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NEW RESEARCH PAPER

CAC for Risk Stratification Among Individuals With Hypertriglyceridemia Free of Clinical Atherosclerotic Cardiovascular Disease

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ABSTRACT

OBJECTIVES In this study, we sought to evaluate whether the coronary artery calcium (CAC) score can enhance current paradigms for risk stratification among individuals with hypertriglyceridemia in primary prevention. The eligibility criteria for icosapent ethyl (IPE) were used as case example.

BACKGROUND Recent trials of atherosclerotic cardiovascular disease (ASCVD) risk-reduction therapies for individuals with hypertriglyceridemia without clinical ASCVD restricted enrollment to participants with diabetes or various other risk factors. These criteria were mirrored in the Food and Drug Administration product label for IPE.

METHODS We pooled 2,345 participants with triglycerides 150 to <500 mg/dL (or >178-<500 mg/dL if not on a statin) and without clinical ASCVD from MESA, CARDIA, the Dallas Heart Study, and the Heinz Nixdorf Recall study. We evaluated the incidence of ASCVD events overall, by IPE eligibility (as defined in the product label), and further stratified by CAC scores (0, >0-100, >100). The number needed to treat for 5 years (NNT_5) to prevent 1 event was estimated among IPE-eligible participants, assuming a 21.8% relative risk reduction with IPE. In exploratory analyses, the NNT_5 was also estimated among noneligible participants.

RESULTS There was marked heterogeneity in CAC burden overall (45% CAC 0; 24% CAC >100) and across IPE eligibility strata. Overall, 17% of participants were eligible for IPE and 11.9% had ASCVD events within 5 years. Among participants eligible for IPE, 38% had CAC >100, and their event rates were markedly higher (15.9% vs 7.2%) and the NNT_5 2.2-fold lower (29 vs 64) than those of the 25% eligible participants with CAC 0. Among the 83% participants not eligible for IPE, 20% had CAC >100, their 5-year incidence of ASCVD (13.9%) was higher than the overall incidence among IPE-eligible participants.

CONCLUSIONS CAC can improve current risk stratification and therapy allocation paradigms among individuals with hypertriglyceridemia without clinical ASCVD. Future trials of risk-reduction therapies in hypertriglyceridemia could use CAC >100 to enroll a high-risk study sample, with implications for a larger target population.
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ABBREVIATIONS AND ACRONYMS

ASCVD = atherosclerotic cardiovascular disease

CAC = coronary artery calcium

CARDIA = Coronary Artery Risk Development in Young Adults

DHS = Dallas Heart Study

FDA = Food and Drug Administration

GLP-1RA = glucagon-like peptide 1 receptor agonist

HNR = Heinz Nixdorf Recall study

hsCRP = high-sensitivity C-reactive protein

MESA = Multi-Ethnic Study of Atherosclerosis

NNT_5 = number needed to treat for 5 years

REDUCE-IT = Reduction of Cardiovascular Events With Icosapent Ethyl—Intervention Trial

RRR = relative risk reduction

STRENGTH = Long-Term Outcomes Study to Assess Statin Residual Risk With Epanova in High Cardiovascular Risk Patients With Hypertriglyceridemia

There is renewed interest in the role of triglycerides and triglyceride-rich particles as independent risk factors for atherosclerotic cardiovascular disease (ASCVD) (1,2). In the United States, 1 out of 4 adults has hypertriglyceridemia (3), and the identification of therapies that can further reduce ASCVD risk among these individuals beyond statins is an active area of research. This includes publication in the past 2 years of the landmark trials of omega-3 fatty acids REDUCE-IT (Reduction of Cardiovascular Events With Icosapent Ethyl—Intervention Trial) and STRENGTH (Long-Term Outcomes Study to Assess Statin Residual Risk With Epanova in High Cardiovascular Risk Patients With Hypertriglyceridemia) (4,5).

In both of those trials, identification of high risk among individuals with hypertriglyceridemia without clinical ASCVD was based on the presence of diabetes or high estimated risk plus additional risk factors or markers (4,5). Specifically, to be enrolled in the primary prevention component of REDUCE-IT, besides triglyceride levels of 150 to 499 mg/dL, participants had to have diabetes mellitus and 2 or more additional risk factors (4). These inclusion criteria were subsequently mirrored by the Food and Drug Administration (FDA) label update for icosapent ethyl (IPE), which in December 2019 included an indication for cardiovascular risk reduction on top of statin therapy among individuals with hypertriglyceridemia and diabetes plus 2 or more risk factors (6).

The coronary artery calcium (CAC) score accurately stratifies risk within subgroups defined by most risk factors and markers used for enrollment in those studies, including age, diabetes, number of traditional risk factors, levels of high-sensitivity C-reactive protein (hsCRP), and the ankle-brachial index, among other (4,5,7-12). In addition, a high CAC score identifies high absolute risk among individuals with a low burden of traditional risk factors (8). CAC is a guideline-endorsed aid for the allocation of statins (13), can help personalize blood pressure-lowering targets and aspirin allocation (14-16), and, in patients with diabetes, augments risk factors and measures of end-organ damage in the identification of highest-risk candidates for ASCVD risk reduction with the use of glucagon-like peptide 1 receptor agonists (GLP-1RAs) (17,18).

An enhanced identification of high risk among individuals with hypertriglyceridemia can help inform the allocation of currently approved and potential future therapies for ASCVD risk reduction in this large population (6) and may have implications for the design of primary prevention trials in this space (19). The aim of the present study was to evaluate whether CAC can further improve current paradigms for risk stratification among individuals with hypertriglyceridemia without clinical ASCVD. For this purpose, we used the risk factor/marker enrollment criteria used in REDUCE-IT and the FDA product label for IPE eligibility as a case example (4,6).

METHODS

SETTING AND COHORTS. We pooled individual-level data from 4 U.S. and European prospective cohort studies: the Multi-Ethnic Study of Atherosclerosis (MESA) (20), Coronary Artery Risk Development in Young Adults (CARDIA) (21), and the Dallas Heart Study (DHS) (22) in the United States, and the Heinz Nixdorf Recall Study (HNR) in Germany (23). MESA is a community-based prospective cohort study of individuals free of clinical ASCVD at baseline, started in 2000 and including 6,814 participants aged 45 to 84 years from 6 U.S. sites (20). CARDIA is a prospective cohort study started in 1985 and including 5,115 young adults aged 18 to 30 years from 4 U.S. cities (21). DHS is a population- and probability-based

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prospective cohort study of 3,072 participants from Dallas County, Texas, started in 2000, with intentional oversampling of African Americans to constitute approximately 50% of the cohort. (22) HNR is a population-based prospective cohort study of 4,814 Caucasian participants, aged 45 to 75 years, from the metropolitan area of Ruhr, Germany (23). The study populations of DHS and HNR included a small proportion of participants with established ASCVD at enrollment (2.5% in DHS, 14% in HNR), all of whom were excluded from the present analysis.

