Chronic Postoperative Pain after Cardiac Surgery

Dor Crónica Pós-operatória após Cirurgia Cardíaca

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July 2017

Doctoral Program in Clinical and Health Services Research

Dissertação de candidatura ao grau de Doutor apresentada à Faculdade de Medicina da Universidade do Porto, no âmbito do Programa Doutoral em Investigação Clínica e em Serviços de Saúde.

This PhD thesis has been submitted in fulfilment of the requirements for the PhD degree in Clinical and Health Services Research at the Faculty of Medicine of the University of Porto.

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Dor Crónica Pós-operatória após Cirurgia Cardíaca

Chronic Postoperative Pain after Cardiac Surgery

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Artigo 48º, parágrafo 3º: A Faculdade não responde pelas doutrinas expendidas na dissertação (Regulamento da Faculdade de Medicina do Porto. Lei nº 19337, de 29 de Janeiro de 1931)

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Maria Isabel Amorim de Azevedo

Rui Manuel Almeida Mota Cardoso

Serafim Correia Pinto Guimarães

Valdemar Miguel Botelho dos Santos Cardoso

Walter Friedrich Alfred Osswald

To

my family

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I. Acknowledgments

A PhD thesis is never a work of a sole person, so I would like to express my most deep gratitude to all those who have contributed to this thesis, in particular, to my supervisors. I must recognize that it was a privilege and an honour to work with them.

I would like to thank to my supervisor, Professor Doutor José Castro Lopes, for being my mentor and my professor, and above all, for the supervision and guidance during this thesis. Additionally, I would like to express my most deep admiration for his dedication and important contribute in the study of pain and its promotion.

I would like to thank to my co-supervisor, Professor Doutor Fernando Abelha, for introducing me to the area of clinical research and for all his motivation and guidance. Furthermore, I would like to express my esteem for his contribution in the research of postoperative outcomes and all the encouragement provided to young anaesthesiologists to perform clinical research.

I would like to thank to my co-supervisor, Professor Doutor Luís Azevedo, for teaching me the essential tools to conduct relevant clinical research, particularly in the field of systematic reviews. Likewise, I thank his support and guidance during this thesis.

I thank to all members of the Department of Health Information and Decision Sciences (CIDES) and members of the Centre for Research in Health Technologies and Information Systems (CINTESIS), at the Faculty of Medicine of the University of Porto (FMUP). Particularly to Professor Doutor Altamiro Pereira I would like to thank the opportunity that he provided by allowing me to accomplish this PhD. Moreover, I thank

Professor Doutor Mário Dinis Ribeiro, Professor Doutor Armando Teixeira Pinto and Professor Doutor João Fonseca, for their essential teachings.

I would like to express my gratitude to Professor Doutor Jorge Tavares, for the continuous motivation to advance my academic career. Beyond that, I would like to express my esteem for his contribution to the teaching of anaesthesiology in Portugal.

I thank to all my teachers and tutors of the Faculty of Medicine of the University of Porto for all they taught me.

I also thank to the research team that collaborated with me throughout this project, namely, Dra. Filomena Farinha and Dr. Pedro Reis. Moreover, I thank to all members of the Anaesthesiology Department and Cardiothoracic Surgery Department of Centro Hospitalar de São João, who helped me during these years, especially their directors.

I am also grateful to Chronic Pain Unit of Centro Hospitalar de São João, particularly to its coordinator, Dra. Armanda Gomes, for welcoming me and introducing me to the comforting mission of chronic pain treatment.

I would like to thank to all patients, for their unengaged and anonymous participation in this research; ultimately, they are the reason of all our work.

I would like to thank my family and close friends for the encouragement and constant support. To my parents and grandmother, thank you very much for believing in me and for all the sacrifices. Finally, I would like to thank my best friend and wife, Ditza, for the love, constant encouragement and emotional support. Without you this thesis would not have been possible.

II. List of Publications

This thesis was based in the following publications:

- Guimaraes-Pereira L, Farinha F, Azevedo L, Abelha F, Castro-Lopes J. Persistent Postoperative Pain after Cardiac Surgery: Incidence, Characterization, Associated Factors and its impact in Quality of Life. European journal of pain (London, England) 2016;20(9):1433-1442.

  The European Journal of Pain (EJP) is the official journal of the European Pain Federation EFIC®. It is a multi-disciplinary, international journal that aims to be a global forum on all aspects of pain research and pain management. The journal publishes clinical and basic science research papers relevant to all aspects of pain and its management, including specialties such as anaesthesiology, dentistry, neurology and neurosurgery, orthopaedics, palliative care, pharmacology, physiology, psychiatry, psychology and rehabilitation; socio-economic aspects of pain are also covered.
  The 2016 Impact Factor of the EJP is 3.019 and has a five-year mark of 3.267.

- Guimaraes-Pereira L, Reis P, Abelha F, Azevedo LF, Castro-Lopes JM. Persistent postoperative pain after cardiac surgery: a systematic review with meta-analysis regarding incidence and pain intensity. Pain 2017;158(10):1869-1885.

  PAIN is an official journal of International Association for the Study of Pain (IASP). Published monthly, PAIN presents original research on the nature, mechanisms, and treatment of pain. This peer-reviewed journal provides a forum for the dissemination of multidisciplinary research in the basic and clinical sciences. It is cited in Current Contents and Index Medicus.
  PAIN continues to be the premier journal in the field of anaesthesiology, according to the “Journal Citation Reports,” attaining an Impact Factor in 2016 of 5.445 and a five-year mark of 6.458, the top ranking during the recent five-year period. The Impact Factor measures, among other things, how often journal articles are cited during a specific period. PAIN had 35,333 total citations in 2016, far outdistancing its nearest competitor and tops in the anaesthesiology field. PAIN also was highly ranked in other journal categories. In the field of clinical neurology, PAIN ranked in the top 9 percent of 194 journals, and in the neurosciences category, it finished in the top 14 percent of 258 journals.

III. Acronyms

BMI: Body Mass Index

BPI-SF: Brief Pain Inventory – Short Form

CABG: Coronary Artery Bypass Graft

CC: Cirurgia Cardíaca

CI: Confidence Interval

CPP: Chronic Postoperative Pain

CPPCS: Chronic Postoperative Pain after Cardiac Surgery

CRC: Cirurgia de Revascularização Coronária

CS: Cardiac Surgery

DCPO: Dor Crónica Pós-Operatória

DCPOCC: Dor Crónica Pós-Operatória após Cirurgia Cardíaca

DN: Dor Neuropática

DN4: Douleur Neuropathique en 4 questions

EFIC: European Federation of IASP Chapters

EPM: Endogenous Pain Modulation

HRQL: Health-Related Quality of Life

HVR: Heart Valve Replacement

IASP: International Association for the Study of Pain

ICD: International Classification of Diseases

ITA: Internal Thoracic Artery

MPQ-SF: McGill Pain Questionnaire – Short Form

NP: Neuropathic Pain

QST: Quantitative Sensory Test

QVRS: Qualidade de Vida Relacionada com a Saúde

RCT: Randomized Controlled Trial

WHO: World Health Organization

IV. Summary

Background

Postoperative pain is perceived by patients as one of the more intolerable aspects of surgical procedures. Today, surgeons and anaesthesiologists recognize the importance of postoperative pain; and pain control is considered a mandatory part of the comprehensive postoperative experience. The recognition of this importance, led the International Association for the Study of Pain (IASP) to declare the 2017 as the “Global Year against Pain after Surgery”. Currently, there is ample evidence that surgery not only leads to acute pain but also causes chronic pain in a significant number of patients. The IASP defines Chronic Postoperative Pain (CPP) as pain that develops after surgical intervention and lasts at least three months, with other causes of pain excluded. Data on CPP incidence vary significantly, depending on the definitions used and types of surgeries performed. Lately, there was an increasing recognition that CPP is difficult to treat and prevention is desirable, namely with the identification of its predictive factors. CPP can have devastating consequences, not only in terms of suffering and reduced health-related quality of life (HRQL) for the individual patient but also with regard to the subsequent costs to the health care and social support systems. Therefore, due to its relevance, CPP has become a health priority and a hot topic in pain investigation.

Cardiac surgery (CS), such as coronary artery bypass grafting (CABG) and heart valve replacement, ranks among the most frequently performed interventions worldwide. Several studies describe CPP as an important complication of CS. However, the precise magnitude of the incidence of CPP after CS (CPPCS) was still under debate, limiting the perception of the true dimension of this problem. Although some studies have focused on CPPCS, several gaps were present in the literature. Therefore, firm evidence about the epidemiology of CPPCS and its clinical properties were still lacking.

Aims

The research work that constitutes this PhD thesis had two general aims: to study the epidemiology of CPPCS, namely, its incidence and the existence of predictive factors; and to study CPPCS' clinical properties, namely, pain intensity, pain interference and patients' HRQL, temporal evaluation, location and the presence of Neuropathic Pain (NP). With the view to achieve these general aims, we have proposed to conduct two studies: an observational prospective study in patients submitted to CS, in one of the reference centres of CS in Portugal, to evaluate the incidence of CPP and its clinical properties (Paper A); and a systematic review of the literature about CPPCS' incidence, intensity, location and the presence of NP (Paper B).

Methods

Firstly, we have conceived, designed, and completed an observational prospective study in patients undergoing CS. We have calculated the CPPCS' incidence in one of the reference centres of CS in Portugal, and investigated its predictive factors, using a multivariate logistic regression analysis. Furthermore, we have characterized CPPCS in terms of pain intensity, pain interference and patient's HRQL, pain temporal evaluation, pain descriptors and presence of NP, applying validated instruments. Secondly, we have designed and materialized a systematic review of the literature about CPPCS' incidence, intensity, location and the presence of NP. The review comprised three phases: a methodological assessment of 6 different databases to identify potential papers and screening according to inclusion criteria by two independent reviewers; data extraction; and study's quality assessment. Additionally, we have performed a set of meta-analyses to provide estimates regarding incidence and intensity of CPPCS.

Results

The results of this thesis are based in the findings of two published studies: an observational prospective study (Paper A), which included 310 patients who undergone CS (93% patients completed the study); and a systematic review with meta-analysis (Paper B), which identified 442 potentially relevant studies through database searching and included 23 studies, involving 11,057 patients.

CPP is a frequent outcome after CS, according to both studies performed. CPPCS' incidence in one of the reference centres of CS in Portugal was 43% (95% CI: 37–49%) at 3 months and 40% (95% CI: 34–46%) at 6 months (Paper A). The pooled estimated incidence of CPP obtained in our meta-analysis was 37% (95%CI: 32–42%) in the first 6 months after CS and 17% (95%CI: 8–25%) more than two years after CS (Paper B). More recent studies report a higher incidence of CPP during the first 6 months after CS, compared to older studies (Paper B). The proportion of patients with CPPCS under any treatment is lacking in the literature (Paper B), but seems to be very low, as shown in our observational study, where only 16% of the patients with CPP were being treated (Paper A).

Concerning predictive factors, we have identified several independent predictors of CPPCS (Paper A): younger age, female gender, higher body mass index, history of osteoarthritis, history of previous surgery (excluding sternotomy), catastrophizing, CABG and more intense acute postoperative pain. Additionally, we have identified two strong independent predictors of CPPCS (Paper A): age lower than 69 years (Odd Ratio: 10.45) and moderate to severe classification in worst pain item of Brief Pain Inventory - Short Form (BPI-SF), at the third postoperative day (Odd Ratio: 15.07). Moreover, preoperative angina pectoris was a predictor for NP in patients with CPP (Paper A).

Pain intensity was addressed by both studies. In our observational study (Paper A), 57.3% of patients with CPPCS rated their average pain as mild and 42.7% as

moderate. Regarding BPI-SF worst pain item, 17.7% rated it as mild, 54.9% as moderate and 27.4% as severe. In the performed systematic review (Paper B), large heterogeneity was found concerning recording and reporting CPP intensity's assessment. The results obtained in our meta-analysis (Paper B), revealed that a large proportion of patients with CPPCS present moderate to severe pain (regarding their average pain: 40 to 50%; regarding their worst pain: 49 to 53%; variation according the time frame), that did not reduce over time.

Patients' HRQL and pain interference was investigated in the observational study (Paper A). Globally, patients who underwent CS, presented an improvement in their HRQL 3 months after CS, however, patients with CPPCS presented lower HRQL compared with those without CPPCS. CPPCS caused substantial interference in patients' daily life, and the most affected activities were: "sleep", "general activity" and "normal work".

According to our both studies, chest is the main location of CPPCS, followed by the leg (Paper A and B). Additionally, in most patients with CPPCS, pain was not permanently present and it had paroxysms (Paper A).

The presence of NP in patients with CPPCS was addressed by both studies. NP was detected in 50% of these patients, using a validated questionnaire (Paper A). Patients with CPPCS who reported moderate to severe pain presented NP more often (Paper A), and CPPCS located in the leg was more often identified as NP than CPPCS located in the chest (Paper A). According to our systematic review, NP seems to be present in the majority of patients with CPPCS; however, only 5 of the included studies addressed this issue, and there was a lack of uniformity in the methods used to measure NP (Paper B).

Conclusion

This thesis provides the most complete assessment and discussion of the current best evidence regarding the epidemiology and clinical properties in the context of CPPCS. Therefore, the aims of this thesis were accomplished with success.

Our research indicates that more than one third of the patients develop CPP in the first 6 months after CS, and approximately half of those patients present moderate to severe pain. Additionally, CPPCS causes substantial interference in patient's life and lower HRQL. Given the foregoing and associating the fact that CS is one of the most frequently performed interventions worldwide, CPPCS should be considered a relevant health problem and deserves special attention from health care professionals and health authorities. Our research identified a set of predictive factors that should be taken into account, in order to prevent its establishment, and highlighted the scarcity of treatment in patients with CPPCS.

There is room for improvement not only in terms of prevention and treatment, but also regarding the assessment of CPPCS in clinical practice and in future studies. CPPCS should not be neglected and this thesis is expected to provide an important scientific impetus that will foster and support improvements in prevention, diagnosis, follow-up and treatment.

V. Resumo

Introdução

A dor pós-operatória é compreendida pelos pacientes como um dos aspetos mais intoleráveis dos procedimentos cirúrgicos. Atualmente, os cirurgiões e os anestesiologistas reconhecem a importância da dor pós-operatória; e o controlo da dor é considerado um componente obrigatório na abordagem pós-operatória. O reconhecimento desta importância levou *a International Association for the Study of Pain* (*IASP*) a declarar o ano de 2017 como *"*O ano da luta contra a dor pós-operatória*".* Atualmente, existe ampla evidência a demonstrar que a cirurgia desencadeia não apenas dor aguda, mas também dor crónica num significativo número de doentes. A *IASP* define dor crónica pós-operatória (DCPO) como uma dor que se desenvolve após uma cirurgia e com uma duração de pelo menos 3 meses, após exclusão de outras causas de dor. Os dados sobre a incidência de DCPO variam bastante, dependendo da definição utilizada e do tipo de cirurgia realizado. Ao longo dos últimos anos, houve um reconhecimento crescente sobre a dificuldade de tratamento da DCPO e a necessidade de a prevenir, nomeadamente através da identificação de fatores preditivos. A DCPO pode ter consequências devastadoras, não só para o individuo, em termos de sofrimento e redução da qualidade de vida relacionada com a saúde (QVRS), mas também para a sociedade, devido aos custos associados aos sistemas de saúde e de apoio social. Sendo assim, devido à sua relevância, a DCPO tornou-se uma prioridade na saúde e um tópico atual na investigação em dor.

A cirurgia cardíaca (CC), nomeadamente a cirurgia de revascularização coronária (CRC) e de substituição valvular, é considerada uma das cirurgias mais frequentemente realizadas em todo o mundo. Vários estudos descrevem a DCPO como uma importante complicação após cirurgia cardíaca. No entanto, o valor preciso

da incidência de DCPO após CC (DCPOCC) ainda estava por determinar, limitando a perceção da dimensão deste problema. Apesar de existirem estudos sobre a DCPOCC, várias lacunas estavam presentes na literatura. Sendo assim, havia necessidade de uma evidência mais forte sobre a epidemiologia da DCPOCC e suas propriedades clínicas.

Objetivos

O projeto de investigação que constitui esta tese de doutoramento teve dois objetivos gerais: estudar a epidemiologia da DCPOCC, nomeadamente, a sua incidência e a existência de fatores preditivos; e estudar as propriedades clínicas da DCPOCC, nomeadamente, intensidade da dor, interferência causada pela dor e QVRS nos pacientes, avaliação temporal, localização, e presença de dor neuropática (DN). De modo a alcançar estes objetivos gerais, propusemos a elaboração de dois estudos: um estudo observacional prospetivo em pacientes submetidos a CC, num dos centros de referência de CC em Portugal, para avaliar a incidência e as propriedades clínicas da DCPOCC (Artigo A); e uma revisão sistemática sobre a incidência, intensidade de dor, localização, e presença de DN na DCPOCC (Artigo B).

Métodos

Em primeiro lugar, projetámos e completámos um estudo observacional prospetivo em pacientes submetidos a CC. Neste estudo, calculámos a incidência de DCPOCC num dos centros de referência de CC em Portugal, e investigámos os seus fatores preditivos, usando uma análise de regressão logística multivariada. Para além disso, caracterizámos a DCPOCC em termos de intensidade, interferência e QVRS nos pacientes, avaliação temporal, descritores de dor e presença de DN, aplicando instrumentos validados. Em segundo lugar, projetámos e concretizámos uma revisão sistemática da literatura sobre a incidência, intensidade, localização e presença de DN

na DCPOCC. A revisão compreendeu três fases: uma pesquisa metódica de 6 bases de dados, para identificar potenciais artigos com relevância, e seleção destes de acordo com os critérios de inclusão, por dois revisores independentes; extração de dados; e avaliação da qualidade dos estudos. Além disso, realizámos um conjunto de meta-análises para fornecer estimativas sobre incidência e intensidade da DCPOCC.

Resultados

Os resultados desta tese baseiam-se nos resultados de 2 estudos publicados: um estudo observacional prospetivo (Artigo A), que incluiu 310 pacientes submetidos a CC (93% completaram o estudo); e uma revisão sistemática com meta-análise (Artigo B), que identificou 442 estudos potencialmente relevantes na pesquisa da base de dados, e incluiu 23 estudos referentes a 11.057 pacientes.

Com base nos estudos realizados, a DCPO é frequente após CC. A incidência de DCPOCC, num dos centros de referência de CC em Portugal, foi de 43% (95% CI: 37–49%) aos 3 meses e 40% (95% CI: 34–46%) aos 6 meses. (Artigo A). A incidência estimada de DCPO obtida na nossa meta-análise foi de 37% (95%CI: 32–42%), nos primeiros 6 meses após CC, e 17% (95%CI: 8–25%), após mais de dois anos da realização de CC (Artigo B). Estudos mais recentes apresentaram uma maior incidência de DCPO nos primeiros 6 meses após CC, em relação a estudos mais antigos (Artigo B). A literatura é escassa, em relação à proporção de pacientes com DCPOCC sob tratamento (Artigo B), mas esta parece ser muito baixa, como demonstrado no nosso estudo observacional, onde apenas 16% dos pacientes com DCPOCC estavam sob tratamento (Artigo A).

Relativamente aos fatores preditivos, identificámos vários preditores independentes de DCPOCC (Artigo A): idade mais jovem, sexo feminino, índice de massa corporal superior, história de osteoartrite, história de cirurgia prévia (excluindo esternotomia), catastrofização, CRC e dor aguda pós-operatória mais intensa. Além disso,

identificámos dois fortes preditores independentes de DCPOCC (Artigo A): idade inferior a 69 anos (*Odd ratio*: 10,45) e classificação moderada a severa no item “pior dor” do questionário *Brief Pain Inventory - Short Form* (BPI-SF), no terceiro dia pós-operatório (*Odd ratio*: 15.07). Além disso, a presença de angina de peito antes da CC foi um preditor de presença de DN em pacientes com DCPO (Artigo A).

A intensidade da DCPOCC foi abordada em ambos os estudos. No nosso estudo observacional (Artigo A), 57,3% dos pacientes com DCPOCC classificaram a sua “dor em média” como ligeira e 42,7% como moderada. Em relação ao item “pior dor” do BPI-SF, 17,7% classificou-a como ligeira, 54,9% como moderada e 27,4% como severa. Na revisão sistemática realizada (Artigo B), registou-se grande heterogeneidade em relação à recolha e registo da avaliação da intensidade da DCPOCC. Os resultados obtidos na nossa meta-análise (Artigo B) revelaram que uma grande proporção de pacientes com DCPOCC apresenta dor moderada a grave (relativamente à “dor em média”: 40 a 50%; relativamente à sua “pior dor”: 49 a 53%; variação de acordo com o período de tempo analisado), que não se reduziu ao longo do tempo.

A QVRS dos pacientes e a interferência causada pela dor foram investigadas no estudo observacional (Artigo A). Globalmente, os pacientes submetidos a CC apresentaram melhoria na sua QVRS, 3 meses após CC; no entanto, os pacientes com DCPOCC apresentaram pior QVRS, em relação aos pacientes sem DCPOCC. A DCPOCC provocou interferência considerável na vida diária dos pacientes, e as atividades mais afetadas foram: o "sono", a "atividade geral" e o "trabalho normal".

De acordo com os nossos dois estudos, o peito é o principal local da DCPOCC, seguido pela perna (Artigo A e B). Além disso, na maioria dos pacientes com DCPOCC, a dor não esteve permanentemente presente e ocorreram episódios de agudização da dor (Artigo A).

A presença de DN nos pacientes com DCPOCC foi abordada em ambos os estudos. Detetou-se DN em 50% destes pacientes, usando um questionário validado (Artigo A).

Os pacientes com DCPOCC moderada a severa apresentaram DN com maior frequência (Artigo A), e a DCPOCC localizada na perna foi mais frequentemente identificada como DN, comparativamente à DCPOCC localizada no peito (Artigo A). De acordo com a nossa revisão sistemática, a DN parece estar presente na maioria dos pacientes com DCPOCC; no entanto, apenas 5 dos estudos incluídos abordaram esta questão, e houve uma falta de uniformidade nos métodos utilizados para medir a DN (Artigo B).

Conclusão

Esta tese apresenta a mais completa avaliação e discussão da melhor evidência atual sobre a epidemiologia e as propriedades clínicas no âmbito da DCPOCC. Portanto, os objetivos desta tese foram alcançados com sucesso.

A nossa investigação indica que mais de um terço dos pacientes desenvolvem DCPO nos primeiros 6 meses após CC, e aproximadamente metade desses pacientes apresentam dor moderada a grave. Além disso, a DCPOCC provoca interferência considerável na vida do paciente e menor QVRS. Por tudo isto, e associando o facto de que a CC é uma das intervenções mais frequentemente realizadas em todo o mundo, a DCPOCC deve ser considerada um problema de saúde importante, que merece especial atenção dos profissionais e autoridades de saúde. A nossa investigação identificou um conjunto de fatores preditivos que devem ser considerados no âmbito da prevenção, e destacou a carência de tratamento nos pacientes com DCPOCC.

É possível introduzir melhorias, não só em termos de prevenção e tratamento, mas também em relação à avaliação da DCPOCC na prática clínica e em estudos futuros. A DCPOCC não deve ser negligenciada, e esta tese pretende ser um importante contributo científico na promoção de melhorias na sua prevenção, diagnóstico, seguimento e tratamento.

1. INTRODUCTION

1.1. Pain as a universal experience

Pain is a universal experience from birth until the end of life. Generally, it is mild and inconsequential, as is the case when we feel a tingling in the legs after keeping them in the same position too long or when we accidentally hit our fingers against the edge of the table. Nevertheless, all too often, pain is intolerable and requires treatment, or else it persists beyond the healing of the injury and becomes chronic, reducing activities and sometimes making life unbearable. Therefore, pain may have an essential role in survival and a negative impact in one's life, concurrently. The effects of pain should never be underestimated and its relief is essential to protect the integrity of the organism, which contradicts the popular saying "It hurts, but it won't kill you" [83].

According to the International Association for the Study of Pain (IASP), pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [61; 95]. More recently, there was a proposal to update this definition to "a distressing experience associated with actual or potential tissue damage with sensory, emotional, cognitive, and social components" [141]. However, this proposal has led to substantial criticism [2; 121; 139; 142].

1.2. Temporal aspect as a key variable

Pain will be considered physiological following an injury, but it will become pathological if it persists beyond a certain period of time [19]. Temporal aspect is a key variable in understanding and treating pain [94]. This characteristic could help us to distinguish acute pain from chronic pain, which is essential. However, this distinction should not be based solely on a temporal criterion [62; 92].

Acute pain is generally identified as pain that lasts for no more than 30 days [19; 62; 92]. It is essential to our survival and enables us to recognize that there is a problem [19]. Therefore, it acts as an alarm and is directly linked to pathological conditions, following its progression [19; 59]. Furthermore, it plays a protective role that allows us to live in an environment fraught with potential dangers. Acute pain usually signals impending or actual tissue damage and thus allows the individual to avoid further injury. It may also prevent harmful movement, for example, in the case of a fracture. Reduced mobility associated with acute pain may consequently aid healing [94]. Therefore, without a doubt, pain is necessary for our survival and we cannot live very long without this essential information. However, the organism benefits only briefly from this effect and its prolongation results in adverse outcomes. Pain also initiates complex neurohumoral responses that help initially to maintain homeostasis in the face of an acute disease or injury; if these changes are excessive or unduly prolonged, they may cause morbidity or mortality [94]. Psychological responses to acute pain may initially be helpful in coping with the physical insult; however, if excessively severe or prolonged, they may become deleterious [94].

Chronic pain, on the other hand, does not have a protective role and may persist even after the triggering event is resolved [19; 59; 92]. It has gradually emerged as a distinct phenomenon in comparison with acute pain [93]. Chronic pain does not seem to have any purpose or use for the individual, and moreover, it leads us to consider pain as pathological and to try to alleviate it, even when its organic components are unknown

[92; 94]. Chronic pain has been recognized as pain which persists past the normal time of healing [18]. In practice this may be less than one month, or more often, more than six months. With non-malignant pain, three months is the most convenient point of division between acute and chronic pain [62]. Those who treat cancer pain find that three months is sometimes too long to wait before regarding a pain as chronic. The definition related to the time of normal healing is not sufficient, nor is it honoured consistently. Pain that persists for a given length of time would be a simpler concept. This length of time should be determined by common medical experience, and reflects the time needed for inflammation to subside or for acute injuries, such as lacerations or incisions, to repair with the union of separated tissues [62]. A longer period is required if we wait for peripheral nerves to grow back after trauma. In these circumstances, chronic pain is recognized when the process of repair is apparently completed [62].

The current version of the International Classification of Diseases (ICD-10) of the World Health Organization (WHO) includes some diagnostic codes for chronic pain conditions, but these diagnoses do not reflect the actual epidemiology of chronic pain, nor are they categorized in a systematic manner [125]. Recently and responding to these shortcomings, the IASP contacted the WHO and established a Task Force for the classification of chronic pain. Thus, IASP Task Force has developed a new and pragmatic classification of chronic pain for the upcoming 11th revision of the ICD. The goal was to create a classification system that is applicable in primary care and in clinical settings for specialized pain management [125]. The new ICD category for “Chronic Pain” comprises the most common clinically relevant disorders and they were divided into 7 groups: chronic primary pain, chronic cancer pain, chronic posttraumatic and postsurgical pain, chronic neuropathic pain, chronic headache and orofacial pain, chronic visceral pain, and chronic musculoskeletal pain. Additionally, they defined chronic pain as persistent or recurrent pain lasting longer than 3 months [125]. This definition according to pain duration has the advantage that it is clear and easily

operationalized [125]. Optional specifiers for each diagnosis record evidence of psychosocial factors and the severity of the pain. Pain severity can be graded based on pain intensity, pain-related distress, and functional impairment [125].

1.3. Chronic pain as a disease in its own right

Chronic pain is a disease in its own right and a very relevant public health problem, as proposed by the European Federation of IASP Chapters (EFIC) [42]. Classically, a public health problem has to be viewed from a population perspective and consequently will have a measurable and relevant impact on the population [32]. This implies to be frequent and to have important consequences for the individuals and populations.

Recently, a review showed huge inconsistency in the definition of chronic pain in the epidemiological literature, making comparison of prevalence estimates across existing studies of questionable value [118]. The inconsistency in operational definitions may weaken the recognition of chronic pain as an important health issue. Researchers and clinicians should be aware of the probability that interview survey method of collecting data may give lower chronic pain reporting than questionnaire survey method and that this effect may be stronger in men than women [118].

Nevertheless, existing estimates indicate a prevalence of chronic pain in developed countries of 37% [126]; however the evidence shows high heterogeneity with systematic reviews finding prevalence between 2% and 64% [99; 112; 118; 135]. Chronic pain of moderate to severe intensity occurs in 19% of adult Europeans, seriously affecting the quality of their social and working lives [21]. It can lead to reduced mobility and a consequent loss of strength, compromise the immune system and interfere with a person's ability to eat, concentrate, sleep, or interact with others [22]. People who live with chronic pain are four times more likely to suffer from depression or anxiety [56; 108]. The physical and psychological effects of chronic pain influence the course of disease [84]. Pain can manifest its harmful effects in several ways. It is known that people who are in pain lose sleep and have reduced appetite. They are then deprived of energy input and restorative functions necessary for healing

or even supporting life [32; 92]. In addition, the direct effect of pain on quality of life can easily be observed: intense suffering reduces the desire to live and sometimes can lead to suicide [93]. Pain can accelerate the growth of tumours by inhibiting the immune system [13; 77; 80]. Thus, controlling pain is of vital importance to patients with cancer [124].

In 2004, it was recognized that failure to treat pain appropriately should be considered substandard medicine with adverse outcomes, being unethical, and susceptible to both legal and professional action [30]. Chronic pain should receive great attention as a global health priority because adequate pain treatment is a human right, and it is the duty of any health care system to provide it [52]. Failure to take reasonable steps to ensure that people who suffer pain have access to adequate pain treatment may result in the violation of the obligation to protect against cruel, inhuman and degrading treatment [84]. The Declaration of Montreal was an important step in addressing inadequate pain management worldwide [31]. Regarding its awareness as a public health problem, in 2013, the Portuguese Directorate-general of Health published a strategic plan for prevention and control of pain [109]. One of its guiding principles is the duty of pain control, and it states that all health professionals should adopt strategies for prevention and control of pain in their patients. Beyond that, it is mentioned that particular attention should be given to the prevention and management of pain caused by diagnostic or therapeutic acts [109].

1.4. Chronic Postoperative Pain

Postoperative pain is perceived by patients as one of the more intolerable aspects of surgical procedures. Acute postoperative pain is a complex physiological reaction to tissue injury, visceral distention, or disease. It is a manifestation of autonomic, psychological, and behavioural responses that result in patient-specific unpleasant, unwanted sensory and emotional experiences [92]. Studies show that effective control of acute postoperative pain decreases rates of morbidity and mortality [57; 83]. Today, surgeons and anaesthesiologists recognize the importance of postoperative pain; and pain control is considered a mandatory part of the comprehensive postoperative experience [92]. The recognition of this importance, led the IASP to declare the 2017 as the “Global Year against Pain after Surgery”. The main purposes according to IASP are: to disseminate information worldwide about pain after surgery; to educate pain researchers as well as health-care professionals who see the issues associated with such pain first-hand in their interactions with patients; to increase awareness of postoperative pain among public officials, members of the media, and the general public; and to encourage government leaders, health-care organizations, and others to support policies that result in improved management of pain after surgery [63].

In 1998, Crombie et al. identified injury and surgery as major risks for chronic pain [33]. They reported that around 40% of 5130 chronic pain patients in 10 pain clinics in the United Kingdom had developed their chronic pain problem after surgery or trauma [33]. This finding has led to a dramatic increase in interest in this subject, and consequently, Chronic Postoperative Pain (CPP) has transitioned from a silent epidemic to a more broadly recognized and widespread problem that urgently requires attention [73].

Currently, there is ample evidence that surgery not only leads to acute pain but also causes chronic pain in a significant number of patients [45; 69; 82; 100; 114]**.** The problem is not limited to major surgery; even common minor surgical procedures such

as hernia repair and skin excisions carry significant risk of chronic pain [106; 116]. Some consider it the most common and serious long-term problem after repair of an inguinal hernia [66]. These CPP syndromes are commonly observed all over the world, following all types of surgery, and they can have devastating consequences, not only in terms of suffering and reduced health-related quality of life (HRQL) for the individual patient but also with regard to the subsequent costs to the health care and social support systems [16; 73; 111].

It is crucially important to develop consistent definitions of terms such as CPP, and the IASP defines CPP as pain that develops after surgical intervention and lasts at least three months, with other causes of pain excluded [73]. Before making a diagnosis of CPP, it is critical that other common causes of pain from surgery be ruled out. The lack of use of a unanimous definition of CPP makes comparisons of different studies and incidence estimations difficult [24]. There is substantial variability in the postoperative time frame for CPP studies, generally from 2 to 6 months [73], though some have used even shorter time frames [116]. In general, the 3-month time frame allows for the patient, surgical care team, and postoperative health care providers to undertake a variety of clinical tests to rule out other pathological causes for the pain at the surgical site [73].

It is alarming that CPP has assumed an epidemic proportion and deserves greater attention as the number of procedures being performed annually increases in the world [24]. A cross-sectional survey performed in 13000 northern Norwegians reported that 25% of the individuals had undergone one or more surgical procedures during the three preceding years [69]. CPP was reported by 40.4% of these patients and moderate to severe CPP was reported by 18.3% [69]. In Portugal, a cross-sectional nationwide epidemiological study, aiming to describe the prevalence and impact of chronic pain, detected that 6% of patients with chronic pain attributed its aetiology to surgery [10]. Data on CPP incidence vary significantly (between 5 and 50%), depending on the definitions applied and types of surgeries performed [75]. Recently, a

multicentre, prospective, observational study, conducted in patients undergoing different kinds of surgery from 21 hospitals in 11 European countries, identified an incidence of moderate to severe CPP of 11.8% at 12 months after surgery [45].

