Journal of the American Heart Association

ORIGINAL RESEARCH

Risk Factors, Subsequent Disease Onset, and Prognostic Impact of Myocardial Infarction and Atrial Fibrillation

Stephan Camen, MD*; Dora Csengeri, MD*; Bastiaan Geelhoed, PhD; Teemu Niiranen, PhD; Francesco Gianfagna, MD; Julie K. Vishram-Nielsen, PhD; Simona Costanzo, PhD; Stefan Söderberg, PhD; Erkki Vartiainen, PhD; Christin S. Börschel, MD; Maria Benedetta Donati, PhD; Maja-Lisa Løchen, PhD; Francisco M. Ojeda, PhD; Jukka Kontto, MSc; Ellisiv B. Mathiesen, MD; Steen Jensen, PhD; Wolfgang Koenig, MD; Frank Kee, MD; Giovanni de Gaetano, MD; Tanja Zeller, PhD; Torben Jørgensen, DMSci; Hugh Tunstall-Pedoe, MD; Stefan Blankenberg, MD; Kari Kuulasmaa, MD; Allan Linneberg, PhD; Veikko Salomaa, PhD; Licia Iacoviello, PhD; Renate B. Schnabel, MD

BACKGROUND: Although myocardial infarction (MI) and atrial fibrillation (AF) are frequent comorbidities and share common cardiovascular risk factors, the direction and strength of the association of the risk factors with disease onset, subsequent disease incidence, and mortality are not completely understood.

METHODS AND RESULTS: In pooled multivariable Cox regression analyses, we examined temporal relations of disease onset and identified predictors of MI, AF, and all-cause mortality in 108 363 individuals (median age, 46.0 years; 48.2% men) free of MI and AF at baseline from 6 European population-based cohorts. During a maximum follow-up of 10.0 years, 3558 (3.3%) individuals were diagnosed exclusively with MI, 1922 (1.8%) with AF but no MI, and 491 (0.5%) individuals developed both MI and AF. Association of sex, systolic blood pressure, antihypertensive treatment, and diabetes appeared to be stronger with incident MI than with AF, whereas increasing age and body mass index showed a higher risk for incident AF. Total cholesterol and daily smoking were significantly related to incident MI but not AF. Combined population attributable fraction of cardiovascular risk factors was >70% for incident MI, whereas it was only 27% for AF. Subsequent MI after AF (hazard ratio [HR], 1.68; 95% CI, 1.03–2.74) and subsequent AF after MI (HR, 1.75; 95% CI, 1.31–2.34) both significantly increased overall mortality risk.

CONCLUSIONS: We observed different associations of cardiovascular risk factors with both diseases indicating distinct pathophysiological pathways. Subsequent diagnoses of MI and AF significantly increased mortality risk.

Key Words: atrial fibrillation ■ cohort study ■ mortality ■ myocardial infarction ■ risk factors

Myocardial infarction (MI) and atrial fibrillation (AF) are common comorbidities. The onset of 1 condition increases the risk of the other disease significantly. A history of MI has been known to be a risk factor for incident AF independent of clinically overt heart failure.[1,2] Vice versa, AF also increases the risk of MI, in particular non–ST-segment–elevation MI.[3,4] Both lifetime diseases share common cardiovascular risk factors such as increased body mass index (BMI) or hypertension.[2,5] Thus, pathophysiological pathways may overlap.[6] If both diseases concur, mortality is increased after MI.[7] A meta-analysis revealed that AF diagnosis in patients with MI is related to a 1.37-fold increased risk of mortality.[8]

Correspondence to: Renate B. Schnabel, University Heart Center Hamburg-Eppendorf, Martinistraße 52, 20246 Hamburg, Germany. Email: r.schnabel@uke.de

*S. Camen and D. Csengeri contributed equally.

Supplemental Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.121.024299

For Sources of Funding and Disclosures, see page 9.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Atrial fibrillation and myocardial infarction show different risk factor associations with common cardiovascular risk factors.
- Classical cardiovascular risk factors explain a higher proportion of the risk for myocardial infarction compared with atrial fibrillation.
- Incident atrial fibrillation increases the risk for subsequent myocardial infarction and vice versa, and diagnoses of both diseases significantly increase mortality risk, irrespective of the first event.

What Are the Clinical Implications?

- Consequent population-level risk factor management could help reduce the burden of atrial fibrillation and myocardial infarction, in particular if either condition has already occurred.
- Low-threshold screening for (paroxysmal) atrial fibrillation should be performed in patients who have suffered from myocardial infarction.

Nonstandard Abbreviations and Acronyms

BiomarCaRE	Biomarker for Cardiovascular Risk Assessment Across Europe
MORGAM	Monica Risk, Genetics, Archiving and Monograph
PAF	population attributable fraction

Data on the (temporal) relationship of both diseases and the prognostic importance of subsequent disease onset on mortality in the general population are rare.

Therefore, our goal was to examine the temporal relationship of MI and AF, potential differential risk factor associations for both diseases, and their impact on mortality using cohorts from the BiomarCaRE (Biomarker for Cardiovascular Risk Assessment Across Europe) consortium.[9] We expected to find a bidirectional temporal relationship between the incidence of AF and MI. In addition, we hypothesized that traditional cardiovascular risk factors would have a stronger association with the incidence of MI than with the incidence of AF and that subsequent disease diagnosis would be associated with increased all-cause mortality.

METHODS

Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to the corresponding author.

Study Population

We pooled participant-level data from 6 community-based cohort studies of the BiomarCaRE project with available information on AF and MI status at baseline and follow-up (http://www.biomarcare.eu/), the DANMONICA study, the FINRISK study, the Moli-sani study, the Northern Sweden MONICA study, the SHHEC (Scottish Heart Health Extended Cohort), and the Tromsø Study, comprising 129 027 unique individuals.[9] Each cohort is based on representative population samples with baseline examinations between 1982 and 2010. Details on the enrollment and follow-up procedures of each cohort are provided in Data S1. The data from the cohorts were carefully harmonized in the MORGAM (Monica Risk, Genetics, Archiving and Monograph) project.[10] These community-based cohorts permit the examination of the prognostic relevance of the subsequent disease occurrence during long-term follow-up.

Individuals with a positive history of AF based on self-report, prior diagnosis by a physician, or on the baseline ECG (N=917) were excluded from all analyses as well as individuals with a positive history of MI based on self-report or prior physician's diagnosis (N=3213). Furthermore, individuals with missing information on baseline or follow-up variables for AF, MI, or mortality or on covariates used in the regression analysis were excluded (N=16 534). Thus, 108 363 individuals were included for analyses across all cohorts.

Definition of Outcomes and Follow-Up

Incident AF was defined by date of the first documentation on ECG or assignment of the relevant code (427.4 for *International Classification of Diseases, Eighth Revision* [*ICD-8*], 427.3 for *International Classification of Diseases, Ninth Revision* [*ICD-9*], and I48 for *International Classification of Diseases, Tenth Revision* [*ICD-10*]).

Incident MI was defined as the first definite or possible fatal or nonfatal acute coronary event according to the MORGAM criteria, excluding individuals with unstable angina pectoris whenever separation was possible. Overall mortality was defined as mortality attributed to any cause during the follow-up period (details on all outcome classifications are provided in Data S2).

Follow-up for AF and MI was based on linkage with national (hospitalization) registries. Follow-up for mortality was obtained from central death registries.

The follow-up for the cohorts was completed in 2009 (SHHEC), 2010 (DAN-MONICA, FINRISK, Tromsø), or 2011 (Moli-sani, Northern Sweden). All participating

cohort studies complied with the Declaration of Helsinki and were approved by local ethics committees, and informed consent was obtained from each participant.

