SUPPLEMENTAL MATERIAL

Supplemental Figure S1 and Figure Legend

Supplemental Tables S1 through S8

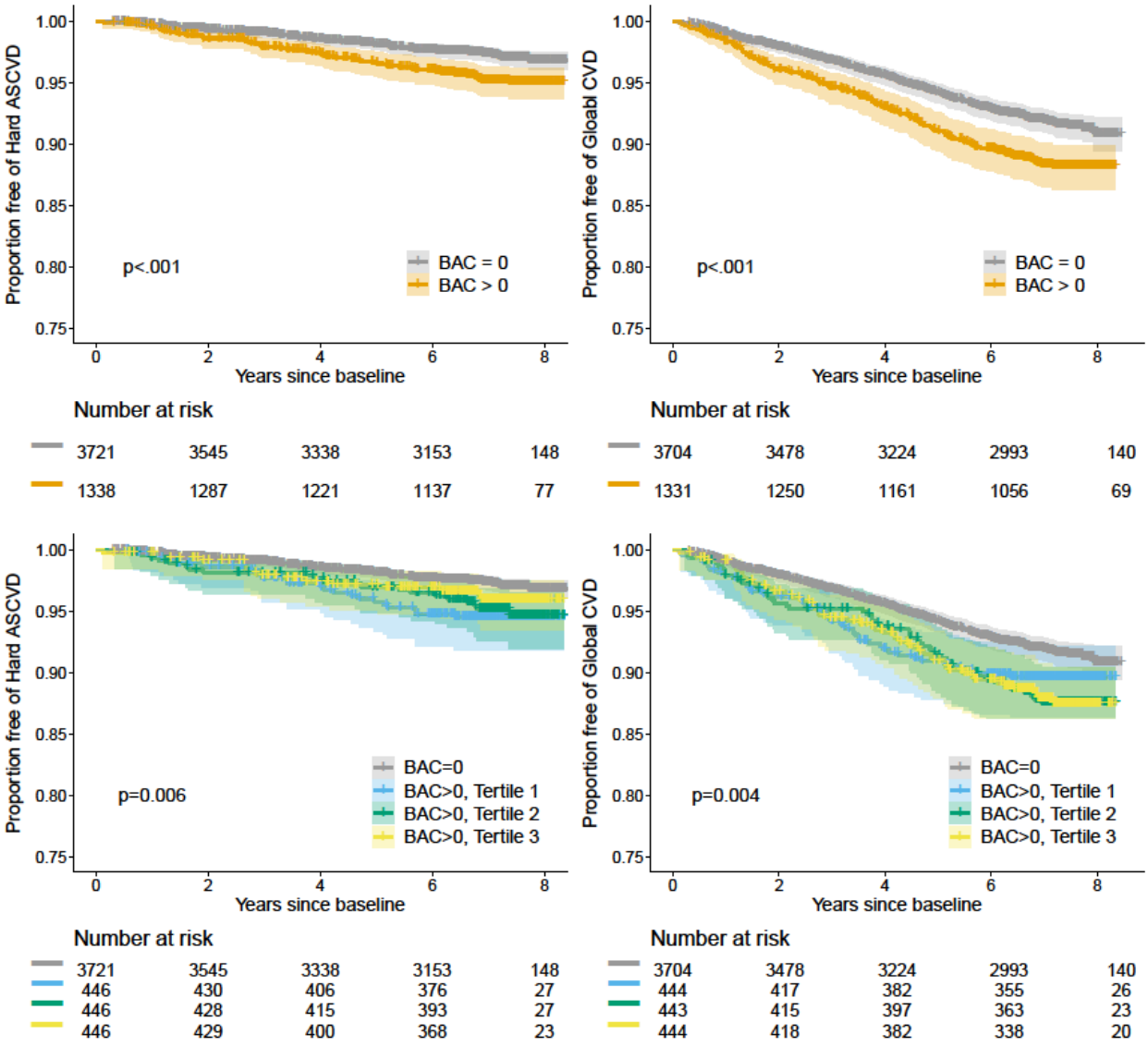
Proportion free of Hard ASCVD
1.00
0.95
0.90
0.85
0.80
0.75
p<.001
BAC = 0
BAC > 0
0
2
4
6
8
Years since baseline
Number at risk
3721 3545 3338 3153 148
1338 1287 1221 1137 77
Proportion free of Gloabl CVD
p<.001
BAC = 0
BAC > 0
Years since baseline
Number at risk
3704 3478 3224 2993 140
1331 1250 1161 1056 69
Proportion free of Hard ASCVD
p=0.006
BAC=0
BAC>0, Tertile 1
BAC>0, Tertile 2
BAC>0, Tertile 3
Years since baseline
Number at risk
3721 3545 3338 3153 148
446 430 406 376 27
446 428 415 393 27
446 429 400 368 23
Proportion free of Global CVD
p=0.004
BAC=0
BAC>0, Tertile 1
BAC>0, Tertile 2
BAC>0, Tertile 3
Years since baseline
Number at risk
3704 3478 3224 2993 140
444 417 382 355 26
443 415 397 363 23
444 418 382 338 20

Figure Legend

Kaplan-Meier Survival Curves for BAC=0 mg vs. BAC > 0 mg and Tertiles of BAC when BAC Present; BAC: breast arterial calcification.

