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Medical (Nonsurgical) Intervention Alone Is Now Best for Prevention of Stroke Associated With Asymptomatic Severe Carotid Stenosis

Results of a Systematic Review and Analysis

Anne L. Abbott, PhD, MBBS, FRACP

Abstract—Significant advances in vascular disease medical intervention since large randomized trials for asymptomatic severe carotid stenosis were conducted (1983–2003) have prompted doubt over current expectations of a surgical benefit. In this systematic review and analysis of published data it was found that rates of ipsilateral and any-territory stroke (+/– TIA), with medical intervention alone, have fallen significantly since the mid-1980s, with recent estimates overlapping those of operated patients in randomized trials. However, current medical intervention alone was estimated at least 3 to 8 times more cost-effective. In conclusion, current vascular disease medical intervention alone is now best for stroke prevention associated with asymptomatic severe carotid stenosis given this new evidence, other cardiovascular benefits, and because high-risk patients who benefit from additional carotid surgery or angioplasty/stenting cannot be identified. (*Stroke*. 2009;40:e573-e583.)

Key Words: asymptomatic carotid stenosis ■ carotid endarterectomy ■ endovascular treatment ■ health policy
■ stroke prevention

The best intervention is prevention and the best prevention is noninvasive.

Asymptomatic severe carotid stenosis generally means atherosclerotic narrowing of the proximal internal carotid artery (ICA) exceeding $\approx 50\%$ to 60% in the absence of previous referable symptoms of stroke or transient ischemic attack (TIA). This lesion, at least in Westernized communities, becomes increasingly prevalent from the fifth decade, affecting $\approx 10\%$ of those aged over 80 years.¹ It accounts for $\approx 12\%$ to 21% of all anterior circulation ischemic strokes,¹ ≈ 2 to 3 times higher than the risk for less severe asymptomatic stenosis.^{2,3}

In many countries surgery (or carotid endarterectomy [CEA]) for asymptomatic severe carotid stenosis is supported by best practice guidelines^{4–6} and commonly recommended⁷ or performed^{8,9} to prevent stroke. This is largely because of the results of 3 major randomized surgical trials: the Veterans' Affairs Cooperative Study (VACS),¹⁰ the Asymptomatic Carotid Atherosclerosis Study (ACAS),¹¹ and the Asymptomatic Carotid Surgery Trial (ACST)¹² conducted 1983 to 2003.

Despite differing primary outcome measures, there was an overall reduction of $\approx 1\%$ in average annual absolute stroke risk among patients who received CEA plus medical intervention.¹³ However, for decades this expensive approach has been questioned because the estimated surgical benefit was marginal and highly dependent on patient selection, nature of the medical and surgical interventions used, and reporting methods.¹ Further, nonoperated patients with higher than average stroke risk who particularly benefit from CEA cannot be identified.¹⁴ Now carotid angioplasty/stenting, with higher procedural costs¹⁵ and similar major complication rates (at least for symptomatic patients¹⁶) is being proposed as the best prophylactic intervention¹⁷ without even randomized trial evidence of efficacy.

Vascular disease medical intervention is the combination of noninvasive strategies to avoid or minimize the impact of vascular disease, includes ongoing diagnosis, education, support of healthy lifestyle practices, and drugs. The first reliable measures of stroke rate associated with asymptomatic severe carotid stenosis managed with medical intervention alone

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date back to the early-1980s when carotid duplex made direct detection relatively cheap and noninvasive. Since then, there have been major improvements in understanding of vascular disease. However, there has been no systematic analysis of reported stroke rate associated with isolated medical management of this lesion accounting for study size, quality and date of publication. This systematic review and analysis was performed to address this problem with three specific goals:

1. To investigate temporal changes in reported stroke (+/-TIA) rate and baseline characteristics among patients with asymptomatic severe carotid stenosis receiving medical intervention alone.
2. To compare the above stroke (+/-TIA) rates with those of patients who received CEA in major randomized surgical trials.
3. To compare stroke prevention cost-effectiveness of current medical intervention alone with medical intervention and CEA as employed in major randomized surgical trials.

Method

Literature Search

A Medline literature search was performed for prospective studies of direct imaging identified nonoperated, angioplasty/stenting-free, asymptomatic severe (nonsubcategorized 50% to 75%+) proximal ICA stenosis with sufficient original data to calculate an average annual patient rate of stroke (fatal/nonfatal, infarct/hemorrhage). To allow meaningful rate comparison, additional requirements were inclusion of >100 patients eligible at baseline and <25% receiving instrumental intervention (CEA, angioplasty/stenting) for the still asymptomatic study artery during follow-up. Follow-up had to be continual from baseline with inclusion of only the first event of interest/patient in rate calculations. When more than one publication was identified referring to the same data, the first publication was selected. Data clarification was sought from authors if necessary.

"Asymptomatic" was defined as the absence of any previous symptoms of ipsilateral stroke or TIA and included patients with previous contralateral or vertebrobasilar stroke or TIA or clinically silent imaging-identified stroke. Search was conducted using Ovid and PubMed software using the following combinations of terms: asymptomatic/unoperated or nonoperated carotid stenosis/plaque/disease/atherosclerosis or narrowing; asymptomatic extracranial disease; asymptomatic cervical/carotid or neck bruit and neck bruit.

Rate Calculation and Statistical Analysis

Average annual ipsilateral and any-territory stroke (+/-TIA) rates were calculated and analyzed separately from raw data (event number, sample size, mean/median follow-up since baseline) and Kaplan-Meier (KM) risk estimates. Rates excluded angiographic risk. Baseline vascular risk factors investigated were age, sex, current smoking, ever (past or present) smoking, and diagnosis of hypertension, hypercholesterolemia, coronary heart disease, atrial fibrillation, diabetes mellitus, peripheral vascular disease (PVD), and previous nonipsilateral stroke/TIA. Variation in outcome and risk factor definition was noted. Baseline use of antiplatelet, hypertensive, and lipid-lowering agents was also investigated.

