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Short Report

Global assessment improves risk stratification for major adverse cardiac events across a wide range of triglyceride levels: Insights from the KP REACH study

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ABSTRACT

Objective: Patients with risk factors for or established atherosclerotic cardiovascular disease (ASCVD) remain at high risk for subsequent ischemic events despite statin therapy. Triglyceride (TG) levels may contribute to residual ASCVD risk, and the performance of global risk assessment calculators across a broad range of TG levels is unknown.

Methods: We performed a retrospective cohort study of Kaiser Permanente Northern California members aged ≥45 years with ≥1 ASCVD risk factor (primary prevention cohort) or established ASCVD (secondary prevention cohort) between 2010 and 2017 who were receiving statin therapy and had a low-density lipoprotein cholesterol between 41–100 mg/dL. Global ASCVD risk assessment was performed using both the Kaiser Permanente ASCVD Risk Estimator (KPARE) and the ACC/AHA ASCVD Pooled Cohort Equation (PCE). Outcomes included major adverse cardiovascular events (MACE) defined as myocardial infarction, stroke, or peripheral artery disease, and expanded MACE (MACE + coronary revascularization + hospitalization for unstable angina).

Results: Among 373,389 patients in the primary prevention cohort, median TG was 122 mg/dL (IQR 88–172 mg/dL) and there were 0.2 MACE events and 0.3 expanded MACE events per 100-person years. Among 97,832 patients in the secondary prevention cohort, median TG level was 116 mg/dL (IQR 84–164 mg/dL) and there were 9.6 MACE events and 22.0 expanded MACE events per 100-person years. KPARE and the ACC/AHA PCE stratified patients for MACE and expanded MACE over the entire range of TGs.

Conclusion: In a cohort receiving statin therapy for primary or secondary prevention, we found global assessment further improves risk stratification for initial and/or recurrent ASCVD events irrespective of baseline TG level.

1. Introduction

Patients with risk factors for or established atherosclerotic cardiovascular disease (ASCVD) may experience subsequent ischemic events despite treatment with lipid-lowering therapies [1–4]. Global assessment of risk with the ACC/AHA ASCVD Pooled cohort equation (PCE) has been observed in primary prevention cohorts to identify high-risk patients but have seldom been applied to populations already

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receiving low-density lipoprotein cholesterol (LDL-C) lowering therapy and/or with established ASCVD (secondary prevention). Additionally, triglyceride (TG) levels are not included in the ACC/AHA PCE and may play a causal role in atherogenesis and contribute to residual risk among patients on LDL-C lowering agents [5–8]. Thus, the primary objective of this analysis of the *KP REACH* (*Kaiser Permanente Residual Risk by Ethnicity, Gender, and Age in a Statin-Treated CoHort*) study was to understand how global assessment of ASCVD risk performs over a wide range of TG levels in a diverse and cohort of adults with ASCVD risk factors (primary prevention) or established ASCVD (secondary prevention), a well-controlled LDL-C, and receiving statin therapy.

2. Methods

KP-REACH is a retrospective cohort study of Kaiser Permanente Northern California (KPNC) members age ≥45 years receiving statin therapy with LDL-C 41–100 mg/dL and ≥1 ASCVD risk factor(s) (primary prevention cohort) or established ASCVD (secondary prevention cohort) (Supplemental Appendix). Patients were enrolled between January 1, 2010 and December 31, 2017. Risk factors for ASCVD included diabetes, men age ≥55 years and women age ≥65 years, active tobacco use, hypertension, high-density lipoprotein cholesterol ≤40 mg/dL for men or ≤50 mg/dL for women, estimated glomerular filtration rate <60 mL/min/1.73m^2, and microvascular complications of diabetes (retinopathy, albuminuria, or asymptomatic peripheral artery disease). Established ASCVD (secondary prevention cohort) was determined using *International Classification of Disease, Ninth or Tenth edition* (ICD-9/10) or *Current Procedural Terminology* codes for coronary heart disease, prior stroke or transient ischemic attack, myocardial infarction, and coronary or peripheral arterial revascularization. Patients were excluded who had unknown gender, <12 months of continuous prior membership or drug benefit before index date, a known non-cardiovascular life-limiting diagnosis (i.e., metastatic cancer, receiving chronic dialysis, and/or cirrhosis), prior organ transplant, or no outpatient TG measured within 2 years before index date. The study was approved by the KPNC Institutional Review Board, and a waiver of informed consent was obtained due to the nature of the study.

