JACC: CARDIOVASCULAR IMAGING
VOL. 10, NO. 8, 2017

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jcmg.2017.04.014

Implications of Coronary Artery Calcium Testing for Treatment Decisions Among Statin Candidates According to the ACC/AHA Cholesterol Management Guidelines

A Cost-Effectiveness Analysis

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ABSTRACT

This review evaluates the cost-effectiveness of using coronary artery calcium (CAC) to guide long-term statin therapy compared with treating all patients eligible for statins according to 2013 American College of Cardiology/American Heart Association cholesterol management guidelines for atherosclerotic cardiovascular disease. The authors used a microsimulation model to compare costs and effectiveness from a societal perspective over a lifetime horizon. Both strategies resulted in similar costs and quality-adjusted life years (QALYs). CAC resulted in increased costs (+$81) and near-equal QALY (+0.01) for an incremental cost-effectiveness ratio of $8,100/QALY compared with the treat-all strategy. For 10,000 patients, the treat-all strategy would theoretically avert 21 atherosclerotic cardiovascular disease events, but would add 47,294 person-years of statins. With CAC costs <$100, and higher cost and/or disutility associated with statin therapy, CAC strategy was favored. These findings suggest the economic value of both approaches were similar. Clinicians should account for individual preferences in context of shared decision making when choosing the most appropriate strategy to guide statin decisions. (J Am Coll Cardiol Img 2017;10:938–52) © 2017 by the American College of Cardiology Foundation.

In 2013, the American College of Cardiology (ACC) and American Heart Association (AHA) expanded the number of patients eligible for statin therapy in the primary prevention settings (1,2). Consequently, it is estimated that 56 million adults in United States will be statin eligible on the basis of their predicted 10-year atherosclerotic cardiovascular disease (ASCVD) risk derived from the Pooled Cohort Equations (1,3). The majority of individuals who are newly eligible have no known ASCVD and are at the lower spectrum of risk. The rationale for widening the scope of statin eligibility has been widely debated

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Manuscript received April 6, 2017; revised manuscript received April 19, 2017, accepted April 20, 2017.

(4,5), considering the fact that the net benefit accrued from treatment is directly proportional to absolute baseline risk (1); many newly eligible for statins may not have a clinically meaningful benefit from long-term treatment. Among these individuals where there is clinical equipoise, the guidelines suggest using shared decision-making principles where patient-centered choices are promoted by understanding and considering the patient's preferences, values, and risk tolerance, and whether the estimated benefits are worth the decades of statin therapy (1,6).

Coronary artery calcium (CAC) detected by low radiation, noncontrast cardiac computed tomography is an established method to quantitate the presence and burden of coronary atherosclerosis, providing robust risk stratification above and beyond traditional risks scores in the primary prevention settings (7,8). More importantly, the absence of CAC in an asymptomatic adult confers a very low risk for future cardiac events (7,9). Multiple studies have demonstrated a significant proportion of statin candidates according to current guidelines have no detectable CAC, and subsequently, these individuals have a lower 10-year observed ASCVD risk than the threshold recommended for statin treatment (10–12).

The value from CAC testing lies in its likelihood of reclassifying risk where a decision for statin therapy changes. The value of additional information can be measured by considering the effectiveness and opportunity costs of alternative treatment strategies, and the diagnostic performance of CAC testing (13). In particular, the absence of CAC reclassifies individuals to a lower risk category and this information can give patients more flexibility in their treatment decisions. The cost-effectiveness of CAC testing in the primary prevention setting has been previously described (14–18). However, there are gaps in knowledge in whether CAC testing to guide statin decisions among those eligible for treatment is cost-effective in the context of the ACC/AHA cholesterol management guidelines. We contribute to the existing literature by using recently described observed ASCVD rates in the MESA study (Multi-Ethnic Study of Atherosclerosis) stratified by CAC score and ACC/AHA risk in a microsimulation model to estimate costs and effectiveness (10). In this study, we evaluate the cost-effectiveness of CAC testing among statin candidates according to updated cholesterol management guidelines by comparing 2 strategies: 1) CAC testing among statin-eligible individuals, where long-term statin therapy is guided by the reclassification of risk; versus 2) treating all statin-eligible individuals according to the ACC/AHA guideline recommendations.

ABBREVIATIONS AND ACRONYMS

ACC = American College of Cardiology

AHA = American Heart Association

ASCVD = atherosclerotic cardiovascular disease

CAC = coronary artery calcium

CHD = coronary heart disease

CI = confidence interval

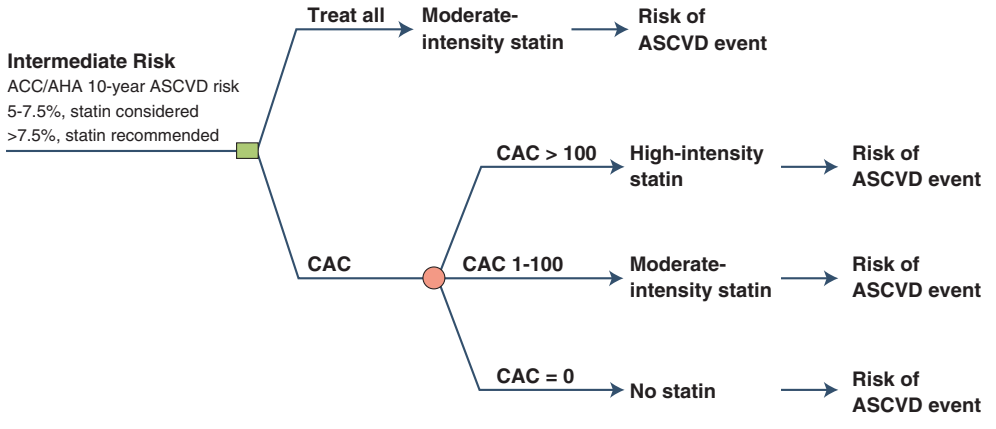
ICER = incremental cost-effectiveness ratio

QALY = quality-adjusted life year

METHODS

MODEL OVERVIEW. We used a state-transition, microsimulation model that has been previously described in the published reports and was developed using TreeAge Pro version 2016 (Williamstown, Massachusetts) (16). The model simulates the clinical and economic consequences of ASCVD in a primary

FIGURE 1 Schematic of Cost-Effectiveness Analysis



We compared 2 strategies: 1) treating all statin-eligible patients at intermediate risk of atherosclerosis (ASCVD); versus 2) CAC testing to guide treatment. ACC/AHA = American College of Cardiology/American Heart Association; CAC = coronary artery calcium.

