Long-Term Survival Among Patients With Myocardial Infarction Before Age 50 Compared With the General Population
A Danish Nationwide Cohort Study

Morten Schmidt, MD, PhD; Szimonetta Szépligeti, MSc; Erzsébet Horváth-Puhó, MSc, PhD; Lars Pedersen, MSc, PhD; Hans Erik Bøtker, MD, PhD, DMSci; Henrik Toft Sørensen, MD, PhD, DMSci

Background—The long-term prognosis for young myocardial infarction (MI) survivors remains poorly understood.

Methods and Results—We conducted a nationwide population-based cohort study using prospectively collected medical data from all hospitals in Denmark during 1980 to 2009. We examined 30-year cause-specific death rates among 21,693 MI patients <50 years versus 216,930 sex- and age-matched people from the general population. We calculated mortality rate ratios (MRRs) based on Cox regression. Between 1980 to 1989 and 2000 to 2009, MI mortality declined from 12.5% to 3.2% within 30 days, 5.1% to 1.6% within 31 to 365 days, and 24.2% to 8.9% within 1 to 10 years. Compared with the general population, the MRR adjusted for sex, age, and cardiovascular and noncardiovascular comorbidity decreased 4.5-fold within 30 days (from 468 to 97), 3-fold within 31 to 365 days (from 11.32 to 3.70), and 2.5-fold within 1 to 10 years (from 4.77 to 1.89). The remaining 1.89-fold increased mortality rate among 1-year survivors in 2000 to 2009 corresponded to 6 additional deaths each year per 1000 patients compared with the general population. Long-term causes of death were primarily because of cardiovascular and chronic pulmonary diseases. The excess 10-year MRR among 1-year survivors was consistent within MI subtypes, did not differ substantially between comorbidity categories, but was higher for women than men (3-fold versus 1.7-fold).

Conclusions—The long-term mortality rate after MI before age 50 has decreased remarkably over the last 3 decades, but remains increased relative to the general population, mainly because of deaths from ischemic heart disease and other smoking-related diseases. (Circ Cardiovasc Qual Outcomes. 2016;9:523-531. DOI: 10.1161/CIRCOUTCOMES.115.002661.)

Key Words: age • cohort study • general population • mortality • myocardial infarction • prognosis

Thirty-day mortality after myocardial infarction (MI) has declined by >50% over the last 3 decades.1 Although patients <50 years of age have the lowest absolute short-term mortality risk,1 these patients still have concerns about their long-term mortality risk and whether it remains elevated compared with the general population after the initial critical postinfarction period.

Few MI cohorts have complete long-term follow-up. The previous 2 studies, which were able to compare mortality of young MI patients with that of the general population, lacked data beyond 4 years of follow-up.2,3 To understand and potentially prevent post-MI deaths, it is necessary to examine causes of death and potentially effect-modifying comorbidities. We, therefore, examined long-term cause-specific death rates among patients hospitalized with MI before age 50 compared with the general population overall and in subgroups of patients according to sex and cardiometabolic comorbidity.

Methods

Setting
We conducted this nationwide population-based cohort study in Denmark. The cumulative Danish population between 1980 and 2009 was 7,543,591 inhabitants.4 The Danish National Health Service provides universal tax-supported health care, guaranteeing unfettered access to general practitioners and hospitals and partial reimbursement for prescribed medications.5 Accurate and unambiguous linkage of all registries at the individual level is possible in Denmark using the unique Central Personal Register number assigned to each Danish citizen at birth and to residents on immigration.6

Myocardial Infarction
We used the Danish National Patient Registry6 to identify all Danish-born patients <50 years of age with a first-time hospital inpatient diagnosis of MI in the 30-year period from January 1, 1980, to December 31, 2009. This registry contains data on dates of admission and discharge from all Danish nonpsychiatric hospitals since 1977.
WHAT IS KNOWN

• The long-term prognosis of young myocardial infarction survivors remains poorly understood.

WHAT THE STUDY ADDS

• In this nationwide population-based cohort study, using prospectively collected medical data from all hospitals in Denmark during 1980 to 2009, we examined 30-year cause-specific death rates among 21,693 myocardial infarction patients below age 50 years compared with 216,930 sex- and age-matched people from the general population, adjusting for sex, age, and cardiovascular and noncardiovascular comorbidity.

• The mortality rate ratio after myocardial infarction decreased over the study period by 4.5-fold within 30 days (from 468 to 97), 3-fold within 31 to 365 days (from 11.32 to 3.70), and 2.5-fold within 1 to 10 years (from 4.77 to 1.89).

• The remaining 1.89-fold increased mortality rate among 1-year survivors corresponded to 6 additional deaths each year per 1000 patients compared with the general population.

• Long-term mortality after MI before age 50 has decreased remarkably over the last 3 decades, but remains elevated relative to the general population, mainly because of deaths from ischemic heart disease and other smoking-related diseases.

and on dates of emergency room and outpatient clinic visits since 1995.

Each hospital discharge or outpatient visit is recorded with one primary diagnosis and one or more secondary diagnoses classified according to the International Classification of Diseases, Eighth Revision (ICD-8) until the end of 1993 and Tenth Revision (ICD-10) thereafter.

