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Decreased Kidney Function

An Unrecognized and Often Untreated Risk Factor for Secondary Cardiovascular Events After Carotid Surgery

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Background and Purpose—Chronic kidney disease is an important risk factor for development and progression of atherosclerosis. The objective of the current study was to investigate the contribution of moderate kidney failure to cardiovascular (CV) mortality and morbidity after carotid endarterectomy (CEA). In addition, we investigated which proportion received optimal medical treatment or underwent diagnostic workup of the kidneys prior to CEA.

Methods—Between 2002 and 2009, 1085 patients undergoing CEA were included in this study. Estimated glomerular filtration rate (eGFR) was assessed at baseline. Moderate kidney failure was defined as an eGFR 30–59 and compared with normal or mildly reduced kidney function (eGFR \geq 60). Primary endpoint was CV death, composed of fatal myocardial infarction, fatal stroke, and ruptured abdominal aneurysm. Secondary endpoints were CV morbidity.

Results—Moderate kidney failure (eGFR 30–59) was observed in 26.5% (288/1085) of the patients. During a median follow-up of 2.95 years (0.0 to 3.0 years), the adjusted hazard ratio for CV death with an eGFR 30–59 was 2.22 (1.27 to 3.89). Adjusted hazard ratio for MI with an eGFR 30–59 was 1.90 (1.04 to 3.47). No higher risk for stroke and peripheral interventions was observed. Of all patients with an eGFR 30–59, 38.3% (105/274) received angiotensin-converting enzyme inhibitors, 74.5% (204/274) received statins, and 34.4% (99/288) visited a nephrologist.

Conclusions—Patients with an eGFR 30–59 have a 2.2-fold increased risk for CV death and 1.9-fold increased risk for myocardial infarction the 3 years after CEA compared with patients with an eGFR \geq 60, independent of other CV risk factors. A minority of these patients receive optimal medical treatment, which might explain the increased risk for progression of chronic kidney disease and CV morbidity and mortality. (*Stroke*. 2011;42:307-312.)

Key Words: carotid endarterectomy ■ carotid stenosis ■ renal disease ■ outcome ■ risk factors

Chronic kidney disease (CKD) is a common and predominantly a silent condition but an important risk factor for development of atherosclerosis and cardiovascular disease (CVD). With the rising incidence of diabetes and hypertension, the incidence of CKD is expected to rise.¹ With accelerated impairment of kidney function, the risk of death, cardiovascular (CV) events, and hospitalization increases gradually in a community-based population.² There is an ongoing debate about the cost effectiveness of population-based screening programs for CKD.³ Although CKD is irreversible, therapeutic interventions may slow or prevent progression of kidney failure. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II antagonists have been shown to delay progression of CKD.^{4–6}

The prevalence of CKD for noninstitutionalized individuals has been estimated to be 9.6% in the US population.⁷ Previous studies have shown that kidney failure is an important risk factor

for adverse outcome in patients with manifest atherosclerotic disease.⁸ The aim of this study was to investigate the prevalence of CKD among patients undergoing carotid endarterectomy (CEA) and the impact of CKD on CV outcome after CEA. Large series concerning peri-operative 30-day morbidity and mortality have shown the impact of CKD on outcome after CEA.^{9–11} However, the impact of kidney function on CV outcome in the first 3 years after CEA is underexposed.

The aim of guidelines for the management of CKD is to reduce the risk of deterioration of kidney function and progression of CVD, but these guidelines are often not met.^{12,13} To investigate the management of CKD among patients undergoing carotid surgery, we examined which proportion of patients was being treated pharmaceutically with antihypertensive drugs or statins for the benefit of risk factor management or had received a diagnostic workup of the kidneys prior to carotid surgery.

