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

Jenifer H. Voeks, PhD; George Howard, DrPH; Gary S. Roubin, MD, PhD; Mahmoud B. Malas, MD; David J. Cohen, MD; W. Charles Sternebergh, 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

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 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.
Too few deaths occurred during the periprocedural period to permit meaningful analyses of this component on its own.

The focus of these analyses is to assess if the age of the patient influences the relative efficacy of CAS versus 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 procedure 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 distribution of the ages for CAS and CEA). There were no significant differences between treatment groups for these factors in any age strata. Figure 1 shows 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.

Finally, to identify potential causes underlying the age–treatment interaction, we conducted a mediation analysis 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 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). The increasing CAS-to-CEA risk at older ages is associated with increasing stroke event rates for those CAS-treated (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: 4.5% youngest, 4.6% middle, 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, 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>Treatment by Age Interaction</th>
<th>Primary End Point (Any Stroke)†</th>
<th>Death</th>
<th>Stroke End Point (Any Stroke)</th>
<th>Periprocedural Period†</th>
<th>Four-Year Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAS</td>
<td>N of Events (Rate ± SE)</td>
<td>CAS N of Events (Rate ± SE)</td>
<td>Treatment</td>
<td>N of Events (Rate ± SE)</td>
<td>N of Events (Rate ± SE)</td>
</tr>
<tr>
<td>Younger than 65</td>
<td>14 (3.9 ± 1.1)</td>
<td>22 (6.1 ± 1.3)</td>
<td>0.37</td>
<td>0.13</td>
<td>14 (3.9 ± 1.1)</td>
</tr>
<tr>
<td>CAS</td>
<td>32 (6.3 ± 1.1)</td>
<td>29 (6.8 ± 1.3)</td>
<td>0.51</td>
<td>0.27</td>
<td>32 (6.3 ± 1.1)</td>
</tr>
<tr>
<td>CEA</td>
<td>38 (12.7 ± 1.9)</td>
<td>25 (7.4 ± 1.4)</td>
<td>0.16</td>
<td>0.19</td>
<td>38 (12.7 ± 1.9)</td>
</tr>
<tr>
<td>Younger than 65</td>
<td>13 (3.7 ± 1.0)</td>
<td>16 (4.5 ± 1.1)</td>
<td>0.85</td>
<td>0.27</td>
<td>13 (3.7 ± 1.0)</td>
</tr>
<tr>
<td>CAS</td>
<td>26 (5.1 ± 1.0)</td>
<td>18 (4.6 ± 1.1)</td>
<td>0.08</td>
<td>0.02</td>
<td>26 (5.1 ± 1.0)</td>
</tr>
<tr>
<td>CEA</td>
<td>33 (10.9 ± 1.8)</td>
<td>16 (4.9 ± 1.2)</td>
<td>0.035</td>
<td>0.05</td>
<td>33 (10.9 ± 1.8)</td>
</tr>
<tr>
<td>Younger than 65</td>
<td>21 (6.7 ± 1.5)</td>
<td>20 (6.0 ± 1.4)</td>
<td>0.85</td>
<td>0.27</td>
<td>21 (6.7 ± 1.5)</td>
</tr>
<tr>
<td>CAS</td>
<td>46 (11.4 ± 1.9)</td>
<td>30 (8.1 ± 1.6)</td>
<td>0.08</td>
<td>0.02</td>
<td>46 (11.4 ± 1.9)</td>
</tr>
<tr>
<td>CEA</td>
<td>38 (13.1 ± 2.1)</td>
<td>28 (9.4 ± 2.2)</td>
<td>0.035</td>
<td>0.02</td>
<td>38 (13.1 ± 2.1)</td>
</tr>
<tr>
<td>Younger than 65</td>
<td>19 (6.6 ± 1.6)</td>
<td>16 (8.2 ± 2.2)</td>
<td>0.05</td>
<td>0.02</td>
<td>19 (6.6 ± 1.6)</td>
</tr>
<tr>
<td>CAS</td>
<td>36 (9.7 ± 1.7)</td>
<td>30 (12.3 ± 2.6)</td>
<td>0.038</td>
<td>0.02</td>
<td>36 (9.7 ± 1.7)</td>
</tr>
<tr>
<td>CEA</td>
<td>39 (18.2 ± 3.0)</td>
<td>37 (18.0 ± 3.0)</td>
<td>0.38</td>
<td>0.01</td>
<td>39 (18.2 ± 3.0)</td>
</tr>
</tbody>
</table>

