Age and Outcomes After Carotid Stenting and Endarterectomy
The Carotid Revascularization Endarterectomy Versus Stenting Trial

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**Background and Purpose**—High stroke event rates among carotid artery stenting (CAS)-treated patients in the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST) lead-in registry generated an a priori hypothesis that age may modify the relative efficacy of CAS versus carotid endarterectomy (CEA). In the primary CREST report, we previously noted significant effect modification by age. Here we extend this investigation by examining the relative efficacy of the components of the primary end point, the treatment-specific impact of age, and contributors to the increasing risk in CAS-treated patients at older ages.

**Methods**—Among 2502 CREST patients with high-grade carotid stenosis, proportional hazards models were used to examine the impact of age on the CAS-to-CEA relative efficacy, and the impact of age on risk within CAS-treated and CEA-treated patients.

**Results**—Age acted as a treatment effect modifier for the primary end point ($P_{interaction} = 0.02$), with the efficacy of CAS and CEA approximately equal at age 70 years. For CAS, risk for the primary end point increased with age ($P < 0.0001$) by 1.77-times (95% confidence interval, 1.38–2.28) per 10-year increment; however, there was no evidence of increased risk for CEA-treated patients ($P = 0.27$). Stroke events were the primary contributor to the overall effect modification ($P_{interaction} = 0.033$), with equal risk at $\approx 64$ years. The treatment-by-age interaction for CAS and CEA was not altered by symptomatic status ($P = 0.96$) or by sex ($P = 0.45$).

**Conclusions**—Outcomes after CAS versus CEA were related to patient age, attributable to increasing risk for stroke after CAS at older ages. Patient age should be an important consideration when choosing between the 2 procedures for treating carotid stenosis.

**Clinical Trial Registration**—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00004732. (Stroke. 2011;42:3484-3490.)

Key Words: carotid artery ■ carotid endarterectomy ■ cerebrovascular disease ■ stents ■ vascular surgery

Patient age has been shown to influence the outcomes after carotid revascularization.1–6 The Carotid Revascularization Endarterectomy vs Stenting Trial (CREST) protocol was developed in 1997,7 when age and vascular anatomy8,9 were not yet recognized as predictors of complications of carotid artery stenting (CAS). To the contrary, it was postulated that CAS might be safer than carotid endarterectomy (CEA) in the elderly. However, during the conduct of the lead-in phase of the study, a high risk of stroke events was observed among the CAS-treated patients, and octogenarians were subsequently excluded from this portion of the trial (but were continued in the randomized phase to assess if equivalent risks were present for the CEA-treated patients).10 At this time (on the basis of lead-in data only and before unblinding of randomized data), the study investigators committed to the preplanned formal assessment of the impact of age on relative efficacy reported herein.

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Materials and Methods

Study Participants and Measurement

CREST is a randomized clinical trial assessing the relative efficacy of CAS versus CEA. The study enrolled 1321 symptomatic patients and 1181 asymptomatic patients. End points were adjudicated by committees blinded to treatment assignment. Details of the study are provided elsewhere.11–13 The protocol was approved by the Institutional/Ethics Review Board of all participating sites. All patients gave written informed consent.

Statistical Analysis

The focus of these analyses is to assess if the age of the patient influences the relative efficacy of CAS and CEA and, if so, what are the contributors of the effect modification. As such, the primary evaluation of efficacy was assessed on an intention-to-treat analysis using proportional hazards analysis to evaluate the potential of an age-by-treatment interaction after adjustment for symptomatic status and sex. The primary outcome of the trial was stroke, myocardial infarction (MI), or death during a periprocedural period (30 days after randomization for those not receiving treatment within 30 days, or 36 days after randomization for those not receiving treatment within 30 days), or ipsilateral stroke over a follow-up period extending 4 years from randomization. Potential effect modification by age was analyzed assuming a linear effect of age (after confirming the linear distribution of the ages for CAS and CEA).

We also assessed if any potential age-by-treatment effect modification was consistent by symptomatic status or sex by adding higher-order interaction terms to the model. Proportional hazards models were fit separately for those CAS-treated and CEA-treated patients to describe the age-related changes in risk within each treatment contributing to their relative CAS-to-CEA efficacy differences.

Finally, to identify potential causes underlying the age–treatment interaction, we conducted a mediation analysis14 to identify if the increased risk at older ages for CAS-treated patients was attributable to an increased prevalence of risk factors (hypertension, diabetes, or dyslipidemia), differences in the characteristics of the lesion (lesion length, eccentric lesions, ulcerated lesion, or percent stenosis), or differences in the procedure (fluoroscopy time or total procedure time) by entering these factors into the model and observing the change in the estimated hazard ratio associated with age. Characteristics of the lesion were determined by the local clinic. Anatomic characteristics such as aortic arch anatomy, vessel tortuosity, and calcification known to be associated with age and CAS complications were not available for analysis. The standard error of the mediation was estimated using bootstrap techniques.

Results

For both treatment groups in CREST, with increasing age participants were more likely to be female, white, and to have higher levels of systolic blood pressure and lower levels of diastolic blood pressure; however, they were less likely to have diabetes, dyslipidemia, or to be current smokers (Table 1). There were no significant differences between treatment groups for these factors in any age strata. Figure 1 shows the distribution of the ages for CAS and CEA.

Table 1. Description of Study Population by Treatment and Age Strata*

<table>
<thead>
<tr>
<th>Age Strata</th>
<th>CAS (n=404)</th>
<th>CEA (n=387)</th>
<th>CAS (n=525)</th>
<th>CEA (n=500)</th>
<th>CAS (n=333)</th>
<th>CEA (n=335)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Younger Than 65</td>
<td>64.6</td>
<td>66.7</td>
<td>67.4</td>
<td>67.4</td>
<td>57.7</td>
<td>64.6</td>
</tr>
<tr>
<td>65–74</td>
<td>70.6</td>
<td>72.8</td>
<td>73.1</td>
<td>72.8</td>
<td>75.2</td>
<td>75.5</td>
</tr>
<tr>
<td>75 and Older</td>
<td>43.8</td>
<td>41.6</td>
<td>53.1</td>
<td>53.0</td>
<td>41.4</td>
<td>45.6</td>
</tr>
</tbody>
</table>

**Risk factor status**

- Hypertension %: 81.4, 84.4, 88.7, 87.9, 86.4, 85.2
- Diabetes %: 32.9, 30.6, 31.6, 34.2, 26.0, 25.0
- Dyslipidemia %: 84.1, 85.9, 84.3, 88.3, 79.3, 82.2
- Current smoker %: 46.3, 47.9, 22.3, 21.0, 8.6, 9.0
- Prior cardiovascular disease %: 36.3, 40.8, 46.9, 50.1, 42.9, 42.4
- Previous coronary artery bypass %: 15.9, 18.2, 22.3, 24.7, 21.1, 20.8
- Systolic blood pressure (mean±SD) mm Hg: 137±20, 138±20, 142±20, 141±21, 147±20, 145±20
- Diastolic blood pressure (mean±SD) mm Hg: 76±12, 76±12, 74±11, 73±11, 72±12, 73±12

