SUPPLEMENTAL MATERIAL

Appendix

Swiss-AF investigators

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Table S1. Outcome definitions.

Hospitalization for heart failure	Hospitalization for acute heart failure is defined as: any hospitalization for acute heart failure that is associated with at least one overnight stay. If it's not clear whether the reason for a patient's hospitalization is acute heart failure or not, this event/incidence should in doubt be classified as acute heart failure. The following references mentioned under clinical examination, or in the progress entry could be used as an indication for heart failure: leg swelling/leg edema, distension of the neck veins, positive hepato-jugular reflux, rales and 3rd heart sound
Mortality	Deaths will be classified as either cardiovascular or non-cardiovascular. All deaths will be assumed to be cardiovascular in nature unless a non-cardiovascular cause can be clearly provided. Cardiovascular death: includes cardiac deaths (e.g. cardiogenic shock, arrhythmia/sudden death, cardiac rupture) and other vascular deaths (e.g., stroke, pulmonary embolism, ruptured aortic aneurysm or dissection). All hemorrhagic deaths will be classified as cardiovascular deaths. Non-cardiovascular death: includes all deaths due to a clearly documented non-cardiac and non-vascular cause, such as respiratory failure (excluding cardiogenic pulmonary edema), infections/sepsis, neoplasm, and trauma (including suicide and homicide).

Ischemic stroke	Defined as a rapid onset of focal neurological dysfunction with clinical, imaging or pathological evidence of focal infarction of the brain, retina (excluding anterior ischaemic optic neuropathy [AION]), or spinal cord explaining the dysfunction. Clinical evidence of infarction is based on symptoms persisting ≥24 hours or until death, and exclusion of other aetiologies (such as brain infection, trauma, tumour, seizure, severe metabolic disease, or degenerative neurological disease). Transient neurological symptoms associated with cerebral infarction on imaging should be classified as ischaemic stroke, not TIA.
Systemic embolism	A systemic arterial embolism will be considered to have occurred where there is clear evidence of abrupt occlusion of a systemic artery consistent with an embolic event. Pulmonary embolism or deep vein thrombosis should not be reported.
Myocardial infarction	Myocardial infarction is defined according to the universal definition of MI as rise and/or fall of cardiac troponin with at least one value above the 99th percentile of the upper reference limit in a clinical setting consistent with myocardial ischemia, and with at least one of the following: - symptoms of ischemia - new ST elevation at the J point in two contiguous leads >0.1 mV except for V2-V3. For leads V2-V3 the following cut points apply: ≥0.2 mV in men ≥40 years, ≥0.25 mV in men <40 years and ≥0.15 mV in women on ECG

	- new horizontal or down-sloping ST depression ≥0.05 mV in two contiguous leads and/or T inversion ≥0.1 mV in two contiguous leads with prominent R wave or R/S ratio >1 - new left bundle brunch block on ECG - development of pathological Q waves on ECG - imaging evidence of new loss of viable myocardium or new regional wall motion - identification of an intracoronary thrombus by angiography or autopsy

Table S2. Association of the inflammation score with adverse outcome events (sensitivity and competing risk analyses).

Outcome	Inflammation score	Sensitivity analysis		Competing risk analysis		Primary analysis	
		Adjusted HR (95% CI)	p-value for trend	Adjusted HR (95% CI)	p-value for trend	Adjusted HR (95% CI)	p-value for trend
Hospitalization for heart failure	0	Reference category		Reference category		Reference category	
	1	1.27 (0.92-1.76)	<0.001	1.24 (0.90-1.71)	<0.001	1.32 (0.96-1.82)	<0.001
	2	1.38 (0.99-1.91)		1.31 (0.94-1.83)		1.45 (1.04-2.00)	
	3	1.95 (1.41-2.70)		1.78 (1.28-2.47)		2.04 (1.48-2.83)	
	4	2.29 (1.68-3.11)		2.08 (1.51-2.85)		2.43 (1.80-3.30)	
All-cause mortality	0	Reference category				Reference category	
	1	2.17 (1.48-3.17)	<0.001			2.20 (1.50-3.21)	<0.001
	2	2.76 (1.89-4.02)				2.85 (1.95-4.15)	
	3	3.74 (2.57-5.45)				3.85 (2.64-5.60)	
	4	4.79 (3.34-6.87)				4.96 (3.47-7.09)	
	0	Reference category		Reference category		Reference category	