In all 4 studies, participants provided written informed consent at study entry. The respective protocols were approved by the institutional review committees of each of the sites participating in each of the studies. Further details of these cohorts have been reported elsewhere (20-23).

STUDY DESIGN. For the present analysis, the pooled study baseline was defined at the time of the first CAC scanning in each cohort. This corresponded to visit 1 in MESA (years 2000-2002) (20), year 15 in CARDIA (years 2000-2001) (21), phase 1 in DHS (years 2000-2002) (22), and visit 1 in HNR (years 2000-2003) (23). We conducted a longitudinal analysis and used all follow-up data available for each participant from the pooled baseline onward.

STUDY POPULATION. Pharmacotherapies aimed at reducing ASCVD risk among individuals with hypertriglyceridemia would be expected to be used on top of statin therapy (6). Therefore, we included participants with either baseline triglyceride levels of 150 to <500 mg/dL on statin therapy, or >178 to <500 mg/dL if statin naïve. The 178 mg/dL cutoff point was defined based on the fact that in JUPITER (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin), 20 mg rosuvastatin once daily reduced triglyceride levels by 16% (150/0.84 = 178.5 mg/dL) (24). Individuals with prevalent ASCVD at baseline, those with missing baseline data for CAC, and those with missing follow-up information were excluded. Also, participants from HNR who had not fasted for at least 8 hours at baseline were excluded from the analyses.

The study population was evaluated overall, as well as stratified into 2 groups defined by the FDA label risk factor/marker criteria for IPE eligibility in primary prevention (6). Among individuals without established ASCVD or triglycerides ≥500 mg/dL, the FDA approved IPE "as an adjunct to maximally tolerated statin therapy to reduce the risk of myocardial infarction, stroke, coronary revascularization, and unstable angina requiring hospitalization in adult patients with triglyceride levels ≥150 mg/dL and diabetes mellitus and 2 or more additional risk factors for cardiovascular disease" (7). The specific risk factors/markers used in REDUCE-IT included age ≥55 years (men) or ≥65 years (women), hypertension, active smoker or quit within 3 months, high-density lipoprotein cholesterol ≤40 mg/dL (men) or ≤50 mg/dL (women), hsCRP >3 mg/L, creatinine clearance >30 to <60 mL/min, retinopathy, micro- or macroalbuminuria, and ankle-brachial index <0.9 without symptoms of claudication (4). Based on this, in our study, participants were considered to be "eligible" for IPE if they had diabetes and at least 2 of the risk factors/markers listed above at the time of the CAC scan. Retinopathy was not included in the definition, because this information was not available in most cohorts. The ankle-brachial index was available in participants from MESA and HNR, but not from CARDIA or DHS, and proteinuria was not evaluated in DHS.

Diabetes was defined as either self-reported, use of diabetes medications, or fasting plasma glucose levels ≥126 mg/dL (25). HbA_{1c} levels ≥6.5% also were used in HNR, where this measurement was available in the majority of participants at the time of CAC scanning (25,26). Hypertension was defined as blood pressure ≥130 mm Hg systolic or ≥80 mm Hg diastolic, or use of antihypertensive medications. Participants not meeting these criteria were considered to be "not eligible" for IPE therapy according to the FDA product label.

CAC SCORES. Baseline CAC scores were available for all participants included in this analysis. CAC was measured using noncontrast cardiac computed tomography, and scored with the use of the Agatston method. For the analyses, CAC was categorized as 0, >0 to 100, or >100.

STUDY OUTCOMES. Details on the event definitions and ascertainment methods used in each cohort have been reported previously and were similar across the studies (20-23). For the purposes of the present analysis, the outcome was defined to mimic as closely as possible the primary composite ASCVD end point used in REDUCE-IT (4) and included cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, and unstable angina. REDUCE-IT also included silent myocardial infarctions in the primary composite end point (4), but this information was not available in our study.

STATISTICAL ANALYSES. The baseline characteristics of study participants were described overall and by FDA label-based IPE eligibility. Categorical variables were presented as n (%), and continuous variables as mean ± SD or median (IQR) depending on whether or not they followed a normal distribution.

TABLE 1 Baseline Characteristics of the Study Participants

		Risk Factor/Marker Criteria for IPE		
	Overall	**Eligible (n = 406)**	**Not Eligible (n = 1,939)**	***P* Value**
Age, y	57 (48-66)	62 (54-69)	56 (47-65)	<0.001
Women	1,043 (44.5)	177 (43.6)	866 (44.7)	0.694
Race/ethnicity				<0.001
Non-Hispanic White[a]	1,315 (56.1)	177 (43.6)	1,138 (58.7)	
Asian (American)	198 (8.4)	35 (8.6)	163 (8.4)	
Black (American)	326 (13.9)	76 (18.7)	250 (12.9)	
Hispanic (American)	506 (21.6)	118 (29.1)	388 (20.0)	
Diabetes	450 (19.2)	406 (100.0)	44 (2.3)	<0.001
Fasting glucose, mg/dL	98 (88-111)	142 (126-183)	95 (87-104)	<0.001
Total cholesterol, mg/dL	214 ± 43	208 ± 45	215 ± 42	<0.001
LDL-C, mg/dL	125 ± 40	120 ± 43	125 ± 39	0.023
HDL-C, mg/dL	43 ± 11	41 ± 9	43 ± 11	<0.001
Triglycerides, mg/dL	221 (195-269)	227 (196-275)	220 (195-268)	0.136
Statin use	389 (19.2)	103 (27.5)	286 (17.3)	<0.001
Any lipid-lowering medication use	446 (19.2)	112 (28.1)	334 (17.4)	<0.001
Systolic blood pressure, mm Hg	129 ± 20	136 ± 22	128 ± 20	<0.001
Use of blood pressure-lowering medication	794 (34.0)	224 (55.5)	570 (29.5)	<0.001
Risk factor/marker criteria for IPE eligibility[b]				
Age ≥55 y (men) or ≥65 y (women)	1,020 (43.5)	249 (61.3)	771 (39.8)	<0.001
Hypertension	1,559 (66.5)	341 (84.0)	1,218 (62.8)	<0.001
Current smoker	464 (19.8)	79 (19.5)	385 (19.9)	0.855
HDL-C <40 mg/dL (men) or <50 mg/dL (women)	1,441 (61.5)	271 (66.8)	1,170 (60.3)	0.016
eGFR 30-60 mL/min/1.73 m^2	306 (13.1)	70 (17.2)	236 (12.2)	0.006
Proteinuria	304 (13.0)	131 (32.3)	173 (8.9)	<0.001
ABI <0.9	80 (3.4)	35 (8.6)	45 (2.3)	<0.001
hsCRP >3.0 mg/L	887 (37.8)	197 (48.5)	690 (35.6)	<0.001

Values are n (%), mean ± SD or median (IQR). Eligibility for IPE was defined based on the FDA product label for primary ASCVD prevention in adult patients with triglyceride levels 150 to <500 mg/dL: presence of diabetes mellitus and ≥2 additional risk factors for cardiovascular disease. Triglyceride levels of >178 mg/dL were required for study inclusion in participants who were not on a statin at baseline. Data on proteinuria and ABI was not available in the Dallas Heart Study (n = 225). [a]Includes White participants from CARDIA, non-Hispanic White participants from MESA and the Dallas Heart Study, and all participants from the Heinz Nixdorf Recall study (Germany). [b]In addition to diabetes, at least 2 required, as defined in REDUCE-IT.

