Renin-angiotensin system antagonists and clinical outcomes in stable coronary artery disease without heart failure

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Aims	The aim of this study was to determine whether angiotensin-converting enzyme inhibitor (ACEI) or angiotensin-II receptor blocker (ARB) use is associated with lower rates of cardiovascular events in patients with stable coronary artery disease (CAD) but without heart failure (HF) receiving contemporary medical management.
Methods and results	Using data from the Reduction of Atherothrombosis for Continued Health (REACH) registry, we examined, using propensity score approaches, relationships between cardiovascular outcomes and ACEI/ARB use (64.1% users) in 20 909 outpatients with stable CAD and free of HF at baseline. As internal control, we assessed the relation between statin use and outcomes. At 4-year follow-up, the risk of cardiovascular death, MI, or stroke (primary outcome) was similar in ACEI/ARB users compared with non-users (hazard ratio, 1.03; 95% confidence interval [CI], 0.91–1.16; $P = 0.66$). Similarly, the risk of the primary outcome and cardiovascular hospitalization for atherothrombotic events (secondary outcome) was not reduced in ACEI/ARB users (hazard ratio, 1.08; 95% CI, 1.01–1.16; $P = 0.04$), nor were the rates of any of its components. Analyses using propensity score matching yielded similar results, as did sensitivity analyses accounting for missing covariates, changes in medications over time, or analysing separately ACEI and ARB use. In contrast, in the same cohort, statin use was associated with lower rates for all outcomes.
Conclusions	Use of ACEI/ARB was not associated with better outcomes in stable CAD outpatients without HF. The benefit of ACEI/ARB seen in randomized clinical trials was not replicated in this large contemporary cohort, which questions their value in this specific subset.
Keywords	Angiotensin-converting enzyme inhibitors • Angiotensin-II receptor blockers • Statins • Stable coronary artery disease

Introduction

Angiotensin-converting enzyme inhibitors (ACEIs) are beneficial in the management of patients with heart failure (HF), left ventricular (LV) dysfunction,[1–3] myocardial infarction (MI),[4] hypertension,[5] diabetes mellitus,[6,7] and chronic kidney disease.[8] Angiotensin-II receptor blockers (ARBs) provide similar results in patients with cardiovascular disease and no HF[9] and are an alternative for patients who are intolerant to ACEI.[10] However, whether these benefits are replicated in routine in stable patients with coronary artery disease (CAD) and without HF is uncertain.

In patients with CAD, both American[11–13] and European[14–16] guidelines for the management of stable angina, acute coronary syndromes, or ST-elevation MI give broad recommendations for the use

of ACEI (or ARB in ACEI intolerant patients). In CAD patients without HF or LV dysfunction, a group at lower risk of events, meta-analyses of randomized clinical trials (RCTs) have shown a modest benefit of ACEI, with a reduction in major cardiovascular outcomes ranging from 13 to 19%.[17−19] Moreover, as mentioned in the 2013 ESC guidelines on the management of stable CAD,[14] 'not all clinical trials have demonstrated that ACEI reduce all-cause mortality, cardiovascular mortality, non-fatal MI, stroke and HF in patients with atherosclerosis and preserved LV function'. While the HOPE[20] and EUROPA[21] trials had found benefit of ACEI in patients at high-risk of cardiovascular disease or with stable CAD and no apparent HF, the more recent PEACE[22] and IMAGINE[23] trials found no impact of ACEI in patients with stable CAD or recent coronary artery bypass graft (CABG) and without HF. In addition, there have been major changes in medical practice in the past 10 years, which make older trials less relevant to the current therapeutic environment. Finally, RCTs tend to enrol highly selected patients. All of these factors result in uncertainty regarding the benefit of ACEI/ARB in stable patients without HF, a cohort at low risk.[24−27]

Large observational studies have more external validity than RCTs and may be useful when evaluating the impact of long-term use of drugs in broad patient populations.[28] Because of conflicting results of RCTs, of their somewhat outdated nature and of the intervening changes in patient management and improved outcomes, and acknowledging that RCTs remain the gold standard to compare effectiveness of medical management strategies,[29] the Reduction of Atherothombosis for Continued Health (REACH) cohort provides an opportunity to study whether the clinical benefit of ACEI/ARB seen in RCTs translates into benefit in routine practice, in a contemporary large cohort of stable CAD patients, with a variety of co-morbidities and conditions, and broad geographic representation. We used data from this cohort in order to assess the incidence of cardiovascular events according to ACEI or ARB use in patients with stable CAD and without HF.

