

Incidence of cerebral ischemic events after discontinuation of clopidogrel in patients with intracranial aneurysms treated with stent-assisted techniques

Clinical article

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Object. The optimal antiplatelet medication protocol for prevention of thrombotic complications after stent-assisted coil embolization of cerebral aneurysms is unclear. Early cessation of antiplatelet agents may be associated with an increased risk of cerebral ischemic events. In this study, the authors assess the incidence of stroke or transient ischemic attack (TIA) following discontinuation of a 6-week course of clopidogrel in patients with cerebral aneurysms treated with stent-assisted techniques.

Methods. A retrospective review was conducted in all patients with cerebral aneurysms undergoing stent-assisted coil embolization or stent-in-stent flow diversion at the University of Iowa during a 24-month period. The antiplatelet protocol was 81 mg aspirin and 75 mg clopidogrel daily for 6 weeks, followed by 325 mg aspirin daily indefinitely. The incidence of stroke or TIA was determined by a retrospective review of medical records generated during a 3-month period following discontinuation of clopidogrel.

Results. A total of 154 patients underwent aneurysm treatment with stent techniques during this interval. Documentation of neurological follow-up 3 months after discontinuation of a 6-week clopidogrel treatment was available in 121 (78.6%) of 154 patients. Of these 121 patients, 114 were treated with stent-assisted coil embolization and 7 with stent-in-stent flow diversion. Six patients (5%) suffered an ischemic event after cessation of clopidogrel, with 2 events occurring within the first 2 weeks. Specifically, the rate of ischemic events was 5 (4.3%) of 114 in the “stent-coil” treatment group and 1 (14.3%) of 7 in the stent-in-stent group. Treatment had been performed in the setting of a subarachnoid hemorrhage in 1 patient. Atypical aneurysm features and technical factors predisposing to thrombotic events were found in all but one of these patients. Similarly, cardiovascular risk factors were present in 5 of the 6 patients in whom ischemic events developed after clopidogrel discontinuation.

Conclusions. Clopidogrel discontinuation is associated with a 5% risk of ischemic events in patients treated with stent techniques. Any stroke related to clopidogrel discontinuation is avoidable, and longer treatment is therefore clearly necessary. Patients with cardiovascular risk factors, high-risk aneurysm features, and those undergoing stent-in-stent flow diversion might benefit the most from longer clopidogrel therapy.

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KEY WORDS • aspirin • clopidogrel • intracranial aneurysm • ischemia • stent • vascular disorders

A REMARKABLE evolution in the technique of endovascular aneurysm treatment over the past decade is the adjunctive use of intracranial stents either for stent-assisted coil embolization or for primary endovascular reconstruction with stent-in-stent flow diversion. This has expanded the spectrum of intracranial

aneurysms that are amenable to endovascular therapy to include complex, wide-necked, and terminally located aneurysms.⁵ A major drawback of stent-assisted techniques, however, is the propensity for acute and delayed thromboembolic complications.^{8,9} The use of DAT with aspirin and clopidogrel has been shown to reduce the rate of symptomatic thromboembolic complications.¹⁴ As neoendothelialization progresses, the thrombogenicity of intracranial stents decreases over weeks to months, thereby avoiding the need for DAT.

Abbreviations used in this paper: DAT = dual antiplatelet therapy; SAH = subarachnoid hemorrhage; TIA = transient ischemic attack.

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A regimen combining aspirin and clopidogrel initially, followed by aspirin monotherapy indefinitely is generally recommended for both coronary and intracranial stents. However, the optimal duration of DAT following intracranial stent insertion is unclear. Because no data are available today to guide neurointerventionists, current practice is based on extrapolation from the cardiology experience, which might not be applicable for intracranial stent procedures. Protocols for DAT have therefore varied widely across neurovascular centers, with treatment durations ranging from 3 weeks to 6 months.⁴ Any assessment of the optimal duration of DAT should be based on the rate of thrombotic events occurring after discontinuation of clopidogrel. In other words, the risk of thrombotic events should remain low after switching from DAT to monotherapy. No study has yet examined the rate of ischemic events occurring after DAT discontinuation in patients with intracranial stents.

In the present report, we assess our 6-week protocol of DAT after intracranial stent placement. Specifically, we examine the incidence of cerebral ischemic events occurring after discontinuation of a 6-week course of clopidogrel in a cohort of patients treated with stent-assisted techniques, and we attempt to identify factors predisposing to such events.