TABLE 1 Input Parameters for the Microsimulation Model Comparing Statin Therapy Strategies for Individuals at Intermediate Risk for a ASCVD Event

	Base-Case Value	Distribution	Ref. #
ASCVD rate per 1,000 person-yrs			
Statin recommended			(10)
CAC 0	5.2 (4.0–7.0)	Beta	
CAC 1–100	8.8 (6.8–11.4)	Beta	
CAC >100	15.4 (12.5–18.9)	Beta	
Statin considered			(10)
CAC 0	1.5 (0.6–3.6)	Beta	
CAC 1–100	7.8 (4.6–13.2)	Beta	
CAC >100	6.3 (2.4–16.8)	Beta	
Subgroup of statin eligible			(10)
CAC 0	3.5 (2.5–4.9)	Beta	
CAC 1–100	8.0 (6.0–10.7)	Beta	
CAC >100	12.1 (9.0–16.2)	Beta	
Probabilities			
ASCVD mortality in first year, age <65 yrs	0.10 (0.02)	Beta	(16,49,50)
ASCVD mortality in first year, age ≥65 yrs	0.16 (0.03)	Beta	(16,49,50)
ASCVD mortality, annual after first year	0.05 (0.01)	Beta	(49,51)
Death from non-ASCVD	U.S. Life Table	N/A	(26)
Mild adverse effect from a statin	0.18 (0.01)	Beta	(52)
Severe adverse effect from a statin	0.000055	No distribution	(53)
Death given severe adverse reaction from a statin	0.09 (0.03)	Beta	(53)
Statin adherence with no CAC testing	0.55 (0.40–1.00)	Triangular	(22)
Statin adherence with CAC testing	0.65 (0.50–1.00)	Triangular	(16,22–24)
Lifetime cancer risk due to CT-scanning–caused radiation exposure	0.00002	No distribution	(54)
1-yr case fatality given cancer due to radiation risk	0.65	No distribution	(55)
Relative risk ASCVD of statins			
Moderate-intensity statin	0.65 (0.55–0.75)	Triangular	(16,20,21), expert opinion
High-intensity statin	0.55 (0.45–0.65)	Triangular	(16,20,21), expert opinion
Costs, $			
CT CAC	200 (160–240)	Triangular	(29,32)
Statin per year	85 (68–102)	Triangular	(33)
ASCVD, fatal	15,250 (7,625)	Gamma	(16,27)
ASCVD, nonfatal in first year	48,165 (24,080)	Gamma	(16,27)
ASCVD, nonfatal annual after first year	6,170 (3,085)	Gamma	(16,27)
Productivity cost of ASCVD, annual		Gamma	(28)
50–59	6,700 (3,350)		
60–69	2,500 (1,250)		
70–79	650 (325)		
80–89	215 (108)		
>90	215 (108)		
Non-ASCVD health care costs		Gamma	(42,56)
50–54	1,426 (70)		
55–64	2,112 (87)		
65–74	2,766 (80)		
>75	3,108 (105)		
Statin complications (mild)	195 (30)	Gamma	(25)
Statin complications (severe)	6,960 (3,480)	Gamma	(25)
Follow-up for incidental noncardiac abnormalities	250 (125)	Gamma	(30)
Follow-up physician visit and additional laboratory tests (lipid panel and liver function tests)	100 (20)	Gamma	(29,57)

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prevention setting for individuals at intermediate risk. Statin-eligible patients were defined by the ACC/AHA guideline recommendations using 10-year ASCVD predicted risk from the Pooled Cohort Equations. Individuals were statin eligible if their predicted 10-year ASCVD risk was ≥5% and were further classified into a statin-recommended group (10-year ASCVD risk ≥7.5%) or a statin-considered

TABLE 1 Continued

	Base-Case Value	Distribution	Ref. #
Quality-of-life weights			
Disutility from taking a statin	0.9962 (0.9923-1.0000)	Triangular	(15), expert opinion
Mild statin complications	0.9941 (0.9890-0.9986)	Triangular	(25), expert opinion
Severe statin complications	0.9553 (0.9233-0.9986)	Triangular	(25), expert opinion
Nonfatal ASCVD	0.827 (0.026)	Beta	(16,58)
Death	0.000	No distribution	
Age-specific QALYs, healthy		N/A	(59)
50–59	0.84		
60–69	0.82		
70–79	0.79		
80–89	0.74		
>90	0.68		

Values are mean or most likely value (SE or uncertainty range)
ASCVD = atherosclerotic cardiovascular disease; CAC = coronary artery calcium; CT = computed tomography; QALYs = quality-adjusted life years.

group (10-year ASCVD risk 5.0% to 7.5%). We conducted analyses for each of these subgroups.

The following strategies were compared (Figure 1):

1. "CAC testing strategy." Individuals underwent a 1-time CAC test, and their CAC score guided statin therapy. If the CAC score was between 1 and 100, then a moderate-intensity statin was prescribed. If the CAC score was >100, then a high-intensity statin was prescribed. However, if there was no CAC, then the patient was not prescribed a statin.
2. "Treat all." Individuals did not receive a CAC test and were all prescribed a moderate-intensity statin.

Our model simulated the accumulated costs and quality-adjusted life years (QALYs) of each strategy. Individual patients were assigned an initial age and a CAC category using the distribution in the MESA study population. Patients cycled through the model until they experienced an ASCVD event or died from another cause. The number of years of statin therapy and whether or not they experienced an ASCVD event was tracked for each patient. We used a societal perspective over a lifetime time horizon with 1-year cycles. All costs and outcomes were discounted at 3% per year. Assumptions and uncertainty in the base-case analysis were assessed by sensitivity analysis. The incremental cost-effectiveness ratio (ICER) was calculated to compare the difference in costs and QALYs between the CAC testing and treat-all strategies.

DATA SOURCES. Probabilities, effectiveness of treatment, cost data, and quality-of-life weights were obtained from the published reports and expert consultation. The parameters used in the model are summarized in Table 1 with their data sources.

