Original Article

Total and Cause-Specific Mortality After Percutaneous Coronary Intervention: Observations From the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease Registry

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ABSTRACT

Background: Patients undergoing percutaneous coronary intervention (PCI) are increasingly older and have a higher comorbidity burden. This study evaluated trends in 30-day, 1-year, and 2-year total and cause-specific mortality using a large, contemporary cohort of patients who underwent PCI in Alberta, Canada.
Methods: We used the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) registry to identify patients aged ≥ 20 years who underwent PCI between 2005 and 2013. All patients were followed until death or being censored by August 2016. Cause of death was from the Vital Statistics database and classified as cardiac or noncardiac. Multivariable logistic regression was used to calculate predicted mortality at 30 days, 1 year, and 2 years post-PCI.
Results: Of the 35,602 patients who underwent PCI, 5284 (14.8%) had died. Mean (standard deviation) follow-up was 74.9 (35.1)

RÉSUMÉ

Contexte : Les patients devant subir une intervention coronarienne percutanée (ICP) sont de plus en plus âgés et subissent un fardeau accru de comorbidités. La présente étude a évalué les tendances de la mortalité totale et due à une cause particulière à 30 jours, 1 an et 2 ans, au sein d'une vaste cohorte contemporaine de patients ayant subi une ICP en Alberta, au Canada.
Méthodologie : Nous avons utilisé le registre APPROACH (*Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease*) pour recenser les patients âgés de 20 ans ou plus qui avaient subi une ICP entre 2005 et 2013. Tous les patients ont fait l'objet d'un suivi jusqu'au décès ou à la censure des données en août 2016. La cause du décès était issue de la Base de données sur l'état civil et classée comme étant d'origine cardiaque ou non cardiaque. On a eu recours à un modèle de régression logistique multivarié pour calculer la mortalité prédite 30 jours, 1 an et 2 ans après l'ICP.

Percutaneous coronary intervention (PCI) is the most frequently performed revascularization procedure worldwide.[1] Over the past 2 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,[2,3] and a marked decline in cardiovascular mortality.[4-6] The characteristics of patients undergoing PCI has also changed, and the procedure is being performed in older individuals with greater comorbidity burden in recent years.[2,3,7] Despite changes in clinical patient profiles, data regarding the contribution of cardiac and noncardiac causes of death after PCI are sparse.[8-10] A retrospective study from a tertiary care center found a mortality rate of 2% within 30 days of PCI, with 58% being attributed to a cardiac cause of death.[8] In the multicenter Evaluation of Drug Eluting Stents and Ischemic Events registry (EVENT) registry,[10] patients who died within the first month post-PCI were more likely to experience a cardiac death; however, the rates of cardiac and noncardiac deaths were similar after the first month up to 1 year.

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months. Over the study period, patients were older and more likely to undergo PCI for an acute coronary syndrome indication. Thirty-day (2005: 1.3%; 2013: 3.2%; *P* < 0.001), 1-year (2005: 2.7%; 2013: 5.7%; *P* < 0.001), and 2-year (2005: 4.5%; 2013: 7.5%; *P* < 0.001) predicted mortality after PCI increased over the study period. Cardiac cause of death dominated in the short-term, but the proportion of noncardiac deaths increased as time from PCI to death increased (30 days = 11.5%, 1 year = 31.5%, 2 years = 39.6%; *P* < 0.001).

Conclusions: In this population-based study, we found all-cause mortality at 30 days, 1 year, and 2 years after PCI increased over time. Cardiac causes of death dominate in the short-term after PCI; however, noncardiac cause becomes a major driver of mortality in the long-term.

