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Original article

Impact of lipid-lowering therapies on cardiovascular outcomes according to coronary artery calcium score. A systematic review and meta-analysis

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A B S T R A C T

Introduction and objectives: Coronary artery calcium (CAC) score improves the accuracy of risk stratification for atherosclerotic cardiovascular disease (ASCVD) events compared with traditional cardiovascular risk factors. We evaluated the interaction of coronary atherosclerotic burden as determined by the CAC score with the prognostic benefit of lipid-lowering therapies in the primary prevention setting.

Methods: We reviewed the MEDLINE, EMBASE, and Cochrane databases for studies including individuals without a previous ASCVD event who underwent CAC score assessment and for whom lipid-lowering therapy status stratified by CAC values was available. The primary outcome was ASCVD. The pooled effect of lipid-lowering therapy on outcomes stratified by CAC groups (0, 1-100, > 100) was evaluated using a random effects model.

Results: Five studies (1 randomized, 2 prospective cohort, 2 retrospective) were included encompassing 35 640 individuals (female 38.1%) with a median age of 62.2 [range, 49.6-68.9] years, low-density lipoprotein cholesterol level of 128 (114-146) mg/dL, and follow-up of 4.3 (2.3-11.1) years. ASCVD occurrence increased steadily across growing CAC strata, both in patients with and without lipid-lowering therapy. Comparing patients with (34.9%) and without (65.1%) treatment exposure, lipid-lowering therapy was associated with reduced occurrence of ASCVD in patients with CAC > 100 (OR, 0.70; 95%CI, 0.53-0.92), but not in patients with CAC 1-100 or CAC 0. Results were consistent when only adjusted data were pooled.

Conclusions: Among individuals without a previous ASCVD, a CAC score > 100 identifies individuals most likely to benefit from lipid-lowering therapy, while undetectable CAC suggests no treatment benefit.

Impacto de los tratamientos hipolipemiantes en los resultados cardiovasculares según la puntuación de calcio coronario. Revisión sistemática y metanálisis

Palabras clave:
Puntuación de calcio arterial coronario
Prevención primaria
Tratamiento hipolipemiante
Enfermedad cardiovascular ateroesclerótica
Metanálisis

R E S U M E N

Introducción y objetivos: La puntuación de calcio arterial coronario (CAC) mejora la precisión de la estratificación del riesgo de enfermedad cardiovascular ateroesclerótica (ECVA) en comparación con los factores de riesgo cardiovascular tradicionales. Se evaluó la interacción de la carga ateroesclerótica coronaria determinada por la puntuación de CAC con el beneficio pronóstico de los tratamientos hipolipemiantes en el contexto de la prevención primaria.

Métodos: Se revisaron las bases de datos MEDLINE, EMBASE y Cochrane en busca de estudios que incluyeran a individuos sin ECVA previa y con datos sobre la puntuación de CAC y el tratamiento hipolipemiante según los valores de CAC. El objetivo primario fue la aparición de ECVA. Se evaluó el efecto del tratamiento hipolipemiante agrupado y estratificado por grupos de CAC (0, 1-100 y > 100) mediante un modelo de efectos aleatorios.

Resultados: Se incluyeron 5 estudios (1 aleatorizado, 2 de cohortes prospectivas y 2 retrospectivas) que incluyeron a 35.640 individuos (el 38,1% mujeres) con medias de edad de 62,2 (rango, 49,6-68,9) años,

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colesterol unido a lipoproteínas de baja densidad de 128 (114-146) mg/dl y seguimiento de 4,3 (2,3-11,1) años. La aparición de la ECVA aumentó de manera constante en los estratos crecientes de CAC tanto en los pacientes con como en aquellos sin tratamiento hipolipemiante. Al comparar a los pacientes con (34,9%) y sin (65,1%) exposición al tratamiento hipolipemiante, este se asoció con menos aparición de ECVA en los pacientes con CAC > 100 (OR = 0,70; IC95%, 0,53-0,92), pero no en aquellos con CAC de 1-100 o 0. Los resultados concordaron al agrupar los datos ajustados.

Conclusiones: Entre los individuos sin ECVA previa, una puntuación de CAC > 100 identifica a los sujetos con mayor probabilidad de beneficiarse del tratamiento hipolipemiante, mientras que un CAC indetectable indica ausencia de beneficio.

Abbreviations

ASCVD: atherosclerotic cardiovascular disease
CAC: coronary artery calcium

INTRODUCTION

Lipid-lowering therapy improves cardiovascular outcomes among patients with a prior atherosclerotic cardiovascular disease (ASCVD) event.[1] Hence, lipid-lowering therapy is universally recommended for the secondary prevention of ASCVD.[2]

In the primary prevention setting, lipid-lowering therapy reduces ASCVD occurrence.[1,3] However, the absolute risk reduction in the overall population may be offset by adverse effects, cost-benefit considerations, and clinical disutility. Identification of high-risk patients is thus pivotal to ensure clinical efficacy and cost-effectiveness when prescribing lipid-lowering therapy in asymptomatic individuals.

