Using existing data for epidemiologic research of cardiovascular diseases

By

Yongzhe Hong

A thesis submitted in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

Department of Medicine

University of Alberta

Abstract

Cardiovascular diseases (CVDs) are the leading cause of morbidity and mortality and have placed a significant burden on our society both regionally and globally. With the development of information technology, we are accumulating digitalized data at an exponential speed. This growing volume of existing data has provided researchers tremendous opportunities and resources to generate real-world evidence for healthcare decision making. Leveraging data from overwhelming numbers of available databases could effectively speed up the progress of scientific advances and provide a significant impact on clinical practice and public health. Despite that plenty of resources and efforts have been put to address health-related questions, countless unanswered questions remain and new hypotheses keep arising with the advance in healthcare system. Many of them can be addressed by epidemiologic studies using the available data without the primary data collection. Meanwhile, the challenges CVD researchers are facing when conducting research using existing data are less frequently discussed. In the thesis, I aim to address several clinical epidemiologic research questions and controversies in the field of cardiovascular diseases using available data, and discuss the challenges during the research process from a data user's perspective to raise the awareness and to stimulate discussions.

Chapter 2 is a diagnostic and community-wide study that evaluated the feasibility of using administrative health data to identify peripheral arterial disease (PAD) patients. The results show that using administrative data to identify PAD patients was highly specific but not sensitive in the community.

Chapter 3 is a systematic review that compared and summarized the admission rates and length of stay (LOS) for venous thromboembolism (VTE) patients with different anticoagulant therapies. We found that the admission rates were lower and the LOS was shorter comparing low molecular weight heparin (LMWH) to unfractionated heparin (UFH) and comparing oral therapy to parenteral therapy for acute VTE in RCTs. These crucial clinically relevant outcomes were underreported in the existing VTE clinical trials.

Chapter 4 is a retrospective and population-based cohort study that measured the association between chronic obstructive pulmonary disease (COPD) and angiographically diagnosed CAD. COPD was found to be negatively associated with CAD with and without adjustment for classic cardiovascular risk factors.

Chapter 5 is a case-crossover study that evaluated the association between acute atmospheric pressure changes and the occurrence of ST-Elevation Myocardial Infarction (STEMI). We found that there was no association between acute air pressure changes and the onset of STEMI 1 to 6 days after the exposure, while there was a higher likelihood of STEMI occurrence for patients experiencing acute air pressure decrease in a lag time of 7 days.

This thesis shows that reutilizing existing data is time-saving and economical to generate evidence for important clinical epidemiologic research questions in the field of cardiovascular diseases despite some practical challenges. Timely access to data, lacking detailed data documentation, establishing causality, data conversion, data consistency, and data validity are the main challenges for CVD researchers conducting epidemiologic research using existing data. Overcoming these challenges would streamline and speed up the research process for investigators conducting epidemiologic research.

Preface

This dissertation contains both published and unpublished work, which is the original work of myself.

Chapter 2 of this thesis has been published as *Hong Y, Sebastianski M, Makowsky M, Tsuyuki R, McMurtry MS. Administrative data are not sensitive for the detection of peripheral artery disease in the community. Vascular Medicine. 2016 Aug; 21(4):331-6.* My contribution to this paper includes the data cleaning, analysis and exhibition as well as writing and revising the manuscript. This project received ethics approvals from the University of Alberta Research Ethics Board: first project name "Epidemiology of lower extremity peripheral arterial disease in hospitalized and ambulatory patients." No. Pro00002292, May 11, 2012; second project name "Ankle-brachial index-determined peripheral arterial disease as an independent risk factor for cardiovascular outcomes following cardiac catheterization" No. Pro00009942, November 7, 2011.

Chapter 3 of this thesis has been published as *Hong Y, Mansour S, Alotaibi G, Wu C, McMurtry MS. Effect of anticoagulants on admission rates and length of hospital stay for acute venous thromboembolism: A systematic review of randomized control trials. Crit Rev Oncol Hematol. 2018;125:12-8.* Dr. Sola Mansour and I contributed equally to this work. We shared equal responsibility for study selection, data extraction and data analysis, and writing and revising the manuscript.

Chapter 4 of this thesis is currently under peer-review as *Hong Y, Graham M, Southern D, McMurtry MS. The association between chronic obstructive pulmonary disease and coronary artery disease in patients undergoing coronary angiography. Submitted to COPD journal.* I was

responsible for requesting, cleaning and analyzing data as well as writing and revising the manuscript. This project received ethics approvals from the University of Alberta Research Ethics Board: project name "The APPROACH longitudinal study comparing sex and gender differences of patients treated in Alberta for coronary artery disease." No.Pro00060498, December 15, 2015.

Chapter 5 of this thesis will be submitted to a peer-review journal as *Hong Y, Graham M, Rosychuk RJ, Southern D, McMurtry MS. The effects of acute atmospheric pressure changes on the occurrence of ST-segment elevation myocardial infarction: a case-crossover study.* My contribution to this project includes study design, data acquisition, cleaning and analysis as well as writing and revising the manuscript. This project received ethics approvals from the University of Alberta Research Ethics Board: project name "Do altitude-related air pressure differences influence susceptibility to cardiovascular disease?" No. Pro00053029, March 4, 2015.

Dedication

This thesis is dedicated to my beloved wife, Xueyi Chen, who has always been a constant source of support and encouragement.

This work is also dedicated to my parents Yuanjin Hong and Huanhuan Cai for their unconditional love and support.

Acknowledgements

First and foremost, I would like to offer my heartfelt thanks to my supervisor, Dr. Michael Sean McMurtry. The dissertation would not be possible without his excellent guidance and support. My time in his lab has enriched me with opportunities for professional development and personal growth.

I also would like to thank my supervisory committee members, Dr. Rosychuk and Dr. Graham, for their constructive suggestions and encouragement throughout my graduate studies.

I am also grateful to Dr. Cynthia Wu for her timely and beneficial feedback on conducting the systematic review.

I would like to acknowledge the Li Ka Shing Foundation, for covering the tuition and stipends during my PhD study in Canada. This generous sponsorship has changed my life profoundly.

I would like to extend my gratitude to all of my colleagues within the laboratory, including Sola, Anmol, and Ghazi, for their continuous encouragement and help.

I would like to thank technician Kyoko Hashimoto for her kind help.

I wish to thank Danielle Southern for providing the assistance during the data acquisition from APPROACH registry.

Table of Contents

List of Tables

Chapter 2

Chapter 3

Chapter 4

Chapter 5

List of Figures

Chapter 3

Chapter 4

Chapter 5

List of Abbreviations

CVDs	Cardiovascular Diseases
CI	Confidence Interval
CAD	Coronary Artery Disease
APPROACH	Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease
CIHR	Canadian Institutes of Health Research
PAD	Peripheral Arterial Disease
ABI	Ankle-Brachial Index
RCTs	Randomized Control Trials
VTE	Venous Thromboembolism
COPD	Chronic Obstructive Pulmonary Disease
STEMI	ST-Elevation Myocardial Infarction
ICD	International Classification of Diseases
CCI	Canadian Classification of Interventions
PPV	Positive Predictive Value
NPV	Negative Predictive Value
DAD	Discharge Abstract Database
ACD	Ambulatory Care Data
PPD	Practitioner Payments Database
LR+	Positive Likelihood Ratio
LR-	Negative Likelihood Ratio

CLI	Critical Limb Ischemia
OR	Odds Ratio
LOS	Length Of Stay
LMWH	Low-Molecular-Weight Heparin
UFH	Unfractionated Heparin
RR	Relative Risk
DVT	Deep Vein Thrombosis
PE	Pulmonary Embolism
VKAs	Vitamin K Antagonists
DOAC	Direct Oral Anticoagulants
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
aPTT	activated Partial Thromboplastin Time
IQR	Interquartile Range
SD	Standard Deviation
OD	Once per Day
BID	Twice per Day
LM	Left Main
LAD	Left Anterior Descending Artery
RCA	Right Coronary Artery
LCX	Left Circumflex
BMI	Body Mass Index
AMI	Acute Myocardial Infarction
NSTEMI	Non-ST Elevation Myocardial Infarction

SPOR	Strategy for Patient-Oriented Research
SUPPORT	Support for People and Patient-Oriented Research and Trials
NO	Nitric Oxide
NO2	Nitrogen Dioxide
CO	Carbon Monoxide
PM2.5	Particulate Matter with an Aerodynamic Diameter ≤2.5 μm

Chapter 1: Introduction

1.1 Cardiovascular diseases: the leading cause of public health burden

Cardiovascular diseases (CVDs) are defined as diseases of the circulatory system affecting the anatomy and physiology of the heart and blood vessels. [1] CVDs consist of a variety of conditions including congenital heart disease, coronary artery disease (CAD), heart failure, cardiomyopathies, valvular heart disease, arrhythmias, pericardial diseases, aneurysm, peripheral and cerebrovascular diseases, systemic hypertension, vasculitides, venous thromboembolic disease, and pulmonary hypertension. [2]

CVDs are the leading cause of morbidity and mortality and have placed a significant burden on our society both regionally and globally.

1.1.1 Prevalence

Globally, the crude prevalence of CVDs was 422.7 million (95% confidence interval [CI] 415.5–427.9 million) in 2015, increased 24.8% compared to that in 2005; and the age-adjusted prevalence in 2015 was 6304.0 per 100,000 (95% CI 6196.1–6382.8), representing a decrease of 1.8% from 2005.[3] The leading cause of CVDs is CAD, followed by stroke.[3] In Canada, there were about 2.4 million (8.5%) Canadian adults aged 20 years and older that were diagnosed with ischemic heart disease including 578,000 (2.1%) with a history of a heart attack in 2012.[4] There were 315,000 Canadians reported living with a stroke in 2009.[5] Despite showing dramatic declines in CVD prevalence in regions with high income, CVDs remain a major contributor to disease burden worldwide because of the growing and ageing population.[6]

1.1.2 Mortality

According to the World Health Organization, CVDs are the number one cause of death globally, and an estimate of 17.7 million people died from CVDs in 2015, accounting for 31% of all global deaths.[7] Among these deaths, an estimated 7.4 million was attributed to CAD and 6.7 million were due to stroke. [7] Over 75% of CVD deaths took place in low- and middle-income countries[7] because of the poor access to effective and equitable healthcare services.[8] In Canada, CVD was the second leading cause of death following cancer, accounting for 22.7% of all deaths in 2009.[9] Attributed to the advances in medicine and the increased awareness of CVD risk factors, the global mortality of CVD has declined over the past 3 decades, with extensive variation between and within regions.[10] However, CVDs should be taken seriously and the trends in mortality should be constantly updated as these diseases are still the leading causes of mortality worldwide.

1.1.3 Economic impact

The 2010 global expense of CVDs was estimated at $863 billion USD (equivalent to an average per capita cost of $125 USD).[11] The expense of CVDs accounted for 14% of total health expenditures from 2013 to 2014, more than the cost of any major diagnostic group.[3] CVDs cost Canadians 22.2 billion in 2000 with 7.6 billion direct costs and 14.6 billion indirect costs, making CVDs the most costly diseases in Canada.[5] With increased obesity rates, increases in elderly members of the population, and increased post-CVD survival rates, the economic cost of CVDs is expected to grow dramatically from $272.5 billion in 2010 in the US to $818.1 billion in 2030.[12]

1.2 Data explosion

With the rapid development of information technology, digitalized data are accumulating at an exponential speed. A study has shown that only 5 exabytes (10^{18} bytes) of data were created by the year 2003. [13] In contrast, about 2.5 exabytes of data were generated each day as of 2012, and this number is doubling every 40 months or so.[14] Entering the era of big data, tremendous opportunities have arisen for clinicians and scientists to explore health-related questions using the enormous amount of data in healthcare system. About 500 petabytes of data were created by the electronic health records in 2012, and this number is projected to reach 25,000 petabytes by 2020.[15]

Additionally, with the increased permissibility of worldwide access to scientific data, every scientist is capable of investigating healthcare questions and hypotheses through data analyses after proper training. Since 2013, both national and international scientific organizations, including the European Commission, the US Office of Science and Technology Policy, and the Global Research Council, have promoted data sharing, which broadens worldwide collaboration and accelerates the pace of scientific studies.[16] Journals such as PLOS One have required authors to fully disclose all the data underlying the findings described in their manuscript.[17] Moreover, governments are facilitating the access to health data by providing a more integrated and centralized database. For instance, Connect Care, a clinical information system from Alberta Health Services, gathers electronic health records from various healthcare providers and provides well-organized secondary data in ways that will literally transform how the health information is recorded and monitored.[18] With the support of enhancing data availability from scientific journals and the government, secondary data uses have become more accessible and attractive for many purposes.[19] In addition, data generated from sequencing platforms, real-time imaging

systems, point-of-care testing, as well as wearable and mobile health devices have also contributed to the rapid expansion of information.[20]

The growing volume of existing data has provided researchers with tremendous opportunities and resources to general real-world evidence to tackle clinically relevant questions, including those regarding CVDs. Leveraging available data could effectively speed up the progress of scientific advances.

Research utilizing existing data is different from research using primary data because secondary data are collected before a research question is defined. There are three critical components involved in this type of research including the formulation of the research question, a rigorous study design, and reliable data sources, which have to be compatible with each other to make the research feasible.

Overall, with the dramatic increase in data availability, reusing the existing data has contributed to a better understanding of CVDs and better healthcare policies.

1.4 Strengths of using existing data for epidemiologic research

Secondary studies are essential complements to the primary studies. Many of the epidemiologic questions may not be necessary for conducting a primary study if the use of existing data can provide the answers in a more efficient and cost-effective approach. There are a number of strengths of using existing data for epidemiologic research compared to primary studies. Each of them is discussed as follows.

1.4.1. Cost-effectiveness

Using existing data could substantially reduce the cost of conducting a study, as it skips the steps of subject recruitment and data collection. The acquisition of existing datasets is often at minimal or no cost. Also, since there is no requirement to provide incentives to study participants, this type of research can be done at a much lower cost.[21] In comparison, in a clinical trial cost study in 2016, the median cost of conducting a study was varied because of the difference in study design; and the number varied from US$3.4 million to $21.4 million.[22] In the context of shrinking research budgets and increasing health expenses, it is especially advantageous to do research using existing data. With a steady increase over the last 20 years, healthcare expenses have accounted for 17.6 percent of the United States' GDP—nearly $600 billion.[23] Therefore, it is vital to maximize the value of existing data to improve the efficiency of healthcare system while also lower the health expenditure.

1.4.2 Efficiency

Because of the availability of the existing data, research using secondary data can generate valuable insights in shorter time compared to primary studies which typically require a long period of time to recruit patients and collect data. Rather than spending a large amount of time on waiting for the outcomes in studies require long-term follow-up, researchers would spend their time on investigating more research questions through analyzing large volumes of existing data.[24]

1.4.3 Large sample size

Researchers who access large provincial or national administrative data are able to conduct research with a larger sample size. This will allow the investigators to study exposures that have a small effect size and to increase the precision of the estimates. It can also reduce the

potential selection bias in single-institution studies. In addition, with a large sample size, studies using available data may elicit more attention from the public, researchers, and policy-makers, generating marked impacts on the society.

1.4.4 Less ethical barriers

Research using existing data avoids exposing patients to potential harms associated with research participation, which could also help the researchers get ethics approval more easily, since it does not involve further intervention on the patients.[25] With minimum identifiable information from each participant, administrative data acquisition normally have fewer requirements from the researchers.

1.4.5 Greater generalizability

One of the strengths of a randomized controlled trial is its high internal validity. However, since the study subjects are highly selected participants, it also reduces the generalizability of the results to the public population.[26] Therefore, research using existing data is an essential supplement by generalizing the results from clinical trials to a broader population. Few researchers would be able to collect a representative sample from every province or state, while utilizing national data from the federal government or combining multiple data sources that cover different regions make the nation-wide analysis more approachable.[27]

1.5 Limitations of using existing data for epidemiologic research

Despite all the advantages, epidemiologic research using existing data has several limitations. And the awareness of these disadvantages allows researchers to optimize study design, effectively utilize databases, and scientifically perform the analysis.

1.5.1 Data quality

Researchers using existing data are dependent on the quality of the original data which varies significantly and depends largely on the owners of the data and the purpose for data collection, methods of data collection and information computerization, and the availability of appropriate strategies to control the accuracy of the data. Nevertheless, rigorous study design and appropriate statistical methods are able to mitigate the influence of sub-optimal data. For instance, regression methods can be used to control potential confounding bias. Multiple imputations may be employed to limit the impact of incomplete patient information. As for conducting a systematic review, the lack of enough numbers of clinical trials and high heterogeneity between trials impede the researchers from generating high-quality evidence.

1.5.2 Confounding bias

Research using existing data, particularly the secondary data analysis, is more prone to confounding bias, since the data are collected in advance without randomizing study subjects into different groups. As a result, the association between an exposure and the outcome may be distorted by confounders. However, advanced statistical methods may enable good and reliable control over many confounders.[28]

1.5.3 Lack of comprehensive data in one database

Because the data are not collected for a particular research question, it is commonplace that some important variables and some population subgroups are not available. Therefore, conducting a successful analysis for a given research question commonly requires linking two or more existing databases. Many administrative data have the potential to be linked by a unique health number. However, when there is no unique identifier available for the databases linking, it

has been suggested that probabilistic matching is an effective way to link multiple existing databases.[29]

1.6 Existing data sources

With increasing volumes of databases opening to the public, studies using existing data will contribute substantially to the understanding of the diseases and provide essential information to improve healthcare practice. Choosing appropriate databases is crucial to the success of research using existing data. Here we have compiled some of the most common sources of data that are publicly open or can be obtained by request.

1.6.1 Administrative data from Alberta Health

Alberta Health is the custodian of extensive administrative data in the health system in Alberta, Canada. A number of datasets, which can be linked by unique lifetime identifiers, are available for request. These datasets include Inpatient Discharge Abstract Database, Ambulatory Care Data, Alberta Blue Cross Claims, Practitioner Claims, Vital Statistics, Alberta Continuing Care Information System data, Pharmaceutical Information Network (PIN) Dispenses data, Population Registry, and Longitudinal Demographic Profile data. Detailed information of individual datasets is available online.[30]

1.6.2 APPROACH registry

Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease (APPROACH) is a prospective clinical collection registry capturing all patients receiving cardiac intervention and revascularization in Alberta, Canada, since 1995.[31] The research files in APPROACH are routinely merged with administrative data. This registry contains detailed

clinical information including demographics, common cardiac risk factors, comorbidities, procedure indications, and coronary anatomy.[32] Researchers and administrators may request access to APPROACH data by filling out the data request form.[33]

1.6.3 Alberta's Tomorrow Project

Alberta's Tomorrow Project is a longitudinal cohort launched in 2000, aiming to track the health condition of 55,000 men and women for 50 years in an effort to identify potential causes of chronic diseases and provide guidance for cancer and chronic diseases prevention.[34]

1.6.4 CIHR

Canadian Institutes of Health Research (CIHR) has compiled a list of CIHR funded and non-funded data and analytic platforms,[35] including but not limited to Population Data BC, Canadian Research Data Centre Network, Canadian Longitudinal Study on Aging Data Platform, and Canadian Chronic Disease Surveillance System.

1.6.5 Statistics Canada

Statistics Canada is the national statistical office which provides high-quality information in a variety of aspects, such as births and deaths, taxation records, and population records. There are abundant of data sources that are open to the public or can be accessed through sending a request to Canadian Research Data Centres (RDC) network.[36]

1.6.6 WHO Global Health Observatory data

The Global Health Observatory data repository shares data on global health with an extensive list of indicators, which can be selected by specific themes or through a multi-

dimensional query functionality. It is the World Health Organization's main health statistics repository.[37]

1.6.7 Open data repository

The open data repository is a place where researchers deposit and share data with the scientific community. Here are a list of popular repositories and their official websites.

- Mendeley Data https://data.mendeley.com/
- Figshare https://figshare.com/
- Fairsharing https://fairsharing.org/
- Datadryad https://datadryad.org/amework
- Harvard Dataverse https://dataverse.harvard.edu/

The above data sources are not exhaustive, and more existing data can be found by identifying what data sources have been used in the publications (books, articles, websites etc.) on the topic that you are interested in.[38] If the data cannot be obtained easily, try to contact the original researchers. Governments all over the world collect lots of data, and many of them are publicly available. Identifying the government agencies that tracking or regulating the data on the topic of your research and finding out what data they have made available is another feasible option.[38] Besides, there is a wide range of international organizations, non-profit research centres foundations and academic association that also collect and share data. Researchers are encouraged to visit their websites and check if they possess the data that focus on your research topic. [38]

1.7 Objectives

Despite that a great deal of resources and efforts have been put to address health-related questions, countless unanswered questions remain and new hypotheses keep arising with the advance in healthcare system. Many of them can be addressed by epidemiologic studies using the available data without the primary data collection. Meanwhile, the challenges CVD researchers are facing when conducting research using existing data are less frequently discussed. In the thesis, I aim to address several clinical epidemiologic research questions and controversies in the field of cardiovascular diseases using available data, and discuss the challenges during the research process from a data user's perspective to raise the awareness and to stimulate discussions. The specific aims of this thesis are shown below.

1. To evaluate whether administrative health data can accurately ascertain peripheral artery disease (PAD) in the community when compared to the gold standard ankle-brachial index (ABI) through linking data from administrative database and data from original investigators.

2. To compare and summarize admission rates and hospital length of stay, as well as described the frequency of reporting these two outcomes in randomized control trials (RCTs) comparing different anticoagulant therapies in patients with venous thromboembolism (VTE). (Systematic review)

3. To investigate the relationship between chronic obstructive pulmonary disease (COPD) and angiographically diagnosed CAD by analyzing a large population-based cohort of patients undergoing coronary angiography. (Registry data)

4. To investigate the association between acute atmospheric pressure changes and the occurrence of ST-Elevation Myocardial Infarction (STEMI) by linking registry data and meteorological data.

1.8 References

1. Balakumar P, Maung-U K, Jagadeesh G. Prevalence and prevention of cardiovascular disease and diabetes mellitus. *Pharmacological Research.* 2016;113, Part A:600-609.

2. Donald M. Lloyd-Jones. Epidemiology of Cardiovascular Disease. In: Goldman, Lee. Goldman-Cecil Medicine. 25th ed. New york: Elsevier; 2016. p. 257-262.

3. Benjamin EJ, Virani SS, Callaway CW, et al. Heart disease and stroke statistics—2018 update: a report from the American Heart Association. *Circulation.* 2018;137:e67-e492.

4. Heart disease in Canada. Government of Canada. Available from: https://www.canada.ca/en/public-health/services/publications/diseases-conditions/heart-disease-canada-fact-sheet.html. Accessed on July 31, 2018.

5. Dai S, Bancej C, Bienek A, Walsh P, Stewart P, Wielgosz A. Report summary tracking heart disease and stroke in canada 2009. *Chronic Dis. Inj. Can.* 2009;29.

6. Mozaffarian D. Global Scourge of Cardiovascular Disease: Time for Health Care Systems Reform and Precision Population Health∗. *J. Am. Coll. Cardiol.* 2017;70:26-28.

7. Cardiovascular diseases. World Health Organization. Available from: http://www.who.int/mediacentre/factsheets/fs317/en/. Accessed on June 29, 2018.

8. Agyemang C, van den Born B-J. Limited access to CVD medicines in low-income and middle-income countries: poverty is at the heart of the matter. *The Lancet Global Health.* 2018;6:e234-e235.

9. Cardiovascular Disease. Public Health Agency of Canada. Available from: http://cbpp-pcpe.phac-aspc.gc.ca/chronic-diseases/cardiovascular-diseases/. Accessd on June 29, 2018.

10. Roth GA, Huffman MD, Moran AE, et al. Global and regional patterns in cardiovascular mortality from 1990 to 2013. *Circulation.* 2015;132:1667-1678.

11. Bloom DE, Cafiero, E.T., Jané-Llopis, E., Abrahams-Gessel, S., Bloom, L.R., Fathima, S., Feigl,, A.B. G, T., Mowafi, M., Pandya, A., Prettner, K., Rosenberg, L., Seligman, B., Stein, A., & Weinstein, C. The Global Economic Burden of Noncommunicable Diseases. World Economic Forum, Geneva (2011).

12. Laslett LJ, Alagona P, Clark BA, et al. The worldwide environment of cardiovascular disease: prevalence, diagnosis, therapy, and policy issues: a report from the American College of Cardiology. *J. Am. Coll. Cardiol.* 2012;60:S1-S49.

13. Sagiroglu S, Sinanc D. Big data: A review. *Collaboration Technologies and Systems (CTS), 2013 International Conference on*: IEEE; 2013:42-47.

14. McAfee A, Brynjolfsson E, Davenport TH, Patil D, Barton D. Big data: the management revolution. *Harv. Bus. Rev.* 2012;90:60-68.

15. Feldman B, Martin EM, Skotnes T. Big data in healthcare hype and hope. *Dr. Bonnie.* 2012;360:122-125.

16. Gewin V. Data sharing: An open mind on open data. *Nature.* 2016;529:117-119.

17. Data availability. Public Library of Science(PLOS). Available from: http://journals.plos.org/plosone/s/data-availability. Accessd on June 29, 2018.

18. Connect care. Alberta Health Services. Available from: https://www.albertahealthservices.ca/info/cis.aspx. Accessed on July 2, 2018.

19. Molloy JC. The open knowledge foundation: open data means better science. *PLoS Biol.* 2011;9:e1001195.

20. Srinivasan U, Arunasalam B. Leveraging big data analytics to reduce healthcare costs. *IT professional.* 2013;15:21-28.

21. Dunn SL, Arslanian-Engoren C, DeKoekkoek T, Jadack R, Scott LD. Secondary data analysis as an efficient and effective approach to nursing research. *West. J. Nurs. Res.* 2015;37:1295-1307.

22. Martin L, Hutchens M, Hawkins C, Radnov A. How much do clinical trials cost? *Nat Rev Drug Discov.* 2017;16:381-382.

23. Kayyali B, Knott D, Van Kuiken S. The big-data revolution in US health care: Accelerating value and innovation. *Mc Kinsey & Company.* 2013;2:1-13.

24. Doolan DM, Froelicher ES. Using an existing data set to answer new research questions: a methodological review. *Res. Theory Nurs. Pract.* 2009;23:203.

25. Doolan DM, Winters J, Nouredini S. Answering Research Questions Using an Existing Data Set. *Medical Research Archives.* 2017;5.

26. Hannan EL. Randomized clinical trials and observational studies: guidelines for assessing respective strengths and limitations. *JACC Cardiovasc. Interv.* 2008;1:211-217.

27. Boslaugh S. An introduction to secondary data analysis. *Secondary data sources for public health: A practical guide.* 2007:2-10.

28. Mariani AW, Pego-Fernandes PM. Observational studies: why are they so important? *Sao Paulo Med. J.* 2014;132:01-02.

29. Waien SA. Linking large administrative databases: a method for conducting emergency medical services cohort studies using existing data. *Acad Emerg Med.* 1997;4:1087-1095.

30. Health research in Alberta. Alberta Heath. Available from: http://www.health.alberta.ca/initiatives/health-research.html. Access on June 29, 2018.

31. Shavadia J, Norris CM, Graham MM, Verma S, Ali I, Bainey KR. Symptomatic graft failure and impact on clinical outcome after coronary artery bypass grafting surgery: Results from the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease registry. *Am Heart J.* 2015;169:833-840.

32. Kaila KS, Norris CM, Graham MM, Ali I, Bainey KR. Long-term survival with revascularization in South Asians admitted with an acute coronary syndrome (from the Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease Registry). *Am J Cardiol.* 2014;114:395-400.

33. APPROACH forms. APPROACH. Available from: http://www.approach.org/support_pages/forms.html. Accessed on June 30, 2018.

34. All About Alberta's Tomorrow Project. Alberta's Tomorrow Project. Available from: https://myatp.ca/about-atp . Accessed on July 27,2018.

35. Health research data: resources. Canadian Institutes of Health Research. Available from: http://www.cihr-irsc.gc.ca/e/49941.html. Accessed on June 30, 2018.

36. The Research Data Centres (RDC) network. Statistic Canada. Available from: https://www.statcan.gc.ca/eng/rdc/network. Accessed on Aug 3, 2018.

37. Global Health Observatory (GHO) data. World Health Organization(WHO). Available from: http://www.who.int/gho/database/en/. Accessed on July 2, 2018.

38. Using Existing Data. DeWitt Wallace Library. Available from: https://libguides.macalester.edu/c.php?g=545757&p=3743355. Accessed on July 27,2018.

Chapter 2: Administrative data are not sensitive for the detection of peripheral artery disease in the community*

Abstract

We sought to evaluate whether case ascertainment using administrative health data would be a feasible way to identify peripheral arterial disease (PAD) patients from the community. Subjects' ankle-brachial index (ABI) scores from two previous prospective observational studies were linked with International Classification of Diseases (ICD) and Canadian Classification of Interventions (CCI) codes from three administrative databases from April 2002 to March 2012, including the Alberta Inpatient Hospital Database (ICD-10-CA/CCI), Ambulatory Care Database (ICD-10-CA/CCI), and the Practitioner Payments Database (ICD-9-CM). We calculated diagnostic statistics for putative case definitions of PAD consisting of individual code or sets of codes, using ABI score ≤ 0.90 as the gold standard. Multivariable logistic regression was performed to investigate additional predictive factors for PAD. Different combinations of diagnostic codes and predictive factors were explored to find out the best algorithms for identifying a PAD study cohort. A total of 1459 patients were included in our analysis. The average age was 63.5 years, 66% were male, and the prevalence of PAD was 8.1%. The highest sensitivity 34.7% was obtained using the algorithm of at least one ICD diagnostic or procedure code, with specificity 91.9%, positive predictive value (PPV) 27.5% and negative predictive value (NPV) 94.1%. The algorithm achieving the highest PPV of 65% was age ≥70 years and at least one code within 443.9 (ICD-9-CM), I73.9, I79.2 (ICD-10-CA/CCI) or all procedure codes, validated with ABI< 1.0 (sensitivity 5.56%, specificity 99.4% and NPV 84.6%). In conclusion,

ascertaining PAD using administrative data scores was insensitive compared with the ABI, limiting the use of administrative data in the community setting.

