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Polypill Therapy, Subclinical Atherosclerosis, and Cardiovascular Events—Implications for the Use of Preventive Pharmacotherapy

MESA (Multi-Ethnic Study of Atherosclerosis)

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Objectives This study examines whether the coronary artery calcium (CAC) score can be used to define the target population to treat with a polypill.

Background Prior studies have suggested a single polypill to reduce cardiovascular disease (CVD) at the population level.

Methods Participants from MESA (Multi-Ethnic Study of Atherosclerosis) were stratified using the criteria of 4 polypill studies (TIPS [The Indian Polycap Study], Poly-Iran, Wald, and the PILL [Program to Improve Life and Longevity] Collaboration). We compared coronary heart disease (CHD) and CVD event rates and calculated the 5-year number needed to treat (NNT) after stratification based on the CAC score.

Results Among MESA participants eligible for TIPS, Poly-Iran, Wald, and the PILL Collaboration, CAC = 0 was observed in 58.6%, 54.5%, 38.9%, and 40.8%, respectively. The rate of CHD events among those with CAC = 0 varied from 1.2 to 1.9 events per 1,000 person-years, those with CAC scores from 1 to 100 had event rates ranging from 4.1 to 5.5, and in those with CAC scores >100 the event rate ranged from 11.6 to 13.3. The estimated 5-year NNT to prevent 1 CVD event ranged from 81–130 for patients with CAC = 0, 38–54 for those with CAC scores from 1 to 100, and 18–20 for those with CAC scores >100.

Conclusions In MESA, among individuals eligible for treatment with the polypill, the majority of CHD and CVD events occurred in those with CAC scores >100. The group with CAC = 0 had a very low event rate and a high projected NNT. The avoidance of treatment in individuals with CAC = 0 could allow for significant reductions in the population considered for treatment, with a more selective use of the polypill and, as a result, avoidance of treatment in those who are unlikely to benefit. (J Am Coll Cardiol 2014;63:434–43) © 2014 by the American College of Cardiology Foundation

In recent years, the concept of using a single polypill in primary prevention has gained significant attention. Proponents of such a strategy have suggested that wider-scale use of preventive therapies could prevent a larger proportion of cardiovascular disease (CVD) events in individuals who have "average" risk factor levels. Yusuf (1) hypothesized that a combination of aspirin, a beta-blocker, an angiotensin-converting enzyme inhibitor, and a statin ("polypill") could reduce CVD events by up to 75%, while Wald and Law (2) suggested that such an approach with 6 medications could reduce up to 80% of coronary heart disease (CHD) and stroke events. These

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authors suggested that either all patients above the age of 55 years or those with at least 1 risk factor should be indiscriminately treated with pharmacotherapy. Nevertheless, such an approach would result in expansion of treatment for millions of asymptomatic men and women. Due to the considerable potential healthcare and economic implications of the polypill strategy, the World Health Organization, Centers for Disease Control and Prevention, National Heart, Lung and Blood Institute, and the Wellcome Trust have called for research to test the impact of various polypills on CVD outcomes (3,4).

Coronary artery calcium (CAC), measured by noncontrast cardiac computed tomography, is a well-known measure of subclinical coronary atherosclerosis that has been well-validated for CVD risk assessment in asymptomatic individuals (5). Higher CAC scores are directly associated with future risk of CVD events and provide risk information that is incremental to traditional risk factors (6). Moreover, CAC can improve risk discrimination and reclassification beyond scores such as the Framingham risk score (FRS) (7,8). As importantly, the absence of calcium is associated with an excellent prognosis and very low event rates in asymptomatic individuals (9,10).

We hypothesized that a simple test with a high negative predictive value could be used to identify individuals with an extremely low event rate, in whom indiscriminate polypill therapy might be safely deferred. In this study, we evaluated whether the CAC score may be used for more selective application of the various proposed polypill strategies for reducing CVD events.

Methods

Ethics statement. The institutional review boards at all participating centers approved the study, and all participants gave informed consent.

MESA (Multi-Ethnic Study of Atherosclerosis). MESA is a National Institutes of Health/National Heart, Lung, and Blood Institute–funded study that was designed to prospectively evaluate the development and progression of atherosclerotic disease. The complete design and protocols have previously been published (11). Briefly, the study included 6,814 individuals between the ages of 45 and 84 years, from both sexes, and free from known CVD at baseline. The selection included patients from the resident list of individuals from the urban areas of the recruiting centers with emphasis on ethnic diversity.

Abbreviations and Acronyms

CAC = coronary artery calcium

CHD = coronary heart disease

CVD = cardiovascular disease

FRS = Framingham risk score

HR = hazard ratio

NNT = number needed to treat

Patient population. Using baseline data (MESA, 2000 to 2002), we identified individuals who met eligibility criteria for 4 polypill-based published trials. The trials and criteria used to identify individuals who may be eligible for treatment with a polypill included: 1) TIPS (the Indian Polycap Study) (12), ages 40 to 80 years without CVD and 1 CVD risk factor; 2) Poly-Iran (13,14), ages 50 to 80 years with or without any risk factor; 3) the initial Wald publication (2), which suggested use by all adults above the age of 55 years; and 4) the PILL (Program to Improve Life and Longevity) Collaboration criteria (15), which used an FRS above 7.5% as the inclusion criterion. Patients meeting inclusion and not meeting exclusion criteria as detailed in those studies were included in the present analysis (Fig. 1).

