

**Supplemental Table 1** Impact of each variable on cluster structure and cluster definition

<b>Variables</b>	<b>Absolute Discriminative Power</b>	<b>Relative Discriminative Power (%)</b>	<b>Adjusted Rand Index</b>
<b>Systolic blood pressure</b>	5193,81	23,74	0,27
<b>Pulse pressure</b>	2793,79	12,77	0,61
<b>Age</b>	2261,09	10,34	0,41
<b>Glomerular filtration rate</b>	2088,37	9,55	0,39
<b>Left ventricular ejection fraction</b>	1398,2	6,39	0,78
<b>Smoker status</b>	974,36	4,45	0,77
<b>Diabetes</b>	963,85	4,41	0,81
<b>White blood cell</b>	770,52	3,52	0,80
<b>Platelet</b>	691,93	3,16	0,85
<b>Body mass index</b>	665,79	3,04	0,85
<b>Hypertension</b>	658,68	3,01	0,86
<b>Gender</b>	505,42	2,31	0,84
<b>Diuretics</b>	487,47	2,23	0,86
<b>Heart rate</b>	369,14	1,69	0,89
<b>Haemoglobin</b>	255,07	1,17	0,90
<b>Angina pectoris</b>	232,31	1,06	0,91
<b>Atrial fibrillation</b>	229,62	1,05	0,93
<b>Diastolic blood pressure</b>	201,46	0,92	0,90
<b>Sodium</b>	198,37	0,91	0,91
<b>Statins</b>	185,09	0,85	0,91
<b>P2Y12 inhibitors</b>	155,88	0,71	0,91
<b>Calcium channel blockers</b>	138,82	0,63	0,93
<b>Myocardial infarction</b>	127,82	0,58	0,93
<b>Cerebrovascular incident</b>	117,88	0,54	0,95
<b>Beta-blockers</b>	94,31	0,43	0,95
<b>Peripheral artery disease</b>	80,01	0,37	0,94
<b>Potassium</b>	20,51	0,09	0,96
<b>Aspirin</b>	14,64	0,07	0,96
<b>Angiotensin II receptor blockers</b>	0	0	1,00