**Stenosis measures**

- Moderate (<70%): 11.1, 12.4, 13.3, 17.6, 15.0, 13.9
- Severe (≥70%): 88.9, 87.6, 86.7, 82.4, 85.0, 86.1
- Left carotid treated %: 50.7, 53.2, 47.8, 52.6, 55.0, 50.7
- Contralateral occlusion %: 3.4, 4.7, 1.9, 3.3, 3.3, 1.5
- Median day from randomization to treatment: 6.0, 7.0, 7.0, 7.0, 6.0, 7.0

*Sample sizes vary for specific characteristics (rows) because of missing data on specific items for a small number of patients.
Table 2 provides the observed number of MI, strokes, and primary end points within approximate tertiles of age strata for both the periprocedural period and for the 4-year outcome. Figure 2 provides the associated Kaplan-Meier estimates of the proportion of participants with a primary end point for each age–treatment strata, showing the similarity of time-to-event across age strata for CEA-treated patients, but the differences of time-to-event across age strata for CAS-treated patients. As previously reported for the primary end point at 4 years, there was evidence of a treatment-by-age interaction ($P_{H11005} = 0.02$). The CAS-to-CEA risk increased with advancing age, from 0.60 (95% confidence interval [CI], 0.31–1.18) for patients younger than 65 years to approximate equal risk for those aged 65 to 74 years (hazard ratio, 1.08; 95% CI, 0.65–1.78), and to 1.63 (95% CI, 0.99–2.69) for those aged 75 years and older. This increasing risk was associated with increasing event rates in the CAS-treated patients (3.9% in the youngest age strata, 6.3% in the middle, and 12.7% in the oldest), whereas risk was relatively stable in the CEA-treated patients (respective rates: 6.1% youngest, 6.8% middle, and 7.4% oldest). This increasing risk was driven by the stroke end point, with a higher ($P_{H11005} = 0.033$) CAS-to-CEA risk across age strata, with hazard ratios of 0.78 (95% CI, 0.37–1.62), 1.42 (95% CI, 0.78–2.60), and 2.15 (95% CI, 1.19–3.91) for those aged 75 years and older. The wider 95% CI bounds imply greater uncertainty for the stroke outcome compared to the primary outcome. There was no evidence ($P_{H11005} = 0.35$) of effect modification by the MI component of the primary end point (Figure 3C).

Although we urge caution in interpretation, Supplemental Table I (https://stroke.ahajournals.org) provides results similar to Table 2, stratified by symptomatic status. This Table requires stratification by both age and symptomatic status, and as such the small sample size in specific stratum could lead to misleading results. We have considered age-by-symptomatic status interactions and found none to be significant ($P > 0.1$), and differences between symptomatic and asymptomatic patients in the relationships of risk with age could have easily occurred by chance alone. However, these data are provided for comparisons with the results of other studies that do not include both asymptomatic and symptomatic patients.

The primary analysis for this report is shown in Figure 3. Figure 3A shows the CREST primary end point as a continuous function of age (identical Figure to that shown in primary study results article, all other Figures and analyses are novel to this article). The risk of the 2 procedures is approximately equal at age 70 years, with CAS showing superiority in younger patients, and there is an increasing benefit for CEA in older patients. The stroke component of the composite end point as a function of age is shown in Figure 3B. The steeper slope in this Figure implies a larger magnitude of effect modification by age on the occurrence of stroke ($P = 0.033$) than for occurrence of the primary end point. We note that unlike the composite outcome in which CAS-to-CEA risk approaches a significant advantage for CAS at younger ages, the wider CI the stroke end point implies the upper limit of the 95% CI bounds remains $>1.0$; however, the a priori focus of this article was on the trend of risk with differences in age (rather than differences at any specific age). The point of equal risk for CAS and CEA is at age 64 years, 6 years younger than for the primary end point. The wider 95% CI bounds imply greater uncertainty for the stroke outcome compared to the primary outcome. There was no evidence ($P = 0.35$) of effect modification by the MI component of the primary end point (Figure 3C).
Table 2. Number of Events and Event Rates by Age Category for Patients Treated With Carotid Artery Stenting and Carotid Endarterectomy

