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Effects of patient age on outcomes after carotid endarterectomy
A retrospective, single-center study in Korea

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Abstract

In this single-center, retrospective study, we aimed to compare early and late outcomes after carotid endarterectomy (CEA) between younger and elderly patients and to investigate the impact of patient age on the overall incidence of cardiovascular events after CEA.

A total of 613 patients with 675 CEAs between January 2007 and December 2014 were stratified by patient age into 2 groups: younger ($\leq$60 years, n = 103 CEAs, 15.3%) and elderly (>60 years, n = 572 CEAs, 84.7%) groups. The study outcomes were defined as the occurrence of major adverse events (MAEs), including fatal or nonfatal stroke or myocardial infarction (MI), or any-cause mortality, and overall cardiovascular events (meaning the composite incidence of stroke or MI) during the perioperative period and within 4 years after CEA.

Although there were no significant differences in the incidence of 30-day MAEs and any of the individual MAE manifestations between the 2 groups, the differences in the MAE incidence (P = .006) and any-cause mortality (P = .023) within 4 years after CEA were significantly greater in patients in the elderly group. For overall incidence of cardiovascular events, no significant difference was noted between the 2 groups (P = .096). On multivariate analysis, older age (>60 years) did not affect the incidence of perioperative MAEs and individual MAE manifestations; however, older age was significantly associated with an increased risk of 4-year MAEs (hazard ratio [HR], 3.68, 95% confidence interval [CI], 1.35–10.0; P = .011) and any-cause mortality (HR, 3.26, 95% CI, 1.02–10.5; P = .047). With regard to the 4-year overall incidence of cardiovascular events, older age was not an independent predictor of increased risk of these cardiovascular events.

Our study indicates that the risks of perioperative MAEs and the 4-year overall incidence of cardiovascular events do not significantly differ between younger and elderly Korean patients undergoing CEA, although there was a higher risk of 4-year any-cause mortality in the elderly patients. Older age does not appear to be an independent risk factor for perioperative MAEs and overall cardiovascular events within 4 years after CEA.

Abbreviations: CAD = coronary artery disease, CEA = carotid endarterectomy, CI = confidence interval, CKD = chronic kidney disease, CTA = computed tomography angiography, DM = diabetes mellitus, DUS = duplex ultrasound, HR = hazard ratio, IQR = interquartile range, MAE = major adverse event, MI = myocardial infarction, MRA = magnetic resonance angiography, OR = odds ratio.

Keywords: age factors, cardiovascular diseases, carotid artery stenosis, carotid endarterectomy, treatment outcome

1. Introduction

Stroke is the second leading cause of death worldwide.[1] Despite the gradual decline of stroke mortality in South Korea, it remains as high as 30 deaths per 100,000 individuals, in parallel with a growing elderly population. Stroke is the third leading cause of death in Korea, after cancer and heart disease, according to Statistics Korea's annual report, *Cause of Death Statistics*.[2,3] Recently, the prevalence of stroke has been increasing in younger adults, who account for 10% to 15% of all stroke patients.[1,4] Considering that stroke is the third most common cause of disability-adjusted life years[5] worldwide, its prevention in this younger subgroup population is less costly than the treatment of its complications. In large randomized clinical trials, carotid endarterectomy (CEA) has been confirmed as a safe and effective treatment modality for prevention of recurrent neurological symptoms and stroke in symptomatic or asymptomatic patients with moderate to severe carotid stenosis.[6–8] There have been several previous subgroup analyses on different factors affecting the outcomes after CEA.[9–16] However, there is a lack of data

regarding the long-term outcomes after CEA according to patient age. Furthermore, there may be ethnic disparities in the risk of major adverse event (MAE) incidence following CEA. Therefore, it is worthwhile to evaluate the long-term outcomes of CEA according to age in Asian patients with significant carotid stenosis.

The aims of this study were to compare early and late outcomes after CEA between younger and elderly Asian patients and to investigate the impact of patient age on the overall incidence of cardiovascular events after CEA.

2. Subjects and methods

2.1. Study design and population

This single-center, retrospective, observational study involved analysis of data extracted from patient medical records. The present study protocol was reviewed and approved by the institutional review board of our hospital (IRB No. 2018–1472), which waived the need for informed consent because of its retrospective nature.

Between January 2007 and December 2014, 717 patients who underwent 789 consecutive CEAs at our hospital were screened for inclusion in this study. Among these, 104 patients with 114 CEAs were followed up after CEA at our tertiary medical center for a specified period (<1 year), and subsequently followed up at other hospitals; these patients were excluded from this analysis. The study population consisted of 613 patients with 675 CEAs (85.6% of the total number of CEAs performed during the study period). The patients were stratified by age[16–18] into 2 groups: younger (under 60) and elderly (over 60).

