

# Dual Antiplatelet Therapy Prior to Expedited Carotid Surgery Reduces Recurrent Events Prior to Surgery without Significantly Increasing Peri-operative Bleeding Complications

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## WHAT THIS PAPER ADDS

A reconfiguration of TIA services reduced the median delay from symptom to CEA to 9 days. However, an audit revealed that during the median 3-day period between transfer from the TIA clinic to undergoing CEA, 13% of patients suffered recurrent events, despite having been previously started on aspirin. In the current audit, a change to early implementation of dual antiplatelet therapy (in the TIA clinic after CT/MR exclusion of parenchymal haemorrhage) was associated with a fivefold reduction in recurrent neurological events prior to expedited CEA and a fourfold reduction in spontaneous embolization, compared with data observed in the preceding audit. This was achieved without a significant increase in major peri-operative bleeding complications.

**Objective:** A daily Rapid-Access TIA Clinic was introduced in 2008, where symptomatic patients were started on 75 mg aspirin + 40 mg simvastatin by the referring doctor, before attending the clinic. Following clinic assessment, patients with 50–99% stenoses were transferred to the vascular unit for carotid endarterectomy (CEA). In two audits ( $n = 212$  patients), the median delay from transfer to the vascular unit to undergoing CEA was 3 days, during which time 28 patients (13%) suffered recurrent neurological events. It was hypothesized that early introduction of dual antiplatelet therapy (by adding clopidogrel 75 mg once parenchymal haemorrhage was excluded in the TIA clinic) might significantly reduce recurrent events between transfer to the surgical unit and undergoing CEA.

**Methods:** Prospective audit in 100 consecutive, recently symptomatic patients receiving dual antiplatelet therapy. Endpoints were: prevalence of recurrent events between transfer from the TIA clinic and undergoing CEA; rates of spontaneous embolization prior to undergoing CEA; and prevalence of haemorrhagic complications

**Results:** The median delay from symptom to CEA was 8 days (IQR 5–15). The median delay between transfer from the TIA clinic to CEA was 3 days (IQR 2–5), during which time three patients (3%) suffered recurrent TIAs. This represents a fivefold reduction compared with previous audit data (OR 4.9, 95% CI 1.5–16.6,  $p = .01$ ) and was matched by a fourfold reduction in the prevalence of spontaneous embolization from 39/189 (21%) previously to 5/83 (5%) in the current audit (OR 4.1, 95% CI 1.5–10.7,  $p = .0047$ ). The 30-day death/stroke rate was 1%. There were three haemorrhagic complications: stroke caused by haemorrhagic transformation of an infarct; exploration for neck haematoma; and debridement and skin grafting for spontaneous shin haematoma.

**Conclusion:** Early introduction of dual antiplatelet therapy was associated with a significant reduction in recurrent neurological events and spontaneous embolization prior to CEA, without incurring a significant increase in major peri-operative bleeding complications.

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## INTRODUCTION

There has been an international move towards performing carotid endarterectomy (CEA) as soon as possible after onset of symptoms, driven by increasing awareness that the highest risk period for recurrent stroke is the first few days after suffering a transient ischaemic attack (TIA) or minor stroke.<sup>1–7</sup>

To deliver expedited CEA, a daily Rapid Access TIA service was established in Leicester in October 2008.<sup>8</sup> The referring

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family doctor/emergency room doctor started anyone with a suspected TIA/minor stroke on 300 mg aspirin and 40 mg simvastatin at the time of seeing the patient. A consultant physician (who specialized in stroke medicine) then saw each referral in the daily TIA clinic and was responsible for optimizing risk factors and ensuring the patient was still taking aspirin and a statin. Anyone with an ipsilateral 50–99% ICA stenosis was transferred from the TIA clinic to the vascular unit for urgent CEA.<sup>8</sup>

This protocol was associated with a reduction in the delay from symptom to CEA to a median of 9 days (95% CI 7–10).<sup>9</sup> Following transfer from the TIA clinic, patients underwent CEA within a median of 3 days. However, two sequential audits showed that during this 3-day time period (between transfer from the TIA clinic and undergoing CEA), 11% and 15% of patients (respectively) suffered recurrent TIAs or strokes,<sup>9,10</sup> emphasizing just how unstable underlying carotid plaques were during this early time period.

