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4 Statin but not Aspirin Treatment is Associated with Reduced Cardiovascular Risk  
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7 in Patients with Diabetes without Obstructive Coronary Artery Disease  
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10 *A Cohort Study from the Western Denmark Heart Registry*  
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4 ABSTRACT  
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7 *Aims:* Patients with diabetes and no obstructive coronary artery disease (CAD) as assessed by  
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9 coronary angiography (CAG) are frequently treated with aspirin and statins. We examined the  
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11 effectiveness of aspirin and statin treatment on cardiovascular and bleeding incidence in patients  
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13 with diabetes and absent obstructive CAD.  
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16 *Methods and results:* The study included patients with diabetes and absent obstructive CAD as  
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18 assessed by CAG from 2003 to 2016 in Western Denmark. We stratified patients by aspirin and  
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20 statin treatment within 6 months after CAG in two separate analyses. Outcomes were MACE  
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22 (major adverse cardiovascular events, a composite of myocardial infarction, ischemic stroke, and  
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24 death) and bleeding (aspirin only). To account for confounding, we used propensity score-based  
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26 weights to estimate the inverse probability of treatment-weighted hazard ratios (HR<sub>IPTW</sub>). We  
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28 included 4,124 patients with diabetes but without CAD as assessed by CAG, among whom 2,474  
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30 (60%) received aspirin and 2,916 (71%) received statin treatment within 6 months following  
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32 CAG. Median follow-up was 4.9 years. Aspirin did not reduce 10-year MACE (21.3% vs 21.8%,  
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34 HR<sub>IPTW</sub> 1.01, 95% confidence interval (CI) 0.82-1.25), all-cause death (HR<sub>IPTW</sub> 0.96, 95% CI  
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36 0.74-1.23), or bleeding (HR<sub>IPTW</sub> 0.95, 95% CI 0.73-1.23), compared to those not receiving  
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38 aspirin treatment. Statin treatment reduced MACE (25% versus 37%, HR<sub>IPTW</sub> 0.58, 95% CI 0.48-  
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40 0.70) compared to those not receiving statin treatment.  
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48 *Conclusion:* Among patients with diabetes and no obstructive CAD, aspirin neither reduced  
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50 MACE nor increased bleeding. In contrast, statin treatment was associated with a major reduction  
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52 in risk of MACE.  
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58 *Keywords:* diabetes, coronary artery disease; statin; aspirin; myocardial infarction; death  
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## INTRODUCTION

Individuals with diabetes have a twofold greater risk of cardiovascular disease compared to persons without diabetes.[1] Patients with diabetes and coronary artery disease (CAD) are at substantially higher risk of cardiovascular outcomes compared to patients with CAD but without diabetes.[2] About 40% of patients undergoing elective coronary angiography (CAG) do not have obstructive CAD.[2] In the absence of obstructive CAD as assessed by CAG or coronary computed tomography angiography, persons with and without diabetes reportedly have a low and comparable risk of myocardial infarction (MI).[2-4] Still, patients with diabetes have an increased risk of ischemic stroke and death.[5] Current guidelines do not routinely recommend aspirin in patients with diabetes without established cardiovascular disease.[6, 7] However, many patients with diabetes continue aspirin treatment after CAG despite no sign of obstructive CAD or other indications for antiplatelet treatment. In such patients, the effectiveness of aspirin treatment remains unclear.

Statins are the first-choice lipid-lowering drugs. However, lipid-lowering therapy – similar to aspirin – is not generally recommended for patients with diabetes considered at low risk of cardiovascular events.[6] Since the efficacy of statins or aspirin in patients with diabetes with documented angiographic absence of CAD has not been examined in a randomized setting, it remains unknown whether aspirin or statins should be initiated, continued, or discontinued, as a primary prevention strategy, in such individuals.

We hypothesized that neither aspirin nor statins would reduce the risk of major adverse cardiovascular events (MACE) in patients with diabetes but without obstructive CAD as assessed by CAG in a routine clinical care setting in Western Denmark.