ABI = ankle-brachial index; eGFR = estimated glomerular filtration rate; HDL-C = high-density lipoprotein cholesterol; hsCRP = high-sensitivity C-reactive protein; IPE = icosapent ethyl; LDL-C = low-density lipoprotein cholesterol.

We used Kaplan-Meier survival functions to generate 5- and 10-year cumulative incidence estimates of ASCVD events. These were computed overall, in the 2 study subpopulations (eligible and not eligible for IPE), and by baseline CAC score strata. Crude incidence rates of the study end point were also computed (expressed per 1,000 person-years) for each of those groups, using all follow-up data available for each participant. To avoid confounding by differential baseline statin use, 5-year ASCVD event rates were also estimated restricted to eligible and not eligible participants not treated with statins at baseline.

Cox proportional hazards regression models were used to evaluate the independent associations between CAC >0 to ≤100 and CAC >100 (compared with CAC 0) and incident ASCVD events, adjusting for demographics, traditional cardiovascular risk factors, statin use, and level of triglycerides. Adjustment in the IPE eligible group was a priori restricted to demographics given the expected low number of participants and events.

In REDUCE-IT, the incidence of the primary composite study end point at a median 4.9 years of follow-up was 22.0% in the control arm and 17.2% in the IPE arm. This defined a relative risk of 0.78 and a relative risk reduction (RRR) of 21.8% (4). No statistical evidence of effect modification was observed in the primary prevention subpopulation (4). Among study participants considered to be eligible for IPE, we used these estimates to compute the number needed to treat for 5 years (NNT_5) to prevent 1 ASCVD event, applying the RRR to the observed 5-year incidence of ASCVD events overall and by CAC strata. This defined the expected incidence at 5 years in each group. The absolute risk reduction was then

computed as the difference between the observed and the expected incidence, and the NNT_5 to prevent 1 ASCVD event was computed as the reciprocal.

We conducted 2 sensitivity analyses. Among IPE-eligible candidates not taking statins at baseline, the NNT_5 calculations were repeated assuming first a 25% RRR with statins (27), and then an additional 21.8% 5-year RRR in ASCVD events with IPE. In a second sensitivity analysis, we also modeled an RRR in ASCVD events of 10.4% with the use of GLP-1RAs in primary prevention patients with diabetes before modeling the effect of IPE (28).

Finally, in exploratory analyses we replicated all NNT_5 calculations described above among individuals considered to be not eligible for IPE, overall and by CAC strata. No statistically significant effect measure modification was detected in any of the subgroup analyses conducted in REDUCE-IT (4); therefore, the same 21.8% 5-year RRR in ASCVD events with IPE was used for this analysis.

A P value < 0.05 was considered to be statistically significant. All statistical analyses were performed with the use of Stata version 16.

RESULTS

STUDY PARTICIPANTS. The study population comprised 2,345 individuals with triglyceride levels from 150 to <500 mg/dL (or ≥178 mg/dL if statin naïve) and no previous history of ASCVD. This included 1,376 participants from MESA (63%), 286 from CARDIA (12%), 225 from DHS (10%), and 458 from HNR (20%). Median age was 57 years, and 45% of participants were women. According to the FDA label risk factor/marker criteria, 406 participants (17%) would be eligible for IPE therapy and 83% would not (**Table 1**). Individuals eligible for IPE were older, were more frequently Black and Hispanic, all had diabetes, and had a higher burden of cardiovascular risk factors than their noneligible counterparts. The prevalence of diabetes among noneligible individuals was 2%.

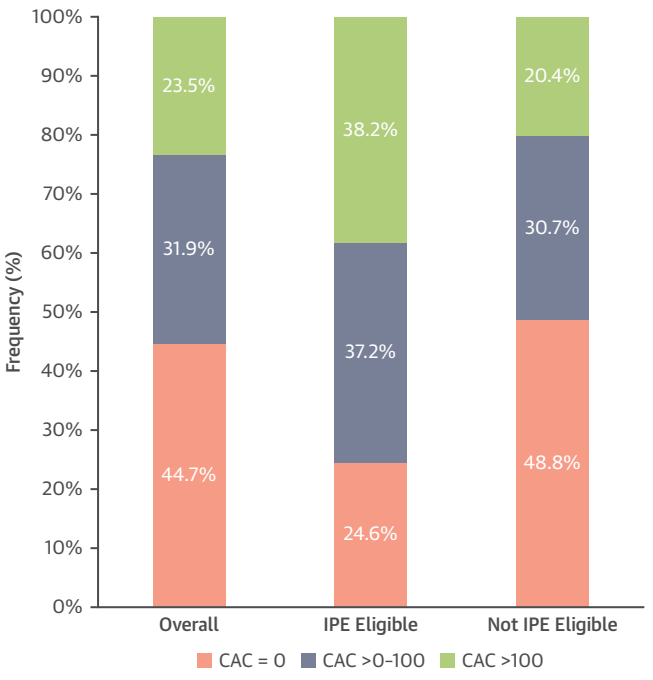
INTERPLAY BETWEEN IPE ELIGIBILITY AND CAC. In the overall study population, 45% had CAC 0, 32% had CAC >0 to ≤100, and 24% had CAC >100 (**Figure 1**). Among participants eligible for IPE, those with CAC >100 represented the largest stratum, and 25% had CAC 0. Among noneligible participants, 51% had CAC >0, including 20% who had CAC >100. The number of participants who were noneligible for IPE and had CAC >100 (n = 396; 17% of the study population) was similar to the number of eligible participants (n = 406; 17%).

INCIDENT ASCVD EVENTS. Over 5 years of follow-up, the incidence of ASCVD events was 6.2% overall, and there was a marked increase with higher CAC scores, the incidence being 7-fold higher in those with CAC >100 compared with those with CAC 0 (**Figure 2**). The incidence was higher among participants eligible vs not eligible for IPE (11.9% vs 5.1%), and in both groups the increase in events with higher CAC scores was evident, particularly among noneligible participants. The 5-year incidence in participants not eligible for IPE with CAC >100 was higher than the overall incidence in eligible participants (13.9% vs 11.9%).

