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ORIGINAL ARTICLE

Postoperative stroke in patients on oral anticoagulation undergoing coronary artery bypass surgery

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Abstract

Objective. Patients on long-term warfarin treatment have an inherent high risk of stroke and here we aimed to identify the determinants of postoperative stroke after coronary artery bypass grafting (CABG) in these patients. *Methods*. A consecutive series of 270 patients on long-term warfarin treatment who underwent isolated CABG in two university hospitals was assessed by logistic regression as well as classification and regression tree (CART) analysis. *Results*. Postoperative stroke occurred in 10 patients during in-hospital stay (3.7%). Logistic regression showed that $CHADS_2 > 2$ ($p = 0.036$), recent thrombolysis ($p < 0.0001$) and history of deep vein thrombosis ($p = 0.025$) were independent predictors of postoperative stroke (area under the ROC curve 0.77). CART analysis showed that $CHADS_2 > 2$, history of stroke/TIA, no preoperative use of aspirin and preoperative use of low molecular weight heparins were associated with an increased risk of stroke (area under the ROC curve of 0.77). *Conclusions*. Both CART and logistic regression analyses showed that the patient characteristics included in $CHADS_2$ score are important also in the prediction of postoperative stroke risk. Preoperative antiplatelet treatment may be beneficial in the high risk patients and the preoperative bridging with low molecular weight heparins may even be harmful in this respect.

Key words: *coronary artery bypass surgery, anticoagulation, stroke, warfarin, aspirin*

It has been estimated that about 7% of patients undergoing isolated coronary artery bypass surgery (CABG) are on long-term oral anticoagulation because of underlying chronic medical conditions (1). The perioperative management of this increasing patient group is challenging, and it is not possible to draw firm conclusions on the relative efficacy and safety of different antithrombotic strategies, since randomized controlled studies are missing and even the cohort studies are few and based on small and heterogeneous patient populations.

Data from our case control and propensity score analysis study showed that the mortality or bleeding risks are not increased in patients on chronic warfarin treatment, but the risk of postoperative stroke was high (2). Since the risk of stroke may be related to the strategy of anticoagulation in the period immediately before and after CABG, we investigated this issue in a relatively large series of patients on chronic warfarin treatment who underwent CABG.

Material and methods

This study complies with the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Turku University Hospital and a waiver of the requirement of written informed consent was obtained.

This study is part of a wider protocol in progress to assess thrombotic and bleeding complications of cardiac procedures in Western Finland (2–5). It included a consecutive series of 270 patients on long-term preoperative treatment with warfarin who underwent isolated CABG in two university hospitals, Turku

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University Hospital and Oulu University Hospital, Finland, between 2004 and 2009. Patients' characteristics and operative data are summarized in Table I.

Baseline and operative data were provided by local institutional clinical registries which prospectively collect information in computerized databases. Furthermore, the full medical records of the eligible patients were reviewed in order to determine the perioperative antithrombotic strategies and the incidence of major operative complications. Operative risk was assessed by the EuroSCORE risk scoring method (6). The risk of stroke was estimated in all patients by the $CHADS_2$, although this index is mainly validated for patients with atrial fibrillation (7). $CHADS_2$ assigns 1 point to congestive heart failure, 1 point to hypertension, 1 point to age > 75 years, 1 point to diabetes and 2 points to prior stroke or transient ischemic attack.

Table I. Baseline characteristics and operative data on patients on preoperative warfarin treatment who underwent isolated coronary artery bypass surgery. Results of univariate and logistic regression in predicting postoperative stroke are reported as well.

