



Carotid artery screening at the time of coronary artery bypass - Does it influence neurological outcomes?



P. Narayan^{a,*}, Md. W. Khan^a, D. Das^a, R. Guha Biswas^b, M. Das^a, E. Rupert^b

^a Department of Cardiac Surgery, NH Rabinranath Tagore International Institute of Cardiac Sciences, Kolkata, India

^b Department of Cardiac Anaesthesia, NH Rabinranath Tagore International Institute of Cardiac Sciences, Kolkata, India

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ABSTRACT

Objective: Patients undergoing coronary artery bypass graft (CABG) are recommended to undergo carotid duplex study in presence of risk factors. Aim of the study was to quantify the relationship between risk factors and presence of carotid disease and examine if screening influenced outcomes.

Methods: Over a four year period in a single institution, 4364 consecutive patients presenting for primary isolated CABG were enrolled to undergo carotid duplex scanning. Patients were grouped as no significant carotid artery stenosis (<50%), moderate stenosis (50%–70%) and severe stenosis (>70%). Sub group analysis of patients with severe carotid stenosis was performed. Sensitivity of risk factors thought to be associated with carotid disease was also assessed.

Results: Of the 4364 patients, 406 patients (9.3%) had moderate or severe carotid artery stenosis. 32 (7.88%) had bilateral disease. Age > 65, hypertension, left main stem stenosis, peripheral vascular disease, and previous neurological injury were all associated with carotid artery disease ($p < 0.01$). Diabetes ($p = 0.06$) and smoking ($p = 0.79$) were not significant risk factors.

In patients with moderate carotid artery stenosis there was no difference in the incidence of major 4 (0.98%) vs. 18 (0.45%) $p = 0.14$ or minor 8 (1.9%) vs. 56 (1.41%); $p = 0.38$ neurological outcomes. However, severe carotid stenosis was associated with an increase in all-cause mortality but no increase in neurological events.

Conclusions: In the presence of risk factors carotid screening identifies at risk population. Severe carotid stenosis was associated with increased all-cause mortality. However, moderate stenosis did not influence neurological outcomes or mortality in patients undergoing coronary artery bypass grafting.

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1. Introduction

The incidence of adverse neurological outcomes following coronary artery bypass grafting (CABG) has been reported to be about 1–3% with an even distribution between major neurological deficits (type 1) and minor neurological deficits (type 2) [1,2]. The two major problems in patients suffering a stroke following coronary artery bypass are increase in mortality which can be up to ten times higher and a prolonged hospital stay [3].

In the past presence of extra-cranial disease of the internal carotid artery has been considered to be a risk factor for adverse neurological outcomes [4] and based on this observation some centres carry out mandatory screening in all patients undergoing coronary artery surgery. However, in more recent times carotid artery stenosis has been thought to be a surrogate marker for diffuse atherosclerotic disease [5] rather than a direct etiological factor and no direct causal relationship between

significant carotid stenosis and postoperative stroke has been established [6]. This has led to the suggestion that screening should perhaps be guided by presence of cerebrovascular symptoms [7]. In accordance to the recommendations by the American Heart Association guidelines some centres selectively screen patients for carotid artery disease only in presence of risk factors like age > 65 years, left main coronary artery stenosis, peripheral arterial disease (PAD), history of cerebrovascular disease, hypertension, smoking, and diabetes mellitus [8–10].

Despite screening for carotid artery disease, either on a mandatory or selective basis it is not clear if it leads to any improvement in neurological outcome which is the sole purpose of pre-operative carotid artery screening. Also any observed benefit of screening in improving neurological outcomes is not uniform. While the subgroup with history of previous cerebro-vascular event may show improved neurological outcomes, there is not enough evidence to prove that screening for carotid artery stenosis leads to any reduction in adverse neurological outcomes in asymptomatic patients [11]. Another observation that undermines the importance of screening for carotid artery disease is the fact that a substantial proportion of strokes after coronary artery

* Corresponding author at: RTIICS, Kolkata 700099, India.

E-mail address: pradeep.narayan.dr@narayanahealth.org (P. Narayan).

bypass grafting, occur in patients without significant carotid artery disease or in an anatomic distribution not consistent with a known significant carotid artery stenosis [11,12].

The aim of our study was to examine the association between the risk factors and presence of carotid artery disease. We also sought to examine if identifying patients with concomitant carotid artery disease undergoing elective coronary artery bypass grafting influenced the incidence of adverse neurological events and mortality.