Patients were considered to be asymptomatic in the absence of neurological symptoms—transient ischemic attack, stroke, or amaurosis fugax—within 6 months before CEA. The indications for CEA were 50% to 99% luminal narrowing in patients with symptomatic carotid stenosis and 70% to 99% in those with asymptomatic carotid stenosis as defined by velocity criteria and the criteria established by the North American Symptomatic Carotid Endarterectomy Trial.[19,20] Velocity criteria were defined as 50% to 69% luminal narrowing, determined by analysis of the peak systolic velocity in the range of 125 to 230 cm/s and end-diastolic velocity in the range of 40 to 100 cm/s, and 70% to 99% luminal narrowing, determined by the peak systolic velocity ≥230 cm/s and end-diastolic velocity ≥100 cm/s.[21] In the case of a discrepancy in the degree of carotid stenosis determined using velocity criteria and luminal narrowing, the estimation of carotid stenosis was based primarily on the velocity criteria. In patients with bilateral significant carotid stenosis, the most symptomatic or higher-grade carotid stenosis was treated first.

Demographics, risk factors of interest, imaging and procedural data, and clinical perioperative and long-term outcomes for all patients were collected prospectively in an Excel database (Microsoft Corp, Redmond, WA) and analyzed retrospectively.

2.2. Preoperative evaluation and index procedure

Preoperative imaging studies included carotid duplex ultrasound (DUS) in all cases. All patients had either computed tomography angiography (CTA) or magnetic resonance angiography (MRA) of the aortic arch and the supra-aortic extracranial and intracranial vessels with concomitant evaluation of the cerebral parenchyma. Neurological assessment was performed by a team of neurologists who conducted a complete evaluation of the presence, type, and severity of the symptoms using the National Institute of Health Stroke Scale[22] and the modified Rankin scale.

The CEA procedure has been previously detailed.[20] In the initial years of the study period, CEA was preferentially performed under regional anesthesia with selective carotid shunting, whereas in more recent years, we changed the anesthetic technique to general anesthesia with routine shunting. Postoperatively, all patients were administered dual antiplatelet and statin therapy in combination with stringent control of blood pressure and close observation in an intensive care unit for at least 24 hours. All patients underwent CTA or MRA before discharge.

2.3. Outcomes of interest and follow-up

The study outcomes of interest included the occurrence of MAEs, defined as fatal or nonfatal stroke or myocardial infarction (MI), or all-cause mortality, during the perioperative (within 30 days) and late (within 4 years) period following CEA. The overall cardiovascular events were defined as the composite incidence of stroke or MI. Only the first event of each outcome was included in the analysis of MAE occurrence. We included only ischemic stroke in the analysis. Stroke, categorized as major or minor, and MI were defined as previously detailed.[20] Restenosis following CEA was defined as the development of ≥70% stenosis, diagnosed on the basis of DUS findings of luminal narrowing and velocity criteria with a peak systolic velocity threshold of ≥274 cm/s, according to previous report.[23]

Follow-up visits with independent neurological examination were scheduled within 1 month after CEA, at 1, 6, and 12 months, and annually thereafter. Follow-up laboratory evaluations and carotid DUS were performed depending on individual patients' atherosclerosis risk factors. When stability was established and at least 3 years had elapsed since CEA, surveillance was performed at longer intervals of approximately 2 years.

2.4. Statistical analysis

The baseline and clinical characteristics and outcomes of the study population are presented as counts and percentages for categorical variables and as means and standard deviations for continuous variables. Categorical variables were compared using the chi-squared test or Fisher exact test, as appropriate, whereas continuous variables were compared using Student t test. Patient age values, not distributed normally and presented as medians and interquartile ranges (IQRs), were analyzed using the Mann–Whitney U test. The cumulative probabilities of long-term outcomes in terms of 4-year MAE-free, stroke-free, and overall survival rates in the 2 groups were estimated with Kaplan–Meier curves and compared by means of the log-rank test. To identify the clinical variables associated with perioperative outcomes (within 30 days after CEA), univariate and multivariate logistic regression analyses were used, and odds ratios (ORs) with 95% confidence intervals (CIs) are reported. Univariate and multivariate analyses to identify the clinical variables associated with long-term outcomes (within 4 years after CEA) were conducted with Cox proportional hazard regression modeling, using the event of interest and the period from CEA to the date of the event or last follow-up as the outcomes. Univariate Cox proportional hazard regression models were fitted to calculate hazard ratios (HRs) with 95% CIs to estimate the associations between clinical variables and long-term outcomes. Variables with a $P < .1$ on

univariate analysis were included in the multivariate analysis using the backward elimination method. $P < .05$ was considered statistically significant. Statistical analyses were performed using SPSS version 21.0 (SPSS Inc, Chicago, IL).

