Trends in Cause of Death after Percutaneous Coronary Intervention

Running title: Spoon et al.; Cause of death after PCI

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Abstract

Background—The impact of changing demographics upon causes of long-term death after percutaneous coronary intervention (PCI) remains incompletely defined.

Methods and Results—We evaluated trends in cause-specific long-term mortality after index PCI performed at a single center from 1991-2008. Deaths were ascertained by scheduled prospective surveillance. Cause was determined via telephone interviews, medical records, autopsy reports and death certificates. Competing-risks analysis of cause-specific mortality was performed using three time-periods of PCI (1991-1996, 1997-2002, 2003-2008). Final follow-up was 12/31/2012. A total of 19,077 patients survived index PCI-hospitalization, of whom 6,988 subsequently died (37%, 4.48/100 person-years). Cause was determined in 6,857 (98.1%). Across three time-periods, there was a 33% decline in cardiac deaths at 5 years after PCI (incidence 9.8%, 7.4%, 6.6%) but a 57% increase in non-cardiac deaths (7.1%, 8.5%, 11.2%). Only 36.8% of deaths in the recent era were cardiac. Similar trends were observed regardless of age, extent of coronary disease or PCI indication. After adjustment for baseline variables there was a 50% temporal decline in cardiac mortality but no change in non-cardiac mortality. The decline in cardiac mortality was driven by fewer deaths from myocardial infarction/sudden death (p<0.001) but not heart failure (p=0.85). The increase in non-cardiac mortality was due primarily to cancer and chronic diseases (p<0.001).

Conclusions This study found a marked temporal switch from predominantly cardiac to predominantly non-cardiac cardiac causes of death after PCI over two decades. The decline in cardiac mortality was independent of changes in baseline clinical characteristics. These findings have implications for patient care and clinical trial design.

Key words: cardiovascular disease, cardiac disease, cardiac catheterization, mortality, percutaneous coronary intervention
Introduction

As percutaneous coronary intervention (PCI) enters its fourth decade of use, it is now the most commonly performed revascularization therapy worldwide.¹ The majority of randomized trials of PCI with a long-term mortality endpoint have shown cardiac causes to predominate as mode of death during follow-up.²⁻⁸ Moreover, the available evidence demonstrating a mortality benefit of PCI over medical therapy for acute coronary syndromes²⁻⁶ or of coronary artery bypass grafting (CABG) over PCI⁷,⁸ has been driven by a reduction in cardiac rather than non-cardiac causes of death.

Mortality from coronary artery disease in the US has been in decline since the late 1960’s⁹,¹⁰ principally due to reduction in atherosclerotic risk factors and implementation of preventative therapies.⁹ Whether there have been temporal changes in the cause of death in populations with established coronary disease undergoing PCI remains incompletely understood. US and European registries have shown the age and atherosclerotic risk factor burden of patients undergoing PCI to have increased over time.¹¹,¹² Despite concurrent improvements in PCI technologies and preventative therapies, long-term mortality after PCI has also increased in recent time-periods.¹¹,¹² Older registry studies indicated cardiac causes of death proportionately outweighed non-cardiac causes during longer term follow-up.¹³⁻¹⁵ Contemporary PCI studies from large registries report all-cause rather than cause-specific mortality.¹¹,¹⁶ In order to appropriately align efforts toward reducing long-term mortality in patients with established coronary disease, it is crucial to understand cause-specific mortality in this population and temporal changes therein. This information will additionally assist in the design of future clinical trials involving PCI. Accordingly, we performed a large retrospective single-center study to
determine cause-specific mortality during long-term follow-up after index PCI-hospitalization, and to evaluate temporal trends in cause of death over a twenty-two year period.

**Methods**

**Patient population**

The study was approved by the Mayo Clinic Institutional Review Board. Patients undergoing PCI at Mayo Clinic in Rochester, Minnesota, are prospectively followed in a registry that includes demographic, clinical, angiographic, and procedural data. We considered the first PCI performed at Mayo Clinic for all patients between January 1, 1991 and December 31, 2008. During this period, 27,001 PCIs were performed on 19,982 consecutive patients. Of these, 476 refused use of records for research purposes and were excluded, leaving 19,506 patients for analysis, of which 19,077 survived to discharge. This cohort was divided into three 6-year eras for analysis according to date of PCI: 1991-1996 (n=5,115 patients), 1997-2002 (n=7,326 patients), and 2003-2008 (n=6,636 patients). Final follow-up was December 31, 2012.