CPP may be somatic, visceral or neuropathic [58]; which seems to be linked to its underlying mechanisms, namely, surgical injury to the nerves, central sensitization, ongoing inflammatory processes, injury to the somatic or visceral structures, or other causes [39; 58]. The likelihood of iatrogenic nerve injury and subsequent Neuropathic Pain (NP) varies among surgical procedures. The prevalence of NP or pain with a neuropathic component was reported to be higher in patients with CPP after thoracic (including sternotomy) and breast surgeries (approximately 67%) [58]. Thus, neuropathic or nociceptive elements of CPP should be assessed in a clinical setting, in order to understand the underlying mechanisms and provide important implications for the prevention and treatment of this type of chronic pain.

Additionally, CPP offers a unique opportunity to study factors that are related to the transition of acute to chronic pain [70]. CPP patients can be assessed before, during, and after the surgical injury [73]. Therefore, CPP is an area that might enable us to better understand the development of chronic pain in general, as it provides an ideal setting for the study of risk and protective factors in a very controlled environment [72]. Factors involved in the pathogenic mechanisms of CPP are multiple and can be grouped into preoperative, intraoperative, and postoperative factors [104]. Preoperative pain, female gender, younger age, preoperative anxiety and pain catastrophizing are well-stablished preoperative factors [75; 101]. The exact role of genetic mechanisms remains to be established. Additionally, the preoperative function of the nociceptive system may be important and where several studies have shown a variable predictive value of different preoperative nociceptive tests [1; 85; 102; 138]. Intraoperatively, type of surgery and its technique are the most important recognized risk factors in CPP, and it is likely that intraoperative nerve injury plays a role in many of the surgeries

associated with the development of CPP [75; 101]. Regarding the postoperative period, the intensity of acute postoperative pain is the most relevant well-known postoperative factor [75; 82; 86; 101].

There is increasing recognition that CPP is difficult to treat, given the substantial percentages (over 20% in many studies) of patients who are long-term attendees at pain clinics having treatment-refractory postoperative pain syndromes, which are associated with enormous costs to the health care systems of many countries [106]. Consequently, prevention is desirable and a potential strategy to address it is to identify factors that may predict an increased likelihood to develop CPP. If we could do this, we may be able to target specific interventions to the most vulnerable patients or use the information when considering the need for surgery, its extent, or both [101]. Recently, a prospective multicentre cohort study enrolling patients scheduled for inguinal hernia repair, hysterectomy and thoracotomy, concluded that clinical factors (type of surgery, age, physical and mental health, and preoperative pain) predict approximately 70% of CPP risk [98]. Additionally, preoperative use of opioids and severe postoperative pain were also associated with the CPP [45; 134].

To this regard, a prospective risk-factor analysis identified five key predictive factors: emotional overload/overstrain, preoperative pain at the operative site, other chronic preoperative pain, acute postoperative pain, and comorbid stress symptoms such as tremulousness, anxiety, or disturbed sleep [4]. However, like many clinical risk-predictive instruments, these above findings lack perfect specificity or sensitivity and so are best viewed as broad guides rather than precise formulas. To date, a search for genetic risk factors has produced negative results [98].

Therefore, due to its relevance, CPP has become a health priority and is scheduled to be included in the upcoming version of the International Classification of Diseases, ICD-11 [125]. Searches in electronic databases for key words about CPP reveal hundreds of publications and this condition has been described by several terms. Recently, there has been an appeal to design better clinical studies about CPP, which

should ideally take a prospective and procedure-specific approach [76]. In addition, future CPP studies should define in detail the location, characteristics, and consequences from CPP on physical and social function [35].

1.5. Motivation for the thesis "Chronic Postoperative Pain after Cardiac Surgery"

As previously stated, CPP is an important health problem and a current investigation topic in the field of pain. However, pain is by definition a subjectively felt experience, and, as such, poses a challenge to epidemiological science to measure objectively the occurrence of events in populations [32]. Good epidemiological research on chronic pain provides important information on occurrence and factors associated with its onset and persistence [132]. Therefore, it is essential to perform good epidemiological research on CPP, and more specifically, on CPP after a specific procedure.

Concurrently, throughout my brief medical career as anaesthesiologist I have followed the perioperative course of several patients through different surgical procedures. Moreover, I have witnessed that postoperative pain and its need for analgesic treatment vary tremendously between procedures, and also between patients. This experience led me to an increased concern for this topic. As I could expect, pain after surgery is a common and not an unexpected symptom. However, although many treatments options are available and established guidelines and evidence-based recommendations exist, postoperative pain is considered to remain predominantly undertreated [7; 14; 140]. The study of postoperative pain guided me to an increasing awareness about its potential for chronification. Gradually, I realized that there was ample evidence that surgery leads to chronic pain in a significant number of patients. Throughout my anaesthesiologist formation, I have contacted with chronic pain patients in our Chronic Pain Unit. There, I have witnessed the suffering and the complaints of patients with CPP. Many of these patients arrived at Chronic Pain Unit after several months of incomprehension, affliction, torment and hardship.

Therefore, I decided to study CPP more deeply and actively bring more knowledge to this field. As I deepened my study, I became aware of the appeal to design better clinical studies about CPP, which should ideally take a prospective and procedure-

specific approach [76], and specify the location, characteristics, and consequences of CPP on physical and social function [35]

Cardiac surgery (CS), such as coronary artery bypass grafting (CABG) and heart valve replacement (HVR), ranks among the most frequently performed interventions worldwide [107]. In the 23 European Union Member States, there were near 181,000 CABG operations in 2015 [44]; and in Portugal, approximately 6,000 CS are performed per year [110]. In 1989, Defalque and Bromley described for the first time a pain syndrome called poststernotomy neuralgia [36]. Since then, several studies were conducted and CPP has been described as an important complication of CS [27; 50; 91]. However, the precise magnitude of the incidence of CPP after CS (CPPCS) was still under debate, and this limited the perception of the true dimension of the problem.

Patients experiencing CPPCS report a significantly lower physical and mental health status compared with patients without it [23; 49; 120]. Although some studies have focused on CPPCS, several gaps were present in the literature. In a recent review, it was stated that risk factors for CPPCS were not well established [50]. Studies have found patient-related factors such as younger age, increased body mass index (BMI) and female gender to predict CPPCS, however the evidence related to the role of psychological and surgery-related factors was inconclusive [50]. Additionally, previous reviews of CPPCS have combined narrative review with expert opinion, with potential risk of bias [27; 50; 91].

Therefore, firm evidence about the incidence of CPPCS and its properties were still lacking. Consequently, I have proposed to study this topic in order to achieve a complete assessment and discussion of the current best evidence regarding CPPCS. This may allow appropriate resource allocation and research planning, and could better inform patient decisions about treatment.

To achieve this goal I had to equip myself with tools to perform relevant clinical research and the PhD program in Clinical and Health Services Research was essential

for this achievement. This PhD program is a unique program in Portugal and it was created with the intention to respond to the needs and demands increasingly felt and expressed by healthcare professionals, regarding high quality educational offer and research training opportunities in clinical research and in health services research. The PhD program in Clinical and Health Services Research allow me: to promote and develop the ability to conceive, design, adapt and perform relevant and original clinical research, in accordance with the requirements imposed by the higher standards of academic quality and integrity; to foment and evolve the competence to critically appraise, evaluate and synthesize new and complex ideas and research work; and to stimulate the skill to effectively communicate with peers, with the academic community and with the general public about the specialty research area.

2. AIMS

The research work that constitutes this PhD thesis had two general aims:

- To study the epidemiology of CPPCS, namely, its incidence and the existence of predictive factors;

- To study CPPCS' clinical properties, namely, pain intensity, pain interference and patients' HRQL, temporal evaluation, location and the presence of NP.

With the view to achieve these general aims, we have proposed to conduct two studies:

1. An observational prospective study in patients submitted to CS, in one of the reference centres of CS in Portugal, to evaluate the incidence of CPPCS and its clinical properties (Paper A).

2. A systematic review of the literature about CPPCS' incidence, intensity, location and the presence of NP (Paper B).

The specific aims of the observational prospective study conducted in patients submitted to CS (Paper A) were:

- to evaluate CPPCS' incidence
- to identify CPPCS' predictive factors

- to comprehensively identify CPPCS' clinical properties, namely, pain intensity, pain interference and patients' HRQL, pain temporal evaluation, pain descriptors and NP presence, using adequately validated instruments;

Additionally, the specific aims of the systematic review of the literature about CPPCS' incidence, intensity, location and the presence of NP (Paper B) were:

- to conduct a rigorous systematic search through the literature about CPPCS' incidence, intensity, location and the presence of NP;
- to identify, appraise, select and synthesize all high-quality research evidence relevant to CPPCS' incidence, intensity, location and the presence of NP;
- to perform a quality assessment for each selected study based on defined criteria;
- to provide, whenever possible, pooled estimates about CPPCS' incidence, CPPCS' intensity and presence of NP in patients with CPPCS;
- to analyse whether the incidences of CPPCS have changed over time

Consequently, our general aim was to contribute to improved knowledge of CPPCS, and a better understanding of CPP.

3. PUBLICATIONS

3.1. Paper A - Persistent Postoperative Pain after Cardiac Surgery: Incidence, Characterization, Associated Factors and its impact in Quality of Life

3.2. Paper B - Persistent postoperative pain after cardiac surgery: a systematic review with meta-analysis regarding incidence and pain intensity

3.1. Paper A

EJP
European Journal of Pain

ORIGINAL ARTICLE

Persistent Postoperative Pain after Cardiac Surgery: Incidence, Characterization, Associated Factors and its impact in Quality of Life

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Funding sources
None declared.

Conflicts of interest
All authors have no conflicts of interest.

Accepted for publication
31 January 2016

doi:10.1002/ejp.866

Abstract

Background: Cardiac surgery (CS) ranks among the most frequently performed interventions worldwide and persistent postoperative pain (PPP) has been recognized as a relevant clinical outcome in this context. We aimed to evaluate its incidence, characteristics, associated factors and patient's quality of life (QoL).
Methods: Observational prospective study conducted in patients undergoing CS in a tertiary university hospital. PPP was defined as persistent pain after surgery with higher than 3 months' duration, after excluding other causes of pain. We used a set of questionnaires for data collection: Pain Catastrophizing Scale, Duke Health Profile, Brief Pain Inventory Short Form, McGill Pain Questionnaire Short Form, Douleur Neuropathique en 4 Questions and standardized questions regarding pain periodicity.
Results: A total of 288 patients have completed the study and 43% presented PPP assessed at 3 months (PPP3M); out of which 84% were not under any treatment. PPP patients reported significantly lower QoL, and a neuropathic pain (NP) component was present in 50% of them. Younger age, female gender, higher body mass index, catastrophizing, coronary artery bypass graft, osteoarthritis, history of previous surgery (excluding sternotomy) and moderate to severe acute postoperative pain were independent predictors of PPP3M.
Conclusion: This is the first study comprehensively describing PPP after CS and identifying NP in half of them. Our results support the important role that PPP plays after CS in considering its interference in patients' daily life and their lower QoL, which deserves the attention of health care professionals in order to improve prevention, assessment and treatment of these patients.
What does this study add? This study comprehensively describes PPP after CS and identifies NP in half of them. Our results support the important role that PPP plays after CS in considering its interference in patients' daily life and their lower quality of life.

Paper A

1. Introduction

The International Association of the Study of Pain (IASP) defines persistent postoperative pain (PPP) as persistent pain after surgery with higher than 3 months' duration, after exclusion of other common causes of pain (Kehlet et al., 2014). PPP is considered to be a common, but underdiagnosed complication of surgery that has significant consequences for the individual patient and for society (Kehlet et al., 2014). In a cross-sectional epidemiological study, 6% of patients with chronic pain attributed its aetiology to surgery (Azevedo et al., 2012). The prevalence of PPP varies across surgeries, with the highest rates observed for thoracotomies and amputations. Recently, there has been an appeal to design better clinical studies about PPP, which should ideally take a prospective and procedure-specific approach (Kehlet and Rathmell, 2010).

Cardiac surgery (CS), such as coronary artery bypass grafting (CABG) and heart valve replacement (HVR), ranks among the most frequently performed interventions worldwide (Roger et al., 2012). Defalque and Bromley (1989) described for the first time a new pain syndrome called poststernotomy neuralgia. Since then, several studies were conducted and recently PPP was recognized as an important clinical outcome after CS, with an estimated incidence between 11% and 56% (Mazzeffi and Khelemsky, 2011). Quality research focusing on the incidence, burden and characteristics of PPP after CS is important to elucidate and improve the prevention, assessment, management and treatment of patients presenting this relevant pain syndrome.

Persistent postoperative pain may be somatic, visceral or neuropathic pain (NP; Haroutiunian et al., 2013), and the prevalence of NP or pain with a neuropathic component was reported to be higher in patients with PPP after thoracotomies and breast surgeries (approximately 66%) (Haroutiunian et al., 2013). Regarding PPP after CS, it has been described that 23% patients with PPP in the chest had NP only, and a combination of NP and non-NP in 20% of the cases based on the reporting of numbness, pins and needles, burning, stabbing (neuropathic) and ache (non-neuropathic) (Bruce et al., 2003). In the current literature regarding PPP after CS, it is noteworthy the lack of adequate NP assessments with validated instruments.

Persistent postoperative pain after CS affects the patients' quality of life (QoL) and may impair activities of daily life. The consequences of PPP are important not only in terms of suffering and reduced QoL for the individual patient but also regarding the subsequent health care and societal costs (Blyth et al., 2003).

In order to further address these issues regarding PPP after CS, the purposes of our study were: to evaluate its incidence; to identify its associated factors; to comprehensively characterize it, in terms of severity, interference, NP, pain descriptors and periodicity, using adequately validated instruments; and to assess the patients' QoL.

2. Methods

2.1 Population and study design

After approval by the Institutional Ethics Committee (CES CHSJ 23-11, 16/04/2013), an observational prospective study was conducted in patients undergoing CS from July to December 2013 in a tertiary university hospital. The inclusion criteria were: patient informed consent, elective CS with sternotomy and age higher than 18 years. Surgeries included CABG, HVR and combination of HVR with CABG. Exclusion criteria were pregnancy or breast-feeding, reoperation and non-Portuguese-speaking patients. The anaesthetic protocol was standardized in all patients: midazolam, fentanyl and propofol were used for induction of anaesthesia and patients were paralysed with rocuronium. Anaesthesia was maintained with propofol, with or without sevoflurane, and either fentanyl or remifentanil, as preferred by the attending anaesthesiologist. These intraoperative data, type of surgery performed and technical details such as extracorporeal circulation, skeletonized internal thoracic artery (ITA) harvesting and saphaenous vein harvesting were appropriately registered. Upon arrival in the Intensive Care Unit after the surgery, patients received a continuous intravenous infusion of morphine (2 mg/h) in combination with acetaminophen (1 g, 4 times a day). Additional administration and tapering of morphine was executed by the attending physician and nurses based upon the reported pain scores, according to local protocol.

2.2 Data collection and assessment instruments

Data collection was performed using validated Portuguese versions (Silva et al., 2001; Azevedo et al., 2007) of several validated questionnaires at different moments: one day before the surgery (T0), 3 days after surgery (T1), 3 and 6 months after surgery (T3

and T6). T0 and T1 questionnaires were administered in a face-to-face interview, and T3 and T6 questionnaires in a telephone interview. The T0 questionnaires included standard demographic questions, Pain Catastrophizing Scale (Sullivan et al., 1995), Duke Health Profile (DHP) (Parkerson et al., 1990) and Brief Pain Inventory Short Form (BPI-SF) (Cleeland and Ryan, 1994; Keller et al., 2004; Mendoza et al., 2004). BPI-SF was also performed at T1 and T3. To evaluate the presence of PPP assessed at 3 months (PPP3M) after CS, at T3, the first question asked was 'Do you still have any pain that you could relate to the surgical procedure?' This is an adaptation of the BPI-SF first question on pain prospection and it has been performed in other similar studies (Gjeilo et al., 2010; Pinto et al., 2012). If the answer was 'yes' and other causes of pain were excluded (different from possible earlier experiences with angina or infection), patients were considered to have PPP3M, according to IASP definition (Kehlet et al., 2014). To identify the presence of PPP assessed at 6 months (PPP6M) after CS, at T6, patients were solely asked for the presence of pain related with the procedure. BPI-SF evaluates pain severity and pain interference in daily activities on an 11-point numerical rating scale, and also pain location (Cleeland and Ryan, 1994). For analysis purposes and according to previous studies (Lahtinen et al., 2006; Taillefer et al., 2006), we converted the numeric rating used in BPI-SF into categorical variables: '0' as none, 1–3 as mild, 4–6 as moderate and 7–10 as severe. We defined moderate to severe PPP3M as PPP3M with a BPI-SF overall pain severity higher than 3. In patients with PPP3M, we applied the McGill Pain Questionnaire Short Form (MPQ-SF) (Melzack, 1987), the Douleur Neuropathique en 4 Questions (DN4) (Bouhassira et al., 2005), and two questions regarding pain periodicity: 'During the past 24 h, how long was your spontaneous pain present?' and 'During the past 24 h, how many pain attacks have you had?'. For the feasibility of this study, the last three items of DN4 resulting from the sensory examination were not performed and patients were classified to have NP in accordance with Bouhassira et al. (2008) guidelines. QoL was evaluated with DHP at T0 and T3. The DHP is a 17-item generic self-report instrument containing six health measures (physical, mental, social, general, perceived health and self-esteem) and four dysfunction measures (anxiety, depression, pain, and disability) (Parkerson et al., 1990).

2.3 Statistical analyses

Using a predicted incidence of pain of 50% (to generate the most conservative or largest sample size), we calculated that 278 participants would ensure a 95% confidence interval for pain incidence estimation with a 6% margin of error. Descriptive statistics of patient characteristics and clinical variables were expressed as frequencies with percentages (%), median with interquartile range or mean with standard deviation (SD) when appropriate. Nonparametric and parametric tests were performed for comparisons between numerical variables according their distribution and chi-squared test for categorical variables. A p-value of 0.05 was considered significant for all tests. Multivariate logistic regression analysis was performed. Univariate predictors of outcome with a p-value <0.10 were selected for multivariate logistic regression analysis with stepwise backward elimination. The dependent variable was PPP3M and possible predictors were used as independent variables. All statistical analyses were performed using Statistical Package for the Social Sciences (version 22.0 for Windows; SPSS, Chicago, IL, USA).

3. Results

A total of 310 patients were included in the study and 288 patients (92.9%) completed the study. Most of the patients were men (70.1%) and underwent CABG without HVR (43.3%); the median age was 68 years. The main characteristics of our sample are described in Table 1.

3.1 Incidence, severity, interference and QoL

One-hundred and twenty-four patients developed PPP3M [incidence: 43%; 95% confidence interval (CI): 37–49%]. Eighty-four per cent of these patients were not under any treatment or referral. The incidence of moderate to severe PPP3M was 17% (95% CI: 12–21%). PPP6M was present in 40% of the sample (115 patients) and none of the patients without PPP3M reported PPP6M.

Table 2 describes the severity and interference of PPP3M, as measured by the BPI-SF. The majority of the patients with PPP3M (61.2%) classified their pain's overall severity as mild, but in 19.4% the overall severity was moderate and in other 19.4% it was severe. Regarding the worst pain item, 54.9% had moderate pain and 27.4% had severe pain. When we assessed their pain interference, 35.5% of the patients with PPP3M had a mild overall interfer-

Paper A

Table 1 Patients' characteristics (N = 288)

Gender, *N* (%)	
Male	202 (70.1)
Female	86 (29.9)
Age in years, M [P_{25}–P_{75}]	68 [60–77]
Age groups, *N* (%)	
18–40 years	5 (1.7)
41–60 years	67 (23.3)
61–80 years	178 (61.8)
>80 years	38 (13.2)
Body mass index (kg/m^2), M [P_{25}–P_{75}]	26.7 [24.3–26.7]
Body mass index categories, *N* (%)	
Normal	89 (30.9)
Overweight	136 (47.2)
Obese Class I (Moderately obese)	49 (17.0)
Obese Class II (Severely obese)	14 (4.9)
Surgery, *N* (%)	
CABG	124 (43.1)
HVR	95 (33.0)
CABG and HVR	69 (23.9)
Extracorporeal circulation, *N* (%)	
Yes	235 (82.7)
No	49 (17.3)
Saphaenous vein harvest, *N* (%)	
Yes	99 (34.4)
No	189 (65.6)
Skeletonized ITA harvest, *N* (%)	
Yes	78 (44.6)
No	97 (55.4)
Worst pain* at T1, M [P_{25}–P_{75}]	4.5 [4.0–5.0]
Pain's Overall Severity* at T1, M [P_{25}–P_{75}]	3.0 [2.0–4.0]

CABG, coronary artery bypass graft; HVR, heart valve replacement; ITA, internal thoracic artery; M, Median; *N*, Number of patients; P_{25}, Percentile 25; P_{75}, Percentile 75; T1, Third postoperative day.
*Obtained with Brief Pain Inventory Short Form.

Table 2 Persistent postoperative pain severity and interference using brief pain inventory short form at 3 months (N = 124)

	None	Mild	Moderate	Severe
Pain severity, *N* (%)				
Worst pain	0 (0.0)	22 (17.7)	68 (54.9)	34 (27.4)
Least pain	90 (72.6)	30 (24.2)	4 (3.2)	0 (0.0)
Average pain	0 (0.0)	71 (57.3)	53 (42.7)	0 (0.0)
Pain right now	61 (49.1)	24 (19.4)	39 (31.5)	0 (0.0)
Overall severity	0 (0.0)	76 (61.2)	24 (19.4)	24 (19.4)
Pain interference, *N* (%)				
General activity	41 (33.2)	39 (31.5)	30 (24.2)	14 (11.3)
Mood	28 (22.6)	62 (50.0)	29 (23.4)	5 (4.0)
Walking ability	95 (76.7)	19 (15.3)	5 (4.0)	5 (4.0)
Normal work	60 (48.3)	25 (20.2)	29 (23.4)	10 (8.1)
Relations with other people	65 (52.4)	49 (39.5)	10 (8.1)	0 (0.0)
Sleep	29 (23.4)	46 (37.0)	39 (31.5)	10 (8.1)
Enjoyment of life	33 (26.6)	66 (53.3)	20 (16.1)	5 (4.0)
Overall Interference	19 (15.3)	44 (35.5)	37 (29.8)	24 (19.4)

N, Number of patients.

ence, 28.9% moderate and 19.4% severe. Fifteen per cent of patients with PPP3M denied any overall interference brought by their pain.

Patients reported higher DUKE scores at T3, compared to T0 (all DUKE scores with $p < 0.001$, except pain score with $p = 0.598$; Table S1). However, when we analyse DUKE scores at T3, patients with PPP3M presented significantly worse results in eight of the 11 scores: Physical Health Score, $p < 0.001$; Mental Health Score, $p = 0.001$; Social Health Score, $p = 0.017$; General Health Score, $p < 0.001$; Anxiety Score, $p < 0.001$; Depression Score, $p = 0.033$; Anxiety–Depression Score, $p < 0.001$; Pain Score $p < 0.001$ (Table S2).

3.2 Pain periodicity, descriptors and NP

Regarding pain periodicity, 27% of patients with PPP3M reported pain permanently, 29% reported pain present between 8 and 12 h during 1 day and 33% between 4 and 7 h. When we assessed their pain paroxysms, 54% had between one and five pain attacks during 1 day and 20% had between six and 10. Nineteen per cent of patients with PPP3M had no pain attacks. A detailed evaluation of pain periodicity can be seen in Table S3.

Relatively to MPQ-SF pain descriptors in patients with PPP3M, 'Tender' was the descriptor mentioned more often as severe, followed by 'Hot-Burning', 'Sharp' and 'Aching' (Table S4). Regarding DN4, the most common DN4 descriptors identified by patients with PPP3M were 'Pins and needles' (77.4%) and 'Tingling' (46.8%). The less reported was 'Painful cold' (15.3%). A detailed evaluation of the DN4 responses can be seen in Table S5. Fifty per cent of the patients with PPP3M presented NP, and those with moderate to severe PPP3M presented significantly more often NP (68.8% vs. 38.2%, $p = 0.001$).

3.3 PPP Predictive Factors

Table 3 presents associations between demographic, psychological factors, clinical, surgical and early postoperative characteristics and the incidence of PPP3M. Younger patients ($p < 0.001$), female gender ($p = 0.02$), higher body mass index (BMI) ($p < 0.001$), CABG ($p = 0.001$), off-pump technique ($p = 0.003$) and more severe BPI-SF worst pain at T1 ($p = 0.008$) were significantly associated with higher incidence of PPP after CS. There were no differences in the incidence of PPP3M related with the presence of preoperative angina pectoris ($p = 0.171$), even when we exclude patients with only valvular disease

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Table 3 Factors associated with PPP at 3 months

	Patients with PPP (*N* = 124)	Patients without PPP (*N* = 164)	*p*
Gender, *N* (%)			
Male	78 (38.6)	124 (61.4)	
Female	46 (53.5)	40 (46.5)	**0.02**[a]
Age in years, M [P_{25}–P_{75}]	61 [56–73]	72 [64–78]	**<0.001**[b]
Age groups, *N* (%)			
21–40 years	0 (0.0)	5 (100.0)	
41–60 years	44 (65.7)	23 (34.3)	
61–80 years	71 (39.9)	107 (60.1)	
>80 years	9 (23.7)	29 (76.3)	**<0.001**[a]
Body mass index (kg/m^2), M [P_{25}–P_{75}]	27.4 [26.1–29.7]	25.5 [23.1–28.7]	**<0.001**[b]
Body mass index categories, *N* (%)			
Normal	18 (20.2)	71 (79.8)	
Overweight	83 (61.0)	53 (39.0)	
Obese Class I	29 (59.2)	20 (40.8)	
Obese Class II	9 (64.3)	5 (35.7)	**<0.001**[a]
Preoperative angina presence, *N* (%)			
Yes	14 (56.0)	11 (44.0)	
No	110 (41.8)	153 (58.2)	0.171[a]
History of previous surgery (excluding sternotomy), *N* (%)			
Yes	100 (49.2)	101 (50.2)	
No	24 (27.6)	63 (72.4)	**<0.001**[a]
Osteoarthritis, *N* (%)			
Yes	18 (66.7)	9 (33.3)	
No	106 (40.6)	155 (59.4)	**0.009**[a]
CABG performed, *N* (%)			
Yes	95 (49.2)	98 (50.8)	
No	27 (28.4)	68 (71.6)	**0.001**[a]
Extracorporeal circulation, *N* (%)			
Yes	90 (38.3)	145 (61.7)	
No	30 (61.2)	19 (38.8)	**0.003**[a]
Saphaenous vein harvest, *N* (%)			
Yes	45 (45.9)	54 (55.1)	
No	76 (40.2)	113 (59.8)	0.364[a]
Skeletonized ITA harvest, *N* (%)			
Yes	40 (51.3)	38 (48.7)	
No	48 (49.5)	49 (50.5)	0.813[a]
Remifentanil during anaesthesia, *N* (%)			
Yes	104 (43.5)	135 (56.5)	
No	20 (40.8)	29 (59.2)	0.728[a]
Worst pain* at T1, M [P_{25}–P_{75}]	4 [4–5]	4 [3–5]	**0.008**[b]
Pain's overall severity* at T1, M [P_{25}–P_{75}]	3 [2–3]	3 [2–3]	0.392[b]
T0 DUKE Anxiety Score [P_{25}–P_{75}]	42 [25–50]	42 [25–50]	0.547[b]
T0 DUKE depression score [P_{25}–P_{75}]	40 [30–50]	40 [20–50]	0.112[b]
T0 DUKE anxiety-depression score [P_{25}–P_{75}]	43 [29–50]	43 [21–50]	0.307[b]
T0 DUKE self-esteem score [P_{25}–P_{75}]	90 [80–100]	100 [90–100]	**0.007**[b]
PCS total score, M [P_{25}–P_{75}]	8 [2–13]	4 [2–9]	**0.034**[b]
Clinically relevant level of catastrophizing (PCS >30), *N* (%)			
Yes	19 (59.4)	13 (40.6)	
No	105 (41.0)	151 (59.0)	**0.048**[a]

CABG, Coronary artery bypass graft; HVR, heart valve replacement; ITA, internal thoracic artery; PCS, Pain Catastrophizing Scale; PPP, persistent postoperative pain; T0, One day before surgery; T1, Third postoperative day; M, Median; P_{25}, Percentile 25; P_{75}, Percentile 75; *N*, number of patients.

Bold = group difference significant at $p < 0.05$ level.

*Assessed with Brief Pain Inventory short form.

[a]Obtained with chi-squared test.

[b]Obtained with Mann–Whitney *U*-test.

(47.6% vs. 49.1%, $p = 0.897$). We also failed to detect differences in the incidence of PPP3M regarding saphaenous vein harvesting ($p = 0.364$), skeletonized ITA harvesting ($p = 0.813$) and remifentanil during CS ($p = 0.728$). Regarding associations between medical history and PPP3M, history of previous surgery (excluding sternotomy) and osteoarthritis were associated with higher incidence of PPP3M ($p < 0.001$ and $p = 0.009$, respectively). We didn't detect differences in other comorbidities (renal, respiratory, diabetes, neurological and gastrointestinal). With respect to psychological factors at T0, lower self-esteem and catastrophizing were associated with the presence of PPP3M. We were unable to detect differences in anxiety and depression.

Table 4 presents the independent predictors of PPP3M after CS based on a multivariate logistic regression analysis. Worst pain classified as moderate to severe at T1 and age lower than 69 were found to be strong independent predictors of PPP3M with odd ratios higher than 10.

3.4 Pain location and NP predictors

In terms of pain location, PPP3M was reported in the thorax (92%), sternum (88%) and leg (16%). Forty-four per cent of the patients who underwent

Table 4 Predictors of PPP3M identified in multivariate logistic regression analysis with stepwise backward elimination (Hosmer–Lemeshow test; $p = 0.069$)

	OR	95% CI	*p*-value
CABG	5.28	2.38–11.72	<0.001
Female gender	3.37	1.37–8.31	0.008
Worst pain at T1[a] classified as moderate to severe	15.07	4.99–45.40	<0.001
Age <69 years	10.45	4.73–23.05	<0.001
BMI >27 kg/m^2	5.98	2.90–12.36	<0.001
Osteoarthritis	3.98	1.03–15.89	0.047
History of previous surgery[b]	3.08	1.42–6.67	0.004
Relevant PCS (PCS >30)	4.80	1.11–20.80	0.036

BMI, body mass index; CABG, coronary artery bypass graft; CI, confidence interval; OR, odds ratio; PCS, Pain Catastrophizing Scale; PPP, persistent postoperative pain at 3 months; T1, Third postoperative day.

[a]Assessed with Brief Pain Inventory short form.

[b]Excluding sternotomy.

saphaenous vein harvesting presented PPP3M in the leg, and these patients presented more often NP ($p < 0.001$), as described in Table 5. It should be noted that all patients who had preoperative angina pectoris and developed PPP3M ($n = 14$) had NP, while only 44% of those with PPP3M but without preoperative angina pectoris had NP ($p < 0.001$).

4. Discussion

The main findings of our study can be summarized as follows. First, an important number of patients developed PPP3M after CS, and the majority were not being treated. PPP3M caused interference in their daily life and lower QoL. Second, in the majority of the patients, PPP3M after CS wasn't permanently present and it had paroxysms. Third, a NP component was reported by half of the cases, using a validated screening instrument. Fourth, applying a multivariate logistic regression analysis, we have identified several independent predictors of PPP3M after CS: CABG, age <69 years, female gender, BMI >27 kg/m^2, moderate to severe classification in BPI-SF worst pain item at the third postoperative day, catastrophizing, osteoarthritis and history of previous surgery (excluding sternotomy). Fifth, preoperative angina pectoris was a predictor for NP in patients with PPP3M.

4.1 Incidence and description of PPP after CS

The incidence of PPP3M and moderate to severe PPP3M after CS found is in accordance with the literature (Bruce et al., 2003; Lahtinen et al., 2006; van Leersum et al., 2010; van Gulik et al., 2011; Choiniere et al., 2014). Although its incidence has been reported to decrease over time after surgery (Gjeilo et al., 2014), the proportion of patients with pain remained almost the same between 3 and 6 months, which could be justified by the enormous lack of PPP treatment. All patients who reported PPP6M had PPP3M, which supports the current evidence that the 3-month time frame, used by IASP for PPP definition (Kehlet et al., 2012), is adequate.

The majority of our patients with PPP3M had an overall severity of pain classified as mild (61.2%), which is higher than found in some studies (Eisenberg et al., 2001; Bruce et al., 2003), but lower than shown by others (Ho et al., 2002). The worst pain was moderate and severe in a slightly higher percentage (54.9% and 27.4%, respectively) when

Table 5 Factors associated with a Neuropathic Pain* in PPP3M patients ($N = 124$)

	Patients with NP ($N = 62$)	Patients without NP ($N = 62$)	*p*
Gender, *N* (%)			
Male	44 (56.4)	34 (43.6)	
Female	18 (39.1)	28 (60.9)	0.063[a]
Age in years, M [P_{25}–P_{75}]	63 [54–74]	61 [58–71]	0.703[b]
Body Mass Index (kg/m^2), M [P_{25}–P_{75}]	26.6 [25.9–28.3]	29.7 [27.3–33.5]	**<0.001**[b]
Preoperative angina, *N* (%)			
Yes	14 (100.0)	0 (0.0)	
No	48 (43.6)	62 (56.4)	**<0.001**[a]
CABG performed, *N* (%)			
Yes	49 (50.5)	48 (49.5)	
No	13 (48.1)	14 (51.9)	0.828[a]
Saphaenous vein harvest, *N* (%)			
Yes	25 (55.6)	20 (44.4)	
No	33 (44.0)	42 (56.0)	0.220[a]
Extracorporeal circulation, *N* (%)			
Yes	43 (47.8)	47 (52.2)	
No	15 (50.0)	15 (50.0)	0.833[a]
Skeletonized ITA harvest, *N* (%)			
Yes	25 (62.5)	15 (37.5)	
No	20 (41.7)	28 (58.3)	0.058[a]
PPP3M in the leg, *N* (%)			
Yes	15 (75.0)	5 (25.0)	
No	47 (45.2)	57 (54.8)	**0.015**[a]

CABG, Coronary artery bypass graft; ITA, internal thoracic artery; NP, neuropathic pain; PPP 3M, persistent postoperative pain at 3 months; M, Median; P_{25}, Percentile 25; P_{75}, Percentile 75; *N*, number of patients.

