Preoperative Noninvasive Coronary Risk Stratification in Candidates for Carotid Endarterectomy

Stefano Urbinati, MD; Giuseppe Di Pasquale, MD, FACC, FESC; Alvaro Andreoli, MD; Anna Maria Lusa, MD; Giancarlo Carini, MD; Paola Grazi, MD; Graziana Labanti, MD; Paola Passarelli, MD; Claudio Corbelli, MD; Giuseppe Pinelli, MD

Background and Purpose Patients with symptomatic carotid stenosis who are candidates for carotid endarterectomy are at high short- and long-term risk of coronary events. To stratify patients at different risk of coronary events we investigated the usefulness of a noninvasive preoperative cardiological workshop.

Methods We studied 172 consecutive patients admitted to the Neurosurgical Department for symptomatic high-grade (70% to 99%) carotid stenosis (age, 42 to 74 years; mean, 57.8 years). Patients without history of coronary artery disease (CAD) and able to exercise were submitted to exercise electrocardiographic testing (EET) and, if abnormal, to exercise thallium myocardial imaging (TMI). Patients were classified into four groups: group 1, patients without CAD: no history of CAD, normal EET, or normal TMI in the presence of indeterminate EET (n=93, 54%); group 2, patients with silent CAD: no history of CAD and concordant abnormal EET and TMI (n=28, 16%); group 3, patients unable to exercise: no history of CAD and inability to perform adequate EET because of previous stroke or claudication (n=29, 17%); and group 4, patients with known CAD: history of angina or myocardial infarction (MI) (n=22, 13%).

Results The four groups were comparable in regard to age, sex, and computed tomographic scan of the brain. The prevalence of stroke was higher in patients unable to exercise; hypercholesterolemia was more frequent in patients with known CAD. During the perioperative period (≤30 days after carotid endarterectomy), coronary events occurred in 3 patients (2%); fatal MI in 2 patients in group 4 and 1 patient in group 3. One hundred percent of patients were followed up for 6.2 years. Coronary events occurred in 23 of the 168 patients discharged from the hospital (13.7%); these were fatal in 11 (6.5%): 3 patients of group 1 (3%; sudden death in 2, fatal MI in 1), 8 patients of group 2 (29%; fatal MI in 5, unstable angina in 3), 8 patients of group 3 (28%; fatal MI in 4, nonfatal MI in 4), and 4 patients of group 4 (18%; fatal MI in 2, sudden death in 1, unstable angina in 1). Kaplan-Meier estimated curves of survival free from fatal and nonfatal coronary events were 97%, 51%, 49%, and 59%, respectively (P<.001, group 1 versus groups 2 and 3; P<.01, group 1 versus group 4).

Conclusions Among patients undergoing carotid endarterectomy, coronary events occurred twice as often as cerebral recurrences. A preoperative noninvasive cardiac investigation, including EET, can adequately identify groups of patients with diverse short- and long-term prognoses. In addition to patients with known CAD, those with silent CAD or who are unable to exercise represent, without the need of further investigation, groups at high risk of coronary events in long-term follow-up. (Stroke. 1994;25:2022-2027.)

Key Words • carotid artery diseases • carotid endarterectomy • coronary disease • preoperative evaluation • vascular surgery

Patients who are candidates for vascular surgery are considered to have a particularly high prevalence of coronary artery disease (CAD).1 A comprehensive analysis of candidates for vascular surgery, including nearly 10,000 patients in approximately 50 series, showed that clinical evidence of CAD was detectable in 50% of patients.2 In the subset of nearly 2000 patients who underwent routine coronary angiography, significant CAD was detected in more than 60% of patients and in 37% of those without history or symptoms of CAD. In candidates for carotid endarterectomy the prevalence of coexisting coronary lesions was 93%; among those without history of CAD, coronary angiography disclosed lesions in 86% of patients, and these were significant in 40%.3 The high prevalence of coexisting CAD accounts for the risk of coronary events being twice that of cerebral recurrences in patients undergoing carotid endarterectomy.4 Overall, these data support the need for a routine cardiac investigation for detecting CAD in patients undergoing vascular surgery and particularly in those undergoing carotid endarterectomy. The aim of the present study was to validate a cardiological study protocol, based on clinical and noninvasive investigation, for stratifying coronary risk both perioperatively and in the long term in patients with high-grade carotid stenosis who are candidates for carotid endarterectomy.

