Journal of the American Heart Association

ORIGINAL RESEARCH

Compliance in Primary Prevention With Statins and Associations With Cardiovascular Risk and Death in a Low-Risk Population With Type 2 Diabetes Mellitus

Morten Malmborg, MD; Michelle D. S. Schmiegelow, MD, PhD; Thomas Gerds, Dr.rer.nat; Morten Schou, MD, PhD; Caroline Kistorp, MD, PhD; Christian Torp-Pedersen, MD, DMSci; Gunnar Gislason, MD, PhD

BACKGROUND: We examined whether primary prevention with statins and high adherence to statins reduce the associated risk of cardiovascular events or death in a low-risk population with type 2 diabetes mellitus (T2D).

METHODS AND RESULTS: Using Danish nationwide registers, we included patients with new-onset T2D, aged 40 to 89 years, between 2005 and 2011, who were alive 18 months following the T2D diagnosis (index date). In patients who purchased statins within 6 months following T2D diagnosis, we calculated the proportion of days covered (PDC) within 1 year after the initial 6-month period. We studied the combined end point of myocardial infarction, stroke, or all-cause mortality, whichever came first, with Cox regression. Reported were standardized 5-year risk differences for fixed comorbidity distribution according to statin treatment history, stratified by sex and age. Among 77 170 patients, 42 975 (56%) were treated with statins, of whom 31 061 (72%) had a PDC ≥80%. In men aged 70 to 79 years who were treated with statins, the standardized 5-year risk was 22.9% (95% CI, 21.5%–24.3%), whereas the risk was 29.1% (95% CI, 27.4%–30.7%) in men not treated, resulting in a significant risk reduction of 6.2% (95% CI, 4.0%–8.4%), $P<0.0001$. The risk reduction associated with statins increased with advancing age group (women: age 40–49 years, 0.0% [95% CI, –1.0% to 1.0%]; age 80–89 years, 10.8% [95% CI, 7.2%–14.4%]). Standardizing to all patients treated with statins, PDC <80% was associated with increased risk difference (reference PDC ≥80%; PDC <20%, 4.2% [95% CI, 2.9%–5.6%]).

CONCLUSIONS: This study supports the use of statins as primary prevention against cardiovascular diseases or death in 18-month surviving low-risk patients with T2D, with the highest effect in the elderly and adherent patients.

Key Words: cardiovascular disease ■ diabetes mellitus ■ statins

Statins are commonly used in both primary and secondary prevention of cardiovascular disease (CVD) in patients with diabetes mellitus. Prior studies have elucidated the beneficial effect of statin therapy in primary prevention of CVD in patients with diabetes mellitus.[1–4] Although a low proportion had diabetes mellitus, a meta-analysis further observed a CVD rate reduction of almost 40% per 1-mmol/L reduction of low-density lipoprotein (LDL) cholesterol in patients at low CVD risk.[5] Studies exploring the cardiovascular risks associated with treatment with statins in a low-risk population with diabetes mellitus are,

Correspondence to: Morten Malmborg, MD, Danish Heart Foundation, Vognmagergade 7, 1120 Copenhagen K, Denmark. E-mail: mmalmborg@hjerteforeningen.dk

Supplementary Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.120.020395

For Sources of Funding and Disclosures, see page 10.

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

CLINICAL PERSPECTIVE

What Is New?

- In a low-risk, nationwide, contemporary population with type 2 diabetes mellitus, use of statins was associated with a lower 5-year risk of a major adverse cardiovascular events or death in all age groups for men and from age >50 years in women, and the risk reduction increased with advancing age.
- A low adherence of statins was associated with a higher 5-year risk of major adverse cardiovascular events or death.

What Are the Clinical Implications?

- This nationwide study supports the use of statins as primary prevention against major adverse cardiovascular events or death in low-risk patients with type 2 diabetes mellitus, with the highest effect in elderly patients.
- A high adherence of statins was important to maintain this effect.

Nonstandard Abbreviations and Acronyms

PDC	proportion of days covered
T2D	type 2 diabetes mellitus

however, limited. In addition, there are discrepancies between European[6] and American[7,8] guidelines on the use of LDL levels to guide primary prevention treatment of dyslipidemia in patients with diabetes mellitus. Generally, suboptimal adherence to primary prevention therapies of CVD may contribute significantly to increased risk of CVD and death,[9] but whether high levels of adherence to primary prevention therapy with statins are associated with reduced risk of CVD or death in patients with diabetes mellitus is unknown. Last, emerging evidence for the potential benefits of statins in elderly people remains limited and to date only examined in relative rather than absolute terms, which limits the understanding of the size of the statin treatment effect.

The aims of this study were, therefore, first to investigate whether statins are associated with reduced 5-year risks of myocardial infarction, ischemic stroke, or all-cause death by sex and age groups in individuals with short type 2 diabetes mellitus (T2D) duration and without prior CVD, chronic kidney failure, or cancer, and second, to investigate the associations between adherence levels to statins and 5-year risk of the composite outcome.

METHODS

Data obtained through the nationwide registers in Denmark can be made available only through research on Danish servers hosted in highly protected research environments where researchers can be granted access and permission with encrypted person identification. Access to raw data can be gained only through collaboration with the authors or other Danish institutions that already have been granted access. Please contact the first author with any questions on data access.

Data Sources

All residents in Denmark receive a unique and permanent civil registration number at birth or immigration that enables individual-level linkage between nationwide registries. We obtained data from the following: (1) the Danish Civil Registration System registry (sex, date of birth, immigration, emigration, and vital status), (2) the Danish National Patient Registry (discharge diagnoses coded according to the *International Classification of Diseases, Eighth Revision* [*ICD-8*] since 1977, and *International Classification of Diseases, Tenth Revision* [*ICD-10*] system since 1994), (3) the Danish National Prescription Registry (all prescriptions claimed since 1995 according to the Anatomical Therapeutic Classification, including date of dispensing, strength, and quantity), and (4) the Danish National Causes of Death Registry (date of death as well as assumed primary and contributing causes of death from death certificates). All registries have been validated previously.[10–13]

Population

The index date was defined as 18 months following the diagnosis of T2D (Figure S1). The study population comprised all individuals in Denmark with incident T2D at age 40 to 89 years between January 1, 2005, and December 31, 2011, who were alive at the index date. Incident T2D was defined as either initiation of treatment with an antidiabetic medication (Anatomical Therapeutic Classification=A10; positive predictive value, 95%; sensitivity, 72%[14]) or discharge diagnosis of T2D (*ICD-10* code E11; positive predictive value, 97%; sensitivity, 64%[14]), whichever came first. We excluded individuals with assumed type 1 diabetes mellitus (monotherapy of insulin [Anatomical Therapeutic Classification code A10A] before the age of 30 years) as well as patients with a diagnosis of coronary artery disease, heart failure, ischemic stroke, peripheral arterial disease, and chronic kidney failure before index, and further excluded patients who were diagnosed with any cancer 6.5 years before index or emigrated before the index date (diagnosis codes in

Table S1). Antidiabetic drug dispensations that were prescribed for possible polycystic ovary syndrome or gestational diabetes mellitus were excluded, as done previously.[15]

Exposure

The method used to determine the dose and treatment duration is shown in Data S1 and has been described previously.[16] Individuals were considered treated with statins, if they were covered at diagnosis of T2D or initiated treatment within the first 6 months (365.25 days/2) following T2D diagnosis. Among individuals who were treated, we used consecutive claimed prescriptions to calculate the drug adherence level as proportion of days covered (PDC), which was calculated as days exposed to statins within 1 year before index (PDC=days covered/365.25).

Comorbidities

Comorbidities (atrial fibrillation and chronic obstructive pulmonary disease) and medications (antidiabetic agents, antihypertensive agents, lipid-lowering drugs, and anticoagulant drugs) at index were identified based on *ICD-8* and *ICD-10* codes and Anatomical Therapeutic Classification codes (Table S1). Medications were defined as dispensed prescriptions within 180 days before the index date.

Outcomes

The primary outcome was the composite of first myocardial infarction, first ischemic stroke, or all-cause death (*ICD-10* codes in Table S1), whichever came first. The diagnoses for myocardial infarction and ischemic stroke have been validated in Danish registers with high positive predictive values (ie, 97% for myocardial infarction and 97% for ischemic stroke).[17,18] The definition of ischemic stroke included diagnoses of ischemic stroke and unspecified stroke, as most unspecified strokes have been observed to be of ischemic origin.[18]

Statistical Analysis

All individuals were followed up from the index date until the primary event, emigration, or 5 years following the index date, whichever came first.

We present population characteristics at the index date as medians with 25th and 75th percentiles for continuous variables, and as counts with percentages for categorical variables. We calculated the probability of initiating treatment within the first 6-month period by sex and age at time of T2D diagnosis (age, 40–49, 50–59, 60–69, 70–79, and 80–89 years). The main analyses were based on a multiple Cox regression model for the hazard rate of the composite outcome in subgroups defined by sex and age. The model was adjusted for comorbidities and use of comedications at the index date (Table S2). On the basis of the Cox regression analyses, we computed the standardized 5-year risks of the composite outcome according to possible drug adherence levels (ie, untreated, PDC levels <20%, 20%–40%, 40%–60%, 60%–80%, or ≥80%), keeping the observed values of the other patient characteristics. We reported average treatment effects as differences of the crude and standardized 5-year risk. We set the significance level at 5%.

In sensitivity analyses, we used multivariable Cox model with the same set of exposure variables for the rate of "any hospital discharge due to a skin lesion" (*ICD-10* codes S00–99). We further moved the index date further away from the date of first T2D diagnosis and repeated all analyses at landmark times set 30, 42, 54, 66, and 78 months following T2D diagnosis. Last, we used a nested case-control design with 10 age- and sex-matched controls from the risk set of each case to fit a Cox regression model with time-dependent exposure and time-dependent covariates and baseline hazard function stratified for age and sex (Table S2).[19,20] The current statin exposure was defined in an 18-month long exposure window before case date, and the comorbidities and comedication were evaluated before the exposure window (Figure S1). Population characteristics at the index date, including comorbidities, medications, as well as coverage and PDC level during the 18 months before the case date, were registered (Tables S1 and S3).

All statistical analyses were conducted using R, version 3.6.1.[21]

Ethical Approval

Retrospective register studies do not need ethical approval in Denmark. The Danish Data Protection Agency has approved the project (approval number P-2019-393).

RESULTS

We included 88 175 individuals with incident T2D between January 1, 2005, and December 31, 2011, and following exclusion of another 11 005 individuals during the 18-month period following T2D diagnosis (23% attributable to death); the final population comprised 77 170 patients (Figure S2). During our study period, 10 209 patients (13.2%) had a first-time myocardial infarction, had a first ischemic stroke, or died. Compared with patients not treated, patients treated with statins as well as treated patients with a high adherence level (PDC ≥80%) compared with lower PDC levels were slightly older, were more frequently ethnically Danish, had lower level of education, and generally claimed prescriptions for antidiabetic agents (except insulin), antihypertensive agents, and anticoagulants more frequently (Table).

Initiation of Medication, Coverage, and Adherence Level

During the 6 months following T2D diagnosis, the proportion of individuals initiating treatment of statins increased rapidly during the first few days after T2D diagnosis and subsequently stabilized, leaving 56% treated with statins following 6 months (Figure 1). Overall, a higher proportion of women (except those aged 40–49 years; Figure 1 and Figure S3) and a higher proportion of patients aged 50 to 79 years initiated treatment with statins. In patients who initiated treatment with statins, most had a high adherence level (PDC ≥80%: 72%; Table and Figure 2), and the adherence level of statins between men and women was largely similar (Figure S3).

The 5-Year Risks According to Coverage and Adherence Level

Use of statins was associated with a significantly lower standardized 5-year risk of the composite outcome of myocardial infarction, ischemic stroke, and all-cause mortality in all age groups for men and from age >50 years in women (ie, men aged 70–79 years: treated, 22.9% [95% CI, 21.5%–24.3%]; not treated, 29.1% [95% CI, 27.4%–30.7%]; risk difference, 6.2% [95% CI, 4.0%–8.4%]; and number needed to treat, 16; Figures 3 and 4 and Figures S4 and S5). Crude 5-year risks and risk differences of the composite according to use of statins are presented in Figures S4 and S5. Although the standardized 5-year risk reduction associated with statins increased with advancing age group in men (age 40–49 years, 1.1% [95% CI, 0.0%–2.3%]; 50–59 years, 2.4% [95% CI, 1.3%–3.4%]; 60–69 years, 3.6% [95% CI, 2.4%–4.8%]; 70–79 years, 6.2% [95% CI, 4.0%–8.4%]; 80–89 years, 12.9% [95% CI, 7.6%–18.2%]) and in women (age 40–49 years, –0.0% [95% CI, –1.0% to 1.0%]; 50–59 years, 1.6% [95% CI, 0.6%–2.7%]; 60–69 years, 2.3% [95% CI, 1.2%–3.5%]; 70–79 years, 7.1% [95% CI, 5.1%–9.2%]; 80–89 years, 10.8% [95% CI, 7.2%–14.4%]), the standardized risk ratio remained largely constant with advancing age for both

