

Impact of Clinical Trial Results on the Temporal Trends of Carotid Endarterectomy and Stenting From 2002 to 2014

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Background and Purpose—Randomized trials provide conflicting data for the efficacy of carotid-artery stenting compared with endarterectomy. The purpose of this study was to examine the impact of conflicting clinical trial publications on the utilization rates of carotid revascularization procedures.

Methods—We conducted a population-level time-series analysis of all individuals who underwent carotid endarterectomy and stenting in Ontario, Canada (2002–2014). The primary analysis examined temporal changes in the rates of carotid revascularization procedures after publications of major randomized trials. Secondary analyses examined changes in overall and age, sex, carotid-artery symptom, and operator specialty-specific procedure rates.

Results—A total of 16 772 patients were studied (14 394 endarterectomy [86%]; 2378 stenting [14%]). The overall rate of carotid revascularization decreased from 6.0 procedures per 100 000 individuals ≥ 40 years old in April 2002 to 4.3 procedures in the first quarter of 2014 (29% decrease; $P < 0.001$). The rate of endarterectomy decreased by 36% ($P < 0.001$), whereas the rate of carotid-artery stenting increased by 72% ($P = 0.006$). We observed a marked increase ($P = 0.01$) in stenting after publication of the SAPPHIRE trial (Stenting and Angioplasty With Protection in Patients at High Risk for Endarterectomy) in 2004, whereas stenting remained relatively unchanged after subsequent randomized trials published in 2006 ($P = 0.11$) and 2010 ($P = 0.34$). In contrast, endarterectomy decreased after trials published in 2006 ($P = 0.04$) and 2010 ($P = 0.005$).

Conclusions—Although the overall rates of carotid revascularization and endarterectomy have fallen since 2002, the rate of carotid-artery stenting has risen since the publication of stenting-favorable SAPPHIRE trial. Subsequent conflicting randomized trials were associated with a decreasing rate of carotid endarterectomy. (*Stroke*. 2016;47:2923-2930. DOI: 10.1161/STROKEAHA.116.014856.)

Key Words: carotid-artery stenting ■ carotid endarterectomy ■ carotid stenosis ■ health services research ■ trends

The optimal revascularization strategy for significant carotid-artery atherosclerosis is highly debated. Carotid endarterectomy had been long considered the gold-standard treatment since large randomized controlled trials established its superiority over medical therapy in the 1990s¹—this led to a dramatic rise in the rates of endarterectomy in both Canada and the United States between 1989 and 1995.² Carotid-artery stenting, however, has more recently gained popularity as

an alternative to endarterectomy because of its less invasive nature and ability to perform in a nonsurgical setting.

Several high-quality randomized trials have compared the safety and efficacy of carotid-artery stenting to endarterectomy.¹ Early trials provided conflicting results, with some suggesting noninferiority of stenting compared with endarterectomy,³ whereas others failed to prove the noninferiority of carotid-artery stenting.^{4,5} Initial results of the largest 2 carotid

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revascularization trials, the 1713-patient ICSS (International Carotid Stenting Study) and the 2502-patient CREST (Carotid Revascularization Endarterectomy Versus Stenting Trial), were published in 2010 with conflicting results.^{6,7} ICSS examined 120-day composite outcomes and showed significantly higher rates of stroke and death with carotid-artery stenting.⁶ CREST, on the contrary, suggested that carotid-artery stenting is noninferior to endarterectomy because the higher risk of stroke with stenting was balanced with a higher risk of myocardial infarction with endarterectomy.⁷ Inclusion of myocardial infarction in the primary composite outcome is, however, debatable because stroke has a greater negative impact on health-related quality of life than myocardial infarction.

Despite this conflicting evidence, numerous authors have noted that clinicians have increased the overall uptake of carotid-artery stenting in practice at the expense of endarterectomy.^{8–18} These studies, however, are limited to the United States; the study periods have generally been short; accuracy of the data sources used are not known; and they have not objectively examined the impact of clinical trial results on procedure rates. Long-term effects of the largest carotid revascularization trials (ICSS and CREST) on clinical practice are also not known. To address these shortcomings, we conducted a population-based analysis to examine the influence of clinical trial publications on temporal trends of carotid endarterectomy and stenting over a 12-year period.

Methods

Study Design and Setting

We conducted a population-level, cross-sectional, time-series analysis to study temporal trends in the rates of carotid endarterectomy and carotid-artery stenting in Ontario, Canada. The 13.5 million Ontario residents have universal access to healthcare funded from a single-payer health system. The St Michael's Hospital Research Ethics Board approved this study.

Sources of Data

We used the following linked population-level health databases: the Canadian Institute for Health Information Discharge Abstract Database (captures patient demographic and clinical information from hospital discharges), the Registered Personal Database (demographic and vital statistics data), and the Institute for Clinical Evaluative Sciences Physicians Database (information on Ontario physicians).

