Chronic Kidney Disease and Alcohol Consumption
Are Asians at Particular Risk for Hemorrhagic Stroke?

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See related article, pages 2531–2537.

Stroke represents one of the major challenges of the 21st century. More than 15 million people suffer from stroke each year worldwide. Enormous efforts in public awareness and prevention of the disease have led in industrialized countries to a slightly declining incidence. Mortality and morbidity (measured in disability-adjusted life years) are, however, expected to rise substantially during the next 2 decades; stroke will climb from 8th rank in 2010 to the 5th rank in 2030 worldwide; compared with 1990, the disability-adjusted life years attributed to stroke will nearly double over these 40 years.1

One important comorbidity that dramatically influences stroke and its outcome is chronic kidney disease (CKD), a clearly underestimated cardiocerebrovascular risk factor. CKD is defined as the combination of kidney damage (with albuminuria) and reduced glomerular filtration rate, as estimated from serum creatinine levels.2 The prevalence of CKD is substantially and/or continuously increasing, from 10% to 13.1% during the last decade (US National Health and Nutrition Examination Survey).2 Currently, more than 20 million Americans are affected by this disease, many of them not even aware of it. Preventing and treating CKD was therefore declared a global challenge.3 In addition to the fact that such a substantial number of people are affected and may finally require renal replacement therapy or transplantation, even more important is that CKD dramatically drives cardiocerebrovascular morbidity and mortality.2,4

CKD is highly associated with important stroke risk factors such as hypertension, diabetes, myocardial hypertrophy, and atrial fibrillation.4 Apart from these, CKD is associated with a number of disturbances in hemostasis and was found to be an independent risk factor of cardiocerebrovascular events. Consequently, risk of stroke in CKD patients was significantly higher than in those without CKD.4 Once a stroke in these patients occurred, it appeared to be a grave prognosis: the little existing data reported 2-year mortality rates of 74% in patients with end-stage renal failure, and even 55% in a combined subgroup with earlier stages of CKD.4

Dr. Shimizu and colleagues add in this issue of Stroke5 some important aspects to the currently very rare data set on CKD and stroke. The authors identified in a prospective cohort of 11780 Japanese men and women without previous cardiovascular disease the estimated glomerular filtration rate (eGFR) as the main factor driving stroke risk in men and women. The total occurrence of strokes in patients with a normal eGFR (>89 mL/min) was 4.3% in men, and 2.4% in women. With a declining eGFR (<60 mL/min, to be classified as CKD stages 3–5), stroke increased markedly to 13.1% in men and 7.6% in women. Even in the subgroup with an eGFR between 90 and 60 mL/min (mild renal failure, to be classified as CKD stage 2) a clear, but not significant, trend for higher stroke rates could be seen in both men and women (6.7 and 3.6%, respectively). As seen in other cardiovascular complications and events, we have to be aware that CKD increases the risk for both ischemic and hemorrhagic strokes already in early stages, with an eGFR <90 mL/min, and significantly below 60 mL/min, respectively.

The most interesting finding of the present study is the association between alcohol drinking habits, CKD, and occurrence of hemorrhagic strokes. A particular strength of the study is the documentation of stroke subtype by brain imaging (MRI or CT) in 93% of stroke patients. Whereas rates of hemorrhagic strokes were very similar in men and women without CKD (0.6–1.5%, respectively) regardless of whether they were drinkers, men and women with CKD suffered from a markedly higher rate of hemorrhagic strokes when drinking alcohol (5.3% and 6.1%, respectively) compared with never-drinkers with CKD (0.7% and 1.7%, respectively) and those without CKD. This is important and suggests a recapitulation: drinking in the present study was defined as consumption of 0.3 go or more per week (1 gō, is a traditional Japanese unit of volume equal to 23 g of ethanol, 2 glasses of wine, 1 bottle of beer, or 75 mL whisky). Although this is substantially lower than the current accepted recommendation of alcohol per day for cardiocerebrovascular protection, in patients with CKD, it led to more brain hemorrhages in this study. A potential reason for the finding could be the decreased activity of the alcohol dehydrogenase in this Japanese population that may have increased alcohol toxicity in the brain much more than in a comparable white population. Although this is a speculation, if just a part of these findings were true, it would have an enormous impact on current recommendations and guidelines. Of note, about 78% of men and 12% of women in this Japanese cohort were current or former drinkers according to this definition. One conclusion from the present study could therefore be a strict alcohol prohibition in at least all Asian patients with eGFR <60 mL/min.
A bit surprising in the present analysis was that the rate of ischemic strokes in men was not significantly different between distinct subgroups with CKD. However, because the time of occurrence of strokes was not reported, it could simply be that in this cohort with 78% currently or formerly drinking men, hemorrhagic stroke was the overriding and early determining factor. In comparison, in women, the higher stroke rates in advanced stages of CKD were mainly because of the marked increase in ischemic strokes (whereas the increase in hemorrhagic stroke rates with a decline in eGFR was not significant).

We understand that each study has its particular focus and cannot answer all questions. However, apart from aforementioned interesting and novel findings, the study has also weaknesses. It is well known that stroke is tightly correlated with atrial fibrillation, particularly in CKD patients. The low incidence of atrial fibrillation in the present study (56 patients = 0.4% of the cohort) is surprising and might be confounded by a lack of systematic screening for atrial fibrillation in the study design. One may argue that study patients were rather young, with average ages between 50 and 60 years, but associated comorbidities such as diabetes, hypertension, and especially CKD were as frequent as in other studies with higher rates of atrial fibrillation. Overall, it is unexpected and not plausible that atrial fibrillation could here not be identified as a risk factor for the occurrence of ischemic strokes in men and women. Lack of data assessment continues in anticoagulation regimens with oral anticoagulation or antiplatelet drugs that were not recorded, but may have influenced total stroke rate, and particularly influenced hemorrhagic strokes.

In summary, this work shows that CKD is an independent risk factor for higher stroke rates in men and women. Although moderate alcohol consumption is widely accepted to have protective effects against cardiocerebrovascular events, it appears in this Japanese cohort to be harmful in patients with CKD because it caused many more brain hemorrhages. This finding is clearly important, impacts current recommendations and guidelines of stroke care, and definitely requires more investigations. A direct and reasonable conclusion might be a strict alcohol prohibition in Asian patients with an eGFR < 60 mL/min.

Disclosures
None.

References
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