PCSK-9 Inhibitor (Evolocumab) Plus Statins Decreases MI, Stroke, MALE, And Death More In PAD And Recent MI Patients Than Others: From A FOURIER RCT Trial Subanalysis: What LDL-C Level Should We Aim For

Background

FOURIER trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk)

FOURIER was a randomized trial of evolocumab versus placebo in 27,564 patients with atherosclerotic disease on statin therapy followed for a median of 2.2 years.

The primary end point was a composite of cardiovascular death, myocardial infarction, stroke, hospital admission for unstable angina, or coronary revascularization.

The key secondary end point was a composite of cardiovascular death, myocardial infarction, or stroke. An additional outcome of interest was major adverse limb events defined as a composite of amputation or urgent peripheral vascular revascularization for ischemia.

Peripheral Arterial Disease

Investigated the efficacy and safety of evolocumab in patients with PAD as well as the effect on major adverse limb events.

Patients were identified as having PAD at baseline if they had intermittent claudication and an ankle brachial index <0.85, or if they had a prior peripheral vascular procedure.

Three thousand six hundred forty-two patients (13.2%) had PAD
Evolocumab significantly reduced the primary end point consistently in patients with PAD (hazard ratio 0.79).

**Cardiovascular Efficacy With Evolocumab**

- In patients with PAD, evolocumab significantly reduced the primary end point by 21% and the composite of CV death, MI, or stroke by 27%.

**MALE Reduction With Evolocumab**

- Overall, evolocumab reduced the risk of MALE by 42%.

**Composite Outcome of MACE and MALE in Patients With PAD**

- Overall, evolocumab reduced the composite of MACE (CV death, MI, or stroke) or MALE (ALI, major amputation, or urgent revascularization) by 21%.

**Safety of Evolocumab in Patients With PAD**

- There were no differences in the incidence of adverse or serious adverse events in patients randomized to evolocumab as compared with placebo in patients with PAD.

- There was no excess of adverse events leading to treatment discontinuation (1.5% vs. 1.5%; hazard ratio 1.0).

- There was a consistent relationship between lower achieved low-density lipoprotein cholesterol and lower risk of two events (all deaths and TVR) that extended down to <10 mg/dL.
Evolocumab significantly reduced the primary end point consistently in patients with PAD (hazard ratio 0.79).

Because of their higher risk, patients with PAD had larger absolute risk reductions for the primary end point (3.5% with PAD, 1.6% without PAD) and the key secondary end point (3.5% with PAD, 1.4% without PAD).

Evolocumab reduced the risk of major adverse limb events in all patients (HR, 0.58; 95% CI, 0.38–0.88; P=0.0093) with consistent effects in those with and without known PAD.

**CONCLUSIONS**

Patients with PAD are at high risk of cardiovascular events, and PCSK9 inhibition with evolocumab significantly reduced that risk with large absolute risk reductions.

Moreover, lowering of low-density lipoprotein cholesterol with evolocumab reduced the risk of major adverse limb events.

Within the group of patients with prior MI, it was hypothesized that readily ascertainable features would identify subsets who derive greater clinical risk reduction with evolocumab.

The 22,351 patients with a prior MI were characterized on the basis of time from most recent MI, number of prior MIs, and presence of residual multivessel coronary artery disease (≥40% stenosis in ≥2 large vessels).

A total of 8402 patients (38%) were within 2 years of their most recent MI.

In a multivariable-adjusted model more recent MI, multiple prior MIs, and residual multivessel coronary disease remained independent predictors of cardiovascular outcomes, with adjusted hazard ratios (HRs) for the primary end point of 1.37, 1.78 and 1.39.

The relative risk reductions with evolocumab for the primary end point were greater in these high-risk subgroups and were 20% for those with more recent MI.

In the placebo arm, compared with patients with a remote MI, those with a recent MI were at significantly higher risk of the primary end point (3-year Kaplan-Meier rate, 16.0% versus 14.0%).
The relative risk reductions with evolocumab for the primary end point were greater in these high-risk subgroups and were 20% for those with more recent MI.

The relative risk reductions with evolocumab for the end point of CV death, MI, or stroke were greater in these high-risk subgroups and were 24% for those with more recent MI.

CONCLUSIONS: Patients closer to their most recent MI, with multiple prior MIs, or with residual multivessel coronary artery disease are at high risk for major vascular events and experience substantial risk reductions with low-density lipoprotein cholesterol lowering with evolocumab.

How low should we go?

LDL Targets – constantly changing…….

How low should we go?
Clinical studies with PCSK9 inhibitors had either no restrictions on the absolute achieved LDL-C level or had a lower limit of <15 mg/dl in 1 case or <25 mg/dl in 2 cases. Because of the anticipated extreme reductions in LDL-C, regulatory agencies required enhanced monitoring of treatment-emergent adverse events. In pooled analyses from phase II and IIIA trials, treatment with fully human monoclonal anti-PCSK9 antibody lowered LDL-C levels to <25 mg/dl in 37.0% of alirocumab-treated participants and 26.0% (773 of 2,976) of evolocumab-treated patients. Levels of LDL-C <15 mg/dl were reported in 9.4% of alirocumab-treated participants. Neurocognitive events were recorded as delirium (including confusion), cognitive and attention disorders and disturbances, dementias and amnestic conditions, disturbances in thinking and perception, and mental impairment disorders. Although differences were suggested in the initial phase III trials—1.6% for evolocumab versus 1.5% for placebo (p = not significant)—these dissipated after larger numbers of patients were studied. In a substudy of FOURIER, there were no group differences in the spatial working memory strategy index of executive function (primary endpoint) or in working memory or psychomotor change (secondary endpoint). These findings are supported by a Mendelian randomization study in which LOF variants in PCSK9 were not associated with impairment in tests of verbal memory.

Fat-soluble vitamin concentrations (A, D, E, and K) and steroid hormones were measured as part of the prespecified safety analysis in phase II trials with PCSK9 inhibitors. Data from 52-week double-blind, controlled trials did not demonstrate changes in levels of fat soluble vitamins (A, D, E, or K), serum adrenocorticotropic hormone ratio, or sex steroids. In FOURIER, the reduction in the primary and secondary composite endpoints was linearly related to the achieved LDL-C concentration. In a post hoc analysis of FOURIER patients, 5% (n = 1,335) achieved LDL-C levels <15 mg/dl. In this subgroup, there were no associations between achieved LDL-C concentrations and predetermined safety events. In FOURIER, the reduction in the primary and secondary composite endpoints was linearly related to the achieved LDL-C concentration. In a post hoc analysis of FOURIER patients, 5% (n = 1,335) achieved LDL-C levels <15 mg/dl. In this subgroup, there were no associations between achieved LDL-C concentrations and predetermined safety events.

Thank you!