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 ≈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.

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 versus 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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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>
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<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>
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<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>
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<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>1.9</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.

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 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.

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. Characteristic 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%, 6.3%, and 12.7%), 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,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).
**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><strong>Younger than 65</strong></td>
<td><strong>Older than 65</strong></td>
<td><strong>Younger than 65</strong></td>
<td><strong>Older than 65</strong></td>
<td><strong>Younger than 65</strong></td>
</tr>
<tr>
<td>65–74 N = 404</td>
<td>65–74 N = 387</td>
<td>75–84 N = 500</td>
<td>75–84 N = 387</td>
<td><strong>N of Events</strong></td>
</tr>
<tr>
<td>Primary end point (any stroke, MI or death) within periprocedural period‡</td>
<td>10 (2.5 ± 0.8)</td>
<td>14 (3.6 ± 0.8)</td>
<td>0.69 (0.31–1.55)</td>
<td>0.37</td>
</tr>
<tr>
<td>Stroke end point (any stroke within periprocedural 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</td>
</tr>
<tr>
<td>Death</td>
<td>30 (0.6 ± 1.0)</td>
<td>21 (5.9 ± 1.3)</td>
<td>1.49 (0.85–2.60)</td>
<td>0.16</td>
</tr>
<tr>
<td>Stroke end point (any stroke within periprocedural period‡)</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</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</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.
‡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% 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\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 \(\approx 70\) 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 StentProtected 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). 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. 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. 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.8 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 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

| Covariate Potentially Mediating Impact of Age (Sample Size/N of Events) | Hazard Ratio for a 10-y Difference in Age After Adjustment for Gender and Symptomatic Status | Hazard Ratio for a 10-y Difference in Age After Further Adjustment for Covariate | Coefficient | Change in P
<table>
<thead>
<tr>
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<th></th>
<th></th>
<th></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>
<td>0.79</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>
<td>0.39</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>
<td>0.58</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>
<td>0.060</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>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>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>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>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>0.43</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
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경동맥 스템트 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 스템트(carotid artery stenting, CAS) 치료를 받은 환자들에서의 높은 뇌졸중 발생률은 나이가 경동맥네막절제술(carotid endarterectomy, CEA)에 대비한 CAS의 상대적 효과를 변화(modify)시킬 수 있을 것이라는 가설을 실현적으로 제시하였다. CREST 일차 보고에서는 모든 환자들이 모두 집중된 각 요소에 대한 상대적인 효과, 나이의 치료 특이적 영향 및 고령의 CAS 치료군에서의 위험성을 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 치료군에서의 위험에 대한 나이의 영향을 분석하기 위해 비례위험모형이 적용되었다.

결과: 나이는 일차 종말점에 대해 70세를 기준으로 치료 효과와 변화 요인으로 작용하였다(Interaction=0.02). CAS의 경우 일차 종말점 발생 위험율은 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 위험이 증가는 유의하지 않았다(P=0.27). 뇌졸중 발생은 전체 효과 변화의 일차적 기여 인자였고(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 대한 CAS의 효과는 환자의 나이에 영향을 주었으며, 고령에서는 CAS 치료 이후 뇌졸중 위험률이 증가하였다. 경동맥 혈착을 치료할 경우 이 두 가지 시술을 선택할 때 나이는 중요하게 고려되어야 할 요인이다.

환자 나이는 경동맥 재건술 이후의 예후에 영향을 미칠 수 있는 것으로 보고되고 있다.1-4 1997년 CREST (Carotid Revascularization Endarterectomy vs Stenting Trial) 연구에서 프로토콜이 마련되어 당시 나이와 혈관 해부5-8는 경동맥 스템트(cardiac artery stenting, CAS) 이후 혈관질환 발생의 예측 인자로 고려되지 않았다.7 반대로 CAS는 고령에서 경동맥네막

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<table>
<thead>
<tr>
<th></th>
<th>Younger Than 65</th>
<th>65–74</th>
<th>75 and Older</th>
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<tbody>
<tr>
<td></td>
<td>CAS (n=404)</td>
<td>CAS (n=525)</td>
<td>CAS (n=333)</td>
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<tr>
<td>Male %</td>
<td>64.6</td>
<td>67.4</td>
<td>57.7</td>
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<tr>
<td>White %</td>
<td>90.6</td>
<td>93.1</td>
<td>95.2</td>
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<tr>
<td>Asymptomatic arteries %</td>
<td>43.8</td>
<td>53.1</td>
<td>41.4</td>
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<tr>
<td>Risk factor status</td>
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<tr>
<td>Hypertension %</td>
<td>81.4</td>
<td>84.7</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>
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<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>
</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.*

대상과 방법

연구 참가자 및 측정
CREST는 CEA와 CAS의 상대적 효과를 평가하기 위한 무작위 임상시험이다. 이 연구는 증상성 환자 1,321명과 무증상 성 환자 1,181명을 모집하였다. 증심동맥은 치료 항암에 대해 논 가압된 위험요소에서 발전하였다. 연구에 대한 다양한 설명은 이전 논문에서 확인할 수 있다. 프로토콜은 모든 참여 간기관의 임상시험/윤리 심사 위원회에 의해 승인되었다.

