Original Paper

Personalized Statin Therapy and Coronary Atherosclerotic Plaque Burden in Asymptomatic Low/Intermediate-Risk Individuals

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Keywords

Atherosclerosis · Coronary computed tomography angiography · Personalized therapy · Statin therapy

Abstract

Background: Current guidelines for the primary prevention of atherosclerotic cardiovascular disease are based on the estimation of a predicted 10-year cardiovascular disease risk and the average relative risk reduction estimates from statin trials. In the clinical setting, however, decision-making is better informed by the expected benefit for the individual patient, which is typically lacking. Consequently, a personalized statin benefit approach based on absolute risk reduction over 10 years (ARR₁₀ benefit threshold $\geq 2.3\%$) has been proposed as a novel approach. However, how this benefit threshold relates with coronary plaque burden in asymptomatic individuals with low/intermediate cardiovascular disease risk is unknown.

Aims: In this study, we compared the predicted ARR₁₀ obtained in each individual with plaque burden detected by coronary computed tomography angiography. **Methods and**

Results: Plaque burden (segment volume score, segment stenosis score, and segment involvement score) was assessed in prospectively recruited asymptomatic subjects ($n = 70$;

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52% male; median age 56 years [interquartile range 51–64 years]) with low/intermediate Framingham risk score (<20%). The expected ARR_{10} with statin in the entire cohort was 2.7% (1.5–4.6%) with a corresponding number needed to treat over 10 years of 36 (22–63). In subjects with an ARR_{10} benefit threshold $\geq 2.3\%$ (vs. <2.3%), plaque burden was significantly higher ($p = 0.02$). **Conclusion:** These findings suggest that individuals with higher coronary plaque burden are more likely to get greater benefit from statin therapy even among asymptomatic individuals with low cardiovascular risk.

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Introduction

Cardiovascular disease (CVD) remains a leading cause of mortality in the United States [1–3]. Consequently, the combined assessment of the Framingham risk score (FRS), which predicts 10-year CVD risk [4], and low-density lipoprotein cholesterol (LDL-C) levels was routinely used to initiate statin therapy for primary prevention according to the Third Adult Treatment Panel (ATP III) guidelines [5]. However, these recommendations for treatment of dyslipidemia have been substantially modified by the 2013 American College of Cardiology (ACC) and American Heart Association (AHA) guidelines for the assessment and reduction of atherosclerotic cardiovascular disease (ASCVD) [6, 7]. These guidelines for primary prevention of ASCVD recommend a comprehensive assessment of the estimated 10-year risk for an ASCVD event. This risk-based treatment strategy is typically based on risk prediction equations and average relative risk reduction (RRR) estimates from randomized interventional studies and prospective studies of large cohorts. This downloadable risk calculator includes race and diabetes among other FRS variables to estimate the 10-year ASCVD risk using the pooled cohort risk equation (PCRE). These new guidelines recommend statin therapy for individuals with an LDL-C level ≥ 70 mg/dL and a calculated ASCVD risk of 7.5% [7].

It is well recognized that a majority of ASCVD events occur in people with low CVD risk (<10%) [8, 9]. Similarly, significant numbers of CVD events occur in individuals younger than 65 years [10]. However, age is a major driver of 10-year CVD risk as determined by the PCRE. Thus, guideline-driven, risk-based “one size fits all” approaches are usually at odds with shared clinical decision-making in the clinical setting where net benefit for the individual patient is important. Recognizing this limitation, an individualized benefit approach based on a predicted absolute risk reduction over 10 years (ARR_{10}) of 2.3% has been proposed [11]. Individualized ARR_{10} of major cardiovascular events by statin therapy was calculated as the difference in estimated CVD risk during baseline and while on statin treatment [11]. The off-treatment risk was estimated by the PCRE and the 10-year on-statin treatment risk was determined by the RRR from a 40% reduction in plasma LDL-C concentration. Using this approach and the data from the National Health and Nutrition Examination Survey (NHANES), they identified an additional 9.5 million low-risk individuals eligible for statin therapy and prevention of 265,000 CVD events over 10 years (ARR_{10} benefit threshold $\geq 2.3\%$ vs. PCRE $\geq 7.5\%$) [11].