2. Methods

Between January 2011 and December 2013, in a single institution, 4364 patients undergoing elective, multi-vessel, isolated, primary coronary surgery prospectively underwent carotid artery duplex scanning. It was a non-selective screening where all patients meeting the criteria were recruited. Ethics committee was contacted who opined that a formal ethics approval was not required in this instance.

Inclusion Criteria:

- Patients presenting for primary CABG
- Patients with elective presentation

Exclusion Criteria:

- History of pericarditis, median sternotomy, thoracotomy, chest irradiation, or pleurodesis,
- Associated valvular pathology requiring a combined procedure
- Re-operative surgery

All eligible patients included in the study underwent carotid Doppler scan irrespective of presence or absence of risk factors for carotid artery disease. However, presence of risk factors for carotid artery disease as advised by the 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery; age > 65 years, presence of left main coronary stenosis, peripheral vascular disease, and history of cerebro-vascular disease, hypertension, smoking, and diabetes mellitus were recorded [8].

The risk factors were individually assessed for association with presence of carotid artery disease in these patients. All internal carotid artery (ICA) examinations were performed with gray-scale, color Doppler, and spectral Doppler ultrasound with an angle of insonation less than or equal to 60° as recommended. ICA peak systolic velocity (PSV) and presence of plaque on gray-scale and/or color Doppler images were used in diagnosis and grading of ICA stenosis along with ICA-to-common carotid artery PSV ratio and ICA end-diastolic velocity [13].

Based on the degree of carotid artery stenosis patients were divided into

- No significant carotid artery stenosis (Carotid artery stenosis < 50%)
- Moderate carotid artery stenosis (Carotid artery stenosis 50%–70%)
- Severe carotid artery stenosis (Carotid artery stenosis > 70%)

During the study period carotid Doppler screening was performed on all patients. However, our current policy of carotid screening is based on the criteria recommended by the American Heart Association [8]. Further investigation protocol was based on the presence or absence of symptoms. In patients with no previous history of neurological event, where the carotid stenosis was not severe no further imaging was carried out. In all patients undergoing CABG with previous history of neurological event irrespective of the carotid status a CT brain was performed. In addition, in patients where the carotid duplex was not conclusive or where the carotid stenosis was considered to be severe on duplex scan a CT angiography of the carotid arteries along with intra-cranial angiography to assess the circle of Willis was also performed.

With regards to the management of concomitant carotid artery stenosis the decision was jointly taken by the cardiac and the vascular surgeons and the options discussed with the patient. In patients with moderate stenosis (50%–70%) we did not intervene on the carotid artery. In patients with severe stenosis (>70%) the decision was taken on an individual basis. In patients with severe carotid artery stenosis but no history of any previous neurological insult we chose to perform isolated CABG. Also, in presence of unstable angina, severe symptoms, or left main stem stenosis we chose to perform coronary artery bypass and the patient was followed up for further management of carotid stenosis. In patients with previous history of neurological injury and significant carotid artery stenosis where the patient was not very symptomatic from the cardiac point of view (Canadian Cardiovascular Society class I) and only if the coronary lesions were not critical i.e. solitary, short segment stenosis of <80% with no left main stem stenosis or left main stem equivalent the patients were referred for intervention on the carotid artery. During the study period patients requiring carotid intervention underwent carotid artery stenting. This was because in some cases endarterectomy was thought to be high risk. In other cases the decision was influenced by patient choice and the availability of an experienced operator with low procedure related risks.

All patients undergoing carotid stenting were maintained on dual anti-platelet agents (aspirin 150 mg and Clopidogrel 75 mg) for a minimum of 3 months after carotid artery stenting. Strict diabetic control, and anti-hypertensive treatment was ensured, and smoking cessation was advised in all cases. All patients in the study population, including those with no significant carotid artery stenosis, were maintained on statin therapy. However, in

patients with moderate to severe carotid stenosis we started with higher dosage of statins which was then titrated with tolerance with an aim to maintain the LDL level < 70 mg/dL.