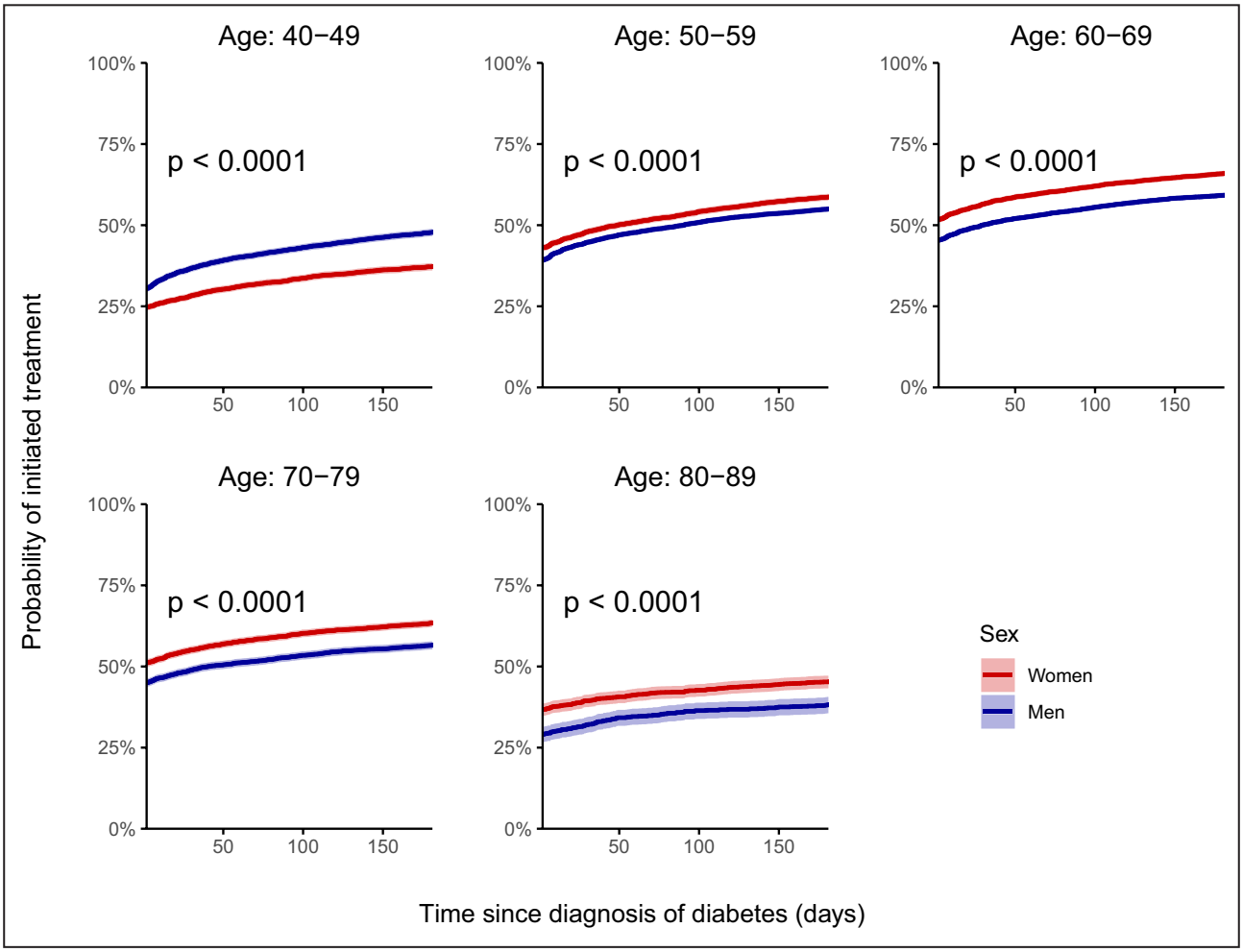


Figure 1. Initiation of statins according to time since diagnosis of type 2 diabetes mellitus, stratified by age at time of diagnosis.

Table 1. Population Characteristics According to Treatment With Statins

Characteristics	Coverage		Proportion of Days Covered				
	Not Treated	Treated	<20%	20%–40%	40%–60%	60%–80%	>80%
Count	34 195	42 975	2651	1486	2099	5678	31 061
Women	15 473 (45.2)	20 287 (47.2)	1149 (43.3)	661 (44.5)	925 (44.1)	2501 (44.0)	15 051 (48.5)
Age, Q_1–Q_3, y	59 (50–68)	62 (54–68)	59 (50–67)	58 (50–65)	59 (51–67)	60 (52–67)	62 (55–69)
Ethnic Danish	30 383 (88.9)	39 319 (91.5)	2225 (83.9)	1222 (82.2)	1778 (84.7)	5064 (89.2)	29 030 (93.5)
Comorbidities							
Atrial fibrillation	1311 (3.8)	1662 (3.9)	92 (3.5)	41 (2.8)	70 (3.3)	198 (3.5)	1261 (4.1)
COPD	1640 (4.8)	1759 (4.1)	116 (4.4)	51 (3.4)	88 (4.2)	242 (4.3)	1262 (4.1)
Highest attained education*							
Basic school	14 255 (41.7)	18 064 (42.0)	1025 (38.7)	601 (40.4)	830 (39.5)	2307 (40.6)	13 301 (42.8)
Upper secondary	1141 (3.3)	1109 (2.6)	91 (3.4)	57 (3.8)	69 (3.3)	156 (2.7)	736 (2.4)
Vocational	12 794 (37.4)	16 765 (39.0)	1055 (39.8)	568 (38.2)	803 (38.3)	2222 (39.1)	12 117 (39.0)
Short- or medium-length higher education	4583 (13.4)	5559 (12.9)	357 (13.5)	192 (12.9)	311 (14.8)	764 (13.5)	3935 (12.7)
Master's degree or higher	1422 (4.2)	1478 (3.4)	123 (4.6)	68 (4.6)	86 (4.1)	229 (4.0)	972 (3.1)
Medication							
Metformin	22 340 (65.3)	34 583 (80.5)	1414 (53.3)	1017 (68.4)	1532 (73.0)	4653 (81.9)	25 967 (83.6)
Insulin	2492 (7.3)	1665 (3.9)	150 (5.7)	72 (4.8)	105 (5.0)	234 (4.1)	1104 (3.6)
Sulfonylureas	6723 (19.7)	7266 (16.9)	340 (12.8)	224 (15.1)	337 (16.1)	964 (17.0)	5401 (17.4)
DPP-4 inhibitor	1289 (3.8)	2107 (4.9)	104 (3.9)	62 (4.2)	104 (5.0)	324 (5.7)	1513 (4.9)
GLP-1 analogue	442 (1.3)	706 (1.6)	43 (1.6)	33 (2.2)	37 (1.8)	115 (2.0)	478 (1.5)
Aspirin	5233 (15.3)	13 030 (30.3)	433 (16.3)	275 (18.5)	559 (26.6)	1647 (29.0)	10 116 (32.6)
ADP inhibitor	61 (0.2)	209 (0.5)	6 (0.2)	10 (0.7)	7 (0.3)	25 (0.4)	161 (0.5)
Anticoagulants	1089 (3.2)	1546 (3.6)	74 (2.8)	37 (2.5)	54 (2.6)	176 (3.1)	1205 (3.9)
RASi	14 153 (41.4)	26 245 (61.1)	1039 (39.2)	671 (45.2)	1105 (52.6)	3410 (60.1)	20 020 (64.5)
Cholesterol-lowering drugs (nonstatins)	251 (0.7)	206 (0.5)	103 (3.9)	44 (3.0)	24 (1.1)	22 (0.4)	13 (0.0)
β Blocker	4623 (13.5)	7916 (18.4)	286 (10.8)	190 (12.8)	297 (14.1)	922 (16.2)	6221 (20.0)
Calcium channel blockers	6149 (18.0)	11 477 (26.7)	436 (16.4)	272 (18.3)	447 (21.3)	1407 (24.8)	8915 (28.7)
Thiazides	5591 (16.4)	8778 (20.4)	338 (12.7)	239 (16.1)	322 (15.3)	986 (17.4)	6893 (22.2)
Furosemide	2826 (8.3)	3193 (7.4)	130 (4.9)	67 (4.5)	132 (6.3)	365 (6.4)	2499 (8.0)
Aldosterone	917 (2.7)	887 (2.1)	40 (1.5)	15 (1.0)	39 (1.9)	105 (1.8)	688 (2.2)

Data are given as number (percentage), unless otherwise indicated. COPD indicates chronic obstructive pulmonary disease; DPP4, dipeptidyl peptidase 4; GLP1, glucagon-like peptide 1; Q_1–Q_3, 25th percentile–75th percentile; and RASi, renin-angiotensin system inhibitors.

*Basic school (primary, lower secondary; 9 years); upper secondary (general secondary, technical secondary; "high-school"); vocational (eg, electrician or chef); short- or medium-length higher education (academy professional degree, professional bachelor's degree, university bachelor's degree; 2–4 years following upper secondary); master's degree or higher.

sexes (except women aged 40–49 years; Figure 4 and Figure S6).

Although the standardized risks were higher in men than in women (*P* for interaction: statins, <0.001; Figure S4), the standardized risk differences were largely similar in men and women (Figure 4). When standardizing to all patients treated with statins, we observed higher standardized risks with a PDC level of <80% compared with a PDC level of 80% to 100% (reference PDC ≥80%; PDC=60%–80%, 1.5% [95% CI, 0.7%–2.4%]; PDC=40%–60%, 4.2% [95% CI, 2.7%–5.7%]; PDC=20%–40%, 2.4% [95% CI, 0.6%–4.2%]; PDC <20%, 4.2% [95% CI, 2.9%–5.6%]; Figure 3 and Figure S4).

Exchanging the main outcome showed lower crude and standardized 5-year risks of hospital discharge attributable to any skin lesion associated with statins as well as lower crude and standardized 5-year risks associated with an increasing adherence level of statins (Figure S7). However, when stratifying by age group,

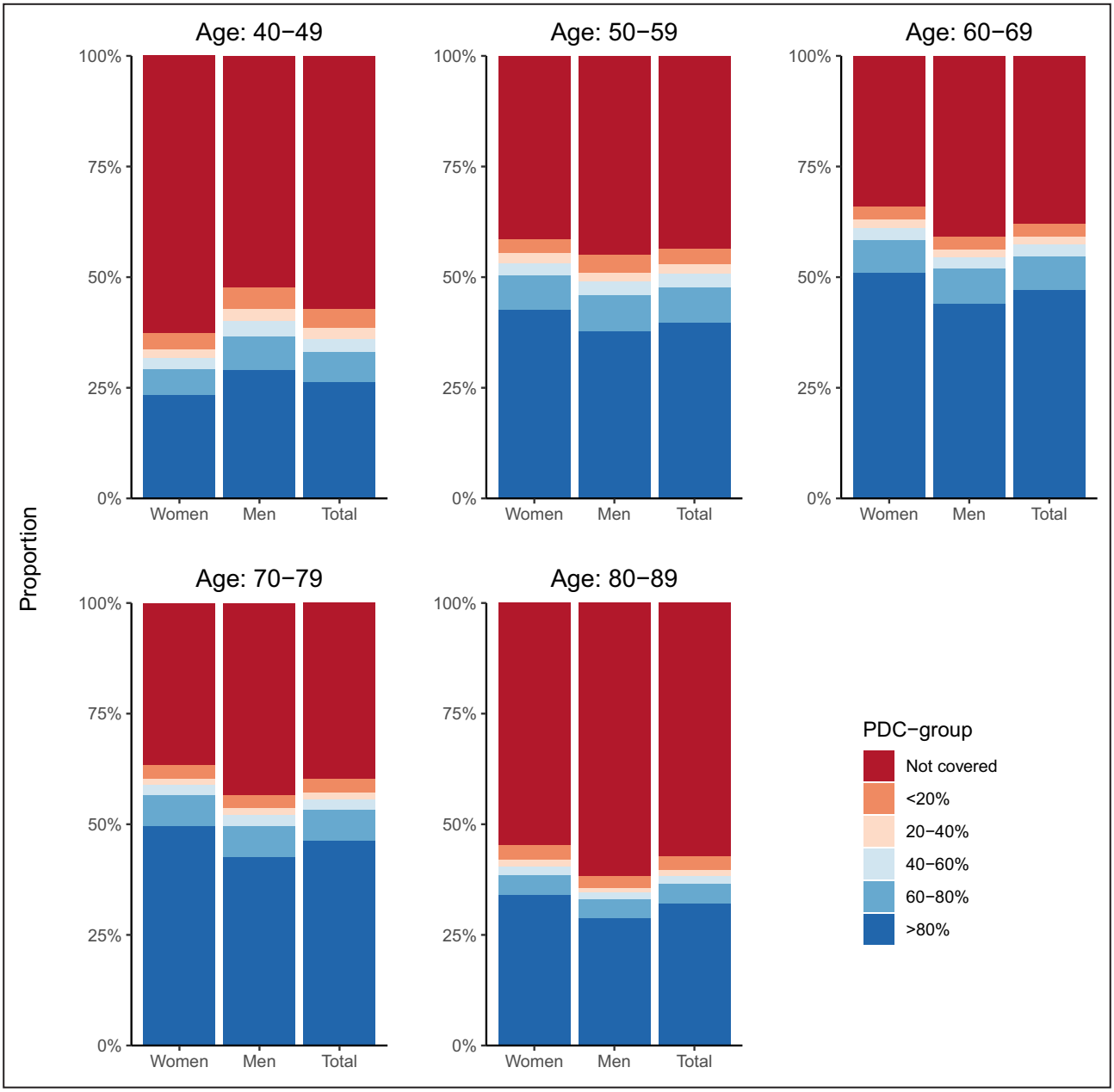


Figure 2. Coverage of statins at index date.
PDC indicates proportion of days covered.

the standardized 5-year risks were largely similar between individuals treated and not treated with statins (Figure S7).

Sensitivity Analyses: Nested Case-Control Population

In event-free survivors, we observed that the proportion of patients treated with statins as well as individuals with a PDC level of 80% to 100% increased over study time regardless of age and sex (Figure S8). The associations between both treatment initiation (yes/no) and PDC levels and associated risk of the primary outcome were comparable in main analyses and the nested case-control population (Figure S9; hazard ratios [HRs] for adjustment variables for main analyses in Tables S4 and S5 and for nested case-control population in Tables S6 and S7).

