

Supplemental Materials

Additional Expanded Materials & Methods

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Table S1. Details for Anatomical Therapeutic Chemical (ATC) Classification System codes for angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs)

ACE inhibitors (C09A)	+ diuretic (C09BA)	+ calcium blocker (C09BB)	
Captopril (C09AA01) Enalapril (C09AA02) Lisinopril (C09AA03) Perindopril (C09AA04) Ramipril (C09AA05) Quinapril (C09AA06) Benazepril (C09AA07) Cilazapril (C09AA08) Fosinopril (C09AA09) Trandolapril (C09AA10) Moexipril (C09AA13) Zofenopril (C09AA15) Imidapril (C09AA16)	Captopril (C09BA01) Enalapril (C09BA02) Lisinopril (C09BA03) Perindopril (C09BA04) Ramipril (C09BA05) Quinapril (C09BA06) Benazepril (C09BA07) Fosinopril (C09BA09) Zofenopril (C09BA15)	Enalapril (C09BB02) Perindopril (C09BB04) Trandolapril (C09BB10)	
ARB (C09C)			+ calcium blocker + diuretic (C09DX)
Losartan (C09CA01) Eprosartan (C09CA02) Valsartan (C09CA03) Irbesartan (C09CA04) Candesartan (C09CA06) Telmisartan (C09CA07) Olmesartan (C09CA08)	Losartan (C09DA01) Valsartan (C09DA03) Irbesartan (C09DA04) Candesartan (C09DA06) Telmisartan (C09DA07) Olmesartan (C09DA08)	Valsartan (C09DB01) Olmesartan (C09DB02) Telmisartan (C09DB04)	Valsartan (C09DX01) Olmesartan (C09DX03)

Table S2. International Classification Disease (ICD-10) codes for diagnosis of cancer (hospitalization discharge diagnosis or long-term disease registration)

Anatomic site	ICD-10 codes
Lip, oral cavity and pharynx	C00-14
Digestive organs	C15-26
Respiratory and intrathoracic organs (non-lung)	C30-33, C35-39, C450
Lung	C34
Bone and articular cartilage	C40-41
Skin	C43-44
Mesothelial and soft tissue	C45-49
Breast	C50
Female genital organs	C51-58
Male genital organs	C60-63
Urinary tract	C64-68
Central nervous system including eye	C69-72, C751-753
Endocrine glands	C73-74, C750, C754-759
Lymphoid tissue	C81-90
Hematopoietic tissue	C91-96
Other *	C76-80, C97
In situ neoplasms	D00-D09
Personal history of malignant neoplasm	Z85%

* Cancers of ill-defined, secondary and unspecified sites and cancers of independent multiple primary sites.

Table S3. International Classification Disease (ICD-10) codes for diagnosis of cardiovascular disease (i.e., ischemic stroke, hemorrhagic stroke, myocardial infarction, ischemic heart disease, heart failure, or peripheral vascular disease) or chronic renal insufficiency, based on hospitalization discharge diagnosis or long-term disease registration

Variable	ICD-10 codes	Medical act codes
Cardiovascular disease	I11.0, I12%, I13%, I15%, I20%, I21%, I22%, I23%, I24%, I25%, I42%, I43%, I50%, I61%, I62%, I63%, I64%, I65%, I66%, I67.2, I70%, Z94.1, Z94.3, Z95%	DDAF001, DDAF003 to DDAF010, DDMA003 to DDMA009, DDMA011, DDMA012, DDMA013, DDMA015 to DDMA038, DDAA002, DDFF001, DDFF002, DDPF002, DDQH006, DDQH009-DDQH015, EEAF%, ECPF%, ECFA%, EBFA%, EENF%, EEPF%, EEFA%, EECA%, ENNF%, ENFA%, DGAF%, EDAF%, DGFP%, EDPF%, DGFA%, EDFA%, DGCA%, EDCA%, EDPF%, EDJF%, EDKA%, EDEA%, EDLF%, EDNF%, EDPF%, EDJF%, EDMA%, EANF002, ECNF002, ECJF001, ECCA007, ECCA009, ECCA003, ECCA002, ECMA001, ECKA002, EBNF001, EDEA001, EDLF007, EEJF001, EDCA005, ENAF001, ENAF002, DGKA004, EDNF003, EDKA002
Chronic renal insufficiency	N18%, Z49.1, Z49.2, Z94.0, Z99.2	

