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Antiplatelet Therapy in Carotid Artery Stenting and Carotid Endarterectomy in the Asymptomatic Carotid Surgery Trial-2

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WHAT THIS PAPER ADDS

Strokes are infrequent but potentially serious complications following carotid intervention, but antiplatelet therapy can reduce these risks. There are currently no specific guidelines on dose and duration of peri-procedural antiplatelet treatment to help clinical proposal design for patients undergoing carotid intervention. The Asymptomatic Carotid Surgery Trial-2 (ACST-2) is the largest clinical trial of interventional treatment for asymptomatic carotid disease, randomising patients to either carotid endarterectomy (CEA) or carotid artery stenting (CAS). The present study reports the "real-world" practice in peri-procedural antiplatelet therapy among collaborators in ACST-2.

Objective: Strokes are infrequent but potentially serious complications following carotid intervention, but antiplatelet therapy can reduce these risks. There are currently no specific guidelines on dose or duration of peri-procedural antiplatelet treatment for patients undergoing carotid intervention. Within the ongoing Asymptomatic Carotid Surgery Trial-2 (ACST-2), this study aimed at assessing the current use of antiplatelet therapy before, during, and after CEA and CAS in patients with asymptomatic carotid stenosis.

Methods: Questionnaires were sent to ACST-2 collaborators seeking information about the use of antiplatelet therapy during the pre-, peri-, and post-operative periods in patients undergoing carotid intervention at 77 participating sites and also whether sites tested for antiplatelet therapy resistance.

Results: The response rate was 68/77 (88%). For CAS, 82% of sites used dual antiplatelet therapy (DAPT) pre-operatively and 86% post-operatively with a mean post-procedural duration of 3 months (range 1–12), while 9% continued DAPT life-long. For CEA only 31% used DAPT pre-operatively, 24% post-operatively with a mean post-procedural duration of 3 months (range 1–5), while 10% continued DAPT life-long. For those prescribing post-procedural mono antiplatelet (MAPT) therapy (76%), aspirin was more commonly prescribed (59%) than clopidogrel (6%) and 11% of centres did not show a preference for either aspirin or clopidogrel. Eleven centres (16%) tested for antiplatelet therapy resistance.

Conclusion: There appears to be broad agreement on the use of antiplatelet therapy in ACST-2 patients undergoing carotid artery stenting and surgery. Although evidence to help guide the duration of peri-procedural antiplatelet therapy is limited, long-term treatment with DAPT appears similar between both treatment arms.

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INTRODUCTION

Stroke is a leading cause of morbidity and mortality worldwide.[1] Randomised trials in patients with carotid artery narrowing have shown that carotid endarterectomy (CEA) with medical treatment reduces 5 and 10 year stroke risk compared with medical treatment alone.[2,3] A feared peri-operative complication is embolism from the narrowed carotid plaque leading to distal vascular occlusion and ischaemic stroke.[4,5] Antiplatelet therapy reduces the risk of occlusive vascular events, but can also cause bleeding (the risk of which may be increased substantially with more intensive regimens).[6,7] There are no specific guidelines on dose and duration on peri-procedural antiplatelet treatment to help clinical proposal design for patients undergoing carotid intervention.[8,9] In previous carotid trials comparing CEA and CAS, single antiplatelet therapy (usually

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aspirin) was used for CEA, and dual antiplatelet therapy (usually clopidogrel and aspirin) was either recommended or mandated.[10–12]

The Asymptomatic Carotid Surgery Trial-2 (ACST-2) is the largest clinical trial of interventional treatment for asymptomatic carotid disease, randomising patients to either CEA or carotid artery stenting (CAS). ACST-2 will compare the immediate hazards of both procedures and subsequent stroke rates over the next 5–10 years.[13] Collaborators from 26 countries worldwide are experienced surgeons and interventionists, and the choice of peri-procedural antithrombotic treatment is at the clinicians' discretion. This gives a unique opportunity to study "real-world" practice in peri-procedural antiplatelet therapy. Therefore, the aim of the present study was to describe the use of antiplatelet therapy for both carotid surgery and stenting among collaborators in the ACST-2 trial.

