Generalizability of the REDUCE-IT trial in patients with stable coronary artery disease.

An analysis from the CLARIFY registry

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Abbreviations

REDUCE-IT: Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention

CLARIFY: ProspeCtive observational LongitudinAl RegIstry oF patients with stable coronary arterY disease

CAD: coronary artery disease

LDL: low density lipoprotein

Epidemiological studies suggest that both moderate and severe hypertriglyceridemia are associated with increased long term cardiovascular risk and mortality. Interestingly, the Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention (REDUCE-IT) randomized trial recently enrolled 8179 statin-treated patients with elevated triglycerides levels (≥135mg/dL and <500mg/dL) and either established cardiovascular disease or diabetes plus at least one risk factor, and demonstrated that 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 to the placebo group (12.5% vs 16.9% HR:0.72, 95%CI (0.63-0.82).

Using a large contemporary international cohort of patients with stable coronary artery disease, we sought to evaluate what proportion of patients would be potentially eligible for enrollment. The CLARIFY (ProspeCtive observational LongitudinAl RegIstry oF patients with stable coronary arterY disease) registry is an international prospective observational longitudinal registry that has been previously described (2). Briefly, stable coronary artery disease (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 up to 5 years.

The REDUCE-IT selection criteria were applied to CLARIFY patients. Key inclusion criteria included statin-treated men or women age ≥45 years with either established cardiovascular disease or age ≥50 years with diabetes mellitus in combination with at least one additional risk factor for cardiovascular disease, with triglycerides levels

≥135mg/dL and <500 mg/dL, and low density lipoprotein (LDL)-cholesterol >40mg/dL 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 greater than 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 with missing triglycerides dosage) allowing evaluation of eligibility. Overall, 15.5% (3738/24146 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=13791) had triglyceride levels<135mg/dL, 0.6% (n=144) had levels≥500mg/dL, and 47.0% (n=11 342) of patients did not fulfil the LDL-cholesterol inclusion criteria (12.6% [n=3034] had LDL-cholesterol≤40mg/dL and 34.4% [n=8308]>100 mg/dL).

Our study demonstrates that in a large international registry, 15.5% of patients with stable coronary artery disease met the REDUCE-IT inclusion criteria, thus being eligible for treatment with icosapent ethyl to reduce cardiovascular risk. The most frequent reasons for non-eligibility were triglycerides<135mg/dL (57.1%) and LDL-cholesterol>100mg/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 in a prevalence of 6.3% in

American adults. (4) Therefore, 15.5% of 16.5 million represent 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.

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Figure Legend

Figure: Frequency of the various non-inclusion criteria ranked by descending order of frequency. *In the CLARIFY registry, 15.5% (3738/24146 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=13791) had triglyceride levels<135mg/dL, 0.6% (n=144) had levels≥500mg/dL, and 47.0% (n=11 342) of patients did not fulfil the LDL-cholesterol inclusion criteria (12.6% [n=3034] had LDL-cholesterol≤40mg/dL and 34.4% [n=8308]>100 mg/dL).*

Relationship with industry:

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