Outcome		Model 1	p-value	Model 2	p-value	Model 3	p-value
Cardiovascular death	1	2.32 (1.46-3.70)	<0.001	2.36 (1.47-3.77)	<0.001	2.36 (1.49-3.76)	<0.001
	2	2.16 (1.33-3.51)		2.10 (1.26-3.50)		2.24 (1.38-3.63)	
	3	3.49 (2.18-5.56)		3.40 (2.09-5.52)		3.61 (2.26-5.77)	
	4	4.10 (2.62-6.42)		3.93 (2.46-6.28)		4.26 (2.72-6.65)	
Ischemic stroke, myocardial infarction or cardiovascular death	0	Reference category		Reference category		Reference category	
	1	1.74 (1.27-2.37)	<0.001	1.72 (1.26-2.34)	<0.001	1.80 (1.32-2.45)	<0.001
	2	1.50 (1.07-2.11)		1.46 (1.03-2.06)		1.55 (1.11-2.17)	
	3	2.58 (1.87-3.56)		2.49 (1.79-3.45)		2.65 (1.92-3.65)	
	4	2.74 (2.00-3.75)		2.60 (1.90-3.57)		2.86 (2.10-3.90)	
Ischemic stroke or systemic embolism	0	Reference category		Reference category		Reference category	
	1	1.18 (0.71-1.98)	0.054	1.17 (0.70-1.97)	0.161	1.23 (0.74-2.06)	0.03
	2	0.77 (0.41-1.46)		0.75 (0.38-1.45)		0.81 (0.43-1.53)	
	3	1.77 (1.01-3.09)		1.59 (0.89-2.85)		1.84 (1.05-3.20)	
	4	1.60 (0.90-2.83)		1.45 (0.81-2.63)		1.76 (1.00-3.07)	

All analyses were adjusted for age, sex, history of heart failure, hypertension, diabetes, prior stroke or transient ischemic attack, history of coronary artery disease, estimated glomerular filtration rate (eGFR) as per MDRD formula, body mass index, smoking status, anticoagulation use and study cohort (BEAT-AF or Swiss-AF). Sensitivity analyses were additionally adjusted for statin use

and cardiac rhythm at baseline. The competing risk analyses additionally accounted for death (first hospitalization for heart failure; composite of ischemic stroke or systemic embolism) and non-cardiovascular death (cardiovascular death; composite of ischemic stroke, myocardial infarction or cardiovascular death), respectively. Observations in model for the sensitivity analyses: 3,624 (95.8% complete cases due to missing information on plasma levels of hs-CRP or IL-6, or missing cardiac rhythm at baseline). Observations in primary model: 3,650 (96.5% complete cases due to missing information on plasma levels of hs-CRP or IL-6). HR hazard ratio, CI confidence interval.