Table S1. Codes for CVD Outcome Ascertainment.

	ICD-9	ICD-10	CPT4 Procedure Codes
Coronary Heart Disease			
Acute myocardial infarction	410, 412	I21, I22, I25.6	
Coronary angioplasty/stent/bypass graft surgery	36.01, 36.02,36.03,36.05, 36.06, 36.07, 36.09, 36.10, 36.11, 36.12, 36.13, 36.14, 36.15, 36.16, 36.17, 36.19, 36.03, 36.2, 36.3, 00.66, 295.5, V45.81, V45.82	ICD-10-PCS: 0210*, 0211*, 0212*, 0213*, 2703*, 02713*, 02723*, 02733*, Z95.5, Z98.61	92980, 92981, 92982, 92984, 92995, 92996, 92975, 92977, 33510, 33511, 92920, 92921, 92924, 92925, 92928, 92929, 92933, 92934, 92937, 92938, 92941, 92943, 92944, 33510-33536
Cerebrovascular Disease			
Ischemic stroke	433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91, 437.0, 437.1	I63, I67.89, I69.320, I69.398	
Hemorrhagic stroke	430, 431, 432.1, 432.9	I60, I61, I62	
Heart failure	428.**, 402.01, 402.11, 402.91, 398.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93	I50.**, I11.0, I09.81, I13.0, I13.2	
Cardiomyopathy	425.0, 425.18, 425.2, 425.3, 425.4, 425.5, 425.6, 425.7, 425.8, 425.9, 429.8	I42.0, I42.1, I42.2, I42.3, I42.4, I42.5, I42.6, I42.7, I42.8, I42.9, I43.**, I25.5, I51.81	

Deep vein thrombosis\pulmonary embolism	451.9, 362.36, 415.11, 415.12, 415.13, 415.19, 453.2, 453.6, 453.81, 453.82, 453.9	I26.0, I26.99, I80.01, V12.51	
Cardiac arrest	427.5	I46,2, I46.8, I46.9	
Peripheral arterial disease	440, 441, 442, 443, 444, 445, 447, 448	I70, I71, I72, I73, I74, I75, i77, I78, I79	37220, 37221, 37222, 37223, 37224, 37225, 37226, 37227, 37228, 37229, 37230, 37231, 37232, 37233, 37234, 37235
Retinal vascular occlusion	362.3	G45.3, H34.00, H34.01, H34.02, H34.03, H34.9, H34.10, H34.11, H34.12, H34.13, H34.211, H34.212, H34.213, H34.219, H34.231, H34.232, H34.233, H34.239, H34.821, H34.822, H34.823, H34.829, H34.8110, H34.8111, H34.8112, H34.8120, H34.8121, H34.8122, H34.8130, H34.8131, H34.8132, H34.8190, H34.8191, H34.8192, H34.8310, H34.8311, H34.8312, H34.8320, H34.8321, H34.8322, H34.8330, H34.8331, H34.8332, H34.8390, H34.8391, H34.8392	
CVD Death	390-459	I00-I99	

CVD: cardiovascular disease; ICD-9: International classification of diseases 9th revision; ICD-10: International classification of diseases 10th revision; CPT4: current procedure terminology, 4th edition

Table S2. Results of electronic chart review adjudication of 20% of events (n=85)

		Confirmed			Notes
	Total	Yes	No	PPV	
Acute myocardial infarction	10	10	0	100%	
Coronary revascularization	2	2		100%	
Ischemic stroke	14	14	0	100%	
CVD death	7	6	1	86%	see a
Hemorrhagic stroke	3	2	1	67%	see b
PAD	23	22	1	96%	see c
Heart failure	23	20	3	87%	see d
Cardiac arrest	1	1	0	100%	
Cardiomyopathy	1	1	0	100%	
Retinal occlusion	1	1	0	100%	
	85	79	6	93%	

a: 1 false + case was PE in metastatic glioblastoma multiforme of the brain

b: 1 false + case was traumatic subdural hematoma

c: 1 false + case was peripheral neuropathy

d: 3 false + cases: 1 diastolic dysfunction in the context of sepsis, 1 mitral regurgitation, 1 traumatic subdural hematoma and hypervolemia following motor vehicle accident

PPV: positive predictive value; CVD: cardiovascular disease; PE: pulmonary embolism; PAD: peripheral arterial disease

Table S3. Hazard Ratios of ASCVD and Global CVD Associated with BAC Gradation Using Three Different Upper BAC Thresholds.