3. Results

3.1. Study population

During the study period, the study cohort consisted of 613 patients who underwent 675 CEAs at our hospital. The younger group (≤60 years) had 103 CEAs (15.3%), and the elderly group (>60 years) had 572 CEAs (84.7%). The baseline and clinical characteristics of the study population according to patient age are presented in Table 1. The mean ages of the patients in the younger and elderly groups were 55.9 ± 3.9 years and 70.8 ± 5.7 years, respectively. To test whether medians of the compared groups (younger group vs. elderly group) were significantly different, the age values were analyzed with the Mann–Whitney U test. The distribution of age values in all enrolled patients (younger group vs. elderly group; median [IQR], 57 years [54.0–59.0 years] vs. 71 years [66.0–74.8 years]) revealed a significant difference between the 2 groups ($P < .001$) (Supplemental Figure 1, http://links.lww.com/MD/D165). With regard to atherosclerotic risk factors and comorbidities, patients in the elderly group had a higher prevalence of hypertension (66.0% vs. 77.8%; $P = .010$) and chronic kidney disease (CKD) (8.7% vs. 18.0%, $P = .020$), and a lower prevalence of past smoking (75.7% vs. 65.0%, $P = .034$) than those in the younger group. There was no significant difference in the proportion of coronary artery disease (CAD) or subclinical CAD between the 2 groups. The degree of carotid stenosis showed a numerically higher trend

in patients in the elderly group ($74.7 \pm 9.7\%$ vs. $76.5 \pm 9.4\%$, $P = .075$); however, no significant differences were noted in the proportion of patients with symptomatic stenosis (45.6% vs. 48.4%; $P = .601$) and the anesthetic and CEA reconstruction techniques between the 2 groups.

3.2. Comparison of study outcomes between the younger and elderly groups

Patients in the younger and elderly groups did not differ significantly in the incidence of MAE occurrence (1.0% vs. 2.04%; $P = .713$) and any of the individual MAE manifestations during the perioperative period. However, within 4 years after CEA, the MAE incidence was found to be 3.9% in the younger group and 14.2% in the elderly group (Table 2); the difference was significant ($P = .006$). Analysis of the individual MAE manifestations indicated a significantly higher risk of any-cause mortality in the elderly group (2.9% vs. 9.8%, $P = .023$), whereas there were no significant differences in the risks of stroke and MI between the 2 groups. No significant difference was noted in the overall incidence of cardiovascular events—the composite incidence of stroke or MI—between the 2 groups (1.9% vs. 5.9%, $P = .096$). During the study period, restenosis was found after 12 CEAs (1.8%): 5 CEAs (4.9%) in the younger group and 7 CEAs (1.2%) in the elderly group. No restenosis-related stroke occurred and the incidence of restenosis was significantly higher in patients in the younger group ($P = .024$).

The mean duration of follow-up was 74.1 ± 31.1 months (median, 69 months; range, 13–139 months) in the younger group and 64.5 ± 30.5 months (median, 64 months; range, 12–166 months) in the elderly group. On Kaplan–Meier survival

Table 1

Baseline and clinical characteristics of the study population stratified according to patient age.

	Total (n=675)	Younger group (n=103)	Elderly group (n=572)	P
Mean age, years	68.5 ± 7.7	55.9 ± 3.9	70.8 ± 5.7	
Male sex	590 (87.4)	89 (86.4)	501 (87.6)	.740
BMI, kg/m²	24.1 ± 2.9	24.4 ± 2.8	24.0 ± 2.9	.247
Risk factors				
Smoking	450 (66.7)	78 (75.7)	372 (65.0)	.034
DM	265 (39.3)	33 (32.0)	232 (40.6)	.103
Hypertension	513 (76.0)	68 (66.0)	445 (77.8)	.010
Dyslipidemia*	466 (69.0)	75 (72.8)	391 (68.4)	.368
Comorbidities				
CAD	131 (19.4)	15 (14.6)	116 (20.3)	.177
Subclinical CAD	23 (3.3)	4 (3.9)	19 (3.3)	.767
CKD	112 (16.6)	9 (8.7)	103 (18.0)	.020
PAOD	45 (6.7)	5 (4.9)	40 (7.0)	.423
Carotid stenosis				
Degree of stenosis, %	76.2 ± 9.5	74.7 ± 9.7	76.5 ± 9.4	.075
SCSO	72 (10.7)	13 (12.6)	59 (10.3)	.485
Symptomatic stenosis	324 (48.0)	47 (45.6)	277 (48.4)	.601
CEA				
General anesthesia	405 (60.0)	67 (65.0)	338 (59.1)	.256
Use of shunt	421 (62.4))	70 (68.0)	351 (61.4)	.203
Reconstruction technique				.027
Patch angioplasty	653 (96.7)	96 (93.2)	557 (97.4)	
Primary closure	10 (1.5)	2 (1.9)	8 (1.4)	
Others	12 (1.8)	5 (4.9)	7 (1.2)	