METHODS

ACST-2

The aims and methods used in ACST-2 have been described previously.[13] Briefly, patients with severe asymptomatic carotid stenosis in which revascularisation is felt to be indicated, are randomised in a 1:1 fashion between CAS and CEA. The trial is multicentre and international, thereby facilitating large-scale recruitment of an appropriately heterogeneous and representative group. However, the majority of recruiting centres (93%) are located in Europe and therefore the study largely reflects antiplatelet therapy in Europe. The trial protocol states that all patients should receive appropriate medical treatment, including antiplatelet therapy, but the use and dose of specific antiplatelet drugs (and other drugs) are left to the discretion of the treating physician.

Study

This study questionnaire was administered in August 2014 and addressed four areas of practice: (1) pre-procedural antiplatelet therapy (in CAS and CEA); (2) intra-procedural antiplatelet therapy (CAS and CEA); (3) post-procedural antiplatelet therapy (CAS and CEA); and (4) testing of antiplatelet resistance; Collaborators who failed to respond were sent a reminder e-mail to participate in the study after 4 and 8 weeks. Seventy-seven of the currently active and recruiting centres in ACST-2 were studied; these studies had recruited a total of 1645 patients to ACST-2. In these centres, 75 performed both CAS and CEA and two performed CEA only.

Statistical analysis

Statistical analysis was performed using SPSS (IBM version 22, 2013). If an answer to duration of antiplatelet therapy was given as a range, the midpoint was taken for the subsequent analysis. Chi-square test was applied to compare pre-, intra- and post-procedural antiplatelet therapy, and a Mann-Whitney *U* test was used to compare means between two treatments. A *p*-value was considered significant when $<.05$.

RESULTS

Response

This study was completed in 66 of 75 centres (88% for CAS) and 61 of 77 centres (79% for CEA). These centres had randomised 1407/1645 patients in ACST-2 (85% of the overall randomisation) from 20 different countries.

Carotid artery stenting

Nearly all responding collaborators who performed CAS had a specific protocol for pre-procedural antiplatelet therapy (65/66 [98%]). The majority treated patients with dual antiplatelet therapy (DAPT) prior to stenting (53/65 [82%]). In nearly all centres (52/53 [98%]) DAPT consisted of aspirin and clopidogrel. One centre prescribed aspirin in combination with either clopidogrel or ticagrelor. Other pre-procedural treatment regimens consisted of aspirin only (3/65 [5%]), clopidogrel only (6/65 [8%]), or triple antiplatelet therapy (3/65 [5%]).

During CAS, all patients received heparin and pre-procedural antiplatelet therapy was continued. One centre also routinely used intra-procedural dextran.

After stenting, all patients received at least aspirin or clopidogrel as life-long therapy. The majority of centres (51/66 [77%]) used DAPT for a defined period post-stenting, followed by life-long single antiplatelet therapy. The drug of preference for life-long treatment was aspirin in 68% of the centres (45/66) and clopidogrel in 6/66 centres (9%). In 51 centres, 12 (24%) administered DAPT for up to 4 weeks and 39 centres (76%) extended DAPT beyond the procedural period (median 3; range 1–12 months). A small proportion of respondents stated that they would give life-long DAPT (6/66 [9%]) or just use life-long single antiplatelet therapy (5/66 [8%]). Four centres treated patients with 9 months of prasugrel or cilostazol (4/66 [6%]) in addition to DAPT (Table 1).

Carotid endarterectomy

For CEA, collaborators had a protocol for pre-operative antiplatelet therapy protocol in 55 out of the 61 responding centres (90%). The remaining six centres continued baseline therapy at randomisation.

Prior to the procedure, most patients received aspirin as single antiplatelet therapy (36/55 [65%]). In 17 centres (31%) dual antiplatelet therapy was used. The number of centres that prescribed DAPT prior to CEA was significantly lower than the use of DAPT prior to CAS ($p < .05$). DAPT consisted of aspirin and clopidogrel in 14 centres. Three centres prescribed aspirin in combination with dipyridamole. In one centre (2%) clopidogrel was used as a single antiplatelet agent. Other pre-procedural treatments consisted of triple antiplatelet therapy in one centre. Patients undergoing CEA received similar intra-operative antiplatelet treatment to patients undergoing CAS: in all centres heparin

Table 1. Peri-procedural antiplatelet therapy for carotid artery stenting (CAS) and carotid endarterectomy (CEA) among 68 centres.[a]