CAC score protocol. MESA participants underwent noncontrast cardiac-gated computed tomography for CAC score evaluation as previously described (16). Approximately

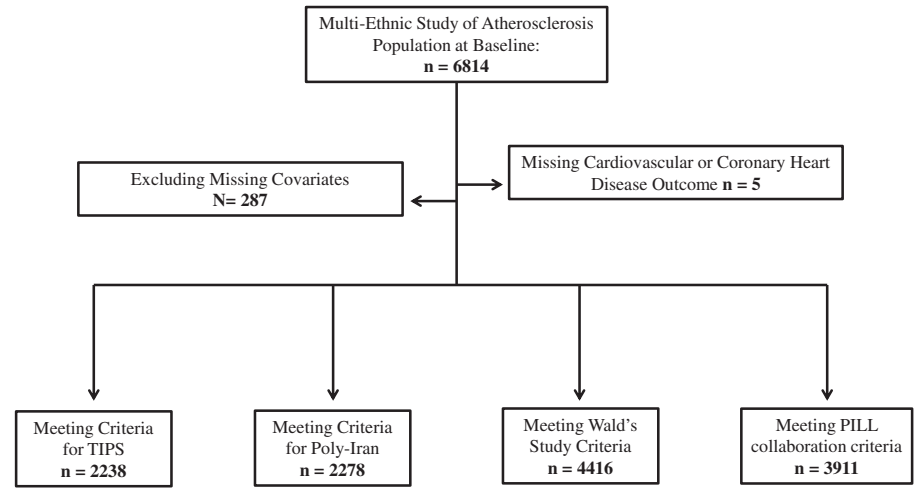

Figure 1 Study Population

Flowchart of participants included in the analysis. PILL = Program to Improve Life and Longevity; TIPS = the Indian Polycap Study.

one-half of the scans were performed with a 4-detector computed tomography scanner, and electron beam tomography was used for the remainder. The average estimated radiation dose was 0.89 mSv. The kappa statistic was 0.92 for agreement on the presence of CAC.

Follow-up of cardiovascular events. Participants were followed up for a median of 7.6 years for incident CVD events from their baseline examinations. Follow-up consisted of 3 follow-up visits conducted by each participating center. In addition, patients were contacted by telephone every 9 to 12 months and questioned on hospital admissions, CVD events, deaths, and outpatient diagnoses. Copies of all medical records for all hospitalizations and outpatient contacts that resulted in new CVD diagnoses as well as death certificates were obtained.

Every event was adjudicated by 2 independent physicians from the MESA events committee after review of all medical records. Endpoints were then classified, and an incident date was defined. The classification followed strictly pre-defined criteria. In case of discordant review, differences were adjudicated. If differences still persisted, a final decision was made by the full events committee.

Coronary heart disease (CHD) events included both myocardial infarction and death from CHD. Myocardial infarction was defined as definite, probable, or absent based on symptoms, electrocardiographic abnormalities, and cardiac biomarkers. CHD death was classified as present or absent based on review of hospital records and interview of families. A fatal CHD event was defined as a documented myocardial infarction within 28 days of death, chest pain in the 72 h prior to death, or a history of CHD and no other known nonatherosclerotic or noncardiac cause for death.

The CVD events consisted of CHD plus stroke (not transient ischemic attack), stroke death, other atherosclerotic death, and other CVD death. A detailed description of the MESA follow-up methods is available at www.mesa-nhlbi.org.

Statistical analysis. Baseline characteristics of the study participants were analyzed according to the presence or absence of CAC. Frequencies and proportions were calculated for categorical variables, and either mean ± SD or median (interquartile range) were calculated for continuous variables based on normality of distribution. We used Kaplan-Meier estimates of cumulative event-free survival to describe the occurrence of CHD and CVD events over time. To determine if CAC can further risk-stratify the individuals meeting the criteria for polypill based on the above-mentioned studies, we compared absolute CHD and CVD event rates as well as Cox multivariable-adjusted hazard ratios (HRs) after stratifying by the presence or absence of CAC. Models were adjusted for age, sex, race/ethnicity, education level (a measure of socioeconomic status), and MESA site.