Continuous data are presented as means ± standard deviation; categorical data are given as number (%).
BMI = body mass index, CAD = coronary artery disease, CEA = carotid endarterectomy, CKD = chronic kidney disease, DM = diabetes mellitus, PAOD = peripheral arterial occlusive disease, SCSO = severe contralateral extracranial carotid stenosis or occlusion.
* All patients received statins before CEA.

Table 2

Major adverse events[*] and the individual major adverse event components among patients who underwent carotid endarterectomy, according to patient age.

	Within 30-day outcomes after CEA				Within 4-year outcomes after CEA[†]			
	Total (n = 675)	Younger (n = 103)	Elderly (n = 572)	P	Total (n = 675)	Younger (n = 103)	Elderly (n = 572)	P
MAE	15 (2.2)	1 (1.0)	14 (2.4)	.713	85 (12.6)	4 (3.9)	81 (14.2)	.006
Stroke/MI	11 (1.6)	1 (1.0)	10 (1.7)	.999	36 (5.3)	2 (1.9)	34 (5.9)	.096
Any stroke	9 (1.3)	1 (1.0)	8 (1.4)	.999	30 (4.4)	2 (1.9)	28 (4.9)	.295
Major	1 (0.1)	0	1 (0.2)	.999	6 (0.9)	1 (1.0)	5 (0.9)	.999
Minor	8 (1.2)	1 (1.0)	7 (1.2)	.999	24 (3.6)	1 (1.0)	23 (4.0)	.154
MI	2 (0.3)	0	2 (0.3)	.999	2 (0.3)	0	2 (0.3)	.999
Death	4 (0.6)	0	4 (0.7)	.999	59 (8.7)	3 (2.9)	56 (9.8)	.023

Values in parentheses are percentages.

CEA = carotid endarterectomy, DM = diabetes mellitus, MAE = major adverse event, MI = myocardial infarction.

[*] Any stroke, MI, or death.

[†] Including the occurrence of MAEs during the perioperative period.

analysis, although there was a similar stroke-free survival rate (P = .138) between the 2 groups, patients in the elderly group had decreased MAE-free (P = .005) and overall (P = .026) survival rates compared with those in the younger group (Fig. 1). For the overall incidence of cardiovascular events, there was no significant difference between the 2 groups (P = .093) (Supplemental Figure 2, http://links.lww.com/MD/D165). The MAE-free, stroke-free, and overall survival rates at 4 years in the younger and elderly groups were 96.1% and 87.2%, 98.0% and 96.0%, and 97.1% and 90.2%, respectively. The 4-year overall cardiovascular events-free survival rate was 98.1% in the younger group and 94.5% in the elderly group.

3.3. Analysis of clinical variables associated with study outcomes

Multivariate analyses adjusting for confounding variables indicated dyslipidemia had a protective effect on perioperative MAE occurrence (OR, 0.30; 95% CI, 0.10–87.0; P = .027), whereas CAD was associated with 3.74-fold increased odds of MAE during the perioperative period (95% CI, 1.25–11.2; P = .018) (Table 3). For the incidence of individual MAE manifestations, dyslipidemia (OR, 0.16; 95% CI, 0.04–0.67; P = .012) and CAD (OR, 5.22; 95% CI, 1.30–20.90; P = .020) were independent predictors of a decreased and an increased perioperative risk of any stroke occurrence, respectively (Supplemental Table 1, http://links.lww.com/MD/D165). For the incidence of perioperative MI and all-cause mortality, univariate analysis identified no statistically significant factor (all P > .1), which precluded the execution of multivariate analysis (data not shown). Older age (>60 years) was not a significant risk factor associated with perioperative MAEs and individual MAE manifestations.