Temporal changes in stroke/TIA rates and baseline characteristics were sought using ordinary least squares linear regression analysis, weighted according to sample sizes¹⁸ (SYSTAT 12, Systat Software Inc). The regression model was:

$$\text{Rate (dependent variable [or } y]) = a + b (\text{publication date [or } x])$$

where a = Y intercept, b = slope of regression. In regression analyses, 1980 was taken as Time=0, as reflected in Y intercepts. Regression lines were characterized by the probability Pb that in the real

population the slope was zero; by Pa (the probability that $a=0$ when $x=0$) and by r^2 (a measure of degree of linear "correlation" between variables x and y) where " r " is the Pearson product-moment correlation coefficient. Further, the Ryan-Holm stepdown Bonferroni procedure for multiple comparisons¹⁹ was used to correct for multiple hypothesis testing, so converting raw probability values into P' values. $P' < 0.05$ and $r^2 > 0.20$ were considered statistically significant. 95% confidence limits (for population event rate regression lines) and 95% prediction limits (for new population stroke +/-TIA rate estimates) were calculated.²⁰

It was hypothesized that stroke/TIA rates and prevalence of baseline characteristics may be higher when derived from hospital-rather than community-based studies or when patients with known nonipsilateral carotid sources of cerebral embolism (such as atrial fibrillation, prosthetic heart valves) were included. Therefore, separate regression analyses were performed for these patient selection criteria.

Comparison of Event Rates According to Intervention Used

Reported average annual event rates of patients receiving medical intervention alone were compared with rates of operated patients from the major randomized surgical trials. Randomized trial results were selected if a statistically significant surgical benefit had been reported for the particular outcome measure. Such a result was reported only from ACAS for ipsilateral stroke, only from ACST for any-territory stroke, only from VACS for any-territory stroke/TIA, and from ACAS and VACS for ipsilateral stroke/TIA.¹⁰⁻¹² Randomized trial event rates included perioperative stroke/death in ACAS and ACST and only perioperative stroke/TIA in VACS. Therefore, ACAS was selected for comparison of ipsilateral stroke/TIA rate.

Cost-Effectiveness of Medical Intervention Alone

A conservative estimate was made of cost/stroke (+/-TIA) prevented with current medical intervention alone using temporal changes in reported event rates. Comparison was made with a previously published cost-effective analysis of medical intervention and CEA as used in major randomized surgical trials.¹

Results

Studies Identified

Sixty-seven publications were identified allowing calculation of average annual stroke rates with respect to direct-imaging-identified asymptomatic severe (>50%) carotid stenosis. However, 56 were excluded because at least one other search criteria (listed above) was not met.^{12,21-75} Of the 11 remaining studies, 10 were hospital^{2,3,10,11,76-81} and 1 community-based.⁸² The major results below are presented, first, with respect to all 11 selected studies (when data were available) and then the 10 hospital-based studies in isolation. Community-based event rates were only available for ipsilateral and any-territory stroke. Data extraction from 4 studies^{10,79,81,82} involved author personal communication (Hobson, 2006; Nicolaides, 2006, 2008; Groessens, 2007; Longstreth and O'Meara, 2008).

Patients from the 11 selected studies were recruited from Europe,^{77,79,81} the United States,^{3,10,11,76} Canada,^{2,3,11,78} and Australia.^{79,80} Patients were allocated medical intervention alone within an observational cohort study^{2,76,78-82} or randomized trial of CEA for ipsilateral asymptomatic^{10,11} or contralateral symptomatic^{3,77} carotid stenosis. Sample sizes varied from 113 to 1115 and involved 3724 patients in total (overall mean age approximately 66 years, 61% male; mean age of the 3539 hospital-based patients approximately 64

Table 1. Average Annual Stroke +/-TIA Rates of Patients With Asymptomatic Severe (>50%) Carotid Stenosis Managed With Medical Intervention Alone (%)*

Study	Sample Size	Ipsilateral Stroke		Ipsilateral Stroke/TIA		Any Territory Stroke		Any Territory Stroke/TIA	
		Raw Data	KM Estimates	Raw Data	KM Estimates	Raw Data	KM Estimates	Raw Data	KM Estimates
Johnson, 1985 ⁷⁶	121	3.3	...	19.0
Toronto, 1986 ²	113	0	...	7.9 (all TIA)	...	1.9	...	10.7	11.0
VACS, 1993 ¹⁰	233	2.4	...	5.2	...	3.0	...	6.1	...
ACAS, 1995 ¹¹	834	2.3	2.2	4.5	3.8	3.8	3.5
ECST, 1995 ⁷⁷	127	2.3	1.9
ACBS, 1997 ⁷⁸	357	1.2	1.4	3.4	4.2	2.1	2.5	5.8	...
CHS, 1998 ⁸²	185	1.3	1.0	2.6	2.3
NASCET, 2000 ³	216	...	3.2
ACSRS, 2005 ⁷⁹	1115	1.3	1.7	3.1	3.4	...	2.1	...	4.1
ASED, 2005 ⁸⁰	202	1.2	1.0	3.2	3.1	2.4	2.2	5.6	5.1
SMART, 2007 ⁸¹	221	0.6	0.7

*ACAS indicates Asymptomatic Carotid Atherosclerosis Study; ECST, European Carotid Surgery Trial; ACBS, Asymptomatic Cervical Bruit Study; NASCET, North American Symptomatic Carotid Endarterectomy Trial; ACSRS, Asymptomatic Carotid Stenosis and Risk of Stroke Study; ASED, Asymptomatic Stenosis Embolus Detection Study; SMART, Second Manifestations of ARterial disease Study.

years, 62% male; mean age of the 185 community-based patients 73 years, 46% male). Patients with known nonipsilateral carotid sources of cerebral embolism were excluded from four studies, all published since 1995,^{3,77,78,80} and also censored from one.⁸⁰ Where stated, recruitment started and finished, respectively, about 4 to 11^{3,10,11,76–82} and 2 to 6^{3,10,11,76–78,80} years before publication.