Figure S1. Cumulative incidence of all-cause mortality across inflammation score categories (Kaplan-Meier method).
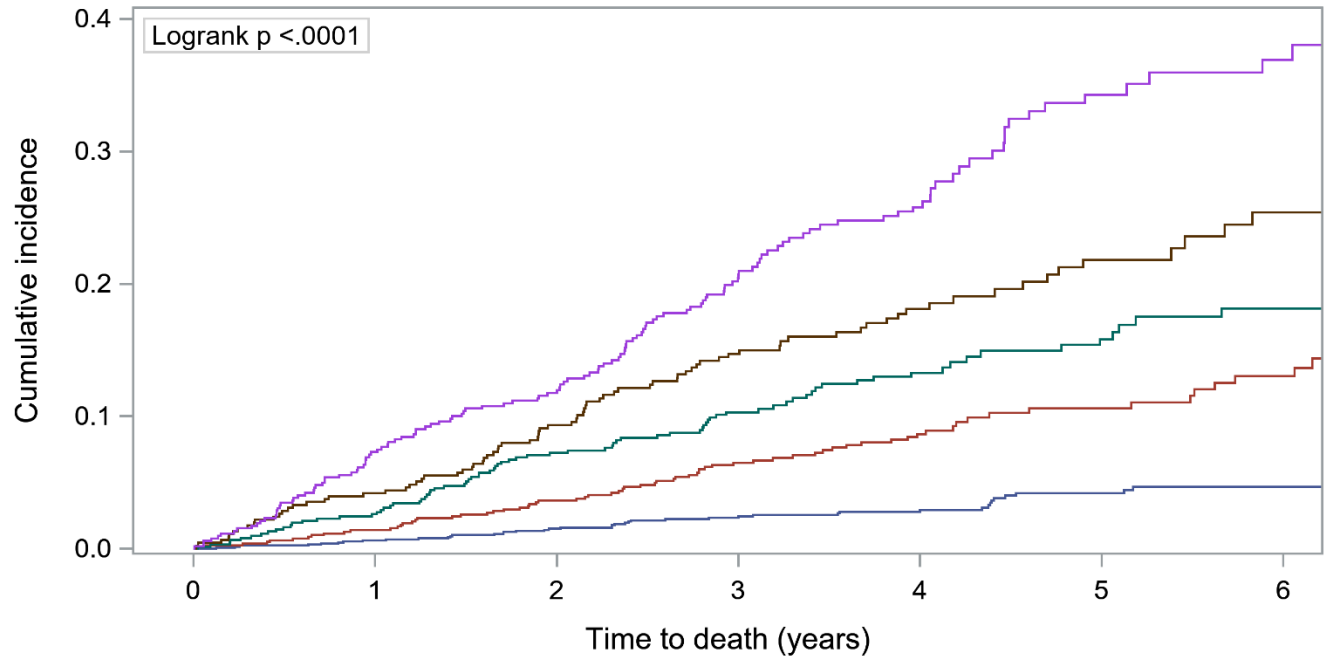
Inflammation score							
0	1280	1268	1157	966	724	500	362
1	779	764	695	582	396	243	164
2	616	596	532	413	272	186	118
3	454	435	383	306	206	133	76
4	521	482	424	304	197	100	64

Figure S2. Cumulative incidence of cardiovascular death across inflammation score categories (Kaplan-Meier method).
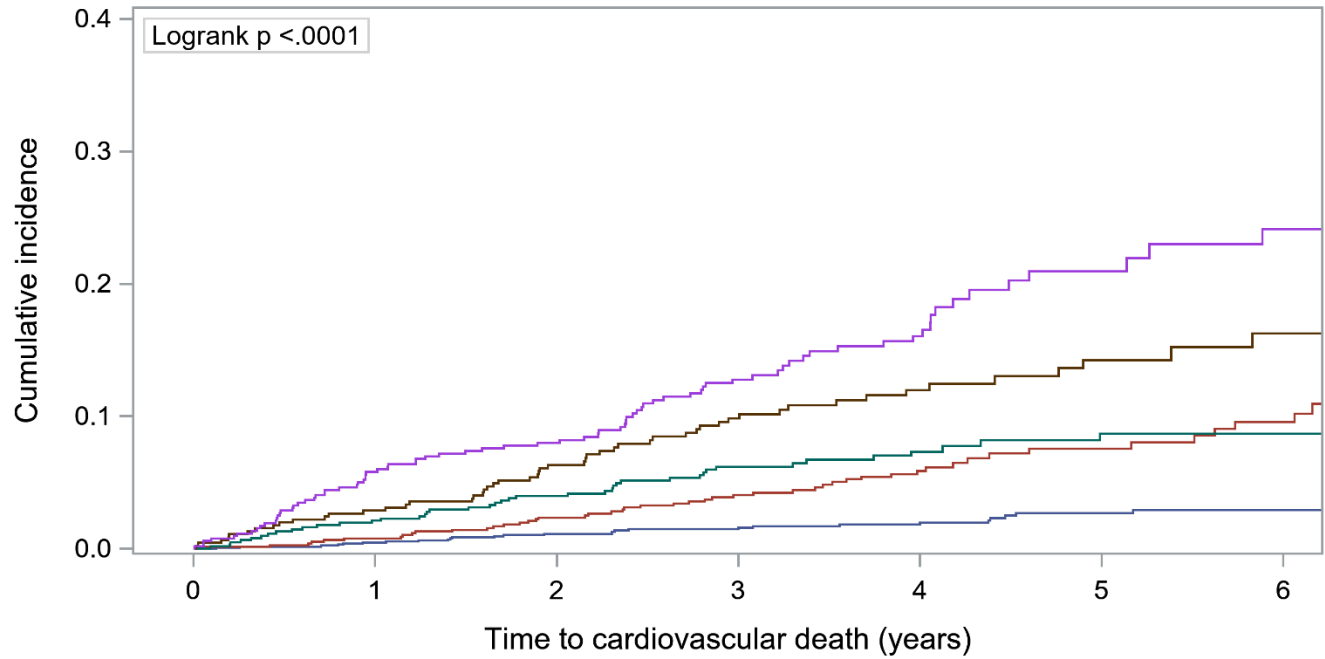
0	1280	1268	1157	966	724	500	362
1	779	764	695	582	396	243	164
2	616	596	532	413	272	186	118
3	454	435	383	306	206	133	76
4	521	482	424	304	197	100	64

