Patient age has been shown to influence the outcomes after carotid revascularization. The Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST) protocol was developed in 1997, when age and vascular anatomy 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). 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.
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. 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 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 assumption was reasonable). The stroke component was defined as elevated enzymes plus either symptoms or electrocardiographic evidence of an event during the periprocedural period.

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>Risk factor status</th>
<th>Younger Than 65</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension %</td>
<td>81.4</td>
<td>84.4</td>
<td>88.7</td>
<td>87.9</td>
<td>86.4</td>
<td>85.2</td>
<td></td>
</tr>
<tr>
<td>Diabetes %</td>
<td>32.9</td>
<td>30.6</td>
<td>31.6</td>
<td>34.2</td>
<td>26.0</td>
<td>25.0</td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia %</td>
<td>84.1</td>
<td>85.9</td>
<td>84.3</td>
<td>88.3</td>
<td>79.3</td>
<td>82.2</td>
<td></td>
</tr>
<tr>
<td>Current smoker %</td>
<td>46.3</td>
<td>47.9</td>
<td>22.3</td>
<td>21.0</td>
<td>8.6</td>
<td>9.0</td>
<td></td>
</tr>
<tr>
<td>Prior cardiovascular disease %</td>
<td>36.3</td>
<td>40.8</td>
<td>46.9</td>
<td>50.1</td>
<td>42.9</td>
<td>42.4</td>
<td></td>
</tr>
<tr>
<td>Previous coronary artery bypass %</td>
<td>15.9</td>
<td>18.2</td>
<td>22.3</td>
<td>24.7</td>
<td>21.1</td>
<td>20.8</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mean±SD) mm Hg</td>
<td>137±20</td>
<td>138±20</td>
<td>142±20</td>
<td>141±21</td>
<td>147±20</td>
<td>145±20</td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure (mean±SD) mm Hg</td>
<td>76±12</td>
<td>76±12</td>
<td>74±11</td>
<td>73±11</td>
<td>72±12</td>
<td>73±12</td>
<td></td>
</tr>
</tbody>
</table>

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

**SD indicates standard deviation; CEA, carotid endarterectomy; CAS, carotid artery stenting.**
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 \( (P = 0.02) \). 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 \( (P = 0.033) \) 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 increasing CAS-to-CEA risk at older ages is associated with increasing stroke event rates for those CAS-treated (3.7%, 5.1%, and 10.9%), but not in those CEA-treated (4.5%, 4.6%, and 4.9%). A similar pattern of effects (increasing CAS-to-CEA risk largely driven by increasing risk at older ages in the CAS-treated patients) was observed during the periprocedural period for both the composite and stroke end points; however, these trends failed to reach a level of statistical significance \( (P > 0.1) \). Contralateral strokes occurring during the periprocedural period were a component of the composite outcome and the stroke outcome, but contralateral strokes after the periprocedural period are not part of these outcomes. For the “all stroke” end point (including contralateral strokes occurring after the periprocedural period), the treatment differences across the age spectrums are diluted \( (P = 0.19) \) by the addition of the stroke events beyond the periprocedural period.

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,\textsuperscript{11} 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).

**Figure 1.** Histogram of the number of patients within age strata by treatment assignment. CAS indicates carotid artery stenting; CEA, carotid endarterectomy.

![Histogram of the number of patients within age strata by treatment assignment. CAS indicates carotid artery stenting; CEA, carotid endarterectomy.](http://stroke.ahajournals.org/ Downloaded from)
For those treated with CAS, there was a 1.77-times increase in risk of primary end point event (P=0.0001; 95% CI, 1.38–2.28) and a 1.76-times increase (95% 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

---

**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>Younger than 65</td>
<td>Younger than 65</td>
<td>CAS N of Events (Rate ± SE)</td>
<td>CEA N of Events (Rate ± SE)</td>
<td>Hazard Ratio (95% CI)</td>
</tr>
<tr>
<td>N=525</td>
<td>N=500</td>
<td>10 (2.5±0.8)</td>
<td>14 (3.6±0.9)</td>
<td>0.69 (0.31–1.55)</td>
</tr>
<tr>
<td>65–74</td>
<td>500</td>
<td>26 (5.0±0.9)</td>
<td>21 (4.2±0.9)</td>
<td>1.22 (0.68–2.16)</td>
</tr>
<tr>
<td>75 or older</td>
<td>30 (0.1±0.1)</td>
<td>25 (5.9±1.3)</td>
<td>1.49 (0.85–2.60)</td>
<td>0.16</td>
</tr>
</tbody>
</table>