In addition, we calculated the 5-year number needed to treat (NNT) for both CHD and CVD by applying the HR for the expected event reduction associated with the use of the polypill according to the TIPS study (reduction of 62% in the CHD events) (12) to the event rates at the median follow-up for the groups with and without CAC. NNT was calculated directly as the reciprocal of the absolute risk difference at median follow-up of the cohort (7.6 years) based on Kaplan-Meier estimates, and was subsequently adjusted to a 5-year NNT according to the Altman-Anderson method (17). A supplemental analysis of the ability of CAC to stratify risk across different levels of clinical risk using the FRS for each patient was performed. For this analysis, the NNTs for 5 years for CHD and CVD events were calculated for each CAC level stratified by 3 groups of FRS defined as low risk (<10%), intermediate risk (10% to 20%), and high risk (>20%). Sensitivity analyses were performed from a wide range of risk reductions to evaluate the consistency of the findings. Although some groups have proposed a reduction in the relative risk of as high as 80%, we chose an estimate based on the most widely accepted estimates from more recent publications (12). Similar estimates have also been estimated by Muntner et al. (18).

Results

Baseline characteristics. Among the 6,814 individuals initially included in MESA, 2,238 (32.8%) met the eligibility criteria for TIPS, 2,278 (33.4%) for Poly-Iran, 4,416 (64.8%) were above the age of 55 years as proposed in the initial Wald proposal, and 3,911 (57.4%) were eligible by the PILL Collaboration criteria. The overall distribution of age, sex, race/ethnicity, risk factors, education, baseline laboratory results, and CAC scores for each of the groups is presented in Table 1.

Distribution of CAC in eligible patients for each polypill regimen. The distribution of CAC among subjects meeting inclusion criteria for each of the 4 polypill regimens was variable, as would be expected based on the respective patient populations included in each study (Fig. 2). For instance, the TIPS and the Poly-Iran studies included younger individuals (i.e., above 40 and 50 years of age), but excluded individuals above the age of 80 years. Additionally, the TIPS study excluded individuals with very high cholesterol low-density lipoprotein or elevated creatinine. Therefore, those 2 studies resulted in a lower-risk population and accordingly had a lower prevalence of any CAC (i.e., CAC scores >0) as well as CAC scores >100.

Event rates by presence or absence of CAC. The rates of CHD and CVD events stratified by the presence or absence of CAC for each polypill study population are presented in Table 2. The overall rates of CHD and CVD events for patients with CAC = 0 (i.e., CAC score of zero) were low in all 4 groups, ranging from 1.2 to 1.9 CHD events per 1,000 person-years. On the other hand, CAC scores from 1 to 100 were associated with a 2.9- to 4.1-fold increase in CHD events, ranging from 4.1 to 5.5 events per 1,000 person-years. For patients with a CAC score >100, there was a 6- to 11-fold increase in the risk of CHD events, with a rate of events ranging from 11.6 to 13.3

Table 1 Baseline Characteristics According to the Inclusion Criteria for Each Polypill Study

Characteristic	TIPS (12)	Poly-Iran (13,14)	Wald (2)	PILL Collaboration (15)
Number of subjects eligible in MESA	2,238	2,278	4,416	3,911
Age (yrs)	58.6 ± 9.4	62.2 ± 7.9	67.7 ± 7.2	63.8 ± 9.9
Male	1,126 (50.3%)	1,080 (47.4%)	2,094 (47.4%)	2,506 (64.1%)
Race				
White	766 (34.2%)	831 (36.5%)	1,696 (38.4%)	1,385 (35.4%)
Black	573 (25.6%)	531 (23.3%)	1,250 (28.3%)	1,150 (29.4%)
Hispanic	620 (27.7%)	555 (24.4%)	931 (21.1%)	933 (23.9%)
Asian	279 (12.5%)	361 (15.8%)	539 (12.2%)	443 (11.3%)
Diabetes	191 (8.5%)	169 (7.4%)	644 (14.6%)	735 (18.8%)
Hypertension	452 (20.2%)	443 (19.5%)	2,574 (58.3%)	2,301 (58.8%)
Smoking				
Never	1,062 (47.5%)	1,131 (49.8%)	2,194 (49.9%)	1,763 (45.3%)
Former	716 (32.0%)	813 (35.8%)	1,757 (39.9%)	1,517 (39.0%)
Current	457 (20.5%)	328 (14.4%)	449 (10.2%)	611 (15.7%)
Education				
<High school	1,173 (53.1%)	1,182 (52.7%)	2,437 (56.2%)	2,090 (54.3%)
College	294 (13.3%)	284 (12.7%)	474 (10.9%)	477 (12.4%)
Bachelor or above	741 (33.6%)	775 (34.6%)	1,429 (32.9%)	1,279 (33.3%)
Family history of CAD	826 (39.1%)	830 (38.9%)	1,854 (45.1%)	1,650 (45.6%)
BMI (kg/m^2)	28.5 ± 5.5	27.3 ± 5.1	28.2 ± 5.3	29.2 ± 5.4
LDL-C (mg/dl)	124.1 ± 26.8	123.0 ± 31.6	116.7 ± 31.5	121.0 ± 32.0
HDL-C (mg/dl)	48.8 ± 13.9	51.9 ± 15.3	51.7 ± 14.9	46.2 ± 12.1
Triglycerides (mg/dl)	115 (80–162)	110 (77–158)	111 (79–159)	126 (87–179)
Calcium scores				
0	1,312 (58.6%)	1,241 (54.5%)	1,718 (38.9%)	1,596 (40.8%)
1–100	581 (26%)	628 (27.6%)	1,324 (30.0%)	1,161 (29.7%)
>100	345 (15.4%)	409 (17.9%)	1,374 (31.1%)	1,154 (29.5%)

Values are mean ± SD, n (%), or mean (interquartile range).
BMI = body mass index; CAD = coronary artery disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; MESA = Multi-Ethnic Study of Atherosclerosis; PILL = Program to Improve Life and Longevity; TIPS = the Indian Polycap Study.

events per 1,000 person-years (Table 2). The Kaplan-Meier estimates for CHD event–free survival for each of the polypill populations are presented in Figure 3A.

