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CLINICAL RESEARCH

Long-term mortality, cardiovascular events, and bleeding in stable patients 1 year after myocardial infarction: a Danish nationwide study

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Abstract

Aims Outcomes after myocardial infarction (MI) improved during recent decades alongside better risk factor management and implementation of guideline-recommended treatments. However, it is unknown whether this applies to stable patients who are event-free 1 year after MI.

Methods and results Using nationwide Danish registries, we included all patients with first-time MI during 2000–17 who survived 1 year free from bleeding and cardiovascular events ($n = 82\,108$, median age 64 years, 68.2% male). Follow-up started 1 year after MI and continued through January 2022. Crude risks of mortality, cardiovascular events, and bleeding were estimated in consecutive 3-year periods. Standardized risks were calculated with respect to the distribution of age, sex, comorbidities, and treatments in the latter period. Guideline-recommended treatment use increased during the study period: e.g. statins (68.6–92.5%) and percutaneous coronary intervention (23.9–68.2%). The crude 5-year risks of outcomes decreased (all *P*-trend <0.001): Mortality, 18.6% (95% confidence interval [CI]: 17.9–19.2) to 12.5% (CI: 11.9–13.1); Recurrent MI, 7.5% (CI: 7.1–8.0) to 5.5% (CI: 5.1–6.0); Bleeding, 3.9% (CI: 3.6–4.3) to 2.7% (CI: 2.4–3.0). Crude 5-year risk of mortality in 2015–17 was as low as 2.6% for patients aged <60 years. Use of guideline-recommended treatments was associated with improved outcomes: After standardization for changes in treatments, 5-year risk of mortality in 2000–02 was 15.5% (CI: 14.9–16.2).

Conclusions For patients who were event-free 1 year after MI, the long-term risks of mortality, cardiovascular events, and bleeding decreased significantly, along with an improved use of guideline-recommended treatments between 2000 and 2017. In the most recent period, 1 year after MI, the risk of additional events was lower than previously reported.

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Structured Graphical Abstract

Key Question

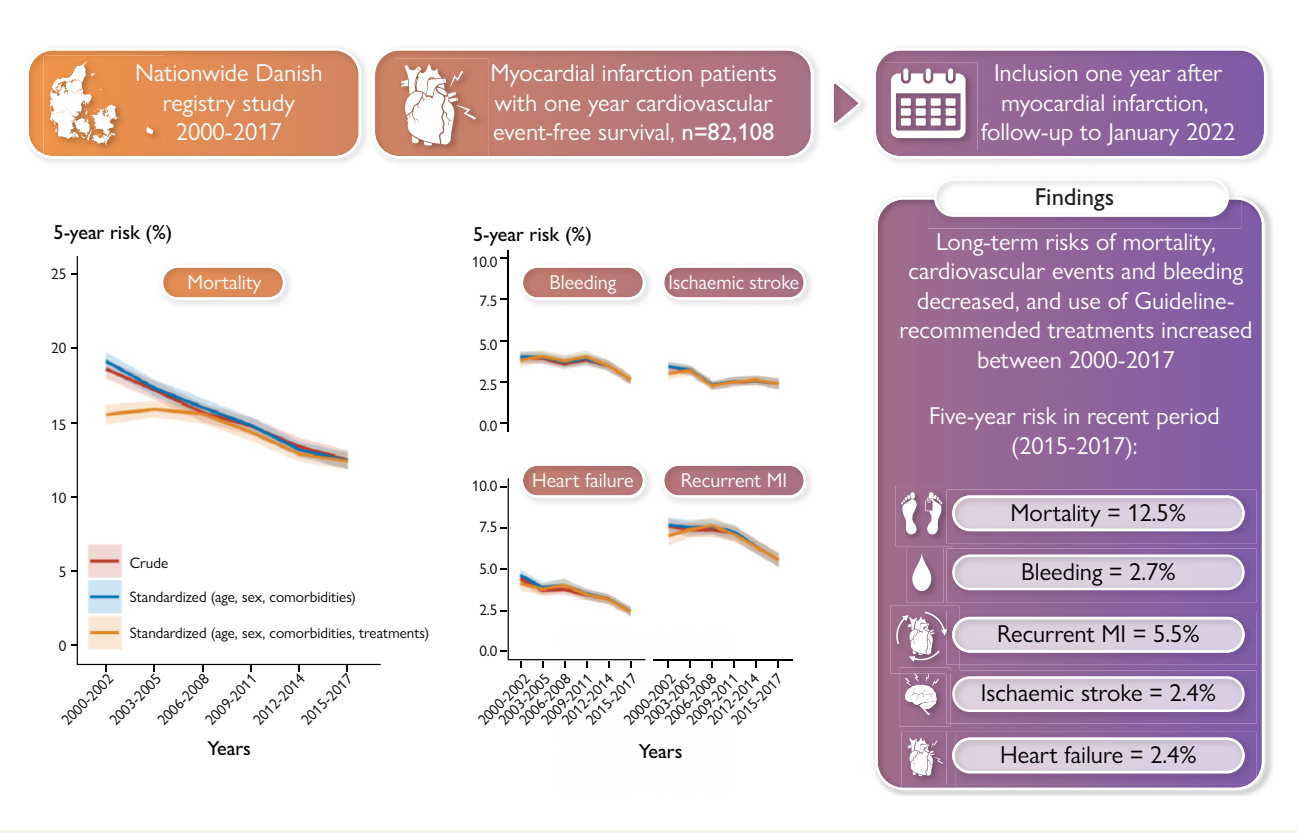
What is the long-term risk of mortality, cardiovascular events, and bleeding in patients with stable disease one year after myocardial infarction, and how have these risks developed in the era of modern Guideline recommended treatments?

Key Finding

In 82,108 patients included in the study through nationwide Danish registries, long-term outcomes improved substantially between 2000 and 2017. This improvement was associated with an increased use of Guideline-recommended treatments during the early study period.

Take Home Message

In patients who are stable one year after myocardial infarction, risk of future adverse events generally appears low. Implementation of Guideline-based delivery of care is important to continuously improve outcomes.



Overview of the study design and the main findings. MI, myocardial infarction.

