EMERGING METHODS FOR USE OF REAL-WORLD CLINICAL DATA FOR CARDIOVASCULAR OUTCOMES RESEARCH

A DISSERTATION IN

Bioinformatics

and Entrepreneurship & Innovation

Presented to the Faculty of the University
of Missouri-Kansas City in partial fulfillment of
the requirements for the degree

DOCTOR OF PHILOSOPHY

by

JEREMY BURTON PROVANCE

B.A., William Jewell College, 2014

M.S., University of Missouri-Kansas City, 2017

Kansas City, Missouri

2021

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Jeremy Burton Provance, Candidate for Doctor or Philosophy Degree

University of Missouri-Kansas City, 2021

ABSTRACT

The purpose of this dissertation is to describe methods for use of real-world data resources to study quality of care and outcomes for patients with critical limb ischemia. We used the Cerner Health Facts de-identified EHR database to 1) exclude patient records except those with critical limb ischemia from clinical sites in the Health Facts database, 2) document variability in patient outcomes after critical limb ischemia care, and 3) document variability in evidence-based medical therapy for the treatment of critical limb ischemia.

We derived a data mart from the Health Facts database and identified 31,490 unique patients seen in 79,359 unique encounters at 233 unique clinical sites in the Health Facts database between 2010 and 2017. Of these, 20,204 encounters included endovascular peripheral vascular intervention. Within 30 days of the intervention, 2.8% of patient encounters resulted in a major amputation. We documented the association of modifiable patient factors with 30-day amputation and significant variation in 30-day amputation rates at the clinical site level. In addition to procedural quality outcomes, we examined rates of guideline directed medical therapy—medications indicated to reduce risk of adverse outcomes in all patients with critical limb ischemia. Only 27.2% of patient encounters documented complete medical therapy while 72.4% documented some component of therapy. As with 30-day amputation outcomes, rates of the medical therapy quality metric

varied widely between sites with a median rate of 38.2% and interquartile range of 16.3-60.1%.

This work demonstrates the use of a national, EHR database for cardiovascular outcomes research. We documented 30-day amputation outcomes after peripheral vascular intervention--a metric of CLI treatment outcomes. We also documented quality of care—guideline directed medical therapy—surrounding an inpatient encounter for CLI. We documented site variability for both treatment outcomes and quality of care to inform future quality improvement work in the treatment of CLI nationally.

APPROVAL PAGE

The faculty listed below, appointed by the Dean of the School of Graduate Studies have examined a dissertation "Emerging Methods for Use of Real-World Clinical Data for Cardiovascular Outcomes Research," presented by Jeremy Burton Provance, M.S., candidate for the Doctor of Philosophy degree, and certify that in their opinion it is worthy of acceptance.

Supervisory Committee

Kim G. Smolderen, Ph.D., F.A.H.A., F.A.C.C.; Research Advisor
Internal Medicine, Yale School of Medicine

John A. Spertus, M.D., M.P.H., F.A.C.C.; Committee Chair
Biomedical & Health Informatics, University of Missouri-Kansas City School of Medicine

Brian S. Anderson, Ph.D.; Co-discipline Advisor
Entrepreneurship & Innovation, Bloch School of Management

Matthew C. Bunte, M.D., M.S.
Medicine, University of Missouri-Kansas City School of Medicine

Mark A. Hoffman, Ph.D.
Biomedical & Health Informatics, University of Missouri-Kansas City School of Medicine

Philip G. Jones, M.S.
Biomedical & Health Informatics, University of Missouri-Kansas City School of Medicine

Todd R. Vogel, M.D.
Surgery, University of Missouri School of Medicine

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ACKNOWLEDGEMENTS

I have so many individuals to thank who helped me to reach this point of finishing my formal education. First, to my research advisor Dr. Kim Smolderen for her research guidance and mentorship over the last 5 years. Kim invested considerable time and energy into helping me grow into the researcher I am today. Kim's commitment to nothing less than excellent work has been such a great example for me to learn from and hopefully to emulate. Thank you to Dr. John Spertus, who is such a great mentor to many students seeking to understand clinical research. Dr. Spertus always asks the hard questions, but they are also the right questions and I have learned so much from him.

Thank you to Dr. Mark Hoffman, who is certainly a role model for anyone who aspires to be a serious informatician as well as a kind human being. Mark was one of the first people who took me under his wing when I showed up to UMKC and my tempered perspectives on data are in large part due to Mark. Thanks to Phil Jones for his always pragmatic, always realistic approach to clinical data analysis. Phil has a real gift for sharing knowledge with others and he's one of the wisest statisticians I have ever met. Thank you to Dr. Brian Anderson, whose enthusiasm for data science methods and platforms started me down a pathway for using reproducible methods that I am confident will continue for the rest of my career. Thank you to the clinical members of my dissertation committee, Dr. Matthew Bunte and Dr. Todd Vogel, who kept me on track with what actually happens and matters in healthcare rather than what we might hope or expect to see.

I am only here because of an army of educators who cared enough to spend time investing in me and my development. They have given great time and effort to my growth from the very beginning. Some, but certainly not all, of these educators are as follows: Anne

House (kindergarten), Kiley Simpson (first grade), Rita Rodgers and Melissa Staples (second grade), Lesa West (third grade), Karen Marlborough (fourth grade), Shelli Cornell (fifth grade), Laura Griffin (sixth grade), Wanda Harter (ASPIRE program coordinator), Christine Lake (seventh grade science), Laura Tewes (eighth grade science), Kat Jones (ninth and twelfth grade advanced biology), who also made me certain science was the career path for me. Educators also include Amy Middaugh (eleventh grade advanced biology), Paul Morales (middle school and high school orchestra), Dr. Tara Allen (undergraduate advisor and biology professor), Dr. Scott Falke (undergraduate research advisor and mentor), the faculty of the biology, chemistry, and physics departments including Dr. Blane Baker, Dr. Patrick Bunton, Dr. Paul Klawinski, Dr. Jason Morrill, Dr. Shane Price, and Dr. Lori Wetmore at William Jewell College, and the faculty in the Department of Biomedical and Health Informatics department including Dr. Jenifer Allsworth, Dr. Julie Banderas, Dr. An-Lin Cheng, Dr. Monica Gaddis, Dr. Mark Nichols, and Dr. Steve Simon at the University of Missouri-Kansas City School of Medicine.

To my mother Karen, my father Joe, and my brother Brad, I owe many debts that cannot be repaid. I appreciate all of your great efforts to make sure I was able to take advantage of the opportunities that life presented. Your love and guidance have made it possible to be where I am today.

To my wife, Olivia, I cannot quantify my gratitude. Thank you for my daily reminders to always work hard and always be nice. I am grateful to have taken this journey alongside you and am so proud that very soon you will be Dr. Olivia Provance. There is so much more in store for us, and I am glad we will get to experience it together.

CHAPTER 1

GENERAL INTRODUCTION

Patients with critical limb ischemia (CLI), an advanced form of peripheral artery disease (PAD), are at significant risk for lower extremity amputation and other adverse cardiac events, including myocardial infarction and stroke, and death due to cardiovascular disease.[1-4] Timely and thorough medical intervention, including early diagnosis, revascularization procedures as appropriate, and overall risk factor modification are crucial to prevent disease progression and complications.[1, 5] There is an unmet need to provide contemporary and comprehensive data sources including CLI patient quality of care and outcomes information. This work aims to leverage a contemporary and national database of real-world data to quantify quality and variability in procedural outcomes in patients with CLI, to quantify variability in medical management of patients with CLI undergoing amputations, as well as exploring patient perspectives for whether or not they wish to partner with providers in their care through evidence-based data.

Clinical registries, such as the National Cardiovascular Disease (NCDR) Peripheral Vascular Intervention (PVI) registry, are typically used to study patients with peripheral vascular disease.[6] As more clinical sites participate in these collaborative registries, this increased representation provides greater opportunity to generalize results and describe a diversity of experiences that patients with CLI have with their care. Although clinical registries offer high-quality data for use in clinical research, they have significant limitations. Patients enrolled in registries are highly selected and may not provide data representing the experience of the patient population as a whole. Clinical registries, including the NCDR PVI registry, attempt to follow patients through time to create longitudinal insights, however,

patient attrition for any study results in censored data. These registries are often de-coupled from other data sources, such as the electronic health record (EHR), and are de-identified to protect patient privacy. This de-identification offers protection for the patients and clinical sites who contribute data but results in loss of the ability to provide updated or additional data to a study record and limits the ability of the researcher to validate results using other data sources such as clinical notes. Given de-identification is often a feature of EHR research databases, a primary aim of this work is to describe methods for creating a high-quality data resource using a de-identified, real-world EHR database that might be applied to clinical problems such as cardiovascular outcomes research. Previous work has been successful in both the use of EHR data to automatically phenotype PAD from discrete data elements and to predict risk of mortality, however, these efforts did not represent patients at a national level.[7]

The Cerner Health Facts resource is an ideal database to address these gaps. Health Facts provides a database of 63 million unique patients seen at 863 participating Cerner health care sites across the US between years 2000 and 2017. Patient level data can be queried for demographics, diagnoses, inpatient medications, procedures, and site characteristics to provide large cohorts with high-resolution data for longitudinal analysis. The overall objective of this dissertation is to understand the magnitude of the problem of non-traumatic amputations in patients with PAD, study the risk profile of patients who have undergone an amputation, as well as the quality of care these patients receive and their subsequent outcomes. The collective insights gained from this work will help us *identify priority areas for preventive action* and *design quality of care improvements*.

In the United States, it is estimated that 8.5 million patients have PAD[3] and approximately 1-3% of these PAD patients will progress to CLI.[8] It is estimated that up to 1.4 million US patients live with non-traumatic amputations[9] and the majority of non-traumatic amputations have origins with CLI and other comorbid cardiovascular diseases.[10] Patients with amputations due to CLI have been shown to have limb-free mortality rates of up to 44%, 66%, and 85% after 1, 3, and 5 years, respectively.[11] The presence of microvascular disease, a manifestation of diabetes, has been shown to be a contributor to lower-extremity amputation rates when it occurs with comorbid CLI.[12, 13] Patients with CLI and diabetes are also at high risk for other cardiovascular events (stroke, myocardial infarction, cardiac death) as compared with individuals who are free from these conditions.[14, 15]

As amputation is a devastating outcome, it is of utmost importance to understand the scope of the problem, identify at-risk populations, study variability in care patterns, and associated outcomes. Overall non-traumatic amputations rates have declined in the last decade,[12, 16, 17] but recent reports signal that they may be increasing, particularly among patients who have complex disease states such as CLI.[12] There is significant variability in the attempts to restore blood flow with revascularization in the year preceding an amputation among Medicare patients.[17] The variability in rates of revascularization varied as much as two-fold across regions of the United States and the intensity of vascular care, or revascularization attempts, was inversely correlated with rates of major amputation. The evidence that we have, however, is *fragmented*, and *contemporary national estimates of non-traumatic amputation are lacking*, and *it is unclear how often vascular testing and revascularization attempts are performed* among patients who ended up with an amputation complication. Some analyses have focused on disease rates within specific regions of the

United States,[12] others national cohorts have focused on quality of care but not rates,[17] and others have focused on both rates and quality of care but only in specific cohorts such as Medicare patients.[16, 18, 19]

The purpose of this work is to examine the quality of care and outcomes in a nationally representative cohort of patients with CLI in the Health Facts database. "Quality of care" is the framework by which the optimal treatment of a medical condition is measured. Following national guidelines, such as the AHA/ACC Guideline for Management of Patients with Lower Extremity Peripheral Artery Disease[4], is considered critical to providing evidence-based treatment regimens for a medical condition. Specific to CLI, recent global guidelines have been released[20] to describe the quality of care metrics that should occur for all patients with diagnosed CLI. These guidelines suggest referral of patients with suspected CLI to a vascular medicine specialist, to perform diagnostic peripheral vascular testing to confirm vessel occlusion,[21-23] to prescribe guideline directed medical therapy (a statin, antihypertensives for patients with documented hypertension, and antiplatelet medications), and to assess a patient's suitability for artery revascularization and complete these procedures as appropriate. All patients should be placed on guideline directed medical therapy including use of lipid-lowering, antihypertensive, and glycemic controlling medications, and should be subjected to lifestyle management counseling for smoking cessation, diet, and exercise changes.

Once CLI is diagnosed as the underlying pathophysiology of a patient's rest pain, ulcer, or gangrene, the patient should be evaluated for a revascularization procedure in an attempt to restore the blood flow to the limb and increase the chances of limb preservation. Revascularization can be an endovascular procedure, such as in the case of balloon

angioplasty or stenting, or surgical with peripheral vascular bypass grafting. Results from the BEST-CLI trial will evaluate the comparative effectiveness of endovascular versus surgical care.[24] These peripheral vascular disease guidelines work in parallel to others for patients with other cardiovascular conditions such as coronary artery disease and cerebral vascular disease.[1] For patients with open CLI foot wounds, quality of care metrics include wound care, infection control, and offloading.[1] The best quality of care for a CLI patient requires a multi-disciplinary and comprehensive approach for each patient including disciplines such as vascular medicine, nutritional and social support, wound care, and diabetes management among others.[5]

Given guidelines for the treatment of CLI have been established but the quality of care patients with CLI receive and the outcomes they experience in real-world care are unclear, the following specific aims were proposed for the research that follows: Specific Aim 1: Develop methods to create a high-fidelity data warehouse from the national Cerner Health Facts electronic health record database for use in cardiovascular outcomes research. Specific Aim 2: Apply the real-world data warehouse to examine quality of care and outcomes in patients with critical limb ischemia. Specifically, this work aims to identify variability in 30-day amputation outcomes after endovascular peripheral vascular intervention documented in the Health Facts database (Aim 2A) and variability in guideline directed medical therapy after amputation, a quality of care treatment metric, documented for patients who have CLI (Aim 2B).

We expect that substantial variability will exist for both treatment quality of care and relevant clinical outcomes for patients with CLI.[25-28] We expect that by using the national, real-world, de-identified, Health Facts database derived from the EHR rather than a clinical

registry or aggregated claims data (such as Medicare), we will both document the amount of variability that exists in this clinical population and provide insights using a new methodology for documentation of CLI care.

By documenting and providing new methodologies for the use of EHR data in real-world analyses, we are providing a path forward for the expanded use of these data resources to generate high-quality evidence using real-world data. Use of the high-fidelity data resource derived from Health Facts will provide evidence for continued use of these resources and guidance on their key limitations for use in cardiovascular outcomes research. Describing variability in the quality of care and outcomes in patients who seek care for CLI using nationally representative, real-world data, we can continue to inform the discussion surrounding CLI care guidelines and inform national quality initiatives for excellence in CLI care.

CHAPTER 2

AIM 1: METHODS FOR IDENTIFYING CLINICAL SITES WITH COMPREHENSIVE DATA FOR CARDIOVASCULAR OUTCOMES RESEARCH IN A NATIONAL ELECTRONIC HEALTH RECORD DATABASE

Introduction

Passage of the Health Information Technology for Economic and Clinical Health Act of 2009[29] has accelerated electronic health record (EHR) adoption in the United States,[30] which has enabled the digital collection of more discrete phenotypic data than ever before for patients seen at health care sites in the United States. These data enter the electronic health record (EHR) to accommodate order sets and billing, which then can be extracted, transformed, and loaded onto secondary platforms for research use. Multi-site, observational databases present an opportunity for real-world epidemiological, quality improvement, and outcomes research.

There is no public, federated system for the uniform organization of data and most data collected by a health care site is governed by individual clinical sites who interface with EHR vendors to adopt electronic data management solutions.[31] Secondary efforts can be applied to transform data into a common data model framework such as the Observational Medical Outcomes Partnership (OMOP) common data model[32] or the Patient Centered Outcomes Research Network (PCORNet) common data model. This normalizes the data structure but does not solve for data completeness. At any given time, a health care system may use multiple EHR vendors and may not provide complete data to the vendors with which they have data usage agreements. This contrasts with health data sets with prospective designs, such as clinical trial registries, where data dictionaries are developed and shared

with sites a-priori and attention is given to ensure data completeness over time. The quality and quantity of data in EHR-derived databases can vary substantially over time.[31] This problem may be exacerbated if a health system has EHR products from multiple vendors (for example, EHR components from both Epic and Cerner) and if they change EHR vendors or add or remove individual EHR modules. Given these variations in observational data, using observational EHR databases for research presents unique challenges particularly when the database aggregates data from multiple non-affiliated sites and health systems.

Understanding the challenges for using aggregated multi-site EHR data for research purposes is key to answering clinically relevant questions with EHR-based data. Each observational research database may require unique data checks at encounter, patient, provider, site, health system, or any combination of these levels. The aim of this study was to derive a critical limb ischemia data mart from the Cerner Health Facts EHR database that is suitable for use in cardiovascular outcomes research. Critical limb ischemia (CLI) is the most advanced form of peripheral artery disease and presents significant opportunity for research into quality of care and outcomes patients experience.[5] Health Facts is a research data warehouse that contains over 69 million unique patients seen at over 460 million unique encounters at 782 distinct clinical sites across the United States. Health Facts is a resource that can be used to characterize quality of care and outcomes research-related questions at the encounter-, patient-, and site-levels of analysis for patients with CLI. This work aimed to describe a workflow for identifying data from sites with comprehensive data in a national, observational, EHR-derived database and applying it through the creation of a cardiovascular outcomes research database.