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4 METHODS

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7 *Study design and setting:* We conducted a cohort study using existing regional and national  
8 health care registries. Denmark has a free tax supported health care system. The Western Denmark  
9 Heart Registry has recorded every CAG performed in Western Denmark since 1999.<sup>[8]</sup> The Civil  
10 Registration System, which contains information on the vital status of each Danish resident,  
11 assigns a unique 10-digit number to each resident at birth or immigration. This identifier is used  
12 in every registry in the country, allowing for linkage of patient-level information among health  
13 care registries.  
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24 *Study population:* The study population included adult patients examined by CAG between  
25 January 1, 2003 and December 31, 2016 in Western Denmark (Figure 1). In case of multiple  
26 examinations of the same patient, the first CAG was considered the index procedure. Exclusions  
27 were a previous history of MI, percutaneous coronary intervention (PCI) or coronary artery bypass  
28 grafting (CABG) prior to CAG, missing CAD registration, obstructive CAD ( $\geq 50\%$  coronary  
29 stenosis in  $\geq 1$  coronary vessel), diffuse CAD (non-obstructive CAD in  $\geq 2$  coronary vessels), an  
30 indication for anti-platelet therapy (ischemic stroke, peripheral artery disease, or coronary  
31 revascularization  $< 6$  months after CAG), treatment with adenosine diphosphate inhibitors or oral  
32 anti-coagulant treatment, atrial fibrillation, or death/emigration  $< 6$  months after CAG. Inclusion  
33 criteria were a diabetes diagnosis recorded in the Danish National Patient Registry, a record of  
34 diabetes in the Western Denmark Heart Registry, or active treatment with anti-diabetes  
35 medications [ $\geq 1$  redeemed prescription(s) 6 months after CAG as recorded in the Danish  
36 Prescription Registry].  
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4       *Aspirin and statin treatment:* Active drug treatment with aspirin or statins at the start of  
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6 follow-up was defined as redemption of  $\geq 1$  prescription(s) within 6 months after the CAG date  
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8 (Supplemental material, Table S1).  
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11       *Outcomes:* The main outcome was MACE, defined as MI, ischemic stroke, or all-cause  
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13 death (Supplemental material, Table S1). We separately examined **cardiovascular death**, all-  
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15 cause death, as well as any hospitalization for bleeding for aspirin.  
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19       *Statistical analysis:* We performed two separate analyses for aspirin treatment and statin  
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21 treatment. Start of follow-up was postponed for 6 months after the CAG date to ensure that patients  
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23 were classified according to aspirin and statin treatment after CAG examination. Follow-up  
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25 continued for up to 10 years, until occurrence of an outcome, death, emigration, or end of follow-  
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27 up (December 31, 2018). For aspirin treatment, patient follow-up was censored upon occurrence  
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29 of an indication for aspirin therapy (coronary revascularization, peripheral artery disease, or atrial  
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31 fibrillation) or initiation of other anti-thrombotic treatment (ADP-inhibitor or oral anti-coagulant  
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33 treatment). Follow-up also was censored when non-treated patients initiated aspirin treatment. We  
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35 used propensity score-based weights to account for confounding.<sup>[9]</sup> The propensity score was  
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37 estimated using a logistic regression model including variables associated with both treatment  
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39 exposure and outcome, or outcome alone (sex, age, hypertension, heart failure, duration of  
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41 diabetes, referral to evaluate acute coronary syndrome, procedural urgency, active smoking,  
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43 previous hospitalization for bleeding, statin treatment within six months following CAG, other-  
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45 lipid lowering treatment, and year of examination).<sup>[10]</sup> A total of 9.8% of patients had missing  
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47 values for smoking. Missing values were handled through multiple imputation using chained  
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49 equations, generating 10 imputations.<sup>[11]</sup>  
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4 We used stabilized inverse-probability of treatment weighting (IPTW) to estimate the  
5 average treatment effect, and standardized mortality ratio weighting (SMRW) to estimate the  
6 average treatment effect among treated patients.<sup>[9, 12]</sup> We estimated baseline characteristics in  
7 IPTW and SMRW pseudo-populations to assess the balance among treated and non-treated  
8 patients after weighting. We used Cox regression to compute crude and weighted hazard ratios  
9 (HRs) with a robust variance-covariance estimator using non-treated patients as reference.<sup>[9, 13]</sup>  
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11 The proportional hazards assumption was evaluated using log -log plots and found to be satisfied.  
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13 We also computed 10-year cumulative incidence and cumulative incidence curves weighted by  
14 IPTW. We performed sex-stratified analyses, considering that previous results suggest potential  
15 sex-dependent effects of aspirin.<sup>[14]</sup> We performed a similar analysis using post-procedural statin  
16 treatment as the exposure. Follow-up started 6 months after the CAG examination date and  
17 continued until occurrence of an outcome, emigration, or 10 years after start of follow-up. Follow-  
18 up of patients not treated with statins was censored if statin treatment was initiated. The propensity  
19 for statin treatment at start of follow-up was estimated using a multivariable logistic regression  
20 model similar to that previously described, also including aspirin treatment. We tested for  
21 interaction between aspirin treatment and statin treatment and the risk of MACE. A p-value <0.05  
22 was considered statistically significant. We used Stata/MP version 16 and R version 4 with R  
23 package ‘tableone’.

