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Equal efficacy of clopidogrel versus ticagrelor as monotherapy in peripheral artery disease

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ABSTRACT A critical appraisal and clinical application of Hiatt H, Fowkes G, Heizer G, et al. Ticagrelor versus clopidogrel in symptomatic peripheral artery disease. *N Engl J Med.* 2017;376:32-40. doi: 10.1056/NEJMoa1611688.

Keywords: *peripheral artery disease, antiplatelet, ticagrelor, clopidogrel*

Clinical Context

The patient is a 55 year old male presenting to the emergency department two hours after a syncopal event just minutes after passing a bloody bowel movement. With a past medical history significant for peripheral artery disease (PAD) and myocardial infarction (MI) nearly 15 years prior, he had been on a daily regimen of aspirin and clopidogrel dual antiplatelet therapy. In the setting of a gastrointestinal bleed, these antiplatelet medications were held on admission to the inpatient floor until the patient was cleared by medical teams to continue therapy. The patient, appropriately concerned by his gastrointestinal hemorrhage, approved of this decision and showed minimal concern for complications regarding his PAD. When the patient reported a history of recent angioplasty of the right femoral artery, the primary team began to question the best approach for long-term medical management of his PAD after discharge.

Clinical Question

What is the most effective antiplatelet therapy regimen for secondary prevention of vascular events in the setting of symptomatic PAD?

Research Article

Hiatt H, Fowkes G, Heizer G, et al. Ticagrelor versus clopidogrel in symptomatic peripheral artery disease. *N Engl J Med.* 2017;376:32-40. doi: 10.1056/NEJMoa1611688

Related Literature

Literature review through the PubMed database was conducted using keywords “antiplatelet therapy,” “peripheral vascular disease,” “clopidogrel,” “aspirin,” and “ticagrelor.” The same keywords were used in a search on Uptodate. Both databases provided information based on five different primary double-blind trials comparing three antiplatelet monotherapy agents as well as dual

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antiplatelet therapy. The PubMed literature search also provided multiple review articles discussing the results and implications of these studies.

While medical management for coronary artery disease has been well studied, the standard of practice for PAD antiplatelet management is not as well developed. The CAPRIE trial in 1996 formed the basis of medical management of PAD when it supported monotherapy with clopidogrel over aspirin alone.[1] With a favorable efficacy/safety ratio, clopidogrel has stood as first line management for secondary prevention of atherothrombotic disease in the setting of PAD since the study was published.[2] However, many alternative options have been proposed since 1996. In 2006, the CHARISMA trial studied whether dual antiplatelet therapy consisting of clopidogrel with aspirin was more effective than aspirin alone, and found no additional benefit of dual antiplatelet therapy in preventing cardiovascular incident.[3] A third antiplatelet agent was introduced in 2010 when the PLATO trial suggested that the more potent P2Y12 inhibitor, ticagrelor, had better efficacy than clopidogrel in acute coronary syndrome.[4] These same two agents were compared in the setting of PAD three years later when Torngren et al. conducted a study suggesting the benefit of ticegrelor for peripheral endothelial function over that of no ADP inhibitors, clopidogrel, or prasugrel treatment.[5] Dual antiplatelet therapy with ticagrelor and aspirin had a larger reduction in major adverse cardiovascular events and major adverse limb events than aspirin alone in the setting of PAD after MI in the PEGASUS-TIMI 54 study published in 2016.[6]

These studies attempted to identify the best antiplatelet therapy in various clinical settings. It appears monotherapy with clopidogrel was the favored therapy, but there was reason to believe ticagrelor monotherapy could also be of benefit. However, none of them compared ticagrelor and clopidogrel in a head to head trial in preventing cardiovascular incidents in the setting of PAD until the EUCLID trial in 2016.[7-8]

Critical Appraisal

The EUCLID trial was a double-blind, parallel-group, end point-driven trial that randomly assigned 13,885 patients with symptomatic PAD to antiplatelet monotherapy with either ticagrelor 90 mg twice daily (n=6,930) or clopidogrel 75 mg once daily (n=6,955). The goal of the study was to show superiority of ticagrelor over clopidogrel in preventing primary end points of cardiovascular death, MI, or ischemic stroke and secondary endpoints including acute limb ischemia and revascularization. Major bleeding served as a safety endpoint. Patient recruitment occurred from December 2012 until March 2014.[9] Eligible patients were at least 50 years old and had an ankle-brachial index ≤ 0.80 or history of previous revascularization of the lower limbs. Exclusion criteria was clearly stated. Our patient fits enrollment criteria with his recent femoral angioplasty and is similar to a majority of the study's patients given his male gender, history of hypertension and hyperlipidemia, and previous aspirin and statin use. The study population included an adequate number of patients with prior myocardial infarction, similar to our patient. However, he is younger than the average age of 66 years.