MESA STUDY AND EVENT RATES. Our base-case population included study participants in the MESA study who were eligible for statins according to the ACC/AHA guidelines (10). Full details of the MESA study design have been previously published (19). The baseline characteristics of the study population are described in Table 2. MESA is a community-based, prospective cohort of 6,814 men and women from 6 different field centers in the United States (Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles, California; New York, New York; and St. Paul, Minnesota). The 10-year ASCVD risk for MESA study participants was calculated using age, total cholesterol, high-density lipoprotein cholesterol levels, current smoking, history of diabetes mellitus, systolic blood pressure, and treatment of hypertension using race/sex-specific parameters from the ACC/AHA Pooled Cohort Equations. MESA study participants were considered eligible for a statin on the basis of their 10-year ASCVD risk. The CAC score distribution of this population was used to further reclassify these patients into CAC 0; CAC 1 to 100; and CAC >100 categories (Table 3). We used observed ASCVD event rates specific to the category of CAC derived from a recent analysis of the MESA study (10). The person-year rates were converted to annual probabilities using the exponential decay function. We validated the model by comparing observed ASCVD time-to-event data in the MESA study to the predicted ASCVD events from the model, assuming that all patients were not treated with a statin, and determined that the resulting event rates were similar (Online Appendix).

EFFECTIVENESS AND TREATMENT ADHERENCE. The benefit of statins was based on meta-analyses of randomized controlled trials on statin efficacy (20,21).

TABLE 2 Baseline Characteristics and Distribution of CAC of MESA Study Population Based on Category of ASCVD Risk

	Statin Recommended (n = 2,377)	Statin Considered (n = 538)
Age, yrs	64.7 ± 7.3	58.4 ± 6.5
Male	1,434 (60)	299 (51)
Race		
White	795 (33)	220 (37)
Black	791 (33)	180 (31)
Hispanic	534 (23)	124 (21)
Asian	527 (11)	65 (11)
Diabetes	472 (20)	0 (0)
Hypertension	1,439 (61)	193 (33)
Smoking		
Never	1,023 (43)	280 (47)
Former	918 (39)	211 (36)
Current	436 (18)	98 (17)
Education		
<High school	1,306 (56)	290 (50)
College	918 (12)	71 (12)
Bachelor or above	753 (32)	224 (38)
Family history of CHD	948 (43)	237 (43)
BMI, kg/m^2	28.7 ± 5.3	28.5 ± 5.4
Total cholesterol, mg/dl	201.5 ± 34.8	199.8 ± 30.6
LDL-C, mg/dl	126.4 ± 31.2	124.6 ± 26.4
HDL-C, mg/dl	48.5 ± 13.8	49.9 ± 13.9
Triglycerides, mg/dl	132.8 ± 67.0	126.4 ± 64.4

Values are mean ± SD or n (%).

BMI = body mass index; CHD = coronary heart disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; MESA = Multi-Ethnic Study of Atherosclerosis; other abbreviations as in Table 1.

TABLE 3 CAC Distribution According to the ACC/AHA Cholesterol Management Guidelines From the MESA Study

Statin recommended	2,377
CAC 0	978 (33.0)
CAC 1–100	714 (24.1)
CAC >100	685 (23.1)
Statin considered	589
CAC 0	338 (11.4)
CAC 1–100	184 (6.2)
CAC >100	67 (2.3)
Total	2,966 (100.0)

Values are n or n (%).

ACC/AHA = American College of Cardiology/American Heart Association; other abbreviations as in Tables 1 and 2.

The meta-analyses only reported the relative risks for the components of the ASCVD composite outcome, and we used expert opinion to synthesize the evidence to determine the relative risk by intensity of statin. Our estimates were similar to the relative risk reductions of ASCVD described in the 2013 ACC/AHA cholesterol management guidelines (1). Patients in the treat-all strategy received a moderate-intensity statin with a mean risk reduction of 35% (relative risk 0.65) on ASCVD (16,20,21). Patients in the CAC strategy received a high-intensity statin with a mean risk reduction of 45% (relative risk: 0.55) if their CAC score was >100, a moderate-intensity statin if their CAC score was 1 to 100, or no statin if there was no evidence of CAC (16,20,21). Statin dose adjustments or tapering of statin efficacy were not included in the model. We did not model the benefits of other therapies such as antihypertensive agents and aspirin that may be relevant in a primary prevention setting.

In the treat-all strategy, we assumed that 55% of patients were adherent to the prescribed statins (22). Studies have shown that patients who visualize calcium deposits in their coronary arteries have a higher likelihood of adherence to statin therapy (23,24). To model this increase in adherence, we assumed that 65% of patients who were prescribed a statin were adherent to therapy for the CAC testing strategy (16). The probability of mortality for an ASCVD event in the first year was 10.3% for patients under the age of 65 years and was 16.3% for patients 65 years and older (16,25). We also modeled age-specific non-ASCVD-related deaths using the life tables from the Centers for Disease Control and Prevention (26).

COSTS. All costs were adjusted for inflation and reported in 2016 U.S. dollars. Costs reflected payments to providers, instead of charges. Such payments offer a conservative assumption, because they remain higher than actual costs which are based on resource allocation. We estimated the costs of an ASCVD event as a weighted average of costs for specific events, using the relative frequencies in the MESA study sample as weights (16). A costing study using Medicare insurance claims data to calculate attributable costs by taking the difference between cases and controls was used to determine the cost of fatal and nonfatal myocardial infarction, resuscitated cardiac arrest, death related to coronary heart disease (CHD), and nonfatal and fatal strokes over the first year and the annual costs after the first year (27). We also included age-specific productivity losses due to ASCVD (28).

Because the costs of CAC testing and statins can vary considerably, we conducted our analysis using a wide range of assumptions. In the base case, the mean cost of a CAC test was an estimated $215, which included the direct cost of a CAC test, an extra physician visit to review results, additional costs for investigating incidental findings, and the opportunity cost of a CAC test (29). CAC testing discovers incidental findings that require additional follow-up in 4% to 8% of patients (30,31). We modeled the

additional cost incurred for 8% of patients who require additional imaging and follow-up. We did not include potential health benefits from investigating incidental findings. For the opportunity cost of CAC, we assumed the productivity cost of a CAC test to be 1 h, valued at the U.S. national median hourly wage (32). The annual cost of statins was $85 per year (approximately $7 per month), reflecting the increasing prevalence of generic use and the downward trend of statin costs in recent years (33,34). In the model, the costs of moderate- and high-intensity statins were the same.