Methods

Patient population

Design, methods, and main results of the large international contemporary REACH registry have been published previously.[30−33] Patients included in the present analysis were those with documented CAD defined as stable angina, or history of unstable angina, percutaneous coronary intervention, CABG, or MI. Patients with prior HF (defined by signs or symptoms of left or right ventricular failure or both) were excluded from the analysis: first, there are ample data to demonstrate the major benefit of ACEI/ARB in patients with HF, and second, in many REACH patients, information on LV function was missing, and it was desirable to assess a composite outcome and a population which would not be affected by HF.

Outcome measures

The primary outcome of REACH was the composite of cardiovascular death, MI, or stroke during 4-year follow-up.[33] We also examined the REACH secondary outcome consisting of the quadruple composite of cardiovascular death, MI, stroke, or cardiovascular hospitalization for atherothrombotic event.[33] Tertiary outcomes were all-cause mortality, all components of the secondary outcome, and HF.

Statistical analysis

Data were expressed as means ($\pm$ standard deviation) for continuous variables and numbers (percentages) for qualitative variables. Because of significant differences in a large number of baseline characteristics between treatment groups (see Supplementary material online, *Table S1*), propensity score adjustment was performed.

As main analysis, propensity score was calculated and used to adjust the between-group comparisons of cardiovascular outcomes. Propensity score was estimated using a non-parsimonious multivariate logistic regression model, with ACEI/ARB use as the dependent variable and all the characteristics which are listed in the Supplementary material online, *Table S1* as covariates.[34]

An additional analysis was performed on matched pairs of patients with vs. without ACEI/ARB: in order to assemble well-balanced groups, patients with or without ACEI/ARB were matched on the propensity score, using the Greedy matching protocol (i.e. a 1:1 matching algorithm without replacement) with a calliper width of 0.1.[34−36] Absolute standardized differences for all covariates before and after matching were estimated to evaluate bias reduction using the propensity score matching method. After propensity score matching, all absolute standardized differences were <10%, indicating adequate matching[37] (see Supplementary material online, *Figure S1*). Comparisons in baseline characteristics between the matched groups were done using the paired Student t-test for continuous variables and the Cochran−Mantel−Haenszel χ^2 test for qualitative variables.

We compared the risk of cardiovascular outcomes between the two groups in the propensity score-adjusted cohort using a Cox proportional hazard regression model with the propensity score as a covariate.[34] Adjusted cumulative incidence curves were calculated using the corrected group prognosis method, after categorization of propensity scores into deciles.[38] A secondary analysis was done using a Cox proportional hazard regression model stratified on the matched pairs. Proportional hazard assumptions were checked by using the log−log survival plot and Schoenfeld residuals. Subgroup analyses were also performed in the propensity score-adjusted and propensity score-matched cohorts based on history of MI (no prior history, prior MI >1 year before enrolment, prior MI ≤1 year), diabetes and hypertension, high baseline blood pressure (BP) values (systolic/diastolic ≥140/90 mmHg) and overall risk as measured from the REACH risk score for prediction of recurrent events.[39] Heterogeneity across subgroups was quantified by introducing multiplicative terms into the Cox proportional hazard regression models.

As an internal validity check of the present analyses, we assessed the impact of statins on cardiovascular outcomes in the same cohort using the same propensity score approaches.

Sensitivity analyses were performed with various statistical models and methods, accounting for missing covariates, for changes in medications or including patients with incident HF during follow-up. Methods are explained in the Supplementary material online, Appendix.

To differentiate the effects of ACEI and ARB use, the main analysis was repeated first in a cohort with ACEI but no ARB use, and secondly in a cohort with ARB but no ACEI use.

Statistical testing was conducted at the two-tailed α-level of 0.05. Data were analysed using the SAS software version 9.3 (SAS Institute, Cary, NC, USA).

Results

Study population

From the 67 888 stable patients with CAD, cerebrovascular disease (CVD), peripheral artery disease (PAD), or ≥3 risk factors only

included at baseline, 45 227 were enrolled for a 4-year follow-up. Of them, 26 389 patients had established CAD but no CVD or PAD at baseline. Among these, 20 936 patients free of HF at baseline constituted the study cohort. Information on baseline use of ACEI or ARB was available in 20 909 patients (99.9% of the study cohort). Patients were divided into two groups on the basis of ACEI or ARB use (13 404 users, 7505 non-users) at enrolment (*Figure 1*). Median follow-up was 44 months (interquartile range, 37−45 months),

with 2- and 4-year follow-up data available for 95.0 and 71.6% of the patients, respectively.

