Predicting early mortality following single-stage coronary artery or valve surgery and carotid endarterectomy

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Abstract

Background: Surgical management of coexisting cardiac disease and extra-cranial carotid artery disease is a controversial area of debate. Thus, in this challenging scenario, risk stratification may play a key role in surgical decision making. Aim: To report the results of single stage coronary/valve surgery (CVS) and carotid endarterectomy (CEA), and to identify predictive factors associated with 30-day mortality. Methods: This was a multicenter, retrospective study of prospectively maintained data from three academic tertiary referral hospitals. For this study, only patients treated with single stage CVS, meaning coronary artery bypass surgery or valve surgery, and CEA between March 1, 2000 and March 30, 2020, were included. Primary outcome measure of interest was 30-day mortality. Secondary outcomes were neurologic events rate, and a composite endpoint of postoperative stroke/death rate. Results: During the study period, there were 386 patients who underwent the following procedures: CEA with isolated coronary-artery bypass graft in 243 (63%) cases, with isolated valve surgery in 40 (10.4%), and combination of coronary artery bypass grafting and valve surgery in 103 (26.7%). Postoperative neurologic event rate was 2.6% (n = 10) which includes 5 (1.3%) TIA’s and 5 (1.3%) strokes (major n = 3, minor n = 2). The 30-day mortality rate was 3.9% (n = 15). Predictors of 30-day mortality included preoperative left heart insufficiency (OR: 5.44, 95%CI: 1.63-18.17, p = 0.006), and postoperative stroke (OR: 197.11, 95%CI: 18.28-2124.93, p < 0.001). No predictor for postoperative stroke and for composite endpoint was identified. Conclusions: Considering that postoperative stroke rate and mortality was acceptably low, single stage approach is an effective option in such selected high-risk patients.
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Word count: 266

Key words: single stage intervention; carotid endarterectomy and coronary artery bypass graft surgery; carotid endarterectomy and valve surgery; postoperative stroke

Introduction
Surgical management of coexisting cardiac disease and extra-cranial carotid artery disease is a controversial area of debate, especially when carotid lesion is asymptomatic.\textsuperscript{1,2} Meta-analyses reported contradictory results, adequately powered randomized clinical trials do not exist demonstrating the superiority of one treatment strategy over another, and clinical practice guidelines from professional cardiovascular societies have not recommended or precluded the adoption of a specific strategy.\textsuperscript{3-10} Currently, the timing of the intervention primarily depends on clinical presentation and institutional experience.\textsuperscript{11} Thus, in this challenging scenario, risk stratification may play a key role in surgical decision making. Utilization of a risk index model when approaching patient selection and treatment modality recommendations could give physicians a more accurate way of predicting postoperative outcomes by and providing them with additional information with high-risk patients.\textsuperscript{12} While most of the single-center experiences focused on overall stroke and mortality risk analysis, there are no specific data reporting on specific predictors for these major outcomes.

The aim of this study was to identify predictors for 30-day mortality, on a cohort of consecutive patients treated with single stage coronary/valve surgery (CVS) and carotid endarterectomy (CEA).

**Methods**

**Study cohort**

This is a multicenter, retrospective, observational cohort study that includes three academic tertiary referral hospitals. Checklist of items followed the STROBE statement.\textsuperscript{13} Clinical data were collected prospectively at each center and entered a merged database, which was analysed retrospectively. For this study, patients of interest were those treated with single stage CVS and CEA between March 1\textsuperscript{st}, 2000, and March 30\textsuperscript{th}, 2020. Data entry was managed by physicians involved in patient care. Information collected included demographics, co-morbidities, presenting symptoms, carotid artery characteristics, the type of concomitant cardiac (coronary artery bypass surgery, valve surgery or their combination) intervention, as well as postoperative events (cerebrovascular events, death, complications, reintervention) within 30 days. Informed consent was obtained from all individual participants included in the study. For this type of study consent for publication is not required by the local Institutional Review Board, accordingly to our National Policy in the matter of Privacy Act on retrospective analysis of anonymized data.

**Operative details**

Preoperative evaluation has been already described in previously published papers of this collaborative group.\textsuperscript{14,15} Specifically for this study, indications for CEA are consistent with the guidelines for the management of extra-cranial carotid disease of the Society for Vascular Surgery (SVS).\textsuperscript{11} Single stage CVS and CEA intervention was considered reasonable in patients:

- with severe and/or symptomatic coronary/valve disease that cannot be emended by endovascular means or exposed to a high-risk of perioperative cardiac complications
- with \([?]50-99\%\) carotid stenosis with a history of stroke or transient ischemic attack (TIA) in the preceding 6-months
- with bilateral asymptomatic 70-99\% carotid stenosis
- with unilateral asymptomatic 70-99\% stenosis and contralateral occlusion.