We identified MI using both primary and secondary hospital discharge diagnoses. The primary diagnosis is the main reason for a hospital contact. Secondary diagnoses supplement primary diagnoses by identifying other diseases relevant to the current hospital contact.

To restrict our study population to patients with incident diagnoses, we excluded patients with inpatient or outpatient MI diagnoses before the index admission date during our study period. For the most recent calendar period (2000–2009), we also differentiated between MI subtypes (ST-segment-elevation myocardial infarction (STEMI) versus non-STEMI).

The Danish National Patient Registry also contains information on interventional procedures, including percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), and heart transplantation. In Denmark, CABG was introduced in the late 1980s, PCI in the late 1990s, and primary PCI as a routine procedure in 2002.

Comparison Cohort

We used the Danish Civil Registration System to sample a population-based comparison cohort from the general population. This registry has recorded all changes in vital status and migration for the entire Danish population since 1968, with daily electronic updates.

For each MI patient, we randomly selected (without replacement) 10 people from the entire general population matched on sex and year of birth. The selection of a comparison cohort member occurred on the admission date of the corresponding MI patient to whom the comparison cohort member was matched. To be eligible for the study, people in the general population cohort could not have had an inpatient hospitalization or hospital outpatient visit for MI before the hospital admission date (index date) for the corresponding MI patient. If a member of the general population cohort subsequently experienced an MI before age 50 years, they joined the MI cohort and was not followed further in the comparison cohort.

Mortality

All-cause mortality data were obtained from the Danish Civil Registration System up to December 31, 2012. We obtained information on underlying and immediate causes of death from the Danish Registry of Causes of Death. This registry contains information abstracted from all Danish death certificates since 1943, coded according to ICD-8 from 1972 through 1993 and ICD-10 thereafter (currently available through 2011).

Comorbidity

We obtained information on comorbid conditions from hospital inpatient and outpatient clinic diagnoses recorded in the Danish National Patient Registry. We included comorbid conditions also recorded during the index admission for MI, except for heart failure, stroke, and venous thromboembolism because these disorders may represent complications of MI, antithrombotic treatment, or immobilization during hospitalization.

As previously described, we categorized the severity of noncardiovascular comorbidity (low, moderate, severe, and very severe) using the Charlson Comorbidity Index, a scoring system previously validated for MI patients. MI, congestive heart failure, and diabetes mellitus were not included in the Charlson Comorbidity Index for the current study. Instead, we separately identified cardiovascular comorbidities of special prognostic interest, including congestive heart failure, diabetes mellitus, stable angina pectoris, atrial fibrillation or flutter, venous thromboembolism, hypertension, and obesity.

Statistical Analysis

We characterized study subjects according to sex, age, decade of diagnosis (1980–1989, 1990–1999, and 2000–2009), cardiovascular comorbidity, and Charlson Comorbidity Index level. We followed all study subjects from their MI admission date (irrespective of later transfers) until date of death, emigration, completion of 30 years of follow-up, or December 31, 2012, whichever came first. The percentage of patients who received PCI, CABG, and heart transplantation during follow-up was computed for each calendar period. We used the Kaplan–Meier estimator to calculate mortality risks and to illustrate graphically 30-year cumulative mortality functions.

We used Cox proportional hazards regression to compute hazard ratios of death as measures of mortality rate ratios (MRRs) and 95% confidence intervals (CIs), comparing the MI and general population cohorts. Visual inspection of the log–log plots revealed that the proportionality of hazards across the full 30 years of follow-up was questionable. Consequently, we applied a piecewise Cox regression model to address the time-dependent risk of death within 0 to 30 days, 31 to 365 days, 1 to 10 years, and 11 to 30 years after MI.

In the analyses, we dissolved the matching (to allow for stratified analyses) and instead adjusted for the matching factors in an ordinary Cox regression. Thus, the unadjusted model included only the matching factors. To control more completely for potential confounding comorbidities, we applied a fully adjusted model also including cardiovascular comorbidities and Charlson Comorbidity Index scores. We also computed mortality rates and mortality rate differences per 1000 person-years (standardized to the age distribution of people diagnosed with MI in 2000). Analyses were repeated within each decade of diagnosis. Within the most recent decade of diagnosis (2000–2009), we stratified the analyses according to MI subtype, cardiovascular comorbidities, and interventional treatments. Finally, we compared cause-specific mortality rates between the MI and general population cohorts. The study was approved by the Danish Data Protection Agency (record number 1-16-02-1-08). Because this study did not involve any contact with patients or any intervention, it was not necessary to obtain permission from the Danish Scientific Ethical Protection Agency (record number 1-16-02-1-08).
Committee. All ICD codes used are provided in Table I in the Data Supplement.