Bold = group difference significant at $p < 0.05$ level.

*Patients were classified to have NP in accordance with Bouhassira et al. (2008) guidelines.

[a]Obtained with chi-squared test.

[b]Obtained with Mann–Whitney *U*-test.

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compared to the results of a previous study using the same methodology (40.4% and 19.1%, respectively) (Gjeilo et al., 2010). Patients with PPP3M reported a substantial overall interference in daily life and moderate to severe sleep interference caused by their pain, in keeping with other studies (Eisenberg et al., 2001; Taillefer et al., 2006; Gjeilo et al., 2010; van Gulik et al., 2011). Improved QoL is a major objective for CS (Eagle et al., 2004; Bonow et al., 2008) and it's well proven (Stoll et al., 2000; Gjeilo et al., 2013). Our study found that PPP3M brought lower QoL, which was previously suggested (Bruce et al., 2003; Taillefer et al., 2006; Gjeilo et al., 2010). The interference in daily life and lower QoL highlight the detrimental outcomes of PPP after CS.

To our knowledge, this is the first time that temporal evaluation of spontaneous ongoing pain and paroxysmal pain was assessed in PPP. The two temporal items represent an important aspect of the evaluation of pain patients and their treatment strategy (Marchand, 2012).

For the first time, NP was detected in 50% of the patients with PPP after CS, using a validated questionnaire. Nerve injury–induced NP has been proposed as a major cause of PPP and a recent review suggests that the prevalence of NP among PPP cases differs in various types of surgery, probably depending on the likelihood of surgical iatrogenic nerve injury (Haroutiunian et al., 2013). Persistent harvest-site pain occurs with astonishing frequency after CABG (Dick et al., 2011) and the most common location reported by our patients was the thorax. Nevertheless, PPP3M was also present in the legs in a high proportion of patients who underwent saphaenous vein harvesting, as previously suggested (Kalso et al., 2001; Bruce et al., 2003; Lahtinen et al., 2006; Taillefer et al., 2006). PPP3M in the leg was more often identified as NP than chest PPP3M, which confirms previous findings (Bruce et al., 2003). A possible explanation is that saphaenous nerve injury can occur as a result of surgical handling or postoperatively from compression caused by subcutaneous suturing. Relevant literature addressed alternative techniques to avoid this injury (Bonde et al., 2004; Allen et al., 2005; Simek et al., 2007).

4.2. Predictive factors

Recently, younger age, female gender and higher BMI were identified as predictors of PPP after CS (Gjeilo et al., 2014). Previous findings have shown that younger age was associated with higher acute postoperative pain, independently of the type and extent of surgery (Gerbershagen et al., 2014), and with PPP after CS (Choiniere et al., 2014; Gjeilo et al., 2014). According to Gerbershagen et al. (2014), 'many factors could influence the pain differences with age, such as biopsychosocial and life-stage factors, as well as changes in the complex cascade of immune, inflammatory and neural responses (Janig and Levine, 2006; Gagliese, 2009)'.

Women are more likely to develop chronic pain conditions, and several epidemiological studies reported a higher prevalence of chronic painful diseases in women (Marchand, 2012). CS in patients with higher BMI is technically more difficult, with prolonged retraction and more probable nerve damage, and thus a higher incidence of PPP (Bruce et al., 2003).

In contrast to some reports (Meyerson et al., 2001; Taillefer et al., 2006; van Gulik et al., 2011; Choiniere et al., 2014), there was a higher incidence of PPP in patients who underwent CABG, which could be explained by the higher probability of damage of the intercostal nerves during ITA harvesting (Mazzeffi and Khelemsky, 2011). Some authors have confirmed that skeletonized ITA harvesting reduces intercostal nerve injury, and consequently reduces PPP (Markman et al., 2010; Bawany et al., 2014), but we have failed to prove it.

There are conflicting reports regarding the role of angina pectoris in PPP (Bruce et al., 2003; Steegers et al., 2007). Preoperative angina pectoris wasn't associated with higher incidence of PPP3M, but patients with preoperative angina pectoris who developed PPP3M were more prone to develop NP, which is a new finding and suggests that it could be involved in the pathophysiology of NP in patients who underwent CS.

Contrary to previously found (van Gulik et al., 2012), remifentanil during CS wasn't significantly associated with a higher risk of PPP, though this study wasn't specifically designed to investigate it.

Although current evidence suggests that psychological factors are important in pain perception (Thibault et al., 2008; Ip et al., 2009; Doering et al., 2014), we didn't find differences regarding anxiety or depression in the development of PPP3M. DHP has been shown to be an effective brief screener for both anxiety and depression (Parkerson et al., 1996); notwithstanding, the distinction between state and trait anxiety could have been important because there are reports of association between state but not trait anxiety with postoperative pain (Martinez-Urrutia, 1975; Scott et al., 1983).

Catastrophizing is a known risk factor for PPP (Theunissen et al., 2012) and acute postoperative pain after CS (Khan et al., 2012); however, its identification as an independent predictor of PPP after CS occurred for the first time.

Osteoarthritis and history of previous surgery were also identified as independent predictors of PPP3M after CS. A possible explanation for this result could rely on the concept of deficient endogenous pain modulation (EPM). EPM is a wide-ranging term, delineating the array of processes taking place in the central nervous system to reduce or increase pain (Yarnitsky, 2015). Enhanced temporal summation and less efficient conditioned pain modulation can both occur in patients with pain, such as in patients with osteoarthritis (Arendt-Nielsen et al., 2010). Use of pain-modulating drugs may rectify the deficient EPM (Yarnitsky, 2015).

Regarding acute postoperative pain, moderate to severe classification in BPI-SF worst pain item at T1 was an independent predictor of PPP3M. Higher pain ratings and analgesic requirements during the first postoperative days have been associated with increased risk of PPP (van Gulik et al., 2011; Mazzeffi and Khelemsky, 2011; Choiniere et al., 2014). The relationship between acute pain and PPP could be associative or causal (Gjeilo et al., 2014). Although this uncertainty remains, interventions to decrease acute pain should be an imperative. Once again, EPM seems to be involved. Weissman-Fogel et al. (2009) proposed the role of pain temporal summation assessed preoperatively as a significant psychophysical predictor for acute postoperative pain intensity.

4.3. Strengths and limitations

Our study has several strengths. It was an observational prospective study regarding PPP after a specific procedure, with detailed assessment based on validated questionnaires, and a low number of loss-to-follow-up and missing data. It is likely that our cohort was representative, favouring external validity. There are also some limitations in this study. Our sample comes from a single hospital, which could bring some bias, with respect to surgical techniques and acute pain treatment, and might be a threat to generalizability.

5. Conclusion

This study relevantly contributes to a better understanding of PPP after CS. Although some studies have focused on PPP after CS, this study adds new knowledge to the field and supports its important role, which should deserve special attention from health care professionals in order to prevent, inform and treat these patients.

Acknowledgements

Cristiana Pinho and Joana Freitas are thanked for patient's interview assistance.

Author contribution

L.G.-P., L.A., F.A., J.C.-L: study conception and design; L.G.-P., F.F: acquisition of data; L.G-P., L.A., F.A: analysis and interpretation of data;. L.G.-P., F.F: drafting of manuscript; L.A., F.A., J.C.-L: critical revision. All authors have read and approved this paper.

References

Allen, K., Cheng, D., Cohn, W., Connolly, M., Edgerton, J., Falk, V., Martin, J., Ohtsuka, T., Vitali, R. (2005). Endoscopic vascular harvest in coronary artery bypass grafting surgery: a consensus statement of the International Society of Minimally Invasive Cardiothoracic Surgery (ISMICS) 2005. *Innovations* 1, 51–60.

Arendt-Nielsen, L., Nie, H., Laursen, M. B., Laursen, B. S., Madeleine, P., Simonsen, O. H., Graven-Nielsen, T. (2010). Sensitization in patients with painful knee osteoarthritis. *Pain* 149, 573–581.

Azevedo, L. F., Pereira, A. C., Dias, C., Agualusa, L., Lemos, L., Romão, J., Patto, T., Vaz-Serra, S., Abrunhosa, R., Carvalho, C. J., Cativo, M. C., Correia, D., Correia, J., Coucelo, G., Lopes, B. C., Loureiro, M.d. C., Silva, B. and Castro-Lopes, J. M. (2007) Tradução, Adaptação Cultural e Estudo Multicêntrico de Validação de Instrumentos para Rastreio e Avaliação do Impacto da Dor Crónica. *Dor* 15, 6–56.

Azevedo, L. F., Costa-Pereira, A., Mendonca, L., Dias, C. C., Castro-Lopes, J. M. (2012). Epidemiology of chronic pain: a population-based nationwide study on its prevalence, characteristics and associated disability in Portugal. *J Pain* 13, 773–783.

Bawany, F. I., Khan, M. S., Khan, A., Hussain, M. (2014). Skeletonization technique in coronary artery bypass graft surgery reduces the postoperative pain intensity and disability index. *J Card Surg* 29, 47–50.

Blyth, F. M., March, L. M., Cousins, M. J. (2003). Chronic pain-related disability and use of analgesia and health services in a Sydney community. *Med J Aust* 179, 84–87.

Bonde, P., Graham, A. N., MacGowan, S. W. (2004). Endoscopic vein harvest: advantages and limitations. *Ann Thorac Surg* 77, 2076–2082.

Bonow, R. O., Carabello, B. A., Chatterjee, K., de Leon, A. C., Jr, Faxon, D. P., Freed, M. D., Gaasch, W. H., Lytle, B. W., Nishimura, R. A., O'Gara, P. T., O'Rourke, R. A., Otto, C. M., Shah, P. M., Shanewise, J. S. (2008). 2008 focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 1998 guidelines for the management of patients with valvular heart disease). Endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol* 52, e1–e142.

Bouhassira, D., Attal, N., Alchaar, H., Boureau, F., Brochet, B., Bruxelle, J., Cunin, G., Fermanian, J., Ginies, P., Grun-Overdyking, A., Jafari-Schluep, H., Lanteri-Minet, M., Laurent, B., Mick, G., Serrie, A., Valade, D., Vicaut, E. (2005). Comparison of pain

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syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). *Pain* 114, 29–36.

Bouhassira, D., Lanteri-Minet, M., Attal, N., Laurent, B., Touboul, C. (2008). Prevalence of chronic pain with neuropathic characteristics in the general population. *Pain* 136, 380–387.

Bruce, J., Drury, N., Poobalan, A. S., Jeffrey, R. R., Smith, W. C. S., Chambers, W. A. (2003). The prevalence of chronic chest and leg pain following cardiac surgery: a historical cohort study. *Pain* 104, 265–273.

Choiniere, M., Watt-Watson, J., Victor, J. C., Baskett, R. J., Bussieres, J. S., Carrier, M., Cogan, J., Costello, J., Feindel, C., Guertin, M. C., Racine, M., Taillefer, M. C. (2014). Prevalence of and risk factors for persistent postoperative nonanginal pain after cardiac surgery: a 2-year prospective multicentre study. *CMAJ* 186, E213–E223.

Cleeland, C. S., Ryan, K. M. (1994). Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singapore* 23, 129–138.

Defalque, R. J., Bromley, J. J. (1989). Poststernotomy neuralgia: a new pain syndrome. *Anesth Analg* 69, 81–82.

Dick, F., Hristic, A., Roost-Krähenbühl, E., Aymard, T., Weber, A., Tevaearai, H. T., Carrel, T. P. (2011). Persistent sensitivity disorders at the radial artery and saphenous vein graft harvest sites: a neglected side effect of coronary artery bypass grafting procedures. *Eur J Cardiothorac Surg* 40, 221–226.

Doering, L. V., Chen, B., McGuire, A., Bodan, R. C., Irwin, M. R. (2014). Persistent depressive symptoms and pain after cardiac surgery. *Psychosom Med* 76, 437–444.

Eagle, K. A., Guyton, R. A., Davidoff, R., Edwards, F. H., Ewy, G. A., Gardner, T. J., Hart, J. C., Herrmann, H. C., Hillis, L. D., Hutter, A. M. Jr, Lytle, B. W., Marlow, R. A., Nugent, W. C., Orszulak, T. A., Antman, E. M., Smith, S. C. Jr, Alpert, J. S., Anderson, J. L., Faxon, D. P., Fuster, V., Gibbons, R. J., Gregoratos, G., Halperin, J. L., Hiratzka, L. F., Hunt, S. A., Jacobs, A. K., Ornato, J. P. (2004). ACC/AHA 2004 guideline update for coronary artery bypass graft surgery: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for Coronary Artery Bypass Graft Surgery). *Circulation* 110, 1168–1176.

Eisenberg, E., Pultorak, Y., Pud, D., Bar-El, Y. (2001). Prevalence and characteristics of post coronary artery bypass graft surgery pain (PCP). *Pain* 92, 11–17.

Gagliese, L. (2009). Pain and aging: the emergence of a new subfield of pain research. *J Pain* 10, 343–353.

Gerbershagen, H. J., Pogatzki-Zahn, E., Aduckathil, S., Peelen, L. M., Kappen, T. H., van Wijck, A. J., Kalkman, C. J., Meissner, W. (2014). Procedure-specific risk factor analysis for the development of severe postoperative pain. *Anesthesiology* 120, 1237–1245.

Gjeilo, K. H., Klepstad, P., Wahba, A., Lydersen, S., Stenseth, R. (2010). Chronic pain after cardiac surgery: a prospective study. *Acta Anaesthesiol Scand* 54, 70–78.

Gjeilo, K. H., Wahba, A., Klepstad, P., Lydersen, S., Stenseth, R. (2013). Survival and quality of life in an elderly cardiac surgery population: 5-year follow-up. *Eur J Cardiothorac Surg* 44, e182–e188.

Gjeilo, K. H., Stenseth, R., Klepstad, P. (2014). Risk factors and early pharmacological interventions to prevent chronic postsurgical pain following cardiac surgery. *Am J Cardiovasc Drugs* 14, 335–342.

van Gulik, L., Janssen, L. I., Ahlers, S. J., Bruins, P., Driessen, A. H., van Boven, W. J., van Dongen, E. P., Knibbe, C. A. (2011). Risk factors for chronic thoracic pain after cardiac surgery via sternotomy. *Eur J Cardiothorac Surg* 40, 1309–1313.

van Gulik, L., Ahlers, S. J., van de Garde, E. M., Bruins, P., van Boven, W. J., Tibboel, D., van Dongen, E. P., Knibbe, C. A. (2012). Remifentanil during cardiac surgery is associated with chronic thoracic pain 1 yr after sternotomy. *Br J Anaesth* 109, 616–622.

Haroutiunian, S., Nikolajsen, L., Finnerup, N. B., Jensen, T. S. (2013). The neuropathic component in persistent postsurgical pain: a systematic literature review. *Pain* 154, 95–102.

Ho, S. C., Royse, C. F., Royse, A. G., Penberthy, A., McRae, R. (2002). Persistent pain after cardiac surgery: an audit of high thoracic epidural and primary opioid analgesia therapies. *Anesth Analg* 95, 820–823.

Ip, H. Y., Abrishami, A., Peng, P. W., Wong, J., Chung, F. (2009). Predictors of postoperative pain and analgesic consumption: a qualitative systematic review. *Anesthesiology* 111, 657–677.

Janig, W. and Levine, J. D. (2006). Autonomic-endocrine-immune interactions in acute and chronic pain. In *Melzack and Wall's Textbook of Pain*, M. Koltzenburg, S. B. McMahon, eds. (Edinburgh: Elsevier) pp. 205–218.

Kalso, E., Mennander, S., Tasmuth, T., Nilsson, E. (2001). Chronic post-sternotomy pain. *Acta Anaesthesiol Scand* 45, 935–939.

Kehlet, H., Rathmell, J. P. (2010). Persistent postsurgical pain: the path forward through better design of clinical studies. *Anesthesiology* 112, 514–515.

Kehlet, H., Edwards, R. R., Buvanendran, A. (2012). Persistent postoperative pain: pathogenic mechanisms and preventive strategies. In *Pain 2012 — Refresher Courses*. I. Tracey, ed. (Seattle, WA: International Association for the Study of Pain/IASP Press) pp. 133–143.

Kehlet, H., Edwards, R. R., Brennan, T. (2014). Persistent postoperative pain: pathogenic mechanisms and preventive strategies. In *Pain 2014 — Refresher Courses*. S. Raja, C. Sommer, eds. (Seattle, WA: International Association for the Study of Pain/IASP Press) pp. 113–123.

Keller, S., Bann, C. M., Dodd, S. L., Schein, J., Mendoza, T. R., Cleeland, C. S. (2004). Validity of the brief pain inventory for use in documenting the outcomes of patients with noncancer pain. *Clin J Pain* 20, 309–318.

Khan, R. S., Skapinakis, P., Ahmed, K., Stefanou, D. C., Ashrafian, H., Darzi, A., Athanasiou, T. (2012). The association between preoperative pain catastrophizing and postoperative pain intensity in cardiac surgery patients. *Pain Med* 13, 820–827.

Lahtinen, P., Kokki, H., Hynynen, M. (2006). Pain after cardiac surgery: a prospective cohort study of 1-year incidence and intensity. *Anesthesiology* 105, 794–800.

van Leersum, N. J., van Leersum, R. L., Verwey, H. F., Klautz, R. J. M. (2010). Pain symptoms accompanying chronic poststernotomy pain: a pilot study. *Pain Med* 11, 1628–1634.

Marchand, S. (2012). *The Phenomenon of Pain*. (Seattle: IASP Press - International Association for the Study of Pain).

Markman, P. L., Rowland, M. A., Leong, J. Y., Van Der Merwe, J., Storey, E., Marasco, S., Negri, J., Bailey, M., Rosenfeldt, F. L. (2010). Skeletonized internal thoracic artery harvesting reduces chest wall dysesthesia after coronary bypass surgery. *J Thorac Cardiovasc Surg* 139, 674–679.

Martinez-Urrutia, A. (1975). Anxiety and pain in surgical patients. *J Consult Clin Psychol* 43, 437–442.

Mazzeffi, M., Khelemsky, Y. (2011). Poststernotomy pain: a clinical review. *J Cardiothorac Vasc Anesth* 25, 1163–1178.

Melzack, R. (1987). The short-form McGill Pain Questionnaire. *Pain* 30, 191–197.

Mendoza, T. R., Chen, C., Brugger, A., Hubbard, R., Snabes, M., Palmer, S. N., Zhang, Q., Cleeland, C. S. (2004). The utility and validity of the modified brief pain inventory in a multiple-dose postoperative analgesic trial. *Clin J Pain* 20, 357–362.

Meyerson, J., Thelin, S., Gordh, T., Karlsten, R. (2001). The incidence of chronic post-sternotomy pain after cardiac surgery–a prospective study. *Acta Anaesthesiol Scand* 45, 940–944.

Parkerson, G. R. Jr, Broadhead, W. E., Tse, C. K. (1990). The Duke Health Profile. A 17-item measure of health and dysfunction. *Med Care* 28, 1056–1072.

Parkerson, G. R., Broadhead, W. E., Tse, C. K. (1996). Anxiety and depressive symptom identification using the Duke Health Profile. *J Clin Epidemiol* 49, 85–93.

Pinto, P. R., McIntyre, T., Nogueira-Silva, C., Almeida, A., Araujo-Soares, V. (2012). Risk factors for persistent postsurgical pain in women undergoing hysterectomy due to benign causes: a prospective predictive study. *J Pain* 13, 1045–1057.

Roger, V. L., Go, A. S., Lloyd-Jones, D. M., Benjamin, E. J., Berry, J. D., Borden, W. B., Bravata, D. M., Dai, S., Ford, E. S., Fox, C. S.,

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Fullerton, H. J., Gillespie, C., Hailpern, S. M., Heit, J. A., Howard, V. J., Kissela, B. M., Kittner, S. J., Lackland, D. T., Lichtman, J. H., Lisabeth, L. D., Makuc, D. M., Marcus, G. M., Marelli, A., Matchar, D. B., Moy, C. S., Mozaffarian, D., Mussolino, M. E., Nichol, G., Paynter, N. P., Soliman, E. Z., Sorlie, P. D., Sotoodehnia, N., Turan, T. N., Virani, S. S., Wong, N. D., Woo, D., Turner, M. B. (2012). Heart disease and stroke statistics–2012 update: a report from the American Heart Association. *Circulation* 125, e2–e220.

Scott, L. E., Clum, G. A., Eoples, J. B. (1983). Preoperative predictors of postoperative pain. *Pain* 15, 283–293.

Silva, C., Pinto, E., Pereira, A. (2001). *Duke: Perfil de saúde Braga*. (Portugal: Universidade do Minho).

Simek, M., Nemec, P., Bruk, V., Gwozdziewicz, M., Fluger, I., Langova, K. (2007). Postoperative and midterm outcomes of minimally invasive and endoscopic great saphenous vein harvesting for coronary artery bypass grafting - a prospective analysis. *Thorac Cardiovasc Surg* 55, 428–432.

Steegers, M. A., van de Luijtgaarden, A., Noyez, L., Scheffer, G. J., Wilder-Smith, O. H. (2007). The role of angina pectoris in chronic pain after coronary artery bypass graft surgery. *J Pain* 8, 667–673.

Stoll, C., Schelling, G., Goetz, A. E., Kilger, E., Bayer, A., Kapfhammer, H. P., Rothenhausler, H. B., Kreuzer, E., Reichart, B., Peter, K. (2000). Health-related quality of life and post-traumatic stress disorder in patients after cardiac surgery and intensive care treatment. *J Thorac Cardiovasc Surg* 120, 505–512.

Sullivan, M. J. L., Bishop, S. R., Pivik, J. (1995). The Pain Catastrophizing Scale: development and validation. *Psychol Assess* 7, 524–532.

Taillefer, M. C., Carrier, M., Belisle, S., Levesque, S., Lanctot, H., Boisvert, A. M., Choiniere, M. (2006). Prevalence, characteristics, and predictors of chronic nonanginal postoperative pain after a cardiac operation: a cross-sectional study. *J Thorac Cardiovasc Surg* 131, 1274–1280.

Theunissen, M., Peters, M. L., Bruce, J., Gramke, H. F., Marcus, M. A. (2012). Preoperative anxiety and catastrophizing: a systematic review and meta-analysis of the association with chronic postsurgical pain. *Clin J Pain* 28, 819–841.

Thibault, P., Loisel, P., Durand, M. J., Catchlove, R., Sullivan, M. J. (2008). Psychological predictors of pain expression and activity intolerance in chronic pain patients. *Pain* 139, 47–54.

Weissman-Fogel, I., Granovsky, Y., Crispel, Y., Ben-Nun, A., Best, L. A., Yarnitsky, D., Granot, M. (2009). Enhanced presurgical pain temporal summation response predicts post-thoracotomy pain intensity during the acute postoperative phase. *J Pain* 10, 628–636.

Yarnitsky, D. (2015). Role of endogenous pain modulation in chronic pain mechanisms and treatment. *Pain* 156 (Suppl. 1), S24–S31.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. Duke Health Profile preoperatively and 3 months after cardiac surgery (N = 288).

Table S2. Duke Health Profile at 3 months and presence of persistent postoperative pain.

Table S3. Persistent Postoperative Pain at 3 months and its periodicity (N = 124).

Table S4. Persistent postoperative pain at 3 months after cardiac surgery and pain descriptors using Short-form McGill Pain Questionnaire (N = 124).

Table S5. Persistent postoperative pain at 3 months after cardiac surgery and DN4 descriptors (N = 124).

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Table S1 - Duke Health Profile preoperatively and three months after cardiac surgery (N total = 288)

Duke Health Profile [1]	**Preoperative** M [P_{25}-P_{75}]	**3 Months after** M [P_{25}-P_{75}]	**p ***
Physical Health Score	40 [20-50]	90 [70-90]	**< 0.001**
Mental Health Score	60 [60-80]	90 [90-100]	**< 0.001**
Social Health Score	100 [80-100]	100 [100-100]	**< 0.001**
General Health Score	66.7 [60-73]	93.3 [86.7-96.7]	**< 0.001**
Perceived Health Score	35 [25-40]	50 [45-70]	**< 0.001**
Self-Esteem Score	100 [80-100]	100 [90-100]	**< 0.001**
Anxiety Score	42 [25-50]	8.3 [0-12.5]	**< 0.001**
Depression Score	40 [30-50]	10 [0-20]	**< 0.001**
Anxiety-Depression Score	42.9 [28.6-50.0]	7.1 [0-14.3]	**< 0.001**
Pain Score	0 [0-50]	0 [0-50]	0.598
Disability Score	0 [0-50]	0 [0-0]	**< 0.001**

* obtained with Wilcoxon signed-rank test
M – Median ; P_{25} – Percentile 25; ; P_{75} – Percentile 75.
[1] For physical health, mental health, social health, general health, self-esteem, and perceived health, 100 indicates the best health status, and 0 indicates the worst health status. For anxiety, depression, anxiety-depression, pain, and disability, 100 indicates the worst health status and 0 indicates the best health status.

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Table S2 - Duke Health Profile at 3 months and presence of Persistent Postoperative Pain at 3 months

Duke Health Profile at 3 months [1]	**With PPP (N=124)** M [P_{25}-P_{75}]	**Without PPP (N=164)** M [P_{25}-P_{75}]	***p*** *
Physical Health Score	80 [60-90]	90 [80-90]	**< 0.001**
Mental Health Score	90 [70-100]	90 [90-100]	**0.001**
Social Health Score	100 [90-100]	100 [100-100]	**0.017**
General Health Score	90 [77-93]	97 [90-97]	**< 0.001**
Perceived Health Score	50 [50-100]	50 [50-100]	0.213
Self-Esteem Score	100 [90-100]	100 [90-100]	0.211
Anxiety Score	8 [8-25]	8 [0-8]	**< 0.001**
Depression Score	10 [0-20]	0 [0-0]	**0.033**
Anxiety-Depression Score	7 [0-21]	7 [0-7]	**< 0.001**
Pain Score	50 [50-50]	0 [0-0]	**< 0.001**
Disability Score	0 [0-0]	0 [0-0]	0.08

* obtained with Mann–Whitney U test
M – Median; P_{25} – Percentile 25; ; P_{75} – Percentile 75; PPP- Persistent Postoperative Pain
[1] For physical health, mental health, social health, general health, self-esteem, and perceived health, 100 indicates the best health status, and 0 indicates the worst health status. For anxiety, depression, anxiety-depression, pain, and disability, 100 indicates the worst health status and 0 indicates the best health status

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Table S3 – Persistent Postoperative Pain at three months and its periodicity (N total = 124)

	N (%)
"During the past 24 hours, how long was your spontaneous pain present?"	
Permanently	33 (27)
Between 8 and 12 hours	36 (29)
Between 4 and 7 hours	41 (33)
Between 1 and 3 hours	13 (10)
Less than 1 hour	1 (1)
"We wish to know if you have brief attacks of pain. During the past 24 hours, how many pain attacks have you had?"	
More than 20	4 (3)
Between 11 and 20	5 (4)
Between 6 and 10	25 (20)
Between 1 and 5	66 (54)
Absent	24 (19)

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Table S4 – Persistent postoperative pain at three months after cardiac surgery and pain descriptors using Short-form McGill Pain Questionnaire (N total = 124)

	None (%)	Mild (%)	Moderate (%)	Severe (%)
1. Throbbing	76.6	15.3	8.1	0.0
2. Shooting	100.0	0.0	0.0	0.0
3. Stabbing	70.1	10.5	19.4	0.0
4. Sharp	15.3	41.1	39.6	4.0
5. Cramping	96.0	0.0	0.0	4.0
6. Gnawing	23.4	41.1	35.5	0.0
7. Hot-Burning	58.9	18.5	15.3	7.3
8. Aching	24.2	48.4	23.4	4.0
9. Heavy	92.0	4.0	0.0	4.0
10. Tender	24.2	41.1	20.2	14.5
11. Splitting	92.7	3.2	4.0	0.0
12. Tiring-Exhausting	84.7	11.3	4.0	0.0
13. Sickening	100.0	0.0	0.0	0.0
14. Fearful	80.6	11.3	8.1	0.0
15. Punishing-Cruel	81.4	10.5	8.1	0.0

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Table S5 – Persistent postoperative pain at three months after cardiac surgery and DN4 descriptors (N total = 124)

Result of the sum of DN4	N (%)	Cumulative %
0	19 (15.3)	15.3
1	15 (12.1)	27.4
2	28 (22.6)	50.0
3	32 (25.8)	75.8
4	20 (16.1)	91.9
5	10 (8.1)	100.0
6	0 (0.0)	100.0
7	0 (0.0)	100.0

Presence of DN4 descriptors (%)	Yes	No
Burning	17.7	82.3
Painful cold	15.3	84.7
Electric shocks	19.4	80.6
Tingling	46.8	53.2
Pins and needles	77.4	22.6
Numbness	31.5	68.5
Itching	31.5	68.5

3.2. Paper B

Systematic Review and Meta-Analysis

PAIN

Persistent postoperative pain after cardiac surgery: a systematic review with meta-analysis regarding incidence and pain intensity

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Abstract

Persistent postoperative pain (PPP) has been described as a complication of cardiac surgery (CS). We aimed to study PPP after CS (PPPCS) by conducting a systematic review of the literature regarding its incidence, intensity, location, and the presence of neuropathic pain, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. The review comprised 3 phases: a methodological assessment of 6 different databases identifying potential articles and screening for inclusion criteria by 2 independent reviewers; data extraction; and study quality assessment. Meta-analysis was used to estimate the pooled incidence rates using a random effects model. We have identified 442 potentially relevant studies through database searching. A total of 23 studies (involving 11,057 patients) met our inclusion criteria. Persistent postoperative pain affects 37% patients in the first 6 months after CS, and it remains present more than 2 years after CS in 17%. The reported incidence of PPP during the first 6 months after CS increased in recent years. Globally, approximately half of the patients with PPPCS reported moderate to severe pain. Chest is the main location of PPPCS followed by the leg; neuropathic pain is present in the majority of the patients. This is the first systematic review and meta-analysis to provide estimates regarding incidence and intensity of PPPCS, which elucidates its relevance. There is an urgent need for adequate treatment and follow-up in patients with PPPCS.

Keywords: Cardiac surgery, Incidence, Meta-analysis, Neuropathic pain, Pain intensity, Persistent postoperative pain, Systematic review

1. Introduction

1.1. Rationale

Crombie et al.[19] identified injury and surgery as major risks for chronic pain in 1998. This finding has led to a dramatic increase of interest in this subject. The International Association for the Study of Pain defines persistent postoperative pain (PPP) as pain that develops after surgical intervention and lasts at least 3 months, with other causes of pain excluded.[40] Depending on the definitions applied and types of surgeries performed, data on PPP incidence vary significantly (between 5% and 50%).[41] The consequences of PPP are significant, not only in terms of suffering and reduced health-related quality of life (HRQL) for the individual patient, but also regarding the subsequent costs to the health care and social support systems.[6,67]

Persistent postoperative pain may be somatic, visceral, or neuropathic,[35] and the prevalence of neuropathic pain (NP) or pain with a neuropathic component was reported to be higher in patients with PPP after thoracic (including sternotomy) and breast surgeries (approximately 67%).[35] Cardiac surgery (CS), such as coronary artery bypass grafting (CABG) and heart valve replacement (HVR), ranks among the most frequently performed interventions worldwide.[62] In 1989, Defalque and Bromley[21] described for the first time a pain syndrome called poststernotomy neuralgia. Since then, several studies were conducted and PPP has been described as an important complication of CS.[16,30,53] However, the precise magnitude of the incidence of PPP after CS (PPPCS) is still under debate, and this limits the perception of the true dimension of the problem. Patients experiencing PPPCS report a significantly lower physical and mental health status compared with patients without it.[10,29,71] It is, therefore, important to provide a more precise measure of the incidence of PPPCS and its properties, namely intensity, location, and NP presence, to allow appropriate resource allocation and research planning, and to inform patient decisions about treatment.[17] Previous reviews of PPPCS have combined narrative review with expert opinion, with potential risk of bias.[16,30,53] Therefore, firm evidence about the incidence of PPPCS and its properties is

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.painjournalonline.com).

PAIN 158 (2017) 1869–1885

http://dx.doi.org/10.1097/j.pain.0000000000000997

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still lacking. Here, we present what we believe to be the first systematic review and meta-analysis regarding PPPCS' incidence and intensity.

1.2. Objectives

We aimed to conduct a systematic review of the literature about PPPCS' incidence, intensity, location, and the presence of NP. Moreover, we have analysed whether the incidences of PPPCS have changed over time. Consequently, our aim was to contribute to improved knowledge of PPPCS and a better understanding of PPP.

2. Methods

2.1. Protocol and registration

This systematic review was developed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[57] The systematic review protocol was registered previously in the PROSPERO International Prospective Register of Systematic Reviews (ID: CRD42014009775).

2.2. Eligibility criteria

We have included quantitative epidemiologic and interventional studies that have reported on the incidence and/or intensity of PPPCS. Studies could have cross-sectional, cohort (prospective and retrospective) or randomized controlled trial (RCT) designs in patients of any age. Included studies had to have similar definition of PPPCS, which is persistent pain after CS of greater than 3 months' duration, with other causes of pain excluded.[40] Studies reporting only on specific subgroups of patients were excluded. Finally, we did not impose any language or follow-up time restrictions (ie, studies of all durations were included).