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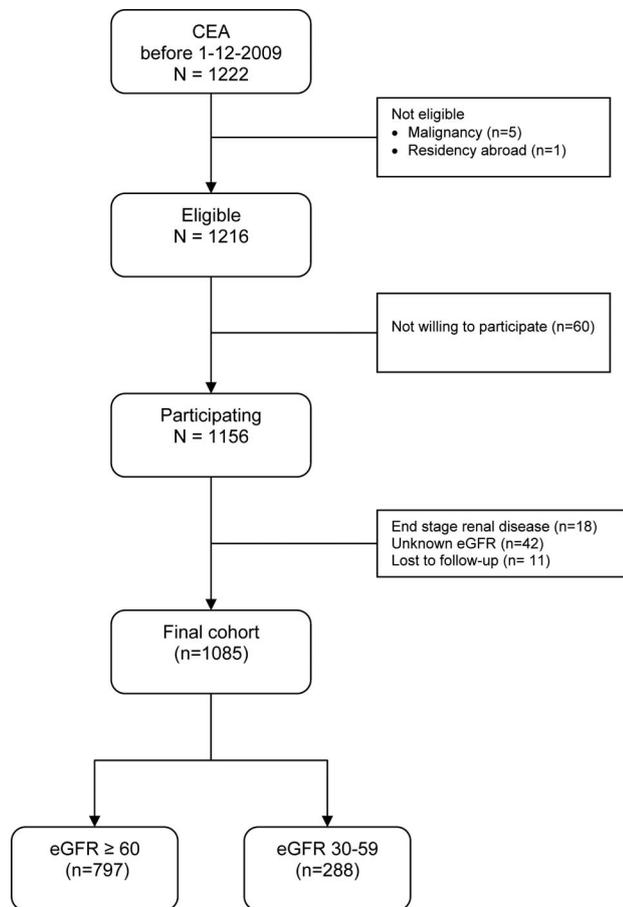


Figure 1. Inclusion flow chart of patients undergoing carotid endarterectomy between March 2002 and December 2009.

Methods

Patient Characteristics

Between March 2002 and December 2009, 1222 consecutive patients underwent CEA at 1 of the hospitals that participate in the Athero-Express biobank study (Figure 1). The study design has been described previously.¹⁴ Medical ethics boards of the 2 participating hospitals approved the study and all participating patients provided written informed consent. Selection for CEA was based on international guidelines of the European Carotid Surgery Trial (ECST), the North American Symptomatic Carotid Endarterectomy Trial (NASCET), and the Asymptomatic Carotid Surgery Trial (ACST) for symptomatic and asymptomatic carotid stenoses, respectively.^{15–17} Patient selection for the current study, based on several inclusion and exclusion criteria, is depicted in Figure 1. Of the 1222 patients, 6 were excluded for follow-up due to malignancy (n=5) or residency abroad (n=1). Sixty patients were unwilling to participate. Patients with end-stage kidney disease (estimation of the glomerular filtration rate [eGFR] <30) were identified (n=18) and excluded given that only the impact of moderate CKD is the subject of the current study and the group was too small to compare with the other groups. Another 42 patients were excluded because of an unknown kidney function. After CEA, 11 patients were lost to follow-up, 0.9% of the total cohort.

Hypertension was defined as systolic tension >130 mm Hg or usage of blood pressure-lowering drugs; diabetes was defined as use of insulin or oral glucose inhibitors. The type of symptomatic presentation was divided into stroke, transient ischemic attack, and asymptomatic presentation.

Patient characteristics and information regarding previous diagnostic tests were obtained from questionnaires that were completed prior to CEA or from preoperative patient charts. Preoperative

medical treatments (ie, statins and antihypertensive drugs including ACE-inhibitors, angiotensin II antagonists, beta blockers, and diuretics) were registered. Previous kidney investigations included ultrasound imaging, renogram, or an angiography of the renal arteries.

Kidney Function Assessment

eGFR is the best overall measure for estimating kidney function.¹⁸ Estimation of GFR was performed at baseline for all patients and calculated using the Modification of Diet in Renal Disease formula and expressed in ml/min per 1.73 m².^{18–21} Cutoff value for CKD based on eGFR was adapted from The Kidney Foundation.^{22,23} An eGFR ≥60 mL/min per 1.73 m² was considered normal or mildly reduced kidney function (CKD stage 1 and 2), and an eGFR 30–59 was considered moderate kidney failure (CKD stage 3).

Follow-Up

Follow-up procedure of the Athero-Express study has been described previously.¹⁴ Briefly, CV events were prospectively registered for 3 consecutive years after carotid surgery. All patients were contacted yearly after CEA and filled in a questionnaire about any vascular event they had experienced or had been hospitalized for in the past year. If any of the questions were answered positively, further research was performed by a research physician, and if necessary, correspondence, laboratory tests, or imaging reports were requested from the relevant institution. Adjudication of all endpoints was performed by an outcome assessment committee consisting of 3 authors (F.L.M., J.V., and G.L.). All endpoints were independently assessed by 2 independent observers. If no consensus was reached, the third observer was consulted. Endpoint registration and validation occurred blind from kidney function. When patients did not respond, the General Practitioner was contacted for the current status.