<table>
<thead>
<tr>
<th>CAS</th>
<th>Younger than 65</th>
<th>Younger than 65</th>
<th>Periprocedural Period†</th>
<th>Treatment by Age</th>
<th>Four-Year Period</th>
<th>Treatment by Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>404</td>
<td>353</td>
<td>0.69 (0.31–1.55)</td>
<td>0.37 ± 0.13</td>
<td>N</td>
<td>0.60 (0.31–1.18)</td>
</tr>
<tr>
<td>65–74</td>
<td>500</td>
<td>500</td>
<td>14 (3.9 ± 1.1)</td>
<td>22 (6.1 ± 1.3)</td>
<td>2 (0.3 ± 1.1)</td>
<td></td>
</tr>
<tr>
<td>MI end point (any periprocedural† stroke, MI or death within 30 days period)</td>
<td>26 (5.0 ± 0.9)</td>
<td>21 (4.2 ± 0.9)</td>
<td>1.22 (0.68–2.16)</td>
<td>0.51 ± 0.16</td>
<td>32 (6.3 ± 1.1)</td>
<td>29 (6.8 ± 1.3)</td>
</tr>
<tr>
<td>75 or older</td>
<td>30 (6.0 ± 1.6)</td>
<td>21 (5.9 ± 1.3)</td>
<td>1.49 (0.85–2.60) (2.14^\times)</td>
<td>0.16 ± 0.08</td>
<td>39 (12.7 ± 1.9)</td>
<td>25 (7.4 ± 1.4)</td>
</tr>
<tr>
<td>Stroke end point (any stroke within 30 days postprocedural period)</td>
<td>9 (2.2 ± 0.7)</td>
<td>8 (2.1 ± 0.7)</td>
<td>0.03 (0.01–0.1)</td>
<td>0.85 ± 0.27</td>
<td>13 (3.7 ± 1.0)</td>
<td>16 (4.5 ± 1.1)</td>
</tr>
<tr>
<td>75 or older</td>
<td>20 (3.8 ± 0.8)</td>
<td>10 (2.0 ± 0.6)</td>
<td>5.93 (2.23–15.38)</td>
<td>0.08 ± 0.04</td>
<td>26 (5.1 ± 1.0)</td>
<td>18 (4.6 ± 1.1)</td>
</tr>
<tr>
<td>All strokes (any stroke up to 4–y follow-up)</td>
<td>23 (6.9 ± 1.4)</td>
<td>11 (3.1 ± 0.9)</td>
<td>2.17 (1.06–4.45)</td>
<td>0.035 ± 0.01</td>
<td>33 (10.9 ± 1.8)</td>
<td>16 (4.9 ± 1.2)</td>
</tr>
<tr>
<td>Younger than 65</td>
<td>9 (2.2 ± 0.7)</td>
<td>8 (2.1 ± 0.7)</td>
<td>1.10 (0.42–2.84)</td>
<td>0.85 ± 0.27</td>
<td>21 (6.7 ± 1.5)</td>
<td>20 (6.0 ± 1.4)</td>
</tr>
<tr>
<td>65–74</td>
<td>20 (3.8 ± 0.8)</td>
<td>10 (2.0 ± 0.6)</td>
<td>1.98 (0.93–4.23)</td>
<td>0.08 ± 0.04</td>
<td>46 (11.4 ± 1.9)</td>
<td>30 (8.1 ± 1.6)</td>
</tr>
<tr>
<td>75 or older</td>
<td>23 (6.9 ± 1.4)</td>
<td>11 (3.1 ± 0.9)</td>
<td>2.17 (1.06–4.45)</td>
<td>0.035 ± 0.01</td>
<td>30 (13.1 ± 2.1)</td>
<td>20 (9.4 ± 2.2)</td>
</tr>
<tr>
<td>Death</td>
<td>0 (0.0 ± 0.0)</td>
<td>0 (0.0 ± 0.0)</td>
<td>NA††</td>
<td>NA†† ± 0.00</td>
<td>19 (6.6 ± 1.6)</td>
<td>18 (8.2 ± 2.2)</td>
</tr>
<tr>
<td>Younger than 65</td>
<td>4 (0.8 ± 0.4)</td>
<td>0 (0.0 ± 0.0)</td>
<td>NA††</td>
<td>NA†† ± 0.00</td>
<td>36 (9.7 ± 1.6)</td>
<td>30 (12.3 ± 2.6)</td>
</tr>
<tr>
<td>65–74</td>
<td>4 (1.2 ± 0.6)</td>
<td>0 (0.0 ± 0.0)</td>
<td>0.03 (0.01–0.1)</td>
<td>0.38 ± 0.04</td>
<td>39 (18.2 ± 3.0)</td>
<td>37 (18.0 ± 3.0)</td>
</tr>
<tr>
<td>M1 end point (periprocedural† MI†)</td>
<td>1 (0.2 ± 0.2)</td>
<td>0 (0.0 ± 0.0)</td>
<td>0.03 (0.01–0.1)</td>
<td>0.09 ± 0.04</td>
<td>39 (18.6 ± 3.0)</td>
<td>37 (18.0 ± 3.0)</td>
</tr>
<tr>
<td>Younger than 65</td>
<td>6 (1.1 ± 0.5)</td>
<td>11 (2.2 ± 0.7)</td>
<td>0.53 (0.20–1.42)</td>
<td>0.21 ± 0.07</td>
<td>5 (1.8 ± 0.5)</td>
<td>11 (2.2 ± 0.7)</td>
</tr>
<tr>
<td>75 or older</td>
<td>7 (2.1 ± 0.8)</td>
<td>3 (1.1 ± 0.9)</td>
<td>0.67 (0.26–1.72)</td>
<td>0.40 ± 0.12</td>
<td>26 (8.1 ± 1.6)</td>
<td>21 (8.2 ± 2.2)</td>
</tr>
</tbody>
</table>

CAS indicates carotid artery stenting; CEA, carotid endarterectomy; NA, not available; SE, standard error.

*Univariate proportional hazards model used because of the small N of events.
†Periprocedural period was defined as the 30-day period after the procedure for all patients receiving treatment within 30 days of randomization, or day 36 for patients not receiving therapy within 30 days of randomization.
‡Event rates for MI end point was calculated as the proportion exposed patients experiencing the end point with SE calculated from the binomial distribution, whereas event rates for the stroke end point and primary end point were calculated using Kaplan-Meier survival function with SE calculated from the Greenwood formula.
§Hazard ratios for the primary end point and stroke end point and death end point were adjusted for symptomatic status and sex, but no adjustments were made in the MI end point because of a small N of events.

For those treated with CAS, there was a 1.77-times increase in risk of primary end point event \(P<0.0001; 95\% \text{ CI}, 1.38–2.28\) and a 1.76-times increase \(95\% \text{ CI}, 1.35–2.31\) for stroke events with each 10-year difference in age. For those treated with CEA, there was no evidence of a difference in risk across the age spectrum for either the primary end point (hazard ratio, 1.16; 95% CI, 0.89–1.50; \(P=0.27\)) or for stroke events (hazard ratio, 1.12; 95% CI, 0.82–1.54; \(P=0.47\)). Introduction of higher-order interaction terms did not suggest that the age modification of treatment effect was influenced by either symptomatic status \(P=0.96\) or by sex \(P=0.45\). The sensitivity analysis using the alternative definition of MI, including 20 biomarker-only MI, showed a nonsignificant effect modification of age \(P=0.75\).

**Mediation Analysis**

Mediation analysis was performed to assess factors potentially contributing to the age-related risk differences in the CAS treatment group (Table 3), but it was not performed for those randomized to CEA because of the lack of evidence for age-related changes for those randomized to CEA. There was no evidence that the effect of age in the CAS group was mediated by differences in the prevalence of hypertension, diabetes, or dyslipidemia, or by differences in observed lesion characteristics or procedure duration \(P>0.05\). Although...
total fluoroscopy time was identified as a potential mediator ($P = 0.046$), its effect was modest, only reducing the age hazard ratio from 1.68 to 1.62 for a 10-year difference in age.

**Discussion**

The current analysis indicates that the age-related differential efficacy observed in CREST is primarily attributable to the stroke component of the primary end point. In turn, the impact of the stroke component is largely driven by an increasing risk of stroke with increasing age among CAS-treated patients, but little change in the increasing risk of stroke with increasing age among CEA-treated patients.

The point of similarity for the risk of stroke for CAS and CEA is at 64 years, compared to approximately 70 years for the risk of the primary end point. The occurrence of MI after either procedure did not differ with age, suggesting CAS results in fewer MI across the entire age spectrum. However, because there were fewer MI events ($N = 42$) than stroke events ($N = 122$), there was lesser power to detect effect modification for MI than stroke. There was no evidence that the age-by-treatment relationships differed by symptomatic status or sex.

