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Hiatt WR, Fowkes FG, Heizer G, et al. Ticagrelor versus clopidogrel in symptomatic peripheral artery disease. NEJM 2017; 376:32-40.

The recent study Examining Use of Ticagrelor in Peripheral Artery Disease is known as the EUCLID clinical trial. Investigators reported a dearth of evidence to support the use of a particular antiplatelet agent in patients with peripheral artery disease (PAD). The EUCLID study was a large, randomized, double-blind trial with 13,885 patients from 811 sites in 28 countries with symptomatic PAD. It compared the cardiovascular effects of antiplatelet agents, ticagrelor and clopidogrel, in patients who were at least 50 years old and had a previous lower limb revascularization or vascular studies indicating significant PAD (screening ankle brachial index of 0.80 or less or toe brachial index of 0.60 when the ABI value was 1.40 or more). The dosage for ticagrelor was 90 mg twice daily and clopidogrel 75 mg once daily. The median age of study patients was 66 years, and 72% were men; there was a median patient follow up of approximately 30 months. Although, the clinical trial was sponsored by AstraZeneca, the makers of ticagrelor, independent committees designed and managed the study. The investigators theorized that monotherapy with ticagrelor would be superior to therapy with clopidogrel in preventing cardiovascular death, myocardial infarction, or ischemic stroke in patients with symptomatic PAD. Results did not support their hypothesis of ticagrelor superiority.

EUCLID exclusion criteria included current or planned dual antiplatelet therapy (e.g., use of aspirin with an anti-platelet agent), treatment with long-term anticoagulant, or poor clopidogrel metabolizers as measured by genotype testing (3.8% of the initial 16,237 patients assessed for eligibility). The primary endpoint in the investigation was the first occurrence of any cardiovascular event including cardiovascular death, myocardial infarction or ischemic stroke. This endpoint occurred in 751 patients (10.8%) in the ticagrelor group and 740 patients (10.6%) in the clopidogrel group (hazard ratio, 1.02; 95% confidence interval ([CI], 0.92 to 1.13; P=0.65). The only significant difference between the groups in this category was rate of ischemic stroke which occurred in 1.9% of patients in the ticagrelor group versus 2.4% in the clopidogrel group. Secondary endpoint was acute limb ischemia leading to hospitalization and this was similar in the two groups at 1.7% (hazard ratio, 1.03; 95% CI, 0.79 to 1.33; P=0.85). Primary safety endpoint was major bleeding and it occurred in 1.6% (hazard ratio, 1.10; 95% CI, 0.84 to 1.43; P=0.49) of patients in both groups. There were fewer fatal bleeding events in the ticagrelor group (10 vs. 20) but there were more overall bleeding events in this group which lead to premature discontinuation of the drug. Ticagrelor was also stopped more frequently for complaints of dyspnea (4.8% in the ticagrelor vs. 0.8% in the clopidogrel group).

In conclusion, the EUCLID trial did not show ticagrelor superiority vs. clopidogrel in reducing the rate of cardiovascular events in the study patients with symptomatic PAD. The rate of major bleeding was similar in both groups and ticagrelor was discontinued more frequently than clopidogrel due to adverse effects including dyspnea and minor bleeding. Further investigations are warranted in the PAD population including studies in patients taking dual antiplatelet therapy, patients with established cardiac disease, patients with stable PAD, and patients who have undergone peripheral revascularization.