OUTCOMES. An ASCVD event was defined as myocardial infarction, resuscitated cardiac arrest, CHD death, and nonfatal and fatal stroke (10). Transient ischemic attacks were not included in our study. We modeled outcomes using QALYs that use quality-of-life weights for different health states. The QALY of an ASCVD event was a weighted average of utilities using the distribution of events in the MESA study as weights. To incorporate potential adverse events associated with statin use, such as myopathy or hepatitis, we included health states for mild and severe statin complications. We assumed utility decrements of 2 days and 2 weeks of lost healthy life, respectively (25). If a patient experienced an adverse event from a statin, the patient discontinued statin therapy for the duration of the model. Other complications of statin therapy such as an increased risk of diabetes were not included in the model. The quality-of-life weights were multiplied by the age-specific healthy QALYs at the end of each cycle and were the same across subgroups.

There is a modest exposure to ionizing radiation (~1.0 mSv) for patients undergoing a CAC test (35). We assumed an incremental lifetime risk of cancer risk due to ionizing radiation and modeled this risk into the time horizon of the model (14). If an individual developed a cancer, then we assumed the probability of mortality was 65% (14).

SENSITIVITY ANALYSIS. The uncertainty of our model was assessed using deterministic and Bayesian multivariate probabilistic sensitivity analysis. The deterministic sensitivity was conducted by varying key assumptions of the model across their uncertainty range. Specifically, we varied the costs of CAC testing from $50 to $300 and the cost of statins from $50 to $500 a year. We also considered whether the patients in the treat-all strategy were prescribed a high-intensity statin; if those with CAC >100 were prescribed a moderate-intensity statin; and conservative estimates of the effect of statin therapy (relative risk of 0.70 for high-intensity and 0.80 for moderate-intensity statins); perfect adherence to statins; a payer perspective; and various disutility decrements associated with ongoing statin use. In other sensitivity analyses, we also included the follow-up outpatient clinic visit and laboratory investigations (lipid panel and liver function tests) within 6 months of patients who were prescribed a statin and included unrelated health care costs in separate scenario analyses. For the probabilistic sensitivity analysis, we performed second-order Monte Carlo simulations, where we drew values from each distribution for 1,000 individuals, whose costs and outcomes we simulated, and repeated this process over 1,000 simulations. Cost-effectiveness acceptability curves were calculated for willingness-to-pay thresholds between $0 to $100,000/QALY to predict the probability that a strategy was cost-effective. We used beta distributions for probabilities, gamma distributions for costs, and triangular distributions for utilities and relative risks of ASCVD with statin therapy. The distribution of the costs of statin therapy and CAC testing was modeled using a triangular distribution bounded by 80% and 120% of the baseline value.

RESULTS

In the base case of the statin-eligible study population, the CAC testing strategy accumulated costs of $11,579 (95% confidence interval [CI]: $5,417 to $19,183) and QALYs of 11.859 (95% CI: 10.859 to 12,838), whereas the treat-all strategy accumulated costs of $11,498 (95% CI: $2,048 to $19,135) and QALYs of 11.849 (95% CI: 10.834 to 12.829). We found that CAC increased costs by $81 and only resulted in a small increase of 0.010 QALYs per patient, resulting in an ICER of $8,100/QALY (**Table 4**). For 10,000 patients, the treat-all strategy averted only 21 incremental ASCVD events, but added 47,294 person-years of statin therapy. In our cost-effectiveness acceptability curves, the CAC strategy was the most cost-effective strategy in 51% of all simulations for a willingness-to-pay threshold of $50,000/QALYs compared with the treat-all strategy (**Central Illustration**).

In our sensitivity analysis, the findings of our model changed considerably when varying the cost of statins, cost of CAC testing, and the disutility associated with statin use (**Table 4**). When the annual costs of statin were low, then a treat-all strategy resulted in lower total costs compared with a CAC strategy. However, when the annual cost of statins was above $150, then a CAC strategy was dominant (lower costs and more QALYs). Similarly, when the cost of CAC testing rose, then a treat-all strategy

TABLE 4 Results of the Base Case and Sensitivity Analysis

	Sensitivity Analysis	Incremental Cost-Effectiveness Ratio ($/QALY)
Statin eligible*		
1	Base-case assumptions	8,100
2	Statin cost: $50/yr	19,200
3	Statin cost: $150/yr	CAC dominates
4	Statin cost: $300/yr	CAC dominates
5	Statin cost: $500/yr	CAC dominates
6	CAC cost: $50	CAC dominates
7	CAC cost: $150	1,500
8	CAC cost: $250	11,500
9	CAC cost: $300	16,500
10	Same intensity statin for both strategies	Treat all dominates
11	High-intensity statin for treat-all strategy	Treat all dominates
12	Lower RR reduction for statins (RR: 0.70 for high intensity, RR: 0.80 for moderate intensity)	CAC dominates
13	Full adherence to statins for both strategies	18,556
14	No disutility with statin therapy	Treat all dominates
15	Increased disutility with statin therapy, trade 4 weeks of life for 10 yrs of not taking a statin	4,050
16	Increased disutility with statin therapy, trade 8 weeks of life for 10 yrs of not taking a statin	2,132
17	Included statin follow-up at 6 months (physician visit and laboratory tests)	3,700
18	Payer perspective	8,100
19	5-yr time horizon	38,750
20	10-yr time horizon	21,000
21	Included unrelated health care costs	2,800
Statin recommended only†		
1	Base-case assumptions	15,000
2	Statin cost: $50/yr	31,667
3	Statin cost: $150/yr	CAC‡ dominates
4	Statin cost: $300/yr	CAC dominates
5	Statin cost: $500/yr	CAC dominates
6	CAC cost: $50	CAC dominates
7	CAC cost: $150	4,167
8	CAC cost: $250	20,833
9	CAC cost: $300	29,167
10	Same intensity statin for both strategies	Treat all dominates
11	High-intensity statin for treat-all strategy	Treat all dominates
12	Lower relative risk reduction for statins (RR: 0.70 for high intensity, RR: 0.80 for moderate intensity)	CAC dominates
13	Full adherence to statins for both strategies	59,750
14	No disutility with statin therapy	Treat all dominates
15	Increased disutility with statin therapy, trade 4 weeks of life for 10 yrs of not taking a statin	6,000
16	Increased disutility with statin therapy, trade 8 weeks of life for 10 yrs of not taking a statin	2,727
17	Included statin follow-up at 6 months (physician visit and laboratory tests)	8,167
18	Payer perspective	15,000
19	5-yr time horizon	52,333
20	10-yr time horizon	18,750
21	Included unrelated health care costs	8,500

Continued on the next page

became more favorable. If patients in the treat-all strategy were treated with a high-intensity statin or if patients in both strategies were treated with the same moderate-intensity statin, then a treat-all strategy was dominant. When all patients in both strategies were treated with a similar moderate-intensity statin irrespective of a high CAC score, then the treat-all strategy averted 54 ASCVD events for 10,000 patients. When we used conservative estimates for the benefit of statins or included the unrelated health costs, then the CAC strategy was more favorable.

