From the Canadian Society for Vascular Surgery

Impact of diabetes on carotid artery revascularization

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Objective: **Diabetes has been suggested as a marker of higher operative risk during carotid artery revascularization. The aim of this study was to summarize the current evidence comparing the effectiveness of carotid revascularization in diabetic vs nondiabetic patients.**

Methods: **We conducted a systematic search of MEDLINE, Embase, and the Cochrane Library databases (1946 to January 2015) for all studies comparing the clinical outcomes of diabetic vs nondiabetic patients who underwent carotid endarterectomy (CEA) or carotid artery stenting (CAS) in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Two authors independently reviewed the studies for inclusion and quality and extracted the data. A third author validated study selection and data extraction. We calculated treatment effects as odds ratios (ORs) and 95% confidence intervals (CIs). We quantified heterogeneity using the I^2 statistic. All pooled analyses were based on random-effects models. The predefined review protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO 2015:CRD42015015873).**

Results: **Of the 1241 abstracts screened, we included 14 observational studies involving 16,264 patients. There was excellent agreement in study selection between the two reviewers (κ statistic, 0.83; 95% CI, 0.72-0.94). CEA was used in 10 studies, CAS was used in 3 studies, and both CEA and CAS were used in 1 study. All included studies were published after 1984, and 93% were published after 1997. Carotid revascularization in diabetic patients was associated with a higher risk of the following outcomes: perioperative stroke (OR, 1.38; 95% CI, 1.02-1.88; $P = .04$; $I^2 = 13\%$), death (OR, 1.94; 95% CI, 1.36-2.75; $P = .0002$; $I^2 = 0\%$), composite risk of stroke or death (OR, 1.80; 95% CI, 1.32-2.47; $P = .0002$; $I^2 = 26\%$), and long-term risk of death (OR, 1.57; 95% CI, 1.22-2.03; $P = .0005$; $I^2 = 0\%$). No association was found between diabetes and perioperative risk of myocardial infarction (MI); composite risk of MI, stroke, or death; and long-term risk of stroke. Study quality was limited by selection bias, minimal control for confounders, and single-center retrospective design. Sensitivity analyses excluding low-quality studies did not change the effect of diabetes on the risk of stroke, death, or MI.**

Conclusions: **Diabetic patients are at an increased risk of perioperative stroke, death, and long-term mortality compared with nondiabetic patients who undergo carotid artery revascularization. This knowledge can help further risk stratify patients with carotid artery stenosis before treatment. Future studies should focus on evaluating which mode of revascularization (CEA or CAS) is more effective in diabetic patients with carotid artery stenosis. (J Vasc Surg 2016;63:1099-107.)**

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Carotid endarterectomy (CEA) and carotid artery stenting (CAS) are two revascularization procedures used to treat patients with significant carotid artery stenosis. Several high-quality randomized controlled trials (RCTs) have compared the effectiveness of these revascularization procedures in patients with carotid artery stenosis.[1] Data from these trials have allowed identification of patient, disease, and health care provider factors that increase the risk of perioperative events, which are reflected in major international committee guidelines.[2,3] However, no RCT has examined the safety and efficacy of carotid artery revascularization specifically in the diabetic population.

Although diabetes mellitus has been suggested as a marker for higher perioperative risk during carotid revascularization in some observational studies, the evidence has been conflicting, with varied conclusions across different studies. Consequently, we set out to conduct a systematic review and a meta-analysis to provide a contemporary and objective estimate of the strength and magnitude of

the association between diabetes and adverse cardiovascular outcomes after CEA and CAS.

METHODS

Protocol and registration. We conducted a systematic review and meta-analysis using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines.[4] Our predefined review protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO 2015:CRD42015015873).

Eligibility criteria and outcomes. We searched for all studies comparing the outcomes of diabetic and nondiabetic individuals who underwent carotid artery revascularization. No study type, publication date, or publication status restrictions were imposed. Primary outcome was perioperative (30-day) risk of stroke. Secondary outcomes included the following: perioperative risk of death; myocardial infarction (MI); composite of stroke, death, or MI; and long-term risk of stroke and death. Non-English studies and studies that did not examine either a primary or secondary outcome were excluded.