Considering the natural progression of coronary atherosclerosis and the anti-atherosclerotic effects of statins, whether this individual benefit threshold relates to coronary plaque burden in asymptomatic individuals with low/intermediate CVD risk is unknown. In this study, we examined the relationship between plaque burden in asymptomatic, untreated individuals with low/intermediate CVD risk and predicted individual benefit due to statin therapy as assessed by ARR_{10} .

Methods

Study Subjects

Written informed consent was obtained from all participants and the study was approved by the local institutional review board (ClinicalTrials.gov identifier: NCT01399385). Consecutive asymptomatic subjects with at least one modifiable ASCVD risk factor, without known or clinically overt ASCVD, were recruited prospectively between May 2008 and September 2013. The cardiovascular risk factors for inclusion were as follows: hypertension (clinically diagnosed and on antihypertensive medications for systolic blood pressure >140 mm Hg); known history of diabetes mellitus; dyslipidemia, defined as serum triglycerides >150 mg/dL, total cholesterol >200 mg/dL, low-density lipoprotein (LDL) >100 mg/dL, high-density lipoprotein (HDL) <40 or <50 mg/dL for women; and tobacco use, defined as current smoker or ex-smoker within the year preceding the study [12–14].

After an overnight fast, blood was drawn to measure high-sensitivity C-reactive protein (hs-CRP), total cholesterol, HDL, LDL, and triglycerides [4]. The 10-year CVD risk was calculated using the FRS tool [1, 3] and categorized as low ($\leq 10\%$), intermediate (11–20%), or high ($> 20\%$). In this report, we use a subset of the original cohort, which excluded patients with diabetes, LDL >190 mg/dL, and patients on statin therapy.

Image Acquisition, Reconstruction, and Analysis

Images were acquired using 64- to 320-slice multidetector computed tomography (CT) scanners using previously described scanning protocols [15–17]. Oral metoprolol was given 30–60 min prior to the scan to reduce the heart rate to approximately 65 bpm. Breathing instructions to reduce motion artifacts were practiced. A noncontrast cardiac CT was performed to obtain the Coronary Artery Calcium (CAC) score (Agatston score [18]), followed by standard coronary computed tomography angiography (CCTA). Axial, multiplanar reformatted coronary images were obtained using a 3-dimensional software tool (Virtual Place; AZE, Tokyo, Japan). Images were assessed by two blinded readers in consensus. A modified 16-segment model was used to identify coronary segments [19, 20].

Four CCTA-based scores were calculated to characterize plaque burden: (1) luminal stenosis, (2) segment involvement score (SIS), (3) segment stenosis score (SSS), and (4) plaque size. Luminal stenosis was categorized as nonobstructive ($< 50\%$ luminal narrowing) or obstructive ($> 50\%$ luminal narrowing) [15, 19]. The SIS (1–16) was calculated based on the number of segments involved with any atherosclerotic plaque. The SSS is similar to the SIS weighted by the degree of coronary artery stenosis (1–3 based on severity of stenosis) in individual segments as previously described [19]. Since subjects were asymptomatic and in the low/intermediate FRS risk group, they were unlikely to have significant coronary stenosis. Therefore, the SIS may be more representative of the atherosclerotic plaque burden. We used SIS > 5 as the cutoff point as previously described [19] to divide the population into two groups for comparison. Finally, plaque size was determined based on relation to coronary segment length; small plaque involved less than one-third, moderate plaque one-third to two-thirds, and large plaque more than two-thirds of segment wall length. Plaque composition was reported as noncalcified, mixed, or calcified [12].

Assessment of ARR_{10}

The 10-year predicted risk for each subject was first calculated using the PCRE [6]. The predicted ARR_{10} for each subject was calculated as previously reported [11]. Relative cardiovascular risk reduction associated with a 40% lowering of LDL-C using midpotency statins was predicted based on the data from the Cholesterol Treatment Trialists. ARR_{10} was estimated as the difference in baseline, without-statin-treatment cardiovascular risk for each subject using the PCRE and the predicted RRR due to statin treatment from the Cholesterol Treatment Trialists [11].

