Original Article

Long-term health benefits and costs of measurement of carotid intima–media thickness in prevention of coronary heart disease

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Objective: Recently, it was demonstrated that information on carotid intima–media thickness (CIMT) and plaque may improve coronary heart disease (CHD) risk prediction through reclassification of some individuals to the correct risk category using the Framingham risk score. Our objective was to assess the currently unknown cost-effectiveness of CIMT measurements in primary prevention.

Methods: A hypothetical cohort of men and women aged 50–59 years and at intermediate or high CHD risk based on data from the Atherosclerosis Risk in Communities Study was simulated using a Markov model. Myocardial infarction (MI) events were used as a proxy for CHD. The effectiveness of pharmaceutical treatment was varied in the analysis. Sensitivity analysis was performed to obtain robust results.

Results: CIMT-based reclassification induced a 1% lower absolute risk of MI and 0.01–0.02 increase in quality-adjusted life years (QALYs) for men, and a 1–3% lower risk, and 0.03–0.05 increase in QALYs for women, over a period of 20–30 years. Corresponding costs were an additional $100 per man, and a cost-saving of $200–300 per woman. Over a 10-year period CIMT measurements were cost-effective with a probability of 66% (men), and 94% (women). Over a 30-year period, CIMT measurements had acceptable cost-effectiveness for men and women.

Conclusion: Performing CIMT measurements in asymptomatic men and women aged 50–59 years results in additional, but small, health benefits. It takes time for these health benefits to outweigh the initial CIMT measurement costs. Our results support CIMT measurements for cardiovascular risk stratification, in particular for women, when focusing on long-term health.

Keywords: coronary heart disease, cost–benefit analysis, imaging, prevention

Abbreviations: ARIC, Atherosclerosis Risk in Communities Study; CHD, coronary heart disease; CIMT, carotid intima–media thickness; FRS, Framingham risk score; ICER, incremental cost-effectiveness ratio; MI, myocardial infarction; NMB, net monetary benefit; NRI, net reclassification improvement; QALY, quality-adjusted life year; WTP, willingness-to-pay

INTRODUCTION

Cardiovascular disease is the leading cause of mortality in the United States. A recent report by the American Heart Association calculated medical costs for cardiovascular disease to triple to $818 billion by 2030 [1]. This alarming increase in health expenditure underscores the need for effective and efficient preventive strategies against cardiovascular disease.

Several risk scores exist to assist clinical practice in cardiovascular risk classification of asymptomatic individuals, and to guide treatment allocation [2]. Established risk factors include male sex, increasing age, blood pressure, LDL cholesterol and current smoking. The most widely used risk prediction score for coronary heart disease (CHD) events is the Framingham risk score (FRS) [3,4]. However, the accuracy of risk classification by the FRS varies between populations and leaves room for improvement [5,6].

Measurement of carotid intima–media thickness (CIMT) has been suggested as a tool to improve identification of high-risk individuals [7]. On the basis of CIMT information, individuals first classified by FRS may be reclassified to either below or above the predefined threshold for medical treatment of 10-year CHD risk exceeding 20%. A recent article from the Atherosclerosis Risk in Communities (ARIC) Study indicated that a CIMT and plaque measurement in addition to established risk factors in asymptomatic individuals with a mean age of 54 (range 45–64) indeed improves risk stratification. Here, a net reclassification improvement (NRI), over all risk categories, of 9.9% was

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observed, and 16.7% in those at intermediate risk [8]. This is another step towards indication that CIMT measurement may also be of clinical benefit. However, it is currently unknown if the expected additional health benefits from treatment after reclassification, as compared to treatment based on FRS only, outweigh the initial CIMT test costs. In this study we examined the cost-effectiveness of adding a single CIMT measurement to the routine evaluation of CHD risk in a Markov model, based on data from participants of the ARIC Study.

METHODS

The risk classification strategies

Figure 1 shows an overview of the analysis used in this study. First, in all individuals, established risk factors are assessed and the absolute 10-year risk for CHD is predicted using the Framingham risk score (assess FRS). These risks are categorized as either below or above 10%. Individuals in the low-risk category (≤10%) are ignored in this analysis as the ARIC results show that CIMT information in these individuals will never cause reclassification to the highest risk category (>20%) and will therefore never alter treatment decisions [8]. Thus, our analysis concerns only individuals in the intermediate to high-risk group (>10%).

In Figure 1, the first strategy is based on the FRS alone. In this strategy, an individuals' risk to develop CHD is based on established risk factors according to the FRS. The second strategy is called CIMT. This strategy adds CIMT and plaque information to FRS and individuals are (re)classified into low (<5%), low-intermediate (5–10%), intermediate (10–20%) and high risk (>20%) categories. Here, reclassification tables, for men and women, from the ARIC article are used (Table 4 and 5, page 1604 and 1605 of the article) [8]. In both strategies (FRS and CIMT) pharmacological treatment is started in all high-risk individuals (>20% risk in 10 years), and in 20% of the individuals in the intermediate risk category (10–20% risk in 10 years). Throughout the article, CIMT information refers to both the CIMT and plaque measurement.

