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Polypill Therapy, Subclinical Atherosclerosis, and Cardiovascular Events – Implications for the Use of Preventive Pharmacotherapy: Multi-Ethnic Study of Atherosclerosis (MESA)

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Abstract

OBJECTIVES—Examine whether the coronary artery calcium score (CAC) can be used to define the target population to treat with a polypill.

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

METHODS—Participants from the Multi-Ethnic Study of Atherosclerosis (MESA) were stratified using the criteria of four polypill studies (TIPS, Poly-Iran, Wald's, and the PILL collaboration). We compared coronary heart disease (CHD) and CVD event rates and calculated 5-year number needed to treat (NNT) after stratification based on the CAC score.

RESULTS—Among MESA participants eligible for the TIPS, Poly-Iran, Wald's and PILL collaboration, a CAC=0 was observed in 58.6%, 54.5%, 38.9% and 40.8%, respectively. The rate

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of CHD events among those with CAC=0 varied from 1.2 to 1.9 events per 1000 person-years, those with CAC 1- 100 had event rates ranging from 4.1 to 5.5, and in those with CAC>100 the event rate ranged from 11.6 to 13.3. The estimated 5-year NNT to prevent one CVD event ranged from 81 to 130 for individuals with CAC=0, 38 to 54 for those with CAC 1-100, and 18 to 20 for those with CAC>100.

CONCLUSION—Among individuals eligible for treatment with the polypill, the majority of events occurred in those with CAC>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, avoiding treatment in those who are unlikely to be benefit

Keywords

subclinical atherosclerosis; risk stratification; polypill

INTRODUCTION

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 et al (1) hypothesized that a combination of aspirin, a beta-blocker, an angiotensin-converting enzyme (ACE) inhibitor and a statin could reduce CVD events by up to 75%, while Wald has suggested that such an approach with 6 medications, could reduce up to 80% of coronary heart disease (CHD) and stroke events(2). These authors suggest that either all patients above the age of 55 or those with at least one 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 WHO, CDC, NHLBI 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 non-contrast 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.(7,8) As importantly, the absence of calcium as associated with an excellent prognosis and very low event rates in asymptomatic individuals. (9,10).

We hypothesize 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 have evaluated whether coronary artery calcium (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.

The Multi-Ethnic Study of Atherosclerosis

The Multi-Ethnic Study of Atherosclerosis (MESA) is a NIH/NHLBI-funded study that has been 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 6814 individuals between the ages of 45 and 84, from both genders, free from known cardiovascular 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.

Patient population

Using baseline data (MESA, 2000-2002), we identified individuals who meet eligibility criteria for four polypill based published trials. The trials and criteria used to identify individuals who may be eligible for treatment with a polypill included: (1) Indian Polycap Study (TIPS): age 40 – 80 without CVD and 1 CVD risk factor.(12) (2) Poly-Iran: age 50 – 80 with or without any risk factor.(13,14) (3) The initial Wald publication suggested use by all adults above the age of 55.(2) (4) The PILL collaborative group criteria used a Framingham risk score above 7.5% as the inclusion criteria (15). Individuals meeting inclusion and not meeting exclusion criteria as detailed in those studies have been included in the present analysis. (Figure 1.)

Coronary artery calcium score protocol

MESA participants underwent non-contrast cardiac-gated computed tomography for coronary calcium score evaluation as previously described.(16) Approximately half of the scans were performed with a four detector CT scanner and electron beam tomography (EBT) was used for the others. 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 for a median of 7.6 years for incident CVD events from their baseline examinations. Follow-up consisted of three follow-up visits conducted by each participating center. In addition, subjects 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 two 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.

CHD events included both myocardial infarction and death from CHD. Myocardial infarction was defined as definite, probable, or absent based on symptoms, ECG 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 hours prior to death or a history of CHD and no other known non-atherosclerotic or non-cardiac cause for death.