---

**Figure 2.** Kaplan-Meier estimates of the proportion of study participants with a primary end point. CAS indicates carotid artery stenting; CEA, carotid endarterectomy.
Discussion

The current analysis indicates that the age-related differential efficacy observed in CREST\textsuperscript{11} 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 \( P \approx 70 \) 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,\textsuperscript{11} 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).\textsuperscript{15} 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,
increase in aortic arch and carotid artery tortuosity and predictor of stroke risk8,19,20 potentially related to the marked findings confirmed in the analyses reported herein. Observations (the observation leading to this preplanned analysis), a among the CAS-treated patients in the CREST lead-in regist-

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 factors, consistent with previous reports.25 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). Nonetheless, the finding that the interaction test was significant provides prima facie confirmation that there are sufficient

### 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-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>
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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경동맥 스텐트 및 내막절제술 이후 나이와 예후의 관계
The Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST) 연구
Age and Outcomes After Carotid Stenting and Endarterectomy
The Carotid Revascularization Endarterectomy Versus Stenting Trial

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

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

배경과 목적: CREST (Carotid Revascularization Endarterectomy Versus Stenting Trial) 등록 초기에 경동맥 스텐트(carotid artery stenting, CAS) 치료를 받을 환자들에서의 높은 뇌졸중 발생률은 나이가 경동맥내막절제술(carotid endarterectomy, CEA)에 대비한 CAS의 상대적 효과를 변화(modify)시킬 수 있을 것이라는 가설을 실험적으로 시도하였다. CREST 일차 보고에서 서로 저자들은 일차 중절점의 각 요소에 대한 상대적인 효과, 나이의 치료 특이적 영향 및 고령의 CAS 치료군에서의 위험도를 높이는 기여 인자에 대하여 문헌하였다.

방법: 고도의 경동맥 혈착을 가진 2,502명의 CREST 환자를 대상으로 CAS 대 CEA의 상대적 효과에 대한 나이의 영향 및 CAS 치료군과 CEA 치료군에서의 위험에 대한 나이의 영향을 분석하기 위해 비례위험모형이 적용되었다.

결과: 나이는 일차 중절점에 대해 70세를 기준으로 치료 효과 변화 인자로 작용하였다(P interaction=0.02). CAS의 경우 일차 중절점 발생 위험률은 나이가 많아짐에 따라 유의하게 증가하며(P<0.0001), 10세 증가할 때마다 1.77배(95% CI, 1.38~2.28)로 증가하였다. 그러나 CEA 환자에서 나이에 따른 위험률 증가는 유의하지 않았다(P=0.27), 뇌졸중 발생은 전체 효과 변화의 일차 기여 인자였고(P interaction=0.033), 64세를 기준으로 발생 위험은 유사하였다. CAS와 CEA에 대한 치료와 나이의 상호 작용은 증상 유무(P=0.96)와 성별(P=0.45)에 의해 변경되지 않았다.

결론: CEA에 대한 CAS의 효과는 환자의 나이와 연관되어 있어, 고령에서는 CAS 치료 이후 뇌졸중 위험률이 증가하였다. 경 동맥 혈착을 치료할 경우 두 가지 시술을 선택할 때 나이는 중요하게 고려되어야 할 요인이다.

자기의 나이가 경동맥 재건술 이후의 예후에 영향을 미칠 수 있는 것으로 보고되고 있다.1-4 1997년 CREST (Carotid Revascularization Endarterectomy vs Stenting Trial) 프로토콜이 만들어진 당시 나이와 혈관 해부는 경동맥 스텐트(carotid artery stenting, CAS) 이후 혈중 증상의 예측 인자로 고려되지 않았다.1 반대로 CAS는 고령에서 경동맥내막

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<table>
<thead>
<tr>
<th>Risk Factor Status</th>
<th>CAS (n=404)</th>
<th>CEA (n=387)</th>
<th>CAS (n=529)</th>
<th>CEA (n=500)</th>
<th>CAS (n=333)</th>
<th>CEA (n=353)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male %</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>White %</td>
<td>90.6</td>
<td>92.8</td>
<td>93.1</td>
<td>92.8</td>
<td>95.2</td>
<td>95.5</td>
</tr>
<tr>
<td>Asymptomatic arteries %</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>

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

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.