Subjects and Methods A consecutive series of patients admitted to the Neurosurgical Department of our institution for carotid endarterectomy were enrolled in this study. All the patients were candidates for carotid endarterectomy for symptomatic high-grade carotid stenosis (70% to 99%). The neurological preoperative investigation included computed tomographic scan of the brain and
four-vessel cerebral angiography. The percent stenosis of carotid vessels was calculated on the angiograms by an expert neuroradiologist according to the criteria adopted in the North American Symptomatic Carotid Endarterectomy Trial. The cardiological study protocol consisted of history, 12-lead electrocardiography (ECG), chest roentgenography, two-dimensional echocardiography, exercise ECG testing, and, if abnormal but asymptomatic, exercise 201Tl myocardial scintigraphy. Coronary angiography was performed only in selected cases.

Exercise ECG testing was performed by treadmill with a Marquette Case II recorder according to a modified Bruce protocol (exercise stages of 2 minutes starting from level 0). A 12-lead ECG and blood pressure were recorded at rest, at the end of each stage, at peak exercise, and at 2-minute intervals during the recovery phase. During exercise the 12-lead ECG was continuously monitored. Exercise ECG testing was maximal or limited by exhaustion, symptoms, systolic blood pressure ≥240 mm Hg, or ST depression >3 mm. The test was considered abnormal if ST depression horizontal or downsloping ≥1 mm or ST elevation >1.5 mm 0.08 seconds after the J point was present.

Patients with abnormal exercise ECG test results underwent bicycle exercise 201Tl myocardial imaging within 2 weeks. At the appearance of ≥1.0 mm ST segment depression, 74 MBq of 201Tl was injected intravenously, and the patients were requested to continue exercise for another 60 to 90 seconds. Each patient underwent imaging in the supine position with a PHO gamma V scintillation camera immediately after isotope administration and 4 hours later (delayed imaging) for the redistribution scan. Each image was subdivided into three or four segments corresponding to the territories of distribution of left anterior descending, circumflex, and right coronary arteries for a total of eight segments. Images were stored in a computer for processing and semiquantitative analysis by circumferential profiles. Myocardial scintigraphy was considered positive for ischemia if transient perfusional abnormalities or limited by exhaustion, symptoms, systolic blood pressure >240 mm Hg, or ST depression >3 mm. The test was considered abnormal if ST depression horizontal or downsloping ≥1 mm or ST elevation >1.5 mm 0.08 seconds after the J point was present.

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According to history and noninvasive cardiac screening, patients were classified into four groups. Group 1 included patients without CAD, with no history of CAD, normal exercise ECG testing at ≥75% of the predicted maximal heart rate, or normal 201Tl myocardial scintigraphy in the presence of abnormal or indeterminant exercise ECG testing. Group 2 included patients with silent CAD, with no history of CAD and abnormal concordant exercise ECG testing and 201Tl myocardial scintigraphy in the absence of angina. Group 3 included patients unable to exercise, with no history of CAD and inability to achieve 75% of their predicted maximal heart rate at exercise ECG testing because of previous stroke or coexisting intermittent claudication. Group 4 included patients with known CAD, with previous myocardial infarction or angina pectoris.

Patients with known CAD and those with silent CAD were treated preoperatively and during and after surgery with anti-ischemic and antiplatelet drugs. During the follow-up period clinical evaluation was performed every 6 months.

The statistical analysis was performed by Student's t test for differences between the mean of different observations and by χ2 test to determine the difference between proportions. Survival free from fatal and nonfatal coronary events was estimated by Kaplan-Meier curves.

