Impact of Chronic Kidney Disease Under Nephrology Care on Outcomes of Carotid Endarterectomy

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WHAT THIS PAPER ADDS

Patients with chronic kidney disease under nephrology care with optimal medical treatment, including better controlled risk factors, and tighter medical surveillance, may benefit from carotid endarterectomy for major adverse cardiovascular event risk reduction because of their higher baseline cardiovascular risks. Considering that there is a paucity of consistent data regarding the association between nephrology care and outcomes of carotid endarterectomy among patients with chronic kidney disease, the present findings may provide more insight into the long term impact of nephrology care on outcomes after carotid endarterectomy among Asian patients with chronic kidney disease.

Objective: This study aimed to investigate the impact of chronic kidney disease (CKD) and the delivery of nephrology care on outcomes of carotid endarterectomy (CEA).

Methods: This was a single centre, retrospective observational study. Between January 2007 and December 2014, 675 CEAs performed on 613 patients were stratified by pre-operative estimated glomerular filtration rate (eGFR) values (CKD [eGFR $<$ 60 mL/min/1.73m^2] and non-CKD [eGFR $\geq$ 60 mL/min/1.73m^2] groups) for retrospective analysis. The study outcomes included the occurrence of major adverse cardiovascular events (MACEs), defined as fatal or non-fatal stroke, myocardial infarction, or all cause mortality, during the peri-operative period and within four years after CEA.

Results: The CKD group consisted of 112 CEAs (16.6%), and the non-CKD group consisted of 563 CEAs (83.4%). The MACE incidence was higher among patients with CKD compared with non-CKD patients during the peri-operative period (4.5% *vs.* 1.8%; p = .086) and within four years after CEA (17.9% *vs.* 11.5%; p = .066), with a non-statistically significant trend. In a subgroup analysis of patients with CKD under nephrology care (63/112, 56.3%; with better controlled risk factors and tighter medical surveillance by a nephrologist), patients with CKD without nephrology care (49/112, 43.8%), and non-CKD patients, the risk of both peri-operative (4.1% *vs.* 0.4%; p = .037) and four year post-operative (20.4% vs. 7.3%; p = .004) all cause mortality was statistically significantly higher among patients with CKD without nephrology care compared with non-CKD patients. However, there were no statistically significant differences between patients with CKD who received nephrology care and non-CKD patients in peri-operative and four year post-operative MACE occurrence, both in terms of the composite MACE outcome and the individual MACE components.

Conclusion: Despite the higher risk of peri-operative and four year MACE after CEA among patients with CKD, and the statistically significantly higher peri-operative and four year post-operative all cause mortality rates among patients with CKD without nephrology care, patients with CKD under nephrology care had similar outcomes to non-CKD patients.

Keywords: Carotid endarterectomy, Chronic kidney disease, Outcomes
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INTRODUCTION

The increasing incidence of chronic kidney disease (CKD), an independent risk factor for cardiovascular disease (CVD), is largely a result of the increasing prevalences of type 2 diabetes mellitus (DM) and hypertension, as well as ageing populations.[1–3] CKD and CVD share atherosclerosis as a common pathophysiological mechanism.[4,5] Indeed, the prevalences of conventional cardiovascular (CV) risk factors are high among patients with impaired kidney function,[6] and most patients with low estimated glomerular filtration rates (eGFRs) die of CV causes rather than progression to end stage kidney disease (ESKD).[1,7]

Cerebrovascular disease is among the leading causes of morbidity and mortality worldwide, and is associated with a heavy socioeconomic burden.[8] Among patients with CKD, there may be ethnic disparities in the incidence of stroke,[9] which has been reported to be statistically significantly higher among Asians compared with Western populations.[1] Despite previous large randomised trials that demonstrated carotid endarterectomy (CEA) — compared with medical management — reduced the risk of ipsilateral stroke among symptomatic or asymptomatic patients with moderate to severe carotid artery stenosis,[10–12] there have been varied conclusions reported regarding the risk associated with CKD among patients undergoing CEA, from no increase in peri-operative risk to a detrimental increase in peri-operative complications and risk of death.[2,13–15] It is well known that structured and early nephrology care, including lifestyle modifications, antihypertensive medication, lipid modification, and achieving glycaemic control, for type two DM patients is effective for kidney function preservation and reducing mortality, and early intervention by a nephrologist has been generally recommended for patients with CKD.[16,17] However, there is a lack of evidence supporting the benefits of nephrology care for patients with CKD undergoing CEA.[18]