Stenosis was measured by conventional angiography,^{3,10} 77 carotid duplex,^{2,76,78–82} or both¹¹ using NACSET criteria for >50% to 75% stenosis^{3,10,11,78,80–82} or comparable criteria,^{2,76,77,79} except for 194 ACSRS study⁷⁹ patients with 50% to 69% stenosis by European Carotid Surgery Trial (ECST) criteria (about 12% to 49% stenosis by North American Symptomatic Carotid Endarterectomy Trial [NASCET] criteria⁷⁹). In some studies asymptomatic occlusion was included as asymptomatic severe carotid stenosis,^{2,76,78,81} making up (where stated) 10% to 23% of patients.^{78,81} In other studies such occlusions were excluded.^{3,10,11,77,79,80,82} In some studies all ipsilateral strokes were ischemic^{2,80} and only specifically carotid territory in two.^{77,80} Where defined, stroke and TIA generally consisted of focal neurological deficits of presumed vascular origin differentiated by 24 hours,^{2,3,10,11,78–80,82} although in one case stroke was defined as lasting >7 days.⁷⁷ TIA, where applicable, specifically included amaurosis fugax in some studies^{2,10,78,79} (raw data rates),⁸⁰ and also retinal infarction in one.⁸⁰ The proportion of patients with still asymptomatic severe carotid stenosis who received CEA during follow-up (where stated) varied from 5% to 13%.^{77,79,83} CEA related stroke was excluded from some studies^{2,3,78–80,82} and included in others, particularly in ECST where this comprised 46% of strokes.⁷⁷

Changes in Stroke and TIA Rates

Average annual stroke (+/-TIA) rates calculated using raw data and KM estimates are given in Table 1. At least 1 raw data-derived rate was available from all except 1 study.³ At least 1 KM-derived rate was available from all except 3 studies.^{10,76,81} In 2 cases (for “ipsilateral stroke” in ACAS¹¹

and “any-territory stroke/TIA” in the Toronto Study²) more than 1 KM-derived rate/study could be used in a regression analysis. In the first case, the KM-derived rate of 3.2% (all causes of stroke) was used being more comparable with other studies. In the second case, the KM-derived rate of 11.0% (derived from the 2-year risk estimate) was used, being more closely related to the actual mean patient follow-up interval (1.9 years). Absolute differences in rates derived from these 2 methods ranged from 0.1% to 0.8% and were higher when derived from raw data in all except 2 studies.^{78,79} Raw data-derived rates were more readily available (28 versus 19 total rates), involved less variability in mean follow-up duration (1.9 to 4.5 versus 3.0 to 7.0 years), and allowed rate comparison over longer time intervals (20 to 22 versus 10 to 19 years). Therefore, raw-data-derived rates are emphasized and presented first.

Raw data-derived event rates for patients allocated medical intervention alone were plotted by publication year and given with statistical results in Figure 1. Mean follow-up was used in rate calculations except for ACAS,¹¹ where only median (2.7 years) was available. Considering all 11 studies, there were statistically significant falls in reported rates of ipsilateral stroke (1.4% from 1985 to 2007), ipsilateral stroke/TIA (7.0% from 1985 to 2005), any-territory stroke (2.3% from 1986 to 2007), and any-territory stroke/TIA (4.2% from 1986 to 2005, P' for slope <0.0012, r^2 >0.200 in each case). Where applicable, falls were amplified when the only community-based study⁸² was excluded (1.5% fall in ipsilateral stroke rate from 1985 to 2007, $y=2.86-0.0643x$, P' for slope <0.0012, $r^2=0.322$; 3.2% fall in any-territory stroke rate from 1986 to 2007, $y=4.63-0.1080x$, P' for slope <0.0012, $r^2=0.307$). Among hospital-based studies, exclusion of 194 ACSRS patients with 50% to 69% stenosis (ECST criteria)⁷⁹ made no significant difference (ipsilateral stroke; $2.75-0.056x$, P' for slope <0.0012, $r^2=0.245$; ipsilateral stroke/TIA $y=11.17-0.352x$, P' for slope <0.0012, $r^2=0.455$).