	No. (%)	Univariate analysis p-value	Logistic regression analysis p-value, O.R. 95% CI
Age (years)	69.4 ± 8.6	0.74	
Age ≥ 75 years	89 (32.9)	0.63	
Females	45 (16.7)	0.38	
Diabetes	97 (35.9)	0.34	
Hypertension	149 (55.2)	1.00	
History of stroke/transient ischemic attack	68 (25.2)	0.13	
Extracardiac arteriopathy	61 (25.2)	0.60	
Previous PCI	36 (13.3)	0.37	
Previous CABG	10 (3.7)	1.00	
Previous cardiac surgery	18 (6.7)	1.00	
Unstable angina pectoris	89 (32.9)	0.24	
Left main stenosis	102 (37.8)	0.51	
Left ventricular ejection fraction < 50%	131 (48.5)	1.00	
Recent myocardial infarction	114 (42.2)	0.33	
Indication for warfarin treatment			
Atrial fibrillation	203 (75.2)	0.71	
Stroke/transient ischemic attack	29 (10.7)	1.00	
Deep vein thrombosis	14 (5.2)	0.09	0.025, 7.73, 12.92–3619.27
Prosthetic heart valve	10 (3.7)	1.00	
Other reasons	14 (5.2)	0.42	
Drug treatment			
Warfarin until day of surgery	43 (15.9)	0.69	
Enoxaparin	146 (54.1)	0.52	
Enoxaparin until day of surgery	121 (44.8)	0.19	
Aspirin	169 (62.6)	0.18	
Clopidogrel	21 (7.8)	0.18	
Glycoprotein inhibitors	12 (4.5)	0.37	
Thrombolysis during same hospitalization	3 (1.1)	0.004	< 0.0001, 216.25, 12.92–3619.27
Aprotinin	18 (6.7)	1.00	
Aminocaproic acid	133 (49.3)	0.34	
Hemoglobin (g/l)	138 ± 17	0.61	
INR	1.9 ± 0.6	0.80	
Platelets (10^9/l)	236 ± 82	0.21	
Creatinine (micromol/l)	93 ± 40	0.13	
Emergency/urgent operation	147 (54.4)	0.76	
Additive EuroSCORE	6.3 ± 3.3	0.44	
$CHADS_2$ score	2.2 ± 1.3	0.27	
$CHADS_2$ score > 2	95 (35.2)	0.17	0.036, 5.80, 1.12–30.02
Aortic cross-clamp time (min)	74 ± 29	0.62	
Cardiopulmonary bypass time (min)	105 ± 41	0.96	
Length of operation (min)	241 ± 61	0.92	
Beating heart surgery	121 (44.8)	1.00	

Continuous variable are reported as mean ± standard deviation; Values in parentheses are percentages. O.R., odds ratio; CI, confidence interval; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; INR, International normalized ratio; *, Definition criteria for preoperative variables are according to EuroSCORE (6); $CHADS_2$, score for prediction of stroke in patients with atrial fibrillation (7).

Perioperative antithrombotic treatments

The main strategy in patients referred for elective surgery was that warfarin was discontinued two days before surgery and heparins were not given preoperatively when feasible. INR was measured on the day before surgery and, when was found to be >2.0, it was checked again on the day of surgery. Enoxaparin was used preoperatively instead of warfarin only in selected patients with acute coronary syndromes or with mechanical heart valve. Aspirin and/or clopidogrel was discontinued for five to seven days when feasible, i.e. when patients conditions allowed to postpone surgery for a few days. Heparin (3.0 mg/kg) was administered intravenously after sternotomy to maintain an activated clotting time of more than 400 s and it was neutralized at the end of the procedure by protamine sulphate (3.0 mg/kg). Further dose of protamine sulphate was given in case of bleeding during closure of the chest or within the first hours after surgery according to activated coagulation time. Tranexamic acid 2000 mg was used intraoperatively and also postoperatively in case of bleeding at the Turku University Hospital. Fresh-frozen plasma as well as platelets were transfused according to the amount of bleeding, INR levels and platelets count. Enoxaparin (40–60 mg once-a-day) was administered postoperatively in all patients since the evening of the operation day. Warfarin was restarted on the first postoperative day unless significant bleeding occurred, i.e. blood loss from drainages more 1000 ml or bleeding requiring re-exploration. Clopidogrel 75 mg once-a-day was administered in patients with recently deployed coronary stents or in patients with aspirin allergy or side effects.

