Background—The impact of changing demographics on 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 to 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 3 time periods of PCI (1991–1996, 1997–2002, and 2003–2008). Final follow-up was December 31, 2012. A total of 19077 patients survived index PCI hospitalization, of whom 6988 subsequently died (37%, 4.48 per 100 person-years). Cause was determined in 6857 (98.1%). Across 3 time periods, there was a 33% decline in cardiac deaths at 5 years after PCI (incidence: 9.8%, 7.4%, and 6.6%) but a 57% increase in noncardiac deaths (7.1%, 8.5%, and 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 noncardiac 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 noncardiac mortality was primarily attributable to cancer and chronic diseases (P<0.001).

Conclusions—This study found a marked temporal switch from predominantly cardiac to predominantly noncardiac causes of death after PCI over 2 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. (Circulation. 2014;129:1286-1294.)

Key Words: cardiovascular diseases coronary disease death percutaneous coronary intervention

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

Editorial see p 1267
Clinical Perspective on p 1294

Mortality from coronary artery disease in the United States has been in decline since the late 1960s, principally as a result of reduction in atherosclerotic risk factors and implementation of preventative therapies. 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. Despite concurrent improvements in PCI technologies and preventative therapies, long-term mortality after PCI has also increased in recent time periods. Older registry studies indicated that cardiac causes of death proportionately outweighed noncardiac causes during longer-term follow-up. Contemporary PCI studies from large registries report all-cause rather than cause-specific mortality. 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 22-year period.

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From the Divisions of Cardiovascular Diseases (D.B.S., P.J.P., M.S., D.R.H., B.J.G., C.S.R., R.D.S., R.G.) and Biomedical Statistics and Informatics (R.J.L.), Mayo Clinic, Rochester, MN; and Division of Cardiovascular Diseases (I.D.M.), Mayo Clinic, Jacksonville, FL.

The online-only Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.113.006518-

Correspondence to Rajiv Gulati, MD, PhD, Mayo Clinic, 200 First St SW, Rochester, MN 55905. E-mail gulati.rajiv@mayo.edu

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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 the 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 3 6-year eras for analysis according to date of PCI: (1) 1991 to 1996 (n=5115 patients); (2) 1997 to 2002 (n=7326 patients); and (3) 2003 to 2008 (n=6636 patients). Final follow-up was December 31, 2012.

Definitions
Current smoking status was defined as having smoked cigarettes within the past 6 months, and 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 mellitus 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 ≥3.0 mg/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, and presence of chronic occlusion. Definitions for 17 disease components of the Charlson index are as described previously 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 previous 7 days together with an urgent or emergency procedure. The coronary artery disease comorbidity index was calculated as described previously.18 The Charlson index, a measure of overall disease burden, was calculated based on 17 diseases and weights as described previously.17 Comorbidities were captured from the Mayo Diagnosis Index database for all times before index PCI to 30 days after PCI. Additionally, the index was split into cardiac and noncardiac 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. On 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 (D.B.S., R.G.) reviewed each death, rescreened medical records when appropriate, and resolved disparity by consensus. Final classification (subclassification) was performed into 1 of 26 causes as follows. (1) cardiac: myocardial infarction, sudden cardiac death, congestive heart failure/structural heart disease, interventional/surgical procedure related, other cardiac; (2) noncardiac: vascular (hemorrhagic stroke, ischemic or undefined stroke, abdominal aortic aneurysm rupture, other vascular), cancer (solid organ, hematologic), infectious, chronic diseases (neurological, pulmonary, renal failure, liver/multiorgan failure, natural causes), hemorrhage (gastrointestinal, other), pulmonary embolus, iatrogenic (noncardiac procedure/surgery related), trauma (accident/truma, soft tissue, acute surgical noncardiac, other noncardiac; and (3) 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 arrhythmic death or the out-of-hospital occurrence of an unexpected presumed pulseless condition together with the absence of an obvious noncardiac explanation. When the only information was the death certificate and when 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 noncardiac and cardiac causes of death, we favored cardiac classification. Fatal motor vehicle accidents were classified as accident/truma, recognizing that sudden cardiac death as a substrate could not be excluded. For equally competing noncardiac causes, we favored death certificate classification.