Résultats : Sur les 35 602 patients ayant subi une ICP, 5 284 (14,8 %) étaient décédés. La durée moyenne de suivi (écart type) était de 74,9 (35,1) mois. Au cours de la période de l'étude, les patients étaient plus âgés et plus susceptibles de subir une ICP pour une indication de syndrome coronarien aigu. On observe une augmentation de la mortalité prédite après l'ICP au cours de la période de l'étude selon les taux suivants : à trente jours (2005 : 1,3 % ; 2013 : 3,2 % ; *p* < 0,001), à 1 an (2005 : 2,7 % ; 2013 : 5,7 % ; *p* < 0,001) et à 2 ans (2005 : 4,5 % ; 2013 : 7,5 % ; *p* < 0,001). Les causes cardiaques de décès dominaient à court terme, mais la proportion de décès d'origine non cardiaque augmentait avec le temps au fur et à mesure de l'allongement de l'intervalle entre la date de l'ICP et le décès (30 jours = 11,5 %, 1 an = 31,5 %, 2 ans = 39,6 % ; *p* < 0,001).

Conclusions : Dans cette étude de population, nous avons trouvé que la mortalité toutes causes confondues à 30 jours, 1 an et 2 ans après une ICP augmente au fil du temps. Les causes cardiaques de décès dominent peu de temps après l'ICP, tandis que les causes non cardiaques jouent un rôle déterminant dans la mortalité à long terme.

Cause-specific mortality in the long-term post-PCI was examined in a large single-center study[9] from 1991 to 2008 showing a 50% decline in 5-year cardiac mortality. Little is known about the trend of total and cause-specific mortality in the short- and long-term among patients undergoing PCI in more recent years in an integrated health care setting reflecting real-world practice. Accordingly, we used the **A**lberta **Pr**ovincial **Pr**oject for **O**utcome **A**ssessment in **C**oronary **H**eart Disease (APPROACH) registry to answer this question.

Methods

APPROACH registry

The APPROACH registry is an ongoing prospective cohort study of all Alberta residents undergoing coronary angiograms since 1995.[11] The database contains information on demographic characteristics, patient comorbidities, medications, laboratory, electrocardiogram and imaging, indication for angiogram, and procedural details. The information is entered into the registry by physicians and trained cardiac catheterization laboratory and health information specialists. The APPROACH research team meets routinely to generate reports and ensure database quality control. Data from APPROACH are supplemented and enhanced by merging the clinical registry data with the administrative data sets.[12,13]

Study population

Using the APPROACH registry, we included patients aged ≥ 20 years who underwent PCI between January 2005 and December 2013. Patients who underwent PCI during the previous 3 years were excluded to ensure new PCI episodes. If a patient had multiple PCIs during the study period, the first PCI was designated as the index PCI. All patients were followed until death or being censored by August 31, 2016, representing a minimum follow-up of 32 months for all patients.

Patient survival and time from angiogram or revascularization until death were ascertained through linkage with the Alberta Administrative Health Dataset/Vital Statistics.[13] We

used the International Classification of Diseases, 10th revision code on the death certificate, which was recorded by each patient's attending physician to identify the most responsible cause of death and categorized it into cardiac (eg, ischemic heart diseases) and noncardiac (eg, neoplastic, respiratory, and digestive causes) groups. Details on cause of death are presented in Supplemental Table S1. Previous studies have confirmed the high accuracy of coding of cardiovascular diseases and stroke in administrative databases.[14-16]

Outcomes

The main outcomes were temporal trends of all-cause mortality at 30 days, 1 year, and 2 years after the index PCI. Other outcomes included mortality over time from the last PCI and distribution of cardiac and noncardiac cause of death at each of the 30-day, 1-year, and 2-year time points after the last PCI according to PCI indication. The last PCI was selected for cause of death assessment to reflect the most proximal intervention for patients who had more than 1 PCI during the study period.