Clinical interpretation of reclassification

In the model, we investigated whether this reclassification indeed results in a lower risk to develop myocardial infarction (MI). For this analysis we used the combined Kaplan–Meier estimates from the ARIC tables for the two separate strategies. We investigated the extent to which this risk reduction was dependent on the effectiveness of the pharmacological treatment when the high category is treated.

Model structure

We used a Markov decision-analytic model and Monte Carlo sampling to assess the differences in long-term health benefits and costs of the CIMT strategy compared with the FRS strategy [9]. Markov decision models are useful when events can occur at various points in time and with varying probabilities, as they are based on probabilities of transitions between health states [10].

The distribution of individuals across risk categories is obtained from the ARIC study [8]. Individuals were first classified based on their 10-year risk of developing CHD based on the FRS alone. Those who were considered low risk (<10%) were excluded from this analysis because no further medical treatment would be indicated. The remaining individuals were classified as either moderate risk (10–20%) or high risk (>20%). Individuals were then re-classified after adding CIMT information to the FRS. The addition of CIMT data results in a reclassification of risk category in a percentage of cases. Thus, results yielded four classifications of 10-year risk of developing CHD: very

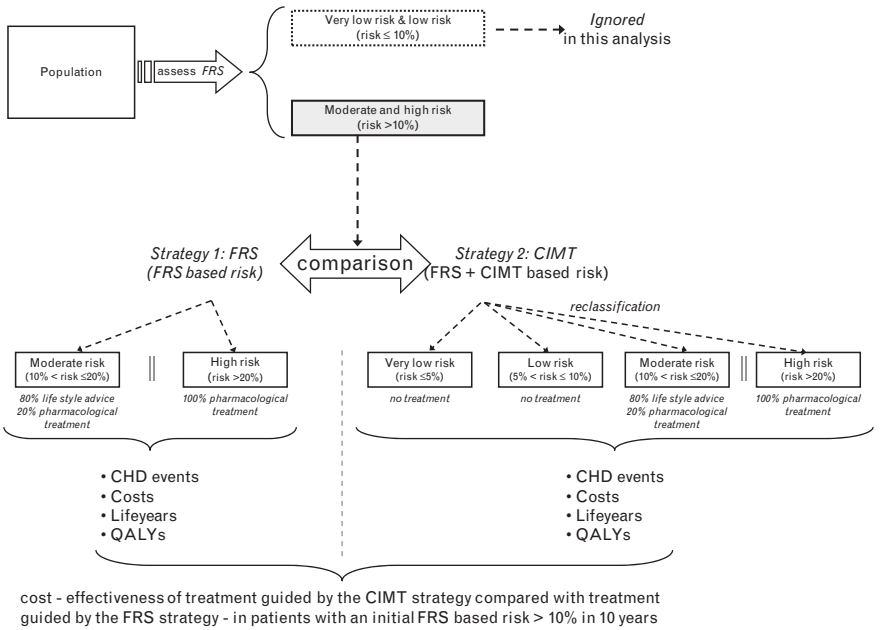

FIGURE 1 Flowchart of the analytic procedure. First, the risk of individuals is assessed based on FRS. Only individuals with a CHD risk exceeding 10% in 10 years are then considered eligible for CIMT measurement. In these individuals, treatment can either be based on the FRS risk classification (strategy 1) or on results from the additional CIMT measurement (strategy 2). Finally, results in terms of CHD events, complications, costs, life years and QALYs are used to determine the cost-effectiveness of strategy 2:CIMT compared with strategy 1:FRS. CIMT, carotid intima–media thickness; FRS, Framingham risk score.

