POST-OPERATIVE OPIOID PRESCRIPTION AND USE IN ADULT CARDIAC SURGERY

by

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POST-OPERATIVE OPIOID PRESCRIPTION AND USE IN

ADULT CARDIAC SURGERY

submitted by Edward D. Percy in partial fulfillment of the requirements for

the degree of Master of Science

in Surgery

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Abstract

Introduction: Persistent opioid use following cardiac surgery occurs in up to 13% of opioid-naïve patients, however there is little data available to guide analgesic prescription at the time of discharge. The purpose of this research was to examine opioid prescription in adult cardiac surgery through two specific aims: (i) to characterize current discharge opioid prescribing practices in Canada and the United States, and (ii) to characterize patient-level opioid use patterns in the post-discharge period.

Methods: Prescription practices in Canada and the United States were examined through a survey of the Canadian Society of Cardiac Surgeons, and a sample of the Centers for Medicare and Medicaid Services dataset, respectively. Patient-level post-discharge opioid use was assessed in a cohort study of patients undergoing sternotomy-based procedures at a tertiary care hospital. Opioid use over the first 10-days after discharge was collected via diary, and confirmed with a follow-up researcher-directed pill count.

Results: In our survey of Canadian prescribers, 81% reported routinely prescribing opioids at discharge, however, the medication type and dose were highly variable. Furthermore, there was an association between a lack of formal education in opioid prescription and a higher number of pills prescribed ($p<0.05$). In the United States, there was also wide variation in the dose of opioids prescribed at the provider, state and regional levels ($p<0.001$ for all). In total, 116 providers (4.2%) across 32 states prescribed more than two standard deviations above the national mean. Furthermore, on average patients filled only 47% of opioid pills prescribed. Finally, in a prospective cohort study of 104 patients following sternotomy-based procedures,

35% used none and 19.0% used fewer than half of the pills prescribed. Median total consumption was the equivalent of 9 Oxycodone 5mg tablets. Following risk-adjustment, mean pain score ≥3 on the day of discharge was predictive of opioid use (OR 2.9, 95% CI 1.8-4.8; $p<0.001$).

Conclusion: Opioid prescribing practices after cardiac surgery are highly variable throughout North America. Many patients develop persistent use, possibly contributing to chronic dependence. A large portion of these patients can be managed without opioids at discharge. Our findings may serve as a preliminary benchmark for quality improvement.

Lay Summary

The prescription of opioid pills has contributed significantly to the ongoing opioid epidemic. Close to 1 in 10 patients continue to use opioids more than 3 months after heart surgery, however we know very little about how we should be prescribing these medications. In two studies examining opioid prescribing practices in Canada and the United States, we found that surgeons' individual practices varied widely and that there has been a lack of formal education in this important area. In another study, following 104 patients who went home after heart surgery, we found that most patients used none, or very few of the opioid pills prescribed. We also found that a patient's pain on the day of discharge is a good indicator of whether they will require any opioid medication at home. We hope that his data can form a basis for evidence-based recommendations and education in the future.

Preface

This manuscript describes three individual studies which I designed and managed:

1. I designed a survey of Canadian cardiac surgeons and trainees regarding opioid prescribing practices at discharge, and led the Delphi process for question development. I worked with the Canadian Society of Cardiac Surgeons, and individual representatives from across Canada, to ensure dissemination of the survey and I managed the data. The statistical analysis in this project was conducted by my colleague Dr. Sameer Hirji, MD, MPH. This study was exempt from ethics board review.
2. I designed a study of Centers for Medicare and Medicaid Services data on opioid prescription after coronary bypass in the United States. I obtained the data, which was previously compiled as part of an open-source collaboration between the Johns Hopkins Bloomberg School of Public Health, and Kaiser Health. I designed the study and analytic plan, and the statistics were performed by Olena Cherkasky, BS. This study was exempt from ethics board review
3. I designed a prospective study of patient-level post-discharge opioid use, and undertook the process of obtaining ethics board approval, designing consent forms and other study documents. The study was conducted within the Department of Surgery, Division of Cardiac Surgery, at Brigham and Women's Hospital in Boston, Massachusetts. I screened patients prospectively and worked with our Division's research assistant to consent patients and conduct follow-up. I designed the analytic plan, which was performed by Olena Cherkasky, BS. The study was approved by the

Human Research Committee within the Partner's Healthcare Internal Review Board (Protocol #2019P000731) in Boston, Massachusetts.

The studies described herein have been published in the following forms. My contributions to the research is detailed above and I was primarily responsible for the writing of the manuscripts and the associated conference proceedings.

1. Percy ED, Hirji S, Cote C, et al. Variability in opioid prescribing practices among cardiac surgeons and trainees [published online ahead of print, 2020 Jul 27]. *J Card Surg*. 2020;10.1111/jocs.14885.
2. Percy ED, Hirji S, Leung N, et al. Prospective Cohort Evaluation of Opioid Use and Pain Following Cardiac Surgery. *Can J Cardiol.* 2020. [Published abstract of oral conference presentation]

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List of Abbreviations

ANOVA – Analysis of variance

AVR – Aortic valve replacement

BMI – Body mass index

CABG – Coronary artery bypass grafting

CI – Confidence interval

CMS – Centers for Medicare and Medicaid Services

CSCS – Canadian Society of Cardiac Surgeons

EMR – Electronic medical record

IQR – Interquartile range

MME – Morphine milligram equivalents

NRS – Numerical rating scale

OR – Odds ratio

PDD – Post-discharge day

SD – Standard deviation

Acknowledgments

I offer my profound gratitude to my supervisors who provided support and mentorship throughout all aspects of this research. I particularly wish to thank Dr. Marc Pelletier, who has been an influential figure and mentor since my time in medical school. His guidance led me to pursue my research fellowship in Boston, and he has been instrumental in the design and conduct of this research program. My deep appreciation also goes out to Dr. Tsuyoshi Kaneko, who welcomed me into his clinical research group at Brigham and Women's Hospital and oversaw the conduct and completion of these studies. I cannot overstate the impact that Dr. Kaneko's teaching has had on my understanding of, and appreciation for, all aspects of clinical research. The skills that I developed under the mentorship of Dr. Pelletier and Dr. Kaneko will serve as invaluable tools as I strive to become an academic surgeon in the future. I also owe a debt of gratitude to Dr. Richard Cook, who has become a trusted mentor both clinically and academically since the beginning of my residency in Vancouver. I appreciate his guidance and look forward to our ongoing work as I rejoin the clinical residency program.

In addition to my supervisors, I would like to thank my colleagues in the Division of Cardiac Surgery at Brigham and Women's Hospital. In particular, Dr. Sameer Hirji, Dr. Farhang Yazdchi, Dr. Morgan Harloff and Dr. Paige Newell, who's help was indispensable in the design and management of these studies and others. It has been an honour to be part of this productive and collaborate research group. Additionally, none of this would have been possible without the guidance of the Division's data manager and statistician Siobhan McGurk who provided thoughtful supervision throughout these and other projects. I am also incredibly grateful for the

help of Olena Cherkasky and Nicholas Leung for their efforts in helping to complete these studies.

I must also acknowledge the involvement of the Clinician Investigator Program (CIP) at the University of British Columbia. Through the provision of salary funding and various training courses, the CIP was truly an indispensable part of my research program. Thank you to Dr. Sian Spacey for your support in the development to these projects and to Tessa Feuchuk for your coordination of the Program.

I have also received support from Dr. Alice Mui as part of this degree program. Dr. Mui provided guidance as I began this journey and has been an important advocate for my studies and research along the way. I would also like to recognize my colleague in the program, Dr. Najah Adreak, for her friendship and support throughout the past 2 years.

Finally, I wish to thank my family. My wife Alana Green has been my greatest supporter throughout this work. I love you and will always cherish our time together in Boston. And my son Leo, who joined us as this data was being collected, has made this time in my life incredibly joyful and special. I am so grateful to have you in my life.

Dedication

This work is dedicated to our surgical patients, who put their trust in us during trying personal times. We hope that this research will contribute, in some small way, as we continuously strive to provide better care to these strong individuals.

Chapter 1: Introduction

1.1 Background and Epidemiology of the Opioid Epidemic

The opioid epidemic has become a major public health concern throughout North America.(1–3) Initial signs of an emerging crisis in Canada date back to the early 1990's, when results of a task force on illicit overdose deaths in British Columbia noted a "very real and very serious drug problem" and warned of a growing health and social crisis.(4) Since then, the epidemic has continued to escalate, surpassing motor-vehicle accidents as the leading cause of premature death, and in April 2016 the Government of British Columbia declared opioid-overdose deaths to be a public health emergency.(5,6) Between January 2016 and December 2019, 15,393 apparent opioid-related deaths occurred in Canada.(7) British Columbia, in particular, continues to be the most severely impacted jurisdiction in the country, with 19.6 opioid-related deaths per 100,000 population in 2019. Additionally, almost 20,000 opioid-related poisoning hospitalizations were recorded throughout the country, excluding Quebec.

The course of the opioid epidemic has been described in terms of three distinct waves.(8) Throughout the 1990's, the first wave began with the increasing prescription of natural and semi-synthetic opioid medications. This has been largely attributed to a proliferation of novel opioid formulations, combined with the increasing focus on the treatment of pain as the "fifth vital sign", and growing concerns over the potential toxicity of non-opioid alternatives.(9–11) Additionally, marketing and lobbying from the pharmaceutical industry has been recognized as an important factor in the steady rise of opioid analgesic prescription and consumption.(9,12,13) Several lawsuits have been recently settled against American-based pharmaceutical companies for enabling the supply of opioid medications "without legitimate medical purpose" as part of

this first wave.(14) A second phase began with a rapid increase in deaths related to heroin around 2010, attributable to an increase in dependency in the context of greater availability of heroin, and the growing presence of anti-abuse reformulations of prescription opioids.(15,16) Finally, a third wave began in 2013, at which time there was a steep rise in the availability of synthetic, and extremely potent, opioids such as fentanyl and its analogues.(17) Between 2012 and 2016, the rate of illicit drug deaths attributable to fentanyl increased from 4% to 68% in British Columbia.(17) Underlying all phases of this epidemic are complex and multifactorial interactions of social determinants and economic disparities, which add additional barriers to any public health response.(9) As society continues to grapple with the immense challenge of the ongoing opioid crisis, the role of perioperative analgesic prescribing in contributing to opioid dependence remains under-studied and inadequately addressed.(18)

1.2 The Role of Prescription Opioids

1.2.1 Prescription Opioids and the Opioid Epidemic

Prescription opioids have played a major role in the current epidemic of chronic use and overdose death.(19–21) In the United States, 240 million opioid prescriptions were dispensed in 2015 and this rise in dispensing has been strongly associated with the increase in chronic use and death.(22) The vast majority of heroin users have reported using prescription opioids prior to illicit drugs.(23,24)

Although the frequency of opioid prescription has decreased slightly in recent years, they remain extremely prevalent. An estimated 4.6 million Canadians (12% of the population) were prescribed an opioid in 2018, over half of whom were starting a new prescription.(25)

Additionally, there was little change in the size or duration of opioids prescribed between 2013 and 2018. Size and duration remain important factors, as prescription sizes of >50 morphine milligram equivalents (MME) per day are associated with a two-fold increase in the rate chronic use compared to prescriptions of less than 20 MME per day.(26) Furthermore, each additional week of opioid prescription increases the risk of chronic use or overdose death by 20%.(27) Although the majority of opioid-related deaths in the current era are primarily caused by illicit synthetic opioids, prescription opioids continue to play a significant role; responsible for over 35% of overdose deaths.(28)

Several studies have demonstrated evidence of significant excess opioid prescription following surgery.(29–34) In one multicenter study of nearly 20,000 patients, 45% of those who received no inpatient opioid administration within 24-hours of discharge were still prescribed narcotic medication when they went home.(35) Excess prescription is concerning in its own right, given the established links between prescription size and chronic use. However, excess prescription is also a major contributor to diversion of opioids within the community. Over 70% of those who abuse prescription opioids have received them through some form of diversion, and it has been reported that 55% of these individuals received pills from a family member or friend with excess pills.(36) Most concerning, Khan et al. showed recently that opioid prescriptions to family members were a significant risk factor for overdose death in a large insurance database (Odds ratio (OR) 2.89, 95% CI 2.59-3.23), with a clear dose-dependent effect.(37)

1.2.2 Prescription and Chronic Use

Given the frequency of opioid prescription and its associated risks, there has been increased scrutiny of prescribing habits within the medical community.(38,39) Surgical

specialties are of particular interest given their routine prescription of opioids to narcotic-naïve patients. Surgeons are responsible for over half of all new opioid prescriptions and even short courses can lead to persistent use and long-term dependence.(40–44) In one survey of patients receiving treatment for chronic opioid use, Callinan et al. demonstrated that almost one-third of patients had their initial opioid prescription originate from a surgeon.(45)

Rates of new chronic opioid use following surgery, which is typically defined as ongoing use 3 months following surgery, range between 1% and 14%, depending on the operation performed.(46) Given the invasive nature of the cardiothoracic procedures, these are often associated with significant pain, and cardiac surgery has been associated with a particularly high rate of persistent opioid use following discharge.(47–49) The rate of new persistent opioid use between 90 and 180 days following discharge has been reported up to 5.5% following valve surgery.(50) Furthermore, Brescia et al. examined new persistent use in the United States Centers for Medicare and Medicaid Services Database and reported that 13% of patients were still using opioids 3 months after coronary artery bypass grafting (CABG).(51) On multivariate analysis, they showed that gastrointestinal complications, history of drug abuse and history of tobacco use were associated with ongoing opioid use. Perioperative prescription size was also independently associated with increased rates of new persistent use across all cardiothoracic procedures. Similarly, Clement et al. showed in a separate Medicare analysis that female gender (OR 1.30), anxiety (OR 1.40), tobacco use (OR 1.34), prior substance abuse (OR 1.99), living in the Southern United States (OR 1.46), and prescription sizes were independently associated with persistent use after CABG.(52)

1.2.2 Prescribing Variability

Despite the links between opioid prescription, chronic use, and the subsequent risks of longer-term addiction, prescription practices remain highly variable among individual patients and across medical and surgical specialties. In 2017, Barnett et al. showed wide variation in the rates of opioid prescribing among physicians within the same emergency department.(53) After adjusting for patient-level differences, patients treated by physicians within the highest quartile of prescribing rates were at significantly increased risk of developing long-term opioid use, compared to those treated by lowest-quartile prescribers (OR 1.30; 95% CI, 1.23-1.37; $p<0.001$). Similarly, high rates of variability and overprescribing have been reported among general surgical, urologic, and hand specialties.(33,36,54–56) This variation has been attributed to a lack of evidence regarding optimal prescription sizes, in addition to the absence of standardized guidelines, and the impact of clinical "inertia" leading to continued practices based on previous experiences.(53,57) Following from the known associations with prescription sizes and chronic use, variability in prescribing practices has become a major target for policy across medical specialties.

Despite the significance of the opioid epidemic, and the prevalence of cardiac surgical procedures (over 30,000 annually in Canada), little is known about current prescribing practices within the specialty.(58) The potential for significant variability in the cardiac surgical community, as a potential cause of the increased rates of persistent use seen in the specialty, along with the added potential for overprescribing and pill diversion, remain critical and understudied areas.