Statistical Analysis

Categorical variables are given as absolute and relative frequencies, and continuous variables are given as median (25th, 75th percentiles). The diagnoses of AF and MI over time were assessed in the overall cohort, limited to a maximum follow-up time of 10 years to meet the proportional hazard assumption. We performed univariable and multivariable-adjusted Cox proportional hazards regression analyses with incident AF, incident MI, and sequential incident AF and MI as end points using time since baseline as the time scale to determine the association of cardiovascular risk factors with incident disease diagnosis. Death was treated as a censoring event because we wanted to estimate cause-specific hazard ratios (HRs).[11] All Cox proportional hazards regressions were adjusted for age, sex, and cohort. In multivariable-adjusted analyses, systolic blood pressure, BMI, total serum cholesterol concentration, diabetes, daily smoking, antihypertensive treatment, and prevalent stroke at baseline were used as additional covariates. This set of risk factors was chosen based on previously reported associations with incident AF and MI and was used for all analyses.[2,5]

When incident AF or incident MI were covariates, they were included as time-dependent covariates.

To understand the prognostic impact of subsequent diagnosis of AF after MI for all-cause mortality, we computed multivariable-adjusted Cox regressions for all-cause mortality, including only those individuals who were diagnosed with MI during follow-up and no diagnosis of AF up to that point. Individuals for whom the date of the index MI corresponded with the date of death were excluded from the analyses. Similar analyses were performed exchanging the role of MI and AF. The time after the initial diagnosis (MI or AF) was used as the time scale in both models, and subsequent incident AF or MI were again treated as time-dependent covariates.

To avoid nonlinearity in all multivariable Cox proportional hazards models, the statistical significance of all possible second-order interactions and of quadratic terms of the variables in the model was assessed, and an interaction was included as an additional covariate if its Bonferroni-corrected P value was <0.05. Interactions with time since baseline were added when needed to avoid violations of the proportional hazards assumption, which were identified using the R function cox.zph with parameter "global" set to false. When included in an interaction, continuous variables were centered on their overall mean (more details on the statistical approach are provided in Data S3). To examine possible secular trends attributed to the long study period, we performed additional Cox regressions using the date of the baseline examination/risk factor assessment or the date of the first documentation of incident AF and MI as covariates.

Population attributable fractions (PAFs) were calculated using the fully adjusted estimated HR to replace the risk ratios in the original formula for PAF. Hence, the PAF of each risk category of each risk factor was calculated using pd×(HR-1)/HR, where pd is the proportion of those in the risk category among the cases (incident AF or MI) during a 5-year follow-up. The combined PAF of the risk factors was calculated according to the method suggested by Bruzzi et al.[12] For each PAF, bootstrapping with 500 repetitions was used to estimate its associated 95% CI and the P values for the differences between PAFs and associated 95% CI.

For the calculation of PAFs, systolic blood pressure, BMI, and total cholesterol were categorized using 4 (<120 mm Hg, 120 to <140mm Hg, 140 to <160 mm Hg, ≥160 mm Hg), 3 (<25 kg/m^2, 25 to <30 kg/m^2, ≥30 kg/m^2), and 2 categories (based on the cutoff value 5.17 mmol/L), respectively. The lowest risk category was taken as reference level during the PAF calculation. Analyses were performed with R version 3.6.3 (http://www.R-project.org).

RESULTS

Population Characteristics and Temporal Relations of MI and AF

The median age of the included individuals was 46.0 years (25th/75th percentiles, 36.1/56.4), 48.2% were men (further baseline characteristics are presented in Table 1 and by cohort in Table S1). During a maximum follow-up of 10.0 years, 3558 (3.3%) individuals were diagnosed exclusively with MI, 1922 (1.8%) with AF but no MI, and 491 (0.5%) individuals developed both MI and AF. Of these individuals, 183 (37%) were diagnosed with both diseases within 30 days, 158 (32%) had an MI >30 days after AF diagnosis, and 150 (32%) were diagnosed with AF >30 days after MI (Figure 1).

Association of Different Risk Factors With Incident Disease

Multivariable-adjusted Cox regression analyses revealed different associations of common cardiovascular risk factors with incident AF and MI (Table 2). Increasing age, male sex, systolic blood pressure, BMI, diabetes, and antihypertensive treatment were associated with both incident AF and MI, whereas total cholesterol and daily smoking were only associated with

Table 1. Characteristics of the Study Population (N=108 363)

General characteristics	
Years of baseline examinations, range	1982–2010
Age at baseline examination, y	46.0 (36.1/56.4)
Male sex, n (%)	52 250 (48.2)
Cardiovascular characteristics	
Systolic blood pressure, mm Hg	131 (120/145)
Body mass index, kg/m²	25.3 (22.9/28.4)
Total cholesterol, mmol/L	5.7 (5.0/6.6)
Diabetes, n (%)	3422 (3.2)
Daily smoker, n (%)	33 052 (30.5)
Antihypertensive treatment, n (%)	12 063 (11.1)
Prevalent stroke, n (%)	1182 (1.1)
Events during follow-up	
Atrial fibrillation, n (%)	2413 (2.2)
Myocardial infarction, n (%)	4049 (3.7)
Death, n (%)	6933 (6.4)

Pooled characteristics of the 6 cohorts are presented as absolute and relative frequencies for categorical variables and medians (25th/75th percentiles) for continuous variables.

incident MI. While increasing age and BMI showed higher HRs for incident AF than MI, male sex, systolic blood pressure, antihypertensive treatment, and diabetes had stronger associations with incident MI than AF. Interim incident MI was associated with an increased risk of subsequent AF diagnosis and vice versa (HR, 7.71 [95% CI, 5.54–9.87; $P<0.01$] and HR, 2.61 [95% CI, 1.74–3.48; $P<0.01$], respectively). All evaluated risk factors were associated with subsequent diagnoses of both AF and MI with male sex and diabetes showing the highest HRs (Figure 2). The strength of the association between cardiovascular risk factors and the incidence of disease, in particular MI, depended on the study period and decreased over the years (Table S2). The PAFs of the cardiovascular risk factors for 5-year incidence for AF and MI are presented in Figure 3. The combined PAFs for incident AF and MI were 26.9% and 71.2%, respectively.

Impact of Subsequent Disease Diagnosis on Overall Mortality

In multivariable-adjusted Cox regression analysis with MI and AF as time-dependent covariates, MI subsequent to incident AF (HR, 1.68; 95% CI, 1.03–2.74; $P=0.04$) as well as AF subsequent to incident MI (HR, 1.75; 95% CI, 1.31–2.34; $P<0.01$) were both associated with an increased mortality risk (Table 3). The evaluation of the proportional hazards assumption revealed a significant interaction between the time interval from AF to subsequent MI and its impact on overall mortality. The reported HR for incident MI after AF represents the geometric mean of the HRs obtained by adding incident MI according to 2-year intervals (eg, within the first 2 years, 2 to 4 years) as separate time-dependent variables to the model. We observed the highest HR for subsequent MI within the first 2 years after AF (for details on the HR of subsequent MI after AF, please refer to Table S3). We did not observe any other violations of the proportional hazards assumption.

DISCUSSION

Based on carefully harmonized data from 6 European population-based cohorts, we were able to demonstrate different associations of common cardiovascular risk factors with incident AF and MI. These risk factors accounted for a substantially higher proportion of the PAF of MI compared with AF, indicating the complex, heterogeneous underlying pathophysiology of AF. Subsequent diagnoses of both diseases were associated with an increased overall mortality risk, irrespective of the first event.

Temporal Relations of AF and MI

Focusing on individuals with both AF and MI during follow-up, we observed a clustering of disease diagnosis of 1 disease within 30 days of the other disease. The nonrandom clustered temporal distribution of disease diagnosis in individuals with both incident diseases is in line with prior findings from a diseased cohort study in which 46% of all incident AF cases were diagnosed within the first 30 days after acute MI, with a gradual decline in AF diagnosis during the duration of follow-up.[7] This observation might be explained by 3 factors. First, both AF and MI might make the treating physician alert to potential clinically silent concomitant cardiac disease and therefore enhance the diagnosis of the respective condition. Second, AF might induce MI and vice versa as outlined in more detail next.[6] Third, the number of individuals at risk of developing AF or MI is likely to decline over time as a result of mortality in these patients who are sick and might therefore also partly explain the lower absolute incidence rates with longer follow-up. Nevertheless, our findings provide further evidence for intensified screening for silent AF in case of the (first) diagnosis of MI.

