Trends in Cause-Specific Mortality after Percutaneous Coronary Intervention (PCI): Observations from the Alberta Provincial Project for Outcome assessment in Coronary Heart disease (APPROACH) Registry

by

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Abstract

Objectives: This study evaluated trends in 30-day, 1-, and 2-year cause-specific mortality using a large, contemporary cohort undergoing percutaneous coronary intervention (PCI).

Background: Prior work has shown that patients undergoing percutaneous coronary intervention (PCI) are older with higher comorbidities in the past decade, yet population-based data examining the impact of these demographic shifts on cause-specific mortality after PCI remain scant.

Methods: We used the APPROACH registry (Alberta Provincial Project for Outcome assessment in Coronary Heart disease) which captures demographic, clinical, and angiographic data on all the patients undergoing coronary angiogram in Alberta, Canada to identify consecutive patients $\geq$ 20 years undergoing PCI from the year 2005 to 2013. The cause of death was provided by the Bureau of Vital Statistics and was classified as cardiac or non-cardiac.

Results: Of the 35,602 patients who underwent PCI, 5284 (14.8%) died over a median follow-up of 66 months. In more recent years, patients were older, had more cardiovascular comorbidities, and more PCIs were done for acute coronary syndrome. The 30-day, 1-and 2-year adjusted total mortality after PCI increased significantly over the 9 years ($p<0.001$). Overall, the most common cause of death was cardiac but non-cardiac deaths increased 28% as time from PCI increased (proportion of non-cardiac deaths: 30-day=11.5%, 1-year=31.5%, 2-year=39.6%; p for trend=<0.001). By 3 years post-PCI, the most common cause of death was non-cardiac for all indications other than ST-elevation myocardial infarction (STEMI); where cardiac remained the predominant cause of death to 6 years.

Conclusion: In this real-world registry, as clinical profiles of patients undergoing PCI worsen, total mortality is increasing. The primary contributor to short-term mortality is cardiac but by 3 years post-PCI non-cardiac mortality predominates except in STEMI patients.

Preface

The research project, of which this thesis is a part of, received research ethics approval from the Human Research Ethics Board of the Research Ethics Office of the University of Alberta - Pro00040868, July 5, 2016.

The research conducted for this thesis forms part of a provincial wide research collaboration in Alberta, led by Dr. Roopinder K Sandhu at the University of Alberta. Chapter 2 of this thesis was published as an abstract as Barake W., Tran D., Galbraith D., Norris C., Knudtson ML., Kaul P., McAlister FA., Sandhu RK. (2017) *Nine Year Trends in Cause-Specific Mortality after Percutaneous Coronary Intervention (PCI): Observations from the Alberta Provincial Project for Outcome assessment in Coronary heart disease (APPROACH) Registry***.** Journal of the American College of Cardiology. 11 (69): 986. I was responsible for the initial study proposal, data collection, analysis, and manuscript composition. D. Tran assisted with data collection, statistical analysis, and manuscript composition. D. Galbraith assisted with the data collection, and contributed to the manuscript edits. C. Norris assisted with the data collection, as well as manuscript edits. ML. Knudtson assisted with the study proposal, data analysis, and manuscript edits. P. Kaul assisted with the study proposal, statistical analysis, and manuscript edits. FA. McAlister assisted with the study proposal, data analysis, manuscript composition, as well as manuscript edits. RK. Sandhu was the supervisory author and was involved with conception of the study, statistical analysis, manuscript composition, and manuscript editing. All authors approved the final work and agreed to the data presented in this research study.

Dedications

This thesis is dedicated to my wife, Lina, my two angels Serena and Rana, as well as my parents who have helped me all along to achieve this goal.

Acknowledgements

I would like to acknowledge Dr. Roopinder Sandhu as my supervisor for this project who has provided dedicated mentorship and brilliant guidance over the last three years. I would like to acknowledge Dr. Finlay McAlister for his excellent guidance, supervision and continuous support for this project. I would also like to acknowledge Dr. Padma Kaul and Dr. Merril Knudtson for their help to conduct this research study.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

PCI	Percutaneous coronary intervention
STEMI	ST-segment elevation myocardial infarction
NSTEMI	Non-ST-segment elevation myocardial infarction
APPROACH	Alberta Provincial Project for Outcome assessment in Coronary Heart disease
ARIC	Atherosclerosis Risk in Communities

Introduction

Percutaneous coronary intervention (PCI) is the most frequently performed revascularization procedure worldwide [1]. Over the past three decades, the management of coronary artery disease has been revolutionized with advancements in PCI technique, equipment, and adjuvant therapies leading to increased procedural safety and success, reduced need for emergency coronary bypass artery graft surgery and a marked decline in cardiovascular mortality [2-5]. The characteristics of patients undergoing PCI has also changed and in recent years the procedure is being performed in older individuals with greater comorbidity burden [2,3,6]. Despite changes in clinical patient profiles and contemporary therapies, data regarding the contribution of cardiac and non-cardiac causes to mortality following PCI are sparse [7-9].

A retrospective study from a tertiary care center found a mortality rate of 2% within 30 days of PCI, with more than half being attributed to a cardiac cause [7]. In the multi-center EVENT registry, patients who died within the first month post-PCI were more likely to experience a cardiac death; however, the rates of cardiac and non-cardiac deaths were similar after the first month up to one year [9]. Cause-specific long-term mortality post-PCI was examined in a large single-center study from 1991-2008: a 50% temporal decline was observed in 5-year cardiac mortality after adjusting for covariates [8]. No study has examined trends in cause-specific mortality in recent years and the contribution of cardiac and non-cardiac causes to short- and long-term mortality among all patients undergoing PCI in an entire healthcare setting reflecting real-world practice. Accordingly, we used the APPROACH registry (Alberta Provincial Project for Outcome assessment in Coronary Heart disease), which captures demographics, clinical and angiographic data, as well as indication for the procedure, to answer this question.

