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Running Title: Statins and Primary Prevention

Word count: 7,027 (including abstract, manuscript, text, references and figure legends)

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Abstract

Aims: We undertook a propensity match-weighted cohort study to investigate whether statin treatment recommendations for statins translate into improved cardiovascular (CV) outcomes in the current routine clinical care of the elderly.

Methods and results: We included in our analysis (ISACS Archives -NCT04008173) a total of 5,619 Caucasian patients with no known prior history of CV disease who presented to hospital with a first manifestation of CV disease with age of 65 years or older. The risk of ST segment elevation myocardial infarction (STEMI) was much lower in statin users than in nonusers in both patients aged 65 to 75 years (14.7 % absolute risk reduction; relative risk [RR]: 0.55, 95% CI 0.45 to 0.66) and those aged 76 years and older (13.3 % absolute risk reduction; RR: 0.58, 95% CI 0.46 to 0.72). Estimates were similar in patients with and without history of hypercholesterolemia (interaction test; p value= 0.2408). Proportional reductions in STEMI diminished with female sex in the old (p for interaction=0.002), but not in the very old age (p for interaction=0.26). We also observed a remarkable reduction in the risk of 30- day mortality from STEMI with statin therapy in both age groups (10.2 % absolute risk reduction; RR: 0.39; 95%CI 0.23 – 0.68 for patients aged 76 or over and 3.8 % absolute risk reduction; RR 0.37; 95%CI 0.17 – 0.82 for patients aged 65 to 75 years old; interaction test, p value=0.4570)

Conclusions: Preventive statin therapy in the elderly reduces the risk of STEMI with benefits in mortality from STEMI, irrespective of the presence of a history of hypercholesterolemia. This effect persists after the age of 76 years. Benefits are less pronounced in women. Randomized clinical trials may contribute to more definitively determine the role of statin therapy in the elderly.

Keywords: Prevention therapy; statins; myocardial infarction; 30-day mortality

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Translational perspective

In this register-based cohort study with match propensity-based design of patients without known prior history of CV disease, we compared statin users versus nonusers in two age groups: 65 to 75 years and 76 years and older. Statin use was associated with a 13% absolute reduction in the risk of ST segment elevation myocardial infarction (STEMI) in patients 76 years and older irrespective of the presence of a history of hypercholesterolemia. Statin use was also significantly related to a 10.2 % reduction in 30-day mortality from STEMI. Estimates were similar in patients aged 65 to 75 years. Benefits were less pronounced in women. This study demonstrates that preventive statin therapy is broadly effective at reducing the risk of major cardiovascular events and mortality in the elderly. Results may inform future research and current guidelines.

Introduction

Since 2016, five major guidelines on statin use to prevent cardiovascular (CV) disease have been released by: the UK National Institute for Health and Care Excellence (NICE)[1], the Canadian Cardiovascular Society (CCS)[2], the U.S. Preventive Services Task Force (USPSTF)[3], the European Society of Cardiology/European Atherosclerosis Society (ESC/EAS)[4] and the American College of Cardiology/American Heart Association (ACC/AHA)[5]. Although these guidelines are based on the same evidence originating predominantly from randomized controlled trials on statin therapy in hypercholesteremic patients, the recommendations for using statins to prevent CV disease in the elderly differ substantially. Only the NICE guidelines provide a strong, statin indication over 75 years of age.

To further complicate matters, some guidelines endorsed a treat-to target strategy with primary prevention LDL-C targets ranging from 77 to 100 mg/dL for high versus low risk individuals [2, 4]. Other guidelines suggested a specific intensity of statin for each risk category with intended LDL-C reduction threshold varying from 30 to 50% [1, 5]. This approach is of concern for treatment of the elderly as LDL-C increases up until the midpoint of life, and then it gradually decreases in the latter decades of life [6]. Removing treatment targets or treat-to-target strategies and replacing them with a global evaluation of risk profile may facilitate decision-making in the elderly.

One of the most notable global risk estimation tools is the Pooled Cohort Equations (PCE) [7]. The USPSTF endorsed the PCE to calculate 10-year risk of CV disease events and to determine whether patients are at sufficient risk to merit treatment with statins. Still there are limitations. No statin clinical trials enrolled patients based on a specific risk threshold. Limited data exist on the performance and use of the 10-year risk scores, especially among people 76 years and older. Consequently, the USPSTF judges the magnitude of the potential benefits of statins to be too poorly documented to merit a decisive recommendation in the older population.

Concern also applies for the more widespread use of concomitant preventive medications that may blunt the cardio-protective effect of statins. Better management of blood pressure, and other risk factors is likely to lower the risk of developing disease, and these medications are mostly used in persons aged more than 65 years. While this issue is clearly important, concomitant medications have been poorly tracked in prior statin randomized work.

On this background, we carried out a statin prevention study using a register-based cohort data in a match-propensity weighted design. Framing our questions around the current USPSTF algorithm for the primary prevention of CV disease in adults, we sought to determine whether statin therapy may lead to reduction in clinically significant outcomes of healthy older adults aged 65 years and above. The main outcome of interest was ST segment elevation myocardial infarction (STEMI) and its relation with 30-day mortality. We matched patients using a parametric balancing strategy by weighting to adjust for differences among sex, ages and concurrent medications. Statin users versus nonusers had a similar pattern of exposure to the most common risk factors and preventive therapies.

Methods

Derivation cohort

From October 2010 to January 2019, we analyzed information from the International Survey of Acute Coronary Syndromes (ISACS) Archives (NCT04008173). The ISACS Archives provides access to de-identified, research cohorts and clinical trials in acute coronary syndromes (ACSs) [8-11] . As the aim of the current investigation was to analyze the relation between CV outcomes and prior evidence-based medication use, we identified two large clinical registries providing such information, namely the ISACS-TC (NCT01218776) and the EMMACE-3X (Long-term Follow-up of Health-Related Quality of Life in Patients with Acute Coronary Syndrome; NCT01955525). In brief, the ISACS-TC registry collected data from 41 centers in 12 European countries: Bosnia and Herzegovina, Croatia, Italy, Kosovo, Lithuania, Macedonia, Hungary, Moldova, Montenegro, Romania, Russian Federation, and Serbia. Among these sites, there were 22 tertiary health care services providing percutaneous coronary intervention (PCI) [12, 13]. The EMMACE-3X gathered routine clinical information from 47 hospitals in England. CV facilities including PCI were available in 33 hospitals[14]. This study complies with the Declaration of Helsinki. The local research ethics committee from each hospital approved the study. Because patient information was collected anonymously, institutional review boards waived the need for individual-informed consent. Both registries had independent source documentation. All data were transferred to the Department of Electrical and Computer Engineering, University of California, Los Angeles, where final statistical analyses were done.

Patient Population

Routine clinical information was gathered from hospital records. The designated physician collected the registry data at the time of clinical assessment. Patients were admitted with a diagnosis of ACS and had at least one of the following: ECG changes consistent with ACS, increases in serum

biochemical markers of cardiac necrosis, and/or documentation of coronary artery disease[15]. The initial population consisted of 23,567 patients with ACS. Patients presenting with a history of CV (coronary heart disease, peripheral vascular disease, and cerebrovascular disease) events or heart failure were excluded leaving a study population in the primary prevention setting of 14,542 patients. Of these patients 5,619 were 65 years and older. **(Supplemental Figure 1).**

Outcome Measures and Definitions

The main outcome measure was the incidence of STEMI. A further key outcome measure was the association between STEMI and all-cause mortality at 30 days. The 30-day window was selected to enrich the data over that acquired during the index hospitalization while mitigating survivor bias. We noted the type of evidence-based medications (aspirin, statins, angiotensin-converting enzyme inhibitors [ACE-inhibitors], angiotensin receptor blockers [ARB] and beta-blockers) given on a regular basis at least for two weeks before the onset of the qualifying event. Medications received immediately before hospitalization or in the emergency department were not considered prior medication use. Multivessel disease was defined as at least two main branches of the epicardial coronary artery with ≥70% stenotic lesions or ≥50% stenosis in the left main coronary artery. All patients with a glomerular filtration rate <60 ml/min/1.73 m^2 for 3 months were defined as having chronic kidney disease. Patients with a history of cough, breathlessness and evidence of airflow limitation documented through spirometry were classified as affected by chronic obstructive pulmonary disease. Smoking habits were self-reported **(Methods in the Supplemental Material)**. Hypertension, hypercholesterolemia and diabetes were assessed by designation of medical history prior to admission in the database. The 10-year CV risk for each patient was calculated by using the Pooled Cohort Equations. We set the cut-off for increased level of CV disease risk at 10% according to the 2017 recommendation statement of the USPS Task Force[3].

