Impact of Carotid Atherosclerosis on the Risk of Adverse Cardiac Events in Patients With and Without Coronary Disease

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Background and Purpose—Carotid atherosclerosis (CA) is reportedly a strong predictor of imminent cardiac events even in the absence of established coronary artery disease (CAD). We examined the differential impact of CA on the risk of major adverse cardiovascular events in patients with and without CAD diagnosed angiographically.

Methods—We conducted a follow-up survey of 1391 patients who underwent clinically driven coronary angiography and a same-day carotid ultrasound and Doppler study. Definitions of CAD, CA, and carotid artery stenosis were in accordance with current practice guidelines.

Results—Of 1391 patients, angiographic CAD was present in 1105 (79%) patients. Mean and median follow-up was 1574 and 1702 days, respectively. Rates of the primary composite major adverse cardiovascular event end point were higher among patients with CAD compared with those without CAD (48% versus 20%; P<0.001), whereas the rates of all-cause mortality (10% versus 9%; P=0.81) and stroke (7% versus 5%; P=0.3) did not differ significantly between both groups. Carotid artery stenosis and CA were associated with an increased risk of the composite major adverse cardiovascular event end point among patients without CAD (hazard ratio=3.17 [95% confidence interval, 1.52–6.60]; P<0.01; and hazard ratio=1.69 [0.95–3.01]; P=0.07, respectively) though not in patients with CAD. Carotid artery stenosis was associated with an increased risk of all-cause mortality among patients without CAD (hazard ratio=2.93 [1.09–7.87]; P=0.03)) though not among those with CAD.

Conclusions—CA and carotid artery stenosis are independent predictors of major adverse cardiovascular event in patients undergoing coronary angiography. The prognostic implications of carotid disease are imparted predominantly in patients without pre-existent CAD. (Stroke. 2014;45:2311-2317.)

Key Words: carotid stenosis ■ coronary artery disease

The presence of atherosclerotic lesions of the common and internal carotid arteries portends an adverse prognosis with respect to future coronary artery disease (CAD) events across a broad clinical spectrum, spanning asymptomatic individuals with vascular risk factors to patients with manifest arterial disease.1–4 In fact, progressive carotid artery stenosis (CAS) is reportedly a stronger predictor of imminent myocardial infarction (MI) than of future stroke events.3

Previous outcome studies relating the presence of atherosclerotic carotid artery lesions to the risk of future coronary events have varied methodologically in the definition of carotid atherosclerosis (CA) and CAD. Therefore, the prognostic implications of CA in specific patient subsets require further definition. This explains, at least in part, the fact that widespread screening for asymptomatic carotid disease is not recommended as of yet although CA is an accepted CAD equivalent.6,8 Specifically, the relative impact of CA on the risk of subsequent coronary events in patients with or without established CAD defined angiographically is unknown.

We have previously reported on the prevalence of concomitant carotid and coronary disease in a large group of consecutive patients undergoing clinically driven coronary artery angiography.4 In this study, we sought to examine the differential impact of CA on the risk of all-cause mortality and major adverse cardiovascular events (MACEs) in patients with and without pre-existent CAD determined angiographically.

Methods

Study Population and Data Collection

Consecutive hospitalized and ambulatory patients undergoing non-emergent coronary angiography between January 2007 and May 2009 were enrolled in the Tel-Aviv Prospective Angiography Study, as previously described.9 Patients undergoing a carotid ultrasound...
and Doppler study within 24 hours of the coronary procedure were candidates for this study (n=1490).

Follow-up was performed by means of (1) review of electronic data obtained from hospital records, which, in the case of death, are continuously synchronized with the database of the Israeli Ministry of Interior; (2) investigator-initiated telephone interviews (by B.S., M.K., O.H., and S.G.) using a prespecified MACE outcome questionnaire; (3) review of hospital records in the case of patients hospitalized at the Tel Aviv Medical Center subsequent to the index coronary and carotid imaging procedures. The index event date was defined as the date of coronary angiography. Mortality data and dates were available for all included patients (n=1391), telephone interviews were conducted between May and October 2012, and outcome questionnaires were available for 1113 patients. For each participant, follow-up was defined as the time period between the index date and either the date of death or the date of a nonfatal MACE in cases in which data were obtained by telephone interview or chart review. The study was approved by the institutional ethics committee.