Figure S3. Cumulative incidence of ischemic stroke, myocardial infarction or cardiovascular death across inflammation score categories (Kaplan-Meier method).
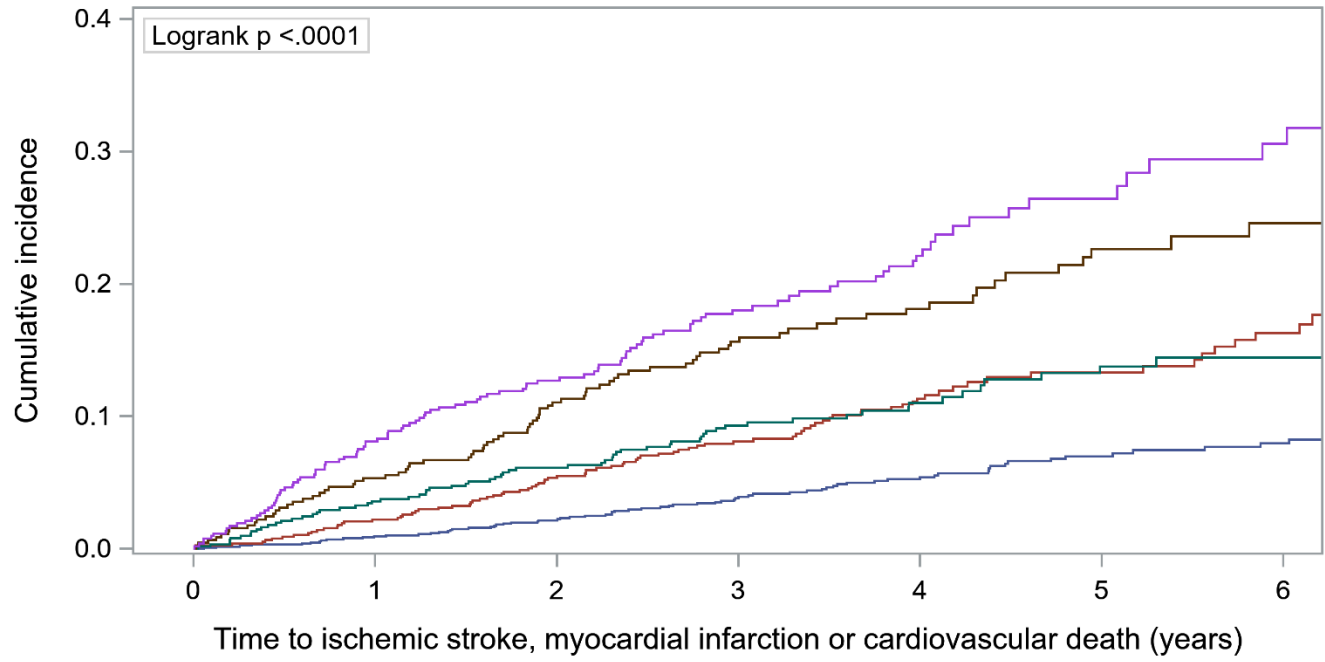
Inflammation score						
0	1280	1261	1144	943	701	481	350
1	779	753	674	562	376	233	156
2	616	587	522	400	263	177	109
3	454	424	366	288	193	123	71
4	521	470	402	283	179	94	60