Statistical analysis

Patient characteristics were stratified according to treatment-group: statin users versus statin nonusers. Baseline characteristics were reported as percentages for categorical variables and means with standard deviation for continuous variables. We had complete data on sex, age, index event and outcomes. Some patients had missing data on other variables. We used k-nearest neighbour (KNN) algorithms as imputation method to treat missing data[16]. **(Methods in the Supplemental Material)**. The existence of associations between outcomes and statin therapy was evaluated with the use of inverse probability of treatment weighting models[17] **(Methods in the Supplemental Material)**. We calculated odds ratios (OR) or relative risks (RR) with their 95% confidence interval (CI) from logistic regression and inverse probability of treatment weighting models, respectively. Comparisons of outcomes between groups were assessed by two-sided p-value. The characteristics incorporated into the logistic regression and inverse probability of treatment weighting models are reported in **Table 1**. Variables included demographics, CV risk factors, medical history and angiographic findings. Standardized differences after weighting were calculated to ensure balanced treatment groups with respect to baseline characteristics. Groups were considered balanced when the standardized difference was less than 20% **(Methods in the Supplemental Material)**. We quantified the impact of statin use on STEMI rates in two age groups (65 to 75 years and ≥76 years). Subsidiary analyses were also conducted to assess differences in the main outcome in subgroups based on sex, history of hypercholesterolemia and diabetes. To minimize concern about comparison of the treatment effect in subgroups, estimates were compared by test of interaction on the log scale[18]. A *P* value < 0.05 was taken to indicate that the difference between the effects in subgroups was unlikely to have occurred simply by chance **(Methods in the Supplemental Material)**.

Results

Of 23,567 patients with information on prior evidence-based medication use, 14,542 had no prior CV event. Statin users showed a slightly higher predicted 10-year CV risk compared with nonusers (**Supplemental Table 1)**. Age was a major determinant for the estimation of CV risk with PCE (SD=0.27)**.** In our cohort, a 10-year CVD risk <10% was rarely reached by people aged 65 to 75 years (N=193 of 3,469; 5.5%) and by those aged 76 years or over (N=18 of 2,361; 0.8%). We therefore restricted our analysis only to those individuals who were 65 years and older with a 10-year CV risk exceeding 10%. In total 5,619 patients were eligible for participation (**Supplemental Figure 1).** The outcome of first STEMI was available in 3,576 patients**,** with 393 (11%) of 3,576 first STEMI classified as deaths from STEMI. The baseline characteristics, stratified by age group (65-75 years and ≥76 years) and by treatment group (statin users versus nonusers), are listed in **Supplemental Table 2**. Slightly more than 15% of patients reported use of statins. Statin users were more often former smokers. Diabetes, hypertension, hypercholesterolemia were more frequent among statin users versus nonusers. Statin users were also more likely to take concomitant evidence-based medications.

After adjustment for inverse probability of treatment weighting, no statistically significant or clinically relevant standardised differences were observed between statin users and nonusers. **(Table 1).** Prior statin use was associated with a significantly decreased rate of STEMI compared with no prior statin use. The effect of statins was consistent in both patients aged 65 to 75 years (absolute difference 14.7%; RR 0.55, 95% CI 0.45 to 0.66) and those aged 76 years and above (absolute difference 13.3%; RR 0.58, 95% CI 0.46 to 0.72; interaction test, p value= 0.3620) **(Supplemental Table 3).**

Among participants aged 76 years and above **(Table 2)**, statin therapy was associated with a 17.1% absolute risk reduction and a 51% RR reduction in STEMI (0.49; 95% CI, 0.35 to 0.68) compared to non-statin therapy in women. Similarly, men had a 13.7% absolute risk reduction and a 43% RR reduction in STEMI (0.57; 95% CI, 0.42 to 0.78; interaction test, p

value=0.26). Reduction of STEMI lost statistical significance in women **(Table 3)** aged 65 to 75 years (5.9 % absolute risk reduction; RR 0.78; 95% CI: 0.56 to 1.08) whereas men still showed a statistically significant and clinically relevant reduction in STEMI (20.7 % absolute risk reduction; RR 0.43; 95% CI: 0.34 to 0.54; interaction test, p value=0.002). The results of the interaction tests are reported in **Supplemental Table 4.**

Figure 1 depicts the RRs of the outcome measure when treatment with statins was stratified based on the presence of hypercholesterolemia and diabetes. (**Supplemental Tables 5–8**). There was no evidence of heterogeneity in the results for any subgroup evaluated **(Supplemental Table 4)**. For subjects with hypercholesterolemia in the age group 65 to 75 years, the benefit of statins was similar to that for those without hypercholesterolemia (RRs: 0.62; 95% CI, 0.48 to 0.79 versus 0.57; 95% CI, 0.40 to 0.80; interaction test, p value =0.35). Similar benefit was observed for subjects aged 76 years and above (RRs: 0.48; 95% CI, 0.35 to 0.66 versus 0.57; 95% CI, 0.40 to 0.82; interaction test, p value =0.24). In line with these findings, the benefit of statins was seen also in patients with and without a history of diabetes either for those 65 to 75-year-old (RRs: 0.56; 95% CI: 0.41 to 0.78 versus 0.50; 95% CI: 0.40 to 0.64; interaction test, p value=0.29) or for those 76 years and older (RRs 0.48; 95% CI: 0.33 to 0.70 versus 0.61; 95% CI: 0.46 to 0.81 interaction test, p value=0.16)**.**

Clinical presentation with STEMI as index event was strongly related to 30-day mortality (ORs: 7.44; 95%CI: 5.26–10.54 in subjects aged 65 to 75 years and 5.77; 95% CI, 4.45 - 7.48 in those 76 years and above) (**Supplemental Figure 2**). To investigate at individual level the relationships among statin therapy, STEMI and death, we restricted our analysis to patients presenting with STEMI on admission. The observed reduction in mortality associated with statins for patients aged 76 or over (10.2 % absolute risk reduction; RR: 0.39; 95%CI 0.23 – 0.68) was nearly 3 times greater than that seen in the 65 to 75 years old risk group (3.8 % absolute risk reduction; RR 0.37; 95%CI 0.17 – 0.82; interaction test, p value=0.46) **(Table 4 and Supplemental Table 9).**

Discussion

In the current study, use of statin therapy in adults 65 to 75 years and 76 years and above without prior evidence of CV disease led to a significant reduction in the incidence of the most severe clinical manifestations of CV disease, namely STEMI. Benefits were irrespective of history of diabetes and hypercholesterolemia. The effect of statin use varied across sex, with men deriving the most gain in prevention of STEMI. Our data also provided evidence for a beneficial effect of statins on 30-day mortality in patients presenting with STEMI on hospital admission suggesting that statin therapy lowers the risk of death through other mechanisms in addition to the prevention of STEMI. These results support the use of statins as a prevention therapy in people 75 years and above in concert with current NICE guidelines recommendations.

Whether the elderly, and especially individuals aged 75 years and above, should receive statin treatment in the primary prevention of CV disease continues to spur much debate [19]. Criticism is based on facts. Some scientists question that although there have been many systematic reviews and meta-analyses of statin treatment there is little evidence concerning the older population alone for primary and secondary prevention. These studies have, indeed, reported on trials that mostly included participants with a history of CV disease.

Two recent studies might help to navigate some of these uncertainties, as they fully disaggregated primary from secondary prevention data in the very elderly. The first study is a cooperative metanalysis performed by the Cholesterol Treatment Trialists (CTT) [20], which included 6,449 people whose age was older than 75 years and who were taking statins versus placebo or less intensive statin treatment in the absence of history of CV disease. Overall, the study observed an 8% nonsignificant reduction in the risk of major vascular events per mmol/L reduction in LDL cholesterol (LDL-C rate ratio 0.92; 95% CI:0.73 to 1.16). The second study is a trial, the HOPE-3 (Heart Outcomes Prevention Evaluation 3)[21], which evaluated statin primary prevention treatment among 3,086 men and women aged 70 year and above free of prior CV disease, but with at least one

major CV risk factor. The reduction of serious vascular events with statins was 17%, but this reduction was not statistically significant (hazard ratio 0.83; 95% CI:0.64 to 1.07). In sum, based on outcome data from CTT metanalysis and HOPE-3 trial, statins seem to confer no substantial benefit among people aged 70 years and above.

Nonetheless, the debate is still open as queries about the evidence base for statin use in the prevention therapy of the elderly continue to emerge from many quarters. Uncertainties remain with regard to numerous issues such as: how strong is the weight to be given to the different components of the composite outcome of major vascular events commonly defined as non-fatal myocardial infarction, coronary death, coronary revascularization, and stroke, is there a discrepancy between the benefits in women and men, and is cholesterol level the only reliable target to guide prevention of CV disease in the elderly?

An important aspect is the selection of outcomes. The effects of primary prevention therapy on mortality from coronary heart disease may be confounded by the changing epidemiology of ACSs with ageing. The elderly represents a growing proportion of the population that present with non-ST elevation acute ACSs[22]. Despite this, STEMI remains much more closely associated with subsequent high rates of short-term mortality than non-ST elevation ACSs[23]. Lack of information on the type of ACS may lead to underestimation of the effect of statins on CV mortality in the elderly as a result of a "dilution bias" due to combination of two intermediate different outcome measures carrying a different weight on mortality, specifically STEMI and non-ST elevation ACSs [24].

