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Original research

Increased risk of recurrent stroke in patients with impaired kidney function: results of a pooled analysis of individual patient data from the MICON international collaboration

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ABSTRACT

Background Patients with chronic kidney disease are at increased risk of stroke and frequently have cerebral microbleeds. Whether such patients also encounter an increased risk of recurrent stroke has not been firmly established. We aimed to determine whether impaired kidney function is associated with the risk of recurrent stroke, and microbleed presence, distribution and severity.

Methods We used pooled data from the Microbleeds International Collaborate Network to investigate associations of impaired kidney function, defined as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2. Our primary outcome was a composite of recurrent ischaemic stroke (IS) and intracranial haemorrhage (ICrH). Secondary outcomes included: (1) individual components of the primary outcome; (2) modification of the primary outcome by microbleed presence or anticoagulant use and (3) microbleed presence, distribution and severity.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Patients with chronic kidney disease (CKD) are at increased risk of stroke.
⇒ CKD has been shown to be associated with cerebral microbleeds.
⇒ Cerebral microbleeds were found to associate with the risk of both ischaemic stroke and intracerebral haemorrhage.

Results 11 175 patients (mean age 70.7±12.6, 42% female) were included, of which 2815 (25.2%) had impaired kidney function. Compared with eGFR ≥60, eGFR <60 was associated with a higher risk of the primary outcome (adjusted HR, aHR 1.33 (95% CI 1.14 to 1.56), p<0.001) and higher rates of the recurrent IS (aHR 1.33 (95% CI 1.12 to 1.58)). Reduced eGFR was not associated with ICrH risk (aHR 1.07 (95% CI 0.70 to

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WHAT THIS STUDY ADDS

⇒ Impaired kidney function is independently associated with recurrent stroke.
⇒ Estimated glomerular filtration rate <60 was associated with presence and severity of microbleeds, mainly strictly lobar and mixed distributions.
⇒ No association was found between impaired renal function and symptomatic intracerebral haemorrhage.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Impaired kidney function may identify a high-risk group for recurrent stroke.
⇒ Optimising treatment in these patients may prevent both CKD progression and recurrent vascular events.

1.60)). eGFR was also associated with microbleed presence (adjusted OR, aOR 1.14 (95% CI 1.03 to 1.26)) and severity (aOR 1.17 (95% CI 1.06 to 1.29)). Compared with having no microbleeds, eGFR was lower in those with strictly lobar microbleeds (adjusted mean difference (aMD) −2.10 mL/min/1.73 cm^2 (95% CI −3.39 to −0.81)) and mixed microbleeds (aMD −2.42 (95% CI −3.70 to −1.15)), but not strictly deep microbleeds (aMD −0.67 (95% CI −1.85 to 0.51)).

Conclusions In patients with IS or transient ischaemic attack, impaired kidney function was associated with a higher risk of recurrent stroke and higher microbleeds burden, compared with those with normal kidney function. Further research is needed to investigate potential additional measures for secondary prevention in this high-risk group.

INTRODUCTION

Chronic kidney disease (CKD) is an established risk factor for cerebrovascular events in community populations, both ischaemic stroke (IS) and intracerebral haemorrhage (ICH).[1–3] However, there are very few studies investigating the risk of recurrent stroke according to impaired kidney function. The PROGRESS investigators and the Fukuoka Stroke Registry Investigators demonstrated a modest association between estimated glomerular filtration rate (eGFR) and increased risk of recurrent stroke.[4 5] Another observational study investigating associations of low and high eGFR with long-term stroke outcomes did not find an independent association of eGFR <60 with recurrent stroke.[6]

Cerebral microbleeds (CMB) are small (<10 mm), round or ovoid hypointense regions on paramagnetic MRI sequences, usually either T2*-weighted gradient-recalled echo (GRE) or susceptibility-weighted imaging (SWI).[4] They have been shown to be associated with the risk of both IS and ICH.[5 6] CKD has previously been shown to be associated with microbleeds, particularly deep microbleeds,[7 8] but also mixed distributions.[9] Most existing evidence did not investigate microbleed distribution and comes from lower-risk community populations.[10 11] Associations of impaired kidney function with microbleed severity and distribution have not been comprehensively investigated in stroke populations.

Using data from a large, multicentre, international individual-patient data pooled analysis, we aimed to investigate whether impaired kidney function is associated with (1) microbleed presence, distribution and severity; (2) stroke recurrence risk, including whether any increased risk found is related to ICH or recurrent IS and (3) whether microbleed presence or anticoagulant use modifies the risk of IS or intracranial haemorrhage (ICrH) according to kidney function.

METHODS

The design and inception of the Microbleeds International Collaborate Network (MICON) have been described previously.[12] Briefly, suitable prospective cohort studies of patients with IS or transient ischaemic attack (TIA), collecting data on microbleeds and recurrent stroke for at least 3 months and up to 5 years, were identified by a systematic literature search. We contacted the authors of suitable studies and invited them to contribute data to an individual patient data meta-analysis. Each study performed its neuroimaging analyses according to local study protocols. For this study, we invited the original MICON collaborators to contribute data on renal function.