Methods

Study Design

The Health Facts EHR database is a de-identified, EHR-derived data resource that includes encounter, diagnosis, procedure, medication data from 782 unique clinical sites. The 2018 version of Health Facts was used for the purposes of this study, which contains data between the years 2000 and 2017. However, only data from 2010 to 2017 were used as Cerner re-engineered the database in 2010 and data after 2010 are more likely to be complete. The Health Facts data reside in a relational database on a distributed computing system at the University of Missouri-Kansas City (UMKC). Data were queried using structured query language (SQL) and were analyzed within the RStudio integrated development environment version 1.3.1073 and R version 4.0.2.[33] The UMKC School of Medicine and Truman Medical Centers joint institutional review board has reviewed the de-identified Health Facts database and has determined subsequent research from its use is considered "non-human subjects research".

Health Facts Database Composition and Data Structure

EHR data may be organized in different places depending on the module adoption of a certain site. For example, a site may use Cerner as their core EHR to document encounters, medical history, and medication lists, but may use a different system provider for their laboratory results. In the Health Facts database, data modules are divided into a star schema with the patient encounter as the primary fact table with secondary fact tables (diagnoses, procedures, medications, etc.) linked to it through an encounter ID (Figure 1). Dimension tables with descriptive data can be linked to each fact table to provide information like data

labels and data to further describe the fact table. The encounter-level data required for this analysis included encounter characteristics, patient characteristics, site characteristics, diagnoses, procedures, and medications.

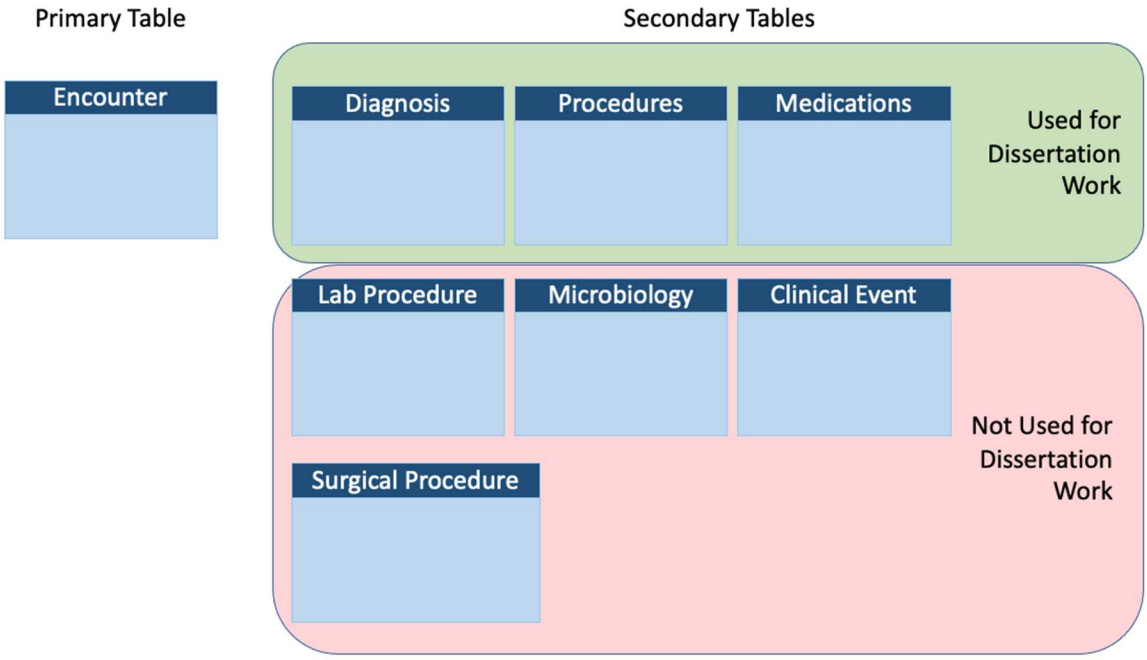


Figure 1. Overview of the Cerner Health Facts Primary and Secondary Tables with Highlights of Tables Used or Not Used to Complete This Dissertation

Data Preparation: Identifying Sites with Comprehensive Data

To classify clinical sites by the volume and presence of data in each of their data tables included in Health Facts, descriptive statistics were derived for unique counts of encounter ID in the encounter, diagnosis, procedure, and medication fact tables stratified by each of the 782 Health Facts sites. As a primary exclusion step, sites with less than 100 or missing unique encounter IDs in the encounter, diagnosis, procedure, or medication table were excluded (Table 1).

Table 1. Steps for Identifying Sites with Comprehensive Clinical Data in the Health Facts Database

Steps for Site-Level Data Checks
1. Exclude any site with fewer than 100 unique encounters in the patient encounter table
2. Exclude any site with fewer than 100 unique encounters in the diagnosis encounter table
3. Exclude any site with fewer than 100 unique encounters in the medication encounter table
4. Exclude any site with fewer than 100 unique encounters in the procedure encounters table

To further refine the data included in our vascular cohort, patients were excluded through a secondary step if they did not have a history of documented CLI in a Health Facts database encounter. Patients with a documented history of CLI diagnoses were identified using International Classification of Diseases, Version 9 (ICD-9) and Version 10 (ICD-10) administrative codes. ICD-9/10 codes to identify patients with CLI have previously been documented.[8, 34] The unique patient identifier in Health Facts was collected for the list of patients who had encounters for CLI, and all encounter identifiers were aggregated for these patients. Data from the diagnoses, procedures, and medication secondary tables were joined to the patient encounter primary table using left joins on the CLI patient encounter IDs.

Data Analysis

Descriptive statistics describing the data mart variable means, counts, and proportions, where applicable, were computed to characterize the derived patient cohort. To examine encounter- and patient-level variables summarized at the clinical site level, the Health Facts unique identifier for site was used to group encounters and summary descriptive statistics were computed. Data contributions from unique encounters in the secondary Health Facts tables (diagnoses, procedures, and medications) were quantified and represented as a proportion of total unique encounters. Heat maps were created to qualitatively describe the

level of completeness (from 0% to 100%) of the secondary tables (diagnoses, procedures, and medications) compared to the primary patient encounter table.

Results

The Health Facts database contains data for 782 distinct clinical sites. These 782 sites on average had 589,172 (± 1,571,564) unique encounters per site (Table 2). These sites were mostly representative of the southern United States census region (N = 269, 35.0%) and least representative of the northeastern (146, 19.0%). Most sites were classified as urban (568, 74.0%), non-acute (425, 54.3%), and non-teaching (665, 82.5%). Over half of sites in the overall Health Facts were classified as having fewer than 5 beds (425, 54.7%) and are likely to be ambulatory clinics.

Table 2. Health Facts Site Characteristics Overall, Characteristics Sites with Comprehensive Data After Excluding Sites with Fewer than 100 Encounters, Diagnosis Encounters, Procedure Encounters, or Medication Encounters, Characteristics of Sites Without Comprehensive Data

Characteristic	Overall Health Facts Site Counts (Percent) N = 782	Included Health Facts Site Counts (Percent) N = 348	Excluded Health Facts Site Counts (Percent) N = 434
Unique Encounters (Mean [SD])	589,172 (1,571,564)	1,090,427 (1,915,309)	187,245 (1,072,906)
Unique Diagnosis Encounters (Mean [SD])	302,555 (697,892)	558,520 (903,412)	45,111 (157,796)
Unique Procedure Encounters (Mean [SD])	68,879 (168,711)	109,697 (204,296)	3,720 (20,792)
Unique Medication Encounters (Mean [SD])	101,281 (185,686)	141,233 (208,875)	8,593 (32,034)
United States Census Region			
Midwest	176 (22.9)	90 (25.9)	86 (20.5)
Northeast	146 (19.0)	51 (14.7)	95 (22.6)
South	269 (35.0)	118 (33.9)	151 (36.0)
West	177 (23.0)	89 (25.6)	88 (21.0)
Urban Status (vs. Rural)	568 (74.0)	263 (74.0)	305 (72.6)
Acute Status (vs. Non-Acute)	357 (45.7)	43 (12.4)	314 (72.4)

Teaching Status (vs. Non-Teaching)	117 (17.5)	79 (31.3)	38 (9.2)
Facility Bed Size Range			
Less than 5 Beds	425 (54.7)	61 (17.8)	364 (83.9)
6-99 Beds	146 (18.8)	130 (38.0)	16 (3.7)
100-199 Beds	78 (10.0)	66 (19.2)	12 (2.8)
200-299 Beds	61 (7.9)	39 (11.4)	22 (5.1)
300-499 Beds	40 (5.1)	30 (8.7)	10 (2.3)
500 or More Beds	27 (3.5)	17 (5.0)	10 (2.3)

Filtration of sites after the year 2010 and for sites with more than 100 encounters in the encounters, diagnosis, procedure, or medications tables yielded 342 (44.5%) remaining sites (Figure 2, Figure 3). These sites with comprehensive data had an average of 1,090,427 (± 1,915,309) unique encounters per site (Table 3). A heat map showing qualitative data presence by clinical site in the overall Health Facts database is shown in Figure 4.

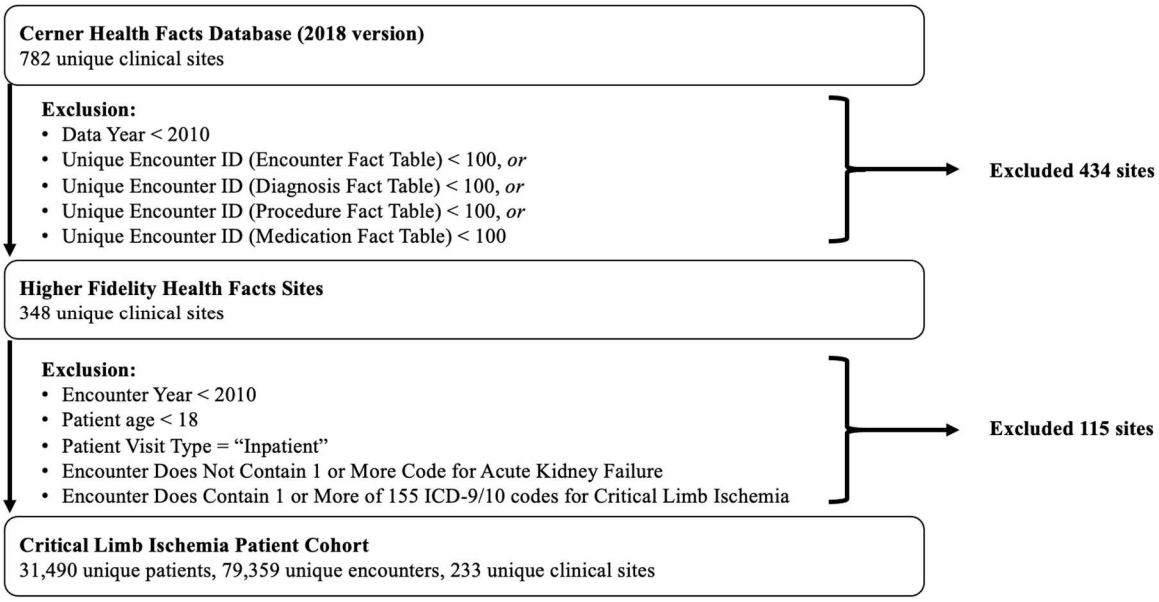


Figure 2. Overall Health Facts Sites, Patients, and Encounters; Exclusion Criteria for Sites without Comprehensive Data and Patients without Critical Limb Ischemia; Counts for Excluded Data

Table 3. Patient Characteristics for the Derived Set of Patients with Critical Limb Ischemia with Encounters Documented at Sites with Comprehensive Data in the Health Facts Database

Characteristic	Patient Encounters (Percent) Total N = 79,413
Mean Age (Standard Deviation)	68.7 (12.4)
Race (White)	52,048 (69.6)
Marital Status (Married)	45,923 (58.9)
Census Region	
Midwest	16,854 (21.2)
Northeast	17,535 (22.1)
South	35,372 (44.5)
West	9,652 (12.2)
Site Teaching Status (Teaching)	46,948 (77.5)
Site Urban vs. Rural Status (Urban)	63,024 (79.4)
Clinical History	
Acute Kidney Failure	16,520 (20.8)
Atrial Fibrillation	17,038 (21.5)
Back Pain	1,122 (1.4)
Chronic Kidney Disease	35,180 (44.3)
Chronic Wound	34,760 (43.8)
Coronary Artery Disease	44,583 (56.1)
Depressive Disorder	9,911 (12.5)
Diabetes	50,994 (64.2)
Dyslipidemia	42,586 (53.6)
Heart Failure	28,722 (36.2)
Lower Limb Amputation	15,675 (19.7)
Malignant Cancer	6,568 (8.3)
Hypertension	65,802 (82.9)
Malnutrition	6,519 (8.2)
Myocardial Infarction	5,069 (6.4)
Obesity	12,104 (15.2)
Osteomyelitis	11,318 (14.3)
Sepsis	10,547 (13.3)
Thyroid Disorder	9,991 (12.6)
Tobacco Use	35,297 (44.4)
Transient Ischemic Attack	10,829 (13.6)

These sites were mostly urban (263, 75.6%), non-acute (305, 87.6%), and non-teaching (79, 31.3%). Only 17.8% (N = 61) of these sites had a documented bed size range of less than 5. Sites that were excluded were typically smaller in bed size categorization (83.9% vs. 17.8%) and were typically acute care facilities (72.4% vs. 12.4%).

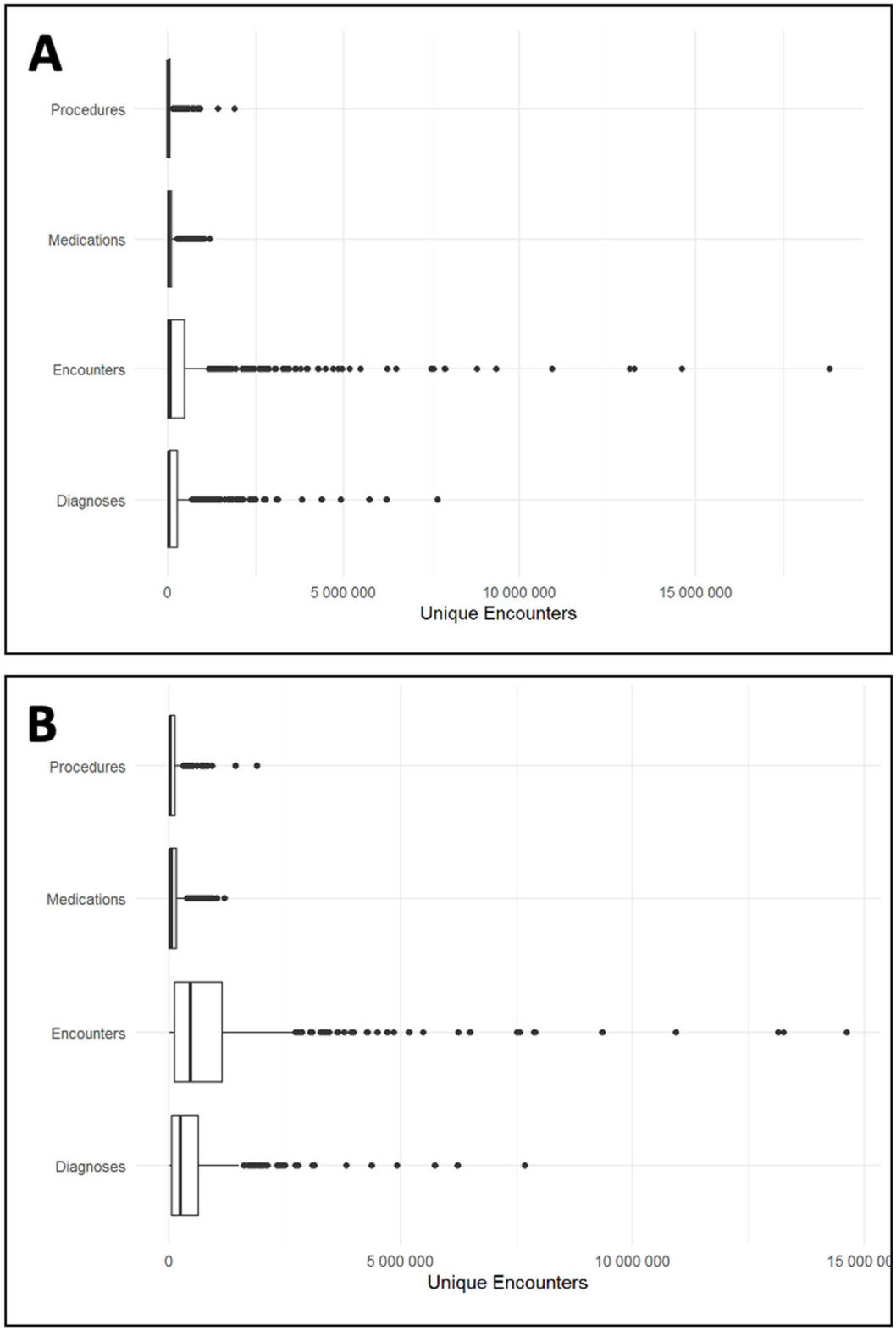


Figure 3. Box and Whisker Plot of Unique Encounter Volume by Module Type Before (A) and After (B) Filtration