통계 분석
이 연구의 핵심은 환자의 나이가 CAS와 CEA의 상대적 효과에 영향을 줄 수 있다는 점, 그리고 이러한 효과 변화의 기여 인자가 무엇인지 평가하는 것이다. 따라서 효과의 일차적 평가는 절제술의 유무 및 성별을 보정한 이후 나이와 치료의 상호작용 가능성을 평가하기 위해 비례 위험 분석을 이용한 치료-의도(intention-to-treat) 분석으로 시행되었다. 연구의 일자 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 병증, 심근경색증(myocardial infarction) 및 사망, 또는 무작위 배정 후 4년까지 추적 관찰 기간 동안의 합병 증의 병증으로 정의하였다. 나이에 의한 잠재적인 효과 변화는 나이의 선형 효과를 가정하여 분석하였다. 병증은 시술 전후 모든 병증 및 이후 4년간 시술 동증에서 발생한 병증으로 정의하였다. 심근경색은 시술 전후 기간 중 심근 효소치의 상승과 함께 중성이 있거나 심전도상 근기의 경우로 정의하였다. 시술 전후 기간 중 사망이 매우 적어서 이에 대한 의미 있는 분석은 이루어지지 않았다.

모형적 접근은 복합 종합생, 병종 종합생 및 심근경색증 종합생을 예측하기 위한 비례위험모형에 상호작용항을 추가하여 분석하였다. 십형적으로 P<0.10의 변수들만 효과 변화와 관련되어 있는 것으로 간주하였다. 또한 (1) 날은 연령대에서의 발생 사항 수, (2) 치료와 나이의 상호작용의 일자 분석에서의 신형성에 대한 평가, (3) 다른 연구와의 비교를 위해 각 시술에 따른 각 연령층에서의 사전 발생률, (4) 각 연령층에서의 CAS와 CEA의 상대적 효과에 대한 대체적 추정 값을 제시하기 위해 각 연령층(65세 미만, 65~74세, 75세 이상) 내에서의 이
차 분석도 이루어졌다.

저자들은 또한 모형에 고위 상호작용을 추가하여 중상 여부 및 성별에 따라 치료와 나의 상호작용에 입항성이 있는지 평가하였다. CAS와 CEA의 상대적 효과의 차이에 기여하는
나이에 따른 위험 변화를 치료군에 따라 보기 위해 CAS 치료
군과 CEA 치료군으로 분리하여 비례위험모형을 적용하였다.

마지막으로 치료와 나이의 상호작용에 영향을 미치는 임계
적 원인을 파악하기 위해 매개 변수를 수렴하여 CAS 치료
받은 환자의 환자들에게 위험을 증가하는 위험 인자 증가(고혈
압, 당뇨병 및 이상지질혈증(dyslipidemia), 뇌병의 특정의
차이(뇌병 길이, 비도심성 뇌병, 뇌양성 뇌병 및 혈착 정도), 또
는 시술의 차이(투시 활염 기간 혹은 총 시술 시간)에 기인한
것인지를 알아보고자 이러한 요인들을 모형에 포함시키고 나
이에 따른 추정 HR의 변화를 관찰하였다. 뇌병의 특정은 각
병원에서 결정하였다. 대동맥군(aortic arch) 해부, 혈관 비률
암, 나이와 연관된 석화 상도, CAS 합병증 중도 분석에 포함
되지 않았다. 매개 분석의 표준오차는 부트스트랩(bootstrap)
기법을 이용하여 추정하였다.

결과

두 치료군 모두에서 나이 증가에 따라 여성과 빈이 많아지
고 수축기 혈압은 높았으며 이완기 혈압은 낮은 경향을 보였으
나 당뇨병, 이상지질혈증, 현재 흡연 여부는 감소하는 경향을
보였다(Table 1). 이러한 연령층에서도 이 인자들에 대해 치료군
간의 유의한 차이가 없었다. Figure 1에 CAS와 CEA 환자들
의 연령 분포가 제시되어 있다.