Patient selection

Patients were eligible for inclusion in the study if they were part of the original MICON meta-analysis and had data available on renal function. Exclusion criteria included exclusion from the original meta-analysis; no outcome data available and no renal data available and missing data needed to estimate GFR.

Estimation of glomerular filtration rate

As recommended by the European Renal Association[13] and the European Federation of Clinical Chemistry and Laboratory Medicine),[14] we chose to use the original 2009 CKD-EPI equation to estimate GFR,[15] omitting the ethnicity coefficient. Although Kidney Disease International has recently recommended using the updated 2021 CKD-EPI equation,[16] this equation has recently been shown not to be as accurate in European populations compared with measured GFR,[17] nor predict clinical outcomes as well as the 2009 equation does.[18] A very large international consortium of studies has validated the original Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation for use in a significant majority of populations.[19]

Study outcomes

The primary outcome was the time to a composite of recurrent IS and symptomatic ICH according to eGFR group. Secondary outcomes included: (1) the individual components of the primary outcome; (2) modification of the risk of the primary outcome, recurrent IS or symptomatic ICrH by either microbleed presence or anticoagulant use; (3) microbleed presence and severity according to the eGFR group and (4) eGFR as a continuous variable according to microbleed distribution. We inverted the outcome and predictor variables for the analysis of microbleed distribution to maximise statistical power to detect a difference.

Statistical analysis

We divided the cohort into those with normal and abnormal eGFR, choosing the definition of reduced eGFR as <60 mL/min/1.73m^2, as recommended by Kidney Disease International (KDIGO).[20 21] To investigate differences according to the severity of impaired kidney function, we used the CKD severity categories also recommended by KDIGO[21]: eGFR ≥60, normal eGFR; eGFR 45–60 mild renal impairment (grade 3a); eGFR 30–45 moderate renal impairment (grade 3b) and eGFR <30 severe renal impairment (grades 4–5). We investigated the association of eGFR as a continuous variable with microbleed distribution by dividing the cohort into groups according to microbleed distributions: no microbleeds; strictly deep and infratentorial

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microbleeds; strictly lobar microbleeds and both lobar and non-lobar (mixed) microbleeds.

We compared study groups using mean (SD) or median (IQR) according to numerical variable distributions, and t-tests or Mann-Whitney U tests as appropriate. We accounted for multiple comparisons using a Bonferroni correction.

We investigated associations of microbleed presence with impaired kidney function by fitting logistic regression models, and associations of microbleed severity with impaired kidney function by fitting ordinal logistic regression models. Since the proportional odds assumption was violated, we fitted a negative binomial regression model of microbleed count against eGFR <60 as a sensitivity analysis. We investigated associations of eGFR with microbleed distribution by fitting linear regression models. Potential confounders were included in the final multivariable models based on biological plausibility and a univariable association of $p<0.1$. This prespecified list included age, sex, East Asian study centre, presentation with IS (rather than TIA), susceptibility-weighted MRI sequence (reference gradient echo), hypertension, diabetes, ischaemic heart disease, hyperlipidaemia and smoking status. We adjusted for potential clustering by including the study centre as a random effect.

To investigate recurrent stroke, we calculated absolute event rates according to eGFR group and compared them using the log-rank test. We displayed the difference between the groups using Kaplan-Meier failure graphs. We assessed the proportional hazards assumption by inspecting log-log plots and went on to fit Cox regression models using a shared frailty term to adjust for clustering, and adjusting for age, sex, East Asian study centre, presentation with IS, hypertension, diabetes, ischaemic heart disease, atrial fibrillation (AF), hyperlipidaemia and smoking status. Because of a high death rate in the eGFR <60 group, we did a competing risks analysis with time to death as the competing event. To further adjust for the underlying stroke aetiology of the qualifying event, we also adjusted for the Trial of Org 10172 classification[22] after first excluding patients from the study sites that did not collect this variable. As a sensitivity analysis, to estimate the effect of potential bias caused by missing data, we repeated this Cox regression analysis after imputing missing values using multiple imputations with chained equations (50 imputations).

We investigated whether microbleed presence, anticoagulation treatment or a combination of both modified the risk of recurrent stroke according to the eGFR group as secondary analyses, by repeating the regression analyses, including interaction terms for microbleed presence, anticoagulant use and both risk factors with eGFR <60. We also applied a Bonferroni correction for the subgroup analyses. We assessed our power to detect an interaction using the calculation of Schmoor *et al*.[23] For the primary outcome, we determined that our study has 97.8% power to detect an interaction between CKD and microbleed presence, and 98.8% power to detect an interaction between CKD and anticoagulant use. This is based on the observed event rate of 7.2% and assumes a HR of 2 for the interaction term. If we assume a lower HR of 1.5, the power drops to 64.3% and 69.4%, respectively.

