EXAMINATION OF NURSE-MODIFIABLE RISK FACTORS FOR CHRONIC POST-SURGICAL PAIN AFTER CARDIAC SURGERY

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ABSTRACT

Background: Thousands of Canadians undergo cardiac surgery each year with the aim of relieving symptoms (e.g., angina) and improving health-related-quality-of-life (HRQoL). Despite the demonstrated symptom-related benefits of these surgeries, evidence suggests that the development of chronic post-surgical pain (CPSP) is a major clinical problem. To date, several perioperative factors have been examined for their potential to confer risk for CPSP.

Purpose: The purpose of the study was to explore the association between preoperative moderate to severe anxiety and depressive symptoms; moderate to severe acute postoperative pain; and cumulative opioid dose consumption with the development of CPSP at six months and 12 months after cardiac surgery.

Method: *Design.* This thesis was a prospective observational cohort sub-study of adults undergoing cardiac surgery in a tertiary care hospital setting (n=735), recruited from Hamilton Health Sciences, Canada over a five year period. *Measures.* The independent variables included state anxiety, depressive symptoms, acute postoperative pain intensity, and opioid dose consumption. At baseline, the Spielberger State-Trait Anxiety Inventory (STAI) assessed state anxiety and the Hospital Anxiety and Depression Scale (HADS) assessed depressive symptoms. The Brief Pain Inventory-Short Form (BPI-SF) assessed acute postoperative pain intensity on postoperative days three (in-hospital) and 30 (at home via telephone). All instruments have established reliability and validity in cardiac surgery patients (e.g., STAI Cronbach's alpha (α) =0.82; HADS α=0.81; BPI-SF α=0.87). Medical records were reviewed and total dose of opioids consumed up to three days postoperatively, were collected via analgesic chart audit and converted into milligrams of parenteral morphine equivalent dose using standard dosage tables. *Dependent variable*. The primary outcome of CPSP was assessed dichotomously (i.e., yes/no) at

six months and 12 months after cardiac surgery. If present, CPSP was assessed via the BPI-SF. At baseline, data was collected on pre-specified model covariates (e.g., age, sex). *Data Analyses*. Logistic regression was used to model the primary outcome with the presence of CPSP at six months and 12 months, while adjusting for model covariates. Secondary linear regression models were constructed to examine the effect of the independent variables on the severity of CPSP with statistical significance set at *p*-values <0.05.

Results: The incidence of CPSP was 8.7% at six months and 4.1% at 12 months after cardiac surgery. Baseline demographics (i.e., age, sex) and medical status (i.e., diabetes mellitus) were significantly associated with the presence of CPSP. Moderate to severe preoperative anxiety was not significantly associated with CPSP at six months (adjusted OR 0.629, 95% CI [0.300, 1.322], *p*=0.222) or 12 months (adjusted OR 0.743, 95% CI [0.242, 2.285], *p*=0.604). Moderate to severe preoperative depressive symptom was not significantly associated with CPSP at six months (adjusted OR 0.676, 95% CI [0.152, 3.005], *p*=0.607) or 12 months (adjusted OR 3.216, 95% CI [0.835, 12.382], *p*=0.089). Acute postoperative pain rated as pain '*right now*' on day three was significantly associated with CPSP at six months (adjusted OR 2.263, 95% CI [1.255, 4.081], *p*=0.007) and 12 months (adjusted OR 2.749, 95% CI [1.174, 6.441], *p*=0.020). Acute postoperative pain '*right now*' on day 30 was significantly associated with CPSP at six months (adjusted OR 2.913, 95% CI [1.304, 6.505], *p*=0.009). Cumulative opioid dose consumed was significantly associated with the development of CPSP at six months (adjusted OR 1.001, 95% CI [1.000, 1.002], *p*=0.003) and 12 months (adjusted OR 1.001, 95% CI [1.000, 1.001], *p*=0.033) after cardiac surgery.

Significance: The findings demonstrate that acute postoperative pain '*right now*' and cumulative opioid dose consumed are risk factors for CPSP after cardiac surgery. These findings offer

targets for nursing staff to identify potentially at-risk patients, implement evidence-based pain management strategies, as well as contribute to nursing-led research designed to target CPSP after cardiac surgery.

Keywords: acute postoperative pain, anxiety, cardiac surgery, chronic post-surgical pain, depressive symptom, nursing, opioid, risk factor

DEDICATION

This doctoral work is dedicated to the Henry ‘T-Rex’ Family: Alexander Junior Henry, Jaivien Xavier Henry, Kamani DeShaun Henry, Alexander Noah Henry and Janet Taylor for inspiring, supporting, encouraging and being the family that lifted me up each time I wavered along the journey.

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Love Mommy ‘T-Rex’, Shaunattonie Henry

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PREFACE

For many individuals living with coronary artery disease, cardiac surgery is required to relieve their symptoms, improve their health-related quality of life (HRQoL) and increase the chances of their survival. However, many patients develop chronic post-surgical pain (CPSP) after cardiac surgery, which affects their health and functional quality of life well after their surgical wounds have healed.

The purpose of this study was to explore the association between severity of risk factors with the development of CPSP at six months and 12 months after cardiac surgery. These risk factors included preoperative anxiety, preoperative depressive symptom, acute postoperative pain intensity, and cumulative opioid dose.

This dissertation was prepared according to the publication manual of the American Psychological Association (APA 7th edition) and submitted to the School of Nursing Graduate Program, McMaster University, in partial fulfillment of the requirements for the Degree Doctor of Philosophy in Nursing.

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List of Abbreviations

BMI: Body Mass Index

BPI: Brief Pain Inventory

BPI-SF: Brief Pain Inventory Short Form

CABG: Coronary Artery Bypass Graft

CAD: Canadian Dollars

CCSA: Canadian Cardiovascular Society Angina

CI: Confidence Interval

CPSP: Chronic Post-Surgical Pain

DM: Diabetes Mellitus

DSM-V: Diagnostic and Statistical Manual of Mental Disorders V (5th edition)

GEE: Generalized Estimation Equation

HADS: Hospital Anxiety and Depression Scale

HRQoL: Health Related Quality of Life

IASP: International Association for the Study of Pain

ICD: International Classification of Diseases

MME: Morphine Milligram Equivalent

NRS: Numerical Rating Scale

NYHAFC: New York Heart Association Functional Classification of Heart Failure

OR: Odds Ratio

PHAC: Public Health Agency of Canada

POD: Postoperative Day

QUIPS: Quality in Prognostic Studies

RCT: Randomized Controlled Trial

RNAO: Registered Nurses Association of Ontario

SD: Standard Deviation

STAI: State Trait Anxiety Inventory

USD: United States Dollars

WHO: World Health Organization

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CHAPTER 1: INTRODUCTION, SIGNIFICANCE AND PROBLEM STATEMENT

Introduction

Heart disease is a global problem, accounting for an estimated 45% or 8.9 million global deaths in 2015 (Public Health Agency of Canada [PHAC], 2018; Wang et al., 2016). Approximately 2.4 million Canadians were diagnosed with heart disease in 2012-2013; of these, 64% were aged 65 years and older (PHAC, 2018). Heart disease is the second leading cause of mortality for both men and women, accounting for approximately 25.9% (*n*=53,134) of all deaths in Canada in 2018 (Statistics Canada, 2015). Among Canadians, aged 20 years and older, the prevalence of diagnosed heart disease was higher in men (10%, 95% confidence interval [CI] [10.0, 10.0]) than women (6.3%, 95% CI [6.3, 6.3]) (PHAC, 2018).

For many individuals living with coronary artery disease—a subset of heart disease, cardiac surgery is required to ameliorate symptoms (e.g., angina, shortness of breath), improve health-related quality of life (HRQoL), and increase the likelihood of survival (PHAC, 2009). Cardiac surgeries, such as coronary artery bypass grafting (CABG), valve repair and/or valve replacement surgeries, are among the most commonly performed surgical interventions globally (Choinière et al., 2014; Roger et al., 2012). Estimates indicate that over 30,000 Canadians undergo cardiac surgery each year (Noly et al., 2017). In 2016, approximately 21.5% of cardiac surgeries (*n*=8,159) were performed in Ontario for 79.7% males and 20.3% females (CorHealth Ontario, 2018). The average age of adult patients having cardiac surgery in Ontario is 65.94 years (standard deviation [SD] ± 9.90), with 57.2% of patients being over the age of 65 years (CorHealth Ontario, 2018).

The invasiveness of cardiac surgeries subject patients to substantial amounts of trauma and injury to nerves and tissue (Delfalque & Bromley, 1989; Mazzeffi & Khelemsky, 2011). For example, CABG surgery, as performed through open sternotomy, involves manipulation and

retraction of many pain-sensitive structures throughout the sternum, intercostal muscles, nerves, ribs, visceral and soft tissues, and donor vein (e.g., saphenous vein) and artery (e.g., internal thoracic artery) sites (Diodato & Chedrawy, 2014; Kehlet et al., 2006; Mazzeffi & Khelemsky, 2011) for various lengths of time during the surgery. Pain, as defined by the International Association for the Study of Pain (IASP), is "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage, or described in terms of such damage" (Raja et al., 2020, p. 1977). For some, unrelieved acute postoperative pain is associated with slower rehabilitation, impaired HRQoL, and transition to chronic post-surgical pain (CPSP) following cardiac surgery (Bjørnnes et al., 2014; Watt-Watson et al., 2004; Katz & Seltzer, 2009). Mounting evidence indicates that postoperative pain that persists beyond normal tissue healing time (i.e., CPSP), is increasingly being recognized as an important chronic complication. CPSP is frequently correlated with serious negative outcomes interfering with patients' postoperative recovery and impose substantial costs to the healthcare system (Choinière et al., 2014; Lahtinen et al., 2006; Mazzeffi & Khelemsky, 2011).

This chapter reviews background information on CPSP including incidence and prevalence, outcomes associated with the development of CPSP, risk factors associated with the transition to CPSP, as well as the significance of nursing in identifying potentially at-risk patients and implementing evidence-based strategies to prevent the development of CPSP after cardiac surgery. This chapter concludes with a problem statement, clarifying the need and purpose of the study.

Incidence and Prevalence of CPSP After Cardiac Surgery

Despite the demonstrated survival and symptom-related benefits of cardiac surgeries, substantial numbers of patients have been reported to develop CPSP and related poor functional recovery in relation to their pain experiences well after their surgery (Bruce et al., 2003; Choinière et al., 2014; King et al., 2008; Lahtinen et al., 2006). The incidence of CPSP has been reported between 28% (*n*=90 of 318) at 12 months (Meyerson et al., 2001) and 45% (*n*=9 of 20) at three months (Ucak et al., 2011) after cardiac surgery.

Globally, prevalence estimates for CPSP after cardiac surgery have ranged from 7.5% (*n*=3 of 40) at six months postoperative (Onan et al., 2013) to 56% at 16 months postoperative (Eisenberg et al., 2001). In Canada, similar CPSP prevalence estimates across multiple surgical centers, have ranged between 9.5% (*n*=93 of 976) at two years (Choinière et al., 2014) and 41% (*n*= 87 of 212) at 12 weeks after cardiac surgery (Routledge et al., 2009).

Variance in CPSP incidence and prevalence estimates reported may be attributable to differences in study designs, sample sizes, lengths of follow-up period and variability in approaches to CPSP measurement across published studies to date (Choinière et al., 2014; Gjeilo et al., 2010; Lahtinen et al., 2006; Lee et al., 2010). For example, Choinière et al. (2014) conducted a prospective multi-center study (CARD-Pain) (*N*=1247), which aimed to determine the prevalence of CPSP, as well as identify risk factors for the presence and severity of CPSP up to two years after cardiac surgery. The results demonstrated that the prevalence of CPSP decreased significantly from 40.1% (*n*=423 of 1054) at three months, to 9.5% (*n*=93 of 976) at two years postoperative (generalized estimating equation [GEE], $p<0.001$). Small, single-site studies, report different prevalence rates. For example, van Gulik et al. (2012) conducted a prospective sub-study, embedded within a single-site RCT (*N*=120), to identify predictors of

CPSP following cardiac surgery. The results demonstrated that 20% (*n*=18 of 90) of patients had CPSP 12 months after cardiac surgery. Similarly, Taillefer et al.'s (2006) single-site, cross-sectional study (*N*=736)–designed to assess the prevalence, characteristics, effect and predictors of CPSP–reported that 23% (*n*=129 of 564) of patients experienced CPSP between one year to three years after cardiac surgery.

In summary, although incidence and prevalence estimates reported across studies varies, these estimates support that CPSP is a problem following cardiac surgery.

Outcomes Associated With CPSP After Cardiac Surgery

Health-Related Quality of Life Outcomes

Irrespective of differences in prevalence rates reported, the correlated outcomes of CPSP following cardiac surgery are unequivocal. According to Hays and Reeve (2010), HRQoL refers to how well individuals are able to function or carry out activities of daily living as well as their perceived physical, mental and social wellbeing. The term HRQoL outcome includes the impact of pain-related complications as well as anxiety and depressive symptoms. In cohorts of patients who develop CPSP following cardiac surgery, the presence of CPSP has been correlated with reported poor to fair perceived HRQoL outcomes (Hunt et al., 2000; Parson et al., 2013), fatigue (Herlitz et al., 2010), reduced activity, sleep disturbances, pain-related interference with mood and activities of daily living (Gjeilo et al., 2010), as well as anxiety and depressive symptoms (Bruce et al., 2003; Bruce & Quinlan, 2011; Choinière et al., 2014; Taillefer et al., 2006; Watt-Watson et al., 2004).

For example, Gjeilo et al. (2010) conducted a single-site prospective study (*N*=534) in Norway, to assess the presence of CPSP and measure HRQoL in relation to CPSP at six months and 12 months after cardiac surgery. HRQoL was assessed by the Norwegian version of Medical

Outcome Study Short Form-36 questionnaire. CPSP point prevalence was reported by 11% of patients at six months (*n*=52 of 462) and at 12 months (*n*=52 of 465) after cardiac surgery. Moderate to severe pain intensity (numerical rating scale [NRS] ≥ 4 of 10) interfered with 33% (*n*=15 of 46) of patients 'walking' and ability to undertake 'general activity' as well as 'work', up to one year after surgery (Gjeilo et al., 2010).

Hunt et al. (2000) conducted a single-site, cross-sectional comparative study (*N*=123) in Australia, to assess the relationship between preoperative risk factors, CPSP, sleep and gender on HRQoL at one year after cardiac surgery. Medical Outcome Study Short Form-36 questionnaires were mailed to participants and used to obtain self-report data on patient's level of physical activity and activity limiting symptoms 12 months following cardiac surgery. At 12 months, 21% of patients reported severe or very severe pain intensity in their sternal wound or donor site (Hunt et al., 2000). CPSP was found to be significantly associated with poor HRQoL, (Spearman rank order, rho (ρ)=0.23, *p*=0.017), wherein patients were 5.1 times more likely to report poor to very poor HRQoL (95% CI [1.89, 13.7], *p*=0.002) (Hunt et al., 2000).

Herlitz et al. (2010) conducted a large, multi-centre prospective study (*N=2000*) in Sweden, which aimed to describe changes in chest pain and dyspnea symptoms as well as define associated factors after cardiac surgery. Mailed questionnaires were used to obtain self-report data on patients' level of physical activity and activity limiting symptoms (i.e., tiredness, palpitations, dyspnea and chest pain) three months before surgery, and at five, 10, and 15 years follow-up (Herlitz et al., 2010). CPSP-related physical limitations, due to tiredness and dyspnea, had increased in patients after cardiac surgery. Between five years (*n*=1,359) and 15 years (*n*=639), restrictions due to tiredness significantly increased from 17% to 28%, (Wilcoxon's signed-rank test, *p*=<0.001); restrictions due to dyspnea also changed significantly from 36% to

44%, (Wilcoxon's signed-rank test, p=<0.001) (Herlitz et al., 2010). These data suggest that tiredness and dyspnea are symptoms which likely exacerbate decline in functional status associated with CPSP. Age-related decline may also contribute to observed changes in functional status over the long-term.

In summary, negative health-related outcomes including: fatigue, sleep disturbance, activity interference, and changes in mood, are often correlated with the presence of CPSP. These symptoms and states have been shown to interfere with patients' ability to effectively cope, as well as recover optimally following cardiac surgery (Bruce et al., 2003; Choinière et al., 2014; Gjeilo et al., 2010).

Economic Correlates

In addition to poor HRQoL, available evidence is clear that CPSP and related factors pose economic burden to patients, families, healthcare facilities, and society. Across studies, meaningful comparisons about magnitude of CPSP-related economic burden are challenging to make, due to differences in approach to economic modeling, variability in patient populations examined (e.g., cancer, surgical-orthopedic, hernia etc.), as well as utilization of various indirect sources of cost data (Hogan et al., 2016; Huang et al., 2016; Parson et al., 2013). For example, using Ontario healthcare databases and the Canadian Community Health Survey from 2000 to 2011, Hogan et al. (2016), conducted a retrospective matched cohort study, to estimate healthcare utilization for patients with chronic pain and the annual incremental medical cost per-person borne by Canadian taxpayers. Cases and controls (n=19,138 pairs) were paired using a matching algorithm based on age (≥12 years), sex, index year and propensity score (Hogan et al., 2016). Expenses were available on a year-to-year basis from 2007-2008 and 2009-2010, for 13,336 pairs of respondents.

Mean annualized healthcare utilization costs per person were $5,177 in Canadian dollars (CAD) for patients with chronic pain and $3,435 CAD for patients without chronic pain (Hogan et al., 2016). Among matched pairs, these data represent an annual incremental cost of $1,742 CAD, 95% CI [$1,488, $2,020], to manage chronic pain (Hogan et al., 2016). Annualized healthcare and incremental costs also increased with the patient's age. For example, annual healthcare utilizations costs were $8,966 CAD, in the group of patients 65 years and over (*n*=4,493 pairs) with chronic pain, and $6,257 CAD in their matched controls; with an incremental cost of $2,710 CAD, 95% CI [$2,090, $3,316] (Hogan et al., 2016). Incremental cost also increased with self-reported pain severity, wherein the cost per-person reporting moderate pain intensity was $1,643 CAD, 95% CI [$1,479, $2,008], and the cost for severe pain intensity was $3,960 CAD, 95% CI [$3,186, $4,680] (Hogan et al., 2016). Overall, the cost per-person to manage chronic pain is reported more than 50% higher than a similar patient without chronic pain (Hogan et al., 2016).

While Hogan et al.'s (2016) large-scale economic study has contributed to our understanding of the incremental costs of chronic pain in Canada, there are some notable limitations. For example, the study did not capture some publicly funded costs associated with technical and overhead charges, as well as alternative funding payments made to smaller hospital-based physicians. Direct out-of-pocket expenses, at the per-patient level, also remain unknown. As such, the study probably under-represents the economic burden of chronic pain to the individual and society. Moreover, clinical characteristics of the cohort include painful conditions classified by the International Classification of Diseases (ICD) 9th and 10th Revisions; these include: abdominal pain, arthritis, back and neck problems, fibromyalgia, migraine and neuropathy (Hogan et al., 2016). However, cause or contributors to pain (e.g., surgery) were not

identified; as such, the representativeness of point estimates generated, in terms of cardiac surgery per se, is unknown.

In a smaller cross-sectional study (*N*=100), Parson et al. (2013), aimed to characterize pain, HRQoL, and economic burden among adult patients with post-traumatic or post-surgical neuropathic pain living in the United States. At the time of enrollment, participants completed a single questionnaire with demographic information, measures of pain intensity and interference, as well as out-of-pocket expenses (Parson et al., 2013). The mean (± SD) pain intensity score was NRS 5.6 of 10 (± 2.1), with 48% (*n*=48) experiencing moderate pain and 35% (*n*=35) experiencing severe pain (Parson et al., 2013). Using stepwise regression, the total mean annualized adjusted direct costs were $11,846 in U.S. dollars (USD), 95% CI [$9,925, $13,767]; indirect costs were $29,617 USD, 95% CI [$25,271, $33,962] per patient (Parson et al., 2013). Potential limitations of this study include the survey method, which required patients to recall lost productivity and out-of-pocket costs over the past seven days; hence, results of this study may be subject to recall bias and underestimating or overestimating costs. The cost estimates generated were derived from those experiencing unspecified chronic post-traumatic or post-surgical (including cardiac surgery) neuropathic pain for over two years following their index traumatic event or surgery (*n*=90); as such, reported cost estimates are not in direct relation to cardiac surgery alone.

Overall, important points of critique to consider include the fact that Hogan et al.'s (2016) and Parson et al.'s (2013) studies include different healthcare payment systems in Canada and the United States and each study employed a different cost calculation method for incremental cost (Hogan et al., 2016) and total cost (Parson et al., 2013) of chronic pain. Additional cost, such as indirect and direct-out-of-pocket expenses, as well as alternative funding

payment options, were not clearly reported and probably under-represent the economic burden of CPSP on patients and the healthcare system at large. Irrespective of costing methods used and their associated strengths and limitations, evidence is clear that CPSP has a significant economic impact on patients and the healthcare system.

Risks Factors for Transition to CPSP

According to the World Health Organization (WHO) (2017), any attribute of an individual that creates or suggests the likelihood or susceptibility for hazard, injury or a disease is known as a risk factor. Offord and Kraemer (2000) claim that risk factors play an important role in prediction and prevention of an outcome. Risk factors can be associated, either positively or negatively, with an outcome, and as such, should be measured before the outcome manifests (Offord & Kraemer, 2000; Weinrib et al., 2017). The presence of a risk factor, can divide a population into two groups: low-risk and high-risk of outcome susceptibility (Offord & Kraemer, 2000; Weinrib et al., 2017). Offord and Kraemer (2000) argue that a risk factor may be either modifiable or non-modifiable, as well as causal or correlated in nature. Modifiable risk factors for CPSP are attributes or behaviours that can be changed to affect the likelihood of developing CPSP after cardiac surgery (e.g., smoking), while a non-modifiable risk factor (e.g., age) cannot be changed.

Causal risk factors are factors that directly impact the likelihood of developing CPSP after cardiac surgery if they are modified (e.g., anterior intercostal nerve sparing incision during internal thoracic artery grafting). Correlated risk factors, on the other hand, are factors found to have an association with CPSP, yet their modification may not necessarily result in a change in the likelihood of developing CPSP after cardiac surgery (e.g., type of anesthetic used intra-operatively) (Offord & Kraemer, 2000; Weinrib et al., 2017). Weinrib et al. (2017) argued that if

well-conceived intervention strategies (targeting putative risk factors for CPSP) are implemented and reduce the likelihood of developing CPSP, then their risk factor targets would be considered clinically important.

Over the last decade, several studies have examined putative risk factors for the development of CPSP after cardiac surgery. These risk factors can be categorized as preoperative, intraoperative, and postoperative risk factors (Katz & Seltzer, 2009)–a number of which may be amenable to nursing intervention in the perioperative context.

Twenty-seven published studies to date have examined risk factors associated with the transition to CPSP following cardiac surgery. From the present standpoint of reviewing modifiable nursing targets, there is little utility in reviewing, in depth, the strength and magnitude of association in a vast majority of these perioperative risk factors, as they are outside the scope of nursing practice (e.g., surgery-related risk factor such as duration of surgery, type of surgical technique used, or type of intraoperative anesthetic used). There are, however, four clinical factors that may hold promise as potentially modifiable nursing targets in the perioperative context; these include preoperative anxiety, preoperative depressive symptoms, acute postoperative pain intensity and cumulative opioid dose consumed in the days after cardiac surgery. These risk factors were examined in seven published studies for their association with the transition to CPSP after cardiac surgery. Several of these studies employed univariate analyses, or had small non-representative samples which limited multivariate modeling analyses, as well as lacked the correct temporal sequencing to make definitive inferences about the putative association with the transition to CPSP following cardiac surgery (Choinière et al., 2014; King et al., 2008; Lahtinen et al., 2006; Lee et al., 2010; Steegers et al., 2007; Taillefer et al., 2006; van Gulik et al., 2011).

Of the evidence that demonstrates significant relationships between risk factors examined and CPSP, the strength of the associations appears to be weak. One plausible explanation for this is that patients who reported mild anxiety or depressive symptoms, or mild pain intensity were included in unadjusted and adjusted analyses reported, potentially diluting the relationship. It is plausible that moderate to severe intensity in preoperative anxiety symptoms, preoperative depressive symptoms, and postoperative pain severity may confer greater risk for CPSP; however, these hypotheses require confirmation. A detailed review of the evidence is provided in chapter two to support these plausible hypotheses.

Significance

Potential Impact

CPSP following cardiac surgery is a prevalent healthcare problem associated with substantial costs to society. To date, multiple perioperative risk factors have been examined for their role in the development of CPSP. The available evidence base has produced mixed results with the vast majority of risk factors for CPSP examined being outside of the scope of nursing practice. There are a few exceptions, which, based on the state of the available evidence, warrant further investigation as possible targets for nursing intervention in the perioperative context. These risk factors include: preoperative anxiety, preoperative depressive symptoms, acute postoperative pain intensity, and cumulative opioid dose.

The findings of this doctoral study offer nurse modifiable risk factors that confer vulnerability for CPSP following cardiac surgery, as well as offer support for development of nurse-led interventions and robust CPSP related research to address the identified risk factors (Barley et al., 2012; Wells-Federman et al., 2002). For example, Wells-Federman et al., (2002), completed an experimental study (*N*=154), to examine the effect of a nurse-led cognitive-

behavioral pain management program on self-efficacy, coping and pain management among patients with chronic pain. Patients' who had undergone several evaluation and suboptimal chronic pain treatments, were referred by physicians to participate in the study. The program lead by experienced chronic pain advanced practice nurses, consisted of a weekly outpatient cognitive behavioural and pain management program, where the role of lifestyle factors (e.g., physical and emotional tension), self-efficacy, coping and management skills were taught for 10 weeks. The visual analog pain intensity scale, chronic pain efficacy scale, pain disability index and center for epidemiological study–depression scales were used to assess key variables. The patients had been experiencing chronic pain for 50 months on average. At baseline, patients reported moderate levels of mean (± SD) pain intensity 6.3 (± 2.6) and depressive symptoms 28 (± 12.7) (Wells-Federman et al., 2002). Following the program, mean (± SD) pain intensity and depressive symptoms sores decreased to 4.9 (± 2.5) and 20 (± 12), respectively. Patients in this study reported significant improvements from pre-program to post-program, in pain intensity scores (*t*-test=5.6, effect size 0.5, 95% CI [0.9, 1.9], *p*=0.001), disability (*t*-test=7.6, effect size 0.6, 95% CI [5.2, 8.9], *p*=0.001), depressive symptoms (*t*-test=9.3, effect size 0.8, 95% CI [5.9, 9], *p*=0.001), and self-efficacy (*t*-test= -1.5, effect size 0.9, 95% CI [-57, -40], *p*=0.001). The results of this investigation provide support that nurses can facilitate an integrated cognitive-behavioral treatment program to reduce effectively chronic pain and depressive symptoms.

Role of Nursing

Available literature shows that pain is a considerable source for symptoms of anxiety and emotional distress in patients following surgery (Theobald et al., 2005; Theobald & Murray, 2004; Tolmie et al., 2006; Leegaard & Fabermoen, 2008). Prolonged and severe pain intensity as well as suboptimal pain treatment, may have serious implications for patients' HRQoL and

functional status after cardiac surgery (Doering et al., 2002; Vilīte et al., 2019; Yin et al., 2015). Challenges in adequately treating postoperative pain may arise from patient-related factors and healthcare-related factors. Patient-related factors include under-reporting of pain, the subjective nature of pain and pain thresholds, patient's knowledge about opioid use for postoperative pain management, and patient's satisfaction with the belief that postoperative pain must be experienced (Dawson et al., 2002; Leegaard et al., 2011; van Gulik et al., 2011; Vilīte et al., 2019; Watt-Watson et al., 2001; Yin et al., 2015). Healthcare-related factors include ineffective pain assessments, suboptimal pain medications prescribed and administered treatment protocols, nurses' knowledge and attitudes about effective pain management, and current healthcare policies and best practice guidelines available (Dawson et al., 2002; Leegaard et al., 2011; van Gulik et al., 2010; Vilīte et al., 2019; Watt-Watson et al., 2001; Yin et al., 2015). For example, Leegaard et al. (2011), completed a multi-center qualitative descriptive study (*N*=22) in Toronto, Canada, to identify cardiac surgery nurses learning needs associated with peri-operative pain management. Leegaard et al. (2011) conducted focused group interviews and found that nurses identified the use of opioids, the need to use multi-faceted pain management strategies, and gaps in knowledge as challenges to effective pain management.

Nurses play an essential role in the assessment, planning, monitoring, management and evaluation of patients' pain throughout the perioperative period (Registered Nurses' Association of Ontario, 2013; Wells et al., 2008). The role of nursing in the management of CPSP after cardiac surgery begins with the early identification of at-risk patients, advocating for effective pain management and treatment strategies, implementation of evidence based strategies, as well as contributing to nurse-led research designed to target the development of CPSP (Courtenay & Carey, 2008; Watt-Watson et al., 2001; Wells et al., 2008).

Problem Statement

For many individuals living with coronary artery disease, cardiac surgery is required to ameliorate symptoms, improve HRQoL and increase the likelihood of survival (PHAC, 2009). Despite the demonstrated survival and symptom-related benefits of cardiac surgeries, CPSP is prevalent in 7.5% to 56% of patients from three months to 15 years after cardiac surgery (Bar-El et al., 2005; Bruce et al., 2003; Choinière et al., 2014; Cogan, 2010; Eisenberg et al., 2001; Garland et al., 2003; Gjeilo et al., 2010; Herlitz et al., 2010; King et al., 2008; Mailis et al., 2000; Onan et al., 2013; Routledge et al., 2009; Steegers et al., 2007; Taillefer et al., 2006; van Gulik et al., 2012). Mounting evidence demonstrates that CPSP after cardiac surgery is increasingly being recognized as a serious negative complication with tremendous economic burden. High incidence and prevalence rates of CPSP also emphasize the need to proactively identify potentially modifiable perioperative risk factors, and to establish risk minimizing prevention and intervention strategies (Horn-Hofmann et al., 2017).

Several studies have examined the association between perioperative risk factors for their prognostic role in the transition to CPSP after cardiac surgery; however, the vast majority are not tenably modifiable by nurses. Risk factors that show potential for nurse-modification, in the perioperative context, include anxiety, depressive symptoms, acute postoperative pain intensity and cumulative opioid dose consumption.

In order to determine whether these factors confer risk for transition to CPSP after cardiac surgery, further robust, prospective observational data are needed from representative samples. The purpose of this study was to explore the association of the following risk factors with CPSP: i) moderate to severe preoperative anxiety symptoms, ii) moderate to severe preoperative depressive symptoms, iii) moderate to severe acute postoperative pain intensity, and

iv) cumulative opioid dose consumption. To inform future intervention development, whether or not the intensity/severity of identified risk factors is associated with the intensity of CPSP in cases where it develops.

CHAPTER 2: LITERATURE REVIEW

Literature Review

The development of CPSP is a complex multi-dimensional issue, in which the presence and persistence of pain meets the following established criteria: i) developed after surgery, ii) present for at least three months in duration, iii) localized to the surgical site and/or projected to an area or dermatome innervated by a nerve at the surgical site, iv) be an extension of acute postoperative pain or develops after an asymptomatic period, v) not a result of a pre-existing condition, vi) all other causes or sources of the pain have been excluded (e.g., infection), and vii) interferes significantly with HRQoL (Kehlet et al., 2006; Macrae, 2008; Raja et al., 2020; Weinrib et al., 2017). CPSP is a major, debilitating health problem, imposing substantial negative outcomes on HRQoL and costs to society. Fundamental to addressing the management of CPSP (and related negative outcomes) is understanding potential risk factors–especially those which may be feasible targets for nursing intervention.

This chapter reviews a) the etiology and nature of acute pain after cardiac surgery including the relevance of pain mechanisms, b) relevance of Gate Control Theory and pain pathophysiology, c) transition from acute to chronic pain states, as well as d) key psychobiological pain-related considerations (i.e., anxiety and depressive symptoms) as they pertain to the development of CPSP. A subsequent review of the available evidence was limited to risk factors that are potentially modifiable in the perioperative context, and hence, potentially amendable to future nursing intervention. These risk factors include: i) anxiety, ii) depressive symptoms, iii) acute postoperative pain, and iv) cumulative opioid dose consumption. The evidence reviewed featured a risk of bias assessment and related arguments that supported the current doctoral study. Conclusions are summarized following the literature review.

Etiology and Nature of Pain After Cardiac Surgery

According to the International Association for the Study of Pain, pain is defined as "an unpleasant sensory and emotional experience associated with, or resembling that associated with actual or potential tissue damage" (Raja et al., 2020, p. 1977). During cardiac surgery, the skin, fascia and visceral tissue are surgically incised, and vessels are electrocauterized to control bleeding, both at the sternum and the donor sites. The bony surfaces of the sternum and ribs are manipulated and mechanically retracted open (Diodato & Chedrawy, 2014; Kehlet et al., 2006). The left internal mammary artery is dissected from the chest wall; the resulting trauma and injury to the internal mammary artery has been associated with intercostal neuralgia as a result of the nerve damage sustained during surgery (Bruce, 2003; Kehlet et al., 2006). Surgical incisions are simultaneously made along one or both legs, from the groin to the ankle, to harvest the saphenous veins from its donor sites. The trauma and injury to saphenous vein donor sites has also been associated with the development of CPSP in the legs following cardiac surgery (Bruce et al., 2003; Garland et al., 2003). The length of donor site incisions and related areas of tissue insult typically depend on the number of vessels to be bypassed (Diodato & Chedrawy, 2014).

Postoperatively, the amount of pain experienced is not directly proportional to the degree of tissue damage/injury sustained (Meyer et al., 2006). Pain after surgery can be inflammatory, nociceptive, and/or neuropathic in nature (Ho et al., 2002; Kalso et al., 2001; Meyer et al., 2006; Parry et al., 2010). Like any other type of pain, postsurgical pain is complex and multi-dimensional, with sensory-discriminative, cognitive-evaluative, and affective-motivational features, which vary by individual (Melzack & Wall, 1965). A review of possible postsurgical pain mechanisms, as well as fundamental conceptual understanding of pain pathophysiology can help to shed light on the complexity of this phenomenon.

Potential Pain Mechanisms Following Surgery

Nociceptive Pain Mechanism

The cutting and handling of tissues during surgery produces noxious stimuli which activate primary afferent nociceptors, A-delta (Aδ) and C-fibers, in the peripheral nervous system (Reddi & Curran, 2014; Schaible & Richter 2004). These neurons encode and process noxious stimuli—a process known as nociception (Belmonte & Cervero, 1996; Schaible & Richter, 2004). During nociception, the sensory endings of these myelinated A-delta (Aδ) and unmyelinated C-fibers transduce, or convert mechanical, thermal and chemical stimuli into an electrical potential, which triggers an action potential and permits conduction by the axon of a primary afferent nerve fiber (Meyer et al., 2006; Reddi & Curran, 2014; Schaible & Richter, 2004). Primary and secondary afferent neurons synapse in the dorsal horn of the spinal cord and transmit excitatory electric impulses, via the ascending pain pathways of the spinothalmic tract, to the brain stem (e.g., thalamus), and the primary somatosensory cortex of the parietal lobe, where central processing of impulses are interpreted as painful (Garland, 2012; Reddi & Curran, 2014; Schaible & Richter, 2004). These somatosensory fibers respond to different stimulus modalities in a fairly predictable and consistent manner, activating ascending tracts to relay nociceptive stimulus to the brain (Ossipov & Porreca, 2014).

Following surgery, continued noxious stimuli at the surgical site(s) lower the activation threshold of nociceptors, and results in an increase in the excitability, or responsiveness of nociceptive neurons, known as sensitization (Meyer et al., 2006; Salter, 2014). Persistent spontaneous activity may develop, which may present clinically as hyperalgesia–increased pain in response to a natural stimulus, or allodynia–pain in response to stimuli that do not normally evoke pain (Gold & Gebhart, 2010; Reddi & Curran, 2014). The processes of peripheral and

central sensitization are widely recognized for their central roles in the development of CPSP (Gereau & Golden, 2014; McMahon et al., 2006).

Inflammatory Pain Mechanism

Inflammation also plays a role in the development of CPSP following cardiac surgery. Intra- and post-operatively, local tissue injury causes the release of concentrations of biochemical and inflammatory mediators that facilitate the inflammatory process in the peripheral environment. These chemical mediator substances include prostaglandins, cytokines, leukotrienes, bradykinin, adenosine, histamine, serotonin, lactate, potassium, adenosine, ATP, thromboxanes, glutamate, protons, platelet-activating factor, nerve growth factors, substance P and calcitonin gene-related peptide released from nociceptor terminals (Gereau & Golden, 2014; Meyer et al., 2006; Schaible & Richter, 2004). A few of these endogenous mediator substances (e.g., bradykinin, serotonin) can directly activate nociceptors, or sensitize nociceptors via modification of ion-channel function (e.g., cytokines) (Gereau & Golden, 2014; Reddi & Curran, 2014) resulting in neuronal excitability and triggering of pain impulses to the spinal cord and brain. Most endogenous mediator substances (e.g., nerve growth factor) act indirectly, via inflammatory cells in the peripheral environment of primary afferent nerve fibers, to orchestrate the signaling cascade of the inflammatory response, as well as have a synergistic effect in potentiating nociceptor transduction and responses (Gereau & Golden, 2014; Meyer et al., 2006; Reddi & Curran, 2014).

Neuropeptides exert efferent functions in the tissue, inducing vasodilation, plasma extravasation and attraction of macrophages or degranulation of mast cells at the site of tissue damage (Schaible & Richter, 2004). The inflammation produced by nociception is called neurogenic inflammation. Following cardiac surgery, endogenous inflammatory mediator-

initiated signaling activates modulation of ion-channel mechanisms to produce increased sensitivity—peripheral sensitization (Gereau & Golden, 2014). In the acute postoperative period, inflammatory pain, secondary to local excitability, usually lessens, as tissue healing occurs (Reddi & Curran, 2014). However, these inflammatory mediators have diverse pain mechanisms and receptor sites of action which may proliferate neuronal excitability and the transmission of pain perception.

Neuropathic Pain Mechanism

Fundamental to understanding the role of neuropathic pain in the development of CPSP after cardiac surgery, is understanding neuronal plasticity. Unlike nociception and inflammation pain mechanisms, neuropathic pain is not stimulated directly by nociceptors (Schaible & Richter, 2004). Neuropathic pain may result from trauma and injury to the neurons in the peripheral or central nervous system (Schaible & Richter, 2004). During cardiac surgery, nerves may be cut, stretched or crushed during incision or retraction of the skin, fascia, or visceral tissue and become disconnected from their principal target (McMahon et al., 2006; Reddi & Curran, 2014). The processing of neuronal information is a dynamic process reliant on changes in the intensity of neuronal excitability and synaptic strength (Woolf & Salter, 2006). As a result of nerve injury, phenotypic changes occur in the neurochemistry and functional properties within the sensory neurons (McMahon et al., 2006). Typically, an innocuous stimulus would not elicit a painful response. However, intraoperative nerve injury may alter properties of the neurons in the somatosensory system resulting in spontaneous, ectopic discharges from injured and proximally located uninjured nerves (Reddi & Curran, 2014; Woolf & Salter, 2006) and an innocuous stimulus would thus elicit spontaneous pain impulses. Such plasticity of the central nervous

system may be responsible for the neuropathic pain experienced well after the initial incision has healed (Kehlet et al., 2006; van Gulik, 2011; Woolf & Salter, 2006).

Relevance of Gate Control Theory and Pain Pathophysiology

What is clear from the description of nociceptive, inflammatory and neuropathic pain mechanisms, above, is that our understanding of the complex, multidimensional nature of pain—and related complexity of the nervous system—have greatly evolved over the last several decades. Classically, however, Melzack and Wall's (1965) Gate Control Theory of pain remains influential—and indeed central—to our conceptual understanding of pain. Gate Control Theory proposed that pain perception was based on the transmission of an impulse from the periphery through to the spinal cord and was subject to modulation by both intrinsic neurons and controls originating from the brain (Cervero, 2005; Dickenson, 2002; Melzack & Wall, 1965). Melzack and Wall (1965) developed Gate Control Theory to challenge two prevalent and mutually-exclusive theories of pain: Specificity Theory and Pattern Theory proposed by von Frey (1894) and Goldscheider (1894). According to Melzack and Wall (1965), von Frey's Specificity Theory proposed that specific pain receptors in the cutaneous tissue transmit nociceptive impulses via A-delta (Aδ) and C-fibers, in the peripheral nervous system. These impulses are transmitted along a dedicated pathway–the lateral spinothalamic tract in the spinal cord–to the thalamus and cerebral cortex, or the 'pain center' of the brain (Melzack & Wall, 1965).

Specificity Theory was based on the proposition that the skin contained 'pain receptors' which only responded to intense noxious stimulation, which once stimulated, would always elicit pain and only the sensation of pain (Melzack & Wall, 1965). This tenet of Specificity Theory suggested that pain intensity was directly related, and proportional to, the degree of tissue damage sustained (Melzack & Wall, 1965). However, Specificity Theory served as a partial

explanation of pain intensity, as it is not wholly supported by clinical evidence (Melzack & Wall, 1965). For example, following amputation of a limb, the presence and intensity of phantom limb pain cannot be explained by Specificity Theory's key proposition of a dedicated pathway to the brain, given the peripheral nerve and pathway have been surgically severed and the limb removed (Melzack & Wall, 1965).

Pattern Theory, a collective heading, used to refer to a body of seminal works by Goldscheinder (1894), Nafe (1934), Hardy, Wolff and Goodell (1940), Livingston (1943), Weddell and Sinclair (1955), as well as Noordenbos (1959), proposed that noxious stimulus intensity and central summation mechanisms were the key determinants of pain, as opposed to peripheral stimulation (Melzak & Wall, 1965). Conceptually, Pattern Theory claimed that in the absence of obvious stimulation, the spinal cord is continually transmitting afferent stimuli– carried by the slow conducting small fiber system. However, when strong noxious stimuli are directed to cutaneous tissue, there is an increase in the number of active receptor fibers transmitting afferent impulses to the spinal cord and brain. The rapidly conducting afferent fibers inhibit synaptic transmission of the slower conducting fiber system, where 'fast blocks slow' transmission to the central nervous system (Melzack & Wall, 1965). It is this notion of balance of neuronal activity between large and small fibers that formed the basis of the 'gating' concept proposed by Melzack and Wall (1965).

Melzack and Wall (1965) claimed that physiologically speaking, Pattern Theory took into consideration that a specialized input controlling system normally prevents summation from occurring and that destruction of the system leads to pathological pain states. For example, mechanical and thermal stimuli activate the transmission of noxious impulses via rapidly conducting, large myelinated fibers. Once activated, these fibers can inhibit synaptic

transmission in the slower conducting, small unmyelinated system–which also transmit noxious stimuli (Melzack & Wall, 1965). Pathological damage to these systems following trauma or tissue injury has been purported to be responsible for diffuse pain states, such as slow burning pain and hyperalgesia pain (Melzack & Wall, 1965). Melzack and Wall (1965) argued that overall, the different proposed pattern-related theories of pain fell short in terms of constituting a satisfactory general theory of pain, as previously proposed theories of pain do not integrate the diverse theoretical mechanisms of pain (i.e., nociceptive, inflammatory and neuropathic—previously described).

Gate Control Theory proposed that when noxious impulses are transmitted from peripheral nerves, via large myelinated (A-delta) and small unmyelinated (C-fiber) receptors, to the dorsal horn in the spinal cord, depending on afferent modulation and relative activity of each receptor fiber in the spinal cord, small densely, packed inter-neurons of the substantia gelatinosa act as a gate to inhibit and potentiate impulses, by regulating the input of large and small fibers to and from peripheral to central cells (Melzack & Wall, 1965). A spinal *'gate'* in the substantia gelatinosa *'opens'*–allowing the release of pro-nociceptive substances (e.g., substance P) into the synaptic cleft, activation of post-synaptic receptors and activation of second order neurons involved in the modulation of noxious impulse to transmission (T) cells along the spinal tract, or '*closes*'–does not allow noxious impulse to transmit to T cells along the spinal tract and to the brain, therefore no pain is felt (Melzack & Wall, 1965). Primarily, this gating mechanism allows spontaneous noxious impulse transmission following damage to A-delta (Aδ) fibers or activation of the C-fibers following excessive stimulation through inflammation or pressure on the C-fibers at the local site (Cope, 2006). The *spinal gate* can be modulated by the number of active fibers, the frequency of nerve impulses, descending inhibitory signals from the brain, or by the balance

in activity in large myelinated and smaller unmyelinated fiber afferents (Melzack & Wall, 1965).

Gate Control Theory (Melzack & Wall, 1965) claimed that pain is not a simple sensory experience, but involves central mechanisms—sensory-discriminative, motivational-affective, and cognitive-evaluative—that result in the complex pain experience. Beyond Gate Control Theory, and as described under pain mechanisms—nociceptive, inflammatory and neuropathic pain involves both dynamic interactions between ascending and descending neural systems, with an ongoing balancing of excitatory and inhibitory mechanisms and endogenous neurotransmitters (e.g., opioids, serotonin and norepinephrine) (Basbaum & Jessell, 2000). As such, pain perception and patient response are not predictable, but highly variable for each person and experience. This variability is a result of the modulation of noxious stimuli at several levels of the central nervous system (Basbaum et al., 2008; Basbaum & Jessell, 2000).