Methods

A retrospective review of 275 patients with intracranial aneurysms treated at the University of Iowa Hospitals and Clinics by a single surgeon (D.H.) between July 2009 and June 2011 was performed. Patients were included for data analysis if they were treated with stent-assisted coil embolization or stent-in-stent flow diversion and if they met the following criteria: 1) discharge medications included aspirin and clopidogrel according to our standard protocol of 81 mg aspirin and 75 mg clopidogrel daily until a clinic visit scheduled at 6 weeks postprocedure, followed by 325 mg aspirin daily for an indefinite period; 2) postprocedure care was provided at our center; and 3) follow-up assessment of the patient by a neurologist or neurosurgeon was performed at least 3 months after the date of clopidogrel discontinuation.

Of note, patients treated in the setting of an SAH received a loading dose of 600 mg clopidogrel after insertion of the stent or the first coil, and were maintained on daily doses of 75 mg clopidogrel and 81 mg aspirin. Patients with unruptured aneurysms were either pretreated with aspirin and clopidogrel or received 600 mg clopidogrel intraprocedurally, with a 0.10 $\mu\text{g}/\text{kg}/\text{min}$ maintenance infusion of tirofiban after insertion of the stent or the first coil.

Patients were assessed for occurrence of stroke or TIA as diagnosed by a neurologist or neurosurgeon. Patient and aneurysm characteristics including ruptured/unruptured aneurysm status were recorded. Initial angiograms obtained in patients in whom delayed ischemic events developed were carefully reviewed by the senior author to identify high-risk aneurysm features and technical factors predisposing the patient to thrombosis. High-risk aneurysm features were defined as giant aneurysms

(≥ 20 mm), fusiform aneurysms, multilobed aneurysms, or aneurysms without a definable neck.

Results

Of 275 patients treated with endovascular procedures in our department during the 2-year interval, 154 patients (56%) underwent stent-assisted coil embolization. Documentation of neurological follow-up after discontinuation of clopidogrel treatment was available in 121 (78.6%) of 154 patients. This cohort consisted of 72 women (59.5%) and 49 men (40.5%), with an average age of 55.3 ± 13.3 years (mean \pm SD; see Table 1). Of 121 patients, 35 (29%) were treated in the acute phase of SAH. Treatment consisted of stent-assisted coil embolization in 114 patients (94.2%) and stent-in-stent flow diversion in the remaining 7 patients (5.8%). Only bare platinum coils were used for aneurysm embolization. In the so-called stent-coil group, the Neuroform stent (Stryker Neurovascular) was used in 86 patients and the Enterprise stent (Cordis Neurovascular, Inc.) was used in 28 patients. In the 7 patients treated with stent-in-stent flow diversion, 2 Enterprise stents were used in 5 patients, 2 Neuroform stents were used in 1 patient, and a combination of both was used in 1 patient.

Overall, 6 (5%) of the 121 patients suffered 7 ischemic events after discontinuation of clopidogrel (Table 2). A TIA occurred in 1 woman after clopidogrel discontinuation; she suffered a stroke 5 months later despite restarting clopidogrel. None of the 7 events were fatal. All patients were taking aspirin at the time of the ischemic event. Treatment had been performed for a ruptured aneurysm in 1 patient (16.7%). In 5 of the 6 patients, aneurysms were located in the anterior circulation. Initial treatment consisted of stent-assisted coil embolization in 5 patients and stent-in-stent flow diversion for a vertebrobasilar fusiform aneurysm in the remaining patient. The rate of ischemic events was 1 (14.3%) of 7 in the stent-in-stent flow diversion group versus 5 (4.3%) of 114 in the stent-coil group. Ischemic events developed over a wide range of intervals from the time of clopidogrel discontinuation (7–90 days), with only 2 events occurring within 2 weeks. All but one patient with an ischemic event had one or more cardiovascular risk factors for stroke (Table 2). Atypical aneurysm anatomical features or technical factors that may predispose to ischemic complications were present in 5 of 6 patients. These factors included prolapse of a coil loop into the parent artery, use of “waffle cone” intraaneurysmal stent placement, giant aneurysm size, and a large fusiform vertebrobasilar aneurysm.

Discussion

The dual antiplatelet drug regimen of aspirin plus clopidogrel as the standard of care for prophylaxis against intraarterial stent thrombosis was based on studies comparing this regimen to aspirin alone or aspirin plus a vitamin K antagonist following stent placement for atherosclerotic coronary artery disease.^{3,11} Ticlopidine was initially used but was replaced by clopidogrel because of similar efficacy, easier administration, and fewer side effects.⁶ Coronary stent thrombosis was reduced with the

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TABLE 1: Characteristics of patients with intracranial aneurysms treated with stent-assisted techniques