RESULTS

18 of the original MICON collaborating groups contributed data to this study, providing 11 660 participants to consider for eligibility, of which 485 were excluded, leaving 11 175 subjects for analysis (70.7±12.6 years, 42% female). The reasons for exclusion included missing renal or outcome data, and missing baseline characteristics meaning calculation of eGFR was impossible. For full details, see the study selection flow chart (figure 1). Compared with those included in the study, in the excluded group, there was a slightly higher rate of female participants, higher rates of ischaemic heart disease and antiplatelet use, and a lower proportion of patients with reduced kidney function. For full details, see online supplemental table S1. The eGFR <60 group was older than the eGFR ≥60 group (mean age 77.3±9.8 vs 68.4±12.8), with a higher proportion of female participants (51.6% vs 39.1%), and higher rates of all comorbidities (for full details, see table 1).

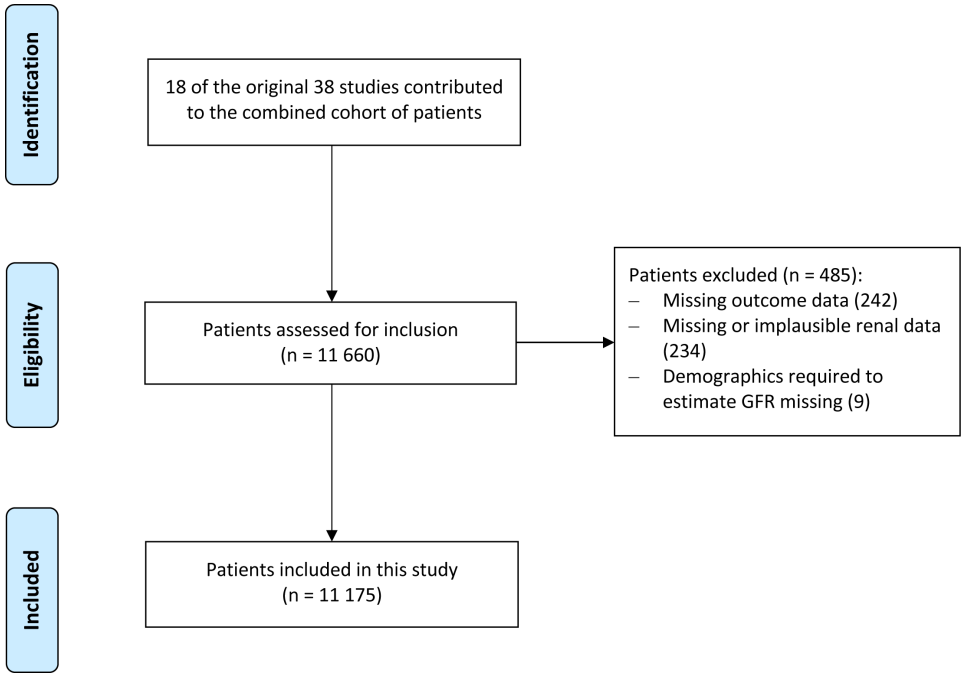


Figure 1 Study flow chart of patient selection. GFR, glomerular filtration rate.

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Table 1 Baseline characteristics of the study participants

	All (n=11 175)	eGFR ≥60 (n=8360)	eGFR <60 (n=2815)	P value*
Clinical data				
Age; years; mean (SD)	70.7 (12.6)	68.4 (12.7)	77.3 (9.7)	**<0.001**
Sex; female; n	4722 (42.3%)	3270 (39.1%)	1452 (51.6%)	**<0.001**
East Asian study centre	6673 (59.7%)	5234 (62.6%)	1439 (51.1%)	**<0.001**
Atrial fibrillation	5418 (48.8%)	3677 (44.3%)	1741 (62.1%)	**<0.001**
Hypertension	8019 (72.0%)	5674 (68.0%)	2345 (83.6%)	**<0.001**
Diabetes	2739 (25.0%)	1859 (22.7%)	880 (31.7%)	**<0.001**
Hyperlipidaemia	4156 (38.0%)	2948 (36.1%)	1208 (43.5%)	**<0.001**
Previous ischaemic stroke	1632 (14.6%)	1107 (13.3%)	525 (18.7%)	**<0.001**
Previous ICH	167 (1.5%)	111 (1.4%)	56 (2.0%)	0.235
Ischaemic heart disease	1463 (13.6%)	898 (11.2%)	565 (20.7%)	**<0.001**
Heart failure	606 (11.4%)	356 (9.5%)	250 (15.7%)	**<0.001**
Current smoker	1955 (18.6%)	1629 (20.8%)	326 (12.3%)	**<0.001**
Alcohol use	922 (19.8%)	664 (21.3%)	258 (16.9%)	**0.009**
eGFR; mean (SD)	75.0 (22.7)	85.2 (14.7)	44.7 (12.8)	
Index event				1.000
Transient ischaemic attack	1331 (11.9%)	1017 (12.2%)	314 (11.2%)	
Ischaemic stroke	9844 (88.1%)	7343 (87.8%)	2501 (88.8%)	
TOAST classification				**<0.001**
Large artery atherosclerosis	1775 (19.1%)	1434 (20.6%)	341 (14.7%)	
Cardioembolic	4355 (46.9%)	3070 (44.1%)	1285 (55.3%)	
Small vessel disease	1342 (14.4%)	1088 (15.6%)	254 (10.9%)	
Other known cause	367 (4.0%)	299 (4.3%)	68 (2.9%)	
Unknown cause	1449 (15.6%)	1075 (15.4%)	374 (16.1%)	
Neuroimaging CMB data				
Microbleeds present	3315 (29.7%)	2368 (28.3%)	947 (33.6%)	**<0.001**
Microbleed severity category				**<0.001**
0	7860 (70.3%)	5992 (71.7%)	1868 (66.4%)	
1	1422 (12.7%)	1065 (12.7%)	357 (12.7%)	
2–4	1175 (10.5%)	818 (9.8%)	357 (12.7%)	
≥5	718 (6.4%)	485 (5.8%)	233 (8.3%)	
Microbleed distribution				**<0.001**
None	7860 (70.3%)	5992 (71.7%)	1868 (66.4%)	
Strictly deep CMB	1161 (10.4%)	883 (10.6%)	278 (9.9%)	
Strictly lobar CMB	993 (8.9%)	679 (8.1%)	314 (11.2%)	
Mixed CMB	997 (8.9%)	693 (8.3%)	304 (10.8%)	
CMB distribution unknown	164 (1.5%)	113 (1.4%)	51 (1.8%)	