Methods

Study Population

We included all patients 20 years or older who underwent PCI in Alberta, Canada from January 2005 to December 2013 (n=37,195). In order to select a more homogeneous sample, we excluded patients who underwent PCI in the previous 3 years (n=1,953) leaving 35,602 patients for our final cohort. If patients had multiple PCI (n=5580) during the years studied, we designated their last PCI as their index PCI to avoid survival bias. All patients had 2 years of follow-up.

APPROACH Registry

The APPROACH (Alberta Provincial Project for Outcome assessment in Coronary Heart disease) registry is an ongoing prospective cohort study of all Alberta residents undergoing coronary angiograms since 1995 [10]. The database contains detailed information on demographic characteristics, cardiovascular risk factors, other comorbidities, medications, laboratory, electrocardiogram and imaging details, indication for angiogram, and procedural details. Data from APPROACH is supplemented and enhanced by merging the clinical registry data with administrative data records [11]. The information is entered into the registry by physicians, trained cardiac catheterization lab and health information specialists. The APPROACH research team meets routinely to generate reports and ensure database quality control.

Ascertainment of Death

Patient survival and time from angiogram and/or revascularization until death were ascertained through semiannual linkage with the Alberta Bureau of Vital Statistics up until August 2016. We used the International Classification of Diseases (ICD) code from the tenth

revision documented on the death certificate completed by each patient's attending physician to identify the most responsible cause of death. The cause of death was classified into the following categories (Appendix: Table 1S): cardiac (myocardial infarction, sudden cardiac death, heart failure/structural heart disease, other) and non-cardiac (neoplastic, respiratory, digestive, endocrine, cerebrovascular, circulatory system excluding cerebrovascular and heart, external causes/injury/poisoning, nervous/mental, genitourinary and other). Previous studies have confirmed the high accuracy of coding of cardiovascular diseases in administrative databases [12,13].

Outcomes

The primary outcome was mortality at 30-days, 1-year, and 2-years following last PCI over the study period. The secondary outcomes included determining the proportion of cardiac and non-cardiac causes of mortality at each time point post-PCI according to PCI indication for the entire cohort. We also evaluated the cumulative incidence of cause-specific mortality over 6 years follow-up overall and according to PCI indication.

Statistical Analysis

Baseline characteristics were reported for each year of the study and according to categories of survivors and non-survivors (cardiac and non-cardiac cause of death) within 30 days, 1-year, and 2-years after index PCI. Descriptive statistics were reported as counts, percentage for categorical variables, and mean $\pm$ SD for continuous variables. The 30-days, 1- and 2-year total, cardiac and non-cardiac mortalities were calculated as a frequency. Logistic models were constructed for trends in total mortality at 30-days, 1-, and 2-years adjusted for year of PCI, sex, age, comorbidities, history of smoking, indication for angiogram and procedural characteristics described in Table 1. The proportion of cardiac and non-cardiac deaths at 30-days,

1-year, and 2-years were reported as a percentage of the total deaths at each time period for each year of the study and for the entire cohort and according to PCI indication (using last PCI). Linear regression was used to calculate trend test. Cumulative incidence of cause-specific mortality was presented up to 6 years from last PCI. All analyses were performed using Stata version 14 (Stata Corporation, College Station, Texas) and two-sided p value< 0.05 was considered statistically significant. The study was approved by the Health Research Ethics Board at the University of Alberta (Pro00040868).

Results

Baseline Characteristics

A total of 35,602 patients underwent a PCI over the nine-year study period and 5284 (14.8%) died over a median follow-up of 66 months. The mean age at time of the PCI was 62.6 $\pm$ 11.9 where females contributed to 23.4%. The majority had a history of hypertension (69.1%) and hyperlipidemia (71.0%), 62.7% were smokers (past or current) and the indication for PCI was ST-elevation myocardial infarction (STEMI) in 33.0%, non-STEMI in 28.6%, unstable angina in 12.0% and stable angina in 20.3% (Table 1). Over the 9 years we studied, patients undergoing PCI became older; more had a history of hypertension, diabetes, and peripheral vascular disease while history of heart failure, prior myocardial infarction and cerebrovascular disease decreased; and the proportion of PCIs done for an acute coronary syndrome (STEMI or NSTEMI) indication increased. Non-cardiovascular comorbidities remained similar over the study period. Characteristics were compared for patients who died within 30-days, 1- and 2 years according to cardiac or non-cardiac cause of death (Appendix: Table 2S). There was no significant difference in age or sex at each time point by cause of death and although comorbidity patterns varied, patients who died a cardiac death were more likely to have undergone PCI for STEMI indication than those who died a non-cardiac death.

Table 1. Baseline Characteristics and Mortality Rates for 35,602 Patients Undergoing Percutaneous Coronary Intervention from 2005-2013.

Variable	All	2005	2006	2007	2008	2009	2010	2011	2012	2013	P for trend
N patient	35,602	3,906	3,829	3,616	3,821	3,836	4,037	4,143	4,139	4,275	
Age (years), mean (SD)	62.6 (11.9)	62.2 (11.9)	62.2 (11.7)	62.1 (11.9)	62.5 (11.9)	62.7 (12)	62.4 (11.9)	62.5 (11.8)	63 (12.1)	63.5 (12)	<0.001
Female (%)	23.4	25.3	22.6	23.9	23	23	21.4	22.2	25.7	23.6	0.68
Cardiovascular Comorbidities (%)											
Hypertension	69.1	67	67.5	69.6	68.9	69.9	71	69.5	69.7	68.8	0.007
Hyperlipidemia	71	79.5	77.3	72.5	71.7	69.9	70.5	67	66.4	65.8	<0.001
Diabetes mellitus	25	23.9	23.9	24.5	23.9	26	25.4	26.2	24.9	26.5	0.001
Renal disease	4	4.1	4	3.9	4.2	4	3.8	4.2	4.1	3.8	0.81
Heart failure	8.3	9.4	8.1	8.8	10.2	8.3	8.1	7.2	7.2	7.3	<0.001
Prior myocardial infarction	16.2	20.7	20.4	17.3	17.1	16.7	14.2	14.3	12.4	13.2	<0.001
Peripheral vascular disease	9.8	6.3	6.2	5.8	11	11.6	11.7	12.4	11.3	11.1	<0.001
Non-cardiac Comorbidities (%)											
Pulmonary	12.9	13.6	12.5	11.6	12.4	12.8	13.7	13.2	14.1	12.1	0.46
Malignancy	3.5	3.8	3.5	4	3.2	3.3	3.9	3.3	3.6	3.2	0.16
Liver disease	0.7	.8	.5	.5	.5	.4	.8	.7	.9	.7	0.17
Cerebrovascular disease	5.1	6	5.9	6.1	4.7	5.2	5.1	5.1	4.4	4	<0.001
Repeat PCI within 90 days	8.1	7.7	7.1	7.4	7.9	7.7	8	8.4	9.5	8.9	<0.001
History of smoking (%)											
Never	37.2	30	34.2	36.9	38.1	37.6	37.8	37	40	42.7	<0.001