This study aimed to test the hypothesis that CKD, evaluated by eGFR, is an independent predictor of the peri-operative and long term outcomes of CEA in Asian populations. It was also investigated whether clinical outcomes after CEA were associated with nephrology care, better controlled risk factors and tighter medical surveillance by a nephrologist, among patients with CKD.

MATERIALS AND METHODS

Study design and patient population

This single centre, observational study was conducted retrospectively using data extracted from the medical records of patients who had undergone CEA. Approval for data collection and publication was granted by the institutional review board of the Asan Medical Centre (IRB No. 2019–0165), Republic of Korea, which waived the requirement for written informed consent because of the study's retrospective design.

Between January 2007 and December 2014, 717 consecutive patients who underwent 789 CEAs at the study hospital were screened for inclusion in this study. Among these patients, 104 (114 CEAs) who were followed up at other hospitals were excluded to ensure that the impact of CKD under nephrology care on long term outcomes of CEA specifically was analysed. Ultimately, 613 patients were included (675 CEAs, 85.6%) stratified by pre-operative eGFR values (with a CKD group including patients with ESKD [eGFR $<$ 60 mL/min/1.73m^2] and a non-CKD group [eGFR $\geq$ 60 mL/min/1.73m^2]). An analysis was also conducted with the CKD group split into subgroups of patients with CKD who received nephrology care and patients with CKD without nephrology care, comparing these subgroups with one another and with non-CKD patients. In the CKD group, the key exposure of interest was nephrology care, defined as referral to a nephrologist (associated with better control of risk factors and tighter medical surveillance) for at least one outpatient visit or hospitalisation care during the study period with an index eGFR measurement $<$ 60 mL/min/1.73m^2.[18] All CEAs were performed according to the Vascular Surgery guidelines for the management of extracranial carotid disease with 50% – 99% luminal narrowing in patients with symptomatic carotid stenosis and $>$ 70% in those with asymptomatic carotid stenosis.[19] The demographics, risk factors of interest (including DM, hypertension, dyslipidaemia, smoking history, and history of CVD), and clinical characteristics and outcomes for all consecutive patients were recorded in an Excel (Microsoft Corp., Redmond, WA, USA) database and analysed retrospectively.

Kidney function assessment and risk factor definitions

Kidney function was assessed according to eGFR values.[20,21] GFR was estimated at baseline for all patients before CEA, calculated using the Modification of Diet in Renal Disease (MDRD) equation and expressed in mL/min/1.73m^2.[20,21] Patients were categorised according to the cutoff value of 60 mL/min/1.73m^2 for CKD, according to the National Kidney Foundation's Kidney Disease Outcome Quality Initiative (NKF KDOQI) guidelines.[22] Patients with eGFR values $\geq$ 60 mL/min/1.73m^2 were classified as having normal or mildly reduced kidney function (CKD stages 1 and 2, non-CKD group), whereas patients with eGFR values $<$ 60 mL/min/1.73m^2 for longer than three months were classified as having CKD (CKD stages 3–5, CKD group, including patients with ESKD). ESKD was defined as dialysis dependent renal failure with uraemia, and patients with severe renal insufficiency (eGFR $<$ 15 mL/min/1.73m^2, CKD stage 5) were not defined as having ESKD as long as they were not yet actually dialysis dependent, although definitions used in previous trials were slightly different. The most recent eGFR values were used to determine the progression of kidney disease, which was defined as progression of the CKD stage: from a normal baseline eGFR to a low eGFR ($<$ 60 mL/min/1.73m^2) in the non-CKD group and from stage 3 to stage 4–5 or from stage 4 to stage 5 in the CKD group.

