Atherosclerosis is a systemic inflammatory vascular disorder, involving multiple arterial beds (1). Although modern pharmacotherapy and revascularization have markedly enhanced the prognosis of patients with atherosclerotic vascular disease, myocardial infarction (MI) and stroke remain leading causes of mortality and morbidity due to this disease (2). Concomitant atherosclerotic lesions of the extracranial internal carotid arteries (ICA) and the coronary circulation portend an adverse prognosis in various clinical settings, including asymptomatic individuals, stroke patients, and patients undergoing coronary artery bypass surgery (3–5). Previous postmortem (6,7) and clinical (8–11) studies, often small in sample size, have reported a variable prevalence of concomitant carotid and coronary lesions in patients with or without clinically evident cardiovascular disease. Thus, the prevalence of clinically important, concomitant carotid artery stenosis (CAS) and coronary artery disease (CAD) requires further definition in larger populations.

We performed ICA duplex ultrasound studies in consecutive patients undergoing nonemergent coronary angiography. The prevalence and predictors of severe ICA stenosis in patients with CAD were analyzed using current consensus guidelines for the definition of CAS (12).

### Methods

**Study population.** Consecutive hospitalized and ambulatory patients undergoing nonemergent coronary angiography between January 2007 and May 2009 were enrolled in the Tel-Aviv Prospective Angiography Study, as previously described (13). Of these, 1,490 patients underwent a carotid ultrasound and Doppler study within 24 h of the coronary procedure. Eighty-five individuals were excluded from the present analyses due to missing data.
Definitions of CAS. Atherosclerosis of both the left and right ICA was assessed by a sonography technician who was blinded to clinical and coronary angiographic data. The ICA were scanned with carotid duplex equipment (HD11 XE, Philips Healthcare, Andover, Massachusetts) with a 3- to 12-MHz linear array transducer, using a previously described protocol (14). ICA atherosclerosis was evaluated by the maximum percentage of diameter reduction recorded by B-mode ultrasound, and by the peak systolic velocity (PSV) and peak diastolic velocity per Doppler. Lesion severity was defined as the greatest stenosis observed either on the right or left ICA. Ultrasound and Doppler findings were classified into 1 of the following 5 categories (12): normal (PSV < 125 cm/s with no signs of atherosclerotic lesions); mild CAS (defined as PSV < 125 cm/s and the presence of a sonographic atherosclerotic lesion correlating to diameter stenosis of < 50%); moderate CAS (defined as PSV between 125 and 230 cm/s correlating to diameter stenosis of 50% to 70%); severe CAS (defined as PSV > 230 cm/s correlating to diameter stenosis of > 70%); and total or near occlusion (defined as 0 PSV and no visible flow). Evidence of clinically significant ICA disease was defined as PSV > 125 cm/s.

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) 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 > 70% in a major epicardial artery (left anterior descending artery, left circumflex artery, right coronary artery) or one of its major branches (15). Clinically significant left main disease was defined as a lumen diameter stenosis > 50% (15). 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), 1VD, 2VD, 3VD (significant lesions in 1, 2, and 3 vessels, respectively), and LMD (significant disease of the left main coronary artery, with or without concomitant lesions in other vessels) (15).

Statistical analysis. Continuous variables are presented as mean ± SD. Spearman correlation was used to evaluate the relation between CAS severity and CAD extent. Multinomial logistic regression models were fitted for CAS severity, defined by either PSV or end-diastolic volume as the dependent variable, with adjustment for CAD extent, age, sex, smoking status, hypertension, diabetes mellitus, hyperlipidemia, chronic renal failure, history of MI, history of coronary artery bypass graft surgery (CABG), stroke, or transient ischemic attack. For all analyses, a 2-tailed p < 0.05 was considered statistically significant. The SPSS statistical package (SPSS Inc., Chicago, Illinois) was used.

Results

The final study population consisted of 1,405 patients. Their demographic and clinical features are presented in Table 1. The prevalence of the various categories of CAS severity and the CAD extent are presented in Table 2.
the entire study population, 42% had patent carotid arteries without any evidence of atherosclerotic plaque, whereas the prevalence of moderate and severe CAS was 12.8% and 4.6%, respectively. The severity of CAS and CAD extent were directly correlated (r = 0.255, p < 0.001). Clinically significant CAS (>50%) was found in 5.9%, 6.6%, 13%, 17.8%, and 31.3% among patients with normal or nonobstructive CAD, 1VD, 2VD, 3VD, and LMD, respectively. Severe CAS (>70%) was found in 2.1%, 3.1%, 3.6%, 7%, and 10.8% of patients with normal or nonobstructive CAD, 1VD, 2VD, 3VD, and LMD, respectively.