Statistical Analyses
Continuous variables are summarized as mean (SD) and were compared between the 3 eras using one-way ANOVA. Categorical variables are summarized as frequency (group percentage) and are compared between the groups using Pearson’s χ2 test for nominal variables and the Kruskal-Wallis test for ordinal variables. Survival analyses were conducted in 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 to 25 miles from the institution undergoing PCI (n=4057) was additionally performed. Because 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/noncardiac deaths at 5 years after PCI was the same between the 3 time eras. Two thousand permutation datasets were created by randomly permuting the time era group with the outcomes data. Within each permuted dataset, the ratio of cardiac/noncardiac deaths at 5 years for the 3 time groups was calculated. Of the 3 possible pairwise era comparisons, the maximum absolute difference in log ratios was calculated for the 2000 datasets to generate an approximate null distribution for the statistic. The observed statistic was then compared with 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 used as well as an offset by the log of the length of follow-up, and overdispersion was assessed by deviance/df. To investigate whether the differences in cause-specific incidence between the 3 eras could be attributable to differences in comorbidity burden, we used strata-weighted estimation. We stratified all subjects by sex, age (<65, 65−79, ≥80 years), multivessel disease, previous revascularization, history of myocardial infarction >7 days, Charlson score for cardiac diagnoses, Charlson score for noncardiac diagnoses, Charlson score for noncardiac 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. Because some strata were not present in all 3 eras, in particular strata with high comorbidity burden, 3283 patients were excluded (559 from 1991–1996, 1145 from 1997–2002, and 1579 from 2003–2008). Otherwise, patients in the 1991 to 1996 and
Baselined Characteristics

Clinical, angiographic, and procedural characteristics of patients undergoing PCI across three eras (1991–1996, 1997–2002, and 2003–2008) are shown in Table 1. There was a temporal increase in mean age, proportion of women, body mass index, and prevalence of all atherosclerotic risk factors except smoking. However, there was a temporal decrease in history of remote myocardial infarction and previous CABG. The prevalence of multiple noncardiac 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.

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Clinical characteristics</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (y), 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>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>3660 (72)</td>
<td>5106 (70)</td>
<td>4607 (69)</td>
<td>0.028</td>
</tr>
<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>
</tr>
<tr>
<td>Current smoking, n (%)</td>
<td>1027 (20)</td>
<td>1412 (20)</td>
<td>1270 (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>
</tr>
<tr>
<td>Cardiovascular comorbidities</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<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>
</tr>
<tr>
<td>Current CHF, n (%)</td>
<td>399 (8)</td>
<td>682 (10)</td>
<td>763 (12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of cholesterol ≥240, n (%)</td>
<td>2252 (51)</td>
<td>4722 (72)</td>
<td>4773 (80)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of MI (&gt;7 days), n (%)</td>
<td>1595 (32)</td>
<td>1796 (25)</td>
<td>1211 (19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous CABG, n (%)</td>
<td>1018 (20)</td>
<td>1338 (18)</td>
<td>1142 (17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peripheral vascular disease, n (%)</td>
<td>339 (12)</td>
<td>670 (9)</td>
<td>630 (10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>1020 (20)</td>
<td>1655 (23)</td>
<td>1696 (26)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>2687 (53)</td>
<td>4592 (65)</td>
<td>4761 (76)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Angiographic and procedural characteristics</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multivessel disease (70%/50%), n (%)</td>
<td>3395 (67)</td>
<td>4868 (69)</td>
<td>3968 (64)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Type C lesion, n (%)</td>
<td>1483 (35)</td>
<td>2891 (44)</td>
<td>3114 (52)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total stents placed, mean (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, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>4766 (72)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Noncardiac comorbidities</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Charlson: noncardiac 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>
</tr>
<tr>
<td>Moderate/severe renal disease, n (%)</td>
<td>119 (4)</td>
<td>206 (3)</td>
<td>270 (4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>COPD, n (%)</td>
<td>552 (11)</td>
<td>937 (13)</td>
<td>1030 (16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peptic ulcer disease, n (%)</td>
<td>396 (8)</td>
<td>567 (8)</td>
<td>572 (9)</td>
<td>0.10</td>
</tr>
<tr>
<td>Cerebrovascular disease, n (%)</td>
<td>585 (11)</td>
<td>897 (12)</td>
<td>1016 (15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dementia, n (%)</td>
<td>32 (1)</td>
<td>66 (1)</td>
<td>70 (1)</td>
<td>0.046</td>
</tr>
<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, n (%)</td>
<td>0 (0)</td>
<td>5 (0)</td>
<td>9 (0)</td>
<td>0.026</td>
</tr>
<tr>
<td>Metastatic solid tumor, n (%)</td>
<td>130 (3)</td>
<td>204 (3)</td>
<td>210 (3)</td>
<td>0.12</td>
</tr>
<tr>
<td>Other cancer, n (%)</td>
<td>624 (12)</td>
<td>1102 (15)</td>
<td>1218 (18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Liver disease, n (%)</td>
<td>95 (2)</td>
<td>154 (2)</td>
<td>310 (5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Discharge medications</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aspirin, n (%)</td>
<td>4622 (90)</td>
<td>6943 (95)</td>
<td>6443 (97)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Thienopyridine, n (%)</td>
<td>1008 (20)</td>
<td>6652 (91)</td>
<td>6439 (97)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>β-blockers, n (%)</td>
<td>2999 (59)</td>
<td>5543 (76)</td>
<td>5671 (86)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any lipid-lowering drugs, n (%)</td>
<td>1274 (25)</td>
<td>4842 (66)</td>
<td>5911 (90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACEI, n (%)</td>
<td>988 (19)</td>
<td>2959 (41)</td>
<td>4157 (63)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