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

Statistical Analysis

Baseline characteristics of the study participants criteria were analyzed according to the presence or abscence of CAC. Frequencies and proportions were calculated for categorical variables, and either means with standard deviations or medians with interquartile ranges were be 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 have compared absolute CHD and CVD event rates as well as Cox multivariable-adjusted hazard ratios after stratifying by the presence or abscence of CAC. Models were adjusted for age, gender, race/ethnicity, education level (a measure of socioeconomic status), and MESA site.

In addition, we have calculated 5-year number needed to treat (NNT) for both CHD and CVD by applying the hazard ratio associated with 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 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 accross different levels of clinical risk using the the Framingham risk score for each individual was performed. For this analysis the NNT for 5 years for CHD and CVD events was calculated for each CAC level stratified by three groups of Framingham risk socre defined as low-risk (<10%), intermediate-risk (10-20%) and high-risk (>20%). Sensitivity analysis were performed from a wide range of risk reductions to evualuate the consistency of the findings. While some groups have proposed a reduction in the relative risk of as high as 80%, we have chosen an estimate based on the most widely accepted estimates from more recent publications(12). Similar estimates have also been estimated by Muntner (18).

RESULTS

Baseline Characteristics

Among the 6814 individuals initially included in the MESA study, 2238 (32.8%) met the eligibility criteria for the TIPS, 2278 (33.4%) for the Poly-Iran, 4416 (64.8%) were above the age of 55 years as proposed in the initial Wald proposal, and 3911 (57.4%) were eligible by the PILL collaboration criteria. The overall distribution of age, gender, 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 four polypill regimens was variable, as would be expected based the respective patient populations included in each study (Figure 2). For instance, the TIPS and the Poly-Iran studies included younger individuals (i.e. above 40 and 50 years of age) while excluding individuals above the age of 80. Additionally, the TIPS study excluded individuals with very high low-density lipoprotein cholesterol or elevated creatinine. Therefore, those two studies resulted in a lower risk population and accordingly had a lower prevalence of any CAC (i.e. CAC>0) as well as CAC >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 rate of CHD and CVD events for individuals with CAC=0 (i.e. CAC score of zero) was low in all four groups, ranging from 1.2 to 1.9 CHD events per 1000 person-years. On the other hand, the CAC 1-100 were associated to a 2.3 to 2.8-fold increase in CHD events, ranging from 4.1 to 5.5 events per 1000 person-years. For patients with a CAC score > 100 there was a 4.7 to 6.4-fold increase in the risk of CHD events, with a rate of events ranging from 11.6 to 13.3 events per 1000 person-years (table 2). The Kaplan-Meier estimates for CHD event free survival for each of the polypill populations is presented in figure 3A.

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 1000 person-years. For individuals with CAC between 1 and 100 the rates ranged from 6.0 to 8.5 events per 1000 person-years, whereas individuals with a CAC >100 had rates between 15.8 and 18.4 per 1000 person-years (table 2). The Kaplan-Meier estimates for CVD event free survival for each of the polypill populations is presented in figure 3B.

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

Number need to Treat 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 TIPS study(12); the NNT for 5 years to prevent one CVD event would range from 81 to 130 for patients with a CAC = 0. For the patients with CAC between 1 and 100, the NNT would range from 38 to 54. For CAC > 100 the NNT to prevent 1 CVD event would be between 18 and 20 (figure 4).

Because the exact reduction in the relative risk with the use of the polypill is not clearly defined, a sensitivity analysis of was performed. For individuals with a CAC=0, the NNT to prevent one CVD event over 5 years was greater than 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 one 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 one CVD event increases and approaches 80 when the risk reduction is 40%. On the other hand, for patients with CAC > 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% (figure 5).

