Eur J Vasc Endovasc Surg (2011) 41, 214–221

Second-generation Thienopyridine use is not Associated with Better Early Perioperative Outcome During Carotid Stenting

P. De Rango [a,*], G. Parlani [a], L. Romano [a], F. Verzini [a], G. Giordano [a], E. Cieri [a], M. Barbante [a], P. Cao [b]

[a] *Vascular and Endovascular Surgery, Hospital S. M. Misericordia, University of Perugia, Perugia, Italy*
[b] *Vascular Surgery, Department of Cardioscience, Hospital S. Camillo-Forlanini, Rome, Italy*

Submitted 6 September 2010; accepted 15 October 2010
Available online 23 November 2010

KEYWORDS
Carotid stenting;
Thienopyridine;
Clopidogrel;
Stroke risk;
Carotid angioplasty

Abstract *Objective:* Management of anti-platelet therapy during carotid artery stenting (CAS) is mainly based on indirect evidence from coronary stenting experience. There is common agreement on the use of thienopyridine (mainly second-generation) during CAS, but some patients are unsuitable for clopidogrel treatment and data on the benefit of its use in large CAS populations are lacking. The aim of this study was to investigate whether clopidogrel was associated with reduced perioperative morbidity in patients undergoing CAS.
Methods: Consecutive patients undergoing CAS for primary carotid stenosis from 2004 to 2009 were reviewed. The independent association of clopidogrel and perioperative morbidity was assessed using multivariable analysis.
Results: A total of 1083 patients were treated (29% females, mean age 71.6 years); 825 (76%) patients were given clopidogrel starting before treatment. Clopidogrel use was associated with a non-significant reduction of perioperative stroke/death (4.3% vs. 2.4%; $p = 0.13$) and disabling stroke (1.2% vs. 1.0%; $p = 1$) rates. The non-significant stroke/death difference was similar in symptomatic (5.8% vs. 4.0%, $p = 0.37$) and asymptomatic (3.7% vs. 1.9%; $p = 0.17$) patients. After adjusting for demographics, co-morbidities and other therapies with multivariable analysis, clopidogrel use failed to show any significant independent association in decreasing operative risks. The only independent protective factor was use of statins ($p = 0.010$). The additional use of dual anti-platelet therapy did not add any advantage to the use of clopidogrel alone.
Conclusions: The suggested benefit of clopidogrel in decreasing the incidence of complications in patients undergoing CAS may be overestimated due to the overlapping effect of other more

* Corresponding author. P. De Rango, Vascular and Endovascular Unit, Hospital S. M. Misericordia, University of Perugia, 06134 Perugia, Italy. Tel.: +39075 5786436; fax: +39075 5786435.
E-mail addresses: plderango@gmail.com, pderango@unipg.it (P. De Rango).

doi:10.1016/j.ejvs.2010.10.007

relevant factors (e.g., pleiotropy and plaque stabilisation from statins). More data and level I evidence are needed to understand which is the best medical management of CAS that will help improve outcomes of the procedure.

Thienopyridines are now one of the most widely used drugs for the treatment and prevention of cardiovascular disease, and their use has been increasingly implemented among individuals with acute coronary syndromes, who are at high-risk of thrombosis and ischaemic complications.[1–4] Today, there is little debate that clopidogrel therapy (the most largely studied thienopyridine) prevents complications and mortality in patients with coronary heart syndromes. Nevertheless, insight is significantly lacking regarding the effects of clopidogrel treatment on periprocedural or long-term outcome in patients undergoing carotid artery stenting (CAS). Although anti-platelet therapy is unquestionably beneficial in CAS, the routine use of clopidogrel in this setting has been mainly extracted from coronary artery literature.[5,6] In the context of current randomised controlled trials (RCTs), patients with cerebrovascular disease or multiple cardiovascular risk factors without a primary event do not appear to obtain a net benefit from dual aspirin and clopidogrel therapy.[1,7–11] Clopidogrel efficacy in decreasing the risk of acute/sub-acute carotid stent thrombosis, a rare but potentially fatal complication of CAS, is also mainly derived from coronary data.[12] Furthermore, there is still large uncertainty in the use of clopidogrel with respect to appropriate regimen, starting time, length of therapy, dosing, combination strategy with other anti-platelet drugs, risk of bleeding and potential for variable platelet response.[1,2,10,11] In the absence of convincing data in carotid procedures, the routine use of clopidogrel during and after CAS might be an object of debate.

To provide additional information in this field, we reviewed our experience with CAS to investigate whether second-generation thienopyridine use was associated with reduced perioperative mortality and morbidity.

