JACC: ADVANCES VOL. 2, NO. 10, 2023

ORIGINAL RESEARCH

OUTCOMES AND QUALITY

Impact of Active vs Passive Statin Selection for Primary Prevention

The CorCal Vanguard Trial

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ABSTRACT

BACKGROUND Statins can improve outcomes in high-risk primary prevention populations. However, application in clinical practice has lagged.

OBJECTIVES The objective of this study was to compare an active vs a passive strategy (ie, usual care) to statin prescription for primary prevention of atherosclerotic cardiovascular disease (ASCVD).

METHODS A total of 3,770 patients ≥50 years of age without a history of ASCVD or statin use were invited to enroll in CorCal, with 601 consenting to participate. These patients were randomized 1:1 to statin initiation guided by the pooled cohort equation or by coronary artery calcium scoring (CACS). Outcomes (2.8-year follow-up) compared patients managed actively vs passively (randomly invited but declined or did not respond).

RESULTS Patient demographics were well matched. Statin recommendation was common among enrolled patients (41.7%). During follow-up, 25.3% of active patients were taking a statin vs 9.8% managed passively ($P < 0.0001$). Active patients had more lipid panels (median 2.0 vs 1.0), lower low-density lipoprotein cholesterol (109 vs 117 mg/dL) (both $P < 0.0001$), and a low rate of major adverse cardiovascular events during follow-up (0.6% vs 1.0%, $P = 0.47$). Statistical comparisons included *t*-tests, chi-squared tests, nonparametric tests, and time-to-event tests as appropriate.

CONCLUSIONS An active approach to statin selection for primary ASCVD prevention identified a large treatment opportunity and led to over twice as many patients on statins compared to passive (usual care) management. A large CorCal Outcomes Trial is underway to more definitively assess the impact on outcomes of active management of statins for primary prevention. (JACC Adv 2023;2:100676) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received April 27, 2023; revised manuscript received August 9, 2023, accepted August 30, 2023.

ISSN 2772-963X https://doi.org/10.1016/j.jacadv.2023.100676

ABBREVIATIONS AND ACRONYMS

ASCVD = atherosclerotic cardiovascular disease

CACS = coronary artery calcium scoring

CAD = coronary artery disease

CV = cardiovascular

EDW = enterprise data warehouse

LDL-C = low-density lipoprotein cholesterol

MACE = major adverse cardiovascular events

MI = myocardial infarction

PCE = pooled cohort equation

Cardiovascular (CV) diseases continue to be the leading cause of morbidity and mortality in the United States and globally.[1-3] Of CV disease burden, the leading contributor is atherosclerotic CV disease (ASCVD), including coronary artery disease (CAD), ischemic stroke, and peripheral arterial disease. Four classical modifiable risk factors for ASCVD include smoking, diabetes, hypertension, and hyperlipidemia.

The 3-hydroxy-3-methylglutaryl coenzyme A-reductase inhibitors (statins) have been shown to be highly effective in the prevention of ASCVD in individuals at elevated primary and secondary ASCVD risk.[4-6] Accordingly, statins represent the foundational therapy in cholesterol treatment guidelines.[7,8] Unfortunately, studies have consistently noted a major lag/gap in risk assessment, statin initiation, and statin persistence.[9-14] Furthermore, a high percentage of individuals, especially younger individuals with a first ASCVD event (eg, myocardial infarction [MI]) would not have been identified as at high enough risk to warrant prior preventive therapy based on current risk assessment algorithms,[9-11,15] indicating an ongoing need for improved primary risk prediction tools.

We therefore performed a randomized study to test the effectiveness of a proactive cardiovascular primary prevention strategy using either the pooled cohort equation (PCE) or coronary calcium scoring (CACS) named CorCal (Effectiveness of a Proactive Cardiovascular Primary Prevention Strategy, With or Without the Use of Coronary Calcium Screening, in Preventing Future Major Adverse Cardiac Events). The Vanguard portion of CorCal has been completed, with the larger outcomes study ongoing. Objectives of the randomized CorCal Vanguard Trial were: 1) to compare 2 primary risk assessment strategies for statin selection, and 2) to compare an active approach (ie, using either of these 2 strategies) to a passive approach to statin prescription (ie, usual care) for primary prevention of ASCVD. The results of the first objective have recently been published.[16] This report addresses the second objective.