Figure S4. Cumulative incidence of ischemic stroke or systemic embolism across inflammation score categories (Kaplan-Meier method).
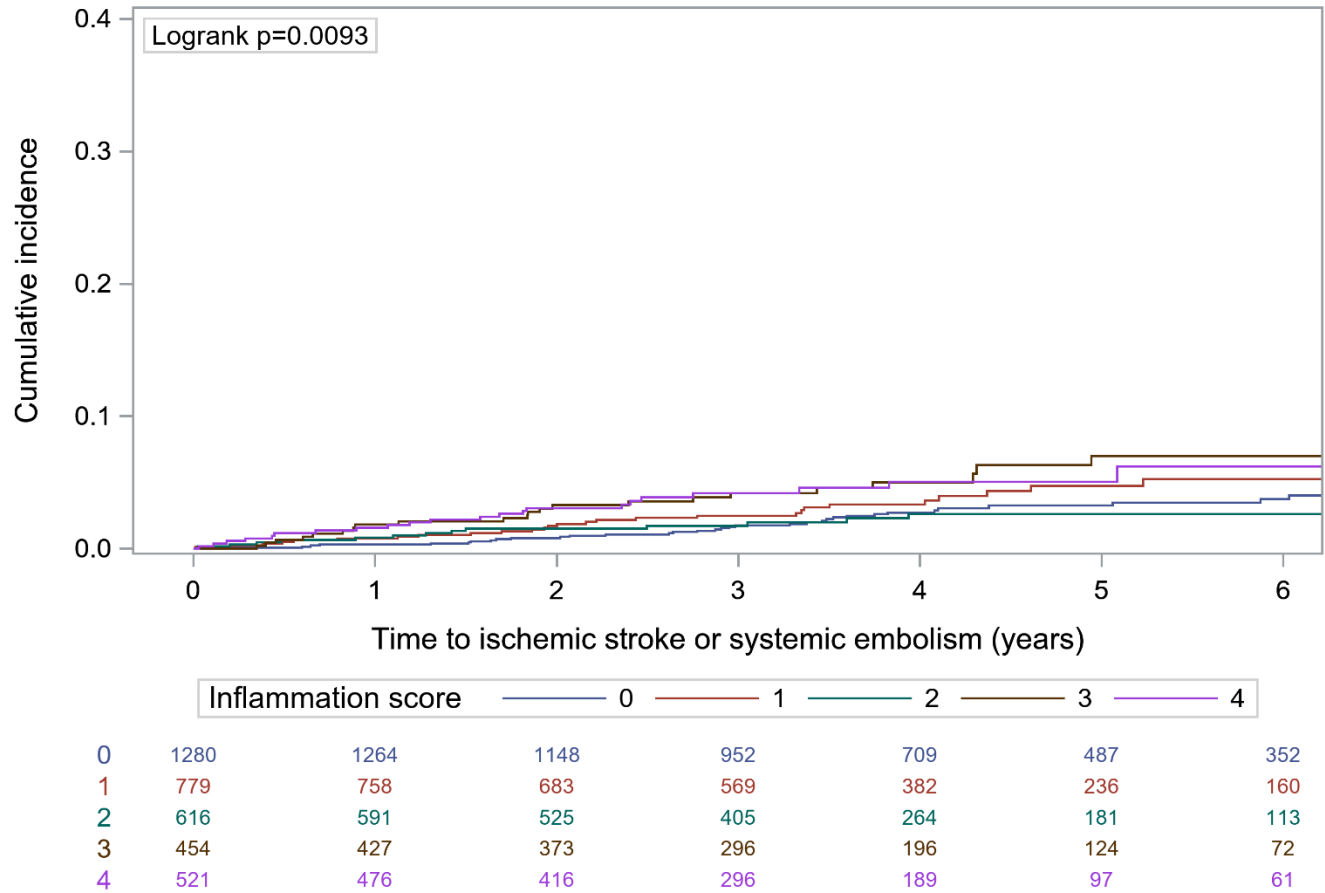
Figure S5. Cumulative incidence function of heart failure hospitalization