Since the development of Gate Control Theory, pain knowledge has greatly evolved. Cumulative research has led to more advanced understanding of the nature of pain mechanisms including peripheral and central sensitization, cortical processing, and spinal and supra-spinal mechanisms of pain modulation. However, the tenets of Gate Control Theory remain relevant to understanding the complexity of pain. Not-with-standing recent advances in our understanding of pain mechanisms, Katz and Rosenbloom (2015) posited that at its core, the *'gate'* metaphor continues to serve as an easily understood concept, which theoretically explains how pain is encoded, and which illustrates how pain can change over time.

In what follows, current conceptual thinking about the notion of 'transition' from acute to chronic pain, and how CPSP per se, is defined and further discussed.

Transition From Acute to Chronic Post-Surgical Pain

Traditionally, pain was conceptually divided into acute and chronic states with the belief that different mechanisms were involved in the development of each (Neil & Macrae, 2009). Generally, these acute and chronic postoperative pain states, were based on 'duration' of time one experiences pain following surgery (Merskey & Bogduk, 1994). For example, if pain was present up to two months postoperatively, it was considered acute pain, which served an adaptive and protective function (Woolf, 2010). However, pain continuing after two months was termed chronic and maladaptive, irrespective of the pain mechanism (i.e., nociceptive, inflammatory or neuropathic—previously described) associated with its development (Woolf, 2010). At present, there is no definition of acute postoperative pain that differentiates it, mechanistically, from CPSP (Shipton, 2011), per se. As such, the definition of acute pain is limited to quantification of a specific duration of pain, i.e., up to two months postoperatively.

The use of a 'duration' based approach to differentiate acute and chronic pain is contradictory to more contemporary understanding of pain as a complex and multidimensional experience. For example, Von Korff (2011) argued against the duration based definition of chronic pain citing four reasons: 1) the time typically used to separate acute from chronic pain states, does not parallel the time-scale of neurophysiological mechanisms theorized to result in chronic pain (i.e., milliseconds versus months), 2) chronic pain by duration alone, is inadequate to distinguish individuals with clinically significant pain, 3) duration based definitions for chronic pain do not provide a foundation for targeting patients at risk of developing CPSP early in its course, when prevention might be most effective, and 4) the available evidence that patients typically become progressively dysfunctional as a result of pain over time is not compelling. Von Korff (2011) believes that important correlates of chronic pain (e.g., anxiety

and depressive symptoms) are often present in the acute period and the transition to CPSP is often described as a failure of these factors to resolve, irrespective of time.

The International Association for the Study of Pain (IASP), in collaboration with WHO, has worked to improve the representation of chronic pain in healthcare. The collaboration cites the inadequacies with the traditional classification of CPSP, the need to improve the impact of CPSP on patients and their HRQoL after surgery, and the need to improve the consistency of diagnosing, reporting, and treatment of chronic pain, including of CPSP (Schug et al., 2019; Treede et al., 2015).

For the purpose of this doctoral work—to examine potentially modifiable risk factors of CPSP in the perioperative period—Von Korff's (2011) argument supports CPSP being operationalized by the following criteria, previously described: it must i) have developed after surgery, ii) be present for at least three months in duration, iii) be localized to the surgical site and/or projected to an area or dermatome innervated by a nerve at the surgical site, iv) be an extension of acute postoperative pain or developed after an asymptomatic period, v) not be the result of a pre-existing condition, vi) interfere significantly with HRQoL (Weinrib et al., 2017; Werner & Kongsgaard, 2014). In addition, all other causes or sources of the pain should be excluded (e.g., infection) (Kehlet et al., 2006; Macrae, 2008).

Overall, this definition gives credence to the belief that pain which was once acute can become chronic by virtue of a complex transition phase (Neil & Macrae, 2009; Katz & Seltzer, 2009). In keeping with the understanding that such a transition can indeed be complex, it is important to understand CPSP not only from a physiologic perspective (as outlined in pain mechanisms), but also from a psychobiological perspective. Key concepts of the

psychobiological perspective are reviewed in the next section, in relation to common emotional states (i.e., anxiety, depressive symptoms) experienced in the context of CPSP.

Chronic Post-Surgical Pain: Key Psychobiological Considerations

Emotional distress is frequently observed in individuals experiencing chronic pain. It has been argued that varying degrees of aversive emotional qualities such as fear, anxiety, and depressive symptoms may have a temporal and correlated relationship with experiences of chronic pain (Craig, 2006; Katz et al., 2014; Turk et al., 2010). Negative emotions may be associated with anticipation of pain, may be an outcome of pain, may be a cause of pain, or may also represent a problem concomitant with pain (Craig, 2006). As Craig (2006) and Garland (2012) argued, pain perception is multidimensional and involves several psychological processes including paying attention to the source of potential harm or a painful stimulus, cognitive appraisal of the meaning of the painful sensation in the body and deciding the degree to which they signify the presence of an actual or potential harm, and the subsequent feedback from emotional, psychobiological and behavioral reaction.

Cognitive appraisal of pain may vary in relation to the activation of different sensory and affective dimensions, wherein change in pain intensity leads to altered activation of somatosensory cortex, whereas change in pain unpleasantness results in altered activation of the anterior cortex (Garland, 2012). Understanding this change is relevant to understanding how individual interpretation of pain as ‘intense’ or ‘unpleasant’ can change when pain intensity and duration increases (Horn et al., 2012). The interpretation of potential harm is also reliant on whether or not the individual perceives that he or she can cope with the sensation. Garland (2012) argued that if available coping resources are deemed insufficient, then pain can be perceived as intense and uncontrollable, regardless of measures implemented to control the pain.

This inference is relevant to understanding that the feelings of inability to cope can also influence negative emotions (e.g., anxiety and depressive symptoms), which in turn influence the interpretation of pain.

The aversive nature of pain elicits strong emotional reactions which give rise to subjective feelings that accompany skeletal (e.g., muscle contraction), autonomic (e.g., changes in heart rate), endocrine (e.g., norepinephrine), and immune (e.g., pro-inflammatory cytokines) responses which may exacerbate pain via psychophysiological pathways (Blair et al., 2003; Craig, 2006; Flor, 2014; Garland, 2012; Price & Busnell, 2004). As an example, negative emotions and stress initiate sympathetic nervous system activity, marked by increased heart rate and muscle tissue contractility in anticipation of avoidance reactions (Garland, 2012). Such sympathoexcitatory activation, if prolonged, may increase blood flow to injured tissue, increase muscle tension, and may augment pain intensity at the site of injury (Garland, 2012).

On the other hand, as previously described above, the presence and rumination of negative emotional states may reduce one's perceived ability to cope with pain, which intensify pain perception and cardiovascular autonomic responses (Garland, 2012; Philips & Rachman, 1996). Garland (2012) cautioned that painful perceptions from the viscera and muscles may also activate cardiac vagal premotor neurons, resulting in decreased blood pressure and heart rate. This autonomic response corresponds with depressive states and affect (Garland, 2012; Philips & Rachman, 1996); adding to the temporal and correlated relationship with experiences of chronic pain which may be present following cardiac surgery.

Garland (2012) also claimed that pro-inflammatory cytokines and cortisol are released during the experience of stress and negative emotion; these can enhance nociception and transmission of aversive information to the brain, motivating the individual to alleviate or avoid

further pain. Typically, individuals are motivated to avoid situations of pain and related experiences that will potentially cause acute pain or further injury (Craig, 2006).

In summary, the complexity of psychobiological systems related to pain supports the fact that as a phenomenon, pain is a complex, subjective, multidimensional experience with sensory-discriminative, cognitive-evaluative and affective-motivational components (Philips & Rachman, 1996; Melzack & Wall, 1965). The tenets of Gate Control Theory are relevant to understanding how negative emotional states (i.e., anxiety and depressive symptoms) and pain pathophysiology can influence the transition to CPSP after cardiac surgery. For example, in the perioperative period, negative emotions (e.g., anxiety) can be associated with the anticipation of pain related to cardiac surgery or represent a problem concomitant with pain (Craig, 2006). The cognitive appraisal of pain as potential harm, may further elicit strong emotional reactions, as well as result in the rumination of the negative emotional state (Garland, 2012). Following cardiac surgery, continuous noxious stimuli at the surgical incision site, lower the activation threshold of nociceptors and results in the excitability and responsiveness of nociceptive neurons (Meyers et al., 2006; Salter, 2014). Similarly, endogenous mediator substances activate nociceptors resulting in neuronal excitability and triggering of pain impulses to the spinal cord and brain (Reddi & Curran, 2014). Both nociceptive and inflammatory pain mechanism may be involved with peripheral sensitization (Gereau & Golden, 2014). Noxious impulses are transmitted from the peripheral nerves via A-delta (Aδ) and C-fiber receptors to the dorsal horn in the spinal cord. Depending on afferent modulation and relative activity of each receptor fiber in the spinal cord, a spinal gate ‘opens’ to allow impulse transmission or ‘closes’ to prevent transmission to T cells (Melzack & Wall, 1965). Primarily, the gating mechanism allows for spontaneous noxious impulse transmission and is modulated by the degree of excitatory activity of nerve impulses as

well as descending inhibitory signals from the brain (Melzack & Wall, 1965). Transmission of cognitive and affective impulse information via the descending neural pathways, influence the gating mechanism (Asmundson & Wright (2004). According to Asmundson & Wright (2004), the summation of ascending nociceptive input (from the periphery) and the descending information (from the brain) regarding cognition and emotional states, "determines whether the spinal gate is 'open' or 'closed', and as such influences the perception of pain" (p. 40). This understanding of Gate Control Theory and pain pathophysiology support the examination of anxiety and depressive symptoms—as key cognitive-emotional states, for their role in the transition to CPSP.

Anxiety and Depressive Symptom

Two key emotion-related concepts that illustrate how common psychobiological systems can be aroused synchronously, in the context of pain, include anxiety and depression (Craig, 2006; Hinrich-Rocker et al., 2009; Theunissen et al., 2012; Turk et al., 2010).

Anxiety. According to the Diagnostic and Statistical Manual of mental disorders (DSM-V), anxiety is described as a subjective experience of cognitive somatic, emotional and behavioral responses, which manifest into fear and worry (American Psychiatric Association, 2013). Several studies have examined the relationship between anxiety and the development of CPSP. A number of these studies were included in Theunissen et al.'s 2012 systematic review and meta-analysis (n=29 studies), designed to investigate whether high levels of preoperative anxiety were associated with an increased risk of CPSP following surgery (e.g., thoracotomy, inguinal hernia, hysterectomy, knee replacement). Of the studies identified for inclusion, approximately half were included for meta-analysis (n=15 of 29). Theunissen et al., (2012) found that overall, anxiety may play a significant role in the occurrence of CPSP (observed minimum

pooled effect, OR 1.55, 95% CI [1.10, 2.20], χ^2 45.89, *df 14*, *p*=<0.001; observed maximum pooled effect, OR 2.10, 95% CI [1.49, 2.95], χ^2 25.37, *df 14*, *p*=0.031).

Other available data also suggest that anxiety is prevalent in cardiac surgery patients throughout the perioperative period (Kovivula et al., 2001; Koivula et al., 2002). For example, Koivula et al. (2002), conducted a follow-up cohort study in Finland (*n*=171) to examine cardiac surgery patient's fears and anxiety at different phases of the perioperative period. Data were collected via mailed survey at three time points (i.e., pre-operative period, hospitalization, and three months postoperatively) via the Bypass Grafting Fear Scale, the Spielberger State Trait Anxiety Inventory (STAI), and the Hospital Anxiety Depression Scale (HADS). Overall, mean (± SD) anxiety scores on the STAI at baseline was 39.0 (± 10.6, 95% CI [37.4, 40.6]) and 41.4 (± 95, 95% CI [40.0, 42.8]) suggesting mild to moderate levels of anxiety on the state and trait scales, respectively. Specifically, Koivula et al. (2002) found that 43% of patients reported moderate situational anxiety and 6% reported severe levels of situational anxiety while waiting for surgery and 18% continued to experience moderate situational anxiety three months after cardiac surgery. What is clear from Koivula et al.'s (2002) study is that patients experience moderate to severe levels of anxiety preoperatively and throughout the postoperative course.

Depressive symptom. Depressive symptoms are well-recognized in chronic pain literature for their association with chronic pain states (Craig, 2006; Turk et al., 2012). Carr (2003) claimed that in some instances, pain-related distress dominates the clinical picture and that an accompanying, underlying depressive disorder may not be recognized for months or even years. Depression, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), consists of a spectrum of signs and symptoms which include: irritable mood, loss of interest, suicidal ideations, significant changes in weight or appetite, sleep, activity, energy, and

concentration, experienced at differing severities (American Psychiatric Association, 2013). Of these signs and symptoms, fatigue, reduced activity, and sleep disturbances have also been established as correlates of CPSP following cardiac surgery.

Hinrich-Rocker et al. (2009) conducted a systematic review of 50 studies, published between January 1996 to June 2006, to identify psychosocial risk factors and correlates of CPSP. Hinrich-Rocker et al. (2009) found that duration of depressive symptoms and psychological vulnerability were more likely to have an association (i.e., Grade of 1) with the development of CPSP following various surgeries (e.g., thoracotomy, breast, spine and knee) (Hinrich-Rocker et al., 2006). Similarly, Blair et al., (2003), conducted a literature review to determine the prevalence of depression and pain symptoms, as well as the effects of co-morbidity on diagnosis, clinical outcomes and treatment. Blair et al., (2003) found that moderate to severe pain intensity in individuals with depression impairs function, and is associated with more depressive symptoms and worse outcomes (e.g., HRQoL). More importantly, the presence of pain negatively affects the identification and management of depression in clinical studies. Although Hinrich-Rocker et al.'s (2009) and Blair et al.'s (2003) reviews were not specific to CPSP among cardiac surgery patients, both reviews support the position that there is a correlation between the presence of depressive symptoms and chronic pain in general.

Data also suggest that depressive symptoms are prevalent in patients undergoing cardiac surgery (Mitchell et al., 2005; Ravven et al., 2013). For example, Ravven et al., (2013), conducted a meta-analysis of 39 studies, published between October 1, 1995 to June 15, 2011, to determine the presence of depressive symptoms in adult patients after cardiac surgery. Ravven et al. (2013) found that within the first two weeks postoperatively (n=4), the risk for depression was increased relative to baseline, relative risk (RR)=1.27, 95% CI [1.01, 1.61], I^2 =79.7%, p=<.001.

However, there was a decreased risk for depression during the recovery period: a) from two weeks to two months (*n*=8), (RR=0.78, 95% CI [0.67, 0.90], I^2 =0.0%, *p*=0.82), b) from two months to six months (*n*=13), (RR=0.64, 95% CI [0.58, 0.70], I^2 =13.8%, *p*=0.31) and c) over six months postoperatively (*n*=6), (RR=0.68, 95% CI [0.58, 0.79], I^2 =38.3%, *p*=0.15). This study found that depressive symptoms are prevalent in the patients undergoing cardiac surgery.

Overall, there is evidence to suggest that preoperative assessment of depressive symptom is important. Given the psychobiological association of depressive symptom and development of chronic pain states, it is important to assess preoperative depressive symptom, as the potential for increased risk for vulnerability, negative emotions, and impaired coping may compromise effective postoperative recovery (Ravven et al., 2013).

To summarize, a review of key psychobiological concepts is helpful in further understanding the complex and multi-dimensional nature of the transition from acute to CPSP. Common psychobiological systems (e.g., endocrine and immune) which operate in the context of pain as well as emotional distress not related to noxious stimuli can be aroused synchronously, and facilitate ongoing arousal in another. Evidence suggest that negative emotional states, namely anxiety and depressive symptoms, can be present in the context of patients who have undergone surgery, including cardiac surgery. The next section of this literature review addresses putative risk factors for transition to CPSP following cardiac surgery per se, and includes discussion of the role that anxiety and depressive symptoms may play in that transition.

Risk Factors for CPSP After Cardiac Surgery

Over the last decade, several studies have examined putative risk factors for the development of CPSP following cardiac surgery. These risk factors can be categorized as

preoperative, intraoperative and postoperative risk factors (Katz & Seltzer, 2009)—a number of which may be amenable to nursing intervention in the perioperative context.

Preoperative Risk Factors

Several preoperative risk factors examined to date include: i) demographic risk factors including age (Bruce et al., 2003; Bruce & Quinlan, 2011; Gjeilo et al., 2010; Kalso et al., 2001; Markman et al., 2010; Steegers et al., 2007; Taillefer et al., 2006; van Gulik et al., 2012 & 2011), sex (Choinière et al., 2014; Gjeilo et al., 2010; Kalso et al., 2001; Markman et al., 2010; Parry et al., 2010; Taillefer et al., 2006; van Gulik et al., 2012 & 2011; van Leersum et al., 2010), and level of education (Choinière et al., 2014); ii) psychological factors including anxiety and depression (Choinière et al., 2014; Taillefer et al., 2006); iii) medical and health status risk factors such as body mass index (Bruce et al., 2003; Choinière et al., 2014; Gjeilo et al., 2010; Steegers et al., 2007; Taillefer et al., 2006; van Gulik et al., 2012), diabetes mellitus (Garland et al., 2003; Gjeilo et al., 2010; Markman et al., 2010; Lahtinen et al., 2006; Lee et al., 2010; Steegers et al., 2007), smoking (Lahtinen et al., 2006) and iv) preoperative angina and other pain problems (Bruce et al., 2003; Kalso et al., 2001; Lahtinen et al., 2006; Lee et al., 2010; Steegers et al., 2007; van Gulik et al., 2012 & 2011).

While a considerable volume of evidence is available pertaining to these preoperative factors, they are, for the most part, non-modifiable (e.g., age). Of these known preoperative risk factors, fewer studies have examined psychological factors, as compared to demographic, medical and health status preoperative factors.

Intraoperative Risk Factors

A number of intra-operative risk factors have been examined for their association with the transition to CPSP following cardiac surgery, these include: i) type of surgical technique used

(Bar–El et al., 2005; Bruce et al., 2003; Boodhwaini et al., 2006; Choinière et al., 2014; Eng & Wells, 1990; Gjeilo et al., 2010; Ho et al., 2002; Lee et al., 2010; Markman et al., 2010; Meyerson et al., 2001; Momeni et al., 2010; Taillefer et al., 2006; van Gulik et al., 2012 & 2011; van Leersum et al., 2010; Wiklund et al., 2000), ii) duration of surgery (Choinière et al, 2014; Kalso et al., 2001; Taillefer et al., 2006; van Gulik et al., 2012), iii) number and type of bypass grafts per surgery (Boodhwaini et al., 2006, Kalso et al., 2001; King et al., 2008; van Gulik et al., 2011; Steegers et al., 2007), and iv) previous cardiac surgery and sternotomy (Gjeilo et al., 2010; van Gulik et al., 2012 & 2011).

From a nursing perspective, there is little utility in reviewing these risk factors for direction or strength of association with CPSP, given that there is no feasible opportunity for nurses to modify the above listed intra-operative factors, considering a nurse's scope of practice. Nevertheless, known intra-operative risk factors, should be controlled for in any future examination of nurse-modifiable risk factors due to potential confounding effects.

Postoperative Risk Factors

A number of clinical (patient or care-process related) postoperative risk factors have also been examined for their association with the transition to CPSP following cardiac surgery, these include: i) length of intensive care unit (ICU) stay and length of hospital stay (Choinière et al., 2014; Taillefer et al., 2006; van Gulik et al., 2012), ii) postoperative complications (Choinière et al., 2014; Gjeilo et al., 2010; Kalso et al., 2001; Lahtinen et al., 2006; Markman et al., 2010; Taillefer et al., 2006; van Gulik et al., 2012 & 2011), iii) postoperative pain (Bjørnnes et al., 2014; Choinière et al., 2014; King et al., 2008; Lee et al., 2010; Momeni et al., 2010; Lahtinen et al., 2006; Steegers et al., 2007; van Gulik et al., 2012 & 2011;) and iv) analgesic consumption (Choinière et al., 2014; Ho et al., 2002; Jensen & Andersen, 2004; Kalso et al., 2001; Lee et al.,

2010; Onan et al., 2013; Taillefer et al., 2006; Ucak et al., 2011). Again, there is little utility in reviewing, in depth, the strength and magnitude of association of the majority of these risk factors with CPSP as they largely fall outside the scope of nursing practice in terms of possible intervention. There are, however, two clinical factors that may hold promise as potentially modifiable nursing targets in the perioperative context; these include acute postoperative pain intensity and cumulative opioid analgesic consumption.

Modifiable Risk Factors for CPSP After Cardiac Surgery

Search Method. An electronic database search of the health sciences literature was conducted using CINAHL, Cochrane Library, Embase, Medline, PsychINFO, and ProQuest Dissertations and Thesis databases to find available research studies that examined the variables: anxiety, depressive symptoms, acute postoperative pain and opioid dose consumption as predictive risk factors for the development of CPSP after cardiac surgery. All databases were searched from inception to January 15, 2021. Variations were made to subject headings, medical subject heading (MeSH) terms and key search words (Appendix A: Search Methodology).

Inclusion Criteria. Studies that examined the variables of either anxiety, depressive symptoms, acute postoperative pain or opioid dose consumption as predictive risk factors for the development of CPSP after cardiac surgery in adults 18 years of age and older. Studies that met the following criteria were included in the review of the related literature: evidence in the form of a guideline, systematic review or single study, available in full-text English. Available reference lists were reviewed for studies that included the variables and meets the inclusion criteria. Abstracts meeting the inclusion criteria, were further searched to find the evidence in English, full text. Although this is not an exhaustive systematic review, the aim was to conduct a thorough review of the available published evidence.

Exclusion Criteria. Evidence was excluded if they were commentaries, editorials, reports, white papers, abstracts with no available English full text, or included surgical procedures other than cardiac surgeries. Available evidence was not excluded based on study design, time of publication, and time to follow-up for outcome measures.

Selection of Studies. The electronic searches produced 549 hits, on all databases combined. A total of 542 results did not meet the inclusion criteria (Appendix B: PRISMA Flow Diagram of Literature Search). The remaining seven articles met the inclusion criteria and were selected for review (Appendix C: Summary of Included Articles).

Critical Appraisal. A single reviewer (SH) critiqued the evidence and assessed for a risk of bias. Prognostic studies were assessed according to the Quality in Prognostic Studies tool (QUIPS) (Hayden et al., 2013). The QUIPS tool was used to assess the methodological quality of six studies on six domains: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, statistical analysis and reporting (Appendix D: Quality in Prognostic Studies Tool). For each domain, three to seven "prompting items for consideration" were used to rate the adequacy of reporting by a study. Based on appraisal, an overall rating of 'high bias', 'moderate bias' or 'low bias' was assigned for each domain, in all seven studies, if there was a potential for a risk of bias in the domain (Appendix E: Risk of Bias Assessment for Included Studies). The cross-sectional study was assessed according to AXIS, the cross sectional study critical appraisal tool (Downes et al., 2016). The AXIS tool uses 20 questions to examine the quality of the cross sectional study design on five domains: introduction, methods, results, discussion, and other. For each domain, the assessment for adequacy of reporting by the study was appraised as 'yes', 'no' and 'do not know' (Appendix F: AXIS Cross Sectional Study Tool)

Critical Appraisal and Synthesis of Risk Factors for CPSP After Cardiac Surgery

Anxiety

A search of the literature found two quantitative studies—one prospective (Choinière et al., 2014) and one cross-sectional (Taillefer et al., 2006)—which examined the predictive role of anxiety in the development of CPSP following cardiac (Appendix G: Studies Examining Anxiety as a Risk Factor for CPSP). Both studies, were conducted in Canada and measure anxiety via the Hospital Anxiety and Depression Scale (HADS). HADS is a 14-item self-evaluation questionnaire that consists of two measures of psychological morbidity: Anxiety and Depressive Symptoms.

To date, Choinière et al. (2014) is the only large-scaled prospective study to examine the prognostic value of psychological morbidity as a putative risk factor for the transition to CPSP and overall, the evidence examining anxiety as a risk factor for CPSP is mixed. Choinière et al. (2014) conducted a multi-center, prospective study (*N*=1247)—CARD-Pain, aimed at determining the prevalence of CPSP and related risk factors for its presence and severity up to two years following cardiac surgery. Choinière et al. (2014) found that CPSP was prevalent in 40.1% of patients (*n*=423 of 1054) at three months following cardiac surgery and remained in 9.5% of patients (*n*=93 of 976) at 24-months postoperative. Through multivariable generalized estimate equation (GEE) regression modelling, it was found that preoperative anxiety, as measured by the HADS, was a significant independent risk factor (adjusted odds ratio [OR] 1.04, 95% CI [1.00, 1.09], *n*=975) for the development of CPSP up to two years postoperatively.

The evidence suggests that preoperative anxiety has the potential to be an independent risk factor of CPSP following cardiac surgery; however, this must be interpreted with caution. The lower limit of the 95% confidence interval included the value of one, and the study did not

report an associated *p*-value. Taken together this may indicate the possibility of a null association between baseline anxiety and CPSP in the real world (Szumilas, 2010). Moreover, mean (± SD) baseline HADS anxiety scores were not reported, precluding inference about the severity of anxiety in the study sample.

In addition, Taillefer et al. (2006) conducted a single-site cross-sectional study (*N*=736), to assess the prevalence, characteristics, effect, and predictors of CPSP. Via mailed survey, between one year and three years after cardiac surgery, patients were asked to report the presence, severity and interference of pain in the past four weeks, their psychological well-being, as well as the use of pharmacological and non-pharmacological methods to treat pain. CPSP was prevalent in 23% (*n*=129 of 564) patients between one year and three years after cardiac surgery. Of these, patients with CPSP (*n*=129) were found to have significantly higher baseline anxiety scores compared to those without CPSP (*n*=394), (*t*-test, *p*=<0.001). Those with CPSP had a mean (± SD) HADS anxiety score of 7.0 (± 4.4); HADS anxiety scores ranging between eight and 10 are considered mild or 'borderline abnormal' and scores between 11 and 21 are deemed moderate to severe or 'abnormal' (Carmines & Zeller, 1979). Considering that the mean reported score had SD ± 4.4, a number of individuals would have reported anxiety in the 'abnormal' or moderate to severe range.

While these data also suggest that anxiety may be of prognostic significance, there are important methodological limitations to consider. For example, Taillefer et al. (2006) study used self-report questionnaires mailed to participants to collect data at approximately 30 months after their cardiac surgery. The use of a mailed self-report survey introduces the risk of bias in sample selection. Specifically, patients might be more inclined to return completed surveys if they experienced the outcome of CPSP leading to over estimation in the prevalence of CPSP after

cardiac surgery. Additionally, the time gap from index surgery to data collection, presents an opportunity for recall bias wherein, participants may have had difficulty recalling their pain experiences and psychological well-being at the time, accurately (Appendix E: Risk of Bias Assessment for Included Studies).

Overall, preliminary evidence suggests an association between baseline anxiety and the development of CPSP following cardiac surgery; however, the strength of this association appears to be weak.

Depressive Symptom

Two quantitative studies—one prospective (Choinière et al., 2014) and one cross-sectional (Taillefer et al., 2006)—which examined preoperative depression via HADS were reviewed (Appendix H: Studies Examining Depressive Symptoms as a Risk Factor for CPSP). These results further add to the mixed evidence base of studies examining an associated between depressive symptoms and the development of CPSP following cardiac surgery. For example, Choinière et al.'s 2014 study, as pervious described, found that preoperative depressive symptoms were not significantly associated with the development of CPSP following cardiac surgery in either adjusted (OR 0.98, 95% CI [0.93, 1.04]) or unadjusted (OR 1.06, 95% CI [1.03, 1.10]) analyses.

Conversely, Taillefer et al.'s 2006 cross-sectional study, as previously described, found that patients with CPSP had significantly higher baseline depression scores (mean 5.1, SD ± 4.3), as measured by HADS, compared to those without CPSP (n=394), *(*t-test, p=<0.001).

Between these two studies, the evidence pertaining to preoperative depressive symptoms as a risk factor for CPSP following cardiac surgery was mixed. A methodological limitation of this evidence was the fact that both studies refer to measuring "depression", but in fact are

measuring depressive symptoms in medically ill patients using a rating subscale; presenting an opportunity for risk of bias in the prognostic factor measurement domain (Appendix E: Risk of Bias Assessment for Included Studies). The rating subscale screens for depressive symptoms and prompts the need for further medical evaluation.

Acute Postoperative Pain Intensity

Six quantitative studies to date—one retrospective (Steegers et al., 2007) and five prospective (Choinière et al., 2014; King et al., 2008; Lahtinen et al., 2006; Lee et al., 2010; van Gulik et al., 2011)—have attempted to identify whether a significant relationship exists between unrelieved acute postoperative pain intensity and the development of CPSP following cardiac surgery (Appendix I: Studies Examining Acute Postoperative Pain Intensity as a Risk Factor for CPSP). The results across studies are mixed, likely due to heterogeneity of measurement approaches and lack of consensus in operationalizing the acute postoperative period with respect to study follow up duration.

Steegers et al. (2007) conducted a single-site retrospective study (N=256), to examine the relationship between chest pain and CPSP at 16 months following cardiac surgery in the Netherlands. At the time of assessment, 16 months after cardiac surgery, patients were asked to recall and self-report their chest pain intensity, categorized as '*slight'*, '*moderate'*, '*major'* and '*severe'*, in the periods before surgery, in the first week, and 12th weeks postoperatively. During the first postoperative week, 87% of patients with CPSP reported acute pain of at least '*moderate'* intensity, as compared to 68% of respondents without CPSP (Mann-Whitney U test, p<0.00002) after cardiac surgery (Steegers et al., 2007). A significant, positive correlation existed between the severity of acute postoperative wound pain and the severity of CPSP after CABG (Spearman r=0.40, p=<0.05) (Steegers et al., 2007).

While these data suggest a prognostic relationship between acute postoperative pain intensity and the transition to CPSP, they must be interpreted with caution. The retrospective nature of the study design, as well as the use of a mailed questionnaire for follow-up data collection (more than a year after cardiac surgery), presents an opportunity for recall bias. Participants may have had difficulty accurately recalling their pain intensity during the time of the acute postoperative period, as such this presents an opportunity for risk of bias in the prognostic factor measurement and outcome measurement domains (Appendix E: Risk of Bias Assessment for Included Studies). In addition, Steegers et al. (2007) used categorical-level measurement, with unknown reliability and validity, to categorize pain intensity experiences. The ranked categories do not permit adequate interpretation of the magnitude of differences demonstrated (Jensen et al., 1986). The use of categories results in a low degree of measurement precision; as well as the accuracy of the results can be challenged in the absence of established reliability estimates.

Fundamentally, greater confidence could be placed in the results of the prospective studies reported, which consistently employed well-established, reliable and valid tools to measure pain following cardiac surgery. However, there was notable heterogeneity in which reliable and valid outcome measures were used, making it difficult to summarize overall conclusions about the role of postoperative pain intensity in the transition to CPSP following cardiac surgery. For example, Lee et al. (2010) conducted a multi-site prospective study (*N*= 53) aimed at describing pain intensity and examining predictors of CPSP within the first 90 days following cardiac surgery in three Taiwanese healthcare facilities. Based upon a pain numerical rating scale (NRS), pain intensity was trichotomized into ‘no pain’ (NRS 0), ‘mild pain’ (NRS 1

to 4) or 'moderate to severe' pain (NRS 5 to 10) for both *'average'* and *'worst'* pain at baseline and seven, 10, 30 and 90 days postoperatively.

Via univariate logistic regression, Lee et al. (2010) found that moderate to severe pain (NRS 5 to 10) for *'worst'* and '*average'* pain intensity at postoperative days seven and 10, were not predictors of the presence or severity of CPSP at three months. That is, on postoperative day seven '*worst'* pain: OR 0.946, 95% CI [0.752, 1.190]; '*average'* pain: OR 1.159, 95% CI [0.815, 1.648]; and on postoperative day 10 '*worst'* pain: OR 0.911, 95% CI [0.724, 1.147]; '*average'* pain: OR 1.182, 95% CI [0.838, 1.669] (Lee et al., 2010). However, greater likelihood for transition to CPSP was associated with moderate to severe pain intensity for '*worst*' pain at 30 days postoperative (univariate logistic regression, OR 1.451, 95% CI [1.043, 2.019], $p<0.05$) (Lee et al., 2010).

These results must be interpreted with caution; a key limitation of the study was the relatively small sample size, which may not be representative of the population and sample size calculation was performed *a priori.* Given that just eight CPSP events were observed, the study likely was underpowered (McCrum-Gardner, 2010) and may be at risk for bias in study participation and statistical analysis and reporting domains (Appendix E: Risk of Bias Assessment for Included Studies).

Similarly, van Gulik et al. (2011) conducted a prospective study (N=120) of patients admitted to the Intensive Care Unit following cardiac surgery in the Netherlands. The study aimed to investigate the effect of predictive factors such as patient demographics, perioperative and postoperative factors on the incidence of CPSP up to one year after cardiac surgery. Postoperative pain intensity was measured via the NRS on the scale '0=no pain' to '10=maximum pain imaginable'. NRS scores ≥4 were classified as 'severe' pain. Pain was

assessed on the patient's self-report of their '*best*' and '*worst*' day. The '*best*' day was considered the day with the lowest pain score, while the '*worst*' day had the highest pain score. van Gulik et al. (2011) found that up to one year after surgery, 35% (*n*=42 of 120) patients reported CPSP. On the patients' self-report of their '*worst*' day, 29.2% (*n*=35 of 120) of patients had severe (NRS ≥4) pain intensity. NRS ≥4 on postoperative days one and two, did not emerge as significant predictors of CPSP following cardiac surgery (univariate analysis, unadjusted OR 1.06, 95% CI [0.47, 2.37], *p*=0.90; unadjusted OR 1.80, 95% CI [0.81, 4.00], *p*=0.15, respectively).

Multivariate logistic regression analysis identified four risk factors to be significant (adjusted) predictors for transition to CPSP (van Gulik et al., 2011). These risk factors include: a) non-elective surgery (adjusted OR 4.22, 95% CI [1.29, 13.84], *p*=0.02), b) re-sternotomy during admittance (adjusted OR 3.38, 95% CI [1.08, 10.54], *p*=0.04), c) severe pain (NRS ≥4) on postoperative day three (adjusted OR 2.89, 95% CI [1.15, 7.23], *p*=0.02), and d) female gender (adjusted OR 2.39, 95% CI [1.01, 5.65], *p*=0.05) (van Gulik et al., 2011).

Methodological limitations of this study included a small sample size and heterogeneity of the sample. van Gulik et al. (2011) did not provide a sample size justification, and included patients with previous sternotomy, non-elective cardiac surgery, and re-sternotomy during admittance; presenting a high risk for bias in the study participation and study confounding domains. A strength of the study is the exploration of these patient characteristics that are typically excluded in other studies. However, given the nociceptive, inflammatory and neuropathic nature of pain, it stands to reason that previous sternotomy and re-sternotomy during admission, may potentially confer further vulnerability to the development of CPSP, given peripheral and central sensitization occurring from repeated trauma.

King et al. (2008) conducted a follow-up sub-study embedded in a RCT, to examine incision and breast pain and discomfort, as well as their predictors in women one year after sternotomy in 10 Canadian Centers. Both the presence of pain and discomfort were assessed as dichotomous (i.e., yes/no) responses. King et al. (2008) found that 79.7% (*n*=47 of 59) of patients reported the presence of pain at 12 weeks following sternotomy.

Using logistic regression analysis, it was found that incision pain at 12 weeks was a significant predictor for the development of CPSP at one year (unadjusted OR 3.26, 95% CI [1.51, 7.07]) (King et al., 2008). Conversely, acute postoperative incisional pain measured at five days after cardiac surgery was not a significant predictor for transition to CPSP (unadjusted OR 1.82, 95% CI [0.92, 3.61]) (King et al., 2008). The major limitation of this study included the fact that standardized pain assessment tools were not utilized. Given that pain was only examined in a dichotomous fashion (i.e., yes/no), it is not feasible to make inferences on the impact of moderate to severe pain intensity as a predictive risk factor for the transition to CPSP after cardiac surgery; presenting a high risk for bias in the prognostic factor measurement domain (Appendix E: Risk of Bias Assessment for Included Studies).

Lahtinen et al.'s (2006) conducted a prospective single-site study (*N*=213) to evaluate the incidence and intensity of pain following cardiac surgery in Finland. Pain was measured via the 11-point NRS (0=no pain and 10=worst pain) at rest, during coughing, and on movement. Pain severity was classified as mild (NRS scores 1 to 3), moderate, (NRS scores 4 to 6) and severe (NRS scores 7 to 10). Pain outcome data were collected prior to surgery, on the fourth postoperative day, and one, three, six and 12 months after cardiac surgery. Lahtinen et al. (2006) found that, on average, patients reported moderate to severe (NRS ≥4) acute postoperative pain intensity at rest, during coughing, and on movement at one month postoperative. At one year

following cardiac surgery, one percent (*n*=1) reported moderate pain and two percent (*n*=2) reported severe pain intensity at rest, while three percent (*n*=5) reported moderate pain and four percent (*n*=7) reported severe pain intensity with movement (Lahtinen et al., 2006). Lahtinen et al. (2006) concluded that patients who had moderate to severe acute postoperative pain (NRS >3) were more likely to have any chronic post sternotomy pain at rest one year after cardiac surgery (Wilcoxon signed-rank test, *p*=0.042). Similar to previous prospective studies examined thus far, this study has the same methodological limitations of no *a priori* sample size calculations presenting risk for moderate bias in study participation (Appendix E: Risk of Bias Assessment for Included Studies).

The largest prospective study on risk factors for CPSP following cardiac surgery to date, by Choinière et al. (2014) (*N*=1247), employed the Brief Pain Inventory (BPI) which measures pain intensity on a NRS ranging from '0=no pain' to '10=worst pain imaginable'. Pain intensity was rated at two points: '*worst in the last 24 hours on movement*' and '*average in last 24 hours on movement*' (Choinière et al., 2014). Pain outcome data were assessed pre-operatively, as well as postoperative days one, two, three, and seven, and months three, six, 12 and 24 postoperatively. The study found that moderate to severe pain intensity (NRS≥4) for '*average* pain' and '*worst* pain' on postoperative day three predicted the presence of any CPSP up to two years following cardiac surgery, (GEE, adjusted OR 1.48, 95% CI [1.10, 2.00]; adjusted OR 1.69, 95% CI [1.16, 2.47]), respectively (Choinière et al., 2014). Moreover, '*average* pain' of moderate to severe intensity on the third postoperative day, also predicted the moderate to severe intensity of CPSP following cardiac surgery (GEE, adjusted OR 2.67, 95% CI [1.74, 4.11]) (Choinière et al., 2014).

In summary, the results of the available studies suggest that the severity of unrelieved acute postoperative pain may confer vulnerability for the development of CPSP following cardiac surgery (Choinière et al., 2014; Lee et al., 2010; Lahtinen et al., 2006; van Gulik et al., 2011). Across studies, there are methodological limitations (i.e., heterogeneity of measurement approaches and variability in outcome follow-up) which detract from the reliability of observed results (Appendix E: Risk of Bias Assessment for Included Studies). For example, one retrospective study measured pain as a categorical measure—'slight', 'moderate', 'major' and severe' (Steegers et al., 2007), one prospective study assessed pain dichotomously (i.e., yes/no) (King et al., 2008) and four prospective studies measured acute postoperative pain intensity using the NRS (Choinière et al., 2014; Lahtinen et al., 2006; Lee et al., 2010; van Gulik et al., 2011). While there is consistency across studies in terms of a positive relationship between acute postoperative pain intensity and CPSP, heterogeneity of approaches to measuring CPSP limits our ability to be conclusive about the nature of the strength of this relationship.

Across studies, there is variability with respect to time points for acute postoperative pain outcome measurement. For example, the presence and intensity of acute postoperative pain were measured on the third postoperative day (Choinière et al., 2014; Steegers et al., 2007; van Gulik et al., 2011), the fourth postoperative day (Lahtinen et al., 2006), the seven postoperative day (Steegers et al., 2007), 30 days (Lee et al., 2010), and 12 weeks postoperatively (King et al., 2008) and were found to be significant (adjusted and unadjusted) predictors for the transition to CPSP following cardiac surgery in some studies and not in others.

Opioid Dose Consumption

Three studies—one cross-sectional (Taillefer et al., 2006) and two prospective (Choinière et al., 2014; Lee et al., 2010)—have examined the relationship between opioid dose consumption

(converted to milligrams of morphine equivalents) and the development of CPSP following cardiac surgery, adding to the mixed evidence base of studies (Appendix J: Studies Examining Opioid Consumption as a Risk Factor for CPSP).

For example, via a chart audit of patients' medical-surgical hospital records, Taillefer et al.'s (2006) cross-sectional study (*N*=579), (previously described) extracted postoperative opioid medications administered in the intensive care unit and on the surgical ward. Opioid dosage was converted into parenteral morphine equivalents by standard dosing tables and summed over time (Taillefer et al., 2006). Via multivariate logistic regression, cumulative opioid dose, on the surgical ward during the first postoperative week, was found to be a significant predictor for the development of CPSP one year following cardiac surgery (adjusted OR 1.05, 95% CI [1.00, 1.10], *p*=0.032) (Taillefer et al., 2006). Specifically, for every five milligram increase in total parenteral morphine equivalent dose, patients were 1.05 times likely to develop CPSP up to three years following cardiac surgery.

Taillefer et al.'s study suggested that postoperative cumulative analgesic dose may be associated with CPSP following cardiac surgery. However, this inference must be stated with caution. Although the study reported a significant relationship between the total amount of opioids received on the surgical ward and the development of CPSP, the lower limit of the associated 95% confidence interval included the value of one, indicating the possibility of a null association between postoperative opioid dose consumed and CPSP after cardiac surgery in the real world (Szumilas, 2010).

Conversely, prospective studies examined to date have not found a significant association between opioid analgesics consumed—dose or cumulative—in the perioperative period with the transition to CPSP following cardiac surgery. For example, Lee et al.'s (2010) prospective study

(*N*=53) (previously described) utilized a chart review process to collect total opioid analgesics (converted to milligrams of morphine equivalents) used during and after cardiac surgery. Via univariate logistic regression, morphine equivalent opioid consumption on the 'day of surgery' and during the 'first postoperative week' were not significant predictors of CPSP at three months after cardiac surgery (unadjusted OR 1.022, 95% CI [0.275, 1.022], unadjusted OR 1.003, 95% CI [0.986, 1.021]), respectively (Lee et al., 2010). Similarly, Choinière et al.'s (2014) larger, multi-center, prospective CARD-PAIN study (*n*=975) (previously described), did not find a significant association between cumulative opioid dose (expressed as milligrams of parenteral morphine equivalents) administered during the first postoperative week following surgery and the presence of CPSP over time (multivariable GEE regression, adjusted OR 1.00, 95% CI [1.00, 1.00]).

In summary, the available evidence examined to date was mixed in relation to the association between postoperative opioid dose consumption and the transition to CPSP after cardiac surgery. Of the studies that suggest that postoperative opioid dose may play a role in the transition to CPSP, the strength of the association appears weak.

Summary of Modifiable Risk Factors Associated With CPSP

It is clear that the cumulative evidence to date, reviewed in this chapter, was equivocal, as to the role preoperative anxiety, preoperative depressive symptoms, acute postoperative pain intensity and opioid dose consumption play in the transition to CPSP after cardiac surgery. To determine whether these potentially modifiable risk factors, in the perioperative context, confer vulnerability for transition to CPSP after cardiac surgery, robust prospective study designs with representative samples are required to potentially corroborate the available evidence.

CHAPTER 3: METHODOLOGY

Methodology

Purpose

The purpose of this study was to explore the association between the following risk factors with CPSP at six months and 12 months after cardiac surgery: i) moderate to severe preoperative anxiety symptoms, ii) moderate to severe preoperative depressive symptoms, iii) moderate to severe acute postoperative pain intensity, and iv) cumulative opioid dose consumption.

Research Questions

1. What is the incidence of CPSP in the study sample at six months and 12 months after cardiac surgery?
2. In patients who undergo cardiac surgery, what is the association between severity of preoperative anxiety and the development of CPSP, adjusting for baseline demographic and clinical characteristics? Specifically, are patients with moderate to severe anxiety scores more likely to develop CPSP as compared to patients with mild anxiety scores?

2a. Among patients experiencing CPSP, what is the association between severity of baseline preoperative anxiety and the intensity of CPSP following cardiac surgery?

3. In patients who undergo cardiac surgery, what is the association between severity of preoperative depressive symptoms and the development of CPSP, adjusting for baseline demographic and clinical characteristics? Specifically, are patients with moderate to severe depressive symptom scores more likely to develop CPSP as compared to patients with mild depressive symptom scores?

3a. Among patients experiencing CPSP, what is the association between severity of baseline preoperative depressive symptoms and the intensity of CPSP following cardiac surgery?

4. In patients who undergo cardiac surgery, what is the association between acute postoperative pain intensity scores and the development of CPSP, adjusting for baseline demographic and clinical characteristics? Specifically, are patients with moderate to severe pain scores more likely to develop CPSP as compared to patients with mild pain scores?

4a. Among patients experiencing CPSP, what is the association between acute postoperative pain intensity and the intensity of CPSP following cardiac surgery?

5. In patients who undergo cardiac surgery, what is the association between cumulative opioid dose consumed in the first three postoperative days and the development of CPSP, adjusting for baseline demographic and clinical characteristics?

Research Method

Design

A prospective observational study design was used in which a cohort of patients who have undergone cardiac surgery were followed for 12 months after their cardiac surgery. The prospective design allowed for examination of the strength of the relationship between the selected variable risk factors and their influence on a specific outcome (Song & Chung, 2011). A prospective cohort is ideal for establishing the correct temporal relationship, wherein perioperative risk factors (i.e., preoperative anxiety, preoperative depressive symptoms, acute postoperative pain intensity and cumulative opioid dose consumption) are situated as antecedents to the development of CPSP after cardiac surgery (Song & Chung, 2011).

