

SUPPLEMENTAL MATERIAL

Supplemental Table 1. Definition of Microvascular Diseases

Microvascular Disease	ICD-9 Code/Condition
Peripheral neuropathy	
Due to secondary diabetes	249.6
Diabetes	250.6, 355.8, 355.9
Idiopathic	337.0, 337.00, 337.09, 337.1
Polyneuropathy	356.9
Uremic	585.9
Retinopathy	
Secondary Diabetes with Ophthalmic manifestations	249.5
Diabetes with Ophthalmic manifestations	250.5
Diabetic retinopathy	362.01-6
Other intraretinal microvascular abnormalities	362.17
Other background retinopathy	362.11-14
Retinal vascular occlusion	362.3
Nephropathy	
Renal Disease	Presence of Proteinuria

Supplemental Table 2. Definition of PAD

ICD-9 Diagnosis and ICD-9 Procedure codes used in ascertaining PAD cases (Inclusion Codes)		
<i>Description</i>	<i>ICD-9 Diagnosis Codes</i>	
Atherosclerosis of Native Arteries of the Lower Extremities	440.20, 440.21, 440.22, 440.23, 440.24, 440.29, 440.30, 440.31, 440.32, 440.8, 440.9, 443.9	
<i>Description</i>	<i>ICD-9 Procedure Codes</i>	<i>CPT Codes</i>
Lower Extremity Peripheral Angioplasty, Atherectomy, or Endarterectomy	38.81, 39.50	35302, 35303, 35304, 35305, 35306, 35331, 35351, 35355, 35361, 35363, 35371, 35372, 35381, 35452, 35454, 35456, 35459, 35470, 35472, 35473, 35474, 35481, 35482, 35483, 35485, 35491, 35492, 35493, 35495
Lower Extremity Peripheral Bypass	39.25, 39.29	35521, 35533, 35537, 35538, 35539, 35540, 35541, 35546, 35548, 35549, 35551, 35556, 35558, 35563, 35565, 35566, 35571, 35582, 35583, 35585, 35587, 35621, 35623, 35637, 35638, 35641, 35646, 35647, 35651, 35654, 35656, 35661, 35663, 35665, 35666, 35671
Repair, Exploration, Revision, Resection of Lower Extremity Arteries, or Thrombectomy of Graft	38.08, 38.38, 38.48, 39.49, 39.56, 39.57, 39.58	35226, 35256, 35286, 35700, 35721, 35741, 35876, 35879, 35881, 35883, 35884
Non-Coronary Vessel Percutaneous Transluminal Mechanical Thrombectomy, or Stents	39.90	37184, 37185, 37186, 37205, 37206, 37207, 37208
Diagnostic Procedures	38.29, 88.42, 88.48, 88.77	75630, 75631, 75710, 75711, 75712, 75716, 75717, 75718, 93925, 93926, 93978, 74175, 72191, 73706, 75635, 74185, 72198, 73725, 93922, 93924
ICD-9-CM Diagnosis Codes Used to Exclude Non-Atherosclerotic Causes of PAD and Procedures with Non-PAD Indications (Exclusion Codes)		
<i>Description</i>	<i>ICD-9 Diagnosis Codes</i>	