Risk factor matrices developed from epidemiological studies have only moderate ability to predict ASCVD,[4,5] as there is substantial heterogeneity between clinical risk and actual atherosclerotic burden.[5,6] Coronary artery calcium (CAC) is a highly specific marker of atherosclerotic burden,[7] able to improve ASCVD prediction among asymptomatic individuals over traditional risk factors.[6,8–10] Patients with no detectable CAC are at very low risk of ASCVD events, suggesting that the benefit of lipid-lowering therapy may be trivial in this subset.[8] However, the relative impact of lipid-lowering therapies on *de novo* ASCVD occurrence, as stratified by increasing CAC values, remains poorly characterized. For this reason, recommendations by the European Society of Cardiology regarding CAC use to drive lipid-lowering therapy remain weak and a statement has been made on the need to further investigate the incremental value of reclassifying total cardiovascular risk and defining eligibility for lipid-lowering therapy based on CAC score.[11]

We thus performed a systematic review and meta-analysis to evaluate the interaction of the coronary atherosclerotic burden as determined by the CAC score with the prognostic benefit of lipid-lowering therapies in the primary prevention setting.

METHODS

Study design

This meta-analysis was reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) Statement; the PRISMA checklist is available in the supplementary data.[12] The original study protocol was prospectively submitted for registration in PROSPERO and protocol amendments have been updated (registration code CRD42020171930).

All published clinical studies including patients without a previous ASCVD who underwent CAC score assessment were evaluated for inclusion in this meta-analysis. We considered for inclusion randomized clinical trials (RCT) or observational studies reporting ASCVD outcomes (defined as a composite endpoint including at least myocardial infarction or a proxy for myocardial infarction such as coronary revascularization) and lipid-lowering therapy status stratified by CAC values. Studies reporting the main study outcomes described in insufficient detail or not written in the English language were excluded. The main study outcome was ASCVD occurrence at last follow-up. ASCVD definition for each included study is reported in table 1. Patients were categorized by CAC strata (CAC 0, CAC 1-100, CAC > 100) and by lipid-lowering therapy status (yes vs no). The impact of lipid-lowering therapies on ASCVD occurrence stratified by CAC categories was evaluated. The ASCVD risk stratification ability of CAC score, overall and stratified by lipid-lowering therapy status was also evaluated.

Database search, study selection, data extraction and risk of bias assessment

Five authors (E. Elia, F. Bruno, F. Angelini, G. Gallone, and P.P. Bocchino) independently searched EMBASE, MEDLINE/PubMed, and the Cochrane Central Register of Controlled Trials (CENTRAL) using a combination of the following free-text words: "calcium artery score", "calcium score", "CAC", "statin", "lipid lowering", "preventive therapy" (detailed search strategy in the supplementary data) from inception to June 15, 2021. Backward snowballing was also performed (no additional studies found).

All authors independently assessed identified studies for possible inclusion. Nonrelevant articles were excluded based on the title and abstract. Two investigators (U. Annone, and F. Piroli) independently extracted data on study designs, measurements, patient characteristics, and outcomes using a standardized data extraction form. Conflicts regarding inclusion and data extraction were discussed and resolved with another investigator (L. Franchin). Data collection included authors, year of publication, inclusion and exclusion criteria, sample size, baseline clinical features of patients, observed adverse events, and medical treatment, as available. To improve data extraction, supplementary data and pertinent substudies were also examined.

Two independent reviewers (M. Bertaina, and E. Elia) assessed the risk of bias (low, intermediate, or high) of the included studies following the Agency for Healthcare Research and Quality recommendations.[16]

Data synthesis and analysis

The analysis was by aggregate data. Cumulative event rates for study endpoints were obtained and reported. Pooled effect