Demographic information and comorbid conditions were ascertained from electronic health records. Laboratory results, including TG levels (fasting and non-fasting measurements), were obtained from a non-emergency, ambulatory setting within 2 years of index date. Baseline medication use was based on dispensed prescriptions within 120 days before index date using health plan pharmacy databases. Global assessment of ASCVD event risk was estimated using both the Kaiser Permanente ASCVD Risk Estimator (KPARE) and the 2013 ACC/AHA PCE [8]. KPARE is the ACC/AHA PCE that was recalibrated to the KPNC membership across four racial/ethnic groups (Black, White, Asian/Pacific Islander and Hispanic). Outcomes included major adverse cardiovascular events (MACE) and expanded MACE. MACE was defined as myocardial infarction, ischemic stroke, or peripheral artery disease, while expanded MACE included the aforementioned criteria in addition to coronary revascularization or hospitalization for unstable angina. Baseline characteristics were stratified by KPARE risk estimates (<5%, 5.0–7.4%, 7.5–9.9%, and ≥10%) and presented as frequencies with percentages or means with standard deviations. Outcomes are presented as the number of events per 100 person-years. *KP REACH* was an investigator-initiated study funded by Amarin Pharma, Inc. (Bridgewater, NJ, USA). The sponsor had no role in protocol development or study execution. All data collection and statistical analyses were performed at KPNC's Division of Research (Oakland, CA). A.P.A and A.S.G. take full responsibility for the manuscript's integrity and had complete control and authority over its preparation and the decision to publish.

3. Results

A total of 373,389 patients met criteria for the primary prevention cohort and 97,832 patients for the secondary prevention cohort. Baseline characteristics are shown in Table 1. In the primary prevention cohort, mean age was 65 (SD 10) years, 51% were women, and there was diverse representation with 44% self-reporting as non-white. The secondary prevention cohort was older with mean (SD) age of 71 (11) years and fewer self-reported female (37%) and non-white (34%) participants. The primary prevention cohort had a higher median TG level (122 mg/dL, IQR 88–172 mg/dL) compared with the secondary prevention cohort (116 mg/dL, IQR 84–164 mg/dL). Overall, use of non-statin lipid lowering agents was low in both the primary and secondary prevention cohorts. Higher KPARE scores were associated with older age, non-Hispanic white race, a history of hypertension, higher glycosylated hemoglobin, and higher TG levels (Table 1).

Over a median (IQR) 5.9 (3.0–8.3) years of follow-up, there were 0.2 MACE and 0.3 expanded MACE events per-100-person years in the primary prevention cohort. Event rates for MACE (9.6 per-100-person years) and expanded MACE (22.0 per-100-person years) were higher in the secondary prevention cohort over a median (IQR) of 4.5 (2.3–7.3) years. For both KPARE and the ACC/AHA PCE, the high predicted risk group (>10%) experienced MACE at an event rate twice that of the moderate predicted risk (7.5–9.9%) group (Fig. 1). When MACE rate was stratified by TG level and global assessment score, both KPARE and the ACC/AHA PCE provided graded risk assessment across a wide range of TG levels. Baseline characteristics are shown in Table 1 and 2.

4. Conclusion

In adults at risk for or with established ASCVD with a well-controlled LDL-C on statins, we found that a global assessment of risk effectively stratified patients for MACE and expanded MACE across a wide range of TG levels. We have previously shown that a TG >150 mg/dL is associated with higher risks of MACE and expanded MACE in primary and secondary prevention cohorts within KP REACH [9]. Our current findings suggest that this modest association between TG levels and ASCVD events does not meaningfully affect the performance of contemporary ASCVD risk calculators.

A novel aspect of this study was the application of ASCVD risk calculators to a secondary prevention cohort. Event rates were much higher in secondary prevention cohorts and more closely aligned with the historical 10-year risk estimates produced by both KPARE and AHA/ACC PCE risk calculators, compared with event rates in the primary prevention cohort. Identifying residual risk in patients with established ASCVD has become increasingly relevant in the era of novel cardioprotective medications, many of which have been shown to reduce ASCVD events via pleiotropic effects in addition to and/or independent of lipid-lowering [10–12]. Global risk assessment may facilitate the identification of patients with high residual ASCVD risk who may be more likely to derive a robust benefit from emerging and/or novel therapies.