There were major differences in baseline characteristics between groups (see Supplementary material online, *Table S1*), which disappeared after matching with all absolute standardized differences <10% suggesting adequate matching (see Supplementary material online, *Figure S1*). Among patients with ACEI/ARB use at baseline, discontinuation was relatively rare: the proportion of patients remaining
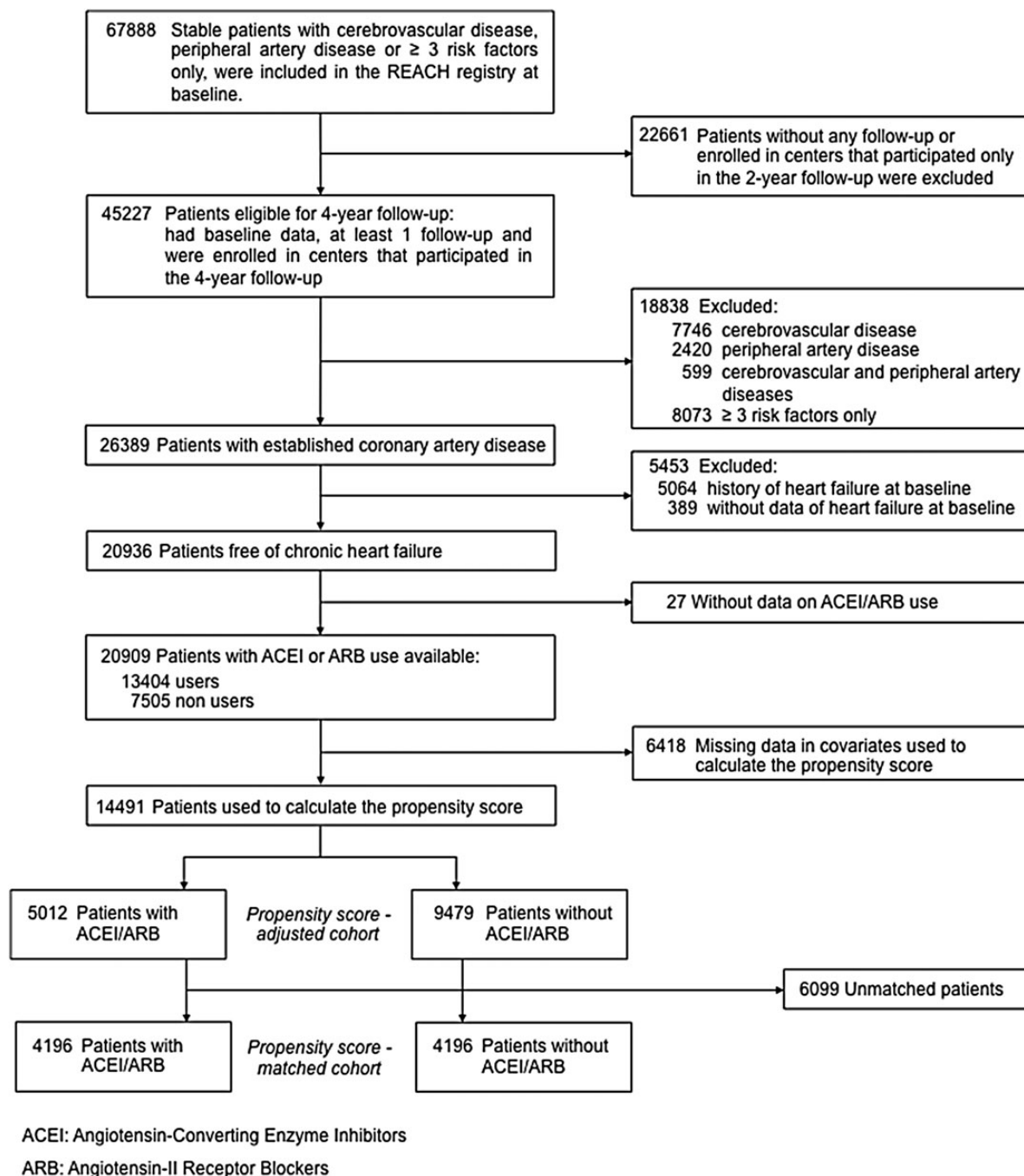
Figure 1 Flow diagram of study patients.

on ACEI/ARB was 94.5 at 6-months, 92.5 at 12-months, 91.5 at 18-months, 91.4 at 2-years, 90.0 at 3-years, and 89.1% at 4-years.