METHODS

The CorCal Vanguard trial methodology has been published in greater detail elsewhere.[16] The CorCal study was approved by the Intermountain Health Institutional Review and Privacy Board and registered with clinicaltrials.gov (NCT03439267). The purpose of this current study is to report the prospective CorCal Vanguard objective to compare an active approach to statin selection for primary prevention (by either of 2 active strategies) to a passive strategy (ie, usual care).

STUDY INSTITUTION. The CorCal Vanguard trial was conducted within the Intermountain Health system. Intermountain Health (Intermountain) is a nonprofit, integrated health care system that included 24 hospitals and 215 clinics in Utah, Idaho, and Nevada during the study period. Intermountain Health has a long-standing, integrated electronic medical records system, the enterprise data warehouse (EDW).

STUDY PROTOCOL. CorCal enrolled Intermountain subjects aged 50 to 85 who were at primary risk for ASCVD and who had an established relationship with an Intermountain health care provider, which was defined as at least 2 visits in the past 5 years with 1 within the past 2 years. Excluded were subjects with a prior history of CAD, peripheral arterial disease, or cerebrovascular arterial disease, diabetes, use of a statin, or a life expectancy of <2 years, based on study investigator's judgment (eg, active cancer, except for a diagnosis of nonmelanoma skin cancer, not in remission or end-stage organ disease).

Potentially eligible subjects were identified by a query of Intermountain health records, and a random sample of 3,770 patients living near Salt Lake City, Utah was invited by mail between March 2018 and April 2019 to participate in the study. Of these, 601 gave written consent to participate in the study and formed the active treatment group. The others, who either declined or did not respond to the letter of invitation, formed the passive treatment group.

STUDY INTERVENTIONS. The 601 patients in the active group consented to be randomized 1:1 to statin initiation guided by either the PCE (n = 299) or by CAC scoring (CACS) (n = 302). Of these, 259 of PCE-assigned patients and 281 of CACS-assigned patients completed required baseline tests (ie, lipid panel; CACS if assigned) and received a statin assignment. The study criteria for statin recommendation and intensity in each arm have been previously published[16] and are summarized in Supplemental Table 1. In brief, PCE recommendations followed the existing guidelines of the American Heart Association/American College of Cardiology for primary prevention.[7] In the CAC arm, an Agatston score of $\geq$100 or a qualifying PCE score for those with a score of 1 to 100 led to a statin recommendation. No therapy was recommended for a CACS = 0 unless low-density lipoprotein cholesterol (LDL-C) exceeded 189 mg/dL.

Therapies in subjects in the control group, that is, those declining to participate or not responding to the

letter of invitation, including initiation of statin therapy during the study observation period, were left to their primary care physicians.

SUBJECT DEMOGRAPHICS AND OUTCOMES. Physicians of subjects enrolled in the active arms received individualized statin treatment and intensity recommendations (ie, to not treat or to treat with a statin and, if so, with moderate or high-intensity dosing), and they then were left to act on their own personal judgment and initiative to interact with patients and implement the study treatment recommendations.

Demographics and statin prescription and lipid testing information in both active and passive groups were obtained through Intermountain EDW records. Clinical outcomes of interest at 1 year included all-cause death, MI, stroke, and arterial revascularization and were determined by EDW query. MI and stroke were determined by International Classification of Diseases (ICD) codes (MI: ICD-9 code 410.x1 or ICD-10 codes: I21.x; CVA: ICD-9 code 433.x1, 434.x1 or ICD-10: I63.x, I64.x). Start date for the outcomes query for each group began with the time the letter of invitation was sent.

STATISTICAL ANALYSIS. For the primary comparisons, all patients signing consent were included in the active group (intention to treat, n = 601). They were compared to all others randomly selected and meeting study entry criteria but not responding or not consenting to be enrolled (passive group, n = 3,169). Baseline characteristics are described using frequencies and proportions for categorical variables. Continuous variables are summarized by mean ± SD or median (IQR). Categorical comparisons used the chi-squared statistic. Since the evaluation of outcomes was exploratory in this Vanguard study, and the event total was small, all events were considered and compared even though the length of follow-up differed slightly between the patient groups. Statistical analyses used SPSS for Windows (version 26.0).