**Supplemental Table 2** Baseline characteristics of the CAPRICORN and EPHEBUS trials and of the pooled cohort.

Variable	CAPRICORN trial (N = 1,959)	EPHEBUS trial (N = 6,632)	p-value	N.	Pooled cohort
<b>Demographic</b>					
Age, years	64 (54, 71)	65 (55, 73)	<0.001	8,591	64 (55, 72)
Female, n. (%)	519 (26)	1,918 (29)	0.04	8,591	2,437 (28)
Current smokers, n. (%)	801 (41)	2,587 (39)	0.002	8,580	3,388 (39)
<b>Medical history</b>					
Diabetes, n. (%)	427 (22)	2,142 (32)	<0.001	8,591	2,569 (30)
Atrial fibrillation, n. (%)	161 (8.2)	874 (13)	<0.001	8,591	1,035 (12)
Angina pectoris, n. (%)	1,073 (55)	3,091 (47)	<0.001	8,591	4,164 (48)
Cerebrovascular accidents, n. (%)	143 (7.3)	595 (9.0)	0.02	8,591	738 (8.6)
Previous MI,* n. (%)	589 (30)	1,802 (27)	0.01	8,591	2,391 (28)
Peripheral artery disease, n. (%)	155 (7.9)	823 (12)	<0.001	8,591	978 (11)
Hypertension, n. (%)	1,041 (53)	4,007 (60)	<0.001	8,591	5,048 (59)
<b>Clinical</b>					
BMI, Kg/m <sup>2</sup>	27.0 (24.0, 30.0)	27.0 (24.0, 30.0)	0.2	8,518	27.0 (24.0, 30.0)
Pulse pressure, mmHg	46 (40, 55)	45 (40, 54)	0.01	8,569	45 (40, 55)
Diastolic BP, mmHg	72 (68, 80)	70 (65, 80)	<0.001	8,569	70 (65, 80)
Systolic BP, mmHg	120 (110, 130)	120 (109, 130)	<0.001	8,569	120 (110, 130)
Heart rate, bpm	76 (70, 84)	74 (67, 80)	<0.001	8,561	74 (68, 82)
LVEF, %	35 (30, 38)	35 (30, 38)	0.3	8,565	35 (30, 38)
<b>Laboratory</b>					
eGFR, mL/min/1.73 m <sup>2</sup>	66 (54, 78)	68 (55, 81)	<0.001	7,609	67 (54, 80)
Potassium, mmol/L	4.50 (4.20, 4.80)	4.30 (4.00, 4.60)	<0.001	7,830	4.30 (4.00, 4.60)
Sodium, mmol/L	138.0 (136.0, 141.0)	139.0 (137.0, 142.0)	<0.001	7,839	139.0 (137.0, 142.0)
White blood cells, 1000/mm <sup>3</sup>	7.80 (6.50, 9.30)	8.30 (6.80, 10.30)	<0.001	7,785	8.20 (6.70, 10.10)
Haemoglobin, gr/L	13.60 (12.40, 14.50)	13.30 (12.20, 14.40)	<0.001	6,580	13.30 (12.20, 14.40)
Platelets, 1000/mm <sup>3</sup>	244 (198, 302)	242 (197, 300)	0.4	7,709	242 (197, 300)
<b>Medical treatment</b>					
P2Y12 inhibitors, n. (%)	211 (11)	1,787 (27)	<0.001	8,586	1,998 (23)
Aspirin, n. (%)	1,679 (86)	5,717 (86)	0.5	8,586	7,396 (86)
Statins, n. (%)	454 (23)	2,730 (41)	<0.001	8,586	3,184 (37)
ARB, n. (%)	16 (0.8)	156 (2.4)	<0.001	8,586	172 (2)
Betablockers, n. (%)	0 (0)	4,616 (70)	>0.9	6,627	4,616 (70)
CCB, n. (%)	69 (3.5)	473 (7.1)	<0.001	8,586	542 (6.3)
Diuretics, n. (%)	738 (38)	3,621 (55)	<0.001	8,586	4,359 (51)
Loop diuretics, n. (%)	596 (30)	3270 (49)	<0.001	8,591	3,866 (45)

Abbreviations: AF, atrial fibrillation; ARB, angiotensin receptor blockers; BMI, body mass index; CCB, calcium channel blockers; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PP, pulse pressure; WBC, white blood cells

\* before study randomization

**Supplemental Table 3** Distribution of cluster membership in the CAPRICORN and EPHEBUS cohorts

<b>Cluster</b>	<b>CAPRICORN</b>	<b>EPHEBUS</b>
1	22% (433)	26% (1728)
2	20% (391)	15% (985)
3	11% (213)	14% (944)
4	26% (509)	24% (1564)
5	21% (413)	21% (1411)

**Supplemental Table 4** Risk of multiple heart failure hospitalizations by clusters in the learning and in the validation set.

	Learning set (EPHESUS/CAPRICORN)			Validation set (COMMANDER-HF)		
	N <sub>events</sub> /N (%)	Adjusted for age and sex		N <sub>events</sub> /N (%)	Adjusted for age and sex	
		HR (CI 95 %)	p-value		HR (CI 95 %)	p-value
<b>Cluster 1</b>	274/2161 (12.7)	5.31 (3.68, 7.66)	<0.001	361/1512 (23.9)	2.53 (2.02, 3.17)	<0.001
<b>Cluster 2</b>	68/1376 (4.9)	2.07 (1.37, 3.13)	<0.001	135/1155 (11.7)	1.13 (0.88, 1.47)	0.34
<b>Cluster 3</b>	117/1157 (10.1)	5.14 (3.54, 7.46)	<0.001	115/582 (19.8)	2.35 (1.82, 3.04)	<0.001
<b>Cluster 4</b>	38/2073 (1.8)	1.00	-	122/1201 (10.2)	1.00	-
<b>Cluster 5</b>	74/1824 (4.1)	2.44 (1.65, 3.62)	<0.001	130/572 (22.7)	3.06 (2.38, 3.93)	<0.001

Multiple heart failure hospitalizations defined as at least two HF hospitalizations during follow-up or one HF hospitalization followed by death

**Supplemental Table 5** Reclassification performance and improvement in discrimination provided by clusters for the main endpoints.

