Low risk of rebound events after a short course of clopidogrel in acute TIA or minor stroke

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ABSTRACT

Objective: The combination of aspirin and clopidogrel is indicated after acute coronary events and possibly for a short period after TIA or minor ischemic stroke. Early discontinuation of clopidogrel results in a transient rebound increase in risk of recurrence in acute coronary syndromes, but there are no published data on any similar rebound effect in patients with TIA or stroke that might inform the design of clinical trials of aspirin and clopidogrel in the acute phase.

Methods: A 30-day course of aspirin and clopidogrel (both 75 mg daily) was given to high-risk patients with TIA or minor ischemic stroke seen acutely in the EXPRESS study clinic from April 1, 2002, to March 31, 2009. Clopidogrel was stopped after 30 days and aspirin continued. Recurrent events were ascertained at face-to-face follow-up.

Results: A total of 320 patients were prescribed a 30-day course of aspirin and clopidogrel acutely after TIA or minor stroke. There were 5 recurrent ischemic strokes and 7 TIAs during the aspirin and clopidogrel treatment period, but no strokes and 4 TIAs during the 30 days after stopping clopidogrel. A similar temporal trend in stroke risk was seen in the 487 patients prescribed aspirin alone in the acute phase, with 12 and 5 strokes in the equivalent time periods. The upper 95% confidence intervals of the observed 0% risk of stroke during the 30 days after stopping clopidogrel was 1.15% overall.

Conclusion: Although larger studies are required, our findings suggest there is unlikely to be a large rebound effect after discontinuation of a 30-day course of clopidogrel in acute TIA and minor ischemic stroke. However, planned trials of aspirin and clopidogrel in the acute phase after TIA or stroke should still follow-up beyond the cessation of clopidogrel treatment. *Neurology*® 2010;74:1891-1896

GLOSSARY

ACS = acute coronary syndrome; **CI** = confidence interval; **NIHSS** = NIH Stroke Scale; **N-STEMI** = non-ST-elevation myocardial infarction; **OXVASC** = Oxford Vascular study; **STEMI** = ST-elevation myocardial infarction.

Antithrombotic therapy is recommended after TIA and ischemic stroke. Addition of clopidogrel to aspirin reduces risk of recurrent events after acute coronary syndromes (ACS).¹⁻⁴ Given the high early risk of stroke following TIA and minor stroke,⁵ a short course of treatment with aspirin plus clopidogrel might also be beneficial. Current trial evidence is limited,⁶⁻⁹ but larger trials are planned.^{10,11} However, the optimal duration of dual treatment to prevent early recurrence without excessive increased bleeding risk is unknown. Premature discontinuation of clopidogrel after ACS is associated with a substantial rebound increase in risk of recurrent events in stented patients¹²⁻¹⁵ and probably also in patients who are not stented,¹⁵ and clinical guidelines were revised accordingly.¹⁶⁻¹⁸ Limited published data suggest that the risk of recurrent ischemic stroke is also increased after discontinuation of antiplatelet therapy in general after TIA or stroke,¹⁹⁻²¹ but there are no published data on any rebound effect following discontinuation of a short course of clopidogrel in this group. No unpublished data are avail-

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able from the CARESS Trial⁷ (personal communication, Hugh Markus, 2010), the Leicester trial⁸ (personal communication, Ross Naylor, 2010), or the FASTER pilot⁹ (personal communication, James Kennedy, 2010) because follow-up was not continued after discontinuation of trial treatment. In the absence of trial data, we sought to identify any rebound effect after discontinuation of a 30-day course of clopidogrel in consecutive patients treated with aspirin and clopidogrel after TIA or minor ischemic stroke in our population-based cohort study.

METHODS The methods of the Oxford Vascular study (OXVASC) and details of the EXPRESS study clinic have been reported previously.²²⁻²⁴ Briefly, the study population comprised all 91,000 individuals, irrespective of age, registered with 63 family physicians in 9 general practices in Oxfordshire, UK. Standard definitions of TIA and stroke were used.

