



Leveraging Administrative Data for
Clinical Profiling in Coronary Artery Bypass Grafting

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Insights and Applications

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Doctoral Thesis

Leveraging Administrative Data for Clinical Profiling in Coronary Artery Bypass Grafting

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Armando Abreu

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Disclaimer

This doctoral thesis is submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy at Faculty of Medicine of the University of Porto. The research presented in this thesis represents the original work of the author, conducted under the supervision of Prof. Dr. Adelino Leite-Moreira, and has not been submitted for any other degree or award.

Colophon

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*The aim of science is not to open the door to infinite wisdom,
but to set a limit to infinite error.*

Bertolt Brecht

Abstract

This thesis examines leveraging administrative data for clinical profiling to deepen our understanding of long-term survival outcomes in patients who have undergone coronary artery bypass grafting (CABG). By analysing a large and diverse cohort, this research investigates the interactions among patient demographics, modifiable risk factors, and surgical techniques, contributing to evidence-based cardiac care advancements.

Key findings indicate that obesity does not confer a protective effect on long-term survival, demonstrating its correlation with traditional atherosclerosis risk factors. This underscores the necessity of weight management in secondary prevention strategies. The study also emphasises the benefits of smoking cessation during the initial hospital admission in reducing cardiac mortality. Furthermore, it reveals the negative impact of preoperative anaemia and blood transfusions on survival, highlighting the importance of perioperative optimisation. Additionally, the research uncovers sex-based disparities in CABG outcomes; however, these disparities disappear after adjusting for baseline characteristics, suggesting a need to revise traditional risk models that disproportionately weigh female sex. Procedural findings also demonstrate that bilateral internal thoracic artery grafting yields superior long-term outcomes in selected populations while providing nuanced insights into the relative risks and benefits of off-pump versus on-pump CABG.

This thesis illustrates the significant role of administrative data in tackling clinically relevant questions, providing a strong, real-world perspective that enhances the evidence gathered from traditional clinical trials. Incorporating advanced statistical techniques such as propensity score methodologies, competing-risk analysis, and spline modelling establishes a solid foundation for refining risk stratification models and advancing personalised treatment strategies. The implications of these findings are far-reaching, contributing to improved patient outcomes, shaping clinical guidelines, and fostering data-driven innovations within healthcare.

Resumo

Esta tese examina a utilização de dados administrativos para o perfilamento clínico, com o objectivo de aprofundar a compreensão sobre os resultados de sobrevivência a longo prazo em doentes submetidos a cirurgia de revascularização do miocárdio (CABG). Através da análise de uma coorte ampla e diversificada, esta investigação explora as interações entre as características demográficas dos doentes, os fatores de risco modificáveis e as técnicas cirúrgicas, contribuindo para avanços nos cuidados cardíacos baseados na evidência.

Os principais resultados indicam que a obesidade não apresenta um efeito protector na sobrevivência a longo prazo, mas demonstra uma forte correlação com os fatores de risco tradicionais para a aterosclerose, destacando a importância da gestão de peso nas estratégias de prevenção secundária. Este estudo evidencia também os benefícios da cessação tabágica durante a admissão hospitalar inicial na redução da mortalidade cardiovascular. Além disso, revela o impacto negativo da anemia pré-operatória e das transfusões de sangue na sobrevivência, sublinhando a necessidade de uma optimização perioperatória eficaz. Adicionalmente, a investigação identificou disparidades relacionadas com o sexo nos resultados da CABG; contudo, estas diferenças desaparecem após o ajustamento para as características basais, sugerindo a necessidade de rever os modelos de risco tradicionais que atribuem um peso desproporcional ao sexo feminino. Os resultados relacionados com a técnica cirúrgica demonstram que a utilização de enxertos bilaterais da artéria torácica interna proporciona melhores resultados a longo prazo em populações seleccionadas, ao mesmo tempo que oferece uma análise detalhada dos riscos e benefícios relativos entre CABG com e sem circulação extracorporeal.

Esta tese ilustra o papel crucial dos dados administrativos na abordagem de questões clinicamente relevantes, fornecendo uma perspectiva sólida e realista que complementa a evidência obtida nos ensaios clínicos tradicionais. A integração de técnicas estatísticas avançadas, como metodologias baseadas em *propensity scores*, análise de riscos competitivos e modelagem com *splines*, estabelece uma base robusta para o aperfeiçoamento de modelos de estratificação de risco e para o desenvolvimento de estratégias de tratamento personalizadas. As implicações destes resultados são abrangentes, contribuindo para a melhoria dos resultados dos doentes, para a formulação de *guidelines* clínicas e para a promoção da inovação baseada em dados no sector da saúde.

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Completing this PhD thesis marks a significant milestone in my academic journey, a path enriched by the unwavering support and contributions of numerous individuals and institutions. While it is not possible to mention everyone who has played a role in this process, I would like to take this opportunity to express my heartfelt gratitude to those who have been pivotal in helping me reach this point.

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This thesis is dedicated to the memory of my father, whose life was tragically cut short by coronary artery disease during my doctoral journey. His loss has deeply shaped my perspective and strengthened my commitment to the work presented in these pages. I am profoundly grateful to my family for their unwavering support throughout this challenging time. Their encouragement, love, and understanding provided me with the strength to persevere, even during the most difficult moments. To my father, whose memory continues to inspire me, and to my family, who stood by me every step of the way, this work is as much theirs as it is mine.

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Moving forward, I hope to pay forward the generosity and kindness shown to me. My aim is to foster environments that support learning, inquiry, and collaboration, much like those I have been fortunate to be part of during my doctoral studies. This acknowledgment, though undoubtedly limited in capturing the full breadth of support, stands as an expression of my deep appreciation. Thank you all for being integral parts of my academic journey and for your contributions toward my success. I am excited to see how the knowledge gained through this research can lead to tangible improvements in clinical practices and patient outcomes, ideally benefiting the community and the fields at large.

Armando Abreu

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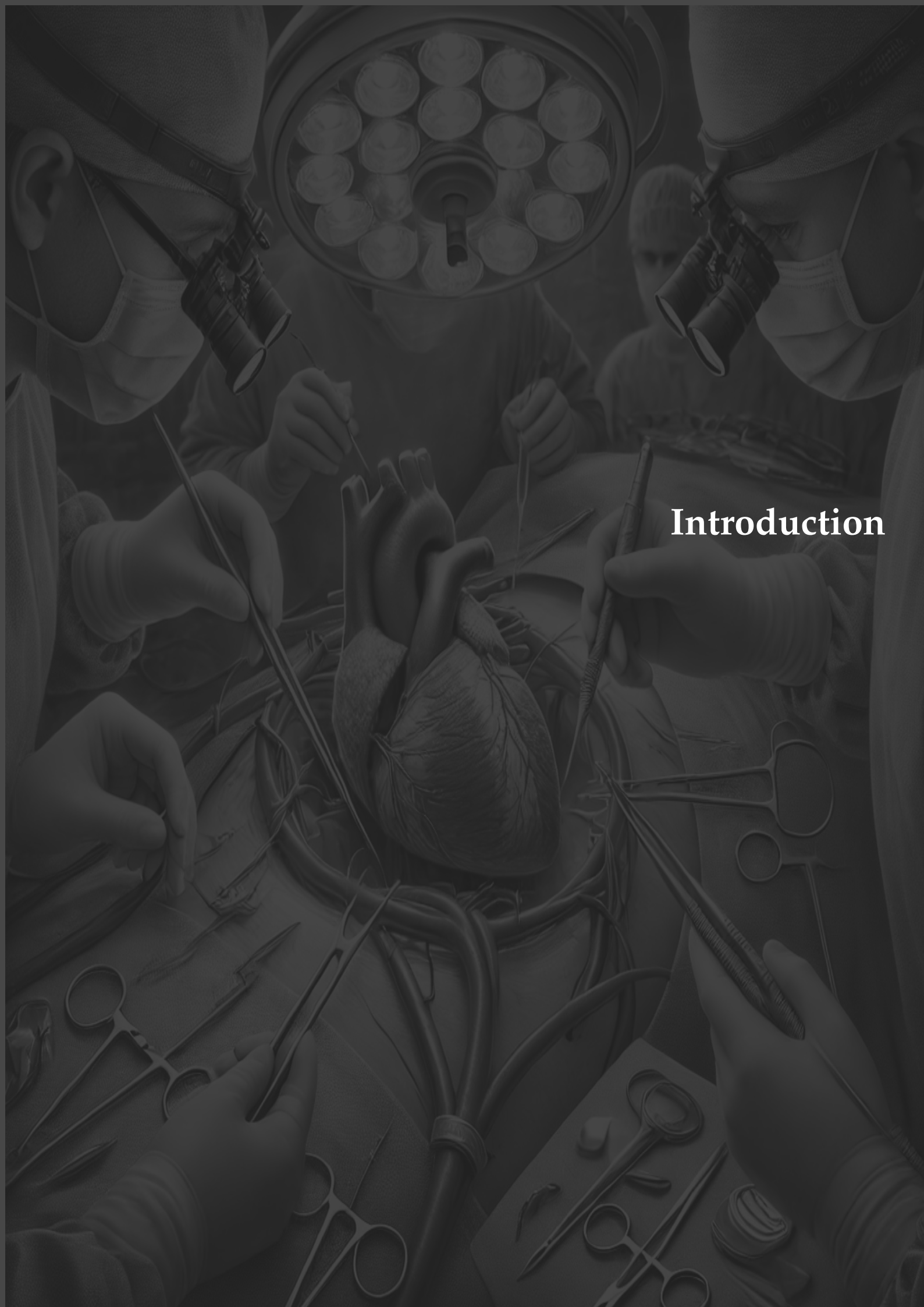
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Introduction

"The idea that the future is unpredictable
is undermined every day
by the ease with which the past is explained."
Daniel Kahneman

1.1. Background

Ischaemic heart disease (IHD), also known as coronary artery disease (CAD), remains a leading cause of mortality and morbidity worldwide, casting a long shadow over global health [1, 2]. Fueled by the increasing adoption of Western lifestyles, the prevalence of risk factors, such as high blood pressure, high cholesterol, smoking, diabetes, and obesity, is on the rise [3, 4]. The vascular response to these diverse causes of endothelial injury exhibits a consistent pattern – the atherosclerotic process. Atherosclerosis consists of a pathological reaction to an arterial endothelium insult that promotes the intimal buildup of lipids and inflammatory cells resulting in plaque formation and arterial blood flow obstruction [5]. All the clinical presentations of IHD stem from the resulting imbalance between myocardial oxygen supply and demand [6]. Despite significant advances in medical, interventional, and surgical therapies, managing IHD remains a complex and evolving challenge, demanding innovative approaches to risk stratification, treatment selection, and long-term care.

For patients with advanced CAD, particularly those with multivessel involvement, significant left main (LM) coronary artery stenosis, or left ventricular (LV) dysfunction, coronary artery bypass grafting (CABG) has long been established as a cornerstone therapy [7, 8]. In these select high-risk populations, CABG offers superior outcomes in terms of survival, symptom relief, and prevention of major adverse cardiovascular events compared to medical therapy or percutaneous coronary intervention (PCI) [9–13]. By restoring blood flow to the ischaemic myocardium, CABG addresses the underlying imbalance between myocardial oxygen supply and demand, thereby reducing anginal symptoms and improving quality of life [14–16]. The procedure involves the creation of new routes to bypass obstructed coronary artery segments using conduits such as the greater saphenous vein (GSV) or internal thoracic artery (ITA). Advances in surgical techniques, anaesthesia, and perioperative care have significantly improved the safety and efficacy of CABG, making it a durable option for the long-term management of complex CAD. However, the complexity of the procedure, the heterogeneity of patient characteristics, and the influence of numerous perioperative factors necessitate a nuanced, data-driven

approach to optimise outcomes – underscoring the critical need for innovative tools for clinical profiling and risk stratification.

Despite the established benefits of CABG, achieving optimal patient outcomes depends heavily on accurate clinical profiling and risk stratification [17]. However, the complexity and heterogeneity of CABG patients, combined with the reliance on traditional data collection methods, pose significant challenges to personalised care. Many institutions lack prospective clinical databases, and retrospective chart abstraction remains labour-intensive, time-consuming, and prone to error [18]. These limitations hinder the ability to identify meaningful patterns, assess patient-specific risks, and ensure evidence-based decision-making. Furthermore, clinical guidelines often rely on data from controlled trials that may not fully represent the real-world diversity of CABG populations [8]. In this context, leveraging alternative data sources, such as administrative data, offers an underexplored yet promising opportunity to bridge these gaps, improve clinical profiling, and advance patient care [19].

Routinely collected for billing, regulatory, and operational purposes, administrative data represents a vast and largely untapped resource for advancing clinical profiling and research in CABG [20]. Unlike traditional data collection methods, administrative data is readily available, cost-effective, and encompasses large populations, often reflecting real-world diversity more accurately than controlled trial data [18, 19, 21]. These datasets typically include critical information, such as patient demographics, diagnoses, procedures, and outcomes, which can be leveraged to develop risk models, assess treatment effectiveness, and identify patterns of care [22]. Moreover, the administrative data scale enables advanced statistical methods, such as propensity score matching (PSM) and inverse probability weighting (IPW), to account for confounding variables and mimic randomised controlled trial (RCT) conditions [23, 24]. Despite its limitations – such as lack of granularity and potential coding inaccuracies – when integrated with clinical data and analysed judiciously, administrative data has the potential to assist in risk stratification, optimise treatment selection, and inform quality improvement efforts in CABG [19].

The convergence of these trends – the enduring burden of CAD, the complexity of CABG, and the availability of administrative data – presents a compelling opportunity to transform clinical profiling and improve patient outcomes in cardiac surgery. By applying advanced analytical techniques to these comprehensive datasets, researchers can uncover hidden patterns, identify high-risk subgroups, personalise treatment strategies, and drive quality improvement initiatives. These efforts have the potential to translate into tangible benefits for patients undergoing CABG, fostering more precise, personalised, and value-based cardiac care. This thesis explores the untapped potential of administrative data to

illuminate the CABG landscape and chart a path toward innovative and data-driven approaches in cardiac surgery.

1.2. Statement of the Problem

Cardiac surgeons bear a profound responsibility to master the substantive issues underlying the quality of care, as this directly impacts patient outcomes and the advancement of the healthcare system [25]. However, translating this responsibility into actionable insights remains a significant challenge, particularly in settings where data infrastructure is limited.

Over its fifty-year history, our department has struggled to maintain a consistent prospective database. This has resulted in a fragmented information landscape, with patient records dispersed across multiple paper-based sources. Consequently, retrospective data abstraction becomes an arduous, error-prone process, severely limiting the availability of reliable outcome reports for a population of nearly four million in Northern Portugal. Without a structured and accessible data repository, critical insights into patient demographics, comorbidities, procedural details, perioperative complications, and long-term survival remain unattainable.

Administrative data, on the other hand, represents a promising alternative. Readily available and inherently broad in scope, these datasets mitigate several challenges posed by traditional data sources. They reduce the risk of informative bias, facilitate linkage to other databases, and enable the study of rare events and population-level trends over time [19]. While not originally intended for clinical profiling, the strategic application of administrative data can fill critical gaps in understanding, particularly when used to examine the quality of care and outcomes in cardiac surgery.

This thesis stems from the belief that the enthusiastic engagement of cardiac surgeons in research, education, and policy development concerning the quality of care is essential for improving the overall performance of the healthcare system. By addressing the barriers to reliable data access and leveraging the potential of administrative datasets, this work aims to bridge the gap between existing knowledge and actionable solutions for enhancing CABG outcomes.

1.3. Aim and Scope of the Study

Long-term survival is, arguably, the most critical outcome for patients undergoing coronary artery bypass grafting (CABG), as it reflects both the immediate and sustained benefits of surgical intervention. The overarching aim of this thesis is to examine

long-term survival in patients with ischaemic heart disease (IHD) undergoing primary, isolated CABG within a contemporary Northern Portuguese population. This research seeks to elucidate how demographic, comorbid, and technical factors influence survival, identifying both protective and detrimental determinants of long-term outcomes.

To achieve this aim, the study is structured around the following specific objectives:

Objective 1. To evaluate differences in long-term survival between female and male patients undergoing primary isolated coronary artery bypass grafting for ischaemic heart disease.

Objective 2. To assess the impact of body mass index, as a surrogate measure of obesity, on long-term survival in patients undergoing primary isolated coronary artery bypass grafting.

Objective 3. To analyse the effect of smoking status on long-term survival in patients undergoing primary isolated coronary artery bypass grafting.

Objective 4. To evaluate the independent and combined effects of preoperative anaemia and perioperative red blood cell transfusion on long-term survival in patients undergoing primary isolated coronary artery bypass grafting.

Objective 5. To compare long-term survival between single and bilateral internal thoracic artery grafting in patients under 70 years of age with multivessel ischaemic heart disease.

Objective 6. To compare long-term survival outcomes between off-pump and on-pump techniques in patients with multivessel ischaemic heart disease undergoing primary isolated coronary artery bypass grafting.

The scope of this study is intentionally regional, focusing on a Northern Portuguese population. This approach facilitates direct linkage to clinical, laboratory, imaging, and vital status databases, which might otherwise be cumbersome with nationwide data. Although this regional focus may limit the sample size, it enables the integration of high-quality, detailed datasets, enhancing the reliability and relevance of the findings to this specific population.

This research also narrows its focus to a pre-specified set of demographic, comorbid, and technical factors. This targeted approach is designed to address key questions in healthcare, such as the impact of sex equity on access and outcomes, the role of risk factor modification in prognosis, and the importance of procedural nuances in optimising long-term survival. By shedding light on these critical factors, this thesis aims to contribute actionable insights that can improve both clinical decision-making and policy formulation in cardiac surgery.

1.4. Significance of the Study

This thesis holds significant potential to impact clinical research and practice in coronary artery bypass grafting (CABG) through four primary contributions:

Extending Knowledge to a Specific Population. By revising current knowledge on CABG and applying it to a contemporary Northern Portuguese population, this thesis bridges the gap between global evidence and local practice. It aims to uncover insights specific to this regional cohort, enhancing the applicability of CABG research to diverse and underrepresented populations.

Addressing Practical Data Challenges. The absence of prospective clinical databases is a widespread challenge faced by many surgical groups, including our department. This study demonstrates the feasibility and reliability of leveraging administrative datasets, coupled with cross-linkage to clinical, laboratory, imaging, and vital status databases. By showcasing a practical solution to this problem, the thesis provides a replicable model for institutions grappling with similar data limitations.

Employing Advanced Statistical Methodology. To ensure robust and reliable results, this study employs sophisticated statistical techniques, including propensity score methods to account for confounding and competing risks analysis to explore causes of late mortality. These approaches enhance the validity and reproducibility of the findings, contributing methodological advancements to CABG outcome research.

Catalysing the Development of Prospective Clinical Databases. The findings of this thesis are evaluated against existing literature to validate their relevance and reliability. Beyond this, the study aims to catalyse the definitive creation and maintenance of a prospective clinical database, incorporating standardised variables and outcomes. This effort has the potential to elevate the quality of clinical data collection and analysis, fostering improvements in patient care and surgical outcomes.

Through these contributions, this thesis not only addresses critical gaps in CABG knowledge and practice but also sets a foundation for future research and quality improvement initiatives. By integrating advanced analytical methods with readily available administrative data, this work aspires to enhance the precision, personalisation, and value of cardiac surgery outcomes, both regionally and beyond.

1.5. Overview of the Study

This thesis is organized into five main parts, each designed to systematically address the overarching aim and objectives of the

study. Following this introductory chapter, the **Second Part** of the thesis focuses on the background, comprising three chapters that explore the foundational aspects of the research. The first chapter in this part, Ischaemic Heart Disease, delves into the pathophysiology, clinical manifestations, and current management strategies of ischaemic heart disease (IHD), emphasising its relevance to coronary artery bypass grafting (CABG). The second chapter, Coronary Artery Bypass Grafting, reviews the evolution, techniques, and clinical outcomes of CABG, highlighting its pivotal role in the treatment of high-risk patients with IHD. The third chapter, Administrative Data, investigates the characteristics, advantages, and limitations of administrative datasets, discussing their applicability to clinical research and their potential to enhance CABG outcome analyses.

The **Third Part** of the thesis, General Methods, comprises a single chapter that outlines the datasets, statistical techniques, and analytical approaches employed in the study. This section serves as the methodological foundation for the research, detailing the processes and tools used to achieve the study's objectives.

The **Fourth Part** of the thesis includes a compilation of six published studies, which together address the core objectives of this research. Each study examines specific factors influencing long-term survival in patients undergoing CABG, with a focus on demographic, comorbid, and technical variables. Presented in their original published formats, these studies retain their scholarly integrity while contributing to the comprehensive exploration of the thesis topic.

The **Fifth Part**, General Discussion and Conclusions, consists of a single chapter that synthesises and critically evaluates the findings from the compiled studies. This chapter contextualises the results within the existing body of literature, discusses the implications for clinical practice and research, and addresses the limitations of the study. It concludes by proposing directions for future research and summarising the overall contributions of the thesis to cardiac surgery and healthcare.

This structure ensures a logical progression from foundational background knowledge to detailed analyses and integrative discussions, providing a cohesive framework for addressing the research aims and objectives.



Background

"There is a disorder of the breast marked with strong and peculiar symptoms... and appears to deserve some notice. The seat of it, and the sense of strangling and anxiety with which it is attended, may make it not improperly be called the angina pectoris."

William Heberden

Ischaemic heart disease (IHD) refers to a spectrum of closely related syndromes caused by an imbalance between cardiac blood supply (perfusion) and myocardial oxygen and nutritional demands. In the overwhelming majority of cases, IHD is a consequence of reduced coronary blood flow secondary to obstructive atherosclerotic vascular disease [26]. Thus, IHD is usually synonymous with coronary artery disease (CAD).

IHD is the leading cause of morbidity and mortality worldwide [1], bringing about an immense impact and economic burden on public health systems [27]. In the past several decades, high-income countries have seen a consistent decline in IHD incidence due to the implementation of preventive and therapeutic strategies targeting modifiable risk factors such as smoking, hypertension, and hyperlipidaemia. Meanwhile, the adoption of Western lifestyles, including tobacco consumption, sedentary behaviour, and poor dietary habits, has contributed to a rising incidence of CAD in low- and lower-middle-income countries, posing a growing health hazard. This increasing burden is further amplified by demographic shifts, such as increased life expectancy [3].

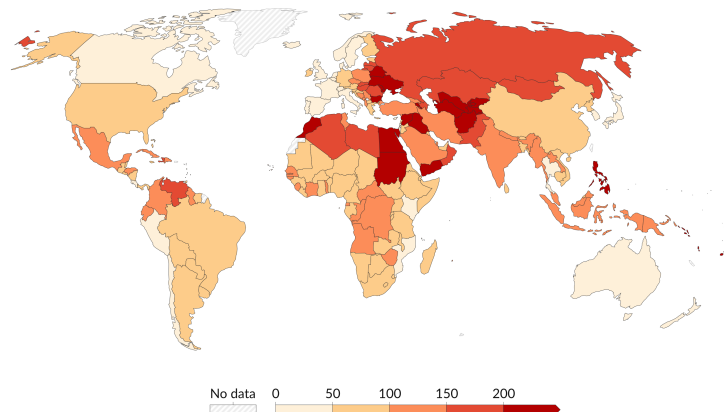
This chapter provides a comprehensive analysis of IHD, including its epidemiology, global trends, underlying mechanisms, and clinical manifestations, with an overview of its management strategies. While a detailed exploration of diagnostic and therapeutic modalities exceeds the scope of this chapter, it is essential to gain a thorough understanding of IHD's pathophysiology, as this underlies the condition treated by coronary artery bypass grafting (CABG). Therefore, this chapter serves as a prelude to the subsequent sections, providing essential context before delving into the central themes of the thesis.

2.1. Epidemiology and Global Trends

Ischaemic heart disease (IHD) remains the leading cause of death and disability worldwide, contributing significantly to the global burden of cardiovascular diseases (CVDs). According to the World Health Organization (WHO), approximately 17.9 million deaths

Death rate from ischaemic heart disease, 2021

Estimated annual death rate from ischaemic heart disease¹, also known as coronary artery disease, per 100,000 people in the population.



Data source: World Health Organization (2024)

OurWorldinData.org/cardiovascular-diseases | CC BY

Note: To allow for comparisons between countries and over time, this metric is age-standardized².

Figure 2.1.: Estimated annual mortality rate from ischaemic heart disease per 100,000 people in the population (Source: OurWorldinData.org, Licence: CC BY).

were attributed to cardiovascular diseases in 2019, with IHD accounting for nearly 9 million of those fatalities, making it the most prevalent cause of cardiovascular mortality [2]. The Global Burden of Disease Study further highlights that IHD was responsible for 182 million disability-adjusted life years (DALYs) globally in 2019 [4]. This enormous burden underscores the public health significance of IHD and the necessity for effective prevention, diagnosis, and treatment strategies (Figure 2.1).

2.1.1. Global Prevalence and Regional Variations

The prevalence of IHD varies considerably across different regions, reflecting disparities in risk factors, healthcare access, and economic development. In high-income countries, the implementation of robust preventive strategies targeting smoking, hypertension, hyperlipidaemia, and sedentary lifestyles has led to a notable decline in IHD incidence over the past several decades [1]. For example, countries like the United States, Canada, and many parts of Western Europe have seen reductions in IHD-related mortality. The improvement is largely attributed to interventions that have diminished cardiac risk factors (behaviours or conditions that promote atherosclerosis), particularly smoking cessation programs, hypertension and diabetes treatment, and the use of cholesterol-lowering agents [28]. However, the epidemic of obesity and type 2 diabetes affecting Western countries endangers this trend.

Meanwhile, in low- and lower-middle-income countries (LMICs) across the world, the increasing adoption of Western lifestyles contributes to an increased incidence of IHD, posing a growing health hazard. Several factors account for this increasing burden, such as increased life expectancy, tobacco consumption, sedentary lifestyles, and poor dietary habits [3]. What makes the IHD

challenge particularly daunting for many developing countries is that, compared to their higher-income counterparts, they will face higher levels of IHD at earlier stages of economic development, with fewer resources and less time to respond effectively. Addressing this tendency calls for policy and legislative interventions for health promotion and primary prevention, similar to those successfully implemented in many high-income nations [29].

2.1.2. Factors Contributing to Global Trends

A consistent body of evidence identifies a core set of risk factors that substantially impact trends in ischaemic heart disease (IHD) incidence and mortality on a global scale [30]. Key contributors such as dietary habits, tobacco use, physical inactivity, excessive alcohol consumption, and psychosocial factors stand out as significant drivers of increasing IHD incidence, particularly in comparisons between high-income and lower-income countries [31].

- ▶ *Ageing Population:* The global increase in life expectancy has led to a growing population of elderly individuals, who are at higher risk for IHD. In both high- and low-income countries, age is one of the strongest predictors of IHD incidence [31].
- ▶ *Nutritional Transition:* Epidemiological evidence suggests that dietary changes associated with the nutritional transition, specifically the increasing consumption of energy-dense diets high in unhealthy fats, oils, sodium, and sugars, have contributed to an increase in IHD incidence in low and middle income countries [32].
- ▶ *Tobacco Use:* Despite global efforts to reduce smoking, it remains a major contributor to IHD, particularly in regions where tobacco control policies are less stringent. Smoking prevalence has declined significantly in high-income countries but remains high in many low- and middle-income nations [33]. In fact, three of the top five cigarette-consuming countries are LMICs (China, Russia, and Indonesia). China alone consumes approximately 2.163 trillion cigarettes every year – 37% of the world’s annual consumption [31].
- ▶ *Sedentary Lifestyles:* An emerging body of evidence suggests that rapid dietary changes associated with nutritional transition, along with a decrease in levels of physical activity in many rapidly urbanising societies, may play a particularly important role in the rise of IHD observed in developing countries [34].
- ▶ *Psychosocial Factors:* Psychosocial factors, including stress at work and at home, financial stress, and major life events in the past year, have been reported to be independently associated with IHD. The presence of psychosocial stressors is associated with an increased risk of acute myocardial infarction [35].

2.1.3. Morbidity and Mortality

The IHD impact on morbidity and mortality is staggering. In 2019, IHD alone was responsible for nearly 16% of all deaths worldwide [2]. While high-income countries have seen a marked decrease in IHD-related mortality attributed to interventions that have diminished cardiac risk factors, in particular smoking cessation programs, hypertension and diabetes treatment, and use of cholesterol-lowering agents, IHD continues to cause a substantial number of deaths, especially among older populations. In the United States, for example, the Centers for Disease Control and Prevention (CDC) reports that IHD accounts for approximately one in every five deaths [36].

Age-adjusted mortality rates for IHD are consistently higher in developing countries compared to their developed counterparts. For example, the proportion of IHD deaths reported for 35 to 64 years is 41 percent in South Africa, 35 percent in India, and 28 percent in Brazil, compared to only 12 percent in the United States and 9 percent in Portugal [37]. Furthermore, a notably greater proportion of IHD-related deaths among younger populations is observed in these developing nations, highlighting a stark contrast in demographic impact between the two contexts [4]. The growing burden of IHD in these regions is particularly concerning because it disproportionately affects working-age adults, leading to significant economic losses and reduced productivity.

2.1.4. Economic Burden

The economic burden of IHD is immense, both in terms of direct healthcare costs and indirect costs related to lost productivity and disability. In high-income countries, IHD treatment costs have risen due to the increasing use of advanced medical technologies, including revascularisation procedures like percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG). In the United States alone, the direct and indirect costs of IHD increased from \$103.5 billion in 1996 to 1997 to \$213.8 billion in 2014 to 2015 [38].

The burden of IHD is disproportionately higher in low- and middle-income countries (LMICs) compared to high-income countries (HICs), with over 80% of IHD-related deaths occurring in these regions [39–41]. Moreover, IHD affects working-age populations much more in LMICs compared to HICs [42]. For example, in Sub-Saharan Africa, half of cardiovascular deaths occur in the 30–69 years age group, at least a decade earlier than in HICs [43]. Between 2011 and 2015, the total economic loss attributable to cardiovascular diseases in LMICs was estimated to be \$3.7 trillion (2010), accounting for approximately half of the overall non-communicable diseases (NCD) economic burden and 2% of the Gross Domestic Product (GDP) of these countries [44].

2.1.5. Summary

IHD remains the most significant contributor to global cardiovascular mortality and morbidity. While high-income countries have made substantial progress in reducing IHD incidence and mortality through preventive strategies and medical advancements, LMICs face a growing burden due to lifestyle changes and insufficient healthcare resources. Understanding these global trends is essential for addressing the challenges posed by IHD and developing targeted interventions. The increasing incidence of IHD worldwide underscores the importance of effective management strategies, including coronary artery bypass grafting (CABG), which remains one of the most effective treatments for advanced IHD.

2.2. Pathophysiology

Atherosclerosis is the fundamental underlying pathogenic mechanism of CAD. In such a circumstance, this term is used interchangeably with IHD. Atherosclerosis is a stereotypical, pathological vascular response to endothelial injury involving a complex interplay between endothelial dysfunction, lipid metabolism, inflammation, and thrombosis [45]. This process impacts the coronary arteries by limiting their ability to provide oxygen-rich blood to the heart muscle. Its clinical manifestations are a direct consequence of inadequate oxygen delivery to the heart, including such disparate clinical syndromes as chronic and acute coronary syndromes, ischaemic cardiomyopathy, and sudden cardiac death [6].

2.2.1. Normal Arterial Wall

The artery wall has the same components and organisation throughout the body, consisting of three layers, the intima, the media, and the adventitia, arranged from the inside out (Figure 2.2) [46].

A single layer of endothelial cells lines the interior surface of the intima, forming a biologically active barrier between circulating blood and the subendothelial space. Beyond containing blood within the vessel's lumen, the endothelium facilitates metabolite exchange between the blood and tissues. It also secretes antithrombotic molecules, maintaining a non-thrombogenic surface that allows smooth blood flow. Additionally, endothelial cells regulate local vascular tone and blood flow by releasing substances influencing smooth muscle contraction or relaxation. Finally, they modulate immune responses by expressing adhesion molecules on their surface, inducing specific white blood cells to adhere and migrate across the endothelium at sites of injury or infection.

The intima is separated from the media – the artery's thickest layer – by the internal elastic lamina. The media comprises smooth

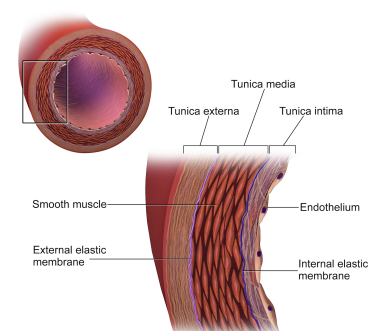


Figure 2.2.: The structure of an artery wall (Source: Wikimedia Commons, Licence: © CC BY 3.0).

muscle cells (SMCs) and extracellular matrix (ECM), providing the vessel with both contractile and elastic properties. SMCs in the medial layer have dual roles: they regulate vessel contraction in response to vasoactive substances, leading to vasoconstriction or vasodilation, and they synthesise key ECM components such as collagen, elastin, and proteoglycans. Additionally, SMCs produce vasoactive and inflammatory mediators, playing an active role in the chronic inflammatory response.

The media is separated from the adventitia by the external elastic lamina. This layer contains nerves, lymphatics, and blood vessels (*vasa vasorum*) that nourish the arterial wall cells.

2.2.2. Initiation of Atherosclerosis

Beyond its anatomical role as a physical barrier between blood and tissue, the endothelium regulates vascular tone, maintains an antithrombotic surface, and controls inflammatory cell adhesion [47]. Exposure to atherogenic risk factors, such as hypertension, hyperlipidaemia, and toxins in tobacco smoke, disrupts this balance, leading to endothelial dysfunction. This dysfunction manifests as increased permeability, tendency for thrombus formation, and leukocyte adhesion, all contributing to atherosclerosis.

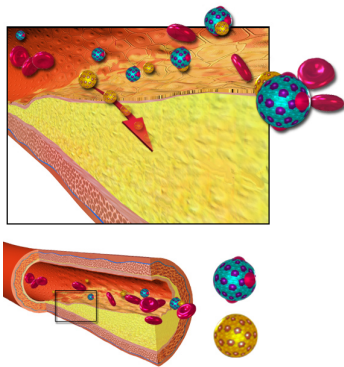


Figure 2.3.: Atherosclerosis is associated with inflammatory processes in the endothelial cells of the vessel wall associated with retained low-density lipoprotein particles (Source: WikiCommons, Licence: CC BY 3.0).

The dysfunctional endothelium can no longer effectively prevent circulating lipoproteins from entering the arterial wall. Low-density lipoproteins (LDL), which transport water-insoluble cholesterol through the bloodstream, become key participants in atherosclerosis when their levels exceed physiological needs. While the human body typically maintains LDL cholesterol levels around 25 mg/dL, individuals on a typical Western diet high in fat and cholesterol often have levels exceeding 100 mg/dL [48]. Both the absolute levels and the cumulative duration of exposure to elevated LDL cholesterol are crucial in the initiation and progression of atherosclerosis [49].

LDL particles contribute to developing atherosclerotic plaques by penetrating the dysfunctional endothelium and infiltrating the arterial walls (Figure 2.3) [50]. Once in the intima, these particles are retained by extracellular matrix proteoglycans, which increase their residence time within the vessel wall. This extended retention allows them to undergo oxidation, catalysed by powerful oxidants produced through the lipoxygenase and myeloperoxidase pathways [51]. These modified LDL particles promote leukocyte recruitment.

Under normal conditions, leucocytes travel in the centre of the bloodstream due to higher shear forces. However, during inflammation, changes in blood flow facilitate leukocyte movement toward the endothelial surface, a process known as margination. Activated endothelial cells upregulate adhesion molecules, such as selectins and integrins, which promote leukocyte binding to the vascular

wall [52]. This process is essential for leucocyte rolling, firm adhesion, and eventual transmigration through the endothelium to reach sites of inflammation or injury. Following margination and adhesion, leucocytes undergo diapedesis, squeezing between endothelial cells and entering surrounding tissues. This chain of events sets a complex pathogenic sequence into motion, involving the selective recruitment of circulating leukocytes from the bloodstream into the intima, where they differentiate into macrophages [53]. Consequently, biomarkers of inflammation, such as C-reactive protein (CRP), have been shown to prospectively predict cardiovascular risk and increase alongside many well-established cardiovascular risk factors [54].

Finally, macrophage scavenger receptors recognise and internalise modified LDL particles through endocytosis, forming cholesterol-laden foam cells – the hallmark of early fatty streak lesions [55, 56]. On gross inspection, these lesions appear as yellowish discolourations on the arterial inner surface without significantly protruding into the lumen or obstructing blood flow. Fatty streaks are commonly present in the coronary arteries by age 20, are typically asymptomatic, and may even regress over time.

2.2.3. Progression of Atherosclerosis

The transition from fatty streak to fibrous atheromatous plaque involves the migration of SMCs from the arterial media into the intima [6]. These contractile vascular SMCs recruited from the media undergo phenotypic conversion to proliferative synthetic cells that generate an extracellular matrix (ECM) to create a fibrous cap over the lipid core and stabilise plaques [57].

In addition to providing structural stability to plaques, ECM macromolecules, namely proteoglycans, play a central role in the progression of atherosclerosis. These negatively charged molecules interact with positively charged apolipoproteins (particularly apolipoprotein B), leading to the retention and accumulation of LDL cholesterol [58]. Once retained in the intima, these lipoproteins undergo oxidation, thereby enhancing macrophage recruitment and the inflammatory response characteristic of atherosclerosis [59]. These recruited macrophages, in turn, support further vascular SMC migration, proliferation, and phenotype switching through the production of factors such as platelet-derived growth factor (PDGF) [60].

This phase of atherosclerosis (fibroatheroma) depends on the extensive accumulation of macrophages on the luminal side of the lipid pools, where they phagocytose deposited lipids to become foam cells [61]. In the absence of resolution, the ensuing inflammatory reaction is self-perpetuating. Furthermore, macrophages and vascular SMCs eventually undergo apoptosis. Given that the plaque milieu suppresses the effective removal of apoptotic cells

Table 2.1.: Complications of Atherosclerosis

Pathologic consequence	Clinical correlate
Progressive plaque growth	Chronic coronary syndromes
Acute plaque changes	Acute coronary syndromes
Vessel wall disruption	Aneurysm formation

(efferocytosis), their accumulation forms a necrotic core within the plaque and releases further inflammatory mediators [58].

This chronic inflammatory response leads to increased secretion of matrix metalloproteinases (MMPs) and cathepsins by foam cells [62]. These proteases degrade the structural components of the fibrous cap, weakening the plaque and increasing the risk of rupture. The balance between matrix synthesis, steered by SMCs, and degradation, driven by foam cells, ultimately determines the integrity of the fibrous cap [63]. This dynamic process ultimately influences the likelihood of plaque complications.

2.2.4. Consequences of Atherosclerosis

The principal pathophysiologic outcome stemming from coronary artery atherosclerotic lesions varies depending on the size and stability of the plaques, as well as the degree to which plaques disrupt the vessel wall (Table 2.1).

The tug-of-war between matrix synthesis and degradation continues for decades, affecting the structure of the fibrous cap and, consequently, plaque integrity [6]. In a simplistic conceptual framework, plaques with thick fibrous caps and smaller lipid cores may lead to pronounced arterial narrowing and cause ischaemic symptoms like angina. However, they are less likely to rupture (stable plaques) [64]. Conversely, plaques with thinner caps and a larger lipid core tend to be more fragile, making them prone to rupture, leading to thrombosis and acute coronary events such as myocardial infarction [65].

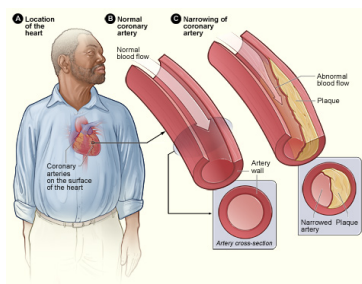


Figure 2.4.: Figure A shows the location of the heart in the body. Figure B shows a normal coronary artery with normal blood flow. The inset image shows a cross-section of a normal coronary artery. Figure C shows a coronary artery narrowed by plaque. The buildup of plaque limits the flow of oxygen-rich blood through the artery. The inset image shows a cross-section of the plaque-narrowed artery (Source: National Heart Lung and Blood Institute, Licence: Public domain).

Progressive Plaque Growth. During much of its life history, the atherosclerotic plaque grows outward rather than inward, a process known as positive remodelling [66]. This process preserves the coronary artery lumen by increasing the overall vessel circumference. However, the expanding atheroma may eventually impinge on blood flow, limiting myocardial perfusion and thus creating an imbalance between oxygen supply and demand. In the coronary circulation, this turning point typically occurs with a 70% reduction in the artery's cross-sectional area [64]. In this circumstance, affected patients have adequate cardiac perfusion at rest, but physical or emotional stress may precipitate myocardial ischaemia (stable angina) (Figure 2.4).

Acute Plaque Change. Acute plaque changes fall into three general categories: plaque rupture, ulceration, or erosion; intraplaque

haemorrhage; atheroembolism. First, *rupture, ulceration, or erosion of an atherosclerotic plaque* exposes procoagulants to blood, leading to thrombus formation at that site. This event may occlude the vessel and cause myocardial infarction, or the thrombus may become organised and added to the plaque [65]. Second, disruption of the overlying fibrous cap or the thin-walled vessels in areas of neovascularisation may lead to *intraplaque haemorrhage* [26]. The resulting haematoma may cause rapid plaque expansion or rupture. Finally, a ruptured plaque may unleash debris into the distal arterial bed, producing microemboli composed of plaque contents (*atheroembolism*) [26].

Vessel Wall Disruption. The fibrous plaque subjects the adjacent medial layer to an increased pressure, inducing atrophy and loss of elastic tissue. This process ultimately weakens the vessel wall, with subsequent aneurysm formation [6].

2.3. Risk Factors

Coronary artery disease (CAD) develops from a complex interaction between genetic predisposition and environmental factors that accelerate the process of atherosclerosis. Identifying and managing the risk factors for CAD is essential for reducing both the incidence of the disease and its clinical consequences, such as myocardial infarction and heart failure. These risk factors are generally divided into two categories: modifiable risk factors, which can be altered through lifestyle changes or medical treatment, and non-modifiable (constitutional) risk factors, which are intrinsic to the individual and cannot be changed (Table 2.2) [67].

2.3.1. Modifiable Risk Factors

While exploring the underlying physiologic causes of death is essential, rigorously assessing upstream drivers of disease offers further avenues to guide public health policies. Research has demonstrated that nine easily measured risk factors account for an overwhelmingly large (over 90%) proportion of ischaemic heart disease risk [30]. In addition, just five risk factors (smoking, dyslipidaemia, hypertension, diabetes, and obesity) contribute to approximately 80% of the attributed risk. Furthermore, their effect is consistent in men and women across different geographic regions and by ethnic group. These actual causes of death are direct modifiable, nongenetic risk factors causing the disease [68]. These factors can be effectively influenced through targeted behavioural modifications or medical interventions.

Cigarette Smoking. Smoking is one of the most significant modifiable risk factors for CAD. The harmful chemicals in tobacco smoke damage the endothelium, promote inflammation, and increase

Table 2.2.: Major risk factors for atherosclerosis.

Constitutional	Modifiable
Genetic causes	Cigarette smoking
Family history	Hypertension
Increasing age	Hyperlipidaemia
Male sex	Obesity and sedentary lifestyle
	Diabetes mellitus
	Diet and alcohol consumption

oxidative stress, which accelerates the atherosclerotic process [69, 70]. Smoking also increases the likelihood of plaque rupture, as it enhances thrombosis by increasing platelet aggregation and reducing fibrinolysis [70]. Epidemiological studies have shown that smokers have a two- to four-fold increased risk of developing CAD compared to non-smokers [70]. Additionally, second-hand smoke exposure has been linked to an increased risk of CAD [71]. Smoking cessation, therefore, represents one of the most effective interventions for reducing the risk of coronary events and improving outcomes in patients with established CAD [72–75].

Hypertension. Hypertension, or high blood pressure, is a major risk factor for CAD [76]. Elevated blood pressure causes mechanical damage to the endothelium, predisposing the arterial wall to infiltrating lipoproteins and developing atherosclerotic plaques [77]. Hypertension also contributes to the progression of plaque instability, increasing the risk of myocardial infarction and stroke [78]. Managing hypertension through lifestyle changes (such as diet, exercise, and weight control) and medications (such as angiotensin-converting enzyme inhibitors or beta-blockers) has been shown to reduce the risk of CAD and its complications significantly [79].

Hyperlipidaemia. Elevated levels of low-density lipoprotein (LDL) cholesterol, commonly referred to as hyperlipidaemia, are a critical driver of atherosclerosis and CAD development [60]. LDL cholesterol is prone to oxidation within the arterial wall, which triggers an inflammatory response, leading to plaque formation [80]. Reducing LDL cholesterol levels through diet, exercise, and pharmacologic agents like statins significantly lowers the risk of CAD events [81]. On the other hand, high-density lipoprotein (HDL) cholesterol plays a protective role by transporting cholesterol away from the arteries to the liver for excretion [82]. Thus, therapies that lower LDL and raise HDL cholesterol levels are central to CAD prevention strategies.

Obesity and Sedentary Lifestyle. Obesity, defined as a body mass index (BMI) greater than 30 kg/m², is an independent risk factor for CAD. Excess body fat, particularly visceral fat, is associated with insulin resistance, dyslipidemia, and systemic inflammation, all of which contribute to atherosclerosis [83]. Obesity also increases the risk of other CAD risk factors, such as hypertension and

diabetes [84]. Physical inactivity exacerbates the risk by reducing cardiorespiratory fitness and promoting visceral fat accumulation. Regular physical activity has been shown to improve cardiovascular health by reducing blood pressure, improving lipid profiles, and enhancing endothelial function [73, 74].

Diabetes Mellitus. Diabetes mellitus, particularly type 2 diabetes, significantly increases the risk of CAD by accelerating atherosclerosis. Patients with diabetes have a higher prevalence of endothelial dysfunction, increased oxidative stress, and abnormal lipid metabolism, all of which contribute to plaque formation [85, 86]. Chronic hyperglycaemia promotes the glycation of proteins and lipids, resulting in advanced glycation end-products (AGEs) that further damage the vascular endothelium [87]. Tight control of blood glucose levels, along with the management of coexisting conditions like hypertension and dyslipidaemia, is essential for reducing CAD risk in diabetic patients [88].

Diet and Alcohol Consumption. Diet plays a central role in the development of CAD. Diets high in saturated fats, trans fats, sodium, and sugars contribute to hyperlipidaemia, hypertension, and obesity, all of which are significant risk factors for CAD [31]. Conversely, diets rich in fruits, vegetables, whole grains, and unsaturated fats (e.g., the Mediterranean diet) have been shown to reduce the risk of CAD by improving lipid profiles and reducing inflammation [89]. Excessive alcohol consumption is also a risk factor for CAD. While moderate alcohol intake has been associated with some cardiovascular benefits, excessive consumption leads to hypertension, arrhythmias, and an increased risk of heart failure [90].

2.3.2. Non-Modifiable Risk Factors

Non-modifiable risk factors are inherent to the individual and cannot be altered, but they are crucial for identifying individuals at higher risk of CAD. These factors highlight the importance of early detection and prevention strategies in at-risk populations.

Age. Advancing age is one of the most significant risk factors for CAD. The risk of developing CAD increases markedly after the age of 45 in men and 55 in women [91]. This increased risk is attributed to the cumulative effect of atherogenic risk factors over time, as well as age-related changes in the arterial wall, such as reduced elasticity and endothelial dysfunction [26].

Sex. Men generally have a higher risk of developing CAD than women, particularly before menopause. However, after menopause, the risk of CAD in women increases due to the loss of the protective effects of estrogen on the cardiovascular system [6]. Estrogen is believed to have favourable effects on lipid metabolism, endothelial function, and inflammation, which may explain the lower risk in premenopausal women. This sex difference in CAD risk is

particularly important in understanding survival outcomes after coronary interventions, such as coronary artery bypass grafting (CABG) [92].

Family History and Genetics. A family history of premature CAD (defined as CAD occurring before the age of 55 in men and 65 in women) is the most important independent risk factor for atherosclerosis [26]. Most familial risk is related to multifactorial traits that go hand in hand with atherosclerosis, including hypertension and diabetes. Inherited genetic mutations that affect lipid metabolism (e.g., familial hypercholesterolaemia) are strongly associated with atherosclerosis, but these account for only a small percentage of cases.

2.3.3. Summary

The development of CAD is influenced by a combination of modifiable and non-modifiable risk factors. While non-modifiable factors such as age, sex, and genetics contribute to inherent risk, modifiable factors like smoking, hypertension, hyperlipidaemia, and diabetes present opportunities for preventive interventions. Effective management of these modifiable risk factors, through lifestyle changes and medical treatment, is critical to reducing the global burden of CAD. On the other hand, understanding these risk factors is essential for identifying high-risk individuals and guiding appropriate preventive and therapeutic strategies, including the use of revascularisation procedures like coronary artery bypass grafting (CABG).

2.4. Clinical Manifestations

Cardiac myocytes generate energy almost exclusively through mitochondrial oxidative phosphorylation, and their proper function and survival strictly depend upon the continuous flow of oxygenated blood through the coronary arteries [26]. As the atherosclerotic process restricts blood flow to the myocardium, the clinical manifestations of coronary artery disease (CAD) are a direct consequence of an inadequate oxygen supply to the heart. Depending on the underlying pathophysiologic process and the timing and severity of a myocardial ischaemic insult, a spectrum of distinct clinical syndromes may result [6].

2.4.1. Chronic Coronary Syndromes

Chronic coronary syndromes (CCS) are generally caused by the progressive luminal encroachment of atheromatous plaque in the proximal epicardial segments of the coronary arteries. The distal arterial bed (arterioles) is usually free of flow-limiting plaques,

allowing it to adjust its vasomotor tone in response to metabolic needs – resistance vessels.

Silent Ischaemia. If a given stenosis narrows the coronary artery lumen diameter by 50-70%, the resting blood flow is not significantly altered [93]. However, the distal resistance vessels dilate during increased physical or emotional stress to accommodate the inflated oxygen myocardial demands. In these asymptomatic individuals, epicardial CAD may be detected during an imaging test to refine cardiovascular risk assessment, screen for personal or professional purposes, or as an incidental finding for another indication [94].

Stable Angina. When a stenosis narrows the coronary artery lumen diameter by more than 70%, resting blood flow is normal. However, when oxygen demand increases with physical or emotional stress, maximal blood flow is reduced even with full dilatation of the resistance vessels. Therefore, myocardial oxygen demand exceeds supply, and ischaemia ensues. If the stenosis compromises the vessel lumen by more than 90%, then even with maximal dilatation of the resistance vessels, blood flow may be inadequate to meet basal requirements, and ischaemia may develop at rest [6].

The clinical correlate to this pathophysiological process is stable angina, the most common manifestation of chronic CAD. It refers to a chronic pattern of transient chest pain or discomfort, typically described as a sensation of pressure, heaviness, or squeezing in the chest, often radiating to the arms, neck, or jaw [95]. It is generally predictable, occurring with physical activity or emotional upset, and is relieved by rest or nitroglycerin (a coronary artery vasodilator). These episodes are often associated with temporary depression of the ST segment on the EKG, but permanent myocardial damage does not result [6].

Ischaemic Cardiomyopathy. Ischaemic cardiomyopathy refers to progressive heart muscle dysfunction resulting from chronic or recurrent ischaemic damage, often following myocardial infarction or ongoing myocardial ischaemia in CAD. Over time, the affected myocardium undergoes fibrosis and remodelling as fibrotic tissue replaces healthy muscle tissue, leading to a strained heart with diminished pumping capacity. This condition is a primary cause of heart failure with reduced ejection fraction (HFrEF) among patients with CAD [26].

As ischaemic cardiomyopathy progresses, patients may experience worsening symptoms, advancing from mild exertional dyspnoea to severe limitations in daily activities and increased hospitalisations. Left untreated, ischaemic cardiomyopathy can lead to severe heart failure, arrhythmias, and eventually death. Management focuses on optimising heart failure therapy (e.g., ACE inhibitors, beta-blockers, diuretics) and, in some cases, revascularisation procedures like CABG to improve blood flow and limit further myocardial damage.

Table 2.3.: Spectrum of acute coronary syndromes.

	UA	NSTEMI	STEMI
Coronary pathology	Partially occlusive thrombus	Partially occlusive thrombus	Completely occlusive thrombus
Myocyte necrosis	No	Yes	Yes

NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; UA, unstable angina

2.4.2. Acute Coronary Syndromes

Acute coronary syndromes represent a spectrum of clinical conditions caused by the rupture or erosion of an unstable atherosclerotic plaque, leading to a sudden reduction in coronary blood flow [65]. ACS is subdivided into three major clinical entities: unstable angina, non-ST-elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI) (Table 2.3).

Unstable Angina. Unstable angina (UA) arises from the partial occlusion of a coronary artery, typically precipitated by plaque rupture accompanied by a superimposed thrombus. Research indicates that approximately two-thirds of these ruptured plaques are associated with less than 50% stenosis prior to disruption, while 97% have stenosis below 70% [96]. Clinically, UA is defined as myocardial ischaemia at rest or on minimal exertion without acute cardiomyocyte injury or necrosis. Specific clinical symptoms include prolonged angina lasting more than 20 minutes at rest, new onset of severe angina, increasing frequency, longer duration, or diminished threshold of angina, or angina that follows a recent myocardial infarction [97].

Myocardial Infarction. Myocardial infarction results from acute thrombotic occlusion of a coronary artery, which reduces blood flow to the myocardium and causes irreversible damage to the myocardium [65]. It is classified into two types based on the electrocardiographic (EKG) findings: non-ST-elevation myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI). Pathologically, NSTEMI is associated with partial or temporary occlusion of a coronary artery, whereas STEMI results from complete coronary artery occlusion. Symptoms of myocardial infarction typically include severe chest pain, often described as a crushing or squeezing sensation that may radiate to the arms, neck, or back. Patients may also experience shortness of breath, diaphoresis, nausea, and a sense of impending doom.

2.4.3. Sudden Cardiac Death

Sudden cardiac death (SCD) is one of the most severe and dramatic complications of CAD, accounting for approximately half of all deaths from cardiovascular disease [98]. It occurs when the heart

suddenly and unexpectedly stops beating, usually due to a fatal arrhythmia such as ventricular fibrillation. The primary cause of SCD in CAD patients is ventricular arrhythmia, which is often triggered by acute ischaemia or infarction, or in patients with ischaemic cardiomyopathy and left ventricular dysfunction [99].

2.4.4. Summary

Coronary artery disease (CAD) can present across a spectrum, from silent ischaemia and stable angina to life-threatening events such as myocardial infarction and sudden cardiac death. Understanding these clinical manifestations is essential for prompt diagnosis and effective management. Recognising the patterns and progression of CAD highlights the importance of timely interventions, including coronary artery bypass grafting (CABG), to control ischaemic symptoms, mitigate myocardial damage, and improve survival in high-risk patients.

2.5. Diagnosis and Management Strategies

The evaluation of IHD begins with an assessment of the likelihood of clinically significant disease, based on a detailed medical history, symptom assessment, physical examination, resting EKG, and laboratory blood tests. These preliminary assessments help identify patients at high risk of IHD and guide the choice of further testing [94]. However, a definitive diagnosis requires imaging tests that can either visualise atherosclerotic plaques directly (e.g., coronary CT angiography, invasive coronary angiography) or document ischaemia using stress tests with imaging (e.g., stress echocardiography, nuclear imaging) [95].

Once clinically significant IHD is confirmed, risk stratification is essential to tailor the management approach. This involves evaluating the patient's risk of future events, incorporating imaging findings, symptom severity, and comorbidities. Most IHD patients benefit from aggressive atherosclerotic risk factor management. Implementing lifestyle changes and pharmacological therapies aimed at reducing these risk factors and addressing features linked to "vulnerability" is essential for preventing the progression and complications of atherosclerosis [6].

Further intervention choices – optimal medical therapy, percutaneous coronary intervention (PCI), or coronary artery bypass grafting (CABG) – depend on the extent, severity, location, and characteristics of the plaques [8]. Risk stratification tools, such as the SYNTAX score, help determine whether patients are better suited for PCI or CABG based on the complexity of coronary lesions and overall risk profile [100]. Each intervention, whether alone or in combination, aims to alleviate ischaemic symptoms,

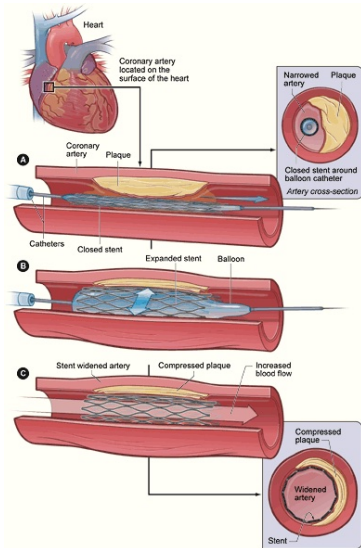


Figure 2.5.: Diagram of coronary angioplasty and stent placement: A, the catheter /DES device is inserted across the lesion. B, the balloon is inflated using saline fed through the catheter portion into the DES/Balloon component, expanding the DES and compressing it against the artery wall. C, the catheter and deflated balloon removed leaving the DES firmly embedded in the artery wall (Source: National Institutes of Health, Licence: Public Domain).

improve quality of life, prevent acute coronary events, and extend survival.

Medical management in CAD prioritises symptom control and slowing disease progression. This approach is essential for all patients and emphasises the importance of long-term adherence to treatment regimens. Some patients might experience long-term reduction of cardiovascular events and anginal symptoms through revascularisation in conjunction with medical therapy and lifestyle modifications [16]. However, for other patients, revascularisation may not be necessary, or the risks associated with the procedure could outweigh the potential long-term benefits, making medical therapy alone the preferred treatment option.

PCI and CABG are mechanistically and clinically very different interventions. PCI specifically addresses flow-limiting stenoses, improving perfusion to distal myocardium. Its technical complexity is largely contingent upon the characteristics of the lesion, including its anatomical location, degree of calcification, and length (Figure 2.5) [101]. Therefore, PCI is typically used for limited disease.

Surgery effectively restores blood flow to the distal myocardium by enabling distal anastomoses while reducing the risk of progressing proximal plaques that were not significantly limiting during the revascularisation procedure [16]. Notably, the technical complexities involved in the surgical intervention are independent of the specific characteristics of the lesions being addressed. Consequently, CABG is often the preferred option for complex cases, such as multivessel disease or left main coronary artery disease, due to its durability and impact on survival. The next chapter will explore the role of CABG in greater detail, examining its indications, procedural considerations, and impact on patient survival and quality of life.

Coronary Artery Bypass Grafting

3.

"To act honestly for the sake of human dignity
is the most important commitment
in our short time on earth."

René Favaloro

Ischaemic heart disease (IHD), or coronary artery disease (CAD), represents a spectrum of conditions caused by impaired blood, nutrient, and oxygen supply to meet myocardial demands. It is a leading cause of morbidity and mortality worldwide, bringing about an immense impact and economic burden on public health systems and profound suffering for millions. Lifestyle modifications and pharmacological interventions are essential in the management of early-stage disease. However, as the disease progresses, more invasive approaches are often required to achieve acceptable myocardial perfusion.

Among these interventions, coronary artery bypass grafting (CABG) has emerged as a cornerstone of IHD treatment, offering a lifeline to countless patients with complex or high-risk disease. This intricate procedure, involving the surgical creation of new conduits to bypass partially or entirely obstructed coronary arteries, represents a triumph of medical innovation and a testament to the relentless pursuit of improving patient outcomes. Since its inception, CABG has undergone a remarkable evolution, driven by a deeper understanding of the pathophysiology of IHD, technological advancements, and refined surgical techniques.

This chapter delves into the multifaceted landscape of CABG, tracing its historical trajectory, exploring current practices and emerging trends, and examining the challenges and opportunities ahead. From the pioneering efforts of early cardiac surgeons to the cutting-edge technologies employed in modern operating rooms, we will navigate the key milestones that have shaped CABG into the sophisticated and life-altering procedure it is today.

This chapter aims to provide a nuanced perspective on the role of CABG in the contemporary management of IHD through a comprehensive examination of patient selection criteria, surgical techniques, operative outcomes, and long-term results. Furthermore, we will explore the evolving landscape of myocardial revascularisation, considering the emergence of minimally invasive approaches and optimal conduit choice, laying the groundwork for the ongoing quest for the optimal treatment paradigm for each patient.

3.1. Historical Perspective

Coronary artery bypass grafting (CABG) is a surgical procedure that uses autologous arteries or veins as grafts to create alternative routes for blood flow. By bypassing coronary arteries partially or entirely obstructed by atherosclerotic plaque, this approach restores adequate blood supply to the heart muscle [14]. Since its introduction in the 1960s, over 20,000,000 CABG procedures have been performed worldwide, firming its status as a cornerstone treatment for coronary artery disease (CAD) [15].

3.1.1. Early Attempts at Managing CAD

In the early twentieth century, the limited understanding of CAD pathophysiology posed a significant challenge in developing reliable techniques to directly address coronary artery obstructions. Without a clear grasp of the disease's underlying mechanisms, early cardiac surgeons were compelled to experiment with various surgical interventions, often relying on indirect methods to manage CAD in the absence of targeted revascularization strategies. These approaches, though not addressing the coronary obstructions directly, were based on managing the symptoms of angina pectoris – a manifestation of CAD – at a time when surgeons lacked the tools and knowledge to intervene on the arteries themselves.

One of these approaches relied on sensory nerve pathway interruption, a concept introduced by the physiologist Charles-Émile François-Franck in 1899 [102]. Based on the hypothesis that the stimuli causing angina pectoris originate in the heart and travel through a nervous pathway to the spinal cord, he admitted that dividing the cervicothoracic sympathetic chain would prevent patients from recognising the symptoms of pain [103]. In 1916, Thoma Ionescu performed sympathectomy on a thirty-year-old man, becoming the first person to treat angina pectoris surgically (Figure 3.1) [104]. Despite the success of the initial case, cervicothoracic sympathectomy failed to gain widespread traction due to its complexity and the ongoing World War I [105].



Figure 3.1.: Thoma Ionescu was the first person to treat angina pectoris surgically in 1916 (Licence: Public Domain).

In the 1920s, thyroidectomy emerged as another popular surgical approach to managing angina pectoris. Previous research had established that addressing the underlying thyroid disease led to symptomatic improvement in hyperthyroid patients with preexisting CAD [106]. Hence, inducing a hypothyroid state in euthyroid patients with angina pectoris was hypothesised to alleviate symptoms by reducing the metabolic workload on the heart [107]. With this objective, Ernst Boas performed a partial thyroidectomy in 1926 without success [108]. In contrast, Elliott Cutler successfully carried out the first total thyroidectomy in 1932, aiming to completely eliminate thyroid activity and further reduce cardiac demand [109].

However, by the early 1940s, clinicians recognised that chemically inducing hypothyroidism was both safer and more effective, ultimately rendering the surgical approach obsolete [110].

These early methods were symptom-focused, aiming to alleviate the pain of angina without improving blood flow to the heart. As the understanding of CAD advanced, surgeons began exploring methods that targeted the root cause of the disease – obstructed coronary arteries – paving the way for the development of coronary revascularisation techniques like CABG.

3.1.2. The Rise of Surgical Revascularisation Attempts

In the early 1930s, a growing understanding of the link between angina and myocardial ischaemia shifted the focus of treatment. Surgeons recognised that angina resulted from inadequate oxygen supply to the myocardium due to coronary artery obstructions and sought to devise procedures to improve coronary circulation directly. The goal was to establish alternative pathways through which oxygenated blood could reach the ischaemic myocardium, addressing the root cause of angina. This objective differed from earlier indirect approaches, such as sympathectomy and thyroidectomy, which focused on symptom management without improving blood flow.

Two pieces of evidence influenced the decision to pursue this surgical revascularisation approach. First, in 1880, Ludwig Langer demonstrated the existence of extensive connections between the coronary circulation and the vascular supply of surrounding intrathoracic structures such as the pericardium, bronchi, and diaphragm [111]. These anastomotic networks were thought to be capable of providing sufficient blood supply to the myocardium beyond atherosclerotic obstructions, offering a potential pathway for bypassing diseased coronary arteries. Second, in 1903, Charles Thorel documented the presence of blood vessels in pericardial adhesions, which he believed could supply blood to ischaemic areas of the heart [112]. These insights provided the theoretical framework for several ingenious operations designed to induce neovascularisation and improve collateral circulation to the myocardium [113, 114]. Although some of these procedures reached clinical application and received temporary acclaim for relieving angina, they ultimately proved less effective in achieving sustained revascularisation [115].

Building on these principles, Claude Beck introduced the use of abrasion of the surface of the heart with a metal burr in the treatment for CAD, a procedure known as cardiopericardiopexy [116]. As granulation tissue proliferated to repair the injury, new arterioles were expected to develop, potentially forming arterial communications between coronary arteries [117]. Beck believed these newly formed blood vessels could function under certain

conditions, providing an additional blood supply to the heart during ischaemic events. However, while this technique showed promise in some cases, it lacked the reliability and long-term efficacy that would be achieved through direct revascularization techniques.

Another approach to establishing a new coronary circulation was creating a vascular network by introducing various grafts onto the myocardium. Anastomoses between the grafts and the heart typically formed within three weeks, driven by the physiological demand for blood in the ischaemic myocardium. In 1935, Beck reported on his cardiomyopexy technique, which involved mechanical abrasion of the epicardium, the instillation of powdered bone into the pericardial space to promote granulation tissue formation, and the use of a pedicled *pectoralis major* muscle graft sutured to the epicardium [116]. Other surgeons experimented with various graft materials, including pericardial and mediastinal fat, omentum, lung, jejunum, pedicled skin, stomach, and spleen, in their efforts to create a functional vascular bed [118]. While innovative, these techniques proved labor-intensive and less effective than the more direct methods that would later emerge.

While Beck and others persevered with their operations for angina pectoris, a few other procedures became popular with surgeons elsewhere. In the early 1940s, after experimental research on coronary anatomy at the Universities of Milan, Padua, and Genoa, Davide Fieschi proposed a novel surgical technique, which was later performed by Zoja and Cesa-Bianchi [119]. The procedure involved ligating the two internal thoracic arteries in the second intercostal space through small incisions in the chest to direct blood flow to the pericardiophrenic arteries, which supply branches to the pericardium. Fieschi hypothesised that the increased blood flow to the heart would alleviate chest pain. This simple procedure afforded spectacular results, namely symptomatic improvement in nearly 95% of cases [120]. However, scepticism arose, leading a group at the University of Washington to conduct a double-blind, randomised, placebo-controlled study to evaluate the technique [121]. The study's findings suggested that the procedure did not affect the underlying pathophysiology of CAD, leading the authors to conclude that any observed benefits were probably attributable to psychological factors.

In 1945, Arthur Vineberg introduced another ingenious surgical technique to address CAD [122]. Vineberg realised that when there was a severe obstruction to coronary artery blood flow, attaching other structures to the cardiac surface would not deliver enough blood to the parched myocardium. Therefore, he proposed a more radical approach: developing an artificial third coronary artery. The Vineberg operation entailed directly implanting the left internal thoracic artery (ITA) into the ventricular myocardium to restore blood flow to ischaemic cardiac tissue [123]. After successive technical refinements in the ensuing years, he performed

this procedure on humans for the first time in 1950 [124]. Upon conducting the procedure on human subjects for several years, Vineberg released a case series encompassing 57 patients in 1958. Within this publication, he outlined a remarkable 60% survival rate over up to 7 years [125]. Although Vineberg's technique was an important step forward, the transition to CABG in the late 1960s and early 1970s marked a turning point in the treatment of CAD. CABG provided a more straightforward, reproducible, and reliable method of restoring blood flow to ischemic heart tissue, achieving the same physiological goals with greater efficiency [126].

3.1.3. Early Direct Coronary Revascularisation Attempts

As the limitations of indirect approaches became more apparent, surgeons began exploring direct interventions on the coronary arteries themselves. The 1950s and 1960s marked a turning point in coronary surgery, as focus shifted toward removing arterial obstructions and directly improving myocardial perfusion. These early attempts at direct coronary revascularisation laid the groundwork for the modern techniques that would follow.

The previously described procedures succeeded in providing a new blood supply to the myocardium but left the coronary arteries untouched. In the 1960s, surgeons flirted with many novel techniques as they attempted to shift their focus to the vessels actually affected by the disease [127]. The logical, yet hazardous, method for addressing obstructed arteries involved directly removing the obstruction.