In this context, the main outcome of interest of the current study was STEMI because of its strong association with short-term CV mortality. Although based on a retrospective analysis, our study provides robust evidence not only of an association between reduction in the incidence of STEMI and prior statin therapy in individuals 65 to 75 years and in those 76 years and above who had not yet experienced a CV event, but also suggests a decreased risk of death among people with STEMI who have undergone treatment with statins before the index events.

Although we cannot identify the mechanism of the associations between reduced incidence and mortality from STEMI and prior statin therapy, our data suggest that some hypotheses can be discounted. The association is not attributable to age, diabetes or impaired renal function[25, 26], as we created a sample in which treatment was independent of the above measured baseline covariates. The association does not reflect a proxy for more unrecognized coronary artery disease and worse outcomes in statin nonusers, since in our study the angiographic severity of coronary artery disease was similar in statin users and nonusers.

A possible mechanism may involve the potential pleiotropic actions of statins. Animal studies demonstrated changes in plaque structure including reduction of macrophage numbers and matrix metalloproteinase-1 expression and increases in interstitial collagen content resulting in increased plaque stability[27]. Stabilization of atherosclerotic plaques translates into reduction of platelet aggregation, a chief factor influencing the degree of coronary occlusion, and distal embolization of plaque materials, a major culprit for microvascular dysfunction and related infarct expansion[28]. Direct cardioprotective effects of statins have been reported at ischemic biomarker level, cardiac function and remodeling after experimental MI followed by cardiac magnetic resonance imaging[29-31].

Another source of uncertainty merit attention. Data on sex difference in the primary prevention in the elderly are lacking as most primary prevention trials and observational studies included few women and the vast majority of these studies provided no sex-specific results[32]. We compared in our analysis the older and the very older populations and identified sex-specific differences in response to statins. In the age group 65 to 75 years, the greatest gain was attained in male subjects with a 20.7% absolute risk reduction of STEMI, which was statistically significant, compared with a 5.9% absolute risk reduction seen in women which was not significant. There was a significant interaction by sex. On the other hand, in the age group 76 years or older, the absolute risk in women was reduced by 17.1% compared with a 13.7 % in men with no significant interaction by sex. There was thus good evidence to support a different treatment effect in the older

women versus men, but not in the very older women versus men. The reasons for the less pronounced benefit of statins in women 65 to 75 years old are not known. It should not go unnoticed, however, that 65 to 75 years old is the age group in which myocardial infarction can be considered premature in women[13, 33] When the potential benefit is low, the number of women needed to be treated to prevent a major CV disease event is generally higher than that for men. Additionally, women who develop myocardial infarction prematurely may be those who are highly predisposed to the disease. Genetic susceptibility to coronary heart disease in women is strongest up to 75 years old and is independent of other risk factors for CV disease[34]. While the evaluation of such mechanisms is beyond the scope of our study, it may be possible that heritable hypercoagulable states may support increased liability for thrombosis and facilitate myocardial infarction in women[35, 36]. It should not surprise us, therefore, that statins, which acts mainly by lowering LDL cholesterol, should confer less benefit in women. Clearly, additional research is needed to confirm (or not) whether the observed sex differences reflect true biological effect.

A second issue of importance relates to the role of diabetes. A relatively recent retrospective cohort study suggested that the presence of diabetes might be necessary to confer CV benefit in people aged over 75 [37]; however, this analysis did not test for the heterogeneity of treatment effects through interaction terms and the confidence intervals in diabetic patents versus nondiabetic patients overlapped the two estimates. In addition, because the composite CV outcome measure of such population was mainly constituted by coronary revascularization, this study primarily identified the effects of statin on the prevention of revascularization, not on the determinants of the "natural history" of disease, namely myocardial infarction and death. As so, tradeoffs remain uncertain. In the current study, statins were associated with a remarkable reduction in the incidence of STEMI on admission in diabetic patients independently of their older or very older age. Still nondiabetic patients had similar benefits. It is possible that the inclusion of chronically ill patients with stable angina and coronary revascularization in prior studies shifted the

nondiabetic population at lower risk of major adverse outcomes such as myocardial infarction and death compared with the presented results.

No treatment is without some risk. Statins can cause muscle pain and injury and rarely diabetes, liver dysfunction, and acute renal failure [38-40]. They have also been associated with decline in cognition[41], but this evidence is still unclear. Our study was addressed to search benefits, not harms. Nevertheless, our retrospective findings may give some insights to further our understanding on the balance between benefits and side effects. We found that a PCE derived 10-year CV disease event risk <10% was rarely reached by people aged 65 to 75 years (5.5%) and by those aged 76 years and above (0.8%). Therefore, the paradox that we face is that the elderly people are at increased risk for CV disease and yet they might be more sensitive to medication side effects. As so, it is a tricky balance and we must stay on the lookout for side effects and interactions, to ensure that we do not overtreat this often-vulnerable population. Two large trials (ClinicalTrials.gov NCT04262206 and NCT02099123) are ongoing. They both included dementia and physical disability into the primary outcomes. As such, these trials may answer important questions on whether there are meaningful harms associated with use of statins in people of 70 years and older.

The outcomes from these two trials are awaited in 2023 and 2026. It is unlikely that further trials will be performed to randomize specific subgroups of subjects such as women versus men and young old ages (65 to 75 years) versus very advanced ages (76 years or over). As so, our data have the potential to inform clinical practice in the interim. In our study, we noted a 10.2 % absolute risk reduction in all-cause mortality in the very old statin users presenting with STEMI. This magnitude of benefit was nearly 3 times greater than that seen in old people at lower ages (3.8%). Despite this, given the higher risk of CV events in the overall older population, these benefits could translate to a considerable reduction in the risk of mortality in both people aged 65 to 75 years and in those aged 76 years and above.

The current study has some potential limitations. First, residual confounding might exist even if mitigated by matching using propensity-based methods. Second, all patients in our cohort

are Caucasians, so ethnic variations in response to statin treatment cannot be assessed. Third, some of the risk factors were ascertained by the general practitioner, which might have led to errors in the dataset. Nonetheless, this was the closest attainable estimate of factors such as blood pressure and glycemic values that are potentially confounded by the severity of the disease. Additionally, information on length of previous treatment, statin type, and daily doses of statins was not addressed by the present analysis. We were unable to adjust for the use of postmenopausal hormone therapy, which may predict a favorable change in cholesterol levels of elderly women. However, its use is not associated with substantial reduction of coronary heart disease[42], and therefore is unlikely to explain the fact that statins confer in women approximately half the benefit that accrues in men. Our data are based on hospital-based patients with ACS and are therefore unlikely to reflect the effects of statins as primary prevention medication in entire countries or regions. Nevertheless, data were available from several countries, and as so this study is representative of a real-world population. As a result, our overall conclusions that preventive statin therapy in the elderly reduces the risk of STEMI with benefits in mortality from STEMI is probably broadly applicable. We cannot rule out that a number of people with STEMI may have died before presentation to hospitals. This fact would have contributed to a smaller proportion of STEMI patients included in the study. Even so, the effect of statins on prevention of STEMI and related mortality was strong and independent of use of concomitant medications.

Finally, patients' baseline risk was categorized using the current USPSTF algorithm. Risk scores of other guidelines could not be used in our study because we investigated areas outside the remit of the remaining guidelines, specifically the role of statin therapy in the clinical management of subjects without hypercholesterolemia, but with other conditions considered to be risk factors for CV disease, including hypertension, diabetes and smoking[4].

In conclusion, preventive statin therapy was significantly associated with a lower risk of STEMI and early mortality from STEMI in the elderly aged 65 years and even 75 years and older with a 10% or greater 10‐year risk of developing CV disease, irrespective of the presence of a

history of hypercholesterolemia. Benefits are less pronounced in women. Based on these data, age is not a reason to withhold statins. In the absence of definitive evidence from trials, we believe that our data provide sufficient grounds for supporting the use of statins in the elderly according to USPSTF cardiovascular risk approach and NICE recommendations.

Funding

EMMACE was funded by the National Institute for Health Research and the British Heart Foundation

Author contributions

RB contributed to study design, data verification and interpretation, literature search, writing and editing of the manuscript. JY and MvdS contributed to data analysis and data interpretation. JY was also responsible for data verification. SK, MZ, ZV contributed to data collection and editing of the manuscript. DM contributed to data collection and editing of the manuscript. OM and GM contributed to data interpretation and editing of the manuscript. CPG contributed to data interpretation and critical revision of the manuscript. LB contributed to data interpretation and editing of the manuscript. EC and MB contributed to study design, literature search, data interpretation, writing and critical revision of the manuscript.