Demographics and other risk factors were defined as described elsewhere.[23] Patients were considered to be symptomatic if they had a transient ischaemic attack, amaurosis fugax, or a non-disabling stroke ipsilateral to the carotid stenosis within the previous six months. Coronary artery disease (CAD) was defined as acute myocardial infarction (MI) or unstable angina pectoris, according to the American College of Cardiology/American Heart Association

Table 1. Baseline and clinical characteristics of 613 patients with or without chronic kidney disease (CKD) undergoing 675 carotid endarterectomies (CEA)

Characteristics	Total	CKD group	Non-CKD group	*p* value
Number of CEAs	675	112 (16.6)	563 (83.7)	
Age − y	68.5 ± 7.7	71.5 ± 7.8	67.9 ± 7.5	<.001
Male sex	590 (87.4)	94 (83.9)	496 (88.1)	.22
BMI − kg/m^2	24.1 ± 2.9	24.4 ± 3.0	24.0 ± 2.9	.20
CKD stage[*]				
Stage 3	99 (14.7)	99 (88.4)	−	NA
Stage 4	9 (1.3)	9 (8.0)	−	NA
Stage 5	4 (0.6)	4 (3.6)	−	NA
ESKD	3 (0.4)	3 (2.7)	−	NA
Risk factors and comorbidities				
DM	265 (39.3)	59 (52.7)	206 (36.6)	.001
Hypertension	513 (76.0)	102 (91.1)	411 (73.0)	<.001
Dyslipidaemia[†]	466 (69.0)	75 (67.0)	391 (69.4)	.60
Smoking[‡]	450 (66.7)	69 (61.6)	381 (67.7)	.21
CAD	131 (19.4)	26 (23.2)	105 (18.7)	.27
PAOD[§]	45 (6.7)	14 (12.5)	31 (5.5)	.007
Pre-operative medication use				
Statin	466 (69.0)	75 (67.0)	391 (69.4)	.60
Antiplatelet	518 (76.7)	76 (67.9)	442 (78.5)	.015
Calcium channel blocker	318 (47.1)	64 (57.1)	254 (45.1)	.020
Beta blocker	143 (21.2)	36 (32.1)	107 (19.0)	.002
ACE inhibitor	36 (5.3)	11 (9.8)	25 (4.4)	.021
Angiotensin II receptor blocker	233 (34.5)	54 (48.2)	179 (31.8)	.001
Kidney disease progression	135 (20.0)	27 (24.1)	108 (19.2)	.23
Carotid stenosis				
Degree of stenosis − %	76.2 ± 9.5	77.0 ± 9.1	76.0 ± 9.6	.30
SCSO	72 (10.7)	14 (12.5)	58 (10.3)	.49
Symptomatic	324 (48.0)	46 (41.1)	278 (49.4)	.11
CEA				
General anaesthesia	405 (60.0)	71 (63.4)	334 (59.3)	.42
Shunt implantation	421 (62.4)	70 (62.5)	351 (62.3)	.98
Patch angioplasty	653 (96.7)	110 (98.2)	543 (96.4)	.41

Data are presented as *n* (%) or mean ± standard deviation. ACE =angiotensin converting enzyme; BMI = body mass index; CAD = coronary artery disease; CEA = carotid endarterectomy; CKD = chronic kidney disease; DM = diabetes mellitus; ESKD = end stage kidney disease; NA = not applicable; PAOD = peripheral arterial occlusive disease; SCSO = severe contralateral extracranial carotid stenosis or occlusion.

* CKD stage at the time of CEA.

† All patients received statins prior to CEA.

‡ Past and current smoking.

§ PAOD was defined as patients who had a history of surgical or radiologic intervention or an ankle brachial index ≤ 0.9 during pre-operative examination.

guidelines. All patients received radionuclide myocardial perfusion imaging or coronary computed tomography angiography for pre-operative cardiac risk assessment.[24] Patients with a pre-operative diagnosis of dyslipidaemia were treated pre-operatively with statins, and regardless of dyslipidaemia status, all patients received statins after CEA.