Statistical analysis

Baseline characteristics were reported for each year of the study and survival status (cardiac and noncardiac cause of death) within 30 days, 1 year, and 2 years after PCI. Descriptive statistics were reported as counts and percentage for categorical variables and mean ($\pm$ standard deviation) for continuous variables. Univariate linear and logistic regression were used for trend test of continuous and binary variables, respectively. We developed 3 multivariable logistic regression models to calculate predicted mortality at 30 days, 1 year, and 2 years after index PCI using marginal standardization.[17] For each model, the primary independent variables were patient sex, age, and year of index PCI as a categorical variable (with the year 2005 as the reference). We used the likelihood ratio test to examine inclusion of additional risk factors. They were patient comorbidities (Table 1) and angiographic and procedural characteristics (multivessel disease, left main > 70%, using drug-eluting or bare metal stents, complete revascularization, and radial access) as binary variables and history of

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

Variable	All	2005	2006	2007	2008	2009	2010	2011	2012	2013	P for trend
N patient	35,602	3906	3829	3616	3821	3836	4037	4143	4139	4275	
Age (y), 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	0.676
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	0.805
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
Noncardiac comorbidities (%)											
Pulmonary disease	12.9	13.6	12.5	11.6	12.4	12.8	13.7	13.2	14.1	12.1	0.464
Malignancy	3.5	3.8	3.5	4	3.2	3.3	3.9	3.3	3.6	3.2	0.155
Liver disease	0.7	.8	.5	.5	.5	.4	.8	.7	.9	.7	0.171
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 d (%)	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	0.980
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	0.019
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 (%)											
Multivessel 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
Complete revascularization	67.9	-	-	84.5	76.4	65.9	64.6	63.5	62.8	60.6	< 0.001
Total mortality (%)											
30 d	2.1	1.5	1.8	2.1	2.1	1.9	2.6	2.3	2	2.7	0.001
1 y	4.2	3.3	3.6	3.9	4.1	3.9	4.8	4.5	4.3	5.1	< 0.001
2 y	6	5.2	5.1	5.6	5.6	6.1	6.7	6	6.3	6.9	< 0.001

NSTEMI, non−ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; SD, standard deviation; STEMI, ST-elevation myocardial infarction.
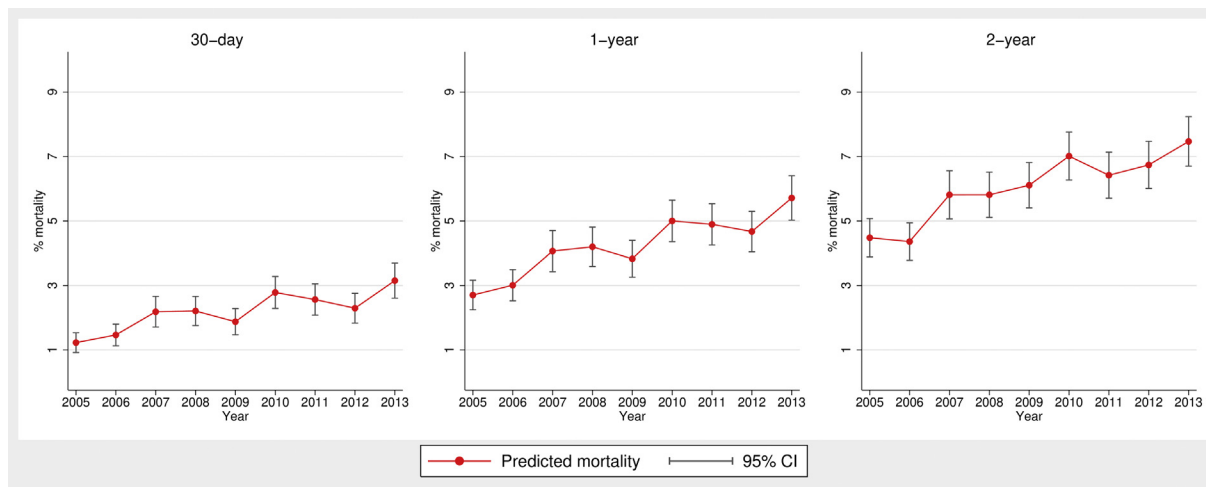
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Figure 1. Temporal trends of all-cause mortality in patients undergoing percutaneous coronary intervention (PCI) in Alberta, 2005-2013.

smoking and indication for PCI as categorical variables. Except for the primary variables, an independent variable remained in the final models if the likelihood ratio test was significant at a $P < 0.05$. Hosmer–Lemeshow goodness-of-fit test was used to check for model fits.