Current	32.8	30.7	33.3	33.9	33.3	32.6	34.2	34	32.7	31	0.98
Past	29.9	39.3	32.5	29.2	28.6	29.8	27.9	29	27.3	26.3	<0.001
Indication for catheterization (%)											
STEMI	33.0	30.7	31.2	32.9	32.2	32.4	34.1	34.3	34.8	34.1	<0.001
NSTEMI	28.6	20.3	27.8	30.2	29.8	29.6	28.6	30.3	29.9	30.8	<0.001
Unstable Angina	12.0	15.6	13.7	11.6	12.6	12	11.2	10.2	10.3	10.8	<0.001
Stable Angina	20.3	21.3	21.8	18.8	20	21.2	20.6	20.5	19.3	19.4	0.02
Other	6.1	12.1	5.5	6.5	5.5	4.8	5.5	4.8	5.7	4.9	<0.001
Angiographic and procedural characteristics (%)											
Multi-vessel disease (%)	48.4	64.2	63	44.8	44.7	43.2	43.3	44.4	43.3	45.6	<0.001
Left main >70% (%)	2.3	1.8	1.9	1.5	2.1	2.3	2.6	2.4	2.6	2.9	<0.001
Drug-eluting stent	41.1	48.7	37.1	27.7	32.7	37.2	38.5	40.5	47.4	56.8	<0.001
Bare metal stent	55.4	51.7	59.5	68.1	63.4	59.2	57.8	55.1	48.3	39.1	<0.001
Total mortality (%)											
30-day	2.1	1.5	1.8	2.1	2.1	1.9	2.6	2.3	2	2.7	0.001
1-year	4.2	3.3	3.6	3.9	4.1	3.9	4.8	4.5	4.3	5.1	<0.001
2-year	6	5.2	5.1	5.6	5.6	6.1	6.7	6	6.3	6.9	<0.001

Trends in 30-day, 1- and 2-year Cause-Specific Mortality

The overall mortality at 30-day, 1-, and 2-years was 2.1%, 4.2% and 6% (Figure 1). Over the nine-years we studied, total mortality increased at 30-day, 1-, and 2-years. After adjusting for covariates, trends in total mortality remained significant ($p<0.001$).

Of the total mortality, cardiac causes of death ranged from 78.3% -89.5% at 30-days, 55.5%-70.5% at 1-year and 49.8%-60.7% at 2-years.