Endpoint Definitions

Primary endpoint for the current study was CV-related death and encompassed fatal myocardial infarction (MI), fatal stroke, and fatal aneurysm rupture. Fatal MI was considered if death occurred more than 1 hour after onset of complaints and at least 2 of the following criteria were met: chest pain for at least 20 minutes, not disappearing after administration of nitrates; electrocardiographic changes: ST elevation >1 mm in 2 following leads or a left bundle branch block; creatine kinase (CK) elevation of at least 2 times the normal value of CK and a CK-MB fraction >5% of the total CK. Definition for stroke was adapted from the World Health Organization.²⁴ Fatal stroke was defined as focal neurologic impairment of sudden onset, lasting more than 24 hours and leading to death, and of presumed vascular origin. Fatal stroke was considered if patients died as a direct consequence of stroke or because of severe handicap caused by stroke. Fatal aneurysm rupture was defined as rupture of the abdominal aortic aneurysm confirmed by laparotomy or imaging.

Secondary endpoints included non-fatal CV events in 3 different vascular territories. A myocardial infarction was defined as stated above without fatal result and required documented enzyme course and changes. Non-fatal stroke was defined as focal neurologic impairment of sudden onset, lasting more than 24 hours not leading to death, and of presumed vascular origin. All strokes were confirmed with computed tomography scan or magnetic resonance imaging. Peripheral interventions were defined as peripheral percutaneous transluminal angioplasty, surgical peripheral arterial revascularization, or lower limb amputation.

Statistical Analysis

SPSS version 15.0 (SPSS, Inc.) was used for all statistical analyses. Baseline differences among the different groups were calculated with χ^2 or Mann Whitney U-test where appropriate. A 2-sided probability value <0.05 was considered statistically significant.

Kaplan Meier survival analysis was performed to estimate the cumulative event rates after CEA. To assess the independent effect of moderate kidney failure on CV outcomes, we performed analyses through multivariable Cox proportional hazards model. Factors that

Table 1. Baseline Patient Characteristics

Patient Characteristics	Estimated Glomerular Filtration Rate (ml/min per 1.73 m ²)		P
	≥60	30–59	
No. of patients (n)	797	288	
Male	71.6% (571/797)	64.6% (186/288)	0.025
Age, mean years (±SD)	66.5 (±8.8)	71.8 (±7.4)	<0.001
Current smoker	36.8% (278/755)	32.6% (88/270)	0.213
Diabetic status	19.4% (137/707)	26.6% (70/263)	0.014
Hypertension	82.9% (600/724)	93.6% (249/266)	<0.001
Body mass index (kg/m ²), mean (±SD)	26.3 (±3.7)	26.7 (±4.0)	0.240
History of myocardial infarction	7.7% (54/699)	12.4% (31/251)	0.028
History of peripheral intervention	15.9% (124/781)	21.4% (59/276)	0.038
Ipsilateral carotid stenosis			
50–70%	5.5% (42/764)	4.0% (11/277)	
70–99%	94.5% (722/764)	96.0% (266/277)	0.322
Contralateral carotid stenosis			
0–50%	56.9% (412/724)	52.7% (139/264)	
50–70%	10.8% (78/724)	9.5% (25/264)	
70–99%	16.6% (120/724)	19.7% (52/48)	
100%	15.7% (114/724)	18.2% (48/164)	0.436
Clinical presentation			
Asymptomatic	14.9% (117/783)	18.4% (52/282)	
Transient ischemic attack	61.4% (481/783)	56.0% (158/282)	
Stroke	23.6% (185/783)	25.5% (72/282)	0.232

showed a possible relation with CV outcome in an univariate analysis ($P < 0.20$) were entered in the multivariable model together with 2 groups of eGFR. Results from univariate and multivariable analyses are presented as (adjusted) hazard ratios (HR) with 95% CI. An HR with a CI not including 1 was considered statistically significant.

Results

Baseline Characteristics

Among 1085 patients, eGFR ≥ 60 (CKD stage 1 and 2) was observed in 797 cases (73.5%) and eGFR 30–59 (CKD stage 3, moderate kidney failure) was observed in 288 patients (26.5%). Baseline characteristics for both groups are provided in Table 1. The group with an eGFR 30–59 encompassed more women, older patients, patients with a higher prevalence of diabetes mellitus and hypertension, and patients who more frequently had history of MI and peripheral intervention.