Table 1
General characteristics of the included studies

Study name First author, publication year	The St. Francis Heart Study Waheed et al., [13] 2016	Korean registry Hwang et al.,[14] 2015	The BioImage Study Mortensen et al.,[4] 2016	Walter Reed Army Medical Center study Mitchell et al.,[15] 2018	Multi-Ethnic Study of Atherosclerosis Budoff et al.,[9] 2018
General characteristics	Double-blind RCT of atorvastatin and vitamins C-E vs placebo in ASCVD primary prevention among patients with elevated CAC	Registry including consecutive patients undergoing CCTA at 3 Korean medical centers with evidence of nonobstructive CAD (1-49% stenosis)	Cohort study in the ASCVD primary prevention setting to identify predictive biomarkers for near-term events	Registry including consecutive patients in ASCVD primary prevention to determine whether CAC can stratify statin treatment benefit	Longitudinal, population-based multiethnic study of patients in the ASCVD primary prevention setting
Study type	RCT	Retrospective study	Prospective observational study	Retrospective study	Prospective observational study
Number of patients	1005	8372	5805	13 644	6814
Year of publication	2016	2015	2016	2018	2018
Enrolment period	1996-1999	2007-2011	2008-2009	2002-2009	2000-2002
Follow-up	4.3 y	2.3 [IQR 1.1-3.7] y	2.7 y	9.4 [IQR 7.2 - 11.2] y	11.1 y
Major inclusion criteria	Healthy men and women aged 50 to 70 y with CAC scores at or above the 80th percentile for age and sex	Men and women not taking aspirin or statins, undergoing coronary CCTA with evidence of nonobstructive CAD	Men 55-80 y and women 60-80 y without known ASCVD at baseline examination	Consecutive patients without pre-existing ASCVD who underwent CAC scoring	Men and women, free of ASCVD, aged 45-84 y, including 4 racial/ethnic groups from 6 US communities
Major exclusion criteria	Insulin-dependent diabetes, triglycerides > 500 mg/dL, LDL > 175 mg/dL (men), LDL < 90 mg/dL, weight > 136 kg, expected survival < 5 y, therapy with estrogens or glucocorticoids, refusal to discontinue lipid-lowering drugs, vitamin C or vitamin E, uncontrolled hypertension	Obstructive CAD, no CAD, statins, or aspirin use before CCTA, history of revascularization	Previous ASCVD	Foreign military members, < 12 mo in the military health care system before their initial CAC scan, no follow-up, no prescriptions filled, previous ASCVD (CAD, MI, stroke, or cerebral revascularization, peripheral vascular disease) or malignancy	Previous ASCVD
Lipid-lowering therapy definition	Atorvastatin 20 mg (100%)	Statin therapy, dose not specified	Lipid-lowering therapy, type and dose not specified	Statin therapy (atorvastatin 20 mg, 15.3%; rosuvastatin 10 mg, 0.4%; lovastatin 20 mg, 0.3% pravastatin 20 mg, 2.5%; simvastatin 20 mg, 81.4%)	Lipid-lowering therapy, type and dose not specified
Lipid-lowering therapy definition relative to CAC assessment	Following CAC assessment	Following CAC assessment	Prior to CAC assessment	Before or within 5-y from CAC assessment	Prior to CAC assessment
ASCVD definition	Coronary death, nonfatal MI, coronary revascularization, nonhemorrhagic stroke, or peripheral vascular surgery	Mortality and late coronary revascularization (> 90 d after CCTA)	Spontaneous MI, UA, coronary revascularization, stroke, or cardiovascular death	MI, stroke, or cardiovascular death	MI, stroke, resuscitated cardiac arrest or cardiovascular death

ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; IQR, interquartile range; LDL, low-density lipoprotein; MI, myocardial infarction; RCT, randomized controlled trial; UA, unstable angina.

estimates of the outcomes were calculated as the weighted mean difference using a random effects model and are presented with 95% confidence intervals (95%CI). Subgroup analysis was performed including only RCTs and studies with multivariate adjustment. Heterogeneity across studies was assessed using Cochrane Q statistics and I^2 values. I^2 values of less than 25% indicate low heterogeneity, 25% to 50% moderate heterogeneity, and greater than 50% high heterogeneity. Statistical significance was set at $P < .05$ (2-sided). Statistical analyses were conducted with RevMan 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

RESULTS

A search of electronic databases, from inception March 1, 2020, identified a total of 276 records. Of these, a total of 5 studies fulfilled the inclusion criteria, for an overall population of 35 640 patients[4,9,13–15,17] (outcome data available for 97.4% of the study population). The consort diagram is shown in figure 1. The PRISMA checklist is provided in the supplementary data. The bias assessment for each RCT is shown in table 1 of the supplementary data.

A summary of included studies is available in table 1 and detailed baseline characteristics are reported in table 2. Of the included studies, 1 was an RCT, 2 were prospective cohort studies, and 2 were retrospective studies. Publication year ranged from 2015 to 2018 and study sample size from 1055 to 13 644 patients, with an overall female prevalence of 38.1%. Study follow-up ranged between 2.3 and 11.1 years. Median age ranged from 49.6 to 68.9 years and median low-density lipoprotein cholesterol ranged between 114.2 and 146.4 mg/dL. Patients on lipid-lowering therapy accounted for between 23.7% and 50.5% (overall 34.9% of the study population). Two studies included patients with CAC >

