**Editor’s Choice – Risk of Bleeding Complications With Different Peri-Operative Antithrombotic Regimens During Carotid Endarterectomy: a National Registry Analysis**

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**WHAT THIS PAPER ADDS**

The dual antiplatelet therapy (DAPT) recommendation after ischaemic stroke or transient ischaemic attack (TIA) is based on large randomised controlled trials that excluded patients undergoing carotid endarterectomy (CEA). The current study supports the safety of DAPT during the peri-operative period of CEA. Given the high recurrent risk of stroke in symptomatic patients and the thromboembolic risk in the early post-operative period, the present authors recommend urgent DAPT after ischaemic stroke/TIA until 30 days after CEA followed by single antiplatelet therapy.

**Objective:** Antithrombotic therapy is one of the cornerstones of the prevention of (recurrent) ocular or cerebral ischaemic events in patients with carotid artery stenosis. Randomised controlled trials on antithrombotic therapy for patients with minor ischaemic stroke and transient ischaemic attack (TIA) have recommended dual antiplatelet therapy (DAPT) in the three weeks following the index event. However, these trials excluded patients undergoing carotid revascularisation. To date, the optimal antithrombotic therapy during the peri-operative period of carotid endarterectomy (CEA) remains unclear.

**Methods:** Symptomatic and asymptomatic patients with carotid artery stenosis undergoing primary CEA from the Dutch Audit for Carotid Interventions registry between June 2013 and December 2020 were eligible for inclusion. The primary outcome was defined as post-operative cervical bleeding needing re-intervention or intracranial haemorrhage during the first 30 days following CEA. The secondary outcomes were ischaemic stroke or TIA or all cause mortality during the first 30 days following CEA. Descriptive statistics and multiple logistic regressions analyses were applied, with acetylsalicylic acid (ASA) as the reference value.

**Results:** A total of 12 317 patients were included. In the peri-operative phase, 31.0% of patients were treated with ASA, 32.4% with clopidogrel, 11.1% with ASA plus clopidogrel, 10.4% with ASA plus dipyridamole, 10.3% with vitamin K antagonist, and 4.8% with direct acting oral anticoagulants therapy. After multiple logistic regression analysis, no association was seen with the primary outcome in ASA plus clopidogrel (odds ratio [OR] 0.81; confidence interval [CI] 0.58 – 1.13; p = .23), and ASA plus dipyridamole (OR 0.69; CI 0.47 – 1.00; p = .059). Both the DAPT therapies were not associated with the secondary outcome.

**Conclusion:** The effectiveness and safety of DAPT did not differ from single antiplatelet therapy (SAPT) in patients undergoing CEA and further evaluation is needed in prospective studies. Considering additional data from the literature and guideline recommendations, DAPT should be started immediately after stroke until 30 days after CEA followed by SAPT, due to a possible reduction in the risk of recurrence.

**Keywords:** Bleeding complications, Carotid endarterectomy, Carotid stenosis, Stroke

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**INTRODUCTION**

Ischaemic stroke can result from thromboembolism originating from a proximal source such as an atherosclerotic carotid artery stenosis. Thromboembolism can be prevented by antithrombotic therapy, which therefore plays a crucial role in the prevention of (recurrent) ocular or cerebral ischaemic events. Both the Platelet Oriented
Inhibition in New TIA and Minor Ischaemic Stroke (POINT)\(^4\) and Clopidogrel in High Risk Patients with Acute Non-disabling Cerebrovascular Events (CHANCE)\(^5\) studies showed that dual antiplatelet therapy (DAPT) consisting of clopidogrel and acetylsalicylic acid (ASA) reduced the early risk of a recurrent stroke (ischaemic or haemorrhagic) after the event when compared with single antiplatelet therapy (SAPT).\(^6\) The greatest benefit was observed with a therapy duration of 21 days.\(^7\) Of note, both POINT and CHANCE included symptomatic patients with a recent ischaemic event, but excluded patients undergoing carotid revascularisation. Of major concern, the effect of DAPT on the risk of peri-operative bleeding complications remained unknown. The recent 2023 clinical practice guidelines of the European Society for Vascular Surgery (ESVS) recommend considering early institution of DAPT after TIA or minor stroke to reduce the risk of early recurrent ischaemic events in patients with a > 50% carotid artery stenosis awaiting carotid endarterectomy (CEA).\(^3\)

