Adding aspirin to clopidogrel increased bleeding without reducing recurrent ischemic vascular events in high-risk patients

Diener HC, Bogousslavsky J, Brass LM, et al. **Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial.** Lancet. 2004;364:331-7.

QUESTION

In high-risk patients who have had a transient ischemic attack (TIA) or recent ischemic stroke, is aspirin plus clopidogrel more effective than clopidogrel alone for reducing recurrent ischemic vascular events?

METHODS

Design: Randomized, placebo-controlled trial (Management of ATherothrombosis with Clopidogrel in High-risk patients [MATCH]).

Allocation: Concealed.*

Blinding: Blinded (clinicians, patients, {data collectors, data analysts, and outcome assessors}†).*

Follow-up period: 18 months of treatment.

Setting: 507 centers (stroke units and neurology departments) in 28 countries.

Patients: 7599 patients (mean age 66 y, 63% men) who had had a TIA or ischemic stroke ≤ 3 months before enrollment in addition to having ≥ 1 of previous stroke or myocardial infarction (MI), angina pectoris, diabetes mellitus, or symptomatic peripheral arterial disease within the previous 3 years. Exclusion criteria included age < 40 years, severe comorbid conditions, increased risk for bleeding (e.g., current peptic ulceration), major or vascular surgery, and contraindications to study medication.

Intervention: Aspirin, 75 mg once daily (n = 3797), or matching placebo tablet (n = 3802) for 18 months. All patients received clopidogrel, 75 mg once daily.

Outcomes: Composite outcome of ischemic stroke, MI, vascular death (including hemorrhagic death of any origin), or rehospitalization for an acute ischemic event (including unstable angina pectoris, worsening of peripheral arterial disease requiring therapeutic intervention or urgent revascularization, or TIA); and life-threatening or major bleeding.

Patient follow-up: 96% (intention-to-treat analysis).

MAIN RESULTS

The groups did not differ for the composite outcome (Table). The rates of life-threatening and major bleeding were greater in the aspirin group than in the placebo group (Table).

CONCLUSIONS

In high-risk patients who have had a transient ischemic attack or recent ischemic stroke, aspirin plus clopidogrel did not differ from clopidogrel alone for reducing recurrent ischemic vascular events and increased the risk for bleeding complications.

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*See Glossary.

†Information provided by author.

Aspirin plus clopidogrel vs placebo plus clopidogrel in high-risk patients who have had a transient ischemic attack or ischemic stroke‡

Outcomes at 18 mo	Aspirin plus clopidogrel	Placebo plus clopidogrel	RRR (95% CI)	NNT
Composite endpoint	16%	17%	6.4% (–4.6 to 16.3)	Not significant
			RRI (CI)	NNH (CI)
Life-threatening bleeding	2.6%	1.3%	97% (40 to 177)	80 (53 to 155)
Major bleeding	1.9%	0.6%	234% (109 to 434)	74 (53 to 115)

‡Composite endpoint = ischemic stroke, myocardial infarction, vascular death (including hemorrhagic death of any origin), or rehospitalization for an acute ischemic event. Abbreviations defined in Glossary; RRR, RRI, NNT, NNH, and CI calculated from data in article.

COMMENTARY

The results of the MATCH trial are consistent with the known effects of aspirin in patients with TIA or ischemic stroke (1) and with the effects of the combination of aspirin and clopidogrel in acute coronary syndromes (2). The MATCH trial compared aspirin plus clopidogrel with clopidogrel alone, rather than with aspirin alone. Statistical power for efficacy and safety were compromised because clopidogrel (the comparator) is more effective than aspirin (by about 9% in relative terms) and safer with respect to gastrointestinal hemorrhage (3). Furthermore, patients in the MATCH trial were not treated until a median of 15 days after their stroke, during which time at least 10% could have had another stroke (4); half of the patients had symptomatic small-vessel disease, which is associated with low risk for early recurrent ischemic stroke (5) and higher risk for intracranial hemorrhage (6); only a third of patients had symptomatic large artery atherothromboembolism, which is associated with high risk for early recurrent stroke (5); and a loading dose of clopidogrel was not used.

The MATCH trial highlights the effectiveness and safety of clopidogrel monotherapy (i.e., adding aspirin does not give any further benefit). However, trials are needed to evaluate the potential additional benefit and safety of the combination of aspirin and clopidogrel when given immediately after TIA and ischemic stroke (i.e., within 12 to 24 h, rather than 15 d), with a loading dose of clopidogrel (300 or 600 mg), in patients with symptomatic large artery atherothromboembolism (at high risk for early recurrent ischemic stroke), and for a short period of about 3 months (when the benefits are likely to be greatest and the cumulative risks for bleeding lessened).

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