Similar patterns were observed at 10 years of follow-up (Supplemental Figure 1). Consistent trends were also observed in terms of incident rates per 1,000 person-years (**Table 2**), with event rates among participants not eligible for IPE with CAC >100 being higher than the overall rates in eligible participants (26.6 vs 26.1 per 1,000 person-years). Analyses of 5-year incident events excluding baseline statin users from both study groups also yielded consistent findings (Supplemental Figure 2).

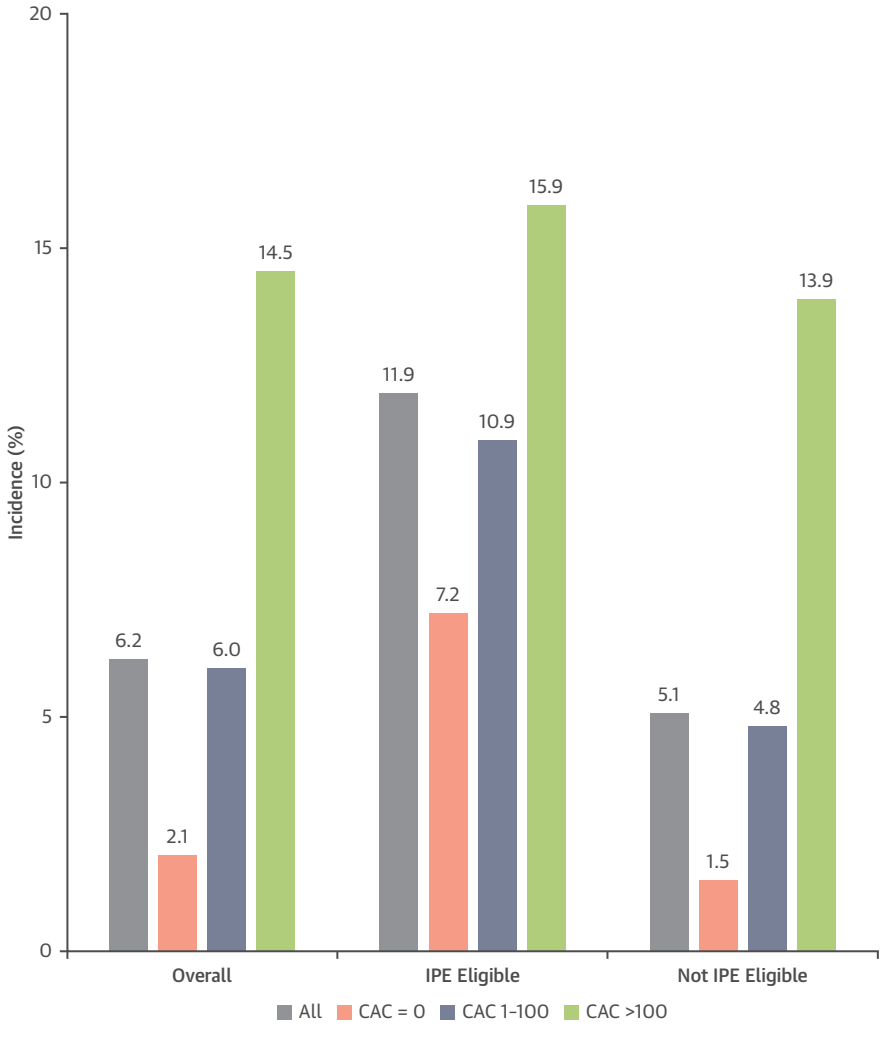
ASSOCIATIONS BETWEEN CAC AND ASCVD EVENTS. Among individuals eligible for IPE, the HR of ASCVD events for CAC >100 compared with CAC = 0 was 2.42 (95% CI: 1.34-4.39) in models

FIGURE 1 Distribution of CAC Scores Overall and by IPE Eligibility



Eligibility for IPE therapy was defined based on the risk factor/marker criteria in the Food and Drug Administration product label for primary prevention. CAC = coronary artery calcium; IPE = icosapent ethyl.

FIGURE 2 **Five-Year Cumulative Incidence of ASCVD Events by IPE Eligibility and CAC Burden**



Results are based on 5-year Kaplan-Meier cumulative incidence estimates. ASCVD = atherosclerotic cardiovascular disease; other abbreviations as in Figure 1.

adjusting for sociodemographic characteristics (Table 3). The associations were also strong among participants not eligible for IPE: The multivariable-adjusted HR for CAC >100 vs CAC = 0 was 2.86 (95% CI: 1.95-4.20).

NNT_5 TO PREVENT 1 ASCVD EVENT. CAC identified the subgroups in which the NNT_5 would be lowest (CAC >100) and highest (CAC 0), overall and among strata defined by IPE eligibility (Figure 3). In exploratory analyses, the NNT_5 to prevent 1 ASCVD event among participants not eligible for IPE with CAC >100 would be at least as low as among eligible participants (33 vs 39). The same was true in analyses that modeled the effect of background therapy with high-intensity statins among statin-naïve participants at baseline (44 vs 49) (Figure 4A). Additional consideration of background therapy with GLP-1RAs in the IPE-eligible population led to a slightly higher NNT_5 in this group (Figure 4B).

DISCUSSION

To the best of our knowledge, this is the largest cohort study to date of individuals with hypertriglyceridemia without clinical ASCVD, carefully phenotyped at baseline, including data on subclinical coronary atherosclerosis, and followed for a median

of >10 years. Combination of 4 landmark cohorts allowed for detailed clinically relevant analyses stratified by CAC burden and FDA criteria for IPE eligibility, which were used as case example, as well as sensitivity analyses that modeled the expected background effect of other guideline-recommended therapies. Inclusion of a multiethnic population, combination of American and European cohorts, and the large proportion of female participants contribute to the external validity of the study findings.

In this study, the proportion of individuals with hypertriglyceridemia who would meet the FDA risk factor/marker eligibility criteria for IPE was modest (17.3%). In this context, among the large group of individuals considered to be noneligible according to the product label, CAC >100 was relatively frequent (20.4%), and the ASCVD event rates in these individuals were higher than those of IPE candidates. Importantly, the absolute number of IPE noncandidates with CAC >100 was similar to that of participants eligible for IPE therapy (**Central Illustration**). These findings suggest that trial enrollment and pharmacotherapy allocation approaches based on the presence of diabetes and/or various additional risk factors may miss a large proportion of individuals with hypertriglyceridemia at high risk of ASCVD events, who could perhaps derive benefit from current/future therapies that further reduce ASCVD risk. Even if all of those individuals were treated with high-intensity statins, the 10-year event rates would likely remain high, leaving room for additional interventions.

