SUPPLEMENTAL MATERIAL

Supplemental Methods

Subcategories of Peripheral Vascular Disease (PVD) Data Set

Studies of primary and secondary prevention of vascular events were included if there was specific inclusion of patients with history of stroke, carotid disease, or lower extremity peripheral artery disease (PAD). Within the category of lower extremity PAD, given that critical limb ischemia (CLI) by definition includes ulceration or ischemic rest pain secondary to significant PAD, the subcategory of CLI trials included those trials that explicitly enrolled PAD patients with arterial ulceration or rest pain and investigated CLI treatment. Meanwhile, the arterial ulceration subcategory of lower extremity PAD studies included those studies that did not specifically define whether patients had flow-limiting PAD and those studies which specifically documented that patients had adequate arterial perfusion (such as therapies investigating treatment of diabetic foot ulcers). Studies enrolling patients with extra-cardiac vascular disease with the endpoints examining plaque regression, plaque stabilization, decrease in inflammatory biomarkers, improvements in endothelial function, and measurements of arterial vessel intimal medial thickness were categorized under the prevention of vascular events category. The subgroups of venous studies are described in Figure 1. Studies were allowed to be in more than 1 subgroup if they enrolled patients categorized within different subgroups (e.g., studies enrolling patients with both arterial and venous ulceration were included in both the arterial ulceration subgroup and venous ulceration subgroup). Venous ulcers were included if they were CEAP class 5 or above. Trials of therapies for pressure ulcers were excluded if they enrolled patients with only pressure ulcers but did not include patients with arterial or venous ulcers.

Development of Cardiology Data Set

The cardiology subset was identified using the same method used to identify the PVD subset. Two Duke cardiologists reviewed a subset of the 2010 MeSH thesaurus and frequently occurring free-text condition terms for relevance to cardiovascular disease. An initial subset of 3503 studies were identified with at least 1 MeSH or condition term relevant to cardiovascular disease.

The cardiologists manually reviewed individual studies and their listed conditions to identify those related to cardiovascular disease in adult patients. They included only those that enrolled adults (maximum age ≥18 years) and studied conditions related to the diagnosis, treatment, or prevention of diseases of the heart (e.g., cardiovascular diseases, disorders of heart structure or function, or cardiovascular imaging). Conditions related to venous and pulmonary embolic disease; general risk factors such as diabetes, smoking, and hypertension in patients without coexisting cardiology disease; and other non-cardiology populations or conditions were excluded. Studies enrolling healthy volunteers were reviewed, and those that specified no cardiac

disease state were excluded. This left a final population of 2325 clinical studies. Those 248 studies that were also identified under the PVD data set were excluded from the cardiology data set (n=2077) for the analysis presented in this manuscript.

Derivation of Assumed Funding Source

If the lead sponsor was from private industry, or the National Institutes of Health (NIH) was neither a lead sponsor nor collaborator and at least 1 collaborator was from industry, then the study was categorized as industry-funded. If the lead sponsor was not from industry, and the NIH was either a lead sponsor or a collaborator, then the study was categorized as NIH-funded. Otherwise, if the lead sponsor and collaborator fields were non-missing, then the study was considered to be funded by other sources.