The logistic regression modeling results are presented in Table 3. Independent predictors of severe CAS or total internal carotid occlusion were the presence of LMD or 3VD, increasing age, a history of stroke, smoking status, diabetes mellitus. A similar analysis using end-diastolic volume did not yield statistically significant results (data not shown).

### Discussion

The present study represents the largest analysis to date of the prevalence of concomitant coronary and carotid atherosclerotic arterial disease. The principal finding of this analysis is that the presence of ICA stenosis is directly related to the extent of CAD, though the prevalence of moderate and severe CAS in patients with CAD is lower than previously reported.

**Clinical importance of concomitant CAD and CAS.** Concurrent CAD and CAS is frequently detected in clinical practice and has important prognostic implications in symptomatic patients who are considered for revascularization of one or both of these vascular beds as well as in entirely asymptomatic individuals. In patients with traditional atherosclerotic risk factors but not necessarily a prior cardiovascular event, the mere presence of a carotid bruit predicts increased risk of MI and cardiac death (4). In fact, progression of CAS on sequential Doppler studies has been shown to be a stronger correlate of future MI events than of stroke (16). The presence of CAS has been shown in multiple (17), though not in all (18), studies to increase the risk of perioperative stroke in patients undergoing CABG. Conversely, the presence of CAD increases the risk of peripheral vascular surgery including carotid endarterectomy (19). Notwithstanding, the role of pre-emptive interventions on asymptomatic carotid or coronary lesions prior to coronary or carotid revascularization, respectively, is controversial (18,20), and guideline recommendations regarding screening for asymptomatic CAS in patients with CAD are unsettled (21,22). Our data indicate that although at least some degree of atherosclerotic carotid disease is frequently detected among patients with extensive CAD (i.e., 3VD and/or LMD), the prevalence of CAS potentially mandating intervention is lower than previously reported (i.e., in the range of 7% to 11% in the highest-risk anatomic subsets of CAD).

**Previous studies.** The reported prevalence of asymptomatic CAS has ranged from 2% to 18% among screened populations, although in high-risk individuals, including those with coronary artery disease, the prevalence of significant CAS has been reported to be as high as 30% (21). In a small study (n = 223), a CAS >50% was found in 5%, 13%, 25%, and 40% of patients with 1VD, 2VD, 3VD, and LMD, respectively (9). In a separate study in 632 Japanese patients, the prevalence of CAS >50% was 14%, 21%, and 36%, in patients with 1VD, 2VD, and 3VD, respectively (8). These rates of CAS are

### Table 3 Multivariate Correlates of Doppler-Defined CAS

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mild CAS</th>
<th>Moderate CAS</th>
<th>Severe CAS or Total Occlusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal or nonobstructive CAD</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>1-vessel CAD</td>
<td>1.86 (1.26–2.74)</td>
<td>1.26 (0.49–3.25)</td>
<td>1.85 (0.60–5.71)</td>
</tr>
<tr>
<td>2-vessel CAD</td>
<td>2.26 (1.56–3.29)</td>
<td>3.92 (1.81–8.46)</td>
<td>2.50 (0.88–7.13)</td>
</tr>
<tr>
<td>3-vessel CAD</td>
<td>2.49 (1.68–3.68)</td>
<td>3.91 (1.79–8.57)</td>
<td>4.20 (1.53–11.52)</td>
</tr>
<tr>
<td>Left main CAD</td>
<td>2.47 (1.27–4.79)</td>
<td>8.77 (3.18–24.16)</td>
<td>7.20 (2.00–25.95)</td>
</tr>
<tr>
<td>History of smoking</td>
<td>1.68 (1.27–2.23)</td>
<td>1.88 (1.44–3.11)</td>
<td>3.25 (1.80–5.85)</td>
</tr>
<tr>
<td>Age (for each 10-yr increase)</td>
<td>1.98 (1.74–2.26)</td>
<td>2.77 (2.17–3.53)</td>
<td>2.42 (1.79–3.26)</td>
</tr>
<tr>
<td>Male</td>
<td>0.80 (0.58–1.29)</td>
<td>0.65 (0.38–1.11)</td>
<td>0.57 (0.29–1.09)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.14 (0.88–1.47)</td>
<td>1.31 (0.82–2.08)</td>
<td>1.23 (0.68–2.21)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.31 (1.01–1.68)</td>
<td>1.58 (1.02–2.47)</td>
<td>1.83 (1.05–3.19)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>0.94 (0.71–1.25)</td>
<td>0.94 (0.55–1.61)</td>
<td>1.21 (0.57–2.57)</td>
</tr>
<tr>
<td>Post-MI</td>
<td>0.94 (0.70–1.27)</td>
<td>1.22 (0.75–2.01)</td>
<td>1.53 (0.84–2.78)</td>
</tr>
<tr>
<td>Post-stroke</td>
<td>1.44 (0.68–3.04)</td>
<td>2.59 (0.94–7.16)</td>
<td>4.71 (1.69–13.15)</td>
</tr>
<tr>
<td>Post-CABG</td>
<td>1.36 (0.91–2.04)</td>
<td>1.59 (0.87–2.87)</td>
<td>1.99 (0.99–4.02)</td>
</tr>
<tr>
<td>CRF</td>
<td>1.15 (0.66–2.02)</td>
<td>2.77 (1.36–6.51)</td>
<td>1.81 (0.72–4.54)</td>
</tr>
</tbody>
</table>