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...
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$^{11}$ 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 ∼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,$^{11}$ 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).$^{15}$ 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, 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.
increase in aortic arch and carotid artery tortuosity and translational studies completed before CREST documented age as a finding 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 registry, this position was challenged by the observation of high risk performance of CAS in younger individuals were unexpected. 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. 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. 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. 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. 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 (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>

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 separate effect modification by the stroke and MI components of the outcomes.

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 among the CAS-treated patients in the CREST lead-in registry10 (the observation leading to this preplanned analysis), a finding confirmed in the analyses reported herein. Observational studies completed before CREST documented age as a predictor of stroke risk8,19,20 potentially related to the marked increase in aortic arch and carotid artery tortuosity and calcification in the elderly. In CREST, characteristics of the carotid lesion such as the degree of stenosis, lesion length, eccentricity, and ulceration had no detectable effect on risk of CAS at older ages. However, the degrees of arterial tortuosity or lesion calcification were not available in the data set and could contribute to the increased CAS event rates in the elderly.9,21–24
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.

Sources of Funding
This work was supported by the National Institute of Neurological Disorders and Stroke (NINDS) and the NIH (R01 NS 038384), and by supplemental funding from Abbott Vascular Solutions (formerly Guidant), including donations of Accunet and Acculink systems, equivalent to approximately 15% of the total study cost, to CREST centers in Canada and to CREST centers in the United States that were at Veterans Affairs sites.

Disclosures
G.H. is a Consultant/Advisory Board for Bayer Healthcare, member of the ARRIVE Executive Committee, received research support from Amgen and Bayer Healthcare, and is a consultant to Abbott Vascular for preparation of FDA materials. G.S.R. received royalties from Abbott Vascular and Cook. D.J.C. received research support from Boston Scientific, Abbott Vascular, Edwards Lifesciences, MedRad, Merck/Schering-Plough, Medtronic, and Eli Lilly-Daiichi Sankyo, is a consultant to Schering-Plough, Eli Lilly, Medtronic, and Cordis, and is a member of the Speakers’ Bureau for Eli Lilly and The Medicines Company. H.D.A. is a member of the Speakers’ Bureau/Advisory Board for Medtronic.

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


Stroke. 2011;42:3484-3490; originally published online October 6, 2011;
doi: 10.1161/STROKEAHA.111.624155

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/42/12/3484

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2012/08/08/STROKEAHA.111.624155.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/
경동맥 스테нт 및 내막질제술 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

Jennifer H. Vocks, PhD; George Howard, DrPH; Gary S. Roubin, MD, PhD; Mahmoud B. Malas, MD; David J. Cohen, MD; W. Charles Sternbergh, 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

배경과 목적: CREST (Carotid Revascularization Endarterectomy Versus Stenting Trial) 등록 초기에 경동맥 스테нт(carotid artery stenting, CAS) 치료를 받은 환자들에서의 높은 뇌졸중 발생률은 나이가 경동맥내막질제술(carotid endarterectomy, CEA)에 비해 CAS의 상대적 효과를 변화(modify)시킬 수 있을 것이라는 가설을 실험적으로 제시하였다. CREST 일차 보고에서 서도 저작들은 나이에 따른 효과 변화에 주목하였다. 이 연구에서 저작들은 일차 종합검의 각 요소에 대한 상대적인 효과, 나이의 치료 특이적 영향 및 고령의 CAS 치료군에서의 위험률을 높이는 기여 인자에 대하여 분석하였다.