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26 *Subgroup analyses:* We performed subgroup analyses limited to (1) patients with stable  
27 angina pectoris as the indication for an elective procedure, and (2) patients with type 2 diabetes,  
28 i.e., excluding patients who had redeemed a prescription only for insulin prior to the start of follow-  
29 up. We also compared patients in high-intensity statin treatment (atorvastatin  $\geq 40$  mg or  
30 rosvastatin  $\geq 20$  mg) to patients in moderate-intensity statin (any other statin treatment).[7]

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4       *Sensitivity analyses:* We performed a sensitivity analysis in which follow-up of aspirin-  
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6 treated patients was censored if aspirin was discontinued. We first counted the number of days that  
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8 each prescription redemption would cover assuming consistent daily intake, i.e., one pill per day.  
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10 Discontinuation was defined as not redeeming a new aspirin prescription >90 days, >60 days, >30  
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12 days, or >15 days, respectively, since the last day that the previous prescription would cover. We  
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14 did not perform a similar sensitivity analysis of statin treatment. Contrary to aspirin, the effect of  
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16 statins on atherosclerosis is not immediate. In addition, the effect of statin would offer some lasting  
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18 protection after discontinuation if preceded by long-term treatment. We performed sensitivity  
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20 analysis using asymmetrical trimming of propensity scores with a 5th percentile to 95th percentile  
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22 range to reduce residual confounding.<sup>[15]</sup> Finally, we performed a new-user analysis of statin  
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24 treatment, excluding patients who had received statin treatment (i.e., redeemed a statin  
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26 prescription) within 6 months prior to CAG.  
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33       *Ethical considerations:* This study was approved by the Danish Data Protection Agency  
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35 (record no. 1-16-02-193-18). Observational registry-based studies do not require approval from  
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37 ethics committees or informed consent from patients according to Danish regulations.  
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## 43 RESULTS

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45       A total of 4,124 patients with diabetes but with no CAD or non-obstructive CAD, as  
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47 assessed by CAG, and no indication for aspirin were included in the study. Among participants,  
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49 2,474 (60%) were receiving aspirin treatment and 2,916 (71%) were receiving statin treatment  
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51 (Figure 1). Median follow-up was 4.9 years (interquartile range 2.2-8.1 years).  
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54       *Baseline characteristics:* Patients receiving aspirin treatment 6 months after CAG were  
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56 older and more often female than patients not treated with aspirin (Table 1). Aspirin-treated  
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4 patients were also more likely to have hypertension and heart failure, and were more frequently  
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6 treated with statins, non-insulin diabetes medication, and anti-hypertensive drugs than non-treated  
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8 patients. After weighting aspirin users and nonusers, treatment groups were well-balanced, with  
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10 absolute standardized differences for all covariates  $<0.10$  after weighting (Supplemental material,  
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12 Table S2). Two year after start of follow-up, 87.2% of aspirin-treated patients remained in  
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14 treatment.

