Faculdade de Engenharia da Universidade do Porto

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The use of drug-eluting versus bare-metal stents in percutaneous coronary intervention after an acute coronary syndrome: practices and determinants in routine care

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Dissertação de candidatura ao grau de Mestre apresentada à Faculdade de Engenharia da Universidade do Porto

Ao longo desta dissertação, colaborei na definição das hipóteses em estudo e dos objetivos a responder em cada um dos artigos, bem como na análise estatística dos dados. Fui responsável pela redação da versão inicial de todos os manuscritos e colaborei ativamente na preparação das suas versões finais.

Esta investigação foi realizada no Departamento de Epidemiologia Clínica, Medicina Preditiva e Saúde Pública da Faculdade de Medicina da Universidade do Porto e no Instituto de Saúde Pública da Universidade do Porto, sob orientação da Professora Doutora Ana Azevedo (Faculdade de Medicina da Universidade do Porto e Instituto de Saúde Pública da Universidade do Porto) e co-orientação do Dr. José Pedro Braga (Serviço de Cardiologia do Centro Hospitalar Vila Nova de Gaia/Espinho).

“All of science is nothing more than refinement of everyday thinking”

Albert Einstein, 1936

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ABBREVIATIONS AND ACRONYMS

ACS	Acute Coronary Syndrome
AMI	Acute Myocardial Infarction
AF	Atrial Fibrillation
BMS	Bare-Metal Stent
CHD	Coronary Heart Disease
CVD	Cardiovascular Diseases
DALYs	Disability-Adjusted Life Years
DAPT	Dual Antiplatelet Therapy
DES	Drug-Eluting Stent
ESC	European Society of Cardiology
LDL	Low-Density Lipoprotein
NSTEMI	Non-ST-Elevation Myocardial Infarction
OAC	Oral Anticoagulation
PCI	Percutaneous Coronary Intervention
STEMI	ST-Elevation Myocardial Infarction
UA	Unstable Angina
YLL	Years of Life Lost
YLD	Years Lived with Disability

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ABSTRACT

Cardiovascular diseases (CVD) are the main cause of death worldwide. CVD and in particular the acute coronary syndrome is responsible for high rates of morbidity and a reduced life expectancy, thus contributing to an enormous medical, social and economic burden worldwide.

Despite the increasing use of coronary stents in angioplasty, there are no clear European recommendations and guidelines regarding the selection of the stent selection. Therefore, the decision process of the appropriate stent to be used remains under discussion within the medical community. In this study our aim was to contribute to a better knowledge of the stent selection process in routine practice and in different clinical conditions in Portugal and in Europe. In this regard, with the elaboration of two articles, this dissertation aims to answer some questions listed and described briefly below:

i) To assess the demographic, clinical and institutional determinants of the use of drug-eluting (DES) *versus* bare-metal (BMS) stents in patients undergoing percutaneous coronary interventions (PCI) after an acute coronary syndrome in Portuguese hospitals (Paper I).

Within the EURopean HOspital Benchmarking Processes study, we retrospectively evaluated 3009 consecutive patients in 10 Portuguese hospitals in 2009. Only patients with stent implantation during PCI (n=1194) were analysed.

A total of 425 patients (36%) received a BMS and 769 patients (64%) received a DES. A history of previous PCI, current non-ST-elevation acute coronary syndrome, anterior descendent artery as the infarct-related artery and being treated in hospitals with catheterization laboratory were independent predictors of DES implantation. Young and old age, anaemia and previous anticoagulation and/or atrial fibrillation were associated with BMS use.

ii) To quantify the variability in the stent utilization and to identify determinants of such variation among hospitals of six European countries (Paper II).

Within the EURopean HOspital Benchmarking Process (EURHOBOP) study, we retrospectively assessed 5958 consecutive patients with acute coronary syndrome who had a stent implanted in Finland, France, Germany, Greece, Portugal and Spain. Due to the hierarchical structure of the data, including patients clustered into hospitals and hospitals clustered into countries, multilevel logistic regression models were used to estimate median odds ratios (MOR) and intra-cluster coefficients (ICC).

The use of drug-eluting stents ranged from 36% in Finland to 80% in Greece.

There was a large inter-hospital variation in the stent type choice (MOR=2.91), slightly attenuated when the country-level was considered (MOR=2.39). Patients' and hospitals' characteristics did not contribute to explain the variance at hospital- and country level. GDP per capita accounted for approximately 30% of total variance at the country level. In the final model, over 85.6% of the variance at hospital level remained unexplained, with a MOR for the difference among hospitals of 2.50 and an ICC for the agreement in type of stent implanted among patients from the same hospital of 21%.

Drug-eluting stents were less often used in octogenarians (OR=0.365), in patients with anticoagulation and/or atrial fibrillation (OR=0.600), and anaemia (OR=0.761). Diabetes *mellitus* (OR=1.557), previous history of PCI (1.824) and non-ST-elevation acute coronary syndrome (OR=2.043) were associated with a higher likelihood of DES use. The odds of use of DES decreased 5% per 1 PPS of GDP.

RESUMO

As doenças cardiovasculares são a primeira causa de morte no mundo, particularmente a síndrome coronária aguda é responsável por elevadas taxas de morbilidade e por esperança de vida reduzida contribuindo, desta forma, para um enorme impacto social, médico e económico.

Apesar da crescente utilização de stents coronários na angioplastia após síndrome coronária aguda, não existem claras recomendações nas guidelines europeias para a seleção do stent e o processo de decisão do stent mais adequado na prática clínica permanece sobre discussão dentro da comunidade médica. Deste modo, o nosso objectivo foi contribuir para um melhor conhecimento do processo de decisão na prática clínica em Portugal e na Europa. Neste sentido, com a elaboração de dois artigos, esta dissertação visa responder a algumas questões enumeradas e descritas resumidamente de seguida:

i) Avaliar os determinantes demográficos, clínicos e institucionais da utilização de stents revestidos *versus* metálicos em pacientes submetidos a angioplastia após síndrome coronária aguda (Artigo I)

Recorrendo ao estudo EURHOBOP, avaliamos 3009 pacientes consecutivamente em 10 hospitais portugueses. De um total de 1194 pacientes implantados com stent, 425 (36%) receberam um stent metálico e 769 (64%) um stent revestido. Verificamos que pacientes com uma história prévia de angioplastia, diagnosticados síndrome coronária aguda sem elevação do segmento-ST, intervencionados na artéria descendente anterior e tratados num hospital com laboratório de hemodinâmica foram associados com a implantação de um stent revestido. Contudo, um stent metálico foi frequentemente mais usado quer em pacientes jovens e idosos, anémicos e com uma história prévia de anticoagulação e/ou fibrilhação auricular.

ii) Quantificar a variabilidade na utilização do tipo de stent e identificar os determinantes responsáveis pela variação entre hospitais de seis países europeus (Artigo II)

No âmbito do mesmo estudo EURHOBOP, avaliamos retrospectivamente 5958 pacientes consecutivos implantados com stent na Finlândia, França, Alemanha, Grécia, Portugal e Espanha. Devido à estrutura hierárquica da informação, com pacientes agrupados em hospitais e estes em países, decidimos implementar modelos de regressão logística multinível para estimar o "median odds ratio (MOR)" e o "intra-cluster coefficients (ICC)".

Podemos constatar que a utilização de stents revestidos variou entre 36% na Finlândia e 80% na Grécia. Foi encontrada uma grande variação entre hospitais na escolha do tipo de stent (MOR=2.91), ligeiramente atenuada quando o país foi considerado (MOR=2.39). As características dos pacientes e dos hospitais não contribuíram para explicar a variância ao nível do hospital e do país. O produto interno bruto per capita foi responsável aproximadamente por 30% da variância total ao nível do país. No modelo final, mais de 85.6% da variância ao nível do hospital permaneceu inexplicada, com um MOR para a diferença entre hospitais de 2.50 e um ICC entre pacientes do mesmo hospital de 21%.

Os stents revestidos foram frequentemente menos usados em octogenários (OR=0.365), em pacientes com anticoagulação e/ou fibrilhação auricular (OR=0.600) e anemia (OR=0.761). A presença de diabetes *mellitus*, história prévia de angioplastia (OR=1.824) e síndrome coronária aguda sem elevação de segmento-ST foi associada com uma maior probabilidade de utilização de stent revestido. A probabilidade de um paciente ser implantado com um stent revestido diminuiu 5% por cada unidade de PPS do produto interno bruto per capita.

1 Introduction

Cardiovascular diseases (CVDs) are the main cause of death worldwide. CVD and in particular the acute coronary syndrome (ACS) is responsible for high rates of morbidity and a reduced life expectancy, thus contributing to an enormous medical, social and economic burden worldwide. Despite the increasing use of coronary stents in angioplasty, the stent selection process in routine practice and in different clinical conditions remains under discussion within the medical community.

1.1 Acute coronary syndrome

1.1.1 Atherosclerosis

The main underlying pathological process that leads to coronary heart disease (CHD) is known as atherosclerosis[1-3]. Atherosclerosis is a continuous process of plaque formation that develops slowly over the person´s lifetime until it manifests as an acute ischemic event[1]. This complex pathological process, mainly a chronic inflammatory process, is located in the wall of blood vessels. This event is directly associated with an array of risk factors of diverse nature, including behavioural risk factors (for example, tobacco use or physical inactivity), metabolic risk factors (hypertension, diabetes, dyslipidaemia, overweight and obesity) and other non-modifiable factors such as age, gender and genetic predisposition[2].

Atherogenesis begins when these risk factors damage the endothelium of the blood vessel leading to a qualitative change in the intact endothelial cells. In a mechanistic perspective, this dysfunctional endothelium subjected to oxidative, hemodynamic or biochemical stimuli is characterized by reduced bioavailability of nitric oxide and by excessive production of endothelin 1 which impairs vascular haemostasis. The permeability change in the blood wall due to increased expression of adhesion molecules (e.g., selectins, vascular cell adhesion molecules, and intercellular adhesion molecules) promotes the entry and retention of blood-borne monocytes and cholesterol-containing low-density lipoprotein (LDL) particles[1, 3].

Once the endothelium has been damaged, the monocytes migrate into the subendothelium and it differentiates into macrophages. The macrophages digest oxidized LDL transforming into foam cells causing the fatty streaks formation. In the presence of activated macrophages which release chemoattractants and cytokines, other macrophages and vascular smooth muscle cells (which produce extracellular matrix) are recruited and there is a fibrous cap formation over the developing atheromatous plaque[1, 3]. The atherosclerotic plaques lead to clinical symptoms due to flow-limiting stenosis (causing stable angina) or by inducing the formation of a thrombus that interrupts blood flow on either a temporary basis (causing unstable angina (UA)) or in a permanent one (causing acute myocardial infarction (AMI))[3]. Macrophages also produce matrix metalloproteiases which lead to physical disruption (rupture) of the plaque that exposes procoagulant material within the core of the plaque to coagulation proteins and platelets, triggering thrombosis[1, 3]. Although plaque rupture may result in ACS, in approximately 99% of cases it is clinically silent. The rate of progression of atherosclerotic lesions is variable, non-linear and unpredictable[1]. After either rupture of the plaque (75% of fatal AMI) or endothelial erosion (25% of fatal AMI), the endothelial matrix (rich in tissue factor, a potent coagulant) is exposed to the circulating blood leading to a platelet adhesion followed by platelet activation and aggregation that cause a thrombus formation (Figure 1). Two types of thrombi can be formed: a platelet-rich clot referred to as a white clot that partially occludes the artery, or a fibrin-rich clot referred to as a red clot that is the result of an activated coagulation cascade and decreased flow in the artery[1]. White clots are found in patients with unstable angina/non-ST-elevation myocardial infarction (UA/NSTEMI), red clots form in patients with ST-elevation myocardial infarction (STEMI)[4].