Methods

Patients with high-grade (>70% as assessed with duplex ultrasound and confirmed at angiography) primary carotid stenosis treated by CAS at a single vascular surgery centre after the training phase were analysed. For the purpose of the study, patients who received CAS for recurrent carotid stenosis and CAS performed within the training phase (2001–2003) were excluded. Patients were analysed according to the treatment they actually received (on-treatment analysis). Patients scheduled for CAS and eventually converted to surgery (carotid endarterectomy, CEA) because of CAS failure were not included.

Medical records were entered in a prospectively compiled database and were reviewed for the present study.

Study variable

The exposure variable for this study was medication with clopidogrel at the time of the CAS procedure. Patients scheduled for CAS usually received anti-platelet therapy consisting of a dual-drug regimen: acetylsalicylic acid (ASA) (125–325 mg once daily) and clopidogrel (75 mg/die) for at least 30 days after a 300 mg loading dose administered 6–12 h before CAS. A loading dose was not used when clopidogrel therapy was started more than 3 days before CAS. A number of patients could not follow the used regimen and were not started on clopidogrel as:

- they demonstrated intolerance to clopidogrel;
- were already on anticoagulation;
- were already on other thienopyridine drug (usually first-generation ticlopidine);
- there was lack of preprocedural window time (emergency treatment).

All these patients were considered clopidogrel non-takers and were counted together as a single variable for the purpose of the analysis. Patients under ticlopidine (250 mg twice daily) or receiving anticoagulation for co-existing medical co-morbidities continued to receive their baseline therapy at their usual dose.

Patients who were not compliant with dual anti-platelet therapy (e.g., previous reaction to one or other anti-platelet drug, recent history of bleeding and gastric intolerance) were left on a single-drug regimen (including or not clopidogrel, depending on the reasons stated above).

Written consent was obtained from all patients before revascularisation.

Patient evaluation

Features and time of preoperative symptoms were evaluated by external neurological audit. Patients were defined symptomatic when ipsilateral hemispheric or retinal symptoms occurred within 6 months from the procedure.

The degree and characteristics of carotid stenosis were assessed with duplex ultrasound. 'Complex carotid plaque' was judged by ultrasound when a lack of uniform pattern and prevalence of soft appearance was evident. Contrast-enhanced computed tomography (CT) was performed selectively, in the case of uncertainty at ultrasound examination. Cerebral CT scan was used in symptomatic patients to assess the extent of recent lesions, if any.

CAS procedure

CAS was carried out following a standardised protocol in an endovascular room equipped with a high-quality fixed imaging system (Axiom Artis FA, Siemens).

All procedures were performed with cerebral protection devices (CPDs) and different stent models (open cell, close cell or hybrid configuration; tapered or straight). The choice of specific material depended on vessel anatomy and lesion characteristics.

Stent size and length were chosen according to preoperative measurements of the target vessel by Doppler

ultrasound or CT examination. Closure devices for access control have been used since 2006.

Outcome measures and definitions

The pre-specified primary outcome was the combined risk of any stroke or death within 30 days or during hospitalisation (perioperative). Secondary outcomes were any perioperative stroke, disabling stroke, transient ischaemic attack (TIA), myocardial infarction (MI), local complications (haematoma and pseudo-aneurysm) and stent thrombosis/occlusion.

In the presence or suspicion of new neurological or cardiac events, a team of neurologists and cardiologists was routinely consulted and documented the presence, the type and the severity (National Institute of Health (NIH) Stroke Scale) of the event. Neurological condition was constantly monitored in all the patients. New-onset postoperative neurological deficits lasting less than 24 h in the absence of new focal cerebral lesions were defined as TIAs. Stroke was defined as any new hemispheric or retinal neurological event persisting $>$24 h and classified as fatal, disabling (modified Rankin Score $\geq$3) or non-disabling (modified Rankin Score $<$3).

Statistical analysis

Tests of statistical significance comparing clopidogrel takers and non-takers were conducted using χ^2 and Fisher's exact test for categorical variables and analysis of variance (ANOVA) and *t*-test for continuous variables. Unadjusted and adjusted odds ratios (ORs) with correspondent 95% confidence intervals (CIs) were used to compare outcomes between clopidogrel takers and non-takers.

Patient characteristics, including demographics, plaque, technical issues, co-morbidities and medication that might be associated with increased cerebrovascular risk complication during CAS were analysed. A list of patients' assessed variables is reported in Table 1.

The association between variables and the combined periprocedural (within 30 days) risk of any stroke or death was first assessed by the univariate logistic method.