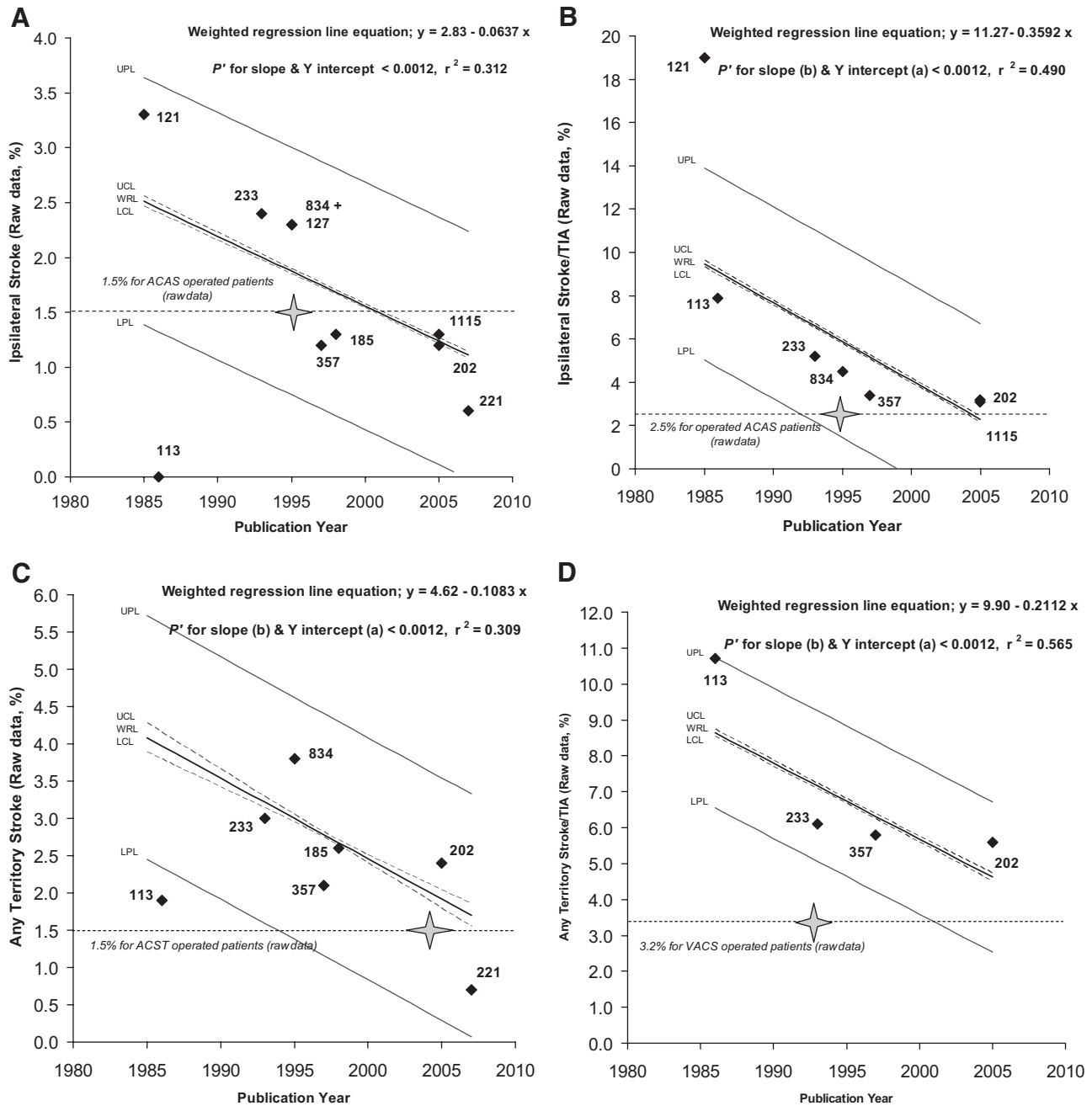


Figure 1. Reported average annual stroke (+/-TIA) rates with medical intervention alone by publication year, sample sizes, and statistical results. UPL and LPL, respectively, indicate upper and lower 95% prediction limits for new population rate estimates; UCL and LCL (dashed lines), respectively, upper and lower 95% confidence limits for the population regression line; WRL, weighted regression line; ACAS, Asymptomatic Carotid Atherosclerosis Study¹¹; ACST, Asymptomatic Carotid Surgery Trial¹²; VACS, Veterans Affairs Cooperative Study.¹⁰ A, Ipsilateral Stroke; Rates from 9 hospital^{2,10,11,76-81} and 1 community-based study⁸² compared with ACAS operated patients. B, Ipsilateral Stroke/TIA; Rates from 7 hospital-based studies^{2,10,11,76,78-80} compared with ACAS operated patients. C, Any-territory Stroke; Rates from 6 hospital^{2,10,11,78,80,81} and 1 community-based study⁸² compared with ACST operated patients. D, Any-territory Stroke/TIA; Rates from 4 hospital-based studies^{10,76,78,80} compared with VACS operated patients.

Again, considering only hospital-based studies, event rate falls were not significantly different when 4 recent studies excluding patients with known nonipsilateral carotid sources of cerebral embolism^{3,77,78,80} were removed from weighted regression analysis of ipsilateral stroke (1.4% fall from 1985 to 2007, $y = 2.95 - 0.0658x$, P' for slope < 0.0012 , $r^2 = 0.343$), ipsilateral stroke/TIA (7.5% fall from 1985 to 2005, $y = 11.83 - 0.3798x$, P' for slope

< 0.0012 , $r^2 = 0.521$), and any-territory stroke (2.5% fall from 1986 to 2007, $y = 4.96 - 0.1224x$, P' for slope < 0.0012 , $r^2 = 0.334$). There were insufficient rates for isolated analysis of any-territory stroke/TIA among these 6 hospital-based studies with known nonipsilateral carotid cerebral embolic sources.

Figure 1 also shows rates of the corresponding outcome measure for operated patients from the major randomized

Table 2. Baseline Characteristics of Patients With Asymptomatic Severe (>50%) Carotid Stenosis Managed With Medical Intervention Alone (%)^{*†}

	Johnson ⁷⁶	Toronto ²	VACS ¹⁰	ACAS ¹¹	ECST ⁷⁷	ACBS ⁷⁸	CHS ⁸²	NASCET ³	ACSRS ⁷⁹	ASED ⁸⁰	SMART ⁸¹
Male	...	60	100	66	71	40‡	46	68	61	68	73
Mean age, y	...	67	65	67‡	64	65‡	73.3	66	70	74	65
Current Smoker	49	24	50	35‡	18	33	18	14	42
Ever smoker	...	77	91	61	...	71	73	90
Hypertension	...	66	64	64	50‡	47‡	71	60	63	72	...
Ischemic heart disease	...	77	57	69	33	39‡	38	36	34	52	59
High cholesterol	...	32	50‡	...	32‡	60	67	...
Diabetes	...	14	27	21	14	20‡	26	22	21	17	21
Atrial arrhythmia	14	0	4	0	3	0	...
PVD	...	70	59	...	24	23‡	8	15‡	40	33	45
Nonipsilateral stroke/TIA	0	0	33	27	100	0	0	100	20	42	0
Antiplatelet therapy†	0	≤51	100*	100*	56‡	50	about 0	95%‡	84	88	63
Antilipid therapy	10	...	25	75D	45
Antihypertension therapy	62	...	60	77D	63
Other known embolic sources excluded	no	no	no	no	yes	yes	no	yes	no	yes	no

*See Table 1 for abbreviations.