1.3 Current Evidence for Best Practices

There is little information available to guide best practices with respect to opioid prescription after surgery, and cardiac surgery in particular. In the absence of clear data, some individual hospitals have had success in reducing variability and overall prescription size by implementing institution-level quality improvement initiatives in specific subspecialties.(59–62) These initiatives are generally limited to a narrow band of common procedures and may be specific to the institutions and populations treated. In an effort to create a set of broad recommendations across several specialties, Overton et al. published a guidance document in *The Annals of Surgery* in 2018 for patients undergoing common surgical procedures.(63) The authors make a consensus recommendation of 0-to-20 Oxycodone 5mg tablets (150 MME) for opioid naïve patients following CABG. They do not, however, provide recommendations for other cardiac surgical procedures, and they provide no evidence upon which these recommendations are based. There remains a significant need to increase the evidence base for opioid prescribing recommendations following cardiac surgery.

1.4 Project Aims

Given the severity of the opioid problem and the potential contribution of cardiac surgery as a specialty, there is a significant need to address knowledge gaps related to current prescribing practices and optimal recommendations. The overall purpose of this research program was to explore issues related to current prescription patterns and ideal practices through two specific aims:

- Specific Aim 1: *To characterize current discharge opioid prescribing practices in both Canada and the United States.*

- Specific Aim 2: *To characterize patient-level opioid use patterns in the post-discharge period.*

Chapter 2: Materials and Methods

Three separate studies were conducted in order to test hypotheses across our two specific aims. In order to address the current state of opioid prescribing practices in cardiac surgery (*Specific Aim 1*), a national survey was conducted in Canada, and a separate study of a national database was conducted among Medicare beneficiaries in the United States. In order to address actual patient-level use (*Specific Aim 2*), a prospective cohort study of patients undergoing cardiac surgery at a large tertiary referral center was conducted.

2.1 Methods Related to Specific Aim 1

2.1.1 Opioid Prescribing Practices Among Cardiac Surgeons in Canada

2.1.1.1 Survey Development and Dissemination

A collection of 16 open and closed-ended survey questions were developed and refined through a systemic 3-round Delphi method conducted by four researchers with experience in treating post-operative cardiac surgery patients and taking into account existing literature. Questions were designed to test hypotheses across three major domains: participant demographics and practice information, discharge analgesic prescribing practices, and the role of education and guidelines surrounding opioid prescription. A French-language version of the survey was also developed to facilitate full inclusion of all programs in Canada. The complete list of survey questions is presented in **Appendix A**.

The survey was disseminated electronically via mailing lists from the Canadian Society of Cardiac Surgeons (CSCS). The CSCS is a primary societal body for cardiac surgeons in Canada and represents 117 of the approximately 175 cardiac surgeons in the country.(58,64) The

CSCS also represents 115 trainee members at the residency or fellowship level. The survey was disseminated twice through societal mailing lists and once via societal newsletter between April and August 2019. Furthermore, resident trainees from programs across the country contributed to facilitate further participation within their institutions, as part of the Canadian Cardiac Surgery Trainee Opioid Working Group (**Appendix B**). Survey responses were collected anonymously and compiled electronically through the Google Forms platform (Mountain View, California, USA).

2.1.1.2 Statistical Analysis

All opioid doses listed were converted to Morphine Milligram Equivalents (MME), for standardization (**Table 2.1**). Normally distributed continuous variables are expressed as a mean with standard deviation and were compared using independent t-tests. Non-normally distributed variables are expressed as median and interquartile range (IQR) and were compared using Mann-Whitney U-tests. Categorical variables are presented as number and percentages and were compared using $\chi 2$ or Fisher's exact tests depending on expected cell counts. Two-sided p-value < 0.05 was conventionally regarded as statistically significant. Analysis was conducted using STATA version 13.1 (College Station, TX).

Opioid	**Conversion factor**
Tramadol	0.1
Codeine	0.15
Morphine	1
Hydrocodone	1
Oxycodone	1.5
Hydromorphone	4

Table 2.1. Conversion factors for commonly-used opioids to Morphine Milligram Equivalents.

2.1.2 Opioid Prescribing Practices Among Cardiac Surgeons in the United States

2.1.2.1 Data Source, Selection, and Outcomes

John Hopkins Bloomberg School of Public Health, in collaboration with Kaiser Health News, developed a publicly available, open-access database of opioid prescribing patterns following various common surgical procedures, including CABG, in the United States.(65) The database was compiled from Centers of Medicare and Medicaid Services (CMS) from 2011-2016. This database identified the average number of 5-mg Oxycodone pills prescribed within one week of CABG for each cardiac surgeon prescribing under Medicare. The average number of pills filled by each patient was also reported. Exclusion criteria were cardiac surgeons who operated on fewer than 10 Medicare patients per year, and patients who consumed opioids within a year before their surgery.

2.1.2.2. Statistical Analysis

Our primary outcome of interest was mean MME per patient prescribed following CABG, stratified based on the surgeon, state, and region (Northeast, Midwest, South, West) to assess provider and geographical variation in opioid practices. We also examined the mean number of pills filled by patients of each surgeon. Normally distributed continuous variables are expressed as means ± standard deviation and were compared using independent t-tests between provider, states, regions. Non-normally distributed variables are expressed as median and interquartile range (IQR) and were compared using analysis of variance (ANOVA). Two-sided p-value < 0.05 was used for statistical significance. Analysis was conducted using R version 3.6.1 (2019).

2.2. Methods Related to Specific Aim 2

In order to assess patterns of real-world post-discharge opioid requirements, a prospective cohort trial was designed to enroll consecutive adult patients undergoing cardiac surgery at Brigham and Women's Hospital in Boston, Massachusetts.

2.2.1 Eligibility Criteria

2.2.1.1 Inclusion Criteria:

i. Able to consent to participation in the study

ii. Have undergone a sternotomy-based cardiac surgical procedure with planned discharge home within 24-48 hours.

2.2.1.2 Exclusion Criteria:

i. History of chronic pain

ii. Age > 85

iii. Prior opioid use (Opioid use within 3 months of surgery)

iv. Cardiac or cardiopulmonary transplant procedure

v. Re-do sternotomy or prior cardiac surgery

vi. Discharge to a facility other than home

2.2.2 Data Collection and Study Procedures

All patients who underwent cardiac surgery between June 2019 and January 2020 were considered. Each day, a clinical liaison sent a list of post-operative patients and noted those being considered for discharge in the next 1-2 days. Patients on this list were prospectively

screened to assess eligibility for enrollment in the study according to pre-specified inclusion and exclusion criteria. Clinical healthcare providers involved in direct in-hospital management or discharge planning had no role in the patient screening, data collection, or conduct of the study.

Following consent, baseline characteristics and in-hospital variables of interest were collected through a patient interview and through a search of our institutional electronic medical record (EMR). All variables of interest were defined according to the Society of Thoracic Surgeons Adult Cardiac Surgery Database Version 2.9.(66) The data collection form used for baseline and follow-up collection is presented in **Appendix C**. Patients were assigned a unique study ID to protect privacy.

2.2.3 Post-Discharge Opioid Tracking

All in-hospital pain and opioid use data were collected from routine nursing records through the EMR. Patients were provided with a standardized diary prior to discharge to record daily opioid use and pain. Each of the first 10 post-discharge days, starting on the day following discharge (Post-discharge Day (PDD) #1), patients recorded the number of opioid pills taken as well as their pain on a validated Numerical Rating Scale (NRS) from 1-10 (**Figure 2.1**). The full patient-directed diary instrument is shown in **Appendix D**. To encourage compliance, patients were instructed to keep their booklets alongside their opioid medication. At the completion of the booklet, patients also rated their overall satisfaction with their pain management on a 4-point scale as very unsatisfied, unsatisfied, satisfied, very satisfied. Following the 10-day diary collection period, patients mailed their completed booklets back to researchers in pre-paid envelopes.

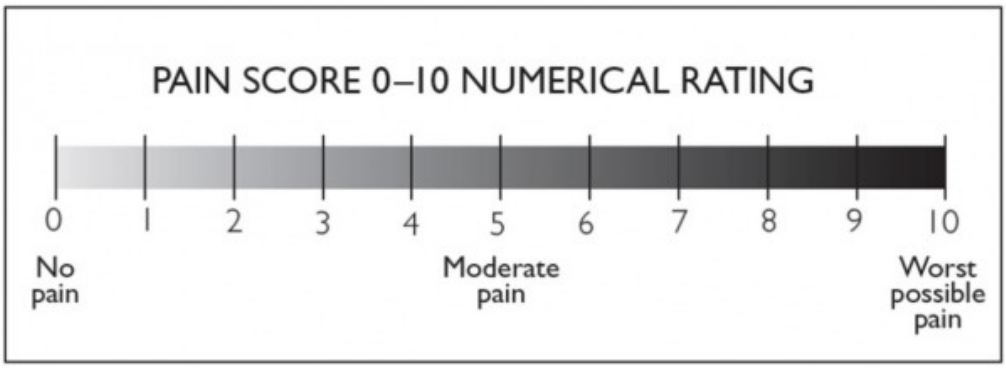


Figure 2.1 Visual analogue numerical pain rating scale used to record pain levels in the post-discharge period.

At Post-discharge day 10 (the last day of booklet recording), patients received a phone call from a study researcher in which they were asked to count pills remaining of their opioid prescription, and were asked about other analgesics used (**Appendix C**). They were again reminded to mail the completed diary via the pre-paid envelope.

2.2.4 Informed Consent

All consecutive patients undergoing cardiac surgery at Brigham and Women's Hospital during the study period were screened for eligibility. If patients were considered eligible they were approached by a study researcher between 24- and 48-hours prior to planned discharge home. All potential risks and benefits of the study were discussed with patients and they were assured that their interest or refusal to enter the study would have no bearing on the care they received. Patients signed institution-specific informed consent documentation, in paper-version. For those patients who did not speak English as a primary language, translation services and a short-form translated consent document were available.

Chapter 3: Results

3.1 Results of Specific Aim 1 – Variability in North American Prescribing Practices

3.1.1 Prescribing Practices Among Cardiac Surgeons in Canada

3.1.1.1 Response Rate and Participant Characteristics

In total, the survey was disseminated to 117 attending surgeons and 100 trainee members. Response rates were 35.9% among attending surgeons and 49.0% among trainees, for an overall response rate of 41.9%. Respondent characteristics are presented in **Table 3.1**. Attending cardiac surgeons with < 10 years, 10-20 years, and > 20 years in practice accounted to 16.5%, 16.5%, and 13.2% of all respondents, respectively. Responses were received from residents at all levels of the 6-year Royal College of Physicians and Surgeons cardiac surgery training curriculum and 6.6% of respondents were at the fellowship level. Among Canadian provinces, Ontario accounted for the greatest proportion of responses (29.7%) and Newfoundland was the only province in which cardiac surgery is performed which was not represented.

		Respondents N = 91
Attending Surgeon		
	Total Number	42 (46.2 %)
	> 20 years experience	12 (13.2 %)
	10 – 20 years experience	15 (16.5 %)
	5 – 10 years experience	11 (12.1 %)
	< 5 years experience	4 (4.4 %)
Trainee		
	Total Number	49 (53.8 %)
	Fellow	6 (6.6 %)
	PGY ≥6	6 (6.6 %)
	PGY 5	6 (6.6 %)
	PGY 4	8 (8.8 %)
	PGY 3	9 (9.9 %)
	PGY 2	5 (5.5 %)

	PGY 1	9 (9.9 %)
Province		
	British Columbia	15 (16.5 %)
	Alberta	13 (14.3 %)
	Saskatchewan	1 (1.1 %)
	Manitoba	8 (8.8 %)
	Ontario	27 (29.7 %)
	Quebec	18 (19.8 %)
	New Brunswick	4 (4.4 %)
	Nova Scotia	5 (5.5 %)
	Newfoundland	0 (0 %)
Center Classification		
	Teaching Center	85 (93.4 %)
	Non – Teaching Center	6 (6.6 %)

PGY – Post-graduate year

Table 3.1 Demographic, experience and practice details of survey respondents.

3.1.1.2 Discharge Prescribing Practices

Overall, 81% of respondents reported prescribing opioids at discharge for patients following routine sternotomy-based procedures, with 31% reporting "Always" prescribing opioids at discharge (**Figure 3.1A**). The median number of pills prescribed was 30 (20-30) pills with a median total dose of 135 (113-200) MME (**Figure 3.1B**). Eighty-nine percent reported never prescribing refills at the time of discharge and 82% reported never prescribing refills at follow-up or any time following discharge, although the timing of these follow-up refills was not examined.

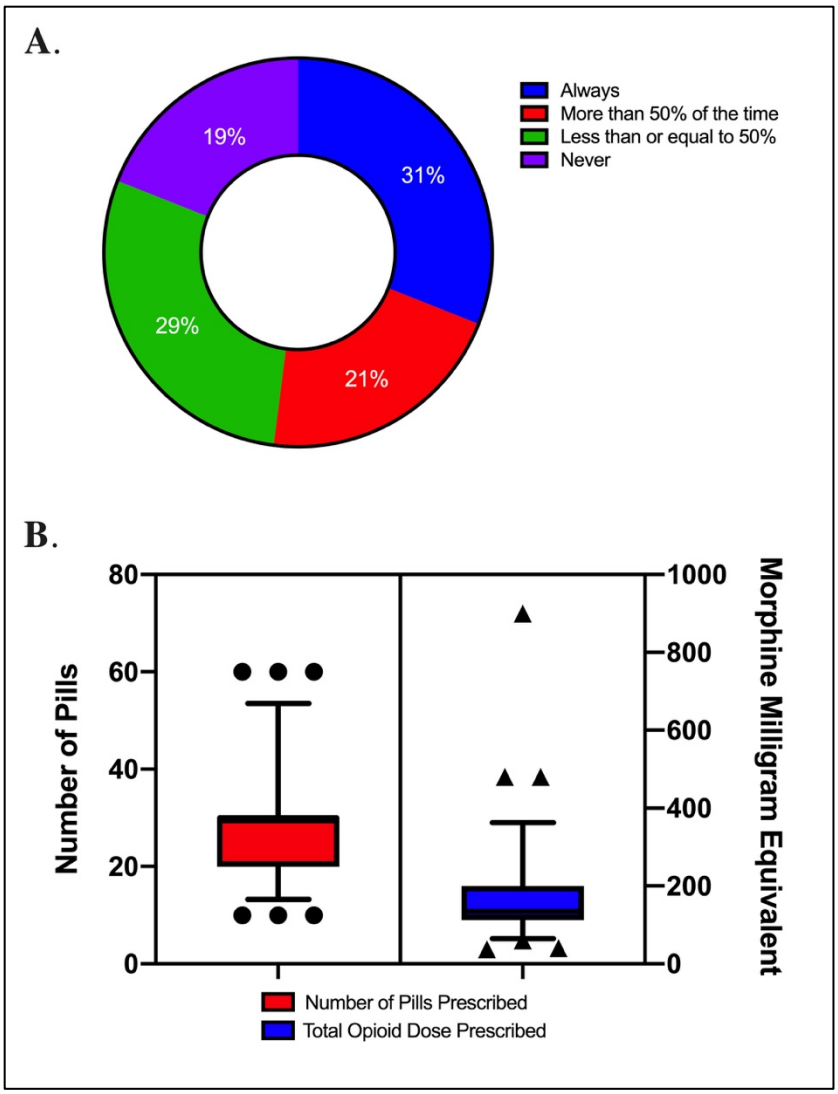


Figure 3.1 A. Frequency of opioid prescription at discharge for patients undergoing routine sternotomy-based procedures, and B. box chart of standard prescription sizes among surgeons who reported opioid prescription.