Non-Atherosclerotic Causes of PAD	237.70, 237.71, 237.72, 237.73, 237.79, 443.1, 446.0, 446.4, 446.5, 446.6, 446.7, 447.6, 710.1, 747.1, 747.22, 747.64
Lower Extremity Trauma/Injury and Others	736.30, 736.31, 736.32, 736.39, 736.4, 736.41, 736.42, 736.5, 736.6, 736.70, 736.71, 736.72, 736.73, 736.74, 736.75, 736.76, 736.79, 736.81, 736.89, 736.9, 735.0, 735.1, 735.2, 735.3, 735.4, 735.5, 735.8, 735.9, 754.30, 754.31, 754.32, 754.33, 754.35, 754.40, 754.41, 754.42, 754.43, 754.44, 754.50, 754.51, 754.52, 754.53, 754.59, 754.60, 754.61, 754.62, 754.69, 754.70, 754.71, 754.79, 755.02, 755.13, 755.14, 755.30, 755.31, 755.32, 755.33, 755.34, 755.35, 755.36, 755.37, 755.38, 755.39, 755.4, 755.60, 755.61, 755.62, 755.63, 755.64, 755.65, 755.66, 755.67, 755.69, 755.8, 759.7, 759.89, 890.0, 890.1, 890.2, 891.0, 891.1, 891.2, 895.0, 895.1, 896.0, 896.1, 896.2, 896.3, 897.0, 897.1, 897.2, 897.3, 897.4, 897.5, 897.6, 897.7, 820.00, 820.01, 820.02, 820.03, 820.09, 820.10, 820.11, 820.12, 820.13, 820.19, 820.20, 820.21, 820.22, 820.30, 820.31, 820.32, 820.8, 820.9, 821.00, 821.01, 821.10, 821.11, 821.20, 821.21, 821.22, 821.23, 821.29, 821.30, 821.31, 821.32, 821.33, 821.39, 822.0, 822.1, 823.00, 823.01, 823.02, 823.10, 823.11, 823.12, 823.20, 823.21, 823.22, 823.30, 823.31, 823.32, 823.40, 823.41, 823.42, 823.80, 823.81, 823.82, 823.90, 823.91, 823.92, 824.0, 824.1, 824.2, 824.3, 824.4, 824.5, 824.6, 824.7, 824.8, 824.9, 825.0, 825.1, 825.20, 825.21, 825.22, 825.23, 825.24, 825.25, 825.29, 825.30, 825.31, 825.32, 825.33, 825.34, 825.35, 825.39, 826.0, 826.1, 827.0, 827.1, 828.0, 828.1, 829.0, 829.1, 835.00, 835.01, 835.02, 835.03, 835.10, 835.11, 835.12, 835.13, 836.0, 836.1, 836.2, 836.3, 836.4, 836.50, 836.51, 836.52, 836.53, 836.54, 836.59, 836.60, 836.61, 836.62, 836.63, 836.64, 836.69, 837.0, 837.1, 838.00, 838.01, 838.02, 838.03, 838.04, 838.05, 838.06, 838.09, 838.10, 838.11, 838.12, 838.13, 838.14, 838.15, 838.16, 838.19, 904.0, 904.1, 904.2, 904.3, 904.40, 904.41, 904.42, 904.50, 904.51, 904.52, 904.53, 904.54, 904.6, 904.7, 904.8, 904.9, 928.00, 928.01, 928.10, 928.11, 928.20, 928.21, 928.3, 928.8, 928.9, 929.0, 929.9, 959.6, 959.7, 996.40, 996.41, 996.42, 996.43, 996.44, 996.45, 996.46, 996.47, 996.49, 996.66, 996.67, 996.78
Amputation with Non-PAD Indications	170.6, 170.7, 170.8, 170.9, 171.3, 172.7, 173.70, 173.71, 173.72, 173.79, 198.5, 344.1, 711.00, 711.01, 711.02, 711.03, 711.04, 711.05, 711.06, 711.07, 711.08, 711.09, 728.6, 733.20, 733.21, 733.22, 733.29, 736.30, 736.31, 736.32, 736.39, 736.41, 736.42, 736.5, 736.6, 736.70, 736.71, 736.72, 736.73, 736.74, 736.75, 736.76, 736.79, 736.81, 736.89, 736.9, 735.0, 735.1, 735.2, 735.3, 735.4, 735.5, 735.8, 735.9, 754.30, 754.31, 754.32, 754.33, 754.35, 754.40, 754.41, 754.42, 754.43, 754.44, 754.50, 754.51, 754.52, 754.53, 754.59, 754.60, 754.61, 754.62, 754.69, 754.70, 754.71, 754.79, 755.02, 755.13, 755.14, 755.30, 755.31, 755.32, 755.33, 755.34, 755.35, 755.36, 755.37, 755.38, 755.39, 755.4, 755.60, 755.61, 755.62, 755.63, 755.64, 755.65, 755.66, 755.67, 755.69, 755.8, 759.7, 759.89, 890.0, 890.1, 890.2, 891.0, 891.1, 891.2, 895.0, 895.1, 896.0, 896.1, 896.2, 896.3, 897.0, 897.1, 897.2, 897.3, 897.4, 897.5, 897.6, 897.7, 820.00, 820.01, 820.02, 820.03, 820.09, 820.10, 820.11, 820.12, 820.13, 820.19, 820.20, 820.21, 820.22, 820.30, 820.31, 820.32, 820.8, 820.9, 821.00, 821.01, 821.10, 821.11, 821.20, 821.21, 821.22, 821.23, 821.29, 821.30, 821.31, 821.32, 821.33, 821.39, 822.0, 822.1, 823.00, 823.01, 823.02, 823.10, 823.11, 823.12, 823.20, 823.21, 823.22, 823.30, 823.31, 823.32, 823.40, 823.41, 823.42, 823.80, 823.81, 823.82, 823.90, 823.91, 823.92, 824.0, 824.1, 824.2,