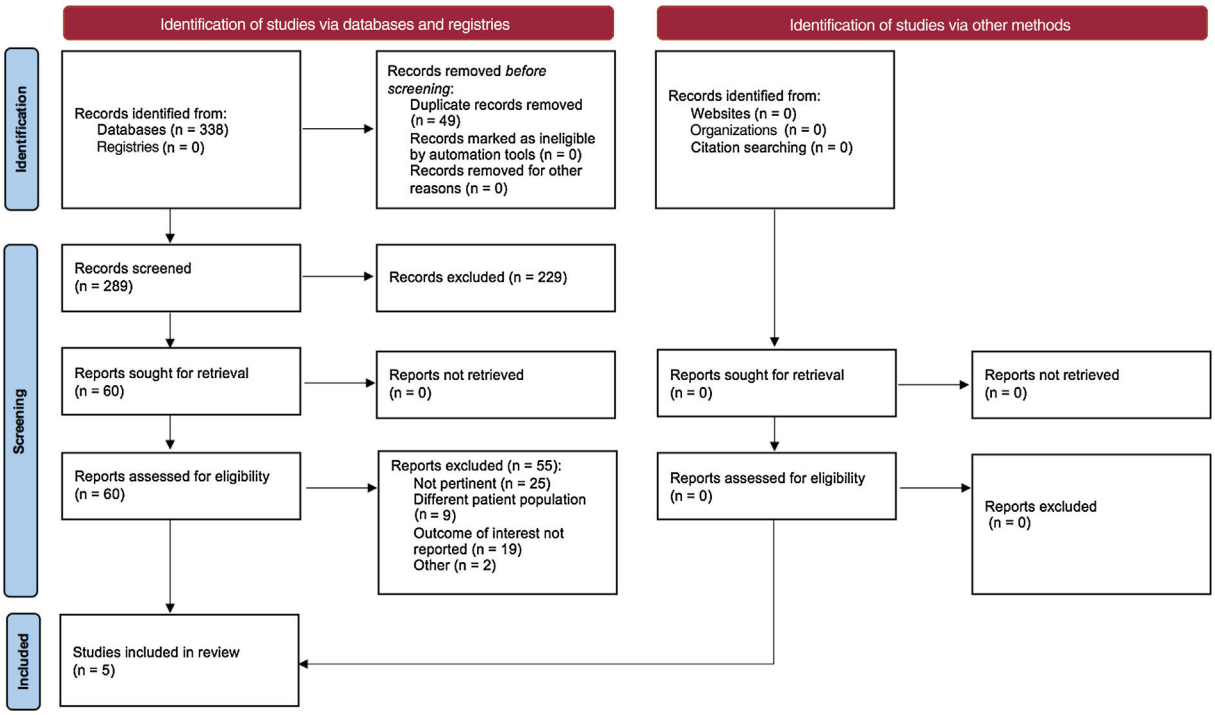

Figure 1. PRISMA 2020 flow diagram for new systematic reviews including searches of databases, registries, and other sources.

0 exclusively. Overall, 14 612 (42.1%) patients had CAC 0, 12 166 (35.1%) patients had CAC 1-100 and 7909 (22.8%) patients had CAC > 100.

Impact of lipid-lowering therapies on ASCVD according to coronary artery calcium

Forest plots for the risk of ASCVD occurrence with vs without lipid-lowering therapy in the overall population and stratified by CAC categories are reported in figure 2. In the overall primary prevention population, numerically reduced ASCVD events were observed among patients on lipid-lowering therapy (hazard ratio, 0.84; 95%CI, 0.68-1.04, $I^2 = 54\%$), a difference that became statistically significant when only adjusted data were pooled (hazard ratio, 0.59; 95%CI, 0.38-0.91, $I^2 = 85\%$), figure 3). A significant interaction was observed among CAC subgroups ($P = .004$, figure 2), so that lipid-lowering therapy was associated with reduced occurrence of ASCVD in patients with CAC > 100 (odds ratio [OR], 0.69; 95%CI, 0.53-0.91, $I^2 = 48\%$), but not in patients with CAC 1-100 or CAC 0. Results were consistent when adjusted data-only were pooled (figure 3). An assessment of the plausibility of the observed subgroup differences[18] is detailed in the supplementary data.

Atherosclerotic cardiovascular disease risk stratification by coronary artery calcium score

ASCVD incidence rates for each study are reported in table 2 of the supplementary data. A graded increase in ASCVD occurrence was observed for increasing CAC strata (table 3). Compared with patients with CAC 1-100, patients with CAC 0 were at lower (OR, 0.56; 95%CI, 0.44-0.67), and patients with CAC > 100 were at higher (OR, 2.45; 95%CI, 2.15-2.75) risk of ASCVD. The results were consistent both in patients with and without lipid-lowering therapy (table 3) and remained similar in a sensitivity analysis limited to patients on lipid-lowering therapy prior to CAC assessment (table 3 of the supplementary data).

DISCUSSION

The main findings of this systematic review and meta-analysis assessing the interaction between lipid-lowering therapy and CAC score in relation to ASCVD occurrence among asymptomatic individuals are as follows:

- A CAC score > 100 identified patients most likely to benefit from lipid-lowering therapy, while no such association was observed among patients with CAC ≤ 100 or no detectable CAC.
- The CAC score effectively stratified ASCVD occurrence, with preserved risk stratification ability among patients on lipid-lowering therapy.

No prospective evidence is currently available to support the impact of a CAC stratification-based strategy to guide lipid-lowering therapy on ASCVD outcomes among asymptomatic individuals. The single RCT available to date randomizing patients to lipid-lowering therapy vs placebo following CAC score assessment showed a nonsignificant trend of ASCVD event reduction, reaching significance only among patients with CAC > 400 (post hoc analysis).[17] However, the study was limited by its small sample size and low event rate, along with high crossover and dropout rates.

