lysosomes under such physiologically relevant conditions will undoubtedly provide insights into how the spatial distribution of NCC is coordinated in health and misregulated in disease.

ACKNOWLEDGMENTS

This work was supported by a US Department of Veterans Affairs Mid-Level Career Development Award (A.R.S.) and National Institutes of Health grants DK084566 (A.R.S) and DK051496 (D.H.E.).

We thank Ora Weisz for critical review of the manuscript and Paul Welling, James Wade, and members of the Ellison laboratory for helpful discussions.

DISCLOSURES

None.

REFERENCES


Management of Symptomatic Carotid Stenosis in Individuals with CKD

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Despite recent interest in carotid stenting for treatment of carotid stenosis, carotid endarterectomy remains the standard of care, particularly for individuals with symptoms referable to that carotid and with moderate to severe stenosis. Interest in stenting has increased in individuals with more medical comorbidities, including renal disease, despite lack of clear data contraindicating endarterectomy in these patients.

The article by Mathew et al. in this issue of JASN analyzes existing data from the North American Symptomatic Carotid Endarterectomy trial (NASCET), the only large randomized carotid endarterectomy trial in which creatinine levels were routinely measured. The authors show that carotid endarterectomy not only may benefit individuals with symptomatic carotid stenosis and chronic kidney disease (CKD) but also is safe and without major operative complications. In their anal-

Published online ahead of print. Publication date available at www.jasn.org.

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ysis, the number needed to treat to prevent one stroke among individuals with CKD was only four, compared with 10 among individuals without CKD.

The primary reason for the results in this article, strongly supportive of carotid endarterectomy in symptomatic patients, is that individuals who have GFR <30 ml/min per 1.73 m² with symptomatic high-grade carotid stenosis (≥70%) and are treated medically have much higher rates of stroke, myocardial infarction, or death than do their equivalents with a normal GFR. In contrast, the risks associated with the surgical group were not elevated to the same extent; in fact, the perioperative stroke or death rate is lower among individuals with CKD than among individuals without CKD. Their results emphasize the poor outcomes among individuals who have CKD and do not undergo revascularization of high-grade carotid stenosis. Individuals who had CKD and were randomly assigned to the surgical treatment group did, however, have significantly higher rates of the composite adverse event of myocardial infarction, congestive heart failure, and arrhythmia (adjusted relative risk 3.98).

In general, the subgroups who have had the least clear benefit from endarterectomy are those with higher rates of surgical complications. Women tend to have higher surgical complication rates than do men and in the NASCET trial do not have as much benefit for treating stenoses <70%. As a result, surgery for symptomatic carotid stenosis has maximum benefit among men, individuals who are aged ≥75 yr, and individuals who are treated within 2 wk of a minor stroke or transient ischemic attack.

Because the NASCET is a randomized trial in which kidney function was not taken into account upon enrollment and the study is now being subjected to a subgroup analysis, there still may be unmeasured confounders that could exist in the relationship between kidney function and outcomes after endarterectomy. Individuals with CKD are likely to have significant small vessel disease of the brain, and it is possible that individuals with more extensive cerebral small vessel disease and symptomatic carotid stenosis may be at higher risk for stroke. Among individuals with asymptomatic carotid stenosis, silent infarcts associate with higher risk for stroke. In addition, more extensive white matter disease of the brain associates with worse outcome after stroke and may be a predictor of having a stroke in general. The other major consideration in management decisions of individuals with carotid stenosis is that primary carotid endarterectomy trials were conducted in an era before routine statin use; it is likely that the same studies done in the current climate would reveal lower rates of stroke in individuals in both treatment groups as a result of the use of statins. Optimal medical management differs in the current era when compared with the era when these large carotid surgery trials were conducted.

It should be emphasized that these results should not be automatically applied to individuals who do not have symptoms and are found to have carotid stenosis, including those found as part of routine clinical care or as part of a transplant evaluation. In a pooled analysis of the asymptomatic carotid stenosis trials, the net relative risk reduction was 0.71 among individuals with >60% stenosis but without symptoms; however, perioperative complication rates in these trials were particularly low. Because perioperative complications are likely to increase in individuals with more comorbidities and because risk for ischemic stroke is lower in the setting of asymptomatic carotid stenosis, it is less clear that a benefit would still favor surgery for patients with CKD and asymptomatic carotid stenosis. In addition, although this study included patients with advanced CKD and a GFR <30 ml/min per 1.73 m², the results cannot be extrapolated to those with even more severe stages, including ESRD.

