

EDITORIAL COMMENT

The Cat Has 9 Lives, Until it Dies*



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The identification of the proprotein convertase subtilisin-kexin type 9 (PCSK9) as a sterol-regulated autocatalytic enzyme in 2003 and its role in regulating the cell surface expression of the low-density lipoprotein receptor (LDLR) represents a seminal discovery in cell and molecular biology (1). This led to the identification, by positional cloning, of rare mutations within the PCSK9 gene that cause familial hypercholesterolemia (FH) (2). Insight on the mechanism by which PCSK9 bind the LDLR and chaperons it to a lysosomal degradation pathway allowed the identification of gain of function mutations in PCSK9 that cause FH (3). In a remarkable analysis of the ARIC (Atherosclerosis Risk in Community) cohort, Cohen et al. (4) found that loss of function variants in PCSK9 are associated with lifelong reductions in low-density lipoprotein cholesterol (LDL-C) and protection against atherosclerosis. The molecular basis of the PCSK9=LDLR interaction was elucidated by examining the crystal structure of a complex between the epidermal growth factor-like domain of the LDLR and PCSK9 (5). Blocking this interaction proved challenging; to date, no small molecules have been found to block this interaction, and monoclonal antibodies (mAb) were developed for this purpose. Evolocumab and alirocumab are fully human mAb that block PCSK9 from interacting with the LDLR and allow for the recycling of the LDLR on the cell membrane for uptake of apolipoprotein B-containing lipoproteins, especially LDL.

It is well known that statins increase PCSK9, an apparently unavoidable consequence of the regulation of the PCSK9 gene by sterol responsive element binding protein-2 (6). This explains why increasing the statin dose is not associated with a proportional reduction in LDL-C, but with an exponentially blunted dose-response relationship. Thus, the use of PCSK9 inhibitors have shown a remarkable synergy when used on a background of statin therapy. The first large, placebo-controlled randomized clinical trial of a PCSK9 mAb examined the effect of evolocumab in the FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) study. In this trial, 27,564 patients with stable CAD were randomized to evolocumab 140 mg administered subcutaneously every 2 weeks or placebo in patients on maximally tolerated dose of statin and an LDL-C >70 mg/dl (1.8 mmol/l). After a median of 2.6 years, the LDL-C was reduced by 59% and the primary combined endpoint of cardiovascular death, nonfatal myocardial infarction, strokes, hospitalization for unstable angina, and coronary revascularization was significantly reduced (hazard ratio [HR]: 0.85; 95% CI: 0.79 to 0.92; $p = 0.0001$) (7).

In parallel, the ODYSSEY group examined the effect of the PCSK9 mAb alirocumab on clinical outcomes in high-risk patients. The ODYSSEY OUTCOMES trial—a multicenter, double-blind study—included 18,924 patients from 57 countries, and randomized patients who had been hospitalized in the previous 1 to 12 months for an acute coronary event and met a specific threshold of LDL-C (or non-high-density lipoprotein cholesterol or apolipoprotein B) and were receiving high-intensity statin therapy, at maximally tolerated dose to alirocumab, or placebo. After an average of 2.8 years of follow-up, the group found a decrease in both the primary outcome of composite death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, and unstable angina requiring hospitalization (HR: 0.85; 95% CI: 0.78 to 0.93), as well as

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a modest reduction of all-cause mortality (HR: 0.85; 95% CI: 0.73 to 0.98) compared with placebo, which proved to be nominally significant ($p = 0.026$) (8).

These studies added considerable support to the CTT (Cholesterol Treatment Trialists') Collaborators meta-analysis of statin trials showing that a reduction in LDL-C level translates into a reduction in major coronary events, strokes, coronary revascularization, and major vascular events and that "lower is better" (9). The PCSK9 inhibitor trials now suggest that "lowest is best" with regards to LDL-C. National cholesterol treatment guidelines have now incorporated these findings in their recommendations (10,11).

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With this background, in this issue of the *Journal*, the ODYSSEY group now report a pre-specified analysis, ODYSSEY Events (12), which takes the atypical, and perhaps controversial, path of analyzing recurring events, as well as the correlation between nonfatal events within a patient and a fatal event. The authors applied a joint frailty model, allowing for multiple nonfatal cardiovascular events within individual patients and assessing for possible censoring of the nonfatal event process by death. The patients enrolled in the ODYSSEY OUTCOMES trial were encouraged to remain on the assigned randomized therapy even after a first reported nonfatal event.

Overall, there were 3,064 first events and 5,425 total events in ODYSSEY, and 190 fewer first and 385 fewer total nonfatal events with alirocumab versus placebo (HR: 0.87; 95% CI: 0.82 to 0.93) and death (HR: 0.83; 95% CI: 0.71 to 0.97) with a strong association between nonfatal and fatal event risk. Furthermore, in a post-hoc analysis, they found that two-thirds of this absolute event reduction came from patients who had an LDL-C equal or above 100 mg/dl (2.6 mmol/l).

One must keep in mind some important caveats. First and foremost, to analyze recurrent events in a clinical trial is atypical but, in the present case, very informative. The authors argue that this helps us measure the total clinical impact to the patient. As an adjunct to the primary study based on first events only, which was positive, this pre-specified analysis does indeed provide us with data that further guides us in assessing the clinical impact alirocumab may have on our patients' outcomes.

Second, the study uses a model that not only allows the possibility that patients may have multiple nonfatal events, but also takes into account the potential censoring of nonfatal outcomes by death. This is performed by first applying a joint semiparametric model that allows for multiple nonfatal cardiovascular events within a given patient, simultaneously

assessing and adjusting for possible informative censoring of the nonfatal event process by death. They then analyzed the association between nonfatal events and death. They argue that if the risk of nonfatal events is associated with the risk of death, then this confirms that the deaths did indeed censor nonfatal events that would have occurred, thus causing noninformative censoring. As they found that there was a positive association, albeit with the limitation that there may have been baseline characteristics that were not included in the pre-specified or post hoc models, which may have partially driven the association between the two, they conclude that there was indeed some censoring, and therefore the assumption that death censored nonfatal events is correct.

Third, as this is a study measuring the modification of the impact of the disease on the patients' experience, it is important to note that the different events that form the totality of the composite outcome are not all equal. All cardiovascular events are not the same. Stafinski et al. (13) tried to examine this issue by assigning a weight to events on a scale from 1 to 10, with death having a score of 10, based on patients' perception of the severity of these events. It would be interesting to perform an analysis with a weight given to each individual type of event in ODYSSEY Events, to measure the impact of these events on patients. It is interesting, however, that they did perform the analysis excluding ischemia-driven coronary revascularization and hospitalization for congestive heart failure and found that these events had a minimal impact on the results.

Finally, this analysis should be included in an economic analysis. Such a dramatic reduction in nonfatal events on alirocumab should have an impact on health care costs. To conclude, ODYSSEY Events is a very positive study that reinforces the role of PCSK9 inhibitors in the treatment of patients post-acute coronary syndrome who have high LDL-C despite maximal statin therapy. Although the study does have some acknowledged limitations, it provides a very encouraging signal that should prompt us to strongly consider the use of PCSK9 inhibitors in patients, especially in the subset who have an LDL-C of 100 mg/dl (2.6 mmol/l) and above despite maximal statin therapy.

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