Table S4. List of codes used to classify confounders and effect modifiers, all assessed within a time frame of 12 months before the inclusion date

Variables	ICD-10 codes	ATC codes
Diabetes	E10%, E11%	A10A%, A10B%
Diabetes with chronic complication *	E10.2–E10.5, E10.7, E11.2–E11.5, E11.7, E12.2–E12.5, E12.7, E13.2–E13.5, E13.7, E14.2–E14.5, E14.7	
Renal disease *	N03.2–N03.7, N05.2–N05.7, N19.x, N25.0, Z49.0	
Rheumatic disease *	M05%, M06%, M31.5, M32%–M34%, M35.1, M35.3, M36.0	
Dementia treated		N06D%
Chronic pulmonary disease (except COPD) *	I27.8, I27.9, J40%–J43%, J45%–J47%, J60%–J67%, J68.4, J70.1, J70.3 except J44%	
COPD	J44%	
Atrial fibrillation	I48%	
Beta-blockers		C07A% except (C07AA07, C07AG02), C07B%, C07CA03, C07DA06, C07FB0%
Calcium channel blockers		C08C% except C08CA06, C08DA01, C08DB01
Thiazides		C03AA%, C03BA%, C03BX03, C03EA%
Anti-platelet drug		B01AC04, B01AC05, B01AC06, B01AC07, B01AC08, B01AC22, B01AC24, B01AC30, C10BX02 or pha_cip_c13='3400931893639'
Anticoagulants		B01AA02, B01AA03, B01AA07, B01AA11, B01AE07, B01AF01, B01AF02 or pha_cip_c13 in ('3400931183280', '3400931183112', '3400933484132')
Lipid lowering drug		C10AA%, C10AB%, C10AX%, C10B%
Drinking	F100%–F109%, K70%, E244%, G3012%, G621%, G721%, I426%, K292%, K825%, K860%, Z502%, Z714%, Z721%, R780%, Y90%	M03BX01%, N07BB%
Smoking	Z720%, F172%	N07BA01%, N07BA02%

* components of Charlson score (as proposed by Quan et al.)

Algorithm for further splitting diabetes mellitus as severe or not, and known for long ago or not

Variable label	Definition
Severity of diabetes	Yes, if two (or more) oral anti-diabetic drug or chronic complication (ICD-10 codes: E10.2–E10.5, E10.7, E11.2–E11.5, E11.7, E12.2–E12.5, E12.7, E13.2–E13.5, E13.7, E14.2–E14.5, E14.7) or insulin plus oral anti-diabetic drug
Long history of diabetes	Long-term registration date < 1999;

We acknowledge that laboratory values are not available; Laboratory values are also unobserved simply because they were never ordered during the observation period. However, whether a laboratory report was ordered might itself be informative. We, therefore, created an indicator variable that a given laboratory was observed in the year prior to the inclusion date (the test was ordered and reimbursed; equal to 0 otherwise); this was made for: renal function assessment: serum urea nitrogen, GFR), potassium, lipids (triglycerides, cholesterol, LDL, HDL) or HbA1c (glycated hemoglobin). We also created a variable that was a count of the number of measurements in the year prior to the inclusion date.

Table S5. Dose levels (high, medium, low) for angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB) and for other drug components which were available in fixed-dose combination (with ACE inhibitor or ARB); Medium dose was based on defined daily dose (WHO definition); any delivery of a package with a lower or higher unit dose was then classified as a low or high dose, respectively.