In a sub analysis we also assessed the utility of CAC testing to identify groups that may benefit the least and the most from adding CAC in addition to traditional risk classification by the Framingham risk score. Approximately one third of individuals eligible for poly-pill in the two studies which included lower risk and 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 poly-pill criteria in the other two studies focusing on slightly older population were intermediate-high risk (Wald's=51% and PILL Collaboration=56%). For all studies, the NNT in those at least intermediate risk was less than 48 individuals for preventing one CHD event and 34 individuals for preventing one CVD event. (Supplement figure 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 intermediate risk (NNT range 135-162 for hard CHD) and high risk (68-126 for hard CHD) groups. On the other hand among those with low FRS and CAC >100 across all criteria, the calculated NNT for preventing one hard CHD event was 38-56 and 26-38 for hard CVD, respectively.

DISCUSSION

In the present study, we have 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 sub-groups that met the inclusion and exclusion criteria for the 4 suggested polypill regimens, the NNT in 5 years to prevent one CVD event ranged from 36 to 57. However, if the strategy of treating only individuals with CAC >100 is chosen, the majority of persons that 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 four strategies. Accordingly, the NNT for 5 years to reduce one 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 prevention.(21,22) On the other extreme, the groups 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 > 100 are extremely robust, as even if the actual efficacy of the polypill is 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 even rate in 7.6 years of follow up, that even if the reduction in the relative risk was 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 is 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 is still around 50%, the expected NNT would be as high as 65.

Irrespective of which of the four inclusion criteria is used, our current data supports 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 are 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 (23) in which we showed that among those MESA participants meeting the “JUPITER criteria” for statin therapy, 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 only treating 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 would be appropriate candidates. Our study, as well as other(24), supports the notion that treatment based on CAC, may identify a larger proportion of individuals at risk for events than other approaches which are based on age or risk factors.

Our analysis demonstrated that even after taking after additional risk stratification with global risk scores such as FRS, among the population considered eligible for polypill based on predefined risk factor based criteria, CAC was still able to provide clinically meaningful information to guide treatment. Among individuals considered intermediate-high risk, absence of CAC was associated with a considerably higher NNT to prevent one 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 sub-groups among whom the benefit may be limited. For example if one decides that the

acceptable NNT for CVD for the polypill is 30-40, among the individuals who would be candidates for the Wald regimen, only those with CAC >100 or the high FRS with CAC >0 would be the most appropriate groups who are likely to derive the greatest benefit from polypill. However in the same process, the initial candidate population could be reduced from by 64% (from 4416 to 1617 individuals requiring treatment) and as a result have tremendous impact when the proposal of widespread use of the polypill 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 4-5 years.(26) Finally, the polypill is expected to be an intervention which would be able to prevent CVD events at a low cost. Since CAC scanning is associated with a small additional cost (European costs are approximately 115 euros,(27) however, as 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 is warranted.(28) Importantly, the CAC can be performed on the vast majority of the currently available scanners around the world, and this technology will not be 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, since a single combined pill formulation is proposed, individuals with contra-indication to any of the components would not be eligible. For instance, individuals with asthma (contra-indications to beta-blockers) and aspirin intolerance may not tolerate such therapy. Second, there is a significant rate of discontinuation due to side effects from the polypills. Although not significantly higher than placebo on short 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 is 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 suggests 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(30). 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 non-diabetics, like the population included in our study. The use of aspirin increased the incidence rate of bleeding by approximately 2.0 events per 1000 person-years.(31) These results are particularly concerning when considering treatment of individuals with a CAC=0 have very low CVD rates of 2.5 to 4.0 per 1000 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 while the exact magnitude of the combined benefit is

unknown, it is fair to state 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 which affirms the findings that once CAC is present, and particularly when CAC >100, the favorably low NNT will persists across a wide range of risk reduction.