In addition, we calculated cardiac and noncardiac mortality after the last PCI using Kaplan–Meier curve and reported as a percentage of the total deaths at each of the 30-day, 1-year, and 2-year time points. All analyses were performed using Stata version 14 (StataCorp LP, College Station, TX). A 2-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

Between 2005 and 2013, there were 37,195 patients aged ≥ 20 years who underwent PCI in Alberta, Canada. After excluding patients who had PCI during the previous 3 years (n = 1953), the final study cohort included 35,602 patients with a mean (standard deviation) follow-up time of 74.9 (35.1) months. Of them, 5580 (15.7%) had more than 1 PCI during the study period. Patient age (mean = 62.6 years) increased over time (2005: mean = 62.2 years; 2013: mean = 63.5 years; $P <$ 0.001). There were less female (23.4%) than male patients, and this trend remained during the study period ($P = 0.676$). Hypertension (69.1%) and hyperlipidemia (71%) were the most prevalent cardiovascular comorbidities. Although hypertension increased (2005: 67%; 2013: 68.8%; $P = 0.007$), hyperlipidemia decreased (2005: 79.5%; 2013: 65.8%; $P < 0.001$). ST-elevation myocardial infarction (STEMI, 33%) was the most common indication for catheterization, and it increased over time (2005: 30.7%; 2013: 34.1%; $P < 0.001$). The proportion of patients who underwent drug-eluting stent increased (2005: 48.7%; 2013: 56.8%; $P < 0.001$), whereas that of those undergoing bare metal stent decreased (2005: 51.7%; 2013: 39.1%; $P < 0.001$) during the study period (Table 1). Characteristics of patients by survival status is presented in Supplemental Table S2.

All-cause mortality

Overall, 5284 patients (14.8%) died during the study period. Unadjusted mortality increased over time at all 3 time points: 30 days (2005: 1.5%; 2013: 2.7%; $P = 0.001$), 1 year (2005: 3.3%; 2013: 5.1%; $P < 0.001$), and 2 years (2005: 5.2%; 2013: 6.9%; $P < 0.001$) (Table 1). The increasing trends remained after risk adjustments. The predicted 30-day mortality increased from 1.3% (95% confidence interval [CI], 0.9-1.6) in 2005 to 3.2% (95% CI, 2.6-3.7) in 2013 ($P < 0.001$). Likewise, the predicted mortality increased from 2.7% (95% CI, 2.2-3.2) in 2005 to 5.7% (95% CI, 5-6.4) in 2013 ($P < 0.001$) and from 4.5% (95% CI, 3.9-5.1) in 2005 to 7.5% (95% CI, 6.7-8.2) in 2013 ($P < 0.001$) at 1 year and 2 years post-PCI, respectively (Fig. 1). Results of multivariable logistic regression models for mortality at 30 days, 1 year, and 2 years after index PCI are presented in Supplemental Table S3.

Cause-specific mortality

Of all deaths, 40% were cardiac and 48% were noncardiac (Fig. 2). The most common cardiac causes of death were chronic ischemic heart disease (18%) and acute myocardial infarction (17%), and the most common causes of noncardiac causes were malignant neoplasm (20%) and diseases of the respiratory system (6%). The proportion of cardiac and noncardiac cause of death from last PCI at 30 days, 1 year, and 2 years by PCI indication is presented in Table 2. Cardiac causes of death were the most common at all 3 time points, but the proportion of noncardiac causes increased as time from PCI did (30 days: 11.5%; 1 year: 31.5%; 2 years: 39.6%; $P < 0.001$). The major drivers for this trend were fewer fatal myocardial infarctions (63.3% and 29.7% of all deaths at 30 days and 2 years post-PCI, respectively, $P <$ 0.001) and more deaths resulting from lung neoplasms (0.7% and 4.5% of all deaths at 30 days and 2 years post-PCI, respectively, $P < 0.001$).