Results

Patient Characteristics

Characteristics of the 21693 patients diagnosed with MI before age 50 and the 216930 matched individuals from the general population are shown in Table 1. Four out of 5 (79.5%) MI patients were men. Median age was 45 (interquartile range 42–48 years), reflecting that 83.6% of patients were between 40 and 49 years, 14.6% between 30 and 39 years, and 1.8% <30 years. As expected, the prevalence of cardiovascular comorbidities was consistently higher in the MI cohort than in the general population cohort, particularly stable angina pectoris (11.7% versus 0.4%), hypertension (10.6% versus 1.2%), diabetes mellitus (7.4% versus 1.1%), and obesity (4.6% versus 0.8%). Although noncardiovascular comorbidity was relatively low in both cohorts, MI patients on average also had a higher degree of such morbidity. The median follow-up period was 11.4 years (interquartile range 5.5–18.8 years) for the MI cohort and 16.6 years (interquartile range 9.4–23.9 years) for the general population cohort. A total of 103 (0.47%) MI patients and 2181 (1.01%) people from the general population cohort emigrated during the study period. No coronary interventions were performed in the patient cohort diagnosed with MI during 1980 to 1989. Thereafter, the percentage of patients receiving PCI or CABG (during admission or subsequent 4 weeks) increased from 1990 to 1999 (5% PCI and 1% CABG) to 2000 to 2009 (58% PCI and 3% CABG). The number of MI patients undergoing heart transplantation was similar in 1980 to 1989 (n=36), 1990 to 1999 (n=34), and 2000 to 2009 (n=33).

Mortality Risk

As shown in Table 2, the 30-day mortality risk within the general population cohort was negligible (0.0%). In comparison, the 30-day mortality risk after an MI diagnosed in patients under age 50 years was 8.3% overall. However, substantial improvement in mortality occurred over time for these patients. This is illustrated in Figure 1 by the decreasing intervals between the cumulative mortality functions across calendar periods. Thirty-day mortality risk decreased from 12.5% during 1980 to 1989 to 8.4% during 1990 to 1999 and to 3.2% during 2000 to 2009. A similar pattern was also observed for long-term survival. Although 31- to 365-day mortality remained at 0.3% for the general population cohort across calendar periods, it decreased among the MI patients from 5.1% during 1980 to 1989 to 2.3% during 1990 to 1999 and to 1.6% during 2000 to 2009. Similarly, 1 to 10 year mortality decreased in the MI cohort from 24.2% during 1980 to 1989 to 12.7% during 1990 to 1999 and to 8.9% during 2000 to 2009. Corresponding decreases in the general population cohort were 4.7%, 4.2%, and 3.6%, respectively.

Comparing MI versus general population mortality rates (Table 3), the overall MRR adjusted for age, sex, cardiovascular comorbidities, and noncardiovascular comorbidities was 298 (95% CI 231–385) within 30 days, 7.13 (95% CI 6.32–8.04) within 31 to 365 days, 3.36 (95% CI 3.20–3.52) within 1 to 10 years, and 2.69 (95% CI 2.59–2.79) within 11 to 30 years. Although the MRR remained increased for the MI cohort compared with the general population cohort across all calendar periods, the magnitude of the increase in mortality rates decreased markedly in each consecutive decade. Thus, between 1980 to 1989 and 2000 to 2009, the MRR decreased 4.5-fold within 30 days (from 468 to 97), 3-fold within 31 to 365 days (from 11.32 to 3.70), and 2.5-fold within 1 to 10 years (from 4.77 to 1.89). The remaining 1.89-fold increased mortality rate corresponded in absolute terms to a mortality rate difference of 6 per 1000 people (versus 25 per 1000 people during 1980–1989; Table 3).

Myocardial Infarction Subtypes

When examining the prognosis for STEMI and non-STEMI patients separately (Table 4), STEMI patients had a substantially higher 30-day MRR compared with the general population than non-STEMI patients (120 versus 12.4). However, after 30 days, the mortality rate became similar (30–365 day MRR: 2.8 for STEMI versus 2.5 for non-STEMI). Also, no
substantial difference was observed for 10-year mortality rate among 1-year survivors; if anything, the point estimates indicated that non-STEMI (MRR: 1.94, 95% CI 1.52–2.47) was associated with worse long-term outcome than STEMI (MRR: 1.50, 95% CI 1.07–2.09).

Patient Subgroups
When we examined the 10-year mortality rate in 1-year survivors of MI during 2000 to 2009 according to cardiovascular comorbidity, the increased MRR was not substantially different in patient subgroups (Figure 2). Patients treated with PCI or CABG had a markedly reduced 1- to 10-year mortality risk (MRR=1.67, 95% CI 1.42–1.97) compared with patients not receiving interventional treatment (MRR=2.29, 95% CI 1.93–2.73). Finally, female MI patients had a higher 1- to 10-year MRR (3.00, 95% CI 2.32–3.87) than men (1.68, 95% CI 1.46–1.93; Tables II–III in the Data Supplement).

Cause of Death
The increased mortality rate among MI patients compared with the general population was attributable to higher death rates from cardiovascular diseases, pulmonary diseases, and...
cancer (Table 5). With a >2-fold increased adjusted MRR, ischemic heart disease (MRR=2.07, 95% CI 1.96–2.18) was the most important underlying cause of death. Other diseases, such as stroke (MRR=1.06, 95% CI 0.89–1.26), were not prominent. Regarding immediate causes of death, other cardiovascular diseases and pulmonary diseases were significant, with an adjusted MRR of 2.18 (95% CI 1.68–2.84) for venous thromboembolism, 2.14 (95% CI 1.67–2.75) for chronic pulmonary disease, and 1.68 (95% CI 1.46–1.94) for pneumonia. The 30-year cause of death rate was increased by only 36% for heart failure as an immediate cause of death (MRR=1.36, 95% CI 1.12–1.65). However, for the most recent calendar period (2000–2009), with ≤10 years of follow-up, heart failure had a greater impact on mortality rates (adjusted MRR=2.71, 95% CI 1.14–6.47).