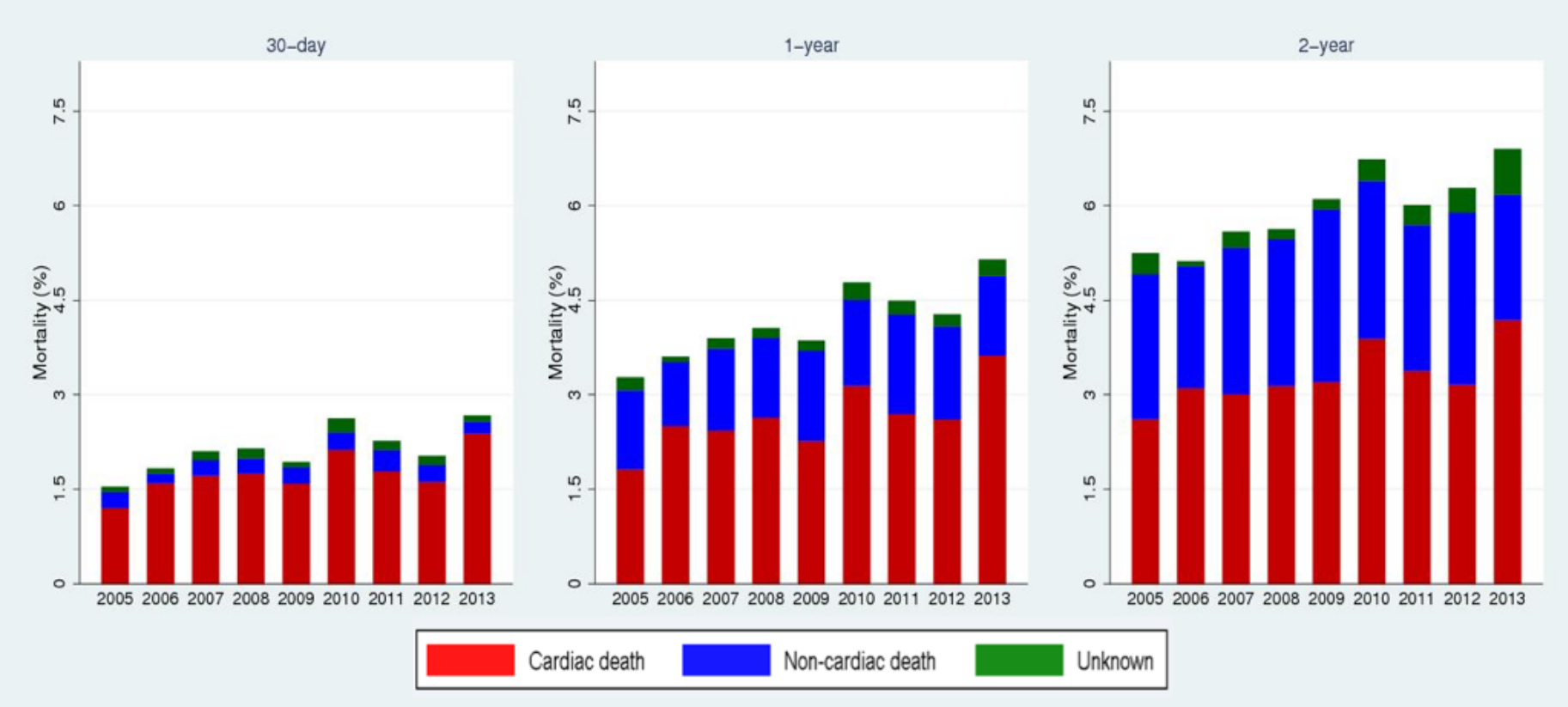


Figure 1. Total mortality and the proportion of cardiac and non-cardiac causes of mortality overall and each year of the study period.

Differential Timing of Cardiac and Non-Cardiac Causes

Of all deaths during median follow-up of 66 months, 40% were cardiac, 48% non-cardiac, and 12% had an unclear etiology (Figure 2). Overall, the most common cardiac causes of death were chronic ischemic heart disease (18%) and acute myocardial infarction (17%) and the most common causes of non-cardiac death were malignant neoplasm (20%) and diseases of the respiratory system (6%).

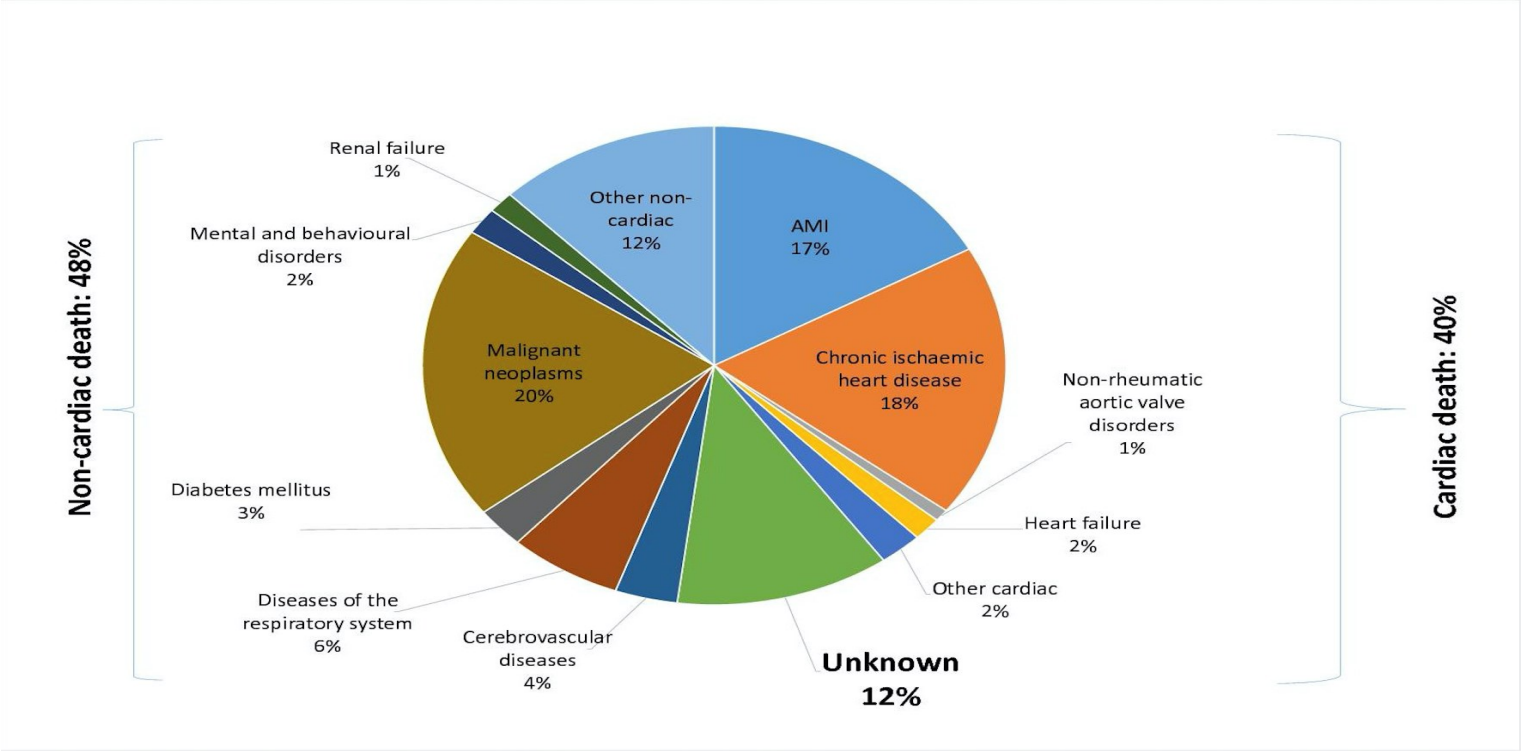


Figure 2. Detailed causes of death following percutaneous coronary intervention over the entire study period.

The proportion of cardiac and non-cardiac deaths at 30-day, 1-, and 2-years after PCI by PCI indication is shown in Table 2. Cardiac causes were the most common cause of death up to 2-years after PCI, however the proportion of deaths that were non-cardiac increased as time from PCI increased (non-cardiac: 30-day=11.8%, 1-year=31.9%, 2-year=39.9%; p for trend=<0.001). The major drivers for this trend were fewer fatal myocardial infarctions (76.6% of all deaths at 30 days but only 53.9% of all deaths at 2 years, p <0.001) and more deaths resulting from lung neoplasms (6.5% to 11.3% p=0.03).