Operative techniques

Epiaortic ultrasound was performed according to the surgeon's preference. Similarly, off-pump coronary surgery was also performed according to surgeon's preference and epiaortic ultrasound findings. Intermittent antegrade and retrograde cold blood cardioplegia was used during conventional CABG. Proximal anastomoses were sutured to the ascending aorta during cross clamping, when the latter was considered safe. Octopus and Starfish stabilizers (Medtronic, Minneapolis, MN, USA) as well as intracoronary shunts were routinely used in patients who underwent off-pump coronary surgery.

Outcome end-point

The main outcome end-point of interest was postoperative stroke as occurred during in-hospital stay. This was defined as a new neurologic deficit following surgery lasting >24 hours with or without new structural changes detected at computed tomography (CT) or magnetic resonance imaging (MRI). Diagnosis of stroke was confirmed by a neurologist in those cases in whom no new structural changes were detected at CT or MRI scan. Other major postoperative complications are listed in Table II.

Statistical analysis

Statistical analysis was performed using a SPSS statistical software (SPSS v. 15.0, SPSS Inc., Chicago, Ill., USA). Continuous variables are reported as the mean $\pm$ standard deviation, range as well as median and 25% and 75% interquartile range (IQR). Fisher's exact test and Mann-Whitney U-test were used for univariate analysis. Logistic regression with backward selection was performed to identify predictors of postoperative stroke after CABG. Hosmer-Lemeshow's test was used to assess the regression model fit. Only variables listed in Table I and having a $p<0.2$ at univariate analysis have been included in the regression model.

Classification and regression tree (CART) analysis was also performed to identify independent risk factors for postoperative stroke. Validation of the classification tree procedure was assessed by cross-validation through 25 folds. Because of the relatively small database, the minimum number of patients for parent node was set to 20 and the minimum for child node was 10. The maximum classification tree depth was 5. Gini's method was used to measure impurity, which is the extent to which a node does not represent a homogenous subset of cases. Minimum change in improvement was set at 0.0001. Bar charts of model importance by independent variable have been developed. Receiver operating characteristic (ROC) curve analysis was used to estimate the area under the curve of probabilities values estimated by logistic regression and CART analysis models in

Table II. Immediate outcome after isolated coronary artery bypass surgery in patients on preoperative warfarin treatment.

In-hospital adverse events	No. (%)
Mortality	10 (3.7)
Stroke	10 (3.7)
Transient ischemic attack	2 (0.7)
Reoperation	23 (8.5)
Prolonged need of inotropics	137 (50.7)
Blood loss at ICU (ml)	865 ± 682
Red blood cells units	2.2 ± 3.1
Fresh-frozen plasma units	2.1 ± 2.7
Platelet units	1.1 ± 2.8
ICU stay (days)	3.3 ± 4.1

Values in parentheses are percentages; continuous variables are reported as mean ± standard deviation.

predicting adverse outcome events. A $p < 0.05$ was considered statistically significant.

Results

Baseline clinical characteristics

The baseline clinical characteristics of the study population are detailed in Table I. Atrial fibrillation was the most common indication for warfarin followed by history of stroke/TIA. The mean $CHADS_2$ score was 2.2 ± 1.3 (median 2.0, IQR 1.0–3.0, range, 0–6). The patients had a rather high operative risk as indicated by additive EuroSCORE (mean 6.3 ± 3.3, median 6.0, IQR 4.0–8.0, range 0–19).

CABG was performed after a pause in warfarin of a mean of 2.4 ± 2.7 days (median 2.0, IQR 1–3 days, range 0–22 days) in 246 patients. The exact day of warfarin interruption was not available in 24 patients. The mean INR at the time of operation was 1.9 ± 0.6 (median 1.9, IQR 1.5–2.2, range, 1.0–5.7).

Short heparin bridging with enoxaparin was used in 146 patients (54.1%) and 121 patients (44.8%) received enoxaparin until the day of surgery.