In the early 1950s, Zoll et al. documented that coronary artery obstructions are typically confined to the epicardial vessels [128]. Their research demonstrated that the majority of these obstructions do not occur directly at the vessel's origin but rather a short distance beyond it. Their detailed research demonstrated that 50% of the obstruction were within 3 cm and 70% within 4 cm of the coronary ostia. Furthermore, these lesions were primarily focal in nature, a finding that revolutionised the understanding of CAD. Through meticulous dissection of 1271 human hearts, Zoll's efforts revealed that the coronary system beyond that specific point was not extensively affected by the disease, although it showed some atherosclerotic changes.

Zoll's experimental work provided Charles Bailey with the fundamental background to perform a closed coronary endarterectomy in 1957 [129]. Using a hollow metal instrument with a curet-like tip, Bailey carefully passed the tool through the coronary arterial tree, either along the line of blood flow or in a retrograde fashion, to detach and remove isolated atheromatous plaques. This technique allowed for safe and efficient plaque removal without encountering significant difficulty or risk, representing a less invasive alternative to more extensive surgical approaches.

Similarly, in 1958, William Longmire and colleagues reported on five patients treated for incapacitating angina pectoris with direct-vision coronary endarterectomy, performed without cardiopulmonary bypass (CPB) support [130, 131]. Among the diverse surgical interventions devised to improve myocardial blood flow in individuals with angina pectoris, none have garnered widespread approval due to the absence of conclusive evidence of their therapeutic efficacy. Consequently, Longmire believed that removing the obstructive atheromatous plaques from the coronary arteries was the most effective approach to augmenting myocardial blood flow, as evidenced by the positive outcomes observed in his small patient cohort.

However, enthusiasm for endarterectomy to treat angina pectoris soon subsided. In most instances, the rapid recurrence of anginal pain and the angiographic evidence of occlusion of the previously endarterectomised site fueled the search for an alternative method to nourish the ischaemic myocardium – one that would come in the form of CABG in the following decade [132].

3.1.4. Key Technological Advances Enabling CABG

The development of direct surgical approaches to the coronary arteries as a transformative treatment for coronary artery disease (CAD) heavily depended on parallel technological progress. Two innovations in particular – the heart-lung machine and selective coronary angiography – played crucial roles in enabling surgeons to perform those precise and complex techniques. These breakthroughs expanded the possibilities of cardiac surgery and revolutionised the diagnosis and management of CAD. They were instrumental in establishing coronary artery bypass grafting (CABG) as the cornerstone of modern revascularisation procedures by providing greater control during surgery and more accurate preoperative planning.

The introduction of the heart-lung machine, also known as the cardiopulmonary bypass (CPB) machine, revolutionised cardiac surgery and was a major breakthrough in the development of CABG. Before its invention, surgeons could only perform procedures on the heart for brief periods, limiting their ability to intervene directly on the coronary arteries or other internal cardiac structures. Open-heart surgery was fraught with challenges because the heart had to remain beating, limiting precision and increasing risk.

In 1953, John Gibbon Jr. successfully perfected the first effective heart-lung bypass machine, an invention he had been working on since the 1930s (Figure 3.2) [133]. The machine temporarily takes over the functions of the heart and lungs during surgery by oxygenating the blood and circulating it through the body, thus

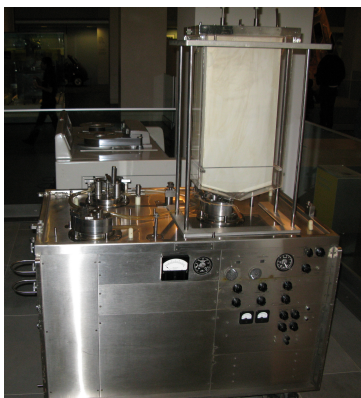


Figure 3.2.: Heart-lung machine used in 1958 (Licence: CC BY SA 4.0, via Wikimedia Commons).

allowing the heart to be stopped and maintained in a motionless state while surgeons operate in a clear, bloodless field [118].

The heart-lung machine has significantly contributed to cardiac surgery, most notably by allowing prolonged operating times. Surgeons could now perform complex procedures on the heart without the constant concern of maintaining circulation and oxygenation, opening the door to operations that were once deemed impossible. Additionally, working on a motionless surgical field enhanced the accuracy of procedures like CABG, reducing the risk of inadvertently damaging surrounding tissues. Finally, the heart-lung machine has been vital in developing CABG itself, enabling surgeons to stop the heart and create a controlled surgical setting to perform direct revascularisation. Surgeons could bypass obstructed arteries using grafts while ensuring that blood circulation remained safe and effective throughout the procedure.

The heart-lung machine laid the foundation for the routine use of CABG in treating CAD and remains a crucial component of cardiac surgery today. While the heart-lung machine enabled precise and controlled cardiac surgeries, another critical innovation – selective coronary angiography – revolutionised the ability to diagnose and locate coronary obstructions, allowing surgeons to plan revascularisation with unprecedented accuracy.

The development of selective coronary angiography in the late 1950s was another landmark innovation that significantly impacted the evolution of CABG. Before its introduction, diagnosing CAD relied on indirect assessments, and the visualisation of coronary arteries during surgery was highly limited. This lack of precision made it challenging to localise obstructions and plan effective interventions.

In 1958, F. Mason Sones inadvertently performed the first selective coronary angiogram at the Cleveland Clinic (Figure 3.3) [135]. While conducting an aortography, Sones accidentally injected contrast dye directly into the patient's right coronary artery, rather than the aorta, which provided a clear and detailed image of the coronary arteries. This serendipitous discovery changed cardiac diagnostics forever by allowing for real-time visualisation of coronary anatomy.

Selective coronary angiography had a profound impact on cardiovascular care by providing clinicians with precise, real-time images of coronary arteries. This technique is essential for planning CABG, allowing surgeons to accurately target obstructions and place grafts effectively. Additionally, Sones' technique proved invaluable for identifying specific focal lesions within the coronary arteries. Understanding the locations of these lesions is critical for CABG, as it allows for effective bypassing of coronary artery stenoses with grafts. This focus on pinpointing obstructions greatly reinforced the foundational concepts underpinning CABG.

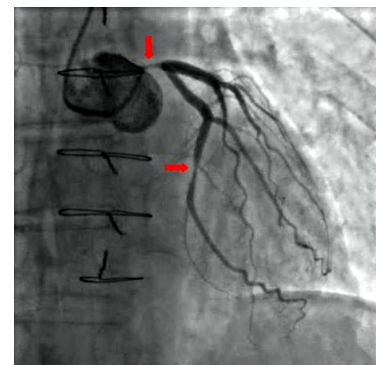


Figure 3.3.: Selective coronary angiography (Licence: © CC BY 2.0, via Wikimedia Commons [134]).

Coronary angiography has also established itself as a diagnostic standard for determining the severity of CAD. It helps clinicians discern which patients are suitable candidates for CABG and which might benefit more from alternative interventions, such as percutaneous coronary intervention (PCI). The ability to evaluate lesion complexity and disease extent plays a vital role in clinical decision-making regarding surgical options. Finally, the insights gained from coronary angiography enhance surgical planning by allowing surgeons to map the coronary anatomy before surgery. This preparation significantly improves outcomes by minimising the need for guesswork during surgery and ensuring that grafts are placed in the most effective locations. This detailed preoperative planning significantly improves outcomes by reducing intraoperative risks and increasing the likelihood of success.

After Sones' discovery, coronary angiography rapidly became the gold standard for diagnosing CAD and remains so today. It is still widely used to assess patients for CABG and other revascularisation procedures. By enabling the accurate visualisation of coronary obstructions, selective coronary angiography played a crucial role in the advancement of CABG, ensuring that the procedure is performed on carefully selected patients and targets the most critical lesions.

Together, the heart-lung machine and selective coronary angiography revolutionized both the technical and diagnostic aspects of cardiac surgery. These innovations laid the foundation for CABG, transforming it into the life-saving, cornerstone procedure it is today.

3.1.5. The Birth of Modern CABG

Advancements in understanding the pathophysiology of coronary artery disease (CAD) in the late 1950s, alongside technological progress, set the stage for early efforts in direct coronary artery bypass surgery. It became widely accepted that CAD resulted from obstructions in the coronary arteries, which limited blood flow to the myocardium under certain circumstances. Importantly, it was also recognised that these obstructions typically occurred proximally, while the distal arterial bed was often relatively spared [128]. This understanding suggested that bypassing the proximal obstructions could restore adequate blood flow to the ischaemic myocardium, laying the theoretical foundation for developing direct surgical revascularisation techniques [15].

In addition, since no idea comes from a vacuum, Alexis Carrel had first described operating on the coronary circulation over a century ago [136]. In 1910, Carrel reported performing an arterial anastomosis between the descending aorta and a coronary artery in a canine model, using the carotid artery as a conduit. However, he humbly acknowledged that surgical procedures required further

refinement before being applied to human subjects. In addition to establishing this conceptual framework, Carrel made significant contributions to the technique of vessel anastomosis, perfecting the suturing of both large blood vessels and those under a millimetre in diameter. His suturing method proved highly effective at preventing major complications such as haemorrhage, thrombosis, embolism, and stricture. Carrel's pioneering work laid the foundation for the advanced techniques of coronary surgery that would follow in later decades.

This conceptual ferment gave Gordon Murray a strong argument for pursuing direct coronary revascularisation [137]. He hypothesised that restoring adequate circulation distal to a coronary artery obstruction could reduce the risks associated with CAD. In 1954, Murray introduced a groundbreaking operation for direct arterial anastomosis of the coronary arteries. Through experiments on dogs, he found that using a carotid artery as a free graft produced the best outcomes. This innovative technique allowed for the occlusion of the coronary artery while maintaining adequate perfusion of the distal segment to prevent infarction. By anastomosing the coronary artery to a branch of the aorta or an aorta-derived graft, Murray was able to preserve coronary circulation and avoid infarction.

In 1958, Edwin Carter and colleagues documented their use of polyethylene rings to perform a sutureless anastomosis between the internal mammary artery and the left circumflex coronary artery in canine subjects [138]. They noted patent anastomoses in 20 of 24 dogs, with an average observation period of seven to eight weeks after the procedure. Carter's team suggested that the nonsuture approach could offer advantages over traditional suture-based methods, such as reducing operative complexity. In 1961, Robert Goetz expanded on this work by performing mammary artery-coronary artery bypass grafting in dogs using a novel nonsuture tantalum ring technique on the beating heart (Figure 3.4) [139]. In an interesting side note, Goetz reported the world's first successful clinical coronary artery bypass surgery on May 2, 1960, when a 38-year-old patient underwent a right mammary artery-right coronary artery bypass at Van Etten Hospital in New York. An initial angiogram on the fourteenth postoperative day confirmed a patent graft, and the patient remained free of angina for a year [140].

Although Goetz's early success in 1960 was groundbreaking, technical challenges and the prevailing skepticism about the procedure limited its further development [141]. This hesitancy left room for other surgeons, such as David Sabiston Jr., to explore direct coronary revascularisation further. In 1962, Sabiston and his team successfully performed the first hand-sewn, saphenous vein-coronary artery bypass on a patient with severe angina pectoris and complete occlusion of the right coronary artery [142]. The immediate postoperative results signaled a potentially novel approach to treating coronary artery disease. Unfortunately, the

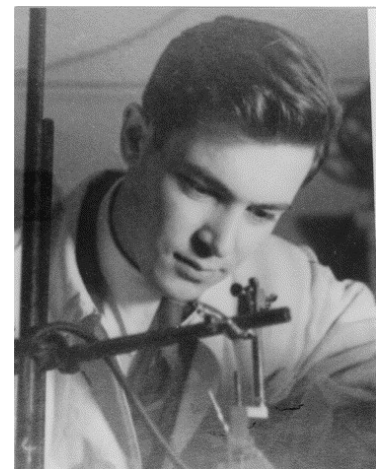


Figure 3.4.: Robert H. Goetz performed the first successful clinical coronary artery bypass operation on May 2, 1960 (Licence: Public Domain).

patient experienced a cerebrovascular accident and passed away three days later. Upon autopsy, a thrombus was present at the site of the proximal anastomosis in the ascending aorta. Sabiston did not report this influential event until 1974.

In 1964, Edward Garrett and associates performed a saphenous vein-left anterior descending artery bypass on a 42-year-old man suffering from severe angina. Garrett reported the case seven years later after demonstrating its angiographic patency [143].

So, history more frequently attributes the first successful hand-sewn anastomosis to the Russian surgeon Vasilii Kolessov [144]. In 1964, he performed a hand-sewn anastomosis between the left internal thoracic artery and one of the marginal branches of the circumflex artery in a 44-year-old man without cardiopulmonary bypass support [145].

In 1968, George Green and colleagues performed the first left ITA to left anterior descending artery anastomosis, which would soon become the absolute gold standard of CABG surgery [146]. The ITA later became the preferred graft due to its superior long-term patency, significantly improving patient outcomes.



Figure 3.5.: René Favaloro: the father of coronary artery bypass grafting (Licence: Public Domain).

Although not the first to perform the procedure, René Favaloro deserves full credit for bringing CABG to its full fruition [132]. In the late 1960s, he introduced CABG to its adulthood (Figure 3.5) [147]. In May 1967, Favaloro performed the first successful coronary bypass operation using an interposed saphenous vein graft to treat a segmental occlusion of the right coronary artery [148]. This innovation led to a hospital mortality rate of just 5.6%, a remarkable achievement at the time [149]. Initially, Favaloro and his team did not plan to use the aortocoronary vein bypass, but they quickly discovered that vein interpositions, requiring two anastomoses, were ineffective for treating ostial or very proximal lesions. They then adopted the vein bypass grafting technique with an end-to-side distal anastomosis, which soon became the worldwide standard [118]. Between May 1967 and October 1970, Favaloro performed 1697 saphenous vein grafts at the Cleveland Clinic, achieving a hospital mortality rate of just 3.5% [150]. The procedure's low mortality, reproducibility, and relative simplicity captivated the cardiovascular community and sparked the CABG revolution [151]. As Denton A. Cooley aptly remarked, Favaloro's contribution to surgical revascularisation was transformative [152].

"Although he was always hesitant to carry the moniker of 'father' of coronary artery bypass surgery, he is the surgeon we should credit with introducing coronary bypass surgery into the clinical arena."

Favaloro's adoption of the vein bypass grafting technique, with its reproducibility and low mortality, laid the groundwork for CABG to become the cornerstone of coronary revascularisation. His contributions, alongside those of other pioneering surgeons,

transformed CABG from an experimental procedure into a routine and life-saving surgery performed on millions of patients worldwide.

3.1.6. CABG as the Gold Standard

Between 1967 and 1970, Favaloro and colleagues gained sufficient experience to report the feasibility of operating on large numbers of patients with low operative mortality and a high incidence of anginal pain relief [150]. This success soon encouraged others to adopt the procedure, and by 1970, several centres had gained substantial experience. The growth of coronary artery bypass grafting (CABG) was remarkable.

However, despite more than 300,000 CABG procedures being performed by the mid-1970s, the indications for its use remained controversial. While there was a general recognition of the low operative mortality and graft closure rates, the available literature did not convincingly demonstrate that initial symptomatic improvement would be sustained. Furthermore, it did not provide strong evidence that CABG effectively prevented myocardial infarctions, arrhythmias, or congestive heart failure, nor that it significantly prolonged life for most patients undergoing the procedure [153].

Therefore, critics have revived an early 20th-century quote from Sir James MacKenzie on another therapy to suggest the need for a solid comparison between CABG and the best available medical therapy [154]:

"A great mass of observations has been accumulated but there has been divergence of opinion as to their interpretation. The divergence is an indication that there is something lacking in the knowledge of the subject. Seeing that the considerations of this subject have failed to bring an agreement, it may be assumed that the method of inquiry has been defective."

Landmark Clinical Trials. To address these uncertainties, three large multicentre randomised controlled trials – the Veterans Administration (VA) Cooperative Study, the European Coronary Surgery Study (ECSS), and the Coronary Artery Surgery Study (CASS) – were conducted between 1972 and 1984 [155–158], along with several smaller trials [159–161]. These studies laid the historical groundwork for comparing the outcomes of medical and surgical therapy and were crucial in shaping the understanding and practice of CABG, particularly as percutaneous coronary intervention had only just emerged in 1977 (Table 3.1).

Main Findings from Key Trials. The VA study, conducted between 1970 and 1974, was the first major clinical trial to compare surgical and medical treatments for patients with stable angina [155]. This landmark study enrolled 1,015 patients from thirteen hospitals and

Table 3.1.: Early clinical trials comparing CABG and medical therapy in patients with stable coronary artery disease.

Study	Period	Patients, n	Inclusion criteria	Main outcomes
VA Cooperative Coronary Surgery Study [155]	1972-1974	686	Angina $\geq$ 6 months Medical therapy $\geq$ 3 months Angiographic evidence of $\geq$ 50% stenosis of $\geq$ 1 major coronary artery with distal target	Operative mortality: 5.6% Mortality (4 years) – – CABG vs medical therapy: 14% vs 17% (all-comers) 15% vs 14% (without LMCAD) 7% vs 36% (with LMCAD)
European Coronary Surgery Study [156]	1973-1976	768	Men Age < 65 years Angina $\geq$ 3 months Angiographic evidence of $\geq$ 50% stenosis of $\geq$ 2 major coronary arteries with distal targets LVEF > 50%	Operative mortality: 3.6% Mortality (5 years) – – CABG vs medical therapy: 6.5% vs 16% (all-comers) 7.1% vs 38% (with LMCAD) 5.1% vs 15% (with 3VD)
Coronary Artery Surgery Study [158]	1975-1979	780	Age $\leq$ 65 y CCS class I or II angina Angiographic evidence of $\geq$ 50% stenosis of left main or $\geq$ 70% stenosis of other major coronary artery LVEF > 35%	Operative mortality: 1.4% Mortality (annual rate) – CABG vs medical therapy: 1.1% vs 1.6%

3VD, three-vessel disease; CABG, coronary artery bypass grafting; CCS, Canadian Cardiovascular Society; LMCAD, left main coronary artery disease; LVEF, left ventricular ejection fraction.

set the stage for future trials by implementing stringent inclusion criteria, including angiographic evidence of significant coronary artery stenosis and a three-month period of medical management before surgery.

The study demonstrated a clear survival advantage for CABG in patients with left main (LM) CAD, showing a four-year mortality rate of 7% for CABG compared to 36% for medical therapy. However, after excluding these patients from the analysis, the other subgroups showed minimal survival benefit (four-year mortality rate, 15% for CABG vs 14% for medical therapy).

The ECSS, conducted between 1973 and 1976, involved 768 patients from twelve European centres [156]. This trial focused on men under 65 with multivessel disease and preserved left ventricular function. The ECSS found that CABG significantly improved five-year survival rates compared to medical therapy, particularly in patients with three-vessel disease or severe stenosis of the proximal left anterior descending artery [157].

Finally, the CASS, conducted between 1975 and 1979, included 780 patients with stable ischaemic heart disease. While the study did not show statistically significant survival differences between medical and surgical groups for all-comers, it highlighted the high rates of crossover to surgery among patients initially assigned to

medical therapy, underscoring the challenges of managing CAD without revascularisation [158].

Consensus and Acceptance of CABG. Although these trials did not unanimously identify an overall survival benefit for CABG over medical therapy, their findings were remarkably consistent in demonstrating significant advantages for high-risk patients. The main conclusion from these studies is that CABG offered the greatest survival benefits for patients at the highest risks, as defined by the severity of angina and ischaemia, the number of diseased vessels, and the presence of left ventricular dysfunction. Consequently, in 1980, the National Institutes of Health in the United States would issue a consensus document emphatically supporting CABG. They asserted that the procedure enhanced quality of life, reduced myocardial ischaemia, and improved survival [127].

Long-Term Impact and Meta-Analysis. In the early 1990s, a landmark meta-analysis by Yusuf et al. of these seven randomised trials demonstrated a significantly lower mortality in the surgical group compared to the medical treatment group at five, seven, and ten years (five-year mortality: 10.2% vs 15.8%; OR 0.61 [95% CI 0.48-0.77], $p=0.0001$). This meta-analysis established the long-term superiority of CABG in high-risk patients and played a pivotal role in promoting its adoption as the gold standard for coronary revascularisation [7].

By consistently demonstrating benefits in reducing mortality and improving quality of life for high-risk patients, CABG solidified its role as the gold standard for revascularisation, especially in cases where medical therapy or PCI proved insufficient.

3.2. Clinical Indications and Patient Selection

The decision to perform coronary artery bypass grafting (CABG) hinges on carefully balancing the risks and benefits of revascularisation in patients with coronary artery disease (CAD). Over the decades, advances in surgical techniques, medical therapies, and diagnostic modalities have led to a deeper understanding of which patients benefit most from CABG. Historically, CABG was primarily indicated for patients with severe, refractory angina or left main coronary artery disease (LMCAD), particularly when medical therapy alone was insufficient to relieve symptoms or improve survival rates [153]. However, evolving evidence from landmark clinical trials [155, 156, 158] and their seminal meta-analysis [7] have expanded the criteria for selecting patients for CABG. Contemporary guidelines from leading cardiovascular societies, including the American College of Cardiology / American Heart Association (ACC/AHA) [162] and the European Society of Cardiology / European Association for Cardio-Thoracic Surgery (ESC/EACTS)

Table 3.2.: Indications for revascularisation in patients with chronic coronary syndromes.

	CAD extent	COR	LOE
For prognosis	Proximal LAD stenosis >50%	I	A
	Left main stenosis >50%	I	A
	Two- or three-vessel disease with stenoses >50% and impaired LV function	I	A
	Large area of ischaemia detected by functional testing (>10% LV)	I	B
For symptoms	Haemodynamically significant coronary stenosis in the presence of limiting angina or angina equivalent, with insufficient response to optimised medical therapy	I	A

CAD, coronary artery disease; COR, class of recommendation; LAD, left anterior descending artery; LOE, level of evidence; LV, left ventricle.

[8], now emphasise a patient-centred approach to revascularisation, considering factors such as anatomical complexity, symptom burden, and overall risk profile.

3.2.1. General Indications for Revascularisation

Revascularisation strategies, including coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI), play a crucial role in managing patients with coronary artery disease (CAD). The choice of revascularisation aims to achieve two main goals: improving patient survival and relieving symptoms of angina [8]. Contemporary guidelines recommend a balanced, patient-centred approach to decide between these strategies based on clinical characteristics, coronary anatomy, and overall risk profile.

Indications for Revascularisation to Improve Survival. Clinical evidence and guideline recommendations emphasise revascularisation to improve survival in the following key anatomical and clinical scenarios:

- The presence of clinically significant stenosis in the *proximal left anterior descending (LAD) artery* increases the long-term mortality rate in medically treated patients with one-, two-, or three-vessel disease [7]. This observation supports the general principle that the greater the amount of myocardium at risk (i.e., more extensive or proximal coronary disease), the greater the improvement in prognosis with revascularisation procedures.
- Clinically significant *left main coronary artery disease (LMCAD)*, characterised by luminal narrowing exceeding 50%, occurs in 4-6% of patients who undergo coronary angiography and in 30% of those with acute coronary syndromes [163]. Additionally, LMCAD is associated with multivessel CAD in over 70% of cases [163]. The medical management of clinically significant LMCAD is associated with a 3-year

mortality rate of 31% [164]. Consequently, a revascularisation procedure, either with CABG or PCI, is indicated in patients with clinically significant stenosis of the left main coronary artery [8].

- *Multivessel coronary artery disease* (two- or three-vessel coronary artery disease, MVCAD) is found in approximately 30% of patients undergoing elective coronary angiography [165]. When medically managed, these patients have their long-term survival significantly curtailed compared to those with single-vessel disease [166]. The extensive myocardial mass at risk associated with MVCAD justifies the need for a revascularisation procedure, either with CABG or PCI [8].
- *Left ventricular dysfunction* and heart failure are major long-term consequences of CAD. In a study involving patients with ischaemic cardiomyopathy, those who underwent CABG, in addition to receiving medical therapy, experienced substantially lower rates of overall mortality, cardiovascular deaths, and combined rates of mortality or hospitalisations for cardiovascular causes over ten years compared to those who received only medical therapy [167].

Indications for Revascularization to Relieve Symptoms. While improving survival is a key consideration in selecting candidates for revascularisation, alleviating symptoms and enhancing quality of life are equally crucial. Revascularisation is indicated in patients experiencing severe, limiting angina that persists despite optimised medical therapy. Revascularisation in this context aims to enhance quality of life by improving myocardial blood flow and alleviating symptoms [8].

3.2.2. General Principles of Patient Selection

When selecting patients for revascularisation, whether with CABG or PCI, guidelines emphasise evaluating three core principles: predicted surgical risk, anatomical complexity of CAD, and completeness of revascularisation. These principles serve as a framework for the Heart Team to make informed, patient-centered decisions based on both clinical and anatomical considerations.

Predicted Surgical Risk. Assessing the predicted surgical risk is a vital component of patient selection for revascularisation procedures. Risk prediction models, such as the Society of Thoracic Surgeons (STS) Risk Score [168] and EuroSCORE II [169], provide reliable estimates of mortality and morbidity associated with surgical interventions. These scoring systems empower clinicians to stratify patients into clear risk categories, facilitating informed decisions regarding the advantages of CABG in light of potential perioperative complications. The Heart Team decisively explores alternative therapeutic strategies for patients with a high predicted surgical risk, including PCI or optimal medical therapy, especially

when the anticipated surgical risks outweigh the potential benefits [8].

Anatomical Complexity of CAD. The anatomical complexity of CAD plays a significant role in determining the appropriate treatment approach, whether CABG or PCI. The SYNTAX Score is a well-validated tool that grades the complexity of coronary lesions based on factors such as the number of lesions, their location, and the involvement of bifurcations or calcifications [100]. Patients with a high SYNTAX Score, indicating complex or extensive CAD, are generally better suited for CABG due to the procedure's ability to achieve complete revascularisation. In contrast, patients with a low or intermediate SYNTAX Score and suitable coronary anatomy may achieve favourable outcomes with PCI.

Completeness of Revascularisation. Another important consideration is the completeness of revascularisation, which refers to the extent to which all significant coronary artery stenoses are treated during the procedure. Studies have shown that achieving complete revascularisation improves long-term outcomes, including reduced mortality and fewer recurrent ischaemic events [170]. CABG often provides more complete revascularisation, particularly in patients with multivessel disease or diffuse CAD. In contrast, PCI may be more suitable for achieving completeness in patients with focal lesions or less complex coronary anatomy.

3.3. Choice of Revascularisation Strategy

Selecting the appropriate revascularisation strategy – either coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI) – depends on the specific anatomical presentation of coronary artery disease (CAD) [8]. Key anatomical subsets include isolated proximal left anterior descending (LAD) artery disease, left main coronary artery disease (LMCAD), and multivessel disease (MVD). Current guidelines and evidence-based clinical practice highlight which approach offers the most favourable long-term outcomes based on factors such as lesion complexity, risk of complications, and patient comorbidities.

3.3.1. Isolated Proximal LAD Disease

Significance. Given the importance of the LAD artery in supplying blood to a considerable portion of the left ventricle (LV), a proximal LAD artery stenosis places a substantial amount of LV myocardium at risk [7].

Literature Overview. Currently, there are only a limited number of randomised controlled trials (RCTs) comparing percutaneous coronary intervention with drug-eluting stents (PCI-DES) to coronary artery bypass surgery (CABG) [171–173]. These studies often

Table 3.3.: Randomised Controlled Trials Comparing CABG and PCI for left main coronary artery disease.

Trial	Patients (n)	Stent	Follow-up	Primary endpoint	Results (PCI vs CABG)
PRECOMBAT [10]	600	DES	1 year	MACCE	6.7% vs 8.7% (p=0.01 for noninferiority)
SYNTAX [11]	705	DES	5 years	MACCE	36.9% vs 31.0% (p=0.12)
NOBLE [12]	1201	DES	5 years	MACCE	28% vs 18% (p=0.0044)
EXCEL [13]	1905	DES	5 years	Composite of all-cause mortality, stroke, or myocardial infarction	22.0% vs 19.2% (p=0.13)

CABG, coronary artery bypass grafting; DES, drug-eluting stents; MACCE, major adverse cardiac and cerebrovascular events; PCI, percutaneous intervention

have small sample sizes and divergent results. As a result, much of the data supporting the guidelines and best practices in this area comes from a relatively small number of registries, which are inherently subject to the typical limitations associated with observational studies [174].

Evidence Synthesis. The available evidence indicates that, among patients with isolated proximal LAD artery disease, there are no significant medium-term differences in mortality, myocardial infarction, or stroke between CABG and PCI. However, PCI is associated with an increased risk of repeat revascularisation [8, 175, 176].

3.3.2. Left Main Coronary Artery Disease

Significance. Patients presenting with left main coronary artery disease (LMCAD) are among the highest-risk patients with atherosclerosis due to the critical nature of the left main coronary artery, which supplies a large portion of the myocardium. Effective revascularisation in these patients can significantly impact prognosis [7].

Literature Overview. The data informing decisions regarding the type of revascularisation procedure in this specific cohort of patients primarily stems from four randomised controlled trials (RCTs) comparing PCI-DES with CABG. These trials include the subgroup of patients from the SYNTAX trial focusing on LMCAD [11], the PRECOMBAT [10], the NOBLE [12], and the EXCEL [13] trials (Table 3.3).

Evidence Synthesis. Available evidence indicates that PCI is an appropriate alternative to CABG for patients with LMCAD and low or intermediate SYNTAX scores (<32) since the two procedures yield similar major clinical endpoints. On the other hand, CABG

is generally recommended in patients with high SYNTAX scores (>32) due to its association with improved long-term survival [8]. Nevertheless, there are important trade-offs to consider regarding the risks of spontaneous myocardial infarction, stroke, and the need for repeat revascularisation. Engaging in shared decision-making with patients is essential to assess these trade-offs properly [177, 178].

3.3.3. Multivessel Coronary Artery Disease

Significance. The presence of extensive CAD affecting different coronary artery territories proportionately increases the amount of myocardium at risk.

Literature Overview. In the late 1990s, a series of four pivotal randomised, multicenter studies — the ARTS, SoS, ERACI-2, and AWESOME trials — were conducted [179–182]. While these trials do not reflect current medical practices, they hold significant historical importance. They were instrumental in comparing the effectiveness of PCI with coronary stenting using *bare-metal stents* (BMS) versus surgery in multivessel CAD. The evidence on the comparative effectiveness of PCI-DES and CABG derives from the contemporary BEST [183] and SYNTAX [9] trials (Table 3.4).

Evidence Synthesis. The SYNTAX trial reinforced CABG as the preferred treatment for patients with multivessel CAD and complex lesions, i.e., those with high or intermediate SYNTAX scores [9]. Conversely, it demonstrated that PCI is a suitable option for patients with less complex disease, i.e., those with low SYNTAX scores. This trial emphasised the importance of considering the severity and complexity of CAD when determining the most appropriate treatment strategy for patients [8].

3.3.4. Left Ventricular Systolic Dysfunction

Significance. Recurrent or prolonged ischaemic events lead to maladaptive remodelling of cardiomyocytes and expanding extracellular matrix, culminating in cavity dilation and systolic dysfunction [186]. Patients presenting with left ventricular (LV) systolic dysfunction pose a significant challenge in revascularisation decision-making, as LV dysfunction is both a consequence of ischaemic cardiomyopathy and a significant predictor of adverse outcomes following any revascularisation procedure.

Literature Overview. Revascularisation strategies are superior to medical treatment in improving survival rates in patients with CAD and reduced LV ejection fraction [187]. Revascularisation strategies are superior to medical treatment in improving survival rates in patients with CAD and reduced LV ejection fraction. The STICH trial has provided robust evidence in favour of CABG for patients with

Table 3.4.: Randomised Controlled Trials Comparing CABG and PCI for multivessel coronary artery disease.

Trial	Patients (n)	Stent	Follow-up	Primary endpoint	Results (PCI vs CABG)
ARTS [179]	1205	BMS	12 months	Freedom from MACCE	73.8% vs 87.8% (p<0.001)
SoS [180]	988	BMS	2 years	Repeat revascularisation	21% vs 6% (p<0.0001)
ERACI-II [184]	450	BMS	5 years	Freedom from MACE	65.3% vs 76.4% (p=0.013)
AWESOME [182]	454	BMS	4.8 years	All-cause mortality	22.0% vs 27.0% (p=0.46)
SYNTAX [9]	1095	DES	5 years	Freedom from MACCE	62.5% vs 75.8% (p<0.001)
BEST [183]	880	DES	4.6 years	MACE	15.3% vs 10.6% (p=0.04)
SYNTAXES [185]	1095	DES	10 years	All-cause mortality	28.0% vs 21.0% (p<0.05)

BMS, bare-metal stents; **DES**, drug-eluting stents; **CABG**, coronary artery bypass grafting; **MACCE**, major adverse cardiac and cerebrovascular events; **PCI**, percutaneous intervention

ischaemic cardiomyopathy [167]. The study demonstrated that CABG, in addition to optimal medical therapy, reduces overall mortality and cardiovascular events compared to medical therapy alone in patients with LV dysfunction (defined as an ejection fraction of 35% or lower). CABG's benefits are attributed to improved myocardial perfusion and potential reversal of hibernating myocardium, which may enhance cardiac function over time.

However, these patients have generally been excluded from randomised controlled trials (RCTs) comparing PCI and CABG. As a result, most data that inform the choice of revascularisation strategy are derived from observational studies.

Evidence Synthesis. In a propensity score matching analysis of 4,616 patients with multivessel disease and severe LV systolic dysfunction (defined as an ejection fraction of 35% or lower) from the New York State registries, Bangalore et al. have demonstrated that PCI-DES had comparable long-term survival to CABG [188]. However, PCI-DES was associated with a higher risk of myocardial infarction in cases of incomplete revascularisation, as well as a higher risk of repeat revascularisation procedures. Conversely, CABG was associated with a higher risk of stroke.

Similarly, Khan et al. reported on a meta-analysis of clinical outcomes comparing PCI and CABG in patients with LV systolic dysfunction (defined as an ejection fraction of 40% or lower) [189]. This analysis encompassed seventeen studies, sixteen of which

were observational in nature. The findings indicated that CABG was associated with lower long-term mortality rates, whereas PCI exhibited a higher incidence of repeat revascularisation during long-term follow-up. However, the long-term rates of stroke and myocardial infarction were found to be comparable between the two procedures.

The ESC/EACTS guidelines suggest that PCI should be considered for older patients without diabetes when complete revascularisation is feasible [8]. In contrast, CABG is preferred for younger patients with more extensive CAD or for those who have diabetes.

3.3.5. Summary

This section has laid out the general principles guiding the choice of revascularisation strategy, emphasising that the final decision should be personalised. An individualised approach, informed by anatomical complexity and patient risk profile, is crucial. The involvement of a multidisciplinary Heart Team is essential to ensure optimal patient outcomes.

3.4. Role of Heart Team in Decision-Making

The concept of a multidisciplinary Heart Team has become a cornerstone in managing complex coronary artery disease (CAD), particularly when considering revascularisation strategies such as coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI). The Heart Team typically comprises clinical and interventional cardiologists, cardiac surgeons, and other healthcare professionals, including cardiac imaging subspecialists, anesthesiologists, and neurologists, among others [190]. Together, they collaboratively assess the risks and benefits of each treatment option, customising the strategy to meet each patient's specific needs.

3.4.1. Importance and Rationale

Shared Expertise. The Heart Team model leverages the collective expertise of specialists to ensure that clinical decisions are based on a comprehensive evaluation of scientific evidence within the context of each patient's unique medical and anatomical circumstances. This approach facilitates evidence-based, patient-centred care, which has been shown to improve outcomes, particularly in cases with high anatomical complexity, such as left main coronary artery disease (LMCAD) and multivessel CAD. Furthermore, it is

well established that collegial decision-making enhances the implementation of clinical recommendations and decreases variability in healthcare delivery [191].

Balancing Perspectives. One of the main advantages of the Heart Team approach is its ability to balance the perspectives of different specialities. For instance, cardiologists may favour PCI due to its minimally invasive nature, while surgeons may emphasise the long-term benefits of CABG for more complex coronary anatomies. This balance helps to mitigate speciality bias and ensures a more comprehensive evaluation of treatment options [192].

3.4.2. Process of Decision-Making

Comprehensive Patient Evaluation. The Heart Team reviews the patient's clinical history, comorbidities, and functional status. Discussing diagnostic imaging results, such as coronary angiography and computed tomography (CT), plays a crucial role in assessing the complexity of CAD using tools like the SYNTAX Score [100].

The SYNTAX score assigns points based on each lesion's complexity and the overall disease burden. It can range from 0 to over 60, with higher scores indicating more complex anatomical situations. In general, scores ≤ 22 indicate low complexity and comparable outcomes with either PCI or CABG. On the other hand, scores between 23 and 32 (intermediate complexity) and those ≥ 33 (high complexity) derive better outcomes with CABG.

In the SYNTAX trial and subsequent external validation cohorts, the SYNTAX score has been identified as an independent predictor of long-term major adverse cardiac and cerebrovascular events (MACCE) and mortality in patients undergoing PCI but not CABG [193–195].

Risk Stratification and Prognosis. Risk assessment models, such as the EuroSCORE II [169] and the Society of Thoracic Surgeons (STS) Risk Score [168], estimate surgical risk. Both scoring systems demonstrate similar discrimination for 30-day mortality in patients undergoing isolated CABG [196]. Although these models include different variables, risk factors can be classified into a common set of categories [17].

Despite the comprehensive nature of these models, they do not account for other comorbid factors such as pulmonary hypertension, liver disease, previous chest radiation, and the patient's frailty status. These factors can increase surgical risk and may play an important role. Nevertheless, these models are pivotal for guiding the choice between CABG and PCI.

Individualised Treatment Planning. The Heart Team discusses the advantages and drawbacks of each revascularisation strategy. Factors considered include the patient's coronary anatomy, left ventricular function, frailty, and personal preferences. Shared

Table 3.5.: Core risk assessment model variables.

Variables	Examples
Demographic	Age Sex
Previous cardiovascular events	Prior cardiovascular surgery or intervention Myocardial infarction Stroke or transient ischaemic attack
Cardiovascular	Left ventricular function Diabetes mellitus Hypertension Arrhythmias Peripheral vascular disease
Noncardiovascular	Renal failure Chronic obstructive pulmonary disease
Disease complexity and pathology	Number of diseased vessels Degree of valve stenosis and regurgitation Presence of endocarditis
Haemodynamic status and urgency of operation	Self-explanatory

decision-making is integral, ensuring that the patient is actively involved in the treatment planning process and understands the potential risks and benefits.

3.4.3. Evidence Supporting the Heart Team Approach

Studies have demonstrated that the Heart Team model improves the quality of clinical decision-making and patient outcomes. For instance, analyses from the SYNTAX trial highlighted that Heart Team discussions led to more appropriate treatment recommendations, aligning with guideline-directed care and improving survival rates and quality of life [197]. Furthermore, the 2018 European Society of Cardiology (ESC) and European Association for Cardio-Thoracic Surgery (EACTS) Guidelines emphasise using a Heart Team, particularly in complex cases of CAD and in patients with high surgical or procedural risk [8].

3.4.4. Summary

The Heart Team approach represents a paradigm shift toward collaborative, patient-centred care in managing complex coronary artery disease. By integrating diverse clinical expertise and focusing on shared decision-making, the Heart Team ensures that patients receive optimal, individualised care that aligns with the latest evidence and their personal values and preferences.

3.5. Special Populations and Considerations

Certain patient groups present unique challenges in managing coronary artery disease (CAD) that warrant special attention when deciding on revascularisation strategies. This section will focus on two key populations: patients with diabetes mellitus and those with chronic kidney disease (CKD). These populations often present unique pathophysiological and procedural challenges that influence the choice between coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI).

3.5.1. Diabetes Mellitus

Significance. Global statistics indicate that approximately 422 million individuals are affected by diabetes, with 1.5 million deaths directly attributable to the condition each year [198]. Among the myriad complications associated with diabetes, atherosclerotic cardiovascular disease – which encompasses coronary artery disease (CAD), cerebrovascular disease (CVD), and peripheral artery disease (PAD) of presumed atherosclerotic origin – emerges as the leading cause of morbidity and mortality in this population [199].

Diabetes mellitus is strongly associated with an increased risk of CAD. According to a 2010 meta-analysis by the Emerging Risk Factors Collaboration, which included 698,782 individuals from 102 prospective studies, diabetes was found to independently double CAD, regardless of other conventional risk factors [200]. Furthermore, diabetic patients often present with multivessel CAD and more diffuse and rapidly progressing atherosclerotic lesions, making revascularisation decisions particularly complex.

Literature Overview. The evidence supporting myocardial revascularisation in patients with diabetes stems from three pivotal randomised controlled trials (RCTs) that have evaluated the outcomes of percutaneous coronary intervention (PCI) and CABG in individuals with multivessel CAD. These trials include the BARI-2D trial [201], a secondary analysis of the SYNTAX trial [202], and the FREEDOM trial [203]. Each of these studies provides critical insights into the comparative effectiveness of these revascularisation strategies, thereby informing clinical decision-making for managing diabetic patients with multivessel CAD (Table 3.6).

Evidence Synthesis. The FREEDOM trial was the first large-scale randomised study comparing the efficacy of CABG versus PCI using DES, specifically in patients with diabetes mellitus and multivessel CAD [203]. Earlier studies often compared both revascularisation strategies but lacked focus on diabetic patients or a clear comparative framework, making it challenging to draw definitive conclusions. This study involved 1,900 patients from 140 international participating sites. The primary outcome measured a

Table 3.6.: Randomised Controlled Trials Comparing CABG and PCI in diabetic patients with multivessel coronary artery disease.

Trial	Patients (n)	Stent	Follow-up	Primary endpoint	Results
BARI-2D [201]	2638	BMS (65.3%) DES (34.7%)	5 years	Survival Freedom from major cardiovascular events	Survival (vs OMT): PCI: 89.2% vs 89.8% (p=0.48) CABG: 86.4% vs 83.6% (p=0.33) Freedom from major cardiovascular events (vs OMT): PCI: 77% vs. 78.9% (p=0.15) CABG: 77.5% vs. 69% (p=0.01)
SYNTAX [202]	1800	DES	5 years	MACCE Composite of all-cause death, stroke, and myocardial infarction MACCE components	MACCE (PCI vs CABG) 46.5% vs 29.0% (p<0.001) Repeat revascularisation (<i>idem</i>) 35.3% vs 14.6% (p<0.001) No differences in any other specified outcomes
FREEDOM [203]	1900	DES	5 years	Composite of all-cause death, stroke, and myocardial infarction	PCI 26.6% vs CABG 18.7% (p=0.005)

BMS, bare-metal stents; **CABG**, coronary artery bypass grafting; **DES**, drug-eluting stents; **MACCE**, major adverse cardiac and cerebrovascular events; **PCI**, percutaneous intervention

composite of death from any cause, nonfatal myocardial infarction, or stroke. Over five years, the primary outcome was observed in 26.6% of patients in the PCI group, as opposed to 18.7% in the CABG group (p=0.005). The superiority of CABG was attributed to differences in the rates of both myocardial infarction (CABG, 6% vs PCI, 13.9%; p<0.001) and all-cause mortality (CABG, 10.9% vs PCI, 16.3%; p=0.049). Although PCI exhibited lower stroke rates (2.4%) compared to CABG (5.2%), the higher incidence of strokes in the CABG group was primarily observed within the initial 30 days post-procedure. The study's findings revealed that, for individuals with diabetes and advanced CAD, CABG provides a clear edge over PCI in terms of reducing the rates of all-cause mortality and myocardial infarction. However, it is worth noting that CABG is linked to an increased risk of early strokes.

In a meta-analysis of four RCTs, Hakkeem and colleagues examined the best revascularisation approach for diabetic patients with multivessel CAD, comparing PCI using DES with CABG [204]. Their analysis, based on 3,052 patients, focused on the primary endpoint of major adverse cardiac events (MACE), including death, myocardial infarction, and stroke, tracked over an average follow-up of four years. This study revealed a higher MACE rate in the PCI group (22.5%) compared to the CABG group (16.8%), with a relative risk (RR) of 1.34 (95% confidence interval [CI] 1.16-1.54; p<0.0001). Furthermore, all-cause mortality (RR 1.51, 95% CI 1.09-2.10; p=0.01) and repeat revascularisation procedures (17.4% vs. 8.0%, RR 1.85, p = 0.05) were notably higher in the PCI group. Conversely, the risk of stroke was significantly lower with PCI (2.3% versus 3.8%, RR 0.59,

95% CI 0.39-0.90; $p=0.01$). The nonfatal myocardial infarction (MI) rates were 10.3% for PCI and 5.9% for CABG, but this difference was not statistically significant (RR 1.44, 95% CI 0.79-2.60; $p=0.23$). The authors concluded that CABG significantly outperforms PCI with DES in decreasing overall mortality, nonfatal MI, and the need for repeat revascularisation in diabetic patients with multivessel CAD at low to intermediate surgical risk (EuroSCORE <5). However, the study also highlights an increased risk of stroke associated with CABG. For these reasons, the researchers advocate for CABG as the preferred option for long-term outcomes in this patient population.

Overall, the current evidence favours CABG as the preferred revascularisation approach for patients with diabetes and multivessel coronary disease [8]. When patients present with a comorbidity that increases surgical risk, the choice of revascularisation method should be determined through a multidisciplinary and individualised risk assessment process.

3.5.2. Chronic Kidney Disease

Significance. Coronary artery disease (CAD) is the leading cause of morbidity and mortality among patients with chronic kidney disease (CKD). As renal function declines, the risk of cardiovascular mortality rises linearly, driven by both traditional risk factors and CKD-specific mechanisms, such as chronic inflammation, oxidative stress, and abnormal mineral metabolism [205]. These factors accelerate atherosclerosis and vascular calcification, leading to more complex and diffuse coronary artery disease [206]. Consequently, CKD patients not only face a higher likelihood of perioperative complications, such as acute kidney injury and infection, but also have worse long-term outcomes, necessitating meticulous risk assessment and specialised perioperative management.

Literature Overview. In general, clinical trials assessing the effect of revascularisation in patients with chronic coronary syndromes have routinely excluded those with advanced CKD. This has led to a lack of robust, high-quality evidence to guide clinical decision-making in this vulnerable population. However, the recent ISCHEMIA-CKD trial was specifically designed to address this information gap [207].

On the other hand, studies that compare the effectiveness of PCI and CABG in managing these patients face significant limitations [208]. First, available randomised controlled trials (RCTs) include small numbers of patients with estimated glomerular filtration rate (eGFR) under 60 ml/min per 1.73 m² and are thus underpowered to provide a definitive response [209]. Second, while observational analyses of revascularisation strategies represent the largest body of evidence and mitigate the issue of power, they lack the control over

confounding variables and biases that a randomised controlled study design provides [210, 211].

Evidence Synthesis. In the ISCHEMIA-CKD trial, 777 patients with chronic coronary syndromes and advanced kidney disease who exhibited moderate to severe ischaemia on stress testing were randomly assigned to one of two treatment strategies [207]. One group underwent an initial invasive approach that included coronary angiography and, if deemed appropriate, revascularisation, in addition to medical therapy. The other group received a conservative strategy, consisting of optimal medical therapy alone, with angiography being reserved for patients for whom medical treatment was ineffective. At a median follow-up of 2.2 years, there was no significant difference in the primary outcome measure, a composite of death or nonfatal myocardial infarction, between the two treatment strategies.

A *post hoc* analysis of the Arterial Revascularization Therapies Study (ARTS) compared long-term clinical outcomes after CABG or PCI with multivessel stenting in patients with CKD (defined as an eGFR ≤ 60 mL/min) [211]. Of 290 participants (25% of the total patients) with CKD at enrollment, 151 underwent PCI, while 139 received CABG. With a mean follow-up of three years, there were no significant differences in the primary outcome – a composite of death, myocardial infarction, or stroke – between the two groups. However, CABG was associated with a lower risk of repeat revascularisation.

Ashrith et al. examined the short- and long-term outcomes of CABG and PCI-DES for multivessel CAD among 812 non-haemodialysis-dependent patients with CKD (defined as an eGFR ≤ 60 mL/min) [210]. The results showed no significant differences in long-term survival between the two treatment strategies; however, patients undergoing CABG had a higher risk of requiring permanent haemodialysis.

Bangalore et al. reported on a propensity score matching analysis of 11,305 patients with CKD who underwent PCI-DES or CABG for multivessel CAD [211]. The two groups had no significant long-term differences regarding the primary outcome of all-cause mortality, except for patients on haemodialysis, for whom CABG demonstrated superior long-term survival. However, PCI was linked to an increased risk of myocardial infarction, limited to those patients with incomplete revascularisation, and repeat revascularisation. Conversely, CABG was associated with an increased stroke risk.

Despite the limited data available, significant insights have emerged from these analyses. Patients with limited disease (one- or two-vessel) have similar outcomes following PCI-DES or CABG. In contrast, the subset of patients with three-vessel disease and possibly those on haemodialysis may benefit from CABG, particularly

when complete revascularisation cannot be achieved through PCI [208].

3.5.3. Summary

Managing CAD in special populations, such as those with diabetes mellitus or chronic kidney disease, requires nuanced decision-making that considers these groups' unique pathophysiology and increased risk profile. While CABG often provides superior outcomes in terms of long-term survival and reduced MACE for diabetic and high-risk CKD patients, PCI remains an essential option for those with prohibitive surgical risks. The involvement of a multidisciplinary Heart Team and shared decision-making with the patient are crucial to ensure optimal, personalised care.

3.6. Surgical Techniques and Technological Advances

The landscape of coronary artery bypass grafting (CABG) has been profoundly transformed since its early days in the 1960s. Initial procedures were rudimentary compared to today's sophisticated techniques, but they laid the groundwork for what has become a cornerstone of modern cardiac surgery. Over the years, advancements in surgical approaches and the integration of cutting-edge technologies have dramatically improved outcomes for patients with coronary artery disease (CAD). These developments have not only enhanced the safety and efficacy of CABG but have also expanded its applicability to a wider range of patients, including those previously deemed too high-risk for surgery.

The evolution of CABG techniques can be broadly categorized into traditional on-pump coronary artery bypass (ONCAB) and more recent innovations, such as off-pump CABG (OPCAB), minimally invasive direct coronary artery bypass (MIDCAB), totally endoscopic coronary artery bypass (TECAB), and hybrid coronary revascularization (HCR). Each approach comes with its unique advantages, challenges, and clinical indications. For example, while ONCAB remains the gold standard for achieving complete and durable myocardial revascularization, it is associated with certain complications linked to cardiopulmonary bypass. In contrast, OPCAB offers a less invasive alternative by operating on a beating heart, potentially reducing perioperative complications.

Technological advancements have further propelled the field forward. Robotic systems, enhanced imaging modalities, and refined grafting techniques have contributed to more precise and effective surgeries. This section will explore the key surgical techniques

and technological innovations that have shaped CABG, providing a comprehensive understanding of how each advancement contributes to improved patient care and long-term outcomes.

3.6.1. On-Pump Coronary Artery Bypass

On-pump coronary artery bypass (ONCAB) surgery represents the traditional and most widely performed method for coronary artery bypass grafting (CABG) [16]. This procedure involves using a cardiopulmonary bypass (CPB) machine, which takes over the function of the heart and lungs, allowing surgeons to operate on a still, bloodless heart. By stopping the heart temporarily and maintaining systemic perfusion with the CPB, ONCAB provides a controlled surgical environment, enabling precise anastomosis of the grafts to the coronary arteries.

Surgical Procedure Overview. After induction of general anaesthesia, the procedure begins with a chest midline incision and median sternotomy, granting access to the heart and great vessels. The surgical team then proceeds with graft take-down, tailored to the patient's needs and surgical strategy, which may include the left internal thoracic artery (LITA), radial artery (RA), or greater saphenous vein (GSV).

Once systemic anticoagulation is achieved through heparin administration, an inverted T pericardial incision is made, and pericardial stay sutures are placed to enhance the exposure of the heart and great vessels. Arterial cannulation is generally performed in the ascending aorta, while venous return is managed through right atrial cannulation. This setup enables the cardiopulmonary bypass (CPB) system to assume the roles of the heart and lungs, ensuring continuous systemic circulation and oxygenation throughout the surgical procedure.

The surgeon conducts a thorough visual and manual assessment of the coronary arteries, integrating preoperative coronary angiography findings. To prepare for grafting, the epicardium is dissected, exposing the targeted coronary site for precise anastomosis. Following aortic cross-clamping, the perfusionist delivers a potassium-rich cardioplegic solution into the coronary arteries, halting cardiac activity and safeguarding the myocardium from ischaemic injury. This controlled environment allows for meticulous anastomosis of the conduits to the coronary vessels, free of cardiac motion or blood flow.

Upon completion of the grafting, the aortic cross-clamp is released, and cardiac activity resumes. The patient is then gradually weaned from CPB, with close monitoring of hemodynamic stability. Graft patency is assessed using transit-time flowmetry (TTFM), while ventricular function is evaluated by the anaesthesiologist employing intraoperative transesophageal echocardiography. Finally, chest

tubes are positioned for drainage, and the sternum is secured using stainless steel wires. The surgical wound is closed in layers, ensuring haemostasis and optimal wound integrity.

Advantages and Limitations. One of the primary advantages of ONCAB is the ability to achieve complete revascularisation, especially in patients with complex coronary anatomy or multivessel disease. The motionless and bloodless surgical field facilitates the creation of precise and enduring graft anastomoses. Furthermore, ONCAB provides better visualisation of the coronary artery tree, which is particularly valuable when dealing with small or heavily calcified vessels.

However, the use of CPB introduces certain drawbacks. The systemic inflammatory response associated with CPB may lead to complications, including coagulopathy, acute kidney injury, and neurological dysfunction, especially in high-risk patients. The myocardial injury related to cardioplegic arrest and the potential for prolonged operative times further underscore the limitations of this approach. These concerns have driven the pursuit of less invasive alternatives, such as off-pump coronary artery bypass (OPCAB) and minimally invasive techniques, including MIDCAB, TECAB, and HCR, which aim to mitigate the physiological impact of conventional CABG [15].

3.6.2. Off-Pump Coronary Artery Bypass

Benetti and Buffolo first introduced off-pump coronary artery bypass grafting (OPCAB) in 1985 [212, 213]. The main objective of OPCAB is to achieve coronary revascularisation without CPB. By eliminating the need for CPB, OPCAB reduces the inflammatory response commonly associated with using a heart-lung machine, potentially resulting in fewer postoperative complications [214]. Moreover, maintaining normal physiological conditions during surgery may help preserve organ function and lower postoperative issues such as renal dysfunction, respiratory problems, and neurological deficits. Consequently, this approach could lead to shorter patient recovery times and overall improved patient safety.

Surgical Procedure Overview. OPCAB is performed under general anaesthesia, much like ONCAB, with a midline sternotomy to access the heart. However, in OPCAB, the heart remains beating throughout the procedure, necessitating specialised stabilisation devices and positioning techniques to provide a motion-restricted field for anastomosis (Figure 3.6) [215]. These stabilisers often use suction or mechanical devices to immobilise the target coronary artery segment while minimising interference with overall cardiac function.

The surgical team employs tissue stabilisers, such as the Octopus or Starfish devices, to restrict heart movement and expose the appropriate coronary vessel. Additionally, intracoronary shunts

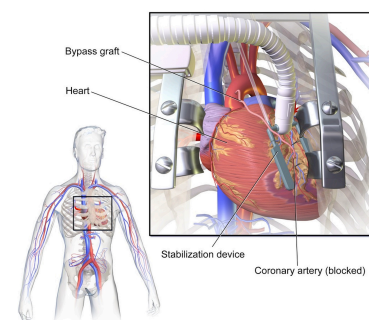


Figure 3.6.: Off-Pump Coronary Artery Bypass (Source: WikiCommons, Licence: © CC BY-SA 4.0).

Table 3.7.: Landmark Randomised Controlled Trials Comparing Off-Pump and On-Pump CABG (5-Year Outcomes).

Trial	Study period	Patients (n)	Inclusion criteria	Clinical outcomes
ROOBY [216]	2002-2007	2203	Male veterans Urgent or elective isolated CABG	OPCAB led to lower rates of 5-year survival and event-free survival than ONCAB
CORONARY [217]	2006-2011	4752	Urgent or elective isolated CABG ≥1 risk factors: ≥70 years, peripheral arterial disease, cerebrovascular disease, or renal insufficiency	The rate of the composite outcome of death, stroke, myocardial infarction, renal failure, or repeat revascularisation was similar among patients who underwent OPCAB and those who underwent ONCAB
GOPCABE [218]	2008-2011	2539	Urgent or elective isolated CABG ≥75 years	The 5-year survival rates and the combined outcome of death, myocardial infarction, and repeat revascularisation were similar after OPCAB and ONCAB

CABG, coronary artery bypass grafting; **ONCAB**, on-pump coronary artery bypass; **OPCAB**, off-pump coronary artery bypass

may be inserted to maintain distal myocardial perfusion during coronary artery occlusion. This technique demands a high degree of precision and expertise from the surgeon, as the beating heart introduces challenges in performing proper anastomoses.

Heparin is administered to achieve systemic anticoagulation but at a lower dose than ONCAB. The surgeon performs the grafting procedures, usually starting with the most critical vessel. Once all grafts have been placed and their patency is confirmed, the chest is closed in layers, and chest tubes are inserted for drainage.

Comparative Effectiveness. Numerous randomised controlled trials (RCTs) comparing off-pump and on-pump techniques for CABG have been reported; however, the debate regarding the preferred technique remains unresolved. Recently, 5-year outcome data have been published for three notable off-pump RCTs: ROOBY [216], CORONARY [217], and GOPCABE [218] (Table 3.7).

In the ROOBY trial, 2203 patients at 18 medical centres were randomly assigned to undergo either on-pump or off-pump CABG [216]. The study focused on two primary 5-year outcomes: death from any cause and a composite outcome of major adverse cardiovascular events, including death from any cause, repeat revascularisation (surgical or percutaneous), or nonfatal myocardial infarction. The five-year death rate was 15.2% in the off-pump group and 11.9% in the on-pump group ($p=0.02$). The major adverse cardiovascular events rate at five years was 31.0% in the off-pump group and 27.1% in the on-pump group ($p=0.046$).

Although its findings were not unique, no trial comparing off-pump with on-pump CABG has sparked as much controversy [219]. Crit-

ics of the trial, particularly those favouring OPCAB, raised concerns about its design, pointing out the inclusion of low-risk patients and the recruitment of surgical residents and inexperienced surgeons for OPCAB procedures, which might have introduced bias. In response, advocates of the OPCAB technique initiated two multi-centre trials: CORONARY [217] and GOPCABE [218]. Both of these trials had much more stringent criteria regarding prior experience for surgeons performing OPCAB.

In the CORONARY trial, 4752 patients with coronary artery disease from 19 countries were randomised to undergo either off-pump or on-pump CABG [217]. The primary outcome was a composite of death, stroke, myocardial infarction, renal failure, or repeat coronary revascularisation (surgical or percutaneous). The rate of the composite outcome and its individual components at five years was similar among patient groups.

In the GOPCABE trial, 2539 patients aged >75 years were randomly assigned to undergo off-pump or on-pump CABG at 12 centres in Germany [218]. The primary outcome was all-cause mortality at five years. The secondary 5-year outcomes were a composite of death, myocardial infarction, and repeat revascularisation. After a median follow-up of five years, 31% of the patients assigned to off-pump CABG and 30% of those assigned to on-pump CABG had died ($p=0.71$). The composite outcome of death, myocardial infarction, and repeat revascularisation occurred in 34% of the patients after off-pump and in 33% of those after on-pump CABG ($p=0.704$).

None of these trials has demonstrated a long-term survival advantage associated with OPCAB. Furthermore, recent large-scale, rigorously adjusted observational studies [220, 221] and meta-analyses [214, 222–224] have raised doubts about its long-term effectiveness. For instance, Chikwe et al. analysed the mandatory clinical and administrative registries from the New Jersey Department of Health, identifying 42,570 patients who underwent CABG between 2005 and 2011 by surgeons who had performed at least 100 OPCAB or ONCAB operations [221]. The OPCAB strategy exhibited increased rates of incomplete revascularisation, repeat revascularisation, and mortality at ten years compared with ONCAB. Furthermore, a meta-analysis by Smart et al. incorporating the results of 5-year follow-ups from the trials mentioned above showed that ONCAB surgery offers better long-term survival outcomes [223].

Summary. While the debate about ONCAB versus OPCAB is ongoing, it may be prudent to shift the focus towards determining the specific patient characteristics that make each procedure more beneficial. OPCAB is more suitable for specific patient profiles, whereas ONCAB is preferable for others, although most patients will have successful outcomes with either approach [219].

While OPCAB has reduced the invasiveness of conventional on-pump surgery by minimising the physiological impact of CPB and ischaemic cardioplegic arrest, other approaches have focused on reducing access invasiveness by performing CABG through smaller incisions rather than the traditional full sternotomy. These approaches, including MIDCAB, TECAB, and HCR, represent the next frontier in surgical strategies, explicitly targeting patients who would benefit from precise yet less invasive interventions.

3.6.3. Minimally Invasive Direct Coronary Artery Bypass

Another approach focuses on reducing access invasiveness by performing CABG through smaller incisions rather than the traditional full sternotomy. In the early days of direct coronary artery procedures, Kolessov performed the ITA to coronary artery anastomoses using a small left anterior thoracotomy through the fifth intercostal space [145]. In the 1990s, given the competitive nature of percutaneous transluminal coronary angioplasty (PTCA) and coronary artery stenting, there was a growing interest in promoting minimally invasive direct coronary artery bypass (MIDCAB) grafting. The most common MIDCAB involves performing an LITA to LAD anastomosis. Subramanian et al. reintroduced this procedure using a left anterior thoracotomy through the fourth intercostal space (Figure 3.7) [225].

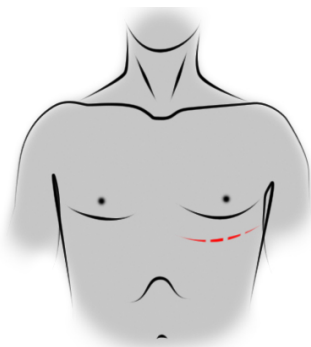


Figure 3.7.: Left anterior thoracotomy (Source: WikiCommons, Licence: © CC BY-SA 4.0).

Surgical Procedure Overview. MIDCAB is currently the most standardised of all minimally invasive coronary procedures [226]. During this procedure, surgeons perform both the LITA take-down as well as the distal LITA to LAD artery anastomosis through a small inframammary thoracotomy in the fourth left intercostal space. Using new retractor systems, single-lung anaesthesia, and video assistance greatly facilitates ITA exposure and dissection.

Advantages. MIDCAB offers several advantages, including a lower stroke rate stemming from the absence of aortic manipulation and cross-clamping, decreased inflammatory response from the bypass circuit resulting in reduced rates of acute kidney injury, and decreased need for blood transfusions [226, 227]. Additionally, smaller incisions facilitate faster extubation, leading to fewer respiratory complications [228]. By eliminating the risk of sternal wound infection and not requiring postoperative bone healing, a small thoracotomy allows patients to resume their normal activities more quickly [229].

Evidence Overview. In a study published in 2007, Holzhey et al. reported on MIDCAB outcomes in 1347 patients operated on between 1996 and 2004 [230]. The analysis found a low intraoperative conversion to sternotomy or CPB in only 1.7% of cases, a perioperative stroke in 0.4%, and postoperative mortality of 0.8%,

highlighting the procedure's safety. In addition, a routine postoperative angiogram revealed 95.6% early graft patency. Furthermore, the 5-year data demonstrated an 89.5% freedom from major adverse events and angina, as well as a 5-year survival rate of 91.9%. These results compared favourably with those of percutaneous intervention and conventional surgery.

Surgical Limitations and Evolution. While MIDCAB has proven highly effective for single-vessel disease, such as LITA to LAD grafting, it does face some limitations. Specifically, its primary constraint lies in its inability to achieve comprehensive multivessel revascularisation, a crucial factor for patients with complex or extensive CAD. MIDCAB is generally limited to anterior myocardial territories and may not address the complete needs of patients with extensive coronary atherosclerosis.

Therefore, in 2005, Mark Ruel pioneered minimally invasive coronary artery bypass grafting (MICS CABG), which provides access to all myocardial territories through a 4- to 6-cm left fifth intercostal thoracotomy [227]. This technique involves using an apical positioner and epicardial stabiliser introduced through the subxiphoid and left seventh intercostal spaces to facilitate heart mobilisation and exposure. The LITA allows the revascularisation of the anterior wall while using the RA or SVG to graft the lateral and inferior myocardial territories, with its proximal anastomoses performed directly onto the aorta or from the LITA as a T-graft. The ability to perform complete multivessel bypass through minimally invasive techniques represents a significant step forward in cardiac surgery, meeting the needs of more complex patient cases while preserving the benefits of reduced trauma and quicker recovery times.

In the first 450 consecutive such procedures, the average number of grafts was 2.1 ± 0.7 , with complete revascularisation achieved in 95% of patients [231]. Thirty-four patients (7.6%) required cardiopulmonary bypass, 17 patients (3.8%) needed conversion to sternotomy, 10 patients (2.2%) had reinterventions for bleeding, and perioperative mortality occurred in 6 patients (1.3%).

The Minimally Invasive Coronary Artery Bypass Grafting Patency Study conducted a prospective evaluation of angiographic graft patency six months after MICS CABG, using 64-slice computed tomography angiography [232]. The study found that the six-month graft patency rate was 92% for all grafts and 100% for LITA grafts.

The ongoing quest to refine and optimise coronary revascularisation has also led to the development of even less invasive methods, such as TECAB and HCR. These cutting-edge approaches aim to further reduce the invasiveness of cardiac surgery while enhancing precision and patient outcomes.

3.6.4. Totally Endoscopic Coronary Artery Bypass

Robotic, totally endoscopic coronary artery bypass (TECAB) is the least invasive form of surgical coronary revascularisation [233]. First introduced by Loulmet et al. and Falk et al. in 1999, TECAB uses robotic assistance to harvest ITA conduits and perform the anastomosis endoscopically – the procedure’s most critical and challenging part [234, 235].

Surgical Procedure Overview. TECAB relies on video-assisted thoracoscopy (VATS) or robot-assisted thoracoscopy (RATS) to complete the procedure. Inducing a controlled pneumothorax using carbon dioxide insufflation can help establish a clear visual field without requiring single-lung ventilation. Subsequently, the surgeon harvests the ITA from the left hemithorax using VATS or RATS instruments via ports in the second, third, and fourth intercostal spaces, approximately 2 cm above and below the anterior axillary line, while triangulating towards the mediastinum. After systemic heparinisation and the transection of the ITA’s distal ends, opening the pericardium allows for identifying all coronary targets.

The procedure proceeds with or without CPB support. With CPB support, peripheral cannulation through the femoral vessels establishes total CPB. An endoscopic transthoracic clamp inserted in the second right intercostal space in the anterior axillary line permits aorta cross-clamping, and using an endoscopically-placed vent needle enables cardioplegia administration. Without CPB support, tissue-stabilising devices passed through one of the ports facilitate the performance of anastomoses on the beating heart. At this point, the surgeon completes the procedure manually using the MIBCAB technique or using the robotic arms to manipulate the heart and perform the anastomoses.

Evidence Overview. The FDA-sanctioned multicentre study by Argenziano et al. examined the efficacy of TECAB for single-vessel revascularisation, reporting promising outcomes such as a 91% rate of freedom from reintervention or angiographic failure and low rates of conversion and perioperative complications [236]. Similarly, De Cannière et al. documented a 97% procedural efficacy rate and a 5% incidence of major adverse cardiac events within six months, underscoring the technique’s safety and reliability [237].

Comparative Effectiveness. Comparative studies, such as the propensity score-matched analysis by Kofler et al., have revealed no significant differences in perioperative mortality, myocardial infarction, or stroke rates between TECAB and conventional CABG [238]. However, TECAB is associated with longer CPB and cross-clamp times. Long-term survival and freedom from major adverse cardiac and cerebrovascular events (MACCE) are comparable between TECAB and conventional CABG. Kitahara et al. literature

review further validates TECAB's graft patency rates, which are similar to those achieved with traditional methods [239].