Patient Cohort

We included all adults aged ≥ 40 years who underwent carotid endarterectomy or carotid-artery stenting between April 1, 2002, and March 31, 2014. We used previously validated *Canadian Classification of Health Intervention* procedure codes to identify patients treated with carotid endarterectomy (1JE57Lx; positive predictive value, 99%; sensitivity, 90%) and carotid-artery stenting (1JE50x; positive predictive value, 87%; sensitivity, 93%).¹⁹ In addition, we established the following patient baseline characteristics: age, sex, region, treating institution type, carotid-artery symptoms, and operator specialty. Symptomatic carotid-artery stenosis was defined as a previous hospital admission or an emergency department visit within the last 6 months with a diagnosis of ischemic stroke or transient ischemic attack.²⁰

Primary and Secondary Analyses

In the primary analysis, we examined temporal changes in the rates of carotid endarterectomy and stenting after publications of major

carotid revascularization randomized trials at 3 time points: the fourth quarter of 2004 (SAPPHIRE trial [Stenting and Angioplasty With Protection in Patients at High Risk for Endarterectomy]); the fourth quarter of 2006 (EVA-3S trial [Endarterectomy Versus Angioplasty in Patients With Severe Symptomatic Carotid Stenosis] and SPACE trial [Stent-Supported Percutaneous Angioplasty of the Carotid Artery Versus Endarterectomy]); and the second quarter of 2010 (ICSS and CREST). Publication dates of the 2006 and 2010 trials were clustered within 2 to 3 months of each other and, thus, were combined into common time points. Secondary analyses examined temporal changes in overall rates of carotid revascularization procedures during the entire study period. In addition, we also examined procedure rates stratified by patient age quintile, sex, carotid-artery symptoms, and operator specialty.

Analytic Approach

We first divided the study time frame into 48 quarterly intervals between April 1, 2002, and March 31, 2014. We then calculated quarterly rates of carotid revascularization procedures per 100 000 Ontario adults ≥ 40 years old. The denominator (population of Ontario ≥ 40 years old) for each year was determined by using data from Stats Canada (Statistics Canada; available at <http://www.statcan.ca>).

We used time-series analysis to study the patterns in utilization rates of carotid revascularization procedures during the study period. Time series analysis is a statistical technique used for modeling autocorrelation in temporally sequenced data that is measured repeatedly in equal intervals of time.²¹ In the primary analysis, we built interventional autoregressive integrated moving average models with ramp functions to examine the effects of clinical trial publications on the temporal trends of carotid endarterectomy and stenting.²² Interventional autoregressive integrated moving average modeling is used to model the effect of an event on time series data, and ramp functions are used to model the response in time series data when there seems to be a gradual change in slope after an event.²³

In the secondary analyses, we used exponential smoothing models to assess temporal trends in the overall rates of carotid revascularization procedures, and rates were stratified according to predefined variables.²⁴ We assessed for model parameter appropriateness and seasonality using the autocorrelation, partial autocorrelation, and inverse autocorrelation functions. Stationarity was assessed using the autocorrelation function and the augmented Dickey–Fuller test.²⁵ The Ljung–Box χ^2 statistic was used to test for the presence of white noise by examining the autocorrelations at various lags.²⁶ All *P* values are 2-sided, and *P* values < 0.05 were considered to be statistically significant. All statistical analyses were conducted using SAS, version 9.4 (SAS Institute, Cary, NC).

Results

Cohort Characteristics

A total of 16 772 individuals who underwent carotid revascularization were included, of which 14 394 (86%) underwent endarterectomy and 2378 (14%) underwent stenting (Table). Mean age (SD) of the total cohort was 69.8 (9.4) years, and 34% were female. Most patients resided in urban areas (81%), were treated at nonacademic institutions (53%), and had asymptomatic carotid-artery stenosis (58%). Of note, among patients ≥ 75 years old, 59% were symptomatic in the stenting group and 46% were symptomatic in the endarterectomy group. With respect to operator specialty, vascular surgeons (55%), followed by neurosurgeons (21%), general surgeons (16%), and cardiac surgeons (8%), most commonly performed carotid endarterectomy. Radiologists (79%) and neurosurgeons (16%), on the contrary, almost exclusively performed carotid-artery stenting.

Primary Analysis

A decreasing trend in the rate of carotid endarterectomy was observed after publication of SAPPHIRE in 2004, although this did not reach statistical significance ($P=0.06$). Subsequent trials appeared to further influence the rate of endarterectomy because it markedly decreased after publication of SPACE and EVA-3S in 2006 ($P=0.04$) and CREST and ICSS in 2010 ($P=0.005$). The utilization rate of carotid-artery stenting, on the contrary, significantly increased after publication of SAPPHIRE in 2004 ($P=0.01$). Rates of stenting did not change after publications of subsequent trials in 2006 and 2010 ($P=0.11$ and $P=0.34$, respectively). See Figure 1 for quarterly rates of carotid endarterectomy and stenting

Table. Characteristics of Individuals Undergoing Carotid Revascularization

Variable	Carotid Endarterectomy (n=14 394)	Carotid Stenting (n=2378)
Age, y		
Mean (SD)	69.8 (9.2)	69.9 (10.6)
Median (IQR)	71 (64–77)	71 (63–78)
Range, n (%), y		
≤64	3969 (27.6)	693 (29.1)
65–69	2625 (18.2)	368 (15.5)
70–74	2886 (20.1)	429 (18.0)
75–79	2808 (19.5)	434 (18.3)
≥80	2106 (14.6)	454 (19.1)
Sex, n (%)		
Male	9534 (66.2)	1560 (65.6)
Female	4860 (33.8)	818 (34.4)
Region, n (%)*		
Urban	11 472 (79.7)	2073 (87.3)
Rural	2917 (20.3)	303 (12.7)
Institution type, n (%)		
Academic	6672 (46.0)	1325 (55.7)
Nonacademic	7767 (54.0)	1053 (44.3)
Symptomatic status, n (%)*		
Symptomatic	5814 (40.4)	1241 (52.2)
Asymptomatic	8578 (59.6)	1137 (47.8)
Operator specialty, n (%)*		
Vascular surgery	7956 (55.3)	22 (0.9)
Neurosurgery	3005 (20.9)	388 (16.3)
General surgery	2252 (15.7)	14 (0.6)
Cardiac surgery	1132 (7.9)	≤5†
Radiology	≤5†	1882 (79.1)
Other	32 (0.2)	40 (1.7)

IQR indicates interquartile range; and SD, standard deviation.