Outcome

Median duration of follow-up was 2.95 years (0.0 to 3.0 years). Fatal CV endpoints were observed in 8.7% (25/288) of the patients with an eGFR 30–59, compared with 3.4% (27/797) for patients with an eGFR ≥ 60 (adjusted $P = 0.001$; Figure 2A). CV death for patients with an eGFR 30–59 was caused by fatal MI ($n = 13$), fatal stroke ($n = 8$), and abdominal aneurysm rupture ($n = 4$). Adjusted HR for CV death with an eGFR 30–59 was 2.22 (1.27 to 3.89), independent from other CV risk factors and baseline differences (Table 2). Other risk

factors that contributed to CV death were age (HR, 1.06; CI, 1.02–1.10) and male sex (HR, 2.53; CI, 1.19–5.38).

MI during follow-up occurred in 7.6% (22/288) of patients with eGFR 30–59 compared with 3.0% (24/797) of patients with eGFR ≥ 60 (adjusted $P = 0.013$; Figure 2B). Adjusted HR for MI with an eGFR 30–59 was 1.90 (1.04–3.47; Table 2). The risk of stroke or peripheral interventions was not significantly higher for patients with moderate kidney failure. (Figure 2C and 2D).

Clinical Management

For patients with eGFR 30–59, only 34.4% (99/288) ever visited a nephrologist for additional diagnostic tests or medication optimization before carotid surgery, compared with 16.4% (131/797) of patients with an eGFR ≥ 60 , respectively (Table 3). From all 288 patients who had an eGFR 30–59, 25.7% (74/288) reported a diagnostic test of the kidneys executed before the CEA procedure. This was significantly more compared with patients with an eGFR ≥ 60 : 13.2% (105/797; $P < 0.001$). The different types of diagnostic tests are displayed in Table 3; performance of the different types of investigations was more prevalent among patients with moderate kidney failure.

Patients with an eGFR 30–59 were prescribed relatively less aspirin, 79.9% (219/274), and more oral anticoagulants, 17.5% (48/274), compared with patients with an eGFR ≥ 60 : 86.8% (692/754) and 12.1% (91/754), respectively (Table 3). Prescription of statins was comparable between groups: 74.8% (564/754) versus 74.5% (204/274). ACE inhibitors