As TECAB has demonstrated safety and efficacy in highly selected patients, it continues to push the boundaries of minimally invasive cardiac surgery. Yet, the need for even more sophisticated and tailored revascularisation strategies remains. This necessity has fueled the development HCR techniques, which seek to combine the advantages of minimally invasive procedures with the comprehensive revascularisation capabilities seen in more invasive procedures.

3.6.5. Hybrid Coronary Revascularisation

Hybrid coronary revascularisation (HCR) integrates traditional coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) techniques to optimise patient outcomes in coronary artery disease (CAD). This innovative strategy was first reported by Angelini et al. in the late 1990s [240], and the advent of drug-eluting stents (DES) in the mid-2000s has renewed interest in its clinical utility.

The core rationale behind HCR lies in leveraging the well-documented survival advantage of left internal thoracic artery (LITA) grafting to the left anterior descending (LAD) artery while recognising that saphenous vein grafts (SVGs) for non-LAD territories may not confer the same long-term benefit [241]. With advancements in DES technology, PCI offers a viable and less invasive option for revascularizing these non-LAD lesions.

Definition. A consensus document has outlined the essential elements for defining HCR to standardise comparative studies and guide clinical practice (Table 3.8) [242]. In its most refined form, HCR employs minimally invasive LITA-LAD grafting combined with PCI to treat other significant non-LAD lesions. This 'best of both worlds' hypothesis underlines the strategy's rationale, aiming to achieve the durability of LITA-LAD bypass while minimising invasiveness for other coronary artery territories [226].

Evidence Overview. Evidence on HCR's efficacy and safety is growing. The POLMIDES trial demonstrated comparable 12-month outcomes between HCR and conventional CABG concerning mortality, myocardial infarction, major bleeding, and repeat revascularisation [243]. Meta-analyses have echoed these findings, indicating similar clinical outcomes between HCR and CABG, alongside faster recovery and reduced hospitalisation times. However, these benefits are counterbalanced by a higher rate of repeat revascularisation and greater overall procedural costs [244–248].

Despite encouraging results, most current data are derived from nonrandomised studies or single-centre experiences, underlining the urgent need for more robust, multicentre randomised trials.

Table 3.8.: Key elements for hybrid coronary revascularisation.

Key elements for hybrid coronary revascularisation
1. Planned use of CABG and PCI techniques for revascularisation of different coronary territories
2. Both CABG and PCI should be performed within 60 days of each other, either during the same or different hospital encounters, regardless of each procedure’s location
3. Neither the CABG nor the PCI portion of the procedure is performed for complications of the other
4. May include concurrent or staged approaches
5. Is irrespective of surgical approach/choice of incision
6. Excludes cases in which PCI is performed of infarct-related artery in acute STEMI followed by CABG that also involves revascularisation of the infarct-related territory

CABG, coronary artery bypass grafting; **PCI**, percutaneous coronary intervention; **STEMI**, ST-elevation myocardial infarction

As hybrid strategies continue to evolve, their role in personalised and precision-based cardiovascular care remains a critical area of investigation.

While these advancements in revascularisation techniques provide innovative ways to treat CAD with reduced invasiveness, the long-term success of any coronary artery bypass strategy still hinges critically on the selection of appropriate conduits. The next section will explore the importance of conduit choice, focusing on the comparative durability and patency rates of commonly used grafts, such as the left internal thoracic artery (LITA), saphenous vein grafts (SVGs), and alternative arterial conduits. Understanding these options is essential for optimising surgical outcomes and CABG efficacy.

3.7. Optimal Conduit Choice

Coronary artery bypass grafting (CABG) remains one of the most effective treatments for coronary artery disease (CAD), largely due to advancements in surgical techniques and the strategic selection of conduits. The choice of graft conduit plays a pivotal role in determining the long-term success of the procedure, as it influences graft patency rates, patient outcomes, and the risk of complications. Studies have consistently shown that conduit choice can affect both short-term recovery and long-term survival, making it a critical consideration in surgical planning .

In the early days, Favaloro demonstrated the benefits of using the saphenous vein graft (SVG) as a conduit for CABG due to its accessibility, versatility, and ease of harvesting. Additionally, within five years of operation, the difference in patency between the internal thoracic artery (ITA) graft and the SVG was deemed

insignificant [249]. For these reasons, the SVG was extensively used as a conduit for CABG [150].

However, initial reports also noted the tendency of the SVG to fail [250]. From five to twelve years after the operation, vein graft occlusion and angiographic evidence of vein graft atherosclerosis increase [251]. This realisation led to a broader recognition of Green's pivotal contribution in 1970 [252, 253], which underscored the superiority of the ITA as a graft, particularly in terms of long-term patency.

The modern approach to CABG endorses the left internal thoracic artery (LITA) to the left anterior descending (LAD) artery bypass as the absolute gold standard, primarily due to its superior long-term patency and resistance to atherosclerosis. However, debates persist regarding the optimal use of other arterial conduits, like the radial artery (RA) and the right internal thoracic artery (RITA), especially in multi-arterial grafting strategies.

Choosing the appropriate conduit requires a nuanced understanding of each patient's specific anatomical and physiological conditions. Factors such as age, comorbidities (e.g., diabetes, chronic kidney disease), and the extent of CAD must be carefully weighed. This section will explore the anatomical and physiological characteristics of various conduits, evidence from landmark studies, and innovative techniques that have influenced the evolution of CABG. By comprehensively reviewing the advantages and limitations of each conduit, we aim to provide a thorough understanding of the strategies that optimise graft longevity and patient outcomes.

3.7.1. Left Internal Thoracic Artery

The left internal thoracic artery (LITA) is widely regarded as the optimal conduit for coronary artery bypass grafting (CABG), particularly for bypassing the left anterior descending (LAD) artery. Its unparalleled long-term patency rates, exceeding 90% at ten years, make it a fundamental component in modern revascularisation strategies. This exceptional performance is attributed to several key physiological characteristics, including the LITA's inherent resistance to atherosclerosis, endothelial integrity, and capacity for long-term adaptation to increased blood flow.

Anatomical Considerations. The LITA arises from the inferior surfaces of the first parts of the ipsilateral subclavian artery at the root of the neck, descending behind the clavicle and the first costal cartilage into the thorax (Figure 3.8) [254]. As they continue their descent, the arteries course along the internal surface of the thorax, slightly lateral to the sternum and posterior to the upper six costal cartilages and intervening internal intercostal muscles. Along their way caudally, they give rise to multiple branches, including the anterior intercostal branches, before dividing into the

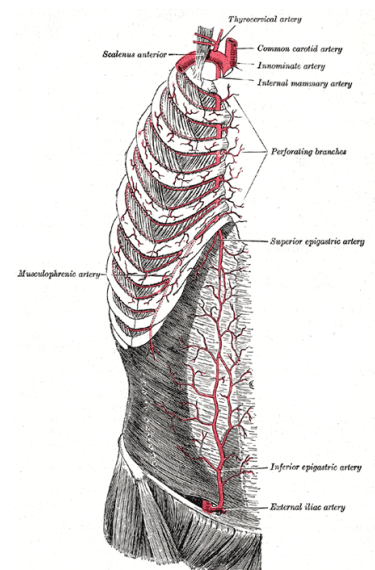


Figure 3.8.: Course of the internal thoracic artery (Source: Gray's Anatomy of the Human Body, Licence: Public Domain).

musculophrenic and the superior epigastric arteries approximately at the level of the sixth intercostal space.

Physiological Characteristics. The ITAs exhibit several unique properties that render them resistant to intimal growth and atherosclerotic plaque formation [255]. Indeed, their media exhibits circumferentially aligned vascular smooth muscle cells (VSMC) firmly encircled by a plethora of longitudinally and circularly interwoven elastic fibres, which might limit VSMC proliferation and migration. In addition, their well-defined, continuous internal elastic lamina might offer an added barrier to the migration of these cells. On the other hand, their inner layer, the intima, demonstrates low permeability, even in individuals with diffuse atherosclerosis. This structural integrity makes it difficult for inflammatory cells and lipids to squeeze into the artery wall. Finally, the ITAs reveal high endothelial nitric oxide synthase (eNOS) expression levels, increasing the production of nitric oxide (NO) [256]. NO is a potent vasodilator and inhibitor of platelet aggregation, both of which contribute to preventing plaque formation. These properties contribute to the superior patency rate of ITAs compared to other conduits [257].

Harvesting Techniques. Henriquez-Pino et al. demonstrated that the length of ITA varies from 15.1 to 26.0 cm, with a mean of 20.4 ± 2.1 cm, from its origin to the terminal bifurcation. In addition, while the left internal thoracic artery (LITA) ranges from 16.2 to 26.0 cm (mean, 20.7 ± 2.1 cm), the right internal thoracic artery (RITA) countered from 15.1 to 25.1 cm (mean, 20.1 ± 2.0 cm), a significant difference ($p=0.00003$) [258]. Harvesting the ITAs with a skeletonised technique, instead of the pedicled strategy, allows surgeons to maximise their length and prevent extensive devascularisation of the sternum. Preserving the collateral blood supply and venous drainage to the sternum through skeletonisation can potentially decrease the risk of sternal wound infections, particularly in high-risk patients such as those with diabetes mellitus or obesity [259, 260]. Skeletonisation also facilitates better visualisation and more efficient use of the artery for multiple grafts when necessary.

Long-Term Outcomes. In 1985, Bruce Lytle et al. established the superior ten-year patency rate of the LITA to the left anterior descending (LAD) artery graft compared to saphenous vein grafts (SVGs) within the same vascular territory (94% vs 78%, respectively) [251]. Later, larger studies on the long-term performance of LITA have revealed a patency rate exceeding 90% at 20 years when grafted on the LAD artery. Furthermore, grafting the ITA to other territories, such as the circumflex (patency rate of 91% at 15 years) or the right coronary arteries (patency rate of 84% at 15 years), still outperforms SVGs, with ten-year patency rates around 50% [261].

In 1986, Floyd Loop et al. demonstrated that this notably higher

long-term patency rate likely accounts for the prognostic benefit of LITA grafting on the LAD artery [262]. Specifically, it afforded a 38% reduction in the risk of death throughout the ten-year follow-up. In addition, patients with an internal thoracic artery to the left anterior descending artery bypass had a 29% decrease in the risk of late myocardial infarction, a 20% reduction in the risk of hospitalisation for cardiac events, a 50% decline in the risk of cardiac reoperation, and a 21% decrease in the risk of all late cardiac events, as compared with patients who received (SVGs).

Summary. An extensive body of observational evidence attests to the superiority of the LITA-LAD graft. While no appropriately powered randomised controlled trial (RCT) has formally tested this hypothesis, there is no professional nor individual equipoise in the surgical community for such a study [263].

3.7.2. Right Internal Thoracic Artery

The left internal thoracic artery (LITA) to the left anterior descending (LAD) artery bypass has become the absolute gold standard in coronary artery bypass grafting (CABG). Its powerful influence on long-term outcomes [262, 264–267] has encouraged several groups to extend the use of the internal thoracic arteries (ITAs) to bypass other coronary artery territories. It was plausible that if a single internal thoracic artery (SITA) graft was effective, bilateral internal thoracic artery (BITA) grafting could be even better [268].

In fact, in 1973, Suzuki et al. introduced using two ITA grafts [269]. In 1983, Lytle et al. reported excellent outcomes from 76 patients with multivessel disease who received revascularisation with BITA grafts from 1971 to 1980. This strategy resulted in excellent graft patency, symptom relief, and long-term survival. As a result, they cautiously suggested using BITA grafts when the saphenous vein was not a suitable option for grafting [270].

Moreover, Mills and colleagues introduced the concept of composite grafts, which involves anastomosing another bypass graft end-to-side to a pedicled internal thoracic artery [271]. This innovative technique helps to avoid placing the proximal anastomosis into a severely atherosclerotic ascending aorta. Using internal thoracic artery grafts, Sauvage and his team have successfully applied this method to bypass all coronary arteries supplying the left ventricle [272]. Tector and associates have also employed a strategy to anastomose the free RITA graft to the side of the pedicled LITA, creating a T or Y graft [273, 274]. This approach allowed for consistent use of the latter to bypass the left anterior descending artery and effectively overcome the limitation in the free RITA graft length to reach the marginal branches of the circumflex artery.

Anatomical and Physiological Considerations. The anatomical and physiological attributes of the right internal thoracic artery (RITA) closely mirror those of the LITA, including its resistance

to atherosclerosis, well-developed elastic fibers in the media, and high levels of endothelial nitric oxide production. These shared characteristics account for the RITA's durability as a graft conduit.

Harvesting Techniques. It is essential to note that using BITA grafts carries a higher risk of sternal wound complications and mediastinitis. According to a meta-analysis of 32 observational studies conducted by Dai and colleagues, patients undergoing BITA grafting showed a 61% increased relative risk of sternal wound infection (SWI) compared to those undergoing SITA grafting [259]. Older age and diabetes mellitus further increase this adverse event risk. However, careful patient selection and the appropriate harvesting technique can significantly reduce the incidence of severe wound problems [275]. For example, two meta-analyses of observational studies have shown that skeletonisation, rather than a pedicled harvesting technique, significantly reduces deep sternal wound infections (DSWI), even in diabetic patients [259, 260].

Long-Term Outcomes. Multiple single-institution observational studies have confirmed the association of BITA grafting with significantly reduced long-term mortality. By contrast, no single study has ever been published that shows superior long-term outcomes with SITA and saphenous vein grafts, or for vein grafts only, over BITA [276]. Several meta-analyses of these trials have documented the association of BITA grafting with significantly reduced long-term mortality [277–282]. However, even though they provide essential information when prospective randomised trials are unavailable, they remain limited by their potential for selection bias.

Nevertheless, the Arterial Revascularization Trial [283], designed to answer whether BITA can improve 10-year survival compared with SITA, failed to demonstrate a significant between-group difference in the death rate from any cause at ten years despite its intensely debated methodological limitations [284, 285]. Several proposed justifications could explain the neutral effect of BITA grafting in this trial [284–286]. First, the sample size calculations predate guideline-directed medical therapy (GDMT), so the sample size might be too small to demonstrate a significant decrease in the proposed endpoints. Second, there was a high crossover rate (14% of patients assigned to the BITA group had a SITA) that might be related to surgeon inexperience. Third, nearly 22% of SITA patients also received a radial artery (RA) graft, which appears to have superior patency rates than SVGs, resulting in improved long-term outcomes [287]. Finally, adherence to GDMT was extremely high in this trial, and noncompliance with GDMT after CABG seems to decrease long-term survival, freedom from myocardial infarctions, and the need for repeat coronary revascularisation procedures [288].

Summary. Overall, the current use of BITA grafting in clinical

practice remains relatively low, with fewer than 5% of patients in the USA and fewer than 10% in Europe receiving it [289]. The reasons for the low uptake of BITA grafting need further elucidation [276]. They may result from factors such as prolonged operative time, perceived technical complexity, unfamiliarity with the surgical techniques, concerns about perioperative outcomes, potential myocardial hypoperfusion, lack of randomised trials, and the increased susceptibility of patients to deep sternal wound infections (DSWIs).

3.7.3. Radial Artery

The radial artery (RA) has emerged as an increasingly popular conduit in coronary artery bypass grafting (CABG). In the early 1970s, CABG primarily relied on saphenous vein grafts (SVGs) to restore coronary blood flow – a procedure known for its simplicity, reproducibility, and excellent short-term results [150]. However, research soon revealed a notable incidence of late graft occlusion and angiographic changes over time. Johnson et al. identified substantial subintimal hyperplasia in explanted SVGs [290], a phenomenon commonly attributed to the vein's adaptation to arterial pressures and associated with an elevated risk of graft failure [291, 292]. These findings underscored the need for more durable grafts to improve long-term outcomes.

In light of these limitations, several surgical groups began exploring alternative conduits, leading to the successful adoption of the internal thoracic artery (ITA), inspired by Green's pioneering work [252, 253]. While the ITA demonstrated superior patency rates and resistance to atherosclerosis, it posed several limitations: its smaller lumen compared to coronary arteries, a more challenging dissection process, the fragility of its distal wall complicating distal sutures, and an insufficient length for bypassing certain coronary targets, such as the right and distal branches of the left coronary arteries [293]. These constraints motivated the search for additional arterial grafts with improved versatility and ease of use.

Introduced by Carpentier and colleagues in 1971, the RA offered an advantageous alternative to both SVG and ITA grafts [293]. The RA features a lumen diameter closer to that of coronary arteries and a muscular, resilient wall, facilitating handling and suturing. Positioned superficially along the forearm, it also supports a straightforward harvesting technique. Moreover, collateral circulation from the ulnar artery minimises the risk of hand ischaemia post-harvest, reinforcing its viability. Additionally, the RA's resistance to atherosclerosis and its adaptability to arterial pressures made it an appealing choice for long-term graft patency, establishing its role in contemporary revascularisation strategies.

Anatomy. The radial artery (RA) originates from the brachial artery at the antecubital fossa (Figure 3.9) [254]. It advances dis-

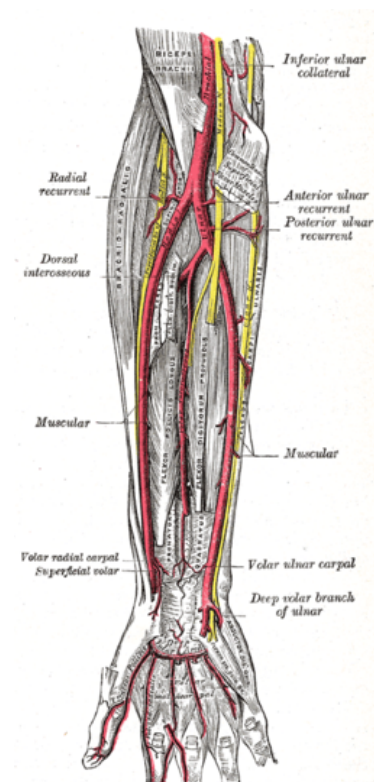


Figure 3.9.: Course of the radial artery – deep view (Source: Gray's Anatomy of the Human Body, Licence: Public Domain).

Table 3.9.: Randomised controlled trials comparing radial artery and greater saphenous vein patency rates.

Trial	Year	Patients (n)	Mean follow-up	Patency rates (RA vs GSV)
Muneretto et al. [295]	2004	160	1.3 years	98.6% vs 88.5% (p=0.033)
Gaudino et al. [296]	2005	120	4.3 years	88.7% vs 60.6% (p=0.001)
Collins et al. [297]	2008	142	5 years	98.3% vs 86.4% (p=0.04)
Goldman et al. [298]	2011	757	1 year	86% vs 89% (p=0.98)
Deb et al. [299]	2012	561	7.7 years	91.1% vs 81.4% (p=0.002)
Song et al. [300]	2012	60	1 year	97.4% vs 94.7% (p=0.437)
Dreifaldt et al. [301]	2013	108	3 years	82% vs 94% (p=0.01)
Buxton et al. [302]	2020	225	10 years	85% vs 71% (p=0.05)

GSV, greater saphenous vein; RA, radial artery

tally along the anterolateral aspect of the forearm, running deep to the *brachioradialis* muscle in the proximal forearm and becoming superficial near the wrist, lying between the tendons of the *brachioradialis* and *flexor carpi radialis* muscles. Along its course, the RA supplies blood to the lateral aspect of the forearm and hand, eventually forming part of the superficial and deep palmar arches in the hand.

Physiological Characteristics. Histologically, the RA is a muscular artery with a thick media layer containing several layers of smooth muscle cells interspersed with a variable number of elastic lamellae [46]. Its intima has a thin subendothelial layer and a prominent internal elastic lamina with multiple fenestrations. These features explain its greater propensity for spasm and intimal hyperplasia compared to the ITA.

Harvesting Techniques. Surgeons usually remove the RA from the non-dominant arm. The modified Allen test is the simplest method for assessing the adequacy of ulnar functional compensation following RA harvesting. However, issues with its reliability often evoke the need for more objective information, such as percutaneous oximetry and Doppler ultrasound [294].

Long-Term Outcomes. The RA is the arterial conduit supported by the most evidence from randomised controlled trials (RCTs) [275]. In general, these RCTs have demonstrated that RAs have a significantly higher patency rate compared to SVGs (Table 3.9) [295–302]. Similarly, the findings of several systematic reviews and meta-analyses, which include a similar core of randomised studies comparing the patency rates of the RA and the GSV, support the conclusion that selected patients with critical coronary artery stenosis may have better midterm angiographic outcomes with the RA [303–306].

The design of most of these trials allowed for a thorough assessment of angiographic outcomes. However, clinical results comparisons

Table 3.10.: Randomised controlled trials comparing radial artery and greater saphenous vein clinical outcomes.

Trial	Year	Patients (n)	Mean follow-up	Clinical outcomes
Muneretto et al. [295]	2004	160	1.3 years	Lower incidence of angina recurrence in the RA arm
Gaudino et al. [296]	2005	120	4.3 years	Superior freedom from clinical and instrumental evidence of ischemia recurrence in the RA arm
Collins et al. [297]	2008	142	5 years	No difference in the 5-year survival rate
Nasso et al. [307]	2009	815	2 years	No difference in 2-year freedom from all-cause death. Better adverse cardiac event-free survival (adverse cardiac events included cardiac death, acute myocardial infarction, recurrent angina, graft occlusion at coronary angiography, redo coronary surgery, or percutaneous transluminal coronary angioplasty) in the RA arm
Petrovic et al. [308]	2015	200	8 years	No difference in composite of cardiac death, non-fatal myocardial infarction and repeat revascularization
Buxton et al. [302]	2020	225	10 years	Survival: RA 72.6% vs GSV 65.2% (p=0.26)

GSV, greater saphenous vein; RA, radial artery

are primarily descriptive and serve as a basis for generating hypotheses [295–297, 302, 307, 308]. Therefore, limited evidence is available for comparing the clinical outcomes of using the RA versus the GSV for CABG (Table 3.10).

Most of the existing data concerning clinical outcomes comes from single-centre observational studies. Generally, they demonstrate an improved long-term survival rate associated to RA use, as well as reduced myocardial infarction rates and need for repeat revascularisation [309–311]. However, it is critical to note that biases in participant selection or treatment assignment and unmeasured or uncontrolled factors may lead to results that are not broadly applicable. Additionally, these reports originate from highly specialised institutions, and their findings may not be universally applicable across all clinical settings [312].

While there is extensive RCT-derived data on the comparative effectiveness of RA and GSV in CABG, only two trials have compared RA and RITA grafts. Buxton et al. reported on a trial involving 394 patients under 70 (or under 60 years if they had diabetes mellitus) who were randomly assigned to receive either a RA or a free RITA graft to the second most important coronary artery target [302]. The RA showed superior 10-year patency (89%) compared to the

free RITA (80%), along with a 47% reduction in mortality hazard for patients receiving RA grafts. Whether the conclusions should apply to in situ RITA grafts is uncertain [313]. On the other hand, Nasso et al. examined 815 patients across three revascularisation strategies and found similar short-term mortality and morbidity rates among groups, but patients with two arterial grafts – either ITAs or a combination of ITA and RA – had significantly improved cardiac event-free survival [307].

In a network meta-analysis, Benedetto et al. compared different CABG graft options, including the RITA, RA, right gastroepiploic artery (RGEA), and GSV [306]. The analysis incorporated data from nine randomised controlled trials involving 2780 patients and 1620 angiographic results. The findings suggested that using the RITA graft resulted in a non-significant 27% absolute risk reduction for functional graft occlusion compared to using the RA. While the study authors anticipate a superior patency rate for the RITA relative to the RA, they emphasise the need for additional research to validate these results. Additionally, in a recent meta-analysis, Urso et al. compared twelve matched populations, comprising 6450 patients with BITA grafting and 9428 patients with SITA plus RA grafting [314]. The study revealed a statistically significant survival benefit in the BITA group. These findings underscore a nuanced balance between graft choices, patient-specific factors, and long-term outcomes in CABG.

Summary. The RA is a valuable alternative conduit in CABG, offering superior long-term patency compared to SVGs and demonstrating promising outcomes in select patient populations. Comparative studies suggest the RA may even outperform the free RITA in specific scenarios, though results for in situ RITA grafts remain inconclusive. While multiple trials and meta-analyses highlight the RA's benefits, including improved event-free survival and graft longevity, the choice between RA and RITA grafting often depends on individual patient factors and institutional expertise. Ultimately, the RA expands surgical options in revascularisation, allowing for a tailored approach to enhance CABG outcomes.

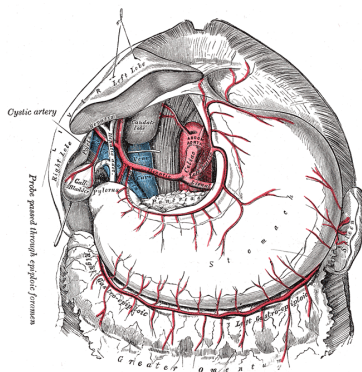


Figure 3.10.: Course of the right gastroepiploic artery along the greater curvature of the stomach (Source: Gray's Anatomy of the Human Body, Licence: Public Domain).

3.7.4. Right Gastroepiploic Artery

The right gastroepiploic artery (RGEA) is a lesser-used coronary artery bypass grafting (CABG) conduit. It primarily serves as an alternative when other arterial grafts are unavailable or complete arterial revascularisation is sought. Edwards and colleagues pioneered using the RGEA as a direct bypass graft to the right coronary artery (RCA) in 1973 [315, 316]. Despite several reports advocating for its broader clinical application in the 1980s [317–320], the use of the RGEA has remained limited compared to more commonly employed conduits, such as the internal thoracic and radial arteries, primarily due to its anatomical position and certain practical limitations.

Anatomy. The RGEA constitutes one of the four arterial vessels responsible for supplying blood to the stomach [254]. It is the principal terminal branch of the gastroduodenal artery, which originates from the common hepatic artery, a branch of the coeliac trunk (Figure 3.10). In most patients, the RGEA is of adequate length and calibre. The average length of the RGEA with an internal diameter of $>3.0\text{mm}$ is $11.3 \pm 9.3\text{cm}$, with a diameter of $>2.5\text{mm}$ is $18.5 \pm 9.2\text{cm}$, and with a diameter of $>2.0\text{mm}$ is $25.0 \pm 7.5\text{cm}$ from the origin.

Physiological Considerations. The RGEA, a muscular artery, possesses fewer elastic fibres and more smooth muscle cells in its media layer than the internal thoracic artery (ITA). However, its internal elastic lamina exhibits minimal defects [321], rendering significant atherosclerotic involvement within this artery a rare occurrence [322].

Harvesting Techniques. Harvesting the RGEA requires a laparotomy or laparoscopy due to its intra-abdominal origin, which may increase operative time. For most patients, taking down the RGEA carries minimal risk of gastric ischaemia, making it a generally safe option with few contraindications [323]. According to Suma et al. [324], the intraoperative endoscopic laser Doppler study revealed no significant change in gastric mucosal blood flow before and after the division of the RGEA.

Long-Term Outcomes. Evidence on RGEA patency rates is variable. In one of the most extensive series available, Suma et al. reported cumulative patency rates of 97.1% at one month, 85.5% at five years, and 66.5% at ten years, attributing lower ten-year patency to symptomatic patients and limited graft samples at risk [325]. By contrast, Suzuki et al. documented improved long-term patency with a skeletonized RGEA graft to critically ($>90\%$) stenotic coronary targets, reporting an 8-year patency of 90.2% [326]. Furthermore, studies by Glineur et al. and Suzuki et al. observed significant long-term survival benefits when the RGEA replaced the great saphenous vein (GSV) to graft the RCA in patients also receiving bilateral internal thoracic artery grafts to the left coronary system [327, 328].

However, a network meta-analysis of RCTs suggested that the RGEA might have a higher risk of functional and complete occlusion compared to other conduits, achieving the highest probability of being the least favorable conduit (82%) in terms of patency [306]. While this finding underscores potential limitations, RGEA remains a viable choice in specific patient populations requiring alternative or additional arterial conduits.

Summary. The RGEA serves as a viable but secondary option in CABG, particularly when complete arterial revascularisation is pursued or conventional arterial conduits are unavailable. Despite its advantageous length, diameter, and resistance to atherosclerosis, the RGEA's intra-abdominal origin complicates harvesting, which

may deter its widespread use. While studies have demonstrated satisfactory mid-term patency rates and low gastric ischaemia risk, long-term outcomes remain inconsistent, with some data suggesting a higher risk of graft occlusion compared to more commonly used arterial conduits. As such, the RGEA remains an important but selective option in the surgeon's repertoire, suited to specific clinical contexts where alternative grafts are necessary.

3.7.5. Greater Saphenous Vein

The greater saphenous vein (GSV) has historically been a cornerstone in coronary artery bypass grafting (CABG) for over five decades, primarily due to two key advantages [150]. First, it offers ample length and versatility, enabling multivessel grafting to reach diverse peripheral targets without needing multiple harvesting sites. Second, venous graft preparation is straightforward, fast, and safe, with minimal complications. However, despite these practical advantages, the long-term patency of saphenous vein grafts remains a significant challenge, with failure often occurring at both early and late stages due to structural and functional limitations under arterial pressure [329].

Graft patency is a critical factor in the success of CABG procedures. Research has shown that the saphenous vein graft (SVG) is prone to intimal hyperplasia, characterised by smooth muscle cell proliferation within the vein wall, and accelerated atherosclerosis, both of which lead to higher failure rates compared to arterial conduits such as the internal thoracic artery (ITA) [330, 331]. However, advanced techniques, such as the "no-touch" harvesting method [332], which preserves the vein's surrounding tissue, and pharmacologic interventions targeting inflammation and platelet activity, have significantly improved SVG patency by minimising trauma to the vein and addressing endothelial damage [333].

Given the ongoing reliance on the GSV in contemporary CABG, optimising outcomes with this conduit requires careful patient selection, meticulous surgical technique, and integrative patient management, alongside continuous research into graft-preserving strategies and alternative conduit options to further improve patient outcomes.

Anatomy. The great saphenous vein (GSV) is the largest and most prominent superficial vein of the lower extremity [254]. It originates from the confluence of the dorsal vein of the hallux and the dorsal venous arch of the foot. Positioned within a fascial compartment between the muscular fascia and the dermis, the GSV begins its upward course just anterior to the medial malleolus. From here, it ascends along the medial aspect of the lower leg, crossing the tibia and coursing behind the medial condyle of the femur. It then follows a path along the medial-posterior aspect of the thigh before

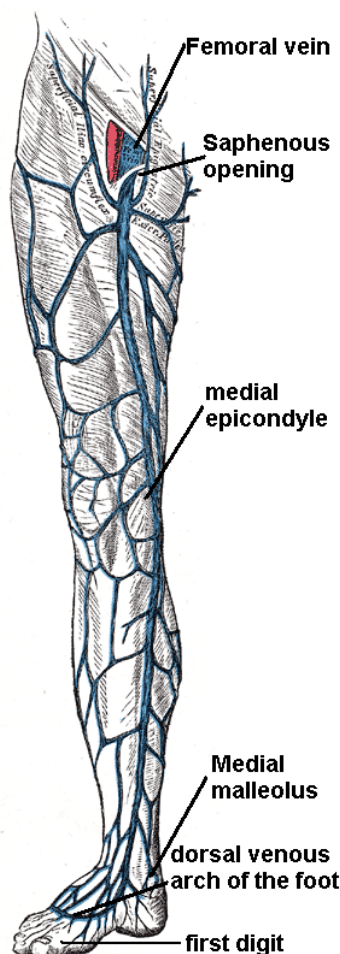


Figure 3.11.: Course of the greater saphenous vein (Source: Gray's Anatomy of the Human Body, Licence: Public Domain).

Table 3.11.: Phases of vein graft failure.

Phase	Time frame	Mechanism	Contributing factors
Acute	< 1 month	Thrombosis	Ischaemia-reperfusion injury Exposure to arterial pressure Endothelial dysfunction Exposure of ECM proteins Prothrombotic mediator release
Early	< 12 months	Intimal hyperplasia	Endothelial cell dysfunction Excessive ECM deposition SMCs recruitment
Late	> 12 months	Atherosclerosis	Atherosclerosis risk factors Endothelial cell dysfunction SMCs proliferation Inflammation

ECM, extracellular matrix; SMC, smooth muscle cell.

reaching the groin, where it traverses the saphenous opening in the *fascia lata* to ultimately drain into the femoral vein (Figure 3.11).

Physiological Considerations. The greater saphenous vein (GSV) remains the most commonly used conduit worldwide for non-left anterior descending (LAD) coronary territories, valued for its generous length, straightforward accessibility, and strategic versatility. However, despite its widespread use, 10-25% of these grafts occlude within the first year, with 40-50% failing by ten years after surgery [331, 334, 335]. These alarming rates of saphenous vein graft failure (VGF) significantly impact long-term outcomes of coronary artery bypass grafting (CABG), leading to increased recurrence of angina, higher incidences of myocardial infarction, greater need for repeat revascularisation, and ultimately compromising long-term survival.

VGF arises from three primary mechanisms: acute thrombosis, which can manifest within hours to days; neointimal hyperplasia, typically developing over weeks to months; and accelerated atherosclerosis, a longer-term issue associated with late-stage graft failure. These pathological events differ in their timing of onset and underlying contributing factors (Table 3.11) [336]. Nevertheless, they all compromise graft patency, offering suitable targets for ongoing surgical and medical management improvements to enhance CABG outcomes [337].

Harvesting Techniques. Greater saphenous vein (GSV) harvesting techniques significantly influence both short-term clinical outcomes and long-term patency. The conventional open vein harvesting (OVH) method involves a continuous incision along the leg, which enables full-length visualisation of the vein, allowing for careful segment selection with minimal damage [336]. However, OVH's drawbacks – namely higher wound complication rates,

postoperative pain, and reduced patient satisfaction – have spurred interest in alternative methods.

One such alternative is the no-touch technique, introduced by Domingos Souza in 1996, which preserves a cushion of surrounding tissue around the vein to minimise trauma and reduce spasm risks [332]. Souza emphasized avoiding high-pressure manual perfusion to protect the graft's intima. The efficacy of this technique was reinforced in a large randomised controlled trial by Tian et al., involving 2,655 patients across seven hospitals. Results showed significantly lower vein graft occlusion rates in the no-touch group at three months (2.8% vs. 4.8%, $p < 0.001$) and at 12 months (3.7% vs. 6.5%, $p < 0.001$) [338]. Despite these patency benefits, the no-touch technique was linked to a higher frequency of surgical wound interventions at three months (10.3% vs. 4.3%, $p < 0.001$).

Similarly, Dreifalldt et al. demonstrated the long-term durability of the no-touch SVG technique in a prospective trial comparing the 8-year patency of the no-touch SVG with the radial artery (RA) in patients with three-vessel disease [339]. Patency rates were comparable (86% for no-touch SVG vs. 79% for RA), with a higher coronary artery patency rate in the no-touch SVG group (91% vs. 81%, $p = 0.046$). These results highlight the no-touch SVG's potential as a versatile, durable conduit in CABG.

Conversely, the endoscopic vein harvesting (EVH) approach was developed to prioritise reduced patient morbidity by minimising incision size. Despite EVH's advantages in reducing leg wound complications, some studies suggest it may compromise graft patency. For example, a *post hoc* analysis of the PREVENT IV trial found higher rates of vein graft failure with EVH at 12 to 18 months compared to OVH (46.7% vs. 38.0%, $p < 0.001$) [340]. The ROOBY trial also noted lower SVG patency rates with EVH (74.5% vs. 85.2%, $p < 0.00001$) and a higher repeat revascularisation rate (6.7% vs. 3.4%, $p < 0.05$) [341]. Criticism arose over surgeon experience, with findings from Kiani et al. indicating that inexperienced harvesters were more likely to damage the vein during EVH, resulting in higher tissue injury markers and reduced graft function [342].

In response to this concern, the REGROUP trial limited participation to experienced EVH practitioners and found no significant differences in major adverse cardiac events between EVH and OVH after three years (13.9% vs. 15.5%, $p = 0.47$) [343]. A meta-analysis by Sastry et al., which included 267,525 patients, concluded that EVH did not significantly differ from OVH in mortality, myocardial infarction, repeat revascularisation, or vein graft patency, while showing reduced wound complications and pain with the endoscopic method [344].

In summary, each harvesting technique offers unique trade-offs. The no-touch technique shows promising results for long-term patency but poses higher risks of wound-related complications. Endoscopic harvesting, while associated with improved wound

healing and less pain, may require experienced practitioners to achieve optimal graft quality and avoid patency issues. Ultimately, selecting the appropriate harvesting method is crucial for optimising both short- and long-term outcomes in CABG.

3.7.6. Summary

The selection of conduits in coronary artery bypass grafting (CABG) aims to maximise long-term patency while considering each graft's specific strengths and limitations. Arterial conduits – particularly the LITA for the LAD artery– demonstrate superior patency and adaptability, making them the preferred choice for durable revascularisation. The RITA and RA serve as valuable alternatives, especially in multivessel grafting, while the RGEA offers additional flexibility in complex cases despite its lower patency. SVGs remain widely used due to their accessibility and length, though their patency rates fall short of arterial grafts; innovations like the no-touch technique aim to address these limitations. In summary, prioritising the LITA and other arterial conduits for critical targets, complemented by SVGs as necessary, represents the most effective strategy for optimising CABG outcomes.

3.8. Outcomes

Coronary artery bypass grafting (CABG) remains a cornerstone in the treatment of coronary artery disease (CAD), especially for patients with multivessel disease or significant left main coronary artery stenosis. Unlike other revascularisation methods, CABG offers a combination of symptom relief, reduced cardiac events, and extended survival, making it a durable solution for many CAD patients. Assessing CABG outcomes involves examining both clinical metrics and quality-of-life improvements, highlighting the surgery's impact on mortality, long-term health, and patient satisfaction. This section will focus on the primary short- and long-term outcomes of CABG, emphasising its value in enhancing patient longevity, functional capacity, and overall well-being.

3.8.1. Short-Term Clinical Outcomes

The immediate clinical outcomes of CABG are crucial in evaluating the procedure's success and guiding postoperative care. Within the first 30 days, two primary metrics – mortality and complication rates – provide insight into the short-term risks associated with the surgery.

30-Day Mortality. CABG has historically been associated with a significant 30-day postoperative mortality rate, establishing early mortality as a core measure of surgical care quality. This metric

is publicly reported as a policy measure to reduce mortality and standardise care among hospitals in the United States, the United Kingdom, and Canada [345–347]. Reporting these outcomes helps drive continuous improvements in surgical standards and patient management.

The risk profile of patients undergoing isolated CABG has changed substantially over recent decades. Today's CABG patients are often older, with a higher prevalence of comorbid conditions and more advanced coronary artery disease (CAD), including extensive atherosclerosis and compromised left ventricular function [16]. Despite these challenges, 30-day mortality following CABG has improved steadily, thanks to advancements in surgical techniques and perioperative care. In low-risk elective cases, current operative mortality rates are as low as 1-2%, a testament to these ongoing improvements [348, 349].

Perioperative Stroke. Perioperative stroke refers to a sudden onset of focal or global neurological impairment resulting from a disruption in the normal blood flow to the brain. This event persists for more than 24 hours, or less than 24 hours if available neuroimaging documents a new haemorrhage or infarct, or if the neurological deficit results in death. Additionally, it occurs from the time of surgery until a specified period postoperatively, typically within 30 days following the procedure.

Stroke is an infrequent yet dreaded complication of CABG, with a prevalence in contemporary series ranging between 0.5% and 1.5% [350, 351]. However, heterogeneity in outcome descriptions, specifically regarding stroke, remains a significant issue in cardiac surgery studies. Thus, researchers should use standardised definitions consistently across all studies [352].

The onset of symptoms helps differentiate perioperative strokes as either intraoperative (occurring during the procedure and diagnosed upon emergence from anaesthesia) or postoperative (occurring after emergence from anaesthesia). Most strokes occur within 24 hours of surgery, suggesting that intraoperative events are the primary cause of most neurological incidents [353, 354].

Intraoperative strokes most frequently occur due to thromboembolism (60%), multiple etiologies (10%) or cerebral hypoperfusion (9%), with haemorrhagic strokes (1%) being rare [355]. Embolic debris may dislodge from the aorta (during cannulation, cross-clamping, or partial clamping for proximal anastomoses) or heart (left ventricular thrombus, left atrial appendage thrombus, gaseous emboli) manipulation (Figure 3.12). Additionally, the heart-lung machine may generate gaseous or particulate emboli. Conversely, cerebral hypoperfusion results from intraoperative or immediate postoperative hypotension or diminished embolic material washout.

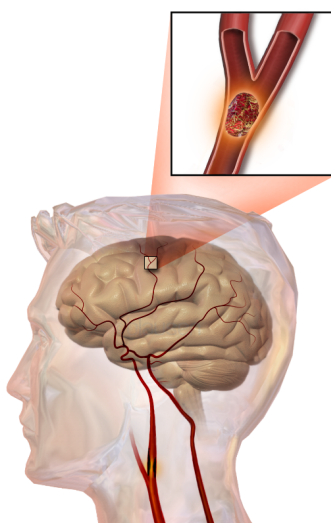


Figure 3.12.: Illustration of an embolic stroke, showing a thrombus lodged in a blood vessel (Source: WikiCommons, Licence: © CC BY 3.0).

The likely culprits during the early postoperative period are haemodynamic instability or postoperative atrial fibrillation. The latter is a common finding in about 30% of patients who undergo CABG and is a major determinant of postoperative stroke [356].

Cognitive Dysfunction. Cognitive dysfunction is the most prevalent manifestation of brain injury following cardiac surgery, significantly impacting patients' quality of life and daily functioning. Its incidence varies based on the definitions used, but it is estimated to affect 50-70% of patients within the first postoperative week, declining to 30-50% after six weeks and 20-40% at six months to one year [357].

Cognitive impairment in CABG patients is primarily linked to three factors associated with cardiopulmonary bypass (CPB): embolism, hypoperfusion, and the inflammatory response [358]. However, these mechanisms are not exclusive to CPB. Cognitive dysfunction has also been observed in patients undergoing off-pump CABG (OPCAB) and in non-surgical patients who undergo transcatheter interventions, suggesting a broader range of contributing factors [359, 360]. Clinically, cognitive dysfunction typically manifests as reduced memory, attention, psychomotor speed, and visuospatial abilities, which can interfere with daily activities and reduce patient independence.

Myocardial Injury. Several factors can contribute to procedural myocardial injury during a CABG procedure. These factors include the details of the myocardial protection technique, the extent of direct traumatic injury to the myocardium, and any potential ischaemic injury. Therefore, CABG unavoidably results in increases in cardiac troponin levels, which reflect procedural myocardial injury.

The diagnosis of myocardial infarction associated with CABG (type 5 myocardial infarction) relies on a cardiac troponin level over ten times the 99th percentile upper reference limit during the first 48 hours following surgery, occurring from a normal baseline value [361]. In addition, clinicians should associate these postprocedural increases in cardiac troponin levels with electrocardiographic, angiographic, or imaging evidence of new myocardial ischaemia or new loss of myocardial viability [362].

However, marked isolated elevation of cardiac troponin levels within the 48-hour postoperative window, even without other evidence of myocardial infarction, indicates prognostically significant procedural myocardial injury [363]. Furthermore, in the presence of significant procedural myocardial injury in patients with operative problems (e.g., difficulty weaning from CPB, technically challenging proximal anastomoses in a heavily calcified aorta, or perioperative evidence of myocardial ischaemia), the surgical team should conduct a thorough review of the procedure and consider additional diagnostic testing to assess the possibility of perioperative myocardial infarction.

Due to variable definitions across studies, reported rates of postoperative myocardial infarction vary, but a 2-4% incidence is generally accepted [17]. Approximately 3% of these cases result in significant haemodynamic instability from early graft failure. While PCI can manage most patients, a subset may require reoperation.

Postoperative Atrial Fibrillation. Postoperative atrial fibrillation (POAF) represents a significant clinical concern following CABG. Despite its often brief, paroxysmal and asymptomatic nature, POAF leads to short-term and long-term morbidity and mortality, prolonging hospital stays and soaring healthcare costs. Epidemiological data suggests that approximately 20-40% of patients undergoing CABG experience POAF, although the reported incidence varies significantly across studies [364]. These discrepancies are likely due to variations in definitions, monitoring practices, and screening protocols used in different clinical settings.

The pathophysiology of POAF is multifactorial, involving a combination of autonomic dysregulation, inflammatory responses, and structural atrial remodelling that can precipitate atrial electrical instability [365]. Most of these mechanisms are typically transient phenomena specific to the postoperative state. Conversely, older age, male gender, a history of atrial fibrillation, congestive heart failure, hypertension, obesity, and chronic obstructive pulmonary disease are all notable risk factors in the onset of this arrhythmia [366]. It is crucial to comprehend the fundamental pathophysiological mechanisms and the interplay of these risk factors to develop practical preventive and therapeutic approaches.

Management of POAF requires a comprehensive approach that addresses immediate and long-term outcomes. The most common interventions to prevent POAF are β -blocker use postoperatively (74%), magnesium (64.5%), and maintaining a serum potassium level over 4.5 mmol/L (84%) [367]. While solid evidence supports β -blocker use, the beneficial effects of magnesium are more disputable [368]. Additional pharmacological options such as amiodarone and sotalol and nonpharmacological alternatives like posterior pericardiotomy and atrial pacing are viable recourses.

Therapeutic interventions may encompass rate control, rhythm control, and anticoagulation to reduce the risk of thromboembolic events. However, the evidence supporting these approaches is ambiguous regarding their efficacy [369, 370].

Surgical Wound Infection. Surgical wound infections includes superficial surgical wound infection (SSWI) and deep surgical wound infection (DSWI). The available epidemiologic data indicates incidence rates of 0.5-8% and <1%, respectively [351, 371, 372]. In SSWI, the infection occurs at the incision site within 30 days after surgery and involves the skin, subcutaneous tissue, or muscle above the fascial layer. This infection may present as purulent discharge from the incision or drain above the fascial layer, isolation of an organism from the culture of fluid from a primarily closed

wound, deliberate opening of the wound by the surgeon (unless the wound is culture-negative), or establishment of the diagnosis of infection by the surgeon. In DSWI, the infection involves tissues or spaces at or beneath the fascial layer and occurs within 30 days after surgery. Its manifestations include purulent discharge from a drain placed beneath the fascial layer, spontaneous wound dehiscence or wound deliberately opened in patients with systemic inflammatory signs (unless the wound is culture-negative), an abscess or other evidence of infection seen on radiologic studies, surgical exploration, or histopathologic examination [373].

The risk factors for surgical wound complications following CABG underscore the importance of thorough preoperative evaluation and postoperative monitoring. Research has identified several independent predictors of these complications, such as older age, obesity, diabetes mellitus, smoking, chronic obstructive pulmonary disease, peripheral vascular disease, NYHA class $\geq$ III, bilateral internal thoracic artery grafting, and prolonged mechanical ventilation support [374].

Surgeons should support preventive measures to avoid surgical wound complications [375]. These measures include obtaining nasal swabs or polymerase chain reaction (PCR) testing for *Staphylococcus aureus*. If these are unavailable, intranasal mupirocin should be administered within 24 hours of surgery and continued for five days to eliminate staphylococcal colonisation. Patients should use a chlorhexidine solution to shower the night before surgery. Moreover, administering a cephalosporin antibiotic intravenously within 60 minutes of surgery, redosing for procedures of more than four hours, and prolonging the prophylaxis for not more than 48 h is effective against staphylococcal species, the most common organisms found in DSWI. Focusing on optimising patients' nutritional status and implementing aggressive glycemic control using insulin are also effective strategies.

All healthcare professionals should recognise that these complications impact the postoperative quality of life but also lead to increased overall mortality, in-hospital mortality, medium-term mortality, and major adverse cardiovascular events (MACE) [376].

Reexploration for Bleeding. Severe postoperative bleeding is a common occurrence after coronary artery bypass grafting (CABG). As a result, reexploration for bleeding is a well-known complication of the procedure, with reported incidence rates of 2-6% [377].

Research in the field indicates that older age, smaller body surface area, longer cardiopulmonary bypass times, a greater number of distal anastomoses, dialysis-dependent renal failure, and the use of the internal mammary artery are all identified as risk factors for reexploration for bleeding [378, 379]. The most frequent locations for bleeding identified during reexploration were the conduit or the anastomosis (57.5%), the sternum or internal mammary artery bed

(31.5%), the mediastinum (8.2%), and cannulation and cardiectomy sites (2.8%) [380].

Reexploration for bleeding seriously increases perioperative mortality and morbidity, including new-onset postoperative atrial fibrillation (POAF), acute kidney injury (AKI), longer mechanical ventilation, intensive care unit (ICU) readmission, and wound infection [381]. Furthermore, delaying the reexploration worsens this scenario significantly.

Functional Recovery and Symptom Relief. CABG generally leads to significant improvements in symptoms and physical function, often within the first months after surgery. Most patients experience relief from angina and increased exercise tolerance, reflecting the success of the revascularisation in restoring blood flow to the myocardium. Studies report that up to 95% of patients achieve symptom relief [382], with improvements in physical activity, reduction in dyspnoea, and enhanced overall vitality [383].

Hospital Length of Stay and Readmissions. The typical length of stay after CABG ranges from 5 to 7 days, depending on patient recovery and the occurrence of complications.

Readmission rates are an essential metric of healthcare quality. High readmission rates suggest inadequate quality of care during the initial hospital stay, including inadequate postoperative monitoring, failure to manage complications, or unsatisfactory discharge planning [16]. Most importantly, they undermine patients' satisfaction and trust in the healthcare system.

The 30-day readmission rate after CABG exceeds 12%, with common causes being infection, sepsis, cardiac arrhythmias, congestive heart failure, respiratory complications, and pleural effusion [384]. The preponderance of noncardiac causes for readmission indicates that efforts to lower readmission rates should prioritise comprehensive postoperative care, specifically managing infections and other complications.

3.8.2. Long-Term Clinical Outcomes

The long-term outcomes of surgical myocardial revascularisation hinge on a complex interplay of patient- and procedure-related factors. Critical patient-related factors include demographic data (such as age and sex), the presence and severity of associated comorbidities, the anatomic distribution and severity of coronary artery atherosclerosis, and the physiologic impact of ischaemia on ventricular function at the time of operation. Conversely, procedure-related factors comprise the completeness of revascularisation, the surgical technique strategies, the selection of bypass conduits, and the occurrence of operative complications.

The interaction of these factors plays a crucial role in the effectiveness of coronary artery bypass grafting (CABG) in meeting

its primary objectives: prolonging survival, providing symptom relief, and enhancing quality of life (QOL). These outcomes hold significant importance, as CABG aims not only to deliver immediate revascularisation benefits but also to promote enduring improvements in both cardiac and overall functional status.

Survival and Freedom from Major Adverse Cardiac Events. Classical studies have established 95%, 80%, and 50% risk-unadjusted survival rates at one, ten, and twenty years, respectively [385]. In contrast, contemporary research has demonstrated survival rates of 96.5% [386], 88.6% [387], and 76% [185] for one year, five years, and ten years, respectively.

Major adverse cardiac event (MACEs) rates are another critical measure of CABG success. They include incident myocardial infarction and the need for repeat revascularisation. Incident myocardial infarction does impact long-term survival after CABG. The unadjusted risk for the first infarct after surgery is 3.5% at one year, 14% at ten years, and 27% at fifteen years [388]. Contemporary research reports slightly reduced risk rates of 3.3% and 3.8% at one and five years after the operation, respectively [386, 387].

Although often considered a clinical endpoint of lesser importance compared with death, stroke, or myocardial infarction (MI), the need for repeat revascularisation significantly impacts patients' quality of life (QoL) and increases their risk of new hospitalisations and procedural complications [389]. Moreover, the performance of any such procedure is an independent predictor of a subsequent increase in long-term all-cause and cardiovascular mortality [390].

Symptom and Functional Stability Over Time. CABG generally affords significant angina relief and improves physical performance and exercise tolerance. However, the recurrence of angina after the operation is inexorable. One year after surgery, 5% of patients will experience angina, in contrast to 20%, 40%, and 80% at five, ten, and twenty years, respectively [382]. Despite its relentless nature, recurring angina has minimal impact on survival and does not serve as a reliable predictor of an impending myocardial infarction.

Quality of Life and Patient Satisfaction. Improvement in quality of life (QoL) is a central goal of CABG, as the procedure seeks to alleviate the symptoms and functional limitations caused by coronary artery disease (CAD). QoL metrics, often measured through tools such as the Seattle Angina Questionnaire (SAQ) and the SF-36 Health Survey, typically show substantial gains in physical functioning, social participation, and emotional well-being [391–394]. Patients frequently report enhanced quality of life and satisfaction with CABG outcomes, especially when symptom relief is maintained, functional limitations are minimised, and repeat revascularisation procedures are not necessary [383].

3.8.3. Summary

The long-term outcomes of coronary artery bypass grafting (CABG) highlight its crucial role in managing complex coronary artery disease (CAD). By prolonging survival, reducing major adverse cardiac events (MACEs), alleviating symptoms, and enhancing quality of life (QoL), CABG demonstrates its enduring benefits across diverse patient populations. These outcomes are influenced by a variety of patient- and procedure-related factors, including comorbidities, conduit selection, and surgical techniques. Understanding these factors is essential for optimising both immediate and long-term results.

Despite the substantial insights provided by clinical studies, accurately tracking and analysing CABG outcomes over time requires the use of robust data sources. Administrative data, encompassing large-scale, real-world patient records, offers a valuable resource for evaluating long-term survival, complications, and healthcare utilisation at a population level. The following chapter explores how administrative data can enhance the understanding of CABG outcomes, support quality improvement initiatives, and inform decision-making in contemporary cardiac surgery.

Administrative Data in Healthcare Research

4.

While traditional clinical trials offer valuable insights, their strict inclusion criteria, limited sample sizes, and resource-intensive nature often restrict their generalisability and scope. In contrast, administrative data – large-scale datasets collected from routine healthcare operations, such as hospital admissions, discharge records, and billing information – provides a powerful resource for supplementing clinical research. These datasets offer real-world evidence, enabling the analysis of healthcare utilisation patterns, patient outcomes, and long-term survival trends across diverse populations.

As healthcare systems increasingly integrate digital records, the role of administrative data has expanded, providing new opportunities for risk stratification, predictive modelling, and healthcare quality improvement. In the broader ischaemic heart disease (IHD) and the specific coronary artery bypass grafting (CABG) contexts, leveraging administrative data to characterise clinical profiles, identify trends in procedural success, monitor postoperative complications, and assess the effectiveness of different treatment strategies is particularly appealing.

This chapter explores the nature of administrative data, focusing on its sources, strengths, and limitations. Additionally, it examines methods for data linkage, highlighting how integrating multiple data sources can enrich datasets. Finally, it reviews practical applications found in contemporary literature, demonstrating the transformative potential of administrative data in advancing healthcare research.

4.1. Definition and Sources of Administrative Data

Administrative data refers to the extensive, routinely collected information generated during healthcare delivery for administrative, billing, and regulatory purposes [20]. Unlike clinical data, which focuses on direct patient care, administrative data records operational and managerial aspects of healthcare. Increasingly, this data has been repurposed for research, policy-making, and quality improvement initiatives, offering insights into healthcare utilisation, patient outcomes, and system performance. By leveraging its extensive coverage and longitudinal nature, researchers can analyse healthcare trends and outcomes across diverse populations in a cost-effective manner.

Multiple sources provide healthcare data at a national or institutional level, enabling comprehensive analysis of patient outcomes,

resource allocation, and healthcare trends on a large scale [21]. Some examples include:

1. *National health systems*. Numerous countries maintain extensive national databases that compile a wide range of health-related data, including patient demographics, comorbidities, treatment records, and health outcomes. These databases typically integrate information from hospitals, outpatient clinics, and primary care facilities.
2. *Health insurance claims data*. Health insurance providers, both public and private, compile claims data that include information about patient visits, treatments, prescriptions, and costs. This data can be invaluable for understanding healthcare utilisation and expenditures across various settings.
3. *Mortality registries*. Registries that record causes of death and demographic information are crucial for understanding public health trends and conducting epidemiological research. Government health departments or statistical agencies typically maintain these registries.
4. *Public health surveillance systems*. These systems collect data related to disease outbreaks, health behaviours, and risk factors at the population level. Government health agencies usually operate them and are essential for monitoring public health issues.
5. *Primary care databases*. Many countries have databases that aggregate data from primary care providers, capturing routine information on patient visits, diagnoses, treatments, and outcomes. Researchers can use this information to study chronic disease management and preventive care.
6. *Emergency department data*. Data collected from emergency departments (ED) provide insights into acute healthcare needs and patient demographics. This data often includes the reasons for visits, treatment received, and outcomes.
7. *National health surveys*. Countries frequently conduct national health surveys to gather data on health behaviours, service utilisation, and health status among their populations. These surveys contribute to understanding health trends and inform policy decisions.
8. *Pharmacy databases*. Pharmacist databases can provide insights into medication usage patterns, adherence, and the impact of pharmaceuticals on public health.

Understanding these data sources is crucial for leveraging administrative data in healthcare research. Each source provides a unique set of variables, such as patient demographics, clinical diagnoses, procedures, and healthcare costs, which form the foundation for analysing healthcare utilisation, outcomes, and quality. The next section delves into these key variables, highlighting their significance and role in administrative data-based research.

4.2. Key Variables in Administrative Data

Administrative data provides a wealth of variables critical for healthcare research, particularly in the context of coronary artery bypass grafting (CABG). These datasets predominantly capture information related to the provision of services within the public sector [18]. Key variables include demographic information, diagnostic codes, procedural codes, complication codes, healthcare utilisation metrics, and cost-related data. Together, these variables offer insights into patient populations, health conditions, and treatment patterns, enabling comprehensive analyses for clinical profiling, risk adjustment, and outcome monitoring.

1. *Demographics*. Patient-identifying information:
 - ▶ Date of birth
 - ▶ Sex
 - ▶ Area of residence
 - ▶ Individual identifying number
2. *Comorbidities*. Detailed coding of the patients' baseline characteristics (i.e., risk factors and secondary diagnoses that affect CABG outcomes), recorded using standardised classification systems like the International Classification of Diseases:
 - ▶ Hypertension
 - ▶ Diabetes mellitus
 - ▶ Hyperlipidaemia
 - ▶ Obesity
 - ▶ Smoking status
 - ▶ Previous stroke
 - ▶ Congestive heart failure
 - ▶ Peripheral vascular disease
 - ▶ Chronic obstructive pulmonary disease
 - ▶ Chronic kidney disease
 - ▶ Liver disease
 - ▶ Anaemia
 - ▶ Coagulation disorders
 - ▶ Cancer
3. *Procedures and interventions*. Detailed coding of the CABG procedure, recorded using standardised classification systems like the International Classification of Diseases (ICD):
 - ▶ Heart-lung machine used
 - ▶ Bypass conduits selected
 - ▶ Number of anastomoses performed
4. *Complication*. Detailed coding of postoperative complications, recorded using standardised classification systems like the International Classification of Diseases (ICD):
 - ▶ Stroke
 - ▶ Intra-aortic balloon counterpulsation
 - ▶ Atrial fibrillation

- ▶ Prolonged mechanical ventilation
 - ▶ Haemodialysis
 - ▶ Reexploration for bleeding
 - ▶ Surgical site wound complication
5. *Utilisation data*. Refers to information on the frequency, type, amount, and results of healthcare services used by patients:
 - ▶ Date of admission
 - ▶ Date of surgery
 - ▶ Date of discharge
 - ▶ Length of hospital stay
 - ▶ Intensive care use
 - ▶ Postoperative care
 - ▶ Discharge disposition
 6. *Cost data*. Direct and indirect costs associated with the CABG procedure, including:
 - ▶ Medications
 - ▶ Length of stay
 - ▶ Resource utilisation

The comprehensive capture of these variables highlights the potential of administrative data to support a wide range of healthcare research objectives. By offering large-scale, real-world insights, administrative datasets enable robust analyses that inform clinical practices, guide policy decisions, and advance quality improvement initiatives. The next section explores the specific advantages of using administrative data in healthcare research.

4.3. Advantages of Using Administrative Data in Healthcare Research

Administrative data has become an invaluable resource for healthcare research, offering numerous advantages that make it an essential tool for studying healthcare trends, outcomes, and disparities [19]. Collected during routine healthcare delivery processes, such as hospital admissions, billing, and insurance claims, administrative data provides large, representative samples that support diverse research objectives. Its cost-effectiveness, capacity for longitudinal tracking, and potential for linkage with other datasets enhance its utility. Moreover, administrative data reflects real-world clinical practices, improving the generalisability of findings. This section explores these key advantages and their implications for advancing healthcare research.

1. *Large sample size and population coverage*. Administrative data sets often include entire populations or significant subsets, yielding extensive sample sizes suitable for rigorous statistical analysis. This extensive scale is suitable for studying rare conditions, treatments, or health outcomes, which may

- not be adequately captured in smaller clinical datasets [19]. The broad coverage also ensures that the data highly represents diverse populations, allowing researchers to examine contrasts and outcomes across distinct demographic groups.
2. *Cost-effectiveness.* Since administrative data is already collected during routine healthcare managerial operations, it is more cost-effective than gathering primary data through surveys, prospectively maintained datasets or clinical trials [395]. Researchers can leverage this preexisting data, minimising the resources required for data collection.
 3. *Longitudinal tracking.* Administrative data typically contains patient records spanning multiple years, enabling longitudinal research. This characteristic allows for tracking health outcomes, disease progression, and healthcare utilization over time. Longitudinal studies are crucial for understanding chronic conditions, treatments' long-term effects, and healthcare use patterns.
 4. *Real-world data and generalisability.* Randomised clinical trials (RCTs) cannot provide all the necessary details about all patient management strategies [396]. On the other hand, treatments that produce excellent outcomes in a research setting (efficacy) may not be beneficial (effectiveness) when applied to a different clinical context. Administrative data enables effectiveness studies that yield outcome findings based on representative samples from all hospitals and physicians. The data reflects real-world clinical practice and healthcare delivery, enhancing research findings' external validity and generalisability. It captures information from various healthcare settings, including hospitals, clinics, and outpatient facilities, making it ideal for studies that apply findings to broader, real-world populations [397].
 5. *Data linkage potential.* The potential for data linkage is a crucial feature of administrative datasets [398]. These datasets can be effectively linked with electronic health records (EHRs), disease registries, or survey data. This process involves matching records from different sources based on common identifiers, such as patient ID or date of birth, to create a more comprehensive dataset. The linked data enriches the dataset with clinical details, patient-reported outcomes, and sociodemographic information, facilitating more in-depth analyses and insights.
 6. *Recall bias.* Patient reports of drug exposure, hospitalisations, physician visits, and medical conditions are subject to recall biases. Most evidence suggests that hospitalisations and physician visits are well-recorded in healthcare managerial systems [19]. Accurate recording of past health events is critical in developing lifetime estimates of exposure or when the timing of an event is essential. Administrative data have many desirable attributes that reduce recall bias.
 7. *Unobtrusive nature.* A great advantage of administrative data

is that it permits relatively unobtrusive research [397]. Since studies using this data are conducted through statistical analyses, patient consent is not required. This approach eliminates biases that may arise from individuals refusing to participate or from individuals involved in the study having prior knowledge of it.

8. *Efficient for Health Policy Evaluation*. Administrative data is ideal for evaluating health policy interventions or system-level changes in healthcare. Researchers can study the impact of new policies on healthcare utilisation, patient outcomes, and cost-effectiveness over time with minimal delay, providing evidence to guide future decision-making.

The numerous strengths of administrative data have established it as a foundational resource for healthcare research. By leveraging its large-scale, cost-effective, and real-world insights, researchers can address a broad spectrum of questions, from policy evaluations to clinical outcomes. These strengths, combined with the ability to integrate other data sources, highlight the expanding potential of administrative datasets. The following section explores strategies for further enriching administrative datasets to enhance their research value.

4.4. Expanding Administrative Databases

The current thesis revolves around the central role of data linkage in expanding administrative databases. This process involves integrating information from multiple records about the same individual, substantially enhancing individual data's breadth and quality [22]. Such ability is essential because, no matter how much data is recorded in any database, specific items desired for a given study may not be available. Furthermore, linkage can help clinicians become more comfortable using administrative data since an expanded amount of information can provide many details they associate with the practice of medicine [397]. For instance, the integration of electronic health records in a national cohort of over 54 million individuals in the United Kingdom exemplifies the growing use of such approaches in healthcare research [399].

Linking records is straightforward when datasets include unique identifiers such as health card or social insurance numbers [400]. This method, known as deterministic record linkage, reliably connects records corresponding to the same individual. However, not all data contain such precise identifiers. In these cases, probabilistic record linkage is employed, using "soft" identifiers such as name, date of birth, gender, and postal code to match records with a degree of confidence.

Researchers may operate various relevant applications of record linkage as described below.

1. *Vital statistics*. Linkage of administrative datasets with vital statistics files allows for verifying deaths and providing cause-of-death information. These methods underlie several longitudinal studies.
2. *Registries*. Linkage of administrative datasets with independently collected data from clinical registries to provide higher-quality information and validity checks.
3. *Anaesthesiology applications*. Linking administrative datasets with anaesthesiology applications produces a rich data set on patients' preoperative status and operative outcomes. These data can help assess the efficacy of several surgical procedures by providing covariates to increase the credibility of claims-based analyses.
4. *Laboratory test results*. Administrative databases typically do not contain laboratory test results. Integrating these datasets with laboratory applications to include such information can address this issue.
5. *Imaging study results*. Administrative databases typically do not contain imaging study results. Integrating these datasets with imaging applications to include such information can address this issue.
6. *Prescriptions*. The absence of medical treatment details, including specific drugs used, in administrative datasets poses a challenge for comparing different medical options for treating various conditions. Integrating these datasets with pharmacy applications can address this issue.
7. *Surveys*. Combining survey data with claims data enables a comprehensive analysis of the relationships between functional status, self-reported health, and surgical results.

By enabling the integration of diverse data sources, linkage enhances the utility of administrative datasets, allowing researchers to address complex questions about healthcare delivery, outcomes, and disparities. Despite its advantages, this process is not without challenges. The next section explores the limitations of administrative data and their implications for healthcare research.

4.5. Disadvantages of Using Administrative Data in Healthcare Research

While administrative data is a vital resource for informing healthcare policy and decision-making, it is essential to recognize its limitations when used for research purposes. Originally designed for administrative functions like service delivery and regulatory compliance, these datasets are not inherently tailored for clinical research or statistical analysis. This misalignment can pose several challenges for healthcare studies, particularly for clinical profiling in CABG [18].

1. *Incorrect number of cases for analysis.* A change of perspective occurs when dealing with administrative data instead of standard observational studies. The researcher has an available dataset but must find the patients of interest [401]. In many cases, patient selection relies on specific disease codes. Several countries have adopted the ICD9 and ICD10 disease classification systems for coding diseases treated during a hospital stay in discharge abstracts. By leveraging these codes and their placement in the discharge abstract, which differentiates between primary and secondary diagnoses, researchers can establish extraction criteria for selecting patients of interest. When using these codes to identify patients, the correlation between the codes and the documented diseases in the health records must be considered. Furthermore, it is crucial to determine the optimal combination of codes for patient selection in specific studies. Numerous studies have explored the most effective algorithms for identifying patients with a particular disease, comparing results obtained from code sets or data sources such as hospital discharge abstracts or outpatient care data sets. However, some authors argue that errors in diagnosis or procedure coding and software algorithms cannot reliably identify isolated CABG cases [402].
2. *Restricted study populations.* Depending on the country, the population represented in these administrative data sets may be limited. For instance, in the United States, the Medicare system includes individuals 65 or older. Consequently, studies based on these data do not necessarily represent overall program quality and may bias the profiling results. However, other countries, such as Denmark, Italy, Portugal, and Sweden, accomplish total resident population representation.
3. *Misalignment of data sources with intended use.* Administrative databases were initially created to handle claims submission and benefits coordination, with coding practices and software algorithms tailored for reimbursement purposes rather than clinical outcomes profiling. The data captured by administrative data systems may not be the most relevant to health outcome studies [403]. Although the data system may document certain events, such as laboratory tests, radiologic studies, or specific examinations, the results of these tests are usually not included in an administrative data system. Consequently, before initiating a study using an administrative dataset, it is crucial to ascertain whether the events of interest and central outcomes are accessible in the dataset.
4. *Coding accuracy and completeness.* Administrative data coding accuracy may be problematic due to imprecise, ambiguous or vague definitions [404]. In addition, some comorbidities or complications are highly dependent on physician documentation and coder interpretation, and healthcare units have difficulty reporting them consistently. On the other

hand, completeness issues may also be challenging. While accurate diagnoses are a critical clinical skill, recording them all together is not a priority for most physicians. Furthermore, even those who underline proper documentation as an integral part of sound clinical reasoning are unlikely to be exhaustive about additional diagnoses since it may not be clear how they will affect patient care [405].