It must be noted that in REDUCE-IT, diabetes was used as a study enrichment criterion (4), which is consistent with FDA recommendations for clinical trials, and increased the average risk of the primary prevention subpopulation (29). However, in subgroup analyses in REDUCE-IT, there was no effect measure modification by diabetes status ($P = 0.56$) (4). In JELIS (Japan EPA Lipid Intervention Study), which did not use diabetes as an inclusion criterion, eicosapentaenoic acid reduced ASCVD events compared with placebo (30). Diabetes was not a requirement in other recent and ongoing trials of IPE either (31,32). Our analyses could also be used to inform future primary prevention trials of IPE among individuals with hypertriglyceridemia, in which the enrichment criterion could be a high CAC score, regardless of diabetes status. Enrichment of study populations of trials through inclusion of participants with high CAC scores may improve trial efficiency (33).

In addition, among participants who met the FDA risk factor/marker criteria for IPE eligibility in primary prevention (6), we observed heterogeneity in CAC burden as well as in incident ASCVD events. This is likely the consequence of differences in lifetime exposure to risk factors and individual-level susceptibility to atherosclerosis (34). Particularly noteworthy was the 25% prevalence of CAC 0 among IPE eligible candidates despite the presence of hypertriglyceridemia, diabetes, and at least 2 additional risk factors. In this context, the NNT_5 analyses suggest that CAC could be a valuable aid in the identification of best candidates for IPE therapy (CAC >100) among those already considered eligible. And, perhaps more importantly, CAC may help to identify eligible individuals in whom IPE would yield the smallest absolute benefit (CAC 0). Indeed, more than twice as many eligible individuals with CAC 0 would

TABLE 2 Crude Incidence Rates per 1,000 Person-Years of All ASCVD Events

	No. of Events	Person-Years	Event Rates[a]
Overall			
All	371	29,783	12.5 (11.3-13.8)
CAC 0	75	14,804	5.1 (4.0-6.4)
CAC >0 to 100	123	9,099	13.5 (11.3-16.1)
CAC >100	173	5,880	29.4 (25.3-34.2)
Eligible for IPE			
All	114	4,361	26.1 (21.8-31.4)
CAC 0	17	1,211	14.0 (8.7-22.6)
CAC >0 to 100	40	1,630	24.5 (18.0-33.5)
CAC >100	57	1,520	37.5 (28.9-48.6)
Not eligible for IPE			
All	257	25,422	10.1 (8.9-11.4)
CAC 0	58	13,593	4.3 (3.3-5.5)
CAC >0 to 100	83	7,469	11.1 (9.0-13.8)
CAC >100	116	4,360	26.6 (22.2-31.9)

[a]Values are incidence rate per 1,000 person-y (95% CI).

ASCVD = atherosclerotic cardiovascular disease; other abbreviations as in Table 1.

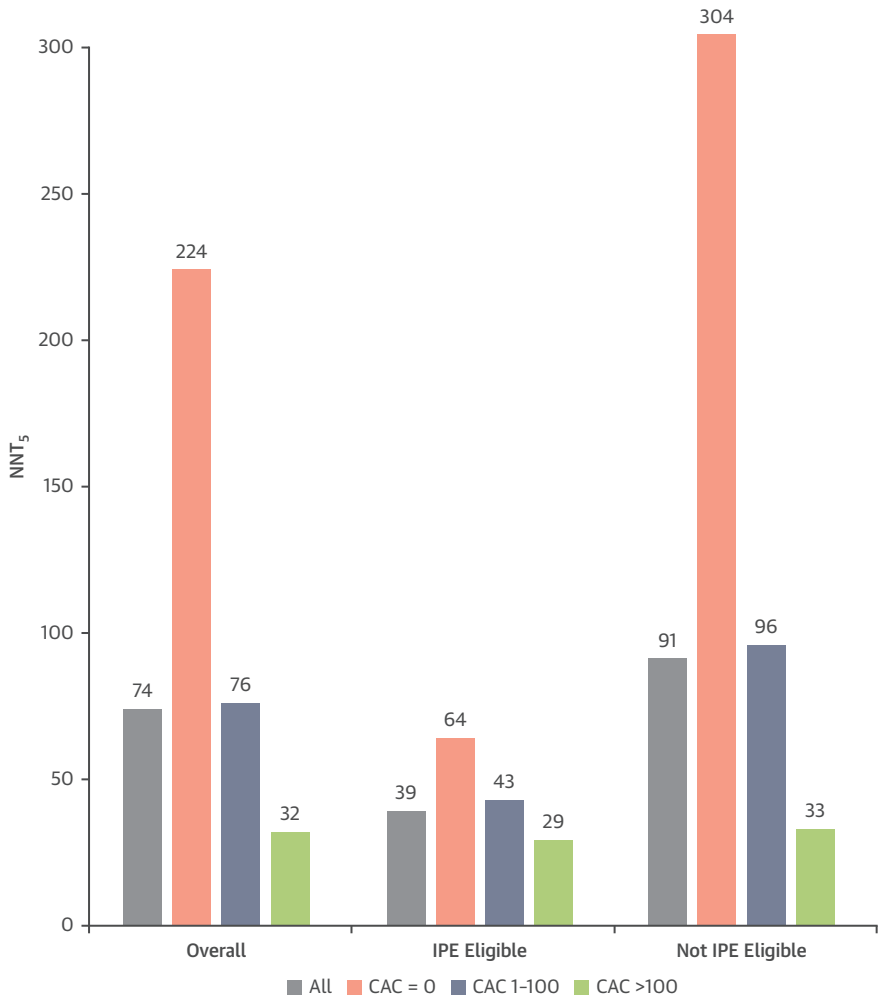
TABLE 3 Associations Between CAC and ASCVD Events

	Model 1	Model 2	Model 3
Eligible for IPE			
CAC 0	1.00 (Ref.)	1.00 (Ref.)	–[a]
CAC >0 to 100	1.73 (0.98-3.06)	1.75 (0.98-3.14)	–[a]
CAC >100	2.68 (1.56-4.61)	2.42 (1.34-4.39)	–[a]
Not eligible for IPE			
CAC 0	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
CAC >0 to 100	2.65 (1.90-3.71)	2.08 (1.47-2.94)	1.70 (1.16-2.49)
CAC >100	6.39 (4.65-8.77)	3.77 (2.64-5.40)	2.86 (1.95-4.20)

Values are HR (95% CI) from Cox proportional hazards regression model. Model 1 was unadjusted; model 2 adjusted for age, sex, and race/ethnicity; and model 3 further adjusted for systolic and diastolic blood pressure, hypertension medication use, tobacco use, LDL-C level, HDL-C level, statin use, diabetes, and level of triglycerides. [a]Model 3, which adjusted for 14 covariates, was not used in the subgroup of participants eligible for IPE because of the low absolute number of events.