Table 2에 대략적 3분위 연령층에 따른 시술 전후 기간 및
4년 경과 동안의 심근경색증, 뇌졸중 및 치료 증상의 관측치
가 제시되어 있다. Figure 2는 각 연령층에서 시술 전후
기간을 보인 환자의 분율의 Kaplan–Meier 추정값을 보여 주는데,
CEA 치료군에서는 각 연령층 간 시술, 사전 발생이 유사하나,
CAS 치료군에서는 각 연령층 간 시술, 사전 발생의 차이가 나
타났다. 4년간 치료 증상 발병에 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, 0.98~2.69)으로 나이에
따라 증가하였다. 이러한 위험 증가는 상대적으로 연령적인
CEA 치료군에서는의 위험률(질은 연령층 6.1, 중간 연령층
6.8, 고령층 7.4%)과는 달리 CAS 치료군에서는 사전 발생
증가(질은 연령층 3.9, 중간 연령층 6.3%, 고령층 12.7%)와
관련하였다. 이러한 위험 증가는 나이 증가와 증가와 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)(P<0.03). 고령에서 CEA 대비 치료 위험 증
가는 CAS 치료군에서의 나이 증가 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 증상 및 뇌졸중 증상에 대해서도 관찰되
었으나 통계적 유의성은 없었다(P>0.1). 시술 전후 기간 동안
발생한 병변 반대측 뇌졸중의 경우 복합 및 뇌졸중 증상의
요소로 포함되었으나, 시술 전후 기간 이후에 발생한 병변 반
대측 뇌졸중은 이 증상에 포함되지 않았다. 모든 뇌졸중
증상(시술 전후 기간 이후에 발생한 병변 반대측 뇌졸중의
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.](image-url)
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</th>
<th>Four-Year Period</th>
<th>Treatment by Age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N of Events (Rate=SE)</td>
<td>Hazard Rate (95% CI)</td>
<td>N of Events (Rate=SE)</td>
<td>Hazard Rate (95% CI)</td>
</tr>
<tr>
<td>Younger</td>
<td>Younger</td>
<td>10 (2.5±0.7)</td>
<td>0.69 (0.31–1.55)</td>
<td>14 (3.9±1.1)</td>
<td>0.60 (0.31–1.18)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>26 (5.2±0.9)</td>
<td>1.22 (0.65–2.16)</td>
<td>32 (6.3±1.1)</td>
<td>1.08 (0.65–1.78)</td>
</tr>
<tr>
<td>75 or older</td>
<td>30 (8.0±1.6)</td>
<td>1.14 (0.59–2.60)</td>
<td>39 (13.7±1.9)</td>
<td>1.83 (0.99–3.39)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 (2.1±0.6)</td>
<td>1.10 (0.57–2.60)</td>
<td>13 (3.7±1.0)</td>
<td>0.78 (0.37–1.72)</td>
</tr>
<tr>
<td>75 or older</td>
<td>23 (6.3±1.4)</td>
<td>2.17 (1.06–4.45)</td>
<td>33 (10.9±1.8)</td>
<td>2.15 (1.19–3.91)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 (2.1±0.6)</td>
<td>1.10 (0.57–2.60)</td>
<td>21 (3.6±1.1)</td>
<td>3.05 (1.54–5.24)</td>
</tr>
<tr>
<td>75 or older</td>
<td>23 (6.3±1.4)</td>
<td>2.17 (1.06–4.45)</td>
<td>33 (10.9±1.8)</td>
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</tbody>
</table>

CAS indicates carotid artery stenting; CEA, carotid endarterectomy; CI, confidence interval; MI, myocardial infarction; NA, not available; SE, standard error.
†Per-procedural 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.
*P was calculated from hazard ratio.
**Per protocol, P value was calculated with age as a continuous variable.
††Not available because of unreliable estimates.

발생한 뇌졸중이 추가됨으로써 그 차이가 희석되었다(P=0.19).

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 주요한 점이나, Supplemental Table 1 (https://stroke.ahajournals.org)은 증상 유무에 따른 분 석에서도 2 Table와 유사한 결과를 보여 준다. 이 표에서는 나이와 증상 유무 모두에 따른 경향이 있어야 하고 이로 인해 특 정군에서의 표본 크기가 작아 잘못된 결과를 초래할 수 있다. 지자들은 나이와 증상 유무에 따른 상호작용을 고려하였으나 유의성을 발견할 수 없었고(P>0.1), 나이와 위험률의 관계에 대한 무증상성 혹은 증상성 환자를 각 차이의 유의에 의해 쉽게 발생할 수 있다. 그러나 이러한 결과는 무증상성 혹은 증상 성 환자를 모두 포함하지 않는 다른 연구들의 결과와의 비교 를 위해 제공되었다.