This report concerns all patients with TIA or minor stroke referred to the EXPRESS study daily outpatient clinic during the first 7 years of OXVASC, from April 1, 2002, to March 31, 2009. Over 95% of patients with suspected TIA and minor stroke in our study population are referred directly to our study clinic by their family practitioner or from accident and emergency.²² The same antiplatelet treatment protocol after TIA or minor ischemic stroke was used throughout.

All patients were given aspirin if not already on antiplatelet therapy (300 mg loading and 75 mg daily), or clopidogrel if aspirin was contraindicated, and anticoagulation as required. In patients seen within 48 hours of their event or those seen later who were thought to be at particularly high early risk (ABCD score >4 or large artery etiology), clopidogrel (300 mg loading followed by 75 mg daily once daily) was given in addition to aspirin with a recommendation that it be stopped after 30 days and substituted with dipyridamole 200 mg twice daily. Brain imaging was required prior to starting combination antiplatelet treatment after a minor stroke to exclude cerebral hemorrhage. Patients with recent symptomatic gastrointestinal or other bleeding events, gastrointestinal or urologic malignancy, coagulation disorders, or other known severely increased tendency for bleeding were not given aspirin plus clopidogrel.²³

Patients were assessed by a study physician in the EXPRESS clinic in a standardized manner. Detailed data were collected on times and methods of first contact with medical attention after the presenting event. All patients were followed up by a research nurse or clinical research fellow after 1, 6, 12, 24, and 60 months and asked about new neurologic symptoms, medication compliance, and any bleeding that had required medical attention. All medication prescribed in the clinic or recommended to the family physician was recorded and data on prescription of all medications after the presenting TIA or stroke were obtained from the databases of the collaborating primary care practices.

Severity of stroke was assessed with the NIH Stroke Scale (NIHSS). Other vascular outcomes were also identified on follow-up. Acute coronary events were defined as ST-elevation myocardial infarction (STEMI) and non-ST-elevation myocardial infarction (N-STEMI) by using standard criteria.²⁵ Acute

peripheral arterial events were defined as ischemic events affecting a limb or organ other than the heart, brain, or eye.

Standard protocol approvals, registrations, and patient consents. The OXVASC study was approved by the Oxford Research Ethics Committee and we received written informed consent from all patients or assent from relatives.

Analysis. All patients with TIA or minor ischemic stroke referred to the EXPRESS clinic were included.

Baseline characteristics of patients started on aspirin and clopidogrel at clinic and those started on aspirin alone were compared by use of χ^2 test for categorical variables and a *t* test for continuous variables. Although it was recommended that clopidogrel be stopped after 30 days, some patients continued clopidogrel in addition to aspirin (deliberately or inadvertently) for longer before stopping. We therefore compared the risk of recurrent ischemic events during 30 days prior to discontinuation with that during the 30 days after discontinuation. In a sensitivity analysis, we restricted this comparison to those patients in whom the recommendation to stop clopidogrel at exactly 30 days had been adhered to. All analyses were performed with SPSS software version 15.0.

RESULTS Of the 952 patients with TIA or minor stroke seen in the EXPRESS clinic from April 1, 2002, to March 31, 2009, 522 (54.8%) presented with TIA and 430 (45.2%) with a minor stroke. Mean age was 71 years and 271 (29%) were ≥ 80 years. A total of 114 (12%) patients had a previous TIA and 105 (11%) had a previous stroke. At the time of assessment in the EXPRESS clinic, the median NIHSS score was 0 (interquartile range 0–1), 894 (94%) patients had a score of 3 or less, and 933 (98.1%) had a score of 5 or less.

A total of 338 (36%) patients were on antiplatelet treatment prior to their presenting event: 308 (91%) on aspirin alone, 8 (0.8%) on aspirin plus clopidogrel 75 mg daily, and 11 (1.2%) on aspirin plus dipyridamole. A total of 11 (1.2%) patients were on clopidogrel 75 mg alone and none were on dipyridamole alone prior to their event. Premorbid aspirin dose was 75 mg in 267 (87%) cases.

