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Supplement 1

Appendix Item 1 Protocol amendments

Date	Record	Reason	Detail
15/02/2008	Amendment 1	Correction to protocol on details of sponsor and responsible institution	
24/09/2008	Amendment 2	Extension of the recruitment phase of the study for an additional 12 months.	
22/10/2009	Amendment 3	Extension of the recruitment phase of the study for an additional 12 months.	
14/07/2010	Amendment 4	Review of the primary endpoint, inclusion criteria, and sample size.	To document a reduced risk of all-cause mortality of at least 12% with combined therapy compared to single monotherapies (RR = 0.88), the required sample size is 3600 patients with diabetes and albuminuria. The subgroup of subjects with these characteristics in the ONTARGET study (N = 2601) was an insufficient sample size to detect a definitive lowering of all-cause mortality, if it existed. Therefore, in this second phase, the LIRICO study will aim to enroll 1200 patients with albuminuria in total, including 1000 patients with diabetes. The final analysis will be scheduled to achieve 225 events according to an "event driven" design. Depending on the expected rate of events, it is estimated that the final analysis can be performed after a follow-up median of about 4 years. Depending on the number of patients already recruited in the study, (n=509, including 344 with diabetes), recruitment of another 656 patients with diabetes and albuminuria is expected. These data will be cumulated with those of the ONTARGET study in order to verify the primary hypothesis with the use of individual patient data analysis.
06/04/2011	Amendment 5	Extension of the recruitment phase of the study for an additional 12 months.	

Appendix Item 2 Study Administration and Investigators

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Supplement 2

Appendix Table 1. Doses of medications at baseline and at final observation.

	ACE inhibitor			ARB			Combined ACE inhibitor/ ARB		
		Dose, mg/day			Dose, mg/day			Dose, mg/day	
	N	Baseline	(final visit)	N	Baseline	(final visit)	N	Baseline	(final visit)
ACE inhibitor									
Benazepril	1	10	(10)	–	–	(–)	2	7.5	(7.5)
Captopril	1	50	(50)	–	–	(–)	–	–	(–)
Cilazapril	1	5	(5)	–	–	(–)	–	–	(–)
Delapril	1	30	(30)	–	–	(–)	–	–	(–)
Enalapril	35	20	(20)	–	–	(–)	24	20	(20)
Fosinopril	5	20	(20)	–	–	(–)	4	15	(15)
Lisinopril	26	20	(20)	–	–	(–)	25	15	(20)
Perindopril	11	10	(10)	–	–	(–)	12	7.5	(10)
Quinapril	4	20	(20)	–	–	(–)	8	10	(10)
Ramipril	294	10	(10)	–	–	(–)	315	5	(10)
Zofenopril	22	30	(30)	–	–	(–)	18	30	(30)
Angiotensin receptor blocker									
Candesartan	–	–	(–)	13	16	(16)	9	16	(16)
Eprosartan	–	–	(–)	–	–	(–)	1	600	(600)
Irbesartan	–	–	(–)	145	300	(300)	122	300	(300)
Losartan	–	–	(–)	64	50	(50)	81	50	(50)
Olmesartan	–	–	(–)	54	20	(20)	50	20	(20)
Telmisartan	–	–	(–)	56	80	(80)	58	80	(80)
Valsartan	–	–	(–)	70	160	(160)	82	80	(80)

Doses are shown as median. – indicates that the medication was not prescribed in the assigned treatment group at the specified time point.

Appendix Table 2. Baseline characteristics of 1059 participants with diabetes.