Our study has 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 robust CAC may perform in identifying groups who are most likely to benefit from therapy. In this sense, the current data supports 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 still ensure treatment to the majority of individuals who are likely to experience CHD and CVD events.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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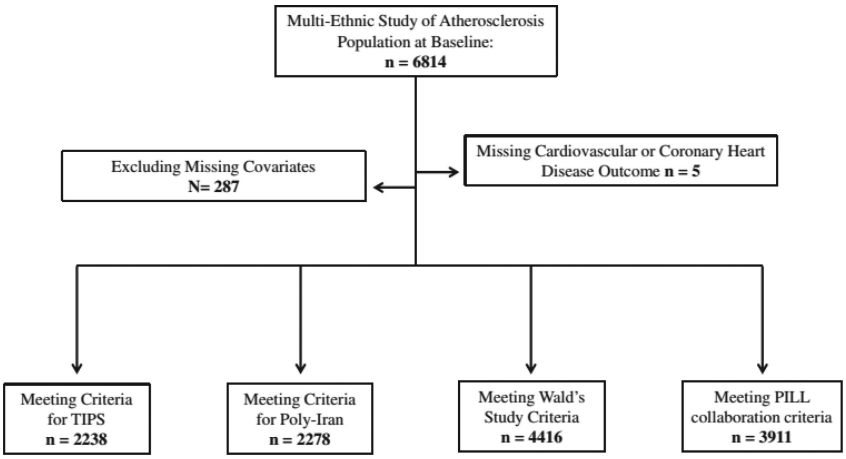

Figure 1.
Flowchart of participants included in the analysis.

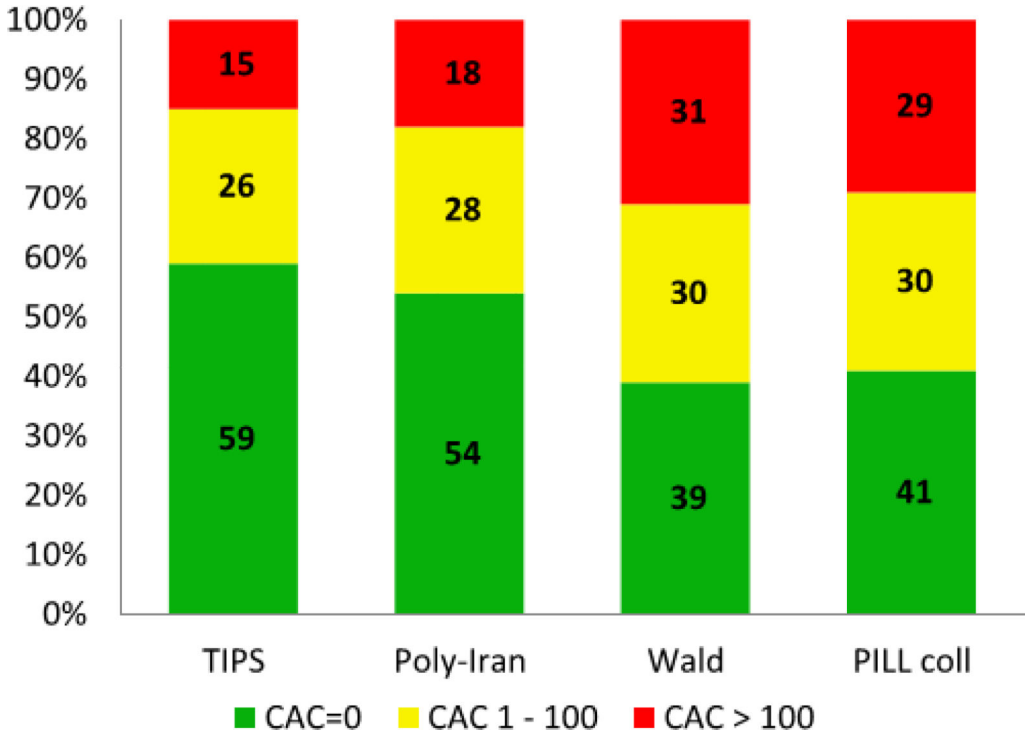

Figure 2.
Distribution of Coronary Artery Calcium (CAC) in each of the four proposed polypill regimens.