The most commonly prescribed opioid pill was hydromorphone (30%), followed by codeine-containing pills (27%) (**Figure 3.2**). Twenty respondents (21%) reported most often prescribing non-opioid analgesics only at discharge. Of these, 65% used primarily acetaminophen, 10% non-steroidal anti-inflammatories and 25% did not list a preference.

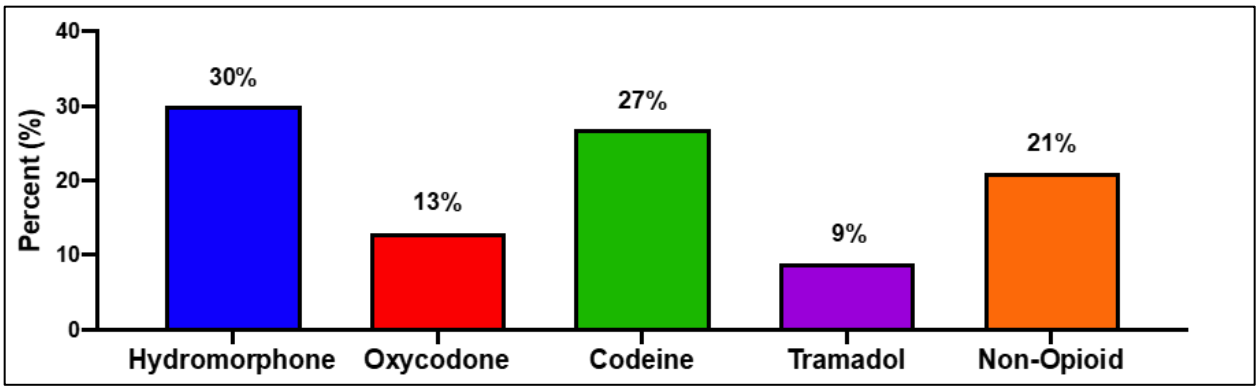


Figure 3.2 Most commonly prescribed opioid medications at discharge following routine sternotomy-based procedures.

There was a significant association between a lack of formal opioid prescribing education and a higher number of opioid pills prescribed (30 vs. 20 pills, p=0.039). There were no associations between level of training, practice location and amount of opioid prescribed. Furthermore, there were no significant differences in the proportion of those who "always" prescribe opioids based on years of practice, location of practice, or beliefs regarding the risk of chronic use.

3.1.1.3 Education and Guidelines

Respondents were asked to rank factors that most influenced their discharge analgesic prescribing practices (**Table 3.2**). Overall, informal education during training or from colleagues was the most commonly reported primary influence on prescribing habits (28.6%), followed by personal experience (25.3%) and formal education during medical school or subsequent accredited sessions (20.9%). Only 3.3% of respondents listed information from pharmaceutical companies as having any influence on their prescribing habits. Overall, only 26.0% of respondents had received formal education regarding dosing of opioids on discharge (**Figure**

3.3). The majority (91.2%) felt that there would be value in establishing guidelines for post-operative opioid prescription following routine cardiac surgical procedures.

Category	First Influence	Second Influence	Third Influence	Any Influence
Formal Education	19 (20.9 %)	18 (19.8 %)	16 (17.6 %)	53 (58.2 %)
Informal Education	26 (28.6 %)	25 (27.5 %)	12 (13.2 %)	63 (69.2 %)
Personal Experience	23 (25.3 %)	26 (28.6 %)	19 (20.9 %)	68 (74.7 %)
Published Literature	8 (8.8 %)	8 (8.8 %)	14 (15.4 %)	30 (33.0 %)
Institutional Policy	10 (11.0 %)	11 (12.2 %)	13 (14.3 %)	34 (37.4 %)
Pharmaceutical Information	1 (1.1 %)	0 (0 %)	2 (2.2 %)	3 (3.3 %)

Table 3.2 Sources of education regarding opioids, ranked by respondents in order of most to least influence on their prescribing practices.

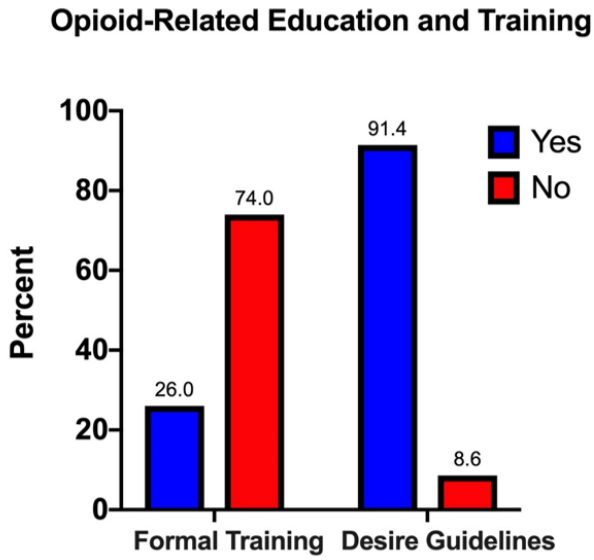


Figure 3.3 Proportions of respondents who had received formal training in opioid prescription and those who felt that there would be value in establishing guidelines in this area for routine cardiac surgical procedures.

Finally, respondents were asked about their perceptions of post-discharge opioid use. The majority (62.6%) believe that between 1% and 10% of opioid-naïve patients become chronic users following a routine post-operative prescription, whereas the 33.0% of respondents believe that fewer than 1% of these patients develop chronic use. Only 4% of respondents believed that the rate of chronic use was over 10%.

3.1.2 Prescribing Practices Among Cardiac Surgeons in the United States

Post-CABG prescription practices of 2742 cardiac surgeons in the United States were studied between 2011 and 2016 in the CMS dataset. Detailed information on patient or provider characteristics was not available in our limited dataset. Overall, the mean amount of opioids prescribed following CABG was 356 MME (±40). However, patients filled an average of only 188 MME (±62). The median difference between opioid pills prescribed and opioid pills filled, by state, was 50% (interquartile range (IQR) 40% - 57%) (**Figure 3.4**).

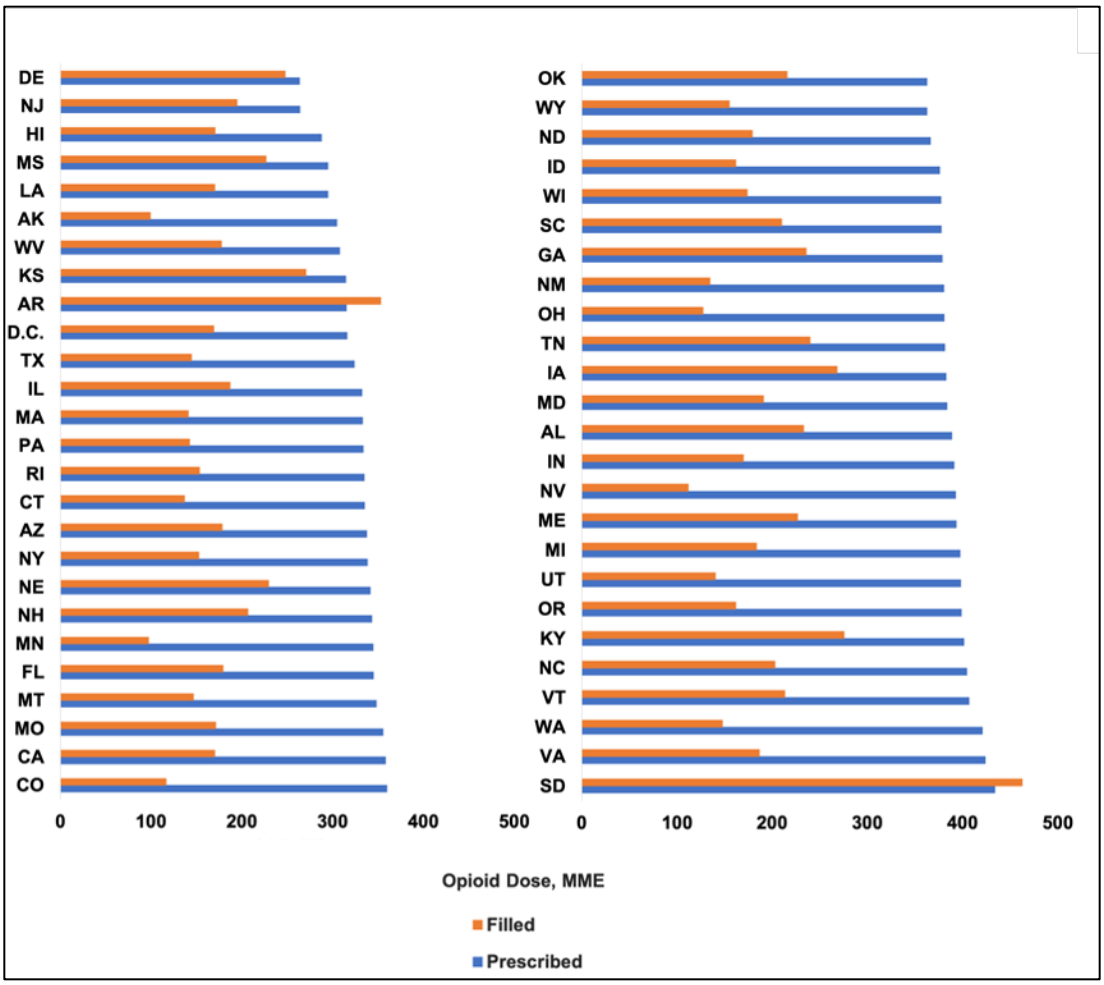


Figure 3.4 Differences between opioid pills prescribed and filled by Medicare patients following CABG between 2011 and 2016, by state (in order of ascending prescription sizes).

There was significant variability in opioid prescribing practices among cardiac surgeons, indicated by a wide range of mean prescription sizes, from a minimum of 120 MME to a maximum of 1252.5 MME. Furthermore, 116 providers (4.2%) across 32 states, prescribed more than two standard deviations above the mean for all providers. Nationally, South Dakota was the only state to prescribe more than one standard deviation above the mean compared to the rest of the country. Overall significant variability in mean opioid prescribing practices were observed at the state level ($p<0.001$) (**Figure 3.5**).

Variability was also evident between regions in the United States ($p<0.001$). The Midwest had the highest median amount of opioid prescriptions postoperatively (135 MME, IQR 68-225 MME), while the Northeast had the lowest (128 MME, IQR 68-218 MME) (**Figure 3.6**).

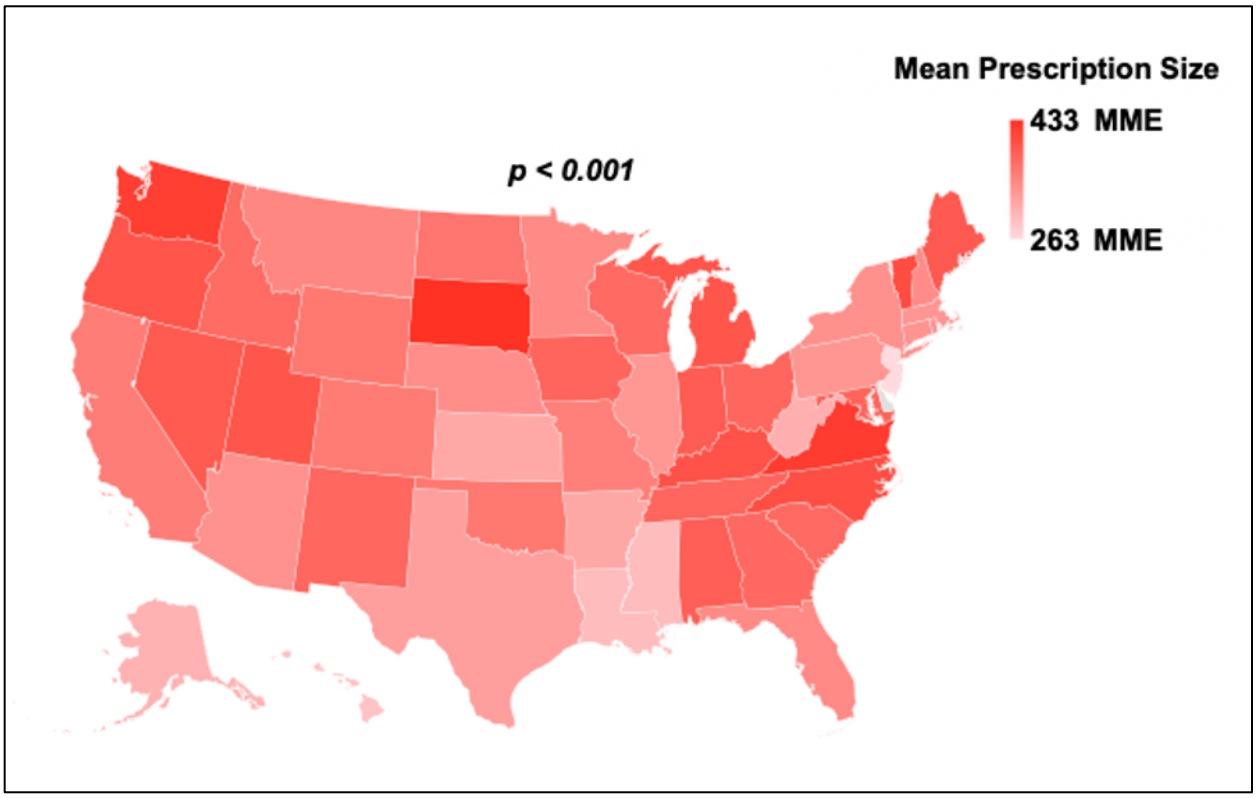


Figure 3.5 United States national heat map showing geographic variation of opioid prescribing practices across the nation after CABG.