**Definitions**

Current smoking status was defined as having smoked cigarettes within the last 6 months while a former smoker was defined as having smoked in the past but quit >6 months ago. A history of high cholesterol was defined as having a total cholesterol value >240 mg/dL or on drug therapy. Peripheral vascular disease was defined as a history of classic claudication or peripheral vascular surgery (including nontraumatic amputation) or peripheral angioplasty. Diabetes was defined as a documented diagnosis requiring treatment with medication or diet. Hypertension was defined as a documented history, or treatment with medication. Moderate or severe renal disease was defined as creatinine >3.0mg/dl or on dialysis or previous kidney transplant. Multivessel disease
(70/50) was defined as ≥2 major coronary arteries with at least 50% stenosis, provided at least 1 artery had ≥70% stenosis. Patients with ≥50% stenosis in the left main coronary artery were considered to have multivessel disease. Type C lesion represents the most severe of American Heart Association/American College of Cardiology coronary artery lesion classifications, based on markers such as lesion length, tortuosity, calcification, thrombus, presence of major side branch, presence of chronic occlusion. Definitions for 17 disease components of the Charlson index are as previously described by Deyo et al.17

For analysis by PCI indication, we defined acute coronary syndrome as unstable angina or any type of myocardial infarction within the prior 7 days together with an urgent or emergency procedure. The coronary artery disease comorbidity index was calculated as previously described.18 The Charlson index, a measure of overall disease burden, was calculated based on 17 diseases and weights as previously described.17 Comorbidities were captured from the Mayo Diagnosis Index database for all time prior to index PCI to 30 days after PCI. Additionally, the index was split into cardiac and non-cardiac components by summing the weights for myocardial infarction and congestive heart failure separate from all other diseases.

**Ascertainment of death and determination of cause**

Deaths were primarily ascertained via scheduled surveillance telephone contact of all PCI patients performed routinely at 6 months, 12 months and yearly thereafter. Communication with the Mayo Clinic registration office, which serves as a central repository of all patient death notifications, provided an additional source. Upon identification of a death, details were obtained through telephone contact with family and external providers and through review of local and external medical records. Death certificates were requested for all patients. Experienced data technicians recorded details of each death and performed initial classification. When cause of
death could not initially be obtained (n = 731, 10% total deaths), information was requested from
the National Death Index. Two physicians (DBS, RG) reviewed each death, re-screened medical
records where appropriate and resolved disparity by consensus. Final classification
(subclassification) was performed into one of 26 causes as follows. **Cardiac:** Myocardial
infarction, sudden cardiac death, congestive heart failure/structural heart disease,
interventional/surgical procedure related, other cardiac. **Non-cardiac:** Vascular (hemorrhagic
stroke, ischemic or undefined stroke, abdominal aortic aneurysm rupture, other vascular), cancer
(solid organ, hematologic), infectious, chronic diseases (neurologic, pulmonary, renal failure,
liver/multiorgan failure, natural causes), hemorrhage (gastro-intestinal, other), pulmonary
embolus, iatrogenic (non-cardiac procedure/surgery related), trauma (accident/trauma, suicide),
aacute surgical non-cardiac, other non-cardiac. **Unknown or unobtainable.**

In view of overlap in the classification of certain modalities of death, and potential
ambiguity, we created operative rules for classification, including the following: Sudden cardiac
death was defined as either a documented arrhythmogenic death or the out-of-hospital
occurrence of an unexpected presumed pulseless condition together with the absence of an
obvious non-cardiac explanation. Where the only information was the death certificate and
where primary cause was stated as ischemic heart disease, this was classified as myocardial
infarction. Fatal valvular heart disease was classified as congestive heart failure/structural heart
disease. When there were competing non-cardiac and cardiac causes of death, we favored cardiac
classification. Fatal motor vehicle accidents were classified as accident/trauma, recognizing that
sudden cardiac death as a substrate could not be excluded. For equally competing non-cardiac
causes, we favored death certificate classification.
Statistical analysis