*Missing values: region (n=7); symptomatic status (n=2); operator specialty (n=46).

†Cells containing 5 or less observations are suppressed.

per 100 000 adults ≥40 years old in relation to clinical trial publications.

Secondary Analyses

The overall rate of carotid revascularization decreased from 6.0 procedures per 100 000 in April 2002 to 4.3 procedures per 100 000 in the first quarter of 2014 (29% decrease; $P<0.001$; Figure 1). The rate of endarterectomy decreased by 36% from 5.6 to 3.6 procedures per 100 000 ($P<0.001$), whereas the rate of stenting increased by 72% from 0.39 to 0.67 procedures per 100 000 ($P=0.006$). Similar to the overall carotid revascularization rates, we observed marked decreases in endarterectomy among men (38% decrease; $P<0.001$) and women (31% decrease; $P<0.001$), whereas the rates of carotid-artery stenting increased among men (74% increase; $P<0.001$) and women (66% increase; $P=0.001$; Figure 2).

With respect to revascularization rates by age, time-series analysis found that the rates of carotid endarterectomy decreased significantly ($P\leq 0.001$) among all age groups, except for those aged ≥80 years, who received endarterectomy at a relatively stable rate during the study period (from 0.78 to 0.71 procedures per 100 000; $P=0.99$). Among the youngest (≤64 years old) group of patients, the rate of carotid-artery stenting increased by 57% (from 0.13 to 0.20 per 100 000; $P<0.001$). Carotid-artery stenting rates also increased among the 2 oldest groups (75–79 and ≥80 years old) of patients ($P=0.004$ and $P<0.001$, respectively); however, these increases largely occurred between 2005 and 2010, and the rates of stenting among these older groups have since stabilized. See Figure I in the [online-only Data Supplement](#) for rates of carotid revascularization stratified by age.

In regard to temporal trends by carotid-artery symptoms, we found that carotid endarterectomy was being performed less frequently in both symptomatic (43% decrease; from 2.8 to 1.6 procedures per 100 000; $P=0.003$) and asymptomatic patients (28% decrease; from 2.8 to 2.0 procedures per 100 000; $P<0.001$; Figure 3). Interestingly, endarterectomy for asymptomatic stenosis initially increased from 2002 to the last quarter of 2006, at which point it was being performed more than twice as frequently for asymptomatic (4.1 procedures per 100 000) compared with symptomatic (2.0 procedures per 100 000) stenosis. Beginning in 2008, however, there was a rapid decline in endarterectomy for asymptomatic carotid stenosis, whereas the rate of endarterectomy for symptomatic stenosis remained relatively stable. Carotid-artery stenting, on the contrary, increased among both symptomatic (76% increase; from 0.22 to 0.39 procedures per 100 000; $P<0.001$) and asymptomatic (65% increase; from 0.17 to 0.27 procedures per 100 000; $P<0.001$) patients during the study period.

Rates of carotid revascularization by operator specialty over the study period also varied (Figure 4). Vascular surgeons most commonly performed endarterectomy, and this rate remained relatively stable between 2002 and 2014 (from 2.3 to 2.5 procedures per 100 000; $P=0.13$). The rate of carotid endarterectomy performed by general surgeons did not change significantly either ($P=0.52$), whereas cardiac surgeons and neurosurgeons performed significantly less endarterectomy (both $P<0.001$).

