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Review article ■

Renal Dysfunction and Ischemic Stroke

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SUMMARY

Chronic kidney disease (CKD) is an important worldwide public health problem and stroke represents a continuously evolving medical and social problem. Renal dysfunction carries a substantial risk for cardiovascular morbidity and mortality, the risk increases with a decline in kidney function. In the last 15 years the link between CKD and cerebrovascular disease has become more apparent. Nowadays, in dialysis patients suffering from stroke, ischemic subtype is present in approximately 70%. In high risk patients with different stages of CKD, renal dysfunction is clearly associated with subsequent ischemic stroke. In population-based studies, conflicting results have been reported. Furthermore, in patients with ischemic stroke renal dysfunction is associated with short- and long-term mortality.

Authors present different studies published in this field and also add some of their own results.

Key words: **cerebrovascular disease, chronic kidney disease, end-stage renal failure, mortality, renal dysfunction**

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INTRODUCTION

Chronic kidney disease (CKD) is a worldwide health problem; up to 15% of the adult population in industrialized countries has CKD (1,2). Renal dysfunction carries a substantial risk for cardiovascular morbidity and mortality, and the risk increases with a decline in kidney function (3-5). The association between uremia and an increased risk of cardiovascular disease was first documented in 1974 by Lindner et al. (6). The prevalence of coronary artery disease in patients with end stage renal disease is approximately 40% and cardiovascular mortality is 10 to 20 times higher than in the general population (7, 8). The high prevalence of cardiovascular disease in patients starting dialysis treatment suggests that cardiovascular disease begins in earlier stages of CKD (9). Later, an independent, graded association was observed between renal dysfunction estimated with glomerular filtration rate (GFR) and the risk of death, cardiovascular events, and hospitalization in a large, community-based population (5).

Patients with CKD have high prevalence of atherosclerosis (10) and despite atherosclerosis being a systemic disease attention has centered mainly on cardiac aspects and/or manifestations. Less is known about the association of renal dysfunction and stroke. Stroke represents a continuously evolving medical and social problem, being the third leading cause of death in developed countries (11). In this paper, some important studies in this field will be presented.

Chronic kidney disease and ischemic stroke

In 1998, the National Kidney Foundation convened a Task Force on Cardiovascular Disease in Chronic Renal Disease and members were unable to draw any conclusions about cerebrovascular disease because the literature was scant (12). In the next 15 years, the link between CKD and cerebrovascular disease become more apparent, especially in dialysis patients. From the decade of 1990s, higher incidence of hemorrhagic stroke was reported compared to ischemic stroke (13). In the study by Iseki et al. the relative risk compared to general population was 5.2 in stroke, 2.0 in cerebral infarction and 10.7 in cerebral hemorrhage (13). Another study from Japan by Kawamura et al. also confirmed higher incidence of cerebral hemorrhage (14). Seliger et al. in the study published in 2003 confirmed high age-gender-adjusted relative risk of stroke among dialysis patients compared to the general population in the United States (15). In this study, also an increased risk of ischemic stroke was found (15). In the study by Toyoda et al. Japanese dialysis patients with acute stroke in 22-year period were included (16). In the first 17 years cerebral hemorrhage was more frequent, but in the last 5 years ischemic stroke replaced hemorrhage as the leading cause of stroke (16). In the DOPPS (the Dialysis Outcomes and Practice Patterns Study) study the prevalence of cerebrovascular disease was similar in Japanese and European dialysis patients and was higher in US dialysis patients (17). Similar prevalence of cerebrovascular disease in US dialysis patients was found also in HEMO (Hemodialysis) study (18). Ischemic cerebrovascular accident was the cause of death in 69% of patients in HEMO study (18). In the study by Sozio et al., published in 2009, ischemic stroke was the most common in dialysis patients; ischemic stroke was confirmed in 76 % of all 200 events registered in the study (19). Recently, a high prevalence of ischemic stroke in patients with end stage renal disease at the start of dialysis as well as a high incidence of ischemic stroke in the course of dialysis treatment has been reported (20). These changes in the distribution of cerebrovascular events in dialysis patients (higher prevalence of ischemic stroke) are probably due to the fact that patients currently accessing dialysis are older and with higher comorbidity (20). Recently published data from ERA-EDTA registry showed increased age- and sex- standardized mortality rates for stroke compared with general population (21).