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

결과: 나이는 일차 종합검에 대해 70세를 기준으로 치료 효과 변화 인자로 작용하였다(P interaction=0.02). CAS의 경우 일차 종합검 발생 위험률은 나이가 많아짐에 따라 유의하게 증가하여(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 변화되지 않았다.

결론: CEA에 비해 CAS의 효과는 환자의 나이와 연관되어 있어, 고령에서는 CAS 치료 이후 뇌졸중 위험률이 증가하였다. 경동맥 혈착을 치료할 경우 이 두 가지 시술을 선택함에 있어 나이는 중요하게 고려되어야 할 요인이다.

차기의 나이는 경동맥 재건술 이후의 예후에 영향을 미칠 수 있는 것으로 보고되고 있다.1 1997년 CREST (Carotid Revascularization Endarterectomy vs Stenting Trial) 프로토타이포 더어빌 당시 나이와 관련 해부는 경동맥 스테 임의의 치료 (carotid artery stenting, CAS) 이후 합병증 발생의 예측 인자로 고려되지 않았다.1 반대로 CAS는 고령에서 경동맥내막

From the Department of Epidemiology (J.H.V.) and Department of Biostatistics (G.H.), University of Alabama at Birmingham, Birmingham, AL; Department of Cardi ovascular Medicine (G.S.R.), Lenox Hill Hospital, New York, NY; Department of Vascular & Endovascular Surgery (M.B.M.), Johns Hopkins Bayview Medical Center and the Johns Hopkins Hospital, Baltimore, MD; Saint Luke’s Mid America Heart and Vascular Institute (D.J.C.), Kansas City, MO; Vascular and Endovascular Surgery (W.C.S.), Ochsner Health Systems, New Orleans, LA; Michigan Heart & Vascular Institute (H.D.A.), Ypsilanti, MI; Division of Vascular Surgery (M.E.K.), Northwestern Memorial Hospital, Chicago, IL; Department of Surgery (A.J.S.), UMDNJ-New Jersey Medical School, Newark, NJ; Vascular Surgery (B.K.L.), University of Maryland Medical Center, Baltimore, MD; Department of Neurology (J.F.M., T.G.B.), Mayo Clinic, Jacksonville, FL. Correspondence to Thomas G. Brott, MD, Mayo Clinic, 4500 San Pablo Rd, Griffin Bldg 3rd Floor, Jacksonville, FL 32224. E-mail brott.thomas@mayo.edu

© 2011 American Heart Association, Inc.
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=340)</td>
<td>CAS (n=520)</td>
<td>CAS (n=333)</td>
</tr>
<tr>
<td>Male %</td>
<td>64.6</td>
<td>67.4</td>
<td>57.7</td>
</tr>
<tr>
<td>White %</td>
<td>90.6</td>
<td>93.1</td>
<td>95.2</td>
</tr>
<tr>
<td>Asymptomatic arteries %</td>
<td>43.8</td>
<td>53.1</td>
<td>41.4</td>
</tr>
<tr>
<td>Risk factor status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension %</td>
<td>81.4</td>
<td>88.7</td>
<td>86.4</td>
</tr>
<tr>
<td>Diabetes %</td>
<td>32.9</td>
<td>31.6</td>
<td>26.0</td>
</tr>
<tr>
<td>Dyslipidemia %</td>
<td>84.1</td>
<td>84.3</td>
<td>79.3</td>
</tr>
<tr>
<td>Current smoker %</td>
<td>46.3</td>
<td>22.3</td>
<td>8.6</td>
</tr>
<tr>
<td>Prior cardiovascular disease %</td>
<td>36.3</td>
<td>46.9</td>
<td>42.9</td>
</tr>
<tr>
<td>Previous coronary artery bypass %</td>
<td>15.9</td>
<td>22.3</td>
<td>21.1</td>
</tr>
<tr>
<td>Systolic blood pressure (mean±SD) mm Hg</td>
<td>137±20</td>
<td>142±20</td>
<td>147±20</td>
</tr>
<tr>
<td>Diastolic blood pressure (mean±SD) mm Hg</td>
<td>76±12</td>
<td>74±11</td>
<td>72±12</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>13.3</td>
<td>15.0</td>
</tr>
<tr>
<td>Severe (≥70%)</td>
<td>88.9</td>
<td>86.7</td>
<td>85.0</td>
</tr>
<tr>
<td>Left carotid treated %</td>
<td>50.7</td>
<td>47.8</td>
<td>55.0</td>
</tr>
<tr>
<td>Contralateral occlusion %</td>
<td>3.4</td>
<td>1.9</td>
<td>3.3</td>
</tr>
<tr>
<td>Median days from randomization to treatment</td>
<td>6.0</td>
<td>7.0</td>
<td>6.0</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.