Following a review of practice, and with the aim of trying to prevent recurrent symptoms between referral and surgery, the stroke physicians and vascular surgeons proposed adding 75 mg clopidogrel (i.e. implementing early dual antiplatelet therapy) as soon as intracranial haemorrhage (ICH) or parenchymal haemorrhage was excluded on CT/MRI in the TIA clinic.

The principle aims of the current audit were to establish whether earlier introduction of dual antiplatelet therapy reduced the prevalence of recurrent events between transfer from the TIA clinic and undergoing CEA, without increasing the risk or peri-operative haemorrhagic complications.

## MATERIALS AND METHODS

Between August 17, 2013 and July 27, 2014, 100 consecutive, recently symptomatic patients undergoing CEA were recruited. Asymptomatic patients undergoing CEA during this time period were excluded. All patients had been transferred to the vascular unit at the Leicester Royal Infirmary via the Rapid Access TIA clinic, or acute stroke unit. The Leicestershire, Northamptonshire and Rutland Research ethics committee advised that this study did not fall under the remit of the NHS research ethics committee, as it was audit/service evaluation. This prospective audit was registered with the University Hospitals of Leicester Clinical Audit and Quality Improvement Project (ref 6625).

### Rapid Access TIA clinic

**October 2008–August 2013.** The Rapid Access TIA clinic started in October 2008 and operates every day of the year.<sup>8</sup> The referring family doctor/emergency department doctor starts 300 mg aspirin and 40 mg simvastatin in anyone suspected of having suffered a TIA/minor stroke. Electronic referrals were triaged based on the patient's ABCD<sup>2</sup> score.<sup>11</sup> Patients with an ABCD<sup>2</sup> score of 0–3 (7-day predicted stroke risk = 1%) were seen within 7 days of referral. Patients with an ABCD<sup>2</sup> score of 4–7 (7–10%

predicted stroke risk within 7 days) were seen either the same day or the following morning.

At the TIA clinic, baseline bloods were taken (haematology/biochemistry) and patients underwent CT/MRI plus carotid Duplex ultrasound assessment. A consultant stroke physician then saw each patient and assumed responsibility for optimizing risk factors and ensuring the patient was taking aspirin and a statin. Any patient who had an ipsilateral 50–99% carotid stenosis was transferred to the vascular unit for urgent CEA. Following transfer, the aspirin dose was reduced from 300 mg to 75 mg daily and this was continued throughout the peri-operative period. Between October 1, 2008 and August 16, 2013, it was unit policy for all CEA patients to receive a single 75 mg dose of clopidogrel the night before surgery (in addition to regular aspirin therapy) to prevent early post-operative thromboembolic stroke.<sup>12</sup> However, no other doses of clopidogrel were administered between admission and surgery during this time period.

**August 2013–July 2014: the current audit.** The main protocol change related to the start date for dual antiplatelet therapy. All other aspects of referral, investigation, and treatment remained the same. Patients with an ipsilateral 50–99% stenosis and who had no evidence of ICH or parenchymal haemorrhage on CT/MRI were started on 75 mg clopidogrel (in addition to their regular aspirin). Dual antiplatelet therapy (75 mg aspirin, 75 mg clopidogrel) was then continued throughout the peri-operative period. Immediately prior to hospital discharge, aspirin was stopped, but clopidogrel was continued as per NICE guidelines.<sup>13</sup> No patients in the current audit were taking warfarin at the time of TIA clinic attendance.

### Expedited CEA

The protocol for performing CEA did not change during the 6-year period from 2008 to 2014. Following admission, each patient underwent work-up for theatre, the goal being to perform CEA safely and as soon as possible. Poorly controlled hypertension was relatively common and treatment was started prior to surgery and then 'finetuned' following the procedure. Where necessary, referrals were made to other medical disciplines for advice regarding the treatment of comorbid conditions that might otherwise delay surgery. Two half-day theatre lists were 'ring-fenced' for CEAs on Tuesdays and Fridays. If these lists were filled, alternative arrangements were made (emergency theatre, ad hoc space on elective lists, deferral to next unfilled CEA list). During the current audit, CEA was performed only once on a Saturday/Sunday.