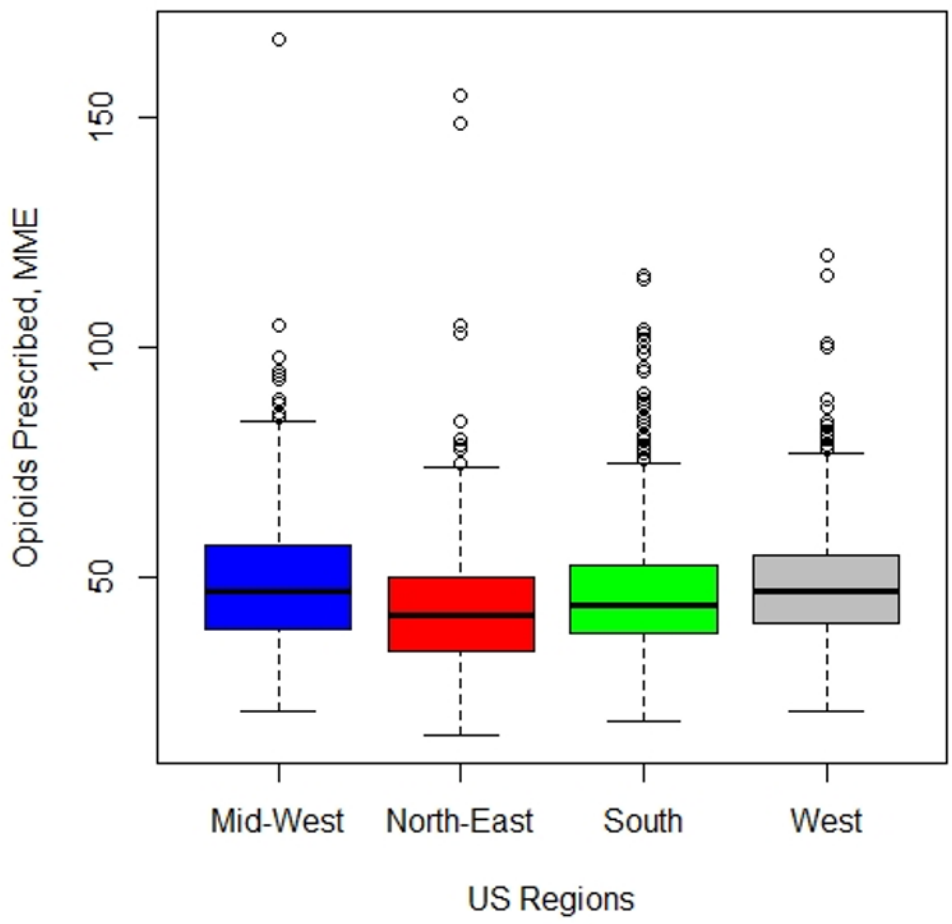


Figure 3.6 Regional variation in opioid prescribing practices after coronary artery bypass grafting. Midwest (MW), Northeast (NE), South (S), and West (W).

3.2 Results of Specific Aim 2 – Prospective Cohort Study of Opioid Use

3.2.1 Patient Recruitment and Cohort Characteristics

Of 111 patients approached for participation, 5 (4.5%) declined to participate and 2 (1.8%) were subsequently lost to all follow-up after discharge, leaving a total of 104 patients in the final analysis. The mean age was 65.8 years (±10.5) and 29 (27.9%) participants were female. Baseline characteristics and procedures performed in the cohort are presented in **Table**

3.3. A history of substance abuse was present in only one patient (1.0%). The largest proportion (45.1%) of patients underwent isolated CABG and the majority of cases were elective (85.5%). Overall, an internal mammary artery graft was used in 49.0% of cases, saphenous vein graft in 52.9%, and radial artery in 3.8%.

Characteristic	N = 104
Age, mean (SD)	65.8 (10.5)
Female, n (%)	29 (27.9)
BMI, mean (SD)	28.3 (4.9)
Smoking history, n (%)	
Never	52 (50.0)
Former	44 (42.3)
Current	8 (7.7)
Hypertension, n (%)	77 (74.0)
Dyslipidemia, n (%)	73 (70.2
Diabetes, n (%)	24 (23.1)
Renal failure, n (%)	3 (2.9)
Prior stroke, n (%)	7 (6.7)
Chronic lung disease, n (%)	6 (5.8)
Peripheral vascular disease, n (%)	4 (3.8)
Atrial fibrillation, n (%)	12 (11.5)
History of substance abuse, n (%)	1 (1.0)
History of depression, n (%)	8 (7.7)
Ejection Fraction, %, (SD)	57.9 (10.4)
Procedure, n (%)	
Isolated CABG	47 (45.1)
Isolated AVR	14 (13.4)
Isolated mitral surgery	14 (13.4)
CABG plus valve	9 (8.6)
Aorta procedure	16 (15.4)
Other procedure	4 (3.8)
Case status, n (%)	
Elective	89 (85.5)
Urgent	10 (9.6)
Emergent	5 (4.8)
Internal mammary artery use, n (%)	51 (49.0)
Saphenous vein use, n (%)	55 (52.9)
Radial artery use, n (%)	4 (3.8)
Total bypass time, mean (min) (SD)	114 (50)
Aortic cross-clamp time, mean (min) (SD)	86 (37)
Post-operative pacemaker implant, n (%)	2 (1.9)

SD: standard deviation; BMI: body mass index; CABG: coronary artery bypass grafting; AVR: aortic valve replacement;

Table 3.3 Baseline characteristics and operative factors of the discharge opioid use cohort.

3.2.2 Post-operative Pain and Opioid Use

The mean length of stay was 7 days (±4). All patient except for 8 (7.7%) required some form of opioid in hospital following surgery. The mean total dose in-hospital was 118.3 MME (±118.5), or 15.1 MME/day of hospitalization (±16.3). Both pain scores and opioid use were highest on post-operative day #1, and decreased subsequently throughout the in-hospital period (**Figure 3.7**).

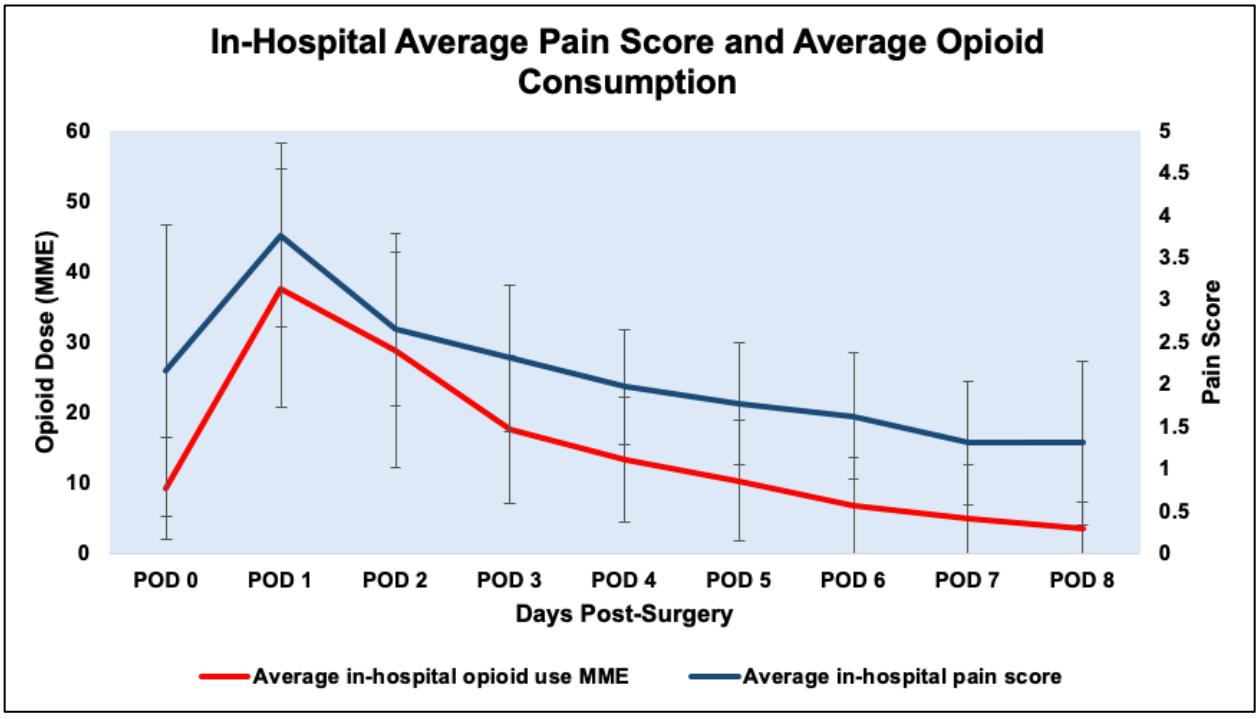


Figure 3.7 In-hospital post-operative pain scores and opioid consumption.

Within the last 24 hours prior to discharge, 32 patients (30.8%) received an oral opioid, with a mean dose of 22.1 MME (±17.5) over that time period. Of those who had not received an opioid within the 24 hours prior to discharge, 26 (50.0%) did still go on to receive an opioid prescription at discharge. The median pain score on the day of discharge was 1 (IQR 0-2).

3.2.3 Post Discharge Opioid Use

At the time of discharge, a total of 63 patients (60.6%) were given an oral opioid prescription. The majority of those were prescribed oxycodone (91.0%), while the remainder received hydromorphone. The mean number of pills prescribed was 16 (±6) and the mean total dose was 128.8 MME (±66.8).

In the first 10 days after discharge, 77 (74.0%) used daily or occasional acetaminophen, 12 (11.5%) used non-steroidal anti-inflammatory analgesics, and 4 (3.8%) used gamma-aminobutyric acid (GABA) analogues. Of those discharged with an opioid, 22 (34.9%) used none and 12 (19.0%) used fewer than half of the pills prescribed (**Figure 3.8**). No patients who had not received an opioid prescription at discharge reported using any opioids within the first 10 days after discharge.

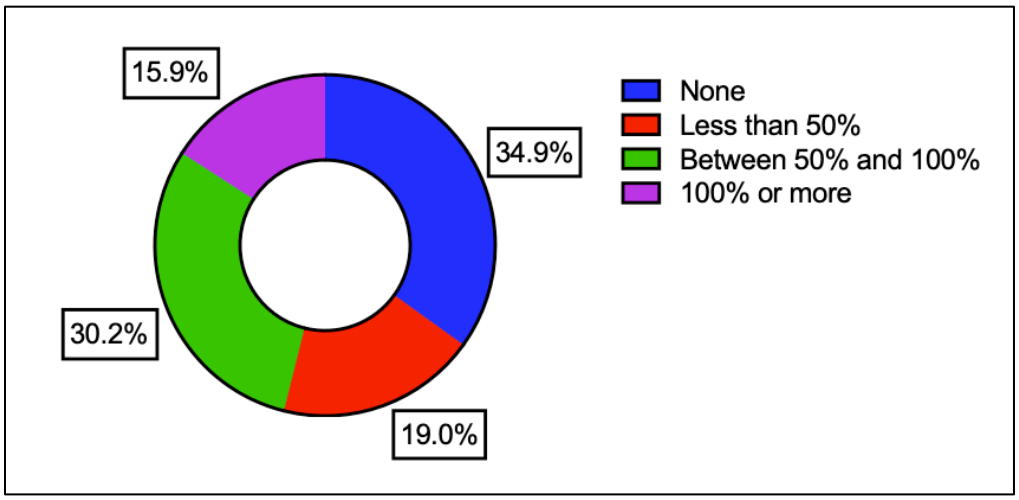


Figure 3.8 Proportion of patients who used none, < 50%, 50%-99%, or ≥ 100% of opioid pills prescribed in the first 10 days following discharge.

Both pain and opioid consumption decreased significantly throughout the post-discharge period (p-trend<0.001) (**Figure 3.9**). Of those who used any opioids in the first 10 days after discharge, median total consumption was 64 MME (IQR 38-128), or the equivalent of 9 Oxycodone 5mg tables. Five (4.8%) patients did receive a refill within the first 10 days after discharge. On the 10th day after discharge, only 11 patients (10.6%) were still taking opioids.

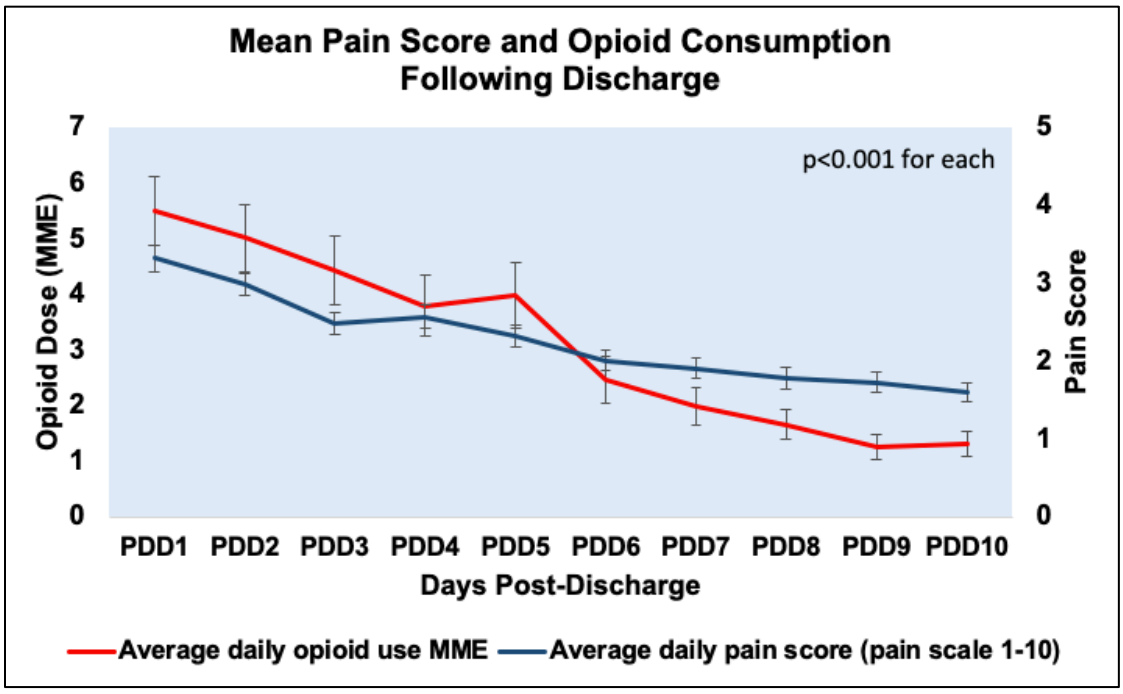


Figure 3.9 Post-discharge pain scores and opioid consumption within the first 10 days after discharge.

3.2.4 Post-Discharge Opioid Use by Age Group

There were significant differences in mean dosages of opioid consumed in the 10 days following discharge, when stratified by age group (**Figure 3.10**). Patients younger than 60 years, on average, consumed more opioids than those between 60-69, 70-79, and over 79 (76.4 MME vs. 41.2 MME vs. 12.1 MME vs. 37.5 MME, p=0.03).