Keywords myocardial infarction stable • Guidelines • long-term risk • Registry • outcomes

Introduction

The incidence of myocardial infarction (MI) has declined substantially in several populations during the past decades.[1–3] Concomitantly, important advances have been made in risk factor management and delivery of care for MI,[4–8] leading to improvements in short- and long-term prognosis.[9–13] Despite these developments, the global burden of coronary artery disease remains high.[14] Due to the improved survival, patients with stable disease post-MI represent an increasingly important and prevalent population.[15] The 1 year mark represents an important timepoint as patients who are considered stable have often left specialist care to be managed in the primary care setting. Notably, this is also when dual antiplatelet therapy is most often withdrawn.[4,5,16,17] Worryingly, prior data have suggested that the long-term risk of cardiovascular events remains persistently high, even in patients with stable disease 1 year after MI.[18]

Because previous studies have mainly focused on outcomes immediately following MI,[2,9–13] there is a lack of available data regarding the developments in post-MI prognosis in the increasingly important and prevalent population of patients with stable disease. It is unclear whether they remain a high-risk population following the general improvements in treatment and risk. Finally, contemporary data on

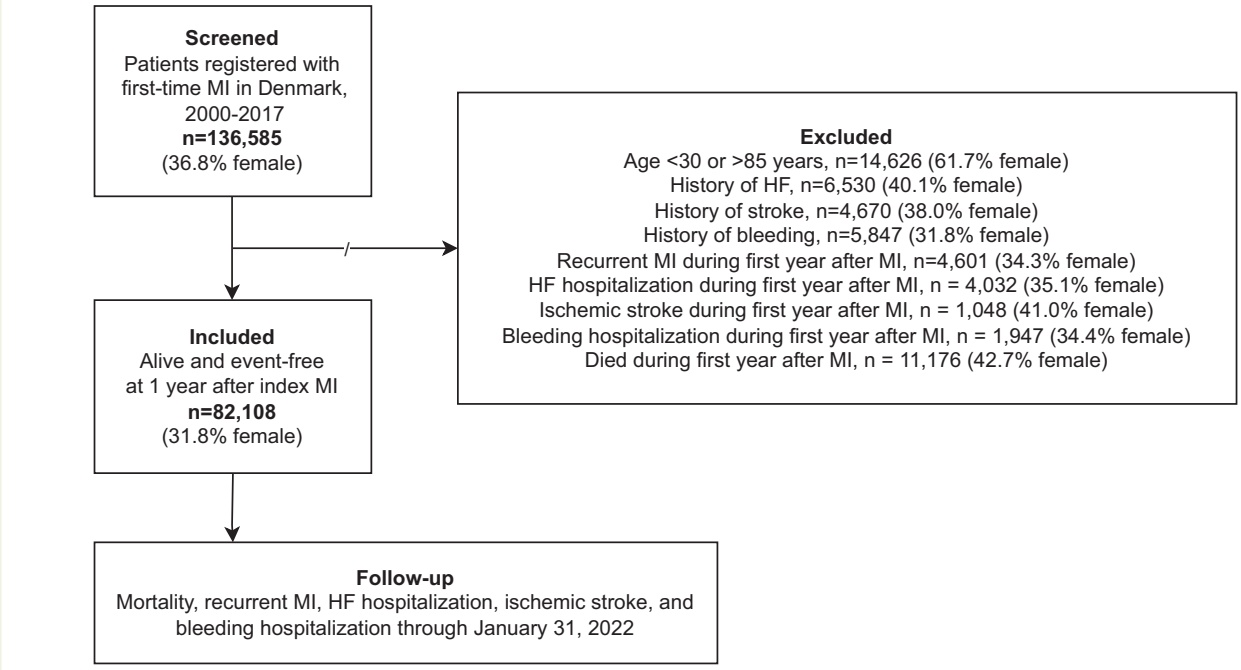


Figure 1 Flowchart of the study population selection, exclusions, and follow-up. Abbreviations: MI, myocardial infarction; HF, heart failure.

prognosis in this population are necessary to aid patient-physician discussions, to guide allocation of resources to public health-level secondary prevention efforts, to determine the need for continued specialist care, and to inform future clinical trials. Thus, using Danish registries, we investigated developments in long-term post-MI outcomes in a nationwide cohort of patients hospitalized from 2000 to 2017 who were alive and event-free at 1 year after index MI, with follow-up conducted through January 2022.

Methods

Data sources

All Danish residents are assigned a unique and personal Civil Registration Number at birth or immigration, which allows cross-linkage of registries with nationwide coverage and negligible loss to follow-up, containing administrative and health care data. This framework has been used extensively for population-based research.[19,20] In the present study, we used data from the Danish Civil Registration System (age and sex), the Danish National Patient Registry (hospital contacts [since 1978] and procedures [since 1996]), the Danish National Prescription Registry (pharmacy redeemed prescriptions with Anatomical Therapeutic Chemical [ATC] classification codes, redemption date, number of tablets, and tablet strength [since 1995]), and the National Causes of Death Registry (date of death). Diagnoses in the Danish National Patient Registry has been validated through manual chart review with high positive predictive values (PPV) for cardiovascular outcomes research.[21]

Study population

All patients between 30 and 85 years of age admitted to hospital in Denmark with a first-time primary diagnosis of MI (International Classification of Diseases, 10th revision [ICD-10]: I21) without a history of heart failure (HF), stroke, or bleeding from 2000 through 2017 were identified. This ICD-10 code has previously yielded a PPV of 97% for first-time MI in the Danish National Patient Registry.[21] Patients who survived 1 year after index MI without an event of recurrent MI, HF hospitalization, ischaemic stroke, or bleeding were included in the study population (*Figure 1*).

Outcome definitions

The outcomes of interest were all-cause mortality, recurrent MI, hospitalization for bleeding, hospitalization for HF, and ischaemic stroke. Recurrent MI was defined as a new hospital admission with a primary discharge diagnosis of MI, which has previously been validated with a PPV of 88%.[21,22] All other non-mortality outcomes were defined by inpatient hospitalizations with a primary discharge diagnosis of the respective outcome. HF (PPV 79%),[21] ischaemic stroke (PPV 97%),[23] and individual components of our bleeding definition (e.g. peptic ulcer bleeding, PPV 93%)[24] have been validated in our registry previously.