Hard ASCVD (n=5,059; 155 events)					
	Model 1 HR* (95% CI)	**P**	**Model 2 HR†** (95% CI)	**p**	**Number events/Number subjects**
80th Percentile Threshold					
BAC present ≤ 80th percentile vs. BAC = 0 mg	1.66 (1.17-2.35)	0.004	1.61 (1.13-2.28)	0.008	50/1071
BAC present > 80th percentile vs. BAC = 0 mg	1.24 (0.64-2.42)	0.53	1.21 (0.62-2.35)	0.58	10/267
90th Percentile Threshold					
BAC present ≤ 90th percentile vs. BAC = 0 mg	1.59 (1.31-2.24)	0.008	1.54 (1.10-2.17)	0.01	54/1205
BAC present > 90th percentile vs. BAC = 0 mg	1.45 (0.62-3.37)	0.39	1.39 (0.60-3.22)	0.44	6/133
95th Percentile Threshold					
BAC present ≤ 95th percentile vs. BAC = 0 mg	1.56 (1.11-2.18)	0.01	1.51 (1.08-2.11)	0.02	56/1272
BAC present > 95th percentile vs. BAC = 0 mg	1.96 (0.71-5.42)	0.19	1.79 (0.65-4.94)	0.26	4/66
Global CVD (n=5,035; 427 events)					
80th Percentile Threshold					
BAC present ≤ 80th percentile vs. BAC = 0 mg	1.26 (1.01-1.57)	0.04	1.23 (0.99-1.54)	0.07	113/1065
BAC present > 80th percentile vs. BAC = 0 mg	1.34 (0.92-1.94)	0.12	1.32 (0.91-1.91)	0.14	33/266
90th Percentile Threshold					
BAC present ≤ 90th percentile vs. BAC = 0 mg	1.19 (0.96-1.48)	0.11	1.17 (0.94-1.45)	0.16	121/1198
BAC present > 90th percentile vs. BAC = 0 mg	2.04 (1.34-3.12)	0.0009	1.98 (1.30-3.01)	0.002	25/133
95th Percentile Threshold					
BAC present ≤ 95th percentile vs. BAC = 0 mg	1.20 (0.97-1.48)	0.10	1.17 (0.95-1.45)	0.14	129/1265
BAC present > 95th percentile vs. BAC = 0 mg	2.90 (1.75-4.79)	<.0001	2.68 (1.62-4.44)	0.0001	17/66

80th, 90th and 95th BAC percentiles among those with BAC present

*age, race, education level

† + glycemic status, smoking, LDL-C and hypertension

BAC: breast arterial calcification; LDL: low-density lipoprotein; CVD: cardiovascular disease; ASCVD: atherosclerotic cardiovascular disease; HR: hazard ratio.

Table S4. ASCVD Risk by Joint Categories of 10-year Pooled Cohort Equations and BAC (n=5,059).

Joint Categories of 10-year Pooled Cohort Equations Risk and Presence vs. Absence of BAC	Number of Women in Category	Number of events	Raw rates per 1,000 person-years	Unadjusted HR (95% CI)	p	Adjusted* HR (95% CI)	p
< 5% with BAC = 0 mg	1343	15	1.73	1.00		1.00	
< 5% with BAC > 0 mg	343	9	3.96	2.28 (1.00-5.21)	0.05	2.28 (1.00-5.21)	0.05
5 to < 7.5% with BAC = 0 mg	852	25	4.49	2.60 (1.37-4.93)	0.004	2.60 (1.37-4.94)	0.003
5 to < 7.5% with BAC > 0 mg	272	6	3.31	1.91 (0.74-4.92)	0.18	1.93 (0.75-4.97)	0.17
7.5 to < 10% with BAC = 0 mg	498	15	4.58	2.64 (1.29-5.41)	0.008	2.65 (1.30-5.42)	0.008
7.5 to < 10% with BAC > 0 mg	190	12	9.49	5.47 (2.56-11.69)	<.0001	5.53 (2.59-11.81)	<.0001
≥ 10% with BAC=0	1028	40	6.00	3.47 (1.92-6.29)	<.0001	3.52 (1.94-6.38)	<.0001
≥ 10% with BAC>0	533	33	9.26	5.35 (2.91-9.85)	<.0001	5.43 (2.94-10.01)	<.0001

Global CVD Risk by Joint Categories of 10-year Pooled Cohort Equations and BAC (n=5,059).