<b>HF hospitalization or all cause death</b>		
<b>Index</b>	<b>Estimate (CI 95%)</b>	<b>p-value</b>
cNRI	0.429 (0.327 to 0.504)	<0.0001
IDI	0.026 (0.019 to 0.034)	<0.0001
C-index Model 0	0.631 (0.617 to 0.645)	<0.0001
C-index Model 1	0.669 (0.655 to 0.682)	<0.0001
Increase C-index	0.037 (0.028 to 0.047)	<0.0001
<b>Cardiovascular hospitalization or all cause death</b>		
cNRI	0.213 (0.166 to 0.278)	<0.0001
IDI	0.015 (0.010 to 0.021)	<0.0001
C-index Model 0	0.547 (0.537 to 0.558)	<0.0001
C-index Model 1	0.577 (0.567 to 0.587)	<0.0001
Increase C-index	0.029 (0.021 to 0.037)	<0.0001
<b>Major adverse cardiovascular events (MACE)</b>		
cNRI	0.345 (0.255 to 0.393)	0.004
IDI	0.012 (0.007 to 0.018)	0.48
C-index Model 0	0.607 (0.591 to 0.623)	<0.0001
C-index Model 1	0.632 (0.617 to 0.647)	<0.0001
Increase C-index	0.025 (0.016 to 0.034)	0.001

Model 0, MAGGIC score; Model 1, MAGGIC score + Clusters

Abbreviations: cNRI, continous net reclassification improvement; HF, heart failure; IDI, integrated discrimination improvement

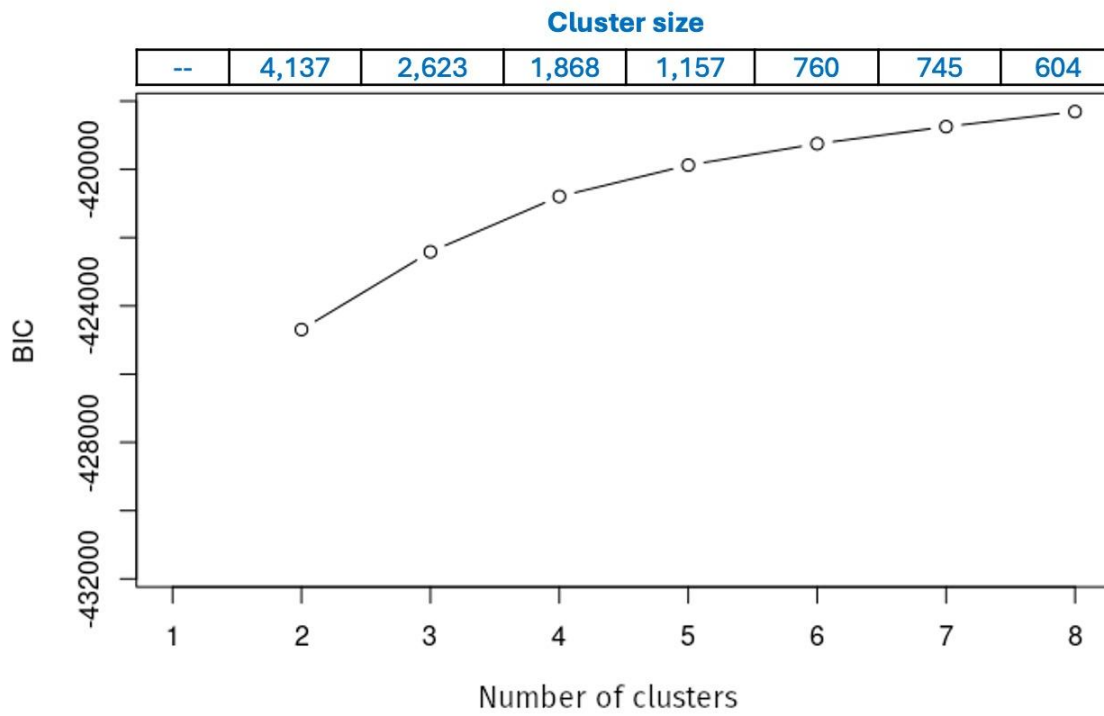
**Supplemental Table 6** Cluster membership prediction ability by random forest model