Discussion

In this nationwide 30-year cohort study, short- and long-term mortality in patients having MI before age 50 years decreased remarkably over the last 3 decades. Still, the mortality rate remained ≥2-fold increased relative to the general population. This increased risk was mainly because of deaths from ischemic heart disease and other smoking-related diseases. The results were consistent within MI subtypes and patient subgroups, except that females experiencing an MI at a young age retained a higher long-term risk of dying than their male counterparts.
Strengths and Limitations

Several issues should be considered in interpreting the results of our study. Its population-based design within a universal tax-supported healthcare system reduced selection biases arising from selective inclusion of specific hospitals or health insurance systems. The Danish Civil Registration System allowed accurate accounting of censoring because of emigration or death and provided a unique opportunity to sample a sex-and age-matched comparison cohort from the entire population.4

All routine clinical data were prospectively recorded.4,6

Table 4. Mortality Among Patients With STEMI and Non-STEMI Before Age 50 Compared With the General Population, 2000 to 2009

<table>
<thead>
<tr>
<th>Type*</th>
<th>People/No of Deaths</th>
<th>Mortality Rate† (95% CI)</th>
<th>Mortality Rate Difference† (95% CI)</th>
<th>Mortality Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Crude‡</td>
<td>Adjusted§</td>
<td></td>
</tr>
<tr>
<td>STEMI patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GP cohort</td>
<td>12970/309</td>
<td>4 (3–4)</td>
<td>0 (reference)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>MI cohort</td>
<td>30 d</td>
<td>1297/34</td>
<td>322 (214–431)</td>
<td>320 (211–428)</td>
</tr>
<tr>
<td></td>
<td>31–365 d</td>
<td>1263/17</td>
<td>15 (8–23)</td>
<td>12 (4–19)</td>
</tr>
<tr>
<td></td>
<td>1–10 y</td>
<td>1245/48</td>
<td>7 (5–9)</td>
<td>4 (1–6)</td>
</tr>
<tr>
<td>Non-STEMI patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GP cohort</td>
<td>17920/510</td>
<td>4 (4–4)</td>
<td>0 (reference)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>MI cohort</td>
<td>30 d</td>
<td>1792/17</td>
<td>113 (59–167)</td>
<td>107 (53–161)</td>
</tr>
<tr>
<td></td>
<td>31–365 d</td>
<td>1775/30</td>
<td>19 (12–26)</td>
<td>16 (9–23)</td>
</tr>
<tr>
<td></td>
<td>1–10 y</td>
<td>1745/102</td>
<td>10 (8–12)</td>
<td>6 (4–8)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; GP, general population; MI, myocardial infarction; and STEMI, ST-segment–elevation myocardial infarction.

*Results for unspecified myocardial infarctions (n=3684) not shown.
†Rates per 1000 person-years standardized to the age distribution of people diagnosed with myocardial infarction in 2000.
‡Adjusted for matching factors (age, sex, and calendar year).
§Additional adjustments for congestive heart failure, diabetes mellitus, stable angina pectoris, atrial fibrillation or flutter, venous thromboembolism, hypertension, obesity, and the modified Charlson Comorbidity Index score.

Figure 2. Ten-year mortality among 1-year survivors of myocardial infarction before age 50 compared with the general population cohort in 2000 to 2009, stratified on cardiovascular comorbidities and interventional treatment. Adjustments were made for age, sex, congestive heart failure, diabetes mellitus, stable angina pectoris, atrial fibrillation or flutter, venous thromboembolism, hypertension, obesity, and the modified Charlson Comorbidity Index score. In each stratum, the myocardial infarction cohort was compared with the general population cohort (reference). PCI and CABG were identified during hospitalization or within 4 weeks after the discharge date. CABG indicates coronary artery bypass grafting; GP, general population; MI, myocardial infarction; MRR, mortality rate ratios; PCI, percutaneous coronary intervention; and SMR, standardized mortality rate.
Although a large proportion (54%) of all MIs during 2000 to 2009 were unexplained with regard to subtype, the positive predictive values for STEMI and non-STEMI are high, and the results are, therefore, not susceptible to information bias. A potential limitation is that patients who suffer sudden cardiac death outside of a hospital or ambulance, or who do not undergo attempted resuscitation in the emergency room are not registered in the Danish National Patient Registry. However, we previously showed that such patients could not account for observed trends in mortality. Another concern is that cause of death, as recorded in the Danish Registry of Causes of Death, is based on subjective clinical judgment rather than autopsy. Consequently, it may not always be correct. Reassuringly, MI was found to be the underlying cause of death that differed most substantially between the MI cohort and the general population cohort. Although we controlled for a range of lifestyle-related comorbidities, including other cardiovascular diseases, cancer, chronic obstructive pulmonary disease, and obesity, it should be acknowledged as a limitation that detailed data on lifestyle factors, including smoking, were not available. The comprehensive adjustment for cardiovascular comorbidities, however, also carries a risk of overadjustment. We, therefore, presented both the crude and adjusted estimates, both of which supported the overall conclusion.