This doctoral study is embedded within the **F**urther **O**bservation for chronic pain and poor functional recovery **R**isk Factor **E**xamination at participating **SITE**s (FORESITE) prospective cohort study of 1,200 patients undergoing cardiac surgery, recruited from Hamilton Health Sciences (Canada), Kingston General (Canada), Ronald Reagan University of California, Los Angeles Medical Center (U.S.A.) and Prince of Wales Hospital (Hong Kong). Led by McGillion et al. and funded by the Canadian Institutes of Health Research, the objectives of FORESITE study are to examine the influence of cognitive factors, namely, pain-related beliefs and gender-based pain expectations, on the following outcomes up to one year following cardiac surgery: the development of CPSP, functional status, and patient-level cost of illness (McGillion et al., 2019). With a view to comprehensive examination of the impact of CPSP on patients, an additional aim of FORESITE is to determine the impact of CPSP on the quality of adjusted life years borne by cardiac surgery, as well as the incremental cost for one additional quality of adjusted life years gained for patients, by virtue of cardiac surgery, among those who develop CPSP compared to those who do not (McGillion et al., 2019) (see Appendix K: Summary of FORESITE Research Proposal for a detailed overview of the study).

This doctoral sub-study is distinct from FORESITE, in its purpose and variables of interest examined as potentially nurse modifiable risk factors for transition to CPSP after cardiac surgery. Firstly, the independent variables in this study—preoperative anxiety, preoperative depressive symptoms, acute postoperative pain intensity and postoperative opioid dose consumption—were examined as putative risk factors for CPSP after cardiac surgery in a subset of FORESITE patients. These independent variables were not addressed in the FORESITE study objectives, but were controlled for in the FORESITE study as model covariates. Secondly, the current study did not examine pain-related interference as an outcome, as pain-related

interference and functional status were outcome variables examined in FORESITE. Following this thesis and completion of the FORESITE study, results pertaining to pain-related interference in FORESITE will be taken into consideration for future intervention development, along with the results of this FORESITE sub-study. Therefore, the importance of pain-related interference as an outcome will not be overlooked in the overall FORESITE research program. Thirdly, in this study, postoperative opioid dose data was collected on postoperative days one, two and three in order to establish the relevance of cumulative opioid dose consumption as a risk factor. In contrast, FORESITE collected postoperative opioid dose data on postoperative day three only. Additionally, the statistical modeling strategy, the sample size calculation, and the analysis plan used in this study are also distinct from that conducted in the FORESITE study. Finally, as an embedded thesis, this study was executed at Hamilton Health Sciences, Ontario, Canada only—a sub-site of the FORESITE study. All methodological details are elaborated upon in the remainder of this chapter.

Study Setting. The study was conducted at Hamilton Health Sciences, Ontario, Canada. Hamilton Health Sciences consists of seven unique hospitals that serve more than 2.3 million residents in Hamilton and southwestern Ontario, Canada (Hamilton Health Sciences, 2019). As the second largest hospital group in Ontario, Hamilton Health Sciences serves as the regional referral center for cardiac, stroke, trauma, neurosurgery, burns, high-risk obstetrics, pediatrics, digestive diseases, orthopedics and rehabilitation services (Hamilton Health Sciences, 2019).

Study Population. The target population of 645 cardiac surgery patients were recruited from Hamilton Health Sciences, Ontario, Canada.

Sample Size. Sample size calculations were performed for each of the five primary questions. The analytic approach for all primary questions was the same, therefore the sample

size calculation could be generalized. To determine the association between preoperative anxiety score, depressive symptom score, pain intensity score or cumulative opioid dose and the development of CPSP while adjusting for baseline risk factors, methods used by Hsieh et al. (1998), where used for multivariable logistic regression. In this validated method, the sample size for a simple logistic regression modeling a single independent variable X1 on the outcome is inflated by a variance inflation factor equal to $1 / (1-\rho^2_{x2\ldots xp})$, where $\rho^2_{x2\ldots xp}$ is equal to the proportion of the variance of X_1 explained by the regression relationship with $X_2 \ldots X_p$. (Hsieh et al., 1998). A conservative scenario was assumed in which

a. The type 1 error (i.e., alpha) = 0.05
b. The proportion of the variance of the primary independent variable (anxiety, depressive symptoms, or pain intensity) explained by baseline covariates was as high as 0.5.
c. The prevalence of CPSP to be as low as 10% (as found in some previous studies).

Under this scenario, a change in the odds of as little as 5% (i.e., an OR = 1.05 or larger) in the association between the primary independent variable and the odds of CPSP development could be detected with 80% power (i.e., type II error of 0.20) with a sample size of 548 patients or more. Should the prevalence of CPSP be higher or the variance explained in the independent variables be smaller, 548 participants will provide > 80% power. To account for a potential of up to 15% loss-to-follow-up, the sample size was increased to 645 (548/85%).

Selection of Participants. ***Inclusion Criteria****:* Inpatients who: 1) are ≥18 years of age and 2) undergo first time cardiac surgery including coronary artery bypass grafting and open heart procedures such as valve repair. ***Exclusion Criteria****:* 1) patients with previous cardiac surgery, thoracotomy or mastectomy, 2) scheduled for an isolated pericardial window procedure

(due to malignancy), pericardectomy, permanent pacemaker, or defibrillator implantation, 3) have a major cognitive disorder precluding participation, or 4) have a hearing impairment or speech impairment precluding telephone-based follow up. Cognitive impairment included: a physician's diagnosis of Alzheimer, or dementia listed in the chart; reported confusion; postoperative delirium assessed by the Confusion Assessment Method delirium screening tool.

Procedure

Cardiac surgery inpatients were recruited from either the Hamilton Health Sciences preoperative assessment clinical, if their surgery was pre-booked, or from the cardiac surgical ward if they were admitted to hospital via the Emergency Department or the Heart Investigation Unit. In either case, the research office used a comprehensive monitoring system to ensure that all potentially eligible cardiac surgery patients were identified and approached.

At the beginning of each day, the research coordinator and the study nurse screened the preoperative assessment clinic, the operating room, the pre-operative hold area, and the cardiac surgery ward patient lists to identify all patients who meet the surgical criteria and who do not meet the surgical exclusion criteria (e.g., permanent pacemaker).

The pre-operative assessment clinic nursing staff—who were in communication with the research coordinator and the study nurse—asked potential participants, that the research coordinator and/or study nurse had identified and screened from the daily lists, if they were willing to speak to the study nurse about the study. If they agreed to hear about the study, the study nurse further screened for eligibility (Appendix L: Registration/ Eligibility), described the study to eligible patients, and obtained voluntary written consent to participate (Appendix M: Consent Form). All patients who consented to participate were electronically enrolled and registered by the study nurse, using the Population Health Research Institute's central

registration system, and obtained a system generated participant identification number (Appendix N: Interact Web Response System Registration). The study enrollment period concluded once the 12-month follow-up telephone interview was completed.

The recruitment and enrollment procedures were identical for patients who were not pre-assessed for cardiac surgery at the preoperative assessment clinic, except that patients were approached, initially by nursing staff on the cardiac surgery ward prior to surgery.

Following enrollment, the study nurse collected baseline data, demographic, independent variable data, and data on co-variates via interview and chart audit. Postoperatively, the study nurse collected data on surgical details via chart audit, and pain intensity scores via participant interview and the BPI. The study nurse contacted patients by phone at 30 days, six months and 12 months after surgery for postoperative pain monitoring and outcome assessment (see Appendix O: Study Visit Schedule, which details data collection and the study timeline).

To enhance the likelihood of completed follow-up, the study nurse at the time of consent, obtained participants address and telephone number, and phone numbers of three people at different addresses who were likely to know the patient's whereabouts (Appendix P: Patient Contact Information). The study nurse confirmed the patient's contact information prior to hospital discharge. To minimize attrition at follow-up, each participant was allowed up to six follow-up telephone calls.

Measurements and Instruments

Demographic Data

For descriptive purposes, standard demographic data collected include: i) participant's age (i.e., years); ii) sex (i.e., male, female, other); iii) ethnicity (i.e., Aboriginal/Indigenous, Asian, African American/Black, Caucasian, East Indian/Pakistani, Hispanic/Latin American, Middle Eastern, Other); iv) highest level of education (i.e., elementary school, high school,

college or technical school, university); v) employment status (i.e., full-time, part-time, retired, unemployed) (Appendix Q: Baseline Assessment).

Dependent Variable

The dependent variable was measured at six months and 12 months after cardiac surgery. The timing of the follow-up outcome measurement is in compliance with the 2013 recommendations set forth by the Initiative for Methods, Measurements and Pain assessment in Clinical Trials (IMMPACT) to standardize the timing of outcome assessment for prognostic studies (VanDenKerkhof, 2013). The primary outcome of CPSP was measured dichotomously (i.e., yes/no). Participants were asked to respond (i.e., yes or no) to three criteria-based questions to confirm the presence of CPSP: 1) have you had (or do you have) any pain in your body related to your cardiac surgery? 2) have you had (or do you have) any pain that is different from pain experienced prior to surgery? 3) have you had (or do you have) any pain that has been present for a while (not just a few days)? (Appendix R: Chronic Post-surgical Pain Assessment)

If pain was present, it was then measured via the Brief Pain Inventory-Short Form (BPI-SF) (Appendix S: Brief Pain Inventory). Cleeland (2009) claimed the BPI-SF was designed as a practical measurement tool for assessing pain severity and its impact on the patient's function in the clinical setting. The BPI was devised to capture two dimensions of pain: severity and interference–with activity and affect (emotion) (Cleeland, 2009). These two dimensions represent Melzack's sensory-affective-evaluative model of pain response (McDowell, 2006).

The BPI-SF is a 15-item tool that assesses the presence of pain today, the location of pain on the body, as well as which area hurts the most. The BPI-SF measures pain intensity on an 11-point numerical rating scale, where '0=no pain' and '10=pain as bad as you can imagine'. Pain intensity is measured via five items: '*worst pain in the last 24 hours with lying down*', '*worst*

pain in the last 24 hours with movement', '*least pain in last 24 hours*', '*average pain in the last 24 hours*' and pain '*right now*'. The BPI-SF captures self-reported treatments or medications received for pain, and the amount of relief obtained in the last 24 hours. The BPI-SF also assesses the impact of pain on seven daily activities (Cleeland, 2009; McDowell, 2006). Pain interference with 'general activity', 'mood', 'walking ability', 'normal work', 'relations with other people', 'sleep' and 'enjoyment of life' are rated on an 11-point Likert scale, where '0=does not interfere' and '10=completely interferes'. BPI-SF pain interference data were not examined as part of this sub-study.

Psychometric Properties. The English version of the BPI-SF has established internal consistency, coefficient alpha (α)=0.87 (McDowell, 2006). The test-retest reliability coefficients among pain intensity rating is from 0.59 to 0.93, and the coefficients among interference rating is from 0.44 to 0.95 (Cleeland, 2009; McDowell, 2006)

Independent Variables

Independent variables include state anxiety, depressive symptoms, acute postoperative pain intensity and opioid dose consumption. Anxiety and depressive symptoms were measured preoperative while acute pain intensity and opioid dose consumption was assessed postoperatively.

Anxiety. Anxiety was measured with the Spielberger State-Trait Anxiety Inventory (STAI) (Appendix T: Spielberger State-Trait Anxiety Inventory). The STAI was developed to assess two constructs: state anxiety and trait anxiety (McDowell, 2006; Spielberger, 1980). Spielberger (1979; 1980; 1983) claimed state anxiety is a transitory condition experienced in a specific condition, while trait anxiety refers to a general tendency to perceive situations as threatening. State anxiety was measured preoperatively using the State-Anxiety Inventory Scale

Form Y-1. The STAI Y-1 takes approximately 10 minutes to complete and was administered via paper and pencil format (Spielberger, 1983).

The STAI Form Y-1 consists of 20 self-evaluation statements that evaluate how respondents feel '*right now'* at this moment (Spielberger, 1980). Patients read and chose a number on the STAI Form Y-1, to the right of each item-statement, that best described the intensity of their feelings: (1) not at all; (2) somewhat; (3) moderately so; or (4) very much so (Spielberger, 1979; 1980; 1983). The instrument was scored by adding all the weighted responses for a total score (Spielberger, 1980). Possible scores range from minimum 20 to maximum 80, wherein, higher scores indicated higher levels of state anxiety. All raw scores were totaled and categorized as low state anxiety (score 20-39), moderate state anxiety (40-59) and severe state anxiety (60-80) (Spielberger, 1983). McDowell (2006) argue that if one to three questions were not answered, a score can be derived by calculating the mean score on items answered, multiplying by 20 and rounding up to the next whole number (Spielberger, 1983). If four or more questions are unanswered, the validity of the scale is challenged (Spielberger, 1983).

***Psychometric Properties*.** Reliability: Several studies have reported consistently high alpha consistency. For example, van Knippenberg et al. (1990) reported internal consistency coefficient of 0.93, for state anxiety measurement in surgical patients, Novy et al. (1993), reported coefficient range 0.93 to 0.95, for pain patients and Ramesh et al. (2017) reported coefficient of 0.82 for state anxiety and 0.86 for trait anxiety in cardiac surgery patients. Test-retest coefficient range from 0.69 to 0.89 (Spielberger, 1983). Validity: The STAI–state and trait aspects–are considered conceptually distinct, but related, as such they have been assessed for factorial validity and found coefficients ranged from 0.7 to 0.8; convergent coefficients were

reported between 0.75 to 0.83; and discriminant validity was compared between the STAI and the Beck Depression Inventory, and found coefficients were 0.71 for STAI state anxiety (McDowell, 2006). Koivula et al. (2001) reported reliability coefficients as 0.92 while waiting for surgery, 0.91 in hospital before surgery, and 0.91 at three months after cardiac surgery. The anticipation of cardiac surgery may induce emotional changes in patients during the preoperative period, as such the STAI Form Y-1 (with demonstrated validity and reliability) is an appropriate tool to measure state anxiety while patients are awaiting cardiac surgery (Fathi et al., 2014).

Depressive Symptom. Depressive symptom was measured with the Hospital Anxiety and Depression Scale (HADS) (Appendix U: Hospital Anxiety and Depression Scale). HADS is a self-evaluation questionnaire that consists of two measures of psychological morbidity: Anxiety and Depressive Symptoms (Zigmond & Snaith, 1983). The HADS tool takes approximately five minutes to complete and was administered by paper and pencil format (Zigmond & Snaith, 1983).

For this study, the seven-item depressive symptom scale, inquiring about respondents' feelings of enjoyment or disposition was used. The HADS measured depressive symptoms with five positively stated questions: 1) I still enjoy the things I used to do enjoy, 2) I can laugh and see the funny side of things, 3) I feel cheerful, 4) I look forward with enjoyment to things, and 5) I can enjoy a good book or radio or TV program (Zigmond & Snaith, 1983). These questions were scored according to the responses selected: (0) "often"/ "definitely as much", (2) "sometimes"/ "not as much", (2) "not often"/ "only a little" (3) "very seldom"/ "hardly at all" (Zigmond & Snaith, 1983). There are two negatively stated questions: 1) I feel as if I have slowed down, and 2) I have lost interest in my appearance (Zigmond & Snaith, 1983). These questions were scored: (3) nearly all the time/ definitely, (2) very often / not as much as I should,

(1) sometimes/ not quite as much as I should, and (0) not at all (Zigmond & Snaith, 1983). The response scores were summed and categorized as either normal (score zero to seven), mild (eight to 10), moderate (11-14) and severe (15 to 21) for depressive symptoms (Zigmond & Snaith, 1983; Carmines & Zeller, 1979). Scores greater than 10 were considered 'abnormal' (Carmines & Zeller, 1979).

Psychometric Properties. Validity: in a comprehensive review (Bjelland et al., 2002) deemed the concurrent validity of the HADS as 'good' to 'very good', with sensitivity of 0.66 and specificity of 0.97 in primary care populations. Reliability: internal consistency is high with Cronbach's (α) ranging from 0.84 to 0.90 in community, psychiatric and medical patients (Julian, 2011). The HADS is an appropriate tool to use to measure depressive symptoms in patients awaiting cardiac surgery as it was designed for use in the hospital setting, it separates anxiety from depression symptoms, is not confounded by physical illness, and has demonstrated validity and reliability (Zigmond & Snaith, 1983).

Acute Postoperative Pain Intensity. Pain intensity was measured on postoperative days three and 30, via the BPI-SF, previously described above. The BPI-SF is a 15-item tool that, measures pain on an 11-point numerical rating, Likert-scale, where '0=no pain' and '10=Pain as bad as you can imagine'. Pain was measured via five items: '*worst in the last 24 hours while lying*', '*worst in the last 24 hours with movement*', '*least in last 24 hours*', '*average pain in last 24 hours*' and pain '*right now*' (Appendix S: Brief Pain Inventory).

Opioid Dose Consumption. Via an adapted chart-audit tool, used in previous cardiac surgery population (Choinière et al., 2014; Watt-Watson et al., 2004), participant's medical charts were reviewed and audited for opioid medications consumed up to three days postoperatively (see Appendix V: Analgesic Chart Audit Tool). For the purposes of

documentation, medications containing opioids were separated into their opioid and non-opioid components. For example, a Tylenol one tablet was separated into Acetaminophen 300mg non-opioid component and a Codeine 15mg opioid component per tablet. All opioids consumed for the first three postoperative days were recorded, unless the nurse indicated a reason for non-administration (e.g., emesis). Using a previously developed standard dose opioid equivalence table, opioids consumed as either milligram per day or micrograms per hour, were converted into milligrams of parenteral morphine equivalents dose by multiplying by the opioid equivalence table conversion factor.

Data Analyses

Categorical data: sex, ethnicity, highest level of formal education, employment status, diabetes mellitus, peripheral artery disease, preoperative chronic pain, New York Heart Associate Functional Classification, Canadian Cardiovascular Society Angina Grading, and presence of preoperative pain are summarized with frequencies and proportions for descriptive demographic data. Continuous data: age and body mass index are summarized using measures of central tendency and dispersion for descriptive demographics. Pain intensity scores are summarized using measures of central tendency and dispersion.

Univariable logistic regression was used to model each covariate and independent variable with the presence of CPSP at both six months and 12 months after cardiac surgery. Multivariable logistic regression was used to model the primary outcome with the presence of CPSP at six months and 12 months, while adjusting for pre-specified model covariates which may contribute to confounding (e.g., age, sex). Model diagnostics performed consisted of influential observation examination and Hosmer-Lemeshow tests for goodness-of-fit. Variance inflation factors were also assessed to determine multi-collinearity in the model.

When important relationships were identified, a secondary univariable linear regression model was constructed to examine the effect of the independent variable on the severity of CPSP as measured by the NRS (0-10 scale). A secondary multivariable linear regression was also constructed to model the independent variables with the severity of CPSP at six months and 12 months, while adjusting for pre-specified model covariates, which may contribute to confounding (e.g., age, sex).

Model diagnostics performed included, examination of potential influential observations, and tests of normality and heteroscedasticity of residuals. The Hosmer-Lemeshow test was completed to assess goodness of fit, specifically how well the data best fit the 'line of fit' in the proposed risk prediction model (Hosmer et al., 1988; Hosmer et al., 2013). The Hosmer-Lemeshow test calculates if the observed event rates match the expected event rates in proposed population subgroups (Hosmer et al., 2013). According to Hosmer et al. (2013), a *p*-value less than 0.05 indicates the model is not a good fit, while a larger *p*-value indicates there is not enough evidence to indicate the model is not a good fit.

The C-Statistic or measure of concordance, measures the goodness of fit for the binary outcomes in a logistic regression model (Austin & Steyerberg, 2012; Pencina & D'Agostino, 2015). The C-Statistic provides the probability at random, that a patient who experienced the event had a higher risk score than a patient who did not experience the event (Harrell, 2015; Pencina & D'Agostino, 2015). A value below 0.5 indicates a poor model, a value of 0.5 means random concordance–that the model is no better than predicting an outcome than by random chance, a value over 0.7 indicates a good model, a value over 0.8 indicate a strong model, and a value of one indicates that the model perfectly predicts the group members who will experience the outcome event and those who will not (Pencina & D'Agostino, 2015).

Additionally, the variance inflation factor (VIF) was examined to assess for multicollinearity between the independent variables. “The VIF indicates whether a predictor has a strong linear relationship with the other predictors” (Field, 2012, p. 325). According to Craney and Surles (2002), an acceptable VIF cut off value is between five and 10. A VIF of ‘10 implies that 90% of the variability in the *i*th independent variable is explained by the remainder of the independent variables in the model” (Craney & Surles, 2002, p. 393). Similarly, “VIF five implies that 80% of the variability in the *i*th independent variable is explained by the remainder of the independent variables in the model” (Craney & Surles, 2002, p. 393). Additionally, Fields (2012) states, “if the largest VIF is greater than 10, then there is cause for concern, if the average VIF is substantially greater than one, then the regression may be biased” (p. 325). Reciprocal to the VIF is the tolerance statistic: 1/VIF (Fields, 2012). According to Fields (2012), a “tolerance [value] below 0.2 indicate a potential problem” (p. 325).

Model diagnostics are reported and interpreted with their goodness of fit to determine how well the independent variable predicts which patients would develop the outcome of CPSP after cardiac surgery in the logistic regression models.

Ethical Consideration

As a sub-study of FORESITE, this study was approved by the Hamilton Integrated Research Ethics Board (Appendix W: Hamilton Integrated Research Ethics Board Project# 12-696). As the doctoral student who conducted this work, I have completed the Hamilton Integrated Research Ethics Board tutorial for researchers conducting retrospective review of health records (certificate number 351677) (Appendix X: Hamilton Integrated Research Ethics Certificate). I have also completed certification in the Good Clinical Practice CITI program, and the Tri-Council Policy Statement: Ethical conduct of research involving humans (2014).

CHAPTER 4: RESULTS

Results

The purpose of this sub-study was to explore the association between the following risk factors with the development of CPSP at six months and 12 months after cardiac surgery: i) moderate to severe preoperative anxiety symptoms, ii) moderate to severe preoperative depressive symptoms, iii) moderate to severe acute postoperative pain intensity, and iv) cumulative opioid dose consumption.

This chapter presents the study results in three sections. Section one: derivation of the study sample, and sample characteristics at baseline and attrition, as well as sample characteristics and known predictors for CPSP. Section two: results of the research questions pertaining to incidence, the association between anxiety symptoms, depressive symptoms, acute postoperative pain intensity and opioid dose consumption and the development of CPSP at six months and 12 months after cardiac surgery. Section three: multivariable logistic regression model containing significantly associated independent variables with the presence of CPSP following cardiac surgery at six months and 12 months, respectively.

Section One: Sample Characteristics

Derivation of the Study Sample

Selection of participants was based on the inclusion criteria: inpatients who: 1) ≥18 years of age and 2) undergo first time cardiac surgery including coronary artery bypass grafting and open heart procedures such as valve repair. Within FORESITE study, a total of *n*=1,138 participants met the inclusion criteria, were enrolled and written consent obtained over a five-year study period.

Following enrollment, baseline data, demographic and descriptive data were collected via telephone interview and chart audit. Potential participants were excluded if they met the

exclusion criteria: patient with previous cardiac surgery (*n*=2), thoracotomy or mastectomy (*n*=0), sternotomy (*n*=34, previous coronary artery bypass graft (*n*=2), previous cardiac transplant (*n*=1), previous valve surgery (*n*=3), scheduled for isolated pericardial window procedure (*n*=0), pericardectomy (*n*=0), permanent pacemaker or defibrillator implantation (*n*=0), have a major cognitive disorder precluding participation, or have a hearing impairment or speech impairment (*n*=0) precluding telephone based follow-up. Following cardiac surgery, patients who had a minimally invasive surgical approach (*n*=4) were excluded from analysis. A total of 46 patients were excluded based on these exclusion criteria.

The research questions were based on the existence of preoperative anxiety and depressive symptoms. Patients who did not complete the baseline Spielberger State Trait Anxiety Inventory (STAI) Form Y-1 (*n*=24) and the Hospital Anxiety Depression Scale (HADS) (*n*=315) were excluded from analysis. The depressive symptom assessment was approved by the Hamilton Integrated Research Ethics Board on December 15, 2014, to be added to the FORESITE baseline assessment. The amendment was made one year after the initial study Research Ethics Board approval, December 3, 2013. The majority of patients excluded based on missing HADS assessment were enrolled prior to the study amendment date, and baseline FORESITE data collection preceded this doctoral thesis. A total of *n*=753 patients, met the inclusion criteria and baseline requirement for analysis.

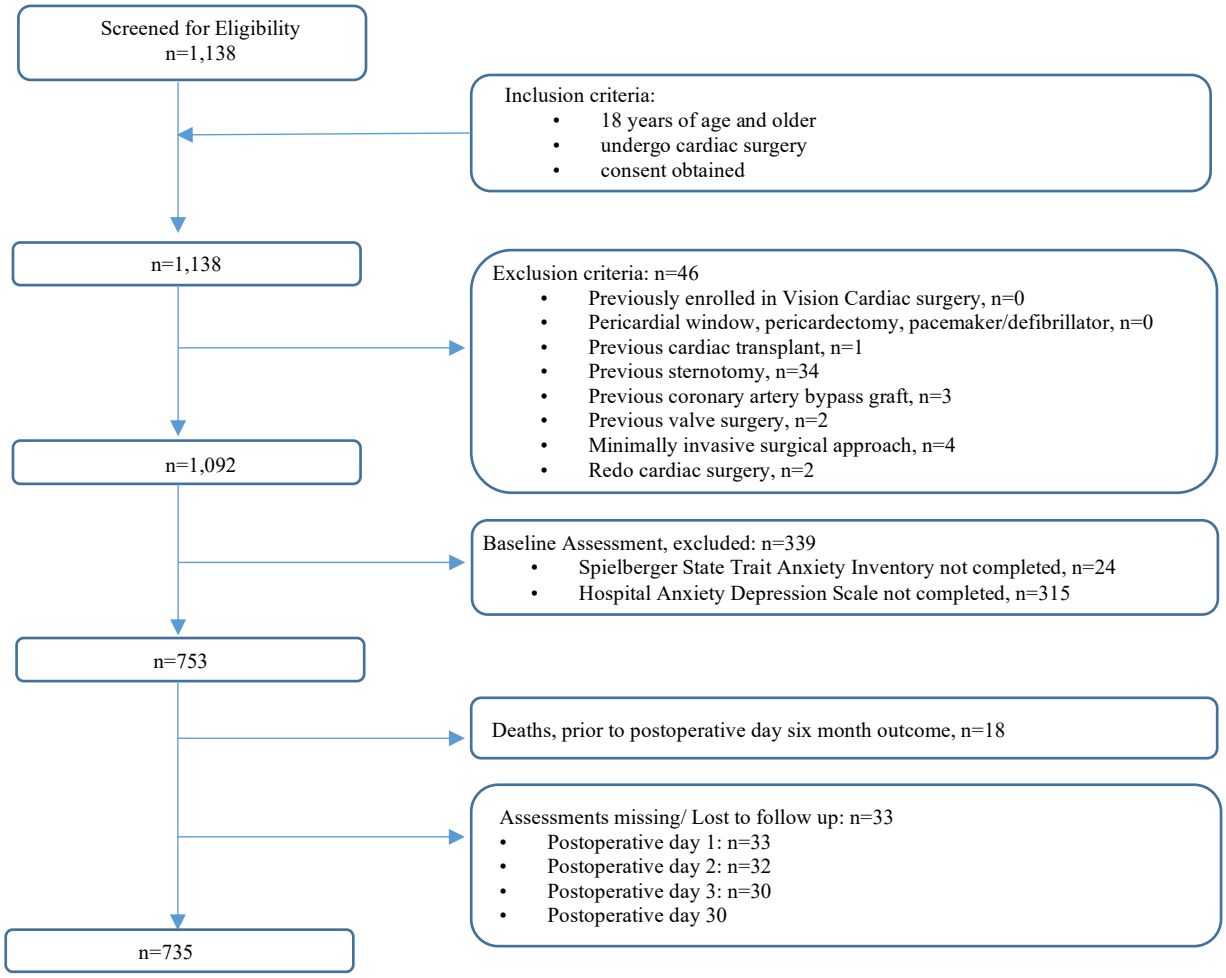
A total of 18 patient deaths were reported between the intraoperative period and up to 40 days postoperatively. Primary cause of death was not reported for this sub-study as it was not included on FORESITE study data collection forms. Baseline characteristics of these deceased patients include: Caucasian, mean age 69.37 years, 50% (*n*=9) males, 78% (*n*=14) grade school education, 44% (*n*=8) Class III on the New York Heart Association Functional Classification

(NYHAFC) of heart failure and 50% (*n*=9) had a Class III by the Canadian Cardiovascular Society Angina (CCSA) grading score, suggesting marked physical limitations. These 18 patients were excluded from analysis as outcome data was not collected at six months or 12 months after cardiac surgery.

All available patient data were analyzed if baseline data and at least one CPSP outcome assessment was completed at six months or 12 months. Thirty-three patients were unable to be reached by telephone and were lost to follow-up. The baseline and outcome data at postoperative days one, two, three, 30, six months and 12 months were pulled for *n*=735 patients from the FORESITE study and included for analysis in this doctoral study (see Figure 2: Flow Diagram of Included Participants).

Figure 2

Flow Diagram of Included Participants



Sample Characteristics at Baseline and Attrition

IBM® SPSS Statistics Version 26 was used to analyze sample characteristics at baseline and study attrition at each data collection time point for postoperative days one, two, three, 30, and six and 12 months. Study participants were primarily males (*n*=537, 73%), Caucasian ethnicity (*n*=530, 72.3%), with a mean (± SD) age 66.99 years (± 10.27). The majority had retired prior to their cardiac surgery (*n*=431, 59%) and had high school-level education (*n*=352, 48.7%) (see Table 1: Sample Demographics).

Table 1

Sample Demographics

Sample demographics	Number (%) of patients or Mean ± SD
Sex	Males: n=537 (73%) Females: n=198 (27%)
Ethnicity	Caucasian: n=530 (72.3%) Hispanic/Latino: n=186 (25.3%) Asian: n=6 (0.8%) Aboriginal: n=7 (1%) African Descent: n=3 (0.4%) Middle Eastern: n=1 (0.1%) Pacific Islander: n=1 (0.1%)
Education	Grade school: n=55 (7.6%) High school: n= 352 (48.7%) College: n=155 (21.4%) University: n=135 (18.7%) Post Graduate: n= 26 (n=3.6%)
Employment	Retired: n=431 (59%) Employed: n=226 (31%) Unemployed: n=67 (9%) Disability: n=11 (1%)
Age (year)	Mean 66.99 ± 10.27 Minimum age: 24, Maximum age: 90 Males 66.67 (± 9.99), Females 67.85 (± 10.99)
Height (cm)	Mean 171.21 ± 9.55 Minimum height: 137, Maximum height: 199
Weight (kg)	Mean 88.39 ± 19.15 Minimum weight: 44, Maximum weight: 170
Body mass index	30.2 ± 2.7

Note: Mean and SD values rounded to nearest tenth

Legend: CM: Centimeter; KG: Kilogram; SD: Standard Deviation; %: Percentage

Sample Characteristics and Known Predictors for CPSP

At baseline, participants reported a history of: hypertension (*n*=573, 78%), myocardial infarction (*n*=296, 40%), tobacco usage (*n*=480, 65%), diabetes mellitus (*n*=255, 35%), atrial fibrillation (*n*=104, 15%), congestive heart failure (*n*=110, 15%), obstructive sleep apnea (*n*=100, 15%), chronic obstructive pulmonary disease (*n*=83, 11%), mobility limited by calf pain (*n*=51, 7%), and peripheral vascular disease (*n*=46, 6%) (Appendix Y: Preoperative and Operative Sample Characteristics). Body mass index (BMI) was calculated based on the mean height (cm) and mean weight (kg) of the sample. A BMI <18.5 is underweight, a BMI between 18.5 and 24.9 is normal weight, a BMI between 25 and 29.9 is overweight, and a BMI ≥30 is obese (Health Canada, 2003; WHO, 2000). The calculated sample mean (± SD) BMI was 30.2 (± 2.7), reflective of obesity (see Table 1: Sample Demographics).

In terms of limitations during ordinary physical activity, patients with cardiac disease may experience symptoms of angina and heart failure (e.g., undue fatigue, dyspnea, palpitations, chest pain) with ordinary physical activity such as walking, stair climbing and personal grooming (Campeau, 1976; New York Heart Association, 1994). According to the New York Heart Association Functional Classification of heart failure (NYHAFC) approximately 39% (*n*=276) of participants were classified Class III, with marked limitation in physical activity due experiencing symptoms and 33% (*n*=230) were Class II with mild limitation in their physical activity due to symptoms (New York Heart Association, 1994). According to the Canadian Cardiovascular Society Angina (CCSA) classification, 41% (*n*=283) of participants were classified as Class II, where there is a slight limitation in physical activity with symptoms of angina experienced during ordinary physical activity (e.g., walking or climbing one flight of stairs at a normal pace under normal conditions) (Campeau, 1976).

At baseline, the mean (± SD) anxiety score was 43.97 (± 5.059); with approximately 14% (*n*=102 of 735) reporting mild anxiety scores, 85% (*n*=629 of 735) reporting moderate anxiety scores, and 1% (*n*=4 of 735) reporting severe situational anxiety scores via the Spielberger STAI Form Y-1.

At baseline, the mean (± SD) depressive symptoms score was 8.08 (± 1.583); with approximately 29% (*n*=214 of 735) reporting normal depressive symptoms scores, 66% (*n*=483 of 735) reporting mild scores, 4% (*n*=34 of 735) reported moderate scores, and 1% (*n*=4 of 735) reporting severe depressive symptom scores via the HADS.

Twenty-five percent (*n*=183) of patients reported having pain in any part of the body, prior to surgery. Of these, 1.6% (*n*=3 of 183) reported cancer related pain. One patient reported having metastatic cancer. The majority of participants (*n*=568, 77%) reported zero pain intensity/ 'no pain' prior to surgery, with the remainder of participants reporting mild to severe pain intensity (*n*=163, 23%) prior to cardiac surgery. Baseline pain intensity prior to cardiac surgery was mean (± SD) 0.91 (± 2.042) rating on the NRS scale. A complete summary of baseline detail is included in Appendix Y: Preoperative and Operative Sample Characteristics.

In terms of operative details, approximately 65% (*n*=480) of patients had elective cardiac surgery. Approximately 82% (*n*=606) had a coronary artery bypass graft and 34.9% (*n*=257) had any valve surgery, majority of patients had severe aortic valve stenosis prior to surgery (*n*=152, 28.5%). The average (± SD) duration of surgery was 3.35 hours (± 0.43), with 82.81 minutes (± 33.047) on cardiopulmonary bypass. A complete summary of intraoperative detail is included in Appendix Y: Preoperative and Operative Sample Characteristics.

Section Two: Results of Research Questions

Question 1: Incidence

What is the incidence of CPSP in the study sample at six months and 12 months after cardiac surgery?

The primary outcome, CPSP, was measured dichotomously (i.e., yes/no). Participants were asked to respond (i.e., yes or no) to three criteria-based questions to confirm the presence of CPSP: 1) have you had (or do you have) any pain in your body related to your cardiac surgery? 2) have you had (or do you have) any pain that is different from pain experienced prior to surgery? 3) have you had (or do you have) any pain that has been present for a while (not just a few days)? (Appendix R: Chronic Post-Surgical Pain Assessment). At six months, 8.7% of patients (*n*=54 of 618; 20 females and 34 males) and at 12 months, 4.1% of patients (*n*=25 of 610; 11 females and 14 males) met the criteria for the presence of CPSP after cardiac surgery. A total of nine patients (seven females and two males), reported CPSP both at six months and 12 months after cardiac surgery.

If CPSP was reported, pain intensity was then measured via the Brief Pain Inventory-Short Form (BPI-SF), on an 11-point numerical rating scale (NRS), where '0=no pain' and '10=pain as bad as you can imagine'. Pain intensity was captured through five items: '*worst in the last 24 hours while lying down*', '*worst in the last 24 hours while moving*', '*least in last 24 hours*', '*average pain in the last 24 hours*' and pain '*right now*'. Within the sample, overall mean (± SD) pain intensity for pain '*right now*' on the NRS was 2.76 (± 3.04) at six months and 1.58 (± 2.01) at 12 months, indicating overall mild pain intensity. Patients who reported '*worst pain in last 24 hours while moving*' had a higher mean (± SD) pain intensity at both six months (4.05 ± 2.98) and 12 months (2.68 ± 2.54), compared to other items measured by the BPI-SF (see Table 2: Mean Postoperative Pain Intensity over Time).

Table 2

Mean Postoperative Pain Intensity over Time

Brief Pain Inventory	**POD 3 Mean (± SD)**	**POD 30 Mean (± SD)**	**6 Months Mean (± SD)**	**12 Months Mean (± SD)**
Worst pain in last 24 hours while lying	4.27 (± 2.92)	2.35 (± 2.67)	3.15 (± 3.18)	2.18 (± 2.35)
Worst pain in last 24 hours while moving	4.76 (± 2.82)	2.87 (± 2.83)	4.05 (± 2.98)	2.68 (± 2.54)
Least pain in last 24 hours	1.39 (± 1.81)	0.70 (± 1.42)	1.27 (± 2.19)	1.11 (± 1.487)
Average pain in last 24 hours	2.98 (± 2.13)	1.43 (± 1.98)	2.76 (± 2.88)	2.16 (± 2.04)
Pain right now	2.24 (± 2.43)	1.13 (± 1.92)	2.76 (± 3.04)	1.58 (± 2.01)

Legend: POD: Postoperative Day; SD: Standard Deviation

Within the sample, 2.6% (*n*=16 of 618) of patients reported CPSP of moderate to severe intensity (i.e., pain score NRS ≥4 of 10) for pain '*right now*' at six months and 0.7% (*n*=4 of 610) reported moderate to severe intensity at 12 months after cardiac surgery.

Specifically, among patients with CPSP at six months (*n*=54) and 12 months (*n*=25), rated NRS ≥4 of 10, CPSP was reported at a moderate intensity across all five items measured by the BPI-SF (see Table 3: Mean Postoperative Pain Intensity for Patients with Moderate to Severe CPSP).

Table 3

Mean Postoperative Pain Intensity for Patients with Moderate to Severe CPSP

Brief Pain Inventory	**6 Months (Mean ± SD) (*n*=54)**	**12 Months (Mean ± SD) (*n*=25)**
Worst pain in last 24 hours while lying	6.46 (± 2.332) (*n*=13, 24%)	5.75 (± 0.957) (*n*=4, 16%)
Worst pain in last 24 hours while moving	6.45 (± 2.041) (*n*=22, 40.7%)	6.00 (± 0.894) (*n*=6, 24%)
Least pain in last 24 hours	5.83 (± 2.229) (*n*=6, 11%)	5.0 (± 0) (*n*=1, 4%)
Average pain in the last 24 hours	6.33 (± 1.589) (*n*=15, 27.8%)	5.00 (± 0.707) (*n*=5, 20%)
Pain right now	6.38 (± 1.746) (*n*=16, 29.7%)	5.00 (± 0.816) (*n*=4, 16%)

Note: Moderate to severe pain intensity assessed as NRS ≥ 4 of 10

Legend: CPSP: Chronic Post-Surgical Pain; NRS: Numerical Rating Scale; SD: Standard Deviation

Covariates. Univariate logistic regression analyses were completed for baseline demographics (i.e., sex, age) and clinical characteristics (i.e., diabetes mellitus prior to cardiac surgery, duration of surgery [length of surgery time measured in hours] and baseline pain intensity) to establish their association with the development of CPSP at six months and 12 months after cardiac surgery. Following unadjusted univariate analysis, younger age (measured in year at time of surgery) (unadjusted OR 0.967, 95% CI [0.943, 0.992], p=0.009), and diabetes mellitus (unadjusted OR 1.834, 95% CI [1.044, 3.222], p=0.035) were statistically significant for an association with CPSP at six months. At 12 months after surgery, sex (unadjusted OR 0.420, 95% CI [0.187, 0.947], p=0.036) and younger age (unadjusted OR 0.936, 95% CI [0.943, 0.992], p=<0.01) were statistically significant for an association with the development of CPSP (see Table 4: Unadjusted Analysis of Covariates and CPSP at Six Months and 12 Months). Duration

of surgery and baseline pain intensity were not statistically significant for an associated with CPSP at six months or 12 months after cardiac surgery.

Overall, the odds of patients with a history of diabetes prior to cardiac surgery experiencing CPSP at six months were 1.834 times greater than those that did not have a history of diabetes. The odds of males experiencing CPSP was lower than females developing CPSP at 12 months after cardiac surgery. Specifically, the odds of females experiencing CPSP was 2.379 times greater than males at 12 months after cardiac surgery. For each year increase in patients' age at baseline, the odds of developing CPSP at six and 12 months decreased.

In the multivariable logistic regression models for each independent variable (i.e., anxiety, depressive symptom, acute postoperative pain and opioid dose) that follow, models will be adjusted for sex, age and diabetes mellitus at six months, and adjusted for sex and age at 12 months after cardiac surgery.

Table 4

Unadjusted Analysis of Covariates and CPSP at Six Months and 12 Months

	Covariates				
	Sex	Age	DM	Duration of Surgery	Baseline Pain Intensity
CPSP 6 Months					
Wald 1df	3.600	6.795	4.453	0.567	2.707
p-value	0.058	0.009*	0.035*	0.451	0.100
OR	0.568	0.967	1.834	1.000	1.855
95% CI	0.317, 1.019	0.943, 0.992	1.044, 3.222	1.000, 1.000	0.889, 3.875
Nagelkerke R^2	0.012	0.023	0.016	0.400	0.009
Hosmer-Lemeshow *p*-value	<0.001	0.625	<0.001	0.002	<0.001
C-Statistic	0.560	0.613	0.572	0.521	0.538
CPSP 12 Months					
Wald 1*df*	4.379	14.36	0.003	0.20	1.75
p-value	0.036*	<0.001*	0.955	0.654	0.185
OR	0.420	0.936	0.976	1.000	1.985
95% CI	0.187, 0.947	0.904, 0.969	0.414, 2.301	1.000, 1.000	0.720, 5.467
Nagelkerke R^2	0.042	0.077	<0.001	0.001	0.009
Hosmer-Lemeshow *p*-value	<0.001	0.299	<0.001	0.893	<0.001
C-Statistic	0.596	0.720	0.503	0.534	0.544

Note: *significant at alpha=0.05, reference groups: female sex, no DM, no/mild baseline pain intensity. Age assessed in years. Duration of surgery assessed in hours. At 6 months female unadjusted OR 1.761, 95% CI [0.892, 3.158], p=0.058. At 12 months female unadjusted OR 2.379, 95% CI [1.056, 5.357], p=0.036.

Legend: CI: Confidence Interval; CPSP: Chronic Post-Surgical Pain; *df*: Degree of Freedom; DM: Diabetes Mellitus; OR: Odds Ratio

The Hosmer-Lemeshow test was completed to assess goodness of fit, specifically how well the data best fit the 'line of fit' in the proposed risk prediction model (Hosmer et al., 1988; Hosmer et al., 2013). A p-value less than 0.05 indicates the model is not a good fit, while a larger p-value indicates there is not enough evidence to indicate the model is not a good fit (Hosmer et al., 2013). At both six and 12 months, the Hosmer-Lemeshow p-values for age were greater than 0.05, indicating the data are a good fit in the prediction model. However, at six months and 12 months, both Hosmer-Lemeshow p-values for covariates sex and diabetes were less than 0.05, indicating that the data may not be a good fit in the respective univariate prediction models.

The C-Statistic or measure of concordance, measures the goodness of fit for the binary outcomes in a logistic regression model (Austin & Steyerberg, 2012; Pencina & D'Agostino, 2015). The C-Statistic provides the probability at random, that a patient who experienced the event had a higher risk score than a patient who did not experience the event (Harrell, 2015; Pencina & D'Agostino, 2015). A value below 0.5 indicates a poor model, a value of 0.5 means random concordance–that the model is no better than predicting an outcome than by random chance, a value over 0.7 indicates a good model, a value over 0.8 indicate a strong model, and a value of one indicates that the model perfectly predicts the group members who will experience

the outcome event and those who will not (Pencina & D'Agostino, 2015). At both six and 12 months C-Statistics were greater than 0.5, indicating that the model for unadjusted analysis of covariates and CPSP was an acceptable model for predicting which patients would have the outcome of CPSP after cardiac surgery (see Table 4: Unadjusted Analysis of Covariates and CPSP at Six Months and 12 Months).

Secondary Analysis

In an attempt to identify and target specific age groups who may be at increased odds for CPSP and to corroborate the findings of existing studies, a secondary analysis was conducted to categorize age into two groups (i.e., ≤ 65 years and ≥ 66 years). In the sample, following univariate unadjusted analysis, there was a significant association observed in patients under 65 years of age, as compared to patients over 66 years of age developing CPSP at six months and 12 months. Specifically, the odds of patients' ≤ 65 years experiencing CPSP were 2.037 times and 3.422 times greater than patients' ≥ 66 years of age at six months and 12 months respectively. Further, age groups were not examined as the number of events of CPSP were small (i.e., *n*=54 at 6 months and *n*=25 at 12 months); this may have inadequate statistical power to detect a relationship between additional age groups and the presence of CPSP, if a relationship existed.

Across age groups, mean pain scores rated as pain '*right now*' at both six months and 12 months indicate mild pain severity after cardiac surgery (see Table 5: Unadjusted Analysis of Covariate Age Group and CPSP at Six Months and 12 Months).