Statistical Analysis

The D'Agostino-Pearson test was used to test frequency distribution (normality). Continuous variables were described as mean $\pm$ standard deviation for normally distributed variables or as median and interquartile range (IQR) for nonnormal distributions. Categorical variables were described as number and percentage. The Spearman rho test was used for correlation analyses. The Mann-Whitney U or Pearson χ^2 tests were used, as appropriate, for comparative analysis. p values < 0.05 were considered statistically significant. Statistical analysis was performed using JMP statistical software version 12.0.

Table 1. Clinical characteristics
(*n* = 70)

Clinical parameters	
Age, years	57±9
Sex, F/M	37/33
Body mass index	27±7
History of hypertension	39 (55)
History of smoking	21 (30)
SBP, mm Hg	131±14
DBP, mm Hg	75±10
Total cholesterol, mg/dL	201±40
LDL-C, mg/dL	118 (46)
HDL-C, mg/dL	50 (19)
Triglycerides, mg/dL	112 (104)
Glycated hemoglobin, %	5.5±0.4
hs-CRP, mg/L	0.71 (2.17)
Framingham risk score	5.7 (7.5)
PCRE score	6.4 (9.1)
CAC score	0 (0–64)
Calcium (percentile)	0 (0–70)
SIS	5 (6)
SSS	6 (14)

Continuous variables are presented as median (interquartile range) or mean ± standard deviation. Categorical variables are presented as *n* (%). CAC score, Coronary Artery Calcium score; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; PCRE, pooled cohort risk equation; SBP, systolic blood pressure; SIS, segment involvement score; SSS, segment stenosis score.

Results

Characteristics of the Study Population

Table 1 describes the characteristics and CVD risk markers of the cohort (*n* = 70). The median age was 57 years (IQR 51–64 years), 53% (*n* = 37) of the cohort were women, and the median body mass index was 27 (IQR 24–31). Thirty-three percent (*n* = 23) of the subjects were prediabetic with a glycated hemoglobin level between 5.7 and 6.4%. The median 10-year FRS was 5.7% (IQR 2–10%). The FRS was in the low category in 70% (*n* = 49) subjects and intermediate in the remainder (30%; *n* = 21). Similarly, the baseline 10-year risk of developing ASCVD as determined by the PCRE was <7.5% in 70% of the study population, and thus only 21 subjects (30%) were eligible for potential statin therapy.

Coronary Atherosclerotic Plaque Burden Characteristics and Distribution

Online supplementary Figures 1 and 2 demonstrate examples of CCTA findings of ASCVD in this asymptomatic population (see www.karger.com/doi/10.1159/000487205). Table 2 describes the distribution and characteristics of the plaque burden. Plaque was not detected in 6 subjects (9%), all of whom had a low FRS. Atherosclerotic plaque was present in the remaining 64 subjects (91%), in whom 387 out of 1,120 (35%) segments were affected. A similar proportion of subjects (84%, *n* = 59) had noncalcified plaque. Plaque burden was detected most often in the left main or left anterior descending coronary artery (38%, *n* = 147 segments); the remaining burden was distributed in the left circumflex and right coronary arteries (18 and 27%, respectively). Approximately 47% of the subjects had moderate to large plaque size affecting more than one-third of segment length, and 11% had obstructive

Table 2. Distribution of plaque and plaque characteristics

	Subjects, n (%)	Segments, n (%)
Total	70	1,120
Presence of plaque	64 (91)	387 (35)
Plaque >1/3 of segment length	33 (47)	79 (7)
Obstruction >50% stenosis	8 (11)	10 (1)
Noncalcified plaque	59 (84)	264 (24)
Mixed plaque	33 (47)	97 (9)
Calcified plaque	11 (16)	26 (2)