Results

One hundred seventy-two consecutive patients (125 men, 47 women; mean age, 57.8±8.9 years; range, 42 to 74 years) admitted for carotid endarterectomy were included in the study. All patients had symptomatic cerebral ischemia (transient ischemic attack in 119 cases and minor stroke in 53). Computed tomographic scan of the brain showed ischemia in 65 patients (38%) and was normal in 107 (62%). According to the inclusion criteria, in all patients cerebral angiography disclosed high-grade carotid stenosis (70% to 99%) ipsilateral to symptoms; in particular, a tight stenosis (90% to 99%) was observed in 55 patients (32%) and a coexisting significant contralateral stenosis in 65 patients (38%).

After cardiac evaluation, 93 patients (54%) were classified into group 1 (no CAD), 28 patients (16%) into group 2 (silent CAD), 29 patients (17%) into group 3 (unable to exercise), and 22 patients (13%) into group 4 (known CAD). The exercise ECG test was abnormal or indeterminant in 38 patients; among them, exercise 201Tl

<table>
<thead>
<tr>
<th>TABLE 1. Prevalence of General Findings, Coronary Risk Factors, and Coexisting Peripheral Vascular Disease</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 (No CAD)</td>
</tr>
<tr>
<td></td>
<td>(n=93)</td>
</tr>
<tr>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Mean±SD age, y</td>
<td>60±7</td>
</tr>
<tr>
<td>Male</td>
<td>61</td>
</tr>
<tr>
<td>TIA</td>
<td>69</td>
</tr>
<tr>
<td>Minor stroke</td>
<td>24</td>
</tr>
<tr>
<td>Current smoking</td>
<td>62</td>
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<tr>
<td>Systemic hypertension</td>
<td>56</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>21</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>41</td>
</tr>
<tr>
<td>Contralateral carotid stenosis</td>
<td>25</td>
</tr>
<tr>
<td>Claudication</td>
<td>25</td>
</tr>
</tbody>
</table>

CAD indicates coronary artery disease; TIA, transient ischemic attack.

*P<.05, group 3 vs groups 1, 2, and 4.
†P<.05, group 4 vs groups 1, 2, and 3.
TABLE 2. Morbidity and Mortality in 172 Candidates for Carotid Endarterectomy

<table>
<thead>
<tr>
<th>Group</th>
<th>1 (No CAD) (n=93)</th>
<th>2 (Silent CAD) (n=28)</th>
<th>3 (Unable to Exercise) (n=29)</th>
<th>4 (Known CAD) (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early (&lt;30 days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total deaths (n=4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Stroke</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Nonfatal events (n=1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIA</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Late (&gt;30 days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total deaths (n=20)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>2</td>
<td>5</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Stroke</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Cancer</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Nonfatal events (n=16)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1</td>
<td>0</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>TIA/stroke</td>
<td>6</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Total coronary events (n=23)</td>
<td></td>
<td>3 (3)*</td>
<td>8 (29)*</td>
<td>8 (28)*</td>
</tr>
<tr>
<td>Total TIA/stroke recurrences (n=11)</td>
<td></td>
<td>7 (8)</td>
<td>1 (4)</td>
<td>1 (3)</td>
</tr>
</tbody>
</table>

CAD indicates coronary artery disease; TIA, transient ischemic attack. Values in parentheses are percentages.

*P<.01, group 1 vs group 4; P<.001, group 1 vs groups 2 and 3.

myocardial scintigraphy was normal in 9 (classified into group 1 as having false-positive exercise ECG tests) and abnormal in 29 (classified into group 2). Among patients of group 3, 15 patients had previous stroke and 9 claudication (5 patients had both); 19 of them underwent exercise ECG testing, but they were unable to exercise at ≥75% of the predicted maximal heart rate. Finally, patients with known CAD (group 4) had a clinical history of myocardial infarction in 17 cases and of angina pectoris in 5. The four groups did not show significant differences in regard to mean age, sex, current smoking, hypertension, diabetes mellitus, contralateral carotid stenosis, and claudication. Hypercholesterolemia was more frequent in group 4 than in groups 1, 2, and 3 (P<.05) (Table 1). Stroke occurrence was higher in group 3. Coronary angiography was performed in 6 patients with known CAD and in 2 patients with silent CAD with large thallium defects.