Joint Categories of 10-year Pooled Cohort Equations Risk and Presence vs. Absence of BAC	Number of Women in Category	Number of events	Raw rates per 1,000 person-years	Unadjusted HR (95% CI)	p	Adjusted* HR (95% CI)	p
< 5% with BAC = 0 mg	1339	67	7.88	1.00		1.00	
< 5% with BAC > 0 mg	340	17	7.67	0.98 (0.57-1.66)	0.93	0.98 (0.57-1.66)	0.93
5 to < 7.5% with BAC = 0 mg	849	57	10.49	1.33 (0.93-1.89)	0.12	1.33 (0.93-1.89)	0.12
5 to < 7.5% with BAC > 0 mg	272	23	13.15	1.68 (1.04-2.69)	0.03	1.67 (1.04-2.68)	0.03
7.5 to < 10% with BAC = 0 mg	496	47	14.96	1.89 (1.30-2.75)	0.0008	1.89 (1.30-2.74)	0.0008
7.5 to < 10% with BAC > 0 mg	188	19	15.42	1.96 (1.18-3.26)	0.01	1.95 (1.17-3.24)	0.01
≥ 10% with BAC=0	1020	110	17.31	2.19 (1.62-2.97)	<.0001	2.18 (1.61-2.95)	<.0001
≥ 10% with BAC>0	531	87	26.08	3.32 (2.41-4.56)	<.0001	3.29 (2.39-4.53)	<.0001

*adjusted for education level

BAC: breast arterial calcification; CVD: cardiovascular disease; ASCVD: atherosclerotic cardiovascular disease; HR: hazard ratio.

Table S5. Calibration, Discrimination and Reclassification of ASCVD (n=5,059).

Variables in the Model	
Calibration (Greenwood-D'Agostino-Nam Test) Chi-square (df); p-value	
PCE only	8.0 (df=9); 0.53
PCE, BAC (0 vs > 0 mg)	8.3 (df=9); 0.51
PCE, BAC (4-level variable)*	16.9 (df=9); 0.05
Discrimination C-index (95% CI); p-value	
PCE only	63.4 (59.3, 67.4)
PCE, BAC (0 vs > 0 mg)	64.3 (60.3, 68.5) 0.28
PCE, BAC (4-level variable)*	64.0 (60.0, 68.0) 0.27
Overall Category-based† Net Reclassification Improvement [NRI] (95% CI); p-value	
Adding BAC (0 vs > 0 mg)	0.12 (0.03,0.22); 0.01
Adding BAC (4-level variable)*	0.07 (0.00,0.14); 0.06
Bias-corrected clinical Net Reclassification Improvement [cNRI] (95% CI); p-value	
Adding BAC (0 vs >0 mg)	0.11 (0.01,0.22); 0.04
Adding BAC (4-level variable)*	0.07 (0.00,0.15); 0.07

* 4-levels of BAC: BAC=0 and tertiles when BAC > 0 mg
PCE was transformed using a log(-log(1-x)) function
Categories of PCE: <5%, 5 to <7.5%, 7.5 to <20%, ≥ 20%

Table S6.

NRI reclassification table for expected ASCVD events by Kaplan-Meier using 5-year time horizon

Model with PCE only	Model with PCE + BAC (0 vs. > 0 mg)			
	<5%	5 to < 7.5%	7.5 to < 20%	>=20%
<5%	13	4	1	0
5 to < 7.5%	2	17	6	0
7.5 to < 20%	0	4	47	7
>=20%	0	0	3	7

NRI reclassification table for expected non-ASCVD events by Kaplan-Meier using 5-year time horizon

Model with PCE only	Model with PCE + BAC (0 vs. > 0 mg)			
	<5%	5 to < 7.5%	7.5 to < 20%	>=20%
<5%	1,446	187	34	0
5 to < 7.5%	372	460	265	0
7.5 to < 20%	0	357	1,310	157
>=20%	0	0	107	246

NRI + = 0.084; NRI - = 0.039; NRI = 0.123
Crude clinical NRI = 0.189; Expected clinical NRI = 0.074; corrected clinical NRI = 0.115
BAC: breast arterial calcification; ASCVD: atherosclerotic cardiovascular disease; NRI: net reclassification improvement; PCE: pooled cohorts equation

NRI reclassification table for expected ASCVD events by Kaplan-Meier using 5-year time horizon