The disutility associated with long-term statin use also changed the results of the model considerably. If there was no disutility associated with statin use, then a treat-all strategy was dominant, and if the

TABLE 4 Continued

	Sensitivity Analysis	Incremental Cost-Effectiveness Ratio ($/QALY)
Statin considered only‡		
1	Base-case assumptions	CAC dominates
2	Statin cost: $50/yr	12,000
3	Statin cost: $150/yr	CAC dominates
4	Statin cost: $300/yr	CAC dominates
5	Statin cost: $500/yr	CAC dominates
6	CAC cost: $50	CAC dominates
7	CAC cost: $150	CAC dominates
8	CAC cost: $250	1,182
9	CAC cost: $300	5,727
10	Same intensity statin for both strategies	5,222
11	High-intensity statin for treat-all strategy	113,667
12	Lower relative risk reduction for statins (RR: 0.70 for high intensity, RR: 0.80 for moderate intensity)	CAC dominates
13	Full adherence to statins for both strategies	CAC dominates
14	No disutility with statin therapy	7,333
15	Increased disutility with statin therapy, trade 4 weeks of life for 10 yrs of not taking a statin	CAC dominates
16	Increased disutility with statin therapy, trade 8 weeks of life for 10 yrs of not taking a statin	CAC dominates
17	Include statin follow-up at 6 months (physician visit and laboratory tests)	CAC dominates
18	Payer perspective	CAC dominates
19	5-yr time horizon	31,000
20	10-yr time horizon	9,000
21	Included unrelated health care costs	CAC dominates

*Statin-eligible individuals had a predicted 10-yr ASCVD risk of ≥5% using the pooled cohort equations (PCE). †Statin-recommended individuals had a predicted 10-yr ASCVD risk of ≥7.5% using the PCE. ‡Statin-considered individuals had a predicted 10-yr ASCVD risk of 5% to 7.5% using the PCE.

RR = relative risk; other abbreviations as in Table 1.

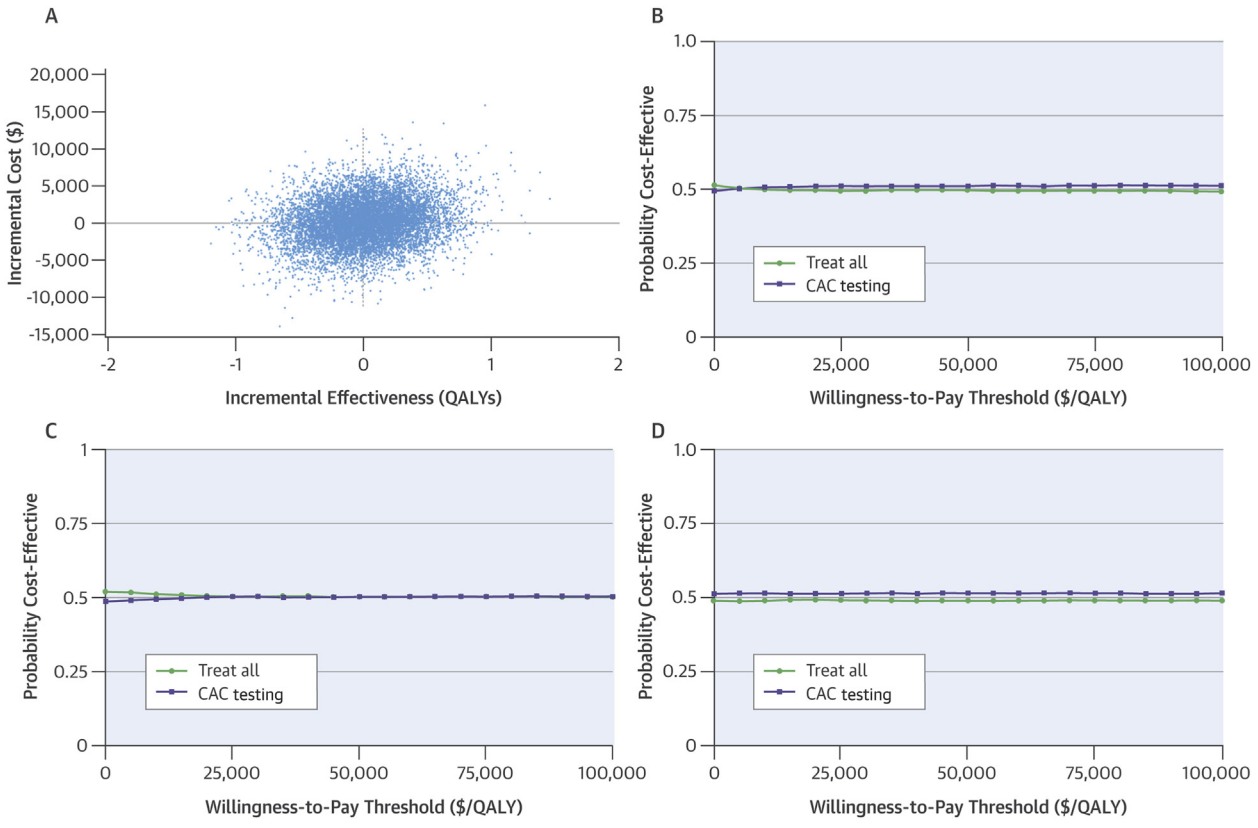
disutility increased, then a CAC strategy was even more cost-effective. In our subgroup analysis, we found a favorable ICER for CAC testing in the statin-recommended group ($15,000/QALY) and a CAC testing strategy was dominant where the risks of ASCVD are lower. In our cost-effectiveness acceptability curves, we found that CAC was the most cost-effective strategy at 50% for the statin-recommended subgroup; and 51% for the statin-considered subgroup for a willingness-to-pay threshold of $50,000/QALYs (Central Illustration).