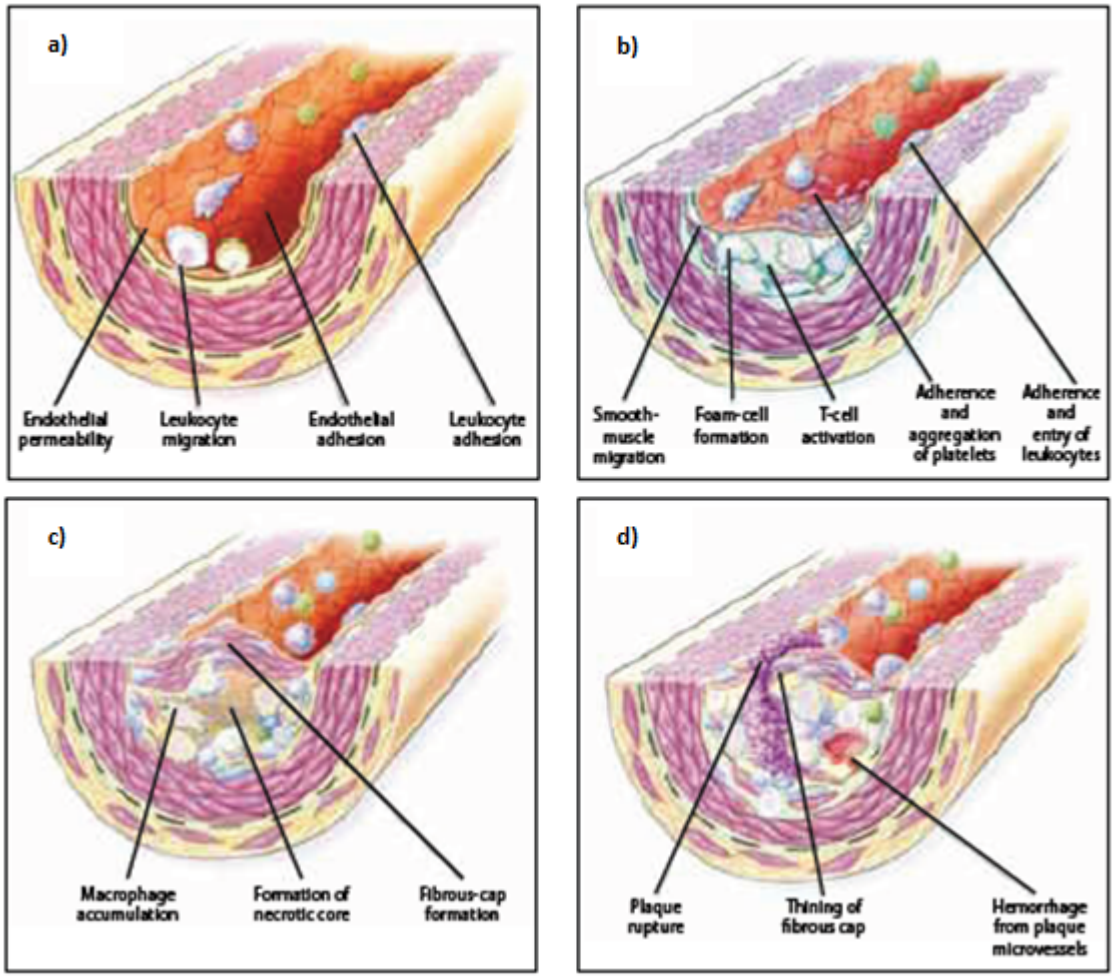


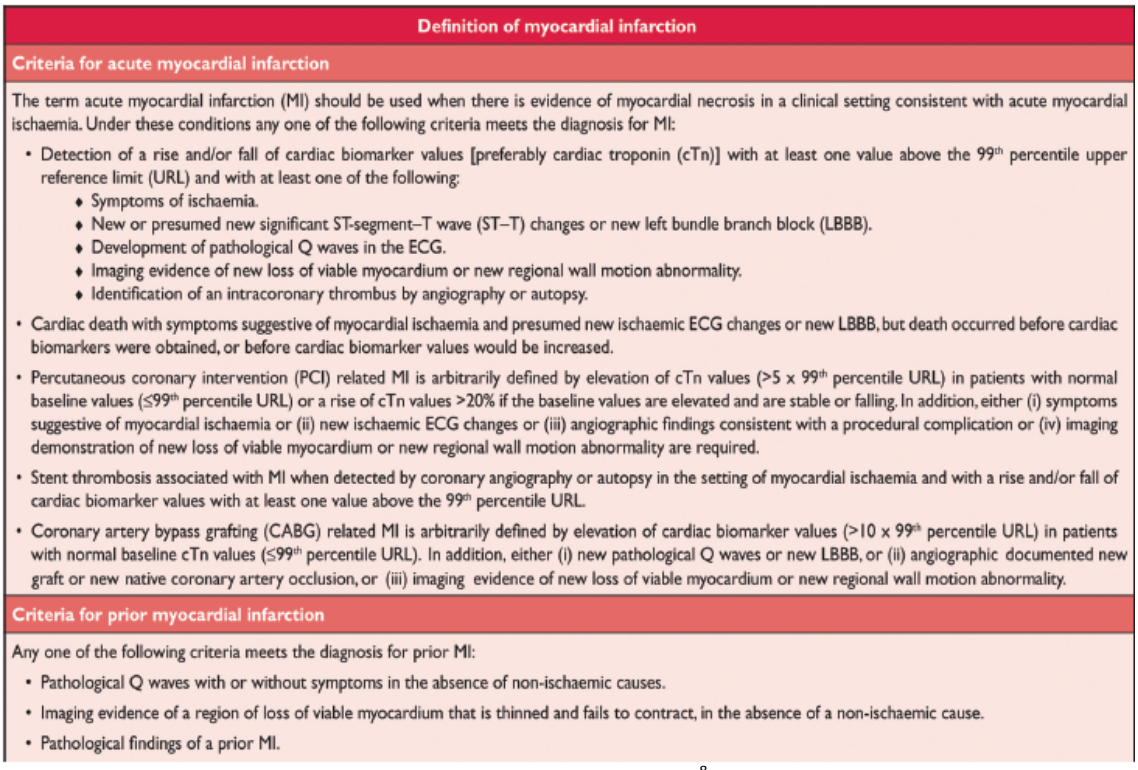
Figure 1. Schematic description of biological events associated with atherogenesis: a) Endothelial dysfunction: Leukocyte adhesion and migration into the deep layer of the intima; b) Fatty streak formation revealing platelet aggregation on the endothelial surface, foam-cell formation and smooth muscle migration; c) Fibrous cap formation and the necrotic core; d) The ruptured plaque[2].

These pathophysiologic differences have consequences in the recommended approaches to the treatment of STEMI and NSTEMI. In UA/NSTEMI, the main aim of antithrombotic therapeutic is to prevent the thrombosis or to allow the thrombus dissolution recurring to fibrinolysis reducing the degree of coronary stenosis. On the other hand, in STEMI, the infarct-related artery is usually totally occluded and there is the necessity of an immediate pharmacological or catheter-based reperfusion as initial approaches with the goal of restoring normal coronary blood flow [5].

1.1.2 Definition and clinical presentation

The ACS includes AMI and UA. The clinical criteria utilized to define AMI have been subject of alterations over time. Until the year 2000, the AMI diagnosis was supported in epidemiologic criteria that were established in 1979 by the World Health Organization. After the year 2000, a definition of AMI was proposed by the European Society of Cardiology (ESC) and the American College of Cardiology based on clinical criteria [6]. In 2007, a redefinition of AMI was published by Joint ESC/ACCF/AHA/WHF Task Force[7]. It was then proposed to simply define AMI as a clinical event that results from myocardial necrosis in a clinical setting consistent with myocardial ischemia. One of the critical changes relied on the use of troponin as gold standard to the diagnosis of AMI. This document also introduced a clinical classification for different types of AMI. However, the development of even more sensitive assays for markers of myocardial necrosis led to a AMI revision by the Third Global Myocardial Infarction Task Force (Figure 2) which recognizes that very small amounts of myocardial injury or necrosis can be detected by biochemical markers and/or imaging[8].

Nowadays, the AMI diagnosis is established with a typical elevation on plasma concentrations of myocardial tissue-specific cardiac biomarkers associated with one of the following criteria: ischemic symptoms; imagiologic evidence of wall motion abnormalities; electrocardiographic changes suggestive of ischemia (ST-elevation or ST-depression and/or T-wave inversion) or development of pathologic Q-waves on the electrocardiogram[9-11]. The ST-segment alterations allow the distinction of patients presenting with ST- segment elevation myocardial infarction (STEMI) and without persistent ST-segment elevation (NSTEMI). Separate guidelines have recently been developed by another Task Force of the ESC for patients presenting ischemic symptoms due to STEMI and NSTEMI[9].



Definition of myocardial infarction

Criteria for acute myocardial infarction

The term acute myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischaemia. Under these conditions any one of the following criteria meets the diagnosis for MI:

- Detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:
  - Symptoms of ischaemia.
  - New or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB).
  - Development of pathological Q waves in the ECG.
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
  - Identification of an intracoronary thrombus by angiography or autopsy.
- Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased.
- Percutaneous coronary intervention (PCI) related MI is arbitrarily defined by elevation of cTn values (>5 x 99th percentile URL) in patients with normal baseline values (≤99th percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischaemia or (ii) new ischaemic ECG changes or (iii) angiographic findings consistent with a procedural complication or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.
- Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischaemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL.
- Coronary artery bypass grafting (CABG) related MI is arbitrarily defined by elevation of cardiac biomarker values (>10 x 99th percentile URL) in patients with normal baseline cTn values (≤99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Criteria for prior myocardial infarction

Any one of the following criteria meets the diagnosis for prior MI:

- Pathological Q waves with or without symptoms in the absence of non-ischaemic causes.
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischaemic cause.
- Pathological findings of a prior MI.

Figure 2. Description of the criteria used to define myocardial infarction[8].

The symptoms of STEMI and UA/NSTEMI in consequence of total or partial occlusion of coronary arteries are similar, and differentiating the two requires medical evaluation and a 12-lead electrocardiogram[1]. Patients with either STEMI[9] or UA/NSTEMI[10] typically present a chest pain lasting for at least 20 min, which frequently further radiates to the neck, jaw, or left arm. Some patients present less-typical symptoms, such as nausea/vomiting, shortness of breath, fatigue, palpitations or syncope in the case of STEMI[9] or diaphoresis, nausea, abdominal pain, dyspnoea, and syncope in the case of UA/NSTEMI[10]. However, atypical presentations are not uncommon either for STEMI[12] or UA/NSTEMI[13].

The current guidelines[9, 10] recommend several diagnostic tools to assess and distinguish ACS patients, including the physical examination with the goal of excluding non-cardiac causes of chest pain and non-ischemic cardiac disorders, the 12-lead electrocardiogram as tool to differentiate STEMI and UA/NSTEMI, the levels of biomarkers of myocardial necrosis as a diagnostic tool and risk stratification, the utilization of non-invasive imaging techniques and the results of stress tests.

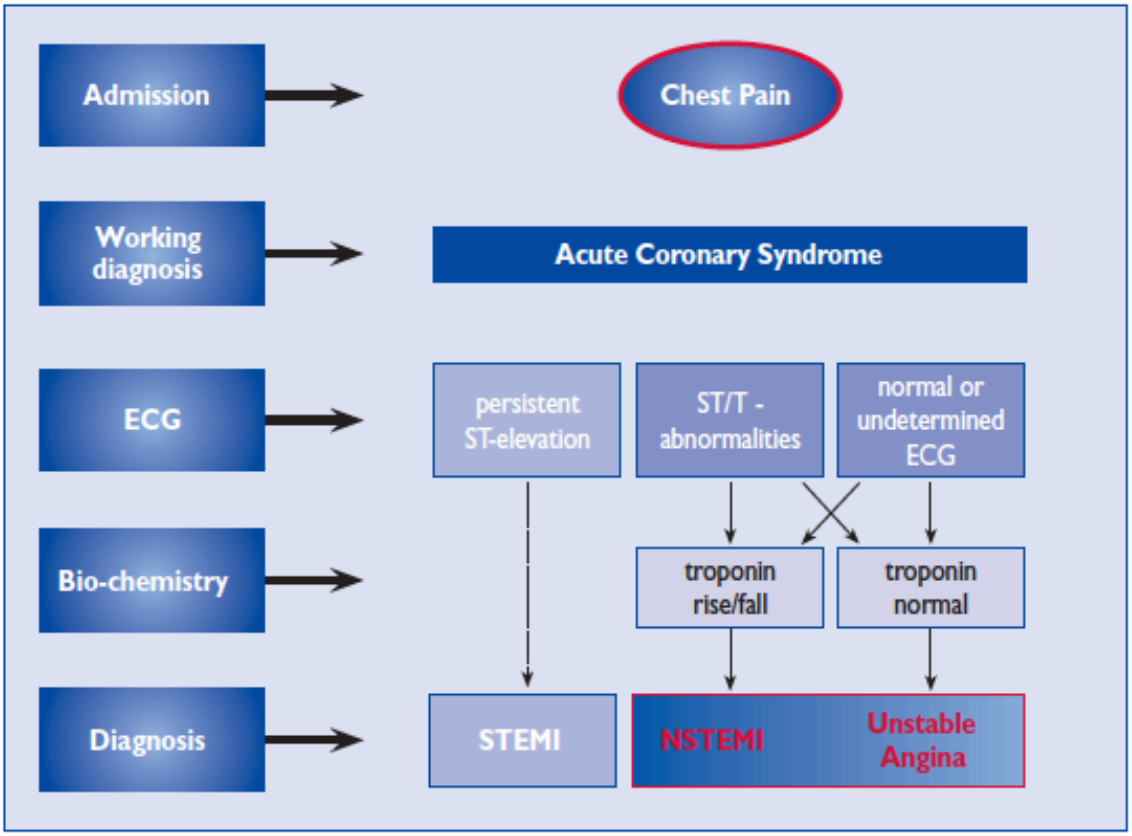


Figure 3. Evaluation of patients with suspected acute coronary syndrome[10].

The algorithm for diagnosis of ACS is depicted in figure 3 and details about treatment decisions will be given in a section about management of ACS.

1.1.3 Burden of disease

Despite the advances in the treatment of ACS, this disease remains a source of high morbidity, mortality and it is associated with a reduced life expectancy contributing to an enormous medical, social and economic burden worldwide[14, 15].

CVDs remains the most frequent cause of death worldwide accounting for 31% of all causes of death in 2008, representing over 17.3 million deaths per year[2]. Of cardiovascular deaths, 46% in males and 38% in females are due to CHD, among which 7.3 million people (42%) died due to ACS in 2008[2].

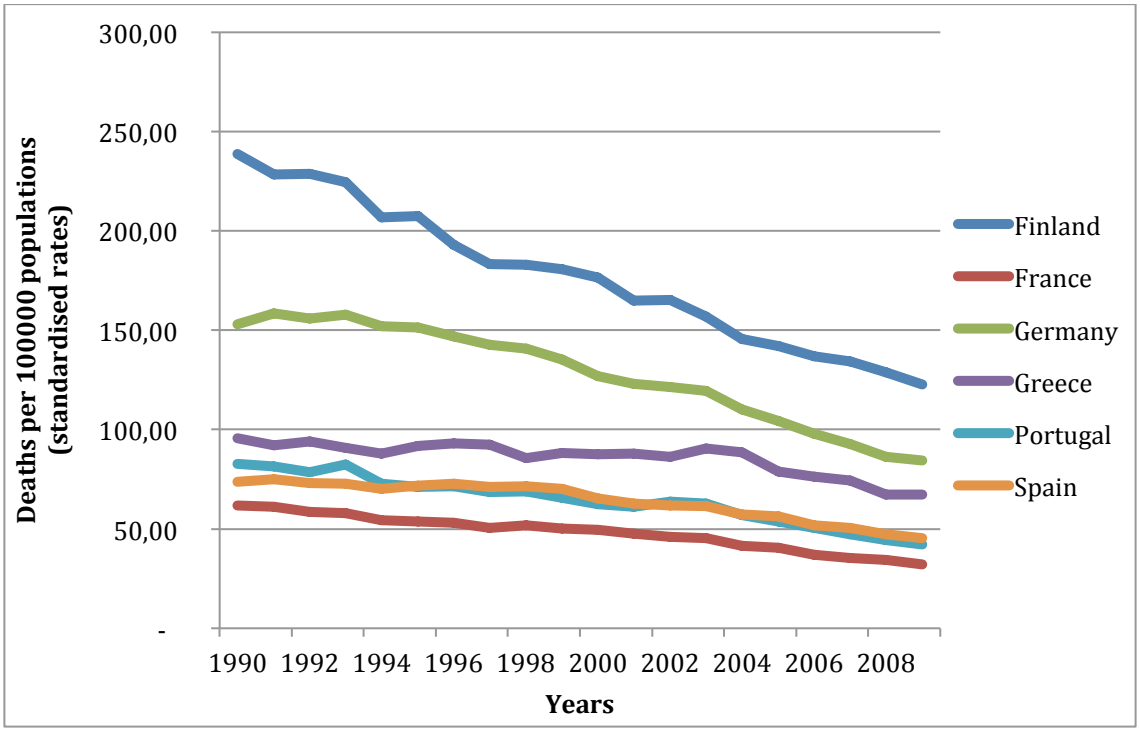


Figure 4. Deaths per 100000 population due to coronary heart disease, all ages, 1990 to 2009, in European Countries (data source[16]).