Carotid endarterectomy procedures

The surgical procedures were performed as detailed previously.[24] A conventional endarterectomy with patch angioplasty in the standard fashion under general anaesthesia with routine carotid shunting or regional anaesthesia with selective shunting was performed. Post-operatively, patients without contraindications were given dual antiplatelet therapy (low dose aspirin plus clopidogrel)[25] with a statin in combination with stringent blood pressure control and close observation in an intensive care unit for at least 24 hours. All patients were followed up both clinically and by magnetic resonance imaging with angiography or carotid duplex ultrasonography (DUS) before discharge.

Study outcomes and follow up

The study outcomes included the occurrence of major adverse cardiovascular events (MACEs), defined as fatal or non-fatal stroke or transient ischaemic attack, MI, or all cause mortality, during the peri-operative period (within 30 days after CEA) and within four years after CEA. Individual MACE components were defined as detailed previously.[23] Only the first event of each outcome was included in the analysis of the MACE composite outcome, whereas each MACE outcome was analysed individually.

Every effort was made to observe the patients post-operatively at regular intervals, with DUS as well as independent neurological examinations: within 30 days, six months, 12 months, and annually. Once stability, general health status, including follow up DUS findings and renal function, had been established over three years, surveillance was performed at longer intervals of about two years.

Statistical analysis

Statistical analysis was performed using SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY, USA). Categorical variables are reported as frequencies or percentages, and continuous variables as means and standard deviations (SDs) or medians and interquartile ranges (IQRs). Categorical variables were compared using the chi square test, or Fisher's exact test when the chi square test was not appropriate. Student *t* test was used for comparisons of normally distributed continuous variables, and the Mann—Whitney *U* test for comparison of non-normally distributed continuous variables. Logistic regression analysis was performed to identify statistically significant variables associated with peri-operative MACEs and the individual MACE components, and odds ratios (ORs) with 95% confidence intervals (CIs) are reported. A Cox proportional hazards regression model was constructed to identify statistically significant variables associated with long term outcomes, and hazard ratios (HRs) with 95% CIs are reported. Variables with a p value $< .1$ on univariable analysis were subjected to multivariable analysis. Long term outcomes, MACE free, stroke free, and overall survival rates for four years, in the CKD and non-CKD groups were analysed using Kaplan—Meier survival curves, and the log rank test was used to compare the occurrence of MACEs and the individual MACE components. A p value $< .05$ was considered to be statistically significant.

RESULTS

Study sample and baseline characteristics

Among the study sample of 675 CEAs, the CKD group included 112 CEAs (16.6%), and the non-CKD group 563 CEAs (83.4%). The demographic and clinical characteristics of the study sample are presented in Table 1. Patients in the CKD group were more likely to be older ($p < .001$) and to have DM ($p = .001$), hypertension ($p < .001$), and peripheral arterial occlusive disease ($p = .007$). The prevalence of pre-operative use of antihypertensive medications was statistically significantly higher in the CKD group, whereas the use of antiplatelet medications was statistically significantly higher in the non-CKD group ($p = .015$).

The median follow up duration was 65 months (IQR 1 — 166 months) for the entire study sample: 61 months (IQR 1 — 131 months) in the CKD group and 65 months (IQR 1 — 166 months) in the non-CKD group. During follow up, the incidence of kidney disease progression was not statistically significantly different between the two groups (24.1% *vs.* 19.2%, $p = .23$). In the non-CKD group, 108 patients experienced kidney disease progression according to the present definition, and in the CKD group, 25 patients progressed from stage 3 to stage 4—5, and two patients progressed from stage 4 to stage 5.

Study outcomes and subgroup analysis according to nephrology care

Based on eGFR, the incidence of MACEs was higher in the CKD group compared with the non-CKD group during the peri-operative period (4.5% *vs.* 1.8%; $p = .086$) and within four years after CEA (17.9% *vs.* 11.5%; $p = .066$), with a non-statistically significant trend. When the individual MACE components were analysed separately, there was a statistically significantly higher risk of all cause mortality within four years in the CKD group (16.1% *vs.* 7.3%; $p = .003$) (Table 2). For the analysis excluding the peri-operative MACEs, there was an increased post-operative four year all cause mortality in the CKD group compared with the non-CKD group (12.1% *vs.* 6.7%; $p = .051$) (Supplementary Table S1). In terms of the occurrence of MACEs and individual MACE components between symptomatic and asymptomatic patients, there were no statistically significant differences between the CKD and non-CKD groups, respectively (data not shown).

