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Benefits Associated with Achieving Optimal Risk Factor Levels for the Primary Prevention of Cardiovascular Disease in Older Men

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Responsibilities

Jennifer G. Robinson, MD, MPH, Catherine Rahilly-Tierney, MD, MPH, and Elizabeth Lawler, MPH, ScD had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Catherine Rahilly-Tierney, MD, MPH, and Elizabeth Lawler, MPH, ScD performed the statistical analyses independently of the sponsor, and were paid by a subcontract with the University of Iowa

Disclosures

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Abstract

Context—Most cardiovascular disease (CVD) occurs after age 65. The additive benefits of aggressive risk factor management with advancing age are not well established.

Objective—Evaluate the relationship between control of 4 modifiable risk factors [smoking, non-high density lipoprotein cholesterol (non-HDL-C), blood pressure, and aspirin use] and CVD risk in a primary prevention population of older men.

Design—Physicians' Health Study participants who in 1997 were ≥ 65 years and had a blood sample. Cox proportional hazard models were adjusted for age and competing causes of death.

Setting—U.S. male physicians from epidemiologic follow-up of a randomized trial of aspirin and beta-carotene.

Participants—4182 men aged ≥ 65 years free of CVD and diabetes.

Main outcome measure—First of any CVD event, defined as cardiovascular death, non-fatal myocardial infarction, angina, coronary revascularization, non-fatal stroke, transient ischemic attack, carotid artery surgery, and other peripheral vascular disease surgery.

Results—Mean follow-up was 9.3 years, mean age was 73 years, and 96% were nonsmokers. Compared to when 4 of 4 risk factors were controlled (6.0% of participants), control of 0 of 4 risk factors almost quadrupled CVD risk (0.4% of participants; event rate 41.2%; HR 3.83, 95% CI 1.72–8.55); control of 1 of 4 risk factors more than double the risk (14.2% of participants; HR 2.53, 95% CI 1.80–3.57); control of 2 of 4 risk factors almost doubled risk (43.8% of participants; HR 1.94, 95% CI 1.41–2.69), and those with control of 3 of 4 risk factors also were at increased risk (35.6% of participants; HR 1.80, 95% CI 1.30–2.50). Control of each additional risk factor was associated with greater cardiovascular protection (p for trend $p=0.002$). Depending on the number of risk factors controlled, the number-needed to control to prevent one CVD event ranged from 5 to 22.

Conclusion—Control of 4 treatable risk factors (nonsmoking, control of non-HDL-C and blood pressure, and aspirin use) were associated with substantial protection against incident cardiovascular events in older men even after adjustment for competing causes of mortality.

The vast burden of cardiovascular disease occurs after age 65.^{1, 2} However, relatively few data are available regarding the benefits of aggressive risk factor management with advancing age. Addressing this knowledge gap is becoming increasingly important as Americans live longer with less disability.³ As “baby-boomers” age, the potential for prevention is even greater, since the number of persons >65 years will double to $>20\%$ of the US population by 2030.⁴

Numerous clinical trials have shown that management of individual risk factors is beneficial in older patients. Moderate-dose statin therapy has been shown to reduce cardiovascular risk in those as old as 80 years with cardiovascular disease or diabetes.⁵ Emerging evidence suggests high dose statin therapy may result in a further reduction in cardiovascular risk over that obtained with moderate dose statin therapy in those aged 65–75 as well as in those <65 years.^{6, 7} Over 80% of those ≥ 70 years have hypertension.⁸ Treatment of hypertension has been shown to be of benefit in those aged 65–80 years and in those >80 years.^{9, 10} Aspirin prophylaxis has also been shown to be beneficial for cardiovascular prevention in those ≥ 65 years.¹¹ Smoking cessation is universally recommended for all smokers.¹²

Physicians are hesitant to treat risk factors in elderly patients for a number of reasons. There is a paucity of efficacy and safety data from statin trials, which have typically excluded subjects >70 –80 years of age.¹³ Competing risks, such as cancer, are often cited as reasons for the futility of preventive efforts in older patients.¹⁴ This is a misconception since of

those <75 years, 25% will die of cardiovascular causes, whereas after age 75, >40% will die of cardiovascular disease.¹⁵ Other factors may also contribute to the hesitation to treat risk factors in older patients, including co-morbid conditions, polypharmacy and drug interactions, tolerability, safety, and perhaps even differing pathophysiology of cardiovascular disease may alter the benefit-harm balance in older patients.^{16–20}

We undertook this study to evaluate the relationship between the intensity of risk factor control and the risk of cardiovascular events in a primary prevention population of men ≥ 65 years. All analyses were adjusted for deaths from noncardiovascular causes in order to determine absolute benefit of risk factor control in the face of competing causes of mortality in aging men.

