Simultaneous Hybrid Revascularization with Carotid Stenting and Coronary Artery Bypass Grafting: Long-Term Results of the SHARP Study

Luigi Chiariello, MD, Paolo Nardi, MD*, Francesco Versaci, MD, Jacob Zeitani, MD, Giovanni A. Chiariello, MD

Abstract — We have recently introduced a new therapeutic strategy (“SHARP protocol”) consisting of a simultaneous hybrid revascularization by carotid artery stenting (CAS), immediately followed by coronary artery bypass grafting (CABG) with the aim to reduce operative risk and minimize surgical trauma as compared to traditional approaches. Ninety-five consecutive patients (mean age 68.8±7.8 years, 79 males) underwent simultaneous CAS-CABG from January 2005 to July 2013 for treatment of concomitant critical (>70% stenosis) carotid and multivessel coronary artery obstructive disease. In-hospital mortality was 2.1%, perioperative myocardial infarction 0%, CAS periprocedural stroke 0%, TIA 3.2%. Actuarial 9-year survival was 82±10%. Freedom from cardiac death was 96±2%, from myocardial infarction 95±3%, from neurological events 90±7%, from CAS procedure-related stroke 100%. The proposed hybrid approach confers a mortality rate comparable to that of isolated CABG; CABG immediately following CAS minimizes the risk of periprocedural myocardial infarction. At a long-term period a high rate of event-free survival and freedom from neurological events can be expected using the SHARP protocol.

Keywords — Coronary Artery Disease, Cardiovascular Disease Carotid Artery Stenting, Coronary Artery Bypass Grafting.

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I. INTRODUCTION

The incidence of perioperative stroke following coronary artery bypass grafting (CABG) surgery has been reported to increase in patients affected by concomitant carotid artery disease.1 The optimal surgical management to prevent stroke and cardiac events in this subset of patients remains unclear. 2-5 The combined surgical approach is associated with an increased risk for mortality and morbidity.5 Nevertheless, the optimal timing of the two procedures, whether carotid artery stenting (CAS) and CABG should be performed in a staged or synchronous step, remains controversial. In the staged surgical approach, which addresses the carotid artery lesion with CEA first, followed several days to several weeks by CABG, incidence of perioperative stroke during CABG is reduced. However, the risk of myocardial infarction (MI) during the CEA procedure and in the period preceding CABG remains high (6%).6 CAS using cerebral protection devices is rapidly evolving as a less invasive alternative to traditional CEA,7 mainly for patients with severe carotid artery stenosis with a high surgical risk, such as patients with coronary artery disease.8 A planning staged CAS-CABG approach has been recently proposed, but the need of a dual anti-platelet aggregation therapy and the need of a prompt coronary revascularization lasting 3-4 weeks after stenting may represent a limitation for this approach.9 Since 2005 we have proposed a new therapeutic strategy consisting of a simultaneous hybrid revascularization by CAS, immediately followed by CABG and cases have been collected in the SHARP study (“Simultaneous hybrid revascularization by carotid artery stenting and coronary artery bypass grafting”). As compared to the combined or staged surgical strategy currently adopted, the new hybrid approach CAS-CABG has the rationale to reduce the incidence of serious perioperative adverse events and minimize surgical trauma. Surgical time and surgical trauma are shorter and less extensive as compared to combined CEA and CABG. Risk of MI is expected to be reduced, by shortening the interval between the two procedures.10
The aim of the current study was to evaluate in-hospital results (mortality, incidence of periprocedural transient ischemic attacks, stroke, myocardial infarction) and long-term outcomes up to 9 years of the synchronous hybrid revascularization strategy by CAS and CABG, to analyze risk factors for in-hospital morbidity and mortality, survival and event-free survival. Major non-cardiac in-hospital complications were also analyzed: pulmonary complication was defined as an episode of primary lung failure requiring mechanical ventilation for more than 48 hours, reintubation, or intermittent application of positive end-expiratory pressure by mask; a neurological complication was defined as an episode of stroke due to a focal or general cerebral lesion; renal insufficiency was defined as a two-fold increase of preoperative serum creatinine or oliguria necessitating renal replacement therapy.