Study outcomes

In the propensity score-adjusted cohort, 1527 patients experienced at least one primary event (cardiovascular death, non-fatal MI, or non-fatal stroke) during 4-year follow-up (Kaplan−Meier estimate, 11.8%). The rate of the primary outcome was similar in ACEI/ARB users compared with non-users (adjusted hazard ratio, 1.03; 95% CI, 0.91−1.16; $P = 0.66$) (Figure 2A). A slight increase in the risk of secondary outcome in patients with ACEI/ARB (HR, 1.08, 95% CI, 1.01−1.16; $P = 0.04$), driven by an increase in hospitalization and HF was found. There was no difference for any others tertiary outcomes (Figure 3A). When these analyses were repeated in the matched cohorts, there was no difference between groups in the rate of primary, secondary, or tertiary outcomes (Figure 4A). The matched hazard ratio was 1.03 (95% CI, 0.90−1.19; $P = 0.66$) for the primary outcome and 1.07 (95% CI, 0.98−1.17; $P = 0.13$) for the secondary outcome.

Subgroup analyses

The main analyses by propensity score-adjusted approach were repeated in key patient subgroups. A history of hypertension, BP measured at baseline, or the level of risk as measured by baseline REACH risk score did not affect the results. However, there was borderline interaction between a history of MI and the effect of ACEI/ARB ($P = 0.06$): a history of recent MI ($\leq$1 year) was associated with a reduction of the primary outcome with ACEI/ARB (see Supplementary material online, Figure S3A). This was no longer significant with the secondary outcome (see Supplementary material online, Figure S3B). However, no such heterogeneity was found in the propensity score-matched cohorts (see Supplementary material online, Figure S4).

Sensitivity analyses

Sensitivity analyses, accounting for missing covariates, for changes in medications or including patients with incident HF during follow-up showed no association between ACEI/ARB use and a reduction of either the primary or secondary outcomes (see Supplementary material online, Appendix 2 and Table S2). There was just a modestly higher risk of the secondary outcome, which included hospitalizations, in the propensity score-adjusted cohort by multiple imputation analysis, with ACEI/ARB use.

Similar findings were observed when the analyses were restricted to ACEI alone, excluding patients with ARB use (see Supplementary material online, Table S3 and Figures S5−S7) with hazard ratios for primary outcome of 1.04 (95% CI, 0.91−1.18; $P = 0.58$) in propensity score-adjusted model and 0.98 (95% CI, 0.84−1.14; $P = 0.78$) in propensity score-matched model. Likewise, the analyses restricted to ARB use alone, excluding patients with ACEI use, showed no detectable impact of ARB on the primary or secondary outcomes (see Supplementary material online, Table S4 and Figures S8−S10).

Statin use and clinical outcomes

There were substantial differences in baseline characteristics between the 16 000 patients receiving statins and the 4915 who did not (see Supplementary material online, Table S5). Using the same propensity score approach as for ACEI/ARB, a propensity score for statin use could be calculated for 14 479 patients (77.3% statin users), and 3096 statin users were matched with 3096 statin non-users. All absolute standardized differences were <10%, also suggesting adequate matching (see Supplementary material online, Figure S2).

In the propensity score-adjusted cohort, 1524 patients reached the primary outcome (Kaplan−Meier estimate, 11.7%). The rate of the primary outcome was lower in patients with statins than in those without (hazard ratio, 0.74; 95% CI, 0.65−0.83; $P<0.001$) (Figure 2B). Statins were also associated with lower rates of secondary and tertiary outcomes, except for non-fatal MI ($P = 0.07$) and HF ($P = 0.09$) (Figure 3B). Similar results were found in the propensity score-matched cohort analysis, although in that analysis, statin use was not associated with lower rates of non-fatal stroke and cardiovascular hospitalizations (Figure 4B). As for ACEI/ARB use, several sensitivity analyses were performed. Regardless of the analytic method, there was a consistent association between statin use and lower rates of the primary and secondary outcomes (see Supplementary material online, Table 2).