In the past, registries and retrospective cohort studies showed higher bleeding rates in patients on DAPT undergoing CEA compared with patients on SAPT.\(^8\)–\(^10\) These observations might vary from local neck haematoma, to increased re-interventions for post-operative bleeding, and a higher prevalence of intracranial haemorrhage (ICH). More recently, a meta-analysis reported an increase in bleeding complications in patients treated with DAPT compared with those treated with SAPT, without any benefit from DAPT in the prevention of peri-operative thrombotic events after CEA.\(^11\) Studies analysing alternative peri-operative antithrombotic regimens, such as direct acting oral anticoagulants (DOAC) or vitamin K antagonists (VKA), in CEA patients are scarce.

The optimal treatment strategy regarding the use of antithrombotic therapy in the CEA peri-operative period remains unresolved.\(^12\) In the Netherlands, all patients undergoing CEA for atherosclerotic stenotic disease are prospectively registered in the Dutch Audit for Carotid Interventions (DACI) registry. Using this nationwide ongoing prospective audit database, the primary aim of the present study was to investigate the association between SAPT and DAPT with the risk of bleeding complications after CEA, taking into account the risk of peri-procedural ischaemic events. Secondly, comparable analyses were performed for the DOAC and VKA regimens.

**METHODS**

**Data source**

The DACI is a nationwide mandatory and ongoing prospective Dutch audit, in which data of all consecutive patients undergoing carotid revascularisation for atherosclerotic stenotic disease are registered with a total follow up of 30 days since June 2013. A detailed description of the registry has been published before.\(^13\) In short, the DACI was initiated by the Dutch Society for Vascular Surgery, a professional national association for vascular surgeons, with the objective to measure and improve the quality of care in patients requiring carotid revascularisation. The DACI is facilitated by the Dutch Institute for Clinical Auditing.\(^6\) The eligibility for each patient undergoing carotid artery revascularisation was reviewed by a multidisciplinary vascular team in each of the 53 participating Dutch centres. CEA was performed following the recommendations of international randomised controlled trials (RCTs) and ESVS guidelines.\(^3\)

**Study population**

A retrospective analysis was performed using the prospectively collected data of the DACI registry. A total of 17 884 patients who underwent CEA between June 2013 and December 2020 were registered in the DACI database. All patients were eligible for inclusion except when no antithrombotic therapy was registered (given this may involve inaccurate data), unusual antithrombotic therapy combinations (as judged by consensus among the authors) were prescribed, redo CEA was performed, or patients were under the age of 40 years (as carotid revascularisation is not performed regularly in patients < 40 years and a history of, e.g., coagulation disorders or fibromuscular dysplasia were not documented within the DACI registry). In all centres, the use and dose of heparin during surgery was left to the discretion of the treating physician. The data were collected with a waiver of patient consent, as is common in clinical audits.

**Data collection**

Patient demographics and characteristics, including age, sex, medication use (peri-procedural antithrombotic, anti-hypertensive, and lipid lowering drugs), peri-operative systolic blood pressure, haemoglobin and creatinine, date and type of index event, surgical technique, shunt use, and date of procedure were obtained from the DACI registry. The index event was classified as patients with carotid artery stenosis presenting with cerebral ischaemic events from the ipsi- or contralateral carotid artery, ocular ischaemic events from the ipsi- or contralateral stenotic carotid artery, or cerebral events from the posterior circulation within the previous six months. Patients who did not experience any ischaemic event or had symptoms longer than six months ago were considered to be asymptomatic patients. The peri-operative antithrombotic regimens that are included in the current study are categorised into the following groups: SAPT including ASA and clopidogrel, and DAPT including ASA plus clopidogrel or ASA plus dipyridamole. As antithrombotic therapy with DOAC and VKA is available from the DACI registry, these anticoagulation regimens were added to the analysis in addition to the conventional regimens.