Our observation of an age effect modification, originally reported in the primary results article, was subsequently confirmed by the meta-analysis of the Stent-Protected Angioplasty vs Carotid Endarterectomy (SPACE) trial, the Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial, and the International Carotid Stenting Study (ICSS). For patients 70 years and older, the risk of events in CAS-treated patients was approximately twice that for CEA-treated patients (hazard ratio, 2.04; 95% CI, 1.48–2.82). This differential age effect in the meta-analysis was also driven by stroke because MI was not a component of the primary end point for this meta-analysis. This meta-analysis showed no differences in risk for patients younger than age 70 (hazard ratio, 2.04; 95% CI, 1.48–2.82). This differential age effect in the meta-analysis was also driven by stroke because MI was not a component of the primary end point for this meta-analysis. This meta-analysis showed no differences in risk for patients younger than age 70 (hazard ratio, 1.11; 95% CI, 0.73–1.71), a finding not supported by our analysis in which younger CAS-treated patients were shown to be at lower risk. Separately, the SPACE investigators reported a risk of 0.54-times (95% CI,
0.28–1.03) less for CAS relative to CEA for those younger than aged 68, and a risk of 1.80-times (95% CI, 0.96–3.40) greater for CAS relative to CEA in those aged 68 and older.16 This age effect is also consistent with reports from the lead-in series of CREST, the Carotid Acculink/Accunet Post-Approval Trial to Uncover Unanticipated or Rare Events (CAPTURE) registry, and in ICSS.10,17,18 All of these trials used eligibility criteria similar to CREST that did not incorporate anatomic exclusion criteria for CAS now thought to be important in elderly patients.9 None of the analyses included a detailed examination of the factors, consistent with previous reports.25

When CREST was designed, we anticipated that the less invasive CAS would be superior in older age groups compared to the more invasive CEA. Accordingly, the superior performance of CEA in older individuals and the superior performance of CAS in younger individuals were unexpected. This position was challenged by the observation of high risk patients, and age results consistent with results from CAS and CEA) and smaller proportions of patients at the tails anticipated (because of better than expected safety for both CAS and CEA) and smaller proportions of patients at the tails of the age distribution, 161 (6.4%) aged 55 years and younger and 240 (9.6%) aged 80 years and older (Figure 1). Nonetheless, the finding that the interaction test was significant provides prima facie confirmation that there are sufficient
table

<table>
<thead>
<tr>
<th>Covariate Potentially Mediating Impact of Age (Sample Size/N of Events)</th>
<th>Hazard Ratio for a 10-y Difference in Age After Adjustment for Gender and Symptomatic Status</th>
<th>Hazard Ratio for a 10-y Difference in Age After Further Adjustment for Covariate</th>
<th>Change in Coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension (1259/85)</td>
<td>1.77 (1.38–2.27)</td>
<td>1.77 (1.37–2.27)</td>
<td>−0.0021±0.0078</td>
</tr>
<tr>
<td>Diabetes (1257/85)</td>
<td>1.77 (1.38–2.27)</td>
<td>1.79 (1.39–2.30)</td>
<td>0.0132±0.0153</td>
</tr>
<tr>
<td>Dyslipidemia (1254/85)</td>
<td>1.78 (1.38–2.28)</td>
<td>1.76 (1.37–2.26)</td>
<td>−0.0077±0.0139</td>
</tr>
<tr>
<td>Lesion length (mm) (1189/83)</td>
<td>1.73 (1.35–2.23)</td>
<td>1.68 (1.31–2.17)</td>
<td>−0.0286±0.0152</td>
</tr>
<tr>
<td>Eccentric lesion (1212/84)</td>
<td>1.75 (1.36–2.25)</td>
<td>1.75 (1.36–2.25)</td>
<td>0.0025±0.0094</td>
</tr>
<tr>
<td>Ulcerated lesion (1207/84)</td>
<td>1.75 (1.36–2.25)</td>
<td>1.73 (1.34–2.22)</td>
<td>−0.0127±0.0149</td>
</tr>
<tr>
<td>Procedural angiogram percent stenosis (1200/83)</td>
<td>1.73 (1.35–2.23)</td>
<td>1.73 (1.35–2.22)</td>
<td>−0.0001±0.0055</td>
</tr>
<tr>
<td>Fluoroscopy time (min) (1156/78)</td>
<td>1.68 (1.30–2.18)</td>
<td>1.62 (1.26–2.09)</td>
<td>−0.0370±0.0185</td>
</tr>
<tr>
<td>Total procedure time (min) (1210/83)</td>
<td>1.78 (1.38–2.30)</td>
<td>1.77 (1.37–2.27)</td>
<td>−0.0097±0.0123</td>
</tr>
</tbody>
</table>

We hypothesize that the risk of embolization during CAS is increased during navigation of tortuous extracranial arteries, particularly in patients with heavily calcified vessels and “extended” type II and III aortic arches. Consistent with this hypothesis, we observed that the elderly required longer fluoroscopy time for CAS. Adjustment for this factor partially mediated the magnitude of the increased risk at older ages. Of note, the higher event rates in the elderly were not associated with increase in cardiovascular risk factors, consistent with previous reports.25

The interaction between patient selection, operator experience, and technology may be relevant to the age interaction in this analysis. Recent reports of CAS using updated patient selection criteria suggest that the age differential for CAS may be absent or blunted.26,27 These studies of CAS, also using new proximal protection devices designed to be less affected by arterial tortuosity, were notable for low event rates in the elderly.28,29 Further studies are required to confirm these findings.

Strengths of the CREST analysis include a large cohort of patients with a broad age distribution, inclusion of asymptomatic patients, and age results consistent with results from the CREST credentialing study and subsequent randomized trials. Limitations include smaller numbers of events than anticipated (because of better than expected safety for both CAS and CEA) and smaller proportions of patients at the tails of the age distribution, 161 (6.4%) aged 55 years and younger and 240 (9.6%) aged 80 years and older (Figure 1).
numbers of individuals in the tails of the age distribution to describe the effect of age.

**Conclusions**
This prespecified analysis of the CREST trial demonstrates that the differential efficacy of CAS compared to CEA across the age spectrum is primarily attributable to stroke events. The pattern of lower relative risk in the CAS group at younger ages and higher relative risk at older ages is driven by increased risk for stroke at older ages for CAS. For CEA, the risk for stroke is relatively constant across the entire age spectrum. We conclude that patient age should be an important factor in selecting the treatment option for carotid stenosis. The anatomic factors that may contribute to these observations require further study.