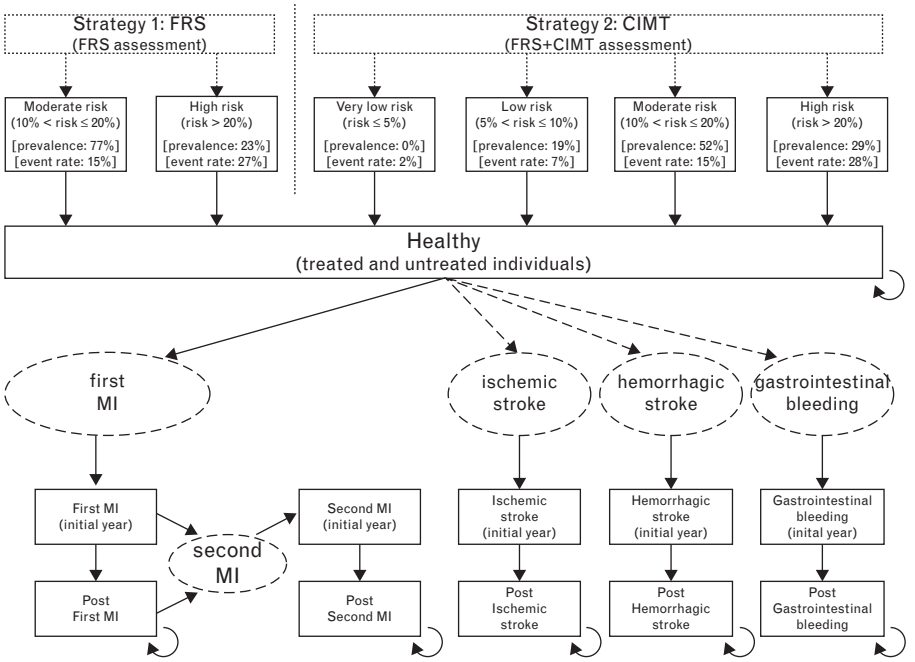

FIGURE 2 Following risk stratification based on one of the two strategies, individuals are classified into one risk category. Per strategy, the proportion of individuals per risk category is indicated with prevalence. The event rate reflects the average risk of myocardial infarction (MI) for all individuals in that risk category. Health states in the model are represented by boxes, starting with the 'Healthy' box. Ellipses represent events, and arrows represent transitions between health states due to events. At baseline, all individuals in the model are healthy after which they can stay healthy, experience a first MI (our main focus, solid arrow), or an ischemic stroke, hemorrhagic stroke, or gastrointestinal bleeding (dashed arrows). Individuals could die from other causes in all health states (event and transitions not shown for visual clarity). CIMT, carotid intima–media thickness; FRS, Framingham risk score.

low risk (<5%), low risk (5–10%), moderate risk (10–20%) and high risk (>20%). In our model (Fig. 2), we used costs and utility information on MI as a proxy for coronary events, as this comprises the majority of coronary events within ARIC [8]. Individuals in our model can stay alive and healthy, experience a fatal or nonfatal MI, or die from other causes. In addition, individuals may experience a fatal or nonfatal ischemic stroke, hemorrhagic stroke, or gastrointestinal bleeding, with the risk of these events modified in individuals receiving pharmacological treatment (eTable 2, http://links.lww.com/HJH/A234). Individuals surviving a first MI can stay alive (with a reduced quality of life), experience a second MI, which again can be fatal or nonfatal, or die from other causes. Each health state was assigned a utility value, expressed in quality-adjusted life years (QALYs).

Model parameters: risk prediction and (re)classification

All risks, risk classification, reclassification parameters and recurrence rates of (fatal) MI used in the model are based on the ARIC Study, Northern American data and Dutch registry data [8,11–14] (eTable 1, http://links.lww.com/HJH/A234). The age-specific and sex-specific 'all-cause' mortality rates were obtained from the National Center of Statistics in the Netherlands (CBS, 2011).

Reclassification according to the CIMT strategy may result in additional health benefits, compared with the FRS strategy by altering individual treatment decisions, as we assume that individuals reclassified to the high-risk category will receive pharmacological treatment.

Model parameters: pharmacological treatment

The use of multiple drugs is common and is recommended by international guidelines in the high-risk category (>20% absolute risk) for CHD. Treatment with combinations of a lipid modifying drug(s), one or more blood pressure lowering drugs, and a platelet aggregation inhibitor is thought to reduce CHD risk up to 40–90% [15–17]. However, in practice only half of the individuals may actually adhere to the medications prescribed [18,19]. We have accounted for this nonadherence in our analysis by shrinking the initial estimates and range of risk reduction due to treatment (40–90%) by half to 20–45%. The effect of pharmacological treatment on the risk of MI, ischemic stroke, hemorrhagic stroke, and gastrointestinal bleeding was included in our model (eTable 2, http://links.lww.com/HJH/A234). We assumed that mild side-effects caused by the drugs are accounted for through our adjustment for nonadherence.

Model parameters: costs

Costs on acute care of fatal and nonfatal MI and the subsequent MI-related care were obtained from published literature from the United States [20]. Costs of ischemic stroke, hemorrhagic stroke, and gastrointestinal bleeding were adapted from a previous cost-effectiveness analysis (eTable 2, http://links.lww.com/HJH/A234) [21]. The cost of a single CIMT measurement was based on the commercial price set by the University of Chicago Medical Center, that is, $325 [22]. Annual costs of pharmacological treatment were assumed equal to annual post-MI pharmacological treatment costs and were estimated at $1116. All costs were estimated

and recalculated to 2011 US dollars, if necessary (1 US$ = 0.615 euro, 05–05–2011).

Model parameters: utilities

Health state utilities were obtained from the published literature [20,23]. The utility values for individuals free of MI stratified for age and sex were based on the EQ-5D US score [23]. Individuals surviving a first MI had a reduced utility value, and this utility value was reduced even further for individuals experiencing a second MI. Utilities of individuals surviving ischemic stroke, hemorrhagic stroke, or gastrointestinal bleeding were adapted from a previous cost-effectiveness analysis (eTable 2, http://links.lww.com/HJH/A234) [21].