RESULTS

PATIENT CHARACTERISTICS. Baseline characteristics of the study cohort, stratified by active and passive arm, are shown in **Table 1**. The 2 study arms were generally well matched. Smoking was slightly more frequent in the passive arm (14.5% vs 11%), with minor increases in non-White race and high-density lipoprotein cholesterol. Patients were followed for clinical care, lipid levels, and outcomes over an average of 2.85 years. Baseline characteristics within the active group are shown by randomization arm (PCE vs CAC) in Supplemental Table 2.

TABLE 1 Baseline Characteristics Stratified by Enrolled (Active) and Invitation Nonresponder/Declined (Passive) Status

	Active (n = 601, 15.9%)	Passive (n = 3,169, 84.1%)	*P* Value
Age (y)	60.2 ± 6.9	60.0 ± 7.5	0.67
Male	34.9	35.2	0.91
Hypertension (%)	39.6	37.1	0.25
Antihypertensive use (%)	15.8	14.2	0.31
Smoking (%)	11.0	14.5	0.02
BMI (kg/m^2)	28.6 ± 6.8	28.2 ± 6.5	0.22
Race			0.02
White (%)	97.3	95.0	
SBP (mm Hg)	123.6 ± 15.1	124.0 ± 15.4	0.62
DBP (mm Hg)	75.7 ± 10.0	75.9 ± 10.3	0.74
Lipid panel			
Total cholesterol	196.5 ± 31.8	199.5 ± 33.6	0.08
LDL-C	120.1 ± 26.7	121.3 ± 28.1	0.53
HDL-C	53.7 ± 14.8	55.3 ± 15.9	0.02
Triglycerides	114.4 ± 62.3	115.8 ± 67.1	0.94
Statin recommendation (%)	41.7[a]	-	-

Values are mean ± SD or %. [a]Percent of patients recommended a statin of 540 consenting patients who completed baseline lipid and CAC (CAC-arm) testing and were randomized to a risk-based statin recommendation.

BMI = body mass index; DBP = diastolic blood pressure; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; SBP = systolic blood pressure.

STATIN RECOMMENDATIONS AND PRESCRIPTIONS. Study algorithms (Supplemental Table 1) recommended a statin prescription in 41.7% of active arm primary prevention subjects based on their calculated ASCVD risk. During follow-up, 25.3% of active arm patients overall were taking a statin based on medical records prescription information. Passive arm subjects received usual care from their primary caregivers. During follow-up in passive arm subjects, medical records indicated a new statin prescription in 9.8% ($P < 0.0001$ vs active arm) (**Table 2**) (**Central Illustration**). Statin recommendations and adherence at 1 year in the active group are shown by randomization arm (PCE vs CAC) in Supplemental Table 2.

LIPID PARAMETER RESPONSES. Active arm patients had more lipid panels during follow-up, averaging 2.2 (median 2.0) versus 1.4 (median 1.0) in passive arm patients ($P < 0.0001$) (**Table 2**). Active arm patients also had lower total cholesterol (187 vs 196 mg/dL) and LDL-C (109 vs 117 mg/dL) at last testing (both $P < 0.0001$) (**Table 2**); high-density lipoprotein cholesterol and triglyceride levels on follow-up did not differ significantly.

CLINICAL OUTCOMES. During an average overall follow-up of 2.85 years, ASCVD event rates were low in this primary prevention cohort (**Table 3**). Major

TABLE 2 Follow-Up Lipids and Statin Use Stratified by Enrolled (Active) and Invitation Nonresponder/Declined (Passive) Status

	Active	Passive	*P* Value
Mean number of follow-up LDL-C measurements	2.2 ± 1.5 (median: 2.0)	1.4 ± 1.3 (median: 1.0)	<0.0001
Last lipid panel			
Years	2.04 ± 1.05 (median: 2.33)	2.15 ± 0.87 (median: 2.32)	
Total cholesterol	187.2 ± 39.8	196.0 ± 36.4	<0.0001
LDL-C	109.5 ± 34.6	116.8 ± 30.4	<0.0001
HDL-C	54.7 ± 14.8	55.7 ± 16.2	0.42
Triglycerides	116.2 ± 65.9	118.7 ± 65.1	0.44
Follow-up statin	25.3	9.8	<0.0001

Values are mean ± SD.
HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

adverse CV events (MACE) occurred in 3 patients (0.6%) in the active group and 31 patients (1.0%) in the passive group, a nonsignificant difference. Death occurred in none (0%) among active patients and in 19 (0.6%) among passively managed subjects ($P = 0.10$). Individual event rates were low, and no difference trends emerged for nonfatal MI, nonfatal stroke, and arterial revascularization.