Note: CMB distribution unknown, not included in hypothesis tests.
Bold values denote statistical significance at the $p < 0.05$ level.
*Adjusted for multiple comparisons using a Bonferroni correction.
CMB, cerebral microbleed; eGFR, estimated glomerular filtration rate; ICH, intracranial haemorrhage; TOAST, Trial of ORG 10172 in Acute Stroke Treatment.

Primary outcome

Over a median follow-up period of 1.0 years (IQR 0.8–2.1), there were 802 primary outcome events, at a rate of 45 per 1000 patient years of follow-up. Compared with the group with normal eGFR, there was a higher rate of the composite outcome in the eGFR <60 group, with event rates of 40 and 58 per 1000 patient follow-up years in the respective groups (log-rank test p<0.001). The risk of the primary outcome according to renal function was significant after multivariable adjustments. Compared with those with eGFR ≥60, the adjusted HR (aHR) for the eGFR <60 group was 1.33 (95% CI 1.14 to 1.54, p<0.001). The full multivariable model is shown in online supplemental table S2. After excluding 5 study centres that did not collect TOAST classification (1230 participants), we included this important risk factor in the multivariable models, but this did not change the results (for the composite outcome, aHR according to eGFR <60 1.37, 95% CI 1.15 to 1.64, online supplemental table S3). The sensitivity analysis, using an imputed Cox regression model, had similar results (aHR 1.37, 95% CI 1.17 to 1.59, online supplemental table S3). In the competing risks regression analysis, accounting for the high rate of death in the eGFR <60 group (135 per 1000 person-years), there was no change in the estimates (aHR 1.32, 95% CI 1.14 to 1.51, online supplemental table S4). The increased event rate in the eGFR <60 group was consistent across all aetiologies of the index event, with the exception of TOAST classification 'other known cause' (online supplemental figure S1). As the severity of renal impairment increased, there was a graded increase in the rate of recurrent stroke, as shown in table 2. Kaplan-Meier event rate plots are shown in figure 2.

All Cox regression models adjusted for age, sex, East Asian Study Centre, atrial fibrillation, hypertension, diabetes,

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Table 2 Recurrent stroke events according to renal function

	Any stroke (ischaemic stroke or intracranial haemorrhage) during follow-up			Recurrent ischaemic stroke during follow-up			Symptomatic intracranial haemorrhage during follow-up		
	Rate per 1000 patient-years	Absolute rate increase per 1000 patient-years	Adjusted HR (95% CI)	Rate per 1000 patient-years	Absolute rate increase per 1000 patient-years	Adjusted HR (95% CI)	Rate per 1000 patient-years	Absolute rate increase per 1000 patient-years	Adjusted HR (95% CI)
Whole cohort	45 (42–48)	–	–	40 (37–43)			7 (6–9)	–	–
Normal eGFR	40 (37–44)	–	Ref.	35 (32–39)	–	Ref.	7 (6–9)	–	Ref.
eGFR<60	58 (51–65)	17 (14–21)	1.33 (1.14 to 1.56)	51 (45–58)	16 (13–19)	1.33 (1.12 to 1.58)	8 (6–11)	2 (0–3)	1.07 (0.7 to 1.60)
eGFR group									
45–59	53 (44–61)	13 (7–17)	1.27 (1.05 to 1.53)	47 (40–56)	12 (8–17)	1.30 (1.06 to 1.59)	7 (5–11)	0 (-1–3)	1.02 (0.62 to 1.66)
30–44	62 (50–78)	21 (13–34)	1.42 (1.11 to 1.82)	56 (44–70)	20 (11–31)	1.38 (1.05 to 1.81)	8 (4–15)	1 (-1–7)	1.06 (0.55 to 2.03)
<30	76 (53–104)	35 (16–60)	1.45 (1.03 to 2.04)	63 (43–90)	28 (11–51)	1.40 (0.96 to 2.02)	16 (7–32)	9 (1–24)	1.64 (0.78 to 3.42)

eGFR, estimated glomerular filtration rate.

hyperlipidaemia, ischaemic heart disease, previous stroke, presentation with IS (rather than TIA), smoking and CMB presence; shared frailty term included to adjust for potentially correlated data within centres.