824.3, 824.4, 824.5, 824.6, 824.7, 824.8, 824.9, 825.0, 825.1, 825.20, 825.21, 825.22, 825.23, 825.24, 825.25, 825.29, 825.30, 825.31, 825.32, 825.33, 825.34, 825.35, 825.39, 826.0, 826.1, 827.0, 827.1, 828.0, 828.1, 829.0, 829.1, 835.00, 835.01, 835.02, 835.03, 835.10, 835.11, 835.12, 835.13, 836.0, 836.1, 836.2, 836.3, 836.4, 836.50, 836.51, 836.52, 836.53, 836.54, 836.59, 836.60, 836.61, 836.62, 836.63, 836.64, 836.69, 837.0, 837.1, 838.00, 838.01, 838.02, 838.03, 838.04, 838.05, 838.06, 838.09, 838.10, 838.11, 838.12, 838.13, 838.14, 838.15, 838.16, 838.19, 904.0, 904.1, 904.2, 904.3, 904.40, 904.41, 904.42, 904.50, 904.51, 904.52, 904.53, 904.54, 904.6, 904.7, 904.8, 904.9, 905.4, 928.00, 928.01, 928.10, 928.11, 928.20, 928.21, 928.3, 928.8, 928.9, 929.0, 929.9, 959.6, 959.7, 996.40, 996.41, 996.42, 996.43, 996.44, 996.45, 996.46, 996.47, 996.49, 996.66, 996.67, 996.78
--

Supplemental Table 3: Baseline Risk of Amputation by combination of Microvascular disease and PAD

Group	N	Events	Incidence Rate per 1000 PY	Unadjusted Model		Adjusted Model	
				Hazard Ratio [95% CI]	p-value	Hazard Ratio [95% CI]	p-value
No Microvascular disease or PAD	109,447	650	0.71	1.00	--	1.00	---
Microvascular disease	9125	252	3.72	5.35 [4.62, 6.19]	<0.0001	2.15 [1.84, 2.51]	<0.0001
PAD	5313	165	4.41	6.37 [5.37, 7.56]	<0.0001	2.83 [2.36, 3.40]	<0.0001
Microvascular disease and PAD	1789	118	11.40	17.47 [14.35, 21.26]	<0.0001	3.62 [2.90, 4.52]	<0.0001
Adjusted Model includes age, sex, race, HIV, prevalent CVD, hypertension, diabetes mellitus, LDL cholesterol, HDL cholesterol, triglycerides, smoking status, HCV Infection, renal failure, BMI, anemia, total bilirubin, alcohol abuse or dependence, cocaine abuse or dependence, and COPD.							