For patients presenting with STEMI and undergoing PCI, cardiac causes of death remained the most common mode of death at 1- and 2-years (Table 2). Non-cardiac causes of death became predominant by 1-year for patients who had PCI for stable angina and by 2 years for those who had NSTEMI or unstable angina.

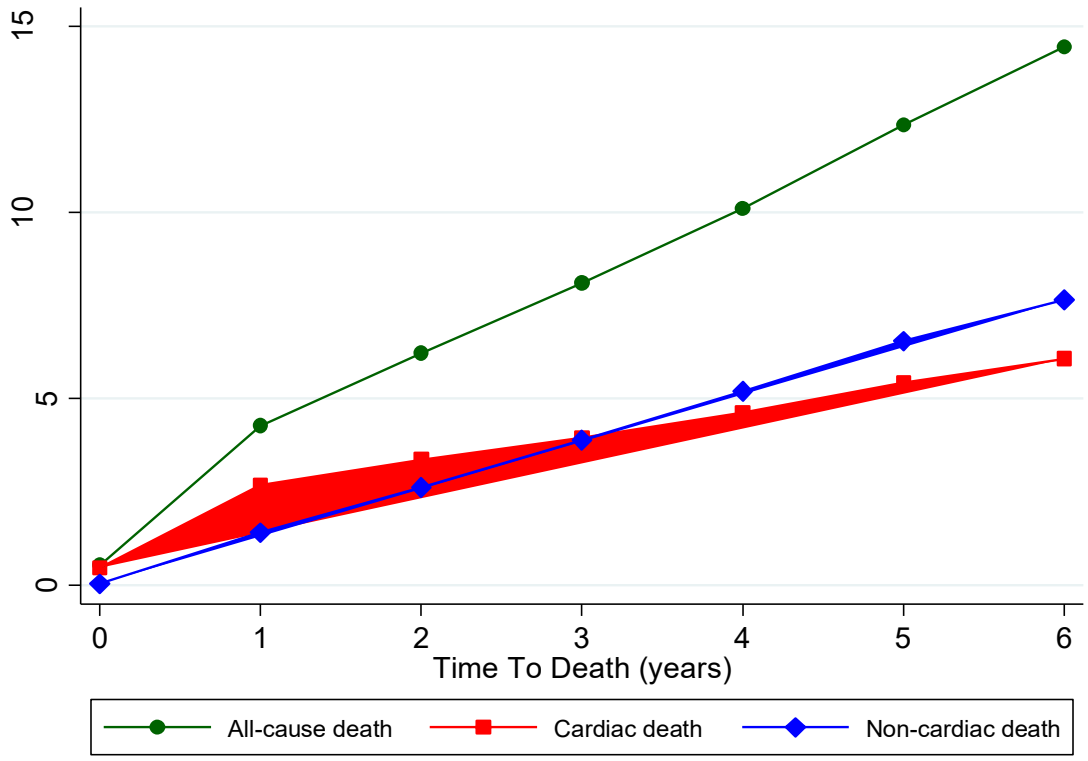
Table 2. Frequency of cardiac and non-cardiac mortality at 30-days, 1 and 2-years according to indication for percutaneous coronary intervention (N=35,602).

Indication for percutaneous coronary intervention	**30-day**	**1-year**	**2-year**
All Indications			
All-cause mortality, n (%)	806 (2.3)	1,590 (4.5)	2,259 (6.4)
Cardiac mortality, n (%)	666 (82.6)	1,019 (64.1)	1,245 (55.1)
Non-cardiac mortality, n (%)	93 (11.5)	501 (31.5)	895 (39.6)
STEMI			
All-cause mortality, n (%)	519 (4.6)	758 (6.8)	921 (8.2)
Cardiac mortality, n (%)	438 (84.4)	554 (73.1)	611 (66.3)
Non-cardiac mortality, n (%)	51 (9.8)	165 (21.8)	259 (28.1)
NSTEMI			
All-cause mortality, n (%)	139 (1.4)	414 (4.2)	621 (6.2)
Cardiac mortality, n (%)	109 (78.4)	226 (54.6)	302 (48.6)
Non-cardiac mortality, n (%)	22 (15.8)	177 (42.8)	298 (48)
Unstable angina			
All-cause mortality, n (%)	33 (0.8)	102 (2.3)	198 (4.5)
Cardiac mortality, n (%)	28 (82.4)	57 (55.9)	88 (44.4)
Non-cardiac mortality, n (%)	5 (14.7)	42 (41.2)	98 (49.5)
Stable angina			
All-cause mortality, n (%)	15 (0.2)	118 (1.5)	246 (3.1)
Cardiac mortality, n (%)	8 (53.3)	51 (43.2)	85 (34.6)
Non-cardiac mortality, n (%)	5 (33.3)	61 (51.7)	144 (58.5)

Long-term Cause-specific Mortality after PCI

The timing of cardiac, non-cardiac and total mortality over 6 years from last PCI is shown in Figure 3: non-cardiac causes of death surpassed cardiac causes after 3 years and remained the most common cause of death the longer the follow-up after PCI.

For STEMI, cardiac mortality rates were higher than non-cardiac mortality over the entire follow-up period (Appendix: Figure 1S). There was a shift in cause-specific mortality with non-cardiac causes of death surpassing cardiac causes of death after 1-year for patients undergoing PCI for unstable and stable angina and 2-years for NSTEMI. The lowest long-term cause-specific mortality rates occurred for those patients with stable angina.



Time to death (years)	0	1	2	3	4	5	6
All cause (%)	0.5	4.3	6.2	8.1	10.1	12.3	14.4
Cardiac Death (%)	0.5	2.7	3.4	4.0	4.6	5.4	6.1
Non-cardiac Death (%)	0.0	1.4	2.6	3.9	5.2	6.5	7.7

Figure 3. The cumulative incidence curves for cardiac and non-cardiac mortality over long-term follow-up.

Discussion

This large population-based registry of consecutive patients undergoing PCI provides a unique perspective on trends in contemporary cause-specific mortality rates.