Association between CKD and stroke is less conclusive; most studies suggest an independent association between the presence of CKD and cardiovascular disease. In most studies, authors had included stroke as part of an aggregate cardiovascular event. In community-based population graded association between renal function and cardiovascular events was found, a cardiovascular event was defined as hospitalization for coronary disease, heart failure, stroke, or peripheral arterial disease (5). Over 1 million adults were included in this investigation (5). Secondary evaluation of four-community based studies (Atherosclerosis Risk in Communities Study, the Cardiovascular Health Study, the Framingham Heart Study and the Framingham Offspring Study) showed that CKD was an independent risk factor for the primary composite study outcome (22). The primary study outcome was a composite of myocardial infarction, fatal coronary heart disease, all-cause mortality, and fatal and non-fatal stroke (22). In a separate analysis, no increased risk of stroke was found in patients with CKD as compared with the patients without CKD (22). In NOMAS (Northern Manhattan) study, a prospective population-based study designed to document the incidence of stroke, estimated glomerular filtration rate (Cockrof-Gault formula) was associated with significant 43% increased stroke risk in the overall cohort, also in multivariate analysis (23). Interestingly, in a separate analysis, renal dysfunction was a significant predictor of incident stroke in blacks and not in whites and Hispanics (23). In general Japanese population, Nakayama et al. found an association between increase in relative hazard for the first symptomatic stroke and decreasing renal function (24). The risk of stroke increased progressively with declining glomerular filtration rate also in

study using data from 10 community-based Japan studies (25).

In studies including high risk patients, defined by the presence of either cardiovascular disease or cardiovascular risk factors, renal dysfunction was an independent risk factor for outcomes. In the study by Shlipak et al. in postmenopausal women with coronary heart disease, even mild and moderate renal insufficiency was associated with cerebrovascular disease (including both stroke and transient ischemic attack) (26). In the secondary analysis from VALLIANT (Valsartan in Acute Myocardial infarction Trial) study the risk of death for stroke increased with declining estimated glomerular filtration rate (MDRD formula) (27). Recently, meta-analysis has been carried out to determine whether a link exists between reduced glomerular filtration rate and incident stroke (28). Most previously mentioned studies and some other were added in this meta-analysis. Incident stroke risk increased among participants with an estimated glomerular filtration rate <60 ml/min/1.73m^2 and not among those with glomerular filtration rate of 60-90 ml/min/1.73m^2 (28). Increased risk was found for subsequent ischemic and hemorrhagic stroke in participants with glomerular filtration rate <60 ml/min/1.73m^2 (28) (Table 1).