Model assumptions

The following assumptions were required for our model:

1. All coronary events in our model were MIs.
2. A first MI implied a low, but permanently increased risk of death, as well as an increased risk of recurrent MI, a second MI did not alter these increased risks.
3. Twenty percent of the individuals in the intermediate risk category (10–20%) received pharmacological treatment for cardiovascular disease risk.

Model simulation

We assessed the cost-effectiveness of the CIMT strategy compared with the FRS strategy by simulating cohorts of 100 000 hypothetical individuals for each of the two strategies. Evidence was based on the ARIC study comprising 13 145 individuals; a larger cohort was simulated to ensure robustness of the results. We simulated separate cohorts for men aged 50–59 years and women aged 50–59 years, which is the main age range of the ARIC study population. We assessed the cost-effectiveness of CIMT versus FRS for time horizons of 10, 20 and 30 years, and applied discounting rates of 3% for costs and effects according to US guidelines [24]. We evaluated three scenarios, with respect to the reduction in the risk of MI offered by pharmacological treatment, based on expert opinion: a moderate scenario with the expected relative risk of MI of 0.675 (effectiveness of 32.5%), a conservative scenario with a relative risk of MI of 0.80 (effectiveness of 20%), and an optimistic scenario with a relative risk of MI of 0.55 (effectiveness of 45%). In addition, we assessed the effect of varying the proportion of treated patients in the intermediate (10–20%) risk category from 20% to either 10 or 30%, and of reducing the cost of a CIMT measurement from $325 to $150.

Initially we calculated the incremental cost-effectiveness ratio (ICER) based on the difference in health benefits and costs. However, when the difference in health benefits is very small, as was the case in our analysis, this ratio is less suitable. Therefore, we calculated the Net Monetary Benefit (NMB) instead. The NMB is defined as the difference in health benefits multiplied by the willingness-to-pay (WTP) threshold to gain one QALY, minus the difference in costs. We calculated the NMB for WTP thresholds of US$ 50 000/QALY and US$ 100 000/QALY. A positive NMB value implies that the balance between additional health effects and additional costs is favorable, whereas a negative NMB value implies that this balance is unfavorable. Uncertainty in model outcomes was assessed with probabilistic sensitivity analysis and Monte Carlo simulation based on 5000 samples (distributions are shown in eTables 1–2, http://links.lww.com/HJH/A234). Results were represented in cost-effectiveness planes and cost-effectiveness acceptability curves [25].

RESULTS

Carotid intima–media thickness measurements and reclassification

Only individuals with more than 10% cardiovascular risk in 10 years are eligible for a CIMT measurement. In the ARIC population (age 50–59 years) this means that, after FRS assessment, one in two men, and one in 11 women received a CIMT measurement. CIMT information would change the subsequent treatment decision in $(290 + 166)/(2229 + 659) = 15.8\%$ of these men, and in $(68 + 43)/(521 + 173) = 16\%$ of these women. The CIMT strategy reduced the overall absolute risk to develop a MI. In our moderate scenario (effectiveness of pharmacological treatment of 32.5%), the absolute 10-year risk of MI decreased from 15.3 to 15.0% in men (Fig. 3) and from 15.1 to 14.5% in women (Fig. 3).

Table 1 displays the main results of the moderate scenario for pharmacological benefit (relative risk 0.675) for men, and Table 2 displays the corresponding results for women. After reclassification, the number of individuals treated in the CIMT strategy is equal to or slightly lower than the number of individuals treated in the FRS strategy. The risks of stroke and of gastrointestinal bleeding are very similar for both strategies, for men and women. Over time, the CIMT strategy resulted in a small reduction in the total risk of MI compared with the FRS strategy, at additional costs. This lower risk of MI translates into a small increase in life years and QALYs. For a WTP of $50 000/QALY the NMB becomes positive for men after at least 20 years, but for women this occurs within 10 years (eTable 3, http://links.lww.com/HJH/A234). For a WTP of $100 000/QALY the NMB is also positive for men within 10 years (eTable 3, http://links.lww.com/HJH/A234). This implies a favorable balance between the additional costs and additional health effects of the CIMT strategy compared with the FRS strategy.

eFigure 1A, http://links.lww.com/HJH/A234 shows the incremental cost-effectives plane for the moderate scenario of pharmacological benefit. The cost-effectiveness plane is divided into four quadrants. The x-axis represents the incremental health effects, the y-axis represents the incremental costs induced, and the gray line indicates the WTP threshold of $100 000/QALY. eFigure 1A, http://links.lww.com/HJH/A234 shows confidence ellipses of the CIMT strategy compared with the FRS strategy, for men and women, over a 10 and 30-year time horizon. Here, the largest portion of the ellipses is located in the upper and lower right quadrants, with positive health effects. For men, CIMT is likely to result in additional health benefits at additional costs, for a 10 and 30-year horizon. Conversely, for women CIMT is likely to result in additional health