Aspirin was used preoperatively in 169 patients (62.6%). The date of discontinuation of aspirin treatment was missing in 22 patients. Seventy-three patients (27.0%) underwent surgery without discontinuation of aspirin treatment. Aspirin was discontinued for a mean of 8.3 ± 8.0 days (median 7.0, IQR 1.0–15.0, range 1–34 days) in the remaining 74 patients. Clopidogrel was administered preoperatively in 21 patients (7.8%).

Postoperative stroke and preoperative antithrombotic strategy

Postoperative stroke occurred in 10 patients during in-hospital stay (3.7%) and three of them died during the in-hospital stay. Data on these patients are summarized in Table III. Two other patients (0.7%) suffered transient ischemic attack.

Preceding thrombolysis for ST-elevation myocardial infarction was associated with high risk of stroke, since all three such patients suffered from stroke after surgery. Neither preoperative INR nor the timing of warfarin discontinuation was predictive of stroke or in-hospital mortality. Preoperative use of enoxaparin failed to prevent stroke (4.8% vs. 2.1%, $p = 0.52$, and the rate of postoperative stroke was even higher in those patients in whom enoxaparin was not discontinued (5.8% vs. 2.1%, $p = 0.19$). Preoperative use of aspirin or clopidogrel did not have any impact on the risk of stroke at univariate analysis by Fisher's exact test.

Table III. Details on patients on chronic oral anticoagulation treatment who suffered stroke after coronary artery bypass surgery.

Patient no.	Indication for warfarin treatment	Preop. TT-INR	Preoperative warfarin discontinuation	Length of warfarin discontinuation (days)	LMWH until surgery	Aspirin use	History of stroke/TIA	Type of surgery	$CHADS_2$ score	Additive EuroSCORE	Off-pump surgery	Diseased ascending aorta	Timing of postop. stroke (days)	LMWH treatment at the time of stroke	In-hospital outcome
1	AF	1.6	No pause	0	Yes	Yes	Yes	Emergency		15	Yes	NA	12	Yes	Dead
2	DVT	2.1	Pause	2	Yes	No	Yes	Elective	4	5	No	Yes	3	Yes	Dead
3	AF	1.7	No pause	0	Yes	No	Yes	Urgent	2	7	No	NA	12	Yes	Dead
4	AF	3.3	Pause	1	No	No	No	Elective	3	4	No	Yes	1	No	Alive
5	AF	1.4	Pause	5	No	No	Yes	Elective	4	1	Yes	Yes	2	Yes	Alive
6	DCM	1.0	Pause	15	No	Yes	No	Elective	1	4	No	NA	3	No	Alive
7	AF	1.3	Pause	4	Yes	Yes	Yes	Urgent	3	8	Yes	No	8	Yes	Alive
8	DVT	2.4	Pause	2	Yes	No	No	Emergency	4	14	No	NA	15	No	Alive
9	AF	3.5	Pause	1	Yes	No	No	Urgent	0	6	Yes	No	13	Yes	Alive
10	AF	1.6	Pause	4	No	Yes	No	Urgent	1	10	No	NA	3	Yes	Alive

AF, atrial fibrillation; DVT, deep vein thrombosis; DCM, dilated cardiomyopathy; LMWH, low molecular weight heparin; TIA, transient ischemic attack; NA, not assessed.

Postoperative stroke and postoperative atrial fibrillation

Patients who had postoperative atrial fibrillation did not have a higher risk postoperative stroke (4.0% vs. 3.5%, $p = 0.83$). Among patients with a preoperative INR < 2.0, those who having experienced postoperative atrial fibrillation had a postoperative stroke rate of 3.9%, whereas patients with no postoperative atrial fibrillation had a postoperative stroke rate of 3.4% (3/87 vs. 3/76, $p = 0.87$).