Discussion

In this contemporary international cohort, we found no evidence that routine use of ACEI/ARB in outpatients with stable CAD but without HF was associated with a lower rate of major cardiovascular events. These findings were consistent across several adjustment methods and sensitivity analyses, and were observed for ACEI/ARB, ACEI alone, or ARB alone. Sub-group analyses found similar results regardless a history of hypertension or the cardiovascular risk level as measured by the REACH risk score for the prediction of recurrent events. There was a borderline interaction suggesting possible benefit in patients with recent MI ($\leq$1 year).

Conversely, with similar methods, statin use was associated with markedly lower rates of both primary and secondary outcomes, consistently across all models and subsets. This 'internal control' reinforces the validity of the present analytic strategy.

Overall, the benefit of routine ACEI/ARB use seen in most RCTs in stable CAD patients without history of HF was not confirmed in this large observational cohort.

In RCTs, the greatest benefit of ACEI/ARB was seen in patients with HF, recent MI, or patients with high cardiovascular risk.[20,21] Interestingly, the PEACE[22] trial, in stable CAD patients without HF, did not find a reduction in the primary outcome of cardiovascular death, MI, or coronary revascularization. Likewise, the IMAGINE[23] trial found no benefit of quinapril on clinical outcomes, after CABG in stable patients without HF. In both of these trials as well as in REACH, the rates of statins and antiplatelet agents use were high and event rates were lower than in HOPE[20] and EUROPA,[21] suggesting that with modern evidence-based secondary prevention medications, patients without HF do not necessarily derive benefit of ACEI/ARB beyond that provided by any effective well-tolerated antihypertensive.