이 연구의 일차 분석 결과는 Figure 3에 제시되어 있다. Figure 3A는 CREST 인자 종합점에서 나아지를 연속변수로 함축화한 관계를 설명한 것으로, 연구 결과의 1차 보고 논문의 그림과 동일하다. 두 시술의 위험률은 70세에서 유사하였
고, CAS는 젊은 환자들에서 우수한 효과를 보였고 나이가 많
은 환자들에서는 CEA의 효과가 더 우월하였다. 뇌졸중 종말
점과 나이의 함수 관계는 Figure 3B에 제시되어 있다. 이 그
림에서 기울기가 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 장점은 보인다는 복
합 종말점에 대한 결과와 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
강점을 보이므로 한 것이지, 특정 연령에서의 위험률의 차이를
보기 위한 것이 아니다. CEA와 CAS의 뇌졸중 발생 위험률이
유사한 시점을 64세로, 일차 종말점의 경우보다 6년 더 높게
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 많아질수록 일차 종
말점의 위험률은 1.77배(P<0.0001; 95% CI, 1.38~2.28), 뇌
졸중의 위험률은 1.76배 증가하였으나(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
하였다. 고위 상호작용을 추가하여 분석한 결과, 나이에 의
한 치료 효과의 변화는 동일 유무(P=0.96) 혹은 성별(P=0.45)
에 영향을 받지 않았다. 젊은 심근경색증의 경우 대신 20년의
생체지표만 양성인 심근경색증까지 포함시킨 만감도 분석에서
나이에 의한 효과 변화는 유의하지 않았다(P=0.75).
매개 분석

CAS 치료군에서 나이와 연관된 위험요인의 차이에 잠재적으로 기여하는 요인을 평가하기 위한 매개 분석이 이루어졌으나 (Table 3), CEA 치료군에 대해서는 나이와 연관된 위험요인의 차이가 유의하지 않아 이러한 분석이 수행되지 않았다. CAS 치료
군에서의 나이의 영향은 고혈압, 당뇨병, 이완성혈관증, 혹은 관측된 병변의 특성 또는 시술 기간의 차이에 의해 매개가된다는
근거는 없었다(P > 0.05). 총 뇌졸중 발생 기간(P = 0.046)이 임계
적 매개 요인으로 확인되었으나, 나이 10세 증가당 HR이 1.68
에서 1.62로 소폭 감소하여 그 효과는 미미하였다.

고찰

본 분석 결과는 CREST 연구1에서 관찰된 나이와 연관된 효
과의 차이가 일차 증발점 중 2주 뇌졸중에 의한 것임을 보여
준다. 바꾸어 말하면 뇌졸중의 영향은 CAS 치료군에서 나이가
많아지면서 뇌졸중의 위험이 증가하지만 CEA 치료군에서는
나이에 따른 뇌졸중 위험 변화가 거의 없는 것에 주로 기인
한다.

CAS 치료군과 CEA 치료군에서 뇌졸중 위험이 유사한 시점
은 64세였고, 일차 증발점의 경우는 약 70세였다. 두 군에서
나이에 따른 심근경색증 발생은 차이가 없어, CAS의 경우 모
든 연령대에서 심근경색증 발생이 더 적은 것을 시사한다. 그
러나 뇌졸중 발생(122건)에 비해 심근경색증 발생(42건)이 더
작아 심근경색보다 심근경색증에 대한 효과 변화를 확인하기 위
한 검증이 필요하였다. 중상 유무 혹은 생병에 따른 치료와 나이
의 상호작용 관계의 변화는 유의하지 않았다.

일차 결과 논문에 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)를 이용한 메타분석에서도 확인되었다.15 70세 이상의
환자들에서는 CAS 치료군에서 사전 발생의 위험률은 CEA 치
료를 받은 환자들에 비해 약 2배 정도였다(HR, 2.04: 95%
CI, 1.48~2.82). 이 메타분석에서 일차 중발점의 요소로 심근
경색증은 제외되었으므로, 나이에 의한 효과는 역시 뇌졸중에
의한 것으로 해석된다. 이 메타분석에서 70세 미만의 환자들
의 위험률은 차이가 없었다(HR, 1.11: 95% CI, 0.73~1.71).

참고: CEA 치료군에서 위험률이 낮았던 본 분석 결과와는 차이
가 있다. SPACE 연구진들은 별도로 68세 미만에서 CEA 대
비 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.17 이러한 나이의 효과는 CREST
 초기 자료, Carotid Acculink/Accunet Post-Approval Trial to Uncover Unanticipated or Rare Events (CAP-

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Potential 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 (1259/85)</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>
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<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>
<td>P = 0.39</td>
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<tr>
<td>Dyslipidemia (1254/85)</td>
<td>1.78 (1.38–2.28)</td>
<td>1.96 (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>-0.026±0.0152</td>
<td>P = 0.90</td>
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<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>
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<tr>
<td>Ucerated 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>
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<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>-0.037±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>
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</table>
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