ARB	ACE inhibitor	Calcium-channel blocker	Thiazide-like diuretic	Medium dose
Eprosartan				600 mg
Irbesartan				150 mg
Valsartan				80 mg
Losartan	Captopril			50 mg
Telmisartan				40 mg
	Zofenopril			30 mg
			Hydrochlorothiazide	25 mg
Olmesartan	Lisinopril			20 mg
	Fosinopril, Quinapril			15 mg
	Enalapril, Imidapril	Lercanidipine		10 mg
Candesartan				8 mg
	Benazepril, Moexipril			7.5 mg
		Amlodipine		5 mg
	Perindopril			4 mg
	Cilazapril, Ramipril			2.5 mg
			Indapamide	1.25 mg

Table S6. International Classification Disease (ICD-10) codes classifying the cause of death

	Label	ICD-10 codes
Strict definition	CV1 Ischemic heart diseases, cardiac arrest, Ventricular tachycardia, Ventricular fibrillation and flutter, Cerebral infarction, Stroke, not specified as hemorrhage or infarction, Occlusion and stenosis of carotid artery, Cerebro-vascular diseases, Sequelae of cerebral infarction, stroke, or of other and unspecified cerebro-vascular diseases CV1R Precordial pain, Chest pain, unspecified Respiratory arrest Dysphasia and aphasia, Dysarthria and anarthria, Agnosia, Apraxia Other sudden death, cause unknown Unattended death, Other ill-defined and unspecified causes of mortality	I20-I25 I460;I461;I469;I472;I490; I630;I631;I632;I633;I634;I635;I638;I639; I64; I652; I678;I679; I693;I694;I698; R072;R074; R092; R470;R471;R481;R482; R960; R98;R99;R999
Broad definition	CV2 Acute rheumatic fever Chronic rheumatic heart diseases Hypertensive diseases Ischemic heart diseases Pulmonary heart disease and diseases of pulmonary circulation Other forms of heart disease Cerebrovascular diseases Diseases of arteries, arterioles and capillaries Diseases of veins, lymphatic vessels and lymph nodes Other and unspecified disorders of the circulatory system CV2R Abnormalities of heart beat Gangrene, not elsewhere classified Nonspecific low blood-pressure reading Syncope and collapse Cardiogenic shock	I00-I02 I05-I09 I10-I15 I20-I25 I26-I28 I30-I52 I60-I69 I70-I79 I80-I89 I95-I99 R000;R001;R002; R02; R031; R55; R570

Table S7. International Classification Disease (ICD-10) codes (as main diagnostic at the medical unit level) or medical act codes for outcomes

Variable label	Value	Definition
Type of major cardiovascular events	1 = 'Intracranial hemorrhage' 2 = 'Ischemic stroke' 3 = 'Heart failure' 4 = 'Myocardial infarction'	Equal 4 if DGN_PAL in (I21%, I22%, I23%) Equal 2 if DGN_PAL in (I63%) Equal 1 if DGN_PAL in (I61%, I62%) Equal 3 if DGN_PAL in (I50%) else missing
Type of non-major cardiovascular events	1 = 'Coronary artery bypass graft surgery' 2 = 'Percutaneous coronary angioplasty' 3 = 'Peripheral revascularization procedure'	Equal 1 if ACT_LIST from table RSS_FUP in (DDAA002, DDMA003 to DDMA009, DDMA011, DDMA012, DDMA013, DDMA015 to DDMA038) Equal 2 if ACT_LIST from table RSS_FUP in (DDAF001, DDAF003 to DDAF010, DDFF001, DDFF002, DDPF002) Equal 3 if ACT_LIST from table RSS_FUP in (EEAF%, ECPF%, ECFA%, EBFA%, EENF%, EEPF%, EEFA%, EECA%, ENNF%, ENFA%, DGAF%, EDAF%, DGFP%, EDPF%, DGFA%, EDFA%, DGCA%, EDCA%, EDPF%, EDJF%, EDKA%, EDEA%, EDLF%, EDNF%, EDPF%, EDJF%, EDMA%, EANF002, ECNF002, ECJF001, ECCA007, ECCA009, ECCA003, ECCA002, ECMA001, ECKA002, EBNF001, EDEA001, EDLF007, EEJF001, EDCA005, ENAF001, ENAF002, DGKA004, EDNF003, EDKA002); else missing

Expanded Materials & Methods S8. Medication possession ratio.