대상과 방법

연구 참가자 및 측정

CREST는 CEA와 CAS의 상대적 효과를 평가하기 위한 무작위 임상시험이다. 이 연구는 중증성 환자 1,321명과 무중상 성 환자 1,181명을 모집하였다. 중증자는 치료 환자에 대해 눈 가림된 환자에게 환장하였다. 연구에 대한 상세한 설명은 이 전 논문에서 확인할 수 있다. 프로토콜은 모든 참가자 기관의 임상시험/통계 심사 위원회에 의해 승인되었다.

통계 분석

이 연구의 핵심은 환자의 나이가 CEA와 CAS의 상대적 효과에 영향을 줄 수 있다는 점, 그렇지 않으면 이러한 효과의 변화는 기여 인자가 무엇인지 평가하는 것이다. 따라서 효과의 일치성을 평가는 혈착의 중상성 유무 및 성별을 보정한 이후 나이와 치료 의 상호작용 가능성을 평가하기 위해 비교 위험 분석을 이용한 치료-의도(mention-to-treat) 분석으로 시행되었다. 연구 의 일차 결과 변수는 시술 전후(30일 이내에 치료를 받은 경우 시술 후 30일 이내, 30일 이내에 치료를 받지 않은 경우 무작위 배정 후 36일 이내)의 뇌졸중, 심근경색증(myocardial infarction) 및 사망, 또는 무작위 배정 후 4년까지 추적 관찰 기간 동안의 협착 동증의 뇌졸중으로 정의하였다. 나이에 의한 잠재적인 효과 변화는 나이의 성별 효과를 가정하여 분석하였다. 뇌졸중은 시술 전후 모든 뇌졸중 및 이후 4년간 시술 동 측에서 발생한 뇌졸중으로 정의하였다. 심근경색증은 시술 전후 기간 중 심근 효소치의 상승과 함께 증상이 있거나 심전도상 근기장이 있는 경우로 정의하였다. 시술 전후 기간 중 사망 또는 우 뛰어 이에 대한 의미 있는 분석은 이루어지지 않았다.

모형적 접근은 복합 종합점, 뇌졸중 종합점 및 심근경색증 종합점을 예측하기 위한 비례위험모형에 상호작용항을 추가하 여 분석하였다. 설계적으로 P<0.10의 변수들이 효과 변화와 관련되어 있는 것으로 간주하였다. 또한 (1) 고은 연령대에서의 발생 사례 수, (2) 치료와 나이의 상호작용의 임자 분석에서의 신경성에 대한 평가, (3) 다른 연구와의 비교를 위해 각 시술에 따른 각 연령층에서의 사전 발생률, (4) 각 연령층에서의 CAS와 CEA의 상대적 효과에 대한 대략적 추정값 등을 제시하기 위해 각 연령층(65세 미만, 65~74세, 75세 이상) 내에서의 이
차 분석도 이루어졌다.

지자들은 또한 모형에 고위 상호작용량을 추가하여 증상 여부 및 성별에 따라 치료와 나이의 상호작용에 인용성이 있는지 평가하였다. CAS와 CEA의 상대적 효과의 차이에 기여하는 나이에 따른 위험 변화를 차용기로 따라 보기 위해 CAS 치료군과 CEA 치료군으로 분류하여 비례위험모형을 적용하였다.

마지막으로 치료와 나이의 상호작용에 영향을 미치는 잔재적 원인을 파악하기 위해 매개 분석을 수행하여 CAS 치료를 받은 고령의 환자들에서 위험을 증가하는 치료의 증가(고혈압, 당뇨병 및 이상지질혈증(dyslipidemia), 병변의 특성의 차이(병변 길이, 비등심 병변, 계양성 병변 및 혈착 정도), 또는 시술의 차이( '*', aortic arch 이형, 혈관 비품

결과

두 치료군 모두에서 나이 증가에 따라 여성과 임신이 많아지 고 수축기 혈압은 높았으며 이완기 혈압은 낮은 경향을 보였으나 당뇨병, 이상지질혈증, 현재 혈연 여부는 감소하는 경향을 보였다(Table 1). 어떤 흡연증에서도 이 인자들에 대해 치료군 간의 유의한 차이는 없었다. Figure 1에 CAS와 CEA 환자들의 연령 분포가 제시되어 있다.