During the perioperative period (0 to 30 days after surgery), 4 patients died (2%) (3 of fatal myocardial infarction and 1 of a fatal recurrence of stroke). Moreover, 1 patient had a recurrence of transient cerebral ischemia. Coronary deaths occurred in no patient of group 1 (no CAD) or group 2 (silent CAD), in 1 of 29 patients (3%) of group 3 (unable to exercise), and in 2 of 22 patients (9%) of group 4 (known CAD) (P=NS). Nonfatal cardiac events did not occur during the perioperative period (Table 2).

One hundred percent of the patients were followed up for 6.2 years. Twenty of the 168 patients discharged from the hospital died: 11 of fatal myocardial infarction, 2 of stroke recurrences, and 7 of cancer. Nonfatal events occurred in 16 additional patients: myocardial infarction in 5, unstable angina in 4, and stroke or transient ischemic attack in 7. In total, fatal and nonfatal coronary events occurred in 23 of the 168 patients (13.7%; 2.2% per year) and cerebral recurrences in 11 (6.5%; 1.1% per year) (Table 2). Comparing the four groups, coronary events occurred in 3 (3%) patients of group 1, in 8 (29%) patients of group 2, in 8 (28%) of group 3, and in 4 (18%) of group 4. Coronary events in groups 2, 3, and 4 were significantly more frequent than in group 1 (P<.01, group 1 versus group 4; P<.001, group 1 versus groups 2 and 3). Specifically, coronary deaths occurred in 2 of 93 patients (2%) of group 1 (no CAD), in 5 of 28 patients (18%) of group 2 (silent CAD), in 3 of 29 patients (10%) of group 3 (unable to exercise), and in 1 of 22 patients (4%) of group 4 (known CAD).

Kaplan-Meier estimated curves of survival free from coronary events were 97%, 51%, 49%, and 59%, respectively, in the four groups during 6.2 years of follow-up (Figure). No significant differences were detected in the prevalence of cerebral recurrences or nonvascular events.

Discussion

CAD has a high prevalence in patients undergoing vascular surgery and strongly influences their perioperative course and long-term follow-up. A possible explanation for the high prevalence of coexisting severe CAD...
in vascular patients, and in particular in those with symptomatic carotid stenosis, may be that atherosclerosis develops earlier in coronary vessels than in carotid or peripheral vessels. When patients with carotid stenosis become symptomatic, in most cases coexisting CAD is already severe. A recent study confirmed the time lag between the appearance of coronary and carotid lesions. Two hundred patients undergoing coronary angiography routinely underwent ultrasonographic study of carotid vessels. In patients with normal coronary arteries or one- to two-vessel CAD, the prevalence of coexisting significant carotid artery disease (>70%) was only 2.9%, whereas in those with three-vessel or left main CAD the prevalence was 25%.