Comorbidities and treatments

Comorbidities were defined by hospital diagnoses or prescription redemptions in the 5 years prior to the start of follow-up. We studied the use of invasive procedures (coronary angiography [CAG], percutaneous coronary intervention [PCI], and coronary artery bypass graft surgery [CABG]) and use of guideline-recommended pharmacological treatments (aspirin, statin, adenosine diphosphate [ADP] receptor inhibitors, beta blockers, renin-angiotensin-system [RAS] inhibitors, and oral anticoagulants). CAG and PCI were defined as procedures performed during index MI admission and CABG was defined as surgery performed within 30 days of index MI admission. Use of guideline-recommended pharmacological treatments was defined by prescription redemptions. Prescriptions were categorized according to date of redemption in relation to index MI (0–12, 0–6, and 6–12 months after index MI). See supplementary material online, *Table S1* for ICD-10 and ATC codes.

Statistical analyses

We divided the study period into consecutive 3-year intervals from 2000 through 2017. For each period, we showed baseline characteristics as frequencies with percentages for categorical variables and median with interquartile range for age. Use of guideline-recommended treatments and

Table 1 Characteristics of the study population at 1 year after index MI

Variable	2000–02 (*n* = 14 098)	2003–05 (*n* = 14 393)	2006–08 (*n* = 13 296)	2009–11 (*n* = 13 329)	2012–14 (*n* = 13 355)	2015–17 (*n* = 13 637)
Age (years), median [IQR]	64 [55, 74]	64 [55, 74]	64 [55, 73]	64 [54, 72]	64 [54, 72]	64 [55, 72]
Male sex	9474 (67.2)	9704 (67.4)	9124 (68.6)	9125 (68.5)	9150 (68.5)	9457 (69.3)
Procedures related to index MI						
CAG	5084 (36.1)	9776 (67.9)	10 600 (79.7)	11 496 (86.2)	11 902 (89.1)	12 389 (90.8)
PCI	3364 (23.9)	7208 (50.1)	7927 (59.6)	8433 (63.3)	8719 (65.3)	9301 (68.2)
CABG	1078 (7.6)	1085 (7.5)	941 (7.1)	985 (7.4)	1086 (8.1)	1011 (7.4)
Comorbidities						
Atrial fibrillation	1233 (8.7)	1292 (9.0)	1189 (8.9)	1257 (9.4)	1418 (10.6)	1406 (10.3)
Chronic kidney disease	326 (2.3)	370 (2.6)	404 (3.0)	411 (3.1)	504 (3.8)	569 (4.2)
Cancer	645 (4.6)	694 (4.8)	736 (5.5)	873 (6.5)	983 (7.4)	1082 (7.9)
Diabetes	1553 (11.0)	1651 (11.5)	1633 (12.3)	1838 (13.8)	2024 (15.2)	2132 (15.6)
Peripheral arterial disease	845 (6.0)	900 (6.3)	906 (6.8)	887 (6.7)	909 (6.8)	904 (6.6)
COPD	879 (6.2)	992 (6.9)	922 (6.9)	988 (7.4)	950 (7.1)	859 (6.3)
Hypertension	7057 (50.1)	8383 (58.2)	7881 (59.3)	7587 (56.9)	7105 (53.2)	6680 (49.0)
Previous PCI	178 (1.3)	300 (2.1)	313 (2.4)	395 (3.0)	422 (3.2)	391 (2.9)
Previous CABG	86 (0.6)	100 (0.7)	73 (0.5)	78 (0.6)	84 (0.6)	76 (0.6)

Values are given as *n* (%), unless otherwise indicated.
IQR, interquartile range; CAG, coronary angiography; COPD, chronic obstructive pulmonary disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; MI, myocardial infarction.

procedures were reported as relative frequencies. Time zero was set 365 days after the date of the index MI. We analyzed the time to outcome, death, or 31 January 2022. We calculated absolute risks of the primary and secondary outcomes using the Kaplan–Meier method for all-cause mortality and the Aalen–Johansen method for the other outcomes where death was a competing risk. Additionally, we calculated the 5-year risks of each outcome in strata defined by age (<60 years, 60–74 years, ≥ 75 years) and sex. To calculate standardized absolute 5-year risks of each outcome with respect to the characteristics of the reference (2015–17) population, we used a Cox regression model for the hazard rate of mortality and cause-specific Cox regression models for the hazard rate of the other outcomes where the hazard rate of the competing risk of death without outcome was modelled by a second cause-specific Cox regression model.[25] Based on the Cox regression models, we predicted the risk of each outcome in every calendar period based on the observed distribution of confounders of the reference (2015–17) population and reported standardized averages of the 5-year predictions. The following variables entered the Cox regression models in two steps: (i) sex, age (<60 years, 60–74 years, ≥ 75 years), the comorbidities shown in *Table 1*, and (ii) invasive procedures (CAG, PCI, and CABG) and guideline-recommended pharmacological treatments (aspirin, statin, ADP receptor inhibitors, beta blockers, RAS inhibitors, and oral anticoagulants). We analyzed linear time trends with calendar year as a continuous variable using Fine–Gray regression for time-to-event outcomes where death was a competing risk, Cox regression for time-to-event outcomes where death was not a competing risk, and logistic regression for pharmaceutical treatments. The level of statistical significance was set at 5%. All analyses were conducted using R version 4.0.3.[26]

Additional analyses

To facilitate comparisons of risk estimates with previous studies, we calculated the absolute 3-year and 5-year risk of major adverse cardiovascular events (MACE). We defined MACE as a composite of all-cause mortality, recurrent MI, hospitalization for HF, or ischaemic stroke. We obtained cause of death from death certificates. Any cause of death including ICD-10: I00-99 was defined as cardiovascular mortality. Crude risks of death were calculated according to calendar year period using the Aalen–Johansen estimator considering the competing risk of non-cardiovascular death, with follow-up through 31 December 2018. To put our main results into context, we presented crude 5-year risks of outcomes in (i) age-, sex-, and date-matched controls from the background population, and (ii) in patients who suffered a non-fatal outcome event during the first year following index MI or had a history of HF, stroke, or bleeding prior to index MI and were thus excluded from the main analyses.

Ethics and data availability

In Denmark, studies based on pseudonymized registry data do not require ethical approval. The data-responsible institution (Capital Region of Denmark) approved the study (approval number P-2019-191). The raw data underlying the study cannot be shared publicly.