Characteristic	ACE inhibitor (n=353)	ARB (n=351)	Combination (n=355)
Age at randomization, mean (SD) in years	63.0 (10.4)	63.7 (9.9)	64.1 (9.2)
Sex, *n* (%)			
Women	251 (72.1)	250 (73.1)	254 (73.4)
Men	97 (27.9)	92 (26.9)	92 (26.6)
Ethnicity,			
African American, *n* (%)	3 (0.9)	5 (1.5)	2 (0.6)
Other	341 (99.1)	338 (98.5)	346 (99.4)
Diabetes, *n* (%)			
Type 1	11 (3.2)	11 (3.2)	10 (2.9)
Type 2	331 (96.8)	329 (96.5)	337 (97.1)
Albuminuria, *n* (%)			
Moderate albuminuria	249 (73.7)	252 (73.7)	264 (76.5)
Severe albuminuria	88 (26.0)	90 (26.3)	81 (23.5)
Smoker, *n* (%)			
Current	82 (23.8)	82 (23.8)	81 (23.1)
Former	105 (30.4)	92 (26.7)	124 (35.3)
Never			
Body mass index mean (SD) in kg/m^2	30.8 (5.5)	31.0 (5.6)	30.5 (5.4)
Weight, mean (SD) in kg	85.0 (16.6)	85.8 (17.5)	83.7 (16.4)
Waist circumference, mean (SD) in cm	105.4 (14.2)	105.4 (12.7)	104.8 (12.8)
Heart rate, mean (SD) per minute	76.0 (10.4)	74.8 (10.5)	74.6 (8.9)
Blood pressure, mean (SD) in mmHg			
Systolic	138.7 (17.0)	139.1 (15.5)	138.4 (16.4)
Diastolic	80.5 (9.3)	79.8 (9.0)	80.2 (9.1)
Fasting glucose, mean (SD) in mg/dl	148.4 (45.1)	155.5 (52.2)	150.8 (47.3)
HbA1C, mean (SD) in %	7.6 (1.6)	7.7 (1.6)	7.6 (1.5)
Estimated GFR, mean (SD) in ml/min per 1.73 m^2	71.5 (27.0)	68.5 (26.1)	67.0 (27.4)
Estimated GFR <60 ml/min per 1.73 m^2, *n* (%)	112 (34.3)	129 (39.7)	142 (43.3)
Serum creatinine, mean (SD) in mg/dl	1.06 (0.72)	1.09 (0.76)	1.09 (0.51)
Urinary albumin-to-creatinine ratio (median, IQR) in mg/g	102 (53-280)	103 (52-294)	120 (56-282)
Serum potassium, mean (SD) in mEq/L	4.5 (0.6)	4.5 (0.6)	4.5 (0.6)
Total cholesterol, mean (SD) in mg/dl	175.3 (38.7)	174.9 (38.5)	173.4 (41.4)
LDL cholesterol, mean (SD) in mg/dl	99.0 (33.2)	100.2 (33.2)	99.1 (33.2)
Triglycerides, mean (SD) in mg/dl	155.8 (91.1)	143.6 (76.3)	147.8 (83.4)
Symptomatic neuropathy, *n* (%)	62 (18.3)	47 (14.2)	55 (16.2)
Diabetic retinopathy, *n* (%)	97 (28.3)	92 (26.9)	92 (26.6)
Previous cardiovascular event, *n* (%)	85 (24.8)	95 (27.6)	94 (26.8)
Family history of cardiovascular disease, *n* (%)	34 (9.6)	34 (9.7)	36 (10.1)
Medications prior to randomization, *n* (%)			
Blood pressure-lowering	290 (85.0)	282 (83.7)	308 (88.5)

Characteristic	ACE inhibitor (n=353)	ARB (n=351)	Combination (n=355)
ACE inhibitor	145 (42.5)	144 (42.7)	146 (42.0)
ARB	142 (41.6)	159 (47.2)	179 (51.4)
ACE inhibitor or ARB	264 (77.4)	262 (77.7)	283 (81.3)
Beta blocker	82 (24.6)	66 (19.6)	62 (17.8)
Calcium channel blocker	89 (26.1)	96 (28.5)	101 (29.0)
Diuretic	124 (36.4)	126 (37.4)	155 (44.5)
Lipid lowering	208 (61.0)	213 (62.3)	227 (65.2)
Statin	191 (56.0)	191 (56.7)	205 (58.9)
Ezetimibe	17 (5.0)	16 (4.7)	18 (5.2)
Fibrate	11 (3.2)	10 (3.0)	13 (3.7)
Omega-3 PUFA	29 (8.5)	44 (13.1)	37 (10.6)
Platelet aggregation inhibitors	143 (41.9)	153 (45.4)	154 (44.3)
Acetylsalicylic acid	125 (36.7)	133 (39.5)	136 (39.1)

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker. GFR = glomerular filtration rate; PUFA = polyunsaturated fatty acid. Numbers and percentages may not sum to 100% due to missing data.