**Clinical outcome**

The primary outcome was a composite endpoint consisting of post-operative cervical bleeding for which a re-intervention was performed or ICH within the first 30 days following CEA. In addition, post-operative cervical bleeding for which a re-intervention was performed was analysed separately. The secondary outcomes were
ischaemic stroke or TIA and all cause mortality within the first 30 days following CEA. Ischaemic stroke or TIA consists of an ipsilateral or contralateral ischaemic event. In sub-analysis, the association with cranial nerve palsy (CNP) was examined in patients who underwent a re-intervention because of post-operative cervical bleeding.

**Statistical analysis**

Baseline characteristics and the primary and secondary outcomes were compared between the five antithrombotic regimens and ASA separately, using ASA as the reference group. The data were inspected for patterns of missing values. The proportion of randomly missing values for baseline characteristics did not exceed 2% and was considered eligible. Baseline characteristics were compared between the different regimens by chi square test for categorical variables and Student t test for continuous variables. To investigate the independent association between antithrombotic regimens and clinical outcome, multivariable logistic regression analysis was performed. Baseline characteristics that showed an association of $p < .20$ with the determinant (antithrombotic therapy) and outcome of interest (post-operative cervical bleeding for which a re-intervention was performed, ICH, any stroke/TIA, all cause mortality, and CNP) were considered as potential confounders for multivariable analyses (Supplementary Fig. S1). Based on the literature, type of procedure and index event were added as confounders.\(^{15,16}\) Values with $p < .050$ were considered to be statistically significant. All statistical analyses were performed using R computing platform version 4.0 (R Project for Statistical Computing, Vienna, Austria).

**RESULTS**

A total of 12 317 patients registered in the DACI database were included in the current study (Fig. 1). The study population was predominantly male (70.7%) with a mean age of 73.1 ± 8.9 years and had a symptomatic presentation (93.7%). The majority underwent CEA with patch angioplasty (78.4%) and were treated within two weeks after the presenting symptom (56.4%). A total of 3 819 (31.0%) patients were treated with ASA, 3 994 (32.4%) with clopidogrel, 1 362 (11.1%) with ASA plus clopidogrel, 1 282 (10.4%) with ASA plus dipyridamole, 1 264 (10.3%) with VKA, and 596 (4.8%) with DOAC antithrombotic therapy (Table 1).

The primary composite outcome occurred in 494 (4.0%) patients. With respect to the different antithrombotic regimens, the risk of the primary outcome was 4.3% in patients receiving ASA, 3.6% in clopidogrel, 3.5% in ASA plus clopidogrel, 2.9% in ASA plus dipyridamole, 6.4% in VKA, and 3.3% in DOAC. The secondary outcome ischaemic stroke or TIA occurred in 2.4% of patients, whereas all cause death occurred in 1.1% within 30 days after CEA (Table 2).

In multiple logistic regression analysis, correcting for confounders such as index event, both SAPT with clopidogrel and the two DAPT groups were not associated with a higher risk of the primary composite outcome. Treatment with ASA plus dipyridamole was inversely associated with the risk of post-operative cervical bleeding for which re-interventions were performed (odds ratio [OR] 0.64; 95% confidence interval [CI] 0.42 — 0.94; $p = .028$). The secondary outcomes of ischaemic stroke or TIA and all cause death did not differ statistically significantly between the antiplatelet regimens. VKA treatment was independently associated with a higher risk of the primary composite outcome (OR 1.45; CI 1.08 — 1.93; $p = .013$). Also, a statistically significantly higher risk of ischaemic stroke or TIA (OR 2.09; CI 1.43 — 3.03; $p < .001$) and all cause mortality (OR 2.44; CI 1.41 — 4.21; $p = .001$) was seen in patients treated with VKA. DOAC treatment was only independently associated with a higher risk of any stroke or TIA (OR 3.06; CI 1.94 — 4.73; $p < .001$) (Fig. 2). Because of the low event rate of ICH, no multivariable analysis could be performed.