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**References**
Age and Outcomes After Carotid Stenting and Endarterectomy: The Carotid Revascularization Endarterectomy Versus Stenting Trial


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The Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST) Study

Age and Outcomes After Carotid Stenting and Endarterectomy

The Carotid Revascularization Endarterectomy Versus Stenting Trial

Jennifer H. Vocks, PhD; George Howard, DrPH; Gary S. Roubin, MD, PhD; Mahmoud B. Malas, MD; David J. Cohen, MD; W. Charles Sterneck, III, MD; Herbert D. Aronow, MD, MPH; Mark K. Eskandari, MD; Alice J. Sheffet, PhD; Brajesh K. Lal, MD; James F. Meschia, MD; Thomas G. Brott, MD; for the CREST Investigators

(Stroke. 2011;42:3484-3490.)

Key Words: carotid artery • carotid endarterectomy • cerebrovascular disease • stents • vascular surgery
Table 1. Description of Study Population by Treatment and Age Strata*

<table>
<thead>
<tr>
<th></th>
<th>Younger Than 65</th>
<th>65–74</th>
<th>75 and Older</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CAS (n=404)</td>
<td>CEA (n=387)</td>
<td>CAS (n=525)</td>
</tr>
<tr>
<td>Male %</td>
<td>64.6</td>
<td>66.7</td>
<td>67.4</td>
</tr>
<tr>
<td>White %</td>
<td>90.6</td>
<td>92.8</td>
<td>93.1</td>
</tr>
<tr>
<td>Asymptomatic arteries %</td>
<td>43.8</td>
<td>41.6</td>
<td>53.1</td>
</tr>
<tr>
<td>Risk factor status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension %</td>
<td>81.4</td>
<td>84.4</td>
<td>88.7</td>
</tr>
<tr>
<td>Diabetes %</td>
<td>32.9</td>
<td>30.6</td>
<td>31.6</td>
</tr>
<tr>
<td>Dyslipidemia %</td>
<td>84.1</td>
<td>85.9</td>
<td>84.3</td>
</tr>
<tr>
<td>Current smoker %</td>
<td>46.3</td>
<td>47.9</td>
<td>22.3</td>
</tr>
<tr>
<td>Prior cardiovascular disease %</td>
<td>36.3</td>
<td>40.8</td>
<td>46.9</td>
</tr>
<tr>
<td>Previous coronary artery bypass %</td>
<td>15.9</td>
<td>18.2</td>
<td>22.3</td>
</tr>
<tr>
<td>Systolic blood pressure (mean±SD) mm Hg</td>
<td>137±20</td>
<td>138±20</td>
<td>142±20</td>
</tr>
<tr>
<td>Diastolic blood pressure (mean±SD) mm Hg</td>
<td>76±12</td>
<td>76±12</td>
<td>74±11</td>
</tr>
<tr>
<td>Stenosis measures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate (&lt;70%)</td>
<td>11.1</td>
<td>12.4</td>
<td>13.3</td>
</tr>
<tr>
<td>Severe (≥70%)</td>
<td>88.9</td>
<td>87.6</td>
<td>86.7</td>
</tr>
<tr>
<td>Left carotid treated %</td>
<td>50.7</td>
<td>53.2</td>
<td>47.8</td>
</tr>
<tr>
<td>Contralateral occlusion %</td>
<td>3.4</td>
<td>4.7</td>
<td>4.9</td>
</tr>
<tr>
<td>Median day from randomization to treatment</td>
<td>6.0</td>
<td>7.0</td>
<td>7.0</td>
</tr>
</tbody>
</table>

SD indicates standard deviation; CEA, carotid endarterectomy; CAS, carotid artery stenting.

*Sample sizes vary for specific characteristics (rows) because of missing data on specific items for a small number of patients.

점절술(carotid endarterectomy, CEA)에 비해 안전한 것이 라 가정되었다. 그러나 연구 초기 수행 시부터 CAS 치료군 중 고령의 환자에서 뇌졸중 발생 위험이 증가하였기 때문에 이는 80세 이상의 환자들은 연구에서 제외하였다.(그나 CEA 치료
군과의 동등한 위험들이 있는지를 평가하기 위해 무작위 단계
까지는 80세 이상의 환자들도 지속적으로 모집하였다. 1) 지자
들은 상대적 효과에 대한 나이의 영향에 대하여 미리 계획된
공식적 평가를 하였다.

대상과 방법

연구 참가자 및 측정

CREST는 CEA와 CAS의 상대적 효과를 평가하기 위한 무
작위 임상시험이다. 이 연구는 중증성 환자 1,321명과 무증상
성 환자 1,181명을 모집하였다. 종합점은 치료 함당에 대해 논
가된 위험요소에서 변동하였다. 연구에 대한 상세한 설명은 이
전 논문에서 확인할 수 있다. 2-3 프로토콜은 모든 참여 기관의
임상시험/오리 심사 위협에 의해 승인되었다.

통계 분석

이 연구의 핵심은 환자의 나이가 CEA와 CAS의 상대적 효
과에 영향을 줄 수 있는지, 그렇다면 이러한 효과 변화의 기여
인자가 무엇인지를 평가하는 것이다. 따라서 효과의 일차적 평
가는 혈착의 중상성 유무 및 성별을 보정한 이후 나이와 치료
의 상호작용 가능성을 평가하기 위해 랜덤화 분석을 이용한
치료-의도도(intention-to-treat) 분석으로 시행되었다. 연구
의 인자 결과 변수는 시술 전후(30일 이내에 치료를 받는 경우
시술 후 30일 이내, 30일 이내에 치료를 받지 않은 경우 무작
위 배정 후 36일 이내)의 뇌졸중, 심근경색증(myocardial
infarction) 및 사망, 또는 무작위 배정 후 4년까지 추적 관찰
기간 동안의 혈착 동족의 뇌졸증으로 정의하였다. 나이에 의한
잠재적인 효과 변화는 나이의 선형 효과를 가정하여 분석하였
다. 뇌졸중은 시술 전후의 모든 뇌졸중 및 이후 4년간 시술 동
측에서 발생한 뇌졸증으로 정의하였다. 심근경색증은 시술 전후
기간 중 심근 효소의 상승과 함께 증상이 있거나 심전도상
근기이 있다는 것으로 정의하였다. 시술 전후 기간 중 사망이 매
우 적어 이에 대한 의미 있는 분석은 이루어지지 않았다.

모형적 접근은 복합 중합점, 뇌졸중 종합점 및 심근경색증
종합점을 예측하기 위한 비례위험모형에 상호작용요인을 추가
되 분석하였다. 선행적으로 P<0.10의 변수들이 효과 변화와
관련되어 있는 것으로 간주하였다. 또한 (1) 난은 영역대에서의
발생 가능 수, (2) 치료와 나이의 상호작용의 일자 분석에서의
선형성에 대한 평가, (3) 다른 연구와의 비교를 위해 각 시술에
따르는 각 영역증에서의 차간 발생률, (4) 각 영역증에서의 CAS
와 CEA의 상대적 효과에 대한 대략적 추정값 등을 제시하기
위해 각 영역증(65세 미만, 65~74세, 75세 이상) 내에서의 이
차 병설도 이루어졌다.