Acknowledgments

The graphical abstract was created with Biorender.com

Conflict of interest

Professor Badimon reports other from Bayer, personal fees and other from International Aspirin Foundation, UK, during the conduct of the study; other from SANOFI, personal fees from LILLY, grants from ASTRAZENECA, personal fees from ASTRAZENECA, other from Glycardial, personal fees from BMS/Pfizer, personal fees from PACE, personal fees and other from FICYE

(FORUM TO STUDY BEER & LIFESTYLE), outside the submitted work; In addition, Professor Badimon has a patent APOj-Gly licensed, a patent IV_STATIN pending, and a patent DJ1-F pending.

Prof. Gale reports personal fees from AstraZeneca, personal fees from Amgen, personal fees from Bayer, grants from BMS, personal fees from Boehrinher-Ingelheim, personal fees from Daiichi Sankyo, personal fees from Vifor Pharma, grants from Abbott, personal fees from Menarini, personal fees from Wondr Medical, personal fees from Raisio Group, personal fees from Oxford University Press, grants from British Heart Foundation, grants from NIHR, grant from Horizon 2020, grants from ESC, outside the submitted work. .

The remaining Authors declare no conflict of interest

Data availability statement

The source codes for this manuscript are uploaded on- https://github.com/jsyoon0823/Treatment_Phenotype

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FIGURE LEGEND

Figure 1. Estimated effects of statins on CV outcomes: distribution by CV risk factors and age

Horizontal lines indicate corresponding 95% confidence intervals around relative risk ratios. All models were balanced for age, female sex, major CV risk factors, chronic obstructive pulmonary disease, chronic kidney disease, medications before admission [aspirin, ACE-inhibitors/angiotensin receptor blockers, beta-blockers] and multivessel disease

Abbreviations: CI, Confidence Interval; CV, cardiovascular; RR, Relative Risk; STEMI, ST elevation myocardial infarction;

Table 1 Inverse probability of treatment weighting: outcomes sorted by age and statin use before index event.

Characteristics	Age 65 to 75 years			Age≥76 years		
	Statin users N=506	Statin nonusers N=2,770	Standardized difference	Statin users N=362	Statin nonusers N=1,981	Standardized difference
Age, y	69.4±3.1	69.3±2.9	0.0584	79.6±3.6	80.0±4.4	-0.0985
Female sex	36.9	32.5	0.0930	46.0	44.6	0.0286
Cardiovascular risk factors						
Diabetes	30.1	26.8	0.0985	26.5	26.0	0.0119
History of hypertension	71.3	68.7	0.0676	76.2	73.1	0.0708
History of hypercholesterolemia	39.7	37.7	0.0415	35.5	31.4	0.0984
Current smokers	32.2	31.6	0.0118	16.5	13.9	0.0727
Former smokers	18.0	15.2	0.0738	15.8	14.4	0.0385
Clinical history						
COPD	5.6	6.5	-0.0370	6.8	7.9	-0.0414
Chronic kidney disease	4.7	5.2	-0.0215	13.5	10.4	0.0937
Medications before admission						
Aspirin	21.8	19.2	0.0642	27.1	23.5	0.0816
ACE inhibitors/ ARBs	43.1	39.3	0.0773	43.7	43.1	0.0121
Beta blockers	24.7	23.2	0.0359	31.8	28.0	0.0963

Angiographic findings						
Multivessel disease	49.4	47.7	0.0350	56.5	59.2	-0.0549
Outcome			**P value**			**P value**
STEMI	50.3	65.0	<0.0001	51.2	64.5	<0.0001
Risk Ratio (95% CI)	0.55 (0.45 – 0.66)		<0.0001	0.58 (0.46 – 0.72)		-<0.0001

Data are percentages or means ± Standard deviation unless stated otherwise

Abbreviations: ACE, angiotensin converting enzyme; ARBs, angiotensin receptor blockers; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; STEMI, ST elevation myocardial infarction·

Table 2. Inverse probability of treatment weighting: outcomes sorted by sex and statin use before index event in patients aged ≥76 years

Characteristics	Women			Men		
	Statin users N=170	Statin nonusers N=878	Standardized difference	Statin users N=192	Statin nonusers N=1103	Standardized difference
Age, years	80.2±3.7	80.4±4.6	-0.0648	78.9±3.2	79.6±4.2	-0.0822
Cardiovascular risk factors						
Diabetes	24. 2	27.9	-0.0880	27.5	24.2	0.0809
History of hypertension	76.6	78.6	-0.0483	72.6	68.9	0.0716
History of hypercholesterolemia	38.0	33.9	0.0866	33.5	29.2	0.0753
Current smokers	9.1	9.4	-0.0092	20.6	17.7	0.0829
Former smokers	10.4	7.8	0.0831	19.4	19.6	-0.0064
Clinical history						
COPD	4.8	6.9	-0.0913	9.1	8.8	0.0115
Chronic kidney disease	12.5	10.5	0.0608	13.0	10.4	0.0911
Medications before admission						
Aspirin	26.2	22.9	0.0750	26.9	23.9	0.0833
ACE inhibitors/ ARBs	48.2	49.1	-0.0173	39.5	38.2	0.0266
Beta blockers	36.2	32.1	0.0866	27.6	24.6	0.0647
Angiographic findings						
Multivessel disease	51.3	56.4	-0.0927	63.6	61.5	0.0450

Outcome			**P value**			**P value**
STEMI	51.5	68.6	0.0001	47.3	61.0	0.0005
Risk Ratio (95% CI)	0.49 (0.35 – 0.68)		<0.0001	0.57 (0.42 – 0.78)		0.0004

Data are percentages or means ± Standard deviation unless stated otherwise.

Abbreviations: ACE, angiotensin converting enzyme; ARBs, angiotensin receptor blockers; COPD, chronic obstructive pulmonary disease; STEMI, ST elevation myocardial infarction.

Table 3. Inverse probability of treatment weighting: outcomes sorted by sex and statin use before index event in patients aged 65 to 75 years ·

Characteristics	Women			Men		
	Statin users N=186	Statin nonusers N=871	Standardized difference	Statin users N=320	Statin nonusers N=1899	Standardized difference
Age, years	69.8±2.8	69.7±2.9	0.0191	69.2±3.3	69.0±2.9	0.0670
Cardiovascular risk factors						
Diabetes	34.4	32.7	0.0363	29.6	24.2	0.0884
History of hypertension	80.4	76.1	0.0659	67.6	65.5	0.0709
History of hypercholesterolemia	45.1	41.7	0.0674	34.6	35.8	-0.0252
Current smokers	27.7	24.5	0.0740	33.5	35.1	-0.0333
Former smokers	7.8	8.9	-0.0415	21.2	18.3	0.0445
Clinical history						
COPD	5.9	7.3	-0.0565	5.1	6.0	-0.0414
Chronic kidney disease	7.0	7.0	0.0006	3.2	4.3	-0.0535
Medications before admission						
Aspirin	23.1	19.8	0.0791	19.8	18.8	0.0255
ACE inhibitors/ ARBs	50.5	47.0	0.0713	35.2	35.6	-0.0085
Beta blockers	26.8	27.6	-0.0190	21.9	20.9	0.0242
Angiographic findings						

Multivessel disease	43.2	42.8	0.0073	54.2	50.0	0.0848
Outcome			**P value**			**P value**
STEMI	58.7	64.6	0.1400	44.6	65.3	<0.0001
Risk Ratio (95% CI)	0.78 (0.56 – 1.08)		0.1316	0.43 (0.34 – 0.54)		<0.0001

Data are percentages or means ± Standard deviation unless stated otherwise.

Abbreviations: ACE, angiotensin converting enzyme; ARBs, angiotensin receptor blockers; COPD, chronic obstructive pulmonary disease; STEMI, ST elevation myocardial infarction.

Table 4. Inverse probability of treatment weighting in patients with STEMI on admission: clinical factors and outcomes sorted by statin use before index event and age.