For on-treatment population subjects were censored at the time they stopped (or switched) their initial drug (ACE inhibitor or ARB). This date was identified as the last dispensing date that precedes end-of-study date or a censoring date (hospitalization for a cardiovascular event or death). End of exposure is defined as the date of last dispensing plus the number of day's supply provided by this last dispensing, possibly censored if an event occurs by this time. We identified all deliveries of ACE inhibitor (or ARB) between first and last delivery as previously defined; for each delivery, a number of units is retained; we then summed all these numbers to get one number (translated as days' supply) for each patient.

Based on those dates (first and last dispensing), we calculate a medication possession ratio (MPR): MPR is a measure of medication availability that estimated the proportion (or percentage) of day supply obtained during a specified time period. The MPR is estimated as the day's supply of medication dispensed during a period divided by the number of days from the first dispensing to the last dispensing. Day's supply is based on the number of tablets multiplied by the number of boxes dispensed (based on the rule that these drugs are prescribed as one tablet per day).

Hospitalization or residence in a long-term care facility was accounted for by subtracting the number of days the patient was hospitalized from the denominator. We identified all hospital stays between first and last delivery as previously defined; for each stay, the length (number of days) is retained; we then summed all these numbers to get one number for each patient.

The measure was dichotomized so that patients are considered adherent if a specified threshold was attained: say 80% or higher. MPR value > 1 has to be interpreted (complete adherence or an oversupply of medication). This definition (threshold) considers the need to account for short-term fluctuations in the timing of refill intervals. Each patient contributes person-time to an exposed group (ARB or ACE inhibitor) equal to the number of days between first delivery and end of exposure multiplied by MPR if its value is below 80%, otherwise MPR equals unity.

Table S9. Death dedicated algorithm

Variable label	Variable name	Value	Definition
End of follow-up	END_DTE	31/12/14	End of study follow-up
Death date in IR_BEN_R	BEN_DCD_DTE	Date	Exist already in IR_BEN_R file
Death date in T_MCO	MCO_DCD_DTE	Date	In T_MCO_B = max(SOR_DAT) if SOR_MOD=9
Death date in T_SSR	SSR_DCD_DTE	Date	In T_SSR = max(SOR_DAT) if SOR_MOD=9
Death date in T_HAD	HAD_DCD_DTE	Date	In T_HAD = max(SOR_DAT) if SOR_MOD=9
Death date in PRS	PRS_DCD_DTE	Date	In PRS, BEN_DCD_DTE

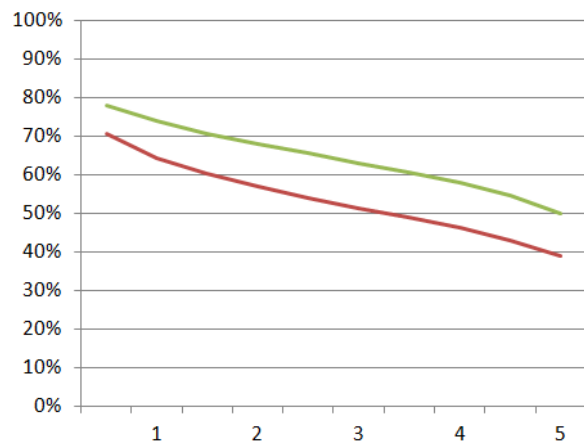
Alive date in PRS	PRS_LAST_DTE	Date	= max(EXE_SOI_DTD) in PRS
Death date	DCD_DTE	Date	If BEN_DCD_DTE NE '.' then DCD_DTE= BEN_DCD_DTE; else if PRS_DCD_DTE NE '.' and >= PRS_LAST_DTE then DCD_DTE = PRS_DCD_DTE; else if MCO_DCD_DTE NE '.' then DCD_DTE=MCO_DCD_DTE; else if SSR_DCD_DTE NE '.' then DCD_DTE = SSR_DCD_DTE; else if HAD_DCD_DTE NE '.' then DCD_DTE=HAD_DCD_DTE;
Min death date	DCD_DTE_MIN	Date	Min(all death dates) if exist; else = ""
Max death date	DCD_DTE_MAX	Date	Max(all death dates) if exist; else = ""
Problem for death date	DCD_DTE_PB	0 = 'No' 1 = 'Yes'	if DCD_DTE is not null then if DCD_DTE_MAX -DCD_DTE_MIN>1 then 1 if (PRS_LAST_DTE-DCD_DTE) >30 AND sum(PRS_ACT_NBR) group by PRS_NAT_REF>0 then 1; else = 0
Primary outcome (overall mortality)	OUTCOME	0 = 'No' 1 = 'Yes' '.'	= 1 if DCD_DTE <= END_DTE); else = 0; if EXPO_START >= DCD_DTE then = '.';
End of follow-up	FUP_DTE	Date	min(DCD_DTE, END_DTE)
Follow-up (observed)	FUP	Num	FUP_DTE - EXPO_START