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19 Patients receiving statin treatment were older and more often female than non-treated  
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21 patients. Statin treatment was more frequently associated with hypertension, but less frequently  
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23 associated with heart failure and renal disease. Aspirin, non-insulin diabetes medications, and anti-  
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25 hypertensive drugs were more frequently used by statin-treated patients. After weighting statin  
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27 users and nonusers, treatment groups were well-balanced, with absolute standardized differences  
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29 for all covariates  $<0.10$  after weighting (Supplemental material, Table S3). Among statin-treated  
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31 patients, 90.0% were still in treatment 2 years after inclusion. Simvastatin was the most frequently  
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33 used type of statin, followed by atorvastatin. Median statin treatment duration prior to start of  
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35 follow-up prior was 4.8 years (interquartile range: 2.1-7.9 years) among statin-treated patients.

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41 *Aspirin treatment:* The weighted 10-year cumulative incidence of MACE was similar in  
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43 aspirin-treated and non-treated patients (21.3% versus 21.8%, Table 2, Figure 2). When estimating  
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45 the average treatment effect of aspirin, we found no difference in 10-year MACE (HR<sub>IPTW</sub> 1.01,  
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47 95% CI 0.82-1.25). Results were similar when estimating the average treatment effect among  
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49 treated patients [HR<sub>SMRW</sub> 1.01, 95% confidence interval (CI) 0.80-1.28, Table 2]. We found similar  
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51 results for **cardiovascular death and** all-cause death. Hospitalizations for bleeding were not  
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53 increased in patients treated with aspirin. When applying increasingly strict censoring criteria for  
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55 treatment discontinuation among aspirin-treated patients, results were similar (Supplemental  
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4 material, Tables S4-S6, Figure S1). However, with stricter censoring criteria point estimates  
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6 showed a reduced MACE rate and an increased bleeding rate associated with aspirin treatment,  
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8 corresponding to an assumption of greater compliance. We found similar results using  
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10 asymmetrical trimming (Supplemental material, Table S7). We found no sex differences in MACE  
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12 (Supplemental material, Table S8).  
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16 *Statin treatment:* Treatment with statin after CAG was associated with reduced 10-year  
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18 risk of MACE compared to non-treated patients (24.6% versus 37.2%, HR<sub>IP<sub>TW</sub></sub> 0.58, 95% CI 0.48-  
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20 0.70, Table 2, Figure 2). This was driven by lower risk of MI and death, but not ischemic stroke.  
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22 Similar results were seen after asymmetrical trimming and among new users (Supplemental  
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24 material, Tables S9-S10). We found no interaction between aspirin and statin treatment (p=0.58).  
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28 **We found no significant effect of high-intensity statin treatment compared to moderate-**  
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30 **intensity statin treatment (Supplemental material, Tables S11).**  
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34 Among patients undergoing an elective procedure due to stable angina pectoris, aspirin did  
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36 not reduce MACE. We also observed a more modest MACE reduction associated with statin  
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38 treatment than in the main analysis (Supplemental material, Table S12). Subgroup analysis of  
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40 patients with type 2 diabetes yielded results similar to the main analysis (Supplemental material,  
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42 Table S13).  
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## 45 46 47 48 DISCUSSION