After adjustment for potential confounding variables, multivariate analysis indicated that older age increased the risk of 4-year MAEs 3.68-fold (95% CI, 1.35–10.0; P = .011). Although diabetes mellitus (DM) (HR, 1.50; 95% CI, 0.98–2.30; P = .062) showed trends associated with an increased risk of 4-year MAE occurrence, this was not statistically significant (Table 4). For the analyses of the association between clinical variables and individual MAE manifestations, DM (HR, 2.55; 95% CI, 1.20–5.41; P = .015) was significantly associated with an increased risk of any stroke within 4 years after CEA (Supplemental Table 2, http://links.lww.com/MD/D165). Older

age (HR, 3.26; 95% CI, 1.02–10.50; P = .047) and CKD (HR, 2.79; 95% CI, 1.57–4.96; P < .001) increased the risk of 4-year any-cause mortality (Supplemental Table 3, http://links.lww.com/MD/D165). There was no statistically significant factor associated with an increased risk of 4-year MI incidence (data not shown). For the analysis of the overall incidence of cardiovascular events, DM (HR, 2.23; 95% CI, 1316–4.40; P = .021) and CAD (HR, 2.05; 95% CI, 1.03–4.08; P = .042) were significantly associated with increased risk of 4-year overall cardiovascular events, whereas older age was not independently associated with these cardiovascular events (Table 5). For the association between clinical variables and carotid restenosis following CEA, older age (>60 years) (HR, 0.29; 95% CI, 0.09–0.91; P = .034) and higher body mass index (HR, 1.22; 95% CI, 1.01–1.47; P = .044) had a protective and a negative effect on restenosis, respectively (Table 6).

4. Discussion

Although CEA has been accepted as a safe and effective procedure for the prevention of recurrent neurological symptoms and stroke in symptomatic or asymptomatic patients with moderate to severe carotid stenosis,[6–8] there have been few reports to document the impact of patient age on outcomes after CEA in Asian populations, and therefore, the long-term benefits of stroke prevention after CEA according to age remains to be defined. In our study, we compared the outcomes after CEA between younger and elderly patients and found that there were no significant differences in the incidence of early MAEs and individual MAE manifestations between the 2 groups; however, we found that the risk of MAE occurrence and any-cause mortality were significantly greater among elderly patients. On multivariate analysis, older age (>60 years) was significantly associated with an increased risk of late any-cause mortality but was not an independent predictor of increased risk of overall incidence of cardiovascular events. During the study period, the rate of late restenosis was significantly greater in the younger patients compared with the elderly patients. The present observations partly corroborate a recent study reported by Dorigo et al,[16] performed in a Western population, which found that younger patients had a more favorable late outcome in terms of overall survival but an increased risk of late restenosis compared with elderly patients. However, the elderly participants in the study of Dorigo et al[16] had a poorer long-term stroke-free
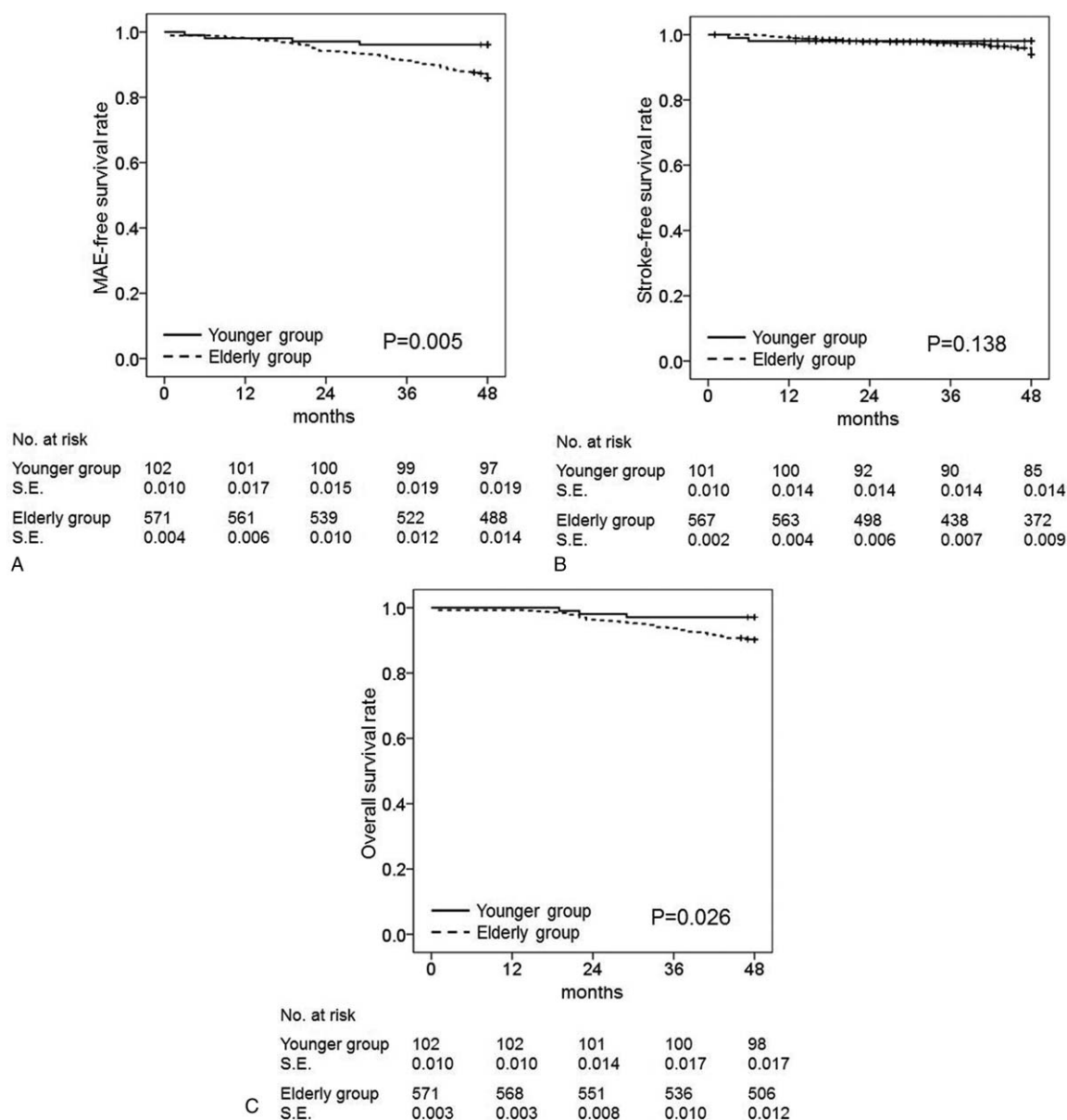
Figure 1. Kaplan–Meier analyses of the cumulative event-free rates. Kaplan–Meier analysis of cumulative event-free rates of (A) 4-year MAE-free, (B) stroke-free, and (C) overall survival in patients undergoing carotid endarterectomy in the younger and elderly groups. MAE = major adverse event, MI = myocardial infarction, SE = standard error.