Table 2에 대략적 3분위 연령층에 따른 시술 전후 기간 및 4년 경과 동안의 심근경색증, 뇌졸중 및 임상 종합점의 관측치가 제시되어 있다. Figure 2는 각 연령층에서 치료 종합점을 보인 환자들의 분포의 Kaplan–Meier 추정값을 보여 주는데, CEA 치료군에서는 각 연령층 간 시간–사건 발생이 유사하나, CAS 치료군에서는 각 연령층 간 시간–사진 발생의 차이가 나타났다. 4년간 임상 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, 0.99–2.69)으로 나이에 따라 증가하였다. 이러한 위험 증가는 상대적으로 안정적인 CEA 치료군에서의 위험률(절은 연령층 6.1%, 중간 연령층 6.8%, 고령층 7.4%)과는 달리 CAS 치료군에서의 사전 발생 증가(절은 연령층 3.9%, 중간 연령층 6.3%, 고령층 12.7%)와 연관되었다. 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). 고령에서 CEA 대비 CEA 치료 위험 증 가는 CAS 치료군에서의 뇌졸중 발생과 연관이 있었고(3.7%, 5.1%, 10.9%) CEA 치료군에서는 연관이 없었다 (4.5%, 4.6%, 4.9%). 이와 유사한 경향의 효과가 시술 전후 기간 동안의 복합 종합점 및 뇌졸중 종합점에 대해서도 관찰되 었으나 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 포함)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>Age Category</th>
<th>CAS</th>
<th>CEA</th>
<th>Periprocedural Period 1/</th>
<th>Four-Year Period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Younger</td>
<td>Younger</td>
<td>(Rate ± SE)</td>
<td>(Rate ± SE)</td>
</tr>
<tr>
<td>Primary end point (any stroke, MI or death)</td>
<td>Younger</td>
<td>N=287</td>
<td>1.0 (2.0±0.8)</td>
<td>1.0 (4.2±0.8)</td>
</tr>
<tr>
<td>within periprocedural period (postprocedural)</td>
<td>75 or older</td>
<td>N=137</td>
<td>1.0 (2.0±0.8)</td>
<td>1.0 (4.2±0.8)</td>
</tr>
<tr>
<td>Stroke end point (any stroke within 30 days of hospitalization)</td>
<td>Younger</td>
<td>N=287</td>
<td>1.0 (2.0±0.8)</td>
<td>1.0 (4.2±0.8)</td>
</tr>
<tr>
<td>Death</td>
<td>Younger</td>
<td>N=287</td>
<td>1.0 (2.0±0.8)</td>
<td>1.0 (4.2±0.8)</td>
</tr>
</tbody>
</table>

1/Perioperative 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.
2/Events rates for MI end point were calculated as the proportion exposed patients experiencing the end point with SE calculated from the binomial distribution, whereas event rates for stroke end point and primary end point were calculated using Kaplan-Meier survival function with SE calculated from the Greenwood formula.
3/CI indicates carotid artery stenting; CEA, carotid endarterectomy; CI, confidence interval; MI, myocardial infarction; NA, not available; SE, standard error.

Figure 2. Kaplan-Meier estimates of the proportion of study participants with a primary end point. CAS indicates carotid artery stenting; CEA, carotid endarterectomy.

결과 해석에 매우 주의할 점이 있으나, Suplemental Table 1 (https://stroke.ahajournals.org)은 증상 유무에 따른 분석에서도 Table 2와 유사한 결과를 보여준다. 이 표에서는 나이와 증상 유무 모두에 따른 계층화가 필요하고 이로 인해 특정군에서의 표본 크기가 작아 잘못된 결과를 초래할 수 있다. 자료들은 나이와 증상 유무에 따른 상호작용을 고려하였으나 유의성을 발견할 수 없었고(P>0.1), 나이와 위험군의 관계에 대한 무증상성 혹은 증상성 환자간 차이는 유의로도 쉽게 발견할 수 있다. 그러나 이러한 결과는 무증상성 혹은 증상성 환자들 모두를 포함하지 않는 다른 연구들의 결과와의 비교를 위해 제공되었다.