In a separate multiple logistic regression analysis, no association was seen between post-operative cervical bleeding for which a re-intervention was performed and the risk of CNP (OR 1.23; CI 0.65 — 2.12, $p = .48$) (Supplementary Table S2).

**DISCUSSION**

This study investigated the risk of bleeding complications after CEA based on a nationwide registry. It was demonstrated that DAPT has a similar risk to SAPT for peri-procedural bleeding complications. The results indicated that DAPT might safely be continued during the CEA peri-

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**Figure 1.** Flowchart of included symptomatic and asymptomatic patients treated with primary carotid endarterectomy (CEA) from the Dutch Audit for Carotid Interventions (DACHI) registry to study the effect of peri-operative antithrombotic regimen on outcome.
operative period in patients who are at high risk of early recurrent cerebral or retinal ischaemic events.

Large RCTs\(^4\)\(^5\) consistently showed a clear benefit of DAPT to prevent recurrent stroke after acute minor ischaemic stroke or TIA, while the evidence of DAPT during CEA procedures in patients with carotid artery stenosis remains lacking. This study did not demonstrate any benefit of DAPT over SAPT in terms of prevention of peri-operative ischaemic events after CEA in mainly recently symptomatic patients.

Today, the treatment of choice during CEA depends on the clinical preference of the treating interventionist, as confirmed with a current worldwide electronic survey for the management of acute symptomatic carotid artery stenosis.\(^1\)\(^7\)

In contrast to the present study, a 2022 meta-analysis including two RCTs and nine observational studies\(^11\) found that DAPT was associated with an increased risk of re-reoperation for bleeding and neck haematoma after CEA vs. SAPT with aspirin. In line with the present results, no