Ref. = reference; other abbreviations as in Tables 1 and 2.

FIGURE 3 **NNT_5 With IPE to Prevent 1 ASCVD Event**



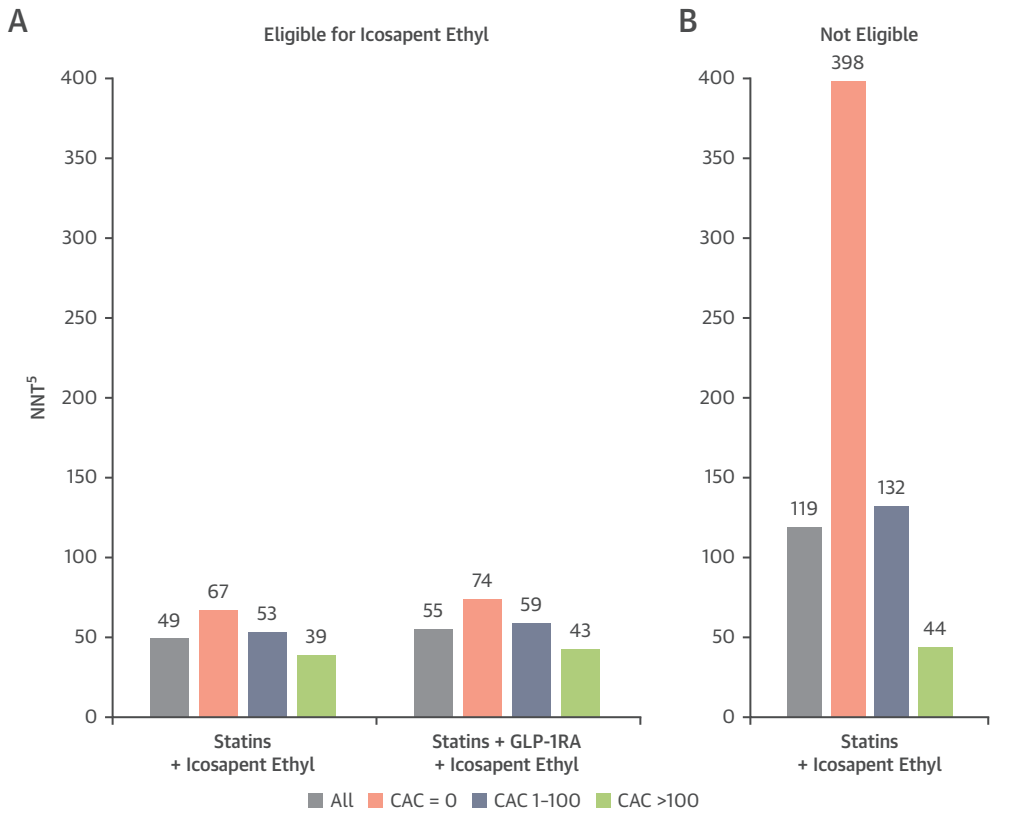
The NNT_5 was estimated assuming a 21.8% relative risk reduction with the use of IPE. NNT_5 = 5-year number needed to treat; other abbreviations as in Figures 1 and 2.

need to be treated compared with those with CAC >100 to prevent 1 event over 5 years.

Although it could be argued that the incidence of ASCVD events at 10 years was rather high among IPE-eligible participants with CAC 0 (10.8%), it is important to note that the study outcome included all ASCVD events, including angina and revascularization, rather than hard events, which is the end point typically used to define risk thresholds for preventive therapy allocation purposes in relevant guidelines (13). Also, baseline use of statins was relatively low in our population, so event rates would be expected to be significantly lower with background therapy with high-intensity statins in the CAC 0 stratum. In a context of finite health care resources, expanding populations with diabetes, and a high prevalence of hypertriglyceridemia in the general population (3), our results suggest that relatively low-cost CAC testing may help to further refine the allocation of IPE to patients most likely to derive a large benefit. There is a growing body of literature suggesting a potential use of CAC for the allocation of multiple preventive pharmacotherapies (14-18), and a recent scientific statement from the National Lipid Association explicitly endorsed the use of CAC for this purpose (35).

STUDY LIMITATIONS. Despite combining 4 cohorts, the number of individuals with CAC >400 and >1,000

FIGURE 4 Sensitivity Analyses: NNT_5 With IPE To Prevent 1 ASCVD Event, Modeling the Effect of Background Therapy With High-Intensity Statins and GLP-1RAs



(A) Eligible for IPE: assuming a 25% RRR with high-intensity statin therapy **(left)** and an additional 10.4% RRR with GLP-1RA **(right)**. All participants eligible for IPE had diabetes. **(B)** Not eligible for IPE: assuming a 25% RRR with high-intensity statin therapy. For both subgroups, analyses were restricted to participants not using statins at baseline. GLP-1RA = glucagon-like peptide 1 receptor agonist; RRR = relative risk reduction; other abbreviations as in Figures 1-3.