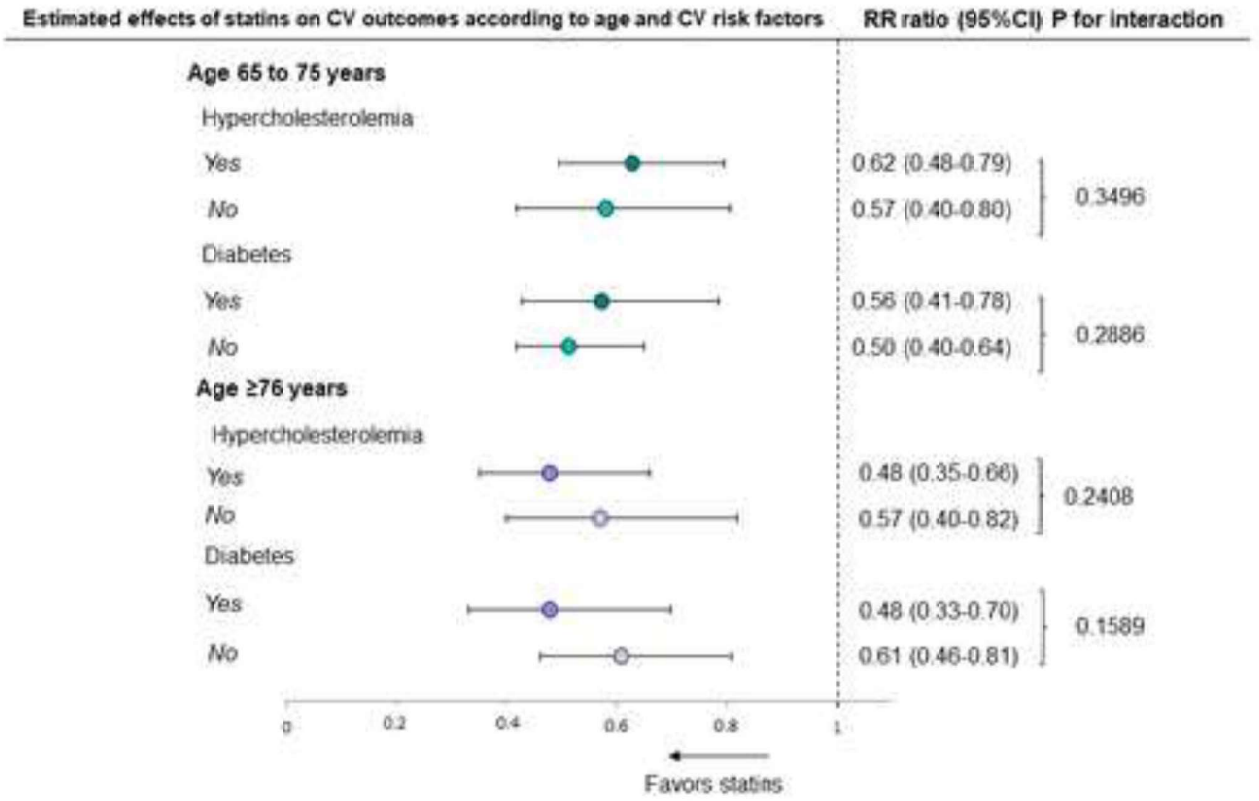
Characteristics	Age 65 to 75 years			Age ≥76 years		
	Statin users N=270	Statin nonusers N=1,826	Standardized difference	Statin users N=187	Statin nonusers N=1,293	Standardized difference
Age, years	69.0±3.0	69.2±2.9	-0.0549	79.4±3.5	80.0±4.4	-0.1513
Female sex	41.3	32.3	0.1873	48.0	47.7	0.0051
Cardiovascular risk factors						
Diabetes	32.7	26.5	0.1361	26.5	26.7	-0.0029
History of hypertension	71.7	66.5	0.1757	70.6	71.7	-0.0250
History of hypercholesterolemia	41.4	37.3	0.0839	36.0	31.7	0.0903
Current smokers	30.6	34.3	-0.0810	21.1	15.5	0.1461
Former smokers	19.7	13.1	0.1784	13.0	11.6	0.0444
Clinical history						
COPD	6.7	6.1	0.0264	6.0	7.6	-0.0603
Chronic kidney disease	4.8	4.8	-0.0005	12.7	10.0	0.0867
Medications before admission						
Aspirin	20.4	16.2	0.1076	24.1	20.3	0.0925
ACE inhibitors/ ARBs	45.9	36.3	0.1950	43.1	41.3	0.0376

Beta blockers	23.3	22.0	0.0311	35.4	26.3	0.1977
Angiographic findings						
Multivessel disease	47.8	47.7	0.0025	58.6	58.8	-0.0041
Outcome			**P value**			**P value**
30-day mortality	2.5	6.3	0.0005	8.2	18.4	<0.0001
Risk Ratio (95%CI)	0.37 (0.17 – 0.82)		0.0148	0.39 (0.23 – 0.68)		0.0008

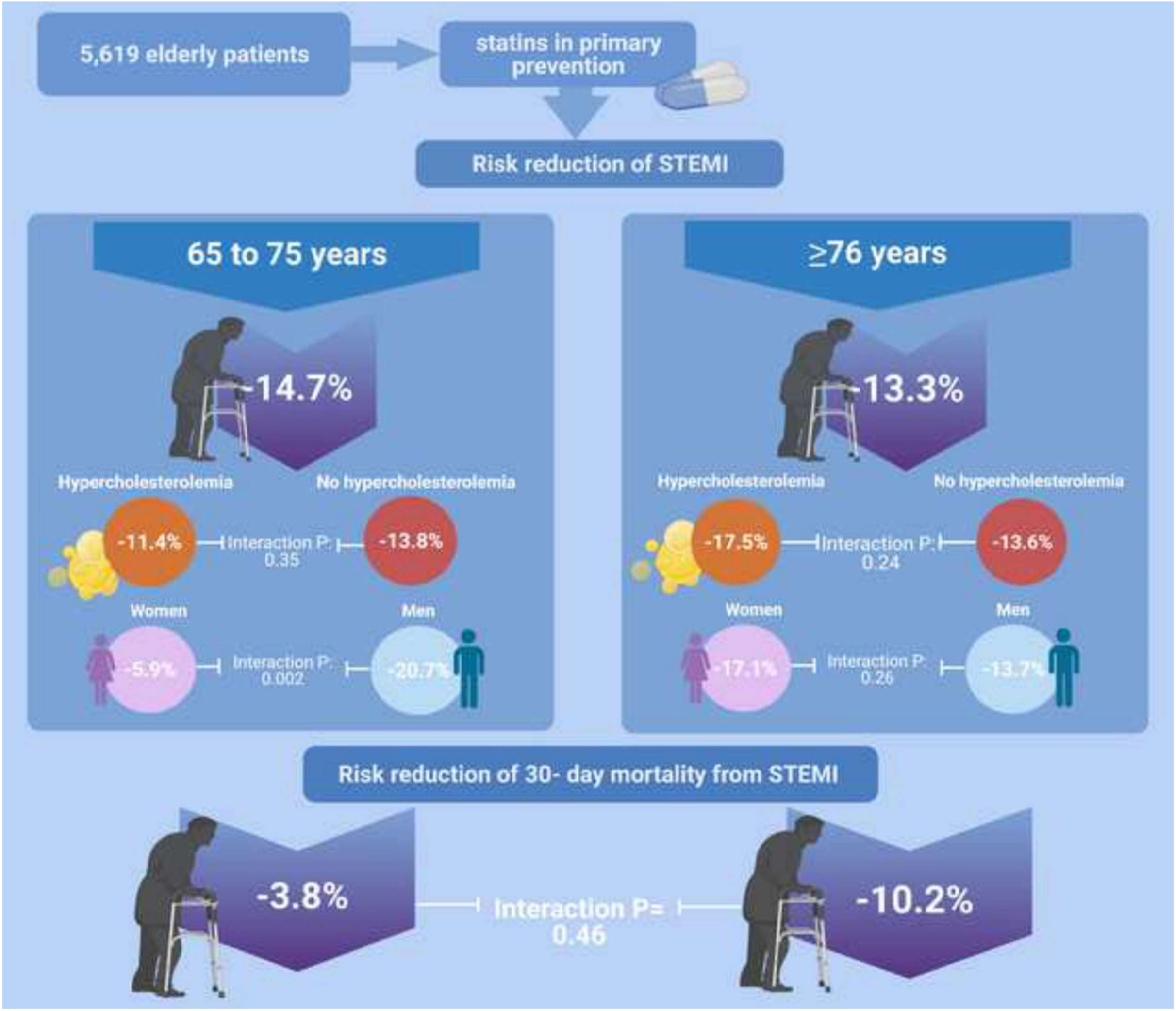
Data are percentages or means ± Standard deviation unless stated otherwise.

Abbreviations: ACE, angiotensin converting enzyme; ARBs, angiotensin receptor blockers; COPD, chronic obstructive pulmonary disease

Figure 1



Graphical Abstract



SUPPLEMENTAL MATERIAL

Statins for Primary Prevention Among Elderly Men and Women

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SUPPLEMENTAL METHODS

Risk factors definitions

Smoking habits were self-reported. We defined current smokers as individuals who smoked 100 cigarettes in his or her lifetime and who smoked cigarettes, cigars, and cigarillos at the time of the index event. Everyday smokers or someday smokers were all included in this definition according to recommendations from the National Health Interview Survey[1]. Participants who have smoked at least 100 cigarettes in their lifetime but who were not active smokers at the time of the index event were labelled as former smokers regardless of time since they quit. The remaining patients were classified as never smokers. Hypertension, hypercholesterolemia and diabetes were assessed by designation of medical history prior to admission in the database. Hypercholesterolemia was defined as total cholesterol >240 mg/dL or LDL cholesterol >160 mg/dL irrespective of current treatment, according to ATP III guidelines[2].

Inverse probability of treatment weighting

We used Inverse probability of treatment weighting to balance the distribution of covariates between two patient groups. If e denotes the estimated propensity score (i.e. e=\hat{P}(Z=1 | x), where the patient x is included in patient group 1; then, 1-e = \hat{P}(Z=0 | x)), then the original sample is weighted by the following weights: Z/e+(1−Z)/ 1−e where Z represents the patient group. For instance, women (Z=1) are assigned a weight equal to the reciprocal of the propensity score (1/e), while men (Z=0) are assigned a weight equal to the reciprocal of one minus the propensity score (1/1-e). The weighting procedure for each sample balances the covariate distributions between two patient groups[3].