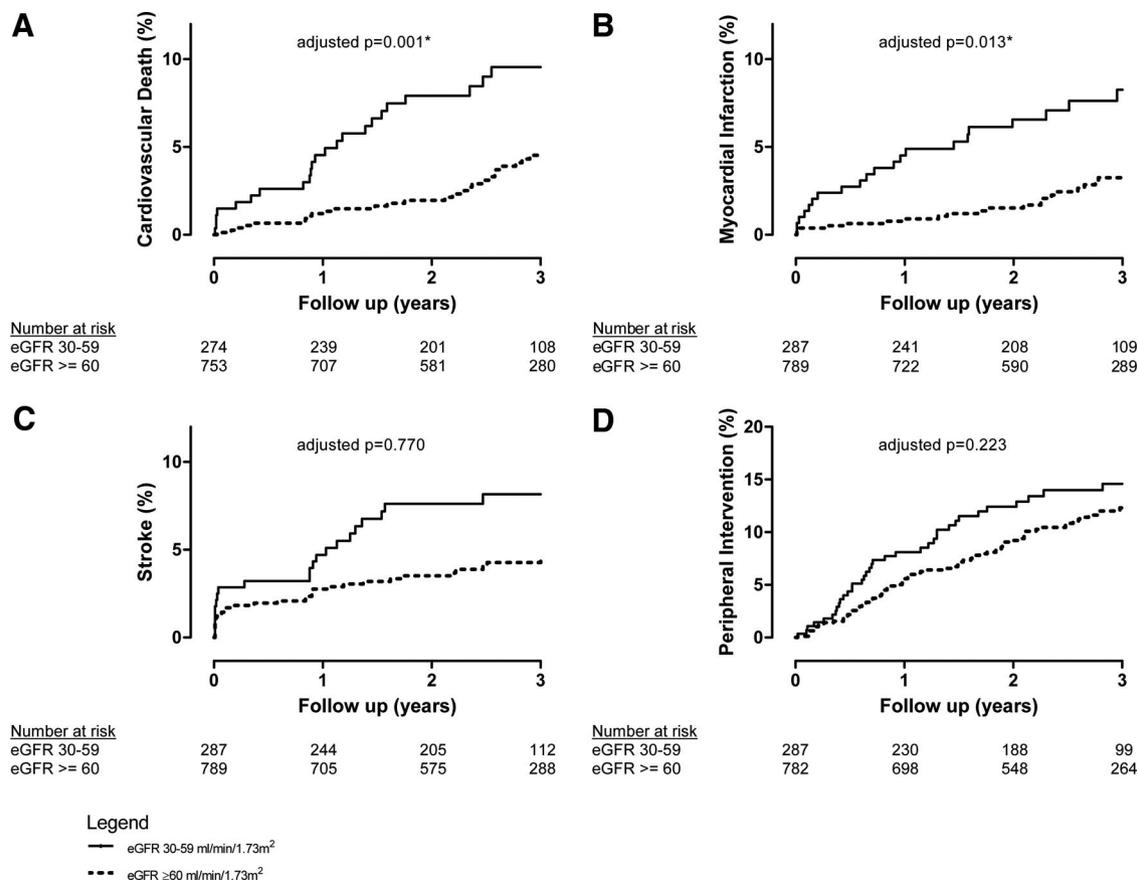


Figure 2. Hazard functions for cardiovascular death (A), myocardial infarction (B), stroke (C), and peripheral interventions (D) after carotid endarterectomy. Probability values were corrected for cardiovascular risk factors and baseline differences.

were prescribed more frequently for patients with an eGFR 30–59: 38.3% (105/274) versus 29.3% (221/754) for eGFR ≥60 ($P=0.006$; Table 3). A similar difference was observed for other antihypertensive drugs including Angiotensin II antagonists, beta blockers, and diuretics (Table 3).

Discussion

We show that in a large cohort of patients undergoing carotid surgery, moderate kidney failure is associated with an increased risk for CV death and myocardial infarction during

midterm follow-up, independent of other CV risk factors. The observation of the independent relation of eGFR 30–59 with CV death emphasizes the vulnerability of patients with moderate kidney failure and thus influences outcome after CEA.

Given that moderate kidney failure is associated with a higher risk of CV death, it is important to prevent deterioration of kidney function and progression of CVD. Deterioration of kidney function can be prevented in part by prescription of ACE inhibitors or angiotensin II antagonists.^{4–6} Although patients

Table 2. Multivariable Cox Regression of Proportional Hazard Ratios for Myocardial Infarction and Cardiovascular-Related Death During 3-Year Follow-Up

Characteristic	HR for Cardiovascular Death (95% CI)	Adjusted HR (95% CI)	HR for Myocardial Infarction (95% CI)	Adjusted HR (95% CI)
Male	2.31 (1.09–4.92)	2.53 (1.19–5.38)	1.54 (0.77–3.10)	
Age	1.07 (1.03–1.11)	1.06 (1.02–1.10)	1.06 (1.03–1.10)	1.06 (1.02–1.10)
Current smoker	1.22 (0.69–2.16)		0.98 (0.53–1.80)	
Diabetic status	1.36 (0.71–2.66)		1.12 (0.55–2.28)	
Hypertension	2.40 (0.74–7.74)		3.44 (0.83–14.23)	
Body mass index	0.95 (0.87–1.04)		1.02 (0.94–1.10)	
History of myocardial infarction	1.44 (0.61–3.37)		2.78 (1.34–5.76)	2.33 (1.12–4.85)
History of peripheral intervention	1.58 (0.85–2.98)		2.34 (1.26–4.33)	2.14 (1.15–3.99)
eGFR ≥60 mL/min per 1.73 m ²	Reference	Reference	Reference	Reference
eGFR 30–59 mL/min per 1.73 m ²	2.69 (1.56–4.63)	2.22 (1.27–3.89)	2.64 (1.48–4.71)	1.90 (1.04–3.47)

Table 3. Nephrologist Visits, Additional Diagnostic Tests, and Medication Use

Characteristic	Estimated Glomerular Filtration Rate (mL/min per 1.73 m ²)		P
	≥60	30–59	
Patients (n)	797	288	
Visited a nephrologist	16.4% (131/797)	34.4% (99/288)	<0.001
Diagnostic test kidneys			
No investigation	86.8% (692/797)	74.3% (214/288)	
Ultrasound	8.3% (66/797)	12.5% (36/288)	
Renogram	1.0% (8/797)	3.1% (9/288)	<0.001
Angiography	1.8% (14/797)	4.5% (13/288)	
Combination of tests*	2.1% (17/797)	5.6% (16/288)	
Pre-operative medication use			
Aspirin	86.1% (649/754)	79.9% (219/274)	0.016
Oral Anti-coagulants	12.1% (91/754)	17.5% (48/274)	0.024
Statin	74.8% (564/754)	74.5% (204/274)	0.910
ACE inhibitor	29.3% (221/754)	38.3% (105/274)	0.006
Diuretic	27.1% (204/754)	50.7% (139/274)	<0.001
Beta-blocker	42.7% (322/754)	54.0% (148/274)	0.001
Angiotensin II antagonist	17.9% (135/754)	24.5% (67/274)	0.019