Table 5

Unadjusted Analysis of Covariate Age Group and CPSP at Six Months and 12 Months

	Covariate Age Group	
	≤ 65	**≥ 66**
Sample n	289	446
6 Months		
Wald 1 *df*	6.229	-
p-value	0.013*	-
OR	2.037	-
95% CI	(1.165, 3.561)	-
CPSP ***n***	30	24
Pain right now	2.92 (± 3.346)	2.69 (± 2.798)
12 Months		
Wald 1 *df*	7.974	-
p-value	0.005	-
OR	3.422	-
95% CI	(1.457, 8.037)	
CPSP *n*	17	8
Pain right now	2.27 (± 2.328)	1.00 (± 1.155)

Note: *significant at alpha=0.05; Age group ≥66 years is comparison group; NRS mean (± SD).

Legend: CI: Confidence Interval; CPSP: Chronic Post-Surgical Pain; *df*: Degree of Freedom; n: number in the sample; NRS: Numerical Rating Scale; OR: Odds Ratio; SD: Standard Deviation.

Question 2: Preoperative Anxiety

Question 2a: In patients who undergo cardiac surgery, what is the association between severity of preoperative anxiety symptoms and the development of CPSP, adjusting for baseline demographic and clinical characteristics? Specifically, are patients with moderate to severe anxiety scores more likely to develop CPSP as compared to those with mild anxiety scores?

Question 2b: Among patients experiencing CPSP, what is the association between severity of baseline preoperative anxiety and the intensity of CPSP after cardiac surgery?

Preoperative state anxiety was assessed via the Spielberger STAI Form Y-1 via 20 questions. The responses were scored, weighted and summed for a total state anxiety score. Total

scores then categorized as mild anxiety (scores 20 to 39), moderate anxiety (scores 40 to 59) and severe anxiety (scores 60 to 80) (Spielberger, 1980). The sample had a mean (± SD) anxiety score of 43.97 (± 5.059); approximately 14% (*n*=102 of 735) reported mild anxiety scores, 85% (*n*=629 of 735) reported moderate anxiety scores, and 1% (*n*=4 of 735) reported severe anxiety scores at baseline.

For patients who developed CPSP at six months (*n*=54), there was a mean (± SD) anxiety score of 44.63 (± 5.048); of these, 18.5% (*n*=10 of 54) of patients had mild anxiety at baseline and 81.5% (*n*=44 of 54) of patients had moderate to severe anxiety at baseline. For patients with CPSP at 12 months (*n*=25), there was a mean (± SD) anxiety score of 45.96 (± 6.426); of these, 16% (*n*=4 of 25) reported mild anxiety and 84% (*n*=21 of 25) reported moderate to severe anxiety at baseline. Overall, mean preoperative state anxiety scores were higher in patients who developed CPSP at 12 months after cardiac surgery.

Univariate logistic regression analysis indicated that moderate to severe preoperative anxiety was not significant for an association with the development of CPSP at six or 12 months. In patients who underwent cardiac surgery, adjusting for baseline demographic and clinical characteristics, moderate to severe preoperative anxiety was not significant for an association with the development of CPSP at either or 12 months.

Overall, in the adjusted models, there were no statistically significant differences in the odds of developing CPSP at six months or 12 months for those with moderate to severe preoperative anxiety, therefore, additional sub-analyses between moderate to severe preoperative anxiety and the intensity of CPSP following cardiac surgery were not conducted.

At six months, the model adjusted for sex, age, diabetes mellitus prior to surgery and anxiety explained 5.4% (Nagelkerke R^2 0.054) of the variance in CPSP. At 12 months, the model

adjusted for sex, age and anxiety explained 10.2% (Nagelkerke R^2 0.102) of the variance in CPSP after cardiac surgery. At six months and 12 months, both Hosmer-Lemeshow *p*-values (0.807 and 0.832, respectively) were greater than 0.05, indicating that data were a good fit in both prediction models. At both six months and 12 months C-Statistics were 0.660 and 0.636 respectively, indicating that the model was an acceptable model for predicting which patients with moderate to severe anxiety, and baseline adjusted covariates, would have the outcome of CPSP after cardiac surgery (see Table 6: Unadjusted and Adjusted Models for Moderate to Severe Preoperative Anxiety and CPSP at Six Months and 12 Months).

Table 6

Unadjusted and Adjusted Models for Moderate to Severe Preoperative Anxiety and CPSP at Six Months and 12 Months

	Unadjusted	**Adjusted**
CPSP 6 Months		
Wald 1*df*	1.025	1.494
p-value	0.311	0.222
OR	0.687	0.629
95% CI	0.332, 1.422	0.300, 1.322
Nagelkerke R^2	0.003	0.054
Hosmer-Lemeshow *p*-value	<0.001	0.807
C-Statistic	0.525	0.660
CPSP 12 Months		
Wald 1*df*	0.051	0.269
p-value	0.822	0.604
OR	0.882	0.743
95% CI	0.295, 2.634	0.242, 2.285
Nagelkerke R^2	<0.001	0.102
Hosmer-Lemeshow *p*-value	<0.001	0.832
C-Statistic	0.525	0.636

Note: alpha=0.05. Independent variable is preoperative Anxiety score (categorical variable, reference no/mild). Reference groups: female sex, no DM. Age assessed in years.

Model at six months adjusted for covariates: Sex, Age and DM. Omnibus likelihood ratio test of model $X^2(4)=15.122$, $p=0.004$

Model at 12 months adjusted for covariates: Sex and Age. Omnibus likelihood ratio test of model $X^2(3)=18.374$, $p=<0.001$

Legend: CI: Confidence Interval; CPSP: Chronic Post-Surgical Pain; *df*: Degree of Freedom; DM: Diabetes Mellitus; OR: Odds Ratio

Secondary Analysis

In an attempt to identify if the presence of any level of state anxiety would confer risk for CPSP and to corroborate the findings of existing studies, a secondary analysis was conducted, which examined state anxiety, scored as a continuous variable.

The sample had a mean (± SD) anxiety score of 43.97 (± 5.059) according to the Spielberger STAI Form Y-1. Univariate logistic regression analysis indicated that preoperative anxiety scores, as a continuous variable, was statistically significant for an association with the development of CPSP at 12 months after cardiac surgery. Specifically, for each unit increase in anxiety scores, the odds of patients experiencing CPSP at 12 months were 1.092 times greater, compared with patients with lower anxiety scores at baseline. However, when analyses were adjusted for demographic and clinical covariates, preoperative anxiety was not significantly associated with the development of CPSP at six or 12 months. Overall, in the adjusted models, there were no statistically significant differences in the odds of developing CPSP at six months or 12 months for preoperative anxiety score, therefore, no additional sub-analyses between preoperative anxiety score and the intensity of CPSP following cardiac surgery were conducted.

The models, adjusted for baseline demographic and clinical characteristics and state anxiety score, explained 5% (Nagelkerke R^2 0.050) of the variance in CPSP six months and 10.9% (Nagelkerke R^2 0.109) of the variance in CPSP seen at 12 months after cardiac surgery.

At six and 12 months, both Hosmer-Lemeshow *p*-values (0.224 and 0.305, respectively) were greater than 0.05—not significant, indicating that data were a good fit in both prediction models. At both six and 12 months C-Statistics were 0.656 and 0.627 respectively, indicating that the model was an acceptable model for predicting which patients with anxiety and baseline adjusted covariates, would have the outcome of CPSP after cardiac surgery (see Table 7: Unadjusted and Adjusted Models for Preoperative Anxiety Score and CPSP at Six Months and 12 Months).

Table 7

Unadjusted and Adjusted Models for Preoperative Anxiety Score with CPSP at Six Months and 12 Months

	Unadjusted	**Adjusted**
CPSP 6 Months		
Wald 1*df*	1.906	0.244
p-value	0.167	0.621
OR	1.040	1.014
95% CI	0.984, 1.099	0.959, 1.073
Nagelkerke R^2	0.007	0.050
Hosmer-Lemeshow *p*-value	0.015	0.224
C-Statistic	0.559	0.656
CPSP 12 Months		
Wald 1*df*	5.655	1.468
p-value	0.017*	0.226
OR	1.092	1.047
95% CI	1.016, 1.174	0.972, 1.128
Nagelkerke R^2	0.029	0.109
Hosmer-Lemeshow *p*-value	0.600	0.305
C-Statistic	0.606	0.627

Note: alpha=0.05. Independent variable is preoperative anxiety score (continuous variable). Reference groups: female sex, no DM. Age assessed in years.

Model at six months adjusted for covariates: Sex, Age and DM. Omnibus likelihood ratio test of model $X^2(4)=13.974$, $p=0.007$

Model at 12 months adjusted for covariates: Sex and Age. Omnibus likelihood ratio test of model $X^2(3)=19.550$, $p=<0.001$

Legend: CI: Confidence Interval; CPSP: Chronic Post-Surgical Pain; *df*: Degree of Freedom; DM: Diabetes Mellitus; OR: Odds Ratio

Question 3: Preoperative Depressive Symptom

Question 3a: In patients who undergo cardiac surgery, what is the association between severity of preoperative depressive symptom and the development of CPSP, adjusting for baseline demographic and clinical characteristics? Specifically, are patients with moderate to severe depressive symptom scores more likely to develop CPSP as compared to those with mild depressive symptom scores?

Question 3b: Among patients experiencing CPSP, what is the association between severity of baseline preoperative depressive symptom and the intensity of CPSP after cardiac surgery?

Preoperative depressive symptom was assessed by the HADS, via seven questions. The responses were scored, weighted and summed for a total depressive symptom score. Scores were categorized as mild (scores 0 to 10), moderate (score 11 to 14), and severe (scores 15 to 21) depressive symptom (Zigmond & Snaith, 1983). The sample had a mean (± SD) depressive symptom score of 8.08 (± 1.583), representing overall mild depressive symptom. Approximately 29% (*n*=214 of 735) reported normal depressive symptom scores, 66% (*n*=483 of 735) reported mild scores, 4% (*n*=36 of 735) reported moderate scores, and 1% (*n*=4 of 735) reported severe depressive symptom score at baseline.

For patients who developed CPSP at six months (*n*=54), there was a preoperative mean (± SD) depressive score of 7.93 (± 1.439); of these, 96% (*n*=52 of 54) of patients had mild symptoms and 4% (*n*=2 of 54) of patients had moderate to severe depressive symptom at baseline. For patients with CPSP at 12 months (*n*=25), there was a mean (± SD) preoperative

depressive score of 8.08 (± 1.824); of these, 88% (*n*=22 of 25) reported mild symptom and 12% (*n*=3 of 25) reported moderate to severe depressive symptom. Overall, mean preoperative depressive score was higher in patients who developed CPSP at 12 months after cardiac surgery.

Univariate logistic regression analysis indicated that moderate to severe preoperative depressive symptom was not significantly associated with the development of CPSP at six months or 12 months. In patients who underwent cardiac surgery, adjusting for baseline demographic and clinical characteristics, moderate to severe preoperative depressive symptom was not significantly associated with the development of CPSP at either six months or 12 months after cardiac surgery.

At six months, the model adjusted for sex, age, diabetes mellitus prior to surgery and preoperative depressive symptoms explained 5% (Nagelkerke R^2 0.050) of the variance in CPSP. At 12 months, the model adjusted for sex, age and preoperative depressive symptoms explained 11.4% (Nagelkerke R^2 0.114) of the variance in CPSP seen after cardiac surgery. At six months and 12 months, both Hosmer-Lemeshow *p*-values (0.157 and 0.760, respectively) were greater than 0.05, indicating the data were a good fit in both prediction models. At six months and 12 months the C-Statistics were 0.654 and 0.739 respectively, indicating that each model was a good model at predicting which patients with moderate to severe depressive symptom and baseline adjusted covariates, would have the outcome of CPSP after cardiac surgery (see Table 8: Unadjusted and Adjusted Models for Moderate to Severe Preoperative Depressive Symptom and CPSP at Six Months and 12 Months).

Overall, in the adjusted models, there were no statistically significant differences in the odds of developing CPSP at six months or 12 months for those with moderate to severe preoperative depressive symptoms. Therefore, no additional sub-analyses to examine the

relationship between the intensity of preoperative depressive symptoms and the intensity of CPSP after cardiac surgery were conducted.

Table 8

Unadjusted and Adjusted Models for Moderate to Severe Preoperative Depressive Symptom and CPSP at Six Months and 12 Months

	Unadjusted	Adjusted
CPSP 6 Months		
Wald 1*df*	0.132	0.265
p-value	0.716	0.607
OR	0.762	0.676
95% CI	0.176, 3.296	0.152, 3.005
Nagelkerke R^2	0.001	0.050
Hosmer-Lemeshow *p*-value	<0.001	0.157
C-Statistic	0.506	0.654
CPSP 12 Months		
Wald 1*df*	3.163	2.884
p-value	0.075	0.089
OR	3.176	3.216
95% CI	0.889, 11.350	0.835, 12.382
Nagelkerke R^2	0.014	0.114
Hosmer-Lemeshow *p*-value	<0.001	0.760
C-Statistic	0.539	0.739

Note: alpha=0.05. Independent variable is preoperative depressive symptom score (categorical variable, reference no/mild). Reference groups: female sex, no DM. Age assessed in years.

Model at six months adjusted for covariates: Sex, Age and DM. Omnibus likelihood ratio test of model $X^2(4)=13.976$, $p=0.007$

Model at 12 months adjusted for covariates: Sex and Age. Omnibus likelihood ratio test of model $X^2(3)=20.395$, $p=<0.001$

Legend: CI: Confidence Interval; CPSP: Chronic Post-Surgical Pain; *df*: Degree of Freedom; DM: Diabetes Mellitus; OR: Odds Ratio

Secondary Analysis

In an attempt to identify if the presence of any level of depressive symptom would confer increased odds for CPSP and to corroborate the findings of existing studies, a secondary analysis were conducted, which examined depressive symptom score as a continuous level of measurement.

The sample had a mean (± SD) preoperative depressive symptom score of 8.08 (± 1.583) according to the HADS. Univariate logistic regression analysis indicated that preoperative depressive symptom score was not significant for an association with the development of CPSP at six months or 12 months. In patients who underwent cardiac surgery, adjusting for baseline demographic and clinical characteristics, preoperative depressive symptom was not significant for an association with and the development of CPSP at either six months or 12 months after cardiac surgery.

Overall, in the adjusted models for preoperative depressive symptoms, there were no statistically significant differences in the odds of developing CPSP at six months or 12 months; therefore, no additional sub-analyses between intensity of preoperative depressive symptom score, as a continuous variable, and the intensity of CPSP after cardiac surgery were conducted.

At six months, the model adjusted for sex, age, diabetes mellitus prior to surgery and preoperative depressive symptoms explained 5.1% (Nagelkerke R^2 0.051) of the variance in CPSP. At 12 months, the model adjusted for sex, age and preoperative depressive symptoms explained 10.1% (Nagelkerke R^2 0.101) of the variance in CPSP seen after cardiac surgery. The Hosmer-Lemeshow goodness of fit test was not statistically significant (p=0.792 and p=0.456) indicating the prediction models were a good fit at both six months and 12 months respectively. At six months and 12 months the C-Statistics were 0.652 and 0.741 respectively, indicating that

each model was a good model at predicting which patients with preoperative depressive symptom and baseline adjusted covariates, would have the outcome of CPSP after cardiac surgery (see Table 9: Unadjusted and Adjusted Models for Preoperative Depressive Symptom Score and CPSP at Six Months and 12 Months).

Table 9

Unadjusted and Adjusted Models for Preoperative Depressive Symptom Score and CPSP at Six Months and 12 Months

	Unadjusted	**Adjusted**
CPSP 6 Months		
Wald 1*df*	1.063	0.589
p-value	0.302	0.443
OR	0.909	0.932
95% CI	0.759, 1.089	0.780, 1.115
Nagelkerke R^2	0.004	0.051
Hosmer-Lemeshow *p*-value	0.026	0.792
C-Statistic	0.567	0.652
CPSP 12 Months		
Wald 1*df*	0.008	0.047
p-value	0.930	0.829
OR	0.989	1.029
95% CI	0.765, 1.277	0.797, 1.327
Nagelkerke R^2	<0.001	0.101
Hosmer-Lemeshow *p*-value	0.887	0.456
C-Statistic	0.533	0.741

Note: alpha=0.05. Independent variable is preoperative depressive symptom score (continuous variable). Reference groups: female sex, no DM. Age assessed in years.

Model at six months adjusted for covariates: Sex, Age and DM. Omnibus likelihood ratio test of model $X^2(4)=14.270$, $p=0.006$

Model at 12 months adjusted for covariates: Sex and Age. Omnibus likelihood ratio test of model $X^2(3)=18.104$, $p=<0.001$

Legend: CI: Confidence Interval; CPSP: Chronic Post-Surgical Pain; *df*: Degree of Freedom; DM: Diabetes Mellitus; OR: Odds Ratio

Question 4: Acute Postoperative Pain Intensity

Question 4a: In patients who undergo cardiac surgery, what is the association between acute postoperative pain intensity and the development of CPSP, adjusting for baseline demographic and clinical characteristics? Specifically, are patients with moderate to severe pain scores more likely to develop CPSP as compared to those with mild pain scores?

The BPI-SF measured the presence and location of pain via five items: '*worst in the last 24 hours while lying*', '*worst in the last 24 hours while moving*', '*least in last 24 hours*', '*average in last 24 hours*' and pain '*right now*' on postoperative days three and 30. On average (± SD), patients reported moderate intensity pain as '*worst pain in last 24 hours while lying*' (4.27 ± 2.92), '*worst pain in last 24 hours while moving*' (4.76 ± 2.82) on postoperative day three. On postoperative day 30, acute pain intensity was reported as mild pain on the BPI (see Table 2: Mean Postoperative Pain Intensity over Time).

The body location of pain indicated on the BPI. The majority of patients reported that the chest, legs and back 'hurt the most' across postoperative days three, 30, six months and 12 months (see Table 10: Brief Pain Inventory Location of Pain 'Hurt the Most' Across Postoperative Days). The chest and leg(s) locations are sternal incisional and vein harvesting sites during cardiac surgery. Approximately, 69% (*n*=511) of patients had the saphenous vein(s) harvested from the leg(s) (See Table 11: Brief Pain Inventory Pain Intensity for Saphenous Vein Site).

Table 10

Brief Pain Inventory Location of Pain 'Hurt the Most' Across Postoperative Days

Location of pain	Postoperative Days			
	POD 3 (*n*=297)	**POD 30 (*n*=138)**	**6 Months (*n*=24)**	**12 Months (*n*=6)**
Chest/Sternum	71% (*n*=212)	60% (*n*=83)	58% (*n*=14)	83% (*n*=5)
Leg(s)	14% (*n*=41)	23% (*n*=31)	8% (*n*=2)	17% (*n*=1)
Back	6% (*n*=17)	4% (*n*=5)	8% (*n*=2)	-
Other	9% (*n*= 27)	13% (*n*=19)	26% (*n*=6)	-

Note: Other sites include head, neck, arms, abdomen, hip/pelvis, generalized, knees, feet.

Legend: n: number in sample; POD: Postoperative Day

Table 11

Brief Pain Inventory Pain Intensity for Saphenous Vein Harvest Sites

Brief Pain Inventory	Postoperative Days			
	POD 3	**POD 30**	**6 months**	**12 months**
Worst pain in last 24 hours while lying	4.30 (± 2.901) (*n*=385)	2.53 (± 2.737) (*n*=133)	3.12 (± 3.362) (*n*=26)	2.50 (± 2.473) (*n*=14)
Worst pain in last 24 hours while moving	4.81 (± 2.793) (*n*=446)	3.03 (± 2.871) (*n*= 290)	3.94 (± 2.906) (*n*=32)	3.14 (± 2.770) (*n*=14)
Least pain in last 24 hours	1.49 (±1.784) (*n*=454)	0.88 (±1.592) (*n*=290)	1.30 (± 2.430) (*n*=33)	1.36 (± 1.646) (*n*=14)
Average pain in last 24 hours	3.11 (± 2.079) (*n*=451)	1.61 (± 2.110) (*n*= 290)	2.91 (± 2.909) (*n*=33)	2.64 (± 2.170) (*n*=14)
Pain right now	2.36 (±2.375) (*n*=455)	1.33 (± 2.073) (*n*=289)	2.82 (± 3.066) (*n*=33)	1.79 (± 2.259) (*n*=14)

Note: Pain intensity measured on 0-10 numerical rating scale; Mean (± SD)

Legend: n: number in sample; POD: Postoperative Day; SD: Standard Deviation

Postoperative day three and CPSP at six months. In unadjusted logistic regression models, at postoperative day three, '*least pain in last 24 hours*' (unadjusted OR 2.161, 95% CI [1.076, 4.341], *p*=0.030), and pain '*right now*' (unadjusted OR 2.602, 95% CI [1.464, 4.626], *p*=0.001) were found to be significantly associated with CPSP at six months. However, '*worst pain in the last 24 hours while lying*', '*worst pain in the last 24 hours while moving*', and '*average pain in last 24 hours*' were not significantly associated with CPSP at six months.

In patients who underwent cardiac surgery, adjusting for baseline demographics and clinical characteristics, pain '*right now*' (adjusted OR 2.263, 95% CI [1.255, 4.081], *p*=0.007) was found to be significant for an association with the development of CPSP at six months after cardiac surgery. In the adjusted model, for those with moderate to severe pain intensity rated at pain '*right now*' on postoperative day three, there was an approximate two-fold increase in the odds of developing CPSP at six months. However, '*worst pain in the last 24 hours while lying*', '*worst pain in the last 24 hours while moving*', '*least pain in last 24 hours*' and '*average pain in last 24 hours*' were not significantly associated with the development of CPSP at six months in adjusted models.

The model adjusted for sex, age, diabetes mellitus prior to surgery and acute postoperative pain intensity for pain '*right now*' explained 7.8% (Nagelkerke R^2 0.078) of the variance in CPSP at six months. The Hosmer-Lemeshow goodness of fit test was not statistically significant (*p*=0.765) indicating the prediction model for pain '*right now*' was a good fit. The C-Statistic was 0.683, indicating the model was a good model at predicting which patients with moderate to severe acute pain intensity rated at pain '*right now*' and baseline adjusted covariates, would have the outcome of CPSP at six months (see Table 12: Unadjusted and Adjusted Models for Acute Pain Intensity on Postoperative Day Three and CPSP at Six Months).

Table 12

Unadjusted and Adjusted Models for Acute Pain Intensity on Postoperative Day Three and CPSP at Six Months

BPI Pain Intensity	Unadjusted	Adjusted
Worst pain in last 24 hours while lying		
Wald 1*df*	0.533	0.232
p-value	0.465	0.630
OR	1.280	1.181
95% CI	0.660, 2.484	0.600, 2.323
Nagelkerke R^2	0.003	0.022
Hosmer-Lemeshow *p*-value	<0.001	0.324
C-Statistic	0.529	0.605
Worst pain in last 24 hours while moving		
Wald 1*df*	3.745	3.211
p-value	0.053	0.073
OR	2.034	1.944
95% CI	0.991, 4.176	0.940, 4.024
Nagelkerke R^2	0.017	0.007
Hosmer-Lemeshow *p*-value	<0.001	0.722
C-Statistic	0.569	0.667
Least pain in last 24 hours		
Wald 1*df*	4.688	3.821
p-value	0.030*	0.051
OR	2.161	2.044
95% CI	1.076, 4.341	0.998, 4.186
Nagelkerke R^2	0.016	0.064
Hosmer-Lemeshow *p*-value	<0.001	0.615
C-Statistic	0.554	0.665
Average pain in last 24 hours		
Wald 1*df*	0.749	0.030
p-value	0.387	0.862
OR	1.290	1.055
95% CI	0.725, 2.295	0.579, 1.921
Nagelkerke R^2	0.003	0.045
Hosmer-Lemeshow *p*-value	<0.001	0.550
C-Statistic	0.531	0.645
Pain right now		
Wald 1*df*	10.622	7.365
p-value	0.001*	0.007*
OR	2.602	2.263
95% CI	1.464, 4.626	1.255, 4.081
Nagelkerke R^2	0.039	0.078
Hosmer-Lemeshow *p*-value	<0.001	0.765
C-Statistic	0.608	0.683

Note: *significant at alpha 0.05. Reference groups: female sex, no DM. Age assessed in years. *Model adjusted for covariate*: Sex, Age and DM. Omnibus likelihood ratio test of model for '*worst pain in last 24 hours while lying*' $X^2(4)=4.467$, $p=0.347$; '*worst pain in last 24 hours*

while moving' $X^2(4)=16.766$, $p=0.002$; '*least pain in last 24 hours*' $X^2(4)=16.918$, $p=0.002$; '*average in last 24 hours*' pain $X^2(4)=11.725$, $p=0.020$ and pain '*right now*' $X^2(4)=20.732$, $p=<0.001$

Legend: BPI: Brief Pain Inventory; CPSP: Chronic Post-Surgical Pain; CI: Confidence Interval; *df*: Degrees of Freedom; DM: Diabetes Mellitus; OR: Odds Ratio

Postoperative day three and CPSP at 12 months. In unadjusted logistic regression models, at postoperative day three, pain '*right now*' (unadjusted OR 3.399, 95% CI [1.488, 7.765], $p=0.004$) was found to have a significant association with the development of CPSP at 12 months after cardiac surgery. However, '*worst pain in the last 24 hours while lying*', '*worst pain in the last 24 hours while moving*', '*least pain in last 24 hours*', and '*average pain*' were not significantly associated with the development of CPSP at 12 months.

In the adjusted model, pain '*right now*' (adjusted OR 2.749, 95% CI [1.174, 6.441], $p=0.020$), on postoperative day three was found to have a significant association with the development of CPSP at 12 months after cardiac surgery. In the adjusted model, for those with moderate to severe pain intensity rated at pain '*right now*' on postoperative day three, there was an approximate two-fold increase in the odds of developing CPSP at 12 months after cardiac surgery.

In patients who underwent cardiac surgery, adjusting for baseline demographics and clinical characteristics—'*worst pain in the last 24 hours while lying*', '*worst pain in the last 24 hours while moving*', '*least pain in last 24 hours*' and '*average pain in last 24 hours*' on postoperative day three, were not significantly associated with the development of CPSP at 12 months after cardiac surgery.

The model adjusted for sex, age and postoperative day three pain intensity explained 13.5% (Nagelkerke R^2 0.135) of the variance in CPSP at 12 months postoperative in pain *'right now'* adjusted model. The Hosmer-Lemeshow goodness of fit test was not statistically significant (p=0.677) indicating the prediction model for pain *'right now'* was a good fit at 12 months postoperatively. The C-Statistic was 0.743, indicating the model was a good model at predicting which patients with moderate to severe acute pain intensity rated at pain *'right now'* and baseline adjusted covariates, would have the outcome of CPSP at 12 months after cardiac surgery (see Table 13: Unadjusted and Adjusted Models for Acute Pain Intensity on Postoperative Day Three and CPSP at 12 months).

Table 13

Unadjusted and Adjusted Models for Acute Pain Intensity on Postoperative Day Three and CPSP at 12 Months

BPI Pain intensity	**Unadjusted**	**Adjusted**
Worst pain in last 24 hours while lying		
Wald 1*df*	2.641	1.387
p-value	0.104	0.239
OR	2.891	2.197
95% CI	0.804, 10.400	0.59, 8.147
Nagelkerke R^2	0.028	0.151
Hosmer-Lemeshow *p*-value	<0.001	0.736
C-Statistic	0.610	0.791
Worst pain in last 24 hours while moving		
Wald 1*df*	2.567	2.165
p-value	0.109	0.141
OR	2.445	2.301
95% CI	0.819, 7.297	0.758, 6.985
Nagelkerke R^2	0.019	0.112
Hosmer-Lemeshow *p*-value	<0.001	0.787
C-Statistic	0.583	0.754
Least pain in last 24 hours		
Wald 1*df*	1.383	0.831
p-value	0.240	0.362
OR	1.842	1.639
95% CI	0.665, 5.100	0.56, 4.742
Nagelkerke R^2	0.007	0.107
Hosmer-Lemeshow *p*-value	<0.001	0.932
C-Statistic	0.542	0.736
Average pain in last 24 hours		
Wald 1*df*	0.583	0.013
p-value	0.445	0.910
OR	1.378	1.051
95% CI	0.605, 3.135	0.447, 2.471
Nagelkerke R^2	0.003	0.103
Hosmer-Lemeshow *p*-value	<0.001	0.695
C-Statistic	0.539	0.738
Pain right now		
Wald 1*df*	8.424	5.421
p-value	0.004*	0.020*
OR	3.399	2.749
95% CI	1.488, 7.765	1.174, 6.441
Nagelkerke R^2	0.049	0.135
Hosmer-Lemeshow *p*-value	<0.001	0.677
C-Statistic	0.515	0.743

Note: * significant at alpha=0.05. Reference group: female sex. Age assessed in years.

Model adjusted for covariate: Sex and Age. Omnibus likelihood ratio test of model for '*worst pain in last 24 hours while lying*' $X^2(3)=17.233$, $p=0.001$; '*worst pain in last 24 hours while*

moving' $X^2(3)=18.162$, $p=<0.001$; '*least pain in last 24 hours*' $X^2(3)=18.132$, $p=0.001$; '*average pain in last 24 hours*' $X^2(3)=17.286$, $p=<0.001$ and pain '*right now*' $X^2(3)=22.876$, $p=<0.001$

Legend: BPI: Brief Pain Inventory; CPSP: Chronic Post-Surgical Pain; CI: Confidence Interval; *df*: Degrees of Freedom; OR: Odds Ratio

Postoperative day 30 and CPSP at six months. In unadjusted logistic regression models, '*worst pain in the last 24 hours while moving*' (unadjusted OR 2.418, 95% CI [1.197, 4.882], $p=0.014$), '*least pain in last 24 hours*' (unadjusted OR 2.923, 95% CI [1.011, 8.447], $p=0.048$), '*average pain in last 24 hours*' (unadjusted OR 2.469, 95% CI [1.146, 5.319], $p=0.021$) and pain '*right now*' (unadjusted OR 3.726, 95% CI [1.731, 8.022], $p=0.001$) were all found to be statistically significant for an association with the development of CPSP at six months following cardiac surgery. However, '*worst pain in the last 24 hours while lying*' on postoperative day 30 was not found to have a statistically significant association with the development of CPSP at six months.

In adjusted models at postoperative day 30, '*worst pain in the last 24 hours while moving*' (adjusted OR 2.147, 95% CI [1.048, 4.400], $p=0.037$) and pain '*right now*' (adjusted OR 2.913, 95% CI [1.304, 6.505], $p=0.009$) were both found to be significant for an association with the development of CPSP at six months after cardiac surgery. In the adjusted model, for those with moderate to severe pain intensity rated at '*worst pain in the last 24 hours while moving*' and pain '*right now*' on postoperative day 30, there was a two-fold increase in the odds of developing CPSP at six months after cardiac surgery, respectively.

In adjusted models at postoperative day 30, '*worst pain in the last 24 hours while lying*', '*least pain in last 24 hours*', and '*average pain in last 24 hours*' were not significantly associated with the development of CPSP at six months after cardiac surgery.

The models adjusted for baseline demographic and clinical characteristics and postoperative day 30 pain intensity explained 6.6% (Nagelkerke R^2 0.066) and 9.3% (Nagelkerke R^2 0.093) of the variance in CPSP at six months in '*worst pain in the last 24 hours while moving*' and pain '*right now*' adjusted models respectively. The Hosmer-Lemeshow goodness of fit test was not statistically significant (p=0.620 and p=0.082) indicating that each prediction model for '*worst pain in the last 24 hours while moving*' and pain *'right now'* was a good fit at six months postoperatively. Also, the C-Statistics were 0.666 and 0.675, indicating the model was a good model at predicting which patients with moderate to severe acute pain intensity rated at '*worst pain in the last 24 hours while moving*' and pain *'right now'* and baseline adjusted covariates, would have the outcome of CPSP at six months after cardiac surgery (see Table 14: Unadjusted and Adjusted Models for Acute Pain Intensity on Postoperative Day 30 and CPSP at Six Months).

Table 14

Unadjusted and Adjusted Models for Acute Pain Intensity on Postoperative Day 30 and CPSP at Six Months

BPI Pain Intensity	**Unadjusted**	**Adjusted**
Worst pain in last 24 hours while lying		
Wald 1*df*	3.140	2.185
p-value	0.076	0.139
OR	2.548	2.263
95% CI	0.906, 7.168	0.766, 6.685
Nagelkerke R^2	0.044	0.083
Hosmer-Lemeshow *p*-value	<0.001	0.759
C-Statistic	0.612	0.679
Worst pain in last 24 hours while moving		
Wald 1*df*	6.063	4.356
p-value	0.014*	0.037*
OR	2.418	2.147
95% CI	1.197, 4.882	1.048, 4.400
Nagelkerke R^2	0.035	0.066
Hosmer-Lemeshow *p*-value	<0.001	0.620
C-Statistic	0.607	0.666
Least pain in last 24 hours		
Wald 1*df*	3.923	1.930
p-value	0.048*	0.165
OR	2.923	2.191
95% CI	1.011, 8.447	0.724, 6.626
Nagelkerke R^2	0.019	0.068
Hosmer-Lemeshow *p*-value	<0.001	0.399
C-Statistic	0.542	0.655
Average pain in last 24 hours		
Wald 1*df*	5.331	2.509
p-value	0.021*	0.113
OR	2.469	1.913
95% CI	1.146, 5.319	0.857, 4.271
Nagelkerke R^2	0.027	0.072
Hosmer-Lemeshow *p*-value	<0.001	0.490
C-Statistic	0.576	0.665
Pain right now		
Wald 1*df*	11.306	6.802
p-value	0.001*	0.009*
OR	3.726	2.913
95% CI	1.731, 8.022	1.304, 6.505
Nagelkerke R^2	0.056	0.093
Hosmer-Lemeshow *p*-value	<0.001	0.082
C-Statistic	0.605	0.675

Note: *significant at 0.05. Reference groups: female sex; no DM. Age assessed in years.

Model adjusted for covariate: Sex, Age and DM. Omnibus likelihood ratio test of model for '*worst in the last 24 hours while lying*' $X^2(4)=5.878$, $p=0.208$; '*worst in the last 24 hours while*

moving' $X^2(4)=11.592$, $p=0.021$; '*least in last 24 hours*' $X^2(4)=12.304$, $p=0.015$; '*average in last 24 hours*' pain $X^2(4)=12.928$, $p=0.012$ and pain '*right now*' $X^2(4)=16.891$, $p=0.002$

Legend: BPI: Brief Pain Inventory; CI: Confidence Interval; CPSP: Chronic Post-Surgical Pain; *df*: Degrees of Freedom; DM: Diabetes Mellitus; OR: Odds Ratio

Postoperative day 30 and CPSP at 12 months. In unadjusted logistic regression models, '*worst pain in the last 24 hours while lying*' (unadjusted OR 10.972, 95% CI [1.237, 97.346], $p=0.031$), '*average pain in last 24 hours*' (unadjusted OR 2.817, 95% CI [0.859, 4.378], $p=0.045$) and pain '*right now*' (unadjusted OR 3.767, 95% CI [1.351, 10.508], $p=0.011$) were found to have a significant association with the development of CPSP at 12 months after cardiac surgery. Although statistically significant, the unadjusted odds ratio and associated 95% CI for '*worst pain in the last 24 hours while lying*' and pain '*right now*' are wide, suggesting a lack of precision in the estimate of effect. In unadjusted models, '*worst pain in the last 24 hours while moving*' and '*least pain in last 24 hours*' at postoperative day 30 were not found to be significantly associated with the development of CPSP at 12 months after cardiac surgery.

In the model adjusted for sex, age, and postoperative day 30 pain intensity, no BPI pain intensity assessments were significantly associated with the development of CPSP at 12 months after cardiac surgery.

The model explained between 12.5% and 23.3% of the variance in CPSP at 12 months across all BPI pain intensity models. The Hosmer-Lemeshow goodness of fit test was not statistically significant in any of the models, indicating the each prediction model for '*worst pain in the last 24 hours while lying*' ($p=0.614$), '*worst pain in the last 24 hours while moving*' ($p=0.773$), '*least pain in last 24-hours*' ($p=0.405$), '*average pain in last 24 hours*' ($p=0.948$) and

pain *'right now'* (p=0.630) on postoperative day 30 was a good fit at six months postoperatively. The C-Statistics were between 0.7 and 0.8, indicating the models were acceptable models for predicting which patients with moderate to severe acute pain intensity on postoperative day 30 and baseline adjusted covariates (age and sex), would have the outcome of CPSP at 12 months after cardiac surgery (see Table 15: Unadjusted and Adjusted Models for Acute Pain Intensity on Postoperative Day 30 and CPSP at 12 Months).

Table 15

Unadjusted and Adjusted Models for Acute Pain Intensity on Postoperative Day 30 and CPSP at 12 Months

BPI Pain intensity	**Unadjusted**	**Adjusted**
Worst pain in last 24 hours while lying		
Wald 1*df*	4.626	3.093
p-value	0.031*	0.079
OR	10.972	7.462
95% CI	1.237, 97.346	0.795, 70.080
Nagelkerke R^2	0.163	0.233
Hosmer-Lemeshow *p*-value	<0.001	0.614
C-Statistic	0.760	0.854
Worst pain in last 24 hours while moving		
Wald 1*df*	3.295	2.198
p-value	0.069	0.138
OR	2.424	2.119
95% CI	0.932, 6.309	0.785, 5.715
Nagelkerke R^2	0.028	0.132
Hosmer-Lemeshow *p*-value	<0.001	0.773
C-Statistic	0.608	0.747
Least pain in last 24 hours		
Wald 1*df*	3.543	1.341
p-value	0.060	0.247
OR	3.574	2.320
95% CI	0.949, 13.458	0.558, 9.639
Nagelkerke R^2	0.023	0.124
Hosmer-Lemeshow *p*-value	0.001	0.405
C-Statistic	0.554	0.728
Average pain in last 24 hours		
Wald 1*df*	4.006	1.406
p-value	0.045*	0.236
OR	2.817	1.923
95% CI	0.859, 4.378	0.652, 5.671
Nagelkerke R^2	0.029	0.125
Hosmer-Lemeshow *p*-value	<0.001	0.948
C-Statistic	0.588	0.743
Pain right now		
Wald 1*df*	6.422	2.784
p-value	0.011*	0.095
OR	3.767	2.535
95% CI	1.351, 10.508	0.850, 7.562
Nagelkerke R^2	0.045	0.135
Hosmer-Lemeshow *p*-value	<0.001	0.630
C-Statistic	0.603	0.748

Note: *significant at 0.05. Reference groups: female sex. Age assessed in years.

Model adjusted for covariate: Sex and Age. Omnibus likelihood ratio test of model for '*worst in the last 24 hours while lying*' $X^2(3)=9.544$, $p=0.023$; '*worst in the last 24 hours while moving*'

$X^2(3)=15.948$, $p=0.001$; '*least in last 24 hours*' $X^2(3)=15.407$, $p=0.001$; '*average in last 24 hours*' pain $X^2(3)=15.534$, $p=0.001$ and pain '*right now*' $X^2(3)=16.814$, $p=0.001$

Legend: BPI: Brief Pain Inventory; CI: Confidence Interval; CPSP: Chronic Post-Surgical Pain; *df*: Degrees of Freedom; OR: Odds Ratio

Diagnostics were completed for multicollinearity between intensity of pain (as continuous level data) as measured by the Brief Pain Inventory at: '*worst pain in the last 24 hours while lying*', '*worst pain in the last 24 hours while moving*', '*least pain in last 24 hours*', '*average in last 24 hours*' pain and pain '*right now*' on postoperative days three and 30. Diagnostics revealed a variance inflation factor (VIF) for '*average*' pain = 5.019 and pain '*right now*' = 4.636 at postoperative day 30, all other VIF results were less than 4 for '*worst pain in the last 24 hours while lying*', '*worst pain in the last 24 hours while moving*' and '*least pain in last 24 hours*', on postoperative day three and 30 following cardiac surgery (see Appendix Z: Collinearity Diagnostics).

According to Fields (2012), the VIF indicates the strength of a linear relationship between predictors. Additionally, "if the largest VIF is greater than 10, then there is cause for concern, if the average VIF is substantially greater than one, then the regression may be biased" (Fields, 2012, p. 325). The average VIF for postoperative day three was 2.026 and for postoperative day 30 was 3.589 and does not indicate a cause for concern.

Reciprocal to the VIF is the tolerance statistic: 1/VIF (Fields, 2012). According to Fields (2012), a "tolerance [value] below 0.2 indicate a potential problem" (p. 325). The tolerance values on postoperative day three were between 0.412 and 0.606, indicating there is no cause for concern. The tolerance value for '*worst pain in the last 24 hours while lying*', '*worst pain in the*

last 24 hours while moving', '*least pain in last 24 hours*' and pain '*right now*' was between 0.216 and 0.454. The tolerance value for '*average pain in last 24 hours*' was 0.199, indicating a potential problem, however, when interpreted in conjunction with the VIF 5.019, it implies that 80% of the variability in the independent variable of '*average pain in last 24 hours*' is explained by the remainder of the independent variables—'*worst pain in the last 24 hours while lying*', '*worst pain in the last 24 hours while moving*', '*least pain in last 24 hours*' and pain '*right now*'—in the model and is not a cause for concern.

Question 4a: Among patients experiencing CPSP, what is the association between acute postoperative pain intensity and the intensity of CPSP after cardiac surgery?

Following adjusted logistic regression analysis, acute postoperative pain intensity on postoperative days three and 30 were found to have a significant association with the development of CPSP at six months and 12 months after cardiac surgery. Secondary linear regression analyses were conducted to explore the association between the intensity of acute postoperative pain with the intensity of CPSP at both six months and 12 months (see Table 16: Unadjusted and Adjusted Models for Acute Postoperative Pain Intensity and CPSP Intensity at Six Months and 12 Months).

Postoperative day three and CPSP at six months. In unadjusted linear regression models, at postoperative day three, the intensity of '*least pain in last 24 hours*' and pain '*right now*' were not found to be significantly associated with the intensity of CPSP at six months. However, in the model adjusting for age, sex, and prior history of diabetes mellitus–pain '*right now*' (*t* statistic=2.837, *p*=0.013) was found to have a significant association with the intensity of CPSP at six months after cardiac surgery.

Postoperative day 30 and CPSP at six months. In unadjusted linear regression models, at postoperative day 30, the intensity of '*worst pain in the last 24 hours while moving*' and pain '*right now*' were not significantly associated with the intensity of CPSP at six months. However, in adjusted models, '*worst pain in the last 24-hours while moving*' (*t* statistic=4.613, *p*=0.002) and pain '*right now*' (*t* statistic=4.846, *p*=0.001) were found to have a significant association with the intensity of CPSP at six months after cardiac surgery.

Postoperative day three and CPSP at 12 months. In unadjusted and adjusted linear regression models, at postoperative day three, the intensity of pain '*right now*' was not significantly associated with the intensity of CPSP at 12 months (see Table 16: Unadjusted and Adjusted Models for Acute Postoperative Pain Intensity and CPSP Intensity at Six Months and 12 Months).

Table 16

Unadjusted and Adjusted Models for Acute Postoperative Pain Intensity and CPSP Intensity at Six Months and 12 Months

	6 Months		12 Months	
BPI Pain Intensity	**Unadjusted**	**Adjusted**	**Adjusted**	**Unadjusted**
POD 3				
Least pain in last 24 hours				
Unstandardized Beta	0.213	0.178	-	-
SE	0.190	0.334	-	-
95% CI	- 0.172, 0.599	-0.538, 0.894	-	-
t-test statistic	1.121	0.534	-	-
p-value	0.269	0.602	-	-
Pain now				
Unstandardized Beta	0.251	0.587	0.309	0.165
SE	0.178	0.207	0.249	0.793
95% CI	- 0.109, 0.610	0.143, 1.031	-0.230, 0.847	-1.874, 2.205
t-test statistic	1.411	2.837	1.239	0.209
p-value	0.166	0.013*	0.237	0.843
POD 30				
Worst pain in last 24 hours while moving				
Unstandardized Beta	0.033	0.806	-	-
SE	0.171	0.175	-	-
95% CI	- 0.317, 0.384	0.393, 1.220	-	-
t-test statistic	0.195	4.613	-	-
p-value	0.847	0.002*	-	-
Pain Now				
Unstandardized Beta	0.141	0.760	-	-
SE	0.209	0.157	-	-
95% CI	- 0.285, 0.567	0.405, 1.115	-	-
t-test statistic	0.676	4.846	-	-
p-value	0.504	0.001*	-	-

Note: *significant at 0.05; Reference groups: female sex, no DM. Age assessed in years.

At six months, model adjusted for covariate: Sex, Age and DM.

At 12 months, model adjusted for covariate: Sex and Age.

Legend: BPI: Brief Pain Inventory; CI: Confidence Interval; CPSP: Chronic Post-Surgical Pain; POD: Postoperative Day; SE: Standard Error

Question 5: Opioid Dose

Question 5: In patients who undergo cardiac surgery, what is the association between cumulative opioid dose consumed in the first three postoperative days and the development of CPSP, adjusting for baseline demographic and clinical characteristics?

Following cardiac surgery and unless contraindicated, patients were routinely prescribed scheduled acetaminophen 650mg oral/per rectum for 48 hours, as needed, and hydromorphone 0.5mg to 2mg oral/subcutaneous/intramuscular/intravenous every two hours, as needed for pain rated NRS ≥4/10. Patients consumed any Codeine, Fentanyl, Hydrocodone, Hydromorphone, Oxycodone, Oxycontin, Oxymorphone, Methadone, Morphine, or Tramadol as opioid containing analgesics. All identified medications containing opioids were converted to standardized parenteral morphine milligram equivalent dose using standardized conversion tables (Centers for Disease and Control, 2018).