CEA was performed in the same standardized manner between 2008 and 2014, using general anaesthesia with routine shunting/patching, intra-operative transcranial Doppler (TCD) monitoring and completion angiography.<sup>12</sup> The policy regarding the type of patch closure did, however, change. Between October 1, 2008 and December 31, 2011, ultrathin collagen-coated polyester patches were used to close the arteriotomy (Hemagard Ultrathin, Atrium

Maquet Getinge Group) and each patient received a single 75 mg dose of clopidogrel the night before surgery in addition to regular aspirin. Between January 1, 2012 and August 16, 2013, a bovine pericardial patch was used to close the arteriotomy (XenoSure Biologic Vascular Patch, LeMaitre). Patients undergoing CEA during this time period still received a single 75 mg dose of clopidogrel the night before surgery in addition to regular aspirin. Between August 17 and July 27, 2014 (the current audit period), bovine pericardial patches were used to close the arteriotomy but every patient now started 75 mg clopidogrel once ICH was excluded in the TIA clinic, in addition to regular aspirin therapy.

### Post-operative care

Patients were monitored for 3 hours in the recovery area of theatre. Provided there was no haemodynamic instability or neurological complications, patients were transferred back to the vascular ward for ongoing care and were usually discharged within 48 hours. Since 2008, the unit has maintained an aggressive policy towards the management of post-CEA hypertension. Written guidance on the management of post-CEA hypertension<sup>12</sup> was placed in the case notes of each patient so that treatment was never delayed. Unit policy regarding the treatment of post-CEA hypertension policy did not change between October 2008 and July 2014.

**Current audit.** The current audit documented recurrent neurological events in the time period between transfer from the TIA clinic and undergoing CEA, along with 30-day rates of death/stroke and any major peri-operative bleeding complication (defined as stroke caused by ICH, haemorrhagic transformation of a cerebral infarct, return to theatre for evacuation of neck haematoma, gastro-intestinal blood loss, and any spontaneous bleeding/haematoma that otherwise delayed discharge). Two additional analyses were undertaken to evaluate the effect of dual antiplatelet therapy on reducing spontaneous embolization and peri-operative haemorrhagic problems. Patients with an accessible temporal window underwent a 30-minute period of TCD monitoring on the afternoon prior to CEA to identify patients with spontaneous embolization in the ipsilateral middle cerebral artery.<sup>12</sup> Similar data (regarding spontaneous embolization rates) were available from the two preceding audits in 2010 and 2011.<sup>9,10</sup>

In addition, the time from flow restoration to removal of drapes was used as a surrogate for the delay to achieving haemostasis. In view of the temporal changes in patch type (and the effect/bias this might have had on haemostasis), three consecutive patient cohorts were analyzed: (i) January 1, 2011 to December 31, 2011: polyester patch with regular aspirin + 75 mg clopidogrel the night before surgery ( $n = 96$ ); (ii) January 1, 2012 to May 31, 2013: bovine pericardial patch with regular aspirin + 75 mg clopidogrel the night before surgery ( $n = 122$ ); and (iii) August 17, 2013 to July 27, 2014 (the current audit): bovine pericardial patch

with regular aspirin + 75 mg clopidogrel starting once ICH was excluded in the TIA clinic ( $n = 100$ ).

### RESULTS

Between August 17, 2013 and July 27, 2014, 100 consecutive patients with recent onset carotid territory symptoms entered the audit. The cohort included 64 males and 36 females with a mean age of 74 years (range 51–92). Sixty-six (66%) presented with a TIA, 18 (18%) with a stroke, and 16 (16%) with amaurosis fugax (Table 1). Seventy-six patients (76%) were on treatment for hypertension, 33 (33%) were diabetic, 21 (21%) had a history of ischaemic heart disease, while 70 (70%) were current/ex-smokers. Table 1 indicates how patient demographics in the current audit compared with the 212 patients in the preceding audits. With the exception of a significantly higher prevalence of stroke as a presentation in the preceding audits, there was no systematic difference between the two patient cohorts. The median ABCD<sup>2</sup> score in the 100 patients in the current audit was 5 (range 1–7). Thirty-five of the 100 patients (35%) had CT/MRI evidence of recent acute infarction or evolving ischaemic change.

### Delays to CEA

The median delay from presenting symptom to undergoing CEA was 8 days (IQR 5–15), compared with a median of 9.5 days (IQR 6–18) in the 212 patients in the preceding audits ( $p = .231$ ). The median delay from transfer from the TIA clinic to undergoing CEA in the current audit was 3 days (IQR 2–5 days), compared with a median of 3 days (IQR 1–4) in the preceding audits (Table 1,  $p = .786$ ). Forty-four patients (44%) in the current audit underwent surgery within 48 hours of transfer from the TIA clinic, while 74 (74%) underwent surgery within 96 hours.