DISCUSSION

We observed that in a low-risk, nationwide, contemporary population with T2D, use of statins was associated

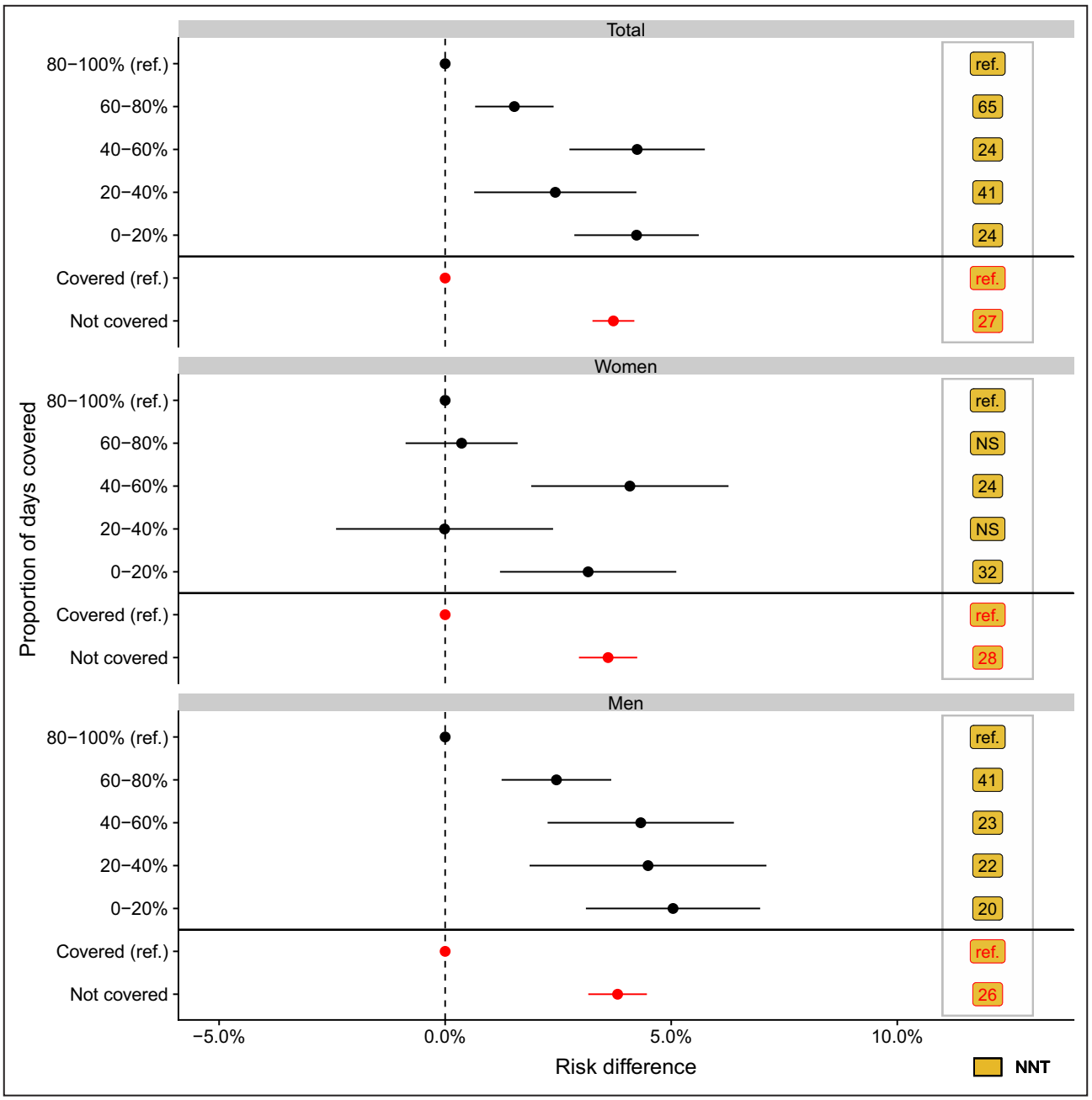


Figure 3. Standardized 5-year risk difference of the composite of myocardial infarction, ischemic stroke, or all-cause death, according to treatment with statins (reference [ref.]=risk$_{treated}$) and proportion of days covered (PDC; reference=risk$_{PDC\ 80\%–100\%}$) and stratified by sex.
Number needed to treat (NNT) is the NNT with PDC level 80% to 100% or NNT with statins (yes/no) to prevent a cardiovascular disease event. NS indicates not significant.

with a lower 5-year risk of a composite outcome of first myocardial infarction, first ischemic stroke, or all-cause mortality in all age groups for men and from age >50 years in women, and that the risk reduction increased with advancing age group. Second, a high adherence of statins was important to maintain this effect. Finally, we observed that women were more frequently treated with statins, and that a high proportion of patients (44%) were not treated with statins 6 months following T2D diagnosis.

Although no prior study has used exactly the same outcome as our study, prior clinical trials[1–3] and meta-analyses[4,5] have demonstrated beneficial effects of statins as primary prevention of CVD in patients with T2D. However, data are sparse for the effects of statins in a contemporary low-risk population

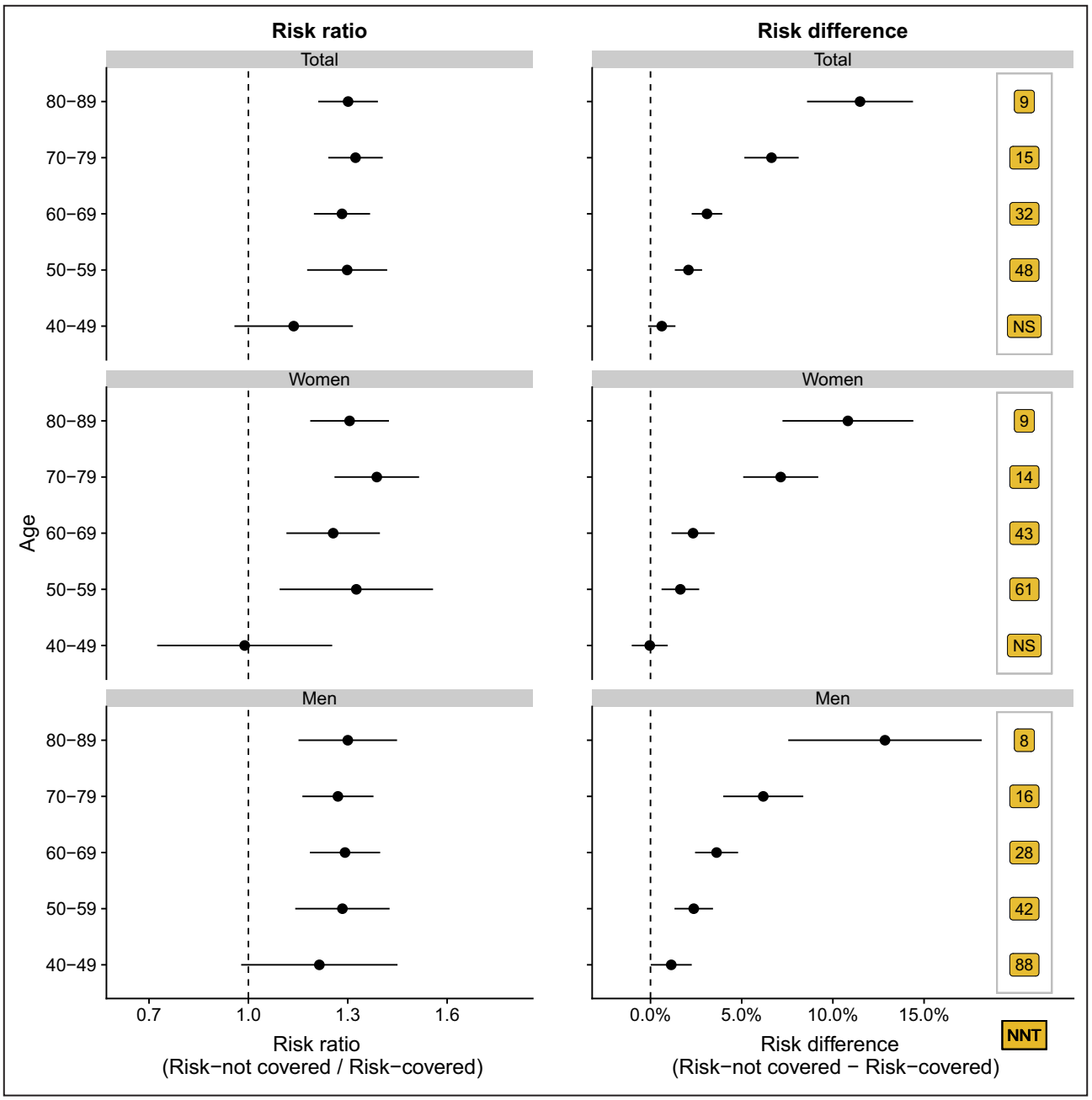


Figure 4. Standardized 5-year risk ratios and risk difference of the composite of myocardial infarction, ischemic stroke, or all-cause death, according to treatment with statins (reference=risk$_{treated}$) and stratified by sex and age group.
Number needed to treat (NNT) is the NNT with statins (yes/no) to prevent a cardiovascular disease event. NS indicates not significant.

with T2D. A meta-analysis observed that reducing LDL levels resulted in a reduction in cardiovascular rate in individuals with predicted <5% and 5% to 10% 5-year cardiovascular risk (HR, 0.61 and 0.66 per 1-mmol/L reduction in LDL, respectively),[5] but only a low proportion of these patients had type 1+2 diabetes mellitus (7% and 18%, respectively), and competing risks of noncardiovascular death were not taken into account when stratifying by the calculated cardiovascular risk groups. Another meta-analysis with patients with type 1+2 diabetes mellitus only observed a beneficial effect of reducing the LDL level on CVD rate in individuals without prior myocardial infarction, stroke, and peripheral arterial disease, but diabetes mellitus duration was unknown.[4] As in our study, both meta-analyses observed slightly higher associations in men than in women. In both meta-analyses, the results were reported in relative terms (HRs), and not on an absolute scale. Although we did not have access to the patients' lipid profile, the

latter meta-analysis showed a similar effect of statins regardless of the baseline lipid profile.[4]

To date, meta-analyses[4,5,22] and a recent retrospective cohort study[23] have only examined the statin treatment effect on major vascular events by age in relative rather than absolute terms, which makes it difficult to interpret the size of the treatment effect.[24] Although one meta-analysis stated that there is less direct evidence of benefit among patients aged >75 years without evidence of occlusive vascular disease,[22] all 4 studies have largely observed a benefit of statins in primary prevention of major vascular events in relative terms in various subpopulations, excluding patients with heart failure and chronic renal failure in all age groups. We observed similar results in relative terms. In our study, we focused on absolute risk differences and observed a clear and increasingly beneficial effect of statins with advancing age in absolute terms, which resulted in lower numbers needed to treat in elderly patients. Thus, the conclusions of the referred studies may have been different if a risk difference had been used. Of note, we did not have access to information on LDL levels, the outcomes were slightly different, and our study used risks, whereas the meta-analyses used hazards limiting the comparison.

We did not observe a significant effect of statins in women aged 40 to 49 years, which particularly in the youngest age group could be because cardiovascular events are rare in these age groups in women, which may explain why we were unable to detect an effect of statins. Furthermore, expected to be a minor limitation, this age category includes pregnant women with T2D, and possibly some women with polycystic ovary syndrome, for whom statins are not recommended. This is supported by more men than women aged 40 to 49 years initiating treatment with statins in our study.

Similar to our study, some studies have previously shown a beneficial effect of a high adherence of statin therapy as primary prevention of CVD and death,[9] but none of the studies was based on a population of patients with diabetes mellitus only, and the methods varied greatly between the studies. Many studies only stratified by good versus poor adherence (typically defined as PDC <80% versus ≥80%); however, this might not really exist because the dose-response phenomenon is more likely a continuum. Although dose-response effects are difficult to mimic in a real-life setting, they are crucial for decision-making on operational adherence thresholds for different therapies.[25] In this context, our study showed that the risk of the composite outcome increased with decreasing PDC group for statins. Because more than every fourth individual claiming prescriptions for statins had a PDC level of <80%, there is an urgent need to improve the adherence to statins, so that patients can benefit fully from the protective effects of statin therapy.

Our study used coverage status and PDC level of statins at the index date to calculate a 5-year risk of myocardial infarction, ischemic stroke, or all-cause mortality, but coverage status and PDC level may change over time, which could have influenced the outcome. We therefore conducted a sensitivity analysis exploring use in the 18 months before outcome event, which confirmed our overall findings for statins, as well as the associations with PDC level of statins.

Strengths and Limitations

The major strengths of this contemporary nationwide study include minimal risk of selection bias, minimal loss to follow-up ensured by the comprehensive Danish registries, and the large sample size. However, important limitations need to be addressed.