The present findings are derived from observational analyses which are subject to well-known limitations. The first is the potential for confounding by measured or unmeasured variables, which cannot be ruled out, even after propensity score adjustment. Indeed, residual
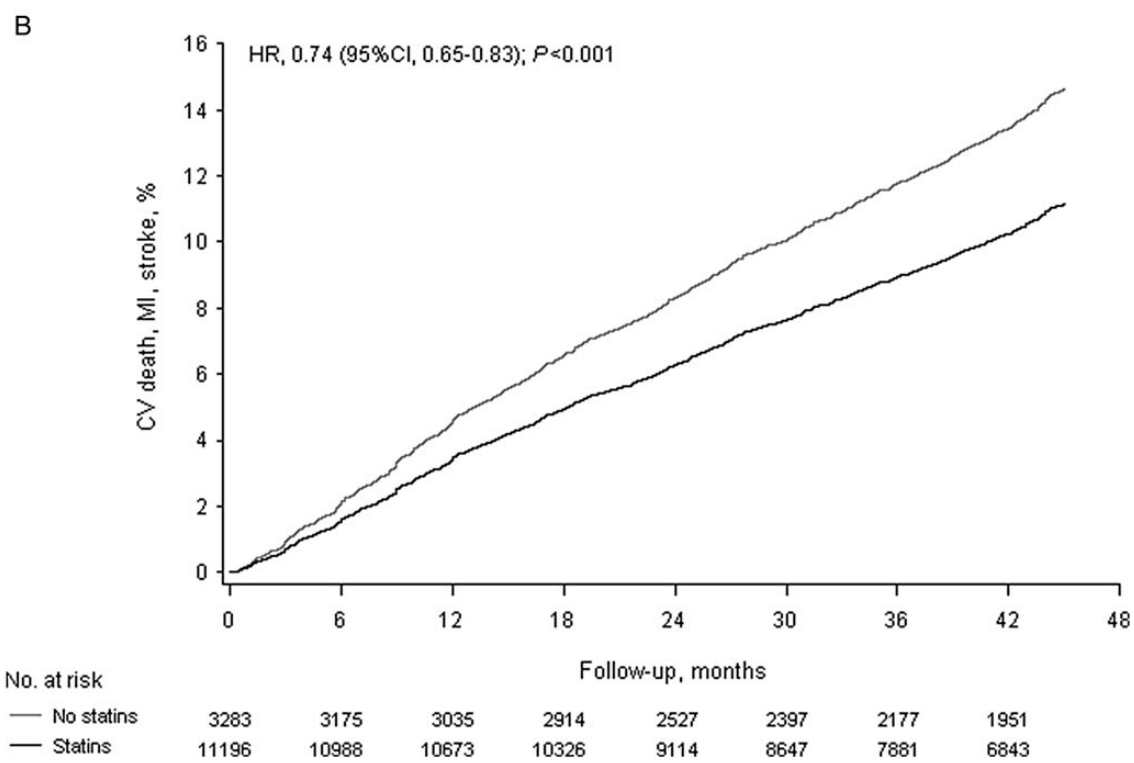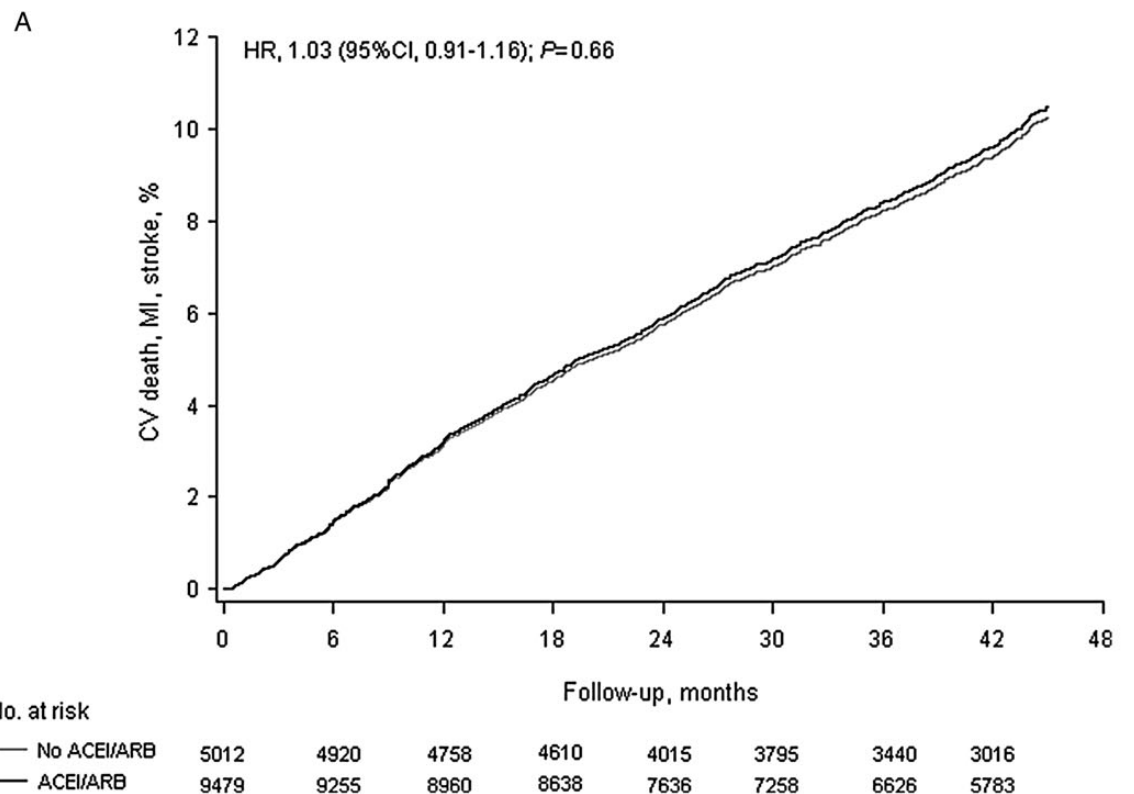
Figure 2 Cumulative incidence curve for the risk of primary outcome by ACEI/ARB use (*A*) and statin use (*B*) in propensity score-adjusted