5. *Absence of critical clinical variables.* A relatively small number of clinical variables provide much of the prognostic information in patients undergoing CABG. Although some of these variables are present in administrative datasets (e.g., age, gender, previous cardiac surgery, and admission status), others are not (e.g., left ventricular function, percentage stenosis of the left main coronary artery, and number of major coronary arteries with over 70% stenoses) [406]. Therefore, adding a few such clinical variables to administrative models may substantially improve their performance [407].
6. *Complications and comorbidities.* When using administrative data, accurately translating ICD-9-CM codes into clinically relevant comorbidities or complications, consistently capturing all comorbidities, and differentiating them from complications is challenging. Generally, undercoding of comorbidities in administrative databases appears to be a more prevalent issue than overcoding, despite advanced coding algorithms [408]. Failing to differentiate complications from comorbidities may exaggerate the performance of risk models based on administrative data. This results from including predictors in the risk model, such as late hospitalisation and preterminal events, and is thus highly predictive of subsequent mortality [18]. Using an indicator for the condition present at admission or employing date stamping of secondary diagnoses can improve the distinction between complications and comorbidities in administrative databases.

While these limitations underscore the challenges of using administrative data for healthcare research, they also highlight areas for improvement through enhanced data collection, linkage, and validation techniques. The following section explores strategies for leveraging administrative data to optimise clinical profiling in CABG and address some of these shortcomings.

4.6. Leveraging Administrative Data for Clinical Profiling in CABG

Administrative data plays a pivotal role in clinical profiling for coronary artery bypass grafting (CABG). It supports a range of studies, from evaluating outcomes and healthcare utilisation to developing risk models and assessing cost-effectiveness. By leveraging demographic, clinical, and procedural data, researchers can

optimise resource allocation, refine clinical practices, and address disparities in care. This section explores key methodologies and their applications in contemporary academic literature.

4.6.1. Outcomes and Performance Measures

Outcomes and performance measures studies in CABG focus on evaluating critical metrics such as mortality rates, hospital readmissions, and long-term survival. These studies aim to assess the effectiveness of surgical procedures, monitor patient recovery, and gauge the quality of care provided by healthcare institutions. By analysing performance indicators, these studies promote the identification of opportunities for clinical improvement and the establishment of benchmarks for successful CABG outcomes.

For instance, Hannan et al. retrospectively analysed 30-day readmissions for 33,936 New York State patients who underwent CABG between 2005 and 2007 [409]. The study sought to document the primary causes of readmission (principal diagnoses) and the significant independent readmission predictors using administrative and clinical databases. Furthermore, the researchers explored the hospital-level relationship between risk-adjusted mortality rate and risk-adjusted readmission rate to determine the value of readmission rate as a complementary quality measure.

The most prevalent causes of readmission included postoperative infection (16.9%), heart failure (12.8%), and "other complications of surgical and medical care" (9.8%). Factors such as older age, female gender, African-American race, higher body mass index, multiple comorbidities, postoperative issues like renal failure and unplanned cardiac reoperation, being on Medicare or Medicaid, discharge to a skilled nursing facility, saphenous vein grafts, and longer hospital stays were all linked to higher readmission rates. There was a correlation of 0.32 ($p = 0.047$) between hospital risk-adjusted 30-day readmission rate and risk-adjusted in-hospital/30-day mortality rate. The readmission rates varied across hospitals, ranging from 8.3% to 21.1%.

The authors concluded that despite decreasing short-term mortality rates, the 30-day readmission rate for CABG surgery remained high, suggesting a need for vigilant monitoring of patients with multiple risk factors for readmission. Furthermore, they considered hospital readmission rates an independent quality measure despite not correlating strongly with mortality rates.

While outcome studies provide essential benchmarks, comparative effectiveness studies delve deeper into evaluating the relative benefits of alternative treatment approaches.

4.6.2. Comparative Effectiveness

Comparative effectiveness studies evaluate and compare treatment outcomes to identify the most effective approach for specific patient populations. In the context of CABG, these studies may assess different surgical techniques (e.g., off-pump versus on-pump procedures) or compare alternative therapies such as medical management versus surgery. By leveraging clinical and administrative data, these studies aim to inform clinical decision-making by identifying the most effective treatment options based on real-world evidence.

Chikwe et al. linked mandatory clinical and administrative registries from the New Jersey Department of Health to identify patients who underwent CABG between 2005 and 2011 by surgeons who had performed a minimum of 100 off-pump or on-pump CABG operations [221]. The authors conducted a comparative analysis of survival rates, incidences of stroke, myocardial infarction, repeat revascularisations, and new dialysis requirements across the different patient groups.

Among 42,570 CABG patients, 6,950 underwent off-pump CABG and 15,295 underwent on-pump CABG met the study criteria. After a median follow-up of 6.8 years, off-pump CABG was associated with higher mortality (33.4% vs 29.6% at ten years; hazard ratio [HR]: 1.11; 95% confidence interval [CI]: 1.04 to 1.18; $p = 0.002$) compared with on-pump CABG. Off-pump CABG was associated with a higher risk of incomplete revascularisation (15.7% vs 8.8%; $p < 0.001$), which was a predictor of late mortality (HR: 1.10; 95% CI: 1.03 to 1.17; $p = 0.006$); and higher rates of repeat revascularisation (15.4% vs 14.0% at ten years; HR: 1.17; 95% CI: 1.01 to 1.37; $p = 0.048$). However, there were no significant differences in the rate of stroke, myocardial infarction, or new dialysis between the two groups.

The authors concluded that off-pump was associated with increased incomplete revascularisation, repeat revascularisation, and mortality at ten years compared with on-pump CABG. These findings suggest that on-pump CABG may be the appropriate choice for most patients undergoing surgical revascularisation.

In addition to comparing treatment approaches, risk prediction models harness administrative data to personalise care and optimise surgical decision-making.

4.6.3. Risk Prediction Models

Risk prediction models use statistical algorithms to estimate the likelihood of specific patient outcomes, such as mortality or complications, based on their clinical and demographic characteristics. In CABG, these models analyse factors like age, comorbidities,

and procedural details to predict risks, enabling clinicians to personalise care, assess patient suitability for surgery, and improve decision-making to minimise adverse outcomes.

Aktuerk et al. developed the Hospital Episode Statistics (HES) risk prediction model using administrative data linked to the national mortality statistics register of patients undergoing CABG (35,115), valve surgery (18,353), and combined CABG and valve surgery (8392) from 2008 to 2011 in England [410]. The authors constructed specific models to predict mortality within one year after discharge, comparing their performance with EuroSCORE models.

The discrimination of the HES model demonstrated good performance for early and up to one year following surgery (C-statistic: CABG 81.6%, 78.4%; isolated valve 78.6%, 77.8%; CABG and valve 76.4%, 72.0%), respectively. Calibration of the HES model has demonstrated a slight difference (CABG 0.15%; isolated valve 0.39%; CABG and valve 0.63%) between observed and expected mortality rates and delivered a reasonable estimate of risk. The discrimination performance of the HES model for in-hospital deaths was consistent for both CABG and combined CABG and valve surgery patients, and it outperformed the EuroSCORE models for valve patients. Additionally, the C-statistics of the HES model were numerically higher than those of the EuroSCORE models for extended periods.

The authors emphasise the national administrative dataset's ability to produce an accurate, stable, and clinically useful early and one-year mortality prediction after cardiac surgery.

Complementing risk prediction, cost-effectiveness studies assess the economic implications of CABG interventions, guiding resource allocation and policy-making.

4.6.4. Cost-Effectiveness and Resource Utilisation

Cost-effectiveness and resource utilisation studies evaluate the economic implications of healthcare interventions by comparing their costs to the health outcomes they generate. In the context of coronary artery bypass grafting (CABG), these studies analyse the cost efficiency of various surgical techniques and treatment methods, considering factors such as hospital stays, postoperative complications, and long-term care requirements. They are crucial in identifying the most cost-effective strategies, informing resource allocation and policy-making to enhance overall healthcare efficiency and patient care quality.

Ho et al. examined whether higher procedure volumes for CABG or percutaneous coronary interventions (PCI) were associated with lower costs per patient and, if so, estimated the financial savings from regionalising cardiac procedures [411].

The authors performed cost regressions with hospital-specific dummy variables measured within-hospital cost reductions associated with increasing hospital volume. They used these regression estimates to predict the change in total costs from moving patients from low-volume hospitals to higher-volume facilities.

According to the study, a 10% increase in PCI procedure volume resulted in a 0.7% reduction in costs per patient. In comparison, a 10% increase in CABG procedure volume led to a 2.8% decrease in costs per patient. However, despite these cost reductions, the overall potential savings from centralising cardiac procedures were relatively modest, at 1.1% for PCI and 3.5% for CABG.

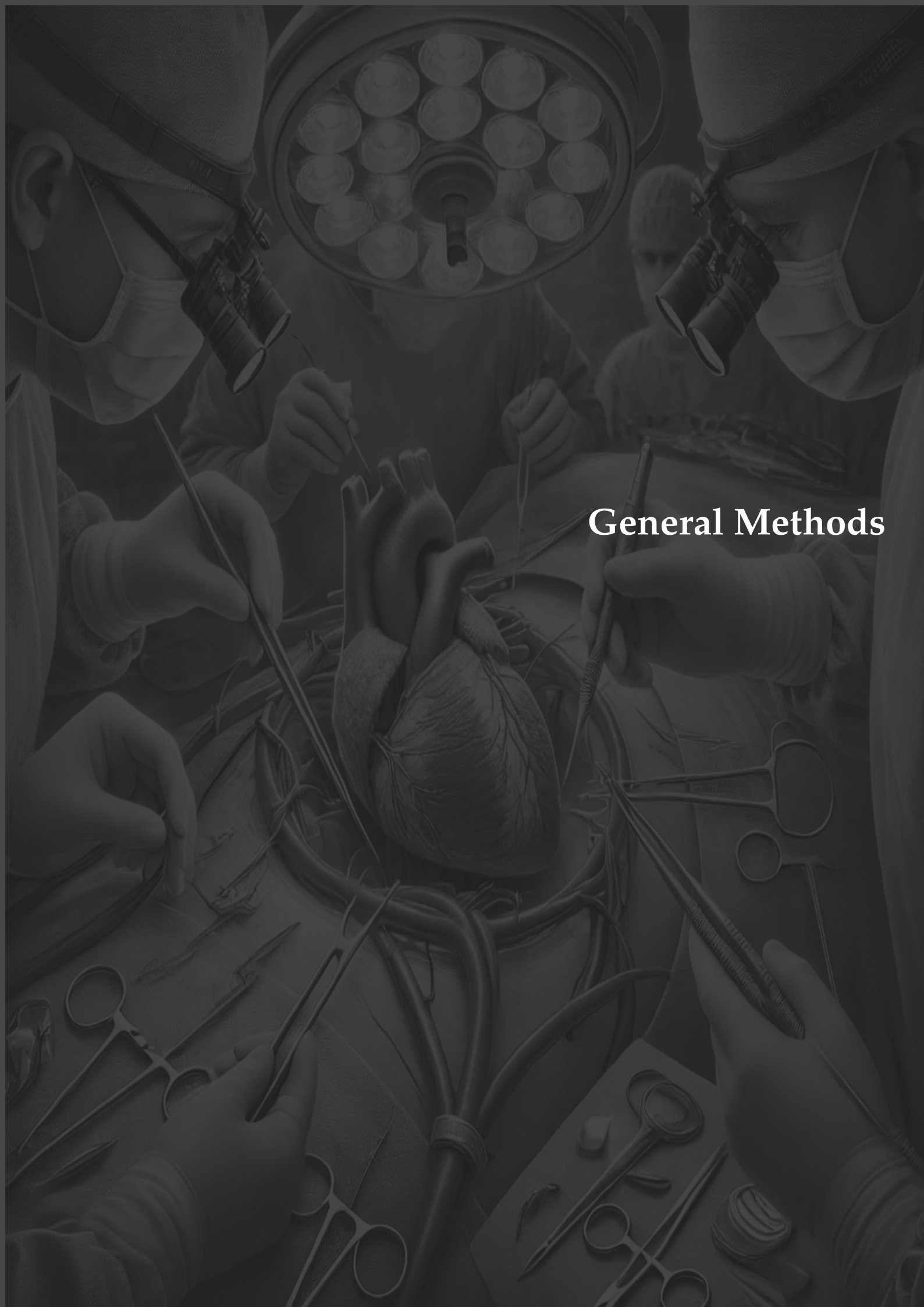
The authors have demonstrated that higher volumes were associated with lower costs per procedure. However, the total potential savings from regionalising cardiac procedures were relatively minor, and the risks of reducing access to needed services may need to be justified.

4.7. Summary

Administrative data has emerged as an indispensable resource for advancing healthcare research, offering unparalleled insights into clinical outcomes, healthcare utilisation, and cost-effectiveness across diverse patient populations. In the context of coronary artery bypass grafting (CABG), administrative datasets provide a foundation for evaluating short- and long-term patient outcomes, refining risk prediction models, and comparing treatment approaches in real-world settings. By leveraging these datasets, researchers may improve our understanding of CABG performance, identify disparities in care delivery, and inform policy decisions aimed at enhancing healthcare quality.

Despite its advantages, administrative data comes with inherent limitations. Issues such as incomplete clinical variables, variability in coding practices, and restricted study populations can hinder its utility for certain research applications. However, through data linkage, the integration of administrative datasets with complementary sources, such as electronic health records and clinical registries, has demonstrated the potential to overcome many of these challenges. These expanded datasets enable richer analyses that support precision in clinical profiling and drive innovations in care delivery.

Looking forward, advancements in technology, such as machine learning and real-time data analytics, promise to further unlock the potential of administrative data. By addressing current limitations and embracing emerging methodologies, researchers and clinicians can continue to leverage these datasets to optimise CABG outcomes, reduce healthcare disparities, and guide evidence-based decision-making.



General Methods

The methodological framework of this thesis is grounded in the use of administrative data to study outcomes and optimise care in coronary artery bypass grafting (CABG). Across the six embedded studies, shared methodologies were employed to ensure consistency and rigour while addressing the unique objectives of each research question. This chapter outlines the key methods utilised throughout the thesis, focusing on the use of large-scale administrative datasets, patient population definitions, and statistical approaches.

Administrative data serves as the backbone of the studies presented, offering extensive sample sizes, longitudinal tracking capabilities, and insights into real-world healthcare delivery. These datasets were supplemented with linked data sources to enhance their depth and applicability. By leveraging such data, the research examines clinical outcomes, resource utilisation, and healthcare disparities, providing actionable insights for improving CABG care.

While the methodological approaches were tailored to the specific aims of each study, this chapter highlights the common frameworks that underpin the thesis. Technical details specific to individual studies are presented in their respective sections, and additional content – such as detailed coding algorithms – is provided in the appendix where appropriate. The goal of this chapter is to offer a cohesive overview of the shared methodologies, ensuring clarity and alignment across the body of work.

5.1. Study Design

The studies in this thesis are based on retrospective analyses of administrative datasets from the University Hospital Centre São João (UHC São João), a level III hospital in Porto, Portugal. This dataset encompasses all hospitalisations recorded at the institution, offering a comprehensive view of healthcare delivery, clinical outcomes, and resource utilisation within a single-centre context.

The analysis focused on patients undergoing primary isolated coronary artery bypass grafting (CABG) from January 1, 2000, to September 30, 2015. This 15-year study period was chosen to align with consistent coding practices under the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), before the transition to ICD-10-CM coding in late 2015. This consistency was critical to ensuring accurate data interpretation and minimising disruptions associated with coding transitions.

Another key advantage of using a single-centre dataset was the ability to seamlessly link administrative data with other clinical databases maintained at UHC São João. This approach enriched the dataset with detailed clinical variables while avoiding the logistical complexities of managing data from multiple hospitals with varying protocols and data systems. The single-centre focus ensured homogeneity in surgical practices and institutional protocols, further strengthening the reliability of the analyses.

Key features of the study design include:

- ▶ **Population Scope:** Inclusion of all patients undergoing primary isolated CABG, with exclusion of those undergoing concomitant procedures to maintain population homogeneity.
- ▶ **Data Linkage:** Leveraging the single-centre dataset facilitated integration with complementary clinical databases, providing enhanced clinical detail without introducing undue complexity.
- ▶ **Time Frame Justification:** A predefined study period aligned with stable ICD-9-CM coding practices ensured consistency in the coding and analysis of clinical variables.
- ▶ **Retrospective Approach:** The use of preexisting data enabled efficient evaluation of long-term trends and outcomes, addressing research objectives within the constraints of available data.

This study design underscores the practicality of administrative data in addressing key research questions, particularly when prospective data is unavailable and retrospective data is challenging to utilise. The following section outlines the criteria used to define the study population.

5.2. Study Population

Patients were included in the study if they underwent primary isolated coronary artery bypass grafting (CABG) during the study period, as identified by the following International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) procedure codes: 3610, 3611, 3612, 3613, 3614, 3615, 3616, 3617, and 3619. The extraction process was performed using R, leveraging a reproducible and systematic script to filter eligible records from the institutional patient discharge datasets [412]. Below is the R code used for this step:

```
1 # Define ICD-9-CM procedure codes for CABG
2 > cabg_codes <- c("3610", "3611", "3612", "3613", "3614",
3   "3615", "3616", "3617", "3619")
4 # Filter dataset for patients with isolated CABG
5 > cabg_patients <- dataset %>%
```

```
6 | filter(procedure_code %in% cabg_codes)
```

Detailed exclusion criteria, including prior cardiac surgery, concomitant valve procedures, aortic surgeries, and correction of myocardial infarction mechanical complications, were implemented using specific ICD-9-CM codes (provided in Appendix A). The exclusion process was performed programmatically in R to ensure consistency and precision [412]. Below is the R code snippet used to apply these criteria:

```
1 | # Define ICD-9-CM codes for exclusion criteria
2 | > exclusion_codes <- c(Exclusion criteria -- provided in
   |   Appendix A)
3 |
4 | # Filter dataset to exclude patients with exclusion
   |   criteria
5 | > filtered_dataset <- cabg_patients %>%
6 |   filter(!procedure_code %in% exclusion_codes)
```

This script systematically excludes ineligible patients based on predefined criteria, resulting in a dataset that contains all primary isolated CABG procedures and defines the final study population for analysis.

5.3. Data Sources and Variables

The data used in this thesis were sourced from the institutional patient discharge datasets, which provide comprehensive documentation of hospitalisations, including demographic information, associated diagnoses, and procedures performed. Primary and secondary diagnoses (Appendix B) and procedures (Appendix C) were coded using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), ensuring consistency and accuracy in defining baseline characteristics and procedural details.

The comorbidities were extracted from the diagnostic codes using the *comorbidity* package in R and subsequently used to calculate the Charlson Comorbidity Index (CCI) for each patient [412–414]. The R code for this process is as follows:

```
1 | # Load required libraries
2 | > library(tidyr)
3 | > library(dplyr)
4 | > library(comorbidity)
5 |
6 | # Convert the dataset from wide to long format
7 | > long_data <- filtered_dataset %>%
8 |   pivot_longer(
9 |     cols = starts_with("diagnosis"), # Specify columns to
   |     pivot
10 |     names_to = "diagnosis_type", # Primary vs secondary
```

```

11     values_to = "diagnosis_code"
12   )
13
14   # Use the 'comorbidity' package to extract comorbidities
    and calculate Charlson Comorbidity Index
15 > charlson_scores <- comorbidity(
16   long_data,
17   id = "patient_id",      # Identifier column
18   code = "diagnosis_code", # Diagnosis code column
19   score = "charlson",     # Specify Charlson score
20   icd = "icd9"           # Specify ICD version
21 )

```

The procedure codes were extracted automatically from the dataset using an R script based on the relevant ICD-9-CM codes [412]. This automated process ensured consistency and accuracy in characterising the conduct of the operation and analysing procedural details relevant to CABG.

```

1 # Load required library
2 > library(dplyr)
3
4 # Define the relevant ICD-9-CM codes for the procedure of
    interest
5 > relevant_codes <- c(Procedure codes -- provided in
    Appendix C)
6
7 # Create a new column to indicate if the patient underwent
    any of the relevant procedures
8 > filtered_dataset <- filtered_dataset %>%
9   mutate(
10     procedure_flag = ifelse(
11       rowSums(across(starts_with("procedure"), ~ . %in%
12         relevant_codes), na.rm = TRUE) > 0,
13       1, # Assign 1 if any procedure matches the relevant
14         codes
15       0 # Assign 0 otherwise
16     )
17 )

```

The independent variables used in the analyses are specific to each study and are detailed in the corresponding papers. This ensures that the selection and definition of variables align with the unique objectives and methodologies of each study within this thesis.

5.4. Outcomes

The primary outcome variable in the analyses was long-term all-cause mortality. This was determined by linking the institutional discharge dataset to the National Patient Registry using individual Social Security numbers to ascertain patients' life status.

Secondary outcomes included the relative incidence of cardiovascular and noncardiovascular mortality. The cause of death was identified through interrogation of the Death Certificate Information System, which categorised deaths as cardiovascular or noncardiovascular based on the primary cause. Allocation to the cardiovascular category ensued in patients whose primary cause of death was cardiovascular, cerebrovascular, or peripheral vascular diseases. Noncardiovascular mortality resulted from all other diagnoses. Finally, all-cause mortality included these cardiovascular and noncardiovascular components and those patients without any specified diagnosis (unknown cause of death).

Other studies focused on a set of postoperative complications as secondary outcomes. These complications, detailed in Appendix D, were systematically identified and coded from the institutional discharge dataset, enabling robust analysis of short-term and long-term postoperative morbidity [412].

```

1 # Load required library
2 > library(dplyr)
3
4 # Define the relevant ICD-9-CM codes for the diagnoses of
   interest
5 > relevant_codes <- c(Diagnosis codes -- provided in
   Appendix D)
6
7 # Create a new column to indicate if the patient had any of
   the relevant diagnoses
8 > filtered_dataset <- filtered_dataset %>%
9   mutate(
10     procedure_flag = ifelse(
11       rowSums(across(starts_with("diagnosis"), ~ . %in%
12         relevant_codes), na.rm = TRUE) > 0,
13       1, # Assign 1 if any diagnosis matches the relevant
14         codes
15       0 # Assign 0 otherwise
16     )
17 )

```

The selection and definition of specific outcome variables varied across studies to align with their respective research objectives. Details of these outcomes and their relevance are discussed in the corresponding papers.

5.5. Statistical Analysis

The statistical analyses were designed to ensure robust evaluation of outcomes while accounting for potential confounding factors. Two primary methodologies were employed to address confounding: propensity score-based (PS) methodologies and competing risk (CR) analyses. These strategies were selected based on the specific research question and the nature of the data in each study.

Before implementing these advanced statistical techniques, a descriptive analysis was conducted to summarise the baseline characteristics, procedural details, and outcomes of the study population.

Descriptive Analyses. The data were initially subjected to descriptive statistical analysis to summarise baseline characteristics, procedural details, and outcomes across the study population. Continuous variables were expressed as means with standard deviations or medians with interquartile ranges, depending on their distribution. Categorical variables were reported as frequencies and percentages. Comparisons between groups were conducted using appropriate statistical tests, such as the Student's t-test or Mann–Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables.

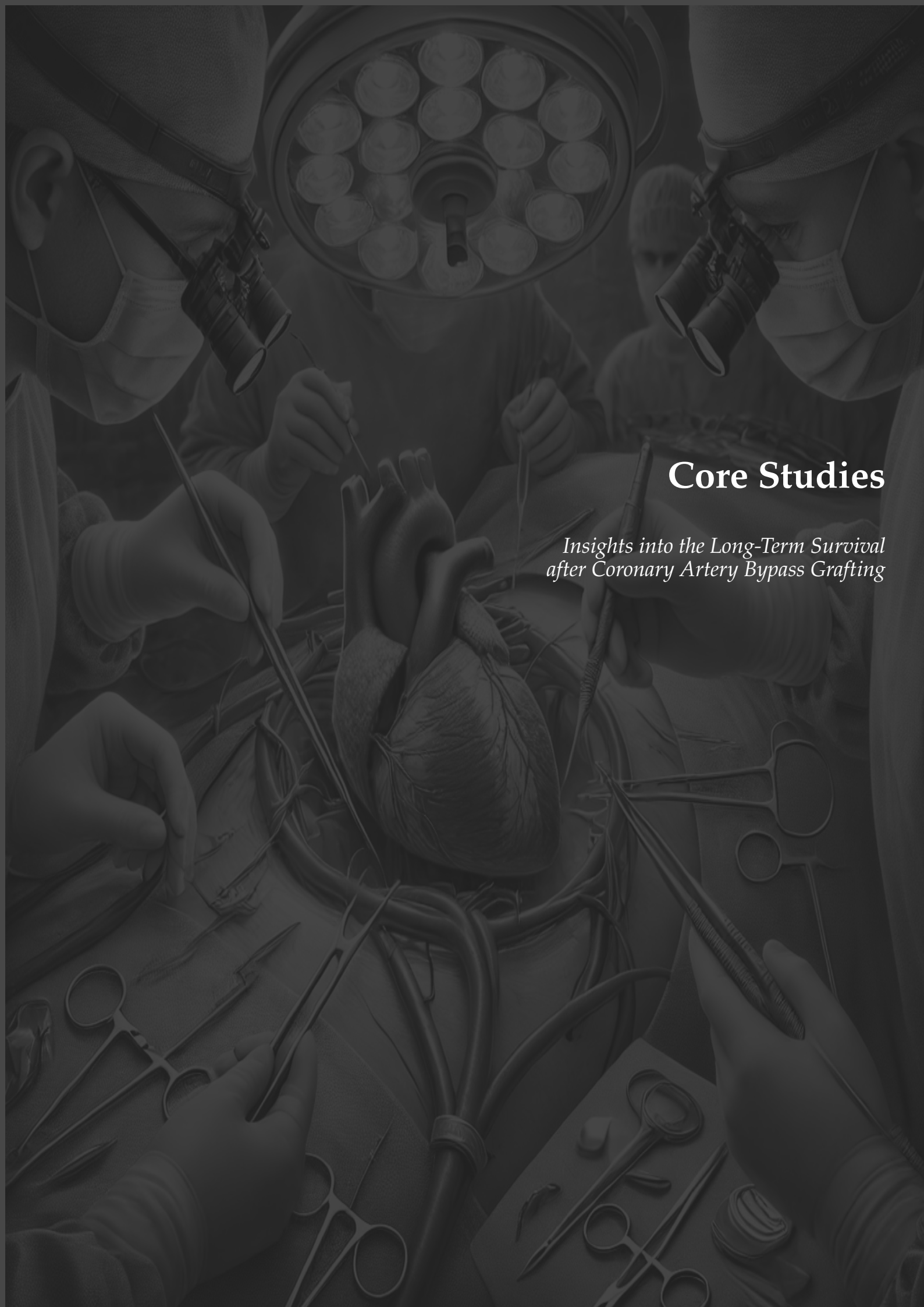
Comparisons between groups were generally expressed as standardised mean differences (SMD), providing a measure of the magnitude of differences that is independent of sample size. An SMD of less than 0.10 was considered indicative of a negligible difference. This approach was particularly relevant in studies employing propensity score methodologies.

In studies using competing risk analyses, group differences were expressed as p-values, with a threshold of <0.05 considered statistically significant. This ensured consistent interpretation of findings in analyses where event-specific probabilities and hazards were evaluated.

Unadjusted Outcome Analyses. To evaluate outcomes without adjusting for baseline differences, inferential statistical analyses were performed. For categorical outcomes, such as postoperative complications, odds ratios were calculated along with their corresponding 95% confidence intervals. The Kaplan–Meier method provided estimates of overall survival probabilities for time-to-event outcomes, with differences between groups assessed using the log-rank test.

Adjusted Outcome Analyses. To account for potential confounding, adjusted analyses incorporated all relevant baseline and procedural variables. Different methodologies were employed depending on the specific objectives and nature of the outcomes in each study.

Propensity score methodologies, such as inverse probability weighting (IPW) or overlap weighting (OW), were used to balance covariates between comparison groups. These methods aimed to approximate a randomised controlled trial by reducing confounding effects and were particularly useful for comparing treatment strategies or surgical techniques. IPW was applied to generate a pseudo-population where the distribution of baseline covariates was independent of the treatment assignment [23]. In those cases where extreme weights were unduly destabilising the analysis,



Core Studies

*Insights into the Long-Term Survival
after Coronary Artery Bypass Grafting*

Gender-Specific Survival

6.

6.1. Background

A consistent finding among patients undergoing coronary artery bypass grafting (CABG) is the superior perioperative mortality seen in female patients compared to male patients [417–419]. Women are likely to present at an older age with a more significant burden of cardiovascular comorbidities and a worse functional status at baseline [420]. Consequently, two of the most extensively used risk prediction tools for CABG outcomes, the Society of Thoracic Surgeons (STS) score and the EuroSCORE, include female sex as an independent risk factor for post-CABG outcomes [169, 421, 422]. It is not clear whether this putative increased surgical risk impacts long-term survival.

6.2. Problem Statement and Knowledge Gap

Multiple studies reported the impact of the female gender on long-term clinical outcomes after isolated CABG with conflicting results. A meta-analysis of 20 observational studies documented that women who underwent isolated CABG experienced higher mortality at short-term and long-term follow-up than their male counterparts [423]; on the other hand, other more recent studies report that the female sex does not constitute a significant predictor of long-term prognosis [424–426]. Therefore, the role of sex on long-term clinical outcomes after CABG remains uncertain and deserves further clarification.

6.3. Research Objectives

This study compares long-term survival in female and male patients with ischaemic heart disease admitted to primary, isolated CABG, in a single level III institution, between 2000 and 2015. We employed an overlap weighting (OW) algorithm to minimise confounding. Its target population highlights patients with the most overlap in their observed characteristics, and its corresponding estimand is the average treatment effect (ATE) in the overlap population [415].

6.4. Reader's Note

The subsequent section of this chapter reproduces the full text of the study, “Long-term survival of female versus male patients

after coronary artery bypass grafting”, by Armando Abreu, José Máximo, and Adelino Leite-Moreira [92] and published in *Plos One* (2022). The paper has been included with the publisher’s permission under the terms of the Creative Commons Attribution License.

For proper citation, please refer to the original publication: Abreu, A., Máximo, J., & Leite-Moreira, A. (2022). Long-term survival of female versus male patients after coronary artery bypass grafting. *PloS one*, 17(9), e0275035. DOI: 10.1371/journal.pone.0275035.

6.5. Original Publication

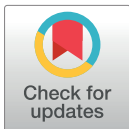
The full text of the study, titled "Long-term survival of female versus male patients after coronary artery bypass grafting", is included in the following pages.

RESEARCH ARTICLE

Long-term survival of female versus male patients after coronary artery bypass grafting

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Abstract

Background

Several of the most extensively used risk prediction tools for coronary artery bypass grafting outcomes include female sex as an independent risk factor for postoperative outcomes. It is not clear whether this putative increased surgical risk impacts long-term survival. This study aimed to assess sex differences in 10-year all-cause mortality.

Methods

Retrospective analysis of 5340 consecutive patients undergoing primary isolated coronary artery bypass surgery, performed from 2000 to 2015, in a Portuguese level III Hospital. The primary endpoint was all-cause mortality at ten years. We employed an overlap weighting algorithm to minimize confounding. Its target population highlights patients with the most overlap in their observed characteristics, and its corresponding estimand is the average treatment effect in the overlap population.

Results

We identified that 5340 patients underwent isolated CABG: 1104 (20.7%) were female, and 4236 (79.3%) were male. Sixteen patients were lost to follow-up (0.3%). The median follow-up time was 12.79 (IQR, 9.52–16.66) years: 12.68 (IQR, 9.48–16.54) years for the male patient group and 13.13 (IQR, 9.75–16.98) years for the female patient group. The primary endpoint of all-cause mortality at ten years occurred in 1106 patients (26.1%) in the male patient group, compared with 315 (28.5%) in the female patient group. The unweighted survival analysis for both groups reveals the worst long-term prognosis for the female cohort (hazard ratio, 1.22; 95% CI, 1.10 to 1.35; $p < 0.001$), while in the overlap weighted survival analysis, such long-term difference in prognosis disappears (hazard ratio, 0.98; 95% CI, 0.88 to 1.09; $p = 0.693$).

Conclusion

In this longitudinal, population-level analysis of patients undergoing primary, isolated CABG, we demonstrated that the female sex is not associated with increased long-term all-

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cause mortality compared to their male counterparts. Thus, sex should not influence the undertaking of an adequate revascularization strategy.

Introduction

A consistent finding among patients undergoing coronary artery bypass grafting (CABG) is the superior perioperative mortality seen in female patients compared to male patients [1–3]. Women are likely to present at an older age with a more significant burden of cardiovascular comorbidities and a worse functional status at baseline [4]. Consequently, two of the most extensively used risk prediction tools for CABG outcomes, the Society of Thoracic Surgeons (STS) score and the EuroSCORE, include female sex as an independent risk factor for post-CABG outcomes [5–7]. It is not clear whether this putative increased surgical risk impacts long-term survival.

Multiple studies reported the impact of the female gender on long-term clinical outcomes after isolated CABG with conflicting results. A meta-analysis of 20 observational studies documented that women who underwent isolated CABG experienced higher mortality at short-term and long-term follow-up than their male counterparts [8]; on the other hand, other more recent studies report that the female sex does not constitute a significant predictor of long-term prognosis [9–11]. Therefore, the role of sex on long-term clinical outcomes after CABG remains uncertain and deserves further clarification.

This study compares 10-year survival in female and male patients with ischemic heart disease admitted to primary coronary artery bypass grafting, in a single level III institution, between 2000 and 2015. We employed an overlap weighting (OW) algorithm to minimize confounding. Its target population highlights patients with the most overlap in their observed characteristics, and its corresponding estimand is the average treatment effect (ATE) in the overlap population [12].

Methods

Ethics

Our Institution's Ethics Committee approved this research, and the need for informed consent was waived.

Study design

We conducted an observational retrospective study to evaluate sex-related differences in baseline characteristics, utilization trends, in-hospital complications, length of hospital stay, discharge disposition, and long-term (10 years) survival in patients with isolated coronary artery disease undergoing CABG. Thus, we analyzed an administrative dataset containing all hospitalizations occurring in a level III hospital from January 1, 2000, to September 30, 2015 (chosen as the cutoff date because of ICD-10-CM implementation). The corresponding diagnoses and procedures were coded for each hospitalization based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM).

Study population

Patients were included in the study if they underwent primary coronary artery bypass surgery (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM]

codes 36.10, 36.11, 36.12, 36.13, 36.14, 36.15, 36.16, 36.17 or 36.19) during the study period. Exclusion criteria included previous cardiac surgery, concomitant valve replacement or repair, concurrent aorta surgery, and simultaneous correction of myocardial infarction mechanical complications ([S1 Table](#)).

Data sources and variables

From an administrative dataset containing all hospitalizations occurring in our Institution from 2000 to 2015, we identified all hospitalizations with at least one associated procedure code of CABG. The predictive or independent variable was the sex of the patient. We obtained patients' baseline characteristics from our institution patient's discharge datasets. After extracting the relevant ICD-9-CM codes, we computed the Charlson Comorbidity Index using the Quan et al. coding scheme [13, 14]. We provide definitions of coexisting conditions in [S2 Table](#).

Outcomes

We compared episodes concerning female patients to those of male patients. The primary outcome variable was 10-year survival. The patient discharge database was linked to the National Patient Registry (RNU) to ascertain patient life status. Secondary outcomes included a set of predefined in-hospital complications (see [S3 Table](#) for detailed definitions), the length of hospital stay, and discharge disposition (categorized as home discharge, transfer to other health-care facilities or in-hospital death).

Statistical analysis

Data are presented as absolute frequencies and percentages for categorical variables and as means and standard deviations or median and interquartile range, where appropriate, for continuous variables. We used the standardized mean difference to assess discrepancies in covariates between treatment groups, as it allows for the judgment of the relative balance of variables measured in different units. We held values less than 0.1 to indicate a negligible difference in the mean or frequency of a covariate between treatment groups [15].

In the univariate analysis, we computed summary measures of risk (odds ratio), and its associated 95% confidence interval, using simple logistic regression for each predefined outcome.

We performed overlap propensity score weighting to address potential confounding. The properties of overlap weights relative to inverse probability weighting include improved covariate balance and increased precision of effect measures estimates [12]. Multivariable logistic regression was used in each treatment group to estimate each patient's propensity score. The propensity model included the following variables: age, admission status (scheduled vs unscheduled), disease presentation (stable coronary disease, unstable angina / NSTEMI, and STEMI), hypertension, diabetes mellitus, hyperlipidemia, obesity, smoking history, cerebrovascular disease, congestive heart failure, chronic obstructive pulmonary disease, peripheral vascular disease, chronic kidney disease, liver disease, anemia, coagulation disorders, cancer history, the Charlson comorbidity index, use of cardiopulmonary bypass (i.e., whether the procedure was performed off-pump or on-pump), number of internal mammary arteries used (i.e., none, single, or bilateral), and the total number of grafts performed. Finally, we assessed the balance between treatment groups using standardized mean differences, with an ideal balance represented by a standardized difference of 10% or less. We included visual depictions of distributional balance as they are a helpful complement to numerical summaries [16].

We derived weighted logistic regression models with a robust variance estimator with the outcome as the dependent variable and the group on which the propensity score balances (e.g., the treatment group) as the only independent/predictor variable [17–19].

Estimates of survival probabilities were calculated using the Kaplan–Meier method and compared with the log-rank test [20–22]. Follow-up time, described by median and interquartile range, was obtained using the same estimator by reversing the event indicator so that the outcome of interest became being censored [23]. We employed a weighted Cox proportional hazards regression model with a robust variance estimator to compare long-term mortality between groups [17–19].

P values were two-sided with a significance threshold of 0.05. All statistical analyses were performed using R version 4.1.3 [24].

Results

Between 2000 and 2015, 5340 patients underwent isolated CABG: 1104 (20.7%) were female, and 4236 (79.3%) were male patients (Fig 1). This relative difference persisted during the study period (Fig 2).

Baseline characteristics

Regarding baseline characteristics (Table 1), women were older (66.7 ± 9.4 vs 62.9 ± 10.0), were more likely to have hypertension (77.4% vs 64.5%; SMD 0.287), diabetes mellitus (50.4% vs 35.5%; SMD 0.317), excessive body weight (30.1% vs 20.9%; SMD 0.212), and anemia

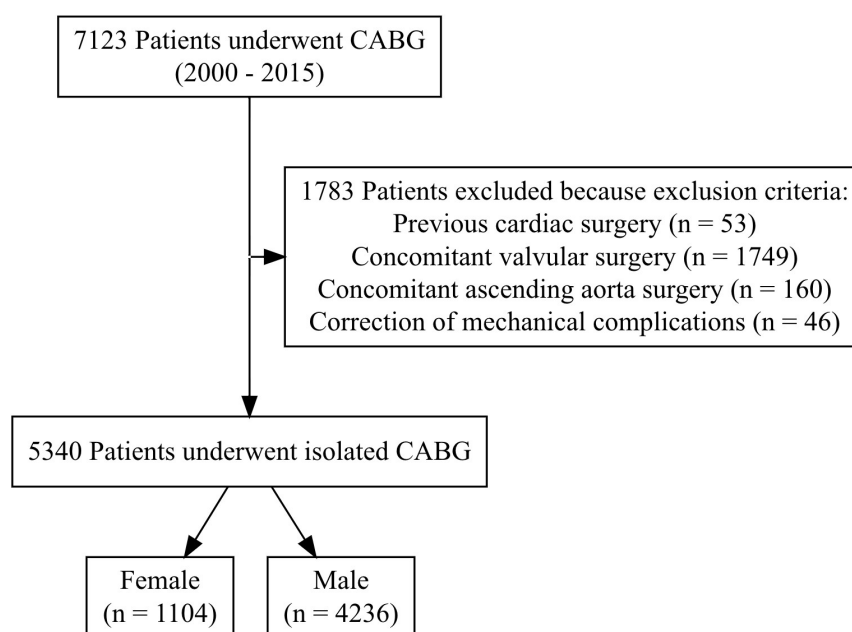


Fig 1. Study flowchart. Exclusion criteria for 7123 patients who underwent coronary artery bypass grafting (CABG) in Northern Portugal.

<https://doi.org/10.1371/journal.pone.0275035.g001>

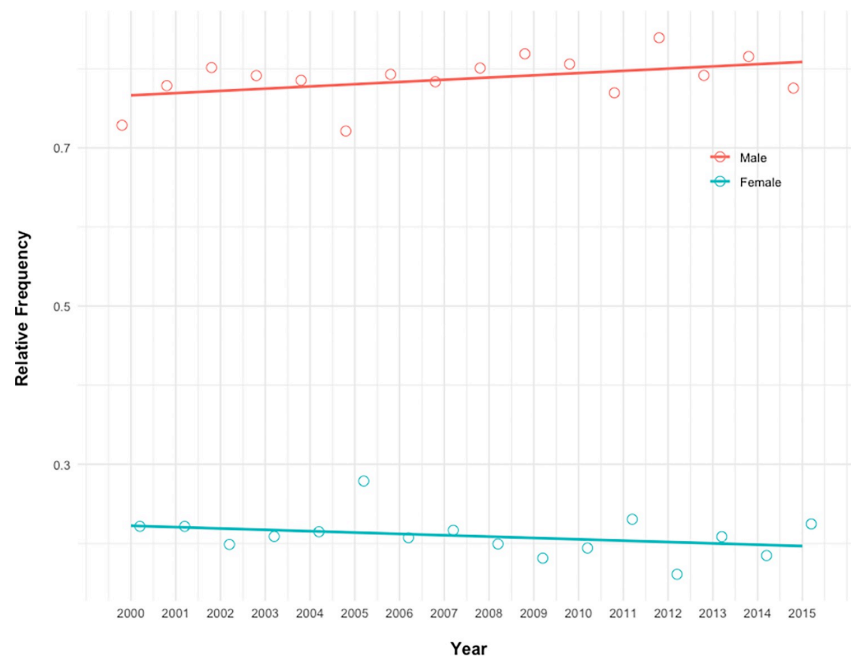


Fig 2. Temporal trends. Temporal trends in the relative frequency of isolated coronary artery grafting (CABG) by sex.
<https://doi.org/10.1371/journal.pone.0275035.g002>

Table 1. Baseline characteristics.

	Unadjusted			Overlap weighted		
	Male (n = 4236)	Female (n = 1104)	SMD ^k	Male (n = 726.9)	Female (n = 726.9)	SMD ^k
Characteristic						
Age, mean (SD) ^a	62.9 (10.0)	66.7 (9.4)	0.391	66.0 (9.1)	66.0 (9.8)	0
Admission, n (%)			0.046			0
Scheduled	1988 (46.9)	493 (44.7)		407.5 (46.4)	407.5 (46.4)	
Unscheduled	2248 (53.1)	611 (55.3)		389.4 (53.6)	389.4 (53.6)	
Presentation, n (%)			0.042			0
Chronic CAD ^b	2705 (63.9)	702 (63.6)		477.2 (65.7)	469.7 (64.6)	
UA / NSTEMI ^c	1112 (26.3)	304 (27.5)		180.1 (24.8)	195.2 (26.9)	
STEMI ^d	419 (9.9)	98 (8.9)		69.5 (9.6)	62.0 (8.5)	
Hypertension, n (%)	2731 (64.5)	854 (77.4)	0.287	537.8 (74.0)	537.8 (74.0)	0
Diabetes mellitus, n (%)			0.317			0
No diabetes	2733 (64.5)	547 (49.5)		394.9 (54.3)	391.8 (53.9)	
Non-insulin-treated	1322 (31.2)	465 (42.1)		282.0 (38.8)	288.1 (39.6)	
Insulin-treated	181 (4.3)	92 (8.3)		50.0 (6.9)	47.0 (6.5)	
Hyperlipidemia, n (%)	2645 (62.4)	736 (66.7)	0.088	465.4 (64.0)	465.4 (64.0)	0
Obesity, n (%)	885 (20.9)	332 (30.1)	0.212	190.8 (26.3)	190.8 (26.3)	0
Smoking history, n (%)			1.127			0
No smoking history	2181 (51.5)	1047 (94.8)		642.0 (88.3)	671.6 (92.4)	
Previous smoker	1163 (27.5)	19 (1.7)		76.9 (10.6)	17.7 (2.4)	
Current smoker	892 (21.1)	38 (3.4)		8.0 (1.1)	37.6 (5.2)	
CVD ^e , n (%)	688 (16.2)	185 (16.8)	0.014	119.6 (16.4)	119.6 (16.4)	0
CHF ^f , n (%)	832 (19.6)	211 (19.1)	0.013	139.1 (19.1)	139.1 (19.1)	0
COPD ^g , n (%)	323 (7.6)	60 (5.4)	0.089	41.0 (5.6)	41.0 (5.6)	0

(Continued)

Table 1. (Continued)

Characteristic	Unadjusted			Overlap weighted		
	Male (n = 4236)	Female (n = 1104)	SMD ^k	Male (n = 726.9)	Female (n = 726.9)	SMD ^k
PVD ^b , n (%)	187 (4.4)	34 (3.1)	0.070	22.4 (3.1)	22.4 (3.1)	0
CKD ⁱ , n (%)			0.069			0
No chronic kidney disease	4010 (94.7)	1033 (93.6)		681.9 (93.8)	680.4 (93.6)	
Non-dialysis dependent	196 (4.6)	66 (6.0)		40.2 (5.5)	43.2 (5.9)	
Dialysis dependent	30 (0.7)	5 (0.5)		4.8 (0.7)	3.3 (0.5)	
Liver disease, n (%)	89 (2.1)	25 (2.3)	0.011	15.3 (2.1)	15.3 (2.1)	0
Anemia, n (%)	363 (8.6)	135 (12.2)	0.120	78.2 (10.8)	78.2 (10.8)	0
Coagulation disorders, n (%)	68 (1.6)	25 (2.3)	0.048	14.1 (1.9)	14.1 (1.9)	0
Cancer, n (%)	46 (1.1)	7 (0.6)	0.049	5.6 (0.8)	5.6 (0.8)	0
CCI ^j , mean (SD ^a)	4.14 (1.70)	4.57 (1.57)	0.266	4.46 (1.63)	4.46 (1.59)	0

Baseline characteristics for unweighted and overlap weighted cohorts: male vs female.

^a standard deviation

^b coronary artery disease

^c unstable angina/non-ST-elevation myocardial infarction

^d ST-elevation myocardial infarction

^e cerebrovascular disease

^f congestive heart disease

^g chronic obstructive pulmonary disease

^h peripheral vascular disease

ⁱ chronic kidney disease

^j Charlson comorbidity index

^k standardized mean difference

<https://doi.org/10.1371/journal.pone.0275035.t001>

Table 2. Procedural details.

Characteristic	Unadjusted			Overlap weighted		
	Male (n = 4236)	Female (n = 1104)	SMD ^h	Male (n = 726.9)	Female (n = 726.9)	SMD
CBP ^a , n (%)			0.003			0
OPCAB ^b	1575 (37.2)	409 (37.0)		266.7 (36.7)	266.7 (36.7)	
ONCAB ^c	2661 (62.8)	695 (63.0)		460.2 (63.3)	460.2 (63.3)	
IMA utilization, n (%)			0.251			0
No IMA ^d	94 (2.2)	51 (4.6)		22.1 (3.0)	29.5 (4.1)	
SIMA ^e	2932 (69.2)	843 (76.4)		560.5 (77.1)	545.6 (75.1)	
BIMA ^f	1210 (28.6)	210 (19.0)		144.4 (19.9)	151.8 (20.9)	
Distal anastomosis, mean (SD ^g)	2.55 (0.86)	2.40 (0.85)	0.179	2.45 (0.84)	2.45 (0.86)	0

Procedural details for unweighted and overlap weighted cohorts: male vs female.

^a cardiopulmonary bypass

^b off-pump coronary artery bypass

^c on-pump coronary artery bypass

^d internal mammary artery

^e single internal mammary artery

^f bilateral internal mammary artery

^g standard deviation

^h standardized mean difference

<https://doi.org/10.1371/journal.pone.0275035.t002>

(12.2% vs 8.6%; SMD 0.120). This disproportionate risk profile translated into a higher Charlson comorbidity index (4.57 ± 1.57 vs 4.14 ± 1.70 ; SMD 0.266).

Considering intra-operative procedure details (Table 2), although there was no significant difference in the relative utilization of OPCAB or ONCAB techniques between groups, there was a higher proportion of women not receiving any internal mammary artery graft (4.6% vs 2.2%), and a lower proportion of women received bilateral internal artery mammary grafting (19.0% vs 28.6%; SMD 0.251). Similarly, the mean number of grafts performed was lower in the female cohort (2.40 ± 0.85 vs 2.55 ± 0.86 ; SMD 0.179).

Crude outcome analysis

In the crude outcome analysis (Table 3), women had 25% higher odds of requiring a blood transfusion (30.8% vs 26.3%; OR = 1.25; 95% CI 1.08, 1.44; $p = 0.003$) and 74% higher odds of having a surgical wound complication (2.4% vs 1.4%; OR = 1.74; 95% CI 1.07, 2.74; $p = 0.021$) in the index hospitalization. Likewise, women had higher odds of being discharged to another healthcare facility following the index hospitalization (7.4% vs 3.7%; OR 2.08; 95% CI 1.58,

Table 3. Crude outcome analysis.

	Male	Female			
Outcome	(n = 4236)	(n = 1104)	OR ^f	(95% CI ^h)	p
Stroke, n (%)	44 (1.0)	6 (0.5)	0.52	0.20, 1.13	0.135
Cardiac, n (%)					
POAF ^a	528 (12.5)	151 (13.7)	1.11	0.91, 1.35	0.282
Pacemaker implantation	17 (0.4)	8 (0.7)	1.81	0.74, 4.08	0.167
IABP ^b	137 (3.2)	40 (3.6)	1.12	0.78, 1.59	0.520
Cardiac arrest	19 (0.4)	3 (0.3)	0.60	0.14, 1.78	0.419
Respiratory, n (%)					
Prolonged ventilation	184 (4.3)	47 (4.3)	0.98	0.70, 1.35	0.900
Reintubation	101 (2.4)	21 (1.9)	0.79	0.48, 1.25	0.341
Tracheotomy	21 (0.5)	4 (0.4)	0.73	0.21, 1.92	0.565
Acute kidney injury, n (%)	37 (0.9)	12 (1.1)	1.25	0.62, 2.33	0.508
Hemorrhage, n (%)	158 (3.7)	35 (3.2)	0.85	0.57, 1.21	0.375
RBC ^c transfusion, n (%)	1114 (26.3)	340 (30.8)	1.25	1.08, 1.44	0.003
Surgical wound, n (%)	58 (1.4)	26 (2.4)	1.74	1.07, 2.74	0.021
Discharge disposition, n (%)					< 0.001
Home	4013 (94.7)	1002 (90.8)	0.55	0.43, 0.70	
Other hospital	157 (3.7)	82 (7.4)	2.08	1.58, 2.74	
Death	66 (1.6)	20 (1.8)	1.17	0.69, 1.89	
	Male	Female			
Outcome	(n = 4236)	(n = 1104)	CIE ^g	(95% CI ^h)	p
LOS ^d , median (IQR ^e)	7 (6, 9)	7 (6, 10)	1.17	0.57, 1.78	< 0.001

Crude outcome analysis (unweighted cohort): male vs female.

^a postoperative atrial fibrillation

^b intra-aortic balloon pump counterpulsation

^c red blood cell

^d length of stay

^e interquartile range

^f odds ratio

^g change in estimate

^h confidence interval

<https://doi.org/10.1371/journal.pone.0275035.t003>

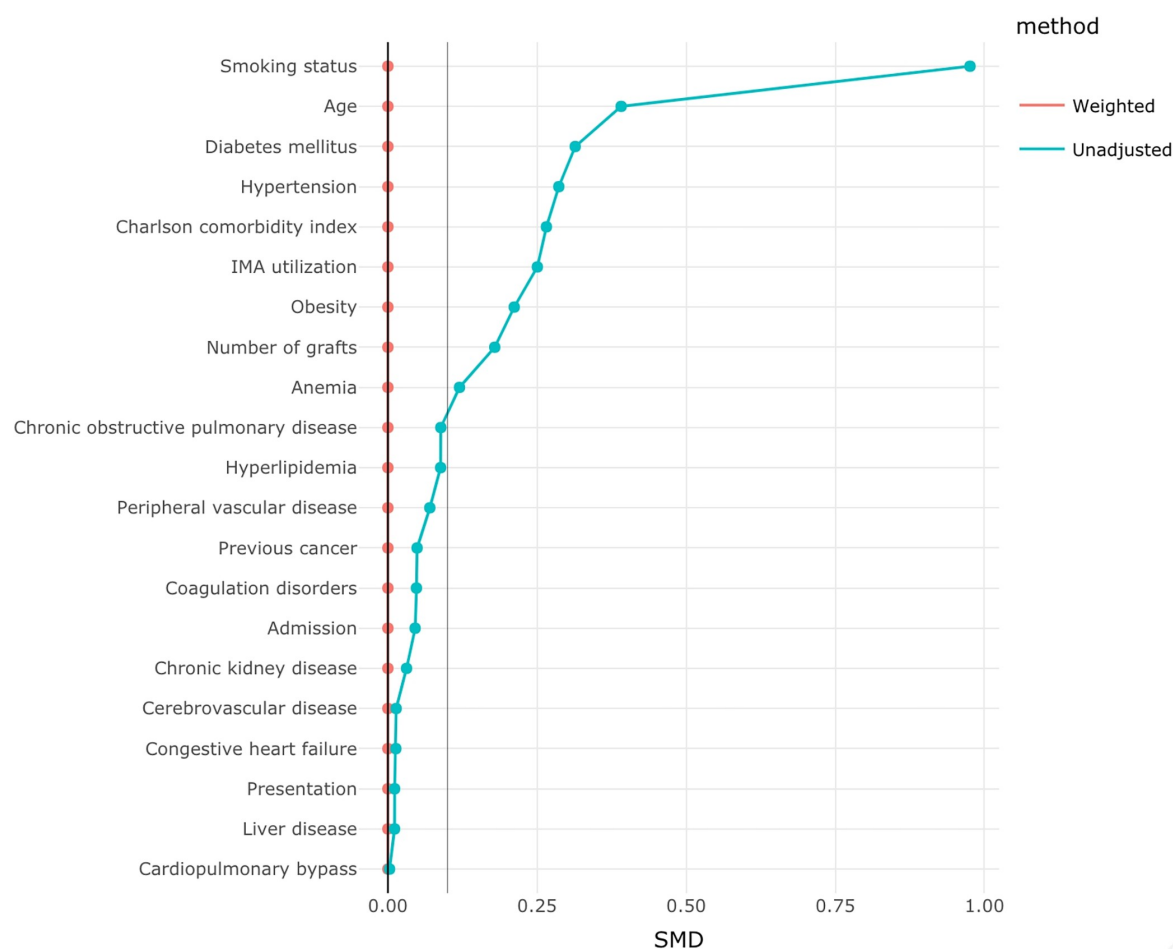


Fig 3. Covariate balance. Covariate balance: unweighted vs overlap weighted cohorts.

<https://doi.org/10.1371/journal.pone.0275035.g003>

2.74; $p < 0.001$). On the other hand, women required longer hospitalization periods [7 (IQR 6, 10) days vs 7 (6, 9) days; CIE 1.17 days; 95% CI 0.57, 1.78; $p < 0.001$].

Weighted outcome analysis

Overlap weighting balanced baseline characteristics in each group (Table 1 and Fig 3). As depicted in Fig 4, female patients had 18% more odds of requiring an RBC transfusion (OR 1.18, 95% CI 1.00, 1.38, $p = 0.046$), and 73% more odds of having surgical wound complications (OR 1.73, 95% CI 1.02, 2.92, $p = 0.042$). We have not noted any other differences in pre-specified complications or discharge disposition rates. Concerning the length of hospital stay, there were no significant differences between groups (CIE 0.59 days, 95% CI -0.12–1.31, $p = 0.105$).

Survival analysis

Sixteen patients were lost to follow-up (0.3%). The median follow-up time was 12.79 (IQR, 9.52–16.66) years: 12.68 (IQR, 9.48–16.54) years for the male patient group and 13.13 (IQR,

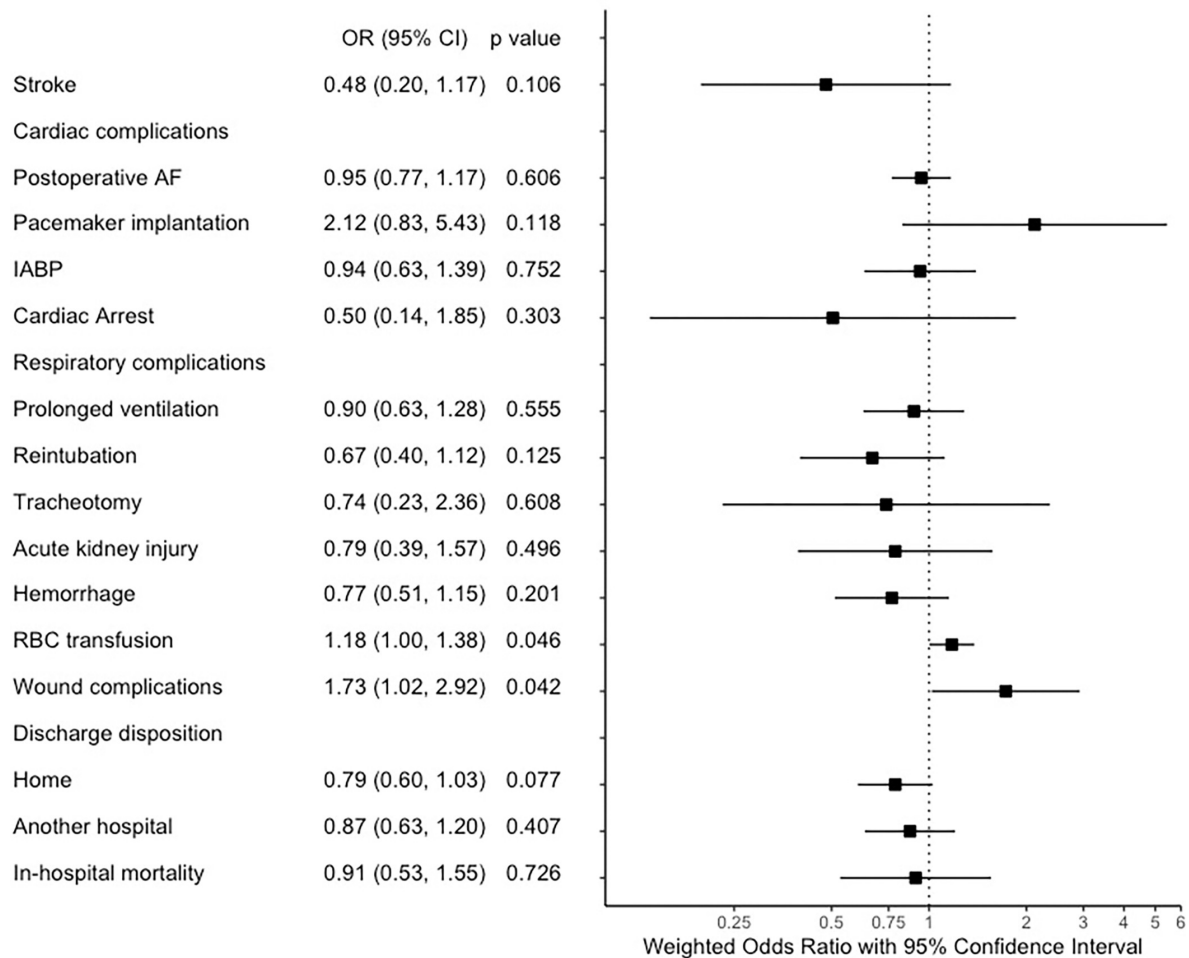


Fig 4. Odds ratio plot. Overlap weighted outcome analysis: male vs female.

<https://doi.org/10.1371/journal.pone.0275035.g004>

9.75–16.98) years for the female patient group. The primary endpoint of all-cause mortality at ten years occurred in 1106 patients (26.1%) in the male patient group, compared with 315 (28.5%) in the female patient group. Thirty-day, one, five and ten-year survival rates were 98.8, 96.3, 87.9 and 72.1% in the male patient group and 98.6, 95.6, 88.1, and 69.4% in the female patient group. Fig 5 depicts the unweighted survival function plot for both groups, revealing the worst long-term prognosis for the female cohort (hazard ratio, 1.22; 95% CI, 1.10 to 1.35; $p < 0.001$). Fig 6 illustrates the overlap weighted survival function plot for both groups, where such long-term difference in prognosis disappears (hazard ratio, 0.98; 95% CI, 0.88 to 1.09; $p = 0.693$).

Discussion

In this contemporary, longitudinal, population-level analysis of patients undergoing primary, isolated CABG, we demonstrated that the female sex is not associated with an increased risk of

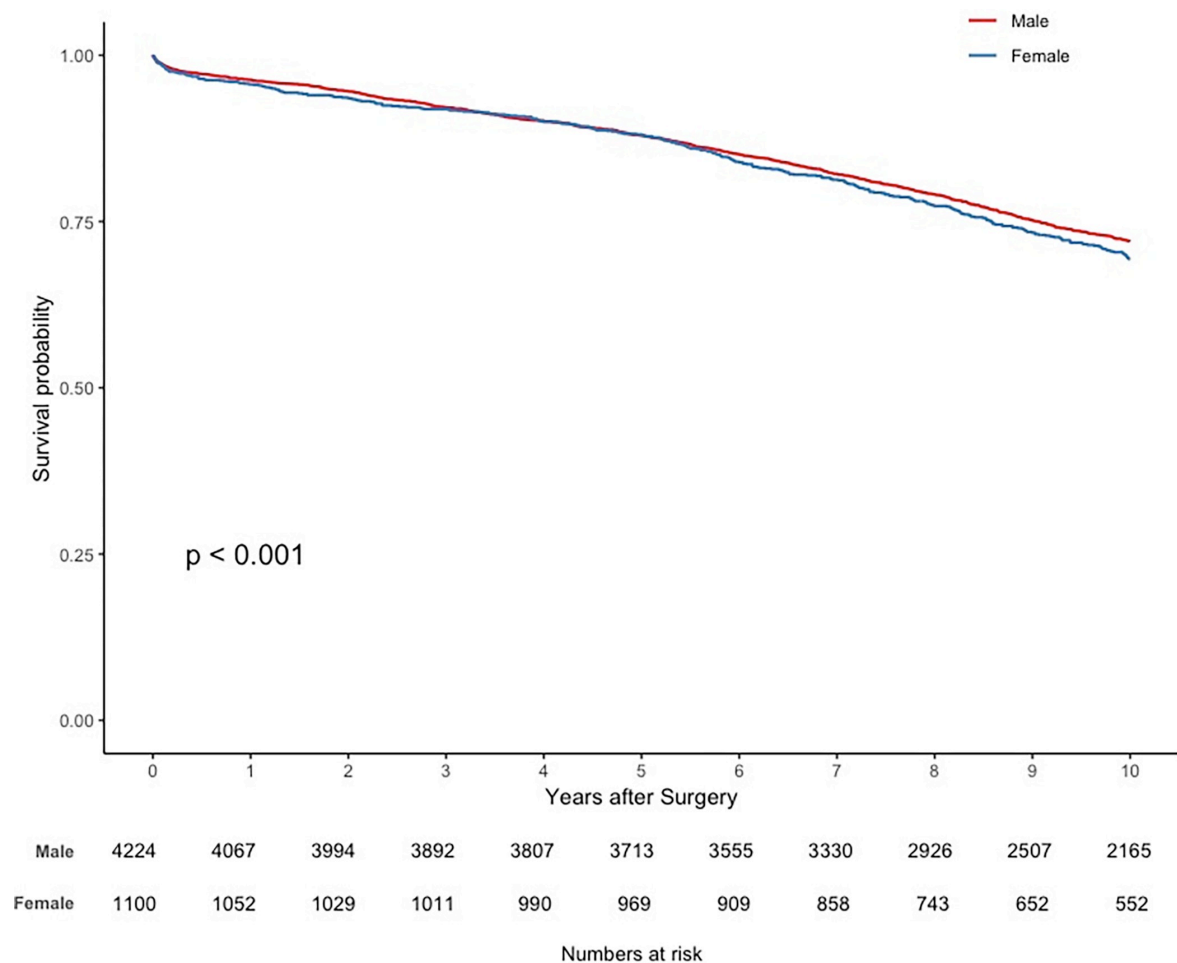


Fig 5. Unweighted survival function plot. Unadjusted survival function (Kaplan-Meier method): male vs female.

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death at ten-year follow-up, after extensive adjustment for baseline and procedural characteristics.

In our cohort, women were older and had a more substantial burden of comorbidities at baseline. Furthermore, they were less likely to receive additional arterial grafts and received fewer distal anastomosis. Nevertheless, we employed a strategy to control for possible confounding (OW) that emphasizes patients with the most overlap in their observed characteristics [12]. Its corresponding estimand, the average treatment effect in the overlap population, is of natural relevance to this investigation because it highlights the portion of the population where the most treatment equipoise exists in clinical practice. Therefore, the significant difference in 10-year found in the unadjusted analysis faded after down-weighting the extremes of the PS distribution.

In a propensity score-matched analysis of 68774 patients (21.9% women), Guru et al. describe similar survival rates in women to those seen in men at 10-year follow-up [25].

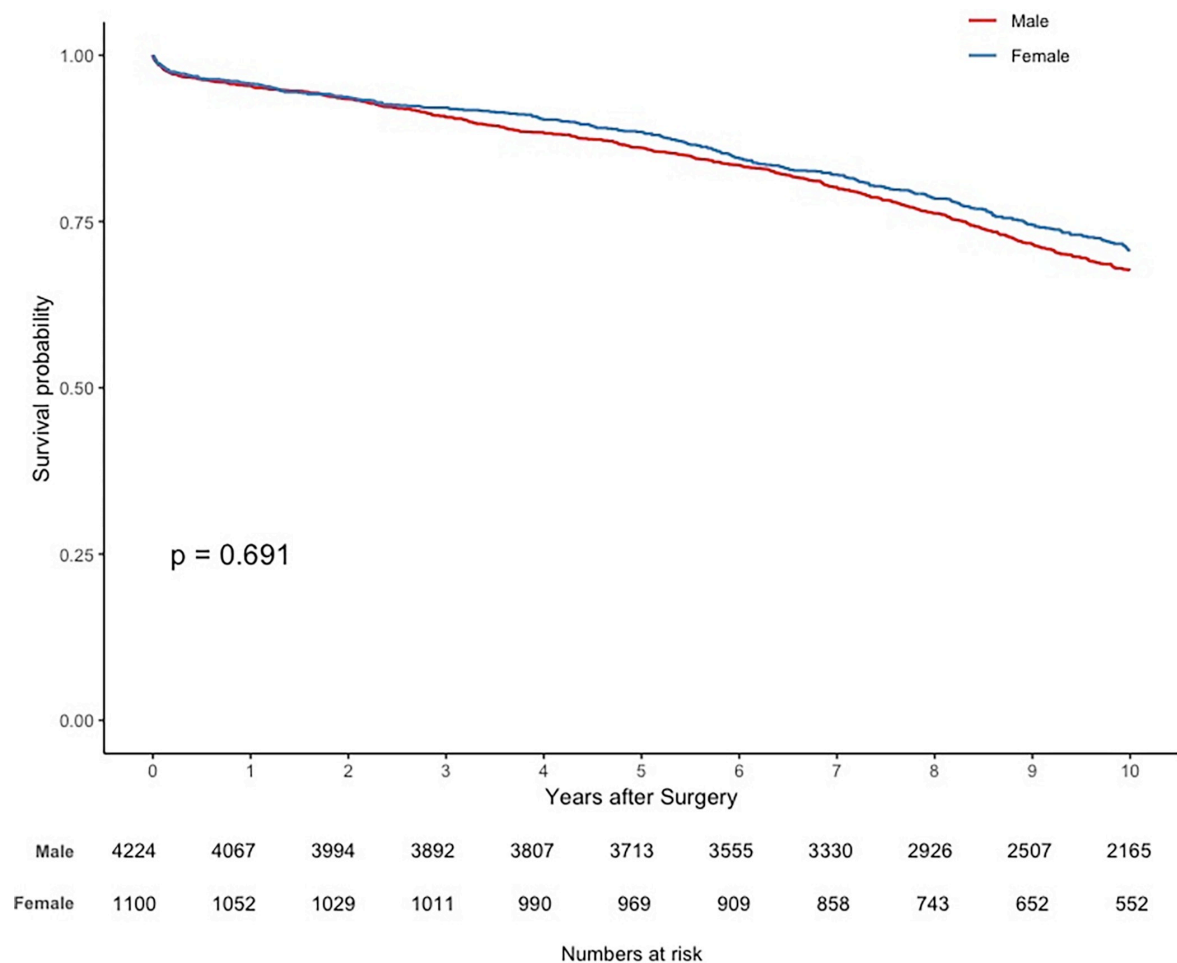


Fig 6. Overlap weighted survival function plot. Adjusted survival function: male vs female.

