

## Editorial

# More news from IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial)

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The IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) reported a significant reduction in first primary endpoint (PEP) post-acute coronary syndrome (ACS) in patients (n=18,144) on ezetimibe + simvastatin compared with placebo + simvastatin.<sup>1</sup> The low-density lipoprotein cholesterol (LDL-C) levels in the combination group were significantly lower than in the monotherapy group (53.7 vs 69.5 mg/dl; 1.4 vs 1.8 mmol/l).

A recent analysis of IMPROVE-IT considered all PEP events [cardiovascular (CV) death, myocardial infarction (MI), stroke, unstable angina leading to hospitalization, coronary revascularization  $\geq 30$  days post-randomization].<sup>2</sup> The duration of the trial was a median of 6 years (25th, 75th percentiles: 4.3 and 7.1 years). Often trials only consider the first vascular event.<sup>2</sup> However, this may not represent the clinical situation, since patients with ACS may have recurrent events (except when the initial event is death). Assessing all events is an advantage in trials which last longer, as for IMPROVE-IT.

Not surprisingly, the *all events* analysis<sup>2</sup> of IMPROVE-IT is more impressive than the initial first

event only analysis.<sup>1</sup> There were 9,545 total PEP events [5,314 (56%) first events + 4,231 (44%) subsequent events]. Thus, the first event analysis did not include >4000 events. Total PEP events were significantly reduced by 9% with ezetimibe/simvastatin vs placebo/simvastatin [incidence-rate ratio (RR): 0.91; 95% confidence interval (CI): 0.85 to 0.97; p=0.007]. There were an additional 251 fewer events in the combination therapy group after considering *all events*. This should be added to the 170 first events prevented making a total of 421 fewer events in the combination therapy group. This translates into 11 total PEP events prevented with ezetimibe plus simvastatin compared with simvastatin monotherapy for every 100 patients treated for 10 years.

In the *all events* analysis<sup>2</sup> of IMPROVE-IT, the exploratory composite endpoint of CV death, MI or stroke was significantly reduced (RR: 0.88; 95% CI: 0.81 to 0.96; p=0.002). The reduction in total events was mainly driven by a decrease in non-fatal MI (RR: 0.87; 95% CI: 0.79 to 0.96; p=0.004) and non-fatal stroke (RR: 0.77; 95% CI: 0.65 to 0.93; p=0.005).

When the total number of PEP events were considered, 70.7% of the participants had no events, 16.6% had 1 event, 7.3% had 2 events and 5.4% had  $\geq 3$  events. The greatest number of events was 14 events in 2 patients; 13% of the 18,144 subjects had >1 PEP event.

Compared with patients with only 1 event, those with multiple events had more comorbidities at study

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entry, including hypertension and diabetes mellitus (DM), and more had previously experienced MI, angina or revascularization.

The *all events* analysis<sup>2</sup> of IMPROVE-IT also provides additional evidence for the LDL-C hypothesis (i.e. *lower is better*). The 1-month LDL-C levels were lowest in those without a subsequent PEP event and highest in those with >1 PEP event (mean 58.3 mg/dl for no event, 59.6 mg/dl for 1 event and 60.1 mg/dl for >1 event;  $p < 0.001$  for 3-way comparison). However, there was no difference when LDL-C levels in those with 1 PEP event were compared with those with >1 PEP event. An LDL-C of <70 mg/dl at 1 month was most common among subjects without a PEP event during the trial compared with subjects with 1 or >1 event ( $p < 0.001$  for 3-way comparison). However, there was no significant difference when comparing subjects with 1 PEP event with those who had >1 PEP event.

The *all events* analysis<sup>2</sup> of IMPROVE-IT suggests that sustained long-term lipid lowering treatment that achieves low LDL-C levels is necessary to achieve a continuous decrease in events. However, this *all events* analysis<sup>2</sup> also has limitations, as outlined by the authors. For example, after a first nonfatal event, many subjects discontinue their blinded study drug, which may influence subsequent events occurring off study drug. To address this limitation, an on-treatment analysis was performed<sup>2</sup> which showed findings consistent with the intent to treat analysis.

The IMPROVE-IT results<sup>1</sup> suggest a greater benefit for patients with DM in terms of event reduction. Furthermore, there was no increase in statin-associated new onset DM (NOD) in the combination therapy group despite achieving significantly lower LDL-C levels [<http://www.tctmd.com/show.aspx?id=130400>; abstract presented at the European Society of Cardiology meeting, London, August 2015]. There may be several reasons for this result.<sup>3</sup> Because there are risk factors that increase the risk of NOD, it would be of interest to assess the incidence of NOD in patients with different numbers of these risk factors. The rationale is that there is some evidence of beneficial effects of ezetimibe on insulin resistance.<sup>3</sup> As one predictor of statin-associated NOD is the duration of statin treatment, the duration of IMPROVE-IT (up

to 7.1 years) may prove to be an advantage. There is also evidence that lowering LDL-C levels with statins helps preserve kidney function.<sup>4</sup> This effect could extend to ezetimibe.<sup>5,6</sup> However, this renal effect of statins or ezetimibe is only likely to be seen in those with some degree of chronic kidney disease. Again, the duration of IMPROVE-IT could prove useful because there is evidence that statins may not protect kidney function in long-term studies.<sup>7</sup>

The cost effectiveness of ezetimibe will increase when this drug becomes a generic product in several countries within the next few years. This drug remains the only add-on to a statin with convincing event-based evidence.<sup>8</sup>

It is surprising that with this level of evidence the Endocrinologic and Metabolic Drugs advisory committee of the food and drug administration did not accept the recommendation of ezetimibe use as add-on to statin therapy in coronary heart disease patients [[http://www.medscape.com/viewarticle/855958?nlid=93603\\_2566&src=wnl\\_edit\\_medp\\_card&uac=182515FR&spon=2&impID=921006&faf=1](http://www.medscape.com/viewarticle/855958?nlid=93603_2566&src=wnl_edit_medp_card&uac=182515FR&spon=2&impID=921006&faf=1)]. In contrast, the European Society of Cardiology guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-Segment elevation recommend ezetimibe as the only add-on to statins.<sup>9</sup>

A survey of a large health care system (n=219,625 patients with ACS) concluded that 31.6% could qualify for ezetimibe if used outside of the strict IMPROVE-IT trial inclusions.<sup>10</sup> It follows that defining the role of ezetimibe in patients with ACS already taking high-intensity statins or those with statin intolerance is important. In this context, statin intolerance remains a clinically relevant problem.<sup>11</sup>

Undoubtedly there will be further sub-analyses of the IMPROVE-IT trial. Obviously, there is a need to consider the effect of additional events on quality of life and health expenditure. An economic analysis of IMPROVE-IT has been planned.

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