Secondary outcomes

eGFR <60 was independently associated with the risk of recurrent IS, aHR 1.33 (95% CI 1.12 to 1.58) but not with symptomatic ICrH, aHR 1.07 (95% CI 0.70 to 1.60). For the primary outcome, there were no interactions of microbleed presence with eGFR <60 ($p_{interaction}$=1.000), anticoagulation use with eGFR <60 ($p_{interaction}$=0.953) or the combination of microbleed presence and anticoagulant use with eGFR <60 ($p_{interaction}$=1.000). Regarding the risk of recurrent IS, there were no interactions of microbleed presence with eGFR <60 ($p_{interaction}$=1.000), anticoagulation use with eGFR <60 ($p_{interaction}$=0.715) or the combination of microbleed presence and anticoagulant use with eGFR <60 ($p_{interaction}$=1.000). Similarly, for the risk of symptomatic ICH, there were no interactions of microbleed presence with eGFR <60 ($p_{interaction}$=1.000), anticoagulation use with eGFR <60 ($p_{interaction}$=1.000) or the combination of microbleed presence and anticoagulant use with eGFR <60 ($p_{interaction}$=1.000). The effects of these variables on renal function as a predictor of recurrent stroke events are shown in online supplemental figure S2.

Compared with eGFR ≥60, eGFR <60 was associated with microbleed presence, adjusted OR (aOR) 1.14 (95% CI 1.03 to 1.26) and microbleed severity category (0, 1, 2–4 and ≥5), aOR 1.17 per point on the ordinal scale (95% CI 1.06 to 1.29). A negative binomial regression model of microbleed count against eGFR <60 also showed an independent association, incidence rate ratio 1.20 (95% CI 1.05 to 1.37) (for full details, see table 3). Compared with having no microbleeds, the adjusted mean differences in eGFR (units mL/min/1.73 cm^2) (95% CIs) were −0.67 (−1.85 to 0.51) for strictly deep microbleeds; −2.10 (95% CI −3.39 to −0.81) for strictly lobar microbleeds and −2.42 (95% CI −3.70 to −1.15) for mixed distribution microbleeds (table 4). For complete regression models, see online supplemental tables S5−S8. As the severity of kidney impairment increased, the microbleed prevalence, microbleed severity and proportion of those with strictly lobar and mixed microbleeds increased, as shown in figure 3.

Since there were high rates of AF (62%) and antithrombotic use (39%) in the eGFR <60 group, to explore whether this might account for our findings we compared the microbleed neuroimaging phenotype in those with eGFR <60 either taking or not taking antithrombotics. There was no difference in microbleed presence, distribution or severity between the groups (online supplemental table S9).

DISCUSSION

In this large multicentre collaborative study involving patients from 13 countries on 3 continents, we found that impaired kidney function was independently associated with the risk of recurrent stroke. This patient group was 33% more likely to have a recurrent cerebrovascular event, mainly due to an increased risk of IS, with risk rising with the severity of kidney impairment. This underscores that kidney disease is an important independent risk factor for recurrent stroke.

Previous studies have linked impaired renal function and reduced eGFR to increased stroke risk, independently of conventional cardiovascular risk factors, including hypertension.[2 24 25] This effect was further modulated by Asian or West