On Kaplan—Meier survival analyses of the cumulative event free rates, although there was a similar stroke free survival rate ($p = .65$) between the two groups, the CKD group had a statistically significantly lower overall survival rate ($p = .002$) than the non-CKD group (Fig. 1). For the post-operative four year occurrence of the MACE composite outcome, the CKD group had a lower MACE free survival rate than the non-CKD group ($p = .070$), probably because of a statistically significantly higher all cause mortality rate in this group. The MACE free survival rates at four years after CEA in the CKD and non-CKD groups were 82.1% and 88.8%, stroke free survival rates were 96.2% and 95.7%, and overall survival rates were 83.9% and 92.7%, respectively.

In the CKD group, 56.3% (63/112) of patients were under nephrology care; most of the patients with stage 4—5 CKD (12/13, 92.3%) received nephrology care. In the subgroup analysis of patients in the CKD group according to delivery of nephrology care, the mean pre-operative eGFR value was statistically significantly lower among patients who received nephrology care compared with those who did not (41.0 $\pm$ 13.4 mL/min/1.73m^2 *vs.* 49.6 $\pm$ 8.1 mL/min/1.73m^2; $p < .001$). There were no statistically significant differences in terms of the occurrence of peri-operative (3.2% *vs.* 6.1% *vs.* 1.8%; $p = .083$) and four year post-operative MACEs (14.3% *vs.* 22.4% *vs.* 11.5%; $p = .080$) after CEA among patients with CKD with nephrology care, patients with CKD without nephrology care, and non-CKD patients. The risk of both peri-operative (4.1% *vs.* 0.4%; $p = .037$) and four year post-operative (20.4% *vs.* 7.3%; $p = .004$) all cause mortality was statistically significantly higher among patients with CKD without nephrology care compared with non-CKD patients, whereas there were no statistically significant differences in

Table 2. **Occurrence of the major adverse cardiovascular event (MACE)[*] composite outcome and the individual MACE components within 30 days and at four years after 675 carotid endarterectomies (CEA) in patients with or without chronic kidney disease (CKD) according to estimated glomerular filtration rate**

Outcome	30 day outcomes after CEA				Four year outcomes after CEA[†]			
	Total (n = 675)	CKD group (n = 112)	Non-CKD group (n = 563)	p value	Total (n = 675)	CKD group (n = 112)	Non-CKD group (n = 563)	p value
MACE	15 (2.2)	5 (4.5)	10 (1.8)	.086	85 (12.6)	20 (17.9)	65 (11.5)	.066
CV events[‡]	11 (1.6)	3 (2.7)	8 (1.4)	.40	32 (4.7)	5 (4.5)	27 (4.8)	.88
Any stroke	9 (1.3)	2 (1.8)	7 (1.2)	.65	30 (4.4)	4 (3.6)	26 (4.6)	.80
Major	1 (0.1)	1 (0.9)	0	.17	6 (0.9)	1 (0.9)	5 (0.9)	1.0
Minor	8 (1.2)	1 (0.9)	7 (1.2)	.99	24 (3.6)	3 (2.7)	21 (3.7)	.78
MI	2 (0.3)	1 (0.9)	1 (0.2)	.31	2 (0.3)	1 (0.9)	1 (0.2)	.31
Death	4 (0.6)	2 (1.8)	2 (0.4)	.13	59 (8.7)	18 (16.1)	41 (7.3)	.003

Data are presented as n (%). CEA = carotid endarterectomy; CKD = chronic kidney disease; CV = cardiovascular; MACE = major adverse cardiovascular event; MI = myocardial infarction.
* Any stroke, MI, or death.
† Including the occurrence of MACEs during the peri-operative period.
‡ Composite incidence of any stroke or MI.

the peri-operative and four year post-operative occurrence of the MACE composite outcome or the individual MACE components between patients with CKD with nephrology care and non-CKD patients (Table 3).