On these bases, recommendations by the European Society of Cardiology regarding CAC use to drive lipid-lowering therapy remain weak and a statement was made on the need to further investigate the incremental value of reclassifying total cardiovascular risk and defining eligibility for lipid-lowering therapy based on CAC score.[11]

Although similar statements have been issued for years, RCTs of CAC-guided prevention powered for hard endpoints have not been

Table 2
Baseline characteristics of the study populations overall and stratified by lipid-lowering therapy status

Study Name First author, publication year	The St. Francis Heart Study Waheed et al.,[13] 2016			Korean registry Hwang et al.,[14] 2015			The BioImage Study Mortensen et al.,[4] 2016			Walter Reed Army Medical Center study Mitchell et al.,[15] 2018			Multi-Ethnic Study of Atherosclerosis Budoff et al.,[9] 2018		
	Overall (N = 990)	L-L drugs (n = 481)	Non-L-L drugs (n = 509)	Overall (N = 8372)	L-L drugs (n = 1983)	Non-L-L drugs (n = 6389)	Overall (N = 5805)	L-L drugs (n = 1991)	Non-L-L drugs (n = 3814)	Overall (N = 13644)	L-L drugs (n = 6886)	Non-L-L drugs (n = 6758)	Overall (N = 6783)	L-L drugs (n = 1101)	Non-L-L drugs (n = 5657)
Age, y	58.9	60.0	58.9	61.4 ± 10.9	62.6 ± 10.3	61.0 ± 11.1	68.9 ± 6.0	70.1	68.6 ± 6.0	49.6	51.1 ± 8.9	48.1 ± 7.6	62.2	-	-
Female sex	26.2	26.4	26.1	29.7	34.1	28.3	56	39.1	65.0	29.4	24.9	34	52.4	-	-
Hyperlipidemia	-	-	-	-	-	-	-	-	-	49.5	75.0	23.5	-	-	-
Lipid profile															
Total cholesterol, mg/dL	225.5	224.3 ± 35	226.6 ± 34	194.2 (41.3)	207.5 (45.0)	189.9 (39.1)	202.5 (38.6)	-	-	-	-	-	-	-	-
Triglyceride, mg/dL	143.4	137.1 ± 83	149.3 ± 97	137.1 (87.2)	133.5 (68.5)	148.0 (88.5)	-	-	-	-	-	-	-	-	-
LDL mg/dL	146.4	146.1 ± 30	146.7 ± 30	116.6 (30.3)	126.0 (32.6)	113.6 (23.9)	114.2 (33.2)	-	-	-	-	-	140.3	-	-
HDL mg/dL	50.3	50.7 ± 15	50 ± 14	50.4 (12.5)	50.5 (12.4)	50.4 (12.5)	55.7 (15.3)	-	-	-	-		51.2	-	-
Hypertension	31.6	30.6	32.6	31.3	47.0	26.4	62	70.3	58.0	34.0	45.1	22.8	-	-	-
Diabetes	7.1	7.3	7.1	15.2	24.6	12.3	15	24.8	10.0	6.8	10.0	3.6	-	-	-
Current smoker/ tobacco use	67.2	67.6	66.8	-	-	-	9	9	9.0	7.1	8.9	5.3	13.1	-	-
CAC score															
CAC score	374.4	379 [148-636]	370 [183-671]	94.1 ± 221.5	90.4 ± 218.0	106.1 ± 232.5	-	-	-	-	-	-	-	-	-
0	-	-	-	-	-	-	1852 (32.0)	495 (24.9)	1352 (35.4)	9360 (68.6)	3742 (54.3)	4855 (83.1)	3400 (50.2)	361 (32.8)	3029 (53.5)
1-100	95 (9.6)	44 (9.1)	51 (10.2)	5755 (76.9)	1265 (74.8)	4490 (77.5)	1675 (29.0)	582 (29.2)	1089 (28.6)	2877 (21.1)	1081 (28.1)	945 (14.0)	1787 (26.3)	348 (31.6)	1437 (25.4)
> 100	895 (90.4)	437 (90.0)	458 (90.3)	1733 (23.1)	426 (25.2)	1307 (22.5)	2278 (39.0)	914 (45.9)	1367 (35.8)	1407 (10.3)	1211 (17.6)	196 (2.9)	1596 (23.5)	390 (35.6)	1201 (20.1)
Therapy															
Lipid-lowering therapy	48.6	100	0	23.7	100	0	34	100	0	50.5	100	0	-	100	0
Aspirin	100	100	100	44.8	66.1	35.1	-	-	-	16.0	24.8	7	-	-	-
ACEI/ARB	-	-	-	17.1	28.1	13.7	-	-	-	15.4	22.9	7.7	-	-	-
Beta-blocker	-	-	-	10	16.1	8.1	-	-	-	6.6	9.3	3.8	-	-	-
CCB	-	-	-	9.3	16.1	7.2	-	-	-	4.6	6.3	2.8	-	-	-

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CAC, coronary artery calcium; CCB, calcium channel blockers; HDL, high-density lipoprotein; L-L, lipid-lowering; LDL, low-density lipoprotein. Values are expressed as rates (%) or mean ± standard deviation.