Two different multivariate logistic regression models were then used to adjust the crude OR and assess the independent association between use of clopidogrel and primary end point (perioperative stroke/death): the first using all patient characteristics, and the second using only significant patient characteristics identified by backward elimination, univariate analysis or which were imbalanced between the clopidogrel and not-clopidogrel takers. Given the virtually identical findings from these two modelling approaches, and the small number of outcome events that had occurred, only results from the second are presented.

The model fit was assessed by using the Hosmer–Lemeshow goodness-of-fit method.

Subgroup analyses by preoperative symptoms gender and age (less or more than 75 years) were performed.

For all tests, a probability value of $p < 0.05$ was considered statistically significant. Statistical Package for Social Sciences (SPSS)/PC version 13.00 Win package (SPSS for Windows Chicago, IL, USA 2003) was used for all data analyses.

Results

A total of 1083 CAS procedures in 1007 patients were performed for severe primary carotid stenosis between January 2004 and March 2009. There were 314 (29%) females and 769 (71%) males with a mean age of 71.53 $\pm$ 7.47 (range 48–92 years). As many as 268 (24.8%) CAS procedures were performed in patients with documented neurological symptoms in the last 6 months before the procedure, whereas the remaining 815 (75.2%) were in patients without clinical symptoms. Co-morbidities, demographics and baseline medications are shown in Table 1.

At the time of operation, 825 (76%) patients were taking clopidogrel according to the standardised protocol, while in 258 (24%), clopidogrel could not be used. In 754 (70%) CAS procedures, clopidogrel was employed within dual antiplatelet regimen (associated with ASA). Any type of dual

Table 1 Characteristics in clopidogrel and non-clopidogrel groups.

	Total *n* 1083	NO clopidogrel *n* 258	Clopidogrel *n* 825	*P* value
Age (mean), years	71.6	71.9 $\pm$ 7.0	71.4 $\pm$ 7.5	0.26
Age $\geq$75 years	439	109 (42.2%)	330 (40%)	0.56
Female	314	72 (27.9%)	242 (29.3%)	0.69
Diabetes	333	87 (33.7%)	246 (29.8%)	0.24
Hypertension	905	217 (84.1%)	688 (83.4%)	0.84
CAD	397	111(43.0%)	286 (34.6%)	0.018
Hyperlipidemia	671	156 (60.4%)	515 (62.4%)	0.55
Statins	465	94 (36.4%)	371 (44.9%)	0.017
PAD	147	42 (16.2%)	105 (12.7%)	0.15
Symptomatic	268	69 (26.7%)	199 (24.1%)	0.4
Contralateral Occlusion	82	22 (8.5%)	60 (7.3%)	0.5
Complex Plaque	338	83 (32.1%)	255 (30.9%)	0.75
Open cell stent	314	66 (25.6%)	248 (30%)	0.20
Debris[a]	423	107 (41.5%)	316 (38.3%)	0.38

CAD: Coronary artery disease; PAD: Peripheral artery disease.
[a] Macroscopic debris during procedure.

Table 2 Perioperative outcome.

	NO Clopidogrel *n* 258	Clopidogrel *n* 825	Absolute difference	OR	CI 95%	*P* value
Stroke/Death	11 (4.3%)	20 (2.4%)	1.9	0.56	0.26—1.18	0.13
Stroke	11 (4.3%)	20 (2.4%)	1.9	0.56	0.26—1.18	0.13
Death	—	—				
Disabling stroke	3 (1.2%)	9 (1.1%)	0.1	0.93	0.25—3.49	1.0
TIA	10 (3.9%)	29 (3.5%)	0.4	0.87	0.42—1.82	0.7
MI	1 (0.4%)	2 (0.2%)	0.2	0.62	0.06—6.92	0.6
MACE	13 (5.0%)	23 (2.8%)	2.2	0.54	0.27—1.08	0.1
Hematoma/pseudo-aneurysm	6 (2.3%)	9 (1.1%)	1.2	0.46	0.16—1.31	0.2
Stent removal/acute thrombosis	3 (1.2%)	1 (0.1%)	1.1	0.10	0.01—0.99	0.04

TIA: Transient Ischemic Attack; MI: Myocardial infarction; MACE: Major Adverse Clinical Events (Stroke, death and MI).

anti-platelet (with or without clopidogrel) therapy was employed in 814 CAS (75.2%) procedures. There were 42 (3.8%) patients under anticoagulation, 145 (13.4%) under ticlopidine and 863 (80%) under ASA, either alone or in combination anti-platelet strategy.