†Proportion applies at baseline unless indicated with D-meaning at least for some time during follow-up.

‡Proportion applies to a larger sample from which patients with >50% stenosis were selected (without statistical comparisons).

surgical trials. To facilitate comparison, surgical event rates were also calculated from raw data. For patients allocated medical intervention alone, average annual ipsilateral stroke rates fell below those of ACAS operated patients¹¹ from 2001, and average annual ipsilateral stroke/TIA rates matched those of ACAS operated patients by 2005. In addition, among patients allocated medical intervention alone, average annual any-territory stroke and any-territory stroke/TIA rates, respectively, closely approximated those of ACST operated patients¹² by 2007 and VACS operated patients¹⁰ by 2005. Further, 95% confidence limits for regression lines were tight. 95% prediction limits indicated loss of a statistically significant surgical advantage by the mid-1980s for ipsilateral stroke, the early-1990s for ipsilateral stroke/TIA, the mid-1990s for any-territory stroke, and by 2001 for any-territory stroke/TIA.

In a separate weighted regression analysis of event rates derived only from KM risk estimates, significant falls were again measured in average annual rate of ipsilateral stroke/TIA (0.6% from 1995 to 2005, $y=4.76-0.0566x$, P' for slope <0.0012 , $r^2=0.680$), any-territory stroke (1.1% from 1995 to 2005, $y=5.00-0.1174x$, P' for slope <0.0012 , $r^2=0.785$) and any-territory stroke/TIA (6.7% from 1986 to 2005, $y=13.13-0.3551x$, P' for slope <0.0012 , $r^2=0.965$). The fall in ipsilateral stroke rate was also significant (0.4% fall from 1995 to 2005, $y=2.62x-0.0391x$, P' for slope <0.0012). However, the weighted regression accounted for $<20\%$ of total variance ($r^2=0.107$). These results were not significantly different when the only community-based study was excluded. There were insufficient KM estimates for isolated analyses of stroke/TIA rates from the 6 hospital-based studies which included patients with known nonipsilateral carotid cerebral embolic sources.

Changes in Baseline Vascular Disease Risk Factors

Where available, prevalence of baseline risk factors of patients receiving medical intervention alone is given in Table 2. In 4/10 hospital-based studies some^{3,11,77} or most⁷⁸ baseline proportions refer to a larger sample from which patients were selected, without statistical comparisons. Results of weighted regression analyses and rate changes appear in Table 3. Considering all 11 studies, there was a significant 5.5-year increase in mean patient age and a 32% increase in the proportion of patients classified hypercholesterolemic. There were also significant falls in the proportion of current smokers (14%), patients with a history of ischemic heart disease (36%), and atrial fibrillation (5.5%). Falls were noted in baseline proportion of males, ever smokers, and those with PVD and an increase in baseline diagnosis of hypertension ($P' < 0.01$ in each case), although the regression accounted for $<20\%$ of total variance ($r^2 < 0.2$ in each case). Baseline proportions for diabetes and previous nonipsilateral stroke/TIA were unchanged.

When hospital-based data underwent separate weighted regression analyses, the above significant changes in baseline risk factors remained (P' for slope <0.01) and were amplified in the case of age (6% increase, $y=62.3+0.275x$, $r^2=0.349$), hypertension (5% increase, $y=57.3+0.220x$, $r^2=0.035$), ischemic heart disease (37% decrease, $y=83.8-1.776x$, $r^2=0.403$), current smokers (15% decrease, $y=48.4-1.054x$, $r^2=0.233$), ever smokers (12% decrease, $y=89.1-0.568x$, $r^2=0.166$), male sex (8% decrease, $y=71.8-0.361x$, $r^2=0.025$), and PVD (11% decrease, $y=48.9-0.527x$, $r^2=0.048$). These analyses made no difference to observed changes in baseline proportions for diabetes ($y=20.2+0.0232x$, P' for slope $=0.0043$, $r^2=0.0024$), previous nonipsilateral stroke/TIA ($y=27.1-0.0104x$, P' for slope $=0.888$, $r^2 < 0.0001$), and hypercholesterolemia (only hospital-based data available).

Table 3. Results of Weighted Linear Regression Analysis of Baseline Characteristics

Characteristic	No. of Studies Analyzed*	WRL Equation	Date Interval	Rate Change	P' for Slope (b)	r ²
Increasing prevalence						
High total cholesterol	5†	$y = 17.7 + 1.669x$	1986–2005	32% increase	<0.01	0.589
Age	10	$y = 62.9 + 0.259x$	1986–2007	5.5 years increase	<0.01	0.256
Antiplatelet therapy	10†	$y = 61.3 + 0.977x$	1985–2007	22% increase	<0.01	0.068
Hypertension	9	$y = 58.2 + 0.197x$	1986–2005	4% increase	<0.01	0.025
Diabetes	10	$y = 20.8 + 0.008x$	1986–2007	<1% increase	>0.999	0.0002
Decreasing prevalence						
Ischemic heart disease	10	$y = 82.3 - 1.736x$	1986–2007	36% decrease	<0.01	0.377
Atrial fibrillation	6	$y = 12.6 - 0.437x$	1993–2005	5.5% decrease	<0.01	0.233
Current smoker	9	$y = 46.7 - 1.001x$	1993–2007	14% decrease	<0.01	0.205
Ever smoker	6	$y = 83.0 - 0.364x$	1986–2007	8% decrease	<0.01	0.055
Male sex	10	$y = 69.7 - 0.305x$	1986–2007	7% decrease	<0.01	0.016
Peripheral vascular disease	9	$y = 42.2 - 0.311x$	1986–2007	6.0% decrease	<0.01	0.013
Nonipsilateral stroke/TIA	11	$y = 24.9 - 0.0339x$	1985–2007	1% decrease	>0.999	0.0001

*No. of studies providing data and available for inclusion.