The patients underwent coronary artery revascularization either on the beating heart or on cardiopulmonary bypass depending on the preference of the operating surgeon and there was no randomization of patients to any particular intervention. Efforts to minimize neurological events were made in all patients. In the pre-operative evaluation if there was any suspicion of aortic disease like calcification in the aortic knuckle or unusually calcified coronaries, severely calcific carotid arteries a CT scan was performed to evaluate the ascending aorta. In the absence of any concerns routine digital palpation of the aorta was carried out at the outset to plan the strategy of conduits and proximal anastomosis. In cases where there was doubt about aortic plaques an intra-operative transoesophageal echocardiography was performed. During the study period we did not perform epi-aortic ultrasound. Apart from identifying and avoiding plaques in ascending aorta a number of other measures were undertaken to minimize the neurological events. Off pump coronary artery bypass (OPCAB) is the preferred strategy of revascularisation at our institution. In order to minimize episodes of hypotension we aimed to keep the mean pressure > 80 during distal anastomosis. During proximal anastomosis constructed on the aorta a minimum mean pressure of 60 and a systolic blood pressure of 100 were acceptable during OPCAB. To minimize hypotension and to ensure minimum handling of the aorta composite grafts were constructed commonly and we also undertook total arterial revascularisation in a small proportion of patients. In cases where revascularisation was performed using cardiopulmonary bypass similar haemodynamic parameters were used. The aortic cannulation site was determined using digital palpation coupled with transoesophageal echocardiography and a single clamp technique was deployed for construction of proximal anastomosis. In the immediate post-operative period we aimed to keep the mean pressure between 80 and 100.

Primary outcome measure included incidence of major neurological deficits (type 1) and minor neurological deficits (type 2) and in hospital mortality directly related to cerebro-vascular accidents. Type 1 or major neurological deficits neurological deficit was defined as presence of major, focal neurological deficits, stupor, or coma; and type 2 or minor neurological deficits, as deterioration in intellectual function and delirium. Neurological assessment was done daily till the time of discharge and further imaging of the brain arranged if there were any concerns.

In the post-operative period in all major neurological events a CT or MRI scan was performed. In patients with minor neurological events advice was sought from a neurologist and a MRI was performed in selected cases.

2.1. Statistical analysis

Categorical data are reported as number and percentage. Categorical outcomes were compared using chi square test and a p value < 0.05 was considered to be significant. When the outcome was <5 in any cell the 2-tailed Fisher's exact test was employed. Prevalence of risk factors in the study population and sensitivity of these risk factors in predicting the presence of concomitant carotid artery disease was calculated. The adverse outcomes were compared between the 2 groups and effect sizes are reported as odds ratios. One way ANOVA was used to compare the 3 groups created by sub-group analysis. All statistical analysis was performed using SPSS v.20.0 (IBM Corp., Armonk, NY, USA).

3. Results

Of the 4364 patients, 406 patients (9.3%) had moderate or severe carotid artery stenosis. Of these 406 patients 106 (26.1%) patients had severe carotid artery stenosis. Overall, 32 (7.88%) patients had bilateral disease. Age > 65, hypertension, presence of left main stem stenosis, peripheral vascular disease, and previous neurological injury were all significantly more common in the group which had moderate to severe carotid artery disease. Diabetes ($p = 0.06$) as a risk factor had borderline association in our study and incidence of smoking ($p = 0.79$) was similar in both the groups (Table 1).

Table 1
Comparison of risk factors in patients with carotid artery stenosis.

	Patients with moderate or severe carotid stenosis (n = 406)	Patients with no significant carotid stenosis (n = 3958)	p value
Age > 65	69 (16.9%)	385 (9.7%)	<0.01
Diabetes mellitus	203 (50%)	1785 (45%)	0.06
Smoker	187 (46%)	1792 (45.2%)	0.80
Peripheral vascular disease	57 (14%)	174 (4.3%)	<0.01
Hypertension	317 (78%)	2746 (69%)	<0.01
Previous cerebro-vascular accident	24 (5.9%)	63 (1.5%)	<0.01
Left main stem stenosis	81 (19.9%)	420 (10.6%)	<0.01

Table 2
Prevalence and sensitivity of risk factors in patients with moderate or severe carotid stenosis.