Supplemental Tables

Table 1. Characteristics of Arterial Disease Trials

	Acute stroke		Renal vascular disease	Supra-aortic vascular disease		Aortic		Lower extremity peripheral artery disease				Primary and secondary prevention	Raynaud's or scleroderma
	Ischemic N=77	Hemorrhagic N=46	N=9	Intra-cranial N=15	Extra-cranial N=18	Thoracic N=29	Abdominal/ aortoiliac N=39	Intermittent claudication N=98	Critical limb ischemia N=91	Acute limb ischemia N=3	Arterial ulceration N=48	N=82	N=12
Masking													
Open	28/76 (36.8%)	20/46 (43.5%)	7/9 (77.8%)	12/15 (80.0%)	13/16 (81.3%)	22/29 (75.9%)	32/39 (82.1%)	57/98 (58.2%)	64/91 (70.3%)	2/3 (66.7%)	26/48 (54.2%)	20/82 (24.4%)	4/12 (33.3%)
Single blind	6/76 (7.9%)	6/46 (13.0%)	0/9 (0.0%)	0/15 (0.0%)	2/16 (12.5%)	0/29 (0.0%)	3/39 (7.7%)	21/98 (21.4%)	10/91 (11.0%)	0/3 (0.0%)	4/48 (8.3%)	9/82 (11.0%)	0/12 (0.0%)
Double blind	42/76 (55.3%)	20/46 (43.5%)	2/9 (22.2%)	3/15 (20.0%)	1/16 (6.3%)	7/29 (24.1%)	4/39 (10.3%)	20/98 (20.4%)	17/91 (18.7%)	1/3 (33.3%)	18/48 (37.5%)	53/82 (64.6%)	8/12 (66.7%)
Allocation													
Randomized	62/76 (81.6%)	32/46 (69.6%)	7/9 (77.8%)	8/15 (53.3%)	7/16 (43.8%)	9/29 (31.0%)	10/38 (26.3%)	62/98 (63.3%)	50/91 (54.9%)	2/3 (66.7%)	39/48 (81.3%)	77/82 (93.9%)	8/12 (66.7%)
Non-randomized	14/76 (18.4%)	14/46 (30.4%)	2/9 (22.2%)	7/15 (46.7%)	9/16 (56.3%)	20/29 (69.0%)	28/38 (73.7%)	36/98 (36.7%)	41/91 (45.1%)	1/3 (33.3%)	9/48 (18.8%)	5/82 (6.1%)	4/12 (33.3%)
Intervention types*													
Drug	51/77 (66.2%)	34/46 (73.9%)	4/9 (44.4%)	3/15 (20.0%)	3/18 (16.7%)	9/29 (31.0%)	5/39 (12.8%)	20/98 (20.4%)	15/91 (16.5%)	0/3 (0.0%)	18/48 (37.5%)	68/82 (82.9%)	11/12 (91.7%)
Device	13/77 (16.9%)	4/46 (8.7%)	7/9 (77.8%)	10/15 (66.7%)	12/18 (66.7%)	18/29 (62.1%)	26/39 (66.7%)	52/98 (53.1%)	45/91 (49.5%)	2/3 (66.7%)	17/48 (35.4%)	3/82 (3.7%)	1/12 (8.3%)
Procedure	4/77 (5.2%)	6/46 (13.0%)	4/9 (44.4%)	4/15 (26.7%)	6/18 (33.3%)	3/29 (10.3%)	10/39 (25.6%)	18/98 (18.4%)	18/91 (19.8%)	1/3 (33.3%)	11/48 (22.9%)	4/82 (4.9%)	0/12 (0.0%)
Behavioral	1/77 (1.3%)	0/46 (0.0%)	0/9 (0.0%)	0/15 (0.0%)	0/18 (0.0%)	0/29 (0.0%)	0/39 (0.0%)	10/98 (10.2%)	1/91 (1.1%)	0/3 (0.0%)	1/48 (2.1%)	7/82 (8.5%)	0/12 (0.0%)
Genetic or biologic	7/77 (9.1%)	2/46 (4.3%)	0/9 (0.0%)	0/15 (0.0%)	0/18 (0.0%)	0/29 (0.0%)	0/39 (0.0%)	2/98 (2.0%)	15/91 (16.5%)	0/3 (0.0%)	3/48 (6.3%)	1/82 (1.2%)	0/12 (0.0%)
Arm types†													
Active comparator	25/68 (36.8%)	15/43 (34.9%)	5/9 (55.6%)	8/15 (53.3%)	8/16 (50.0%)	8/19 (42.1%)	9/28 (32.1%)	39/82 (47.6%)	29/79 (36.7%)	2/3 (66.7%)	20/42 (47.6%)	45/81 (55.6%)	3/8 (37.5%)
No intervention arm	9/68 (13.2%)	6/43 (14.0%)	0/9 (0.0%)	1/15 (6.7%)	0/16 (0.0%)	0/19 (0.0%)	2/28 (7.1%)	6/82 (7.3%)	7/79 (8.9%)	0/3 (0.0%)	3/42 (7.1%)	4/81 (4.9%)	0/8 (0.0%)