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n = 12 317)</th>
<th>ASA (n = 3 819)</th>
<th>Clopidogrel (n = 3 994)</th>
<th>ASA + clopidogrel (n = 1 362)</th>
<th>ASA + dipyridamole (n = 1 282)</th>
<th>VKA (n = 1 264)</th>
<th>DOAC (n = 596)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — y</td>
<td>73.1 ± 8.9</td>
<td>73.2 ± 8.7</td>
<td>72.1 ± 9.2</td>
<td>72.2 ± 9.1</td>
<td>72.4 ± 9.1</td>
<td>76.6 ± 7.6</td>
<td>75.8 ± 7.2</td>
</tr>
<tr>
<td>Female sex</td>
<td>3 608 (29.3)</td>
<td>1 133 (29.7)</td>
<td>1 278 (32.0)</td>
<td>416 (30.5)</td>
<td>345 (26.9)</td>
<td>288 (22.8)</td>
<td>148 (24.8)</td>
</tr>
<tr>
<td>Statin use at baseline</td>
<td>9 630 (78.2)</td>
<td>2 759 (72.5)</td>
<td>3 312 (83.0)</td>
<td>1 164 (85.6)</td>
<td>1 062 (83.2)</td>
<td>890 (70.6)</td>
<td>443 (74.5)</td>
</tr>
<tr>
<td>Antihypertensive drug use at baseline</td>
<td>8 445 (66.8)</td>
<td>2 718 (76.3)</td>
<td>2 569 (64.5)</td>
<td>980 (72.2)</td>
<td>669 (70.2)</td>
<td>1 026 (85.7)</td>
<td>483 (81.0)</td>
</tr>
<tr>
<td><strong>Index event</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>776 (6.3)</td>
<td>227 (5.9)</td>
<td>218 (5.5)</td>
<td>59 (4.3)</td>
<td>186 (14.5)</td>
<td>68 (5.4)</td>
<td>18 (3.0)</td>
</tr>
<tr>
<td>Cerebral symptoms from SCA</td>
<td>9 252 (75.1)</td>
<td>2 880 (75.5)</td>
<td>3 049 (76.4)</td>
<td>1 055 (77.5)</td>
<td>897 (70.1)</td>
<td>934 (74.0)</td>
<td>437 (73.3)</td>
</tr>
<tr>
<td>Ocular symptoms from SCA</td>
<td>2 215 (18.0)</td>
<td>681 (17.8)</td>
<td>709 (17.8)</td>
<td>243 (17.9)</td>
<td>186 (14.5)</td>
<td>255 (20.2)</td>
<td>141 (23.7)</td>
</tr>
<tr>
<td>Cerebral symptoms from posterior circulation</td>
<td>66 (0.5)</td>
<td>28 (0.7)</td>
<td>17 (0.4)</td>
<td>4 (0.3)</td>
<td>11 (0.9)</td>
<td>6 (0.5)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Treated side right side</td>
<td>5 725 (46.5)</td>
<td>1 812 (50.5)</td>
<td>1 925 (48.2)</td>
<td>668 (49.2)</td>
<td>466 (47.9)</td>
<td>567 (47.1)</td>
<td>287 (48.2)</td>
</tr>
<tr>
<td>Pre-operative systolic blood pressure (mmHg)</td>
<td>148 ± 23.0</td>
<td>148 ± 23</td>
<td>149 ± 23</td>
<td>148 ± 23</td>
<td>147 ± 23</td>
<td>145 ± 23</td>
<td>146 ± 23</td>
</tr>
<tr>
<td>Pre-operative serum haemoglobin (mmol/L)</td>
<td>8.6 ± 1.1</td>
<td>8.6 ± 1.4</td>
<td>8.7 ± 1.0</td>
<td>8.6 ± 1.1</td>
<td>8.7 ± 1.0</td>
<td>8.5 ± 1.1</td>
<td>8.5 ± 1.1</td>
</tr>
<tr>
<td>Pre-operative serum creatinine (mmol/L)</td>
<td>94.3 ± 38.2</td>
<td>94.5 ± 38.7</td>
<td>91.3 ± 36.3</td>
<td>94.0 ± 41.3</td>
<td>92.0 ± 28.8</td>
<td>105.2 ± 49.5</td>
<td>94.9 ± 26.6</td>
</tr>
<tr>
<td><strong>Type of procedure</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CEA without patch angioplasty</td>
<td>1 234 (10.0)</td>
<td>386 (10.1)</td>
<td>338 (8.5)</td>
<td>122 (9.0)</td>
<td>197 (15.4)</td>
<td>143 (11.3)</td>
<td>48 (8.1)</td>
</tr>
<tr>
<td>CEA with patch angioplasty</td>
<td>9 661 (78.4)</td>
<td>3 100 (81.2)</td>
<td>3 119 (78.1)</td>
<td>1 058 (77.7)</td>
<td>933 (72.8)</td>
<td>968 (76.6)</td>
<td>483 (81.0)</td>
</tr>
<tr>
<td>Eversion CEA</td>
<td>1 422 (11.5)</td>
<td>333 (8.7)</td>
<td>537 (13.4)</td>
<td>182 (13.4)</td>
<td>152 (11.9)</td>
<td>153 (12.1)</td>
<td>65 (10.9)</td>
</tr>
<tr>
<td>Shunting during surgery</td>
<td>2 392 (19.4)</td>
<td>820 (22.3)</td>
<td>622 (16.2)</td>
<td>287 (22.0)</td>
<td>294 (25.6)</td>
<td>253 (21.2)</td>
<td>116 (19.7)</td>
</tr>
<tr>
<td><strong>Time index event to CEA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 2 weeks</td>
<td>6 946 (56.4)</td>
<td>2 238 (59.4)</td>
<td>2 218 (56.0)</td>
<td>831 (61.3)</td>
<td>566 (45.0)</td>
<td>700 (56.0)</td>
<td>393 (65.9)</td>
</tr>
<tr>
<td>&gt; 2 weeks</td>
<td>4 467 (36.3)</td>
<td>1 304 (34.6)</td>
<td>1 525 (38.5)</td>
<td>465 (34.3)</td>
<td>506 (40.2)</td>
<td>482 (38.6)</td>
<td>185 (31.0)</td>
</tr>
<tr>
<td>Not applicable as asymptomatic status</td>
<td>776 (6.3)</td>
<td>227 (6.0)</td>
<td>218 (5.5)</td>
<td>59 (4.4)</td>
<td>186 (14.8)</td>
<td>68 (5.4)</td>
<td>18 (3.6)</td>
</tr>
</tbody>
</table>

