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Letters

Generalizability of the REDUCE-IT Trial in Patients With Stable Coronary Artery Disease

Epidemiological studies suggest that both moderate and severe hypertriglyceridemia are associated with increased long-term cardiovascular risk and mortality. Interestingly, the REDUCE-IT (Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention) randomized trial recently enrolled 8,179 statin-treated patients with elevated triglyceride levels (≥135 and <500 mg/dl) and either established cardiovascular disease or diabetes plus at least 1 risk factor, and demonstrated that a high dose (4 g/day) of icosapent ethyl reduced the risk of ischemic events, including cardiovascular death (1). Indeed, the secondary prevention cohort represented 70.7% of the total cohort, which experienced a lower rate of the key secondary efficacy composite endpoint of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke as compared with the placebo group (12.5% vs. 16.9%; hazard ratio: 0.72; 95% confidence interval: 0.63 to 0.82).

Using a large contemporary international cohort of patients with stable coronary artery disease (CAD), we sought to evaluate what proportion of patients would be potentially eligible for enrollment. The CLARIFY (ProspeCtive observational Longitudi-nAl RegIstry oF patients with stable coronary arterY disease) registry is an international, prospective, observational, longitudinal registry that has been previously described (2). Briefly, stable CAD patients from 45 countries were enrolled between November 2009 and June 2010. The inclusion criteria were any of the following: previous myocardial infarction, evidence of coronary stenosis >50%, proven symptomatic myocardial ischemia, or prior coronary revascularization procedure. Follow-up visits were planned annually for ≤5 years.

The REDUCE-IT selection criteria were applied to CLARIFY patients. Key inclusion criteria included statin-treated men or women either age ≥45 years with established cardiovascular disease or age ≥50 years with diabetes mellitus in combination with at least 1 additional risk factor for cardiovascular disease, with triglyceride levels ≥135 and <500 mg/dl, and low-density lipoprotein (LDL) cholesterol >40 and ≤100 mg/dl (1). In the REDUCE-IT trial, patients were excluded if they had severe heart failure, active severe liver disease, a glycated hemoglobin level >10.0%, a planned coronary intervention or surgery, a history of acute or chronic pancreatitis, or known hypersensitivity to fish, shellfish, or ingredients of icosapent ethyl or placebo (1). As data on exclusion criteria were not all recorded in the CLARIFY registry, they were not included to the present analysis.

In CLARIFY, 24,146 out of 32,703 patients had complete data (505 patients were missing triglycerides values) allowing evaluation of eligibility. Overall, 15.5% (3,738 of 24,146 patients) were eligible for enrollment in REDUCE-IT. Among those not eligible, 3.8% of the patients (n = 926) were younger than 45 years, 57.1% (n = 13,791) had triglyceride levels <135 mg/dl, 0.6% (n = 144) had levels ≥500 mg/dl, and 47.0% (n = 11,342) of patients did not fulfil the LDL cholesterol inclusion criteria (12.6% [n = 3,034] had LDL cholesterol ≤40 mg/dl and 34.4% [n = 8,308] >100 mg/dl) (**Figure 1**).

Our analysis demonstrates that in a large international registry, 15.5% of patients with stable coronary artery disease met the REDUCE-IT inclusion criteria, and were thus eligible for treatment with icosapent ethyl to reduce cardiovascular risk. The most frequent reasons for noneligibility were triglycerides <135 mg/dl (57.1%) and LDL cholesterol >100 mg/dl (34.4%), which may depend on lifestyle and adherence to evidence-based recommended intensive statin therapy, which are likely to vary across geographic regions. Global data indicate there are approximately 110.55 million patients with stable CAD similar to the definition in CLARIFY (3). If 15.5% of these patients are eligible for icosapent ethyl, that works out to approximately 17.14 million patients who may benefit. On the basis of data from the National Health and Nutrition Examination Survey from 2011 to 2014, an estimated 16.5 million Americans have CAD, which translates into a prevalence of 6.3% in American adults (4). Therefore, 15.5% of 16.5 million represents 2.56 million American adults who could benefit from

such treatment. Of note, the CLARIFY registry did not include patients from the United States, where the prevalence of high triglycerides and the use of intensive statin treatment are likely higher than in other parts of the world, and therefore where eligibility may be more frequent. In addition, the REDUCE-IT trial also enrolled patients with peripheral artery disease or cerebrovascular disease as well as patients with diabetes mellitus and an additional cardiovascular risk factor, and therefore has a much broader recruitment base than solely stable CAD patients as in CLARIFY.

Fabien Picard, MD, MSc
Deepak L. Bhatt, MD, MPH
Grégory Ducrocq, MD, PhD
Yedid Elbez, MSc
Roberto Ferrari, MD, PhD
Ian Ford, PhD
Jean-Claude Tardif, MD
Michal Tendera, MD
Kim M. Fox, MD
***Philippe Gabriel Steg, MD**

*Service de Cardiologie
Hôpital Bichat
46 rue Henri-Huchard
75018 Paris
France
E-mail: gabriel.steg@aphp.fr

