Use of real-world evidence in pharmacoeconomic analysis

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Comparing the effect of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on renal function decline in diabetes

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ABSTRACT

Aim:

To compare effectiveness of ACEis/ARBs for protecting DM2 patients from renal function decline in a real world setting.

Methods:

Retrospective cohort study of new ACEi/ARB users in 2007-2012 in an unselected primary care DM2 population. Outcome is decline in renal function stage (combining eGFR and albuminuria). Patients were matched on a propensity score. Extended Cox models with time-varying covariates were used to estimate hazard ratios of outcome.

Results:

The time to renal function decline for ARB users was slightly, but not significantly longer than for ACEi users (HR = 0.80, 95%CI [0.58-1.10], p=0.166).

Conclusion:

This study did not show significant differences between the classes in preventing renal function decline in DM2 patients in primary care.

Keywords: Angiotensin Converting Enzyme inhibitors; Angiotensin Receptor Blockers; Comparative effectiveness research; Primary care; Renal function decline; Type 2 diabetes; observational research; cohort study

BACKGROUND

Diabetic patients with renal complications are at increased risk for cardiovascular events and, if untreated, of increased renal function decline [1,2]. Diabetic nephropathy occurs in 20–40% of all diabetic patients and has become the leading cause of end stage renal disease (ESRD) in the western world [1]. As the most clinically relevant pharmacological agents that block the renin-angiotensin-aldosterone system (RAAS), angiotensin converting enzyme inhibitors (ACEis) and angiotensin receptor blockers (ARBs) have been extensively studied in randomized controlled trials (RCTs) on their beneficial effects on cardiovascular morbidity and mortality across various populations. Although differences in modes of action between ACEis and ARBs introduce controversial discussion about effects on mortality or myocardial infarction risk [3-5], both ACEis and ARBs have been shown to be renoprotective in diabetic patients [6,7], and either of these drug classes are recommended as first choice treatment in diabetic patients with hypertension [1,8]. Head-to-head comparisons in RCTs (i.e. comparing an ACEi directly with an ARB) are relatively rare, and the findings in protective effects between the two classes are still inconclusive [9,10]. Recently, two network meta-analyses of antihypertensive treatment in diabetic patients on ESRD and on secondary kidney function outcomes from RCTs found that both ACEi and ARB monotherapy showed significant protective effects in preventing ESRD and doubling of serum creatinine, but comparison between ACEis and ARBs did not reach statistical significance [6,7]. RCTs may have the limitation, due to the patient selection criteria, that observed benefits do not easily translate to a real world, where patients are older and often have multimorbidity [11]. In actual practice, both ACEis and ARBs seem to be less effective because patients are older, leading to the call for more observational studies assessing the effects of these drug classes in populations different from those in trials [12].

In recent years observational studies have compared the effectiveness of ACEis and ARBs in patients with hypertension, heart failure, kidney disease and other metabolic diseases, applying propensity score matching in order to reduce bias due to confounding [13-16]. For type 2 diabetes mellitus (DM2), a study in the US [17] showed that in an older population with macroalbuminuria ACEis were associated with lower ESRD development and all-cause mortality than ARBs. But since the population in that study was restricted to patients with macroalbuminuria, the comparative effectiveness of ACEis and ARBs on nephropathy in more generalized DM2 patients still needs to be explored. To our knowledge no studies have been reported comparing the effectiveness of ACEis and ARBs for protecting patients from renal function decline in an unselected DM2 population.

Outcome measures for renal function in studies comparing ACEis and ARBs include albuminuria, estimated glomerular filtration rate (eGFR), doubling of serum creatinine, occurrence of ESRD, or mortality. The use of this variety of indicators of renal function complicates comparison between studies. Instead of using a single biomarker, a functional classification into renal function stages has been developed [18], acknowledging that glomerular filtration rate and albumin secretion are independently associated with adverse outcomes. Several studies have used this measure of renal function stages to analyse kidney function in patients with diabetes or cardiovascular diseases [19,20], with the advantage of enabling the quantification of early onset renal function decline. To our knowledge no observational drug effectiveness studies have used this classification as an outcome measure.