across inflammation score categories, accounting for the competing risk of death.
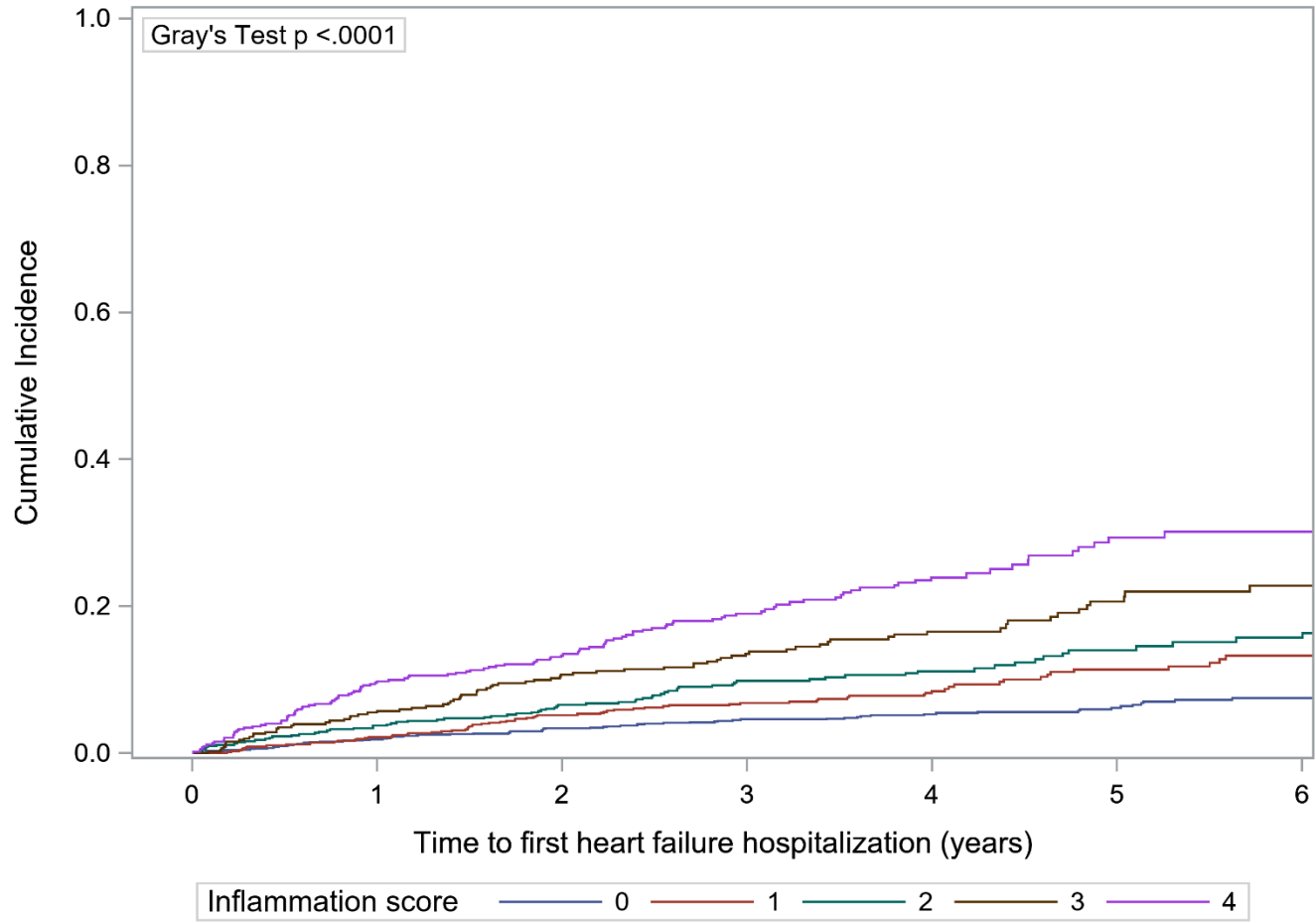
Figure S6. Cumulative incidence function of cardiovascular death across inflammation score categories, accounting for the competing risk of non-cardiovascular death.