Association of Risk Factors With Incident Diseases

We found that the association of male sex, systolic blood pressure, antihypertensive treatment, and diabetes appeared to be stronger with incident MI than with AF, whereas increasing age and BMI showed stronger associations with a newly diagnosed AF. Total cholesterol and daily smoking were significantly related to incident MI, but not AF. The directions of the associations are

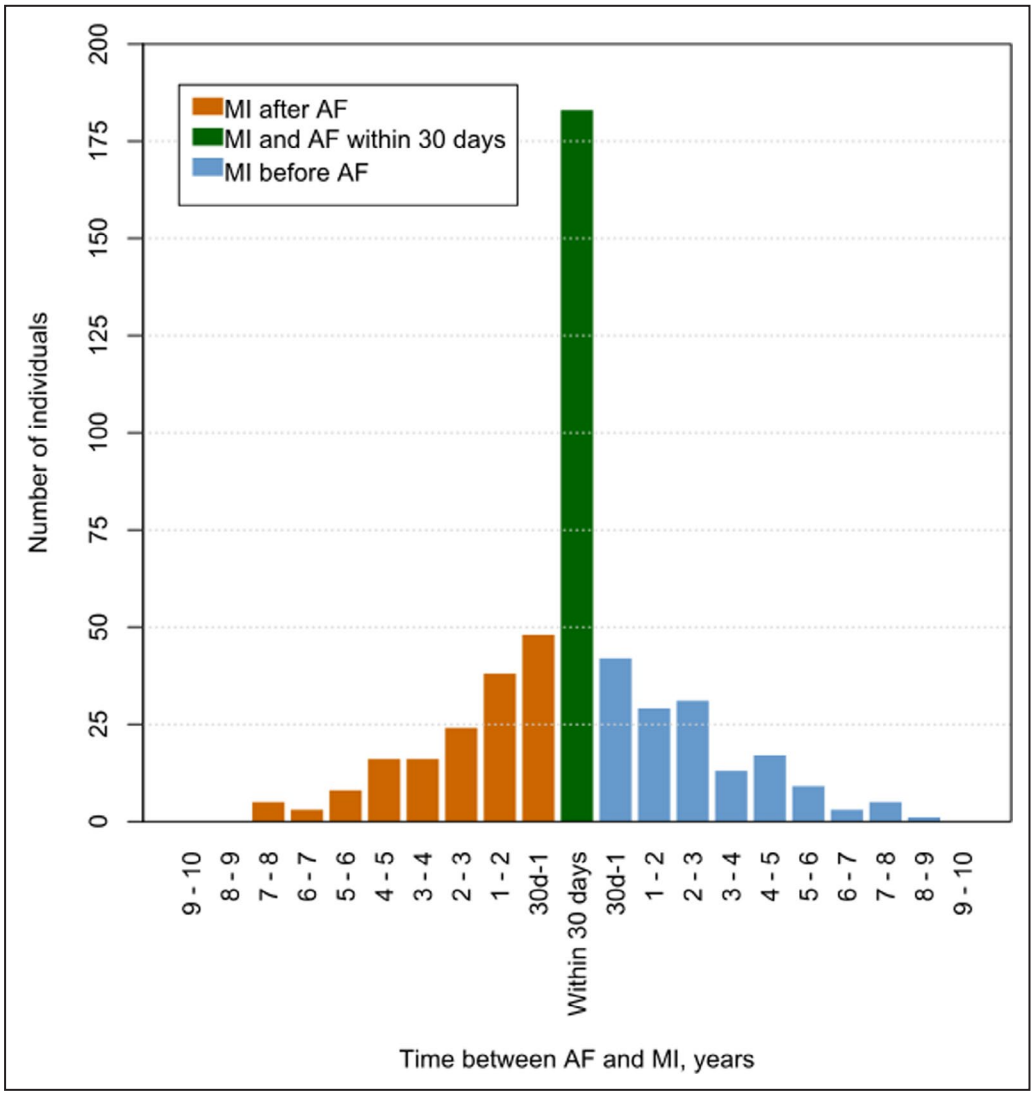

Figure 1. Temporal relations of myocardial infarction (MI) and atrial fibrillation (AF).
This graph shows the distribution of individuals who developed both AF and MI based on the time that elapsed between diagnoses of both events. Overall, 491 individuals were diagnosed with both diseases during a maximum follow-up of 10.0 years.

in line with previous reports. Data on smoking have remained inconsistent. Although a recent meta-analysis of population-based cohorts showed a relationship between smoking and incident AF, other reports did not demonstrate a clear association.[2,5,6,13] Similarly, prior reports on the association of diabetes with incident AF have been inconclusive, whereas the association with incident MI is well established.[1,5,14] We observed an attenuation of the association of cardiovascular risk factors with the risk of incident disease in more recent study periods, potentially reflecting increasing awareness and treatment options for the cardiovascular risk factors. The observed difference of the cardiovascular risk factors' associations with incident AF and MI might be explained by distinct pathophysiological pathways. MI often is the consequence of acute plaque rupture with subsequent occlusion of the vessel or a supply–demand mismatch attributed to coronary artery disease as the cardiac manifestation of arteriosclerosis, whereas the underlying etiology of AF seems to be more complex and is only partially explained by vascular disease caused by classic cardiovascular risk factors.[6] In addition, misclassification in the case of asymptomatic AF might have weakened the associations and could help explain the observed differences.

The observed stronger association of modifiable cardiovascular risk factors with incident MI than with AF, except for BMI, led to a higher combined PAF for incident MI compared with AF. Previous population-based studies demonstrated a PAF of similar strength for hypertension and increased BMI with both incident AF and MI, whereas the PAF of smoking and diabetes seemed to

Table 2. Association of Risk Factors With Incident AF and MI

Risk factor	Disease	HR (95% CI)	*P* value
Age, per 5 y increase	AF	1.84 (1.75–1.92)	<0.01
	MI	1.65 (1.59–1.72)	<0.01
Male sex	AF	2.72 (2.32–3.11)	<0.01
	MI	3.86 (3.42–4.30)	<0.01
Systolic blood pressure, per 10 mm Hg increase	AF	1.03 (1.01–1.05)	<0.01
	MI	1.12 (1.10–1.13)	<0.01
Body mass index, per 5 kg/m² increase	AF	1.31 (1.22–1.40)	<0.01
	MI	1.18 (1.11–1.24)	<0.01
Total cholesterol, per 1 mmol/L increase	AF	0.95 (0.89–1.00)	0.05
	MI	1.57 (1.49–1.64)	<0.01
Diabetes	AF	1.19 (1.02–1.36)	0.03
	MI	2.18 (1.95–2.42)	<0.01
Daily smoker	AF	1.05 (0.95–1.15)	0.35
	MI	2.21 (2.04–2.39)	<0.01
Antihypertensive treatment	AF	1.35 (1.04–1.66)	0.03
	MI	1.76 (1.50–2.02)	<0.01
Incident interim MI during follow-up	AF	7.71 (5.54–9.87)	<0.01
Incident interim AF during follow-up	MI	2.61 (1.74–3.48)	<0.01

P values and CIs were estimated by bootstrapping with 500 repetitions. Analyses were additionally adjusted for cohorts. AF indicates atrial fibrillation; HR, hazard ratio; and MI, myocardial infarction.

be higher for incident MI than AF.[2,5] Whereas increased total cholesterol concentrations contribute a large PAF for incident MI, they have shown an inverse association with incident AF.[2,15] We present a direct comparison of the PAF of the cardiovascular risk factors for both diseases, demonstrating that it is about 70% for incident MI, whereas it is only about a quarter for incident AF in our cohorts. As known, total cholesterol, daily smoking, and systolic blood pressure contributed substantially to the incidence of MI in the community, highlighting the importance and potential benefit of strict risk factor management. Based on our results and a dearth of specific disease prevention programs, AF prevention is more complex.[16] For now, blood pressure treatment and weight control appear to be the most promising strategies for a reduction of the AF burden in the community.