### Comparison With Other Studies
An analysis of 23 studies from the prethrombolytic era indicated a mortality risk of 10% within the first year post MI and 5% within each subsequent year, regardless of age or sex. Most but not all studies support our finding of a substantial improvement in the survival rate of young MI patients over the last 3 decades. A cohort study of 2142 MI patients aged 35 to 54, conducted in Worcester, Massachusetts, demonstrated that 2-year postdischarge mortality rates decreased by 30% between 1975 to 1986 and 1997 to 2007 (MMR=0.69, 95% CI 0.43–1.10). A Swiss cohort study reported that among all patients under age 30 diagnosed with acute coronary syndrome during 1994 to 2010 (n=27), the 5-year mortality risk was 7%. In comparison, among patients diagnosed in our study during 2000 to 2009, who survived the critical first 30-day period (3.2% died), the risk of dying within the remainder of the first year was only 1.6% and only 9% in the subsequent 9 years.

The low long-term absolute mortality risk in these young patients makes comparison with the general population highly relevant. It puts temporal trends in young MI patients’ survival into the public health context of overall improvement in survival compared with the general population. Until now, only 2 other studies have made this comparison. The first was a UK cohort study, including 59308 MI patients aged 30 to 54 years who were diagnosed during 2000–2010. It showed that among 30-day survivors, the MRRs were 2.6 for men and 5.6 for women aged 30 to 54 years after 4 years compared with people of equivalent age in the general population. The other study was a Swedish population–based 4-year cohort study of MI patients aged 25 to 55 years diagnosed during the 20-year period from 1987 to 2006. Here, young 28-day male survivors of acute MI before age 50 had low absolute long-term mortality rates (between 0.5 and 0.59 per 100 person-years for men and between 1.2 and 1.5 per 100 person-years for women), although they remained 2- to 4-fold higher than in the general population. Despite overlapping confidence intervals, we note that the higher 1- to 10-year mortality among non-STEMI patients is consistent with previous reports and is

### Table 5. Causes of Death After Myocardial Infarction Before Age 50 Compared With the General Population Cohort

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>n (%)</th>
<th>Standardized Mortality Rate (95% Confidence Interval)*</th>
<th>Mortality Rate Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>MI Cohort</td>
<td>GP Cohort</td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
<td>11266 (4.7)</td>
<td>135 (131–139)</td>
<td>65 (63–67)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>7280 (3.1)</td>
<td>145 (141–150)</td>
<td>69 (66–73)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>4587 (1.9)</td>
<td>210 (202–218)</td>
<td>76 (71–82)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>272 (0.1)</td>
<td>58 (45–72)</td>
<td>50 (40–60)</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>178 (0.1)</td>
<td>97 (59–135)</td>
<td>69 (57–80)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1240 (0.5)</td>
<td>76 (65–88)</td>
<td>59 (54–63)</td>
</tr>
<tr>
<td>Pulmonary diseases</td>
<td>1865 (0.8)</td>
<td>270 (-117–657)</td>
<td>55 (52–59)</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>1317 (0.6)</td>
<td>257 (-129–644)</td>
<td>54 (50–58)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>348 (0.1)</td>
<td>98 (55–140)</td>
<td>56 (49–64)</td>
</tr>
<tr>
<td>Neoplasms</td>
<td>12010 (5.0)</td>
<td>201 (21–381)</td>
<td>63 (61–64)</td>
</tr>
</tbody>
</table>

GP indicates general population; and MI, myocardial infarction.
*Reported numbers and rates (per 1000 person-years) are for underlying causes of death. Cause of death was missing for 856 myocardial infarction patients.
†Adjusted for matching factors (age, sex, and calendar year).
‡Additional adjustments for congestive heart failure, diabetes mellitus, stable angina pectoris, atrial fibrillation or flutter, venous thromboembolism, hypertension, obesity, and the modified Charlson Comorbidity Index score.

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likely because of the more pronounced systemic disease and comorbidity in these patients compared with STEMI patients.15,16

Mechanisms
It is estimated that half of the decline in MI mortality since 1980 is attributable to primary MI prevention, in particular reduction in smoking prevalence.17–19 The other half, that is, the effect observed in our study, is likely attributable to (1) the introduction of early reperfusion strategies (thrombolysis and PCI) that improve myocardial salvage,20,21 (2) follow-up revascularization with PCI and CABG when appropriate,22 (3) awareness and organization,23 and (4) tertiary medical treatment, also including treatment of hypertension, hypercholesterolemia, and other comorbidities.24–26

Younger patients are also more likely than elderly patients to receive evidence-based medical care and reperfusion therapy.27 Even in the absence of contraindications, proven therapies are underused in the elderly.28,29 Although frailty is not a strict contraindication for CABG or PCI, reluctance toward using aggressive interventional therapy in older patients with comorbidity may exist in some circumstances because noncardiovascular comorbidities and declining health status may affect life expectancy.30 Frailty is less likely to be influential in our young cohort, with little comorbidity compared with older age groups.1 Changes in diagnostic criteria during the study period, with troponins introduced as the main diagnostic biomarker of MI,31 likely increased the detection rate of smaller infarcts and, hence, boosted survival compared with the general population. Reports from the United States show that, over the long term, cause of death has shifted more toward noncardiovascular causes.32 Consistent with those reports, we found that noncardiovascular diseases, in particular those also related to smoking, are important long-term causes of death in young MI patients.