저자들은 또한 모형에 고위 상호작용을 추가하여 증상 여부 및 성별에 따라 치료와 나이와 상호작용에 일관성이 있는지 평가하였다. CAS와 CEA의 상대적 효과의 차이에 기여하는 나이에 따른 위험 변화를 치료군에 따라 보기 위해 CAS 치료군과 CEA 치료군으로 분리하여 비교함으로써를 적용하였다.

마지막으로 치료와 나이의 상호작용에 영향을 미치는 임계적 원인을 파악하기 위해 매개 변수를 수정하여 CAS 치료를 받은 환자들의 인지도에 더 중요한 인자들이 연구되었다(고혈압, 당뇨병 및 이상지질혈증, 병변의 특성의 차이가 영향, 비등성 병변, 계양성 병변 및 혈착 정도, 또는 수술의 차이 등)를 하였다. 대동맥경(aortic arch) 해부, 혈관의 절개, 나이와 성별의 영향도, CEA 치료병중 증후군 통계적으로 정의되는 결과를 이용하여 추정하였다.

결과

두 치료군 모두에서 나이 증가에 따라 어성과 백인이 많아지고 수축기 혈압은 높았으며 이관절 혈압은 낮은 경향을 보였으나 당뇨병, 이상지질혈증, 현재 흡연 여부는 감소하는 경향을 보였다(Table 1). 이점에 관계없이도 이 인자들에 대해 치료군간의 유의한 차이가 없었다. Figure 1에 CAS와 CEA 치료군의 연령 분포가 제시되어 있다.

Table 2에 대략적인 3분위 연령층에 따른 시술 전후 기간 및 4년 결과 동안의 심근경색증, 뇌졸중 및 일차 종합점의 관측치가 제시되어 있다. Figure 2는 각 연령층에서 각각의 종합점을 보인 환자들의 분율의 Kaplan-Meier 추정값을 보여 주는데, CEA 치료군에서는 각 연령층 간 사건-사건 발생이 유사하다. CAS 치료군에서는 각 연령층 간 사건-사건 발생의 차이가 나타났다. 4년간 일차 종합점 발생에 대한 이전의 보고와 같이, 치료와 나이의 유의한 상호작용이 확인되었다(P=0.02).

CEA 대비 CAS의 HR은 65세 미만군의 0.60 (95% CI, 0.31 - 1.18)에서 65~74세군의 유사한 HR (1.08; 95% CI, 0.65 - 1.78), 75세 이상군의 1.63 (95% CI, 0.90 - 2.69)으로 나이에 따라 증가하였다. 이러한 위험 증가는 상대적으로 안정적인 CEA 치료군에서의 위험도(절반 연령중 6.1%, 중간 연령중 6.8%, 고혈압 7.4%)과는 달리 CAS 치료군에서의 사건 발생 증가(절반 연령중 3.9%, 중간 연령중 6.3%, 고혈압 12.7%)가 관찰되었다. 이러한 위험 증가는 뇌졸중 종합점에 의한 것으로 각 연령층에 걸쳐 CEA 대비 CAS의 HR은 각각 0.78 (95% CI, 0.37 - 1.62), 1.42 (95% CI, 0.78 - 2.60), 2.15 (95% CI, 1.19 - 3.91)였다(P=0.033). 그래프에서 CEA 대비 CAS 위험 증가는 CAS 치료군에서의 뇌졸중 발생과 연관이 있었고 (3.7%, 5.1%, 10.9%) CEA 치료군에서는 연관이 없었다 (4.5%, 4.6%, 4.9%)이었다. 이와 유사한 경향의 효과가 시술 전후 기간 동안의 복합 종합점 및 뇌졸중 종합점에 대해서도 관찰되었으나 통계적 유의성은 없었다(P>0.1). 시술 전후 기간 동안 발생한 병변 반대측 뇌졸중의 경우 복합 및 뇌졸중 종합점의 요소로 포함되었으나, 시술 전후 기간 이후에 발생한 병변 반대측 뇌졸중은 이 종합점에 포함되지 않았다. 모든 뇌졸중 종합점(시술 전후 기간 이후에 발생한 병변 반대측 뇌졸중 및 그)에 대한 연령층에 따른 치료 효과는 시술 전후 기간 이후에

---

Figure 1. Histogram of the number of patients within age strata by treatment assignment. CAS indicates carotid artery stenting; CEA, carotid endarterectomy.
Table 2. Number of Events and Event Rates by Age Category for Patients Treated With Carotid Artery Stenting and Carotid Endarterectomy

<table>
<thead>
<tr>
<th>CAS</th>
<th>CEA</th>
<th>Periprocedural Period†</th>
<th>Treatment by Age Interaction</th>
<th>Four-Year Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAS N of</td>
<td>CAS N of</td>
<td>Hazard Rate</td>
<td>N of Events</td>
<td>N of Events</td>
</tr>
<tr>
<td>Events</td>
<td>Events</td>
<td>(95% CI)</td>
<td>(Rate=SE)</td>
<td>(Rate=SE)</td>
</tr>
<tr>
<td>CAS</td>
<td>CEA</td>
<td>P</td>
<td>P</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CAS</th>
<th>CEA</th>
<th>Periprocedural Period†</th>
<th>Treatment by Age Interaction</th>
<th>Four-Year Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAS N of</td>
<td>CAS N of</td>
<td>Hazard Rate</td>
<td>N of Events</td>
<td>N of Events</td>
</tr>
<tr>
<td>Events</td>
<td>Events</td>
<td>(95% CI)</td>
<td>(Rate=SE)</td>
<td>(Rate=SE)</td>
</tr>
<tr>
<td>CAS</td>
<td>CEA</td>
<td>P</td>
<td>P</td>
<td></td>
</tr>
</tbody>
</table>

CAS indicates carotid artery stenting; CEA, carotid endarterectomy; CI, confidence interval; MI, myocardial infarction; NA, not available; SE, standard error.

†Per protocol. P value was calculated with age as a continuous variable.

**Available because of unreliable estimate.

발생한 뇌졸중이 추가됨으로써 그 차이가 희석되었다(P=0.19).

결과 해석에 매우 주의할 점이 있으나, Supplemental Table 1 (https://stroke.ahajournals.org)은 증상 유무에 따른 분석에서도 Table 2와 유사한 결과를 보여 준다. 이 표에서는 나이와 증상 유무 모두에 따른 코호트가 필요하고 이로 인해 특정군에서의 표본 크기가 작아 잘못된 결과를 초래할 수 있다. 지자는 나이와 증상 유무에 따른 상호작용을 고려하였거나 유의성을 발견할 수 없었고(P>0.1), 나이와 위험들의 관계에 대한 무중상성 혹은 중상성 환자들 간 차이는 연구에 의해 쉽게 발생할 수 있다. 그러나 이러한 결과는 무중상성 혹은 중상성 환자들 모두를 포함하지 않는 다른 연구들의 결과와의 비교를 위해 제공되었다.