We acknowledge several limitations of our study. First, our study was conducted among insured adults in Northern California between 2010–2017 and may not be completely generalizable to uninsured persons, persons in other geographic regions, or other timeframes. Second, KPARE has only been internally validated within Kaiser Permanente populations. Additionally, the ACC/AHA PCE has been shown to overestimate and misclassify risk in certain contemporary populations [13]. Lastly, non-fasting TG levels are impacted by recent dietary intake and could introduce systematic bias if physician ordering patterns (fasting vs non-fasting) were non-random, although we only used TG tests from non-emergency ambulatory settings.

The broader use of global risk assessment may help identify high-risk patients who might benefit from novel treatments.

CRediT authorship contribution statement

Jeffrey R. Wagner: Investigation, Writing – original draft, Writing –

Table 1
Baseline characteristics for primary prevention cohort by KPARE risk stratification.

Characteristics	Overall $N = 373,389$	<5.0% $N = 123,119$	5.0–7.4% $N = 57,557$	7.5–9.9% $N = 44,665$	≥10% $N = 148,048$
Age, years, mean (SD)	65 (10)	57 (7)	62 (8)	65 (8)	72 (9)
Women, *N* (%)	190,576 (51)	84,359 (57)	29,452 (48)	20,537 (48)	56,228 (47)
Non-Hispanic White, *N* (%)	210,004 (56)	61,100 (50)	30,735 (53)	24,658 (55)	93,511 (63)
Non-Hispanic Black, *N* (%)	25,903 (7)	9382 (8)	4025 (7)	2685 (6)	9811 (7)
Hispanic, *N* (%)	56,127 (15)	20,603 (17)	8859 (15)	6652 (15)	20,013 (14)
Asian-Pacific Islander, *N* (%)	72,002 (19)	28,288 (23)	12,265 (21)	9518 (21)	21,931 (15)
Unknown Race, *N* (%)	9353 (3)	3746 (3)	1673 (3)	1152 (3)	2782 (2)
Current tobacco use, *N* (%)	86,056 (23)	26,950 (22)	13,438 (23)	10,782 (24)	34,886 (24)
Former tobacco use, *N* (%)	70,757 (19)	18,046 (15)	10,117 (8)	8463 (19)	34,131 (23)
Diabetes mellitus, *N* (%)	162,198 (43)	27,951 (23)	23,025 (40)	20,700 (46)	90,522 (61)
Hypertension, *N* (%)	315,926 (85)	87,701 (71)	48,520 (84)	39,705 (89)	140,000 (96)
Dyslipidemia, *N* (%)	372,914 (99.9)	123,014 (99.9)	57,498 (99.9)	44,619 (99.9)	147,783 (99.8)
Chronic kidney disease, *N* (%)	67,484 (18)	10,322 (8)	6390 (11)	6463 (15)	44,309 (30)
Statin potency, *N* (%)					
Low-intensity	55,248 (15)	12,305 (12)	7026 (13)	6067 (14)	29,850 (17)
Moderate-intensity	276,995 (74)	77,859 (76)	39,671 (75)	32,059 (75)	127,406 (73)
High-intensity	41,141 (11)	12,255 (12)	6102 (12)	4703 (11)	18,081 (10)
Unknown	5 (0)	2 (0)	2 (0)	0 (0)	1 (0)
Non-statin lipid lowering agent, *N* (%)	18,927 (5)	4394 (4)	3020 (5)	2508 (6)	9005 (6)
Body mass index, kg/m^2, Mean (SD)	29 (6)	29 (6)	30 (6)	30 (6)	30 (6)
Hemoglobin A1c, %, Median (IQR)	6.4 (5.8–7.2)	6.0 (5.7–6.9)	6.4 (5.8–7.4)	6.5 (5.9–7.4)	6.5 (6.0–7.3)
Total cholesterol, mg/dL, Median (IQR)	161 (144–177)	163 (147–179)	162 (146–178)	162 (145–178)	158 (141–175)
High density lipoprotein mg/dL, Median (IQR)	48 (41–58)	51 (43–62)	49 (41–58)	48 (40–57)	46 (39–55)
Low density lipoprotein mg/dL, Median (IQR)	83 (71–93)	85 (73–93)	84 (72–93)	83 (71–93)	81 (58–91)
Triglycerides lipoprotein mg/dL, Median (IQR)	122 (88–172)	111 (81–157)	122 (88–174)	125 (90–178)	129 (94–182)
Non-high density lipoprotein mg/dL, Median (IQR)	109 (95–123)	108 (95–121)	110 (96–124)	110 (96–125)	110 (95–125)