Pre-procedural	CAS ($n = 66$)	CEA ($n = 61$)
Do you have a pre-procedural protocol?	Yes (98%)	Yes (90%)
	No (2%)	No (10%)
Do you generally give?		
MAPT		
Aspirin	5%	65%
Clopidogrel	8%	2%
DAPT	82%	31%
TAPT	5%	2%
Intra-procedural		
Do you generally give?		
Heparin + continued antiplatelet	98%	98%
Dextran additionally	2%	2%
Post-procedural		
Do you generally give?		
DAPT	86%	24%
MAPT		
Aspirin	6%	59%
Clopidogrel	1%	6%
Aspirin or clopidogrel (no preference)	1%	11%
TAPT	6%	0%
Duration		
MAPT (aspirin or clopidogrel) life-long	100%	100%
DAPT life-long	9%	10%
DAPT for (median; range)	77% (3; 1—12)	14% (3; 1—5)
then aspirin life-long	68%	14%
then clopidogrel life-long	9%	0%
Resistance		
Do you test for antiplatelet resistance?		
Yes	11/68 centres (16%)	
Aspirin	6 centres	
Clopidogrel	11 centres	

MAPT = mono antiplatelet therapy; DAPT = dual antiplatelet therapy; TAPT = triple antiplatelet therapy.

[a] Response to both CAS and CEA questionnaire = 59 centres; response to CAS questionnaire only = 7 centres; response to CEA questionnaire only = 2 centres.

was administered and pre-procedural antiplatelet therapy was continued. The same centre that routinely prescribed dextran during the CAS procedure also prescribed dextran during CEA.

Post-procedurally, centres used life-long aspirin or clopidogrel for all CEA patients, similar to present findings in the CAS group. Fifteen centres (24%) prescribed DAPT after CEA, and usually for a defined period; thus the use of DAPT after surgery was significantly lower than after CAS ($p < .05$). Six of 61 centres (10%) continued dual antiplatelet therapy life-long. Of the remaining nine centres, two prescribed DAPT for up to 4 weeks and seven extended the use of DAPT beyond the procedural period (median 3; range 1—5 months). The median duration of DAPT use was not significantly different between CAS and CEA ($p = .74$). The drug of choice for life-long use following CEA was aspirin.

Regional variation

Table S1 (supplementary material) gives an overview of participating countries in this survey and their pre-and post-procedural antiplatelet therapy for CAS and CEA. Fig. 1 shows the prescription rates described within different regions. Before the procedure antiplatelet treatment regimens did not vary widely between different regions (Figs. 1A, C). Post CAS, life-long DAPT was more often prescribed in Western Europe compared with other regions (Fig. 1B). After CEA, all centres in Northern Europe prescribed MAPT therapy, all Eastern European centres prescribed DAPT, whereas both MAPT and DAPT treatments regimens were used in other countries (Fig. 1D).

Antiplatelet resistance

A small proportion (11/68; 16%) of responding centres performs platelet function tests for detection of resistance to antiplatelet drugs. Eleven centres tested for resistance to aspirin. In addition, six of these 11 centres also tested for clopidogrel resistance. The current survey was not designed to answer the question of how centres tailored their procedural antiplatelet therapy based on platelet function tests.

DISCUSSION

In this study describing the use of antiplatelet therapies by collaborators in ACST-2 during the pre- and post-procedural periods, most patients undergoing CAS were treated with DAPT, whereas patients undergoing CEA received a single antiplatelet drug. Intra-operative regimens were similar for both procedures, all collaborators using heparin and continued antiplatelet therapy. After the procedures, more CAS than CEA patients received DAPT, and the median duration of DAPT (30 days) was similar for both procedures.

This is the first large survey comparing pre-, intra- and post-procedural antiplatelet therapy for CAS and CEA. Previous surveys addressing procedural antiplatelet treatment have focused on vascular surgical procedures in general,[14] on only carotid endarterectomy[15] or on technical aspects of the procedure.[16] In 2009, in a survey of 650 European surgeons, Hamish et al. found broad agreement between vascular surgeons in the peri-procedural management of patients undergoing CEA. For symptomatic patients and asymptomatic patients 95% and 88% of surgeons would continue aspirin prior to CEA. Of those surgeons prescribing clopidogrel, about half would stop this drug prior to treatment.[15] The present survey allowed assessment of antiplatelet variations across regions. More variation existed in post-procedural treatment. For CAS, DAPT was more often prescribed in Western Europe. Following CEA, all centres in Northern Europe prescribed MAPT, all Eastern European

