Acute arterial events across all vascular territories in the FOURIER trial

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Background: In the FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Patients With Elevated Risk) trial, adding the PCSK9 inhibitor evolocumab to statin therapy reduced low-density lipoprotein cholesterol (LDL-C) and cardiovascular risk. Although atherosclerotic coronary, cerebrovascular, and peripheral vascular events share a related pathobiology, the effect of aggressive LDL-C lowering with PCSK9 inhibition on the risk of acute arterial events across all three vascular beds is not well-described.

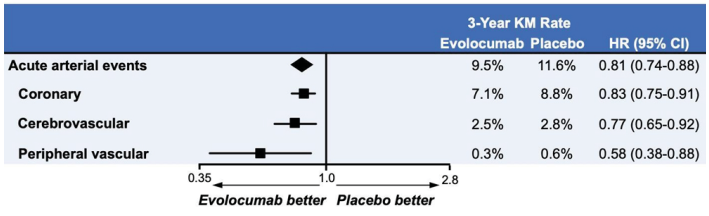
Purpose: To assess the efficacy of evolocumab on acute arterial events in all vascular territories including coronary, cerebral, and peripheral vascular beds.

Methods: In the FOURIER trial, patients (n=27,564) with stable atherosclerotic cardiovascular disease and LDL-C $\geq$70 mg/dL on a statin were randomly assigned to evolocumab versus placebo and followed for a median of 2.2 years (1.8–2.5). Acute arterial events were defined as a composite of coronary (coronary heart disease [CHD] death, myocardial infarction [MI], or urgent coronary revascularization), cerebrovascular (ischemic stroke, transient ischemic attack [TIA], or urgent cerebral revascularization), or peripheral vascular (acute limb ischemia, major amputation, or urgent peripheral revascularization) events. Cox proportional-hazard models were used to assess the efficacy of evolocumab on these outcomes. Landmark and total event analyses were also done.

Results: Of the 2,210 first acute arterial events occurring during follow-up, 74% were coronary, 22% were cerebrovascular, and 4% were peripheral vascular. Evolocumab reduced the risk of a first acute arterial event by 19% (HR 0.81, 95% CI 0.74–0.88; P<0.001), with significant individual reductions in acute coronary (HR 0.83; 95% CI 0.75–0.91; P<0.001), acute cerebrovascular (HR 0.77; 95% CI 0.65–0.92; P=0.004), and acute peripheral vascular (HR 0.58; 95% CI 0.38–0.88; P=0.01) events (Figure, top). The magnitude of the risk reduction with evolocumab tended to increase over time, with a 16% reduction (HR 0.84; 95% CI 0.75–0.96) in the first year followed by a 24% reduction (HR 0.76; 95% CI 0.67–0.85) thereafter (Figure, bottom). There were 3,780 total acute arterial events (first plus recurrent), with a 22% reduction with evolocumab (incidence rate ratio [RR] 0.78; 95% CI 0.70–0.87). Evolocumab prevented 496 total acute arterial events as compared to 222 first events.

Conclusions: The addition of the PCSK9 inhibitor evolocumab to statin therapy reduced the risk of acute arterial events across all vascular territories with a robust effect over time. These findings indicate a pan-vascular impact of aggressive lipid-lowering therapy on these acute and clinically meaningful events.

Efficacy of evolocumab on acute arterial events across all vascular territories



Landmark analyses