The objective of this study is to compare the effectiveness of ACEis and ARBs for protecting DM2 patients from renal function decline in a real world setting. In addition we will explore the effect modification of the initial renal function stage.

METHODS

Study design

This study is a retrospective, longitudinal cohort study in an unselected primary care population of about 35,000 patients with type 2 diabetes in the Northern Netherlands. Patients receiving diabetes care from their general practitioner (GP) between 2007 and 2012 were eligible for inclusion in the study.

Cohort definition

Data from the GIANTT (Groningen Initiative to Analyse Type 2 diabetes Treatment) cohort are used. The GIANTT database contains anonymized data extracted from structured tables and free text parts of electronic medical records using an automated and validated method [21].

We included patients who initiated treatment with ACEi or ARB between 2007 and 2012.

Initiation of ACEis or ARBs is defined as a prescription during the study period, without a prescription of any RAAS-inhibitors in the preceding 365 days. Apparent non-use in this period due to temporary absence from the general practice was manually checked with full patient data; false initiators due to temporary non-use were excluded. The date of this first

prescription is the index date. Within class switches during follow-up are allowed, since the different ACEis or ARBs drugs are considered to have similar effects [22].

Exclusion criteria were: (1) treatment stopped within 6 months; (2) no baseline eGFR measurement (last 12 months before the index date); (3) no eGFR measurements after 90 days of the index date, since the first 3 months of treatment were usually for changing therapies or titrating dose [23] so that eGFR measurements after 3 months were assumed to reflect effectiveness of a stable treatment regimen.

Patient characteristics

Patient characteristics used were demographic characteristics (age, gender, time since DM2 diagnosis), risk factor measurements (systolic/diastolic blood pressure (SBP/DBP), HbA1c, total cholesterol (TC), high/low density lipoprotein cholesterol (HDL-C/LDL-C), triglycerides (TG), renal function stage, body mass index (BMI) and smoking status). The last observed value of these characteristics during the year before the index date was used as baseline value, and all observations during follow-up were recorded. Baseline status of cardiovascular comorbidities (ischaemic heart disease with angina, acute myocardial infarction, ischaemic heart disease without angina, heart failure, atrial fibrillation, cardiac arrhythmia, stroke/cerebrovascular accident, cerebrovascular disease, atherosclerosis/peripheral vascular disease) was defined as a diagnosis ever before index. The use of other antihypertensives (diuretics, calcium channel blockers, beta-blockers) during the year before index date was assessed to obtain baseline co-medication status, and the exposure to these drugs, as well as the ACEi or ARB during follow-up was recorded.

Outcome measure

Outcome is renal function decline, as measured by the combination of eGFR and albuminuria-to-creatinine ratio (ACR) in five renal function stages [18] (**Supplementary Table 1**). Baseline renal function stage was determined by the last available eGFR and ACR in the year before the index date. During follow-up, each measurement of eGFR and/or ACR was used to update the renal function stage. We consider an ACR within 2 days from a measurement of eGFR as originating from the same observation due to expected variation in availability of blood and urine test results. For an ACR measurement without an eGFR measurement on the same date, the last available eGFR value before that date was used to calculate the renal function stage. In case of an eGFR measurement without a coinciding ACR observation, the last available ACR value was used to calculate the renal stage.

Follow-up

Patients were followed from the index date until the first occurrence of: (1) reaching the outcome: confirmed renal function decline, defined by two consecutive stage observations worse than baseline; (2) moving out of the general practice; (3) death; (4) end of data availability.