<b>Cluster</b>	<b>Precision</b>	<b>Recall</b>	<b>F-Measure</b>	<b>ROC Area</b>
1	0.833	0.894	0.863	0.978
2	0.796	0.908	0.849	0.986
3	0.887	0.507	0.645	0.961
4	0.828	0.879	0.853	0.979
5	0.887	0.894	0.89	0.989
Weighted Avg.	0.845	0.841	0.835	0.98

Supplemental Figure 1



**Supplemental Figure 2**



<b>Number of clusters (n)</b>	<b>BIC</b>	<b>BIC variation (BIC<sub>n</sub>-BIC<sub>n-1</sub>)</b>
2	-424,693.9	NA
3	-422,416.6	2,277.3
4	-420,793	1,623.6
5	-419,876.2	916.8
6	-419,249.9	626.3
7	-418,748.1	501.8
8	-418,308	440.1



Supplemental Figure 3

Association of clusters with outcomes

All cause death

**A**

Variable	Learning set			Validation set		
	N	Hazard ratio	p-value	N	Hazard ratio	p-value
<b>Cluster 4</b> – Young man, higher LVEF	2073	Reference		1172	Reference	
<b>Cluster 1</b> – Oldest, AF, high CV events burden	2161	2.36 (1.93, 2.89)	<0.001	1545	1.93 (1.58, 2.35)	<0.001
<b>Cluster 2</b> – Old woman, hypertensive, smokers	1376	1.37 (1.09, 1.71)	0.007	1199	1.17 (0.95, 1.45)	0.1
<b>Cluster 3</b> – Hypertensive, diabetic, PAD	1157	2.25 (1.82, 2.79)	<0.001	561	1.85 (1.47, 2.33)	<0.001
<b>Cluster 5</b> – Youngest, low CV events burden	1824	1.70 (1.37, 2.10)	<0.001	545	2.59 (2.08, 3.23)	<0.001

Cardiovascular death

**B**

Variable	Learning set			Validation set		
	N	Hazard ratio	p-value	N	Hazard ratio	p-value
<b>Cluster 4</b> – Young man, higher LVEF	2073	Reference		1172	Reference	
<b>Cluster 1</b> – Oldest, AF, high CV events burden	2161	2.52 (2.02, 3.13)	<0.001	1545	1.96 (1.58, 2.42)	<0.001
<b>Cluster 2</b> – Old woman, hypertensive, smokers	1376	1.40 (1.09, 1.78)	0.008	1199	1.12 (0.89, 1.42)	0.3
<b>Cluster 3</b> – Hypertensive, diabetic, PAD	1157	2.17 (1.72, 2.73)	<0.001	561	1.78 (1.38, 2.29)	<0.001
<b>Cluster 5</b> – Youngest, low CV events burden	1824	1.68 (1.33, 2.11)	<0.001	545	2.65 (2.09, 3.36)	<0.001