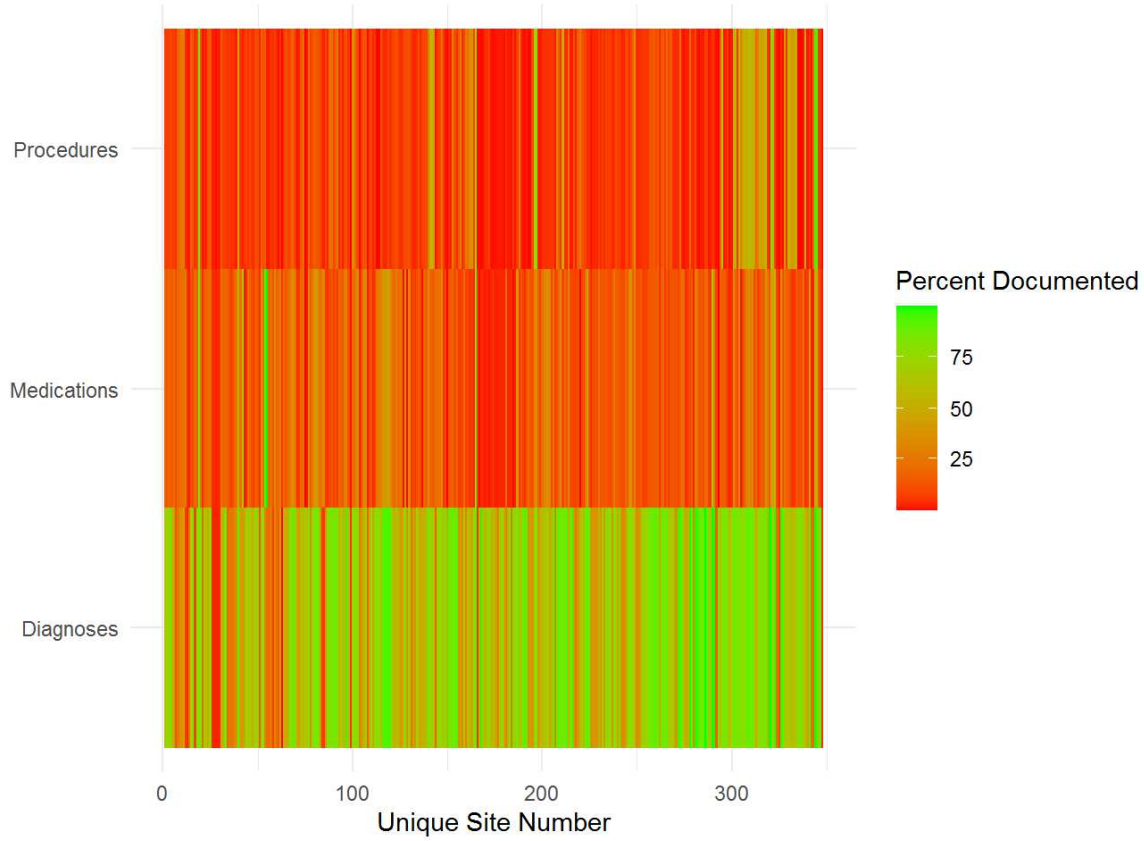


Figure 4. Heat Map for Percent of Encounters Containing Data for Secondary Modules in Filtered Site Set

Filtration of patient records within the 342 included sites yielded 31,490 unique patient records containing data for 79,359 unique encounters at 233 unique clinical sites from the years 2010 to 2017 (Figure 2). Patients were on average 68.9 years old (± 12.4) at the time of encounter, were more often documented as having a white race (69.6%), and were most often documented as married (58.9%) (Table 3). Nearly 4/5 of patient encounters were at sites documented as teaching and urban sites. Over half of all encounters had documented coronary artery disease (56.1%), diabetes (64.2), dyslipidemia (53.6), and hypertension (82.9). More than one-third of encounters contained documented chronic kidney disease (44.3%), chronic non-healing extremity wounds (43.8), heart failure (36.2), and previous tobacco use (44.4).

Discussion

This work, using the Cerner Health Facts database, describes a methodology for identifying sites with comprehensive data in a national, real-world database and for excluding sites less suitable for examining quality of care and outcomes in CLI patient treatment. We used administrative billing codes to exclude patients without a history of CLI diagnosis to derive the final research data mart. This study used a method that is reproducible in other aggregated EHR databases to exclude sites with fewer encounters overall, and with fewer encounters documented in diagnosis, medication, and procedures tables, which tended to be smaller acute care facilities. Both of these methods are useful across multi-site, observational databases derived from clinical data. As these research databases are frequently synthesized from disparate data sources, the requirement to verify data quality and remove systematically incomplete data will become critical to produce high-quality output.

Previous work has sought to use reproducible methods to examine EHR data such that it might be used to study conditions such as vascular disease.[7] Efforts to facilitate reproducible research, through the creation and implementation of common data models has resulted in the adoption of standards such as OMOP and PCORNet to achieve these aims.[35] These standards allow for disparate data sources to be compiled for analysis purposes. However, data within the same data model paradigm will not always provide comparable data quality. Particularly for larger, longitudinal databases, data contributions may vary over time, by the type of data contributed, and by the quality and quantity of data contributed at any given point in time.[31] Given this variance in data contribution, synthesis into a common data model is not sufficient to create high-quality data resources that might be used for

analysis. Data quality must be further explored within a common data model to understand the volume, type, and quality of data disparate sources contributed over time.

As a primary filtration step, data were excluded from over half of the unique clinical sites in the database with low or no contribution of data to the Cerner Health Facts data tables. As a secondary filtration step, the study also excluded patients who met prespecified exclusion criteria using administrative codes—a commonly used method—to identify patients with the clinical condition of interest. We specifically limited our analysis to sites with more than 100 unique encounters per clinical site in the Health Facts database. Distinct clinical sites in the Health Facts database ranged widely in their number of encounters by site (Figure *3*). We explored several options for low-volume site exclusion. Excluding the lower quartiles of encounter numbers disproportionately penalized sites with smaller bed sizes. Generating a ratio of encounters between different modules (for example, the ratio of diagnosis encounters to overall patient encounters) was unsuccessful as it has been documented that not every site in Health Facts use modules in a uniform manner.[31] We excluded sites with zero encounters or those with no data (classified as "NA"), however, some sites have large discrepancies between different modules with millions of encounters in one module and tens in another. In an effort to exclude low and no module usage without penalizing sites with fewer encounters proportionally, we set an exclusion criterion of 100 or fewer encounters in any of the four modules (patient, diagnosis, procedure, and medication) used for this analysis.

Future work should perform sensitivity analyses for excluding sites with lower quality data contributions from aggregated EHR databases. These analyses in a database such as Health Facts could further classify how sites contribute data overall to a specific database

and over time. As different analyses will require different data to answer a clinical question, a sensitivity analysis to a specific project would be appropriate to identify the highest quality sites suitable for answering the specific question identified.

This work suggests a standardized, simple method for excluding data from lower-quality sites in the Cerner Health Facts database. Within Health Facts, encounter-level data contributed by each of the 782 distinct clinical sites is stratified into separate data tables. For analyses that require specific types of data (inpatient vs. outpatient, diagnoses vs. procedures) investigators must characterize the availability of data required for their analysis within a specific database. Removing portions of a data set may reduce the robustness and representativeness in analysis, but this trade off may be warranted given a higher quality analysis result.

Our study is limited due to the observational nature of the data used to derive these results. Given our study variables were derived using discrete data and administrative codes, there is the possibility that there is unobserved confounding within our data. Health Facts does not contain clinical narrative data and is de-identified, therefore it is not possible to verify a CLI diagnosis using a secondary method such as chart abstraction that would occur in a clinical registry. It has been shown that administrative codes alone may not be sufficient to sensitively identify vascular disease[36] and future work should validate and refine sensitive and specific identification of CLI in administrative databases. Data may be misclassified or missing, though as the Health Facts Database is de-identified there is no current method to independently verify the integrity of the data. To validate our method of site exclusion against a known contributor to the Health Facts database, it would require the unmasking of the Health Facts site identifier, which is desirable but not possible at this time.

Documentation of data discontinuity in other clinical databases has been performed and once completed, data that is of lower quality can be excluded from analysis to reduce information bias.[37]

Conclusions

Our study describes a data workflow for excluding low quality data contributions for deriving research-quality data sets. We developed a method for deriving a data mart from the Health Facts database to address cardiovascular outcomes research questions in critical limb ischemia. This work can inform future work for the use of EHR databases to address similar questions in quality of care and outcomes in other clinical populations.

CHAPTER 3

AIM 2A: VARIABILITY IN 30-DAY MAJOR AMPUTATION RATES FOLLOWING ENDOVASCULAR PERIPHERAL VASCULAR INTERVENTION FOR CRITICAL LIMB ISCHEMIA

Introduction

Critical limb ischemia (CLI), the most advanced form of peripheral artery disease (PAD), is associated with a high risk of adverse cardiovascular events, including one-year mortality rates up to 20%, increasing up to 50% at 5 years post diagnosis.[5, 9] Treatment goals for CLI are focused on cardiovascular risk management and limb preservation.[1] Invasive strategies improve blood flow include endovascular peripheral vascular intervention (PVI) and lower-extremity bypass grafting. While the comparative effectiveness of PVI to bypass grafting is still being evaluated,[38-41] the endovascular approach offers the benefit of fewer upfront procedural risks, and has quickly become the primary mode of treatment.[34] Key performance benchmarks for the safety evaluation of CLI treatments include avoiding major adverse cardiac events and major adverse limb events, including lower extremity major amputations within 30 days after treatment,[42] which have been adopted into performance metrics for the evaluation of CLI treatments.[43]

While rates of major amputation in the context of a CLI-related admissions overall have decreased, the risk of undergoing an amputation 30 days after endovascular PVI still remains between 2 and 6 percent.[44, 45] The suggested performance goal for rates of amputation 30 days after endovascular PVI is 3%.[42] There is, however, a relative lack of national data registries that have or can reliably track vascular outcomes following a CLI-related admission, as a way to monitor and improve performance.

To address this gap, we used the multicenter Cerner Health Facts database, which contains de-identified electronic health record (EHR) data from 2000-2017 from 782 participating sites using the Cerner EHR across the United States, to describe the rates of 30-day major amputation among patients diagnosed with CLI and underwent PVI across care centers in the United States. We also examined the association of patient-level and site-level factors associated with variability in 30-day rates of major amputation. Understanding institutional performance, and the factors associated with this outcome may offer the opportunity to further refine the use of 30-day major amputation as a metric of CLI care quality.

Methods

Study Design and Patient Selection

The de-identified Cerner Health Facts (Cerner Corporation, Kansas City, Missouri) electronic health record (EHR) database is a data warehouse derived from the EHR intended for use in research and quality improvement. Data in Health Facts are extracted from the EHR at health systems with a data use agreement with Cerner. Encounters may include pharmacy, clinical and microbiology laboratory, admission, and billing information from affiliated patient care locations. Admissions, medication orders and dispensing, laboratory orders and specimens are date and time stamped (though date-shifted at the patient level during de-identification), providing a temporal relationship between treatment patterns and clinical information. Cerner Corporation has established Health Insurance Portability and Accountability Act-compliant operating policies to establish de-identification for Health Facts.

The Health Facts data represent over 69 million unique patients from inpatient, outpatient, and emergent visits, and provide encounter-level data that includes diagnoses, medications, procedures, and laboratory results. We filtered the Health Facts database patients for those with documented CLI using International Classification of Diseases, versions 9 and 10 (ICD-9/10) administrative codes (Table A-1). Patients eligible for this analysis were those with a documented Current Procedural Terminology, version 4 (CPT-4) codes for at least one endovascular peripheral vascular intervention procedure. Our unit of analysis the patient encounter, so a patient may have been included more than once if they had more than one documented PVI. Patient encounters were selected from 2010 to 2017. Patients were excluded from analysis if they were under the age of 18 or did not have at least one of 152 ICD-9/10 administrative codes documenting CLI (Table A-1). We included all sites in our statistical analysis as even sites with low PVI volumes can add informative value to a model. We excluded sites with fewer than 50 endovascular peripheral vascular interventions overall when examining rates of amputation since sites with low volumes significantly skewed these rates.

The University of Missouri-Kansas City School of Medicine and Truman Medical Centers joint Institutional Review Board determined research performed with the de-identified Health Facts database qualifies as Not Human Subjects Research (Protocol 14-567).

Primary Outcome

Major amputation within 30 days of PVI outcomes were defined as major lower extremity amputations that occurred within 30 days following an endovascular peripheral vascular intervention discharge. These amputation outcomes are typically unexpected as the effort had

been made to restore perfusion through the PVI procedure and the patient had been discharged from the care facility. Patients with amputations within the same encounter as the PVI procedure were not included as it is not possible to discern whether these amputations were unexpected. Non-traumatic, lower-limb major amputations were identified using ICD-9/10 codes and CPT-4 codes (Table A-1). Conversions between ICD-9 and ICD-10 were based on previously published methodologies.[46]

Patient Characteristics

Demographic and socio-economic variables included age, sex, race, and marital status. Race was categorized as white vs. non-white groups (non-white includes African American, Asian, Hispanic, and "Other" races), and marital status as married vs. not married.

Medical history was derived from patient encounters using ICD-9, ICD-10-CM, and CPT-4 codes (Table A-1). History variables include previous limb amputation, transient ischemic attack, sepsis, renal disease, osteomyelitis, malnutrition, malignant cancer, hypertension, heart failure, diabetes mellitus, depression, and coronary artery disease. Clinical variables were defined by starting with Elixhauser[47] definitions and were supplemented and supported by clinician review and review of previously published administrative code definitions.[8, 48]

Site Characteristics

Site characteristics included academic status (teaching vs. non-teaching), categorized bed size (1-5, 6-99, 100-199, 200-299, 300-499, and 500+ beds), United States census regions (Midwest, Northeast, South, and West), and rurality (urban vs. rural).

Statistical Analysis

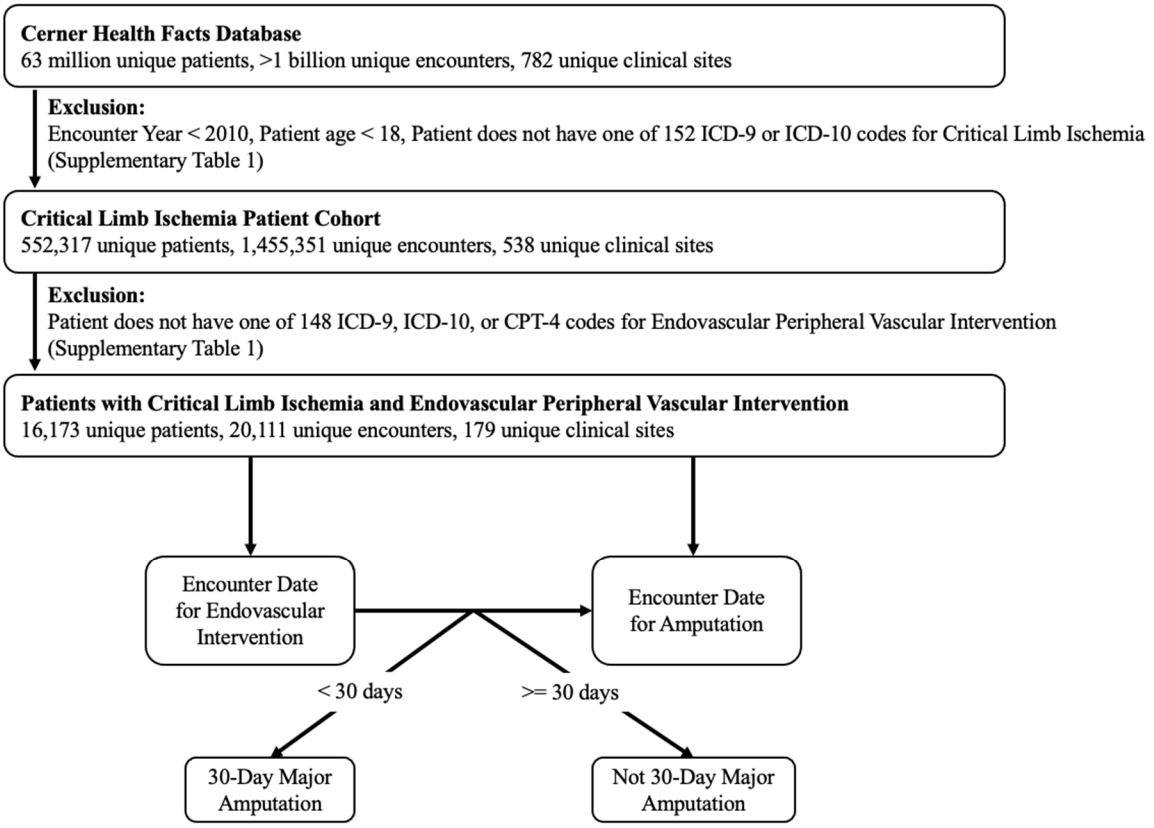
Unique patient, encounter, and site counts were computed along with proportions of each demographic, socioeconomic, medical history, and site-level characteristic for all patient encounters in the data set. Median risk ratios (MRR) were calculated, with a random effect for site, to describe variation in the 30-day amputation outcome across clinical sites. A median risk ratio describes the average likelihood a patient would experience a 30-day major amputation event at one random site versus any other site after adjusting for patient covariates such that the average variability for statistically identical patients is examined.[49] The model accommodates variability in sample size and down-weights sites with smaller sample sizes that may otherwise be outliers in raw 30-day major amputation rates.