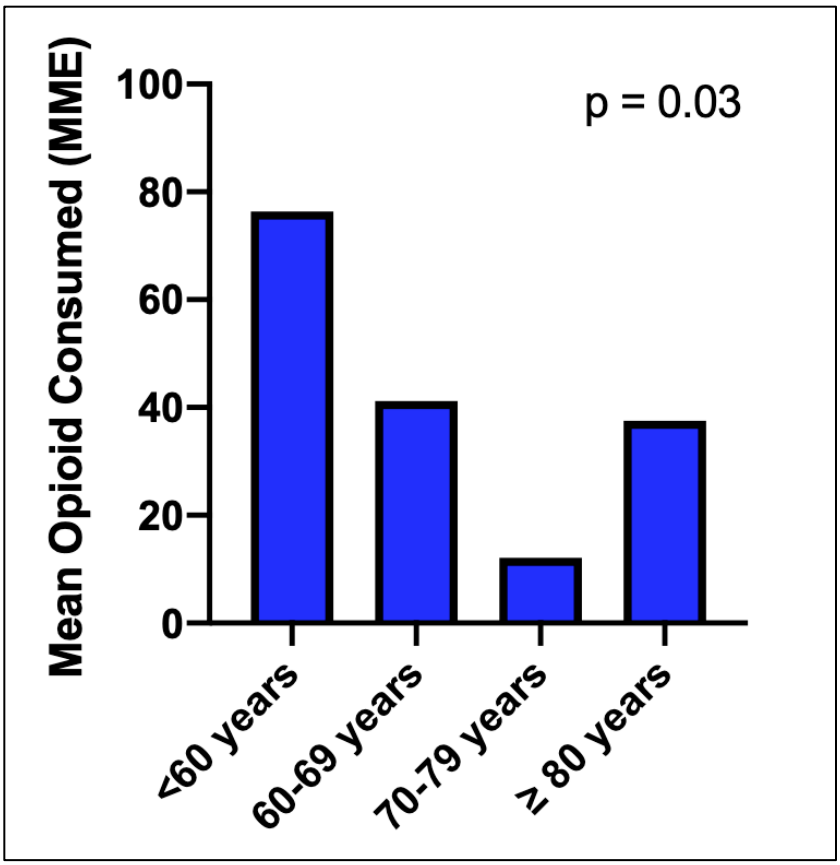


Figure 3.10 Opioid consumption by age group in the first 10 days following discharge.

3.2.5 Predictors of Opioid Use

Baseline characteristics and operative differences between those who did or did not use opioids after discharge are presented in **Table 3.4**. Patients who used opioids were younger (60.9 vs. 70.0 years, p<0.001), however there were no differences in opioid use based on sex, history of substance use, depression, smoking, or procedure type.

Characteristic	Used Opioid (n=44)	No Opioid (n=60)	p-value
Age, mean (SD)	60.9 (11.8)	69.7 (7.7)	0.01
Female, n (%)	10 (22.7)	19 (31.7)	0.42
BMI, mean (SD)	29.5 (4.9)	27.7 (3.3)	0.06

Current Smoker, n (%)	4 (9.1)	3 (5.0)	0.23
Hypertension, n (%)	33 (75.0)	44 (73.3)	0.97
Dyslipidemia, n (%)	26 (59.1)	45 (75.0)	0.18
Diabetes, n (%)	13 (29.5)	11 (18.3)	0.27
Renal failure, n (%)	1 (2.3)	2 (3.3)	1.00
Prior stroke, n (%)	1 (2.3)	6 (10.0)	0.25
Chronic lung disease, n (%)	2 (4.5)	4 (6.7)	0.97
Atrial fibrillation, n (%)	6 (13.6)	6 (10.0)	0.25
History of substance abuse, n (%)	1 (2.3)	0 (0.0)	0.88
History of depression, n (%)	1 (2.3)	7 (11.7)	0.16
Procedure, n (%)			0.49
Isolated CABG	20 (45.5)	27 (45.0)	
Isolated AVR	5 (11.3)	9 (15.0)	
Isolated mitral surgery	4 (9.1)	10 (16.7)	
CABG plus valve	3 (6.8)	6 (10.0)	
Aorta procedure	10 (22.7)	6 (10.0)	
Other procedure	2 (4.5)	2 (3.3)	
Internal mammary artery use, n (%)	22 (50.0)	29 (48.3)	0.867
Saphenous vein use, n (%)	23 (52.3)	32 (53.3)	0.915
Radial artery use, n (%)	2 (4.5)	2 (3.3)	0.751
Total bypass time, mean (min)	121	105	0.203
Aortic cross-clamp time, mean (min)	92	79	0.115

SD: standard deviation; BMI: body mass index; CABG: coronary artery bypass grafting; AVR: aortic valve replacement;

Table 3.4 Baseline characteristics and operative factors associated with opioid use in the first 10 days after discharge.

Additionally, there were no differences in the rates of non-steroidal anti-inflammatory or acetaminophen use between those who did or did not use opioids (29.5% vs. 31.7%, p=1.00) and (81.8% vs. 68.3%, p=0.10), respectively. Those who used opioids reported higher pain score within the 10-day post-discharge period (3.3 vs. 1.7, p=0.01).

In a logistic regression model adjusting for baseline and procedural differences, both the presence of diabetes (OR 4.9, 95% CI 1.19-20.1, p=0.03) and mean pain score ≥3 on the day of discharge (OR 2.9, 95% CI 1.8-4.8; p<0.01) were independently associated with post-discharge opioid use (**Figure 3.11**). Increasing age appeared inversely proportional to the likelihood of using opioids, however, this did not reach significance (OR 0.8, 95% CI 0.8-2.6, p=0.01).

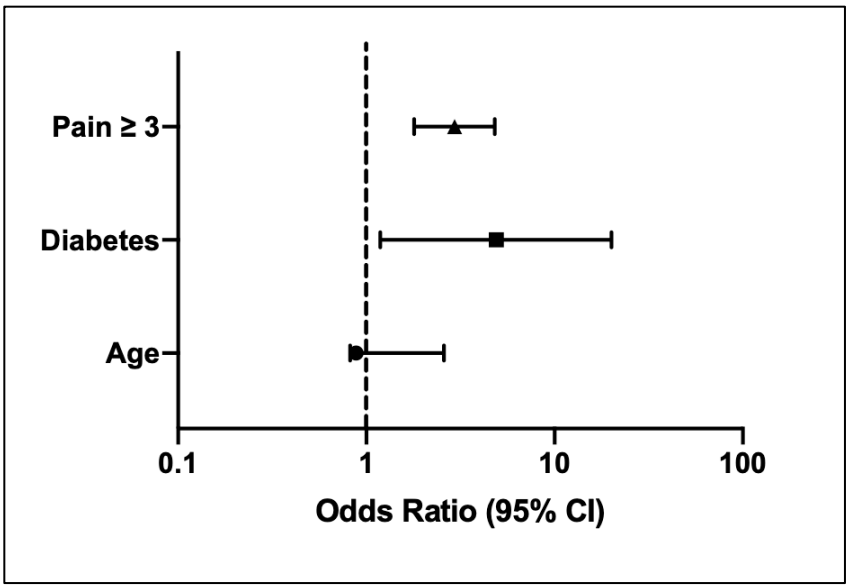


Figure 3.11 Forest plot of factors associated with opioid use after discharge following sternotomy-based procedures.

Chapter 4: Discussion

4.1 Summary and Key Findings

The opioid epidemic remains a major public health crisis and there is abundant evidence linking medically prescribed opioids to the initiation and perpetuation of problematic use. While there has been preliminary study of optimal prescribing practices in several surgical subspecialties, there is very little data addressing the potential impact of cardiac surgery. We examined current patterns of discharge opioid prescription after cardiac surgery in North America, and evaluated real-world patient-level opioid use following discharge. The key findings of this research program can be summarized as follows:

1. Significant variability exists with respect to discharge opioid prescription practices following cardiac surgery in both Canada and the United States.
2. The majority of education on opioid prescription has come from informal sources and there is a strong desire for guidelines in this area.
3. There was evidence of excess opioid prescription on a nationwide level, both in our analysis of Medicare prescription trends, and in a single-centre prospective cohort study.
4. In those patients who did use opioids following discharge, median consumption was the equivalent of just 9 Oxycodone 5mg tablets.
5. The presence of diabetes and moderate pain on the day of discharge may be useful as indicators for opioid requirement in the post-discharge period.

4.2 Variability in Prescribing Practices (Specific Aim 1)

Prescription opioids have played a major role in the current epidemic.(19,20) Furthermore, increasing sizes of post-operative prescriptions are associated with increasing rates of misuse.(68) Our studies of variability in prescribing patterns in Canada and the United States had several important findings. First there exists wide variability with respect to the type and dose of discharge opioid prescriptions following cardiac surgical procedures. Second, education regarding opioid prescription has come primarily from informal teaching during training, from colleagues or from personal experience. Third, there was evidence of excess prescription in our analysis of U.S.-based Medicare prescription patterns. Finally, a lack of formal education in opioid prescribing was associated with increased number of pills given, and over 90% of prescribers believe that there is value in establishing practice guidelines in this area.

Opioid prescribing practices in cardiac surgery have not previously been characterized and there remains little data to guide prescribers. Importantly, provider-dependent variability in opioid prescription has been linked to chronic use and pill diversion.(53,69) In our study of Canadian prescribers, 19% of respondents reported never prescribing opioids at discharge following routine sternotomy-based procedures, while 31% reported always prescribing them. Furthermore, among those who did prescribe opioids at discharge, the total dose of routine prescriptions varied widely, ranging from 37.5 to 900 MME. This variability was not explained by associations with practice location, level of training or beliefs about the risk of chronic use. Practice patterns were highly variable in all levels of training, which may explain why there were no significant differences in patterns between attending surgeons and trainees.

The link between these variable patterns and the development of chronic use remains unknown. However, this variability in routine practices is concerning in itself.(69,70) A previous study on prescription variability by Barnett et al. showed that doses on the higher end of a high-

variability prescribing group were associated with increased rates of long-term opioid use.(53) Similar concerns have been raised in several other surgical subspecialties.(33,36,54–56) A reduction in this variability through the establishment of standard practices may serve to decrease the high rate of new persistent opioid use following cardiac surgery.

An important cause of the variability seen in our studies appeared to be related to informal educational sources. Notably, 74% of respondents to our Canadian survey had not had previous formal education relating to opioid prescription and these providers prescribed significantly more opioids at discharge compared to those who had received formal education. Furthermore, the primary source of knowledge about prescribing came from informal sources during training or from colleagues. This is in keeping with other research which has demonstrated that opioid prescribing practices are generally based on unstandardized, informal experience.(71,72) Along with further research into optimal prescription sizes, education may represent a target for curbing the opioid crisis.

In response to the opioid epidemic, medical schools have been increasingly expanding curricula to encompass further education regarding substance use disorders and appropriate prescription. Within health systems, multilevel intervention strategies such as prescriber and patient education, the replacement of standard prescription orders with evidence-based guidelines, and the introduction of electronic medical record based tools have led to a reduction in opioid prescribing.(73) Furthermore, the introduction of Prescription Drug Monitoring Programs have shown promising results for curbing patterns of abuse in some jurisdictions.(74)

There should also be an increased educational focus on provider best practices in multimodal pain management and opioid alternatives, with attention paid to the strength of opioids prescribed. In our survey of Canadian prescribers, 21% of respondents reported routinely

avoiding opioid prescription at discharge, opting primarily for acetaminophen or non-steroidal anti-inflammatories. These stark differences in routine practices within the cardiac surgery community should provide a stimulus for a more thoughtful and graded approach to opioid prescribing. Greater collaboration and interaction with pain management specialists and addiction medicine experts, and maximization of non-opioid analgesic strategies prior to considering opioids may further combat the problem of chronic and mis-use of post-operative opioids.

Over 90% of prescribers felt that there would be value in establishing guidelines for post-operative opioid prescription following routine cardiac surgical procedures. Despite the scope of the opioid problem, little evidence-base exists for the establishment of these recommendations. Consensus prescribing guidelines were created in 2018 for patients undergoing common surgical procedures.(63) The authors note the lack of evidence in this area but do make a consensus recommendation of 0-to-20 Oxycodone 5mg tablets (0-150 MME) for opioid naïve patients following CABG. In our Canadian survey, 37% of routine prescriptions exceeded this maximum and in the United States experience, the mean prescription dose of 356 MME was well above this maximum threshold. Further characterization of actual use is necessary, in order to reduce this gap, which serves as the stimulus for our prospective cohort study of patient-level opioid use and pain after discharge.

4.3 Post-Discharge Opioid Use (Specific Aim 2)

Recommendations for opioid prescription after cardiac surgery remain consensus-based, which may partially explain the large variability seen in practice patterns. Several surgical subspecialties have had success in standardizing opioid prescription through the implementation

of quality improvement measures, however there is currently insufficient data in cardiac surgery to make such recommendations. In our cohort study of patient-level opioid use following discharge from sternotomy-based procedures, several important findings were evident. First the majority of patients used none or fewer than 50% of the opioid pills prescribed to them in the post-discharge period. Second, in those who did use opioids in the post-discharge period, the median consumption was just 64 MME. Third, opioid use was greatest among the youngest patient group, under the age of 60 years. Finally, after controlling for baseline and operative characteristics, the presence of diabetes and mean pain score ≥ 3 on the day of discharge were significant predictors of opioid use in the post-discharge period. These findings may serve as a preliminary basis for the creation of quality improvement recommendations for opioid prescription after cardiac surgery.

Studies in various surgical subspecialties have shown lower rates of post-discharge opioid use than expected. For example, Bartels et al. showed that 71% of patients used fewer than half of their opioid pills after thoracic surgical procedures.(75) Several experiences in orthopedic and general surgery have shown similar results.(33,59,62,76,77) Furthermore, our study of U.S.-based Medicare patients showed that patients filled only half of the opioid prescriptions given, suggesting a significant amount of excess prescription in that population. In our prospective cohort study, 54% of patients reported taking none or fewer than half of the opioid pills prescribed at discharge. Furthermore, half of patients who used no opioids in the last 24 hours were still prescribed opioids at the time of discharge. Excess prescription in this context raises concern for increased risks of chronic use, pill diversion, and even risks of overdose among family members.(36,37) This emphasizes the need for research in this area and for the establishment of benchmark values.

Large administrative database studies have previously examined predictors for persistent opioid use at 3 months following cardiac surgery. Clement et al. showed female gender (OR 1.30), anxiety (OR 1.40), tobacco use (OR 1.34), prior substance abuse (OR 1.99), living in the Southern United States (OR 1.46), and prescription sizes to all be associated with persistent use after CABG.(52) Additionally, Brescia et al. showed that gastrointestinal complications, history of drug abuse and history of tobacco use were associated with persistent opioid use.(51) While these factors are important to consider in the reduction of long-term opioid use, they do not provide information on which patients require opioid prescriptions at the time of discharge. Conversely, our study focused primarily on factors that determined opioid use in the short-term. Specifically, the presence of diabetes, as well as mean pain score ≥ 3 on the day of discharge were associated with patients requiring opioids after discharge. The use of these patient-level factors may serve as a useful metric for provider decision-making regarding the need for opioid prescriptions at the time of discharge.

Our study, which to our knowledge is the first in cardiac surgery, also provides important data which may be used to generate recommendations. This process was outlined by Howard et al. recently in *The Annals of Surgery*.(78) They describe a pragmatic process of evidence-based prescribing guideline development and implementation (**Figure 4.1**). Notably, they report that, based on prior studies of post-operative opioid use, a sample size of 100 patients is more than enough to achieve an appropriate margin of error with 95% confidence. The authors suggest basing the recommended prescription size on the 80th percentile of patient-reported opioid use. In our study, taking into account data from all patients who were prescribed an opioid at discharge, this would equate to a recommendation of 96 MME, or the equivalent of approximately 13 Oxycodone 5mg pills. If we include all patients, even those who were not prescribed opioids, this

drops to 57 MME, or 8 Oxycodone 5mg pills. Both of these values remain much lower than the current consensus recommendation of up to 150 MME. Stakeholder engagement, continual assessment, and adaptability remain important additional steps in the pathway to creating and implementing prescribing guidelines.