In Europe, CHD is the single most common cause of death and it is responsible for 1.8 millions deaths per year[17]. Death rates are generally higher in Central and Eastern Europe as compared with the Northern, Southern and Western Europe regions[18]. Over the past 20 years death rates from CHD have been consistently falling in the countries assessed in our study (Figure 4). For example, Finland, Portugal and France denoted a remarkable decrease in death rates from CHD between the period of 1990 until 2009 (decrease rate of 49%, 49% and 48% respectively) followed of Germany (45%), Spain (38%) and Greece (29%).

Table 1. Percentage of global disability-adjusted life years due to coronary heart disease in some European Countries (data source[19]).

	% DALYs		
	1990	**2010**	**% variation**
Finland	16.0	11.0	-31%
France	7.2	5.8	-19%
Germany	14.0	10.0	-29%
Greece	12.0	12.0	0%
Portugal	8.4	6.5	-23%
Spain	8.8	7.3	-17%

DALYs – Disability-adjusted life years

Another indicator that provides data about the burden of CHD is morbidity measured in the so-called potential disability-adjusted life years (DALYs), which are the sum of years of life lost due to premature mortality (YLL) and years lived with disability (YLD)[20]. Data from the Global Burden of Disease study[19] showed a decrease of CHD contribute in the DALYs percentage between the years of 1990 and 2010 with the exception of Greece (Table 1).

This decrease in mortality rate and DALYs due to CHD reflect advances in prevention and treatment of CHD[21]. Among treatments, the largest contributions came from a greater use of reperfusion therapy, primary PCI, modern anti-thrombotic therapy and secondary prevention treatments[9].

Beyond the medical and social burden, there are substantial costs associated with CHD that include treatment-related medical costs (i.e. hospital, nursing home, physicians and drugs), as well as costs due to loss of productivity (mortality and morbidity)[15]. In 2009, the direct medical costs for CHD were estimated at €19.87 billion in European Union and €72.67 in United States of America representing about 53% of total costs. In addition, the loss of productivity for CHD has been estimated to be worth €17.54 billions in European Union and €61.39 in United States of America (Table 2).

Table 2. Estimated direct and indirect costs (in billions of euros) of coronary heart disease in European Union (2009) and United States of America (2010) (data source[22, 23])

	European Union		United States of America	
	€ billions	**% of total**	**€ billions**	**% of total**
Direct costs	**19.87**	**53%**	**72.67**	**54%**
Indirect costs				
Lost productivity/morbidity	**5.53**	**15%**	**8.55**	**6%**
Lost productivity/mortality	**12.01**	**32%**	**52.84**	**39%**
Total costs	**37.41**		**134.06**	

1.2 Management of acute coronary syndrome

1.2.1 Main advances in treatment

Considerable progress with the advance of cardiovascular science has been achieved since the 1960s contributing to a change in the understanding and management of CHD (Figure 5).

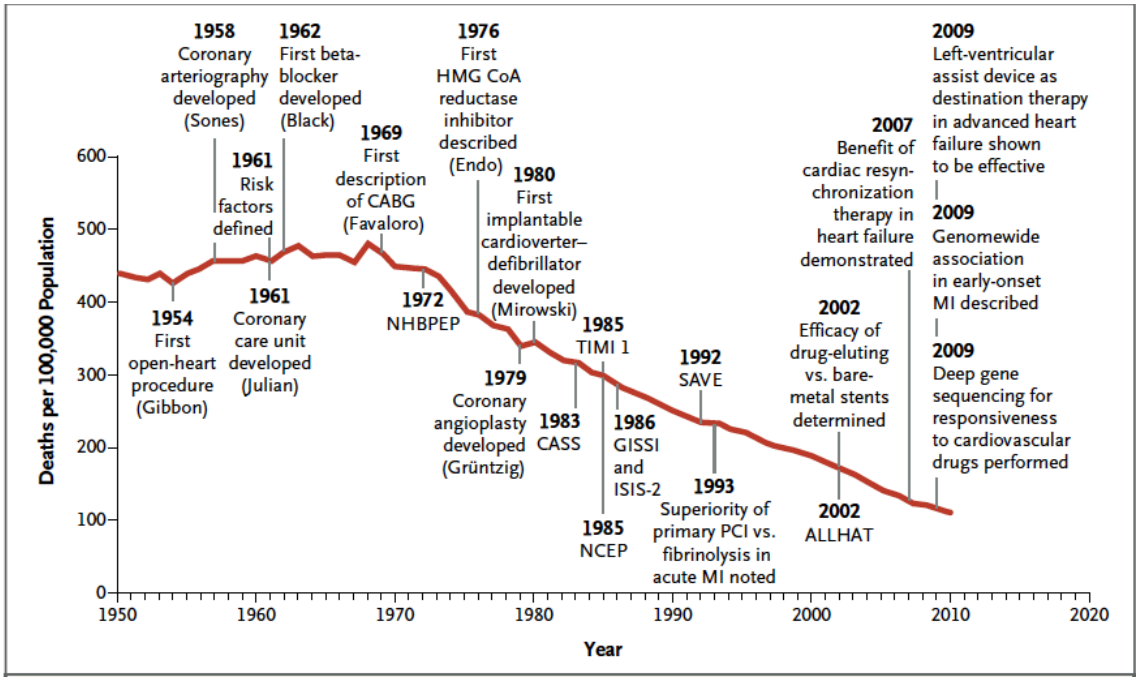


Figure 5. Decline in deaths from cardiovascular disease with major advances in cardiovascular science and medicine[3].

In 1948, the Framingham Heart study was initiated with the goal of understanding the development of heart disease by studying the lifestyles of the residents of Framingham, Massachusetts. In 1961, a publication entitled "Factors of Risk in the Development of Coronary Heart Disease"[24] reported that elevations in blood pressure and cholesterol levels were associated with an increased incidence of CHD. The identification of these risk factors led to the emergence of prevention in CHD, comprising primary and secondary prevention approaches for the first time. This knowledge, coupled with the education of clinicians and society, and the development of drugs to control these risk factors, a dramatic reduction in cardiac death rates was achieved[3].

Before 1961, the case-fatality of AMI was approximately 30%[3]. With the development of coronary care units providing a continuous monitoring of the electrocardiogram, closed-chest cardiac resuscitation and external defibrillation, the in-hospital mortality was reduced by half, to approximately 15%[25].

Another important point in the history of cardiovascular disease leads us to 1976 when the cardiologists were able to open acutely occluded coronary arteries through the coronary non-invasive infusion of the fibrinolytic agent streptokinase, allowing a reduction in early mortality in patients with the ACS[26, 27]. After three years, in 1979, Andreas Gruntzig, considered the father of percutaneous interventional cardiology,[28] develops a technique that allows to open an occluded coronary artery percutaneously using a balloon angioplasty. This initial technique was followed by the insertion of bare-metal stents (BMS) and, more recently, drug-eluting stents (DES) that are used to prevent the coronary restenosis[29].

Coronary angioplasty and stenting together with fibrinolytic agents, aspirin[30] and newer potent platelet inhibitors contributed to a reduction of in-hospital mortality to about 7%[3]. In 2004, the crude in-hospital mortality due to AMI was about 4% in high-income countries[31, 32].

1.2.2 Selection of a strategy of revascularization

Selection of a strategy of revascularization represents a key aspect in the ACS treatment. Angioplasty, coronary artery bypass graft and fibrinolysis are available approaches currently used to restore blood flow[9, 10, 33]. Today, in patients diagnosed with severe myocardial ischemia, a revascularization procedure should be considered promptly, preferably using emerging coronary angiography with a view to primary percutaneous coronary intervention (PCI) or, if unavailable, intravenous thrombolysis[9, 10, 33].

Several clinical factors including diabetes *mellitus*, chronic kidney disease, completeness of revascularization, left ventricle systolic dysfunction, previous coronary artery bypass graft, type of ACS (STEMI *versus* UA/NSTEMI), expected dual antiplatelet therapy (DAPT) compliance and stent thrombosis may influence the choice of revascularization[34].

1.2.3 Percutaneous coronary intervention

Angioplasty or PCI is a procedure used for coronary revascularization in CHD patients. Primary PCI is considered effective in securing and maintaining coronary artery patency and avoids some of the bleeding risks of fibrinolysis[9, 10, 33] being, currently, one of the most common procedures in clinical practice[3, 35].

The goals of coronary angiography and revascularization in UA/NSTEMI patients are to reduce the risk of death and myocardial infarction and provide symptom relief. Indications for revascularization depend on the patient´s clinical risk characteristics and coronary anatomy and are in general stronger in the presence of high-risk clinical presentation (Table 3)[36]. To improve prognosis, it is important to stratify the patients with UA or NSTEMI in high-risk versus low-risk groups[34, 36]. PCI is recommended only in the high-risk groups[34, 36].

Table 3. Characteristics of patients with non-ST-elevation myocardial infarction at high acute, that should undergo coronary angiography within 48 h[36].

(1)	Recurrent resting pain
(2)	Dynamic ST-segment changes: ST-depression ≥0.1 mV or transient (<30 min) ST-segment elevation ≥0.1 mV
(3)	Elevated Troponin-I, Troponin-T, or CK-MB levels
(4)	Hemodynamic instability within the observation period
(5)	Major arrhythmias (ventricular tachycardia, ventricular fibrillation)
(6)	Early post-infarction unstable angina
(7)	Diabetes *mellitus*

According to the 2011 ACCF/AHA/SCAI guidelines, an early (within 24 hours of admission) PCI is indicated in UA/NSTEMI patients who have refractory angina or hemodynamic or electrical instability (without serious comorbidities or contraindications to procedure) and it is indicated in initially stabilized UA/NSTEMI patients who have an elevated risk for clinical events. Still, according to these guidelines, an early PCI in not recommended in patients with extensive comorbidities (e.g., liver, pulmonary failure or cancer)[34]. Outcome after PCI in NSTEMI has been improved markedly with the use of intracoronary stenting and contemporary antithrombotic and antiplatelet therapies[10].

In Portugal, as described in figure 6, there has been a tendency towards higher PCI utilization instead of fibrinolysis as reperfusion therapy in STEMI patients over the last 10 years.

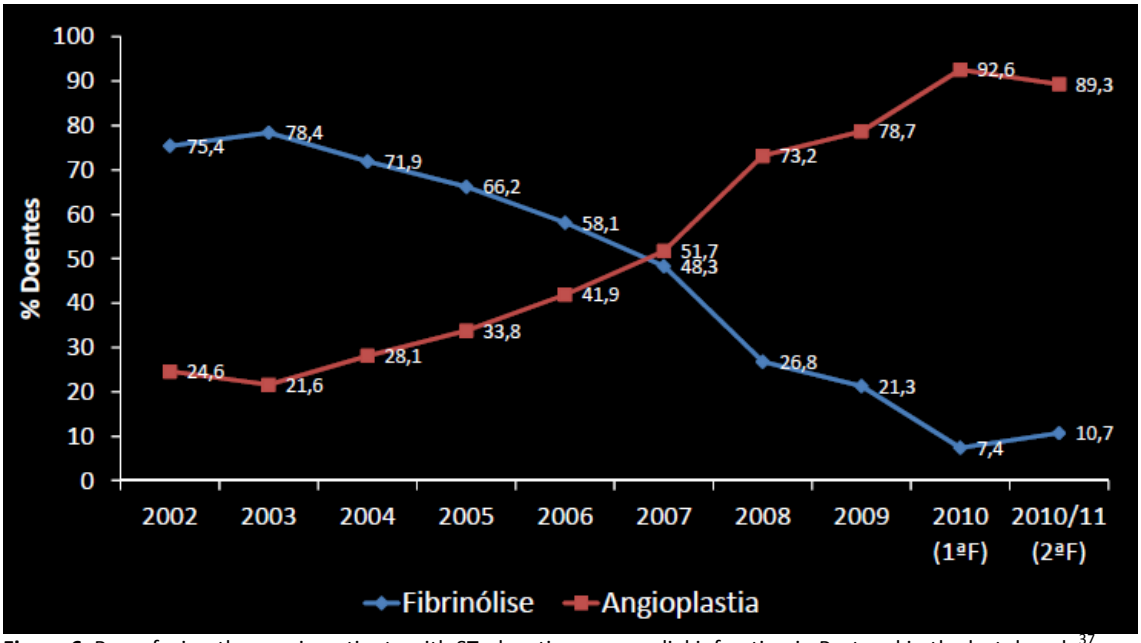


Figure 6. Reperfusion therapy in patients with ST-elevation myocardial infarction in Portugal in the last decade[37].

Primary PCI is defined as an emergent PCI in patients with STEMI without previous fibrinolytic treatment. It is the reperfusion strategy preferred in patients with STEMI. It can be performed expeditiously (i.e. within guideline-recommended times) by an experienced team when the patient presents to a PCI-capable hospital[9, 34, 36].

Primary PCI when compared with fibrinolytic therapy in randomized studies produces higher rates for infarct artery patency, TIMI flow grade 3, and lower rates for recurrent ischemia, re-infarction, emergency repeat revascularization procedures, intracranial haemorrhage[34, 36]. Lower mortality rates among patients undergoing primary PCI are observed in centers with a high volume of PCI procedures[9, 34].

For patients diagnosed with STEMI within 12h of symptom onset, a pharmacologic or mechanic (PCI) reperfusion should be performed as soon as possible [9, 34]. However, there is no consensus about PCI benefit in patients presenting >12h from symptoms onset in the absence of clinical and/or electrocardiographic evidence of ischemia[9]. In situations where primary PCI cannot be performed within 120 min after first medical contact by an experienced team, fibrinolysis should be considered - particularly when it can be administered in pre-hospital environment and within the first 120 min of symptoms onset (Figure 7)[9].