**Bold values indicate statistical significance.** Multinomial logistic regression model for CAS severity as the dependant variable. The CAS severity variables are referenced to the presence of normal CAS. Carotid artery stenosis defined as: normal (PSV <125 cm/s) with no signs of atherosclerotic lesions; mild CAS (defined as PSV <125 cm/s) and the presence of a sonographic atherosclerotic lesion correlating to diameter stenosis of <50%; moderate CAS (defined as PSV between 125 and 230 cm/s correlating to diameter stenosis of 50% to 70%); severe CAS (defined as PSV ≥230 cm/s correlating to diameter stenosis of >70%); and total or near occlusion (defined as 0 PSV and no visible flow). CI = confidence interval; OR = odds ratio; other abbreviations as in Tables 1 and 2.
higher than found in our patients, a difference most prominent (≥1.5–2-fold) among patients with 3VD and LMD. Several explanations might account for the difference between our findings and those reported by others. First, the definition of “significant” CAS has differed across studies. Whereas other authors have used a definition of >50%, our study analyzed stenoses exceeding both 50% and 70% diameter stenosis. It should be noted the 70% definition for severe CAS conforms to current guidelines (12) and is clinically relevant for decisions regarding revascularization therapy. Second, studies have differed in their sample sizes as well as the methodology employed. Kallikazaros et al. (9) defined diameter stenosis using B-mode ultrasonography in mild CAS, whereas Doppler flow velocities were used for severe CAS. In contrast, in the present study, we used flow velocity for all lesions (12,23). Third, the velocities were used for severe CAS. In contrast, in the present study, we used flow velocity for all lesions (12,23). Third, the Tanimoto study was limited to Japanese patients (8), whereas our study was conducted in an ethnically diverse population. Finally, our study was conducted several years after the aforementioned studies. It is possible that better adherence to optimal medical therapy for cardiovascular disease accounts in part for the decreasing prevalence of severe CAS among patients with symptomatic CAD (24).

Study limitations. The patients included in this study were referred for nonemergency coronary angiography for suspected CAD. Therefore, the prevalence of concomitant carotid and coronary disease in asymptomatic individuals could not be evaluated. Additionally, the study provides no information on the prevalence of clinically-important coronary artery disease among patients with acutely symptomatic carotid artery lesions. Lastly, due to the small numbers of moderate and severe CAS, the multinomial logistic regression model may be overfitted, and cross-validation is needed.

Summary and clinical implications. This analysis confirms the findings of previous studies that have reported a direct relation between the extent of CAD and the prevalence of CAS among patients referred for coronary angiography, though the prevalence of clinically significant CAS in these patients appears to be lower than previously reported.

Our findings support current guidelines that do not endorse nonselective screening for CAS among individuals without symptoms attributable to the carotid circulation, including those with CAD (21). This study also lends further credence to the recommendation to screen high-risk individuals with CAD (including those with multivessel disease or LMD, a history of stroke, advanced age, and smokers) (21). Of note, percutaneous intervention is increasingly utilized in CAD subsets previously treated almost exclusively by CABG (e.g., LMD) (25). Guideline recommendations on screening for CAS prior to CABG should probably be extended to this increasing population of patients (21).

Acknowledgment
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References

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