Trends in Mortality

Over the last four decades, major advances in prevention and treatment have led to a significant decline in mortality from coronary artery disease all over the world [15]. Although improvements in PCI technique and use of secondary prevention therapy have contributed to lower cardiac death rates, long-term mortality after PCI has increased in recent years [3,6,8]. A single-center study of PCI patients found an increase in 1-, 3- and 5-year unadjusted mortality rates between 1991 and 2008 [8]. In an unselected nationwide cohort from Sweden spanning 20 years, the 1-year mortality rate also increased from 2.2% in 1990 to 1995 to 5.9% in 2009 to 2010 among patients treated with PCI [6]. Similarly, we found a significant increasing trend in mortality rates over the nine years we studied (2005-2013) and this finding was consistent at 30-days, 1- and 2- years post PCI. This finding may be explained by changes in the patient population with a higher risk profile and changes in PCI indications over time. Also, in a large study by Bønaa et al [27] looking at mortality outcomes after PCI by stent type, no difference in outcomes was seen in patients who received older generation drug-eluting stents (DES) versus those who received bare metal stents (BMS) after six years of therapy. Although newer generation DES have been shown to reduce cardiovascular events and mortality in comparison to BMS and older generation DES [28,29,30], they have been used widely in Alberta only in the last 5 years and their potential effect would not be reflected in our study sample which was pre-2014.

Changes in Cause-specific Mortality

Few studies have evaluated the differential timing of cardiac and non-cardiac causes of death after PCI in clinical practice [7-9]. Within 30-days of PCI, the major cause of death is cardiac, contributing anywhere from 58% to 70% of all deaths in prior studies but 83% in our cohort [7,9]. After 30-days, the EVENT registry found similar rates of cardiac and non-cardiac causes of death however an etiology could not be determined in 26% of patients [9]. In our study, cardiac causes remained the most common cause of death up to 2 years post-PCI. At 5 years, cardiac deaths accounted for only 37% of deaths from the Mayo clinic [8]. The difference in the proportion of cardiac and non-cardiac deaths at various time points among studies likely reflects differences in patient profiles and indications for PCI. A third of our cohort had undergone PCI for STEMI whereas this represented only 5% of the EVENT registry and this was not reported from the Mayo clinic.

Older registry data from the 1980's and 1990's and the recent EVENT registry evaluating long-term cause-specific mortality have found the incidence of cardiac mortality consistently higher than non-cardiac mortality rates [8,9,16]. However, single-center data from across three eras demonstrates the incidence of non-cardiac mortality surpassing cardiac mortality less than one year post-procedure in 2003-2008 compared to earlier years [8]. In the APPROACH registry, we also found a shift in long-term cause-specific mortality with a higher incidence of non-cardiac mortality than cardiac mortality by 3 years after PCI. Similar to the 1990s study from the Mayo clinic, the decline in cardiac mortality was due to fewer fatal myocardial infarctions while increasing malignancy rates have resulted in increased non-cardiac mortality [8]. Prior work suggests the shift in cause-specific mortality may be explained by changing patient characteristics (i.e. older patients with a higher burden of non-cardiovascular

comorbidities) which would influence the rates of non-cardiac mortality while advancements in technology (thrombolytics versus stenting, DES vs. BMS stents), improving procedural success rates, and increasing use of secondary prevention therapies have lowered long-term cardiac mortality [3,6,7,17,18].

Cardiac and Non-Cardiac Mortality According to PCI Indication

Our study is novel in reporting the proportion of cardiac and non-cardiac causes of mortality at 30-day, 1-, and 2-years post-PCI and the cumulative incidence in cause-specific mortality in long-term follow-up according to the indication for PCI for the entire cohort.

In our study, there was a higher proportion of death due to cardiac causes at 30-day, 1-, 2 years for patients who underwent PCI for STEMI while the proportion of non-cardiac deaths was higher after 1-year for stable angina and 2-years for NSTEMI and unstable angina. Among STEMI patients, we found the incidence rates for cardiac mortality were consistently higher than non-cardiac mortality and did not begin to converge until 5-years after the PCI. The Coronary Revascularization Demonstrating Outcomes study in Kyoto (CREDO-Kyoto AMI) registry also demonstrated higher rates of cardiac death compared to non-cardiac death in long-term follow-up among 3942 patients who underwent PCI for STEMI with differences in cause-specific mortality becoming similar by 7 years [19]. Similarly, a single-center study in Denmark found non-cardiac mortality rates surpassed cardiac mortality after 7-year of follow up in 2861 consecutive patients with STEMI undergoing primary PCI [20]. In contrast to STEMI patients, our study found patients who underwent PCI for NSTEMI had a higher risk of non-cardiac death after 2 years following PCI whereas this risk occurred earlier, at less than 1 year, for unstable and stable angina patients. Similar trends were seen among stable disease patients in the Spoon et al study, however direct comparisons cannot be made with acute coronary syndrome patients as they were

defined as unstable angina or any type of myocardial infarction within the prior 7 days together was an urgent or emergent procedure [8]. It is possible that STEMI patients have higher cardiovascular disease burden than patients undergoing PCI for other indications and could explain the difference in cause-specific mortality in those patients. Further confirmatory research is needed to fully explain the causes of mortality trends differences.