The main limitation of the study is its observational nature; thus, only hypothesis-generating associations and not causal relations can be explored. As with any statistical analysis, our ability to adjust for potential confounding is limited to data availability. In this study, we did not have access to information on metabolic control (glucose levels, lipids, blood pressure, and urine albumin levels), imaging findings (echocardiography and computed tomographic angiography, including coronary artery calcium scores), or lifestyle factors (smoking, alcohol consumption, body mass index, physical activity level, or diet). Although the Danish registries do not have information on smoking, we included chronic obstructive pulmonary disease as we consider it a strong marker of smoking. Similarly, we did not have information on hypertension, which is largely diagnosed from general practitioners. Discharge diagnoses of hypertension would therefore strongly underestimate the number of patients with hypertension. Instead, we chose to adjust for claimed prescriptions of antihypertensive medication groups separately. In addition, the group of cholesterol-lowering drugs (nonstatins) was considered as a common group. These drugs were claimed only by a small number of patients at index, and we would therefore not expect subgrouping of this medication group to have a large impact on our results. PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors are not registered in the Danish National Prescription Registry as they have been delivered from hospital lipid clinics directly since October 2015, using rather restrictive rules because of the high price. Because the population of the current study was a low-risk population with T2D, PCSK9 inhibitors may only have been given to a minor group of patients toward the end of the study period, which we consider unlikely to have affected our results.

Furthermore, a "healthy adherer" effect cannot be excluded,[26] because exchanging the outcome to hospital discharge attributable to any skin lesion showed greater reduction of the composite outcome, particularly with increasing PDC level. However, when stratifying by age, a healthy adherer effect was less obvious. It has previously been suggested that, on the basis of the differential class effects of drug adherence on long-term survival, adherence-related benefits associated with evidence-based pharmacotherapies are mediated by drug effects more than by healthy adherer behaviors.[27,28] Last, others have observed that individuals who are more ill appear to adhere to statins better.[29] These findings challenge the concept of the "healthy adherer effect."

Third, we did not know the indication for the statins, and the calculations of dose and treatment periods represent approximations. During our study period, Danish guidelines recommended initiation of statins as primary prevention at time of T2D diagnosis at LDL levels >2.5 mmol/L, which was in line with European Association for the Study of Diabetes/European Society of Cardiology guidelines.[30] To minimize inclusion of secondary prevention statin therapy, we excluded individuals with coronary heart disease, ischemic stroke, peripheral arterial disease, heart failure, cancer, and chronic kidney disease before and 18 months following a T2D diagnosis. Although these diagnoses have high positive predictive values[17,18,31,32] in the Danish registers, and high sensitivity for myocardial infarction,[33] the sensitivity for heart failure is low[32] and unknown for the remaining diseases. Thus, we cannot rule out that the indications for the claimed prescriptions of statins have been prescribed because of indications other than primary prevention of CVD.

Last, most of the Danish population is White individuals, and we did not include individuals immigrating to Denmark during our study period because of unknown medical history; thus, our results may not be generalizable to non-White individuals.

CONCLUSIONS

This nationwide study supports the use of statins as primary prevention against CVDs or death in 18-month surviving low-risk patients with T2D, with the highest effect in the elderly patients. Second, a high adherence of statins was important to maintain this effect. Finally, women were more frequently treated with statins, and a high proportion of patients were not treated with statins 6 months following T2D diagnosis.

ARTICLE INFORMATION

Received January 4, 2021; accepted May 3, 2021.

Affiliations

Danish Heart Foundation, Copenhagen, Denmark (M.M., T.G., G.G.); Department of Cardiology, Holbæk Sygehus, Holbæk, Denmark (M.D.S.); Department of Biostatistics, University of Copenhagen, Denmark (T.G.); Department of Cardiology, Herlev and Gentofte Hospital, Hellerup, Denmark (M.S., G.G.); Department of Endocrinology, Copenhagen University Hospital, Copenhagen, Denmark (C.K.); and Department of Clinical Investigation and Cardiology, Nordsjaellands Hospital, Hillerød, Denmark (C.T.).

Sources of Funding

This work was funded by the Danish Heart Foundation (grant number: 18-R121-A8218).

Disclosures

None.

Supplementary Material

Data S1
Tables S1–S7
Figures S1–S9

REFERENCES

1. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HAW, Livingstone SJ, Thomason MJ, Mackness MI, Charlton-Menys V, Fuller JH; CARDS Investigators. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet*. 2004;364:685–696. DOI: 10.1016/S0140-6736(04)16895-5.
2. Collins R, Armitage J, Parish S, Sleigh P, Peto R; Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet*. 2003;361:2005–2016. DOI: 10.1016/s0140-6736(03)13636-7.
3. Knopp RH, d'Emden M, Smilde JG, Pocock SJ. Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes: the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus (ASPEN). *Diabetes Care*. 2006;29:1478–1485. DOI: 10.2337/dc05-2415.
4. Cholesterol Treatment Trialists' (CTT) Collaborators, Kearney PM, Blackwell L, Collins R, Keech A, Simes J, Peto R, Armitage J, Baigent C. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. *Lancet*. 2008;371:117–125. DOI: 10.1016/S0140-6736(08)60104-X.
5. Cholesterol Treatment Trialists' (CTT) Collaborators, Mihaylova B, Emberson J, Blackwell L, Keech A, Simes J, Barnes EH, Voysey M, Gray A, Collins R, Baigent C. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet*. 2012;380:581–590. DOI: 10.1016/S0140-6736(12)60367-5.
6. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, Federici M, Filippatos G, Grobbee DE, Hansen TB, et al; ESC Scientific Document Group. 2019 ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J*. 2020;41:255–323. DOI: 10.1093/eurheartj/ehz486.
7. American Diabetes Association. 10: Cardiovascular disease and risk management: standards of medical care in diabetes-2019. *Diabetes Care*. 2019;42:S103–S123. DOI: 10.2337/dc19-S010.
8. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, Himmelfarb CD, Khera A, Lloyd-Jones D, McEvoy JW, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;140:e596–e646. DOI: 10.1161/CIR.0000000000000678.
9. De Vera MA, Bhole V, Burns LC, Lacaille D. Impact of statin adherence on cardiovascular disease and mortality outcomes: a systematic review. *Br J Clin Pharmacol*. 2014;78:684–698. DOI: 10.1111/bcp.12339.

10. Pedersen CB. The Danish Civil Registration System. *Scand J Public Health*. 2011;39:22–25. DOI: 10.1177/1403494810387965.
11. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health*. 2011;39:30–33. DOI: 10.1177/1403494811401482.
12. Kildemoes HW, Sørensen HT, Hallas J. The Danish National Prescription Registry. *Scand J Public Health*. 2011;39:38–41. DOI: 10.1177/1403494810394717.
13. Helweg-Larsen K. The Danish register of causes of death. *Scand J Public Health*. 2011;39:26–29. DOI: 10.1177/1403494811399958.
14. Carstensen B, Kristensen JK, Marcussen MM, Borch-Johnsen K. The national diabetes register. *Scand J Public Health*. 2011;39:58–61. DOI: 10.1177/1403494811404278.
15. Malmborg M, Schmiegelow MDS, Nørgaard CH, Munch A, Gerds T, Schou M, Kistorp C, Torp-Pedersen C, Hlatky MA, Gislason G. Does type 2 diabetes confer higher relative rates of cardiovascular events in women compared with men? *Eur Heart J*. 2020;41:1346–1353. DOI: 10.1093/eurheartj/ehz913.
16. tagteam/heaven. GitHub. https://github.com/tagteam/heaven. Accessed March 27, 2020.
17. Sundbøll J, Adelborg K, Munch T, Frøslev T, Sørensen HT, Bøtker HE, Schmidt M. Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study. *BMJ Open*. 2016;6:e012832. DOI: 10.1136/bmjopen-2016-012832.
18. Krarup L-H, Boysen G, Janjua H, Prescott E, Truelsen T. Validity of stroke diagnoses in a National Register of Patients. *Neuroepidemiology*. 2007;28:150–154. DOI: 10.1159/000102143.
19. Borgan O, Goldstein L, Langholz B. Methods for the analysis of sampled cohort data in the cox proportional hazards model. *Ann Stat*. 1995;23:1749–1778. DOI: 10.1214/aos/1176324322.
20. Borgan O, Samuelsen SO. Nested case-control and case-cohort. In: Klein JP, van Houwelingen HC, Ibrahim JG, Scheike TH, eds. *Handbook of Survival Analysis*. Routledge Handbooks Online; 2013:343–367. https://www.routledgehandbooks.com/doi/10.1201/b16248-22. Accessed March 10, 2021.
21. R: the R project for statistical computing. https://www.r-project.org/. Accessed March 23, 2020.
22. Cholesterol Treatment Trialists' Collaboration. Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials. *Lancet*. 2019;393:407–415. DOI: 10.1016/S0140-6736(18)31942-1.
23. Orkaby AR, Driver JA, Ho Y-L, Lu B, Costa L, Honerlaw J, Galloway A, Vassy JL, Forman DE, Gaziano JM, et al. Association of statin use with all-cause and cardiovascular mortality in US veterans 75 years and older. *JAMA*. 2020;324:68–78. DOI: 10.1001/jama.2020.7848.
24. Akobeng AK. Understanding measures of treatment effect in clinical trials. *Arch Dis Child*. 2005;90:54–56. DOI: 10.1136/adc.2004.052233.
25. Organisation mondiale de la santé, Organization WH, WHO. *Adherence to Long-Term Therapies: Evidence for Action*. World Health Organization; 2003:1–230. https://www.who.int/chp/knowledge/publications/adherence_report/en/. Accessed March 10, 2021.
26. Simpson SH, Eurich DT, Majumdar SR, Padwal RS, Tsuyuki RT, Varney J, Johnson JA. A meta-analysis of the association between adherence to drug therapy and mortality. *BMJ*. 2006;333:15. DOI: 10.1136/bmj.38875.675486.55.
27. Rasmussen JN, Chong A, Alter DA. Relationship between adherence to evidence-based pharmacotherapy and long-term mortality after acute myocardial infarction. *JAMA*. 2007;297:177–186. DOI: 10.1001/jama.297.2.177.
28. Daskalopoulou SS, Delaney JAC, Filion KB, Brophy JM, Mayo NE, Suissa S. Discontinuation of statin therapy following an acute myocardial infarction: a population-based study. *Eur Heart J*. 2008;29:2083–2091. DOI: 10.1093/eurheartj/ehn346.
29. Hope HF, Binkley GM, Fenton S, Kitas GD, Verstappen SMM, Symmons DPM. Systematic review of the predictors of statin adherence for the primary prevention of cardiovascular disease. *PLoS One*. 2019;14:e0201196. DOI: 10.1371/journal.pone.0201196.
30. Rydén L, Standl E, Bartnik M, Van den Berghe G, Betteridge J, de Boer M-J, Cosentino F, Jönsson B, Laakso M, Malmberg K, et al; Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC), European Association for the Study of Diabetes (EASD). Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). *Eur Heart J*. 2007;28:88–136. DOI: 10.1093/eurheartj/ehl260.
31. Thygesen SK, Christiansen CF, Christensen S, Lash TL, Sørensen HT. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. *BMC Med Res Methodol*. 2011;11:83. DOI: 10.1186/1471-2288-11-83.
32. Kümler T, Gislason GH, Kirk V, Bay M, Nielsen OW, Køber L, Torp-Pedersen C. Accuracy of a heart failure diagnosis in administrative registers. *Eur J Heart Fail*. 2008;10:658–660. DOI: 10.1016/j.ejheart.2008.05.006.
33. Madsen M, Davidsen M, Rasmussen S, Abildstrom SZ, Osler M. The validity of the diagnosis of acute myocardial infarction in routine statistics: a comparison of mortality and hospital discharge data with the Danish MONICA registry. *J Clin Epidemiol*. 2003;56:124–130. DOI: 10.1016/S0895-4356(02)00591-7.

SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

Description of method used to determine the dose and treatment duration of statins.

The national prescription registry does not include information on prescribed daily dosage of the medication, but rather date of dispensing, strength and quantity. For each of the statins dispensed between 1 January 2004 and 31 December 2018, we created an algorithm in which a minimum, maximum and typical daily dosage of used medication was defined. For patients who had not been in treatment in the period preceding the day of a prescription claim, the typical daily dosage was assigned, and treatment length was calculated by dividing the amount of claimed medications by the daily dosage. For patients who were covered by a previous prescription claim at the time of claiming a new prescription, the daily dosage was reset and a new daily dosage was calculated as the amount of claimed medications during the preceding period divided by time between prescription claims. If calculated dosages exceeded the predefined highest daily dosages, patients were assigned the maximally dosages and exceeding tablets were assumed to be stored and consumed during the immediate period after duration of last prescription. Based on these assumptions, we calculated whether patients at any time had tablets available or not. We defined a patient as receiving treatment if tablets were available.

Table S1. ICD-8, ICD-10 and ATC codes used.