IR_BEN_R is a file containing some demographic data at an individual level; T_MCO, T_SSR, T_HAD are concatenated files from French hospital discharge database (PMSI), MCO, SSR and HAD referring to "medical, surgical, obstetrical wards", "rehabilitation wards" and "at home health care" respectively; PRS is a file containing all ambulatory care claims.

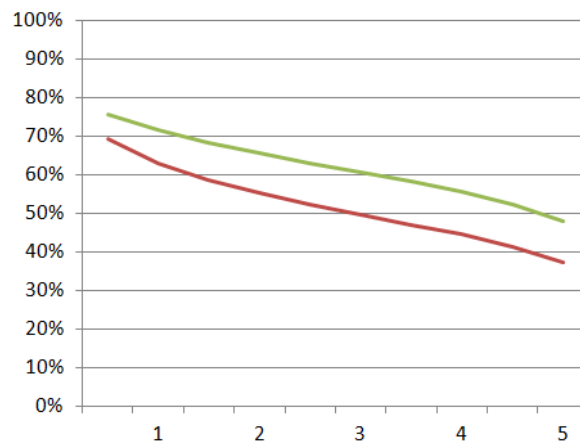
For quality control we selected patients where DCD_DTE_PB=1 and printed those patients with all death dates for further investigation.

Online Figure I. Adherence to initial regimen (ACE inhibitor, red line; ARB green line) over time (in years) expressed as 1 minus the cumulative frequency of switching/stopping; panel A: all doses; panel B: high doses; panel C: medium doses; panel D: low doses

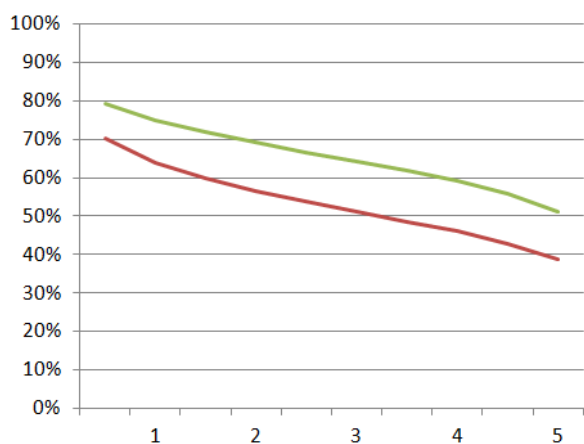
A. Adherence to initial regimen over the years: all doses



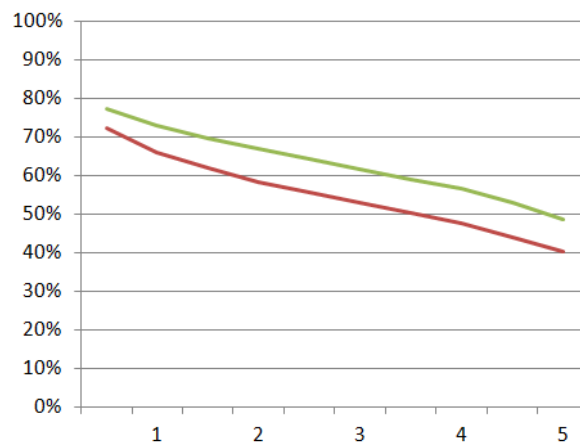
B. Adherence to initial regimen over the years: high doses