Table 3. Differences between study variables based on SIS >5

Clinical parameters	SIS ≤5	SIS >5	p value
Age, years	54 (13)	59 (11)	0.13
Male	13	20	0.06
Body mass index	27 (10)	27 (4)	0.65
SBP, mm Hg	130±13	130±16	0.85
Total cholesterol, mg/dL	190±38	211±40	0.03
LDL-C, mg/dL	113 (47)	127 (45)	0.07
HDL-C, mg/dL	54 (17)	48 (21)	0.07
Glycated hemoglobin, %	5.4 (0.4)	5.6 (0.6)	0.13
hs-CRP, mg/L	0.42 (1.06)	1.10 (2.47)	0.01
Framingham risk score	3.9 (4.5)	8.8 (9.4)	0.006
PCRE score	5.9 (4.2)	10.2 (9.3)	0.007
CAC score	0 (0)	33 (184)	<0.001

Continuous variables are presented as median (interquartile range) or mean ± standard deviation. Categorical variables are presented as n (%). CAC score, Coronary Artery Calcium score; HDL-C, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; PCRE, pooled cohort risk equation; SBP, systolic blood pressure; SIS, segment involvement score.

plaque causing >50% stenosis of the lumen. An SSS >5 and an SIS >5 was noted in 53% ($n = 37$) and 50% ($n = 35$), respectively.

The CAC score correlated significantly ($p < 0.001$) with CCTA-measured parameters of plaque burden including plaque size ($r = 0.52$), SIS ($r = 0.37$), and SSS ($r = 0.50$). Age, body mass index, systolic blood pressure, total cholesterol, LDL-C, HDL-C, glycated hemoglobin, and hs-CRP were unrelated to plaque burden. Using the cutoff SIS >5, the population was almost equally divided without significant differences in age and sex (Table 3). However, the subjects with an SIS >5 had significantly higher total cholesterol, hs-CRP, CAC score, FRS, and 10-year ASCVD score by PCRE when compared to subjects with an SIS ≤5 (Table 3).

Individual Absolute Risk Reduction and Coronary Plaque Burden

The expected ARR_{10} with statin in the entire cohort was 2.7% (1.5–4.6%) with a corresponding number needed to treat over 10 years of 36 (22–63). An expected ARR_{10} of ≥2.3% has been suggested as an optimal threshold for absolute benefit [11]. Using this individualized threshold, 57% ($n = 40$) of this cohort would benefit from statin treatment for primary prevention. Expected ARR_{10} was significantly associated with plaque burden including plaque size ($r = 0.34$), SIS ($r = 0.35$), and SSS ($r = 0.50$). The predicted ARR_{10} with statin treatment

Fig. 1. Cardiovascular risk and atherosclerotic burden in asymptomatic low-risk individuals. **a** Baseline cardiovascular risk. **b** Predicted ARR₁₀ with statin treatment in individuals with an SIS ≤5 and >5. **c** SIS in individuals with an ARR₁₀ <2.3 and ≥2.3%. Bars represent mean (95% CI). * $p < 0.05$. ARR₁₀, absolute risk reduction over 10 years; SIS, segment involvement score.

Fig. 2. ROC curve analysis for the expected ARR₁₀ of subjects treated with statins versus coronary atherosclerotic burden. The AUC for the coronary atherosclerotic burden parameters (**a**, SIS >5; **b**, SSS >5) are presented as mean (95% CI). ARR₁₀, absolute risk reduction over 10 years; AUC, area under the curve; ROC, receiver operating characteristic; SIS, segment involvement score; SSS, segment stenosis score.