	ICD-8, ICD-10 and ATC codes	Comments
Outcomes of interest (ICD)		From the National Patient Registry and National Causes of Death Registry
Myocardial infarction	ICD-10: I21	
Ischemic stroke	ICD-8: 433, 443, 436 ICD-10: I63-64	
Comorbidities (ICD)		From the National Patient Registry
Coronary artery disease	ICD-8: 410-414 ICD-10: I20-25	
Congestive heart failure	ICD-8: 42709-42711, 42719, 42899, 78249 ICD-10: I110, I130, I132, I420, I426-429, I500-503, I508-509	
Peripheral arterial disease	ICD-8: 44389-44399 ICD-10: I73	
Chronic renal failure	ICD-8: 585, T858-859, Z992 ICD-10: N18, I12-13	
Atrial fibrillation	ICD-8: 42793, 42794 ICD-10: I48	
Chronic obstructive pulmonary disease	ICD-8: 490-492 ICD-10: J42, J44	
Cancer	ICD-8: 140-209 ICD-10: C00-99	
Medication (ATC)		From the National Prescription Registry. Medications at the index date were defined as dispensed prescriptions within 180 days prior to the index date. For the nested case-control population, medications were defined as dispensed prescriptions within 180 days prior to one year before the case date.
Exposure		
Statins	C10AA	
Antidiabetics		

Metformin	A10BA02, A10BD02, A10BD03, A10BD05, A10BD07, A10BD08, A10BD10, A10BD11, A10BD13, A10BD14, A10BD15, A10BD16, A10BD17, A10BD18, A10BD20, A10BD22, A10BD23, A10BD25	
Insulin	A10A	
Sulfonylureas	A10BB, A10BD02, A10BD04, A10BD06	
DPP4-inhibitors	A10BH, A10BD07, A10BD08, A10BD10, A10BD11, A10BD12, A10BD13, A10BD18, A10BD21, A10BD22, A10BD24	
GLP1-analogs	A10BJ, A10AE54, A10AE56	
Antithrombothic agents		
Aspirin	B01AC06, N02BA01	
ADP-receptor inhibitors	B01AC04, B01AC22, B01AC24	
Anticoagulants	BB01AA, BB01AE, BB01AF	
Other		
Cholesterol-lowering drugs (non-statins)	C10A, except C10AA	
RASi	C09	
Betablockers	C07, C09BX	
Calcium channel blockers	C08, C07F, C09BB, C09DB	
Thiazides	C03A, C07B, C07D, C09XA52, C03EA01	
Furosemide	C03C, C03EB01, C03EB02	
Aldosterone	C03DA	

Table S2. Variables standardized (main analysis) and adjusted (nested case-control) for in the models.

Models	Variables
Main analysis	Sex, age (1-year bands), atrial fibrillation, chronic obstructive pulmonary disease, ethnicity (Danish, 1st generation immigrants, 2nd generation immigrants), highest attained education (ground school, high school, vocational, bachelor, master/research), metformin, sulfonylureas, DPP-4 inhibitors, GLP-1 analogues, aspirin, ADP inhibitors, anticoagulants, RASi, cholesterol-lowering drugs (non-statins), betablockers, calcium-channel blockers, thiazides, furosemide, aldosterone, year of type 2 diabetes diagnosis (2005, 2006, 2007, 2008, 2009, 2010, 2011).
Nested case-control	Matching variables: sex and age (10-year bands). Atrial fibrillation, chronic obstructive pulmonary disease, cancer, ethnicity (Danish, 1st generation immigrants, 2nd generation immigrants), highest attained education (ground school, high school, vocational, bachelor, master/research), metformin, sulfonylureas, DPP-4 inhibitors, GLP-1 analogues, aspirin, ADP inhibitors, anticoagulants, RASi, cholesterol-lowering drugs (non-statins), betablockers, calcium-channel blockers, thiazides, furosemide, aldosterone, year of type 2 diabetes diagnosis (2005, 2006, 2007, 2008, 2009, 2010, 2011).

Table S3. Population characteristics according to coverage of statins in the nested case-control population.

	Coverage		PDC				
	Not treated	**Treated**	**<20%**	**(20-40%]**	**(40-60%]**	**(60-80%]**	**≥80%**
Count (%)	37625	73574	3956	3552	4241	9059	52766
Women	15,812 (42.0)	31,400 (42.7)	1,606 (40.6)	1,449 (40.8)	1,635 (38.6)	3,661 (40.4)	23,049 (43.7)
Age (Q_1-Q_3*)	71 [62, 81]	69 [62, 76]	68 [58, 77]	68 [59, 77]	68 [60, 76]	69 [61, 76]	70 [63, 77]
Ethnic Danish	34,744 (92.3)	69,051 (93.9)	3,552 (89.8)	3,210 (90.4)	3,851 (90.8)	8,303 (91.7)	50,135 (95.0)
Comorbidities							
Diabetes duration (Q_1-Q_3*)	3.9 [2.6, 5.1]	4 [2.8, 5.3]	3.6 [2.5, 5.0]	3.8 [2.6, 5.1]	3.8 [2.6, 5.1]	3.9 [2.7, 5.2]	4.1 [2.9, 5.3]
Coronary heart disease	416 (1.1)	1375 (1.9)	63 (1.6)	67 (1.9)	83 (2.0)	160 (1.8)	1002 (1.9)
Heart failure	411 (1.1)	590 (0.8)	32 (0.8)	25 (0.7)	30 (0.7)	91 (1.0)	412 (0.8)
PAD	160 (0.4)	537 (0.7)	28 (0.7)	36 (1.0)	42 (1.0)	65 (0.7)	366 (0.7)
Chronic renal failure	212 (0.6)	370 (0.5)	16 (0.4)	15 (0.4)	14 (0.3)	65 (0.7)	260 (0.5)
Atrial fibrillation	3130 (8.3)	5084 (6.9)	286 (7.2)	241 (6.8)	261 (6.2)	620 (6.8)	3676 (7.0)
COPD	2793 (7.4)	4264 (5.8)	230 (5.8)	217 (6.1)	250 (5.9)	579 (6.4)	2988 (5.7)
Cancer	3670 (9.8)	6187 (8.4)	359 (9.1)	267 (7.5)	372 (8.8)	783 (8.6)	4406 (8.4)
Highest attained education							
Basic school	18,130 (48.2)	33,715 (45.8)	1,764 (44.6)	1,611 (45.4)	1,809 (42.7)	3,879 (42.8)	24,652 (46.7)
Upper secondary	869 (2.3)	1394 (1.9)	98 (2.5)	78 (2.2)	97 (2.3)	209 (2.3)	912 (1.7)
Vocational	12747 (33.9)	27573 (37.5)	1491 (37.7)	1325 (37.3)	1652 (39.0)	3504 (38.7)	19601 (37.1)
Short or medium length higher education	4334 (11.5)	8568 (11.6)	464 (11.7)	382 (10.8)	522 (12.3)	1153 (12.7)	6047 (11.5)
Master's degree or higher	1545 (4.1)	2324 (3.2)	139 (3.5)	156 (4.4)	161 (3.8)	314 (3.5)	1554 (2.9)
Medication							
Metformin	22613 (60.1)	58368 (79.3)	2678 (67.7)	2534 (71.3)	3146 (74.2)	7192 (79.4)	42818 (81.1)
Insulin	2376 (6.3)	3908 (5.3)	277 (7.0)	238 (6.7)	268 (6.3)	493 (5.4)	2632 (5.0)

Sulfonylureas	8174 (21.7)	14668 (19.9)	788 (19.9)	751 (21.1)	883 (20.8)	1800 (19.9)	10446 (19.8)
DPP-4 inhibitor	1548 (4.1)	4736 (6.4)	238 (6.0)	213 (6.0)	259 (6.1)	616 (6.8)	3410 (6.5)
GLP-1 analogue	488 (1.3)	1540 (2.1)	74 (1.9)	77 (2.2)	92 (2.2)	207 (2.3)	1090 (2.1)
Aspirin	7538 (20.0)	24409 (33.2)	906 (22.9)	943 (26.5)	1144 (27.0)	2772 (30.6)	18644 (35.3)
ADP inhibitor	155 (0.4)	844 (1.1)	32 (0.8)	39 (1.1)	41 (1.0)	102 (1.1)	630 (1.2)
Anticoagulants	2398 (6.4)	4467 (6.1)	222 (5.6)	175 (4.9)	207 (4.9)	521 (5.8)	3342 (6.3)
RAS inhibitor	16378 (43.5)	47010 (63.9)	1943 (49.1)	1930 (54.3)	2356 (55.6)	5454 (60.2)	35327 (67.0)
Non-statin lipid-lowering drugs	487 (1.3)	264 (0.4)	75 (1.9)	50 (1.4)	37 (0.9)	34 (0.4)	68 (0.1)
Beta blocker	6751 (17.9)	15915 (21.6)	657 (16.6)	652 (18.4)	769 (18.1)	1820 (20.1)	12017 (22.8)
CCB	8251 (21.9)	22343 (30.4)	859 (21.7)	871 (24.5)	1080 (25.5)	2507 (27.7)	17026 (32.3)
Thiazides	7383 (19.6)	16279 (22.1)	753 (19.0)	701 (19.7)	832 (19.6)	1843 (20.3)	12150 (23.0)
Furosemide	4960 (13.2)	7788 (10.6)	347 (8.8)	301 (8.5)	382 (9.0)	958 (10.6)	5800 (11.0)
Aldosterone	1436 (3.8)	1971 (2.7)	96 (2.4)	75 (2.1)	102 (2.4)	226 (2.5)	1472 (2.8)

PDC = proportion of days covered, Q_1-Q_3 = 25th percentile-75th percentile, PAD = peripheral arterial disease, COPD = chronic obstructive pulmonary disease, DPP4 = dipeptidyl peptidase 4, GLP1 = glucagon-like peptide 1, ADP = adenosine diphosphate, NOAC = novel oral anticoagulant, RAS inhibitor = renin-angiotensin system inhibitor, CCB = calcium channel blockers.
Highest attained education: Basic school (primary, lower secondary; 9 years); Upper secondary (general secondary, technical secondary; “high-school”); Vocational (e.g., electrician or chef); Short or medium length higher education (academy professional degree, professional bachelor’s degree, university bachelor’s degree; 2 to 4 years following upper secondary); Master’s degree or higher.

Table S4. Hazard ratios of adjustment variables used for the main analysis according to coverage (reference = $risk_{treated}$).

Variable	Units	Hazard ratio	P-value
Sex	Men vs. women	1.46 [1.40;1.52]	< 0.001
Age		1.06 [1.06;1.07]	< 0.001
Atrial fibrillation	Yes vs. no	1.30 [1.19;1.43]	< 0.001
COPD	Yes vs. no	1.98 [1.86;2.11]	< 0.001
Ethnicity	1st generation immigrant vs. Danish	0.78 [0.71;0.85]	< 0.001
	2nd generation immigrant vs. Danish	0.56 [0.27;1.17]	0.121
Highest attained education	Highschool vs. ground school	1.03 [0.89;1.18]	0.73
	Vocational vs. ground school	0.90 [0.86;0.94]	< 0.001
	Bachelor vs. ground school	0.82 [0.77;0.88]	< 0.001
	Master vs. ground school	0.72 [0.64;0.81]	< 0.001
Metformin	Yes vs. no	0.86 [0.82;0.90]	< 0.001
Insulin	Yes vs. no	1.72 [1.59;1.86]	< 0.001
Sulfonylurea	Yes vs. no	1.06 [1.01;1.12]	0.023
DPP4 inhibitor	Yes vs. no	1.04 [0.94;1.16]	0.465
GLP-1 analog	Yes vs. no	0.92 [0.74;1.14]	0.436
Aspirin	Yes vs. no	1.06 [1.01;1.11]	0.01
ADP-inhibitor	Yes vs. no	2.09 [1.67;2.61]	< 0.001
Anticoagulants	Yes vs. no	0.92 [0.83;1.02]	0.13
Non-statin lipid-lowering drugs	Yes vs. no	1.05 [0.81;1.36]	0.701
RASi	Yes vs. no	0.85 [0.81;0.88]	< 0.001
Betablocker	Yes vs. no	1.07 [1.02;1.13]	0.007
Calcium channel blocker	Yes vs. no	1.03 [0.98;1.07]	0.288
Thiazide	Yes vs. no	1.08 [1.03;1.13]	0.003
Furosemide	Yes vs. no	1.61 [1.52;1.71]	< 0.001
Aldosterone	Yes vs. no	1.50 [1.37;1.65]	< 0.001
Year	2006 vs. 2005	1.00 [0.93;1.08]	0.93

2007 vs. 2005	0.97 [0.90;1.05]	0.452
2008 vs. 2005	0.92 [0.85;0.99]	0.035
2009 vs. 2005	0.90 [0.83;0.97]	0.009
2010 vs. 2005	0.87 [0.81;0.94]	< 0.001
2011 vs. 2005	0.89 [0.83;0.96]	0.003

Table S5. Hazard ratios of adjustment variables used for the main analysis according to proportion of days covered (reference = risk$_{PDC\ 80\text{-}100\%}$).

Variable	Units	Hazard ratio	P-value
Sex	Men vs. women	1.45 [1.37;1.54]	< 0.001
Age		1.06 [1.06;1.07]	< 0.001
Atrial fibrillation	Yes vs. no	1.33 [1.15;1.53]	< 0.001
COPD	Yes vs. no	2.06 [1.87;2.27]	< 0.001
Ethnicity	1st generation immigrant vs. Danish	0.77 [0.67;0.88]	< 0.001
	2nd generation immigrant vs. Danish	0.48 [0.12;1.91]	0.294
Highest attained education	Highschool vs. ground school	0.96 [0.77;1.19]	0.688
	Vocational vs. ground school	0.87 [0.81;0.93]	< 0.001
	Bachelor vs. ground school	0.83 [0.75;0.92]	< 0.001
	Master vs. ground school	0.78 [0.66;0.93]	0.006
Metformin	Yes vs. no	0.91 [0.85;0.99]	0.02
Insulin	Yes vs. no	1.75 [1.54;1.99]	< 0.001
Sulfonylurea	Yes vs. no	1.09 [1.00;1.18]	0.039
DPP4 inhibitor	Yes vs. no	1.12 [0.98;1.29]	0.108
GLP-1 analog	Yes vs. no	1.10 [0.84;1.45]	0.48
Aspirin	Yes vs. no	1.07 [1.01;1.14]	0.026
ADP-inhibitor	Yes vs. no	2.13 [1.64;2.78]	< 0.001
Anticoagulants	Yes vs. no	1.07 [0.92;1.24]	0.394
Non-statin lipid-lowering drugs	Yes vs. no	1.13 [0.78;1.63]	0.529
RASi	Yes vs. no	0.93 [0.87;0.98]	0.014
Betablocker	Yes vs. no	1.08 [1.01;1.16]	0.032
Calcium channel blocker	Yes vs. no	1.05 [0.99;1.12]	0.118
Thiazide	Yes vs. no	1.08 [1.01;1.16]	0.029
Furosemide	Yes vs. no	1.63 [1.49;1.77]	< 0.001
Aldosterone	Yes vs. no	1.10 [0.94;1.29]	0.246
Year	2006 vs. 2005	1.01 [0.89;1.14]	0.901

2007 vs. 2005	0.91 [0.80;1.03]	0.129
2008 vs. 2005	0.88 [0.78;0.99]	0.037
2009 vs. 2005	0.83 [0.73;0.94]	0.002
2010 vs. 2005	0.81 [0.72;0.91]	< 0.001
2011 vs. 2005	0.84 [0.75;0.95]	0.004

Table S6. Hazard ratios of adjustment variables used for the nested case control population according to coverage (reference = $risk_{treated}$).