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50 The major findings of this study, performed in a cohort of patients with diabetes and  
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52 without obstructive CAD, were that statin treatment reduced MACE and all-cause death, while  
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54 aspirin did not affect these outcomes.  
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4 Our group and others have shown previously that patients with diabetes have a low risk of  
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6 MI and an intermediate risk of ischemic stroke in the absence of obstructive CAD.<sup>[2, 4, 5]</sup> In the  
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8 current study, we examined the effect of aspirin and statins, hypothesizing that neither aspirin nor  
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10 statins would improve outcomes in this population. We found no effect of aspirin treatment for  
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12 patients with diabetes and without obstructive CAD. These results align with the ASCEND (A  
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14 Study of Cardiovascular Events in Diabetes) trial, which examined the effect of aspirin as primary  
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16 prophylaxis in patients with diabetes but no clinical history of cardiovascular disease  
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18 (n=15,480).[16] Aspirin reduced the risk of serious vascular events by 1.1%. This was offset by a  
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20 absolute increase in major bleeding of 0.9%. Aspirin failed to reduce serious cardiovascular events  
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22 and mortality in a meta-analysis of 11,618 patients with diabetes.<sup>[14]</sup> In both the ASCEND trial and  
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24 the meta-analysis, eligible patients had no clinical history of cardiovascular disease and unknown  
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26 coronary status. The latter characteristic suggests that our cohort, with documented absence of  
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28 obstructive CAD, may have been at lower risk of cardiac events than the ASCEND cohort.  
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30 However, our results are consistent with those of the ASCEND trial.  
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38 In contrast to aspirin, we found that statin treatment of patients with diabetes but without  
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40 obstructive CAD was associated with a 12.6% absolute risk reduction in MACE over ten years.  
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42 **Primary prophylactic treatment with statins significantly reduces cardiovascular risk in**  
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44 **diabetes patients.[17] However, randomized studies have primarily included patients with**  
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46 **unknown coronary status.[18] The use of statins for primary prevention among patients**  
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48 **without angiographically-documented absence of obstructive CAD has not yet been**  
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50 **examined in a randomized setting.** Treating asymptomatic patients with an intermediate risk of  
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52 cardiovascular disease with statins – independent of cholesterol levels – reduced a composite end-  
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54 point of cardiac death, MI, stroke, cardiac arrest, heart failure, or revascularization by 24% and  
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4 yielded a 35% relative reduction in MI.<sup>[19]</sup> After 5.6 years of follow-up of statin-treated patients,  
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6 0.7% had experienced MI, 1.1% had experienced stroke, and 5.6% had died. After median follow-  
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8 up of 4.9 years, we observed a 2.4% MI risk, 3.0% ischemic stroke risk, and 13.5% mortality. We  
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10 included symptomatic patients with diabetes, a high prevalence of hypertension and heart failure,  
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12 and a high body mass index, with an indication for CAG. This may explain the increased event  
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14 rates compared to the randomized trials. A 1 mmol/L reduction in LDL cholesterol among patients  
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16 prescribed statins as primary prevention was associated with a 43% relative reduction in major  
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18 coronary events among patients with low risk of vascular disease and no history of CAD.<sup>[20]</sup> In a  
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20 pooled cohort of 11,730 randomized patients with diabetes and without known atherosclerotic  
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22 cardiovascular disease, statin treatment significantly reduced major vascular events (MI, coronary  
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24 death, stroke, or revascularization) by 27% per mmol/L reduction in LDL cholesterol.<sup>[18]</sup> A Danish  
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26 study found that new statin users on average reduced their LDL cholesterol levels by 1.7 mmol/L,  
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28 and that 82% of high-risk patients (including patients with diabetes without previous  
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30 cardiovascular disease) reached the recommended 2.5 mmol/L treatment target.<sup>[21]</sup> Assuming a  