II. METHODS

Ninety-five consecutive patients (79 males, 16 females, mean age 68.8 ± 7.9 years) affected by concomitant severe carotid and coronary artery obstructive disease scheduled for treatment at Cardiac Surgery Division of Tor Vergata University Policlinic of Rome from January 2005 to July 2013 were included in the current study. The study was approved by our local Institutional Review Board, which waived the need for patient consent. Preoperative characteristics are reported in Table I. Eligible criteria for the enrollment: 1) concomitant critical carotid and coronary disease with coronary arteries suitable for CABG; 2) EuroSCORE I ≥5; 3) A carotid artery stenosis ≥50% in the symptomatic disease or ≥80% in asymptomatic disease, as determined by the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria.2 Since 2008 we extended the treatment also for patients with lower EuroSCORE I and in presence of a carotid artery stenosis greater than 70% regardless of symptoms. The presence and the degree of carotid artery stenosis was evidenced by eco duplex scanning, then confirmed by catheter angiography and either magnetic resonance angiography or computed tomography scan angiography. A computed tomography scan with or without angiographic dye, depending on preprocedural serum levels of creatinine, was performed in all patients to provide the maximum information regarding the aortic arch, the extent of aortic disease and the brain. In case of bilateral carotid artery stenosis the choice of the carotid artery to treat was made according to clinical criteria or to the severity and morphology of plaque. In a very few instances of bilateral subocclusive carotid stenosis, successful bilateral CAS has been performed, immediately followed by CABG. Carotid artery stenting was performed under local anaesthesia through a percutaneous transfemoral access with the use of stents and protection devices. An introducer sheath was positioned in the femoral artery, and heparin (1 mg /kg) was administered intra-arterially as a bolus. Then a guiding catheter was placed in the common carotid artery, proximally to the bifurcation. A distal filter protection was used in all patients. At the end of the procedure, patients were transferred directly to the operating room; CABG procedure was performed according to the choice of surgeon and co-morbid disease of patient.

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Periprocedural pharmacological protocol

Aspirin 100 mg daily was started at least 2 days before CAS and daily after combined procedure was performed. Heparin was administered 1 mg /Kg as a bolus intra-arterially immediately before the stent implantation procedure and in the operating room before the cardiopulmonary bypass 2 mg/Kg as a bolus. Activated clotting time was checked every 30 minutes and was constantly maintained ≥ 250 sec. until the CABG procedure and ≥480 seconds until the end of the cardiopulmonary bypass. Tranexamic acid 2 g in bolus was administered as an antifibrinolytic agent over 20 minutes before sternotomy and then as endovenous infusion (0.5 g/h) until the patient was admitted to the postoperative intensive care unit in most of cases. Clopidogrel, 300 mg as a loading dose, followed by 75 mg per day for 1 month was started in the intensive care unit via a nasogastric tube.

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### Table I: Preoperative Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CAS + CABG (n = 95)</th>
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</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>68.8 ± 7.9</td>
</tr>
<tr>
<td>Male gender, n. (%)</td>
<td>79 (83)</td>
</tr>
<tr>
<td>Logistic EuroSCORE I, %</td>
<td>8.6 ± 7.3</td>
</tr>
<tr>
<td>Logistic EuroSCORE II, %</td>
<td>3.4 ± 2.4</td>
</tr>
<tr>
<td>CCS class, mean value</td>
<td>2.9 ± 1.0</td>
</tr>
<tr>
<td>NYHA class, mean value</td>
<td>2.0 ± 1.0</td>
</tr>
<tr>
<td>Previous myocardial infarction, n. (%)</td>
<td>44 (46)</td>
</tr>
<tr>
<td>Hypertension, n. (%)</td>
<td>82 (86)</td>
</tr>
<tr>
<td>Smoking habit, n. (%)</td>
<td>74 (78)</td>
</tr>
<tr>
<td>Diabetes mellitus, n. (%)</td>
<td>46 (48)</td>
</tr>
<tr>
<td>- Insulin Therapy, n. (%)</td>
<td>20 (21)</td>
</tr>
<tr>
<td>Hyperlipidemia, n. (%)</td>
<td>59 (62)</td>
</tr>
<tr>
<td>Obesity, n. (%)</td>
<td>19 (20)</td>
</tr>
<tr>
<td>Chronic renal dysfunction, n. (%)</td>
<td>17 (18)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease, n. (%)</td>
<td>42 (44)</td>
</tr>
<tr>
<td>Bilateral carotid artery stenosis ≥50%, n. (%)</td>
<td>62 (65)</td>
</tr>
<tr>
<td>Contra-lateral carotid occlusion, n. (%)</td>
<td>8 (8.4)</td>
</tr>
<tr>
<td>Previous stroke /TIA, n. (%)</td>
<td>18 (19)</td>
</tr>
<tr>
<td>Urgent CABG, n. (%)</td>
<td>48 (51)</td>
</tr>
<tr>
<td>No. diseased coronary vessels /patient</td>
<td>2.8 ± 0.4</td>
</tr>
<tr>
<td>LVEF, mean value</td>
<td>0.52 ± 0.11</td>
</tr>
</tbody>
</table>