Keywords: ankle-brachial index, ICD, CCI, administrative data, peripheral arterial disease

* A version of this work has been published: *Hong Y, Sebastianski M, Makowsky M, Tsuyuki R, McMurtry MS. Administrative data are not sensitive for the detection of peripheral artery disease in the community. Vascular Medicine. 2016 Aug; 21(4):331-6.*

2.1 Background

Lower extremity peripheral arterial disease (PAD) is an atherosclerotic disease that is often overlooked clinically[1] and is understudied relative to other important medical conditions.[2] The ascertainment of PAD involves measurement of the ankle-brachial index (ABI), which is used to diagnose PAD when less than or equal to 0.90.[3] Despite guideline recommendations to use the resting ABI to establish a PAD diagnosis in patients with exertional leg symptoms, non-healing wounds, age 65 and older, or age 50 with a history of smoking or diabetes,[3] many subjects with PAD are not identified by routine care.[1] Population-based studies evaluating PAD epidemiology using the ABI to ascertain the true prevalence PAD are expensive and time-consuming and typically limited by small numbers of cases as well as cross-sectional design, precluding analyses of trends over time or estimates of incidence.[4-10]

Collected as part of routine care, administrative data utilize the standard International Classification of Disease (ICD) codes and procedure codes that describe a patient's diagnosis and medical care and are an inexpensive and powerful tool for epidemiology and outcomes research. An important criterion for use of administrative data to study a specific disease state is an adequately accurate case definition, as diagnostic algorithms based on administrative data have variable sensitivity, specificity, and positive and negative predictive values.[11] Often a single ICD code is inadequate to accurately identify a disease, especially those of low prevalence, and derivation of an algorithm from multiple data points such as age, gender or related disease and procedure codes can provide better case definitions with improved diagnostic statistics.[12]

Administrative data have been used to study various forms of PAD, but typically ascertain forms of PAD requiring revascularization,[13, 14] such as critical limb ischemia (CLI).[15, 16]

While validated case definitions for CLI exist,[17] most patients with PAD do not have CLI, do not require revascularization, and may be asymptomatic[18]; therefore, relying on hospitalizations or revascularization procedures to ascertain PAD is not sensitive, or will bias towards advanced disease or severe symptoms. Fan et al evaluated the validity of ICD-9 PAD codes as well as a multivariable combination of diagnostic and procedural codes to ascertain PAD compared with the ABI in 22,712 subjects attending the vascular laboratory at the Mayo Clinic between 1998 and 2008 and 4420 subjects from the community.[19] They found that the ascertainment of PAD based on ICD-9 diagnostic codes solely was limited by low sensitivity (38.7%, 95% CI 27.6%-50.6%) when applied to the community sample, but the incorporation of procedure codes using a multivariable model improved sensitivity (68%, 95% CI 56.2%-78.3%) when compared to the gold standard of chart review in the community sample.[19] A key limitation of this study was that ABI was not used for diagnosis in the community sample, which was the final validation set, and the authors stated that "additional work is needed to assess the performance of algorithms for identifying PAD cases and controls at other institutions."[19]

We sought to evaluate whether administrative health data can accurately ascertain PAD in the community when compared to the gold standard ABI, based on ICD diagnostic codes, procedure codes, or a combination of codes and common clinical factors in a multivariable model. [20]

2.2 Methods

We conducted a validation study of administrative data, including ICD and Canadian Classification of Intervention (CCI) codes, to identify a PAD cohort using the ABI as the

reference standard. This study was approved by The Health Research Ethics Board of the University of Alberta.

2.2.1 Study population

We combined data from two prospective cohorts identified in Alberta, Canada, to form our dataset. EpiPAD is a prospective study of lower extremity PAD in ambulatory health settings.[21] Patients 50 years of age or older were consecutively screened in community pharmacies (urban and rural), family medicine clinics (urban) and a community cardiology clinic (urban) in Alberta during 2008 with 361 undergoing ABI measurement. Patients were excluded from the study if they: (1) had dementia; (2) had undergone recent major surgery; (3) had a prior lower extremity amputation; (4) were wheelchair bound; (5) had open ulcers or sores on their lower extremities; (6) were medically unstable; (7) or were unable to communicate in English. The ABI study is a prospective observational cohort study of ABI as a predictor of outcomes in coronary artery disease.[22] Adults with the suspected coronary disease who had been referred for a coronary angiogram were consecutively sampled from the Cardiac Catheterization Lab waiting room and the Cardiology inpatient wards at the Mazankowski Alberta Heart Institute and the Royal Alexandra Hospital in Edmonton, Alberta. Patients were excluded from this study if they: (1) were heart transplant patients; (2) were being assessed for pulmonary hypertension, valve disease or congenital heart disease; (3) had open ulcers or sores on their lower extremities; (4) were emergency cases/medically unstable; (5) or were unable to communicate in English. Both outpatients and inpatients waiting for their angiogram were included in the study and had their ABI measured prior to their catheterization procedure. Data collection began in March 2010 and concluded in August 2012 (n=1100).

2.2.2 Reference Standard – ABI scores

ABI ≤ 0.90 was used as the gold standard for the ascertainment of PAD.[23] ABI was assessed by a trained research assistant on each patient.[21, 22] After the patient rested in a supine position for at least five minutes, manual non-simultaneous systolic blood pressure was measured at the brachial, posterior tibial, and dorsalis pedis arteries bilaterally using an L150 Summit Doppler (Wallach Surgical, Trumbull, Connecticut) with an 8-MHz vascular probe. [21, 22] The ABI was calculated as the ratio of the highest systolic pressure of either the dorsalis pedis or posterior tibialis arteries in each leg and the highest systolic pressure in either of the brachial arteries.[22]

2.2.3 Administrative Data

Three administrative databases were used in this study. The Inpatient Discharge Abstract Database (DAD) and Ambulatory Care Data (ACD) include the diagnosis and procedure codes for patients discharged from any inpatient bed in Alberta.[24] Since 2002 the International Classification of Diseases, Tenth Revision, Canada/Canadian Classification of Health Interventions (ICD-10-CA/CCI) coding has been used where up to 25 diagnosis codes can be listed per patient in DAD and 10 diagnosis codes per patient in ACD, which allows practitioners to input more diagnostic or procedure codes in the system.[24, 25] This difference did not affect the codes, since all of our patients were enrolled after 2002. The Practitioner Payments Database (PPD) includes the fee for service claims from 1994 to present with up to three ICD codes.[24, 25] The PPD only uses International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) coding, therefore we combined ICD-9-CM with ICD-10- CA/CCI. As inpatients are more likely to have more severe diseases and comorbidities, using multiple databases decreases potential selection bias in future research studies that apply our derived PAD case definition since both inpatients and patients in the community are represented. Three

administrative databases were linked with the ABI and EpiPAD cohorts using personal health numbers as the unique identifier. We selected ICD codes related to atherosclerosis, cardiovascular disease, diabetes, peripheral arterial disease and procedure codes related to the same diseases or conditions for validation (Table 1). Putative case definitions for PAD using individual or combinations of codes, as well as PAD codes combined with other demographic and comorbidity variables ascertained by subjects' responses and chart information, were evaluated.

2.2.4 Statistical Analysis

Descriptive statistics were used for demographic variables. Multivariable logistic regression was performed to develop the optimal algorithm. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+) and negative likelihood ratio (LR-) were calculated for each ICD code related to a PAD diagnosis with corresponding 95% CIs. The performances for these codes within the databases informed the development of potential algorithms. Once potential algorithms were developed, sensitivity, specificity, PPV, NPV, LR+ and LR- were calculated for each algorithm. ABI is accepted in the literature as a dichotomous measure for PAD, and an ABI score of ≤ 0.90 is considered a diagnostic standard for PAD.[3] To potentially enhance sensitivity, a repeat calculation of the sensitivity, specificity, PPV, NPV, LR+ and LR- was done using ABI < 1.0 as the gold standard, which is interpreted as either abnormal or borderline abnormal.[3] We performed similar analyses using ABI < 0.4 as our reference standard to examine if CLI, as the severe form of PAD, could yield a better performance.

All statistical analyses were performed with the statistical software STATA (version13.1; StataCorp LP, College Station, TX, USA).

2.3 Results

A total of 1459 patients were included in our analyses. Two patients were excluded due to incomplete ABI data. The average age of the study subjects was 63.5 years, and 66% of them were male. There were 23 patients who underwent an endovascular procedure and six patients who had evidence of CLI. Other standard cardiovascular risk factors, including smoking (58%, 95% CI 56-61%), diabetes (31%, 95% CI 28-33%), hypertension (73%, 95% CI 70-75%), and hyperlipidemia (76%, 95% CI 74-79%) were commonly present in the subjects. The ABI-based prevalence of PAD in the dataset was 8.1% (Table 1). The PAD-related ICD codes and their associated numbers of cases identified are listed in Table 2.

Multivariable logistic regression demonstrated that the standard risk factors were associated with PAD in our dataset. Patients who were elderly (OR 1.08, 95% CI 1.05-1.11), had diabetes (OR 2.12, 95% CI 1.28-3.52) or were smokers (OR 2.45, 95% CI 1.40-4.31) had significantly higher odds of having PAD (Table 3).

The validity of ICD-9-CM and ICD-10-CA/CCI for each code is shown in Table 4 and 5. The sensitivity for single ICD code was low, ranging from 0.85 to 30.5%. The prevalence of PAD was low based on ICD codes with the prevalence measured at only 1% when ascertained by 443.9 (ICD-9-CM). The most specific ICD code in ICD-9-CM coding system identifying PAD patients was 443.9, with sensitivity 10.1% (95% CI 4.7-18.3%), specificity 99.4% (95% CI 98.7-99.8%), PPV 64.3% (95% CI 35.1-87.2%), NPV 91.6% (95% CI 89.7-93.3%), LR+ 17.8 (95% CI 6.09-51.9), and LR- 0.90 (95% CI 0.84-0.97). For the ICD-10-CA/CCI codes, the ICD code

identifying PAD patients with the highest PPV was the procedure code KG.57.^^, with sensitivity 3.39% (95% CI 0.93-8.45%), specificity 99.7% (95% CI 99.2-99.8%), PPV 50% (95% CI 15.7-84.3%), NPV 92.1% (95% CI 90.6-93.5%), LR+ 11.4 (95% CI 2.88-44.9), and LR- 0.97 (95% CI 0.94-1.00).

For putative case definitions for PAD, including the combinations of ICD codes and additional comorbidity or demographic data, the highest sensitivity 34.7% (95% CI 26.2-44.1%) was obtained by the algorithm of at least one ICD PAD diagnostic code, with specificity 91.9% (95% CI 90.4-93.3%), PPV 27.5% (95% CI 20.5-35.4%) and NPV 94.1% (95% CI 92.7-95.3%; Table 6). The case definition achieving the highest PPV 65% (95% CI 40.8-84.6%) was age ≥ 70 years and at least one code within 443.9 (ICD-9-CM), I73.9, I79.2 (ICD-10-CA/CCI) or any procedure code, validated with the alternative gold standard of ABI< 1.00, which is interpreted as abnormal or borderline abnormal, with sensitivity 5.56% (95% CI 2.99-9.31%), specificity 99.4% (95% CI 98.8-99.8%) and NPV 84.6% (95% CI 82.7-86.5%).

2.4 Discussion

We found that using administrative data to identify PAD patients was specific but not sensitive in the community. The highest sensitivity 34.7% was obtained by ascertaining PAD using at least one ICD diagnostic or procedure code, with a specificity of 91.9%. The most specific algorithm with the highest PPV 65% was age ≥ 70 years and at least one code within 443.9 (ICD-9-CM), I73.9, I79.2 (ICD-10-CA/CCI) or any procedure code, but this result was achieved by relaxing the ABI criterion to ABI < 1.0 (sensitivity 5.56%, specificity 99.4% and NPV 84.6%). Our data support that many true cases of PAD, defined as ABI ≤ 0.90, which were asymptomatic or minimally symptomatic, fail to be identified in the community, and thus do not

appear in the administrative data. There are at least two key implications of these findings: 1) PAD remains under-diagnosed in the community, and 2) administrative data are likely too insensitive to be reliably used to ascertain the complete burden of PAD in epidemiological research since most cases would not be identifiable using administrative data alone.

Fan et al[19] found that ascertainment of PAD based on ICD-9-CM codes had 68-85.5% sensitivity and 82.6-87.6% of specificity in their Mayo Clinic dataset, but also found low sensitivity (38.7%, 95% CI 27.6%-50.6%) when their ascertainment algorithm was applied to the community sample using chart review as the gold standard. Our study, in which the ABI was used as the gold standard for all subjects, confirmed a relatively low sensitivity of 34.7% (95% CI 26.2-44.1%) for ascertaining PAD using administrative data. The better performance of administrative data in the Mayo Clinic subset used in the Fan paper might be explained by differences in clinical practice within and outside the Mayo Clinic, including different rates in using screening ABI tests, and different PAD prevalence within and outside the Mayo Clinic. However, both our data and the data from Fan et al support that administrative data is an insensitive approach to ascertain PAD in the community.

Our study has limitations. The inclusion of the participants in the study was not random, but they were consecutively sampled. Also, a large portion of our participants was referred for a coronary angiogram, and so it is possible our sample differs from the community population due to referral bias. However, since the prevalence of PAD we found in our sample is similar to the prevalence expected based on demographic and comorbidity data, we believe our sample likely does accurately represent our community. Moreover, it is likely that any bias in our sample would toward having more cases of PAD, rather than less, so the low sensitivity for ICD codes for ascertaining PAD in our sample would likely also be seen in a true population-based sample.

Also, some selection bias may exist, as patients who had a prior lower extremity amputation were excluded from the EpiPAD dataset. We were unable to include patients with non-compressible vessels in our PAD definition, as we did not have data on toe brachial index which may underestimate the accuracy of the coding. It is possible that some values of ABI could possibly be measured after remote lower extremity revascularization outside Alberta, which might result in some misclassification bias. In addition, our study evaluated data from the province of Alberta, which has a single-payer universal healthcare system, and our findings may not be completely generalizable to other regions with different healthcare providers.

Our study also has several strengths. First of all, we used the ABI to ascertain PAD in all subjects. To our knowledge, this is the first study to use the ABI to validate the diagnostic accuracy of administrative data using subjects not recruited from a vascular laboratory. In addition, not only did we investigate the validity of each proposed diagnostic code, but also utilized multivariable logistic regression to create an algorithm from the administrative dataset to improve diagnostic accuracy. In addition, we also explored the reference standard of ABI < 1.0, which enable us to achieve the highest PPV of 65%. We also examined the CLI standard of ABI<0.4 to explore if there is any difference in the sensitivity and specificity of the coding in subjects with severe forms of PAD. However, the validity was still low. The case definition achieving the best result was Age ≥ 70 plus at least one of ICD 443.9, I73.9, I79.2 or any procedure code (sensitivity 33.3%, specificity 98.8% and PPV 10%, NPV 99.7%, LR+ 26.9, LR-0.675).

2.5 Conclusion

In conclusion, administrative data are specific but not sensitive for the ascertainment of PAD when compared to ABI ≤ 0.90, suggesting that PAD is under-diagnosed in the community and that administrative data cannot be used reliably to identify all forms of PAD in the community. While restrictive case definitions can increase PPV to more accurately identify true cases, this approach is very insensitive.

Table 2. 1. Baseline Characteristics of Study Subjects (Total N=1459)

Characteristics	**Point estimates**	**95% confidence interval**
Age, years	63.5±11.1	(62.9, 64.1)
Gender, male	66%	(64, 69)
Smoking	58%	(56, 61)
Diabetes	31%	(28, 33)
Hypertension	73%	(70, 75)
Hyperlipidemia	76%	(74, 79)
PAD (ABI ≤ 0.90)	8.1%	(6.7, 9.6)

PAD, peripheral artery disease; ABI, ankle-brachial index.

Table 2. 2. International Classification of Diseases (ICD) and Canadian Classification of Intervention (CCI) codes for validation with ankle–brachial index scores

ICD Code	Disease or Procedure	Numbers of subjects identified by each code, n, (%)
ICD-9-CM		
440	Any atherosclerosis	92 (6.3%)
440.2	Atherosclerosis of native arteries of the extremities	0
440.21	Intermittent claudication	0
440.23	Atherosclerosis, extremities with ulceration	0
443	Other peripheral vascular disease	0
443.9	Peripheral vascular disease, unspecified	14 (1.0%)
38.08	Incision of vessel, embolectomy, thrombectomy, lower limb arteries	0
38.18	Endarterectomy, lower limb vessels	0
39.25	Aorta-iliac-femoral bypass	0
39.29	Other peripheral shunt or bypass	0
39.50	Angioplasty of non-coronary vessel	0
39.90	Insertion of non-drug-eluting peripheral vessel stent	0
ICD-10-CA		
I70	Atherosclerosis	0

I70.2	Atherosclerosis of arteries of extremities	4 (0.3%)
I70.8	Atherosclerosis of other arteries	0
I70.9	Generalized and unspecified atherosclerosis	0
I73	Other peripheral vascular diseases	0
I73.9	Peripheral vascular disease, unspecified	33 (2.3%)
I79.2	Peripheral angiopathy in diseases classified elsewhere (diabetes E10)	23 (1.6%)
E10.50	Type I diabetes mellitus with peripheral angiopathy	0
E10.51	Type I diabetes mellitus with peripheral angiopathy with gangrene	0
E10.59	Type I diabetes mellitus with circulatory complication, unspecified	0
ICD-10-CCI		
1.KG.50.^^	Dilation, arteries of leg NEC (angioplasty, lower limb arteries)	10 (0.7)
1.KG.57.^^	Extraction, arteries of leg NEC (endarterectomy, lower limb arteries)	8 (0.5%)
1.KG.76.^^	Bypass, arteries of leg NEC	11 (0.8%)

Six of the patients were identified with 2 procedure codes.

ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CA, International Classification of Diseases, Tenth Revision, Canada; CCI, Canadian Classification of health Interventions; NEC, not elsewhere classified.

Table 2. 3. Results of multivariable logistic regression of ankle-brachial index ≤ 0.90

Characteristics	**Odds ratio**	**p-value**	**95% CI**
Age	1.08	0.000	1.05-1.11
Gender, male	0.57	0.038	0.34-0.96
Hypertension	1.39	0.329	0.72-2.71
Hyperlipidemia	1.21	0.579	0.61-2.39
Diabetes	2.12	0.004	1.28-3.52
Smoking	2.45	0.002	1.40-4.31

CI, confidence interval.

Table 2. 4. The validity of ICD-9-CM codes compared with ankle-brachial index ≤ 0.90

ICD codes*	Sensitivity	Specificity	PPV	NPV	LR+	LR-
440	27.7% [18.9-37.8%]	93.1% [91.3-94.6%]	28.3% [19.4-38.6%]	92.9% [91.1-94.5%]	4.01 [2.69-6]	0.78 [0.69-0.89]
443	20.2% [12.6-29.8%]	97.8% [96.7-98.6%]	47.5% [31.5-63.9%]	92.6% [90.8-94.1%]	9.22 [5.15-16.5]	0.82 [0.74-0.90]
443.9	10.1% [4.73-18.3%]	99.4% [98.7-99.8%]	64.3% [35.1-87.2%]	91.6% [89.7-93.3%]	17.8 [6.09-51.9]	0.90 [0.84-0.97]
440 or 443 or 443.9	30.5% [22.4-39.7%]	94.1% [92.7-95.3%]	31.3% [23.0-40.6%]	93.9% [92.5-95.1%]	5.18 [3.66-7.32]	0.74 [0.66-0.83]

* Diagnostic codes or procedure codes with no cases are not shown.

95% confidence intervals are shown in square brackets.

ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; PPV, positive predictive value; NPV, negative predictive value; LR+, positive likelihood ratio; LR-, negative likelihood ratio.

Table 2. 5. The validity of ICD-10-CA/CCI codes compared with ankle-brachial index ≤ 0.90

ICD codes[a]	Sensitivity	Specificity	PPV	NPV	LR+	LR-
I70.2	0.85% [0.02-4.63%]	99.8% [99.3-100%]	25% [0.63-80.6%]	92% [90.4-93.3%]	3.79 [0.40-36.1]	0.994 [0.98-1.01]
I73.9	10.2% [5.37- 17.1%]	98.4% [97.6-99%]	36.4% [20.4-54.9%]	92.6% [91.1-93.9%]	6.49 [3.28-12.9]	0.91 [0.86-0.97]
I79.2	8.47% [4.14- 15%]	99% [98.3-99.5%]	43.5% [23.2-65.5%]	92.5% [91-93.8%]	8.74 [3.92-19.5]	0.92 [0.88-0.98]
KG.50.^^	3.39% [0.93-8.45%]	99.6% [99-99.8%]	40% [12.2-73.8%]	92.1% [90.6-93.5%]	7.58 [2.17-26.5]	0.97 [0.94-1]
KG.57.^^	3.39% [0.93-8.45%]	99.7% [99.2-99.9%]	50% [15.7-84.3%]	92.1% [90.6-93.5%]	11.4 [2.88-44.9]	0.97 [0.94-1]
KG.76.^^	4.24% [1.39-9.61%]	99.6% [99-99.8%]	45.5% [16.7-76.6%]	92.2% [90.7-93.5%]	9.47 [2.93-30.6]	0.96 [0.93-0.99]
Combination[b]	19.5% [12.8-27.8%]	97% [96-97.9%]	36.5% [24.7-49.6%]	93.2% [91.7-94.5%]	6.53 [4.06-10.5]	0.83 [0.76-0.91]

[a]I70, I70.9, I73 were not shown since there were no cases.

[b]At least one of the above ICD10 codes.

95% confidence intervals are shown in square brackets.

ICD-10-CA/CCI, International Classification of Diseases, Tenth Revision, Canada/Canadian Classification of Interventions; PPV, positive predictive value; NPV, negative predictive value; LR+, positive likelihood ratio; LR-, negative likelihood ratio.

Table 2. 6. The combinatorial case definitions of peripheral artery disease using administrative data

ICD codes	Sensitivity	Specificity	PPV	NPV	LR+	LR-
Definition 1	34.7% [26.2-44.1%]	91.9% [90.4-93.3%]	27.5% [20.5-35.4%]	94.1% [92.7-95.3%]	4.31 [3.18-5.86]	0.71 [0.62-0.81]
Definition 2	18.6% [12.1-26.9%]	97.8% [96.8-98.5%]	42.3% [28.7-56.8%]	93.2% [91.7-94.4%]	8.33 [4.97-14]	0.83 [0.76-0.91]
Definition 3	11.9% [6.64-19.1%]	98.9% [98.2-99.4%]	48.3% [29.4-67.5%]	92.7% [91.3-94%]	10.6 [5.25-21.4]	0.89 [0.83-0.95]
Definition 4	9.32% [4.75-16.1%]	99.3% [98.7-99.7%]	55% [31.5-76.9%]	92.6% [91.1-93.9%]	13.9 [5.87-32.8]	0.91 [0.86-0.97]
Definition 5	5.56% [2.99-9.31%]	99.4% [98.8-99.8%]	65% [40.8-84.6%]	84.6% [82.7-86.5%]	9.72 [3.92-24.1]	0.95 [0.92-0.98]
Definition 6	33.3% [4.33-77.7%]	98.8% [98.0-99.3%]	10% [1.23-31.7%]	99.7% [99.3-99.9%]	26.9 [7.93-91.2]	0.67 [0.38-1.19]

Definition 1: At least one of the codes listed in the proposed codes list.

Definition 2: At least one of ICD443.9, I73.9, I79.2 or any procedure code.

Definition 3: Definition 2 and age $\geq$ 65.

Definition 4: Definition 2 and age $\geq$ 70.

Definition 5: Definition 4 validated with ankle-brachial index < 1.0 and as the gold standard.

Definition 6: Definition 4 validated with ankle-brachial index < 0.4 and as the gold standard.

95% confidence intervals are shown in square brackets.

ICD, International Classification of Diseases; PPV, positive predictive value; NPV, negative predictive value; LR+, positive likelihood ratio; LR−, negative likelihood ratio.

2.6 References

1. Hirsch AT, Criqui MH, Treat-Jacobson D, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. *JAMA.* 2001;286:1317-1324.

2. Jaff MR. Why patients know more about cars than peripheral artery disease. *Circulation.* 2014;130:1778-1779.

3. Rooke TW, Hirsch AT, Misra S, et al. Management of patients with peripheral artery disease (compilation of 2005 and 2011 ACCF/AHA Guideline Recommendations): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2013;61:1555-1570.

4. Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999-2000. *Circulation.* 2004;110:738-743.

5. Liang Y, Yan Z, Sun B, et al. Cardiovascular risk factor profiles for peripheral artery disease and carotid atherosclerosis among Chinese older people: a population-based study. *PLoS One.* 2014;9:e85927.

6. Diage TR, Johnson G, Ravipati G. Digital ankle-brachial index technology used in primary care settings to detect flow obstruction: a population based registry study. *BMC Res Notes.* 2013;6:404.

7. Ohnishi H, Sawayama Y, Furusyo N, Maeda S, Tokunaga S, Hayashi J. Risk factors for and the prevalence of peripheral arterial disease and its relationship to carotid atherosclerosis: the Kyushu and Okinawa Population Study (KOPS). *J Atheroscler Thromb.* 2010;17:751-758.

8. Kroger K, Dragano N, Stang A, et al. An unequal social distribution of peripheral arterial disease and the possible explanations: results from a population-based study. *Vascular medicine.* 2009;14:289-296.

9. Blanes JI, Cairols MA, Marrugat J, Estime. Prevalence of peripheral artery disease and its associated risk factors in Spain: The ESTIME Study. *Int Angiol.* 2009;28:20-25.

10. Sigvant B, Wiberg-Hedman K, Bergqvist D, et al. A population-based study of peripheral arterial disease prevalence with special focus on critical limb ischemia and sex differences. *Journal of vascular surgery.* 2007;45:1185-1191.

11. Tonelli M, Wiebe N, Fortin M, et al. Methods for identifying 30 chronic conditions: application to administrative data. *BMC Med Inform Decis Mak.* 2015;15:31.

12. Van Walraven C, Austin PC, Manuel D, Knoll G, Jennings A, Forster AJ. The usefulness of administrative databases for identifying disease cohorts is increased with a multivariate model. *Journal of clinical epidemiology.* 2010;63:1332-1341.

13. Al-Omran M, Tu JV, Johnston KW, Mamdani MM, Kucey DS. Outcome of revascularization procedures for peripheral arterial occlusive disease in Ontario between 1991 and 1998: a population-based study. *Journal of vascular surgery.* 2003;38:279-288.

14. Al-Omran M, Tu JV, Johnston KW, Mamdani MM, Kucey DS. Use of interventional procedures for peripheral arterial occlusive disease in Ontario between 1991 and 1998: a population-based study. *Journal of vascular surgery.* 2003;38:289-295.

15. Kolossvary E, Ferenci T, Kovats T, et al. Trends in Major Lower Limb Amputation Related to Peripheral Arterial Disease in Hungary: A Nationwide Study (2004-2012). *European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery.* 2015;50:78-85.

16. Malyar N, Furstenberg T, Wellmann J, et al. Recent trends in morbidity and in-hospital outcomes of in-patients with peripheral arterial disease: a nationwide population-based analysis. *European heart journal.* 2013;34:2706-2714.

17. Bekwelem W, Bengtson LG, Oldenburg NC, et al. Development of administrative data algorithms to identify patients with critical limb ischemia. *Vascular medicine.* 2014;19:483-490.

18. Widener JM. Peripheral arterial disease and disability from NHANES 2001-2004 data. *J Vasc Nurs.* 2011;29:104-112.

19. Fan J, Arruda-Olson AM, Leibson CL, et al. Billing code algorithms to identify cases of peripheral artery disease from administrative data. *Journal of the American Medical Informatics Association : JAMIA.* 2013;20:e349-354.

20. Criqui MH, Aboyans V. Epidemiology of peripheral artery disease. *Circ Res.* 2015;116:1509-1526.

21. Makowsky M, McMurtry MS, Elton T, et al. Prevalence and treatment patterns of lower extremity peripheral arterial disease among patients at risk in ambulatory health settings. *The Canadian journal of cardiology.* 2011;27:389 e311-388.

22. Sebastianski M, Narasimhan S, Graham MM, et al. Usefulness of the ankle-brachial index to predict high coronary SYNTAX scores, myocardium at risk, and incomplete coronary revascularization. *Am J Cardiol.* 2014;114:1745-1749.

23. Abramson BL, Huckell V, Anand S, et al. Canadian Cardiovascular Society Consensus Conference: peripheral arterial disease-executive summary. *The Canadian journal of cardiology.* 2005;21:997-1006.

24. The Overview of Administrative Health Datasets. Alberta Health. Available from: https://open.alberta.ca/dataset/overview-of-administrative-health-datasets. Accessed on July 12,2018.

25. Chen G, Khan N, Walker R, Quan H. Validating ICD coding algorithms for diabetes mellitus from administrative data. *Diabetes Res. Clin. Pract.* 2010;89:189-195.

Chapter 3: Effect of anticoagulants on admission rates and length of hospital stay for acute venous thromboembolism: a systematic review of randomized control trials*

Abstract

Background: There is a paucity of studies available on hospitalization and length of stay (LOS) for different anticoagulant therapies. We sought to compare and summarize admission rates and LOS and describe the frequency of reporting these two outcomes in randomized control trials (RCTs) comparing different anticoagulant therapies for venous thromboembolism (VTE).

Methods: A literature search was conducted from inception to August 15, 2016 on RCTs of anticoagulant therapy for patients with VTE. Study selection, data extraction and risk of bias analysis were done by two reviewers independently. Meta-analyses were conducted for admission rates and LOS.

Results: A total of 4064 articles were identified. There were 74 articles of 70 studies included in the analysis. Hospitalization rates and LOS were reported in 13 (18.6%) and 12 (17.1%) of the 70 included studies, respectively. Low-molecular-weight heparin (LMWH)-treated patients were 33.0% less likely to be admitted to hospitals compared to unfractionated heparin (UFH) (RR=0.67, 95% CI [0.58, 0.78]). The mean difference in LOS between LMWH and UFH was 2.54 days in favor of LMWH (95% CI [-4.94, -0.14]). Compared to parenteral therapy, using rivaroxaban was associated with a lower admission rate for a difference of 1.4-5.1% in VTE, 2.5% in DVT and 0.2% in PE. The LOS of patients receiving rivaroxaban was significantly shorter than that in the parenteral therapy group for a difference of 1-5 days in VTE, 3 days in DVT and 1 day in PE.