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32 similar reduction in our cohort, we would expect a 34% relative reduction in MACE with statin  
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34 use, but actually observed a 42% reduction.<sup>[22]</sup> Current guidelines recommend exceedingly low  
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36 LDL cholesterol target levels depending on cardiovascular risk status.<sup>[6]</sup> American guidelines  
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38 recommend statin treatment as primary prevention for all patients with type 2 diabetes aged 40-  
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40 70.<sup>[23]</sup> In the absence of randomized trial evidence, our findings support statin treatment of patients  
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42 with diabetes and without obstructive CAD, since statin treatment is inexpensive and has few side  
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44 effects.<sup>[24]</sup> However, statin treatment did not lower the risk of ischemic stroke in our cohort. A  
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46 possible explanation is that increased risk of subclinical episodes of atrial fibrillation in patients  
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48 with diabetes causing embolic strokes that cannot be prevented by statin.<sup>[25]</sup> The Danish Steno-2  
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4 study found that an intensive, target-driven, multifactorial intervention, including medication  
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6 (lipid-lowering medication and aspirin) and lifestyle changes in patients with diabetes, led to a  
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8 20% absolute decrease in mortality over 13 years of follow-up, as well as a decrease in  
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10 cardiovascular events.<sup>[26]</sup> These results led to the implementation of an intensive risk management  
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12 strategy for Danish patients with diabetes, as observed in our patient cohort. However, this  
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14 intervention may not be uniformly implemented in other countries.  
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19 *Limitations:* The results of the observational study reported here are in line with those from  
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21 randomized clinical trials. However, several limitations must be mentioned. First, we did not have  
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23 access to LDL cholesterol values. While LDL cholesterol currently guides the decision to initiate  
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25 statins, it is not considered in the decision to initiate aspirin.<sup>[6]</sup> Second, it is possible that residual  
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27 confounding and confounding by indication may have biased the results of our study. However,  
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29 we employed statistical methods to reduce the possibility of confounding.[9, 12] Third, drug  
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31 exposure was determined by prescription redemption. We cannot attest to whether patients took  
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33 their medication, but that limitation applies to both observational studies and clinical trials.  
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35 However, prescription redemption indicates an active effort to collect and pay for medication. This  
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37 perhaps indicates a higher probability of taking the medication. Fourth, patients included in this  
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39 study may have had mild, non-obstructive CAD in a single vessel. CAD represents a continuum  
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41 rather than a dichotomous condition, with varying extent of affected vessels and stenosis severity.  
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43 We were unable to differentiate between patients with no apparent CAD and mild CAD. However,  
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45 a study of American veterans found no difference in one-year MI incidence and mortality between  
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47 patients with diabetes with no CAD and with mild-single vessel disease.<sup>[27]</sup> **Subclinical**  
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49 **atherosclerosis cannot be detected by CAG. Some of the patients may have had subclinical**  
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51 **coronary plaque burden, which has been found to be stronger predictor of cardiovascular**  
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4 **disease than luminal stenosis.[28]** Finally, our study cohort represents symptomatic patients with  
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6 diabetes examined by CAG and should not be generalized to all patients with diabetes.  
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9         In conclusion, statins, but not aspirin, reduced cardiovascular risk as assessed by CAG in  
10 patients with diabetes and without obstructive CAD. However, aspirin did not increase  
11 hospitalizations for bleeding. Unless proven otherwise by future randomized trials, our results  
12 suggest that statin treatment should be recommended to patients with diabetes, even with  
13 documented absence of CAD. Continued aspirin treatment cannot be discouraged based on our  
14 results, but should be carefully weighed by patients in consultation with their physicians in the  
15 context of their individual risk profiles.  
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16 None  
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21 DATA AVAILABILITY STATEMENT