Variables associated with the occurrence of major adverse cardiovascular events

Multivariable analyses adjusting for confounding variables indicated that pre-operative use of statins had a protective effect on peri-operative MACE occurrence (OR 0.31; 95% CI 0.11 − 0.90; p = .031), whereas CAD was associated with 3.59 fold increased odds of MACE occurrence (95% CI 1.20 − 10.70; p = .022). CKD stage 3 trended towards an association with an increased incidence of MACEs (OR 2.84; 95% CI 0.94 − 8.65; p = .065) (Supplementary Table S2). In terms of the incidence of the individual MACE components, the use of statins was an independent predictor of a decreased peri-operative risk of any stroke occurrence (OR 0.16; 95% CI 0.04 − 0.68; p = .013) (Supplementary Table S3). The univariable analyses for the incidence of MI and all cause mortality identified no statistically significant risk factor, which precluded the execution of multivariable analysis (data not shown).

Multivariable analyses for determining factors associated with the four year risk of MACE occurrence indicated that older age (HR 1.05; 95% CI 1.02 − 1.08; p = .001) and DM (HR 1.62; 95% CI 1.06 − 2.48; p = .026) were negative independent risk factors for MACE occurrence (Supplementary Table S4). Regarding the four year post-operative incidence of the individual MACE components, DM (HR 2.59; 95% CI 1.23 − 5.44; p = .012) was statistically significantly associated with an increased risk of four year stroke occurrence (Supplementary Table S5), whereas older age (HR 1.05; 95% CI 1.02 − 1.19; p = .005), hypertension (HR 0.40; 95% CI 0.23 − 0.69; p = .001), and CKD stage 3 (HR 2.45; 95% CI 1.34 − 4.48; p = .005) were found to be significant predictors associated with death from any cause (Supplementary Table S6). Kidney disease progression was associated with a 1.69 fold increased likelihood of death from any cause within four post-operative years (95% CI 0.95 − 3.00; p = .073), with a non-statistically significant trend. There were no MIs identified in the present study sample within four years after CEA.

DISCUSSION

CKD is an important risk factor for the development of atherosclerosis and CVD.[2] A systematic review of observational studies showed that a reduced eGFR was associated with an increased risk of CVD,[26] and a recent meta-analysis found that a low eGFR (< 60 mL/min/1.73 m^2) was linked to a risk of future stroke that was 43% greater than that associated with a normal baseline eGFR.[1] This association was consistent across diverse population subgroups, that is, those with or without traditional CV risk factors.[1] In fact, CKD of even mild severity has been shown to be associated with worse clinical outcomes among patients with stroke, including a higher risk of all cause mortality and CV mortality.[27,28]

CEA is established as an effective treatment option for primary or secondary prevention of stroke among patients with major extracranial carotid artery stenosis.[10−12] Although CKD severity increases the risk of both peri-operative and late death, patients with mild to moderate CKD could equally benefit from stroke free survival after CEA compared with those without CKD, with no observed increase in the risk of peri-operative death or stroke.[13,14] Determining the risk of poor outcomes after CEA among individual patients with CKD is confounded by many factors, especially comorbidities.[5] Furthermore, there may be ethnic disparities in anatomic characteristics and the prevalence of extracranial carotid lesions[9]; however, little is known about the effectiveness and safety of CEA among Asian patients with CKD,[14] and few studies have examined the association between nephrology care and outcomes in such patients.