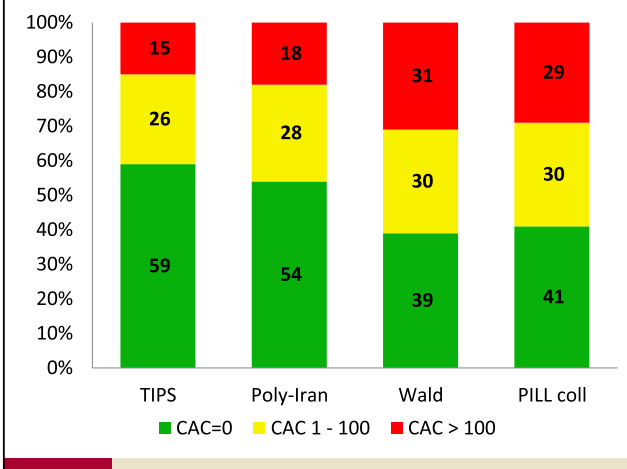

Figure 2 CAC Distribution

Distribution of coronary artery calcium (CAC) scores in each of the 4 proposed polypill regimens. Abbreviations as in Figure 1.

Similarly, among individuals with no CAC, the rate of CVD was low across all populations, with a rate of 2.5 to 4.0 events per 1,000 person-years. For individuals with CAC scores between 1 and 100 the rates ranged from 6.0 to 8.5 events per 1,000 person-years, whereas individuals with a CAC score >100 had rates between 15.8 and 18.4 per 1,000 person-years. The Kaplan-Meier estimates for CVD event–free survival for each of the polypill populations are presented in Figure 3B.

These results remained largely unchanged after adjustment for age, sex, race, education, and MESA site from which the patient was recruited. The HRs for CAC scores between 1 and 100 to predict CHD and CVD ranged from 2.3 to 2.8 and 1.7 to 1.9, respectively. For CAC scores >100, the HRs for CHD and CVD ranged from 4.7 to 6.4 and 3.3 to 4.4, respectively (Table 3).

NNT according to CAC. Using the estimates of events from the survival model at median follow-up, and assuming the proposed benefit of 62% event reduction, as per the TIPS study (12), the NNT for 5 years to prevent 1 CVD event would range from 81 to 130 for patients with CAC = 0. For the patients with CAC scores between 1 and 100, the NNT would range from 38 to 54. For CAC scores >100, the NNT to prevent 1 CVD event would be between 18 and 20 (Fig. 4).

Table 2 CHD and CVD Event Rates per 1,000 Person-Years and 5-Year NNT for Each of the Polypill Studies

	TIPS (12)			Poly-Iran (13,14)			Wald (2)			PILL Collaboration (15)		
	CAC = 0	CAC 1–100	CAC >100	CAC = 0	CAC 1–100	CAC >100	CAC = 0	CAC 1–100	CAC >100	CAC = 0	CAC 1–100	CAC >100
Total	1,312 (58.6%)	581 (26%)	345 (15.4%)	1,241 (54.5%)	628 (27.6%)	409 (17.9%)	1,718 (38.9%)	1,324 (30%)	1,374 (31.1%)	1,596 (40.8%)	1,161 (29.7%)	1,154 (29.5%)
CHD events	11 (0.8%)	19 (3.3%)	31 (9.0%)	12 (1.0%)	18 (2.9%)	33 (8.1%)	23 (1.3%)	46 (3.5%)	106 (7.7%)	19 (1.2%)	44 (3.8%)	96 (8.3%)
CHD event rate (1,000 pr-yrs)	1.2	4.6	13.3	1.3	4.1	12.0	1.9	5.1	11.6	1.7	5.5	12.5
CVD events	23 (1.8%)	25 (4.3%)	42 (12.2%)	22 (1.8%)	26 (4.1%)	43 (10.5%)	45 (2.6%)	75 (5.7%)	148 (10.8%)	45 (2.8%)	67 (5.8%)	130 (11.3%)
CVD event rate (1,000 pr-yrs)	2.5	6.1	18.4	2.5	6.0	15.8	3.7	8.3	16.5	4.0	8.5	17.2

Values are n (%) unless otherwise indicated. The numbers needed to treat (NNTs) were calculated directly as the reciprocal of the absolute risk difference at the median follow-up of 7.6 years and were subsequently adjusted to a 5-year period.
CAC = coronary artery calcium; CHD = coronary heart disease; CVD = cardiovascular disease; other abbreviations as in Table 1.

