Risk of Major Adverse Limb Events with Ezetimibe versus Placebo in Addition to Statin Therapy: Insights from the IMPROVE IT Trial

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BACKGROUND

- Patients with peripheral artery disease (PAD) are at risk of developing progressive symptoms leading to revascularization as well as major adverse limb events (MALE) such as critical limb ischemia (CLI) and amputation.
- Two vascular specialists blinded to treatment allocation independently reviewed all adverse events to categorize limb outcomes, including critical limb ischemia (CLI) and related amputation, as well as progressive symptoms leading to lower extremity revascularization (worsening PAD).
- Total limb outcomes over follow up were compared by treatment groups using negative binomial regression and relative risks (RR) are presented.

RESULTS

- Of a total of 18,144 patients, there were 439 CLI or worsening PAD events occurring in a total of 326 patients.
- This included 397 events of worsening symptoms that occurred in 307 patients and 43 CLI events in 30 patients during follow up. Of the 1,005 patients who had PAD at baseline, there were a total of 108 had worsening PAD or CLI events that occurred in 108 patients.
- The risk of total events (CLI or worsening symptoms) was lower with ezetimibe versus placebo (RR 0.77, 95% CI 0.62 –0.96, p=0.018) with a consistent trend for both components (Figure 1).
- When evaluating the relationship of achieved LDL-C at 1 month post-randomization and the risk of first PAD event, there was a linear relationship extending to an LDL-C less than 25 mg/dL (p=0.0119, Figure 2).
- Patients with PAD had a greater frequency of CLI/worsening PAD events per patient over the 6 years of follow up (Figure 3) than the overall population.
- There was a similar pattern for benefit for CLI/worsening PAD in those patients who had known PAD at baseline overall (RR 0.77, 0.49 –1.22) and with first and subsequent events (Figure 3).
- The pattern of benefit was consistent for both first and subsequent events, with some patients experiencing up to six events (Figure 4).

CONCLUSION

Further lowering of LDL-C with ezetimibe on top of statin therapy in patients with ACS lowered the risk of adverse limb events over long-term follow up, including CLI and progressive disease leading to revascularization. These data support the importance of intensive lipid lowering therapies in improving limb outcomes in patients with atherosclerotic vascular disease. In addition, these data support LDL-C as a treatment target for optimizing outcomes in patients with peripheral arterial disease.

DISCLOSURE INFORMATION