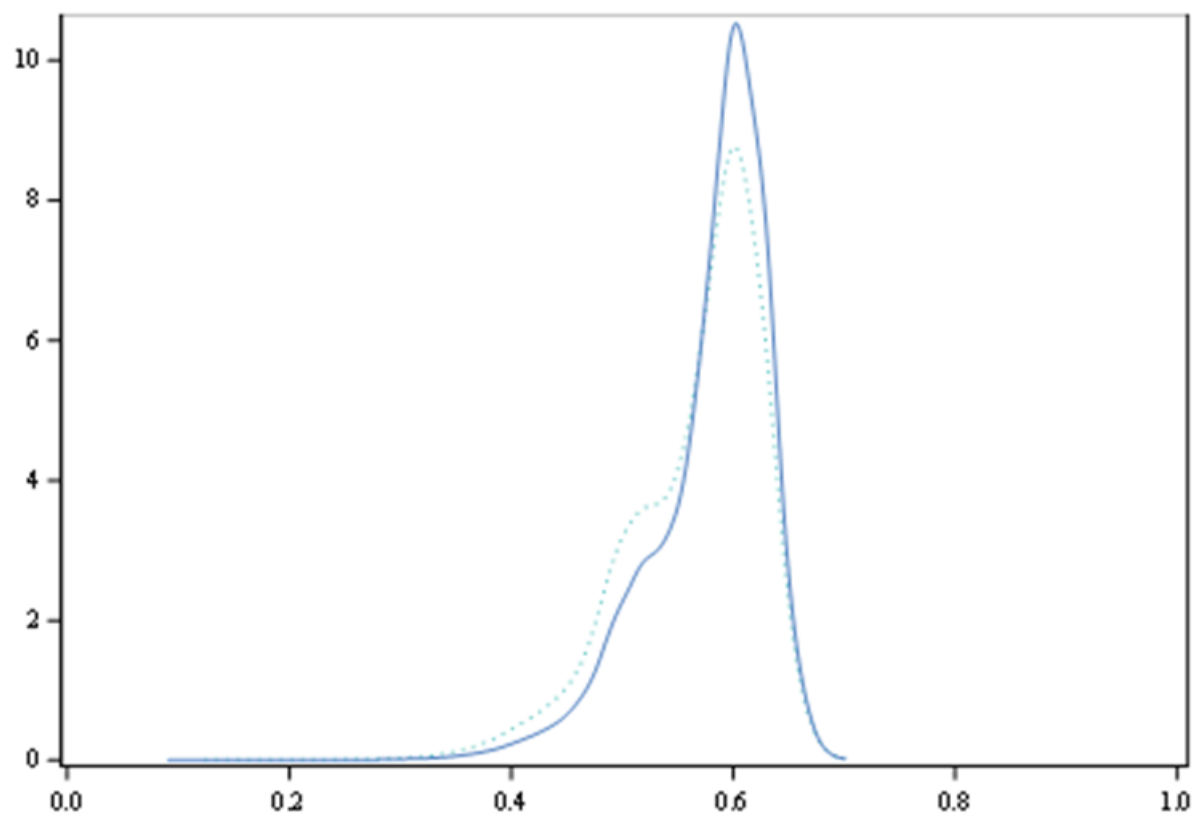
C. Adherence to initial regimen over the years: medium doses