Variable	Units	Hazard ratio	P-value
Atrial fibrillation	Yes vs. no	1.11 [1.01;1.22]	0.027
COPD	Yes vs. no	1.91 [1.78;2.04]	<0.001
Ethnicity	1st generation immigrant vs. Danish	0.71 [0.65;0.78]	<0.001
	2nd generation immigrant vs. Danish	0.44 [0.20;0.95]	0.036
Highest attained education	Highschool vs. ground school	0.95 [0.82;1.10]	0.502
	Vocational vs. ground school	0.86 [0.82;0.90]	<0.001
	Bachelor vs. ground school	0.78 [0.72;0.83]	<0.001
	Master vs. ground school	0.71 [0.62;0.80]	<0.001
Metformin	Yes vs. no	0.91 [0.86;0.96]	<0.001
Insulin	Yes vs. no	1.49 [1.38;1.62]	<0.001
Sulfonylurea	Yes vs. no	1.15 [1.09;1.21]	<0.001
DPP4 inhibitor	Yes vs. no	0.79 [0.72;0.88]	<0.001
GLP-1 analog	Yes vs. no	0.62 [0.51;0.74]	<0.001
Aspirin	Yes vs. no	1.09 [1.03;1.14]	<0.001
ADP-inhibitor	Yes vs. no	1.50 [1.23;1.82]	<0.001
Anticoagulants	Yes vs. no	1.07 [0.97;1.18]	0.205
Non-statin lipid-lowering drugs	Yes vs. no	0.76 [0.58;0.99]	0.045
RASi	Yes vs. no	0.83 [0.79;0.87]	<0.001
Betablocker	Yes vs. no	1.06 [1.01;1.12]	0.027
Calcium channel blocker	Yes vs. no	1.02 [0.97;1.07]	0.526
Thiazide	Yes vs. no	1.12 [1.06;1.18]	<0.001
Furosemide	Yes vs. no	1.59 [1.49;1.69]	<0.001
Aldosterone	Yes vs. no	1.32 [1.20;1.46]	<0.001
Year	2006 vs. 2005	1.00 [0.92;1.09]	0.983
	2007 vs. 2005	0.92 [0.84;1.01]	0.072
	2008 vs. 2005	0.82 [0.75;0.91]	<0.001

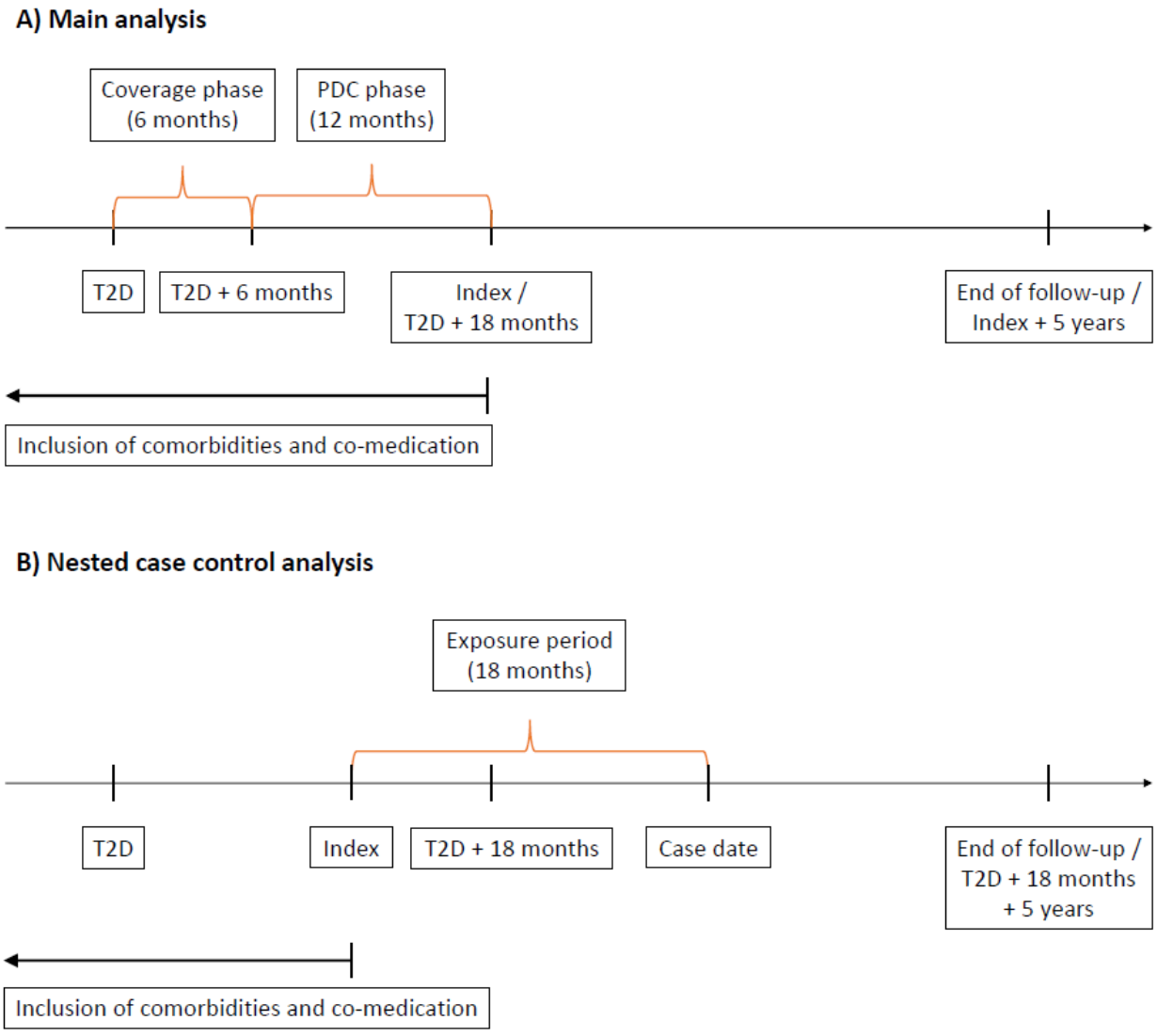
2009 vs. 2005	0.77 [0.70;0.86]	<0.001
2010 vs. 2005	0.72 [0.65;0.81]	<0.001
2011 vs. 2005	0.70 [0.62;0.79]	<0.001

Table S7. Hazard ratios of adjustment variables used for the nested case control population according to proportion of days covered (reference = risk$_{PDC\ 80\text{-}100\%}$).

Variable	Units	Hazard ratio	P-value
Atrial fibrillation	Yes vs. no	1.09 [0.95;1.24]	0.227
COPD	Yes vs. no	1.96 [1.77;2.16]	< 0.001
Ethnicity	1st generation immigrant vs. Danish	0.69 [0.60;0.80]	< 0.001
	2nd generation immigrant vs. Danish	0.34 [0.08;1.44]	0.144
Highest attained education	Highschool vs. ground school	0.87 [0.70;1.09]	0.234
	Vocational vs. ground school	0.85 [0.80;0.91]	< 0.001
	Bachelor vs. ground school	0.77 [0.70;0.85]	< 0.001
	Master vs. ground school	0.75 [0.62;0.90]	0.002
Metformin	Yes vs. no	0.92 [0.85;0.99]	0.031
Insulin	Yes vs. no	1.40 [1.24;1.57]	< 0.001
Sulfonylurea	Yes vs. no	1.14 [1.05;1.23]	0.001
DPP4 inhibitor	Yes vs. no	0.85 [0.75;0.96]	0.01
GLP-1 analog	Yes vs. no	0.65 [0.52;0.82]	< 0.001
Aspirin	Yes vs. no	1.14 [1.07;1.21]	< 0.001
ADP-inhibitor	Yes vs. no	1.56 [1.24;1.96]	< 0.001
Anticoagulants	Yes vs. no	1.25 [1.08;1.43]	0.002
Non-statin lipid-lowering drugs	Yes vs. no	0.69 [0.42;1.13]	0.142
RASi	Yes vs. no	0.91 [0.86;0.97]	0.004
Betablocker	Yes vs. no	1.10 [1.02;1.18]	0.01
Calcium channel blocker	Yes vs. no	1.07 [1.00;1.14]	0.049
Thiazide	Yes vs. no	1.09 [1.02;1.17]	0.012
Furosemide	Yes vs. no	1.55 [1.42;1.69]	< 0.001
Aldosterone	Yes vs. no	1.26 [1.08;1.47]	0.003
Year	2006 vs. 2005	0.90 [0.79;1.02]	0.094
	2007 vs. 2005	0.86 [0.76;0.98]	0.025
	2008 vs. 2005	0.74 [0.65;0.85]	< 0.001

2009 vs. 2005	0.67 [0.58;0.78]	< 0.001
2010 vs. 2005	0.63 [0.54;0.73]	< 0.001
2011 vs. 2005	0.62 [0.53;0.73]	< 0.001

Figure S1. Illustration of the study setup in the main analysis (A) and in the nested case control population (B).



T2D = Type 2 diabetes, PDC = proportion of days covered.

Figure S2. Flowchart.

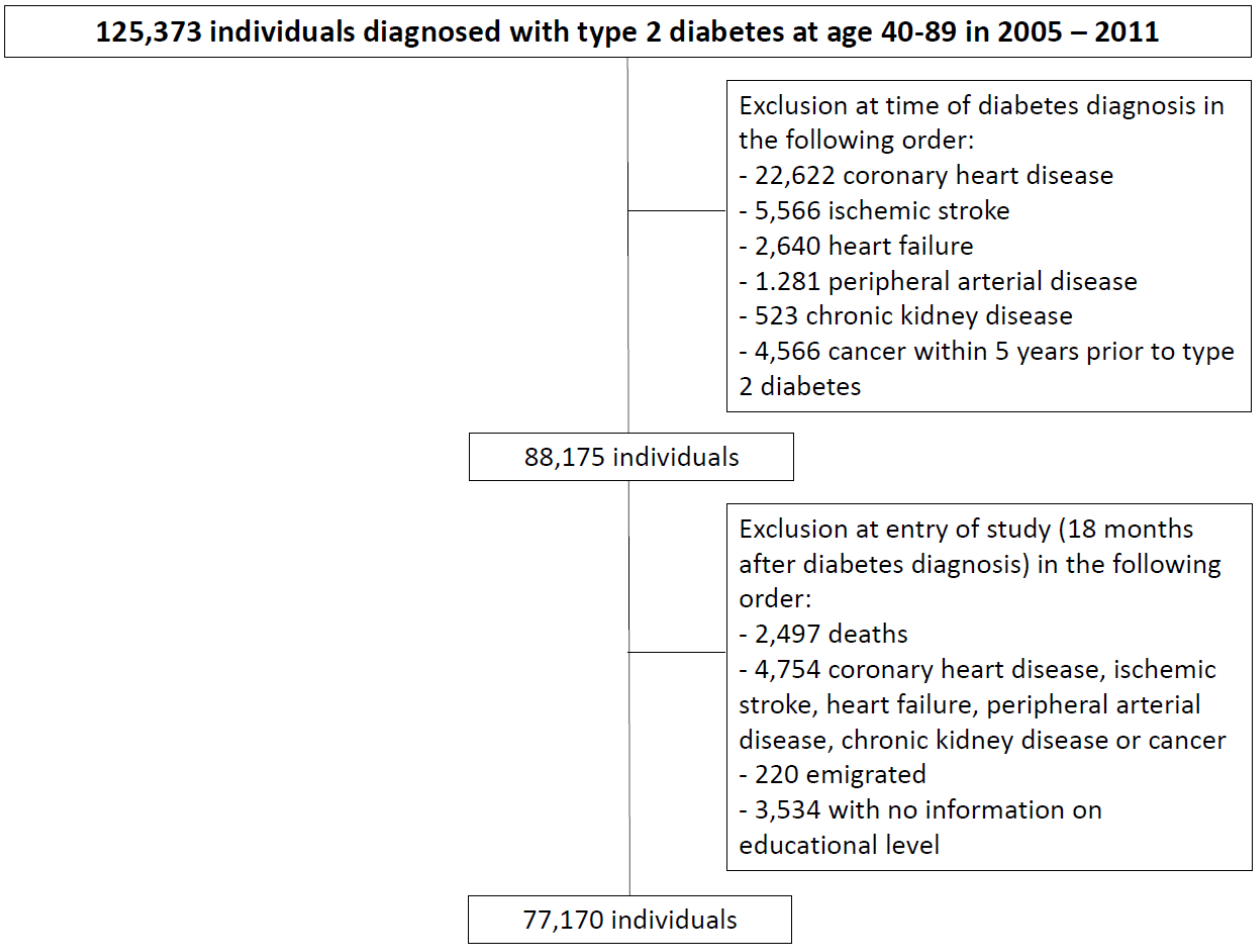


Figure S3. A) Proportion of patients treated with statins at index by age and sex, and B) mean proportion of days covered at index by age and sex in patients treated with statins at index.