결제술(carotid endarterectomy, CEA)에 비해 안전할 것이 라 가정되었다. 그러나 연구 초기 수행 시부터 CEA 치료군 중 고령의 환자에서 뇌졸중 발생 위험이 증가하였기 때문에 이에 80세 이상의 환자들을 연구에서 제외하였다(그러나 CEA 치료
군과의 동등한 환자들이 있는지를 평가하기 위해 무작위 단계
까지는 80세 이상의 환자들도 지속적으로 모집하였다). 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 3,212명과 무증상
성 환자 1,811명을 모집하였다. 측정은 치료 후당에 대해 눈
가릴된 위험군에서 두가지로 분류하였다. 연구에 대한 상세한 설명은 이
전 논문에서 확인할 수 있다. 프로토콜은 모두 참여 기관의
임상시험/윤리 심사 위험에 의해 승인되었다.

통계 분석

이 연구의 핵심은 환자의 나이가 CAS와 CEA의 상대적 효
과에 영향을 줄 수 있는지, 그렇다면 이러한 효과 변화의 기여
인자가 무엇인지 평가하는 것이다. 따라서 효과의 임차적 평
가는 혈압의 증상성 유무 및 성별을 보정한 이후 나이와 치료
의 상호작용 가능성을 평가하기 위해 비례 위험 분석을 이용한
치료-의도(intention-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 무작
위 배정 후 36일 이내)의 뇌졸중, 심근경색증(myocardial
infarction) 및 사망, 또는 무작위 배정 후 4년까지 추적 관찰
g간 동안 혈증 동증의 뇌졸중으로 정의하였다. 나이에 의한
결제의 효과 변화는 나이의 동정 효과를 가정하여 분석하였
다. 뇌졸중은 시술 전후의 모든 뇌졸중 및 이후 4년간 시술 동
측에서 발생한 뇌졸중으로 정의하였다. 심근경색증은 시술 전후
기간 중 심근 고혈압의 사망과 함께 증상이 있거나 심장조음
근기가 있는 경우로 정의하였다. 시술 전후 기간 중 사망이 매
우 적어 이에 대한 의미 있는 분석은 이루어지지 않았다.

모형적 접근은 복합 종합검, 뇌졸중 종합검 및 심근경색증
종합검을 예측하기 위한 비례위험모형에 상호작용항을 추가하
여 분석하였다. 허기를 P<0.10의 변수들이 효과 변화와
관련되어 있는 것으로 간주하였다. 또한 (1) 난은 연령대에서의
발생 사례 수, (2) 치료와 나이의 상호작용의 일차 분석에서의
신뢰성에 대한 평가, (3) 다른 연구와의 비교를 위해 각 시술에
따른 각 연령구에서의 사전 발생률, (4) 각 연령구의 CAS와
CEA의 상대적 효과에 대한 대역적 추정값 등을 제시하기
위해 각 연령구(65세 미만, 65~74세, 75세 이상) 내에서의 이


차 분석도 이루어졌다.

저자들은 또한 모형에서 고위 상호작용을 추가하여 증상 여부 및 성별에 따라 치료와 나이의 상호작용을 일관성이 있는지 평가하였다. CAS와 CEA의 상대적 효과의 차이에 기여하는 나이에 따른 위험 변화를 치료군에 따라 보기 위해 CAS 치료
군과 CEA 치료군으로 분류하여 비례위험모형을 적용하였다.