Conclusions and Implications
Young MI patients often have concerns about their mortality risk after surviving the initial critical postinfarction period. As a response to these concerns, our data show that long-term survival after premature MI has decreased remarkably over the last 3 decades. The results likely apply to most industrial Western societies in which changes in lifestyle, risk factor modification, and healthcare systems have followed international recommendations.

Still, MI patients should be advised that an excess risk of fatal events persists, warranting adherence to prescribed medical therapy and efforts to reduce modifiable lifestyle-related risk factors, particularly smoking.

Acknowledgments
The lead author affirms that the article is a honest, accurate, and transparent account of the study being reported, that no important aspects of the study have been omitted, and that any discrepancies from the study as planned have been explained. Dr Sørensen conceived the study idea and acquired data permissions. Dr Schmidt designed the current study based on previous design development by Dr Sørensen and Dr Pedersen. Dr Pedersen performed data management and established the cohort in collaboration with Dr Horváth-Puhó and Dr Szépligeti. Dr Schmidt reviewed the literature and directed the analyses, which were carried out by S. Szépligeti under the supervision of Dr Horváth-Puhó. All authors participated in the discussion and interpretation of the results. Dr Schmidt organized the writing and wrote the initial drafts. All authors critically revised the article for intellectual content and approved the final version. Dr Sørensen is the guarantor.

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Disclosures
None.

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### eTable 1. International Classification of Diseases (ICD) codes

<table>
<thead>
<tr>
<th>Condition</th>
<th>ICD-8 codes</th>
<th>ICD-10 codes</th>
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<tbody>
<tr>
<td><strong>Myocardial infarction</strong></td>
<td>410</td>
<td>I21</td>
</tr>
<tr>
<td>PCI</td>
<td></td>
<td>KFNG, KFNF</td>
</tr>
<tr>
<td>CABG</td>
<td></td>
<td>KFNH20</td>
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<tr>
<td><strong>Other cardiovascular diseases</strong></td>
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<tr>
<td>Stable angina pectoris</td>
<td>413</td>
<td>I20 (except I20.0), I25.1, I25.9</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>427.09; 427.10; 427.11; 427.19; 428.99; 782.49</td>
<td>I50; I11.0; I13.0; I13.2</td>
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<tr>
<td>Atrial fibrillation</td>
<td>427.93, 427.94</td>
<td>I48</td>
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<tr>
<td>Diabetes</td>
<td>249, 250</td>
<td>E10, E11, H36.0</td>
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<tr>
<td>Venous thromboembolism</td>
<td>450.99, 451.00</td>
<td>I26, I80.1-3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>400-404</td>
<td>D110-D115, I67.4</td>
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<tr>
<td>Obesity</td>
<td>277</td>
<td>E65-E68</td>
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<tr>
<td><strong>Conditions in the Charlson Comorbidity Index</strong></td>
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<tr>
<td>Congestive heart failure</td>
<td>427.09; 427.10; 427.11; 427.19; 428.99</td>
<td>I50; I11.0; I13.0; I13.2</td>
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<tr>
<td>Peripheral vascular disease</td>
<td>440; 441; 442; 443; 444; 445</td>
<td>I70; I71; I72; I73; I74; I77</td>
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<td>Cerebrovascular disease</td>
<td>430-438</td>
<td>I60-I69; G45; G46</td>
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<tr>
<td>Dementia</td>
<td>290.09-290.19; 293.09</td>
<td>F00-F03; F05.1; G30</td>
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<tr>
<td>Chronic pulmonary disease</td>
<td>490-493; 515-518</td>
<td>J40-J47; J60-J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3</td>
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<tr>
<td>Connective tissue disease</td>
<td>712; 716; 734; 446; 135.99</td>
<td>M05; M06; M08; M09; M30; M31; M32; M33; M34; M35; M36; D86</td>
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<td>Ulcer disease</td>
<td>530.91; 530.98; 531-534</td>
<td>K22.1, K25-K28</td>
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<tr>
<td>Mild liver disease</td>
<td>571; 573.01; 573.04</td>
<td>B18; K70.0-K70.3; K70.9; K71; K73; K74; K76.0</td>
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<tr>
<td>Diabetes without end-organ damage</td>
<td>249.00; 249.06; 249.07; 249.09; 250.00; 250.06; 250.07; 250.09</td>
<td>E10.0, E10.1; E10.9; E11.0; E11.1; E11.9</td>
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<tr>
<td>Diabetes with end-organ damage</td>
<td>249.01-249.05; 249.08; 250.01-250.05; 250.08</td>
<td>E10.2-E10.8, E11.2-E11.8</td>
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<tr>
<td>Hemiplegia</td>
<td>344</td>
<td>G81; G82</td>
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<tr>
<td>Moderate to severe renal disease</td>
<td>403; 404; 580-583; 584; 590.09; 593.19; 753.10-753.19; 792</td>
<td>I12; I13; N00-N05; N07; N11; N14; N17-N19; Q61</td>
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<tr>
<td>Non-metastatic solid tumour</td>
<td>140-194</td>
<td>C00-C75</td>
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<tr>
<td>Leukaemia</td>
<td>204-207</td>
<td>C91-C95</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>200-203; 275.59</td>
<td>C81-C85; C88; C90; C96</td>
</tr>
<tr>
<td>Moderate to severe liver disease</td>
<td>070.00; 070.02; 070.04; 070.06; 070.08; 573.00-456.00-456.09</td>
<td>B15.0; B16.0; B16.2; B19.0; K70.4; K72; K76.6; I85</td>
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<tr>
<td>AIDS</td>
<td>195-198; 199</td>
<td>C76-C80</td>
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<tr>
<td><strong>Cause of death</strong></td>
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</tr>
<tr>
<td>Diseases of the circulatory system</td>
<td>390-459</td>
<td>I00-I99</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>410-414</td>
<td>I20-I25 or 150</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>410</td>
<td>I21-I23</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>427.09; 427.10; 427.11; 427.19; 428.99; 782.49</td>
<td>I50; I11.0; I13.0; I13.2</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>450, 451</td>
<td>I26, I80</td>
</tr>
<tr>
<td>Stroke</td>
<td>431-434</td>
<td>I61, I63-164</td>
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<tr>
<td><strong>Diseases of the respiratory system</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>490-493; 515-518</td>
<td>J40-J47; J60-J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3</td>
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<tr>
<td>Pneumonia</td>
<td>471; 480-486</td>
<td>J12-J18</td>
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<tr>
<td>Neoplasm</td>
<td>140-209</td>
<td>C00-C96</td>
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</tbody>
</table>
**ETable 2.** Mortality among female patients with a first-time myocardial infarction (MI) before age 50 compared with women from the general population (GP), by calendar period