CAS = carotid artery stenting; CABG = coronary artery bypass grafting; EuroSCORE = European System for Cardiac Operative Risk Evaluation; CCS = Canadian Cardiovascular Society; NYHA = New York Heart Association; TIA = transient ischemic attack; LVEF = left ventricular ejection fraction.
mammary artery in 19 cases (20%). Mean number of grafts per patient was 2.9 ± 0.8.

In-Hospital mortality was 2.1% (2 deaths /95 patients). One 75-year old patient with a 9.7% Logistic EuroSCORE I died after 25 days from the procedure for a septic shock; another 68-year female patient with a 18.3% Logistic EuroSCORE I died in the first postoperative day for a low-output syndrome. Major non-cardiac complications occurred postoperatively in 13 (13.7%) patients (stroke, n = 1; respiratory insufficiency, n = 6; acute renal injury with or without renal therapy replacement, n = 6).

The presence of preoperative chronic renal dysfunction was found as the only independent predictor of in-hospital morbidity and mortality (P=.018; HR: 6.7) (Table III).

Although diabetes mellitus was associated with a higher incidence of perioperative mortality and morbidity rate (13% vs. 6.1%), it was not recognized as risk factor at the univariate analysis. (P = .20).

Incidence of peri-procedural CAS transient ischemic attacks was 3.2%, of stroke 0%, of myocardial infarction 0%, respectively. Re-exploration for bleeding was required in 4 (4.2%) patients.

Postoperative length of stay was 7.8 ± 5.3 days.

Follow-up Results
Mean duration of follow-up was of 48 ± 34 (range 1-108) months. Three patients were lost at follow-up, thus completeness was 97%. Independent predictor of impaired survival was the preoperative lower value of left ventricular ejection fraction (0.43 ± 0.10 vs. 54 ± 0.12, P=.007; HR:7.7).

At the end of follow-up we found 7 deaths whit an actuarial survival rate of 82 ± 10% at 9 years; furthermore we observed a very low mortality rate for cardiac late death (96 ± 2%) and high rates of freedom from myocardial infarction (95 ± 3%) and neurological events (90 ± 7%) (we registered just one case of fatal stroke during follow-up). Freedom from fatal stroke CAS-related was 100% (Figures 1-5).

Independent predictor of neurological events was a higher preoperative value of the new EuroSCORE II (8.7 ± 13 vs. 3 ± 3.3, P=.005; HR:13.3). CCS class improved from 2.9 ± 1.0 preoperatively to 1.1 ± 0.4 (P<.00001), and NYHA functional class from 2.0 ± 1.0 preoperatively to 1.5 ± 0.6 (P=.0005).

Internal carotid artery systolic blood flow during follow-up, assessed by duplex-scanner Echo-Doppler US, showed significant improvement as compared to preoperative mean value (67 ± 10 cm/sec vs. 325 ± 40 cm/sec, P<.001).

In-stent subcritical re-stenosis was detected in 1 patient.

### TABLE II

**INTRAOPERATIVE CHARACTERISTICS**

<table>
<thead>
<tr>
<th>Variable</th>
<th>CAS + CABG (n = 95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiopulmonary bypass, n. (%)</td>
<td>80 (84)</td>
</tr>
<tr>
<td>Off-pump CABG</td>
<td>15 (16)</td>
</tr>
<tr>
<td>Aortic Cross-clamp time, minutes</td>
<td>46 ± 19</td>
</tr>
<tr>
<td>No. grafts per patient</td>
<td>2.9 ± 0.8</td>
</tr>
<tr>
<td>ITA use, n. (%)</td>
<td>95 (100)</td>
</tr>
<tr>
<td>Bilateral ITA, n. (%)</td>
<td>19 (20)</td>
</tr>
</tbody>
</table>

CAS = carotid artery stenting; CABG = coronary artery bypass grafting; ITA = internal thoracic artery.