**Table 1.** Demographics, spontaneous embolization rates, median delays to referral/treatment, and recurrent events prior to CEA.

	Current audit	Preceding audits	<i>p</i>
<i>n</i>	100	212	
Males:females	64:36	142:70	.610
Median age	74 (range 51–92)	72 (range 37–94)	.768
Past history			
Treated hypertension	76 (76%)	161 (76%)	1.00
Diabetes	33 (33%)	47 (22%)	.052
Ischaemic heart disease	21 (21%)	35 (17%)	.346
Ex/current smoker	70 (70%)	157 (74%)	.496
Presentation			
TIA	66 (66%)	117 (55%)	.085
Stroke	18 (18%)	64 (30%)	.027
Amaurosis	16 (16%)	31 (15%)	.737
Median delays			
Index symptom to CEA	8 days (IQR 5–15)	9.5 days (IQR 6–18)	.231
Referral to CEA	3 days (IQR 2–5)	3 days (IQR 1–4)	.786

### Recurrent events prior to CEA

Three patients in the current audit (3%) suffered recurrent symptoms in the (median) 3-day period between transfer from the TIA clinic and undergoing CEA. All were TIAs and no-one suffered a recurrent stroke. Details regarding presentation, time of starting dual antiplatelet therapy, and timing of recurrent symptoms are detailed in Table 2. Interestingly, none of those patients suffering a recurrent event had severe (70–99%) carotid stenoses; all had 50–60% stenoses using the NASCET measuring method.

The 3% rate of recurrent events in the median 3-day period between transfer from the TIA clinic to undergoing CEA in the current audit represents a fivefold reduction compared with the 28/212 (13%) prevalence in the preceding audits (OR 4.9, 95% CI 1.5–16.6,  $p = .01$ ).

### Prevalence of embolization prior to CEA

Eighty-three of the 100 patients in the current audit had an accessible transcranial window and underwent 30 minutes

**Table 2.** Clinical details regarding the three patients who suffered recurrent TIAs immediately prior to carotid surgery despite early implementation of dual antiplatelet therapy.

Clinical details	
Case 1	Hemispheric TIA at 16:45 on November 10
64-year-old female	Seen in TIA clinic on morning of November 11
	Carotid Duplex scan showed 50–60% stenosis of ipsilateral ICA
	Transferred to vascular unit at 15:00 h on November 11
	Clopidogrel administered at 17:50 h on November 11
	Recurrent hemispheric TIA November 12 (22 h after clopidogrel started)
Case 2	Five hemispheric TIAs in preceding 4 days
86-year-old male	Attended emergency department at 22:40 h on December 22
	Clopidogrel administered 23:45 h on December 22 (stroke physician advice)
	Admitted to stroke unit at 00:44 h on December 23
	Carotid Duplex scan 11:00 h on December 23: 50–60% stenosis of ipsilateral ICA
	Recurrent TIA on evening of December 23 (18 h after clopidogrel started)
Case 3	Two hemispheric TIAs in preceding 7 days; seen in peripheral hospital
70-year-old male	Clopidogrel started on May 2 by referring stroke unit
	CT angiogram on May 3: 60% stenosis of ipsilateral ICA
	Recurrent hemispheric TIA 11:00 h on May 9
	Transferred to vascular unit on afternoon of May 9
	Two hemispheric TIAs on evening of May 10 (had been taking clopidogrel for 8 days)

of TCD monitoring on the afternoon prior to surgery. Five (6%) had evidence of spontaneous embolization. In the preceding audits, 189/212 (89%) had an accessible transcranial window and underwent 30 minutes of TCD monitoring. In this group, 39/189 (21%) had evidence of spontaneous embolization. Compared with the current audit, this represents a fourfold reduction in the prevalence of spontaneous embolization (OR 4.1, 95% CI 1.5–10.7,  $p = .0047$ ).