Following assessment in the clinic, 487 (51%) patients were treated with aspirin only and 320 (34%) with aspirin plus a short course of clopidogrel. The remainder of the results refer only to these 807 patients.

Baseline characteristics of the aspirin and clopidogrel and the aspirin-only treated groups are shown in table 1. There were no major differences in measured risk factors between the aspirin and clopidogrel and the aspirin-treated groups except a higher prevalence of hyperlipidemia, hypertension, and $\geq 50\%$ symptomatic carotid artery disease in the aspirin and clopidogrel group, as expected on the basis of our preferential use of combination treatment in higher-risk patients with large artery disease.

Table 1 Baseline characteristics of the aspirin and clopidogrel group and the aspirin-only group^a

	Aspirin + clopidogrel (n = 320)	Aspirin only (n = 487)	p
Age, y	70 (13)	71.7 (13)	0.17 ^b
Male sex	164 (51)	223 (46)	0.13
Prior TIA	31 (10)	58 (12)	0.36
Prior stroke	29 (9)	58 (12)	0.25
Prior angina	47 (15)	61 (13)	0.39
Prior MI	30 (9)	36 (7)	0.36
Prior PVD	15 (5)	21 (4)	0.86
Hypertension	182 (57) ^c	237 (49)	0.03
Hyperlipidemia	122 (38) ^d	124 (26) ^d	<0.0001
Cardiac failure	16 (5)	40 (8)	0.09
Diabetes	39 (12)	57 (12)	0.82
Antiinflammatory use	35 (14)	64 (15)	0.91
Venous thrombosis	13 (4) ^b	20 (4)	1.0
Post-event acid suppression	113 (35)	75 (15)	<0.0001
Smoking	0.36		
Never	134 (42)	228 (47)	
Ex-smoker	135 (42)	191 (40)	
Current smoker	51 (16)	68 (14)	
≥50% Symptomatic carotid stenosis	49 (15)	50 (10)	0.04
CEA for (≥50%) stenosis	19 (6)	17 (3.5)	0.11

Abbreviations: CEA = carotid endarterectomy; MI = myocardial infarction; PVD = peripheral vascular disease.

^a Data are n (%) and Fisher exact test unless stated otherwise.

^b † Test.

^c One case missing.

^d Two cases missing.

During the 30 days prior to stopping clopidogrel, there were 5 ischemic strokes (1.6%) and 7 TIAs in the aspirin and clopidogrel group. During the 30 days after stopping clopidogrel, there were no strokes and 4 TIAs. The upper 95% confidence interval (CI) of the observed 30-day stroke risk after discontinuation of clopidogrel was 1.15%. A similar temporal trend in stroke risk was seen in the 487 patients prescribed aspirin alone in the acute phase, with 12 and 5 strokes in the equivalent time periods (although aspirin was of course not stopped). The number of ischemic events in other arterial territories was small (table 2), such that the temporal trends in risk of all major acute vascular events were similar to those for stroke alone.

Aspirin and clopidogrel was prescribed in the EXPRESS clinic for 30 days, but 103 (32%) patients continued clopidogrel in addition to aspirin (deliberately or inadvertently) for longer before stopping. However, exclusion of these cases from the above analyses did not alter the findings. A total of 49 patients treated with aspirin and clopidogrel had

≥50% symptomatic carotid stenosis, of whom 19 subsequently had endarterectomy with a median time to carotid endarterectomy of 39 days (interquartile range 12–69). The upper 95% CI of the observed 0% stroke risk after discontinuation of clopidogrel in these 49 patients was 7.2%, so clinically significant stroke risk cannot be excluded. However, there were 4 TIAs during follow-up in this group, all of which occurred during the 30-day period on aspirin plus clopidogrel, with no events during the subsequent 30-day rebound period.