이 연구의 일부 분석 결과는 Figure 3에 제시되어 있다. Figure 3A는 CREST 입자 종합점에 대해 나이와 연속 변수로 함수화한 관계를 도식화한 것으로, 위험 결과의 1차 보고 논문의 그림과 동일하다. 두 사물의 위험률은 70세에서 유사한
고, CAS는 젊은 환자들에서 우수한 효과를 보였고 나이가 많은 환자들에게는 CEA의 효과가 더 우월하였다. 뇌졸중 종말점과 나이의 함수관계는 Figure 3B에 제시되어 있다. 이 그림에서 기울기가 더 가파른 일차 종말점보다 뇌졸중 발생에 대해 (P=0.033) 나이에 의한 효과 변화의 정도가 더 크다는 것을 알 수 있다. 젊은 환자들에게 CAS가 유의한 장점을 보인다는 복합종말점에 대한 결과는 달리, 뇌졸중 종말점의 경우 CI의 폭이 큰 것은 95% CI의 상한이 1.0보다 크다는 것을 시사한다. 그러나 원래의 본 연구의 핵심은 나이 차에 따른 위험률의 경향을 보고한 것이지, 특정 연령에서의 위험률의 차이를 보고한 것이 아니다. CEA와 CAS의 뇌졸중 발생 위험률이 유사한 시기는 64세로, 일차 종말점의 경우보다 6년 더 높게 나타났다. 95% CI의 폭이 넓다는 것은 일차 종말점에 비해 뇌졸중 종말점의 경우 불확실성이 더 크다는 것을 시사한다. 일차 종말점 중 심근경색증에 대해 나이에 의한 효과 변화는 없는 것으로 나타났다 (P=0.35, Figure 3C).

CIA 치료를 받은 환자들의 나이가 10세 많아질수록 일차 종말점의 위험률은 1.77배 (P<0.0001: 95% CI, 1.38~2.28), 뇌졸중의 위험률은 1.76배 증가하였다 (95% CI, 1.35~2.31). CEA 치료를 받은 환자들의 경우 일차 종말점 (HR, 1.16: 95% CI, 0.89~1.50: P=0.27), 뇌졸중 (HR, 1.12: 95% CI, 0.82~1.54: P=0.47)의 위험률은 나이에 따른 차이를 보이지 않았다. 고위 상호작용을 추가하여 분석한 결과, 나이에 의한 치료 효과의 변화는 증상 유무 (P=0.06) 혹은 성별 (P=0.2)에 영향을 받지 않았다. 기존 심근경색증의 정의에 대한 20건의 생체지표가 양상인 심근경색증까지 포함시킨 민감도 분석에서 나이에 의한 효과 변화는 유의하지 않았다 (P=0.75).
매개 분석
CAS 치료군에서 나이와 연관된 위험들의 차이에 잠재적으로
기여하는 요인을 평가하기 위한 매개 분석이 이루어졌으나
(Table 3), CEA 치료군에 대해서는 나이와 연관된 위험들의 차
이가 유의하지 않아 이러한 분석이 수행되지 않았다. CAS 치료
군에서의 나이의 효과는 고혈압, 당뇨병, 이상지점증, 혹은
관측된 병변의 특성 또는 시술 시각의 차이에 의해 매개된다는
근거는 없었다(P>0.05). 중 투시 환영 기간(P=0.046)의 잠재적
매개 요인으로 확인되었으나, 나이 10세 증가당 HR이 1.68
에서 1.62로 소폭 감소하여 그 효과는 미미하였다.

고찰
본 분석 결과는 CREST 연구10에서 관찰된 나이와 연관된 향
과의 차이가 임상 중점점 중 주로 뇌증증에 의한 것임을 보여
준다. 바꾸어 말하면 뇌증증의 영향은 CAS 치료군에서 나이가
많아지면서 뇌증증의 위험이 증가하지만 CEA 치료군에서는
나이에 따른 뇌증증 위험 변화가 거의 없는 것에 주로 기인
한다.
CAS 치료군과 CEA 치료군에서 뇌증증 위험이 유사한 시점
은 64세였고, 일차 중점점의 경우에는 약 70세였다. 두 군에서
나이에 따른 심근경색증 발생은 차이가 없어, CAS의 경우 모
든 연령대에서 심근경색증 발생이 더 적은 것을 시사한다. 그
러나 뇌증증 발생(122건)에 비해 심근경색증 발생(42건)이 더
적어 뇌증증보다 심근경색증에 대한 효과 변화를 확인하기 위
한 검증이 약했다. 중상 유무 혹은 성별에 따른 치료와 나이
의 상호작용 관계의 변화는 유의하지 않았다.
일차 결과 논문10)에 제시되었던 나이에 의한 효과의 변화는 이어
Stent–Protected Angioplasty vs Carotid Endarterectomy
(SP/ACE) 연구, Endarterectomy Versus Angioplasty in
Patients with Symptomatic Severe Carotid Stenosis
(EVA–3S) 연구, International Carotid Stenting Study
(ICSS)을 이용한 메타분석에서도 확인되었다.11 70세 이상의
환자들에서는 CAS 치료군에서 사건 발생의 위험률은 CEA 치
료를 받은 환자들에 비해 약 2배 정도海淀区(HR, 2.04; 95%
CI, 1.48~2.82). 이 메타분석에서 임상 중점점의 요소로 심근
경색증은 제외되었으므로, 나이에 의한 효과는 역시 뇌증증에
의한 것으로 해석된다. 이 메타분석에서 70세 미만의 환자들
의 위험률은 차이가 없었는데(HR, 1.11: 95% CI, 0.73~1.71).
젊은 CAS 치료군에서 위험률이 낮았던 본 분석 결과와는 차이
가 없다. SPACE 연구진들은 별도로 68세 미만에서 CEA 대
비 CAS의 위험률은 0.54 배(95% CI, 0.28~1.03)로 적었으며,
68세 이상에서는 CAS가 1.80배(95% CI, 0.96~3.40) 위험률이
증가하는 것으로 보고하였다.11 이러한 나이에 의한 효과는 CREST
초기 자료, Carotid Acculink/Accunet Post–Approval
Trial to Uncover Unanticipated or Rare Events (CAP–

Table 3. Results of Mediation Analysis Showing the Hazard Ratio for the Primary End Point Based on a
10-Year Change in Age in Patients Treated With CAS Before and After Adjustment for a Potential
Mediating Factor

