

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Sacco RL, Diener H-C, Yusuf S, et al. Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. *N Engl J Med* 2008;359:1238-51. DOI: 10.1056/NEJMoa0805002.

APPENDIX I. Primary, secondary and tertiary outcome events of the PRoFESS trial.

PRIMARY OUTCOME EVENT	TERTIARY OUTCOME EVENTS
<p><u>Stroke (nonfatal or fatal)</u></p> <p>Ischemic OR</p> <p>Hemorrhagic OR</p> <p>Of uncertain cause</p>	<p><u>Stroke or major hemorrhagic event</u></p> <p><u>Death</u></p> <p>Classification of Death:</p> <p>Ischemic stroke, hemorrhagic stroke, stroke of uncertain cause, MI, hemorrhage excluding intracranial bleeding, other vascular causes, non-vascular causes</p>
<hr/> <p>SECONDARY OUTCOME EVENTS</p> <p>Antiplatelet comparison:</p> <p><u>Vascular events</u></p> <p>Stroke (non-fatal or fatal) OR</p> <p>Myocardial infarction (non-fatal or fatal) OR</p> <p>Vascular death</p> <p>Telmisartan Comparison:</p> <p><u>Vascular events or CHF</u></p> <p>Stroke (non-fatal or fatal) OR</p> <p>MI (non-fatal or fatal) OR</p> <p>Vascular death OR</p> <p>New or Worsening CHF¹</p>	<p><u>Major hemorrhagic events</u></p> <p>Life-threatening</p> <p>Non-life-threatening</p> <p>Classifications of hemorrhagic events (both major or minor):</p> <p>Hematuria, hematemesis, gastrointestinal, epistaxis, intraocular, purpura, gynecologic, internal bleeding, intracranial, other</p>
<p><u>New-onset diabetes</u></p>	<p><u>Other designated vascular events</u></p> <p>Pulmonary embolism OR</p> <p>Retinal vascular accidents² OR</p> <p>Deep vein thrombosis OR</p> <p>Peripheral arterial occlusion OR</p> <p>TIA OR</p> <p>Cerebral venous thrombosis³</p> <p><u>New or worsening CHF</u></p>

	<p><u>Thrombotic thrombocytopenic purpura</u></p> <p><u>Neutropenia</u></p> <p style="padding-left: 40px;">Non-severe OR</p> <p style="padding-left: 40px;">severe</p> <p><u>Ischaemic stroke</u></p> <p><u>Ischaemic Stroke Subtype:</u></p> <p>Large-artery atherosclerosis; cardioembolism; small-artery occlusion (lacune); acute stroke of other determined etiology; stroke of undetermined etiology</p> <p><u>Other endpoints:</u> MMSE, modified Rankin, EQ-5D, Barthel, post-stroke chronic pain</p>
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CHF = congestive heart failure; MI = myocardial infarction; TIA = transient ischemic

attack; MMSE = Mini Mental State Examination; QOL = Quality of life

¹New or worsening CHF is defined as a patient who is hospitalized for CHF symptoms, or a patient is seen in the emergency room for CHF symptoms, or a patient is treated with intravenous diuretics.

²Retinal vascular accidents that are not confirmed retinal arterial occlusions. The latter are defined as strokes.

³Cerebral venous thrombosis as opposed to arterial thrombosis.

APPENDIX IIA: Frequency [N(%)] of most commonly reported serious adverse events

(at least 0.4% at the patient level in any group) by treatment, primary system organ

class, and preferred term (randomised patients).