6 hours after the end of CABG surgery, providing that surgical bleeding from the thoracic drains had either stopped, or when it was less than 50 mL /hr for 3 consecutive hours from the sixth postoperative hour.

### STATISTICAL ANALYSIS

Statistical Analysis was performed with Stat View 4.5 (SAS Institute Inc, Abacus Concepts, Berkeley, CA). Univariate analysis of preoperative and perioperative variables considered as potential risk factors for in-hospital morbidity and mortality was performed using the Student’s t test for continuous data and the χ² or Fisher’s exact test for categorical data. Univariate variables with p value of or less than 0.1 were included into a multivariate logistic regression analysis in order to identify independent predictors . Twenty-five variables were selected for the univariate and multivariate analyses, including age, gender, previous myocardial infarction, presence of previous stroke or transient ischemic attack, smoking habit, family history, co-morbid disease (arterial hypertension, diabetes mellitus, chronic renal dysfunction, chronic obstructive pulmonary disease, hyperlipidemia, obesity), the presence of a bilateral carotid stenosis (>/=50%) or contra-lateral carotid occlusion, Canadian Cardiovascular Society (CCS) grade of angina, New York Heart Association (NYHA) functional class, mean value of Logistic EuroSCORE I and the new EuroSCORE II, preoperative value of the left ventricular ejection fraction, number of diseased coronary artery vessels, presence of the left main stem critical disease, need of urgent CABG, number of grafts per patient, cardiopulmonary bypass and aortic cross-clamp times. Overall survival (not including operative mortality), freedom from late cardiac death and freedom from neurological events were expressed as mean values plus or minus 1 standard deviation, and computed by using the Kaplan-Meier method; the Cox proportional hazards methods was used to evaluate the influence of variables on time to death. All other values were expressed as mean plus or minus 1 standard deviation of the mean.

### III. RESULTS

Intraoperative characteristics of the population are reported in Table II. Left internal mammary artery was used as graft to the left anterior descending artery in all patients, bilateral mammary artery in 19 cases (20%). Mean number of grafts per patient was 2.9 ± 0.8.

In-Hospital mortality was 2.1% (2 deaths /95 patients). One 75-year old patient with a 9.7% Logistic EuroSCORE I died after 25 days from the procedure for a septic shock; another 68-year female patient with a 18.3% Logistic EuroSCORE I died in the first postoperative day for a low-output syndrome. Major non-cardiac complications occurred postoperatively in 13 (13.7%) patients (stroke, n = 1; respiratory insufficiency, n = 6; acute renal injury with or without renal therapy replacement, n = 6).

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### TABLE III

**INDEPENDENT PREDICTORS OF IN-HOSPITAL MORBIDITY AND MORTALITY**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>H. Ratio</th>
<th>95% CI</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Renal Dysfunction</td>
<td>6.7</td>
<td>1.37 – 32.4</td>
<td>.018</td>
</tr>
<tr>
<td>Bilateral carotid stenosis ≥50%</td>
<td></td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

NS = not significant for P value > .05.
IV. DISCUSSION

Neurological complications are relatively common after CABG, especially in high-risk patients. Carotid artery disease is significantly associated with a type I adverse neurological outcome (i.e., death due to stroke or hypoxic encephalopathy, nonfatal stroke, TIA, stupor, or coma). Significant carotid artery stenosis is associated with up to 30% of early postoperative strokes following CABG. Preventing stroke and cardiovascular events after CABG is an important and complex issue. Concomitant carotid artery disease might be a major factor contributing to the occurrence of postoperative stroke. Moreover, carotid artery disease might be a marker of diffuse atherosclerosis, affecting also aortic arch, arch vessels, and intracranial vessels. In this high risk population, a simplified operative management like hybrid revascularization by CAS and CABG can minimize the negative impact of diffuse atherosclerotic disease. In fact, our findings indicate that, in patients with combined carotid artery disease and coronary artery disease, the proposed

Fig. 1. Survival during follow-up of 48 ± 34 (1-108) months after CAS and CABG procedure.
CAS = carotid artery stenting; CABG = coronary artery bypass grafting.