Conclusion: Admission rates were lower and LOS was shorter when using LMWH compared to UFH and oral therapy compared to parenteral therapy for acute VTE treatment in RCTs, based on limited eligible RCTs. These crucial clinically relevant outcomes are underreported in the existing VTE clinical trials.

Keywords: Anticoagulants, admission rates, length of stay, venous thromboembolism, systematic review, deep vein thrombosis, pulmonary embolism

* A version of this work has been published: *Hong Y, Mansour S, Alotaibi G, Wu C, McMurtry MS. Effect of anticoagulants on admission rates and length of hospital stay for acute venous thromboembolism: A systematic review of randomized control trials. Crit Rev Oncol Hematol. 2018;125:12-8.*

3.1 Introduction

Venous thromboembolism (VTE), which comprises deep vein thrombosis (DVT) and pulmonary embolism (PE), is the third most common cause of cardiovascular death following myocardial infarction and stroke.[1] VTE places significant clinical and economic burden on the healthcare system. The estimated annual incidence of VTE is approximately 5 persons per 10,000,[2] and the economic burden of VTE is considerable, costing more than $1.5 billion/year in the United States.[3] Anticoagulant therapy is the mainstay of treatment for VTE.[4] Historically, conventional therapy involved parenteral anticoagulants for at least 5 days and vitamin K antagonists (VKAs) started concurrently and continued for at least 3 months.[5]

Over the last few decades, there has been an evolution in antithrombotic therapy with a transition from parenteral to newer anticoagulants. While unfractionated heparin (UFH) was widely used, low-molecular-weight heparin (LMWH) safely replaced it due to convenience and possibility of outpatient administration. Longer term treatment was delivered through VKAs.[6] However, these agents were limited by the need of frequent monitoring and dose adjustment. Direct oral anticoagulants (DOAC) are now available and address some of these limitations.[7]

While recurrent VTE and major bleeding have been the traditional primary efficacy and safety outcomes in VTE trials, the rate of hospitalization and the length of stay (LOS) are also important. The latter two are frequently overlooked outcomes. Hospital admissions are associated with potential complications such as hospital-acquired infections, neurological complications and other life-threatening diagnoses.[8, 9] These complications result in a delay of recovery and return to normal activities. They also prolong hospital stay and add higher costs to the healthcare system.[10, 11] In-hospital complications occur in 5.7% to 7.5% of admitted patients,[12, 13] and result in an increase in the LOS by an average of 8 days.[14] LOS has been

treated as a great marker for measuring patients' quality of care. Within the context of shrinking healthcare budgets and the aging populations with complex healthcare needs,[15] a better understanding of the effect of different anticoagulants therapy on VTE is urgently needed to reduce unnecessary inpatient treatment.

There is no prior review summarizing the impact of different anticoagulants on hospitalization rates and LOS for VTE. We sought to compare and summarize admission rates and hospital LOS and describe the frequency of reporting these two outcomes in randomized control trials (RCTs) comparing different anticoagulant therapies for VTE.

3.2 Methods

The following study was done in accordance with a review protocol established a priori, which is available on request to the authors. This study was registered in PROSPERO. This review was reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

3.2.1 Selection criteria

We included all RCTs comparing two different anticoagulant therapy regimens for acute VTE. The primary outcomes of our study were LOS and admission rates. The secondary outcome was the reporting rate of these two outcomes in the existing RCTs.

To improve the homogeneity of selected trials, studies were excluded if: 1. comparing different doses of the same anticoagulants; 2. evaluating thrombolysis; 3. evaluating inferior vena cava filters; 4. evaluating surgical thrombectomy; 5. focused on a specific group of patients

such as renal diseases, pregnant women, critically ill patients, extended therapy, or cardiac diseases; 5. pharmacokinetic studies; 6. evaluating DVT prophylaxis.

3.2.2 Search methods

A literature search was conducted on MEDLINE and EMBASE via Ovid platform from inception to August 15, 2016. A librarian was consulted during the developing of the search strategy. A full list of the search strategy was provided in Appendix A. The search was limited to the studies of human adult participants. No language or date restriction was applied. We also checked the reference lists of eligible studies for additional relevant articles.

3.2.3 Study selection and data extraction

Two reviewers independently screened for eligible articles by titles and abstracts using the selection criteria. The full-texts of eligible studies were retrieved and reviewed by two reviewers afterward. We solved disagreement by consensus. A senior author was consulted if the disagreement was unresolved. All eligible articles in accordance with the selection criteria were considered for data extraction.

After an agreement on studies included for data extraction was made, two reviewers independently extracted the data using the same pilot tested data extraction form. The main data items collected were patient characteristics, anticoagulants used, and all of the outcomes reported in the trials. Primary authors were contacted if additional information was needed.

3.2.4 Data analyses

Two reviewers independently evaluated included studies which reported admission rate or LOS using the recommended risk of bias tool described in the Cochrane Handbook for Systematic Reviews of Interventions.[16] A high, low, or unclear risk would be assigned to seven

domains including random sequence generation, allocation concealment, blinding of participants, personnel and outcome adjudicators, incomplete outcome assessment, selective reporting, and other sources of bias. Because it is recommended that funnel plot and test for asymmetry should not be used in the meta-analysis if fewer than ten studies are included,[17] we would not use a funnel plot if less than ten studies were included in the meta-analysis stage.

We examined heterogeneity using I-square and Chi-squared tests. Heterogeneity was considered low or high if I-square <25% or >75%, respectively. If the outcomes and interventions were similar between studies, we conducted meta-analyses using RevMan 5.3 software. Risk ratio (RR) and mean difference were employed to pool summary estimates. We performed meta-analyses on admission rate and LOS and used the random effects model if high heterogeneity presented. No sensitivity or subgroup analyses were pre-specified.

3.3 Results

A total of 4062 articles were identified through database searching. Two additional articles were identified, one from the reference list of the included studies and another from the recommendation of content expert (Fig. 1). There were 81 articles eligible for obtaining full-texts and one RCT was available in abstract form only. In the end, 74 articles (70 studies) were included in the analyses, of which, 71 articles were original randomized controlled trials comparing different types of anticoagulant therapies. The remaining three articles are post-hoc analyses of two included trials.[18-20] The characteristics of the included studies were shown in Appendix B.

3.3.1 Risk of bias analyses

In the risk of bias analyses for the individual studies reporting admission rate or LOS, most RCTs did not provide information on random sequence generation (Fig. 2 and 3). More than half of the trials had a low risk with respect to the detection bias, attrition bias and reporting bias. The major drawback of the trials was the blinding of participants and personnel. Since the comparison of anticoagulants often involves distinctive ways of administration (subcutaneous, intravenous or oral), it is relatively difficult to blind the patients. Only the trials comparing fondaparinux to LMWH had a low performance bias, since they were all subcutaneously administrated.

3.3.2 Reporting rate of hospitalization rates and LOS

Hospitalization rates and LOS were reported in 13 (18.6%) and 12 (17.1%) of the 70 included studies, respectively.[18, 19, 21-31] There were 14.3% of RCTs comparing DOAC to other anticoagulants stated admission rates or LOS. And only 19.2% of RCTs comparing LMWH to the anticoagulants other than DOAC reported these two outcomes.

Table 1 shows the LOS and admission rates from 14 articles of 13 studies. Ten trials compared LMWH to UFH,[21-29, 31] and three post-hoc analyses compared rivaroxaban (a DOAC) to either UFH [18] or LMWH.[19, 20] The last study compared fondaparinux, a specific inhibitor of activated Factor X, to enoxaparin (a type of LMWH).[30]

3.3.3 Data synthesis

Only 7 of the 14 articles were included in the quantitative meta-analysis due to 1) The trials did not report both the mean and standard deviation of LOS; 2) admission to hospital were required for all patients; 3) a sparse number of trials which are inappropriate to conduct a meta-analysis. The I-square in both meta-analyses were greater than 75%, therefore, random effect

models were used. The results of the analyses of admission rates and LOS are presented in Fig 4 and 5.

Overall, all patients treated with intravenous UFH were admitted to the hospital, given that hospital admission of patients treated with UFH is usually compulsory, whereas those treated with LMWH, rivaroxaban or fondaparinux were either treated as outpatients or inpatients based on the patient preferences, physician decisions or study protocol.

LMWH-treated patients with VTE were 33% less likely to be admitted to the hospitals compared to patients receiving UFH (RR=0.67, 95% CI [0.58, 0.78], p<0.001) (Fig. 4). For patients with VTE, the admission rate of the rivaroxaban arm was 46.7% in EINSTEIN studies in North America, which was slightly lower than that of the LMWH/VKA arm (48.1%).[19] For EINSTEIN DVT in all regions, the admission rate for the rivaroxaban group was 50.6%, lower than 53.1% in the LMWH/VKA group. For EINSTEIN PE in all regions, the admission rates for two treatment groups were similar (89.7% in the rivaroxaban group and 89.9% in the LMWH/VKA group).[20] In the Japanese EINSTEIN trials,[18] VTE patients receiving rivaroxaban therapy were found to have a lower admission rate than the UFH/VKA group (94.9% vs 100%).

The mean LOS of VTE patients receiving LMWH was 4.74 days compared to 7.28 days for those receiving UFH. The mean difference in LOS between LMWH and UFH was 2.54 days in favor of LMWH (95% CI [-4.94, -0.14], p=0.04) (Fig. 5). The median LOS of hospitalized VTE patients treated with rivaroxaban was 3 days compared to 4 days in the LMWH/VKA group in the EINSTEIN trials in North America ($p < 0.01$).[19] The median LOS was 5 days versus 8 days ($P < 0.01$) and 6 days versus 7 days ($P < 0.01$) in EINSTEIN DVT and PE in all regions, respectively.[20] In the Japanese EINSTEIN trial,[18] the median LOS of VTE patients were 10 days and 15 days in the rivaroxaban group and the UFH groups respectively ($p < 0.05$).

3.4 Discussion

In this review, we found that the admission rate of using LMWH is significantly lower than using UFH. Compared with the parenteral therapy, using rivaroxaban had a lower or similar rate of hospitalization. The LOS was significantly shorter when comparing the LMWH group to the UFH group or comparing rivaroxaban to parenteral treatment. Less than 20% of included RCTs reported admission rates or LOS.

An ideal anticoagulant has the following characteristics: efficacy, safety, convenience of administration, minimal monitoring requirements and low cost.[32] The trend in the development of newer anticoagulants over time has shifted towards drugs that require less monitoring, less expertise in administration and thus can be taken as outpatient regimens earlier on in the treatment course. In this review, VTE patients treated with LMWH were found less likely to be admitted to hospital and had significantly shorter LOS, compared with patients receiving UFH. The unstable pharmacokinetics and close-monitoring requirement with the activated partial thromboplastin time (aPTT) of UFH are the reasons for an inpatient care.[33] In contrast, Not only do LMWH have a more convenient way of administration, it also overcomes the drawbacks of frequent monitoring and dose adjustment. These differences have made it possible for VTE patients to be treated at home or discharged earlier. In addition to the advantages of LMWH, the DOACs now provide these in an oral formulation. Our results suggest a slightly lower admission rate and significant shorter LOS with DOAC versus traditional anticoagulants in patients with DVT or PE.

Compared with efficacy and safety outcomes, the reporting rates of hospitalization rates and LOS were far less frequent, with reporting rates of less than 20%. According to a systematic

review of the outpatient treatment of systematic PE, the rate of recurrent VTE was 1.47% (95% CI: 0.47 to 3.0%; I^2: 65.4%) during the 3 month follow-up period, and the overall 3 month mortality rate was 1.58% (95% CI: 0.71 to 2.80%; I^2: 45%).[34] The authors concluded that low-risk patients with acute PE can be safely treated as outpatients if home circumstances are adequate.[34] However, in a study investigating the trends in admission rates and mean LOS for VTE from 2002 to 2012, no clear temporal trend was found for these two measures.[35] Clearly, the advancement in pharmacotherapy did not reduce the admission rates and LOS for VTE patients.[35] Underreporting of these important outcomes in clinical trials may partly explain the poor knowledge translation on the safety and efficacy of outpatient management of VTE. Despite the fact that LMWH has been developed for more than two centuries, only 19.2% of RCTs comparing LMWH to non-DOAC anticoagulants reported these two outcomes. Similarly, the evidence in terms of admission rates and LOS for DOACs was still sparse, even though DOAC provides more advantages over traditional anticoagulants for implementing outpatient treatment. To resolve this issue, more RCTs reporting admission rate and LOS are needed to potentially improve the reassurance of outpatient therapy and increase the patient compliance. Clinicians can also better appreciate the cost-effectiveness of different anticoagulants for acute VTE treatment should these outcomes be more prominently reported.

This systematic review has several strengths. To our best knowledge, this is the first review to compare and summarize the impact of different anticoagulants on the hospitalization rate and the LOS for acute VTE patients. We highlight the needs of reporting hospitalization rate and LOS along with efficacy and safety outcomes in trials regarding anticoagulants therapy for VTE since these two important outcomes remain underreported.

There are some limitations in this systematic review. Firstly, we pooled the results from trials regardless of the event type (DVT or PE), the type of LMWH, doses and the place of administration. In the meta-analysis, only one study included PE patients, which made the findings more representative for DVT patients. Since these trials have high heterogeneity, random effects model was used, which assumed that the analyzed data was from different hierarchies of populations. A sufficient number of RCTs are needed to reduce the heterogeneity and allow reliable publication bias analysis, as well as sensitivity analysis and subgroup analysis. Secondly, hospitalization and LOS may be affected by patients' and physicians' preferences, the severity of VTE and comorbidities, none of which were adequately captured in the existing trials to assess the appropriateness of each admission and resulting LOS. Thirdly, there were even fewer data on oral anticoagulants, particularly the DOAC, to draw firm conclusions relevant to the current VTE treatment practices. Fourthly, to generalize our findings to the clinical practices, our work will need the confirmation in observational studies, since our results may be biased by the protocol of clinical trials.

3.5 Conclusion

Rates of hospitalization and LOS are slightly shorter comparing LMWH to UFH and comparing the oral therapy to the parenteral therapy, based on limited eligible RCTs. These crucial clinically relevant outcomes are significantly underreported in the existing VTE clinical trials. Further studies including such data are of high priority to better tailor appropriate anticoagulant options.

Table 3. 1. Characteristics of studies reporting admission rate or length of stay

Study	Year of publication	Event Type	Intervention, n		Comparator, n	
			Admission Rates, n (%)	***Length of Stay, mean ± SD or median(IQR)***	***Admission Rates, n (%)***	***Length of Stay, mean ± SD or median(IQR)***
Columbus Investigators[36]	1997	VTE	S/C Reviparin Sodium, 510		IV UFH, 511	
			410(80%)	6.4 ± 7.1	511 (100%)	9.4 ± 7.8
Belcaro et al[26]	1999	DVT	S/C Nadroparin, 98		IV UFH, 97 S/C Heparin, 99	
			65 (66.3%)	5.1 ± 1.0	97 (100%)	5.4 ± 1.4
Tasman Study Group[31]	1996	DVT	S/C Nadroparin, 202		IV UFH, 198	
			130 (64%)	Mean: 2.7	198 (100%)	Mean: 8.1
Naz et al[37]	2005	DVT	S/C Dalteparin Sodium, 15		IV UFH, 15	
			15 (100%)	<10 d: 13 (86.6%) 11-15 d: 1 (6.6%) >15 d: 1 (6.6%)	15 (100%)	<10 d: 3 (20%) 11-15 d: 7 (46.6%) >15 d: 5 (33.3%)
Häfeli et al[38]	2001	VTE	S/C Dalteparin Sodium, 62		IV UFH, 63	
			62 (100%)	Mean: 10.4	63 (100%)	Mean: 11.0
Beckman et al[39]	2003	PE	S/C Enoxaparin, 40		IV UFH + Warfarin, 20	
			40 (100%)	Median: 4.0 95%CI 2.0-24.0	20 (100%)	Median: 6.0 95%CI: 4.0-10.0
Levine et al[40]	1996	DVT	S/C Enoxaparin, 247		IV UFH, 253	
			127	1.1 ± 2.9	253 (100%)	6.5 ± 3.4

			(51.4%)			
CLETRAT Investigators[41]	2004	DVT	S/C Enoxaparin, 104		IV UFH, 97	
			67 (64%)	3.0 ± 3.0	97 (100%)	7.0 ± 3.0
ASTH DVT Study Group[42]	2005	DVT	S/C Enoxaparin, 150		IV UFH, 148	
			116 (77%)	Same day discharge: 18 (12%) 1 night: 51 (34%) 2 nights: 34 (23%) ≥ 3 nights: 12 (8%)	148 (100%)	
Lissovoy et al[24]	2000	DVT	S/C Enoxaparin OD, 112 S/C Enoxaparin BID, 124		IV UFH, 104	
			112 (100%)	8.5 ± 4.7	104 (100%)	8.2 ± 4.1
			124 (100%)	8.2 ± 2.9		
Matisse Investigators[43]	2004	DVT	S/C Fondaparinux, 1,091		S/C Enoxaparin, 1,101	
			1,003 (91.9%)		1,010 (91.7%)	
Matsuo et al (J-EINSTEIN Investigators post-hoc analysis)[44]	2015	VTE	Oral Rivaroxaban, 78		IV UFH + Warfarin, 180	
			74 (94.9%)	10.0 (6.0 - 15.0)	180 (100%)	15.0 (9.0 - 22.0)
Bookhart et al (Post-hoc analysis of	2014	VTE	Oral Rivaroxaban, 405		S/C Enoxaparin / VKA, 401	
			189 (46.7%)	3.0 (3.0 - 5.0)	193 (48.1%)	4.0 (3.0 - 6.0)

EINSTEIN studies in North American)[19]						
Bellen et al (Post-hoc analysis of EINSTEIN studies in all regions)[20]	2014	DVT	Oral Rivaroxaban,1723		S/C Enoxaparin/VKA, 1711	
			872(50.6%)	5.0(3.0-9.0)	909(53.1%)	8.0(4.0-10.0)
		PE	Oral Rivaroxaban, 2412		S/C Enoxaparin/VKA, 2409	
			2163(89.7%)	6.0 (4.0-9.0)	2165(89.9%)	7.0(5.0-10.0)

SD standard deviation; *IQR* interquartile range; *VTE* venous thromboembolism; *DVT* deep vein thrombosis; *PE* pulmonary embolism; *S/C* subcutaneous; *IV* intravenous; *CI* confidence interval; *UFH* unfractionated heparin; *OD* once per day; *BID* twice per day; *VKA* vitamin K antagonist.

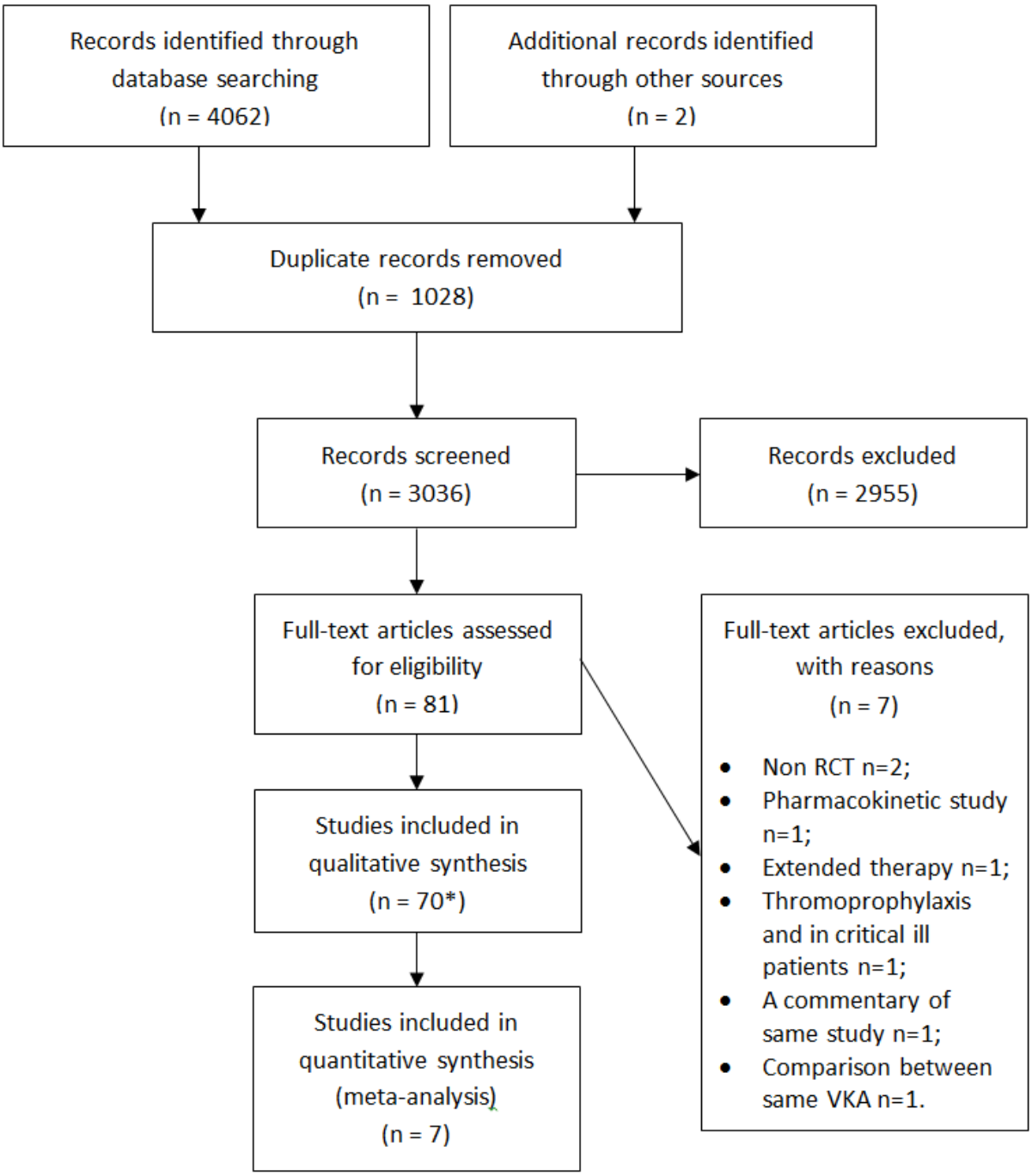

Figure 3. 1. Flowchart of trials identification and selection.

* Six articles came from two studies. *RCT* randomized control trial; *VKA* vitamin K antagonist

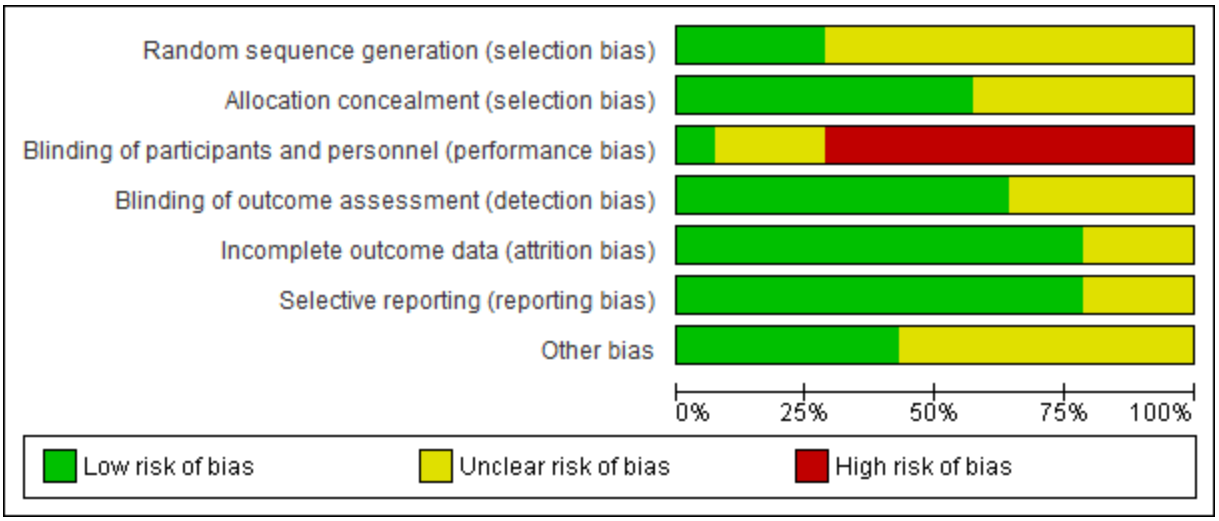

Figure 3. 2. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies reporting admission rate or length of stay

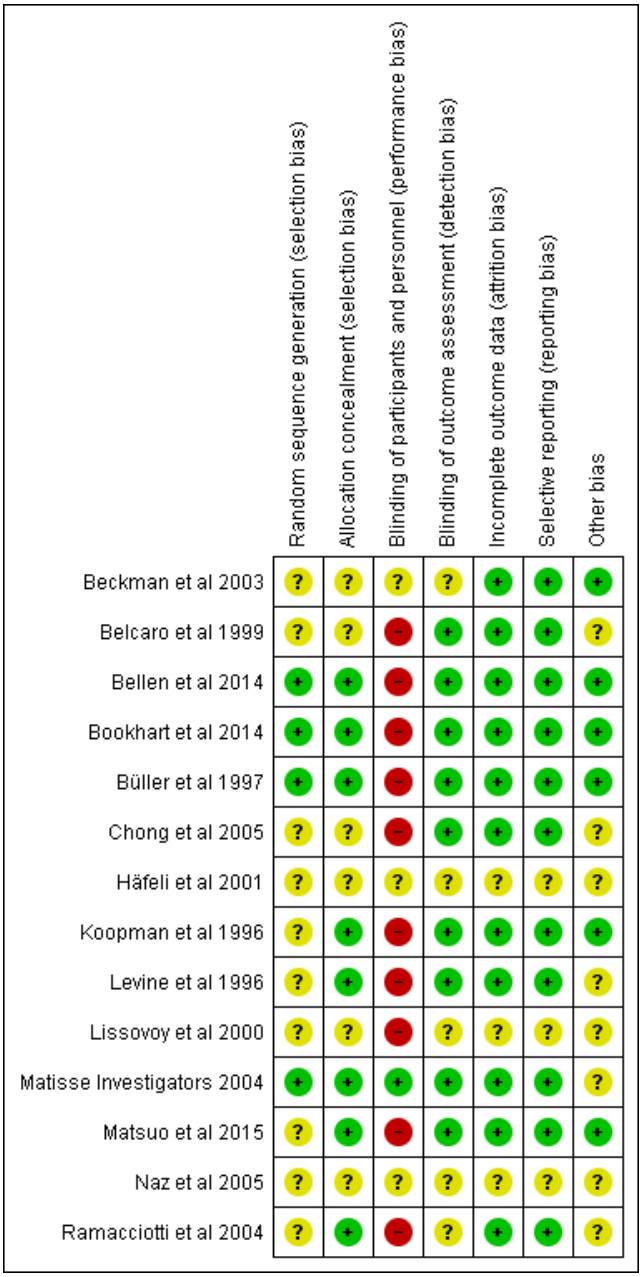

Figure 3. 3. Risk of bias summary: review authors' judgments about each risk of bias item for each included study reporting admission rate or length of stay

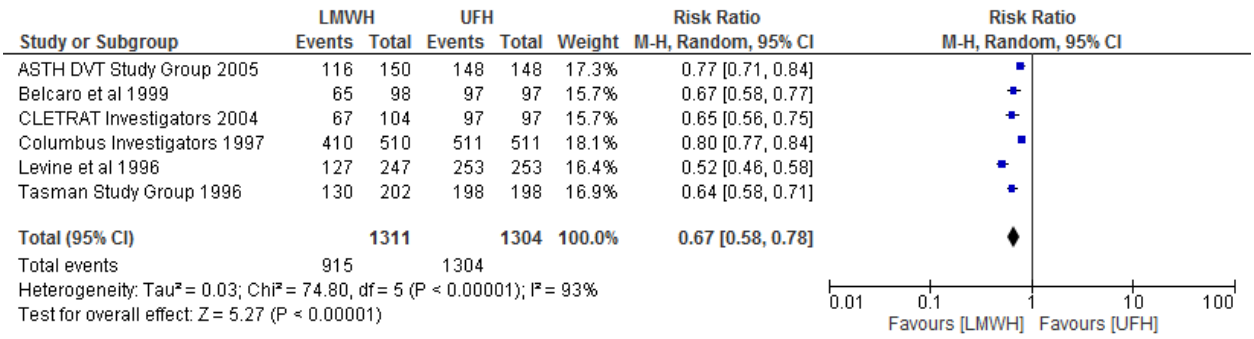

Figure 3. 4. Forest plot of relative risks comparing the admission rates of LMWH versus UFH in patients with VTE.

LMWH low molecular weight heparin; *UFH* unfractionated heparin; *M-H* Mantel–Haenszel, *CI* confidence interval

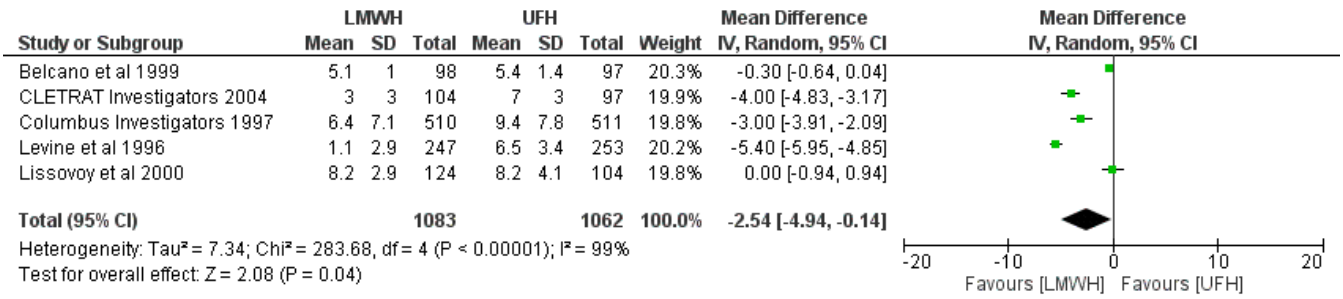

Figure 3. 5. Forest plot of mean differences comparing the length of stay of LMWH versus UFH in patients with VTE.