Impact of Incident Disease on All-Cause Mortality

Subsequent diagnoses of AF and MI were associated with an increased risk of overall mortality in our study,

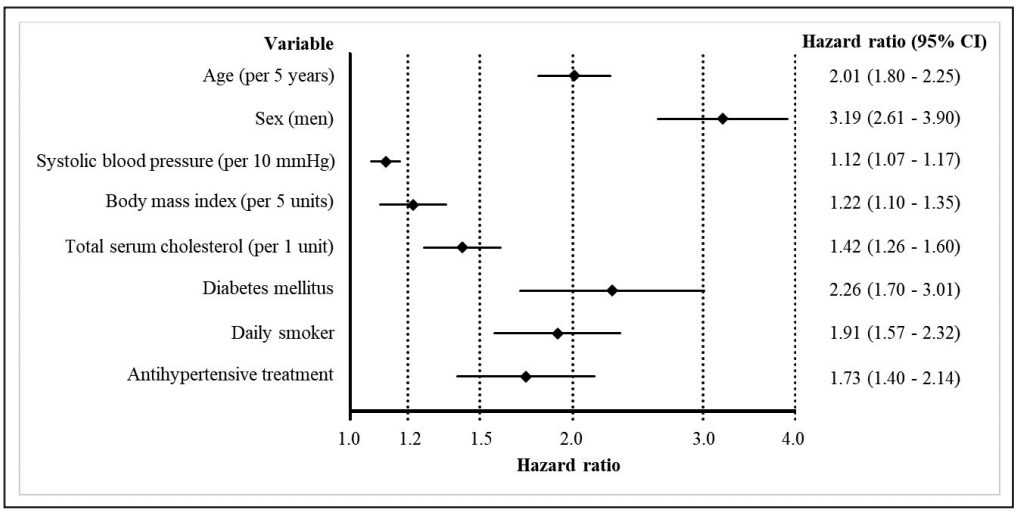

Figure 2. Hazard ratios of cardiovascular risk factors for subsequent diagnoses of atrial fibrillation and myocardial infarction.
Hazard ratios and 95% CIs are provided. Analyses were adjusted for cohorts.

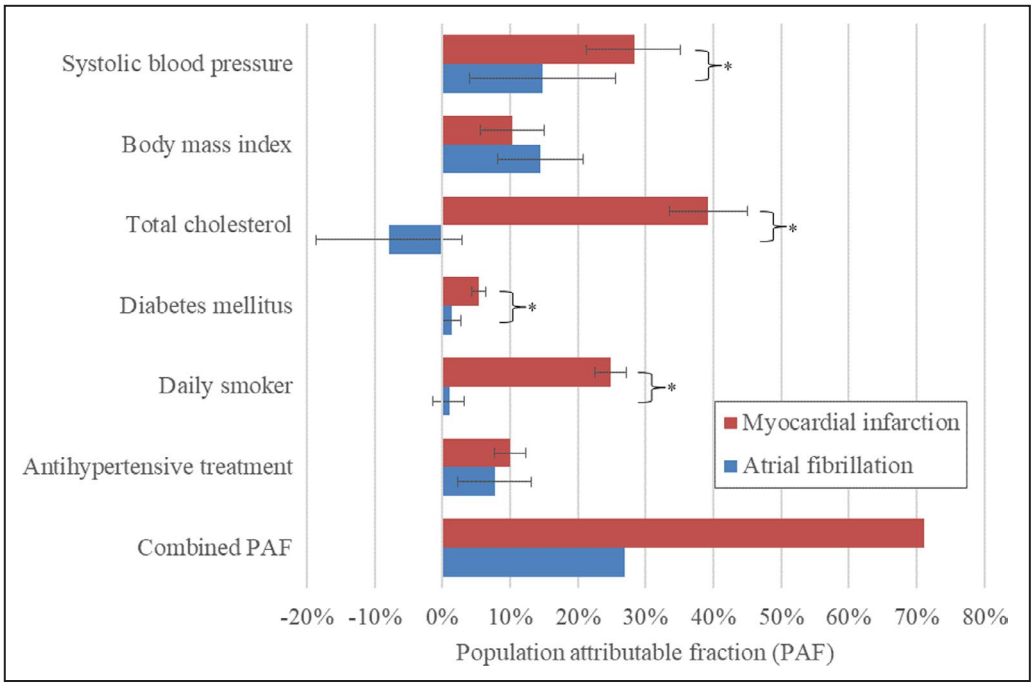

Figure 3. Bar chart showing the population attributable fractions (PAFs) of common cardiovascular risk factors for 5-year incidence of myocardial infarction and atrial fibrillation.
Error bars represent 95% CIs. *P* values and CIs were estimated by bootstrapping with 500 repetitions. *Risk factors with a statistically significant (5% level) difference of the PAF for both diseases.

irrespective of the first event. Furthermore, interim incident AF was associated with an increased risk for subsequent MI and vice versa (Figure 4). MI has previously been shown to increase the risk of incident AF, possibly mediated by atrial ischemia, systemic inflammation caused by MI, and subsequent heart failure attributed to wall motion abnormalities.[1,2,6] Prior studies demonstrated that worse Killip class and left ventricular ejection fraction, but not ST-segment–elevation MI, were associated with incident AF in patients with acute MI.[7,17] AF, on the other hand, might also induce MI, in particular non–ST-segment–elevation MI as a result of an irregular and excessive ventricular response (tachyarrhythmia) with a subsequent oxygen

Table 3. Multivariable-Adjusted HRs for Subsequent Disease Onset of Atrial Fibrillation and Myocardial Infarction for All-Cause Mortality

	Incident index event			
Variables	Atrial fibrillation (n=2232), HR (95% CI)	*P* value	Myocardial infarction (n=2871), HR (95% CI)	*P* value
Subsequent myocardial infarction	1.68 (1.03–2.74)	0.04	…	…
Subsequent atrial fibrillation	…	…	1.75 (1.31–2.34)	<0.01
Age, per 5 y increase	1.55 (1.47–1.64)	<0.01	1.33 (1.28–1.39)	<0.01
Sex (men)	1.69 (1.39–2.06)	<0.01	1.24 (1.06–1.45)	<0.01
Systolic blood pressure, per 10 mm Hg increase	1.04 (0.99–1.08)	0.09	1.07 (1.03–1.10)	<0.01
Body mass index, per 5 kg/m² increase	0.77 (0.69–0.86)	<0.01	0.96 (0.87–1.04)	0.31
Total cholesterol, per 1 mmol/L increase	1.10 (1.03–1.17)	<0.01	1.03 (0.98–1.08)	0.25
Diabetes	1.54 (1.13–2.10)	<0.01	1.81 (1.48–2.23)	<0.01
Daily smoker	1.67 (1.35–2.06)	<0.01	1.38 (1.18–1.62)	<0.01
Antihypertensive treatment	1.06 (0.85–1.32)	0.62	1.28 (1.08–1.51)	<0.01
Prevalent stroke	1.65 (1.20–2.26)	<0.01	1.28 (0.93–1.76)	0.12

In individuals with an index diagnosis of myocardial infarction, 811 died during follow-up; in individuals with an index diagnosis of atrial fibrillation, 503 died. Time since the index event is used as the time scale in both analyses, with subsequent myocardial infarction and atrial fibrillation treated as time-dependent covariates. Analyses were additionally adjusted for cohorts. HR indicates hazard ratio.