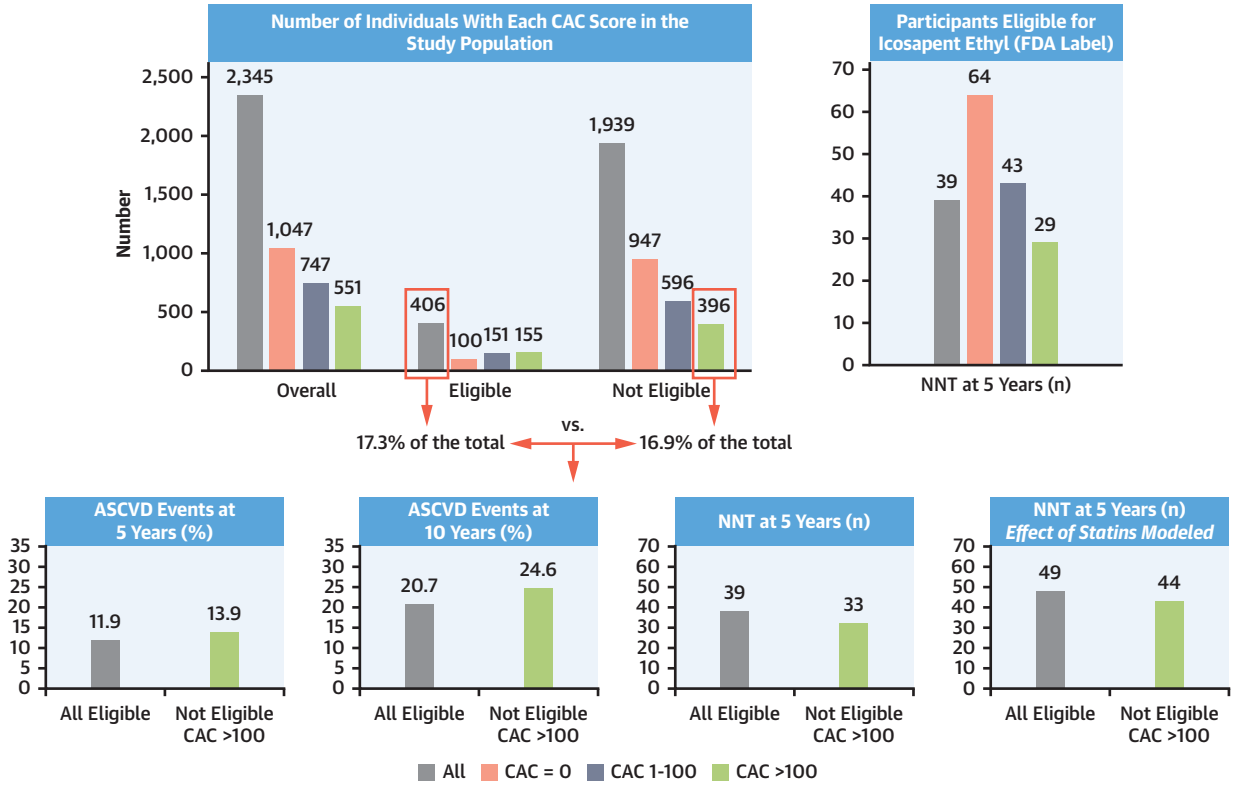
was relatively low. This prevented evaluating these very high CAC thresholds. Nonetheless, event rates among individuals with hypertriglyceridemia and CAC >100 were already high.

Second, baseline use of statins in our study population was relatively low as well. Although the study entry criteria and the NNT_5 calculations modeled the expected effect of background high-intensity statin therapy, it could be argued that the Agatston CAC score may not be as informative among individuals who are already being treated with statins. Nonetheless, various recent analyses among statin users demonstrate that CAC retains independent predictive value also in the setting of statin use (36-38). The results of the NNT analyses modeling the effect of high-intensity statin therapy may be particularly informative, because maximally tolerated statin therapy would be expected before using additional novel therapies for ASCVD risk reduction in these individuals (4,6,13).

Third, the same 21.8% 5-year RRR in ASCVD events with IPE reported in REDUCE-IT was used in the exploratory analyses of IPE-noneligible participants. Although no statistical evidence of effect modification was identified in multiple subgroup analyses in REDUCE-IT (4), a better understanding of the RRR of IPE across primary prevention scenarios and baseline CAC burden is needed. Still, this assumption would not have affected the results for incident events, which showed highly consistent trends.

Finally, although the cohorts pooled in this analysis were drawn from the general primary prevention population, they were assembled more than 20 years ago, and their racial/ethnic distribution is not

CENTRAL ILLUSTRATION **Number of Individuals With Each CAC Score in the Study Population, Overall and by Icosapent Ethyl Eligibility, Potential Role of CAC Among Eligible Individuals, and Comparison Between Eligible Individuals Versus Noneligible Individuals With CAC >100**



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Eligibility for icosapent ethyl therapy was defined based on the FDA product label risk factor/marker criteria for primary prevention in adult patients with triglyceride levels 150 to <500 mg/dL. ASCVD = atherosclerotic cardiovascular disease; CAC = coronary artery calcium; NNT = number needed to treat.

representative of the general population of either the US or Germany. Therefore, although the qualitative trends reported are expected to have high external validity, the specific rates and NNTs observed in these cohorts may differ from those observed in real-world settings in 2021.

CONCLUSIONS

There is significant risk heterogeneity among individuals with hypertriglyceridemia free of clinical ASCVD, and the CAC score can help further improve current ASCVD risk stratification and therapy allocation paradigms in this large population. Future primary prevention trials of ASCVD risk-reduction therapies for individuals with hypertriglyceridemia could use a high CAC score for enrollment of a high-risk study sample, with implications for a larger target population.

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PERSPECTIVES

CLINICAL PERSPECTIVE: In patients with hypertriglyceridemia who are considered eligible for treatment with IPE for ASCVD risk reduction in primary prevention, the CAC score can help identify those likely to derive the largest and smallest absolute risk reduction, respectively.

COMPETENCY IN MEDICAL KNOWLEDGE: One out of 5 individuals without clinical ASCVD with triglyceride levels 150-500 mg/dL who do not qualify for therapy with IPE have CAC scores >100, and this is associated with a high risk of ASCVD events.

TRANSLATIONAL OUTLOOK: Future primary prevention trials of ASCVD risk-reduction therapies for individuals with hypertriglyceridemia could enroll participants on the basis of high CAC scores, regardless of diabetes status and burden of other traditional risk factors.

REFERENCES

1. Raposeiras-Roubin S, Rosselló X, Oliva B, et al. Triglycerides and residual atherosclerotic risk. *J Am Coll Cardiol*. 2021;77:3031-3041.

2. Quispe R, Martin SS, Michos ED, et al. Remnant cholesterol predicts cardiovascular disease beyond LDL and ApoB: a primary prevention study. *Eur Heart J*. 2021;42:ehab432. https://doi.org/10.1093/eurheartj/ehab432

3. Fan W, Philip S, Granowitz C, Toth PP, Wong ND. Prevalence of US adults with triglycerides ≥150 mg/dL: NHANES 2007-2014. *Cardiol Ther*. 2020;9:207-213.

4. Bhatt DL, Steg PG, Miller M, et al, REDUCE-IT Investigators. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med*. 2019;380:11-22.

5. Nicholls SJ, Lincoff AM, Garcia M, et al. Effect of high-dose omega-3 fatty acids vs corn oil on major adverse cardiovascular events in patients at high cardiovascular risk: the STRENGTH randomized clinical trial. *JAMA*. 2020;324:2268-2280.

6. US Food and Drug Administration. FDA news release: FDA approves use of drug to reduce risk of cardiovascular events in certain adult patient groups. Accessed August 30, 2021. https://www.fda.gov/news-events/press-announcements/fda-approves-use-drug-reduce-risk-cardiovascular-events-certain-adult-patient-groups

7. Nasir K, Bittencourt MS, Blaha MJ, et al. Implications of coronary artery calcium testing among statin candidates according to American College of Cardiology/American Heart Association cholesterol management guidelines: MESA (Multi-Ethnic Study of Atherosclerosis). *J Am Coll Cardiol*. 2015;66:1657-1668.