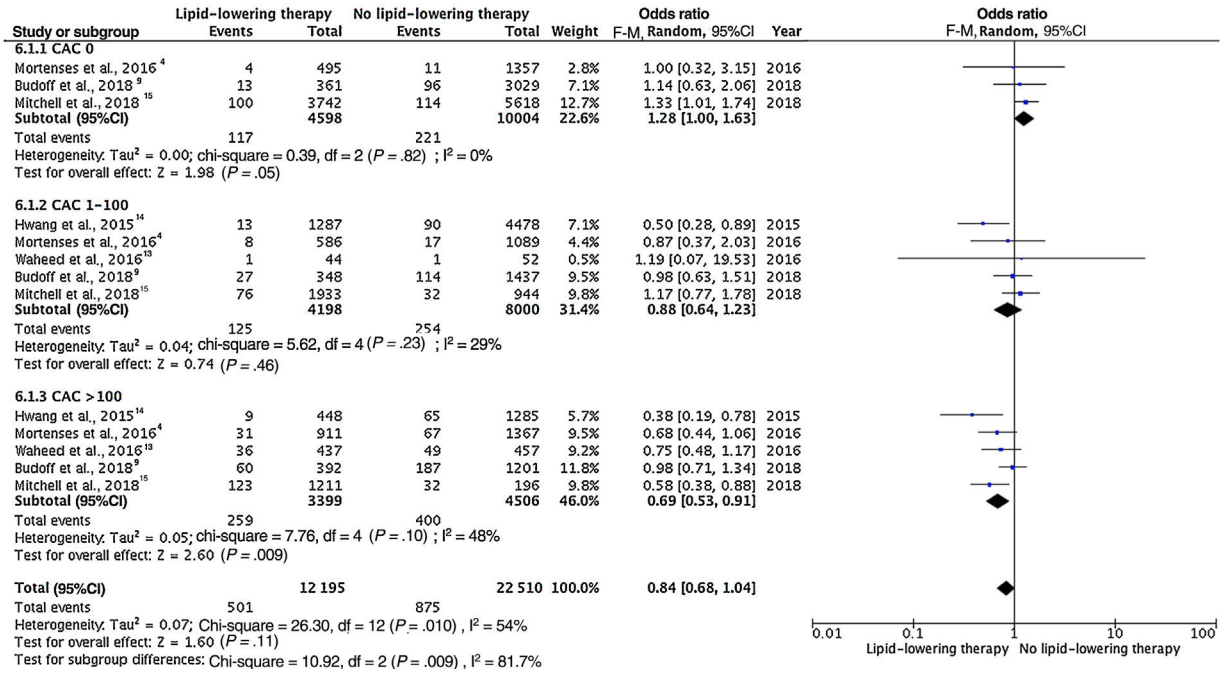

Figure 2. Summary forest plots for the observed risk of atherosclerotic cardiovascular disease occurrence with vs without lipid-lowering therapy stratified by CAC categories. 95%CI, 95% confidence interval; CAC, coronary artery calcium; df, degrees of freedom; F, females; M, males.

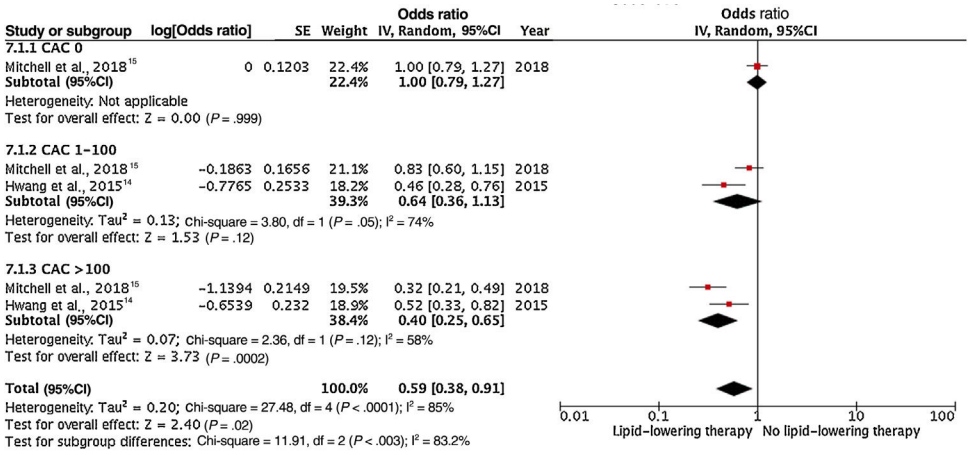

Figure 3. Summary forest plots for the adjusted risk of atherosclerotic cardiovascular disease occurrence with vs without lipid-lowering therapy stratified by CAC categories. 95%CI, 95% confidence interval; CAC, coronary artery calcium; df, degrees of freedom; SE, standard error.

carried out, likely due to anticipated trial size, costs, and ethical concerns about withdrawing lipid-lowering therapy among patients with high CAC score.[19]

We therefore performed a systematic review and meta-analysis of CAC studies reporting CAC-stratified ASCVD outcomes in patients with and without lipid-lowering therapy to gain insight on this issue.