22  
23 The data on which this article is based cannot be shared publicly due to Danish data protection  
24 regulations.  
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31 CONFLICTS OF INTERESTS

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33 K.K.W.O. has received a speaker's fee from Bayer. U.H.J., R.W.T., and H.T.S. report that the  
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TABLES

**Table 1.** Baseline characteristics in diabetes patients without obstructive coronary artery disease by aspirin treatment and statin treatment.

	No aspirin (n=1,650)		Aspirin (n=2,474)		No statin (n=1,208)		Statin (n=2,916)	
	n	%	n	%	n	%	n	%
Mean age (SD)	56 years (12)		61 years (11)		57 years (13)		60 years (11)	
Male sex	864	52.4	1,210	48.9	674	55.8	1,400	48.0
Smoking <sup>a</sup>	350	21.2	517	20.9	289	23.9	578	19.8
Family history of ischemic heart disease <sup>a</sup>	613	37.2	1,026	41.5	432	35.8	1,207	41.4
<b>Comorbidity</b>								
Hypertension	1,155	70.0	2,038	82.4	820	67.9	2,373	81.4
Heart failure	207	12.5	349	14.1	214	17.7	342	11.7
Renal disease	147	8.9	121	4.9	104	8.6	164	5.6
Previous bleeding	151	9.2	165	6.7	90	7.5	226	7.8
Median diabetes duration (IQR)	4 years (1-9)		4 years (1-10)		3 years (0-9)		4 years (1-10)	
Median eGFR (IQR) <sup>a</sup>	99 mL/min (76-119)		95 mL/min (75-115)		99 mL/min (76-118)		96 mL/min (76-115)	
Median BMI, (IQR)	30 kg/m <sup>2</sup> (26-35)		30 kg/m <sup>2</sup> (27-35)		30 kg/m <sup>2</sup> (25-34)		30 kg/m <sup>2</sup> (27-35)	
Median systolic BP (IQR)	140 mmHg (125-154)		140 mmHg (127-154)		140 mmHg (124-153)		140 mmHg (128-155)	
Median diastolic BP (IQR)	80 mmHg (70-88)		80 mmHg (70-87)		80 mmHg (70-87)		80 mmHg (70-88)	
<b>Medication</b>								
Statin	943	57.2	1,973	79.7	0	0.0	2,916	100.0
Aspirin	0	0.0	2,474	100.0	501	41.5	1,973	67.7
Non-insulin	904	54.8	1,683	68.0	595	49.3	1,992	68.3
Insulin	462	28.0	731	29.5	342	28.3	851	29.2
Beta-blocker	560	33.9	1,326	53.6	474	39.2	1,412	48.4
Calcium-blocker	464	28.1	951	38.4	327	27.1	1,088	37.3

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Thiazide	250	15.2	500	20.2	172	14.2	578	19.8
ARB	442	26.8	772	31.2	275	22.8	939	32.2
ACE-inhibitor	575	34.8	1,154	46.6	443	36.7	1,286	44.1
Proton-pump inhibitor	526	31.9	754	30.5	361	29.9	919	31.5
Other lipid-lowering treatment	42	2.5	74	3.0	54	4.5	62	2.1
Fibrates	10	0.6	33	1.3	21	1.7	22.0	0.8
Cholestyramine	2	0.1	3	0.1	2	0.2	3	0.1
Niacine	4	0.2	3	0.1	2	0.2	5	0.2
Ezetimibe	27	1.6	38	1.5	32	2.6	33	1.2
<b>Type of statin</b>								
Simvastatin	687	41.6	1,467	59.3	0	0.0	2,150	73.3
Atorvastatin	190	11.5	372	15.0	0	0.0	560	19.2
Rosuvastatin	45	2.7	94	3.8	0	0.0	138	4.7
Lovastatin	0	0.0	3	0.1	0	0.0	3	0.1
Fluvastatin	4	0.2	4	0.2	0	0.0	8	0.3
Pravastatin	22	1.3	35	1.4	0	0.0	57	2.0
<b>Priority</b>								
Acute	89	5.4	101	4.1	89	7.4	101	3.5
Subacute	298	18.1	423	17.1	223	18.5	498	17.1
Elective	1,263	76.5	1,950	78.8	896	74.2	2,317	79.5
<b>Indication</b>								
STEMI	49	3.0	55	2.2	53	4.4	51	1.7
NSTEMI	75	4.5	157	6.3	60	5.0	172	5.9
Unstable AP	70	4.2	72	2.9	41	3.4	101	3.5
Stable AP	843	51.1	1,428	57.7	576	47.7	1,695	58.1
Arrhythmia	48	2.9	49	2.0	39	3.2	58	2.0
Valvular disease	60	3.6	120	4.9	66	5.5	114	3.9
Cardiomyopathy	135	8.2	200	8.1	121	10.0	214	7.3
Other	370	22.4	393	15.9	252	20.9	511	17.5

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<b>CCTA &lt;3 months prior to examination</b>	<b>124</b>	<b>10.3</b>	<b>180</b>	<b>6.2</b>	<b>141</b>	<b>8.5</b>	<b>163</b>	<b>6.6</b>
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<sup>a)</sup> Missing values: smoking (9.8%), family history of ischemic heart disease (9.4%), eGFR (18.7%)