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Likewise, Piña et al., from the STICH trial, relate similar all-cause mortality, cardiovascular mortality, and the composite of all-cause mortality or cardiovascular hospitalization, although the small representativeness of women (12%) in the study population [11]. On the other hand, a meta-analysis of 20 observational studies with nearly one million patients (29% women) reported higher mortality in women after CABG at a 5-year follow-up [8]. This result was consistent in the subgroup analysis of prospective and propensity score matching data.

Several observational studies reported higher 30-day mortality rates in women [26–30]. We could not confirm this result based on our data in line with other studies [2, 31–33]. The unadjusted and the overlap weighted cohorts presented similar in-hospital mortality rates. Moreover, our reported in-hospital mortality rates are significantly inferior to those reported in the previously cited meta-analysis [8].

As documented in other series, women represented about 25% of patients undergoing CABG from 2000 to 2015 [25, 33]. Whether this might represent a referral bias is not supported by our data. Women often present atypical symptoms of myocardial infarction, with

attending delays in hospital admission [1]. This should translate in an increased proportion of unscheduled procedures (urgent or emergent), which is contrary to our findings.

There are several limitations to our study. First, although using administrative databases allows for the efficient assessment of large populations over long periods, coding practices were developed for reimbursement issues, not for clinical outcome profiling. As such, imprecise or equivocal definitions may compromise coding accuracy. Additionally, surgical risk models are usually based on a limited number of crucial clinical variables that are typically unavailable in administrative databases [34].

Second, we employed OW to restrict confounding by indication, emphasizing patients with the most overlap in their observed characteristics [12]. Nevertheless, propensity score-based methodologies do not consider factors that are not analyzed, such as patients' frailty, quality of coronary artery targets, quality of venous and arterial conduits, or secondary prevention after CABG. Only a prospective randomized trial, where the distribution of known and unknown confounders would be similar in both the intervention and control groups, could address these issues.

Third, although demonstrating that the gap in CABG outcomes between sexes is narrowing, it would be highly relevant to understand its underlying mechanisms thoroughly.

Our results have important implications for clinical practice, as they might imply a revision of traditional risk scores, which continue to weigh the variable female sex significantly. Furthermore, pursuing an aggressive and timely diagnostic work-up and implementing an adequate revascularization strategy, using multiple arterial grafts and striving for complete revascularization could improve immediate and long-term results in female patients.

Conclusion

In this longitudinal, population-level analysis of patients undergoing primary, isolated CABG, we demonstrated that the female sex is not associated with increased long-term all-cause mortality compared to their male counterparts. Thus, sex should not influence the undertaking of an adequate revascularization strategy.

Supporting information

S1 Table. International Classification of Diseases, 9th Edition, Clinical Modification codes of the conditions defined as exclusion criteria.

(DOCX)

S2 Table. International Classification of Diseases, 9th Edition, Clinical Modification codes of the conditions defined as covariates.

(DOCX)

S3 Table. International Classification of Diseases, 9th Edition, Clinical Modification codes of the conditions defined as outcomes.

(DOCX)

S1 File. Minimal anonymized data set.

(CSV)

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Author Contributions

Conceptualization: Armando Abreu.

Data curation: Armando Abreu.

Formal analysis: Armando Abreu.

Methodology: Armando Abreu.

Software: Armando Abreu.

Writing – original draft: Armando Abreu.

Writing – review & editing: Armando Abreu, José Máximo, Adelino Leite-Moreira.

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7.1. Background

In 2016, nearly 2 billion adults were overweight, of whom over 650 million were obese [427]. Obesity is associated with numerous adverse cardiovascular health effects. Specifically, it represents one of the major risk factors for hypertension, diabetes mellitus, heart failure and coronary heart disease [428, 429]. Nevertheless, various lines of clinical investigation suggest the existence of an obesity paradox in which overweight and obese patients with established cardiovascular diseases tend to have a more favourable short- and long-term prognosis [83, 430].

7.2. Problem Statement and Knowledge Gap

Within this conceptual structure, several studies reported an obesity paradox in patients with established coronary artery disease undergoing coronary artery bypass grafting (CABG) [431–440]. In a 2016 meta-analysis reporting on nearly 80 000 patients, Takagi and Umemoto [441] documented the overweight, but not obesity, association with better short-term and mid-to-long-term post-CABG survival relative to normal weight. Additionally, Schwann et al. [11] identified a partial obesity paradox among overweight and mildly obese patients in a retrospective analysis of over 7000 CABG patients. On the other hand, Masoudkabar et al. [442] highlighted obesity as an independent risk factor for worse outcomes, namely 5-year all-cause mortality and major adverse cardiac and cerebrovascular events in a 17 751 isolated CABG sample. Therefore, it seems unclear whether an obesity paradox exists after coronary surgery and how increasing body mass index (BMI) affects these patients' long-term survival.

7.3. Research Objectives

This article aims to explore the influence of BMI on the long-term mortality of patients undergoing primary isolated CABG. Additionally, within a competing risk framework, it seeks to uncover whether any discrepancy found could be attributable to cardiovascular or noncardiovascular causes [416].

7.4. Reader's Note

The subsequent section of this chapter reproduces the full text of the study, "Body mass index effect on long-term survival after coronary artery bypass surgery: a competing risk analysis", by Armando Abreu, José Máximo, Francisca Saraiva, and Adelino Leite-Moreira [443] and published in *Interdisciplinary CardioVascular and Thoracic Surgery (ICVTS)* (2023). The paper has been included with the publisher's permission under the terms of the Creative Commons Attribution License.

For proper citation, please refer to the original publication: Abreu, A., Máximo, J., Saraiva, F., & Leite-Moreira, A. (2023). Body mass index effect on long-term survival after coronary artery bypass surgery: a competing risk analysis. *Interdisciplinary cardiovascular and thoracic surgery*, 37(3), ivad161. DOI: 10.1093/icvts/ivad161.

7.5. Original Publication

The full text of the study, titled "Body mass index effect on long-term survival after coronary artery bypass surgery: a competing risk analysis", is included in the following pages.

Cite this article as: Abreu A, Máximo J, Saraiva F, Leite-Moreira A. Body mass index effect on long-term survival after coronary artery bypass surgery: a competing risk analysis. Interdiscip CardioVasc Thorac Surg 2023; doi:10.1093/icvts/ivad161.

Body mass index effect on long-term survival after coronary artery bypass surgery: a competing risk analysis

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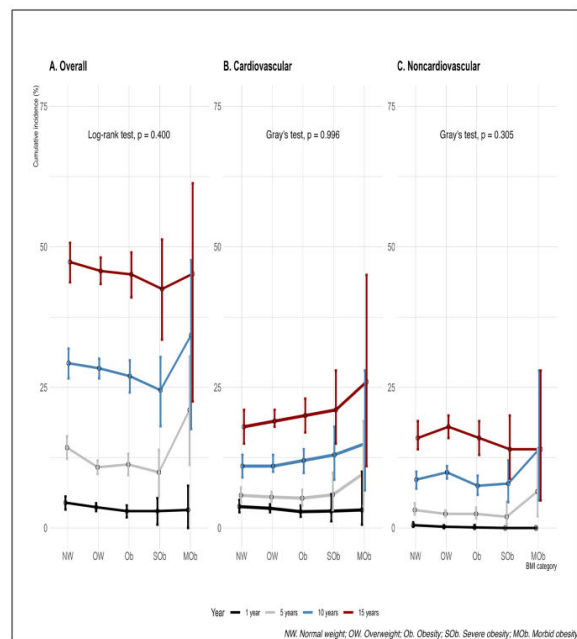
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Body Mass Index Effect on Long-term Survival after Coronary Artery Bypass Surgery

Summary

In a retrospective study of 5242 consecutive patients with BMI over 18.5 kg/m² undergoing primary isolated coronary artery bypass surgery from 2000 to 2015, we analysed long-term overall and cause-specific mortality. We could not demonstrate in-between category differences when the BMI was forced as a categorical variable (using WHO predefined cutoffs).



Legend: Cumulative incidence functions at 1, 5, 10, and 15 years (BMI, Body Mass Index; NW, Normal Weight; Ob, Obesity; OW, Overweight; MOb, Morbid Obesity; SOb, Severe Obesity; WHO, World Health Organization)

Abstract

OBJECTIVES: The aim of this study was to investigate the presence of an obesity paradox on the long-term mortality of patients undergoing primary isolated coronary artery bypass surgery and to uncover whether any discrepancy found could be attributable to cardiovascular or noncardiovascular causes.

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METHODS: Retrospective analysis of 5242 consecutive patients with body mass index (BMI) over 18.5 kg/m² undergoing primary isolated coronary artery bypass surgery, performed from 2000 to 2015, in a Portuguese level III Hospital. The primary end point was long-term all-cause mortality. Secondary outcomes were long-term cause-specific mortality (cardiovascular and noncardiovascular). We fitted overall, and cause-specific hazard models, with BMI forced both as a categorical (using World Health Organization predefined cutoffs) and as a continuous variable.

RESULTS: Follow-up was 99.7% complete. The median follow-up time was 12.79 years (interquartile range, 9.51–16.61). The cumulative incidence functions failed to uncover any difference in 15-year all-cause (log-rank test, $P = 0.400$), cardiovascular (Gray's test, $P = 0.996$) and noncardiovascular mortality (Gray's test, $P = 0.305$) between BMI categories. Likewise, extensive multivariable-adjusted Cox regression and cause-specific hazards models failed to demonstrate in-between category differences, with BMI forced as a categorical variable. On the other hand, using BMI as a continuous variable, the model identified the optimal BMI as between 25.8 and 30.3 kg/m² (nadir around 28.9 kg/m²), albeit this was dependent on the definition of the reference value.

CONCLUSIONS: In this longitudinal, population-level analysis of patients undergoing isolated primary coronary artery bypass grafting, we could not attest to any protective effect of obesity on long-term survival.

Keywords: Coronary artery bypass surgery • Atherosclerosis • Obesity • Survival analysis

ABBREVIATIONS

BMI	Body mass index
CABG	Coronary artery bypass grafting
CI	Confidence interval
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification

INTRODUCTION

In 2016, nearly 2 billion adults were overweight, of whom over 650 million were obese [1]. Obesity is associated with numerous adverse cardiovascular health effects. Specifically, it represents one of the major risk factors for hypertension, diabetes mellitus, heart failure and coronary heart disease [2, 3]. Nevertheless, various lines of clinical investigation suggest the existence of an obesity paradox in which overweight and obese patients with established cardiovascular diseases tend to have a more favourable short- and long-term prognosis [4, 5].

Within this conceptual structure, several studies reported an obesity paradox in patients with established coronary artery disease undergoing coronary artery bypass grafting (CABG) [6–15]. In a 2016 meta-analysis reporting on nearly 80 000 patients, Takagi and Umemoto [16] documented the overweight, but not obesity, association with better short-term and mid-to-long-term post-CABG survival relative to normal weight. Additionally, Schwann *et al.* [11] identified a partial obesity paradox among overweight and mildly obese patients in a retrospective analysis of over 7000 CABG patients. On the other hand, Masoudkabar *et al.* [17] highlighted obesity as an independent risk factor for worse outcomes, namely 5-year all-cause mortality and major adverse cardiac and cerebrovascular events in a 17 751 isolated CABG sample. Therefore, it seems unclear whether an obesity paradox exists after coronary surgery and how increasing body mass index (BMI) affects these patients' long-term survival.

This article aims to explore the influence of BMI on the long-term mortality of patients undergoing primary isolated CABG. Additionally, within a competing risk framework, it seeks to uncover whether any discrepancy found could be attributable to cardiovascular or noncardiovascular causes [18].

METHODS

Ethics

The São João University Hospital Center Ethics Committee approved this research (ID Number 279-13, 25th October 2013) and waived the need for informed consent due to the study's retrospective nature.

Study design

This study was a retrospective analysis of an administrative dataset containing all hospitalizations occurring in a level III hospital (Centro Hospitalar Universitário São João, Porto, Portugal). We included patients undergoing primary isolated CABG, from 1 January 2000 to 30 September 2015 (chosen as the cutoff date because of International Classification of Diseases, Tenth Revision, Clinical Modification implementation).

Study population

Patients were included in the study if they underwent primary isolated coronary artery bypass surgery [International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 3610, 3611, 3612, 3613, 3614, 3615, 3616, 3617 or 3619] during the study period. The dataset was then linked with a clinical database to extract each patient's weight and height to allow computation of their BMI. Exclusion criteria included: BMI <18.5 kg/m²; previous cardiac surgery (ICD-9-CM codes V433 and V4581); concomitant valve replacement or repair (ICD-9-CM codes 3510, 3511, 3512, 3513, 3514, 3520, 3521, 3522, 3523, 3524, 3525, 3526, 3527, 3528 and 3533); concurrent aorta surgery (ICD-9-CM codes 3804, 3814, 3834, 3844, 3845 and 3864); and simultaneous correction of myocardial infarction mechanical complications (ICD-9-CM codes 41410, 4295, 4296, 42971 and 42979).

Data sources and variables

From the selected patients, the corresponding diagnoses and procedures were coded for each hospitalization based on the ICD-9-CM. Patients' preoperative BMI, the predictive or independent variable, was treated both as a categorical variable [using

WHO predefined cutoffs: normal weight (18.50 < BMI < 24.99), overweight (25.00 < BMI < 29.99), obesity (30.00 < BMI < 34.99), severe obesity (35.00 < BMI < 39.99) and morbid obesity (BMI $\geq$ 40.00)] and as a continuous variable. Other baseline characteristics were extracted from our Institution's patient discharge datasets [19]. After obtaining the relevant ICD-9-CM codes, we computed the Charlson Comorbidity Index using the Quan *et al.* [20] coding scheme. Definitions of coexisting conditions in Supplementary Material, Table S1.

Outcomes

The primary outcome variable was long-term all-cause mortality. The discharge dataset, through individual Social Security numbers, allowed linkage to the National Patient Registry (RNU) to ascertain patient life status. Secondary outcomes were long-term cause-specific mortality (cardiovascular and noncardiovascular). Interrogation of the Death Certificate Information System elucidated the cause of death. Allocation to the cardiovascular category ensued in patients whose primary cause of death was cardiovascular, cerebrovascular or peripheral vascular diseases. Noncardiovascular mortality resulted from all other diagnoses. Finally, all-cause mortality included these cardiovascular and noncardiovascular components and those patients without any specified diagnosis (unknown cause of death).

Statistical analysis

Continuous variables were summarized using mean and standard deviation. Categorical variables were summarized using frequencies and percentages. Student's *t*-tests with pooled standard deviation allowed pairwise comparisons between group levels taking normal weight as the reference category. χ^2 -test or Fisher exact test (when values with expected counts below 5 were <20%) permitted pairwise comparisons between group levels assuming normal weight as the reference category. Finally, we employed Benjamini and Hochberg method to correct for multiple testing.

To clarify between-group differences in in-hospital mortality, we fitted a univariable logistic regression model with in-hospital death as the dependent variable and the BMI category as the only independent predictor.

For time-to-event outcomes, using the Kaplan–Meier method provided estimates of overall survival probabilities. Additionally, Kaplan–Meier curves can indicate an unusual pattern suggesting non-proportional hazards. Follow-up time, described by median and interquartile range, was obtained using the same estimator by reversing the event indicator so that the outcome of interest became being censored.

The cumulative incidence function is a valuable summary statistic for analysing competing risk data. Therefore, we estimated the cumulative incidences of cardiovascular and noncardiovascular death and the composite outcome of all-cause mortality in the overall sample and stratified by BMI category by modelling the cause-specific hazard function of all individual causes. Gray's test compares the cumulative incidence function directly.

We fitted overall and cause-specific hazard models, with BMI forced both as a categorical and continuous variable. These Cox proportional hazards regression models relate the hazard function to a set of additional covariates: baseline characteristics (age, sex, admission type, disease presentation, hypertension, diabetes mellitus, hyperlipidaemia, smoking status, previous stroke,

congestive heart failure, peripheral vascular disease, chronic obstructive pulmonary disease, chronic kidney disease, liver disease and preoperative anemia) and procedural details (use of cardiopulmonary bypass, number of internal mammary artery grafts, and total number of grafts). To avoid violations of the proportional hazard assumption, we graphed the continuous explanatory variables against martingale residuals of the null Cox proportional hazards model to explore the functional form of continuous variables. Stratification by nuisance categorical variables, as demonstrated by plots of scaled Schoenfeld residuals, was an additional strategy for dealing with a proportional hazards assumption violation. Finally, we used the Grambsch–Therneau test to evaluate the proportional hazards assumption for the Cox regression model fit.

The graphical display of the effect of BMI, both as a categorical and as a continuous variable, followed the methodology described by Terry Therneau [21].

All the tests of the exposure effect were two-tailed with an alpha threshold of 0.05. All statistical analyses were performed using R software, version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria) [22–28].

RESULTS

The study population comprised 5242 patients: 1211 (23.1%) in the normal weight group, 2723 (51.9%) in the overweight group, 1043 (19.9%) in the obese group, 203 (3.9%) in the severely obese group and 62 (1.2%) in the morbidly obese group. Figure 1A offers a histogram of preoperative BMI. Figure 1B provides a standard Kaplan–Meier curve of post-CABG survival for these patients.

Descriptive statistical analyses

Table 1 presents descriptive statistics for patients in the study population. Regarding traditional atherosclerosis risk factors, with the increasing BMI group, there was a consistent rise in the prevalence of hypertension [normal weight, 684 (56.5%), the reference; overweight, 1857 (68.2%), $P < 0.001$; obese, 785 (75.3%), $P < 0.001$; severely obese, 156 (76.8%), $P < 0.001$; and morbidly obese, 47 (75.8%), $P = 0.008$], diabetes mellitus [normal weight, 372 (30.7%), the reference; overweight, 1055 (38.7%), $P < 0.001$; obese, 479 (45.9%), $P < 0.001$; severely obese, 102 (50.3%), $P < 0.001$; and morbidly obese, 21 (33.8%)] and hyperlipidaemia [normal weight, 655 (54.1%), the reference; overweight, 1778 (65.3%), $P < 0.001$; obese, 717 (68.7%), $P < 0.001$; severely obese, 144 (70.9%), $P < 0.001$; and morbidly obese, 46 (74.2%), $P = 0.007$]. Contrastingly, current smoking status followed a uniform decline with increasing BMI group [normal weight, 280 (23.1%), the reference; overweight, 463 (17.0%), $P < 0.001$; obese, 129 (12.4%), $P < 0.001$; severely obese, 23 (11.3%), $P < 0.001$; and morbidly obese, 8 (12.9%), $P = 0.287$].

Of note, no differences concerning technical details of the surgical procedure were discernible between groups.

In-hospital mortality

Overall, in-hospital mortality was 1.56% (82 patients died in the index episode). Compared to normal-weight patients, there was no difference in unadjusted in-hospital mortality across BMI

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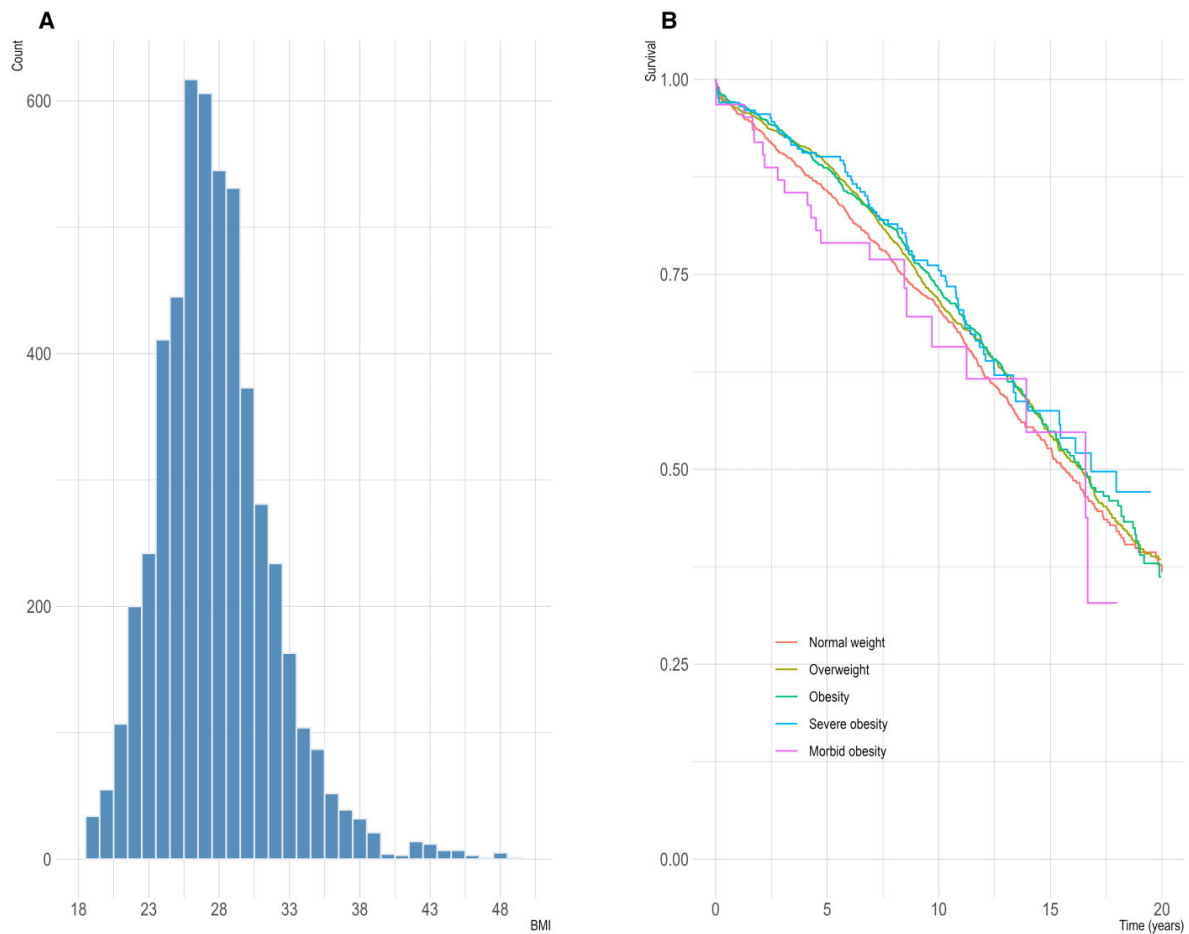


Figure 1: (A) Histogram of preoperative body mass index. (B) Standard Kaplan-Meier curve of post-surgery survival.

categories: the odds ratio for in-hospital mortality was 1.69 [95% confidence interval (CI) 0.91–3.12; $P=0.095$] in overweight patients, 1.25 (95% CI, 0.59–2.68; $P=0.559$) in obese patients, 2.33 (95% CI, 0.82–6.60; $P=0.112$) in severely obese patients and 1.51 (95% CI, 0.19–11.74; $P=0.693$) in morbidly obese patients.

Cumulative incidence functions

Follow-up was 99.7% complete (15 patients were lost to follow-up). The median follow-up time was 12.79 years (interquartile range, 9.51–16.61). A total of 2054 deaths (39.2%) were documented overall: cardiovascular causes accounted for 881 (16.8%), noncardiovascular causes 730 (13.9%) and unknown causes 445 (8.5%).

Figure 2 portrays the cumulative incidences of cardiovascular and noncardiovascular death in the study population, along with the incidence of the composite outcome of all-cause mortality, stratified by the BMI group. As exposed in Fig. 3, there was no difference in 15-year all-cause mortality between BMI categories (log-rank test, $P=0.400$): 47.3% (95% CI 43.7–50.7%) in the normal weight group, 45.7% (95% CI, 43.3–48.1%) in overweight patients, 45.1% (95% CI, 41.0–49.0%) in obese patients, 42.5%

(95% CI, 33.5–51.3%) in severely obese patients and 45.2% (95% CI, 22.5–61.3%) in morbidly obese patients.

When accounting for competing risks, there was no difference in the 15-year cumulative incidence for cardiovascular death between BMI categories (Gray's test, $P=0.996$): 18% (95% CI, 15–21%) in the normal weight group, 19% (95% CI, 18–21%) in overweight patients, 20% (95% CI, 17–23%) in obese patients, 21% (95% CI, 15–28%) in severely obese patients and 26% (95% CI, 11–45%) in morbidly obese patients.

Likewise, there were no between-group differences at 15 years of follow-up in noncardiovascular mortality (Gray's test, $P=0.305$): 16% (95% CI, 14–19%) for the normal weight, 18% (95% CI, 16–20%) for the overweight, 16% (95% CI, 13–19%) for the obese, 14% (95% CI, 8.8–20%) for the severely obese and 14% (95% CI 4.9–28%) for morbidly obese patients.

Cause-specific hazard models

Modelling BMI as a categorical variable. The univariable analysis failed to demonstrate the impact of the BMI category (considering normal weight as the reference category) on overall all-cause mortality (Fig. 4). Likewise, the cause-specific hazard

Table 1: Baseline characteristics per body mass index category

Characteristic	Normal weight (n = 1211)	Overweight (n = 2723)		Obesity (n = 1043)		Severe obesity (n = 203)		Morbid obesity (n = 62)	
Age, n (%)	64.1 (10.4)	63.8 (9.9)	0.318	63.6 (9.5)	0.169	62.6 (9.0)	0.027	64.1 (9.9)	0.863
Female sex, n (%)	224 (18.5)	475 (17.4)	0.502	284 (27.2)	<0.001	81 (39.9)	<0.001	18 (29.0)	0.083
Admission, n (%)			0.054		0.027		0.554		0.556
Scheduled	518 (42.8)	1286 (47.2)		513 (48.2)		94 (46.3)		23 (37.1)	
Unscheduled	693 (57.2)	1437 (52.8)		530 (50.8)		109 (53.7)		39 (62.9)	
Disease presentation, n (%)			0.018		0.026		0.616		0.317
Chronic CAD	732 (60.4)	1765 (64.8)		673 (64.5)		125 (61.6)		45 (72.6)	
UA/NSTEMI	328 (27.1)	712 (26.1)		283 (27.1)		59 (29.1)		14 (22.6)	
STEMI	151 (12.5)	246 (9.0)		87 (8.3)		19 (9.4)		3 (4.8)	
Hypertension, n (%)	684 (56.5)	1857 (68.2)	<0.001	785 (75.3)	<0.001	156 (76.8)	<0.001	47 (75.8)	0.008
Diabetes mellitus, n (%)			<0.001		<0.001		<0.001		0.789
Non-insulin-treated	334 (27.6)	921 (33.8)		404 (38.7)		84 (41.4)		19 (30.6)	
Insulin treated	38 (3.1)	134 (4.9)		75 (7.2)		18 (8.9)		2 (3.2)	
Hyperlipidaemia, n (%)	655 (54.1)	1778 (65.3)	<0.001	717 (68.7)	<0.001	144 (70.9)	<0.001	46 (74.2)	0.007
Smoking history, n (%)			<0.001		<0.001		<0.001		0.287
Never smoked	671 (55.4)	1617 (59.4)		699 (67.0)		147 (72.4)		39 (62.9)	
Former smoker	260 (21.5)	643 (23.6)		215 (20.6)		33 (16.3)		15 (24.2)	
Current smoker	280 (23.1)	463 (17.0)		129 (12.4)		23 (11.3)		8 (12.9)	
Body mass index, n (%)	23.02 ± 1.47	27.31 ± 1.38		31.78 ± 1.30		36.56 ± 1.31		44.83 ± 4.18	
Previous stroke, n (%)	15 (1.2)	28 (1.0)	1.000	7 (0.7)	1.000	1 (0.5)	1.000	0 (0.0)	1.000
Congestive heart failure, n (%)	237 (19.6)	513 (18.8)	0.776	207 (19.8)	0.912	45 (22.2)	0.776	10 (16.1)	0.776
Peripheral vascular disease, n (%)	128 (10.6)	218 (8.0)	0.051	69 (6.6)	0.001	13 (6.4)	0.203	2 (3.2)	0.203
Chronic obstructive pulmonary disease, n (%)	101 (8.3)	173 (6.4)	0.252	81 (7.8)	0.917	16 (7.9)	1.000	3 (4.8)	0.917
Chronic kidney disease, n (%)			0.346		0.346		0.346		1.000
Non-dialysis dependent	65 (5.4)	128 (4.7)		43 (4.1)		15 (7.4)		2 (3.2)	
Dialysis dependent	14 (1.2)	16 (0.6)		4 (0.4)		0 (0.0)		0 (0.0)	
Liver disease, n (%)	34 (2.8)	55 (2.0)	0.660	16 (1.5)	0.447	5 (2.5)	1.000	1 (1.6)	1.000
Anaemia, n (%)	148 (12.2)	228 (8.4)	0.001	79 (7.6)	0.001	26 (12.8)	0.818	3 (4.8)	0.173
Charlson comorbidity index, n (%)	4.29 (1.76)	4.20 (1.67)	0.108	4.23 (1.57)	0.326	4.22 (1.61)	0.579	3.92 (1.37)	0.098
Cardiopulmonary bypass, n (%)			0.714		0.714		0.714		0.714
Off-pump	440 (36.4)	1012 (37.2)		409 (39.2)		80 (39.4)		20 (32.3)	
On-pump	771 (63.7)	1711 (62.8)		634 (60.8)		123 (60.6)		42 (67.7)	
Internal mammary artery, n (%)			0.977		0.611		0.611		0.611
None	34 (2.8)	75 (2.8)		22 (2.1)		10 (4.9)		1 (1.6)	
Single	855 (70.6)	1930 (70.9)		731 (70.1)		144 (70.9)		40 (64.5)	
Bilateral	322 (26.6)	718 (26.4)		290 (27.8)		49 (24.1)		21 (33.9)	
Number of grafts, n (%)	2.54 (0.81)	2.52 (0.86)	0.712	2.51 (0.89)	0.618	2.44 (0.86)	0.314	2.31 (0.97)	0.214

CAD: coronary artery disease; NSTEMI: non-ST elevation myocardial infarction; STEMI: ST elevation myocardial infarction; UA: unstable angina.

models for cardiovascular and noncardiovascular death failed to prove significant differences among BMI categories. These results were consistent after extensive multivariable adjustment of the Cox regression model and the cause-specific hazards models. The Grambsch-Therneau test ($P=0.152$) excluded violations of the proportional hazards assumption for the Cox regression model fit.

Modelling BMI as a continuous variable. Treating BMI as a continuous non-linear variable did not substantiate the categorical analysis (Fig. 5). BMI specification as a penalized spline basis with 3 degrees of freedom was input to the univariable Cox regression model. This strategy highlighted a reduction in the hazard of all-cause mortality for BMI between 24.9 and 35.7 kg/m² (nadir around 32.7 kg/m²). This reduction appeared to take place

at the cost of reduced cardiovascular mortality. The reference point used was the median value in the normal weight category (23.4 kg/m²).

After comprehensive multivariable adjustment, the model identified the optimal BMI as between 25.8 and 30.3 kg/m² (nadir around 28.9 kg/m²). Again, this reduction seemed to occur at the expense of diminished cardiovascular mortality. The Grambsch-Therneau test ($P=0.139$) excluded violations of the proportional hazards assumption for the Cox regression model fit.

DISCUSSION

In this longitudinal, population-level analysis of patients undergoing isolated primary CABG, we could not attest to any protective effect of obesity on long-term survival. Although forcing BMI

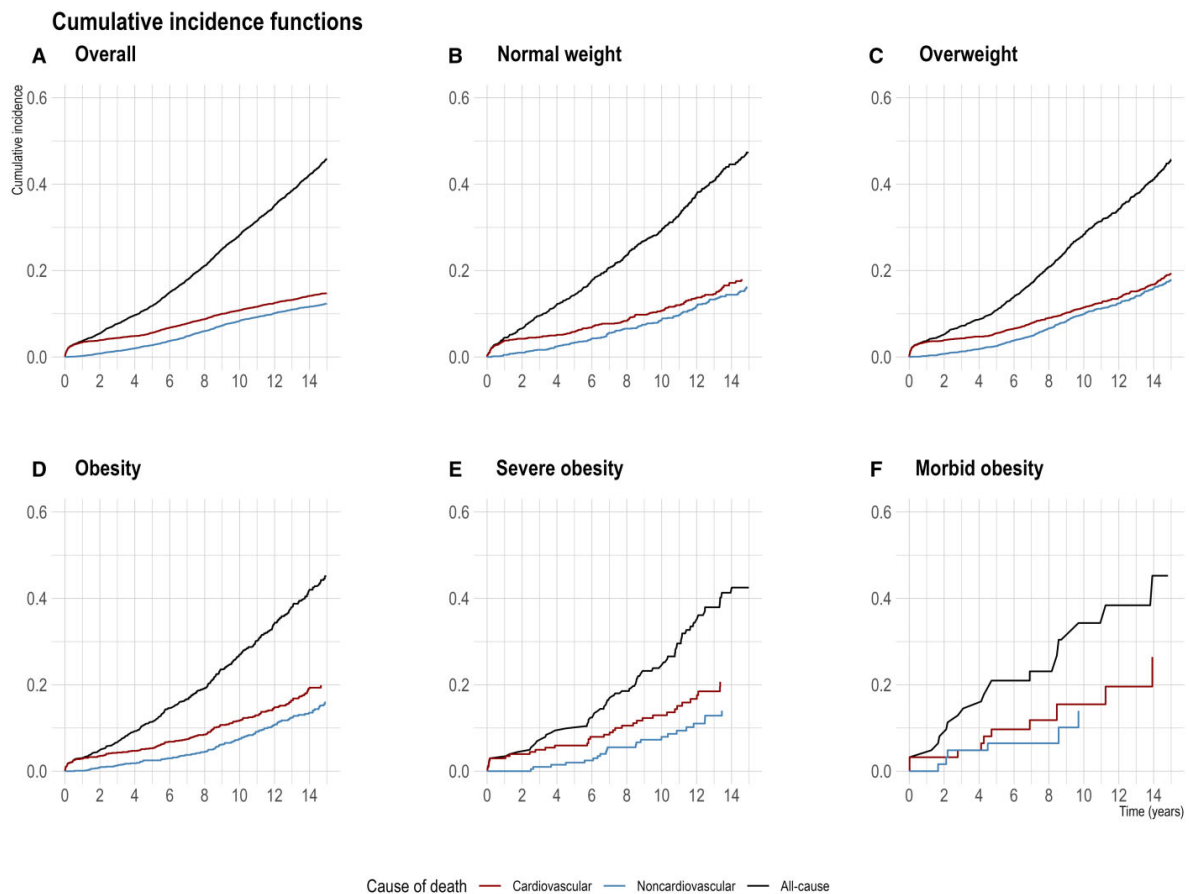


Figure 2: Fifteen-year cumulative incidence functions exhibiting all-cause and cause-specific mortality for the entire cohort and each of the individual body mass index categories. (A) Overall; (B) normal weight; (C) overweight; (D) obesity; (E) severe obesity; and (F) morbid obesity.

as a continuous variable into the model allowed for identifying the optimal BMI as between 25.8 and 30.3 kg/m² (nadir around 28.9 kg/m²), we should recognize that this depended on the definition of the reference value.

A possible explanation for our results might be that the relation of BMI to the long-term hazard of death is significantly non-linear. Modelling BMI as a spline allows us to accommodate this relationship freely. As pointed out by Filardo *et al.* [29], spline smoothing functions provide an efficient approach to dealing with continuous variables, avoiding the risks inherent in the assumptions about the shape of the association between a continuous variable and an outcome when forced into a categorization strategy. Additionally, how the curve is centred is a critical next step. Due to the markedly negative skew BMI distribution within the normal weight category, it seemed correct to centre the curve in the median BMI value of the normal weight strata. Choosing other values, for instance, 18.5 kg/m² (the lower limit of the normal weight category) or 21.75 kg/m² (the centre of the normal weight category), should predictably affect our conclusions.

For example, Benedetto *et al.* used 18.5 kg/m² as the centring point for their elegant analysis and identified a BMI of 27–29 kg/m² as significantly protective against late mortality. Applying

the same comparator to our data would determine a BMI of 21.9–36.1 kg/m² (nadir 28.9 kg/m²) as protective for long-term mortality.

Another issue relates to model definition. The proportional hazards model estimates an average hazard over time, and its use is often reasonable in a clinical setting. One straightforward extension to deal with gross violations of nonproportionality is a step function for $\beta(t)$, i.e. different coefficients over different time intervals. Schwann *et al.* [11] employed this approach, and their results are consistent with ours: they identified a BMI between 28.5 and 29.0 kg/m² associated with the best outcomes.

A pooled analysis of 14 studies, including nearly 80 000 patients, exposed the overweight, but not obesity, association with better short-term and long-term post-CABG survival compared to normal weight [16]. Despite the results of our study of BMI as a continuous variable agreeing with this conclusion, we could not demonstrate such a relationship in the categorical variable analysis. This absence of difference among the various categories of BMI could also be related to insufficient sample size, as transforming continuous to categorical variables always leads to some information loss. Accordingly, the sample size might limit the ability to draw more definitive conclusions.

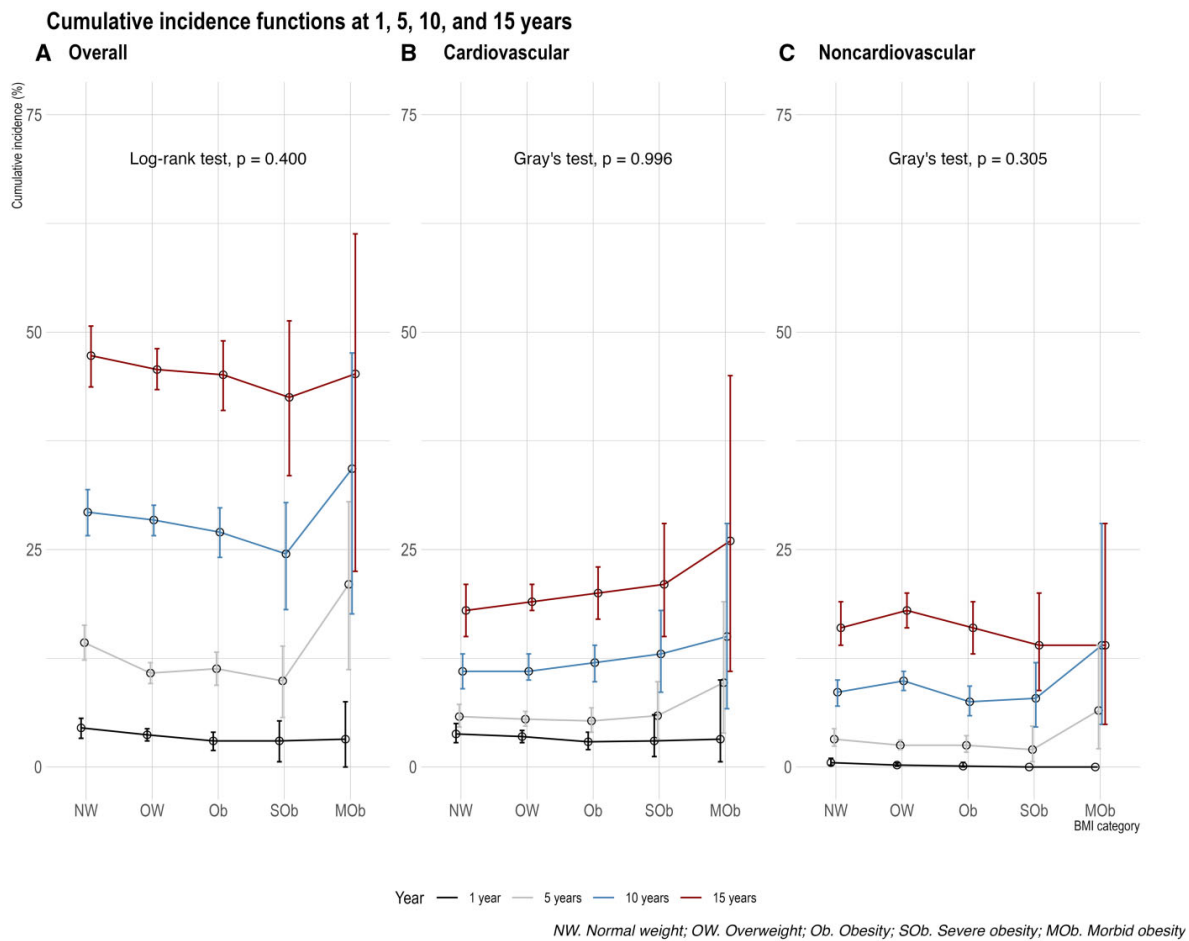


Figure 3: Cumulative incidence functions, expressed as percentages, displaying all-cause and cause-specific mortality for the entire cohort and each of the individual body mass index categories, at 1, 5, 10 and 15 years. (A) Overall mortality; (B) cardiovascular mortality; and (C) noncardiovascular mortality.

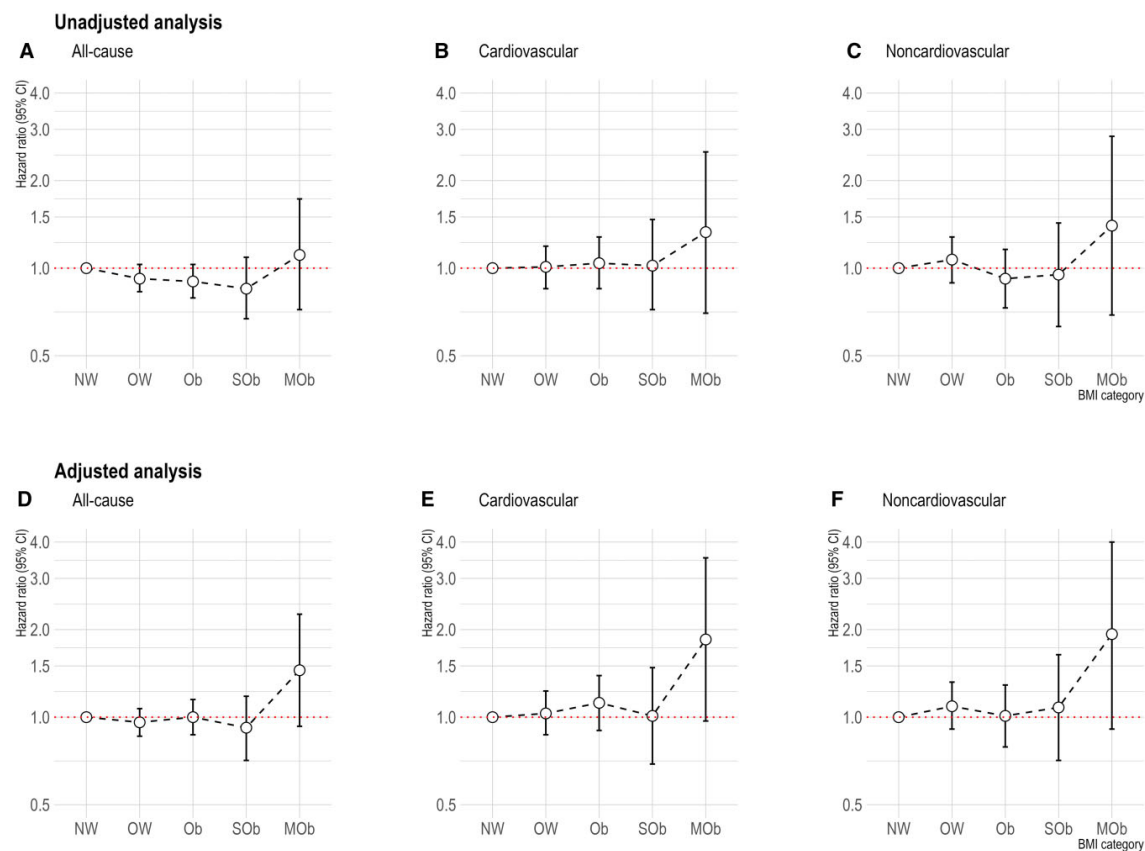
Limitations

The present study does present some limitations. First, we used the BMI as a surrogate measure of obesity. Nevertheless, we should acknowledge it as an imperfect measure of bodily adiposity since it cannot discriminate between fat and lean mass [30, 31]. Other body fat indices, such as waist circumference, proved more accurate [32–34]. Second, all our analyses focus on the weight and height at a particular point in time, i.e., the day of surgery. Beyond precision issues related to these measurements, we did not account for their dynamic nature. With a follow-up period that exceeds twenty years in some patients, we should anticipate substantial oscillations in the BMI. As De Schutter *et al.* [35] suggest, obese patients, with the help of diet and exercise, might lose weight, thereby improving their cardiorespiratory fitness and changing their prognosis. We have no data to support this contention. Third, we should acknowledge that the use of death certificate data to disclose the cause of death is highly unreliable, with nearly 50% lacking agreement with autopsy studies. Therefore, one should exercise extreme caution in discussing

the discrepancy in findings between cardiovascular and noncardiovascular causes of mortality [36]. Finally, although intuitively appealing, treating the BMI as a categorical variable creates unbalanced groups with small numbers of patients in specific categories. This problem might conceal distinctive trends in baseline characteristics and not provide adequate power for time-to-event analysis to reveal the existent contrasts. Nevertheless, the unique J-shaped form disclosed in the relationship between the BMI and the hazard of late mortality suggests an increased risk of all-cause and cardiovascular death in the extremes of the distribution.

CONCLUSION

In this longitudinal, population-level analysis of patients undergoing isolated primary CABG, we could not attest to any protective effect of obesity on long-term survival. Furthermore, it strongly associates with traditional atherosclerosis risk factors, which have a powerful impact on long-term survival. Therefore,



NW. Normal weight; OW. Overweight; Ob. Obesity; SOb. Severe obesity; MOb. Morbid obesity

Figure 4: Unadjusted and comprehensive multivariable-adjusted comparison of all-cause and cause-specific mortality across body mass index categories (body mass index forced in the model as a categorical variable). Unadjusted analysis: (A) all-cause mortality; (B) cardiovascular mortality; and (C) noncardiovascular mortality. Adjusted analysis: (D) all-cause mortality; (E) cardiovascular mortality; and (F) noncardiovascular mortality.

obesity management should be considered an integral part of any secondary prevention program directed at coronary artery disease.

SUPPLEMENTARY MATERIAL

Supplementary material is available at ICVTS online.

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Conflict of interest: none declared.

DATA AVAILABILITY

The article's data will be shared on reasonable request to the corresponding author.

Author contributions

Armando Abreu: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Software; Writing—original draft; Writing—review & editing. **José Máximo:** Writing—original draft; Writing—review & editing. **Francisca Saraiva:** Data curation; Writing—review & editing. **Adelino Leite-Moreira:** Funding acquisition; Supervision; Writing—review & editing.

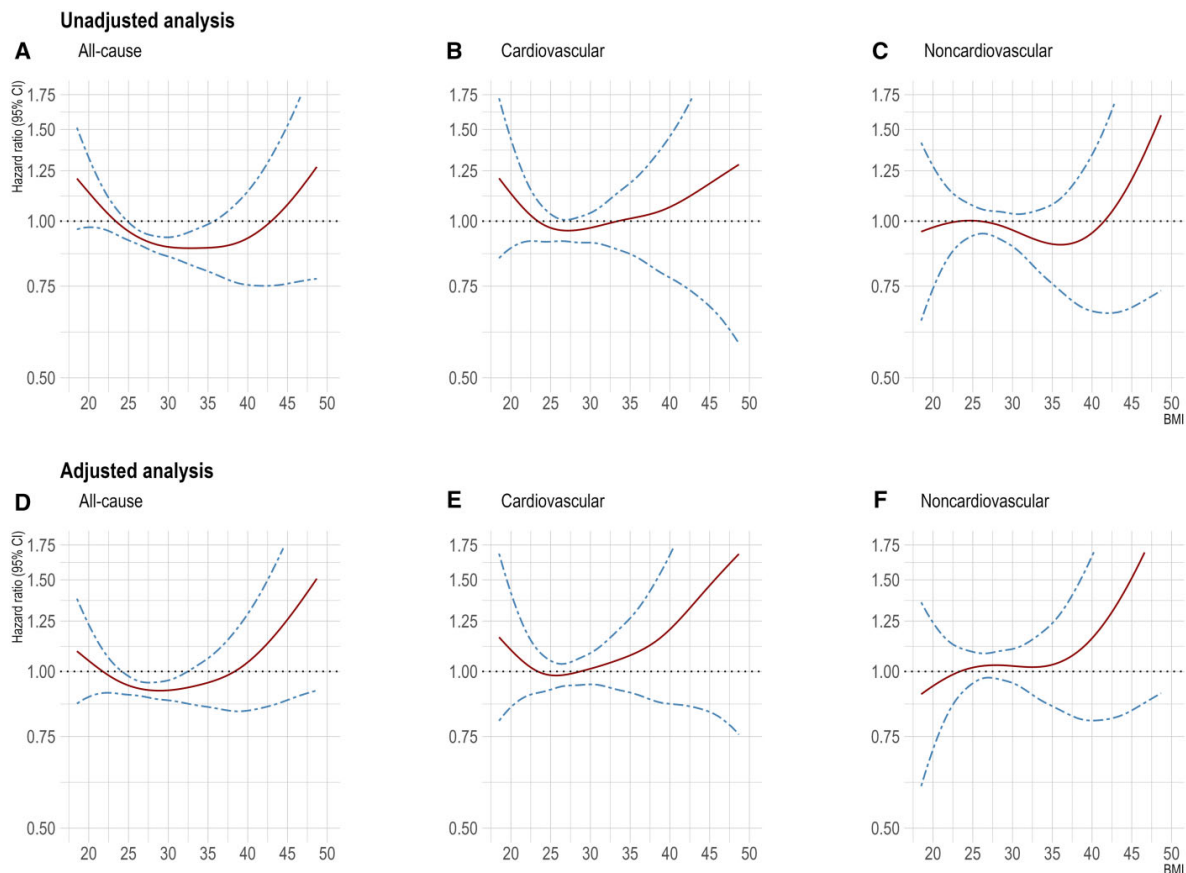


Figure 5: Unadjusted and comprehensive multivariable-adjusted comparison of all-cause and cause-specific mortality along body mass index range (body mass index forced in the model as a continuous variable). Unadjusted analysis: (A) all-cause mortality; (B) cardiovascular mortality; and (C) noncardiovascular mortality. Adjusted analysis: (D) all-cause mortality; (E) cardiovascular mortality; and (F) noncardiovascular mortality.

Reviewer information

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Smoking Status and Survival 8.

8.1. Background

Tobacco consumption is the single largest avoidable health risk, and the most significant cause of premature death in the European Union, responsible for nearly 700 000 deaths every year [444]. It relates to all the processes through which atherosclerosis develops, including endothelial dysfunction, thrombosis, inflammation and abnormal lipid metabolism [70]. Patients with severe coronary artery disease who undergo coronary artery bypass surgery consistently demonstrate that continued smoking after the index procedure increases mortality rates [445]. One potential explanation indicates that smoking may exert its harmful effects through the ongoing chronic process of atherosclerotic progression both in the grafts and the native system. However, it is not clear whether cardiac mortality is primary and solely responsible for the inferior late survival of current smokers.

8.2. Problem Statement and Knowledge Gap

Several observational studies established an association between current smoking status and worse late survival after coronary artery bypass grafting [446–451]. In a meta-analysis of 37 studies including over 125 000 patients, Ma et al. [452] analysed the impact of smoking on all-cause mortality after coronary revascularisation (either a percutaneous coronary intervention or coronary artery bypass graft surgery). They documented that cigarette smokers experienced a 30% increased risk of all-cause mortality during the late follow-up period (over 1 year). On the other hand, they noted no association between smoking and the risk of major adverse cardiovascular events. Therefore, the causes for this excess in late mortality appear currently unknown.

8.3. Research Objectives

The objective of this paper is to investigate the influence of smoking status on long-term mortality in patients undergoing primary isolated coronary artery bypass grafting (CABG). Moreover, within a competing risks framework, it aims to determine the relative contributions of cardiovascular and noncardiovascular causes that might explain any observed differences in mortality rates.

8.4. Reader's Note

The subsequent section of this chapter reproduces the full text of the study, "Body mass index effect on long-term survival after coronary artery bypass surgery: a competing risk analysis", by Armando Abreu, José Máximo, and Adelino Leite-Moreira [453] and published in *European Journal of Cardio-Thoracic Surgery*. (EJCTS) (2024). The paper has been included with the publisher's permission under the terms of the Creative Commons Attribution License.

For proper citation, please refer to the original publication: Abreu, A., Máximo, J., & Leite-Moreira, A. (2024). Preoperative smoking status and long-term survival after coronary artery bypass grafting: a competing risk analysis. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery*, 65(5), ezae183. DOI: 10.1093/ejcts/ezae183.

8.5. Original Publication

The full text of the study, titled "Preoperative smoking status and long-term survival after coronary artery bypass grafting: a competing risk analysis", is included in the following pages.

Cite this article as: Abreu A, Máximo J, Leite-Moreira A. Preoperative smoking status and long-term survival after coronary artery bypass grafting: a competing risk analysis. Eur J Cardiothorac Surg 2024; doi:10.1093/ejcts/ezae183.

Preoperative smoking status and long-term survival after coronary artery bypass grafting: a competing risk analysis

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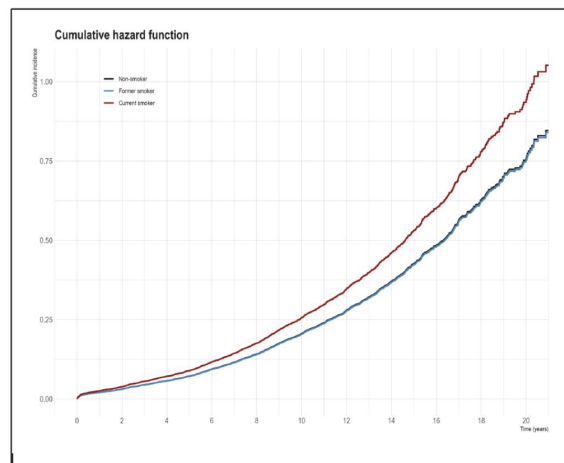
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Preoperative smoking status and long-term survival after coronary artery bypass grafting: a competing-risk analysis

Summary

This longitudinal, population-level analysis emphasises the increase in late all-cause mortality risk in smokers after CABG. On the other hand, ex-smokers (> 1 year) experience identical long-term survival, as compared to patients who never smoked.



Legend: Cumulative hazard function by smoking status. **CABG**, Coronary Artery Bypass Grafting.

Abstract

OBJECTIVES: Patients with severe coronary artery disease who undergo coronary artery bypass grafting consistently demonstrate that continued smoking after surgery increases late mortality rates. Smoking may exert its harmful effects through the ongoing chronic process of atherosclerotic progression both in the grafts and the native system. However, it is not clear whether cardiac mortality is primary and solely responsible for the inferior late survival of current smokers.

METHODS: In this retrospective analysis, we included all consecutive patients undergoing primary isolated coronary artery bypass surgery from 1 January 2000 to 30 September 2015 in an Academic Hospital in Northern Portugal. The predictive or independent variable was the patients' smoking history status, a categorical variable with 3 levels: non-smoker (the comparator), ex-smoker for >1 year (exposure 1) and current smoker (exposure 2). The primary end point was long-term all-cause mortality. Secondary outcomes were long-term cause-specific mortality (cardiovascular and noncardiovascular). We fitted overall and Fine and Gray subdistribution hazard models.

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RESULTS: We identified 5242 eligible patients. Follow-up was 99.7% complete (with 17 patients lost to follow-up). The median follow-up time was 12.79 years (interquartile range, 9.51–16.60). Throughout the study, there were 2049 deaths (39.1%): 877 from cardiovascular causes (16.7%), 727 from noncardiovascular causes (13.9%) and 445 from unknown causes (8.5%). Ex-smokers had an identical long-term survival than non-smokers [hazard ratio (HR) 0.99; 95% confidence interval (CI) 0.88, 1.12; $P = 0.899$]. Conversely, current smokers had a 24% increase in late mortality risk (HR 1.24; 95% CI 1.07, 1.44; $P = 0.004$) as compared to non-smokers. While the current smoker status increased the relative incidence of noncardiac death by 61% (HR 1.61; 95% CI 1.27, 2.05, $P < 0.001$), it did confer a 25% reduction in the relative incidence of cardiac death (HR 0.75; 95% CI 0.59, 0.97; $P = 0.025$).

CONCLUSIONS: Whereas ex-smokers have an identical long-term survival to non-smokers, current smokers exhibit an increase in late all-cause mortality risk at the expense of an increased relative incidence of noncardiac death. By subtracting the inciting risk factor, smoking cessation reduces the relative incidence of cardiac death.

Keywords: Smoking • Coronary artery bypass surgery • Survival analysis

ABBREVIATIONS

CABG	Coronary artery bypass grafting
CI	Confidence interval
HR	Hazard ratio
ICD-9-CM	<i>International Classification of Diseases, Ninth Revision, Clinical Modification</i>
IQR	Interquartile range

INTRODUCTION

Tobacco consumption is the single largest avoidable health risk, and the most significant cause of premature death in the European Union, responsible for nearly 700 000 deaths every year [1]. It relates to all the processes through which atherosclerosis develops, including endothelial dysfunction, thrombosis, inflammation and abnormal lipid metabolism [2]. Patients with severe coronary artery disease who undergo coronary artery bypass surgery consistently demonstrate that continued smoking after the index procedure increases mortality rates [3]. One potential explanation indicates that smoking may exert its harmful effects through the ongoing chronic process of atherosclerotic progression both in the grafts and the native system. However, it is not clear whether cardiac mortality is primary and solely responsible for the inferior late survival of current smokers.

Several observational studies established an association between current smoking status and worse late survival after coronary artery bypass grafting [4–9]. In a meta-analysis of 37 studies including over 125 000 patients, Ma et al. [10] analysed the impact of smoking on all-cause mortality after coronary revascularization (either a percutaneous coronary intervention or coronary artery bypass graft surgery). They documented that cigarette smokers experienced a 30% increased risk of all-cause mortality during the late follow-up period (over 1 year). On the other hand, they noted no association between smoking and the risk of major adverse cardiovascular events. Therefore, the causes for this excess in late mortality appear currently unknown.

The objective of this paper is to investigate the influence of smoking status on long-term mortality in patients undergoing primary isolated coronary artery bypass grafting (CABG). Moreover, within a competing risks framework, it aims to determine the relative contributions of cardiovascular and noncardiovascular causes that might explain any observed differences in mortality rates.

METHODS

Ethics

The São João University Hospital Centre Ethics Committee approved this research (ID Number 279-13, 25 October 2013) and waived the need for informed consent due to the study's retrospective nature. Posteriorly, to include patients operated on between 2013 and September 2015, an addendum was requested and properly accepted by the same committee.

Study design

This study was a retrospective analysis of an administrative dataset containing all hospitalizations in a level III hospital (University Hospital Centre São João, Porto, Portugal). We included patients undergoing primary isolated CABG from 1 January 2000 to 30 September 2015 [chosen as the cut-off date because of International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) implementation].

Study population

Patients were included in the study if they underwent primary isolated coronary artery bypass surgery [International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 3610, 3611, 3612, 3613, 3614, 3615, 3616, 3617, or 3619] during the study period. Exclusion criteria included previous cardiac surgery (ICD-9-CM codes V433 and V4581); concomitant valve replacement or repair (ICD-9-CM codes 3510, 3511, 3512, 3513, 3514, 3520, 3521, 3522, 3523, 3524, 3525, 3526, 3527, 3528 and 3533); concurrent aorta surgery (ICD-9-CM codes 3804, 3814, 3834, 3844, 3845 and 3864); and simultaneous correction of myocardial infarction mechanical complications (ICD-9-CM codes 41410, 4295, 4296, 42971 and 42979).

Data sources and variables

The corresponding diagnoses and procedures were coded for each hospitalization from the selected patients based on the ICD-9-CM. The predictive or independent variable was the patients' smoking history status, a categorical variable with 3 levels, defined by the presence of ICD-9-CM code V1582 (ex-smoker for >1 year, exposure 1) or 3051 (current smoker, exposure 2) or by the absence of any such codes (non-smoker, the comparator). We extracted other relevant baseline

characteristics from our Institution's patient discharge datasets. After obtaining the applicable ICD-9-CM codes, we computed the Charlson Comorbidity Index using the Quan *et al.* coding scheme [11]. We provide definitions of coexisting conditions in [Supplementary Material, Table S1](#).

Outcomes

The primary outcome variable was long-term all-cause mortality. Through individual Social Security numbers, the discharge dataset allowed linkage to the National Patient Registry to ascertain patients' life status. Secondary outcomes were the relative incidence of cardiovascular and noncardiovascular mortality. Interrogation of the Death Certificate Information System revealed the cause of death. Allocation to the cardiovascular category ensued in patients whose primary cause of death was cardiovascular, cerebrovascular, or peripheral vascular diseases. Noncardiovascular mortality resulted from all other diagnoses. Finally, all-cause mortality included these cardiovascular and noncardiovascular components and those patients without any specified diagnosis (unknown cause of death).

Statistical analysis

We report categorical variables as frequency counts and percentages and compare them with the chi-squared test (or Fisher's exact test in cases frequencies are low). After the visual assessment of normality, we express continuous variables as mean (standard deviation) and compare them with Welch's analysis of variance (ANOVA) test, as it is insensitive to unequal variances [12]. Therefore, it completely removes the need to worry about the assumption of homogeneous variances (or homoscedasticity). We assessed the 3 groups of the predictor variable as ordered categories and performed trend tests, accordingly.

The Kaplan-Meier method provided estimates of overall survival probabilities for time-to-event outcomes. Additionally, Kaplan-Meier curves can indicate an unusual pattern suggesting non-proportional hazards. Follow-up time, described by median and interquartile range, was obtained using the same estimator by reversing the event indicator so that the outcome of interest became being censored [13].

The cumulative incidence function is a valuable summary statistic for analysing competing risk data. Thus, we calculated the subdistribution estimates for each cause (cardiovascular and noncardiovascular mortality) in each study group. Gray's test allows the comparison of the subdistribution for each cause across groups [14]. We performed data truncation at a 10-year follow-up to validate the corresponding log-rank and Gray's test.

We focused on estimating incidence or predicting prognosis in the presence of competing risks, so we fitted Fine-Gray subdistribution hazard models for cardiovascular and noncardiovascular deaths [15]. For each of the 2 causes of death, we regressed the hazard of death on twenty covariates. The baseline variables accounted for consisted of age, sex, the particular clinical presentation of the disease (chronic coronary artery disease, unstable angina/non-ST-elevation myocardial infarction or ST-elevation myocardial infarction), arterial hypertension, diabetes mellitus (whether absent, non-insulin treated or insulin-treated), hyperlipidaemia, the body mass index, history of previous stroke, congestive heart failure, chronic obstructive pulmonary disease (COPD), peripheral vascular disease, the creatinine clearance (in ml/min/1.73 m²), the current need for haemodialysis, the

presence of preoperative anaemia and history of previous neoplastic disease. Additionally, we considered the following surgical procedure details: admission type for the surgical procedure (whether it was scheduled or unscheduled), whether performed with or without cardiopulmonary bypass support, the number of arterial conduits used and the number of distal anastomoses [14].

All the tests of the exposure effect were two-tailed with an alpha threshold of 0.05. All statistical analyses were performed using R software, version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria) [16].

RESULTS

During the predefined study period, 5242 patients underwent primary isolated coronary artery bypass surgery: 3173 (60.5%) had no past smoking history, 1166 (22.2%) were ex-smokers and 903 (17.3%) were current smokers. The mean age of the study population was 63.8 (± 9.9) years, and 1082 (20.6%) were females.

Baseline characteristics

Table 1 exposes the in-between group differences in baseline characteristics. Regarding demographic variables, the proportion of female patients among non-smokers (32.3%) was higher than that of ex-smokers (1.6%) or current smokers (4.1%) (Cochran-Armitage trend test $P < 0.001$). Likewise, non-smokers were, on average, older (65.93 ± 9.20 years) than ex-smokers (63.23 ± 9.62 years) and current smokers (56.75 ± 9.13 years) (linear trend test $P < 0.001$).

Considering the clinical presentation, while 31.3% of non-smokers were operated on following an acute coronary syndrome, that proportion rose to 39.5% in ex-smokers and 49.7% in current smokers (Cochran-Armitage trend test $P < 0.001$). Correspondingly, fewer non-smokers were operated on an unscheduled basis than ex-smokers or current smokers (Cochran-Armitage trend test $P < 0.001$).

Concerning the other traditional coronary artery disease risk factors, non-smokers (68.8%) and ex-smokers (70.7%) were more likely to have arterial hypertension (Cochran-Armitage trend test $P < 0.001$). Diabetes mellitus was more prevalent in non-smokers (42.2%) than in ex-smokers (38.3%) or current smokers (27.0%) (Cochran-Armitage trend test $P < 0.001$). Conversely, hyperlipidaemia was less frequent in non-smokers (60.0%) than in ex-smokers (70.5%) or current smokers (67.9%) (Cochran-Armitage trend test $P < 0.001$). The mean body mass index, a surrogate for obesity, was superior in non-smokers (28.06 ± 4.20 kg/m²), as compared to ex-smokers (27.67 ± 3.90 kg/m²) or current smokers (26.88 ± 4.01 kg/m²) (linear trend test $P < 0.001$).

Additionally, there were significant differences in associated comorbidities amongst the study groups. As expected, chronic obstructive pulmonary disease was more prevalent in patients with past (9.3%) or current smoking habits (13.3%) than in non-smokers (4.6%) (Cochran-Armitage trend test $P < 0.001$). Similarly, peripheral vascular disease was more common in patients with previous (11.7%) or current (13.6%) smoking history than in non-smokers (5.4%) (Cochran-Armitage trend test $P < 0.001$). On the other hand, creatinine clearance, a surrogate for chronic kidney disease, was lower in non-smokers (72.68 ± 21.43 ml/min/1.73 m²) than in ex-smokers (77.88 ± 21.14 ml/min/1.73 m²) or current smokers (85.43 ± 20.95 ml/min/1.73 m²)

Table 1: Baseline characteristics stratified by smoking history status

Variable	Non-smoker (n = 3173)	Ex-smoker (n = 1166)	Current smoker (n = 903)	P-value
Female sex, n (%)	1026 (32.3)	19 (1.6)	37 (4.1)	<0.001
Age, mean (SD)	65.93 (9.20)	63.23 (9.62)	56.75 (9.13)	<0.001
Clinical presentation, n (%)				<0.001
Chronic CAD	2180 (68.7)	706 (60.5)	454 (50.3)	
UA/NSTEMI	736 (23.2)	360 (30.9)	300 (33.2)	
STEMI	257 (8.1)	100 (8.6)	149 (16.5)	
Hypertension, n (%)	2184 (68.8)	824 (70.7)	521 (57.7)	<0.001
Diabetes mellitus, n (%)				<0.001
Non-insulin treated	1145 (36.1)	399 (34.2)	218 (24.1)	
Insulin treated	193 (6.1)	48 (4.1)	26 (2.9)	
Hyperlipidaemia, n (%)	1905 (60.0)	822 (70.5)	613 (67.9)	<0.001
Body mass index, n (%)	28.06 (4.20)	27.67 (3.90)	26.88 (4.01)	<0.001
Previous stroke, n (%)	29 (0.9)	10 (0.9)	12 (1.3)	0.481
Congestive heart failure, n (%)	589 (18.6)	252 (21.6)	171 (18.9)	0.075
COPD, n (%)	145 (4.6)	109 (9.3)	120 (13.3)	<0.001
Creatinine clearance, mean (SD)	72.68 (21.43)	77.88 (21.14)	85.43 (20.95)	<0.001
Haemodialysis, n (%)	22 (0.7)	7 (0.6)	6 (0.7)	0.946
Peripheral vascular disease, n (%)	171 (5.4)	136 (11.7)	123 (13.6)	<0.001
Previous cancer, n (%)	25 (0.8)	21 (1.8)	6 (0.7)	0.006
Anaemia, n (%)	1008 (31.8)	380 (32.6)	249 (27.6)	0.029
Charlson comorbidity index, n (%)	4.35 (1.61)	4.32 (1.72)	3.65 (1.69)	<0.001
Admission, n (%)				<0.001
Scheduled	1575 (49.6)	537 (46.1)	322 (35.7)	
Unscheduled	1598 (50.4)	629 (53.9)	581 (64.3)	
Cardiopulmonary bypass, n (%)				0.088
ONCAB	2007 (63.3)	698 (59.9)	576 (63.8)	
OPCAB	1166 (36.7)	468 (40.1)	327 (36.2)	
Internal thoracic artery use, n (%)				<0.001
None	99 (3.1)	25 (2.1)	18 (2.0)	
Single	2368 (74.6)	788 (67.6)	544 (60.2)	
Bilateral	706 (22.3)	353 (30.3)	341 (37.8)	
Distal anastomoses, mean (SD)	2.51 (0.86)	2.52 (0.86)	2.54 (0.83)	0.629

CAD: Coronary artery disease; COPD: Chronic obstructive pulmonary disease; ONCAB: On-pump coronary artery bypass; OPCAB: Off-pump coronary artery bypass; SD: Standard deviation; STEMI: ST-elevation myocardial infarction; UA/NSTEMI: Unstable angina/non-ST-elevation myocardial infarction.