Data are presented as n (%) or mean ± standard deviation. ASA = acetylsalicylic acid; CEA = carotid endarterectomy; DOAC = direct oral anticoagulant; SCA = stenotic carotid artery; VKA = vitamin K antagonist.

* Results of the chi square tests and Student t tests for the five antithrombotic regimens vs. ASA are available in Supplementary Table S1.
benefit was seen in terms of ischaemic stroke and TIA with DAPT in the same meta-analysis. However, the overall quality of evidence was low, and more research was deemed necessary. Later, a German nationwide data study analysing 117,973 patients showed a statistically significantly higher rate of secondary bleeding complications requiring re-intervention without reducing the risk of ischaemic stroke for patients using DAPT. In contrast, in a prospective audit of 100 consecutive patients, early introduction of DAPT was associated with a fivefold reduction in recurrent TIA prior to expedited CEA. Also, a fourfold reduction of spontaneous embolisation in the ipsilateral middle cerebral artery during 30 minutes transcranial Doppler monitoring on the afternoon prior to CEA was observed.

### Table 2. Post-operative clinical outcomes within 30 days after carotid endarterectomy in 12,317 symptomatic and asymptomatic patients with different antithrombotic regimens at baseline registered in the Dutch Audit for Carotid Interventions registry between June 2013 and December 2020

<table>
<thead>
<tr>
<th>Outcome per antithrombotic regimen</th>
<th>Total (n = 12,317)</th>
<th>ASA (n = 3,819)</th>
<th>Clopidogrel (n = 3,994)</th>
<th>ASA + clopidogrel (n = 1,362)</th>
<th>ASA + dipyridamole (n = 1,282)</th>
<th>VKA (n = 1,264)</th>
<th>DOAC (n = 596)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-operative cervical bleeding or intracranial haemorrhage</td>
<td>494 (4.0%)</td>
<td>164 (4.3%)</td>
<td>144 (3.6%)</td>
<td>48 (3.5%)</td>
<td>37 (2.9%)</td>
<td>81 (6.4%)</td>
<td>20 (3.3%)</td>
</tr>
<tr>
<td>Intracranial haemorrhage</td>
<td>36 (0.3%)</td>
<td>13 (0.3%)</td>
<td>12 (0.3%)</td>
<td>5 (0.4%)</td>
<td>4 (0.3%)</td>
<td>0 (0%)</td>
<td>2 (0.3%)</td>
</tr>
<tr>
<td>Ischaemic stroke/TIA</td>
<td>298 (2.4%)</td>
<td>74 (1.9%)</td>
<td>91 (2.3%)</td>
<td>25 (1.8%)</td>
<td>26 (2.0%)</td>
<td>52 (4.1%)</td>
<td>30 (5.0%)</td>
</tr>
<tr>
<td>All cause death</td>
<td>135 (1.1%)</td>
<td>32 (0.8%)</td>
<td>44 (1.1%)</td>
<td>10 (0.7%)</td>
<td>13 (1.0%)</td>
<td>29 (2.3%)</td>
<td>7 (1.2%)</td>
</tr>
</tbody>
</table>

Data are presented as n (%). ASA = acetylsalicylic acid; DOAC = direct oral anticoagulants; TIA = transient ischaemic attack; VKA = vitamin K antagonist.