The use of clopidogrel increased slightly over the years: percentages of clopidogrel takers were 72% ($n = 117$) in 2004, 73.5% ($n = 103$) in 2005, 77.8% ($n = 232$) in 2006, 74.6% ($n = 173$) in 2007 and 80% ($n = 200$) in 2008/2009.

Patients not taking clopidogrel had coronary artery disease more frequently (43.0% vs. 34.6%; $p = 0.018$), while the concurrent preoperative use of statin was more likely (44.9% vs. 36.4%; $p = 0.017$) in the clopidogrel group (Table 1). There were no imbalances between clopidogrel and non-clopidogrel users with regard to age ($p = 0.26$), gender ($p = 0.69$) and symptomatic disease ($p = 0.4$).

Perioperative morbidity

There were 31 perioperative strokes and no perioperative death for a combined perioperative stroke or death rate of 2.8%. Twelve strokes were disabling (1.1%). MI occurred in three (0.3%), TIA in 39 (3.6%) and any major adverse clinical event (MACE: stroke or death or MI) in 36 (3.3%) cases.

The distribution of perioperative complications was not significantly different between clopidogrel and non-clopidogrel takers. The details of perioperative complications are shown in Table 2.

Univariate analysis failed to show significant association between the use of clopidogrel and decreased perioperative rates of stroke/death: 4.3% vs. 2.4%, in non-clopidogrel versus clopidogrel takers (OR 0.56, 95% CI 0.26—1.18; $p = 0.13$). Only the preoperative use of statin was ($p = 0.009$) significantly associated with decreased primary outcome (perioperative death/stroke rate) at univariate analysis (Table 3).

There were no significant associations between the use of clopidogrel and other complications, including disabling stroke, MACE, MI and haematoma/pseudo-aneurysm (Table 2). Similar results were found when only the subgroup of 754 clopidogrel takers within the dual anti-platelet regimen (censoring mono-drug takers) was analysed: stroke and

Table 3 Perioperative stroke or death rate. Univariate analysis.

Variables	CAS with variable	Events in CAS with variable	Events in CAS without variable	OR	95% CI	*P* value
Age (mean), years	71.6[a]	73.6[a]	71.4[a]	1.3	−4.84—0.49	0.11
Age ≥75 years	439	3.4%	2.5%	0.7	0.35—1.47	0.46
Females	314	2.2%	3.1%	0.7	0.30—1.66	0.54
Diabetes	333	2.4%	3.1%	0.8	0.34—1.76	0.69
Hypertension	905	2.8%	3.4%	0.8	0.33—2.00	0.62
CAD	397	2.5%	3.1%	0.8	0.38—1.75	0.71
PAD	147	2.7%	2.9%	0.9	0.32—2.70	1.0
Contralateral occlusion	82	6.1%	2.6%	2.4	0.91—6.51	0.08
Symptomatic	268	4.5%	2.3%	1.9	0.94—4.10	0.09
Complex plaque	338	3.5%	2.6%	1.4	0.67—2.91	0.43
Debris[b]	423	3.8%	2.3%	1.7	0.83—3.45	0.19
Open cell stent	314	2.5%	2.9%	0.9	0.39—2.00	0.84
Clopidogrel	258	2.4%	4.3%	0.6	0.26—1.18	0.13
Clopidogrel dual	754	2.4%	3.7%	0.6	0.29—1.37	0.29
Dual anti-platelet (any type)	814	2.6%	3.3%	0.7	0.33—1.74	0.50
Statin	465	1.3%	4.0%	0.31	0.12—0.76	0.009

CAD: Coronary artery disease; PAD: Peripheral artery disease.
[a] Mean age.
[b] Macroscopic debris during procedure.

death 2.4% ($n = 18$); disabling strokes 1.1% ($n = 8$); TIA 3.6% ($n = 27$); MI 0.3% ($n = 2$); MACE 2.7% ($n = 20$); and haematoma 1.1% ($n = 8$).

Multivariate analysis, adjusting for confounders with backward selection, confirmed the lack of association between perioperative stroke/death rate and use of clopidogrel (OR 0.6; 95% CI: 0.28–1.3; $p = 0.20$). Lack of effect was also detected for clopidogrel used exclusively as dual anti-platelet therapy. Statin use remained independently associated with over threefold reduction of the hazard of perioperative stroke/death: OR 0.31, 95% CI 0.13–0.76; $p = 0.010$ (Hosmer–Lemeshow goodness-of-fit analysis; $p = 0.26$).