Inverse probability of treatment weighting method can potentially result in unstable and biased estimates if some of the weights are very high. To avoid excessive weights, we compared results with other methods for handling confounding. We included probability of treatment variables in a multivariable model. We also used XGBoost, a decision-tree-based ensemble machine learning

algorithm, as an alternative multivariable model for estimating the probability of treatment. Conclusions from theses analyses were the same as our current results. Further, we created a threshold for weights to avoid the impacts of the outliers (we use 20 as threshold). Therefore, the inverse probability of treatment weighting analyses presented in the current analysis were quite stable.

Comparison of means and prevalences in the weighted sample

To evaluate the balance of the baseline covariate distributions between treatment and control groups, standardized difference (SD) is widely used in inverse probability of treatment weighting (IPTW) framework. For the baseline analysis, we use standard SD which is defined as follows: $\frac{m_t - m_c}{\sqrt{\frac{s_t^2 + s_c^2}{2}}}$ for continuous variables and $\frac{m_t - m_c}{\sqrt{\frac{m_t(1-m_t) + m_c(1-m_c)}{2}}}$ for binary variable where m_t, m_c are sample mean of the variables for treatment and control group, and s_t^2, s_c^2 are sample variance of the variables for treatment and control group, respectively. For IPTW analysis, we use weighted SD where m_t, m_c are replaced to weighted sample mean of the variables for treatment and control group, and s_t^2, s_c^2 are replaced to weighted sample variance of the variables for treatment and control group, respectively. Weights are determined by the inverse probability of treatment received. In general, 0.2 is the reasonable threshold to determine whether two distributions are balanced (i.e., if SD > 0.2, the baseline covariate is imbalanced).[4]

Nearest neighbour imputation algorithms

Nearest neighbour (NN) imputation algorithms are efficient methods to fill in missing data where each missing value on some records is replaced by a value obtained from related cases in the whole

set of records. Thus, imputation for clinical features was conducted using the average of measured values from k records (kNN).[5,6]

NN algorithms are similarity-based methods that rely on distance metrics and results may change in relation to the similarity measure used to evaluate the distance between recipients and donors. In our work, we used the following norm as metric to evaluate distance:

$(\sum ni=1|xi-yi|p)1/p$

Before imputation of the recipient Xi, the full set with no missing data C(X) was filtered to select a subset of features relevant to the missing variable to be imputed (Xi_miss). To this end, C(X) was considered as a dataset in the context of a regression problem, where the variable with the missing data (Xmiss) was set as the class variable and the other q variables (X1, X2, …, Xq) as predictors. We also applied the RReliefF algorithm[7].The set was, therefore, filtered to select a subset $Cs(X) \subset C(X)$ where $(X1, X2, \ldots, Xs) \subset (X1, X2, \ldots, Xq)$ and $s < q$. In the present context, we set the number of neighbours for RReliefF equal to 10 and set s as 10 %, 20 % or 30 % of q. As C(X) is invariant to Xi, the filtering step was performed only once before the NN imputation step that, on the contrary was performed separately for each Xi. In sum, we tried multiple imputations using chained equations (MICE) for the initial analyses to address the uncertainty in the imputation process. More specifically, we generated multiple imputed datasets and check whether the conclusions are consistent across the different imputed datasets. Then, we use KNN imputation as the final imputation method (single imputation) to address final estimates.

Interaction test

The comparison of two estimated quantities, each with its standard error, is a general method that can be applied widely[8]. These measures were always analysed on the log scale because the distributions of the log ratios tend to be those closer to normal than of the ratios themselves. If the

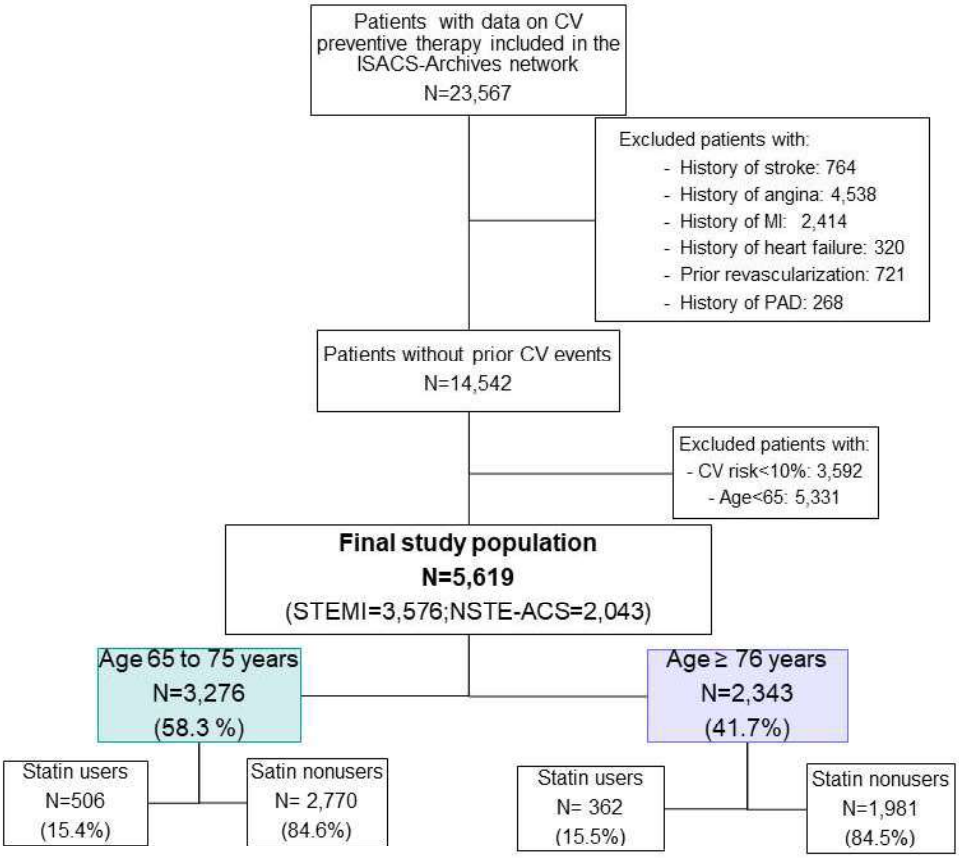
estimates are $E1$ and $E2$ with standard errors SE($E1$) and SE($E2$), then the difference $d=E1 - E2$ has standard error SE(d)=Ö[SE($E1$)2 + SE($E2$)2] i.e., the square root of the sum of the squares of the separate standard errors. The ratio $z=d/\mathrm{SE}(d)$ gives a test of the null hypothesis that in the population the difference d is zero, by comparing the value of z to the standard normal distribution. The 95% confidence interval for the difference is d-1.96SE(d) to d+1.96SE(d).