### Figure 2. Multivariable logistic regression analysis of different antithrombotic therapies in clinical outcomes within 30 days after carotid endarterectomy in a total of 12,317 symptomatic and asymptomatic patients. ASA = acetylsalicylic acid; CI = confidence interval; DOAC = direct oral anticoagulants; OR = odds ratio; TIA = transient ischaemic attack; VKA = vitamin K antagonist.
seen. Surprisingly, the present study demonstrated that DAPT with ASA plus dipyridamole was inversely associated with the risk of post-operative cervical bleeding for which re-interventions were performed. Based on the working mechanism of both drugs, one would suspect a higher risk of peri-operative bleeding complications. A possible explanation could be that the team involved in the procedure was aware of a higher bleeding risk, and extra caution was taken with heparin administration and operation time. This hypothesis needs further validation, however, for which information on total surgery time and total heparin and protamine administered during surgery are needed.

The 2014 ESC/ESA Guidelines on non-cardiac surgery reported that patients treated with anticoagulant therapy are known to have an increased risk of bleeding during surgical procedures, and drug therapy should only be maintained if the risk of bleeding will be outweighed by the benefit of the anticoagulant. In line with the present results, a prospective multicentre study analysing 280 symptomatic carotid patients needing therapeutic anticoagulants during CEA showed that bridging with low molecular weight heparin was independently associated with peri-operative neck haematoma. Also, the present study showed that VKA and DOAC were associated with a higher risk of any stroke or TIA. In general, patients treated with these anticoagulant regimens have a more severe cardiovascular medical history (e.g., atrial fibrillation and venous thromboembolism) and have a higher thromboembolic risk, especially during temporary lowering or interruption of anticoagulant therapy to prevent haemorrhagic transformation during CEA. In the current study it was not possible to correct for medical history and comorbidities in the multiple logistic regression analyses, because these data were only recorded from 2018 onwards. Nonetheless, the hypothesis that patients treated with VKA or DOAC are exposed to a multifactorial higher peri-operative risk of ischaemic events when lowering or bridging antithrombotic therapy is a plausible explanation for concurrent findings.

Besides a thromboembolic cause, peri-operative stroke may also be caused by occlusive, haemodynamic, or haemorrhagic pathways. To date, in the vast majority of studies investigating the safety and efficiency of revascularisation procedures, assessment of the underlying pathophysiological mechanism of stroke is lacking. Consequently, the true effect of antithrombotic regimens on stroke prevention remains unclear. Future studies should focus on identifying the underlying mechanism that causes stroke using 1) transcranial Doppler imaging to assess signals of athero-embolic debris, 2) carotid imaging to check for post-procedure occlusion, 3) haemodynamic event assessment (both hypo- and hypertension) to check for haemodynamic disturbances, and 4) brain imaging to characterise topographic and ischaemic vs. haemorrhagic patterns and to support the identification of subclinical events such as silent brain infarcts and diffusion weighted imaging lesions. Moreover, a Delphi consensus study including 31 experts found that the optimal management of ipsilateral stroke after CEA depends on the phase at which the stroke occurred. Therefore, a clear distinction should be made between intra- and post-procedural strokes to obtain clear insights in the pathophysiology of peri-operative stroke after CEA.

In the present study, 56% of patients were treated within two weeks after the index event. A previous DACI registry based study showed that younger age, previous CEA, ocular symptoms, and indirect referral were hospital dependent factors for delay to CEA. Over the total study period, an upward trend towards earlier intervention over the years was seen (Supplementary Fig. S2). This is in line with the current guidelines recommending performing CEA as soon as possible after the index event in symptomatic patients eligible for carotid artery revascularisation, based on pooled data from the Carotid Surgery Trial and North American Symptomatic Carotid Endarterectomy Trial.