After completion of the procedure, four stents were acutely removed (Table 4). Only one of these patients was under clopidogrel at the time of the primary procedure. Two were on oral anticoagulant for atrial fibrillation and the third was on ASA alone because of treatment in emergency for an acute deficit. In this patient, the stent thrombosis occurred 2 h after CAS, and was associated with a transient ocular deficit that totally recovered in few minutes. In a female patient, repeated TIAs developed after stent deployment for plaque protrusion through the stent struts. Stent removal occurred the day after. Two other male patients developed stent thromboses immediately after procedure for asymptomatic carotid stenosis. In one, this was associated with occurrence of two transient brachial–crural arm deficits (few minutes) after an uneventful procedure. The last patient with stent removal, treated for preocclusive carotid stenosis, had developed alteration of consciousness after stent ballooning, and completion angiography showed complete occlusion of the stent. Due to the preocclusive lesion, it was indicated to proceed immediately with carotid surgery and stent removal. In all these cases, duplex ultrasound was performed immediately upon the occurrence of deficits to diagnose stent patency. All the four patients were uneventfully converted to CEA. Details are shown in Table 4.

Table 4 Characteristics of 4 patients with acute stent removal.

N	Year	Age/gender	indication	therapy	CPD	Stent	Event at time of thrombosis	Timing of stent removal	outcome
1	2006	57y male	Transferred from Stroke unit for acute neurological deficit and severe right carotid stenosis	ASA	EpifilterWire	Wallstent	2 transient (few minutes) brachio-crural deficits	2 h after CAS	No new deficit
2	2006	67y female	80% asymptomatic right carotid stenosis	Dicumarol	EpifilterWire	Wallstent	Repeated facio-brachial deficits 12–24 h after CAS	24 h after CAS	No new deficit
3	2008	79y male	Preocclusive asymptomatic left carotid stenosis	ASA, Clopidogrel	Emboshield	Cristallo Ideale	Immediate alteration of consciousness after ballooning	Immediately after CAS	No new deficit
4	2009	78y male	80% asymptomatic right carotid stenosis	Dicumarol	Mo.Ma	Xact	Transient ocular deficit (few minutes)	2 h after CAS	No new deficit

CPD: Cerebral Protection Device; CAS: Carotid artery Stenting.

Subgroup analyses

Subgroup analyses by symptoms, gender and age were performed. Perioperative stroke/death risk was not significantly lower in asymptomatic (15/815; 1.8%) versus symptomatic (12/268; 4.47%; $p = 0.08$), in females (7/314; 2.2%) versus males (24/769; 3.1%; $p = 0.54$) and in <75 years old (16/644; 2.5%) versus ≥ 75 years old (15/439; 3.4%; $p = 0.45$) patients.

The lack of association between the use of clopidogrel and stroke/death rate by symptoms and gender was confirmed in both univariate (Table 5, Fig. 1) and multivariate analyses (Fig. 2). The non-significant stroke/death difference between clopidogrel takers and not takers was similar in symptomatic (4.0% vs. 5.8%; $p = 0.37$) and asymptomatic (1.9% vs. 3.7%; $p = 0.17$) patients, in females (1.6% vs. 4.2%; $p = 0.20$) and in males (2.7% vs. 4.3%; $p = 0.33$). The addition of dual therapy to clopidogrel did not provide adjunctive benefit (analyses of the subgroup of 754 clopidogrel takers as dual therapy showed similar findings).

There was no association between use of clopidogrel and perioperative stroke/death in the younger (<75 years)

Table 5 Perioperative stroke and death rate in subgroup analysis. Univariate analysis.

	Tot (n = 1083)	No Clopidogrel (n = 258)	Clopidogrel (n = 825)	Absolute difference	OR	95% CI	P value
Gender		*N*	*N*				
Females	314	3/72 (4.2%)	4/242 (1.6%)	2.6	0.4	0.08—1.76	0.20
Males	769	8/186 (4.3%)	16/583 (2.7%)	1.6	0.6	0.26—1.4	0.33
Age							
<75 years	644	4/149 (2.7%)	12/495 (2.4%)	0.3	0.9	0.28—2.84	0.77
≥75 years	439	7/109 (6.4%)	8/330 (2.4%)	4.0	0.3	0.12—1.02	0.06
Indication							
Symptomatic	268	4/69 (5.8%)	8/199 (4.0%)	1.8	0.7	0.19—2.33	0.37
Asymptomatic	815	7/189 (3.7%)	12/626 (1.9%)	1.8	0.5	0.19—1.31	0.17

patients' subgroup: 2.4% versus 2.7% (in clopidogrel vs. non-clopidogrel takers; $p = 0.77$). For the subgroup of older (>75 years) patients, there was a trend towards a protective effect of clopidogrel use on perioperative stroke/death rate: 2.4% versus 6.4% in clopidogrel versus non-clopidogrel takers, OR 0.36; 95% CI 0.12—1.023; $p = 0.06$. This trend was confirmed by multivariate analysis where the use of clopidogrel was selected by backward elimination in the last step of the analysis ($p = 0.07$, OR 0.38, 95% CI 0.13—1.0) as well as contralateral occlusion ($p = 0.018$, OR = 4.3, 95% CI 1.29—14.6), the only significant predictor.