Patients and general practitioners were advised to start dipyridamole 200 mg twice daily following the 30-day course of clopidogrel. However, an audit of 50 consecutive cases showed that only 21 (42%) had ever started dipyridamole, and the median delay from stopping clopidogrel to starting dipyridamole was 49 days.

DISCUSSION We observed no rebound increase in risk of stroke during the 30 days after discontinuation of a short course of clopidogrel in TIA or minor stroke. The number of patients studied (n = 320) was not very large, but the upper 95% CI of the observed stroke risk after discontinuation of treatment was relatively low nevertheless (1.15%) and ours is the only published cohort of patients treated with aspirin plus clopidogrel acutely after TIA or stroke with follow-up after discontinuation of clopidogrel. Moreover, no data are available on the risk of vascular events after discontinuation of clopidogrel in patients randomized to aspirin and clopidogrel in the CARESS,⁷ Leicester,⁸ or FASTER pilot trials.⁹ Furthermore, our sample of 320 patients is actually larger than the aspirin and clopidogrel groups in all 3 of these trials combined, and our subset of 49 patients with ≥50% symptomatic carotid stenosis is equivalent to the aspirin and clopidogrel groups in the Leicester⁸ and CARESS⁷ trials, which were done in this specific patient group.

It is important to stress that no conclusions about efficacy can be drawn from our comparison of the aspirin plus clopidogrel group with the aspirin-only group. Rather, we simply looked at the temporal trend in event rates within the aspirin and clopidogrel group in order to try to detect a rebound effect. We presented the event rates during the equivalent periods in the aspirin-only group simply to give an idea of the temporal trends in event rates that might be expected in the absence of discontinuation of antiplatelet treatment.

Given the strong evidence of a rebound risk of acute ischemic events after discontinuation of clopidogrel in patients with prior acute coronary events,^{12–15} the lack of an obvious rebound effect in

Table 2 Risk of recurrent ischemic events stratified according to the timing of discontinuation of clopidogrel in patients given a short course of clopidogrel in addition to aspirin and in the equivalent periods in patients treated with aspirin alone

Time period ^a	Aspirin + clopidogrel (n = 320)	Aspirin only (n = 487)	p
Risk of ischemic stroke			
–30 to 0 days	5/318 (1.6)	12/487 (2.5)	0.41
0 to 30 days	0/316 (0)	5/485 (1.0)	0.07
30 to 60 days	1/315 (0.3)	4/482 (0.8)	0.37
Risk of TIA			
–30 to 0 days	7/318 (2.2)	5/487 (1.0)	0.16
0 to 30 days	4/316 (1.2)	3/485 (0.61)	0.34
30 to 60 days	5/315 (1.6)	3/482 (0.62)	0.18
Risk of ischemic stroke, myocardial infarction, or acute peripheral vascular events			
–30 to 0 days	6/318 (1.9)	14/487 (2.8)	0.40
0 to 30 days	0/316	6/485 (1.2)	0.048
30 to 60 days	1/315 (0.3)	4/482 (0.82)	0.37
Risk of ischemic stroke, TIA, myocardial infarction, or acute peripheral vascular events			
–30 to 0 days	13/318 (4.0)	19/487 (3.9)	0.83
0 to 30 days	4/316 (1.2)	9/485 (1.8)	0.53
30 to 60 days	6/315 (1.9)	7/482 (1.5)	0.62

^a –30 to 0 days represents the 30 days prior to stopping clopidogrel; 0 to 30 days represents the 30 days after clopidogrel was stopped; and 30 to 60 days represents the period 30 to 60 days after clopidogrel was stopped.