### Peri-operative bleeding complications

Three patients in the current audit (3%) suffered major haemorrhagic complications within 30-days of surgery. One suffered a stroke following haemorrhagic transformation of a recent ischaemic infarction on day 2 after CEA. He had presented with a non-disabling stroke (Rankin grade 2) 4 days prior to CEA. He underwent an uneventful procedure, but suffered an acute worsening of his pre-existing neurological deficit on the second post-operative day, in the absence of post-CEA hypertension. He was transferred to the stroke unit for rehabilitation and scored Rankin grade 2 at 30 days (non-disabling post-operative stroke). There were no other strokes or deaths in the peri-operative period. The second patient developed a neck haematoma that required evacuation, while a third developed a spontaneous shin haematoma that required debridement and skin grafting.

In the preceding audits involving 212 patients who did not receive dual antiplatelet therapy (other than on the night before surgery); no patient suffered an intracranial haemorrhage but seven (3.3%) required re-exploration for neck haematomas.

### Time from restoration of flow to removal of drapes

The time from flow restoration to removal of drapes is a surrogate marker for delays to achieving haemostasis. In view of the temporal changes in patch type (and the effect/bias this might have had on achieving haemostasis), three consecutive patient cohorts were analyzed (Table 3). The median delay from flow restoration to drape removal in patients whose arteriotomy was closed with a collagen-coated, thin-walled polyester patch, and who were taking regular aspirin and a single 75 mg dose of clopidogrel the night before surgery (policy during all of the first audit and 9 months of the second audit) was 31 minutes (IQR 26–41). The change to using bovine pericardial patches, as was practiced during the latter 4 months of the second audit, (regular aspirin plus a single 75 mg dose of clopidogrel the night before surgery), saw a significant decrease in the median time from flow restoration to drape removal (26 minutes, IQR 21–32,  $p = .021$ , Mann-Whitney  $U$  test). In the current audit (where dual antiplatelet therapy was started 3 days pre-operatively once parenchymal haemorrhage had been excluded on CT/MRA), all arteriotomies were closed with bovine pericardial patches. Here, the median delay from flow restoration to drape removal increased non-significantly to 28 minutes (IQR 21–33,  $p = .5619$ , Mann-Whitney  $U$  test), compared with patients

**Table 3.** Median time from restoration of flow to removal of surgical drapes in three cohorts of patients stratified for patch type and antiplatelet strategy.

Assessment period <sup>a</sup>	Patch type	Antiplatelet strategy	n	Median time (IQR)
01/01/11 to 31/12/11	Collagen-coated polyester	75 mg aspirin daily <sup>b</sup> + 75 mg clopidogrel night before CEA	96	31 mins (26–41)
01/01/2012 to 31/05/2013	Bovine pericardial patch	75 mg aspirin daily <sup>b</sup> + 75 mg clopidogrel night before CEA	122	28 mins (21–32)
Current audit 17/08/2013 to 27/07/2014	Bovine pericardial patch	75 mg aspirin daily <sup>b</sup> + 75 mg clopidogrel daily <sup>c</sup> starting in TIA clinic	100	28 mins (21–33)

<sup>a</sup> Because the type of carotid patch changed in the years prior to the current audit, the median delay from flow restoration to drape removal has been listed for two discrete time periods before the current audit was undertaken to see whether the introduction of dual antiplatelet therapy was associated with a significant prolongation in time to achieve haemostasis.

<sup>b</sup> Aspirin was started by the referring family or emergency room doctor once a TIA or minor stroke was suspected.

<sup>c</sup> Clopidogrel (dual antiplatelet therapy) was started once parenchymal haemorrhage was excluded on CT/MRI in the TIA clinic.

undergoing a bovine pericardial patched CEA and who only received a single 75 mg dose of clopidogrel the night before surgery in addition to their regular aspirin.

## DISCUSSION

There has been a worldwide move towards performing CEA as soon as possible after onset of symptoms. This has been driven by awareness that the highest risk period for recurrent stroke in patients with ipsilateral 50–99% stenoses of the internal carotid artery (ICA) is the first few days after onset of symptoms, with published prevalences ranging from 5–8% at 48 hours,<sup>5–7</sup> 17% at 72 hours,<sup>3,7</sup> 8–22% at 7 days,<sup>2,3,5–7</sup> and 11–25% at 14 days.<sup>2,5–7</sup>

The ability to perform CEA as soon as possible after onset of symptoms cannot be achieved through ad hoc changes in referral practices, no matter how enthusiastic some surgeons might be.<sup>14</sup> The Leicester Rapid Access TIA service was introduced in October 2008 through collaboration between vascular surgeons, stroke physicians, radiologists, vascular technologists, hospital management, and health purchasers.<sup>8</sup> The net result was an immediate reduction in delays to treatment for all TIA/minor stroke referrals but, especially, CEA patients. Prior to 2008, the median delay from referral to CEA in Leicester was 28 days,<sup>14</sup> but this fell immediately to 4 days after introduction of the daily TIA clinic.<sup>8</sup>

One unanticipated consequence, however, of expediting all aspects of the referral and admission process was that a significant proportion of patients suffered recurrent neurological events in the (median) 3-day time period between transfer from the TIA clinic and undergoing CEA. Historically, this was something that had not been encountered previously, reflecting the greater delays between onset of symptoms and undergoing CEA that was typical of most vascular units of the time.