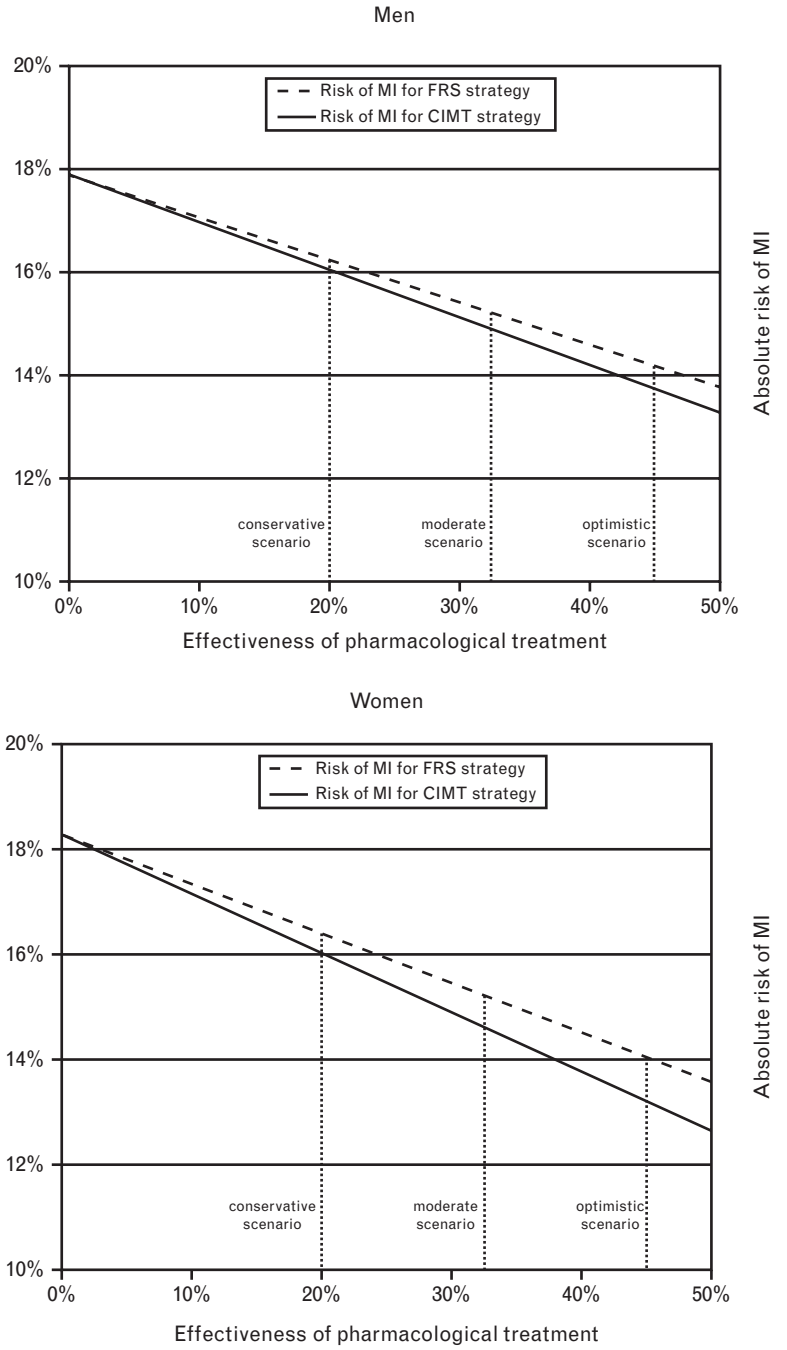

FIGURE 3 The absolute risk of myocardial infarction (MI) in individuals eligible for CIMT, that is with an initial FRS risk more than 10% in 10 years, separately for men and women. Note that the y-axis starts at 10% risk. The effectiveness of pharmacological treatment (x-axis) translates in the analysis as 1 minus the relative risk of MI. The reduction in absolute risk depends on the effectiveness of pharmacological treatment and the reclassification based on CIMT results. The 95% confidence intervals for the absolute risk in both strategies are overlapping for all effectiveness values in the range 0–50% (not shown). CIMT, carotid intima–media thickness; FRS, Framingham risk score.

benefits, at additional costs for a 10-year time horizon, and at reduced costs (cost-saving) for a 30-year time horizon.

eFigure 1B, http://links.lww.com/HJH/A234 displays the cost-effectiveness acceptability curves corresponding to the results shown in eFigure 1A, http://links.lww.com/HJH/A234. From eFigure 1B, http://links.lww.com/HJH/A234 it is clear that the applied time horizon substantially affects the probability of CIMT being cost-effective for men but not for women. For a 10-year time horizon, the CIMT strategy has a 25% probability of being cost-effective for men, and a 87% probability of being cost-effective for women, for a WTP threshold of $50 000/QALY. For a 30-year time horizon, these probabilities increase to 93% for men and 98% for women. Applying a WTP threshold of $100 000/QALY, the probability that the CIMT strategy is cost-effective is already very high within 10 years time for women (94%) but not for men (66%), and probabilities exceed 95% for a 30-year time horizon.