HF hospitalization or CV death

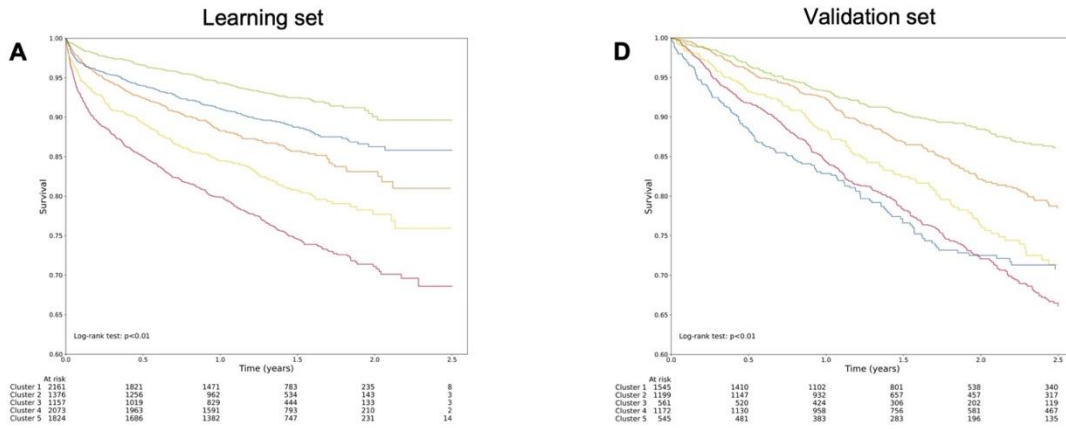
**C**

Variable	Learning set			Validation set		
	N	Hazard ratio	p-value	N	Hazard ratio	p-value
<b>Cluster 4</b> – Young man, higher LVEF	2073	Reference		1172	Reference	
<b>Cluster 1</b> – Oldest, AF, high CV events burden	2161	3.05 (2.57, 3.63)	<0.001	1545	1.97 (1.70, 2.29)	<0.001
<b>Cluster 2</b> – Old woman, hypertensive, smokers	1376	1.56 (1.28, 1.89)	<0.001	1199	1.09 (0.92, 1.28)	0.3
<b>Cluster 3</b> – Hypertensive, diabetic, PAD	1157	2.79 (2.33, 3.34)	<0.001	561	1.97 (1.66, 2.33)	<0.001
<b>Cluster 5</b> – Youngest, low CV events burden	1824	1.83 (1.53, 2.19)	<0.001	545	2.37 (2.00, 2.81)	<0.001