To be included, the studies had to examine our primary or secondary outcomes of interest. The primary outcome was as follows: proportion of participants reporting any pain at the anatomical site of the procedure or pain referred to the surgical site, or both, 3 months after the procedure (with other causes of pain excluded). Our secondary outcomes included the number of patients reporting moderate or severe pain at the anatomical site of the procedure 3 months after the procedure, pain location, and the presence of NP.

2.3. Information sources

We have conducted a systematic search in the electronic databases MEDLINE, Web of Science, SCOPUS, Cochrane Central Register of Controlled Trials (CENTRAL), Google Scholar, and China National Knowledge Infrastructure through 1998 to present (search date: November 2016). In addition, we have noted the citations in the retrieved studies and recent reviews to avoid missing relevant studies in this field. Abstract books or e-books and CD-ROMs from 5 annual scientific meetings (European Society of Anaesthesiology, American Society of Anesthesiologists, IASP, and European Pain Federation and European Association for Cardio-Thoracic Surgery) have been searched for relevant abstracts regarding the last 5 years. The online registry www.clinicaltrials.gov was searched and, in addition, individual researchers, research organisations, pharmaceutical companies, and experts working in the field were contacted for unpublished and on-going trials for studies not retrieved by our search. No language restrictions were applied.

2.4. Search

In conjunction with a researcher with experience in systematic reviews (L.A.), we developed a systematic search strategy with structured terms of Medical Subject Headings (MeSH). The search covered the following themes: PPP, CS, Incidence, Intensity, and NP. Searches included studies from 1998 to November 2016. The search strategy for MEDLINE in PubMed, which was adjusted to search for eligible studies in other databases as well, is described in detail in Supplementary Material 1 (available online at http://links.lww.com/PAIN/A450).

2.5. Study selection

To ensure reliability, a training exercise was conducted before screening. Afterward, 2 reviewers (L.G.-P. and P.R.) screened, separately and independently, the titles and abstracts of studies identified from initial searches. A standard screening checklist based on the eligibility criteria mentioned previously was used for each study. Studies that did not meet the criteria according to the titles or abstracts were excluded. Full-text versions of the remaining studies, including those that were potentially eligible studies and uncertain, were retrieved for a second review by 2 reviewers (L.G.-P. and P.R.), independently, to determine the eligibility. Disagreements regarding study eligibility were discussed among reviewers. If consensus could not be reached, a third reviewer (L.A.) made the ultimate decision. For studies without sufficient information to evaluate their eligibility, we contacted the study authors through email to obtain their clarifications. The studies were excluded if there was insufficient information after this contact. If more than 1 publication reported the results from the same study population, we chose the publication with the largest sample size. The abstracts that were published in academic conferences were evaluated case by case, and we contacted the study authors for details if necessary. The abstracts or full texts of studies not published in English were translated.

2.6. Data collection process

Studies obtained through the search strategy were imported into EndNote X6, and duplicates were deleted. Reasons for exclusion were recorded. The same 2 reviewers (L.G.-P. and P.R.) extracted data from eligible studies using a predesigned and pilot tested electronic data extraction form, independently. Disagreements regarding the data extraction between authors were resolved by discussion. If consensus could not be reached, a third author (L.A.) would review the study and arbitrate. When data were missing for synthesis or assessment of study quality, we attempted to contact the study authors through email at least 2 times. The study was excluded if there was still insufficient data following this procedure.

2.7. Data items

Data were extracted using a standardised data extraction form, including authorship, study's country, study's title, study's design, sample size at baseline and at follow-up, pain's assessment time, inclusion criteria, exclusion criteria, outcomes evaluated, study population characteristics, and interventions/control applied. Data on the following relevant clinical outcomes were extracted:

2.7.1. Primary outcome

1. Persistent postoperative pain's incidence after CS (at 3 to less than 6 months, 6 to less than 12 months, 12 to less than 24 months, and at least 24 months after CS).

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2.7.2. Secondary outcomes

1. Persistent postoperative pain after CS' intensity was rated either using the Numerical Rating Scale (NRS; 0-10, 0-100), the Visual Analogue Scale (VAS; 0-10 cm, 0-100 mm), or the Verbal Rating Scale (VRS). We made simplifications to obtain the proportion of patients with PPPCS reporting at least 4/10 or moderate to severe pain.
2. Persistent postoperative pain's location.
3. The presence of NP in patients with PPPCS.

2.8. Risk of bias in individual studies

The quality of studies was assessed independently by 2 reviewers (L.G.-P. and P.R.) based on the established criteria developed from guidelines on the evaluation of incidence studies.[48] Studies were given a score of 0 to 8 based on 8 criteria relating to the rigor of the clinical assessment, the quality of the statistical analysis, and the extent to which the sample population represented the population at large. Disagreement between authors in respect of study quality assessment was resolved by discussion. The levels of assessment items were displayed for each eligible study. The studies with quality assessment score >5 were considered as having low risk of bias.

2.9. Summary measures

Regarding PPPCS incidence, we have used proportions and corresponding 95% confidence intervals (CIs) or the raw data that could be used to calculate the estimate. The denominator used to calculate the incidence of PPPCS in each study was the total number of patients who completed each study. Regarding PPPCS intensity, we noted whether its assessment was for all patients or only for patients with PPP. We only analysed those data recorded for patients with PPPCS. For continuous data reported in studies using VAS 0 to 10 cm, VAS 0 to 100 mm, or NRS 0 to 10, we used average scores. We also calculated the proportion of patients with PPPCS who reported moderate to severe pain for each study reporting PPP intensity, when possible.

2.10. Synthesis of results

If studies could be combined, meta-analysis of the incidence of PPPCS (proportions, binominal rate) was performed using the DerSimonian and Laird method of moments assuming the random effects model. We used the random-effects model to analyse the data according to the assumption that the effect sizes vary from study to study because of clinical heterogeneity between the analysed patient groups, interventions, and clinical settings.[9] Regarding the outcome "PPPCS intensity," many of the selected studies reported pain intensity data that were recorded for all patients (patients with PPP and without PPP). This underestimates the true intensity of pain, as patients who did not suffer from pain lowered the overall pain intensity. To overcome this underestimation, we extracted data for each study to achieve the pain intensity in patients with PPPCS, and by a combination of similar pain assessments, we were able to identify the proportion of patients with moderate to severe pain for each study, which was defined as pain at least 4/10. Therefore, we calculated the incidences (untransformed proportions) of patients experiencing moderate or severe pain at the different time points postoperatively using the DerSimonian and Laird method of moments assuming the random-effects model. The untransformed proportions and the corresponding 95% CIs were reported. Forest plots of the untransformed proportions were presented. Heterogeneity between studies was examined visually, and then using the χ^2 test for heterogeneity ($P < 0.1$), and quantified by the Higgins I^2 statistic. Furthermore, we reported statistical heterogeneity using the I^2 statistics. Briefly, statistical heterogeneity (inconsistency) was classified as low, moderate, or high in accordance to I^2 values of 25%, 50%, and 75%, respectively. When there were no quantitative data that could be combined, a qualitative synthesis was conducted.

2.11. Additional analyses

Subgroup and sensitivity analyses were performed to study the reasons for existing statistical heterogeneity and to test the robustness of the overall estimate, respectively. We performed subgroup analysis to consider the magnitude of heterogeneity introduced by the study design (RCTs vs observational studies) and study's quality (quality assessment score >5). Data were analysed using the random effects model and heterogeneity I^2 statistics to compare the subgroups. A sensitivity analysis was conducted to identify potential outlying studies. In this regard, an additional pooled effect estimate and 95% CI were generated upon removing exactly one study from the original full set of included studies—leave one-out meta-analysis. This shows how each individual study affects the overall estimate of the rest of the studies. An individual study was considered an outlier if upon removal, the effect estimate for the restricted set differed significantly from that of the full set of included studies. To investigate whether the incidence rates of PPP were changing over time, we performed a random effects meta-regression using the publication year as a covariate.

2.12. Software

Meta-analyses including subgroup analyses, meta-regression analyses, and sensitivity analyses were performed using the open source software OpenMeta (Analyst) (Center for Evidence-based Medicine, Brown University, Providence, RI), http://www.cebm.brown.edu/openmeta/download.html.[81]

3. Results

3.1. Study selection

We identified 442 potentially relevant studies through database searching and 9 through other sources. After removing the duplicates and screening the titles and abstracts, we retrieved 51 articles for further full-text screening. A total of 23 studies (involving 11,057 patients)[5,10,12,15,18,26,29,31,34,37,39,44,45,51,55,60,68,71,73,75–78] met our inclusion criteria and 28 were excluded.[2,4,7,8,11,14,22,36,42,43,46,49,50,52,54,56,58,59,61,63–65,69,79,80,83,84,86] **Figure 1** illustrates the study selection with a flow diagram according to the PRISMA statement.[57]

3.2. Study characteristics

Of the 23 studies included, 10 were observational prospective studies,[15,29,31,34,37,44,55,68,76,77] 6 were observational retrospective studies,[10,18,26,39,51,78] 3 were cross-sectional studies,[12,45,71] and 4 were RCTs.[5,60,73,75] All RCTs were double blinded and have described a sample size calculation. Concerning the types of CS performed, 6 studies concern to CABG solely,[12,26,39,44,68,75] 1 concerns to HVR solely,[37] 1 concerns to pediatric CS through median sternotomy (closure of atrial and ventricular septum defects, correction of Tetralogy of Fallot, arterial switch, and Ross

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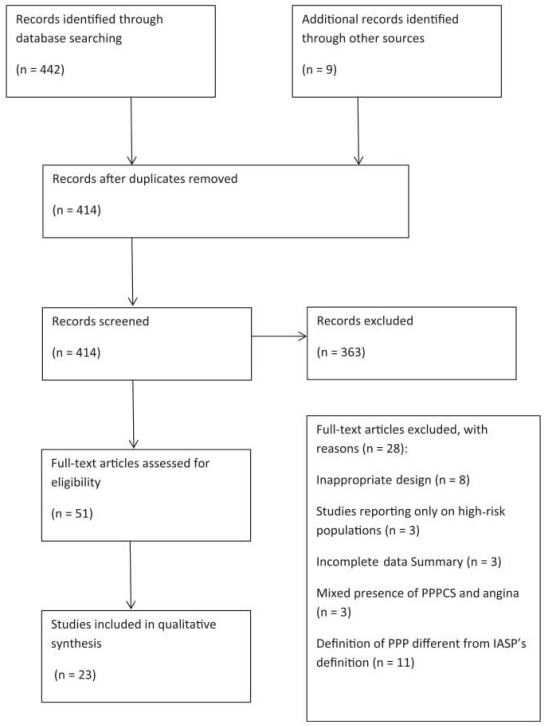

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 flow diagram. PPPCS, persistent postoperative pain after cardiac surgery; PPP, persistent postoperative pain.

operations),[45] and the other 15 studies combine in each study various types of procedures accomplished through median sternotomy (comprising CABG solely, or HVR solely, or CABG with HVR).[5,10,15,18,29,31,34,51,55,60,71,73,76–78] All studies included adult patients, with the exception of one.[45] **Table 1** presents a summary of the general characteristics (type of study, study size, population, intervention, outcomes, and follow-up period) of each study.

3.3. Risk of bias within studies

A quality assessment was performed for each study based on the criteria developed from guidelines on the evaluation of incidence studies.[48] Studies were given a score of 0 to 8 based on the degree to which they fulfilled 8 criteria relating to the rigor of the clinical assessment, the quality of the statistical analysis, and the extent to which the sample population represented the population at large. Studies with quality assessment score >5 were considered as having low risk of bias and we have performed a subgroup analysis in these studies. Average quality assessment score was 6.2, with only 2 studies scoring <4 (for the detailed analysis see Supplementary Material 2, available online at, http://links.lww.com/PAIN/A450).

3.4. Persistent postoperative pain after cardiac surgery incidence

Four studies (n = 2041)[10,18,26,45] reported PPP assessment at widely variable time intervals, which precluded us to cluster it in time frames. Regarding the remaining studies, we pooled 7 (n = 2188),[5,15,34,51,60,68,75] 8 (n = 3645),[5,12,15,29,34,51,73,76] 8 (n = 3089),[5,15,29,37,44,55,77,78] and 5 (n = 2857)[15,31,39,51,71] studies reporting PPP at 3 to less than 6 months, 6 to less than 12 months, 12 to less than 24 months, and at least 24 months after CS, respectively, in the meta-analysis of the incidences of PPPCS. Of these studies, 1^{15} reported pain at all 4 time points, $2^{5,51}$ reported pain at 3 time points, $2^{29,34}$ reported at 2 time points, and $14^{12,31,37,39,44,55,60,68,71,73,75–78}$ reported only once. Ratios of RCTs to observational studies of 3/4, 2/6, 1/7, and 0/5 were observed in all studies assessing PPPCS at 3 to less than 6, 6 to less than 12, 12 to less than 24, and at least 24 months, respectively. We were unable to estimate the PPPCS incidence according the subtype of surgery performed because the majority of the studies present combined data. When the authors of the included studies have tested the influence of subtype of surgery with PPP, they did not find any association,[10,15,29,51,55,71,76,77] except one study where HVR was associated with lower rates of PPP,[34] and another where CABG with internal thoracic artery grafts was associated with higher rates of PPP.[18]

Table 2 presents incidences of PPPCS reported in each study according to time frames (results of individual studies). The results of the meta-analysis and additional analysis performed at each time frame are summarized in **Table 3**. Forest plots of the meta-analyses performed are presented in **Figure 2** and those concerning additional analyses are shown in Supplementary Material 3 (available online at, http://links.lww.com/PAIN/A450). The overall estimated incidence of PPPCS ranged from 37% (3 to less than 6 months after CS) to 17% (at least 24 months after CS). Regarding the subgroup of studies with low risk of bias (quality assessment score >5), the incidence of PPPCS ranged from 40% (3 to less than 6 months after CS) to 17% (at least 24 months after CS). Concerning the type of study, the observational studies subgroup presented higher incidences compared with RCTs (**Table 3**).

The proportion of patients with PPPCS under treatment was absent from all included studies, except in 1 study[34] that addressed this issue and reported that 16% of patients with PPPCS were under treatment and follow-up.

To assess whether the incidences of PPPCS were changing over time, we performed a random effects meta-regression using the publication year of the study as a predictor. All studies reporting PPP incidences after CS were published after 2001. Therefore, the time span is mainly restricted to the previous 15 years. Using the publication year as a predictor in this analysis, we detected a positive trend over time on the incidence rates at 3 to less than 6 months after CS (**Fig. 3A**). We did not detect any trend over time on the incidence rates at 6 to less than 12 months or 12 to less than 24 months (**Fig. 3B, C**), but a negative trend over time was found on the incidence rates at least 24 months after CS (**Fig. 3D**).

3.5. Persistent postoperative pain after cardiac surgery intensity

We identified 17 studies which reported pain intensity assessment for PPPCS.[5,15,18,26,29,31,34,37,39,44,51,55,60,71,73,77,78] In total, 5 studies reported intensity of PPPCS at 3 to less than 6 months,[5,15,34,51,60] 4 at 6 to less than 12 months,[5,15,73,77] 8 at 12 to less than 24 months,[5,15,29,37,44,51,55,78] and 5 studies reported at least 24 months[15,31,39,51,71] after CS. Two studies[18,26] reported intensity of PPPCS in a variable time range, which does not allow grouping it in the established time frames. **Table 4** summarizes the data regarding the intensity of PPPCS reported in

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Table 1

Studies characteristics.

Study	Country	Type of study	Sample size (Baseline; Follow-up/analyzed)	Pain's assessment time	Population and selection criteria	Exclusion Criteria	Outcomes	Intervention/Control
Bjornnes 2016	Norway	RCT	n = 416; n = 349.	3; 6; 12 mo.	Adult patients scheduled for elective CABG and/or HVR.	More than 12 h spent in the intensive care unit, not anticipated to be at home to receive the follow-up telephone call at 10 d after CS or predicted to be unable to care for themselves after hospital discharge.	Primary outcome: worst pain intensity at rest in the previous 24 h measured using an 11-point NRS grading system. Secondary outcomes: pain-related interference with activities, patients' concerns about pain and pain medication and self-report of pharmacological management in the previous week. Additional exploratory data included assessing pain location and pain relief from pain treatments in the previous 24 h.	Standard discharge care plus a pain management education intervention/ standard discharge care.
Bruce 2003	Scotland	Observational retrospective	n = 1195; n = 1080.	28 mo ± 15.3 (mean ± SD).	Adult patients scheduled for elective CABG and/or HVR.	None stated.	Frequency, location, and nature of chronic pain after median sternotomy; impact of chronic pain on quality of life; possible risk factors associated with the development of chronic pain after CS.	No intervention.
Carle 2006	United Kingdom	Cross-sectional study	n = 100; n = 79.	8-10 mo.	Adult patients scheduled for elective CABG.	Patients with incomplete data.	PPP presence and its characteristics.	No intervention.
Choiniere 2014	Canada	Observational prospective	n = 1247; n = 1054 at 3 mo, 1023 at 6 mo, 1011 at 12 mo and 976 at 24 mo.	3; 6; 12; 24 mo.	Adult patients scheduled for elective CABG and/or HVR who had never undergone thoracotomy or mastectomy.	Patients who could not complete the questionnaires because of physical or mental incapacity or had insufficient knowledge of French or English.	Presence of PPP; severity of pain in terms of intensity with NRS.	No intervention.
Costa 2015	Brazil	Observational retrospective	n = 453; n = 453.	From 6 to 279 mo; 58 mo (mean).	Patients undergoing CS through sternotomy (HVR, CABG, interatrial communication closure, aortic surgery, left ventricle aneurysm repair, myxoma resection).	Patients with less than 6 mo after surgery and patients with connective tissue disorders.	Presence of chest pain, its characteristics, and intensity ranging from 1 to 10.	No intervention.
Eisenberg 2001	Israel	Observational retrospective	n = 504; n = 387.	16.1 mo ± 6.3 (mean ± SD).	Adult patients scheduled for elective CABG.	Inability to contact patients due to either change in address or language difficulties.	Presence of chest wall PPP. Main outcome measures included a preliminary pain questionnaire, pain localization on a body scheme, a 5-point verbal scale and the VAS for measuring pain intensity.	No intervention.
Gjeilo 2010	Norway	Observational prospective	n = 534; n = 462 at 6 mo, and 465 at 12 mo.	6 and 12 mo.	All patients undergoing CS.	Emergency surgery; lack of ability to write or read Norwegian; cognitive impairments or mental problems; poor physical health	Presence of PPP and HRQL at 6 and 12 mo.	No intervention.

(continued on next page)

Table 1 (*continued*)

Study	Country	Type of study	Sample size (Baseline; Follow-up/analyzed)	Pain's assessment time	Population and selection criteria	Exclusion Criteria	Outcomes	Intervention/Control
						condition or refusal to participate.		
Gjeilo 2016	Norway	Observational prospective	n = 454; n = 373.	5 y.	All patients undergoing CS.	Emergency surgery; lack of ability to write or read Norwegian; cognitive impairments or mental problems; poor physical health condition or refusal to participate.	Presence of PPP, its characteristics and HRQL.	No intervention.
Guimaraes-Pereira 2016	Portugal	Observational prospective	n = 310; n = 288.	3 and 6 mo.	Adult patients scheduled for elective CABG and/or HVR.	Pregnancy or breast-feeding, reoperation and non-Portuguese speaking patients.	PPP presence and its characteristics, and HRQL after surgery.	No intervention.
Jensen 2004	Denmark	Observational prospective	n = 53; n = 49.	18 mo.	Patients scheduled for elective HVR.	Acute operation, re-VR and combination surgery (HVR plus CABG).	Acute pain evaluation, complications related to the use of thoracic epidural analgesia, and incidence of chronic pain related to the sternotomy and its severity.	Thoracic epidural analgesia/ Conventional analgesia.
Kalso 2001	Finland	Observational retrospective	n = 791 (71 thymectomy and 720 CABG); n = 687 (62 thymectomy and 625 CABG).	Thymectomy 6 mo to 12 y vs CABG 24 to 36 mo.	Patients who underwent surgery through sternotomy, ie, either a thymectomy operation for myasthenia gravis or CABG.	None stated.	Primary outcome measure: presence of chronic pain related to sternotomy operations at the time of the interview. Pain characteristics and risk factors for chronic poststernotomy pain were also evaluated.	No intervention.
Lahtinen 2006	Finland	Observational prospective	n = 230; n = 186.	12 mo.	Patients with age <70 scheduled to undergo elective CABG with CPB.	Patients who were unable to express themselves verbally or who were unable to fill out the questionnaires were excluded.	Presence of PPP and its characteristics.	No intervention.
Lauridsen 2014	Denmark	Cross-sectional study	n = 171; n = 121.	4 (0.8-5.1) y.	Children who had undergone CS via median sternotomy.	Cognitive impairment or other severe systemic disease.	Presence of PPP and its characteristics.	No intervention.
Marcassa 2015	Italy	Observational retrospective	n = 972; n = 945 (3 groups: 3 mo 313, 1 y 313 and 3 y 319).	3 mo, 1 y and 3 y.	Adult patients scheduled for elective CABG and/or HVR.	None stated.	Presence of PPP and its characteristics.	No intervention.
Meyerson 2001	Sweden	Observational prospective	n = 349; n = 318.	13 mo ± 0.11 (mean ± SD); range 9-18 mo.	Adult patients scheduled for elective CABG and/or HVR.	Patients not willing to participate, unable to be contacted, or medical reasons.	Presence of PPP. Pain characteristics, such as severity.	No intervention.
Pesonen 2011	Finland	RCT	n = 70; n = 57.	3 mo.	Patients with age >74 scheduled for elective CABG and/or HVR with CPB.	LVEF <30%; renal failure (plasma creatinine level >150 μmol-L^{-1}); liver disease; CHF; type 1 diabetes mellitus; neurological disease; preoperative infections; BMI >35 Kg/m^2; psychiatric disease or alcohol abuse; chronic pain syndrome; recent use of gabapentinoids.	Incidence of PPP (3 mo after surgery); Consumption of oxycodone; Postoperative confusion; side-effects of opioids.	150 mg pregabalin before operation and 75 mg pregabalin twice daily for 5 postoperative days/placebo.

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Table 1 (*continued*)

Study	Country	Type of study	Sample size (Baseline; Follow-up/analyzed)	Pain's assessment time	Population and selection criteria	Exclusion Criteria	Outcomes	Intervention/Control
Setala 2016	Finland	Observational prospective	n = 100; n = 87.	4 to 6 mo.	Adult patients scheduled for elective CABG.	Previous CS and lack of cooperation.	Presence of PPP.	No intervention.
Taillefer 2006	Canada	Cross-sectional study	n = 736; n = 564.	29.9 mo ± 10.5 (mean ± SD); range 13.5-49.4 mo.	Patients randomly selected from a computerized list of individuals who survived a first elective CABG and/or HVR.	Patients who underwent an urgent operation, those who could not be reached, and those who died after their hospitalization.	Pain presence, pain characteristics, HRQL and psychologic well-being, 1 y or more after surgery.	No intervention.
Turan 2015	4 Countries	RCT	n = 1043; n = 1023.	1 and 6 mo.	Adult patients undergoing elective, urgent, or emergent CS; undergoing CBP with a EuroSCORE >6.	Patients taking systemic steroids or who will undergo planned systemic steroid therapy in the immediate postoperative period; history of bacterial or fungal infection in the last 30 d; allergy, or intolerance to corticosteroids.	Primary outcomes were incisional pain assessment using an 11-point verbal response scale. Secondarily, evaluate the potential risk factors for incisional pain at 6 mo: smoking, age, sex, preoperative history of pain, BMI, and deep sternal wound infection.	Methylprednisolone 500 mg (250 mg during anesthetic induction + 250 mg on CPB initiation)/placebo solution, given comparably.
Ucak 2011	Turkey	RCT	n = 40; n = 40.	3 mo.	Patients with age <80 scheduled for elective CABG surgery with CPB.	LVEF <50%; obstructive lung disease; renal insufficiency (preoperative creatinine level >2.0 mg/dL); known allergy to any of the study medications; height <145 cm; weight >100 kg; history of alcohol or drug abuse; neurologic dysfunction.	Assessment of postoperative pain at 1 mo and at 3 mo.	Oral gabapentin 1.2 g/d, before and 2 d after surgery/ placebo capsule instead.
van Gulik 2011	The Netherlands	Observational prospective	n = 143; n = 120.	10-12 mo.	Adult patients admitted to the ICU after CS via sternotomy (CABG and/or HVR, and/or ascending aorta surgery).	None stated.	Presence of PPP at 10 to 12 mo.	No intervention.
van Gulik 2012	The Netherlands	Observational prospective	n = 120; n = 90.	13 mo.	Adult patients with age <85 admitted to the ICU after CS via sternotomy (CABG and/ or VR, and/or ascending aorta surgery).	Pregnancy or breast-feeding; inability to communicate in either Dutch or English; coma or brain death; known morphine or acetaminophen (paracetamol) allergy.	Presence of PPP after 1 y.	No intervention.
van Leersum 2010	The Netherlands	Observational retrospective	n = 1097; n = 631.	19.1-19.7 mo.	Adult patients who underwent open heart surgery via median sternotomy.	Patients who underwent multiple sternotomies (either before the cohort started or due to direct postoperative bleeding).	Pain presence and location after surgery.	No intervention.

BMI, body mass index; CABG, coronary artery bypass grafting; CHF, congestive heart failure; CPB, cardiopulmonary bypass; CS, cardiac surgery; HRQL, health-related quality of life; HVR, heart valvular replacement; ICU, intensive care unit; LVEF, left ventricular ejection fraction; mo, month; N, number; NRS, Numerical Rating Scale; PPP, persistent postoperative pain; RCT, randomized controlled trial; VAS, Visual Analog Scale.

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Table 2

Study data for the estimation of the incidences of PPPCS at 3 to less than 6, 6 to less than 12, 12 to less than 24, and at least 24 mo after CS.

Source	3 to <6 mo		6 to <12 mo		12 to <24 mo		≥24 mo		Variable range	
	Rate (%)	Total (n)	Rate (%)	Total (n)	Rate (%)	Total (n)	Rate (%)	Total (n)	Rate (%)	Total (n)
Bjornnes et al. (2016)	39	349	35	337	29	339				
Bruce et al. (2003)									36	1080
Carle et al. (2009)			46	79						
Choiniere et al. (2014)	40	1054	21	1023	17	1011	10	976		
Costa et al. (2015)									39	453
Eisenberg et al. (2001)									56	387
Gjeilo et al. (2010)			15	462	15	465				
Gjeilo et al. (2016)							4	373		
Guimaraes-Pereira et al. (2016)	43	288	40	288						
Jensen et al. (2004)					33	49				
Kalso et al. (2001)							28	625		
Lahtinen et al. (2006)					58	186				
Lauridsen et al. (2014)									52	121
Marcassa et al. (2015)	35	313	27	313			20	319		
Meyerson et al. (2001)					28	318				
Pesonen et al. (2011)	16	57								
Setala et al. (2016)	44	87								
Taillefer et al. (2006)							23	564		
Turan et al. (2015)			16	1023						
Ucak et al. (2011)	40	40								
van Gulik et al. (2011)			35	120						
van Gulik et al. (2012)					20	90				
van Leersum et al. (2010)					36	631				

PPPCS, persistent postoperative pain after cardiac surgery.

each study (results of individual studies). We detected large heterogeneity concerning recording and reporting of the PPPCS assessment, including recording time, pain rating scales, rating conditions, pain assessment group, and summary measures. **Table 3** summarizes the meta-analysis results regarding the intensity of PPPCS at each time frame, and **Figure 4** presents the respective forest plots. Supplementary Material 4 presents the data used for their estimation (available online at, http://links.lww.com/PAIN/A450). Regarding average pain (**Fig. 4A–C**), moderate to severe pain was estimated to be present in 40% (3 studies,[15,34,51] n = 658), 43% (4 studies,[15,29,51,78] n = 529), and 50% (5 studies,[15,18,31,39,71] n = 588), at 3 to less than 6 months, at 12 to less than 24 months, and at least 24 months after CS, respectively, in patients presenting with PPPCS. At 6 to less than 12 months, we were unable to perform the estimation of pain intensity, as only 1 study[15] reported it in this time frame. Regarding worst pain (**Fig. 4D, E**), moderate to severe pain was estimated to be present in 49% (3 studies,[29,51,55] n = 224), and 53% (2 studies,[31,71] n = 143) at 12 to less than 24 months and at least 24 months after CS, respectively, in patients presenting with PPPCS. We were unable to perform the estimation of worst pain for the other time frames. As only a minority of studies reported intensity of pain as continuous data, either on a VAS 0 to 100 mm or NRS 0 to 10, we were not able to perform a meta-analysis for continuous pain data.

3.6. Persistent postoperative pain after cardiac surgery location

Twelve studies[5,10,26,29,31,34,44,51,68,71,77,78] reported the location of PPPCS. Five studies[5,10,26,34,44] assessed pain location on a body outline diagram and 7 studies[29,31,51,68,71,77,78] assessed it with a question regarding pain location. Only 1 study[78] added a physical examination. The main location reported was the chest, in the sternum more specifically, followed by the limbs. Between 8%[68] and 75%[10] of the patients with PPPCS reported pain in the leg. Some of the patients had pain at more than 1 site, such as in the sternum and leg simultaneously,[5,10,26,29,31,34,44,51,71,78] and others reported pain in areas not linked with the surgical wound, such as head, neck, shoulders, and back.[29,31,68,71,78] Supplementary Material 5 resumes the studies data regarding pain location (available online at, http://links.lww.com/PAIN/A450).

3.7. Neuropathic pain in persistent postoperative pain after cardiac surgery

Five studies[26,34,39,45,73] addressed heterogeneously the issue of NP in patients with PPPCS. Two of them[34,73] used validated questionnaires to identify it, 1[39] reported NP descriptors, and 2[26,45] applied quantitative sensory test. Eisenberg et al.[26] performed physical examination to evaluate hypoesthesia or

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Table 3

Estimated incidences of PPPCS and its intensity at 3 to less than 6, 6 to less than 12, 12 to less than 24, and at least 24 mo after CS.

	3 to <6 mo	6 to <12 mo	12 to <4 mo	≥24 mo
PPPCS incidence				
All studies	37% (CI: 32%-42%) I^2 = 79%	29% (CI: 22%-35%) I^2 = 95%	29% (CI: 21%-38%) I^2 = 97%	17% (CI: 8%-25%) I^2 = 98%
Leave-one-out meta-analysis	36%-40%	27%-31%	25%-31%	14%-20%
Studies with quality assessment score > 5 subgroup meta-analysis	40% (CI: 37%-42%) I^2 = 11%	27% (CI: 20%-33%) I^2 = 95%	29% (CI: 20%-38%) I^2 = 97%	17% (CI: 8%-25%)* I^2 = 98%
Observational studies subgroup meta-analysis	40% (CI: 37%-43%) I^2 = 32%	30% (CI: 22%-38%) I^2 = 94%	29% (CI: 20%-39%) I^2 = 97%	17% (CI: 8%-25%) * I^2 = 98%
RCTs subgroup meta-analysis	31% (CI: 15%-48%) I^2 = 89%	26% (CI: 7%-44%) I^2 = 98%	Nonapplicable (only 1 study[3])	Nonapplicable (no study)
PPPCS intensity (patients with PPPCS reporting moderate to severe pain)				
Regarding their average pain	40% (CI: 34%-46%) I^2 = 53%		43% (CI: 31%-56%) I^2 = 88%	50% (CI: 38%-63%) I^2 = 89%
Regarding their worst pain			49% (CI: 42%-56%) I^2 = 13%	53% (CI: 44%-61%) I^2 = 0%

CI, confidence interval; PPPCS, persistent postoperative pain after cardiac surgery; RCT, randomized controlled trial.
* All studies have a quality assessment score >5 and are observational studies.

mechanical allodynia, mechanical hyperalgesia, and temporal summation of repeated noxious stimuli, also known as "wind-up"-like pain. They reported that only less than 20% of patients with PPPCS have normal sensation in the painful site, which clearly indicated an underlying neuropathic mechanism in the majority of those patients. Guimarães-Pereira et al.[34] concluded that 50% of the patients with PPPCS presented NP, and those with moderate to severe PPPCS presented significantly more often NP (68.8% vs 38.2%, $P = 0.001$). These authors also reported that patients with PPP located in the leg had more NP (PPP in the leg: 75% NP vs PPP in other locations: 42% NP, $P = 0.015$). Turan et al.[73] found that among patients who reported PPPCS, only 6% seemed to be neuropathic. Lauridsen et al.[45] reported that quantitative sensory testing revealed sensory abnormalities in 10 of 13 children. Kalso et al.[39] stated that pricking was present in 29% of the answers, and that patients also had paraesthesias.

4. Discussion

4.1. Summary of evidence

This systematic review summarizes the available evidence concerning PPPCS incidence, intensity, location, and NP presence. We performed meta-analysis for its incidence and intensity. For data on the location and NP presence, a qualitative synthesis of the evidence was performed because of the impossibility of combining quantitative outcomes. The majority of the included studies (78%) present an individual low risk of bias, which strengthens our findings.

Persistent postoperative pain affects 37% of patients in the first 6 months after CS, and it remains present more than 2 years after CS in 17% of them. More recent studies report a higher incidence of PPP during the first 6 months after CS, compared with older studies. Regarding the subtypes of surgery performed and its association with PPPCS, the available data are inconclusive, because there are few studies addressing this issue included in our analysis and those which did, had low power to detect associations. The proportion of PPPCS patients under any treatment is not known, but seems to be low. Regarding PPPCS intensity, we were unable to include all the selected studies in the analysis because of inconsistencies concerning the methods of pain measurement and reporting. Overall, approximately half of patients with PPPCS reported moderate to severe pain. The chest is the main location of PPPCS followed by the leg. Neuropathic pain seems to be present in the majority of patients with PPPCS; however, only a minority of the included studies addressed this issue, and there was a lack of uniformity in the methods used to measure NP.