Methods

This study was approved by the University of Iowa Human Subject's Office and the Institutional Review Board of the Brigham & Women's Hospital. The Physicians' Health Study (PHS; NCT00000500) was a randomized, double-blind, placebo-controlled trial designed to evaluate the roles of aspirin and beta-carotene in the primary prevention of cardiovascular disease and cancer among 22,071 predominantly Caucasian male physicians aged 40–84 years.²¹ At baseline in 1982, all participants were apparently free of diagnosed cardiovascular disease. Data on lifestyle and medical diagnoses were collected by questionnaires prior to randomization, after 6 months, and annually thereafter.

Anthropometric measures including height, weight, and blood pressure on all subjects and blood lipids on a subgroup of the cohort were performed at baseline and again in 1997. This study included only subjects who were ≥ 65 years and free of CVD in 1997 who had information on lipids and other CVD risk factors available in 1997. Approximately 9 years of follow-up occurred after the 1997 blood samples were received.

In 1997, all PHS participants were mailed blood kits which consisted of Vacutainer tubes containing EDTA, instructions for blood draws, and cold packs. Nonfasting blood samples were returned via overnight carrier, and stored at -80°C . A total cholesterol and high density lipoprotein cholesterol were directly measured using laboratory techniques according to the Lipid Research Clinics standards and procedures on a Hitachi 911 analyzer (Roche Diagnostics). Non-HDL-C was calculated by subtracting HDL-C from total cholesterol (mg/dl). Triglycerides were not measured, therefore low density lipoprotein cholesterol (LDL-C) was not calculated. Blood pressure was reported at baseline and in each follow-up questionnaire. Information regarding cholesterol and anti-hypertensive medication was collected at annually.

Subjects were monitored for incident cardiovascular disease with follow-up questionnaires. Deaths were reported by family members and confirmed by review of medical records. All outcomes were confirmed after blinded (to treatment assignment) review of medical records by an Endpoints Committee consisting of a neurologist, a cardiologist, and 2 internists. In PHS, follow-up was 99.7% for nonfatal events and 100% for fatal events.²²

Because diabetes is considered a coronary heart disease (CHD) risk equivalent by widely accepted Adult Treatment Panel (ATP) III guidelines subjects with diabetes diagnosed prior to 1997 were not included in this analysis.²³ Subjects with missing information regarding aspirin use, lipids, smoking, blood pressure, or cholesterol or antihypertensive medication were excluded. The primary endpoint of this study was the first of any cardiovascular disease event, defined as cardiovascular death, non-fatal myocardial infarction, angina, coronary revascularization, non-fatal stroke, transient ischemic attack, carotid artery surgery, and other peripheral vascular disease surgery. The cardiovascular events included in the

primary endpoint were chosen to be similar to the atherosclerotic cardiovascular events included in the general Cardiovascular Risk Profile recently developed by D'Agostino and colleagues.²⁴ Serious comorbidities were self-reported and included chronic obstructive pulmonary disease, congestive heart failure, history of gastrointestinal bleeding, liver disease, renal disease, non-fatal cancer, and cerebrovascular disease, excluding stroke but including transient ischemic attack or carotid artery surgery.

Each of 4 treatable risk factors was assessed for control (dichotomized as yes or no; *high risk* level italicized) as defined by the most recent U.S. prevention guidelines^{25, 26} and classified by drug treatment: non-HDL-C (<130 vs ≥ 130 mg/dl) by cholesterol-modifying drug use, blood pressure (<140/<90 vs ≥ 140 or ≥ 90 mm Hg) by antihypertensive medication use, smoking (no vs yes), and regular aspirin use (yes vs no). HDL-C (<40 vs ≥ 40 mg/dl) was included for informational purposes, pending the results of randomized trials of drugs targeting HDL-C levels. Each subject was given a score according to how well their risk factors are controlled (0, 1, 2, 3, or 4).

