John Witucki, PharmD 04 August 2017

Sabatine MS, Giugliano RP, Keech AC, et al.

Evolocumab and clinical outcomes in patients with cardiovascular disease

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Background and Overview	

Background	• High low-density lipoprotein cholesterol (LDL-C) is a long-established, modifiable risk factor for cardiovascular disease (CVD)
	• Statins have been extensively used in the past, not only for their cholesterol reduction capabilities, but also for their cardiovascular benefit.
	  o Many patients are unable/unwilling to take statins because of the possibility of myalgias, which severely limits their maximal use in patients that may greatly benefit
	• Previous studies:
	  o PROVE IT-TIMI 22 and TNT
	  ▪ Suggested that aiming for LDL-C targets led to significant reductions in major cardiovascular events
	  ▪ Showed that more intensive statin regimens lowered LDL-C from 100 mg/dL to 70 mg/dL
	  o IMPROVE-IT
	  ▪ Lowered LDL-C from 70 mg/dL to 54 mg/dL and showed significantly reduced cardiovascular events
	  o GLAGOV
	  ▪ Showed that continued CV benefit can be seen as LDL-C is reduced even to 20-25 mg/dL
	• Proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors are an emerging class of medications that have been shown to decrease LDL-C levels by 60%
	  o The LDL receptor binds LDL-C in the circulation and transports it into the cell, out of the bloodstream. Once this is complete, the receptor cycles back to the membrane to repeat this process.
	  o When PCSK9 is bound to the LDL receptor, the receptor is not recycled after delivering the LDL-C into the cell, and cannot return to the cell membrane.
	  o Thus, inhibiting PCSK9 would allow more of the receptors to be recycled, providing greater reductions in circulating LDL
	• In the past, marginal CV benefit has been shown when adding additional lipid-lowering therapies to statins. However, none of the other classes tested with a background of statin therapy has shown the potential to have as profound an effect on LDL-C as PCSK9 inhibitors

Objective	To test the clinical efficacy and safety of evolocumab when added to high-intensity or moderate-intensity statin therapy in patients with clinically evident atherosclerotic cardiovascular disease.
Methods	
Study Design	Randomized, double-blind, placebo-controlled, multinational clinical trial
Funding	Amgen pharmaceuticals

Inclusion Criteria	• Adults age 40-85
	• History of clinically-evident cardiovascular disease (MI, non-hemorrhagic stroke, systemic PAD)
	• At lease 1 major or 2 minor risk factors:
	  o Major
	  ▪ Diabetes (type 1 or 2)
	  ▪ Age 65-85
	  ▪ MI or non-hemorrhagic stroke within 6 months of screening
	  ▪ Additional diagnosis of MI or non-hemorrhagic stroke, excluding qualifying event
	  ▪ Current daily cigarette smoking
	  ▪ History of symptomatic PAD
	  o Minor
	  ▪ History of non-MI-related coronary revascularization
	  ▪ Residual CAD with $\geq$40% stenosis in $\geq$2 large vessels
	  ▪ Most recent HDL-C <40 mg/dL (men) and <50 mg dL (women)
	  ▪ Most recent hsCRP >2.0 mg/dL
	  ▪ Most recent LDL-C $\geq$130 mg/dL or non-HDL-C $\geq$160 mg/dL
	  ▪ Metabolic syndrome
	• Most recent fasting LDL-C $\geq$70 mg/dL or non-HDL-C $\geq$100 mg/dL during screening after $\geq$2 weeks of stable lipid lowering therapy