Data sources and search strategy. We systematically searched OVID versions of MEDLINE (1946 through January 2015, week 2), Embase Classic and Embase (1947 through 2015, week 2), and the Cochrane Central Register of Controlled Trials (Issue 11, November 2014) for relevant studies using a combination of search terms, including the following: *carotid stenosis*; *carotid endarterectomy*; *stents*; *cerebrovascular accident*; and *diabetes mellitus*. The complete search strategy is described in Supplementary Fig 1 (online only). We also searched bibliographies of included studies for relevant articles.

Study selection. After duplicate records were removed, two reviewers (S.A.B-A., O.Q.S.) independently screened the titles and abstracts identified by the search strategy for relevance and full-text review. Two reviewers (S.A.B-A., O.Q.S.) also independently conducted full-text reviews of all potentially relevant articles to establish eligibility. Disagreements between reviewers were resolved by consensus with two additional reviewers (M.A.H., M.A-O.).

Data extraction. We developed an electronic data extraction form, piloted it on four randomly selected included studies, and refined it accordingly. Two reviewers (S.A.B-A., O.Q.S.) independently extracted data from the included studies in duplicate, and a third reviewer (M.A.H.) checked the extracted data to minimize measurement bias. Disagreements between reviewers were resolved by consensus. Information extracted from each study included study characteristics (author, year of publication, country, study design, number of patients, follow-up period), type of carotid revascularization procedure, history of diabetes, method of diagnosing diabetes, other patient characteristics (age, gender, symptomatic disease, smoking, hypertension, dyslipidemia, coronary artery disease), and outcomes of interest.

Quality assessment. Two reviewers (S.A.B-A., O.Q.S.) independently examined the methodologic quality of included studies using the Newcastle-Ottawa Scale (NOS).[5] This instrument assesses the quality of cohort studies in terms of selection of study cohorts, comparability of the cohorts, and outcomes ascertainment using a "star system." Disagreements between reviewers were resolved by consensus with a third reviewer (M.A.H.).

Statistical analysis. We calculated the κ statistic to determine the level of agreement between reviewers for study selection using SAS 9.4 (SAS Institute, Cary, NC). A κ value of $\geq$0.8 indicates near-perfect agreement.[6] The meta-analyses were performed by computing odds ratios (ORs) and 95% confidence intervals (CIs) for the primary and secondary outcomes, with the nondiabetic group as reference. For each outcome, overall results and results divided into subgroups by type of carotid revascularization procedure (CEA or CAS) were presented in forest plots. We also conducted sensitivity analyses by excluding studies that were at high risk for bias (NOS score $\leq$5). All pooled analyses were based on random-effects models. We quantified heterogeneity using the I^2 statistic, which provides an estimate of the percentage of variation across studies arising from study heterogeneity rather than chance.[7] An I^2 statistic value of $\geq$50% generally indicates moderate to high heterogeneity.[8] We deemed an α level of $< .05$ statistically significant. All meta-analyses were performed using Review Manager 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark).

RESULTS

Study selection. As shown in Fig 1, a total of 1558 studies were identified with our search strategy. After adjusting for duplicates, 1241 studies remained. Of these, 1220 were excluded after title and abstract screening because it appeared that these studies did not meet our inclusion criteria. The remaining 21 studies were subjected to a full-text review, and an additional 7 were excluded for the following reasons: abstract only (n = 2), did not compare diabetics to nondiabetics (n = 2), full-text unavailable (n = 1), irrelevant outcomes (n = 1), and duplicate data source (n = 1). In total, 14 studies were included in this systematic review and meta-analysis. There was excellent inter-reviewer agreement (κ, 0.83; 95% CI, 0.72-0.94) during the study selection process.

Study characteristics. Study characteristics are summarized in Table I.[9-22] All 14 finally selected studies were observational cohort studies published in English, with the majority (93%) being retrospective in design. Nine (64%) studies were from Europe, four (29%) from the United States, and one (7%) from Japan. All studies were published during a 30-year period (1984-2014), with the majority (93%) being published during or after the year 1997. CEA was the revascularization procedure used in 10 (71%) of the studies, whereas 3 (21%) studies used CAS, and 1 (7%) study used both CEA and CAS. The included studies reported on a total of 16,264 patients, with 4204 (26%) of them being diabetic. The majority (64%) of the studies defined diabetes as prior history of insulin or oral hypoglycemic agent use, whereas 21% of the studies used laboratory criteria, and 14% of the studies did not report the method of defining diabetes. Six (43%) studies reported