Statistical analysis

The association between the level of control of risk factors and the 9-year risk of any cardiovascular event was adjusted for competing causes of mortality using the method of Pencina and d'Agostino.^{27, 28} The primary focus was on the age-adjusted models (adjusted for the other 3 modifiable risk factors when modifiable risk factors were examined individually) since these were considered reflective of the effects observed in clinical trials and more representative of clinical decision-making. However, more fully adjusted models were examined to evaluate potential confounders such as body mass index, physical activity, and HDL-C level. The number-needed-to treat was calculated as the inverse of the absolute rate of any cardiovascular event over the approximate 9 years of follow-up, with follow-up beginning on the date the 1997 blood kit was returned for each subject. Using competing risk analysis, the cumulative incidence of CVD events for a man aged 65 years with 0,1,2,3 or 4 risk factors controlled was estimated and graphed.² SAS version 9.2 (SAS Institute, Inc. Cary, North Carolina) was used.

Results

The study population was comprised of 4182 men aged ≥ 65 years who were free of cardiovascular disease or diabetes in 1997 (Table 1). At baseline, the mean age was 73 years, with a mean non-HDL-C of 161 mg/dl and a mean HDL-C of 45 mg/dl and 14% used a cholesterol-modifying drug. Mean blood pressure was 131/78 mm Hg, 46% were normotensive, and 30% used at least one antihypertensive drug. Aspirin was used by 49% and 4% were current smokers. No serious comorbidities occurred in 36% of men, 47% had one serious comorbidity, and 18% had 2 or more serious comorbidities. During the mean 9.3 years of follow-up, 26% of participants died, primarily of non-cardiovascular causes (77%) [Table 2]. A cardiovascular event was experienced by 28% of participants, with 58% of first events due to CHD, 28% due to cerebrovascular events, and 14% due to other cardiovascular events.

Although cardiovascular risk was still high when non-HDL-C was <130 mg/dl, similar rates were observed in those receiving (22%) and not receiving cholesterol modifying therapy (25%) [Table 3]. After adjustment for blood pressure control, smoking and aspirin use, those with a non-HDL-C <130 mg/dl on drug treatment had a nonsignificant 31% higher cardiovascular risk than those with an untreated non-HDL-C <130 mg/dl. In contrast, those with a non-HDL-C ≥ 130 mg/dl on drug-treatment had a 73% higher risk, and those not receiving drug treatment had a 50% higher risk, than those with untreated non-HDL-C <130

mg/dl. These relationships were not substantively influenced by further adjustment for body mass index, physical activity, and HDL-C.

In contrast to non-HDL-c, where drug treatment substantially ameliorated excess cardiovascular risk, those whose blood pressure was <140/<90 mm Hg on drug therapy had a substantially higher absolute cardiovascular risk (31%) compared to normotensive men (23%), which was similar to those with untreated blood pressure ≥ 140 /or ≥ 90 mm Hg (also 32%). After adjusting for non-HDL-c control, smoking, and aspirin use, those with controlled blood pressure were at 34% higher cardiovascular risk than normotensive men, and those with poorly controlled blood pressure on drug treatment had 69% higher CVD risk. Again, these relationships did not substantively change after further adjustment.

Smokers had a 46% risk of a cardiovascular event during the period of follow-up, which was more than twice that of nonsmokers in both adjusted models. Men not taking aspirin had a significant 16% higher risk for CVD compared to men not taking aspirin.