Statistical analysis

Missing values of baseline characteristics

Since in the Netherlands diabetes management is highly protocolized with three-monthly visits resulting in standardized observations of the variables used in this study, we expect the missingness to be at random. Therefore we used multiple imputation to impute missing baseline values of albuminuria, SBP, DBP, HbA1c, TG, TC, HDL-C, LDL-C, BMI and smoking status. In our pre-analyses, 10 multiple imputed datasets were used as suggested in the literature [24]. Baseline and follow-up renal function stages were partly dependent on imputed baseline albuminuria values, causing different follow-up periods and outcomes between imputed datasets. Since there is no guidance on the number of imputations needed for a fair estimate of effects in such a situation, we conservatively chose a high number, 25. To improve computing performance, all further analyses were performed in each imputed dataset separately, after which the results were combined using Rubin's rules [25] and pooled results are reported.

Propensity score matching

To minimize confounding by indication [26], patients starting on ACEi and ARB treatment were matched on a propensity score (PS), using all available baseline characteristics. ACEi users were matched with ARB users at a ratio of 1:1 using a nearest neighbour matching algorithm with a maximum caliper. The post-matching C-statistic [27], a multivariate statistic to assess balance on all covariates simultaneously, was used to identify the caliper at which the number of matched patients decreased faster than the achieved balance. A caliper of 0.01 was identified as optimal. To assess imbalance in individual baseline characteristics, the standardized mean difference (SDD) was calculated [28].

Survival Analysis

The time to renal function decline was analysed using an extended Cox model with time-varying covariates in the propensity score matched cohort. The time-varying covariates were SBP, DBP, BMI, HbA1c, TG, cardiovascular comorbidities, as well as study and co-medication (expressed in units of Defined Daily Dose (DDD) per day [29]).

Patients can leave the cohort due to moving house (for example to a nursing home, or another region) or death. Since these reasons can be related to the study outcome, competing risks models treating moving or death as competing risks, were used instead of a standard Cox model, to calculate hazard ratios (HRs) of confirmed renal function decline. Models incorporating the interaction between renal function stage and drug treatment were used to explore effect modification by the initial renal function stage on ACEi/ARB effectiveness.

Data preparation and statistical analyses were performed using Stata MP Version 12.0 (Stata Corporation, College Station, TX).

Ethics Statement

For research using anonymous medical records no ethics committee approval is needed in The Netherlands. The study protocol was approved by the GIANTT Steering Group.

RESULTS

After applying the inclusion and exclusion criteria, 3,633 patients were selected for the analyses. Among them, 2,830 patients were taking ACEis and 803 patients were taking ARBs (the types of ACEis/ARBs received by the study participants were showed in **Supplementary Table 2**). Patients were excluded mainly due to the exposure of study drugs (ACEis and ARBs) before diagnosis of DM2 and lack of baseline renal function stage measurements (**Figure 1**).

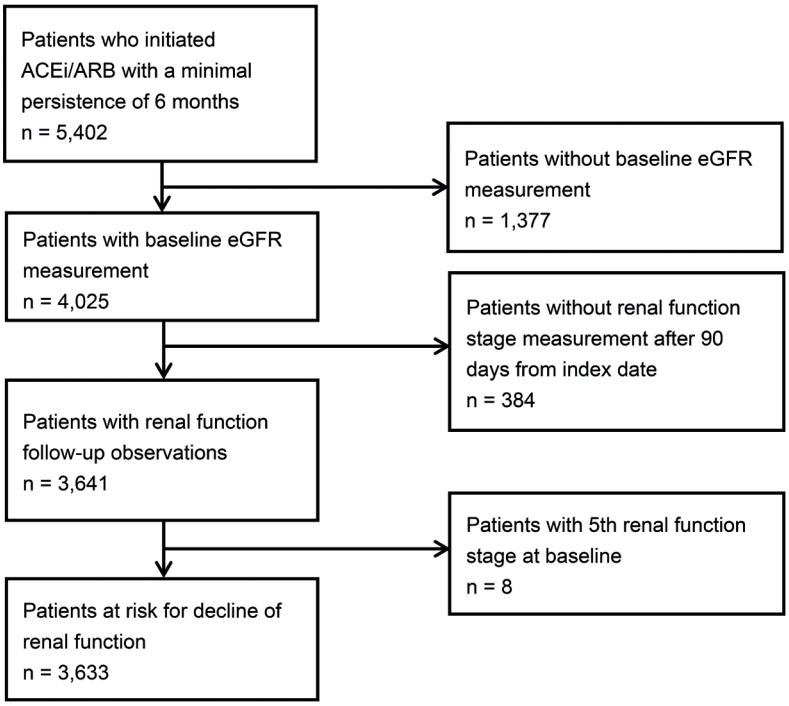

Figure 1. Patient selection flow of study.
ACEi: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; eGFR: Estimated glomerular filtration rate.