Continuous variables are summarized as mean (SD) and were compared between the three eras using one-way ANOVA. Categorical variables are summarized as frequency (group percentage) and are compared between the groups using Pearson’s chi-squared test for nominal variables and the Kruskal-Wallis test for ordinal variables. Survival analyses were conducted on in-hospital survivors only. Kaplan-Meier estimates are used to summarize event rates for all-cause mortality, with the log-rank test used for group comparisons. Competing risks methods were used to estimate the cumulative incidence of cause-specific modes of death over long-term follow-up. To exclude bias from a potential change in referral patterns that may have occurred over time, a separate population analysis confined to residents 0-25 miles from the institution undergoing PCI (n=4,057) was additionally performed. As there are no other PCI centers within 75 miles of the institution, this represented a true local (rather than tertiary referral) population. A permutation test approach was used to test the hypothesis that the ratio of cardiac to non-cardiac deaths at 5-years after PCI was the same between the three time eras. Two-thousand permutation data sets were created by randomly permuting the time era group with the outcomes data. Within each permuted data set, the ratio of cardiac to non-cardiac deaths at 5 years for the three time groups was calculated. Of the 3 possible pairwise era comparisons, the maximum absolute difference in log-ratios was calculated for the 2,000 data sets to generate an approximate null distribution for the statistic. The observed statistic was then compared to the null distribution to determine a p-value. Cox proportional hazards models were used to test differences in cause-specific mortality between groups. Group comparisons of the incidence of PCI and CABG after discharge were tested using a generalized linear model with the number of events as the dependent variable. A log link function (assuming Poisson distribution) was employed as well as an offset by the log of
the length of follow-up, and overdispersion assessed by deviance/df. To investigate whether the differences in cause-specific incidence between the three eras could be due to differences in comorbidity burden, we used strata-weighted estimation. We stratified all subjects by sex, age (<65, 65-79, ≥80), multivessel disease, previous revascularization, history of MI > 7 days, Charlson score for cardiac diagnoses, Charlson score for non-cardiac diagnoses (0,1,2,3,4,5-6,7-9,10-13,>13), and diagnoses for congestive heart failure, moderate/severe renal disease, and metastatic solid tumor. As some strata were not present in all three eras, in particular strata with high comorbidity burden, 3,283 patients were excluded (559 from 1991-1996, 1,145 from 1997-2002, and 1,579 from 2003-2008). Otherwise, patients in the 1991-1996 and 1997-2002 eras were weighted such that all strata distributions were proportional to the 2003-2008 era. All hypotheses tests are 2-sided with a 0.05 Type I error rate. SAS 9.3 (SAS Institute, Cary, NC) was used for all analyses.

Results

Baseline characteristics

Clinical, angiographic, and procedural characteristics of patients undergoing PCI across three eras (1991-1996, 1997-2002, 2003-2008) are shown in Table 1. There was a temporal increase in mean age, proportion of females, body mass index and prevalence of all atherosclerotic risk factors except smoking. However there was a temporal decrease in history of remote MI and prior CABG. The prevalence of multiple non-cardiac comorbidities also increased across eras. The predominant indication for PCI changed from stable angina in the first 6 years to acute coronary syndrome more recently. The use of evidence-based secondary prevention therapies at hospital dismissal significantly increased over time.
In-hospital mortality and unadjusted long-term outcomes

From 19,506 patient PCI-hospitalizations between 1991 and 2008, 429 deaths occurred during initial hospitalization (2.2%). Of the survivors, 6,988 (37%) died during subsequent follow-up. In-hospital mortality decreased over time among patients undergoing PCI for stable angina but not acute coronary syndrome (Table 2). In survivors of initial hospitalization, the unadjusted rate of long-term mortality was higher in the most recent era, at multiple time-points after PCI (Table 2). The incidence of repeat PCI or CABG performed during five years of follow-up decreased across time periods (incidence per 1,000 person-years 73.3, 64.2, 53.7 and 27.7, 17.3, 10.2 respectively; each p<0.001).

Change in causes of long-term death after PCI

Cause of death was obtained in 6,857 of 6,988 deaths in the overall study period (98.1%).

Figure 1 illustrates a major temporal shift in cause of long-term death after PCI from cardiac to non-cardiac diseases over five years of follow-up. This was due both to a decline in cardiac deaths across time periods (incidence 5 years after PCI: 9.8%, 7.4%, 6.6%, p<0.001) and an increase in non-cardiac deaths (7.1%, 8.5%, 11.2%, p<0.001). In the most recent era, cardiac deaths accounted for only 36.8% of deaths at 5 years of follow-up. Non-cardiac disease surpassed cardiac disease as the primary cause of death at 50 days after PCI.