Model patient-level covariates were selected from the pool of available variables if they were associated with 30-day amputation outcomes at the 0.1 level of significance, through univariate testing using Chi-squared, Mann Whitney-U, and student's T-tests where appropriate per a previously documented method.[45] Risk ratios for the correlates of amputation were derived from a modified, binary outcome Poisson regression, with a random site effect and including robust standard errors to account for variance misspecification. The binary Poisson regression was chosen over a logistic regression in order to directly estimate relative risks since rates of the 30-day amputation outcome variable were relatively low.[50]

All analyses were conducted at the patient encounter level in the RStudio integrated development environment (version 1.4.1103) using R[33] (version 4.0.4).

Results

A flowchart describing the patient cohort selection is shown in **Error! Reference source not found.**. A total of 20,204 unique patient encounters from 179 sites undergoing



PVI for CLI indications were identified. Mean age was 69.0 (± 12.6) years, 58.0% were male, and 29.6% were of non-white race (Table 4). Most patient encounters had documented diabetes mellitus (62.6%), hypertension (77.5%), and a third had documented chronic kidney disease (34.8%). Patient encounters most often occurred at sites in the South United States Census region (48.4%), at sites that were designated as teaching facilities (73.4%), and at sites designated at urban (80.4%).

Figure 5. Health Facts Analysis Patient Exclusion Flow Chart and Identification of 30-Day Major Amputation Procedure

Table 4. Descriptive Statistics for Encounters for Patients with Critical Limb Ischemia and Peripheral Vascular Endovascular Intervention in the Health Facts Database

Characteristic	Patient Encounters (N = 20,204)
Age (Mean [SD])	69.04 (12.56)
Age Over 65	12,193 (62.5)
Sex (Male)	11,592 (58.0)
Race (Non-White)	7,184 (29.6)
Marital Status (Married)	10,993 (56.4)
United States Census Region	
Midwest	3,689 (18.3)
Northeast	3,416 (17.0)
South	9,737 (48.4)
West	3,269 (16.3)
Site Teaching Status (Teaching)	10,816 (73.4)
Site Rural Status (Urban)	16,171 (80.4)
History of Coronary Artery Disease	9,328 (46.4)
History of Depression	1,654 (8.2)
History of Diabetes Mellitus	12,597 (62.6)
History of Heart Failure	4,796 (23.8)
History of Lower Limb Amputation	3,029 (15.1)
History of Malignant Cancer	1,244 (6.2)
History of Hypertension	15,595 (77.5)
History of Kidney Disease	6,989 (34.8)
History of Malnutrition	1,405 (7.0)
History of Osteomyelitis	3,990 (19.8)
History of Sepsis	1,901 (9.5)
History of Transient Ischemic Attack	2,255 (11.2)

Across all 179 sites included in the analysis, the rate of non-traumatic major amputation within 30 days after the PVI procedure was 2.8%. Among sites that performed at least 50 PVIs (n=80), the median amputation rate was 2.47% (IQR, 1.29%-3.63%) (**Error! Reference source not found.**).

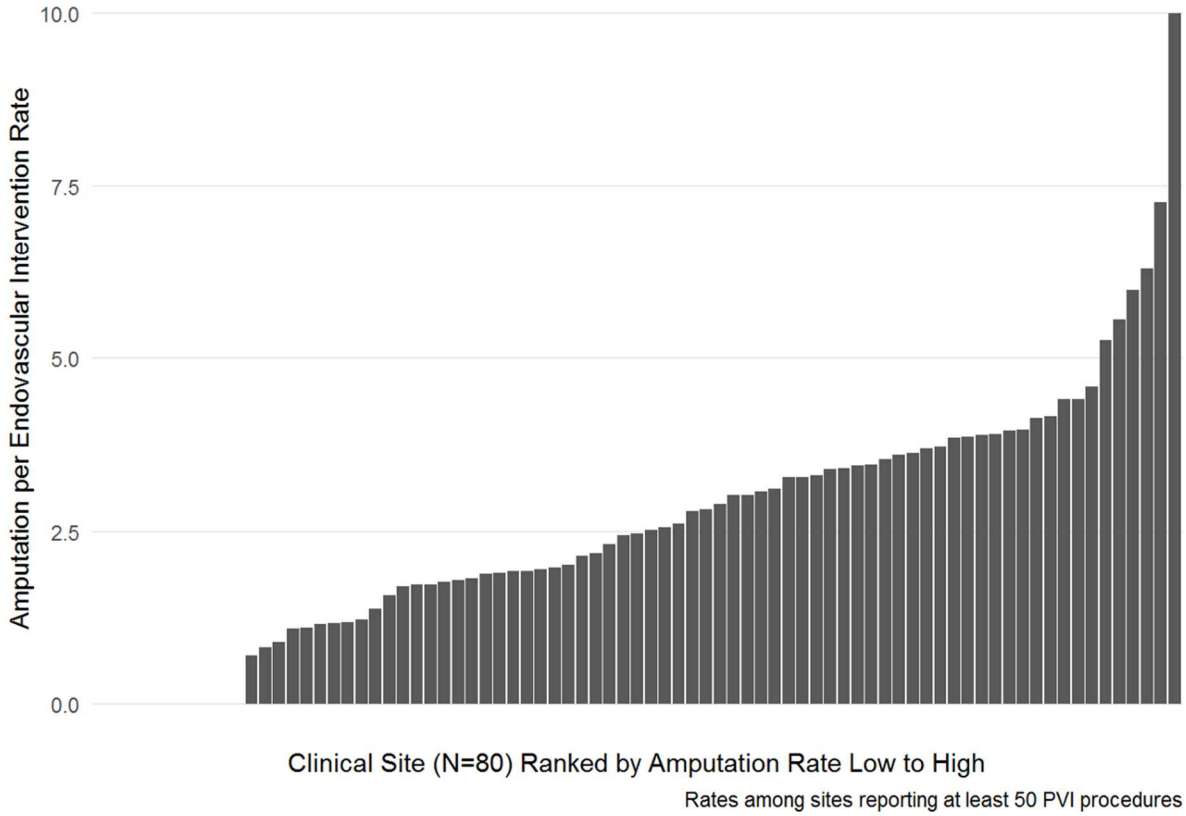


Figure 6. Percent 30-Day Major Amputation Relative to the Number of PVI Procedures by Site in Patients with Critical Limb Ischemia Undergoing Peripheral Vascular Endovascular Intervention

The patient factors that were retained after univariate testing for the model were: dichotomous age greater than or less than 65 years, sex, white race vs. non-white race, marital status, documented coronary artery disease, depressive disorder, diabetes, heart failure, previous lower limb amputation, malignant cancer, hypertension, kidney disease, malnutrition, osteomyelitis, sepsis, and previous transient ischemic attack. The site level

variables were teaching vs. non-teaching site, urban vs. rural status, and bed size classification.

The MRR for site variability in the unadjusted model was 1.40 (95% confidence interval [CI], 1.35-1.46) (Table *5*). After adjusting the model for patient characteristics, the median relative difference in risk of major amputation at 30 days between sites was 30% (MRR 1.30 [95% CI, 1.26-1.35]). Further adjustment for site-level characteristics (teaching vs. non-teaching site, urban vs. rural status, and bed size classification) explained much of the variability (MRR 1.14 [95% CI 1.12-1.16]), while adjusting for geographic region resulted in a small attenuation (MRR 1.11 (95% CI 1.09-1.12). As for patient-level factors, malnutrition (risk ratio [RR] 1.91, 95% CI 1.44-2.53), previous lower-limb amputation (RR 1.84, 95% CI 1.48-2.28), diabetes (RR 1.43, 95% CI 1.14-1.81), and being of non-white race (RR 1.40, 95% CI 1.14-1.71) were all independently associated with an increased risk of 30-day major amputation in the final adjusted model (Figure 7).

Table 5. Median Risk Ratios Demonstrating Variability of Experiencing 30-Day Major Amputation by Site

Model	Number of Sites	Median Risk Ratio (95% Confidence Intervals)
Model 1: Unadjusted	N = 179	1.40 (1.35-1.46)
Model 2: Adjusted for Patient Characteristics[1]		1.30 (1.26-1.34)
Model 3: Adjusted for Patient[1] and Site[2] Characteristics		1.14 (1.12-1.16)
Model 4: Adjusted for Patient,[1] Site,[2] and US Census Region		1.11 (1.09-1.13)

1. Patient characteristics include dichotomous age greater than or less than 65 years, biological sex, white race vs. non-white race, marital status, documented coronary artery disease, depressive disorder, diabetes, heart failure, previous lower limb amputation, malignant cancer, hypertension, kidney disease, malnutrition, osteomyelitis, sepsis, and previous transient ischemic attack.
2. Site characteristics include teaching vs. non-teaching site, urban vs. rural status, and bed size classification.

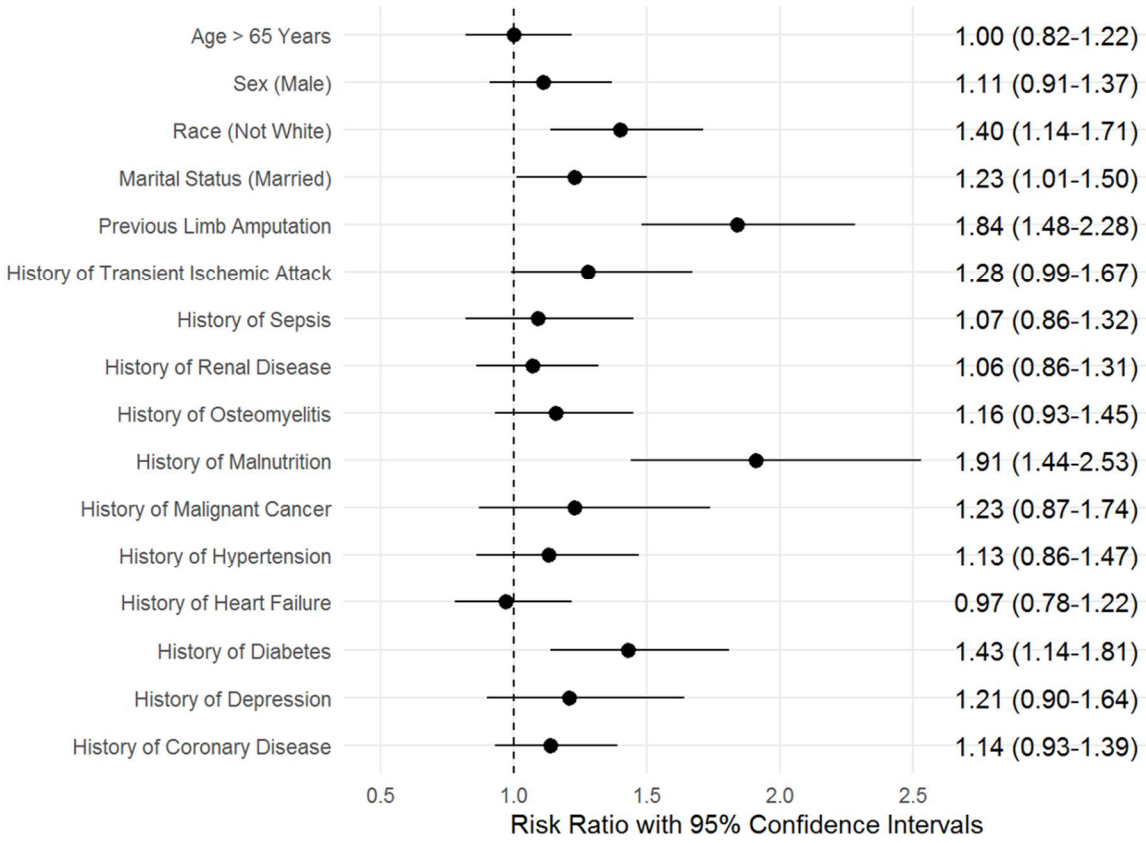


Figure 7. Factors Associated with 30-Day Major Amputation in Patients with Critical Limb Ischemia Undergoing Endovascular Peripheral Vascular Intervention

Discussion

By documenting major amputations within 30 days after PVI for patients with CLI, we can explore the quality of care these patients are receiving. The national Health Facts database is a rich resource to study patients with CLI and is potentially more generalizable than any other current database used to study this disease.[6, 8] This study is the first of its kind to document rates of early major amputation after endovascular intervention at the national level. Our study used the national Health Facts database to identify and describe factors associated with 30-day amputations in patients with CLI who underwent endovascular peripheral vascular intervention.

We found that 2.8% of these patients experienced a 30-day amputation and factors associated with amputation were non-white race, nutritional status, and prior medical history. This rate is within the bounds of the of the previously documented 2-6% of patients experiencing a 30-day amputation, a strong validation of the data source.[44, 45] Amputation rates ranged from 0.0% to 10.0% among sites included in this study. This variability was largely explained by site-level factors including teaching status, rurality status, and bed size classification. We found that there was systematic variance in amputation rates at the site level that was still present after adjusting for patient and site-level factors. Given systemic variation will inevitably exist, future work should aim to explain how much variance might contribute to a disparity in quality of care for one particular care site versus another. Apart from disease severity markers, disparities in outcomes by non-white race were documented and modifiable patient factors such as malnutrition were also identified.

Our work builds on previous work providing a more representative sample but confirming that rates of 30-day major amputations following PVI are a concerning and unexpected outcome that disproportionately affects patients of non-white race and those with prior amputations.[44, 45] Documenting predictors of 30-day amputation outcomes at both the patient and site level of analysis helps to describe factors associated with early major amputation and its value as a quality metric. This study also highlights the need to address both systemic and modifiable factors that may reduce unnecessary major amputation.

Importantly, we also found that there are potentially modifiable patient characteristics predictive of 30-day amputation outcomes, including malnutrition. For patients with peripheral vascular disease, proper nutritional intake has not historically been referenced as a key treatment guideline[1] although more recently, the importance of adequate nutrition for

integral CLI care is being recognized.[5] Whether nutritional status functions as a marker or a mediator for adverse health outcomes in patients with vascular disease warrants further investigation. Our work also identified being of a non-white race as increasing the risk of 30-day amputation. That racial disparities in medical care exist is not a novel insight, both in the early diagnosis of vascular disease, as well as with regards to the quality of care received, with subsequent disparate outcomes of individuals of non-white race and Hispanic ethnicity.[1, 16, 51-53] Deep investigation into the social barriers to health is not within the scope of this work, though future work should identify drivers of this phenomena in effort to intervene and reduce these inequities. Our results add to current evidence of inequality in medical care and in addition, demonstrate that these inequalities also manifest as a higher risk of complications following endovascular procedures in CLI. Identifying systemic factors that explain these disparate outcomes and develop interventions to eradicate these inequities are key priorities when further defining this CLI quality metric.[54]

In addition to further evaluating the standards for high-quality CLI care, further priority should be given to targeted preventative programs to earlier detect PAD progression to CLI both at the health system and community level would be critical to further prevent amputations. If these undesired amputation outcomes can be predicted, it warrants continued investigation into how these key drivers might be modified. Data-driven approaches, such as the one we present here, will be necessary to enable us to proactively redesign CLI prevention and care.

We demonstrate that a large degree of the variability in 30-day amputation outcomes can be explained by site-level variables, a marker of variation in patterns of care. The site factors we examined were rurality, bed-size, and teaching status, which represent broad

categorization of sites and may describe them, on average, compared to other sites but do not identify nuanced differences in care patterns that could be examined if a site, the patients seen at each site, and specific care patterns were identifiable for future work. Previous work describing the regional variability and intensity of revascularization procedures shows that rates can vary widely and increased intensity of vascular care is associated with decreased rates of lower limb amputation.[26] By further comparing outcome metrics following PVI across centers that deliver CLI care, such as 30-day amputation rates, across sites and what characteristics define these sites, one can start identifying potential organizational quality metrics that need to be in place to maintain low complication rates in CLI and define centers of excellence, such as with established centers of excellence in percutaneous coronary intervention,[55] in the treatment of CLI.

Our study is limited due to the observational nature of the data used to derive our results. As with any observational study using electronic health record data based on administrative codes, there is the possibility of important variance in the data that was not captured in the analysis data set. One particular variable that is crucially important in CLI outcomes observation is patient mortality status. Health Facts does not consistently include mortality status, nor does it reconcile this outcome with other sources such as the social security death index.[56] Variables derived from the presence or absence of an administrative code in a list associated with a patient encounter assume no data are missing from analysis and that data are coded correctly at the time of data collection. The Heath Facts database itself has limitation as only clinical sites with a Cerner electronic health record that opt-in to participate in the database are included; there is documented variability between data contributions of sites within Health Facts.[31] For example, if a PVI occurred at a site included

in Cerner Health Facts and an 30-day major amputation occurred at a non-Cerner site, we would not have captured this outcome in our analysis. This systematic site inclusion bias may affect the ability to generalize results since it could be argued they are not representative of the entire CLI population. This study only examined endovascular PVI, and not surgical bypass procedures or amputations associated with surgical procedures. Sites contributing to Health Facts may represent a wide range of health care delivery models. Patients with CLI who undergo surgical procedures may have medical history and outcomes that contrast with the results presented here.