8. Silverman MG, Blaha MJ, Krumholz HM, et al. Impact of coronary artery calcium on coronary heart disease events in individuals at the extremes of traditional risk factor burden: the Multi-Ethnic Study of Atherosclerosis. *Eur Heart J*. 2014;35:2232-2241.

9. Martin SS, Blaha MJ, Blankstein R, et al. Dyslipidemia, coronary artery calcium, and incident atherosclerotic cardiovascular disease: implications for statin therapy from the Multi-Ethnic Study of Atherosclerosis. *Circulation*. 2014;129:77-86.

10. Tota-Maharaj R, Blaha MJ, McEvoy JW, et al. Coronary artery calcium for the prediction of mortality in young adults <45 years old and elderly adults >75 years old. *Eur Heart J*. 2012;33:2955-2962.

11. Yeboah J, McClelland RL, Polonsky TS, et al. Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. *JAMA*. 2012;308:788-795.

12. Blaha MJ, Budoff MJ, DeFilippis AP, et al. Associations between C-reactive protein, coronary artery calcium, and cardiovascular events: implications for the JUPITER population from MESA, a population-based cohort study. *Lancet*. 2011;378:684-692.

13. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2019;74(10):1376-1414.

14. Cainzos-Achirica M, Miedema MD, McEvoy JW, et al. Coronary artery calcium for personalized allocation of aspirin in primary prevention of cardiovascular disease in 2019: the MESA study (Multi-Ethnic Study of Atherosclerosis). *Circulation*. 2020;141:1541-1553.

15. Ajufo E, Ayers CR, Vigen R, et al. Value of coronary artery calcium scanning in association with the net benefit of aspirin in primary prevention of atherosclerotic cardiovascular disease. *JAMA Cardiol*. 2021;6:179-187.

16. McEvoy JW, Martin SS, Dardari ZA, et al. Coronary artery calcium to guide a personalized risk-based approach to initiation and intensification of antihypertensive therapy. *Circulation*. 2017;135:153-165.

17. Cainzos-Achirica M, Patel KV, Quispe R, et al. Coronary artery calcium for the allocation of GLP-1RA for primary prevention of atherosclerotic cardiovascular disease. *J Am Coll Cardiol Img*. 2021;14:1470-1472.

18. Cardoso R, Dudum R, Ferraro RA, et al. Cardiac computed tomography for personalized management of patients with type 2 diabetes mellitus. *Circ Cardiovasc Imaging*. 2020;13:e011365.

19. Sharma G, Martin SS, Blumenthal RS. Effects of omega-3 fatty acids on major adverse cardiovascular events: What matters most: the drug, the dose, or the placebo? *JAMA*. 2020;324:2262-2264.

20. Bild DE, Bluemke DA, Burke GL, et al. Multi-Ethnic Study of Atherosclerosis: objectives and design. *Am J Epidemiol*. 2002;156:871-881.

21. Carr JJ, Jacobs DR Jr, Terry JG, et al. Association of coronary artery calcium in adults aged 32 to 46 years with incident coronary heart disease and death. *JAMA Cardiol*. 2017;2:391-399.

22. Victor RG, Haley RW, Willett DL, et al, Dallas Heart Study Investigators. The Dallas Heart Study: a population-based probability sample for the multidisciplinary study of ethnic differences in cardiovascular health. *Am J Cardiol*. 2004;93:1473-1480.

23. Schmermund A, Möhlenkamp S, Stang A, et al. Assessment of clinically silent atherosclerotic disease and established and novel risk factors for predicting myocardial infarction and cardiac death in healthy middle-aged subjects: rationale and design of the Heinz Nixdorf Recall study. Risk factors, evaluation of coronary calcium and lifestyle. *Am Heart J*. 2002;144:212-218.

24. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med*. 2008;359:2195-2207.

25. American Diabetes Association. Classification and diagnosis of diabetes: standards of medical care in diabetes—2020. *Diabetes Care*. 2020;43:S14-31.

26. Moebus S, Stang A, Möhlenkamp S, et al. Association of impaired fasting glucose and coronary artery calcification as a marker of subclinical atherosclerosis in a population-based cohort—results of the Heinz Nixdorf Recall study. *Diabetologia*. 2009;52:81-89.

27. Silverman MG, Ference BA, Im K, et al. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: a systematic review and meta-analysis. *JAMA*. 2016;316:1289-1297.

28. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet*. 2019;394:121-130.

29. US Food and Drug Administration. Enrichment strategies for clinical trials to support approval of human drugs and biological products. Accessed August 30, 2021. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm332181.pdf

30. Yokoyama M, Origasa H, Matsuzaki M, et al, Japan EPA Lipid Intervention Study (JELIS) Investigators. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded end point analysis. *Lancet*. 2007;369:1090-1098.

31. Budoff MJ, Bhatt DL, Kinninger A, et al. Effect of icosapent ethyl on progression of coronary atherosclerosis in patients with elevated triglycerides on statin therapy: final results of the EVAPORATE trial. *Eur Heart J*. 2020;41:3925-3932.

32. Bhatt DL, Hull MA, Song M, et al. Beyond cardiovascular medicine: potential future uses of icosapent ethyl. *Eur Heart J Suppl*. 2020;22:J54-J64.

33. Cainzos-Achirica M, Bittencourt MS, Osei AD, et al. Coronary artery calcium to improve the efficiency of randomized controlled trials in primary cardiovascular prevention. *J Am Coll Cardiol Img*. 2021;14:1005-1016.

34. Erbel R, Budoff M. Improvement of cardiovascular risk prediction using coronary imaging: subclinical atherosclerosis: the memory of lifetime risk factor exposure. *Eur Heart J*. 2012;33:1201-1213.

35. Orringer CE, Blaha MJ, Blankstein R, et al. The National Lipid Association scientific statement on coronary artery calcium scoring to guide preventive strategies for ASCVD risk reduction. *J Clin Lipidol*. 2021;15:33-60.

36. Miname MH, Bittencourt MS, Moraes SR, et al. Coronary artery calcium and cardiovascular events in patients with familial hypercholesterolemia receiving standard lipid-lowering therapy. *J Am Coll Cardiol Img*. 2019;12:1797-1804.

37. Gallo A, Pérez de Isla L, Charrière S, et al. The added value of coronary calcium score in predicting cardiovascular events in familial hypercholesterolemia. J Am Coll Cardiol Img. http://doi.org/10.1016/j.jcmg.2021.06.011.

38. Rifai MA, Blaha MJ, Patel J, et al. Coronary artery calcification, statin use and long-term risk of atherosclerotic cardiovascular disease events (from the Multi-Ethnic Study of Atherosclerosis). *Am J Cardiol*. 2020;125:835-839.

KEY WORDS cardiovascular disease, coronary artery calcium, hypertriglyceridemia, icosapent ethyl, prevention, primary prevention, risk

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