Randomization occurred using interactive voice-response or Web-response systems to protect proper blinding. Similar groups were created with evenly distributed patient characteristics which eliminated the risk for selection bias.7 Since patients in the ticagrelor group were taking dosages twice per day, patients in the clopidogrel group took a placebo once a day as well as their daily clopidogrel so that they could remain blinded to their treatment regimen preventing the influence of detection bias. Patients were followed for a median of 30 months with follow up visits for all patients at two, four, and 12 months, and every 6 months after the first year to evaluate for occurrence of primary endpoints.

Primary efficacy end points occurred in 10.8% of the ticagrelor group and 10.6% of the clopidogrel group (hazard ratio 1.02; 95% confidence interval: 0.92-1.13, p=0.65). These findings were consistent among all subgroups except those who had undergone previous coronary or carotid revascularization or coronary stenting. In this subgroup, ticagrelor was favored. Considering primary end points separately, the rate of ischemic stroke was significantly lower in the ticagrelor group compared to the clopidogrel group. TIMI major bleeding, the primary safety end point, occurred in both groups at an equal rate.

Analyses were performed by the intention-to-treat principle and included all patients that had been randomized to a group regardless of adherence to protocol, adherence to group assignment, or continuation of participation. Limitations of the EUCLID trial are the possibilities for attrition bias. Both groups had a significant number of participants discontinue their study drug, withdraw consent, or lost to follow up. Following the intention to treat principle offers the possibility that inaccurate data was included in the

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analysis. Discontinuation of ticagrelor was more prevalent due to an increased incidence of bleeding and occurrence of dyspnea—a known adverse side effect of ticagrelor.

Of note, the EUCLID trial was supported by AstraZeneca, the biopharmaceutical business based out of the United Kingdom that is responsible for making ticagrelor. Many of the authors of the EUCLID trial report were employees of AstraZeneca. One of these employees also held equity interest in AstraZeneca. Many of the authors had received consulting fees from pharmaceutical companies or medical device companies. This connection with AstraZeneca offers the possibility of funding bias holding an influence in the paper's results. However, the results confirming clopidogrel as superior to ticagrelor negate the potential for this bias.

Clinical Application

The EUCLID trial shows that ticagrelol is not superior to clopidogrel in preventing cardiovascular incidents in the setting of pure PAD. However, it does suggest some possible superiority in patients with previous coronary or carotid revascularization or coronary stenting. This exception to the main conclusion of the study is significant as our patient fits this subgroup of patients. In fact, the authors of the EUCLID trial warn against the utilization of evidence gathered in the setting of pure PAD for the clinical scenario of CAD with associated PAD. The EUCLID trial focused on patients with pure PAD instead of CAD with concurrent PAD as seen in our patient and generally more often in the clinical setting.8 Therefore, its results are relevant only to a small portion of the atherosclerotic patient population. In the meantime, clopidogrel remains the standard of care for our patient.

The results of these studies must consider the cost-benefit ratio of new medications as the financial state of the patient can often play a role in management. Currently, clopidogrel costs less than ticagrelor making its cost-benefit ratio more desirable. Although less effective, aspirin is often used for PAD as it costs less than both ticagrelor and clopidogrel and may be the only possible therapy given a patient's socioeconomic status. Our patient was comfortable continuing his clopidogrel therapy upon discharge as this medication had an ideal cost-benefit ratio and was covered under his insurance plan. We felt the evidence available demonstrates this was a reasonable choice for this patient.

Learning points:

1. Clopidogrel monotherapy is the first line management of symptomatic peripheral vascular disease despite recent discussions regarding ticagrelor.
2. More research is needed to evaluate the utility of ticagrelor in the setting of CAD with concurrent PAD.
3. Critical appraisal will be vital in determining standard of care as many trials are underway regarding medical management of PAD in various patient subgroups.

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