마지막으로 치료와 나이의 상호작용에 영향을 미치는 잔재적 원인을 파악하기 위해 매개 분석을 수행하여 CAS 치료를 받은 환자들에서 위험률 증가가 위험 인자의 증가(고혈
압, 당뇨병 및 이상지질혈증(dyslipidemia)), 변경의 특성의 차이(변변 길이, 비등심성 변경, 패혈성 변경 및 혈착 정도), 또는 시술의 차이(最初 첫 번째 시술 혹은 총 시술 시간)에 기인한
것인지를 알아보고자 이러한 요인들을 모형에 포함시키고 나
이에 따른 추정 HR의 변화를 관찰하였다. 변경의 특성은 각
병원에서 결정하였다. 대장벽액(aortic arch) 해부, 혈관 비플
림, 나이와 연관된 석화의 정도, CAS 합병증 등은 분석에 포함
되지 않았다. 매개 분석의 표준오차는 부트스트랩(bootstrap)
기법을 이용하여 추정하였다.

결과

두 치료군 모두에서 나이 증가에 따라 여성과 백인이 많아지
고 수축기 혈압은 높았으며 이완기 혈압은 낮은 경향을 보였으
나 당뇨병, 이상지질혈증, 현대 혈관 여부는 감소하는 경향을
보았다(Table 1). 이번 연령층에서도 어느 인자들에 대해 치료군간의 유의한 차이는 없었다. Figure 1에 CAS와 CEA 환자들
의 연령 분포가 제시되어 있다.

Table 2에 대략적 3분위 연령층에 따른 시술 전후 기간 및
4년 경과 동안의 신근경색증, 뇌졸중 및 일차 종합점의 관측치
가 제시되어 있다. Figure 2는 각 연령층에서 인자 중간점을
보인 환자들의 분율의 Kaplan-Meier 추정값을 보여 주는데,

CEA 치료군에서는 각 연령층 간 시간-사전 발생이 유사하나,
CAS 치료군에서는 각 연령층 간 시간-사전 발생의 차이가 나
타났다. 4년간 일차 종합점 발생에 대한 이전의 보고와 같
이, 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, 0.96~2.69)으로 나이에
따라 증가하였다. 이러한 위험 증가는 상대적으로 연령대인
CEA 치료군에서의 위험률(절연령중 6.1, 중간 연령중
6.8, 고령중 7.4)과는 달리 CAS 치료군에서의 사건 발생
증가(절연령중 3.9, 중간 연령중 6.3, 고령중 12.7)가
현관되었다. 이러한 위험 증가는 뇌졸중 중음주에 의한 것으로
각 연령층에 걸친 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 CAS 대비 CEA 위험 중
간은 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 중음주에 대해서도 관찰되
었으나 통계적 유의성이 없었다(P>0.1). 시술 전후 기간 동안
발생한 병변 반대측 뇌졸중의 경우 복합 및 뇌졸중 중음주의
요소로 포함되었으나, 시술 전후 기간 이후에 발생한 병변 반
대측 뇌졸중은 이 중음주에 포함되지 않았다. 모든 뇌졸중
증합점(시술 전후 기간 이후에 발생한 병변 반대측 뇌졸중 포
함)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>
</tr>
</thead>
<tbody>
<tr>
<td>Younger than 65</td>
<td>Younger than 65</td>
</tr>
<tr>
<td>65–74</td>
<td>75 or older</td>
</tr>
<tr>
<td>N=404</td>
<td>515</td>
</tr>
<tr>
<td>N=397</td>
<td>500</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Periprocedural Period†</th>
<th>Treatment by Age Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAS N of Events</td>
<td>CEA N of Events</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Four-Year Period</th>
<th>Treatment by Age Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAS N of Events</td>
<td>CEA N of Events</td>
</tr>
</tbody>
</table>

CAS indicates carotid artery stenting; CEA, carotid endarterectomy; CI, confidence interval; MI, myocardial infarction; 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.