Results

The 82 108 patients included in the study population were followed for a total of 762 541.5 person-years. Their median age was 64 years and 68.2% were male. The baseline characteristics and number of events that occurred during the study were provided by age groups and sex in supplementary material online, *Table S3* and *Table S2*. During the study period, the number of patients with event-free survival at 1 year after index MI remained stable (*Table 1*). Generally, comorbidities remained relatively stable between 2000–02 and 2015–17, apart from

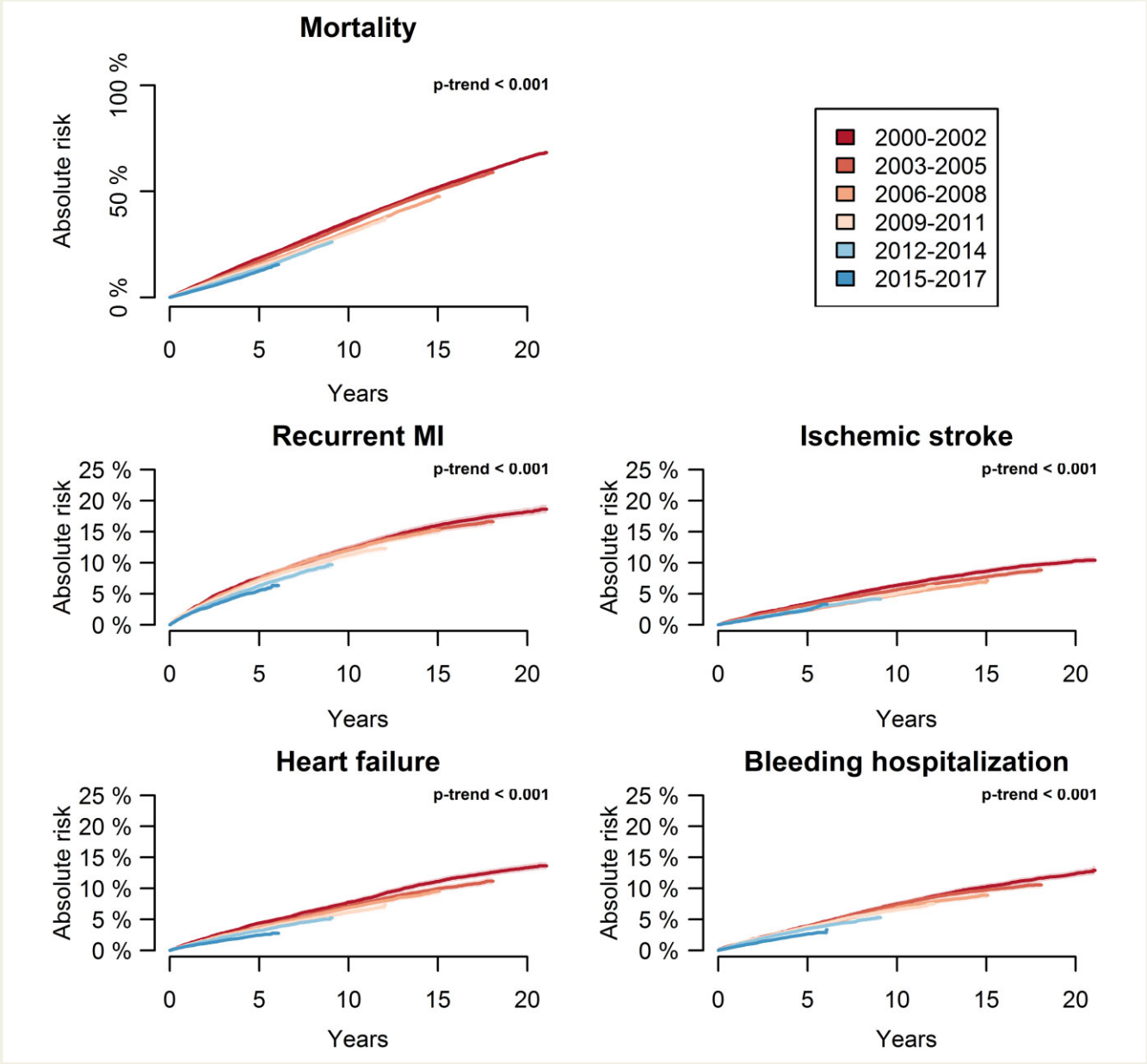


Figure 2 Crude risk curves with 95% confidence intervals for mortality, recurrent myocardial infarction, hospitalization for heart failure, ischaemic stroke, and hospitalization for bleeding according to calendar period in patients with event-free survival 1 year after myocardial infarction.

cancer, which increased from 4.6% to 7.9%, chronic kidney disease, which increased from 2.3% to 4.2%, and diabetes, which increased from 11.0% to 15.6%.

Mortality, cardiovascular events, and bleeding

The long-term mortality risk decreased in consecutive calendar periods (*Figure 2*, see supplementary material online, *Figure S1* for risk set numbers). Calendar time trends for all outcomes were statistically significant (*P*-trend <0.05). As an example, 5-year risk of mortality was 18.6% (95% CI: 17.9–19.2) in 2000–02, 15.6% (95% CI: 15.0–16.3) in 2006–08, and 12.5% (95% CI: 11.9–13.1) in 2015–17. Likewise, 10-year risk of mortality decreased from 35.9% (95% CI: 35.1–36.7) in 2000–02 to 30.2% (95% CI: 29.4–31.0) in 2009–11. The long-term risk for all non-fatal outcomes declined over time (*Figure 2*, supplementary material online, *Figures S2–S5*). For recurrent MI, the 5-year risk was 7.5% (95% CI: 7.1–8.0) in 2000–02 and 5.5% (95% CI: 5.1–6.0) in 2015–17. Similarly, the 5-year risk of ischaemic stroke declined from 3.4% (95% CI: 3.1–3.7) to 2.4% (95% CI: 2.1–2.7), the 5-year risk of hospitalization for HF declined from 4.4% (95% CI: 4.1–4.8) to 2.4% (95% CI: 2.2–2.7), and the 5-year risk of bleeding declined from 3.9% (95% CI: 3.6–4.3) in 2000–02 to 2.7% (95% CI: 2.4–3.0) in 2015–17.