TABLE 1. Main outcomes of the cost-effectiveness analysis for men

Men	Moderate effectiveness of treatment (relative risk of MI: 0.675)	
	10 year time horizon	30 year time horizon
FRS outcomes		
Average fraction treated	0.34 (0.33 to 0.36)	0.31 (0.30 to 0.32)
Total risk of MI*	0.18 (0.16 to 0.20)	0.42 (0.37 to 0.47)
Risk of stroke#	0.016 (0.014 to 0.018)	0.032 (0.028 to 0.036)
Risk of gastrointestinal bleeding	0.009 (0.006 to 0.011)	0.017 (0.013 to 0.021)
Costs (k$)	6.2 (5.8 to 6.5)	13.0 (12.3 to 13.7)
Lifeyears	8.28 (8.27 to 8.30)	14.95 (14.81 to 15.08)
QALYs	6.97 (6.89 to 7.04)	12.17 (11.96 to 12.37)
CIMT outcomes		
Average fraction treated	0.34 (0.33 to 0.35)	0.30 (0.29 to 0.31)
Total risk of MI*	0.17 (0.15 to 0.19)	0.41 (0.36 to 0.46)
Risk of stroke#	0.016 (0.014 to 0.018)	0.032 (0.028 to 0.036)
Risk of gastrointestinal bleeding	0.008 (0.006 to 0.011)	0.017 (0.013 to 0.021)
Costs (k$)	6.4 (6.1 to 6.7)	13.1 (12.4 to 13.9)
Lifeyears	8.29 (8.27 to 8.30)	14.97 (14.82 to 15.09)
QALYs	6.97 (6.89 to 7.04)	12.19 (11.98 to 12.39)
Difference between CIMT and FRS		
Average fraction treated	0.00 (–0.02 to 0.01)	–0.01 (–0.02 to 0.00)
Total risk of MI*	0.00 (–0.01 to 0.00)	–0.01 (–0.02 to 0.00)
Risk of stroke#	0.000 (0.000 to 0.000)	0.000 (0.000 to 0.000)
Risk of gastrointestinal bleeding	0.000 (0.000 to 0.000)	0.000 (0.000 to 0.000)
Costs (k$)	0.2 (0.1 to 0.4)	0.1 (–0.1 to 0.3)
Lifeyears	0.00 (0.00 to 0.00)	0.01 (0.00 to 0.03)
QALYs	0.00 (0.00 to 0.01)	0.02 (0.00 to 0.03)

CIMT, carotid intima–media thickness; FRS, Framingham risk score. Comparison of the FRS and CIMT strategies in men for time horizons of 10 and 30 years, and with all costs, and (quality-adjusted) life years discounted at 3%: *The total risk of MI includes the risk of first and second MIs; #The risk of stroke includes the risk of ischemic and of hemorrhagic stroke.

TABLE 2. Main outcomes of the cost-effectiveness analysis for women

Women	Moderate effectiveness of treatment (relative risk of MI: 0.675)	
	10 year time horizon	30 year time horizon
FRS outcomes		
Average fraction treated	0.36 (0.34 to 0.39)	0.32 (0.30 to 0.35)
Total risk of MI*	0.18 (0.15 to 0.22)	0.47 (0.39 to 0.56)
Risk of stroke#	0.008 (0.007 to 0.009)	0.017 (0.015 to 0.020)
Risk of gastrointestinal bleeding	0.004 (0.002 to 0.005)	0.008 (0.005 to 0.012)
Costs (k$)	5.9 (5.5 to 6.4)	13.0 (12.1 to 14.1)
Lifeyears	8.43 (8.40 to 8.45)	16.47 (16.19 to 16.69)
QALYs	6.88 (6.80 to 6.96)	12.91 (12.63 to 13.17)
CIMT outcomes		
Average fraction treated	0.35 (0.32 to 0.37)	0.30 (0.27 to 0.33)
Total risk of MI*	0.17 (0.14 to 0.20)	0.44 (0.37 to 0.52)
Risk of stroke#	0.008 (0.007 to 0.009)	0.018 (0.015 to 0.020)
Risk of gastrointestinal bleeding	0.004 (0.002 to 0.005)	0.008 (0.005 to 0.012)
Costs (k$)	6.0 (5.6 to 6.5)	12.7 (11.8 to 13.7)
Lifeyears	8.43 (8.40 to 8.46)	16.52 (16.25 to 16.73)
QALYs	6.89 (6.81 to 6.96)	12.97 (12.70 to 13.21)
Difference between CIMT and FRS		
Average fraction treated	–0.02 (–0.04 to 0.01)	–0.02 (–0.05 to 0.00)
Total risk of MI*	–0.01 (–0.02 to 0.00)	–0.03 (–0.06 to 0.00)
Risk of stroke#	0.000 (0.000 to 0.000)	0.000 (0.000 to 0.001)
Risk of gastrointestinal bleeding	0.000 (0.000 to 0.000)	0.000 (0.000 to 0.000)
Costs (k$)	0.1 (–0.2 to 0.3)	–0.3 (–0.9 to 0.2)
Lifeyears	0.01 (0.00 to 0.01)	0.05 (0.00 to 0.10)
QALYs	0.01 (0.00 to 0.02)	0.05 (0.00 to 0.11)