Discussion

Among patients undergoing CAS, use of clopidogrel in the periprocedural period (30 days) was associated with a non-significantly lower periprocedural mortality and stroke rate with respect to no use of clopidogrel: 2.4% versus 4.3%; $p = 0.13$. The decreased perioperative stroke/death risk was not robust when adjusted for the relationship between prognostic variables and outcome, and for the confounding effect by concurrent treatment with a statin. This finding extended to patients undertaking another anti-platelet drug associated with clopidogrel and occurred in both asymptomatic and symptomatic patients undergoing CAS. In addition, there was no evidence of better cardiac outcome associated with clopidogrel. Even though the non-clopidogrel group included more patients with coronary disease and patients treated acutely (without window time for clopidogrel loading dose), outcomes were not significantly different from the clopidogrel group.

The suggested lower procedural risk in clopidogrel takers is mainly based on findings from coronary literature.[1,5,6] Only one small RCT has directly analysed outcomes after carotid stenting in clopidogrel versus non-clopidogrel takers, and the results of this study in favour of clopidogrel may not be generalised.[13] The routine use of clopidogrel during CAS seems to be not supported by adequate evidence.[13,14]

The occurrence of rapid thrombus formation immediately after arterial injury and stenting and potential embolisation of the thrombus to distal sites provides the rationale for early use of clopidogrel therapy during stenting. It has been suggested that intimal injury of the artery during percutaneous interventions can release procoagulant tissue factors and expose collagen and other platelet-adhesive proteins in the subendothelium, thereby triggering the formation of a platelet-rich thrombus that seals the site of injury. However, almost all our information on arterial injury and stent thrombosis is from coronary circulation,[12,15] while there are inconsistent data to support the efficacy of clopidrogrel in preventing acute/sub-acute carotid stent thrombosis, a rare but potentially catastrophic complication reported after CAS.[16,17]

The extent of platelet deposition and thrombus formation on the arterial wall after injury is dependent on the degree of vessel-wall injury and local shear forces, accounting for a number of differences between coronary and carotid vessels.[12,15] During carotid stenting, operator experience has more significance than the formation of a new platelet-rich thrombus on the injured wall in triggering cerebral ischaemic complications. Furthermore, due to the larger size of the carotid vessel and the lower shear stress, thrombosis risk is less likely with respect to coronary arteries. In our experience, the risk of stent removal for early thrombosis was more frequent in the clopidogrel non-takers group. However, data were provided from only four

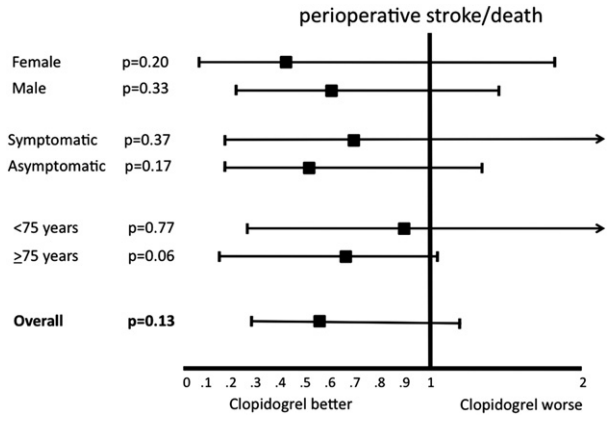

Figure 1 Subgroup analyses by gender, preoperative symptoms and age in clopidogrel takers according to univariate analysis. Risk of perioperative stroke/death is shown as OR (square box) and Confidence intervals (horizontal line boundaries).

