Minor ischaemic stroke and antiplatelet drugs

Very little advantage from adding clopidogrel to aspirin

● **In a double-blind, randomised trial, adding *clopidogrel* to *aspirin* after a minor ischaemic stroke or transient ischaemic attack reduced the risk of recurrent ischaemic stroke, but had no demonstrated effect on mortality or disability. After one month of dual therapy, the incidence of ischaemic events (mainly strokes) fell from 5.8% with *aspirin* alone to 3.9% with dual therapy. Increasing the duration of *clopidogrel* administration to 3 months did not result in any greater efficacy whereas it increased the risk of haemorrhage.**

Low dose *aspirin* is the first-choice antithrombotic after an ischaemic stroke or a transient ischaemic attack (TIA), in the absence of prosthetic valves or heart disease predisposing to embolism (1). A randomised trial in 5170 patients showed that adding *clopidogrel* to *aspirin* (two antiplatelet drugs) for the 3 weeks following a stroke appeared to prevent a few recurrences, but had no demonstrated effect on mortality and did not increase the risk of major bleeding events (1).

Another trial of *clopidogrel* versus placebo in addition to *aspirin,* with a slightly different protocol, in particular a longer duration of dual therapy, has provided further information.

This double-blind randomised trial, the Point trial, included 4881 patients who had had a minor stroke with few sequelae (57% of patients) or a TIA with a high risk of recurrence (**a**)(2). This was a multi-centre trial, carried out largely in the USA and financed principally by public funds.

During the initial 12 hours following the ischaemic event, patients in the dual therapy group received a dose of *clopidogrel* 600 mg, and then beginning on the second day, a combination of *clopidogrel* (75 mg per day) plus *aspirin* (50 mg to 325 mg per day). In both groups, the choice of the *aspirin* dose was left up to investigators (2).

The trial was stopped after major bleeding had been noted on several occasions in the *clopidogrel* group, and because statistically significant efficacy results had been observed. About 93% of patients had at that time completed the 3 months of treatment planned in the protocol or had died, which allows the results to be taken into account, although with caution. About 30% of the patients in the two groups had discontinued at least one of the drugs before the end of the trial, which reduces the level of evidence (2).

During the 3 months of treatment, mortality was around 0.6%, with no statistically significant difference between the two groups (2). A new disability of at least moderate severity was reported in 13% of patients in both groups (2). The frequency of the primary outcome measure (a combination of ischaemic stroke, myocardial infarction or ischaemic vascular death) was reduced in the *clopidogrel* group: 5.0% versus 6.5% in the placebo group (p=0.02), with in particular a lower risk of recurrent ischaemic stroke: 4.6% versus 6.3% (p=0.01) (2).

The efficacy of dual therapy was only apparent during the first month of treatment: 3.9% of patients had an ischaemic event versus 5.8% in the placebo group (p=0.02). During the subsequent two months, 0.9% of patients had an ischaemic event, with no difference between the groups.

The frequency of major bleeding events was increased: 0.9% in the *clopidogrel* group versus 0.4% (p=0.02). The frequency of cerebral haemorrhage was around 0.25%, with no statistically significant difference between the two groups (2).

There was no statistically significant difference regarding an endpoint combining major ischaemic or haemorrhagic events (often chosen as the principal outcome measure in this type of trial), which occurred in 6.6% of patients (2).

In practice This trial confirms that after a minor stroke or TIA, increasing the antiplatelet effect by adding *clopidogrel* to *aspirin* for 3 to 4 weeks prevents some recurrent ischaemic strokes, but increases the risk of some major bleeding events. However, despite the inclusion of thousands of patients, this addition had no apparent effect on mortality or risk of disability. The advantage is tenuous, and it can be predicted that the harm-benefit balance will be less favourable if there is an increased risk of haemorrhage.

Beyond the month immediately following the stroke or TIA, the harm-benefit balance of adding *clopidogrel* seems unfavourable. *Aspirin*, used alone, remains the first-choice antithrombotic.

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***a-** A minor ischaemic stroke was defined as a National Institute of Health Stroke Score (NIHSS) of less than 3. This score ranges from 0 to 42, with a high score indicating severe impairment. An increased risk of recurrence after a TIA was defined as an ABCD 2 score greater than or equal to 4. This score is based on the patient's age, blood pressure, symptoms, presence or absence of diabetes, and duration of the TIA. It ranges from 0 to 7 (ref 1,2).*

Selected references from Prescrire's literature search.

1- Prescrire Editorial Staff "Ischaemic stroke. Addition of clopidogrel to aspirin to prevent recurrence?" *Prescrire Int* 2017; **26** (187): 274-275.
2- Johnston SC et al. "Clopidogrel and aspirin in acute ischemic stroke and high-risk TIA" *N Engl J Med* 2018; **379** (3): 215-225 + supplementary appendix 52 pages.