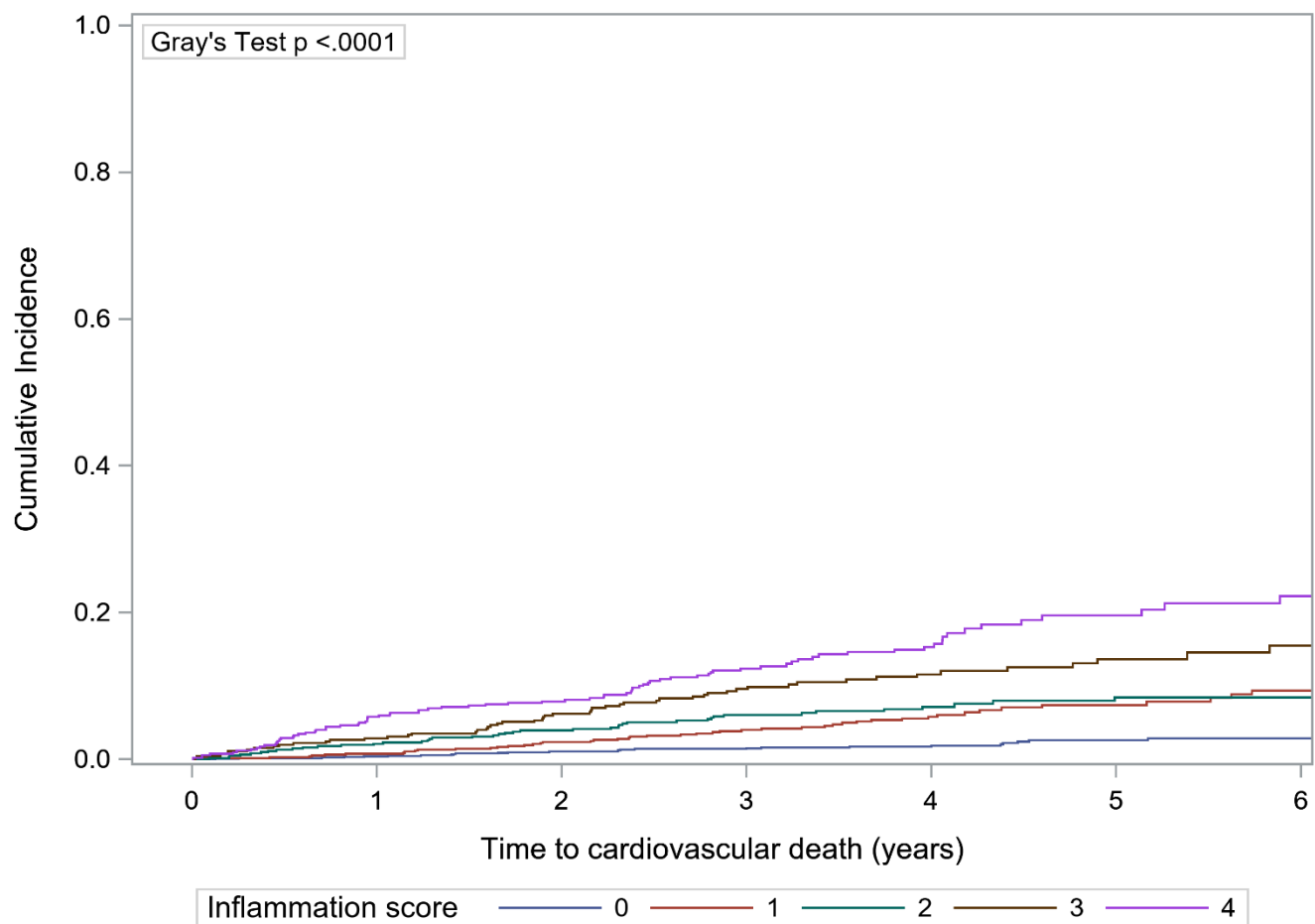
Figure S7. Cumulative incidence function of ischemic stroke, myocardial infarction or cardiovascular death across categories of the inflammation score, accounting for the