DISCUSSION

SUMMARY OF STUDY FINDINGS. In this random sample of primary prevention patients within Intermountain Health, an active approach to statin selection based on PCE or CACS determination of not low-risk status (active arm) led to a more than 2-fold increase in statin prescriptions over the 2.9-year average period of follow-up compared to usual care by primary care physicians (passive arm) (**Central Illustration**). The groups were well balanced demographically, except for a small increase in smokers in the passive arm group. Participation in the active arm was also associated with twice the median number of follow-up lipid panels and lower follow-up levels of total cholesterol and LDL-C. Clinical event rates in this primary prevention population were low in both groups over nearly 3 years of follow-up (0.6% vs 1.0%, P = NS) but with a trend to a lower mortality rate with active therapy (0% vs 0.6%, $P = 0.10$).

LITERATURE COMPARISONS. ASCVD continues to be the leading cause of morbidity and mortality in the Western World and globally.[1-3] LDL-C is not only a well-established risk factor for ASCVD but now generally is accepted to be a causal factor,[17] based on genetic, epidemiologic, preclinical, and clinical studies.[4-8,17] Furthermore, there is strong and consistent evidence, especially for statins, that lowering LDL-C lowers primary and secondary ASCVD risk.[4-6] Hence, current guidelines strongly endorse LDL-C lowering with statins for secondary prevention and in those at elevated primary ASCVD risk.[7,8,18] Concomitant emphasis on a healthy lifestyle also is supported by clinical evidence.[19]

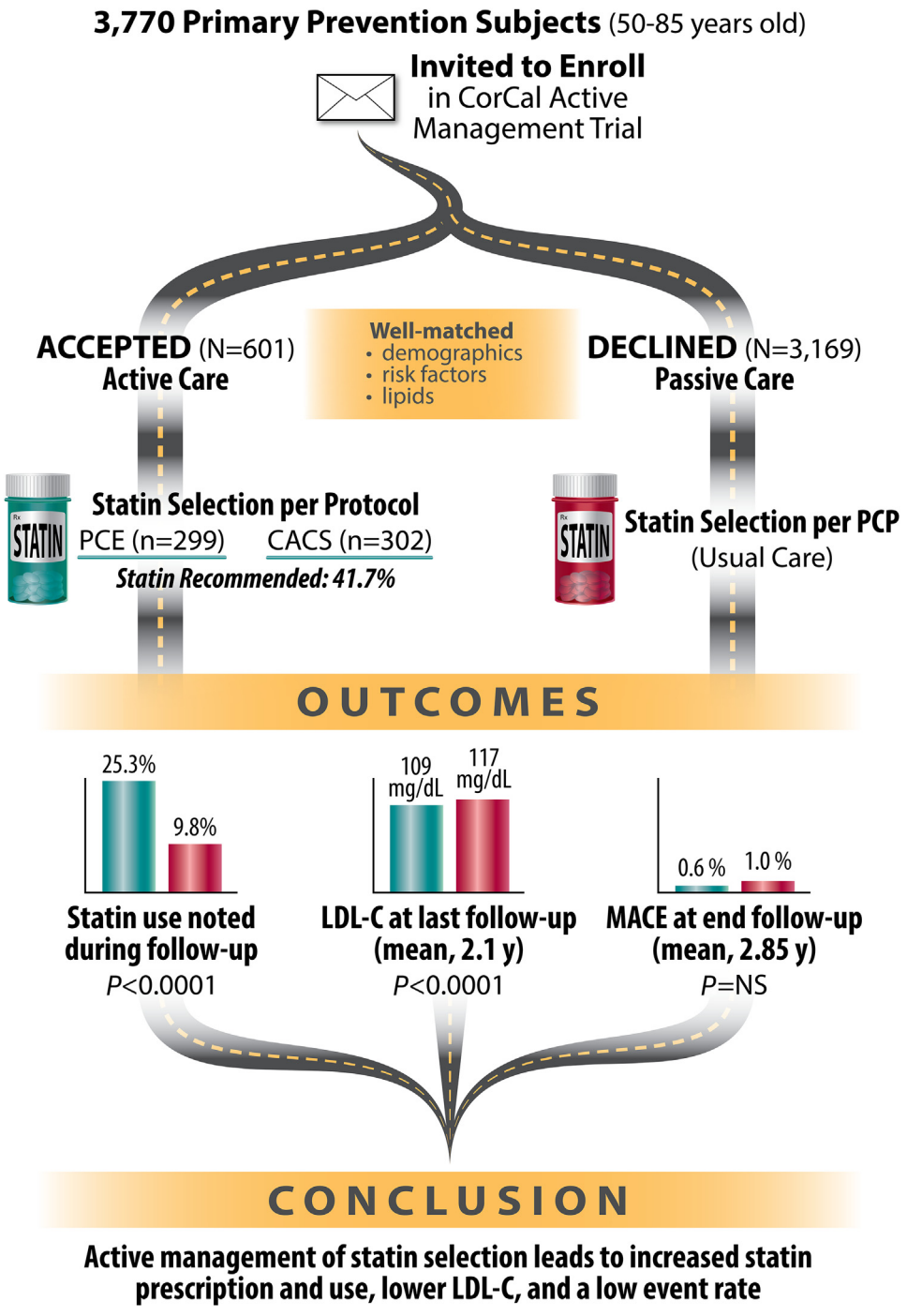
Despite this firm evidence base and guideline recommendations, there remains a large treatment gap and an opportunity for improved prevention, especially for primary prevention.[10,13,20,21] For example, in a study of individuals presenting with premature, angiographically documented CAD, 41% would have qualified for a statin by current guidelines, with an additional 14% who could be considered for treatment. However, only 17% had received a statin and only 11% had achieved guideline-recommended treatment goals. Our 41% of primary prevention patients who were recommended for statin therapy in CorCal endorses a similar treatment opportunity.