LMWH low molecular weight heparin; *UFH* unfractionated heparin; *IV* inverse variance; *SD* standard deviation; *CI* confidence interval

3.6 References

1. Goldhaber SZ, Bounameaux H. Pulmonary embolism and deep vein thrombosis. *The Lancet.* 2012;379:1835-1846.

2. Fowkes FJ, Price JF, Fowkes FG. Incidence of diagnosed deep vein thrombosis in the general population: systematic review. *Eur. J. Vasc. Endovasc. Surg.* 2003;25:1-5.

3. Dobesh PP. Economic burden of venous thromboembolism in hospitalized patients. *Pharmacotherapy.* 2009;29:943-953.

4. Kearon C. Initial Treatment of Venous Thromboembolism. *Thromb. Haemost.* 1999;82:887-891.

5. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic Therapy for VTE Disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141:e419S-e496S.

6. Garcia DA, Baglin TP, Weitz JI, Samama MM. Parenteral anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141:e24S-43S.

7. Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G. Oral anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141:e44S-88S.

8. Ducel G, Fabry J, Nicolle L, Organization WH. Prevention of hospital-acquired infections: a practical guide. 2002.

9. García-Cabrera E, Fernández-Hidalgo N, Almirante B, et al. Neurological complications of infective endocarditis: risk factors, outcome, and impact of cardiac surgery: a multicenter observational study. *Circulation.* 2013;127:2272-2284.

10. Lagoe RJ, Westert GP. Evaluation of hospital inpatient complications: a planning approach. *BMC Health Serv. Res.* 2010;10:200.

11. Hoogervorst-Schilp J, Langelaan M, Spreeuwenberg P, de Bruijne MC, Wagner C. Excess length of stay and economic consequences of adverse events in Dutch hospital patients. *BMC Health Serv. Res.* 2015;15:531.

12. Baker GR, Norton PG, Flintoft V, et al. The Canadian Adverse Events Study: the incidence of adverse events among hospital patients in Canada. *Can Med Assoc J.* 2004;170:1678-1686.

13. Zegers M, de Bruijne MC, Wagner C, et al. Adverse events and potentially preventable deaths in Dutch hospitals: results of a retrospective patient record review study. *Qual Saf Health Care.* 2009;18:297-302.

14. Sari AB-A, Sheldon TA, Cracknell A, et al. Extent, nature and consequences of adverse events: results of a retrospective casenote review in a large NHS hospital. *Qual Saf Health Care.* 2007;16:434-439.

15. Busby J, Purdy S, Hollingworth W. A systematic review of the magnitude and cause of geographic variation in unplanned hospital admission rates and length of stay for ambulatory care sensitive conditions. *BMC Health Serv Res.* 2015;15:324.

16. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ.* 2011;343:d5928.

17. Song F, Hooper L, Loke YK. Publication bias: what is it? How do we measure it? How do we avoid it? *Open Access J Clin Trials.* 2013;5:71-81.

18. Matsuo H, Prins M, Lensing AWA, Fujinuma EW, Miyamoto Y, Kajikawa M. Shortened length of hospital stay with rivaroxaban in patients with symptomatic venous thromboembolism in Japan: the J-EINSTEIN pulmonary embolism and deep vein thrombosis program. *Curr Med Res Opin.* 2015;31:1057-1061.

19. Bookhart BK, Haskell L, Bamber L, Wang M, Schein J, Mody SH. Length of stay and economic consequences with rivaroxaban vs enoxaparin/vitamin K antagonist in patients with DVT and PE: findings from the North American EINSTEIN clinical trial program. *J Med Econ.* 2014;17:691-695.

20. van Bellen B, Bamber L, Correa de Carvalho F, Prins M, Wang M, Lensing AWA. Reduction in the length of stay with rivaroxaban as a single-drug regimen for the treatment of deep vein thrombosis and pulmonary embolism. *Curr Med Res Opin.* 2014;30:829-837.

21. Levine M, Gent M, Hirsh J, et al. A Comparison of Low-Molecular-Weight Heparin Administered Primarily at Home with Unfractionated Heparin Administered in the Hospital for Proximal Deep-Vein Thrombosis. *N Engl J Med.* 1996;334:677-681.

22. Ramacciotti E, Araujo GR, Lastoria S, et al. An open-label, comparative study of the efficacy and safety of once-daily dose of enoxaparin versus unfractionated heparin in the treatment of proximal lower limb deep-vein thrombosis. *Thromb. Res.* 2004;114:149-153.

23. Chong BH, Brighton TA, Baker RI, Thurlow P, Lee CH. Once-daily enoxaparin in the outpatient setting versus unfractionated heparin in hospital for the treatment of symptomatic deep-vein thrombosis. *J Thromb Thrombolysis.* 2005;19:173-181.

24. de Lissovoy G, Yusen RD, Spiro TE, Krupski WC, Champion AH, Sorensen SV. Cost for inpatient care of venous thrombosis: A trial of enoxaparin vs standard heparin. *Arch Intern Med.* 2000;160:3160-3165.

25. Beckman JA, Dunn K, Sasahara AA, Goldhaber SZ. Enoxaparin monotherapy without oral anticoagulation to treat acute symptomatic pulmonary embolism. *Thromb Haemost.* 2003;89:953-958.

26. Belcaro G, Nicolaides AN, Cesarone MR, et al. Comparison of low-molecular-weight heparin, administered primarily at home, with unfractionated heparin, administered in hospital, and subcutaneous heparin, administered at home for deep-vein thrombosis. *Angiology.* 1999;50:781-787.

27. Naz R, Naz S, Mehboob M, Khalid GH. Comparison of unfractionated heparin vs low molecular weight heparin in the treatment of acute deep vein thrombosis. *J Coll Physicians Surg Pak.* 2005;15:601-604.

28. R. Hafeli SK, Ch. Wehrli, J. Goede, D. Conen. Nieder-molekulares heparin (Dalteparin) in der behandlung von patienten mit thromboembolischen (TVT/LE) ereignissen. *Praxis-Bern.* 2001;90:1339-1345.

29. The Columbus Investigators. Low-Molecular-Weight Heparin in the Treatment of Patients with Venous Thromboembolism. *N Engl J Med.* 1997;337:657-662.

30. The Matisse Investigators. Subcutaneous Fondaparinux versus Intravenous Unfractionated Heparin in the Initial Treatment of Pulmonary Embolism. *N Engl J Med.* 2003;349:1695-1702.

31. Koopman MM, Prandoni P, Piovella F, et al. Treatment of venous thrombosis with intravenous unfractionated heparin administered in the hospital as compared with

subcutaneous low-molecular-weight heparin administered at home. *N Engl J Med.* 1996;334:682-687.

32. King CS, Holley AB, Moores LK. Moving toward a more ideal anticoagulant: the oral direct thrombin and factor Xa inhibitors. *Chest.* 2013;143:1106-1116.

33. Byun JH, Jang IS, Kim JW, Koh EH. Establishing the heparin therapeutic range using aPTT and anti-Xa measurements for monitoring unfractionated heparin therapy. *Blood Res.* 2016;51:171-174.

34. Piran S, Le Gal G, Wells PS, et al. Outpatient treatment of symptomatic pulmonary embolism: A systematic review and meta-analysis. *Thromb. Res.* 2013;132:515-519.

35. Mansour S, Alotaibi G, Wu C, McMurtry MS. Trends in admission rates and in-hospital stay for venous thromboembolism. *Thrombosis research.* 2017;156:149-154.

36. Columbus Investigators. Low-molecular-weight heparin in the treatment of patients with venous thromboembolism. *N Engl J Med.* 1997;1997:657-662.

37. Naz R, Naz S, Mehboob M, Khalid GH. Comparison of unfractionated heparin vs low molecular weight heparin in the treatment of acute deep vein thrombosis. *Journal of the College of Physicians and Surgeons--Pakistan: JCPSP.* 2005;15:601-604.

38. Hafeli R, Kraljevic S, Wehrli C, Goede J, Conen D. [Low molecular weight heparin (dalteparin) in treatment of patients with thromboembolism incidents]. *Praxis (Bern 1994).* 2001;90:1339-1345.

39. Beckman JA, Dunn K, Sasahara AA, Goldhaber SZ. Enoxaparin monotherapy without oral anticoagulation to treat acute symptomatic pulmonary embolism. *Thromb. Haemost.* 2003;89:953-958.

40. Levine M, Gent M, Hirsh J, et al. A comparison of low-molecular-weight heparin administered primarily at home with unfractionated heparin administered in the hospital for proximal deep-vein thrombosis. *N Engl J Med.* 1996;334:677-681.

41. Ramacciotti E, Araújo GR, Lastoria S, et al. An open-label, comparative study of the efficacy and safety of once-daily dose of enoxaparin versus unfractionated heparin in the treatment of proximal lower limb deep-vein thrombosis. *Thromb. Res.* 2004;114:149-153.

42. Chong BH, Brighton TA, Baker RI, Thurlow P, Lee CH, Group ADS. Once-daily enoxaparin in the outpatient setting versus unfractionated heparin in hospital for the treatment of symptomatic deep-vein thrombosis. *Journal of thrombosis and thrombolysis.* 2005;19:173-181.

43. Büller HR, Davidson BL, Decousus H, et al. Fondaparinux or Enoxaparin for the Initial Treatment of Symptomatic Deep Venous ThrombosisA Randomized Trial. *Ann Intern Med.* 2004;140:867-873.

44. Matsuo H, Prins M, Lensing AW, Fujinuma EW, Miyamoto Y, Kajikawa M. Shortened length of hospital stay with rivaroxaban in patients with symptomatic venous thromboembolism in Japan: the J-EINSTEIN pulmonary embolism and deep vein thrombosis program. *Curr Med Res Opin.* 2015;31:1057-1061.

Chapter 4: The association between chronic obstructive pulmonary disease and coronary artery disease in patients undergoing coronary angiography

Abstract:

Background: Chronic obstructive pulmonary disease (COPD) and coronary artery disease (CAD) are leading causes of morbidity and mortality. There are conflicting results regarding the association between COPD and CAD. We sought to measure the association between COPD and angiographically diagnosed CAD in a population-based cohort.

Methods: We performed a retrospective analysis using data from The Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease (APPROACH), a prospectively collected registry capturing all patients undergoing coronary angiography in Alberta, Canada, since 1995. We included adult patients who had undergone coronary angiogram between April 1, 2007 and March 31, 2014. CAD was present if at least one coronary artery had a significant stenosis ≥ 50%. COPD was present if the patient had a documented COPD history and was prescribed bronchodilators or inhaled steroids. We evaluated the association between COPD and CAD using univariable and multivariable logistic regression.

Results: There were 26,137 patients included with a mean age of 63.3 ± 12.2 years, and 19542 (74.8%) were male. The crude odds ratio of having CAD was 0.83 (95% CI 0.74-0.92) for patients with COPD compared to those without COPD. The adjusted odds ratio was 0.75 (95%

CI 0.67-0.84) after controlling for age, gender, smoking history, body mass index, hypertension, diabetes, hyperlipidemia, peripheral artery disease, and cardiac family history.

Conclusion: In patients undergoing coronary angiography, COPD was negatively associated with CAD before and after adjustment for classic risk factors.

Keywords: chronic obstructive pulmonary disease, coronary artery disease, angiography, risk factors, association

4.1 Background

Chronic Obstructive Pulmonary Disease (COPD) is a common disease that is characterized by persistent and progressive airflow limitation and is associated with an enhanced chronic inflammatory response to noxious particles or gases in the airways and the lung.[1] Both COPD and Coronary Artery Disease (CAD) are leading causes of morbidity and mortality globally, and result in a significant societal burden.[2, 3] In a thirty years surveillance study in the United States, COPD affected 5%–10% of the population,[4] while CAD caused more than 116 per 100 000 deaths, and accounted for 50% of all cardiovascular-related deaths in the United States in 2009.[5] COPD and CAD share many risk factors such as smoking and age. Campo et al. summarized the main possible mechanisms for the co-existence of COPD and CAD were smoking habit, hypoxia, systematic inflammation, platelet reactivity and arterial stiffness.[6] COPD patients have various concomitant diseases and are especially prone to cardiovascular disease.[1, 7] In patients with ischemic heart disease, Nishiyama et al. have demonstrated that COPD is an independent risk factor for long-term cardiac mortality.[8] COPD severity is independently associated with the severity of coronary calcification, a non-invasive marker of CAD risk,[9] and some have found that COPD is independently associated with the severity of CAD measured by diagnostic coronary angiography.[10] However, one systemic review found that only 5 of the 9 relevant studies reported an increased risk of CAD in patients with COPD.[11] The review authors also pointed out that some negative studies tended to have smaller sample sizes.[11] And in a case-control study, it was found that COPD was not associated with CAD when adjusting for classic cardiovascular risk factors.[12] Therefore, there remains some doubt as to whether COPD is truly an independent risk factor for CAD. Confirming an association between COPD and CAD is important, as it may have implications for the management of the coexistence

of these 2 diseases.[11] Therefore, we sought to determine if there is an independent association between COPD and angiographically diagnosed CAD by analyzing a large population-based cohort of patients undergoing coronary angiography.

4.2 Methods

We obtained data from The Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease (APPROACH). APPROACH is a prospective clinical collection registry capturing information from patients undergoing cardiac intervention and revascularization in the province of Alberta, Canada, since 1995.[13] The research files in APPROACH are routinely merged with Administrative health data. This registry contains detailed clinical information including demographics, common cardiac risk factors, comorbidities, procedure indications and coronary anatomy.[14] All the angiograms were evaluated by an independent cardiologist blinded to the patients' clinical data. Alberta has a population of about 3.6 million, and there are in total 3 cardiac catheterization laboratories located in 2 large cities in Alberta.[15]

This is a retrospective cohort study design. This study was approved by the University of Alberta Health Research Ethics Board. We included patients aged > 18 years who had undergone coronary angiogram for any reason between April 1, 2007 and March 31, 2014 (7 fiscal years). A patient was considered to have CAD if at least 1 coronary artery (left main [LM], left anterior descending artery [LAD], right coronary artery [RCA] or left circumflex [LCX]) had a significant stenosis ≥ 50%. Multi-vessel diseases were defined as more than one coronary artery having significant stenosis ≥ 50%. COPD was present if the patient had a documented COPD history and was on a pharmacological therapy (i.e. bronchodilators or inhaled steroids). This definition has a very high positive predictive value and negative predictive value (PPV=90.8%,

NPV= 92.2%) according to a validation study.[16] Former and current cigarette smokers were all defined as smokers. Diabetes mellitus was defined as a history of diabetes mellitus diagnosed and/or treated by a physician. If a patient had typical symptoms of claudication or had prior corrective surgery, angioplasty or amputation to the extremities, it was diagnosed with peripheral artery disease. Hypertension and hyperlipidemia were defined according to Canadian Medical Association Guideline 2000.[17, 18] A patient's Body Mass Index (BMI) was calculated as the patient's weight in kilograms divided by the patient's height in metres squared. The family history of heart disease was presented if the immediate family of the patient had a cardiac history at the age of fewer than 60 years.

Statistical Analyses

Continuous and categorical variables were expressed as mean ± standard deviation (SD) and frequency (percentage), respectively. Independent samples t-test and chi-square test were used for the comparison between groups. A 2-tailed p-value < 0.05 was considered statistically significant. Univariable logistic regression models were first conducted, followed by a multivariable logistic regression model to evaluate the association between CAD and COPD adjusting for classic cardiovascular risk factors including age, sex, cigarette smoking, cardiac family history, diabetes mellitus, hypertension, hyperlipidemia, BMI and peripheral artery disease. Odds ratios (OR) and their 95% confidence intervals were used and reported to measure the effect of association. The interaction between smoking history and COPD was tested, and Hosmer-Lemeshow goodness of fit test was examined. We also conducted pre-specified subgroup analyses by fitting the multivariable logistic regression model in each fiscal year. All statistical analyses were performed with statistical software STATA version 13.1 (Stata Corp., Houston, Texas, USA).

4.3 Results

There were 26,137 patients included in the analysis, with a mean age of 63.3 ± 12.2 years and 74.8% of which were male (Table 1). COPD was identified in 3523 patients (13.5%). The prevalences of CAD in patients with COPD and without COPD were 86.6% and 88.7%, respectively. The patients in the COPD group were significantly older than the patients without COPD (67.7 ± 11.3 years vs. 62.6 ± 12.2 years, $p < 0.001$). There were significant differences between the 2 groups in terms of smoking history, comorbidities of diabetes mellitus, hypertension, hyperlipidemia, peripheral vascular disease and family history of heart attack. In contrast, the average BMI showed no statistical difference between the two groups ($p = 0.725$).

Table 2 shows the angiographic presentation of the study population. Significant coronary artery stenosis was more likely to be observed in the COPD group than in the non-COPD group in the RCA, LCX and LM ($P<0.001$). Half of the subjects with COPD had multi-vessel diseases, which was significantly greater than the proportion in the non-COPD group (45.1%, $p < 0.001$).

The crude odds ratio of having CAD was 0.83 (95% CI 0.74-0.92) for patients with COPD compared to those without COPD in the univariable logistic regression analysis (Table 3). After controlling for age, gender, smoking history, BMI, hypertension, diabetes, hyperlipidemia, peripheral artery disease, and cardiac family history in the multivariable logistic regression, the OR was 0.75 (95% CI 0.67-0.84). No interaction was found between smoking history and COPD ($P=0.75$). The p-value for the Hosmer-Lemeshow goodness of fit test was 0.36, which indicates that this model fits the data well.

Figure 1 shows the odds ratios of having CAD in the COPD group compared to the non-COPD group and its corresponding 95% CIs in each fiscal year from 2007 to 2013. The odds ratios of having CAD in the COPD group ranged from 0.57 to 0.82 across 7 fiscal years, despite the non-significant findings in 2008, 2010 and 2012.

4.4 Discussion

We found that the patients with COPD had more coronary lesions in the RCA, LCX and LM, compared with the patients without COPD at the segment level. Higher proportions of multi-vessel lesions were also found in the COPD group compared to the non-COPD group. COPD was negatively associated with CAD, with or without controlling for classic cardiovascular risk factors. This negative association between COPD and CAD was roughly consistent across 7 fiscal years.

It is important to investigate the COPD-CAD relationship. Studies have shown that the prevalence of patients with multiple chronic diseases is considerably greater: more than two thirds (68%) have ≥2 chronic diseases, and 14% have ≥6 chronic diseases.[19] And many clinical trials often exclude patients with comorbidities, limiting the potential to generalize the findings to a larger population.[20] Therefore, more real-world evidence studying patients with both COPD and CAD are warranted to complement the limitation of clinical trials.

In our study, the crude odds ratio of having CAD was 0.83 for the COPD group in univariable logistic regression analysis, which was different from the findings in Table 2. The reason was that the COPD group had a significantly higher probability of having multi-vessel lesions than the non-COPD group, and the analysis of angiographic characteristics was on a segment level (RCA, LAD, LCX, LM).

In the literature, the adjusted relative risk of CAD between patients with and without COPD varies between 0.7-6.8, and one systemic review demonstrated that only 5 of the 9 relevant studies reported an increased risk of CAD for patients with COPD,[11] among which some negative studies tended to have smaller sample sizes.[11] However, we found an inverse relationship between CAD and COPD before and after adjustment for risk factors in a large population-based cohort, so this negative association cannot be explained by a small sample size limitation. This association was also showed to be relatively consistent in the subgroup analyses that the point estimates of the odds ratios for CAD in each year were all smaller than one with 5 out of 8 95% CIs being significant (Figure 1). This kind of inconsistent findings in the literature may attribute to the differences in the populations studied as well as study designs, including differences in how CAD is ascertained as well as which risk factor was controlled.

A study comparing carotid intima-media thickness to angiography in patients suspected of CAD have indicated that, in COPD patients, coronary lesions were more frequently seen in LM, and LCX, which is similar to our findings.[21] Both Almagro et al.[22] and Liang et al.[23] have also demonstrated similar findings that the patients with COPD have more coronary vessels affected.

The underlying mechanism for a COPD-CAD association is unknown. Some advocates of positive associations between COPD and CAD believe that low-grade systemic inflammation may contribute to the higher prevalence of cardiovascular complication in COPD patients.[24] However, there are conflicting findings regarding the inflammation hypothesis for atherothrombosis. P Ridker et al. found that anti-inflammatory therapy targeting the interleukin-1β innate immunity pathway with canakinumab significantly reduced the rate of recurrent cardiovascular events compared to the placebo group.[25] In contrast, several randomized

controlled trials of testing anti-inflammatory agents in patients with CAD have not demonstrated any benefit. For example, a randomized controlled trial of using statins as a potential anti-inflammatory agent showed a daily dose of Simvastatin did not affect the exacerbation rate or the time to the first exacerbation in COPD patients with high risk of exacerbation.[26] Another randomized control trial found that almonds, which reduce cardiovascular risk via suppressing inflammation, do not significantly impact vascular function in CAD patients.[27] In addition, colchicine, known for its anti-inflammatory effects, failed to improve the inflammatory profiles or reduce the infarct size in patients admitted for ST-segment elevation myocardial infarction.[28] Hypoxia is one of the common manifestations in patients with COPD. It has been shown that hypoxia could improve the outcome of CAD patients, which may partly support the inverse relationship between COPD and CAD. Liang etc. found that long-term remote hypoxic preconditioning improved the endothelial function in patients with CAD.[29] A systematic review summarizing the remote ischemic conditioning-related effected on myocardial injury biomarkers also demonstrated that remote preconditioning appeared to reduce ischemia and long-term clinical events.[30] This systematic review implies that hypoxia could have a protective effect on CAD, which could be a possible mechanism to explain the paradoxical negative associations between COPD and CAD.

Smoking is a shared risk factor for COPD and CAD. Smoke and other inhaled noxious particles are considered the key factors in the inflammatory responses of the lung and arterial wall, which induce airway obstruction and promote atherosclerosis.[6] In the multivariable analysis, controlling for the smoking effect revealed a more negative relationship between COPD and CAD, confirming that smoking is an important exposure for the development of CAD. The mechanism for an inverse association between COPD and CAD is not clear, but our data do not

support the statement that COPD-associated inflammation contributes to the development of CAD.

Our study has a number of strengths. First of all, this large provincial retrospective cohort study design has enabled us to reduce possible selection bias and random error by capturing all the patients undergoing coronary catheterization in Alberta, Canada, when compared with single-centre regional studies. Secondly, by using coronary angiography, which is the gold standard for diagnosing CAD, the information bias in terms of the outcome of interest has been extensively minimized. In addition, multivariable logistic regression was used to control the confounding effects of classic risk factors for CAD, including the share risk factors age and smoking between CAD and COPD.

There are also some limitations in this study. Firstly, due to the nature of the observational study design, we were unable to adjust for all possible confounders, including diet and physical activities. However, we treated BMI as a proxy in the regression model, since BMI is highly related to diet and physical activities. Secondly, we cannot rule out the risk of bias from the competing risk of death, where severe COPD patients may die before the identification of CAD and therefore will not be included in the analysis. Thirdly, in this cohort of patients suspected of having CAD, the prevalence of CAD in patients with COPD was 86.6%, which was higher than the general COPD population which ranges from 4.7% to 60%.[11] Thus, our findings may not apply to the general population of COPD directly. Lastly, the diagnosis of COPD was based on the medical history and pharmacological therapy records instead of spirometry. Nevertheless, according to a validation study done by H Quan et al,[16] this definition for COPD has a very high PPV (90.8%) and NPV (92.2%), which indicates that our method of identifying true COPD patients is reliable. This is also a very common approach in the literature.[31-33]

4.5 Conclusion

In patients undergoing coronary angiography, COPD was negatively associated with CAD before and after adjustment for classic risk factors.

Table 4. 1. Baseline characteristics of the study population

	Overall cohort N(%) (N=26137)	COPD N(%) (N=3523)	Without COPD N(%) N(22614)	P value
Patient demographics				
Age, years	63.3±12.2	67.7±11.3	62.6±12.2	<0.001
Gender, male	19542(74.8)	2431(69.0)	17111(75.7)	<0.001
Clinical characteristics				
Smoking history	15715(60.1)	2476(70.3)	13239(58.5)	<0.001
Diabetes mellitus	6527(25.0)	1221(31.8)	5406(23.9)	<0.001
Hypertension	17640(67.5)	2703(76.7)	14937(66.1)	<0.001
Hyperlipidemia	17607(67.4)	2485(70.5)	15122(66.9)	<0.001
Peripheral vascular disease	2416(9.2)	408(11.6)	2008(8.9)	<0.001
BMI	28.8±5.5	28.8±6.4	28.8±5.4	0.725
Family history of heart attacks	8925(34.2)	1074(30.5)	7851(34.7)	<0.001
Prevalence of CAD	88.4	86.6	88.7	<0.001

BMI, body mass index; COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease; NA, not applicable.

Table 4. 2. Angiographic characteristics of the study population

Variables		COPD (%)	Without COPD (%)	P value
RCA	≥50%	2009 (57.0)	12125 (53.6)	<0.001
LAD	≥50%	2128 (60.4)	13778 (60.9)	0.554
LCX	≥50%	1285 (36.5)	7495 (33.1)	<0.001
LM	≥50%	388 (11.0)	1720 (7.6)	<0.001
Numbers of vessels affected	0	471 (13.4)	2560 (11.3)	
	1	1278 (36.3)	9859 (43.6)	
	2	965 (27.4)	6147 (27.2)	
	3	634 (18.0)	3227 (14.3)	
	4	175 (4.9)	821 (3.6)	
Multi-vessel disease		1774 (50.4)	10195 (45.1)	P<0.001

COPD, chronic obstructive pulmonary disease; LAD, left anterior descending artery; LCX, left circumflex artery; LM, left main artery; RCA, right coronary artery.

Table 4. 3. The univariable and multivariable logistic regression analysis

Factors	Univarable analysis		Multivariable analysis	
	OR (95% CI)*	P value	OR (95% CI)*	P value
COPD	0.83 (0.74, 0.92)	<0.001	0.75 (0.67, 0.84)	<0.001
Age, years †	1.01 (1.00, 1.02)	<0.001	1.02 (1.01, 1.02)	<0.001
Gender, male	1.62 (1.50, 1.76)	<0.001	1.77 (1.63, 1.92)	<0.001
Smoking history	1.08 (1.01, 1.17)	0.035	1.15 (1.05, 1.24)	0.001
Diabetes mellitus	1.40 (1.27, 1.54)	<0.001	1.41 (1.28, 1.56)	<0.001
Hypertension	1.04 (0.96, 1.13)	0.310	0.96 (0.88, 1.05)	0.352
Hyperlipidemia	1.00 (0.93, 1.09)	0.908	0.96 (0.88, 1.04)	0.296
Peripheral vascular disease	1.50 (1.29, 1.74)	<0.001	1.46 (1.26, 1.70)	<0.001
BMI, kg/m^2 †	1.00 (0.99, 1.01)	0.543	1.00 (0.99, 1.01)	0.283
Family history of heart attacks	0.95 (0.88, 1.03)	0.254	1.04 (0.95, 1.12)	0.408

*Odds ratio of coronary artery disease defined as at least one coronary artery has a significant stenosis ≥ 50%.

†OR presented for one unit of change.

BMI, body mass index; COPD, chronic obstructive pulmonary disease; CI, confidence interval.

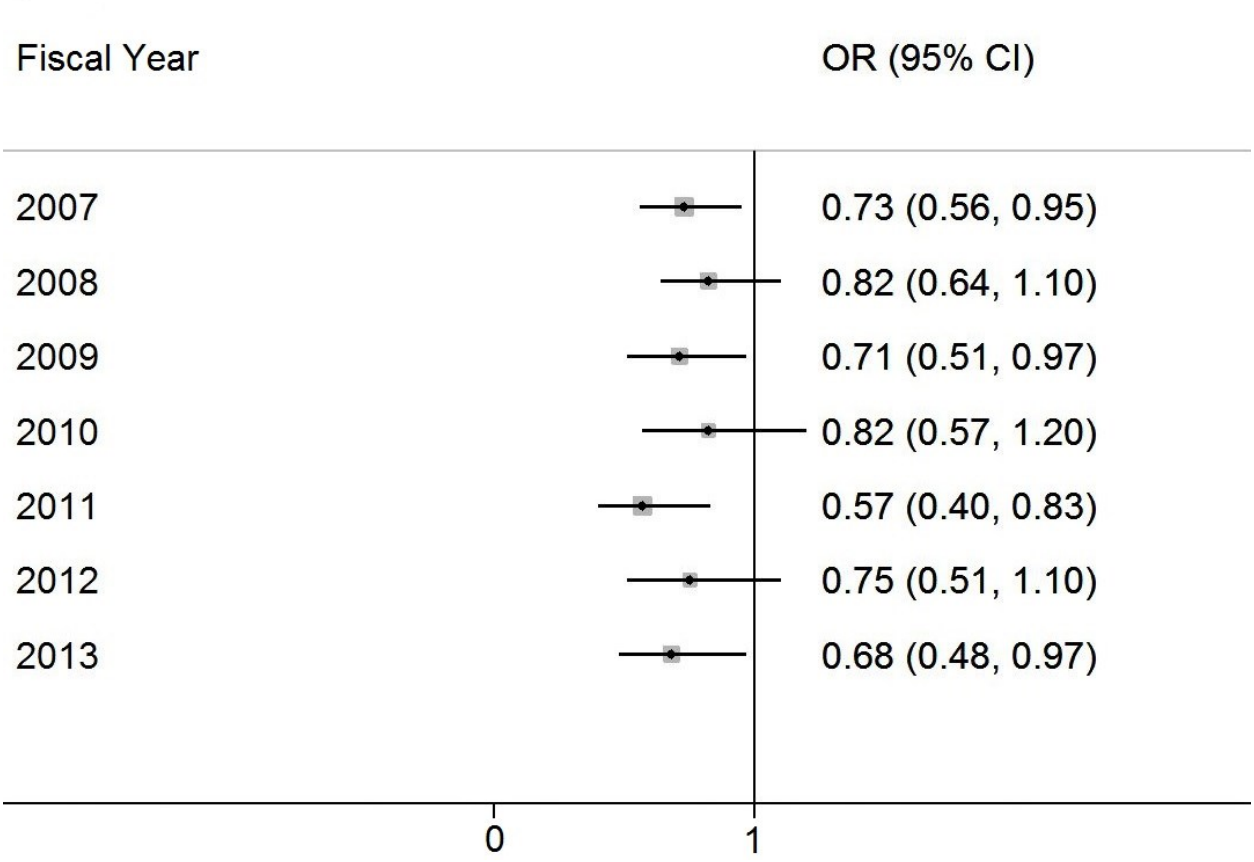

Figure 4. 1. The sensitivity analysis of the association between COPD and CAD by each fiscal year adjusting for classic cardiovascular risk factors.