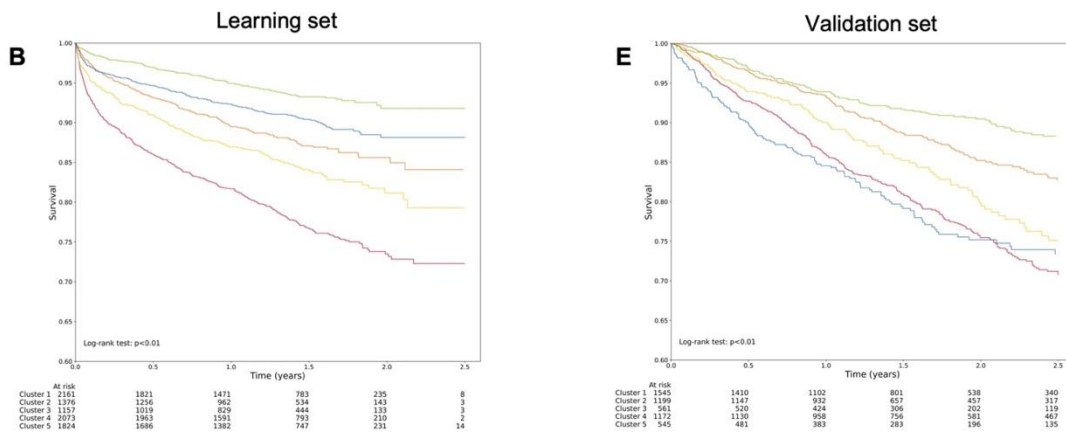
# Supplemental Figure 4



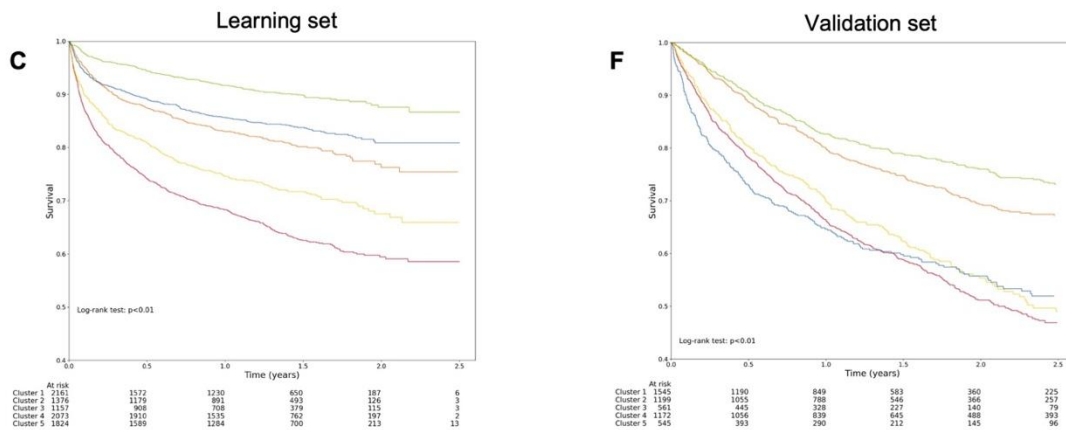
## All cause death



## Cardiovascular death

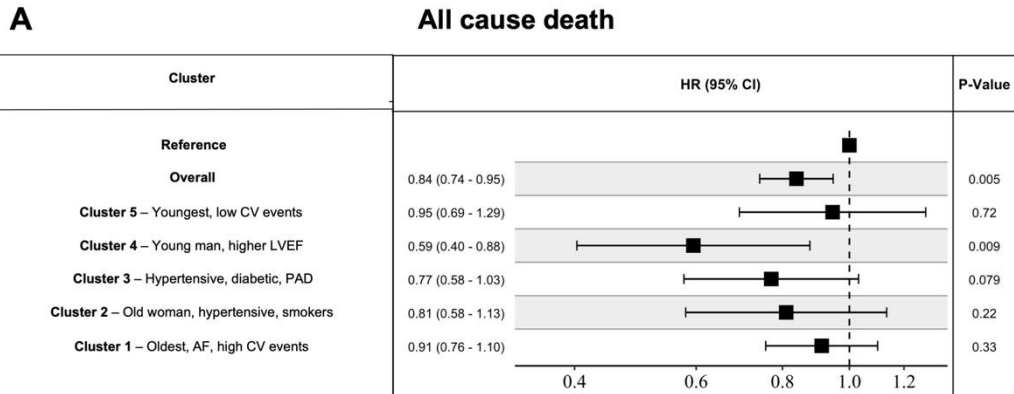


## HF hospitalization or CV death

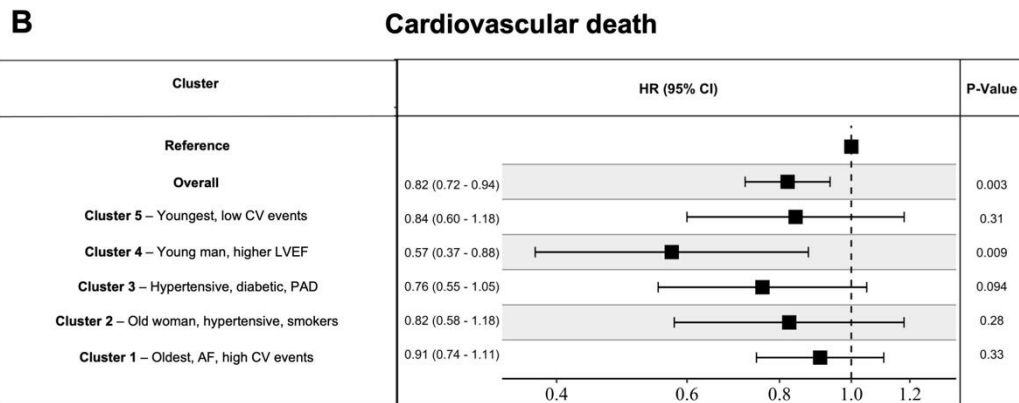


Supplemental Figure 5

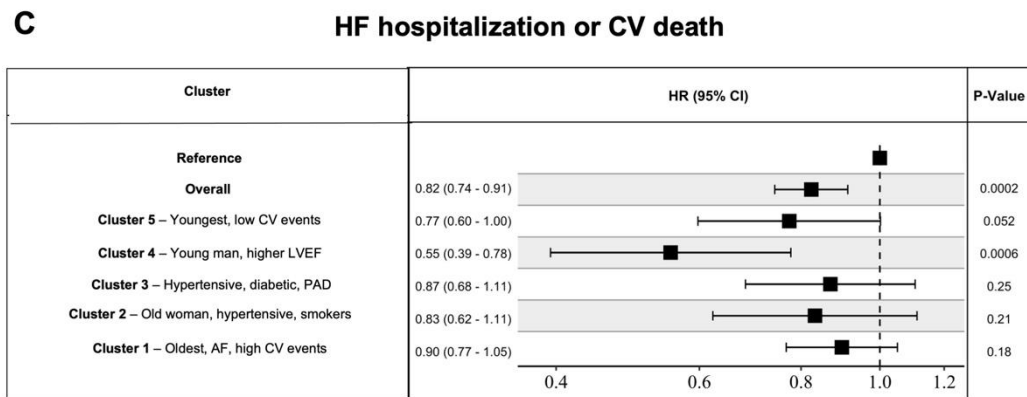
Treatment effect of eplerenone according to clusters