Model with PCE only	Model with PCE + 4-level BAC variable using tertiles when BAC>0			
	<5%	5 to < 7.5%	7.5 to < 20%	>=20%
<5%	14	4	0	0
5 to < 7.5%	1	20	4	0
7.5 to < 20%	0	1	54	3
>=20%	0	0	3	7

NRI reclassification table for expected non-ASCVD events by Kaplan-Meier using 5-year time horizon

Model with PCE only	Model with PCE + 4-level BAC variable using tertiles when BAC>0			
	<5%	5 to < 7.5%	7.5 to < 20%	>=20%
<5%	1,549	117	0	0
5 to < 7.5%	173	792	131	0
7.5 to < 20%	0	165	1,573	85
>=20%	0	0	59	295

*: 4-level categories of BAC: BAC=0 and tertiles of BAC>0

NRI + = 0.056; NRI - = 0.013; NRI = 0.068
Crude clinical NRI = 0.100; Expected clinical NRI = 0.030; corrected clinical NRI = 0.070
BAC: breast arterial calcification; ASCVD: atherosclerotic cardiovascular disease; NRI: net reclassification improvement; PCE: pooled cohorts equation

Table S7. Sensitivity Analysis of Hazard Ratios of ASCVD and Global CVD Associated with BAC Presence and Gradation Among Women not on Cholesterol Lowering Drugs.

	Model 1 HR* (95% CI)	**P**	**Model 2 HR† (95% CI)**	**p**
Hard ASCVD (n=1,143; 25 events)				
BAC Presence vs. Absence Model				
BAC > 0 mg vs. BAC = 0 mg	1.95 (0.88-4.34)	0.10	1.91 (0.86-4.25)	0.11
BAC Gradation Model				
Tertile 1 when BAC is present vs. BAC = 0 mg	2.10 (0.59-6.40)	0.19	2.25 (0.73-6.92)	0.16
Tertile 2 when BAC is present vs. BAC = 0 mg	2.01 (0.66-6.16)	0.22	1.86 (0.59-5.88)	0.29
Tertile 3 when BAC is present vs. BAC = 0 mg	1.71 (0.48-6.07)	0.40	1.62 (0.46-5.76)	0.46
Global CVD (n=1,139; 70 events)				
BAC Presence vs. Absence Model				
BAC > 0 mg vs. BAC = 0 mg	1.05 (0.62-1.75)	0.86	1.07 (0.64-1.80)	0.80
BAC Gradation Model				
Tertile 1 when BAC is present vs. BAC = 0 mg	1.23 (0.58-2.60)	0.59	1.32 (0.62-2.80)	0.47
Tertile 2 when BAC is present vs. BAC = 0 mg	1.13 (0.53-2.40)	0.75	1.12 (0.52-2.40)	0.77
Tertile 3 when BAC is present vs. BAC = 0 mg	0.77 (0.30-1.94)	0.58	0.77 (0.31-1.97)	0.59

*age, race, education level

† + glycemic status, smoking, LDL-C and hypertension

BAC: breast arterial calcification; ASCVD: atherosclerotic cardiovascular disease; CVD: cardiovascular disease; HR: hazard ratio

Table S8. Hard ASCVD Age-adjusted Rates per 1,000 person-years According to PCE Risk Group, BAC Status and Use of Cholesterol Lowering Therapy.

Women not on Cholesterol Lowering Drugs (n=1,351)			
	BAC		**All**
PCE Risk Group	**0 mg**	**>0 mg**	
Low (< 5)	1 532 0.20	1 124 0.70	2 656 0.30
Borderline (5 to < 7.5)	7 218 4.86	2 83 3.91	9 301 4.55
Intermediate (7.5 to < 20)	12 249 10.59	6 113 14.88	18 362 11.62
High (>= 20)	1 17 31.37	2 15 120.14	3 32 60.34
All	21 1016 3.18	11 335 4.60	32 1351 3.62
Women on Cholesterol Lowering Drugs (n=3,708)			
Low (< 5)	14 811 2.70	8 219 5.79	22 1030 3.45
Borderline (5 to < 7.5)	18 634 4.30	4 189 3.11	22 823 4.02
Intermediate (7.5 to < 20)	35 1074 4.84	28 448 8.41	63 1522 5.74
High (>= 20)	7 186 5.61	9 147 7.37	16 333 6.06
All	74 2705 3.98	49 1003 6.34	123 3708 4.60

Cell entries are (from top to bottom): number of events, number of subjects and age-adjusted ASCVD rate
BAC: breast arterial calcification; ASCVD: atherosclerotic cardiovascular disease; PCE: pooled cohorts equation.