이 연구의 이차 분석 결과는 Figure 3에 제시되어 있다. Figure 3A는 CREST 임상 종합점에 대해 나이를 연속 변수로 함수화한 관계를 도식화한 것으로 연구 결과의 1차 보고 논문의 그림과 동일하다. 2) 두 시술의 위험률은 70세에서 유사하였
Figure 3. The impact of age on the relative efficacy of carotid artery stenting (CAS) vs carotid endarterectomy (CEA). A, Hazard for the primary end point of any stroke, death, or myocardial infarction (MI) during the periprocedural period, plus ipsilateral strokes over the subsequent 4-year period. Progressively better outcomes were seen with CAS in patients younger than 70 years and with CEA in those older than 70 years. B, Hazard as a function of age for the stroke component of the primary end point (any stroke during the periprocedural period plus ipsilateral stroke over the subsequent 4-year period). Progressively better outcomes were seen with CAS in patients younger than 64 years, and with CEA in those older than 64 years. C, Hazard for the MI component of the primary end point (MI during the periprocedural period). The third component, deaths during the periprocedural period, is not provided because of the relatively small number of death events.
<table>
<thead>
<tr>
<th>Covariate</th>
<th>Potentially Mediating Impact of Age (Sample Size/N of Events)</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>
<td>P=0.79</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>
<td>P=0.39</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>
<td>P=0.58</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>–0.0268±0.0152</td>
<td>P=0.60</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>
<td>P=0.79</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>
<td>P=0.40</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>
<td>P=0.98</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>
<td>P=0.046</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>
<td>P=0.43</td>
</tr>
</tbody>
</table>

매개 분석
CAS 치료군에서 나이와 연관된 위험요소의 차이에 잠재적으로 기여하는 요인을 평가하기 위한 매개 분석이 이루어졌으나 (Table 3), CEA 치료군에 대해서는 나이와 연관된 위험요소의 차이가 유의하지 않아 이러한 분석이 수행되지 않았다. CAS 치료군에서의 나이의 효과는 고혈압, 당뇨병, 이상혈압증, 혹은 관측된 병변의 특성 또는 시술 시간의 차이에 의해 매개된다는 근거는 없다(P>0.05), 중 다른 환경 허용(P=0.046)의 잠재적 매개 요인으로 확인되었으나, 나이 10세 증가당 HR이 1.68에서 1.62로 소폭 감소하여 그 효과는 미미하였다.

고찰
본 분석 결과는 CREST 연구에서 관찰된 나이와 연관된 효과의 차이가 각각 중앙값 중 주로 나이증에 의한 것임을 보여 준다. 바꾸어 말하면 나이증의 영향은 CAS 치료군에서 나이가 많아지면서 나이증의 위험이 증가하지만 CEA 치료군에서는 나이에 따른 나이증 위험 변화가 거의 없는 것에 주로 기인 한다.
CAS 치료군과 CEA 치료군에서 나이증 위험이 유사한 시점은 64세였고, 일자 종발점의 경우에는 약 70세였다. 두 군에서 나이에 따른 심근경색증 발생은 차이가 없어, CAS의 경우 모든 연령대에서 심근경색증 발생이 더 적은 것을 시사한다. 그

러나 나이증 발생(122건)을 비해 심근경색증 발생(42건)이 더 적어 나이증보다 심근경색증에 대한 효과 변화를 확인하기 위한 기준이 일부 약하였다. 중상 유무 혹은 성별에 따른 치료와 나이의 상호작용 관계의 변화는 유의하지 않았다.
일자 결과 논문에 제시되었던 나이와 연관된 효과의 변화는 이어
Stent–Protected Angioplasty vs Carotid Endarterectomy (SPACE) 연구, Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA–3S) 연구, International Carotid Stenting Study (ICSS)를 이용한 메타분석에서도 확인되었다. 70세 이상의 환자들은 CAS 치료군에서 사기 발생의 위험률은 CEA 치료 받은 환자들에 비해 약 2배 정도였다(3.42; 95% CI, 1.48~2.82). 이 메타분석에서 일부 증점의 요소로 심근
경색증은 제외되었으므로, 나이에 의한 효과는 역시 나이증에 의한 것으로 해석된다. 이 메타분석에서 70세 미만의 환자들의 위험률은 차이가 없었다(3.42; 95% CI, 0.73~1.71), 젊은 CAS 치료군에서 위험률이 낮았던 본 분석 결과와 차이가 있다. SPACE 연구진들은 별도로 68세 미만에서 CEA 대비 CAS의 위험률은 0.54배(95% CI, 0.28~1.03)로 적었으며, 68세 이상에서는 CAS가 1.80배(95% CI, 0.96-3.40) 위험률이 증가하는 것으로 보고하였다. 70세 이상의 나이의 효과는 CREST
 초기 자료, Carotid Acculink/Accunet Post–Approval Trial to Uncover Unanticipated or Rare Events (CAP–
TURE) 등록부 및 ICSS 결과와도 일치한다. 위의 모든 연구 역시 CREST와 유사한 신경 기능을 사용하여, 현재 고혈압에서 중요하다고 생각되는 CAS에 대한 해부학적 계외 기준을 포
함하지 않았다. 또한 뇌졸중 및 심근경색증에 효과 변화를 볼도로 조사한 연구는 없다.