Sex	No. of Patients	Age in Yrs*	No. of Ruptured Aneurysms (%)	No. w/ Coil Embolization (%)	No. w/ Stent-In-Stent Flow Diversion (%)	No. w/ Ischemic Events (%)
female	72	57.0 ± 12.7	18 (25)	68 (94)	2 (2.8)	4 (5.6)
male	49	52.9 ± 13.9	17 (34)	46 (94)	5 (10.2)	2 (4.1)
total	121	55.3 ± 13.3	35 (29)	114 (94)	7 (5.8)	6 (5.0)

* Ages are expressed as the mean ± SD.

administration of thienopyridine prasugrel compared with clopidogrel in patients undergoing stent placement for high-risk acute coronary syndromes.¹³ The risk of thrombosis related to a coronary drug-eluting stent after discontinuation of clopidogrel has led to the recommendation to prolong therapy from 6 to 12 months in these circumstances.⁷ Clustering of adverse clinical cardiac events following clopidogrel withdrawal has led to concern over a prothrombotic “rebound” effect in this setting.¹⁰

The applicability of studies involving antithrombotic therapy used in stent procedures for atherosclerotic coronary disease to stent-assisted cerebral aneurysm coil embolization is uncertain, given the differences in arterial site, disease process, hemodynamic factors, and stent design. Studies directly comparing different drug regimens for ischemia in endovascular treatment of cerebral aneurysm are lacking. The list of potentially useful drugs for prevention of ischemic events after stent-assisted cerebral aneurysm treatment is rapidly expanding, and may include several thienopyridine adenosine diphosphate receptor/P2Y12 inhibitors (ticlopidine, clopidogrel, prasugrel), a thrombin inhibitor (dabigatran), and factor Xa inhibitors (rivaroxaban, apixaban). More comparative studies of antithrombotic therapy in stent-assisted aneurysm treatment are needed.

We performed a retrospective analysis of cerebral

ischemic events following discontinuation of clopidogrel at 6 weeks after stent-assisted coil embolization of intracranial aneurysms. Stroke or TIA was observed in 5% of patients (6 of 121) during the postclopidogrel observation period of at least 3 months. To our knowledge, this is the first systematic assessment of ischemic events after cessation of DAT in patients with cerebral aneurysm. Early discontinuation of DAT may be a risk factor for intracranial stent thrombosis and delayed ischemic events. In their recent report, Mocco and colleagues⁴ observed 7 delayed thrombotic events in a multicenter cohort that included 213 patients treated with stent-assisted coil embolization by using the Enterprise stent. Interestingly, the authors reported that 100% of delayed ischemic events were associated with cessation of DAT, and concluded that these 2 events may be critically related. However, as the authors point out in their report, the antiplatelet protocol was not standardized, thus varying widely across institutions from 3 weeks to 6 months, and the exact course of treatment for individual patients was not recorded either. As a result, no meaningful conclusion could be drawn from this report as to the optimal duration of DAT.

We observed a 5% rate of ischemic events after a 6-week course of clopidogrel in the present study, which suggests that such a protocol may be suboptimal for intracranial stent-placement procedures. A 5% ischemic

TABLE 2: Characteristics of 6 patients suffering an ischemic complication after discontinuation of clopidogrel*

Case No.	Age (yrs), Sex	Ischemic Event	SAH	Aneurysm Location	Coil	Stent-in-Stent	Days From Cessation to Event	Cardiovascular History	Anatomical/ Technical Features
1	73, F	TIA/stroke	no	rt ACA (A ₁ -A ₂)	yes	no	TIA Day 7; Plavix resumed—stroke occurred 5 mos after Plavix resumed	HTN	waffle cone stent placement
2	50, M	stroke	no	rt ICA (supraclinoid)	yes	no	7	none	coil loop prolapse
3	66, M	stroke	no	lt MCA (bifurcation)	yes	no	41	MI, ESRD, HTN, aortic complex atheroma	saccular
4	72, F	stroke	no	lt ICA (supraclinoid)	yes	no	48	PFO	giant aneurysm (21 mm)
5	59, F	stroke	no	basilar	no	yes	30	severe HTN	fusiform aneurysm of the VBJ
6	84, F	stroke	yes	ACoA	yes	no	90	HTN, aortic complex atheroma	waffle cone stent placement

* Every patient suffered a stroke; 1 patient also had TIA symptoms. One patient had a history of SAH, but her ischemic event was remote from aneurysmal rupture. All but 1 of these patients had at least 1 contributing factor from their cardiovascular history. Abbreviations: ACA = anterior cerebral artery; ACoA = anterior communicating artery; ESRD = end-stage renal disease; HTN = hypertension; ICA = internal carotid artery; MCA = middle cerebral artery; MI = myocardial infarction; PFO = patent foramen ovale; VBJ = vertebrobasilar junction.

event rate over only a 3-month period could be very high, considering the typical annual incidence rate of stroke estimated at 200 per 100,000 persons per year.¹ In fact, 6 strokes per 121 individuals for 3 months would translate to 24 strokes per 121 individuals per year (provided the rate remains constant), or 19,835 strokes per 100,000 per year. This rate suggests nearly a 100-fold increased risk of stroke compared with the general population. The need for longer duration of clopidogrel therapy is therefore clearly apparent. However, it should be noted that the population studied had a very high risk of stroke, which should also be taken into account for comparison purposes.