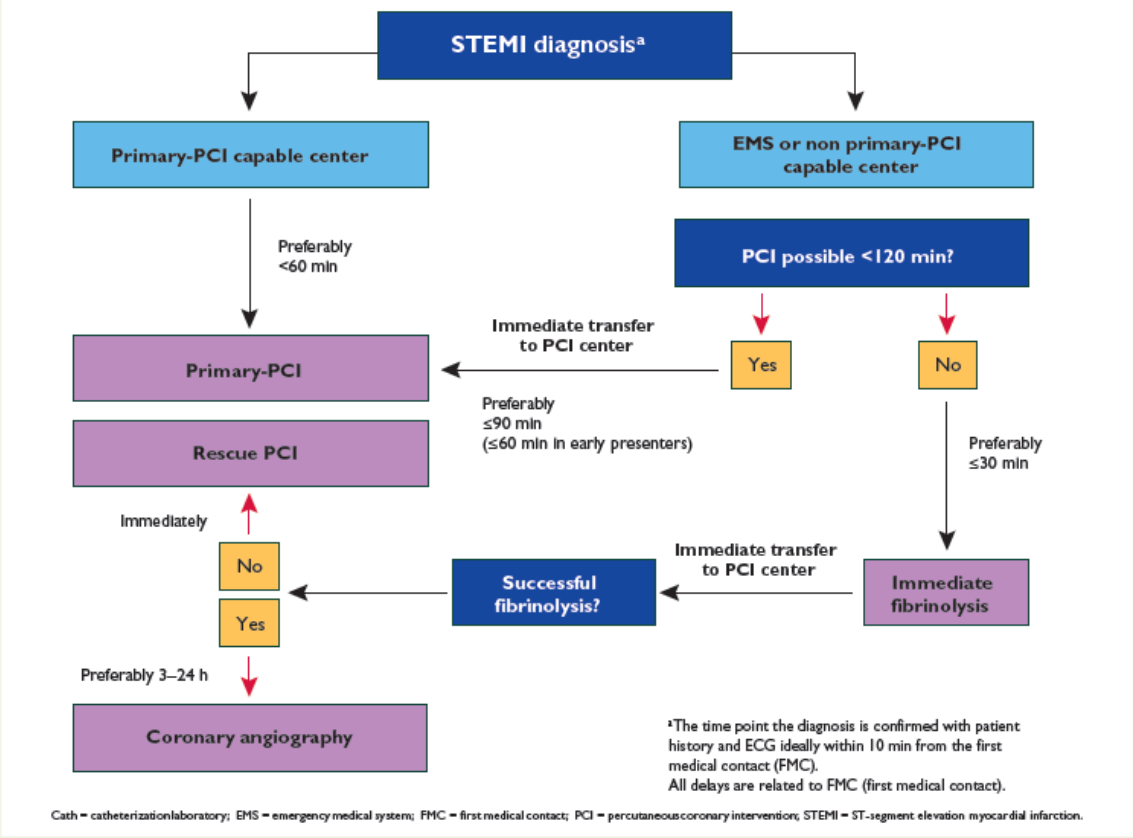


Figure 7. Pre-hospital and in-hospital management and reperfusion strategies within 24h of first medical contact[9].

Successful PCI decreases the complications of STEMI that result from longer ischemic times or unsuccessful fibrinolytic therapy, allowing earlier hospital discharge and resumption of daily activities[34]. Approximately 50% of patients with STEMI have significant multivessel disease[9]. Table 4 summarizes the diverse recommendations for primary PCI and procedural aspects of PCI adapted from European and American guidelines. It is important to note that those recommendations differ with regards to the time allocated to perform PCI and its classification. Only the infarct-related artery should be treated during the initial intervention[36]. In patients with multivessel disease and cardiogenic shock, non-culprit lesions without critic stenosis should not routinely be treated with stents[9, 34]. Due to the need of antithrombotic and antiplatelet drugs, bleeding is more frequent when PCI is performed during ACS when compared with bleeding associated to elective procedures[9].

Table 4. Primary PCI: indications and procedural aspects adapted from European and American guidelines.

Recommendations	[i]Class	[ii]Level	[iii]Ref
Indications for primary PCI			
Primary PCI is the recommended reperfusion therapy over fibrinolysis if performed by an experienced team within 120 min of FMC	I	A	[9]
Primary PCI is indicated for patients with severe acute heart failure or cardiogenic shock, unless the expected PCI related delay is excessive and the patient presents early after symptom onset	I	B	[9]
Primary PCI should be performed as soon as possible in patients with STEMI and contraindications to fibrinolysis therapy with ischemic symptoms for less than 12 hours	I	B	[34]
Primary PCI is reasonable in patients with STEMI if there is clinical and/or electrocardiographic evidence of ongoing ischaemia between 12 and 24 hours after symptom onset	IIa	B	[34]
Procedural aspects of primary PCI			
Stenting is recommended (over balloon angioplasty alone) for primary PCI	I	A	[9]
Primary PCI should be limited to the culprit vessel with the exception of cardiogenic shock and persistent ischaemia after PCI of the supposed culprit lesion	IIa	B	[9]
If performed by an experienced radial operator; radial access should be preferred over femoral access	IIa	B	[9]
If the patient has no contraindications to prolonged DAPT (indication for oral coagulation, or estimated high long-term bleeding risk) and is likely to be compliant, DES should be preferred over BMS	IIa	A	[9]
Routine thrombus aspiration should be considered.	IIa	B	[9]
Routine use of distal protection devices is not recommended.	III	C	[9]
Routine use of IABP (in patients without shock) is not recommended.	III	A	[9]

BMS=bare-metal stent; DAPT=dual antiplatelet therapy; DES=drug-eluting stent; FMC=first medical contact; IABP=intra-aortic balloon pump; PCI=percutaneous coronary intervention. i Class of recommendation. ii Level of evidence. iii Reference

1.2.4 Stents

Coronary stents were developed in the mid-1980s and this innovation changed the paradigm of interventional cardiology (Figure 8). The first coronary stent was implanted by Sigwart et al in 1986[35]. Coronary stenting only became a widely accepted technique after the publication of the landmark BENESTENT[38] (Belgium Netherlands Stent) trial and STRESS[39] (Stent Restenosis Study) in 1994.

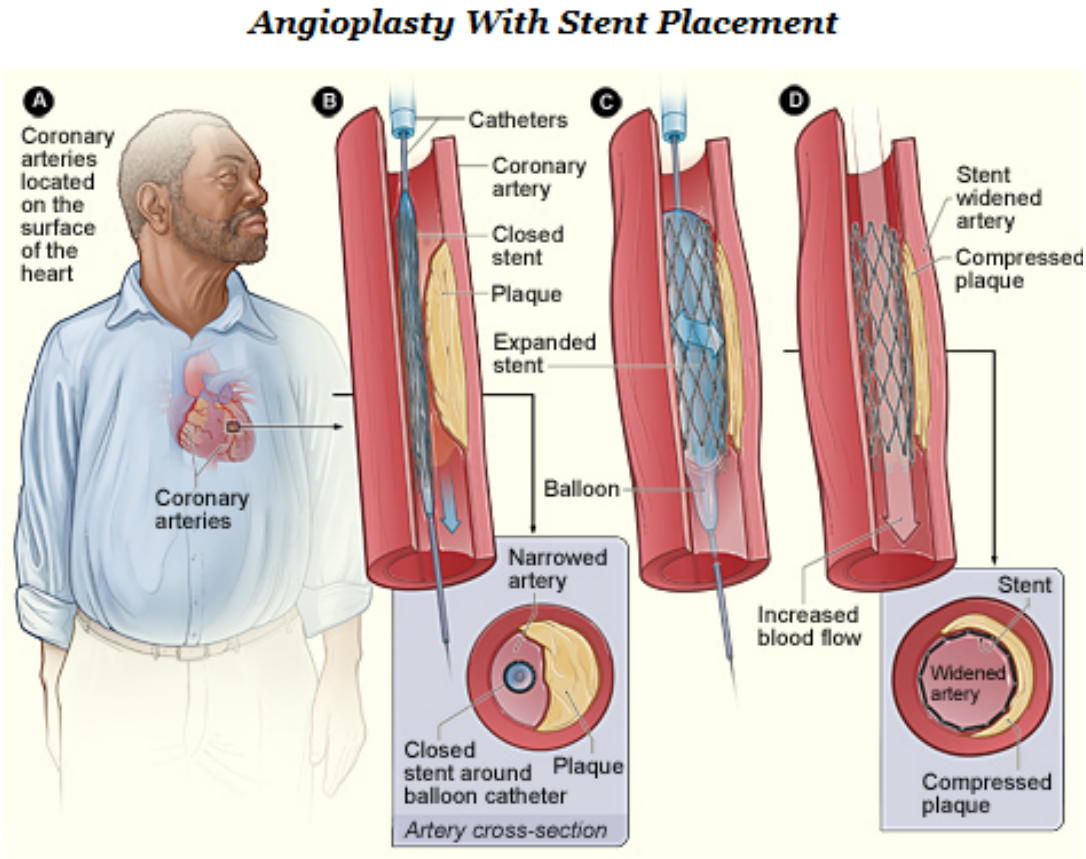


Figure 8. Angioplasty with stent implantation. A) shows the location of the heart and coronary arteries; B) shows the deflated balloon catheter and closed stent inserted into the narrow coronary artery. The inset image shows a cross-section of the artery with the inserted balloon catheter and closed stent. C) the balloon is inflated, expanding the stent and compressing the plaque against the artery wall; D) shows the stent-widened artery. The inset image shows a cross-section of the compressed plaque and stent-widened artery [40].

Due to associated problems (Figure 9) with the utilization of BMS that contribute for high restenosis rates[41] (20% to 30%) a newer generation of stents, DES with controlled local release of anti-proliferative drugs was developed, and currently, DES are used to prevent a coronary restenosis, although BMS continues to be used. A dramatic reduction in restenosis rates when using DES instead of BMS has also contributed to the exponential growth of PCI as a revascularization treatment for patients with coronary disease[42-45].

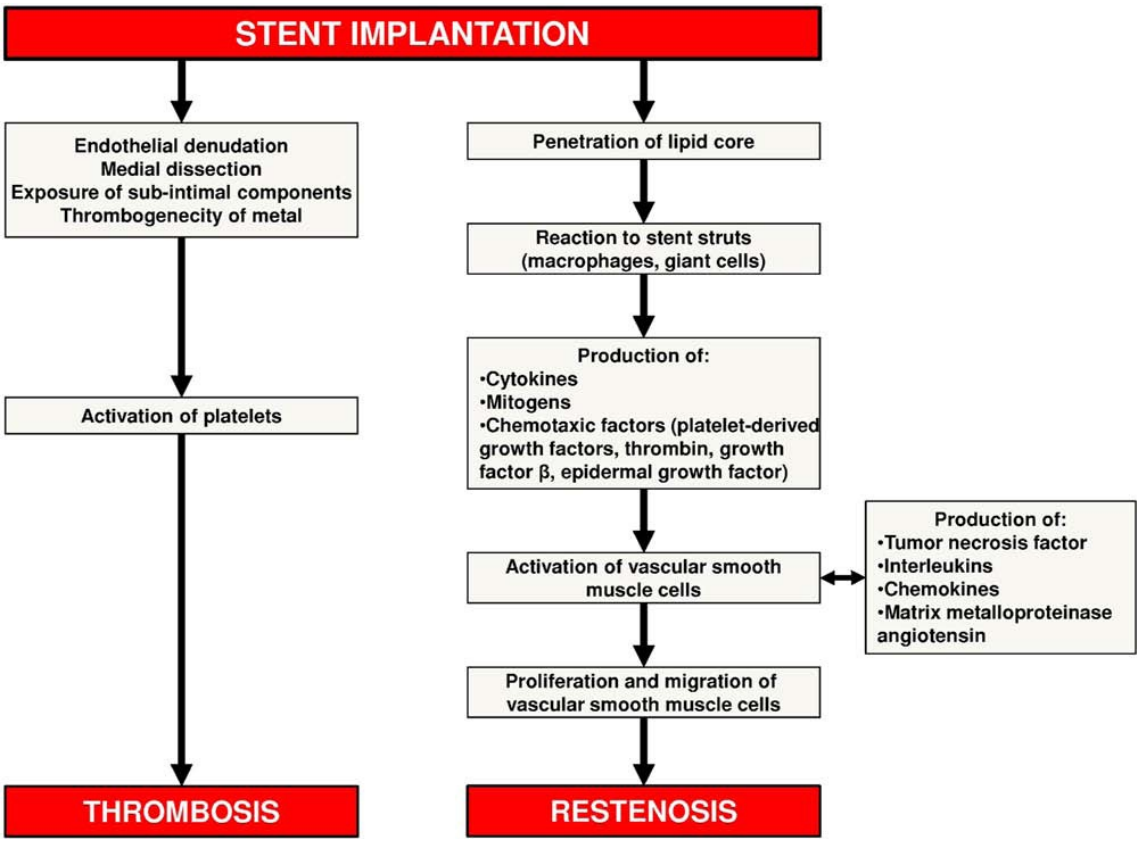


Figure 9. Pathway leading to in-stent restenosis after stent implantation[35].

Today, the majority of PCI procedures involve a coronary stent implantation and, therefore, interventional cardiologists need to select which stent to implant. The selection of stents ranges from conventional BMS that are composed of stainless steel or cobalt chromium alloys and DES that are widely used in contemporary practice. In the USA, 4 types of DES are currently approved: sirolimus-eluting stents, paclitaxel-eluting stents in the first-generation of DES and zotarolimus-eluting stents and

everolimus-eluting stents in the second-generation of DES. These type of stents vary according to stent scaffold material and design, drug content and the polymer used for drug elution[34, 35]. Newer stents such as: DES with biodegradable polymers, DES that are polymer-free, DES with novel coatings, dedicated bifurcation stents, self-expanding stents and biodegradable stents start to appear in the market[35].

The selection of stent type depends on factors including the patient´s condition, the presence of risk factors, co-morbidities and the extent and severity of the lesion identified by coronary angiography and the risk-benefit profile is most favourable for DES over BMS when the risk of restenosis with BMS is high (Table 5)[34]. In 2005, 80% to 90% of all PCI in the USA were performed using a DES, however current rate of PCI procedure with DES is of 75%[35]. DES is now implanted in more than 500000 patients every year in the United States[46].

Table 5. Clinical situations associated with DES or BMS selection preference[34].

DES generally preferred over BMS (Efficacy considerations)	BMS preferred over DES (Safety considerations)
• Left main disease • Small vessels • In-stent restenosis • Bifurcations • Diabetes • Long lesions • Multiple lesions • Saphenous vein grafts	• Unable to tolerate or comply with DAPT • Anticipated surgery requiring discontinuation of DAPT within 12 months • High risk of bleeding

BMS – bare-metal stent(s); DAPT – dual antiplatelet therapy; DES – drug-eluting stent(s)

It is important to note that DES therapy is more expensive than BMS. Cost-effectiveness analysis has shown a reduction in total cost associated with DES because of avoidance of repeat procedures, yet it may be reasonable to consider use of BMS in patient subsets with a low risk of restenosis[47].