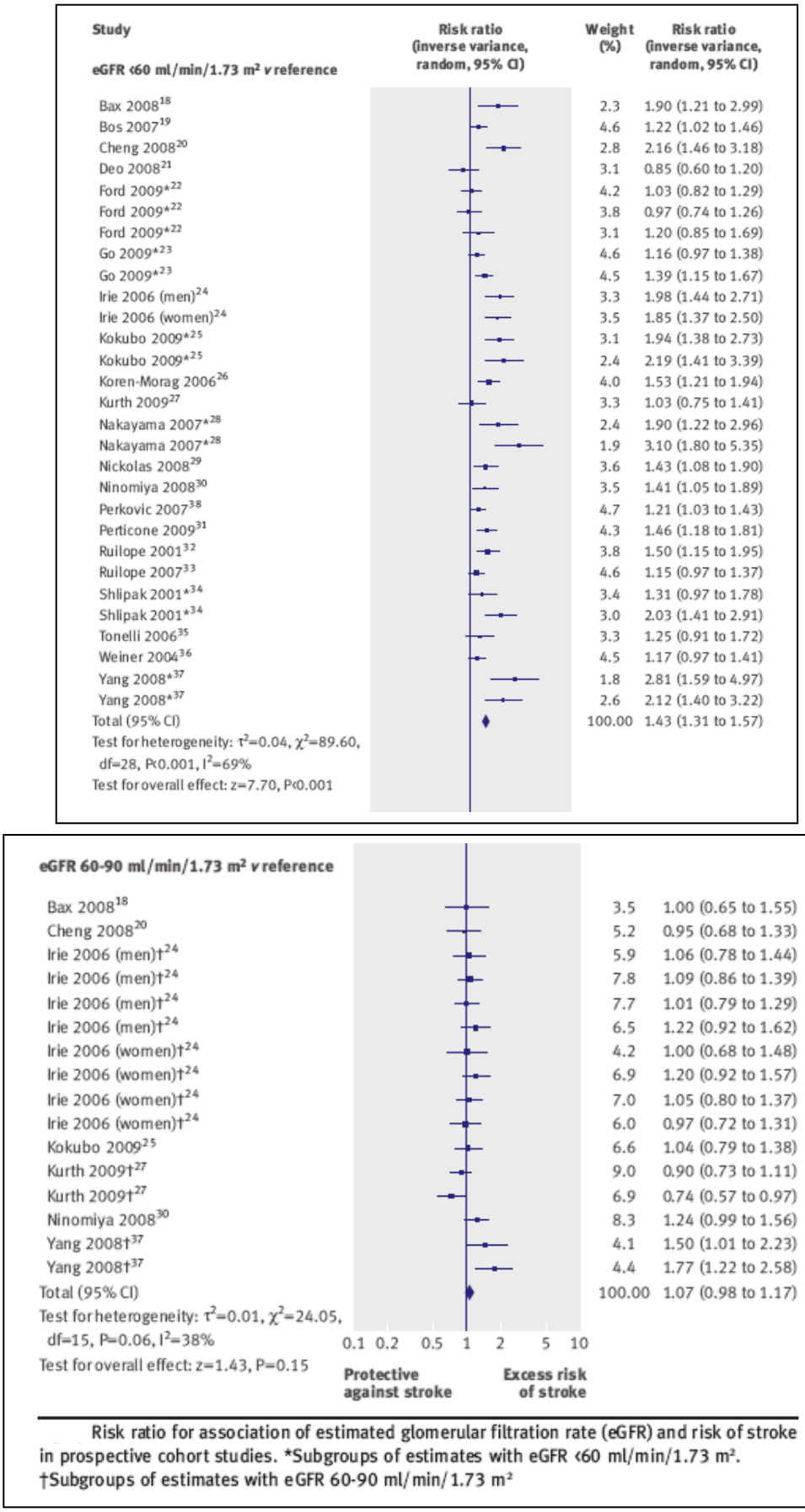
For transplant patients, single-center studies had small sample sizes and consequently few observed events, so it is not surprising that only a limited number of studies about stroke in kidney transplant patients are available. In a Spanish study, the prevalence of stroke was 7.97% at ten years and cerebral hemorrhage appears to be more prevalent than in general population (29). In the study by Lentine et al. (30), data from the United States Renal Data System registry were used; in the analysis 29.614 Medicare-insured kidney transplant recipients were included. Medicare-insured kidney transplant candidates and recipients with allograft failure were also included in the analysis (30). The cumulative, three-year incidence of de novo cerebrovascular disease events after transplantation was 6.8% and was lower than adjusted three-year estimates of 11.8% on the waiting list and 11.2% after graft loss (30). Similar relationships with transplantation and graft loss were observed for each type of cerebrovascular disease event and all forms of cerebrovascular disease event diagnoses after transplantation predicted increased mortality (30).