The analysis by number of risk factors controlled (defined as nonsmoking, non-HDL-C <130 mg/dl, blood pressure <140/<90 mm Hg, and aspirin use) is presented in Table 4. Further adjustment for body mass index, physical activity, and HDL-C minimally attenuated the excess CVD risk of suboptimal risk factor control and the hazard ratios for the fully adjusted models are now presented for each level of risk factor control. Very few participants had none of the four modifiable risk factors controlled (<1%); their 9-year cardiovascular risk was 41%, which was 3.5-fold higher than if all 4 risk factors were controlled. One of four risk factors [usually non-smoking (88%)] was controlled in 14% of men, who had a 37% 9-year cardiovascular risk; their risk was 2.3-fold higher than in those with all 4 risk factors controlled. Two of four risk factors [usually nonsmoking (97%) and blood pressure (63%)] were controlled in 44% of men, who had a 28% 9-year cardiovascular risk; their risk was 1.8-fold higher than in those with all 4 risk factors controlled. Three of four risk factors [usually smoking (100%), blood pressure (93%), and aspirin use (80%)] were controlled in 36% of men, who had a 25% 9-year cardiovascular risk, which was 25% higher than when all 4 risk factors were controlled. Only 6% of men had all 4 risk factors controlled; nonetheless, they still had a 20% 9-year cardiovascular risk. Tests for trend for both the age and adjusted models of risk factor control were significant ($p=0.002$ for the age-adjusted and $p=0.01$ for the fully adjusted models). Most strikingly, only 5 to 8 nonsmoking men needed to have blood pressure or non-HDL-C controlled, or use aspirin, to prevent one cardiovascular event over about 9 years of follow-up.

Figure 1 displays the estimated cumulative incidence of CVD events, adjusted for competing risk of non-CVD death or non-fatal cancer, for a 65 year old man with 0 (blue line), 1 (red line), 2 (green line), 3 (black line), or 4 (purple line) risk factors controlled. Cumulative incidence of CVD events was estimated to be highest among those with no risk factors controlled, and decreased with increasing number of risk factors controlled.

Discussion

In this cohort of older, primarily nonsmoking male physicians, control of non-HDL-C and blood pressure was associated with substantial protection against incident cardiovascular events. Control of none of the 4 risk factors almost quadrupled cardiovascular risk compared to when all 4 risk factors were controlled. Control of each additional modifiable risk factor was associated with significantly reduced risk. Given the high absolute risk of cardiovascular events in this aging cohort, only 5 to 22 additional men needed to have an additional risk factor controlled to prevent one cardiovascular event. Importantly, these benefits occurred after adjustment for competing causes of mortality in these older men.

We found that drug treatment to a non-HDL-C <130 mg/dl largely ameliorated the excess risk of higher non-HDL-C levels. This finding is consistent with an analysis of clinical trials suggesting a log linear relationship between LDL-C lowering and cardiovascular risk reduction exists, with most of the risk reduction benefit occurring when LDL-C reduced to 100 mg/dl (non-HDL-C of 130 mg/dl corresponds to an LDL-C of 100 mg/dl).^{23, 29} This finding is also of interest in light of the results of the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) trial of pravastatin in adults aged 70–82 years.³⁰ PROSPER did not find a significant benefit in the primary prevention population overall, which may have been due to the relatively high proportion of women enrolled in the trial.¹³

Of the 4 treatable risk factors, few had a non-HDL-C <130 mg/dl due to the low rate of cholesterol-lowering medication use (14%). Addressing the treatment gap in non-HDL-C control, with or without control of other risk factors, would therefore be expected to substantially reduce cardiovascular risk in elderly men over a 10 year period. Our findings also suggest that future cholesterol guidelines should identify dual goals of LDL-C <100 mg/dl and non-HDL-C <130 mg/dl for men >65 years. The Third National Cholesterol Education Program Adult Treatment Panel recommended an LDL-C goal <130 mg/dl for those individuals without a coronary heart disease equivalent condition, with drug therapy considered optional for those with LDL-C levels 100–129 mg/dl (corresponding to non-HDL-C levels 130–159 mg/dl).²⁵

In our study, treatment of hypertension was also suboptimal, with only 65% of hypertensive persons receiving antihypertensive medication, and of those, less than half were controlled to <140/<90 mm Hg. Nonetheless treatment of blood pressure was associated with substantial cardiovascular benefit, although not entirely ameliorating all excess risk due to hypertension. Approximately 30% reductions in cardiovascular events were observed in clinical trials of hypertensive therapy,^{9, 13} similar to the risk reduction associated with blood pressure control in this study. Also of interest, we observed a <50% prevalence of hypertension, which was lower than expected compared with 80% population prevalence of hypertension after age 70.⁸ This may have reflected the lack of obesity in our study population of male physicians over time. At the start of our follow-up in 1997 mean body mass index (BMI) was 25 ($\pm$ 3).