Results of logistic regression

Logistic regression showed that $CHADS_2 > 2$ ($p = 0.036$), preceding thrombolysis ($p < 0.0001$) and history of deep vein thrombosis as indication for warfarin treatment ($p = 0.025$) were independent predictors of postoperative stroke (Hosmer-Lemeshow's test: $p = 0.61$). ROC curve showed that this logistic regression prognostic model performed rather well (area under the curve 0.77, 95% CI 0.61–0.94, $p = 0.003$).

Results of classification and regression tree analysis

CART analysis showed that $CHADS_2 > 2$, history of stroke/transient ischemic attack, not use of aspirin before surgery and preoperative use of low molecular weight heparin were associated with an increased risk of stroke (area under the ROC curve of 0.77, 95% CI 0.63–0.91, $p = 0.004$, Figures 1 and 2). This CART model was predictor also of any postoperative stroke or transient ischemic attack (area under the ROC curve 0.73, 95% CI 0.57–0.90, $p = 0.006$).

CART analysis including any preoperative use of aspirin and/or clopidogrel showed that the latter had even greater neuroprotective effect (area under the ROC curve 0.83, 95% CI 0.73–0.93, $p < 0.0001$, Figure 3). This CART model was predictive also of any postoperative stroke or transient ischemic attack (area under the ROC curve 0.78, 95% CI 0.65–0.92, $p = 0.001$). Preoperative use of aspirin or low molecular weight heparins had no significant effect on mortality in these patients.

Discussion

In the present study, we decided to use CART analysis which provides the clinicians with the possibility to investigate multilevel interactions between risk factors (8–11). Beside its intuitive nature and easy-to-understand graphical explanatory trees, this method allows the identification of a relatively small number of patients who are reasonably homogeneous