Overall, noncardiac cause of death surpassed cardiac cause after 3 years from the last PCI and remained the most common cause thereafter (Fig. 3). Cardiac death dominated during the first 6 years after the last PCI for patients with
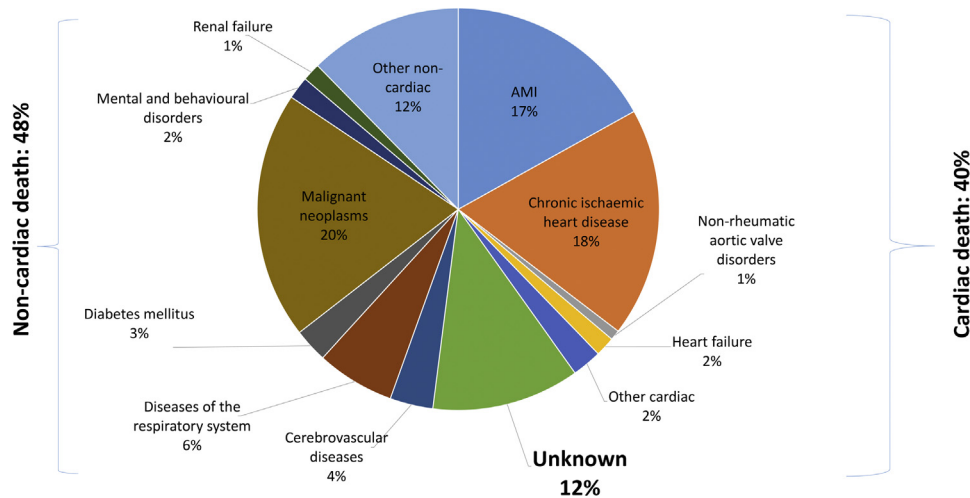
Figure 2. Causes of death after PCI in Alberta, 2005-2013.

STEMI, whereas noncardiac causes did at 1 year for patients who had stable angina and 2 years for those who had non-STEMI or unstable angina (Table 2, Fig. 4).

Discussion

Our population-based study of 35,602 patients undergoing PCI using a real-world prospective clinical registry over 9 years showed that all-cause mortality at 30 days, 1 year, and 2 years after PCI increased over time. Overall, cardiac causes accounted for a smaller proportion of death compared with noncardiac reasons, but it dominated in the short-term after PCI and subsequently decreased as time from PCI increased. By the third year after PCI, noncardiac cause became the major driver of mortality. Patients with STEMI had the highest burden of cardiac mortality, and this remained dominant until the sixth year post-PCI.

Similar to our study, which included a more contemporary time period, studies from both the United States and Sweden have found mortality rates after PCI have increased in recent years.[7,9] When evaluating 1-year mortality rates, Fokkema et al.[7] reported a slight decrease, whereas we found both unadjusted and adjusted 1-year mortality rates after PCI increased over time. The differences in trends could be explained by differences in level of risk adjustment. In our study, we adjusted for not only age and indication for PCI but also patient and angiographic factors. Additionally, the decrease in mortality observed in the Sweden study was mainly among patients with STEMI, which increased 5-fold over the study period, but only increased 3.4% in our cohort.[7] Furthermore, the increasing trends of mortality after PCI in our study may be the result of a patient population with a higher risk profile (ie, the elderly) or broader indication, such as patients with complex lesions for whom it was previously not recommended,[18,19] or the degree of complete revascularization.