To exclude bias from a potential change in referral patterns which may have occurred over time, a separate PCI population analysis of confined to residents 0-25 miles from the institution indicated near identical temporal changes in cause of death (Supplemental Figure 1).

Weighted-comparisons of patients with similar age, gender, and cardiac and non-cardiac co-morbid variables across three eras indicated a 50% decline in the incidence of cardiac deaths at 5-years (8.2%, 5.5%, 4.1%) whereas the incidence of non-cardiac deaths remained relatively
stable (7.5%, 7.1%, 8.1%) (Figure 2). Similar patterns were observed for cardiovascular and non-cardiovascular deaths (Supplemental Figure 2)

**Cause-specific mortality by age, PCI indication and extent of coronary disease**

The change from cardiac to non-cardiac diseases as the primary cause of long-term death occurred in all age-groups, with the largest relative change occurring in the elderly (Figure 3a). Temporal patterns were similar whether PCI was performed for stable disease or for acute coronary syndromes (Figure 3b) and in both single-vessel and multivessel disease subsets (Figure 4).

**Changes in subtypes of cardiac and non-cardiac death**

The decline in absolute incidence of cardiac death was driven by a decline in fatal myocardial infarction/sudden cardiac death, rather than congestive heart failure; the rise in non-cardiac deaths was principally due to deaths from cancer and chronic diseases (Figure 5a). Vascular deaths accounted for a much smaller proportion overall, but increased in the most recent era (5-year incidence: 1.00%, 1.02%, 1.43%, p=0.002, Supplemental Figure 3). This was driven by a non-significant rise in ischemic/undefined strokes (0.62%, 0.62%, 0.80%; p=0.26). There was a significant increase in fatal hemorrhagic strokes (0.14%, 0.16%, 0.29%; p=0.004), with this increase being most pronounced in the first twelve months after PCI (Supplemental Figure 4). Specific causes as a proportion of all deaths in the most recent era are illustrated in Figure 5b.

**Discussion**

The major findings of this study are: 1) There has been a marked temporal switch over two decades from predominantly cardiac to predominantly non-cardiac causes of long-term death after PCI. 2) This change occurred in all age groups, in single and multivessel disease subsets
and whether PCI was performed for stable angina or acute coronary syndromes. 3) The decline in cardiac mortality was independent of changes in baseline clinical characteristics. 4) This decline has been driven by deaths attributable to myocardial infarction and sudden cardiac death, but mortality from heart failure has remained unchanged. 5) The increase in non-cardiac mortality was associated with increased non-cardiac comorbidities at baseline, and has been due primarily to deaths from cancer and chronic diseases.

**Decline in cardiac mortality**

Despite mean age and atherosclerotic risk factor burden increasing over time, weighted comparison of patients with similar cardiac/non-cardiac profiles showed an even more pronounced decline in cardiac mortality than in the overall PCI population. While an effect of unmeasured clinical variables cannot be excluded, this finding suggests the temporal decline in long-term cardiac mortality is robust and independent of changes in baseline clinical characteristics.

A plausible explanation for the decline in long-term cardiac deaths after PCI is the increase in pre-dismissal secondary prevention therapies that was noted across all 3 eras. Multiple randomized trials have indicated mortality benefit of such therapies in patients with established coronary disease, as summarized in current practice guidelines. Moreover, utilization of multiple classes of these medications has previously been found to be independently associated with long-term survival after PCI. A causative relationship between the increased prescription of these therapies and a reduction in cardiac mortality might further be implied by the specific decline in fatal myocardial infarction/sudden cardiac death seen in the current study. This finding is consistent with the established effectiveness of preventative
therapies, particularly statins and ACE inhibitors, in reducing the long-term risk of myocardial infarction and sudden death in patients with established coronary disease\textsuperscript{21-26}.

The time-periods in this study corresponded approximately with balloon angioplasty (early provisional stenting, 1991-1996) as the primary interventional approach, routine bare-metal stent (1997-2002) and routine drug-eluting stent placement (2003-2008).\textsuperscript{27} Randomized studies have failed to show a long-term mortality advantage of bare metal stents over balloon angioplasty or of drug-eluting stents over bare-metal stents in multiple clinical settings.\textsuperscript{28-30} Therefore, while it is possible that these studies were underpowered for detecting mortality differences, it would seem unlikely that temporal improvements in device technologies themselves have had significant impact upon late cardiac mortality in the current study.