Restenosis within BMS has been considered the main problem in coronary angioplasty due to a 20-30 % rate of recurrence of angiographic stenosis within 6-9 months after implantation[42]. Therefore, in the tentative resolution of this problem a new generation of stents, DES, emerged. Randomized studies did not show significant differences in long-term rates of death or myocardial infarction after BMS or DES implantation[42, 48]. However, in non-randomized studies, DES use may reduce death and myocardial infarction, in spite of a slightly increased propensity for late and very late stent thrombosis[42, 48]. Randomized studies suggest that second-generation of DES may provide superior clinical outcomes to first-generation of DES [33].

The use of DES with proved efficacy should be considered by default in all clinical conditions and lesion subsets, except if there are concerns or contraindications for prolonged DAPT[33]. DES use is not recommended in several clinical situations: a) when there is difficulty in access to clinical history of patient, especially in acute severe clinical cases (patients with STEMI or cardiogenic shock); b) when expected poor compliance with DAPT, including patients with multiple comorbidities and polypharmacy; c) when non-elective surgery is scheduled in the short time that will require interruption of DAPT; d) when there is increased risk of bleeding; e) when the patient is allergic to acetylsalicylic acid or clopidogrel/prasugrel/ticagrelor and, finally f) when there is an absolute indication for long-term anticoagulation[33]. Despite the contraindications already mentioned, indications for DES in a few specific patient or lesion subsets remain a matter of debate in the international medical community[33]. The optimal duration of DAPT after DES implantation is not known[33]. However, several clinicians recommend a minimum DAPT use for 6 months until 12 months. Some clinicians defend DAPT use during 12 months independently of stent type used[10]. Recent evidence shows that (very) late stent thrombosis results from delayed hypersensitivity to components of the drug-polymer-device combination that causes necrotizing vasculitis and late malapposition[49].

The interventional cardiologists that perform primary PCI in patients with STEMI should be aware of the importance of selecting an appropriate stent size. Most patients with STEMI have some degree of coronary spasm and therefore the intracoronary administration of nitrates is recommended before starting the coronary angiographic sequence used to select the stent size. The presence of thrombus can also lead to stent undersizing or suboptimal deployment, which is a frequent cause of restenosis or thrombosis in the stent[9].

In primary PCI, DES reduce the risk of repeated revascularization in the treated vessel when compared with BMS[50]. There have been concerns about increased risks of very late stent thrombosis and re-infarction with DES when compared with BMS[50]. However, DES use has not been associated with an increased risk of death, myocardial infarction or stent thrombosis on long-term follow up[51]. In selected STEMI patients, sirolimus-eluting stent and paclitaxel-eluting stents were shown to be safe and effective (TYPHOON, HORIZONS-AMI, PASEO, and ZEST-AMI) with follow-up extending from 2 to 4 years[50, 52].

In a randomized study (HORIZONS AMI) it was shown that the DES use versus BMS use in patients with STEMI did not reveal any safety concerns, whereas a consistent reduction of restenosis and unplanned repeat revascularization was found after DES implantation[53]. Due to the lack of randomized trials in patients with NSTEMI, the choice between the use of a BMS or a DES should be based on an individual assessment of benefit versus risk[54].

1.2.4.1 Special populations and conditions

Elderly patients

In 2007, the American College of Cardiology guidelines defined elderly or older patients as those aged ≥75 years[55]. However, the American Heart Association used a lower threshold, ≥65 years old[56, 57]. Such variation in definitions of who is elderly reflects some ambiguity in the concept.

According to the projections for 2030, the absolute number of the oldest old (≥85 years of age) will double relatively to year 2000[58]. This rapid expanding is of concern because age itself constitutes a fundamental risk factor for CHD due to physiologic changes associated with age. With the ageing population there is the need to evaluate the CHD treatments and their results. If the expectations are confirmed, the number of elderly patients who might benefit from DES will likely increase and it will be necessary to assess the comparative effectiveness of DES *versus* BMS among elderly patients.

Why are the elderly a special population?

Few studies have compared the effectiveness and safety of stents among elderly patients because they are typically excluded from randomized controlled trials. Furthermore, elderly patients involved in trials tend to be healthier than those in the community, reducing the generalizability of the conclusions. Older patients are frequently prescribed with multiple medications resulting in more drug-drug interactions and adverse drug effects[59]. Another important fact is the difficulty in the access to information and resources about their illness and medications. Additionally, increasing age is associated with an increased prevalence of atrial fibrillation and consequently chronic oral anticoagulation[17].

Comparison of DES and BMS in elderly patients

In 2009, Pamela Douglas et al[60] evaluated the outcomes of 262,700 patients ≥65 years of age from 650 National Cardiovascular Data Registry sites during 2004 to 2006 and showed that patients implanted with DES had lower rates of death and myocardial infarction with minimal difference in revascularization. This study showed that patients implanted with DES had significantly better clinical outcomes than BMS patients.

In 2012, a study[61] using the same registry but of a different period (2004 to 2008) reported in-hospital mortality rates significantly higher among patients ≥85 years of age as compared with younger patients. In the same study, DES use decreased with age, both in acute and elective PCI. The outcomes of DES use when compared with BMS use were associated with lower mortality and myocardial infarction risks without significant differences in repeat revascularization. In observational studies[62, 63], the use of DES has also been associated with lower mortality and myocardial infarction. DES use for high-risk patients must be considered in the future[61].

Diabetes *mellitus*

It has been very well established that patients with diabetes have a higher risk of adverse outcomes among patients with CHD. Moreover, these patients have a higher incidence of thrombotic events and re-intervention procedures[64].

The evidence shows that the presence of diabetes *mellitus* is associated with worse results among AMI patients[64]. Diabetic patients have a higher rate of mortality and post-intervention coronary restenosis than non-diabetic patients[64]. This special population displayed smaller calibre vessels, diffuse disease that often progresses rapidly, a greater burden of atherosclerotic disease,[65-68] and exaggerated neo-intimal hyperplasia that contributes to an increase in the likelihood of the need for repeat revascularization[69-71]. The poor prognosis of diabetic patients with AMI has been linked to several factors including hypercoagulability, endothelial and platelet dysfunction, widespread atherosclerosis and comorbidities[64]. Considering that the prevalence of diabetes *mellitus* among AMI patients has increased during the last decade and the prognosis of patients with diabetes has remained worse despite advances in the management of myocardial infarction, the evaluation of efficacy and safety of DES in diabetic patients with STEMI constitutes an issue of great interest[72].

In patients with diabetes, the use of DES when compared with BMS has showed a high efficacy in reduction of target vessel revascularization risk without increases in any adverse safety outcomes including very late stent thrombosis[73]. However, a recent publication that evaluated clinical outcomes in diabetic patients showed that there are significant differences among DES type and the everolimus-eluting stent has been considered the most effective and safe[73].

Despite all the knowledge, there have been inconsistent results of clinical outcomes among various DES as well as when DES are compared with BMS in diabetic patients[73].

History of anaemia

Anaemia has been linked to poor outcomes in patients with CHD. Among patients undergoing PCI, anaemia has been associated with adverse prognosis including high rates of in-hospital mortality, particularly among those presenting with ACS[74-80].

Anaemia may be a result of multiple causes. One of the most common causes is iron deficiency explained by chronic bleeding followed by others causes such as chronic infection, malignancy, autoimmune disease, and chronic kidney disease[81]. This special population has a high risk of bleeding during and after PCI[82, 83]. Thus, the guidelines for the diagnosis and treatment of NSTEMI patients of the ESC recommend quantify baseline haemoglobin levels during the initial risk stratification[84].

Despite the reduction in target vessel revascularization rates with DES use when compared with BMS use, some have raised concerns in the DES use in patients with anaemia[18, 85]. Due to haemorrhagic risk with antiplatelet therapy used and the recommendation for a prolonged course of dual antiplatelet therapy after DES implantation, the operators often choose to implant BMS in anaemic patients[82].

Recently, Pilgrim et al[86] studied the impact of preprocedural anaemia on clinical outcomes with the unrestricted use of DES and the results encountered show high rates of overall mortality and stent thrombosis among patients with severe anaemia. These findings may be explained by several reasons: first, DES use in patients with anaemia due to chronic disease and a procoagulant state may increase the risk of stent thrombosis; second, prolonged DAPT in patients with DES may exacerbate anaemia caused by occult bleeding; third, anaemia may be a mere marker for adverse outcome: patients with anaemia at baseline could be more likely to have adverse events because of conditions that caused anaemia, irrespective of the selected type of stent. If the first 2 reasons apply, DES may be contraindicated. Therefore, it is unclear whether the potential advantages of DES justify its use in patients with severe anaemia.

The available data suggest that unless data from randomized trials indicate otherwise, BMS should be used instead of DES in these patients.

Anticoagulation and/or atrial fibrillation

About 70-80% of patients with atrial fibrillation (AF) have an indication for continuous oral anticoagulation (OAC) and CHD co-exists in 20-30% of these patients[87, 88]. AF is the most common cardiac arrhythmia and it is associated with a risk of mortality and morbidity from stroke and thromboembolism[89]. Therefore, an antithrombotic therapy is fundamental in the management of AF patients[89].

With an estimated prevalence of AF in 1-2% of the population[90, 91], these anticoagulated patients are often candidates for coronary revascularization through PCI, usually including stents. Due to stents' characteristics the DAPT duration after stent implantation is a concern in anticoagulated patients. This particularity increases the complexity of the management of AF patients presenting with an ACS. Moreover, the use of DES of first and second generation, due to the prolonged DAPT needed, should be avoided in patients with an indication for long-term OAC[92].

Increasing evidence suggests that the thrombogenic tendency in AF is related to several underlying pathophysiological mechanisms among which abnormal changes in blood flows, in vessel wall and in blood constituents. Platelets are known to play a limit role in AF due to the thrombus type (mainly fibrin-rich) that is formed in this condition. Indeed, this is consistent with the superior prophylactic effect of OAC observed for AF patients when compared antiplatelet therapy for stroke prevention.

After coronary stent implantation, DAPT is necessary. However, the combination of oral anticoagulation and antiplatelet therapy increases the bleeding risk and the clinicians need to balance the risk of stroke and thromboembolism against the risk of recurrent cardiac ischemia and/or stent thrombosis[92]. Due to this need, current ESC guidelines for AF suggest risk stratification in patients with non-valvular AF for the decision of implementing oral anticoagulation.[93] This risk stratification is based on the CHADS2-Score (Congestive heart failure; Hypertension; Age; Diabetes; previous ischemic Stroke) that is the simplest and most commonly used schema for predicting the risk of thromboembolism in patients with non-valvular AF[92, 93]. As anticoagulation is associated with an increased risk of bleeding, the ESC guidelines on AF also provide a risk score to assess the haemorrhagic risk: the HAS-BLED-Score (Hypertension;

Abnormal renal and liver function; Stroke; Bleeding; Labile INRs; Elderly; Drugs or alcohol)[93].

The recommendations of ESC can be used as a "roadmap" for the management of patients with AF and coronary stenting especially because they are detailed and pragmatic[94]. Depending on the clinical presentation (ACS *versus* elective stenting), the haemorrhagic risk evaluated by CHADS2- and HASBLED-Score and the type of stent used (DES *versus* BMS), these patients can be stratified as having low or high risk of haemorrhage[94] (Table 5).

Another important point to take into consideration, in addition to choice of antithrombotic strategy, it is the vascular access site selection that may also have a great impact on bleeding complications. Radial artery access should be the preferred point of access instead of femoral access because it has been associated with a reduced risk of access site bleeding[95-97].

In summary, an individualized approach is needed for patients with AF and CHD to find the fine balance between the risk of cerebrovascular events and bleeding complications[94]. In patients with high bleeding risk the duration of DAPT should be minimized by avoiding DES or at least strictly limiting DES to those clinical and/or anatomical situations, such as long lesions, small vessels, diabetes, etc. where a significant benefit is expected as compared to BMS[92].

Table 5 Recommended antithrombotic strategies following coronary artery stenting in patients with atrial fibrillation at moderate-to-high thromboembolic risk (in whom oral anticoagulation therapy is required)[92].

Haemorrhagic risk	Clinical setting	Stent implanted	Recommendations
Low or intermediate	Elective	Bare metal	***1 month:*** triple therapy of warfarin (INR 2.0-2.5) + aspirin ≥100mg/day + clopidogrel 75mg/day + gastric protection ***lifelong:*** warfarin (INR 2.0-3.0) alone.
	Elective	Drug eluting	***3 (-olimus group) to 6 (paclitaxel) months:*** triple therapy of warfarin (INR 2.0-2.5) + aspirin ≥100mg/day + clopidogrel 75mg/day; ***up to 12th months:*** combination of warfarin (INR 2.0-2.5) + clopidogrel 75mg/day* (or aspirin 100 mg/day); ***lifelong:*** warfarin (INR 2.0-3.0) alone.
	ACS	Bare metal or drug eluting	***6 months:*** triple therapy of warfarin (INR 2.0-2.5) + aspirin ≥100mg/day + clopidogrel 75mg/day; ***up to 12th months:*** combination of warfarin (INR 2.0-2.5) + clopidogrel 75mg/day* (or aspirin 100 mg/day); ***lifelong:*** warfarin (INR 2.0-3.0) alone.
High	Elective	Bare metal#	***2 to 4 months:*** triple therapy of warfarin (INR 2.0-2.5) + aspirin ≥100mg/day + clopidogrel 75mg/day; ***lifelong:*** warfarin (INR 2.0-3.0) alone.
	ACS	Bare metal#	***4 weeks:*** triple therapy of warfarin (INR 2.0-2.5) + aspirin ≥100mg/day + clopidogrel 75mg/day; ***up to 12th month:*** combination of warfarin (INR 2.0-2.5) + clopidogrel 75mg/day* (or aspirin 100 mg/day); ***lifelong:*** warfarin (INR 2.0-3.0).

* combination of warfarin (INR 2.0-3.0) + aspirin = 100mg/day (with PPI, if indicated) may be considered as an alternative. # drug eluting stents should be avoided. INR= international normalized ratio; PPI=proton group inhibitors; ACS=acute coronary syndrome.

2 Aims

This dissertation is intended to contribute to a better knowledge of the stent selection process in routine practice both in Portugal and among hospitals from several European countries.

Therefore, the specific aims of this dissertation were:

i) To assess the demographic, clinical and institutional determinants of the use of drug-eluting (DES) *versus* bare-metal (BMS) stents in patients undergoing percutaneous coronary interventions (PCI) after an acute coronary syndrome in Portuguese hospitals.

ii) To quantify the variability in the stent type utilization among hospitals in some countries of Europe and to identify determinants of such variation at patient-, hospital- and country-level.

3 Paper I

Barros V, Pereira M, Araújo C, Marrugat J, Braga P, Azevedo A.