D. Adherence to initial regimen over the years: low doses

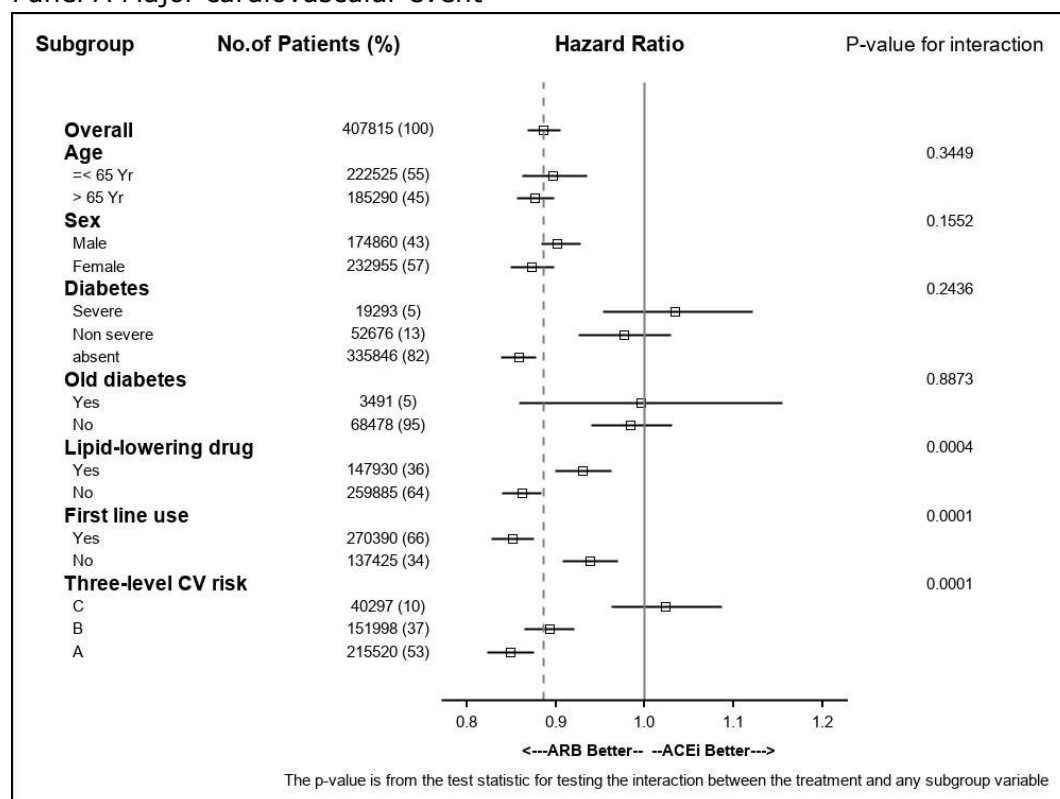


Online Figure II. Kernel density plot of estimated propensity scores stratified by treatment group (ACE inhibitor, dashed line; ARB solid blue line).