	Prevalence (total no = 4364)	Sensitivity 95% confidence interval
Age > 65	454 (10.4%)	15.1% (12%–18.9%)
Diabetes mellitus	1988 (45.5%)	10.2% (8.9%–11.6%)
Smoker	1979 (45.3%)	9.4% (8.2–10.8)
Peripheral vascular disease	231 (5.2%)	24.6% (19.3–30.8)
Hypertension	3063 (70.1%)	10.3% (9.3–11.4)
Previous cerebro-vascular accident	87 (2%)	27.5% (18.8–38.3)
Left main stem stenosis	501 (11.4%)	16.1% (13.1–19.7)

Hypertension was the most prevalent risk factor (70%) in our study population and the history of previous cerebro-vascular accident the least prevalent (2%) (Table 2). However, the history of previous cerebro-vascular accident was the most sensitive risk factor for presence of moderate to severe carotid artery disease and smoking was the least sensitive risk factor.

In our study population, plaques with heterogeneous echogenicity were reported in 131 (32.2%) patients with moderate to severe carotid artery stenosis. Homogenous echo pattern plaques were reported in 80 (19.7%) patients. Of all the plaques reported 22.7% (48 of 211) were reported to be hypoechoic in nature. Ulcerated plaques were seen in 11 (5.2%) of patients.

There was no statistically significant difference between patients with moderate to severe carotid artery stenosis compared to those with no significant carotid artery stenosis in terms of major or minor neurological events (Table 3). However, patients with severe stenosis were associated with a significantly increased all-cause mortality (Table 4). Pre-operative carotid artery stenting was carried out on nine patients with no adverse outcome.

While moderate carotid artery stenosis was not a risk factor for post-operative stroke in our study, presence of previous neurological event appeared to be a powerful independent predictor of post-operative stroke. This was true both in patients with moderate to severe carotid artery stenosis 2 (8.3%) vs. 2 (0.05%); $p = 0.01$ and those who had no significant carotid artery stenosis 7 (11.1%) vs. 11 (0.03%); $p = 0.01$.

Post-operative stroke in symptomatic patients was seen in 2 out of 24 (8.3%) patients with moderate or severe carotid stenosis and 5 out of 63 (7.9%) patients with no significant carotid artery stenosis (odds ratio 1.23; 95% confidence interval 0.22–6.82). In the asymptomatic group, post-operative stroke was seen in 2/382 (0.05%) patients with moderate to severe carotid stenosis and 13/3895 (0.03%) patients with no significant carotid artery stenosis (odds ratio 1.57; 95% confidence interval 0.35–6.99). Thus, there were 4 patients with moderate to severe carotid artery stenosis and 18 patients with no significant carotid artery stenosis who had a neurological event in the post-operative period (Table 4).

Of the 4 strokes in the group with moderate to severe carotid artery stenosis, 2 occurred on the ipsilateral side as that of the carotid artery

Table 3
Adverse neurological, all cause and neurological cause mortality.

Outcomes	Patients with moderate or severe carotid artery stenosis	Patients with no significant carotid artery stenosis	p value	Odds ratio (95% confidence interval)
Major adverse neurological event	4 (0.9%)	18 (0.4%)	0.14	2.17 (0.7 to 6.4)
Minor adverse neurological event	8 (1.9%)	56 (1.4%)	0.38	1.40 (0.6 to 2.9)
All-cause mortality	15 (3.6%)	88 (2.2%)	0.08	1.68 (0.9 to 2.9)
Mortality due to neurological event	3 (0.7%)	10 (0.2%)	0.11	2.9 (0.8 to 10.7)

Table 4
Outcome comparison in patients with severe, moderate and no significant carotid artery stenosis.

Outcomes	Severe carotid artery stenosis (n = 106)	Moderate carotid artery stenosis (n = 300)	No significant carotid artery stenosis (n = 3958)	p value
Major adverse neurological event	2 (1.8%)	2 (0.6%)	18 (0.4%)	0.19
Minor adverse neurological event	3 (2.8%)	5 (1.6%)	56 (1.4%)	0.74
All-cause mortality	7 (6.6%)	8 (2.6%)	88 (2.2%)	0.01
Mortality due to neurological event	2 (1.8%)	1 (0.3%)	10 (0.2%)	0.08

lesion whereas 2 were in areas not related to the side of the carotid artery stenosis. In patients with no significant carotid artery stenosis 18 patients had a stroke of which 16 were infarcts and 2 were haemorrhagic.

The overall mortality was 103 out of 4364 (2.36%). Overall 22 (0.50%) patients had major neurological events of which 2 (9.0%) occurred in the moderate carotid artery stenosis group, 2 in the severe carotid artery stenosis group and 18 in the group with no significant carotid artery stenosis (Table 4). In presence of major neurological event, mortality increased dramatically (13 out of 22, 59%) irrespective of the degree of carotid stenosis.