**Increase in non-cardiac mortality**

The current study showed cardiac and non-cardiac mortality trends in the overall PCI population were mirrored in a population of local residents, lending support to generalizability of the findings. Community studies of myocardial infarction and heart failure have also indicated an increase in the proportions of late non-cardiovascular death, but these studies have been limited by small numbers of deaths within cohorts.\textsuperscript{31,32} 

The present study showed the rise in non-cardiac mortality was related to an increased prevalence of non-cardiac comorbidities at time of PCI. This itself may be a consequence of symptomatic coronary disease having shifted toward older populations.\textsuperscript{9,11} Alternatively, it is possible that older and sicker patients in the contemporary era are preferentially being referred for PCI rather than CABG or medical therapy alone. However, as similar trends in causes of death were seen in all age-groups, in patients with single and multivessel disease, and in patients
undergoing PCI for both stable and acute indications, it seems unlikely that the increase in non-cardiac mortality is accounted for by a temporal bias in referral of sicker patients for PCI.

**Implications**

The present study indicates that in the contemporary era it is the competing risk from non-cardiac diseases that outweighs the long-term mortality risk of progressive cardiac disease. Moreover, the higher risk of non-cardiac mortality occurring in multiple subgroups of patients undergoing PCI suggests an evolution in the prognosis of broad populations of patients with coronary disease. If the primary goal continues to be prolongation of life, these temporal changes have implications for both current care and for strategic priorities in resource allocation for cardiovascular health. Attention to the comprehensive management of non-cardiac comorbidities might arguably offer significant returns in combination with a continued focus upon cardiac strategies. Additionally, the higher likelihood of non-cardiac rather than cardiac mortality after PCI should be considered during patient selection, especially in those with less certain indications for revascularization and multiple non-cardiac comorbidities. There are few risk-models which predict long-term mortality after PCI, and even these are restricted to all-cause mortality.33, 34 The development of risk models that predict cause-specific rather than all-cause death will help further refine revascularization decisions.

Cause-specific mortality (cardiac vs. non-cardiac) is frequently an endpoint in randomized studies, but has been less well studied in registries of PCI which are more reflective of clinical practice at large. Consistent with the current study, comparisons of historic with contemporary randomized trials of PCI for stable angina indicate a decrease in the proportion of cardiac deaths during follow-up.35, 36 Discordant with the current study however, is the continued predominance of cardiac causes of late death in randomized trials of acute coronary syndrome,2, 4,
Our study defines what is meant by a “real-world” population in terms of cause-specific mortality. The data indicates that it is difficult to extrapolate mortality benefit of novel treatments from randomized trials when the increasing frequency of non-cardiac death in real-world PCI cohorts is not adequately represented in trial design due to patient selection bias. The trajectory of rising non-cardiac mortality in the current study suggests that not only will it be increasingly difficult to power randomized studies intending to evaluate mortality benefit of cardiac-directed therapies, but that a focus on cardiac strategies alone may have diminishing relevance for meaningful mortality impact in “real-world” settings.

Limitations

Although analysis confined to local residents yielded similar trends in cause of death, the single-center setting may limit the generalizability of results and may not reflect trends in different geographic, racial or socio-economic backgrounds. While data was collected prospectively and causes of death were mostly collected through scheduled surveillance, there are limitations inherent to all retrospective analyses. A recent study reported death certificates had only 58% accuracy for classifying deaths as cardiac versus non-cardiac. A strength of the current study is the use of multiple methods of cause of death ascertainment. Despite this accuracy cannot be assured and misclassification may have occurred in some. Undiagnosed massive pulmonary embolus, intracerebral hemorrhage or stroke could have been misclassified as sudden cardiac death. This potential for misclassification is a broad issue within most epidemiologic studies of sudden death. Finally, lack of information on non-interventional care of patients between index PCI and death may limit the ability to more directly draw implications from the observed outcomes.
Conclusions

This study found a shift from predominantly cardiac to predominantly non-cardiac causes of long-term death after PCI. Increased utilization of secondary preventative therapies, increase in mean age at PCI and increase in prevalence of non-cardiac comorbidities may have contributed to these changes. The findings underscore the importance of a holistic approach in the care of patients with coronary artery disease and provide cause-specific mortality benchmarks to assess the future impact of survival-directed therapies.

Conflict of Interest Disclosures: None.

References:


Table 1. Baseline clinical, angiographic, and procedural characteristics by PCI-era.