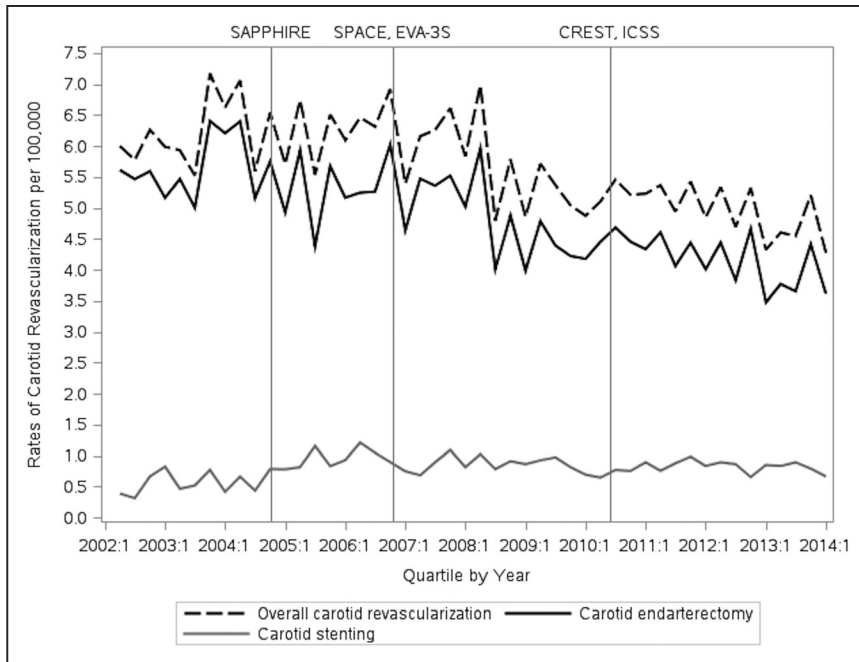


Figure 1. Trends in the rates of carotid revascularization in relation to major clinical trials. These rates (per 100 000 adults ≥ 40 years old) are reported for 3-month periods from April 1, 2002, to March 31, 2014. Vertical lines represent timing of publication of major clinical trials that may have influenced the rates of carotid endarterectomy and stenting. CREST indicates Carotid Revascularization Endarterectomy Versus Stenting Trial; EVA-3S, Endarterectomy Versus Angioplasty in Patients With Severe Symptomatic Carotid Stenosis; ICSS, International Carotid Stenting Study; SAPHIRE, Stenting and Angioplasty With Protection in Patients at High Risk for Endarterectomy; and SPACE, Stent-Supported Percutaneous Angioplasty of the Carotid Artery Versus Endarterectomy.

In fact, cardiac surgeons stopped performing carotid endarterectomy in 2009, whereas neurosurgeons were performing 64% less endarterectomy (from 1.6 to 0.6 procedures per 100 000) by the end of the study period. Neurosurgeons, however, performed nearly 4 \times more carotid-artery stenting (from 0.06 to 0.22 procedures per 100 000; $P < 0.001$), which was second only to carotid-artery stenting performed by radiologists (62% increase; from 0.28 to 0.45 procedures per 100 000; $P < 0.001$).

Discussion

In the current population-level study, we found the overall utilization of carotid revascularization has decreased by 29%

in the province of Ontario between 2002 and 2014—this was driven by a falling rate of carotid endarterectomy (36% decrease), whereas the rate of carotid-artery stenting increased by 72%. The stenting-favorable SAPHIRE trial published in 2004 appeared to be the major driver of rising rates of carotid-artery stenting, whereas SAPHIRE and subsequent conflicting trials published in 2006 (EVA-3S and SPACE) and 2010 (ICSS and CREST) were associated with declining rates of carotid endarterectomy.

Several studies have reported rising rates of carotid-artery stenting and falling rates of endarterectomy in the United States. Kim et al¹¹ recently conducted a cross-sectional analysis of over 1.3 million patients who underwent carotid

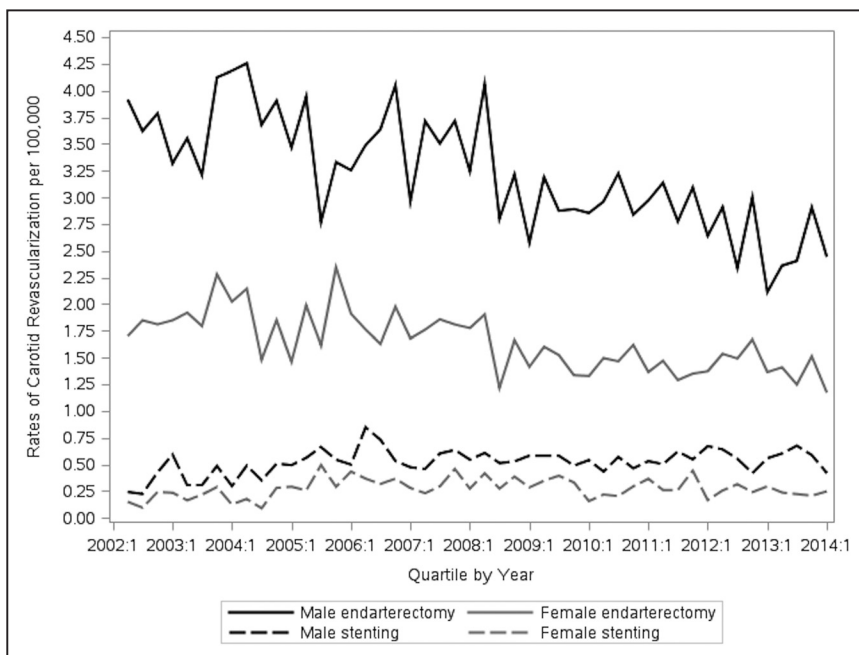


Figure 2. Sex-specific trends in the rates of carotid endarterectomy and stenting. These rates (per 100 000 adults ≥ 40 years old) are reported for 3-month periods from April 1, 2002, to March 31, 2014.