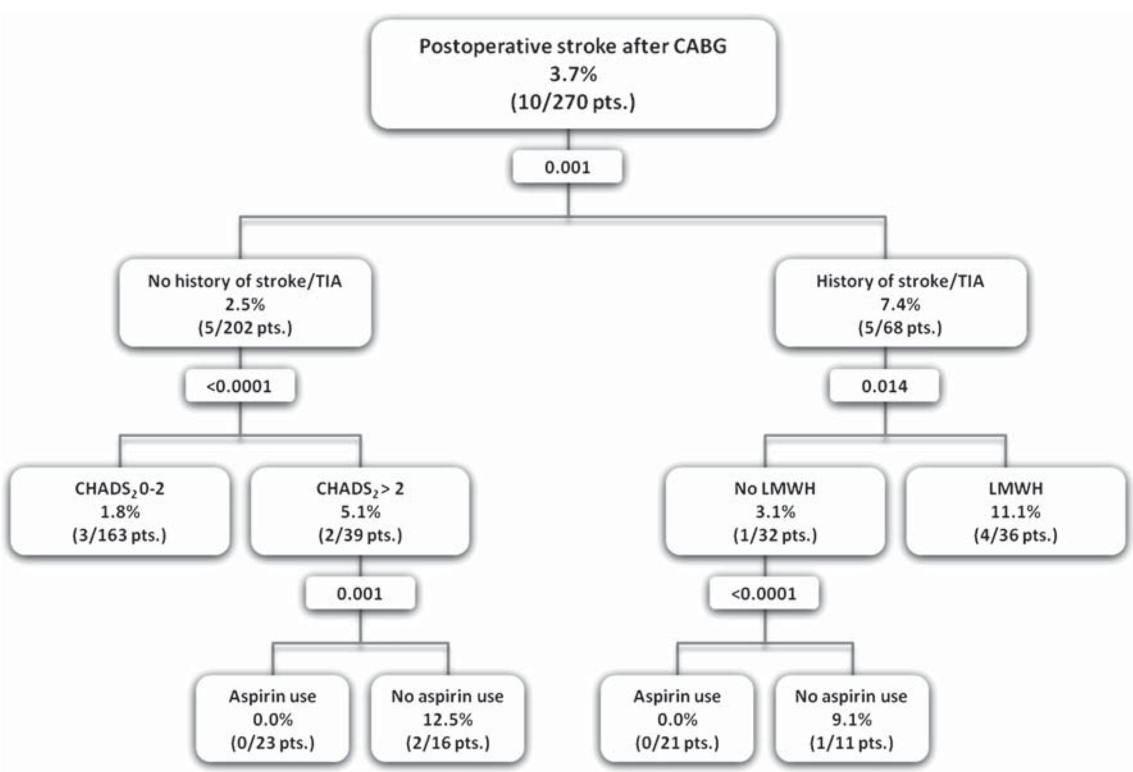

Figure 1. Classification and regression tree summarizing independent predictors of postoperative stroke after coronary artery bypass surgery in patients on chronic oral anticoagulation. Rates of postoperative stroke are reported in percentages and absolute values in parentheses. The improvement values are reported at the splitting of the parent node. CABG, coronary artery bypass grafting; TIA, transient ischemic attack; LMWH, low molecular weight heparin.

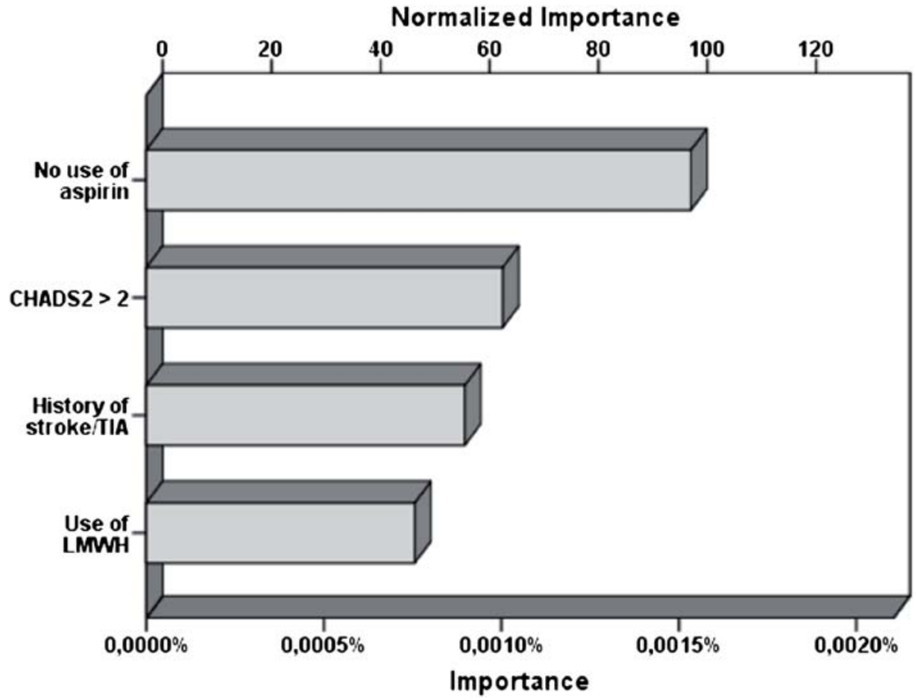

Figure 2. Independent variable importance in predicting in-hospital stroke after coronary artery bypass surgery in patient on oral anticoagulation. LMWH, low molecular weight heparin.

with regard to the outcome. In contrast to traditional regression method which compute prognostic index as a weighted average of patients' characteristics, classification tree analysis provides subgroups based directly on patients characteristics and demonstrate the association between different variables and its direct impact on patients' outcome.

To our knowledge this is the first study to focus on immediate postoperative stroke risk in patients on long-term oral anticoagulation. The present findings show that this fragile patient group is at an increased risk of stroke and the patient's intrinsic propensity to stroke as measured by $CHADS_2$ score is the major predictor of postoperative stroke. Secondly, our findings suggest that effective antiplatelet therapy may help to reduce the stroke risk in the high risk patients. On the other hand, the level of oral anticoagulation had no effect on stroke risk, but the patients treated with low-molecular weight heparins were at high risk of stroke.