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<tr>
<td><strong>Clinical characteristics</strong></td>
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<tr>
<td>Age (yrs), mean (sd)</td>
<td>64.7 (11.4)</td>
<td>66.0 (12.0)</td>
<td>66.3 (12.4)</td>
<td>&lt;0.001</td>
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<tr>
<td>Male gender, no. (%)</td>
<td>3,660 (72)</td>
<td>5,106 (70)</td>
<td>4,607 (69)</td>
<td>0.028</td>
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<tr>
<td>BMI, mean (sd)</td>
<td>28.5 (5.0)</td>
<td>29.4 (5.6)</td>
<td>29.8 (5.9)</td>
<td>&lt;0.001</td>
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<tr>
<td>Current smoking, no. (%)</td>
<td>1,027 (20)</td>
<td>1,412 (20)</td>
<td>1,270 (20)</td>
<td>0.75</td>
</tr>
<tr>
<td>Charlson index, mean (sd)</td>
<td>1.8 (2.1)</td>
<td>2.0 (2.3)</td>
<td>2.6 (2.8)</td>
<td>&lt;0.001</td>
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<tr>
<td><strong>Cardiovascular comorbidities</strong></td>
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<tr>
<td>CAD comorbidity index, mean (sd)</td>
<td>1.6 (2.4)</td>
<td>2.2 (2.6)</td>
<td>2.5 (2.9)</td>
<td>&lt;0.001</td>
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<tr>
<td>History of MI (&gt;7 days), no. (%)</td>
<td>1,595 (32)</td>
<td>1,796 (25)</td>
<td>1,211 (19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior CABG, no. (%)</td>
<td>1,018 (20)</td>
<td>1,338 (18)</td>
<td>1,142 (17)</td>
<td>&lt;0.001</td>
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<td></td>
<td><strong>Angiographic and procedural characteristics</strong></td>
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<tr>
<td>Multivessel disease (70/50), no. (%)</td>
<td>3,395 (67)</td>
<td>4,868 (69)</td>
<td>3,968 (64)</td>
<td>&lt;0.001</td>
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<tr>
<td>Type C lesion, no. (%)</td>
<td>1,483 (35)</td>
<td>2,891 (44)</td>
<td>3,114 (52)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total stents placed, mean no. (sd)</td>
<td>0.4 (0.8)</td>
<td>1.4 (1.0)</td>
<td>1.4 (0.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Use of drug-eluting stents, no (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>4,766 (72)</td>
<td>&lt;0.001</td>
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<tr>
<td><strong>Non-cardiac comorbidities</strong></td>
<td></td>
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<tr>
<td>Charlson: Non-cardiac only, mean (sd)</td>
<td>1.3 (1.9)</td>
<td>1.4 (2.1)</td>
<td>1.9 (2.6)</td>
<td>&lt;0.001</td>
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<tr>
<td>Mod/severe renal disease, no. (%)</td>
<td>119 (4)</td>
<td>206 (3)</td>
<td>270 (4)</td>
<td>&lt;0.001</td>
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<td>COPD, no. (%)</td>
<td>552 (11)</td>
<td>937 (13)</td>
<td>1,030 (16)</td>
<td>&lt;0.001</td>
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<tr>
<td>Peptic ulcer disease, no. (%)</td>
<td>396 (8)</td>
<td>567 (8)</td>
<td>572 (9)</td>
<td>0.10</td>
</tr>
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<td>Cerebrovascular disease, no. (%)</td>
<td>588 (11)</td>
<td>897 (12)</td>
<td>1016 (15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dementia, no. (%)</td>
<td>32 (1)</td>
<td>66 (1)</td>
<td>70 (1)</td>
<td>0.046</td>
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<tr>
<td>Rheumatologic Disease, n (%)</td>
<td>146 (3)</td>
<td>216 (3)</td>
<td>277 (4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HIV/AIDS, no. (%)</td>
<td>0 (0)</td>
<td>5 (0)</td>
<td>9 (0)</td>
<td>0.026</td>
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<tr>
<td>Metastatic Solid Tumor, no. (%)</td>
<td>130 (3)</td>
<td>204 (3)</td>
<td>210 (3)</td>
<td>0.12</td>
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<tr>
<td>Other Cancer, no. (%)</td>
<td>624 (12)</td>
<td>1,102 (15)</td>
<td>1,218 (18)</td>
<td>&lt;0.001</td>
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<td>Liver disease, no. (%)</td>
<td>95 (2)</td>
<td>154 (2)</td>
<td>310 (5)</td>
<td>&lt;0.001</td>
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<td><strong>Discharge medications</strong></td>
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<tr>
<td>Aspirin, no. (%)</td>
<td>4,622 (90)</td>
<td>6,943 (95)</td>
<td>6,443 (97)</td>
<td>&lt;0.001</td>
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<tr>
<td>Thienopyridine, no. (%)</td>
<td>1,008 (20)</td>
<td>6,652 (91)</td>
<td>6,439 (97)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>β-blockers, no. (%)</td>
<td>2,999 (59)</td>
<td>5,543 (76)</td>
<td>5,671 (86)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any lipid-lowering drugs, no. (%)</td>
<td>1,274 (25)</td>
<td>4,842 (66)</td>
<td>5,911 (90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACEI, no. (%)</td>
<td>988 (19)</td>
<td>2,959 (41)</td>
<td>4,157 (63)</td>
<td>&lt;0.001</td>
</tr>
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</table>
Table 2. In-hospital and unadjusted long-term mortality by PCI-era. Data shown is overall and by PCI-indication (stable disease and acute coronary syndrome).