Conclusions

Our study of a national cohort of patients with CLI used EHR data to identify variability in 30-day major amputation outcomes in patients undergoing endovascular PVI. Rates of major amputation remain low, site-level factors account for significant variability in the outcome. Importantly, patient-level and site-level disparities in care represent an opportunity for interventions to reduce early major amputation following PVI. Lastly, 30-day major amputation may be a useful marker of post-PVI care quality. Further development and validation of national quality metrics for CLI care is warranted.

CHAPTER 4

AIM 2B: RATES OF GUIDELINE DIRECTED MEDICAL THERAPY IN PATIENTS WITH CRITICAL LIMB ISCHEMIA AND MAJOR AMPUTATION

Introduction

Critical limb ischemia (CLI), the severe form of peripheral artery disease (PAD), affects approximately 2% of patients with PAD each year with a prevalence of ~200,000 patients per year in the United States.[8] CLI is characterized by rest pain, ulceration, and non-healing wounds.[5] Beyond the cardiovascular risks that patients with PAD face, patients with CLI are at high risk of lower extremity amputation, cardiovascular related death, among other adverse cardiovascular outcomes.[57] Once patients with CLI enter the care system, they have over a 20% chance of readmission in 30 days and over 40% chance of readmission at 6 months.[34] The 1-year risk of amputation in patients with CLI is approximately 10%[34] and risk of mortality at 1-year is between 16 and 33% depending on the level of CLI severity.[58]

CLI-related amputations are preventable outcomes[59] and efforts to prevent amputation and other adverse outcomes in patients have been described through quality of care guidelines for the treatment of CLI.[1, 4] The key to preventing amputation is to reduce overall cardiovascular risk and to improve arterial blood flow to the extremity through revascularization. All patients with CLI, as well as those with PAD, should be put on optimal or guideline directed medical therapy (statin, antiplatelets including aspirin, and angiotensin-converting enzyme [ACE] or angiotensin receptor blocker [ARB] in cases where a patient has documented hypertension) as this is an effective method to reduce overall cardiovascular risk in population with higher risk of events.[4, 60, 61] Patients with PAD, the earliest stage of arterial disease, which can lead to CLI, are typically under treated.[62-65]

Although guidelines for quality of care are implemented at the national level, national rates of quality of care and their association to key outcomes like major amputation in patients with CLI are not well documented especially among the sickest patients who undergo major amputation procedures, though rates of adherence to guidelines have been shown to vary in subsets of the population of patients with CLI.[25, 26, 66, 67]

CLI patients have a poorer prognosis than those patients with PAD, however, CLI patients can would still benefit from cardiovascular risk management including guideline directed medical therapy.[1] This work aimed to use the national, real-world Cerner Health Facts database to document variability in rates of guideline directed medical therapy in patients with CLI who also had documented non-traumatic, lower-extremity major amputation procedures and to examine patient level predictors of GDMT within the cohort. By documenting rates of guideline therapy at a national level for patients with CLI, this work will generate evidence for national rates of guideline directed medical therapy where few studies have previously.[66]

Methods

Health Facts Database

The de-identified Cerner Health Facts (Cerner Corporation, Kansas City, Missouri) electronic health record (EHR) database is an observational database derived from the Cerner EHR intended for use in research and quality improvement. Data in Health Facts is extracted directly from the electronic medical records from hospitals in which Cerner has a data use agreement. Encounters may include pharmacy, clinical and microbiology laboratory, admission, and billing information from affiliated patient care locations. All admissions, medication orders and dispensing, laboratory orders and specimens are date and time

stamped, providing a temporal relationship between treatment patterns and clinical information. Cerner Corporation has established Health Insurance Portability and Accountability Act-compliant operating policies to establish de-identification for Health Facts.

The University of Missouri-Kansas City School of Medicine and Truman Medical Centers joint Institutional Review Board has reviewed the de-identified Health Facts database and determined it qualifies as Not Human Subjects Research and this individual study is exempt from human subject review (Protocol 14-567).

Critical Limb Ischemia Patient Cohort and Health Facts Selection

Sites contributing lower quality data in the Health Facts database were excluded using previously described methods and patients without critical limb ischemia documented in an encounter before a major amputation were excluded using administrative codes (Supplementary Table 1). *Major amputation* was defined as a non-traumatic, lower-extremity, ankle or above amputation procedure as defined by ICD-9/10, and CPT-4 codes (Supplementary Table 1). For GDMT rates by site, any site with fewer than 10 encounters in the data set overall were removed from rate descriptive statistics and the bar chart to reduce outlier rates.

Clinical Variable Creation

Total guideline directed medical therapy was defined as having the presence of all of the following three classes of medications during a patient encounter: statin, anti-platelet (such as aspirin or clopidogrel), and anti-hypertensive (including angiotensin-converting enzyme [ACE] or angiotensin II receptor blockers [ARB], if a patient had documented hypertension). Due to inconsistencies with outpatient medication reconciliation within the

Health Facts database, we used only inpatient medications for generating these variables as we note elsewhere.

Any guideline directed medical therapy was defined as having the presence or absence of any of the following three classes of medications at a patient encounter: statin, anti-platelet (including aspirin), and anti-hypertensive (including ACE/ARB).

Non-Traumatic, Lower Extremity, Major Amputation

Patient Characteristics

Demographic and *socio-economic* variables included age, sex, race, and marital status. Age was a continues variable in years, biological sex as reported in the EHR as male vs. female, race was dichotomized into white vs. non-white categories, and marital status was coded as married vs. not married.

Medical history variables were derived from patient encounters using ICD-9, ICD-10-CM, and CPT-4 codes. History variables include previous limb amputation, transient ischemic attack, sepsis, renal disease, osteomyelitis, malnutrition, malignant cancer, hypertension, heart failure, diabetes mellitus, depression, and coronary artery disease. Clinical variables were defined by starting with Elixhauser[47] definitions and were supplemented and supported by clinician review and review of previously published administrative code definitions.[8, 48]

Site Characteristics

Site characteristics included academic status (teaching vs. non-teaching), categorized bed size, United States census regions (Midwest, Northeast, South, and West), and rurality (urban vs. rural).

Statistical Analysis

Unique encounter and site counts were computed along with proportions of patient encounters within each demographic, socioeconomic, medical history, and site-level characteristic. The rates and proportions of patient encounters that were classified as having complete GDMT were computed and compared against those who did not have a complete GDMT using standardized mean difference and pairwise comparisons using student's t-tests for continuous data and chi-squared tests for categorical data. Comparisons used were student's t-test, Chi-square, or Mann-Whitney U where appropriate. Patient encounters were grouped by site and proportions of GDMT by site were computed.

Median odds ratios (MOR)[68] were computed to quantify the variability in GDMT rates across centers. Adjustments were made for patient demographics and history (age over 65, sex, race, history of diabetes, history of coronary artery disease, history of hypertension, history of heart failure, and history of myocardial infarction), adjusting for site characteristics (teaching status and rurality), and adjusting for revascularization. A median odds ratio describes the likelihood of an encounter documenting complete GDMT designation at one random site versus any other site before and after adjusting for model covariates.[49]

To look at predictors of GDMT, a hierarchical multi-variable logistic regression with a random effect for site was constructed to assess the odds of a covariate predicting GDMT in a patient's clinical encounter. Model covariates were entered as patient characteristics (age, sex, race, marital status), patient medical history (coronary artery disease, acute kidney failure, sepsis, obesity, tobacco use, dyslipidemia, hypertension, diabetes, or a previous revascularization), site-level characteristics (teaching status and rurality), and regionality (US census region).

All analyses were conducted using R[33] (version 4.0.2) in the RStudio integrated development environment (version 1.4.1103).

Results

Within the Health Facts database, 52,381 unique patients with CLI observed at 302,689 encounters were identified (Figure 8). Of these, 10,192 patients with a documented major amputation were seen at 74,669 encounters. After excluding patients with acute limb ischemia and encounters that were not of the type "Inpatient", 9,272 unique patients seen at 30,856 encounters at 196 unique clinical facilities remained.

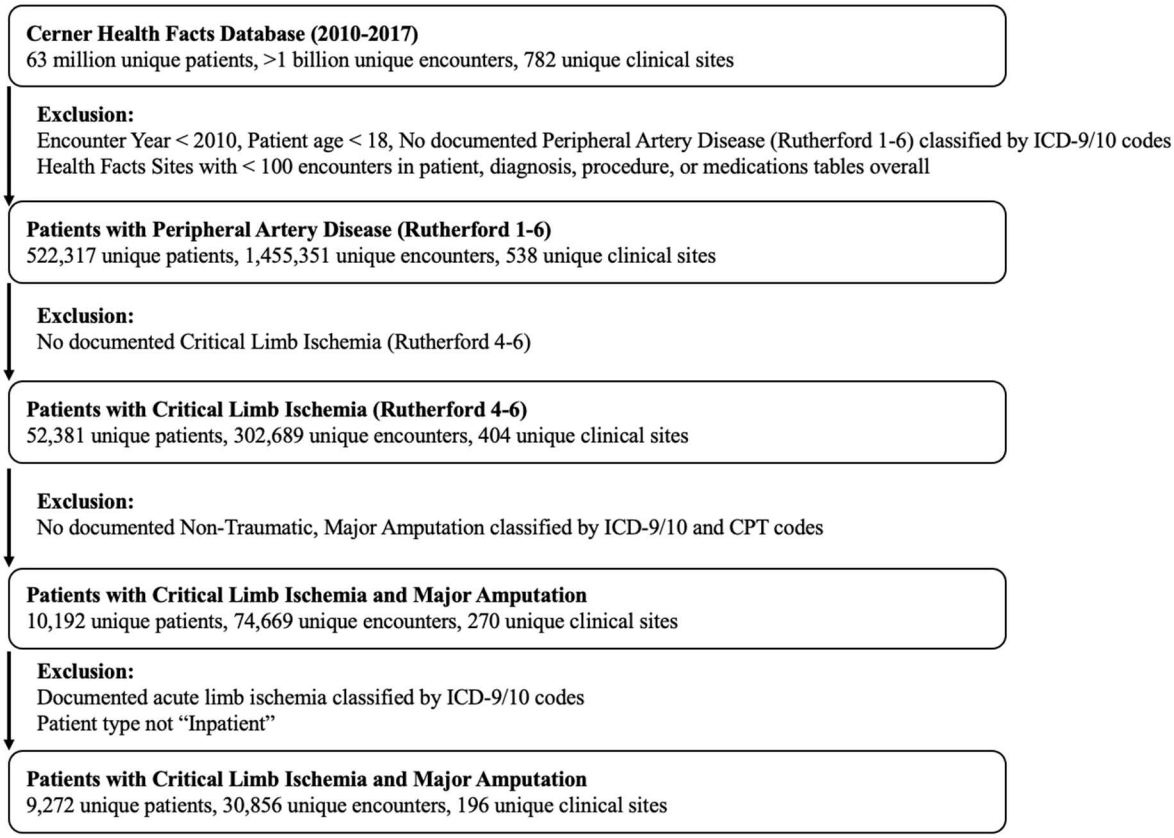


Figure 8. Health Facts Site and Patient Exclusions Flow Chart to Derive Final Analysis Cohort

Mean patient age at clinical encounter was 66.8 years (± 12.3 standard deviation), 55.0% of patients were over the age of 65 years, 63.5% were male, 62.7% were classified as being white race, and 57.8% were classified as having a marital status of married (Table 6).

Table 6. Overall Encounter Characteristics for Patients with Critical Limb Ischemia and Major Amputation in the Health Facts Database

Encounter Characteristic	Encounter Proportions (N = 30,866)
Age (Mean [SD])	66.8 (12.3)
Age > 65	16,425 (55.0)
Sex (Male)	19,601 (63.5)
Race (White)	17,964 (62.7)
Marital Status (Married)	17,503 (57.8)
United States Census Region	
Midwest	5,686 (18.4)
Northeast	6,323 (20.5)
South	14,984 (48.5)
West	3,873 (12.5)
Site Teaching Status (Teaching)	19,022 (80.7)
Site Rural Status (Urban)	24,744 (80.2)
Quality of Care Metrics	
Complete GDMT	8,406 (27.2)
Any GDMT	22,339 (72.4)
GDMT: Statin	15,370 (49.8)
GDMT: Anti-Platelet	17,119 (55.5)
GDMT: Anti-Hypertensive	15,338 (49.6)

Most patient encounters occurred at sites in the South United States census region (48.5%), were at sites classified as teaching facilities (80.7%), and were at sites designated as urban (80.2%). Of the 30,865 unique encounters for these patients, 8,406 encounters (27.2%) had documentation of complete guideline directed medical therapy for the patient at encounter. There were 22,339 patient encounters (72.4%) with any GDMT component medication documented. Statins were documented in 15,370 encounters (49.8%), anti-platelets in 17,119 (55.5%), and anti-hypertensives in 15,338 (58.0%, as a percent of those with documented hypertension).

Patient encounter procedure characteristics associated with complete GDMT were having undergone an endovascular peripheral vascular intervention (19.9 vs. 14.5%) or any peripheral vascular intervention (surgical or endovascular; 32.4 vs. 22.7%) (Table 7).

Table 7. Encounter Characteristics of Patients with CLI and Major Amputation Stratified by Documented Complete Guideline Directed Medical Therapy Status

Encounter Characteristics (N = 30,856)	No Complete GDMT N = 22,460 (72.8%)	Complete GDMT N = 8,406 (27.2%)	Standardized Mean Difference	P-Value
Demographics				
Age (Mean [SD])	66.77 (12.63)	66.83 (11.31)	0.005	0.687
Age > 65	11,912 (54.6)	4,513 (55.9)	0.027	0.042
Sex (Male)	14,223 (63.3)	5,378 (64.0)	0.013	0.302
Race (White)	13,223 (63.0)	4,741 (61.9)	0.024	0.079
Marital Status (Married)	12,778 (58.1)	4,725 (57.0)	0.022	0.089
United States Census Region			0.242	<0.001
Midwest	4,077 (18.2)	1,609 (19.1)		
Northeast	4,137 (18.4)	2,186 (26.0)		
South	11,580 (51.6)	3,404 (40.5)		
West	2,666 (11.9)	1,207 (14.4)		
Site Teaching Status (Teaching)	13,286 (80.0)	5,736 (82.3)	0.058	<0.001
Site Rural Status (Urban)	18,587 (82.8)	6,157 (73.2)	0.231	<0.001
Quality of Care Metrics				
Complete GDMT	0 (0.0)	8,406 (100.0)	--	--
Any GDMT	13,933 (62.0)	8,406 (100.0)	1.106	<0.001
Statin	6,964 (41.2)	8,406 (100.0)	1.690	<0.001
Anti-Platelet	8,713 (38.8)	8,406 (100.0)	1.776	<0.001
Anti-Hypertensive, among hypertensive patients	6,932 (36.8)	8,406 (100.0)	1.696	<0.001
Endovascular Peripheral Vascular Intervention	2,579 (14.5)	1,340 (19.9)	0.145	<0.001
Any Revascularization Procedure	4,042 (22.7)	2,178 (32.4)	0.218	<0.001
Clinical History				
Acute Kidney Failure	4,429 (19.7)	1,905 (22.7)	0.072	<0.001
Coronary Artery Disease	11,439 (50.9)	5,522 (65.7)	0.303	<0.001
Sepsis	3,832 (17.1)	1,162 (13.8)	0.090	<0.001
Obesity	3,395 (15.1)	1,375 (16.4)	0.034	0.034
Tobacco Use	9,021 (40.2)	3,693 (43.9)	0.076	<0.001
Dyslipidemia	10,899 (48.5)	5,374 (63.9)	0.314	<0.001
Dementia	1,925 (8.6)	569 (6.8)	0.068	<0.001

Encounter Characteristics (N = 30,856)	No Complete GDMT N = 22,460 (72.8%)	Complete GDMT N = 8,406 (27.2%)	Standardized Mean Difference	P-Value
Hypertension	18,809 (83.7)	7,623 (90.7)	0.209	<0.001
Osteomyelitis	5,131 (22.8)	2,032 (24.2)	0.031	0.014
Malignant Cancer	657 (2.9)	167 (2.0)	0.061	<0.001
Angina	216 (1.0)	172 (2.0)	0.089	<0.001
Alcohol Abuse	839 (3.7)	274 (3.3)	0.026	0.050
Atrial Fibrillation	4,566 (20.3)	1,359 (16.2)	0.108	<0.001
Malnutrition	2,250 (10.0)	725 (8.6)	0.048	<0.001
Heart Failure	7,498 (33.4)	3,345 (39.8)	0.133	<0.001
Chronic Lung Disease	4,638 (20.7)	1,622 (19.3)	0.034	0.009
Asthma	889 (4.0)	358 (4.3)	0.015	0.245
Myocardial Infarction	866 (3.9)	801 (9.5)	0.229	<0.001
Diabetes	16,628 (74.0)	6,859 (81.6)	0.183	<0.001
Chronic Kidney Disease	11,577 (51.5)	4,224 (50.2)	0.026	0.044
Depression	2,887 (12.9)	1,040 (12.4)	0.015	0.266
Claudication Medication	578 (3.4)	536 (6.4)	0.137	<0.001
Smoking Cessation Medication	1,142 (6.8)	623 (7.4)	0.026	0.057

Patient encounter medical history associated with complete GDMT was previous coronary artery disease (65.7 vs. 50.9%), dyslipidemia (63.9 vs. 48.5%), hypertension (90.7 vs. 83.7%), osteomyelitis (24.2 vs. 22.8%), heart failure (39.8 vs. 33.4%), or having had a previous myocardial infarction (9.5 vs. 3.9%). Patient medical history associated with not having a complete GDMT status was sepsis (17.1 vs. 13.8%), dementia (8.6 vs. 6.8%), atrial fibrillation (20.3 vs. 16.2%), malnutrition (10.0 vs. 8.6%), and chronic lung disease (20.7 vs. 19.3). Being seen at a site in the Northeast United States census region was associated with complete GDMT (26.0 vs. 18.4%) as well as the West census region (14.4 vs. 11.9%). Sites that were classified as “teaching” were more likely to have encounters with complete GDMT (82.3 vs. 80.0%).