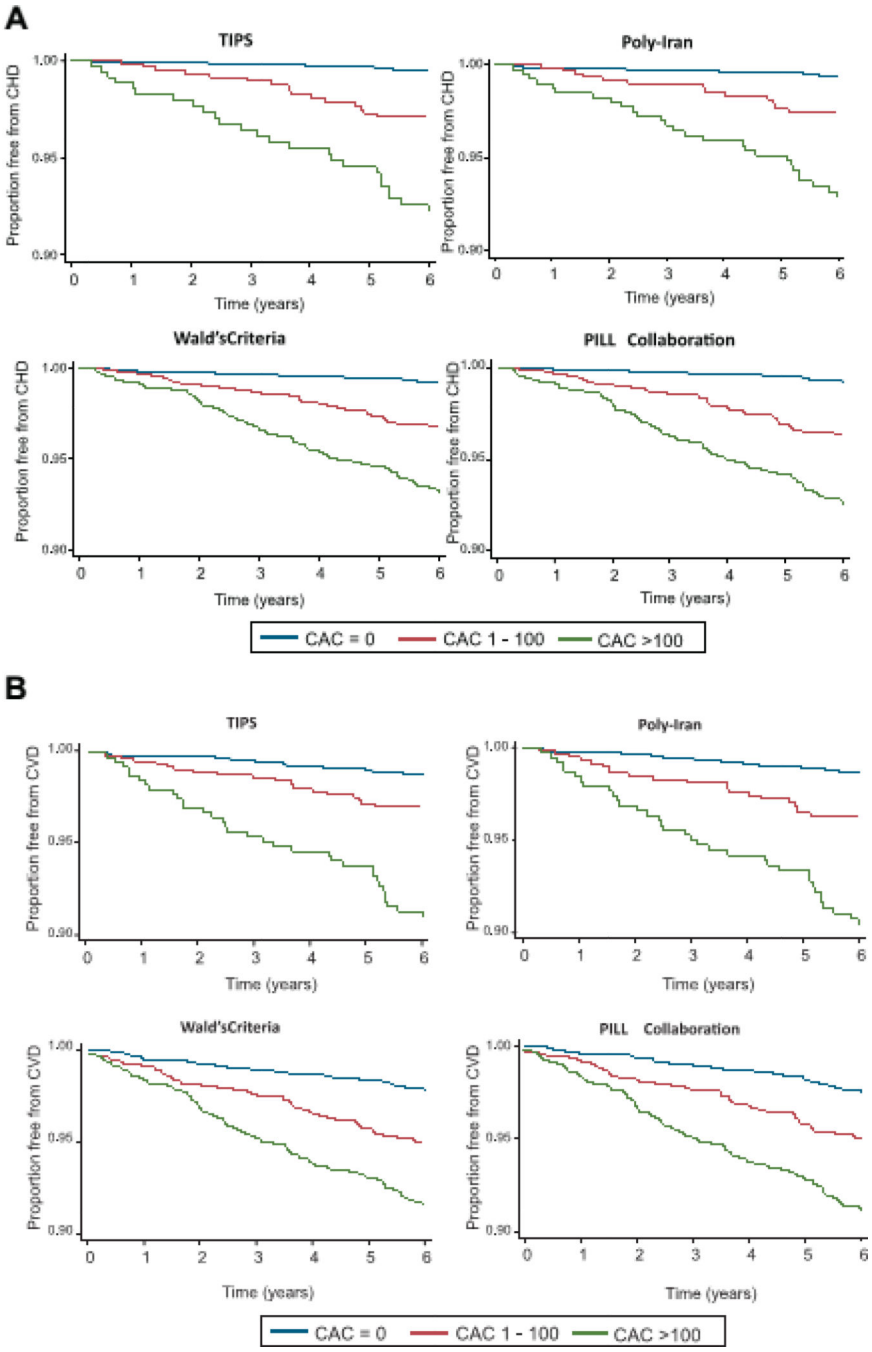

Figure 3.