DISCUSSION

We compared the cost-effectiveness of 2 strategies: 1) a selective approach using CAC testing to guide statin therapy as advocated in recent studies; versus 2) treating individuals according to the ACC/AHA guidelines. We found that a CAC strategy is cost-effective compared with a treat-all strategy among statin-eligible individuals (estimated 10-year ASCVD risk ≥5%); however, the differences in costs and QALYs were small. In 10,000 patients, a treat-all strategy only averted 21 ASCVD events while increasing the person-years of statin therapy by over 47,000. The CAC strategy was more likely to be cost-effective in 51% of simulations compared with a treat-all strategy (49%) at a willingness-to-pay threshold of $50,000/QALY, suggesting that both approaches have generally similar clinical and economic consequences. We found that when focusing on a statin-considered group (estimated 10-year ASCVD risk 5.0% to 7.5%), CAC testing was more cost-effective, suggesting significant value in this specific subgroup of individuals that are at a lower estimated risk. The small decrease in the number of ASCVD events for the treat-all strategy can be attributed to the low risk of ASCVD in the absence of CAC and how a high-intensity statin was prescribed in individuals with a CAC >100 compared with a moderate-intensity statin prescribed to everyone in the treat-all strategy.

It is important to note that the results of our study were sensitive to the underlying assumptions of the model. In scenarios where both strategies were treated with a similar intensity of statins, even when the CAC score was >100, a treat-all strategy was dominant in the statin-eligible and statin-recommended groups. The directionality of cost-effectiveness was highly dependent on the costs of statins as well as CAC testing. In our base case, we used a conservative estimate for the cost of statins ($85/year) using the wholesale price of generic statins

CENTRAL ILLUSTRATION **Cost-Effectiveness Plane and Acceptability Curves**



Hong, J.C. et al. J Am Coll Cardiol Img. 2017;10(8):938–52.

Cost-effectiveness plane **(A)** with incremental quality-adjusted life years on the x-axis and incremental costs on the y-axis for statin-eligible patients using the American College of Cardiology/American Heart Association (ACC/AHA) cholesterol management guidelines. Cost-effectiveness acceptability curves demonstrate the probability that a given strategy is the most cost-effective using a range of willingness-to-pay thresholds for statin eligible **(B)**, recommended **(C)**, and considered **(D)**. CAC = coronary artery calcium; QALY = quality-adjusted life years.

(33). However, a recent analysis of the Medical Expenditure Panel Survey reported a significantly higher average annual costs of generic statins ($227/year) than the estimate we used in our base case (34). The study also found that 82% of all statin users were using generics in a nationally representative population, suggesting that using a generic cost of statins is appropriate for economic models.

In our analysis, we found that when the annual costs of statins rose above $200, the CAC strategy was dominant over the treat-all strategy. In our model, we estimated the cost of CAC testing by including the direct costs of administering the test, a follow-up visit, the cost of investigating incidental findings, and the opportunity costs ($215), whereas in most real-world situations, the cost may be lower, and some have proposed approaches to lower the costs of CAC, which would favor a CAC strategy (10). Our cost-effectiveness analysis also found that individuals who preferred to avoid long-term statin therapy (greater disutility with statin therapy), a CAC-based strategy was more favorable by allowing close to one-half of these individuals to be reclassified into a low-risk category where statins are generally not recommended. This suggests that CAC testing can be a cost-effective tool that clinicians can use to facilitate shared decision-making for flexible treatment goals among uncertain individuals deemed eligible for lifelong statins.

Since the release of the recent ACC/AHA cholesterol management guidelines, various approaches of further refining risk to identify appropriate statin candidates have received considerable attention (4,5,10). Although the risk estimates in the revised guidelines resulted in higher treatment rates among

those expected to have future cardiovascular events, some have argued that the benefit can only be realized if a significant proportion of patients at a much lower risk are willing to accept lifelong commitment to statins (36). This results in the unintended consequences of treating a significant proportion of low-risk patients who will likely derive minimal benefit from these therapies. In addition, evidence suggests that some patients are averse to lifelong pharmacological therapy if the treatment does not result in a meaningful reduction in risk, even if the therapy was free from side effects and had minimal costs (37). Risk assessment strategies are able to identify these lower-risk individuals (7,8,38) and can have a profound impact in facilitating appropriate resource allocation and shared decision making to allow flexible, patient-centered treatment choices.

LITERATURE REVIEW. Although it is difficult to compare previous cost-effectiveness analyses because the models differ in assumptions, strategies compared, study population, and treatment thresholds, our conclusion is fairly consistent with prior studies (14–18). The key features of 5 recent cost-effectiveness analyses of CAC screening in a primary prevention setting are described in **Table 5**. The 5 studies used well-constructed state-transition microsimulation. All of the models incorporated the risk of adverse events from statin therapy, real-world adherence rates, and the risk of radiation-induced cancer from a CAC screening, which are important considerations in a primary prevention setting. The cost-effectiveness analyses used different costs of statin therapy in the base case, but all used sensitivity analysis to include low-cost generic statins. We assessed the quality of the previous economic evaluations using the Quality of Health Economics Studies instrument, a standard, validated tool. The previous economic evaluations were of good quality, with scores ranging from 89 to 96 (maximum score of 100) (**Table 5**). The main issues of the previous studies were the reasons for why a perspective of the analysis was chosen was not stated and/or the analytic horizon did not encompass all relevant and important outcomes (16).

Most studies included a disutility associated with long-term statin use that was independent from adverse events (15–18). The disutility of statin use is attributed to the burden of managing prescriptions, taking the medication every day, and receiving periodic visits with clinicians for pharmacotherapy monitoring (39). Two of the cost-effectiveness analyses derived a disutility on the basis of expert opinion assuming that individuals would trade 2 weeks of life to avoid 10 years of statin therapy (15,16). van Kempen et al. (18) cited a study that found individuals would trade a median of 6 months of life to avoid taking an idealized daily medication over their lifetime (40). There is a paucity of published reports on what is the appropriate disutility associated with daily medication use, but some studies have described a subset of the population that is willing to trade life expectancy to avoid taking a daily medication for cardiovascular prevention (37,41). Thus, it is likely important to include a disutility to long-term statin therapy; further research is needed to confirm these findings.

Four of the 5 studies concluded that CAC was cost-effective or identified situations that were favorable for CAC (14,18). Pletcher et al. (15) found that a treat-all strategy was more cost-effective when the costs of statins were low ($47/year) and there was no disutility associated with statin use. However, when the costs of statins were high ($365/year) and there was a disutility, then CAC was cost-effective. van Kempen et al. (14) in 2011 used a high cost of statins in their base case ($570/year) and did not include a disutility for ongoing statin use. The study reported that CAC testing was cost-effective in men, but not cost-effective in women. This difference was attributed to the fact that women were more likely to be reclassified to a low-risk category that led to less aggressive treatment and this low-risk group had a higher observed incidence of ASCVD compared with men. Similarly, van Kempen et al. (18) in 2016 found that CAC was cost-effective in men, but not in women, when comparing various risk stratification and treat-all strategies to guide statin, antihypertensive, and aspirin therapy. In this analysis, a low annual cost of statins was used ($73/year), and a disutility was included with statin use.