competing risk of non-cardiovascular death.
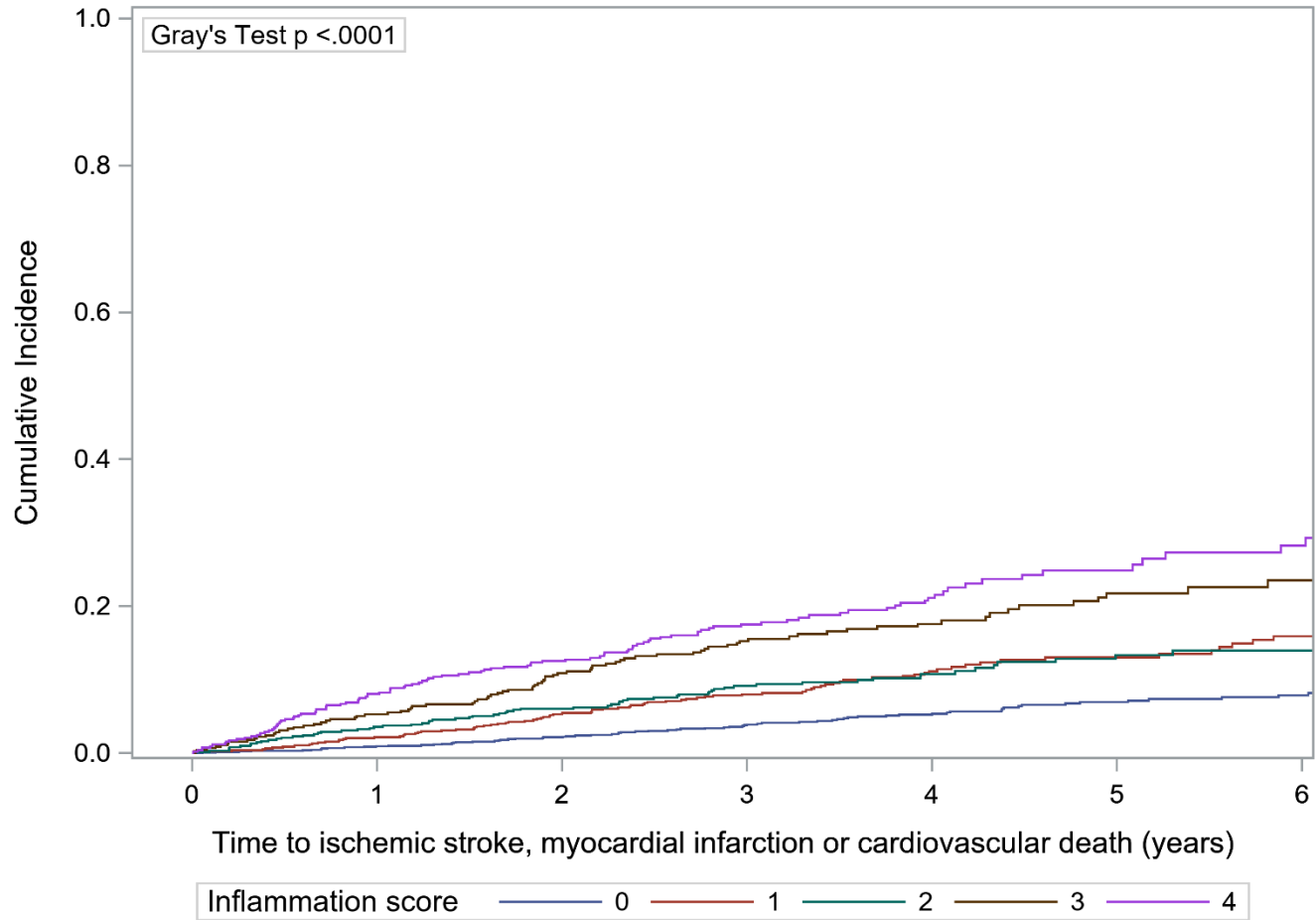
Figure S8. Cumulative incidence function of ischemic stroke or systemic embolism across categories of the inflammation score, accounting for the competing risk of death.