Appendix Table 3. Incidence of primary and secondary outcomes in 1059 participants with diabetes.

	ACE inhibitor, *n* (%) (n=353)	**ARB, *n* (%)** (n=351)	**Combination *n* (%)** (n=355)	**ACE inhibitor *vs* ARB Hazard ratio (95% CI)**	**ACE inhibitor *vs* combination Hazard ratio (95% CI)**	**ARB *vs* combination Hazard ratio (95% CI)**
Primary composite (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, hospitalization secondary to cardiovascular cause)	28 (7.9)	26 (7.4)	34 (9.6)	1.07 (0.62–1.82)	0.81 (0.49–1.33)	0.75 (0.45–1.26)
All-cause mortality	14 (4.0)	19 (5.4)	15 (4.2)	0.73 (0.36–1.45)	0.92 (0.45–1.91)	1.27 (0.64–2.50)
Cardiovascular death	6 (1.7)	6 (1.7)	2 (0.6)	0.99 (0.32–3.06)	2.96 (0.60–14.7)	3.00 (0.61–14.9)
End-stage kidney disease	5 (1.4)	2 (0.6)	2 (0.6)	2.47 (0.48–12.7)	2.50 (0.48–12.9)	1.01 (0.14–7.12)
Nonfatal myocardial infarction	3 (0.9)	4 (1.1)	9 (2.5)	0.74 (0.17–3.31)	0.33 (0.09–1.23)	0.45 (0.14–1.45)
Nonfatal stroke	3 (0.9)	1 (0.5)	5 (1.4)	2.96 (0.31–28.5)	0.60 (0.14–2.49)	0.20 (0.02–1.71)
Hospitalization for cardiovascular cause	24 (6.8)	19 (5.4)	30 (8.5)	1.25 (0.69–2.29)	0.79 (0.46–1.35)	0.63 (0.35–1.12)
Doubling of serum creatinine	20 (5.7)	17 (4.8)	16 (4.5)	1.17 (0.61–2.24)	1.33 (0.68–2.59)	1.13 (0.56–2.26)
eGFR <60 ml/min per 1.73 m^{2*}	66 (31.4)	67 (34.7)	54 (30.2)	0.85 (0.61–1.20)	1.07 (0.74–1.53)	1.25 (0.87–1.79)
Progression to severe albuminuria	41 (15.2)	43 (15.8)	40 (14.8)	0.88 (0.57–1.35)	1.05 (0.68–1.64)	1.08 (0.70–1.66)
Regression to normal or mildly increased albuminuria	78 (22.5)	76 (22.2)	81 (23.3)	0.98 (0.71–1.34)	0.95 (0.70–1.30)	0.96 (0.70–1.32)

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker. eGFR = estimated glomerular filtration rate. Counts correspond to the number of participants who experienced a specific outcome event at least once. *In participants with an estimated glomerular filtration rate >60 ml/min per 1.73 m^2 at baseline (ACE inhibitor n=236, ARB n=227, ACE inhibitor + ARB n=205).

Appendix Table 4. Adverse events in 1059 participants with diabetes.

	ACE inhibitor, *n* (%) (n=353)	ARB, *n* (%) (n=351)	ACE inhibitor + ARB, *n* (%) (n=355)	ACE inhibitor versus ARB P value*	ACE *vs* combination inhibitor P value*	ARB *vs* combination P value*
Serious adverse events*	37 (10.4)	38 (10.8)	41 (11.5)	0.90	0.72	0.82
Permanent discontinuation of therapy	55 (15.6)	25 (7.1)	65 (18.3)	<0.001	0.37	<0.001
Hyperkalemia (>6 mEq/l)	6 (1.7)	5 (1.4)	7 (2.0)	1.00	1.00	0.77
Hypotension	3 (0.9)	2 (0.6)	1 (0.3)	1.00	0.37	0.62
Cough	15 (4.3)	1 (0.3)	7 (2.0)	<0.001	0.09	0.07