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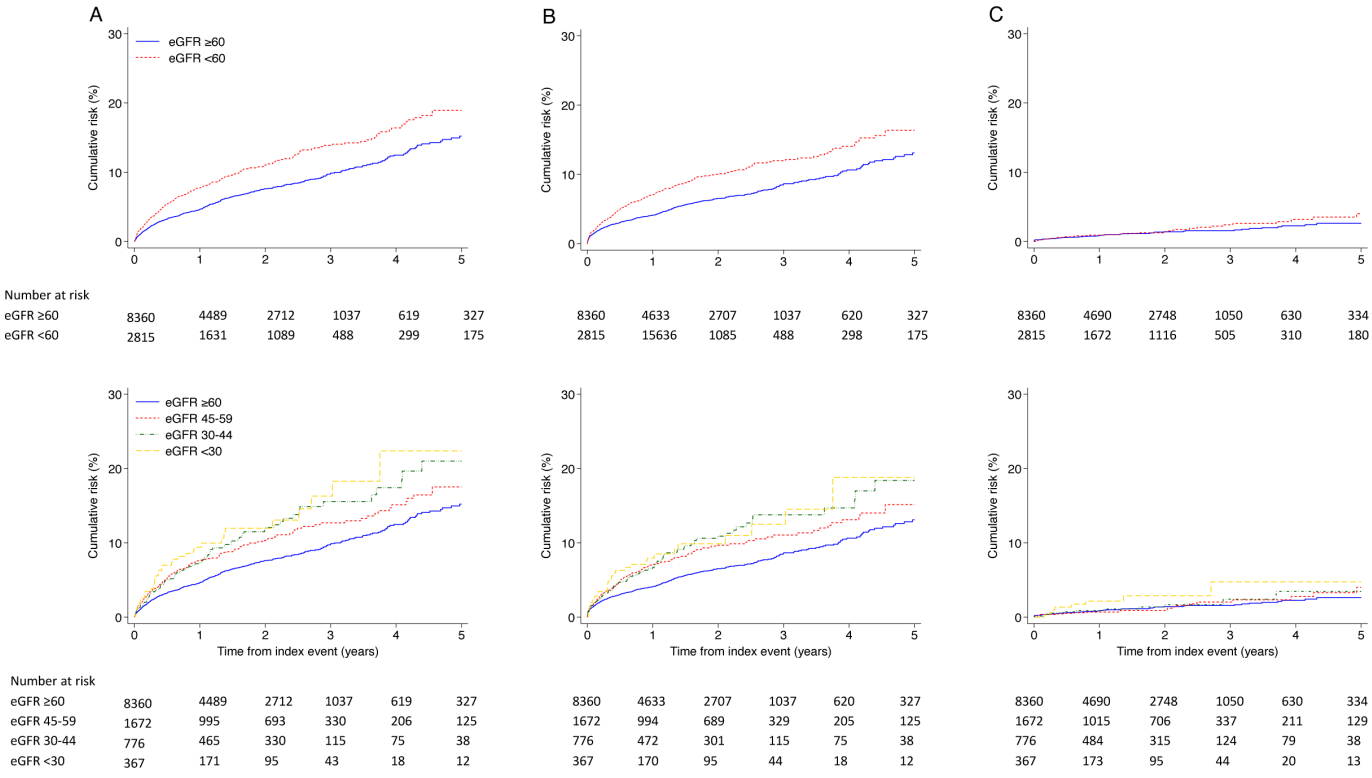


Figure 2 Kaplan-Meier event rate plots for recurrent stroke events according to renal function. (A) Any stroke during follow-up (a composite of recurrent ischaemic stroke and symptomatic intracranial haemorrhage). (B) Recurrent ischaemic stroke. (C) Symptomatic intracranial haemorrhage. eGFR, estimated glomerular filtration rate.

African ancestry.[25 26] Moreover, stroke risk rates were associated with the severity of renal impairment and were extremely high among patients receiving renal replacement therapy.[24 27] CKD was also associated with worse stroke outcomes and higher rates of poststroke cognitive impairment,[27–30] particularly in patients with lacunar stroke and cerebral small vessel disease (SVD). However, associations of renal function with recurrent stroke have scarcely been investigated. A subanalysis of the PROGRESS trial found a mildly increased risk of recurrent stroke for those with eGFR <60[4] but did not adjust for AF or stroke aetiology.

Reduced eGFR and increased albuminuria were reported to correlate with SVD imaging markers.[31 32] Both the brain and the kidneys share low-resistance vascular circuits to maintain continuous high-flow blood supply during systole and diastole, thereby making their small arteries more vulnerable to blood pressure fluctuations and microvascular injury.[27 33] Thus, the connection between CKD and SVD may stem from shared microvascular damage, with renal impairment potentially indicating cerebrovascular injury severity.[34] However, the results of other studies that reported impaired cerebral autoregulation in the setting of acute kidney injury may suggest a possible causative effect.[35 36]

Our study also found higher AF rates in patients with CKD, consistent with previous reports.[37] This may explain the higher rates of anticoagulation treatment among patients with CKD. Indeed, in our population, anticoagulation was linked to a lower risk for recurrent stroke. Unfortunately, as in previous studies, no data regarding the aetiology of recurrent IS were available in the current study, leaving it unclear whether the higher rates of IS among CKD patients derive from SVD, AF or other causes. The absence of association between AF and recurrent stroke in our study suggests other aetiologies of stroke recurrence such as SVD. A better understanding of recurrent stroke mechanisms in CKD patients could improve prevention strategies.