Two sequential audits evaluated the prevalence of recurrent symptoms between transfer from the TIA clinic and undergoing CEA. In the 2011 audit, Salem reported that 18/123 patients (15%) suffered recurrent symptoms in the (median) 3-day time period between transfer from the TIA clinic and undergoing CEA.<sup>9</sup> None, however, were strokes. In a second (2013) audit, Ali observed that 10/89 patients (11%) suffered recurrent neurological events (TIA = 8;

stroke = 2) prior to surgery. Two strokes were disabling and neither patient was fit enough to undergo surgery.<sup>10</sup> When the two audits were combined, 28/212 patients (13%) suffered recurrent neurological events in a median time period of 3 days (IQR 1–4) between transfer from the TIA clinic and undergoing surgery. Overall, the median delay from index symptom to CEA for these 212 patients was 9.5 days (IQR 6–18), that is not significantly different to the 8 days (IQR 5–15) observed in the current audit.

Similar experiences have been reported elsewhere, although few have published data reporting recurrent events so close to the index event. In Blaser's series,<sup>15</sup> the median delay from index event to investigation was 19 days. However, in the 10 days (median) between investigation and undergoing CEA, 15 patients (10%) suffered recurrent events (TIA = 6; non-disabling stroke = 1; disabling stroke = 8), while eight (6%) suffered an asymptomatic occlusion of their ICA. In a similar series, but where patients were seen at a median of 14 days after symptom onset, Kastrup observed that during the next 7 days, 3% suffered a recurrent TIA, while 12% developed new, asymptomatic DWI lesions on MRI.<sup>16</sup> Finally, Johannson observed that the rate of recurrent ipsilateral stroke in patients with 50–99% stenoses who were waiting for CEA was 5% at 48 hours after the index event, 8% at 7 days, and 11% at 14 days.<sup>5</sup> In a recent Swedish study, Stromberg reported that 72% of their cohort of patients who presented with a TIA/minor stroke and a 50–99% stenosis were admitted on the day of the referring neurological event.<sup>17</sup> Thereafter, 2% suffered a stroke within 48 hours of their presenting symptom, increasing to 4% at 7 days. When 'strokes in evolution' were included, 3.2% of patients had suffered a stroke within 48 hours.

The hypothesis underlying the current audit was that earlier institution of dual antiplatelet therapy might reduce the prevalence of recurrent events immediately prior to CEA. This was based on the following clinical/scientific observations: (i) most recurrent events follow continuing embolization from unstable carotid plaques; (ii) embolization rates are highest in the very early time period after onset of symptoms;<sup>9</sup> (iii) the CARESS and CLAIR studies showed that early institution of aspirin and clopidogrel significantly reduced rates of embolization in patients with

recent onset TIA/stroke;<sup>18,19</sup> (iv) when aspirin and clopidogrel were started <24 hours in patients suffering an acute coronary syndrome, there was a significant reduction in cardiovascular death, non-fatal MI, and stroke;<sup>20</sup> and (v) a meta-analysis of four randomized trials showed that the early introduction of aspirin and clopidogrel was associated with a 34% relative risk reduction in stroke, TIA, acute coronary syndrome, and all-cause death.<sup>21</sup>

In the current audit, only three patients (3%) suffered a recurrent TIA during the median 3-day time period between transfer from the TIA clinic and undergoing CEA. This represents a fivefold reduction in the prevalence of recurrent events, when compared with 28/212 patients (13%) in the preceding audits when only aspirin monotherapy was administered in the 3-day time period between transfer from the TIA clinic and CEA<sup>9,10</sup> (OR 4.9, 95% CI 1.5–16.6,  $p = .0102$ ). This significant reduction in recurrent events was also associated with a fourfold reduction in the proportion of patients with spontaneous embolization on pre-operative TCD monitoring. It is, of course, accepted that this is not a randomized comparison, but there were no significant differences in delays from index symptom to CEA and from TIA clinic transfer to CEA in the preceding audits (Table 1). Moreover, patient demographics were very similar and there was no other difference in prescribing practices. One confounding factor that was not considered in this audit (nor in the preceding ones) was to document the proportion of patients who were or were not already taking antiplatelet agents prior to their symptoms starting. This information was not recorded, but there is no reason to believe that a systematic change in antiplatelet prescribing had occurred between the three sequential audits.