Of the 196 sites included with analysis, 86 of these sites had fewer than 10 unique patient encounters and were excluded from site rate calculations. Of the 110 remaining sites,

the median GDMT rate per patient was 38.2% (interquartile range 16.3-60.1%) (Figure 9). At minimum a site's rate of GDMT per patient was 0.0% and at maximum it was 83.3%.

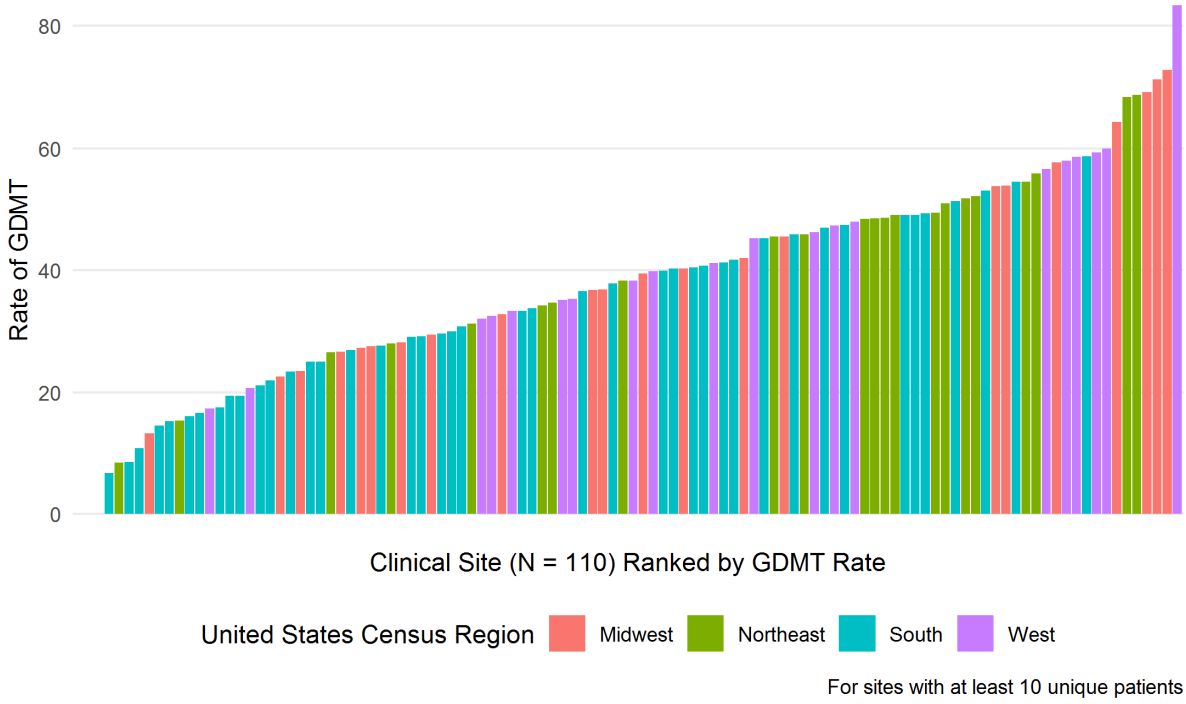


Figure 9. Rate of Guideline Directed Medical Therapy (GDMT) in Patients with Critical Limb Ischemia and Major Amputation Ranked by Clinical Site

The MOR describing site variability in the unadjusted model was 2.31 (95% confidence intervals [CI] 2.19-2.45) (Table 8). Models were adjusted sequentially for patient-level factors (MOR 2.31, 95% CI 2.18-2.44), for previous revascularization procedure (MOR 2.25, 95% CI 2.13-2.38), for site-level factors (MOR 2.11, 95% CI 1.99-2.23), and for census region (MOR 2.07, 95% CI 1.96-2.18).

Table 8. Median Odds Ratios Describing Variability of Guideline Directed Medical Therapy Across Sites

Model	Number of Sites	Median Odds Ratio (95% Confidence Intervals)
Model 1: Unadjusted	N = 196	2.32 (2.19-2.45)
Model 2: Adjusted for Patient-level Covariates[1]		2.31 (2.18-2.44)
Model 3: Adjusted for Revascularization Procedure		2.25 (2.13-2.38)
Model 4: Adjusted for Site-level Covariates[2]		2.11 (1.99-2.23)
Model 5: Adjusted for US Census Region		2.07 (1.96-2.18)

1. Patient-level encounter characteristics included age over 65, sex, race, history of diabetes, history of coronary artery disease, history of hypertension, history of heart failure, and history of myocardial infarction.
2. Site-level encounter characteristics included teaching vs. non-teaching status and urban vs. rural rurality classification.

Predictors of GDMT use included age over 65 years (odds ratio [OR] 1.08, 95% confidence interval [CI] 1.01-1.16), and those who had previously documented coronary artery disease (OR 1.66, 95% CI 1.54-1.80), acute kidney failure (OR 1.21, 95% CI 1.11-1.32), tobacco use (OR 1.15, 95% CI 1.07-1.23), dyslipidemia (OR 1.65, 95% CI 1.54-1.78), hypertension (OR 1.45, 95% CI 1.30-1.63), diabetes (OR 1.27, 95% CI 1.17-1.39), previous revascularization (OR 1.68, 95% CI 1.56-1.82), and those patients seen at sites with teaching designation (OR 1.20, 95% CI 1.09-1.32) (Figure 10). Factors that were predictive of not having complete GDMT designation were non-white race (OR 0.84, 95% CI 0.77 – 0.92), documented malnutrition (OR 0.82, 95% CI 0.73-0.93), sites designated as urban as opposed to rural (OR 0.60, 95% CI 0.54-0.67), and sites in the south census region as compared to the Midwest (OR 0.84, 95% CI 0.77-0.93).

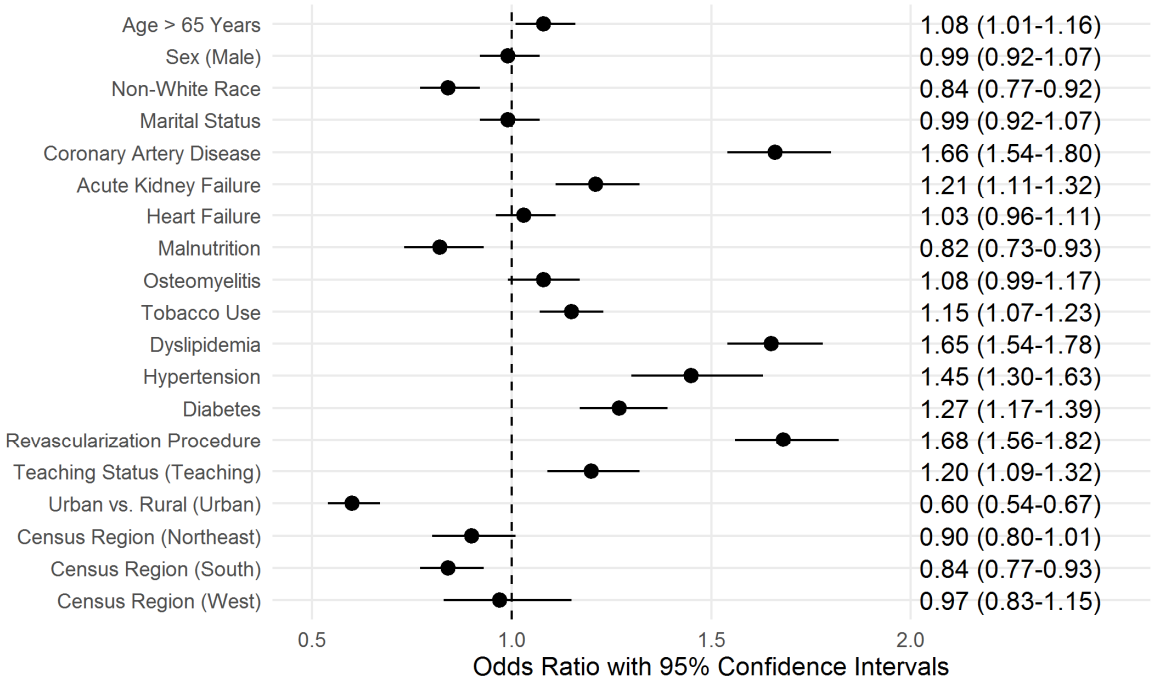


Figure 10. Patient and Site Factors Associated with Complete Guideline Directed Medical Therapy in Patients with Critical Limb Ischemia Who Have Experienced Major Amputation

Discussion

Through this work we document that only one in four patients with documented CLI and a previous major amputation had complete GDMT documented in the Health Facts-derived data mart. Variability in rates of complete GDMT between sites was substantial and the median of complete GDMT between sites was less than 4 out of 10 patients. Predictors of complete GDMT included comorbid cardiovascular diseases such as coronary artery disease, dyslipidemia, hypertension, and diabetes. Patients were more likely to have complete GDMT documented if they had a peripheral vascular intervention or other significant cardiovascular comorbidities for which they were seen. This phenomena of higher GDMT adherence rates in patients with polyvascular disease has been previously documented.[69] Individual medication adherence rates (statins in 49.8% of encounters, anti-platelets in 55.5% of encounters, and anti-hypertensives in 49.6% of encounters) documented in this population are higher than

those documented in a previous cohort of patients with peripheral artery disease,[70] though data documenting any contemporary rates of GDMT in CLI patients are sparse.

We provide new insight into GDMT rates in patients with CLI using nationally-representative, real-world EHR data. The data presented here contrasts with clinical registry data used to describe clinical care for patients with CLI as it may provide estimates that better align with real-world clinical practice.[25] Previous work provides limited perspective on real-world estimates and GDMT in patients with CLI and previous amputations has not been previously documented. However, the evidence supporting GDMT use in patients with CLI has been well-documented.[1, 71-76]

The GDMT rates this study documented at individual site-level, some sites with at least 10 CLI patients with documented major amputation who were seen as inpatients had complete GDMT rates at 0.0%, the median rate was 38.2% of patient encounters, with a maximum rate at 83.3% for the top-performing site. Though this rate had extensive variation between sites, it did not appear to cluster by United States census region as some quality of care metrics, such as revascularization, have been shown to do.[26, 67] When examining the likelihood that a patient would be on a complete GDMT regimen after being seen at one random site versus any other in the included Health Facts data set, the MOR for the unadjusted model was 2.31 indicating substantial variation (no variation between any given sites would result in a MOR of 1). This variation between GDMT between sites was only partially attenuated after adjusting for key patient level covariates, revascularization, site-level variables, and census region (final MOR 2.07, 95% CI 1.96-2.18), indicating that significant variation in complete GDMT remains unmeasured for these patient encounters.

Following the association seen in pairwise comparisons, there were also many key predictors of GDMT in this specific patient population. These predictors include previous procedures specific to the peripheral arteries and complex cardiovascular comorbidities. These comorbid conditions may serve to indicate the advanced cardiovascular risk patients with multiple cardiovascular diseases experience regardless of their CLI, which may explain their increased likelihood of having documented and complete GDMT. It is also notable that the results presented here reinforce previously documented racial disparities in care for patients with CLI.[1, 16, 27, 45, 51, 52, 77, 78] Being of a non-white race or being seen at an urban health care site being documented during an encounter was predictive of not having complete GDMT.

In addition to continued evaluation of the effectiveness of current standards of quality of care for treating patients with CLI, programs that might work to identify patients with high cardiovascular risk profiles (with or without CLI) in effort to reduce the burden of risk in the patients who need it most. By evaluating GDMT adherence by site, we can identify those high-performing sites that may be indicative of clinical care patterns successful at identifying patients with CLI. If this disease can be identified in the early stages of PAD, patients can be enrolled in complete GDMT in effort to prevent disease progression and adverse events such as amputations.

This study should be evaluated against several key limitations. As these data are derived from the EHR and are observational in nature, it is always possible that there is unobserved and important variance not available by these data. Since data are categorized using administrative codes, it is assumed that no data are missing, and data are entered correctly at the time of documentation. The Health Facts database is de-identified and

therefore granular validity cannot be independently verified. There is a systematic inclusion bias for Health Facts database such that only sites with a Cerner EHR can be included and not all EHR data for these potential sites will be included in the database Although the Health Facts database includes data for patient encounters classified as inpatient, outpatient, emergent, and others, the misclassification is possible. For this reason, we chose to only analyze inpatient patient encounters, though patients could be provided the opportunity to adhere to a complete GDMT regimen as an outpatient and we would not detect this event in the current analysis.

Conclusions

Our study of a contemporary, national cohort of patient encounters used EHR data to describe rates of GDMT in CLI patients who have undergone major amputations. Rates of compete adherence to GDMT were low in a population that has had substantial interaction with the health care system for their CLI care. Variability in rates between sites proved substantial and further exploration of high-performing programs is warranted to inform future care programs for the treatment of CLI.

CHAPTER 5

ASSESSING PATIENT PREFERENCES FOR SHARED DECISION-MAKING IN PERIPHERAL ARTERY DISEASE

Introduction

Peripheral artery disease (PAD) increases cardiovascular risk, can cause pain and diminishes patients' quality of life. To obtain claudication symptom relief, patients may have multiple effective treatment options available to address their symptoms, including medications, supervised exercise therapy, and revascularization procedures, each having different risks and benefits. It is unclear what patients' preferences are as to whether they want to be involved in making PAD treatment decisions for PAD symptom relief. Accordingly, in patients with new or worsening symptoms of PAD, we aimed to (1) document their preferences for shared decision-making and (2) determine whether patients' decision-making preferences were honored by their provider.[79]

Methods

The Patient-Centered Outcomes Related to Treatment Practices in Peripheral Arterial Disease: Investigating Trajectories (PORTRAIT) Study is a multi-center, prospective, observational registry that enrolled patients with stable PAD (Rutherford 1–3) from 16 PAD specialty clinics in the United States, the Netherlands, and Australia.[80] Because of the unique health care system and documented cultural differences that may exist for medical decision preferences among countries,[81] we only focused on the US patient cohort in this analysis. Patients were consented and interviewed at baseline by local data collectors after PAD

diagnosis, but before PAD treatment. Interviews collected information about their sociodemographic and psychosocial characteristics and decision-making preferences. Medical chart abstraction was conducted at baseline to collect information about medical history, diagnostic tests, medications, and treatments. Centralized phone follow-up interviews were conducted at 3 months by the data coordinating center at Saint Luke's Mid America Heart Institute in Kansas City, Missouri to collect information about patients' health status and quality of medical decision-making. Institutional review board approval was received from each site participating in PORTRAIT, and all patients provided informed consent. Data can be made available on request by contacting the authors.

Preferences for shared decision-making were measured at enrollment (before PAD care and treatment) with the Problem-Solving Decision-Making Scale (PSDM) Questionnaire.[82] The PSDM Questionnaire asks patients questions about who should determine their medical treatments (Figure 11). The PSDM was scored, and preferred decision-making roles were derived, using a previously described method.[83] Based on the responses, 2 groups were created: patients whose responses were reflective of a shared or autonomous role were grouped into a single active group[84] versus patients who expressed to prefer a passive role (Figure 12). It should be noted that autonomous patients typically differ from shared patients in that they not only want an active role in decision-making, but they also wish to be active in problem-solving (i.e., decide which treatment options are applicable to them). At the 3-month follow-up and after patients received their PAD treatments, we used a purposely designed question to ask patients who actually had made their treatment decision and mirrored the response options after the PSDM scale. We compared responses with the preferred decision-making role and defined discrepancies in responses as *decision*

discordance. For example, if the patient preferred to have a shared role, but the doctor alone made the decision, decision discordance would be present.