Exclusion Criteria	• MI or stroke within 4 weeks of randomization • NYHA class III or IV, or last known LVEF <30% • Known hemorrhagic stroke at any time • Uncontrolled tachycardia • Planned or expected cardiac surgery or revascularization within 3 months after randomization • Uncontrolled HTN • Use of CETP inhibition treatment, mipomersen, or lomitapide within 12 months prior to randomization. Fenofibrate therapy must be stable for at least 6 weeks prior to final screening at a dose that is appropriate for the duration of the study in the judgement of the investigator. Other fibrate therapies are prohibited. • Prior use of PCSK9 inhibition treatment other than evolocumab or use of evolocumab <12 weeks prior to final lipid screening • Untreated or inadequately treated hyperthyroidism or hypothyroidism • Active liver disease or hepatic dysfunction • Recipient of any major organ transplant • Personal or family history of hereditary muscular disorders • LDL or plasma apheresis within 12 months prior to randomization • Severe, concomitant non-cardiovascular disease that is expected to reduce life expectancy to < 3 years • CK >5 times the ULN at final screening • Known major active infection or major hematologic, renal, metabolic, GI, or endocrine dysfunction • Malignancy within the last 10 years • Received systemic drugs that have known major interactions with background statin therapy within 1 month prior to randomization • Currently or recently enrolled in another investigational drug/device study • Females of childbearing potential who have used or are not willing to use acceptable methods of birth control, or who are currently or soon-to-be pregnant/breastfeeding
Interventions	• Patients were assigned 1:1 to receive either evolocumab or placebo ○ Patients were then allowed to choose between 140 mg every 2 weeks or 420 mg monthly evolocumab or matching placebo • Groups were stratified according to final screening LDL-C, and region
Outcome Measures	• Primary endpoint – Composite of:cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization • Secondary endpoint – Composite of: cardiovascular death, MI, or stroke
Statistical Analysis	• Primary analysis was based on the time from randomized study-group assignment to the first occurrence of any element of the primary composite endpoint • If the primary endpoint achieved significance, then it would be tested against the secondary endpoint • Conducted based on an intention-to-treat basis • Safety evaluations included any patient who had received a single dose of study agent, and for whom post-dose data were available • Based on secondary endpoint, 1630 events would be required to provide 90% power to detect a 15% relative risk reduction
Results	

Baseline Characteristics	• 27,564 total patients
	  ○ Evolocumab: 13,784
	  ○ Placebo: 13,780
	• The two groups were very well matched
	• Patients were primarily male and average age was 63 years
	• The majority of included patients had a history of MI
	• Nearly 70% of patients were taking a high-intensity statin, as recommended

LDL	

	• At baseline, median LDL-C was 92 mg/dL
	  ○ Mean absolute LDL-C reduction of 56 mg/dL
	  ○ This reduction was maintained over time
	  ▪ At 48 weeks, 87% of patients had LDL-C <70 mg/dL

Efficacy Endpoints	

	• Primary endpoint occurrence
	  o Evolocumab: 1344 patients (9.8%)
	  o Placebo: 1563 patients (11.3%
	  o HR, 0.85; 95% CI, 0.79 to 0.92; :<0.001)
	• Secondary endpoint occurrence
	  o Evolocumab: 816 patients (5.9%)
	  o Placebo: 1013 patients (7.4%)
	• Risk reduction continued to increase over time
	• The benefits were consistent across all quartiles of baseline LDL-C levels
	• The benefits were consistent, regardless of intensity of statin therapy, regardless of ezetimibe therapy, and with both the bi-weekly and monthly dosing regimens.

Safety Endpoints	

	• No significant between-group differences in:
	  o Overall rates of adverse events
	  o Serious adverse events
	  o Adverse events thought to be related to the study agent and leading to discontinuation of the study regimen
	• Injection site reactions were rare, but more frequent with evolocumab (2.1% vs. 1.6% placebo)

Conclusions and Discussion	
Discussion	• The addition of evolocumab to statin therapy significantly reduced the risk of CV events • The translation of reductions in LDL-C levels into cardiovascular clinical benefit requires time • 74 patients would need to be treated over a period of 2 years to prevent a CV death, MI, or stroke • The magnitude of benefit of evolocumab in reducing the risk of major coronary events, stroke, and urgent coronary revascularization is largely consistent with the benefit seen with statins • Limitations o Relatively short duration of follow-up may limit the number of adverse events
Application	• In the absence of guideline recommendations, this medication is reasonable to add in patients who would benefit from additional lipid lowering therapy. • This medication can also be considered in patients unwilling or unable to take statins. • Price will likely limit use for now.

References

1. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Eng J Med* 2017;376:1713-22.
2. Giugliano RP, Sabatine MS. Are PCSK9 inhibitors the next breakthrough in the cardiovascular field? *J Am Coll Cardiol* 2015;65:2638-51.
3. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004;350:1495-504.
4. LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med* 2005;352:1425-35.
5. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med* 2015;372:2387-97.
6. Nicholls SJ, Puri R, Anderson T, et al. Effect of evolocumab on progression of coronary disease in statin-treated patients: the GLAGOV randomized clinical trial. *JAMA* 2016;316:2373-84.