OR, odds ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease.

4.6 References

1. Vestbo J, Hurd SS, Rodriguez-Roisin R. The 2011 revision of the global strategy for the diagnosis, management and prevention of COPD (GOLD)--why and what? *Clin Respir J.* 2012;6:208-214.

2. Murray CJ, Atkinson C, Bhalla K, et al. The state of US health, 1990-2010: burden of diseases, injuries, and risk factors. *JAMA.* 2013;310:591-608.

3. Kolh P, Windecker S, Alfonso F, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur J Cardiothorac Surg.* 2014;46:517-592.

4. Mannino DM, Homa DM, Akinbami LJ, Ford ES, Redd SC. Chronic obstructive pulmonary disease surveillance---United States, 1971--2000. *Respir. Care.* 2002;76.

5. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics—2012 update a report from the American heart association. *Circulation.* 2012;125:e2-e220.

6. Campo G, Pavasini R, Malagu M, et al. Chronic obstructive pulmonary disease and ischemic heart disease comorbidity: overview of mechanisms and clinical management. *Cardiovasc Drugs Ther.* 2015;29:147-157.

7. Vanfleteren LE, Spruit MA, Groenen M, et al. Clusters of comorbidities based on validated objective measurements and systemic inflammation in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2013;187:728-735.

8. Nishiyama K, Morimoto T, Furukawa Y, et al. Chronic obstructive pulmonary disease—an independent risk factor for long-term cardiac and cardiovascular mortality in patients with ischemic heart disease. *Int J Cardiol.* 2010;143:178-183.

9. Rasmussen T, Køber L, Pedersen JH, et al. Relationship between chronic obstructive pulmonary disease and subclinical coronary artery disease in long-term smokers. *Eur Heart J Cardiovasc Imaging.* 2013;14:1159-1166.

10. Topsakal R, Kalay N, Ozdogru I, et al. Effects of chronic obstructive pulmonary disease on coronary atherosclerosis. *Heart Vessels.* 2009;24:164-168.

11. Müllerova H, Agusti A, Erqou S, Mapel DW. Cardiovascular comorbidity in COPD: systematic literature review. *CHEST Journal.* 2013;144:1163-1178.

12. Izquierdo JL, Martinez A, Guzman E, de Lucas P, Rodriguez JM. Lack of association of ischemic heart disease with COPD when taking into account classical cardiovascular risk factors. *Int J Chron Obstruct Pulmon Dis.* 2010;5:387-394.

13. Shavadia J, Norris CM, Graham MM, Verma S, Ali I, Bainey KR. Symptomatic graft failure and impact on clinical outcome after coronary artery bypass grafting surgery: Results from the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease registry. *Am Heart J.* 2015;169:833-840.

14. Kaila KS, Norris CM, Graham MM, Ali I, Bainey KR. Long-term survival with revascularization in South Asians admitted with an acute coronary syndrome (from the Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease Registry). *Am J Cardiol.* 2014;114:395-400.

15. Bresee LC, Knudtson ML, Zhang J, et al. Likelihood of coronary angiography among First Nations patients with acute myocardial infarction. *CMAJ.* 2014;186:E372-380.

16. Quan H, Li B, Saunders LD, et al. Assessing validity of ICD-9-CM and ICD-10 administrative data in recording clinical conditions in a unique dually coded database. *Health Serv Res.* 2008;43:1424-1441.

17. Fodor JG, Frohlich JJ, Genest JJ, McPherson PR. Recommendations for the management and treatment of dyslipidemia Report of the Working Group on Hypercholesterolemia and Other Dyslipidemias. *Can Med Assoc J.* 2000;162:1441-1447.

18. Feldman RD, Campbell N, Larochelle P, et al. 1999 Canadian recommendations for the management of hypertension. *Can Med Assoc J.* 1999;161:S1-S17.

19. Lochner KA, Goodman RA, Posner S, Parekh A. Multiple chronic conditions among Medicare beneficiaries: state-level variations in prevalence, utilization, and cost, 2011. *Medicare Medicaid Res Rev.* 2013;3.

20. Arnett DK, Goodman RA, Halperin JL, Anderson JL, Parekh AK, Zoghbi WA. AHA/ACC/HHS strategies to enhance application of clinical practice guidelines in patients with cardiovascular disease and comorbid conditions: from the American Heart Association, American College of Cardiology, and US Department of Health and Human Services. *J. Am. Coll. Cardiol.* 2014;64:1851-1856.

21. Koseoglu C, Kurmus O, Ertem AG, et al. Association between carotid intima-media thickness and presence of coronary artery disease in chronic obstructive pulmonary disease patients. *Anatol J Cardiol.* 2016;16:601-607.

22. Almagro P, Lapuente A, Pareja J, et al. Underdiagnosis and prognosis of chronic obstructive pulmonary disease after percutaneous coronary intervention: a prospective study. *Int J Chron Obstruct Pulmon Dis.* 2015;10:1353.

23. Liang B, Xu Z, Yi Q, Ou X, Feng Y. Association of chronic obstructive pulmonary disease with coronary artery disease. *Chin Med J.* 2012;126:3205-3208.

24. Sin DD, Man SP. Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular diseases? *Circulation.* 2003;107:1514-1519.

25. Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. *N Engl J Med.* 2017;377:1119-1131.

26. Criner GJ, Connett JE, Aaron SD, et al. Simvastatin for the prevention of exacerbations in moderate-to-severe COPD. *N Engl J Med.* 2014;370:2201-2210.

27. Chen CY, Holbrook M, Duess MA, et al. Effect of almond consumption on vascular function in patients with coronary artery disease: a randomized, controlled, cross-over trial. *Nutr J.* 2015;14:61.

28. Akodad M, Lattuca B, Nagot N, et al. COLIN trial: Value of colchicine in the treatment of patients with acute myocardial infarction and inflammatory response. *Arch Cardiovasc Dis.* 2017;110:395-402.

29. Liang Y, Li YP, He F, Liu XQ, Zhang JY. Long-term, regular remote ischemic preconditioning improves endothelial function in patients with coronary heart disease. *Braz J Med Biol Res.* 2015;48:568-576.

30. Le Page S, Bejan-Angoulvant T, Angoulvant D, Prunier F. Remote ischemic conditioning and cardioprotection: a systematic review and meta-analysis of randomized clinical trials. *Basic Res Cardiol.* 2015;110:11.

31. Vozoris NT, Wang X, Austin PC, et al. Incident diuretic drug use and adverse respiratory events among older adults with chronic obstructive pulmonary disease. *Br. J. Clin. Pharmacol.* 2017.

32. McGuire K, Avina-Zubieta JA, Esdaile JM, et al. Risk of Incident Chronic Obstructive Pulmonary Disease (COPD) in Rheumatoid Arthritis: A Population Based Cohort Study. *Arthritis Care Res. (Hoboken).* 2017.

33. Lee TM, Tu K, Wing LL, Gershon AS. Identifying individuals with physician-diagnosed chronic obstructive pulmonary disease in primary care electronic medical records: a retrospective chart abstraction study. *NPJ Prim Care Respir Med.* 2017;27:34.

Chapter 5: The effects of acute atmospheric pressure changes on the occurrence of ST elevation myocardial infarction: a case-crossover study

Abstract

Introduction: Few studies have explored the influence of short-term exposure to atmospheric pressure changes on the abrupt onset of ST elevation myocardial infarction (STEMI). We sought to evaluate the association between acute atmospheric pressure changes and the occurrence of STEMI.

Methods: We studied STEMI patients from the Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease (APPROACH) confirmed by angiogram from March 1st, 2002 to December 31st, 2016 in a case-crossover study design. Each case was matched with control intervals by the same day of week in the same month and year. All STEMI patients were linked with the nearest weather station within 40 km radius by residential postal code. The effect of exposing to air pressure changes, rate of air pressure changes, acute air pressure increase and acute air pressure decrease 1 day to 7 days earlier on the onset of STEMI were analyzed with conditional logistic regression. All models were adjusted with daily average temperature, relative humidity and average levels of five air pollutants (carbon monoxide, nitric monoxide, nitric dioxide, particulate matter 2.5 and ozone).

Results: In 11379 STEMI patients, the largest percentage (54.1%, N=6158) of individuals was between 45 and 65 years old, and 77.6% (N=8830) of the patients were male. Positive

associations with the onset of STEMI were only found at 7 days after exposing to acute air pressure decrease (OR, 1.12; 95%CI, 1.03-1.21), which is consistent in the sensitivity analysis and subgroup analysis. All the other models showed no significant associations.

Conclusion: There is no association between acute air pressure changes and the onset of STEMI in a lag time of 1 day to 6 days, whereas acute air pressure decrease is associated with higher odds of STEMI event 7 days after exposure.

Keywords: STEMI, atmospheric pressure changes, case-crossover

5.1 Background

Acute myocardial infarction (AMI), the severest form of coronary artery disease, causes more than 2.4 million deaths in the United States, more than 4 million deaths in Europe and northern Asia, which accounts for more than a third of all deaths in developed nations annually.[1] AMI is traditionally classified into ST elevation myocardial infarction (STEMI) and non-ST elevation myocardial infarction (NSTEMI).[2] STEMI, constituting nearly 25–40 % of all AMI cases, is a medical emergency that requires prompt recognition and treatment.[3]

Atmospheric pressure, also termed barometric pressure or air pressure, is the force per unit area exerted against a surface by the weight of the air above that surface.[4] Several previous studies have shown that atmospheric pressure may have a significant impact on the morbidity and the mortality of AMI.[5, 6] Sanja et al have found that lower air pressure (< 100.9 kPa) adjusted for the temperature and relative humidity was associated with lower AMI incidence among adults and the elderly people.[7] A 10-year survey spanning 1985 to 1994 has revealed a U shape association between atmospheric pressure and MI, showing that increases and decreases in atmospheric pressure from 101.6 kPa were both associated with an increase in daily MI event rates.[8] Moreover, in a study among 1.64 million German-Swiss residents living at altitude between 259 and 1960m, the investigators have found a relative risk reduction of 22% per 1000m of altitude above sea level for myocardial infarction.[9] Since altitude is inversely related with atmospheric pressure, we suspected that atmospheric pressure may be one of the mechanisms to explain the protective effect of living at high altitude. However, few studies have explored the impacts of short-term exposure to atmospheric pressure changes on the abrupt onset of STEMI. Therefore, the objective of this study is to investigate the relationship between acute air pressure changes and the occurrence of STEMI.

5.2 Methods

5.2.1 Study design

We used a case-crossover study design, which is a variant of a case-control design and is widely used to study the association between a transient exposure and an acute event.[10] Since STEMI generally has an abrupt onset and a short latency period for diagnosis, we employed this design to explore the effects of acute atmospheric pressure changes on the onset of STEMI. This design is advantageous because it minimizes confounding from time-independent risk factors such as age, gender, the family history, and comorbidities.[11] In the case-crossover study, each case serves as its own control. The exposure of the case interval was compared to the exposure of the control interval.

5.2.2 Data sources

We requested data of the STEMI population from the Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease (APPROACH) and Alberta Strategy for Patient-Oriented Research (SPOR) Support for People and Patient-Oriented Research and Trials (SUPPORT) Unit. The ethics approval was obtained from the University of Alberta of Health Research Ethics Board. The details of the data sources were addressed below.

1. APPROACH

APPROACH is an ongoing clinical data collection registry capturing all patients undergoing cardiac intervention and revascularization in the province of Alberta, Canada, since 1995.[12] The registry contains detailed clinical information including diagnosis, procedure, demographic profile, ejection fraction, smoking and history of myocardial infarction, comorbidities and indication for revascularization etc. This registry collects exhaustive

standardized information on the presentation of STEMI from the only 3 cardiac catheterization laboratories in Alberta (2 located in Edmonton and 1 in Calgary), covering the entire 3.6 million population of Alberta. [13]

2. SPOR SUPPORT Unit

SPOR is a Canadian Institutes of Health Research (CIHR) initiative, which integrates funding, research and healthcare.[14] SPOR is also a coalition of federal, provincial, and territorial partners comprised of SUPPORT Units and Networks.[14] The SPOR SUPPORT Units are specialized, multidisciplinary research service centres located across Canada aiming to support researchers conducting patient-centred research.[14]

3. Meteorological Data

We obtained historic climate data from Environment Canada.[15] Hourly atmospheric pressure, temperature and relative humidity collected by weather stations across Alberta were used in the study. Any weather stations which did not record hourly air pressure were not considered. Air pollution data were extracted from the Environment Canada National Air Pollution Surveillance database.[16] Hourly records of five air pollutants including nitric oxide (NO), nitrogen dioxide (NO_2), carbon monoxide (CO), Ozone and particulate matter with an aerodynamic diameter $\leq$2.5 μm (PM2.5) were used to calculate daily average levels of the air pollutants.

5.2.3 Population

All patients admitted to the hospital from March 1, 2002 to December 31, 2016 with a primary diagnosis of STEMI confirmed by electrocardiogram and coronary angiogram were

included in this study. Patients who did not have complete data on the meteorological factors or air pollutants were excluded.

5.2.4 Variables of interest

1. Exposures of interest

In this study, we investigated the effects of four exposures including acute atmospheric pressure changes, the rate of atmospheric pressure changes, acute atmospheric pressure increase, and acute atmospheric pressure decrease, on the onset of STEMI.

Acute atmospheric pressure change was referred to the difference between the daily highest air pressure and the lowest air pressure from 12 A.M. to 11 P.M. The rate of air pressure changes was defined as the daily air pressure changes divided by the duration of the change. The mean and standard deviation of daily air pressure changes over the study period were considered as the cut-point to determine if acute air pressure increase or decrease was present. Specifically, acute air pressure increase was deemed present if the daily atmospheric pressure change was greater than its mean plus one standard deviation and the highest air pressure was later than the lowest one. A similar definition was employed for acute air pressure decrease.

2. Outcome variable and covariates

The occurrence of STEMI was the outcome variable for this study. To better describe the study population, the demographic characteristics and comorbidities were also collected, including age, gender, heart failure, cerebrovascular disease, peripheral vascular disease, chronic obstructive pulmonary disease, current/prior smoking, hyperlipidemia, hypertension, and diabetes mellitus.

5.2.5 Statistical analysis

The admission dates were treated as the case intervals. We used a time-stratified referent selection strategy to select the control intervals, which were matched with the cases by the same day of week from the same calendar month and year. This strategy has been proven to be able to limit time-trend bias.[17]

Patients' first admitted hospital and the admission dates requested through Alberta SPOR SUPPORT Unit were first linked with the demographic data from APPROACH registry by the personal health number. Then, the records of all the STEMI cases as well as their self-controls were linked with the meteorological and air pollutants' data from the nearest weather station by the postal code and the date of exposure. We restricted our analysis to the patients who live within 40km radius of the nearest weather stations. A series of lag periods from 1 to 7 days was explored. For example, for 1 day lag period, the patients were considered being admitted to the hospital 1 day after the exposure.

The characteristics of the STEMI patients and the distribution of STEMI events in different seasons were described. Statistics including mean, standard deviation and 25%, 50%, 75% percentiles of continuous predictors were presented.

Unadjusted and adjusted conditional logistic regression was used to evaluate the relationship between the occurrence of STEMI and four exposures of interest. A p-value of less than 0.05 was considered to be statistically significant for all statistical tests. The effects of association were reported as odds ratio with corresponding 95% confidence interval. Daily average temperature, relative humidity and daily average levels of five air pollutants were adjusted in the regression models.

Pre-specified subgroup analyses were performed to determine if there were different effects of air pressure changes on the onset of STEMI in each subgroup. A sensitivity analysis restricting the STEMI population to those who live within 20km radius of the nearest weather station was conducted to examine if the results would be affected by the choice of the distance.

All the data management was implemented in Python 3.6.1. The geodesic distances between patients and weather stations were calculated using GeoPy 1.11.0 package. The statistical analyses were implemented in STATA (version 13.1; StataCorp LP, College Station, TX, USA).

5.3 Results

The characteristics of the STEMI patients are shown in Table 1. In a total of 11379 STEMI patients, the largest percentage (54.1%, N=6158) of individuals was between 45 and 65 years old, and 77.6% (N=8830) of all the STEMI patients were male. Hypertension (55.8%, N=6349), hyperlipidemia (56.2%, N=6393) and smoking history (53.4%, N=6083) were the most common comorbidities in this population. The STEMI events were basically equally distributed in four seasons (26.0%, 24.2%, 24.9%, 24.9% from Spring to Winter). The percentages of patients exposed to acute air pressure increase and air pressure decrease were 7.2% (N=818) and 7.1% (808), respectively.

The statistics of continuous predictors are shown in Table 2. The mean and standard deviation of the daily air pressure change and the rate of air pressure change were 0.66 (0.41) kPa and 0.40 (0.20) hPa/hour. The reason of using hPa/hour as the unit for the rate of air pressure change was for the convenience of interpreting one unit changes regarding the OR in the regression model. The mean and standard deviation of the average daily temperature, relative

humidity, carbon monoxide, nitric oxide, nitrogen dioxide, ozone and PM2.5 that the study population exposed to were 4.33(11.0) °C, 64.5%(14.9%), 0.28(0.22) ppm, 13.08(21.1) ppb, 15.9(10.0) ppb, 21.3(10.0) ppb and 7.6(6.26) $\mu g/m^3$, respectively.

Figure 1 shows the unadjusted and adjusted odds ratios of STEMI associated with four exposures with lag times from 1 day to 7 days for patients who were linked with the nearest weather stations within 40 km of their residences. Acute air pressure changes were found to have no significant association with the onset of STEMI with and without the adjustment of average temperature, relative humidity and air pollutants in the lag periods from 1 day to 6 days. In the lag period of 7 days, this association became significant with an odds ratio of 1.06 (95% CI, 1.01 to 1.11) after the adjustment. There was no significant association between the onset of STEMI and the rate of air pressure changes, with adjusted odds ratios ranged from 0.92 to 1.05. Similarly, acute air pressure increase had no significant effect on the onset of STEMI, with the adjusted odds ratios ranged from 0.98 to 1.05. However, acute air pressure decrease was associated with a higher probability of STEMI onset with and without adjustment (OR, 1.12; 95%CI, 1.03 to 1.21) in the lag time of 7 days, while this association was not found in the lag period from 1 day to 6 days.

In the sensitivity analysis (Figure 2) of restricting the distances between the patients and weather stations to less than 20km, we found that the results were similar to the findings with a restriction of the distance between patients' residence and the weather stations within 40km. The differences were that the odd ratio of STEMI associated with acute air pressure changes was insignificant in the lag period of 7 days (OR, 1.04; 95%CI, 0.98 to 1.10). In the lag period of 7 days, the adjusted odds ratio of STEMI onset associated with acute air pressure decrease was 1.10 (95%CI, 1.01 to 1.19), which remains significant.

Figure 3 and Figure 4 show the odds ratios of STEMI onset associated with four exposures by sex and age from 1 day to 7 days lag periods adjusting for daily mean temperature, relative humidity and air pollutants. The onset of STEMI was found to have no significant association with acute air pressure changes, the rate of air pressure changes, air pressure increase and air pressure decrease, except that air pressure changes were significantly associated with higher likelihood of STEMI onset for males (OR, 1.12; 95%CI, 1.02 to 1.23) and for the non-seniors (OR, 1.12; 95%CI 1.02 to 1.24) at day 7 after the exposure. We also found a borderline significant association between the onset of STEMI and the rate of air pressure changes in a lag time of 5 days (OR, 0.88; 95%CI, 0.77 to 0.99).

5.4 Discussion

In the current study, we found that there were no significant associations between the occurrence of STEMI and four exposures including acute air pressure changes, the rate of air pressure changes, acute air pressure increase and air pressure decrease 1 to 6 days after the exposure, whereas air pressure decrease was significantly associated with higher odds of STEMI onset 7 days after the exposure. Although acute air pressure changes were significantly associated with higher odds of STEMI events in the adjusted model 7 days after the exposure, this association is likely a false positive error, since which is not consistently found in the subsequent sensitivity analysis and subgroup analysis.

There is a growing body of literature reporting that meteorological factors such as air pollutants[18], temperature[8, 19], atmospheric pressure and relative humidity[20] may trigger AMI, which is often induced by a ruptured or eroded atherosclerotic plaque that leads to a sudden and critical reduction in blood flow.[21] Although the effect of climate triggers to any single person is

relatively small compared with the effect of traditional risk factors (e.g. smoking), the public health relevance is considerable, as environmental factors impact hundreds of millions of individuals on a continuous and involuntary basis.[22]

Several studies have indicated that acute air pressure change might have an impact on the onset of myocardial infarction. AMI is one of the common medical emergencies during a commercial flight.[23] During the flight, the passengers experience a reduced ambient air pressure equivalent to the air pressure at an altitude of 6000 to 8000 feet.[24] In an in vitro study, Mitsuhiro et al have demonstrated that subtle changes of atmospheric pressure (5–20 hPa) can induce elevation of intracellular calcium level in cultured human keratinocytes,[25] suggesting that keratinocytes might act as the sensors of atmospheric pressure changes in our bodies. It has also shown that an air pressure changes as small as 5 hPa could have an effect on the bodies. The authors also found that various neurotransmitters and hormones that influence multiple systems (nervous, cardiovascular, endocrine, and immune systems) were generated and released from epidermal keratinocytes after exposing to acute atmospheric pressure changes.[26] Their findings suggest that atmospheric pressure change might be sensed by epidermal keratinocytes, causing the synthesis and release of NO which might subsequently influence the blood vessels. [26] In our study, we found that acute air pressure decrease (>10.7 hPa) increased the odds of STEMI occurrence (OR ranged from 1.10 to 1.12) in a lag time of 7 days with and without adjustment of the confounders, which was consistent with the findings in the sensitivity analysis. In the subgroup analysis, this positive association was also observed in male and in non-senior patients. Primarily, our results indicate that the short-term exposure to daily air pressure decrease may require an induction period of 7 days before the occurrence of STEMI. Our results were partly in line with Houck's findings[27], which showed no relation between the daily occurrence of AMI

and the maximum air pressure changes for a lag period of 1 to 3 days. However, Honck et al[27] did not investigate a longer latency period. Therefore, further investigations are required to confirm the positive association between acute air pressure decrease and STEMI occurrence at 7 day lag period.

Strengths

Our study has several strengths. Firstly, to our best knowledge, this is the first study evaluating the relationship between acute atmospheric pressure changes and the onset of STEMI using a case-crossover study design, which intrinsically adjusts for all measured and unmeasured time-invariant individual-level confounders, such as age, gender, social economic status, lifestyle, body mass index and comorbidities. Secondly, we used the resident postal code of each patient to locate the nearest weather station for personalized atmospheric pressure data, which makes our study more precise than the studies using the city-wide averaged atmospheric pressure. Thirdly, this study has a large sample size covering all STEMI patients undergoing cardiac angiogram in a province, which reduces the selection bias arising from the selection of patients from a single research site. Finally, time stratified referent selection strategy adopted in this study has controlled the time-trend bias.

Limitations

There are some limitations in our study. Since the outcome definitions of STEMI were defined by hospital admissions, major events leading to out-of-hospital mortality were not included in the study. Another limitation is a potential selection bias induced by excluding weather stations which did not record hourly atmospheric pressure. We observed that there were about 90 percent of included patients coming from the urban area. This means that our results

may be more representative for patients who live in urban area. Moreover, we were unable to adjust for other plausible triggers, such as physical exertion, anxiety, loss of a significant person or alcohol. However, it is unlikely that all these rare triggers happened at the same time. Therefore, we expect that the bias would be small. Lastly, some measurement error may exist that would bias the estimate toward the null, since individual-level exposure can only be measured by the nearest weather station to the patients' residences.

5.5 Conclusion

There is no association between acute air pressure changes and the onset of STEMI in a lag time of 1 day to 6 days, whereas acute air pressure decrease is associated with higher odds of STEMI event 7 days after exposure.

Table 5. 1. Characteristics of the STEMI patients (N=11379)

Characteristic	N	%
Age(Years)		
<45	1023	9.0
45-65	6158	54.1
>65	4198	36.9
Gender		
Male	8830	77.6
Female	2549	22.4
Season		
Spring (March to May)	2956	26.0
Summer (June to August)	2749	24.2
Autumn (September to November)	2838	24.9
Winter (December to February)	2836	24.9
Comorbidity		
COPD	1088	9.6
Heart failure	1012	8.9
Cerebrovascular disease	457	4.0
Diabetes	2298	20.2
Hypertension	6349	55.8
Hyperlipidemia	6393	56.2
Smoking history	6083	53.4
PAD	837	7.36
dichotomous Exposure		
Acute air pressure increase	818	7.2%
Acute air pressure decrease	808	7.1%

COPD, chronic obstructive pulmonary disease; PAD, peripheral artery disease.

Table 5. 2. Summary statistics for continuous exposures and covariates.

Variable	Mean	Standard deviation	25% percentile	50% percentile	75% percentile
Air pressure change(kPa)	0.66	0.41	0.35	0.56	0.87
Rate of air pressure change(hPa/hour)	0.40	0.20	0.24	0.35	0.50
Temperature (Celsius)	4.33	11.0	-2.6	5.29	13.1
Relative humidity (%)	64.5	14.9	53.6	64.7	75.4
CO(ppm)	0.28	0.22	0.2	0.3	0.4
NO(ppb)	13.08	21.1	2	6	15
NO2(ppb)	15.9	10.0	8	14	22
O_3(ppb)	21.3	10.0	14	21	29
PM2.5(μg/m^3)	7.5	6.26	4	6	9

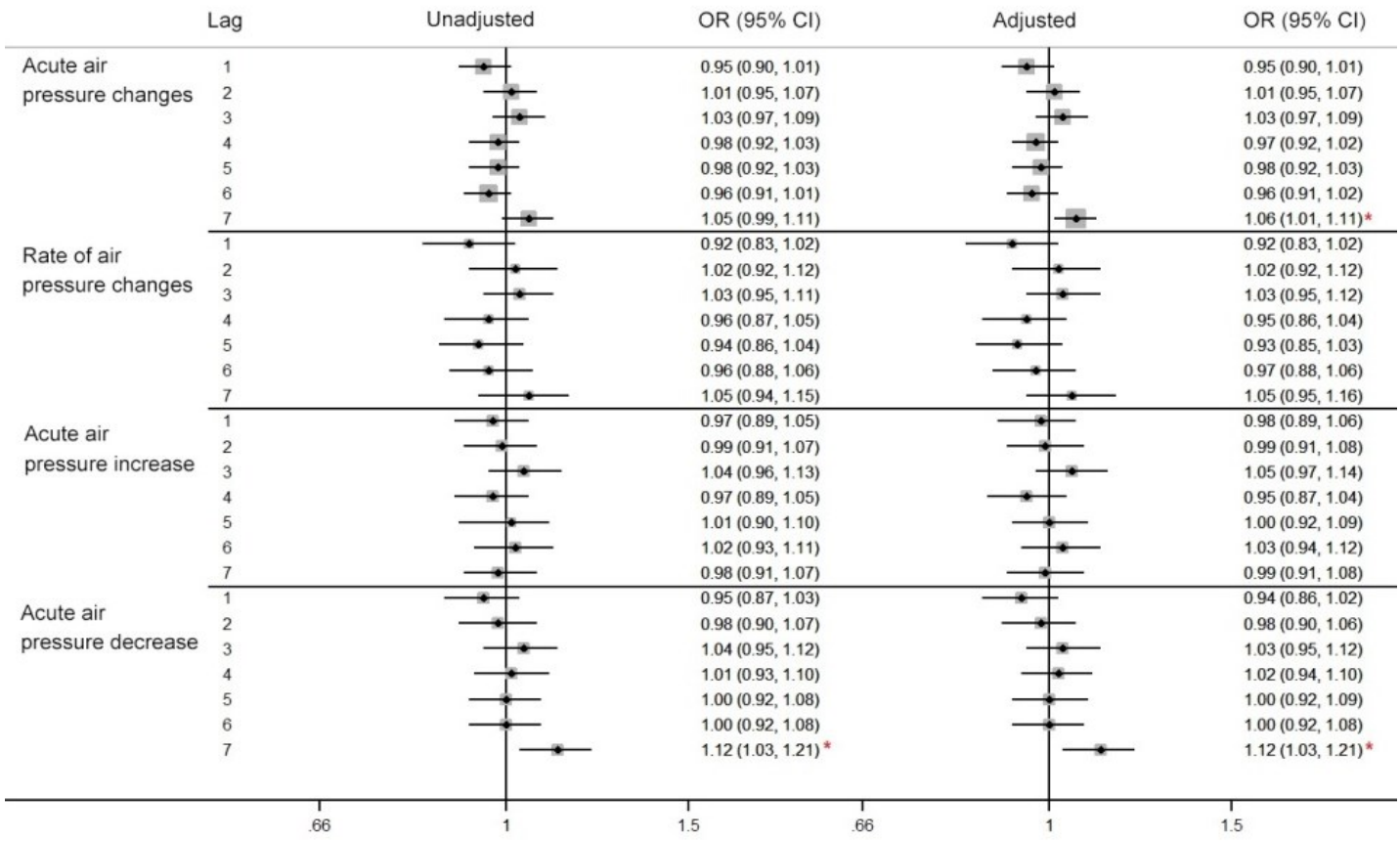

Figure 5. 1. The unadjusted and adjusted odds ratios of STEMI onset associated with four exposures of interest (<40km between patients' residence and the nearest weather station)

One unit increase was 1kPa for acute air pressure changes and 1hPa/hour for the rate of air pressure changes.