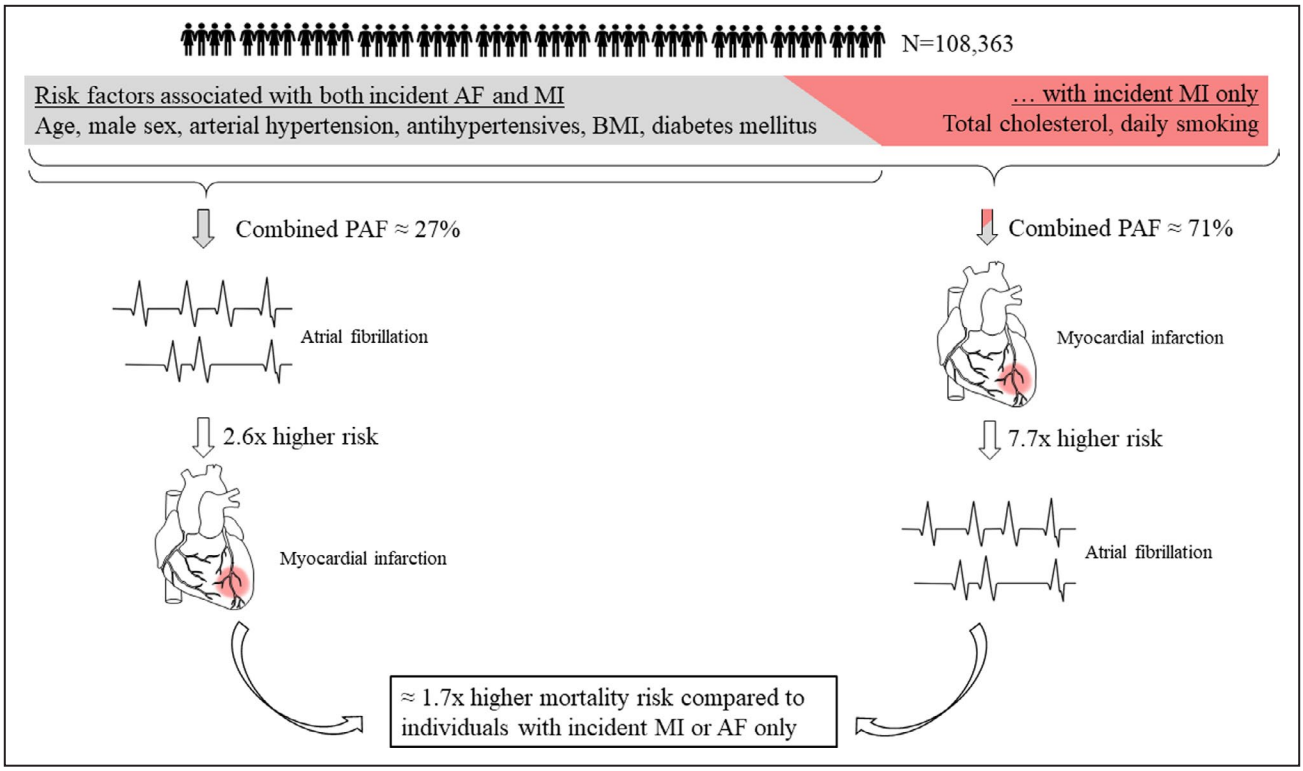

Figure 4. Common cardiovascular risk factors show different associations with incident AF and MI, their subsequent onset, and death.
AF indicates atrial fibrillation; BMI, body mass index; MI, myocardial infarction; and PAF, population attributable fraction.

supply–demand mismatch.[3,6] Another probably rather rare mechanism is embolic occlusion of a coronary artery attributed to thromboembolism caused by AF.[18] Considering these potentially underlying mechanisms for subsequent disease onset, downstream diagnosis of the respective other disease might also be an indicator of disease progression of the primary condition. Whereas a meta-analysis confirmed the negative prognostic impact of AF in individuals with MI,[8] reports from disease cohorts on the prognostic impact of AF according to the timing of disease onset in individuals with MI have yielded inconclusive results.[19,20] The prognostic impact of subsequent MI after AF seemed to vary in our study depending on the time that elapsed between the diagnoses of both diseases. However, these results should be interpreted with caution because the number of incident cases beyond the first 2 years of follow-up after incident disease was comparatively small, resulting in a rather wide CI.

Limitations and Strengths

We excluded 16 534 individuals because of missing information on covariates or follow-up variables. This, together with nonparticipation to the baseline surveys, may have introduced selection bias. Because follow-up was mainly based on linkage to hospital discharge registry data, some cases of incident AF might have been missed because AF does not necessarily require hospital treatment. Furthermore, because of the often paroxysmal and asymptomatic nature of AF, some cases of AF might have misclassified. However, underascertainment of AF would more likely underestimate the true association of incident AF with mortality. Nevertheless, we observed a significant impact of AF on overall mortality. Information about the medical treatment after the diagnosis of AF or MI was not available in this study, which might have affected the results given the comparatively long study period and the considerable change in treatment strategies for both diseases in recent decades. Furthermore, we did not have any information on the severity of MI (eg, Killip class, ST-segment–elevation versus non–ST-segment–elevation MI). Therefore, as usual in community-based studies, residual confounding is likely. Finally, because of the observational nature of the current study, no conclusions can be drawn regarding a causal relationship between AF, MI, and mortality. Strengths of our study are the unique study sample with harmonized long-term follow-up for both cardiovascular diseases and mortality that permits strong insights into the temporal relationship of AF and MI.

CONCLUSIONS

Subsequent diagnoses of incident MI and AF were associated with a significant increase in mortality across

European cohorts, irrespective of the first event. Associations of common cardiovascular risk factors varied for MI and AF, indicating distinct pathophysiological pathways in disease development requiring specific prevention strategies. Our results further emphasize the importance of risk factor management considering that all investigated cardiovascular risk factors were associated with subsequent diagnoses of both diseases.

ARTICLE INFORMATION

Received October 10, 2021; accepted February 16, 2022.

Affiliations

Department of Cardiology, University Heart & Vascular Center Hamburg, University Medical Center Hamburg-Eppendorf, Hamburg, Germany (S.C., D.C., B.G., C.S.B., F.M.O., T.Z., S.B., R.B.S.); German Center for Cardiovascular Research (DZHK), Partner Site Hamburg/Kiel/Luebeck, Hamburg, Germany (S.C., C.S.B., T.Z., S.B., R.B.S.); Finnish Institute for Health and Welfare, Helsinki, Finland (T.N., E.V., J.K., K.K., V.S.); Department of Medicine, Turku University Hospital and University of Turku, Turku, Finland (T.N.); Research Center in Epidemiology and Preventive Medicine, Department of Medicine and Surgery, University of Insubria, Varese, Italy (F.G., L.I.); Mediterranea Cardiocentro, Napoli, Italy (F.G.); Center for Clinical Research and Prevention, Bispebjerg and Frederiksberg Hospital, The Capital Region of Denmark, Copenhagen, Denmark (J.K.V., T.J., A.L.); Department of Cardiology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark (J.K.V.); Department of Epidemiology and Prevention, Istituto Neurologico Mediterraneo è un Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Neuromed, Pozzilli, Italy (S.C., M.B.D., G.d.G., L.I.); Department of Public Health and Clinical Medicine, and Heart Centre, Umeå University, Umeå, Sweden (S.S., S.J.); Department of Community Medicine (M.L.); and Brain and Circulation Research Group, Department of Clinical Medicine (E.B.M.), UiT The Arctic University of Norway, Tromsø, Norway; Department of Neurology, University Hospital of North Norway, Tromsø, Norway (E.B.M.); German Heart Center Munich, Technical University of Munich, Munich, Germany (W.K.); German Centre for Cardiovascular Research (DZHK), Partner Site Munich Heart Alliance, Munich, Germany (W.K.); Institute of Epidemiology and Medical Biometry, University of Ulm, Germany (W.K.); Centre for Public Health, Queens University of Belfast, Belfast, UK (F.K.); Department of Public Health, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark (T.J.); Cardiovascular Epidemiology Unit, Institute of Cardiovascular Research, University of Dundee, Dundee, UK (H.T.); and Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark (A.L.).

Acknowledgments

We thank the participants and staff of the cohorts for their continuing dedication and efforts.