‡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 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.

*P was calculated from hazard ratios.

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

††Not available because of unreliable estimates.

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 계층화가 필요하고 이로 인해 특정군에서의 표본 크기가 작아 잘못된 결과를 초래할 수 있다. 저장은 나이와 증상 유무에 따른 상호작용을 고려하였으나 유의성을 발견할 수 없었고(P>0.1), 나이와 위험군의 관계에 대한 무중상성 혹은 증상성 환자를 간 차이는 우연에 의해 쉽게 발생할 수 있다. 그러나 이러한 결과는 무중상성 혹은 증상성 환자를 모두 포함하지 않는 다른 연구들의 결과와의 비교를 위해 제공되었다.

이 연구의 일부 분석 결과는 Figure 3에 제시되어 있다. Figure 3A는 CREST 일차 종합점에 대해 나이를 연속 변수로 함수화한 곡선을 도식화한 것으로 연구 결과의 1차 보고 논문의 그림과 동일하다. 두 시술의 위험률은 70세에서 유사하였으며

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

Figure 3. Kaplan-Meier estimates of the proportion of study participants with a primary end point, CAS indicates carotid artery stenting; CEA, carotid endarterectomy.

Figure 4. Kaplan-Meier estimates of the proportion of study participants with a primary end point, CAS indicates carotid artery stenting; CEA, carotid endarterectomy.
고, CAS는 젊은 환자들에서 우수한 효과를 보였고 나이가 많 은 환자들에서는 CEA의 효과가 더 우월하였다. 뇌졸중 종말 점과 나이의 영향은 Figure 3B에서 제시되어 있다. 이 그 름에서 가용가 더 가파른 일차 종말점보다 뇌졸중 발생에 대 해(P=0.033) 나이에 의한 효과 변화의 정도가 더 크다는 것을 알 수 있다. 젊은 환자들에서 CAS가 유의한 장점을 보인다는 통 합 종말점에 대한 결과는 달리, 뇌졸중 종말점의 경우 CI의 폭이 큰 것은 95% CI의 상한이 1.0보다 크다는 것을 시사한 다. 그러나 원래의 본 연구의 핵심은 나이 차에 따른 위험률의 경향을 보고한 것이지, 특정 연령대에서의 위험률의 차이를 보기에 위한 것이 아니다. CEA와 CAS의 뇌졸중 발생 위험률이 유사한 시점은 64세로, 일차 종말점을 초과한 나이는 6년 더 늦게 나타났다. 95% CI의 폭이 넓다는 것은 일차 종말점에 비해 뇌 졸중 종말점의 경우 불확실성이 더 크다는 것을 시사한다. 일 차 종말점 중 심근경색증에 대해 나이에 의한 효과 변화는 없 는 것으로 나타났다(P=0.35, Figure 3C).

CAS 치료를 받은 환자는 나이가 10세 놓여질수록 일차 종말점의 위험률은 1.77배(P=0.0001; 95% CI, 1.38~2.28), 뇌 졸중의 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 의 한 치료 효과의 변화는 증상 유무(P=0.06) 혹은 성별(P=0.45) 에 영향을 받지 않았다. 기존 심근경색증의 경의 대신 20년의 생세치표면 양성인 심근경색증까지 포함시킨 민감도 분석에서 나이에 의한 효과 변화는 유의하지 않았다(P=0.75).
**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 (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>
</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>−0.0266±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 (1.36–2.30)</td>
<td>1.77 (1.37–2.27)</td>
<td>−0.0097±0.0123</td>
</tr>
</tbody>
</table>

메개 분석

CAS 치료군에서 나이와 연관된 위험률의 차이에 잠재적으로 기여하는 요인을 평가하기 위한 메개 분석이 이루어졌으나 (Table 3), CEA 치료군에 대해서는 나이와 연관된 위험률의 차이가 유의하지 않아 이러한 분석이 수행되지 않았다. CAS 치료군에서의 나이의 효과는 고혈압, 당뇨병, 이상지질혈증, 혹은 관장된 병변의 특성 또는 시술 시간의 차이에 의해 메개된다는 근거는 없다(7, 0.95). 총 추시 환영 기간(7, 0.046)이 잔재적 메개 요인으로 확인되었으나, 나이 10세 증가량 HR이 1.68에서 1.62로 소폭 감소하여 그 효과는 미미하였다.