Limitations

Our study has some limitations. First, the accuracy of administrative codes from death certificates in Canada has not been well validated [21]. The accuracy of death certificates has been validated in the Framingham Heart Study and the Atherosclerosis Risk in Communities (ARIC) cohort studies, where the positive predictive value of death certificates of cardiac deaths was 67% when compared with the validated cause of death based on physician review of all available clinical and administrative data[22-23]. Death due to coronary heart disease based on death certificates was overestimated by 24% and 20%, respectively. ICD codes have been used in different studies [8,9,12,13,14] to classify the cause of death and were used as the lone ascertainment method in the PCI study performed by Fokkema et al [6]. Prior work has demonstrated a high accuracy rate for coding of cardiovascular disease (myocardial infarction, heart failure, stroke) in Canadian administrative databases and this methodology has been extensively used to evaluate trends in rates of death in Canada [12-14,24,25]. In addition, it is unlikely that attending physicians or medical coroners responsible for determining causes of death drastically changed their approach over the nine-year study period. In order to have homogenous methodology and results that can be interpreted in the context of previous studies, we have classified cause-specific mortality in similar categories to those described by Spoon et al. [8] and Stolker et al. [9] with the exception of cerebrovascular deaths (4% of all of our deaths)

which were classified in the cardiac category by Stolker and colleagues. Second, our study did not capture medications at discharge or during follow-up and this could have impacted the balance between cardiac and non-cardiac mortality rates, particularly since secondary prevention medication have been shown to improve long-term cardiac survival after PCI [17, 26]. Third, this study is observational in nature and the mortality rates were not standardized for changes in underlying risk factors and comorbidities which subject such studies to unmeasured confounders, and residual confounding.

Conclusion

In this large cohort from a single-payer health care system with universal coverage and access, we found increasing rates of total mortality over time in the contemporary era. The most common cause of death at 30-days, 1-, and 2 years was cardiac but as time from PCI increased, the proportion of deaths that were non-cardiac increased and surpassed cardiac mortality after 2 years in patients undergoing PCI for NSTEMI and after 1 year in those undergoing PCI for unstable or stable angina; however, cardiac mortality remained the predominant cause of death after PCI for STEMI even out to 6 years. These data suggest that prognostication for patients undergoing PCI requires careful evaluation of a patient's clinical profile and procedural indication. We would caution clinicians to not only weigh non-cardiac comorbidities in making decisions about cardiac catheterization and PCI but also to treat those which are modifiable in order to reduce total mortality for patients undergoing PCI.

Clinical perspectives

What is known?

Clinical profiles for patients undergoing PCI are changing yet little is known about the impact on cause-specific mortality.

What is new?

In a large, contemporary cohort of consecutive patients undergoing PCI, total mortality at 30-day, 1- and 2 years increased over a nine-year period. The most common cause of death was cardiac at each of these time points. In the longer-term follow-up, a shift in cause-specific mortality was observed with the proportion of non-cardiac causes of death increasing with time from the PCI. Our findings emphasize the importance of considering all-cause outcomes in cardiac patients rather than cause-specific outcomes.

What is next?

Further research of cause-specific mortality is needed both in randomized clinical trials and observational studies to help improve risk prediction and guide appropriate patient selection, as well as optimize management of underlying conditions.

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Appendix

Table 1S. International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM), causes of deaths classified in subgroups of diseases.

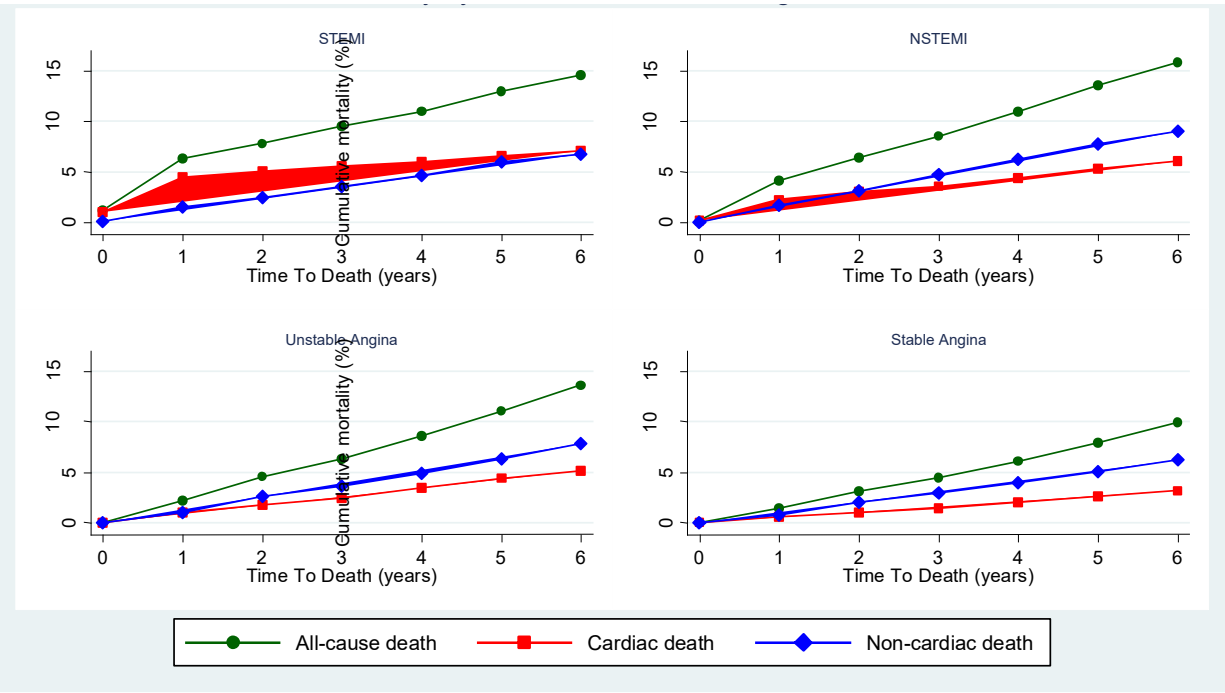
Category	ICD-10
Cardiac Causes	I00-I09 I20-I25 I30-I52 I11 (Hypertensive heart disease) I27 (Other pulmonary heart diseases) Q20-Q24 (Congenital malformations of cardiac chambers and connections, Congenital malformations of cardiac septa, Congenital malformations of pulmonary and tricuspid valves, Congenital malformations of aortic and mitral valves, Other congenital malformations of heart)
Non-Cardiac Causes	
Neoplastic	C00-C97 D00-D48
Respiratory	J00-J99
Digestive	K00-K93
Endocrine, nutrition and metabolic	E00-E90
Cerebrovascular	I60-I69
External causes, injury and poisoning	S00-S99 T00-T98 V01-Y98
Circulatory system excluding Cerebrovascular and heart	I10-I15Hypertensive diseases (excluding I11 Hypertensive heart disease) I26-I28 Pulmonary heart disease and diseases of pulmonary circulation (excluding I27 Other pulmonary heart diseases) I70-I79Diseases of arteries, arterioles and capillaries I80-I89Diseases of veins, lymphatic vessels and lymph nodes, not elsewhere classified I95-I99Other and unspecified disorders of the circulatory system

Category	ICD-10
Nervous and mental	F00-F99 G00-G99(G40*)
Genitourinary	N00-N77
Others	Any others ICD code

Table 2S. Characteristics of survivors and non-survivors at 30-days, 1- and 2-year following percutaneous coronary intervention.