Roberts et al. (16) found that CAC was the dominant strategy because it reduced costs and increased QALYs. In the base case of the Roberts et al. study, the cost of statins was $180/year, and there was a disutility with statin use. CAC was likely favored in this study because patients with a high CAC score were treated with more aggressive statin therapy, lowering risks, whereas only a moderate-intensity statin was prescribed in the treat-all group. Also, there was a disutility for statin use and thus penalized individuals if they used a statin despite having a low observed incidence of ASCVD. The Galper et al. (17) study found that a treat-all strategy was dominant over other risk stratification methods, including CAC testing. The annual cost of statins was $85/year, and disutility associated with statins was lower than the other studies. In their sensitivity analysis, only when

TABLE 5 Review of Key Cost-Effectiveness Analyses of CAC Testing in a Primary Prevention Setting

	van Kempen et al. (14)	Pletcher et al. (15)	Roberts et al. (16)	Galper et al. (17)	van Kempen et al. (18)	Current Study
Year of publication	2011	2014	2015	2015	2016	2017
Population	Primary prevention, intermediate risk	Primary prevention, intermediate risk	Primary prevention, intermediate risk	Primary prevention, adult population	Primary prevention, intermediate risk	Primary prevention, intermediate risk
Setting	United States	United States	United States	United States	United States	United States
CAC strategy	1. Statin, antihypertensive agent, or aspirin depending on reclassification of risk	1. Statin if CAC >300 2. Statin if CAC >100 3. Statin if CAC >0	1. Statin if CAC >0 2. Statin if CAC >100	1. SHAPE 2. Texas*	1. Statin, antihypertensive agent, or aspirin depending on reclassification of risk	1. Statin if CAC >0
Comparators	2. Baseline 3. Guidelines directed: statins if LDL-C >130 mg/dl, antihypertensive agent when SBP >140 mm Hg 4. Treat all with a statin	4. Treat all with a statin 5. Treat none	3. ATP III: statin therapy based on FRS and LDL-C level 4. Treat all with statin	3. Baseline 4. ATP III: statin therapy based on FRS and LDL-C level 5. ACC/AHA: statin therapy based on LDL-C and/or pooled cohort equation risk 6. JUPITER: statin therapy based on age, LDL-C, and CRP 7. Treat all with moderate-intensity statin, men with aspirin 8. Treat all with severe-intensity statin, men with aspirin	2. Baseline 3. Guidelines directed: ACC/AHA for statin therapy, and JNC-8 for antihypertensive agents 4. CRP: statin, antihypertensive agent depending on reclassification of risk 5. Intima-media thickness: statin, antihypertensive agent depending on reclassification of risk 6. Ankle-brachial index: statin, antihypertensive agent depending on reclassification of risk 7. Treat all with statin and JNC-8 guidelines for antihypertensive agents	2. ACC/AHA: statin therapy based on Pooled Cohort Equation risk
Study design	Microsimulation	Microsimulation	Microsimulation	Microsimulation	Microsimulation	Microsimulation
Perspective	Societal	Health care payer	Health care payer Societal	Health care payer	Societal	Societal
Time horizon	Lifetime	Lifetime	5-yr 10-yr	Lifetime	Lifetime	Lifetime
Discounting	3% costs and QALYs	3% costs and QALYs	3% costs and QALYs	3% costs and QALYs	3% costs and QALYs	3% costs and QALYs
Outcomes data source	Rotterdam Coronary Calcium Study	Multi-Ethnic Study of Atherosclerosis	Multi-Ethnic Study of Atherosclerosis	Framingham Heart Study	Framingham Heart Study and Rotterdam Coronary Calcium Study	Multi-Ethnic Study of Atherosclerosis
Model details (cost of CAC and statins; disutility with statin use)	CAC: $105 Statin: $570/yr No disutility with statin use	CAC: $185 Statin: $47/yr, $365/yr Included disutility with statin use	CAC: $100 Statin: $180/yr Included disutility with statin use	CAC: $200 Statin: $85/yr Included disutility with statin use	CAC: $110 Statin: $73/yr Included disutility with statin use	CAC: $200 Statin: $85/yr Included disutility with statin use
Sensitivity analysis	Deterministic Probabilistic	Deterministic Probabilistic	Deterministic Probabilistic	Deterministic Probabilistic	Deterministic Probabilistic	Deterministic Probabilistic

Continued on the next page

the disutility with statins was multiplied by a factor of 100 or 1,000 were other risk stratification methods cost-effective. In general, the previous studies found that CAC was cost-effective when the costs of statins was higher, the cost of CAC testing was low, and there was a disutility with statin therapy.

IMPLICATIONS. A recent analysis of the MESA study data found that between 41% and 57% of individuals who were recommended or considered for statin therapy by the guidelines did not have any presence of CAC (10). These individuals with no detectable CAC had a low rate of ASCVD events in a follow-up extending to 10 years (4.9% for recommended and 1.5% for considered risk categories) (10). Our cost-effectiveness analysis builds on the existing published reports by using recently described ASCVD rates and CAC distributions to evaluate the cost-effectiveness of CAC testing, which improves the generalizability of our findings. Our study addresses a common clinical scenario for patients and clinicians in deciding whether or not to start lifelong statin therapy for patients at intermediate risk for ASCVD in the primary care setting using the ACC/AHA cholesterol guidelines. The key finding of our analysis is that the clinical and economic consequences are