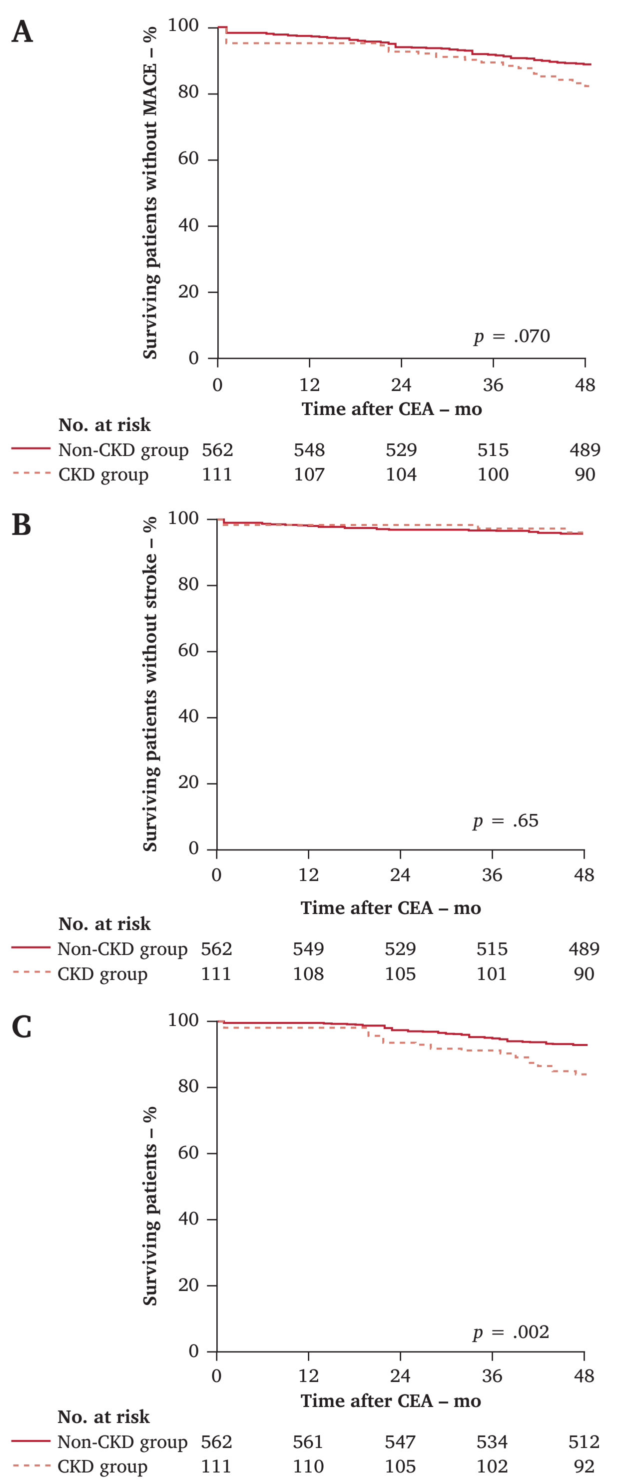

Figure 1. Cumulative Kaplan–Meier estimate of surviving patients without (A) major adverse cardiovascular event (MACE), (B) stroke, and (C) all cause mortality after carotid endarterectomy (CEA) based on a cutoff estimated glomerular filtration rate (eGFR) value of 60 mL/min/1.73m^2 (CKD group *vs.* non-CKD group). The CKD group had a statistically significantly lower overall survival rate ($p = .002$) than the non-CKD group.

It has been recommended that patients with CKD with symptomatic carotid stenosis could be treated according to general guidelines but should be informed that they may be at higher peri-operative risk than non-CKD patients.[29,30] Although Cooper *et al.* reported that peri-operative stroke and death rates were lower in patients with CKD with asymptomatic carotid stenosis than those with symptomatic stenosis,[29] the indications for asymptomatic carotid stenosis have not been well clarified. In the present study of Asian patients who underwent CEA, it was found that patients with CKD who received nephrology care had similar outcomes after CEA to patients in the non-CKD group, despite the higher peri-operative and four year post-operative risk of MACEs in the CKD group. Although patients in the CKD group were older and had more CV comorbidities than patients in the non-CKD group, most patients with stage 4—5 CKD were under nephrology care and were, therefore, managed appropriately. This study suggests that the MACE incidence after CEA could be decreased among patients with CKD with any nephrology care, more aggressive medical treatments, better control of risk factors, and tighter medical surveillance, which perhaps helped to preserve kidney function and minimise death among these patients.[16,17]

Despite this study's small sample size and its retrospective design, its strengths included the comparison of study outcomes according to the assessment of kidney function using eGFR, the close follow up of patients with optimal medical treatment (particularly patients with stage 4—5 CKD under nephrology care), and the long mean follow up period of 66.0 months, which allowed investigation of the effects of nephrology care and medication use on long term outcomes after CEA. The present findings have provided more insight into the CEA outcomes, similar peri-operative and four year post-operative outcomes in patients with CKD under nephrology care compared with non-CKD patients, among Asian patients with CKD over time.