Interaction p-value: 0.32



Interaction p-value: 0.40

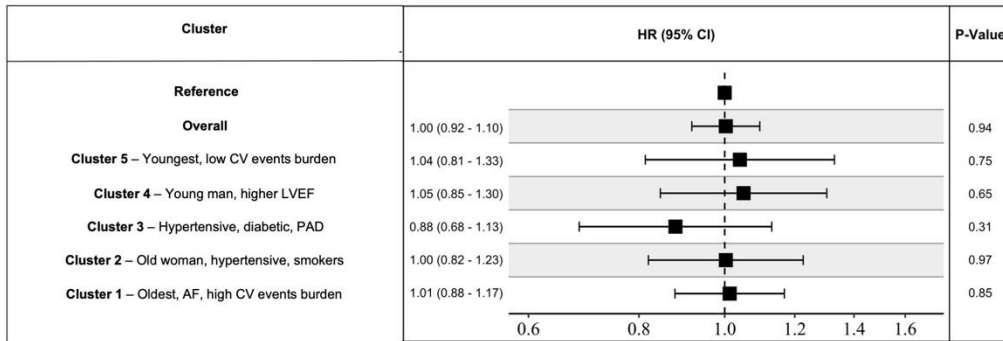


Interaction p-value: 0.14

Supplemental Figure 6

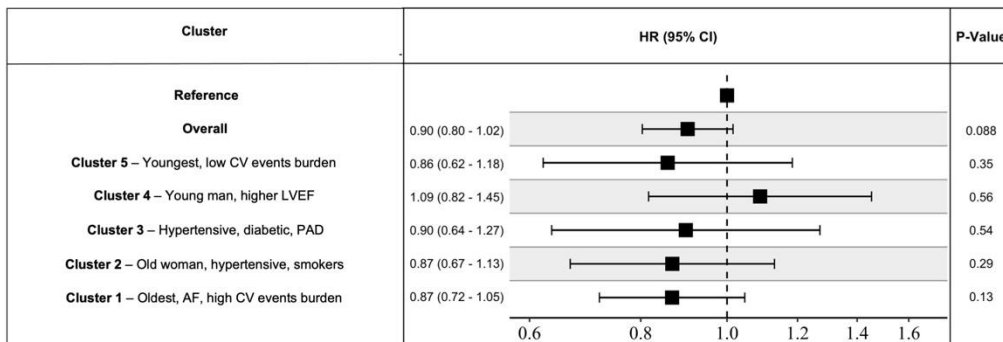
## Treatment effect of low-dose rivaroxaban according to clusters