The mean (± SD) morphine milligram equivalent (MME) dose consumed on postoperative days one, two, three and cumulatively were 84.09 (± 426.67), 32.76 (± 321.42), 35.60 (± 448.97) and 151.49 (± 1,055.39) respectively. On all postoperative days, two patients were outliers, accounting for between 4,560 mg to 8,644 mg of morphine equivalent dose each, per day. A secondary analysis was conducted with the two patient outliers removed. The mean (± SD) MME dose consumed on postoperative days one, two, three, and cumulatively was 71.48 (± 285.39), 20.99 (± 46.40), 11.92 (± 36.97) and 104.09 (± 311.26) respectively.

Opioid dose and CPSP at six months. Following univariate logistic regression analysis, the morphine milligram equivalent dose of opioids consumed on postoperative day one (unadjusted OR 1.001, 95% CI [1.000, 1.002], p=0.001) and cumulative dose (unadjusted OR 1.001, 95% CI [1.000, 1.002], p=0.001) were found to be significant for an association with the

development of CPSP at six months. However, opioid dose consumed on postoperative days two and three were not significant for an association with the development of CPSP at six months.

Adjusting for baseline demographic and clinical characteristics—sex, age and diabetes mellitus prior to cardiac surgery—opioid dose consumed on postoperative day one (adjusted OR 1.001, 95% CI [1.000, 1.002], p=0.004) and cumulative dose (adjusted OR 1.001, 95% CI [1.000, 1.002], p=0.003) remained statistically significant for an association with and the development of CPSP at six months after cardiac surgery. In the adjusted model, morphine milligram equivalent dose of opioid consumed on postoperative days two and three were not found to be significant for an association with the development of CPSP at six months.

Overall, in the adjusted model, each milligram of morphine equivalent dose consumed on postoperative day one was associated with an increase in the odds of developing CPSP (OR 1.001, 95% CI [1.001, 1.002], p=0.004). Similarly, in the adjusted model, with each milligram of morphine equivalent cumulative dose consumed, there was an increase in the odds or developing CPSP (OR 1.001, 95% CI [1.001, 1.002], p=0.003). The increase in the odds for CPSP at six months was statistically significant.

The model adjusted for sex, age, prior history of diabetes mellitus and milligram of morphine equivalent dose consumed on postoperative day one and cumulative dose explained 7.1% (Nagelkerke R^2 0.071) and 7.4% (Nagelkerke R^2 0.074) of the variance in CPSP at six months, respectively. The Hosmer-Lemeshow goodness of fit test was not statistically significant (p=0.389 and p=0.677) indicating the prediction model for morphine milligram equivalent opioid dose consumed on postoperative day one and cumulative dose were a good fit at six months postoperatively. The C-Statistics were 0.648 and 0.654, indicating that each model was a good model at predicting which patients with increased opioid doses and baseline adjusted

covariates, would have the outcome of CPSP at six months after cardiac surgery (see Table 17: Unadjusted and Adjusted Models for Postoperative Opioid Dose and CPSP at Six Months).

Table 17

Unadjusted and Adjusted Models for Postoperative Opioid Dose and CPSP at Six Months

Postoperative Opioid Dose	**Unadjusted**	**Adjusted**
POD1 MME^{+}		
Wald 1*df*	10.835	8.196
p-value	0.001*	0.004*
OR	1.001	1.001
95% CI	1.000, 1.002	1.000, 1.002
Nagelkerke R^2	0.044	0.071
Hosmer-Lemeshow *p*-value	-0.354	0.389
C-Statistic	0.479	0.648
POD2 MME^{+}		
Wald 1*df*	3.761	3.395
p-value	0.052	0.065
OR	1.004	1.004
95% CI	1. 000, 1.007	1.000, 1.007
Nagelkerke R^2	0.012	0.047
Hosmer-Lemeshow *p*-value	0.228	0.132
C-Statistic	0.465	0.638
POD3 MME^{+}		
Wald 1*df*	3.184	2.807
p-value	0.074	0.094
OR	1.000	1.004
95% CI	1.000, 1.009	0.999, 1.009
Nagelkerke R^2	0.012	0.052
Hosmer-Lemeshow *p*-value	0.016	0.056
C-Statistic	0.519	0.648
Cumulative POD1,2,3^{+}		
Wald 1*df*	11.865	9.134
p-value	0.001*	0.003*
OR	1.001	1.001
95% CI	1.000, 1.002	1.000, 1.002
Nagelkerke R^2	0.048	0.074
Hosmer-Lemeshow *p*-value	0.286	0.677
C-Statistic	0.477	0.654

Note: *significant at 0.05; $^{+}$expressed as parenteral morphine milligrams equivalents. Reference groups: female sex, no DM. Age assessed in years.

Interpretation: Due to continuous nature of the independent factor MME, odds ratios can be interpreted as the percentage increase in the odds of developing CPSP. For example, an OR=1.002, would represent a 0.2% increase in the odds of developing CPSP.

Model adjusted for covariate: Sex, Age, and DM. Omnibus likelihood ratio test of model for POD1 $X^2(4)=19.567$, $p=<0.001$, POD2 $X^2(4)=12.834$, $p=0.012$, POD3 $X^2(4)=13.961$, $p=0.007$ and Cumulative $X^2(4)=20.463$, $p=<0.001$

Legend: CI: Confidence Interval; CPSP: Chronic Post-Surgical Pain; *df*: Degrees of Freedom; DM: Diabetes Mellitus; OR: Odds Ratio; MME: Morphine Milligram Equivalent dose; POD: Postoperative Day

Opioid dose and CPSP at 12 months. Following univariate logistic regression analysis, the morphine milligram equivalent dose of opioids consumed on postoperative day one (unadjusted OR 1.001, 95% CI [1.000, 1.002], $p=0.011$), postoperative day two (unadjusted OR 1.005, 95% C [1.000, 1.009], $p=0.032$), and cumulative dose (unadjusted OR 1.001, 95% CI [1.000, 1.002], $p=0.007$) were found to be significant for an association with the development of CPSP at 12 months.

After adjusting for baseline demographic characteristics—sex and age—the morphine milligram equivalent dose of opioids consumed on postoperative days one (adjusted OR 1.001, 95% CI [1.000, 1.001], $p=0.045$), two (adjusted OR 1.005, 95% CI [1.001, 1.010], $p=0.017$), three (adjusted OR 1.005, 95% CI [1.000, 1.010], $p=0.044$, and cumulative dose (adjusted OR 1.001, 95% CI [1.000, 1.001], $p=0.033$) were found to be significant for an association with the development of CPSP at 12 months after cardiac surgery.

Overall, in the model adjusted for sex and age, with each milligram of morphine equivalent opioid dose consumed on postoperative days one, two, three, as well as cumulatively, there was an increase in the odds or developing CPSP. These increases in odds for CPSP at 12 months were statistically significant.

The model adjusted for sex, age and morphine milligram equivalent opioid dose consumed explained between 10.1% (Nagelkerke R^2 0.101) and 10.6% (Nagelkerke R^2 0.106) of the variance in CPSP at 12 months postoperative. The Hosmer-Lemeshow goodness of fit test was not statistically significant indicating the prediction model for morphine milligram equivalent opioid dose consumed on postoperative day one (p=0.064), day three (p=0.504) and cumulative dose (p=0.251) were a good fit at 12 months postoperatively. However, the Hosmer-Lemeshow for postoperative day two was statistically significant (p=0.038) indicating there is evidence to suggest the prediction model for morphine milligram equivalent opioid dose consumed was not a good fit. Overall, the C-Statistics for postoperative day one (0.723), postoperative day two (0.747), postoperative day three (0.753) and cumulative dose (0.729), indicate the models were a good model at predicting which patients with increased opioid doses and baseline adjusted covariates, would have the outcome of CPSP at 12 months after cardiac surgery (see Table 18: Unadjusted and Adjusted Models for Postoperative Opioid Dose and CPSP at 12 Months).

Table 18

Unadjusted and Adjusted Models for Postoperative Opioid Dose and CPSP at 12 Months

Postoperative Opioid	Unadjusted	Adjusted
POD1 MME^{+}		
Wald 1*df*	6.458	4.013
p-value	0.011*	0.045*
OR	1.001	1.001
95% CI	1.000–1.002	1.000–1.001
Nagelkerke R^2	0.030	0.102
Hosmer-Lemeshow *p*-value	0.410	0.064
C-Statistic	0.660	0.723
POD2 MME^{+}		
Wald 1*df*	4.617	5.689
p-value	0.032*	0.017*
OR	1.005	1.005
95% CI	1.000–1.009	1.001–1.010
Nagelkerke R^2	0.020	0.101
Hosmer-Lemeshow *p*-value	0.110	0.038
C-Statistic	0.721	0.747
POD3 MME^{+}		
Wald 1*df*	3.636	4.058
p-value	0.057	0.044*
OR	1.005	1.005
95% CI	1.000–1.010	1.000–1.010
Nagelkerke R^2	0.017	0.106
Hosmer-Lemeshow *p*-value	0.180	0.504
C-Statistic	0.676	0.753
Cumulative POD1,2,3^{+}		
Wald 1*df*	7.228	4.542
p-value	0.007*	0.033*
OR	1.001	1.001
95% CI	1.000–1.002	1.000–1.001
Nagelkerke R^2	0.037	0.106
Hosmer-Lemeshow *p*-value	0.379	0.251
C-Statistic	0.683	0.729

Note: *significant at 0.05; $^{+}$expressed as parenteral morphine milligrams equivalents. Reference groups: female sex. Age assessed in years.

Model adjusted for covariate: Sex and Age. Omnibus likelihood ratio test of model for POD1 $X^2(3)=18.179$, $p=<0.001$, POD2 $X^2(3)=18.171$, $p=<0.001$ and POD3 $X^2(3)=18.361$, $p=<0.001$, and Cumulative $X^2(3)=19.016$, $p=<0.001$,

Legend: CI: Confidence Interval; CPSP: Chronic Post-Surgical Pain; *df*: Degrees of Freedom; OR: Odds Ratio; MME: Morphine Milligram Equivalent dose; POD: Postoperative Day

Section Three: Multivariable Regression Model

The variables, sex, age, presence of pain '*right now*' at postoperative day three, and milligrams of morphine equivalent cumulative dose were entered in a secondary multivariable regression model for their association with the development of CPSP at six months and 12 months postoperatively. The primary variables in the multivariable regression model were derived from the independent variables which demonstrated a significant association with the development of CPSP at both six months and 12 months after cardiac surgery.

Multivariable Model at Six Months

In the adjusted multivariable model, pain '*right now*' at postoperative day three (adjusted OR 2.279, 95% CI [1.248, 4.162], p=0.007) and milligrams of morphine equivalent cumulative opioid dose (adjusted OR 1.001, 95% CI [1.000, 1.002], p=0.001) were significantly associated with the development of CPSP at six months following cardiac surgery. Age and sex were not statistically associated with the development of CPSP at six months.

Overall, in the adjusted model, for those with moderate to severe pain intensity rated at pain *'right now'* on postoperative day three, there was a two-fold increase in the odds of CPSP at six months after cardiac surgery. In the adjusted model, for each milligram increase of cumulative opioid dose consumed, there was an increase in the odds of developing CPSP at six months. These increases in odds were statistically significant; however, the 95% CI for cumulative opioid dose included the value of one, suggesting that in repeated sampling a non-significant finding for opioid dose as a predictor or CPSP would be likely (Szumilas, 2010).

The model adjusted for age, sex, pain *'right now'* at postoperative day three and cumulative opioid dose explained 9.2% (Nagelkerke R^2 0.092) of the variance in CPSP at six months. The Hosmer-Lemeshow goodness of fit test was not statistically significant (p=0.405),

indicating the prediction model was a good fit at six months. The C-Statistic was 0.678, indicating the model was acceptable for predicting which patients would have the outcome CPSP at six months after cardiac surgery (see Table 19: Adjusted Multivariable Models for CPSP at Six Months and 12 Months).

Multivariable Model at 12 Months

In the adjusted multivariable model, age (adjusted OR 0.939, 95% CI [0.904, 0.975], p=0.001) and pain '*right now*' at postoperative day three (adjusted OR 2.881, 95% CI [1.227, 6.767], p=0.015) were significantly associated with the development of CPSP at 12 months following cardiac surgery. However, sex and cumulative opioid dose were not found to have a significant association with the development of CPSP of at 12 months.

Overall, in the adjusted model, for those with moderate to severe pain intensity rated at pain *'right now'* on postoperative day three, there was a two-fold increase in the odds of CPSP at 12 months following cardiac surgery. In the adjusted model, younger age was significant for an increase in the odds of developing CPSP at 12 months following cardiac surgery. These increases in odds were statistically significant.

The model adjusted for age, sex, pain '*right now*' at postoperative day three and cumulative opioid dose explained 14.2% (Nagelkerke R^2 0.142) of the variance in CPSP at 12 months. The Hosmer-Lemeshow goodness of fit test was statistically significant (p=0.044), indicating there is evidence to suggest the prediction model may not be a good fit at 12 months. The C-Statistic was 0.737, indicating the model was acceptable for predicting which patients would have the outcome CPSP at 12 months after cardiac surgery (see Table 19: Adjusted Multivariable Models for CPSP at Six months and 12 Months).

Table 19

Adjusted Multivariable Models for CPSP at Six Months and 12 Months

Variables	**Adjusted Models For CPSP**	
	6 Months	12 Months
Age		
Wald 1*df*	2.276	10.561
p-value	0.131	0.001*
OR	0.979	0.939
95% CI	0.952, 1.006	0.904, 0.975
Sex		
Wald 1*df*	0.244	0.211
p-value	0.621	0.646
OR	0.851	0.802
95% CI	0.448, 1.615	0.316, 2.036
Pain right now		
Wald 1*df*	7.189	5.902
p-value	0.007*	0.015*
OR	2.279	2.881
95% CI	1.248, 4.162	1.227, 6.767
Cumulative POD1,2,3^{+}		
Wald 1*df*	10.333	3.027
p-value	0.001*	0.082
OR	1.001	1.001
95% CI	1.000, 1.002	1.000, 1.002

Note: *significant at 0.05; $^{+}$expressed as parenteral morphine milligrams equivalents. Reference group: female sex. Age assessed in years. Omnibus likelihood ratio test of model for six months $X^2(4)=24.201$, Hosmer-Lemeshow *p*-value=0.405; Nagelkerke R^2 =0.092, C-Statistic=0.678. Omnibus likelihood ratio test of model for 12 months $X^2(4)=24.049$, *p*=<0.001; Hosmer-Lemeshow *p*-value=0.044; Nagelkerke R^2 =0.142, C-Statistic=0.737.

Legend: CI: Confidence Interval; CPSP: Chronic Post-Surgical Pain; *df*: Degrees of Freedom; OR: Odds Ratio; MME: Morphine Milligram Equivalent dose; POD: Postoperative Day

Summary

To summarize, the study examined whether the following risk factors confer greater risk for the development of CPSP following cardiac surgery at six months and 12 months: i) moderate to severe preoperative anxiety, ii) moderate to severe preoperative depressive symptom, iii) moderate to severe acute postoperative pain intensity, and iv) cumulative postoperative opioid dose consumption.

In a sample of 735 patients, the incidence of CPSP of any intensity was 8.7% at six months and 4.1% at 12 months after cardiac surgery. Following univariate analysis to identify baseline covariates, history of diabetes mellitus prior to surgery and younger age were found to be significant covariates at six months postoperatively, while younger age and sex were found to be a significant covariates at both 12 months after cardiac surgery. These baseline covariates were included to adjust the regression models at the six months or 12 months postoperatively.

Moderate to severe preoperative anxiety and depressive symptom were not found to be significantly associated with the transition to CPSP following cardiac surgery at either six months or 12 months in both unadjusted and adjusted models.

In adjusted models, for those with moderate to severe acute pain intensity rated as pain *'right now'* on postoperative day three, there was a significant association with the development of CPSP at six months and 12 months after cardiac surgery. However, only pain *'right now'* on postoperative day three was significantly associated with the transition to CPSP at 12 months following cardiac surgery. Additionally, in an adjusted model, acute postoperative pain intensity rated as pain *'right now'* on postoperative day three as found to be significantly associated with the intensity of CPSP at six months after cardiac surgery.

In adjusted models, for those with moderate to severe pain intensity rated as '*worst pain in the last 24 hours'* and pain *'right now'* on postoperative day 30, there was a significant association with the transition to CPSP pain at six months. However, acute postoperative pain intensity on postoperative day 30 was not found to be significantly associated with the transition to CPSP at 12 months after cardiac surgery in this sample.

In adjusted models with opioid dose consumed on postoperative day one and cumulative dose, there was a significant association with the transition to CPSP pain at six months. There was a significant association found with opioid doses consumed on postoperative days one, two, three, and cumulative dose, with the transition to CPSP at 12 months following cardiac surgery.

Select independent variables that demonstrated a significant relationship with the transition to CPSP after cardiac surgery were included in an omnibus multivariable regression model. These independent variables include age, sex, pain '*right now*' at postoperative day three and cumulative opioid dose. In the omnibus adjusted model, for patients with moderate to severe pain intensity rated as pain '*right now*' on postoperative day three and cumulative opioid dose there was a significant association with the development of CPSP at six months. On-the-other-hand, age and moderate to severe pain intensity rated as pain '*right now*' on postoperative day three were found to be significant of an association with the transition to CPSP at 12 months following cardiac surgery. Overall, in adjusted models at both six months and 12 months, moderate to severe pain intensity rated at pain '*right now*' on postoperative day three, exhibited a two-fold increase in the odds of developing CPSP following cardiac surgery.

CHAPTER 5: DISCUSSION, CONCLUSIONS AND RECOMMENDATIONS

Discussion, Conclusions and Recommendations

The purpose of this study was to explore the association between the following risk factors and the development of CPSP at six months and 12 months after cardiac surgery: i) moderate to severe preoperative anxiety symptom, ii) moderate to severe preoperative depressive symptoms, iii) moderate to severe acute postoperative pain intensity, and iv) cumulative opioid dose consumption. This chapter discusses the observed study findings with respect to the incidence, covariates, and risk factors associated with the development of CPSP after cardiac surgery. Critical, summative comparisons of these results are made to those of previous studies and recommendations for further research are made.

Study Sample

The sample included 735 adult inpatients who met the inclusion criteria and who had reported outcome data at either six months or 12 months after cardiac surgery. Included study participants were primarily Caucasian (*n*=530, 72.3%), males (*n*=537, 73%) who were 66.99 years of age, on average (SD ± 10.27). The study sample characteristics are similar to those reported in previously published prospective and retrospective cardiac surgery pain-related studies (Choinière et al., 2014; Parry et al., 2010; Steegers et al., 2007; Taillefer et al., 2006; van Gulik et al. 2011).

Incidence of CPSP

The observed incidence of CPSP in the study sample was 8.7% (*n*=54 of 618; females=20, males=34) at six months and 4.1% (*n*=25 of 610; females=11, males=14) at 12 months; these incidence rates are less than those previously reported following cardiac surgery (Meyerson et al., 2001; Ucak et al., 2011). Within the sample, the rate of moderate to

severe CPSP pain intensity (NRS ≥4) was 2.6% (*n*=16 of 618) at six months and 0.7% (*n*=4 of 610) at 12 months after cardiac surgery. These moderate to severe pain rates are similar to those reported in previous studies (Lahtinen et al., 2006, Kalso et al., 2001; Meyerson et al., (2001).

Overall, the incidence of CPSP has been reported to be between 28% (*n*=90 of 318) at one year (Meyerson et al., 2001) and 45% (*n*=9 of 20) at three months after cardiac surgery (Ucak et al., 2011). The variability in CPSP incidence estimates reported may be explained by methodological differences in study settings, sample sizes, lengths of follow-up period, variability in time frame and approaches to CPSP measurement across published studies (Choinière et al., 2014; Gjeilo et al., 2010; Guimarães-Pereira et al., 2017; Jensen & Anderson, 2004; Lahtinen et al., 2006; Lee et al., 2010; Meyerson et al., 2001; van Gulik et al., 2011; van Gulik et al., 2012).

For example, van Gulik et al.'s (2011) prospective single-center cohort study in the Netherlands—aimed at examining the influence of patient baseline demographics and operative characteristics on the incidence of CPSP—measured CPSP at one year after cardiac surgery using the following question: "have you experienced thoracic pain related to the surgery" (p. 1310); required responses were dichotomous (i.e., yes/no). van Gulik et al. (2011) found that 35% (*n*=42 of 120) of patients had CPSP one year after cardiac surgery. The use of a single-center, a small sample size, a single follow-up period of one year and the dichotomous approach to CPSP measurement (i.e., yes/no) may serve to overestimate the incidences of CPSP and may not represent the true incidence estimate in the population. For example, by virtue of answering yes/no to the one question posed, participants of van Gulik et al.'s (2011) study may have indicated a positive response to pain that was not chronic in terms

of duration, as the question does not specify CPSP, per se. Similarly, the single question posed does not distinguish pain resulting from a pre-existing condition (e.g., angina pectoris), or pain from all other causes or sources (e.g., infection); these distinctions are key in terms of accurately defining and reporting CPSP incidence (Kehlet et al., 2006; Macrae, 2008; Weinrib, 2017). As reported, the true incidence of CPSP in this sample is uncertain.

Choinière et al.'s (2014) previously described Canadian prospective multi-center CARD-PAIN study (*N*=1247)—utilized a semi-structured telephone interview to assess the presence of CPSP at 3, 6, 12 and 24 months. Choinière et al. (2014) assessed the presence of CPSP with the following criteria: i) pain "first appeared after surgery, ii) not related to pain felt before surgery or to any other cause, and iii) present for at least 3 months" (p. E215). The three question criteria-based approach found that approximately 40.1% (*n*=423 of 1054) of patients reported pain at 3 months postoperatively. Choinière et al.'s (2014) study was conducted at multiple surgical centers where high surgical volumes and complex cardiac surgeries are being performed. Choinière et al.'s (2014) use of a standardized criteria to detect the presence of CPSP, as well as its scope in terms of being multi-site, and enrolling a large population-representative sample, likely resulted in a more accurate estimation of CSP after cardiac surgery than other studies published to date.

Although there are methodological differences between the prospective observational study designs, it is clear that the issue of CPSP after cardiac surgery is a common problem, and the severity or intensity of CPSP as a postoperative problem is fairly consistent among the studies reviewed. In the current thesis study, the observed rates for moderate to severe CPSP pain intensity (NRS $\geq$ 4 /10), were 2.6% (*n*=16) six months and 0.7% (*n*=4) at 12 months. These rates of moderate to severe CPSP intensity are similar to those reported by Lahtinen et

al. (2006), Kalso et al. (2001) and Meyerson et al. (2001). For example, Lahtinen et al.'s (2006) prospective cohort study (*n*=213), aimed at identifying the incidence and intensity of CPSP one year after cardiac surgery, found that at rest, the incidence of moderate pain intensity was 1% (*n*=1), and the incidence of severe pain intensity was 2% (*n*=2). Upon movement, the incidence of moderate pain intensity was reported at 3% (*n*=5) and incidence of severe pain was reported at 4% (*n*=7) up to one year after cardiac surgery.

A potential limitation of Lahtinen et al.'s (2006) study is that the team used a mailed self-report questionnaire, which assessed pain intensity via the numerical rating scale. Although patients reported experiencing moderate to severe CPSP after cardiac surgery, it is not clear what the time frame over which participants are asked about CPSP (e.g., pain the last 4 weeks), or when pain was last experienced (e.g., last 24 hours, pain now).

To yield true incidence rates of CPSP and related severity after cardiac surgery, it is recommended that global-scale multi-center, prospective cohort studies with representative samples and longitudinal outcome assessment time-points are conducted. Essential to accurately estimating the incidence of CPSP after cardiac surgery is ensuring the presence of CPSP is assessed according to established criteria. For example, i) developed after surgery, ii) present for at least three months in duration, iii) localized to the surgical site and/or projected to an area or dermatome innervated by a nerve at the surgical site, iv) be an extension of acute postoperative pain or develops after an asymptomatic period, v) not a result of a pre-existing condition, vi) all other causes or sources of the pain have been excluded (e.g., infection), and vii) interferes significantly with HRQoL (Kehlet et al., 2006; Macrae, 2008; Weinrib et al., 2017). To further aid global reporting of the true incidence of CPSP and to help identify and manage patients living with CPSP, the diagnosis of CPSP as a chronic secondary pain

syndrome has been added to the ICD-11 codes vis-à-vis the recent collaboration between the IASP and WHO previously discussed in Chapter 3. According to the classification for chronic secondary pain, these "pain syndromes are linked to other diseases as the underlying cause, for which pain may initially be regarded as a symptom" (Treede et al., 2019, p. 22). The classification for chronic secondary pain is important as healthcare providers seek to exclude all other causes or sources of pain and the problem of chronic pain becomes a diagnosis its in own right (Treede et al., 2019). Treede et al. (2019) suggest that allowing for further differentiation among chronic pain states, a co-diagnosis such as chronic peripheral neuropathic pain may be included. The integration of an ICD-11 diagnosis can help healthcare professionals appropriately identify patients with CPSP as well as support the development of prevention strategies.

Covariates Associated With CPSP After Cardiac Surgery

In terms of baseline demographic characteristics, patients' sex, age, and history of diabetes mellitus prior to cardiac surgery were found to have a significant association with the development of CPSP at either six months or 12 months after cardiac surgery.

Age

The mean (± SD) age of the sample was 66.99 (± 10.27) years. Following univariate analysis, the results demonstrated that younger patients in the sample, had an increased odds of developing CPSP at both six months and 12 months after cardiac surgery. In an attempt to identify and target specific age groups who may be at increased odds for CPSP and to corroborate the findings of existing studies, a secondary analysis was conducted to categorize age into groups (i.e., ≤ 65 years, ≥ 66 years). In the present sample, the odds of experiencing CPSP at six months in patients aged ≤ 65 years were 2.037 times greater than patients ≥ 66

years; and the odds of experiencing CPSP at 12 months in patients aged ≤ 65 years were 3.422 times greater than patients ≥ 66 years (unadjusted OR 2.037, 95% CI [1.165, 3.561], *p*=0.013) and (unadjusted OR 3.422, 95% CI [1.457, 8.037], *p*=0.005, respectively).

The observed finding in the current study that younger age is a risk factor for CPSP is similar to results reported in previous prospective studies (Choinière et al., 2014; Gjeilo et al., 2010) and cross sectional and retrospective studies (Bruce et al., 2003; Kalso et al., 2001; Steegers et al., 2007). For example, using GEE analysis, Choinière et al.'s (2014) CARD-PAIN study (*n*=975, mean age 61.9 years [SD ± 10.2]) found the odds for developing CPSP in patients between 21 and 55 years were 1.87 times greater compared to patients over 76 years of age (adjusted OR 1.87, 95% CI [1.09, 3.19]). The GEE model was adjusted for:

> age, sex, persistent nonanginal pain before cardiac surgery, HADS anxiety and depression scores, pain catastrophizing scale scores, SF-12v2 mental and physical health summary scores, duration of surgery, time in hospital after discharge from ICU, average pain in previous 24 hours, worst pain in 24 hours, BPI pain interference score on [postoperative] day 7, and total opioid use (Choinière et al., 2014, p. E220).

Gjeilo et al. (2010) conducted a prospective cohort study (*n*=534) in Norway, aimed at assessing CPSP at six months and 12 months after cardiac surgery. Gjeilo et al. (2010) observed that at 12 months after surgery, there was a significant difference in the median age of patients with CPSP (*n*=52, median age 62.2 years), compared to those without CPSP (*n*= 413, median age 69.8 years) (Mann-Whitney *U* test, *p*-value=0.002). Multiple regression analysis—adjusted for sex, DM, surgical site infection and BMI—showed that patient age (in 10-year groups) was significantly associated with the development of CPSP (*n*=52) (adjusted OR 0.7, 95% CI [0.5, 0.9], *p*=0.001). Although Gjeilo et al. (2010) demonstrated an association between age and the

development of CPSP at 12 months, it is not clear what the 10-year age group categories were that were used for the analysis. The lack of sufficient presentation for categories of data to assess the analytic strategy used to build the model, represents moderate statistical analysis and reporting biases on the quality in prognostic studies (QUIPS) critical appraisal tool (Hayden et al., 2013). The QUIPS tool previously described—was used to assess the methodological quality of prognostic studies reviewed on six domains. Based on appraisal, an overall rating of 'high bias', 'moderate bias' or 'low bias' was assigned for each domain, if there is potential for a risk of bias in the domain (Appendix E: Table 2 Risk of Bias Assessment for Included Studies). The lack of sufficient details reported precludes definitive conclusions about the prognostic utility of age categories on the development of CPSP.

Overall, irrespective of study design and methodological limitations identified, the available evidence supports the findings of the current study that younger age in patients undergoing cardiac surgery confers an increased risk for transitioning to CPSP.

Sex

Within the sample, the odds of males experiencing CPSP at 12 months after cardiac surgery was lower compared to females. Specifically, the odds of females experiencing CPSP was 2.379 times greater than males at 12 months postoperatively (unadjusted OR 2.379, 95% CI [1.056, 5.357], p=0.036). There was no statistically significant difference in the odds of females (unadjusted OR 1.761, 95% CI [0.892, 3.158], p=0.058) experiencing CPSP at six months as compared to males; however, the results trended towards statistical significance.

Similar to the findings of this doctoral study, other prospective studies have found that female sex is associated with increased odds of developing CPSP after cardiac surgery (Choinière et al., 2014; Guimarães-Pereira et al., 2017; van Gulik et al., 2011).

For example, following GEE regression modeling, Choinière et al.'s (2014) CARD-PAIN study (*n*=975, female=204, male=770) found that the odds for developing persistent postoperative pain in females were 1.13 times greater than males over time (adjusted OR 1.13, 95% CI [0.85, 1.50]). Moreover, females were 1.62 times greater odds than males to transition to persistent postoperative pain of moderate to severe pain intensity up to two years after cardiac surgery (adjusted OR 1.62, 95% CI [1.11, 2.35]). van Gulik et al.'s (2011) prospective single-center cohort study (*n*= 120, female=38, male=82) also found similar results. Following multivariable logistic regression analysis, van Gulik et al. (2011) found that female sex was significantly associated with chronic thoracic pain, wherein females were 2.39 times greater odds than males, to develop chronic thoracic pain at one year after sternotomy (OR 2.39, 95% CI [1.01, 5.65], *p*=0.05).

The finding that female sex is a risk factor for CPSP after cardiac surgery is in contrast to what has been found in a number of other prospective (Gjeilo et al., 2010; Markman et al., 2010; Lahtinen et al. 2006), case-control and retrospective/cross-sectional studies (Kalso et al., 2001; Taillefer et al., 2006). For example, Gjeilo et al.'s (2010) single-site Norwegian prospective cohort study (*n*=534, female=121, male=413), aimed at assessing CPSP at six months and 12 months after cardiac surgery, did not find female sex to be a significant risk factor for CPSP at one year after cardiac surgery (binary logistic regression analysis, unadjusted OR 0.8, 95% CI [0.4, 1.7], *p*=0.640). Gjeilo et al. (2010) utilized the Norwegian version of the BPI-SF to assess pain intensity at one year following surgery. One possible explanation for the lack of association between female sex and the development of CPSP at one year is the number of females with CPSP (*n*=10 of 52) as compared to those without CPSP (*n*=91 of 413) in the sample. The small number of females may have been inadequate

statistical power to detect a relationship between female sex and the presence of CPSP, if a relationship existed.

Similarly, Taillefer et al. (2006) conducted a single-site cross-sectional study, to assess the prevalence, characteristics, effect, and predictors of CPSP. Via mailed survey (sent between one year and three years after cardiac surgery) patients were asked to report the presence and severity of pain, as well as pain-related interference in the past four weeks. CPSP was prevalent in 23% (*n*=129 of 564) patients between one year and three years after cardiac surgery. Following univariate logistic regression analysis, Taillefer et al.'s (2006) study (*n*=564, females=146, males=418), did not observe a significant association between female sex and the development of CPSP up to three years after cardiac surgery (unadjusted OR 1.33, 95% CI [0.86, 2.08], *p*=0.205). A possible explanation for the lack of association between sex and the development of CPSP observed may be related to the cross-sectional study design and data collection method used. The cross-sectional study design lacks the temporal sequencing that allows establishment of risk factors antecedent to outcome variables (Wang & Cheng, 2020). Additionally, Taillefer et al.'s (2006) sample had a smaller number of females with CPSP (*n*=38 of 129) up to three years after cardiac surgery, as compared to those without CPSP (*n*=95 of 398). The small number of females may have been inadequate statistical power to detect a relationship between female sex and the presence of CPSP, if a relationship existed.

Beyond the methodological limitations of the available studies, the overall evidence for sex as a risk factor for the development of CPSP after cardiac surgery is equivocal and therefore more research is needed to tease out what effect sex has on the development of CPSP after cardiac surgery (Bjørnnes et al., 2014; Choinière et al., 2014; Gjeilo et al., 2010;

Kalso et al., 2001; Lahtinen et al., 2006; Markman et al., 2010; Parry et al., 2010; Taillefer et al., 2006; van Gulik et al., 2011 & 2012; van Leersum et al., 2010).

Diabetes

Within the sample, the odds of experiencing CPSP at six months in patients with a history of diabetes mellitus prior to cardiac surgery were 1.834 times greater as compared to patients without diabetes mellitus (unadjusted OR 1.834, 95% CI [1.044, 3.222], p=0.035).

Although the current study demonstrated a significant association between a history of diabetes mellitus and the development of CPSP, several published prospective studies (Gjeilo et al., 2010; Markman et al., 2010; Lahtinen et al. 2006; Lee et al., 2010) case-control studies, and retrospective/cross-sectional studies (Costa et al., 2015; Garland et al., 2003; Steegers et al., 2007) have not demonstrated a significant association. The difference between the findings of the current study and the existing evidence may be due to methodological differences in study design, a smaller sample size, and fewer incidences of CPSP after cardiac surgery.

For example, Lee et al., (2010) conducted a prospective single-center Taiwanese study (n=53), aimed at examining predictors and patterns of CPSP after cardiac surgery. At baseline, 22.6% (n=12 of 53) of patients reported a history of diabetes mellitus prior to surgery. At three months postoperatively, 15% (n=8 of 53) of patients reported the presence of CPSP rated at moderate to severe intensity as 'worst pain' (Lee et al., 2010). Following univariate logistic regression analysis, Lee et al. (2010) did not find a significant association between diabetes mellitus and the development of CPSP at three months after cardiac surgery (Wald X^2 0.900, OR 0.0, 95% CI [0.0, 0.0]). The small sample size and lower number of

CPSP events observed in Lee at al.'s (2010) prospective study, may explain the lack of association between diabetes mellitus and CPSP.

The retrospective cohort study designs utilized by Garland et al. (2003) and Steegers et al. (2007) may contribute to the lack of an observed significant relationship between diabetes mellitus prior to cardiac surgery and the development of CPSP, as compared to the current study. Retrospective and cross-sectional studies inherently lack the proper temporal sequence necessary to establish the presence of the exposure before the observed outcome (Song & Chung, 2010). For example, Garland et al. (2003) conducted a multi-center retrospective study (n=422) to identify whether diabetes or peripheral vascular disease was a risk factor for pain and other postsurgical complications (e.g., swelling, wound infection) in the lower limbs following coronary artery bypass grafting surgery in New Zealand. Following multivariate analysis, Garland et al. (2003) did not find a significant association between diabetes mellitus and the presence of CPSP (n=29 of 83) up to four years after cardiac surgery (p=0.22). Similarly, Steegers et al. (2007) conducted a single center, retrospective cross-sectional study (n=256) in the Netherlands, aimed at examining the relationship between angina pectoris and CPSP after cardiac surgery. Steegers et al. (2007), reported that 22% of patients (n=22 of 99) with diabetes developed CPSP, as compared to 14% (n=22 of 157). Following Mann-Whitney U test, no statistically significant associations was found between diabetes and CPSP at least three months after cardiac surgery (p=0.07). Overall, the retrospective and cross-sectional study designs do not situate diabetes mellitus as antecedent to the development of CPSP; as such, these designs are not well-positioned to define sub-groups of patients at risk for CPSP, an adverse outcome, or allow more accurate prediction of disease and patient outcomes (Mak & Kum, 2005; Song & Chung, 2011).

Beyond the methodological limitations of these study designs, evidence indicates that the pathogenesis of diabetes mellitus negatively affects the micro-environment of peripheral nerves and neural pathways, which may determine how people experience pain and diabetic-related neuropathy (Irwin, 2004). It has been hypothesized that the change in the experience of pain may be related to systematic inflammation associated with the pathogenesis of diabetes mellitus seen in other surgical patient populations (Rajamäki et al., 2015). Potentially, the natural course of deterioration of the pre-existing neural micro-environment as it pertains to baseline diabetes mellitus prior to cardiac surgery needs to be further examined in the basic and clinical research to provide more insight on how diabetes mellitus becomes a precursor to predicting CPSP.

To summarize, it is clear that the patient's age, sex and history of diabetes mellitus prior to cardiac surgery can influence the experience of CPSP at either six months or 12 months after cardiac surgery; however, the exact strength of prognostic significance of how these baseline covariates affect CPSP remains unclear. Methodological variances such as study design (i.e., retrospective/cross sectional studies), small sample size, and small incidences of CPSP reported by the studies examined to date may explain the observed differences in the evidence. Overall, more robust prospective studies, conducted with population representative samples, should be conducted to bolster confidence in the conclusion that baseline covariates such as age, sex, and diabetes mellitus are associated with the development of CPSP after cardiac surgery.

Anxiety and Depressive Symptoms

The research questions were to identify: i) what is the association between moderate to severe preoperative anxiety and depressive symptoms and the development of CPSP after cardiac surgery, and ii) if an important association was observed, what is the association between severity of preoperative anxiety and depressive scores and the intensity of CPSP.

The present thesis study found that patients had a mean (± SD) baseline anxiety score of 43.97 (± 5.059), with the majority of patients reporting moderate anxiety (85%, *n*=629 of 735). Specifically, for patients who developed CPSP at six months (*n*=54), there was a mean (± SD) anxiety score of 44.63 (± 5.048); of these patients, 81.5% (*n*=44 of 54) had moderate to severe anxiety symptoms at baseline. For patients with CPSP at 12 months (*n*=25), there was a mean (± SD) score of 45.96 (± 6.426); of these patients, 84% (*n*=21 of 25) reported moderate to severe anxiety symptom at baseline. Overall, mean baseline state anxiety scores were higher in patients who developed CPSP at 12 months after cardiac surgery.

This study also found that patients had a mean (± SD) baseline depressive symptom score of 8.08 (± 1.583), with the majority of patients reporting mild depressive symptom (66%, *n*=483 of 735). Specifically for patients who developed CPSP at six months (*n*=54), there was a mean (± SD) depressive score of 7.93 (± 1.439); of these patients, 96% (*n*=52 of 54) had mild depressive symptom at baseline. For patients with CPSP at 12 months (*n*=25), there was a mean (± SD) depressive score of 8.08 (± 1.824); of these patients, 88% (*n*=22 of 25) reported mild depressive symptom at baseline. Overall, mean baseline depressive symptom score was higher in patients who developed CPSP at 12 months after cardiac surgery.

Following adjusted logistic regression analysis—adjusted for sex, age and history of diabetes mellitus prior to cardiac surgery—the presence of moderate to severe preoperative anxiety or moderate to severe depressive symptom were not statistically significant for an association with the presence of CPSP at six months or 12 months.

In an attempt to identify if, the presence of any level of state anxiety or depressive symptoms would confer risk for increased odds of CPSP secondary analyses were conducted which examined STAI Form Y-1 state anxiety and HADS depressive symptom scores as

continuous independent variables. Univariate unadjusted logistic regression analysis indicated that preoperative anxiety score, as a continuous variable, was significant for an association with the development of CPSP at 12 months after cardiac surgery. Specifically, for each unit increase in preoperative anxiety scores, the odds of patients experiencing CPSP at 12 months were 1.092 times greater, compared with patients with lower anxiety scores at baseline. While not statistically significant, (i.e., $p<0.05$), the *p*-values for depressive symptom score, as a continuous variable, may suggest a trend towards statistical significance at 12 months in unadjusted ($p=0.075$, OR 3.176, 95% CI [0.889, 11.350]) and adjusted models ($p=0.089$, OR 3.216, 95% CI [0.835, 12.382]).

At baseline, patients had a mean (± SD) 43.97 (± 5.059) anxiety score, suggestive of overall moderate anxiety; however, the SD around the estimate, i.e. ± 5.059, suggests that the lower limits falls on the low-moderate anxiety range. The SD suggests that at baseline anxiety scores could be as low as 38, or as high as 49. This variance may explain why a significant association was observed with anxiety scored as a continuous variable in an unadjusted model, but not significant for an association in other adjusted models at either six months or 12 months after cardiac surgery. Similarly, the majority of patients had a normal or mild depressive symptom mean (± SD) score 8.08 (± 1.583) at baseline, which was not associated with an increased risk in the odds of developing CPSP.

The results of the current study are consistent with those of Choinière et al.'s (2014) CARD-PAIN study ($n= 1,010$) who found that the presence of baseline depressive symptom—measured by the HADS—was not significantly associated with the development of CPSP after cardiac surgery. Following GEE modeling, Choinière et al. (2014) did not show a significant association between baseline depressive symptom with the presence of CPSP (adjusted OR 0.98,

95% CI [0.93, 1.04]) or the intensity of CPSP (adjusted OR 1.00, 95% CI [0.92, 1.07]) at two years after cardiac surgery.

In contrast, the current study findings differs from those of Choinière et al. (2014) who reported preoperative anxiety symptoms were significantly associated with the development of CPSP. For example, following GEE modeling, Choinière et al., (2014), found that, at baseline, the presence of anxiety was a predictor for the presence of any persistent postoperative pain at two years after cardiac surgery (adjusted OR 1.04, 95% CI [1.00, 1.09]). However, baseline anxiety was not a predictor of the intensity of CPSP observed (adjusted OR 1.04, 95% CI [0.99, 1.10]). The GEE modeling the association between the presence of anxiety with the presence of CPSP was adjusted for:

> age, sex, persistent nonanginal pain before cardiac surgery, HADS anxiety and depression scores, pain catastrophizing scale scores, SF-12v2 mental and physical health summary scores, duration of surgery, time in hospital after discharge from ICU, average pain in previous 24 hours, worst pain in 24 hours, BPI pain interference score on [postoperative] day 7, and total opioid use (Choinière et al., 2014, p. E220).

The GEE modeling the association between the presence of anxiety with the intensity of CPSP was adjusted for:

> sex, CCS class, persistent nonanginal pain before cardiac surgery, HADS anxiety and depression scores, pain catastrophizing scale scores, SF-12v2 mental and physical health summary scores, time in ICU, time in hospital after discharge from ICU, average pain in previous 24 hours, BPI pain interference score on [postoperative] day seven, and total opioid use (Choinière et al. 2014, p. E221).

Although the CARD-PAIN study (Choinière et al., 2014) demonstrated an association between anxiety and CPSP at two years, the lower limit of the 95% confidence interval included the value of one, and the study did not report an associated *p*-value. Taken together this may indicate the possibility of a null association between baseline anxiety and CPSP in the real world (Szumilas, 2010), with repeated population sampling. Additionally, the difference observed in the evidence for an association between anxiety and CPSP may be attributable to methodological differences between the current study and Choinière et al.'s (2014) study with respect to the tools used to measure preoperative anxiety, the cut-off scores of the instruments used to determine severity of anxiety, as well as the rates of CPSP events reported after cardiac surgery.

For example, in the current study, preoperative anxiety symptom was assessed by the Spielberger STAI Form Y-1, via 20 item questionnaire. The STAI Form Y-1 scores are categorized as mild (score 20-39), moderate (score 40-59), and severe (score 60-80) anxiety (Spielberger, 1983). At approximately half of the total score, a score of 40 would suggest a moderate level of state anxiety. In the current study, preoperative state anxiety was analyzed as a categorical variable, specifically comparing moderate to severe scores with mild severity scores. However, Choinière et al. (2014) measured baseline anxiety as a continuous variable using the HADS, via a seven-item questionnaire. According to Zigmond and Snaith (1983), a score zero to 10 represent normal to mild symptoms, scores 11 to 14 represent moderate symptoms and scores 15 to 21 represent severe depressive symptom. This category would suggest that approximately half of the total scores ($\leq$ 10 of 21), would represent mild anxiety symptoms. Choinière el at., (2014) utilized the baseline HADS scores as a continuous variable, wherein the presence of any anxiety symptom, not severity of anxiety symptoms, may be a predictor for CPSP after cardiac surgery. While both tools have demonstrated validity and reliability in surgical populations, it

fundamental to understand that the cut off scores that determine the presence and severity of anxiety for each tool differs. Consequently, using each tool on the same sample to assess severity of anxiety would potentially yield different numbers of people who are categorized as having mild, moderate and severe anxiety symptoms.

To summarize, the evidence pertaining to anxiety and depressive symptom as a risk factor for CPSP is equivocal. The current study does not show an association between severity of baseline anxiety and depressive symptom with the development of CPSP. However, the secondary analysis, suggest a trend towards baseline anxiety and depressive symptoms having a significant association with the development of CPSP up to one year after cardiac surgery. Methodological variances such as the instruments used to measure anxiety and depressive symptoms, how each independent risk factor is examined (i.e., categorical or continuous), and the number of CPSP cases reported at follow up may explain the observed differences in the evidence. Overall, more robust prospective studies, conducted with population representative samples, and valid instruments should be conducted to bolster confidence in the conclusion that baseline anxiety and depressive symptoms may confer risk for the development of CPSP after cardiac surgery.

Acute Postoperative Pain

With respect to acute pain intensity, the research question was to explore the association between moderate to severe acute postoperative pain intensity and the development of CPSP. If an important association was identified, to further explore the association between moderate to severe postoperative pain intensity and the intensity of CPSP after cardiac surgery.