ACE: angiotensin converting enzyme

AP: angina pectoris

ARB: angiotensin II receptor blocker

BMI: body mass index

BP: blood pressure

**CCTA: coronary computed tomography angiography**

eGFR: estimated glomerular filtration rate

IQR: interquartile range

NSTEMI: non-ST elevation myocardial infarction

SD: standard deviation

STEMI: ST-elevation myocardial infarction

**Table 2.** Risk of major adverse cardiovascular events, death, and bleeding by aspirin and statin treatment.

	Patients (events)	Stabilized IP-weighted 10-year incidence proportion	Crude HR (95% CI)	Stabilized IP-weighted HR (95% CI)	SMR-weighted HR (95% CI)
<i>Aspirin treatment</i>					
<i>Major adverse cardiovascular events</i>					
No aspirin	1,650 (149)	21.8%	Reference	Reference	Reference
Aspirin	2,474 (360)	21.3%	1.18 (0.98-1.43)	1.01 (0.82-1.25)	1.01 (0.80-1.28)
<i>Cardiovascular death</i>					
<b>No aspirin</b>	<b>1,650 (31)</b>	<b>6.5%</b>	<b>Reference</b>	<b>Reference</b>	<b>Reference</b>
<b>Aspirin</b>	<b>2,474 (110)</b>	<b>6.2%</b>	<b>1.81 (1.21-2.71)</b>	<b>1.18 (0.76-1.85)</b>	<b>1.07 (0.67-1.73)</b>
<i>All-cause death</i>					
No aspirin	1,650 (111)	16.6%	Reference	Reference	Reference
Aspirin	2,474 (250)	15.4%	1.10 (0.88-1.38)	0.96 (0.74-1.23)	0.99 (0.74-1.31)
<i>Hospitalization for bleeding</i>					
No aspirin	1,650 (98)	12.2%	Reference	Reference	Reference
Aspirin	2,474 (187)	11.9%	0.97 (0.76-1.24)	0.95 (0.73-1.23)	0.91 (0.69-1.20)
<i>Statin treatment</i>					
<i>Major adverse cardiovascular events</i>					
No statins	1,208 (177)	37.2%	Reference	Reference	Reference
Statins	2,916 (500)	24.6%	0.63 (0.53-0.75)	0.58 (0.48-0.70)	0.58 (0.47-0.71)
<i>Cardiovascular death</i>					
<b>No statins</b>	<b>1,208 (53)</b>	<b>11.2%</b>	<b>Reference</b>	<b>Reference</b>	<b>Reference</b>
<b>Statins</b>	<b>2,916 (81)</b>	<b>4.1%</b>	<b>0.36 (0.25-0.51)</b>	<b>0.30 (0.21-0.44)</b>	<b>0.30 (0.20-0.44)</b>
<i>Myocardial Infarction</i>					
No statins	1,208 (23)	6.2%	Reference	Reference	Reference
Statins	2,916 (69)	3.6%	0.65 (0.40-1.04)	0.61 (0.37-1.02)	0.63 (0.36-1.09)
<i>Ischemic stroke</i>					

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No statins	1,208 (19)	3.6%	Reference	Reference	Reference
Statins	2,916 (87)	4.4%	1.05 (0.64-1.73)	0.95 (0.56-1.62)	0.96 (0.55-1.68)
<i>All-cause death</i>					
No statins	1,208 (147)	31.7%	Reference	Reference	Reference
Statins	2,916 (394)	20.0%	0.58 (0.48-70)	0.53 (0.43-0.65)	0.54 (0.43-0.67)

CI: confidence interval  
HR: hazard ratio  
IP: inverse probability  
SMR: standardized mortality ratio

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4 **FIGURE LEGENDS**  
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9 **Figure 1.** Patient selection.  
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14 **Figure 2.** Ten-year inverse probability of treatment-weighted cumulative incidence of major  
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16 adverse cardiovascular events and death by aspirin treatment and statin treatment.  
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