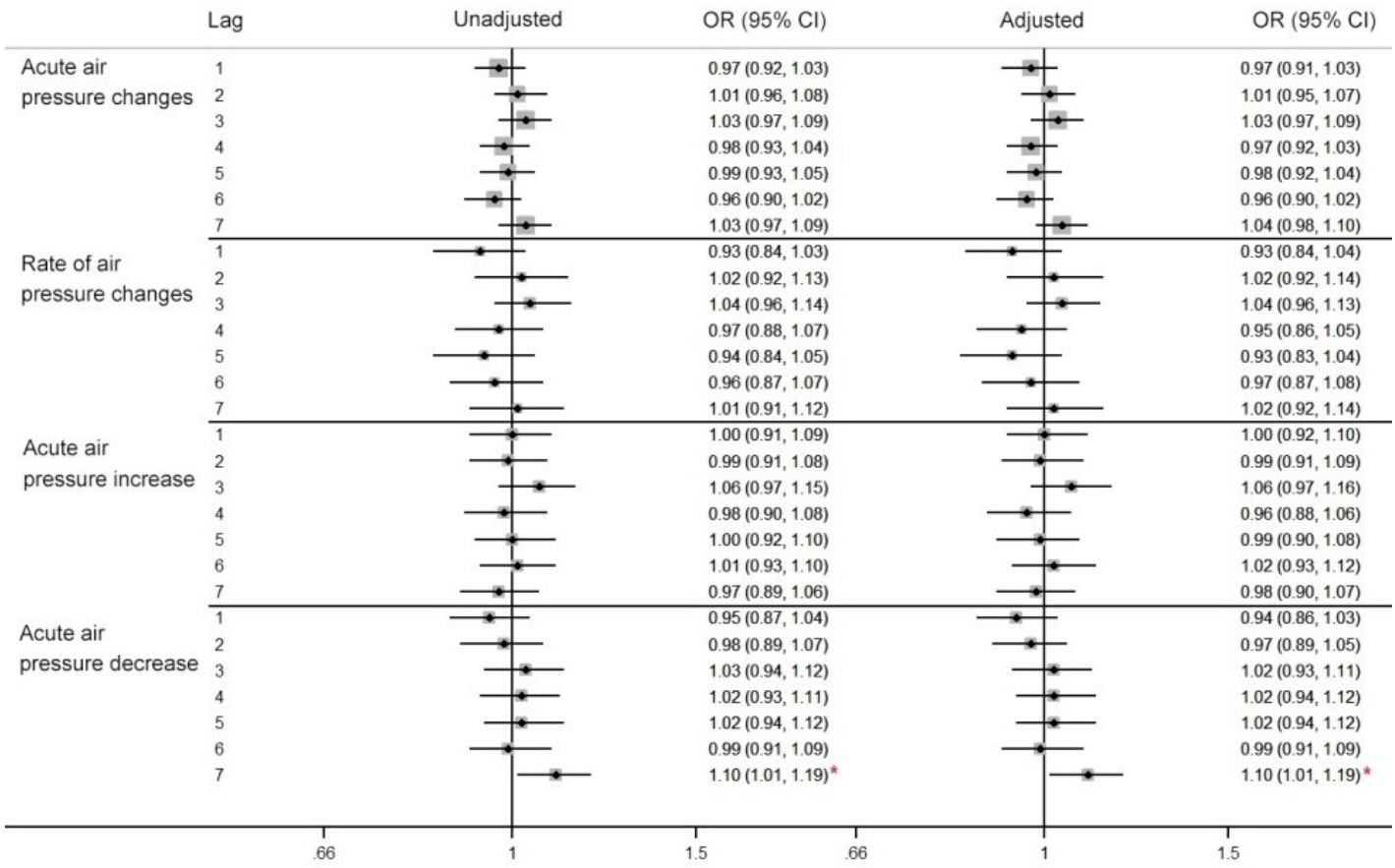

Figure 5. 2. The unadjusted and adjusted odds ratios of STEMI onset associated with four exposures of interest (<20km between patients' residence and the nearest weather station)

One unit increase was 1kPa for acute air pressure changes and 1hPa/hour for the rate of air pressure changes.

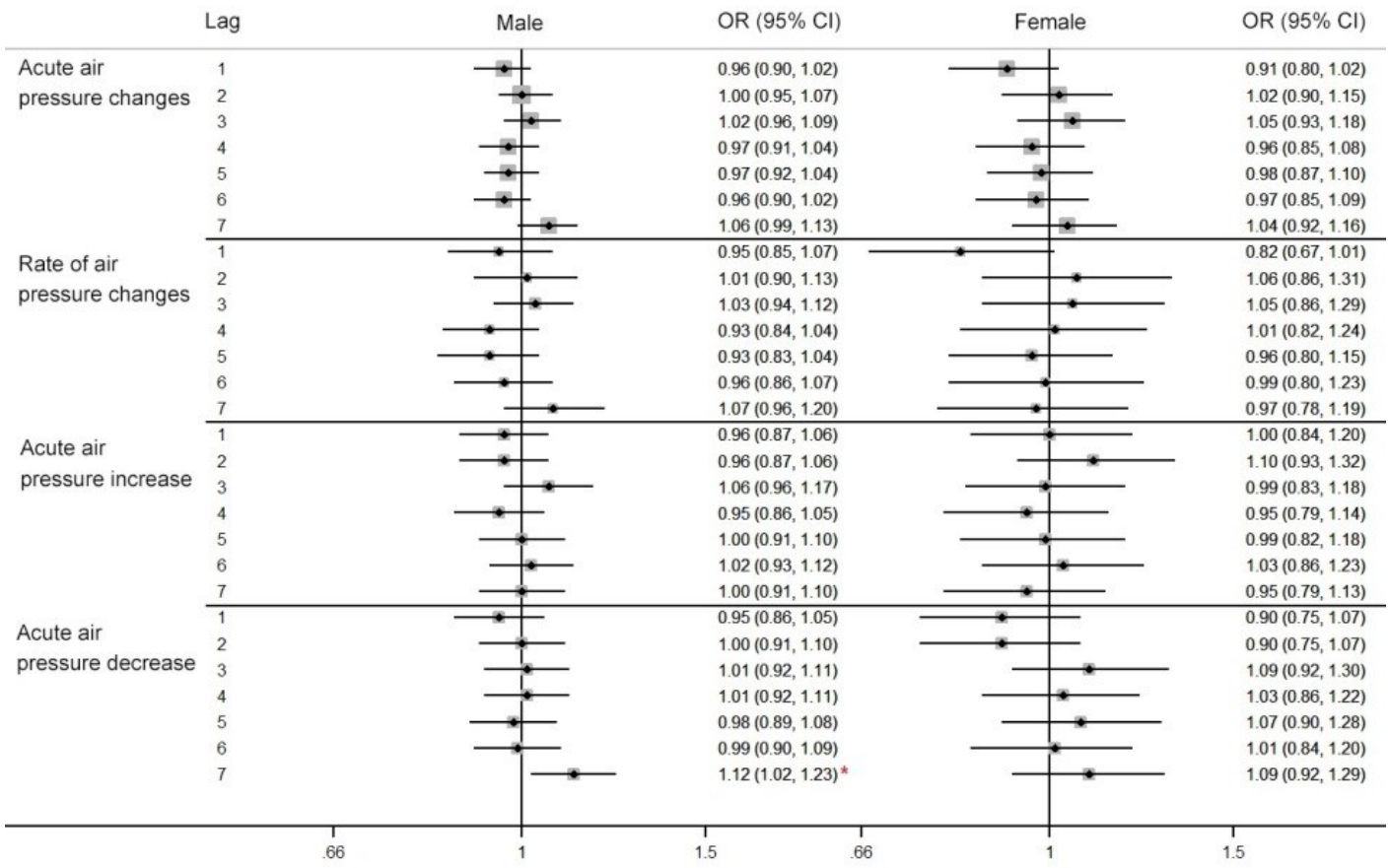

Figure 5. 3. The adjusted odds ratios of STEMI onset associated with four exposures of interest (<40km between patients' residence and the nearest weather station)

One unit increase was 1kPa for acute air pressure changes and 1hPa/hour for the rate of air pressure changes.

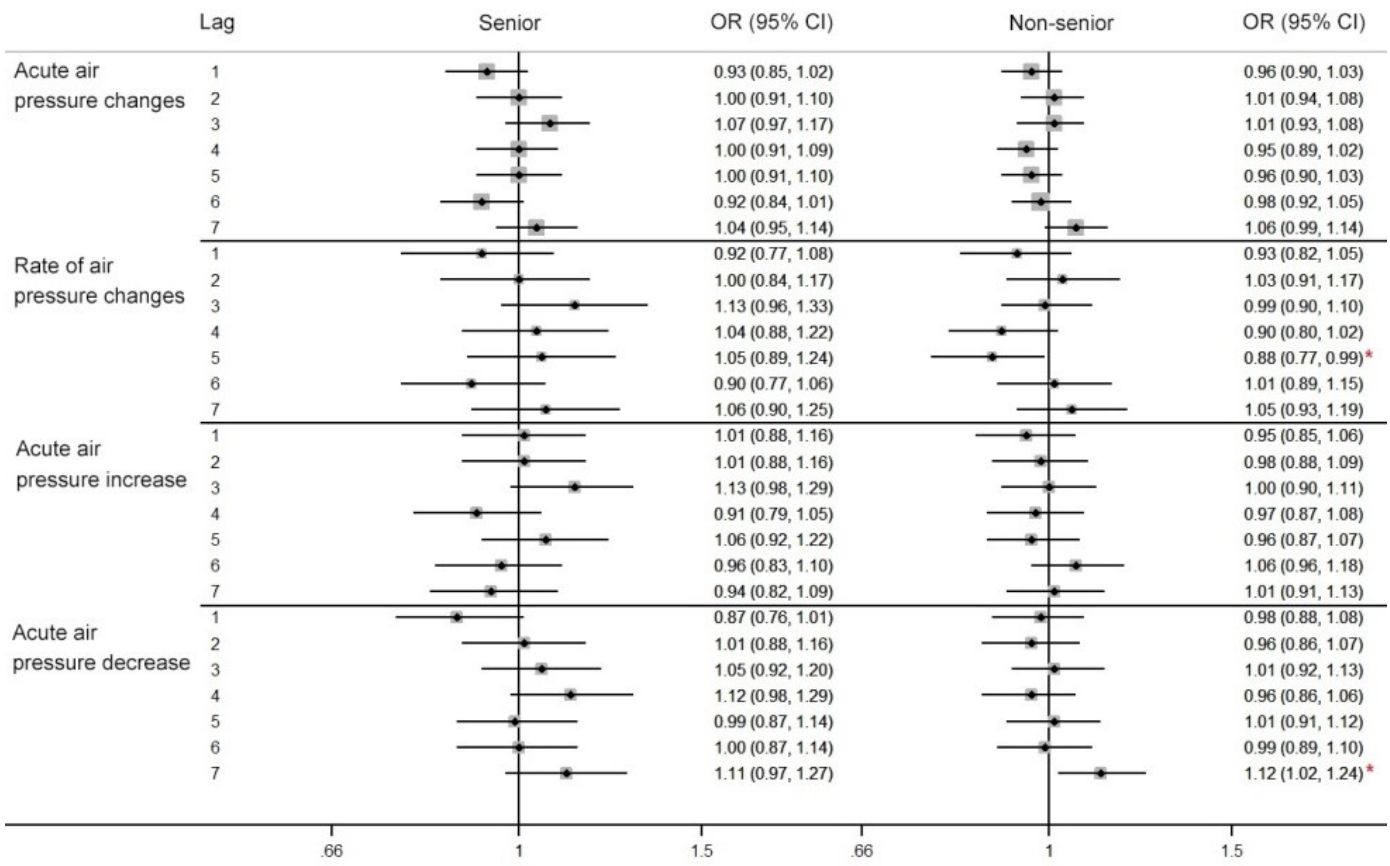

Figure 5. 4. The adjusted odds ratios of STEMI onset associated with four exposures of interest (<40km between patients' residence and the nearest weather station)

One unit increase was 1kPa for acute air pressure changes and 1hPa/hour for the rate of air pressure changes.

5.6 References

1. Reed GW, Rossi JE, Cannon CP. Acute myocardial infarction. *The Lancet.* 2017;389:197-210.

2. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. *Eur. Heart J.* 2012;33:2551-2567.

3. Yadlapati A, Gajjar M, Schimmel DR, Ricciardi MJ, Flaherty JD. Contemporary management of ST-segment elevation myocardial infarction. *Internal and Emergency Medicine.* 2016;11:1107-1113.

4. Department of Atmospheric Sciences (DAS) at the University of Illinois. Available from: http://ww2010.atmos.uiuc.edu/(Gh)/abt/aknw/dvlp.rxml. Accessed on Oct 21, 2017.

5. Wang H, Matsumura M, Kakehashi M, Eboshida A. Effects of atmospheric temperature and pressure on the occurrence of acute myocardial infarction in Hiroshima City, Japan. *Hiroshima J. Med. Sci.* 2006;55:45.

6. Radišauskas R, Vaičiulis V, Ustinavičienė R, Bernotienė G. The effect of atmospheric temperature and pressure on the occurrence of acute myocardial infarction in Kaunas. *Medicina.* 2013;49:447-452.

7. Bijelović S, Dragić N, Bijelović M, Kovačević M, Jevtić M, Ninkovic MO. Impact of climate conditions on hospital admissions for subcategories of cardiovascular diseases. *Medycyna pracy.* 2017;68:189.

8. Danet S, Richard F, Montaye M, et al. Unhealthy effects of atmospheric temperature and pressure on the occurrence of myocardial infarction and coronary deaths. *Circulation.* 1999;100:e1-e7.

9. Faeh D, Gutzwiller F, Bopp M. Lower mortality from coronary heart disease and stroke at higher altitudes in Switzerland. *Circulation.* 2009;120:495-501.

10. Maclure M. The case-crossover design: a method for studying transient effects on the risk of acute events. *American journal of epidemiology.* 1991;133:144-153.

11. Warner L, Macaluso M, Austin HD, et al. Application of the Case-Crossover Design to Reduce Unmeasured Confounding in Studies of Condom Effectiveness. *American Journal of Epidemiology.* 2005;161:765-773.

12. Shavadia J, Norris CM, Graham MM, Verma S, Ali I, Bainey KR. Symptomatic graft failure and impact on clinical outcome after coronary artery bypass grafting surgery: Results from the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease registry. *American Heart Journal.* 2015;169:833-840.

13. Bresee LC, Knudtson ML, Zhang J, et al. Likelihood of coronary angiography among First Nations patients with acute myocardial infarction. *CMAJ.* 2014;186:E372-380.

14. Murphy T. SPOR SUPPORT Unit, November 10, 2015. 2015.

15. Historical data. Environment Canada. Available from: http://climate.weather.gc.ca/historical_data/search_historic_data_e.html. Accessed on Oct 19, 2017

16. Al-Omran M, Tu JV, Johnston KW, Mamdani MM, Kucey DS. Outcome of revascularization procedures for peripheral arterial occlusive disease in Ontario between 1991 and 1998: a population-based study. *Journal of vascular surgery.* 2003;38:279-288.

17. Janes H, Sheppard L, Lumley T. Case-crossover analyses of air pollution exposure data: referent selection strategies and their implications for bias. *Epidemiology.* 2005;16:717-726.

18. Peters A, Dockery DW, Muller JE, Mittleman MA. Increased particulate air pollution and the triggering of myocardial infarction. *Circulation.* 2001;103:2810-2815.

19. Barnett AG, Dobson AJ, McElduff P, Salomaa V, Kuulasmaa K, Sans S. Cold periods and coronary events: an analysis of populations worldwide. *J. Epidemiol. Community Health.* 2005;59:551-557.

20. Ou CQ, Jun Y, Ou QQ, et al. The impact of relative humidity and atmospheric pressure on mortality in Guangzhou, China. *Biomed. Environ. Sci.* 2014;27:917-925.

21. Davies MJ, Thomas AC. Plaque fissuring--the cause of acute myocardial infarction, sudden ischaemic death, and crescendo angina. *Br. Heart J.* 1985;53:363.

22. Claeys MJ, Rajagopalan S, Nawrot TS, Brook RD. Climate and environmental triggers of acute myocardial infarction. *Eur. Heart J.* 2016;38:955-960.

23. Nable JV, Tupe CL, Gehle BD, Brady WJ. In-flight medical emergencies during commercial travel. *N Engl J Med.* 2015;373:939-945.

24. Subcommittee CA, Association AM, Committee AS. Cabin cruising altitudes for regular transport aircraft. *Aviation, space, and environmental medicine.* 2008;79:433-439.

25. Ikeyama K, Nakatani M, Kumamoto J, Denda M. Distinct intracellular calcium responses of individual cultured human keratinocytes to air pressure changes. *Skin Res. Technol.* 2013;19:346-351.

26. Denda M. Keratinocytes at the uppermost layer of epidermis might act as sensors of atmospheric pressure change. *Extreme physiology & medicine.* 2016;5:11.

27. Houck PD, Lethen JE, Riggs MW, Gantt DS, Dehmer GJ. Relation of atmospheric pressure changes and the occurrences of acute myocardial infarction and stroke. *American Journal of Cardiology.* 2005;96:45-51.

Chapter 6: Discussion and conclusion

6.1 General discussion

The preceding chapters of this thesis have demonstrated some practical examples of epidemiologic research of CVDs using existing data. The study carried out in Chapter 2 is a validation study developing new algorithms to identify PAD patients using linked administrative data and ABI data from independent researchers. We found that using administrative data to identify PAD patients had high specificity but low sensitivity in the community, which implies that PAD remains under-diagnosed and therefore undertreated in the community. Even though the current study has demonstrated that using ICD codes with common predictors were not sufficient in PAD diagnosis, the use of ICD codes has been shown to facilitate the identification of patients with COPD,[1] herpes zoster ophthalmicus,[2] and venous thromboembolism[3]. Moreover, ICD codes in the administrative data are useful for chronic disease surveillance.[4, 5] These findings have supported the incredibly helpful role of administrative data in healthcare research. Because the use of ICD codes is commonplace and the awareness of the applicability and potential error sources of ICD codes usage has increased,[6] investigators can critically employ the administrative data in medical research to maximize the impact of findings on healthcare practice and outcomes. To enhance the validity of using ICD codes to identify PAD patients, more studies exploring the use of ICD codes or combining administrative data with other databases are encouraged.

Chapter 3 is a systematic review that summarized the current evidence reporting the comparison of patients receiving different anticoagulants with respect to the admission rate and

length of hospital stay. The main findings were that the admission rate of using LMWH was significantly lower than using UFH. Compared with parenteral therapy, using rivaroxaban had a lower or similar rate of hospitalization. The LOS was significantly shorter when comparing the LMWH group to the UFH group, or comparing rivaroxaban to parenteral treatment. In this information era, there are more than 25 million published journal articles in MEDLINE, and this number has dramatically increased with more than 813,500 newly added citations in 2017.[7] This ever-increasing plethora of studies is challenging busy clinicians and researchers to catch up with the literature which usually guides the clinical decision-making. Thus, systematic review and meta-analysis critically summarize evidence on a specific topic, being a major player in translating primary research evidence into clinical practice.[8-10] Despite that systematic reviews are superior to independent primary study, systematic reviews have potential biases and are required appropriate interpretations from clinicians and researchers.[10] Moreover, the quality of systematic reviews varies, and therefore, efforts should be made to improve the quality of systematic reviews. In the current study, we have found that less than 20% of included RCTs reported admission rates or LOS, which compromise the potential of generalizing our findings because of the small sample size. We urge for more RCTs to report admission rate and LOS. And efforts on improving the primary data transparency will benefit the production of high-quality systematic reviews. Overall, appropriate use of systematic reviews direct patient-care decision based on scientific evidence, contributing to the improvement of health care system.

In Chapter 4, through analyzing a large population-based cohort from APPROACH registry, we investigated whether COPD has an independent relationship with CAD. The results showed that COPD was negatively associated with CAD with and without controlling for classic cardiovascular risk factors. This study suggests that the argument from a systematic review[11]

stated that negative relationship between COPD and CAD might be due to small sample size was not valid, while this association should be interpreted cautiously with regards to causal inference. From a broader perspective, it is vital to study the association between CVD and other common diseases, as it will contribute to the development of evidence-based guidelines to improve CVD prevention and treatment. There are epidemiologic studies have demonstrated the associations of post-traumatic stress disorder[12], obesity[13], and insulin resistance[14] with CVD, which may direct clinicians to launch better interventions to improve patient outcomes, and provide valuable insight to the overall risk prediction for CVD.

In Chapter 5, a case-crossover study was conducted by leveraging administrative data, registry data, meteorological data, and air pollutants data. It was found that there is no association between acute air pressure changes and the onset of STEMI in a lag time of 1 day to 6 days, whereas acute air pressure decrease is associated with higher odds of STEMI event 7 days after exposure. Our results are in line with Houck's findings, [15] which found no relationship between the daily occurrence of AMI and the daily maximum air pressure changes. However, the current evidence regarding the short-term impact of air pressure changes on the occurrence of STEMI is very limited. More studies are needed to further validate our findings. Environmental epidemiology has long existed since Roman and Greek times, which aims to uncover the contribution of environmental exposures to injuries and diseases. The increased awareness of the influence of climate and weather on population health and the urgency of the climate change threat has spurred investigations to elucidate the interactions between meteorological factors and health. Meteorological factors, such as temperature,[16, 17] atmospheric pressure,[18] humidity[19]and air pollutants[20] have been shown to have associations with CVDs across the world. These

epidemiological studies will continue to promote public health programs to prepare and prevent meteorological factors related health effects.[21]

Above all, the available data can be leveraged to address important clinical questions and dilemmas. First of all, epidemiologic studies using existing data are capable of general high-quality evidence in an efficient manner, especially when employing systematic reviews and meta-analyses. The Institute of Medicine has updated the definition of Clinical Practice Guidelines to specify that they are "informed by a systematic review of evidence"[22], highlighting how reutilizing numerous primary data from RCTs contributes to clinical decision making. Secondly, besides directing clinical practices, these studies have filled the knowledge gaps in medicine along with primary studies. Both primary data and secondary data have advantages and disadvantages. Thus, based on research priority, hypotheses, study designs, ethical issues, cost, secondary data availability and others, researchers can balance the use of available data or collecting primary data for a specific research question. Since secondary studies and primary studies are complementary to each other, using secondary data sources can improve the overall efficiency of the medical research by maximizing the available research resources. Last but not least, it also provides important etiologic clues and helps formulate hypotheses to be tested in subsequent studies. In this thesis, I am also able to reflect on my practical experience of using existing data for research and identify the challenges CVD researchers will confront and examine the policy issues that would hinder researchers' timelines.

6.2 Challenges in the research using existing data

6.2.1 Timely access to data

In a survey of provincial ministries and organizations responsible for the access to health data, the authors have found that when researchers actively requesting for data, it took anywhere between 1 to 18 months for them to receive the data.[23] For the project displayed in Chapter 2, it took six months to receive the data from Alberta Health and one month to receive the data from the original researchers. It took six months for the delivery of data for the project in Chapter 4 and four months for the project in Chapter 5. A variety of factors affect the timeline including the data custodian review process, the responsiveness of the researcher, researcher's experience, the complexity of the research project, privacy uncertainty, staffing levels and the availability of fundings.[23] Public data such as published full-text original articles used in the systematic review and the meteorological data can be retrieved faster and the timeline is under the researchers' control. Due to the variation of the data processing time, it is advisable to consider the time required for the proposed project and keep in close contact with the data custodian to ensure a timely delivery of data.

6.2.2 Detailed data documentation

Easily understandable documentation of the existing datasets or databases may be difficult to obtain, but such documentation is especially worthwhile to evaluate the usefulness and the quality of the data. In addition, it also allows the researchers to make precise data request when communicating with the data administrators who responsible for extracting the data. It includes information on data available (list of variables collected), data format (codes and their definition), data collection procedures (population targeted, mode of collection, etc.),[24] and data quality assurance. Although Alberta Health has provided documents on the available variables in

the databases, information on the data collection procedure and data quality are not provided publicly. As for the APPROACH registry, the data quality documentation and the data specification are only available through request after submitting a data application. I found that many of the variables' description are not clearly defined. For instance, the description of cardiac family history is 'a family history of heart disease'. However, detailed information regarding the family members with heart disease, such as first- or second-degree relatives and the age of disease diagnosis, is not given, which resulted in difficulties in describing the variable definition in the research manuscript. It is advised that all this information should be made available publicly online, so that the researchers could have a more detailed evaluation on the data and also reduce the time on response to these types of inquiries for the data custodian.

6.2.3 Establishing causality

Correlation is not equal to causality. RCTs normally are considered the most reliable way to establish causality. However, RCTs are not always feasible due to reasons such as ethical concerns, high cost, and timeliness. [25] Therefore, much of our knowledge of causality must come from non-randomized observational studies.[25] The sampling method for research using existing data generally is not random, which make this type of study prone to the selection bias and the confounding bias. Despite the challenge in making causal inference in research using existing data, new techniques such as instrument variable analysis are attracting more attention as a tool for causal inference since it can control for unmeasured confounding in observational epidemiologic studies.[26] The rationale of instrument variable is that it mimics the process of intervention assignment in the randomized study.[27] Another statistical technique that could draw casual inference for observational study using existing data is propensity score matching. Propensity score balancing non-equivalent groups to allow researchers making more accurate

causal inference in a non-randomized design.[28] Using data from on-going longitudinal cohort and identifying a strong and dose-response relationship between exposure and outcome could also contribute to a causal claim.

6.2.4 Data conversion

There are a variety of data analytic software on the marketing and data are encoded in different formats. Several issues regarding data conversion have not received the attention it deserves. Data conversion is a critical step in the data analysis. For example, R software is growing its popularity due to its open-source policy and a large selection of packages that are free to use. In Chapter 4, during the data inspection process, a portion of the data values was falsely altered when using R to import data stored in SAS format. This issue can be resolved by using the built-in functionality in SAS software to convert the data to excel format first before importing into R. Due to the complexity of the encodings in different formats of data, the data types may be converted from string type to numerical type or vice versa, which will also induce some difficulties during the data analysis process. Performing a careful data inspection will avoid the impact of improper data conversion on the validity of the data. It is also recommended that the investigators could specify the format they would like to receive the data to the data suppliers, so that some data conversion can be avoided.

6.2.5 Data consistency

For the existing data used in the epidemiologic studies of cardiovascular diseases, a high variety and amount of datasets have been collected continuously which is managed by independent organizations or researchers with different intentions. Because of the lack of universal health data collection agreement on what and how information should be recorded, the record consistency among datasets varies, which reinforces the challenges in data merging and

analyses. The main challenge involved in integrating data to build a national-wide healthcare database include the inconsistency of standards across databases and legal/ethical constraints.[24] Researchers undertaking pan-Canadian analysis have therefore confronted huge barriers when looking for data across the provinces.[24] A great deal of efforts is needed to integrate the data across jurisdiction boundaries. Due to the utilization of different data-collecting system among institutions, information exchanges or linking are prohibited, which hinders the potential of maximizing beneficial effects from health data. Thomas and Yahav have shown discrepancy on ethnic and socio-economic data collection among regions by analyzing demographic data collection systems from the US, Israel, and Europe, which prevents comprehensive analyses of minority health and delivery of quality care for minorities.[29] In my experience of working with Alberta administrated data, the implementation of ICD-10 varied in different administrative databases, which creates difficulties in the comparability of the data. Above all, universal agreements on health-care data and routine management information collection are needed, which will greatly benefit health care providers and researchers.

6.2.6 Data validity

Currently, the data suppliers do not provide the information regarding the profile of the missing data in their databases. Therefore, researchers will experience the difficulty in accurately describing the timeframe for the data requests to obtain enough sample size for their research questions. Also, since not every weather stations record hourly air pressure data, part of the cases was excluded from the analysis in Chapter 5. The missing data require the investigators to have better statistical literacy and to use strict and rigorous analytic methods in an effect to minimize the influence of missing data. Proper handling of missing data will mitigate its impact on the validity of the study. Moreover, the accuracy of ICD codes for certain diseases has to be

improved in the administrative database. The results from Chapter 2 have suggested that using ICD codes to identify PAD patients will underestimate the true prevalence of the PAD population. One of the possible reasons was that PAD patients were not accurately coded by the health practitioners especially when PAD is not the primary diagnosis. Therefore, a higher standard of regulations and proper trainings on diagnostic coding may be considered to improve the accuracy of ICD codes, which is also beneficial to the government reporting and health resources planning.

6.3 Major contributions

1. Administrative data are specific but not sensitive to PAD patients when compared to ABI $\leq$ 0.90, suggesting that PAD is under-diagnosed in the community and that administrative data cannot be used reliably to identify all forms of PAD in the community. However, the algorithms we developed have the potential to infer the true prevalence of PAD patients in Alberta.

2. Admission rates were lower and LOS was slightly shorter comparing LMWH to UFH and comparing new oral therapy to parenteral therapy, supporting the use of NOAC in outpatients' care for eligible VTE patients.

3. The admission rates and LOS were significantly underreported in the existing VTE clinical trials. More RCTs reporting admission rates and LOS are needed to potentially improve the reassurance of outpatient therapy and to increase the patient compliance.

4. COPD was negatively associated with CAD before and after controlling for classic cardiovascular risk factors. Our data did not support that the association between COPD and CAD was due to small sample size.

5. There is no association between acute air pressure changes and the onset of STEMI in a lag time of 1 day to 6 days, whereas acute air pressure decrease is associated with higher odds of STEMI event 7 days after exposure. Further studies are warranted to confirm the latency effect of air pressure decrease on STEMI.

6. Several challenges when using existing data for epidemiologic research are discussed in this thesis to raise more awareness and discussion. Relevant policy changes to the access and management of databases should be made to facilitate the use of the digital resources.

6.4 Conclusion

This thesis shows that reutilizing existing data is time-saving and economical to generate evidence for important clinical epidemiologic research questions in the field of cardiovascular diseases despite some practical challenges. Timely access to data, lacking detailed data documentation, establishing causality, data conversion, data consistency, and data validity are the main challenges for CVD researchers conducting epidemiologic research using existing data. Overcoming these challenges would streamline and speed up the research process for investigators conducting epidemiologic research.