Because the exact reduction in the relative risk with the use of the polypill is not clearly defined, a sensitivity analysis was performed. For individuals with a CAC = 0, the NNT to prevent 1 CVD event over 5 years was >50 for all regimens, even if the risk reduction was (unrealistically) as high as 95%. For participants in the intermediate group, the NNT to prevent 1 CVD event was below 50, assuming a risk reduction of approximately 60%, as previous calculations suggest. If the benefit is lower than expected, the NNT for 5 years to prevent 1 CVD event increases and approaches 80 when the risk reduction is 40%. On the other hand, for patients with CAC scores >100, the NNT remains favorable even when the risk reduction is far lower than the estimate used in our analysis. The NNT remains below 30 when the risk reduction decreases to approximately 35% to 40% (Fig. 5).

In a subanalysis, we also assessed the utility of CAC testing to identify groups that may benefit the least and the most from adding CAC scores to traditional risk classification by the FRS. Approximately one-third of individuals eligible for polypill by criteria that included lower risk and a younger population were at least intermediate risk by FRS (TIPS = 37% and Poly-Iran = 40%). On the other hand, more than 50% of individuals meeting polypill criteria focusing on slightly older population were intermediate to high risk (Wald = 51% and PILL Collaboration = 56%). For all criteria, the NNT in those at least intermediate risk was <48 individuals for preventing 1 CHD event and <34 individuals for preventing 1 CVD event (Online Figs. 1A and 1B). Overall, CAC provided significant discrimination in the NNT to prevent CHD/CVD events in individuals across the FRS spectrum, with the highest NNT noted among those who have no CAC, even among the intermediate-risk (NNT range 135 to 162 for hard CHD) and high-risk (68 to 126 for hard CHD) groups. On the other hand, among those with low FRS and CAC scores >100 across all criteria, the calculated NNT for preventing 1 hard CHD event was 38 to 56 and was 26 to 38 for hard CVD.

Discussion

In the present study, we estimated the potential impact of a polypill on CVD risk reduction according to CAC score in a large, asymptomatic cohort of U.S. adults according to 4 different proposed inclusion criteria. Across subgroups that met the inclusion and exclusion criteria for the 4 suggested polypill regimens, the NNT in 5 years to prevent 1 CVD event ranged from 36 to 57. However, if the strategy of treating only individuals with CAC scores >100 is chosen, the majority of persons who experienced events would be eligible for therapy, but the overall population requiring treatment would be less than one-third of the initial sample in any of the 4 strategies. Accordingly, the NNT for 5 years to reduce 1 CVD event decreased to 18 to 20, which is much lower than the threshold used to recommend the treatment of hypertension (19,20) or for the use of statins in primary