In the unmatched population the C-statistic of exposure was 0.606, indicating some relevant differences of baseline characteristics for treatment choice. The worst balanced characteristics were the use of CCB and β-blocker medication, gender, short DM2 duration, SBP, BMI availability and HbA1c with SDDs ranging from 0.194 to 0.102 (**Table 1**). The pooled post-matching C-statistic of 0.544 in the 25 imputed cohorts indicated good balance between the treatment groups. All baseline characteristics had a pooled SDD below 0.1, which means the matching resulted in well-balanced baseline values between the treatment groups.

Table 1. Baseline characteristics before and after propensity score matching.

	Before matching			After matching*		
	ACEi N (%) / Mean (SD)	ARB N (%) / Mean (SD)	SDD	ACEi Pooled Mean	ARB Pooled Mean	Pooled SDD
Number of patients	2,830	803	-	779 (6.4)†	779 (6.4)†	-
Female	1,293 (45.7%)	417 (51.9%)	0.124	53.6%	51.8%	0.040
Age	65.5 (12.0)	66.5 (11.2)	0.084	66.5	66.4	0.034
SBP observed	2,646 (93.5%)	743 (92.5%)	0.038			
SBP value	156.1 (21.0)	158.7 (23.0)	0.120	158.8	158.3	0.027
DBP observed	2,645 (93.5%)	742 (92.4%)	0.041			
DBP value	85.6 (11.9)	85.8 (12.0)	0.017	85.8	85.7	0.027
BMI observed	1,798 (63.5%)	467 (58.2%)	0.110			
BMI value	30.2 (5.7)	30.7 (5.3)	0.077	30.7	30.6	0.025
HbA1c observed	2,685 (94.9%)	773 (96.3%)	0.067			
HbA1c value	7.1 (1.2)	6.9 (1.0)	0.102	6.9	7.0	0.023
Total Cholesterol observed	2,373 (83.9%)	679 (84.6%)	0.019			
Total Cholesterol value	4.7 (1.2)	4.7 (1.1)	0.020	4.7	4.7	0.022
HDL-C observed	2,472 (87.4%)	712 (88.7%)	0.041			
HDL-C value	1.2 (0.3)	1.2 (0.3)	0.085	1.2	1.2	0.028
LDL-C observed	2,437 (86.1%)	702 (87.4%)	0.039			
LDL-C value	2.7 (1.0)	2.7 (1.0)	0.014	2.7	2.7	0.026
Triglycerides observed	2,486 (87.8%)	717 (89.3%)	0.045			
Triglycerides value	2.0 (1.3)	1.9 (1.2)	0.060	1.9	1.9	0.024
Smoking	361 (12.8%)	78 (9.7%)	0.096	9.1%	9.5%	0.022
DM2 duration (months)						
< 12 months	747 (26.4%)	170 (21.2%)	0.123	20.5%	21.3%	0.029
12- 60 months	1,020 (36.0%)	303 (37.7%)	0.035	38.7%	38.1%	0.023
60-120 months	659 (23.3%)	190 (23.7%)	0.009	23.3%	23.6%	0.024
>= 120 months	404 (14.3%)	140 (17.4%)	0.087	17.5%	17.0%	0.020
Reanl stage	1,897 (67.0%)	551 (68.6%)	0.034			
Stage 1	1,037 (54.7%)	327 (59.3%)	0.084	57.9%	57.7%	0.025
Stage 2	621 (32.7%)	161 (29.2%)	0.047	28.8%	29.3%	0.029
Stage 3	174 (9.2%)	45 (8.2%)	0.023	9.8%	8.9%	0.036
Stage 4	65 (3.4%)	18 (3.3 %)	0.004	3.5%	4.1%	0.038
Cardiovascular comorbidity history						