Prevalence and impact of renal dysfunction in patients with ischemic stroke

The prevalence of renal dysfunction in patients with cerebrovascular disease and/or stroke is not known. In study of Koren-Morag et al. where patients with previous coronary heart disease were followed, a fifth of patients suffering from ischemic stroke or transitory ischemic attack (TIA) had renal dysfunction defined as GFR≤60 ml/min/1.73m^2 (31). Recently, the prevalence of renal dysfunction of approximately 30% has been reported in acute stroke patients including patients with ischemic and hemorrhagic stroke (32). CKD was present in 36% of patients with acute stoke based on MDRD formula and in only 18% if based on Mayo Clinic formula in the study by Yahalom et al. (33). In the study by Tsukamoto et al. (34), only patients with ischemic stroke and transitory ischemic attack were included and the prevalence of CKD was 38%. CKD was defined as estimated glomerular filtration rate <60 ml/min/ 1.73m^2; dialysis patients were excluded (34). In age-matched control group, CKD was present in only 22% (34).

There are only few data about the impact of renal dysfunction on mortality in patients suffering from ischemic stroke. In most studies renal dysfunction was associated with worse outcome in these patients. In the study by Hojs Fabjan et al. (35) patients with ischemic stroke and estimated GFR <90 mL/min/1.73m^2 were included. Decreased GFR was associated with higher short-term (in-hospital) mortality (35). Renal dysfunction was an independent predictor also after multivariable adjustment (35). In the study by MacWalter et al. (36), renal dysfunction was highly significant in predicting short-term and long- term mortality after stroke. Patients with ischemic and hemorrhagic stroke were included in this study; renal dysfunction remained highly significant in predicting mortality also among subgroup of patients with ischemic stroke (36). In a prospective study, Tsagalis et al. included hospitalized first-ever stroke patients, after adjusting for basic demographic, stroke risk factors and stroke severity on admission; renal dysfunction was an independent predictor of stroke mortality at 10 years (32). CKD was strong and independent predictor of mortality in patients with acute stroke also in an Israel study (33) (Figure 1). Ovbiagele obtained data from Nationwide Inpatient Sample (NIS) (37). Of over 1 million stroke hospitalizations during the study period, 6.1% had a comorbid diagnosis of CKD, and 9% of those with CKD died in hospital. The presence of CKD was independently associated with higher odds of dying during stroke hospitalization regardless of stroke type. This adverse association was driven by severe CKD and was more pronounced in relatively younger persons and women (37).

Table 1. *Metaanalysis - incident stroke risk among participants with an eGFR < 60 ml/min/1.73m^2 and among those with eGFR 60-90 ml/min/1.73m^2*



Risk ratio for association of estimated glomerular filtration rate (eGFR) and risk of stroke in prospective cohort studies. *Subgroups of estimates with eGFR <60 ml/min/1.73 m². †Subgroups of estimates with eGFR 60-90 ml/min/1.73 m²