Problem-Solving Decision-Making Scale Elements	**Responses (All Elements)**
Problem-Solving Tasks A. Who should determine (diagnose) what the likely cause of your symptoms are? B. Who should determine what the treatment options are? C. Who should determine what the risks and benefits of each treatment options are? **D.** Who should decide how like each of these risks and benefits are to happen?	**Likert Scale:** 1 = The Doctor Alone 2 = Mostly the Doctor 3 = Doctor and You Equally 4 = Mostly Me 5 = Me Alone
Decision-Making Tasks E. Given the risks and benefits of these possible treatments, who should decide how acceptable those risks and benefits are to you? **F.** Given all the information about risks and benefits of the possible treatments, who should decide what treatment options should be selected?	
Mean scores were calculated for the Problem-Solving and Decision-Making domains. A mean score < 3 suggests a preference for "Hand Over", 3-3.99 for "Share", and ≥ 4 for "Keep"	

Figure 11. Overview of the Problem-Solving Decision-Making Scale

	Responsibility for Problem-Solving		
Responsibility for Decision-Making	**Hand Over**	**Share**	**Keep**
Hand Over	Passive	N/A	N/A
Share	Shared	Shared	Autonomous
Keep	Shared	Shared	Autonomous

Figure 12. Overview of Preferred Decision-making Role Assignment

Patient characteristics were described for the overall cohort and compared by PSDM categories using Student *t* test for continuous variables, Mann-Whitney *U* for ordinal variables, and χ^2 for categorical variables. Decision discordance between patients' desired and actual roles in decision- making was quantified by comparing PSDM roles with the actual decision-making process. Missing data were present in <5% of patients (the highest

missing rate for any covariate was 1.8%). Missing values were imputed using sequential regression imputation. Data were analyzed with R software version 3.5.0.[33] All tests were 2-tailed, and *P* values <0.05 were considered statistically significant.

Results

A total of 797 US patients were enrolled for the US cohort of PORTRAIT and 744 completed the PSDM Questionnaire at the baseline interview (Figure 13). The majority of patients preferred shared or autonomous roles (N=523, 70.3%), with less than a third preferring a passive role (N=221, 29.7%) (Figure 14). Of the 523 patients preferring shared or autonomous roles, only 11 patients preferred autonomous roles. Compared with those who preferred shared or autonomous roles, patients who adopted passive roles typically had a lower education level, a history of coronary artery bypass grafting, and expressed more treatment satisfaction on the disease-specific Peripheral Artery Questionnaire (Table 9).[85]

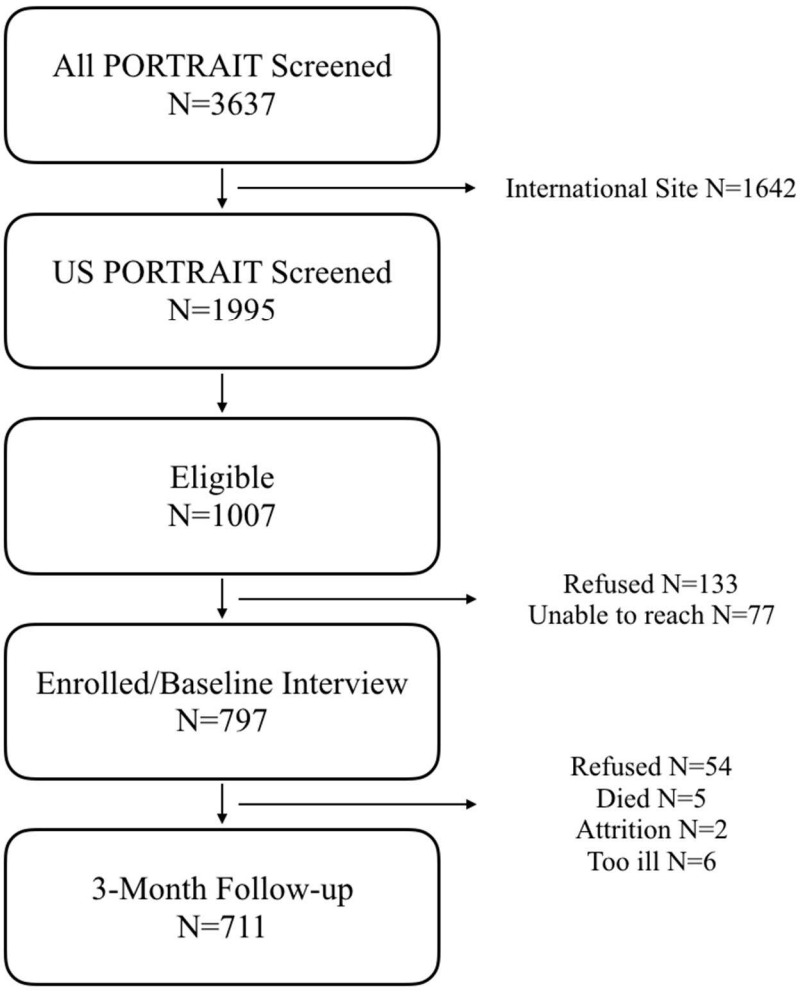


Figure 13. Flowchart of US PORTRAIT Patients Screened, Eligible, Enrolled/Interviewed at Baseline, and 3-Month Follow-up

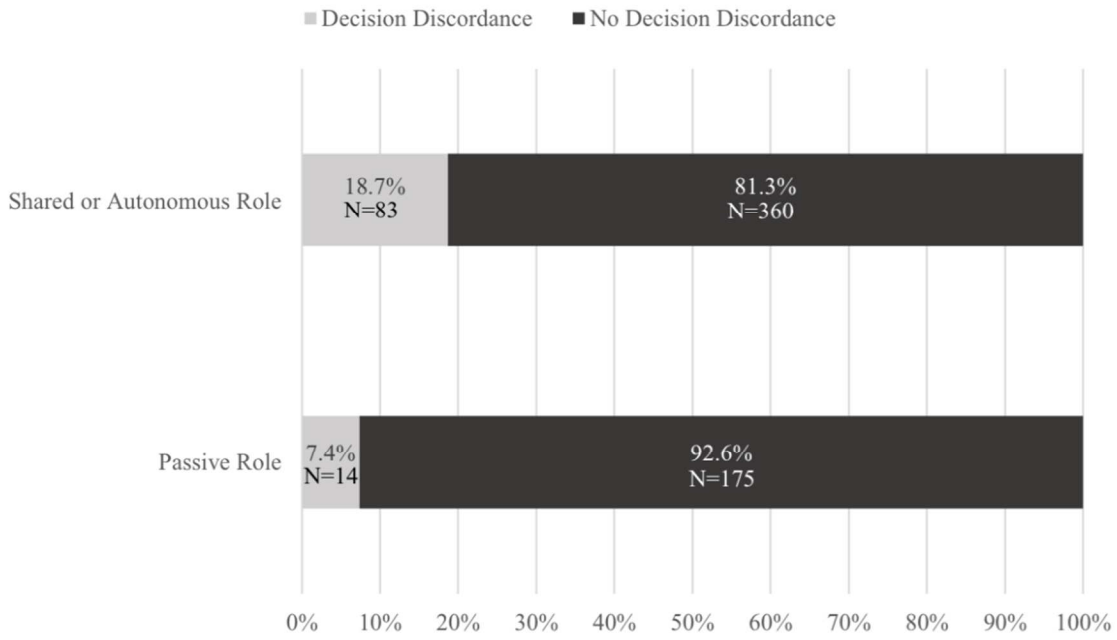


Figure 14. Patient Preferences for Shared Decision-making in Peripheral Artery Disease Treatment Decisions by the Presence of Disease Discordance

Table 9. Overview of Patient Characteristics by Preferred Decision-Making Role (Passive versus Shared/Autonomous)

Characteristic	Passive (N=221, 29.7%)	Shared/Autonomous (N=523, 70.3%)	P-Value
Demographics			
Age, years (mean±SD)	69.1±9.4	68.3±9.7	0.28
Sex			0.34
Male	133 (60.2)	295 (56.4)	
Female	88 (39.8)	228 (43.6)	
White race	153 (69.2)	380 (72.7)	0.34
Hispanic or Latina/o	3 (1.5)	11 (2.1)	0.76
Socio-Economic Factors			
Married	110 (50.5)	294 (56.4)	0.13
Insurance	219 (99.1)	520 (99.4)	0.64
Education high school or above	175 (79.2)	458 (87.6)	0.003
Currently working for pay			0.53
Yes	48 (21.7)	120 (22.9)	
Avoid care due to cost	29 (13.3)	92 (17.7)	0.14
Disease Characteristics			

Characteristic	Passive (N=221, 29.7%)	Shared/Autonomous (N=523, 70.3%)	P-Value
ABI (mean±SD)	0.7±0.2	0.7±0.2	0.77
Typical Symptom Presentation	189 (89.2)	437 (87.8)	0.59
Symptom complaint			0.08
New-onset disease	75 (33.9)	213 (40.7)	
Exacerbation of PAD	146 (66.1)	310 (59.3)	
Rutherford Category			0.23
Mild claudication	38 (17.4)	104 (20.0)	
Moderate claudication	122 (55.7)	254 (48.8)	
Severe claudication	59 (26.9)	162 (31.2)	
Lesion location			0.16
Proximal disease	57 (26.1)	120 (23.1	
Distal disease	96 (44.0)	206 (39.7)	
Both	65 (29.8)	193 (37.2)	
Symptom Duration			0.63
< 1 month	3 (1.4)	6 (1.3)	
1-6 month(s)	51 (24.5)	132 (27.6)	
7-12 months	38 (18.3)	98 (20.5)	
> 12 months	116 (55.8)	242 (50.6)	
Vascular History			
Non-healing ulcer	4 (1.8)	9 (1.7)	1.00
Amputation	5 (2.3)	7 (1.3)	0.35
Peripheral vascular intervention	81 (36.7)	186 (35.6)	0.78
Cardiovascular Risk Factors			
Congestive heart failure	36 (16.3)	65 (12.4)	0.16
Dyslipidemia	201 (91.0)	459 (87.8)	0.21
Hypertension	199 (90.0)	463 (88.5)	0.55
TIA	11 (5.0)	21 (4.0)	0.55
CVA	17 (7.7)	46 (8.8)	0.62
Angina	31 (14.0)	68 (13.0)	0.71
MI	48 (21.7)	115 (22.0)	0.94
PCI	55 (24.9)	149 (28.5)	0.31
CABG	66 (29.9)	115 (22.0)	0.022
Pacemaker	13 (5.9)	16 (3.1)	0.07
ICD	9 (4.1)	16 (3.1)	0.48
Non-Cardiac History			
Chronic kidney disease	34 (15.4)	79 (15.1)	0.92
Chronic lung disease	35 (15.8)	82 (15.7)	0.96
Sleep apnea	24 (10.9)	53 (10.1)	0.77
Osteoarthritis (hip or knee)	19 (8.6)	60 (11.5)	0.24
Chronic back pain	32 (14.5)	68 (13.0)	0.59
Cancer	25 (11.3)	49 (9.4)	0.42
Depression requiring treatment	33 (14.9)	82 (15.7)	0.79

Characteristic	Passive (N=221, 29.7%)	Shared/Autonomous (N=523, 70.3%)	P-Value
Diabetes	77 (34.8)	208 (39.8)	0.21
Treatment Strategy in First 3 Months			0.083
Invasive (Endovascular or Surgery)	33 (16.3)	102 (22.1)	
Non-Invasive	170 (83.7)	359 (77.9)	
Clinician Provider Specialty			0.509
Interventional Cardiologist	146 (66.1)	353 (67.5)	
Cardiologist	36 (16.3)	86 (16.4)	
Vascular Surgeon	11 (5.0)	37 (7.1)	
Vascular Medicine Specialist	25 (11.3)	42 (8.0)	
Other	3 (1.4)	5 (1.0)	
Baseline Health Status (mean score±SD)			
PAQ: physical limitation	36.1±26.3	33.5±24.3	0.21
PAQ: symptom stability	43.8±19.2	43.1±20.8	0.67
PAQ: symptoms	44.8±23.9	42.7±23.3	0.26
PAQ: treatment satisfaction	85.1±18.4	81.5±21.4	0.034
PAQ: quality of life	51.1±26.5	47.4±25.6	0.07
PAQ: social limitation	62.1±30.4	59.3±30.8	0.26
PAQ: summary	48.9±22.3	46.0±21.8	0.10
PHQ-8 depression score	4.3±5.0	4.8±5.1	0.23

Abbreviations: SD, standard deviation; ABI, ankle brachial index; PAD, peripheral artery disease; TIA, transient ischemic attack; CVA, cerebrovascular accident; MI, Myocardial Infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; ICD, implantable cardioverter-defibrillator; PAQ, peripheral artery questionnaire; PHQ-8, Patient Health Questionnaire-8 Item Scale

Decision discordance (i.e., PSDM preferred role did not match with what actually happened) occurred in 97 patients (15.3%) (Table 10) and was more prevalent in patients who preferred shared or autonomous roles (18.7% in shared role versus 7.4% in passive role, *P*=0.00047) (Figure 14). Decision discordance was more prevalent among those without a history of a peripheral vascular intervention, lower PAD-specific treatment satisfaction scores before treatment, and among those with low social support[86] scores. The presence of decision discordance did not statistically vary by site (median odds ratio=1.32; 95% CI, 1.00–2.07; *P*=0.07) or provider (unadjusted median odds ratio=1.56; 95% CI, 1.00– 2.44; *P*=0.06) (Figure 15).

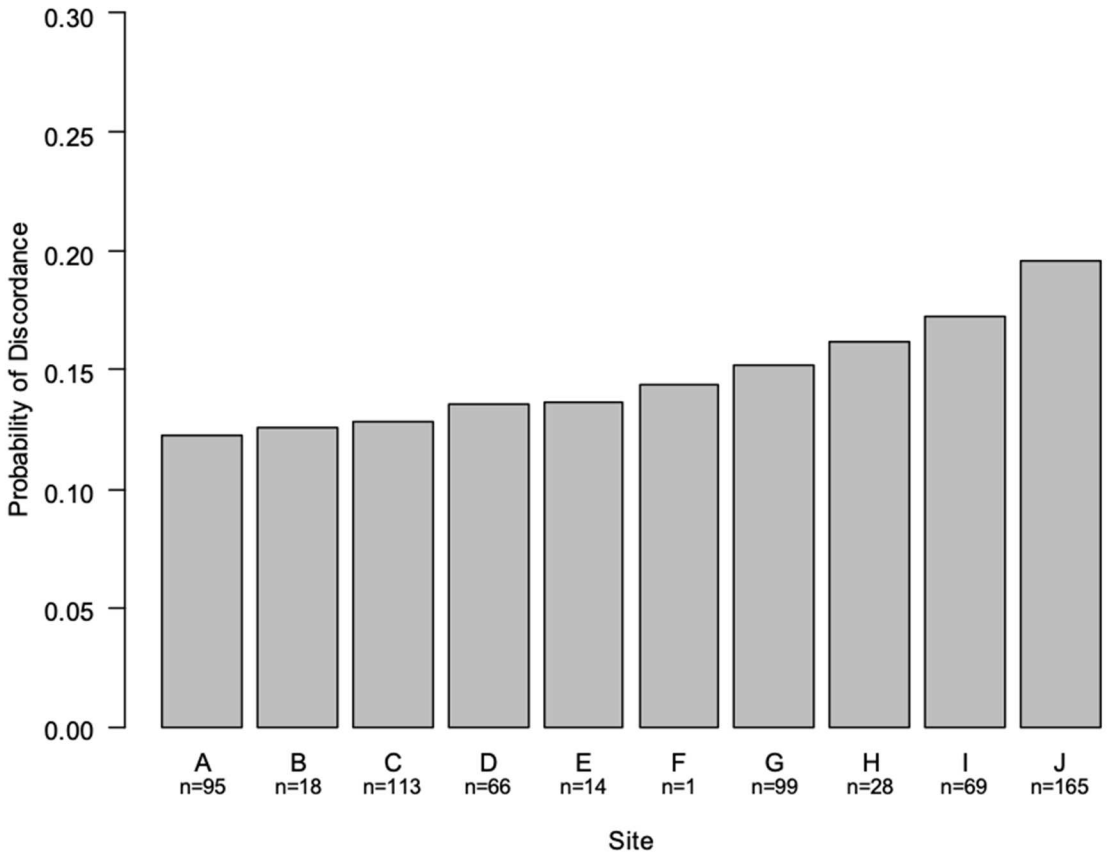
Table 10. Overview of Patient Characteristics by the Presence or Absence of Decision-Making Discordance