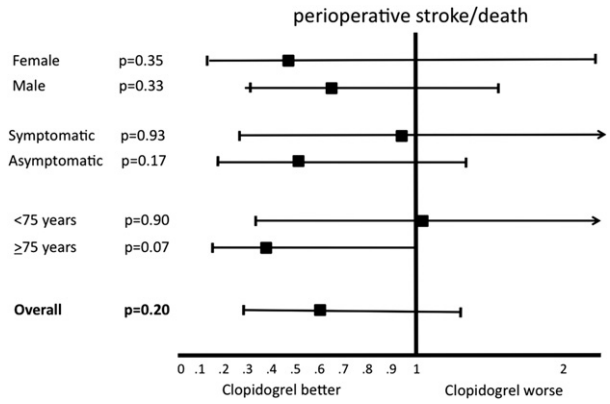

Figure 2 Association between clopidogrel use and rates of perioperative stroke/death in subgroup analyses by gender, preoperative symptoms and age according to multivariate analysis. Risk of perioperative stroke/death is shown as OR (square box) and Confidence intervals (horizontal line boundaries).

CAS procedures, and it was more likely that technical errors have affected the early thromboses and the protrusion of plaque through the stent struts.

In our study, although the majority of patients were taking clopidogrel, the benefit could not be proven with respect to the minority of patients not taking clopidogrel. Our results would not suggest that clopidogrel is not effective in patients undergoing CAS but more likely that the benefit of clopidogrel in endovascular carotid procedures might be overestimated, based on inaccurate assumptions from coronary procedures. However, we cannot exclude that lack of maximal efficacy of clopidogrel in our study was due to the small numbers or patient resistance to clopidogrel, either genetic or related to concurrent assumption of receptor—competitor drug, as we did not investigate these issues. Nevertheless, we should hypothesise that the resistance against the drug was considerable to counterbalance the overall beneficial effect, while literature data on the clinical relevance of clopidogrel resistance are conflicting and not consistent.[18]

Our patients on clopidogrel undergoing CAS were more likely to have a statin as a concurrent medication (this likely reflects factors such as individual physician practice or ability to pay for medication or compliance with drugs, which were not captured in our study). When we analysed the independent effect of statin and clopidogrel on primary outcome (perioperative stroke/death), an association with decreased outcome was confirmed only for statin and not for clopidogrel use. We could infer that the true benefit in outcome might be due to an overlapping 'fog' effect of statins hidden by clopidogrel. Statins exhibit many properties that may be protective at the time of surgery and endovascular procedures, including anti-thrombotic actions, the ability to stabilise atherosclerotic plaque and neuroprotective actions such as attenuating inflammatory response and antioxidant activity.[19] Some of these effects could be shared by statins and clopidogrel, but statins have an additional pleiotropic anti-inflammatory role in plaque stabilisation likely resulting in a stronger benefit in decreasing ischaemic complications. There is increasing evidence that the use of statin is today a mainstay in the management of vascular patients.[19] The findings of our study support this hypothesis.

Use of clopidogrel during CAS might be more beneficial in some subgroups of patients, such as the elderly. In our study, patients $\geq$75 years old without clopidogrel showed a fourfold perioperative stroke risk than clopidogrel takers: 6.4% versus 2.4%; $p = 0.06$. Although the drug might be helpful in decreasing the procedural risk in older patients, it is also known that advanced age is a risk factor for CAS, and most old patients should be excluded from the procedure.[20] More data and prospective analyses are needed to confirm this hypothesis and to investigate the role of clopidogrel in CAS subgroups.

Limitations of this study include, at first, the retrospective analysis and the lack of randomisation. Despite the statistical methods (multivariable analyses) employed, we could not exclude selection biases. Second, the number of clopidogrel non-takers was unbalanced ($n = 258$) when compared with clopidogrel takers ($n = 825$). There is the possibility that a true effect of clopidogrel on outcome might be hidden by the low frequency of outcomes observed and the small numbers at risk. Third, the resistance to drug, as well as the concurrent assumption of proton pump inhibitors invalidating the effect of clopidogrel, was not tested; however, literature data on the clinical relevance of clopidogrel resistance are conflicting. Finally, we analysed exclusively early outcome, as, in most of our patients, clopidogrel was used for 30 days after procedure and then discontinued.

Conclusions

Use of anti-platelet is a mainstay in the management of patients undergoing carotid revascularisation. Although benefit from clopidogrel in decreasing the complication of stroke during CAS is likely, the true effect might be overestimated as the efficacy of clopidogrel during carotid endovascular procedure is supported by insufficient and indirect evidence. Complications of CAS, more than of coronary interventions, benefit from operator experience and case selection. The overlapping adjunctive benefit of other drugs (e.g., statin) should also be considered. More accurate and in-depth knowledge is essential to provide optimal medical management of patients undergoing CAS. Future, prospective, randomised and large studies will be helpful to clarify the extent of efficacy of new and old thienopyiridines in decreasing adverse perioperative outcomes of CAS.

Acknowledgements

We thank Ms. Francesca Zannetti for language supervision and editing.

Conflict of Interest

None.