has higher in individuals with an SIS >5 (Fig. 1). Receiver operating characteristic (ROC) curve analysis was performed to determine how well the expected ARR₁₀ distinguished atherosclerotic load, categorized as an SIS >5 or an SSS >5. The ROC curve for predicting coronary atherosclerosis burden with expected ARR₁₀ is depicted in Figure 2. The area under the curve was 0.68 (95% CI 0.55–0.81) for SIS >5 and 0.69 (95% CI 0.57–0.82) for SSS >5, suggesting that both models performed well in identifying subjects with significant atherosclerotic burden. Using the current guidelines, a 10-year PCRE risk ≥7.5% is the threshold for statin initiation. The baseline cardiovascular risk estimated by the PCRE was related to predicted ARR₁₀ ($r = 0.80$, $p < 0.0001$). We compared the discriminative power of the PCRE score and predicted ARR₁₀ to identify measures of atherosclerotic burden (SIS and SSS). The area under

the curve was 0.69 (95% CI 0.57–0.82) for SIS >5 and 0.65 (95% CI 0.52–0.78) for SSS >5. There was no significant difference between the C statistics of the two scores for the identification of patients with SIS and SSS >5.

Discussion

A personalized approach in choosing therapies that provide the greatest risk reduction may indeed be the coming paradigm shift in clinical practice [21]. In this study, we demonstrated that in asymptomatic individuals with low/intermediate ASCVD risk, a benefit threshold of $ARR_{10} \geq 2.3\%$ identified 40% more individuals for primary prevention when compared with a risk-based approach, and that these individuals also had higher coronary plaque burden. This is the first study to examine the atherosclerotic burden and its relationship to expected risk reduction rather than baseline risk.

Assessment of baseline cardiovascular risk using population-based risk models formed the basis of the recent ACC/AHA guidelines regarding use of the PCRE for CVD risk calculation [6]. These guidelines have incited controversy and debate [22–24], particularly regarding the recommendation to initiate therapy at the 10-year CVD risk cutoff value of 7.5%. This criterion is lower than the earlier threshold of 20% 10-year risk calculated using the FRS [23]. Outcome validation studies are emerging to investigate the utility of the new PCRE and the 2013 ACC/AHA guidelines [25]. Implicit in this risk-targeted approach is the assumption that RRR is similar across the treatment group. However, the efficiency of statin therapy is higher in individuals with higher baseline LDL concentrations and of younger age, and related to statin potency [11, 26, 27]. Thus, this approach will invariably lead to unnecessary treatment of some individuals (e.g., low LDL levels), with the exclusion of others (e.g., younger age group). By estimating the individualized treatment effect from trial-level data, various studies in recent years have examined the impact of individualizing statin treatment for primary prevention [11, 28–31]. In particular, the study by Thanassoulis et al. [11], using the individualized treatment approach with a treatment threshold of $ARR_{10} \geq 2.3\%$, identified an additional 9.5 million patients with a PCRE-calculated risk <7.5% who would benefit from statin therapy.

Temporal progression or “regression” of coronary artery plaque in response to medical management has been evaluated by invasive modalities such as coronary angiography [32] and intravascular ultrasound studies [33] and recently by CCTA [34, 35]. Increased coronary plaque burden is associated with negative cardiovascular outcomes [36], and plaque regression following statin therapy is associated with reduced cardiovascular events [33]. These studies were performed in individuals with high risk for CVD. However, 40% of the US population are at “intermediate” risk and thus account for a significant number of cardiovascular events. Large studies examining the prevalence, natural history, and changes in coronary plaque burden in this population are lacking. In a retrospective study of asymptomatic Korean adults, coronary plaque and stenosis (>50%) was present in 43 and 10%, respectively [37]. In another study of asymptomatic individuals with low to moderate risk, noncalcified plaque accounted for more than half of total plaque, irrespective of the CAC score [38]. In our study, CCTA detected at least one coronary vessel with a significant luminal stenosis (>50%) in 11% of subjects, similar to the South Korean study [37]. Since this prospective study investigated asymptomatic patients with low/intermediate risk, this relatively low prevalence was not surprising. Yet, the presence of potentially obstructive lesions in asymptomatic individuals is notable and underscores the need for better early identification as suggested by the ACC/AHA guidelines.