All the interventions were performed under general anesthesia, antibiotic prophylaxis and heparinization. Intraoperatively, somatosensory-evoked potentials plus electroencephalogram, or transcranial-Doppler was used to monitor cerebral status during surgical intervention, and to indicate when the use of shunt was necessary. Carotid endarterectomy was performed using a standard longitudinal arteriotomy; eversion technique was never used. Patch closure was used in selected patients, based on a combination of factors such as gender, size of internal carotid artery, and distal extension of the plaque. Skin incision was closed after the patient was out of extracorporeal circulation. Immediate neurologic assessment of the patient was accomplished upon awakening, and throughout the entire postoperative course if necessary. Any sudden suspect neurologic deficit was promptly evaluated with the collaboration of an independent neurologist, and with computed tomography to determine the etiologic mechanism, and to guide subsequent treatment.
**Definition and primary outcomes**

Clinical and morphologic features, categorization, and grading of comorbidities as well as outcomes measures were classified accordingly to the reporting standards for carotid interventions appointed by the SVS.\(^\text{16}\) Carotid stenosis was considered symptomatic if TIA or stroke involving the ipsilateral carotid territory occurred within 6-months of the initial assessment. Carotid cross-clamp intolerance and necessity of shunt insertion was defined as a reduction of >75% in baseline wave values of when using somatosensory-evoked potentials, or >50% reduction of the peak systolic value at the ipsilateral middle cerebral artery at transcranial-Doppler. Severity of the complication and neurologic events were classified accordingly to the SVS guidelines.\(^\text{11,16}\)

Neurologic complications were classified as follow: minor stroke was a new neurologic event that persisted for >24 hours but completely resolved or returns to baseline within 30 days and changed the National Institutes of Health Stroke Scale (NIHSS) by 2 to 3 points. A major stroke was a new neurologic event that persisted after 3 days and changed the NIHSS by at least 4 points. Specifically for this study, primary outcome was in-hospital mortality. Secondary outcomes were neurologic events rate, and a composite endpoint of stroke/death rate.

**Statistical analysis** \(^\text{17}\)

Clinical data were recorded and tabulated in Microsoft Excel (Microsoft Corp – Redmond; Wash – USA) database. Statistical analysis was performed by means of SPSS 26.0 for Windows (IBM SPSS – Chicago; Ill – USA). Categorical variables were presented using frequencies and percentages. Continuous variables were presented with mean ± standard deviation (SD), or median with interquartile range (IQR) and ranges, based on data distribution. Categorical variables were analyzed with the $\chi^2$ test, and Fisher’s exact test when appropriate. Continuous variables were tested for normal distribution by the Shapiro-Wilk’s test and compared between groups with unpaired Student’s $T$-test for normally distributed values; otherwise, the Mann-Whitney $U$ test was used. Tukey’s honest significance test was used as single-step multiple comparisons to find significant difference among means. Univariate analysis was used to identify potential predictors of in-hospital mortality. Associations that yielded a $p$ value <0.20 on univariate screen were then included in a binary logistic regression analysis using the Wald’s forward stepwise model. The strength of the association of variables with mortality was estimated by calculating the odd ratio (OR) and 95% confidence intervals [(95%CI): significance criteria 0.20 for entry, 0.05 for removal]. All reported $p$ values were two-sided; $p$ value <0.05 was considered significant.

**Results**

**Study cohort and surgical details**

During the study period 386 patients met the inclusion criteria. There were 364 (94.3%) males and 22 (5.7%) females. The median age was 73 years (IQR, 67-78). Demographic data, comorbidities and risk factors of the entire cohort are reported in Table 1: the median SVS score risk was 9 (IQR, 8-11). Single stage CEA and isolated coronary-artery bypass graft was performed in 243 (63%) cases, CEA and isolated valve surgery in 40 (10.4%); CEA with a combination of coronary-artery bypass and valve surgery was performed in 103 (26.7%) cases. Carotid endarterectomy was performed with shunting in 56 (14.5%) cases, and patch closure was carried out in 197 (51%). Overall, the median clamping time was 29 minutes (IQR, 23-37).