Characteristic	Discordance Present (N=97, 15.3%)	Discordance Absent (N=535 84.7%)	P-Value
Demographics			
Age, years (mean±SD)	69.0±10.4	68.4±9.4	0.55
Sex			0.84
Male	57 (59.4)	307 (58.3)	
Female	39 (40.6)	220 (41.7)	
White/Caucasian Race	68 (70.8)	378 (71.7)	0.86
Hispanic or Latino ethnicity	1 (1.0)	9 (1.7)	0.22
Married	51 (53.7)	282 (53.9)	0.97
Socio-Economic Factors			
Insurance	67 (69.8)	317 (60.2)	0.07
Education high school or above	83 (86.5)	447 (84.8)	0.68
Avoid care due to cost (baseline)	20 (21.3)	81 (15.5)	0.16
Disease Characteristics			
ABI (mean ±SD)	0.70±0.20	0.70±0.20	0.023
Symptom Presentation			0.23
Typical	77 (85.6)	452 (89.9)	
Rutherford Category			0.31
Mild claudication	21 (21.9)	98 (18.7)	
Moderate claudication	52 (54.2)	261 (49.7)	
Severe claudication	23 (24.0)	166 (31.6)	
Symptom Duration			0.77
< 1 month	1 (1.1)	6 (1.2)	
1-6 month(s)	21 (23.3)	131 (27.2)	
7-12 months	22 (24.4)	97 (20.2)	
> 12 months	46 (51.1)	247 (51.4)	
Vascular History			
Amputation	2 (2.1)	6 (1.1)	0.36
Peripheral vascular intervention	23 (24.0)	196 (37.2)	0.012
Cardiovascular Risk Factors			
Arial Fibrillation	8 (8.3)	73 (13.9)	0.14
Congestive heart failure	12 (12.5)	69 (13.1)	0.14
Dyslipidemia	85 (88.5)	468 (88.8)	0.94
Hypertension	90 (93.8)	468 (88.8)	0.14
TIA	8 (8.3)	21 (4.0)	0.11
CVA	8 (8.3)	46 (8.7)	0.89

Characteristic	Discordance Present (N=97, 15.3%)	Discordance Absent (N=535 84.7%)	P-Value
Prior MI	22 (22.9)	117 (22.2)	0.88
PCI	32 (33.3)	141 (26.8)	0.19
CABG	21 (21.9)	132 (25.1)	0.51
Prior pacemaker	4 (4.2)	18 (3.4)	0.761
Prior ICD	2 (2.1)	18 (3.4)	0.75
Non-Cardiac History			
BMI (mean value±SD)	29.4±6.5	29.6±7.0	0.82
Smoking status			0.41
Never	11 (11.5)	62 (11.8)	
Former	61 (63.5)	299 (56.7)	
Current	24 (25.0)	166 (31.5)	
Chronic kidney disease	12 (12.5)	82 (15.6)	0.44
Chronic lung disease	17 (17.7)	82 (15.6)	0.59
Sleep apnea	12 (12.5)	54 (10.2)	0.51
Osteoarthritis (hip or knee)	5 (5.2)	60 (11.4)	0.07
Chronic back pain	16 (16.7)	68 (12.9)	0.32
Cancer	11 (11.5)	52 (9.9)	0.63
Depression requiring treatment	12 (12.5)	88 (16.7)	0.30
Diabetes	34 (35.4)	208 (39.5)	0.45
Treatment Strategy in First 3 Months			0.223
Invasive (Endovascular or Surgery)	16 (16.3)	117 (22.2)	
Non-Invasive	80 (83.3)	410 (77.8)	
Clinician Provider Specialty			0.339
Interventional Cardiologist	61 (63.5)	358 (67.9)	
Cardiologist	22 (22.9)	80 (15.2)	
Vascular Surgeon	8 (8.3)	35 (6.6)	
Vascular Medicine Specialist	5 (5.2)	46 (8.7)	
Nurse Practitioner	0 (0.0)	2 (0.4)	
Other	0 (0.0)	6 (1.1)	
Baseline Health Status (score±SD)			
PAQ: physical limitation	35.5±23.4	34.2±25.2	0.69
PAQ: symptom stability	43.1±20.2	43.5±20.6	0.84
PAQ: symptoms	44.2±24.3	43.4±23.1	0.76
PAQ: treatment satisfaction	78.5±22.3	83.8±19.6	0.023
PAQ: quality of life	50.4±25.8	48.6±25.6	0.52
PAQ: social limitation	61.6±30.3	60.4±30.6	0.71
PAQ: summary	48.8±21.4	47.0±21.9	0.45
PHQ-8 depression score	4.6±4.7	4.6±5.0	0.99
ESSI Social Support Score	21.5±5.0	22.3±4.2	0.07
ESSI Low Social Support Score	23 (24.2)	68 (13.0)	0.004

Characteristic	Discordance Present (N=97, 15.3%)	Discordance Absent (N=535 84.7%)	P-Value
Decision-Making			
PSDM preferred role			<0.001
Passive	14 (13.5)	175 (32.7)	
Shared/Autonomous	83 (86.5)	360 (67.3)	

Abbreviations: SD, standard deviation; ABI, ankle brachial index; TIA, transient ischemic attack; CVA, cardiovascular accident; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; ICD, implantable cardioverter defibrillator; PAQ, peripheral artery questionnaire; PHQ-8, Patient Health Questionnaire-8 Item Scale; ESSI, ENRICHED social support inventory; PSDM, patient shared decision-making



	MOR (95% CI)	P-value
Site variability (n=10)	1.32 (1.00, 2.07)	0.07
Provider variability (n=107)		
Unadjusted	1.56 (1.00, 2.44)	0.06
Adjusted for site	1.39 (1.00, 2.30)	0.20

Figure 15. Computed Odds Ratios Showing Probability of Patient Discordance by US PORTRAIT Site, Median Odds Ratio with 95% Confidence Intervals (MOR, 95% CI)=1.32 (1.00, 2.07), P-value=0.07.

Discussion

Understanding patient values and preferences and how they intersect with medical treatment choices and outcomes has increasingly become important. In PAD, we have not studied these processes yet, even though treatment choices for PAD symptom relief are

preference sensitive.[4] In our prospective, multi-center cohort of patients with newly diagnosed or a recent exacerbation of their PAD, we found that a large majority of patients prefer a shared or autonomous role in their PAD treatment decision-making. Patients who preferred passive roles tended to be less educated, had a history of heart surgery, and typically less satisfied with PAD treatment at baseline. While the majority of patients indicated that their preferences were honored during the actual decision-making process, in 15% of the patients this was not the case. Decision discordance was associated with those patients who had not previously undergone a peripheral vascular intervention, those having lower PAD treatment satisfaction scores before treatment, and with those who had low social support.

Our work significantly extends the literature about shared decision-making in the care of patients with PAD. Patients enrolled in PORTRAIT experienced claudication for which the recommended treatment is optimal medical treatment (statins, antiplatelet therapy, and supervised exercise therapy) before considering invasive options. Invasive options can still be considered with life-limiting symptoms and are thus preference-sensitive, given its risks and benefits against treating PAD symptoms noninvasively. Patients in our study express a desire to be actively involved in conversations as to which treatment would work best for them given their preferences and the evidence-base that is out there.

Decision-support tools can be developed and used to meet the needs of patients who want to have a say and can also be used to educate and invite patients to transition from a more passive role to a more engaged role.[87] In addition, it could help to address to resolve some of the discordance that takes place between patients' preferred role and the way their

treating physician interacts with the patient in the decision-making process. Few patient characteristics were substantively associated with patient preference for treatment decision-making, thus, the best way to determine which treatment a patient prefers is probably to ask them directly. Currently, there are no formal decision-making tools available in routine clinical practice for patients facing a PAD treatment decision. Initial efforts have been directed towards developing tools specific to PAD invasive treatment decisions,[88] but it is unclear whether they are actually used and how these tools affect treatment decision-making. Patient knowledge, value sets associated with individual treatment modalities, and provider skills in shared decision-making will need to be further documented and developed to enable the successful design of standardized shared decision-making platforms in PAD. Future work should seek to develop and test frameworks for PAD treatment decision- making so that treatment decision quality, treatment out- comes, and the shared decision-making process can be studied in patients who are seeking PAD symptom relief.

Our study should be interpreted in the context of the following potential limitations. The PORTRAIT registry is an observational study, and it is possible that we did not collect information on all factors that could have accounted for patients' preferences. Second, our assessment of actual decision-making was assessed at the 3-month follow-up interview. This was done intentionally because it often takes few weeks to implement a treatment plan after an initial outpatient visit, but also introduced the possibility for the treatment type and outcome to influence patients' perceptions and responses. Finally, the enrolling sites were led by PAD specialists who elected to voluntarily participate in the PORTRAIT registry and their processes of interacting with their patients may differ from other practitioners.

Patients in the US receiving care for their PAD symptoms most often prefer to be involved in their PAD treatment decisions. One in 7 patients experienced decision discordance. Exploring shared-decision–making frameworks and decision-support tools that would meet patients' expectations to become involved in their care, and to study its impact on improving the quality and care of PAD outcomes is an important priority in our quest to make PAD care more patient-centric.

CHAPTER 6

GENERAL DISCUSSION

The aims of this dissertation were to 1) use the Health Facts database to create a data mart of CLI patients for use in cardiovascular outcomes research and 2) to use the data mart to examine nationally-representative, real-world quality of care and outcomes for the treatment of CLI. Specifically, we aimed to document 30-day amputations in CLI patients after endovascular peripheral vascular intervention (Aim 2A) and GDMT in patients with CLI who have documented major amputations (Aim 2B). We also documented site variability in both 30-day amputation and GDMT. We documented the methodology used to exclude Health Facts sites that did not contain comprehensive data necessary for specific study context and documented the methods used to exclude patients who did not have documented CLI to create the final analysis data mart. We documented rates of 30-day amputations after intervention, the variability in this outcome between sites, and identified factors associated with 30-day amputation. We also documented rates of GDMT in patients with CLI, variability in GDMT between clinical sites, and identified factors associated with a patient encounter documenting complete GDMT.

By documenting a path forward for the use of real-world data in clinical research, we build on previous work in informatics demonstrating the use of routinely collected EHR data for advanced analytics and highlight the opportunity for future use as methods and data sources are validated and refined. We specifically provide contemporary, nationally-representative, real-world evidence, which has not been documented until now. The use of real-world data resources in cardiovascular outcomes research represents an opportunity for evidence-based research in contrast to clinical registry data, which, although provides

excellent opportunity to understand patient care and outcomes, may not always represent reality for the majority of patients.[89]

Our methodology for identification of these patients is reproducible in other administrative data sets and is agnostic to the EHR and health system in which it is applied. By understanding the source of a research database, we have learned how to perform quality checks to ensure comprehensive data is used to produce insights that are valid. Further validation of this work in other data sets is possible and would be encouraged to verify our results in separate cross-sections of the CLI patient population and to determine if the care quality signals documented in this nationally representative cohort are present.

A lack of national benchmarks for CLI quality of care represents an opportunity to further develop this work to increase awareness of CLI and its risk for adverse cardiovascular events, variability in the care for patients with CLI, and to document the variability in outcomes patients with CLI experience. We specifically contribute variability in 30-day amputation outcomes and guideline directed medical therapy in patients with CLI represented in the Cerner Health Facts database as potential quality markers for CLI care and suggest further work should be done in this context to understand real-world CLI treatment and outcomes patterns. By continuing this work, we can inform national benchmarks and work to establish evidence-based guidelines for CLI care.

This work overall should be interpreted against key limitations. As Health Facts is an observational database of retrospective data, there is the possibility of residual confounding of data and unobserved drivers of variance in the data. Health Facts contributors are limited to those health systems who have purchased a Cerner EHR and have agreed to contribute data for research purposes, presenting a possible inclusion bias for data represented. A key

feature of Health Facts to protect site and patient privacy is its de-identification, however, this also limits efforts to validate results using alternative pathways such as through clinical note review.

Conclusions

With this work, we demonstrate the use of real-world, national EHR data for cardiovascular outcomes research. Use of these aggregated databases requires a multi-disciplinary approach to ensure only the highest quality data are used. By applying this methodology to the quality of care and outcomes in patients with CLI, we demonstrate the promise these EHR databases present for our current and future work and contribute insights that can inform national standards of care for patients with CLI.

APPENDIX

Table A-1. Clinical Definitions Derived from Administrative and Billing Codes

Concept	Code(s)	Clarification
Critical Limb Ischemia	ICD-9: 440.XX ICD-10-CM: I70.XX	Confirming rest pain, ulceration, or gangrene indicated
Endovascular Peripheral Vascular Intervention	ICD-9: 00.55, 00.60, 17.56, 39.50, 39.90 ICD-10-CM: 047(C, D, E, F, H, J, K, L, M, N, P, Q, R, S, T, U, Y)XXX, 04CXXXX CPT-4: 354XX, 37(1, 2)XX	Confirming peripheral artery and percutaneous approach are indicated
Non-traumatic, Major Amputation of Lower Limb	ICD-9: 84.1X ICD-10: 0Y6(2-8, F-J)XXX; 0Y6(M, N)0Z CPT-4: 2729(0, 5), 2759(1, 2, 8), 2788(0, 2, 6, 8, 9)	Confirming lower limb disarticulation (ankle and above) is indicated

Abbreviations: CPT-4, Clinical Procedural Terminology, 4th Revision; ICD-9, International Classification of Diseases, 9th Revision; ICD-10, International Classification of Diseases, 10th Revision

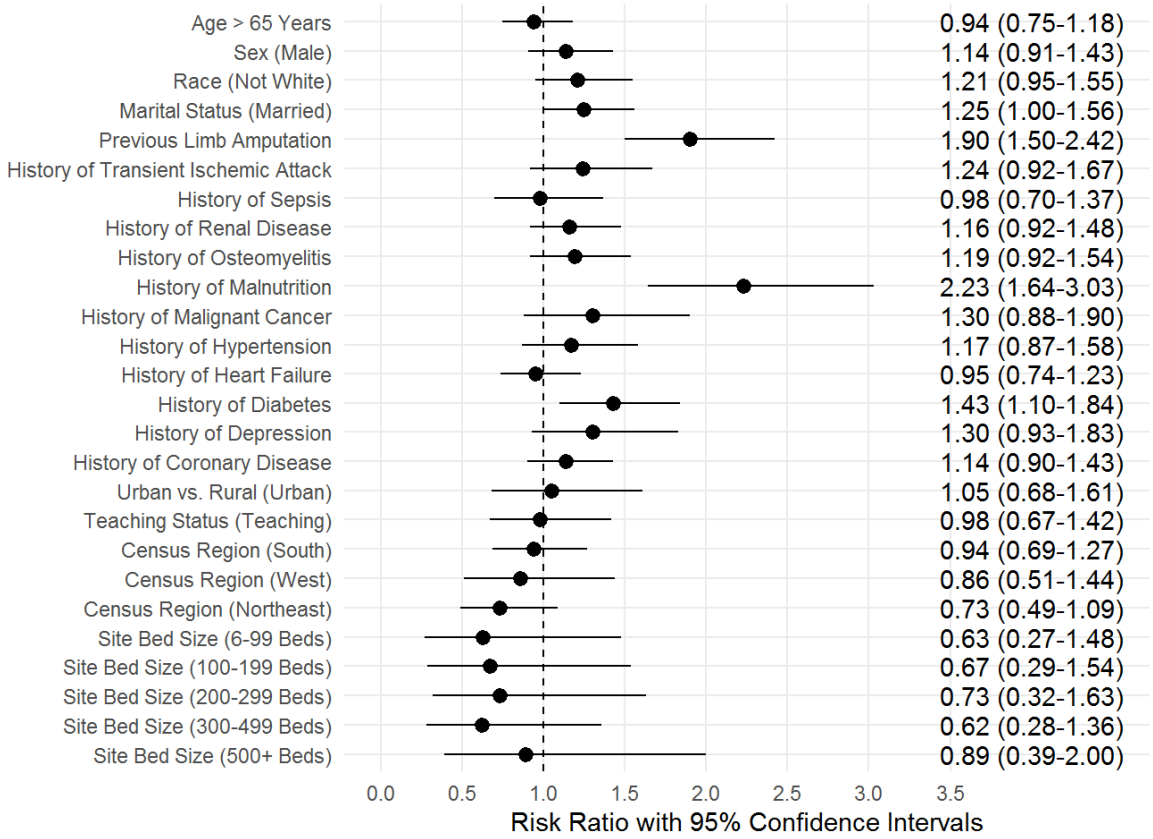


Figure A-1. Patient and Site Factors Associated with 30-Day Amputation in Patients with Critical Limb Ischemia Undergoing Endovascular Peripheral Vascular Intervention

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VITA

Jeremy is an interdisciplinary Ph.D. degree candidate for Bioinformatics and Entrepreneurship & Innovation in the department of Biomedical and Health Informatics at the University of Missouri-Kansas City School of Medicine and the Regnier Institute for Entrepreneurship and Innovation at the Henry W. Bloch School of Management. He graduated from William Jewell College with a Bachelor of Arts degree in biology in 2014. He spent two years working in industry and then attended the University of Missouri-Kansas City School of Medicine receiving a Master of Science degree in Bioinformatics in 2017. While at the UMKC School of Medicine, he has worked as a graduate research assistant under the guidance of Kim G. Smolderen, Ph.D. at the Saint Luke's Mid-America Heart Institute in Kansas City, Missouri. He worked as a teaching assistant for the course *Clinical Trials* for one semester and as graduate instructor for the last two years of his Ph.D. training. Jeremy has written or co-authored many peer-reviewed articles, abstracts, and poster presentations during his time in graduate school and has presented this work at many national, regional, and local professional meetings. Jeremy served his fellow students on the Graduate Student Council and was elected President of the body in 2019. Jeremy is a member of the American Medical Informatics Association, American College of Cardiology, and American Heart Association. Jeremy has accepted a post-doctoral research associate position at Yale University School of Medicine that will begin following completion of his doctoral program.