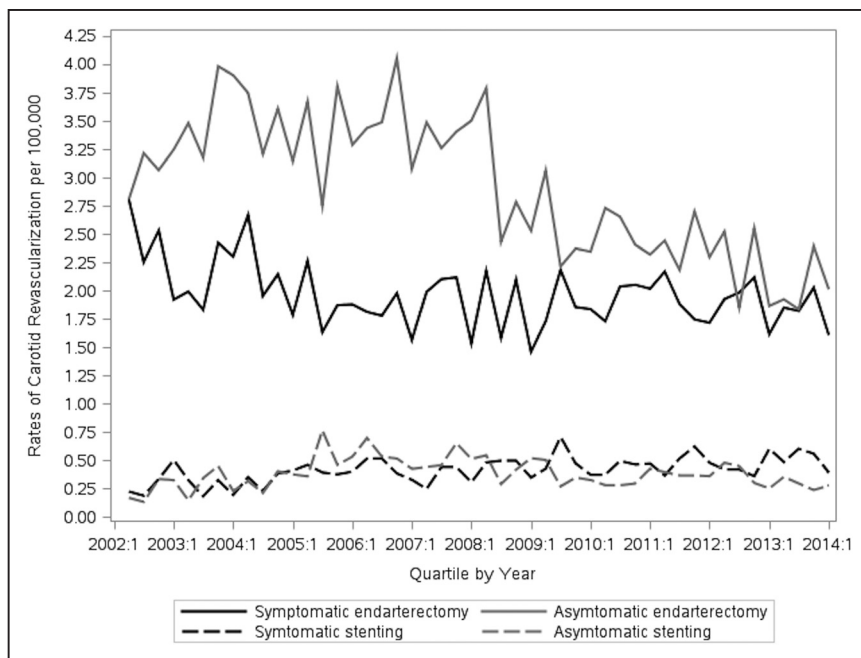


Figure 3. Trends in the rates of carotid endarterectomy and stenting by symptomatic status. These rates (per 100 000 adults ≥ 40 years old) are reported for 3-month periods from April 1, 2002, to March 31, 2014.

revascularization between 2001 and 2010 using the National Inpatient Sample. Similar to the current study, the authors reported declining rates of all carotid revascularization procedures (34% decrease) and endarterectomy (41% decrease), whereas the rate of stenting increased by 2.5-fold. The impact of clinical trial results on revascularization trends, however, was not examined in this study, and utilization rates beyond the year 2010 were also not reported. Siddiq et al⁹ used the National Inpatient Sample to identify changes in the use of carotid revascularization procedures in the years before (2009) and after (2011) publication of the CREST trial. Among 225 191 patients studied, the frequency of carotid endarterectomy and stenting did not change significantly after publication of CREST. However, a small study time period, lack of data on the impact of other clinical trials, and

inability to stratify the results based on key variables limited the conclusions that could be drawn from this study. Other similar studies conducted using either the National Inpatient Sample,^{12–15,27} Medicare data,^{8,10,16–18} or another United States database²⁸ were also limited by short study time periods or lack of longitudinal data on the effect of clinical trial publication on carotid revascularization rates.

Several factors may account for the declining rates of overall carotid revascularization and endarterectomy observed in this study. First, the incidence of ischemic stroke has decreased over the last decade,²⁹ perhaps owing to general improvements in cardiovascular risk reduction therapies, such as statins, antihypertensive agents, and antiplatelet therapies.³⁰ Second, clinicians are performing less endarterectomy for patients with asymptomatic carotid-artery stenosis in Ontario.

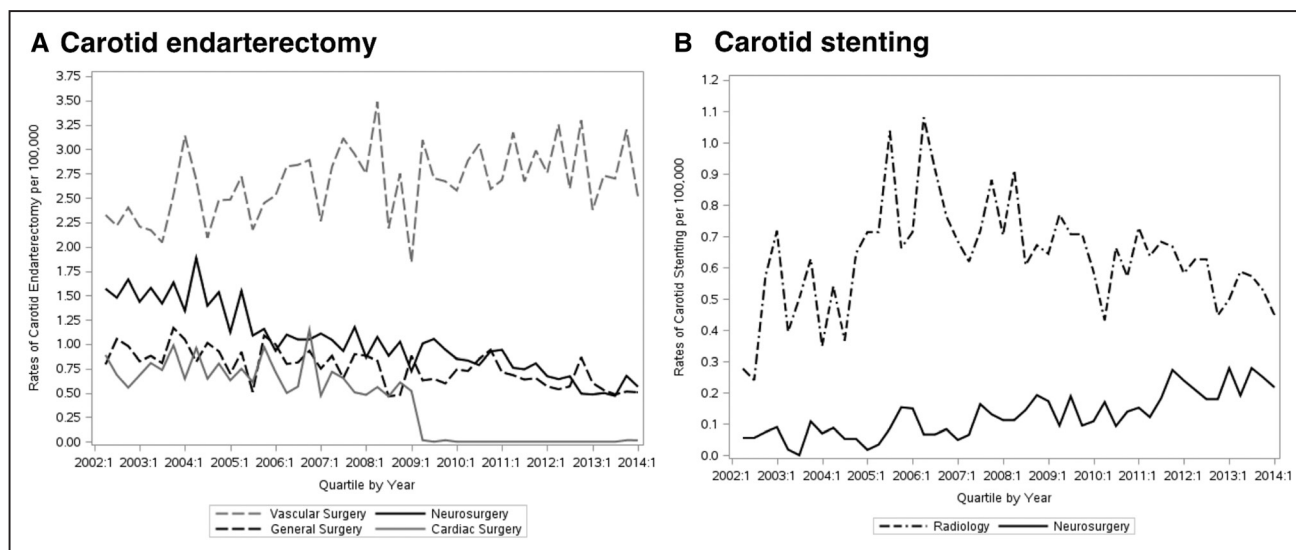


Figure 4. Operator specialty-specific rates of carotid endarterectomy (A) and stenting (B). These rates (per 100 000 adults ≥ 40 years old) are reported for 3-month periods from April 1, 2002, to March 31, 2014.