Table 1. Continued

	Before matching			After matching*		
	ACEi N (%) / Mean (SD)	ARB N (%) / Mean (SD)	SDD	ACEi Pooled Mean	ARB Pooled Mean	Pooled SDD
Ischaemic heart disease with angina	197 (7.0%)	56 (7.0%)	0.000	6.4%	6.8%	0.027
Acute myocardial infarction	207 (7.3%)	59 (7.4%)	0.001	6.9%	7.0%	0.024
Ischaemic heart disease without angina	229 (8.1%)	65 (8.1%)	0.000	7.6%	7.7%	0.025
Heart failure	103 (3.6%)	34 (4.2%)	0.031	4.0%	4.0%	0.018
Atrial fibrillation	118 (4.2%)	47 (5.9%)	0.077	5.4%	5.2%	0.023
Cardiac arrhythmia	70 (2.5%)	18 (2.2%)	0.015	1.7%	1.9%	0.025
Stroke/ cerebrovascular accident	91 (3.2%)	25 (3.1%)	0.006	3.1%	3.1%	0.019
Cerebrovascular disease	31 (1.1%)	9 (1.1%)	0.002	1.1%	1.1%	0.025
Atherosclerosis/ peripheral vascular disease	177 (6.3%)	41 (5.1%)	0.050	4.8%	5.0%	0.021
Co-medication						
Diuretics	967 (34.2%)	300 (37.4%)	0.067	37.8%	37.2%	0.020
Calcium channel blocker	338 (11.9%)	152 (18.9%)	0.194	19.2%	18.0%	0.030
β-blocker	966 (34.1%)	342 (42.6%)	0.175	43.6%	42.1%	0.031
C-statistic of logistic model for PS			0.606			0.544

* Pooled means of value or percentage and their pooled SDD from 25 imputed datasets.
† Pooled mean of number of matched patients (standard deviation) from 25 imputed datasets.
ACEi: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; DBP: Diastolic blood pressure; DM2: Type 2 diabetes mellitus; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; PS: Propensity score; SBP: Systolic blood pressure; SD: Standard deviation; SDD: Standardized mean difference.

The follow-up periods were similar in the ACEi and ARB groups (2,287 and 2,280 person-years respectively), with a pooled average follow-up time of 2.9 years in both groups (**Table 2**). The average drug exposure over the follow-up period, presented as the average DDD, was significantly higher in the ARB than in the ACEi users (1.12 vs. 1.07 DDD/day; p=0.001). This was not caused by a difference in adherence, since the medication possession ratio

(MPR) was similar (ACEi: 85.0%, ARB: 83.9%; p=0.175). The median number of renal stage measurements per year was similar in both groups (1.6, p=0.205).

Table 2. Comparison of follow-up periods in matched sample (25 imputed datasets).

	Pooled mean / median		Pooled
	ACEi	ARB	P-value
Number of renal stage measurement during follow-up per year (median)	1.6	1.6	0.205*
Total follow-up time, person-years (mean)	2,286.6	2,279.7	
Total follow-up time, years (mean)	2.9	2.9	0.727*
Average drug exposure over the follow-up period (DDD/day) (mean)	1.07	1.12	0.001*
Medication possession ratio (MPR) (mean)	85.0 %	83.9 %	0.175
Number of patients with confirmed renal function decline (outcome) (median)	119	99	0.186**

* Rank sum test
** Log-rank test
ACEi: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; DDD: Defined daily dose; MPR: Medication possession ratio.

The pooled average number of outcomes (deterioration of renal function stage) was 217 (13.9%) in the 25 imputed cohorts. The average numbers of occurred competing risk events of moving and death were 31 (2.0%) and 27 (1.8%), respectively. The competing risk regression model favoured ARBs over ACEi (pooled adjusted HR=0.80, 95%CI [0.58-1.10]) to protect against renal function decline but the effect is not statistically significant (p=0.166). Among the 25 analyses in the imputed datasets the p-value ranged from 0.010 to 0.917, with 8 having a value below 0.05 (table in **Supplementary Table 3**). We did not find significant interaction between drug class and baseline renal function stage (pooled p=0.640).