CREST가 고혈압 당시 연구진은 친숙적인 CEA에 비해
비 친숙한 CAS가 고혈압 환자에게 유리한 효과를 보일
것으로 기대하였다. 따라서, 고혈압에서의 CEA의 우열성 및 점
은 뇌졸중 및 심근경색증에 효과 변화를 볼도로 조사한 연구는 없다.

어려운 예상은 CREST 초기 등록부에서 CAS를 받은 환자들에서 위험
을 높다는 결과로 인하여 도저히, 본 연구 결과로 확인
되었다. CREST이전 외래진 관찰 연구에서 나타난 뇌졸중
위험의 중요한 예측 인자로, 23, 24 고혈압에서 대뇌동맥구경과 동맥
의 비결손, 섬회화 정도와 임상적으로 연관되어 있음을 제시하
였다. CREST에서는 혈압의 정도, 병변 길이, 비결손성 및 개
방 등의 경도의 복합성 병변의 특성 고혈압 환자에서 CAS 위
험성을 미치는 영향은 없었다. 그러나 동맥의 비결손이나 병변
의 섬회화의 현계 레이터들에 없었기 때문에 고혈압에서의 CAS 사
건 발생의 증가를 기여하였을 수도 있다. 23, 24 저자들은 비결손
두께의 경도를 지날 때, 특히 혈관 섬회화 정도가 상당하고
제2, 3 유형의 확장된 동맥구경 형태일 경우 CAS 사망 동산의
세전 위험성이 증가할 것으로 가정하였다. 이러한 가정과 부분
계 고혈압의 환자에서는 더 긴 CAS 사망 시간이 필요하였다. 이
요인에 대한 보고가 고혈압에서의 증가된 위험률을 부분적으로
배제하는 것으로 나타났다. 흥미로운 것은 고혈압에서의 뇌 위
험률이 심혈관에 의해 위험 인자와 연관성이 없는 것으로,
이는 이전 보고들과 일치한다. 25

환자의 심장 및 골밀도의 심결과 심장이 이 분석에서 나아
관한 상호작용과 관련을 있을 수 있다. 최신화된 환자 선택 기준을
사용한 CEA에 대한 최근 연구들은 CAS에 대한 나아에 따른
-choice가 없었다고 제시하고 있다고 제시하였다. 25, 26 또한 동맥의 비
결손에 영향을 미친 방식으로 고혈압의 근위부 병변을 사용한 이
연구에서 고혈압의 낮은 사망 발생률은 수락할 만하다. 25, 26 이러한 결과를 확인하기 위해 새로운 연구들이 필
요하다.

CREST 연구의 장점은 많은 연구대상을 포함한 대규모 코호트
연구이며 무상환 환자를 포함하였고, 나아에 대한 결과가
CREST 신뢰 연구 및 후속 무작위 임상시험 연구 결과와 부합
한다는 점 등을 들 수 있다. 단점으로는 기대한 것보다 사망 발
생 수가 적었고(CAS와 CEA 모두 우리보다 훨씬 작은 연구를
보였기 때문), 나아 분포 중 뇌시 작가 적었다는 점(55세
이하 161명, 6.4%; 80세 이상 240명, 9.6%)을 들 수 있다
(Figure 1). 그량에도 불구하고 나아 상호작용이 유의하였다는
결과는 나아 분포 중에 충분히 많은 환자들을 포함하여 반
복시 갱신되는 유의한 근거를 제시한다고 할 수 있다.

결론
사전에 계획된 이 CREST 연구 분석은 나아에 따른 CEA 대
비 CAS 효과의 차이가 주로 뇌졸중 발생에 의한 것임을 증명
하였다. CAS의 RR이 적은 군에서 낮고 고혈압에서 높은 양상은
고혈암 환자들에서 CAS의 뇌졸중 위험이 증가하기 때문이다.
CEA의 경우 뇌졸중 위험은 모든 연구대에 걸쳐 상대적으로 일
정하나, 저자들은 경청동맥 혈관에 대한 치료적 선택에 있어 나
아가 중요한 요인이 되어한다면 결과는 이다. 이러한 관점에
영향을 미칠 수 있는 해부학적 요인에 대한 추가 연구가 필요
할 것이다.

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