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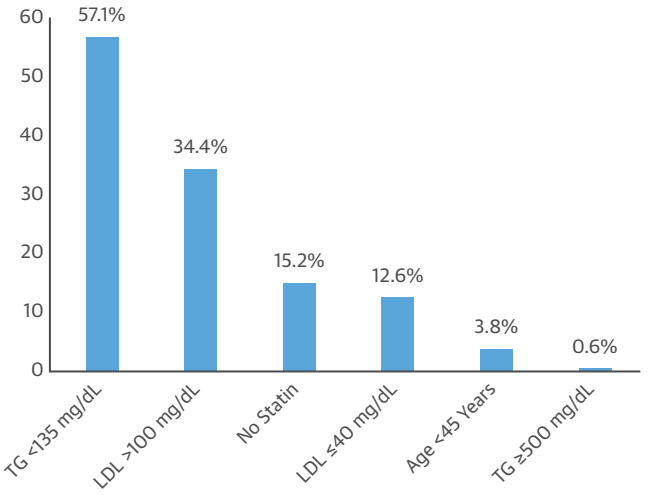
FIGURE 1 **Frequency of the Various Noninclusion Criteria Ranked By Descending Order of Frequency**



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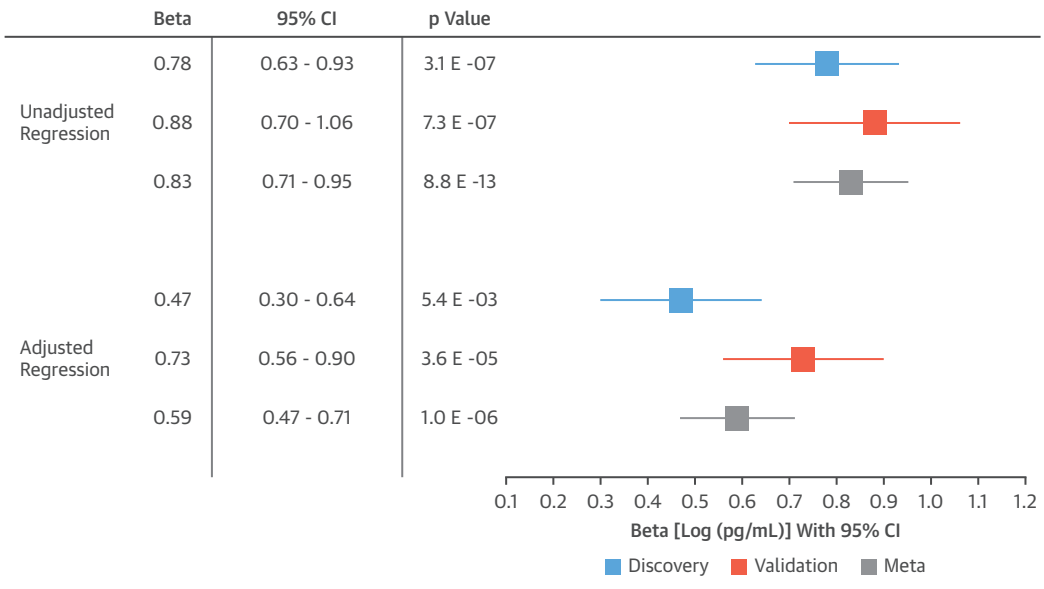
Soluble FMS-Like Tyrosine Kinase-1 Is a Circulating Biomarker Associated With Calcific Aortic Stenosis

Calcific aortic stenosis (CAS) is the end manifestation of calcific aortic valve disease (CAVD). There are no medical therapies to reverse or slow the progression of CAVD (1). Circulating biomarkers may provide insights into CAVD pathogenesis. Biomarkers identified in association with CAVD include osteopontin, osteoprotegerin, fibroblast growth factor (FGF-23), B-type natriuretic peptide (BNP), low-density lipoprotein cholesterol, and lipoprotein(a) [Lp(a)] (2). Lp(a) has been established as a causal risk factor for CAVD through Mendelian randomization (3).

We performed a targeted discovery experiment to identify novel biomarkers of CAS using a multiplexed assay of 48 candidate proteins related to cardiovascular disease. We leveraged a large biobank at the University of Pennsylvania (PennMedicine Biobank) and used text mining of the electronic health record to identify CAS cases and non-CAS control subjects, followed by electronic health record review for confirmation of case status. We then assayed 48 proteins among 711 subjects with CAS and 802 age- and sex-matched controls (cases: 78 ± 10 years of age, 84% Caucasian, 6% Black; control subjects: 74 ± 9 years of age, 85% Caucasian, 6% Black).

In a multiple linear regression model adjusted for age, sex, ethnicity, and common clinical conditions (hypertension, coronary artery disease, heart failure, diabetes, peripheral vascular disease, and renal disease), 17 proteins were significantly (false discovery rate <0.05) associated with CAS. These included BNP, which had increased plasma levels in CAS cases relative to control subjects. Osteopontin, osteoprotegerin, and FGF-23 were significantly increased in cases in unadjusted regression, but were not significant after adjusting for demographic and clinical covariates. Of the novel protein associations, soluble

FIGURE 1 Multiple Linear Regression of sFLT-1 in Discovery/Validation Cohorts With Meta-Analysis



Forest plots for multiple linear regression of sFLT-1 against CAS status adjusted for age, sex, and ethnicity in our discovery/validation cohorts with meta-analysis. We present models both without clinical covariates **(top)** and with clinical covariates **(bottom)**. All models had a significant association (false discovery rate <0.05) between sFLT-1 and CAS. CAS = calcific aortic stenosis; CI = confidence interval; sFLT-1 = soluble FMS-like tyrosine kinase-1.