Diagnosis of carotid stenosis is another important consideration for future research; although iodinated dye is required for the stenting procedure itself, confirmation of stenosis often requires either gadolinium (for magnetic resonance angiography) or iodinated dye (for computed tomographic angiography or conventional angiography). Much has been written about the risks of both iodinated contrast and gadolinium contrast in patients with CKD. Depending on the clinical situation, some surgeons will operate on the basis of carotid ultrasound results alone, but sensitivity and specificity of the diagnosis (as compared with conventional angiography as the gold standard) both increase when carotid duplex is combined with another study, such as magnetic resonance angiography.

That individuals with CKD in the NASCET trial, particularly those with high-grade stenosis, had such a benefit from carotid endarterectomy in this subgroup analysis will change clinical recommendations for individuals with CKD and symptomatic carotid disease. Recent recommendations have included consideration of carotid endarterectomy in only some cases with CKD, but this article emphasizes that it should be considered more routinely, particularly in individuals with >70% stenosis. This is even more important given recent findings that individuals with CKD may have worse outcomes after carotid artery stenting.

Individuals who have symptomatic moderate- to high-grade carotid stenosis and also have CKD benefit from and tolerate carotid endarterectomy. How this compares with the use of carotid stenting or with the use of maximal medical therapy in an era of statin use and good BP management is still unclear and warrants further study.

DISCLOSURES
None.

REFERENCES


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**Protection from Cancer in Kidney Transplant Patients by γδ T Cells: Role of CMV Infection?**

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In this issue of *JASN*, Couzi *et al.* describe a longitudinal case-control study of kidney transplant recipients who developed cancer 2 to 6 years after transplantation. The median percentage of γδ T cells was significantly lower in patients who developed cancer but only in those who had a pre- or posttransplantation cytomegalovirus (CMV) infection.

γδ T cells reside among the epithelia of various organs, particularly in lung, skin, intestine, and tongue, where they serve as a first-line defense against invading viruses, bacteria, and fungi. Activated early, during the interphase between innate and adaptive immunity, γδ T cells attract innate effector cells and help polarize the adaptive immune response. When they recognize cells undergoing environmental stress or infection, they produce cytokines (IFN-γ, TNF-α, IL-1, and IL-17) that activate the adaptive immune system. The site of accumulation and the stimuli that activate γδ T cells depend on their receptor Vδ regions. For example, Vδ2 γδ T cells recognize nonpeptidic phosphorylated metabolites of isoprenoid biosynthesis expressed by mycobacteria, whereas Vδ1 γδ T cells are activated by MIC-A, MIC-B, and UL-16-binding proteins and thus respond to NKG2D ligands through an MHC-independent mechanism that does not require recognition of specific antigens. This makes them particularly interesting in tumor surveillance, because tumor cells often downregulate MHC class I molecules.

γδ T cells are more numerous after CMV infection, and an increase in Vδ2 γδ T cells associate with clearance and control of infection. CMV-infected cells are targets for Vδ2 γδ T cells, and infection induces a memory response. The factors on CMV-infected cells that activate Vδ2 γδ T cells are unknown; however, the expansion of this population is puzzling because CMV downregulates factors that may be involved in their activation, such as MIC-A, MIC-B, and UL-16-binding proteins, as well as MHC class I molecules.

CMV is a common virus in the population, and 50 to 90% of adults have been previously infected with CMV and carry latent virus. The primary infection is generally asymptomatic or causes mild symptoms; however, patients with a suppressed immune system, such as transplant recipients and patients with AIDS, develop clinical CMV infections that may be life-threatening. The virus remains dormant, particularly in blood cells of the myeloid lineage, and can reactivate during inflammation. CMV may also reactivate in patients who have cancer and are immunosuppressed as a