Other CCTA criteria reflective of plaque burden such as plaque size, number of segments involved (SIS), and severity of segment stenosis (SSS) [39] were more common than signif-

icant stenosis. The SIS and the SSS have prognostic value in symptomatic patients when either score is >5 [19]. In this study, plaque size more than one-third of a segment length was present in about half of the subjects (47%). Noncalcified plaque was the most prevalent (84%), whereas calcified plaque was seen in 16% of subjects, findings similar to those reported by Rodriguez et al. [38]. These numbers reflect the underlying burden of coronary disease in asymptomatic subjects, which is much larger than might be expected given the modest amount of calcified plaque.

When the study population was stratified by $SIS \leq 5$ and >5 , the two groups had similar age and sex, but significantly different FRS, 10-year ASCVD risk score, hs-CRP, CAC score, and percentile. These findings highlight the relationship between anatomic atherosclerotic plaque burden and scoring methods and other markers. The $SIS >5$ group had a median 10-year ASCVD risk of 10.2%, which is congruent with the 2013 ACC/AHA recommendation for aggressive management of a 7.5% 10-year calculated risk [6]. However, in the $SIS >5$ group, hs-CRP (1.1 mg/L) levels were substantially lower than the ACC/AHA threshold (2 mg/L). Further studies in larger asymptomatic populations, with ASCVD outcomes, will help determine the predictive value of the CAC score and hs-CRP as surrogate markers for coronary atherosclerotic burden.

The PCRE has been shown to accurately identify high coronary atherosclerotic burden in individuals with high cardiovascular risk [40]. However, in our cohort with low/moderate cardiovascular risk, stratification based on PCRE risk ≥ 7.5 and $<7.5\%$ was able to distinguish subjects with higher atherosclerotic burden. Similarly, when subjects were stratified by $ARR_{10} \geq 2.3\%$ and $<2.3\%$, the group with $\geq 2.3\%$ had a higher coronary plaque burden. Moreover, the ROC analysis showed that the expected ARR_{10} reasonably distinguished angiographic disease ($SIS >5$ and $SSS >5$). This finding of higher atherosclerotic load supports the pathophysiological argument for initiating statin treatment for primary prevention in individuals who are at low to moderate cardiovascular risk. In fact, using the individual benefit threshold (expected $ARR_{10} \geq 2.3\%$), approximately 4% of the US adult population or 8.4 million additional individuals will now be candidates for statin therapy [41].

The role of CCTA in personalizing cardiovascular risk assessment and monitoring therapeutic response is a topic of intense debate. Limited longitudinal data on plaque progression and its relationship to clinical outcomes, risks associated with contrast use and repeated radiation exposure, and the associated costs precludes routine use of CCTA in cardiac risk assessment, especially in low-risk individuals. The PARADIGM registry, a large, prospective, observational registry, seeks to evaluate the progression of atherosclerosis (by serial CCTA) in individuals with low to moderate risk [42]. This ongoing study may provide much-needed insights and strategies to risk stratify this particular population based on clinical outcomes. Novel techniques of functional CT imaging, including CT perfusion and CT-derived fractional flow reserve, when combined with CCTA can simultaneously assess hemodynamically significant coronary lesions [43]. The advent of these newer techniques that are cost-effective, more accurate with lower radiation exposure, and less invasive may provide “personalized imaging” to deliver individualized treatment in the future [44].

In conclusion, this study demonstrates that asymptomatic subjects with a low/intermediate FRS score have a substantial coronary atherosclerotic disease burden. Our novel findings suggest that an individualized statin therapy approach, even in asymptomatic individuals with low cardiovascular risk, targets individuals with higher coronary plaque burden, so that they are more likely to get greater cardiovascular benefit.

Statement of Ethics

Written informed consent was obtained from all participants and the study was approved by the local institutional review board (ClinicalTrials.gov identifier: NCT01399385).

Disclosure Statement

The authors have no conflicts of interest.

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Author Contributions

R. Muniyappa, A. Hamimi, J.R. Matta, R. El Khouli, K. Abd-Elmoniem, R. Noureldin, and A.M. Gharib designed the study, collected the data, and drafted the manuscript. R. Muniyappa, A.M. Gharib, and K. Abd-Elmoniem performed the statistical analysis. All authors interpreted the data and revised the manuscript.

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