The non-neurological causes of death were similar between patients with moderate and severe stenosis and those with no carotid artery stenosis. The number of deaths in moderate to severe stenosis group due to cardiac causes were 3 while in the group with no carotid artery disease were 27 ($p = 0.75$). Non cardiac causes were 9 in the moderate to severe stenosis group and 51 in the no carotid artery stenosis group ($p = 0.17$).

Of the thirty-two patients who had bilateral disease 3 (9.3%) had severe disease on both the sides, 19 (59.3%) had severe stenosis on one side and moderate stenosis on the other and 10 (31.2%) patients had moderate stenosis on both the sides. Comparing the outcomes between patients who had bilateral, unilateral and no significant carotid artery stenosis it was seen that mortality due to neurological causes in the group with bilateral disease was significantly higher (Table 5).

4. Discussion

The main finding of our study was that age > 65 years, hypertension, presence of left main stem stenosis, peripheral vascular disease, and previous neurological injury were all significantly associated with presence of carotid artery disease. And therefore presence of these risk factors warrants pre-operative screening for carotid artery disease. Moderate carotid artery stenosis did not lead to an increase in mortality or adverse neurological outcomes. However, severe carotid stenosis greater led to an increase in all-cause mortality. We also found that

Table 5
Outcome comparison in patients with bilateral, unilateral, and no significant carotid artery stenosis.

Outcomes	Bilateral carotid artery stenosis (n = 32)	Unilateral carotid artery stenosis (n = 374)	No significant carotid artery stenosis (n = 3958)	p value
Major adverse neurological event	1 (3.1%)	3 (0.8%)	18 (0.4%)	0.07
Minor adverse neurological event	1 (3.1%)	7 (1.8%)	56 (1.4%)	0.57
All-cause mortality	1 (3.1%)	12 (3.2%)	88 (2.2%)	0.45
Mortality due to neurological event	1 (3.1%)	2 (0.5%)	10 (0.2%)	0.009

presence of previous history of cerebro-vascular event was an independent predictor of post-operative adverse cerebral events irrespective of the carotid artery stenosis. Moreover, once a neurological event occurred in patients undergoing CABG, the mortality was very high.

While screening is generally recommended, there are two main issues pertaining to screening. Firstly, should it be selective or routine and secondly if it is selective then what criteria should it be based on. Presence of undiagnosed concomitant carotid artery stenosis and the associated risk of stroke have driven some surgeons and institutions to carry out mandatory routine screening for carotid artery stenosis [4]. However, it has been found to be wasteful as criteria based screening reduces the screening load significantly with negligible impact on surgical management or neurologic outcomes [9]. As a result, criteria based screening is generally favored but these are variable across different institutions in different countries. Some centres suggest that below 60 years of age unless there are at least 2 other risk factors from hypertension, diabetes, or smoking; screening for carotid artery disease is not necessary [14]. Other studies have recommended selective screening only in presence of age > 65, presence of carotid bruit, or history of cerebro-vascular disease [9]. The 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery recommends carotid screening in presence of >65 years, left main coronary stenosis, peripheral artery disease, history of cerebrovascular disease, hypertension, smoking, and diabetes mellitus [8]. The more recent 2014 ESC-EACTS Myocardial Revascularization guidelines suggest screening in symptomatic patients (Class of Recommendation 1) and in patients with multivessel coronary artery disease, presence of peripheral arterial disease, and age > 70 (Class of Recommendation IIa) [15].

The findings from our study confirms that apart from smoking which was not a significant risk factor and diabetes which had borderline significance all the other risk factors recommended by the ACCF/AHA were independently associated with carotid artery disease.

While screening for concomitant carotid artery disease has a definite role in risk stratifying the patients and predicting the stroke risk, its role in reducing adverse neurological outcomes remains questionable. Apart from increase in all-cause mortality in patients with severe carotid artery stenosis there was no difference in the incidence of adverse neurological events or mortality in patients who had carotid artery disease when compared to those who did not have carotid artery disease. This finding has been supported by other studies which show no direct causal relationship between postoperative stroke and severe carotid stenosis with a very small proportion of patients developing stroke in the diseased carotid territory [7]. Patients with carotid artery stenosis often have co-existing aortic atheroma, concomitant left main stem stenosis and presence of peripheral vascular disease and therefore carotid artery stenosis has been thought more to be a marker for diffuse systemic atherosclerotic disease, rather than the solitary causal factor [5].