Sources of Funding

The MORGAM (Monica Risk, Genetics, Archiving and Monograph) project has received funding from European Union (EU) projects MORGAM (Biomed, BMH4-CT98-3183), GenomEUtwin (FP5, QLG2-CT-2002-01254), ENGAGE (FP7, HEALTH-F4-2007-201413), CHANCES (FP7, HEALTH-F3-2010-242244), BiomarCaRE (Biomarker for Cardiovascular Risk Assessment Across Europe; FP7, HEALTH-F2-2011-278913), euCanSHare (Horizon 2020, No. 825903), and AFFECT-EU (Horizon 2020; 847770) and Medical Research Council, London (G0601463; 80983: Biomarkers in the MORGAM Populations). This has supported central coordination, workshops, and part of the activities of the MORGAM Data Centre, the MORGAM Laboratories, and the MORGAM Participating Centres. Dr Schnabel has received funding from the European Research Council under the European Union's Horizon 2020 research and innovation program (648131), from the European Union's Horizon 2020 research and innovation program under the Grant Agreement No. 847770 (AFFECT-EU) and German Center for Cardiovascular Research (DZHK e.V.; 81Z1710103), German Ministry of Research and Education (BMBF 01ZX1408A), and ERACoSysMed3 (031L0239). The FINRISK surveys were mainly supported by budgetary funds of THL with additional funding from numerous nonprofit foundations. Dr Salomaa has been supported by the Finnish Foundation for Cardiovascular Research and the Academy of Finland (139635). Dr Niiranen has been supported by the Finnish Foundation for Cardiovascular Research, the Finnish Medical Foundation, the Emil Aaltonen Foundation, and the Academy of Finland (321351). The DANMONICA cohorts at the Research Center for Prevention and Health (currently named Centre for Clinical Research and Prevention) were established during a period of 10 years and have been funded by numerous sources that have been acknowledged, where appropriate, in the original articles. The Moli-sani Project was partially supported by research grants from the Pfizer Foundation (Rome, Italy), the Italian Ministry of University and Research (MIUR, Rome, Italy)–Programma Triennale di Ricerca, Decreto No. 1588 and Instrumentation Laboratory, Milan, Italy. The Northern Sweden MONICA project was supported by Norrbotten and Västerbotten County Councils. Dr Söderberg has been supported by the Swedish Heart–Lung Foundation (20140799, 20120631, 20100635), the County Council of Västerbotten (ALF, VLL-548791), and Umeå University. The SHHEC (Scottish Heart Health Extended Cohort) received funding from the Scottish Health Department Chief Scientist Organization, the British Heart Foundation, and the FP Fleming Trust. The Tromsø Study was supported by the UiT Arctic University of Norway, the municipality of Tromsø, the Norwegian Research Council, and the National Health Screening Service.

Disclosures

Dr Koenig reports consulting fees from AstraZeneca, Novartis, Pfizer, The Medicines Company, DalCor, Kowa, Amgen, Corvidia, Daiichi-Sankyo, Berlin-Chemie, Genentech, OMEICOS, Esperion, Sanofi, Novo Nordisk, and Bristol-Myers Squibb and grants and nonfinancial support from Abbott, Roche Diagnostics, Beckmann and Singulex outside this work. Dr Salomaa has received honoraria for consulting from Novo Nordisk and Sanofi. He also has ongoing research collaboration with Bayer Ltd (all outside this work). Dr Söderberg has received honoraria for lecturing and advisory board from Actelion Ltd. Dr Costanzo has received honoraria for lecturing from The Dutch Beer Institute Foundation–The Brewers of Europe, outside the submitted work. Dr Schnabel has received lecture fees and advisory board fees from Bristol Myers Squibb/Pfizer outside this work. Dr Løchen has received lecture fees from Bristol Myers Squibb/Pfizer and Sanofi outside this work. The remaining authors have no disclosures to report.

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SUPPLEMENTAL MATERIAL

Supplemental Methods

Data S1.

Cohort descriptions

DAN-MONICA[21]

The DAN-MONICA study from the Research Center for Prevention and Health in Glostrup consists of three prospective cohorts with individuals randomly selected from eleven municipalities from the western part of the suburbs of Copenhagen, Denmark. Random sampling was based on the national population register, stratified by sex and year of birth. Cohort 1 (N=4,052; baseline survey 1982-1984) and 3 (N=1,504; 1991-1992) included inhabitants from 30 to 70 years, whereas age range for cohort 2 (N=1,624; 1986-1987) was set at 30 to 60 years. Follow-up was based on linkage to the Civil Registration System, the National Hospital Discharge Register and to the National Cause of Death Register using a unique personal identification number. At the present time, follow-up has been extended up to December 31st 2010.

https://www.thl.fi/publications/morgam/cohorts/full/denmark/den-gloa.htm

FINRISK[22]

The FINRISK study is a large Finnish population-based survey on cardiovascular risk factors carried out every five years since 1972 by the National Public Health Institute in Helsinki, including individuals from up to six regions in eastern and south-western Finland. The cohorts were formed by random sampling based on the Nationwide Central Population Register, stratified by sex and 10-years age group. Baseline examinations were conducted in 1982 for cohort 1 (N=9,029), in 1987 for cohort 2 (N=5,811), in 1992 for cohort 3 (N=5,999), in 1997 for cohort 4 (N=8,444), and in 2002 for cohort 5 (N=9,291), respectively. Follow-up was achieved through linkage to the National Register of Cause of Death, the National Hospital Discharge Register and the National Drug Reimbursement Register. Follow-up for the cohort is completed up to December 31st 2010.

https://www.thl.fi/publications/morgam/cohorts/full/finland/fin-fina.htm

Moli-sani study[23, 24]

The cohort of the Moli-sani study was recruited from residents of the Molise region in Italy by multistage sampling based on the city-hall registries. First, townships were sampled in two

major areas by cluster sampling; then, within each township, individuals aged 35 years or older were selected by simple random sampling. Pregnancy at the time of recruitment, current polytrauma or coma, lack of understanding or refusal to sign the informed consent were exclusion criteria. Baseline examinations and questionnaires were administered by trained staff. Overall, 24,325 individuals were included from 2005 to 2010. Median follow-up for the total cohort was 4.2 years (with a maximum of 6.5 years) from the baseline examination until death or December 31st 2011 for those individuals who remained alive. Follow-up was achieved by record linkage to national mortality registers and hospital discharge registers.

https://moli-sani.org

Northern Sweden MONICA project[25, 26]

The Northern Sweden MONICA project consists of population-based surveys of individuals from the counties of Västerbotten and Norrbotten carried out every five years since 1986. Individuals were randomly selected from population registers, stratified for 10-years age group (with age range from 25 to 64 years in 1986 and 1990, and 25 to 74 years since 1994) and sex.

For every survey 250 men and 250 women were selected in each age group, totalling in 2,000 individuals for the first two surveys and 2,500 individuals from 1994 on, respectively. The participants of the 1986, 1990, and 1994 surveys were re-examined in 1999. Follow-up was achieved through linkage with the national death register and the National registers at the National Board of Health and Welfare (Cause of Death Register, Inpatient Diagnosis Register, Cancer Register, and Medication Register) as well as the MONICA stroke event and myocardial infarction registers, with endpoint diagnosis based on MORGAM criteria. Follow-up is completed until December 31st 2011.

https://www.thl.fi/publications/morgam/cohorts/full/sweden/swe-nswa.htm

https://snd.gu.se/en/catalogue/study/ext0042

Scottish Heart Health Extended Cohort (SHHEC)[27]

The Scottish Heart Health Extended Cohort consists of two overlapping studies which share a common protocol and methods: the Scottish Heart Health Study randomly recruited men and women aged 40-59 across 22 Scottish districts in 1984-1987; Scottish MONICA similarly recruited men and women aged 25-64 in Edinburgh and North Glasgow in 1986, and in North Glasgow again in 1989, 1992 (age range 25-74 years), and in 1995 as part of the WHO MONICA Project [27]. The cohorts comprise respondents of representative sample surveys of

the respective area. As the first sampling stage, a random sample of general practitioners was selected based on a list of all general practitioners as the sampling frame. In the second stage, the lists of persons registered with the selected general practitioners were used as sampling frames. From each of these lists a sample of size proportional to the number of persons within the target age and sex groups in the list was selected. The second stage sampling was stratified by sex and 10-year age group. Follow-up was achieved by record linkage and extends through 2009. Of the original 18,107 individuals, complete data on 16,000 were transferred to Helsinki in 2000 for the MORGAM collaboration and available serum and plasma to the biomarker laboratory in Mainz/ Hamburg some years later, first for use in the MORGAM biomarker study and then for the Biomarker for Cardiovascular Risk Assessment across Europe (BiomarCaRE) project. A more detailed cohort description has been published elsewhere [28]. https://www.thl.fi/publications/morgam/cohorts/full/uk/unk-sco.htm

