PEGASUS-TIMI 54 Subanalysis: Continuing $P2Y_{12}$ Inhibitor Therapy Beyond 1 Year After MI Robustly Reduces Ischemic Events

Written by Toni Rizzo

The PEGASUS-TIMI 54 trial evaluated the efficacy and safety of ticagrelor, a $P2Y_{12}$ receptor antagonist, in 21 162 patients who had a myocardial infarction (MI) event 1 to 3 years earlier. Patients were randomly assigned to treatment with ticagrelor 90 or 60 mg BID or placebo; all patients received aspirin. The primary efficacy end point was the composite of cardiovascular (CV) death, MI, or stroke at a median 33 months of follow-up. The primary safety end point was TIMI major bleeding. The investigators reported that both ticagrelor doses significantly reduced the rate of the composite end point compared with placebo [Bonaca MP et al. *N Engl J Med*. 2015].

Marc P. Bonaca, MD, Brigham and Women's Hospital, Boston, Massachusetts, USA, presented the results of a subanalysis of the PEGASUS-TIMI 54 trial that assessed the effect of ticagrelor on reducing atherothrombotic events in post-MI patients, based on the time from withdrawal of their previous $P2Y_{12}$ inhibitor therapy. The investigators hypothesized that patients withdrawn from $P2Y_{12}$ inhibition at or shortly prior to randomization would have a relatively high ischemic risk compared with patients who had survived event free on aspirin therapy alone for a prolonged period and therefore would have a more robust reduction in ischemic risk with ticagrelor therapy.

The patients were stratified at the time of randomization according to time from $P2Y_{12}$ inhibitor withdrawal: ≤30 days (n=7181), >30 days to 1 year (n=6501), and >1 year (n=5079). Patients taking placebo who recently stopped $P2Y_{12}$ inhibition (≤30 days) had a higher risk for major adverse cardiac events (9.9%; HR, 1.47; 95% CI, 1.12 to 1.93), as did those who had stopped therapy 30 days to ≤1 year previously (8.7%; HR, 1.28; 95% CI, 0.98 to 1.67), compared with patients who had stopped therapy >1 year previously (6.9%; P_{trend}=.0097).

The benefit of ticagrelor treatment was greatest among patients randomized to ticagrelor within 30 days of $P2Y_{12}$ inhibitor withdrawal even if MI was >2 years ago, with a 27% risk reduction for CV death, myocardial infarction, or stroke (Figure 1). Patients who started ticagrelor >30 days to 1 year from $P2Y_{12}$ withdrawal had a 14% reduced risk, while those who started ticagrelor >1 year after $P2Y_{12}$ withdrawal derived no benefit.

Figure 1. Reduction in Major Adverse Cardiac Events With Ticagrelor by Time From $P2Y_{12}$ Inhibitor Withdrawal

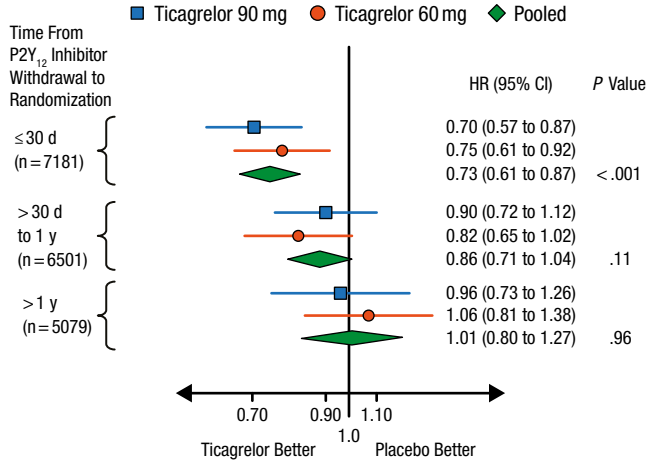

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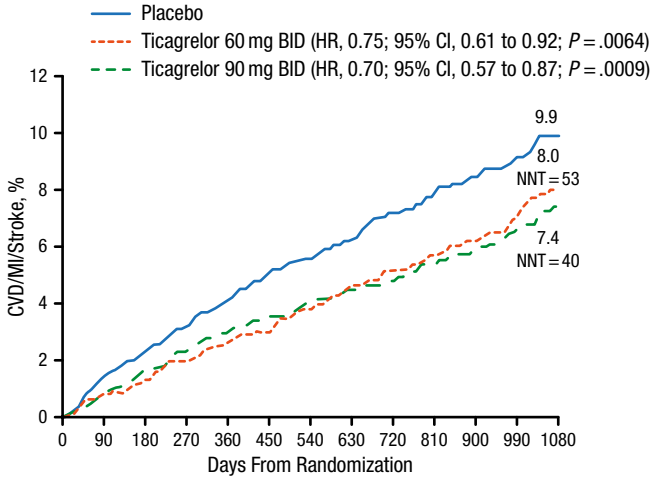
Figure 2. Major Adverse Cardiac Events With Ticagrelor in Patients With P2Y12 Inhibitor Withdrawal ≤30 Days From Randomization



CVD, cardiovascular death; MI, myocardial infarction; NNT, number needed to treat.
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At 3 years, patients treated with ticagrelor within 30 days of randomization had a significantly lower risk of ischemic events vs those treated with placebo (ticagrelor 90 mg, *P*=.0009; ticagrelor 60 mg, *P*=.0064; Figure 2).