This study did have its limitations. Similar to previous studies, it was retrospective and included only a small number of patients with severe CKD. There may have been selection bias in that some patients with severe CKD who were suspected of having other CV comorbidities could have been more appropriately treated medically and were, therefore, excluded from this study. Moreover, because of the small sample size in the CKD group, the results may be affected by type II error and should, therefore, be interpreted with caution. This could have accounted for some of the differences in outcomes relative to other studies. Furthermore, the frequency, length, or intensity of nephrology care or the management decisions implemented could not be determined. Additionally, the included patients in the CKD group were much older and had more CV comorbidities than those in the non-CKD group, which may have influenced the peri-operative and four year post-operative outcomes. Although corrections were made for other confounders potentially influencing the outcomes through multivariable analyses, residual confounding cannot be excluded because of the study's retrospective design.

In conclusion, despite the higher risk of peri-operative and four year MACEs after CEA among patients with CKD,

Table 3. Occurrence of the major adverse cardiovascular event (MACE)* composite outcome and the individual MACE components within 30 days and four years after total 675 carotid endarterectomies (CEA) among patients with chronic kidney disease (CKD) who received nephrology care, patients with CKD without nephrology care, and non-CKD patients

Outcome	30 day outcomes after CEA				Four year outcomes after CEA†			
	Under NPH care (n = 63)	Without NPH care (n = 49)	Non-CKD (n = 563)	p value	Under NPH care (n = 63)	Without NPH care (n = 49)	Non-CKD (n = 563)	p value
MACE	2 (3.2)	3 (6.1)	10 (1.8)	.083	9 (14.3)	11 (22.4)	65 (11.5)	.080
CV events‡	2 (3.2)	1 (2.0)	8 (1.4)	.33	3 (4.8)	2 (4.1)	27 (4.8)	1.0
Any stroke	1 (1.6)	1 (2.0)	7 (1.2)	.46	2 (3.2)	2 (4.1)	26 (4.6)	1.0
Major	1 (1.6)	0	0	.17	1 (1.6)	0	5 (0.9)	.67
Minor	0	1 (2.0)	7 (1.2)	.58	1 (1.6)	2 (4.1)	21 (3.7)	.70
MI	1 (1.6)	0	1 (0.2)	.31	1 (1.6)	0	1 (0.2)	.31
Death	0	2 (4.1)	2 (0.4)	.037§	8 (12.7)	10 (20.4)	41 (7.3)	.004§

Data are presented as n (%). CEA = carotid endarterectomy; CKD = chronic kidney disease; CV = cardiovascular; eGFR = estimated glomerular filtration rate; MACE = major adverse cardiovascular event; MI = myocardial infarction; NPH = nephrology.
* Any stroke, MI, or death.
† Including the occurrence of MACEs during the peri-operative period.
‡ Composite incidence of any stroke or MI.
§ Statistically significant difference between patients with CKD without nephrology care and non-CKD patients.

and the statistically significantly higher peri-operative and four year post-operative all cause mortality rates among patients with CKD without nephrology care, patients with CKD under nephrology care had similar outcomes to non-CKD patients. Any nephrology care with more aggressive medical treatment may reduce the risk of MACEs after CEA among patients of advanced age with CKD and higher baseline CV risks, including those with DM and hypertension. Future prospective trials with larger cohorts should lead to a better understanding of the benefits of nephrology care and a consensus of the standard care for patients with CKD undergoing CEA.

CONFLICT OF INTEREST

None.

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AUTHOR CONTRIBUTIONS

Conception and design: M.J.J. and Y.P.C. Analysis and interpretation of data: M.J.J., E.B., and Y.P.C. Drafting and revising of the article: M.J.J. and Y.P.C. Providing intellectual content of critical importance to the work described: J.W.C., S.U.K., Y.H., T.W.K., and Y.P.C. Statistical expertise: M.J.J., E.B., N.K., and E.C. Collection and assembly of data: M.J.J., E.B., E.C., Y.H., T.W.K. and Y.P.C. Final approval of the version to be published: All authors read and approved the final manuscript.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2021.01.013.

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