The Tromsø Study [29]

The Tromsø Study is a prospective population-based health study carried out in the region of Northern Norway with overall seven surveys taking place from 1974 to 2016. Residents of specific age groups were invited to each survey based on the official population registry of the municipality of Tromsø, enabling the gathering of information on the change of prevalent diseases and risk factors in many individuals over time. The third and the fourth Tromsø surveys, conducted in 1986/87 and 1994/95, participated in the current study. For the third survey men aged 20-61 years, women aged 20-56 years, a randomly selected 10% sample from the 12-19 years age group as well as a subsample, who were included in a family intervention study, were invited, whereas for the fourth and largest survey all resident of Tromsø aged 25 or elder were asked to participate. Analysis of the current study included all individuals of the third survey aged 20-59 years, and all individuals from the fourth survey who were not included from the third survey.

Follow-up for incident events was achieved by linkage to the discharge diagnosis registry at the University Hospital of North Norway, the only hospital in the region of Tromsø, and to the National Causes of Death Registry. Adjudication of all incident events was conducted. Follow-up is completed up to December 31st 2010.

https://thl.fi/morgam/a/publications/cohorts/full/norway/nor-tro.htm

http://tromsoundersokelsen.uit.no/tromso/

Data S2.

Detailed outcome classification

Incident atrial fibrillation was defined as atrial fibrillation of any kind or duration. Self-reported diagnosis as the only information source was considered insufficient during follow-up. Clinical and death certificate diagnosis were scanned and the relevant ICD codes were 427.4 for ICD-8, 427.3 for ICD-9 and I48 for ICD-10, respectively. These codes comprise atrial fibrillation as well as atrial flutter, so that some cases classified as atrial fibrillation in this study might have actually been considered as atrial flutter.

Incident myocardial infarction was defined as first definite or possible fatal or non-fatal acute coronary event with or without cardiac revascularization according to MORGAM criteria[30], excluding individuals with unstable angina pectoris in the cohort, in which angina pectoris could be reasonably separated from possible myocardial infarction (using cardiac troponin measurements).

The follow-up procedure for the assessment and validation of incident coronary events varied between the included cohorts.

In DAN-MONICA follow-up was achieved trough linkage to the National Hospital Discharge Register (ICD codes 410 and 411 for ICD-8 and I21 and I22 for ICD-10, respectively) and the Causes of Death Register (ICD codes 410-414 for ICD-8 and I20-I25 for ICD-10, respectively).

In FINRISK events found in the FINMONICA or FINAMI register, two different diagnostic procedures were used. For events up to year 1996, the MONICA diagnostic category was used.

For an event to be classified as definite myocardial infarction according to MONICA criteria there had to be

- definite signs of myocardial infarction on electrocardiogram (ECG) or
- symptoms typical or atypical or inadequately described, together with probable ECG and abnormal enzymes, or
- symptoms typical and abnormal enzymes with ischaemic or non-codable ECG or ECG not available, or
- naked-eye appearance of fresh myocardial infarction and/or recent coronary occlusion found at necropsy in fatal cases.

Events were considered as a possible myocardial infarction if criteria for definite myocardial infarction were not met, but

- the patient presented with typical symptoms without good evidence for another cause for the attack or
- the case was fatal without good evidence for another cause of death (clinically or at autopsy).

For events from 1997 up to 2002, the AHA/WHF/ESC/CDC/NHLBI definition from year 2003 was used [31]. For events found in the Hospital Discharge Register or the Register of Causes of Death but not in the FINMONICA or FINAMI register, and for all events after year 2002, the diagnostic classification was done using the relevant ICD-codes. For events found in the hospital discharge codes these were 410 for ICD-8/9 and 21 and I22 for ICD-10, respectively. For events identified through the Register of Causes of Death the relevant ICD codes were 410-414 for ICD-8/9 and I21-25 for ICD-10.

Coronary events occurring within 28 days of each other were considered as one event. For events found both in the Hospital Discharge register and the Register of Causes of Death, a coronary event diagnosis was given if it was found in either of them.

In the Moli-sani study potential coronary events were selected for further validation if death certificates presented one of the following as the underlying cause of death:

- ischemic heart disease (ICD-9 codes 410-414)
- sudden death (ICD-9 code 798 and 799)
- diabetes as the underlying cause of death (ICD-9 code 250) or arterial hypertension (ICD-9 codes 401-405) or other form of heart disease (ICD-codes 420-429), associated with ischemic heart disease (ICD-9 codes 410-414) as a secondary cause of death.

Furthermore, events were selected for further evaluation if hospital discharge records revealed a hospitalization with ICD-9 code 410-414.

For all cases selected for further validation, the clinical records were searched and if clinical documentation was found, the event was validated using the procedure of the AHA, WHF, ESC, CDC and NHLBI definition for epidemiology and clinical research studies [31]. If clinical documentation for a fatal event was not available, general practitioners were asked for information and on the basis of their patient description the diagnostic category was assigned.

The Northern Sweden MONICA project used the MONICA criteria (see above) to identify definite and possible myocardial infarctions through linkage to the myocardial infarction register. The cohort was further linked to the National Cause of Death Register, the National Inpatient Diagnosis Register and the Local Diagnosis Registers. For events not found in the myocardial infarction register and for non-fatal events found in the myocardial infarction

register with diagnostic category "possible MI", the MORGAM diagnostic category was derived using the corresponding ICD-codes. For an inpatient diagnosis these were 41000, 41007, and 41099 for ICD-8-SV, 410 and 411A for ICD-9-SV and I21-23 for ICD-10-SE, respectively. The relevant ICD-codes in the National Cause of Death Register were 410 and 412-4, 41007 for ICD-8-SV and ICD-9-SV and I21-25 for ICD-10-SE.

The Scottish Heart Health Extended Cohort used the combination of diagnostic codes found in the Scottish Record Linkage System or the NHS Central Register to assess incident acute coronary events and other coronary diagnoses. The relevant ICD-codes for incident definite or possible myocardial infarction were 410 for ICD-9 and I21-23 for ICD-10, respectively. If information from the official underlying or other death certificates were used, a coding of 410-414 for ICD-9 and I20-25 for ICD-10 were considered as incident myocardial infarction events.

In the Tromsø Study adjudication of hospitalized and out-of-hospital first-ever myocardial infarction was performed by an endpoint committee consisting of experienced physicians. Medical records have been validated for all persons with a relevant cardiovascular discharge diagnosis from the hospital (including visits in out-patient clinics) and/or from the national Causes of Death Registry. For out of hospital deaths, records from pre-hospital care (ambulance service, general practitioners, nursing homes) and/or death certificate were searched for diagnostic criteria (clinical presentation, diagnostic procedures, laboratory tests, and/or autopsy). To be accepted as definite myocardial infarction in the Tromsø Study one of the following had to be present:

- typical, atypical or inadequately described symptoms + a definite new infarction in ECG recordings.
- Typical symptoms + significantly higher myocardial enzyme and/or troponin levels.
- Atypical or inadequately described symptoms + significantly higher myocardial enzyme and/or troponin levels + a probable new infarction in ECG recordings.

To be accepted as probable myocardial infarction one of the following sets of conditions was required:

- Typical, atypical, or inadequately described symptoms + a probable new infarction in ECG recordings + moderately increased myocardial enzyme and/or troponin levels.
- Typical symptoms + moderately higher myocardial enzyme and/or troponin levels.
- Atypical or inadequately described symptoms + significantly higher myocardial enzyme and/or troponin levels.