This impressive gap in implementation of optimal lipid lowering for primary prevention has motivated investigators to study methods to determine optimal implementation strategies.[22] Community-based efforts have been studied to improve blood pressure control, and these could hold lessons for lipid management. A cluster-randomized trial of blood pressure reduction program based in black barbershops attended by specialty-trained pharmacists showed larger reductions in blood pressure than in control shops.[23] In another cluster-randomized trial, a nonphysician community health care team in China achieved important reductions in CV events by implementing an intensive blood pressure reduction program.[24]

These community-based efforts, while effective, require major resource commitments. Blood et al[25] remotely delivered a hypertension and lipid program to patients across a diverse health care network. Of 18,444 patients approached, 10,803 agreed to be enrolled. Education, monitoring, and treatment were managed by nonlicensed navigators and pharmacists, using standardized algorithms and supported by CV clinicians. Those enrolled in the lipid management program experienced a 37.5 mg/dL reduction in LDL-C at 12 months, compared to a 10.2 mg/dL reduction in the education-only cohort. In our current study, a simple letter invitation resulted in a 16% (601/3,770) acceptance rate for remote risk assessment and statin recommendation and achieved a more than doubling of the rate of statin prescription compared to usual care.

To improve initiation and adherence to a statin recommendation, electronic "nudges" to patients and to physicians have been studied. In the ENCOURAGE (the improvEment in medicatioN adherenCe thrOUgh

CENTRAL ILLUSTRATION **Trial Summary of Active Vs Passive Management of LDL-Cholesterol With Statins in the CorCal Study**



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CACS = coronary artery calcium scoring; LDL-C = low-density lipoprotein cholesterol; MACE = major adverse cardiovascular event; PCE = pooled cohort equation; PCP = primary care physician.

TABLE 3 Outcomes Stratified by Enrolled (Active) and Invitation Nonresponder/Declined (Passive) Status

	Active	Passive	*P* Value
Length of follow-up, y	2.93 ± 0.47 (median: 2.98)	2.77 ± 0.57 (median: 2.87)	<0.0001
Outcome events			
MACE	0.6 (3)	1.0 (31)	0.47
Death	0 (0)	0.6 (19)	0.10
Nonfatal MI	0 (0)	0.1 (4)	1.00
Nonfatal stroke	0.4 (2)	0.3 (8)	0.65
PCI	0.2 (1)	0.1 (4)	0.55
CABG	0 (0)	0 (0)	-
Peripheral revascularization	0 (0)	0.03 (1)	1.00

Values are mean ± SD.