Unfortunately, there are no reports in the neurointerventional literature with which to compare our findings. Ideally, protocols with different DAT durations should be compared with respect to ischemic events to identify the minimal necessary duration of DAT after intracranial stent embolization. Nevertheless, our study provides important data for future comparisons in this setting. More studies are needed to determine if continuation of clopidogrel beyond 6 weeks would further reduce the risk of ischemic complications.

The majority of ischemic events in our study occurred in patients with atypical anatomical or treatment features that might predispose them to thrombosis, such as coil loop prolapse, waffle cone stent placement, giant aneurysms, and fusiform aneurysms. Cardiovascular risk factors for stroke were common in these patients as well. Although the impact of these putative high-risk features on thrombotic complications after stent-assisted aneurysm treatment is uncertain, it might be reasonable to extend the duration of antithrombotic therapy further in patients with the aforementioned risk factors. Patients treated with stent-in-stent flow diversion also had a 14.3% rate of ischemic events, versus only 4.3% in patients undergoing stent-coil treatment. Longer treatment durations may therefore be needed after dual-stent procedures. Clopidogrel resistance is another potentially important factor that has been associated with thromboembolic events in stent-coil procedures.^{2,12} It is estimated that almost 40% of patients could have a poor response to clopidogrel.² However, this factor obviously does not play a role in the present study because all patients had discontinued clopidogrel after a 6-week course of DAT.

Our study has several limitations, as follows. 1) A comparison of different antiplatelet regimens was not performed, which precludes any confident conclusion in this regard. 2) Only symptomatic ischemic events were assessed, with no monitoring for clinically silent infarcts on follow-up imaging studies. In fact, a study accounting for silent infarcts would be very difficult to conduct because it would require brain imaging just before discontinuation of clopidogrel, followed by brain imaging at the scheduled follow-up. Otherwise, it would be impossible to determine when the infarct actually occurred, namely before or after clopidogrel discontinuation. 3) A 3-month period following clopidogrel discontinuation may not be long enough to detect all associated ischemic events, and an assessment at later time points was not performed. Nevertheless, the cardiology experience suggests that the average duration between clopidogrel discontinuation and

coronary stent thrombosis is 9 days, which indicates that most relevant ischemic events were indeed detected during the 3-month period in the present study. 4) The impact of loss to follow-up on the rate of ischemic events is uncertain because it would be difficult to tell if patients lost to follow-up differ from those who remained in the study. One could argue that the rate of ischemic events may be higher in this subgroup of patients, which could further increase the overall rate of ischemic events in the studied population. 5) The small number of events in the present study precluded a time-based statistical analysis of the occurrence of ischemic events following clopidogrel discontinuation. Large-scale prospective studies with long follow-up periods are best suited for such analysis.

The risk of cerebral ischemic events after discontinuation of antithrombotic therapy should be included in the considerations of endovascular versus microsurgical obliteration of cerebral aneurysms or expectant care and incorporated in the informed consent process. Our current study may encourage neurointerventionists to favor a more evidence-based policy with regard to the duration of antiplatelet therapy. These measures may lead to better surgical outcomes and decreased treatment costs.

Conclusions

Treatment with 81 mg aspirin and 75 mg clopidogrel daily for 6 weeks after stent-assisted coil embolization, followed by 325 mg oral aspirin daily for an indefinite period seems to be associated with a relatively high risk of cerebral ischemic events (5%). Longer clopidogrel therapy may be needed after stent-assisted procedures to avoid ischemic events, especially in patients with cardiovascular risk factors or high-risk aneurysm and treatment features. Further studies comparing various antiplatelet treatment durations are needed to determine the optimal regimen for DAT in intracranial stent procedures. This question will definitely become the focus of future research because stent-assisted techniques are increasingly being used for a wide array of intracranial aneurysms.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Hasan, Rossen, Chalouhi. Acquisition of data: Hasan, Wassef, Thomas. Analysis and interpretation of data: Hasan, Rossen, Chalouhi, Wassef, Abel. Drafting the article: all authors. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Hasan. Administrative/technical/material support: Hasan, Rossen, Chalouhi. Study supervision: Hasan.

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