System organ class/preferred term	ASA-ERDP N (%)	Clopidogrel N (%)
Number of patients	10181 (100.00)	10151 (100.00)
Total with serious adverse events	2749 (27.0)	2724 (26.8)
Blood and lymphatic system disorders	91 (0.9)	70 (0.7)
Anaemia	58 (0.6)	44 (0.4)
Cardiac disorders	470 (4.6)	463 (4.6)
Angina unstable	119 (1.2)	89 (0.9)
Atrial fibrillation	110 (1.1)	130 (1.3)
Coronary artery disease	62 (0.6)	66 (0.7)
Angina pectoris	60 (0.6)	60 (0.6)
Ear and labyrinth disorders	53 (0.5)	66 (0.7)
Vertigo	30 (0.3)	44 (0.4)
Eye disorders	48 (0.5)	49 (0.5)
Gastrointestinal disorders	390 (3.8)	344 (3.4)
Vomiting	46 (0.5)	36 (0.4)
Diarrhoea	43 (0.4)	37 (0.4)
General disorders and administration site conditions	265 (2.6)	222 (2.2)
Chest pain	107 (1.1)	76 (0.7)
Hepatobiliary disorders	86 (0.8)	87 (0.9)
Infections and Infestations	584 (5.7)	634 (6.2)

Pneumonia	202 (2.0)	202 (2.0)
Urinary tract infection	86 (0.8)	114 (1.1)
Sepsis	41 (0.4)	50 (0.5)
Injury, poisoning and procedural complications	384 (3.8)	392 (3.9)
Fall	121 (1.2)	116 (1.1)
Hip fracture	43 (0.4)	44 (0.4)
Investigations	50 (0.5)	45 (0.4)
Metabolism and nutrition disorders	228 (2.2)	200 (2.0)
Dehydration	65 (0.6)	35 (0.3)
Hyponatraemia	41 (0.4)	36 (0.4)
Musculoskeletal and connective tissue disorders	216 (2.1)	255 (2.5)
Osteoarthritis	61 (0.6)	80 (0.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	358 (3.5)	368 (3.6)
Nervous system disorders	537 (5.3)	514 (5.1)
Syncope	73 (0.7)	74 (0.7)
Convulsion	62 (0.6)	64 (0.6)
Carotid artery stenosis	58 (0.6)	61 (0.6)
Dizziness	48 (0.5)	39 (0.4)
Headache	47 (0.5)	30 (0.3)
Epilepsy	44 (0.4)	31 (0.3)
Psychiatric disorders	142 (1.4)	101 (1.0)
Depression	45 (0.4)	28 (0.3)
Renal and urinary disorders	194 (1.9)	182 (1.8)
Renal failure acute	77 (0.8)	66 (0.7)

Reproductive system and breast disorders	51 (0.5)	61 (0.6)
Respiratory, thoracic and mediastinal disorders	226 (2.2)	202 (2.0)
Chronic obstructive pulmonary disease	41 (0.4)	47 (0.5)
Skin and subcutaneous tissue disorders	40 (0.4)	42 (0.4)
Vascular disorders	185 (1.8)	195 (1.9)
Hypotension	40 (0.4)	42 (0.4)
Hypertension	38 (0.4)	42 (0.4)

APPENDIX IIB: Frequency [N (%)] of most commonly reported adverse events leading to permanent treatment discontinuation (at least 0.1% at the patient level in any group) by treatment, primary system organ class and preferred term (treated patients).

	ASA-ERDP N (%)	Clopidogrel N (%)
Number of patients	10055 (100.00)	10040 (100.00)
Total with adverse events leading to treatment discontinuation	1650 (16.41)	1069 (10.65)
Blood and lymphatic system disorders	16 (0.16)	17 (0.17)
Cardiac disorders	216 (2.15)	249 (2.48)
Atrial fibrillation	122 (1.21)	143 (1.42)
Angina unstable	23 (0.23)	30 (0.30)
Angina pectoris	22 (0.22)	12 (0.12)
Palpitations	13 (0.13)	3 (0.03)
Coronary artery disease	8 (0.08)	12 (0.12)
Ear and labyrinth disorders	20 (0.20)	13 (0.13)
Vertigo	19 (0.19)	13 (0.13)
Gastrointestinal disorders	479 (4.76)	228 (2.27)
Vomiting	158 (1.57)	37 (0.37)
Nausea	155 (1.54)	58 (0.58)
Diarrhoea	102 (1.01)	42 (0.42)
Abdominal pain upper	33 (0.33)	21 (0.21)
Abdominal discomfort	25 (0.25)	7 (0.07)
Abdominal pain	15 (0.15)	9 (0.09)