SUPPLEMENTAL RESULTS

Interaction tests

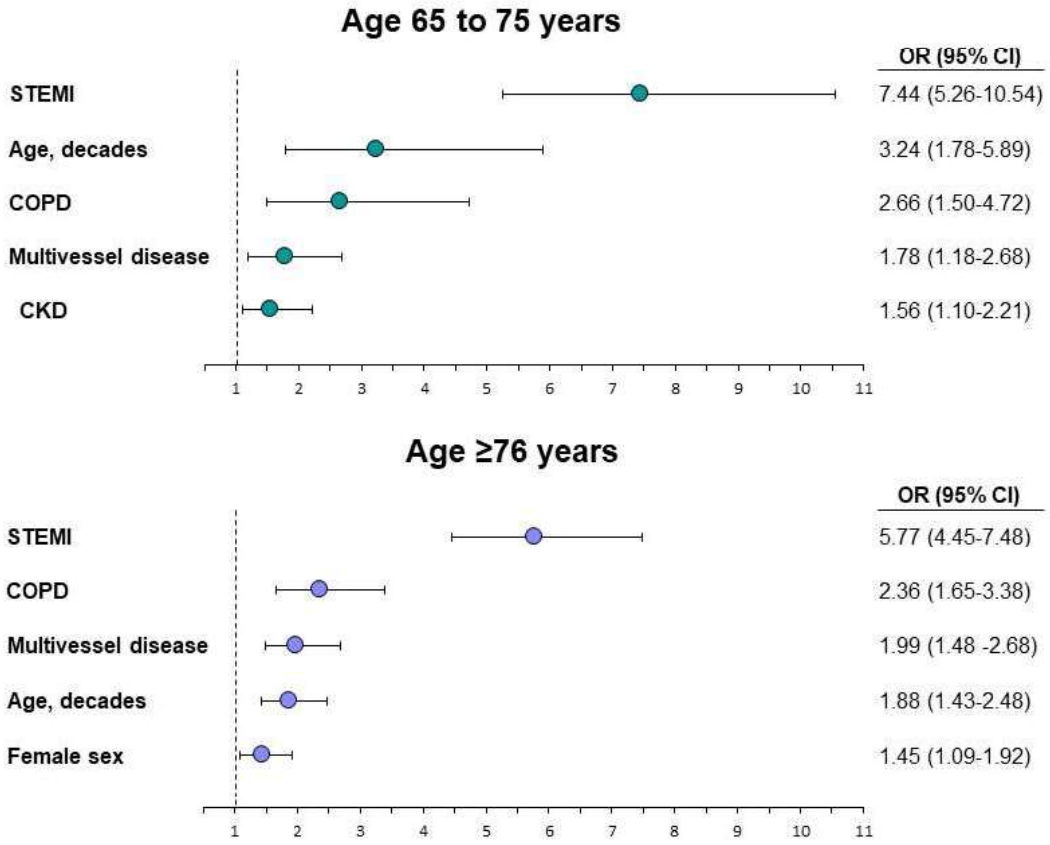
We tested (**Supplemental Table 3**) whether there is a significant interaction between age (65 to 75 years versus 76 years or older) and statin user status (yes versus no) in function of the primary outcome (ST elevation myocardial infarction). We obtained the logs of the risk ratios (relative risks) and their confidence intervals (rows 2 and 4). As 95% confidence intervals were obtained as 1.96 standard errors either side of the estimate, the SE of each log relative risk was obtained by dividing the width of its confidence interval by 2×1.96 (row 6). The estimated difference in log relative risks was *d*=E1- E2= -0.0531 (row 7) and its standard error 0.1504 (row 8). From these two values, we tested the interaction and estimated the ratio of the relative risks (with confidence interval). The test of interaction was the ratio of *d* to its standard error: z=-0.3531, which gives P=0.3620 when we referred it to a table of the normal distribution (row 10). The estimated interaction effect was exp =0.9483 (row 11). The confidence interval for this effect was -0.3479 to 0.2417 on the log scale (row 9). Transforming back to the relative risk scale, we got 0.7062 to 1.2734 (row 12). There was thus no evidence to support a different outcome effect in statin users grouped by age. The same approach was used to compare the effect of sex , history of hypercholesterolemia and diabetes status **(Supplemental Table 4**). Similar analyses were performed to investigate potential heterogeneity of treatment effects for 30-day mortality in elderly patients with STEMI on admission **(Supplemental Table 9).**

Supplemental Figure 1. Study Flow Chart



Abbreviations**:** CV, cardiovascular; MI, myocardial infarction; PAD, Peripheral artery disease

Supplemental Figure 2: Multivariable analysis of clinical factors associated with 30-day all-cause mortality stratified by age··



The full model included the following covariates: female sex, age (decades), diabetes, hypertension, hypercholesterolemia, current smokers, former smokers, Body Mass Index, chronic obstructive pulmonary disease, chronic kidney disease, multivessel disease, ST elevation myocardial infarction

Abbreviations: CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; STEMI, ST-elevation myocardial infarction

Supplemental Table 1. Estimation of 10-year risk for CV disease: Distribution of Pooled Cohort Equations parameters according to statin use

Characteristics	Overall Population (N=14,542)		
	Statin users N=1,824	Statin nonusers N=12,718	Standardized difference
Age, y	64.4±11.0	61.3±12.2	0.2690
Female sex	646 (35.4)	3,674 (28.9)	0.1401
Cardiovascular risk factors			
Diabetes	648 (35.5)	2,340 (18.4)	0.3933
Current smokers	690 (37.8)	5,673 (44.6)	-0.1380
Clinical characteristics			
Total cholesterol, mg/dL	191.8±51.8	209.8±51.0	-0.3493
HDL cholesterol, mg/dL	42.3±14.0	45.0±17.8	-0.1641
SBP, mmHg	137.9±28.3	139.7±27.8	-0.0646
Risk for CV disease			
Mean calculated 10- year risk for CV disease (%)	25.8±17.9	22.5±17.1	0.1890

Data are numbers (%) or means ± Standard deviation unless stated otherwise.

Abbreviations: CV, cardiovascular; SBP. Systolic blood pressure

Supplemental Table 2. Baseline characteristics of the overall population sorted by age and statin use before index event. ··

Characteristics	Age 65 to 75 years (N=3,276)			Age≥76 years (N=2,343)		
	Statin users N=506	**Statin nonusers N=2,770**	**Standardized difference**	**Statin users N=362**	**Statin nonusers N=1,981**	**Standardized difference**
Age, y	69.4±3.0	69.2±2.9	0.0609	79.7±3.7	80.1±4.5	-0.1015
Female sex	186 (36.8)	871 (31.4)	0.1123	170 (47.0)	878 (44.3)	0.0530
Cardiovascular risk factors (overall)						
Diabetes	194 (38.3)	655 (23.6)	0.3218	141 (39.0)	469 (23.7)	0.3339
History of hypertension	415 (82.0)	1815 (65.5)	0.3817	305 (84.3)	1411 (71.2)	0.3171
History of hypercholesterolemia	366 (72.3)	838 (30.3)	0.9281	231 (63.8)	493 (24.9)	0.8516
Current smokers	148 (29.2)	872 (31.5)	-0.0485	44 (12.2)	284 (14.3)	-0.0644
Former smokers	118 (23.3)	372 (13.4)	0.2575	78 (21.5)	262 (13.2)	0.2209
Clinical history (overall)						
COPD	43 (8.5)	170 (6.1)	0.0907	37 (10.2)	150 (7.6)	0.0932
Chronic kidney disease	42 (8.3)	123 (4.4)	0.1585	41 (11.3)	200 (10.1)	0.0398

Medications before admission (overall)						
Aspirin	292 (57.7)	293 (10.6)	1.1453	241 (66.6)	299 (15.1)	1.2294
ACE- inhibitors/ARBs	362 (71.5)	891 (32.2)	0.8574	252 (69.6)	754 (38.1)	0.6672
Beta blockers	268 (53.0)	454 (16.4)	0.8324	189 (52.2)	457 (23.1)	0.6307
Angiographic findings						
Multivessel disease	252 (49.8)	1,307 (47.2)	0.0524	213 (58.8)	1,160 (58.6)	0.0058

Data are numbers (%) or means ± Standard deviation unless stated otherwise.

Abbreviations: ACE, angiotensin converting enzyme; ARBs: angiotensin receptor blockers; COPD, chronic obstructive pulmonary disease.

Supplemental Table 3. Interaction test: calculations for comparing two estimated risk ratios (statin users versus nonusers) for STEMI by inverse probability of treatment weighting: patients aged 65 to 75 years vs patients aged≥76 years.··

		Group 1 [Age 65 to 75 years] (n = 3,276)	Group 2 [Age≥76 years] (n = 2,343)
1	**RR**	0.55	0.58
2	**log RR**	-0.5978	-0.5447
3	**95% CI for RR**	0.45 ~ 0.66	0.46 ~ 0.72
4	**95% CI for log RR**	-0.7985 ~ -0.4155	-0.7765 ~ -0.3285
5	**Width of CI**	0.3830	0.4480
6	**SE (=width / (2*1.96))**	0.0977	0.1143
	Difference between log risk ratios		
7	**d (=$E_1 - E_2$)**	**-0.0531**	
8	**SE (d)**	**0.1504**	
9	**CI (d)**	**-0.3479** ~ 0.2417	
10	**Test of Interaction**	**-0.3531 (p-values: 0.3620)**	
	Ratio of risk ratios		
11	**RRR (=exp(d))**	0.9483	
12	**CI (RRR)**	0.7062 ~ 1.2734	

Supplemental Table 4. Interaction test: calculations for comparing two estimated relative risk ratios (statin users versus nonusers) for STEMI by inverse probability of treatment weighting in patients sorted by sex and traditional risk factors.

	Women	**Men**	***P* interaction**
Patients aged 65 to75 years	0.78 (0.56 – 1.08)	0.43 (0.34 – 0.54)	0.0018
Patients aged ≥76 years	0.49 (0.35 – 0.68)	0.57 (0.42 – 0.78)	0.2569
	History of hypercholesterolemia	**No history of hypercholesterolemia**	***P* interaction**
Patients aged 65 to 75 years	0.62 (0.48 – 0.79)	0.57 (0.40 – 0.80)	0.3496
Patients aged ≥76 years	0.48 (0.35 – 0.66)	0.57 (0.40 – 0.82)	0.2408
	Diabetes	**No diabetes**	***P* interaction**
Patients aged 65 to 75 years	0.56 (0.41 – 0.78)	0.50 (0.40 – 0.64)	0.2886
Patients aged ≥76 years	0.48 (0.33 – 0.70)	0.61 (0.46 – 0.81)	0.1589

Supplemental Table 5. Inverse probability of treatment weighting: outcomes sorted by history of hypercholesterolemia and statin use before index event in patients aged 65 to 75 years.