In the current study, the BPI-SF was used to measure acute pain on postoperative days three and 30, and CPSP at six months and 12 months. The BPI-SF measured the presence and

location of pain via five items: '*worst in the last 24 hours while lying*', '*worst in the last 24 hours while moving*', '*least in last 24 hours*', '*average pain in last 24 hours*' and pain '*right now*' (Cleeland, 2009).

In models adjusted for baseline demographic and clinical characteristics, the odds of experiencing CPSP in patients with moderate to severe pain intensity rated as pain *'right now'* on postoperative day three were 2.263 times greater, and 2.749 times greater at six months and 12 months (adjusted OR 2.263, 95% CI [1.255, 4.081], p=0.007; adjusted OR 2.749, 95% CI [1.174, 6.441], p=0.020, respectively); and on postoperative day 30 were 2.913 times greater at six months after cardiac surgery, as compared to those with no pain/ mild pain (adjusted OR 2.913, 95% CI [1.304, 6.505], p=0.009).

Following a secondary linear regression analysis, the current study also demonstrated a significant association between the intensity of acute postoperative pain with the intensity of CPSP after cardiac surgery. Specifically, in the adjusted model—sex, age, and diabetes mellitus—acute postoperative pain intensity rated as pain *'right now'* on postoperative day three (Unstandardized Beta 0.587, 95% CI [0.143, 1.031], p=0.013) and postoperative day 30 (Unstandardized Beta 0.760, 95% CI [0.405, 1.115], p=0.001) were significantly associated with the intensity of CPSP at both six months. For each one unit increase in the intensity of acute pain '*right now*' on postoperative day three the intensity of CPSP increases by 0.5 and for each unit increase in acute pain '*right now*' on postoperative day 30, the intensity of CPSP increases by 0.7 units. Therefore, if the association between severity of acute postoperative pain and CPSP holds true, by keeping acute pain in the no/pain to mild pain intensity, the likelihood of patients developing CPSP of moderate to severe intensity decreases.

The results of the current study are consistent with the existing published prospective evidence, which demonstrates that the presence and intensity of acute postoperative pain is associated with the development of CPSP after cardiac surgery. However, the temporal nature of pain, the timing of acute postoperative pain outcome assessment, and the psychometric properties of the tools used to assess pain may account for some of the variation in results reported. The variance in the timing of when associations are observed suggest 'moving targets' for modification of acute pain intensity as a putative risk factor for development of CPSP. For instance, Choinière et al. (2014) CARD-PAIN study, assessed pain intensity at postoperative days one, two, three, and seven via the BPI. Choinière et al. (2014) found that moderate to severe acute pain intensity on postoperative day three was a predictor for both the presence and intensity of CPSP at two years after cardiac surgery. Specifically, on postoperative day three, the odds for developing moderate to severe intensity CPSP in patients who reported moderate to severe acute pain intensity for *'average pain in the last 24 hours'* were 1.48 times greater (adjusted OR 1.48, 95% CI [1.10, 2.00]); patients who reported moderate to severe acute pain intensity for *'worst pain in the last 24 hours*' were 1.69 times greater (adjusted OR 1.69, 95% CI [1.16, 2.47]); and patients who reported moderate to severe acute pain intensity for *'average pain in the last 24 hours'* were 2.67 times greater at 24 months after cardiac surgery (adjusted OR 2.67, 95% CI [1.74, 4.11]). Although Choinière et al. (2014) used the BPI for outcome assessment, the temporality of the assessments differ. Choinière et al. (2014) assessed pain only in the context of movement, while the current study found that pain '*right now*' was also significant. The variance in the temporal assessment of CPSP further adds to the burden to identify key targets for intervention.

In a similar prospective cohort study, Lee et al. (2010) (*n*=53), also found that acute postoperative pain intensity was associated with the development of CPSP. Using the numerical rating scale (NRS), Lee et al. (2010) dichotomized the severity of pain to indicate none to mild pain (NRS 0 to 4) and moderate to severe pain (NRS 5 to 10). Via interview questions, Lee et al. (2010), measured the intensity of acute postoperative pain on postoperative days seven, 10, and 30 to indicate *'worst pain in the last 24 hours'* and *'average pain in the last 24 hours'*. Lee et al (2010) found that the odds for experiencing moderate to severe CPSP in patients who reported *'worst pain in the last 24 hours'* at POD 30 were 1.451 times greater at three months after cardiac surgery compared to those who did not report worst pain (OR 1.451, 95% CI [1.043, 2.019]). Lee et al.'s study offers a different interpretation on the NRS measurement scale. In the current study, NRS four to six would indicate moderate pain intensity, however, Lee et al., (2010) includes the NRS value of four to indicate mild pain intensity. The difference in the interpretation of the measurement tool does not allow appropriate comparisons to be made about the intensity of postoperative pain.

The prospective cohort study (*n*=213), conducted by Lahtinen et al.'s (2006) also found acute postoperative pain intensity was associated with the development of CPSP after cardiac surgery. Using the NRS rated 0='no pain' to 10='worst pain imaginable', acute pain was assessed on postoperative days four and 30 after cardiac surgery. Lahtinen et al. (2006) found that moderate to severe acute postoperative pain intensity was associated with the development of CPSP at 12 months after cardiac surgery (Wilcoxon signed-rank test, *p*-value=0.042). However, Lahtinen et al. (2006) did not specify if postoperative day four or day 30 was associated with the CPSP outcome. The lack of sufficient details reported precludes definitive

conclusions about the prognostic utility of the timing of acute postoperative pain with the development of CPSP in the study by Lahtinen et al. (2006).

Overall, there is a need to standardize timing of assessment in order to allow critical comparisons to be made across the pain literature, as well as overcome over- and underestimation of incidence and prevalence rates (Guimarães-Pereira et al., 2017).

In terms of the psychometric properties of the BPI used in the current study: the BPI was used to measure the presence and location of pain as '*worst pain in the last 24 hours while lying*', '*worst pain in the last 24 hours while moving*', '*least pain in last 24 hours*', '*average pain in the last 24 hours*' and pain '*right now*' (Cleeland, 2009) on postoperative days three and at 30 days follow-up. However, these assessment options may potentially limit the patient's ability to rate '*worst pain*' and '*average*' if their worst pain was experienced greater than 24 hours prior to data collection in the acute postoperative period, at six months, or 12 months follow-up. It is plausible that patients' could have experienced *'worst pain'* or higher pain intensities outside of the 24 hours outcome assessment timeframe. For example, at the six month postoperative outcome assessment, if the participant experienced moderate to severe pain (NRS ≥4 of 10) at 48 hours prior to data being collected, this pain experience would not be captured as part of worst pain, or average pain experienced with the BPI-SF 24 hour recall timeframe. In cases where higher moderate to severe pain intensity was experienced outside of the 24 hours prior to data collection, the pain intensity captured as '*average*' pain intensity, may dilute the magnitude of effect seen and preclude definitive conclusions about the prognostic utility of pain intensity as a putative risk factor for transition to CPSP after cardiac surgery.

Existing evidence has demonstrated acceptable reliability and validity of the BPI-SF as an assessment tool to measure the temporal nature of pain in several cardiac surgery patient

studies (Fathi et al., 2014; Koivula et al., 2001; Novy et al., 1993; Spielberger, 1983; van Knippenberg et al., 1990). The IMMPACT consensus confirms that postsurgical pain research to date does not give sufficient attention to the measures of the temporal aspects of pain (Dworkin et al., 2005). These temporal aspects include the severity, frequency of pain, the timing, and duration of pain relief measures (Dworkin et al., 2005). Attention to identifying measures that have demonstrated appropriate psychometric properties with the least participant burden should also be considered in the design of cardiac surgery studies (Dworkin et al., 2005; Turk et al., 2003). It is therefore recommended that future large-scaled multi-center prospective cardiac surgery studies should be designed with consideration for the temporal aspects of pain assessment and reporting tools, and the IMMPACT recommendations for outcomes assessments to specifically identify the crucial postoperative timing and pain intensity measures that confers the risk for CPSP, as well as corroborate findings in the available evidence (Dworkin et al., 2005; Turk et al., 2003).

Cumulative Opioid Dose

With respect to cumulative opioid dose, the question was to examine the association between cumulative opioid dose consumed in the first three postoperative days and the development of CPSP after adjusting for baseline demographic and clinical characteristics.

In models adjusted for sex, age and diabetes, cumulative opioid dose consumed as morphine milligram equivalent dose, was observed to have a significant association with the development of CPSP at both six months (adjusted OR 1.001, 95% CI [1.000, 1.002], p=0.003) and 12 months after cardiac surgery (adjusted OR 1.001, 95% CI [1.000, 1.001], p=0.033). Of specific clinical relevance, is the fact that for each five milligram increase in cumulative opioid

dose consumed during the first three postoperative days, patients were 1.05 times greater odds for developing CPSP at both six months and 12 months after cardiac surgery.

The findings in the current study are similar to those reported by Taillefer et al.'s (2006) with respect to the association between cumulative opioid dose and CPSP after cardiac surgery. Taillefer et al. (2006) conducted a cross-sectional study in Canada (N=579), aimed at assessing the prevalence, characteristics, and predictors of CPSP. Following cardiac surgery, hospital charts were reviewed and audited, relevant medical, surgical and postoperative opioid medication data were extracted and converted into parenteral morphine equivalents doses, using standard dosing tables (Taillefer et al., 2006). Via mailed self-report follow-up surveys, Taillefer et al. (2006) collected follow-up data between one and three years after cardiac surgery. Taillefer et al. (2006) found that the average total amount of opioids consumed on the surgical ward in patients with CPSP was significantly more than total amounts consumed by patients who did not develop CPSP (mean 18.1 mg, mean 11.7 mg, respectively, Pearson X^2, p=0.018). Multivariate logistic regression analysis showed that cumulative opioid dose consumed on the surgical ward during the first postoperative week was significantly associated with the development of CPSP after cardiac surgery (adjusted OR 1.05, 95% CI [1.00, 1.10], p=0.0320). Taillefer et al. (2006) found that for every five mg increase in the total amount of opioids received on the surgical ward, the patient was 1.05 times greater odds for developing chronic postoperative pain.

Overall, Taillefer et al.'s (2006) study suggests that postoperative cumulative opioid dose may be associated with CPSP following cardiac surgery. However, methodological limitations related to study design restrict the inference made about cumulative opioid dose as a putative risk factor for the development of CPSP after cardiac surgery. For example, Taillefer et al. (2006) employed a cross-sectional study designed, which inherently collects both risk factor and

outcome data at the same time. The cross-sectional study design lacks the temporal sequence that allows establishment of risk factors antecedent to outcome variables (Wang & Cheng, 2020). Additionally, Taillefer et al. (2006) used a self-report mailed survey to collect outcome data. The use of a mailed questionnaire for follow-up data collection (more than a year after cardiac surgery), presents an opportunity for recall bias and sample selection bias. Participants may have had difficulty with accurately recalling their pain intensity up to 29.9 (SD ± 10.5) months after their cardiac surgery, and as such this presents an opportunity for risk of bias in the outcome measurement (Appendix E: Risk of Bias Assessment of Included Studies).

The findings of the current study and Taillefer et al.'s (2006) study findings add to the emerging evidence in support of an association between cumulative opioid dosing and CPSP; however, the literature remains mixed. The variance observed may be explained by differences in methodological limitation such as smaller samples sizes, fewer cases of CPSP observed at outcome measurement, the postoperative intensive care unit and ward settings, and the timing of when cumulative opioid doses are consumed. For instance, Choinière et al.'s (2014) multi-center, prospective study CARD-PAIN study (n=975)—previously described, involved a review and audit of hospital charts for relevant medical, surgical and postoperative opioid medication data. Data for the first seven days after cardiac surgery was extracted and converted into parenteral morphine equivalents doses, using standard dosing tables (Choinière et al., 2014). Cumulative opioid dose during the first seven days after surgery was not found to be a significant predictor for the presence or intensity of CPSP up to two years after surgery (adjusted OR 1.00, 95% CI [1.00, 1.00]; (adjusted OR 1.00, 95% CI [1.00, 1.00], respectively). It is plausible that examining cumulative opioid dose after the third postoperative day dilutes the magnitude of association that cumulative opioid dose has with the development of CPSP.

In another multi-center prospective study (previously described), Lee et al. (2010) (*n*=53) completed a chart review similar to the current thesis sub-study, to extract relevant medical, surgical and total opioid medications used during and after cardiac surgery. Opioid dose was converted into milligrams of morphine equivalent dose (Lee et al., 2010). Univariate logistic regression analysis showed that opioid dose consumed on the 'day of surgery' (Wald X^2 1.192, unadjusted OR 1.022, 95% CI [0.275, 1.022]) and during the 'first postoperative week' (Wald X^2 0.146, unadjusted OR 1.003, 95% CI [0.986, 1.021]) were not significantly associated with CPSP at three months after cardiac surgery. Lee et al.'s (2010) study may be under-powered to detect an association between cumulative opioid dose and the development of CPSP at three months after cardiac surgery, due to the lack of samples size calculation and the small sample enrolled (*n*=53).

Overall, there are methodological differences between the studies that could explain the variances in findings across studies as it relates to opioid dose as a putative risk factor for CPSP after cardiac surgery. However, there is some evidence to suggest that genetics and hormones may play a role in the relationship between opioid consumption and pain intensity. For example, Ren et al. (2015) conducted a systematic review (*n*=59) and meta-analysis (*n*=23) to assess the influence of genetics on opioids used for acute postoperative pain relief. Ren et al. (2015) found that there was a significant association between genetics, the dose of opioids consumed and higher acute postoperative pain intensity scores. Although genetics was found to have an association with both opioid consumption and pain intensity, the interaction with other confounding non-modifiable covariates, (i.e., sex, and age)—that have demonstrated an association with development of CPSP must be considered.

In summary, the available evidence examined to date remains mixed in relation to the association between postoperative opioid dose consumption and the transition to CPSP following cardiac surgery. Methodological differences between studies could explain differences in results reported. However, what remains clear is that pain is a complex subjective experience that requires a dynamic approach to assessment, measurement and management. The role of opioid dose consumption as a risk factor for CPSP following cardiac surgery, should be examined in large robust, multi-center prospective samples that examine both prescribing and administration practices following cardiac surgery patients

Relevance of Pain Mechanism and Pain Theory to the Predictors of CPSP

Pain is not a simple sensory experience, but rather it is a complex phenomenon determined by—sensory-discriminative, motivational-affective, and cognitive-evaluative factors (Melzack & Katz, 2013; Basbaum & Jessell, 2000). Like other types of pain, post-surgical pain following cardiac surgery is subjective and complex. In what follows, the relevance of pain mechanisms and theory are examined in relation to the variables examined in this study.

Cardiac Postsurgical Pain: Sensory-Discriminative. During the intraoperative and acute postoperative period the combination of nociceptive, inflammatory and neuropathic pain mechanisms, as well as endogenous neurotransmitters (i.e., opioids) contribute to the variability of pain severity and play a sensory-discriminative role in the perception of pain (Kehlet et al., 2006). The interaction between these pain mechanisms may serve to further explain the results observed with respect to an association between i) acute postoperative pain intensity and CPSP, ii) cumulative opioid dose and CPSP, in this current study as well the dissimilarities between the existing literature.

For instance, intraoperatively, following the initial incision and the surgical manipulation of tissue, muscle, and bones during cardiac surgery, sensitizing pro-inflammatory cell mediators (i.e., cytokines, bradykinins and prostaglandins) are released, activating peripheral nociceptors (Kehlet et al., 2006). High threshold sensory nociceptors continue to respond to noxious chemical stimuli (e.g., medications used intraoperatively), mechanical stimuli (e.g., blade incision), and thermal stimuli (e.g., increased temperature during cauterization) during the surgical procedure resulting in peripheral sensitization (Kehlet et al., 2006). Neuronal excitement is transmitted via afferent Aδ and C-fibers to the dorsal horn of the spinal cord resulting in central sensitization (Kehlet et al., 2006; Woolf & Salter, 2000). Repeated and progressive increase in noxious stimuli resulting from tissue retraction and tissue manipulation associated with multiple vessel harvesting, intensifies the neuronal excitement resulting in dorsal horn windup of the afferent C-fibers (Katz & Seltzer, 2009; Kehlet et al., 2006; Woolf & Salter, 2000). Intense noxious stimuli also activate the release of pain modulating glutamate and peptide neurotransmitters (e.g., endomorphins and enkephalins) into the dorsal horn, these endogenous neurotransmitters activate the μ-opioid receptor mediated anti-nociceptive system (Guan et al., 2006). Within a few seconds to minutes, the initiation and mediation of the nociceptive system is activated, however, the response and duration continues well after the noxious stimuli has been removed (Guan et al., 2006). Additionally, further pro-inflammatory responses occur with the insertion of sternal wires for breastbone closure intraoperatively. Care is normally taken to employ nerve-sparing incisional approaches during cardiac surgery; however, damage may be inflicted to the peripheral nerves (i.e., brachial plexus, phrenic nerve, and saphenous nerve) in the process of harvesting either the internal mammary artery or the saphenous vein used for

cardiac bypass grafting; this neural damage results in the precursor for future neuropathic pain (Kleiman et al., 2017; Sharma et al., 2000).

Over the first three postoperative days, there may be changes in how the nociceptive, inflammatory and neuropathic pain mechanisms respond to stimuli. For example, although the initial noxious stimuli from the cutting of the tissue activated the nociceptive pain mechanism, has been removed, the trauma to the tissue and the associated inflammation will persist for a few days postoperatively. Given the recent injury and trauma to the nerves and tissues, these may become hypersensitive to typical activities that are not noxious in nature. As such, movement and activity (e.g., walking, coughing), can trigger a primary hyperalgesic response, as the patient attempts to do activities (e.g., walking) of daily living or prevent postsurgical complications such as deep vein thrombosis (Milgrom et al., 2004). Intrinsically, the nociceptive mechanism, may not be solely responsible of the experience of acute pain *'right now'* in postoperative days three and 30, but instead the inflammatory and neuropathic mechanisms also may be responsible. The findings of the current study support this conclusion, as patients reported mild pain intensity (mean 2.24, SD ± 2.43) as pain '*right now*', but moderate intensity '*pain in the past 24 hours while lying*' (mean 4.27, SD ± 2.92) and '*pain in the past 24 hours with movement*' (mean 4.76 SD ± 2.82) on postoperative day three. However, it cannot be stated definitively, as to which pain mechanism or mechanisms are responsible for acute postoperative pain, as no validated instruments (e.g., neuropathic pain questionnaire) were used to assess pain characteristics for a neuropathic component. A limitation of the current study is the lack of neuropathic pain assessment following cardiac surgery. This study was a sub-study of FORESITE-VISION, and there were no staffing resources in FORESITE to allow for additional data collection during

telephone-based follow up, given that study personnel were time pressured while running multiple clinical studies in parallel.

With a clearer understanding of pain mechanisms—nociceptive, inflammatory, and neuropathic—and the fact that the body's anti-nociceptive system is responsible for the mediation of endogenous opioids, it stands to reason that in the acute postoperative period i) the need for higher cumulative opioid dose would indicate that patients are experiencing pain, ii) the current treatment is not optimal, and iii) possibly one or more pain mechanism is/are culpable for both acute postoperative pain, and CPSP after cardiac surgery. To understand the association between pain mechanisms, pain intensity and cumulative opioid dose fully, it is recommended that large-scaled prospective studies, guided by IMMPACT recommendations for systematic and temporal pain assessment, characteristics (e.g., movement, rest, sharp, dull, etc.) and discriminative features (e.g. neuropathic pain questionnaire) be conducted at each postoperative follow-up time point.

Cognitive-Evaluative. In the context of the cognitive-evaluative role of Gate Control Theory, understanding how patients cognitively appraise their impending cardiac surgery and their available coping mechanisms has implications for how patients may cognitively evaluate and interpret pain and other complications postoperatively. The current study findings demonstrated that although patients reported moderate to severe preoperative situational anxiety and depressive symptom these baseline symptoms did not play a major role in conferring an increased risk for the development of CPSP at six months or 12 months after cardiac surgery. The small number of events of CPSP observed at six months (n=54) and 12 months (n=25) may be attributed to the lack of a significant association with moderate to severe intensity of preoperative anxiety and depressive states.

Motivational-Affective. In the context of the motivational-affective aspects of pain, it is important to understand how patients utilize different coping strategies and behaviours to manage their pain. Via a chart audit, the current study collected data on the use of pharmacological agents used for acute postoperative pain relief during the first three postoperative days, however, the study did not collect data on non-pharmacological coping strategies used for pain management. Evidence in the available pain literature have demonstrated that non-pharmacological and complement therapies such as yoga (Guddeti et al., 2019), cannabis (Martín-Sánchez et al., 2009), music-therapy (Sendelbach et al., 2006), massage, mindfulness and relaxation therapy (Anderson & Cutshall, 2007; Bauer et al., 2010; Kattan et al., 2002), distraction and coping activities (e.g., social support) have been shown to reduce the perception of both acute and CPSP after cardiac surgery. Moreover, the evidence demonstrates that males and females utilize different coping strategies and behaviours to manage their pain; wherein, males opted to use problem-focused and behaviour-related strategies, while females opted to use cognitive, emotional and social strategies to manage their pain (Bartley & Fillingim, 2009; Fillingim et al., 2009; Racine et al., 2012).

Availability of data on pharmacological and non-pharmacological coping strategies could have further elucidated the motivational-affective aspects of the pain experience following cardiac surgery. Primarily, conclusions can be made as to the types of motivational-affective strategies patients with and without acute and chronic pain use for pain management. It is recommended that in future studies, attention to pain coping strategies and behaviours are explored to provide interpretative context for pain.

Summary

The purpose of this study was to explore the association between the following risk factors with CPSP at six months and 12 months after cardiac surgery: i) moderate to severe preoperative anxiety symptoms, ii) moderate to severe preoperative depressive symptoms, iii) moderate to severe acute postoperative pain intensity, and iv) cumulative opioid dose consumption. The sample included 735 adult inpatients who met the inclusion criteria and who had reported outcome data at either six months or 12 months after cardiac surgery. The observed incidence of CPSP was 8.7% at six months and 4.1% at 12 months. These observed incidence are lower than current global estimates.

Overall, the findings of the current study suggest that younger age in patients undergoing cardiac surgery conferred an increased risk for developing CPSP. At baseline, the odds of males developing CPSP at 12 months after cardiac surgery was lower as compared to females. The presence of diabetes mellitus prior to cardiac surgery increased the odds of developing CPSP at six months. The findings of the current study adds to the available evidence base as to the role of age, sex, and a history of diabetes as significant putative risk factors for CPSP after cardiac surgery.

In terms of risk factors-tenably modifiable through nursing intervention, the current study found that moderate to severe preoperative anxiety and depressive symptoms were not significantly associated with the development of CPSP at six months or 12 months after cardiac surgery. Acute postoperative pain intensity, rated as pain '*right now*' was significantly associated with the development and intensity of CPSP after cardiac surgery. Cumulative opioid dose consumed up to three days postoperatively, had a significant association with the development of CPSP at both six months and 12 months after cardiac surgery. These findings

add to the available evidence base on the role of each putative risk factor in the development of CPSP after cardiac surgery, as well as offer targets for nursing intervention.

Overall, methodological variances such as study design, sample sizes, outcome measurement tools used to assess the presence and intensity of pain in the studies examined to date explain the observed differences in the evidence. However, bio-physiological mechanisms, such as genetics and hormones may offer plausible explanations for the difference in the observed results with respect to diabetes and opioid, and an association with the development of CPSP, compared to the existing evidence.

In order to bolster confidence in the conclusions of the study findings, where: age, sex, diabetes, preoperative anxiety and depressive symptom, acute postoperative pain intensity, and cumulative opioid dose are examined for an associated with the development of CPSP after cardiac surgery, future research should include large scaled prospective studies, conducted with population representative samples, validated anxiety and depressive instruments, validated pain measurement instruments, and designed with attention to IMMPACT recommendations.

CHAPTER 6: IMPLICATIONS FOR NURSING

Implications for Nursing

Evidence to date demonstrates that serious complications (e.g., pain, infection) occur after cardiac surgery, however, the most common complication, i.e. unrelieved postoperative pain, is being 'underdiagnosed' and 'undertreated' (Kleiman et al., 2017). This section describes the implications of the study results for nursing research, education, and practice.

Research

The overall findings of this study add to the growing body of literature surrounding modifiable risk factors and the development of CPSP after cardiac surgery.

Anxiety and Depressive Symptom

This study did not demonstrate a significant association between preoperative anxiety and depressive symptoms with the development of CPSP up to one year after cardiac surgery. However, this does not signify that there is no clinical relevance to examining modification of perioperative anxiety and depressive symptom in patients undergoing cardiac surgery. The findings of the study confirm that at baseline a large number of patients experienced moderate to severe perioperative anxiety and depressive symptoms. In the larger pain-related literature, existing evidence demonstrates that anxiety and depressive symptoms had negative effects on pain perception, physical and psychological recovery, as well as HRQoL (Craig, 2006; Blair et al., 2003; Theunissen et al., 2012; Turk et al., 2010).

Following a review of the literature on the psychological effects of cardiac surgery, Gardner and Worwood (1997) suggested that psychological preparation for cardiac surgery should be patient focused. Patient's may utilize different cognitive appraisal and motivational-affective strategies to cope with their stressors, as such nurses should be knowledgeable of

various non-pharmacological interventions that could be implemented to reduce the patient's anxiety and depressive symptom, in order to aid postoperative recovery. For instance, Leegaard and Fagermoen (2008) conducted a synthesis of qualitative studies that explored patients' experiences after cardiac surgery. Leegaard and Fagermoen (2008) found that patients expressed the need of supportive relationships as a major theme. Patients expressed they received reassurance through information provided by staff and the presence of staff reduced their anxiety in the perioperative periods (Leegaard & Fagermoen, 2008).

In order to get a better understanding of psychological risk factors and their role in the development of CPSP, additional nursing research should be conducted to examine how patients cognitively appraise their impending cardiac surgery, their perception of pain, as well as, what motivational coping strategies they use to manage their stressors during the perioperative period.

Acute Postoperative Pain and Opioid Consumption

In terms of research, several studies have examined the association between perioperative risk factors and the transition to CPSP following cardiac surgery (Choinière et al., 2014; King et al., 2008; Lahtinen et al., 2006; Lee et al., 2010; Steegers et al., 2007; van Gulik et al., 2011). The vast majority of risk factors identified are not tenably modifiable by nurses; however, the results of the current study suggest there may be a role for the nurse to intervene with respect to patients' acute postoperative pain intensity and cumulative opioid dose consumption in the early postoperative period. More large-scaled prospective studies, with systematic and comprehensive pain assessments, are needed to offer modifiable targets for front line nurses to advocate and administer appropriate pharmacological and non-pharmacological interventions to optimize pain relief after cardiac surgery. More nurse-led intervention studies that seek to offer nurse-modifiable risk factors (e.g., pain management, pharmacological and non-pharmacological

interventions/strategies) should be conducted to enable positive patient outcomes and support nursing practice.

One such nurse-led study currently underway is McGillion et al.'s (2016) TecHnology Enabled Self-MAnagemenT–VIsion for Remote Automated Patient Monitoring and EmpoWerment Following Cardiac and VasculaR Surgery (SMArTVIEW). McGillion et al.'s (2016) international collaborative randomized controlled trial seeks to enroll 800 patients in Canada and the United Kingdom. SMArTVIEW, is an e-health enabled program that employs remote monitoring, education, coaching and interactive self-management training program to reduce postoperative pain and other complications (e.g., surgical site infections, hospital readmissions) up to five weeks after cardiac surgery.

SMArTVIEW remote automated monitoring and self-management intervention, is divided into two stages: stage one is focused on remote automated monitoring and pain management education while the patient is in hospital; stage two is focused on specially trained hospital cardiac and vascular trained nurses, virtually interfacing and remotely monitoring and supporting patients after their discharge home and for the 5 weeks of the intervention (McGillion et al., 2016). The remote monitor for patients involves the use of blue-tooth enabled devices to transmit vital signs (e.g., blood pressure), and interactive patient symptom and self-report surveys that assess postoperative recovery (McGillion et al, 2016). Should vital signs or self-reported symptoms trigger the early warning alert system, nurses will be able to triage and prioritize follow-ups with patients and conduct virtual video visits, assessments and counseling (McGillion et al., 2016).

The educational self-management component of SMArTVIEW is called Restore and Recover. As the PhD student on the trial, I led the development of this aspect of the intervention.

Restore and recover espouses an approach to patient recovery self-management which recognizes that following cardiac surgery, patients and health partners (e.g., family) are vulnerable and not well-prepared to manage their postoperative pain and recovery after cardiac surgery. To tackle this, Restore and Recover provides online, interactive education and nursing support for day-to-day decisions and behaviours that patients engage in, with direct linkage to patients' own goals for management of their health and their recovery experience. For example, Week zero of the curriculum, while the patient is still in hospital, the self-management education is focused on acute pain assessment, wherein, the patient is introduced to the pain scale and how to ask ward nurses for help with pain management when their pain is not in the mild range (NRS >4/10) (McGillion et al., 2016). Week two of the curriculum—while the patient is at home, the curriculum focuses on fear-avoidance, mindfulness and relaxation strategies, as cognitive-affective interventions (McGillion et al., 2016).

A large scaled randomized controlled trail such as SMArTVIEW, developed with considerations for IMMPACT recommendations, allows prospective data collection, offers opportunity for patients to self-report data (e.g., pain intensity) consistently, learn and manage postoperative pain management strategies, as well as allows patients to learn cognitive and motivational coping and self-management strategies that will reduce postoperative complications during their recovery. More nurse-lead studies such as SMArTVIEW are needed to evaluate the nurse led-interventions that have been developed and implemented for cardiac surgery patients' recovery.

Education

Anxiety and Depressive Symptom

It is within the scope of nursing to identify potentially vulnerable patients at any point in the perioperative period and offer education (i.e., health teaching, coping strategies) as well as to communicate with the interdisciplinary team as an advocate for hospital or community resources for patients experiencing anxiety and depressive symptoms. For example, Kalogianni et al. (2016) conducted a randomized controlled trial (*n*=395, intervention group=205, control group=190) in Greece, to assess the effectiveness of a nurse-led preoperative education program on anxiety and patient outcomes following cardiac surgery. Anxiety levels were assessed via the Spielberger STAI at three periods: three to four days preoperatively, the day of surgery, and at discharge (Kalogianni et al., 2016). The intervention—a 20 to 40 minute face-to face education program was delivered by trained program nurses (Kalogianni et al., 2016). The education program consisted of an educational booklet, as well a discussion on procedure-related details, and psychoeducational skills (i.e., breathing and coughing exercises, pain management, strategies to control anxiety, meditation) to use after cardiac surgery (Kalogianni et al., 2016). The intervention nurse answered questions regarding postoperative pain and pain management (Kalogianni et al., 2016). Patients allocated to the standard care group received standard postoperative teaching which consisted of unstructured, verbal information about the procedure, from the surgeon, anesthetist, and the cardiac surgery nurses (Kalogianni et al., 2016). Kalogianni et al. (2016) found that preoperative education was effective in significantly reducing mean (± SD) anxiety scores over time from three to four days (36.1 ± 9.6), the day of surgery (34.0 ± 8.4), and prior to discharge (29.1 ± 6.5) in the intervention group (*p*-value=0.001, repeated measurement analysis of variance), as compared to the control group (37.7 ± 10.6),

(36.9 ± 10.7), (34.6 ± 10.2), respectively. The findings add to the evidence that nursing led interventions that offer perioperative health teaching and coping strategies are feasible and effective in reducing negative emotional distress during the perioperative period.

Nursing Practice

Acute Postoperative Pain and Cumulative Opioid Dose

The results of this current study demonstrated a significant association between moderate to severe pain intensity in the acute postoperative period (i.e., day three and 30) and cumulative opioid dose in the first three postoperative days, with the development of CPSP up to one year after cardiac surgery.

What is clear is that patients are experiencing moderate to severe pain intensity when assessed by nurses on the surgical ward, i.e., *'right now'*, and that there is ineffective pain management in the acute postoperative period. It can be reasoned that ineffective acute pain management may be related to ineffective nursing assessment surrounding the impact of unrelieved pain on recovery and interventions—both pharmacological and non-pharmacological. Moreover, it may be the case that patients are under-reporting their pain intensity in an effort to be stoic, or avoid consumption of opioids as a pain relief measure. Cumulative published studies on cardiac surgery patients have demonstrated that patients are concerned about not 'bothering' the nurse and that they want to be what they perceive as 'good patients' who do not ask for help with pain control (Cogan, 2010; Cogan et al., 2014; Leegaard & Fagermoen; 2008; Watt-Watson et al., 2001; 2004).

For instance, Cogan et al. (2014), conducted a prospective study to examine the knowledge and beliefs of cardiac surgery patients. Via the Barriers Questionnaire, Cogan et al. (2014) identified that 31% of patients' perceived addiction was a barrier to pain relief, 36% of

patients believed that pain management interventions should be taken only when pain worsens or is severe in intensity, and 20% of patients believed that voicing concerns about pain does not make you a 'good patient'.

Akin to patients' beliefs about pain management, is the patients' confidence with the nurses' pain knowledge and clinical practice. Patients may also under-report their postoperative pain because they do not belief the nurse possesses the knowledge and or skills to effectively manage their pain. For instance, in Leegaard and Fagermoen's (2008) qualitative synthesis, "fear" emerged a major theme and 'staff making mistakes' was a sub-theme (Leegaard & Fagermoen, 2008). Patients expressed a theme of fear with respect to staff lacking information about postoperative pain management medications following cardiac surgery (Leegaard & Fagermoen, 2008). Leegaard and Fagermoen (2008) thematic analysis highlights the patients' perspective in the need for nurses to be knowledgeable and clinical practice about pain medications in order to bolster confidence in their ability to effectively manage postoperative pain.

Key to effective pain management is understanding the scope of nursing in the decision making and pain management process. At the forefront, the role of nursing is to complete systematic and comprehensive pain assessments, as well as to advocate for multi-modal pharmacological and non-pharmacological pain relieving strategies (RNAO, 2013). The RNAO (2013), clinical best practice guidelines for assessment and management of pain confirm that the nurses' scope of practice requires the nurse to possess the knowledge, skill and clinical competency to employ appropriate pain management interventions. However, patient's postoperative pain remain under-treated. For example, Watt-Watson et al. (2001) conducted a descriptive correlational study (*N*=94 nurses, 225 patients) to examine the relationship between

nurses pain knowledge and postoperative pain management following cardiac surgery. Watt-Watson et al. (2001) found that within the 24 hours prior to data collection on postoperative day three, approximately 86% of patients experienced moderate to severe pain, and nurses administered 47% of their prescribed analgesia. Furthermore, 51% of patients experienced severe pain prior to the next scheduled dose (Watt-Watson et al., 2001). The under-medication of patients was significantly related to inadequate nurses' knowledge (r=0.52, p-value=<0.007). Overall, Watt-Watson et al. (2001) found that nurses need confirmation of their role, their nursing interventions related to pain management, as well as their patient's assessments. Fear and biases associated with opioid-related negative outcomes, such as addiction or constipation, following opioid use, may explain the reason for patients not voluntarily asking for pain medications in the acute postoperative period.

The study found that for each morphine equivalent dose of cumulative opioid received, the patient was more likely to develop CPSP. This finding is an important consideration for nurses as increased pain medication use is reflective of unrelieved pain that requires control. As nurses perform pain assessments, the need for increased opioid consumption to achieve adequate acute postoperative pain relief should serve as a warning flag to nurses, i) to implement pharmacological and non-pharmacological pain interventions, ii) advocate for multimodal treatment options, iii) identify the patient in the early acute postoperative period as being vulnerable for CPSP, and work collaboratively with the healthcare team and the patient to minimize their risk for CPSP after cardiac surgery.

Strengths and Limitations

The current study has several strengths. The study's methodological strengths include its prospective design and large cohort of adult inpatients following cardiac surgery. The primary focus of the study was to examine the risk for, potentially nurse modifiable risk factors: perioperative anxiety, preoperative depressive symptom, acute postoperative pain intensity and cumulative opioid dose on the development of CPSP following cardiac surgery. A prospective cohort is ideal for establishing the correct temporal relationship, wherein perioperative risk factors (i.e., preoperative anxiety, preoperative depressive symptom, acute postoperative pain intensity and cumulative opioid dose consumption) are situated as antecedents to the development of CPSP outcomes at either six months or 12 months after cardiac surgery.

Additionally, the findings of the study, add to the available evidence base as to the role potentially nurse-modifiable risk factors may play in the development of CPSP following cardiac surgery. The findings can be used to further corroborate the existing literature as well as guide clinical decision making in the clinical setting. Prospective study designs are suitable to guide clinical decision making as they aid with identifying sub-groups of patients at risk for an adverse outcome as well as allow more accurate identification of risk factor, given the temporal sequencing (Song & Chung, 2011). The findings offer nursing a means to identify, potentially at-risk patients as well as implement evidence based strategies, to prevent negative health outcomes. The available findings further fill the gap on the pain-related evidence in the Canadian context.

A limitation of the study is the small number of patients that reported CPSP at both six months (n=54) and 12 months (n=25) after cardiac surgery. The small number of patients with CPSP, may limit the extent to which the findings can be generalized to patients following cardiac

surgery. Similarly, another limitation of the current study includes the extent to which the findings can explain the role of moderate to severe preoperative anxiety and depressive symptom, acute postoperative pain intensity and opioid usage in the transition to CPSP. For example, the study did not complete detailed neurophysiological examinations, nor perform sensory assessments to further offer context and explanation of the observed results in the sample. Therefore, the study is unable to evaluate the role of altered neuropathic mechanisms in the development of CPSP. The FORESITE study and current thesis sub-study, utilized multiple data collection instruments. Adding a neuropathic assessment tool may potentially add a burden for the patients to complete and was not feasible for data collection staff. The present consensus for IMMPACT recommendations suggest consideration be given for respondent and administrator burden and feasibility when designing and evaluating potential core outcome measurements (Turk et al., 2005).

Another limitation of the current study is the use of self-reported pain measurements and pain intensity via the NRS (0-10). Given the complex and multi-dimensional nature of pain, a multimodal pain measurement assessment would offer a comprehensive assessment. In order to increase rigor in the current study, a criteria based approach was used to establish the presence of CPSP and validated instrument was used for outcome data collection. The three question criteria, helps to differentiate CPSP from pre-existing pain and non-surgery related pains at outcome assessment at six months and 12 months. Similarly, the BPI assessed pain via five items: '*worst in the last 24 hours while lying down*' '*worst in the last 24 hours while moving*', '*least pain in last 24 hours*', '*average pain in the last 24 hours*' and pain '*right now*' to further capture the context of/ and trend of pain in the last 24 hours, these ensured rigor was maintained in the assessment of pain outcomes.

Lastly, the current study did not examine pain-related interference as an outcome, as pain-related interference and functional status were outcome variables examined in FORESITE (McGillion et al., 2019). Following this thesis and completion of the FORESITE study, results pertaining to pain-related interference in FORESITE will be taken into consideration for future intervention development, along with the results of this FORESITE sub-study. Therefore, the importance of pain-related interference as an outcome will not be overlooked in the overall FORESITE research program.

Conclusion

In conclusion, the observed incidence rates indicate that CPSP after cardiac surgery is still a major health and clinical problem up to one year postoperatively. Pain perception is a complex multidimensional phenomenon that involves several bio-psychological, emotional and behavioral reactions. Negative emotions may be associated with the anticipation of pain, may be an outcome of pain, or may represent a problem concomitant with pain. Existing literature suggests that aversive emotions qualities (e.g., anxiety, depressive symptom) are frequently observed in individuals prior to surgery, and have a temporal and correlated relationship with CPSP following various surgeries. However, the degree to which moderate to severe anxiety and depressive symptom predict CPSP after cardiac surgery, was not observed in this study up to 12 months postoperatively. The lack of observed association may be attributed to the small number of reported events of CPSP at both six and 12 months after cardiac surgery.

Acute postoperative pain intensity and cumulative opioid dose were found to be significant predictors for the development of CPSP up to 12 months after cardiac surgery. The findings of this study add to the growing body of literature surrounding modifiable risk factors and the transition to CPSP. Pain assessment and the administration of opioid doses to manage

acute postoperative pain are feasible and modifiable targets for nursing intervention in the perioperative period.

The role of nursing includes identifying and advocating for vulnerable patients, at risk of psychological morbidity and acute postoperative pain. Nursing is also charged with completing systematic and comprehensive pain assessment, utilizing evidence-based pain management strategies (i.e., pharmacological and non-pharmacological), and educating patients on the management of pain and opioid related side effects.

Finally, in terms of research, and to truly appreciate the complex nature of pain management, a truly expansive exploratory approach has to be taken in order to examine pain transition in the perioperative context. Nursing should collaboratively design large-scale prospective studies with population representative samples, using validated instruments, to support additional insights into modifiable targets that may be amendable to nursing interventions in the perioperative context. It is recommended that the findings of this doctoral study be replicated to bolster confidence in the observed associations between acute postoperative pain intensity and cumulative opioid dose with the development of CPSP after cardiac surgery. For future research, additional data should be collected on the types of non-pharmacological strategies used to minimize pain experiences postoperatively, as well as, information on nursing and patient beliefs regarding opioids.

THE END

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Appendix A

Search Methodology

Evidence on CPSP

Search method. An electronic database search of the health sciences literature was conducted using CINAHL, Cochrane Library, Embase, Medline, PsycINFO, ProQuest Dissertations and Thesis Database to find available research studies that examined anxiety, depressive symptoms, acute postsurgical pain and opioid analgesic as predictive risk factors for the development of CPSP following cardiac surgery.

To ensure relevant studies were retrieved for inclusion, variations were made to subject headings, medical subject heading (MeSH) terms and key search words. Multiple combinations for key words were used in the database search. These key words include: 'OR' combinations of:

Search strategy one: *"coronary artery bypass graft", "CABG", "cardiac surgery", "cardiovascular surgery", "heart surgery"*

Search strategy two: "*post-surgical*", "*postsurgical*", *"post-operative", "postoperative", "postop", "post-op", "postoperative pain", "pain"*

Search strategy three: *"chronic pain", "persistent pain", "chronic postoperative pain", "chronic postsurgical pain"*

Search strategy four: *"acute pain", "acute post-op pain", "acute postoperative pain", "acute postsurgical pain", "pain severity", "pain intensity"*

Search strategy five: *"psychological morbidity", "psychological factor", "anxiety", "nervous", "apprehension", "anxious", "depression", "depressive symptomatology"*

Search strategy six: *"analgesia",* "*analgesic*", "*morphine dose*", "*morphine equivalent*", *"narcotic"*, "*opioid", and "pain medication"*

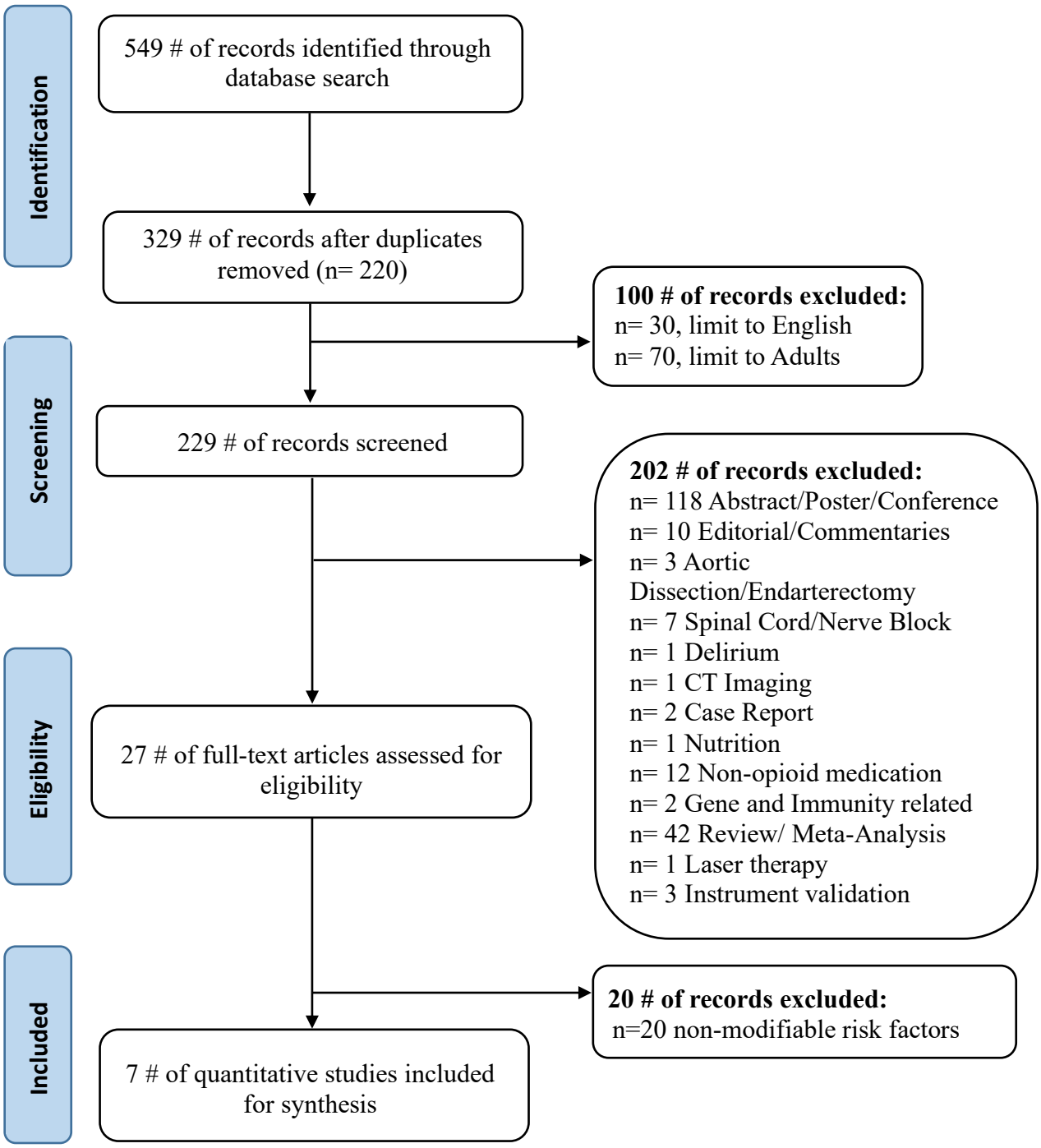
To form the population (P) and outcomes (O) of interest, search strategies one, two and three were combined with 'AND', resulting in search strategy seven. Each search strategy (i.e., four, five, six) was combined with 'AND' to search strategy seven to form the population (P), exposure (E) and outcomes (O) of interest. In addition, a Health Sciences Librarian was consulted throughout the literature search process to refine search terms and strategies to retrieve the best available evidence.