Fig. 2. Freedom from late cardiac death.

Fig. 3. Freedom from myocardial infarction.

Fig. 4. Freedom from neurological events.

Fig. 5. CAS procedure-related fatal stroke.
hybrid approach is a feasible therapeutic option with good immediate and short-term clinical results. The recently reported incidence of perioperative stroke and mortality following CEA and CABG is not negligible, ranging between 8.3% to 10.3%. According to these results, in a previous series of 100 consecutive patients undergoing combined surgical revascularization at our Institution between 1991 and 2002, the 30-day mortality and stroke rate was 10% and 1.1%, respectively, with a mortality rate of 14.5% when the standard EuroSCORE was ≥ 6, and 3.4% when it was lower than 6. These high-risk patients could be treated by an alternative strategy such as the hybrid approach proposed in this study. As compared with combined surgical revascularization, the hybrid strategy requires a shorter surgical time and less extensive surgical trauma, thus reducing cofactors known to increase morbidity and mortality. In particular, in high-risk patients for CEA, mainly due to severe CAD, the SAPPHIRE trial showed that CAS was safer than CEA, because it had a lower postprocedural risk of myocardial infarction at 30 days as compared with surgery. This is likely to be the case mainly in patients with elevated surgical risk, such as the patients involved in the SHARP study. In particular, when the standard EuroSCORE is greter than 5 and the Logistic is 8%, as it is in our study (Table 1), the surgical mortality rate might be greater than 10-12%. In this high-risk subset of patients, specific surgical complications are also increased up to 55%. When both internal carotid arteries have significant stenosis, the risk of stroke after cardiac surgery is particularly high (25%). With the percutaneous hybrid approach, in our study the stroke rate was absent, considering that 65% of our patients had bilateral internal carotid artery disease (Table I). Potential adjunctive advantage of the simultaneous hybrid approach as compared with a combined surgical approach is that during the CAS procedure the patient is awake and the neurological outcome will be known instantly rather than after the patient emerges from general anesthesia. Another most important finding of our study was the absence of peri-procedural rate of myocardial infarction. A recent analysis of Shishehbor and co-workers, comparing three different approaches to carotid revascularization and open heart surgery, found a higher risk of inter-stage myocardial infarction in the staged CEA and cardiac surgery in comparison with concomitant both artery territories revascularization. The staged CAS CABG approach can be a valid alternative in patients at a high surgical risk, but the need of an aggressive antplatelet therapy for one month after stent procedure increases the risk of myocardial infarction. In cases of less extended coronary artery disease, i.e. in presence of single- or two-vascular coronary disease, concomitant CAS and percutaneous coronary revascularization can be a valid option. By observing the proposed protocol, the risk of myocardial infarction, especially during carotid surgery or in the time elapsing between the two procedures (traditional CEA or CAS and CABG after 3-4 weeks from carotid procedure), is virtually eliminated. In the two-stage procedure, the rate of MI when the patient is waiting for CABG after carotid artery procedure is about 5-6%. The proposed hybrid approach conferred an operative mortality rate comparable to that of isolated CABG. During a long-term follow-up we observed very satisfactory results, either in terms of high freedom from neurological events (90%), than in terms of freedom from cardiac death (96%) and myocardial infarction (95%). Freedom from cerebral events CAS procedure-related was 100%.

Limitations of the study
The principal weakness of this study is its retrospective nature, the relatively small sample size and the limited number at risk of patients following the five years of the follow-up. To evaluate the effectiveness of this protocol in reducing in-hospital morbidity and mortality in comparison with other traditional surgical techniques or with other hybrid strategies, a large number of patients should be required.

V. CONCLUSIONS
In conclusions, the new hybrid approach is aiming to reduce risk of myocardial infarction, of bleeding after CABG and risk of death and major cerebrovascular complications. Reduced mortality and morbidity are expected to reduce also in-hospital stay and costs. Therefore, in patients with combined carotid artery and coronary artery disease at higher surgical risk, the proposed hybrid approach seems to be a possible, advantageous and safe alternative therapeutic strategy.

REFERENCES