our study requires explanation. First, the difference may reflect the fact that patients with stroke and TIA are a more heterogeneous group compared to patients with acute coronary events. The subgroup most analogous to cohorts with acute coronary events is probably those patients with $\geq 50\%$ symptomatic carotid stenosis, and the upper 95% CI of our 0% 30-day rebound stroke risk in the 49 such patients in our study was 7.2% and so a clinically important rebound effect in this group cannot be excluded. Second, the rebound effect upon discontinuation of clopidogrel is more likely to occur in those patients with acute coronary syndrome who have coronary stents compared to those without.^{12–14} A small number of case reports highlight premature discontinuation of aspirin and clopidogrel as a potential cause of late carotid stent thrombosis^{26,27} but carotid endarterectomy was the standard treatment for revascularization of extracranial carotid occlusive disease in our study. Third, a rebound phenomenon assumes that the treatment has had some beneficial effect in the first place. It is, of course, possible that the combination of agents is actually no more effective than aspirin alone, in which case we would not expect to see a rebound effect after withdrawal of

clopidogrel. However, the results in trials in acute coronary events,^{3,28–30} and the data available so far from trials in patients with TIA or minor stroke,^{6–9} suggest that there probably is some benefit—the uncertainty in patients with TIA or stroke being more related to whether the risk of bleeding outweighs such benefit.³¹

One potential shortcoming of our study was a theoretical possibility that our advice to primary care physicians that dipyridamole should be commenced after stopping clopidogrel might have reduced any rebound risk of ischemic events. However, the majority of patients did not go onto dipyridamole and there was a considerable delay to prescription in those who did.

Our results have implications for the design of trials of aspirin plus clopidogrel in patients with TIA or minor stroke. We observed no rebound increase in risk of stroke or TIA after discontinuation of a 30-day course of clopidogrel, but larger studies are required and ongoing trials that use a limited duration of clopidogrel should follow-up patients beyond the cessation of trial treatment in order to document any rebound effect.^{10,11,32} In terms of more immediate implications for clinical practice, although use of aspirin plus clopidogrel in the acute phase after TIA or minor stroke is not supported by substantial trial evidence, a short course of combination treatment is used in some centers. Our findings suggest that a 30-day course of clopidogrel is likely to be sufficient (assuming that it actually is of some benefit), given the lack of an obvious rebound effect. It is important to stress, however, that our results do not provide any evidence on the risks of discontinuation of clopidogrel prior to 30 days, as is often required, for example, by some surgeons in patients due to undergo carotid endarterectomy.

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DISCLOSURE

Dr. Geraghty, Dr. Paul, and Dr. Chandratheva report no disclosures. Prof. Rothwell serves on scientific advisory boards for Bayer Schering Pharma, Servier, and, Biotronic; has received funding for travel and speaker honoraria from Sanofi-Aventis, Servier, AstraZeneca, and Bayer Schering Pharma; serves as Assistant Editor of the *International Journal of Stroke* and on the editorial boards of *Lancet Neurology* and *Stroke*; and has received research support from Sanofi-Aventis and from Bristol-Myers Squibb.

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Editor's Note to Authors and Readers: Levels of Evidence coming to *Neurology*®

Effective January 15, 2009, authors submitting Articles or Clinical/Scientific Notes to *Neurology*® that report on clinical therapeutic studies must state the study type, the primary research question(s), and the classification of level of evidence assigned to each question based on the classification scheme requirements shown below (left). While the authors will initially assign a level of evidence, the final level will be adjudicated by an independent team prior to publication. Ultimately, these levels can be translated into classes of recommendations for clinical care, as shown below (right). For more information, please access the articles and the editorial on the use of classification of levels of evidence published in *Neurology*.¹⁻³

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Classification scheme requirements for therapeutic questions

Class I. A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class II. A randomized, controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criterion a-e in Class I or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b-e in Class I. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class III. All other controlled trials (including well-defined natural history controls or patients serving as their own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurements.

Class IV. Studies not meeting Class I, II, or III criteria including consensus or expert opinion.

AAN classification of recommendations

A = Established as effective, ineffective, or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)

B = Probably effective, ineffective, or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)

C = Possibly effective, ineffective, or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.