Determinants of drug-eluting *versus* bare-metal stents use in percutaneous coronary intervention after an acute coronary syndrome in Portugal: EURHOBOP study

Abstract

Aims: To assess demographic, clinical and institutional determinants of the use of bare-metal (BMS) *versus* drug-eluting (DES) stents in patients undergoing percutaneous coronary interventions (PCI) after an acute coronary syndrome in Portuguese hospitals.

Methods and Results: Within the EURopean HOspital Benchmarking Processes study, we retrospectively assessed 3009 consecutive patients in 10 Portuguese hospitals in 2009. Only patients with stent implantation during PCI (n=1194) were analysed.

A total of 425 patients (36%) received a BMS and 769 patients (64%) received a DES. A history of previous PCI, current non-ST-elevation acute coronary syndrome, anterior descendent artery as the infarct-related artery and being treated in hospitals with catheterization laboratory were independent predictors of DES implantation. Young and old age, anaemia and previous anticoagulation and/or atrial fibrillation were associated with BMS use.

Conclusions: Stent type selection was mainly influenced by the bleeding risk and expected prognosis of the acute event. This choice varied according to the hospitals' characteristics, sustaining the need for a standardization of procedures in patients undergoing PCI in the setting of acute coronary syndromes.

Introduction

Treatments for acute coronary syndrome (ACS) have improved considerably in the last century and there are currently several approaches available for revascularization, including fibrinolysis, percutaneous coronary intervention (PCI), coronary artery bypass surgery (CABG) and hybrid procedures[1-3]. Several clinical factors including previous medical history, characteristics of the disease (presentation as unstable angina (UA), non-ST-elevation myocardial infarction (NSTEMI) or ST-elevation myocardial infarction (STEMI)) and other therapeutic options (dual antiplatelet therapy (DAPT) compliance and safety) may influence the choice of the strategy for revascularization[4].

Over the last decade, there has been a growing trend towards the use of PCI both in patients presenting STEMI and intermediate/high-risk patients with non-ST-elevation ACS (NSTE-ACS)[4, 5]. The increasing utilization of PCI is based on studies that support the efficiency of this approach in securing and maintaining coronary artery patency, especially avoiding some of the bleeding risks of fibrinolysis[6-9]. The reduction of restenosis in the target lesion by 60%-70%, when using drug-eluting stent (DES) instead of bare-metal stent (BMS), has also contributed to the exponential growth of PCI as a revascularization treatment for patients with coronary disease[10-13]. In Portugal, according to the Portuguese Registry of ACS, PCI performance in STEMI patients rose from 14.5% in 2002 to 50.2% in 2008 [14].

Currently, the interventional cardiologist decides the specific stent type used based on the risk-benefit profile of each patient. Usually, DES should be considered in all clinical conditions and lesion subsets, except if there are concerns or contraindications for prolonged DAPT[3]. There are particular situations in which the use of DES is strongly recommended, including in presence of left main artery disease, diabetes *mellitus*, saphenous vein grafts, small vessels (<2.5 mm diameter), long lesions, bifurcations, multiple lesions and in-stent restenosis[4]. Beyond all clinical

considerations, it is important to note that DES were two or three times more expensive than BMS in the recent past and this factor may influence the choice of stent used in clinical practice.

Therefore, the aim of this work was to identify and quantify the effect of demographic, clinical and institutional determinants of stent type in patients with ACS undergoing PCI in routine practice in Portuguese hospitals.

Methods

Patient data was collected in the framework of EURopean HOspital Benchmarking by Outcomes in acute coronary syndrome Processes (EURHOBOP) project, which was a multicenter and multinational retrospective study of patients diagnosed with ACS consecutively discharged from 70 European hospitals (Finland, France, Germany, Greece, Italy, Portugal and Spain). This study only considers patients admitted in the ten Portuguese hospitals.

Portuguese hospitals

Data from public hospitals, from North to South and East to West of the country, serving both urban and rural populations and with different levels of specialization (catheterization laboratory and/or cardiac surgery department) were included. Participating hospitals are listed in the acknowledgments section. From the ten Portuguese hospitals, five had a catheterization laboratory and only three had a cardiac surgery department. The number of beds ranged from 280 to 1124.

Study participants

From each hospital, retrospective data from 300 consecutive patients from the year 2009 were collected. In hospitals whose annual number of cases was not enough to obtain the 300-patient sample, we extended the recruitment period backwards to 2008.

A total of 3009 ACS patients were included in the study. For this analysis, we excluded patients without PCI (n=1663), patients who performed PCI without stent implantation (n=73), patients who had both types of stent (DES and BMS) implanted during the same episode (n=24) and patients with missing information in the type of stent (n=55).

Data collection

Data was collected by trained medical record extractors using a standardized data collection form. The main source of information was the discharge letter, however information on emergency room records and laboratory information systems were also accessed, whenever available. We extracted information on the type of diagnosis, demographic characteristics, previous medical history, clinical and laboratory admission data, procedures used during hospitalization, severity indicators and complications during hospitalization.

Statistical analysis

Descriptive statistics were used to characterize the patients included in this study. Chi-squared test or Fisher's exact test, when applicable, were used to compare the characteristics of the patients implanted with BMS or DES. A multivariable logistic regression was used to estimate odds ratios (OR) for the association of patient and hospital characteristics with the stent type used during PCI. All variables were included in the model at first. Age and sex were forced to stay, regardless of their effect in this sample. We then removed the variables that had no significant association with the outcome and no confounding role on the effect of other predictors (based on a change in the regression coefficients over 10%), one at a time, until the final model. Initially patients with STEMI and NSTE-ACS were analysed separately, but since the determinants of stent type used were not significantly different, as assessed by interaction terms, we decided to analyse all ACS together, including the type of ACS as an additional covariate.

STATA version 12.0 (Stata Corporation, College Station, Texas, USA) was used for data analysis and a p value <0.05 was considered statistically significant.

Ethics

The ethics committee of the University of Porto Medical School and the National Commission for Data Protection approved the study. These two entities agreed that it would not be necessary to ask for patients' informed consent, since the study was based on the collection of retrospective clinical data from the medical records during hospitalization, and the confidentiality of patients' identification was assured.

Results

The 1194 consecutive patients with stent implantation had a mean (standard deviation) age of 64 (13) years and three quarters were men. One-third were smokers, one-third had diabetes and two-thirds had a history of hypertension. A total of 425 patients (36%) received a BMS, while 769 patients (64%) received a DES.

In univariate analysis, those who had a previous PCI and male gender had higher rates of DES implanted. On the other hand, BMS had been chosen more frequently in older patients, in patients with previous history of stroke, previous anticoagulation and atrial fibrillation, and anaemia (Table 1). In STEMI patients, the BMS were used more frequently than DES (61.5% versus 47.9%, $p<0.001$). Patients intervened on the anterior descendent artery had a higher rate of DES implanted. On the other hand, a higher rate of BMS was implanted in the right coronary artery (Figure 1).

In multivariate analysis (Table 2), independent predictors of DES use in patients with ACS included previous PCI (OR=2.02), anterior descendent artery intervened (OR=2.58), hospitals with catheterization laboratory (OR=1.40) and NSTE-ACS patients (OR=1.80). Age under 45 (OR=0.63) or above 80 (OR=0.17), anaemia (OR=0.56), and previous anticoagulation and/or atrial fibrillation (OR=0.25) were associated with a lower likelihood of DES use.

Discussion

This study involved a retrospective review of the medical records and discharge letters in a large sample of ACS patients. It enabled us to generate an insightful overview of clinical patterns of stent use in the routine care of patients diagnosed with ACS who underwent elective or primary PCI in ten Portuguese hospitals.

Overall, 65% of patients who were diagnosed with either STEMI or NSTEMI were implanted with a DES. This frequency is similar to the observed in other observational studies examining the use of DES and BMS in patients who underwent PCI across Europe, particularly when compared with Mediterranean countries[15]. Ramcharitar et al showed a higher frequency of DES use in Northern Europe (69.3%) followed by Western European (64.2%), Mediterranean countries (60.4%) and Central Europe (20.1%) for the period 2005-2006[15]. In the same period, DES use in patients with STEMI among seven countries ranged from 6.8% to 72.1% (Poland, 6.8%; Slovenia, 13.5%; Finland, 15.1%; Spain, 16.0%; Sweden, 28.4%; Italy, 37.8%; Germany, 72.1%)[16]. In our study, 59% of the patients with STEMI used DES in 2009. The observed differences between countries may be associated with the uncertainty about benefit/risks of DES use and the variation of characteristics of cardiac patients in Europe around 2006[17]. Later on, the concern with the safety of DES was not validated and there was an increase in DES implantation[18]. However, the representativeness of these studies' samples and the heterogeneity of the population involved may have contributed to the observed differences.

Elderly patients are typically not included in randomized trials due to comorbidities and prescription of multiple medications associated with their age, limiting the evidence on the influence of age on stent type selection [19]. Increasing age is associated with an increase of prevalence of atrial fibrillation and consequently chronic oral anticoagulation[20]. However, DES as compared to BMS among elderly patients was associated with lower mortality and myocardial infarction risks without

significant difference in repeat revascularization risk[21]. Drug-eluting stent seems to be safe and effective in the elderly in clinical practice[22]. Nevertheless, more studies are needed to validate this data and confirm the possible effects of antiplatelet agents[22]. Ours and other studies reported older age as an independent predictor of the stent type with a tendency to decrease of DES use with the increase of age[16, 23]. A higher use of BMS in very young ACS patients can only be explained by the angiographic characteristics of the disease, namely if these patients were often being treated in large caliper vessels. In this retrospective study, we did not have detailed data on the angiography result to be able to test this interpretation, which should be explored in future studies.

Patients with a history of bleeding are typically considered as having the highest risk of re-bleeding with anticoagulation and antiplatelet therapy during and after a coronary intervention[24]. Therefore the use of BMS instead of DES is recommended in patients with anemia[2]. The fulfilment of this recommendation was observed in our results, anaemia was an independent predictor of BMS use.

In this study, patients with a history of anticoagulation and patients with atrial fibrillation were pooled due to an administration of anticoagulation therapy[24, 25] and this fact has been associated with high-risk of bleeding[26]. There is a lack of published data about the more appropriate antithrombotic strategy in patients with anticoagulated AF presenting ACS and submitted to PCI with coronary stent implantation[27]. Nevertheless, guidelines advise the use of CHADS2 Score[28] and HAS-BLED Score[29] to assess the haemorrhagic risk of these patients. Both the European Society of Cardiology[30] and the North American consensus[31] recommend the BMS use in high-risk patients of bleeding and the DES use should be discouraged in patients with AF due to the need of dual antiplatelet therapies administration after stent implantation[32, 33]. In the present study anticoagulation/atrial fibrillation was considered an independent predictor of BMS use, supporting the general respect for these recommendations.

Our study suggests that previous PCI was an independent predictor of DES use, like in the EUROTRANSFER Registry[16]. However, this result must be carefully analysed because data on whether the previous PCI was performed in the same vessel was not available in the data set. The lack of data regarding the type of stent previously implanted was also a limitation. In addition, it is unknown whether the PCI performed was due to restenosis or in-stent thrombosis.

PCI in the left anterior descendent artery (LAD) is associated with a high rate either of restenosis or in-stent thrombosis, so that DES use is recommended, whenever possible[34, 35]. However, there is no evidence of benefit in DES use compared to BMS use in nonostial proximal lesions of LAD and some authors defend BMS use in a cost/benefit perspective in LAD nonostial proximal lesions[36]. LAD as the infarct-related artery was considered a strong independent predictor of the DES use in this study as also reported in EUROTRANSFER Registry[16] and EuroPCI Survey[15]. Due to the retrospective of this study, we did not have detailed angiographic data and the distribution and anatomical lesion characteristics could have influenced the stent used.

We also evaluated whether the hospital characteristics had an influence on the choice of stent type, independently of the patient characteristics. The patients treated in hospitals without catheterization laboratory had a lower probability of having a DES implanted. In fact, the choice of the type of stent in these patients was made in the referral hospitals where they go for the invasive procedure; therefore this observation is difficult to interpret. Probably, the cases referred to other hospitals for intervention had characteristics not considered in this analysis that may have influenced the choice of the type of stent, such as general condition and comorbidities.

Current guidelines recommend the preferential use of DES in diabetic patients[4]. In this study, diabetes was not an independent predictor of the type of stent implanted. In fact, in 2009, when the patients in this study were treated, there was evidence of a higher risk of death with DES compared to BMS in diabetic patients, particularly if the duration of DAPT was < 6 months[37].

NSTE-ACS patients were more often treated with DES. Most likely this difference results from anatomic characteristics of the vessel and the lesion. No detailed information regarding these characteristics was available in our database, but it would be interesting to explore in future studies the putative mechanisms involved.

In-hospital mortality was significantly lower in patients treated with DES than in patients treated with BMS ($p<0.001$), as has also been documented in other studies[38, 39 40, 41]. This difference could be related with the severity of the event, with patients implanted with BMS being more likely to have associated comorbidities.

In this analysis, the choice of stent type was influenced by two main factors: 1) the bleeding risk during and after the intervention in the patient, 2) the characteristics of vessel intervened. This choice also varied according to the hospitals' characteristics, regardless of patients' characteristics. Therefore, this study sustains the need for a standardization of procedures in patients undergoing PCI in the setting of acute coronary syndromes.

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Table 1. Baseline clinical characteristics of patients submitted to percutaneous coronary intervention with stent implantation, according to the type of stent used.

		Overall n (%)	Stent type		
			Bare-metal stent n (%)	Drug-eluting stent n (%)	p
Socio-demographic characteristics					
Age, years					
	<45	102 (8.5)	38 (8.9)	64 (8.3)	<0.001
	45-79	987 (82.7)	309 (72.7)	678 (88.2)	
	≥80	105 (8.8)	78 (18.4)	27 (3.5)	
Sex					
	Male	887 (74.3)	301 (70.8)	586 (76.2)	0.042
	Female	307 (25.7)	124 (29.2)	183 (23.8)	
Previous medical history					
Smoking		398 (33.3)	127 (29.9)	271 (35.2)	0.060
Diabetes *mellitus*		317 (26.6)	100 (23.5)	217 (28.2)	0.079
Hypertension		767 (64.2)	276 (64.9)	491 (63.9)	0.706
Myocardial infarction		191 (16.0)	64 (15.1)	127 (16.5)	0.511
Stroke		55 (4.6)	28 (6.6)	27 (3.5)	0.015
Percutaneous coronary intervention		124 (10.4)	29 (6.8)	95 (12.4)	0.003
Coronary artery bypass graft		44 (3.7)	17 (4.0)	27 (3.5)	0.668
Heart failure		49 (4.1)	17 (4.7)	29 (3.8)	0.436
Anticoagulation and/or atrial fibrillation		54 (4.5)	35 (8.2)	19 (2.5)	<0.001
Renal failure[§]		69 (5.8)	30 (7.1)	39 (5.1)	0.159
Alzheimer´s disease		9 (0.8)	3 (0.7)	6 (0.8)	0.594
Anaemia[+]		227 (19.0)	102 (24.0)	125 (16.3)	0.001
Characteristics of the current acute coronary syndrome					
Type of myocardial infarction					
	STEMI	613 (52.7)	252 (61.5)	361 (47.9)	<0.001
	NSTE-ACS	550 (47.3)	158 (38.5)	392 (52.1)	
Hospital characteristics					
Catheterization laboratory		756 (63.3)	258 (60.7)	498 (64.8)	0.164
Outcome					
Vital status					
	Alive	1162 (97.3)	402 (94.6)	760 (98.8)	<0.001
	Dead	32 (2.7)	23 (5.4)	9 (1.2)	

[+] Anaemia defined as haemoglobin <13 g/dl for male and haemoglobin <12 g/dl for female.