4.2. Interpreting the findings

The incidence of PPPCS obtained in our study represents one of the highest compared with other types of surgeries.[35,40,41] The lack of uniformity in the PPPCS' assessment and reporting time frames led us to divide the assessment time frames using an approach based on previous similar studies.[3,82] This is an important part of the analysis because it allowed us to observe and analyze the incidence of PPPCS decreasing along time after the surgery, in contrast to what was described in a previous systematic review regarding thoracotomies.[3] Fletcher et al.[27] found a similar decline regarding the incidence of moderate PPP between 6 and 12 months. The estimated incidence of PPP was higher in the first months after CS (3 to less than 6 months after CS) compared with other time frames and more than 2 years after CS its value is less than half of the initial. The pathophysiology of this decline is not clear, although as the time with PPP evolves it may be assumed that these patients are identified and given appropriate treatment with better follow-up performed. However, data regarding the proportion of patients with PPPCS under any treatment or referral are lacking, as only 1 of the included studies[34] addressed it and found that 84% of patients with PPPCS were not under any treatment or referral. As recently stated,[1] it would be interesting to know why some patients with pain abstain from using analgesics; whether this is due to poor effect in this pain condition or for other reasons. Alternative hypotheses for the decline of PPPCS incidence

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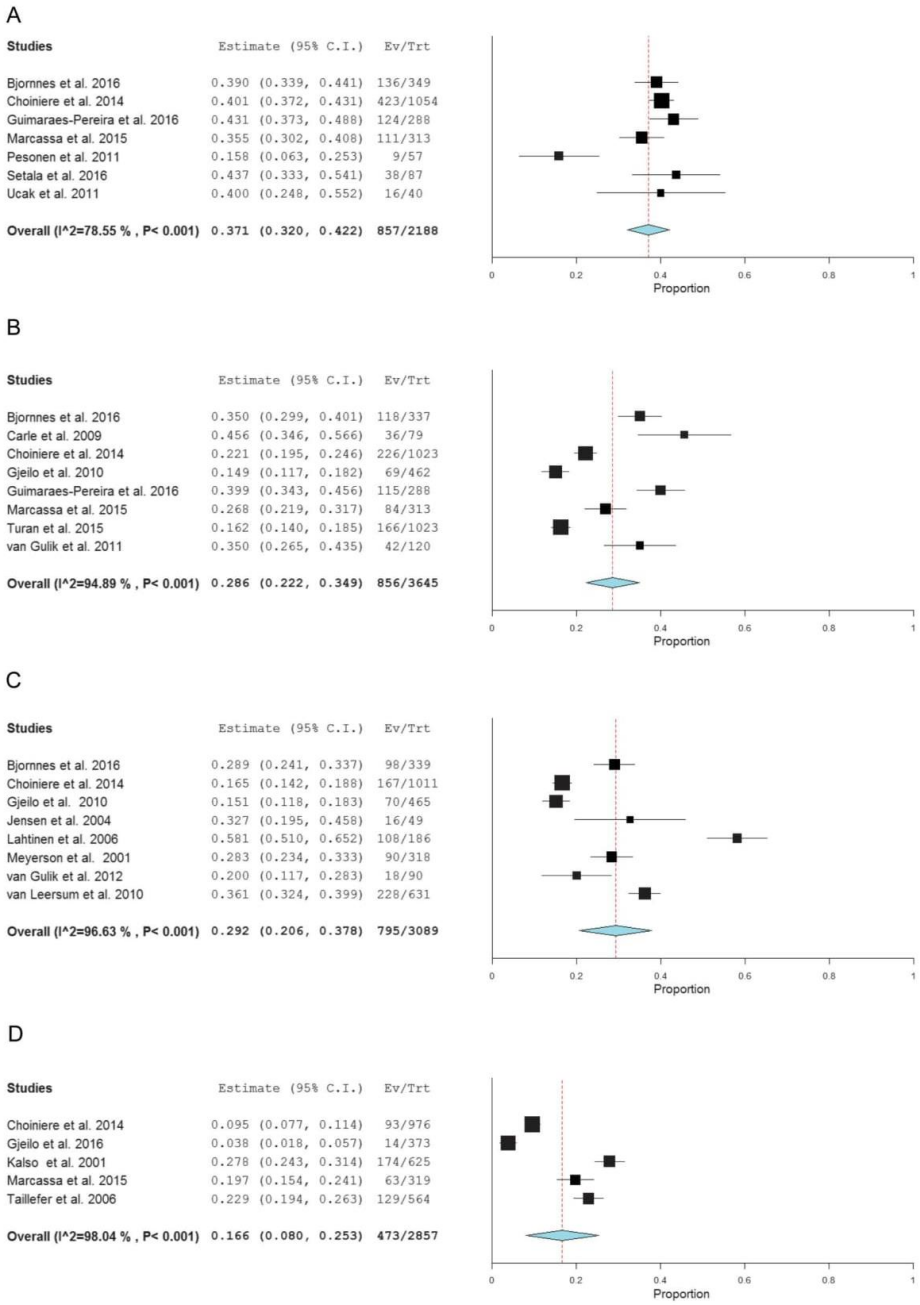

Figure 2. Incidence of PPPCS' forest plots: (A) at 3 to less than 6 months after surgery, (B) at 6 to less than 12 months after surgery, (C) at 12 to less than 24 months after surgery, and (D) at least 24 months after surgery. CI, confidence intervals; PPPCS, persistent postoperative pain after cardiac surgery.

through time are that this may be attributable to psychological factors or PPP pathophysiology. Psychological factors are important in pain perception,[24,72] and resilience and positive affect have shown to reduce chronic pain.[85] In addition, patients who had CS might have an improvement in HRQL and satisfaction with life,[32,70] which may contribute to their psychological profile. Consequently, a possible hypothesis is that HRQL and satisfaction with life improvements over time might lead to continuous pain decline in these patients. However, this hypothesis lacks formal confirmation. The role

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October 2017 • Volume 158 • Number 10 www.painjournalonline.com 1879

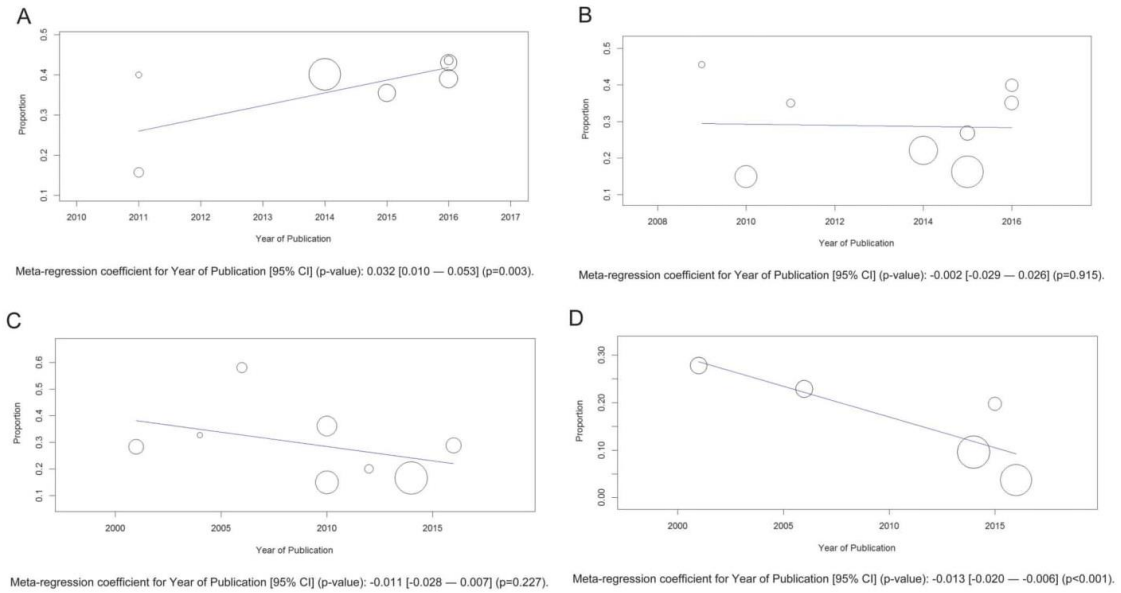

Figure 3. Metaregression with the publication year as covariate: incidence of PPP at (A) 3 to less than 6 months after surgery, (B) 6 to less than 12 months after surgery, (C) 12 to less than 24 months after surgery, and (D) at least 24 months after surgery. CI, confidence intervals; PPP, persistent postoperative pain.

of contextual and cognitive content variables in chronic pain is not only important but also complex.[28] The cause of PPPCS is multifactorial and transcends the aims of this systematic review, yet tissue destruction, nerve trauma, scar formation, rib fractures, stainless-steel wire sutures, and/or costochondral separation may all play relevant roles.[13] Noxious input from acute injury may trigger a state of CNS sensitization. In essence, dorsal horn neurotransmitter release through nociceptive input conditions the CNS such that there is enhanced responsiveness (secondary hyperalgesia). Although experimental evidence exists indicating that enhanced responsiveness outlasts the initial provocative insult, the exact clinical relevance and extent remain to be determined.[13]

Subgroup analysis in the group of patients with PPPCS at 3 to less than 6 months showed that studies with higher quality assessment showed a higher incidence with higher consistency; however, in the other time frames analysed sub-group analysis related with quality assessment did not reduce heterogeneity.

Regarding the subtypes of surgery performed and its association with PPPCS, the available data are inconclusive, because there are few included studies that addressed this issue and those which did, had low power to detect associations.

Concerning the type of studies, the estimated incidences were lower in the RCTs sub-group. These RCT studies[4,60,73,75] address strategies to reduce acute postoperative pain. Although they could not prove the efficacy of their interventions in reducing PPPCS, 2 of them reported reduced acute postoperative pain.[60,75] Intervention studies that aim to reduce acute postoperative pain play a fundamental role in preventing PPP, as acute postoperative pain is a strong predictor of PPPCS[15,34,77] and PPP following other types of surgeries.[40] Although efficacy is not proven for statistical or nonsuperiority reasons, tight and optimal treatment of acute postoperative pain is offered to patients enrolled in these interventional studies. In addition, placebo analgesic effects substantially contribute to the overall effectiveness of analgesic treatments.[17]

According to our inclusion criteria, the first studies regarding the incidence of PPPCS appeared in 2001.[26,39,55] Despite medical progress and improved awareness of PPP, it is surprising that the incidence of PPPCS has a positive trend over time, regarding the first time frame considered (3 to less than 6 months after CS). In addition, it is important to notice that older studies considering this time frame presented lower quality assessment scores, which could underestimate the incidence of PPPCS. On the other hand, a negative trend was found regarding studies evaluating PPP at least 24 months after CS. A possible explanation for this is the improved accessibility of patients with long-term pain states to health care and better analgesic regimens to treat PPP achieved in the latter years.

Regarding PPPCS' intensity, we were unable to include all studies in the analysis because of inconsistencies concerning the methods of pain measurement and reporting. As noted previously, large heterogeneity was found concerning recording and reporting PPP intensity's assessment. Similar problems were reported in other systematic reviews with meta-analysis on PPP after other types of surgeries.[3,82] We have estimated that a large proportion of patients with PPPCS present moderate to severe pain, and this proportion did not reduce over time. This pattern also was obtained in another systematic review regarding thoracotomy.[3] Although the incidence of PPP at least 24 months after CS declines, we estimate that half of these patients present moderate to severe pain, which is a higher proportion than the obtained in the other time frames. This could indicate the existence of a subtype of PPPCS more difficult to treat for several reasons that should be addressed in future studies.

Concerning PPPCS' location, the main locations identified were related to the extent of the surgical wound. However, pain was also present in areas not linked with the surgical wound, which could be explained by the presence of referred pain,

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Table 4
PPPCS intensity data.

Source	Intensity outcomes			Assessment (Patients with pain/all patients)	Summary measure	Results
	Time after surgery	Scale	Pain rating			
Bjornnes 2016	3, 6, and 12 mo.	NRS.	Worst pain at rest in the previous 24 h.	All patients	Mean (±SD).	3 mo: 1.6 (2.1); 6 mo: 1.4 (2.0); 12 mo: 1.2 (2.1).
Bruce 2003	Not available. Although severity was assessed, the authors mixed PPP patients with angina patients with PPP.					
Carle 2009	Not available.					
Choiniere 2014	3, 6, 12 and 24 mo.	NRS.	Average pain in the past 7 d.	All patients	Proportion of patients with moderate to severe pain.	3 mo: 149/1054; 6 mo: 72/1023; 12 mo: 67/1011; 24 mo: 35/976.
Costa 2015	58 mo (mean).	NRS.	Unclear.	All patients	Number of patients (%) according pain stratification.	No pain: 275 (61); 1 and 2: 62 (14); 3 and 4: 32 (7); 5 and 6: 56 (12); 7 and 8: 16 (3); 9 and 10: 12 (3).
Eisenberg 2001	16.1 ± 6.3 mo (mean ± SD).	VRS, VAS and MPQ.	Present pain.	Patients with pain	Number of patients (%) according pain stratification; mean (±SD) for VAS and MPQ.	None 0 (0), Mild 73 (34), moderate 115 (53), severe 19 (9) and very severe 8 (4). VAS 35 ± 22 and MPQ 4.9 ± 3.7.
Gjeilo 2010	12 mo.	NRS.	Present pain; worst pain, least pain, and average pain during the last 24 h.	50 patients with pain	Percentage of patients with moderate (4-6 on the NRS) or severe pain (7-10 on the NRS).	Present pain: 23% moderate and 6% severe; average pain: 37% moderate and 9% severe; worst pain: 40% moderate and 19% severe; least pain: 15% moderate and 0% severe.
Gjeilo 2016	5 y.	NRS.	Present pain; worst pain, least pain, and average pain during the last 24 h.	Patients with pain	Number of patients (%) according pain stratification.	Average pain: 4 (30.8) reported mild pain, 7 (53.8) reported moderate pain and 2 (15.4%) reported severe pain (1 missing). Worst pain: 2 (15.4), 7 (53.8) and 2 (15.4), respectively (1 missing, 2 reported no pain).
Guimaraes-Pereira 2016	3 mo.	NRS.	Present pain; worst pain, least pain, and average pain during the last 24 h.	Patients with pain	Number of patients (%) according to pain stratification.	Pain at the time of responding to the questionnaire: None 61 (49.1), mild 24 (19.4), moderate 39 (31.5) and severe 0 (0.0). Worst pain: none 0 (0.0), mild 22 (17.7), moderate 68 (54.9) and severe 34 (27.4). Least pain: none 90 (72.6), mild 30 (24.2), moderate 4 (3.2) and severe 0 (0.0). Average pain: none 0 (0.0), mild 71 (57.3), moderate 53 (42.7) and severe 0 (0.0). Overall severity: none 0 (0.0), mild 76 (61.2), Moderate 24 (19.4) and severe 24 (19.4).
Jensen 2004	18 mo.	Unclear.	Unclear.	Patients with pain	Number of patients with severe pain.	Severe pain: 2 patients
Kalso 2001	24 to 36 mo.	Mild, moderate, severe, or excruciating.	Present pain.	Patients with pain	Percentage of patients.	Mild: 62; moderate: 35; severe: 3; excruciating: 0.

(continued on next page)

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Source	Intensity outcomes		Assessment (Patients with pain/all patients)	Summary measure	Results
	Time after surgery	Scale	Pain rating		
Lahtinen 2006	12 mo.	NRS.	Pain at rest and on movement.	All patients	Number of patients (%) according to pain stratification.	Rest: 26 (14%) mild, 1 (1%) moderate, 3 (2%) severe pain. Movement: 45 (24%) mild, 5 (3%) moderate, 7 (4%) severe pain.
Lauridsen 2014	Not available.					
Marcassa 2015	3 mo, 1 y and 3 y.	NRS.	Average pain intensity in the last 24 h; worst pain intensity in the last 2 wk.	All patients	Median (IQR). Percentage of patients according to pain stratification, among patients with persistent pain after surgery.	"Average pain" at 3 mo 3.0 (2-5), 1 y 3.0 (2-4), and 3 y 2.0 (1.0-3.75). "Worst pain" at 3 mo 4.0 (2-6), 1 y 3.0 (2-5) and 3 y 3.0 (IQR 2-5). "Average pain moderate to severe" 44.7% at 3 mo, 29.9% after 1 y and 25.4% after 3 y "Worst pain moderate to severe" was 61.8%, and 45.9% and 40%, respectively.
Meyerson 2001	13 ± 0.11 mo (mean ± SD).	VAS.	Intensity of pain at its worst (VASmax) and at its best (VASmin).	All patients	Number of patients (%) according pain stratification.	VASmax >30 mm: 41 (13); VASmax >54 mm: 14 (4); VASmin >30 mm: 8 (3); VASmin >54 mm: 3 (1).
Pesonen 2011	3 mo.	VRS.	VRS pain score at rest and during movement.	All patients	Number of patients (%) according to pain stratification.	At rest: VRS0 56 (98), VRS1 1 (2); During movement: VRS0 48 (84), VRS1 8 (14), VRS2 1 (2).
Setala 2016	Not available					
Taillefer 2006	29.9 ± 10.5 mo (mean ± SD).	NRS.	Present pain and worst and average pain in the past 7 d.	Patients with pain	Number of patients (%) according to pain stratification.	Present pain: 2.1 ± 2.4 (mean). Worst pain in the past 7 d: moderate to severe levels in 79 (61.3); usual pain in the past 7 d: moderate to severe levels in 66 (51.2).
Turan 2015	6 mo.	NRS, BPI, and Neuropathic Pain Questionnaire.	Present pain.	Patients with pain	Mean (±SD).	Average pain: 1.4 (±1.6); worst pain 2.6 (± 2.3).
Ucak 2011	Not available.					
van Gulik 2011	10-12 mo.	NRS.	Pain intensity in best (least pain) and worst (greatest pain) day in the 2 wk prior.	All patients	Number of patients (%) according to pain stratification.	Worst day, NRS >3: 35 (29.2). Best day, NRS = 0: (91.7); NRS >3: 7 (5.8).
van Gulik 2012	Not available.					
van Leersum 2010	19.1-19.7 mo.	NRS.	Unclear.	Patients with pain	Percentage of patients	NRS >3: 57%; Unknown: 22%.

BPI, brief pain inventory; H, hours; IQR, interquartile range; mo, month; MPQ, McGill Pain Questionnaire; NRS, Numerical Rating Scale; PPP, persistent postoperative pain; PPPCS, persistent postoperative pain after cardiac surgery; VAS, Visual Analog Scale; VRS, Verbal Rating Scale.

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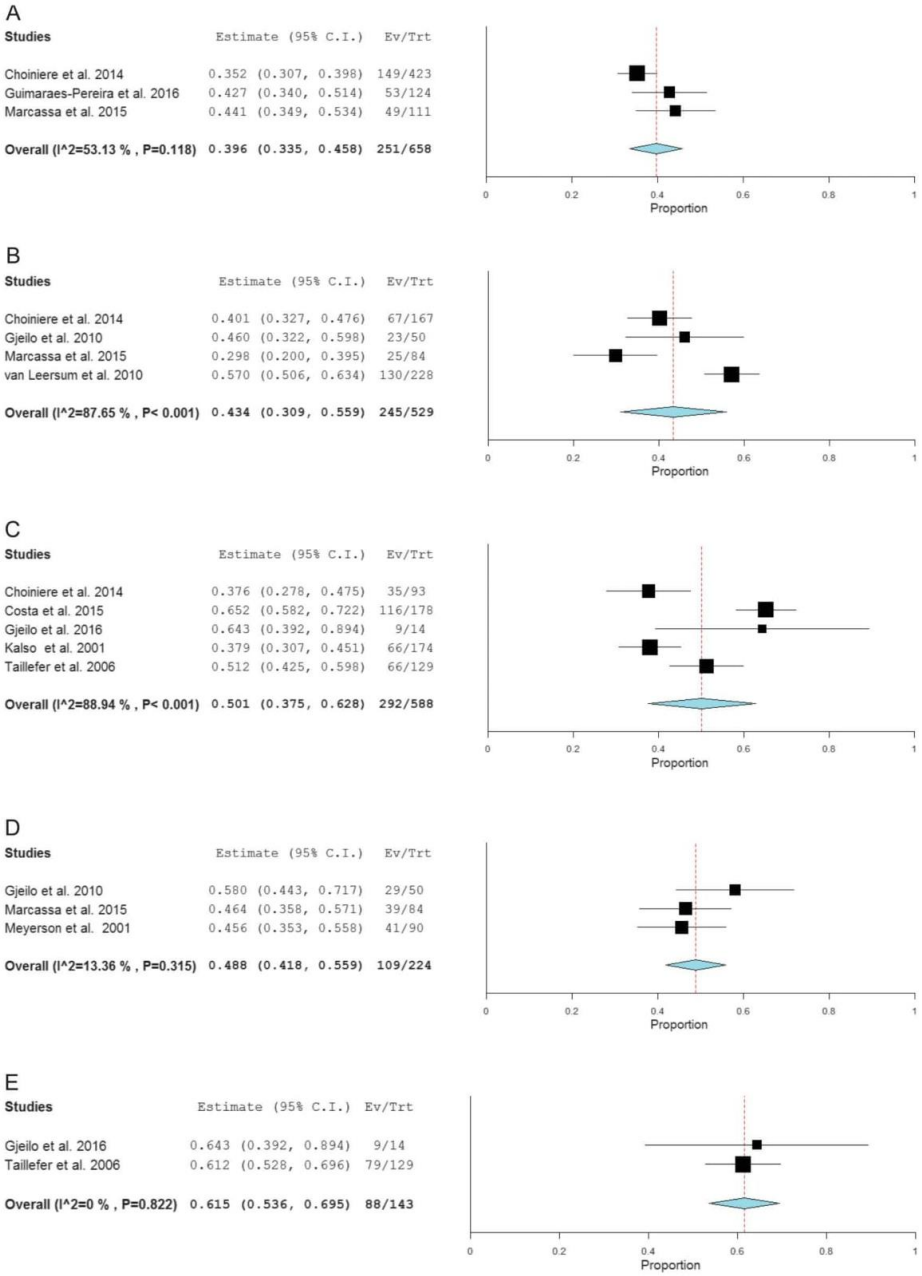

Figure 4. Moderate to severe pain in patients reporting PPPCS' forest plots: (A) Average pain at 3 to less than 6 months after surgery, (B) average pain at 12 to less than 24 months after surgery, (C) average pain at least 24 months after surgery, (D) worst pain at 12 to less than 24 months after surgery, and (E) worst pain at least 24 months after surgery. PPPCS, persistent postoperative pain after cardiac surgery.

suboptimal positioning of patients during surgery, or central venous catheter placement.[13] Vessel harvesting is responsible for some of the pain locations; however, the presented data have a wide range, which limits the recognition of its exact contribution. We have detected large heterogeneity concerning the location assessment and reports which restricts further conclusions.

With respect to NP, only a few of the included studies addressed this issue. Despite the wide variation of proportion of patients with NP and its assessment, the presence of NP in a considerable number of patients with PPPCS seems to be a certainty. Three of the included studies[26,34,45] reported that the majority of patients presented with NP. Nerve injury–induced NP

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has been proposed as a major cause of PPP, and a recent review suggests that the prevalence of NP among PPP cases differs in various types of surgery, probably depending on the likelihood of surgical iatrogenic nerve injury.[35]

4.3. Strengths and limitations

There are some narrative reviews about PPPCS,[16,30,53] but to our knowledge, no systematic review and meta-analysis has been conducted to date, namely about its incidence, intensity, location, and NP presence. One of the strengths of this review is the presentation of pooled estimates regarding the incidence and intensity of PPPCS and the thorough analysis of the magnitude and factors explaining the heterogeneity among those estimates. Second, we have evaluated the PPPCS incidence through different time frames, which is more adequate because the incidence varies depending on the time that has passed after CS. Consequently, that allowed us to understand its trajectory as time evolves. Furthermore, we have analysed the incidences of PPPCS according to publication year with a random-effects meta-regression, which has never been performed. This analysis informs health professionals and authorities about their performance in this pain syndrome. In addition, some of the included studies were not identified by the primary search but rather were retrieved from reference lists of other articles. This issue was expected,[23,47,66] and to overcome it the authors have conducted a systematic search through 6 relevant databases and abstract books of major relevant annual scientific meetings.

The current systematic review has some limitations. First, the performed random effects meta-analyses revealed substantial statistical heterogeneity with I^2 above 80% for most of the analyses. This should be taken into account when analysing and interpreting the meta-analytical measures presented. However, large heterogeneities were expected as we set out to include retrospective and prospective observational studies and RCTs. Sensitivity analysis was used to explain and control for the observed heterogeneity, in some cases reducing it. However, other factors such as population-based differences or differences in perioperative care may have contributed to the high observed heterogeneity. Other meta-analyses of PPP reported similar results, revealing a large statistical heterogeneity as a common problem in this field.[3,82] Second, an important epidemiological consideration is the inconsistent use of the terms incidence and prevalence. Incidence is defined as the fraction of a group of people initially free of the outcome of interest that develops the clinical condition over a given period. This is the most correct epidemiological term for PPP.[35] There is, however, a considerable diversity in assessing and reporting prevalence vs incidence, which could further contribute to unconformities. Reporting cumulative prevalence may lead to overestimation of PPP, as it includes patients who developed transient pain after surgery.

4.4. Implications for clinical practice and research

This systematic review elucidates the relevance and dimension of PPPCS for clinical practice. It is an important problem affecting more than one-third of patients in the first 6 months after CS and it remains present in a considerable number of patients more than 2 years after CS. Patients experiencing PPPCS report a significantly lower HRQL compared with patients without it.[10,29,71] Our results deserve special attention from health care professionals, to prevent, inform, and treat these patients. Despite medical progress, the reported incidence of PPP during the first 6 months after CS increased in recent years, and overall, approximately half of the patients with PPPCS reported moderate to severe pain. As recently commented upon,[33] if the presence of PPP is established at 3 months, it is crucial that a formal diagnosis is made, appropriate treatment given, and that follow-up is performed. Acute pain services should play a role in assessing PPP as an outcome of surgery.[38] The majority of patients with PPPCS present NP; therefore, its presence should be assessed and treated accordingly. Regarding implications for research, future studies should focus on the follow-up and treatment of patients with PPPCS, because data regarding the proportion of PPPCS patients with vs without treatment are lacking and the reasons for treating or not treating this condition are unknown. There is an urgent need for more research in the treatment of different kinds of PPP.[38] Regarding PPPCS intensity assessment, the recommendations of the IMMPACT group should be followed[25,74] to achieve better evidence regarding PPPCS intensity. In addition, studies should present pain intensity in patients with PPPCS and not in all the patients studied, to overcome the risk of underestimation. Neuropathic pain should be better addressed in the future, because it is present in a considerable number of these patients. In an attempt to strengthen the criteria for what is and what is not NP, a probability grading system for categorizing NP was included in the latest European Federation of Neurological Societies guidelines on the NP assessment,[20] and should be followed in future studies focusing this issue. The need to characterize other forms of pain apart from NP should also be addressed in future studies.

In conclusion, this systematic review and meta-analysis importantly adds to the current literature by providing the most complete assessment and discussion of the current best evidence regarding the incidence, intensity, location, and frequency of NP presence in the context of PPPCS. The authors maintain that there is room for improvement not only in terms of treatment, but also regarding the assessment of PPPCS in clinical practice and in future studies. This review is expected and believed to provide an important scientific impetus that will foster and support these improvements.

Conflict of interest statement

The authors have no conflict of interest to declare.

Acknowledgements

The authors thank the contacted eligible study's authors for providing additional data.

Appendix A. Supplemental Digital Content

Supplemental Digital Content associated with this article can be found online at http://links.lww.com/PAIN/A450.

Article history:
Received 21 February 2017
Received in revised form 16 June 2017
Accepted 21 June 2017
Available online 31 July 2017

References

[1] Andersen KG, Duriaud HM, Jensen HE, Kroman N, Kehlet H. Reply. PAIN 2016;157:1174.
[2] Bawany FI, Khan MS, Khan A, Hussain M. Skeletonization technique in coronary artery bypass graft surgery reduces the postoperative pain intensity and disability index. J Card Surg 2014;29:47–50.

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[3] Bayman EO, Brennan TJ. Incidence and severity of chronic pain at 3 and 6 months after thoracotomy: meta-analysis. J Pain 2014;15:887–97.
[4] Bjornnes AK, Parry M, Lie I, Fagerland MW, Watt-Watson J, Rustoen T, Stubhaug A, Leegaard M. Pain experiences of men and women after cardiac surgery. J Clin Nurs 2016;25:3058–68.
[5] Bjornnes AK, Parry M, Lie I, Fagerland MW, Watt-Watson J, Rustoen T, Stubhaug A, Leegaard M. The impact of an educational pain management booklet intervention on postoperative pain control after cardiac surgery. Eur J Cardiovasc Nurs 2017;16:18–27.
[6] Blyth FM, March LM, Cousins MJ. Chronic pain-related disability and use of analgesia and health services in a Sydney community. Med J Aust 2003;179:84–7.
[7] Bonde P, Graham AN, MacGowan SW. Endoscopic vein harvest: advantages and limitations. Ann Thorac Surg 2004;77:2076–82.
[8] Boodhwani M, Lam BK, Nathan HJ, Mesana TG, Ruel M, Zeng W, Sellke FW, Rubens FD. Skeletonized internal thoracic artery harvest reduces pain and dysesthesia and improves sternal perfusion after coronary artery bypass surgery: a randomized, double-blind, within-patient comparison. Circulation 2006;114:766–73.
[9] Borenstein M, Hedges LV, Higgins JP, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. Res Synth Methods 2010;1:97–111.
[10] Bruce J, Drury N, Poobalan AS, Jeffrey RR, Smith WCS, Chambers WA. The prevalence of chronic chest and leg pain following cardiac surgery: a historical cohort study. PAIN 2003;104:265–73.
[11] Bruce J, Poobalan AS, Smith WCS, Chambers WA. Quantitative assessment of chronic postsurgical pain using the McGill Pain Questionnaire. Clin J Pain 2004;20:70–5.
[12] Carle C, Ashworth A, Roscoe A. A survey of post-sternotomy chronic pain following cardiac surgery. Anaesthesia 2009;64:1387.
[13] Chaney MA. Kaplan's cardiac anesthesia. In: Kaplan J, Reich D, Savino J, editors. The Echo Era. St. Louis. MO: Saunders/Elsevier, 2011. p. 1108–10.
[14] Chiu KM, Wu CC, Wang MJ, Lu CW, Shieh JS, Lin TY, Chu SH. Local infusion of bupivacaine combined with intravenous patient-controlled analgesia provides better pain relief than intravenous patient-controlled analgesia alone in patients undergoing minimally invasive cardiac surgery. J Thorac Cardiovasc Surg 2008;135:1348–52.
[15] Choiniere M, Watt-Watson J, Victor JC, Baskett RJ, Bussieres JS, Carrier M, Cogan J, Costello J, Feindel C, Guertin MC, Racine M, Taillefer MC. Prevalence of and risk factors for persistent postoperative nonanginal pain after cardiac surgery: a 2-year prospective multicentre study. CMAJ 2014;186:E213–223.
[16] Cogan J. Pain management after cardiac surgery. Semin Cardiothorac Vasc Anesth 2010;14:201–4.
[17] Colloca L, Klinger R, Flor H, Bingel U. Placebo analgesia: psychological and neurobiological mechanisms. PAIN 2013;154:511–14.
[18] Costa MA, Trentini CA, Schafranski MD, Pipino O, Gomes RZ, Reis ES. Factors associated with the development of chronic post-sternotomy pain: a case-control study. Braz J Cardiovasc Surg 2015;30:552–6.
[19] Crombie IK, Davies HT, Macrae WA. Cut and thrust: antecedent surgery and trauma among patients attending a chronic pain clinic. PAIN 1998; 76:167–71.
[20] Cruccu G, Sommer C, Anand P, Attal N, Baron R, Garcia-Larrea L, Haanpaa M, Jensen TS, Serra J, Treede RD. EFNS guidelines on neuropathic pain assessment: revised 2009. Eur J Neurol 2010;17:1010–18.
[21] Defalque RJ, Bromley JJ. Poststernotomy neuralgia: a new pain syndrome. Anesth Analg 1989;69:81–2.
[22] Dick F, Hristic A, Roost-Krähenbühl E, Aymard T, Weber A, Tevaearai HT, Carrel TP. Persistent sensitivity disorders at the radial artery and saphenous vein graft harvest sites: a neglected side effect of coronary artery bypass grafting procedures. Eur J Cardiothorac Surg 2011;40:221–6.
[23] Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic reviews. BMJ 1994;309:1286–91.
[24] Doering LV, Chen B, McGuire A, Bodan RC, Irwin MR. Persistent depressive symptoms and pain after cardiac surgery. Psychosomatic Med 2014;76:437–44.
[25] Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, Kerns RD, Stucki G, Allen RR, Bellamy N, Carr DB, Chandler J, Cowan P, Dionne R, Galer BS, Hertz S, Jadad AR, Kramer LD, Manning DC, Martin S, McCormick CG, McDermott MP, McGrath P, Quessy S, Rappaport BA, Robbins W, Robinson JP, Rothman M, Royal MA, Simon L, Stauffer JW, Stein W, Tollett J, Wernicke J, Witter J. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. PAIN 2005;113:9–19.
[26] Eisenberg E, Pultorak Y, Pud D, Bar-El Y. Prevalence and characteristics of post coronary artery bypass graft surgery pain (PCP). PAIN 2001;92: 11–17.
[27] Fletcher D, Stamer UM, Pogatzki-Zahn E, Zaslansky R, Tanase NV, Perruchoud C, Kranke P, Komann M, Lehman T, Meissner W. Chronic postsurgical pain in Europe: an observational study. Eur J Anaesthesiol 2015;32:725–34.
[28] Gillanders DT, Ferreira NB, Bose S, Esrich T. The relationship between acceptance, catastrophizing and illness representations in chronic pain. Eur J Pain 2013;17:893–902.
[29] Gjeilo KH, Klepstad P, Wahba A, Lydersen S, Stenseth R. Chronic pain after cardiac surgery: a prospective study. Acta Anaesthesiol Scand 2010;54:70–8.
[30] Gjeilo KH, Stenseth R, Klepstad P. Risk factors and early pharmacological interventions to prevent chronic postsurgical pain following cardiac surgery. Am J Cardiovasc Drugs 2014;14:335–42.
[31] Gjeilo KH, Stenseth R, Wahba A, Lydersen S, Klepstad P. Chronic postsurgical pain in patients 5 years after cardiac surgery: a prospective cohort study. Eur J Pain 2017;21:425–33.
[32] Gjeilo KH, Wahba A, Klepstad P, Lydersen S, Stenseth R. Survival and quality of life in an elderly cardiac surgery population: 5-year follow-up. Eur J Cardiothorac Surg 2013;44:e182–188.
[33] Guimarães-Pereira L. Persistent postoperative pain and the problem of strictly observational research. PAIN 2016;157:1173–4.
[34] Guimaraes-Pereira L, Farinha F, Azevedo L, Abelha F, Castro-Lopes J. Persistent postoperative pain after cardiac surgery: incidence, characterization, associated factors and its impact in quality of life. Eur J Pain 2016;20:1433–42.
[35] Haroutiunian S, Nikolajsen L, Finnerup NB, Jensen TS. The neuropathic component in persistent postsurgical pain: a systematic literature review. PAIN 2013;154:95–102.
[36] Ho SC, Royse CF, Royse AG, Penberthy A, McRae R. Persistent pain after cardiac surgery: an audit of high thoracic epidural and primary opioid analgesia therapies. Anesth Analgesia 2002;95:820–3.
[37] Jensen MK, Andersen C. Can chronic poststernotomy pain after cardiac valve replacement be reduced using thoracic epidural analgesia? Acta Anaesthesiol Scand 2004;48:871–4.
[38] Kalso E IV. Persistent post-surgery pain: research agenda for mechanisms, prevention, and treatment. Br J Anaesth 2013;111:9–12.
[39] Kalso E, Mennander S, Tasmuth T, Nilsson E. Chronic post-sternotomy pain. Acta Anaesthesiol Scand 2001;45:935–9.
[40] Kehlet H, Edwards RR, Brennan T. Persistent postoperative pain: pathogenic mechanisms and preventive strategies. In: Raja S, Sommer C, editors. Pain 2014—Refresher courses. Seattle: International Association for the Study of Pain/IASP Press, 2014. p. 113–23.
[41] Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. Lancet 2006;367:1618–25.
[42] Keita H. Can we prevent the chronic post-surgical pain? Pain and locoregional anesthesia committee and the standards committee of the French society of anesthesia and intensive care. Ann Fr Anesth Reanim 2009;28:e75–77.
[43] King KM, Parry M, Southern D, Faris P, Tsuyuki RT. Women's Recovery from Sternotomy-Extension (WREST-E) study: examining long-term pain and discomfort following sternotomy and their predictors. Heart 2008;94: 493–7.
[44] Lahtinen P, Kokki H, Hynynen M. Pain after cardiac surgery: a prospective cohort study of 1-year incidence and intensity. Anesthesiology 2006;105: 794–800.
[45] Lauridsen MH, Kristensen AD, Hjortdal VE, Jensen TS, Nikolajsen L. Chronic pain in children after cardiac surgery via sternotomy. Cardiol Young 2014;24:893–9.
[46] Lee W, Yan YY, Jensen MP, Shun SC, Lin YK, Tsai TP, Lai YH. Predictors and patterns of chronic pain three months after cardiac surgery in Taiwan. Pain Med 2010;11:1849–58.
[47] Lemeshow AR, Blum RE, Berlin JA, Stoto MA, Colditz GA. Searching one or two databases was insufficient for meta-analysis of observational studies. J Clin Epidemiol 2005;58:867–73.
[48] Loney PL, Chambers LW, Bennett KJ, Roberts JG, Stratford PW. Critical appraisal of the health research literature: prevalence or incidence of a health problem. Chronic Dis Can 1998;19:170–6.
[49] Madan K, Gupta VP, Singh R, Talwar S, Choudhary SK, Airan B, Sampath Kumar A. Comparison of straight sternotomy and interlocking sternotomy in open heart surgery. Indian J Med Res 2006;124:57–62.
[50] Mailis A, Umana M, Feindel CM. Anterior intercostal nerve damage after coronary artery bypass graft surgery with use of internal thoracic artery graft. Ann Thorac Surg 2000;69:1455–8.
[51] Marcassa C, Faggiano P, Greco C, Ambrosetti M, Temporelli Pier L. A retrospective multicenter study on long-term prevalence of chronic pain after cardiac surgery. J Cardiovasc Med 2015;16:768–74.
[52] Markman PL, Rowland MA, Leong JY, Van Der Merwe J, Storey E, Marasco S, Negri J, Bailey M, Rosenfeldt FL. Skeletonized internal