Pathway Element	Description/Examples
Choose procedure or patient cohort to pilot initiative	Elective, low variability, uncomplicated patients
Collect data on prescribing practices	Retrospective chart review, Prescription Drug Monitoring Programs
Collect data on patient-reported opioid use	Prospective patient surveys (medication use, pain scores, satisfaction)
Generate evidence-based prescribing recommendations	Using patient-reported medication use, identify potential prescribing cut-points (such as by percentile treated)
Stakeholder education	Engaging all providers involved in patient care (pre-op, peri-op, post-op residents, faculty, nurses, PAs, NPs)
Patient and caregiver education	Counseling patients and caregivers regarding safe postoperative opioid use, pain control, disposal
Continual assessment and update of recommendations	Prospective chart review to analyze impact of recommendations, patient surveys to analyze medication use and pain scores

Framework for an Evidence-based Postoperative Opioid-prescribing Pathway.

Figure 4.1 A framework for the development of evidence-based postoperative opioid prescribing recommendations. ***Adapted with permission from Howard et al, 2020.***(78)

4.4 Limitations

These findings should be taken in the context of several limitations. Overall, our research on variability in prescribing practices is limited by a lack of granular data, including patient characteristics, postoperative events, and data on prescription refills. This limited the study of risk-adjusted analyses or time-based trends. We were also unable to definitively link variability in prescription sizes to the actual incidence of chronic use. In the survey of Canadian prescribers, we asked respondents to report discharge prescription sizes for routine sternotomy-based procedures, and it is possible that the hypothetical nature of the question accounted for some of the variability seen. This also limited our ability to draw conclusions about other procedure types such as minimally-invasive cases or catheter-based interventions. Additionally, our overall

response rate was 42%, which may introduce an element of selection bias and we were unable to identify granular demographics to determine if some groups were more likely to have responded. In the Medicare analysis of prescribing practices in the United States, patients who were not prescribed opioids, or who did not fill opioid prescriptions were not included. Furthermore, the Medicare dataset was limited to 2011-2016, before a number of important system-level efforts to reduce prescribing had been implemented. It is possible that this represents a dated experience, not fully reflective of contemporary practice. Finally, these studies do not represent the practice of nurse practitioners or physician assistants, who have an important role in discharge prescription in many settings. Nonetheless, our findings reflect significant and inadequately addressed issues related to postoperative prescription which will require further focus and intervention.

Our prospective cohort analysis of patients undergoing sternotomy-based procedures at Brigham and Women's Hospital is limited by the potential for recall bias in patients filling pain and opioid use diaries at home. In order to limit this bias, we followed up with patients on a 10-day telephone encounter which involved a pill count. Additionally, patients may have been subject to the Hawthorne effect, by which an individual changes their behavior when they are aware that they are being observed. Furthermore, the exclusion of patients transferred to non-home facilities may impact the external validity of our results, however, our cohort did appear to reflect a fairly characteristic group of patients and cases undergoing sternotomy-based procedures at a North American center. Finally, the differential experience and reporting of pain scores by post-operative patients may limit the use of the pain as a predictor for opioid use.(79) Despite these limitations, we provide important preliminary data on real-world post-discharge

opioid use in a cardiac surgical cohort, which may be critical in our specialty's response to the ongoing opioid epidemic.

4.5 Future Directions

There is an ongoing need for further confirmatory studies of post-discharge opioid use, particularity in cardiac surgery populations. Our research provides the first such patient-level data, however further similar studies will provide a more robust evidence-base for the development of recommendations. In addition to the development of guidelines, ongoing efforts in education and multi-stakeholder engagement related to the reduction of unnecessary opioid prescription will be key for the implementation of sound recommendations.

With regards to reducing the overall reliance of opioids in the medical context, there have been recent reports of fully opioid-free cardiac surgical procedures in patients with severe allergies.(80–82) In one such report, Landry et al. described a case of open surgical aortic valve replacement performed without opioids used in the intra-operative or post-operative period.(81) An increased reliance on alternate non-opioid analgesics in the perioperative period may serve as an additional target to reduce the prevalence of opioid use disorder after cardiac surgery. In the future, these techniques could theoretically be applied in patients deemed at high-risk for prolonged opioid use, such as those with prior substance use disorders.

While an improved understanding of medical opioid use is important, much larger system-wide interventions are also required to help reduce the scope and significance of the opioid epidemic. Preliminary attempts at harm-reduction, such as the distribution of take-home naloxone kits, have been successful in reducing the incidence of over-dose deaths, however a much larger public health effort is required.(83,84) In a recent report from the Canadian Mental

Health Association, six key recommendations have been identified as priorities in an over-arching approach to the crisis: strengthen the social determinants of health and invest in mental health services; research, fund, and improve access to treatment for opioid use disorders; develop a national pain and addiction strategy for safer pain management; increased overdose prevention sites and supervised consumption sites; support prescription drugs as an alternative to contaminated drugs; and decriminalise the personal possession of illegal drugs.(85) Issues related to discharge opioid prescription, as studied in our research, represent only a small element of this overall strategy, and ongoing implementation of this holistic public health-based approach is necessary to curb the opioid epidemic.

Chapter 5: Conclusion

Post-operative opioid prescription has been linked to the ongoing epidemic of chronic use and overdose death, however current prescribing practices and optimal regimens have been poorly studied in cardiac surgical populations. Throughout this research program, we showed that discharge prescribing practices are highly variable in both Canada and the United States. Furthermore, there was evidence of significant excess prescription on a national level in the U.S.-based Medicare database. Finally, the primary source of education regarding opioid prescription has come from informal sources, and there is a strong desire for evidence-based guidelines in this area. Our findings may help to explain the high rates of new persistent opioid use after cardiac surgery, which has been a recent focus of concern.

In a prospective cohort study of patient-level use, we examined actual opioid usage within the first 10 days after discharge from sternotomy-based cardiac surgical procedures. Again, there was evidence of excess prescription in this population. We also identified predictors of opioid use based on in-hospital pain scores, which may help providers in the determination of patients who require opioids in the post-discharge period. The data presented on opioid consumption within the first 10-days after discharge may also form a preliminary basis for future quality improvement recommendations. Despite the limitations of this research, this data may serve as an important benchmark for future confirmatory studies, as well as education aimed at standardizing practices in this critical area.

Bibliography

1. Hoots BE, Xu L, Kariisa M, Wilson NO, Rudd RA, Scholl L, et al. 2018 ANNUAL SURVEILLANCE REPORT OF DRUG-RELATED RISKS AND OUTCOMES UNITED STATES [Internet]. [cited 2018 Oct 1]. Available from: https://www.cdc.gov/
2. Kanouse AB, Compton P. The Epidemic of Prescription Opioid Abuse, the Subsequent Rising Prevalence of Heroin Use, and the Federal Response. J Pain Palliat Care Pharmacother [Internet]. 2015 Apr 3 [cited 2018 Oct 1];29(2):102–14. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26095479
3. Vadivelu N, Kai AM, Kodumudi V, Sramcik J, Kaye AD. The Opioid Crisis: a Comprehensive Overview. Curr Pain Headache Rep [Internet]. 2018 Mar 23 [cited 2018 Oct 2];22(3):16. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29476358
4. Cain J. Office of the Chief Coroner: report of the Task Force into illicit narcotic overdose deaths in British Columbia. 1994.
5. Government of Canada. National report: apparent opioid-related deaths in Canada. 2018.
6. Wood E. Strategies for reducing opioid-overdose deaths — Lessons from Canada [Internet]. Vol. 378, New England Journal of Medicine. Massachussetts Medical Society; 2018 [cited 2020 Aug 19]. p. 1565–7. Available from: https://pubmed-ncbi-nlm-nih-gov.ezproxy.library.ubc.ca/29694813/
7. Special Advisory Committee on the Epidemic of Opioid Overdoses. Opioid-related Harms in Canada. Ottawa;
8. Understanding the Epidemic | Drug Overdose | CDC Injury Center [Internet]. [cited 2020 Aug 19]. Available from: https://www.cdc.gov/drugoverdose/epidemic/index.html
9. Dasgupta N, Beletsky L, Ciccarone D. Opioid Crisis: No Easy Fix to Its Social and

Economic Determinants [Internet]. Vol. 108, American Journal of Public Health. American Public Health Association Inc.; 2018 [cited 2020 Aug 19]. p. 182–6. Available from: https://pubmed-ncbi-nlm-nih-gov.ezproxy.library.ubc.ca/29267060/

10. Conaghan PG. A turbulent decade for NSAIDs: Update on current concepts of classification, epidemiology, comparative efficacy, and toxicity [Internet]. Vol. 32, Rheumatology International. Rheumatol Int; 2012 [cited 2020 Aug 19]. p. 1491–502. Available from: https://pubmed-ncbi-nlm-nih-gov.ezproxy.library.ubc.ca/22193214/
11. Campbell JN. The fifth vital sign revisited [Internet]. Vol. 157, Pain. Lippincott Williams and Wilkins; 2016 [cited 2020 Sep 9]. p. 3–4. Available from: https://pubmed-ncbi-nlm-nih-gov.ezproxy.library.ubc.ca/26683106/
12. Ayoo K, Mikhaeil J, Huang A, Wąsowicz M. The opioid crisis in North America: facts and future lessons for Europe. Anaesthesiol Intensive Ther [Internet]. 2020 [cited 2020 Aug 19];52(2):139–47. Available from: https://pubmed-ncbi-nlm-nih-gov.ezproxy.library.ubc.ca/32419434/
13. Becker WC, Fiellin DA. Abuse-deterrent opioid formulations - Putting the potential benefits into perspective [Internet]. Vol. 376, New England Journal of Medicine. Massachussetts Medical Society; 2017 [cited 2020 Aug 19]. p. 2103–5. Available from: https://pubmed-ncbi-nlm-nih-gov.ezproxy.library.ubc.ca/28564568/
14. Purdue Pharma to plead guilty in $8bn opioid settlement - BBC News [Internet]. [cited 2020 Nov 12]. Available from: https://www.bbc.com/news/business-54636002
15. Rudd RA, Aleshire N, Zibbell JE, Gladden RM. Increases in Drug and Opioid Overdose Deaths — United States, 2000–2014. MMWR Morb Mortal Wkly Rep. 2016 Jan 1;64(50–51):1378–82.

16. Compton WM, Jones CM, Baldwin GT. Relationship between Nonmedical Prescription-Opioid Use and Heroin Use [Internet]. Vol. 374, New England Journal of Medicine. Massachussetts Medical Society; 2016 [cited 2020 Aug 19]. p. 154–63. Available from: https://pubmed-ncbi-nlm-nih-gov.ezproxy.library.ubc.ca/26760086/

17. Belzak L, Halverson J. The opioid crisis in Canada: A national perspective [Internet]. Vol. 38, Health Promotion and Chronic Disease Prevention in Canada. Public Health Agency of Canada; 2018 [cited 2020 Aug 19]. p. 224–33. Available from: https://pubmed-ncbi-nlm-nih-gov.ezproxy.library.ubc.ca/29911818/

18. Wetzel M, Hockenberry J, Raval M V. Interventions for Postsurgical Opioid Prescribing: A Systematic Review. JAMA Surg [Internet]. 2018 Oct 1 [cited 2020 Aug 19];153(10):948–54. Available from: https://pubmed-ncbi-nlm-nih-gov.ezproxy.library.ubc.ca/30140931/

19. Kolodny A, Courtwright DT, Hwang CS, Kreiner P, Eadie JL, Clark TW, et al. The Prescription Opioid and Heroin Crisis: A Public Health Approach to an Epidemic of Addiction. Annu Rev Public Health. 2015 Mar 18;36(1):559–74.

20. Makary MA, Overton HN, Wang P. Overprescribing is major contributor to opioid crisis. Vol. 359, BMJ (Online). BMJ Publishing Group; 2017.

21. Deyo RA, Hallvik SE, Hildebran C, Marino M, Dexter E, Irvine JM, et al. Association Between Initial Opioid Prescribing Patterns and Subsequent Long-Term Use Among Opioid-Naïve Patients: A Statewide Retrospective Cohort Study. J Gen Intern Med [Internet]. 2017 Jan 1 [cited 2020 Aug 20];32(1):21–7. Available from: https://pubmed-ncbi-nlm-nih-gov.ezproxy.library.ubc.ca/27484682/

22. Guy GP, Zhang K, Bohm MK, Losby J, Lewis B, Young R, et al. Vital signs: Changes in

opioid prescribing in the United States, 2006–2015. Morb Mortal Wkly Rep. 2017 Jul 7;66(26):697–704.

23. Fendrich M, Becker J. Prior prescription opioid misuse in a cohort of heroin users in a treatment study. Addict Behav Reports [Internet]. 2018 Dec 1 [cited 2020 Aug 20];8:8–10. Available from: /pmc/articles/PMC6029944/?report=abstract

24. National Institute on Drug Abuse: Prescription Opioids and Heroin Research Report. 2018.

25. Canadian Institutes for Health Research (CIHI). Opioid Prescribing in Canada: How Are Practices Changing? [Internet]. Ottawa, ON; 2019. Available from: https://www.cihi.ca/sites/default/files/document/opioid-prescribing-canada-trends-en-web.pdf

26. Rosenberg JM, Bilka BM, Wilson SM, Spevak C. Opioid therapy for chronic pain: Overview of the 2017 us department of veterans affairs and us department of defense clinical practice guideline. Pain Med (United States) [Internet]. 2018 May 1 [cited 2020 Aug 20];19(5):928–41. Available from: https://pubmed-ncbi-nlm-nih-gov.ezproxy.library.ubc.ca/29025128/

27. Schieber LZ, Guy GP, Seth P, Young R, Mattson CL, Mikosz CA, et al. Trends and Patterns of Geographic Variation in Opioid Prescribing Practices by State, United States, 2006-2017. JAMA Netw open [Internet]. 2019 Mar 1 [cited 2020 Aug 20];2(3):e190665. Available from: /pmc/articles/PMC6484643/?report=abstract

28. Kariisa M, Scholl L, Wilson N, Seth P, Hoots B. Drug Overdose Deaths Involving Cocaine and Psychostimulants with Abuse Potential — United States, 2003–2017. MMWR Morb Mortal Wkly Rep [Internet]. 2019 May 3 [cited 2020 Sep 2];68(17):388–

95. Available from: http://www.cdc.gov/mmwr/volumes/68/wr/mm6817a3.htm?s_cid=mm6817a3_w

29. Tan WH, Yu J, Feaman S, McAllister JM, Kahan LG, Quasebarth MA, et al. Opioid Medication Use in the Surgical Patient: An Assessment of Prescribing Patterns and Use. J Am Coll Surg [Internet]. 2018 Aug 1 [cited 2018 Oct 1];227(2):203–11. Available from: https://www-sciencedirect-com.ezproxy.library.ubc.ca/science/article/pii/S1072751518303314

30. Chapman T, Kim N, Maltenfort M, Ilyas AM. Prospective Evaluation of Opioid Consumption Following Carpal Tunnel Release Surgery. HAND [Internet]. 2017 Jan 7 [cited 2018 Oct 3];12(1):39–42. Available from: http://journals.sagepub.com/doi/10.1177/1558944716646765