survival rate, in contrast to our observations. Our findings of a higher risk of late MAE occurrence in the elderly group could be explained by the higher late any-cause mortality rate in the elderly group. During the perioperative period, dyslipidemia, diagnosed before CEA, is a significant protective factor for early MAEs and any stroke occurrence, but not for late outcomes. All patients diagnosed with dyslipidemia received statin therapy before CEA in our study population, and our results are consistent with the findings by Texakalidis et al,[24] who reported that statin therapy reduced perioperative complications following CEA.

Our study cohort consisted of only Korean patients and may not be representative of other ethnic groups. The recently published Stroke Statistics in Korea project,[2] the most up-to-date and nationally representative databases analysis, reported

population-attributable risk factors of stroke according to age groups and sex in the Korean population. In young and middle-aged men, smoking is the most important risk factor, and in young and middle-aged women, hypertension is most important. In the elderly, hypertension is the most important factor for both sexes. A large portion of atherosclerotic risk factors and comorbidities is age-related or age-dependent, and therefore, the incidence and severity of atherosclerotic vascular disease increase with increasing age. The changing patient demographics according to age and increasing proportion of elderly patients are similar between Asian and Western countries. However, there may be ethnic differences in environmental and genetic factors, comorbidities, and other characteristics of carotid stenosis that could have an impact on various outcomes after CEA in Asian

Table 3

Factors associated with the occurrence of 30-day major adverse events[*].