Prescription patterns for guideline-recommended treatments

During the study period, the proportion of patients redeeming an aspirin prescription during the first year after MI remained at a stable, high level (>90%, *P*-trend 0.18). Use of statins post-MI increased

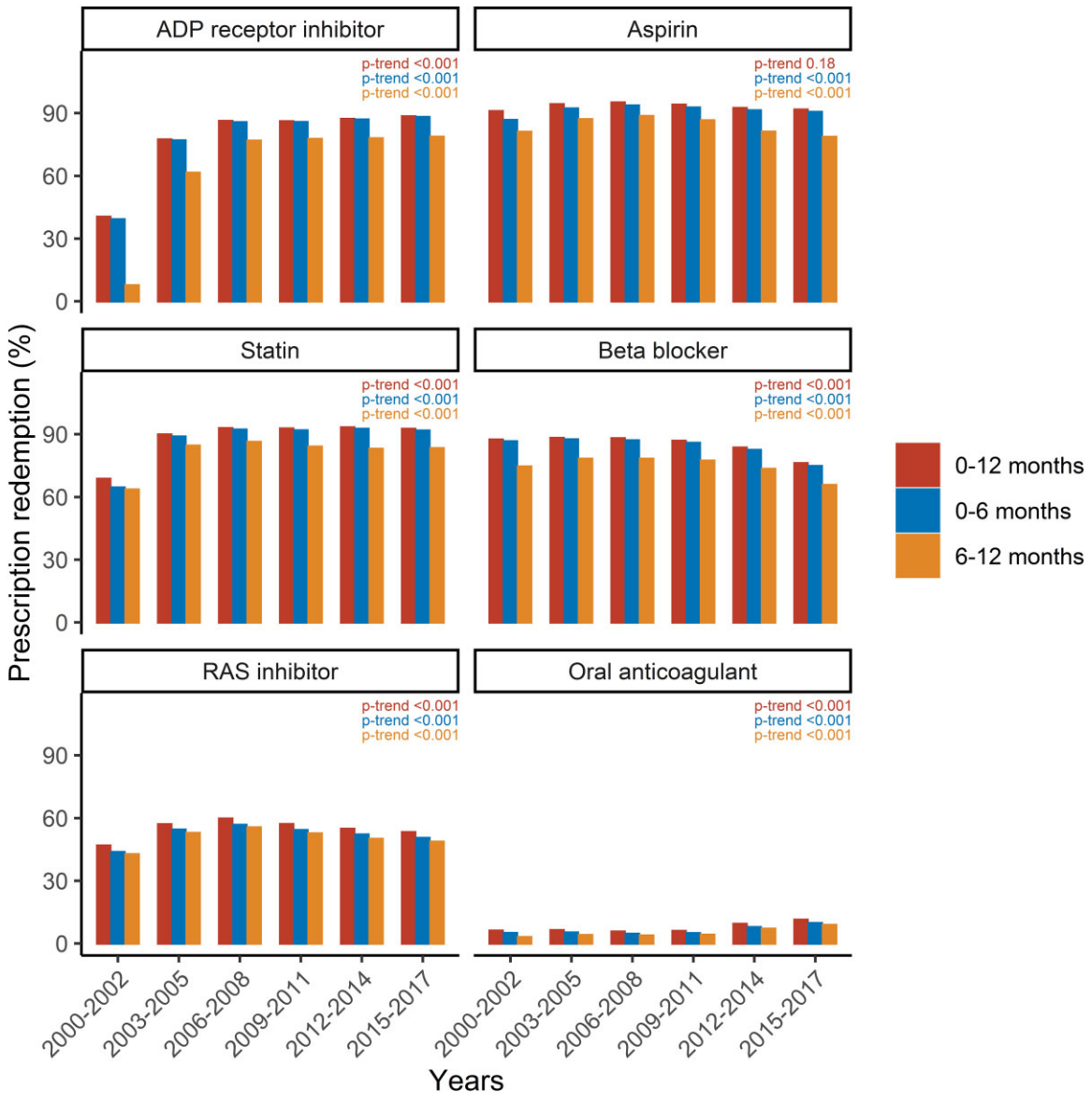


Figure 3 Redemption of prescriptions for guideline-recommended pharmacological treatments according to calendar period between index MI and study inclusion (1 year after index MI). Shown are the relative frequencies for prescription redemptions categorized according to specific periods: from 0 to 12 months after index MI, from 0 to 6 months after index MI, and from 6 to 12 months after index MI. Abbreviations: MI, myocardial infarction; ADP, adenosine diphosphate; RAS, renin-angiotensin system.

from 68.6% to 92.5% and ADP receptor inhibitors from 40.3% to 88.4% between 2000–02 and 2015–17. The initial rise was rapid and became more gradual during the latter calendar periods (*Figure 3*). Use of beta blockers post-MI appeared to decline in the 2015–17 period to 76.1%, where it was at a stable level around 85% for all preceding periods. Use of RAS inhibitors remained stable whereas use of OACs increased during the study, mainly driven by an increased use of direct oral anticoagulants (supplementary material online, *Table S4*). For the treatments that increased during the study period, prescription redemption frequency at 6–12 months after MI (a proxy for longer-term adherence) also increased: statins from 63.4% to 83.2% and ADP receptor inhibitors from 7.6% to 78.6% between 2000–02 and 2015–17 (*Figure 3*). Use of invasive procedures increased between 2000–02 and 2015–17: CAG from 36.1% to 90.8% and PCI from 23.9% to 68.2%. CABG within 30 days from index MI admission remained stable at around 7.5% (*Table 1*).