A. Survival free from CHD events stratified by the presence or absence of coronary artery calcium for each of the four polypill regimens. B. Survival free from CVD events stratified by the presence or absence of coronary artery calcium for each of the four polypill regimens.

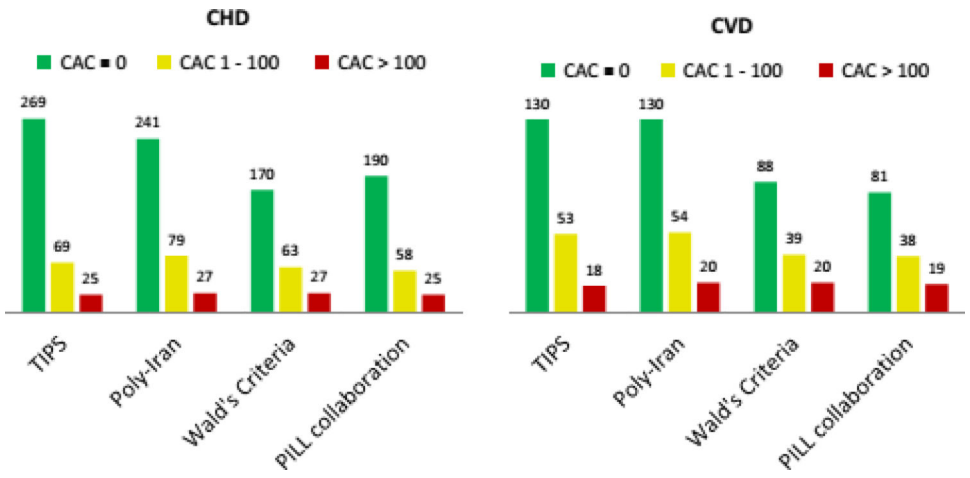

Figure 4.

NNT to prevent one CHD (left) and one 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 subsequently adjusted to a 5-year period.

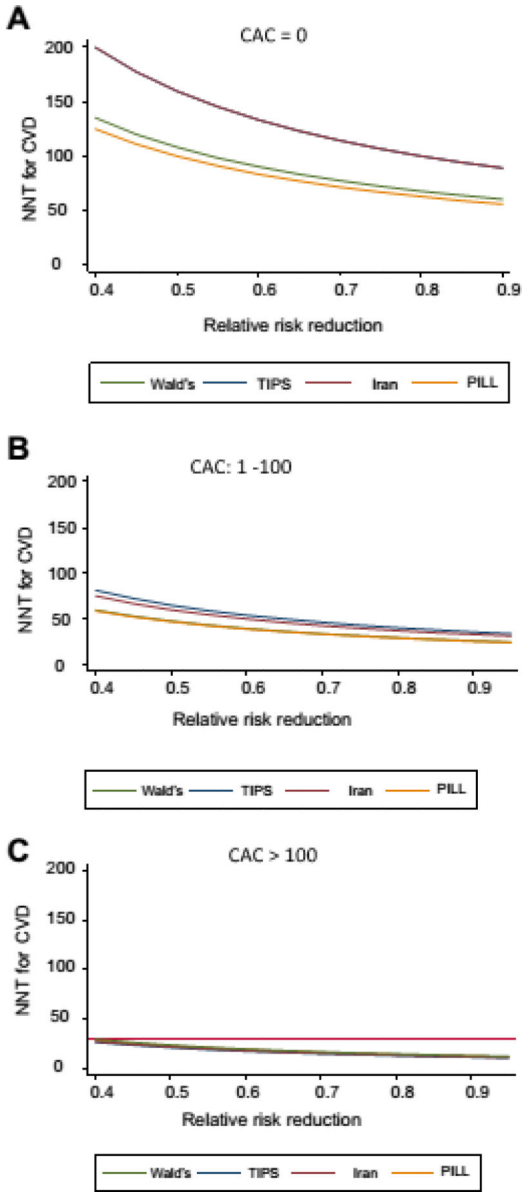

Figure 5.