31. Kim N, Matzon JL, Abboudi J, Jones C, Kirkpatrick W, Leinberry CF, et al. Orthopaedic forum A Prospective Evaluation of Opioid Utilization After Upper-Extremity Surgical Procedures: Identifying Consumption Patterns and Determining Prescribing Guidelines. [cited 2018 Oct 3]; Available from: http://dx.doi.org/10.2106/JBJS.15.00614

32. Kumar K, Gulotta L V., Dines JS, Allen AA, Cheng J, Fields KG, et al. Unused Opioid Pills After Outpatient Shoulder Surgeries Given Current Perioperative Prescribing Habits. Am J Sports Med [Internet]. 2017 Mar 9 [cited 2018 Oct 3];45(3):636–41. Available from: http://journals.sagepub.com/doi/10.1177/0363546517693665

33. Rodgers J, Cunningham K, Fitzgerald K, Finnerty E. Opioid Consumption Following Outpatient Upper Extremity Surgery. 2012 [cited 2018 Oct 3]; Available from: https://ac-els-cdn-com.ezproxy.library.ubc.ca/S0363502312001268/1-s2.0-S0363502312001268-main.pdf?_tid=0c1f1c17-cfb0-41f4-b038-

41073cd062df&acdnat=1538575167_eaf47d63d2c3bacd32a38bfa80a86f00

34. Waljee JF, Zhong L, Hou H, Sears E, Brummett C, Chung KC. The Use of Opioid Analgesics following Common Upper Extremity Surgical Procedures. Plast Reconstr Surg [Internet]. 2016 Feb [cited 2018 Oct 3];137(2):355e-364e. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00006534-201602000-00032

35. Chen EY, Marcantonio A, Tornetta P. Correlation Between 24-Hour Predischarge Opioid Use and Amount of Opioids Prescribed at Hospital Discharge. JAMA Surg [Internet]. 2018 Feb 21 [cited 2018 Oct 3];153(2):e174859. Available from: http://archsurg.jamanetwork.com/article.aspx?doi=10.1001/jamasurg.2017.4859

36. Hill M V., Mcmahon ML, Stucke RS, Barth RJ. Wide variation and excessive dosage of opioid prescriptions for common general surgical procedures. Ann Surg [Internet]. 2017 Apr 1 [cited 2020 Aug 20];265(4):709–14. Available from: https://pubmed-ncbi-nlm-nih-gov.ezproxy.library.ubc.ca/27631771/

37. Khan NF, Bateman BT, Landon JE, Gagne JJ. Association of Opioid Overdose with Opioid Prescriptions to Family Members. JAMA Intern Med [Internet]. 2019 Sep 1 [cited 2020 Aug 5];179(9):1186–92. Available from: https://pubmed.ncbi.nlm.nih.gov/31233088/

38. Zhu W, Chernew ME, Sherry TB, Maestas N. Initial opioid prescriptions among U.S. Commercially insured patients, 2012-2017 [Internet]. Vol. 380, New England Journal of Medicine. Massachussetts Medical Society; 2019 [cited 2020 Aug 20]. p. 1043–52. Available from: https://pubmed-ncbi-nlm-nih-gov.ezproxy.library.ubc.ca/30865798/

39. Dineen KK, DuBois JM. Between a rock and a hard place: Can physicians prescribe

opioids to treat pain adequately while avoiding legal sanction? Am J Law Med [Internet]. 2016 [cited 2020 Aug 20];42(1):7–52. Available from: /pmc/articles/PMC5494184/?report=abstract

40. Brummett CM, Waljee JF, Goesling J, Moser S, Lin P, Englesbe MJ, et al. New Persistent Opioid Use After Minor and Major Surgical Procedures in US Adults. JAMA Surg [Internet]. 2017 Jun 21 [cited 2018 Oct 1];152(6):e170504. Available from: http://archsurg.jamanetwork.com/article.aspx?doi=10.1001/jamasurg.2017.0504

41. Clarke H, Soneji N, Ko DT, Yun L, Wijeysundera DN. Rates and risk factors for prolonged opioid use after major surgery: population based cohort study. BMJ [Internet]. 2014 Feb 11 [cited 2018 Oct 1];348(feb11 3):g1251–g1251. Available from: http://www.bmj.com/cgi/doi/10.1136/bmj.g1251

42. Alam A, Gomes T, Zheng H, Mamdani MM, Juurlink DN, Bell CM. Long-term analgesic use after low-risk surgery: a retrospective cohort study. Arch Intern Med [Internet]. 2012 Mar 12 [cited 2018 Oct 1];172(5):425–30. Available from: http://archinte.jamanetwork.com/article.aspx?doi=10.1001/archinternmed.2011.1827

43. Starting on Opioids – Opioid prescribing patterns in Ontario by family doctors, surgeons, and dentists, for people starting to take opioids [Internet]. [cited 2020 Apr 27]. Available from: http://startingonopioids.hqontario.ca/

44. Levy B, Paulozzi L, Mack KA, Jones CM. Trends in Opioid Analgesic-Prescribing Rates by Specialty, U.S., 2007-2012. Am J Prev Med [Internet]. 2015 Sep [cited 2018 Oct 2];49(3):409–13. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0749379715000896

45. Callinan CE, Neuman MD, Lacy KE, Gabison C, Ashburn MA. The Initiation of Chronic

Opioids: A Survey of Chronic Pain Patients. In: Journal of Pain [Internet]. Churchill Livingstone Inc.; 2017 [cited 2020 Aug 20]. p. 360–5. Available from: https://pubmed-ncbi-nlm-nih-gov.ezproxy.library.ubc.ca/27919771/

46. Lawal OD, Gold J, Murthy A, Ruchi R, Bavry E, Hume AL, et al. Rate and Risk Factors Associated With Prolonged Opioid Use After Surgery: A Systematic Review and Meta-analysis. JAMA Netw open [Internet]. 2020 Jun 1 [cited 2020 Sep 2];3(6):e207367. Available from: https://pubmed-ncbi-nlm-nih-gov.ezproxy.library.ubc.ca/32584407/

47. Huang APS, Sakata RK. Pain after sternotomy – review. Brazilian J Anesthesiol (English Ed [Internet]. 2016 Jul [cited 2018 Oct 2];66(4):395–401. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27343790

48. Cogan J. Pain Management After Cardiac Surgery. Semin Cardiothorac Vasc Anesth [Internet]. 2010 Sep 12 [cited 2018 Oct 2];14(3):201–4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20705642

49. Mueller XM, Tinguely F, Tevaearai HT, Revelly J-P, Chioléro R, von Segesser LK. Pain Location, Distribution, and Intensity After Cardiac Surgery. Chest [Internet]. 2000 Aug 1 [cited 2018 Oct 2];118(2):391–6. Available from: https://www.sciencedirect.com/science/article/pii/S0012369215517972

50. Clement KC, Canner JK, Whitman GJR, Lawton JS, Grant MC, Sussman MS. New Persistent Opioid Use After Aortic and Mitral Valve Surgery in Commercially Insured Patients. In: Annals of Thoracic Surgery [Internet]. Elsevier USA; 2020 [cited 2020 Sep 2]. p. 829–35. Available from: https://pubmed-ncbi-nlm-nih-gov.ezproxy.library.ubc.ca/32004502/

51. Brescia AA, Waljee JF, Hu HM, Englesbe MJ, Brummett CM, Lagisetty PA, et al. Impact

of Prescribing on New Persistent Opioid Use After Cardiothoracic Surgery. Ann Thorac Surg [Internet]. 2019 [cited 2020 Jan 10];108(4):1107–13. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31447051

52. Clement KC, Canner JK, Lawton JS, Whitman GJR, Grant MC, Sussman MS. Predictors of new persistent opioid use after coronary artery bypass grafting. In: Journal of Thoracic and Cardiovascular Surgery. Mosby Inc.; 2020.

53. Barnett ML, Olenski AR, Jena AB. Opioid-Prescribing Patterns of Emergency Physicians and Risk of Long-Term Use. N Engl J Med [Internet]. 2017 Feb 16 [cited 2020 Jan 10];376(7):663–73. Available from: http://www.nejm.org/doi/10.1056/NEJMsa1610524

54. Eid AI, DePesa C, Nordestgaard AT, Kongkaewpaisan N, Lee JM, Kongwibulwut M, et al. Variation of Opioid Prescribing Patterns among Patients undergoing Similar Surgery on the Same Acute Care Surgery Service of the Same Institution: Time for Standardization? Surg (United States) [Internet]. 2018 Nov 1 [cited 2020 Sep 9];164(5):926–30. Available from: https://pubmed-ncbi-nlm-nih-gov.ezproxy.library.ubc.ca/30049481/

55. Thiels CA, Anderson SS, Ubl DS, Hanson KT, Bergquist WJ, Gray RJ, et al. Wide Variation and Overprescription of Opioids After Elective Surgery. Ann Surg [Internet]. 2017 Oct 1 [cited 2020 Apr 13];266(4):564–73. Available from: http://journals.lww.com/00000658-201710000-00003

56. Bates C, Laciak R, Southwick A, Bishoff J. Overprescription of Postoperative Narcotics: A Look at Postoperative Pain Medication Delivery, Consumption and Disposal in Urological Practice. J Urol [Internet]. 2011 Feb [cited 2020 Apr 13];185(2):551–5. Available from: http://www.jurology.com/doi/10.1016/j.juro.2010.09.088

57. Hill M V., Mcmahon ML, Stucke RS, Barth RJ. Wide variation and excessive dosage of opioid prescriptions for common general surgical procedures. Ann Surg [Internet]. 2017 Apr 1 [cited 2020 Aug 19];265(4):709–14. Available from: https://pubmed-ncbi-nlm-nih-gov.ezproxy.library.ubc.ca/27631771/

58. Noly P-E, Rubens FD, Ouzounian M, Quantz M, Shao-Hua W, Pelletier M, et al. Cardiac surgery training in Canada: Current state and future perspectives. J Thorac Cardiovasc Surg [Internet]. 2017 [cited 2018 Nov 7];154:998–1005. Available from: http://dx.doi.org/10.1016/j.jtcvs.2017.04.010

59. Howard R, Waljee J, Brummett C, Englesbe M, Lee J. Reduction in opioid prescribing through evidence-based prescribing guidelines [Internet]. Vol. 153, JAMA Surgery. American Medical Association; 2018 [cited 2020 Sep 9]. p. 285–7. Available from: https://pubmed-ncbi-nlm-nih-gov.ezproxy.library.ubc.ca/29214318/

60. Hill M V., Stucke RS, McMahon ML, Beeman JL, Barth RJ. An Educational Intervention Decreases Opioid Prescribing after General Surgical Operations. Ann Surg [Internet]. 2018 Mar 1 [cited 2020 Sep 9];267(3):468–72. Available from: https://pubmed-ncbi-nlm-nih-gov.ezproxy.library.ubc.ca/28267689/

61. Lee JS, Howard RA, Klueh MP, Englesbe MJ, Waljee JF, Brummett CM, et al. The Impact of Education and Prescribing Guidelines on Opioid Prescribing for Breast and Melanoma Procedures. Ann Surg Oncol [Internet]. 2019 Jan 15 [cited 2020 Sep 9];26(1):17–24. Available from: https://pubmed-ncbi-nlm-nih-gov.ezproxy.library.ubc.ca/30238243/

62. Saini S, McDonald EL, Shakked R, Nicholson K, Rogero R, Chapter M, et al. Prospective Evaluation of Utilization Patterns and Prescribing Guidelines of Opioid Consumption

Following Orthopedic Foot and Ankle Surgery. Foot Ankle Int [Internet]. 2018 Nov 1 [cited 2020 Sep 9];39(11):1257–65. Available from: https://pubmed-ncbi-nlm-nih-gov.ezproxy.library.ubc.ca/30124084/

63. Overton HN, Hanna MN, Bruhn WE, Hutfless S, Bicket MC, Makary MA, et al. Opioid-Prescribing Guidelines for Common Surgical Procedures: An Expert Panel Consensus. J Am Coll Surg [Internet]. 2018 Oct 1 [cited 2018 Oct 1];227(4):411–8. Available from: https://www-sciencedirect-com.ezproxy.library.ubc.ca/science/article/pii/S1072751518311293

64. Canadian Society of Cardiac Surgeons 2019 Annual Report. 2019.

65. Lucas E. Opioid Operators: How Surgeons Ply Patients With Painkillers | Kaiser Health News. Kaiser Health News. 2019.

66. Adult Cardiac Surgery Database | STS [Internet]. [cited 2020 Sep 3]. Available from: https://www.sts.org/registries-research-center/sts-national-database/adult-cardiac-surgery-database

67. Myles PS, Hunt JO, Fletcher H, Solly R, Woodward D, Kelly S. Relation between quality of recovery in hospital and quality of life at 3 months after cardiac surgery. Anesthesiology [Internet]. 2001 Oct [cited 2018 Nov 30];95(4):862–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11605925

68. Brat GA, Agniel D, Beam A, Yorkgitis B, Bicket M, Homer M, et al. Postsurgical prescriptions for opioid naive patients and association with overdose and misuse: Retrospective cohort study. BMJ [Internet]. 2018 Jan 17 [cited 2020 Apr 21];360:j5790. Available from: http://www.bmj.com/lookup/doi/10.1136/bmj.j5790

69. Berger I, Strother M, Talwar R, Ziemba J, Wirtalla C, Xia L, et al. National Variation in

Opioid Prescription Fills and Long-Term Use in Opioid Naïve Patients after Urological Surgery. J Urol [Internet]. 2019 [cited 2020 Jan 22];202(5):1036–43. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31112103

70. Jena AB, Goldman D, Karaca-Mandic P. Hospital Prescribing of Opioids to Medicare Beneficiaries. JAMA Intern Med [Internet]. 2016 Jul 1 [cited 2020 Jan 13];176(7):990. Available from: http://archinte.jamanetwork.com/article.aspx?doi=10.1001/jamainternmed.2016.2737

71. Desveaux L, Saragosa M, Kithulegoda N, Ivers NM. Understanding the behavioural determinants of opioid prescribing among family physicians: a qualitative study. BMC Fam Pract [Internet]. 2019 Dec 10 [cited 2020 Jan 13];20(1):59. Available from: https://bmcfampract.biomedcentral.com/articles/10.1186/s12875-019-0947-2

72. Lee JS, Parashar V, Miller JB, Bremmer SM, Vu J V., Waljee JF, et al. Opioid Prescribing After Curative-Intent Surgery: A Qualitative Study Using the Theoretical Domains Framework. Ann Surg Oncol [Internet]. 2018 Jul 10 [cited 2020 Jan 13];25(7):1843–51. Available from: http://link.springer.com/10.1245/s10434-018-6466-x

73. Meisenberg BR, Grover J, Campbell C, Korpon D. Assessment of Opioid Prescribing Practices Before and After Implementation of a Health System Intervention to Reduce Opioid Overprescribing. JAMA Netw open [Internet]. 2018 [cited 2020 Jan 10];1(5):e182908. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30646184

74. Holmgren AJ, Botelho A, Brandt AM. A History of Prescription Drug Monitoring Programs in the United States: Political Appeal and Public Health Efficacy. Am J Public Health [Internet]. 2020 Aug 1 [cited 2020 Aug 5];110(8):1191–7. Available from: https://ajph.aphapublications.org/doi/full/10.2105/AJPH.2020.305696