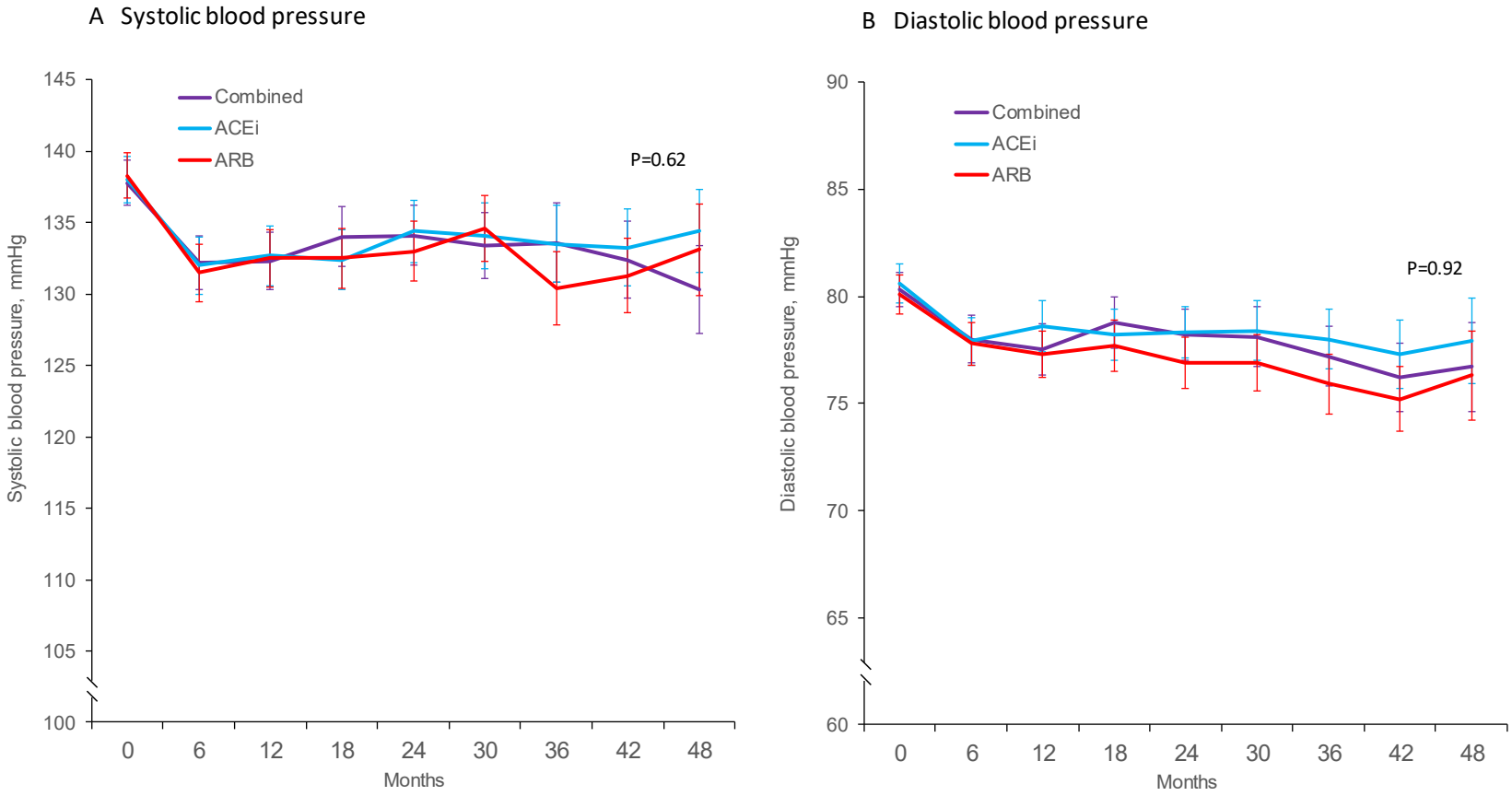
ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker *Number of participants experiencing events were compared using the two-sided Fisher exact test. *Serious adverse events were defined as any unfavorable sign, symptom, or medical event, whether or not due to study intervention, and that resulted in death, life-threatening illness, hospitalization or prolongation of hospitalization, persistent or significant disability, or a serious medical event in the opinion of the responsible investigator.

Appendix Table 5. Subgroup analyses for the primary composite outcome.