	Acute stroke		Renal vascular disease	Supra-aortic vascular disease		Aortic		Lower extremity peripheral artery disease				Primary and secondary prevention	Raynaud's or scleroderma
	Ischemic N=77	Hemorrhagic N=46	N=9	Intra-cranial N=15	Extra-cranial N=18	Thoracic N=29	Abdominal/ aortoiliac N=39	Intermittent claudication N=98	Critical limb ischemia N=91	Acute limb ischemia N=3	Arterial ulceration N=48	N=82	N=12
Enrollment[‡]													
Median	119.5	60.0	120.0	250.0	281.0	115.0	100.0	100.0	80.0	250.0	65.0	185.0	45.5
(Q1,Q3)	(36.0,370.0)	(24.0,184.0)	(80.0,150.0)	(85.0,500.0)	(135.0,453.5)	(50.0,250.0)	(44.0,194.0)	(50.0,170.0)	(36.0,150.0)	(54.0,250.0)	(37.5,120.0)	(74.0,475.0)	(18.5,150.0)

Data are n/N (%) except where indicated. Q1 indicates first quartile; Q3, third quartile.

[*]A study may have more than 1 intervention type.

[†]A study may have more than 1 arm type.

‡Enrollment is either anticipated (for studies that had not completed enrollment on September 27, 2010) or actual.

Table 2. Characteristics of Venous Disease Trials

	DVT treatment	DVT/PE prevention	Venous insufficiency	PE treatment	Venous ulceration	Portal hypertension
	N=27	N=77	N=19	N=19	N=46	N=2
Masking						
Open	17/26 (65.4%)	43/76 (56.6%)	10/19 (52.6%)	7/19 (36.8%)	27/46 (58.7%)	1/2 (50.0%)
Single blind	2/26 (7.7%)	5/76 (6.6%)	4/19 (21.1%)	4/19 (21.1%)	4/46 (8.7%)	1/2 (50.0%)
Double blind	7/26 (26.9%)	28/76 (36.8%)	5/19 (26.3%)	8/19 (42.1%)	15/46 (32.6%)	0/2 (0.0%)
Allocation						
Randomized	16/26 (61.5%)	54/75 (72.0%)	17/19 (89.5%)	17/19 (89.5%)	38/46 (82.6%)	2/2 (100.0%)
Non-randomized	10/26 (38.5%)	21/75 (28.0%)	2/19 (10.5%)	2/19 (10.5%)	8/46 (17.4%)	0/2 (0.0%)
Intervention types*						
Drug	19/27 (70.4%)	63/77 (81.8%)	8/19 (42.1%)	18/19 (94.7%)	12/46 (26.1%)	0/2 (0.0%)
Device	4/27 (14.8%)	10/77 (13.0%)	4/19 (21.1%)	2/19 (10.5%)	23/46 (50.0%)	1/2 (50.0%)
Procedure	0/27 (0.0%)	2/77 (2.6%)	6/19 (31.6%)	0/19 (0.0%)	5/46 (10.9%)	2/2 (100.0%)
Behavioral	1/27 (3.7%)	0/77 (0.0%)	0/19 (0.0%)	0/19 (0.0%)	2/46 (4.3%)	0/2 (0.0%)
Genetic or biologic	0/27 (0.0%)	2/77 (2.6%)	0/19 (0.0%)	0/19 (0.0%)	2/46 (4.3%)	0/2 (0.0%)
Arm types†						
Active comparator	11/23 (47.8%)	41/73 (56.2%)	12/18 (66.7%)	12/17 (70.6%)	20/39 (51.3%)	2/2 (100.0%)
No intervention arm	5/23 (21.7%)	11/73 (15.1%)	2/18 (11.1%)	0/17 (0.0%)	6/39 (15.4%)	0/2 (0.0%)
Enrollment‡						
Median	289.5	300.0	180.0	129.0	62.0	141.5
(Q1,Q3)	(50.0,692.0)	(100.0,669.0)	(105.0,280.0)	(41.0,1000)	(25.0,200.0)	(130.0,153.0)

Data are n/N (%) except where indicated. DVT indicates deep vein thrombosis; PE, pulmonary embolus; Q1, first quartile; Q3, third quartile.

*A study may have more than 1 intervention type.

†A study may have more than 1 arm type.

‡Enrollment is either anticipated (for studies that had not completed enrollment on September 27, 2010) or actual.