75. Bartels K, Mayes LM, Dingmann C, Bullard KJ, Hopfer CJ, Binswanger IA. Opioid use and storage patterns by patients after hospital discharge following surgery. PLoS One [Internet]. 2016 Jan 1 [cited 2020 Sep 13];11(1). Available from: https://pubmed.ncbi.nlm.nih.gov/26824844/

76. Kim N, Matzon JL, Abboudi J, Jones C, Kirkpatrick W, Leinberry CF, et al. A prospective evaluation of opioid utilization after upper-extremity surgical procedures: Identifying consumption patterns and determining prescribing guidelines [Internet]. Vol. 98, Journal of Bone and Joint Surgery - American Volume. Lippincott Williams and Wilkins; 2016 [cited 2020 Sep 13]. p. e89. Available from: https://pubmed-ncbi-nlm-nih-gov.ezproxy.library.ubc.ca/27869630/

77. Wojahn RD, Bogunovic L, Brophy RH, Wright RW, Matava MJ, Green JR, et al. Opioid consumption after knee arthroscopy. J Bone Jt Surg - Am Vol [Internet]. 2018 [cited 2020 Sep 13];100(19):1629–36. Available from: https://pubmed-ncbi-nlm-nih-gov.ezproxy.library.ubc.ca/30277992/

78. Howard R, Vu J, Lee J, Brummett C, Englesbe M, Waljee J. A Pathway for Developing Postoperative Opioid Prescribing Best Practices [Internet]. Vol. 271, Annals of Surgery. Lippincott Williams and Wilkins; 2020 [cited 2020 Sep 9]. p. 86–93. Available from: https://pubmed-ncbi-nlm-nih-gov.ezproxy.library.ubc.ca/31478976/

79. DeLoach LJ, Higgins MS, Caplan AB, Stiff JL. The Visual Analog Scale in the Immediate Postoperative Period. Anesth Analg [Internet]. 1998 Jan [cited 2020 Sep 14];86(1):102–6. Available from: http://journals.lww.com/00000539-199801000-00020

80. Chanowski EJP, Horn JL, Boyd JH, Tsui BCH, Brodt JL. Opioid-Free Ultra-Fast-Track On-Pump Coronary Artery Bypass Grafting Using Erector Spinae Plane Catheters. J

Cardiothorac Vasc Anesth [Internet]. 2019 Jul 1 [cited 2020 Sep 18];33(7):1988–90. Available from: https://pubmed-ncbi-nlm-nih-gov.ezproxy.library.ubc.ca/30424939/

81. Landry E, Burns S, Pelletier MP, Muehlschlegel JD. A Successful Opioid-Free Anesthetic in a Patient Undergoing Cardiac Surgery. J Cardiothorac Vasc Anesth [Internet]. 2019 Sep 1 [cited 2020 Sep 14];33(9):2517–20. Available from: https://pubmed.ncbi.nlm.nih.gov/30611614/

82. Guinot PG, Spitz A, Berthoud V, Ellouze O, Missaoui A, Constandache T, et al. Effect of opioid-free anaesthesia on post-operative period in cardiac surgery: A retrospective matched case-control study. BMC Anesthesiol [Internet]. 2019 Jul 31 [cited 2020 Sep 18];19(1). Available from: /pmc/articles/PMC6668113/?report=abstract

83. The Lancet Public Health. A public health approach to Canada's opioid crisis [Internet]. Vol. 3, The Lancet Public Health. Elsevier Ltd; 2018 [cited 2020 Sep 18]. p. e204. Available from: https://pubmed-ncbi-nlm-nih-gov.ezproxy.library.ubc.ca/29709648/

84. Hyshka E, Anderson-Baron J, Karekezi K, Belle-Isle L, Elliott R, Pauly B, et al. Harm reduction in name, but not substance: A comparative analysis of current Canadian provincial and territorial policy frameworks. Harm Reduct J [Internet]. 2017 Jul 26 [cited 2020 Sep 18];14(1). Available from: https://pubmed-ncbi-nlm-nih-gov.ezproxy.library.ubc.ca/28747183/

85. Care not Corrections Relieving the Opioid Crisis in Canada [Internet]. 2018 [cited 2020 Sep 18]. Available from: www.cmha.ca

Appendices

Appendix A: Canadian Society of Cardiac Surgeons survey questions (English Version)

1. What is your current position?
    a. Attending Physician. *If yes, indicate number of years in practice:*
        i. < 5
        ii. 5-10
        iii. 10-20
        iv. >20
    b. Resident. *If yes, indicate clinical level completed:*
        i. PGY 1
        ii. PGY 2
        iii. PGY 3
        iv. PGY 4
        v. PGY 5
        vi. PGY 6 or higher
    c. Fellow.

2. In which province is your current practice based?
    a. Newfoundland and Labrador
    b. Nova Scotia
    c. New Brunswick
    d. Quebec
    e. Ontario
    f. Manitoba
    g. Saskatchewan
    h. Alberta
    i. British Columbia

3. Which best describes the cardiac surgery program at your hospital?
    a. Teaching Program
    b. Non-teaching Program

4. When discharging a patient after a straight-forward sternotomy-based procedure, how often do you prescribe an opioid or an opioid-containing combination pill (e.g. Tylenol #3):
    a. Always
    b. More than half of the time
    c. Less than half of the time
    d. Never

5. When discharging a patient after a straight-forward sternotomy-based procedure, which opioid medication are you MOST likely to prescribe:
    a. Hydromorphone
    b. Oxycodone

c. Morphine
d. Codeine
e. Tramadol
f. Other opioid not listed
g. Non-opioid medications (write in)

6. *If an opioid was selected* -> Write in the pill number and dose that you prescribe most commonly (e.g. Tylenol #3)
    a. Pill Name _____ (e.g. Tylenol #3 or Oxycodone)
    b. Dose _____ (e.g. Specify in tablets or milligrams per pill)
    c. Number of Pills _____
    d. Number of Refills _____

7. How often do you prescribe refills on opioid medications at the time of discharge?
    a. Always
    b. More than half of the time
    c. Less than half of the time
    d. Never

9. How often do you prescribe refills on opioid medications at follow-up or any time after discharge?
    a. Always
    b. More than half of the time
    c. Less than half of the time
    d. Never

10. Which of the following has MOST informed your approach to analgesic prescription at discharge? (Please rank up to 3)
    a. Formal education during medical school or subsequent accredited sessions
    b. Published literature or guidelines on analgesic dosing
    c. Personal experience
    d. Institutional policies
    e. Informal teaching either during training or from colleagues
    f. Material or informational support from pharmaceutical companies
    g. Other (write in)

11. For how long after discharge would you assume that a typical patient requires opioid medication?
    a. < 1 week
    b. 1-2 weeks
    c. 2-4 weeks
    d. > 4 weeks

12. Have you ever received formal education regarding dosing guidelines for opioid prescription when discharging patients?
    a. No

b. Yes

13. On average, how much of a given post-operative opioid prescription do you believe that a patient typically uses?
    a. Most to all
    b. More than Half
    c. Roughly Half
    d. Less than Half
    e. Little to none
    f. Unsure

14. What percentage of opioid-naïve patients do you think become chronic users following a routine post-operative prescription?
    a. <1%
    b. 1-5%
    c. 5-10%
    d. <10%

15. Do you believe that there is value in establishing guidelines for post-operative opioid prescription following routine cardiac surgical procedures?
    a. Yes
    b. No

Appendix B: Canadian Cardiac Surgery Trainee Opioid Working Group (Alphabetical Order)

Sabin Bozso MD, *Division of Cardiac Surgery, Department of Surgery, University of Alberta, Edmonton, Alberta*

Ryan Buyting, *Dalhousie Medical School, Dalhousie Medicine New Brunswick, Saint John, New Brunswick*

Claudia Cote MD, *Division of Cardiac Surgery, Dalhousie Medical School, Halifax, Nova Scotia*

Ali Fatehi MD MSc, *Department of Cardiac Sciences, University of Calgary, Calgary, Alberta*

Ming Hao Guo MD, *Division of Cardiac Surgery, University of Ottawa Heart Institute, Ontario*

Iqbal Jaffer MBBS PhD, *Division of Cardiac Surgery, McMaster University, Hamilton, Ontario*

Charles Laurin MD, *Division of Cardiac Surgery, Université Laval, Quebec, QC*

Carly Lodewyks MD MS, *Department of Surgery, University of Manitoba, Winnipeg, Manitoba*

Edward Percy MD, *Division of Cardiovascular Surgery, University of British Columbia, Vancouver, British Columbia*

Derrick Tam MD, *Division of Cardiac Surgery, University of Toronto, Toronto, Ontario*

Philippe Tremblay, *Division of Cardiac Surgery, Dalhousie Medical School, Halifax, Nova Scotia*

Appendix C: Data collection form used to collect patient-level information in the prospective cohort study.

DATA COLLECTION FORM
PART I:
Baseline and In-hospital Data

Patient Unique Study ID _____

Variables are defined according to the Society of Thoracic Surgeons Adult Cardiac Surgery Database Version 2.9 (Available via: https://www.sts.org/registries-research-center/sts-national-database/adult-cardiac-surgery-database/data-collection)

Demographic/Baseline Variables of interest

- Age at operation (value, years) ____
- Sex (M/F) ____
- History of substance abuse (Y/N)___
- History of depression (Y/N) ____
- History of opioid abuse (Y/N) ____
- Body mass index (value, kg/m^2) ____
- Smoking history (Never/Current Smoker/Former Smoker) ____
- Hypertension (Y/N) ____
- Dyslipidemia (Y/N) ____
- Diabetes (Y/N) ____
- Renal Failure (Y/N) ____
- Previous stroke or TIA (Y/N) ____
- Peripheral vascular disease (Y/N) ____
- Chronic obstructive pulmonary disease (Y/N) ____
- Atrial fibrillation (Y/N) ____
- Pulmonary Hypertension (Y/N) ____
- Five Meter Walk Test (distance, ft) ___
- Pre-operative Ejection Fraction (value, %) ____

Peri-operative in-hospital variables/outcomes of interest

- Procedure (STS V2.9 codes) _____
- Procedure Status (Elective/Urgent/Emergent) ____
- Length of cardiopulmonary bypass (value, min) ____
- Aortic cross-clamp time (value, min) ____
- Use of saphenous vein graph (Y/N) ____
- Use of internal mammary artery (Y/N) ____
- Use of bilateral internal mammary arteries (Y/N) ____
- Use of radial artery (Y/N) ____
- Length of ICU stay (value, days) ____
- Numerical Rating Scale Pain score on first day on post-operative ward (value, 0 to 10) ___
- Prolonged ventilation (Y/N) ____
- Pneumonia (Y/N) ____
- Renal failure (Y/N) ____

- Atrial fibrillation (Y/N) ____
- Stroke/TIA (Y/N) ____
- Pacemaker implantation (Y/N) ____
- Length of hospital stay (value, days) ____
- Total morphine milligram equivalents used in 24-hr prior to discharge (value) ____
- Non-steroidal anti-inflammatory prescribed at discharge? (Y/N) ____
- GABA analogue medication prescribed at discharge? (Y/N) ____
- Tricyclic antidepressant prescribed at discharge? (Y/N) ____
- Opioid medication prescribed at discharge (medication type) ____
- Opioid dose/pill prescribed (value) ____
- Number of opioid pills prescribed at discharge (value) ____
- Numerical Rating Scale Pain score on day of discharge (value, 0 to 10) ____

DATA COLLECTION FORM
PART II:
Follow-up Outcomes

Patient Unique Study ID _____

2.1 Post-discharge Day 1-10 outcomes of interest recorded in Patient Booklet (Separate Document)

- See booklet

2.2 Post-discharge Day 10 Patient Encounter (Telephone Call)

- Total number of opioid pills used, researcher-directed patient pill count (value) ____
- Numerical Rating Scale Pain score (value) ____
- Use of non-steroidal anti-inflammatory in initial 10-days (never, occasionally, daily) _____
- Use of acetaminophen (unless combined with opioid) in initial 10-days (never, occasionally, daily) ___
- Use of GABA agonists in initial 10-days (never, occasionally, daily) ____
- Use of tricyclic antidepressant in initial 10-days (never, occasionally, daily) ____
- Satisfaction with pain management (Very Unsatisfied, Unsatisfied, Satisfied, Very Satisfied) _____

2.3 Three-month post-discharge Patient Encounter (Telephone Call)

- Ongoing opioid use within last 7 days (Y/N) ____
- Ongoing opioid use, more days than not (Y/N) ____
- Ongoing daily opioid use (Y/N) ____
- Any use of non-steroidal anti-inflammatory medications within last 7 days (Y/N) ____
- Daily use of non-steroidal anti-inflammatory medications (Y/N) ____
- Any use of GABA analogue medications within last 7 days (Y/N) ____
- Daily use of GABA analogue medication (Y/N) ____
- Any use of tricyclic antidepressant within the last 7 days (Y/N) ____

- Daily use of tricyclic antidepressant medication (Y/N)___
- Numerical Rating Scale Pain score (value) ____
- Satisfaction with pain management (Very Unsatisfied, Unsatisfied, Satisfied, Very Satisfied) _____
- Quality of Recovery Questionnaire (QoR – 40 Score) _____

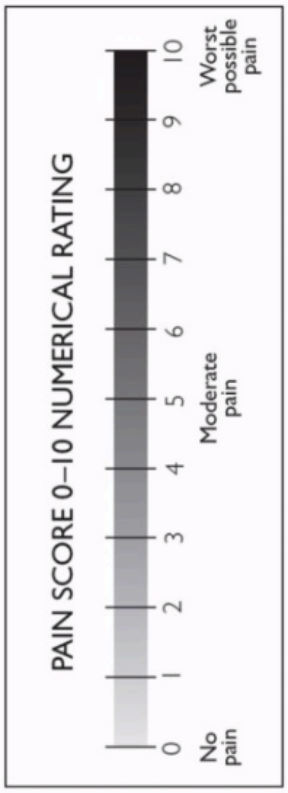
Appendix D: Patient-led post-discharge pain and opioid use diary used in prospective cohort study (printed on front and back of a single 8x11" sheet).

Contact

Thank you for taking part in our study. If you have any questions or concerns, feel free to call us at:

617-732-6781

For any medical issues please call your surgeon's office or visit your local emergency room.



BRIGHAM AND WOMEN'S HOSPITAL

Cardiac Surgery Pain Journal

Your study ID number:

_____

Your pain medication and dose:

_____

Instructions:

- **Please make an entry into this journal each day for the first 10-days after you get home**
- **Each day, mark down:**
  - **The date**
  - **Your pain number from 1-10 (see scale on back)**
  - **The number of _____ pills taken**
- **On Day 10, how satisfied are you with overall pain management since getting home? (circle one)**
  - **Very Unsatisfied**
  - **Unsatisfied**
  - **Satisfied**
  - **Very Satisfied**

- **Mail this brochure back to us in the pre-paid envelope**
- **We will see you at your follow-up visit**

	Date	Pain Score	# of pills
Day 1		__/10	
Day 2		__/10	
Day 3		__/10	
Day 4		__/10	
Day 5		__/10	
Day 6		__/10	
Day 7		__/10	

	Date	Pain Score	# of pills
Day 8		__/10	
Day 9		__/10	
Day 10		__/10	