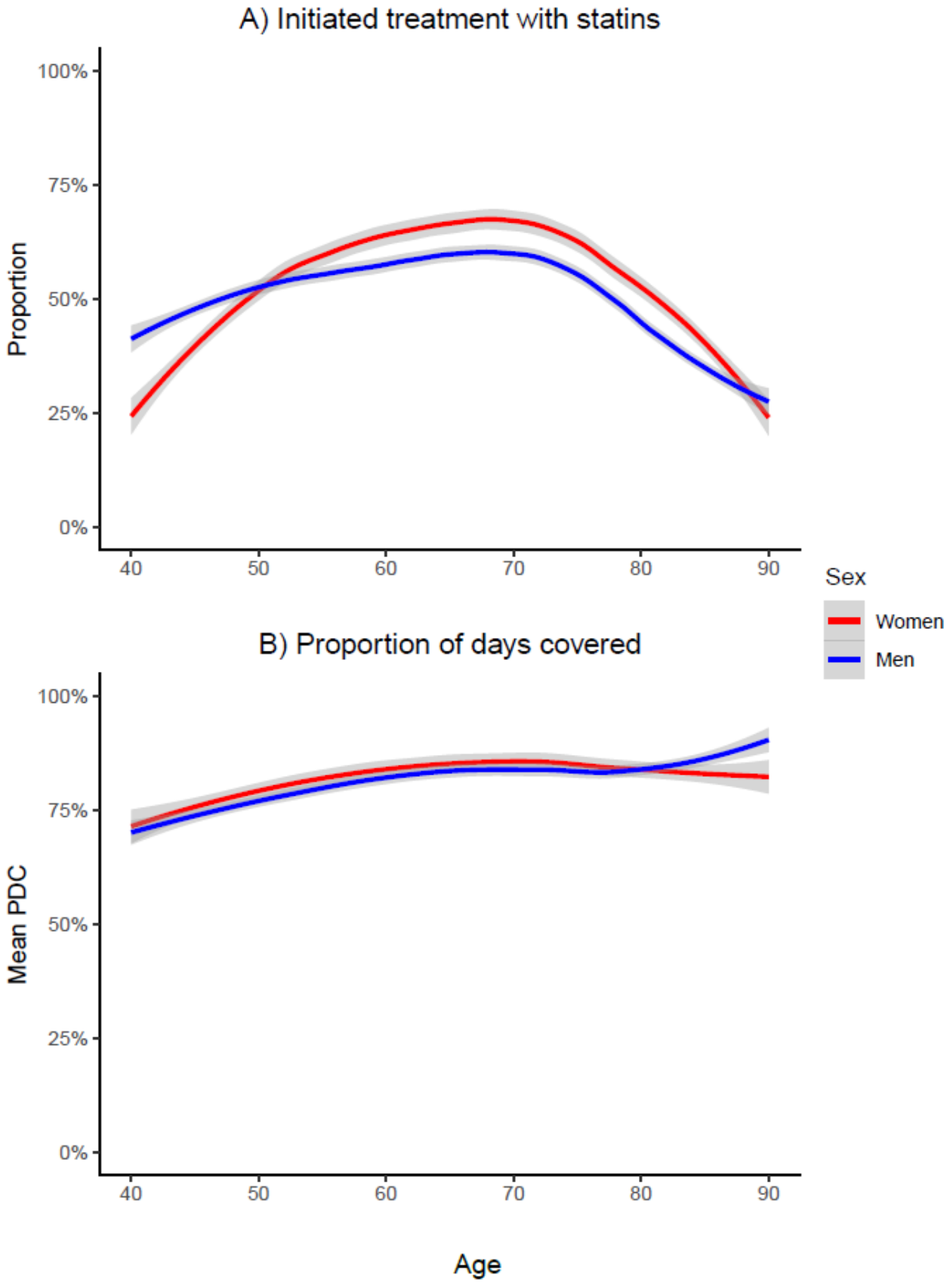


Figure S4. Crude and standardized 5-year risk of myocardial infarction, ischemic stroke or all-cause death according to sex, coverage and proportion of days covered.

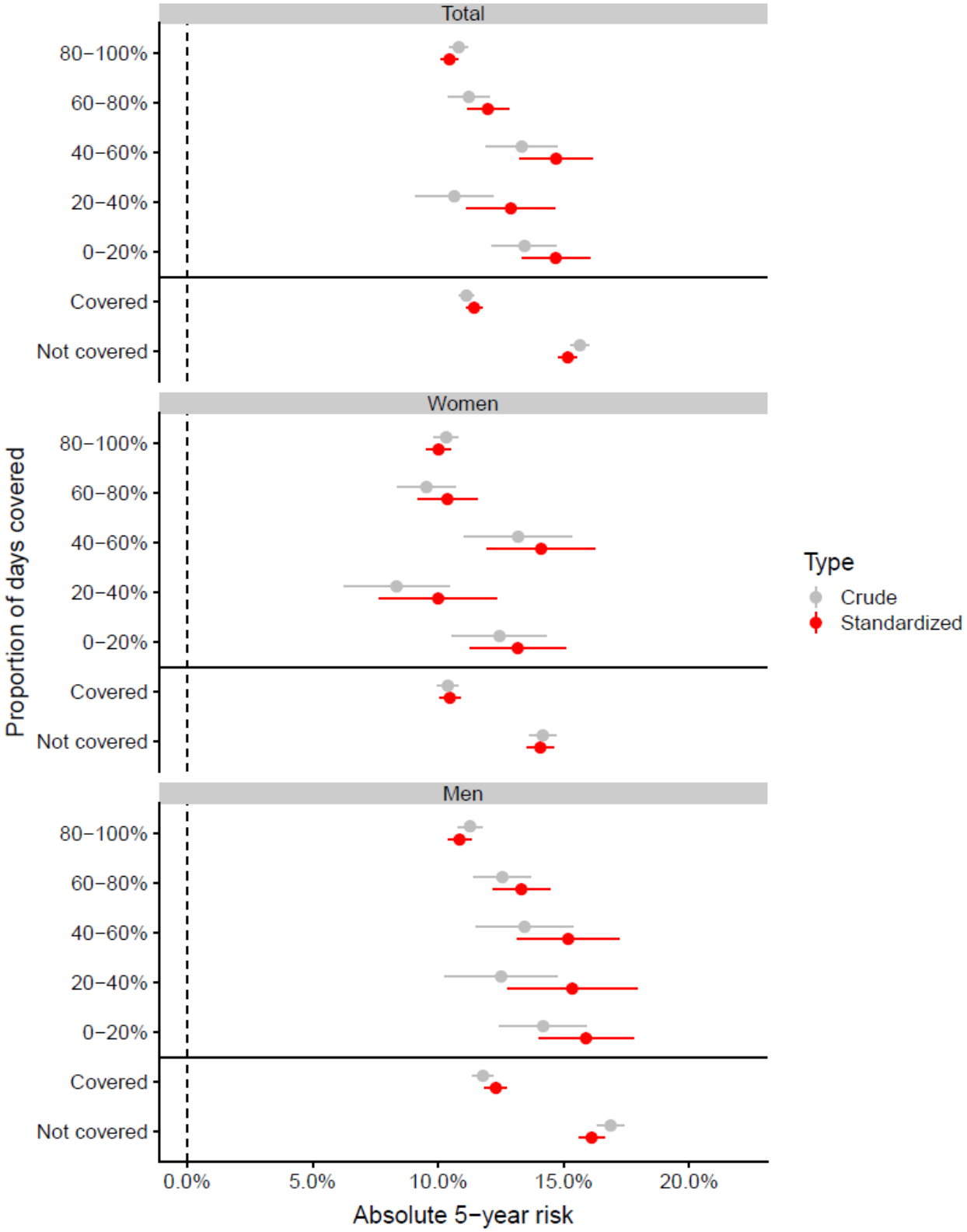
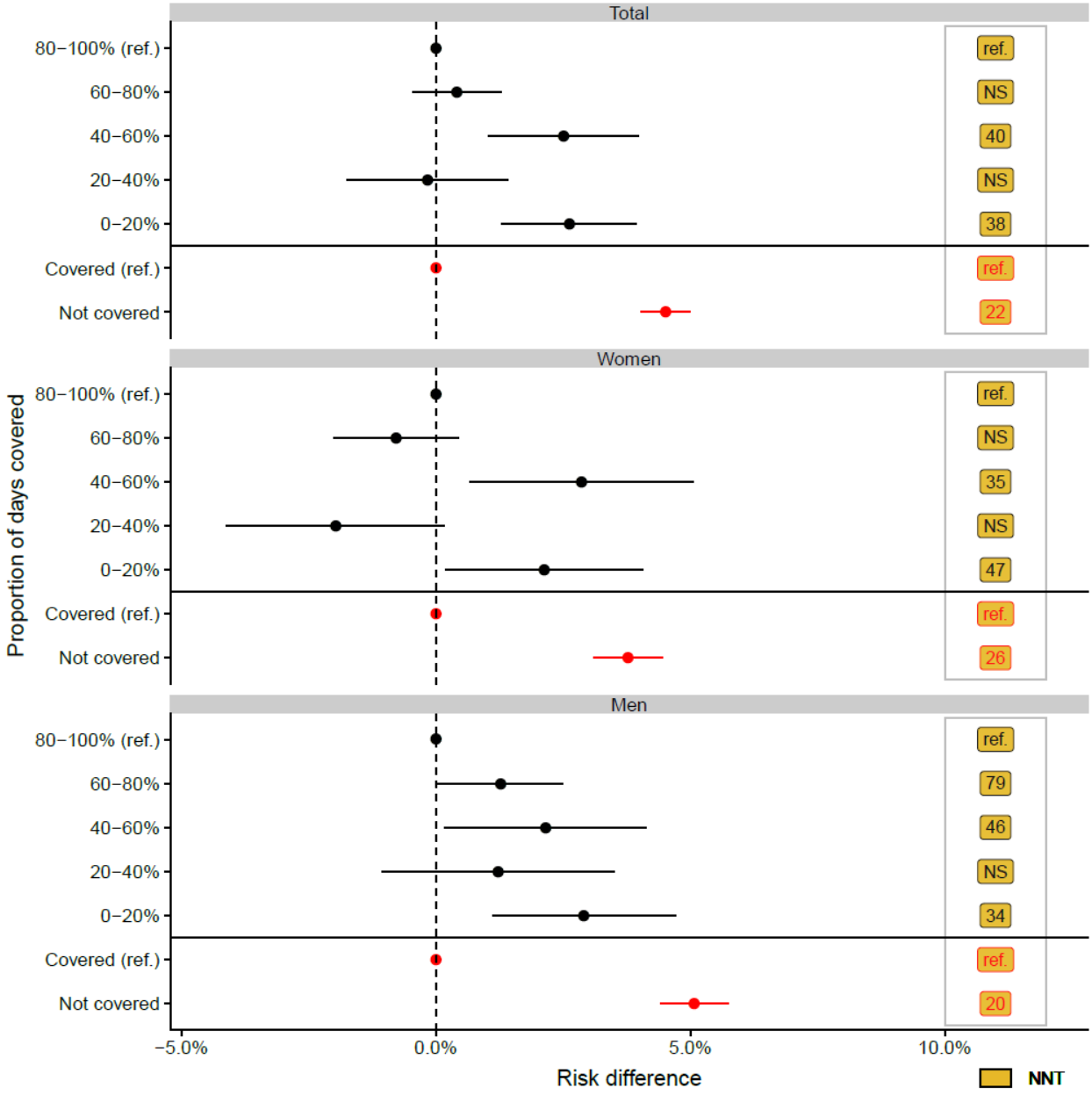


Figure S5. Crude 5-year risk difference of myocardial infarction, ischemic stroke or all-cause death according to sex, coverage of statins (reference = $risk_{treated}$) and proportion of days covered (reference = $risk_{PDC\ 80\text{-}100\%}$).



NNT = Numbers needed to treat, NS = Not significant.

Figure S6. Standardized 5-year risk of myocardial infarction, ischemic stroke or all-cause death according to sex, age and coverage.