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thoracic artery harvesting reduces chest wall dysesthesia after coronary bypass surgery. J Thorac Cardiovasc Surg 2010;139:674–9.
[53] Mazzeffi M, Khelemsky Y. Poststernotomy pain: a clinical review. J Cardiothorac Vasc Anesth 2011;25:1163–78.
[54] Medalion B, Fuks A, Sharoni E, Stamler A, Snir E, Vidne B, Porat E. Limb performance and patient satisfaction after radial artery harvesting: endoscopic versus open techniques. Surg Endosc 2008;22:2638–42.
[55] Meyerson J, Thelin S, Gordh T, Karlsten R. The incidence of chronic post-sternotomy pain after cardiac surgery–a prospective study. Acta Anaesthesiol Scand 2001;45:940–4.
[56] Miller KH, Grindel CG. Comparison of symptoms of younger and older patients undergoing coronary artery bypass surgery. Clin Nurs Res 2004; 13:179–93; discussion 194–178.
[57] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.
[58] Mountney J, Wilkinson GA. Saphenous neuralgia after coronary artery bypass grafting. Eur J Cardiothorac Surg 1999;16:440–3.
[59] Oz BS, Iyem H, Akay HT, Yildirim V, Karabacak K, Bolcal C, Demirkilic U, Tatar H. Preservation of pleural integrity during coronary artery bypass surgery affects respiratory functions and postoperative pain: a prospective study. Can Respir J 2006;13:145–9.
[60] Pesonen A, Suojaranta-Ylinen R, Hammaren E, Kontinen VK, Raivio P, Tarkkila P, Rosenberg PH. Pregabalin has an opioid-sparing effect in elderly patients after cardiac surgery: a randomized placebo-controlled trial. Br J Anaesth 2011;106:873–81.
[61] Rashidi S, Elenbaas TW, Hamad MAS, Van Suijlekom HJ, Van Straten AH. Does removal of steel wires relieve post-sternotomy pain after cardiac surgery? Asian Cardiovasc Thorac Ann 2013;21:409–13.
[62] Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Makuc DM, Marcus GM, Marelli A, Matchar DB, Moy CS, Mozaffarian D, Mussolino ME, Nichol G, Paynter NP, Soliman EZ, Sorlie PD, Sotoodehnia N, Turan TN, Virani SS, Wong ND, Woo D, Turner MB. Heart disease and stroke statistics–2012 update: a report from the American Heart Association. Circulation 2012;125:e2–e220.
[63] Rowe MA, King KB. Long-term chest wall discomfort in women after coronary artery bypass grafting. Heart Lung 1998;27:184–8.
[64] Royse C, Remedios C, Royse A. High thoracic epidural analgesia reduces the risk of long-term depression in patients undergoing coronary artery bypass surgery. Ann Thorac Cardiovasc Surg 2007;13:32–5.
[65] Rudez I, Unic D, Sutlic Z, Biocina B, Baric D, Ivkovic M, Pavlovic M. Endoscopic radial artery harvesting reduces postoperative pain and neurologic complications. Heart Surg Forum 2007;10:E363–365.
[66] Ruppen W, Derry S, McQuay H, Moore RA. Incidence of epidural hematoma, infection, and neurologic injury in obstetric patients with epidural analgesia/anesthesia. Anesthesiology 2006;105:394–9.
[67] Schnabel A, Pogatzki-Zahn E. Predictors of chronic pain following surgery. What do we know? Schmerz 2010;24:517–31. quiz 532–513.
[68] Setala P, Kalliomaki ML, Jarvela K, Huhtala H, Sisto T, Puolakka P. Postoperative hyperalgesia does not predict persistent post-sternotomy pain; observational study based on clinical examination. Acta Anaesthesiol Scand 2016;60:520–8.
[69] Simek M, Nemec P, Bruk V, Gwozdziewicz M, Fluger I, Langova K. Postoperative and midterm outcomes of minimally invasive and endoscopic great saphenous vein harvesting for coronary artery bypass grafting—a prospective analysis. Thorac Cardiovasc Surgeon 2007;55:428–32.
[70] Stoll C, Schelling G, Goetz AE, Kilger E, Bayer A, Kapfhammer HP, Rothenhausler HB, Kreuzer E, Reichart B, Peter K. Health-related quality of life and post-traumatic stress disorder in patients after cardiac surgery and intensive care treatment. J Thorac Cardiovasc Surg 2000;120: 505–12.
[71] Taillefer MC, Carrier M, Belisle S, Levesque S, Lanctot H, Boisvert AM, Choiniere M. Prevalence, characteristics, and predictors of chronic nonanginal postoperative pain after a cardiac operation: a cross-sectional study. J Thorac Cardiovasc Surg 2006;131:1274–80.
[72] Thibault P, Loisel P, Durand MJ, Catchlove R, Sullivan MJ. Psychological predictors of pain expression and activity intolerance in chronic pain patients. PAIN 2008;139:47–54.
[73] Turan A, Belley-Cote EP, Vincent J, Sessler DI, Devereaux PJ, Yusuf S, van Oostveen R, Cordova G, Yared JP, Yu H, Legare JF, Royse A, Rochon A, Nasr V, Ayad S, Quantz M, Lamy A, Whitlock RP. Methylprednisolone does not reduce persistent pain after cardiac surgery. Anesthesiology 2015;123:1404–10.
[74] Turk DC, Dworkin RH, Allen RR, Bellamy N, Brandenburg N, Carr DB, Cleeland C, Dionne R, Farrar JT, Galer BS, Hewitt DJ, Jadad AR, Katz NP, Kramer LD, Manning DC, McCormick CG, McDermott MP, McGrath P, Quessy S, Rappaport BA, Robinson JP, Royal MA, Simon L, Stauffer JW, Stein W, Tollett J, Witter J. Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. PAIN 2003;106:337–45.
[75] Ucak A, Onan B, Sen H, Selcuk I, Turan A, Yilmaz AT. The effects of gabapentin on acute and chronic postoperative pain after coronary artery bypass graft surgery. J Cardiothorac Vasc Anesth 2011;25:824–9.
[76] van Gulik L, Ahlers SJ, van de Garde EM, Bruins P, van Boven WJ, Tibboel D, van Dongen EP, Knibbe CA. Remifentanil during cardiac surgery is associated with chronic thoracic pain 1 yr after sternotomy. Br J Anaesth 2012;109:616–22.
[77] van Gulik L, Janssen LI, Ahlers SJ, Bruins P, Driessen AH, van Boven WJ, van Dongen EP, Knibbe CA. Risk factors for chronic thoracic pain after cardiac surgery via sternotomy. Eur J Cardiothorac Surg 2011;40: 1309–13.
[78] van Leersum NJ, van Leersum RL, Verwey HF, Klautz RJM. Pain symptoms accompanying chronic poststernotomy pain: a pilot study. Pain Med 2010;11:1628–34.
[79] Voegtle TA. A different kind of chest pain. Am J Nurs 2000;100:65.
[80] Vrooman B, Kapural L, Sarwar S, Mascha EJ, Mihaljevic T, Gillinov M, Qavi S, Sessler DI. Lidocaine 5% patch for treatment of acute pain after robotic cardiac surgery and prevention of persistent incisional pain: a randomized, placebo-controlled, double-blind trial. Pain Med 2015;16: 1610–21.
[81] Wallace BC, Dahabreh IJ, Trikalinos TA, Lau J, Trow P, Schmid CH. Closing the gap between methodologists and end-users: R as a computational back-end. J Stat Softw 2012;1:2012.
[82] Weibel S, Neubert K, Jelting Y, Meissner W, Wockel A, Roewer N, Kranke P. Incidence and severity of chronic pain after caesarean section: a systematic review with meta-analysis. Eur J Anaesthesiol 2016;33:853–65.
[83] Weis F, Kilger E, Roozendaal B, De Quervain DJF, Lamm P, Schmidt M, Schmölz M, Briegel J, Schelling G. Stress doses of hydrocortisone reduce chronic stress symptoms and improve health-related quality of life in high-risk patients after cardiac surgery: a randomized study. J Thorac Cardiovasc Surg 2006;131:277–82.e271.
[84] Yun KL, Sintek CF, Fletcher AD, Pfeffer TA, Kochamba GS, Mahrer PR, Khonsari S. Time related quality of life after elective cardiac operation. Ann Thorac Surg 1999;68:1314–20.
[85] Zautra AJ, Johnson LM, Davis MC. Positive affect as a source of resilience for women in chronic pain. J Consult Clin Psychol 2005;73:212–20.
[86] Zhu YY, Hayward PA, Hadinata IE, Matalanis G, Buxton BF, Stewart AG, Hare DL. Long-term impact of radial artery harvest on forearm function and symptoms: a comparison with leg vein. J Thorac Cardiovasc Surg 2013;145:412–19.

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Appendix A. Supplemental Digital Content

Supplementary Material 1 – Search strategy

Search strategy in MEDLINE with PubMed:

1. Incidence (MeSH)

2. Pain measurement (MeSH)

3. Cardiac Surgical Procedures (MeSH)

4. Postoperative Pain (MeSH)

5. Chronic Pain (MeSH)

6. Humans (MeSH)

7. "1998/01/01"[PDAT] : "2016/11/31" [PDAT]

8. 1 OR 2

9. 4 OR 5

10. 3 AND 6 AND 7 AND 8 AND 9

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Appendix A. Supplemental Digital Content

Supplementary Material 2 – Study's quality assessment

Methodological scoring system used to rate studies reviewed	Score	Bjormnes *et al.* (2016)	Bruce *et al.* (2003)	Carle *et al.* (2009)	Choiniere et al. (2014)	Costa et al. (2015)	Eisenberg et al. (2001)	Gjeilo et al. (2010)	Gjeilo et al. (2016)	Guimaraes-Pereira et al. (2016)	Jensen et al. (2004)	Kalso et al. (2001)	Lahtinen et al. (2006)	Lauridsen et al. (2014)	Marcassa et al. (2015)	Meyerson et al. (2001)	Pesonen et al. (2011)	Setala et al. (2016)	Tailleifer et al. (2006)	Turan et al. (2015)	Ucak et al. (2011)	van Gulik et al. (2011)	van Gulik et al. (2012)	van Leersum et al. (2010)
Item																								
1. Random sample or whole population	1 point	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1
2. Unbiased sampling frame (i.e. census data)	1 point	0	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	0	1	1	1
3. Adequate sample size (≥ 278 subjects)	1 point	1	1	0	1	1	1	1	1	1	0	1	0	0	1	1	0	0	1	1	0	0	0	0
4. Measures were the standard	1 point	1	1	0	1	1	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1
5. Outcomes measured by unbiased assessors	1 point	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
6. Adequate response rate (75%), refusers described	1 point	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	0
7. Confidence intervals, subgroup analysis	1 point	0	1	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0
8. Study subjects described	1 point	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Total	**8 points**	**6**	**7**	**3**	**8**	**7**	**7**	**7**	**7**	**8**	**3**	**6**	**6**	**5**	**7**	**7**	**5**	**6**	**7**	**8**	**5**	**6**	**6**	**6**

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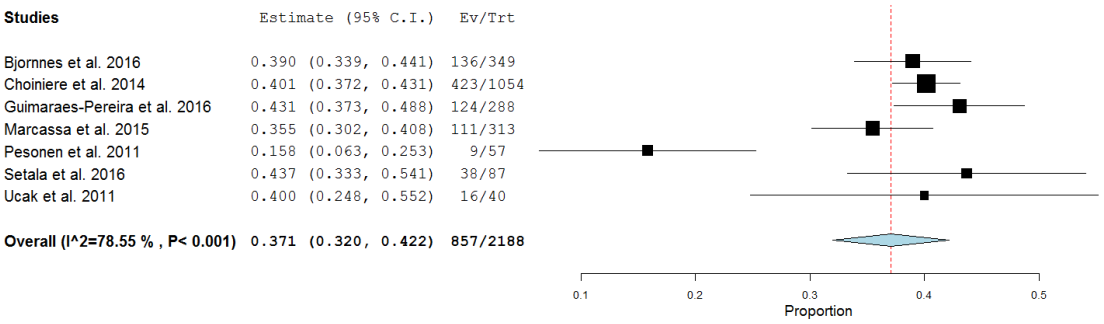
Appendix A. Supplemental Digital Content

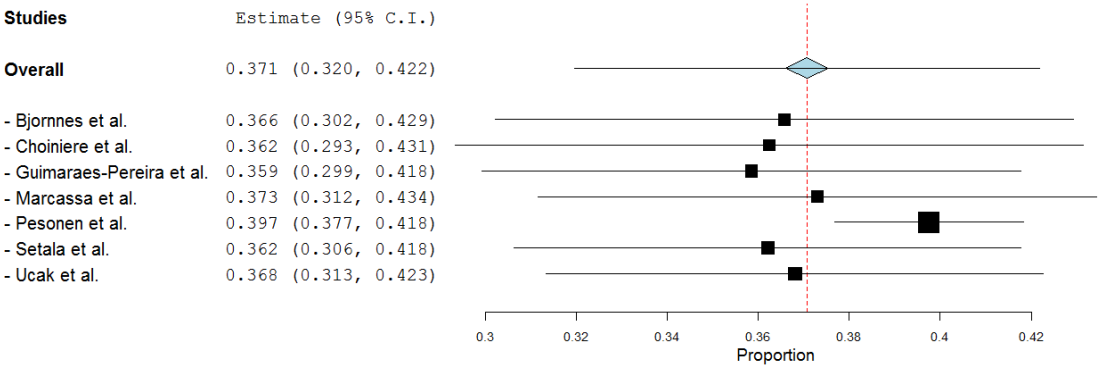
Supplementary Material 3 – Additional analysis

Incidence of PPP at 3 to less than 6 months after Cardiac Surgery: (a) forest plot, (b) leave-one-out meta-analysis, (c) quality assessment score subgroup forest plot, (d) type of study subgroup forest plot

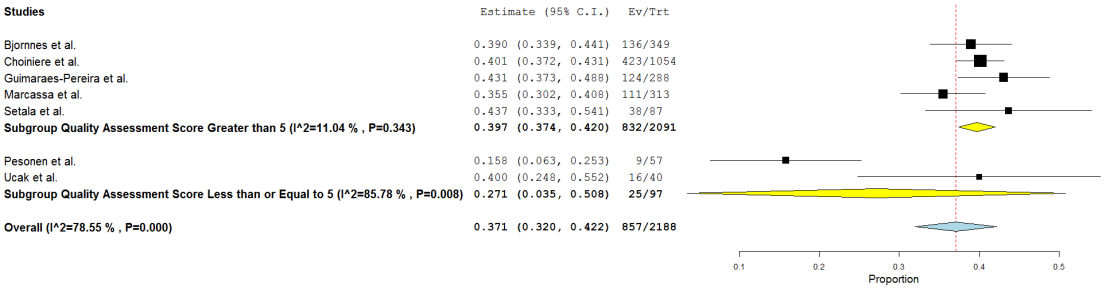
a)



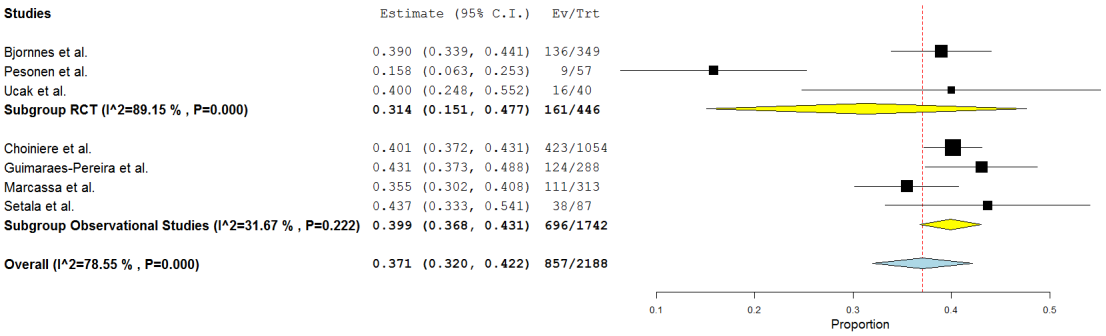
b)



c)

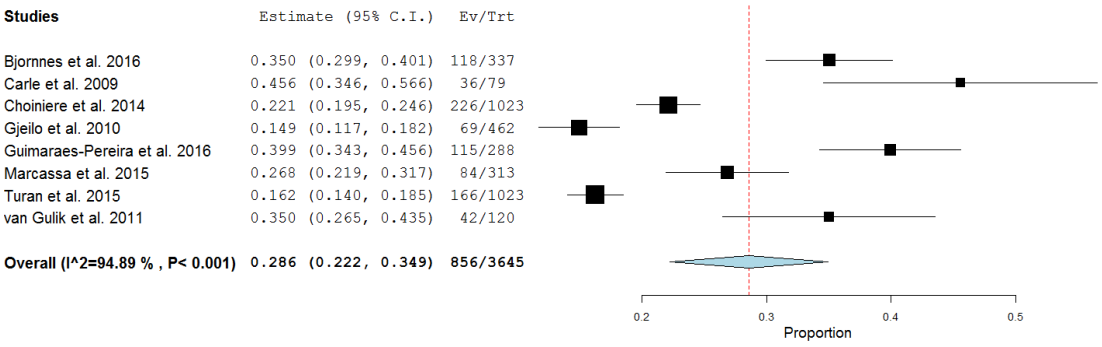


d)

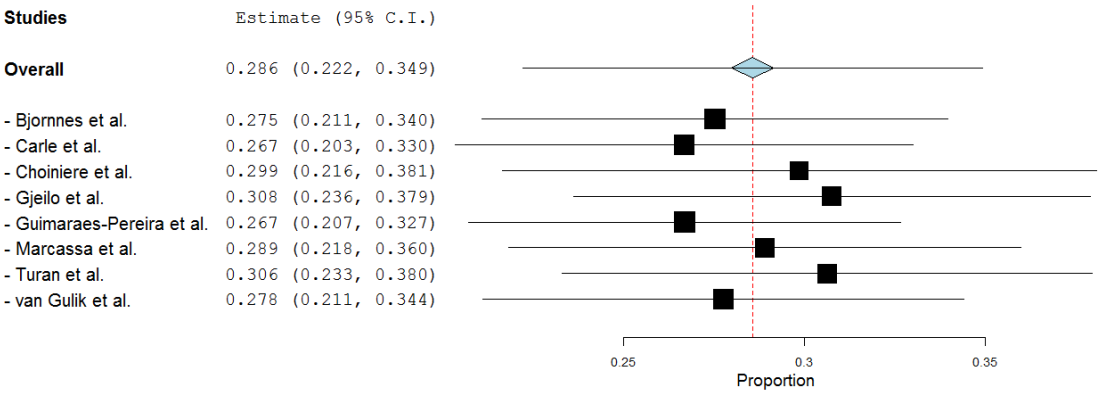


Incidence of PPP at 6 to less than 12 months after Cardiac Surgery: (a) forest plot, (b) leave-one-out meta-analysis, (c) quality assessment score subgroup forest plot, (d) type of study subgroup forest plot

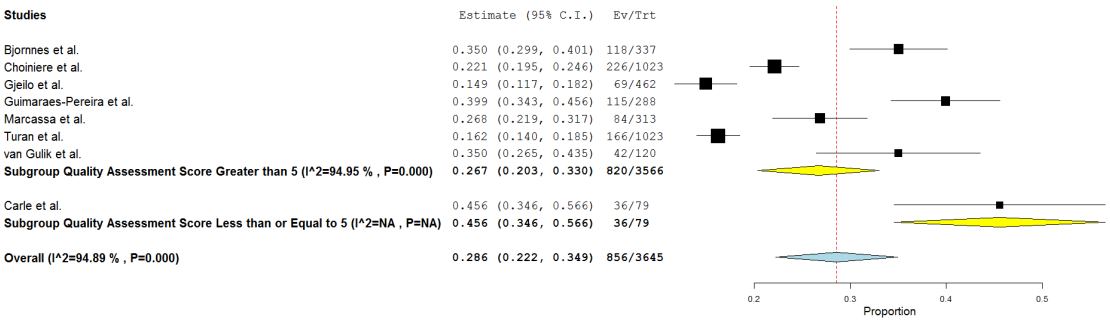
a)



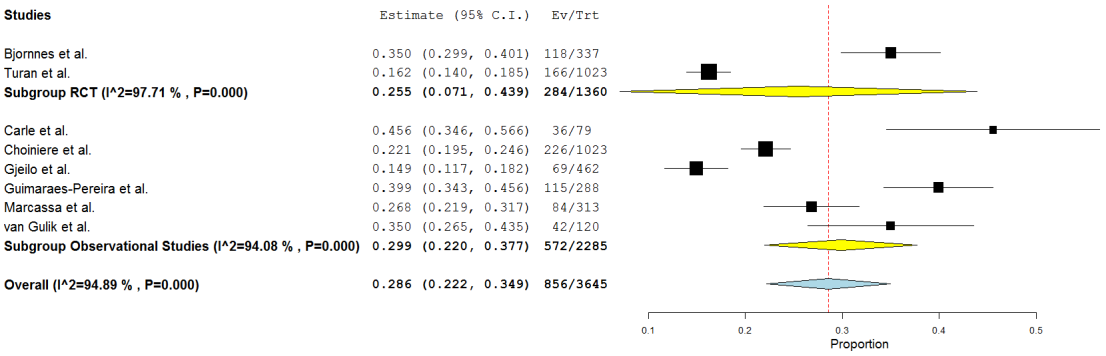
b)



c)

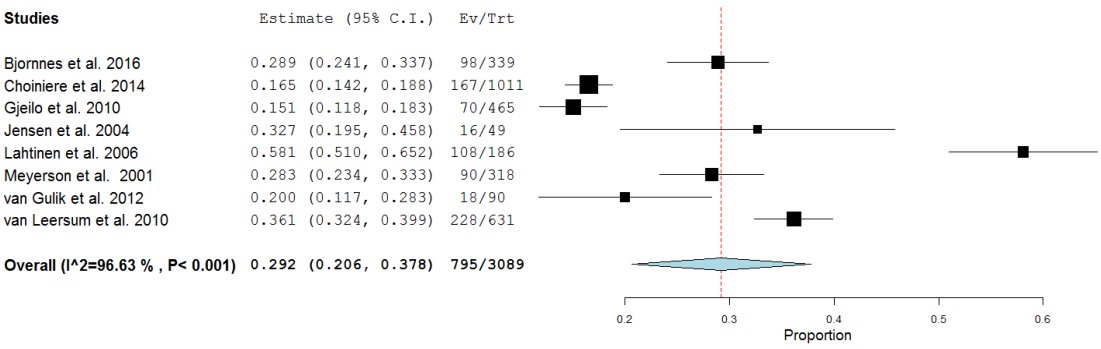


d)

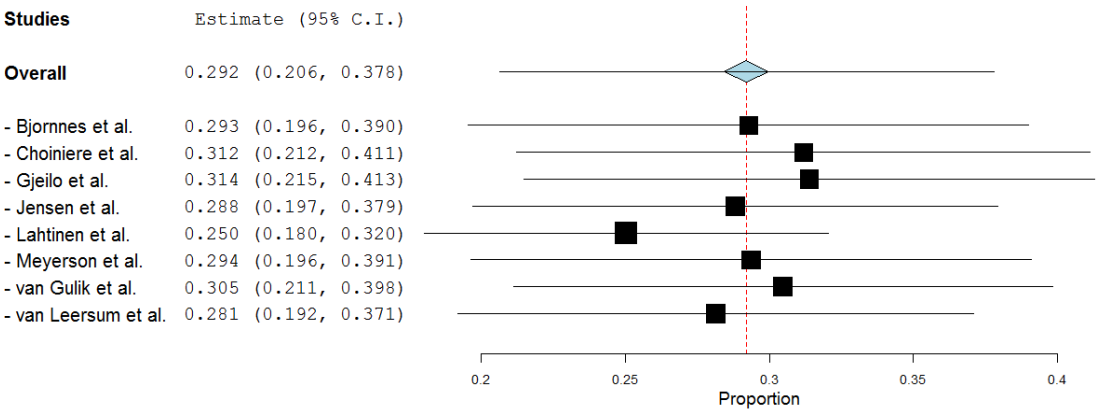


Incidence of PPP at 12 to less than 24 months after Cardiac Surgery: (a) forest plot, (b) leave-one-out meta-analysis, (c) quality assessment score subgroup forest plot, (d) type of study subgroup forest plot

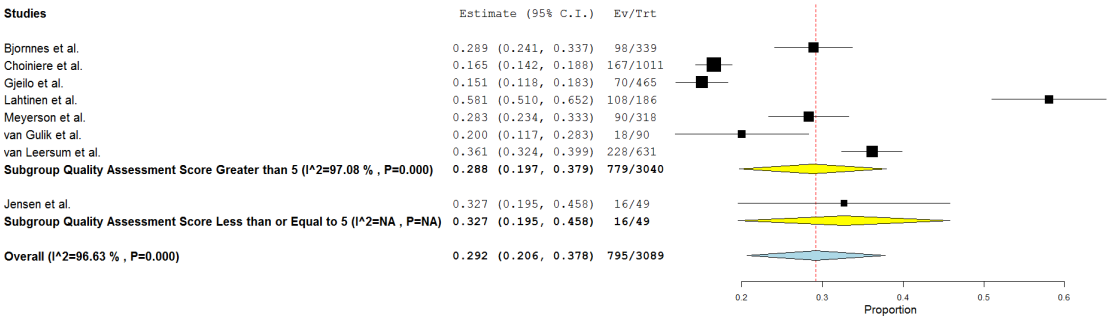
a)



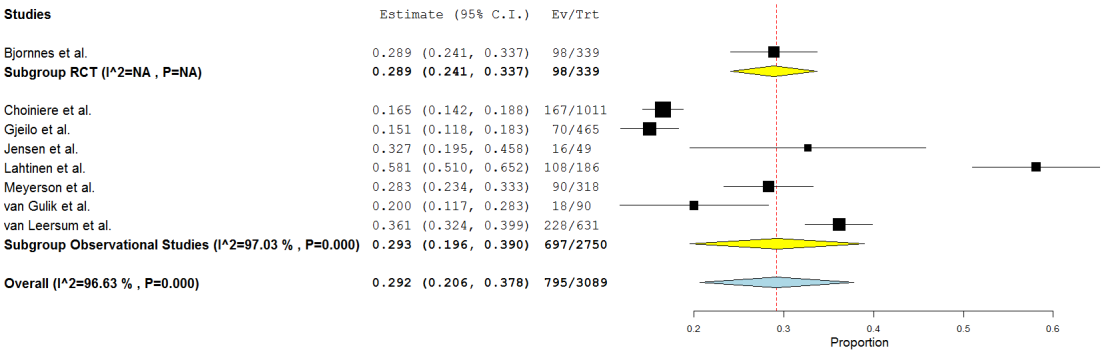
b)


Studies
Estimate (95% C.I.)
Overall 0.292 (0.206, 0.378)
- Bjornnes et al. 0.293 (0.196, 0.390)
- Choiniere et al. 0.312 (0.212, 0.411)
- Gjeilo et al. 0.314 (0.215, 0.413)
- Jensen et al. 0.288 (0.197, 0.379)
- Lahtinen et al. 0.250 (0.180, 0.320)
- Meyerson et al. 0.294 (0.196, 0.391)
- van Gulik et al. 0.305 (0.211, 0.398)
- van Leersum et al. 0.281 (0.192, 0.371)
0.2
0.25
0.3
0.35
0.4
Proportion

c)

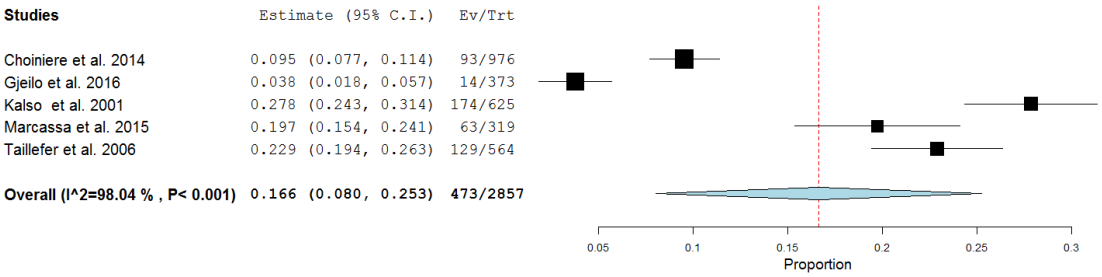

Studies
Estimate (95% C.I.) Ev/Trt
Bjornnes et al. 0.289 (0.241, 0.337) 98/339
Choiniere et al. 0.165 (0.142, 0.188) 167/1011
Gjeilo et al. 0.151 (0.118, 0.183) 70/465
Lahtinen et al. 0.581 (0.510, 0.652) 108/186
Meyerson et al. 0.283 (0.234, 0.333) 90/318
van Gulik et al. 0.200 (0.117, 0.283) 18/90
van Leersum et al. 0.361 (0.324, 0.399) 228/631
Subgroup Quality Assessment Score Greater than 5 (I^2=97.08 % , P=0.000) 0.288 (0.197, 0.379) 779/3040
Jensen et al. 0.327 (0.195, 0.458) 16/49
Subgroup Quality Assessment Score Less than or Equal to 5 (I^2=NA , P=NA) 0.327 (0.195, 0.458) 16/49
Overall (I^2=96.63 % , P=0.000) 0.292 (0.206, 0.378) 795/3089
0.2
0.3
0.4
0.5
0.6
Proportion

d)