Age-, sex-, comorbidity-, and treatment-standardized risks

The age-, sex-, and comorbidity-standardized 5-year risks of all outcomes declined throughout the study period in a largely similar pattern as the crude risks (*Figure 4*). However, there was a significantly lower treatment-standardized 5-year risk of mortality in 2000–02 (15.5% [95% CI: 14.9–16.2]) and 2003–05 (15.9% [95% CI: 15.3–16.4]) compared to the crude risk. There were also numerically lower treatment-

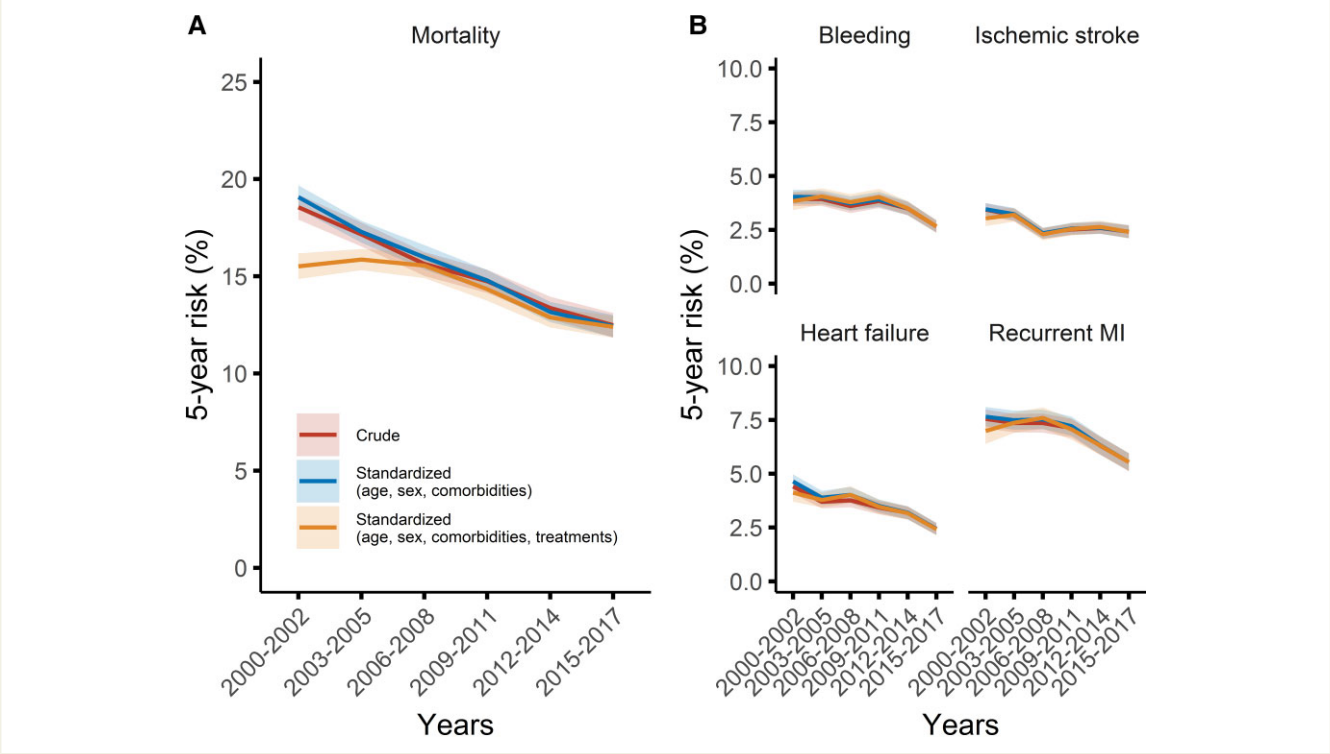


Figure 4 Crude and standardized 5-year risks of (A) mortality, (B) recurrent myocardial infarction, hospitalization for heart failure, ischaemic stroke, and hospitalization for bleeding according to calendar period. Standardization was performed with the 2015–17 population as reference and is interpreted as the predicted 5-year risk had the patients in each calendar period had the same distribution of sex, age, comorbidities, and guideline-recommended treatments as the 2015–17 reference population.

standardized 5-year risks of recurrent MI (7.0% [95% CI: 6.4–7.6]) and ischaemic stroke (3.0% [95% CI: 2.7–3.4]) in 2000–02 compared to the crude risks.

Age- and sex-stratified risks

For all outcomes, the age- and sex-stratified analysis showed declines during the study period largely consistent with the unstratified analysis (*Figure 5*). For example, between 2000–02 and 2015–17, the 5-year mortality risk among females declined from 5.5% (95% CI: 4.2–6.9) to 2.6% (95% CI: 1.6–3.5) in <60 year-olds, from 17.3% (95% CI: 15.6–19.0) to 14.0% (95% CI: 12.2–15.9) in 60–74 year-olds, and from 40.9% (95% CI: 38.5–43.3) to 33.2% (95% CI: 30.0–36.3) in ≥75 year-olds. Risk estimates were largely similar in both sexes and were higher for older compared to younger ages. However, the 5-year risk of recurrent MI was higher for the older age groups during the earlier study period, whereas it was largely similar regardless of age in 2015–17: 6.1% (95% CI: 5.3–7.0) for males and 4.7% (95% CI: 3.5–6.0) for females aged <60 years, and 6.6% (95% CI: 5.2–8.0) for males and 4.9% (95% CI: 3.5–6.2) for females aged ≥75 years. The 5-year risk of hospitalization for HF in 2015–17 was generally low but increased with age: 1.0% (95% CI: 0.7–1.4) for males and 0.5% (95% CI: 0.1–0.9) for females aged <60 years, and 6.0% (95% CI: 4.6–7.4) for males and 4.4% (95% CI: 3.2–5.7) for females aged ≥75 years (*Figure 5*). Characteristics and use of guideline-recommended treatments varied across age groups (supplementary material online, *Table S2*).

Additional analyses

The 5-year risk of MACE decreased from 27.2% (95% CI: 26.5–28.0) in 2000–02 to 19.9% (95% CI: 19.2–20.7) in 2015–17. The 3-year risk of MACE was 12.2% (95% CI: 11.6–12.7) in 2015–17 (supplementary material online, *Figure S6*). This decline was consistent across age and sex (supplementary material online, *Figure S7*). In patients who experienced a non-fatal event during the first year after index MI, the crude 5-year risks for all outcomes were markedly higher than in the main study population (supplementary material online, *Figure S8*). For mortality, MI, and HF, 5-year risks were lower for background population controls. However, for ischaemic stroke and bleeding, the crude 5-year risks in the study population approached that of the background population. The patients in the 'non-stable' MI population were older and had more comorbidities (supplementary material online, *Table S5*), whereas the background population controls had fewer comorbidities (not shown). The risk of cardiovascular mortality declined significantly throughout the study period; the 5-year risk decreased from 12.8% (95% CI: 12.3–13.4) in 2000–02 to 7.7% (95% CI: 7.2–8.2) in 2012–14 (supplementary material online, *Figure S9*). Cause-specific hazard ratios of all outcomes comparing each calendar year period to 2000–02 (reference period) are provided in the supplement (supplementary material online, *Figure S10*).