Meta-analysis of randomized studies reported a cumulative incidence of postoperative stroke after CABG ranging from 0.5% to 1.6% (12,13), whereas observational studies including large series reported slightly higher stroke rates, but still ranging from 1.2% to 2.1% (14–17). Preoperative atrial fibrillation doubles the risk of stroke to a level of 2.6–4.3% (18–20) and a previous study of ours showed that the risk of stroke after CABG in patients on long-term oral anticoagulation treatment is higher than patients with similar operative risk (2). The present study including a much larger number of patients confirmed the high (3.7%) risk of immediate postoperative stroke in these patients, which could not be explained by the increased operative risk of patients on oral anticoagulation.

The present findings could also be affected by the nature and timing of stroke occurring in these patients. Strokes occurring during the first postoperative hours/day may be the result of ascending aortic manipulation as well as the use of cardiopulmonary bypass (14,21). Because the off-pump approach avoids arterial cannulation, cardiopulmonary bypass and aortic cross-clamping, it is thought to be associated with a lower rate of postoperative stroke. This complication often occurs, however, several days after off-pump surgery, possibly due to platelets hyperactivity (22).

Our present findings suggest that perioperative antithrombotic strategy may have an important impact on the occurrence of this severe neurological complication. In the current literature, there are no randomized trials comparing different strategies to manage long-term oral anticoagulation in patients undergoing CABG. The lack of knowledge emphasizes the importance of the present study in shedding light on the unresolved issue of preoperative treatment and outcome of patients with an indication for long-term oral anticoagulation. The importance of this issue is further emphasized by the fact that the