Our study results are consistent with previous CAC literature showing a graded increase in ASCVD events across growing CAC strata and further expands this concept by suggesting an interaction of CAC with the benefit of lipid-lowering therapy.

Indeed, CAC score identifies the presence and extent of subclinical coronary atherosclerotic disease (which is the substratum for ASCVD events) rather than its probability, as is the case for clinical risk scores. The clinical implications of this concept are supported by a wealth of evidence highlighting a disconnect between the clinical risk profile and the atherosclerotic burden of asymptomatic individuals, with significant risk reclassification abilities of CAC over traditional risk estimators.

Individuals with no detectable coronary artery calcium score

Among individuals with no detectable CAC, representing 41% to 57% of individuals eligible for lipid-lowering therapy, the 10-year actual ASCVD event rate was much lower than predicted, ranging between 1.5% and 4.9%.[20] Similarly, among individuals with $\geq$ 3 risk factors, 35% had no detectable CAC and a 7-year ASCVD event rate of around 3/1000 person-years.[21]

Our results, not accounting for the clinical risk profile, consistently suggest that lipid-lowering in this population therapy may not be beneficial. Caution is warranted in translating this

Table 3
Odds ratios (95% confidence intervals) for ASCVD occurrence categorized by CAC strata

	ASCVD OR (95%CI) for increasing CAC strata					
CAC strata	Hwang et al.,[14] 2015	Waheed et al.,[13] 2016	Mortenses et al.,[4] 2016	Mitchell et al.,[15] 2018	Budoff et al.,[9] 2018	POOLED
Overall population (N = 35 640)						
CAC none	-	-	0.54 [0.28-1.03]	0.60 [0.46-0.78]	0.37 [0.29-0.49]	0.56 [0.44-0.67]
CAC 0-100	REF	REF	REF	REF	REF	REF
CAC >100	2.45 [1.81-3.32]	20.39 [1.25-331.18]	2.97 [1.90-4.62]	3.17 [2.46-4.09]	2.13 [1.72-2.63]	2.45 [2.15-2.75]
Lipid-lowering therapies (n = 12 425)						
CAC none	-	-	0.59 [0.18-1.95]	0.67 [0.50-0.91]	0.44 [0.23-0.88]	0.57 [0.41-0.73]
CAC 0-100	REF	REF	REF	REF	REF	REF
CAC >100	2.01 [0.85-4.73]	8.09 [0.49-134.09]	2.56 [1.16-5.59]	2.76 [1.71-4.46]	2.15 [1.33-3.47]	2.36 [1.83-2.88]
No lipid-lowering therapy (n = 23 127)						
CAC none	-	-	0.53 [0.36-0.78]	0.59 [0.40-0.88]	0.38 [0.29-0.50]	0.48 [0.34-0.61]
CAC 0-100	REF	REF	REF	REF	REF	REF
CAC >100	2.60 [1.88-3.60]	12.72 [0.77-209.35]	3.25 [1.94-5.45]	5.56 [3.31-9.33]	2.14 [1.67-2.74]	3.01 [2.05-3.97]

95%CI, 95% confidence interval; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; OR, odds ratio; REF, reference.

finding to specific subsets, including smokers, individuals with severe familial hypercholesterolemia, those with a strong family history of ASCVD and those with a 10-year ASCVD estimated risk $\geq$ 20%, who demonstrated substantial 10-year actual ASCVD risk despite no detectable CAC.[11,20,22,23]

Regarding young individuals (< 45 years), no detectable CAC is highly prevalent (consistently more than 90% across the literature); accordingly its role as a screening strategy in this subset has been questioned.[7] When available, a CAC 0 entails a very benign prognosis with an estimated 10-year mortality of 0.4%.[21] Nevertheless, considering the very long-term expected lifespan of this population and that ASCVD event risk depends on cumulative prior exposure to low-density lipoprotein cholesterol,[24] it remains to be established whether early initiation of lipid-lowering therapy may translate into a very long-term clinical benefit in young hypercholesterolemic individuals.

Individuals with coronary artery calcium score 1-100

We found no significant treatment benefit among patients with CAC 1-100, including in the analysis adjusted for clinical risk factors (aOR, 0.64; 95%CI, 0.36-1.13; $P = .12$, $I^2 = 74\%$). However, the numerical trend toward a benefit of lipid-lowering therapy (against a background of previous studies showing that 10% ASCVD actual risk in patients with CAC 1-100 varies widely between 3.8% and 14.3% according to sex, age and ethnicity[9]) suggests that, in this CAC range, ASCVD clinical risk estimation is warranted to indicate lipid-lowering therapy. This concept has been empirically embraced by the American College of Cardiology/American Heart Association guidelines, which favor lipid-lowering therapy initiation only in adults > 55 years of age, when CAC scores of 1 to 99 are found.[23]

