Editorial

Dual antiplatelet therapy for acute minor ischemic stroke or transient ischemic attack

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A renewed interest in dual antiplatelet (DAP) therapy for patients with acute ischemic neurological events manifested in the form of minor ischemic stroke or transient ischemic attack (TIA) has been recently observed. These events are well-known precursors of recurrent symptomatology (often a fatal stroke), as it has been repeatedly shown by a large number of studies, including the Oxford Vascular Study (OXVASC) (1,2). Although the period of risk often spans up to a few years or even life-long for patients with a cardioembolic cause, only in recent years it has been realized that during the very early period after a non-cardioembolic the risk is extremely high. This observation has led to increased awareness for these conditions—especially for TIAs—and a call for prompt action to manage the exact cause of the ischemic event and eventually prevent its recurrence.

Minor ischemic stroke and TIAs, as mentioned above, are multifactorial in origin thromboembolic events. As such they are usually the result of an overt or often transient arrhythmia not immediately apparent ("cryptogenic"), large artery-to-artery embolism like a symptomatic carotid or vertebral artery atherosclerotic stenosis, intracranial atherosclerosis or lacunar in origin, but also they can be a result of rare conditions including arterial dissections.

Because of their thromboembolic nature and the increased risk for recurrence, minor ischemic stroke and TIAs require proper antithrombotic therapy to decrease this risk. While arrhythmia and cardiac valve disease require anticoagulation, the other causes are thought to be sufficiently managed with antiplatelet therapy. Indeed, in the collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients, the risk for stroke in patients with a previous TIA or stroke with antiplatelet use is reduced by about 2.4% (3), which is generally accepted to be a relatively small figure. In the same group of patients, a larger benefit for all vascular events was seen for DAPs.

About two decades ago, the randomized second European Stroke Prevention Study (ESPS-2) in patients with TIAs, showed that compared to aspirin alone, the combination of aspirin and dipyridamole reduced further the likelihood of recurrent events (4), findings that sparkled further research on the role of DAPs in acute ischemic neurological events. Unlike dipyridamole, which is often not well tolerated because it causes headache, clopidogrel is better accepted. The obvious drawback of long-term DAP use is the significantly increased risk of bleeding.

In the landmark CHANCE trial in high-risk patients with TIAs or acute minor strokes, which first reported some 2 years ago, the early (≤24 h) use of a combination of aspirin and clopidogrel (clopidogrel at an initial dose of 300 mg, followed by 75 mg per day for 90 days, plus aspirin at a dose of 75 mg per day for the first 21 days) was significantly better than placebo plus aspirin (75 mg per day for 90 days), by reducing stroke from 11.7% in the aspirin group down to 8.2% in the clopidogrel-aspirin group [hazard ratio (HR) =0.68; 95% confidence interval (CI), 0.57-0.81; P<0.001] at 90 days of follow-up (5). In CHANCE the benefit was evident only during the first week or so and trial DAPs were prescribed for the first 3 weeks; it remains unknown if DAP use of shorter duration would retain their efficacy. Moderate or severe bleeding was reported to be rare and equally distributed in the two study groups (0.3%,

P=0.73). The CHANCE investigators concluded that the combination of clopidogrel and aspirin is superior to aspirin alone by reducing the risk of stroke in the first 90 days and does not increase the risk of hemorrhage in patients with TIA or minor stroke that can be treated within 24 h after the onset of symptoms.

The CHANCE investigators have just reported the 1-year results of their randomized trial, which were sustained throughout the study period (6). Stroke occurred in 10.6% of patients in the clopidogrel-aspirin group and 14.0% patients in the aspirin group (HR =0.78; 95% CI, 0.65-0.93; P=0.006, number needed to treat 30). Moderate or severe hemorrhage was rare (less than 0.5%, P=0.44) and was equally distributed in the two study groups. The CHANCE investigators concluded that the early benefit of DAPs (clopidogrel plus aspirin) in reducing the risk of subsequent stroke (relative risk reduction of 32% and absolute risk reduction of approximately 3.5%) persisted over the duration of 1-year of follow-up. This large relative risk reduction is attributed to the fact that a population of patients at very high risk for recurrence was recruited into the study.