TABLE 5 Continued

	van Kempen et al. (14)	Pletcher et al. (15)	Roberts et al. (16)	Galper et al. (17)	van Kempen et al. (18)	Current Study
Results	CAC was cost-effective compared with baseline in men ($35,977/QALY) Guidelines was the dominant strategy in women	Treat all was preferred if low cost statins and no disutility with statins CAC was preferred if high cost of statins and disutility with statins	CAC >0 was the dominant strategy	Treat-all with high-intensity statins was the dominant strategy	CAC was cost-effective in men when there was a disutility with statins in men CRP was cost-effective in women	CAC was cost-effective compared with treat all ($8,100/QALY)
Sensitivity analysis findings	CAC was most cost-effective strategy in >50% of simulations for men; but only 20% of simulations for women for willingness-to-pay thresholds >$50,000/QALY For men, when the cost of CAC >$200, then a treat-all strategy was preferred	CAC was more cost-effective when the cost of statins were high and there was a greater disutility with statins	CAC was the most cost-effective strategy in >60% of simulations for a wide range of willingness-to-pay thresholds ATP III was cost-effective when the cost of CAC was high or when the cost of statins was low	Treat-all with high-intensity statin was most cost-effective strategy in >65% of simulations in men, and >40% in women for a wide range of willingness-to-pay thresholds Only when a large disutility was applied to statin adverse effects were risk stratification strategies cost-effective	CAC was the most-effective strategy in > 30% of simulations in men, and >10% in women for willingness-to-pay thresholds >$50,000/QALY	CAC was the most-effective strategy in only 51% of simulations for willingness-to-pay thresholds >$50,000/QALY
Conclusion	CAC screening is cost-effective in men, but not in women	CAC screening is cost-effective when statins are costly and are associated with a disutility to long-term use	CAC screening is cost-effective	CAC screening is not cost-effective compared with treating all strategy	CAC is cost-effective in men when there is a disutility from taking long-term use, but not in women	CAC is cost-effective, but both strategies have similar economic value
QHES Quality Score	96	96	89	96	96	

*In 2009, the State of Texas mandated payers to provide coverage for CAC screening of patients with Framingham Risk Scores (FRS) >10%.

ATP III = National Cholesterol Education Program's Adult Treatment Panel III; CRP = C-reactive protein; JNC-8 = Eighth Joint National Committee Hypertension Guidelines; JUPITER = Justification for the use of Statins in Primary Prevention; QHES = Quality of Health Economic Studies; SBP = systolic blood pressure; SHAPE = Screening for Heart Attack Prevention and Education; other abbreviations as in Tables 1, 2, and 3.

similar between using CAC testing or the ACC/AHA guidelines to guide long-term statin therapy among individuals at intermediate cardiovascular risk. Cost-effectiveness analyses should not be the only criterion for clinical decision making, but understanding the value of treatment strategies is important for clinicians, patients, and policymakers. Our analysis and previous cost-effectiveness analyses are consistent with the notion that CAC testing affords a reasonable option to risk stratify as well as facilitate shared decision making without any significant downstream adverse outcomes, loss of quality of life, and/or increased costs.

Although conservatively low-cost generic statins seem to drive the value toward a treat-all strategy, there are situations where CAC is cost-effective. Studies have demonstrated considerable preference heterogeneity for a daily medication for cardiovascular disease prevention (37,40,41), and a subset of the population would prefer to avoid taking a daily preventive medication to the point that they are willing to give up life expectancy even if the side effects were minimal (40). At the other end of the spectrum, there are individuals who prefer to avoid any cardiovascular events in the future and would gladly take a preventive medication (40). Although the risk estimates are more certain resulting in fewer trade-offs with statin decisions among high-risk (>20% 10-year ASCVD estimates) and low-risk (<5% 10-year ASCVD estimates) populations, evidence exists to point toward significant heterogeneous risk in the broad intermediate-risk group of patients with a 10-year ASCVD risk range of 5% to 20% (10). In this situation, the shared decision-making principles to guide patients toward a patient-centered treatment strategy are important, considering there is clinical equipoise. A treat-all strategy for these individuals may not be appropriate, and allowing options such as CAC testing for informed decisions in these uncertain patients appears reasonable as noted in our cost-effectiveness analyses. It is the role of the clinician to understand their patient's preferences, and CAC testing can supplement the shared decision-making process through more accurate risk prediction and help avoid low-value pharmacological therapy.

STUDY LIMITATIONS. First, our analysis is not a clinical trial, but a decision analysis model that used

assumptions and parameters to compare various statin strategies. A randomized clinical trial studying the comparative effectiveness of CAC testing to guide cardiovascular disease prevention treatment would be helpful to inform our analysis, but the likelihood of such a trial in the future is low. Second, a lifetime time horizon in the model captured the relevant consequences of statin treatment. However, we used modeling to extend the prediction of ASCVD rates beyond the observation period of the MESA study by assuming that the rates of ASCVD stratified by CAC score stayed constant. Third, we did not consider other cardiovascular prevention treatment modalities such as antihypertensive agents and aspirin that may be relevant in patients at intermediate risk for cardiovascular disease, who have an elevated level of subclinical atherosclerosis. Fourth, we did not account for the increase in utility when patient preferences are incorporated in clinical decisions or the decrease in utility for patients who view the decision process as burdensome. Unfortunately, cost-effectiveness analysis is not well-suited to incorporate these effects as they are hard to ascertain. Fifth, using time trade-off methods to determine a disutility associated with long-term statin use may not capture all the implications of a complex behavior and is, at best, a crude estimate. Sixth, the Second Panel of Cost-Effectiveness in Health and Medicine has recently advocated for the inclusion of unrelated health care costs (42). However, this is a point of contention among the research community, and unrelated health care costs have rarely been included in previous economic evaluations (43–45). In 2013, the National Institute for Health Care Excellence in the United Kingdom recommended that these costs should be excluded (46). In order to maintain comparability between previous cost-effectiveness analyses, we did not include unrelated health care costs in our base case, but considered it in a sensitivity analysis. The inclusion of unrelated health care costs favored the CAC strategy; however, it did not change the overall conclusion of our analysis. Lastly, a recent study has shown PCSK-9 inhibitors significantly reduced the clinical outcomes among those with established ASDVD but are associated with a high cost of treatment (47,48). Although it may be useful to examine the clinical and economic implications of using CAC testing to risk stratify individuals for PCSK-9 inhibitor therapy, such analyses are beyond the scope of our study because the impact of PCSK9 inhibitors in the primary prevention setting is unknown, and furthermore, our study focuses on the decision strategies for statin initiation.

CONCLUSIONS

The strategy of CAC testing to guide treatment decisions among statin candidates free of established ASCVD resulted in comparable clinical and economic consequences to a treat-all strategy at a willingness-to-pay threshold of $50,000 using conservative estimates. The results support the role of dynamic shared decision making for individual preferences and values in choosing the most appropriate strategy while considering long-term use of statins among intermediate-risk patients in the primary prevention setting.

ACKNOWLEDGMENT The authors would like to acknowledge Eric Roberts, PhD, for his help in developing the original economic model.

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KEY WORDS atherosclerosis, CAC, cholesterol, cost-effectiveness analysis, risk assessment, statins

APPENDIX For an expanded Methods section with a supplemental table and figure, please see the online version of this paper.