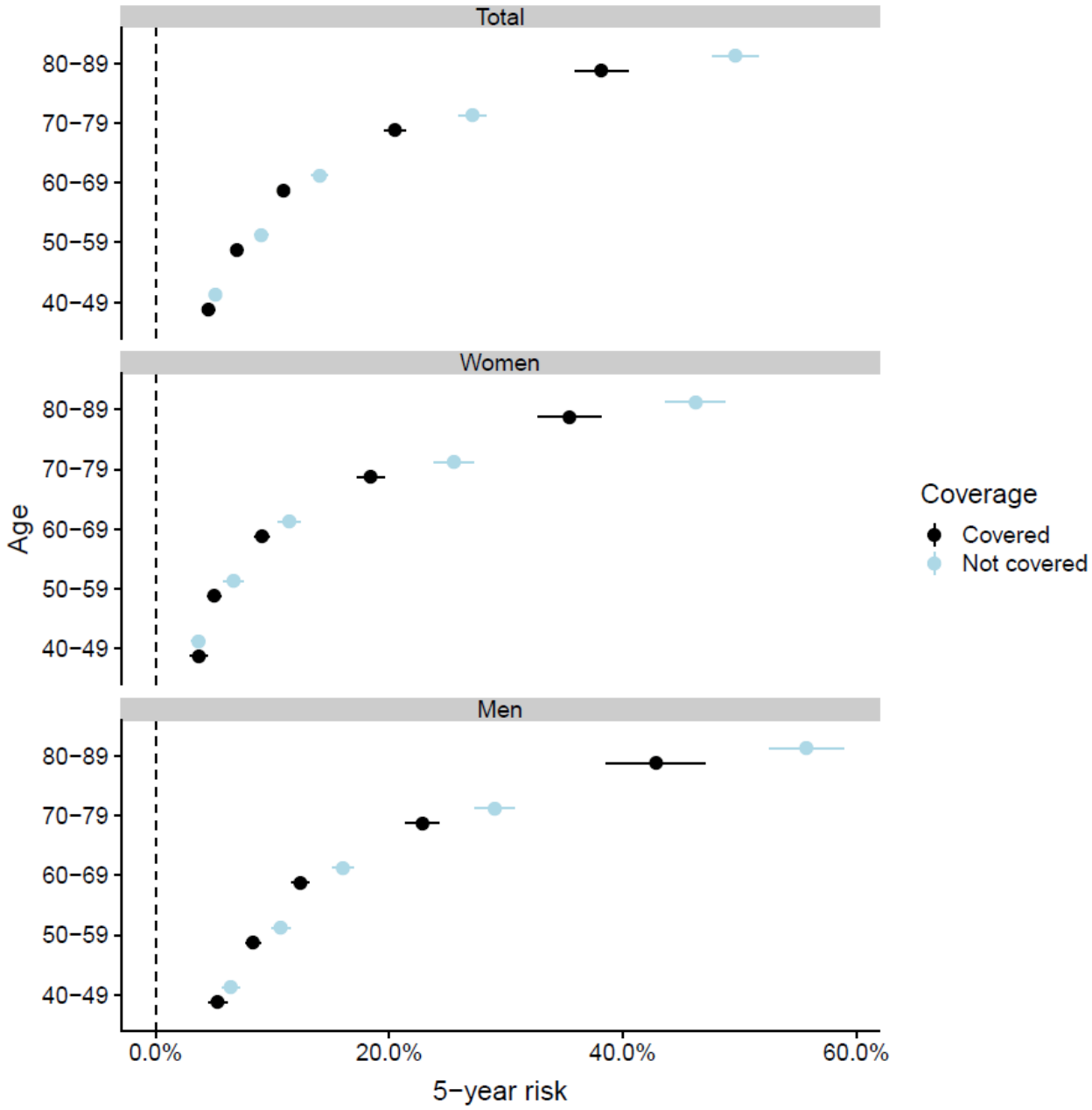


Figure S7. A) Crude and standardized 5-year risk of hospital discharge due to any skin lesion according to sex, coverage of statins and proportion of days covered. B) Standardized 5-year risk of hospital discharge due to any skin lesion according to sex, age-group and coverage of statins.

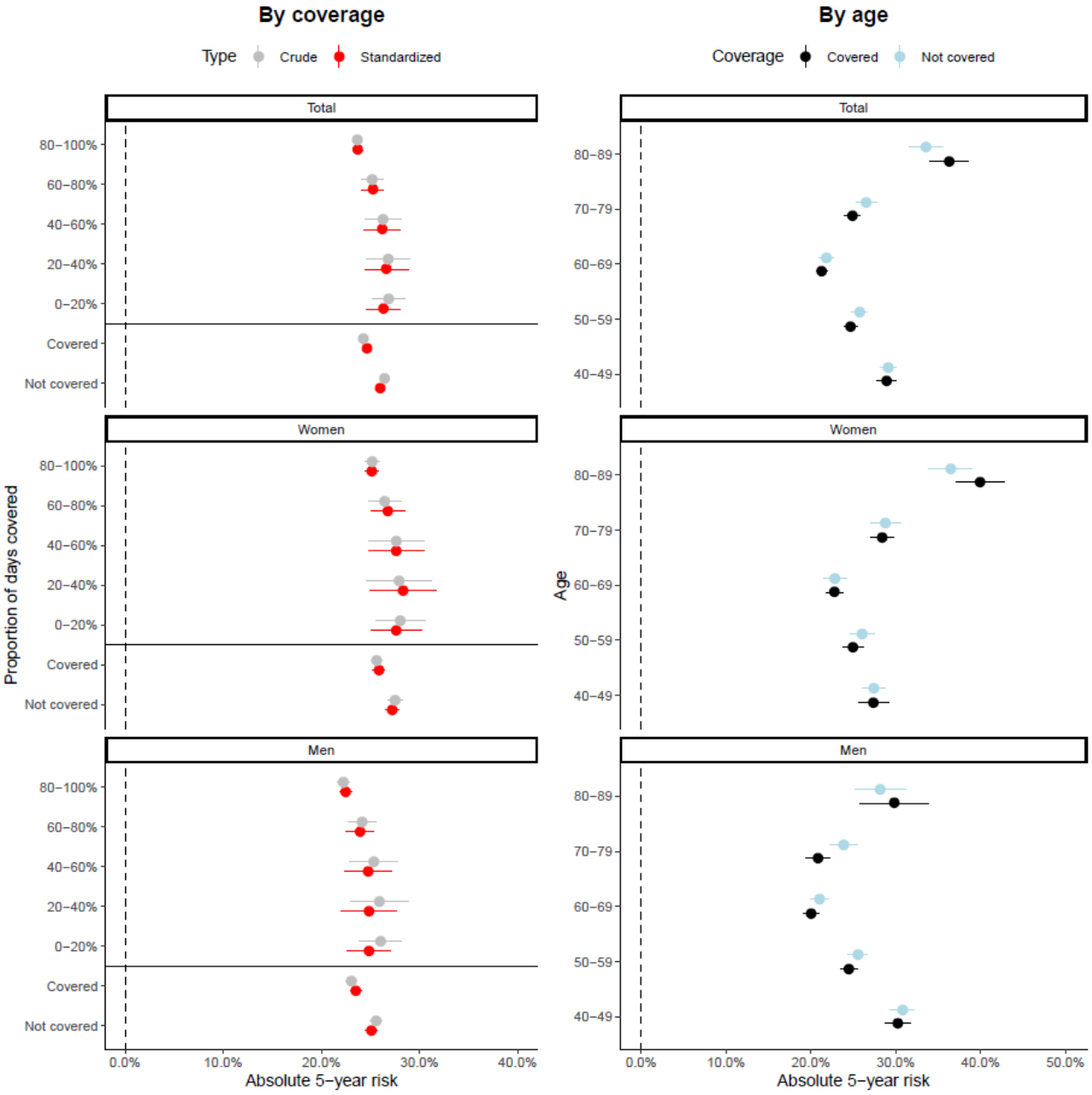
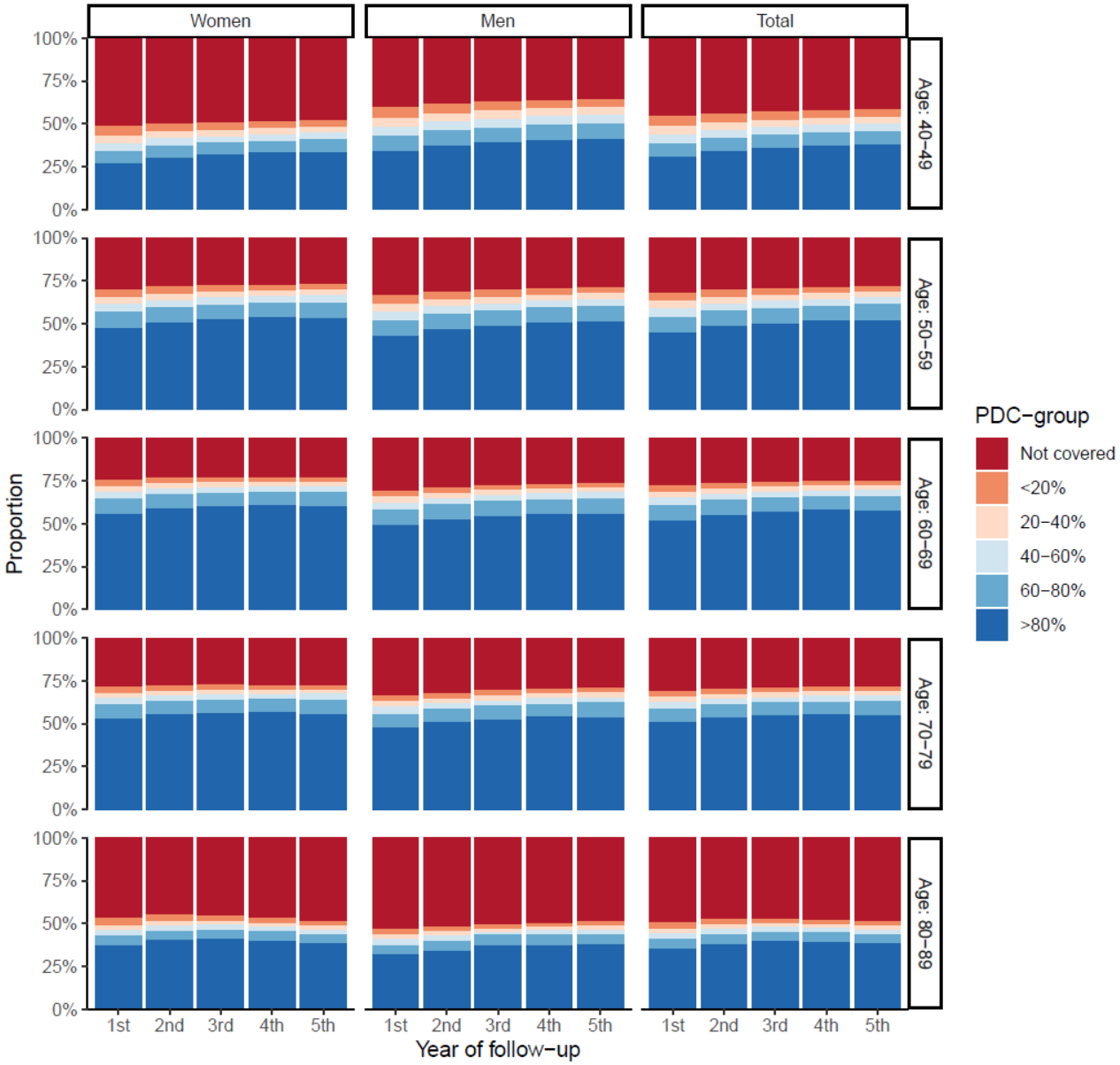
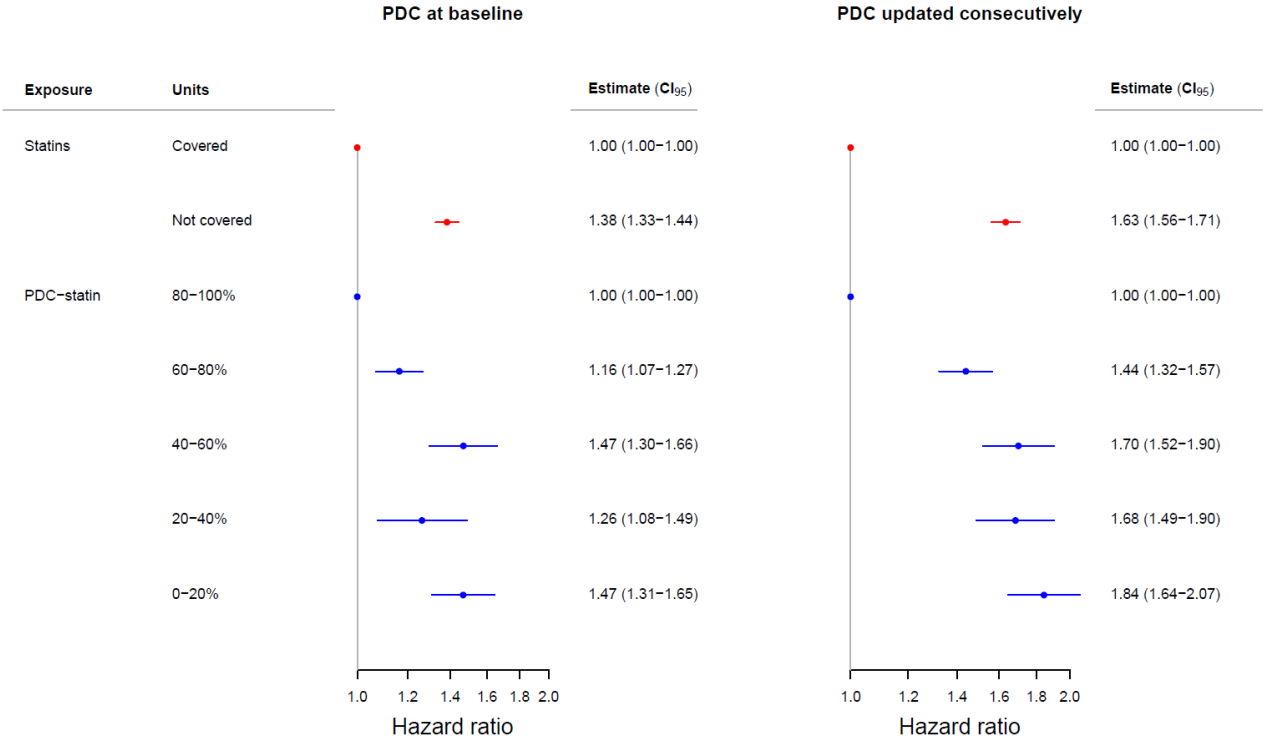


Figure S8. Coverage of statins according to sex, age group at time of type 2 diabetes diagnosis and year of follow-up in event-free individuals.



PDC = Proportion of days covered.

Figure S9. Adjusted Hazard ratios of myocardial infarction, ischemic stroke or all-cause death according to coverage (red) and proportion of days covered (blue) of statins in the main analysis and the nested case-control population.



PDC = proportion of days covered.