Although the present study population is based on a nationwide and validated quality assurance database registering patients over eight consecutive years with a prospective unselected study design, there are a few important shortcomings. There was a lack of information on medical history, exact dose and timing of the antithrombotic regimens, special surgery conditions such as tandem stenosis or simultaneous cardiac and aortic surgery, intra-operative heparin or protamine administration, and duration of operation due to the registry design of the DACI. In future prospective studies regarding optimal antithrombotic therapy in CEA patients, these variables should be included because they may possibly influence the results. Based on a recent meta-analysis, eversion endarterectomy and patching with bovine pericardium or polytetrafluoroethylene was associated with the lowest 30 day combined stroke and death rate and res-tenosis following CEA. In the present study, it was only possible to correct for type of procedure but not for type of patch used. Generally, an international normalised ratio (INR) limit of 1.5 for VKA therapy and a short interruption of DOAC therapy is advised during the peri-operative period, and for some specific indications bridging therapy is recommended. This was not verified in the current study and thus may vary among patients. Given the lack of information mentioned above, recommendations from the present results for clinical practice should be drawn with caution. Second, the cause of death was not registered. Therefore, only all cause mortality was studied without being able to distinguish between death due to a cardiovascular (e.g., cerebral haemorrhage or ischaemia) or other cause. Moreover, the prevalence of post-operative myocardial infarction was only registered from 2019 onwards and was therefore not used in the current analysis. Third, it is known for clopidogrel that users can be intermediate and poor responders attributed to reduced function of cytochrome P450 2C19 (CYP2C19), which may prohibit the mutually comparable therapeutic effect in this group. CYP2C19 effectiveness is not documented in the DACI registry, so for the present study it was not possible to correct for this possible confounder. Fourth, it was not possible to divide the index event into ischaemic stroke vs. TIA. As a result, it was not possible to analyse whether ischaemic stroke was associated with intracerebral haemorrhage, due to haemorrhagic transformation of the
infarct zone. Fifth, subanalysis showed no association between post-operative cervical bleeding for which re-intervention was performed and the risk of CNP. It was not possible to determine whether CNP occurred during primary surgery or during re-intervention. Finally, causality cannot be confirmed due to the lack of additional data.

In conclusion, the effectiveness and safety of DAPT did not differ from those of SAPT and the suggested beneficial effect of early DAPT after cerebral ischaemia needs to be further evaluated in future studies. VKA and DOAC treatment were independently associated with a higher risk of ischaemic stroke or TIA, while VKA was also associated with a higher bleeding risk. Given the high thromboembolic risk arising from the recently operated carotid area in the early post-operative period added to the high recurrent stroke risk in symptomatic patients, the present authors recommend starting urgent DAPT after ischaemic stroke or TIA until 30 days after CEA followed by SAPT.

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CONFLICT OF INTEREST STATEMENT AND FUNDING

None.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2022.08.020.

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Endovascular Treatment of a Giant Iliac Vein Aneurysm After a Traumatic Arteriovenous Fistula

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A 60 year old man with a history of a military mine injury 30 years previously presented with chronic leg swelling and a non-healing ulcer. Computed tomography angiography (CTA) revealed a giant iliac venous aneurysm (Figure A; red arrow) due to a chronic arteriovenous fistula (purple arrow) in the proximal superficial femoral artery (SFA; mine fragments indicated by the blue arrows). An iliac limb stent graft (16 – 23 mm × 100 mm; W.L. Gore & Associates, Flagstaff, AZ, USA) was placed via an open antegrade common femoral artery approach into the SFA. The ulcer healed and follow up CTA showed a patent SFA with exclusion of the venous aneurysm (Figure B).

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