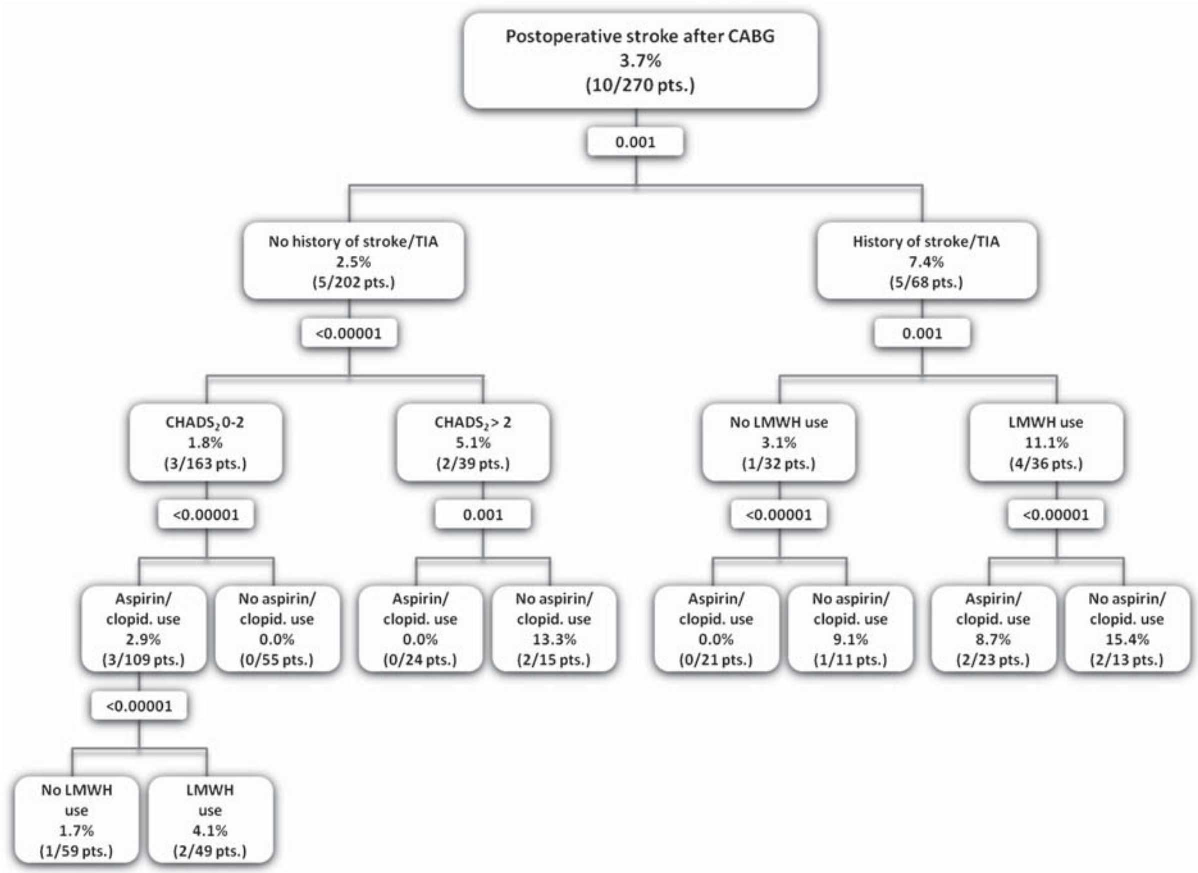

Figure 3. Classification and regression tree including preoperative use of aspirin and/or clopidogrel and summarizing independent predictors of postoperative stroke after coronary artery bypass surgery in patients on chronic oral anticoagulation. Rates of postoperative stroke are reported in percentages and absolute values in parentheses. The improvement values are reported at the splitting of the parent node. CABG, coronary artery bypass grafting; TIA, transient ischemic attack; Aspirin/clopid., aspirin and/or clopidogrel; LMWH, low molecular weight heparin.

magnitude of this problem is rapidly increasing together with the growing number of elderly patients referred for cardiac procedures.

Unexpectedly, the risk of stroke after CABG was not related to the intensity of oral anticoagulation as measured by INR as well as the timing of discontinuation of warfarin. This suggests that a short pause of oral anticoagulation leading to INR values in the low therapeutic range before CABG does not have per se detrimental effects when warfarin was restarted already on the first postoperative day. On the other hand, bridging therapy was associated with a high risk of stroke. This may be due to the fact that bridging therapy was used mostly in acute coronary syndromes, although recent studies suggest that bridging therapy by itself may lead to higher complication risk in coronary interventions (23).

Since off-pump coronary surgery may lead to late thrombin generation and reduced fibrinolysis as well as higher platelet activity during the immediate postoperative period (22), we can speculate that such delayed strokes occurring a few days after CABG may be secondary to an unexpected pronounced platelet aggregation. This may in turn explain the increased risk of stroke in patients on oral anticoagulation not using preoperatively any antiplatelet drug. The beneficial effects of preoperative aspirin in CABG patients are likely, but still not completely proven (24,25). Our results suggest that preoperative antiplatelet treatment may be particularly beneficial in patients on oral anticoagulation who otherwise have a rather high operative risk.

The retrospective nature and the relatively small size of the present series are the main limitations of this study and the present findings on stroke predictors must be ascertained in future prospective studies. This study proved that identification of risk factors in clinical research is far from being simple. The regression methods herein used provide rather different results, despite both univocally indicating the prognostic impact of CHADS$_2$ > 2, an observation which couples that in non-surgical patients. CART is one and the most used of classification tree procedures, but still its results can be affected by several methodological issues. Herein, we attempted to develop classification trees of reduced size and possibly of more clinical relevance. Since our database is relatively small, analysis in the terminal nodes was necessarily allowed in a rather small number of patients and, this may possibly introduce a bias. However, we believe that estimation of these variables' predictive importance effectively guided us in the development of clinically sound and valuable classification trees. Notably, we have obtained with CART analyses rather large areas under the ROC curve, even better than the one obtained with logistic regression.

In conclusion, both CART and logistic regression analyses showed that the patient characteristics included in $CHADS_2$ score are important also in the prediction of postoperative stroke risk. Preoperative antiplatelet treatment may be beneficial in the high risk patients and the preoperative bridging with low molecular weight heparins may even be harmful in this respect.

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Declaration of interest: The authors have no conflict of interest and they are alone responsible for the content and writing of the paper.

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