†Data available from hospital-based studies only.

Of studies reporting a cut-off value for definition of hypercholesterolemia, a total cholesterol of >6.5 mmol/L (250 mg/dL) was used in 2 studies published before 2000^{2,78} and >5.2/5.5 mmol/L (200/212 mg/dL) in 2 published later.^{79,83} Of studies reporting a cut-off value for definition of diabetes, a fasting blood sugar of >8.2 mmol/L (148 mg/dL) was used by 2 published before 2000^{78,82} and of >7.5/7.0 mmol/L (135/126 mg/dL) in 2 published later.^{80,81} Of studies reporting a cut-off value for definition of hypertension, systolic and diastolic values of 160 mm Hg and 90 to 95 mm Hg, respectively, were used in all.^{2,78,80,82} Past smoker was defined in only 1 case.⁸⁰ Definition of ischemic heart disease, where reported, was similar including a history of angina, myocardial infarction, and cardiac bypass surgery with^{2,77,82}/without^{3,78–80} electrocardiographic (ECG) evidence. It included ischemic cardiac failure in 1.⁸⁰ Definition of atrial fibrillation, where reported, included baseline ECG with⁸²/without self-reporting^{3,78,79} or baseline self-reporting, physical examination, and ECG if clinically indicated.⁸⁰ Definition of PVD, where reported, varied. It included vascular insufficiency symptoms with/without past surgical procedures, with/without detection of bruits/pulses, and with/without ankle-brachial pulse pressure measurements.^{2,78,80–82}

Changes in Baseline Use of Vascular Disease Medications

Where reported, the proportion of patients allocated medical intervention alone and receiving baseline antiplatelet therapy is given in Table 2. This proportion was not reported from the community-based study,⁸² nor the Toronto Study.² However, in the latter case ≤51% of patients were on “aspirin” at baseline,² and this figure was used in analysis. In 2 other studies^{3,77} this baseline proportion refers to a larger sample from which patients were selected, without statistical comparisons. Results of weighted regression analysis and rate changes appear in Table 3. Although there was a 22% increase in baseline proportion of patients receiving antiplate-

let therapy from 1985 to 2007 ($P' < 0.01$), the regression accounted for <20% of total variance ($r^2 < 0.2$). From only 3 studies^{79,81,82} was the baseline proportion of patients taking any other medication reported or later available. Here, respectively, 60%, 63%, and 62% of patients were receiving antihypertensive drugs and 25%, 45%, and 10% were receiving lipid lowering drugs.

Cost-Effectiveness of Current Medical Intervention Alone

For comparative purposes, a conservative estimate was made of the cost/stroke (+/-TIA) saved with current medical intervention alone using the falls in reported event rates and a detailed knowledge of the medical intervention received in a most recent study. Unpublished data from the Asymptomatic Stenosis Embolus Detection Study⁸⁰ was used in the absence of published material. In this study, 202 patients underwent biannual neurologist clinical assessment. Soon after recruitment began in 1996, a full drug history was recorded. Table 4 shows the proportion of patients taking various subclasses of “arterial protective” medications at least once during follow-up. Estimated total annual cost of medical intervention for each 100 study patients was AU\$268 000. This estimate was made using current consumer prices⁸⁴ and conservative assumptions that each patient continued each drug throughout the study, using the most expensive agent of its drug subclass and at maximal doses.

As noted above, among hospital-based patients treated with medical intervention alone there were, respectively, 1.5% and 3.2% falls in reported raw data-derived average annual rates of ipsilateral and any-territory stroke since 1985. Being, again, conservative and assuming that cost of medical intervention before 1985 was negligible, then cost/ipsilateral stroke saved with current medical intervention alone is approximately AU\$179 000 (AU\$268 000/1.5) and cost/any-territory stroke saved is approximately AU\$83 750 (AU\$268 000/3.2). Similarly, cost/event saved with current

Table 4. Cost Estimate of Medical Interventions Received by ASED Study⁸⁰ Patients

Intervention	Usage (% of Study Patients)	Annual Cost of Treatment/100 Study Patients (AU\$)
Biannual specialist physician assessment	100	Subtotal: 5000
Antithrombotic drugs	93	Subtotal: 22 756
Aspirin	86	
Persantin	9	
Ticlid (and not Plavix)	6	
Plavix (+/–Ticlid)	10	
Warfarin	9	
Dyslipidaemic drugs	66	Subtotal: 88 074
Statin	64	
Fibrate	5	
Bile acid sequestrant	1	
Antihypertensive drugs	75	Subtotal: 88 139
Calcium blocker	45	
ACE inhibitor	40	
Beta blocker	26	
Low ceiling +/-potassium sparing diuretics	20	
Angiotension receptor blocker	15	
Others*	1–7	
Antiarrhythmic drugs	5	Subtotal: 3 899
Blood sugar lowering drugs	15	Subtotal: 32 664
Other “arterial protective” drugs†	1–23	Subtotal: 26 842
		Grand total‡: 268 000

*Peripherally/centrally acting antiadrenergic agents, combined alpha/beta-blockers, direct arteriolar smooth muscle relaxants.

†High ceiling diuretics, potassium supplements, digoxin, thyroxine, antianginals.

‡Rounded to next 1000.

vascular disease medical intervention alone is about AU\$38 000 (AU\$268 000/7.0) for ipsilateral stroke/TIA and about AU\$64 000 (AU\$268 000/4.2) for any-territory stroke/TIA.