We found that traditional cardiac risk factors (hypertension, hyperlipidemia) confer a reduction in the odds of all-cause mortality. Improved use of evidence-based medicine
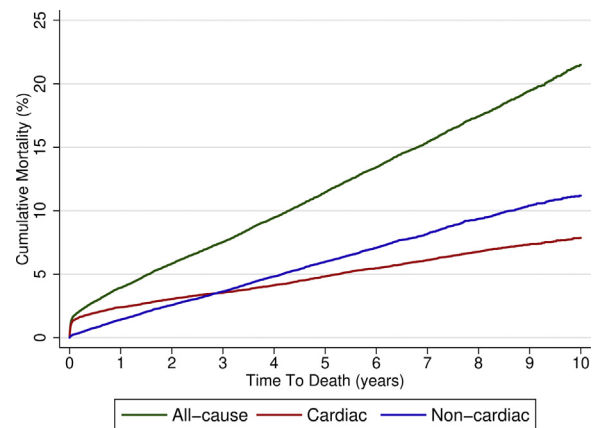
Table 2. Proportion of cardiac and noncardiac mortality at 30 days, 1 year, and 2 years after the last PCI according to indication for PCI

Indication for PCI	30 d	1 y	2 y
All indications			
All-cause mortality (%)	2.3	4.5	6.4
Cardiac mortality (%)	82.6	64.1	55.1
Noncardiac mortality (%)	11.5	31.5	39.6
STEMI			
All-cause mortality (%)	4.6	6.8	8.2
Cardiac mortality (%)	84.4	73.1	66.3
Noncardiac mortality (%)	9.8	21.8	28.1
NSTEMI			
All-cause mortality (%)	1.4	4.2	6.2
Cardiac mortality (%)	78.4	54.6	48.6
Noncardiac mortality (%)	15.8	42.8	48
Unstable angina			
All-cause mortality (%)	0.8	2.3	4.5
Cardiac mortality (%)	82.4	55.9	44.4
Noncardiac mortality (%)	14.7	41.2	49.5
Stable angina			
All-cause mortality (%)	0.2	1.5	3.1
Cardiac mortality (%)	53.3	43.2	34.6
Noncardiac mortality (%)	33.3	51.7	58.5

NSTEMI, non–ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

Figure 3. Cumulative all-cause and cause-specific mortality after PCI in Alberta, 2005-2013.

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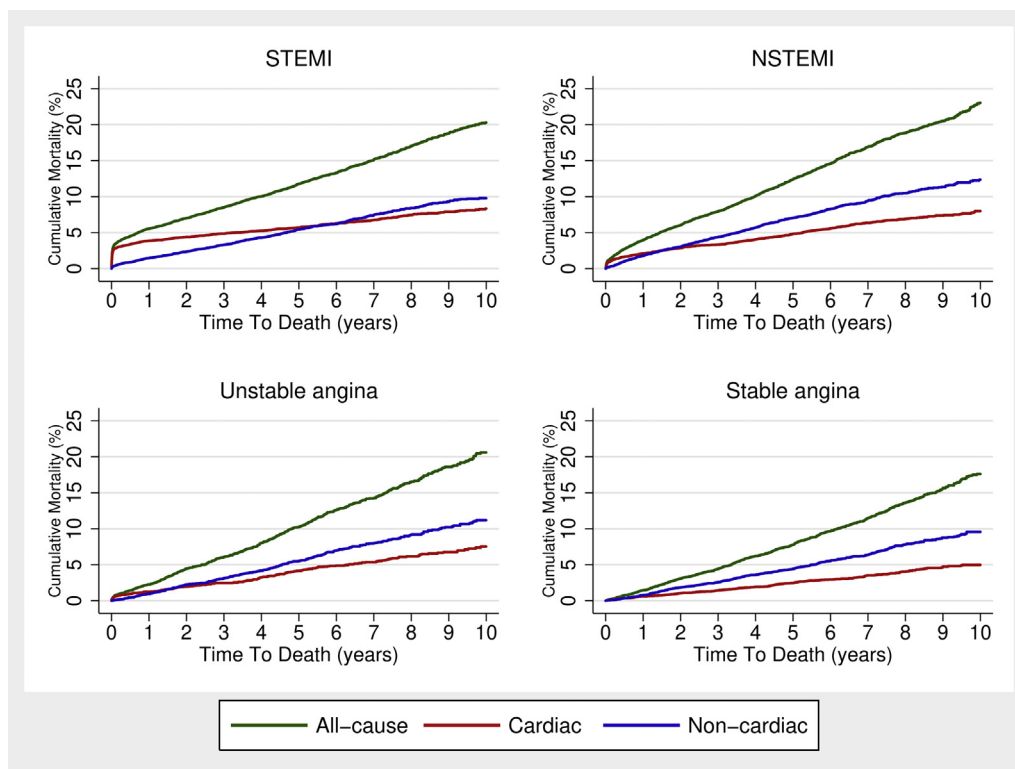Total and Cause-Specific Mortality Post-PCI

