FPIN's Clinical Inquiries

Dual Antiplatelet Therapy for Patients with Cardiovascular Disease

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Clinical Question

Do patients with established cardiovascular disease who do not qualify for coronary stenting or those at increased risk of cardiovascular disease benefit from dual antiplatelet therapy (aspirin plus clopidogrel)?

Evidence-Based Answer

Patients with established cardiovascular disease or risk factors (e.g., ischemic cerebrovascular disease, peripheral arterial disease, high risk of atherothrombotic disease) should receive dual antiplatelet therapy with aspirin plus clopidogrel, which confers additional benefit over aspirin alone. (Strength of Recommendation [SOR]: A, based on meta-analyses of randomized controlled trials [RCTs].) Dual antiplatelet therapy decreases the risk of myocardial infarction (MI) and ischemic stroke (number needed to treat [NNT] = 77 and 43, respectively) with no change in mortality. It also increases the risks of major and minor bleeding (number needed to harm [NNH] = 111 and 30, respectively). Dual antiplatelet therapy has more benefit in patients who have established cardiovascular disease compared with those who have only risk factors (NNT to reduce composite of MI, stroke, and cardiovascular death = 100; NNT for all-cause mortality = 59). (SOR: B, based on a post hoc analysis of RCTs.)

Summary

A 2017 Cochrane meta-analysis found that dual antiplatelet therapy reduced the risk of MI and stroke and increased the risk of bleeding compared with aspirin alone, but it did not reduce mortality in patients with high risk of or known cardiovascular disease.[1] Participants had known coronary artery disease, ischemic cerebrovascular disease, peripheral arterial disease, or a high risk of atherothrombotic disease (mean age: 60 to 65 years in most studies; 50% to 90% men). Patients were randomized to treatment with aspirin (70 to 325 mg daily) plus clopidogrel (75 mg daily in all but one RCT, which used 100 mg) vs. aspirin plus placebo for at least 30 days. Patients were followed for a median of 12 months. Dual antiplatelet therapy decreased fatal and nonfatal MI (relative risk [RR] = 0.78; 95% CI, 0.69 to 0.90; six RCTs; n = 16,175; NNT = 77) and fatal and nonfatal ischemic stroke (RR = 0.73; 95% CI, 0.59 to 0.91; five RCTs; n = 4,006; NNT = 43). There was no difference in cardiovascular mortality (RR = 0.98; 95% CI, 0.88 to 1.10; seven RCTs; n = 31,903) or all-cause mortality (RR = 1.05; 95% CI, 0.87 to 1.25; nine RCTs; n = 32,908). There was an increased risk of major bleeding (RR = 1.44; 95% CI, 1.25 to 1.64; 10 RCTs; n = 33,300; NNH = 111) and minor bleeding (RR = 2.03; 95% CI, 1.75 to 2.36; eight RCTs;

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n = 14,731; NNH = 30). Treating 1,000 patients with dual antiplatelet therapy vs. aspirin alone would prevent 13 MIs and 23 strokes over one year, but would cause nine major bleeds over 10.5 months and 33 minor bleeds over six months. The studies were rated as moderate quality except for those evaluating all-cause mortality, which were rated low quality, and significant publication bias was suspected for effectiveness and safety outcomes.

A post hoc subgroup analysis of a large RCT (N = 15,603) found that dual antiplatelet therapy marginally reduced the composite outcome of MI, stroke, and cardiovascular death in patients with known cardiovascular disease compared with those who had only risk factors (RR = 0.88; 95% CI, 0.77 to 0.998; $P = .046$; NNT = 100), but it increased mortality in patients with cardiovascular risk factors alone (NNH for all-cause mortality = 63; $P = .04$; NNH for cardiovascular mortality = 59; $P = .01$).[2] Participants were primarily men (mean age: 64 years); they were randomized to aspirin (70 to 162 mg daily) plus clopidogrel (75 mg daily) or aspirin plus placebo for a median of 28 months. Patients with known cardiovascular disease had a history of MI, angina, percutaneous intervention, coronary artery bypass grafting, transient ischemic attack, ischemic stroke, or symptomatic peripheral artery disease. Risk factors for cardiovascular disease included diabetes mellitus, ankle-brachial index less than 0.9, 70% or greater carotid stenosis, at least one carotid plaque, poorly controlled hypertension, hypercholesterolemia, smoking more than 15 cigarettes per day, or age at least 65 (men) or 70 (women) years. A higher percentage of patients in the treatment group discontinued the study drug.

Another large RCT (N = 12,562) found that dual antiplatelet therapy produced similar reductions in the composite outcome of death from cardiovascular causes, nonfatal MI, or stroke compared with aspirin alone at one and 12 months.[3] Participants were primarily men in their mid-60s who had unstable angina or non-ST elevation MI. They were randomized to aspirin (81 to 162 mg daily) plus clopidogrel (75 mg daily) or aspirin alone. Both therapies reduced the composite outcome at 30 days (RR = 0.79; 95% CI, 0.67 to 0.92) and 12 months (RR = 0.82; 95% CI, 0.70 to 0.95). Not all patients undergoing percutaneous intervention received dual antiplatelet therapy and the principal investigator changed the selection criteria after the first 3,000 patients were recruited.

Recommendations from Others

A 2012 clinical practice guideline from the American College of Chest Physicians recommends up to one year of dual antiplatelet therapy for patients with acute coronary syndrome or those undergoing elective percutaneous intervention with stenting.[4] It also recommends long-term single antiplatelet therapy for patients with established coronary artery disease.

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