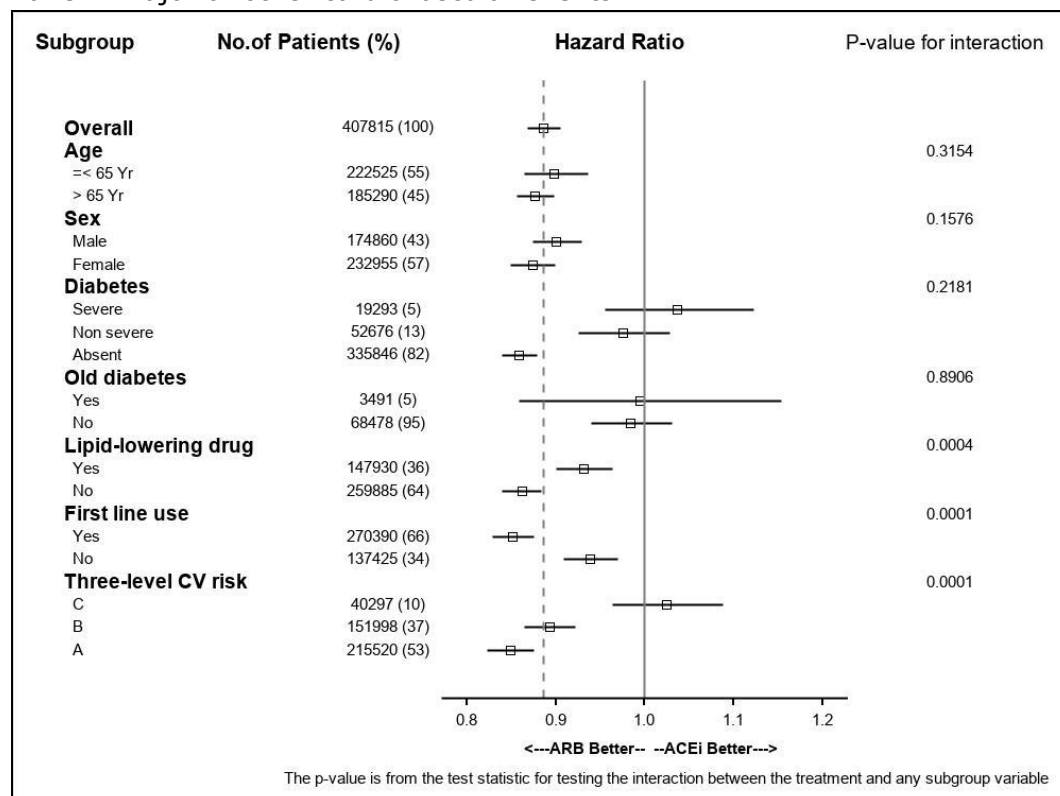


Online Figure III. Analysis of subgroups and interactions for composite secondary outcomes

Panel A Major cardiovascular event



Panel B Major or other cardiovascular events



Severe diabetes if two (or more) oral anti-diabetic drug or insulin plus oral anti-diabetic drug or chronic; long-ago onset of diabetes if long-term registration for more than 10 years; cardiovascular risk: level C: subjects having diabetes and using lipid-lowering drug; level B: subjects having only one of the above risk factors or using antithrombotic drug; level A: subjects with none of the above three conditions.

Table S10. Propensity model

Parameters	p-value *	OR	p-value \$
Female§	<.0001	0.91	<.0001
Age plus quadratic term§	<.0001	-	<.0001
Diabetes§	<.0001	1.27	<.0001
Obesity§	0.0092	1.20	0.6265
Alcohol§	<.0001	2.43	<.0001
Smoking habit§	<.0001	1.63	<.0001
Renal disease§	<.0001	4.04	0.1914
Rheumatic disease§	<.0001	2.94	<.0001
Dementia	<.0001	8.63	<.0001
Dementia treated	<.0001	2.47	0.0007
Chronic pulmonary disease (except COPD)	<.0001	2.48	0.0554
Diabetes with chronic complications	<.0001	2.52	<.0001
Hemiplegia or paraplegia	<.0001	2.31	<.0001
Mild liver disease	<.0001	3.04	Excl.
Moderate or severe liver disease	<.0001	6.11	0.0786
AIDS/HIV	0.0093	2.00	Excl.
Atrial fibrillation	<.0001	2.92	<.0001
COPD	<.0001	4.40	<.0001
Prior delivery of beta-blockers	<.0001	0.79	<.0001
Prior delivery of calcium channel blockers	<.0001	1.64	<.0001
Prior delivery of thiazides	<.0001	1.25	<.0001
Prior delivery of anti-platelet drugs	<.0001	2.41	<.0001
Prior delivery of anticoagulants	<.0001	2.89	<.0001
Prior delivery of lipid lowering drugs	<.0001	0.94	<.0001
BUN observed	<.0001	1.19	<.0001
Potassium observed	<.0001	1.22	<.0001
Triglycerides observed	<.0001	1.13	Excl.
Cholesterol observed	<.0001	1.20	<.0001
LDL observed	0.0070	0.73	Excl.
HDL observed	<.0001	0.64	<.0001
HbA1c observed	<.0001	1.13	<.0001

* univariate, \$ multivariate; § Set of covariates forced in the model; Amid 8 covariates forced in the model, 23 variables were entered in the model from a set of 24 candidates and 19 remained after backward selection: the 4 variables excluded were: LDL (p=0.8445), mild liver disease (p=0.5811), TG (p=0.5652) and AIDS (p=0.2146).