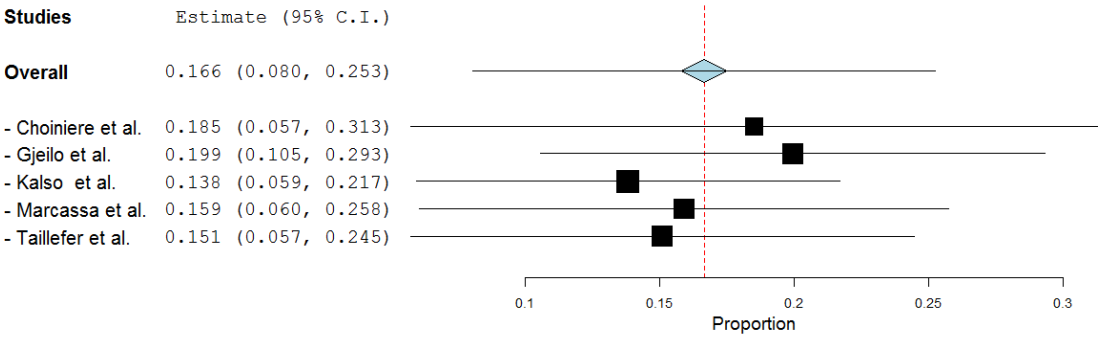

Studies
Estimate (95% C.I.) Ev/Trt
Bjornnes et al. 0.289 (0.241, 0.337) 98/339
Subgroup RCT (I^2=NA , P=NA) 0.289 (0.241, 0.337) 98/339
Choiniere et al. 0.165 (0.142, 0.188) 167/1011
Gjeilo et al. 0.151 (0.118, 0.183) 70/465
Jensen et al. 0.327 (0.195, 0.458) 16/49
Lahtinen et al. 0.581 (0.510, 0.652) 108/186
Meyerson et al. 0.283 (0.234, 0.333) 90/318
van Gulik et al. 0.200 (0.117, 0.283) 18/90
van Leersum et al. 0.361 (0.324, 0.399) 228/631
Subgroup Observational Studies (I^2=97.03 % , P=0.000) 0.293 (0.196, 0.390) 697/2750
Overall (I^2=96.63 % , P=0.000) 0.292 (0.206, 0.378) 795/3089
0.2
0.3
0.4
0.5
0.6
Proportion

Incidence of PPP at least 24 months after Cardiac Surgery: (a) forest plot, (b) leave-one-out meta-analysis

a)



b)



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Appendix A. Supplemental Digital Content

Supplementary Material 4 - Data for the estimation of the intensity of PPP at 3 to less than 6, 6 to less than 12, 12 to less than 24 and at least 24 months after CS

Source	Pain rating (magnitude)	Summary measure	Patients assessed (N)	3 to < 6 months			6 to < 12 months			≥ 12 months to < 24 months			≥ 24 months			Variable range *		
				Average	Worst	Other	Average	Worst	Other	Average	Worst	Other	Average	Worst	Other	Average	Worst	Other
Bjornnes 2016	NRS (0 – 10)	Mean (± SD)	All patients (349, 337, 339)		1.6 (± 2.1)			1.4 (± 2.0)			1.2 (± 2.1)							
Choiniere 2014	NRS (0 – 10)	Proportion of patients reporting ≥ moderate pain (≥4)	Pain Patients (423, 226, 167, 93)	149/423			72/226			67/167			35/93					
Costa 2015	NRS (0 – 10)	Proportion of patients reporting ≥ moderate pain (≥3)	Pain patients (178)										116/178					
Eisenberg 2001	VAS (0 – 100)	Mean (± SD)	Pain patients (217)													35 (± 22)		
	Verbal Scale (mild, moderate, severe, very severe)	Proportion of patients reporting ≥ moderate pain	Pain patients (217)													142/217		
Gjelio 2010	NRS (0- 10)	Proportion of patients reporting ≥ moderate pain (≥4)	Pain patients (50)							23/50	29/50	Present 14/50; Least 8/50;						
Gjelio 2016	NRS (0 – 10)	Proportion of patients reporting ≥ moderate pain (≥4)	Pain patients (14)										9/14	9/14				
Guimaraes-Pereira 2016	NRS (0- 10)	Proportion of patients reporting ≥ moderate pain (≥4)	Pain patients (124)	53/124														
Kalso 2001	Verbal Scale (mild, moderate, severe, excruciating)	Proportion of patients reporting ≥ moderate pain	Pain patients (174)										66/174					
Lahtinen 2006	NRS (0- 10)	Proportion of patients reporting ≥ moderate pain (≥4)	Pain Patients (108)									Rest 4/108; Movement 12/108;						
Marcassa 2015	NRS (0- 10)	Median (IQR)	All patients (313, 313, 319)	3.0 (2–5)	4.0 (2–6)					3.0 (2–4)	3.0 (2–5)		2 (1–3.8)	3.0 (2–5)				
		Proportion of patients reporting ≥ moderate pain (≥4)	Pain patients (111, 84, 63)	49/111	69/111					25/84	39/84							
Meyerson 2001	VAS (0-100)	Proportion of patients reporting ≥ moderate pain (>30)	Pain Patients (90)								41/90	Least Pain 8/90						
Taillefer 2006)	NRS (0- 10)	Mean (±SD)	Pain patients (129)										2.1 (± 2.4)					
		Proportion of patients reporting ≥ moderate pain (≥4)	Pain patients (129)										66/129	79/129				
Turan 2015	NRS (0- 10)	Mean (± SD)	Pain patients (166)				1.4 (± 1.6)	2.6 (± 2.3)										
van Gulik 2011	NRS (0- 10)	Proportion of patients reporting ≥ moderate pain (≥4)	Pain patients (42)					35/42	Least pain 7/42									
van Leersum 2010	NRS (0- 10)	Proportion of patients reporting ≥ moderate pain (≥4)	Pain patients (228)							130/228								

IQR: Interquartile Range; NRS: Numerical Rating Scale; SD: Standard Deviation; VAS: Visual Analog Scale.

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Appendix A. Supplemental Digital Content

Supplementary Material 5 - PPPCS's location

Source	Determination of Pain location	Assessment Time	Number of PPP patients evaluated	Pain location (Number of patients)				Observations
				Chest	Leg	Chest + Leg	Other	
Bjornes 2016	Assessing pain location on a body outline diagram.	12 Ms.	98	Sternotomy area: 44; elsewhere in the torso: 56.	19			Locations are not unique. Imprecisions.
Bruce 2003	Assessing pain location on an upper and lower body pain maps. Chest pain location was coded as right/left/front/back of the neck/shoulder/central chest/arm and side of body. Leg pain location was coded as right/l/eft/front/back of the lower/upper/ankle region and foot.	28 Ms (mean).	394	100	155	139		Data is more detailed, but mixes patients with angina and PPP. We have excluded cases with patients with angina and PPP.
Eisenberg 2001	Assessing pain location on a body outline diagram.	16 Ms (mean).	80	Left anterior chest wall: 53. Midline pain (around the scar): 47. Right-sided pain: 9.				Some patients reported having pain at more than one site.
Gjeilo 2010	Question regarding pain location.	12 Ms.	52 (five of the patients did not undergo vein harvesting)	Sternum only: 15.	2	Sternum and leg: 16 (from 47 patients because 5 didn't undergo vein harvesting from the leg).	Other location (shoulder, neck or back pain) only: 10. Other sites and/or leg and/or sternum: 9.	5 patients didn't undergo vein harvesting from the leg. Pain both at the leg and at the sternum site more intense than pain at one site only.
Gjeilo 2016	Question regarding pain location.	5 Ys.	14	Sternotomy site only: 5 (35.7%);	2 (14.3%)	Sternotomy site + leg: 3 (21.4%).	Sternotomy + other pain sites: 3 (21.4%); Only other sites: 1 (7.1%).	
Guimaraes-Pereira 2016	Assessing pain location on a body outline diagram (BPI-SF).	3 Ms.	124	Thorax (92%), Sternum (88%)	16% *			Some patients had pain at more than one site. *40% of the patients who underwent saphenous vein harvesting present PPP in the leg.
Lahtinen 2006	Assessing pain location on a body outline diagram.	1 Y.	108	73 (39%)	22 (12%)	13 (7%)		
Marcassa 2015	Record of major pain location, in relation to major surgical wounds.	3 Ms; 1 Y; 3 Ys.	111; 84; 63.	Sternum: 70% (3 Ms), 77.1% (1 Y), 74.3% (3 Ys);	17.3% (3 Ms); 16.9% (1 Y); 7.9% (3 Ys)	Sternum + leg: 12.7% (3 Ms), 6.0% (1 Y), 17.5% (3 Ys).		
Setia 2016	Question regarding pain location.	4 to < 6 Ms.	38	Around the sternal wound: 13 (4 of these had pain in several locations).	3		Shoulder: 3; Upper arm: 1; Back: 5; Joints: 1. Could not name a location at all: 7.	
Taillefer 2006	Question regarding pain location.	29.9 Ms (mean)	129	109 (84.5%)	46 (35.7%)		Other areas of the upper body (arms / shoulders / neck / back): 56 (43.4%).	PPP commonly present in more than one site.
van Gulik 2011	Question regarding pain location.	10 – 12 Ms.	42	Around sternotomy: 66%; elsewhere in thorax: 28.6%.			Diffusely in a non-specified anatomical region in the thorax: 4.8%.	
van Leersum 2010	Questionnaire and Physical examination.	19 Ms.	228	22%			Head: 33%; neck: 33%; shoulder: 45%; between the scapulae: 38%; arms: 21%.	Some patients had pain at more than one site.

M: Month; PPP: Persistent Postoperative Pain; PPPCS: Persistent Postoperative Pain after Cardiac Surgery; Y: Year.

4. DISCUSSION

As an inaugural comment, I must say that the general aims of this thesis were accomplished with success, namely the study of CPPCS' epidemiology and clinical properties.

In order to reach these general aims, as proposed, we have concluded two studies. Firstly, we have conceived, designed, and completed an observational prospective study in 310 patients undergoing CS (Paper A). We have calculated the CPPCS' incidence in one of the reference centres of CS in Portugal, and identified its predictive factors. Furthermore, we have characterized CPPCS in terms of pain intensity, pain interference and HRQL, pain temporal evaluation, pain descriptors and presence of NP. To achieve these goals, we have used adequately validated instruments.

Secondly, we have designed and materialized a systematic review of the literature about CPPCS' incidence, intensity, location, and the presence of NP (Paper B). The review comprised three phases: a methodological assessment of 6 different databases to identify potential papers and screening according to inclusion criteria by two independent reviewers; data extraction; and study's quality assessment. Twenty three studies were included in our systematic review, and we have performed a set of meta-analyses to provide estimates regarding incidence and intensity of CPPCS.

After performing an adequate and significant amount of original clinical research, we have composed, reviewed and published two papers in high impact factor journals, in order to disseminate our findings.

4.1. Main Findings

The main findings of this thesis can be outlined as follows.

Epidemiology

Incidence

- The CPPCS' incidence in one of the reference centres of CS in Portugal was 43% (95% CI: 37–49%) at 3 months and 40% (95% CI: 34–46%) at 6 months (Paper A).
- The pooled estimated incidence of CPP obtained in our meta-analysis was 37% (95%CI: 32–42%) in the first 6 months after CS and 17% (95%CI: 8–25%) more than two years after CS (Paper B);
- More recent studies report a higher incidence of CPP during the first 6 months after CS, compared to older studies (Paper B);
- The proportion of patients with CPPCS under any treatment is lacking in the literature (Paper B), but seems to be very low, as shown in our observational study, where only 16% of the patients with CPP were being treated (Paper A);

Predictive Factors

- Applying a multivariate logistic regression analysis (Paper A), we have identified several independent predictors of CPPCS: younger age, female gender, higher BMI, history of osteoarthritis, history of previous surgery (excluding sternotomy), catastrophizing, CABG and more intense acute postoperative pain;
- We have identified two strong independent predictors of CPPCS (Paper A): age lower than 69 years (Odd Ratio: 10.45) and moderate to severe classification in worst pain item of Brief Pain Inventory - Short Form (BPI-SF), at the third postoperative day (Odd Ratio: 15.07).

- Preoperative angina pectoris was a predictor for NP in patients with CPP (Paper A);

Clinical Properties

Intensity

- In our observational study (Paper A), 57.3% of patients with CPPCS rated their average pain (using BPI-SF) as mild and 42.7% as moderate. Regarding BPI-SF worst pain item, 17.7% rated it as mild, 54.9% as moderate and 27.4% as severe.
- Large heterogeneity was found concerning recording and reporting CPP intensity's assessment (Paper B).
- The results obtained in our meta-analysis (Paper B), revealed that a large proportion of patients with CPPCS present moderate to severe pain (regarding their average pain: 40 to 50%; regarding their worst pain: 49 to 53%; variation according the time frame) and these percentages did not reduce over time;

Pain Interference and Health-Related Quality of Life

- CPPCS caused substantial interference in patients' daily life, and the most affected activities were: "sleep", "general activity" and "normal work" (Paper A);
- Patients with CPPCS presented lower HRQL, namely, worse results in several health measures and dysfunction measures (Paper A);

Temporal evaluation

- In most patients with CPPCS, pain was not permanently present and it had paroxysms (Paper A);

CPPCS' location

- Chest is the main location of CPPCS, followed by the leg (Paper A and B);

Presence of Neuropathic Pain

- NP was detected in 50% of the patients with CPPCS, using a validated questionnaire (Paper A);
- Patients with CPPCS who reported moderate to severe pain presented NP more often (Paper A);
- CPPCS located in the leg was more often identified as NP than CPPCS located in the chest (Paper A);
- NP seems to be present in the majority of patients with CPPCS, however, only a minority of the included studies addressed this issue and there was a lack of uniformity in the methods used to measure NP (Paper B);

The main findings of each study are presented in detail in each paper.

4.2. CPPCS' Epidemiology

Epidemiology is the study of the occurrence and distribution of health-related events, states, and processes in specified populations, including the study of the determinants influencing such processes, and the application of this knowledge to control relevant health problems [97]. Good epidemiological research on chronic pain provides important information on occurrence and factors associated with its onset and persistence [132].

4.2.1. Incidence

Incidence is a term describing the frequency of a disease or other event or attribute in a population [97]. Therefore, it is essential to know the incidence of CPPCS. As previously introduced, the precise magnitude of the incidence of CPPCS was still under debate, and this limited the perception of the true dimension of this problem. One of our aims was to identify the incidence of CPPCS. This thesis addressed this issue in two steps, first with an observational prospective single centre study and lately with a systematic review. Our observational prospective single centre study [54] revealed an incidence of 43% (95% CI: 37–49%) 3 months after CS and of 40% (95% CI: 34–46%) 6 months after CS, which were in accordance with the existing literature [23; 26; 79; 131; 133]. Interestingly, none of the patients who deny pain 3 months after CS reported CPP 6 months after CS, and consequently all patients who reported CPP 6 months after CS had CPP 3 months after CS, which supports the current evidence that the 3-month time frame, used by IASP for CPP definition [74], is adequate. The systematic review with meta-analysis performed [55], estimated a CPPCS' incidence of 37% (95%

CI: 32–42%) in the first 6 months after CS and 17% (95% CI: 8–25%) 2 years after CS. Consequently, the incidence of CPPCS is one of the highest compared to other types of surgeries [58; 73; 75]. Despite this, CPPCS is often ignored, when compared with CPP after other types of surgeries. As an example, recently, an important systematic review has focused on therapeutic interventions to reduce CPP on surgical procedures associated with high incidence of CPP [60]. These surgical procedures were: amputation, mastectomy and thoracotomy. Alternatively, other authors aimed to analyse functional genetic polymorphisms and clinical factors that might identify CPP risk after inguinal hernia repair, hysterectomy, and thoracotomy [98].

Although there are some narrative reviews about CPPCS [27; 50; 91], our systematic review constitutes the first systematic review and meta-analysis regarding the incidence of CPPCS. Therefore, these data are expected to provide an important contribution to recognize CPP as a frequent outcome after CS.

The incidence of CPPCS decreases along time after surgery, in contrast to what was described in a previous systematic review regarding thoracotomies [12]. Fletcher et al. [45] found a similar decline regarding the incidence of moderate CPP between 6 and 12 months after several types of surgeries. The estimated incidence of CPP is higher in the first months after CS (3 to less than 6 months after CS) compared to other time frames; and more than two years after CS its value is less than half of the initial. The pathophysiology of this decline is not clear, though as the time with CPP evolves it may be assumed that these patients are identified and given appropriate treatment with better follow-up performed. In our observational study [54], the proportion of patients with pain remained almost the same between 3 and 6 months, which could be justified by the enormous lack of CPP treatment, as 84% of these patients were not under any treatment or referral. However, data regarding the proportion of patients with CPPCS under any treatment or referral are lacking, as only our observational study [54] addressed it. As recently stated [6], it would be interesting to know why some patients with pain abstain from using analgesics; whether this is due to poor effect in this pain

condition or for other reasons. Alternative hypotheses for the decline of CPPCS incidence through time are that this may be attributable to psychological factors or CPP pathophysiology. Psychological factors are important in pain perception [38; 123], and resilience and positive affect have shown to reduce chronic pain [144]. Improved HRQL is a major objective for CS [20; 41] and it's well proven [51; 119]. Likewise, we have witnessed this improvement throughout our observational study as we compared patients' HRQL before CS with patients' HRQL 3 months after CS. As a result, improvement in HRQL and satisfaction with life may contribute to their psychological profile. Consequently, a possible hypothesis is that HRQL improvements over time might lead to continuous pain decline in these patients. However, this hypothesis lacks formal confirmation. The role of contextual and cognitive content variables in chronic pain is not only important but also complex [48]. The cause of CPPCS is multifactorial and tissue destruction, nerve trauma, scar formation, bone fractures, stainless-steel wire sutures, and/or costochondral separation may all play relevant roles [25]. Noxious input from acute injury may trigger a state of CNS sensitization. In essence, dorsal horn neurotransmitter release via nociceptive input conditions the CNS such that there is enhanced responsiveness (secondary hyperalgesia). Although experimental evidence exists indicating that enhanced responsiveness outlasts the initial provocative insult, the exact clinical relevance and extent remain to be determined [25].

According to our search, the first studies regarding the incidence of CPPCS appeared in 2001 [43; 71; 96]. Despite medical progress and improved awareness of CPP, it is surprising that the incidence of CPPCS has a positive trend over time, regarding the first 6 months after CS. However, it is important to notice that older studies considering this time frame presented lower quality assessment scores, which could underestimate the incidence of CPPCS. On the other hand, a negative trend was found regarding studies evaluating CPP at least 2 years after CS. A possible explanation for this is the

improved accessibility of patients with long-term pain states to health care and better analgesic regimens to treat CPP achieved in the latter years.

4.2.2. Predictive factors

One of the essential aims of epidemiology is the prevention of diseases. Primary prevention is intended to prevent a disease or symptom from occurring. Secondary prevention is aimed at early detection so that treatment begins before it becomes chronic. Tertiary prevention seeks not to prevent disease or symptoms, but to minimise disability and handicap arising from it [59]. A potential strategy for primary prevention of CPP is to identify factors that may predict an increased likelihood of its establishment. With this approach, we may be able to target specific interventions to the most vulnerable patients or use the information when considering the need for surgery, its extent, or both [101]. Predictive factors for CPP can be patient specific or surgery specific. Furthermore, these factors can be subdivided into preoperative, intraoperative, and postoperative factors. In our observational study [54], we have performed a multivariate logistic regression analysis in order to identify independent predictors of CPPCS. We have identified 6 preoperative independent predictors: younger age, female gender, higher BMI, history of osteoarthritis, history of previous surgery (excluding sternotomy) and catastrophizing. CABG was found to be an intraoperative independent predictor and more intense acute postoperative pain a postoperative independent predictor. Previously, Gjeilo et al. [50] identified younger age, female gender and higher BMI as predictors of CPPCS. In our study, age lower than 69 years was a strong independent predictor of CPPCS (Odd Ratio: 10.45). Previous findings have shown that younger age was associated with higher acute postoperative pain, independently of the type and extent of surgery [47], and with CPPCS [26; 50]. According to Gerbershagen et al. [47], “many factors could influence the pain

differences with age, such as bio-psychosocial and life-stage factors, as well as changes in the complex cascade of immune, inflammatory, and neural responses [46; 65]". Women are more likely to develop chronic pain conditions, and several epidemiological studies reported a higher prevalence of chronic painful diseases in women [88]. CS in patients with higher BMI is technically more difficult, with prolonged retraction and more probable nerve damage, and thus a higher incidence of CPP [23].

We were unable to estimate the incidence of CPPCS according to the subtype of surgery performed because the majority of the studies included in our systematic review presented combined data. Furthermore, we have not found association between subtype of surgery and CPPCS in the majority of the literature [23; 26; 49; 87; 96; 120; 130; 131], except in our observational study [54] and in another one where CABG with internal thoracic artery (ITA) grafts were associated with higher rates of CPP [29]. A possible explanation for higher incidence of CPP in patients who underwent CABG could be the higher probability of damage of the intercostal nerves during ITA harvesting [91]. Some authors have confirmed that skeletonized ITA harvesting reduces intercostal nerve injury, and consequently reduces CPP [11; 89].

There are conflicting reports regarding the role of angina pectoris in CPPCS [23; 117]. Regarding this factor, we haven't found an association with CPPCS, however patients with preoperative angina pectoris who developed CPPCS were more prone to develop NP, which is a new finding and suggests that it could be involved in the pathophysiology of NP in patients who underwent CS.

Although current evidence suggests that psychological factors are important in pain perception [38; 64; 123], we found no association with anxiety or depression in the development of CPP. Duke Health Profile has been shown to be an effective brief screener for both anxiety and depression [103], notwithstanding, the distinction between state and trait anxiety could have been important because there are reports of association between state but not trait anxiety with postoperative pain [90; 113].

Catastrophizing is a known risk factor for CPP [122] and acute postoperative pain after CS [78]; however, its identification as an independent predictor of CPPCS occurred for the first time in our observational study.

Osteoarthritis and history of previous surgery were also identified as independent predictors of CPPCS. A possible explanation for this result could rely on the concept of deficient endogenous pain modulation (EPM). EPM is a wide-ranging term, delineating the array of processes taking place in the central nervous system to reduce or increase pain [143]. Enhanced temporal summation and less efficient conditioned pain modulation can both occur in patients with pain, such as in patients with osteoarthritis [9]. Use of pain-modulating drugs may rectify the deficient EPM [143].

Regarding acute postoperative pain, moderate to severe classification in worst pain item of BPI-SF, at the third postoperative day, was a strong independent predictor of CPPCS (Odd Ratio: 15.07). Higher pain ratings and analgesic requirements during the first postoperative days have been associated with increased risk of CPPCS [26; 91; 131]. The relationship between acute pain and CPP could be associative or causal [50]. Although this uncertainty remains, interventions to decrease acute pain should be an imperative. Once again, EPM seems to be involved. Weissman-Fogel et al. [137], proposed the role of pain temporal summation assessed preoperatively as a significant psychophysical predictor for acute postoperative pain intensity. Our systematic review [55] revealed that the CPPCS' estimated incidences were lower in the randomized controlled trials (RCTs) sub-group. These RCTs studies [15; 105; 127; 129] address strategies to reduce acute postoperative pain. Although they could not prove the efficacy of their interventions in reducing CPPCS, two of them reported reduced acute postoperative pain [105; 129]. Intervention studies that aim to reduce acute postoperative pain play a fundamental role in preventing CPP, as acute postoperative pain is a strong predictor of CPPCS [26; 54; 131] and CPP following other types of surgeries [73]. Even though efficacy is not proven for statistical or non-superiority reasons, tight and optimal treatment of acute postoperative pain is offered to patients

enrolled in these interventional studies. In addition, placebo analgesic effects substantially contribute to the overall effectiveness of analgesic treatments [28].

4.3. Clinical properties

4.3.1. Pain Intensity

Pain severity can be graded based on pain intensity [125], and large heterogeneity was found concerning recording and reporting CPPCS intensity's assessment [55]. Similar problems were reported in other systematic reviews with meta-analysis on CPP after other types of surgeries [12; 136]. Regarding intensity assessment, the recommendations of the IMMPACT group should be followed [40; 128] to achieve stronger evidence regarding CPPCS' intensity. In addition, studies should present pain intensity in patients with CPP and not in all the patients studied, to overcome the risk of underestimation.

In our systematic review with meta-analysis, we have estimated that a large proportion of patients with CPPCS present moderate to severe pain (regarding their average pain: 40 to 50%; regarding their worst pain: 49 to 53%; variations according to the time frame considered) and this proportion did not reduce over time [55]. This pattern also was obtained in another systematic review regarding thoracotomy [12]. Although the incidence of CPP at least two years after CS declines, we estimate that half of these patients present moderate to severe pain, which is a higher proportion than the obtained in the other time frames. This could indicate the existence of a subtype of CPPCS more difficult to treat for several reasons that should be addressed in future studies.

The issue of pain intensity was also addressed in our observational study [54]. Regarding average pain classification, the results obtained [54] are in accordance with the results estimated in our meta-analysis [55]. However, regarding worst pain classification, we have identified a higher percentage of patients with moderate to severe pain in our observational study (82.3%), which is alarming and should be

addressed by health professionals and authorities of this centre involved in the treatment of these patients.

There is an association between moderate to severe CPP and the presence of NP [39; 45; 54; 69], which highlights the importance of nerve damage in these patients. This finding is discussed with detail later on, in the subsection “Presence of NP”.

4.3.2. Pain Interference and Health-Related Quality of Life

In addition to pain intensity, pain severity can be also graded based on pain-related distress, and functional impairment [125]. This issue was analysed in our observational study [54], namely, pain interference with daily activities and impact in HRQL.

Patients with CPPCS reported a substantial overall interference in daily life, in keeping with other studies [43; 49; 120; 131]. Approximately half of the patients with CPPCS reported a moderate to severe overall interference. More specifically, the most affected activities were: “sleep”, “general activity” and “normal work”. More than three quarters of the patients had interference in their sleep, which has potential adverse effects [5]. Sleep plays a vital role in health and well-being throughout life; and sleep quality is associated with mental health, physical health, quality of life, and safety [5].

Additionally, more than half of patients with CPPCS reported pain interference in “normal work” item, which could lead to job loss, change in professional responsibilities, switching profession/job, early retirement, and long-term sick leave, as it happens in other chronic pain syndromes [10]. Therefore, beyond emotional and financial impact for the patient, CPPCS could have an economic impact for the society.

Concurrently, a small proportion of patients (15%) denied any overall interference brought by their pain.

HRQL is a multidimensional concept that relates specifically to a person's health, to the measure of its functioning, well-being and general health perception in physical, psychological, and social domains [8]. As previously stated, patients who underwent CS improved their HRQL and we have witnessed it [51; 54; 119]. However, we have found a lower HRQL in patients with CPPCS, which is in accordance with previous studies [23; 49; 54; 120]. These patients presented worse results in several health measures, namely, physical health, mental health, social health, general health; they also presented worse results in several dysfunction measures, namely, anxiety, depression and pain.

The substantial interference in daily life and lower HRQL highlight the detrimental outcomes of CPPCS, not only for the patient but also for the society.

4.3.3. Temporal evaluation

Temporal evaluation of spontaneous ongoing pain and paroxysmal pain represent an important aspect of the evaluation of pain in patients and their treatment strategy [88]. This information can be used to adjust medication according to pain temporal characteristics. Nevertheless, the temporal characteristics of CPPCS were lacking in the current literature and were addressed for the first time in our observational study [54]. Regarding pain periodicity, our results are approximately equally tripartite between patients who reported pain permanently present, pain presence between 8 and 12 hours and pain presence between 4 and 7 hours (per day). Regarding pain paroxysms, we have found that approximately half of the patients with CPPCS (54%) presented 1 to 5 pain attacks during one day. A minority of patients with CPP (19%) denied pain attacks.

4.3.4. CPPCS' location

We have detected large heterogeneity concerning the location assessment and reports. The most reported location was the chest, in the sternum more specifically, followed by the legs.

The main locations identified were related to the extent of the surgical wound. Nevertheless, pain was also present in areas not linked with the surgical wound, which could be explained by the presence of referred pain, suboptimal positioning of patients during surgery, or central venous catheter placement [25].

Vessel harvesting is responsible for some of the pain locations; however the presented data have a wide range of results, which limits the recognition of its exact contribution. Additionally, most of the studies did not present the relationship of patients who reported CPP in the leg with patients who had saphenous vein harvesting.

4.3.5. Presence of Neuropathic Pain

Relatively to pain descriptors of McGill Pain Questionnaire – Short Form (MPQ-SF) in patients with CPPCS, our observational study [54] revealed that "Tender" was the descriptor mentioned more often as severe, followed by "Hot-Burning", "Sharp" and "Aching". Regarding *Douleur Neuropathique en 4 questions* (DN4), the most common descriptors identified by patients with CPPCS were "Pins and needles" (77.4%) and "Tingling" (46.8%). The less reported was "Painful cold" (15.3%). Both MPQ-SF pain and DN4 descriptors suggest that a high proportion of patients present CPP with a neuropathic component.

CPP has been considered neuropathic, and a strong association is reported between CPP and sensory abnormalities, but the evidence suggests that mechanisms other than nerve injury such as inflammation, central sensitization, or a combination of these play a role [58]. In order to identify risk factors for CPP, it is essential to understand the underlying mechanisms and to elucidate whether CPP is due to surgical injury to the nerves, ongoing inflammatory processes, injury to the somatic or visceral structures, or other causes [58]. Consequently, we have addressed this issue in our observational study [54] and our systematic review [55].

After a systematic review of the literature [55], we have found only few studies [43; 54; 71; 81; 127] that addressed heterogeneously this issue, including our observational study, where NP was detected in 50% of the patients with CPPCS, using a validated questionnaire. Despite the wide variation of proportion of patients with NP and its assessment, NP seems to be present in a considerable number of patients with CPPCS. Three of the included studies [43; 54; 81] reported that the majority of patients presented with NP. Nerve injury–induced NP has been proposed as a major cause of CPP and a recent review suggests that the occurrence of NP among CPP cases differs in various types of surgery, probably depending on the likelihood of surgical iatrogenic nerve injury [58]. Two studies [43; 81] applied Quantitative Sensory Test (QST) in their assessments. QST in pain research involves a large variety of stimulus modalities (thermal, mechanical, chemical, electrical), assessment methods (psychophysics, electrophysiology, imaging, microdialysis), and target structures (skin, musculoskeletal, and viscera). QST can provide an understanding of the mechanisms involved in pain transduction, transmission, modulation, and perception under normal and pathophysiological conditions; consequently, it may contribute to mechanism-based diagnosis, prevention, and management of pain in future [67]. Eisenberg et al. [43], reported that only less than 20% of patients with CPPCS have normal sensation in the painful site, which clearly indicates an underlying neuropathic mechanism in most of those patients. Additionally, Lauridsen et al. [81] reported that QST revealed sensory

abnormalities in 10 out of 13 children with CPPCS. Translating QST-based mechanistic knowledge into the benefit of patients, as better diagnosis and treatment, is the future research agenda for this field.

We have found that patients with moderate to severe CPPCS presented significantly more often NP [54]. This is in line with previous studies that enrolled patients suffering from CPP [39; 45; 69], and points to nerve damage as a possible important risk factor for CPP in a significant proportion of cases, particularly those with moderate to severe pain. Duale et al. [39], concluded that in a similar way to other types of chronic pain, the neuropathic aspect of CPP may be a factor of severity and chronification. Moreover, Fletcher et al. [45] found an association between CPP with neuropathic characteristics and more pronounced functional impairment.

Persistent harvest-site pain occurs with astonishing frequency after CABG [37]. CPP was present in the legs in a high proportion of patients who underwent saphenous vein harvesting [54], as previously suggested [23; 71; 79; 120]. CPPCS located in the leg was more often identified as NP than CPPCS located in the chest [54], which confirms previous findings [23]. A possible explanation is that saphenous nerve injury can occur as a result of surgical handling or post-operatively from compression caused by subcutaneous suturing. Relevant literature addressed alternative techniques to avoid this injury [3; 17; 115].

Preoperative angina pectoris wasn’t associated with higher incidence of CPPCS, but patients with preoperative angina pectoris who developed CPPCS were more prone to develop NP [54], which is a new finding and suggests that it could be involved in the pathophysiology of NP in patients who underwent CS.

4.4. Strengths and limitations

The major strength of this PhD thesis is the extensive analysis of the current literature about CPPCS. We have performed a careful epidemiological evaluation of CPPCS by providing important information on incidence and factors associated with its onset.

Regarding incidence, we have presented pooled estimates about CPPCS' incidence for the first time. Moreover, we have studied the course of CPPCS as it evolves and its tendency according to publication year, which could inform all those involved in the study of this topic, clinicians who treat pain patients and health authorities.

As recently commented upon [53], if the presence of CPP is established at 3 months, it is crucial that a formal diagnosis is made, appropriate treatment is given and that follow-up is performed. However, data regarding the proportion of patients with CPPCS under treatment is lacking, and our observational study [54] provides important information about it. Therefore, this thesis highlights the need to perform follow-up and to provide adequate treatment in patients with CPPCS.

Concerning factors associated with its onset, we have identified a set of independent predictors of CPPCS, based on a multivariate logistic regression analysis. In addition, we have identified two strong predictors of CPPCS with odd ratios higher than 10. As stated in the preceding sections, the identification of predictive factors could allow target specific interventions to the most vulnerable patients. Moreover, acute postoperative pain is a modifiable predictive factor, and our results emphasize the importance of attempting to reduce it.