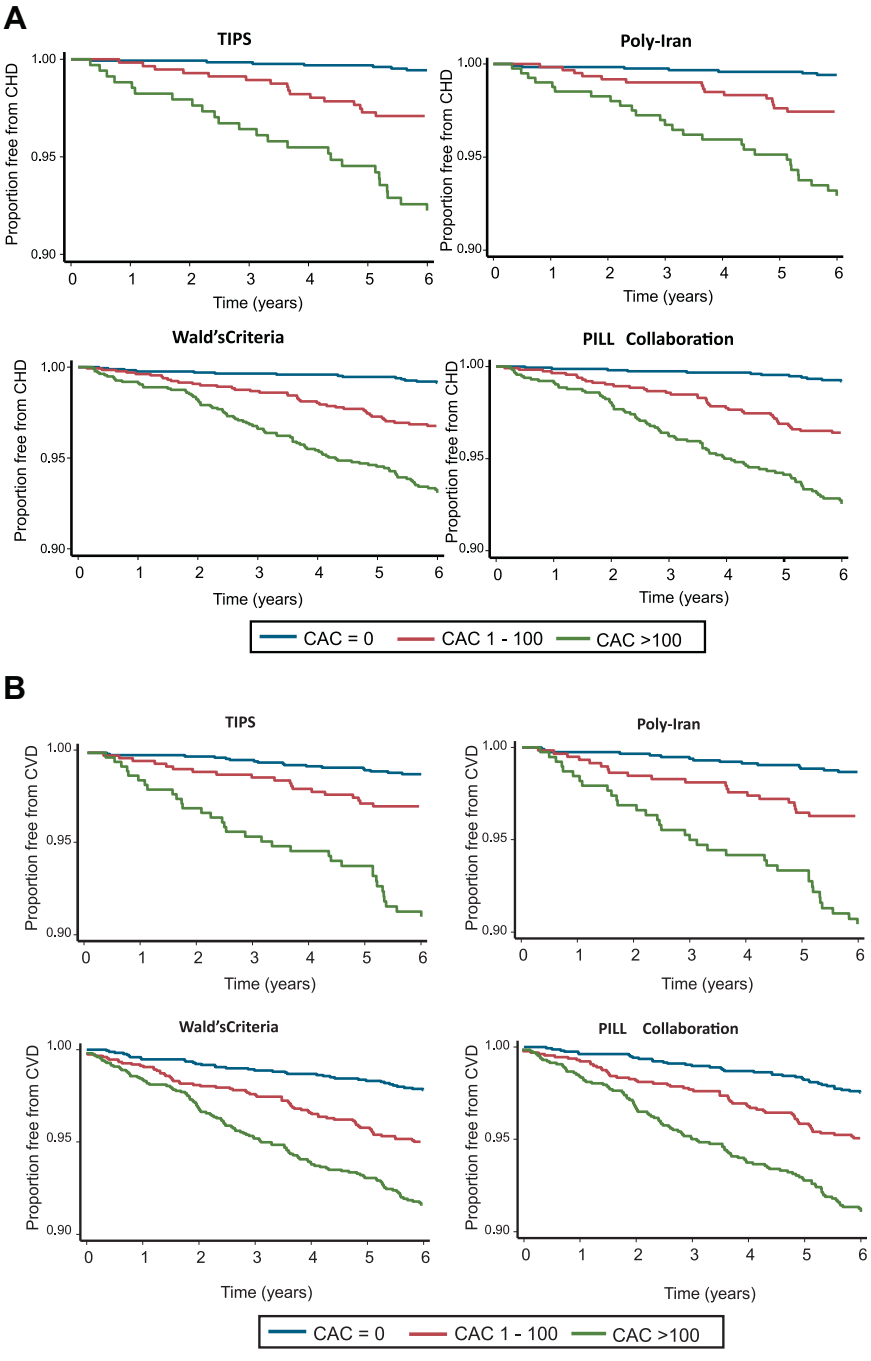

Figure 3 **Survival Free From Events According to CAC Scores**

(A) Survival free from coronary heart disease (CHD) events stratified by the presence or absence of CAC for each of the 4 polypill regimens. **(B)** Survival free from cardiovascular disease (CVD) events stratified by the presence or absence of CAC for each of the 4 polypill regimens. Abbreviations as in Figures 1 and 2.

prevention (21,22). On the other extreme, the group with CAC = 0 had much higher NNT, ranging from 81 to 130. In this group, the strategy of prescribing the polypill would result in an extremely low, if any, net benefit.

Notably, our sensitivity analysis affirms that the benefits of treating individuals with CAC scores >100 are extremely robust, as even if the actual efficacy of the polypill were one-half of expected, treating this population would still result in a highly favorable NNT. The results of the sensitivity analysis showing the lack of expected benefit for the group with CAC = 0 are also robust. This group has such a low event rate in 7.6 years of follow-up that even if the reduction

Table 3 HRs (95% CIs) for CHD and CVD Events With Increasing Burden of CAC for the Polypill Studies

	TIPS (12)		Poly-Iran (13,14)		Wald (2)		PILL Collaboration (15)	
	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
CHD								
CAC = 0	1.0 (ref)	—	1.0 (ref)	—	1.0 (ref)	—	1.0 (ref)	—
CAC 1–100	2.7 (1.2–5.8)	0.014	2.4 (1.1–5.1)	0.022	2.3 (1.4–3.8)	0.002	2.8 (1.6–4.8)	<0.0001
CAC >100	6.4 (2.9–13.8)	<0.0001	5.9 (2.8–12.2)	<0.0001	4.7 (2.9–7.6)	<0.0001	5.6 (3.3–9.5)	<0.0001
CVD								
CAC = 0	1.0 (ref)	—	1.0 (ref)	—	1.0 (ref)	—	1.0 (ref)	—
CAC 1–100	1.7 (0.9–3.1)	0.076	1.9 (1.1–3.4)	0.031	1.9 (1.3–2.7)	0.001	1.8 (1.2–2.7)	0.002
CAC >100	4.4 (2.4–7.8)	<0.0001	4.2 (2.4–7.4)	<0.0001	3.3 (2.3–4.7)	<0.0001	3.3 (2.3–4.8)	<0.0001

Values are hazard ratio (HR) (95% confidence interval [CI]). The results are adjusted for age, sex, race, education, and MESA site.
Abbreviations as in Tables 1 and 2.

in the relative risk were as high as 95%, the benefit would be minimal. Finally, the group with CAC between 1 and 100 is most sensitive to the potential benefit of the polypill. If the actual benefit were as high as the 80%, as initially proposed (2), this group will have a favorable NNT between 29 and 40 and is thus likely to benefit. On the other hand, if the actual risk reduction were still around 50%, the expected NNT would be as high as 65.

Irrespective of which of the 4 sets of inclusion criteria is used, our current data support the use of a single measure of the CAC to improve risk stratification among the population considered eligible for primary prevention with the polypill. If only individuals with CAC >100 were treated, the treated population would be reduced by more than 60%, while about 60% of the individuals who develop an event would still receive treatment. The hypothesis that CAC testing may be able to more appropriately identify those who will not benefit from polypill therapy is also supported by our recent findings MESA participants meeting the JUPITER (Justification of the Use of Statins in Primary Prevention: an Intervention Trial Using Rosuvastatin) criteria for statin therapy (23), in which we showed that among the 47% of the population with CAC = 0, there was an extremely low event rate with a corresponding NNT of 549.