(linear trend test $P < 0.001$). This differential disease burden translated into an identical Charlson comorbidity index in non-smokers (4.35 ± 1.61) as in ex-smokers (4.32 ± 1.72), both superior to current smokers (3.65 ± 1.69) (linear trend test $P < 0.001$).

Finally, considering the surgical procedure details, no significant differences were noted in the relative proportion of patients operated with or without cardiopulmonary bypass support. Similarly, the mean number of distal anastomoses performed was identical among the study groups. Nevertheless, bilateral internal thoracic grafting was less frequent in non-smokers (22.3%) than in ex-smokers (30.3%) and current smokers (37.8%) (Cochran-Armitage trend test $P < 0.001$).

Survival analysis

Follow-up was 99.7% complete (with 17 patients lost to follow-up). The median follow-up time was 12.79 years [interquartile range (IQR), 9.51–16.60]: 13.12 (IQR, 9.62–17.08) years in non-smokers, 12.66 (IQR, 9.58–16.02) years in ex-smokers and 11.98 (IQR, 9.09–15.85) years in smokers. Throughout the study, there were 2049 deaths (39.1%). Among these, cardiovascular causes accounted for 877 (16.7%), noncardiovascular causes for 727 (13.9%) and unknown causes for 445 (8.5%).

Figure 1 provides a standard Kaplan-Meier curve of post-CABG survival for these patients. With non-smokers established

as the reference group, ex-smokers had an 11% decreased unadjusted risk of late mortality [hazard ratio (HR) 0.89; 95% confidence interval (CI) 0.80, 0.99; $P = 0.034$], and current smokers had a 30% decreased unadjusted risk of late mortality (HR 0.70; 95% CI 0.62, 0.80; $P < 0.001$).

Cox regression analysis demonstrated that ex-smokers had an identical long-term survival than non-smokers (HR 0.99; 95% CI 0.88, 1.12; $P = 0.899$), as displayed when survival by smoking status was plotted at the mean of the covariates (Fig. 2). Conversely, current smokers had a 24% increase in late mortality risk (HR 1.24; 95% CI 1.07, 1.44; $P = 0.004$) as compared to non-smokers (Fig. 3).

Crude incidence of cardiovascular and noncardiovascular death

Figure 4 depicts the cumulative incidences of cardiovascular and noncardiovascular death by smoking status. While the cumulative incidence of cardiovascular mortality was higher than noncardiovascular mortality at all time intervals in non-smokers and ex-smokers, the reverse was true in current smokers.

Table 2 quantifies the differences between study groups in cardiovascular, noncardiovascular, and all-cause mortality. At 10-year follow-up, 30.0% of non-smokers had a fatal outcome, compared with 27.9% of ex-smokers and 22.0% of current smokers (log-rank test, $P < 0.001$). When accounting for competing

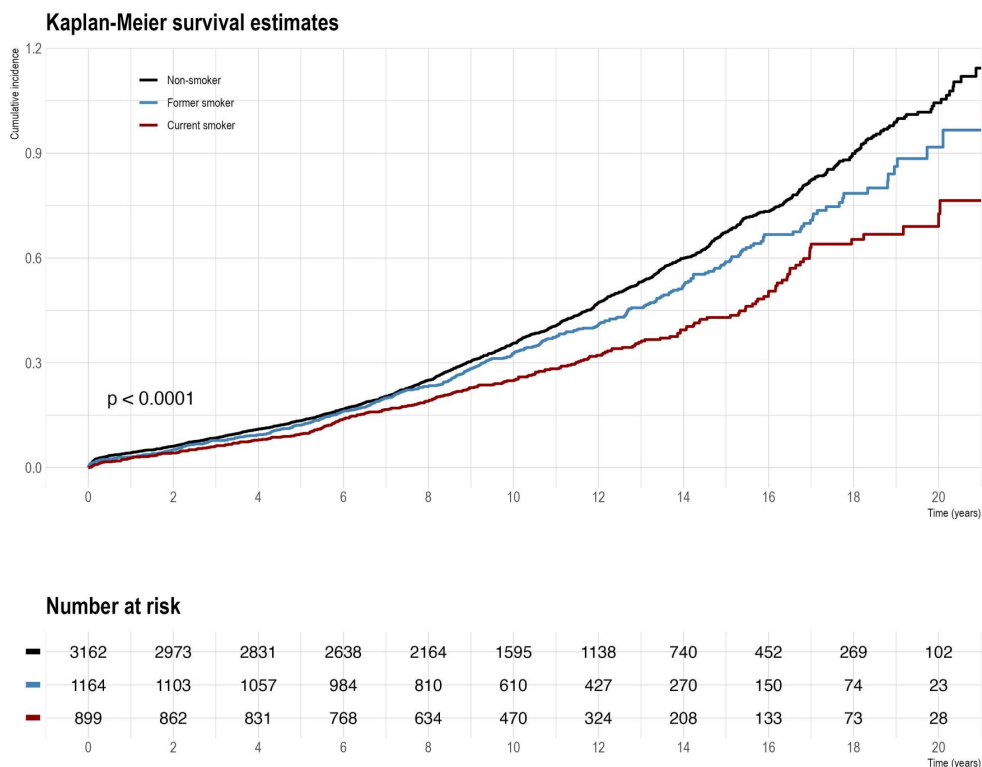


Figure 1: Kaplan–Meier survival estimates.

risks, the 10-year cumulative incidence of cardiovascular death was 13.0% in non-smokers, compared with 11.0% in ex-smokers and 7.6% in current smokers (Gray's test, $P < 0.001$). On the other hand, the 10-year cumulative incidence of noncardiovascular death was 9.0% in non-smokers, compared with 10.0% in ex-smokers and 7.8% in current smokers (Gray's test, $P = 0.300$).

Subdistribution hazard models

As detailed in Table 3, compared to non-smokers, the ex-smoker status increased the relative incidence of noncardiac death by 22% (HR 1.22; 95% CI 1.01, 1.48, $P = 0.045$), while the current smoker status increased the relative incidence of noncardiac death by 61% (HR 1.61; 95% CI 1.27, 2.05, $P < 0.001$). Interestingly, compared to non-smokers, albeit the ex-smoker status did not seem to affect the relative incidence of cardiac death, the current smoker status did confer a 25% reduction in the relative incidence of cardiac death (HR 0.75; 95% CI 0.59, 0.97; $P = 0.025$).

DISCUSSION

This longitudinal, population-based study focused on the association of smoking history status with long-term mortality after primary isolated CABG, as well as on the relative incidence of cardiovascular and noncardiovascular mortality. The 3 study groups presented divergent demographic and comorbid profiles,

such that, at 10-year follow-up, 30.0% of non-smokers had a fatal outcome, compared with 27.9% of ex-smokers and 22.0% of current smokers. Nevertheless, after extensive multivariate adjustment, while ex-smokers had an identical long-term survival to non-smokers, current smokers had a 24% increase in late all-cause mortality risk. By betaking Fine-Gray subdistribution hazard models, we demonstrated that current smoking status increased the relative incidence of noncardiac death by 61%. Interestingly, it conferred a 25% reduction in the relative incidence of cardiac death.

Our results support the association between current smoking status and increased all-cause long-term mortality after coronary artery bypass surgery. This excess in mortality seems to be the result of an increased relative incidence of noncardiac death. Neoplastic disease accounted for >36% of noncardiac deaths in our cohort, making it its leading cause. In this regard, smoking causes about 90% of all lung cancer deaths, the main responsible for cancer-related death in both women and men [17]. Furthermore, it has the potential to cause cancer in virtually any part of the body [18]. Additionally, smoking promotes inflammation and decreased immune function [19], and nearly 35% of noncardiac fatalities resulted from infectious diseases in our cohort (Supplementary Material, Table S2).

On the other hand, we noted a reduction in the relative incidence of cardiac death among current smokers. As proposed by O'Boyle *et al.* [20], this might be secondary to the subtraction of the inciting risk factor, smoking, after coronary artery bypass surgery. According to Ampatzidou *et al.* [21], nearly 76% of patients

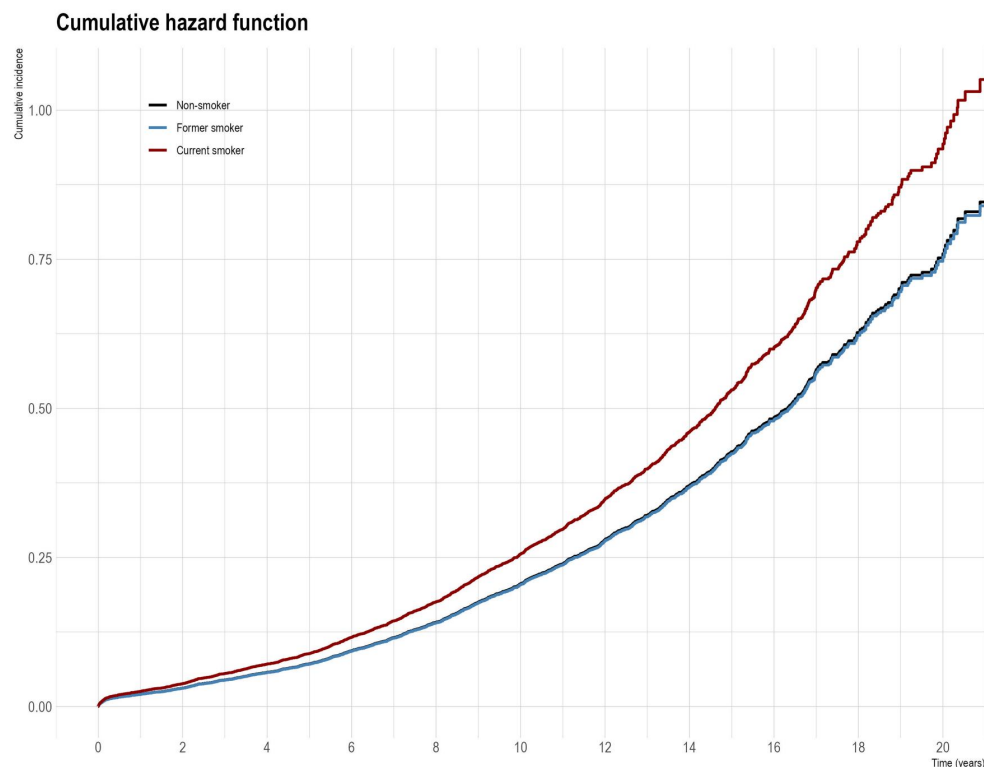


Figure 2: Cumulative hazard function.

report initially quitting tobacco smoking after CABG, but only 57.5% can achieve or maintain abstinence 1 year after surgery. Nevertheless, Masoudkabar *et al.* [9] demonstrated that smoking cessation after CABG could reduce 5-year mortality by 35%. Finally, van Domburg *et al.* [5], in a 20-year follow-up study from Netherlands, showed that patients who continued to smoke after CABG had a greater risk of death than patients who stopped smoking.

Several studies documented the presence of a 'smoker's paradox', which denotes a survival advantage for individuals with cardiovascular disease who smoke compared to those who do not smoke [22, 23]. Similar to other reports [24, 25], our data do not support this claim. The survival advantage observed in the univariable analysis appears to be attributed to smokers' tendency to be younger and have a lower risk profile.

Our results compare with those reported by Ma *et al.* [10]: current smoking status confers a 30% increased risk of late mortality compared to non-smokers. Furthermore, this excess risk does not seem to result from cardiovascular causes. Conversely, van Domburg *et al.* [5] describe a 75% increase in the relative risk of cardiac death. They also quantify the estimated survival benefit for ex-smokers, which increases from 3% at 5 years to 14% at 15 years. This point might clarify the convergence in late mortality between non-smokers and ex-smokers in our cohort.

Finally, Zhang *et al.* [26] report on the SYNTAX Trial at 5-Year follow-up established that smoking was an independent predictor of the composite end-point of death, myocardial infarction, or stroke. Furthermore, the worse clinical outcomes were due to

a higher incidence of recurrent myocardial infarction in both revascularization arms. However, this time frame may be insufficient for other death causes to take their toll. Additionally, in the SYNTAX Extended Survival study, Takahashi *et al.* [27] demonstrate that current smokers had a higher adjusted risk of 10-year all-cause mortality, whereas former smokers did not.

Limitations

The current study does have certain limitations. First, although using administrative databases allows for the efficient assessment of large populations over long periods of time, coding practices were developed for reimbursement issues, not for clinical outcome profiling. As such, imprecise or equivocal definitions may compromise coding accuracy. Additionally, surgical risk models are usually based on a limited number of crucial clinical variables that typically are unavailable in administrative databases [28, 29]. Second, we have no data relating to the duration of abstinence before surgery in ex-smokers nor the smoking status of current smokers after the index procedure. While the decrease in the relative incidence of cardiac death among current smokers gives rise to speculation about the effectiveness of smoking cessation, we remark that this information is indirect. Nevertheless, no interaction between smoking status and COPD was detected in the present analysis; in other words, the COPD effect is not a modifying factor of smoking. Third, with such an extended study period, it would be possible that the surgical techniques, the indication for intervention or the perioperative

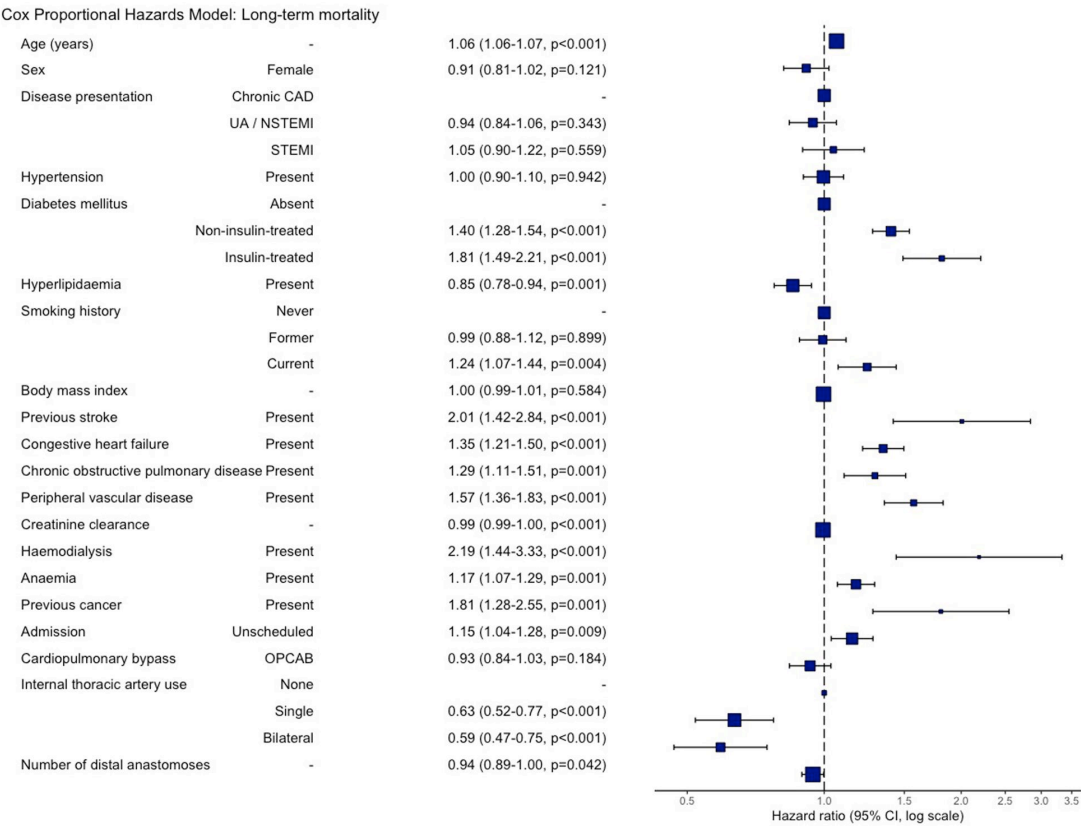


Figure 3: . Odds ratio plot for the specified Cox proportional hazards model.

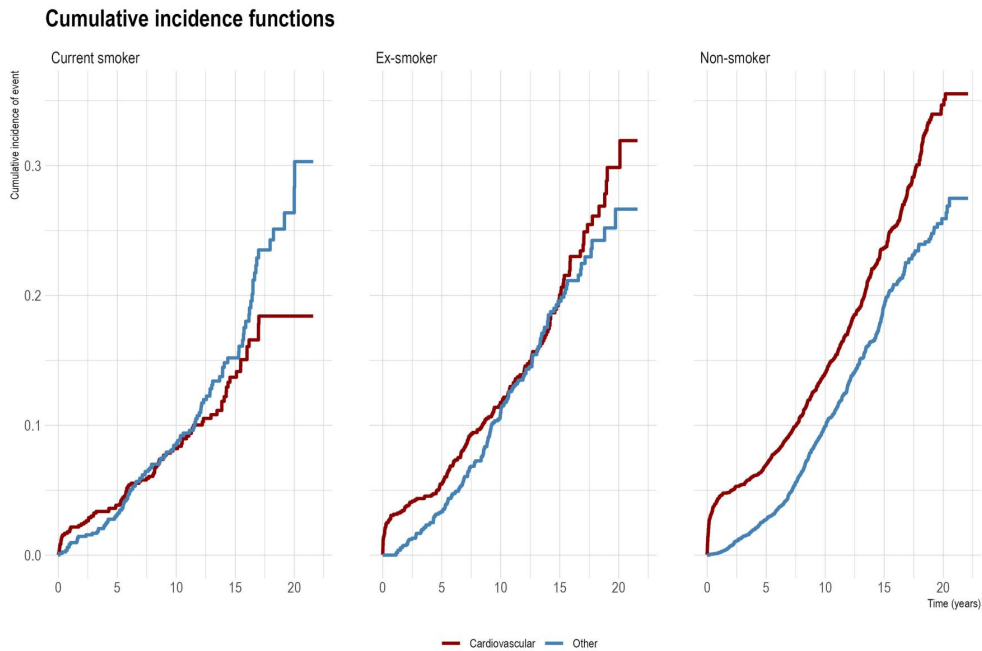


Figure 4: Cumulative incidence functions from competing risks data.

Table 2: Cumulative incidence functions at 1, 5, 10 and 15 years of follow-up, categorized into cardiovascular, noncardiovascular and overall mortality

Mortality (%)	Non-smoker	Ex-smoker	Current smoker	P-value
Cardiovascular				<0.001 ^a
5 years	6.3 (5.5, 7.2)	5.1 (3.9, 6.4)	3.6% (2.5%, 4.9%)	
10 years	13 (11, 14)	11 (9.1, 13)	7.6% (5.9%, 9.5%)	
15 years	21 (20, 23)	19 (16, 21)	13% (10%, 16%)	
20 years	31 (28, 34)	28 (23, 33)	17% (13%, 21%)	
Noncardiovascular				0.500 ^a
5 years	2.5 (2.0, 3.1)	3.1 (2.2, 4.2)	2.9% (1.9%, 4.1%)	
10 years	9.0 (8.0, 10)	10 (8.4, 12)	7.8% (6.1%, 9.8%)	
15 years	17 (16, 19)	18 (15, 21)	14% (11%, 17%)	
20 years	23 (21, 26)	25 (20, 29)	26% (20%, 32%)	
All-cause				<0.001 ^b
5 years	12.6 (11.4, 13.7)	11.5 (9.6, 13.3)	9.2 (7.3, 11.1)	
10 years	30 (28.3, 31.6)	27.9 (25.1, 30.5)	22.0 (19.1, 24.8)	
15 years	49.1 (46.8, 51.2)	44.5 (40.7, 48.1)	34.9 (30.8, 38.8)	
20 years	64.8 (61.7, 67.7)	60 (53.6, 65.6)	51.6 (44.5, 57.9)	

^aGray's test.^bLog-rank test.**Table 3:** Hazard ratios (and 95% confidence intervals) from subdistribution hazard models for cardiac and noncardiac death

Variable	Cardiovascular death			Noncardiovascular death		
	HR	95% CI	P-value	HR	95% CI	P-value
Age (per 1-year increase)	1.03	1.03, 1.04	<0.001	1.06	1.05, 1.07	<0.001
Female sex	0.93	0.79, 1.10	0.420	0.94	0.77, 1.45	0.550
Clinical presentation						
Chronic CAD	Ref	Ref	Ref	Ref	Ref	Ref
UA/NSTEMI	1.12	0.93, 1.34	0.220	1.20	0.99, 1.46	0.069
STEMI	1.38	1.10, 1.74	0.006	1.01	0.76, 1.33	0.970
Hypertension	1.20	1.02, 1.42	0.024	0.92	0.77, 1.09	0.340
Diabetes mellitus						
Absent	Ref	Ref	Ref	Ref	Ref	Ref
Non-insulin treated	1.33	1.15, 1.54	<0.001	1.34	1.15, 1.57	<0.001
Insulin treated	1.54	1.14, 2.08	0.005	1.83	1.31, 2.54	<0.001
Hyperlipidaemia	0.90	0.78, 1.04	0.150	0.88	0.75, 1.04	0.130
Smoking history						
Never smoked	Ref	Ref	Ref	Ref	Ref	Ref
Ex-smoker	0.87	0.72, 1.04	0.130	1.22	1.01, 1.48	0.045
Current smoker	0.75	0.59, 0.97	0.025	1.61	1.27, 2.05	<0.001
BMI (per 1 kg/m ² increase)	1.00	0.98, 1.01	0.680	1.01	0.99, 1.03	0.270
Previous stroke	1.76	1.01, 3.08	0.046	1.09	0.54, 2.16	0.810
Congestive heart failure	1.48	1.26, 1.73	<0.001	1.05	0.87, 1.26	0.630
COPD	1.36	1.07, 1.73	0.011	1.06	0.81, 1.39	0.670
Peripheral vascular disease	1.67	1.34, 2.09	<0.001	1.16	0.89, 1.51	0.280
Creatinine clearance (per 1 ml/min/1.73 m ² increase)	0.99	0.98, 0.99	<0.001	1.00	1.00, 1.01	0.230
Haemodialysis	1.52	0.80, 2.89	0.200	1.71	0.76, 3.88	0.200
Anaemia	1.17	1.01, 1.35	0.040	1.08	0.92, 1.28	0.340
Previous cancer	0.96	0.50, 1.83	0.890	1.26	0.67, 2.36	0.470
Admission						
Scheduled	Ref	Ref	Ref	Ref	Ref	Ref
Unscheduled	1.11	0.95, 1.31	0.200	0.97	0.82, 1.15	0.720
Cardiopulmonary bypass						
ONCAB	Ref	Ref	Ref	Ref	Ref	Ref
OPCAB	0.92	0.78, 1.08	0.320	1.17	0.98, 1.38	0.077
Internal thoracic artery use						
None	Ref	Ref	Ref	Ref	Ref	Ref
Single	0.62	0.46, 0.82	0.001	1.10	0.73, 1.65	0.650
Bilateral	0.51	0.36, 0.73	<0.001	1.12	0.71, 1.76	0.630
Number of distal anastomoses (per 1 graft increase)	0.93	0.85, 1.01	0.078	1.00	0.91, 1.10	0.970

BMI: Body mass index; CI: Confidence interval; CAD: Coronary artery disease; COPD: Chronic obstructive pulmonary disease; HR: Hazard ratio; ONCAB: On-pump coronary artery bypass; OPCAB: Off-pump coronary artery bypass; Ref: Reference; STEMI: ST-elevation myocardial infarction; UA/NSTEMI: Unstable angina/Non-ST-elevation myocardial infarction.

care could have changed throughout the time frame the patients were recruited. However, incorporating the study period as a covariate on the Cox model does not affect our conclusions (Supplementary Material, Table S3). Finally, we should acknowledge that the use of death certificate data to disclose the cause of death is highly unreliable, with nearly 50% lacking agreement with autopsy studies. Therefore, one should exercise extreme caution in discussing the discrepancy in findings between cardiovascular and noncardiovascular causes of mortality [30].

CONCLUSIONS

In this longitudinal, population-based study, we focused on the association of smoking history status with long-term mortality after primary isolated CABG, as well as on the relative incidence of cardiovascular and noncardiovascular mortality. We demonstrated that, while ex-smokers had an identical long-term survival to non-smokers, current smokers had an increase in late all-cause mortality risk at the expense of an increased relative incidence of noncardiac death. By subtracting the inciting risk factor, smoking cessation reduces the relative incidence of cardiac death.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

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Conflict of interest: none declared.

DATA AVAILABILITY

The article's data will be shared on reasonable request to the corresponding author.

Author contributions

Armando Abreu: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Software; Validation; Visualization; Writing—original draft; Writing—review & editing. **José Máximo:** Writing—original draft; Writing—review & editing. **Adelino Leite-Moreira:** Funding acquisition; Supervision; Writing—review & editing.

Reviewer information

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9.1. Background

The World Health Organization defines anaemia as a haemoglobin level of $<13\text{g/dl}$ in men and $<12\text{g/dl}$ in women, translating into a preoperative anaemia prevalence in patients undergoing cardiac surgery from 16% to 54% [454–456]. Hospital-acquired blood loss, iron-deficiency anaemia and anaemia of chronic disease are common causes which are unrelated to the operative procedure itself; nevertheless, the specificities of the surgical practices, such as phlebotomy, intraoperative blood loss and the haemodilution intrinsic to the cardiopulmonary bypass support, might compound the condition [457, 458]. Patients with low haemoglobin concentration have diminished oxygen delivery ability and are prone to end-organ ischaemia. Herein lies the rationale for red blood cell (RBC) transfusion since its primary effect would be increased oxygen delivery and improved organ perfusion.

9.2. Problem Statement and Knowledge Gap

In the past 20 years, a wealth of data analysed the independent influence of preoperative anaemia and perioperative RBC transfusion on outcomes after cardiac surgery. For instance, two meta-analyses [459, 460] established the association between preoperative anaemia and adverse results after surgery. Conversely, several studies described the association of perioperative RBC transfusions with increased long-term mortality [461–464]. However, there is a scarcity of data focusing on the role of the interaction effect of preoperative anaemia and perioperative transfusion on long-term survival.

9.3. Research Objectives

This article strives to describe the independent and combined effects of preoperative anaemia and perioperative RBC transfusion on long-term survival in a large single-centre inverse probability-weighted (IPW) cohort of patients admitted for isolated coronary artery bypass grafting (CABG). IPW creates a pseudo-population of the treatment and the control groups, with the same covariate distribution as the overall treated and untreated population [23]. This methodology allows us to estimate the average treatment effect in the entire population, the same question asked in a randomized controlled trial.

9.4. Reader's Note

The subsequent section of this chapter reproduces the full text of the study, "The additive effects of anaemia and transfusion on long-term survival after coronary artery bypass surgery", by Armando Abreu, José Máximo, Cláudia Almeida, André Lourenço, and Adelino Leite-Moreira [465] and published in *European Journal of Cardio-Thoracic Surgery. (EJCTS)* (2024). The paper has been included with the publisher's permission under the terms of the Creative Commons Attribution License.

For proper citation, please refer to the original publication: Abreu, A., Máximo, J., & Leite-Moreira, A. (2024). Preoperative smoking status and long-term survival after coronary artery bypass grafting: a competing risk analysis. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery*, 65(5), ezae183. DOI: 10.1093/ejcts/ezae183.

9.5. Original Publication

The full text of the study, titled "The additive effects of anaemia and transfusion on long-term survival after coronary artery bypass surgery", is included in the following pages.

Cite this article as: Abreu A, Máximo J, Almeida C, Lourenço A, Leite-Moreira A. The additive effects of anaemia and transfusion on long-term survival after coronary artery bypass surgery. Eur J Cardiothorac Surg 2024; doi:10.1093/ejcts/ezad403.

The additive effects of anaemia and transfusion on long-term survival after coronary artery bypass surgery

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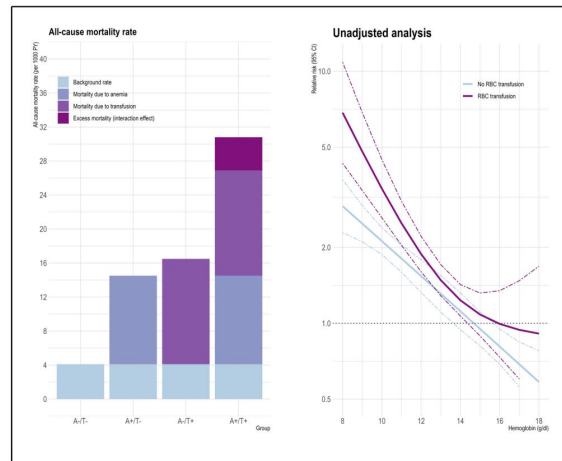
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Interaction of haemoglobin concentration and red blood cell transfusion

Summary

This longitudinal, population-level study emphasises the adverse long-term outcomes of preoperative anaemia and perioperative RBC transfusion. It stresses the importance of an evidence-based, multimodal, and multidisciplinary approach to conserving blood resources and optimising outcomes in patients at high risk for transfusion.



Legend: A. Haemoglobin concentration treated as a dichotomous variable. B. Haemoglobin concentration treated as a continuous variable. RBC, red blood cell.

Abstract

OBJECTIVES: To compare the independent and combined effects of anaemia and red blood cell transfusion on late survival after isolated coronary artery bypass grafting.

METHODS: Retrospective analysis of 5243 consecutive patients undergoing primary isolated coronary artery bypass grafting, performed from 2000 to 2015, in a Portuguese Academic Hospital. We identified 1649 patients with preoperative anaemia (A^+) and 1422 patients who received a perioperative transfusion (T^+)—the 4 possible combinations allowed for the creation of 4 subgroups (A^-/T^- , A^-/T^+ , A^+/T^- and A^+/T^+). The primary endpoint was all-cause mortality at 10 years. We employed inverse probability weighting to control for confounding variables.

RESULTS: Thirty-one percent of the patients had preoperative anaemia, and 27.0% had at least one packed red blood cell transfusion. Inverse probability weighting was effective in eliminating differences in all significant baseline characteristics. The primary endpoint of all-cause mortality at 10 years occurred in 568 patients (20.5%) in the A^-/T^- group, as compared with 204 (24.4%) in the A^-/T^+ group (hazard ratio, 1.14; 95% confidence interval, 1.00 to 1.31; $P = 0.053$), 358 (33.8%) in the A^+/T^- group (hazard ratio, 1.53; 95% confidence interval, 1.38 to 1.71; $P < 0.001$), 254 (43.6%) in the A^+/T^+ group (hazard ratio, 2.25; 95% confidence interval, 1.97 to 2.56; $P < 0.001$).

CONCLUSIONS: This longitudinal, population-level study emphasizes the adverse long-term outcomes of preoperative anaemia and perioperative red blood cell transfusion. It stresses the importance of an evidence-based, multimodal and multidisciplinary approach to conserving blood resources and optimizing outcomes in patients at high risk for transfusion.

Keywords: Coronary artery bypass • Anaemia • Blood transfusion • Survival analysis

ABBREVIATIONS

CABG	Coronary artery bypass grafting
CI	Confidence interval
IPW	Inverse probability-weighted
IQR	Interquartile range
OR	Odds ratio
RBC	Red blood cell
SMD	Standardized mean difference

INTRODUCTION

The World Health Organization defines anaemia as a haemoglobin level of <13 g/dl in men and <12 g/dl in women, translating into a preoperative anaemia prevalence in patients undergoing cardiac surgery from 16% to 54% [1–3]. Hospital-acquired blood loss, iron-deficiency anaemia and anaemia of chronic disease are common causes which are unrelated to the operative procedure itself; nevertheless, the specificities of the surgical practices, such as phlebotomy, intraoperative blood loss and the haemodilution intrinsic to the cardiopulmonary bypass support, might compound the condition [4, 5]. Patients with low haemoglobin concentration have diminished oxygen delivery ability and are prone to end-organ ischaemia. Herein lies the rationale for red blood cell (RBC) transfusion since its primary effect would be increased oxygen delivery and improved organ perfusion.

In the past 20 years, a wealth of data analysed the independent influence of preoperative anaemia and perioperative RBC transfusion on outcomes after cardiac surgery. For instance, 2 meta-analyses [6, 7] established the association between preoperative anaemia and adverse results after surgery. Conversely, several studies described the association of perioperative RBC transfusions with increased long-term mortality [8–11]. However, there is a scarcity of data focusing on the role of the interaction effect of preoperative anaemia and perioperative transfusion on long-term survival.

This article strives to describe the independent and combined effects of preoperative anaemia and perioperative RBC transfusion on long-term survival in a large single-centre inverse probability-weighted (IPW) cohort of patients admitted for isolated coronary artery bypass grafting (CABG). IPW creates a pseudo-population of the treatment and the control groups, with the same covariate distribution as the overall treated and untreated population [12]. This methodology allows us to estimate the average treatment effect in the entire population, the same question asked in a randomized controlled trial.

MATERIALS AND METHODS

Ethical statement

The São João University Hospital Centre Ethics Committee approved this research (ID Number 279-13, 25 October 2013) and waived the need for informed consent due to the study's retrospective nature.

Study design

This study was a retrospective analysis of an administrative dataset containing all hospitalizations in a level III hospital (University Hospital Centre São João, Porto, Portugal). We included patients undergoing primary isolated CABG from 1 January 2000 to 30 September 2015 (chosen as the cut-off date because of ICD-10-CM implementation).

Study population

Patients were included in the study if they underwent primary isolated coronary artery bypass surgery [International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 3610, 3611, 3612, 3613, 3614, 3615, 3616, 3617 or 3619] during the study period. Exclusion criteria included: previous cardiac surgery (ICD-9-CM codes V433 and V4581); concomitant valve replacement or repair (ICD-9-CM codes 3510, 3511, 3512, 3513, 3514, 3520, 3521, 3522, 3523, 3524, 3525, 3526, 3527, 3528 and 3533); concurrent aorta surgery (ICD-9-CM codes 3804, 3814, 3834, 3844, 3845 and 3864); and simultaneous correction of myocardial infarction mechanical complications (ICD-9-CM codes 41410, 4295, 4296, 42971 and 42979).

Data sources and variables

The corresponding diagnoses and procedures were coded for each hospitalization from the selected patients based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). Linkage of this dataset to a laboratory data repository allowed for the extraction of each patient's preoperative haemoglobin concentration (in g/dl). Using the World Health Organization cut-off values (men, $Hb < 13.0$ g/dl; women, $Hb < 12.0$ g/dl), and whether an RBC transfusion performed, intra- or perioperatively (ICD-9-CM code 9904), 4 treatment groups were thus created (the predictive or independent variable): no anaemia/no RBC transfusion (A^-/T^-), no anaemia/RBC transfusion (A^-/T^+), anaemia/no RBC transfusion (A^+/T^-)

and anaemia/RBC transfusion (A^+/T^+). Other baseline characteristics were extracted from our Institution's patient discharge datasets. After obtaining the relevant ICD-9-CM codes, we computed the Charlson Comorbidity Index using the Quan *et al.* coding scheme [13]. We provide definitions of coexisting conditions in [Supplementary Material, Table S1](#).

Outcomes

The primary outcome variable was long-term all-cause mortality. Through individual Social Security numbers, the discharge dataset allowed linkage to the National Patient Registry (RNU) to ascertain patient life status. Secondary outcomes included peri-operative stroke (ICD-9-CM codes 99701 and 99702), prolonged mechanical ventilation (ICD-9-CM codes 9670, 9671 and 9672), acute kidney injury (an increase of over 0.3 mg/dl over baseline creatinine concentration), the length of hospital stay (LOS) and in-hospital mortality.

Statistical analysis

We present the data as absolute frequencies and percentages for categorical variables and as means and standard deviations for continuous variables. We used the standardized mean difference (SMD) to assess discrepancies in covariates between treatment groups, as it allows for the judgement of the relative balance of variables measured in different units. Values <0.1 indicate a negligible difference in the mean or frequency of a covariate between treatment groups.

We utilized IPW to restrict confounding by indication. IPW makes sense with an active comparator, allowing us to estimate the average treatment effect in the entire population. Making these causal contrasts depends on predicting treatment based on relevant covariates, that is, the propensity score estimation. To this end, we performed covariate balancing propensity score weighting. This method relies on estimating propensity scores using a generalized method of moments and then converting those scores into weights using a formula that depends on the desired estimand. The model included the following variables: sex, age, admission status (scheduled vs unscheduled), disease presentation (stable coronary disease, unstable angina/non-ST-elevation myocardial infarction [NSTEMI] and ST-elevation myocardial infarction [STEMI]), hypertension, diabetes mellitus, hyperlipidaemia, body mass index, smoking history, previous stroke, congestive heart failure, chronic obstructive pulmonary disease, peripheral vascular disease, creatinine clearance (as a surrogate for chronic kidney disease), cancer history and the surgical procedural details (such as whether the procedure was conducted on- or off-pump, the number of internal thoracic arteries used as grafts and the total number of distal anastomosis performed).

We derived weighted logistic regression models with a robust variance estimator with the outcome as the dependent variable and the group on which the propensity score balances (e.g. the treatment group) as the only independent/predictor variable.

Estimates of survival probabilities were calculated using the Kaplan-Meier method and compared with the log-rank test. Follow-up time, described by median and interquartile range (IQR), was obtained using the same estimator by reversing the event indicator so that the outcome of interest became being censored. We employed a weighted Cox proportional hazards

regression model with a robust variance estimator to compare long-term mortality between groups.

In order to further clarify the effect of the interaction between anaemia and RBC transfusion, we computed all-cause mortality rates using the number of events and the person-years of follow-up time contributed by the cohort of subjects stratified into subgroups. For transparency, we report the separate effect of each exposure and their joint effect compared to the unexposed group (considered as the background risk).

Finally, we should stress that we did not adjust the 95% confidence intervals (CIs) for multiple comparisons, and inferences drawn from them may not be reproducible.

All the tests of the exposure effect were 2-tailed with an alpha threshold of 0.05. All statistical analyses were performed using R software, version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Of 7123 patients who underwent CABG during the study period, 5243 were eligible for inclusion and constitute the study population. According to the World Health Organization defined cut-off, 31.3% of the patients had preoperative anaemia, and 27.0% had at least one packed RBC transfusion (Fig. 1). The mean age of the study population was $63.4 (\pm 9.9)$ years, and 1082 (20.6%) were females.

Baseline characteristics

Table 1 depicts the baseline characteristics of each one of the study groups. Compared to A^-/T^- patients (mean age 62.31 ± 9.75 years), patients in the A^-/T^+ (mean age 63.48 ± 9.71 years, $SMD = 0.120$), A^+/T^- (mean age 65.52 ± 9.62 years, $SMD = 0.332$) and A^+/T^+ (mean age 67.69 ± 9.61 years, $SMD = 0.556$) were significantly older. Over 46% of patients in the A^-/T^- group were operated on an unscheduled basis, as compared to 46.5% in the A^-/T^+ ($SMD = 0.003$), 67.5 in the A^+/T^- ($SMD = 0.431$) and 71.8% ($SMD = 0.530$) in the A^+/T^+ groups.

As for the traditional risk factors for atherosclerosis, the prevalence of hypertension was 63.5% in the A^-/T^- group, as compared with 71.5% ($SMD = 0.173$) in the A^-/T^+ , 65.9% ($SMD = 0.051$) in the A^+/T^- and 82.1% ($SMD = 0.429$) in the A^+/T^+ groups. Likewise, the prevalence of diabetes mellitus was 34.6% in the A^-/T^- , 38.4% ($SMD = 0.131$) in the A^-/T^+ , 41.9% ($SMD = 0.159$) in the A^+/T^- and 53.4% ($SMD = 0.446$) in the A^+/T^+ groups.

Concerning associated comorbidities, congestive heart failure was present in 14.6% of A^-/T^- patients, 23.1% ($SMD = 0.218$) of A^-/T^+ , 20.4% ($SMD = 0.153$) of A^+/T^- and 34.4% in the A^+/T^+ groups. Similarly, the mean creatinine clearance, a surrogate for chronic kidney disease, was 79.81 ± 19.17 ml/min in A^-/T^- patients, as compared to 78.77 ± 20.22 in A^-/T^+ ($SMD = 0.053$), 69.71 ± 23.70 in A^+/T^- ($SMD = 0.468$) and 65.68 ± 26.02 ($SMD = 0.618$) in the A^+/T^+ groups. Peripheral vascular disease was present in 5.3% of A^-/T^- patients, 10.5% ($SMD = 0.193$) of A^-/T^+ , 8.3% ($SMD = 0.118$) of A^+/T^- and 18.4% ($SMD = 0.412$) of A^+/T^+ patients. Correspondingly, the Charlson Comorbidity Index was 3.83 ± 1.48 in A^-/T^- patients, as opposed to 4.30 ± 1.62 ($SMD = 0.305$) in A^-/T^+ , 4.51 ± 1.66 ($SMD = 0.435$) in A^+/T^- and 5.49 ± 1.81 ($SMD = 1.01$) in the A^+/T^+ patients.

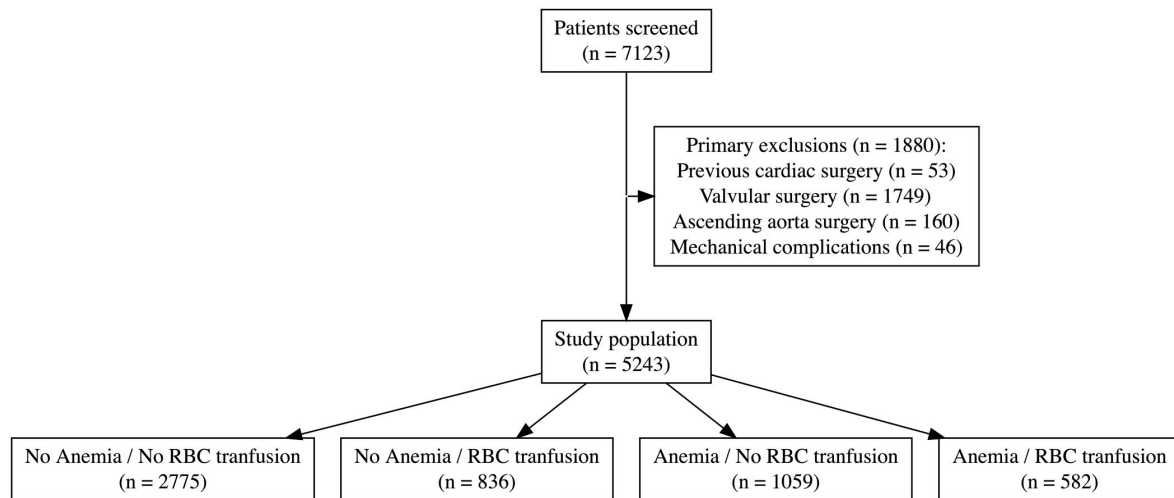


Figure 1: Study population diagram.

Table 1: Baseline characteristics distributed by study group

Variable	A ⁻ /T ⁻ (n = 2775)	A ⁻ /T ⁺ (n = 836)	A ⁺ /T ⁻ (n = 1059)	A ⁺ /T ⁺ (n = 582)
Female sex, n (%)	516 (18.6)	190 (22.7)	236 (22.3)	140 (24.1)
Age, mean (SD)	62.31 (9.75)	63.48 (9.71)	65.52 (9.62)	67.69 (9.61)
Admission, n (%)				
Scheduled	1480 (53.3)	447 (53.5)	344 (32.5)	164 (28.2)
Unscheduled	1295 (46.7)	389 (46.5)	715 (67.5)	418 (71.8)
Presentation, n (%)				
Chronic CAD	1940 (69.9)	516 (61.7)	622 (58.7)	266 (45.7)
UA/NSTEMI	620 (22.3)	241 (28.8)	302 (28.5)	239 (41.1)
STEMI	215 (7.7)	79 (9.4)	135 (12.7)	77 (13.2)
Hypertension, n (%)	1761 (63.5)	598 (71.5)	698 (65.9)	478 (82.1)
Diabetes mellitus, n (%)				
Non-insulin-treated	865 (31.2)	271 (32.4)	390 (36.8)	241 (41.4)
Insulin-treated	94 (3.4)	50 (6.0)	54 (5.1)	70 (12.0)
Hyperlipidaemia, n (%)	1758 (63.4)	568 (67.9)	648 (61.2)	374 (64.3)
BMI, mean (SD)	27.93 (4.01)	27.78 (4.25)	27.70 (4.23)	27.20 (4.33)
Smoking history, n (%)				
Never smoked	1663 (59.9)	503 (60.2)	664 (62.7)	346 (59.5)
Former smoker	601 (21.7)	190 (22.7)	227 (21.4)	155 (26.6)
Current smoker	511 (18.4)	143 (17.1)	168 (15.9)	81 (13.9)
Previous stroke, n (%)	15 (0.5)	18 (2.2)	8 (0.8)	10 (1.7)
Congestive heart failure, n (%)	405 (14.6)	193 (23.1)	216 (20.4)	200 (34.4)
COPD, n (%)	177 (6.4)	57 (6.8)	79 (7.5)	61 (10.5)
Creatinine, mean (SD)	1.01 (0.47)	1.02 (0.63)	1.21 (0.91)	1.37 (1.17)
Creatinine clearance, mean (SD)	79.81 (19.17)	78.77 (20.22)	69.71 (23.70)	65.68 (26.02)
Peripheral vascular disease, n (%)	148 (5.3)	88 (10.5)	88 (8.3)	107 (18.4)
Previous cancer, n (%)	19 (0.7)	5 (0.6)	10 (0.9)	18 (3.1)
CCI, mean (SD)	3.83 (1.48)	4.30 (1.62)	4.51 (1.66)	5.49 (1.81)
Cardiopulmonary bypass, n (%)				
OPCAB	1089 (39.2)	288 (34.4)	359 (33.9)	225 (38.7)
ONCAB	1686 (60.8)	548 (65.6)	700 (66.1)	357 (61.3)
Internal thoracic artery use, n (%)				
None	79 (2.8)	10 (1.2)	36 (3.4)	18 (3.1)
Single	1891 (68.1)	575 (68.8)	817 (77.1)	424 (72.9)
Bilateral	805 (29.0)	251 (30.0)	206 (19.5)	140 (24.1)
Number of grafts, mean (SD)	2.48 (0.86)	2.55 (0.85)	2.56 (0.86)	2.60 (0.82)

BMI: body mass index; CAD: coronary artery disease; CCI: Charlson Comorbidity Index; COPD: chronic obstructive pulmonary disease; NSTEMI: non-ST-elevation myocardial infarction; ONCAB: on-pump coronary artery bypass; OPCAB: off-pump coronary artery bypass; SD: standard deviation; STEMI: ST-elevation myocardial infarction; UA: unstable angina.

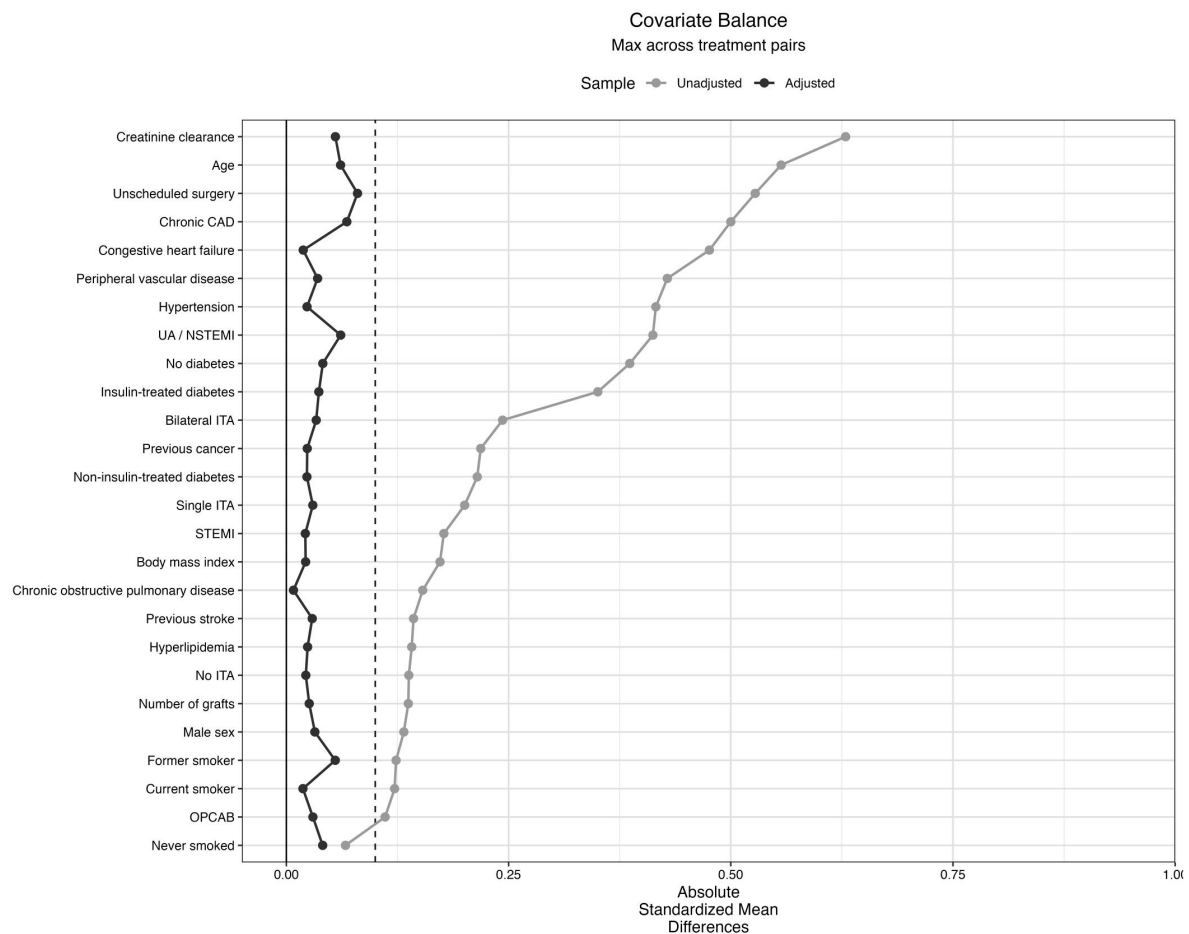


Figure 2: Love plot illustrating covariate balance assessment.

Regarding the technical details of the surgical procedure, despite the slight differences recorded, they did not appear to follow the above-noted gradient.

IPW effectively eliminated differences in all baseline characteristics (Fig. 2), as revealed by SMD values below 0.10.

In-hospital outcomes

When examining predefined secondary outcomes (Table 2), the odds ratio (OR) for perioperative stroke was 3.85 (95% CI, 1.87–8.03; $P < 0.001$) in the A^-/T^+ group, 1.69 (95% CI, 0.70–3.85, $P = 0.223$) in the A^+/T^- group and 3.10 (95% CI, 1.28–7.09, $P = 0.009$) in the A^+/T^+ group, as compared to the reference group, A^-/T^- , in the unadjusted analysis. However, in the adjusted analysis, these differences fell away: the OR was 2.13 (95% CI, 0.97–4.67; $P = 0.059$) in the A^-/T^+ group, 1.37 (95% CI, 0.57–3.27, $P = 0.477$) in the A^+/T^- group and 1.46 (95% CI, 0.53–4.02, $P = 0.464$) in the A^+/T^+ group, as compared to the reference group, A^-/T^- . These results suggest that factors other than preoperative anaemia or RBC transfusion could explain perioperative stroke more reasonably.

Regarding prolonged postoperative mechanical ventilation, the OR was 3.13 (95% CI, 2.19–4.47; $P < 0.001$) in the A^-/T^+ group, 1.64 (95% CI, 1.10–2.41, $P = 0.013$) in the A^+/T^- group and 3.49 (95% CI, 2.37–5.11, $P < 0.001$) in the A^+/T^+ group, as compared to the reference group, A^-/T^- , in the unadjusted analysis. In the adjusted analysis, the OR was 2.85 (95% CI, 1.94–4.20; $P < 0.001$) in the A^-/T^+ group, 1.37 (95% CI, 0.89–2.11, $P = 0.156$) in the A^+/T^- group and 2.81 (95% CI, 1.74–4.53, $P < 0.001$) in the A^+/T^+ group, as compared to the reference group, A^-/T^- . These results suggest that RBC transfusion, but not anaemia itself, might be responsible for the protracted mechanical ventilation times.

Concerning acute kidney injury, the OR was 1.10 (95% CI, 0.90–1.36; $P = 0.349$) in the A^-/T^+ group, 1.78 (95% CI, 1.50–2.12, $P < 0.001$) in the A^+/T^- group and 2.10 (95% CI, 1.70–2.58, $P < 0.001$) in the A^+/T^+ group, as compared to the reference group, A^-/T^- , in the unadjusted analysis. In the adjusted analysis, the OR was 1.09 (95% CI, 0.87–1.37; $P = 0.431$) in the A^-/T^+ group, 1.48 (95% CI, 1.23–1.78, $P < 0.001$) in the A^+/T^- group and 1.38 (95% CI, 1.07–1.78, $P = 0.013$) in the A^+/T^+ group, as compared to the reference group, A^-/T^- . Again, these results

Table 2: In-hospital outcomes: unadjusted and weighted

Outcome	A ⁻ /T ⁻ (n = 2775)	A ⁻ /T ⁺ (n = 836)	A ⁺ /T ⁻ (n = 1059)	A ⁺ /T ⁺ (n = 582)
Stroke, OR (95% CI)				
Unadjusted	Reference	3.85 (1.87, 8.03)	1.69 (0.70, 3.85)	3.10 (1.28, 7.09)
Adjusted	Reference	2.13 (0.97, 4.67)	1.37 (0.57, 3.27)	1.46 (0.53, 4.03)
Prolonged ventilation, OR (95% CI)				
Unadjusted	Reference	3.13 (2.19, 4.47)	1.64 (1.10, 2.41)	3.49 (2.37, 5.11)
Adjusted	Reference	2.85 (1.94, 4.20)	1.36 (0.89, 2.11)	2.81 (1.74, 4.53)
AKI, OR (95% CI)				
Unadjusted	Reference	1.10 (0.90, 1.36)	1.78 (1.50, 2.12)	2.09 (1.70, 2.58)
Adjusted	Reference	1.09 (0.87, 1.37)	1.48 (1.23, 1.78)	1.38 (1.07, 1.78)
LOS (days), Δ estimate (95% CI)				
Unadjusted	Reference	1.45 (0.78, 2.12)	1.98 (1.36, 2.12)	4.07 (3.29, 4.84)
Adjusted	Reference	1.20 (0.08, 2.32)	0.70 (0.14, 1.27)	1.24 (0.41, 2.07)
Mortality, OR (95% CI)				
Unadjusted	Reference	2.40 (1.21, 4.64)	2.52 (1.35, 4.69)	6.13 (3.43, 11.1)
Adjusted	Reference	1.51 (0.72, 3.16)	1.12 (0.56, 2.24)	2.03 (1.03, 4.02)

AKI: acute kidney injury; CI: confidence interval; LOS: length of hospital stay; OR: odds ratio.

suggest that anaemia might be responsible for the acute kidney injury, not RBC transfusion.

In regard the length of hospital stay, it was 1.45 (95% CI, 0.78–2.12; $P < 0.001$) days longer in the A⁻/T⁺ group, 1.98 (95% CI, 1.36–2.59, $P < 0.001$) days longer in the A⁺/T⁻ group and 4.07 (95% CI, 3.29–4.84, $P < 0.001$) days longer in the A⁺/T⁺ group, as compared to the reference group, A⁻/T⁻, in the unadjusted analysis. On the other hand, after extensive covariate adjustment, the length of hospital stay was 1.20 (95% CI, 0.08–2.32; $P = 0.035$) days longer in the A⁻/T⁺ group, 0.70 (95% CI, 0.14–1.27, $P = 0.015$) days longer in the A⁺/T⁻ group and 1.24 (95% CI, 0.41–2.07, $P = 0.003$) days longer in the A⁺/T⁺ group, as compared to the reference group, A⁻/T⁻.

About in-hospital mortality, the OR was 2.40 (95% CI, 1.21–4.64; $P = 0.010$) in the A⁻/T⁺ group, 2.52 (95% CI, 1.35–4.69, $P = 0.003$) in the A⁺/T⁻ group and 6.13 (95% CI, 3.43–11.1, $P < 0.001$) in the A⁺/T⁺ group, as compared to the reference group, A⁻/T⁻, in the unadjusted analysis. However, in the adjusted analysis, the OR was 1.51 (95% CI, 0.72–3.16; $P = 0.274$) in the A⁻/T⁺ group, 1.12 (95% CI, 0.56–2.24, $P = 0.739$) in the A⁺/T⁻ group and 2.03 (95% CI, 1.03–4.02, $P = 0.042$) in the A⁺/T⁺ group, as compared to the reference group, A⁻/T⁻.

Long-term survival

Follow-up was 99.71% complete (15 patients with unidentified vital status). The median follow-up time was 12.80 (IQR, 9.52–16.62) years: 12.90 (IQR, 9.60–17.18) years for the A⁻/T⁻ group, 11.83 (IQR, 8.82–14.57) years for the A⁻/T⁺ group, 13.81 (IQR, 10.90–18.67) years for the A⁺/T⁻ group and 11.16 (IQR, 8.75–13.95) years for the A⁺/T⁺ group. The primary endpoint of all-cause mortality at 10 years occurred in 568 patients (20.5%) in the A⁻/T⁻ group, as compared with 204 (24.4%) in the A⁻/T⁺ group (hazard ratio, 1.14; 95% CI, 1.00 to 1.31; $P = 0.053$), 358 (33.8%) in the A⁺/T⁻ group (hazard ratio, 1.53; 95% CI, 1.38 to 1.71; $P < 0.001$), 254 (43.6%) in the A⁺/T⁺ group (hazard ratio, 2.25; 95% CI, 1.97 to 2.56; $P < 0.001$). Thirty-day, 1-, 5- and 10-year survival rates were 99.3%, 98.0%, 91.9% and 77.9% in the A⁻/T⁻ group, 98.6%, 95.4%, 90.2% and 73.2% in the A⁻/T⁺ group,

98.6%, 95.4%, 82.9% and 64.8% in the A⁺/T⁻ group and 96.7%, 91.6%, 77.4% and 53.4% in the A⁺/T⁺ group. Figure 3 depicts the unweighted survival function plot for all groups. Figure 4 illustrates the weighted survival function plot for all groups. Both reveal the difference in long-term survival between groups.

Interaction of haemoglobin and RBC transfusion

The all-cause mortality rate was lowest in subjects without anaemia and RBC transfusion (the background rate of 4.10/1000 person-years) (Fig. 5A). The mortality rate in subjects with anaemia (the background rate plus the additional effect of anaemia of 14.5/1000 person-years) was substantially increased. Likewise, the mortality rate in subjects with RBC transfusion (the background rate plus the additional effect of RBC transfusion of 16.5/1000 person-years) was further increased. On top of the combined effect of background, anaemia and RBC transfusion, an additional effect was present. This excess effect of 3.9/1000 person-years is termed the interaction effect.

This interaction effect was again noticeable when the haemoglobin concentration was modelled as a continuous variable, using a natural spline with 2 knots to express its complete flexibility (interaction term, $P = 0.005$) (Fig. 5B).

DISCUSSION

This longitudinal, population-level evaluation of the independent and combined effects of preoperative anaemia and perioperative RBC transfusion on long-term survival should highlight several key points. First, the basis for perioperative stroke should lie in explanations other than anaemia or RBC transfusion. Prolonged mechanical ventilation appears associated with RBC transfusion but not anaemia; conversely, acute kidney injury seems to result from anaemia, not RBC transfusion. Both could justify the extended length of hospital stay described. On the other hand, only the combined effects of anaemia and RBC transfusion seem to affect short-term mortality. Second, with a median follow-up time exceeding 10 years, preoperative

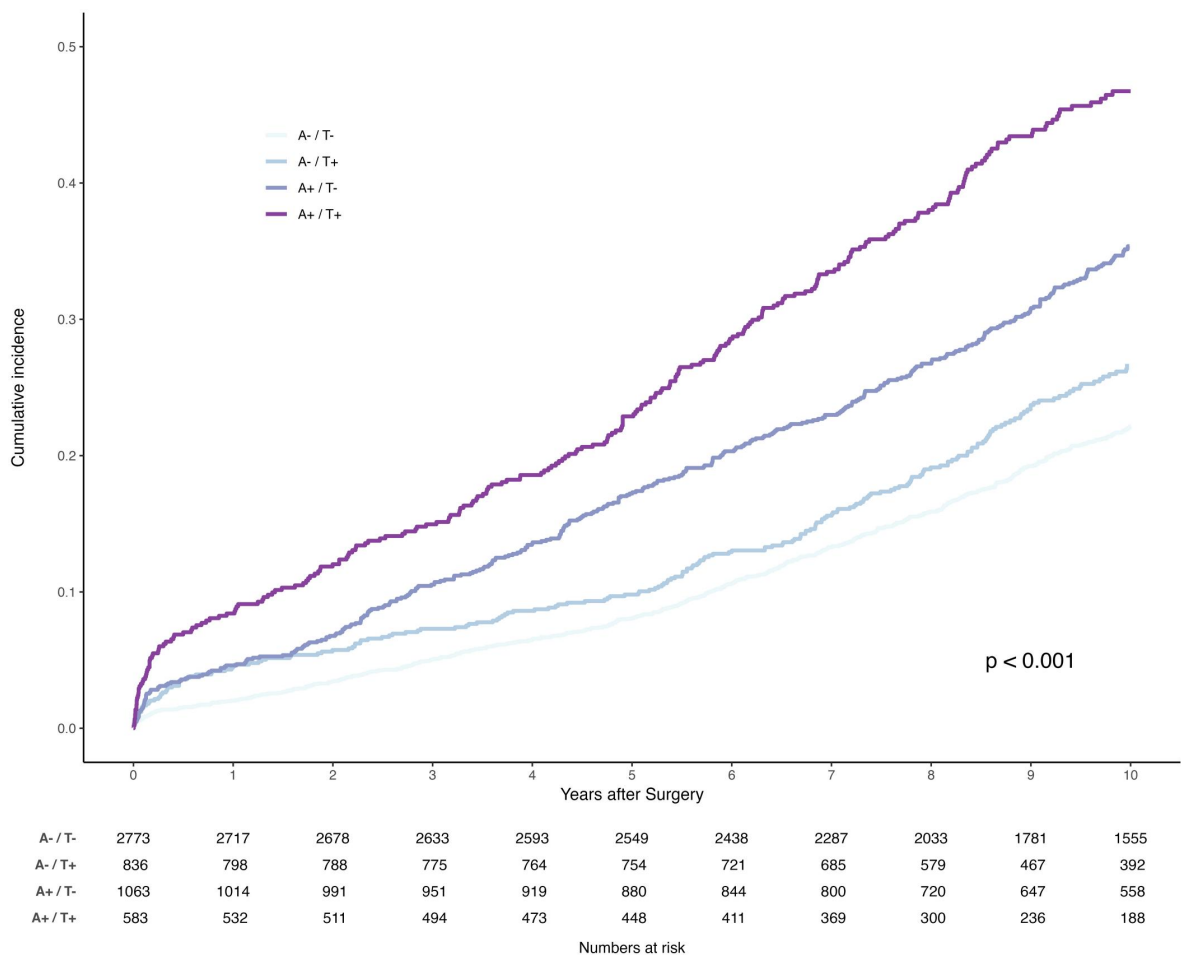


Figure 3: Long-term survival in unweighted cohort (Kaplan–Meier method).

anaemia and perioperative RBC transfusion independently impact late mortality. Finally, it was possible to quantify the interaction effect of the combined anaemia and RBC transfusion on long-term survival.

Regarding immediate postoperative outcomes, a possible explanation for our results might be that preoperative anaemia might be associated with inadequate oxygen delivery ability, impaired tissue oxygenation and subsequent organ dysfunction. This mechanism could justify the increased incidence of postoperative acute kidney injury. On the other hand, RBC transfusion-induced transfusion-related acute lung injury should offer a plausible explanation for increased mechanical ventilation duration. Contrarily, the low event rate of perioperative stroke [$n = 48$ (0.91%)] could undermine our ability to detect significant differences between predefined groups. These, and perhaps other specific complications of cardiac surgery, should explain the extended length of hospital stay described in this study cohort. Finally, only the combined effects of preoperative anaemia and RBC transfusion are associated with an increased risk of in-hospital mortality. Again, with an in-hospital mortality rate of 1.56% ($n = 82$), sample size issues might offer a credible justification for detecting smaller differences between study groups.

The long-term survival impact of anaemia and RBC transfusion appeared to be additive. The effect of preoperative anaemia, compounded by phlebotomy, perioperative blood loss or the haemodilution associated with cardiopulmonary bypass, should extend itself well beyond hospital discharge [14]. Its negative influence exerted over prolonged periods has a well-known association with reduced long-term survival. However, the precise pathophysiological mechanism is not clear. One possible explanation could be the increased haemodynamic overload on the left ventricle, resulting in its remodelling and failure, with an increased mortality risk. Additionally, anaemia is a significant risk factor in ischaemic heart disease, and it correlates with advanced ischaemic heart disease, chronic heart failure, rhythm disturbance, and higher mortality rate [15]. Furthermore, anaemia is associated with higher blood pressure values, and lower dipping status in hypertensive patients [16], thus contributing to an increased cardiovascular risk. Finally, a low haematocrit means hypoxia and cerebral ischaemia; this boosted blood flow and turbulence might enable the migration of a thrombus and embolism [17].