Individuals with coronary artery calcium score > 100

A CAC score > 100 identifies individuals at the higher end of the cardiovascular risk spectrum despite a low burden of traditional risk factors. Specifically, it translates into an 10-year actual risk of ASCVD > 7.5%, regardless of clinically estimated 10-year ASCVD risk.[9] Young individuals (< 45 years) with elevated CAC burden had a much higher mortality risk than elderly individuals (> 75 years) with a CAC score of zero.[25] Similarly, among individuals with no risk factors, 12% had CAC > 100 and experienced an ASCVD rate of 9.2 per 1000 person-years.[21]

Our study findings extend these observations further by showing a substantial benefit of lipid-lowering therapy in patients with CAC > 100. A Report and Systematic Review for the US Preventive Services Task Force assessing the benefits and harms of CAC score suggested that the score may inappropriately reclassify individuals not having ASCVD into higher-risk categories, thus prompting unneeded treatment.[26] Our analysis does not concur with this concept, since a consistent treatment benefit was observed among these patients and in the analysis adjusted by clinical risk factors.

Of note, the utility of a CAC-guided over clinically-guided treatment strategy in primary prevention seems to apply also to aspirin, for which recent studies adopting meta-analysis data on ASCVD relative risk reduction and bleeding risk seem to suggest that, while aspirin allocation guided by the pooled cohort equations may translate in net harm across all ASCVD risk classes, a strategy complemented by CAC evaluation may identify subsets of patients with a risk trade-off favoring aspirin treatment (ie, patients with CAC > 100 in the setting of low bleeding risk and more than low ASCVD risk).[27,28]

Finally, CAC-guided compared with clinical risk-guided lipid-lowering therapy appears to have a cost-effective profile.[29] The single RCT comparing a CAC-based with a risk factor-based strategy consistently showed improved cardiovascular risk factor control without increased downstream resource use by more appropriate resource allocation to at risk patients.[30]

To conclude, we observed that the CAC stratification ability was preserved among patients on lipid-lowering therapies, both among those already on treatment at CAC assessment and among those starting treatment thereafter.

Some authors have raised concerns that the plaque-stabilizing effect of statins, which is reflected by an increase in CAC score, might affect the risk stratification ability of CAC score assessment among patients on lipid-lowering therapies.[30,31] As a consequence, European Society of Cardiology guidelines warrant caution when interpreting CAC score values among patients on lipid-lowering therapy.[11] Our finding is reassuring, by showing that the prognostic implications of CAC score remain valid among patients already on lipid-lowering treatment. This observation is consistent with a recent analysis from the CAC consortium, which showed that CAC retains robust risk prediction in statin users, though with a slightly weaker power compared with a statin nonuser, likely

explained by the changing relationship of CAC density among statin users.[32]

Limitations

The findings of this meta-analysis should be interpreted in the context of some limitations. First, this is a study-level meta-analysis, and the findings provide mean study-level effects. Second, the rate of crossovers and the variable exposures to lipid-lowering drugs in the studies included in the analysis may complicate the interpretation of the results. Third, we report both unadjusted and adjusted pooled effect estimates, as the latter were available for only 2 studies (and 1 study for the CAC 0 group). Moreover, despite adjustment, this analysis cannot account for unmeasured covariates and do not completely eliminate confounding bias. However, the consistency between the results of the analyses support the validity of our observations. Fourth, ASCVD definition varied among studies. Even though the effect size of benefit of lipid-lowering therapy was similar among individual cardiovascular outcomes (with slight attenuation for stroke and cardiovascular death, compared with myocardial infarction and coronary revascularization)[1], the reported relative effect estimates should be interpreted in this context.

CONCLUSIONS

Among individuals without a previous ASCVD, there is an association between increasing CAC strata and the expected benefit from lipid-lowering therapy. A CAC score > 100 identifies individuals most likely to benefit from lipid-lowering therapy, while undetectable CAC suggests no treatment benefit. These findings may stimulate discussion toward a paradigm shift in risk assessment with a focus on the detection of subclinical atherosclerosis rather than the probability of disease presence.

WHAT IS KNOWN ABOUT THE TOPIC?

- CAC score improves the accuracy of risk stratification for ASCVD events compared with traditional cardiovascular risk factors.

WHAT DOES THIS STUDY ADD?

- In the setting of primary prevention, a CAC score > 100 identifies persons most likely to benefit from lipid-lowering therapy, while undetectable CAC suggests no treatment benefit. A paradigm shift in risk assessment with a focus on subclinical atherosclerosis detection rather than disease probability requires exploration.

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AUTHORS' CONTRIBUTIONS

G. Gallone, E. Elia, F. Bruno, L. Baldetti, F. D'Ascenzo, A. Esposito, A. Depaoli, P. Fonio, and G.M. De Ferrari were involved in the conception and design of the study. G. Gallone, E. Elia, F. Angelini, L. Franchin, P.P. Bocchino, F. Piroli, U. Annone, A. Serafini, A. Montabone, M. Beratina, O. De Filippo, A. Palmisano, and G. Marengo performed the analysis and drafted the manuscript. All the authors contributed to the interpretation of data, critically revised the manuscript, approved it in its current form, and are accountable for all aspects of the work.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

APPENDIX. SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.1016/j.rec.2021.08.002

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