Subgroup	ACE inhibitor versus ARB		ACE inhibitor versus combination		ARB versus combination		P value for interaction
	No. of events (no. of participants)	Hazard ratio (95% confidence interval)	No. of events (no. of participants)	Hazard ratio (95% confidence interval)	No. of events (no. of participants)	Hazard ratio (95% confidence interval)	
Men	13 (232)	0.91 (0.31-2.71)	12 (229)	1.04 (0.32-3.40)	13 (227)	1.09 (0.33-3.56)	0.61
Women	46 (578)	1.10 (0.62-1.96)	58 (585)	0.78 (0.45-1.36)	56 (583)	0.71 (0.40-1.25)	
Diabetes type 1	-	-	-	-	-	-	Not estimable
Diabetes type 2	52 (659)	1.08 (0.63-1.86)	60 (667)	0.82 (0.50-1.37)	58 (666)	0.76 (0.45-1.28)	
Hypertension	55 (728)	1.02 (0.60-1.73)	62 (742)	0.90 (0.53-1.54)	63 (750)	0.88 (0.52-1.49)	0.24
No hypertension	4 (99)	2.16 (0.22-20.8)	8 (88)	0.34 (0.08-1.52)	6 (80)	0.14 (0.02-1.28)	
Family history of cardiovascular disease	7 (82)	2.46 (0.48-12.7)	12 (83)	0.94 (0.29-3.07)	9 (85)	0.20 (0.02-1.65)	0.85
No family history of cardiovascular disease	52 (745)	0.95 (0.55-1.63)	58 (746)	0.79 (0.45-1.37)	60 (745)	0.85 (0.50-1.47)	
Prior cardiovascular event	-	-	-	-	-	-	Not estimable
No prior cardiovascular event	32 (313)	0.88 (0.44-1.77)	35 (618)	0.89 (0.43-1.82)	37 (615)	0.98 (0.49-1.99)	
Moderate albuminuria	36 (586)	1.11 (0.58-2.14)	43 (333)	0.95 (0.50-1.81)	41 (599)	0.82 (0.41-1.61)	<0.001
Severe albuminuria	21 (212)	0.88 (0.37-2.10)	25 (205)	0.61 (0.27-1.39)	28 (211)	0.65 (0.30-1.41)	
HbA1C ≤7.5%	22 (279)	0.84 (0.36-1.95)	28 (282)	0.56 (0.26-1.22)	30 (287)	0.66 (0.32-1.37)	0.16
HbA1C>7.5%	37 (548)	1.18 (0.62-2.26)	42 (547)	1.06 (0.54-2.08)	39 (543)	0.85 (0.42-1.75)	
Total cholesterol ≤180 mg/dl	21 (350)	1.11 (0.47-2.62)	22 (334)	1.00 (0.42-2.41)	21 (330)	0.82 (0.33-2.02)	0.56
Total cholesterol >180 mg/dl	38 (477)	1.02 (0.54-1.92)	48 (495)	0.74 (0.40-1.36)	48 (500)	0.74 (0.40-1.37)	
Estimated glomerular filtration rate <60 ml/min/1.73 m^2	25 (299)	0.61 (0.27-1.38)	34 (318)	0.49 (0.22-1.12)	41 (329)	0.73 (0.37-1.44)	0.07
Estimated glomerular filtration rate ≥60 ml/min/1.73 m^2	30 (470)	1.48 (0.71-3.07)	31 (453)	1.34 (0.65-2.79)	31 (453)	0.90 (0.40-2.04)	