[§] Renal failure defined as estimated glomerular filtration rate <60 ml/min using Cockcroft-Gault equation.

NSTE-ACS, non-ST elevation acute coronary syndrome; STEMI, ST elevation myocardial infarction

Table 2. Independent predictors of drug-eluting stent use in acute coronary syndrome patients.

	Adjusted OR	95% confidence interval
Age, years		
<45	0.63	0.40–0.98
45-79	1	
≥80	0.17	0.10–0.28
Female	0.84	0.61–1.15
Previous percutaneous coronary intervention	2.02	1.24–3.28
Anaemia[+]	0.58	0.41–0.82
Previous anticoagulation and/or atrial fibrillation	0.25	0.13–0.48
NSTE-ACS	1.78	1.35 – 2.36
Anterior descendent artery intervened	2.58	1.97–3.38
Catheterization laboratory	1.40	1.05–1.86

[+] Anaemia defined as haemoglobin <13 g/dl for male and haemoglobin <12 g/dl for female;

NSTE-ACS, non-ST-elevation acute coronary syndrome; OR, odds ratio

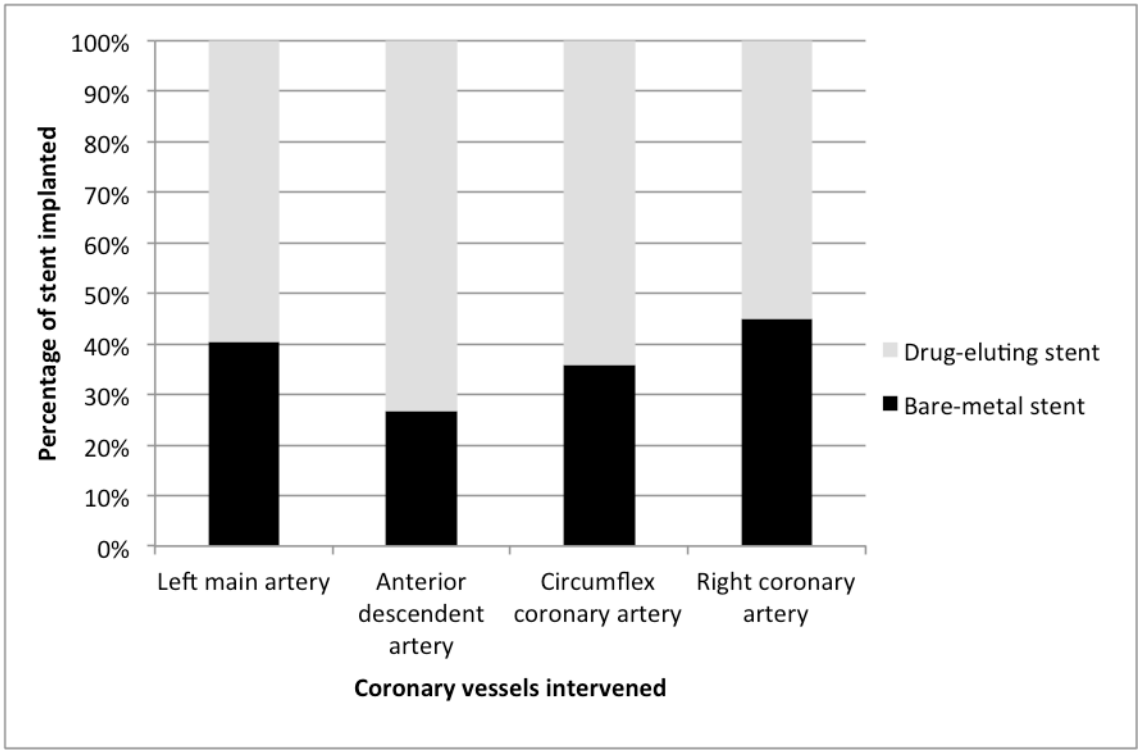

Figure 1. Type of stent used according to the vessel intervened.

4 Paper II

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Variation in utilization of drug-eluting *versus* bare-metal stents in acute coronary syndrome patients among 54 hospitals from six countries: a multilevel analysis in the EURHOBOP study

Abstract

Aims: This study aims to quantify the variability in the stent type utilization and to identify determinants of such variation among hospitals of six European countries.

Methods and Results: Within the EURopean HOspital Benchmarking Process (EURHOBOP) study, we retrospectively assessed 5958 consecutive patients with acute coronary syndrome who had a stent implanted in Finland, France, Germany, Greece, Portugal and Spain. Due to the hierarchical structure of the data, including patients clustered into hospitals and hospitals clustered into countries, multilevel logistic regression models were used to estimate median odds ratios (MOR) and intra-cluster coefficients (ICC).

The use of drug-eluting stents ranged from 36% in Finland to 80% in Greece.

There was a large inter-hospital variation in the stent type choice (MOR=2.91), slightly attenuated when the country-level was considered (MOR=2.39). Patients' and hospitals' characteristics did not contribute to explain the variance at hospital- and country level. GDP per capita accounted for approximately 30% of total variance at the country level. In the final model, over 85.6% of the variance at hospital level remained unexplained, with a MOR for the difference among hospitals of 2.50 and an ICC for the agreement in type of stent implanted among patients from the same hospital of 21%.

Drug-eluting stents were less often used in octogenarians (OR=0.365), in patients with anticoagulation and/or atrial fibrillation (OR=0.600), and anaemia (OR=0.761). Diabetes *mellitus* (OR=1.557), previous history of PCI (OR=1.824) and non-ST-elevation acute coronary syndrome (OR=2.043) were associated with a higher likelihood of DES use. The odds of use of DES decreased 5% per 1 PPS of GDP.

Conclusions: A large variation in the type of stent implanted was observed among European hospitals. Patient characteristics had a low impact on the variance among hospitals and inter-country variance was largely explained by the GDP per capita. Specific recommendations for stent choice are needed in order to reduce the differences in the stents used.

Introduction

Over the past four decades there has been a dramatic progress in the management of coronary heart disease[1]. A considerable reduction in restenosis rates was obtained when drug-eluting stents (DES) started to be used instead of bare-metal stents (BMS), and this has contributed to the exponential growth of percutaneous coronary intervention (PCI) as a revascularization treatment for patients with coronary disease[2-5]. Nowadays, the majority of PCI procedures typically involve a stent implantation and this implies that there is a need to select the type of stent to be implanted. However, few studies have studied the process of choice of stent type in clinical practice and the differences in stent utilization among hospitals and countries.

Previous studies have demonstrated differences in DES utilization among hospitals within one country[6-8]. It is also established that the selection of stent type depend on several factors including patient's condition, the presence of risk factors, co-morbidities and the extent and severity of the lesion identified by coronary angiography[9]. In this study, we hypothesize that the choice of stent is a multifaceted phenomenon grounded in an interplay of patient, but also hospital and country factors. We approached this complex phenomenon using a hierarchical model which takes in consideration patient-, hospital- and country-level measured characteristics, as well as random variation at these levels[10, 11].

The aim of our study was to quantify the variability in the stent utilization among hospitals in some countries of Europe and to identify determinants of such variation at patient-, hospital- and country-level.

Methods

This analysis was performed in the framework of the EURopean HOspital Benchmarking by Outcomes in acute coronary syndrome Processes (EURHOBOP) project, which was a collaborative, multicentre and multinational study oriented to Western Europe. This project was conducted between 2008 and 2010 in seven countries (Finland, France, Germany, Greece, Italy, Portugal and Spain). In each country, 8 to 10 centers contributed with at least 200 consecutive patients diagnosed with myocardial infarction or unstable angina.

Of a total of 15079 patients only 5958 had a stent implanted and were included in this study. We excluded the Italian patients (n=2000) due to lack of information on the stent type implanted, all patients who had both types of stent (DES and BMS) implanted during the index episode (n=242) and all hospitals wherein less than 20 patients with implanted stents were available for analysis.

Data sources

Data was collected by trained medical record extractors using a standardized data collection form. The main source of information was the discharge letter, however information on emergency room records and laboratory systems were also accessed, whenever available. The type of diagnosis, demographic characteristics, previous medical history, clinical and laboratory admission data, procedures used during hospitalization, severity indicators and complications were collected. Finally, for each country, the gross domestic product (GDP) per capita in purchasing power standards (PPS) was abstracted from Eurostat (2009) and it was added to complete EURHOBOP data and to take into account the impact of inter-regional socioeconomic inequalities in the stent choice.

Statistical analysis

Descriptive statistics were used to study the characteristics of the patients implanted with DES or BMS in the several countries through the Chi-squared test. A similar analysis was performed with the aim of describing differences in stent utilization in several countries. We defined a binary outcome based on stent type (DES or BMS) used in each patient.

A multilevel logistic model was designed according to the data hierarchy, with random variation permitted at three levels: patient, hospital and country. We fitted five models. The first model, an empty model, only included the hospital-level with the aim of quantifying the total variance among all hospitals in the stent choice. The second model contained the hospital- and country-level. The third model was extended to include relevant patient comorbidities (identified in a preliminary stepwise logistic regression model), age, sex, presence of diabetes *mellitus*, previous PCI, anticoagulation and/or atrial fibrillation, anaemia and acute coronary syndrome type. Age and sex were forced into the model and the significance level of entry and removal for other variables was set at 0.05. The fourth model results from the addition of characteristics of hospital-level, presence of catheterization laboratory and teaching status. The fifth model adjusted additionally to characteristics of country-level, GDP per capita in PPS. All characteristics of three levels were added as fixed effects. Finally, only for the final model, we present the associations between the characteristics of three levels and the stent type implanted through odds ratios (ORs) and their 95% confidence intervals (CIs). The amount of variance explained intra-cluster was calculated by the proportional change in variance (PCV), $PCV=(V_0-V_i)/V_0$, where V_0 is the initial (null) variance of empty model and V_i is the variance of model adjusted for characteristics added to empty model[12]. The intra-cluster correlation (ICC) is a measure of cluster homogeneity and it was calculated by the linear threshold according to the formula used by Snijders and Bosker in 1999[12], while the median odds ratio (MOR)

indicates the cluster heterogeneity[13]. We used the area the ROC curve to assess the discriminative ability of the model in predicting the stent type implanted. This area (alternatively named c-index) varies from 0.5 to 1, with larger values denoting better model performance).

STATA version 12.0 (Stata Corporation, College Station, Texas, USA) was used for data analysis and a p value <0.05 was considered statistically significant.

Ethics

The International Review Boards of the institutions enrolled approved the study.

Results

The study sample included 5958 patients who had a stent implanted. Three quarters were men and the mean age was 64 years.

Baseline characteristics by country are summarized in Table 1. Finland and Germany displayed a higher percentage of older patients subject to stent implantation as compared to France, Greece, Portugal and Spain. Greek patients displayed the highest smoking rate among the enrolled countries. A higher frequency of previous history of myocardial infarction, PCI, coronary artery bypass graft, anticoagulation and/or atrial fibrillation, anaemia and renal failure was observed in German patients. Patients from Greece had a higher rate of STEMI. On the other hand, a higher rate of patients diagnosed with NSTE-ACS was visible in French and German patients. The majority of hospitals enrolled had catheterization laboratory and about 50% were university teaching hospitals (Table 1).

The use of drug-eluting stents ranged from 36% in Finland to 80% in Greece, and averaged 51% in the EURHOBOP study. Drug-eluting stents were significantly more used in Southern Europe (Greece, Portugal and Spain) and decreased progressively through Western (France and Germany) to Northern Europe (Finland) (Figure 1).

In the overall sample, there was a large inter-hospital variation in the stent type choice (MOR=2.91) (Table 2, Model 1). When the country-level was considered, the inter-hospital variation was attenuated (MOR=2.39) (Table 2, Model 2). The weight of clinical characteristics at patient-level in the variability of stent choice, included as fixed effects, did not contribute to reduce the variance at hospital- and country level (MOR=2.52 and 2.14, respectively) (Table 2, Model 3). The presence of a catheterization laboratory and the teaching status of the hospital did not explain the inter-hospital variation (Table 2, Model 4), which remained unchanged. The adjustment for the GDP *per capita* (in PPS) accounted for a substantial part of unexplained variance at the country level (approximately 30% of total variance was

attributed to GDP and 11% to patients' characteristics) (Table 2). In the final model, over 85.6% of the variance at hospital level remained unexplained, with a MOR for the difference among hospitals of 2.50 and an agreement in type of stent implanted among patients from the same hospital, as measured by the ICC, of 21%. The final model had a c-index of 0.77 denoting a satisfactory performance in predicting the stent type implanted in the study sample.

Table 3 depicts the fixed effects estimates for the variables included in Model 5, the fully adjusted multi-level analysis. Drug-eluting stents were less often used in octogenarians (OR=0.365), in patients with previous history of anticoagulation and/or atrial fibrillation (OR=0.600), and anaemia (OR=0.761). A previous history of diabetes *mellitus* (OR=1.557), previous history of PCI (1.824) and non-ST-elevation acute coronary syndrome patients (OR=2.043) were associated with a higher likelihood of the DES use. Gross domestic product was significantly and inversely associated with the use of DES; specifically, the odds of use of DES decreased 5% per 1 PPS (Table 3).

Discussion

This study evaluated the differences in the stent use in the routine care in 54 hospitals from six European countries (Finland, France, Germany, Greece, Portugal and Spain) and quantified the variation in the stent choice at three levels: patient, hospital and country.