ACEI indicates angiotensin-converting enzyme inhibitor; BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disorder; MI, myocardial infarction; and PCI, percutaneous coronary intervention.
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, 6988 (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 5 years of follow-up decreased across time periods (incidence per 1000 person-years: 73.3, 64.2, 53.7 and 27.7, 17.3, 10.2, respectively; each P < 0.001).

Changing 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 noncardiac diseases over 5 years of follow-up. This was attributable to both 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 noncardiac 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. Noncardiac 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 that may have occurred over time, a separate PCI population analysis of confined to residents 0 to 25 miles from the institution indicated near identical temporal changes in cause of death (see Figure I in the online-only Data Supplement).

Weighted comparisons of patients with similar age, sex, and cardiac and noncardiac comorbid variables across 3 eras indicated a 50% decline in the incidence of cardiac deaths at 5 years (8.2%, 5.5%, 4.1%), whereas the incidence of noncardiac deaths remained relatively stable (7.5%, 7.1%, 8.1%; Figure 2). Similar patterns were observed for cardiovascular and noncardiovascular deaths (see Figure II in the online-only Data Supplement).

Cause-Specific Mortality by Age, PCI Indication, and Extent of Coronary Disease

The change from cardiac to noncardiac 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 acute coronary syndromes (Figure 3B) and in both single-vessel and multivessel disease subsets (Figure 4).

Changes in Subtypes of Cardiac and Noncardiac 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 noncardiac deaths was principally attributable 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: 1.0%, 1.0%, 1.4%; P = 0.002; see Figure III in the online-only Data Supplement). This was driven by a nonsignificant rise in ischemic/undefined strokes (0.6%, 0.6%, 0.8%; P = 0.26). There was a significant increase in fatal hemorrhagic strokes (0.1%, Table 2. In-Hospital and Unadjusted Long-Term Mortality by PCI Era

<table>
<thead>
<tr>
<th>End Point</th>
<th>Overall</th>
<th>ACS</th>
<th>Stable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>5256</td>
<td>7463</td>
<td>6787</td>
</tr>
<tr>
<td>In-hospital deaths, n (%)</td>
<td>141 (2.7)</td>
<td>137 (1.8)</td>
<td>151 (2.2)</td>
</tr>
<tr>
<td>In-hospital survivors, n follow-up deaths (%)</td>
<td>5115</td>
<td>7326</td>
<td>6636</td>
</tr>
<tr>
<td>1 y</td>
<td>214 (4.2)</td>
<td>303 (4.2)</td>
<td>304 (4.6)</td>
</tr>
<tr>
<td>3 y</td>
<td>537 (10.6)</td>
<td>669 (9.3)</td>
<td>722 (11.2)</td>
</tr>
<tr>
<td>5 y</td>
<td>853 (17.0)</td>
<td>1130 (15.9)</td>
<td>1095 (18.2)</td>
</tr>
</tbody>
</table>

Data shown are overall and by PCI indication (stable disease and acute coronary syndrome). ACS indicates acute coronary syndrome; and PCI, percutaneous coronary intervention.

Figure 1. Temporal trends in incidence of cause-specific death (cardiac versus noncardiac) after percutaneous coronary intervention (PCI).
0.16%, 0.29%; \( P = 0.004 \), with this increase being most pronounced in the first 12 months after PCI (see Figure IV in the online-only Data Supplement). 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 include the following. (1) There has been a marked temporal switch over 2 decades from predominantly cardiac to predominantly noncardiac 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 noncardiac mortality was associated with increased noncardiac comorbidities at baseline and has been primarily attributable 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/noncardiac profiles showed an even more pronounced decline in cardiac mortality than in the overall PCI population. Although an effect of unmeasured clinical variables cannot be excluded, this finding suggests that 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 predissmission 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, use of multiple classes of these medications has been found previously to be independently associated with long-term survival.