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Figure 4. Cumulative mortality according to indication for PCI over long-term follow-up. NSTEMI, non—ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction.

to treat risk factors may contribute to this finding.[20-22] A radial approach was also associated with a decreased risk of mortality. Compared with a femoral approach, multiple randomized clinical trials have demonstrated a mortality benefit with a radial approach that is primarily driven by a reduction in bleeding complications.[23-26]

Few studies have evaluated the differential timing of cardiac and noncardiac cause of death after PCI in clinical practice and found a cardiac reason for death in the short-term ranging from 58% to 70% in the United States and 92% in Denmark.[8,10,27] The lower proportions of cardiac cause of death in the US cohorts might be due to differences in patient risk profiles (ie, older population in the US cohorts, possibly making them more vulnerable to noncardiac reasons such as cancer or pulmonary diseases).[8,10,27] Stolker et al.[10] reported 25% undetermined cause of death and variations in patterns of practice between jurisdictions as possibly affecting patient outcomes.[28]

Although cardiac mortality dominates in the short-term post-PCI, we found the proportion of noncardiac deaths surpasses cardiac mortality in the long-term follow-up as previously reported. Spoon et al.[9] reported a significant shift to noncardiac cause of death in 2014. Similar trends from cardiac to noncardiac cause of death after PCI have also been observed specifically in patients with STEMI.[29] Pedersen et al.[27] reported higher noncardiac deaths at 6 years after PCI in patients with STEMI in Denmark, approximately the same as the convergence time for patients with STEMI in our study. Likewise, Yamashita et al.[30] reported only 9% of

noncardiac cause of death at 6 months but 4.5 times increase to 41% at 7 years after PCI in Japan.

This decline in cardiac reasons for mortality in our study and a prior report of long-term follow-up are mainly due to fewer fatal myocardial infarctions and increasing malignancy rates.[9] Patient characteristics (ie, older patients with a higher burden of noncardiovascular comorbidities)[3,7] may predispose to noncardiac reasons for mortality, particularly because advancements in revascularization technology, high procedural success rates, and use of secondary prevention therapies have lowered long-term cardiac mortality.[3,8,20,21] Further research may be warranted to integrate the roles of noncardiac cause of death into clinical guidelines and best practices regarding cardiac health.

Study limitations

Although our study was conducted using a clinical registry in a single-payer, universally covered, and integrated health system, which serves more than 4 million people in a large geographical area of Alberta, there are limitations that warrant discussion. First, our study did not capture medications at discharge or during follow-up, and this could have affected the adjusted balance between cardiac and noncardiac mortality rates, particularly because secondary prevention medication has been shown to improve long-term cardiac survival after PCI.[20,22] Second, we had missing data for the variable complete revascularization in 2005-2006, and we are unable to differentiate the specific causes of death under the broader categories (ie, cause of death under chronic ischemic heart

disease). Third, cause of death validity using International Classification of Diseases, 10th revision coding has not been studied. However, the cause of death in the Canadian Vital Statistics has been used widely in research recently.[31-35] Finally, this study is observational in nature and subject to inherent limitations of this study design, such as misclassification and unobserved confounders, which may affect results.

Conclusion

In this large and contemporary cohort of patients undergoing PCI from a single-payer healthcare system with universal coverage and access, we found increasing rates of mortality over time. The most common cause of death in the short-term after PCI is cardiac, but as time from PCI increases, noncardiac cause of death increases and becomes the predominant mode of death. This pattern in cause-specific mortality occurs earlier in patients with non-STEMI and unstable angina undergoing PCI.

Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

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