In a recent study it has been shown that only one in twenty strokes following cardiac surgery were due to a carotid artery lesion and >75% of the strokes occurred without significant carotid artery stenosis. Moreover, in 60% of the cases the stroke was not confined to a single carotid artery territory [6].

The lack of direct causal relationship between carotid stenosis and stroke could be due to a variety of reasons. It has been shown that adverse neurological outcome following coronary artery bypass grafting is due to supraventricular arrhythmias, low cardiac output or postoperative hypercoagulability in >50% of the cases and can occur after uneventful recovery from CABG [10]. Also post CABG strokes are seen in patients with normal carotid artery in a significant proportion of cases. Presence of aortic atherosclerosis and embolization during cannulation, clamping and construction of proximal anastomosis of the ascending aorta and arch has been demonstrated to be a significant determinant of postoperative stroke. In fact 60% of strokes associated with cardiac surgery are of embolic origin [16]. For this reason alone to reduce

adverse neurological outcomes, other strategies like identification of an atherosclerotic aorta; epi-aortic scanning; use of no touch technique of the aorta maybe more important than routine screening of carotid artery disease in patients undergoing CABG [17–19].

While degree of carotid occlusion is merely a quantitative measure of flow impairment carotid plaques allow a qualitative risk assessment of the disease. Based on the composition of the plaque they can be homogenous or heterogenous and can appear to have low echogenicity or hyperechoic. The presence of echolucent plaques is associated with higher risk of coronary and cerebrovascular ischemic events than echogenic plaques [20]. Evidence from a recently published meta-analysis shows that plaques with complex features, particularly those with echolucency, neovascularization, ulceration and intraplaque motion are associated with ischemic symptoms. The authors concluded that the nature of plaque on ultrasound may provide stroke risk information beyond measurement of luminal stenosis and recommended that evaluation of carotid artery stenosis should focus on the detection of plaque characteristics in addition to quantifying the degree of stenosis [21].

It is generally accepted that while asymptomatic patients with unilateral carotid stenoses do not appear to benefit from carotid revascularization, patients with a less than six month history of TIA/stroke or ipsilateral retinal ischemic symptoms and severe carotid stenosis do benefit from carotid revascularisation [12,22]. Revascularisation has also been shown to be useful in patients with bilateral severe carotid artery stenosis or in patients with severe carotid stenosis and contralateral occlusion [23].

During the study period we carried out carotid artery stenting in nine of our patients before performing the CABG. The problem with this strategy is the need to continue dual anti-platelets for a minimum of one month post stenting. However, we continued it for three months before embarking on CABG. The problem arises if CABG is required within a month of carotid artery stenting. Even though we did not encounter this situation our protocol in this situation is to continue with the dual anti-platelets accepting the risk of increased bleeding rather than risk stent thrombosis by stopping the anti-platelet agents. Currently In light of more recent evidence and guidelines we are using carotid artery stenting in very selective situations [24].

4.1. Limitations

The event rate of adverse neurological events in our study was very low. Therefore, despite a large study population there is a chance of a type II error. Also, the rate of carotid artery intervention in our study population was quite low. It is therefore possible that a more liberal intervention policy in presence of carotid artery stenosis may have shown a difference in adverse neurological outcomes. As we did not perform brain imaging in all patients pre-operatively we were not able to ascertain if preoperative injuries as detected at brain imaging increased risk of postoperative neurological events. Also we were unable to reliably establish in all cases if the pre-operative neurological event was related to the diseased carotid artery territory. Owing to these important limitations a large well-structured randomized trial would be ideally required to determine best management strategies of carotid artery disease for patients referred to CABG.

Based on our study we conclude that carotid screening guided by recommended risk factors reliably identifies patients who have carotid artery stenosis. While carotid artery screening did not make any overall difference in neurological outcomes in patients undergoing coronary artery bypass grafting it is useful in quantifying the risks involved. Bilateral disease increases mortality due to neurological causes. Compared to patients with no significant carotid artery stenosis patients with moderate stenosis do not have any increase in neurological events or mortality however, those with severe stenosis have an associated increase in all-cause mortality.

Authorship declaration

We declare that all the authors listed meet the authorship criteria according to the latest guidelines of the International Committee of Medical Journal Editors, and ii) that all authors are in agreement with the manuscript.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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