In 2006, the rate of endarterectomy for asymptomatic stenosis was 2× higher than that for symptomatic stenosis; however, by 2014, these rates were nearly identical. A shift away from routine revascularization for asymptomatic carotid-artery stenosis likely occurred during this time because of increasing evidence from both randomized trials and observational studies, suggesting a very low annual risk of ipsilateral stroke with contemporary best medical therapy.³¹ Nonetheless, ≈50% of patients continue to receive endarterectomy for asymptomatic carotid-artery stenosis in Canada. In contrast, endarterectomy for asymptomatic stenosis is much more commonly performed in the United States (90%) and Italy (69%), but less commonly in the United Kingdom (17%) and Denmark (0%).^{9,28,32} Variability in provider preference and reimbursement policies may account for these discrepancies, which questions the appropriateness of routine interventions for patients with asymptomatic carotid-artery stenosis.³³

Finally, a part of the decline in endarterectomy is likely attributable to the rise in carotid-artery stenting as an alternative revascularization strategy. We found that carotid-artery stenting uptake increased significantly immediately after publication of the stenting-favorable SAPHIRE trial in 2004, although this trial was criticized for slow recruitment, early termination, narrow inclusion criteria, enrolling <30% patients with symptomatic carotid-artery stenosis, and controversial inclusion of non-Q-wave myocardial infarctions in the primary outcome. Since 2006, stenting has remained stable in Ontario and currently accounts for ≈15% of all carotid revascularization procedures per year, which is similar to the data in United States.^{11,13} Several factors may account for the stagnant rate of stenting observed over the last decade, including variable referral patterns (patients with significant carotid-artery stenosis are most commonly referred to vascular surgeons in Ontario, who almost exclusively perform endarterectomy); reimbursement policies (Medicare only reimburses providers for carotid-artery stenting performed in high-risk patients in the United States); and because a higher risk of periprocedural stroke or death associated with stenting in recent trials such as ICSS (8.0% versus 4.2% for endarterectomy)⁶ and CREST (4.4% versus 2.3% for endarterectomy)⁷ raised caution among clinicians, thus, preventing its widespread use in clinical practice. Furthermore, carotid-artery stenting has yet to be compared with medical management in a large randomized trial—the ongoing CREST-2 trial will provide much needed data in this regard.

We also found that temporal trends in carotid revascularization varied by age. Rates of endarterectomy decreased among all age groups, except for those ≥80 years old. Accumulating high-quality evidence for the superiority of carotid endarterectomy over stenting in older patients³⁴ may account for the stable rate of endarterectomy observed in this group. It is, however, concerning to see that carotid-artery stenting increased among the 2 oldest subgroups of patients, and 41% of patients ≥75 years old treated with stenting had asymptomatic stenosis, despite a paucity of evidence for its relative safety compared with endarterectomy in the elderly population. Unfavorable anatomic and pathological factors

(increased vessel tortuosity, greater burden of atherosclerosis, and decreased plaque stability) may account for the increased stroke and death events observed with stenting in the elderly¹; therefore, clinicians need to exercise caution before offering this therapy to older patients.

With respect to operator specialty-specific rates, we found that vascular surgery is becoming the dedicated specialty to perform the majority of endarterectomy procedures in Ontario. Cardiac surgeons essentially stopped performing endarterectomy in 2009, likely because there were a handful of broadly trained cardiovascular surgeons who performed this procedure who either narrowed their focus or retired. A small number of general surgeons continue to perform endarterectomy—these are likely general surgeons with formal training in vascular surgery who use their general surgery certification for the purposes of billing. Neurosurgeons are moving away from endarterectomy and toward performing more carotid-artery stenting, whereas radiologists perform the majority (≈80%) of stenting procedures in Ontario. These rates differ than those from the United States, where intervention cardiologists (49%), surgeons (36%), and radiologists (15%) most commonly perform carotid-artery stenting procedures,⁸ whereas vascular surgeons (40%), cardiothoracic surgeons (29%), and general surgeons (29%) perform endarterectomy.¹⁰

Our study has some limitations. First, like all population-based studies, inaccurate coding could have confounded our results. To mitigate this risk, we used procedure codes that have been previously validated.¹⁹ Second, our databases did not specify if prior neurological events occurred on the ipsilateral or contralateral side of the carotid revascularization procedure—this may overestimate the actual number of patients with symptomatic carotid-artery stenosis because patients with prior contralateral strokes may have been incorrectly captured as symptomatic patients. Third, the temporal trends in carotid revascularization we report are limited to the province of Ontario, and these findings may not be generalizable to other settings. However, this also highlights the novelty of our study because direct comparisons of our results to those from different healthcare models (such as the United States) will help improve our understanding of how new knowledge from clinical trials has translated into practice across diverse health systems. Finally, our study time frame was limited from 2002 to 2014; effects of clinical trial publications before 2002 and beyond 2014 were not studied. Three additional major carotid revascularization trial results have since been published: 5-year results of the ICSS trial³⁵; 10-year results on the CREST trial³⁶; and initial results of the Asymptomatic Carotid Trial I.³⁷ All 3 of these trials showed either no significant differences in the rates of primary outcomes after carotid endarterectomy and stenting or noninferiority of stenting. Therefore, future carotid revascularization trends may further change, given accumulating evidence for the safety of carotid-artery stenting.