The differences in the stent implantation across the countries enrolled were large and significant, in accordance with previous studies[14]. We hypothesized that these differences could be explained in part by patients', hospitals' and countries' characteristics. The inter-hospital variance was large in all multilevel models even after the adjustment for patient- and country- variables. However, the inter-hospital variance was greatly reduced when the country-level was introduced in the model, suggesting that part of the variance encountered reflected differences among countries, not among individual hospitals within the same country. Despite the substantial heterogeneity of patients implanted with stent in the several countries and associations between patient characteristics and the stent type implanted, only 11% and 14% of the variance among countries and hospital in the stent choice was explained by characteristics of patients, respectively. The introduction of hospital characteristics such as the presence of catheterization laboratory and the teaching status of the hospital did not affect the inter-hospital variance. This result suggests good practices because it is not supposed to patients are treated differently depending on the characteristics of the hospital. Patients should be sent to hospitals that are technically capable of providing what they need and treatment should not be conditioned by the treatments locally available.

The stent choice is considered a complex and multifactorial process that may be influenced by multiple factors at several levels, and some of them were not investigated in this study. Recently, the impact of sale representative presence at the cardiac catheterization laboratory was evaluated and associated with a higher utilization of stents from their respective companies, particularly the DES use

contributing to prove the influence of representatives on stent usage[15]. The production of legislation to regulate the relationship among the hospital, physicians and medical industry could contribute to standardize the stent availability and in this way to reduce the significant differences observed in the stent use. Conflicts of interest among physicians and medical industry are known and this factor could also influence the choice of stent type to be implanted[15]. Another important factor that could influence the unexplained variance encountered at the hospital-level is the presence of financial arrangements among the different hospitals and the stent companies resulting in recommendations by the institution to use preferentially a stent type or even the stent availability in the catheterization laboratory and finally differences on healthcare systems at country-level could play a role[6-8, 15].

The variance among countries and within the different countries was similar in all models, except for the final model when the GDP per capita was added into the multilevel model and variance intra- or inter-country was substantially inferior to variance associated to hospital-level. This country factor decreased substantially the variance intra-country and was responsible by 30% of total variance intra-country. The unexplained variance at country-level (59.2%) was significantly inferior relatively to unexplained variance at hospital-level (85.6%) showing homogeneity among hospitals from the same country in the choice of stent type. It would be expected that countries with higher financial resources available resulted in a higher frequency of DES implantation, however our study and others did not show this trend[14]. The differences in hospital payment systems between countries may explain some of inter-country variance encountered. For example, France, Germany and Spain differentiate between patients treated with DES and BMS, either by classifying cases into specific DES in Spain or by providing additional payments for DES use in France and Germany[16]. However, patients from Finland, France and Germany that have a higher GDP per capita were more implanted with BMS than Greek, Portuguese and Spanish patients (lower GDP per capita).

There are some limitations that should be noted. Given the retrospective nature of this study, the type stent in several countries could be influenced by unmeasured patient-, hospital- level characteristics. Another limitation could be the inability to include at operator-level in order to study their impact in the choice of stent type implanted. Patients admitted in a hospital without catheterization laboratory performed PCI in other hospital being attributed to the index hospital. Finally, the participation of hospitals may not be representative of all hospitals in a respective country.

Conclusion

In conclusion, our study shows differences in the stent type utilization in these European hospitals and contributes to a better knowledge of clinical practices in the Europe. This study sustains the need of intervene locally (hospital-level) and globally (debates between countries) through clear recommendations on stent choice with the aim to reduce the differences observed in the stent use among countries and turn practices more effective clinically and economically.

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Table 1. Baseline characteristics at patient-, hospital- and country-level.

	EURHOBOP	Finland	France	Germany	Greece	Portugal	Spain	p-value
				n (%)				
Level 1: Patient								
Age, years								
<45	435 (7.3)	40 (5.3)	120 (8.1)	59 (5.2)	46 (9.0)	102 (8.5)	68 (7.8)	< 0.001
45-79	4910 (82.4)	619 (81.6)	1229 (82.4)	926 (81.6)	434 (85.3)	987 (82.7)	715 (82.2)	
≥80	613 (10.3)	100 (13.2)	142 (9.5)	150 (13.2)	29 (5.7)	105 (8.8)	87 (10.0)	
Sex								
Male	4498 (75.5)	556 (73.3)	1155 (77.5)	807 (71.1)	419 (82.3)	887 (74.3)	674 (77.5)	< 0.001
Female	1460 (24.5)	203 (26.8)	336 (22.5)	328 (28.9)	90 (17.7)	307 (25.7)	196 (22.5)	
Previous medical history								
Smoking	2160 (36.3)	213 (28.1)	523 (35.1)	342 (30.1)	317 (62.3)	398 (33.3)	367 (42.2)	< 0.001
Diabetes *mellitus*	1460 (24.5)	141 (18.6)	311 (20.9)	306 (27.0)	138 (27.1)	317 (26.6)	247 (28.4)	< 0.001
Myocardial infarction	912 (15.3)	117 (15.4)	212 (14.2)	194 (17.1)	50 (9.8)	191 (16.0)	148 (17.0)	< 0.001
Percutaneous coronary intervention	1082 (18.2)	105 (13.8)	378 (25.4)	304 (26.8)	55 (10.8)	124 (10.4)	116 (13.3)	< 0.001
Coronary artery bypass graft	326 (5.5)	54 (7.1)	50 (3.4)	117 (10.3)	18 (3.5)	44 (3.7)	43 (4.9)	< 0.001
Anticoagulation and/or atrial fibrillation	514 (8.6)	93 (12.3)	95 (6.4)	186 (16.4)	14 (2.8)	54 (4.5)	72 (8.3)	< 0.001
Anaemia	1263 (21.2)	178 (23.5)	217 (14.6)	383 (33.7)	83 (16.1)	227 (19.0)	175 (20.1)	< 0.001
Renal failure	402 (6.8)	27 (3.6)	72 (4.8)	167 (14.7)	5 (1.0)	69 (5.8)	62 (7.1)	< 0.001
Characteristics of the current acute coronary syndrome								
ST-Elevation myocardial infarction	2691 (46.7)	368 (50.7)	516 (35.0)	400 (36.6)	317 (63.3)	613 (52.7)	477 (58.9)	< 0.001
Non-ST-Elevation acute coronary syndrome	3078 (53.3)	358 (49.3)	960 (65.0)	693 (63.4)	184 (36.7)	550 (47.3)	333 (41.1)	
Level 2: Hospital								
Catheterization Laboratory	5236 (87.9)	759 (100)	1231 (82.6)	1135 (100)	509 (100)	756 (63.3)	846 (97.2)	< 0.001
University teaching	3182 (53.4)	485 (63.9)	486 (32.6)	684 (60.3)	261 (51.3)	539 (45.1)	727 (83.6)	< 0.001
Level 3: Country								
GDP per capita in PPS		114	108	116	94	80	103	< 0.001

GDP, gross domestic product; PPS, Purchasing Power Standards.

Table 2. Results from the random effects component of multilevel logistic regression models, measuring variation among hospitals and countries in the choice of the type of stent implanted during PCI in acute coronary syndrome patients.

	Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]	Model 5[e]
Measures of variation					
Country level					
Variance (SE)		0.720 (0.266)	0.799 (0.291)	0.805 (0.289)	0.426 (0.256)
Explained variation (%)		Reference	-11.0	-11.8	40.8
ICC (%)		11.1	13.1	13.3	4.1
MOR		1.99	2.14	2.15	1.50
Hospital level					
Variance (SE)	1.121 (0.128)	0.914 (0.112)	0.969 (0.118)	0.960 (0.117)	0.960 (0.119)
Explained variation (%)	Reference	18.5	13.6	14.3	14.4
ICC (%)	27.6	18.0	19.3	19.0	21.0
MOR	2.91	2.39	2.52	2.50	2.50
Goodness of fit					
c-index	0.72	0.72	0.77	0.77	0.77

ICC, intra-class correlation; MOR, median odds ratio; SE, standard error.

[a] Model 1 is null model for hospital, baseline model without any exposure variable.

[b] Model 2 is null model for country and hospital level, baseline model without any exposure variable.

[c] Model 3 is additionally adjusted for age, sex, diabetes, percutaneous coronary intervention, anticoagulation and/or atrial fibrillation, anaemia and type of acute coronary syndrome.

[d] Model 4 is the model 3 additionally adjusted for presence of catheterization laboratory and university teaching.

[e] Model 5 is the model 4 additionally adjusted for PIB per capita in PPS of the country.

Table 3. Fixed effects component of the fully adjusted model 5.

		Model 5[a]
Measures of association (OR, 95 %)		
Level 1: Patient		
Age, years		
	<45	0.986 (0.788 - 1.234)
	45-79	1
	≥80	0.365 (0.295 - 0.451)
Female sex		0.932 (0.810 - 1.071)
Previous medical history		
Diabetes *mellitus*		1.557 (1.352 - 1.793)
Percutaneous coronary intervention		1.824 (1.553 - 2.143)
Anticoagulation and/or atrial fibrillation		0.600 (0.478 - 0.752)
Anaemia		0.761 (0.650 - 0.892)
Characteristics of the current acute coronary syndrome		
	ST-Elevation myocardial infarction patients	1
	Non-ST-Elevation acute coronary syndrome	2.043 (1.797 - 2.323)
Level 2: Hospital		
Catheterization Laboratory		1.828 (0.699 - 4.779)
University teaching		1.064 (0.592 - 1.914)
Level 3: Country		
GDP per capita in PPS		0.950 (0.917 - 0.985)

GDP, Gross Domestic Product; OR, Odds Ratio; PPS, Purchasing Power Standards.

[a] Model 5 is adjusted for age, sex, diabetes, percutaneous coronary intervention, anticoagulation, type of acute coronary syndrome, catheterization laboratory at the hospital, university teaching hospital and GDP per capita in PPS.

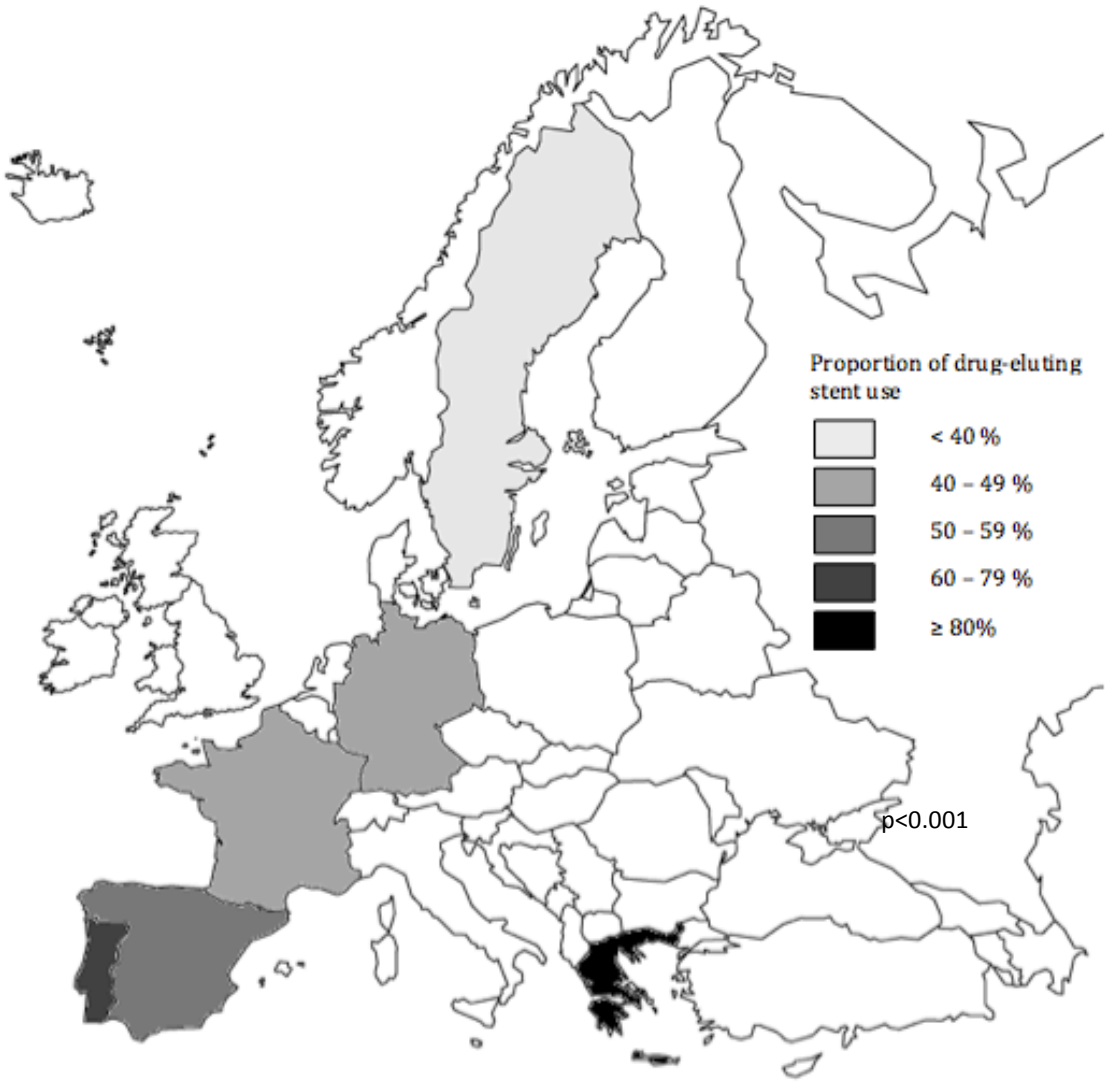

Figure 1. Percentage of type of stent implanted in each country.

5 Conclusions

In the retrospective analysis of 3009 consecutive patients with acute coronary syndrome in 10 Portuguese hospitals in 2009, 1194 patients had a stent implanted. A total of 425 patients (36%) received a BMS and 769 patients (64%) received a DES.

The choice of stent type was influenced by two main factors: 1) the bleeding risk during and after the intervention in the patient, 2) the characteristics of vessel intervened. This choice also varied according to the hospitals' characteristics, regardless of patients' characteristics.

In the analysis of 5958 consecutive patients with acute coronary syndrome who had a stent implanted in 54 hospitals in Finland, France, Germany, Greece, Portugal and Spain, a large variation in the type of stent implanted was observed among hospitals. Patient characteristics had a low impact on the variance among hospitals and inter-country variance was largely explained by the GDP per capita.

The stent selection process showed to be complex and multifactorial. The current European guidelines do not take into consideration the complexity of this process in the "real world". Taken together, the two studies sustain the need for a standardization of procedures in patients undergoing PCI in the setting of acute coronary syndromes in Europe.

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