Abbreviations: N = number; SD = standard deviation; IQR = interquartile range.

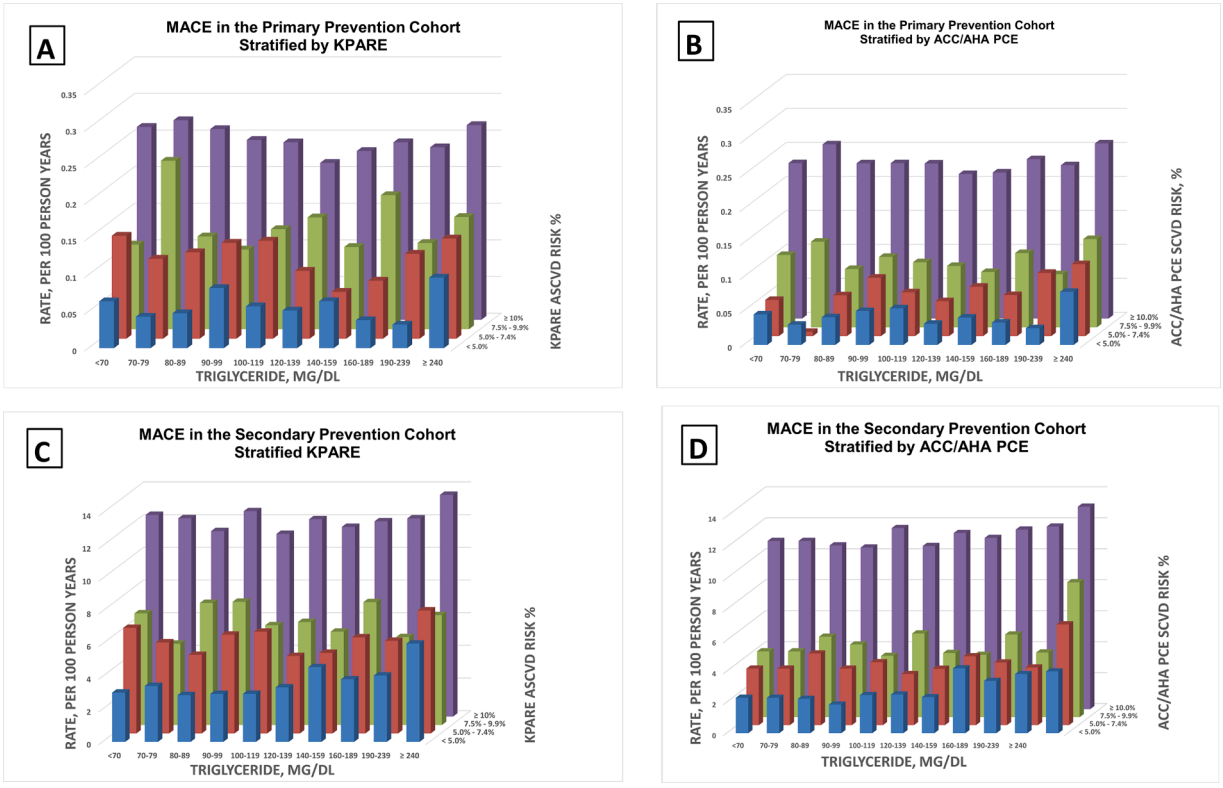

Fig. 1. MACE per 100-person years stratified by global risk assessment score and triglyceride level. Risk assessment with KPARE and the ACC/AHA PCE are shown for both primary (A and B) and secondary prevention (C and D) cohorts.

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Table 2
Baseline characteristics for secondary prevention cohort by KPARE risk stratification.