The results of CHANCE are in full agreement with what reported by recent meta-analyses on this topic (7-10), with DAP therapy significantly reducing the risk of stroke compared to monotherapy (usually aspirin) alone. Several trials in these meta-analyses were not powered to show a difference, because of the small benefit with DAPs. This gain was evident in trials using DAPs for up to a month but also in the long-term; however prolonged use of DAPs in meta-analyses was associated with an increased risk of bleeding, including major and intracranial bleeding, trading-off not only the benefit attained by reducing stroke, but also the gain regarding the composite end-point of stroke, TIA, acute coronary syndrome, and all-cause mortality. Of note, the composite end-point of stroke, myocardial infarction and cardiovascular death was also reduced in CHANCE with DAP use.

The rationale of using DAPs is their different mechanism of action. As a result, DAPs are more effective than single agents. In a randomized-controlled trial, platelet aggregation and platelet-leukocyte aggregates were reduced in patients who were treated with DAPs (clopidogrel and aspirin) compared to patients on aspirin alone, at day 30 of treatment (P<0.001) (11). Also, in a subgroup analysis of CLAIR, performed in patients with ≥50% extracranial or intracranial internal carotid or middle cerebral artery stenosis by carotid duplex, transcranial Doppler, or magnetic resonance angiography with evidence of micro-embolic signals on transcranial Doppler, DAPs reduced micro-embolic signals in patients with TIAs and minor stroke (12). On day 7, the proportion of patients with ≥1 micro-embolic signals was 31% (9/29) with DAPs (clopidogrel and aspirin) and 53% (18/34) with aspirin alone (adjusted relative risk reduction 41.4%; 95% CI, 29.8-51.1; P<0.001). The median number of micro-embolic signals on day 7 was 0 with DAPs and 1.0 with aspirin alone (P=0.046).

Non-cardioembolic stroke is however a heterogeneous condition. In the SPS3 study in patients with a recent lacunar stroke, DAPs (clopidogrel and aspirin) did not significantly reduce the risk of recurrent stroke compared to aspirin alone, but significantly increased the risk of bleeding and death (13). A meta-analysis comparing single antiplatelet agents with placebo in lacunar stroke confirmed the adequacy of the former for secondary stroke prevention after lacunar stroke. However, DAPs non-significantly reduced ischemic stroke compared to single agents (RR =0.80; range, 0.62-1.02), based on three studies. The authors suggested DAP therapy not be used for long-term stroke prevention in lacunar stroke (14).

In a randomized-controlled trial in patients with acute large-artery atherosclerosis stroke, neurologic deterioration (within 1 week) and recurrent ischemic stroke (within 1 month) were less frequent in patients on DAPs compared with those on aspirin (3.52% *vs.* 9.78%; RR =0.69; 95% CI, 0.57-0.83; P<0.001 and 1.76% *vs.* 6.29%; RR =0.72; 95% CI, 0.61-0.96; P=0.006, respectively) (11). There was no additional benefit beyond 1 month and up to 6 months (15). Interestingly, only patients with posterior circulation and basilar artery strokes (and not those with anterior circulation, internal carotid or middle cerebral strokes) demonstrated clinical improvement at 6 months. Subgroup analysis of the CHANCE trial by stroke subtype is eagerly awaited (16,17). "Time is brain" (18), with very early surgery for symptomatic carotid artery stenosis being currently advocated (19), while DAP therapy is thought to confer clinical benefit in the setting of carotid endarterectomy by reducing postoperative stroke (20), therefore we see no contraindication if surgery or carotid stenting is contemplated, provided that these are performed on an expedited fashion. Interestingly, in CHANCE, DAP therapy reduced stroke only in male patients and in those who presented with a minor stroke or hypertension at the time of randomization (6), observations that should be confirmed by future trials. Additionally, patients with TIAs lost the initially reported benefit with DAP use during follow-up (5,6).

It is expected that future studies, like the platelet-oriented inhibition in new TIA and minor ischemic stroke (POINT) trial, will report on certain stroke subgroups, to better inform decision-making (21), taking also into account the higher incidence of intracranial atherosclerosis and also prevalence of genetic polymorphisms affecting the metabolism of clopidogrel in Chinese patients, as the CHANCE investigators have acknowledged (5). Cost-effectiveness analyses for DAP therapy are sparse. One study showed that early 90-day clopidogrel-aspirin DAP for acute TIA or minor stroke is highly cost-effective in China and that treatment with generic clopidogrel and aspirin would have been cost-saving (22).

In summary, a short course of DAP therapy given early in patients with acute minor ischemic stroke or TIA leads to a relative risk reduction of 32% and an absolute risk reduction of approximately 3.5% in reducing recurrent stroke, with a number needed to treat of 30. More trial information on this subject is required.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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