Summary

The current Ontario study demonstrated that overall carotid revascularization has decreased between 2002 and 2014, owing largely to a fall in endarterectomy. Utilization of

carotid-artery stenting, on the contrary, has risen since publication of the stenting-favorable SAPHIRE trial in 2004; subsequent major trial publications did not impact rates of stenting but were associated with declining rates of endarterectomy. Clinical practice seems to have closely followed evidence in some areas (such as declining rates of routine endarterectomy for asymptomatic carotid-artery stenosis), whereas other areas for improvement in knowledge translation remain (such as increased rates of carotid-artery stenting among the elderly). Our findings emphasize the importance for research that describes how knowledge has translated from research into clinical practice—this is particularly important in settings where findings from high-quality clinical trials are contradictory because the potential influence on physician practices is uncertain.

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Disclosures

None.

References

- Hussain MA, Verma S, Gupta N, Al-Orman M. Carotid artery revascularization: what's the best strategy? *Circulation*. 2015;131:2226–2231. doi: 10.1161/CIRCULATIONAHA.114.013017.
- Tu JV, Hannan EL, Anderson GM, Iron K, Wu K, Vranizan K, et al. The fall and rise of carotid endarterectomy in the United States and Canada. *N Engl J Med*. 1998;339:1441–1447. doi: 10.1056/NEJM199811123392006.
- Yadav JS, Wholey MH, Kuntz RE, Fayad P, Katzen BT, Mishkel GJ, et al; Stenting and Angioplasty With Protection in Patients at High Risk for Endarterectomy Investigators. Protected carotid-artery stenting versus endarterectomy in high-risk patients. *N Engl J Med*. 2004;351:1493–1501. doi: 10.1056/NEJMoa040127.
- Mas JL, Chatellier G, Beyssen B, Branchereau A, Moulin T, Becquemin JP, et al; EVA-3S Investigators. Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis. *N Engl J Med*. 2006;355:1660–1671. doi: 10.1056/NEJMoa061752.
- Ringleb PA, Allenberg J, Brückmann H, Eckstein HH, Fraedrich G, Hartmann M, et al; SPACE Collaborative Group. 30 day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomised non-inferiority trial. *Lancet*. 2006;368:1239–1247. doi: 10.1016/S0140-6736(06)9122-8.
- Carotid Stenting Trialists' Collaboration; Bonati LH, Dobson J, Algra A, Branchereau A, Chatellier G, Fraedrich G, et al. Short-term outcome after stenting versus endarterectomy for symptomatic carotid stenosis: a preplanned meta-analysis of individual patient data. *Lancet*. 2010;376:1062–1073. doi: 10.1016/S0140-6736(10)61009-4.
- Brott TG, Hobson RW 2nd, Howard G, Roubin GS, Clark WM, Brooks W, et al; CREST Investigators. Stenting versus endarterectomy for treatment of carotid-artery stenosis. *N Engl J Med*. 2010;363:11–23. doi: 10.1056/NEJMoa0912321.
- Wallaert JB, Nolan BW, Stone DH, Powell RJ, Brown JR, Cronenwett JL, et al. Physician specialty and variation in carotid revascularization