Characteristics	Overall $N = 97,832$	<5.0% $N = 13,778$	5.0–7.4% $N = 9099$	7.5–9.9% $N = 8628$	≥10% $N = 66,327$
Age, years, mean (SD)	71 (11)	57 (7)	63 (8)	66 (9)	75 (9)
Women, *N* (%),	36,600 (37)	5094 (37)	3293 (36)	3142 (36)	25,071 (38)
Non-Hispanic White, *N* (%)	64,972 (66)	7102 (52)	5000 (55)	5096 (59)	47,774 (72)
Non-Hispanic Black, *N* (%)	6688 (7)	s1098 (8)	864 (10)	650 (8)	4076 (6)
Hispanic, *N* (%)	12,270 (13)	2336 (17)	1495 (16)	1363 (16)	7076 (11)
Asian-Pacific Islander, *N* (%)	12,798 (13)	2978 (22)	1609 (18)	1418 (16)	6793 (10)
Unknown Race, *N* (%)	1104 (1)	264 (2)	131 (1)	101 (1)	608 (1)
Current tobacco use, *N* (%)	30,444 (31)	1948 (14)	1995 (22)	2172 (25)	24,329 (37)
Former tobacco use, *N* (%)	27,357 (28)	3218 (23)	2474 (27)	2457 (29)	19,208 (29)
Diabetes mellitus, *N* (%)	38,072 (39)	1727 (13)	2044 (23)	2370 (28)	31,931 (48)
Hypertension, *N* (%)	89,795 (92)	10,555 (77)	7874 (87)	7764 (90)	63,602 (96)
Dyslipidemia, *N* (%)	97,687 (100)	13,768 (100)	9093 (100)	8613 (100)	66,213 (100)
Chronic kidney disease, *N* (%)	31,406 (32.1)	1533 (11.1)	1522 (16.7)	1750 (20.3)	26,601 (40.1)
Statin potency, *N* (%)					
Low-intensity	10,600 (11)	1045 (8)	818 (9)	769 (9)	7968 (12)
Moderate-intensity	60,297 (62)	7698 (56)	5432 (60)	5243 (61)	41,924(63)
High-intensity	26,935 (28)	5035 (37)	2849 (31)	2616 (30)	16,435 (25)
Non-statin lipid lowering agent, *N* (%)	6712 (7)	730 (5)	582 (6)	584 (7)	4816 (7)
Body mass index, kg/m^2, Mean (SD)	28 (6)	29 (6)	29 (6)	29 (6)	28 (6)
Hemoglobin A1c, %, Median (IQR)	6.3 (5.8–7.2)	5.8 (5.6–6.3)	6.0 (5.7–7.0)	6.1 (5.7–7.2)	6.4 (5.8–7.3)
Total cholesterol, mg/dL, Median (IQR)	151 (133–171)	145 (126–165)	150 (132–169)	152 (134–170)	153 (134–172)
High density lipoprotein mg/dL, Median (IQR)	45 (38–55)	47 (39–57)	46 (39–56)	47 (39–57)	45 (38–54)
Low density lipoprotein mg/dL, Median (IQR)	77 (64–89)	74 (60–87)	77 (64–89)	78 (65–89)	78 (65–89)
Triglycerides lipoprotein mg/dL, Median (IQR)	116 (84–164)	99 (73–153)	109 (80–153)	111 (81–159)	121 (88–171)
Non-high density lipoprotein mg/dL, Median (IQR)	103 (87–120)	95 (79–111)	101 (85–117)	102 (86–118)	105 (89–122)

Abbreviations: N = number; SD = standard deviation; IQR = interquartile range.

Declaration of Competing Interest

APA has received relevant research support through grants to his institution from the National Institute on Aging, National Heart, Lung, and Blood Institute, Amarin Pharma, Inc., Abbott, and Novartis, as well as modest reimbursement for travel from Novartis. SP and DA are employees of Amarin Pharma, Inc. CG is an employee of Lexicon Pharmaceuticals, Inc. ASG has received relevant research support through grants to his institution from the National Heart, Lung, and Blood Institute, National Institute of Diabetes, Digestive, and Kidney Diseases, National Institute on Aging, Amarin Pharma, Inc., and Novartis. All other authors have no relevant conflicts of interest to declare.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajpc.2022.100319.

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