<table>
<thead>
<tr>
<th>Covariate Potentially Mediating Impact of Age</th>
<th>Hazard Ratio for a 10–year Difference in Age After Adjustment for Gender and Symptomatic Status</th>
<th>Hazard Ratio for a 10–year Difference in Age After Further Adjustment for Covariate</th>
<th>Change in Coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension (1259/65)</td>
<td>1.77 (1.38~2.27)</td>
<td>1.77 (1.37~2.27)</td>
<td>−0.0021 = 0.0078</td>
</tr>
<tr>
<td>Diabetes (1257/65)</td>
<td>1.77 (1.38~2.27)</td>
<td>1.79 (1.39~2.30)</td>
<td>0.0132 = 0.0153</td>
</tr>
<tr>
<td>Dyslipidemia (1254/65)</td>
<td>1.78 (1.38~2.28)</td>
<td>1.76 (1.37~2.26)</td>
<td>−0.0077 = 0.0139</td>
</tr>
<tr>
<td>Lesion length (mm) (1189/83)</td>
<td>1.73 (1.33~2.23)</td>
<td>1.68 (1.31~2.17)</td>
<td>−0.0236 = 0.0152</td>
</tr>
<tr>
<td>Eccentric lesion (1212/64)</td>
<td>1.75 (1.36~2.25)</td>
<td>1.75 (1.36~2.25)</td>
<td>0.0025 = 0.0094</td>
</tr>
<tr>
<td>Ulcerated lesion (1207/64)</td>
<td>1.75 (1.36~2.25)</td>
<td>1.73 (1.34~2.22)</td>
<td>−0.0127 = 0.0149</td>
</tr>
<tr>
<td>Procedural angiogram percent stenosis (1200/83)</td>
<td>1.73 (1.33~2.23)</td>
<td>1.73 (1.35~2.22)</td>
<td>−0.0001 = 0.0055</td>
</tr>
<tr>
<td>Fluoroscopy time (min) (1156/78)</td>
<td>1.68 (1.30~2.18)</td>
<td>1.62 (1.26~2.09)</td>
<td>−0.0370 = 0.0185</td>
</tr>
<tr>
<td>Total procedure time (min) (1210/83)</td>
<td>1.78 (1.38~2.30)</td>
<td>1.77 (1.37~2.27)</td>
<td>−0.0093 = 0.0123</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Change in Coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>P = 0.79</td>
</tr>
<tr>
<td>P = 0.39</td>
</tr>
<tr>
<td>P = 0.58</td>
</tr>
<tr>
<td>P = 0.60</td>
</tr>
<tr>
<td>P = 0.79</td>
</tr>
<tr>
<td>P = 0.80</td>
</tr>
<tr>
<td>P = 0.046</td>
</tr>
<tr>
<td>P = 0.43</td>
</tr>
</tbody>
</table>
CREST가 고안된 당시 연구진들은 절차적인 CEA에 비해 덜 절차적인 CAS가 고혈압 환자들에게 우수한 효과를 보일 것으로 기대하였다. 따라서, 고혈압에서 CEA의 우월성 및 절차 연구진들 CAS의 우수성은 예상 밖의 결과였다. 이러한 예상은 CREST 초기 등록부에서 CAS를 받은 환자들에게 위험률이 높다는 판찰로 인하여 도전받았고, 본 연구 결과로 확인되었다. CREST 이전의 위험별 관찰 연구들에서 나온의 뇌졸중 위험의 중요한 예측 인자로, 고혈압에서 대동맥질환과 경동맥의 비밀리즘, 석회화 정도 및 임상적으로 운동을 제시하였다. CREST에서는 혈압의 정상, 병변 길이, 비밀리즘 및 갯양 등의 경동맥 질환의 특성을 고혈압의 환자에서 CAS 위험률에 미치는 영향은 없었다. 그러나 동맥의 비밀리즘에 비해 비밀리즘의 원인 데이터에 없었기 때문에 CREST에서의 CAS 사전 발생의 증가에 기여하였을 것으로 생각된다. 이 보고는 대동맥 두께의 경동맥을 포함, 특히 혈관 석회화 정도가 상당히 제3, 3 유형의 확장된 대동맥 질병일 경우 CAS 사전 동안의 서전 위험이 증가할 것으로 가정하였다. 이러한 가정과 부합된 고혈압의 환자에서의 더 큰 CAS 사전 사전 시각치는 필요하였다. 이에 대해 대한 보건 연구에서의 증가된 위험.k를 부분적으로 제가하는 것으로 나타났다. 홍미로운 것은 연구에서의 높은 위험률이 심혈관 관리와 인지차와 연관이 없다는 것으로, 이는 이전 보고들과 일치한다.

환자의 선택, 시술자의 경험 및 기술이 이 분석에서 나아가 상호작용과 관련이 있을 수 있다. 최신화된 결과 선택 기준은 사용한 CEA에 대한 최근 연구들은 CEA에 대한 나아가 선택하기를 권장하고 있다. CREST의 비밀리즘에 영향을 미친 연구로 가진도 연구는 다른 영향을 바탕으로 사용한 이 연구들에서 빛나는 사전 변화는 주요한 사관을 갖는다. 이러한 결과를 확인하기 위해 새로운 연구들이 필요하다.

CREST 연구의 장점은 많은 연구대를 포함한 대규모 코호트 연구이며 무증상 환자를 포함하였고, 나아가 결과가 CREST 신뢰 연구 및 추측 무작위 임상시험 연구 결과와 부합한다는 점 등을 들 수 있다. 단점으로는 기대한 것보다 사전 발생률이 적었다고(CAES 와 CEA 모두 예상보다 개선된 안정성을 보였기 때문), 나이 분포 양 끝의 환자 수가 적었다는 점(55세 이하 161명, 6.4%, 80세 이상 240명, 9.6%)을 들 수 있다 (Figure 1). 그럼에도 불구하고 이 나이 상호작용이 유의하였다는 결과는 나이 분포 양 끝에 충분히 많은 환자를 포함하여 반복기전에 따른 유의한 경향을 제시한다고 하 할 수 있다.

결론
사전에 계획된 이 CREST 연구 분석은 나아가 CEA 대비 CAS 효과의 차이가 주로 뇌졸중 발생에 의한 것임을 증명하였다. CAS의 RR이 제한된 근에서 보고 과학자들로부터 높은 양은 고혈압 환자들 CAS의 뇌졸중 위험이 증가하기 때문이다. CEA의 경우 뇌졸중 위험은 모든 연구본에 걸쳐 상대적으로 일정하다. 저자들은 경동맥 질환에 대한 처방선 선택에 있어 나아가 중요한 요인이 되어야한다고 결론지었다. 이러한 관점에 영향을 미칠 수 있는 해부학적 요인에 대한 추가 연구가 필요할 것이다.

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