Variable	All patients still alive at 2 years	Patients who died within 30 days			Patients who died within 1 year			Patients who died within 2 years		
		CV cause	Non-CV cause	P value	CV cause	Non-CV cause	P value	CV cause	Non-CV cause	P value
N patient	33,343	666	93		1,019	501		1,245	895	
Age (years), mean (SD)	62.3 (11.7)	69.5 (12.7)	69.2 (11.4)	0.86	70.2 (12.6)	70.8 (11.2)	0.38	70.5 (12.4)	71.1 (10.9)	0.22
Female (%)	22.9	31.7	32.3	0.91	31.8	28.9	0.26	31.2	31.3	0.98
Cardiovascular Comorbidities (%)										
Hypertension	70.7	59.9	71	0.04	69.1	74.3	0.04	71.8	78.9	<0.001
Hyperlipidemia	73.9	45.3	47.3	0.72	55.7	63.7	0.003	59.8	68.3	<0.001
Diabetes mellitus	24.7	31.5	35.5	0.45	36.1	39.5	0.20	37.5	39.3	0.39
Renal disease	3	18.6	31.2	0.01	19.7	22.8	0.17	20.4	20	0.82
Heart failure	7.1	28.7	25.8	0.57	32.4	28.1	0.09	33.4	27	0.002
Prior MI	20.4	19.8	23.7	0.39	26.4	28.1	0.47	29.7	31.4	0.41
Peripheral vascular disease	9.6	15	21.5	0.11	15.8	15	0.68	16.1	15.1	0.54
Non-cardiac Comorbidities (%)										
Pulmonary	12.8	19.1	33.3	0.002	22	33.3	<0.001	23.4	32.2	<0.001

Malignancy	3.2	4.5	22.6	<0.001	5.7	21	<0.001	5.3	17.7	<0.001
Liver disease	0.6	2.1	3.2	0.49	2	3	0.21	1.7	3.2	0.02
Cerebrovascular disease	5	9.3	18.3	0.01	11.1	12.8	0.34	11.9	13.1	0.27
History of smoking (%)										
Never	36	57.4	49.5	0.15	51.7	42.1	<0.001	48.7	40.3	<0.001
Current	32.7	24.8	21.5	0.49	25.7	25	0.75	25.6	25.6	0.99
Past	31.3	17.9	29	0.01	22.6	32.9	<0.001	25.7	34.1	<0.001
Indication for catheterization (%)										
STEMI	30.8	65.8	54.8	0.04	54.4	32.9	<0.001	49.1	28.9	<0.001
NSTEMI	28	16.4	23.7	0.08	22.2	35.4	<0.001	24.2	33.3	<0.001
Unstable Angina	12.7	4.2	5.4	0.60	5.6	8.4	0.04	7.5	10.9	0.002
Stable Angina	22.9	1.2	5.4	0.004	5	12.2	<0.001	6.8	16.1	<0.001
Other	5.6	12.4	10.8	0.64	12.9	11.2	0.35	12.8	10.7	0.15
Angiographic and procedural characteristics (%)										
Multi-vessel disease (%)	45.4	63.1	65.6	0.64	64	61.5	0.34	65.1	59.4	0.008
LM>70% (%)	2	11.3	11.8	0.87	10.3	5.4	0.001	10	5.3	<0.001
DES used	45.3	22.2	22.6	0.94	28.2	33.9	0.02	30.9	35.8	0.02
BMS used	52.7	64.3	63.4	0.88	60.6	57.3	0.22	58.8	56.8	0.35
Complete revascularization achieved (%)	59.2	39.9	41.9	0.71	39	47.5	0.001	39	48.7	<0.001



	N patients	Time to death (years)						
PCI Indication		**0**	**1**	**2**	**3**	**4**	**5**	**6**
STEMI	6,044							
All cause (%)		1.2	6.4	7.8	9.5	11.0	13.0	14.6
Cardiac Death (%)		1.0	4.5	5.0	5.6	6.0	6.6	7.1
Non-cardiac Death (%)		0.1	1.6	2.4	3.6	4.6	6.0	6.7
NSTEMI	5,288							
All-cause (%)		0.2	4.2	6.4	8.5	10.9	13.5	15.8
Cardiac Death (%)		0.2	2.3	3.0	3.6	4.4	5.4	6.1
Non-cardiac Death (%)		0.0	1.7	3.1	4.7	6.2	7.8	9.0
Unstable Angina	2,573							
All-cause (%)		0.0	2.2	4.6	6.3	8.6	11.1	13.6
Cardiac Death (%)		0.0	1.0	1.8	2.4	3.5	4.4	5.2
Non-cardiac Death (%)		0.0	1.0	2.6	3.6	4.9	6.3	7.8
Stable Angina	4,222							
All-cause (%)		0.0	1.4	3.1	4.5	6.1	7.9	9.9
Cardiac Death (%)		0.0	0.6	1.0	1.4	2.0	2.7	3.2
Non-cardiac Death (%)		0.0	0.8	2.0	2.9	4.0	5.0	6.2

Figure 1S. The cumulative incidence curves for cardiac and non-cardiac mortality according to indication for percutaneous coronary intervention over long-term follow-up.