6.5 References

1. Cooke CR, Joo MJ, Anderson SM, et al. The validity of using ICD-9 codes and pharmacy records to identify patients with chronic obstructive pulmonary disease. *BMC Health Serv. Res.* 2011;11:37.

2. Pimentel MA, Browne EN, Janardhana PM, et al. Assessment of the accuracy of using ICD-9 codes to identify uveitis, herpes zoster ophthalmicus, scleritis, and episcleritis. *JAMA ophthalmology.* 2016;134:1001-1006.

3. Alotaibi GS, Wu C, Senthilselvan A, McMurtry MS. The validity of ICD codes coupled with imaging procedure codes for identifying acute venous thromboembolism using administrative data. *Vasc. Med.* 2015;20:364-368.

4. Thygesen SK, Christiansen CF, Christensen S, Lash TL, Sørensen HT. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. *BMC Med. Res. Methodol.* 2011;11:83.

5. Khokhar B, Jette N, Metcalfe A, et al. Systematic review of validated case definitions for diabetes in ICD-9-coded and ICD-10-coded data in adult populations. *BMJ open.* 2016;6:e009952.

6. O'Malley KJ, Cook KF, Price MD, Wildes KR, Hurdle JF, Ashton CM. Measuring Diagnoses: ICD Code Accuracy. *Health Serv. Res.* 2005;40:1620-1639.

7. MEDLINE: Description of the Database. U.S. National Library of Medicine. Available from: https://www.nlm.nih.gov/bsd/medline.html. Accessed on September 20, 2018.

8. Garg AX, Hackam D, Tonelli M. Systematic review and meta-analysis: when one study is just not enough. *Clin. J. Am. Soc. Nephrol.* 2008;3:253-260.

9. Mattos CT, Ruellas ACdO. Systematic review and meta-analysis: What are the implications in the clinical practice? *Dental Press J. Orthod.* 2015;20:17-19.

10. Feldstein DA. Clinician's guide to systematic reviews and meta-analyses. *WMJ.* 2005;104:25-29.

11. Müllerova H, Agusti A, Erqou S, Mapel DW. Cardiovascular comorbidity in COPD: systematic literature review. *Chest.* 2013;144:1163-1178.

12. Gradus JL, Farkas DK, Svensson E, et al. Associations between stress disorders and cardiovascular disease events in the Danish population. *BMJ Open.* 2015;5:e009334.

13. Akil L, Ahmad HA. Relationships between Obesity and Cardiovascular Diseases in Four Southern States and Colorado. *J. Health Care Poor Underserved.* 2011;22:61-72.

14. McFarlane SI, Banerji M, Sowers JR. Insulin Resistance and Cardiovascular Disease1. *The Journal of Clinical Endocrinology & Metabolism.* 2001;86:713-718.

15. Houck PD, Lethen JE, Riggs MW, Gantt DS, Dehmer GJ. Relation of atmospheric pressure changes and the occurrences of acute myocardial infarction and stroke. *American Journal of Cardiology.* 2005;96:45-51.

16. Fares A. Winter Cardiovascular Diseases Phenomenon. *N. Am. J. Med. Sci.* 2013;5:266-279.

17. Bai L, Li Q, Wang J, et al. Increased coronary heart disease and stroke hospitalisations from ambient temperatures in Ontario. *Heart.* 2017.

18. Radišauskas R, Bernotienė G, Bacevičienė M, Ustinavičienė R, Kirvaitienė J, Krančiukaitė-Butylkinienė D. Trends of myocardial infarction morbidity and its associations with weather conditions. *Medicina.* 2014;50:182-189.

19. Abrignani MG, Corrao S, Biondo GB, et al. Effects of ambient temperature, humidity, and other meteorological variables on hospital admissions for angina pectoris. *European journal of preventive cardiology.* 2011;19:342-348.

20. Liu H, Tian Y, Xiang X, et al. Air Pollution and Hospitalization for Acute Myocardial Infarction in China. *Am J Cardiol.* 2017;120:753-758.

21. Ballester F, Michelozzi P, Iniguez C. Weather, climate, and public health. *Journal of Epidemiology and Community Health.* 2003;57:759-760.

22. Institute of Medicine (US) Committee on Standards for Developing Trustworthy Clinical Practice Guidelines; Graham R, Mancher M, Miller Wolman D, et al., editors. Clinical Practice Guidelines We Can Trust. Washington (DC): National Academies Press (US); 2011. Summary. Available from: https://www.ncbi.nlm.nih.gov/books/NBK209538/. Access on Sept 20, 2018.

23. Data Access Review Times Study. Population Data BC. Available from: https://www.popdata.bc.ca/sites/default/files/documents/organisational/Data%20Access%20Review%20Times_Report_2013%2006%2020%20Final.pdf. Accessed on July 5, 2018.

24. Accessing Health and Health-Related Data in Canada. Council of Canadian Academies. Available from: http://www.scienceadvice.ca/uploads/eng/assessments%20and%20publications%20and%20news%20releases/Health-data/HealthDataFullReportEn.pdf. Accessed on June 30, 2018.

25. Rubin DB. The design versus the analysis of observational studies for causal effects: parallels with the design of randomized trials. *Stat. Med.* 2007;26:20-36.

26. Klungel O, Jamal Uddin M, de Boer A, Belitser S, Groenwold R, Roes K. Instrumental variable analysis in epidemiologic studies: an overview of the estimation methods. *Pharm Anal Acta.* 2015;6:2.

27. Bennett DA. An introduction to instrumental variables analysis: part 1. *Neuroepidemiology.* 2010;35:237-240.

28. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika.* 1983;70:41-55.

29. Thomas L, Yahav S. Cultural relativism in health care: Bridging global health disparities for minorities and the underserved. *The Journal of MacroTrends in Health and Medicine.* 1016;4:20-24.

Bibliographies

References for Chapter 1

1. Balakumar P, Maung-U K, Jagadeesh G. Prevalence and prevention of cardiovascular disease and diabetes mellitus. *Pharmacological Research.* 2016;113, Part A:600-609.

2. Donald M. Lloyd-Jones. Epidemiology of Cardiovascular Disease. In: Goldman, Lee. Goldman-Cecil Medicine. 25th ed. New york: Elsevier; 2016. p. 257-262.

3. Benjamin EJ, Virani SS, Callaway CW, et al. Heart disease and stroke statistics—2018 update: a report from the American Heart Association. *Circulation.* 2018;137:e67-e492.

4. Heart disease in Canada. Government of Canada. Available from: https://www.canada.ca/en/public-health/services/publications/diseases-conditions/heart-disease-canada-fact-sheet.html. Accessed on July 31, 2018.

5. Dai S, Bancej C, Bienek A, Walsh P, Stewart P, Wielgosz A. Report summary tracking heart disease and stroke in canada 2009. *Chronic Dis. Inj. Can.* 2009;29.

6. Mozaffarian D. Global Scourge of Cardiovascular Disease: Time for Health Care Systems Reform and Precision Population Health∗. *J. Am. Coll. Cardiol.* 2017;70:26-28.

7. Cardiovascular diseases. World Health Organization. Available from: http://www.who.int/mediacentre/factsheets/fs317/en/. Accessed on June 29, 2018.

8. Agyemang C, van den Born B-J. Limited access to CVD medicines in low-income and middle-income countries: poverty is at the heart of the matter. *The Lancet Global Health.* 2018;6:e234-e235.

9. Cardiovascular Disease. Public Health Agency of Canada. Available from: http://cbpp-pcpe.phac-aspc.gc.ca/chronic-diseases/cardiovascular-diseases/. Accessd on June 29, 2018.

10. Roth GA, Huffman MD, Moran AE, et al. Global and regional patterns in cardiovascular mortality from 1990 to 2013. *Circulation.* 2015;132:1667-1678.

11. Bloom DE, Cafiero, E.T., Jané-Llopis, E., Abrahams-Gessel, S., Bloom, L.R., Fathima, S., Feigl,, A.B. G, T., Mowafi, M., Pandya, A., Prettner, K., Rosenberg, L., Seligman, B., Stein, A., & Weinstein, C. The Global Economic Burden of Noncommunicable Diseases. World Economic Forum, Geneva (2011).

12. Laslett LJ, Alagona P, Clark BA, et al. The worldwide environment of cardiovascular disease: prevalence, diagnosis, therapy, and policy issues: a report from the American College of Cardiology. *J. Am. Coll. Cardiol.* 2012;60:S1-S49.

13. Sagiroglu S, Sinanc D. Big data: A review. *Collaboration Technologies and Systems (CTS), 2013 International Conference on*: IEEE; 2013:42-47.

14. McAfee A, Brynjolfsson E, Davenport TH, Patil D, Barton D. Big data: the management revolution. *Harv. Bus. Rev.* 2012;90:60-68.

15. Feldman B, Martin EM, Skotnes T. Big data in healthcare hype and hope. *Dr. Bonnie.* 2012;360:122-125.

16. Gewin V. Data sharing: An open mind on open data. *Nature.* 2016;529:117-119.

17. Data availability. Public Library of Science(PLOS). Available from: http://journals.plos.org/plosone/s/data-availability. Accessd on June 29, 2018.

18. Connect care. Alberta Health Services. Available from: https://www.albertahealthservices.ca/info/cis.aspx. Accessed on July 2, 2018.

19. Molloy JC. The open knowledge foundation: open data means better science. *PLoS Biol.* 2011;9:e1001195.

20. Srinivasan U, Arunasalam B. Leveraging big data analytics to reduce healthcare costs. *IT professional.* 2013;15:21-28.

21. Dunn SL, Arslanian-Engoren C, DeKoekkoek T, Jadack R, Scott LD. Secondary data analysis as an efficient and effective approach to nursing research. *West. J. Nurs. Res.* 2015;37:1295-1307.

22. Martin L, Hutchens M, Hawkins C, Radnov A. How much do clinical trials cost? *Nat Rev Drug Discov.* 2017;16:381-382.

23. Kayyali B, Knott D, Van Kuiken S. The big-data revolution in US health care: Accelerating value and innovation. *Mc Kinsey & Company.* 2013;2:1-13.

24. Doolan DM, Froelicher ES. Using an existing data set to answer new research questions: a methodological review. *Res. Theory Nurs. Pract.* 2009;23:203.

25. Doolan DM, Winters J, Nouredini S. Answering Research Questions Using an Existing Data Set. *Medical Research Archives.* 2017;5.

26. Hannan EL. Randomized clinical trials and observational studies: guidelines for assessing respective strengths and limitations. *JACC Cardiovasc. Interv.* 2008;1:211-217.

27. Boslaugh S. An introduction to secondary data analysis. *Secondary data sources for public health: A practical guide.* 2007:2-10.

28. Mariani AW, Pego-Fernandes PM. Observational studies: why are they so important? *Sao Paulo Med. J.* 2014;132:01-02.

29. Waien SA. Linking large administrative databases: a method for conducting emergency medical services cohort studies using existing data. *Acad Emerg Med.* 1997;4:1087-1095.

30. Health research in Alberta. Alberta Heath. Available from: http://www.health.alberta.ca/initiatives/health-research.html. Access on June 29, 2018.

31. Shavadia J, Norris CM, Graham MM, Verma S, Ali I, Bainey KR. Symptomatic graft failure and impact on clinical outcome after coronary artery bypass grafting surgery: Results from the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease registry. *Am Heart J.* 2015;169:833-840.

32. Kaila KS, Norris CM, Graham MM, Ali I, Bainey KR. Long-term survival with revascularization in South Asians admitted with an acute coronary syndrome (from the Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease Registry). *Am J Cardiol.* 2014;114:395-400.

33. APPROACH forms. APPROACH. Available from: http://www.approach.org/support_pages/forms.html. Accessed on June 30, 2018.

34. All About Alberta's Tomorrow Project. Alberta's Tomorrow Project. Available from: https://myatp.ca/about-atp . Accessed on July 27,2018.

35. Health research data: resources. Canadian Institutes of Health Research. Available from: http://www.cihr-irsc.gc.ca/e/49941.html. Accessed on June 30, 2018.

36. The Research Data Centres (RDC) network. Statistic Canada. Available from: https://www.statcan.gc.ca/eng/rdc/network. Accessed on Aug 3, 2018.

37. Global Health Observatory (GHO) data. World Health Organization(WHO). Available from: http://www.who.int/gho/database/en/. Accessed on July 2, 2018.

38. Using Existing Data. DeWitt Wallace Library. Available from: https://libguides.macalester.edu/c.php?g=545757&p=3743355. Accessed on July 27,2018.

References for Chapter 2

1. Hirsch AT, Criqui MH, Treat-Jacobson D, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. *JAMA.* 2001;286:1317-1324.

2. Jaff MR. Why patients know more about cars than peripheral artery disease. *Circulation.* 2014;130:1778-1779.

3. Rooke TW, Hirsch AT, Misra S, et al. Management of patients with peripheral artery disease (compilation of 2005 and 2011 ACCF/AHA Guideline Recommendations): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2013;61:1555-1570.

4. Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999-2000. *Circulation.* 2004;110:738-743.

5. Liang Y, Yan Z, Sun B, et al. Cardiovascular risk factor profiles for peripheral artery disease and carotid atherosclerosis among Chinese older people: a population-based study. *PLoS One.* 2014;9:e85927.

6. Diage TR, Johnson G, Ravipati G. Digital ankle-brachial index technology used in primary care settings to detect flow obstruction: a population based registry study. *BMC Res Notes.* 2013;6:404.

7. Ohnishi H, Sawayama Y, Furusyo N, Maeda S, Tokunaga S, Hayashi J. Risk factors for and the prevalence of peripheral arterial disease and its relationship to carotid atherosclerosis: the Kyushu and Okinawa Population Study (KOPS). *J Atheroscler Thromb.* 2010;17:751-758.

8. Kroger K, Dragano N, Stang A, et al. An unequal social distribution of peripheral arterial disease and the possible explanations: results from a population-based study. *Vascular medicine.* 2009;14:289-296.

9. Blanes JI, Cairols MA, Marrugat J, Estime. Prevalence of peripheral artery disease and its associated risk factors in Spain: The ESTIME Study. *Int Angiol.* 2009;28:20-25.

10. Sigvant B, Wiberg-Hedman K, Bergqvist D, et al. A population-based study of peripheral arterial disease prevalence with special focus on critical limb ischemia and sex differences. *Journal of vascular surgery.* 2007;45:1185-1191.

11. Tonelli M, Wiebe N, Fortin M, et al. Methods for identifying 30 chronic conditions: application to administrative data. *BMC Med Inform Decis Mak.* 2015;15:31.

12. Van Walraven C, Austin PC, Manuel D, Knoll G, Jennings A, Forster AJ. The usefulness of administrative databases for identifying disease cohorts is increased with a multivariate model. *Journal of clinical epidemiology.* 2010;63:1332-1341.

13. Al-Omran M, Tu JV, Johnston KW, Mamdani MM, Kucey DS. Outcome of revascularization procedures for peripheral arterial occlusive disease in Ontario between 1991 and 1998: a population-based study. *Journal of vascular surgery.* 2003;38:279-288.

14. Al-Omran M, Tu JV, Johnston KW, Mamdani MM, Kucey DS. Use of interventional procedures for peripheral arterial occlusive disease in Ontario between 1991 and 1998: a population-based study. *Journal of vascular surgery.* 2003;38:289-295.

15. Kolossvary E, Ferenci T, Kovats T, et al. Trends in Major Lower Limb Amputation Related to Peripheral Arterial Disease in Hungary: A Nationwide Study (2004-2012). *European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery.* 2015;50:78-85.

16. Malyar N, Furstenberg T, Wellmann J, et al. Recent trends in morbidity and in-hospital outcomes of in-patients with peripheral arterial disease: a nationwide population-based analysis. *European heart journal.* 2013;34:2706-2714.

17. Bekwelem W, Bengtson LG, Oldenburg NC, et al. Development of administrative data algorithms to identify patients with critical limb ischemia. *Vascular medicine.* 2014;19:483-490.

18. Widener JM. Peripheral arterial disease and disability from NHANES 2001-2004 data. *J Vasc Nurs.* 2011;29:104-112.

19. Fan J, Arruda-Olson AM, Leibson CL, et al. Billing code algorithms to identify cases of peripheral artery disease from administrative data. *Journal of the American Medical Informatics Association : JAMIA.* 2013;20:e349-354.

20. Criqui MH, Aboyans V. Epidemiology of peripheral artery disease. *Circ Res.* 2015;116:1509-1526.

21. Makowsky M, McMurtry MS, Elton T, et al. Prevalence and treatment patterns of lower extremity peripheral arterial disease among patients at risk in ambulatory health settings. *The Canadian journal of cardiology.* 2011;27:389 e311-388.

22. Sebastianski M, Narasimhan S, Graham MM, et al. Usefulness of the ankle-brachial index to predict high coronary SYNTAX scores, myocardium at risk, and incomplete coronary revascularization. *Am J Cardiol.* 2014;114:1745-1749.

23. Abramson BL, Huckell V, Anand S, et al. Canadian Cardiovascular Society Consensus Conference: peripheral arterial disease-executive summary. *The Canadian journal of cardiology.* 2005;21:997-1006.

24. The Overview of Administrative Health Datasets. Alberta Health. Available from: https://open.alberta.ca/dataset/overview-of-administrative-health-datasets. Accessed on July 12,2018.

25. Chen G, Khan N, Walker R, Quan H. Validating ICD coding algorithms for diabetes mellitus from administrative data. *Diabetes Res. Clin. Pract.* 2010;89:189-195.

References for Chapter 3

1. Goldhaber SZ, Bounameaux H. Pulmonary embolism and deep vein thrombosis. *The Lancet.* 2012;379:1835-1846.

2. Fowkes FJ, Price JF, Fowkes FG. Incidence of diagnosed deep vein thrombosis in the general population: systematic review. *Eur. J. Vasc. Endovasc. Surg.* 2003;25:1-5.

3. Dobesh PP. Economic burden of venous thromboembolism in hospitalized patients. *Pharmacotherapy.* 2009;29:943-953.

4. Kearon C. Initial Treatment of Venous Thromboembolism. *Thromb. Haemost.* 1999;82:887-891.

5. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic Therapy for VTE Disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141:e419S-e496S.

6. Garcia DA, Baglin TP, Weitz JI, Samama MM. Parenteral anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141:e24S-43S.

7. Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G. Oral anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141:e44S-88S.

8. Ducel G, Fabry J, Nicolle L, Organization WH. Prevention of hospital-acquired infections: a practical guide. 2002.

9. García-Cabrera E, Fernández-Hidalgo N, Almirante B, et al. Neurological complications of infective endocarditis: risk factors, outcome, and impact of cardiac surgery: a multicenter observational study. *Circulation.* 2013;127:2272-2284.

10. Lagoe RJ, Westert GP. Evaluation of hospital inpatient complications: a planning approach. *BMC Health Serv. Res.* 2010;10:200.

11. Hoogervorst-Schilp J, Langelaan M, Spreeuwenberg P, de Bruijne MC, Wagner C. Excess length of stay and economic consequences of adverse events in Dutch hospital patients. *BMC Health Serv. Res.* 2015;15:531.

12. Baker GR, Norton PG, Flintoft V, et al. The Canadian Adverse Events Study: the incidence of adverse events among hospital patients in Canada. *Can Med Assoc J.* 2004;170:1678-1686.

13. Zegers M, de Bruijne MC, Wagner C, et al. Adverse events and potentially preventable deaths in Dutch hospitals: results of a retrospective patient record review study. *Qual Saf Health Care.* 2009;18:297-302.

14. Sari AB-A, Sheldon TA, Cracknell A, et al. Extent, nature and consequences of adverse events: results of a retrospective casenote review in a large NHS hospital. *Qual Saf Health Care.* 2007;16:434-439.

15. Busby J, Purdy S, Hollingworth W. A systematic review of the magnitude and cause of geographic variation in unplanned hospital admission rates and length of stay for ambulatory care sensitive conditions. *BMC Health Serv Res.* 2015;15:324.

16. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ.* 2011;343:d5928.

17. Song F, Hooper L, Loke YK. Publication bias: what is it? How do we measure it? How do we avoid it? *Open Access J Clin Trials.* 2013;5:71-81.

18. Matsuo H, Prins M, Lensing AWA, Fujinuma EW, Miyamoto Y, Kajikawa M. Shortened length of hospital stay with rivaroxaban in patients with symptomatic venous thromboembolism in Japan: the J-EINSTEIN pulmonary embolism and deep vein thrombosis program. *Curr Med Res Opin.* 2015;31:1057-1061.

19. Bookhart BK, Haskell L, Bamber L, Wang M, Schein J, Mody SH. Length of stay and economic consequences with rivaroxaban vs enoxaparin/vitamin K antagonist in patients with DVT and PE: findings from the North American EINSTEIN clinical trial program. *J Med Econ.* 2014;17:691-695.

20. van Bellen B, Bamber L, Correa de Carvalho F, Prins M, Wang M, Lensing AWA. Reduction in the length of stay with rivaroxaban as a single-drug regimen for the treatment of deep vein thrombosis and pulmonary embolism. *Curr Med Res Opin.* 2014;30:829-837.

21. Levine M, Gent M, Hirsh J, et al. A Comparison of Low-Molecular-Weight Heparin Administered Primarily at Home with Unfractionated Heparin Administered in the Hospital for Proximal Deep-Vein Thrombosis. *N Engl J Med.* 1996;334:677-681.

22. Ramacciotti E, Araujo GR, Lastoria S, et al. An open-label, comparative study of the efficacy and safety of once-daily dose of enoxaparin versus unfractionated heparin in the treatment of proximal lower limb deep-vein thrombosis. *Thromb. Res.* 2004;114:149-153.

23. Chong BH, Brighton TA, Baker RI, Thurlow P, Lee CH. Once-daily enoxaparin in the outpatient setting versus unfractionated heparin in hospital for the treatment of symptomatic deep-vein thrombosis. *J Thromb Thrombolysis.* 2005;19:173-181.

24. de Lissovoy G, Yusen RD, Spiro TE, Krupski WC, Champion AH, Sorensen SV. Cost for inpatient care of venous thrombosis: A trial of enoxaparin vs standard heparin. *Arch Intern Med.* 2000;160:3160-3165.

25. Beckman JA, Dunn K, Sasahara AA, Goldhaber SZ. Enoxaparin monotherapy without oral anticoagulation to treat acute symptomatic pulmonary embolism. *Thromb Haemost.* 2003;89:953-958.

26. Belcaro G, Nicolaides AN, Cesarone MR, et al. Comparison of low-molecular-weight heparin, administered primarily at home, with unfractionated heparin, administered in hospital, and subcutaneous heparin, administered at home for deep-vein thrombosis. *Angiology.* 1999;50:781-787.

27. Naz R, Naz S, Mehboob M, Khalid GH. Comparison of unfractionated heparin vs low molecular weight heparin in the treatment of acute deep vein thrombosis. *J Coll Physicians Surg Pak.* 2005;15:601-604.

28. R. Hafeli SK, Ch. Wehrli, J. Goede, D. Conen. Nieder-molekulares heparin (Dalteparin) in der behandlung von patienten mit thromboembolischen (TVT/LE) ereignissen. *Praxis-Bern.* 2001;90:1339-1345.

29. The Columbus Investigators. Low-Molecular-Weight Heparin in the Treatment of Patients with Venous Thromboembolism. *N Engl J Med.* 1997;337:657-662.

30. The Matisse Investigators. Subcutaneous Fondaparinux versus Intravenous Unfractionated Heparin in the Initial Treatment of Pulmonary Embolism. *N Engl J Med.* 2003;349:1695-1702.

31. Koopman MM, Prandoni P, Piovella F, et al. Treatment of venous thrombosis with intravenous unfractionated heparin administered in the hospital as compared with

subcutaneous low-molecular-weight heparin administered at home. *N Engl J Med.* 1996;334:682-687.

32. King CS, Holley AB, Moores LK. Moving toward a more ideal anticoagulant: the oral direct thrombin and factor Xa inhibitors. *Chest.* 2013;143:1106-1116.

33. Byun JH, Jang IS, Kim JW, Koh EH. Establishing the heparin therapeutic range using aPTT and anti-Xa measurements for monitoring unfractionated heparin therapy. *Blood Res.* 2016;51:171-174.

34. Piran S, Le Gal G, Wells PS, et al. Outpatient treatment of symptomatic pulmonary embolism: A systematic review and meta-analysis. *Thromb. Res.* 2013;132:515-519.

35. Mansour S, Alotaibi G, Wu C, McMurtry MS. Trends in admission rates and in-hospital stay for venous thromboembolism. *Thrombosis research.* 2017;156:149-154.

36. Columbus Investigators. Low-molecular-weight heparin in the treatment of patients with venous thromboembolism. *N Engl J Med.* 1997;1997:657-662.

37. Naz R, Naz S, Mehboob M, Khalid GH. Comparison of unfractionated heparin vs low molecular weight heparin in the treatment of acute deep vein thrombosis. *Journal of the College of Physicians and Surgeons--Pakistan: JCPSP.* 2005;15:601-604.

38. Hafeli R, Kraljevic S, Wehrli C, Goede J, Conen D. [Low molecular weight heparin (dalteparin) in treatment of patients with thromboembolism incidents]. *Praxis (Bern 1994).* 2001;90:1339-1345.

39. Beckman JA, Dunn K, Sasahara AA, Goldhaber SZ. Enoxaparin monotherapy without oral anticoagulation to treat acute symptomatic pulmonary embolism. *Thromb. Haemost.* 2003;89:953-958.

40. Levine M, Gent M, Hirsh J, et al. A comparison of low-molecular-weight heparin administered primarily at home with unfractionated heparin administered in the hospital for proximal deep-vein thrombosis. *N Engl J Med.* 1996;334:677-681.

41. Ramacciotti E, Araújo GR, Lastoria S, et al. An open-label, comparative study of the efficacy and safety of once-daily dose of enoxaparin versus unfractionated heparin in the treatment of proximal lower limb deep-vein thrombosis. *Thromb. Res.* 2004;114:149-153.

42. Chong BH, Brighton TA, Baker RI, Thurlow P, Lee CH, Group ADS. Once-daily enoxaparin in the outpatient setting versus unfractionated heparin in hospital for the treatment of symptomatic deep-vein thrombosis. *Journal of thrombosis and thrombolysis.* 2005;19:173-181.

43. Büller HR, Davidson BL, Decousus H, et al. Fondaparinux or Enoxaparin for the Initial Treatment of Symptomatic Deep Venous ThrombosisA Randomized Trial. *Ann Intern Med.* 2004;140:867-873.

44. Matsuo H, Prins M, Lensing AW, Fujinuma EW, Miyamoto Y, Kajikawa M. Shortened length of hospital stay with rivaroxaban in patients with symptomatic venous thromboembolism in Japan: the J-EINSTEIN pulmonary embolism and deep vein thrombosis program. *Curr Med Res Opin.* 2015;31:1057-1061.

References for Chapter 4

1. Vestbo J, Hurd SS, Rodriguez-Roisin R. The 2011 revision of the global strategy for the diagnosis, management and prevention of COPD (GOLD)--why and what? *Clin Respir J.* 2012;6:208-214.

2. Murray CJ, Atkinson C, Bhalla K, et al. The state of US health, 1990-2010: burden of diseases, injuries, and risk factors. *JAMA.* 2013;310:591-608.

3. Kolh P, Windecker S, Alfonso F, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur J Cardiothorac Surg.* 2014;46:517-592.

4. Mannino DM, Homa DM, Akinbami LJ, Ford ES, Redd SC. Chronic obstructive pulmonary disease surveillance---United States, 1971--2000. *Respir. Care.* 2002;76.

5. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics—2012 update a report from the American heart association. *Circulation.* 2012;125:e2-e220.

6. Campo G, Pavasini R, Malagu M, et al. Chronic obstructive pulmonary disease and ischemic heart disease comorbidity: overview of mechanisms and clinical management. *Cardiovasc Drugs Ther.* 2015;29:147-157.

7. Vanfleteren LE, Spruit MA, Groenen M, et al. Clusters of comorbidities based on validated objective measurements and systemic inflammation in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2013;187:728-735.

8. Nishiyama K, Morimoto T, Furukawa Y, et al. Chronic obstructive pulmonary disease—an independent risk factor for long-term cardiac and cardiovascular mortality in patients with ischemic heart disease. *Int J Cardiol.* 2010;143:178-183.

9. Rasmussen T, Køber L, Pedersen JH, et al. Relationship between chronic obstructive pulmonary disease and subclinical coronary artery disease in long-term smokers. *Eur Heart J Cardiovasc Imaging.* 2013;14:1159-1166.

10. Topsakal R, Kalay N, Ozdogru I, et al. Effects of chronic obstructive pulmonary disease on coronary atherosclerosis. *Heart Vessels.* 2009;24:164-168.

11. Müllerova H, Agusti A, Erqou S, Mapel DW. Cardiovascular comorbidity in COPD: systematic literature review. *CHEST Journal.* 2013;144:1163-1178.

12. Izquierdo JL, Martinez A, Guzman E, de Lucas P, Rodriguez JM. Lack of association of ischemic heart disease with COPD when taking into account classical cardiovascular risk factors. *Int J Chron Obstruct Pulmon Dis.* 2010;5:387-394.

13. Shavadia J, Norris CM, Graham MM, Verma S, Ali I, Bainey KR. Symptomatic graft failure and impact on clinical outcome after coronary artery bypass grafting surgery: Results from the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease registry. *Am Heart J.* 2015;169:833-840.

14. Kaila KS, Norris CM, Graham MM, Ali I, Bainey KR. Long-term survival with revascularization in South Asians admitted with an acute coronary syndrome (from the Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease Registry). *Am J Cardiol.* 2014;114:395-400.

15. Bresee LC, Knudtson ML, Zhang J, et al. Likelihood of coronary angiography among First Nations patients with acute myocardial infarction. *CMAJ.* 2014;186:E372-380.

16. Quan H, Li B, Saunders LD, et al. Assessing validity of ICD-9-CM and ICD-10 administrative data in recording clinical conditions in a unique dually coded database. *Health Serv Res.* 2008;43:1424-1441.