Sensitivity analysis for the NNT for 5 years to reduce one 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 of zero. B. Subjects with CAC 1 – 100. C. Subjects with CAC > 100. The panel on the right includes a red reference line on the NNT of 30 for reference.

Table 1

Baseline characteristics according to the inclusion criteria for each polypill study. Continuous variables are presented as mean (± SD) or mean (interquartile range) while categorical data is presented in absolute numbers (proportions).

	TIPS	Poly-Iran	Wald	PILL Collaboration
Number of subjects eligible in MESA	2238	2278	4416	3911
Age	58.6±9.4	62.2±7.9	67.7±7.2	63.8±9.9
Male	1126 (50.3%)	1080 (47.4%)	2094 (47.4%)	2506 (64.1%)
Race				
White	766 (34.2%)	831 (36.5%)	1696 (38.4%)	1385 (35.4%)
Black	573 (25.6%)	531 (23.3%)	1250 (28.3%)	1150 (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%)	2574 (58.3%)	2301 (58.8%)
Smoking				
Never	1062 (47.5%)	1131 (49.8%)	2194 (49.9%)	1763 (45.3%)
Former	716 (32.0%)	813 (35.8%)	1757 (39.9%)	1517 (39.0%)
Current	457 (20.5%)	328 (14.4%)	449 (10.2%)	611 (15.7%)
Education				
< High School	1173 (53.1%)	1182 (52.7%)	2437 (56.2%)	2090 (54.3%)
College	294 (13.3%)	284 (12.7%)	474 (10.9%)	477 (12.4%)
Bachelor or above	741 (33.6%)	775 (34.6%)	1429 (32.9%)	1279 (33.3%)
Family history	826 (39.1%)	830 (38.9%)	1854 (45.1%)	1650 (45.6%)
BMI	28.5±5.5)	27.3±5.1	28.2±5.3	29.2±5.4
LDL	124.1±26.8	123.0±31.6	116.7±31.5	121.0±32.0
HDL	48.8±13.9	51.9±15.3	51.7±14.9	46.2±12.1
Triglycerides	115 (80 – 162)	110 (77 – 158)	111 (79 – 159)	126 (87 – 179)
Calcium Scores				
Zero	1312 (58.6%)	1241 (54.5%)	1718 (38.9%)	1596 (40.8%)
1 – 100	581 (26%)	628 (27.5%)	1324 (30.0%)	1161 (29.7%)
> 100	345 (15.4%)	409 (18.0%)	1374 (31.1%)	1154 (29.5%)

Table 2

CHD and CVD event rates per 1000 person-years and 5-year NNT for each of the polypill studies. The NNTs were calculated directly as the reciprocal of the absolute risk difference at the median follow up of 7.6 years and subsequently adjusted to a 5-year period.

	TIPS			Poly-Iran			Wald			PILL Collaboration		
	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**
N (%)	1312 (58.6%)	581 (26%)	345 (15.4%)	1241 (54.5%)	628 (27.6%)	409 (17.9%)	1718 (38.9%)	1324 (30%)	1374 (31.1%)	1596 (40.8%)	1161 (29.7%)	1154 (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 (1000 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 (1000 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

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Table 3

Hazard ratio for the presence of Coronary Artery Calcium (CAC). The results are adjusted for age, gender, race, education and MESA site

	TIPS		Poly-Iran		Wald		PILL Collaboration	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	
CHD								
CAC = 0	1 (ref)	-	1 (ref)	-	1 (ref)	-	1 (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 (ref)	-	1 (ref)	-	1 (ref)	-	1 (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