**Table 1. Baseline Clinical and Anatomic Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Entire Group (n=1391)</th>
<th>CAD Present (n=1105)</th>
<th>CAD Absent (n=286)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean (±SD)</td>
<td>65 (±11)</td>
<td>66 (±11)</td>
<td>63 (±11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>1071 (77)</td>
<td>913 (83)</td>
<td>158 (55)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>422 (30)</td>
<td>346 (31)</td>
<td>76 (27)</td>
<td>0.120</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>530 (38)</td>
<td>441 (40)</td>
<td>89 (31)</td>
<td>0.006</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>723 (52)</td>
<td>582 (53)</td>
<td>141 (49)</td>
<td>0.320</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>1030 (74)</td>
<td>845 (76)</td>
<td>185 (64)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Post-MI, n (%)</td>
<td>328 (24)</td>
<td>313 (28)</td>
<td>15 (5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Poststroke, n (%)</td>
<td>50 (4)</td>
<td>42 (4)</td>
<td>8 (3)</td>
<td>0.416</td>
</tr>
<tr>
<td>Coronary artery bypass grafting, n (%)</td>
<td>203 (15)</td>
<td>203 (18)</td>
<td>0 (0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Indications for coronary angiography

- Nonspecific chest pain, n (%) 61 (4) 33 (3) 28 (10) <0.001
- Stable angina pectoris, n (%) 179 (13) 151 (14) 28 (10) 0.081
- Unstable angina pectoris, n (%) 555 (40) 451 (41) 104 (35) 0.171
- Myocardial infarction, n (%) 52 (4) 48 (4) 4 (1) 0.019
- Positive stress test, n (%) 212 (15) 162 (15) 50 (18) 0.237
- Before valve surgery, n (%) 66 (5) 33 (3) 33 (12) <0.001
- Staged angioplasty, n (%) 187 (13) 185 (17) 2 (1) <0.001
- Other, n (%) 79 (6) 42 (4) 37 (13) <0.001

CAD extent per angiography

- Single-vessel disease, n (%) 257 (19) 257 (23) 0 (0) NA
- 2-vessel disease, n (%) 382 (28) 382 (35) 0 (0) NA
- 3-vessel disease, n (%) 385 (28) 385 (35) 0 (0) NA
- Left main disease, n (%) 81 (6) 81 (7) 0 (0) NA
- CA, n (%) 810 (58) 696 (63) 114 (40) <0.001
- CAS >50%, n (%) 179 (13) 162 (15) 17 (6) <0.001

**CA** indicates carotid atherosclerosis, CAD, coronary artery disease; CAS, carotid artery stenosis; MI, myocardial infarction; NA, not applicable; and SD, standard deviation.

**Study End Points**

The primary end point was the composite rate of MACE, including all-cause mortality, MI, stroke, and any coronary revascularization procedure, defined as any revascularization procedure (percutaneous or surgical) performed ≥30 days after the index date to exclude elective staged interventions driven by the index procedure.

**Definitions of CA and CAS**

The protocol for carotid duplex scanning has been described. Briefly, atherosclerosis of both the left and the right internal carotid arteries was assessed by a sonography technician blinded to clinical and coronary angiographic data. The internal carotid arteries were scanned using carotid duplex equipment (HD11 XE, Philips Healthcare, Andover, MA) with a 3- to 12-MHz linear-array transducer. Internal CA was evaluated by the maximum percentage of diameter reduction recorded by B-mode ultrasound and by the peak systolic (PSV) and diastolic velocities per Doppler. Lesion severity was defined as the greatest stenosis observed either on the right or on the left internal carotid artery. Ultrasound and Doppler findings were classified according to consensus imaging guidelines: normal study (PSV <125 cm/s with no signs of atherosclerotic lesions); mild CAS (PSV <125 cm/s in the presence of an atherosclerotic lesion); moderate CAS (PSV 125–230 cm/s, corresponding to 50%–70% diameter stenosis); severe CAS (PSV >230 cm/s, >70% diameter stenosis); total or near occlusion (defined as zero PSV and no visible flow). For the purposes of this study, CAS was defined as any carotid lesion exceeding 50% diameter stenosis, whereas evidence of any atherosclerotic lesion (any finding other than normal, regardless of PSV) was considered as CA and designated CA.

**Definitions of CAD**

Coronary angiography was performed by standard techniques. The severity of coronary lesions was determined by visual estimation or by a quantitative coronary angiography program (Xcelera, Philips Healthcare, Andover, MA), at the discretion of the interventional cardiologist performing the procedure. Clinically significant CAD was defined as the presence of a coronary lesion, resulting in a lumen diameter stenosis of either >70% for the left anterior descending artery, left circumflex artery, right coronary artery, or...
their major branches or >50% in the left main coronary artery. Patients were stratified according to the number of involved vessels as follows: normal coronaries or nonobstructive CAD (individuals not meeting the criteria for clinically significant CAD), one vessel disease, two vessel, three vessel disease (significant lesions in 1, 2, 3 vessels, respectively), and left main disease (significant disease of the left main coronary artery, with or without concomitant lesions in other vessels).