Our results provide important insight regarding a key question in primary prevention: should we "treat all" at-risk individuals or instead use a more targeted approach of treating only individuals with evidence of established—albeit subclinical—disease. The initial publication on the polypill suggested that "a large preventive effect would require intervention in everyone at increased risk, irrespective of the risk factor levels" (2). At the time, the authors suggested that anyone above the age of 55 years would be an appropriate candidate. Our study and others (24) support the notion that

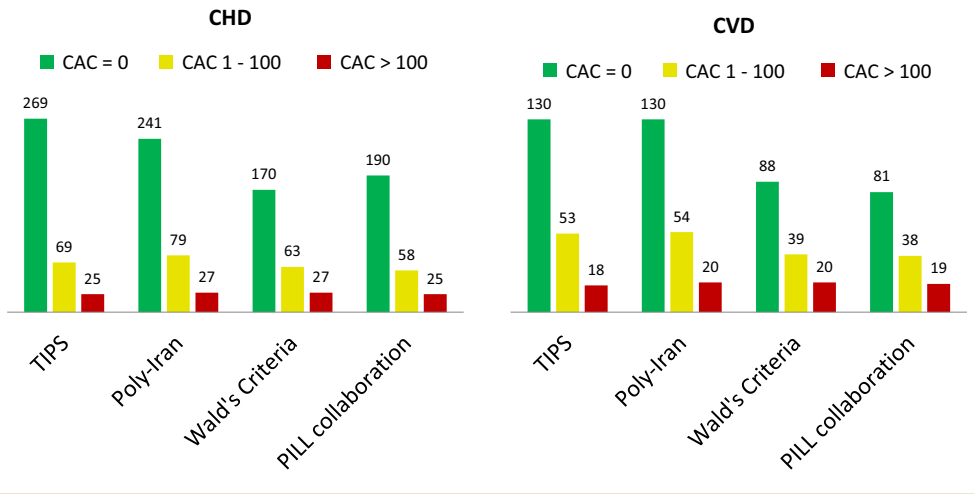

Figure 4 NNT According to CAC Scores

Number needed to treat (NNT) to prevent 1 CHD **(left)** and 1 CVD **(right)** event in 5 years using the entry criteria for each of the polypill regimen. The NNTs were calculated directly as the reciprocal of the absolute risk difference at the median follow-up of 7.6 years and were subsequently adjusted to a 5-year period. CAC = coronary artery calcium; other abbreviations as in Figures 1 and 3.

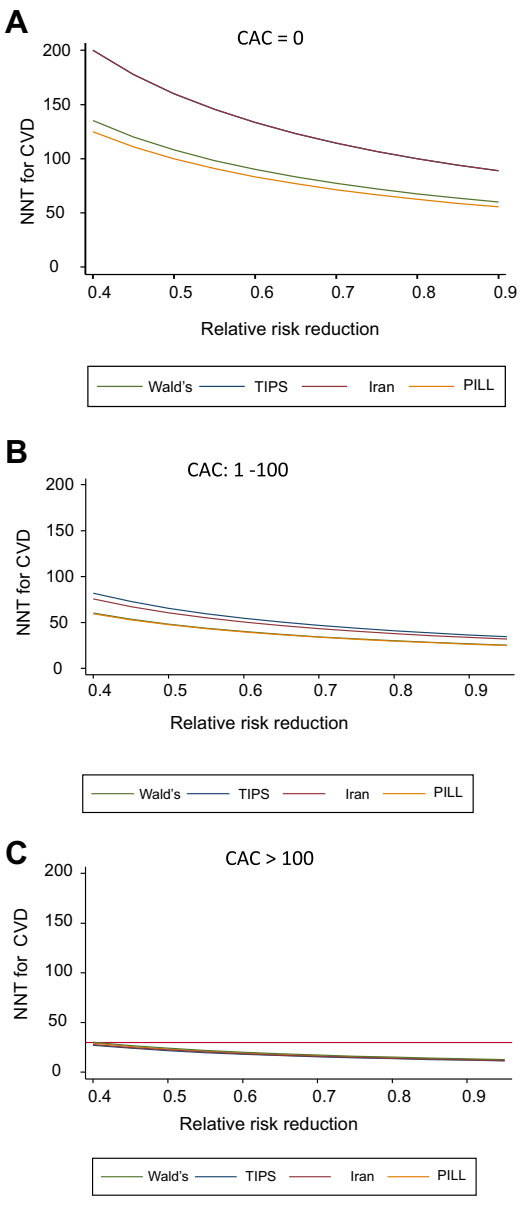

Figure 5 **Sensitivity Analysis for the NNT**

Sensitivity analysis for the NNT for 5 years to reduce 1 CVD event. The **curves** represent the NNT values across the spectrum of reductions in the relative risk with the use of the polypill in each study. **(A)** Subjects with a CAC score of 0. **(B)** Subjects with CAC scores 1 to 100. **(C)** Subjects with CAC scores >100. **The lower panel** includes a **red reference line** on the NNT of 30 for reference. Abbreviations as in Figures 1, 3, and 4.

treatment based on CAC may identify a larger proportion of individuals at risk for events than other approaches that are based on age or risk factors.