The results of the present study raise three main issues. The first issue concerns the possibility that a noninvasive, feasible, low-cost cardiologic protocol could adequately stratify the risk of coronary events in candidates for carotid endarterectomy. The need for noninvasive cardiac investigation in patients with carotid stenosis and transient ischemic attacks was outlined 16 years ago by Whisnant et al, who showed that cardiac mortality was independent of cardiac history, suggesting a high prevalence of asymptomatic CAD in patients without known CAD. Recently, Chimowitz et al confirmed this need in their evaluation of the cardiac prognosis of 444 patients enrolled in the Department of Veterans Affairs Study on the efficacy of surgical treatment of peripheral artery disease. Patients exercised on a treadmill, and those unable to achieve 75% of their predicted maximal heart rate increased their probability of having CAD from 1% to 16% and the inability to achieve 75% of the predicted maximal heart rate from 2% to 11%. In 1988 McPhail et al confirmed these results. Among 100 patients undergoing peripheral vascular surgery, those unable to achieve 85% of maximal heart rate increased their posttest probability of CAD from 7% to 24%; those with positive test results increased their probability from 33% to 56%. Overall, in regard to candidates for peripheral vascular surgery, only one third are able to perform a submaximal exercise test. Therefore, in the past decade, more attention was directed to testing that did not require exercise, i.e., dipyridamole-thallium imaging or echocardiography. Nevertheless, the accuracy of dipyridamole-thallium scintigraphy in the prediction of cardiac risk after vascular surgery has been strongly challenged by the most recent studies. In our experience, most candidates for carotid endarterectomy without known CAD are able to exercise (83% in our series).

The second issue concerns the possibility that a preoperative cardiac protocol could include exercise ECG testing as the method of choice for detecting CAD. Such a protocol would allow extension of the preoperative evaluation to most cardiologic institutions because of the wide availability, low cost, and feasibility of exercise ECG testing. The possible role of routine exercise ECG testing in patients undergoing vascular surgery was first investigated in several studies in the early 1980s. In 1981 Cutler et al studied a series of 130 patients undergoing lower extremity peripheral vascular surgery. Patients exercised on a treadmill, and those unable to achieve 75% of their predicted maximal heart rate exercised further on an arm ergometer. The identification of ECG signs of myocardial ischemia increased the posttest probability of CAD from 1% to 16% and the inability to achieve 75% of the predicted maximal heart rate from 2% to 11%. In 1988 McPhail et al confirmed these results. Among 100 patients undergoing peripheral vascular surgery, those unable to achieve 85% of maximal heart rate increased their posttest probability of CAD from 7% to 24%; those with positive test results increased their probability from 33% to 56%. Overall, in regard to candidates for peripheral vascular surgery, only one third are able to perform a submaximal exercise test. Therefore, in the past decade, more attention was directed to testing that did not require exercise, i.e., dipyridamole-thallium imaging or echocardiography. Nevertheless, the accuracy of dipyridamole-thallium scintigraphy in the prediction of cardiac risk after vascular surgery has been strongly challenged by the most recent studies. In our experience, most candidates for carotid endarterectomy without known CAD are able to exercise (83% in our series).

The third issue concerns the usefulness of reclassifying patients without history of CAD on the basis of the absence (group 1) or the presence (group 2) of abnormal exercise ECG testing and 201TI myocardial scintigraphy and the inability to exercise (group 3). During the perioperative period, coronary events occurred in no
patients in groups 1 and 2, 3% of patients in group 3, and 9% of patients in group 4. In the long-term follow-up, only patients in group 1 were at low risk of coronary events (3%), whereas patients in groups 2, 3, and 4 were similarly at high risk (29%, 28%, and 18%, respectively). Therefore, patients with known CAD and those unable to exercise were at high risk of coronary events in both the short- and long-term periods. Patients with silent CAD were at low risk in the perioperative period and at high risk in the long-term follow-up, confirming that the prognostic role of silent CAD is comparable to that of symptomatic CAD.\textsuperscript{23,24}

In recent years, several authors proposed algorithms or scoring systems for stratifying the risk of coronary events in patients undergoing noncardiac surgery.\textsuperscript{25,26} Although these indexes may be useful in the general population of surgical patients, they are ineffective in adequately stratifying patients with peripheral vascular surgery. In 1989 Eagle et al\textsuperscript{27} suggested that clinical evaluation and resting ECG might be sufficient to select patients at high risk who should undergo coronary angiography, whereas patients at low to moderate risk should be further stratified by noninvasive procedures, ie, dipyridamole testing.\textsuperscript{28} The extremely high risk of coronary events in patients with symptomatic carotid disease supports the need of a routine noninvasive investigation for identifying coexisting CAD in these patients. Preoperative coronary angiography should be performed only in patients who are considered at high risk of coronary events after the noninvasive risk stratification.\textsuperscript{29}