We found that patients with eGFR <60 had independent associations with the presence and severity of microbleeds, including strictly lobar and mixed distributions. This holds significance as both distributions were associated with an increased risk of recurrent stroke in our study and in the inception MICON study.[9] Previous research has shown renal impairment is associated with

Table 3 Regression analyses showing associations of renal function with microbleed presence, distribution and severity

Outcome	Predictor	Adjusted estimate (95% CI)	P value
Microbleed presence*	eGFR <60	1.14 (1.03 to 1.26)	**0.013**
	eGFR 45–59	1.08 (0.95 to 1.22)	**0.030**
	eGFR 30–44	1.18 (1.00 to 1.39)	
	eGFR <30	1.32 (1.05 to 1.65)	
Microbleed category†	eGFR <60	1.17 (1.06 to 1.29)	**0.002**
(0, 1, 2–4 or ≥5)	eGFR 45–59	1.11 (0.98 to 1.25)	**0.005**
	eGFR 30–44	1.19 (1.01 to 1.40)	
	eGFR <30	1.38 (1.11 to 1.71)	
Microbleed count‡	eGFR <60	1.21 (1.06 to 1.39)	**0.005**
	eGFR 45–59	1.25 (1.07 to 1.47)	**0.015**
	eGFR 30–44	1.05 (0.84 to 1.32)	
	eGFR <30	1.35 (1.00 to 1.82)	

All models adjusted for age, sex, East Asian study centre, hypertension, diabetes, hyperlipidaemia, smoking and SWI sequence use.
Bold values denote statistical significance at the p < 0.05 level.
*OR from a mixed effects logistic regression model.
†OR from a mixed effects ordinal logistic regression model (microbleed categories 0, 1, 2–4 and ≥5).
‡Incidence rate ratio from a mixed effects negative binomial regression model.
eGFR, estimated glomerular filtration rate; SWI, susceptibility-weighted imaging.

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Table 4 Kidney function according to microbleed distribution

Microbleed distribution	None (n=7860)	Strictly lobar CMB (n=993)	Strictly deep CMB (n=1161)	Mixed CMB (n=997)	CMB distribution unknown (n=164)	P value
Reduced eGFR (<60)	1868 (66.4%)	314 (11.2%)	278 (9.9%)	304 (10.8%)	51 (1.8%)	**<0.001**
eGFR group						**<0.001**
≥60	5992 (71.7%)	679 (8.1%)	883 (10.6%)	693 (8.3%)	113 (1.4%)	
45–59	1144 (68.4%)	177 (10.6%)	153 (9.2%)	172 (10.3%)	26 (1.6%)	
30–44	503 (64.8%)	88 (11.3%)	89 (11.5%)	81 (10.4%)	15 (1.9%)	
<30	221 (60.2%)	49 (13.4%)	36 (9.8%)	51 (13.9%)	10 (2.7%)	
eGFR; mean (SD)	76.1 (22.5)	70.6 (22.3)	75.9 (22.8)	70.6 (22.8)	70.2 (23.9)	**<0.001**
Adjusted mean difference in eGFR*	Ref.	−2.10 (−3.39 to −0.81)	−0.67 (−1.85 to 0.51)	−2.42 (−3.70 to −1.15)	–	**<0.001**

Note: CMB distribution unknown not included in hypothesis tests.
*Bold values denote statistical significance at the p < 0.05 level.
*Determined using a mixed effects linear regression model adjusted for age, sex, East Asian study centre, hypertension, diabetes, hyperlipidaemia, smoking and SWI sequence use.
CMB, cerebral microbleed; eGFR, estimated glomerular filtration rate; SWI, susceptibility-weighted imaging.

deep and mixed microbleeds, but not strictly lobar microbleeds, independent of hypertension.[10–13 38] Given that this association was not observed for the deep regions, hypertension cannot solely explain these findings,[10 12] and other mechanisms warrant consideration. When seen in the context of lobar ICH, transient focal neurological episodes, or cognitive decline, the presence of multiple lobar haemorrhagic lesions is predictive of the presence of cerebral amyloid angiopathy (CAA). However, lobar microbleeds can result from other arteriopathies.[39] Therefore, the presence of strictly lobar or mixed microbleeds may indicate more extensive microvascular pathologies in this population. Indeed, lobar microbleeds are linked to CAA but also with arteriolosclerosis as confirmed in neuropathological studies.[40 41] This suggests that lobar microbleed development in CKD probably does not arise from CAA. The lack of association between renal function and superficial siderosis in the current cohort also supports this, as well as a high prevalence of lobar microbleeds which was found among patients with Fabry disease.[42] Glomerular dysfunction is known to be associated with endothelial damage and thereby leads to dysfunction of the endothelial junctions in the capillaries.[42–44] A similar process may lead to the development of both deep and lobar microbleeds, as well as other SVD lesions. Another conceivable mechanism involves uraemia and induced oxidative stress resulting in biochemical and structural microvascular changes, potentially contributing to lobar microbleeds.[45] This could partially elucidate the absence of association with symptomatic ICH, as these patients typically carry a lower risk for future ICH than those with CAA. Finally, while CKD is not known to be associated with CAA, there are potential mechanisms by which persons with CKD may be at risk for accelerated brain and cerebrovascular amyloid deposition. The kidney clears beta-amyloid from the peripheral circulation, and failure of this clearance may explain why patients with CKD have elevated plasma beta-amyloid and higher brain beta-amyloid deposition.[46] More studies, ideally with neuropathological validation, are needed to fully understand the effect, potentially multifactorial, of CKD on the cerebral small vessels.