<table>
<thead>
<tr>
<th>Calendar period</th>
<th>Persons/no. of deaths</th>
<th>Mortality rate* (95% CI)</th>
<th>Mortality rate difference* (95% CI)</th>
<th>Mortality rate ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Crude†</td>
<td>Adjusted‡</td>
</tr>
<tr>
<td><strong>1980–2009</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GP cohort</td>
<td>44440/4178</td>
<td>6 (5–6)</td>
<td>0 (reference)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>MI cohort</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–10 years</td>
<td>3879/522</td>
<td>18 (17–20)</td>
<td>15 (14–17)</td>
<td>6.07 (5.46–6.74)</td>
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<tr>
<td>11–30 years</td>
<td>2315/581</td>
<td>30 (28–32)</td>
<td>21 (19–24)</td>
<td>3.64 (3.33–3.98)</td>
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<tr>
<td><strong>1980–1989</strong></td>
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<td></td>
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<tr>
<td>GP cohort</td>
<td>14290/2846</td>
<td>8 (7–8)</td>
<td>0 (reference)</td>
<td>1 (reference)</td>
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<tr>
<td>MI cohort</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 days</td>
<td>1429/201</td>
<td>2172 (1698–2646)</td>
<td>2169 (1695–2643)</td>
<td>542 (202–1459)</td>
</tr>
<tr>
<td>31–365 days</td>
<td>1228/75</td>
<td>68 (52–84)</td>
<td>65 (50–81)</td>
<td>24.33 (16.41–36.07)</td>
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<tr>
<td>1–10 years</td>
<td>1153/262</td>
<td>29 (25–33)</td>
<td>25 (22–29)</td>
<td>7.82 (6.72–9.10)</td>
</tr>
<tr>
<td>11–30 years</td>
<td>891/433</td>
<td>38 (34–41)</td>
<td>27 (24–31)</td>
<td>3.81 (3.44–4.22)</td>
</tr>
<tr>
<td><strong>1990–1999</strong></td>
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</tr>
<tr>
<td>GP cohort</td>
<td>13460/1001</td>
<td>4 (4–5)</td>
<td>0 (reference)</td>
<td>1 (reference)</td>
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<tr>
<td>MI cohort</td>
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<td></td>
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<tr>
<td>30 days</td>
<td>1346/149</td>
<td>1514 (1264–1763)</td>
<td>1512 (1262–1762)</td>
<td>790 (196–3190)</td>
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<tr>
<td>31–365 days</td>
<td>1197/37</td>
<td>35 (24–47)</td>
<td>33 (21–44)</td>
<td>12.79 (8.00–20.44)</td>
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<tr>
<td>1–10 years</td>
<td>1160/147</td>
<td>16 (13–18)</td>
<td>13 (10–15)</td>
<td>5.22 (4.30–6.33)</td>
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<tr>
<td>11–20 years</td>
<td>1013/136</td>
<td>19 (15–22)</td>
<td>12 (9–16)</td>
<td>3.08 (2.56–3.71)</td>
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<tr>
<td><strong>2000–2009</strong></td>
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<tr>
<td>GP cohort</td>
<td>16690/331</td>
<td>3 (2–3)</td>
<td>0 (reference)</td>
<td>1 (reference)</td>
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<td>MI cohort</td>
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<tr>
<td>30 days</td>
<td>1669/67</td>
<td>538 (342–734)</td>
<td>533 (337–729)</td>
<td>98.16 (45.06–214)</td>
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<tr>
<td>1–10 years</td>
<td>1566/113</td>
<td>12 (9–14)</td>
<td>9 (7–11)</td>
<td>4.53 (3.64–5.63)</td>
</tr>
</tbody>
</table>