CIMT, carotid intima–media thickness; FRS, Framingham risk score. Comparison of the FRS and CIMT strategies in women for time horizons of 10 and 30 years, and with all costs, and (quality-adjusted) life years discounted at 3%: *The total risk of MI includes the risk of first and second MIs; #The risk of stroke includes the risk of ischemic and of hemorrhagic stroke.

For the conservative and optimistic scenarios, the results are shown in eFigures 2 and 3, and eTable 3, http://links.lww.com/HJH/A234. For the conservative scenario [relative risk (RR) = 0.8] the probability that CIMT is cost-effective is somewhat lower than for the optimistic scenario, for men and women, and regardless of WTP threshold. However, the general outcome is similar: the cost-effectiveness of CIMT is favorable for men within 30 years and for women within 10 years. Only in the optimistic scenario (RR = 0.55) there is a substantial probability of 78% that the cost-effectiveness of CIMT is favorable for men within 10 years, for a WTP of $100 000/QALY.

We also investigated the effects of a lower cost for the B-mode ultrasound measurement of the carotid artery, by setting its cost to $150 instead of $325.

As a result, the probability of cost-effectiveness in 10 years increased from 66 to 91% for men and from 94 to 98% for women in the moderate scenario, for a WTP of $100 000/QALY. If, in addition, the time horizon was extended to 30 years, CIMT was cost-effective for both men and women. Varying the extent to which individuals in the intermediate (10–20%) risk category were also treated, from 20% (baseline) to 10 and 30%, resulted in, respectively, lower and higher probabilities of cost-effectiveness for men and women, all time horizons and WTP thresholds, but did not affect the overall conclusions (data not shown).

DISCUSSION

This study examined the cost-effectiveness of adding a single CIMT measurement to the routine evaluation of CHD risk. Our analysis was consistent with the 2010 guidelines of the ACC/AHA and was based on best available evidence. We observed that performing CIMT and plaque measurements in asymptomatic men and women aged 50–59 years with an initial FRS intermediate risk (>10% in 10 years) for CHD results in additional, but small, health benefits. It takes time for these health benefits to outweigh the initial CIMT costs. With an increasing time horizon the balance between health benefits and costs becomes more favorable in both men and women, with the balance for women remaining more favorable than the balance for men, in all scenarios. In general, cost-effectiveness is acceptable for men within 30 years and for women within 10 years, regardless of the anticipated effect of pharmacological treatment, and the proportion of patients with intermediate risk that is treated, for any WTP threshold over $50 000/QALY. When the cost of a CIMT and plaque measurement decreases, or treatment effectiveness would be greater than anticipated (optimistic scenario) the cost-effectiveness of the CIMT strategy will become more favorable, in particular within a 10 year horizon in both men and women.

Added value of carotid intima–media thickness measurements: health outcomes and costs

We performed a model-based analysis to estimate the absolute actual risk reduction for MI that would result from reclassification according to CIMT and plaque information. When pharmacological treatment leads to a relative risk of 0.675 for CHD in high-risk individuals, treatment guided by CIMT measurement would reduce the absolute overall 10-year risk of MI by 0.4% for men and 0.9% for women, and the respective 30-year risks by 1.0 and 3.0%. At the same time, the CIMT strategy will not lead to additional complications from treatment, such as hemorrhagic strokes, and gastrointestinal bleedings.

When translating directly to the United States, there will be 20.9 million men, and 22.0 million women aged 50–59 years in 2012, according to the US Census Bureau. Of these individuals, one in two men and one in 11 women is eligible for CIMT measurement. Subsequently, CIMT and plaque measurements would be performed in 12.5 million individuals (screening of $1/2 \times 20.9$ men and $1/11 \times 22.0$ women). Treatment based on screening with CIMT and plaque information would then prevent almost 61 500 CHD events within 10 years, and over 166 000 CHD events within 30 years. This is an overestimation as we assume a participation rate of risk factor assessment of 100%, however, still a considerable number of prevented CHD events would be expected.

At present, the evidence of the added value of a CIMT measurement in 10-year cardiovascular risk prediction is not consistent across studies. Here, we used the reported net reclassification index (NRI) from the ARIC study, which was comparable to the NRI reported by the FATE Study [26]. In the intermediate risk group, the NRI in ARIC was even higher, 16.7% [8]. However, the Framingham Heart Study [27], the German CAPS Study [28], and the Rotterdam Study [29] did not report clinically relevant reclassification with CIMT measurements in the whole population.