We repeated the analyses in patients without missing baseline albuminuria, and found no systematic differences in adjusted HRs with the outcomes from the imputed dataset (**Supplementary Table 3 & Figure 1**). Therefore we consider our assumption that albuminuria missingness is at random, valid.

DISCUSSION

This study compared effectiveness of ACEis and ARBs for protection against renal function decline in patients with type 2 diabetes in a real world setting. We used an PS matching method based on multiple imputed datasets. Survival models with competing risks showed that ACEis and ARBs were similar in protecting DM2 patients from renal function decline (HR=0.80, 95%CI [0.58-1.10], p=0.166), although the effect slightly favoured ARBs.

These results are in line with the majority of head-to-head comparisons between ACEi and ARB [30-37] in diabetic patients, and also in hypertensive patients [38] with some exceptions that favoured one over another [17,39,40]. Our study differs in several aspects from earlier studies. The main differences are the outcome and the population included. Our study focussed on the process of renal decline based on both GFR and albuminuria irrespective of the initial renal function. Therefore, our results apply to patients with different baseline renal function stages. In earlier studies the outcome was defined as either GFR/creatinine or albuminuria, or end stage disease outcome, e.g. ESRD, or all-cause mortality.

In addition, the follow-up in most earlier RCTs [30-34,39] is often relatively short (from 24 weeks to 1 year), and limited to one follow-up measurement. The negative results in these studies must be interpreted with caution because therapy duration may significantly influence the ability to detect meaningful changes in renal function.

Our study used longitudinal time-to-event follow-up that may strengthen the statistical power to detect differences in effectiveness between ACEis and ARBs. The three observational studies with direct comparison used the same time to event follow-up data [17,37,40], but only one included adequate adjustment for confounding by indication [17]. However that study included a selected population with macroalbuminuria and showed ACEis to be more effective.

Another difference from other studies is the unselected population included, with patients ranging from renal function stage one to four, i.e. from normal renal function to severe renal function dysfunction. Therefore our results may be generalizable to the general diabetic population. We found no effect modification of the baseline renal stage. In the earlier studies the population was usually limited to patients with specific renal dysfunction. For instance, the majority of RCTs included patients with microalbuminuria [30-34] and the ONTARGET trial only included patients with end-organ damage [36].

Strength of our study is the use of observational data of an unselected population of patients with DM2 as registered during the regular care process. Through the PS matching we succeeded in reducing the measured confounding. Besides well-balanced baseline characteristics our analysis adjusted for time-varying characteristics as well.

The study also has some limitations. The number of events in the matched population was relatively small, resulting in limited power to differentiate between the effectiveness of ACEi and ARB. Secondly, in studies based on data obtained during regular care missing data are a potential problem [41]. Although we used multiple imputation, our assumption that missingness was random could have been wrong. However, analysis using complete cases showed essentially the same results (**Supplementary Table 3**).

CONCLUSION

The results of this study support earlier studies that ACEi and ARBs have a similar effectiveness for preventing renal function decline in patients with DM2 in primary care. This means that also in an unselected population, and also focusing on renal function decline in the earlier stages, both drug groups seem as effective. As such, the study results support the current recommendations in DM guidelines in primary care.