Statistical Analysis
All data are presented as mean (standard deviation) for continuous variables and as number (percentage) for categorical variables. The Student $t$ and Pearson $\chi^2$ tests were used for comparisons of continuous and categorical variables, respectively. The log-rank test was used for unadjusted Kaplan–Meir survival curves. MACE-free survival was estimated using Cox regression models. All models were adjusted for the presence of CA or CAS separately, age, sex, hypertension, diabetes mellitus, hyperlipidemia, history of smoking, history of MI, or coronary artery bypass grafting. A 2-tailed $P$ value of <0.05 was considered statistically significant. The SPSS statistical package was used to perform all analyses (SPSS, Chicago, IL).

Results
One thousand four hundred ninety patients underwent a carotid ultrasound and Doppler study within 24 hours of the coronary procedure. Eighty-five individuals were excluded from the analysis because of missing angiographic or Doppler data, and 14 nonresident patients were also excluded because

<table>
<thead>
<tr>
<th>Event</th>
<th>CAD Present, n (%)</th>
<th>CAD Absent, n (%)</th>
<th>P Value</th>
<th>CAD Present, n (%)</th>
<th>CAD Absent, n (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>96 (14)</td>
<td>24 (6)</td>
<td>&lt;0.01</td>
<td>14 (12)</td>
<td>11 (6)</td>
<td>0.084</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>54 (10)</td>
<td>27 (9)</td>
<td>0.49</td>
<td>3 (3)</td>
<td>1 (1)</td>
<td>0.17</td>
</tr>
<tr>
<td>Stroke</td>
<td>45 (9)</td>
<td>11 (4)</td>
<td>&lt;0.01</td>
<td>6 (7)</td>
<td>4 (3)</td>
<td>0.22</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>182 (26)</td>
<td>102 (25)</td>
<td>0.66</td>
<td>8 (7)</td>
<td>8 (5)</td>
<td>0.39</td>
</tr>
<tr>
<td>Composite MACE outcome</td>
<td>295 (42)</td>
<td>128 (31)</td>
<td>&lt;0.01</td>
<td>26 (23)</td>
<td>22 (13)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

CA indicates carotid atherosclerosis; CAD, coronary artery disease; and MACE, major adverse cardiovascular event.
of loss to follow-up. Thus, 1391 patients were available for long-term follow-up and data assembly. Of the 1391 patients included in the study, angiographic CAD was present in 1105 patients (79%) and was excluded in the remaining 286 (21%). Mean and median follow-up was 1574 and 1702 days, respectively. Complete follow-up data ≥3, ≥4, and ≥5 years were available for 91%, 60%, and 35% of patients, respectively. Baseline demographic, clinical, and vascular anatomic features are presented in Table 1. Patients with CAD were older and more likely to be men. Diabetes mellitus, hyperlipidemia, and a history of prior coronary revascularization were more prevalent in patients with versus those without CAD, as was ultrasonic evidence for CA and CAS (Table 1).

**Clinical Outcomes by Coronary Disease Status**

MACEs occurred more frequently among patients with versus those without CAD (covariate unadjusted and adjusted rates presented in Figure 1). The rates of the primary composite MACE end point, MI, and coronary revascularization procedures were higher among patients with CAD compared

<table>
<thead>
<tr>
<th>Event</th>
<th>CAD Present</th>
<th>CAD Absent</th>
<th>P Value</th>
<th>CAD Present</th>
<th>CAD Absent</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>29 (18)</td>
<td>91 (10)</td>
<td>&lt;0.01</td>
<td>5 (30)</td>
<td>20 (7)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>18 (14)</td>
<td>63 (9)</td>
<td>0.08</td>
<td>0 (0)</td>
<td>4 (2)</td>
<td>0.59</td>
</tr>
<tr>
<td>Stroke</td>
<td>14 (11)</td>
<td>42 (6)</td>
<td>0.04</td>
<td>4 (27)</td>
<td>6 (3)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>43 (27)</td>
<td>241 (26)</td>
<td>0.79</td>
<td>2 (12)</td>
<td>14 (5)</td>
<td>0.25</td>
</tr>
<tr>
<td>Composite MACE outcome</td>
<td>79 (49)</td>
<td>344 (37)</td>
<td>&lt;0.01</td>
<td>9 (53)</td>
<td>39 (16)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