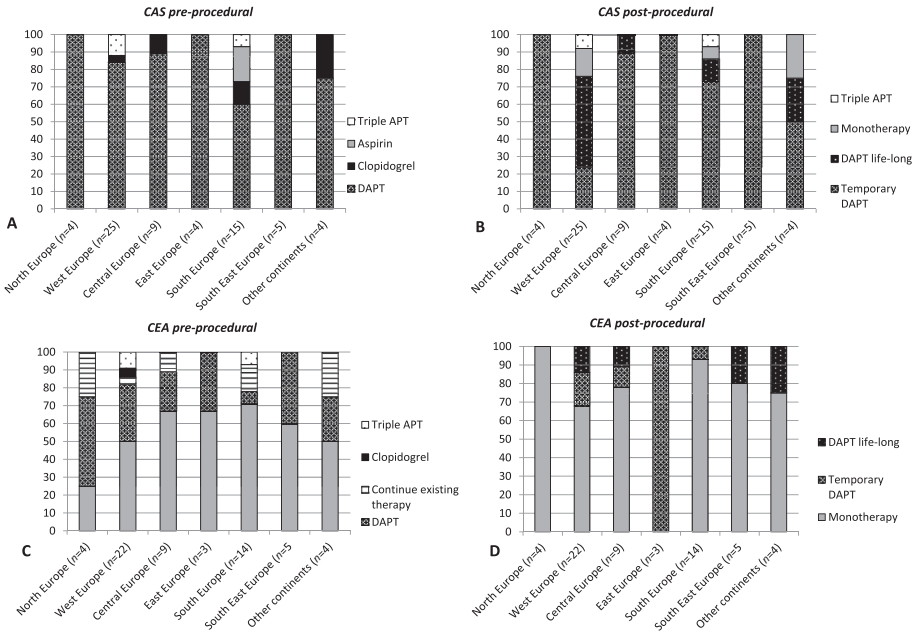

Figure 1. Pre- (A, C) and post-procedural (B, D) antiplatelet therapy per region.

centres prescribed DAPT, whereas both MAPT and DAPT treatments regimens existed in other regions. This could reflect the lack of specific guidelines on dose and duration on peri-procedural antiplatelet treatment. Current guidelines include the following suggestions for antiplatelet treatment in the procedural period: for CEA, "aspirin should be continued in the pre- and postprocedural period,"[17] "aspirin should be given at a dose of 75—325 mg daily", "more data are required to establish the role of clopidogrel,"[9] and "aspirin should not be discontinued before CEA, patients taking combination of aspirin plus clopidogrel are at higher risk of major bleeding."[18] For CAS, guidelines state that the procedure should be performed under DAPT, with aspirin and clopidogrel,[9] or aspirin and ticlopidine.[18] Duration of DAPT after CAS varies from no recommendations,[17] to at least 1 month[18] or 3 months.[9]

The rationale for antiplatelet therapy in patients with severe carotid artery stenosis is twofold: (1) reduction of peri-operative primary embolic or thrombotic stroke and (2) long-term stroke prevention. A clear distinction between these two is found when discussing our results and the current literature. In terms of long-term prevention, a low dose of aspirin (75—150 mg) is thought to be protective in all patients at increased risk of occlusive vascular events.[6] In patients without clear evidence of vascular disease, aspirin is of uncertain value as the beneficial effects may be outweighed by an increased risk of bleeding.[7] Antiplatelet therapy for long-term prevention of atherothrombotic events has been studied in several recent large trials, but these do not relate to peri-procedural stroke prevention.[19,20] In the CHARISMA trial, 15,603 patients with either clinically evident cardiovascular disease or multiple risk factors received clopidogrel plus low-dose aspirin or placebo plus low-dose aspirin, and were followed up for a median of 28 months. Clopidogrel plus aspirin was not significantly more effective than aspirin alone in reducing the rate of myocardial infarction, stroke, or death from cardiovascular causes.[19] In the MATCH trial, 7,599 high-risk patients with recent ischaemic stroke or TIA were randomly assigned to receive either aspirin or a placebo in addition to clopidogrel and were followed up for 18 months. A non-significant reduction of major vascular events was observed when aspirin was added to clopidogrel. However, the risk of life-threatening or major bleeding was increased in the dual antiplatelet cohort.[20] Beneficial effects of DAPT have been observed in the CARESS trial. In this small study of 230 patients with recently symptomatic $\geq$50% carotid stenosis, combination therapy with clopidogrel and aspirin was more effective than aspirin alone in reducing transcranial detected cerebral asymptomatic embolisation.[21] However, the primary end-point consisted of asymptomatic embolisation detected on day 7 and the trial did not report any long-term results. Therefore, the beneficial effect of DAPT in long-term primary and secondary prevention is still unclear.