Discussion

Principal findings

In this nationwide study, we observed decreased long-term risks of mortality, recurrent MI, hospitalization for HF, ischaemic stroke, and bleeding in patients with event-free survival at 1 year after first-time MI between 2000 and 2017 (*Structured Graphical Abstract*). We also

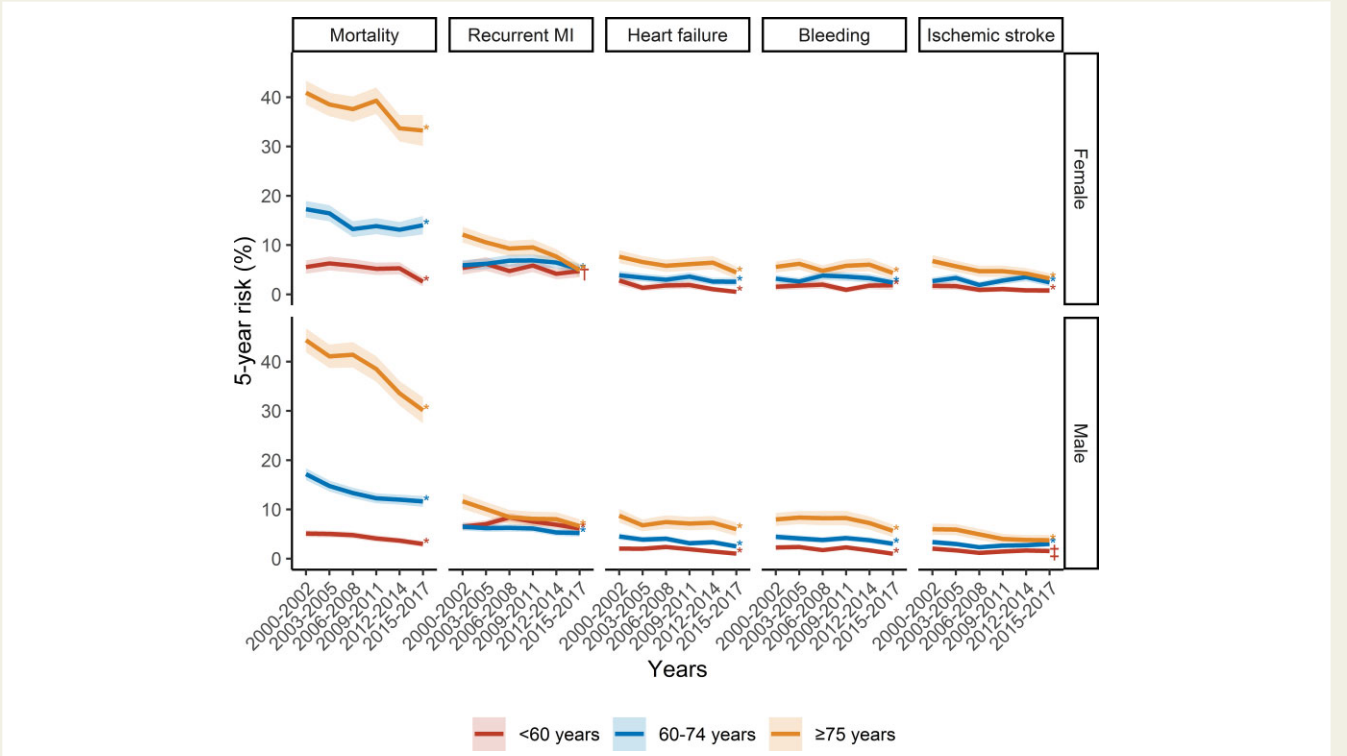


Figure 5 Absolute 5-year risks of mortality, recurrent myocardial infarction, hospitalization for heart failure, ischaemic stroke, and hospitalization for bleeding stratified according to age and sex. *P-trend <0.001, †P-trend =0.031, ‡P-trend =0.038.

found an increased use of guideline-recommended treatments, which may partly explain the improved outcomes. In the latter part of the study period, the risk of future cardiovascular events was lower than expected for these stable patients compared to previous reports.

Interpretation of results and comparison to other studies

The present study builds upon prior studies showing vast improvements in outcomes of MI during the preceding decades.[2,9–13] The overall incidence of MI in Denmark has been declining in recent decades,[1] but the number of patients included throughout our study period was stable. This is because a higher proportion of MI patients achieved event-free 1-year survival, which is corroborated by recent data.[27] This is also underlined by the increased prevalence of high-risk comorbidities such diabetes, chronic kidney disease, and cancer, as these patients are increasingly likely to achieve event-free 1-year survival. Scrutinization of longer-term outcomes is warranted in this growing population of stable patients. Previous studies investigated developments in short- and long-term outcomes immediately following acute MI,[2,9–13] while our study showed that the improvements also pertained to stable post-MI patients. It is well recognized that the risk of cardiovascular events is particularly high during the first year following MI (upwards of 20%).[12,13,18] However, previous studies showed that even in patients with event-free survival 1 year after MI, the risks of mortality and cardiovascular events remained high in the long term.[18,28] A Swedish study reported that the 3-year cumulative risk of cardiovascular events (a composite of cardiovascular death and non-fatal MI or ischaemic stroke) was 20% in the stable population.[18] The 3-year risk of MACE was between 7.7% and 9.0% in patients included in the PEGASUS-TIMI 54 trial who had an MI between 1 and 3 years prior to enrollment (median duration 1.7 years).[29] In contrast, during the latter part of our study, we found a 12.2% composite 3-year risk using a broader definition of MACE which included all-cause (as opposed to only cardiovascular) mortality as well as hospitalization for HF. Specifically, we also report a 5-year all-cause mortality risk of 12.5%, a 5-year risk of recurrent MI of 5.5%, and an even lower risk for HF and ischaemic stroke during the latter part of the study period (2015–17). In patients <60 years of age, the 5-year risk of mortality was as low as 2.6%. However, their 5-year risk of recurrent MI was as high as the older age groups (~5–6%), indicating that prevention of recurrent ischaemic events may be especially warranted among younger patients. The differences in risk of long-term outcomes reported in our study compared to previous studies possibly pertain to the continuous temporal improvements that we have demonstrated, i.e. the risk is likely lower in more contemporary populations. Additionally, our patient selection differed from the Swedish study, as we only included patients between 30 and 85 years of age at index MI, which also explains the difference in long-term mortality risk. Bear in mind, the observed improvement in long-term mortality through calendar periods could be driven by an increased life expectancy in the population generally. Yet, the similar pattern observed for the long-term risk of recurrent MI, HF, and ischaemic stroke suggests an improvement of cardiovascular risk *per se*.