We did find a significant 16% increase in risk for CVD in men who were not treated with aspirin compared to those who were. This is expected given the >10% 10-year coronary heart disease risk, the recommended treatment threshold for aspirin in primary prevention.³¹ The original Physician's Health Study aspirin trial published in 1989 found that aspirin reduced myocardial infarction by 44%, without a stroke benefit in men $\geq$ 50 years who had higher rates of current smoking (15%) and diabetes (5%) than the older men in our analysis.^{32, 33}

In the few men with all 4 risk factors controlled, 20% still experienced a cardiovascular event. As already noted, among this population of primarily middle-aged men, 15% were smokers at the start of the Physician's Health Study aspirin trial in 1982 and long-term blood pressure control was suboptimal.^{21, 34} Few had received cholesterol-lowering drug therapy by 1997. This suggests more aggressive risk factor control in middle-age may be necessary to have a major impact on cardiovascular risk with advancing age. These findings are in line with the findings from long-term follow-up in the Framingham Study, where men with 1 major risk factor at age 50 have a 38% risk of cardiovascular disease by age 75, and a 50% risk by age 95.³⁵

Limitations

Our findings may not be generalizable to populations at high risk of competing causes of noncardiovascular mortality. Participants in the Physician's Health Study would be expected to have healthier lifestyle habits and better risk factor control (primarily lack of smoking) than the general population of men, and indeed only 23% of deaths were due to a cardiovascular cause compared to 34% in a similarly aged general population.³⁶ In populations with higher levels of cardiovascular risk factors and cardiovascular death rates, the benefits of risk factor control would be even more marked due to fewer deaths from competing causes of mortality.²⁷ Even though risk factor levels were lower than the general population of older men³⁷, the estimated 10-year atherosclerotic CVD risk of men in this study was about 26%,²⁴ fairly similar to the observed 28% 9-year CVD risk with carotid revascularizations included.

It could be argued that our analysis overestimates the benefit of risk factor control, since over 50% of men were normotensive and 96% were nonsmokers at the cohort baseline. However, our objective was to establish 4 treatable risk factors and evaluate the merits of maximizing the number of controlled treatable risk factors in older men. Moreover, we were able to demonstrate large improvements in cardiovascular risk associated with intensification of risk factor control, despite temporal trends in improving risk factor control between 1999 and 2006³⁸ (which would have biased the association toward the null).

Control of treatable risk factors is associated with substantially reduced cardiovascular risk with advancing age. Since the control of risk factors is additive, clinicians need to take a comprehensive approach to risk factor management that aims to control all 4 treatable risk factors in older patients, either through lifestyle modification or drug therapy. However, control of cardiovascular risk factors throughout adulthood likely will be needed to limit the burden of atherosclerotic diseases with advancing age, since cardiovascular risk may be only partially reduced if risk factor treatment is delayed until older ages.

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Figure 1. Cumulative incidence of cardiovascular disease events during follow up, by category of risk factors controlled. (Blue=0 Risk Factors controlled; Red=1 risk factor controlled; Green=2 risk factors controlled; Black=3 risk factors controlled; Purple=4 risk factors controlled).