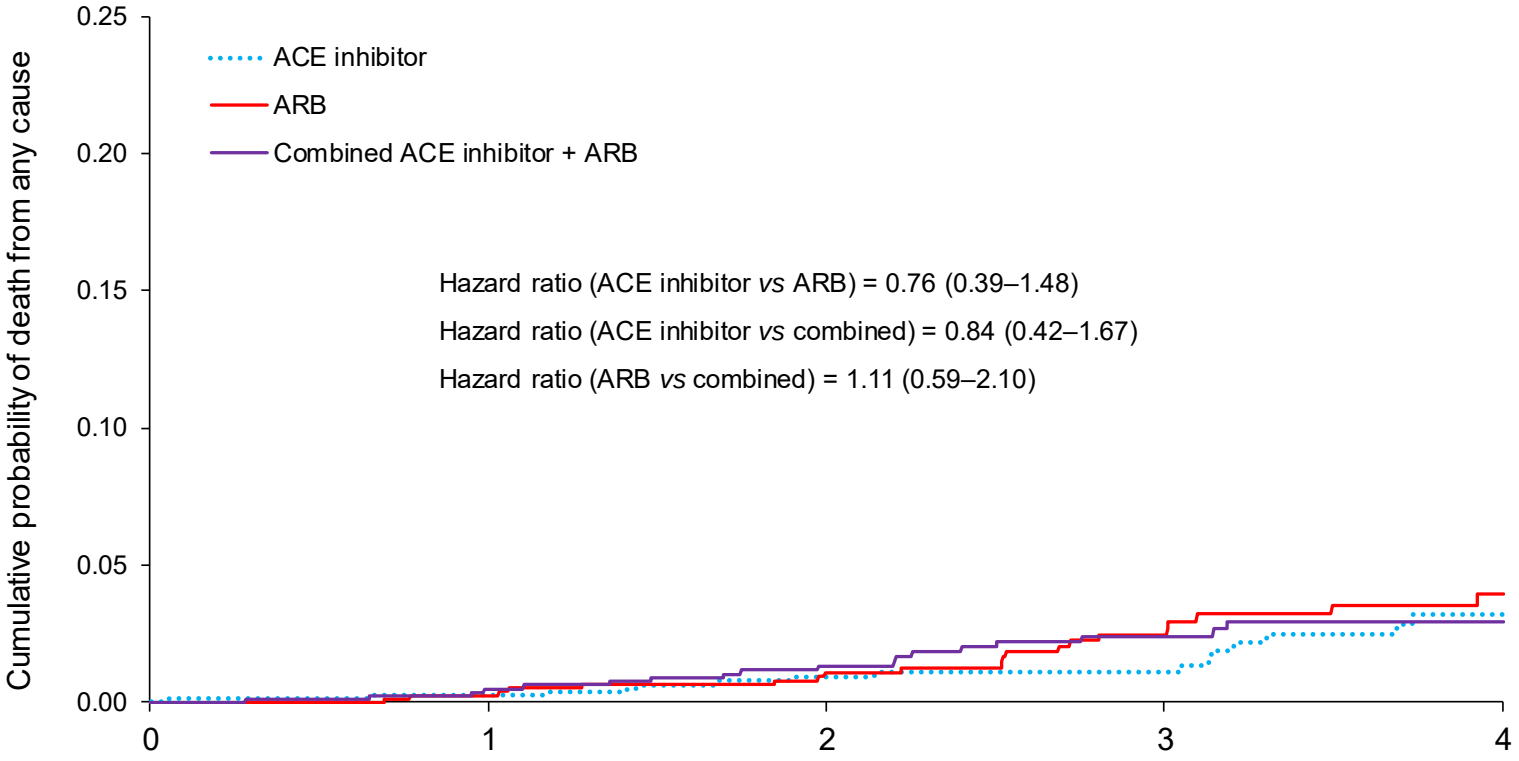
The primary composite outcome was death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, and hospitalization for cardiovascular causes. The P value is for the interaction between treatment comparison and subgroups. ACE=angiotensin converting enzyme. ARB=angiotensin receptor blocker. Subgroup analyses for the groups with type 1 diabetes and type 2 diabetes and those with and without a prior cardiovascular event are not shown as model gave results that were too unreliable due to few events within a group.

Appendix Figure 1. Change in systolic and diastolic blood pressure from baseline to study end.



Data are expressed as estimated mean with 95% confidence interval (CI). Comparative analyses are based on a mixed model for repeated measurements, comparing the values over time between groups, accounting for within-participant correlation. ACEi = angiotensin-converting enzyme inhibitor. ARB, angiotensin receptor blocker. *P* value for interaction between groups over time is shown.