<table>
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<tr>
<th>Endpoint</th>
<th>Overall</th>
<th>ACS</th>
<th>Stable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>5,256</td>
<td>7,463</td>
<td>6,787</td>
</tr>
<tr>
<td>In-hospital deaths, no. (%)</td>
<td>141 (2.7)</td>
<td>137 (1.8)</td>
<td>151 (2.2)</td>
</tr>
<tr>
<td>Follow-up deaths (%)</td>
<td>5,115</td>
<td>7,326</td>
<td>6,636</td>
</tr>
<tr>
<td>1 yr</td>
<td>214 (4.2)</td>
<td>303 (4.2)</td>
<td>304 (4.6)</td>
</tr>
<tr>
<td>3 yr</td>
<td>537 (10.6)</td>
<td>669 (9.3)</td>
<td>722 (11.2)</td>
</tr>
<tr>
<td>5 yr</td>
<td>853 (17.0)</td>
<td>1,130 (15.9)</td>
<td>1,095 (18.2)</td>
</tr>
</tbody>
</table>
Figure Legends:

**Figure 1.** Temporal trends in incidence of cause-specific death (cardiac vs. non-cardiac) after PCI.

**Figure 2.** Temporal trends in incidence of cardiac and non-cardiac mortality after weighted adjustment for multiple cardiac and non-cardiac variables.

**Figure 3.** Temporal trends in incidence of cause-specific mortality by age (a) and PCI-indication (b).

**Figure 4.** Temporal trends in cause-specific death in patients with single vessel disease and patients with multi-vessel disease.

**Figure 5.** Temporal trends in fatal cardiac and non-cardiac disease subtypes (a). Causes of death during five years of follow-up after PCI in the contemporary era (b).
Figure 1

Cumulative incidence (%)


Years after PCI

Cardiac Non-cardiac

p < 0.001
Figure 2

Cumulative incidence (%) by years after PCI:

- Cardiac
- Non-Cardiac

Years after PCI:
- 1991-1996
- 1997-2002
- 2003-2008
Figure 3A

Cumulative incidence (%)

<65 y

65-79 y

≥80 y

Years after PCI

Cardiac

Non-cardiac
Figure 3B
Figure 4
Figure 5A
Figure 5B
Trends in Cause of Death after Percutaneous Coronary Intervention
Daniel B. Spoon, Peter J. Psaltis, Mandeep Singh, David R. Holmes, Jr., Bernard J. Gersh, Charanjit S. Rihal, Ryan J. Lennon, Issam D. Moussa, Robert D. Simari and Rajiv Gulati

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Supplemental Figure 1. Temporal trends in cause-specific death in patients residing within 25 miles of Mayo Clinic, Rochester, MN.
Supplemental Figure 2. Temporal trends in incidence of Cardiovascular (CV) and Non-cardiovascular (Non-CV) mortality after weighted adjustment for multiple clinical variables.
Supplemental Figure 3. Trends in incidence of vascular-specific long-term deaths after PCI
Supplemental Figure 4. Trends in incidence of fatal hemorrhagic strokes after PCI. An increase in fatal hemorrhagic strokes was noted in the most recent era, principally in the first 12 months after PCI.