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ETHICAL CONDUCT OF RESEARCH

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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Supplementary Table 1. Classification of renal function based on both eGFR* and ACR*

	stage		ACR (mg/mmol) Normoalbuminuria M: ACR<2.5 F: ACR<3.5	Microalbuminuria M: 2.5≤ACR<25 F: 3.5≤ACR<35	Macroalbuminuria M: 25≤ACR<167 F: 35≤ACR<233	Macroalbuminuria M: ACR≥167 F: ACR≥233
eGFR (ml/min per 1.73 m^2)	S1	eGFR≥90	Stage 1	Stage 2	Stage 3	Stage 5
	S2	60≤eGFR<90				
	S3A	45≤eGFR<60	Stage 2	Stage 3	Stage 4	Stage 5
	S3B	30≤eGFR<45	Stage 3	Stage 4	Stage 4	Stage 5
	S4	15≤eGFR<30	Stage 4	Stage 4	Stage 4	Stage 5
	S5	eGFR<15	Stage 5	Stage 5	Stage 5	Stage 5

* eGFR = estimated glomerular filtration rate; ACR = albuminuria-to-creatinine ratio.

Supplementary Table 2. Types of ACEis/ARBs received by the study participants.

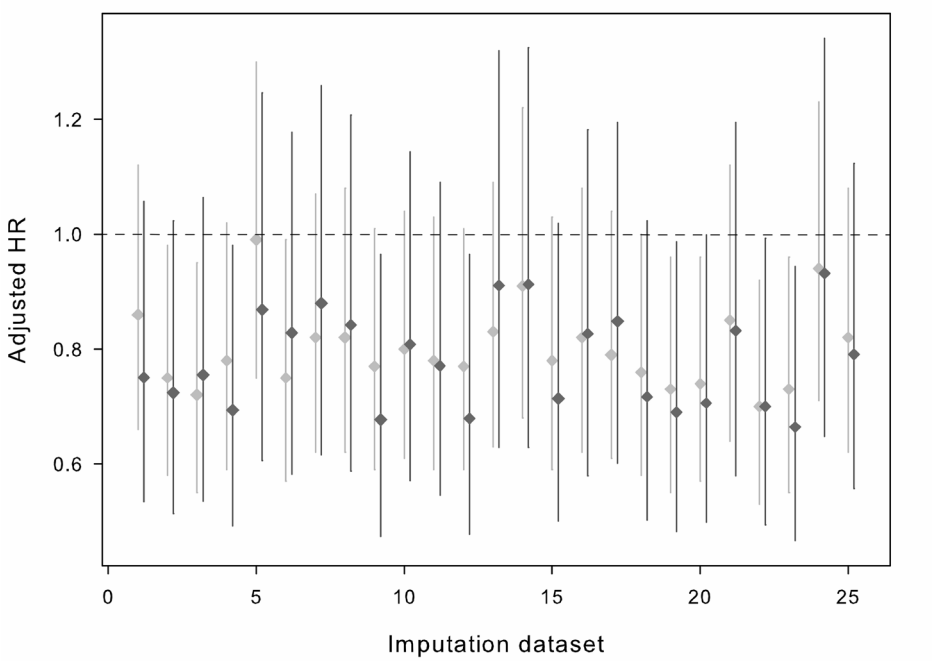
ACEi	N	%
captopril	3	0.1
enalapril	1464	51.6
lisinopril	460	16.2
perindopril	656	23.1
ramipril	210	7.4
quinapril	17	0.6
fosinopril	23	0.8
zofenopril	4	0.1
	2837	
ARB	N	%
losartan	206	25.6
eprosartan	2	0.2
valsartan	140	17.4
irbesartan	265	33.0
candesartan	88	10.9
telmisartan	86	10.7
olmesartan medoxomil	17	2.1
	804	

Supplementary Table 3. Competing risk cox regression model results per individual imputation dataset.