Appendix B

PRISMA Flow Diagram of Literature Search

Figure 1

Flow Diagram of Literature Search



Appendix C

Summary of Included Studies

Author/ Year	Date/ Location	Purpose	Design/ Instrument	Follow-up	Sample Size	Results	Strengths/Limitations
Choinière et al., (2014)	2005-2006; Canada	Find prevalence of CPSP up to 24months after cardiac surgery and to identify risk factors for its presence and severity	Prospective study (4 centres) **Instruments**: Canadian Cardiovascular society grading scale, Hospital Anxiety and Depression Scale; Pain Catastrophizing Scale; SF-12v2 Health Survey	3, 6, 12, 24 months postoperative	*N*=1275, (*n*=770 males, *n*=226 females)	3-month prevalence = 40% (*n*= 423/1054) 6-month prevalence = 22% (*n*= 226/1023) 12-month prevalence = 17% (*n*= 167/1011) 24-month prevalence = 10% (*n*= 93/976)	**Strength:** 1) Prospective design, multicenter, large cohort and 2 years follow up **Limitation:** 1) Reports based on self-reported pain (Reporting Bias). 2) Detailed neurological examinations and quantitative sensory testing were not performed to assess the presence of sensory abnormalities in the area of surgery (e.g. hyperesthesia) in the preoperative and postoperative periods. Therefore, unable to evaluate the potential role of altered pain processing due to intraoperative nerve injury or to some general pre-dispositional factors in the development of pain.
Lee et al., (2010)	Surgery date not reported: Taiwan	Describe the pattern of pain in the first 3 months following cardiac surgery and examine the predictors of surgery-related chronic pain	Prospective study (3 centres) **Instruments:** Pain intensity measured with NRS (0 to 10); The 7-item negative effect belief subscale (of 10-item pain Opioid Analgesics Beliefs Scale - validity and reliability reported	Preoperative day before surgery, 7 days, 10 days, 1 month and 3 months after surgery Survey-face to face interview at the bedside, telephone interview after discharge.	(*N*=53)	Patients (*n*=5/8) with chronic pain at 3-months reported higher levels of negative beliefs in opioids use (Mean=2.91, SD±0.62) compared to patients without chronic pain (*t*= -2.58, p<0.05) Univariate logical regression: A greater likelihood of chronic pain at 3-months postop was associated with higher worst pain intensity 30 days after surgery (OR=1.451, Wald = 4.878, *p*<0.05, 95% C.I. 1.043, 2.019) and more negative beliefs in opioid use (OR=1.225, Wald=5.419, *p*<0.05, 95% C.I. 1.036, 1.512)	**Limitations:** 1) Pre-surgical measure to report pain at all sites and from all possible causes (Confounding/Performance bias). Pain at a single site before surgery (e.g. chest/cardiac pain) might be a significant predictor of developing chronic pain after surgery, but the most important for predictive pain problem might not have been adequately assessed at pretreatment. 2) The sample and the number of patients with CPSP might have been too small for adequate power to detect smaller and more subtle associations between some predictors and the development CPSP (Performance bias) 3) The small sample size contributed to even smaller subsamples of participants.

CPSP=chronic post-surgical pain, CI=confidence interval, OR=odds ratio, NRS=numerical rating scale

Summary of Included Studies

Author/ Year	Date/ Location	Purpose	Design/ Instrument	Follow-up	Sample Size	Results	Strength/ Limitation
Lahtinen et al., (2006)	Surgery date not reported; Finland	Evaluate the incidence and intensity of pain, patients expectations and recovery after CABG sternotomy	Prospective study (1 centre) **Instruments:** intra-op question, POD4, mailed questionnaire, Post-op 1, 3, 6 & 12 months. Telephone call for unreturned questionnaire.	1-day preoperative; POD 4, 1 month, 3 months, 6 months and 12 months postoperative	*N*=213 Males (*n*=176), Females (*n*=37)	Incidence of pain at 12 months= 39% (*n*=73/186), 20% (*n*=40/186) had leg pain, and 14% (*n*=28/186) had pain at both sites Postoperative day 4: 7% (*n*=14/213) patients had severe postop pain and 67% (*n*=143/213) had mild to moderate pain Those patients who had moderate to severe acute post-op pain (NRS>3) were more likely to have any CPSP (NRS1-10) at rest 1 year post op (*p*= 0.042).	**Strength:** 1) Prospective design, 1-year follow up, 2) 85% response rate. **Limitation:** 1) Re-operated patients were included in the sample (Confounding/ Performance bias) 2) No formal sample size calculations were made, estimated sample size (Performance bias). 3) Pain intensity reporting on POD 4 was grouped mild to moderate with 67% (*n*=143), it would have been clearer to report mild and moderate rates as separate numbers, given differing intensities and potential role as a prognostic factor (Bias in statistical analysis and reporting). 4) OR not reported, so uncertainty of magnitude of effect size, given power in sample size, not calculated (Statistical reporting analysis bias) . 5) Inability to distinguish between different types of pain (somatic, neuropathic, visceral and scar pain)
Taillefer et al., (2006)	1999-2002; Canada	Assess the prevalence, characteristics, effect and predictors of chronic postoperative pain 1 to 3 years after cardiac surgery	Cross-sectional (single centre) **Instrument:** Mailed questionnaire, NRS, HRQL – SF-36, HADS	1 to 3 years postoperative	*N*=579, (*n*=418 males, *n*=146 females)	CPSP prevalence = 23% CPSP: Mean 5.1, SD±4.3 No CPSP: Mean 2.9, SD±3.1, *p*=000	Anxiety and depression variable not included in multiple regression (*p*-value does not meet multi-variable inclusion criteria)

CABG=coronary artery bypass graph, CPSP=chronic post-surgical pain, OR=odds ratio, POD=postoperative day, SD=standard deviation

Summary of Included Studies

Author/ Year	Date/ Location	Purpose	Design/ Instrument	Follow-up	Sample Size	Results	Strength/ Limitation
King et al., (2008)	Surgery dates not reported; Canada	Examine incision and breast pain and discomfort, and their predictors in women at 12 months following sternotomy	Extension survey following RCT (10 Canadian centres) in original trial. Standardized interview in hospital and via telephone following hospital discharge. Pain and discomfort measured 'yes/no'	5 days, 3 months, 12 months	(*N*=326 females) Mean age 66.35, SD ±11.17	18% (*n*=59) patients reported pain at 12 months 79.7% (*n*=47/59) patients had pain at 3 months; 46.6% (*n*=152) patients reported any discomfort at 12 months 77.0% (*n*=117/152) had discomfort at 3months; Logistic regression models: incisional pain and discomfort, breast pain at 12 weeks and discomfort predicts CPSP.	**Strength**: Primary focus on female patients **Limitation:** 1) Only women who participated in the original trial were eligible, posing a potential for selection bias in the cohort (Risk of bias for study participation). 2) Clear definition of pain and discomfort were not provided (Risk of bias prognostic factor). 3) Adequate information was not provided regarding the description of the population, baseline sample, the period and place of recruitment. No formal sample size calculations were made, as this was an extension trial to only WREST females. 4) Pain and discomfort scores were dichotomized (presence/absence), unable to make a comment on any change in intensity of these symptoms over the course of follow-up. 5) Although the groups were similar in characteristics, the majority of the women in the intervention group received compression undergarments, may have impacted the experience of pain. While having less women from the usual care group, may have impacted the prevalence (Risk of bias for Outcome measurement and Study confounding).

CPSP=chronic post-surgical pain, SD=standard deviation

Summary of Included Studies

Author/ Year	Date/ Location	Purpose	Design/ Instrument	Follow-up	Sample Size	Results	Strength/ Limitation
Steegers et al., (2007)	Jan 1, 2003-Dec 31, 2003; Netherlands	Investigate the role of angina pectoris in long term pain after CABG	Retrospective/ Cross-sectional;(single hospital) **Instruments:** demographics, questions on the period before CABG surgery, the 1st week after surgery, and the period 3-months after surgery. Rose Angina Questionnaire; pain intensity and description; pain location; and medication and non-medication treatments; activity restriction	Data collection between 9-21 months	*N*=256 (*n*=211 males, n=45 females; Mean age= 65 (SD±10)	Incidence of acute post-operative pain showed a positive correlation with the incidence of CPSP (Spearman R=0.54, $p<0.05$)	**Strengths**: 1) Response rate of 73%, higher than previously published studies of 62%. 2) Pain arising after surgery and persisting either continuously or intermittently for ≥3 months **Limitation:** 1) Retrospective design and limitation of self-reported pain in the context of the questionnaire (Recall bias/ Prognostic Factor). 2) Time interval between questionnaire and date of surgery could be expected to influence recall of pain experienced during the acute and subacute phase after surgery (Recall bias). 4) Difference between responders and non-responders, more females in non-responder group, do not know if the pain was equally distributed between responders and non-responders (Study Participation bias). 5) Pain descriptors used were purely descriptive and do not allow reliable classification regarding underlying cause of the post-op pain (valid instrument not used) (Outcome measurement bias) 6) Observed effect sizes not reported (statistical analysis & reporting bias)

CABG=coronary artery bypass graph, Post-op=postoperative, SD=standard deviation

Summary of Included Studies

Author/ Year	Date/ Location	Purpose	Design/ Instrument	Follow-up	Sample Size	Results	Strength/ Limitation
van Gulik et al., (2011)	June 28 - August 18, 2006; Netherlands	To examine the influence of patient demographics and peri- and postoperative characteristics on the incidence of chronic thoracic pain 1 year after cardiac surgery, as well as the impact of chronic thoracic pain on daily life.	Prospective cohort (single centre) **Instrument** Questionnaire based on McGill Pain Questionnaire. Pain was rated on NRS scale '0' denotes no pain and '10' indicates the maximum pain imaginable. NRS 4 was considered severe pain.	Postoperative Days 0 to 7 and 10-12 months after surgery	*N*=120 enrolled	'Worst' Day 29.2% (*n*=35) reported chest pain NRS ≥4. Multivariate analysis showed non-elective surgery (OR 4.2, 95% CI: 1.29, 13.84, p=0.02), re-sternotomy during admittance, (OR 3.38, 95%CI: 1.08, 10.54, p=0.04) severe pain (NRS ≥4) on postoperative day 3 (OR 2.89, 95%CI: 1.15, 7.23, p=0.02), and Sex (OR 2.39, 95%CI: 1.01, 5.65, p=0.05) were independent predictors of CPSP. 35% (*n*=15/42) patients with CPSP reported sleep disturbance due to pain, compared to those without CPSP (1.3%, *n*=1/78) (Mann—Whitney U-test, p<0.001). 33.3% (*n*=14/42) Patients with CPSP reported more analgesic use compared to those without CPSP (1.3%, *n*=1/78) (Mann—Whitney U-test, p<0.001). 14.3% (*n*=6/42) stated pain impacted daily life, work	**Strength:** 1) prospective study identifying predictors of CPSP. **Limitation:** 1) Included 13% (*n*=16) patients with non-elective surgery and 15% (*n*=18) with re-sternotomy, although these may be viable surgical characteristics, the increased numbers, may not be truly representative of the cardiac surgery population as it relates to non-elective and re-sternotomy (Study Participants & Confounding bias. 2) The small sample size may not be adequate to power the study (Risk of bias Prognostic Factor, & Statistical Analysis and Reporting). 3) Outcome measurement interview survey was based on McGill Questionnaire, however, no report of reliability and validity assessments (Risk of bias Outcome measurement)

CI=confidence interval, CPSP=chronic post-surgical pain, NRS=numerical rating scale, OR=odds ratio

Appendix D

Quality in Prognostic Studies (QUIPS) tool

Domains	Prompting items for Consideration	Ratings
Study Participation	a. Adequate participation in the study by eligible persons b. Description of the source population or population of interest c. Description of the baseline study sample d. Adequate description of the sampling frame and recruitment e. Adequate description of the period and place of recruitment f. Adequate description of inclusion and exclusion criteria	**High bias:** The relationship between the PF and outcome is very likely to be different for participants and eligible nonparticipants **Moderate bias**: The relationship between the PF and outcome may be different for participants and eligible nonparticipants **Low bias**: The relationship between the PF and outcome is unlikely to be different for participants and eligible nonparticipants
Study Attrition	a. Adequate response rate for study participants b. Description of attempts to collect information on participants who dropped out c. Reasons for loss to follow-up are provided d. Adequate description of participants lost to follow-up e. There are no important differences between participants who completed the study and those who did not	**High bias**: The relationship between the PF and outcome is very likely to be different for completing and non-completing participants **Moderate bias**: The relationship between the PF and outcome may be different for completing and non-completing participants **Low bias**: The relationship between the PF and outcome is unlikely to be different for completing and non-completing participants
Prognostic Factor Measurement	a. A clear definition or description of the PF is provided b. Method of PF measurement is adequately valid and reliable c. Continuous variables are reported or appropriate cut points are used d. The method and setting of measurement of PF is the same for all study participants e. Adequate proportion of the study sample has complete data for the PF f. Appropriate methods of imputation are used for missing for missing PF data	**High bias**: The measurement of the PF is very likely to be different for different levels of the outcome of interest **Moderate bias**: The measurement of the PF may be different for different levels of the outcome of interest **Low bias**: The measurement of the PF is unlikely to be different for different levels of the outcome of interest

Outcome Measurement	a. A clear definition of the outcome is provided b. Method of outcome measurement used is adequately valid and reliable c. The method and setting of outcome measurement is the same for all study participants	**High bias**: The measurement of the outcome is very likely to be different related to the baseline level of the PF **Moderate bias**: The measurement of the outcome may be different related to the baseline level of the PF **Low bias**: The measurement of the outcome is unlikely to be different related to the baseline level of the PF
Study Confounding	a. All important confounders are measured b. Clear definitions of the important confounders measured are provided c. Measurement of all important confounders is adequately valid and reliable d. The method and setting of confounding measurement are the same for all study participants e. Appropriate methods are used if imputation is used for missing confounder data f. Important potential confounders are accounted for in the study design g. Important potential confounders are accounted for in the analysis	**High bias:** The observed effect of the PF on the outcome is very likely to be distorted by another factor related to PF and outcome **Moderate bias:** The observed effect of the PF on outcome may be distorted by another factor related to PF and outcome **Low bias:** The observed effect of the PF on outcome is unlikely to be distorted by another factor related to PF and outcome
Statistical Analysis and Reporting	a. Sufficient presentation of data to assess the adequacy of the analytic strategy b. Strategy for model building is appropriate and is based on a conceptual framework or model c. The selected statistical model is adequate for the design of the study d. There is no selective reporting of results	**High bias**: The reported results are very likely to be spurious or biased related to analysis or reporting **Moderate bias**: The reported results may be spurious or biased related to analysis or reporting **Low bias**: The reported results are unlikely to be spurious or biased related to analysis or reporting

Source: Hayden JA, van der Windt DA, Cartwright JL, Côté P, Bombardier C. (2013). Assessing bias in studies of prognostic factors. *Ann Intern Med, 158*(4). 280-286
Abbreviation: PF=prognostic factor

Appendix E

Risk of Bias Assessment for Included Studies

Domains	Choinière et al. (2014)	King et al. (2008)	Lahtinen et al. (2006)	Lee et al. (2010)	van Gulik et al. (2011)	Steegers et al. (2007)	Taillefer et al. (2006)
Study Participation	🟢	🟡	🟡	🟡	🔴	🟡	🟢
Study Attrition	🟡	🟡	🔴	🔴	🟢	🟡	🟡
Prognostic Factor Measurement	🟡	🔴	🟢	🟡	🔴	🟡	🟡
Outcome Measurement	🟢	🟡	🟢	🟡	🟡	🟡	🟡
Study Confounding	🟢	🟡	🟡	🔴	🔴	🟡	🟡
Statistical Analysis and Reporting	🟡	🟢	🟡	🟢	🟢	🟡	🟡
Legend:	🟢 Low Risk		🟡 Moderate Risk			🔴 High Risk	

Appendix F: AXIS Cross sectional Study Appraisal Tool

Appraisal of Cross-sectional Studies

	Question	Yes	No	Don't know/ Comment
Introduction				
1	Were the aims/objectives of the study clear?			
Methods				
2	Was the study design appropriate for the stated aim(s)?			
3	Was the sample size justified?			
4	Was the target/reference population clearly defined? (Is it clear who the research was about?)			
5	Was the sample frame taken from an appropriate population base so that it closely represented the target/reference population under investigation?			
6	Was the selection process likely to select subjects/participants that were representative of the target/reference population under investigation?			
7	Were measures undertaken to address and categorise non-responders?			
8	Were the risk factor and outcome variables measured appropriate to the aims of the study?			
9	Were the risk factor and outcome variables measured correctly using instruments/measurements that had been trialled, piloted or published previously?			
10	Is it clear what was used to determined statistical significance and/or precision estimates? (e.g. p-values, confidence intervals)			
11	Were the methods (including statistical methods) sufficiently described to enable them to be repeated?			
Results				
12	Were the basic data adequately described?			
13	Does the response rate raise concerns about non-response bias?			
14	If appropriate, was information about non-responders described?			
15	Were the results internally consistent?			
16	Were the results presented for all the analyses described in the methods?			
Discussion				
17	Were the authors' discussions and conclusions justified by the results?			
18	Were the limitations of the study discussed?			
Other				
19	Were there any funding sources or conflicts of interest that may affect the authors' interpretation of the results?			
20	Was ethical approval or consent of participants attained?			

Appendix G

Studies Examining Anxiety as a Risk Factor for CPSP

Risk Factor	Study/ Year	Date/ Location	Design/ Instrument	Follow-up	Sample Size	Effect Size	Notes
ANXIETY	Choinière et al. (2014)	2005-2006; Canada	Prospective study (4 centres); Hospital Anxiety and Depression Scale (HADS)	3, 6, 12, 24 months postoperative	*n*=975, (*n*=770 males, *n*=226 females)	GEE Adjusted Odd Ratio (95% CI = 1.04 (1.00-1.09, *p*=0.041) Unadjusted Odds Ratio =1.09 (1.06-1.11)	Multivariable GEE regression model Pain arising after surgery, unrelated to pain felt prior to surgery, and present for ≥3 months
ANXIETY	Taillefer et al. (2006)	1999-2002; Canada	Cross-sectional (single centre) (HADS)	1 to 3 years postoperative	*n*=579, (*n*=418 males, *n*=146 females)	CPSP: Mean 7.0, SD±4.4 No CPSP: Mean 4.5, SD±3.5, *p*=000	Variable not included in multiple regression (p-value does not meet multi-variable inclusion criteria)

CI=confidence interval, **CPSP**=chronic post-surgical pain, **GEE**=Generalized Estimating Equation, **HADS**=Hospital anxiety and depression scale

Appendix H

Studies Examining Depressive Symptoms as a Risk Factor for CPSP

Risk Factor	Study/ Year	Date/ Location	Design/ Instrument	Follow-up	Sample Size	Effect Size	Notes
DEPRESSION	Choinière et al. (2014)	2005-2006; Canada	Prospective study (4 centres); HADS	3, 6, 12, 24 months postoperative	*n*=975, (*n*=770 males, *n*=226 females)	Adjusted Odds Ratio= 0.98 (0.93-1.04) Unadjusted Odds Ratio=1.06 (1.03-1.10)	Multivariable GEE regression model Pain arising after surgery, unrelated to pain felt prior to surgery, and present for ≥3 months
DEPRESSION	Taillefer et al. (2006)	1999-2002; Canada	Cross-sectional (single centre) (HADS)	1 to 3 years postoperative	*n*=579, (*n*=418 males, *n*=146 females)	CPSP: Mean 5.1, SD±4.3 No CPSP: Mean 2.9, SD±3.1, *p*=000	Variable not included in multiple regression (*p*-value does not meet multi-variable inclusion criteria)

CI=confidence interval, **CPSP**=chronic post-surgical pain, **GEE**=Generalized Estimating Equation, **HADS**=Hospital anxiety and depression scale

Appendix I

Studies Examining Acute Postoperative Pain Intensity as a Risk Factor for CPSP

Risk Factor	Study/ Year	Date/ Location	Design/ Instrument	Follow-up	Sample Size	Effect Size	Notes
POST-OP PAIN: Average 24hr NRS ≥ 4/10, POD 3	Choinière et al. (2014)	2005-2006; Canada	Prospective study (4 centres); Brief Pain Inventory	3, 6, 12, 24 months postoperative	*n*=975, (*n*=770 males, *n*=226 females)	Adjusted Odds Ratio=1.48 (1.10- 2.47) Unadjusted Odds Ratio=2.23 (1.78-2.79)	Multivariable GEE regression model
POST-OP PAIN: Worst 24hr NRS ≥ 4/10, POD 3	Choinière et al. (2014)	2005-2006; Canada	Prospective study (4 centres); Brief Pain Inventory	3, 6, 12, 24 months postoperative	*n*=975, (*n*=770 males, *n*=226 females)	Adjusted Odds Ratio=1.69 (1.16- 2.47) Unadjusted Odds Ratio=2.58 (1.94-3.44)	Multivariable GEE regression model
POST-OP PAIN: Acute	Steegers et al. 2007	2003; Netherlands	Retrospective/Cross-sectional; (single hospital); Rose Angina Questionnaire	16 months postoperative	*N*=256, (*n*=211 males, *n*=45 females)	Acute postoperative pain intensity significantly associated with chronic pain (Man-Whitney *U* test, *p*=<0.00002)	Effect size not reported Pain intensity reported as '*slight', 'moderate', major*' or *'severe'*
POST-OP PAIN: Severity	Steegers et al. 2007	2003; Netherlands	Retrospective/Cross-sectional; (single centre); Rose Angina Questionnaire	16 months postoperative	*N*=256, (*n*=211 males, *n*=45 females)	Seriousness of acute wound pain correlated with seriousness of chronic pain (Spearman R=0.40, *p*<0.05)	Effect size not reported
POST-OP PAIN: Severity	Lahtinen et al. 2006	CABG surgery dates not reported; Finland	Prospective cohort; (single centre); Pain assessed with NRS	1 day preoperative; 4 days postoperative; 1, 3, 6, 12 months	*N*=213, (*n*=176 males, *n*=37 females)	Moderate to severe acute post-op pain (NRS >3/10) more likely to have any post-sternotomy pain rest at 12 months (Friedman test, *p*<0.042).	Effect size not reported No formal sample size calculations made NRS-mild=1-3, moderate=4-6, severe=7-10

CABG=coronary artery bypass graph, **CPSP**=chronic post-surgical pain, **GEE**=Generalized Estimating Equation, **NRS**=numerical rating scale, **Post-op**=postoperative, **POD**=postoperative day

Studies Examining Acute Postoperative Pain Intensity as a Risk Factor for CPSP

Risk Factor	Study/ Year	Date/ Location	Design/ Instrument	Follow-up	Sample Size	Effect Size	Notes
POST-OP PAIN: Severity NRS ≥ 4/10, POD 1 and 2	van Gulik et al. 2011	2006; Netherlands	RCT; (single centre) Prospective cohort; Pain assessed with NRS	0-7 days and approx. 1-year (10- 12 months) post-op	*N*=120, (*n*=82 males, *n*=38 females)	No univariate association for moderate to severe (NRS ≥ 4/10) on: POD1 (OR= 1.06 (0.47- 2.37, *p*=0.90, *n*=114) POD2 (OR= 1.80 (0.81- 4.00, *p*=0.15, *n*=113) POD3 (OR= 2.15 (0.93- 4.97, *p*=0.07, *n*=11)	POD1 and POD 2 variables not included in Multiple regression as values did not meet inclusion criteria (p-value <0.10)
POST-OP PAIN: Severity NRS ≥ 4/10, POD 3	van Gulik et al. 2011	2006; Netherlands	RCT; (single centre) Prospective cohort; Pain assessed with NRS	0-7 days and a1-year (10- 12 months) post-op	*N*=120, (*n*=82 males, *n*=38 females)	Multivariate association: NRS ≥4 on Post-op day 3 predicted transition to CPSP: OR=2.89 (1.15- 7.23, *p=0.02*)	Multivariable modelling
POST-OP PAIN: Severity NRS ≥ 4/10, POD 3	van Gulik et al. 2011	2006; Netherlands	RCT; (single centre) Prospective cohort; Pain assessed with NRS	0-7 days and Approx. 1-year (10- 12 months) post-op	*N*=120, (*n*=82 males, *n*=38 females)	Multivariate association: NRS ≥4 on Post-op day 3 predicted transition to CPSP: OR=2.89 (1.15- 7.23, *p=0.02*)	Multivariable modelling
POST-OP PAIN: Severity NRS ≥ 5/10, POD 7	Lee et al. 2010	CABG and/or VR surgery dates not reported; Taiwan	Prospective cohort (3 centers); Pain assessed with NRS	Pre-op, 7, 10, 30, 90 days post-op	*N*=53, (*n*=43 males, *n*=10 females)	Univariate regression: no association between worst pain average pain Worst pain: OR=0.946 (0.752-1.190) Average pain: OR=1.159 (0.815-1.648)	Chronic pain = moderate to severe pain (NRS 5/10) at 3-months follow-up NRS-mild=1-4, moderate to severe=5-10

CABG=coronary artery bypass graph, **CPSP**=chronic post-surgical pain, **NRS**=numerical rating scale, **Post-op**=postoperative, **POD**=postoperative day, **RCT**=randomized control trial, **VR**=valve replacement

Studies Examining Acute Postoperative Pain Intensity as a Risk Factor for CPSP

Risk Factor	Study/ Year	Date/ Location	Design/ Instrument	Follow-up	Sample Size	Effect Size	Notes
POST-OP PAIN: Severity NRS ≥ 5/10, POD 10	Lee et al. 2010	CABG and/or VR surgery dates not reported; Taiwan	Prospective cohort (3 centers)	Preoperative, 7, 10, 30, 90 days post-op	*N*=53, (*n*=43 males, *n*=10 females)	Univariate regression: no association between worst pain average pain Worst pain: OR=0.911 (0.724 - 1.147) Average pain: OR=1.182 (0.838-1.669)	Chronic pain = moderate to severe pain (NRS 5/10) at 3-months follow-up NRS-mild=1-4, moderate to severe=5-10
POST-OP PAIN: Severity NRS ≥ 5/10, POD 30	Lee et al. 2010	CABG and/or VR surgery dates not reported; Taiwan	Prospective cohort (3 centers)	Preoperative, 7, 10, 30, 90 days post-op	*N*=53, (*n*=43 males, *n*=10 females)	Univariate regression: significant association between worst pain: OR=1.1451 (1.043 -2.019) Univariate regression: no significant association between average pain: OR=0.887 (0.8591-1.331)	Chronic pain = moderate to severe pain (NRS 5/10) at 3-months follow-up NRS-mild=1-4, moderate to severe=5-10

CABG=coronary artery bypass graph, **CPSP**=chronic post-surgical pain, **NRS**=numerical rating scale, **OR**=odds ratio, **Post-op**=postoperative, **POD**=postoperative day, **RCT**=randomized control trial, **VR**=valve replacement

Appendix J

Studies Examining Acute Opioid Analgesic Consumption as a Risk Factor for CPSP

Risk Factor	Study/ Year	Date/ Location	Design/ Instrument	Follow-up	Sample Size	Effect Size	Notes
ANALGESIA THERAPY: 1ST WEEK OF SURGERY	Choinière et al. (2014)	2005-2006; Canada	Prospective study (4 centres)	3, 6, 12, 24 months post-op	*n*=975, (*n*=770 males, *n*=226 females)	Adjusted Odds Ratio (continuous)= 1.00 (1.00-1.00) Unadjusted Odds Ratio=1.02 (1.00- 1.04)	Multivariable GEE regression model
ANALGESIA THERAPY: 1ST WEEK OF SURGERY	Lee et al. 2010	CABG and/or VR surgery dates not reported; Taiwan	Prospective cohort (3 centers)	Preoperative, 7, 10, 30, 90 days postoperative	*N*=53, (*n*=43 males, *n*=10 females)	OR=1.003 (0.986 -1.021)	Univariate logistic regression analyses
ANALGESIA THERAPY: DAY OF SURGERY	Lee et al. 2010	CABG and/or VR surgery dates not reported; Taiwan	Prospective cohort (3 centers)	Preoperative, 7, 10, 30, 90 days postoperative	*N*=53, (*n*=43 males, *n*=10 females)	Univariate regression: no significant association OR=1.022 (0.275 -1.022)	Chronic pain = moderate to severe pain (NRS 5/10) at 3-months follow-up NRS-mild=1-4, moderate to severe=5-10
ANALGESIA THERAPY: Total in ICU	Taillefer et al. (2006)	1999-2002; Canada	Cross-sectional (single centre)	1 to 3 years postoperative	*N*=579, (*n*=418 males, *n*=146 females)	Univariate logistic regression Unadjusted Odds Ratio (mg)=1.00 (0.99-1.00, *p*=0.735)	Variable not included in multiple regression (*p*-value does not meet multi-variable inclusion criteria)
ANALGESIA THERAPY: Total on Surgical Ward	Taillefer et al. (2006)	1999-2002; Canada	Cross-sectional (single centre)	1 to 3 years post-op	*N*=579, (*n*=X418 males, *n*=146 females)	Univariate logistic regression Odds Ratio (mg)=1.01 (1.00-1.02, p=0.051) Multivariate logistic regression Odds Ratio =1.05 (1.00-1.10, *p*=0.032)	Multivariate modelling

CABG=coronary artery bypass graph, **CPSP**=chronic post-surgical pain, **NRS**=numerical rating scale, **OR**=odds ratio, **Post-op**=postoperative, **POD**=postoperative day, **RCT**=randomized control trial, **VR**=valve replacement

Appendix K
Summary of FORESITE Research Proposal

Operating Grant/Subvention de fonctionnement Application/Demande: 2013-09-16

Summary of Research Proposal/Résumé de la proposition de recherche

Background: With the growing, global burden of cardiovascular disease, the number of people undergoing cardiac surgery is expected to rise. Recent estimates suggest that approximately 400,000 Americans and 36,000 Canadians undergo cardiac surgery annually. Despite the proven survival and symptom-related benefits of cardiac surgeries, mounting evidence suggests that chronic post-surgical pain (CPSP)—and related poor functional recovery—following these procedures are major clinical problems. Moreover, the economic consequences of these problems remain unknown. Patient risk factors are of high prognostic relevance, yet the majority of putative risk factors examined to date are not tenably modifiable in the peri-surgical context.

Study Objectives. The aims of this study are to examine the influence of modifiable cognitive factors, namely, pain-related beliefs and gender-based pain expectations, on the following outcomes up to 1 year following cardiac surgery: the development of CPSP, functional status, and patient-level cost of illness. With a view to comprehensive examination of the impact of CPSP on patients, an additional aim is to determine the impact of CPSP on quality-adjusted life years (QALY) borne by cardiac surgery, as well as the incremental cost for one additional QALY gained for patients, by virtue of cardiac surgery, among those who develop CPSP compared to those who do not.

Research Plan: Design. We will undertake a prospective cohort study of 1,250 in-patients who undergo cardiac surgery, recruited from the Hamilton Health Sciences over a 2-year period. We will collect data on the putative risk factors for CPSP (independent variables) prior to patient's surgical procedure. The total follow-up period will be 12 months, with data on pre-specified model covariates (e.g., non-modifiable risk factors for CPSP, such as age) collected also at baseline, and post-operative days 3 (in hospital) and 30 (at home via telephone). Outcome data will be collected via telephone interview at 6 and 12 months following surgery.

Participants. Inpatients who: 1) are ≥18 years of age and 2) undergo cardiac surgery including coronary artery bypass grafting and open heart procedures such as valvular repairs.

Sample size. The sample size of 1,250 patients was based on a correlation of ≤0.60 between the 2 follow-up measurements, assuming that at least 16% of the variability of our independent variables will be explained by our covariates, an alpha of 0.05, a power of 80%, a ≥10%, prevalence of CPSP, and allowing for detection of ≥5% in the odds of developing chronic pain after cardiac surgery, we will enroll 1,250 patients in our study.

Measures. Dependent variables- Dependent variables will be measured at 6 and 12 months after surgery. The primary outcome is CPSP; this variable will first be measured dichotomously (i.e., yes/no). If CPSP is present, it will then be measured via the Brief Pain Inventory-Short Form. Additional outcomes include functional status (Short Form-12v2), and cost of illness (Ambulatory Home Care Record). **Independent variables-** Independent variables include pain-related beliefs (Pain Barriers Questionnaire), and gender-based pain expectations (Gender Role Expectations in Pain Questionnaire). Aside from baseline clinical and surgical factors we will control for baseline anxiety (Spielberger State-Trait Anxiety

Inventory). **Data Analyses:** We will employ generalized estimating equations (GEE) to model the primary outcome, 6-month and 1-year presence of CPSP, as well as functional status and cost of illness on pain-related beliefs and gender-based pain expectations while adjusting for pre-specified model covariates. QALYs will be estimated by converting SF-12v2 data collected in the study to a utility score using a validated algorithm. After estimating QALYs, we will analyze it as a dependent variable using regression to estimate the difference in expected QALYs between those who develop CPSP and those who do not.
Integrated and end-of-grant knowledge transfer (KT) and dissemination: We are fortunate to have strong partnerships with organizations including Elsevier and the Heart and Stroke Foundation, allowing for continued access to web-based, international-scale dissemination infrastructure that we previously developed with these partners.
Significance: CPSP is a major problem with well-documented deleterious consequences on functional status for cardiac patients. We aim to investigate putative cognitive risk factors that could be targeted for preventative intervention. We will also examine the economic consequences of CPSP comprehensively, including the impact on QALYs, with no additional data collection required. Given our dedicated partners and KT infrastructure, we are confident we can make a lasting contribution to reducing the risk of CPSP after cardiac surgery.

File Number/Numéro de dossier 00210994

Appendix L: Registration/ Eligibility

REGISTRATION/ELIGIBILITY CRF 1

CRF 1- Registration/ Eligibility CRF #001 Visit #001

PATIENT ID: ☐☐☐ ☐☐☐☐ PATIENT INITIALS: ☐☐☐ (F M L) Reference Page

A. INCLUSION CRITERIA *(Must be 'Yes' to Questions 1 - 2)*

	No	Yes
1. Age ≥ 18 years	☐	☐
2. Patient who has undergone cardiac surgery. This includes coronary artery bypass grafting and and all open heart procedures such as valvular repairs/replacement.	☐	☐

Record details of index cardiac surgery on the Operative Forms (CRFs 5-6)

B. EXCLUSION CRITERIA *(Must be 'No' to Questions 1 - 2)*

	No	Yes
1. Previously enrolled in the VISION Cardiac Surgery Study	☐	☐
2. Patient who has undergone an isolated pericardial window, pericardiectomy, permanent pacemaker or defibrillator implantation.	☐	☐

C. PATIENT CONSENT *(Must be prior to surgery or within 24 hours post-operatively, unless deferred)*

1. Written informed consent obtained: ☐ Prior to surgery ☐ Within 24 hours post-op ☐ Deferred
2. Local time and date of consent: ☐☐☐☐ ☐☐ ☐☐ (year / month / day) ☐☐:☐☐ (24-hour clock)
3. a) Consent for Bio-Bank sub-study: ☐ No ☐ Yes ☐ N/A *(If YES, complete 3b):*

   b) Consent for genetic analyses: ☐ No ☐ Yes
4. a) Is the patient participating in additional substudies? ☐ No ☐ Yes → *Specify participation and confirm consent below*

   ☐☐ ☐☐ ☐☐ ☐☐ ☐☐ ☐☐ ☐☐ ☐☐ ☐☐ ☐☐

   b) Consent obtained for substudies: ☐ No ☐ Yes

   c) Consent obtained for substudy genetic analyses? ☐ No ☐ Yes

D. REGISTRATION CONFIRMATION

1. Date of birth: ☐☐☐☐ ☐☐ ☐☐ (year / month / day)
2. Local date of surgery: ☐☐☐☐ ☐☐ ☐☐ (year / month / day)

	Time of surgery commencement (skin incision)	Time of surgery completion (skin closure)
	a) ☐☐:☐☐ (24-hour clock)	b) ☐☐:☐☐ (24-hour clock)

E. PATIENT REGISTRATION *(Registration must occur no later than 24 hours post-surgery)*

Log-in to PHRI's 24-hour Interactive Web Registration System (IWRS) to register this patient. A unique Patient ID will be provided by the registration service. Use this Patient ID to enter all patient data into iDataFax.

1. Local time and date of Registration: ☐☐☐☐ ☐☐ ☐☐ (year / month / day) ☐☐:☐☐ (24-hour clock)

Name of authorized person completing this CRF: _____ Date: ☐☐☐☐ ☐☐ ☐☐ (year / month / day)

Version 7.0, 2016-11-08

Appendix M: Consent Form

Hamilton Health Sciences

McMaster University Health Sciences

INFORMATION SHEET AND CONSENT FORM (PARTICIPANT)

Title of the Study: **Vascular events In Surgery patIents cOhort evaluatIoN – Cardiac Surgery (VISION Cardiac Surgery)**

Sponsor: Population Health Research Institute, Hamilton Health Sciences

Locally Responsible Investigator: Dr. Andre Lamy
237 Barton Street E., Rm C1-112, Hamilton, ON L8L 2X2
Tel: 905-527-4322 ext. 40325

Co-Investigator(s): Drs. P.J. Devereaux, Richard Whitlock, Victor Chu, Irene Cybulsky, Matt Danter, Adel Dyub, Steve Singh, Lloyd Semelhago, Stephen Hill, Peter Kavsak, Summer Syed and Tomas Vanhelder

INTRODUCTION

You are being asked to participate in a research study involving patients undergoing heart surgery. Please read this form carefully and ask the investigator (study doctor) or research personnel to explain any words or information that are not clear to you. This will help to make sure you understand the details of your participation before you give your consent. The following sections will discuss the requirements of this study, and the details of your role as a participant. The investigator or other research personnel will answer any questions you may have about this consent form and about the study.

PURPOSE OF THIS RESEARCH STUDY

Despite its benefits, people that undergo heart surgery may experience complications (such as death, heart attack, cardiac arrest, and stroke) around the time of their surgery. Although some heart surgery studies have provided useful information to help us predict who may be at risk of having complications, we still do not know the extent to which major complications are currently happening to patients undergoing heart surgery.

The purpose of this study is to determine the relationship between postoperative troponin (a blood marker for heart damage) and the risk of major vascular complications, including death after surgery.

WHERE THE STUDY IS BEING DONE AND NUMBER OF PEOPLE PARTICIPATING

This study will take place in at least 15 sites worldwide with at least 15,000 participants. At least 1,000 patients are expected to be recruited at Hamilton General Hospital.

WHO CAN PARTICIPATE

Patients who are 18 years of age or older, are scheduled for or who have undergone heart surgery) and have provided written informed consent can participate.

Participant Initials _____

LENGTH OF YOUR PARTICIPATION

Your participation in the study will span one year. You will be followed throughout your hospital stay and after discharge, a VISION Cardiac Surgery Study researcher will contact you by phone 30 days and at one year after your surgery to check on your health status.

PROCEDURES TO BE FOLLOWED DURING THIS STUDY

You will:

- Be approached by study personnel either prior to or within 24 hours after your surgery regarding participating in the study. Should you agree to participate, you will be asked to sign the informed consent form at the end of this document.
- Be asked about your previous health history and about the medications you are taking.
- If you wish to take part in the sub-study to monitor your pain after surgery. We would ask you about your feelings on having surgery, as well as your sense of general well-being. We will also ask you some questions about your beliefs and expectations about pain and recovery from your cardiac surgery. We will also ask you some questions about your beliefs and expectations about pain and recovery from your cardiac surgery.
- Have blood collected, equivalent to a teaspoon (5 mL), within 4 hours before your surgery, 6-12 hours after surgery, and on days 1-3 after surgery for the troponin blood test. This tube of blood will be collected along with your other routine blood test. Wherever possible, no additional needle pokes will be required.
- If you agree, have an additional amount of blood (about 20 mL or 1-2 tablespoons) taken at the same times as the above blood collection, so your blood samples can be stored and used to measure various risk factors for heart disease, stroke and other chronic diseases, such as tests of glucose, blood clotting and kidney function. A urine sample will also be collected at these times.
- Be contacted at 30 days and 1 year after your surgery by telephone. During these telephone calls you will be asked about any medical problems you have had since the surgery. These follow-up calls will take approximately 15 minutes. During these calls you will also be asked to a series of questions concerning pain after your heart surgery.
- If you would like to take part in the study to monitor your pain after surgery we will ask you to complete additional questionnaires at30 days, 6 months and at 1 year by telephone. We will ask you about any pain you may still have from your surgery, how active you are, and how much time and money is spent by yourself and care takers after your surgery. These additional questionnaires will take about 20 minutes to complete.

STORAGE AND USE OF BLOOD SAMPLES

Your blood samples will be labeled with a code number. A list linking you to the code number will be kept in a locked secure location at Hamilton General Hospital. After the end of this study, any personal identifying links to your sample will be destroyed. This means that your sample and any further results from it cannot be connected with you. Your blood samples will be frozen and stored at the Clinical Research and Clinical Trials Laboratory at Hamilton General Hospital, Canada for up to 25 years for future research. The samples will be used for research and such use may result in inventions or discoveries that create new products or diagnostic or

Participant Initials _____

therapeutic agents. In some instances, these inventions and discoveries may be of potential commercial value and may be patented and licensed by the researchers/sponsor. You will not receive any money or other benefits derived from any commercial or other products that may be developed from use of the specimens.

COLLECTION OF BLOOD SAMPLES FOR GENETIC ANALYSIS

Some genes may be linked to heart disease, stroke or other chronic diseases, but few have been identified. In this study, researchers may be able to find out more about how a person's genes affect their risk of those diseases. Therefore you are being asked to provide an additional blood sample for genetic analysis. Your decision to participate or not participate in the genetics part of the study will have no effect on your ability to take part in the rest of the study. If you agree to have your sample stored, you may change your mind at a later time and have your sample withdrawn as long as it can still be linked to your code number.

If you decide to take part in the genetics part of the study, no extra blood is required. All blood samples will be assigned a code number. A list linking you to the code number will be kept in a locked secure location at Hamilton General Hospital. After the end of this study, any personal identifying links to your sample will be destroyed. This means that your sample and any further results from it cannot be connected with you.

This study is not meant to test your personal medical status. Results of the genetics part of the study may be communicated to the scientific community in seminars or scientific publications while strictly maintaining confidentiality and anonymity of participants. If you have questions about whether any genetic test would be useful to you, you should ask your personal doctor.

POSSIBLE RISKS OF TAKING PART IN THIS STUDY

This study requires additional tubes of blood taken along with routine blood samples. You may experience some pain from this, or faintness, irritation, bruising, bleeding, and rarely, infection at the site of the needle insertion.

BENEFITS

You may or may not receive any benefits from participating in this trial, however, others may benefit from this study in the future.

PARTICIPATION AND WITHDRAWAL FROM THE STUDY

It is up to you to decide whether or not to take part in this study. If you do decide to take part you will be given this information sheet to keep and asked to sign the attached consent form.

Your decision not to participate will involve no penalty or loss of benefits to which you are otherwise entitled. Should you wish to withdraw your consent, please notify the study doctor or research nurse at the telephone number listed on the last page of this information sheet. You will be free to withdraw from the study before study completion if you decide to do so at any time and irrespective of the reason.

Participant Initials _____

However, even if you withdraw your consent, the information about you that was collected as part of the research study will still be used to protect the quality of the study. We will continue to collect anonymized data related to the outcomes of the study. All information will be kept completely confidential. The study doctor will make the best effort to re-contact you (e.g., contacting your family or private physician, review available registries or health care database) to determine your vital status as well as information concerning occurrence of a complication like a heart attack or stroke. Attempts to contact you will be documented in your records (e.g., times and dates of attempted telephone contact, receipt for sending a registered letter) and this will continue until the common study end date.

COSTS AND PAYMENT FOR PARTICIPATION

There will not be any monetary payment to you for participating in this study. In addition, you are not responsible for any costs for the required study visits and procedures.

RESEARCH ETHICS BOARD

This study has been reviewed and approved by the research ethics board at Hamilton Integrated Research Ethics Board (HIREB). This group of people, independent of your doctor or the sponsor, reviews the science and ethics of a study before it is allowed to start. The purpose of this committee is to protect you as a participant.

CONFIDENTIALITY AND RELEASE OF PERSONAL INFORMATION

All information related to this research study will remain de-identified and to the extent permitted by the applicable laws and/or regulations will not be made publicly available. Data (information) derived from this study will be used for research purposes. The investigator and members of his/her research team, representatives of the sponsor, and Hamilton Integrated Research Ethics Board (HIREB) will be granted direct access to your medical records and other records relating to this study to check that the study information is correct to the extent permitted by applicable laws and/or regulations.

Your collected data will be stored locally and transmitted to the PHRI who are performing this study. Your information will be kept in a secure location with limited access of authorized personnel only. The PHRI will store and process your data with electronic data processing systems. In the electronic database, your data will be identified only with a code number and your initials. At the end of the study all personal identifiers will be destroyed, the remaining information will be stored for 25 years and securely disposed thereafter.