On the other hand, RBC transfusion has profound immunomodulatory effects that render the recipients vulnerable to

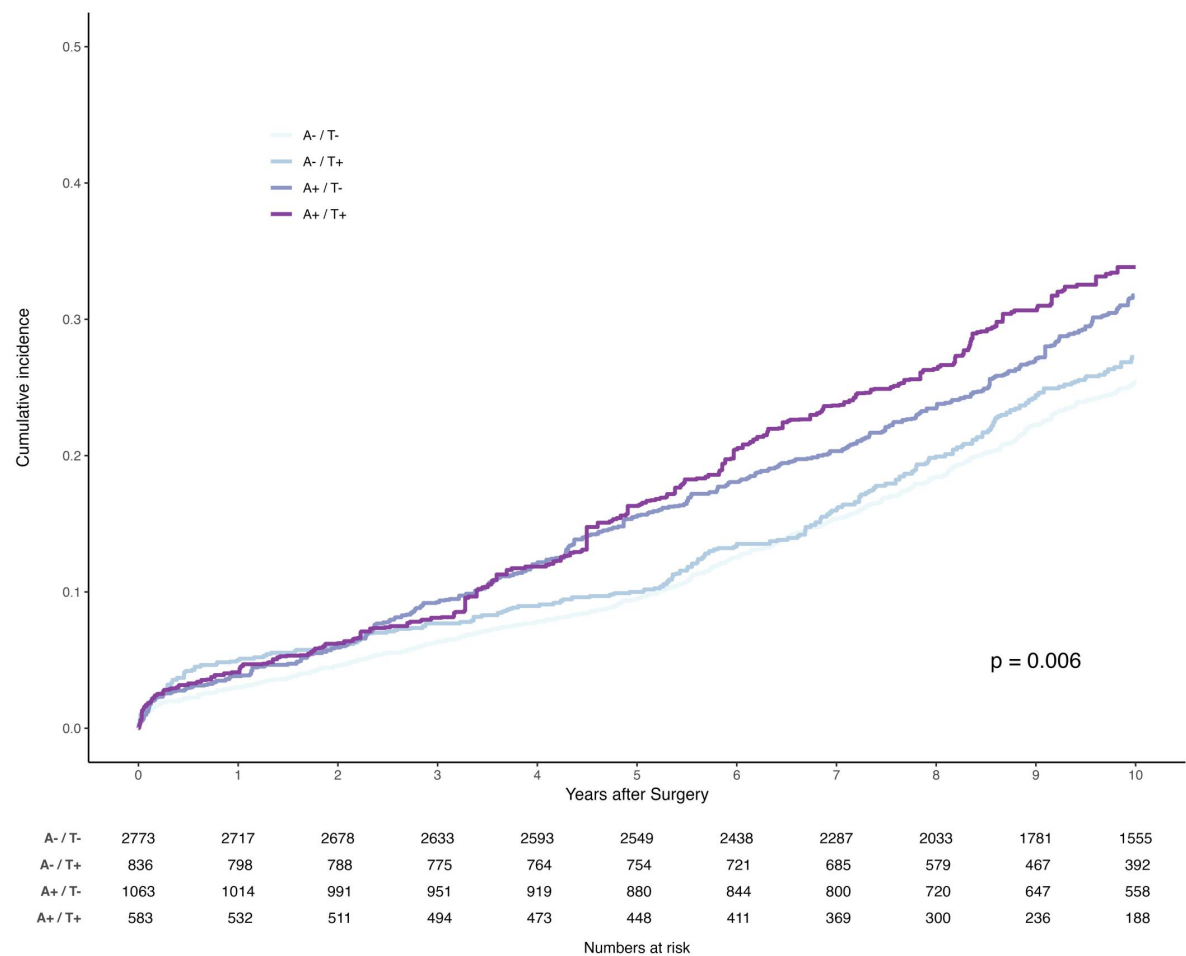


Figure 4: Long-term survival in inverse probability weighted cohort.

infection, coronary graft failure, progression of atherosclerosis, malignancy and reactivation of latent viruses [18–20]. Surprisingly, these consequences persist long after the index transfusion, affecting late mortality [21].

As anaemia frequently triggers RBC transfusion, both circumstances may strike the same patient synchronously. Through the distinct mechanisms mentioned above, they take their toll on late survival [11, 22]. Besides, there seems to be a cooperative effect resulting from their interaction. Demonstrating and quantifying this additional risk lends further insight into the research question.

Several observational studies demonstrated the adverse outcomes of preoperative anaemia [2, 3, 23–30]. For instance, Karkouti *et al.* [31] reported the results from a multicentre cohort study that included 3500 patients (67% of patients underwent isolated CABG). Although their definition of preoperative anaemia (haemoglobin < 12.5 g/dl) differed from ours, as well as the methodology employed to control for confounders (multivariable logistic regression and propensity-score matching), the adjusted OR for the composite end-point of in-hospital death,

stroke or acute kidney injury was 1.8 (95% CI, 1.2 to 2.7). Similarly, Padmanabhan *et al.* [7] documented the association of preoperative anaemia with adverse outcomes after cardiac surgery in their meta-analysis of over 114 000 patients. While the different studies utilized different anaemia definitions and study populations, their combined analysis revealed increased mortality (OR, 2.74; 95% CI, 2.32–3.24; $P < 0.001$), acute kidney injury (OR, 3.13; 95% CI, 2.37–4.12; $P < 0.001$), stroke (OR, 1.46; 95% CI, 1.24–1.72; $P < 0.001$) and infection (OR, 2.65; 95% CI, 1.98–3.55; $P < 0.001$). They found no statistically significant association between mortality and RBC transfusion (OR, 1.35; 95% CI, 0.92–1.98; $P = 0.12$), albeit the severe heterogeneity in the estimate ($I^2 = 83.7\%$). Interestingly, the authors support the addition of preoperative anaemia to future risk prediction models and as a target for risk modification.

Padmanabhan *et al.* [32], in a single-centre retrospective analysis of 1170 propensity-matched pairs of patients, showed that preoperative anaemia was independently associated with long-term mortality, regardless of whether or not patients received RBC transfusion. They found no association between RBC

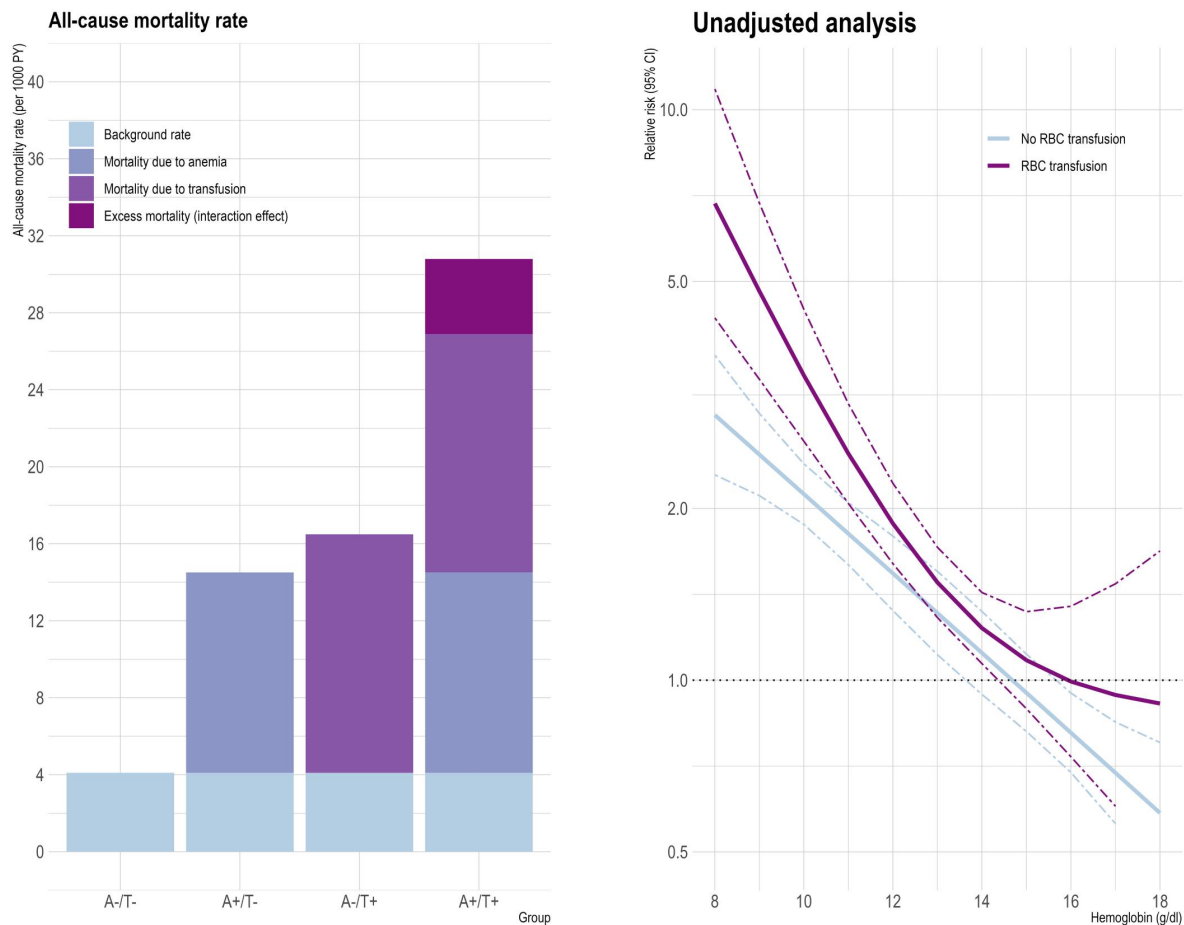


Figure 5: Interaction of haemoglobin concentration and red blood cell transfusion. Haemoglobin concentration treated as a dichotomic variable (left panel). Haemoglobin concentration treated as a continuous variable (right panel).

transfusion and mortality. Furthermore, there was no interaction between preoperative anaemia and blood transfusion on long-term mortality. Differently, in an observational cohort study conducted at a university hospital in Germany that included 3131 patients, von Heymann *et al.* [30] employed multivariate Cox regression analyses to adjust for confounding. Their results indicate that both the severity of preoperative anaemia (mild anaemia: hazard ratio, 1.441; 95% CI, 1.201–1.728; severe anaemia: hazard ratio, 1.805; 95% CI, 1.336–2.440) and intraoperative transfusion (hazard ratio, 1.340; 95% CI, 1.109–1.620) were associated with decreased long-term survival. The authors conclude that long-term survival was worse in anaemic patients receiving intraoperative RBC transfusion. Finally, Schwann *et al.* [21] reported on over 250 000 patients above 65 years undergoing isolated CABG. Using multivariate Cox regression to control for confounding variables, the authors note that both preoperative and intraoperative anaemia are associated with increased mortality, albeit only marginally. They also document a robust and dose-dependent association between RBC transfusion and mortality. However, they failed to demonstrate a significant interaction between the 2 variables.

Limitations

Our study does present some limitations. First, its observational nature qualifies for demonstrating association rather than causality. Despite controlling for confounding variables with a sophisticated IPW algorithm, we cannot account for those that were not measured. Second, treating RBC transfusion as a dichotomic variable precludes establishing a dose-dependent response that further supports our causality contention. Third, exploring an etiologic classification of preoperative anaemia might help refine the management of these patients [5].

CONCLUSION

This longitudinal, population-level study extensively emphasizes the adverse short- and long-term outcomes of preoperative anaemia and perioperative RBC transfusion. It stresses the importance of an evidence-based, multimodal and multidisciplinary approach to conserving blood resources and optimizing outcomes in patients at high risk for transfusion—a Patient Blood Management program. In the face of the information conveyed,

identifying and optimizing scheduled patients for cardiac surgery at risk and non-arbitrary but evidence-based use of a precious resource should be considered standard practice.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

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Conflict of interest: None declared.

DATA AVAILABILITY

The paper's data will be shared on reasonable request to the corresponding author.

Author contributions

Armando Abreu: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Software; Writing—original draft; Writing—review & editing. **José Máximo:** Writing—original draft. **Cláudia Almeida:** Conceptualization; Writing—original draft. **André Lourenço:** Writing—original draft; Writing—review & editing. **Adelino Leite-Moreira:** Funding acquisition; Writing—review & editing.

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Long-Term Survival of Single versus Bilateral Internal Thoracic Artery Grafting

10.

10.1. Background

The World Health Organization defines anaemia as a haemoglobin level of $<13\text{g/dl}$ in men and $<12\text{g/dl}$ in women, translating into a preoperative anaemia prevalence in patients undergoing cardiac surgery from 16% to 54% [454–456]. Hospital-acquired blood loss, iron-deficiency anaemia and anaemia of chronic disease are common causes which are unrelated to the operative procedure itself; nevertheless, the specificities of the surgical practices, such as phlebotomy, intraoperative blood loss and the haemodilution intrinsic to the cardiopulmonary bypass support, might compound the condition [457, 458]. Patients with low haemoglobin concentration have diminished oxygen delivery ability and are prone to end-organ ischaemia. Herein lies the rationale for red blood cell (RBC) transfusion since its primary effect would be increased oxygen delivery and improved organ perfusion.

10.2. Problem Statement and Knowledge Gap

In the past 20 years, a wealth of data analysed the independent influence of preoperative anaemia and perioperative RBC transfusion on outcomes after cardiac surgery. For instance, two meta-analyses [459, 460] established the association between preoperative anaemia and adverse results after surgery. Conversely, several studies described the association of perioperative RBC transfusions with increased long-term mortality [461–464]. However, there is a scarcity of data focusing on the role of the interaction effect of preoperative anaemia and perioperative transfusion on long-term survival.

10.3. Research Objectives

This article strives to describe the independent and combined effects of preoperative anaemia and perioperative RBC transfusion on long-term survival in a large single-centre inverse probability-weighted (IPW) cohort of patients admitted for isolated coronary artery bypass grafting (CABG). IPW creates a pseudo-population of the treatment and the control groups, with the same covariate distribution as the overall treated and untreated population [23]. This methodology allows us to estimate the average treatment effect in the entire population, the same question asked in a randomized controlled trial.

10.4. Reader's Note

The subsequent section of this chapter reproduces the full text of the study, "The additive effects of anaemia and transfusion on long-term survival after coronary artery bypass surgery", by Armando Abreu, José Máximo, Cláudia Almeida, André Lourenço, and Adelino Leite-Moreira [465] and published in *European Journal of Cardio-Thoracic Surgery. (EJCTS)* (2024). The paper has been included with the publisher's permission under the terms of the Creative Commons Attribution License.

For proper citation, please refer to the original publication: Abreu, A., Máximo, J., & Leite-Moreira, A. (2024). Preoperative smoking status and long-term survival after coronary artery bypass grafting: a competing risk analysis. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery*, 65(5), ezae183. DOI: 10.1093/ejcts/ezae183.

10.5. Original Publication

The full text of the study, titled "Long-term survival of single versus bilateral internal mammary artery grafting in patients under 70", is included in the following pages.

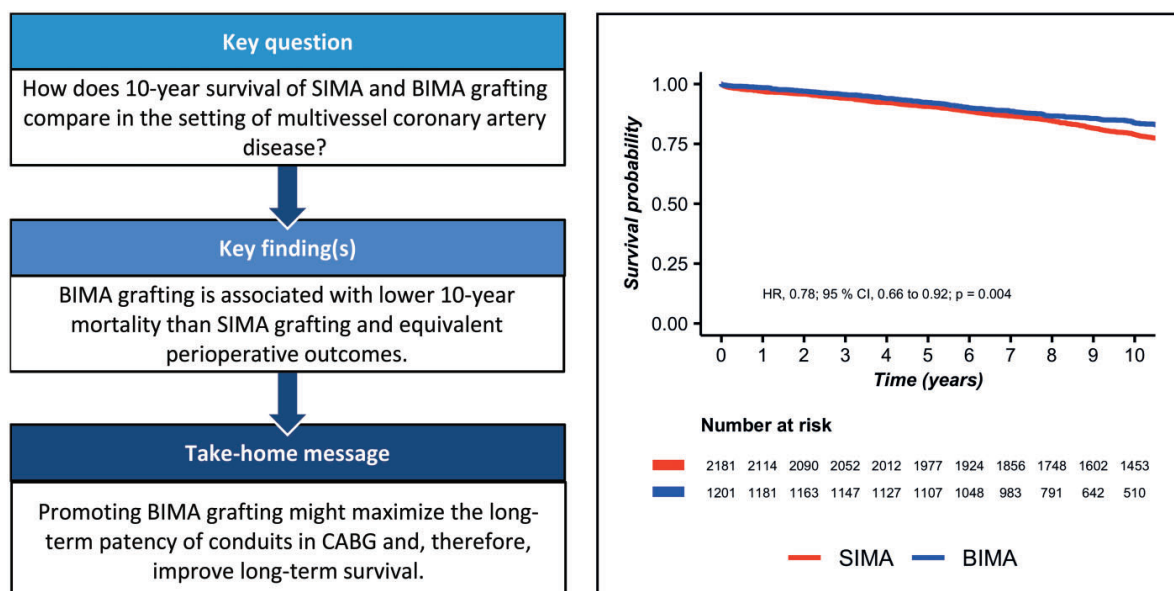
Cite this article as: Abreu A, Máximo J, Leite-Moreira A. Long-term survival of single versus bilateral internal mammary artery grafting in patients under 70. *Interact CardioVasc Thorac Surg* 2022; doi:10.1093/icvts/ivac225.

Long-term survival of single versus bilateral internal mammary artery grafting in patients under 70

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Abstract

OBJECTIVES: As definitive data from randomized controlled trials comparing the effect on long-term survival of using single internal mammary artery (SIMA) or bilateral internal mammary artery (BIMA) grafting are not yet available, observational studies allow for long-term follow-up in large and representative populations, which might complement the information potentially derived from randomized trials. To compare long-term survival in patients under 70 years of age undergoing SIMA or BIMA grafting.

METHODS: Retrospective analysis of 3384 consecutive patients under 70 years undergoing primary isolated coronary artery bypass grafting, performed from 2000 to 2015, in a Portuguese level III Hospital. We identified 2176 and 1208 patients from the study population who underwent SIMA and BIMA grafting, respectively. The primary end point was all-cause mortality at 10 years. We employed inverse probability weighting to restrict confounding by indication.

RESULTS: The mean age of the study population was 59.4 ($\pm$ 7.6) years, and 567 (16.8%) were females. Inverse probability weighting was effective in eliminating differences in all significant baseline characteristics. Follow-up was 99.88% complete. The median follow-up time was 12.82 (interquartile range, 9.65, 16.74) years: the primary end point of all-cause mortality at 10 years occurred in 463 patients (21.3%) and 166 (13.7%) in the SIMA and BIMA grafting groups, respectively (hazard ratio, 0.78; 95% confidence interval, 0.66–0.92; P = 0.004).

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CONCLUSIONS: Bilateral internal mammary grafting is associated with lower long-term mortality than single internal mammary grafting. Moreover, this survival benefit comes at no increased perioperative morbidity or mortality cost.

Keywords: Coronary artery bypass grafting • Internal mammary coronary artery anastomosis • Propensity score • Survival analysis

ABBREVIATIONS

BIMA	Bilateral internal mammary artery
CABG	Coronary artery bypass grafting
CI	Confidence interval
GDMT	Guideline-directed medical therapy
ICD-9-CM	International classification of diseases, 9th edition, clinical modification
IMA	Internal mammary artery
IPW	Inverse probability weighting
IQR	Interquartile range
OR	Odds ratio
SIMA	Single internal mammary artery
SMD	Standardized mean difference
SVGs	Saphenous vein grafts

INTRODUCTION

As outcomes following coronary artery bypass grafting (CABG) are ultimately related to long-term graft patency, the choice of bypass conduits plays a central role in this surgical procedure [1]. The internal mammary artery (IMA) possesses exceptional biological properties that confer relative resistance to atherosclerosis and better long-term patency than saphenous vein grafts (SVGs), making it a conduit of choice for CABG [2–4]. Therefore, Loop *et al.* [5] established the use of the left IMA to the left anterior descending artery as the standard of care and demonstrated that it prolonged survival and improved long-term results after CABG. Consequently, it seems intuitive that if a single IMA (SIMA) was good, bilateral IMAs (BIMA) would be better [6].

Lytle *et al.* [7] from the Cleveland Clinic published the first comprehensive analysis of clinical results of BIMA grafting. Since their publication, several meta-analyses of single-institution observational studies have confirmed that BIMA grafting is associated with significantly reducing long-term mortality [8–13]. Yet, even though they provide important information when prospective randomized trials are unavailable, they remain limited by their potential for selection bias. However, the Arterial Revascularization Trial, designed to answer whether BIMA can improve 10-year survival compared with SIMA, failed to demonstrate a significant between-group difference in the death rate from any cause at 10 years [14], despite its intensely debated methodological limitations [15, 16].

This article aims to compare long-term survival in patients under 70 years of age undergoing SIMA versus BIMA in a large single-centre inverse probability-weighted (IPW) cohort of patients. IPW creates a pseudo-population of the treatment and the control group, with the same covariate distribution as the overall treated and untreated population [17]. This methodology allows us to estimate the average treatment effect in the entire population, the same question asked in a randomized controlled trial.

MATERIALS AND METHODS

Ethical statement

The São João University Hospital Center Ethics Committee approved this research and waived the need for informed consent.

Study design

We conducted an observational retrospective study to evaluate SIMA and BIMA utilization trends, in-hospital complications, length of hospital stay, discharge disposition and long-term (10 years) survival in patients with isolated coronary artery disease undergoing CABG. Thus, we analysed an administrative dataset containing all hospitalizations occurring in a tertiary care hospital from 1 January 2000 to 30 September 2015 [chosen as the cut-off date because of International Classification of Diseases, 9th Revision, Clinical Modification (ICD-10-CM) implementation]. The corresponding diagnoses and procedures were coded for each hospitalization based on the ICD-9-CM.

Study population

Patients were included in the study if they were under the age of 70 years and underwent primary CABG (ICD-9-CM codes 36.10, 36.11, 36.12, 36.13, 36.14, 36.15, 36.16, 36.17 or 36.19) during the study period, with >1 graft performed. Exclusion criteria included previous cardiac surgery, concomitant valve replacement or repair, concurrent aorta surgery and simultaneous correction of myocardial infarction mechanical complications (Supplementary Material, Table S1).

Data sources and variables

From an administrative dataset containing all hospitalizations occurring in our Institution from 2000 to 2015, we identified all hospitalizations with at least 1 associated procedure code of CABG. The predictive or independent variable was the treatment modality of CABG, a dichotomous variable defined by the presence of ICD-9-CM code 36.16 (BIMA, the intervention) or 35.15 (SIMA, the comparator). We obtained patients' baseline characteristics from our institution patient's discharge datasets. After extracting the relevant ICD-9-CM codes, we computed the Charlson Comorbidity Index using the Quan *et al.* coding scheme [18]. We provide definitions of coexisting conditions in Supplementary Material, Table S2.

Outcomes

We compared episodes coded as BIMA grafting to those coded as SIMA grafting. The primary outcome variable was 10-year survival. The patient discharge database was linked to the Portuguese National Patient Registry to ascertain patient life status. Secondary outcomes included a set of predefined in-hospital

complications (see [Supplementary Material, Table S3](#) for detailed definitions), the length of hospital stay and discharge disposition (categorized as home discharge, transfer to other healthcare facilities or in-hospital death).

Statistical analysis

Data are presented as absolute frequencies and percentages for categorical variables and as means and standard deviations for continuous variables. We used the standardized mean difference (SMD) to assess discrepancies in covariates between treatment groups, as it allows for the judgement of the relative balance of variables measured in different units. We held values <0.1 to indicate a negligible difference in the mean or frequency of a covariate between treatment groups.

In the univariable analysis, we computed summary measures of risk [odds ratio (OR)], its associated 95% confidence interval (CI) and a chi-squared test for difference in the observed proportions from count data presented in a two-by-two table for each of the predefined outcomes.

We employed IPW to restrict confounding by indication. IPW makes sense with an active comparator, allowing us to estimate the average treatment effect in the entire population. Making these causal contrasts depends on predicting treatment based on relevant covariates, that is the propensity score estimation. Multivariable logistic regression was used in each treatment group to estimate each patient's probability of undergoing BIMA grafting (i.e. the propensity score). The propensity model

included the following variables: sex, age, admission status (scheduled vs unscheduled), disease presentation (stable coronary disease, unstable angina/non-ST-elevation myocardial infarction and ST-elevation myocardial infarction), hypertension, diabetes mellitus, hyperlipidaemia, obesity, smoking history, cerebrovascular disease, congestive heart failure, chronic obstructive pulmonary disease, peripheral vascular disease, chronic kidney disease, liver disease, anaemia, coagulation disorders, cancer history and the Charlson comorbidity index. We calculated stabilized weights by dividing the marginal probability of the observed treatment by the propensity score for the treatment received. Finally, we assessed the balance between treatment groups using SMDs, with an ideal balance represented by a standardized difference of 10% or less. We included visual depictions of distributional balance as they are a helpful complement to numerical summaries.

We derived weighted logistic regression models with a robust variance estimator with the outcome as the dependent variable and the group on which the propensity score balances (e.g. the treatment group) as the only independent/predictor variable.

Estimates of survival probabilities were calculated using the Kaplan-Meier method and compared with the log-rank test. Follow-up time, described by median and interquartile range (IQR), was obtained using the same estimator by reversing the event indicator so that the outcome of interest became being censored. We employed a weighted Cox proportional hazards regression model with a robust variance estimator to compare long-term mortality between groups.

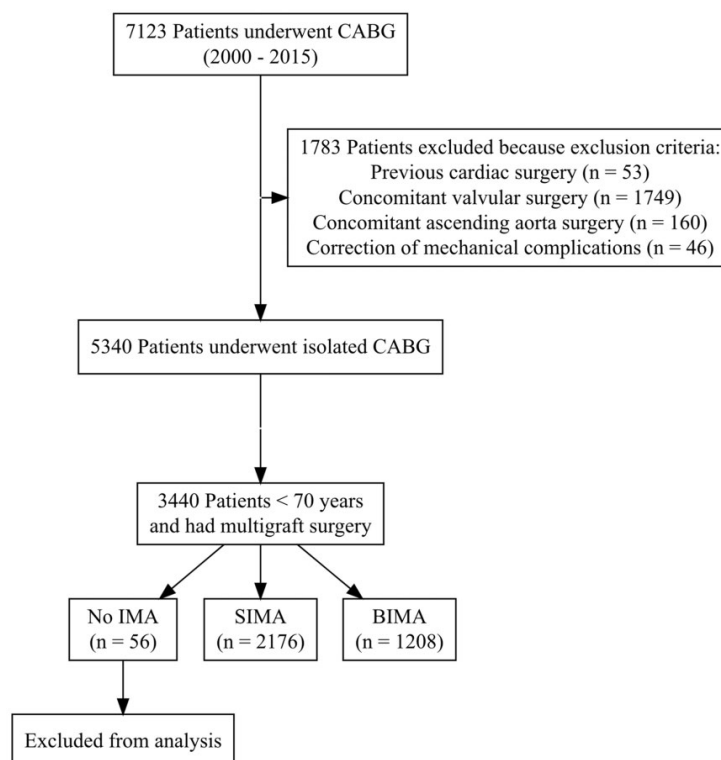


Figure 1: Study flowchart.

P-values <0.05 were considered statistically significant. All statistical analyses were performed using R, version 4.1.2 [19].

RESULTS

Of 7123 patients who underwent CABG during the study period, 3440 were eligible for inclusion in the study (Fig. 1): 2176 patients in the SIMA group (63.3%) and 1208 patients in the BIMA group (35.1%). In this time frame, 3384 (98.4%) received at least 1 IMA graft. The mean age of the study population was 59.4 ($\pm$ 7.6) years, and 567 (16.8%) were females. Figure 2 portrays the annual trend of relative BIMA and SIMA utilization during the study period. In this time frame, BIMA utilization was ~0.5% in 2000, and it rose to ~80% in 2015 in this patient population.

Baseline characteristics

Patients in the BIMA group were less likely to be female (13.2% vs 18.7%, SMD 0.149), were younger (56.82 ± 7.65 vs 60.76 ± 7.24 years, SMD 0.529) and were more likely to be operated on following an acute coronary syndrome (40.2% vs 34.2%, SMD=0.165), less likely to have diabetes mellitus (35.5% vs 40.0%, SMD 0.152) and more likely to have a past or current

smoking history (53.9% vs 40.6%, SMD=0.274). In addition, BIMA patients presented with lower Charlson comorbidity index scores (3.49 ± 1.44 vs 3.81 ± 1.38 , SMD=0.224). IPW effectively eliminated differences in all baseline characteristics (Table 1 and Fig. 3), as revealed by SMD values below 0.10. The mean stabilized weight was close to 1, and its maximum value was inferior to 10 (actually, 5.67), so no trimming procedure was necessary as a sensitivity analysis.

Unadjusted analysis

In the crude univariable analysis (Table 2), BIMA patients were less likely to require longer mechanical ventilation times (2.3% vs 4.5%, OR=0.50, 95% CI 0.32–0.75, $P < 0.001$) and to demand orotracheal reintubation less often (1.4% vs 2.4%, OR=0.58, 95% CI 0.33–0.99, $P = 0.055$). Regarding discharge disposition, BIMA patients were more likely to go directly home after the index hospitalization (96.9% vs 95.3%, OR=1.56, 95% CI 1.07–2.31, $P = 0.023$). We have not noted any other differences in the rates of pre-specified complications. Concerning the length of hospital stay (Table 2), BIMA patients required shorter median hospitalization periods: change in the estimate of -1.6 days (95% CI -2.2 to -1.1, $P < 0.001$).

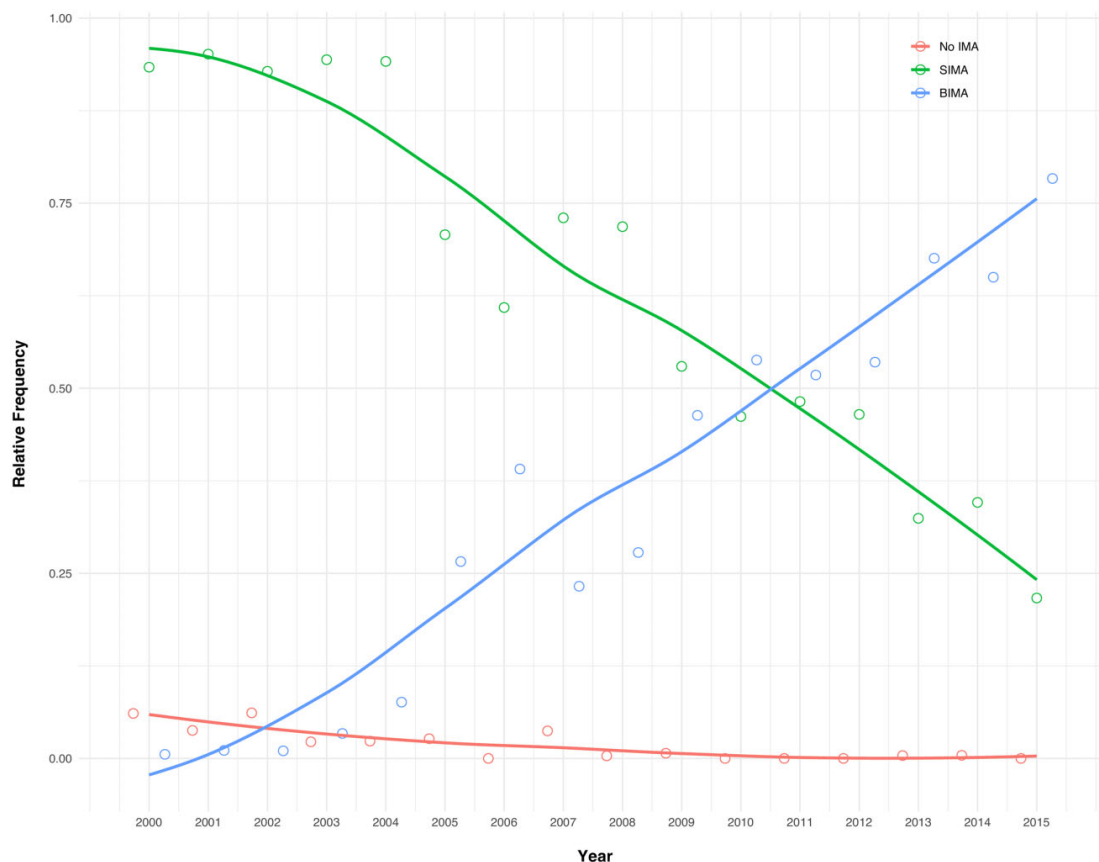


Figure 2: Temporal trends in single internal mammary artery versus bilateral internal mammary artery grafting (2000–2015).

Table 1: Baseline characteristics for unweighted and inverse probability weighting cohorts: single internal mammary artery versus bilateral internal mammary artery

Characteristic	Unadjusted cohort			IPW cohort		
	SIMA (n = 2176)	BIMA (n = 1208)	SMD	SIMA (n = 2184.8)	BIMA (n = 1200.8)	SMD
Female, n (%)	407 (18.7)	160 (13.2)	0.149	367.1 (16.8)	203.8 (17.0)	0.004
Age, mean (SD)	60.76 (7.24)	56.82 (7.65)	0.529	59.20 (8.09)	59.16 (7.23)	0.005
Admission, n (%)			0.040			0.012
Scheduled	1040 (47.2)	553 (45.8)		1024.9 (47.3)	574.6 (47.9)	
Unscheduled	1136 (52.2)	655 (54.2)		1151.9 (52.7)	626.2 (52.1)	
Presentation, n (%)			0.165			0.006
Chronic CAD	1432 (65.8)	722 (59.8)		1394.3 (63.8)	769.3 (64.1)	
UA/NSTEMI	520 (23.9)	377 (31.2)		578.8 (26.5)	314.8 (26.2)	
STEMI	224 (10.3)	109 (9.0)		211.6 (9.7)	116.8 (9.7)	
Hypertension, n (%)	1424 (65.4)	777 (64.3)	0.023	1410.4 (64.6)	772.9 (64.4)	0.004
Diabetes mellitus, n (%)			0.152			0.005
No diabetes	1305 (60.0)	779 (64.5)		1349.7 (61.8)	742.8 (61.9)	
Non-insulin treated	771 (35.4)	350 (29.0)		717.6 (32.8)	394.7 (32.9)	
Insulin treated	100 (4.6)	79 (6.5)		117.5 (5.4)	63.3 (5.3)	
Hyperlipidaemia, n (%)	1392 (64.0)	832 (68.9)	0.104	1437.8 (65.8)	791.6 (65.9)	0.002
Obesity, n (%)	517 (23.8)	330 (27.3)	0.082	544.3 (24.9)	297.5 (24.8)	0.003
Smoking history, n (%)			0.274			0.009
No smoking history	1292 (59.4)	557 (46.1)		1190.5 (54.5)	659.8 (54.9)	
Previous smoker	460 (21.1)	312 (25.8)		494.2 (22.6)	269.2 (22.4)	
Current smoker	424 (19.5)	339 (28.1)		500.1 (22.9)	271.9 (22.6)	
CVD, n (%)	286 (13.1)	176 (14.6)	0.041	292.2 (13.4)	159.6 (13.3)	0.002
CHF, n (%)	401 (18.4)	197 (16.3)	0.056	381.5 (17.5)	202.6 (16.9)	0.016
COPD, n (%)	129 (5.9)	92 (7.6)	0.067	140.3 (6.4)	77.3 (6.4)	0.0005
PVD, n (%)	65 (3.0)	57 (4.7)	0.090	78.0 (3.6)	43.2 (3.6)	0.002
CKD, n (%)			0.031			0.002
No chronic kidney disease	2082 (95.7)	1154 (95.5)		2091 (95.7)	1150 (95.7)	
Non-dialysis dependent	79 (3.6)	48 (4.0)		80.8 (3.7)	44.1 (3.7)	
Dialysis dependent	15 (0.7)	6 (0.5)		13.2 (0.6)	7.2 (0.6)	
Liver disease, n (%)	47 (2.2)	22 (1.8)	0.024	44.2 (2.0)	23.9 (2.0)	0.003
Anaemia, n (%)	198 (9.1)	77 (6.4)	0.102	180.3 (8.3)	103.1 (8.6)	0.012
Coagulation disorders, n (%)	34 (1.6)	11 (0.9)	0.059	27.8 (1.3)	12.2 (1.0)	0.024
Cancer, n (%)	15 (0.7)	8 (0.7)	0.003	14.7 (0.7)	8.4 (0.7)	0.003
CCI, mean (SD)	3.81 (1.38)	3.49 (1.44)	0.224	3.67 (1.43)	3.66 (1.37)	0.008

BIMA: bilateral internal mammary artery; CAD: coronary artery disease; CCI: Charlson comorbidity index; CHF: congestive heart failure; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; CVD: cerebrovascular disease; IPW: inverse probability weighting; PVD: peripheral vascular disease; SD: standard deviation; SIMA: single internal mammary artery; SMD: standardized mean difference; STEMI: ST-elevation myocardial infarction; UA/NSTEMI: unstable angina/non-ST-elevation myocardial infarction.

Weighted analysis

IPW resulted in balanced baseline characteristics in each group (Fig. 3). As depicted in Fig. 4, BIMA patients were less likely to require longer mechanical ventilation times (2.4% vs 4.7%, OR = 0.50, 95% CI 0.32–0.79, $P = 0.003$). We have not noted any other differences in pre-specified complications or discharge disposition rates. Concerning the length of hospital stay, there were no significant differences between groups (change in estimate 0.04 days, 95% CI -0.74 to 0.77, $P = 0.911$).

Survival analysis

Follow-up was 99.88% complete (4 patients with vital status impossible to ascertain). The median follow-up time was 12.82 (IQR, 9.65–16.74) years: 14.93 (IQR, 11.67–18.55) years for the SIMA group and 10.18 (IQR, 8.16–12.56) years for the BIMA group. The primary end point of all-cause mortality at 10 years occurred in 463 patients (21.3%) in the SIMA group, as compared with 166 (13.7%) in the BIMA group (hazard ratio, 0.78; 95% CI, 0.66–0.92; $P = 0.004$). Thirty-day and 1-, 5- and 10-year survival

rates were 99.0%, 96.9%, 90.2% and 78.0% in the SIMA group and 99.5%, 98.4%, 92.7% and 84.8% in the BIMA group. Figure 5 depicts the unweighted survival function plot for both groups. Figure 6 illustrates the weighted survival function plot for both groups. Both reveal the difference in long-term survival between groups.

DISCUSSION

In this longitudinal, population-level analysis of patients undergoing isolated primary CABG, we demonstrated that the use of BIMA for treating multivessel coronary artery disease is associated with lower long-term mortality than SIMA. Moreover, we proved that this survival benefit comes at no increased perioperative morbidity or mortality cost.

A possible explanation for our results might be that the IMA holds exceptional biological properties that grant protection to atherosclerotic plaque formation and its subsequent evolution, thus making it a conduit of choice for CABG [4]. Angiographic studies specifically directed at evaluating right IMA patency rates reported 10-year patency rates over 90%, equivalent to the left

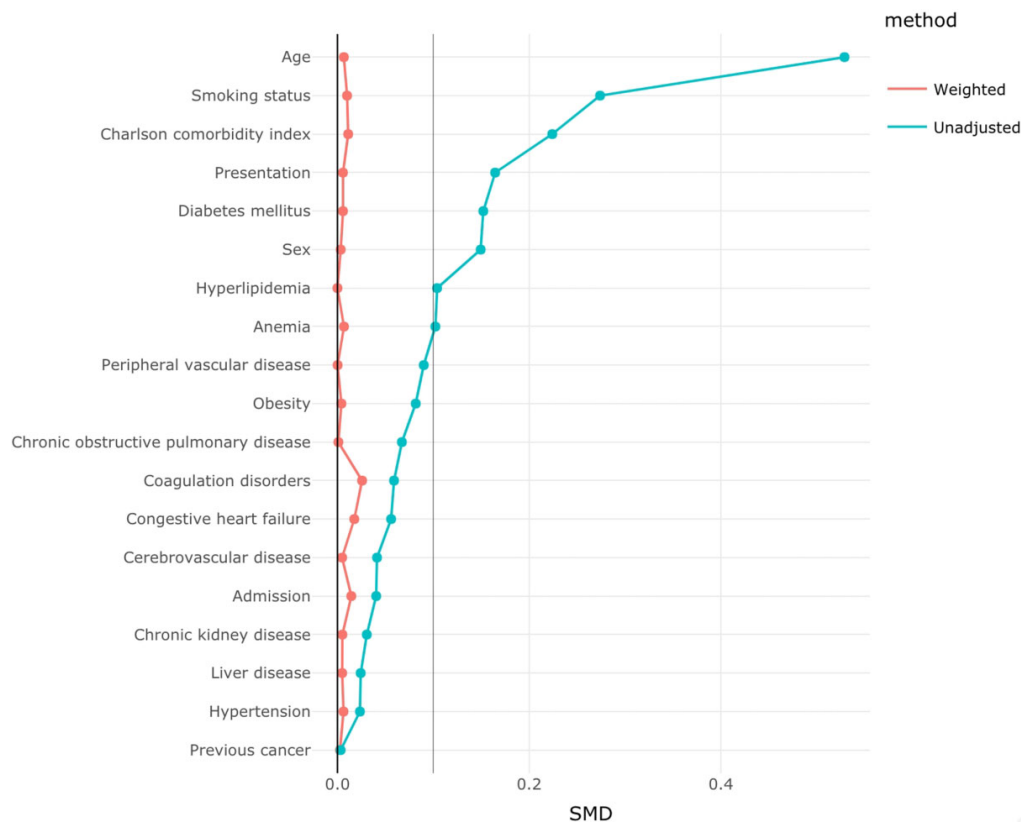


Figure 3: Covariate balance assessment.

Table 2: Crude intra- and postoperative outcomes: single internal mammary artery versus bilateral internal mammary artery

Outcome	SIMA (n = 2186)	BIMA (n = 1208)	OR (95% CI)	P-Value
Stroke, n (%)	19 (0.9)	11 (0.9)	1.04 (0.48, 2.16)	0.911
Cardiac, n (%)				
POAF	225 (10.3)	105 (8.7)	0.83 (0.65, 1.05)	0.122
Pacemaker implantation	9 (0.4)	3 (0.2)	0.60 (0.13, 2.01)	0.443
IABP	63 (2.9)	32 (2.6)	0.91 (0.59, 1.39)	0.678
Cardiac arrest	6 (0.3)	2 (0.2)	0.60 (0.09, 2.61)	0.532
Respiratory, n (%)				
Prolonged ventilation	99 (4.5)	28 (2.3)	0.50 (0.32, 0.75)	0.001
Reintubation	52 (2.4)	17 (1.4)	0.58 (0.33, 0.99)	0.055
Tracheotomy	9 (0.4)	2 (0.2)	0.40 (0.06, 1.55)	0.241
AKI, n (%)	20 (0.9)	5 (0.4)	0.44 (0.15, 1.11)	0.109
Hemorrhage, n (%)	77 (3.5)	34 (2.8)	0.79 (0.52, 1.18)	0.258
RBC transfusion, n (%)	539 (24.8)	326 (27.0)	1.12 (0.96, 1.32)	0.157
Surgical wound, n (%)	32 (1.5)	15 (1.2)	0.84 (0.44, 1.53)	0.586
Discharge disposition, n (%)				0.070
Home	2074 (95.3)	1171 (96.9)	1.56 (1.07, 2.31)	
Other hospitals	77 (3.5)	29 (2.4)	0.67 (0.43, 1.02)	
Death	25 (1.1)	8 (0.7)	0.57 (0.24, 1.22)	
LOS, median (IQR)	7 (6, 9)	6 (5, 8)	-1.6 (-2.2, -1.1)	<0.001

AKI: acute kidney injury; BIMA: bilateral internal mammary artery; CI: confidence interval; CIE: change in estimate; IABP: intra-aortic balloon pump counterpulsation; IQR: interquartile range; OR: odds ratio; POAF: postoperative atrial fibrillation; RBC: red blood cell; SIMA: single internal mammary artery; LOS: length of stay.

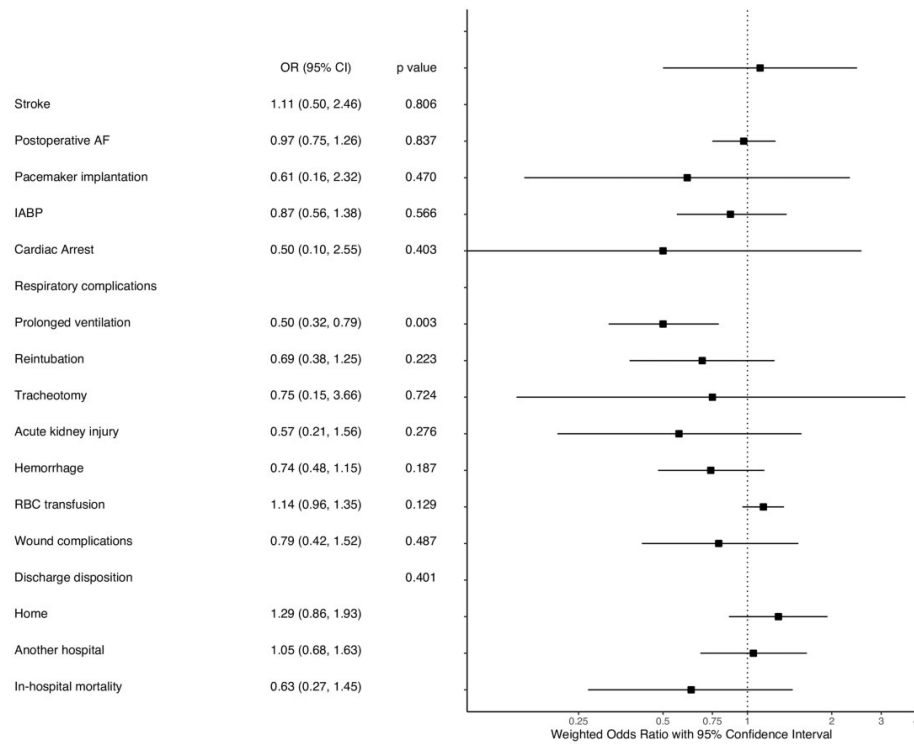


Figure 4: Weighted clinical outcomes: single internal mammary artery versus bilateral internal mammary artery.

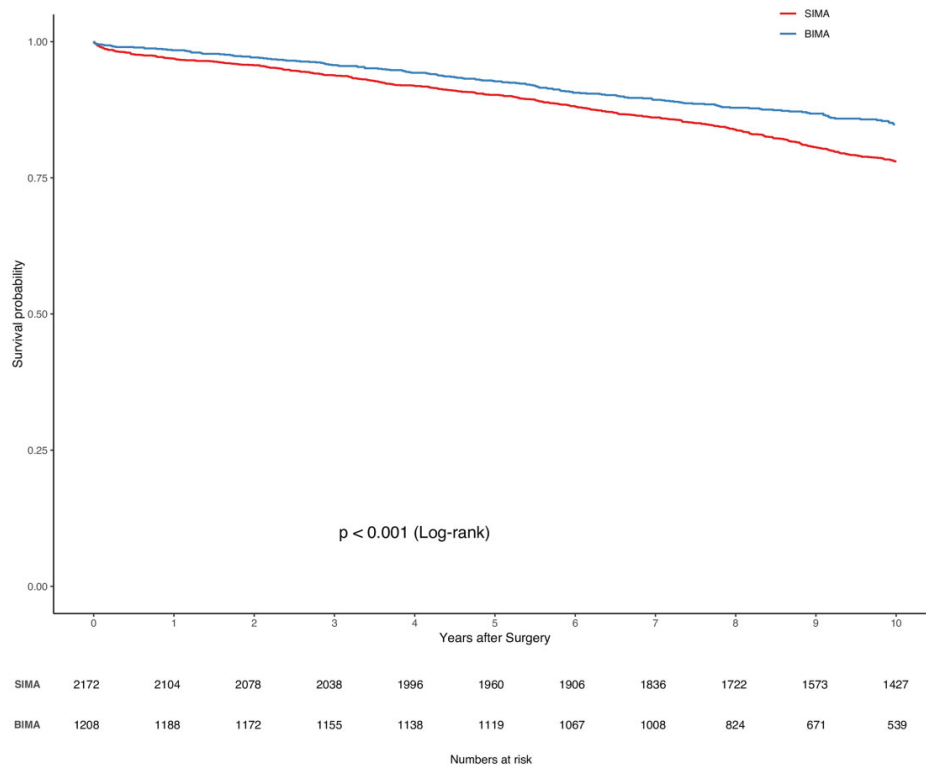


Figure 5: Long-term survival in unweighted cohort (Kaplan-Meier method): single internal mammary artery versus bilateral internal mammary artery.

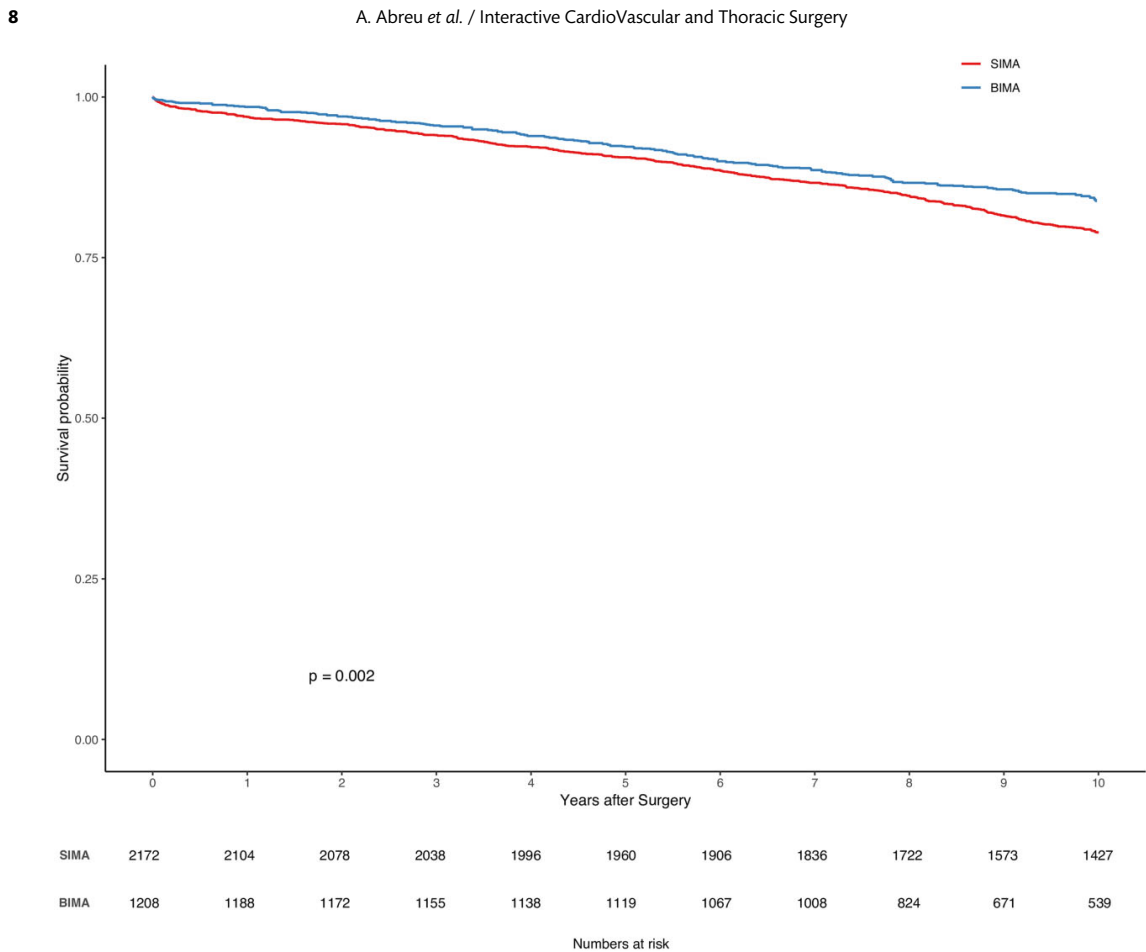


Figure 6: Long-term survival in inverse probability weighting cohort: single internal mammary artery versus bilateral internal mammary artery.

IMA for identical territories, always better than radial artery and SVG, and remain free of atheroma [20]. On the other hand, SVG durability is suboptimal, with reported 10-year patency rates of around 50%, and among these patent conduits, only 50% are free from atherosclerotic disease [21, 22]. As the long-term success of coronary revascularization depends on graft patency [23], it does make sense that BIMA grafting would fare better than SIMA supplemented by SVG.

Consistent with the aggregated findings of other observational studies in the literature [8–13], we demonstrate that BIMA grafting improved long-term survival. With a median follow-up time of over twelve years, patients receiving BIMA grafting had a 22% reduction in all-cause mortality, a survival benefit that becomes more pronounced 7 years after the procedure. One possible explanation for this finding could be the known SVGs attrition rate, which increases to ~5% per year beyond the seventh postoperative year [21].

As to randomized controlled trial-derived information, in the Arterial Revascularization Trial, among patients scheduled for CABG and randomly assigned to undergo bilateral or SIMA grafting, there was no significant between-group difference in the rate of death from any cause at 10 years in the intention-to-treat analysis [14]. Several proposed justifications could explain the neutral effect of BIMA grafting in this trial [15, 16, 24]. First, the

sample size calculations predate guideline-directed medical therapy (GDMT), such that the sample size might be too small to demonstrate a significant decrease in the proposed end-points. Second, there was a high crossover rate (14% of patients assigned to the BIMA group had an SIMA) that might be related to surgeon inexperience. Third, ~22% of SIMA patients also received a radial artery graft, which appears to have superior patency rates than SVGs, resulting in improved long-term outcomes [25]. Finally, adherence to GDMT was extremely high in this trial, and noncompliance with GDMT after CABG seems to decrease long-term survival, freedom from myocardial infarctions and the need for repeat coronary revascularization procedures [26].

Limitations

There are several limitations in our study. First, although using administrative databases allows for the efficient assessment of large populations over long periods of time, coding practices were developed for reimbursement issues, not for clinical outcome profiling. As such, imprecise or equivocal definitions may compromise coding accuracy. In addition, surgical risk models are usually based on a limited number of crucial clinical variables that typically are unavailable in administrative databases [27].

Second, we employed IPW to restrict confounding by indication, which makes sense with an active comparator, allowing us to estimate the average treatment effect in the entire study population. Nevertheless, propensity score-based methodologies do not consider factors that are not analysed, such as patients' frailty, quality of coronary artery targets, quality of venous and arterial conduits or secondary prevention after CABG. Only a prospective randomized trial, where the distribution of known and unknown confounders would be similar in both the intervention and control groups, could address these issues.

Third, although demonstrating an adjusted survival benefit of BIMA grafting is essential, we present no data on the risk of future revascularization procedures, which could lend additional support for greater BIMA use [28].

Our results have significant implications for clinical practice, as promoting BIMA grafting might maximize the long-term patency of CABG conduits and improve long-term survival. Overall, the current use of BIMA grafting in clinical practice remains relatively low, with fewer than 5% of patients in the USA and fewer than 10% in Europe receiving it [29]. The absence of randomized controlled trial-derived data to support its widespread use might explain this finding. In our cohort of patients under 70 years, BIMA grafting use was around 4% in 2000 and rose to 75% by 2015. Behind this growth is a firm conviction in the benefits of arterial revascularization among the surgical staff. In addition, we believe that the choice of revascularization strategy should be tailored to the patient and not dictated by the surgeon's ineptitude. Therefore, removing unjustified operating room time restrictions to BIMA takedown allows for proficiency in IMA harvesting, a paramount detail during training. In our experience, routinely skeletonized arteries by experienced surgeons afford little increased operative time and do not appear to increase sternal wound complications [30], even in diabetic patients.

CONCLUSION

In this longitudinal, population-level analysis of patients under 70 years undergoing primary, isolated CABG, we demonstrated that BIMA for treating multivessel coronary artery disease is associated with lower long-term mortality than SIMA. Moreover, we proved that this survival benefit comes at no increased perioperative morbidity or mortality cost.

SUPPLEMENTARY MATERIAL

[Supplementary material](#) is available at *ICVTS* online.

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Conflict of interest: none declared.

Data availability

The article's data will be shared on reasonable request to the corresponding author.

Author contributions

Armando Abreu: Conceptualization; Data curation; Formal analysis; Methodology; Software; Visualization; Writing—original draft. **José Máximo:** Writing—review & editing. **Adelino Leite-Moreira:** Writing—review & editing.

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Long-Term Survival of Off-Pump versus On-Pump Coronary Artery Bypass Grafting

11.

11.1. Background

Coronary artery bypass grafting (CABG) remains the most common cardiac surgery performed today worldwide [8, 140]. Subject to several technical refinements in its 50-year history, it is still, despite wide geographical variations, usually performed through a midline sternotomy, under cardiopulmonary bypass (CPB) support, and cardioplegic arrest for the construction of coronary anastomosis in a quiet, bloodless field [14, 17]. Since the mid-1980s, in an attempt to overcome some of the conventional on-pump coronary artery bypass (ONCAB) limitations by avoiding potentially harmful adverse effects associated with extracorporeal circulation and aortic cross-clamping, off-pump coronary artery bypass (OPCAB) develops. As it requires making the same anastomosis on a beating heart, its increased technical difficulty with its attending longer learning curve raised concerns about an increased incidence of incomplete revascularisation, early and late graft occlusion, and the need for repeat revascularisation, and consequent inferior long-term survival [466].

11.2. Problem Statement and Knowledge Gap

While both techniques' short- and medium-term results appear to be comparable or even favor OPCAB [467, 468], results from several recent observational studies [220, 221] and meta-analyses [214, 222–224] suggest that OPCAB may confer inferior long-term results. Additionally, the 5-year results of three large randomised controlled trials (RCTs), namely the randomised on/off bypass (ROOBY), the CABG off- or on-pump revascularisation study (CORONARY), as well as the German off-pump coronary artery bypass grafting in elderly patients (GOPCABE) trial became available [216–218]. While the ROOBY trial demonstrated that OPCAB led to lower rates of 5-year survival and event-free survival than ONCAB, the CORONARY and the GOPCABE failed to confirm any such difference. Therefore, it is unclear whether patient-related factors, completeness of revascularisation, graft patency, and the use of multiple arterial grafting are responsible for these long-term outcomes or whether the use of CPB to perform the procedure plays a central role.

11.3. Research Objectives

This paper compares long-term survival in patients with multivessel ischaemic heart disease undergoing OPCAB versus ONCAB in a large Northern Portugal cohort between 2000 and 2015. We employed an overlap weighting (OW) algorithm to minimise confounding. Its target population highlights patients with the most overlap in their observed characteristics, and its corresponding estimand is the average treatment effect in the overlap population [415].

11.4. Reader's Note

The subsequent section of this chapter reproduces the full text of the study, "An overlap-weighted analysis on 10-year survival of off-pump versus on-pump coronary artery grafting in multivessel coronary artery disease", by Armando Abreu, José Máximo, and Adelino Leite-Moreira [469] and published in *Journal of Cardiac Surgery. (JOCS)* (2022). The paper has been included with the publisher's permission under the terms of the Creative Commons Attribution License.

For proper citation, please refer to the original publication: de Abreu, A. J. P., Máximo, J., & Leite-Moreira, A. (2022). An overlap-weighted analysis on 10-year survival of off-pump versus on-pump coronary artery grafting in multivessel coronary artery disease. *Journal of cardiac surgery*, 37(10), 3222–3231. DOI: 10.1111/jocs.16832

11.5. Original Publication

The full text of the study, titled "An overlap-weighted analysis on 10-year survival of off-pump versus on-pump coronary artery grafting in multivessel coronary artery disease", is included in the following pages.

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ORIGINAL ARTICLE

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An overlap-weighted analysis on 10-year survival of off-pump versus on-pump coronary artery grafting in multivessel coronary artery disease

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Email: armandopabreu@gmail.com**Abstract****Background and Objective:** The introduction of off-pump coronary artery bypass surgery intended to overcome some of the conventional on-pump procedure limitations by avoiding potentially harmful adverse effects of extracorporeal circulation and aortic cross-clamping. However, the doubt remains on whether it is associated with worse long-term outcomes. To compare long-term survival in patients with multivessel ischemic heart disease undergoing off-pump versus on-pump coronary artery bypass grafting.**Methods:** Retrospective analysis of 4788 consecutive patients undergoing primary isolated multivessel coronary artery bypass grafting surgery, performed from 2000 to 2015, in Northern Portugal. Among the study population, we identified 1616 and 3172 patients that underwent off-pump and on-pump coronary artery grafting, respectively. We employed a propensity-score-based overlap weighting (OW) algorithm to restrict confounding by indication. The primary endpoint was all-cause mortality at 10 years.**Results:** The mean age of the study population was 63.9 (± 9.8) years, and 951 (19.9%) were females. OW was effective in eliminating differences in all major baseline characteristics. Follow-up was 100% complete. The median follow-up time was 12.80 (9.62, 16.62) years. The primary endpoint of all-cause mortality at 10 years occurred in 431 patients (26.7%) in the off-pump group, as compared with 863 (27.2%) in the on-pump group (hazard ratio, 0.93; 95% confidence interval, 0.83–1.04; $p = .196$).**Conclusions:** In this longitudinal, population-level comparison of off-pump versus on-pump coronary artery bypass surgery for treating multivessel coronary artery disease, the primary outcome of long-term mortality was identical among both patients' groups.**KEYWORDS**

coronary artery bypass grafting, off-pump coronary artery bypass, propensity score, survival analysis

1 | INTRODUCTION

Coronary artery bypass grafting (CABG) remains the most common cardiac surgery performed today worldwide.^{1,2} Subject to several technical refinements in its 50-year history, it is still, despite wide geographical variations, usually performed through a midline sternotomy, under cardiopulmonary bypass (CPB) support, and cardioplegic arrest for the construction of coronary anastomosis in a quiet, bloodless field.^{3,4} Since the mid-1980s, in an attempt to overcome some of the conventional on-pump coronary artery bypass (ONCAB) limitations by avoiding potentially harmful adverse effects associated with extracorporeal circulation and aortic cross-clamping, off-pump coronary artery bypass (OPCAB) develops. As it requires making the same anastomosis on a beating heart, its increased technical difficulty with its attending longer learning curve raised concerns about an increased incidence of incomplete revascularization, early and late graft occlusion, and the need for repeat revascularization, and consequent inferior long-term survival.⁵

While both techniques' short- and medium-term results appear to be comparable or even favor OPCAB,^{6,7} results from several recent observational studies^{8,9} and meta-analyses^{10–13} suggest that OPCAB may confer inferior long-term results. Additionally, the 5-year results of three large randomized controlled trials (RCTs), namely the randomized on/off bypass (ROOBY), the CABG off- or on-pump revascularization study (CORONARY), as well as the German off-pump coronary artery bypass grafting in elderly patients (GOPCABE) trial became available.^{14–16} While the ROOBY trial demonstrated that OPCAB led to lower rates of 5-year survival and event-free survival than ONCAB, the CORONARY and the GOPCABE failed to confirm any such difference. Therefore, it is unclear whether patient-related factors, completeness of revascularization, graft patency, and the use of multiple arterial grafting are responsible for these long-term outcomes or whether the use of CPB to perform the procedure plays a central role.

This paper compares 10-year survival in patients with multivessel ischemic heart disease undergoing OPCAB versus ONCAB in a large Northern Portugal cohort between 2000 and 2015. We employed an overlap weighting (OW) algorithm to minimize confounding. Its target population highlights patients with the most overlap in their observed characteristics, and its corresponding estimand is the average treatment effect in the overlap population.¹⁷

2 | MATERIALS AND METHODS

2.1 | Study design

We conducted an observational retrospective study to evaluate trends in OPCABG and ONCABG utilization, in-hospital complications, length of hospital stay, discharge disposition, and long-term (10 years) survival in patients with isolated coronary artery disease undergoing CABG. Thus, we analyzed an administrative dataset containing all hospitalizations occurring in a tertiary care hospital

from January 1, 2000, to September 30, 2015 (chosen as the cutoff date because of the International Classification of Diseases, 10th revision, clinical modification [ICD-10-CM] implementation). The corresponding diagnoses and procedures were coded for each hospitalization based on the ICD-9-CM.

2.2 | Study population

Patients were included in the study if they underwent primary coronary artery bypass surgery (ICD-9-CM codes 36.10, 36.11, 36.12, 36.13, 36.14, 36.15, 36.16, 36.17, or 36.19) during the study period, with >1 graft performed. Exclusion criteria included previous cardiac surgery, concomitant valve replacement or repair, concurrent aorta surgery, and simultaneous correction of acute myocardial infarction mechanical complications (Supporting Information: Table S1).

2.3 | Data sources and variables

From an administrative dataset containing all hospitalizations occurring in our Institution from 2000 to 2015, we identified all hospitalizations with at least one associated procedure code of CABG. The predictive or independent variable was the treatment modality of CABG, a dichotomous variable defined by the absence or presence of ICD-9-CM code 39.61: OPCAB (the intervention) and ONCAB (the comparator).

We obtained patients' baseline characteristics from our institution patient's discharge datasets. After extracting the relevant ICD-9-CM codes, we computed the Charlson comorbidity index using the Quan et al.¹⁸ coding scheme. We provide definitions of coexisting conditions in Supporting Information: Table S2.

2.4 | Outcomes

We compared episodes coded as OPCAB to those coded as ONCAB. The primary outcome variable was 10-year survival. The patient discharge database was linked to the Portuguese National Patient Registry (RNU) to ascertain patient life status. Secondary outcomes included a set of predefined in-hospital complications (see Supporting Information: Table S3 for detailed definitions), the length of hospital stay, and discharge disposition (categorized as home discharge, transfer to other healthcare facilities, or in-hospital death).

2.5 | Statistical analysis

Data are presented as absolute frequencies and percentages for categorical variables and as means and standard deviations for continuous variables. We used the standardized mean difference (SMD) to assess discrepancies in covariates between treatment

groups, as it allows for the judgment of the relative balance of variables measured in different units. We held values less than 0.1 to indicate a negligible difference in the mean or frequency of a covariate between treatment groups.

In the univariate analysis, we computed summary measures of risk (odds ratio [OR]), its associated 95% confidence interval (CI), and a χ^2 test for difference in the observed proportions from count data presented in a two-by-two table, for each of the predefined outcomes.

We used a propensity-score-based OW algorithm to limit confounding by indication. Multivariable logistic regression was used in each treatment group to estimate each patient's probability of undergoing OPCABG (i.e., the propensity score [PS]). The propensity model included the following variables: sex, age, admission status (scheduled vs. unscheduled), disease presentation (chronic coronary artery disease, unstable angina/non-ST-elevation myocardial infarction, and ST-elevation myocardial infarction), hypertension, diabetes mellitus, hyperlipidemia, obesity, smoking history, previous stroke, congestive heart failure, chronic obstructive pulmonary disease, peripheral vascular disease, chronic kidney disease, liver disease, anemia, coagulation disorders, cancer history, the Charlson comorbidity index, internal mammary artery utilization, and the number of distal anastomoses performed. 1-PS defines the overlap weights for a treated unit and PS for a control unit (Supporting Information: - Figure S1). Thus, they are naturally bound by 0 and 1, which allows them to automatically overcome the uncertainty in dealing with extreme PS, for instance, when using inverse-probability-weighting methodologies. We assessed the balance between treatment groups using SMDs, with visual depictions of distributional balance as a helpful substitute for numerical summaries.

We derived weighted logistic regression models with a robust variance estimator with the outcome as the dependent variable and the group on which the PS balances (e.g., treatment group) as the only independent/predictor variable.

Estimates of survival probabilities were calculated by means of the Kaplan-Meier method and were compared with the use of the logrank test. Follow-up time, described by the median and interquartile range (IQR), was obtained using the same estimator, by reversing the event indicator so that the outcome of interest became censored. Weighted Cox proportional hazards regression with a robust variance estimator was used to compare long-term mortality between groups.

$p < .05$ were considered statistically significant. All statistical analyses were performed using R, version 4.1.2.¹⁹

3 | RESULTS

Of 7123 patients who underwent CABG during the study period, 4788 were eligible for inclusion (Figure 1), of which 1616 (33.7%) were performed without CPB support. The mean age of the study population was 63.9 (± 9.9) years, and 952 (19.9%) were females. Figure 2 portrays the annual trend of isolated CABG procedures

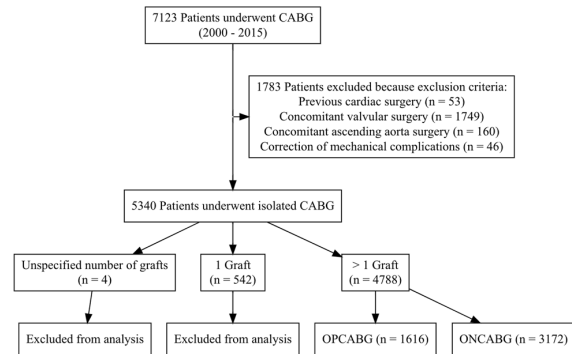


FIGURE 1 Study flowchart. CABG, coronary artery bypass grafting; ONCABG, on-pump coronary artery bypass grafting; OPCABG, off-pump coronary artery bypass grafting.

during the study period, revealing a continuous rise in OPCAB procedures until 2011, followed by a progressive decrease.

3.1 | Baseline characteristics

Table 1 depicts preoperative baseline characteristics and operative details in both treatment groups. Patients who underwent OPCAB were more likely to be operated on following an acute coronary syndrome (40.0% vs. 35.2%, SMD = 0.125), to have arterial hypertension (70.9% vs. 65.7%, SMD 0.112), and to present with a higher Charlson comorbidity index score (4.42 ± 1.71 vs. 4.19 ± 1.63 , SMD = 0.136). Concerning graft utilization, a higher proportion of patients in the OPCAB group had bilateral IMA grafting (52.7% vs. 17.9%, SMD = 0.794) compared to the ONCAB group. On the other hand, OPCAB patients had a lower mean number of bypasses performed (2.53 ± 0.70 vs. 2.77 ± 0.72 , SMD = 0.336).