Very few studies have specifically looked at the effect of early implementation of dual antiplatelet therapy on preventing recurrent events prior to CEA. Shahidi et al. reported that 29% of their cohort of 115 recently symptomatic patients awaiting CEA had suffered a recurrent neurological event in the 90-day time period prior to the neurological event that led to the patient's referral for CEA. Patients were then started on clopidogrel (in addition to regular aspirin), prior to surgery. During a median 6-day period between referral and CEA, only 2.5% suffered recurrent events.<sup>22</sup> Accordingly, the current audit (as well as Shahidi's data) suggest that the early introduction of dual antiplatelet therapy is associated with a significant reduction in the prevalence of recurrent neurological events during this (previously) high-risk period, presumably caused by a significant reduction in spontaneous embolization. It might, however, be speculated that the median 3-day time period between transfer from the TIA clinic to undergoing CEA was too short a time period for dual antiplatelet therapy to exert a meaningful effect. However, a prospective, randomized trial has previously shown that a single 75 mg dose of clopidogrel given the night before surgery reduced platelet aggregation to ADP by 40% by the following day, suggesting that 3 days of dual antiplatelet therapy should be capable of exerting a clinically significant antiplatelet effect.

Notwithstanding the clinically important benefit (to the patient) of reducing recurrent events prior to surgery, surgeons remain concerned that dual antiplatelet therapy will be associated with a significant increase in major bleeding complications during the peri-operative period. However, only three patients (3%) in the current audit suffered major haemorrhagic complications and this does not represent a significantly increased level of risk compared with historical controls in the literature or when compared with the 212 patients in the two preceding audits. The prevalence of re-exploration for neck haematoma (1% in the current audit) was no different to that reported in other contemporary audits. In a series of 5264 CEAs from the Vascular Study Group of New England, the prevalence of re-exploration for neck haematoma was 1.5% in patients not taking any antiplatelet therapy, 1.2% in patients taking aspirin, 0.7% in patients taking clopidogrel, and 1.4% in patients taking aspirin and clopidogrel.<sup>23</sup> Other single centre studies have also reported that performing CEA in patients on dual antiplatelet therapy is not associated with an increase in re-exploration for neck haematomas,<sup>24</sup> while the International Carotid Stenting Study reported a prevalence of 3.4% for neck haematomas requiring re-exploration following 821 CEAs.<sup>25</sup> It is, however, conceded that the spontaneous shin haematoma was probably a direct consequence of dual antiplatelet therapy, but this was the only example of spontaneous peripheral bleeding in this series and there were no cases of acute gastrointestinal haemorrhage.

One patient (1%) did, however, suffer haemorrhagic transformation in an area of recent cerebral infarction. This was the only stroke that occurred in the peri-operative period in the current audit. Interestingly, this happened without any associated increase in blood pressure. It is possible, however, that had such an aggressive policy not been adopted towards the treatment of post-CEA hypertension,<sup>12</sup> untreated surges in blood pressure (in the presence of dual antiplatelet therapy) might have predisposed towards a much higher prevalence of ICH and haemorrhagic infarct transformation. This is probably an important additional message to come from this audit.

Finally, the choice of patch may be an important factor following the introduction of dual antiplatelet therapy prior to CEA. The Leicester unit changed from a collagen-coated, polyester patch to a bovine pericardial patch following publication of a systematic review of prosthetic patch infections, which showed that early patch infection (within 3 months of surgery) was associated with early wound complications including wound haematoma. It has previously been shown that the addition of a single 75 mg dose of clopidogrel (to regular aspirin) the night before surgery adds an average of 20 minutes to the time from flow restoration to removal of drapes, reflecting an increase in the time to achieve haemostasis.<sup>26</sup> It was hypothesized that changing from a prosthetic to a biological patch would achieve more rapid haemostasis (and hence fewer wound haematomas) and this was borne out in this audit where the median delay from flow restoration to drape removal decreased by 5 minutes from 31 minutes (polyester

patch +75 mg clopidogrel the night before surgery) to 26 minutes (bovine pericardial patch + 75 mg clopidogrel the night before surgery). More importantly, starting dual antiplatelet therapy 3 days prior to CEA was only associated with a (non-significant) 2-minute increase in the median time from flow restoration to drape removal, compared with bovine pericardial-patched patients receiving a single dose of clopidogrel the night before surgery (Table 3).