Our analysis demonstrated that even after taking additional risk stratification with global risk scores such as FRS, among the population considered eligible for the polypill based on pre-defined risk factor–based criteria, CAC was still able to provide clinically-meaningful information to guide treatment. Among individuals considered to be at intermediate to high risk, the absence of CAC was associated with a considerably higher NNT to prevent 1 cardiac event. Based on our secondary analyses, we believe there is strong value in using the combination of clinical scores and CAC scores for identifying appropriate groups among whom we may expect the greatest benefit from initiation of polypill, along with identifying subgroups among whom the benefit may be limited. For example, if one decides that the acceptable NNT for CVD for polypill is 30 to 40, among the individuals who would be candidates for the Wald regimen, only those with CAC scores >100 or the high FRS with CAC scores >0 would be the most appropriate group that is likely to derive the greatest benefit from the polypill. However, in the same process, the initial candidate population could be reduced by 64% (from 4,416 to 1,617 individuals requiring treatment) and, as a result, could have tremendous impact when the proposal of widespread use of the polypill is considered.

The use of CAC for screening for coronary atherosclerosis has some disadvantages. First, although the radiation dose is lower than 1 mSV (approximately equivalent to a bilateral mammogram), this poses a small theoretical risk (25). Second, CAC progresses over time and the actual "warranty period" of having no CAC is not completely clear but is likely to approach at least 4 to 5 years (26). Finally, the polypill is expected to be an intervention that would be able to prevent CVD events at a low cost. CAC scanning is associated with a small additional cost (European costs are approximately €115 [27]; however, because the cost is mainly driven by human resources, the cost is expected to be lower in developing countries). Further studies regarding the cost-effectiveness of CAC screening followed by selective treatment versus a treat-all approach are warranted (28). Importantly, CAC scoring can be performed on the vast majority of the currently-available scanners around the world, and this technology will be neither a significant limitation nor responsible for increased costs.

It is noteworthy that the polypill is still under evaluation and also has some undefined limitations. First, because a single combined pill formulation is proposed, individuals with a contraindication to any of the components would not be eligible. For instance, individuals with asthma (a contraindication to beta-blockers) or aspirin intolerance may not tolerate such therapy. Second, there is a significant rate of discontinuation due to side effects from the polypill. Although not significantly higher than placebo in short-term follow-up studies, up to 36% of patients discontinued treatment due to reported side effects in a recent meta-analysis of polypill studies (29).

Our analysis does not address the potential harm of treatment with the polypill. Although no data are yet available for the polypill, vast literature on the side effects of many of the individual drugs is available. One large database study presented observational data that suggested that the

numbers needed to harm with 5 years of treatment with statins are variable, but can be as low as 136 for liver dysfunction, 91 for myopathy, and 346 for acute renal failure (29). Additionally, another large study evaluated the risk of bleeding in a cohort of patients taking aspirin and found a particularly important increase in the risk of bleeding in nondiabetics, similar to the population included in our study. The use of aspirin increased the incidence rate of bleeding by approximately 2.0 events per 1,000 person-years (30). These results are particularly concerning when considering that individuals with a CAC = 0 had very low CVD rates of 2.5 to 4.0 per 1,000 person-years in our study and are thus more likely to be harmed by therapy.

Study limitations. An important limitation of our study is that the long-term efficacy of the polypill remains to be proven. The various therapies (e.g., aspirin, statins) have individually reduced events in primary prevention trials, and thus although the exact magnitude of the combined benefit is unknown, it is fair to state that some benefit—even if lower than predicted by Yusuf et al. (12)—will likely be realized by this strategy. Nevertheless, given the fact that the precise benefit is unknown, we performed a sensitivity analysis that affirmed the finding that once CAC is present, and particularly when CAC scores are >100, the favorably low NNT will persist across a wide range of risk reduction.

Our study evaluated various polypill studies with different inclusion criteria, but we did not aim to compare them. Rather, by presenting the full spectrum of all suggested polypill regimens, our aim was to test how robustly CAC scoring may perform in identifying groups who are most likely to benefit from therapy. In this sense, the current data support the presence of calcium as a simple and accurate tool for the selection of patients most likely to benefit from the polypill.

Conclusions

CAC has the potential to identify patients most likely to receive net benefit from the polypill. Such an approach would significantly reduce the number of individuals requiring treatment, thus reducing important side effects and cost, but would still ensure treatment in the majority of individuals who are likely to experience CHD and CVD events.

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Key Words: polypill ■ risk stratification ■ subclinical atherosclerosis.

APPENDIX

For a supplemental figure, please see the online version of this article.