3.2 | Univariate analysis

In the crude univariate analysis (Table 2), OPCAB patients were less likely to require postoperative intra-aortic balloon pump counterpulsation (2.5% vs. 3.9%, OR = 0.63, 95% CI: 0.44–0.90, $p = .013$), to require prolonged mechanical ventilation times (2.8% vs. 5.3%, OR = 0.52, 95% CI: 0.36–0.71, $p < .001$), to demand orotracheal reintubation (1.5% vs. 2.7%, OR = 0.56, 95% CI: 0.35–0.87, $p = .012$), to suffer any hemorrhagic event (2.7% vs. 4.2%, OR = 0.62, 95% CI: 0.43–0.87, $p = .007$), and to have deep sternal wound complications (0.6% vs. 1.2%, OR = 0.50, 95% CI: 0.24, 0.97, $p = .051$). We have not noted any other differences in the rates of pre-specified complications or discharge disposition, namely in-hospital mortality. Concerning the length of hospital stay (Table 2), OPCAB patients required shorter median hospitalization periods (7 [IQR: 6, 9] vs. 7 days [IQR: 6, 10]): a change in the estimate of -1.46 days (95% CI: -2.02 to -0.90 , $p < .001$).



FIGURE 2 Temporal trends in coronary surgery between 2000 through 2015: OPCAB versus ONCAB. ONCABG, on-pump coronary artery bypass grafting; OPCABG, Off-pump coronary artery bypass grafting.

3.3 | Weighted analysis

OW effectively eliminated differences in all baseline characteristics (Figure 3). As depicted in Figure 4, OPCAB patients were less likely to require postoperative intra-aortic balloon pump counterpulsation (OR = 0.59, 95% CI: 0.40–0.88, $p = .009$), less likely to require prolonged mechanical ventilation (OR = 0.63, 95% CI: 0.44–0.90), less likely to demand orotracheal reintubation (OR = 0.58, 95% CI: 0.35, 0.94, $p = .029$), less likely to experience any hemorrhagic event (OR = 0.66, 95% CI: 0.45–0.96, $p = .031$), less likely to have deep sternal wound infections (OR = 0.44, 95% CI: 0.21–0.92, $p = .030$), and less likely to require a blood transfusion (OR = 0.79, 95% CI: 0.68–0.92, $p = .002$). No difference was noted regarding discharge disposition, namely in-hospital mortality. Nevertheless, OPCAB patients required shorter hospitalization periods (change in estimate -1.32 days, 95% CI: -1.89 , -0.74 , $p < .001$).

3.4 | Survival analysis

Follow-up was 100% complete. The median follow-up time was 12.80 (IQR: 9.62, 16.2) years: 11.32 (IQR: 8.93, 13.66) years for the OPCAB group and 14.03 (IQR: 10.10, 18.11) years for the ONCAB

group. The primary endpoint of all-cause mortality at 10 years occurred in 431 patients (26.7%) in the OPCAB group, compared to 863 (27.2%) in the ONCAB group. Thirty-day, 1, 5, and 10-year survivals were 98.9%, 96.8%, 88.6%, and 71.2% in the OPCAB group and 98.7%, 95.1%, 86.5%, and 71.2% in the ONCAB group. Figure 5 depicts the unweighted survival function plot for both groups (HR = 0.97, 95% CI: 0.87–1.07, $p = .518$). Figure 6 illustrates the weighted survival function plot for both groups (HR = 0.93, 95% CI: 0.83–1.04, $p = .196$). Both fail to demonstrate any difference in 10-year survival between groups.

4 | DISCUSSION

In this longitudinal, population-level comparison of OPCAB versus ONCAB for treating multivessel coronary artery disease, the primary outcome of long-term mortality was identical among both patients' groups. Moreover, short-term secondary outcomes appear to favor the OPCAB approach.

As techniques to facilitate OPCAB were developed to reduce complications associated with CPB and manipulation of the aorta, and reports of improved short-term outcomes were revealed, there was a substantial increase in its use. A surgeon's preference often

Characteristic	Descriptive	ONCAB (n = 3172)	OPCAB (n = 1616)	SMD
Preoperative				
Female sex	n (%)	639 (20.1)	312 (19.3)	0.021
Age	Mean (SD)	63.9 (9.7)	63.9 (10.1)	0.003
Admission	n (%)			0.057
Scheduled		1494 (47.1)	715 (44.2)	
Unscheduled		1678 (52.9)	901 (55.8)	
Presentation	n (%)			0.125
Chronic CAD		2055 (64.8)	969 (60.0)	
UA/NSTEMI		794 (25.0)	495 (30.6)	
STEMI		323 (10.2)	152 (9.4)	
Hypertension	n (%)	2084 (65.7)	1146 (70.9)	0.112
Diabetes mellitus	n (%)			0.077
Non-insulin-dependent		1062 (33.5)	572 (35.4)	
Insulin-dependent		149 (4.7)	97 (6.0)	
Hyperlipidemia	n (%)	1982 (62.5)	1067 (66.0)	0.074
Obesity (BMI > 30)	n (%)	644 (20.3)	352 (21.8)	0.036
Smoking status	n (%)			0.054
Never smoked		1934 (61.0)	958 (59.3)	
Previous smoker		675 (21.3)	380 (23.5)	
Current smoker		563 (17.7)	278 (17.2)	
Previous stroke	n (%)	33 (1.0)	16 (1.0)	0.005
Congestive heart failure	n (%)	599 (18.9)	355 (22.0)	0.077
COPD	n (%)	212 (6.7)	139 (8.6)	0.072
Peripheral vascular disease	n (%)	236 (7.4)	161 (10.0)	0.090
Chronic kidney disease	n (%)			0.060
Non-dialysis-dependent		144 (4.5)	95 (5.9)	
Dialysis-dependent		22 (0.7)	11 (0.7)	
Liver disease	n (%)	68 (2.1)	36 (2.2)	0.006
Anemia	n (%)	304 (9.6)	149 (9.2)	0.012
Coagulation disorders	n (%)	62 (2.0)	21 (1.3)	0.052
Previous cancer	n (%)	27 (0.9)	20 (1.2)	0.038
Charlson comorbidity index	Mean (SD)	4.19 (1.63)	4.42 (1.71)	0.136
Operative				
Internal mammary artery	n (%)			0.794
None		116 (3.7)	11 (0.7)	
Single		2488 (78.4)	754 (46.7)	
Bilateral		568 (17.9)	851 (52.7)	
Distal anastomoses	Mean (SD)	2.77 (0.72)	2.53 (0.70)	0.336

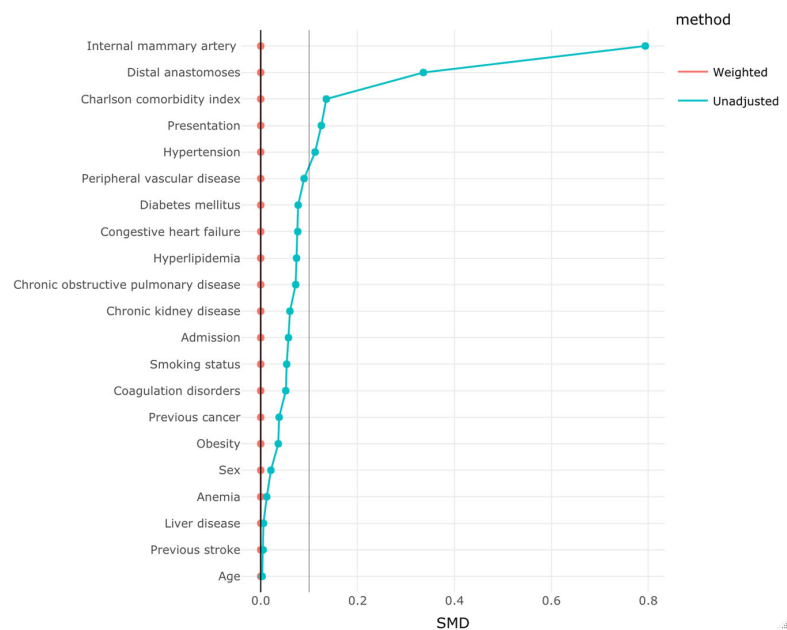
TABLE 1 Baseline characteristics and operative details for unweighted cohort: OPCAB versus ONCAB

Abbreviations: BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; ONCAB, on-pump coronary artery bypass grafting; OPCAB, off-pump coronary artery grafting; SD, standard deviation; SMD, standardized mean difference; STEMI, ST-elevation myocardial infarction; UA/NSTEMI, unstable angina/non-ST-elevation myocardial infarction.

TABLE 2 Crude intra- and postoperative outcomes: OPCAB versus ONCAB

Complication	ONCAB (n = 3172)	OPCAB (n = 1616)	OR	95% CI	p
Postoperative stroke	37 (1.2)	10 (0.6)	0.53	0.25, 1.03	.074
Cardiac complications					
Cardiac arrest	12 (0.4)	8 (0.5)	1.31	0.51, 3.17	.555
IABP	125 (3.9)	41 (2.5)	0.63	0.44, 0.90	.013
POAF	401 (12.6)	221 (13.7)	1.09	0.92, 1.30	.314
Respiratory complications					
Prolonged ventilation	167 (5.3)	45 (2.8)	0.52	0.36, 0.71	<.001
Reintubation	86 (2.7)	25 (1.5)	0.56	0.35, 0.87	.012
Hemodialysis	83 (2.6)	36 (2.2)	0.85	0.56, 1.25	.414
Hemorrhage	134 (4.2)	43 (2.7)	0.62	0.43, 0.87	.007
Reexploration	67 (2.1)	37 (2.3)	1.09	0.72, 1.62	.691
DSWI	39 (1.2)	10 (0.6)	0.50	0.24, 0.97	.051
RBC transfusion	894 (28.2)	434 (26.9)	0.94	0.82, 1.07	.332
Discharge disposition					
Home	2978 (93.9)	1522 (94.2)	1.05	0.82, 1.36	
Other hospitals	141 (4.4)	69 (4.3)	0.96	0.71, 1.28	
In-hospital death	53 (1.7)	25 (1.5)	0.92	0.56, 1.48	
Complication	ONCAB (n = 3172)	OPCAB (n = 1616)	CIE	95% CI	p
LOS (days)	7 (6, 10)	7 (6, 9)	-1.46	-2.02, -0.90	<.001

Abbreviations: CI, confidence interval; CIE, change in estimate; DSWI, deep sternal wound infection; IABP, intra-aortic balloon pump counterpulsation; LOS, length of stay; ONCAB, on-pump coronary artery bypass; OPCAB, off-pump coronary artery bypass; OR, odds ratio; POAF, postoperative atrial fibrillation; RBC, red blood cell.

FIGURE 3 Covariate balance assessment. SMD, standardized mean difference.

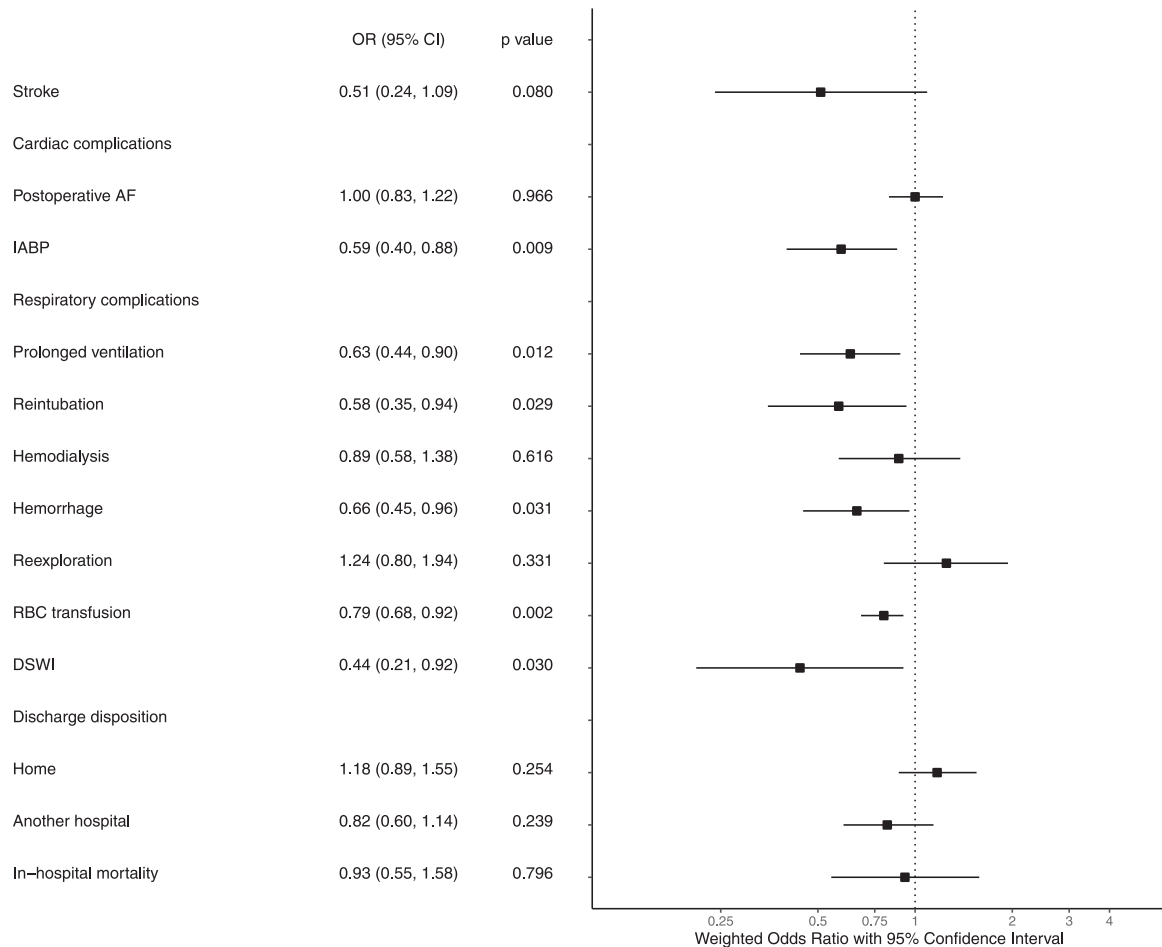


FIGURE 4 Weighted intra- and postoperative outcomes: OPCAB versus ONCAB. AF, atrial fibrillation; DSWI, deep sternal wound infection; IABP, intra-aortic balloon pump counterpulsation; ONCAB, on-pump coronary artery bypass; OPCAB, off-pump coronary artery bypass; RBC, red blood cell.

determines the choice of either technique. However, choosing a given technique assumes that long-term mortality is equivalent between both techniques, which was the case in our analysis. As surgeon inexperience in OPCAB seems associated with late mortality,¹³ dedicated teams might achieve comparable long-term results to the standard ONCAB procedure.

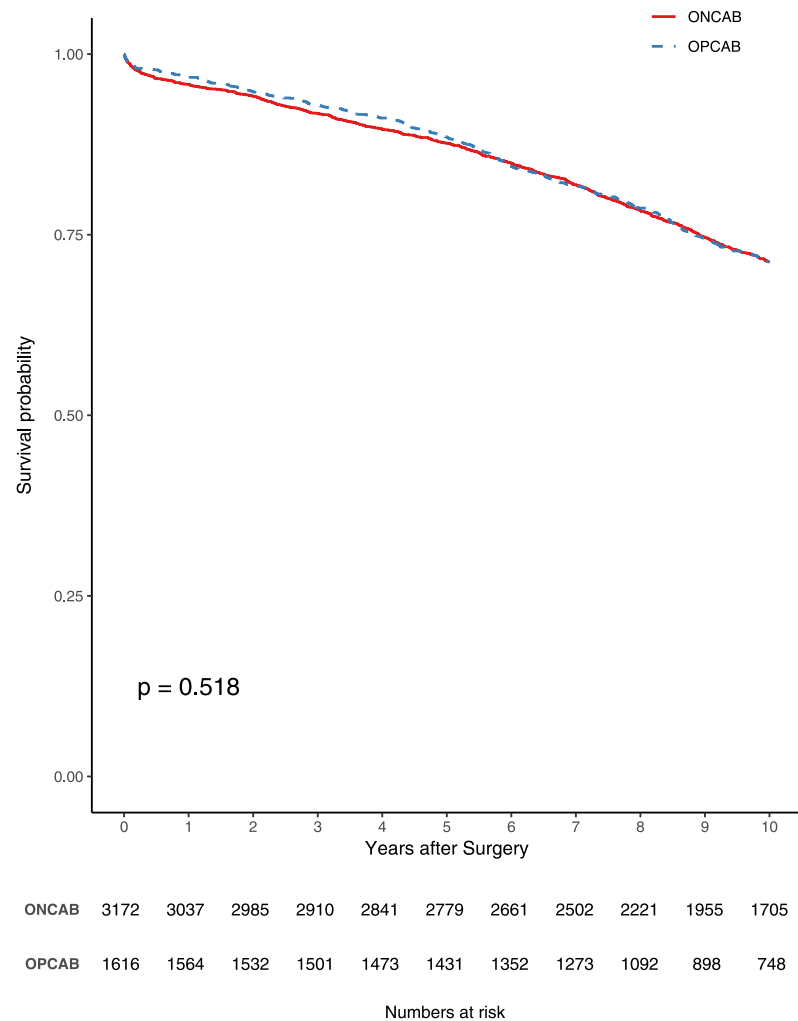
Previous comparisons of both techniques have had divergent results. In the ROOBY trial, OPCAB led to lower rates of 5-year survival than ONCAB.¹⁴ On the other hand, there were no significant differences between the OPCAB and the ONCAB group in the rate of the composite outcome of death, stroke, myocardial infarction, renal failure, or repeat revascularization at 5 years of follow-up (or in the rates of the components of the outcome) in the CORONARY trial.¹⁵ In their meta-analysis of all randomized trials performed to date, Gaudino et al.¹³ concluded that OPCAB was associated with decreased midterm survival compared with ONCAB at a weighted mean

follow-up time of 3.7 years. The same was corroborated in the meta-analysis of Smart et al.,¹¹ which included only studies reporting long-term (>4 years) outcomes from RCTs of OPCAB versus ONCAB.

Randomized surgical trials are the most effective way to control unmeasured confounders and selection bias. However, usually, they involve highly selected patients and surgeons and provide limited follow-up, which reduces the external validity of their findings. Nonrandomized clinical registries allow long-term follow-up in larger populations more representative of clinical practice, which might complement the information derived from RCTs. In their PS matching analysis, Chikwe et al.⁹ found that OPCAB was associated with a higher risk of death at 10 years than ONCAB.

Regarding short-term outcomes, observational studies suggest that, by avoiding the adverse effects of CBP and reducing aortic manipulation, OPCAB may substantially reduce mortality and

FIGURE 5 Unweighted overall survival (Kaplan–Meier method): OPCAB versus ONCAB. ONCAB, on-pump coronary artery bypass; OPCAB, off-pump coronary artery bypass.

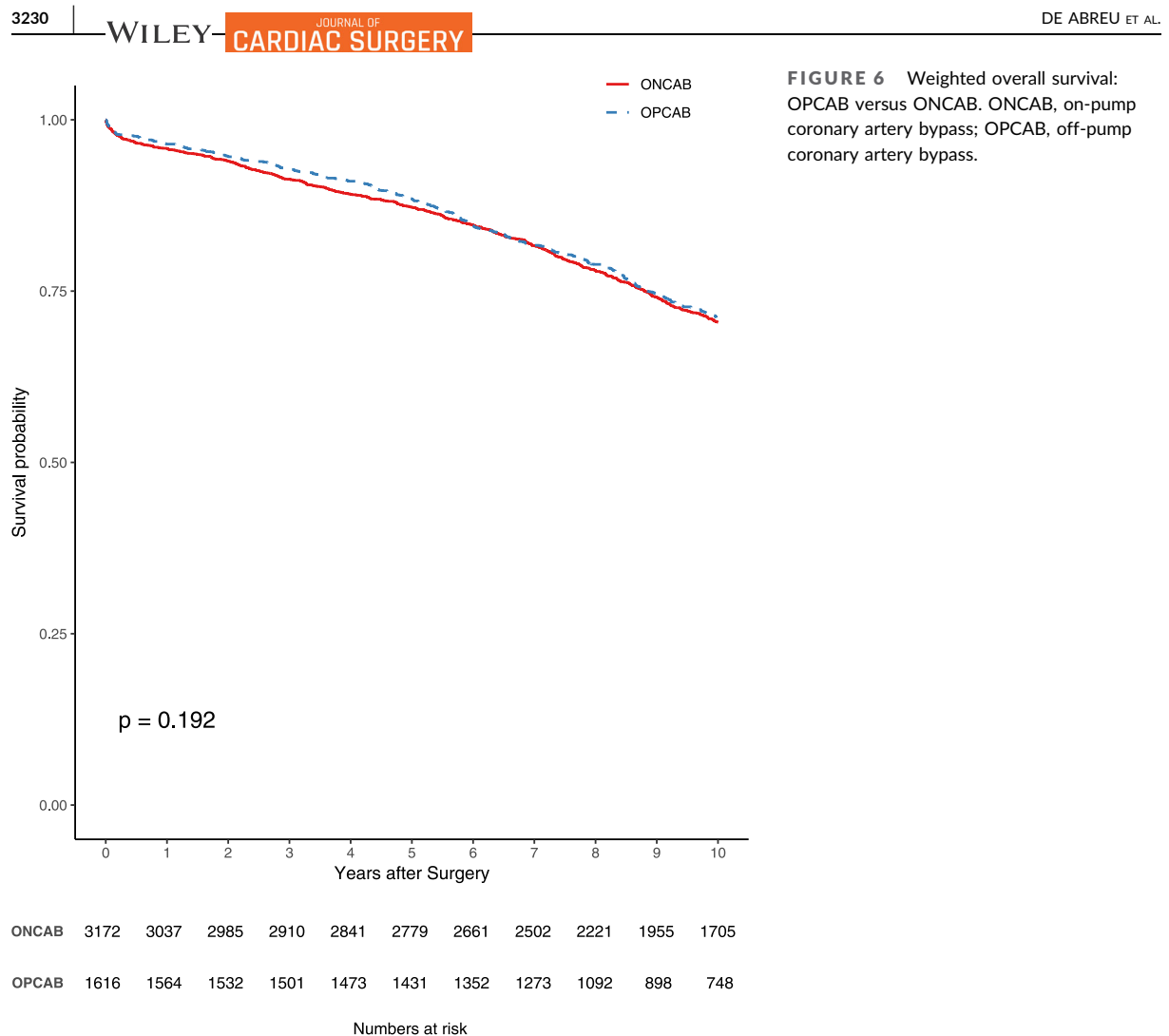


morbidity rates compared with conventional ONCAB. Nevertheless, these theoretical benefits have never been confirmed in a single RCT.⁶ For instance, the ROOBY trial found no significant difference between off-pump and on-pump CABG in the rate of the 30-day composite endpoint of death, reoperation, new mechanical support, cardiac arrest, coma, stroke, or renal failure.²⁰ Similarly, the CORONARY trial showed no significant difference between these two techniques in terms of 30-day rate of mortality, myocardial infarction, stroke, or renal failure requiring dialysis.²¹ In their meta-analysis, Kowalewski et al.⁶ found no difference in the mortality rate between the two techniques. Following these results, we noted no difference in in-hospital mortality.

There are several limitations regarding administrative data sources that should be acknowledged.²² First and foremost, coding practices were developed for reimbursement issues, not for clinical outcome profiling. As such, imprecise or equivocal definitions may compromise coding accuracy. Second, surgical

risk models are usually based on a limited number of crucial clinical variables that are typically unavailable in administrative databases. Finally, it may be challenging to distinguish comorbidities from complications. Despite the fragilities mentioned above, as the Portuguese National Health Service provides universal coverage, studies based on administrative data should probably result in unbiased population samples and represent overall program quality.

Nevertheless, this study has also several strong points, as it appraises a contemporary 16-year practice with both techniques within a regional scope. Furthermore, using administrative databases allows for the efficient assessment of large populations over long periods of time. With a careful study design and sophisticated statistical methodology to control for potential known and unknown confounders, we provide robust treatment effects estimates consistent with the available literature.



5 | CONCLUSION

OPCAB affords significant early postoperative benefits and, with dedicated and experienced surgical teams, does not seem to compromise long-term survival. Patient comorbidities, completeness of revascularization, graft patency, and multiple arterial grafting probably determine long-term outcomes following any CABG procedure more than whether the procedure is performed with or without CPB support.

AUTHOR CONTRIBUTIONS

Armando J. P. de Abreu was responsible for study design, data analysis, and interpretation, and the original article drafting. José Máximo was responsible for the critical revision of the article. Adelino Leite-Moreira was responsible for the critical revision of the article and subsequent approval of its final version.

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ETHICS STATEMENT

The São João University Hospital Center Ethics Committee approved this research and waived the need for informed consent.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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Discussion and Conclusion

"No one ever made a decision because of a number.
They need a story."
Daniel Kahneman

The final chapter of this thesis serves as a synthesis of the key findings derived from six distinct yet interrelated studies on clinical profiling in coronary artery bypass grafting (CABG) using administrative data. While each embedded paper presented a focused analysis and discussion, this chapter integrates these findings into a comprehensive narrative. The aim is to elucidate broader themes, contextualise the research within the wider field of cardiac surgery, and discuss its implications for clinical practice, policy, and future research.

The overarching goal of this thesis has been to leverage administrative data as a powerful tool for clinical profiling, particularly in the context of CABG, a central surgical intervention for managing ischaemic heart disease. This approach aimed to bridge gaps in our understanding of long-term survival outcomes by systematically analysing patient demographics, comorbid conditions, and surgical techniques. By focusing on these factors, this research provides nuanced insights into the determinants of CABG success.

This discussion chapter is structured to achieve several key objectives. First, it seeks to synthesise the collective findings of the six studies, identifying overarching themes and examining their clinical implications. Second, it critically analyses the strengths and limitations of the methodological approach employed throughout this thesis, with particular focus on the use of administrative data as a tool for clinical profiling. Third, it explores how these findings align with and extend the existing body of literature, situating the research within the broader context of cardiac surgery and patient outcomes. Finally, the chapter aims to propose future directions for research and clinical practice, drawing on the insights gained to outline opportunities for advancing the field.

The integration of findings from individual studies offers a unique opportunity to develop a holistic understanding of CABG outcomes. In doing so, this chapter aims to highlight the potential of data-driven methodologies for improving patient stratification, optimising surgical decision-making, and enhancing long-term patient care.

12.1. Synthesis of Findings

The six studies collectively provide a detailed exploration of factors influencing long-term survival in patients undergoing primary isolated coronary artery bypass grafting (CABG). While each study addressed a specific research question, together they offer a cohesive narrative on how patient demographics, modifiable risks factors, and surgical approaches interact to shape outcomes. By integrating these dimensions, we gain a more holistic understanding of the determinants of survival and their implications for clinical practice.

12.1.1. Influence of Patient Demographics

The *first objective* of this research was to examine gender-related differences in CABG outcomes [92]. The analysis revealed significant disparities in baseline characteristics and surgical management strategies between men and women. Women in the cohort were older, had a higher burden of comorbidities, and were less likely to receive additional arterial grafts. They were also more likely to have fewer distal anastomoses performed, a finding that serves as a surrogate indicator for less frequent complete revascularisation. These disparate profiles may explain the objective gender-specific difference in long-term survival detected in the unadjusted analysis. However, this discrepancy was largely eliminated by using an overlap weighting (OW) algorithm to emphasise patients with the most comparable observed characteristics and target the average treatment effect in a population where treatment equipoise is most evident.

These results have important implications for clinical practice. They suggest that traditional risk scores, which continue to weigh female sex significantly, may require revision. Moreover, pursuing an aggressive and timely diagnostic work-up and implementing adequate revascularisation strategies – including the use of multiple arterial grafts and striving for complete revascularisation – has the potential to improve both immediate and long-term outcomes in female patients.

12.1.2. Role of Modifiable Risk Factors

The *second objective* of this research was to evaluate the relationship between body mass index (BMI), a surrogate measure of obesity, and long-term survival in patients undergoing primary isolated CABG [443]. Two general conclusions were drawn by categorising the predictive variable according to the World Health Organisation's (WHO) established cutoffs. While increasing BMI strata did not reduce the hazard of late mortality, there was a strong positive correlation with traditional risk factors for atherosclerosis.

In addition, BMI was treated as a continuous variable to further refine the analysis and account for the potential limitations of its categorisation into discrete strata. Employing spline modelling to accommodate the non-linear relationship between BMI and the hazard of late mortality revealed a distinct U-shaped curve. These results emphasised an optimal BMI range of 25.8–30.3 kg/m² as associated with the most favourable outcomes while indicating an increased risk of death at both extremes of the BMI distribution.

These inconsistent findings are dependent on disputable methodological assumptions. Furthermore, obesity is strongly associated with traditional atherosclerosis risk factors, which have a powerful impact on long-term survival. Consequently, managing obesity should be regarded as a fundamental component of any secondary prevention program for coronary artery disease.

The *third objective* of this research was to analyse the effect of smoking status on long-term survival in patients undergoing primary isolated CABG [453]. This study demonstrated that, while ex-smokers had an identical long-term survival to non-smokers, smokers had an increase in late all-cause mortality risk. It also acknowledged noncardiac death as the catalyst of this increased late fatality risk within a competing risk framework. Interestingly, smokers demonstrated a reduced relative incidence of cardiac death, which may be attributed to the elimination of the precipitating risk factor following smoking cessation.

These findings strongly support the implementation of smoking cessation programs during the index hospital admission to improve long-term outcomes.

The *fourth objective* of this research was to evaluate the independent and combined effects of preoperative anaemia and perioperative red blood cell transfusion on long-term survival in patients undergoing primary isolated CABG [465]. While each of these factors independently compromise late CABG outcomes, their combined effect is multiplicative.

These data stress the importance of an evidence-based, multimodal and multidisciplinary approach to conserving blood resources and optimising outcomes in patients at high risk for transfusion, i.e., a Patient Blood Management (PBM) program. In light of this information, it is essential to identify and optimise scheduled patients for cardiac surgery who are at risk, while ensuring that the use of this precious resource is guided by evidence rather than arbitrary decisions, thereby establishing a new standard of care.

12.1.3. Implications of Surgical Strategies

The *fifth objective* of this research was to compare long-term survival rates between single internal thoracic artery (SITA) grafting and bilateral internal thoracic artery (BITA) grafting in patients under

70 years of age with multivessel coronary artery disease (CAD) [470]. The findings indicate that BITA grafting is associated with reduced long-term mortality compared to SITA. Importantly, this survival advantage was achieved without increased perioperative morbidity or mortality. Using inverse probability-weighting (IPW) allowed for the creation of a pseudo-population that reflected the same covariate distribution as the overall treated and untreated populations. This methodology enabled the estimation of the average treatment effect across the entire population, mirroring the question typically posed in a randomised controlled trial.

These results have significant implications for clinical practice, as promoting BITA grafting might maximise the long-term patency of CABG conduits and improve long-term survival.

The *sixth objective* of this research was to compare long-term survival outcomes between off-pump and on-pump techniques in patients with multivessel CAD undergoing primary isolated CABG [469]. This research revealed that off-pump coronary artery bypass (OPCAB) grafting offers significant early postoperative advantages and, when performed by dedicated and experienced surgical teams, does not appear to compromise long-term survival. Confounding factors were addressed using an overlap weighting (OW) algorithm, emphasising patients with the most comparable observed characteristics and focusing on the average treatment effect in a population where treatment equipoise is most evident.

These findings hold significant implications for clinical practice. The long-term outcomes following any coronary artery bypass grafting (CABG) procedure are likely influenced more by patient comorbidities, the completeness of revascularisation, graft patency, and the utilisation of multiple arterial grafts rather than by the choice of performing the procedure with or without cardiopulmonary bypass support.

12.1.4. Integration of Insights

Taken together, the findings from this research illustrate the multifaceted nature of outcomes in CABG, shaped by the interplay of patient-specific factors, modifiable risk factors, and procedural variables. Each of these dimensions contributes uniquely to long-term survival, underscoring the importance of a holistic approach to patient management.

Patient-specific factors, such as sex and baseline comorbidities, highlight the inherent diversity in clinical populations and the need for tailored surgical strategies. For instance, the disparities observed between men and women emphasise the importance of equitable access to advanced surgical techniques and perioperative care. At the same time, the evaluation of modifiable risk factors, including obesity, smoking, and preoperative anaemia, underscores opportunities for intervention. These findings suggest

that optimising modifiable risk factors through targeted strategies – such as weight management programs, smoking cessation efforts, and anaemia correction – could substantially improve CABG outcomes.

The influence of procedural choices, including the type of grafts used (e.g., SITA versus BITA) and surgical techniques (e.g., OPCAB versus ONCAB), further highlights the dynamic interplay between patient characteristics and surgical decisions. Tailoring these decisions to the clinical and demographic profile of individual patients can maximise survival benefits while minimising potential risks.

The utilisation of administrative data played a crucial role in deriving these insights. Administrative datasets offer robust evidence that mirrors real-world clinical practices by enabling the analysis of large and diverse cohorts. In contrast to traditional clinical trials, which often focus on highly selected populations, these data enhance generalisability and allow the assessment of rare outcomes and long-term trends. This capability is particularly advantageous for refining risk stratification models, as it captures the complex interactions among demographic, clinical, and procedural variables.

The findings of this investigation highlight the transformative potential of utilising administrative data to craft personalised treatment strategies. Advanced statistical methods – such as propensity score-based techniques, competing-risk analysis, and spline modeling – were instrumental in revealing subtle yet clinically significant patterns that might have otherwise gone unnoticed. These methodologies can be further augmented by emerging tools such as machine learning and predictive analytics, offering exciting opportunities to improve precision in clinical profiling.

By synthesising insights across patient, procedural, and modifiable factors, this research reinforces the need for a data-driven, patient-centered approach to CABG. Integrating these findings into clinical decision-making can help clinicians better stratify risks, optimise surgical planning, and implement targeted interventions, ultimately enhancing long-term outcomes for diverse patient populations.

12.2. Contribution to the Field

By integrating these contributions, this research advances both the scientific understanding of CABG and its practical application in clinical settings, offering a strong foundation for future developments in personalised, data-driven cardiac care.

12.2.1. Advances in Knowledge

This investigation makes significant contributions to coronary artery bypass grafting (CABG) by expanding the understanding of how demographic, modifiable, and procedural factors interact to influence long-term outcomes. A key gain lies in the innovative use of administrative data for clinical profiling. By leveraging large-scale, population-level datasets, this research provides robust and generalisable evidence that complements findings from traditional clinical trials. Advanced statistical methodologies, such as propensity score-based methodologies, competing-risk analysis, and spline modelling, enabled nuanced analyses of continuous variables and highlighted the importance of accurately addressing confounders to understand survival outcomes better.

Moreover, this research sheds new light on several critical areas, challenging existing paradigms, and offering evidence-based recommendations to refine clinical risk assessment and intervention strategies.

12.2.2. Implications for Practice

The insights generated by this thesis have direct implications for clinical practice, particularly in the following areas:

1. *Risk Assessment Tools.* This research demonstrates the potential to refine existing risk assessment models by incorporating findings from demographic and modifiable factors. For example, traditional risk scores that disproportionately weigh female sex as a risk factor may require adjustment to account for baseline characteristics that drive disparities in outcomes. Similarly, incorporating non-linear relationships between continuous variables and survival into these models could improve their predictive accuracy.
2. *Perioperative Care Strategies.* Findings on the impact of anaemia and blood transfusion on survival emphasise the need for improved perioperative strategies, such as early identification and correction of anaemia and minimising the use of blood transfusions when feasible. Additionally, the disparities in procedural strategies between sexes highlight the need to ensure equitable access to advanced surgical techniques, such as multiple arterial grafts, to improve outcomes for all patients.
3. *Tailored Interventions for At-Risk Populations.* Modifiable risk factors such as obesity, smoking status, and preoperative anaemia present clear opportunities for targeted intervention. This research underscores the value of integrating weight management, smoking cessation programs, and patient blood management into preoperative and postoperative care. These interventions, coupled with timely and aggressive

diagnostic approaches, can significantly enhance outcomes for at-risk populations.

12.2.3. Alignment with Current Trends

The findings of this research align closely with broader trends in personalised medicine, data-driven healthcare, and surgical innovation. Personalised medicine aims to tailor treatments to individual patients based on their unique clinical and demographic profiles, and this research contributes directly to that goal by providing evidence-based recommendations for stratifying risks and optimising treatment strategies.

In the context of data-driven healthcare, using administrative data exemplifies the power of leveraging large datasets to uncover insights that inform clinical decision-making. These findings pave the way for incorporating advanced analytics, such as machine learning and artificial intelligence, to enhance clinical profiling and risk prediction further.

Finally, this thesis aligns with ongoing advancements in surgical innovation by highlighting the need for individualised procedural planning. The comparative analyses of OPCAB versus ONCAB and SITA versus BITA grafting provide actionable insights for optimising surgical techniques based on patient-specific characteristics.

12.3. Methodological Reflections

By leveraging the strengths of administrative data while addressing its limitations, this research has demonstrated the feasibility and value of using large-scale datasets to inform clinical decision-making. The lessons learned from these methodological reflections provide a foundation for future advancements in data-driven cardiac care and beyond.

12.3.1. Strengths of the Approach

A major strength of this thesis lies in its innovative use of administrative data to address clinically significant questions in CABG. Administrative datasets offer several unique advantages that were integral to achieving the research objectives:

1. *Large-Scale Analysis.* The ability to analyse a vast and otherwise inaccessible population of patients undergoing CABG provided statistical power to detect subtle effects and explore subgroups, such as sex-specific differences or the impact of procedural choices. This large sample size enhanced the robustness and generalisability of the findings.

2. *Real-World Applicability.* Unlike clinical trials, which often include highly selected populations, administrative data reflect routine clinical practice across diverse healthcare settings. This real-world applicability ensures that the insights are directly translatable to everyday clinical care, providing evidence that can inform guidelines and policy.
3. *Longitudinal Tracking of Outcomes.* Administrative data facilitate the study of long-term survival outcomes by enabling comprehensive follow-up over extended periods. This capability was crucial for understanding the enduring effects of demographic, comorbid, and procedural factors on survival after CABG.

Additionally, advanced statistical techniques, including propensity score-based methods (e.g., inverse probability and overlap weighting), competing risk analysis, and spline modelling, allowed for more nuanced data analyses. These approaches helped address potential confounders and captured non-linear relationships, offering a deeper understanding of the variables influencing CABG outcomes.

12.3.2. Challenges and Limitations

While administrative data provide powerful opportunities, they also present inherent challenges and limitations:

1. *Data Granularity and Completeness.* Administrative datasets often lack detailed clinical information, laboratory results, imaging data, or intraoperative metrics, which may limit the ability to explore specific hypotheses. For instance, the absence of precise smoking cessation data limited the ability to differentiate between patients who quit smoking immediately before or after surgery. Moreover, obtaining pack-year calculations – crucial for establishing the dose-response effect in causality assessments – is not feasible when relying solely on administrative data.
2. *Potential for Biases.* Administrative data are subject to coding inaccuracies, missing data, and biases introduced by variations in data collection practices across institutions. While this investigation utilised data from a single tertiary centre to mitigate these issues, such factors may still influence the reliability of certain variables and necessitate thorough data cleaning, manipulation, and validation.
3. *Controlling for Confounders.* Observational data inherently contain confounding variables that necessitate careful consideration to prevent biased outcomes. Although propensity score-based methods and regression analysis techniques are employed to mitigate these biases, it is essential to acknowledge that residual confounding cannot be fully eliminated.

4. *Categorisation Limitations.* Transforming continuous variables into categories, as seen in some BMI analyses, can lead to a loss of information and reduce the ability to detect subtle trends or interactions. This factor highlights the importance of careful variable modelling.

12.3.3. Lessons Learned

The challenges encountered during this research provided valuable insights for future studies:

1. *Data Handling, Manipulation, and Validation.* Thorough pre-processing and validation of administrative data are crucial to address challenges associated with coding inaccuracies and missing information. Future research initiatives should prioritise the maintenance of this essential prerequisite to standardise the data preparation process for subsequent analysis.
2. *Advanced Statistical Techniques.* Using sophisticated methodologies, such as spline modelling, demonstrated the value of flexible approaches in capturing complex relationships. Future studies should continue to explore advanced analytics, including machine learning, address confounding and improve predictive modelling.
3. *Interpretation of Findings.* The limitations of observational data necessitate cautious interpretation of results. Emphasising transparency in methodology and acknowledging potential biases are critical for maintaining the credibility and utility of findings.
4. *Collaboration Across Data Sources.* The integration of administrative data with additional data sources, such as laboratory study results, imaging studies, patient-reported outcomes, or genetic information, has the potential to facilitate more comprehensive analyses in future research endeavors. This multidisciplinary approach would significantly enhance the capacity to investigate complex questions concerning patient-specific and procedural variables in CABG.

12.4. Integrated Clinical Implications

Building on the synthesis of cross-cutting themes, this section distills the key clinical implications of the findings, focusing on actionable strategies to enhance patient outcomes and refine clinical practices in CABG.

1. *Personalised Risk Stratification.* The findings emphasise the need for personalised risk assessment tools that integrate nuanced factors such as non-linear relationships with BMI

and sex-specific disparities in outcomes. Current risk scores may need to be revised to account for these complexities, enabling more accurate predictions and better-informed decision-making.

2. *Enhanced Perioperative and Postoperative Care.* Evidence from this research supports the adoption of targeted interventions, such as timely anaemia correction and smoking cessation programs during the index hospital admission. These efforts could significantly reduce long-term mortality risk and improve quality of life for CABG patients.
3. *Equitable Access to Advanced Techniques.* Addressing disparities in procedural choices, such as the underuse of bilateral arterial grafting in women, will require systematic changes to ensure equitable access to the best surgical techniques. This could include clinician education, updated guidelines, and resource allocation to promote consistency in care.
4. *Integration of Data-Driven Decision-Making.* The use of administrative data demonstrated the value of leveraging large-scale, real-world datasets to uncover clinically meaningful insights. Expanding this approach with emerging tools like machine learning could further refine treatment strategies and optimise outcomes across diverse patient populations.
5. *Policy and Systemic Changes.* The broader implications of this research extend to healthcare policy, such as incorporating evidence from administrative data into national registries or benchmarking systems to improve accountability and standardise care quality.

12.5. Future Directions

The findings of this thesis open several avenues for future research, methodological advancements, and practical applications in clinical and academic settings. Building on the insights gained, this section outlines promising directions that can further advance the field of cardiac surgery and beyond.

12.5.1. Research Opportunities

While this thesis focused on specific risk factors and surgical variables, future research could expand to investigate outcomes in *other patient subgroups with unique characteristics or underexplored comorbidities*. Potential avenues include assessing the impact of diabetes mellitus and chronic kidney disease on long-term survival, as well as evaluating cause-specific mortality in patients with preoperative or postoperative atrial fibrillation. Additionally, disparities in outcomes across geographic or socioeconomic groups warrant further exploration to address health equity concerns. These investigations would provide a deeper understanding of

how diverse patient populations experience CABG and identify opportunities to optimise care for at-risk groups.

Emerging tools such as *machine learning and artificial intelligence* (AI) offer exciting opportunities to enhance clinical profiling and improve predictive accuracy in risk models. AI-driven algorithms could integrate data from diverse sources, including administrative, clinical, laboratory, and imaging datasets, to predict long-term survival more effectively. Natural language processing techniques could also incorporate unstructured data, such as clinical notes, into risk assessments, while deep learning methods might uncover previously unrecognised patterns in patient trajectories. These advanced analytics have the potential to revolutionise risk stratification and personalised care in CABG and beyond.

12.5.2. Administrative Data Potential

Administrative data remain an invaluable resource for studying real-world outcomes on a large scale. Future research can extend the applications of such datasets to other cardiac surgical populations, such as patients undergoing valve repair or hybrid procedures. Moreover, combining administrative data with patient-reported outcomes could provide a holistic perspective on post-operative recovery, bridging the gap between clinical metrics and quality-of-life indicators. These expanded applications hold the potential to inform healthcare policy by establishing national benchmarks for CABG outcomes and supporting initiatives to enhance care quality and equity.

12.5.3. Collaboration and Innovation

Collaboration and innovation will be key to realising these future directions. Interdisciplinary efforts involving clinicians, data scientists, engineers, and behavioral researchers can drive innovation in surgical decision-making and perioperative care strategies. Advances in wearable technology and remote monitoring could also complement administrative data by offering continuous insights into post-operative recovery, helping to identify early complications and improve follow-up care. Furthermore, global collaborations leveraging international datasets could enhance the generalisability of findings and support the development of universally applicable clinical guidelines.

By pursuing these directions, future research can build on the foundation established in this thesis, driving innovation in data-driven medicine, personalised care, and surgical outcomes. These efforts will not only benefit patients undergoing CABG but also extend to broader areas of cardiovascular and surgical care, advancing the field as a whole.

12.6. Conclusion

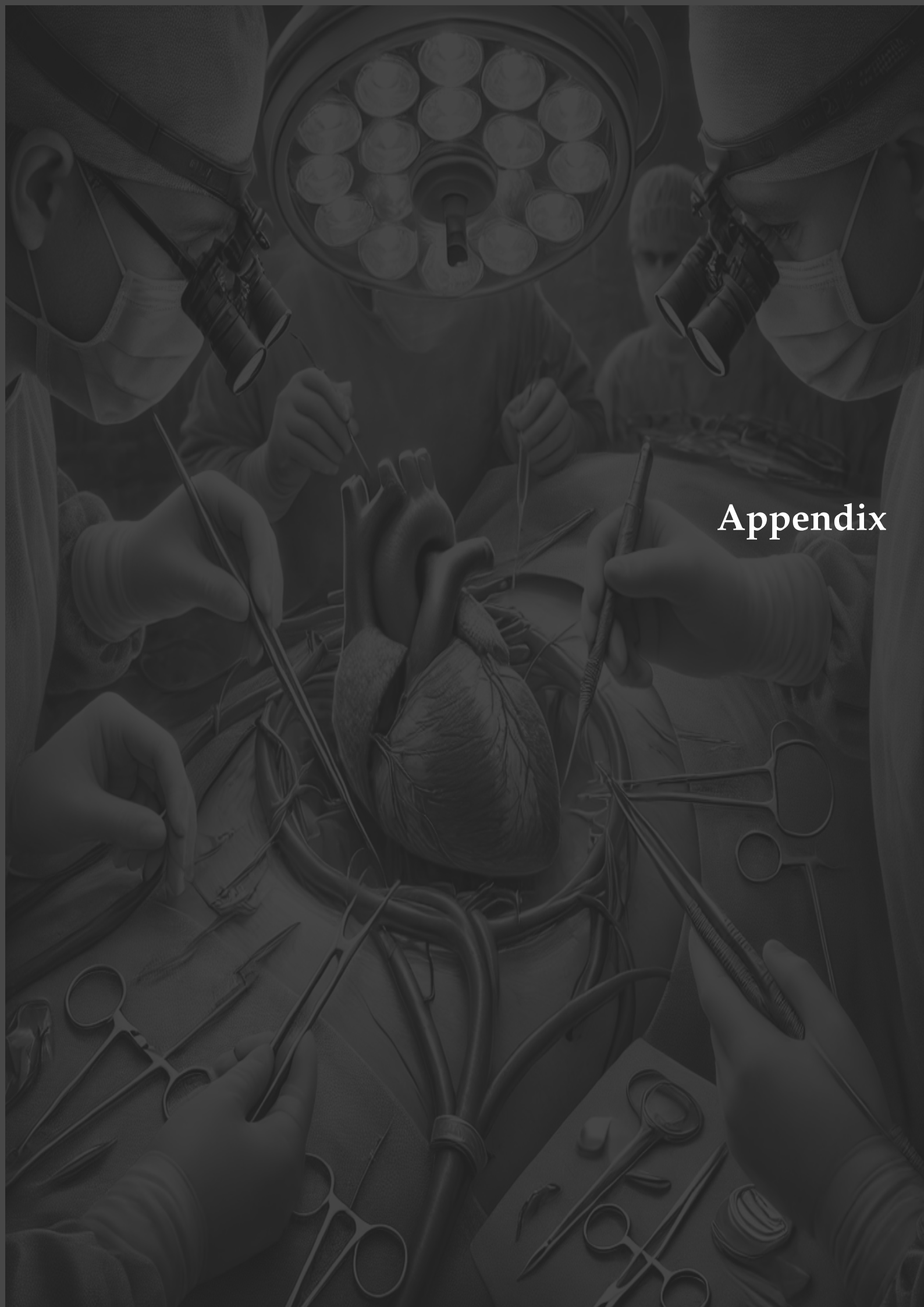
This thesis represents a significant contribution to the understanding of long-term outcomes in CABG by addressing critical gaps in knowledge about the roles of patient-specific factors, modifiable risk factors, and procedural choices. By leveraging administrative data, this research provided a real-world perspective on clinical outcomes, complementing evidence from traditional clinical trials. Key findings included the complex, non-linear relationship between obesity and survival, the importance of smoking cessation during the index hospital admission, and the interplay between preoperative anaemia, blood transfusions, and survival outcomes. The thesis also offered valuable insights into sex-based disparities in CABG outcomes, challenging the reliance on traditional risk scores that disproportionately weigh female sex as a prognostic factor. These findings advance academic knowledge while also informing clinical practices, including refined risk stratification models, improved perioperative care strategies, and targeted interventions for at-risk populations.

The methodologies employed, such as propensity score-based methodologies, competing-risk analysis, and spline modelling, highlight the value of advanced analytical techniques in uncovering subtle but clinically meaningful patterns. This research underscores the transformative potential of administrative data, not only for understanding CABG outcomes but also as a template for exploring broader clinical questions. The findings carry important implications for clinical practice, including the need to revise risk scores, promote equity in access to advanced surgical techniques, and incorporate personalised approaches to patient care. Furthermore, the insights into modifiable risk factors provide actionable strategies for healthcare providers to improve both immediate and long-term outcomes, ultimately contributing to better management of cardiovascular disease.

Beyond CABG, the findings of this thesis align with the growing momentum in healthcare toward data-driven decision-making and personalised medicine. By demonstrating the ability to use administrative data to address real-world clinical problems, this research highlights the role of such datasets in improving healthcare delivery. It also opens opportunities for integrating artificial intelligence and machine learning to refine predictive modeling and support clinical decision-making. These advancements have the potential to drive improvements not only in cardiac surgery but across a range of medical specialties, ensuring more precise, equitable, and effective care for diverse patient populations.

On a personal level, this research has been a deeply enriching experience, combining the intellectual challenge of addressing complex healthcare questions with the practical impact of contributing to improved patient outcomes. The journey has reinforced the importance of evidence-based decision-making and the power of

interdisciplinary collaboration in tackling pressing healthcare challenges. It is my hope that this work will serve as a foundation for further research and inspire innovations in data-driven medicine, ultimately leading to improved care and quality of life for patients undergoing CABG and beyond.



Appendix

Exclusion Criteria

A.

This appendix provides definitions for the key variables used throughout the thesis. Understanding these variables is crucial for interpreting the research findings.

Exclusion criteria are specific characteristics or conditions that disqualify individuals from being included in the analysis (Table A.1). They are crucial in research design as they help to define the population under study, control for potential confounding variables, and enhance the validity and reliability of the research findings.

Table A.1.: Exclusion criteria and corresponding ICD-9-CM procedure codes.

Code	Description
<i>Valve Replacement or Repair</i>	
3500–3509	Closed Heart Valvotomy
3510–3514	Open Heart Valvuloplasty Without Replacement
3520–3528	Open And Other Replacement Of Heart Valve
3531–3539	Operations On Structures Adjacent To Heart Valves
<i>Aorta Surgery</i>	
3804	Incision of vessel, aorta
3814	Endarterectomy, aorta
3834	Resection of vessel with anastomosis, aorta
3845	Resection of vessel with replacement, thoracic vessels
<i>Mechanical Complications of Acute Myocardial Infarction</i>	
3711	Excision of aneurysm of heart
3731	Repair of heart septum
3732	Insertion of heart septal device
<i>Previous Cardiac Surgery</i>	
V151	Personal history of surgery to heart and great vessels
V4581	Aortocoronary bypass status
V433	Heart valve replaced by other means

Baseline Variables

B.

This appendix provides definitions for the key variables used throughout the thesis. Understanding these variables is crucial for interpreting the research findings.

Baseline variables refer to specific characteristics or measurements taken at the beginning of a study or before an intervention is implemented (Table B.1). They are crucial for establishing a common starting point and ensuring that any observed changes or outcomes can be attributed to the intervention rather than preexisting differences.

Table B.1.: Baseline Variables and Corresponding ICD-9-CM Diagnosis Codes.

Code	Description
Age	
-	The time difference, in days, between the dates of surgery and birth, which is then divided by 365.25 to obtain the age in years
Sex	
-	Patient’s biological sex with two possible values – male or female
Disease Presentation	
Chronic Coronary Syndromes	
4130-4139	Angina Pectoris
4140-4149	Other forms of chronic ischaemic heart disease
Unstable angina or non-ST-elevation myocardial infarction	
41070-41072	Subendocardial infarction
4110-4118	Other acute and subacute forms of ischaemic heart disease
ST-elevation myocardial infarction	
41000-41002	Acute myocardial infarction of anterolateral wall
41010-41012	Acute myocardial infarction of other anterior wall
41020-41022	Acute myocardial infarction of inferolateral wall
41030-41032	Acute myocardial infarction of inferoposterior wall
41040-41042	Acute myocardial infarction of other inferior wall
41050-41052	Acute myocardial infarction of other lateral wall
41060-41062	True posterior wall infarction
41080-41082	Acute myocardial infarction of other specified sites

Continued on next page

Table B.1 – continued from previous page

Code	Description
41090-41092	Acute myocardial infarction of unspecified site
<i>Arterial Hypertension</i>	
4010-4019	Essential Hypertension
4020-4029	Hypertensive heart disease
4030-4039	Hypertensive chronic kidney disease
4040-4049	Hypertensive heart and chronic kidney disease
4050-4059	Secondary hypertension
<i>Diabetes Mellitus</i>	
Non-Insulin-Treated	
2490-2499	Secondary diabetes mellitus
2500-2509	Diabetes mellitus
Insulin-Treated	
V5867	Long-term (current) use of insulin
<i>Dyslipidaemia</i>	
2720-2729	Disorders of lipid metabolism
<i>Obesity</i>	
27800-27803	Overweight and obesity
2781	Localised adiposity
<i>Smoking Status</i>	
V1582	History of former tobacco use, last used more than a year ago
3051	Tobacco use disorder
<i>Previous Stroke</i>	
34660-34663	Persistent migraine aura with cerebral infarction
36230-36237	Retinal vascular occlusion
430	Subarachnoid haemorrhage
431	Intracerebral haemorrhage
4320-4329	Other and unspecified intracranial haemorrhage
4330-4339	Occlusion and stenosis of precerebral arteries
4340-4349	Occlusion of cerebral arteries
4350-4359	Transient cerebral ischaemia
436	Acute, but ill-defined, cerebrovascular disease
4370-4379	Other and ill-defined cerebrovascular disease

Continued on next page

Table B.1 – continued from previous page

Code	Description
4380-4389	Late effects of cerebrovascular disease
78043	Transient alteration of awareness
<i>Congestive Heart Failure</i>	
39891	Rheumatic heart failure (congestive)
4280-4289	Heart failure
<i>Peripheral Vascular Disease</i>	
4400-4409	Atherosclerosis
4410-4419	Aortic aneurysm and dissection
4420-4429	Other aneurysm
4440-4449	Arterial embolism and thrombosis
4450-4458	Atheroembolism
4471	Stricture of artery
V434	Blood vessel replaced by other means
<i>Chronic Obstructive Pulmonary Disease</i>	
4910-4919	Chronic bronchitis
4920-4928	Emphysema
4930-4939	Asthma
4940-4941	Bronchiectasis
496	Chronic airway obstruction, not elsewhere classified
<i>Chronic Kidney Disease</i>	
Non-dialysis-dependent	
4030-4039	Hypertensive chronic kidney disease
4040-4049	Hypertensive heart and chronic kidney disease
5820-5829	Chronic glomerulonephritis
5830-5839	Nephritis and nephropathy not specified as acute or chronic
5851-5859	Chronic kidney disease
586	Renal failure, unspecified
587	Renal sclerosis, unspecified
5880-5889	Disorders resulting from impaired renal function
V420	Kidney replaced by transplant
Dialysis-dependent	
V56X	Encounter for dialysis and care involving dialysis

Continued on next page

Table B.1 – continued from previous page

Code	Description
<i>Liver Disease</i>	
0700-0709	Viral hepatitis
4560-4568	Varicose veins of other sites
570	Acute and subacute necrosis of liver
5710-5719	Chronic liver disease and cirrhosis
5720-5780	Liver abscess and sequelae of chronic liver disease
5730-5739	Other disorders of liver
7824	Jaundice, unspecified, not of newborn
7891	Hepatomegaly
7895	Ascites
7904	Nonspecific elevation of levels of transaminase
7905	Other nonspecific abnormal serum enzyme levels
7948	Nonspecific abnormal results of function study of liver
V427	Liver replaced by transplant
<i>Anaemia</i>	
2800-2809	Iron deficiency anaemias
2810-2819	Other deficiency anaemias
2820-2829	Hereditary hemolytic anaemias
2830-2839	Acquired hemolytic anaemias
2840-2849	Aplastic anaemia and other bone marrow failure syndromes
2850-2859	Other and unspecified anaemias
<i>Coagulation Disorders</i>	
2860-2869	Coagulation defects
2870-2879	Purpura and other hemorrhagic conditions
<i>Cancer</i>	
<i>Oropharyngeal Cancer</i>	
1400-1409	Malignant neoplasm of lip
1410-1419	Malignant neoplasm of tongue
1420-1429	Malignant neoplasm of major salivary glands
1430-1439	Malignant neoplasm of gum
1440-1449	Malignant neoplasm of floor of mouth
1450-1459	Malignant neoplasm of other and unspecified parts of mouth

Continued on next page

Table B.1 – continued from previous page

Code	Description
1460-1469	Malignant neoplasm of oropharynx
1470-1479	Malignant neoplasm of nasopharynx
1480-1489	Malignant neoplasm of hypopharynx
1490-1499	Malignant neoplasm of other and ill-defined sites within the lip oral cavity and pharynx
Gastrointestinal Cancer	
1500-1509	Malignant neoplasm of esophagus
1510-1519	Malignant neoplasm of stomach
1520-1529	Malignant neoplasm of small intestine including duodenum
1530-1539	Malignant neoplasm of colon
1540-1548	Malignant neoplasm of rectum rectosigmoid junction and anus
1550-1552	Malignant neoplasm of liver and intrahepatic bile ducts
1560-1569	Malignant neoplasm of gallbladder and extrahepatic bile ducts
1570-1579	Malignant neoplasm of pancreas
1580-1589	Malignant neoplasm of retroperitoneum and peritoneum
1590-1599	Malignant neoplasm of other and ill-defined sites within the digestive organs and peritoneum
Respiratory Tract Cancer	
1600-1609	Malignant neoplasm of nasal cavities middle ear and accessory sinuses
1610-1619	Malignant neoplasm of larynx
1620-1629	Malignant neoplasm of trachea bronchus and lung
1630-1639	Malignant neoplasm of pleura
1640-1649	Malignant neoplasm of thymus heart and mediastinum
1650-1659	Malignant neoplasm of other and ill-defined sites within the respiratory system and intrathoracic organs
Bone and Connective Tissue Cancer	
1700-1709	Malignant neoplasm of bone and articular cartilage
1710-1719	Malignant neoplasm of connective and other soft tissue
1720-1729	Malignant melanoma of skin
1730-1739	Other and unspecified malignant neoplasm of skin
1740-1749	Malignant neoplasm of female breast
1750-1759	Malignant neoplasm of male breast

Continued on next page

Table B.1 – continued from previous page

Code	Description
1760-1769	Kaposi's sarcoma
Genitourinary Cancer	
179	Malignant neoplasm of uterus, part unspecified
1800-1809	Malignant neoplasm of cervix uteri
181	Malignant neoplasm of placenta
1820-1828	Malignant neoplasm of body of uterus
1830-1839	Malignant neoplasm of ovary and other uterine adnexa
1840-1849	Malignant neoplasm of other and unspecified female genital organs
185	Malignant neoplasm of prostate
1860-1869	Malignant neoplasm of testis
1871-1879	Malignant neoplasm of penis and other male genital organs
1880-1889	Malignant neoplasm of bladder
1890-1899	Malignant neoplasm of kidney and other and unspecified urinary organs
Lymphoid Cancer	
2000-2008	Lymphosarcoma and reticulosarcoma and other specified malignant tumors of lymphatic tissue
2010-2019	Hodgkin's disease
2020-2029	Other malignant neoplasms of lymphoid and histiocytic tissue
2030-2038	Multiple myeloma and immunoproliferative neoplasms
Haematologic Cancer	
2040-2049	Lymphoid leukaemia
2050-2059	Myeloid leukaemia
2060-2069	Monocytic leukaemia
2070-2078	Other specified leukaemia
2080-2089	Leukaemia of unspecified cell type
2090-2097	Neuroendocrine tumors
Other Cancer	
1900-1909	Malignant neoplasm of eye
1910-1919	Malignant neoplasm of brain
1920-1929	Malignant neoplasm of other and unspecified parts of nervous system
193	Malignant neoplasm of thyroid gland

Continued on next page

Table B.1 – continued from previous page

Code	Description
1940-1949	Malignant neoplasm of other endocrine glands and related structures
1950-1958	Malignant neoplasm of other and ill-defined sites
1960-1969	Secondary and unspecified malignant neoplasm of lymph nodes
1970-1978	Secondary malignant neoplasm of respiratory and digestive systems
1980-1988	Secondary malignant neoplasm of other specified sites
1990-1992	Malignant neoplasm without specification of site

Charlson Comorbidity Index

-	The CCI is a discrete variable widely used to assess the impact of comorbid conditions on patient outcomes, particularly in predicting mortality and resource utilisation. This index comprises 17 comorbid conditions, each assigned a specific weight based on severity and impact on mortality risk. The total score is derived by summing the weights of all present comorbid conditions
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Procedural Variables

C.

This appendix provides definitions for the key variables used throughout the thesis. Understanding these variables is crucial for interpreting the research findings.

Procedural variables denote the precise methods, techniques, or strategies employed to perform a surgical procedure (Table C.1). These variables encompass all elements of the surgical process that may impact the study’s outcomes, ensuring that the procedures are consistently and systematically carried out across all participants or conditions. A thorough understanding of procedural variables is essential for maintaining the reliability and credibility of research results.

Table C.1.: Procedural Variables and Corresponding ICD-9-CM Procedure Codes.

Code	Description
<i>Admission Status</i>	
-	Surgery admission status is a critical classification that outlines the urgency and nature of a patient’s surgical admission (elective or urgent) and their overall condition upon entry (outpatient or inpatient). This status informs surgical planning, resource allocation, and post-operative care, ensuring patients receive appropriate and timely medical intervention
<i>Cardiopulmonary bypass support</i>	
3961	On-pump CABG
No 3961	Off-pump CABG
<i>Internal thoracic artery use</i>	
3615	Single internal thoracic artery
3616	Bilateral internal thoracic artery
<i>Distal anastomoses</i>	
3610-3616	The number of distal anastomoses depends on a simple arithmetic sum based on the following codes: 3610 (unspecified), 3611 (one), 3612 (two), 3613 (three), 3614 (four), 3615 (one), and 3616 (two)

Postoperative Complications

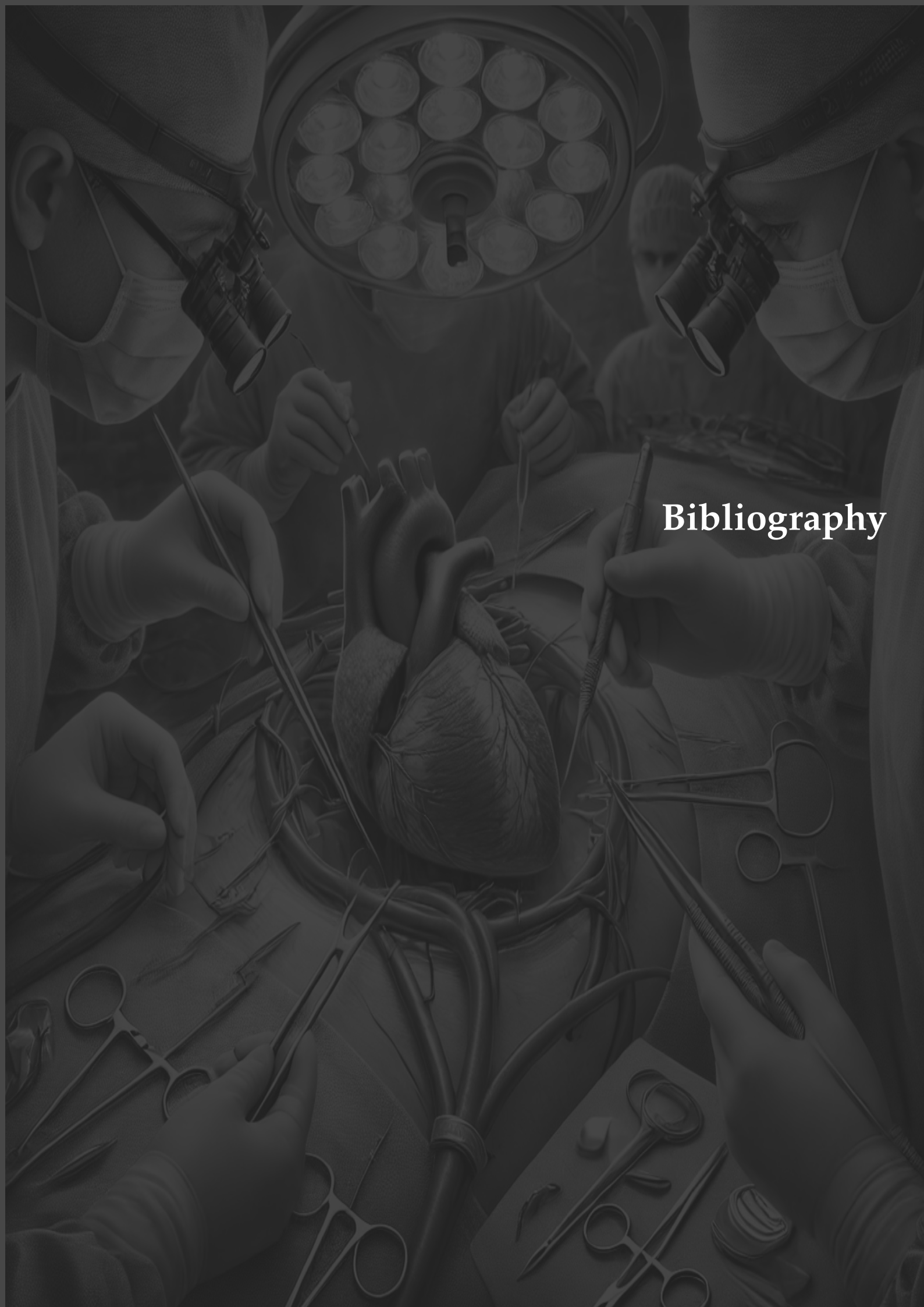
D.

This appendix provides definitions for the key variables used throughout the thesis. Understanding these variables is crucial for interpreting the research findings.

Postoperative complications encompass a wide range of conditions that may arise following surgical procedures, including infections, wound healing issues, graft failures, and organ-specific dysfunctions (Table D.1). Accurate classification and documentation of these complications are essential for monitoring outcomes, improving patient care, and facilitating research on surgical quality and safety.

Table D.1.: Postoperative Complications and Corresponding ICD-9-CM Codes.

Code	Description
<i>Postoperative Stroke</i>	
99700-99709	Nervous system complications
<i>Cardiac Complications</i>	
42731-42732	Atrial fibrillation and flutter (excluding V5681)
3761	Implant of pulsation balloon
4275	Cardiac arrest
<i>Pulmonary Complications</i>	
9670-9672	Prolonged continuous invasive mechanical ventilation
9604	Insertion of endotracheal tube
311	Temporary tracheostomy
<i>Acute Kidney Injury</i>	
5845-5849	Acute kidney failure
<i>Haemorrhage</i>	
99811-99812	Haemorrhage or haematoma complicating a procedure not elsewhere classified
<i>Transfusion</i>	
9904	Transfusion of packed cells
<i>Wound Complications</i>	
99830-99832	Disruption of operation wound
99859	Other postoperative infection



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