In conclusion, the early introduction of dual antiplatelet therapy was associated with a fivefold reduction in recurrent neurological events prior to expedited CEA and a fourfold reduction in spontaneous embolization, when compared with historical controls. This was achieved without a significant increase in major peri-operative bleeding complications or delays to secure haemostasis, although it is accepted that the risk of haemorrhagic stroke might have been considerably higher had the unit not adopted such an aggressive policy towards the treatment of post-CEA hypertension. Given these findings, one might now reasonably speculate that because the vast majority of TIA/AFx patients are unlikely to have underlying parenchymal haemorrhage at the time of presentation, it may be reasonable for the family doctor or emergency room doctor to commence dual antiplatelet therapy as soon as possible in any patient whose symptoms resolve within 24 hours, rather than simply start aspirin and await a CT/MRI scan in the TIA clinic before converting to dual antiplatelet therapy. In that way, it may prove possible to further reduce the risk of recurrent events in the 5–7 days that it takes patients to seek medical advice and be referred to specialist clinics.

### CONFLICT OF INTEREST

None.

### FUNDING

None.

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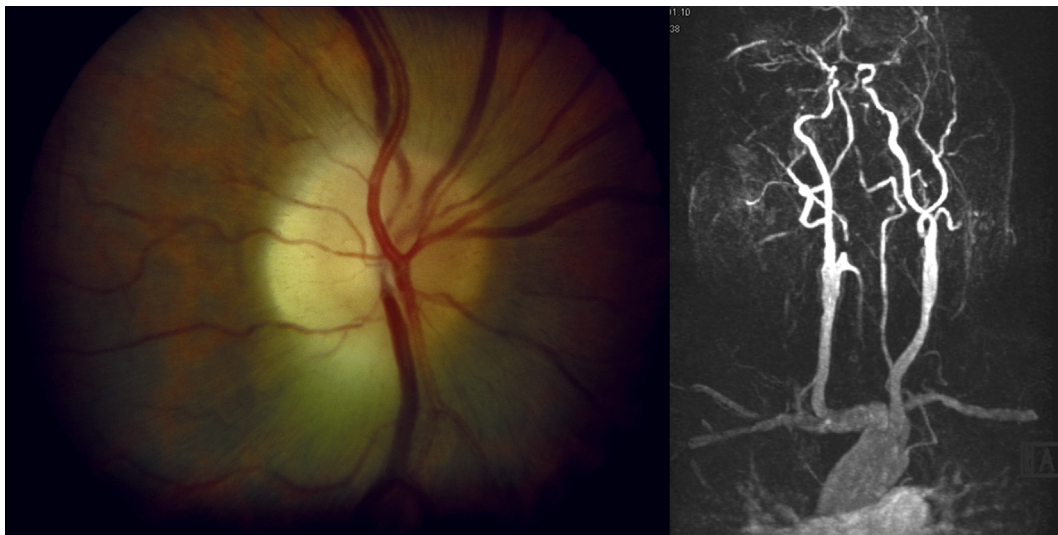
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## COUP D'OEIL

# Acute Monocular Blindness after Carotid Endarterectomy due to Non-arteritic Anterior Ischemic Optic Neuropathy

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A 56 year old non-diabetic male patient with an asymptomatic 90% stenosis of the right internal carotid artery underwent carotid endarterectomy with patch angioplasty. Thirty hours after surgery the patient's right eye was sore and light perception completely vanished without recovery. Nuclear magnetic resonance spectroscopy revealed a new occlusion of the external carotid artery (right). Five days after surgery optic disc edema developed so NAION (non-arteritic anterior ischemic optic neuropathy) was diagnosed (left). This entity has to be distinguished from posterior ischemic optic neuropathy without ophthalmoscopic changes and from central retinal artery occlusion with a "cherry red spot" and surrounding pale retina.

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