- technique selected for Medicare patients. *J Vasc Surg*. 2016;63:89–97. doi: 10.1016/j.jvs.2015.08.068.
- Siddiq F, Adil MM, Malik AA, Qureshi MH, Qureshi AI. Effect of Carotid Revascularization Endarterectomy Versus Stenting Trial results on the performance of carotid artery stent placement and carotid endarterectomy in the United States. *Neurosurgery*. 2015;77:726–732, discussion 732. doi: 10.1227/NEU.0000000000000905.
- Kumamaru H, Jalbert JJ, Nguyen LL, Gerhard-Herman MD, Williams LA, Chen CY, et al. Surgeon case volume and 30-day mortality after carotid endarterectomy among contemporary medicare beneficiaries: before and after national coverage determination for carotid artery stenting. *Stroke*. 2015;46:1288–1294. doi: 10.1161/STROKEAHA.114.006276.
- Kim LK, Yang DC, Swaminathan RV, Minutello RM, Okin PM, Lee MK, et al. Comparison of trends and outcomes of carotid artery stenting and endarterectomy in the United States, 2001 to 2010. *Circ Cardiovasc Interv*. 2014;7:692–700. doi: 10.1161/CIRCINTERVENTIONS.113.001338.
- Choi JH, Pile-Spellman J, Brisman JL. US nationwide trends in carotid revascularization: hospital outcome and predictors of outcome from 1998 to 2007. *Acta Neurol Scand*. 2014;129:85–93. doi: 10.1111/ane.12163.
- Dumont TM, Rughani AI. National trends in carotid artery revascularization surgery. *J Neurosurg*. 2012;116:1251–1257. doi: 10.3171/2012.3.JNS111320.
- Skerritt MR, Block RC, Pearson TA, Young KC. Carotid endarterectomy and carotid artery stenting utilization trends over time. *BMC Neurol*. 2012;12:17. doi: 10.1186/1471-2377-12-17.
- Eslami MH, McPhee JT, Simons JP, Schanzer A, Messina LM. National trends in utilization and postprocedure outcomes for carotid artery revascularization 2005 to 2007. *J Vasc Surg*. 2011;53:307–315. doi: 10.1016/j.jvs.2010.08.080.
- Goodney PP, Travis LL, Malenka D, Bronner KK, Lucas FL, Cronenwett JL, et al. Regional variation in carotid artery stenting and endarterectomy in the Medicare population. *Circ Cardiovasc Qual Outcomes*. 2010;3:15–24. doi: 10.1161/CIRCOUTCOMES.109.864736.
- Patel MR, Greiner MA, DiMartino LD, Schulman KA, Duncan PW, Matchar DB, et al. Geographic variation in carotid revascularization among Medicare beneficiaries, 2003–2006. *Arch Intern Med*. 2010;170:1218–1225. doi: 10.1001/archinternmed.2010.194.
- Goodney PP, Lucas FL, Travis LL, Likosky DS, Malenka DJ, Fisher ES. Changes in the use of carotid revascularization among the medicare population. *Arch Surg*. 2008;143:170–173. doi: 10.1001/archsurg.2007.43.
- Hussain MA, Mamdani M, Saposnik G, Tu JV, Turkel-Parrella D, Spears J, et al. Validation of carotid artery revascularization coding in Ontario Health Administrative Databases. *Clin Invest Med*. 2016;39:E73–E78.
- Kokotailo RA, Hill MD. Coding of stroke and stroke risk factors using international classification of diseases, revisions 9 and 10. *Stroke*. 2005;36:1776–1781. doi: 10.1161/01.STR.0000174293.17959.a1.
- Juurlink DN, Mamdani MM, Lee DS, Kopp A, Austin PC, Laupacis A, et al. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. *N Engl J Med*. 2004;351:543–551. doi: 10.1056/NEJMoa040135.
- Crabtree BF, Ray SC, Schmidt PM, O'Connor PJ, Schmidt DD. The individual over time: time series applications in health care research. *J Clin Epidemiol*. 1990;43:241–260.
- Helffenstein U. Box-Jenkins modelling in medical research. *Stat Methods Med Res*. 1996;5:3–22.
- Gardner ES. Exponential smoothing: the state of the art. *J Forecast*. 1985;4:1–28.
- Dickey DA, Fuller WA. Distribution of the estimators for autoregressive time series with a unit root. *J Am Stat Assoc*. 1979;74:427–431.
- Ljung GM, Box GEP. On a measure of lack of fit in time-series models. *Biometrika*. 1978;65:297–303.
- Eslami MH, Rybin DV, Doros G, Farber A. The association of publication of Center for Medicaid and Medicare Services Guidelines for Carotid Artery Angioplasty and Stenting (CAS) and CREST results on the utilization of CAS in carotid revascularization. *Ann Vasc Surg*. 2015;29:1606–1613. doi: 10.1016/j.avsg.2015.06.091.
- McDonald JS, McDonald RJ, Fan J, Lanzino G, Kallmes DF, Cloft HJ. Effect of CREST findings on carotid revascularization practice in the United States. *J Stroke Cerebrovasc Dis*. 2015;24:1390–1396. doi: 10.1016/j.jstrokecerebrovasdis.2015.02.020.
- Writing Group Members; Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart disease and stroke statistics—2016 update: a report from the American Heart Association. *Circulation*. 2016;133:e38–e60. doi: 10.1161/CIR.0000000000000350.

30. Fang MC, Coca Perrillon M, Ghosh K, Cutler DM, Rosen AB. Trends in stroke rates, risk, and outcomes in the United States, 1988 to 2008. *Am J Med.* 2014;127:608–615. doi: 10.1016/j.amjmed.2014.03.017.
31. Naylor AR. Time to rethink management strategies in asymptomatic carotid artery disease. *Nat Rev Cardiol.* 2011;9:116–124. doi: 10.1038/nrcardio.2011.151.
32. Vikatmaa P, Mitchell D, Jensen LP, Beiles B, Björck M, Halbakken E, et al. Variation in clinical practice in carotid surgery in nine countries 2005–2010. Lessons from VASCUNET and recommendations for the future of national clinical audit. *Eur J Vasc Endovasc Surg.* 2012;44:11–17. doi: 10.1016/j.ejvs.2012.04.013.
33. Spence JD, Naylor AR. Endarterectomy, stenting, or neither for asymptomatic carotid-artery stenosis. *N Engl J Med.* 2016;374:1087–1088. doi: 10.1056/NEJMe1600123.
34. Howard G, Roubin GS, Jansen O, Hendrikse J, Halliday A, Fraedrich G, et al; Carotid Stenting Trialists' Collaboration. Association between age and risk of stroke or death from carotid endarterectomy and carotid stenting: a meta-analysis of pooled patient data from four randomised trials. *Lancet.* 2016;387:1305–1311. doi: 10.1016/S0140-6736(15)01309-4.
35. Bonati LH, Dobson J, Featherstone RL, Ederle J, van der Worp HB, de Borst GJ, et al; International Carotid Stenting Study Investigators. Long-term outcomes after stenting versus endarterectomy for treatment of symptomatic carotid stenosis: the International Carotid Stenting Study (ICSS) randomised trial. *Lancet.* 2015;385:529–538. doi: 10.1016/S0140-6736(14)61184-3.
36. Brott TG, Howard G, Roubin GS, Meschia JF, Mackey A, Brooks W, et al; CREST Investigators. Long-term results of stenting versus endarterectomy for carotid-artery stenosis. *N Engl J Med.* 2016;374:1021–1031. doi: 10.1056/NEJMoa1505215.
37. Rosenfield K, Matsumura JS, Chaturvedi S, Riles T, Ansel GM, Metzger DC, et al; ACT I Investigators. Randomized trial of stent versus surgery for asymptomatic carotid stenosis. *N Engl J Med.* 2016;374:1011–1020. doi: 10.1056/NEJMoa1515706.