Although differences in NRI between studies may have been attributed to differences in CIMT measurement and whether plaque information was included, in study population, in number of events, in cutoff values for risk categories and in chosen endpoints, it appears that evidence is beginning to emerge in support of the use of CIMT measurements in risk stratification, particularly for individuals with an estimated intermediate 10-year cardiovascular disease risk.

As accurate evidence on the benefits of treating patients with a combination of lipid-modifying drugs, blood pressure-lowering drugs, and a platelet aggregation inhibitor is lacking, we evaluated three scenarios, in which the risk reduction due to polypharmacy was varied, to obtain robust results. Combining recent evidence on the risk reduction offered by single drugs (RR of 0.75 95%CI 0.62–0.91 for blood pressure-lowering drugs, OR of 0.70 95%CI 0.61–0.81 for statins, and OR of 0.85 95%CI 0.69–1.06 for aspirin) [30–32], assuming 50% adherence and applying Mant and Hicks cumulative relative benefit approach [33], resulted in a combined risk reduction estimate of 0.29 95%CI (0.19–0.39). This estimate closely corresponds to our moderate scenario, and the wide confidence interval also confirms to need for a robust scenario-based approach as taken here.

Implementation of carotid intima–media thickness measurements

Before CIMT measurements can be implemented on a large scale, several issues must be addressed [34]. Population-based normative data for CIMT and presence of carotid plaque are needed. A validated prediction rule that includes

information on CIMT and plaque is also needed, and unintended consequences of CIMT testing, such as, for example, carotid revascularization surgery, need to be assessed. Finally, a common, recommended protocol that is feasible for a clinical setting is needed. A recently published example of such a protocol [35] uses information from the common, bulb and internal carotid segments and includes a separate measure of focal plaque. This protocol was shown to be reproducible and was feasible for use in an office setting conditional on strict quality control (training, certification, and monitoring).

Cost-effectiveness analyses such as those presented here add to the ability of clinicians and policy makers to appropriately evaluate the value of an imaging test such as CIMT. The Society for Atherosclerosis Imaging and Prevention (SAIP) together with the International Atherosclerosis Society have developed Appropriate Use Criteria for the CIMT measurement as part of a broader initiative to shepherd this technology into clinical practice [36]. This may lead to wider application of CIMT and plaque measurements, which, in turn, may reduce the CIMT measurement costs as modelled in our study. This initiative assumes the following: 'an appropriate imaging study is one in which the expected incremental information, combined with clinical judgment, exceeds the expected negative consequences by a sufficiently wide margin for a specific indication that the procedure is generally considered acceptable care and a reasonable approach for the indication' [37]. When evaluating CIMT, clinicians felt that appropriate indications were primarily for the detection of CHD risk among intermediate risk patients, metabolic syndrome and older patients [38].

Thus, the results of this analysis are consistent with the application of CIMT and plaque measurements in intermediate risk individuals. For individuals with the metabolic syndrome, or older individuals, cost-effectiveness may be assessed when appropriate evidence for these subgroups becomes available.

Study limitations

We assumed all coronary events to be MIs. Although the ARIC study reported that MI was the main contributor to coronary events, the costs and health states associated with coronary events and procedures are quite different. Costs associated with percutaneous coronary interventions and coronary artery bypass grafts are approximately 3–6 times higher than costs associated with MI [39], with health state utilities approximately 10% higher as compared to MI [40]. Accounting only for MIs is therefore likely to result in an underestimation of the costs that may be saved, and an overestimation of the additional health benefits, by CIMT measurements. Also, we were unable to account for lifestyle interventions because limited evidence is available on the costs, effects and compliance. As lifestyle recommendations are similar across all categories of risk, and for both strategies, exclusion is not likely to have influenced our results.

In conclusion, performing CIMT measurements in asymptomatic men and women aged 50–59 years results in additional, but small, health benefits. It takes time for these health benefits to outweigh the initial CIMT measurement costs. Our results support measurement of CIMT for cardiovascular risk stratification, in particular for women, when focusing on long-term health.

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Conflicts of interest

There are no conflicts of interest.

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Reviewers' Summary Evaluations

Reviewer 1

The strength of the article is the subject of cost effectiveness has not been done before according to search of the literature. The weakness of the study is that the relevance may not pertain to developing countries. The article may be more appropriate to publish in a cardiology or stroke specialist journal. I note in a review of published articles no article on this subject has been published in a specialist hypertension journal. Perhaps it may be a first time on this occasion. The final decision is left to the editorial committee.

Reviewer 2

The topic and the data of this paper are interesting. The authors have used the protocol of the ARIC study and an excellent mathematical analysis. The approach is cost-effective on long term. However, IMT measurement is not an easy technique and requires very well trained technicians. Multiple measurements were done, but only from a single point. For classifying cardiovascular risk the authors used the Framingham tables and not the SCORE model system. Hopefully this research will be continued.