Supplemental Table 4: Distribution of Microvascular Disease Manifestation by Level of Amputation at Time of Amputation In Participants with Isolated Microvascular Disease

Manifestation of Microvascular Disease	Level of Amputation			
	Below Ankle Amputation	Below Knee Amputation	Above Knee Amputation	Unknown Location
Retinopathy	43 (9%)	5 (3%)	4 (5%)	2 (14%)
Nephropathy	13 (3%)	4 (3%)	6 (7%)	1 (7%)
Neuropathy	47 (10%)	18 (12%)	15 (18%)	1 (7%)
Retinopathy and Nephropathy	59 (12%)	17 (11%)	3 (4%)	2 (14%)
Retinopathy and Neuropathy	68 (14%)	27 (18%)	16 (19%)	1 (7%)
Nephropathy and Neuropathy	72 (15%)	29 (19%)	24 (28%)	2 (14%)
All Three	183 (38%)	54 (35%)	17 (20%)	5 (36%)
<i>Number of Amputations</i>	<i>485</i>	<i>154</i>	<i>85</i>	<i>14</i>

Cells contain column percentages

There is an association between level of amputation and microvascular disease manifestation ($\chi^2=38.1$, $df=18$, $p=0.004$).

Supplemental Table 5. Time-Updated Risk of Amputation by combination of Microvascular disease and PAD among those with Diabetes Mellitus

Group	Person-Years	Events	Incidence Rate per 1000 PY	Unadjusted Model		Adjusted Model	
				Hazard Ratio [95% CI]	p-value	Hazard Ratio [95% CI]	p-value
No Microvascular disease or PAD	82,199	88	1.07	1.00	---	1.00	---
Microvascular disease	45,345	168	3.70	3.30 [2.55, 4.27]	<0.0001	3.05 [2.35, 3.96]	<0.0001
PAD	13,120	111	8.46	7.71 [5.81, 10.23]	<0.0001	7.85 [5.89, 10.47]	<0.0001
Microvascular disease and PAD	19,420	405	20.85	18.18 [14.35, 23.02]	<0.0001	15.94 [12.35, 20.57]	<0.0001
Adjusted Model includes age, sex, race, HIV, prevalent CVD, hypertension, LDL cholesterol, HDL cholesterol, triglycerides, smoking status, HCV Infection, renal failure, BMI, anemia, total bilirubin, alcohol abuse or dependence, cocaine abuse or dependence, and COPD.							

Supplemental Table 6. Risk of MACE by combination of Microvascular Disease and PAD

MACE defined as Death, AMI, and revascularization							
Group	N	Events	Incidence Rate per 1000 PY	Unadjusted Model		Adjusted Model	
				Hazard Ratio [95% CI]	p-value	Hazard Ratio [95% CI]	p-value
No Microvascular disease or PAD	95,895	16,996	21.65	1.00	--	1.00	---
Microvascular disease	6773	2165	42.64	1.98 [1.90, 2.07]	<0.0001	1.17 [1.11, 1.22]	<0.0001
PAD	2432	1013	58.03	2.70 [2.53, 2.87]	<0.0001	1.60 [1.50, 1.71]	<0.0001
Microvascular disease and PAD	620	314	81.76	3.85 [3.44, 4.31]	<0.0001	1.54 [1.37, 1.73]	<0.0001
MACE defined as AMI and Revascularization							
Group	N	Events	Incidence Rate per 1000PY	Unadjusted Model		Adjusted Model	
				Hazard Ratio [95% CI]	p-value	Hazard Ratio [95% CI]	p-value
No Microvascular disease or PAD	95,895	3660	4.65	1.00	--	1.00	---
Microvascular disease	6773	527	10.37	2.27 [2.07, 2.49]	<0.0001	1.43 [1.30, 1.57]	<0.0001
PAD	2432	218	12.46	2.73 [2.38, 3.13]	<0.0001	1.67 [1.45, 1.92]	<0.0001
Microvascular disease and PAD	620	93	24.14	5.50 [4.47, 6.75]	<0.0001	2.22 [1.79, 2.75]	<0.0001
Adjusted Model includes age, sex, race, HIV, hypertension, diabetes mellitus, LDL cholesterol, HDL cholesterol, triglycerides, smoking status, HCV Infection, renal failure, BMI, anemia, total bilirubin, alcohol abuse or dependence, cocaine abuse or dependence, and COPD.							
Those with Prevalent CVD are excluded from these analyses.							