![Figure 4](image-url)

**Figure 4.** Temporal trends in cause-specific death in patients with single-vessel disease and patients with multivessel disease. PCI indicates percutaneous coronary intervention.

![Figure 5](image-url)

**Figure 5.** Temporal trends in fatal cardiac and noncardiac disease subtypes (A). Causes of death during 5 years of follow-up after percutaneous coronary intervention in the contemporary era (B). AAA indicates abdominal aortic aneurysm; CHF, congestive heart failure; CVA, cerebrovascular accident; MI, myocardial infarction; PCI, percutaneous coronary intervention; and SCD, sudden cardiac death.
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 effectiveness of preventative therapies, particularly statins and angiotensin-converting enzyme inhibitors, in reducing the long-term risk of myocardial infarction and sudden death in patients with established coronary disease.

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). 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. Therefore, although 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 on late cardiac mortality in the current study.

Increase in Noncardiac Mortality

The current study showed that cardiac and noncardiac 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 noncardiovascular death, but these studies have been limited by small numbers of deaths within cohorts.

The present study showed that the rise in noncardiac mortality was related to an increased prevalence of noncardiac comorbidities at the time of PCI. This itself may be a consequence of symptomatic coronary disease having shifted toward older populations. 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, because 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 noncardiac 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 noncardiac diseases that outweighs the long-term mortality risk of progressive cardiac disease. Moreover, the higher risk of noncardiac 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 noncardiac comorbidities might arguably offer significant returns in combination with a continued focus on cardiac strategies. Additionally, the higher likelihood of noncardiac rather than cardiac mortality after PCI should be considered during patient selection, especially in those with less certain indications for revascularization and multiple noncardiac comorbidities. There are few risk models that predict long-term mortality after PCI, and even these are restricted to all-cause mortality. The development of risk models that predict cause-specific rather than all-cause death will help further refine revascularization decisions.

Cause-specific mortality (cardiac versus noncardiac) is frequently an end point in randomized studies but has been less well studied in registries of PCI that 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. However, discordant with the current study is the continued predominance of cardiac causes of late death in randomized trials of acute coronary syndrome. Our study defines what is meant by a “real-world” population in terms of cause-specific mortality. The data indicate that it is difficult to extrapolate mortality benefit of novel treatments from randomized trials when the increasing frequency of noncardiac death in real-world PCI cohorts is not adequately represented in trial design as a result of patient selection bias. The trajectory of rising noncardiac 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 socioeconomic backgrounds. Although data were collected prospectively and causes of death were mostly collected through scheduled surveillance, there are limitations inherent to all retrospective analyses. A recent study reported that death certificates had only 58% accuracy for classifying deaths as cardiac versus noncardiac. 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 epidemiological studies of sudden death. Finally, lack of information on noninterventional 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 noncardiac causes of long-term death after PCI. Increased use of secondary preventative therapies, increase in mean age at PCI, and increase in prevalence of noncardiac 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 impact on survival-directed therapies.

Disclosures

None.

References

The cause of long-term death in populations with established coronary disease remains incompletely understood. We evaluated secular trends in cause-specific long-term mortality after index percutaneous coronary intervention (PCI) performed at a single center between 1991 and 2008. Over 2 decades, we found a marked temporal switch from predominantly cardiac to predominantly noncardiac causes of long-term death after PCI, with cardiac causes accounting for only a minority of 5-year deaths in the contemporary era. These trends occurred in all age groups, in patients with single and multivessel disease and whether PCI was performed for stable angina or acute coronary syndromes. This suggests changes in the prognosis of broad populations of patients with coronary disease. After adjusting for multiple cardiac and noncardiac variables, the decline in cardiac mortality was found to be independent of changes in baseline clinical profile, whereas the rise in noncardiac mortality was directly related to an increased prevalence of noncardiac comorbidities at baseline. Moreover, the reduction in cardiac mortality was driven by fewer deaths from myocardial infarction and sudden death but not heart failure. The rise in noncardiac mortality was driven by deaths from cancer and chronic diseases. We believe the findings of this study have important implications for strategic priorities in resource allocation for cardiovascular health, as well as for design of clinical trials. The findings also 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 influence of survival-directed therapies.
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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.