**Early results ([?]) 30 days**

**primary outcome**

Mortality at 30-days was observed in 15 (3.9%) cases; it was not different among enrolling centers (3.8% vs 3.0% vs 5.7%, $p = 0.632$) and quartile of study (3.9% vs 0.0% vs 5.5% vs 2.8%, $P = 0.431$). Five covariates were associated with the primary outcome as reported in Table 2: however, binary logistic regression analysis identified that 30-days mortality was associated with preoperative left heart insufficiency (OR: 5.44, 95%CI: 1.63-18.17, $p = 0.006$), and postoperative stroke (OR: 197.11, 95%CI: 18.28-2124.93, $p < 0.001$). The ROC analysis (AUROC: 0.77, 95%CI: 0.64-0.91) had reasonably good discrimination for the obtained multivariate model (Figure 1).
Secondary outcomes

There were 10 (2.6%) postoperative cerebrovascular events: 5 (1.3%) TIs and 5 (1.3%) strokes (major n = 3, minor n = 2). This rate was not different among the enrolling centers (1.6% vs. 3.7% vs. 2.9%, p = 0.509); although there was a continuous decrease through the four quartiles of the study period, the difference was not statistically significant (5.9% vs. 3.7% vs. 2.5% vs. 1.4%, p = 0.365). Postoperative stroke was not significantly associated neither with gender (OR: 0.94, P = 1.0) nor with elderly patients aged >80 years (OR: 0.51, p = 0.998), nor with the use of shunt (OR: 1.65, p = 0.655).

Discussion

Cardiovascular operators have not yet reached a definitive consensus regarding the best treatment strategy in the presence of co-existing coronary artery and/or valve disease and extra-cranial carotid lesions amenable of operative repair. During the last decade there have not been systematic high-level evidence published, and two randomized clinical trials failed to establish which should be the recommended treatment strategy due to lack of adequate power and/or because of slow enrollment. Still a pending matter of debate, we believe that the choice to perform a single stage intervention may still be reasonable based on our institutional experience, especially in the presence of a homogeneous treatment protocol among the centers involved. The 3.9% postoperative mortality rate at 30-days observed in our cohort is acceptable considering the magnitude of intervention and the high-risk profile of the cohort: it is in line with the mean 5.1% in-hospital mortality reported in the larger cohort of the National Inpatient Sample analysis of isolated coronary artery bypass grafting, as well as not significantly inferior to the 3.8% reported for the staged treatment of the concomitant diseases.

One modality for optimizing risk assessment is to use a predictive score but, currently, there are no mortality predictive scoring systems for single stage CVS and CEA. The predictors identified in our series are reliable since they have been associated with mortality in other experiences. When it comes to the carotid revascularization component of this complex clinical scenario, the risk of neurologic complications has been correlated to the clinical relevance of the carotid stenosis, namely a history of stroke. While there is no unquestionable evidence that the majority of patients undergoing coronary artery bypass grafting may benefit from CEA, high-grade extra-cranial carotid artery stenosis poses a higher risk of stroke than patients without carotid disease. The fact that stroke rate was lowest at 1.9% in the staged group of the vast cohort of the National Inpatient Sample may support this observation. Furthermore, most of the strokes have been mechanistically unrelated to pre-existing carotid artery occlusive disease. For the sake of comparability, the 1.3% rate found in our experience is favorable in comparison with the 2.8% reported in a recent meta-analysis by Urso et al. in patients undergoing isolated coronary artery bypass grafting, and like the 2.5% in those undergoing isolated percutaneous coronary intervention with drug-eluting stents. Also, in our experience we did not observe a difference in occurrence of new strokes between patients who had symptomatic or asymptomatic carotid lesions. Taking into consideration that the recent clinical practice guidelines of the European Society for Vascular Surgery (ESVS) reported that CEA should be considered in patients with a history of stroke, and considering the favorable data in our cohort, we consider single stage CVS and CEA safe and effective in selected high-risk patients.

Considering that outcomes in patients undergoing carotid artery stenting (CAS) markedly improved in recent years, CAS has been proposed as an alternative strategy for carotid lesions, as transcatheter aortic valve implantation for valve disease. In the cohort of the National Inpatient Sample, the staged approach with CAS preceding coronary-artery bypass grafting showed the lowest risk of mortality. However, CAS was associated with highest risk of stroke, and a higher risk of stroke and higher interstage risk of myocardial infarction for a total number of staged CAS-first strategy that was twenty times fewer than single stage coronary-artery bypass grafting and CEA. Thus, in these patients with concomitant diseases there is minimal reasonable evidence to widely support a CAS-first strategy.

Limitations

This study has several limitations. Though data collection is prospective, analysis is retrospective in nature.
This multicenter dataset relies solely on accurate site reporting. However, important morphologic variables related to the carotid arteries have been collected the study was adequately powered. Therefore, prospective evaluation of the risk score is needed to clarify its utility for risk stratification and decision-making. There is the risk of sampling bias as this is a selected cohort of patients undergoing repair with other techniques were not included for comparison. Nevertheless, this reflects the careful selection process in our cases as well as the homogeneity of the cohort among these centers. Also, the low adverse event rate did not allow for meaningful multivariate analysis as well as subgroup analyses. Despite these limitations, this data compares well with the available literature owing to the consistency and homogeneity of the data. Even so, these limitations may not allow for generalizability of our findings.