17. Fodor JG, Frohlich JJ, Genest JJ, McPherson PR. Recommendations for the management and treatment of dyslipidemia Report of the Working Group on Hypercholesterolemia and Other Dyslipidemias. *Can Med Assoc J.* 2000;162:1441-1447.

18. Feldman RD, Campbell N, Larochelle P, et al. 1999 Canadian recommendations for the management of hypertension. *Can Med Assoc J.* 1999;161:S1-S17.

19. Lochner KA, Goodman RA, Posner S, Parekh A. Multiple chronic conditions among Medicare beneficiaries: state-level variations in prevalence, utilization, and cost, 2011. *Medicare Medicaid Res Rev.* 2013;3.

20. Arnett DK, Goodman RA, Halperin JL, Anderson JL, Parekh AK, Zoghbi WA. AHA/ACC/HHS strategies to enhance application of clinical practice guidelines in patients with cardiovascular disease and comorbid conditions: from the American Heart Association, American College of Cardiology, and US Department of Health and Human Services. *J. Am. Coll. Cardiol.* 2014;64:1851-1856.

21. Koseoglu C, Kurmus O, Ertem AG, et al. Association between carotid intima-media thickness and presence of coronary artery disease in chronic obstructive pulmonary disease patients. *Anatol J Cardiol.* 2016;16:601-607.

22. Almagro P, Lapuente A, Pareja J, et al. Underdiagnosis and prognosis of chronic obstructive pulmonary disease after percutaneous coronary intervention: a prospective study. *Int J Chron Obstruct Pulmon Dis.* 2015;10:1353.

23. Liang B, Xu Z, Yi Q, Ou X, Feng Y. Association of chronic obstructive pulmonary disease with coronary artery disease. *Chin Med J.* 2012;126:3205-3208.

24. Sin DD, Man SP. Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular diseases? *Circulation.* 2003;107:1514-1519.

25. Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. *N Engl J Med.* 2017;377:1119-1131.

26. Criner GJ, Connett JE, Aaron SD, et al. Simvastatin for the prevention of exacerbations in moderate-to-severe COPD. *N Engl J Med.* 2014;370:2201-2210.

27. Chen CY, Holbrook M, Duess MA, et al. Effect of almond consumption on vascular function in patients with coronary artery disease: a randomized, controlled, cross-over trial. *Nutr J.* 2015;14:61.

28. Akodad M, Lattuca B, Nagot N, et al. COLIN trial: Value of colchicine in the treatment of patients with acute myocardial infarction and inflammatory response. *Arch Cardiovasc Dis.* 2017;110:395-402.

29. Liang Y, Li YP, He F, Liu XQ, Zhang JY. Long-term, regular remote ischemic preconditioning improves endothelial function in patients with coronary heart disease. *Braz J Med Biol Res.* 2015;48:568-576.

30. Le Page S, Bejan-Angoulvant T, Angoulvant D, Prunier F. Remote ischemic conditioning and cardioprotection: a systematic review and meta-analysis of randomized clinical trials. *Basic Res Cardiol.* 2015;110:11.

31. Vozoris NT, Wang X, Austin PC, et al. Incident diuretic drug use and adverse respiratory events among older adults with chronic obstructive pulmonary disease. *Br. J. Clin. Pharmacol.* 2017.

32. McGuire K, Avina-Zubieta JA, Esdaile JM, et al. Risk of Incident Chronic Obstructive Pulmonary Disease (COPD) in Rheumatoid Arthritis: A Population Based Cohort Study. *Arthritis Care Res. (Hoboken).* 2017.

33. Lee TM, Tu K, Wing LL, Gershon AS. Identifying individuals with physician-diagnosed chronic obstructive pulmonary disease in primary care electronic medical records: a retrospective chart abstraction study. *NPJ Prim Care Respir Med.* 2017;27:34.

References for Chapter 5

1. Reed GW, Rossi JE, Cannon CP. Acute myocardial infarction. *The Lancet.* 2017;389:197-210.

2. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. *Eur. Heart J.* 2012;33:2551-2567.

3. Yadlapati A, Gajjar M, Schimmel DR, Ricciardi MJ, Flaherty JD. Contemporary management of ST-segment elevation myocardial infarction. *Internal and Emergency Medicine.* 2016;11:1107-1113.

4. Department of Atmospheric Sciences (DAS) at the University of Illinois. Available from: http://ww2010.atmos.uiuc.edu/(Gh)/abt/aknw/dvlp.rxml. Accessed on Oct 21, 2017.

5. Wang H, Matsumura M, Kakehashi M, Eboshida A. Effects of atmospheric temperature and pressure on the occurrence of acute myocardial infarction in Hiroshima City, Japan. *Hiroshima J. Med. Sci.* 2006;55:45.

6. Radišauskas R, Vaičiulis V, Ustinavičienė R, Bernotienė G. The effect of atmospheric temperature and pressure on the occurrence of acute myocardial infarction in Kaunas. *Medicina.* 2013;49:447-452.

7. Bijelović S, Dragić N, Bijelović M, Kovačević M, Jevtić M, Ninkovic MO. Impact of climate conditions on hospital admissions for subcategories of cardiovascular diseases. *Medycyna pracy.* 2017;68:189.

8. Danet S, Richard F, Montaye M, et al. Unhealthy effects of atmospheric temperature and pressure on the occurrence of myocardial infarction and coronary deaths. *Circulation.* 1999;100:e1-e7.

9. Faeh D, Gutzwiller F, Bopp M. Lower mortality from coronary heart disease and stroke at higher altitudes in Switzerland. *Circulation.* 2009;120:495-501.

10. Maclure M. The case-crossover design: a method for studying transient effects on the risk of acute events. *American journal of epidemiology.* 1991;133:144-153.

11. Warner L, Macaluso M, Austin HD, et al. Application of the Case-Crossover Design to Reduce Unmeasured Confounding in Studies of Condom Effectiveness. *American Journal of Epidemiology.* 2005;161:765-773.

12. Shavadia J, Norris CM, Graham MM, Verma S, Ali I, Bainey KR. Symptomatic graft failure and impact on clinical outcome after coronary artery bypass grafting surgery: Results from the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease registry. *American Heart Journal.* 2015;169:833-840.

13. Bresee LC, Knudtson ML, Zhang J, et al. Likelihood of coronary angiography among First Nations patients with acute myocardial infarction. *CMAJ.* 2014;186:E372-380.

14. Murphy T. SPOR SUPPORT Unit, November 10, 2015. 2015.

15. Historical data. Environment Canada. Available from: http://climate.weather.gc.ca/historical_data/search_historic_data_e.html. Accessed on Oct 19, 2017

16. Al-Omran M, Tu JV, Johnston KW, Mamdani MM, Kucey DS. Outcome of revascularization procedures for peripheral arterial occlusive disease in Ontario between 1991 and 1998: a population-based study. *Journal of vascular surgery.* 2003;38:279-288.

17. Janes H, Sheppard L, Lumley T. Case-crossover analyses of air pollution exposure data: referent selection strategies and their implications for bias. *Epidemiology.* 2005;16:717-726.

18. Peters A, Dockery DW, Muller JE, Mittleman MA. Increased particulate air pollution and the triggering of myocardial infarction. *Circulation.* 2001;103:2810-2815.

19. Barnett AG, Dobson AJ, McElduff P, Salomaa V, Kuulasmaa K, Sans S. Cold periods and coronary events: an analysis of populations worldwide. *J. Epidemiol. Community Health.* 2005;59:551-557.

20. Ou CQ, Jun Y, Ou QQ, et al. The impact of relative humidity and atmospheric pressure on mortality in Guangzhou, China. *Biomed. Environ. Sci.* 2014;27:917-925.

21. Davies MJ, Thomas AC. Plaque fissuring--the cause of acute myocardial infarction, sudden ischaemic death, and crescendo angina. *Br. Heart J.* 1985;53:363.

22. Claeys MJ, Rajagopalan S, Nawrot TS, Brook RD. Climate and environmental triggers of acute myocardial infarction. *Eur. Heart J.* 2016;38:955-960.

23. Nable JV, Tupe CL, Gehle BD, Brady WJ. In-flight medical emergencies during commercial travel. *N Engl J Med.* 2015;373:939-945.

24. Subcommittee CA, Association AM, Committee AS. Cabin cruising altitudes for regular transport aircraft. *Aviation, space, and environmental medicine.* 2008;79:433-439.

25. Ikeyama K, Nakatani M, Kumamoto J, Denda M. Distinct intracellular calcium responses of individual cultured human keratinocytes to air pressure changes. *Skin Res. Technol.* 2013;19:346-351.

26. Denda M. Keratinocytes at the uppermost layer of epidermis might act as sensors of atmospheric pressure change. *Extreme physiology & medicine.* 2016;5:11.

27. Houck PD, Lethen JE, Riggs MW, Gantt DS, Dehmer GJ. Relation of atmospheric pressure changes and the occurrences of acute myocardial infarction and stroke. *American Journal of Cardiology.* 2005;96:45-51.

References for Chapter 6

1. Cooke CR, Joo MJ, Anderson SM, et al. The validity of using ICD-9 codes and pharmacy records to identify patients with chronic obstructive pulmonary disease. *BMC Health Serv. Res.* 2011;11:37.

2. Pimentel MA, Browne EN, Janardhana PM, et al. Assessment of the accuracy of using ICD-9 codes to identify uveitis, herpes zoster ophthalmicus, scleritis, and episcleritis. *JAMA ophthalmology.* 2016;134:1001-1006.

3. Alotaibi GS, Wu C, Senthilselvan A, McMurtry MS. The validity of ICD codes coupled with imaging procedure codes for identifying acute venous thromboembolism using administrative data. *Vasc. Med.* 2015;20:364-368.

4. Thygesen SK, Christiansen CF, Christensen S, Lash TL, Sørensen HT. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. *BMC Med. Res. Methodol.* 2011;11:83.

5. Khokhar B, Jette N, Metcalfe A, et al. Systematic review of validated case definitions for diabetes in ICD-9-coded and ICD-10-coded data in adult populations. *BMJ open.* 2016;6:e009952.

6. O'Malley KJ, Cook KF, Price MD, Wildes KR, Hurdle JF, Ashton CM. Measuring Diagnoses: ICD Code Accuracy. *Health Serv. Res.* 2005;40:1620-1639.

7. MEDLINE: Description of the Database. U.S. National Library of Medicine. Available from: https://www.nlm.nih.gov/bsd/medline.html. Accessed on September 20, 2018.

8. Garg AX, Hackam D, Tonelli M. Systematic review and meta-analysis: when one study is just not enough. *Clin. J. Am. Soc. Nephrol.* 2008;3:253-260.

9. Mattos CT, Ruellas ACdO. Systematic review and meta-analysis: What are the implications in the clinical practice? *Dental Press J. Orthod.* 2015;20:17-19.

10. Feldstein DA. Clinician's guide to systematic reviews and meta-analyses. *WMJ.* 2005;104:25-29.

11. Müllerova H, Agusti A, Erqou S, Mapel DW. Cardiovascular comorbidity in COPD: systematic literature review. *Chest.* 2013;144:1163-1178.

12. Gradus JL, Farkas DK, Svensson E, et al. Associations between stress disorders and cardiovascular disease events in the Danish population. *BMJ Open.* 2015;5:e009334.

13. Akil L, Ahmad HA. Relationships between Obesity and Cardiovascular Diseases in Four Southern States and Colorado. *J. Health Care Poor Underserved.* 2011;22:61-72.

14. McFarlane SI, Banerji M, Sowers JR. Insulin Resistance and Cardiovascular Disease1. *The Journal of Clinical Endocrinology & Metabolism.* 2001;86:713-718.

15. Houck PD, Lethen JE, Riggs MW, Gantt DS, Dehmer GJ. Relation of atmospheric pressure changes and the occurrences of acute myocardial infarction and stroke. *American Journal of Cardiology.* 2005;96:45-51.

16. Fares A. Winter Cardiovascular Diseases Phenomenon. *N. Am. J. Med. Sci.* 2013;5:266-279.

17. Bai L, Li Q, Wang J, et al. Increased coronary heart disease and stroke hospitalisations from ambient temperatures in Ontario. *Heart.* 2017.

18. Radišauskas R, Bernotienė G, Bacevičienė M, Ustinavičienė R, Kirvaitienė J, Krančiukaitė-Butylkinienė D. Trends of myocardial infarction morbidity and its associations with weather conditions. *Medicina.* 2014;50:182-189.

19. Abrignani MG, Corrao S, Biondo GB, et al. Effects of ambient temperature, humidity, and other meteorological variables on hospital admissions for angina pectoris. *European journal of preventive cardiology.* 2011;19:342-348.

20. Liu H, Tian Y, Xiang X, et al. Air Pollution and Hospitalization for Acute Myocardial Infarction in China. *Am J Cardiol.* 2017;120:753-758.

21. Ballester F, Michelozzi P, Iniguez C. Weather, climate, and public health. *Journal of Epidemiology and Community Health.* 2003;57:759-760.

22. Institute of Medicine (US) Committee on Standards for Developing Trustworthy Clinical Practice Guidelines; Graham R, Mancher M, Miller Wolman D, et al., editors. Clinical Practice Guidelines We Can Trust. Washington (DC): National Academies Press (US); 2011. Summary. Available from: https://www.ncbi.nlm.nih.gov/books/NBK209538/. Access on Sept 20, 2018.

23. Data Access Review Times Study. Population Data BC. Available from: https://www.popdata.bc.ca/sites/default/files/documents/organisational/Data%20Access%20Review%20Times_Report_2013%2006%2020%20Final.pdf. Accessed on July 5, 2018.

24. Accessing Health and Health-Related Data in Canada. Council of Canadian Academies. Available from: http://www.scienceadvice.ca/uploads/eng/assessments%20and%20publications%20and%20news%20releases/Health-data/HealthDataFullReportEn.pdf. Accessed on June 30, 2018.

25. Rubin DB. The design versus the analysis of observational studies for causal effects: parallels with the design of randomized trials. *Stat. Med.* 2007;26:20-36.

26. Klungel O, Jamal Uddin M, de Boer A, Belitser S, Groenwold R, Roes K. Instrumental variable analysis in epidemiologic studies: an overview of the estimation methods. *Pharm Anal Acta.* 2015;6:2.

27. Bennett DA. An introduction to instrumental variables analysis: part 1. *Neuroepidemiology.* 2010;35:237-240.

28. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika.* 1983;70:41-55.

29. Thomas L, Yahav S. Cultural relativism in health care: Bridging global health disparities for minorities and the underserved. *The Journal of MacroTrends in Health and Medicine.* 1016;4:20-24.

Appendix A

Search Strategy used to search for randomized in trials. Search was done via the Ovid interface for MEDLINE and EMBASE.

No.	Search term
1.	exp Venous Thrombosis/
2.	exp Venous Thromboembolism/
3.	Deep vein thrombosis.mp.
4.	Pulmonary embolism.mp. or exp Pulmonary Embolism/
5.	(PE or DVT).mp. or VTE.ti,ab,kw.
6.	((vein* or ven*) adj5 thromb*).ti,ab,kw.
7.	exp Anticoagulants/
8.	(anticoagul* or anti-coagu* or antithrombotic*).mp.
9.	exp Warfarin/
10.	(warfarin or (vitamin adj3 antagonist*) or VKA or Nicoumalone or phenindione or acenocoumarol* or Sinthrome or dicoumarol* or nicoumalone or phenprocoumon or Marcoumar or Marcumar or Falithrom or AVK or bishydroxycoumarin* or coumarin* or coumadin* or phenprocoumon*).mp.
11.	Direct thrombin inhibitor.mp.
12.	(Ximelagatran or Exanta or Exarta or dabigatran or rivaroxaban or Xarelto or edoxaban or Eliquis or Pradaxa).mp.
13.	(fondaparinux or Arixtra or BAY59-7939 or TTP889 or odiparcil or LY517717 or YM150 or DU-176b).mp.

14.	(apixaban or betrixaban or edoxaban or idraparinux).mp.
15.	exp Acenocoumarol/
16.	dabigatran.mp.
17.	rivaroxaban.mp.
18.	apixaban.mp.
19.	edoxaban.mp.
20.	direct Xa inhibitor.mp.
21.	xarelto.mp.
22.	Pradax$.mp.
23.	xarelto.mp.
24.	eliquis.mp.
25.	coumadin.mp.
26.	exp Heparin, low molecular weight/
27.	(LMWH or UFH or heparin or nadroparin* or fraxiparin* or enoxaparin).mp.
28.	(Clexane or klexane or lovenox or dalteparin or Fragmin or ardeparin).mp.
29.	(normiflo or tinzaparin or logiparin or Innohep or certoparin or sandoparin or reviparin or clivarin*).mp.
30.	(danaproid or danaparoid or antixarin or ardeparin* or bemiparin*).mp.
31.	randomized controlled trial.pt.
32.	controlled clinical trial.pt.
33.	random allocation.sh.
34.	double blind method.sh.

35.	single-blind method.sh.
36.	((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).ti,ab.
37.	or/1-6
38.	or/7-30
39.	or/31-36
40.	37 and 38 and 39

Appendix B

Table B.1. Characteristics of included studies (70 studies)

Intervention	Comparison	Primary outcome	Secondary outcome	Authors	Published Year
Rivaroxaban	Enoxaparin and VKA (warfarin or acenocoumarol)	1- Recurrent VTE 2- Bleeding 3- Death	1- All-cause mortality 2- Vascular events 3- Net clinical benefit 4- Major bleeding	EINSTEIN Investigators	2010, 2012, 2014, 2014 (4 article in total)
SR90107a/ ORG31540 (factor Xa inhibitor) inj 5, 7.5, 10 mg OD	LMWH (dalteparin)	1- Change in thrombus mass 2- Recurrent VTE/ occurrence of PE 3- Major bleeding		Rembrandt Investigators	2000
LMWH (reviparin sodium)	UFH	1- Recurrent, symptomatic DVT, PE or both 2- Major bleeding 3- Death	LOS	COLUMBUS Investigators	1997
LMWH(CY216)	UFH	1- Marder and Arnesen scores 2- Recurrence VTE 3- Bleeding		Duroux et al.	1991
Apixaban	LMWH(Enoxaparin) + Warfarin	1- Recurrent VTE 2- Death	1- Recurrent DVT, PE	AMPLIFY Investigato	2013

		3- Major bleeding	2- Recurrent VTE+death 3- Major+nonmajor bleeding	rs	
Rivaroxaban	LMWH(Enoxaparin) + VKA	1- Improvement in thrombotic burden at day 21 2- Major bleeding during 12 weeks of treatment	1- Improvement of thrombus score of 4 points 2- Recurrent DVT, PE 3- Minor bleeding	ODIXa-DVT Study Investigators	2007
LMWH(Fragmin)	UFH	1- Changes in venography 2- Clinical parameters and iterative biological tests		Aiach M et al.	1989
LMWH(Fragmin)	UFH	1- Major and minor bleeding 2- Recurrence		Albada J et al.	1989
LMWH(enoxaparin)	UFH+warfarin	1- Recurrence of VTE 2- Major bleeding	Hospital LOS	Beckman J et al.	2003
1- UFH in hospital 2- LMWH(nadroparin) at	Subcutaneous calcium Heparin at home	1- Recurrence or extension of DVT in 3 months after randomization 2- Bleeding		Belcaro G et al.	1999

home 3- LMWH(nadroparin) in hospital		3- PE 4- Hospital LOS 5- Numbers of patients treated at home without hospital admission			
Napsagatran (thrombin inhibitor)	UFH	Thrombin activity and thrombin generation measurement		Bounameaux H et al.	1999
LMWH(Fragmin)	UFH	1- Changes of Marder score 2- Blood coagulation and hematological assays 3- Major bleeding 4- Recurrence of DVT or PE		Bratt G et al.	1990
UFH	LMWH(reviparin)	1- Changes of Marder score	1- Recurrence VTE 2- Major bleeding 3- Death	Breddin HK et al.	2001
Apixaban	LMWH(tinzaparin or enoxaparin) +VKA	1- Recurrence VTE and deterioration 2- Major and clinically relevant non-major bleeding	1- Any bleeding 2- All-cause mortality	Buller H et al.	2008
Idraparinux	UFH+VKA	1- Recurrent VTE 2- Major or		Buller H.R. et al.	2007

		clinically relevant non-major bleeding 3- Death			
Fondaparinux	UFH	1- Recurrent VTE 2- Major bleeding 3- Death		Buller H.R. et al.	2003
Edoxaban	Warfarin	1- Recurrent VTE 2- Death 2- Clinically relevant bleeding		Buller H.R. et al.	2013
Idrabiotaparinux	Idraparinux	1- Recurrent VTE 2- Clinically relevant bleeding 3- Death		The Equinox Investigators	2011
Fondaparinux	LMWH(enoxaparin)	1- Recurrent VTE 2- Major and clinically relevant bleeding 3- Death	Hospitalization	The Matisse Investigators	2004
LMWH(enoxaparin)+Idrabiotaparinux	LMWH(enoxaparin)+warfarin	1- Recurrent VTE within 99 days 2- Clinically relevant bleeding 3- Death	Recurrent VTE within 190 days	The Cassiopea Investigators	2012
LMWH(tinzaparin)	UFH+acenocoumarol	1- Degree of thrombus regression, expressed by modified Marder score 2- Development of	1- Recurrence or progression of VTE 2- Bleeding 3- Mortality 4- Incidence of major events	Daskalopoulos M. E. et al.	2004

		venous reflux	5- Cost analysis		
Ximelagatran	LMWH(dalteparin) and warfarin	1- Progression or regression of the thrombus 2- Bleeding 3- Symptoms of recurrent VTE		The THRIVE Investigators	2002
LMWH (dalteparin)	UFH	1- Change in Marder score 2- Bleeding 3- Recurrence of VTE		Fiessinger JN et al.	1996
LMWH(enoxaparin)	UFH	1- Major bleeding 2- Recurrent VTE 3- Death 4- Thrombocytopenia		Findik S. et al.	2002
LMWH	UFH	1- Thrombus progression 2- PE 3- Bleeding 4- Lab tests		Harenberg J et al.	1990
UFH	LMWH(nadroparin)	1- Recurrent VTE	1- Major bleeding 2- Quality of life 3- The duration of treatment 4 -The length	Koopman MM et al.	1996

			of the hospital stay 5- The number of outpatient visits 6- The frequency of telephone calls for medical information 7- Mortality		
LMWH(nadroparin)	UFH	1- Cost 2- Hematologic lab assessment		Levesque H et al.	1994
UFH	LMWH(enoxaparin)	1- Recurrent VTE 2- Bleeding	1- Mortality 2- Hospital stay	Levine M et al.	1996
LMWH(Fragmin)	UFH	1- Change in Marder score	2- Bleeding 3- PE 4- Symptomatic thrombus progression 5- Death 6- VTE recurrence	Lindmarker P et al.	1994
LMWH(nardroparin)	Acenocoumarol +UFH	1- Recurrent VTE or progression	1- Bleeding 2- LOS	LopezBeret P. et al.	2001
LMWH(dalteparin)	UFH	1- Change in Marder score	All adverse events	Luomanmaki K. et	1996

				al.	
Rivaroxaban	UFH+Warfarin	1- Symptomatic recurrent VTE or asymptomatic deterioration 2- Bleeding	2- LOS supplement	J-EINSTEIN investigators*	2015
LMWH(Enoxaparin)	UFH	1- Recurrent VTE 2- Bleeding		Merli G. et al.	2001
LMWH (Fragmin)	UFH	1- Recurrent PE 2- Bleeding	1- Evolution of pulmonary scintigraphic vascular obstruction score 2- Lab tests 3- Death	Meyer G. et al.	1995
LMWH(Dalteparin)	UFH	1- Clinical/radiological effectiveness 2- Side effects: bleeding		MorenoPalomares JJ et al.	2001
Apixaban	UFH and warfarin	1- ISTH-defined major bleeding and CRNM bleeding during the treatment period 2- Recurrent VTE 3- Death	1- ISTH major bleeding events and all bleeding events (ISTH major, CRNM, and minor)	Nakamura M. et al.	2015

Fondaparinux	UFH	1- Recurrent symptomatic VTE 2- Major bleeding	1- Recurrent symptomatic nonfatal PE, symptomatic DVT without concomitant PE, fatal VTE, and all VTEs, including asymptomatic PE and asymptomatic DVT	Nakamura M. et al.	2011
LMWH (Dalteparin)	UFH	1- Pain improvement 2- Bleeding profile 3- Complications 4- Hospital stay 5- Recurrence 6- Mortality		Naz R. et al.	2005
LMWH(CY216)	UFH	1- Symptomatic recurrent DVT 2- Severe bleeding	1- Change in extent of venous thrombosis 2- Minor bleeding	Prandoni P. et al.	1992
LMWH(CY216)	UFH	1- Changes in Marder score 2- Bleeding 3- Recurrence of		Prandoni P. et al.	1990

		VTE 4- PTS(postthromboti c sequelae)			
LMWH(Nad roparin)	UFH	1- Recurrent VTE 2- Major bleeding 3- Death		The Galilei Investigato rs	2004
LMWH(Eno xaparin)	UFH	1- recurrent DVT 2- Bleeding	1- Recurrent DVT 2-Incidence of PE 3- Hospitalization 4- LOS	The CLETRAT Investigato rs	2004
LMWH(Tinz aparin)	VKA (acenocoumarol)	1- Symptomatic DVT or pulmonary embolism 2- Major bleeding		Romera A. et al.	2009
Dabigatran	UFH	1- Recurrent VTE 2- Death 3- Bleeding events 4- Acute coronary syndrome 5- Elevated liver function tests 6- Adverse events		Schulman S. et al.	2011
Dabigatran	Warfarin	1- Recurrent VTE 2- Major bleeding 3- Death 4- Acute coronary syndrome		Schulman S. et al.	2009

		5- Elevated liver function tests 6- Adverse events			
LMWH(Dalteparin)	UFH	Time courses of different coagulation and fibrinolytic markers	Evaluation of changes in perfusion abnormalities	Schutgens R. et al.	2004
LMWH(Enoxaparin)	UFH	1- Changes of the thrombus size 2- Bleeding	1-Changes in the quantitative venographic score 2-Recurrent VTE	Simonneau G. et al.	1993
LMWH(Tinzaparin)	UFH	1- Combined outcome event: symptomatic recurrent VTE major bleeding death	1- Change in extent of scintigraphically detectable PE	Simonneau G. et al.	1997
LMWH(Nadroparin)	UFH	1- Markers of hemostatic activation	1- Hemorrhagic complications by clinical outcome and Marder score.	Stricker H. et al.	1999
LMWH(Enoxaparin)	VKA(Acenocoumarol)	1- Recurrence VTE 2- Bleeding		Veiga F. et al.	2000
LMWH(Enoxaparin)	UFH	Markers of hemostatic system		The DVTENO	1993

				X study group	
UFH+ Acenocoumarol	Acenocoumarol	1- Symptomatic extension of venous thromboembolism, symptomatic PE, symptomatic recurrent DVT 2- Bleeding		Brandjes DP et al.	1992
LMWH(Fragmin)	UFH	1-Marder score 2-Bleeding		Bratt GA et al.	1988
LMWH(Enoxaparin)	UFH	1- Symptomatic recurrent DVT 2- Adverse events 3- Bleeding	1- PE 2- hospital admission	The ASTH DVT Study Group	2005
LMWH(Enoxaparin)	UFH	Cost	1- Readmission 2- LOS	De Lissovoy G. et al.	2000
Ximelagatran	LMWH(Enoxaparin) + warfarin	1- Recurrent VTE 2- Bleeding 3- Death		The THRIVE Treatment Study Investigators	2005
LMWH(Dalteparin)	UFH	1- Recurrence 2- Bleeding 3- HIT(heparin-induced thrombopenia) 4- Mortality	LOS	Hafeli R. et al.	2001

Ximelagatran	LMWH(daltepa rin) + warfarin	1-Marder score 2-Bleeding 3-Recurrent VTE 4-Death		Harenberg J. et al.	2002
LMWH(Cert oparin)	UFH	1- 30 percent or greater improvement in the Marder Score	1- Death, 2- Recurrent venous thromboemboli sm and 3- Major bleeding	Harenberg J. et al.	2000
LMWH(Tinz aparin)	UFH	1- Cost 2- Recurrent VTE 3- Death 4- Major bleeding		Hull RD et al.	1998
LMWH(Tinz aparin)	LMWH(Tinzap arin) + warfarin	1- Symptomatic recurrent VTE 2- Bleeding	1- Death 2- Patient's treatment satisfaction 3- Symptoms of the post-thrombotic syndrome 4- Thrombocytop enia 5- Bone fractures	The LITE Trial Investigato rs	2009
LMWH(Tinz aparin)	UFH + warfarin	1- Recurrent VTE 2- Death 3- bleeding		The LITE Trial Investigato	2007

				rs	
LMWH(Reviparin)+VKA	UFH	1- Symptomatic recurrent thromboembolism 2- Phlebographic response rate 3- Changes in coagulation parameters		Kakkar V. V. et al.	2001
LMWH(Certoparin)	UFH	1- Reduction of phlebographic Marder score	1- Recurrent VTE 2- Bleeding	Kirchmaier CM et al.	1998
LMWH (CY 216)	UFH	1- Recurrent VTE 2- Bleeding 3- Death		Lopaciuk S. et al.	1992
LMWH(Enoxaparin)	UFH	1- Recurrence 2- Severe bleeding		Perez de Llano L.A. et al.	2003
LMWH(Dalteparin)	UFH	Markers of hemostatic system		Peternel P. et al.	2002
Edoxaban	UFH+warfarin	1- Change in MRV-quantified thrombus volume 2- Clinically relevant bleeding	1- Recurrent VTE 2- VTE-related death	Piazza G. et al.	2016
LMWH(Tinzaparin)	LMWH(Daltep arin)	1- Recurrent VTE 2- Bleeding		Wells P. S. et al.	2005
LMWH(CY 222)	UFH	1- Marder score 2- Lab tests		Faivre R. et al.	1987

VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism; UFH, unfractionated heparin; VKA, vitamin K antagonist; LMWH, low molecule weight heparin; LOS, length of stay; OD, once per day.

*Two articles published in the same year.