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P	OR (95% CI)	P
Age >60 years	2.56 (0.33–19.7)	.367	NA	NA
Male sex	0.49 (0.06–3.77)	.493	NA	NA
BMI	1.13 (0.95–1.35)	.155	NA	NA
Smoking	1.38 (0.44–4.40)	.581	NA	NA
DM	1.36 (0.49–3.81)	.554	NA	NA
Hypertension	4.52 (0.59–34.6)	.147	NA	NA
Dyslipidemia	0.38 (0.14–1.07)	.067	0.30 (0.10–0.87)	.027
CAD	2.85 (1.00–8.16)	.051	3.74 (1.25–11.2)	.018
Subclinical CAD	0.00 (0.00–NA)	.998	NA	NA
CKD	2.58 (0.87–7.71)	.089	2.37 (0.78–7.19)	.126
PAOD	1.00 (0.13–7.78)	.999	NA	NA
Symptomatic stenosis	0.95 (0.34–2.64)	.917	NA	NA
Degree of stenosis	0.99 (0.94–1.04)	.685	NA	NA
SCSO	2.14 (0.59–7.78)	.247	NA	NA

BMI = body mass index, CAD = coronary artery disease, CI = confidence interval, CKD = chronic kidney disease, DM = diabetes mellitus, NA = not applicable, OR = odds ratio, PAOD = peripheral arterial occlusive disease, SCSO = severe contralateral extracranial carotid stenosis or occlusion.
[*] Any stroke, MI, or death.

Table 4

Factors associated with the occurrence of 4-year major adverse events[*].

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age >60 years	3.80 (1.39–10.4)	.009	3.68 (1.35–10.0)	.011
Male sex	1.15 (0.63–2.13)	.646	NA	NA
BMI	0.95 (0.88–1.03)	.192	NA	NA
Smoking	1.36 (0.85–2.20)	.204	NA	NA
DM	1.55 (1.02–2.38)	.042	1.50 (0.98–2.30)	.062
Hypertension	0.70 (0.44–1.10)	.123	NA	NA
Dyslipidemia	0.81 (0.52–1.27)	.356	NA	NA
CAD	1.36 (0.83–2.22)	.225	NA	NA
Subclinical CAD	0.33 (0.05–2.34)	.265	NA	NA
CKD	1.60 (0.97–2.65)	.065	1.41 (0.85–2.34)	.185
PAOD	0.88 (0.36–2.17)	.783	NA	NA
Symptomatic stenosis	0.83 (0.54–1.28)	.397	NA	NA
Degree of stenosis	1.01 (0.99–1.03)	.379	NA	NA
SCSO	1.26 (0.67–2.38)	.472	NA	NA

BMI = body mass index, CAD = coronary artery disease, CI = confidence interval, CKD = chronic kidney disease, DM = diabetes mellitus, HR = hazard ratio, NA = not applicable, PAOD = peripheral arterial occlusive disease, SCSO = severe contralateral extracranial carotid stenosis or occlusion.
[*] Any stroke, MI, or death.

populations. For example, in South Korea, it was observed that stroke incidence was higher than the incidence of MI in the general population,[25] and the incidence of perioperative MI was substantially lower in patients undergoing CEA[26] compared with findings from studies in Western populations. Therefore, decisions about the management approach, including the optimal type of carotid revascularization (CEA or carotid artery stenting) may be different according to ethnicity. There are limited data available from studies on Asian populations, and therefore, our findings could help inform clinicians about the best treatment options for younger and elderly Asian patients with significant carotid stenosis. Further studies of larger cohorts are needed to better understand the impact of patient age on clinical outcomes following CEA in Asian populations.

The incidence of carotid restenosis following CEA has been reported to range from 5% to 30%.[27,28] According to prior

publications,[27,29–33] several risk factors may be associated with carotid restenosis following CEA: smoking, gender, age, and metabolic syndrome (at least 3 out of the 4 metabolic syndrome criteria: hypertension, hyperglycemia, dyslipidemia, and body mass index >25 kg/m^2). The mechanism of restenosis differs according to the time interval between CEA and restenosis.[34,35] Restenosis occurring in the first 2 years following CEA is attributed commonly to neointimal hyperplasia characterized by a proliferation of smooth muscle cells, which was thought to be associated with a low risk of thromboembolic events, whereas restenosis occurring later is most likely caused by recurrent atherosclerosis. In the International Carotid Stenting Study, most occurrences of restenosis after CEA arose in the first 2 years.[35] However, whether residual or recurrent stenosis after CEA increases the risk of recurrent stroke remains to be defined. In our study, the median time interval between CEA and restenosis was

Table 5

Factors associated with the overall incidence of cardiovascular events within 4 years after carotid endarterectomy.