analysis. Adjusted event curves were calculated using the corrected group prognosis after categorization of propensity score into deciles.
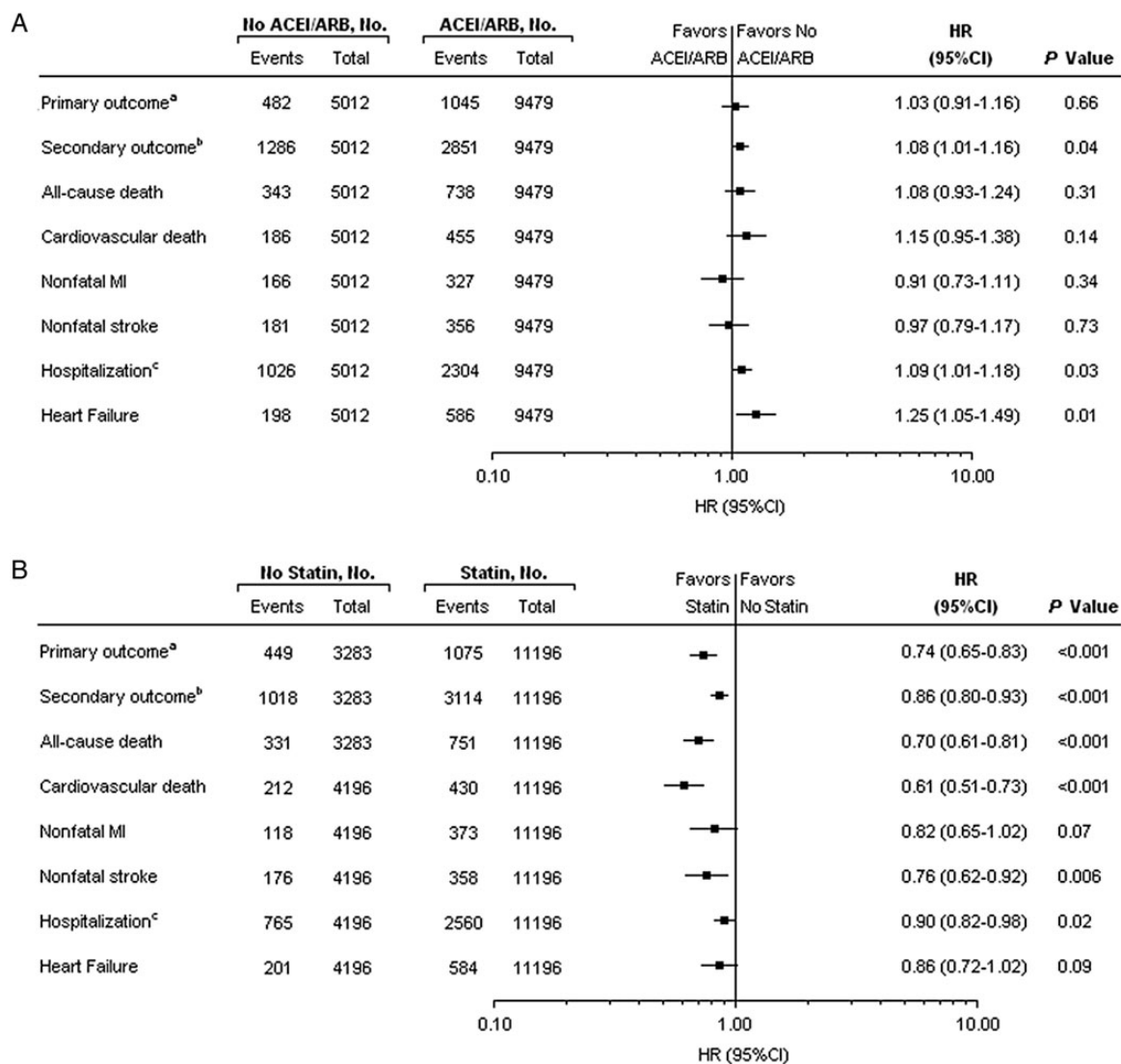
Figure 3 Risk of outcomes by ACEI/ARB use (*A*) and statin use (*B*) in propensity score-adjusted analysis. [a]Cardiovascular death, non-fatal MI, or non-fatal stroke; [b]primary outcome plus hospitalization; [c]hospitalization for atherothrombotic events or revascularization procedure (coronary, cerebral, or peripheral).