CAD indicates coronary artery disease; CAS, carotid artery stenosis; and MACE, major adverse cardiovascular event.
with those without CAD (38% versus 17%; hazard ratio [HR]=2.1 [95% confidence interval [CI], 1.5–2.8]; P<0.001; 10% versus 2%; HR=3.3 [1.2–9.5]; P=0.02; 26% versus 6%; HR=4.6 [2.7–7.7]; P<0.001, respectively), whereas the rates of all-cause mortality (11% versus 9%; HR=0.94 [0.59–1.51]; P=0.81) and stroke (7% versus 5%; HR=0.68 [0.32–1.14]; P=0.30) did not differ significantly between both groups.

Clinical Outcomes by Coronary and Carotid Disease Status

MACE rates in patients stratified according to CAD and carotid disease status are presented in Tables 2 and 3 and in Figures 2 and 3. As can be seen in Figure 2, unadjusted event-free survival rates were lower among patients with any degree of CA compared with those without CA, approximating survival rates observed in patients with CAD.

Multivariate Analysis

Primary Composite MACE End Point

By covariate-adjusted Cox regression analysis (Table 4 and Figure 3), the presence of carotid disease of any degree, CAD, and the combination of the 2 were associated with an increased risk of the composite MACE end point, compared with patients without either carotid artery disease or CAD. Among patients without CAD, the presence of CAS was independently associated with an increased risk of the composite MACE end point (HR=3.17 [95% CI, 1.52–6.60]; P<0.01); the association between CA and the composite MACE end point was of borderline significance (HR=1.69 [95% CI, 0.95–3.01]; P=0.07). Among patients with CAD, rates of the composite MACE end point were similar, regardless of the presence or absence of carotid disease (Table 4).

Secondary End Points

Among patients without CAD, CAS was associated with an increased risk of all-cause mortality (HR=2.93 [95% CI, 1.09–7.87]; P=0.03), as well as with an increased risk of the combined MACE end point excluding revascularization (ie, all-cause mortality, MI, and stroke; HR=2.7 [95% CI, 1.2–5.6]). CA and the composite MACE end point excluding revascularization were not independently correlated. Among patients with CAD, CAS was not independently associated with all-cause mortality rates.

Figure 3. Covariate-adjusted Cox regression results stratified by presence of coronary artery disease (CAD), carotid atherosclerosis (CA), and carotid artery stenosis (CAS). Left, All-cause mortality and major adverse cardiovascular event (MACE; see text) stratified by presence of carotid atherosclerosis (defined as presence of any visible carotid plaque) and presence of CAD. Right, Stratified by carotid stenosis >50% (see text) and presence of CAD.
Table 4. Multivariate Cox Proportional Hazard Ratios for All-Cause Mortality and MACE Among Patients Stratified by Coronary and Carotid Disease Status*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Coronary Disease Absent</th>
<th>Coronary Disease Present</th>
<th>Coronary Disease Absent</th>
<th>Coronary Disease Present</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Carotid Disease Absent</td>
<td>Carotid Disease Present</td>
<td>Carotid Disease Absent</td>
<td>Carotid Disease Present</td>
</tr>
<tr>
<td></td>
<td>HR</td>
<td>P Value</td>
<td>HR (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>1</td>
<td>…</td>
<td>2.93 (1.09–7.87)</td>
<td>0.03</td>
</tr>
<tr>
<td>MACE</td>
<td>1</td>
<td>…</td>
<td>3.17 (1.52–6.60)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CA</td>
<td>1</td>
<td>…</td>
<td>1.05 (0.63–1.78)</td>
<td>0.84</td>
</tr>
<tr>
<td>CA</td>
<td>1</td>
<td>…</td>
<td>2.40 (1.69–3.40)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>MACE</td>
<td>1</td>
<td>…</td>
<td>0.76 (0.366–1.61)</td>
<td>0.48</td>
</tr>
<tr>
<td>MACE</td>
<td>1</td>
<td>…</td>
<td>2.45 (1.54–3.91)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

CA indicates carotid atherosclerosis; CAD, coronary artery disease; CAS, carotid artery stenosis; CI, confidence interval; HR, hazard ratio; and MACE, major adverse cardiovascular events.

*Patients stratified by CAD and CAS/CA status (columns II–IV) are referenced to patients with neither CAD nor carotid disease (column I). The covariate-adjusted models were analyzed for CA and CAS separately (see Methods section for definitions). Covariates used were age, sex, hypertension, diabetes mellitus, hyperlipidemia, smoking history, history of myocardial infarction or coronary artery bypass grafting at the index event.