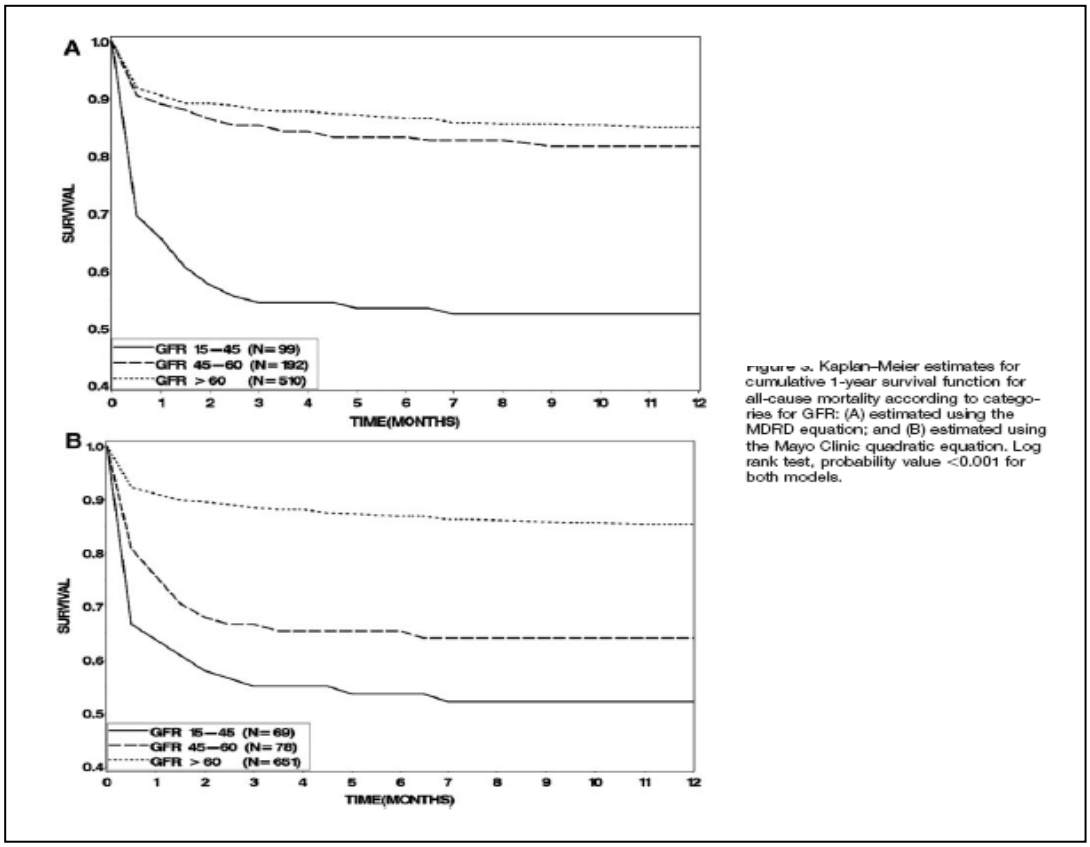


Figure 3. Kaplan–Meier estimates for cumulative 1-year survival function for all-cause mortality according to categories for GFR: (A) estimated using the MDRD equation; and (B) estimated using the Mayo Clinic quadratic equation. Log rank test, probability value <0.001 for both models.

Figure 1. *CKD is strong and independent predictor of mortality in patients with acute stroke*

CONCLUSION

In the first studies from 1990s, a higher incidence of hemorrhagic stroke in dialysis patients was reported compared to ischemic stroke. Afterwards, an increased risk of ischemic stroke was found. In the last studies, ischemic stroke was present in approximately 70% of dialysis patients with stroke. These changes are probably due to the fact that patients currently accessing dialysis are older and with higher co-morbidity. In patients with different stages of CKD before dialysis treatment, the association between CKD and stroke is less conclusive. Conflicting results from population-based studies have been reported. In studies including high risk patients, defined by the presence of either cardiovascular disease or cardiovascular risk factors, renal dysfunction was clearly associated with subsequent stroke (ischemic and hemorrhagic). In patients with ischemic stroke, renal dysfunction is associated with worse short and long-term outcomes.

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BUBREŽNA DISFUNKCIJA I ISHEMIČNI MOŽDANI UDAR

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Sažetak

Hronična bubrežna bolest je važan svetski zdravstveni problem, dok moždani udar predstavlja kontinuirano rastući medicinski i društveni problem. Bubrežna disfunkcija nosi sa sobom značajan rizik za kardiovaskularni morbiditet, a rizik se povećava sa opadanjem bubrežne funkcije. U poslednjih petnaest godina, veza između hronične bubrežne bolesti i cerebrovaskularne bolesti je sve očiglednija. Danas je kod bolesnika na dijalizi, koji su preživeli moždani udar, ishemični podtip prisutan u oko 70%. Kod visoko rizičnih bolesnika, sa različitim stupnjevima hronične bubrežne bolesti, bubrežna disfunkcija je u jasnoj vezi sa posledičnim moždanim udarom. Kod populacione analize prikazani su kontradiktorni rezultati. Štaviše, kod bolesnika sa ishemičnim moždanim udarom bubrežna disfunkcija se dovodi u vezu sa kratkoročnim i dugoročnim mortalitetom.
Autori u ovom radu prikazuju različite studije objavljene u ovoj oblasti, kao i sopstvene rezultate.

Ključne reči: **cerebrovaskularna bolest, hronična bubrežna bolest, završna faza bubrežne insuficijencije, mortalitet, bubrežna disfunkcija**