* Rates per 1000 person-years standardized to the age distribution of persons diagnosed with myocardial infarction in 2000.
† Adjusted for age and calendar year.
‡ Adjusted for matching factors, CCI score, and the individual cardiovascular comorbidities in Table 1 not already included in the CCI (*i.e.*, stable angina pectoris, atrial fibrillation, venous thromboembolism, hypertension, and obesity).
**eTable 3. Mortality among male patients with a first-time myocardial infarction (MI) before age 50 compared with men from the general population (GP), by calendar period**

<table>
<thead>
<tr>
<th>Calendar period</th>
<th>Persons/ no. of deaths</th>
<th>Mortality rate* (95% CI)</th>
<th>Mortality rate difference* (95% CI)</th>
<th>Mortality rate ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crude†</td>
<td>Adjusted‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1980–2009</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GP cohort</td>
<td>44440/4178</td>
<td>6 (5–6)</td>
<td>0 (reference)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>MI cohort</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 days</td>
<td>17249/1395</td>
<td>1054 (998–1110)</td>
<td>1051 (995–1107)</td>
<td>306 (230–408)</td>
</tr>
<tr>
<td>31–365 days</td>
<td>15854/459</td>
<td>32 (29–35)</td>
<td>28 (25–31)</td>
<td>8.79 (7.78–9.94)</td>
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<tr>
<td>1–10 years</td>
<td>15387/2302</td>
<td>20 (19–20)</td>
<td>15 (14–15)</td>
<td>3.91 (3.73–4.10)</td>
</tr>
<tr>
<td>11–30 years</td>
<td>9815/3109</td>
<td>37 (35–38)</td>
<td>23 (21–24)</td>
<td>2.88 (2.77–2.99)</td>
</tr>
<tr>
<td>1980–1989</td>
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<tr>
<td>GP cohort</td>
<td>68010/18432</td>
<td>12 (11–12)</td>
<td>0 (reference)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>MI cohort</td>
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<tr>
<td>30 days</td>
<td>6801/830</td>
<td>1655 (1542–1769)</td>
<td>1652 (1538–1766)</td>
<td>492 (309–785)</td>
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<tr>
<td>31–365 days</td>
<td>5971/288</td>
<td>54 (48–60)</td>
<td>50 (44–56)</td>
<td>13.88 (11.70–16.47)</td>
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<tr>
<td>1–10 years</td>
<td>5680/1390</td>
<td>31 (29–33)</td>
<td>25 (24–27)</td>
<td>5.58 (5.24–5.94)</td>
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<tr>
<td>11–30 years</td>
<td>4281/2290</td>
<td>44 (42–46)</td>
<td>28 (26–30)</td>
<td>2.95 (2.82–3.08)</td>
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<tr>
<td>1990–1999</td>
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<td>GP cohort</td>
<td>53440/6417</td>
<td>7 (7–7)</td>
<td>0 (reference)</td>
<td>1 (reference)</td>
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<td>MI cohort</td>
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<tr>
<td>30 days</td>
<td>5344/411</td>
<td>1018 (918–1118)</td>
<td>1014 (914–1115)</td>
<td>285 (171–478)</td>
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<tr>
<td>31–365 days</td>
<td>4933/102</td>
<td>22 (18–27)</td>
<td>19 (14–23)</td>
<td>6.01 (4.72–7.66)</td>
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<tr>
<td>1–10 years</td>
<td>4828/611</td>
<td>15 (14–16)</td>
<td>10 (9–11)</td>
<td>2.89 (2.64–3.16)</td>
</tr>
<tr>
<td>11–20 years</td>
<td>4199/785</td>
<td>26 (24–28)</td>
<td>16 (14–18)</td>
<td>2.68 (2.48–2.89)</td>
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<td>2000–2009</td>
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<tr>
<td>GP cohort</td>
<td>51040/1711</td>
<td>4 (4–5)</td>
<td>0 (reference)</td>
<td>1 (reference)</td>
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<td>MI cohort</td>
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<tr>
<td>30 days</td>
<td>5104/154</td>
<td>372 (312–431)</td>
<td>368 (309–427)</td>
<td>104 (61.38–177)</td>
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<td>31–365 days</td>
<td>4950/69</td>
<td>15 (12–19)</td>
<td>12 (8–15)</td>
<td>4.59 (3.46–6.10)</td>
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<td>1–10 years</td>
<td>4879/301</td>
<td>10 (9–11)</td>
<td>5 (4–6)</td>
<td>2.25 (1.99–2.55)</td>
</tr>
</tbody>
</table>

*Rates per 1000 person-years standardized to the age distribution of persons diagnosed with myocardial infarction in 2000.
†Adjusted for age and calendar year.
‡Adjusted for matching factors, CCI score, and the individual cardiovascular comorbidities in Table 1 not already included in the CCI (i.e., stable angina pectoris, atrial fibrillation, venous thromboembolism, hypertension, and obesity).