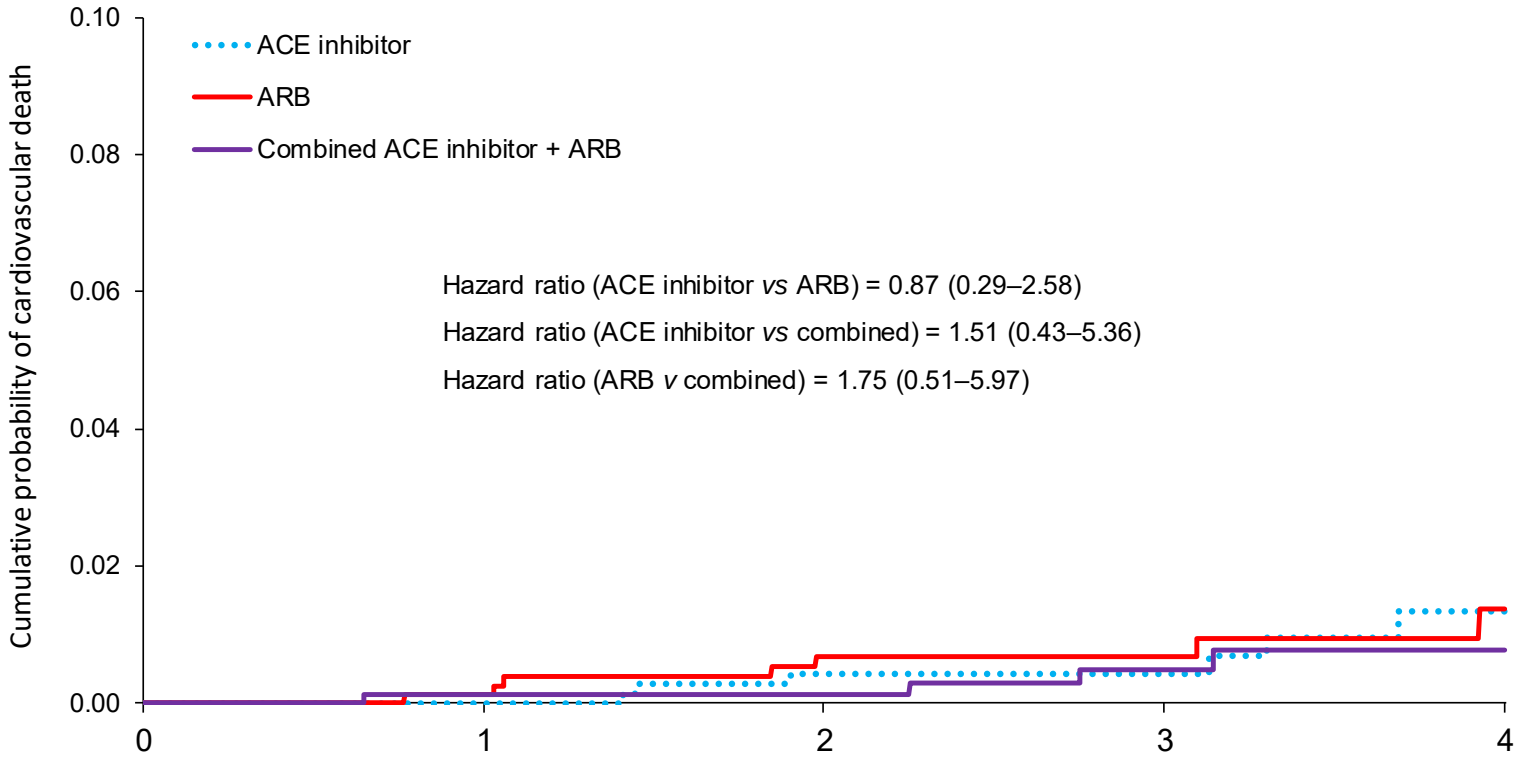
Appendix Figure 2. Kaplan-Meier estimates of all-cause mortality according to treatment allocation.



Number at risk (number of events)				
ACEi	413 (2)	339 (5)	279 (1)	194 (7)
ARB	414 (2)	341 (6)	282 (7)	196 (5)
ACEi + ARB	416 (4)	343 (6)	288 (6)	192 (2)

ACEi = angiotensin-converting enzyme inhibitor. ARB = angiotensin receptor blocker.

Appendix Figure 3. Kaplan-Meier estimates of cardiovascular death according to treatment allocation.



Number at risk (number of events)				
ACEi	413 (0)	339 (3)	279 (0)	194 (3)
ARB	414 (1)	341 (4)	283 (0)	197 (2)
ACEi + ARB	416 (1)	344 (0)	291 (2)	194 (1)

ACEi = angiotensin-converting enzyme inhibitor. ARB = angiotensin receptor blocker.