In accordance with previous studies,[10,12,13] we found an increased use of guideline-recommended treatments during the study period. Expanding upon previous studies, we further reported that the relative frequency of prescription redemptions between 6 and 12 months after index MI, serving as a proxy for adherence, improved over time. The use of

antithrombotic agents increased but was not accompanied by an observed increase in long-term bleeding risk. This may be because prolonged (beyond 12 months) dual antiplatelet therapy for patients with high cardiovascular risk was only incorporated into international guidelines after the end of our inclusion period.[16,17] Thus, dual antiplatelet therapy was likely discontinued around start of follow-up for our population.

We calculated standardized 5-year risks to determine the influence of changes in age, sex, comorbidities, and treatments on our results. These estimates were standardized with respect to the distribution of the characteristics, comorbidities, and treatments of the reference 2015–17 population, i.e. accounting for the lower treatment probability and different comorbidity and demographic distribution in the earlier periods compared to 2015–17. When the curves overlap as they do for the treatment-standardized and crude risks for mortality after 2005 and for the other outcomes after 2002, it implies that the factors with respect to which we standardized did not meaningfully change the observed long-term risks. As such, the observed changes were not explained by differences in age, sex, and comorbidities. Furthermore, if the 2000–02 population had the same high rate of treatment (and same comorbidity distribution, etc.) as the 2015–17 population, 5-year mortality risk would likely have been lower. The lack of difference between the treatment-standardized and crude risks in the subsequent periods may be due to the high use of guideline-recommended treatments observed from 2003-05 and onwards. A further implication of the standardized analysis is that factors other than those studied may have contributed to the observed improvements in long-term risk. Better risk factor management, rehabilitation, quicker recognition of symptoms, smaller infarctions due to improved diagnostic sensitivity, etc. probably played a role in the improvements. For example, previous data indicate an increase in early catheterization during the study period in the overall MI population.[27] Improved attainment of low-density lipoprotein cholesterol target values were also observed in individuals initiating lipid-lowering therapy in Denmark during the study period,[30] while prevalence of smoking decreased in general.[31] These improvements likely also affected our study population and may have driven the continuously decreasing risk.

Limitations

The main limitation of our study was the observational design. This precludes firm conclusions to be drawn on the causality of the findings. Another important limitation is the lack of information about important risk factors such as smoking, blood pressure, lipids, or obesity and diagnostic variables such as cardiac enzymes, angiographic findings, ECGs, type of MI, and echocardiographic findings. Some of these factors likely changed during the study period and may have contributed to explain our results. For example, smoking decreased in Denmark during the study period,[31] which likely contributed to the improved outcomes observed in our data. During the latter part of our study period, COVID-19 lockdowns may have decreased the incidence of cardiovascular hospitalizations.[32] However, in a previous study from our group, we found that the incidence of cardiovascular events dropped by approximately 20% during the initial weeks of the first lockdown in Denmark before returning to normal and remaining stable during subsequent lockdowns.[33]

Future perspectives and clinical implications

Continuous successful real-world implementation of evidence-based treatments from clinical trials remains key to improve long-term prognosis after MI, also in stable patients. In Denmark, guideline implementation has largely been driven by the Danish Society of Cardiology. The 'National Treatment Guidelines' are peer-reviewed and published regularly, based on endorsements of ESC guidelines.[34] The high implementation of guideline recommendations in Denmark may also be linked to a tradition for research with importance for clinical practice. For example, DANAMI-2 led to the national implementation of primary PCI as first-line treatment of ST-elevation MI in 2003.[35] Of note, statin use increased from an already high level during the early part of our study following the landmark trials of the 90s,[36,37] likewise with dual antiplatelet therapy following the landmark trials of the early 2000s.[38,39] Besides this, our data seem to indicate that efforts in additional areas are needed to further improve outcomes, as use of established treatments had reached a stably high level. Newer treatments such as anti-inflammatory treatments and proprotein-convertase subtilisin/kexin type 9 inhibitors (PCSK9-i) may play a role in targeting residual risk.[40] Furthermore, non-cardiac comorbidities such as kidney disease, cancer, and diabetes were gradually more prevalent in our population, and comorbidities and non-cardiac outcomes may represent an increasingly important challenge in the management of the stable post-MI population. Finally, more focus is warranted on the role of cardiac rehabilitation and quality of life interventions considering the improved clinical outcomes for stable post-MI patients shown in our study. Another important consideration is, that treatments established in previous eras may need reevaluation to determine their efficacy in contemporary populations with lower *a priori* risk. An example of this the DANBLOCK trial that will assess the effect of beta blockers in an acute MI population without reduced left ventricular ejection fraction.[41] Also, increasing evidence suggests similar ischaemic benefits of shorter compared with longer durations of antiplatelet therapy,[42,43] which may lead to improvements in bleeding risk management for patients with MI in the future. However, the reported bleeding risk in our population was so low, that it approached that of the background population, implying that it may be difficult to additionally reduce bleeding risk in these patients. As the prognosis varied markedly between stable and non-stable post-MI patients in our study, identifying high-risk patients through individual risk stratification, and applying personalized treatment strategies may be the key to further improve long-term outcomes while reducing the risk of adverse effects.

Conclusions

This nationwide study found that in patients who were stable and event-free 1 year after MI, long-term risks of cardiovascular outcomes decreased significantly, along with an improved use of guideline-recommended treatments between 2000 and 2017. Our results suggest that the residual cardiovascular risk was lower than expected in stable patients compared to earlier findings. Our findings highlight the importance of the long-term perspective in secondary prevention following MI in the modern era.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Data availability

Access to data from the Danish nationwide registries is granted by the Danish Health Data Authority.

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