고찰

본 분석 결과는 CREST 연구3에서 관찰된 나이와 연관된 효과의 차이가 잔치 중단점 중 주로 나이증증에 의한 것임을 보여 준다. 바꾸어 말하면 나이증증의 영향은 CAS 치료군에서 나이가 많아지면서 나이증증의 위험이 증가하지만 CEA 치료군에서는 나이에 따른 나이증증 위험 변화가 거의 없는 것에 주로 기인 한다.

CAS 치료군과 CEA 치료군에서 나이증증 위험이 유사한 시점은 64세였고, 잔치 중단점의 경우에는 약 70세였다. 두 군에서 나이에 따른 심근경색증 발생은 차이가 없어, CAS의 경우 모든 연령대에서 심근경색증 발생이 더 적은 것을 시사한다. 그러나 나이증증 발생(122건)에 비해 심근경색증 발생(42건)이 다르게 나타났으나 심근경색증에 대한 효과와 변화를 확인하기 위한 검증이 약간 않았다. 증상 유무 혹은 성별에 따른 치료와 나이의 상호작용 관계의 변화는 유의하지 않았다.

일차 결과 논문6에서 제시되었던 나이에 의한 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)을 이용한 메타분석에서도 확인되었다. 70세 이상의 환자들에서는 CAS 치료군에서 사전 발생의 위험률은 CEA 치료 받은 환자들에 비해 약 2배 정도였다(HR, 2.04; 95% CI, 1.48~2.82). 이 메타분석에서 잔치 중단점의 요소로 심근 경색증은 제외되었으므로, 나이에 의한 효과는 역시 나이증증에 의한 것으로 해석된다. 이 메타분석에서 70세 이상의 환자들 의 위험은 차이가 있었는데(7, 1.11: 95% CI, 0.73~1.71), 젊은 CAS 치료군에서 위험들이 낮았던 본 분석 결과와는 차이가 있다. SPACE 연구진들은 별도로 68세 이상에서 CAS 대비 CEA의 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. 7 이러한 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 신정 기준을 사용하여, 현재 고혈압에 서 중요한 지적을 생각하는 CAS에 대한 해부학적 제외 기준을 포함하지 않았다. 또한 논증 중 심장경색증과 효과 변화의 별 도로 조사한 연구는 없었다.

CREST가 고안된 당시 연구진들은 침습적인 CEA에 비해 민첩한 임상기 자기고혈압의 환자에게 유리한 효과를 보일 것으로 기대하였다. 따라서, 고혈압에서의 CEA의 유효성 및 점은 인증중의 CAS의 유효성은 예상 밖의 결과였다. 이러한 예 상은 CREST 초기 등록부에서 CAS를 받은 환자들에게 의한 결과로 확인되었다. CREST 이전의 관찰된 환자 연구에서 나타난 논증의 중요한 예측 인자가, 고혈압에서 대동맥경화 및 경동맥의 비밀림, 식취자 정리가 주장되며 보완을 제시하였다. CREST에서는 향후의 성별, 범위 길이, 비밀림부 및 경 동맥의 변화 등과 같은 경동맥 병변의 특성과 고혈압의 환자에서 CAS 위험률에 미치는 영향은 없다. 그러나 동맥의 비밀림이나 범위 의협의 환자에서의 결과에서 있었기에 때문에 고혈압에서의 CAS 사 건 발생의 증가에 기여할 수 있다고 한다. 13,14 저자들은 비밀립 두개의 경동맥 병변을 가진 환자들, 특히 혈관 식취자 정리가 상당히 제2, 3 유형의 확장된 동맥경화 형태의 경우 CAS 사 건 동안의 사전 위험이 증가할 것으로 가정하였다. 이러한 가정과 부합되게 고혈압의 환자에서는 더 높은 합병증의 위험수위가 필요하다. 이 요인에 대한 보고가 고혈압에서의 증가된 위험률을 부문적으로 배제하는 것으로 나타났다. 환자의 절반 이상은 연구에서 높은 위 협률이 심혈관계 정확 기간의 증가와 연관되어 있다고 설명되는 점으로, 이는 이전 보고들과 일치한다. 15