Funding

None.

References

1 Faxon DP, Freedman JE. Facts and controversies of aspirin and clopidogrel therapy. *Am Heart J* 2009;**157**:412—22.
2 Plosker GL, Lyseng-Williamson KA. Clopidogrel: a review of its use in the prevention of thrombosis. *Drugs* 2007;**67**:613—46 [Review].
3 Canadian Cardiovascular Society. 2007 focused update of the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. *J Am Coll Cardiol* 2008;**51**:210—47.
4 Goldstein LB, Adams R, Alberts MJ, Appel LJ, Brass LM, Bushnell CD, et al. American Heart Association American Stroke Association Stroke Council. Primary prevention of ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council. *Circulation* 2006; **113**:e873—923.
5 Berg J, Fidan D, Lindgren P. Cost-effectiveness of clopidogrel treatment in percutaneous coronary intervention: a European model based on a meta-analysis of the PCI-CURE, CREDO and PCI-CLARITY trials. *Curr Med Res Opin* 2008;**24**:2089—101.
6 Mehta SR. Aspirin and clopidogrel in patients with ACS undergoing PCI: CURE and PCI-CURE. *J Invasive Cardiol* 2003;(Suppl. 17B-20B).
7 Diener HC, Bogousslavsky J, Brass LM, Cimminiello C, Csiba L, Kaste M, et al. MATCH investigators. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. *Lancet* 2004;**364**:331—7.
8 Markus HS, Droste DW, Kaps M, Larrue V, Lees KR, Siebler M, et al. Dual antiplatelet therapy with clopidogrel and aspirin in symptomatic carotid stenosis evaluated using doppler embolic signal detection: the Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) trial. *Circulation* 2005;**111**:2233—40.
9 Hankey GJ, Hacke W, Easton JD, Johnston SC, Mas JL, Brennan DM, et al. CHARISMA Trial Investigators. Effect of clopidogrel on the rate and functional severity of stroke among high vascular risk patients: a prespecified substudy of the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) trial. *Stroke* 2010;**41**:1679—83.
10 Beckman JA. Antithrombotic therapies in cerebrovascular disease: what should we use as secondary prevention in patients with carotid artery disease? *Catheter Cardiovasc Interv* 2009;**74**:S12—6.
11 Kiernan TJ, Yan BP, Jaff MR. Antiplatelet therapy for the primary and secondary prevention of cerebrovascular events in patients with extracranial carotid artery disease. *J Vasc Surg* 2009;**50**:431—9.
12 Chaturvedi S, Yadav JS. The role of antiplatelet therapy in carotid stenting for ischemic stroke prevention. *Stroke* 2006; **37**:1572—7.
13 McKevitt FM, Randall MS, Cleveland TJ, Gaines PA, Tan KT, Venables GS. The benefits of combined anti-platelet treatment in carotid artery stenting. *Eur J Vasc Endovasc Surg* 2005;**29**: 522—7.
14 Gortler D, Schlösser FJ, Muhs BE, Nelson MA, Dardik A. Periprocedural drug therapy in carotid artery stenting: the need for more evidence. *Vascular* 2008;**16**:303—9.
15 Hayes PD, Box H, Tull S, Bell PR, Goodall A, Naylor AR. Patients' thromboembolic potential after carotid endarterectomy is related to the platelets' sensitivity to adenosine diphosphate. *J Vasc Surg* 2003;**38**:1226—31.
16 Iancu A, Grosz C, Lazar A. Acute carotid stent thrombosis: review of the literature and long-term follow-up. *Cardiovasc Revasc Med* 2010;**11**:110—3.
17 Setacci C, de Donato G, Setacci F, Chisci E, Cappelli A, Pieraccini M, et al. Surgical management of acute carotid thrombosis after carotid stenting: a report of three cases. *J Vasc Surg* 2005;**42**:993—6.
18 Paré G, Mehta SR, Yusuf S, Anand SS, Connolly SJ, Hirsh J, et al. Effects of CYP2C19 genotype on outcomes of clopidogrel treatment. *N Engl J Med* 2010;**363**:1704—14.
19 Perler BA. The effect of statin medications on perioperative and long-term outcomes following carotid endarterectomy or stenting. *Semin Vasc Surg* 2007;**20**:252—8.
20 Hobson 2nd RW, Howard VJ, Roubin GS, Brott TG, Ferguson RD, Popma JJ, et al. CREST Investigators. Carotid artery stenting is associated with increased complications in octogenarians: 30-day stroke and death rates in the CREST lead-in phase. *J Vasc Surg* 2004;**40**:1106—11.