By signing this consent form, you are agreeing to allow the study monitors, and Research Ethics Board to examine your medical records. Your name will be kept confidential to the extent allowed by law, and you will not be identified in any presentations or reports dealing with this research. When the results of the study are published, your identity will not be revealed.

WHOM TO CONTACT

If you have any questions or concerns about this study now or later or any medical problems related, please feel free to contact:

Participant Initials _____

Principal Investigator:
Dr. Andre Lamy, 237 Barton St. E., Hamilton, ON, 905-527-4322 ext. 40325
Research Coordinator:
Lindsay Doharris, 237 Barton St. E., McMaster Clinic Room 358, Hamilton, ON, 905-521-2100 ext. 44156

If you have any questions regarding your rights as a research participant you may contact the Office of the Chair of the Hamilton Health Sciences/Faculty of Health Sciences Research Ethics Board at 905-521-2100 ext. 42013.

INFORMED CONSENT STATEMENT

I certify the following:

- I have read the above information form and understand that the study involves research. I understand the purpose of the study as well as the potential benefits and risks of participating in the study.
- I have had the opportunity to ask questions. All my questions have been answered to my satisfaction.
- I understand that I am free to withdraw from this study at any time without the need to give a reason and without affecting my future treatment. Similarly, should I choose not to participate in this study in the first place, that decision would not make a difference to my medical treatment.
- I also grant auditors from the Hamilton Integrated Research Ethics Board (HIREB) direct access to my original medical records for verification of clinical trial procedures and/or data to the extent permitted by applicable laws and regulations.

I agree to participate in the VISION Cardiac Surgery study and I understand that I will receive a signed copy of this form.

1) I also agree to have my blood and urine stored (for up to 25 years after the study ends) for future tests when they become available.
   ☐ YES ☐ NO

2) I also agree to give a blood sample for the genetics portion of the study.
   ☐ YES ☐ NO

3) I also agree to participate in the VISION-FORSITE pain sub-study.
   ☐ YES ☐ NO

Participant Initials _____

If you mark "no" to item 1, 2, or 3 you may still participate in the study.

Participant/Legal Representative's name (printed)	Signature	/ / : Date: (DD/MMM/YYYY) and Time (24 hr clock)
Name of person obtaining consent (printed)	Signature	/ / : Date: (DD/MMM/YYYY) and Time (24 hr clock)

Appendix N: Interact Web Response System Registration

IWRS REGISTRATION **CRF 102**

CRF #102 Visit #000

PATIENT ID: ☐☐☐ ☐☐☐☐ **PATIENT INITIALS:** ☐☐☐ *F M L* Reference Page

This form is for PHRI **internal use only** to document registration.

1. Date of registration: ☐☐☐☐☐☐☐☐ *year / month / day* 2. Time of registration: ☐☐:☐☐ *24-hour clock*

3. Has the patient undergone cardiac surgery? ☐ No ☐ Yes

4. Patient's date of birth: ☐☐☐☐☐☐☐☐ *year / month / day*

5. Date of Surgery: ☐☐☐☐☐☐☐☐ *year / month / day*

6. Sub-study participation:

- ☐ Patient not enrolled in any sub-studies
- ☐ Full Biobank
- ☐ Partial Biobank (HsTnI Plus)
- ☐ Prospective BNP
- ☐ FORESITE Chronic Pain
- ☐ APPRAIsE
- ☐ Function and Frailty (PRISMA 7 and 6CIT)
- ☐ Hand Grip Strength

7. Name of person performing registration: _____

Appendix O: Proposed Timeline and Outcome Measurement

Time Period	Preoperative	In Hospital			Follow-up		
		Postoperative Day 1	Postoperative Day 2	Postoperative Day 3	30 Day Follow up	6 Month/ Follow up	12 Month/ Final Follow up
Eligibility Assessment	x						
Informed Consent[1]	x						
STAI Assessment[2]	x[2]						
HADS Assessment[2]	x[2]						
Demographics	x						
Medical History	x						
Surgical Details		x					
Medication Chart Audit		x	x	x			
BPI-SF Questionnaire				x	x	x	x
Outcome Events						x	x

[1]Participants may be consented before or after surgery.

[2]These measures must be completed prior to surgery. Participants that are not consented prior to surgery will not have these baseline measures recorded.

Appendix P: Patient Contact Information

PATIENT CONTACT INFORMATION

Please record Patient ID after enrollment and retain the Patient Contact Information form in the patient's study file. DO NOT send this form to the PHRI Project Office.

PATIENT IDENTIFICATION

Patient Name: _____ (Last Name) _____ (First Name) _____ (Middle Name)

Date of Birth: __ __ / __ __ / __ __ __ __ (day / month / year) Medical record/health number: _____

Resident ID (country specific identifier e.g. SIN, SSN) _____

Primary home address: _____ (Apt/House No. Street City State/Province Postal Code)

Telephone number(s): _____ (Home Mobile Work/Business)

Spouse or significant other: _____ (Last Name) _____ (First Name)

E-mail address: _____

ALTERNATIVE CONTACT INFORMATION (Close relative or family friend not living with the patient)

Contact Name: _____ (Last Name) _____ (First Name)

Relationship to the patient: _____

Address: _____ (Apt/House No. Street City State/Province Postal Code)

Telephone number(s): _____ Best time to Call: _____ ☐ AM ☐ PM

E-mail address: _____

ALTERNATIVE CONTACT INFORMATION (Close relative or family friend not living with the patient)

Contact Name: _____ (Last Name) _____ (First Name)

Relationship to the patient: _____

Address: _____ (Apt/House No. Street City State/Province Postal Code)

Telephone number(s): _____ Best time to Call: _____ ☐ AM ☐ PM

E-mail address: _____

REFERRING/PRIMARY CARE PHYSICIAN/GENERAL PRACTITIONER CONTACT INFORMATION

Physician Name: _____ (Last Name) _____ (First Name) _____ (Role in patient's care)

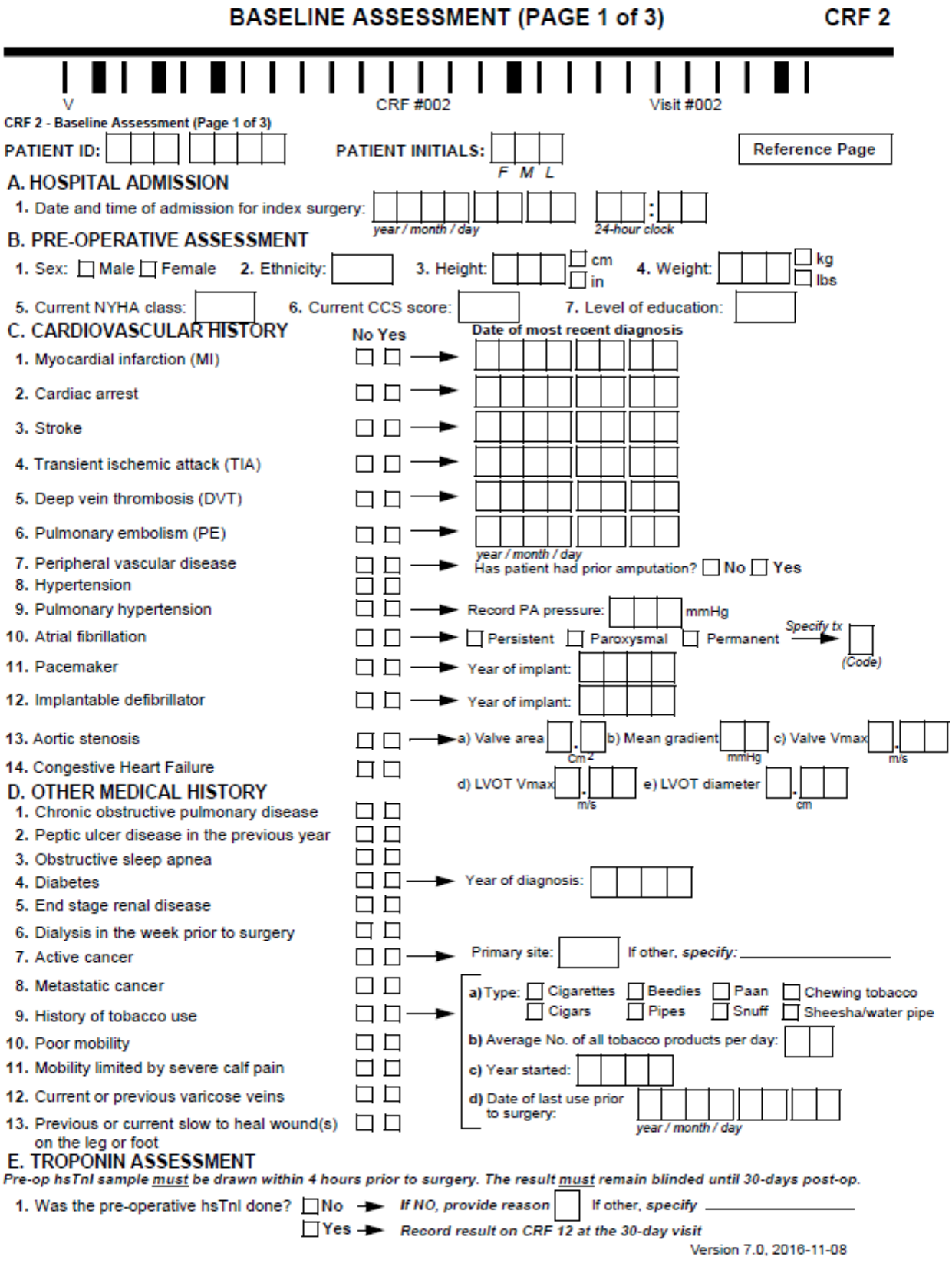
Address: _____ (No. Street City State/Province Postal Code Country)

Office Telephone/Fax: _____ (Office Telephone Number) _____ (Office Fax Number)

Contains Confidential Patient Information

- Please retain this form in the patient's study file. DO NOT send this form to the PHRI Project Office -

Appendix Q: Baseline Assessment



BASELINE ASSESSMENT (PAGE 1 of 3) CRF 2

V CRF #002 Visit #002

CRF 2 - Baseline Assessment (Page 1 of 3)

PATIENT ID: PATIENT INITIALS: F M L Reference Page

A. HOSPITAL ADMISSION

1. Date and time of admission for index surgery: year / month / day 24-hour clock

B. PRE-OPERATIVE ASSESSMENT

1. Sex: Male Female 2. Ethnicity: 3. Height: cm in 4. Weight: kg lbs

5. Current NYHA class: 6. Current CCS score: 7. Level of education:

C. CARDIOVASCULAR HISTORY

	No	Yes	Date of most recent diagnosis
1. Myocardial infarction (MI)			
2. Cardiac arrest			
3. Stroke			
4. Transient ischemic attack (TIA)			
5. Deep vein thrombosis (DVT)			
6. Pulmonary embolism (PE)			
7. Peripheral vascular disease			year / month / day; Has patient had prior amputation? No Yes
8. Hypertension			
9. Pulmonary hypertension			Record PA pressure: mmHg
10. Atrial fibrillation			Persistent Paroxysmal Permanent Specify tx (Code)
11. Pacemaker			Year of implant:
12. Implantable defibrillator			Year of implant:
13. Aortic stenosis			a) Valve area cm² b) Mean gradient mmHg c) Valve Vmax m/s
14. Congestive Heart Failure			d) LVOT Vmax m/s e) LVOT diameter cm

D. OTHER MEDICAL HISTORY

	No	Yes	
1. Chronic obstructive pulmonary disease			
2. Peptic ulcer disease in the previous year			
3. Obstructive sleep apnea			
4. Diabetes			Year of diagnosis:
5. End stage renal disease			
6. Dialysis in the week prior to surgery			
7. Active cancer			Primary site: If other, specify:
8. Metastatic cancer			
9. History of tobacco use			a) Type: Cigarettes Beedies Paan Chewing tobacco Cigars Pipes Snuff Sheesha/water pipe; b) Average No. of all tobacco products per day: c) Year started: d) Date of last use prior to surgery: year / month / day
10. Poor mobility			
11. Mobility limited by severe calf pain			
12. Current or previous varicose veins			
13. Previous or current slow to heal wound(s) on the leg or foot			

E. TROPONIN ASSESSMENT

Pre-op hsTnI sample must be drawn within 4 hours prior to surgery. The result must remain blinded until 30-days post-op.

1. Was the pre-operative hsTnI done? No → *If NO, provide reason* If other, *specify* _____

Yes → *Record result on CRF 12 at the 30-day visit*

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BASELINE ASSESSMENT (PAGE 2 of 3) CRF 3

CRF #003 Visit #002

CRF 3 - Baseline Assessment (Page 2 of 3)

PATIENT ID: ☐☐☐ ☐☐☐☐ PATIENT INITIALS: ☐☐☐ (F M L)

Reference Page

F. BASELINE LABORATORY TESTS *(Most recent prior to surgery)*

1. Date and time of sample: ☐☐☐☐ ☐☐ ☐☐ (year / month / day) ☐☐:☐☐ (24-hour clock)

		Date and time of sample *(record if different from above)* (year / month / day) (24-hour clock)
2. Hemoglobin	☐☐.☐ g/dL	→ ☐☐☐☐ ☐☐ ☐☐ ☐☐:☐☐
3. Total WBC	☐☐.☐ x10^9/L	→ ☐☐☐☐ ☐☐ ☐☐ ☐☐:☐☐
4. Platelet count	☐☐☐ x10^9/L	→ ☐☐☐☐ ☐☐ ☐☐ ☐☐:☐☐
5. aPTT	☐☐☐ sec	→ ☐☐☐☐ ☐☐ ☐☐ ☐☐:☐☐
6. INR	☐.☐	→ ☐☐☐☐ ☐☐ ☐☐ ☐☐:☐☐
7. Glucose	☐☐☐.☐ mmol/L or ☐ mg/dL	→ ☐☐☐☐ ☐☐ ☐☐ ☐☐:☐☐
8. Na^+	☐☐☐ mmol/L	→ ☐☐☐☐ ☐☐ ☐☐ ☐☐:☐☐
9. K^+	☐☐.☐ mmol/L	→ ☐☐☐☐ ☐☐ ☐☐ ☐☐:☐☐
10. Creatinine	☐☐☐☐.☐☐ ☐ mg/dL ☐ µmol/L	→ ☐☐☐☐ ☐☐ ☐☐ ☐☐:☐☐

G. PRE-OPERATIVE ECG *(Most recent prior to surgery)*

1. Date and time of preoperative ECG: ☐☐☐☐ ☐☐ ☐☐ (year / month / day) ☐☐:☐☐ (24-hour clock) 2. ECG sent to PHRI? ☐ No ☐ Yes ☐

H. PREVIOUS CARDIAC INTERVENTIONS AND CARDIOVASCULAR ANATOMY

1. Cardiac catheterization within 12 months prior to surgery or history of any cardiac surgery procedures? ☐ No ☐ Yes → *If YES, complete previous Cardiac Cath/ Cardiac Surgery report (CRF 20)*
2. Cardiac catheterization >12 months prior to surgery with no history of any cardiac surgery procedures? ☐ No ☐ Yes
3. Previous cardiac transplant: ☐ No ☐ Yes → Date of transplant: ☐☐☐☐ ☐☐ ☐☐ (year / month / day)
4. a) LV ejection fraction: ☐☐ % and/or b) LVEF grade: ☐
5. Current valve status:
   a) Aortic stenosis: ☐ b) Aortic regurgitation: ☐
   c) Mitral stenosis: ☐ d) Mitral regurgitation: ☐
   e) Tricuspid stenosis: ☐ f) Tricuspid regurgitation: ☐
   g) Pulmonic stenosis: ☐ h) Pulmonic regurgitation: ☐
6. Aneursymal aortic disease ☐ No ☐ Yes (specify) → ☐ Ascending ☐ Arch ☐ Descending thoracic
7. Atrial septal defect ☐ No ☐ Yes
8. Ventricular septal defect ☐ No ☐ Yes → ☐ Ischemic ☐ Congenital
9. Rheumatic valvular heart disease ☐ No ☐ Yes
10. Aortic plaque ☐ No ☐ Yes
11. Previous sternotomy ☐ No ☐ Yes

BASELINE ASSESSMENT (PAGE 3 of 3) CRF 4

CRF #004 Visit #002

- CRF 4 - BaselinBaseline Assessme Assessmentent (Page 3 ofe 3 of 3)

PATIENT ID: ☐☐☐ ☐☐☐☐ PATIENT INITIALS: ☐☐☐ (F M L) Reference Page

I. PAIN ASSESSMENT *(Prior to index cardiac surgery)*

1. Pain in any part of your body that requires treatment with a drug more than five times per month? ☐ No ☐ Yes
2. a) Pain in any part of your body that has existed for 3 or more months (regularly or intermittently)? ☐ No ☐ Yes
   b) If YES to question 2a), is this pain cancer related? ☐ No ☐ Yes

J. STOPBang QUESTIONNAIRE

1. *Ask patient:* Do you snore loudly (louder than talking or loud enough to be heard through closed doors)? ☐ No ☐ Yes
2. *Ask patient:* Do you often feel tired, fatigued, or sleepy during the daytime? ☐ No ☐ Yes
3. *Ask patient:* Has anyone observed you stop breathing during your sleep? ☐ No ☐ Yes
4. Neck size *(measure around Adam's Apple)* ☐☐.☐ ☐ cm ☐ in

K. REGULAR MEDICATIONS PRIOR TO SURGERY

	≤24 hrs No	≤24 hrs Yes	>24 hrs - 7 days No	>24 hrs - 7 days Yes
1. ACE inhibitor	☐	☐	☐	☐
2. ARB agent	☐	☐	☐	☐
3. Direct renin inhibitors	☐	☐	☐	☐
4. Beta-blocker	☐	☐	☐	☐
5. Alpha 2 agonist	☐	☐	☐	☐
6. Rate controlling CCB	☐	☐	☐	☐
7. Dihydropyridine CCB	☐	☐	☐	☐
8. K^+ sparing diuretics	☐	☐	☐	☐
9. Other diuretic	☐	☐	☐	☐
10. Digoxin	☐	☐	☐	☐
11. Other anti-arrhythmic	☐	☐	☐	☐
12. Long acting nitrate	☐	☐	☐	☐
13. Opiods	☐	☐	☐	☐
14. Statin	☐	☐	☐	☐
15. Other lipid lowering agent	☐	☐	☐	☐
16. Insulin	☐	☐	☐	☐
17. Other oral hypoglycemic	☐	☐	☐	☐
18. Sulfonylurea	☐	☐	☐	☐
19. H_2 antagonist	☐	☐	☐	☐
20. Proton pump inhibitor	☐	☐	☐	☐
21. COX-2 inhibitor	☐	☐	☐	☐
22. NSAID/non-COX-2 inhibitor	☐	☐	☐	☐
23. Nicotine replacement	☐	☐	☐	☐
24. Non-nicotine cessation drugs	☐	☐	☐	☐
25. Cannabis use	☐	☐	☐	☐
26. Benzodiazipines	☐	☐	☐	☐

L. ANTI-PLATELETS/ANTI-THROMBINS/ANTI-COAGULANTS *(within 7 days prior to surgery)*

	No	Yes	*(If YES, record date and time of last dose)*
1. Acetylsalicylic acid	☐	☐	→ ☐☐☐☐ ☐☐ ☐☐ : ☐☐
2. Clopidogrel	☐	☐	→ ☐☐☐☐ ☐☐ ☐☐ : ☐☐
3. Ticagrelor	☐	☐	→ ☐☐☐☐ ☐☐ ☐☐ : ☐☐
4. Prasugrel	☐	☐	→ ☐☐☐☐ ☐☐ ☐☐ : ☐☐
5. GPIIb/IIIa inhibitor	☐	☐	→ ☐☐☐☐ ☐☐ ☐☐ : ☐☐
6. Other anti-platelet	☐	☐	→ ☐☐☐☐ ☐☐ ☐☐ : ☐☐ → Specify type _____
7. LMWH	☐	☐	→ ☐☐☐☐ ☐☐ ☐☐ : ☐☐
8. Unfractionated heparin	☐	☐	→ ☐☐☐☐ ☐☐ ☐☐ : ☐☐
9. Fondaparinux	☐	☐	→ ☐☐☐☐ ☐☐ ☐☐ : ☐☐
10. Vitamin K antagonist	☐	☐	→ ☐☐☐☐ ☐☐ ☐☐ : ☐☐
11. Non VKA OAC	☐	☐	→ ☐☐☐☐ ☐☐ ☐☐ : ☐☐ → ☐ Dabigatran ☐ Apixaban ☐ Rivaroxaban ☐ Other _____

year / month / day *24-hour clock* *specify*

M. FRAILTY ASSESSMENT AND APPRAISE SUB-STUDY QUESTIONNAIRE

1. Was the FRAILTY Assessment completed? ☐ No ☐ Yes → *Complete CRF 21 FRAILTY Assessment*
2. Was the SAGE Questionnaire completed? ☐ No ☐ Yes → *Complete CRFs 22 and 23 SAGE Questionnaire*

Has the PI or Co-PI reviewed source documents and verified completeness and accuracy of the data on CRFs 1-4 (and CRF 20, if applicable)? ☐ No ☐ Yes

Name of authorized person completing this CRF: _____ Date: ☐☐☐☐ ☐☐ ☐☐ *year / month / day*

Version 7.0, 2016-11-08

Appendix R: Chronic Post-Surgical Pain Assessment

6 MONTH - SHORT FORM - 12 QUESTIONNAIRE (SF-12) CRF 411

DataFax #084 CRF #411 Visit #013

PATIENT ID: PATIENT INITIALS: (F M L) Reference Page

FORESITE Substudy- 6 Month Follow up

1. Date of questionnaire completion: (year / month / day)

A. CONFIRMATION OF CHRONIC POST SURGICAL PAIN

1. Have you had (or do you have) any pain in your body related to your cardiac surgery? ☐ No ☐ Yes
2. Have you had (or do you have) pain that is different from pain experienced prior to surgery? ☐ No ☐ Yes
3. Have you had (or do you have) pain that has been present for a while (not just a few days)? ☐ No ☐ Yes

B. SHORT FORM-12 QUESTIONNAIRE

(Please record all responses as reported by patient at time of administration.)

1. In general, would you say your health is: ☐
2. a) Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf: ☐
   b) Climbing several flights of stairs: ☐
3. a) Accomplished less than you would like: ☐
   b) Were limited in the kind of work or other activities: ☐
4. a) Accomplished less than you would like: ☐
   b) Did work or other activities less carefully than usual: ☐
5. During the past 4 weeks how much did pain interfere with your normal work (including both work outside the home and housework)? ☐
6. a) Have you felt calm and peaceful? ☐
   b) Did you have a lot of energy? ☐
   c) Have you felt downhearted and depressed? ☐
7. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)? ☐

Name of authorized person completing this CRF: .....

(year/month/day)

Version 5.0, 2016-11-08

Appendix S: Brief Pain Inventory

FORESITE Substudy

POD 3 - BRIEF PAIN INVENTORY (BPI)

CRF 408

DataFax #084 CRF #408 Visit #011

PATIENT ID: PATIENT INITIALS: (F M L)

Reference Page

FORESITE Substudy- POD3

1. Date of questionnaire completion: (year / month / day)

A. BRIEF PAIN INVENTORY SHORT FORM

Please record all responses as reported by patient at time of administration.

1. Has patient experienced unusual kinds of pain today? ☐ No ☐ Yes
   (related to their cardiac surgery)
2. a) Indicate shaded areas on diagram or locations given by the patient either verbally or by pointing to his/her body.

   _____ _____

   _____ _____

   _____ _____

   b) Indicate which area hurt the most: _____
3. a) Please record **worst** level of pain in the last 24 hrs as reported by patient (while lying down):

   b) Please record **worst** level of pain in the last 24 hrs as reported by patient (while moving):
4. Please record **least** level of pain in the last 24 hrs as reported by patient:
5. Please record **average** level of pain in the last 24 hrs as reported by patient:
6. Please record level of pain patient has right now as reported by patient:
7. Is the patient receiving treatment or medication for pain? → ***Record analgesics on CRF 407 for POD3***
8. How much relief have pain treatments or medications provided to the patient in the last 24hr? %
9. Please record pain interference rate, during the past 24 hrs, as reported by patient:

A. General Activity		E. Relations with other people	
B. Mood		F. Sleep	
C. Walking Ability		G. Enjoyment of life	
D. Normal Work			

Name of authorized person completing this CRF: _____

(year/month/day)

FORESITE Substudy **6 MONTH - BRIEF PAIN INVENTORY (BPI)** **CRF 413**

DataFax #084 CRF #413 Visit #013

PATIENT ID: ☐☐☐ ☐☐☐☐ **PATIENT INITIALS:** ☐☐☐ (F M L) **Reference Page**

FORESITE Substudy- 6 Month Follow up

1. Date of questionnaire completion: ☐☐☐☐ ☐☐ ☐☐ *year / month / day*

A. BRIEF PAIN INVENTORY SHORT FORM

Please record all responses as reported by patient at time of administration.

1. Has patient experienced unusual kinds of pain today? ☐ No ☐ Yes
   (related to their cardiac surgery)
2. a) Indicate shaded areas on diagram or locations given by the patient either verbally or by pointing to his/her body.

   ______________________ ______________________
   ______________________ ______________________
   ______________________ ______________________

   b) Indicate which area hurt the most: ______________________
3. a) Please record **worst** level of pain in the last 24 hrs as reported by patient (while lying down): ☐☐
   b) Please record **worst** level of pain in the last 24 hrs as reported by patient (while moving): ☐☐
4. Please record **least** level of pain in the last 24 hrs as reported by patient: ☐☐
5. Please record **average** level of pain in the last 24 hrs as reported by patient: ☐☐
6. Please record level of pain patient has right now as reported by patient: ☐☐
7. Is the patient receiving treatment or medication for pain? ☐ No ☐ Yes → ***Record analgesics on CRF 407 for POD3 Complete below for 30 Day, 6 month and 1 year follow up.***

(Code)	Drug (provide code, if 99 specify)	Dose	Unit	Route	No. of doses w/in 24hrs	Schedule
☐☐	__________	☐☐☐☐☐☐.☐☐☐	☐☐	☐	☐	☐ Regular ☐ PRN
☐☐	__________	☐☐☐☐☐☐.☐☐☐	☐☐	☐	☐	☐ Regular ☐ PRN
☐☐	__________	☐☐☐☐☐☐.☐☐☐	☐☐	☐	☐	☐ Regular ☐ PRN
☐☐	__________	☐☐☐☐☐☐.☐☐☐	☐☐	☐	☐	☐ Regular ☐ PRN
☐☐	__________	☐☐☐☐☐☐.☐☐☐	☐☐	☐	☐	☐ Regular ☐ PRN

8. How much relief have pain treatments or medications provided to the patient in the last 24hr? ☐☐☐ %
9. Please record pain interference rate, during the past 24 hrs, as reported by patient:

A. General Activity	☐☐	**E.** Relations with other people	☐☐
B. Mood	☐☐	**F.** Sleep	☐☐
C. Walking Ability	☐☐	**G.** Enjoyment of life	☐☐
D. Normal Work	☐☐		

Name of authorized person completing this CRF: ______________________ ☐☐☐☐ ☐☐ ☐☐ *year/month/day*

Version 5.0, 2016-11-08

Appendix T: Spielberger State-Trait Anxiety Inventory

FORESITE Substudy **STATE-TRAIT ANXIETY INVENTORY (STAI)** CRF 404

DataFax #084 CRF #404 Visit #010

PATIENT ID: ☐☐☐ ☐☐☐☐ PATIENT INITIALS: ☐☐☐ (F M L) Reference Page

FORESITE Substudy- Baseline

1. Date of questionnaire completion: ☐☐☐☐ ☐☐ ☐☐ (year / month / day)

A. STATE-TRAIT ANXIETY INVENTORY

Please record all responses as reported by patient at time of administration.

1. I feel calm. ☐
2. I am tense. ☐
3. I feel at ease. ☐
4. I am presently worrying over possible misfortunes ☐
5. I feel nervous. ☐
6. I am jittery. ☐
7. I am relaxed ☐
8. I am worried ☐
9. I feel steady. ☐
10. I feel frightened. ☐
11. I am a steady person ☐
12. I feel satisfied with myself ☐
13. I get in a state of tension or turmoil as I think over my recent concerns and interests. ☐
14. I wish I could be as happy as others seem to be. ☐
15. I feel like a failure. ☐
16. I feel nervous and restless ☐
17. I feel secure. ☐
18. I lack self-confidence. ☐
19. I feel inadequate. ☐
20. I worry too much over something that really doesn't matter ☐

Name of authorized person completing this CRF: .....

☐☐☐☐ ☐☐ ☐☐ (year/month/day)

Version 5.0, 2016-11-08

Appendix U: Hospital Anxiety and Depression Scale

FORESITE Substudy

HOSPITAL DEPRESSION SCALE (HDS)

CRF 400

Study #084 CRF #400 Visit #010

PATIENT ID: ☐☐☐ ☐☐☐☐ PATIENT INITIALS: ☐☐☐ (F M L)

Reference Page

FORESITE Substudy- Baseline

1. Date of questionnaire completion: ☐☐☐☐ ☐☐ ☐☐ (year / month / day)

A. HOSPITAL DEPRESSION SCALE QUESTIONNAIRE

(Please record all responses as reported by patient at time of administration.)

1. I still enjoy the things I used to enjoy:
   - ☐ 0 Definitely as much
   - ☐ 1 Not quite as much
   - ☐ 2 Only a little
   - ☐ 3 Hardly at all

2. I can laugh and see the funny side of things:
   - ☐ 0 As much as I always could
   - ☐ 1 Not quite so much now
   - ☐ 2 Definitely not so much now
   - ☐ 3 Not at all

3. I feel cheerful:
   - ☐ 3 Not at all
   - ☐ 2 Not often
   - ☐ 1 Sometimes
   - ☐ 0 Most of the time

4. I feel as if I am slowed down:
   - ☐ 3 Nearly all the time
   - ☐ 2 Very often
   - ☐ 1 Sometimes
   - ☐ 0 Not at all

5. I have lost interest in my appearance:
   - ☐ 3 Definitely
   - ☐ 2 I don't take as much care as I should
   - ☐ 1 I may not take quite as much care
   - ☐ 0 I take just as much care as ever

6. I look forward with enjoyment to things:
   - ☐ 0 As much as I ever did
   - ☐ 1 Rather less than I used to
   - ☐ 2 Definitely less than i used to
   - ☐ 3 Hardly at all

7. I can enjoy a good book or radio or TV program:
   - ☐ 0 Often
   - ☐ 1 Sometimes
   - ☐ 2 Not often
   - ☐ 3 Very seldom

To calculate the Total Score, add the score to the left of each response for each question.

Total Score = ☐

Name of authorized person completing this CRF: .....

☐☐☐☐ ☐☐ ☐☐ (year/month/day)

Version 5.0, 2016-11-08

Appendix V: Analgesic Chart Audit

FORESITE Substudy **ANALGESIC CHART AUDIT** **CRF 407**

DataFax #084 CRF #407 Visit #011

PATIENT ID: ☐☐☐ ☐☐☐☐ **PATIENT INITIALS:** ☐☐☐ (*F M L*) Reference Page

FORESITE Substudy- POD3

1. Date of form completion: ☐☐☐☐ ☐☐ ☐☐ *year / month / day*

A. ANALGESIC CHART AUDIT FORM

(Record all analgesic medication prescribed on/after post-op day 3)

1. Was the patient prescribed an analgesic on or after the time point specified above? ☐ No ☐ Yes ➔ ***Complete this CRF***

Post-op Day	Drug (provide reference code)		Dose	Unit	Route	No. of doses POD3	Schedule
☐	☐☐	______	☐☐☐☐☐☐.☐☐☐	☐☐	☐	☐	☐ Regular ☐ Single Dose ☐ PRN
☐	☐☐	______	☐☐☐☐☐☐.☐☐☐	☐☐	☐	☐	☐ Regular ☐ Single Dose ☐ PRN
☐	☐☐	______	☐☐☐☐☐☐.☐☐☐	☐☐	☐	☐	☐ Regular ☐ Single Dose ☐ PRN
☐	☐☐	______	☐☐☐☐☐☐.☐☐☐	☐☐	☐	☐	☐ Regular ☐ Single Dose ☐ PRN
☐	☐☐	______	☐☐☐☐☐☐.☐☐☐	☐☐	☐	☐	☐ Regular ☐ Single Dose ☐ PRN
☐	☐☐	______	☐☐☐☐☐☐.☐☐☐	☐☐	☐	☐	☐ Regular ☐ Single Dose ☐ PRN
☐	☐☐	______	☐☐☐☐☐☐.☐☐☐	☐☐	☐	☐	☐ Regular ☐ Single Dose ☐ PRN
☐	☐☐	______	☐☐☐☐☐☐.☐☐☐	☐☐	☐	☐	☐ Regular ☐ Single Dose ☐ PRN
☐	☐☐	______	☐☐☐☐☐☐.☐☐☐	☐☐	☐	☐	☐ Regular ☐ Single Dose ☐ PRN
☐	☐☐	______	☐☐☐☐☐☐.☐☐☐	☐☐	☐	☐	☐ Regular ☐ Single Dose ☐ PRN
☐	☐☐	______	☐☐☐☐☐☐.☐☐☐	☐☐	☐	☐	☐ Regular ☐ Single Dose ☐ PRN
☐	☐☐ Code	______	☐☐☐☐☐☐.☐☐☐	☐☐	☐	☐	☐ Regular ☐ Single Dose ☐ PRN

Name of authorized person completing this CRF: [ ] ☐☐☐☐ ☐☐ ☐☐ *year/month/day*

Version 5.0, 2016-11-08

Appendix W: Hamilton Integrated Research Ethics Board Project Approval Letter

Hamilton Health Sciences | McMaster University | St. Joseph's Healthcare Hamilton

Hamilton Integrated Research Ethics Board
AMENDMENT REQUEST

REB Project #: 12-696

Principal Investigator: Dr. Andre Lamy

Project Title: Vascular events in Surgery patients cOhort evaluatioN - Cardiac Surgery (VISION Cardiac Surgery)

Sub-Study: VISION Cardiac Surgery Sub-Study: FORESITE-VISION

Document(s) Amended with version # and date:

- Application Form - Revised Sections on Funding & Budget Summary
- Protocol Amendment - VISION Cardiac Surgery Sub-Study: Foresite-Vision Ver: 1.0 Dated: 25 November, 2013
- Consent Form Amendment - Information Sheet and Consent Form (Participant) Ver: 2.0 Dated: 22 November, 2013
- Questionnaire - Sub-Study Questionnaire: Brief Pain Inventory (BPI)
- Questionnaire - Sub-Study Questionnaire: Pain Barriers Questionnaire (PBQ) Dated: 8/12/2012
- Questionnaire - Sub-Study Questionnaire: Analgesic Chart Audit Form
- Questionnaire - Sub-Study Questionnaire: Ambulatory Home Care Record (AHCR) Dated: 1998
- Questionnaire - Sub-Study Questionnaire: Gender Role Expectations of Pain (GREP)
- Questionnaire - Sub-Study Questionnaire: Short-Form 12 (SF-12)
- Questionnaire - Sub-Study Questionnaire: State-Trait Anxiety Inventory
- Questionnaire - Sub-Study Questionnaire: Somatic Pre-Occupation and Coping Questionnaire (SPOC)
- Other - Release of Medical Information Form Ver: 1.0 Dated: 22 November, 2013
- Other - TCPS 2: Core Certificate for Michael McGillon dated 24 November 2013
- Administrative Change - Include Dr. Michael McGillion and Jason Busse for the Addendum to the Sub-Study FORESITE-VISION
- Administrative Change - Local Study Coordinator is Lindsay Doharris
- Other - Letter dated November 25, 2013 re summary and rationale of amendment

Research Ethics Board Review
(this box to be completed by HIREB Chair only)

[X] **Amendment approved as submitted**

[ ] **Amendment approved conditional on changes noted in "Conditions" section below**

[ ] **New enrolment suspended**

REB Project #: 12-696 **Page 2 of 2 Pages**

[ ] Study suspended pending further review

Level of Review:

[ ] Full Research Ethics Board

[X] Research Ethics Board Executive

The Hamilton Integrated Research Ethics Board operates in compliance with and is constituted in accordance with the requirements of: The Tri-Council Policy Statement on Ethical Conduct of Research Involving Humans; The International Conference on Harmonization of Good Clinical Practices; Part C Division 5 of the Food and Drug Regulations of Health Canada, and the provisions of the Ontario Personal Health Information Protection Act 2004 and its applicable Regulations; For studies conducted at St. Joseph's Hospital, HIREB complies with the health ethics guide of the Catholic Alliance of Canada

Raelene A Rathbone

Suzette Salama PhD., Chair

Raelene Rathbone, MB, BS, MD, PhD, Chair

12/3/2013

Date

All Correspondence should be addressed to the HIREB Chair(s) and forwarded to:
HIREB Coordinator
293 Wellington St. N, Suite 102, Hamilton ON L8L 8E7
Tel. 905-521-2100 Ext. 42013 Fax: 905-577-8378

Appendix X: Hamilton Integrated Research Ethics Certificate

Hamilton Health Sciences | St. Joseph's Healthcare Hamilton | McMaster University Health Sciences

CERTIFICATE OF COMPLETION

This is to certify that

Shaunattonie Henry

has successfully completed

the Tutorial for Researchers Conducting Retrospective Review of Health Records

Certification Number: 351677

Date: 2017-07-13

HiREB
Hamilton Integrated Research Ethics Board

Hamilton Integrated Research Ethics Board

Appendix Y

Preoperative and Operative Sample Characteristics

Preoperative Sample Characteristics

Characteristics and Predictors of CPSP	**Number (%) of patients**
New York Heart Association Functional Classification	Class 1: n= 68 (10%) Class II: n=230 (33%) Class III: n=276 (39%) Class 1V: n=131 (18%)
Canadian Cardiovascular Society Angina Grading	Class 0: n=38 (5%) Class I: n=218 (32%) Class II: n=283 (41%) Class III: n=67 (10%) Class IVA: n=73 (10%) Class IVB: n=7 (1%)
Cardiac Arrest	No: n=722 (98%) Yes: n=13 (2%)
Prior Stroke	No: n=689 (94%) Yes: n=46 (6%)
Prior Transient Ischemic Attack	No: n=695 (95%) Yes: n=40 (5%)
Deep Vein Thrombosis	No: n=722 (98%) Yes: n=13 (2%)
Pulmonary Embolism	No: n=727 (99%) Yes: n=8 (1%)
Peripheral vascular disease	No: n=689 (94%) Yes: n=46 (6%)
Hypertension	No: n=162 (22%) Yes: n=573 (78%)
Congestive Heart Failure	No: n=625 (85%) Yes: n=110 (15%)
Obstructive Sleep Apnea	No: n=635 (86%) Yes: n=100 (14%)
Chronic Obstructive Pulmonary Disease	No: n=652 (89%) Yes: n=83 (11%)
Peptic Ulcer Disease	No: n=722 (98%) Yes: n=13 (2%)

Characteristics and Predictors of CPSP	Mean ± SD or Number (%) of patients
Myocardial Infarction	No: n=430 (60%) Yes: n=296 (40%)
Atrial Fibrillation	No: n=631 (86%) Yes: n=104 (14%)
Pulmonary Hypertension	No: n=695 (95%) Yes: n=40 (5%)
Diabetes Mellitus	No: n=480 (65%) Yes: n=255 (35%)
End Stage Renal Disease	No: n=723 (98%) Yes: n=12 (2%)
History of Tobacco usage prior to day of surgery	No: n=255 (35%) Yes: n=480 (65%)
Poor mobility	No: n=724 (98%) Yes: n=11 (2%)
Mobility limited by calf pain	No: n=667 (93%) Yes: n=51 (7%)
Previous current slow healing wound	No: n=688 (94%) Yes: n=29 (4%) Not reported: n=18 (2%)
Prior amputation	No: n=44 (6%) Yes: n=1 (0.1%) Not reported: n=690 (93.6%)
Anxiety[+]	Mean 43.97 (± 5.059) Mild: n= 102 (14%) Moderate: n=629 (85%) Severe: n=4 (1%)
Depressive Symptoms[+]	Mean 8.08 (± 1.583) Normal: n=214 (29%) Mild: n=483 (66%) Moderate: n=34 (4%) Severe: n=4 (1%)
Pain Intensity¶	Mean 0.91 (± 2.042) No pain: n=568 (77%) Mild pain: n=75 (10%) Moderate pain: n=56 (8%) Severe pain: n=32 (4%)

Note: [+]percentage values rounded

*New York Heart Association Functional Classification: Class 1-no symptoms; Class II-mild symptoms; Class III-moderate symptoms; Class 1V-severe symptoms.

∞Canadian Cardiovascular Society Angina Grading: Class 0-asymptomatic; Class I-angina with exertion; Class II slight limitation; Class III-symptoms with everyday living activities; Class IVA-symptoms deterioration controlled

on oral medical therapy; Class IVB-continued pain/symptom despite maximal oral medical therapy.
¶Pain intensity categories based on numerical rating scale: no pain (0), mild pain (1-3), moderate pain (4-6) severe pain (7-10).

Operative Sample Characteristics

Operative characteristics	**Number (%) of patients or Mean ± SD**
Urgency rating	Elective: n=480 (65%) Urgent: n=251 (34%) Emergency: n=4 (01%)
Type of Surgery	CABG only: n=606 (82.4%) 1 graft=41 (5.6%) 2 grafts=61 (8.3%) 3 grafts=179 (24.4%) 4 grafts=246 (33.5%) 5 grafts=69 (9.4%) 6 grafts=10 (1.4%) Any valve repair: n=257 (34.9%)
Heart rate (n=732) (beats per minute)	Mean 73 ± 13 Range 45 to 150
Blood pressure (n=734) (mmhg)	Mean Systolic: 150.47 ± 27.14 Mean Diastolic: 70.63 ± 13.06 Range Systolic 70 to 300, Range Diastolic 30 to 122
Hemoglobin (n=735) (mmol)	Mean 12.55 ± 1.82 Range 6 to 20
Total WBC (n=735) (mm^3)	Mean 7.09 ± 2.53 Range 2 to 40
Platelet count (n=734) (mmol)	Mean 210.94 ± 62.64 Range 42 to 644
aPTT (n=533) (mmol)	Mean 32.03 ± 9.10 Range 19 to 105
INR (n=712) (mmol)	Mean 1.00 ± 0.11 Range 1 to 2
Glucose (n=717) (mmol)	Mean 7.03 ± 2.83 Range 3 to 24
Sodium (n=722) (mmol)	Mean 139.41 ± 2.84 Range 120 to 146
Potassium (n=722) (mmol)	Mean 4.27 ± 0.669 Range 3 to 14
Creatinine (n=735) (mmol)	Mean 98.35 ± 62.48 Range 51 to 848
Duration of surgery (n=735) (hours)	Mean 3.35 ± 0.43 Range 1 to 8
Time on bypass (minutes)	Mean 82.81 ± 33.047 Range 23 to 231

Operative characteristics	**Number (%) of patients or Mean ± SD**
Cardiac Valve Status	
Left Ventricle Ejection Fraction	Grade I (≥50%): n= 576, (79.6%) Grade II (35-49%): n=108, (15%) Grade III (20-34%): n=38, (5.2%) Grade IV (<20%): n=2, 0.2%
Aortic Stenosis	None: n=329, (61.6%) Mild: n=22, (4.1%) Moderate: n=31, (5.8%) Severe: n=152, (28.5%)
Aortic Regurgitation	None: n=297, (57.2%) Mild: n=167, (32.2%) Moderate: n=40, (7.7%) Severe: n=15, (2.9%)
Mitral Stenosis	None: n=485, (97%) Mild: n=7, (1.4%) Moderate: n=5, (1%) Severe: n=3, (0.6%)
Mitral Regurgitation	None: n=127, (25%) Mild: n=316, (62%) Moderate: n=46, (9%) Severe: n=20, (4%)
Tricuspid Stenosis	None: n=485, (99.8%) Mild: n=1, (0.2%)
Tricuspid Regurgitation	None: n=156, (31.8%) Mild: n=310, (63.3%) Moderate: n=16, (3.3%) Severe: n=8, (1.6%)
Pulmonic Stenosis	None: n=455, (99.8%) Mild: n=1, (0.2%)
Pulmonic Regurgitation	None: n=249, (54.4%) Mild: n=206, (45%) Moderate: n=2, (0.4%) Severe: n=1, (0.2%)

Note: [+]percentage, means and SD values rounded; %: Percentage
Legend: CABG: Coronary artery bypass surgery; SD: Standard Deviation; mmHG: millimeters of mercury; mmol: millimoles per litre

Appendix Z

Table 20

Collinearity Diagnostics

	95% CI	Tolerance	VIF
Postoperative Day 3			
Worst pain in the last 24 hours while lying	-0.937, -0.112	0.530	1.887
Worst pain in the last 24 hours with movement	-0.113, 0.653	0.606	1.649
Least pain in the last 24 hours	0.002, 1.301	0.538	1.858
Average pain in the last 24 hours	-0.668, 0.588	0.412	2.428
Pain right now	-1.111, -0.008	0.433	2.311
Postoperative Day 30			
Worst pain in the last 24 hours while lying	-1.598, 0.507	0.326	3.067
Worst pain in the last 24 hours with movement	-0.777, 0.865	0.454	2.203
Least pain in the last 24 hours	-1.686, 2.129	0.331	3.020
Average pain in the last 24 hours	-1.323, 2.229	0.199	5.019
Pain right now	-2.307, 1.219	0.216	4.636

Legend: CI: Confidence Interval; VIF: Variance Inflation Factor