Dyspepsia	12 (0.12)	8 (0.08)
Gastrointestinal disorder	12 (0.12)	4 (0.04)
Gastritis	11 (0.11)	9 (0.09)
Gastrointestinal haemorrhage	11 (0.11)	7 (0.07)
Dysphagia	7 (0.07)	11 (0.11)
General disorders and administration site conditions	116 (1.15)	57 (0.57)
Fatigue	25 (0.25)	14 (0.14)
Asthenia	21 (0.21)	12 (0.12)
Chest pain	15 (0.15)	5 (0.05)
Pain	13 (0.13)	2 (0.02)
Malaise	10 (0.10)	7 (0.07)
Immune system disorders	8 (0.08)	11 (0.11)
Infections and Infestations	45 (0.45)	40 (0.40)
Pneumonia	15 (0.15)	16 (0.16)
Injury, poisoning and procedural complications	23 (0.23)	43 (0.43)
Contusion	0 (0.00)	12 (0.12)
Investigations	26 (0.26)	14 (0.14)
Metabolism and nutrition disorders	24 (0.24)	14 (0.14)
Anorexia	10 (0.10)	2 (0.02)
Musculoskeletal and connective tissue disorders	70 (0.70)	43 (0.43)
Myalgia	31 (0.31)	15 (0.15)
Arthralgia	12 (0.12)	9 (0.09)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	81 (0.81)	87 (0.87)
Lung neoplasm malignant	7 (0.07)	10 (0.10)

Neoplasm malignant	5 (0.05)	10 (0.10)
Nervous system disorders	719 (7.15)	180 (1.79)
Headache	593 (5.90)	87 (0.87)
Dizziness	134 (1.33)	52 (0.52)
Syncope	8 (0.08)	10 (0.10)
Psychiatric disorders	46 (0.46)	26 (0.26)
Depression	13 (0.13)	8 (0.08)
Renal and urinary disorders	29 (0.29)	22 (0.22)
Respiratory, thoracic and mediastinal disorders	37 (0.37)	38 (0.38)
Skin and subcutaneous tissue disorders	63 (0.63)	88 (0.88)
Rash	26 (0.26)	35 (0.35)
Pruritus	9 (0.09)	10 (0.10)
Surgical and medical procedures	24 (0.24)	17 (0.17)
Vascular disorders	87 (0.87)	77 (0.77)
Hypotension	54 (0.54)	35 (0.35)

APPENDIX III: Calculation of stroke risk score.

Before database lock, a stroke risk score was generated from the blinded trial data by considering all baseline characteristics from five selected risk scores from the literature (Framingham, SPI-II, Essen, NOMASS-7, NOMAS global vascular risk) in a Cox regression model. The final model included all statistically significant predictors of stroke: age, gender, physical activity, baseline systolic blood pressure, history of hypertension, diabetes, previous MI, atrial fibrillation, peripheral arterial disease, and stroke prior to qualifying event. The risk score for PRoFESS is calculated as the sum of the linear combination of the above 10 variables. The weight of each variable is the corresponding coefficient: ((Age-48) X 0.2 (e.g., add 0.2 for each year older than 48) + Gender male X 2 + Physical activity classified as sedentary X 2 + (Baseline systolic BP – 90) X 0.05 (e.g., add 0.05 for each SBP unit > 90) + History of Hypertension X 2 + Diabetes mellitus X 4 + Previous MI X 2 + Atrial fibrillation X 3 + PAOD X 3 + Stroke in addition to qualifying event X 6).

Within PRoFESS, incidences of stroke for each stroke risk score tertile were: Low risk: 5.5%; Moderate risk: 8.1%; High risk: 13.3%