환자 선택, 식사자의 경험 및 기술이 이 분석에서 나이 관련 상호작용과 관련이 있을 수 있다. 최신화된 환자 선택 기준을 사용한 CAS에 대한 최근 연구들은 CAS에 대한 나이에 따른 차이가 없거나 무시하고 있다고 제시하였다. 16,17 또한 동맥의 비밀림에 영향을 미친 만큼 고혈압이 심혈관계의 특성과 사용한 이 연구들에서 고혈압의 난은 사건 발생률은 주요한 합한. 18,19 이러한 결과를 확인하기 위해 새로운 연구들이 필요하다.

CREST 연구의 장점은 많은 연구대를 포함한 대규모 코호트 연구이며, 무중상 환자를 포함하였고, 나이에 대한 결과가 CREST의 신선 연구 및 후속 무작위 입상시험 연구 결과와 부합 한다는 점 등을 들 수 있다. 단점으로는 기술적 제한은 이 연구 단위 발생의 적절성, CEA와 CAS 모두 예상치를 계산한 인원성을 보였기 때문에, 나이 분포 의 품종, 환자 수가 적었다는 점(55세 이하 161명, 6.4%; 80세 이상 240명, 9.6%)을 들 수 있다 (Figure 1). 그럼에도 불구하고 나이 상호작용이 유의하였다. 결과는 나이 분포 안에 충분히 많은 환자를 포함하여 밸 중하기 전까지는 유의한 근거를 제시한다고 할 수 있다.

결론

사전에 계획된 이 CREST 연구 분석은 나이에 따른 CEA 대 비 CAS 효과의 차이가 주로 논증 중 발생에 의한 것임을 증명하였다. CAS의 RR이 높은 군에서 낮고 고혈압기 높은 양상을 고혈압 환자에서의 CAS의 논증중 위험이 증가하기 때문이다. CEA의 경우 논증중 위험은 모든 연령대에 걸쳐 상대적으로 일 정하나, 저자들은 경동맥 병변에 대한 치료적 선택에 있어 나 이가 중요한 요인이 되어 있다고 결론지었다. 이러한 관점에 영향을 미칠 수 있는 해부학적 요인에 대한 추가 연구가 필요할 것이다.

Sources of Funding

This work was supported by the National Institute of Neurological Disorders and Stroke (NINDS) and the NIH (R01 NS 038384), and by supplemental funding from Abbott Vascular Systems (formerly Guidant), including donations of Accunet and Acculink systems, equivalent to approximately 15% of the total study cost, to CREST centers in Canada and to CREST centers in the United States that were at Veterans Affairs sites.

Disclosures

G.H. is a Consultant/Advisory Board for Bayer Healthcare, member of the ARRIVE Executive Committee, received research support from Amgen and Bayer Healthcare, and is a consultant to Abbott Vascular for preparation of FDA materials. G.S.R. received royalties from Abbott Vascular and Cook. D.I.C. received research support from Boston Scientific, Abbott Vascular, Edwards Lifesciences, MedRad, Merck/Schering-Plough, Medtronic, and Eli Lilly-Daichi Sankyo, is a consultant to Schering-Plough, Eli Lilly, Medtronic, and Cordis, and is a member of the Speakers’ Bureau for Eli Lilly and The Medicines Company. H.D.A. is a member of the Speakers’ Bureau/Advisory Board for Medtronic.

References