Discussion

This study, using coronary angiography and carotid Doppler in all participants, confirms and extends the findings of previous studies that have reported an association between the presence of atherosclerotic carotid artery disease and an increased risk of subsequent MACE. The prognostic implications of carotid artery disease are imparted predominantly in patients without significant CAD.

Previous Studies

Several previous studies have investigated the association between the presence of carotid disease and future CAD-related adverse events (ie, MI and cardiac death). The largest of these studies was an analysis from the international Reduction of Atherothrombosis for Continued Health (REACH) registry. At the time of enrollment, 23,000 registry patients had evidence of CA (defined as any degree of carotid plaque regardless of luminal stenosis, evidenced either by a history of carotid revascularization or by a physician report documenting ≥1 carotid plaque or a carotid stenosis ≥70%). At 4-year follow-up, the presence of CA was associated with a 22% increase in the risk of coronary events; this finding is consistent across all patient subsets, including patients with or without pre-existing CAD. However, the definition of CAD in this study was not standardized and was largely surrogate based (eg, physician- or patient-reported history of unstable or stable anginal symptoms), whereas objective evidence of CAD was not a mandatory inclusion criterion. In a separate single-center study from Korea, 1390 patients with angiographically proven CAD underwent carotid duplex scanning at the time of coronary angiography. At follow-up (mean, 54 months), the presence of carotid plaque at baseline was associated with an ≈7-fold increase in the risk of cardiac death and an ≈2-fold increase in the rates of the composite end point (all-cause mortality, MI, and stroke). Although the rate of cardiac death was significantly higher in patients with versus those without CA, the rates of MI did not differ between both groups. Of note, this study differed from ours, in that the definition of CA was on the basis of the presence of any coronary lesion ≥50%, whereas our definition required the presence of lesions >70% diameter stenosis, in accordance with recent practice guidelines. Considered together, previous reports indicate that the presence of CA is an independent predictor of future CAD-related events though methodological variability across these studies and the broad definitions of CA and CAD used have left the relative prognostic impact of CA in patients with or without CAD inadequately defined.

Prognostic Implications of CA in This Study

Our study differs from previous reports, in that coronary angiography and carotid Doppler were used in all participants to provide quantitative assessment of CAD and CA, respectively, in accordance with current practice guidelines. The data thus obtained demonstrate that the association between CA and subsequent MACE is particularly significant in patients without manifest CAD at the time of carotid disease detection. In fact, the presence of CA of any degree portends a risk of future MACE similar to that seen in patients with established CAD. This finding substantiates the concept that Doppler evidence of CAS (as defined in this study) should be considered a CAD equivalent, with attendant prognostic and therapeutic implications. This is particularly important in patients in whom obstructive CAD has been excluded on the basis of coronary angiography or functional tests of myocardial perfusion. Our data also suggest that angiographically evident CAD probably reflects an advanced stage of vascular disease, in which the prognostic importance of carotid lesions (other than critically obstructive stenosis) is overwhelmed by the burden of atherosclerotic disease in other vascular beds.

Study Limitations

The retrospective design of this analysis is acknowledged. Another limitation of this study lies in the small number of participants without CAD identified as having carotid lesions, especially those with severe stenoses. The relatively small sample size may have also obscured a meaningful association.
between CA of a lesser degree than CAS as defined herein with future MACE. Lastly, detailed information on medication use after discharge (eg, statins, antihypertensive, and antiplatelet agents) was not collected systematically in the Tel-Aviv Prospective Angiography Study registry. Therefore, we cannot exclude the possibility that the increased risk of adverse events in patients with CAS but no CAD might have resulted in part from failure to implement relevant pharmacological therapy because of the misperception that in the absence of CAD such therapy was not indicated.

Summary and Clinical Implications

Although current guidelines on prevention of cardiovascular disease consider the presence of any degree of CA a high-risk marker (>10% per 10 years) of death, routine carotid Doppler disease consider the presence of any degree of CA a high-risk

therapy was not indicated.

from failure to implement relevant pharmacological therapy

exclude the possibility that the increased risk of adverse events

Prospective Angiography Study registry. Therefore, we cannot

future MACE. Lastly, detailed information on medication use

between CA of a lesser degree than CAS as defined herein with

importance in patients without pre-existing CAD, who might

ease in terms of adverse cardiac events are of predominant

data indicate that the prognostic implications of carotid dis-

ting might have a direct bearing on screening strategies for

Disclosures
None.

References

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