By comparison, the stroke prevention benefit reported for patients who received CEA plus medical intervention in major randomized trials was much more expensive. Assuming the surgical benefit reported from these trials exists in current routine clinical practice, that each CEA costs AU\$7000 and using previously published reasoning,^{1,85} it can be estimated that annual procedural costs alone of a surgical approach would approximate AU\$600 000 to “be ahead” by 1 ipsilateral stroke (using ACAS results¹¹), AU\$650 000 to be ahead by 1 stroke in any vascular territory (ACST results¹²), about AU\$320 000 to be ahead by 1 ipsilateral stroke/TIA (ACAS results¹¹), and about AU\$242 000 to be ahead by 1 any-territory stroke/TIA (VACS results¹⁰). Therefore, current vascular disease medical intervention alone is at least 3 to 8 times cheaper in preventing stroke and 4 to 8 times cheaper in preventing stroke/TIA compared to surgery and medical intervention as employed in major randomized surgical trials.

Discussion

Fall in Stroke Symptom Risk With Medical Intervention Alone

The key findings of this systematic review and analysis included significant falls in reported average annual rates of ipsilateral and any-territory stroke (with/without TIA) associated with isolated medical intervention for asymptomatic severe proximal ICA stenosis since the mid-1980s. From 2001, average annual rates of ipsilateral stroke among patients receiving vascular disease medical intervention alone fell below those of patients who received CEA in ACAS,¹¹ the only randomized trial with a reported surgical advantage for this outcome measure. Further, results indicated loss of a statistically significant surgical advantage in prevention of ipsilateral stroke from the mid-1980s, of ipsilateral stroke/TIA from the early-1990s, of any-territory stroke from the mid-1990s, and of any-territory stroke/TIA from about 2001. These findings resulted from limiting analyses to studies sharing fundamental criteria for sound methodology and use of appropriate statistical tests to account for sample size¹⁸ and multiple comparisons.¹⁹

This “25-year” fall in reported stroke and TIA rates relates, in particular, to hospital-based patients. Significant falls in event rates were amplified when the only community-based study was excluded. The falls in reported stroke symptom rates were gradual and progressive and, therefore, not simply explained by comparing outlying studies at time interval extremes. Nor are they explained by the tendency in later hospital-based studies to remove patients with known nonipsilateral carotid sources of cerebral embolism, as the results remained largely unchanged when these studies were excluded. Nor are they attributable to fundamental differences in rate calculation method as significant falls were seen when raw data– and KM-estimate-derived rates were analyzed separately. However, raw data–derived rates were more readily available, usually doubled the time span for testing event rate changes, and were more closely related to the actual mean patient follow-up (important as event rates tend to be higher early in follow-up¹).

Further, these falls in reported stroke event rates are not explained by the exclusion of 2 large studies of carotid disease, the ACST,¹² and 1 reported by Dick et al.⁷¹ The ACST was excluded because patients with ipsilateral stroke/TIA >6 months before entry were recruited, comprising 12% of patients. In ACST, the total number of ipsilateral strokes was not reported and TIA was not an outcome measure; the 1560 patients allocated “deferred CEA” had an average annual any-territory stroke rate of 2.5% (using raw data). If this rate is added to a weighted regression analysis of the selected hospital-based studies of asymptomatic patients, a 1.7% fall in any-territory stroke rate is seen from 1986 to 2007 (Figure 2). This fall, also significant, was lower than the 3.2% fall noted earlier when the selected hospital-based studies were analyzed alone. The study reported by Dick et al was excluded because the proportion of first strokes among the 44 total observed (among 525 patients followed for an average of 38 months) was not reported. However, a subsequent estimate was that 11/44 strokes were recurrent (Schill-

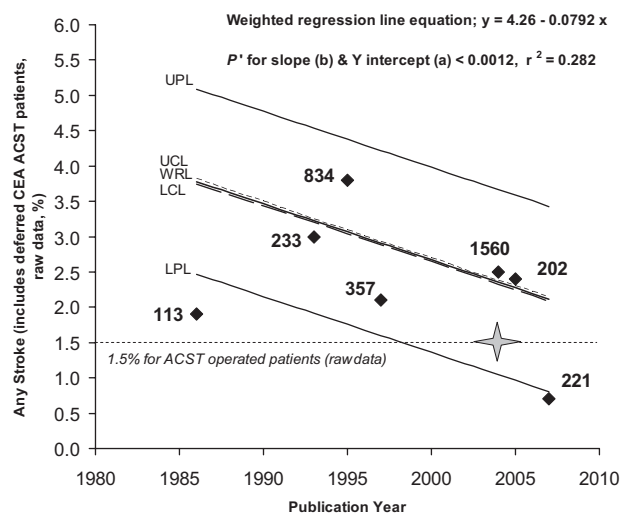


Figure 2. Any-territory stroke rates of hospital-based asymptomatic patients undergoing medical intervention alone^{2,10,11,78,80,81} and 1560 “deferred CEA” ACST patients¹² by publication year with sample sizes, and statistical results (comparison with ACST operated/“immediate CEA” patients). See Figure 1 for abbreviations.

inger, personal communication 2008), producing an average annual, raw data derived rate of first “any-territory” stroke of 2.0%, maintaining a significant rate fall with the selected hospital-based studies (with/without ACST, respective weighted regression line equations $y=4.59-0.1051x$, P' for slope <0.0014 , $r^2=0.382$ and $y=4.34-0.0849x$, P' for slope <0.0014 , $r^2=0.330$).