	Baseline PS matched						Baseline PS matched plus time-varying covariates								
	Imputed						Imputed				Complete case				
Set	N	Events	HR	95% CI		p	HR	95% CI		p	N	Events	HR	95% CI		p
1	1564	222	0.89	0.68	1.15	0.368	0.86	0.66	1.12	0.265	1081	139	0.75	0.53	1.06	0.101
2	1554	230	0.76	0.58	0.98	0.037	0.75	0.58	0.98	0.036	1054	138	0.72	0.51	1.02	0.067
3	1552	215	0.73	0.56	0.96	0.023	0.72	0.55	0.95	0.02	1057	136	0.76	0.54	1.06	0.108
4	1564	220	0.79	0.61	1.04	0.090	0.78	0.59	1.02	0.071	1070	143	0.69	0.49	0.98	0.038
5	1552	208	0.94	0.72	1.24	0.667	0.99	0.75	1.30	0.917	1059	125	0.87	0.61	1.25	0.444
6	1558	213	0.8	0.61	1.05	0.108	0.75	0.57	0.99	0.041	1060	125	0.83	0.58	1.18	0.292
7	1560	216	0.81	0.62	1.06	0.122	0.82	0.62	1.07	0.141	1060	127	0.88	0.62	1.26	0.485
8	1564	213	0.86	0.66	1.13	0.284	0.82	0.62	1.08	0.152	1082	127	0.84	0.59	1.21	0.350
9	1566	226	0.81	0.62	1.05	0.115	0.77	0.59	1.01	0.057	1064	136	0.68	0.47	0.97	0.031
10	1566	223	0.82	0.63	1.07	0.148	0.8	0.61	1.04	0.092	1057	132	0.81	0.57	1.14	0.229
11	1552	218	0.8	0.62	1.05	0.111	0.78	0.59	1.03	0.078	1082	137	0.77	0.55	1.09	0.141
12	1552	225	0.79	0.61	1.03	0.077	0.77	0.59	1.01	0.057	1044	138	0.68	0.48	0.97	0.031
13	1574	218	0.86	0.66	1.12	0.274	0.83	0.63	1.09	0.187	1081	124	0.91	0.63	1.32	0.622
14	1538	197	0.91	0.69	1.21	0.531	0.91	0.68	1.22	0.529	1062	120	0.91	0.63	1.33	0.630
15	1572	215	0.84	0.64	1.10	0.201	0.78	0.59	1.03	0.077	1082	134	0.71	0.50	1.02	0.064
16	1556	217	0.86	0.66	1.13	0.283	0.82	0.62	1.08	0.152	1065	131	0.83	0.58	1.18	0.298
17	1560	222	0.81	0.62	1.06	0.123	0.79	0.61	1.04	0.090	1084	133	0.85	0.60	1.20	0.346
18	1556	224	0.76	0.58	0.98	0.037	0.76	0.58	1.00	0.05	1071	138	0.72	0.50	1.02	0.067
19	1540	210	0.76	0.58	1.00	0.051	0.73	0.55	0.96	0.024	1068	132	0.69	0.48	0.99	0.042
20	1566	225	0.76	0.59	1.00	0.045	0.74	0.57	0.96	0.026	1068	134	0.71	0.50	1.00	0.049

Supplementary Table 3. Continued

			Baseline PS matched				Baseline PS matched plus time-varying covariates									
			Imputed				Imputed				Complete case					
Set	**N**	**Events**	**HR**	**95% CI**		**p**	**HR**	**95% CI**		**p**	**N**	**Events**	**HR**	**95% CI**		**p**
21	1568	211	0.87	0.66	1.14	0.302	0.85	0.64	1.12	0.244	1068	125	0.83	0.58	1.20	0.320
22	1538	222	0.69	0.53	0.90	0.006	0.7	0.53	0.92	0.01	1066	134	0.70	0.49	0.99	0.046
23	1526	217	0.71	0.54	0.93	0.014	0.73	0.55	0.96	0.022	1040	133	0.66	0.47	0.94	0.023
24	1572	208	0.96	0.73	1.26	0.783	0.94	0.71	1.23	0.635	1061	125	0.93	0.65	1.34	0.706
25	1580	214	0.81	0.62	1.06	0.122	0.82	0.62	1.08	0.166	1082	134	0.79	0.56	1.12	0.190
Pooled			**0.81**	**0.59**	**1.12**	**0.197**	**0.8**	**0.58**	**1.1**	**0.166**			**0.78**	**0.55**	**1.11**	**0.23**



Supplementary Figure 1. Adjusted HRs with 95% confidence interval for imputed cases (blue) and complete cases (red), by imputation dataset.