Additionally, we present a comprehensive analysis of CPPCS' clinical properties, namely pain severity, pain temporal evaluation, pain location and NP presence.

This thesis provides an assessment of CPPCS' severity, based on pain intensity and impact in patient's life, namely interference in daily activities and HRQL. Besides large heterogeneity concerning recording and reporting CPP intensity's assessment, we have provided pooled estimates through different time frames. This has never been

done, and allows us to observe that two years after CS, the proportion of patients with CPP who present moderate to severe pain is not lower than the obtained in the other time frames. Although the impact of CPPCS in patient's life was previously studied [23; 43; 49; 120; 131], our observational study reinforces its substantial interference in daily life and its HRQL reduction [54], which highlight the detrimental outcomes of CPPCS.

Considering pain temporal evaluation as an important aspect of the evaluation of pain patients and their treatment strategy, this thesis presents its analysis for the first time.

Finally, this thesis describes the NP presence in CPPCS, which is essential to understand underlying mechanisms and to adjust its prevention and treatment. Only few studies [43; 54; 71; 81; 127], including our observational study, have addressed this issue, and they suggest that NP is present in the majority of the patients with CPPCS.

This thesis has some limitations. Firstly, the identification of predictive factors of CPPCS was performed based on a sample that comes from a single hospital, which could bring some bias, with respect to surgical techniques and acute pain treatment, and might be a threat to generalizability. Although there was a literature framework, this issue should be confirmed with stronger evidence. Secondly, the knowledge of the contribution of NP in CPPCCS was based in few studies [43; 54; 71; 81; 127] and the methodology to assess NP varied across studies. The classic presentation of NP is characterized both in descriptive terms and sensory signs; however, the specificity and the sensitivity of these are suboptimal [58]. Ideally, each patient reporting CPP should have had a validated diagnosis, according to standardized procedures including QST [68]. In an attempt to strengthen the criteria for what is and what is not NP, a probability grading system for categorizing NP, was included in the latest European Federation of Neurological Societies guidelines on NP assessment [34], and should be followed in future studies focusing this issue.

The specific strengths and limitations of each study are discussed in detail in each paper.

5. CONCLUSION

This thesis provides the most complete assessment and discussion of the current best evidence regarding the epidemiology and clinical properties in the context of CPPCS.

Our research indicates that CPP is a frequent and deleterious outcome after CS, apparently poorly recognized and treated. Given the foregoing and associating the fact that CS is one of the most frequently performed interventions worldwide [107], CPPCS should be considered a relevant health problem which deserves special attention from health care professionals and health authorities.

The research work that constitutes this PhD thesis is expected to provide an important scientific impetus that will foster and support improvements in prevention, diagnosis, follow-up and treatment of CPPCS. In the future, the construction of an easily applicable risk index could allow the identification of patients at high-risk of developing CPPCS. This should allow for targeted interventions which consequently may decrease CPPCS' incidence and impact.

To conclude, while some might perceive a PhD thesis as representing the end of a chapter in an individual's scientific career, for me it is the commencement of the path to increased research independence. The ultimate aim is to produce clinical research that may lead to change the outcomes and lives of all those who may suffer from CPPCS, and to a broader extent all those who may suffer from CPP.

6. REFERENCES

[1] Aasvang EK, Gmaehle E, Hansen JB, Gmaehle B, Forman JL, Schwarz J, Bittner R, Kehlet H. Predictive risk factors for persistent postherniotomy pain. Anesthesiology 2010;112(4):957-969.

[2] Alcock MM. Defining pain: past, present, and future. PAIN 2017;158(4):761-762.

[3] Allen K, Cheng D, Cohn W, Connolly M, Edgerton J, Falk V, Martin J, Ohtsuka T, Vitali R. Endoscopic Vascular Harvest in Coronary Artery Bypass Grafting Surgery: A Consensus Statement of the International Society of Minimally Invasive Cardiothoracic Surgery (ISMICS) 2005. Innovations (Philadelphia, Pa) 2005;1(2):51-60.

[4] Althaus A, Hinrichs-Rocker A, Chapman R, Arranz Becker O, Lefering R, Simanski C, Weber F, Moser KH, Joppich R, Trojan S, Gutzeit N, Neugebauer E. Development of a risk index for the prediction of chronic post-surgical pain. European journal of pain (London, England) 2012;16(6):901-910.

[5] Alvarez GG, Ayas NT. The impact of daily sleep duration on health: a review of the literature. Progress in cardiovascular nursing 2004;19(2):56-59.

[6] Andersen KG, Duriaud HM, Jensen HE, Kroman N, Kehlet H. Reply. Pain 2016;157(5):1174.

[7] Apfelbaum JL, Chen C, Mehta SS, Gan TJ. Postoperative pain experience: results from a national survey suggest postoperative pain continues to be undermanaged. Anesthesia and analgesia 2003;97(2):534-540, table of contents.

[8] Apolone G, Mosconi P. Review of the concept of quality of life assessment and discussion of the present trend in clinical research. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 1998;13 Suppl 1:65-69.

[9] Arendt-Nielsen L, Nie H, Laursen MB, Laursen BS, Madeleine P, Simonsen OH, Graven-Nielsen T. Sensitization in patients with painful knee osteoarthritis. Pain 2010;149(3):573-581.

[10] Azevedo LF, Costa-Pereira A, Mendonca L, Dias CC, Castro-Lopes JM. Epidemiology of chronic pain: a population-based nationwide study on its prevalence, characteristics and associated disability in Portugal. The journal of pain : official journal of the American Pain Society 2012;13(8):773-783.

[11] Bawany FI, Khan MS, Khan A, Hussain M. Skeletonization technique in coronary artery bypass graft surgery reduces the postoperative pain intensity and disability index. Journal of cardiac surgery 2014;29(1):47-50.

[12] Bayman EO, Brennan TJ. Incidence and severity of chronic pain at 3 and 6 months after thoracotomy: meta-analysis. The journal of pain : official journal of the American Pain Society 2014;15(9):887-897.

[13] Ben-Eliyahu S. The promotion of tumor metastasis by surgery and stress: immunological basis and implications for psychoneuroimmunology. Brain, behavior, and immunity 2003;17 Suppl 1:S27-36.

[14] Benhamou D, Berti M, Brodner G, De Andres J, Draisci G, Moreno-Azcoita M, Neugebauer EA, Schwenk W, Torres LM, Viel E. Postoperative Analgesic THerapy Observational Survey (PATHOS): a practice pattern study in 7 central/southern European countries. PAIN 2008;136(1-2):134-141.

[15] Bjornnes AK, Parry M, Lie I, Fagerland MW, Watt-Watson J, Rustoen T, Stubhaug A, Leegaard M. The impact of an educational pain management booklet intervention on postoperative pain control after cardiac surgery. European

journal of cardiovascular nursing : journal of the Working Group on Cardiovascular Nursing of the European Society of Cardiology 2016.

[16] Blyth FM, March LM, Cousins MJ. Chronic pain-related disability and use of analgesia and health services in a Sydney community. The Medical journal of Australia 2003;179(2):84-87.

[17] Bonde P, Graham AN, MacGowan SW. Endoscopic vein harvest: advantages and limitations. The Annals of thoracic surgery 2004;77(6):2076-2082.

[18] Bonica J. The management of pain. Philadelphia: Lea & Febiger, 1953.

[19] Bonica JJ. Pain. New York: Raven Press, 1980.

[20] Bonow RO, Carabello BA, Chatterjee K, de Leon AC, Jr., Faxon DP, Freed MD, Gaasch WH, Lytle BW, Nishimura RA, O'Gara PT, O'Rourke RA, Otto CM, Shah PM, Shanewise JS. 2008 focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 1998 guidelines for the management of patients with valvular heart disease). Endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Journal of the American College of Cardiology 2008;52(13):e1-142.

[21] Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. European journal of pain (London, England) 2006;10(4):287-333.

[22] Brennan F, Carr DB, Cousins M. Pain management: a fundamental human right. Anesthesia and analgesia 2007;105(1):205-221.

[23] Bruce J, Drury N, Poobalan AS, Jeffrey RR, Smith WCS, Chambers WA. The prevalence of chronic chest and leg pain following cardiac surgery: a historical cohort study. Pain 2003;104(1-2):265-273.

[24] Buvanendran A. Chronic postsurgical pain: are we closer to understanding the puzzle? Anesthesia and analgesia 2012;115(2):231-232.

[25] Chaney MA. Kaplan's Cardiac Anesthesia: The Echo Era. In: J Kaplan, D Reich, J Savino, editors. USA: Saunders/Elsevier, 2011. pp. 1108-1110.

[26] Choiniere M, Watt-Watson J, Victor JC, Baskett RJ, Bussieres JS, Carrier M, Cogan J, Costello J, Feindel C, Guertin MC, Racine M, Taillefer MC. Prevalence of and risk factors for persistent postoperative nonanginal pain after cardiac surgery: a 2-year prospective multicentre study. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne 2014;186(7):E213-223.

[27] Cogan J. Pain management after cardiac surgery. Seminars in cardiothoracic and vascular anesthesia 2010;14(3):201-204.

[28] Colloca L, Klinger R, Flor H, Bingel U. Placebo analgesia: Psychological and neurobiological mechanisms. Pain 2013;154(4):511-514.

[29] Costa MACd, Trentini CA, Schafranski MD, Pipino O, Gomes RZ, Reis ESdS. Factors Associated With the Development of Chronic Post-Sternotomy Pain: a Case-Control Study. Brazilian Journal of Cardiovascular Surgery 2015;30:552-556.

[30] Cousins MJ, Brennan F, Carr DB. Pain relief: a universal human right. PAIN 2004;112(1-2):1-4.

[31] Cousins MJ, Lynch ME. The Declaration Montreal: Access to pain management is a fundamental human right. PAIN 2011;152(12):2673-2674.

[32] Croft P, Blyth FM, Windt Dvd. Chronic pain epidemiology : from aetiology to public health. Oxford: Oxford University Press, 2010.

[33] Crombie IK, Davies HT, Macrae WA. Cut and thrust: antecedent surgery and trauma among patients attending a chronic pain clinic. PAIN 1998;76(1-2):167-171.

[34] Cruccu G, Sommer C, Anand P, Attal N, Baron R, Garcia-Larrea L, Haanpaa M, Jensen TS, Serra J, Treede RD. EFNS guidelines on neuropathic pain assessment: revised 2009. European journal of neurology 2010;17(8):1010-1018.

[35] Dahl JB, Kehlet H. Preventive analgesia. Current opinion in anaesthesiology 2011;24(3):331-338.

[36] Defalque RJ, Bromley JJ. Poststernotomy neuralgia: a new pain syndrome. Anesth Analg 1989;69(1):81-82.

[37] Dick F, Hristic A, Roost-Krähenbühl E, Aymard T, Weber A, Tevaearai HT, Carrel TP. Persistent sensitivity disorders at the radial artery and saphenous vein graft harvest sites: A neglected side effect of coronary artery bypass grafting procedures. European Journal of Cardio-thoracic Surgery 2011;40(1):221-226.

[38] Doering LV, Chen B, McGuire A, Bodan RC, Irwin MR. Persistent depressive symptoms and pain after cardiac surgery. Psychosomatic medicine 2014;76(6):437-444.

[39] Duale C, Ouchchane L, Schoeffler P, Dubray C. Neuropathic aspects of persistent postsurgical pain: a French multicenter survey with a 6-month prospective follow-up. The journal of pain : official journal of the American Pain Society 2014;15(1):24 e21-24 e20.

[40] Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, Kerns RD, Stucki G, Allen RR, Bellamy N, Carr DB, Chandler J, Cowan P, Dionne R, Galer BS, Hertz S, Jadad AR, Kramer LD, Manning DC, Martin S, McCormick CG, McDermott MP, McGrath P, Quessy S, Rappaport BA, Robbins W, Robinson JP, Rothman M, Royal MA, Simon L, Stauffer JW, Stein W, Tollett J, Wernicke J, Witter J. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain 2005;113(1-2):9-19.

[41] Eagle KA, Guyton RA, Davidoff R, Edwards FH, Ewy GA, Gardner TJ, Hart JC, Herrmann HC, Hillis LD, Hutter AM, Jr., Lytle BW, Marlow RA, Nugent WC, Orszulak TA, Antman EM, Smith SC, Jr., Alpert JS, Anderson JL, Faxon DP, Fuster V, Gibbons RJ, Gregoratos G, Halperin JL, Hiratzka LF, Hunt SA, Jacobs AK, Ornato JP. ACC/AHA 2004 guideline update for coronary artery bypass graft surgery: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for Coronary Artery Bypass Graft Surgery). Circulation 2004;110(9):1168-1176.

[42] EFIC. The European Pain Federation Declaration on Pain: Pain as a major health problem, a disease in its own right, 2001.

[43] Eisenberg E, Pultorak Y, Pud D, Bar-El Y. Prevalence and characteristics of post coronary artery bypass graft surgery pain (PCP). Pain 2001;92(1-2):11-17.

[44] eurostat. Cardiovascular diseases statistics 2016.

[45] Fletcher D, Stamer UM, Pogatzki-Zahn E, Zaslansky R, Tanase NV, Perruchoud C, Kranke P, Komann M, Lehman T, Meissner W. Chronic postsurgical pain in Europe: An observational study. European journal of anaesthesiology 2015;32(10):725-734.

[46] Gagliese L. Pain and aging: the emergence of a new subfield of pain research. The journal of pain : official journal of the American Pain Society 2009;10(4):343-353.

[47] Gerbershagen HJ, Pogatzki-Zahn E, Aduckathil S, Peelen LM, Kappen TH, van Wijck AJ, Kalkman CJ, Meissner W. Procedure-specific risk factor analysis for the development of severe postoperative pain. Anesthesiology 2014;120(5):1237-1245.

[48] Gillanders DT, Ferreira NB, Bose S, Esrich T. The relationship between acceptance, catastrophizing and illness representations in chronic pain. European journal of pain (London, England) 2013;17(6):893-902.
[49] Gjeilo KH, Klepstad P, Wahba A, Lydersen S, Stenseth R. Chronic pain after cardiac surgery: a prospective study. Acta anaesthesiologica Scandinavica 2010;54(1):70-78.
[50] Gjeilo KH, Stenseth R, Klepstad P. Risk Factors and Early Pharmacological Interventions to Prevent Chronic Postsurgical Pain Following Cardiac Surgery. American Journal of Cardiovascular Drugs 2014;14(5):335-342.
[51] Gjeilo KH, Wahba A, Klepstad P, Lydersen S, Stenseth R. Survival and quality of life in an elderly cardiac surgery population: 5-year follow-up. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery 2013;44(3):e182-188.
[52] Goldberg DS, McGee SJ. Pain as a global public health priority. BMC public health 2011;11:770.
[53] Guimarães-Pereira L. Persistent postoperative pain and the problem of strictly observational research. Pain 2016;157(5):1173-1174.
[54] Guimaraes-Pereira L, Farinha F, Azevedo L, Abelha F, Castro-Lopes J. Persistent Postoperative Pain after Cardiac Surgery: Incidence, Characterization, Associated Factors and its impact in Quality of Life. European journal of pain (London, England) 2016;20(9):1433-1442.
[55] Guimaraes-Pereira L, Reis P, Abelha F, Azevedo LF, Castro-Lopes JM. Persistent postoperative pain after cardiac surgery: a systematic review with meta-analysis regarding incidence and pain intensity. Pain 2017;158(10):1869-1885.
[56] Gureje O, Von Korff M, Simon GE, Gater R. Persistent pain and well-being: a World Health Organization Study in Primary Care. Jama 1998;280(2):147-151.
[57] Harmer M. Postoperative pain relief--time to take our heads out of the sand? Anaesthesia 1991;46(3):167-168.
[58] Haroutiunian S, Nikolajsen L, Finnerup NB, Jensen TS. The neuropathic component in persistent postsurgical pain: a systematic literature review. Pain 2013;154(1):95-102.
[59] Holdcroft A, Jaggar, Jaggar SI. Core Topics in Pain, 2005.
[60] Humble SR, Dalton AJ, Li L. A systematic review of therapeutic interventions to reduce acute and chronic post-surgical pain after amputation, thoracotomy or mastectomy. European journal of pain (London, England) 2015;19(4):451-465.
[61] IASP. Classification of chronic pain. Descriptions of chronic pain syndromes and definitions of pain terms. Prepared by the International Association for the Study of Pain, Subcommittee on Taxonomy. Pain Supplement 1986;3:S1-226.
[62] IASP. Classification of chronic pain. Descriptions of chronic pain syndromes and definitions of pain terms. Prepared by the International Association for the Study of Pain, Subcommittee on Taxonomy, Vol. 3, 1986.
[63] IASP. 2017 Global Year Against Pain After Surgery, 2017.
[64] Ip HY, Abrishami A, Peng PW, Wong J, Chung F. Predictors of postoperative pain and analgesic consumption: a qualitative systematic review. Anesthesiology 2009;111(3):657-677.
[65] Janig W, Levine JD. Autonomic-endocrine-immune interactions in acute and chronic pain. In: K M., M S.B., editors. Melzack and Wall's Textbook of Pain. Edinburgh: Elsevier, 2006. pp. 205–218.
[66] Jenkins JT, O'Dwyer PJ. Inguinal hernias. BMJ 2008;336(7638):269-272.
[67] Jensen TS, Baron R. Translation of symptoms and signs into mechanisms in neuropathic pain. PAIN 2003;102(1-2):1-8.
[68] Jensen TS, Kehlet H. Pain following thoracotomy: is it neuropathic? Pain 2011;152(1):12-13.

[69] Johansen A, Romundstad L, Nielsen CS, Schirmer H, Stubhaug A. Persistent postsurgical pain in a general population: prevalence and predictors in the Tromso study. PAIN 2012;153(7):1390-1396.
[70] Kalso E. IV. Persistent post-surgery pain: research agenda for mechanisms, prevention, and treatment. British journal of anaesthesia 2013;111(1):9-12.
[71] Kalso E, Mennander S, Tasmuth T, Nilsson E. Chronic post-sternotomy pain. Acta anaesthesiologica Scandinavica 2001;45(8):935-939.
[72] Katz J, Seltzer Z. Transition from acute to chronic postsurgical pain: risk factors and protective factors. Expert review of neurotherapeutics 2009;9(5):723-744.
[73] Kehlet H, Edwards RR, Brennan T. Persistent postoperative pain: Pathogenic mechanisms and preventive strategies. In: S Raja, C Sommer, editors. Pain 2014 — Refresher Courses. Seattle: International Association for the Study of Pain/IASP Press, 2014. pp. 113-123.
[74] Kehlet H, Edwards RR, Buvanendran A. Persistent postoperative pain: Pathogenic mechanisms and preventive strategies. In: I Tracey, editor. Pain 2012 — Refresher Courses. Seattle: International Association for the Study of Pain/IASP Press, 2012. pp. 133-143.
[75] Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. Lancet 2006;367(9522):1618-1625.
[76] Kehlet H, Rathmell JP. Persistent postsurgical pain: the path forward through better design of clinical studies. Anesthesiology 2010;112(3):514-515.
[77] Keller SE, Weiss JM, Schleifer SJ, Miller NE, Stein M. Suppression of immunity by stress: effect of a graded series of stressors on lymphocyte stimulation in the rat. Science (New York, NY) 1981;213(4514):1397-1400.
[78] Khan RS, Skapinakis P, Ahmed K, Stefanou DC, Ashrafian H, Darzi A, Athanasiou T. The association between preoperative pain catastrophizing and postoperative pain intensity in cardiac surgery patients. Pain medicine (Malden, Mass) 2012;13(6):820-827.
[79] Lahtinen P, Kokki H, Hynynen M. Pain after cardiac surgery: A prospective cohort study of 1-year incidence and intensity. Anesthesiology 2006;105(4):794-800.
[80] Laudenslager ML, Ryan SM, Drugan RC, Hyson RL, Maier SF. Coping and immunosuppression: inescapable but not escapable shock suppresses lymphocyte proliferation. Science (New York, NY) 1983;221(4610):568-570.
[81] Lauridsen MH, Kristensen AD, Hjortdal VE, Jensen TS, Nikolajsen L. Chronic pain in children after cardiac surgery via sternotomy. Cardiology in the young 2014;24(5):893-899.
[82] Lavand'homme P. The progression from acute to chronic pain. Current opinion in anaesthesiology 2011;24(5):545-550.
[83] Liebeskind JC. Pain can kill. PAIN 1991;44(1):3-4.
[84] Lohman D, Schleifer R, Amon JJ. Access to pain treatment as a human right. BMC medicine 2010;8:8.
[85] Lunn TH, Gaarn-Larsen L, Kehlet H. Prediction of postoperative pain by preoperative pain response to heat stimulation in total knee arthroplasty. Pain 2013;154(9):1878-1885.
[86] Macrae WA. Chronic post-surgical pain: 10 years on. British journal of anaesthesia 2008;101(1):77-86.
[87] Marcassa C, Faggiano P, Greco C, Ambrosetti M, Temporelli Pier L. A retrospective multicenter study on long-term prevalence of chronic pain after cardiac surgery. Journal of Cardiovascular Medicine 2015;16(11):768-774.
[88] Marchand S. The Phenomenon of Pain. United States: IASP Press - International Association for the Study of Pain, 2012.
[89] Markman PL, Rowland MA, Leong JY, Van Der Merwe J, Storey E, Marasco S, Negri J, Bailey M, Rosenfeldt FL. Skeletonized internal thoracic artery

harvesting reduces chest wall dysesthesia after coronary bypass surgery. The Journal of thoracic and cardiovascular surgery 2010;139(3):674-679.
[90] Martinez-Urrutia A. Anxiety and pain in surgical patients. Journal of consulting and clinical psychology 1975;43(4):437-442.
[91] Mazzeffi M, Khelemsky Y. Poststernotomy pain: a clinical review. Journal of cardiothoracic and vascular anesthesia 2011;25(6):1163-1178.
[92] McMahon SB, Wall PD. Wall and Melzack's textbook of pain. Philadelphia: Elsevier Saunders, 2013.
[93] Melzack R. The tragedy of needless pain. Scientific American 1990;262(2):27-33.
[94] Melzack R, Wall PD. Handbook of pain management : a clinical companion to Wall and Melzack's "Textbook of pain". Edinburgh: Churchill Livingstone, 2003.
[95] Merskey H, Bogduk N. Classification of chronic pain: descriptions of chronic pain syndromes and definitions of pain terms.: IASP Press, 1994. pp. 206-213.
[96] Meyerson J, Thelin S, Gordh T, Karlsten R. The incidence of chronic post-sternotomy pain after cardiac surgery--a prospective study. Acta anaesthesiologica Scandinavica 2001;45(8):940-944.
[97] Miquel P. A Dictionary of Epidemiology: 'Oxford University Press'.
[98] Montes A, Roca G, Sabate S, Lao JI, Navarro A, Cantillo J, Canet J. Genetic and Clinical Factors Associated with Chronic Postsurgical Pain after Hernia Repair, Hysterectomy, and Thoracotomy: A Two-year Multicenter Cohort Study. Anesthesiology 2015;122(5):1123-1141.
[99] Nickel R, Raspe HH. [Chronic pain: epidemiology and health care utilization]. Der Nervenarzt 2001;72(12):897-906.
[100] Nikolajsen L, Brix LD. Chronic pain after surgery in children. Current opinion in anaesthesiology 2014;27(5):507-512.
[101] Niraj G, Rowbotham DJ. Persistent postoperative pain: where are we now? British journal of anaesthesia 2011;107(1):25-29.
[102] Pan PH, Tonidandel AM, Aschenbrenner CA, Houle TT, Harris LC, Eisenach JC. Predicting acute pain after cesarean delivery using three simple questions. Anesthesiology 2013;118(5):1170-1179.
[103] Parkerson GR, Broadhead WE, Tse CK. Anxiety and depressive symptom identification using the Duke Health Profile. Journal of clinical epidemiology 1996;49(1):85-93.
[104] Perkins FM, Kehlet H. Chronic pain as an outcome of surgery. A review of predictive factors. Anesthesiology 2000;93(4):1123-1133.
[105] Pesonen A, Suojaranta-Ylinen R, Hammaren E, Kontinen VK, Raivio P, Tarkkila P, Rosenberg PH. Pregabalin has an opioid-sparing effect in elderly patients after cardiac surgery: a randomized placebo-controlled trial. British journal of anaesthesia 2011;106(6):873-881.
[106] Reddi D, Curran N. Chronic pain after surgery: pathophysiology, risk factors and prevention. Postgraduate medical journal 2014;90(1062):222-227; quiz 226.
[107] Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Makuc DM, Marcus GM, Marelli A, Matchar DB, Moy CS, Mozaffarian D, Mussolino ME, Nichol G, Paynter NP, Soliman EZ, Sorlie PD, Sotoodehnia N, Turan TN, Virani SS, Wong ND, Woo D, Turner MB. Heart disease and stroke statistics--2012 update: a report from the American Heart Association. Circulation 2012;125(1):e2-e220.
[108] Rosenfeld B, Breitbart W, McDonald MV, Passik SD, Thaler H, Portenoy RK. Pain in ambulatory AIDS patients. II: Impact of pain on psychological functioning and quality of life. PAIN 1996;68(2-3):323-328.
[109] Saúde DGd. Plano Estratégico Nacional de Prevenção e Controlo da Dor (PENPCDor), 2013.

[110] Saúde DGd. Rede Nacional de Especialidade Hospitalar e Referenciação - Cirurgia Cardiotorácica, 2016.
[111] Schnabel A, Pogatzki-Zahn E. [Predictors of chronic pain following surgery. What do we know?]. Schmerz (Berlin, Germany) 2010;24(5):517-531; quiz 532-513.
[112] Schopflocher D, Taenzer P, Jovey R. The prevalence of chronic pain in Canada. Pain Research & Management : The Journal of the Canadian Pain Society 2011;16(6):445-450.
[113] Scott LE, Clum GA, Peoples JB. Preoperative predictors of postoperative pain. Pain 1983;15(3):283-293.
[114] Simanski CJ, Althaus A, Hoederath S, Kreutz KW, Hoederath P, Lefering R, Pape-Kohler C, Neugebauer EA. Incidence of chronic postsurgical pain (CPSP) after general surgery. Pain medicine (Malden, Mass) 2014;15(7):1222-1229.
[115] Simek M, Nemec P, Bruk V, Gwozdziewicz M, Fluger I, Langova K. Postoperative and midterm outcomes of minimally invasive and endoscopic great saphenous vein harvesting for coronary artery bypass grafting - a prospective analysis. The Thoracic and cardiovascular surgeon 2007;55(7):428-432.
[116] Slagelse C, Petersen KL, Dahl JB, Finnerup K, Greene K, Leong SP, Levine J, Rowbotham M, Werner MU, Finnerup NB. Persistent postoperative pain and sensory changes following lymph node excision in melanoma patients: a topical review. Melanoma research 2014;24(2):93-98.
[117] Steegers MA, van de Luijtgaarden A, Noyez L, Scheffer GJ, Wilder-Smith OH. The role of angina pectoris in chronic pain after coronary artery bypass graft surgery. The journal of pain : official journal of the American Pain Society 2007;8(8):667-673.
[118] Steingrimsdottir OA, Landmark T, Macfarlane GJ, Nielsen CS. Defining chronic pain in epidemiological studies - a systematic review and meta-analysis. PAIN 2017.
[119] Stoll C, Schelling G, Goetz AE, Kilger E, Bayer A, Kapfhammer HP, Rothenhausler HB, Kreuzer E, Reichart B, Peter K. Health-related quality of life and post-traumatic stress disorder in patients after cardiac surgery and intensive care treatment. The Journal of thoracic and cardiovascular surgery 2000;120(3):505-512.
[120] Taillefer MC, Carrier M, Belisle S, Levesque S, Lanctot H, Boisvert AM, Choiniere M. Prevalence, characteristics, and predictors of chronic nonanginal postoperative pain after a cardiac operation: a cross-sectional study. The Journal of thoracic and cardiovascular surgery 2006;131(6):1274-1280.
[121] Tesarz J, Eich W. A conceptual framework for “updating the definition of pain”. PAIN 2017;158(6):1177-1178.
[122] Theunissen M, Peters ML, Bruce J, Gramke HF, Marcus MA. Preoperative anxiety and catastrophizing: a systematic review and meta-analysis of the association with chronic postsurgical pain. The Clinical journal of pain 2012;28(9):819-841.
[123] Thibault P, Loisel P, Durand MJ, Catchlove R, Sullivan MJ. Psychological predictors of pain expression and activity intolerance in chronic pain patients. Pain 2008;139(1):47-54.
[124] Tonnesen E. Immunological aspects of anaesthesia and surgery--with special reference to NK cells. Danish medical bulletin 1989;36(3):263-281.
[125] Treede R-D, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, Cohen M, Evers S, Finnerup NB, First MB, Giamberardino MA, Kaasa S, Kosek E, Lavand'homme P, Nicholas M, Perrot S, Scholz J, Schug S, Smith BH, Svensson P, Vlaeyen JWS, Wang S-J. A classification of chronic pain for ICD-11. PAIN 2015;156(6):1003-1007.

[126] Tsang A, Von Korff M, Lee S, Alonso J, Karam E, Angermeyer MC, Borges GL, Bromet EJ, Demytteneare K, de Girolamo G, de Graaf R, Gureje O, Lepine JP, Haro JM, Levinson D, Oakley Browne MA, Posada-Villa J, Seedat S, Watanabe M. Common chronic pain conditions in developed and developing countries: gender and age differences and comorbidity with depression-anxiety disorders. The journal of pain : official journal of the American Pain Society 2008;9(10):883-891.

[127] Turan A, Belley-Cote EP, Vincent J, Sessler DI, Devereaux PJ, Yusuf S, van Oostveen R, Cordova G, Yared JP, Yu H, Legare JF, Royse A, Rochon A, Nasr V, Ayad S, Quantz M, Lamy A, Whitlock RP. Methylprednisolone Does Not Reduce Persistent Pain after Cardiac Surgery. Anesthesiology 2015;123(6):1404-1410.

[128] Turk DC, Dworkin RH, Allen RR, Bellamy N, Brandenburg N, Carr DB, Cleeland C, Dionne R, Farrar JT, Galer BS, Hewitt DJ, Jadad AR, Katz NP, Kramer LD, Manning DC, McCormick CG, McDermott MP, McGrath P, Quessy S, Rappaport BA, Robinson JP, Royal MA, Simon L, Stauffer JW, Stein W, Tollett J, Witter J. Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. Pain 2003;106(3):337-345.

[129] Ucak A, Onan B, Sen H, Selcuk I, Turan A, Yilmaz AT. The effects of gabapentin on acute and chronic postoperative pain after coronary artery bypass graft surgery. Journal of cardiothoracic and vascular anesthesia 2011;25(5):824-829.

[130] van Gulik L, Ahlers SJ, van de Garde EM, Bruins P, van Boven WJ, Tibboel D, van Dongen EP, Knibbe CA. Remifentanil during cardiac surgery is associated with chronic thoracic pain 1 yr after sternotomy. British journal of anaesthesia 2012;109(4):616-622.

[131] van Gulik L, Janssen LI, Ahlers SJ, Bruins P, Driessen AH, van Boven WJ, van Dongen EP, Knibbe CA. Risk factors for chronic thoracic pain after cardiac surgery via sternotomy. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery 2011;40(6):1309-1313.

[132] van Hecke O, Torrance N, Smith BH. Chronic pain epidemiology and its clinical relevance. British journal of anaesthesia 2013;111(1):13-18.

[133] van Leersum NJ, van Leersum RL, Verwey HF, Klautz RJM. Pain Symptoms Accompanying Chronic Poststernotomy Pain: A Pilot Study. Pain Medicine 2010;11(11):1628-1634.

[134] VanDenKerkhof EG, Hopman WM, Goldstein DH, Wilson RA, Towheed TE, Lam M, Harrison MB, Reitsma ML, Johnston SL, Medd JD, Gilron I. Impact of perioperative pain intensity, pain qualities, and opioid use on chronic pain after surgery: a prospective cohort study. Regional anesthesia and pain medicine 2012;37(1):19-27.

[135] Verhaak PF, Kerssens JJ, Dekker J, Sorbi MJ, Bensing JM. Prevalence of chronic benign pain disorder among adults: a review of the literature. PAIN 1998;77(3):231-239.

[136] Weibel S, Neubert K, Jelting Y, Meissner W, Wockel A, Roewer N, Kranke P. Incidence and severity of chronic pain after caesarean section: A systematic review with meta-analysis. European journal of anaesthesiology 2016;33(11):853-865.

[137] Weissman-Fogel I, Granovsky Y, Crispel Y, Ben-Nun A, Best LA, Yarnitsky D, Granot M. Enhanced presurgical pain temporal summation response predicts post-thoracotomy pain intensity during the acute postoperative phase. The journal of pain : official journal of the American Pain Society 2009;10(6):628-636.

[138] Werner MU, Mjobo HN, Nielsen PR, Rudin A. Prediction of postoperative pain: a systematic review of predictive experimental pain studies. Anesthesiology 2010;112(6):1494-1502.

[139] Whitburn LY, Jones LE, Davey M-A, Small R. Supporting the updated definition of pain. But what about labour pain? PAIN 2017;158(5):990-991.
[140] White PF, Kehlet H. Improving postoperative pain management: what are the unresolved issues? Anesthesiology 2010;112(1):220-225.
[141] Williams ACdC, Craig KD. Updating the definition of pain. PAIN 2016;157(11):2420-2423.
[142] Wright A, Aydede M. Critical comments on Williams and Craig's recent proposal for revising the definition of pain. PAIN 2017;158(2):362-363.
[143] Yarnitsky D. Role of endogenous pain modulation in chronic pain mechanisms and treatment. Pain 2015;156 Suppl 1:S24-31.
[144] Zautra AJ, Johnson LM, Davis MC. Positive affect as a source of resilience for women in chronic pain. Journal of consulting and clinical psychology 2005;73(2):212-220.