*Combination of tests was defined as a composition of ultrasound, renogram, or angiography.

with an eGFR 30–59 were prescribed more blood pressure-lowering drugs compared with patients with an eGFR ≥60, only the minority of these patients is treated. In our cohort, only 34.2% of patients with an eGFR 30–59 was treated with ACE inhibitors, and 24.5% received an angiotensin II antagonist, although it is known that these patients especially can benefit from this type of medical treatment.^{4–6} Apart from progression of CKD, a beneficial effect of ACE inhibition on CV outcome has been shown in patients with a moderate kidney failure and stable coronary artery disease.²⁵ Unfortunately, no risk modification by treatment could be observed in our cohort, but this can be explained by selection bias; treatment effect can only be investigated in a randomized controlled setting.

Statins were prescribed in 74.5% (204/274) of the cases with moderate kidney failure. For optimal medical treatment and risk factor management, a higher prescription rate of statins, together with lifestyle adjustments for these vulnerable patients, is justified.

Population-based screening for CKD is already a current subject of discussion.²⁶ Patients with positive test results for CKD should be evaluated and treated according to established guidelines for CKD as defined by the National Kidney Foundation.²³ Current guidelines recommend referral of all patients with CKD stage 4 to 5 (eGFR <30) to nephrologists for specialized care. However, these guidelines are population based. Patients who undergo carotid surgery are already in a more-advanced stage of atherosclerotic disease and thus more prone to worsening of CVD and deterioration of kidney function. The guidelines might, therefore, be less applicable for patients with clinically manifest atherosclerosis and a more aggressive screening program might be justified. Surveillance programs for CKD stage 3 (eGFR 30–59) have been suggested before as an effective way to decrease rates of

CVD and death.²⁶ However, such surveillance programs are expensive and require more resources. It is, therefore, desirable to start with subgroup surveillance of “patients at risk” among all patients with an eGFR 30–59. Patients undergoing carotid surgery probably belong to this subgroup at risk given that they already suffer from manifest atherosclerotic disease of the carotid artery. In addition, patients with diabetes mellitus or hypertension might be considered for regular kidney function assessment, as these conditions are known to be involved in development and deterioration of kidney failure.²⁷

Limitations of the Current Study

It is unlikely that confounders influenced the outcome because we corrected for other CV risk factors and baseline differences through multivariable Cox regression analyses. However, residual confounding cannot be excluded since the design for the current study is a prospective cohort study and not a randomized controlled trial. Nevertheless, we believe that the current study provides good insight in outcome of a consecutive cohort of patients undergoing carotid surgery and has sufficient statistical power.

The assessment of kidney function has been a subject of discussion for many years. Assessment of kidney function was performed for this study by the Modification for Diet in Renal Disease. This merely estimates the actual kidney function, but to our knowledge, it is the most accurate equation when it comes to estimating GFR. The original Modification for Diet in Renal Disease formula also included serum albumin and urea. The requirement of these additional values is clearly a limitation. For practical use, a simplified formula excluding serum albumin and urea was used to maximize the number of patients eligible for this study. We do not expect that use of this equation resulted in appreciable

loss of accuracy. This simplified version of the formula is widely applied and cited.¹⁹

In summary, our data show that moderate kidney insufficiency is a common phenomenon and independent risk factor for CV death and myocardial infarction during follow-up after carotid surgery. Progress of current medical practice can still be made in terms of identifying patients at risk and medication adjustments to prevent deterioration of kidney function and progression of CVD.

Conclusion

Patients with an eGFR 30–59 have a 2.2-fold increased risk for CV death and 1.9-fold increased risk for myocardial infarction the first 3 years after CEA compared with patients with an eGFR \geq 60, independent of other CV risk factors. A minority of these patients receive optimal medical treatment, which might explain the increased risk for progression of CKD and CV morbidity and mortality.

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Disclosures

F.L.M., D.P.V.K., and G.P. are co-founders of Cavadis, a company that specializes in diagnostic plaque biomarker kits. The content of this article is not related to the activities of Cavadis.

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