In the present study we classified patients on the basis of history of CAD, eligibility for exercise, and the result of exercise ECG testing followed, if abnormal, by exercise \textsuperscript{20}TI myocardial scintigraphy. While the prognosis of patients without CAD or with known CAD is rather predictable, the results concerning patients with silent ischemia or who are unable to exercise require further comment. We classified patients with abnormal ECG tests and \textsuperscript{20}TI myocardial scintigraphy in the silent CAD group. The predictive value of an abnormal exercise ECG test alone in asymptomatic subjects is low because of the high rate of false-positive responses. To improve the specificity of exercise ECG testing for detecting silent coexisting CAD in patients with an intermediate to high pretest probability of CAD, as the candidates for vascular surgery are, \textsuperscript{20}TI myocardial scintigraphy could be used successfully.\textsuperscript{30} In 191 asymptomatic subjects with abnormal exercise ECG tests, \textsuperscript{20}TI myocardial scintigraphy identified 97% of subjects correctly regarding the presence or absence of CAD.\textsuperscript{31}

More recently, in the large Baltimore Longitudinal Study on Aging,\textsuperscript{32} after a mean follow-up period of 4.6 years, cardiac events developed in 7% of subjects with both a negative exercise test and negative \textsuperscript{20}TI myocardial scintigraphy, in 8% of those with either test positive, and in 18% of those with both tests positive. The present study confirms that the presence of concordant abnormal exercise ECG testing and \textsuperscript{20}TI myocardial scintigraphy identifies patients with a high prevalence of coronary events in long-term follow-up.

Even patients unable to perform adequate exercise testing were shown to be at very high risk of coronary events. This result is not surprising because similar data have been observed in other series of patients. In a series of 100 patients aged 65 years or older scheduled for noncardiac surgery, Gerson et al\textsuperscript{33} found that the inability to exercise was the only independent predictor of perioperative complications. Moreover, ineligibility for the exercise test was the most important predictor of events among the determinants of 6-month mortality in 10,219 survivors of myocardial infarction after thrombolysis enrolled in the GISSI-2 study.\textsuperscript{34} The authors reported that the relative risk of coronary events was of similar magnitude irrespective of whether cardiac or noncardiac reasons determined ineligibility for exercise testing. Exclusion from the exercise test appears to be an empirical index that incorporates the cumulative risk resulting from known adverse prognostic factors such as a more severe and widespread vascular disease or a significant reduction of cardiac reserve. Recently Goldman\textsuperscript{35} described the unsatisfactory results of preoperative thallium-dipyridamole imaging in candidates for vascular surgery who were unable to exercise, suggesting that the coronary risk of these patients is so high that further noninvasive cardiac testing was not warranted in these cases.

In conclusion, the present study shows that in patients undergoing carotid endarterectomy, coexisting CAD should always be investigated.\textsuperscript{36} Patients without a history of CAD should undergo a cardiac investigative protocol that is noninvasive, easy to perform, relatively inexpensive, and widely feasible. A cardiac investigation consisting of history, clinical investigation, and exercise ECG testing (followed, if abnormal, by exercise myocardial scintigraphy) may adequately identify subgroups of patients with different perioperative and long-term coronary prognoses. Therefore, while recent large clinical trials in patients with high-grade symptomatic carotid stenosis support the efficacy of carotid endarterectomy and antiplatelet drug therapy for preventing cerebrovascular recurrences,\textsuperscript{36,37} concomitant CAD can severely affect the prognosis of patients with carotid disease, probably rendering the benefits of prophylaxis ineffective.\textsuperscript{38} The survival of these patients cannot be improved without planning more aggressive strategies for reducing coronary events.

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References


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