These 25-year falls in reported stroke symptom rate are consistent with other observed falls in incidence of stroke,⁸⁶ heart attack, and sudden death⁸⁷ and are most likely attributable to improving efficacy of vascular disease medical intervention. The falls in stroke symptom rate were statistically significant despite the studies originating from a number of countries and some interstudy methodological differences; this implies the biological effects of vascular disease and its response to medical intervention is not country specific, at least within “Westernized” communities. The falls coincide with great gains in vascular disease understanding. There has been, for example, lowering or expansion of thresholds used to define and treat the diabetic,⁸⁸ hypertensive,⁸⁹ and hyperlipidemic^{90–92} patient. There has also been growing appreciation and exploitation of the vascular protection offered by existing and new drugs. Most important have been antiplatelet drugs (aspirin and more recent alternatives), blood pressure-lowering drugs (including angiotensin converting enzyme inhibitors with possible unique cardioprotective properties⁹³), and effective and better tolerated lipid-lowering drugs (particularly HMG-Coenzyme A reductase inhibitors).⁹⁴

Other findings of this systematic analysis have provided evidence that the falls in stroke symptom rate among nonoperated/stented patients with asymptomatic severe carotid stenosis are not simply due to inclusion of fitter patients over time. Falls occurred despite an observed 5.5-year increase in mean patient age. Further, there was direct evidence that rate falls were attributable, at least in part, to the impact of vascular disease medical intervention with a 14% fall in the

proportion of baseline active smokers, consistent with other observed changes in population vascular risk factors over the last 20 to 25 years.^{86,87,95} Such population studies have also revealed falls in baseline mean blood pressure and total cholesterol. In the present analysis, there were significant increases in baseline proportions of patients classified as hypertensive and hypercholesterolemic. Reporting methods, however, did not allow comparison of mean blood pressure and total cholesterol values over time.

In the present analysis there were also significant falls in the proportion of patients classified at baseline as having ischemic heart disease and atrial fibrillation. These were perhaps influenced by changing patient selection criteria or by patients becoming more likely to avoid cardiovascular symptoms and present later with carotid disease. There was evidence for more frequent baseline use of antiplatelet agents over time among medically treated patients. The absence of published data on baseline use of blood pressure and lipid lowering drugs before 2005 is testament to the unavailability of many now commonly used drugs and the growing appreciation of the significant impact they have on vascular risk.

Why Current Medical Intervention Alone Is Best

Previously, factors which specifically reduce the risk of stroke caused by, and otherwise associated with, asymptomatic severe carotid stenosis were unknown. Medical intervention for this condition was largely driven by contemporary understanding of, and interventions available for, associated vascular disease risk factors and symptoms. Therefore, best evidence now indicates that common-place, current vascular disease medical intervention is now at least as effective in preventing stroke and TIA associated with this lesion as the combination of medical intervention and CEA used in past randomized surgical trials. Although this may be sufficient evidence that patients can now be spared surgery in routine clinical practice, the total evidence for this conclusion is overwhelming when other factors (discussed below) are also considered.

First, evidence has been presented that current, common-place, vascular disease medical intervention is >3 to 8 times cheaper in preventing stroke and >4 to 8 times cheaper in preventing stroke or TIA for hospital-referred patients than the combination of medical intervention and rigorously monitored CEA used in the major randomized surgical trials. There is no evidence that carotid angioplasty/stenting for asymptomatic patients improves the stroke prevention efficacy or cost-effectiveness of current vascular disease medical intervention alone. Further, cost-effectiveness should account for other vascular disease complications, such as fatal/nonfatal myocardial infarction and ischemic legs, which are reduced by medical intervention whereas they are complications of instrumental intervention.

Second, a policy of effective medical intervention alone would bypass the need for rigorous measurement of surgical outcomes in routine practice, measurement prevented by problems including insufficient resources and conflicting clinical interests. Further, vascular disease medical intervention can be more easily administered in the wider community, not being limited to the confines of tertiary referral centers.

Finally, as reported previously, it is not currently possible to identify patients with asymptomatic severe carotid stenosis with higher than average stroke risk despite current best practice medical intervention alone.¹⁴ If such patients are one day reliably identified, randomized trials will be required to establish any potential additional benefit from instrumental intervention in routine practice. Further, if instrumental intervention is found to provide an additional benefit in such randomized trials, the methods and standards that achieved such benefits must be adopted as minimum requirements in routine practice.

Now and the Future

Vascular disease medical intervention is an evolving, powerful, multidisciplinary combination of interventions to avoid or minimize the impact of vascular disease, including ongoing diagnosis, education, support, and drugs. Best evidence indicates that it alone is now best for prevention of stroke associated with asymptomatic severe carotid stenosis. It is no longer appropriate to refer to vascular disease medical intervention as “conservative,” “control,” or “natural history” therapy, as has been done in the past.^{12,71,72,96,97} It is also inappropriate to reserve more effective sounding terminology, like “intervention,” “revascularization,” and “repair,” to surgery, angioplasty, or stenting.^{39,98–100} The appropriate referral path for patients identified with asymptomatic severe carotid stenosis is to an enthusiastic clinician expert in current best practice vascular disease medical intervention.

It has already been acknowledged that the stroke prevention benefit of current best practice medical intervention alone among patients with asymptomatic carotid stenosis has not been measured.¹ Average annual stroke rates of less than 1–1.5% among hospital-referred patients may be relatively easily achieved and further indicate the redundancy or harm of additional instrumental intervention. Further, it is likely that appreciation of vascular disease risk factors and effective medical interventions will continue to evolve and may vary across localities. Therefore, collection of basic, quality observational data, relevant to such important clinical outcomes, should be built into networked practices. This would allow construction of large, locally relevant, up-to-date databases necessary for better patient risk stratification. Randomized trials of invasive, expensive, and difficult to regulate interventions (like carotid surgery, angioplasty/stenting) should be considered only if reliable methods are available to identify patients with sufficiently higher than average ipsilateral stroke risk despite current best practice vascular disease medical intervention alone.

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