Table 1

Baseline characteristics [mean (SD) or number (%)], n=4182

Characteristic	Mean (SD)
Age, years, mean (SD)	72.9 (5.8)
Total cholesterol, mg/dl, mean (SD)	205.6 (36.4)
HDL-C, mg/dl, mean (SD)	44.5 (15.8)
HDL-C<40 mg/dL, no. (%)	1815 (43.4)
HDL-C≥40 mg/dL, no. (%)	2378 (56.6)
Non-HDL-C, mg/dl, mean (SD)	161.1 (36.2)
Non-HDL-C <100 mg/dl, no. (%)	130 (3.1)
Non-HDL-C 100-<130 mg/dl, no. (%)	691 (16.5)
Non-HDL-C ≥130 mg/dl, no. (%)	3361 (80.3)
Systolic blood pressure (SBP), mm Hg, mean (SD)	131.3 (12.9)
SBP <140 mm Hg	2894 (69.2)
SBP ≥140 mm Hg	1288 (30.8)
Diastolic blood pressure (DBP), mm Hg, mean (SD)	78.2 (7.4)
DBP <90 mm Hg	3847 (92.0)
DBP ≥90 mm Hg	335 (8.0)
Body mass index	25.3 (3.4)
Current smoking, no. (%)	145 (3.5)
Regular physical activity, no. (%) *	673 (16.2)
Lipid-lowering drug use, no. (%)	589 (14.0)
Antihypertensive drug use (%)	1254 (30.0)
Aspirin use (%)	2046 (48.9)
Serious comorbidities	

Characteristic	Mean (SD)
0	1497(35.8)
1	1952(46.7)
≥2	733(17.5)
Glomerular filtration rate <30 mg/dl (%)	183 (4.4)

HDL-C = High-density lipoprotein cholesterol

* Defined as exercising to sweat ≥5 time per week, missing in 31 participants

** Serious comorbidities included baseline chronic obstructive pulmonary disease, congestive heart failure, history of gastrointestinal bleeding, liver disease, renal disease, non-fatal cancer or cerebrovascular disease, excluding stroke but including transient ischemic attack or carotid artery surgery.

TABLE 2

Cardiovascular events, cancer, and death rates over 9 years of follow-up (n=4182).

Event	N (percent)
Death, any cause	1094(26.2)
CVD death	248 (22.7)
Non-CVD death	846(77.3)
CHD * - Total	633 (15.1)
Nonfatal CHD	570 (90.0)
Fatal CHD	63 (10.0)
Cerebrovascular events ^{**} - Total	423 (10.1)
Nonfatal cerebrovascular events	358 (84.6)
Fatal stroke	65 (15.4)
Other CVD [†]	216 (5.2)
Any CVD event	1172(28.0)
Cancer - total	984 (23.5)
Incident	600 (61.0)
Fatal	384 (39.0)

* CHD = Coronary heart disease includes fatal and non-fatal myocardial infarction, angina, and coronary revascularizations

** Includes fatal and non-fatal stroke, transient ischemic attack, and carotid artery surgery

[†] Includes peripheral vascular disease surgery

TABLE 3

Absolute risk over 9-years, parameter estimates and hazard ratios (HR) and 95% confidence intervals (95% CI) for categorized cholesterol control, blood pressure control, smoking, and aspirin use, and HDL-C for the combined outcome of any CVD*

Risk Factor/Treatment	Absolute risk of any CVD event over 9 years (95% CI)			
	Age-adjusted (n=4182)		Model 2 (n=4164)	
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Cholesterol-modifying therapy = No				
Non-HDL<130 mg/dL (n=728, 17.4%)	22.4% (19.5–25.6)	Reference	Reference	Reference
Non-HDL≥130 mg/dL (n=2865, 68.5%)	29.1% (27.4–30.8)	1.52 (1.28–1.80)	1.50 (1.26–1.78)	1.44 (1.21–1.72)
Cholesterol-modifying therapy = Yes				
Non-HDL<130 mg/dL (n=93, 2.2%)	24.7% (17.1–34.3)	1.37(0.89–2.13)	1.31 (0.84–2.03)	1.33 (0.85–2.06)
Non-HDL≥130 mg/dL (n=496, 11.9%)	30.7% (26.7–34.8)	1.85 (1.48–2.32)	1.73 (1.38–2.18)	1.65(1.31–2.07)
Antihypertensive therapy = No				
Blood pressure <140/<90 mmHg (n=2251, 53.8%)	23.3% (21.6–25.1)	Reference	Reference	Reference
Blood pressure ≥140/or ≥90 mmHg (n=677, 16.2%)	31.6% (28.2–35.2)	1.34 (1.14–1.57)	1.31 (1.12–1.54)	1.30(1.09–1.50)
Antihypertensive therapy = Yes				
Blood pressure <140/<90 mmHg (n=572, 13.7%)	30.8% (27.1–34.7)	1.40(1.18–1.66)	1.34 (1.12–1.59)	1.31 (1.10–1.56)
Blood pressure ≥140/or ≥90 mmHg (n=682, 16.3%)	37.7% (34.1–41.4)	1.70 (1.46–1.97)	1.69 (1.45–1.96)	1.64 (1.4201.90)
Smoking=No (n=4037, 96.5%)	27.4% (26.0–28.8)	Reference	Reference	Reference
Smoking=Yes (n=145, 3.5%)	45.5% (37.6–53.6)	2.29 (1.79–2.94)	2.24 (1.75–2.88)	2.26 (1.76–2.89)
Aspirin= Yes (n=2046, 48.9%)	29.3% (27.3–31.3)	Reference	Reference	Reference
Aspirin=No (n=2136, 51.1%)	26.8% (25.0–28.7)	1.22(1.09–1.37)	1.16(1.03–1.30)	1.16 (1.03–1.31)
HDL-C ≥40 mg/dL (n=2367, 56.6%)	25.1% (23.3–26.9)	Reference	Reference	Reference
HDL-C <40 mg/dL (n=1815, 43.4%)	31.9% (29.7–34.0)	0.38	1.46 (1.30–1.64)	1.36 (1.21–1.53)