CABG = coronary artery bypass graft surgery; MACE = major adverse cardiovascular event; MI = myocardial infarction; PCI = percutaneous coronary intervention.

the implementation of peRsonAl nudGE) trial, Horne et al[14] used personalized electronic nudges to encourage statin compliance and compared it to usual care in a randomized trial of 182 subjects who had an indication for statin therapy. Adherence was greater in those randomized to nudges than to usual care (66.3% vs 50.5%, $P = 0.036$). Adusumalli et al[26] (2023) performed a cluster randomized clinical trial to assess the impact of active electronic health care record alerts compared to passive alerts or no alerts on statin prescribing and dose among a population of 11,693 patients. At baseline, 40% of patients were on optimal statin dosing. Among patients with clinical ASCVD, an increase in optimal dosing of 3.8% in the active compared to the control arm was observed ($P = 0.0087$). The authors proposed that their results could help guide the design or targeting of future interventions aimed at optimizing statin therapy.

CLINICAL IMPLICATIONS. This study confirms that formal risk assessment and treatment recommendations consistent with current cholesterol treatment guidelines increase statin prescriptions and lower total cholesterol and LDL-C. Our study was too small to provide a definitive assessment of outcomes benefit. However, based on projections from clinical trials, a ~30% reduction in CV risk in those taking statins can be estimated. The absolute differential rate of statin use of 15% in our study and a 3-year MACE event rate of 1% indicates potentially a 3 per 1,000 reduction in CV events or potentially 9,000 fewer events per 3 years (3,000/year) in the estimated 3 million persons covered by Intermountain Health. These figures support an aggressive, system-wide active approach to ASCVD primary risk reduction.

Finally, the best statin selection algorithm remains to be determined. We compared 2 (PCE and CAC) in the CorCal Vanguard study.[16] While PCE enjoys boarder experience and acceptance, CAC has several potential advantages, including the ability to reclassify a large percentage of patients into lower or higher risk categories based on anatomic plaque burden rather than risk-factor dependent probabilistic considerations. This can lead to a net reduction in statin prescription and a favorable economic impact, yet with greater adherence.[16] A larger (>5,000 patients) CorCal Outcomes Trial, now underway, should provide a more exact estimate of the potential for outcome benefit system-wide at Intermountain.

STRENGTHS AND LIMITATIONS. This prospectively defined CorCal ancillary study has strengths and some limitations. A strength is its random selection of patients invited to participate in the risk assessment and statin selection trial. As such, demographics should be representative of the primary prevention population of our region and our health care system as a whole. In addition, the characteristics of patients choosing to participate and not choosing were generally quite comparable, indicating a lack of strong systemic health-related biases influencing the decision to participate in the trial. However, the choice of active vs passive management was not randomized, so that small differences in a few baseline characteristics (ie, smoking) were noted, and other, undetected or unaccounted for biases cannot be excluded, which could have influenced the comparative results. For example, agreement to participate in a clinical trial has been reported to be associated with greater adherence to drug therapy.[27] The majority of patients in both arms were of European-American heritage, so that generalizability to other racial/ethnic groups is uncertain. Also, the number of ASCVD events during follow-up was too few to draw firm conclusions about benefit/risk comparisons, and trends should be considered to be hypothesis generating. However, based on these interesting trends, a larger, longer-term trial (CorCal Outcomes) has been planned and is underway, of which one objective is a comparison of outcomes of active versus passively managed patients for statin selection.

CONCLUSIONS

An active approach to statin selection for primary ASCVD prevention identified a major unmet treatment opportunity and led to more than twice as many at-risk patients taking a statin, more frequent lipid checks, lower LDL-C levels, and a favorably low MACE

rate compared to passive management. A large CorCal Outcomes Trial is underway to more definitively assess the impact on outcomes of active management of statin prescription system-wide for patients at primary risk of ASCVD.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This study was supported by departmental funds. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE: An active approach to statin selection for primary ASCVD prevention identified a large treatment opportunity and led to over twice as many patients on statins, more frequent lipid checks, lower LDL-C levels, and a favorably low event rate compared to passive management.

TRANSLATIONAL OUTLOOK: Although this is a Vanguard study, it provides an opportunity to recognize the potential benefits of an active approach to statin use, at a health care system level, to identify primary prevention patients at increased ASCVD risk.

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KEY WORDS atherosclerotic cardiovascular disease, clinical trial, coronary artery calcium, coronary artery disease, pooled cohort equation, statin

APPENDIX For supplemental tables, please see the online version of this paper.