The TIMI major bleeding rate was significantly higher with ticagrelor compared with placebo at 3 years.

These results showed that continuing $P2Y_{12}$ inhibition beyond 1 year after MI provided a robust benefit for reducing cardiac events. Reinitiation of $P2Y_{12}$ inhibition in patients who had survived without ischemic events on aspirin alone for >1 year did not appear to provide any benefit and increased the risk of bleeding. Ongoing research using clinical, biochemical, and genetic factors may provide further prospective data for defining the optimal patient populations for long-term therapy.

IMPROVE-IT Findings: Benefit of Ezetimibe Particularly Striking in Patients With Diabetes, With No Increase in New-Onset Diabetes Among Nondiabetic Patients

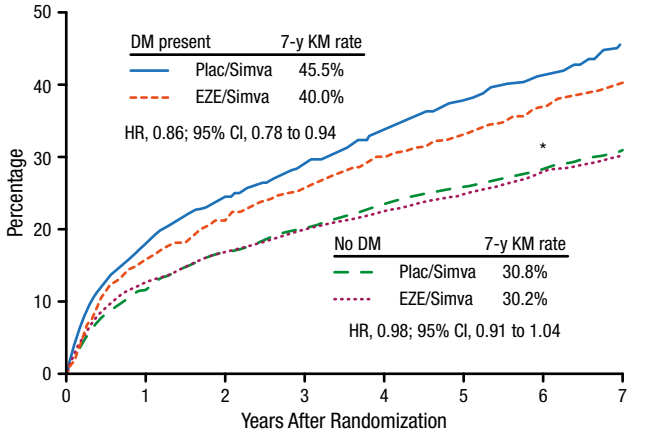
Written by Toni Rizzo

The IMPROVE-IT trial showed that the cholesterol absorption inhibitor ezetimibe, when added to statin therapy, reduced cardiovascular events in patients with acute coronary syndrome (ACS) [Cannon CP et al. *N Engl J Med*. 2015]. Among patients with diabetes, ezetimibe has been shown to reduce the levels of low-density lipoprotein cholesterol (LDL-C) and other lipids, and lower insulin resistance. Data from 2 meta-analyses suggested that intensive-dose statin therapy can increase the risk of new-onset diabetes mellitus (NODM) [Preiss D et al. *JAMA*. 2011; Sattar N et al. *Lancet*. 2010]. A pooled analysis comparing simvastatin alone vs ezetimibe plus simvastatin in patients without diabetes found both arms had small but significant increases in fasting glucose but there were no between-group differences [Toth P et al. *J Am Coll Cardiol*. 2015].

In the IMPROVE-IT trial, a total of 18 144 patients stabilized after ACS ≤10 days were randomized to ezetimibe 10 mg plus simvastatin 40 mg vs placebo plus simvastatin 40 mg for a minimum 2.5 years. A recent analysis of this trial, presented by Robert P. Giugliano, MD, SM, Brigham and Women's Hospital, Boston, Massachusetts, USA, examined the effects of ezetimibe vs placebo in a prespecified subgroup of patients with diabetes (n=4933) vs patients without diabetes (n=13 202). The primary end point was the composite of cardiovascular death, myocardial infarction (MI), documented unstable angina (UA) requiring rehospitalization, coronary revascularization (≥30 days), or stroke.

The intention-to-treat results demonstrated a significantly lower risk for the primary end point among patients with diabetes treated with ezetimibe plus simvastatin vs placebo plus simvastatin (40% vs 46%; HR, 0.86; 95% CI, 0.78 to 0.94) after 7 years (Figure 1). Among patients without diabetes, there was no significant difference in the primary end point between the treatment groups. Patients with diabetes had a significantly greater benefit from ezetimibe than those without diabetes (P_{Int}=.023).

Figure 1. Primary Composite End Point at 7 Years After Randomization (Intention-to-Treat)



Cardiovascular death, myocardial infarction, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 d), or stroke.

DM, diabetes mellitus; EZE, ezetimibe; KM, Kaplan-Meier; plac, placebo; simva, simvastatin.

*P_{int}=.023.

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Analysis of the individual cardiovascular end points in patients with diabetes treated with ezetimibe showed a significant reduction in MI (24% reduction, P_{Int}=.028) and ischemic stroke (39% reduction, P_{Int}=.031) but not in cardiovascular death (P_{Int}=.57), when compared with patients without diabetes who were treated with ezetimibe. There was no significant difference in the safety profile of ezetimibe when stratified by the presence of diabetes.

The IMPROVE-IT trial investigators also analyzed the occurrence of NODM among patients treated with ezetimibe. The results were presented by Michael A. Blazing, MD, Duke Clinical Research Institute, Durham, North Carolina, USA. NODM was defined as the initiation of diabetes medication or 2 consecutive fasting glucose levels ≥7 mmol/L. Patients with pre-existing diabetes were excluded from the analysis population. Pre-existing diabetes was defined as use of a hypoglycemic drug or elevated glucose at randomization (fasting glucose ≥7 mmol/L or nonfasting glucose ≥11.1 mmol/L).

After a mean follow-up of 75 months, a total of 1414 (13.3%) patients were diagnosed with NODM. The risk of