### A HF hospitalization or all cause death



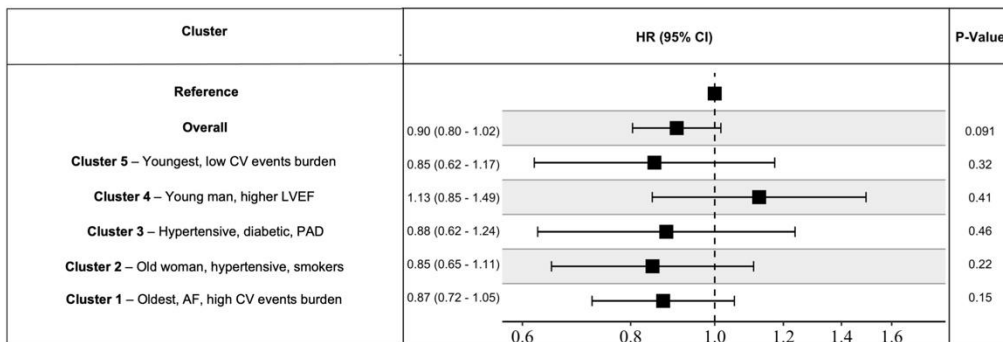
Interaction p-value: 0.85

### B CV hospitalization or all cause death



Interaction p-value: 0.73

### C MACE

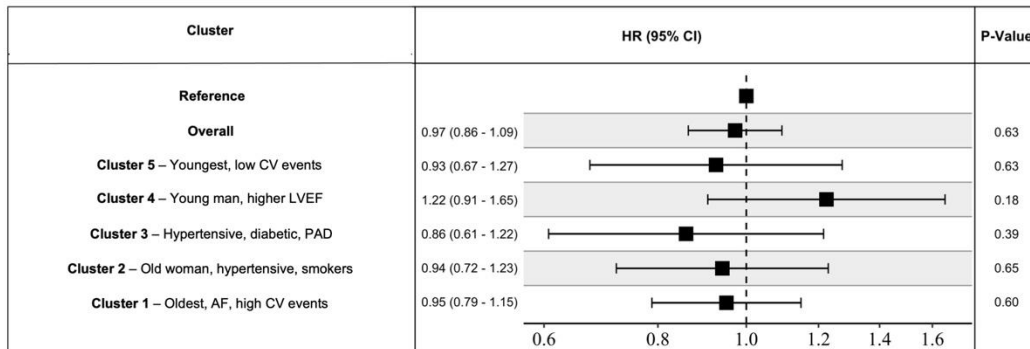


Interaction p-value: 0.59

Supplemental Figure 7

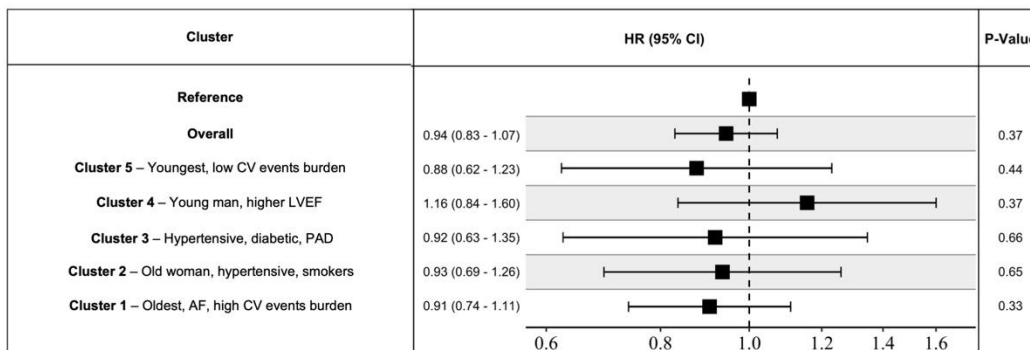
## Treatment effect of low-dose rivaroxaban according to clusters

### A All cause death



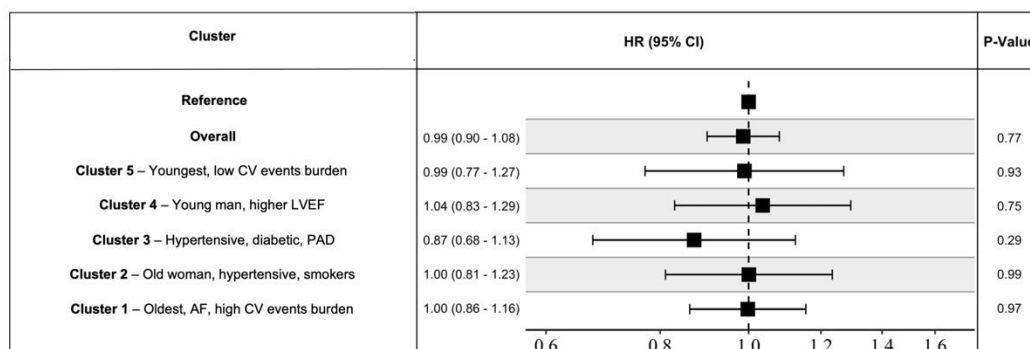
Interaction p-value: 0.56

### B Cardiovascular death



Interaction p-value: 0.75

### C HF hospitalization or CV death



Interaction p-value: 0.88