There is an important distinction to be made between procedural risk and long-term prevention. Thromboembolic stroke as a result of carotid embolisation is a well-known complication of both carotid surgery and stenting; in surgery embolisation can occur intra-procedurally when atherothrombotic debris is released either spontaneously from the unstable carotid plaque, or through surgical manipulation. Post-procedural carotid embolisation can also occur from thrombus formation on the endarterectomised vessel surface. In the present study, the majority of surgeons prescribed aspirin prior to CEA. This is consistent with a recent systematic review showing the significant benefit of antiplatelet therapy over no treatment or placebo in reducing the risk of any stroke, and this supports the routine use of antiplatelet drugs in patients undergoing

CEA.[22] Despite aspirin therapy and adequate heparinisation, thromboembolic stroke still occurs in the peri-procedural period. Therefore, the addition of an antiplatelet drug acting through a different pathway may be of more benefit than aspirin alone. The results of two small studies seem to support this hypothesis and report that a single dose of 75 mg clopidogrel (administered the night before surgery) significantly reduced transcranial detected cerebral embolisation post CEA.[23] However, most of these patients (84%) were symptomatic. In the present study of asymptomatic patients, 30% of surgeons prescribe DAPT therapy prior to CEA.

In carotid artery stenting, two mechanisms can cause peri-procedural thromboembolic stroke: (1) distal embolisation from a destabilised carotid plaque and (2) thrombus formation following intimal injury. Protection devices have been developed to try to reduce distal embolisation but, for the second proposed mechanism, antiplatelet therapy plays an important role. In the present study the majority of interventionists prescribe DAPT before and after CAS. A dual antiplatelet regime has been shown to reduce adverse events without increasing bleeding in several small studies and is now considered to be routine pre-operative practice during CAS.[24–26] The optimal duration for DAPT post stenting is less well established, but treatment for at least 4 weeks is usually recommended.[8] As coronary intervention has a longer history than CAS, the standard peri-procedural antithrombotic therapy is mainly based on large comparative studies in coronary intervention.[27] In the present survey, 39 centres (76%) extended therapy well beyond the procedural period and 9% administered life-long DAPT. Stent endothelialisation takes some time and late stent thrombosis (>30 days) has been reported in coronary artery stenting, with an annual rate reported ranging from 0.6% to 1.6%.[28,29] Prolonged use of clopidogrel and aspirin has also been associated with a decrease in long-term major vascular events.[30,31] It may be important in the future to try to define the optimal duration of dual antiplatelet therapy for carotid artery stenting. Furthermore, this lack of evidence should be made clear in the current guidelines that lead the present clinical practice.

Currently, there is also ongoing interest in the role of antiplatelet reactivity testing in carotid revascularisation. A recent review, including 102 studies (on 44,098 patients) showed that high on-treatment platelet reactivity (HPR), leading to impaired efficacy of antiplatelet therapy was diagnosed in 22% of patients taking aspirin and in 40% of patients taking clopidogrel and that HPR was associated with an increased risk of cerebrovascular events.[32] In the present survey, only 16% of responding centres performed platelet function tests to detect resistance to antiplatelet drugs. Although platelet reactivity testing is an interesting concept and may help provide “personalised medicine” for patients at increased vascular risk, more studies are needed to investigate its utility in routine daily practice. Previous studies used many different antiplatelet tests and there is no single platelet reactivity test that is superior. Furthermore, there is no evidence that change in antiplatelet therapy based on results of platelet reactivity tests will improve clinical outcomes.

The present study has several limitations. First of all, the survey did not address the use of high-dose boluses of clopidogrel, neither the use of vitamin K antagonists. Hence, the present study is limited to reporting the use of antiplatelet therapy among collaborators in ACST-2. Second, although ACST-2 is an international trial, most trial centres (and hence responses) are European. Therefore, the present results might be best interpreted as standard use of antiplatelet therapy in European countries.

CONCLUSION

In conclusion, despite the lack of guidelines, there appears to be broad agreement among ACST-2 collaborators on the long-term use of antiplatelet therapy patients undergoing carotid artery stenting and surgery. However, in the early post-procedural period some variation exists, with more CAS patients receiving DAPT.

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CONFLICT OF INTEREST

None.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejvs.2015.11.002.

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