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age >60 years	3.17 (0.76–13.2)	.113	NA	NA
Male sex	0.87 (0.31–2.46)	.792	NA	NA
BMI	1.03 (0.92–1.15)	.653	NA	NA
Smoking	1.32 (0.64–2.74)	.456	NA	NA
DM	2.47 (1.26–4.83)	.008	2.23 (1.13–4.40)	.021
Hypertension	1.94 (0.75–4.98)	.170	NA	NA
Dyslipidemia	0.78 (0.39–1.54)	.469	NA	NA
CAD	2.37 (1.20–4.68)	.013	2.05 (1.03–4.08)	.042
Subclinical CAD	0.05 (0.00–126.2)	.448	NA	NA
CKD	1.24 (0.54–2.84)	.607	NA	NA
PAOD	0.82 (0.20–3.42)	.787	NA	NA
Symptomatic stenosis	0.96 (0.50–1.85)	.912	NA	NA
Degree of stenosis	1.01 (0.97–1.04)	.785	NA	NA
SCSO	1.06 (0.38–3.00)	.911	NA	NA

BMI = body mass index, CAD = coronary artery disease, CEA = carotid endarterectomy, CI = confidence interval, CKD = chronic kidney disease, DM = diabetes mellitus, HR = hazard ratio, NA = not applicable, PAOD = peripheral arterial occlusive disease, SCSO = severe contralateral extracranial carotid stenosis or occlusion.

Table 6

Factors associated with carotid restenosis within 4 years after carotid endarterectomy.

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age >60 years	0.28 (0.09–0.88)	.030	0.29 (0.09–0.91)	.034
Female sex	2.23 (0.60–8.24)	.229	NA	NA
BMI	1.22 (1.01–1.48)	.042	1.22 (1.01–1.47)	.044
Smoking	1.07 (0.32–3.54)	.918	NA	NA
DM	1.16 (0.37–3.66)	.800	NA	NA
Hypertension	0.96 (0.26–3.54)	.949	NA	NA
Dyslipidemia	2.16 (0.47–9.87)	.319	NA	NA
CAD	0.04 (0.00–19.1)	.299	NA	NA
Subclinical CAD	2.70 (0.35–20.9)	.341	NA	NA
CKD	1.98 (0.54–7.31)	.306	NA	NA
PAOD	0.04 (0.00–697.4)	.528	NA	NA
Symptomatic stenosis	1.14 (0.37–3.52)	.825	NA	NA
Degree of stenosis	0.99 (0.94–1.05)	.787	NA	NA
SCSO	1.67 (0.37–7.64)	.507	NA	NA

BMI = body mass index, CAD = coronary artery disease, CEA = carotid endarterectomy, CI = confidence interval, CKD = chronic kidney disease, DM = diabetes mellitus, HR = hazard ratio, NA = not applicable, PAOD = peripheral arterial occlusive disease, SCSO = severe contralateral extracranial carotid stenosis or occlusion.

16.0 months (range, 6–44 months) in the younger patients and 13.0 months (range, 1–41 months) in the elderly patients. There was no significant difference in time interval between the 2 groups (*P* = .587). Therefore, patient mortality is not considered a confounding factor associated with restenosis in our analysis. We identified younger age and higher body mass index as independent predictors of restenosis, and there was no restenosis-related stroke.

This study has some limitations of note. First, the retrospective nature of the study raises the possibility of selection and information biases on the part of the physicians or patients; indication bias and patient self-selection may also have influenced our findings. Hence, the incidence of MAEs may have been underestimated, and the number of excluded patients was considerable. Although there is a wide age threshold defining the "younger patient," from 45 to 65 years, across multiple studies,

we used the age threshold of 60 years or less to identify younger patients, according to a recent meta-analysis.[15] Furthermore, there was no adjustment for baseline differences between the 2 groups. These differences may have affected the incidence of MAEs between the study populations stratified by patient age; patients in the elderly group had a higher prevalence of atherosclerosis risk factors and comorbidities than those in the younger group. Second, the study cohort was entirely Asian; therefore, these results may not be generalizable to other ethnic groups. However, this may be both a unique feature and a limitation of this study. Considering that there may be ethnic disparities between Asian and Western countries, and limited data are available in the Asian populations, this study would help inform clinicians about the best treatment options according to age for Asian patients with extracranial carotid stenosis. Finally, based on the relatively small sample size of the single-center

cohort, this study was likely underpowered to confirm a causal relationship between patient age and the risk of MAEs incidence.

In conclusion, our study indicates that the risks of perioperative MAEs and the overall incidence of cardiovascular events within 4 years after CEA did not differ significantly between younger and elderly Korean patients undergoing CEA, although there was a higher risk of 4-year any-cause mortality in elderly patients. Older age was not an independent risk factor for perioperative MAEs and the 4-year overall incidence of cardiovascular events, whereas older age was significantly associated with an increased risk of 4-year any-cause mortality.

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