

Title: Updated Literature Search to Accompany AHRQ Main Report “Treatment Strategies for Patients with Peripheral Artery Disease”

Authors: W. Schuyler Jones MD, Sreekanth Vemulapalli MD, Manesh R. Patel MD, Megan Chobot, Gillian Sanders Schmidler PhD, Rowena Dolor MD

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Description of updated literature search:

We performed an updated search of PubMed®, Embase®, and the Cochrane Database of Systematic Reviews for relevant English-language studies published between August 2012 and March 2015. The same search terms and criteria were used from the original search (dated August 2012). A total of 1,739 abstracts were screened by two investigators. After initial screening, 61 full-text articles were screened more carefully for inclusion, and 25 individual articles were considered relevant to the systematic review. Unlike the initial AHRQ report, no formal data abstraction, quality ratings, or evidence grading was performed for this updated literature evaluation but rather the 25 included articles were reviewed specifically to ascertain whether their findings would impact the original report’s conclusions and strength of evidence.

Results:

Seven new studies—4 randomized controlled trials (RCTs), 3 observational studies—evaluated the comparative effectiveness of antiplatelet agents in patients with PAD. A subgroup analysis from the TRA2°P-TIMI 50 study of 3,787 stable patients with intermittent claudication, abnormal ankle-brachial index, and/or prior peripheral revascularization showed consistent results in the PAD subgroup that vorapaxar was associated with a trend towards reduction of the incidence of cardiovascular death, myocardial infarction, or stroke and a significant reduction in limb events including hospitalization for acute limb ischemia. Another subgroup analysis from the PLATO study of 1,144 patients with peripheral artery disease being treated for acute coronary syndrome demonstrated consistent results in the PAD subgroup when compared with the overall study (i.e. trend towards reduction in cardiovascular death, MI, or stroke in patients treated with ticagrelor when compared with clopidogrel). These results are similar to our previous findings that antiplatelet agents are effective in patients with PAD.

A total of 13 studies—1 RCT, 12 observational studies—evaluated the comparative effectiveness of medical therapy, exercise training, endovascular revascularization, or surgical revascularization in patients with intermittent claudication. The single RCT, an assessment of the 18-month results of the CLEVER study, was published in 2014 and demonstrated that supervised exercise training and endovascular revascularization were superior to optimal medical therapy for peak walking time and quality of life measures. There was no significant difference in peak walking time or quality of life in patients treated with supervised exercise training and endovascular revascularization at 18 months. These results are generally consistent with the main AHRQ report, although the endpoints included in the original AHRQ report were typically measured at 3 and 6 months rather than 18 months.

There were 8 observational studies (no RCTs) that evaluated the comparative

effectiveness of endovascular and surgical revascularization in patients with critical limb ischemia (CLI). There was significant heterogeneity between studies and 3 studies involved a mixed population of patients with intermittent claudication and critical limb ischemia. None of the remaining 5 CLI observational studies included more than 500 subjects. In the largest study of 460 patients, Soga et al reported no difference in amputation-free survival, limb salvage, or overall survival between patients treated with endovascular and surgical revascularization. These findings were also consistent with the results of the main AHRQ report.

Conclusions:

There continue to be few direct comparisons between treatment modalities in patients with peripheral artery disease, and it is unlikely that these updated results would change the outcome of the original AHRQ report. The major contributions of the updated literature search to our original report were the subgroup analyses of antiplatelet agents (vorapaxar, ticagrelor). An additional search of upcoming and ongoing studies registered on clinicaltrials.gov demonstrated only two RCTs with >500 subjects [EUCLID study of clopidogrel vs. ticagrelor monotherapy in stable PAD (N=13,500); BEST-CLI study of endovascular vs. surgical revascularization in patients with CLI (N=2,100)]. Further research is required to identify the most effective treatment modalities for patients with PAD.