Characteristics	History of hypercholesterolemia			No history of hypercholesterolemia		
	Statin users N=366	Statin nonusers N=838	Standardized difference	Statin users N=140	Statin nonusers N=1,932	Standardized difference
Age, years	69.3±2.9	69.2±2.8	0.0544	69.5±3.1	69.3±2.9	0.0788
Female sex	40.9	36.7	0.0847	36.5	30.1	0.1372
Cardiovascular risk factors						
Diabetes	31.8	32.8	-0.0217	28.1	22.6	0.1264
History of hypertension	82.5	81.6	0.0236	70.5	60.7	0.1816
Current smokers	32.3	33.9	-0.0332	28.5	29.9	-0.0305
Former smokers	17.5	16.9	0.0152	20.8	14.5	0.1838
Clinical history						
COPD	6.1	5.3	0.0343	5.3	7.1	-0.0727
Chronic kidney disease	8.0	6.8	0.0474	2.4	4.2	-0.0984
Medications before admission						
Aspirin	27.7	27.1	0.0132	15.4	13.5	0.0554
ACE inhibitors/ ARBs	50.4	47.6	0.0557	40.1	33.7	0.1322
Beta blockers	32.9	30.8	0.0442	18.8	18.1	0.0196
Angiographic findings						
Multivessel disease	50.6	52.5	-0.0378	44.8	44.5	0.0065
Outcome			**P value**			**P value**

STEMI	54.4	65.8	0.0002	50.8	64.6	0.0020
Risk Ratio (95% CI)	0.62 (0.48 – 0.79)		0.0002	0.57 (0.40 – 0.80)		0.0012

Data are percentages or means ± Standard deviation unless stated otherwise.

Abbreviations: ACE, angiotensin converting enzyme; ARBs, angiotensin receptor blockers; COPD, chronic obstructive pulmonary disease; STEMI, ST elevation myocardial infarction.

Supplemental Table 6. Inverse probability of treatment weighting: outcomes sorted by history of hypercholesterolemia and statin use before index event in patients aged ≥76 years.

Characteristics	History of hypercholesterolemia			No history of hypercholesterolemia		
	Statin users N=231	Statin nonusers N=493	Standardized difference	Statin users N=131	Statin nonusers N=1,488	Standardized difference
Age, years	79.6±3.9	79.7±4.2	-0.0364	79.5±3.3	80.1±4.5	-0.1588
Female sex	47.1	48.1	-0.0186	44.3	42.9	0.0281
Cardiovascular risk factors						
Diabetes	32.4	33.1	-0.0159	23.4	22.7	0.0170
History of hypertension	83.0	85.6	-0.0737	75.7	67.5	0.1811
Current smokers	16.8	15.9	0.0246	14.4	13.0	0.0396
Former smokers	15.3	15.5	-0.0035	18.5	14.1	0.1193
Clinical history						
COPD	7.4	6.9	0.0204	6.7	8.4	-0.0649
Chronic kidney disease	10.9	10.2	0.0213	14.9	10.5	0.1341
Medications before admission						
Aspirin	34.1	33.9	0.0037	18.6	18.1	0.0127
ACE inhibitors/ ARBs	54.6	54.3	0.0066	36.2	37.9	-0.0341
Beta blockers	42.1	39.5	0.0538	30.1	22.7	0.1690
Angiographic findings						
Multivessel disease	63.8	63.0	0.0160	51.9	57.5	-0.1108
Outcome			**P value**			**P value**

STEMI	49.7	67.2	<0.0001	49.9	63.5	0.0033
Risk Ratio (95% CI)	0.48 (0.35 – 0.66)		<0.0001	0.57 (0.40 – 0.82)		0.0022

Data are percentages or means ± Standard deviation unless stated otherwise.

Abbreviations: ACE, angiotensin converting enzyme; ARBs, angiotensin receptor blockers; COPD, chronic obstructive pulmonary disease; STEMI, ST elevation myocardial infarction.

Supplemental Table 7. Inverse probability of treatment weighting: outcomes sorted by diabetes status and statin use before index event in patients aged 65 to 75 years.

Characteristics	Diabetes			No diabetes		
	Statin users N=194	Statin nonusers N=655	Standardized difference	Statin users N=312	Statin nonusers N=2,115	Standardized difference
Age, years	69.3±3.2	69.2±2.9	0.0341	69.4±3.0	69.3±2.9	0.0506
Female sex	39.8	40.4	-0.0137	37.5	30.0	0.1504
Cardiovascular risk factors						
History of hypertension	88.5	82.2	0.1780	70.1	63.8	0.1766
History of hypercholesterolemia	44.1	45.9	-0.0359	36.5	34.4	0.0432
Current smokers	23.9	25.6	-0.0404	37.2	33.8	0.0728
Former smokers	14.8	14.4	0.0121	18.7	15.5	0.0847
Clinical history						
COPD	7.1	7.8	-0.0258	4.1	6.0	-0.0842
Chronic kidney disease	8.5	10.0	-0.0514	3.7	3.5	0.0066
Medications before admission						
Aspirin	25.5	25.6	-0.0035	19.8	16.4	0.0881
ACE inhibitors/ ARBs	56.7	51.2	0.1107	36.3	34.6	0.0349
Beta blockers	36.5	33.6	0.0617	18.9	19.0	-0.0017
Angiographic findings						
Multivessel disease	61.4	52.2	0.0617	42.7	46.1	-0.0694
Outcome			**P value**			**P value**

STEMI	50.9	64.8	0.0007	48.4	65.0	<0.0001
Risk Ratio (95% CI)	0.56 (0.41 – 0.78)		0.0005	0.50 (0.40 – 0.64)		<0.001

Data are percentages or means ± Standard deviation unless stated otherwise.

Abbreviations: ACE, angiotensin converting enzyme; ARBs, angiotensin receptor blockers; COPD, chronic obstructive pulmonary disease; STEMI, ST elevation myocardial infarction

Supplemental Table 8. Inverse probability of treatment weighting: outcomes sorted by diabetes status and statin use before index event in patients aged ≥76 years.

Characteristics	Diabetes			No diabetes		
	Statin users N=141	Statin nonusers N=469	Standardized difference	Statin users N=221	Statin nonusers N=1,512	Standardized difference
Age, years	79.9±3.5	79.9±4.2	0.0083	79.4±3.6	80.0±4.5	-0.1574
Female sex	45.1	47.8	-0.0556	48.8	43.5	0.1064
Cardiovascular risk factors						
History of hypertension	91.1	85.4	0.1758	72.6	68.9	0.0816
History of hypercholesterolemia	46.0	41.9	0.0834	33.5	28.4	0.1115
Current smokers	16.8	11.1	0.1693	13.3	14.9	-0.0451
Former smokers	13.4	13.2	0.0058	17.7	15.4	0.0628
Clinical history						
COPD	5.2	6.7	-0.0602	6.9	8.2	-0.0483
Chronic kidney disease	20.9	14.2	0.1773	9.7	9.0	0.0254
Medications before admission						
Aspirin	32.7	31.7	0.0204	25.3	21.3	0.0949
ACE inhibitors/ ARBs	58.8	57.1	0.0344	38.9	38.6	0.0060
Beta blockers	42.0	40.4	0.0326	30.5	24.1	0.1440
Angiographic findings						
Multivessel disease	60.5	62.6	-0.0424	54.5	58.1	-0.0727
Outcome			**P value**			**P value**

STEMI	50.3	67.9	0.0003	51.6	63.6	0.0010
Risk Ratio (95% CI)	0.48 (0.33 – 0.70)		0.0002	0.61 (0.46 – 0.81)		0.0007

Data are percentages or means ± Standard deviation unless stated otherwise.

Abbreviations: ACE, angiotensin converting enzyme; ARBs, angiotensin receptor blockers; COPD, chronic obstructive pulmonary disease; STEMI, ST elevation myocardial infarction

Supplemental Table 9. Interaction test: calculations for comparing two estimated risk ratios (statin users versus nonusers) for 30-day mortality by inverse probability of treatment weighting in STEMI patients aged 65 to 75 years vs STEMI patients aged ≥76 years. ··

		Group 1 [Age 65 to 75 years] (n = 2,096)	**Group 2 [Age≥76 years] (n = 1,480)**
1	**RR**	0.37	0.39
2	**log RR**	-0.9943	-0.9416
3	**95% CI for RR**	0.17 ~ 0.82	0.23 ~ 0.68
4	**95% CI for log RR**	-1.7720 ~ -0.1985	-1.4697 ~ -0.3857
5	**Width of CI**	1.5735	1.0840
6	**SE (=width / (2*1.96))**	0.4014	0.2765
	Difference between log risk ratios		
7	**d (=$E_1 - E_2$)**	**-0.0527**	
8	**SE (d)**	**0.4874**	
9	**CI (d)**	**-1.0080** ~ 0.9026	
10	**Test of Interaction**	**-0.1081 (p-value: 0.4570)**	
	Ratio of risk ratios		
11	**RRR (=exp(d))**	0.9487	
12	**CI (RRR)**	0.3649 ~ 2.4660	

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