CVD = Cardiovascular disease

HDL-C = High-density lipoprotein cholesterol

* Includes cardiovascular death, non-fatal myocardial infarction, angina, revascularizations, non-fatal stroke, transient ischemic attack, carotid artery surgery, and other peripheral vascular disease surgery).

Model 1 includes age, categorized cholesterol control, categorized blood pressure control, smoking, and aspirin use.

Model 2 includes covariates in Model 1 plus body mass index, physical activity, and high-density lipoprotein cholesterol

TABLE 4

Absolute risk over 9-years, number-needed-to-control, and age-adjusted parameter estimates and hazard ratios (HR) and 95% confidence intervals (95% CI) for Framingham risk factor control score for the combined outcome of any CVD (includes cardiovascular death, non-fatal myocardial infarction, angina, revascularizations, non-fatal stroke, transient ischemic attack, carotid artery surgery, and other peripheral vascular disease surgery). Score includes cholesterol control, blood pressure control, smoking, and aspirin use

	Absolute risk of any CVD events over 9 years (95% CI)	Age-adjusted HR (95% CI) (n=4182)	Model 1 HR (95% CI) (n=4164)	Number- needed-to control to prevent 1 CVD event over 9 years
0 Risk factors controlled (n= 17, 0.41%)	41.2% (21.6–64.0)	3.83(1.72–8.55)	3.54(1.59–7.91)	
1 Risk factor controlled (n=594, 14.2%)	36.7% (32.9–40.7)	2.53(1.80–3.57)	2.26(1.60–3.17)	22
Non-HDL-C <130 mg/dL (n=3, 0.51%)				
Blood pressure <140/<90 mmHg (n=39, 6.6%)				
Aspirin use (n=28, 4.7%)				
Non-smoking (n=524, 88.2%)				
2 Risk factors controlled (n=1832,43.8%)	28.3% (26.3–30.4)	1.94(1.41–2.69)	1.76(1.27–2.43)	8
Non-HDL-C <130 mg/dL (n=158, 8.6%)				
Blood pressure <140/<90 mmHg (n=1149, 62.7%)				
Aspirin use (n=577, 31.5%)				
Non-smoking (n=1780, 97.2%)				
3 Risk factors controlled (n=1487, 35.6%)	25.4% (23.3–27.7)	1.80(1.30–2.50)	1.65(1.19–2.29)	6
Non-HDL-C <130 mg/dL (n=408, 27.4%)				
Blood pressure <140/<90 mmHg (n=1383, 93.0%)				
Aspirin use (n=1189, 80.0%)				
Non-smoking (n=1481, 99.6%)				
4 Risk factors controlled (n= 252, 6.0%)	20.2% (15.7–25.6)	REFERENCE	REFERENCE	5
		Test for trend P0.002	Test for trend P0.01	

CVD = Cardiovascular disease

HDL-C = High-density lipoprotein cholesterol

Model 1 adjusted for age, body mass index, physical activity, and high-density lipoprotein cholesterol