Conclusions

The risk of postoperative stroke after single stage CVS and CEA progressively decreased over the years in our experience. The development of postoperative stroke showed to have a strong impact on mortality which, however, was very close to the lower limit of the rate reported in the literature. Considering that stroke rate and mortality was not non-inferior to isolated CVS, we consider that single stage approach to concomitant coronary artery, and/or valve disease, and extra-cranial severe carotid stenosis is our operation of choice in such selected high-risk patients.

Authors’ contributions:
Study design: GP, WD, SBo
Data collection: MF, SS, BP, CZ, SF
Data analysis: GP, WD
Writing: GP, WD, SBo, RP, MB
Critical revision and final approval: MF, WD, SB, SS, RP, SBo, MB, GP, SF, BP, MT, PS, CZ
All authors read and approved the final version of the manuscript.

References


Figure 1

Receiver operating characteristic curve for the multivariate model evaluating mortality at 30-days (AUROC = area under the receiver operating characteristic curve).

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Total cohort</th>
</tr>
</thead>
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<tr>
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<td>(n = 386)</td>
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<tr>
<td><strong>Demographics</strong></td>
<td></td>
</tr>
<tr>
<td>M:F</td>
<td>364:22</td>
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<tr>
<td>Age, median (IQR)</td>
<td>73 (67-78)</td>
</tr>
<tr>
<td>&gt;80 years, n (%)</td>
<td>68 (17.6)</td>
</tr>
<tr>
<td><strong>Comorbidity</strong>, n (%)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>348 (90.2)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>272 (70.5)</td>
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<tr>
<td>Active smoking</td>
<td>251 (52.1)</td>
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<tr>
<td>Diabetes</td>
<td>156 (40.4)</td>
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<tr>
<td>Pulmonary hypertension</td>
<td>87 (22.5)</td>
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<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>81 (21.0)</td>
</tr>
<tr>
<td>Left heart insufficiency</td>
<td>75 (19.4)</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>47 (12.2)</td>
</tr>
<tr>
<td><strong>Risk factor</strong>, n (%)</td>
<td></td>
</tr>
<tr>
<td>Symptomatic carotid</td>
<td>50 (13)</td>
</tr>
<tr>
<td>Reintervention</td>
<td>45 (11.7)</td>
</tr>
<tr>
<td>Hostile neck</td>
<td>31 (8.1)</td>
</tr>
<tr>
<td>Preoperative stroke</td>
<td>25 (6.5)</td>
</tr>
<tr>
<td>Contralateral CEA</td>
<td>8 (2.1)</td>
</tr>
<tr>
<td>SVS score, median (IQR)</td>
<td>8 (7-10)</td>
</tr>
<tr>
<td>Carotid stenosis, median (IQR)</td>
<td>80 (75-85)</td>
</tr>
<tr>
<td>Contralateral stenosis, median (IQR)</td>
<td>45 (40-55)</td>
</tr>
</tbody>
</table>

**TABLE 1**

Comorbidities and risk factors of the cohort undergoing single stage valve or coronary artery surgery and carotid artery endarterectomy (n = 386)

**CEA** = carotid endarterectomy

**IQR** = interquartile range; **n** = number

**SVS** = Society for Vascular Surgery

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Univariate</th>
<th>Univariate</th>
<th>Univariate</th>
<th>Univariate</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>30-days mortality</td>
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<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>P</td>
<td>OR</td>
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<td>Reintervention</td>
<td>2.93</td>
<td>1.85-9.62</td>
<td>0.084</td>
<td>5.44</td>
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<td></td>
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<tr>
<td>Left heart insufficiency</td>
<td>3.90</td>
<td>1.37-11.12</td>
<td>0.014</td>
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<tr>
<td>Symptomatic stenosis</td>
<td>2.57</td>
<td>0.78-8.40</td>
<td>0.115</td>
<td>5.44</td>
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<td>History of stroke</td>
<td>3.97</td>
<td>1.04-15.01</td>
<td>0.065</td>
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<tr>
<td>Use of shunt</td>
<td>2.51</td>
<td>0.77-8.19</td>
<td>0.112</td>
<td>5.44</td>
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<tr>
<td>Postoperative stroke</td>
<td>18.3</td>
<td>5.45-89.72</td>
<td>&lt; 0.001</td>
<td></td>
<td></td>
<td>197.11</td>
</tr>
</tbody>
</table>

**TABLE 2**

Univariate screen and multivariable analysis for early (≤30 days) mortality.

**CIs** = confidence intervals; **OR** = odds ratio

![AUROC curve](attachment:image)