bias by indication may have been present particularly as we did not have systematic assessment of LV function. However, even though we could not exclude patients with asymptomatic LV dysfunction (which are known to derive benefit from ACEI/ARB) from our analyses, we did not find evidence of benefit from ACEI/ARB use. Moreover, three factors suggest that these results are valid: first, the remarkable consistency and robustness of the outcomes across the various models, subsets, and adjustment methods used; secondly, the size of the population and the attendant narrow confidence intervals of clinical outcome rates; and thirdly, the contrast between lack of effects of ACEI/ARB on outcomes and the marked consistent benefit of statins, suggesting that drugs rather than analytical methods or study design may account for the results. Another interesting analysis would have been to study the effect of ACEI/ARB in patients with history of HF at baseline, but that subgroup was too

small to allow a robust propensity score-adjusted analysis. The lack of information regarding doses of ACEI/ARB is another limitation. It is well known that the doses of renin–angiotensin system antagonists which have shown efficacy in trials are often higher than those used in routine clinical practice, which may account for some of the present findings. Finally and importantly, our analyses should not be interpreted as detracting in any way from the established value of ACEI/ARB in other patient subsets, particularly in patients with CAD and congestive HF.

In conclusion, in the large international contemporary REACH registry, use of ACEI/ARB, ACEI alone, or ARB alone did not appear associated with lower rates of major cardiovascular outcomes, whereas in the same population, identical methods found a lower rate of ischaemic events in patients on statins. These results question the effectiveness of routine ACEI/ARB use in
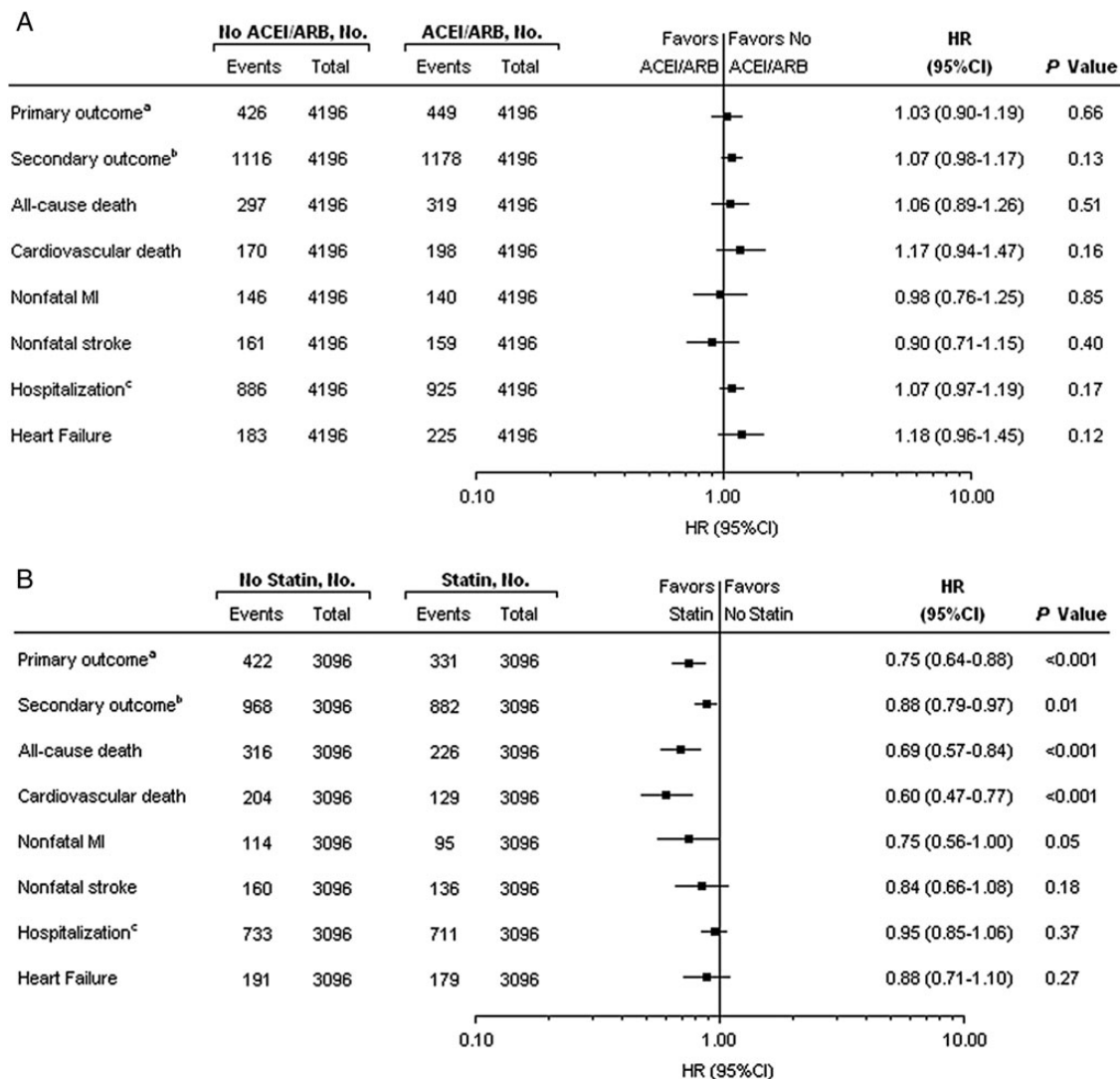
Figure 4 Risk of outcomes by ACEI/ARB use (*A*) and statin use (*B*) in propensity score-matched analysis. [a]Cardiovascular death, non-fatal MI, or non-fatal stroke; [b]primary outcome plus hospitalization; [c] hospitalization for atherothrombotic events or revascularization procedure (coronary, cerebral, or peripheral).

patients with stable CAD and without HF in the modern therapeutic environment.

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