- Fatal events with insufficient evidence for definite MI but a diagnosis of death due to coronary disease on the death certificate.
- Fatal events with a diagnosis of sudden death (ICD 7:795, ICD 8: 795-796, ICD 9: 798-799, ICD 10: I46, R96, R98, R99) on the death certificate with evidence of a history of coronary heart disease or where there is no good evidence for another cause of death and no concomitant diagnosis of cancer, chronic obstructive pulmonary disease, chronic alcoholism, alcohol-related liver disease and/or acute pneumonia.

Furthermore, fatal events with a diagnosis of sudden death (please see above) when no information other than a diagnosis from the Causes of Death Registry was available were also accepted as cases of incident myocardial infarction in the Tromsø Study.

Overall mortality was defined as mortality due to any cause during the follow-up time.

Further details of the follow-up and diagnostic procedures of each participating study have been published elsewhere [32].

Data S3.

Supplementary statistical methods

As outlined in the main manuscript the statistical significance of all possible second-order interactions and quadratic terms of the variables in the model was assessed and an interaction was included as additional covariate if its Bonferroni-corrected p-value was smaller than 0.05 in order to avoid non-linearity in all multivariable Cox proportional hazards models. The number of tests for these Bonferroni corrections was taken each time as the total number of estimable interactions plus the total number of estimable quadratic terms. Interactions with time since baseline were added when needed to avoid violations of the proportional hazard assumption, which were identified using the R function cox.zph with parameter "global" set to false. When included in an interaction, continuous variables were centered on their overall mean. In the analyses were hazard ratios for AF and MI were compared, the interactions and quadratic terms added to the AF model were also added to the MI model and vice versa. After the addition of the interactions with time, a few further changes were implemented:

(i) The interaction of MI and time since MI was added to the model with outcome AF and the interaction of AF and time since AF was added to the model with outcome MI.

(ii) All possible age interactions and the quadratic age term were tested and included in the model when the Bonferroni-corrected p-value was smaller than 0.05. The number of tests

in this Bonferroni-correction was the number of estimable age interactions plus one (to account for the quadratic age term).

(iii) In a final step, it was again assured that all interactions in the model with AF as the outcome were also present in the model with MI as the outcome. Interactions which became non-significant ($p \geq 0.05$) in both models were removed from both models.

Table S1. Characteristics of the study population by cohort.

Cohort	DANMONICA	FINRISK	Moli-sani	TROMSØ	NORTHERN SWEDEN	SHHEC
General characteristics	N=7167	N=33,420	N=16,136	N=26,364	N=10,121	N=15,155
Years of baseline examinations	1982-1992	1982-2002	2005-2010	1986-1995	1986-2009	1984-1995
Age at baseline, years	50.0 (20.2)	45.1 (21.6)	53.6 (17.5)	37.3 (18.6)	47.9 (21.8)	49.4 (12.7)
Men, No. (%)	3540 (49.4)	15874 (47.5)	7556 (46.8)	12857 (48.8)	4903 (48.4)	7520 (49.6)
Cardiovascular characteristics						
Systolic blood pressure, mmHg	121 (23)	134 (26)	137 (27)	130 (22)	126 (26)	129 (26)
Body mass index, kg/m²	24.4 (5.0)	25.8 (5.6)	27.5 (6.1)	23.8 (4.4)	26.2 (5.9)	25.3 (5.0)
Total cholesterol, mmol/L	5.7 (1.5)	5.6 (1.5)	5.5 (1.5)	5.6 (1.8)	5.8 (1.7)	6.2 (1.6)
Diabetes mellitus, No. (%)	155 (2.2)	1423 (4.3)	957 (5.9)	329 (1.2)	329 (3.3)	229 (1.5)
Daily smoker, No. (%)	3198 (44.6)	8268 (24.7)	3311 (20.5)	10585 (40.1)	1875 (18.5)	5815 (38.4)
Antihypertensive treatment, No. (%)	481 (6.7)	3919 (11.7)	4371 (27.1)	1111 (4.2)	1181 (11.7)	1000 (6.6)
Prevalent stroke, No. (%)	72 (1.0)	476 (1.4)	97 (0.6)	258 (1.0)	163 (1.6)	116 (0.8)
Endpoints during follow-up						
Atrial fibrillation, No. (%)	249 (3.5)	550 (1.6)	185 (1.1)	849 (3.2)	384 (3.8)	196 (1.3)
Myocardial infarction, No. (%)	405 (5.7)	1062 (3.2)	91 (0.6)	1329 (5.0)	487 (4.8)	675 (4.5)
Death, No. (%)	1043 (14.6)	1721 (5.1)	245 (1.5)	2059 (7.8)	728 (7.2)	1137 (7.5)

Characteristics of the six cohorts are presented as absolute and relative frequencies for categorical variables, and medians and interquartile range for continuous variables.

Table S2. Secular trends in the association of cardiovascular risk factors with incident myocardial infarction and atrial fibrillation and the risk of sequential disease diagnosis

Variable	Atrial fibrillation HR (95% CI)	Myocardial infarction HR (95% CI)
Age, per 5 years increase	1.00 (1.00 - 1.00)	0.99 (0.99 - 0.99)
Male sex	0.99 (0.98 - 1.00)	0.94 (0.94 - 0.95)
Systolic blood pressure, per 10 mmHg	1.00 (1.00 - 1.00)	0.99 (0.99 - 0.99)
Body mass index, per 5 kg/m²	1.00 (0.99 - 1.01)	0.98 (0.98 - 0.99)
Total cholesterol, mmol/L	1.00 (0.99 - 1.00)	0.98 (0.98 - 0.99)
Diabetes mellitus	1.01 (0.99 - 1.03)	0.97 (0.95 - 0.98)
Daily smoker	0.98 (0.97 - 0.99)	0.96 (0.95 - 0.96)
Prevalent stroke	0.99 (0.96 - 1.03)	0.96 (0.93 - 0.98)
Antihypertensive treatment	1.00 (0.98 - 1.01)	0.95 (0.94 - 0.96)
Incident myocardial infarction *	0.98 (0.95 - 1.01)	-
Incident atrial fibrillation*	-	0.93 (0.90 - 0.96)

This table shows the impact of the date of baseline examination on the strength of the association of the specific risk factors with incident atrial fibrillation or myocardial infarction (per 1 year increase). * For incident myocardial infarction/atrial fibrillation the table shows the relative risk for the subsequent diagnosis of the respective other disease over time (per 1 year increase).

Table S3. Multivariable adjusted hazard ratio for overall mortality after incident atrial fibrillation

Variables	Hazard ratio (95% CI)	p-value
Subsequent myocardial infarction	-	-
… overall*	1.68 (1.03 - 2.74)	0.04
… within the first 2 years after AF	3.27 (2.26 - 4.74)	<0.01
… 2 to 4 years after AF	1.11 (0.70 - 1.75)	0.66
… 4 to 6 years after AF	1.39 (0.76 - 2.55)	0.29
… 6 to 8 years after AF	2.92 (1.11 - 7.69)	0.03
… 8 to 10 years after AF	0.90 (0.12 - 6.79)	0.92
Age, per 5 years increase	1.55 (1.47 - 1.64)	<0.01
Sex (men)	1.69 (1.39 - 2.06)	<0.01
Systolic blood pressure, per 10 mmHg increase	1.04 (0.99 - 1.08)	0.09
Body mass index, per 5 kg/m² increase	0.77 (0.69 - 0.86)	<0.01
Total cholesterol, per 1 mmol/L increase	1.10 (1.03 - 1.17)	<0.01
Diabetes mellitus	1.54 (1.13 - 2.10)	<0.01
Daily smoker	1.67 (1.35 - 2.06)	<0.01
Antihypertensive treatment	1.06 (0.85 - 1.32)	0.62
Prevalent stroke	1.65 (1.20 - 2.26)	<0.01

AF, atrial fibrillation; CI, confidence interval; * The reported hazard ratio is the geometric mean of the five hazard ratios:
exp((log(3.27)+log(1.11)+log(1.39)+log(2.92)+log(0.90))/5) = 1.68