Although microbleed presence and severity were associated with eGFR <60, no association was found between impaired kidney function and symptomatic ICH during follow-up. Previous studies examining CKD influence on ICH rates have demonstrated conflicting results.[3 47] In the current study, a higher rate of ICH was demonstrated only among patients with eGFR <30, and the results were not demonstrated in a multivariable analysis. This is in line with a previous study, which found higher ICH risk only among dialysis patients.[47] Notably, most studies did not report ICH locations.[47–50] The reported microbleed distributions found in the current analysis highlight the importance of determining ICH locations among such patients. Current data are insufficient in order to establish the pathophysiology beyond the reported higher ICH risk among patients with severe renal impairment, and it is uncertain whether blood pressure alterations, use of heparin during dialysis, uraemic platelet dysfunction, endothelial damage or other mechanisms mediate

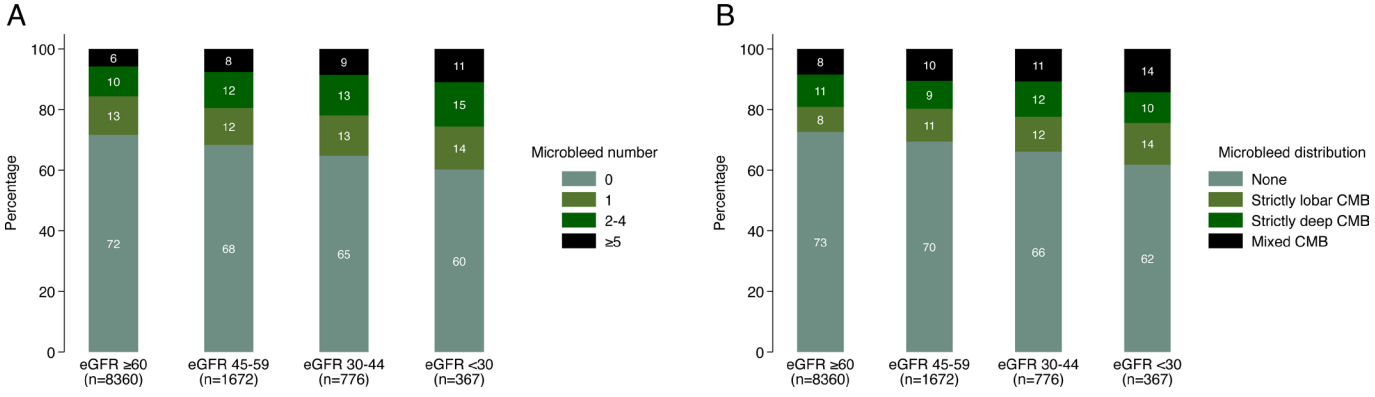


Figure 3 (A) Microbleed distribution and (B) presence and severity according to eGFR stage. CMB, cerebral microbleeds; eGFR, estimated glomerular filtration rate.

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such associations. Future trials should focus on ICH locations and potential mechanisms.

Importantly, the absolute risk of recurrent IS is higher than the absolute risk of ICH in patients with impaired kidney function receiving antithrombotic agents, regardless of accompanying microbleeds or severity of renal impairment. Our study confirms that decreased eGFR provides predictive value for overt IS recurrence in patients with renal impairment receiving antithrombotic agents for secondary stroke prevention and that microbleeds do not alter the net harm of antithrombotic therapy. We also found that anticoagulant use and microbleed presence did not modify the risk of recurrent IS or ICH for patients with eGFR <60. This has implications for clinical practice, as many clinicians have expressed safety concerns regarding anticoagulant treatment in this high-risk population,[51 52] supported by the superior safety and efficacy profile of Direct oral anti-coagulants (DOACs) compared with vitamin-K antagonists among CKD patients.[53] Nevertheless, we must interpret these findings with caution, given the observational nature of the current study, potential indication bias and the potential for incomplete adjustment for confounding variables.

The strengths of our study include its large sample size and geographical reach, increasing the generalisability of the findings, and a long follow-up period for many of the contributing centres. We are unaware of another study that reports microbleed distribution and severity, and recurrent stroke risk according to renal function with this many participants. Our study has some limitations. The observational design has the potential for selection bias. Furthermore, the requirement for MRI-suitable patients may lead to the exclusion of severe stroke patients. The assessment of microbleeds was performed using either GRE or SWI sequences. GRE is likely to underestimate the presence and number of microbleeds compared with SWI. This was addressed by adding SWI sequence use to the multivariate analyses, but a possible underestimation of microbleeds and superficial siderosis cannot be ruled out. Notably, the included patients had a single measurement of eGFR. Thus, we could not differentiate between acute and chronic renal impairment. We also did not obtain data regarding albuminuria or other renal dysfunction measures, nor anticoagulation type and dosage. We had no data regarding cardiovascular risk factor severity, and we cannot rule out that patients with impaired renal function had not only higher rates of vascular risk factors but also poor vascular risk factor control, influencing stroke risk. However, the lack of association between deep microbleeds and renal function does not support this hypothesis. Last, as mentioned, we lacked data regarding the lesion location of the recurrent IS or ICH.

In conclusion, our study reports the novel finding that impaired kidney function is independently associated with recurrent stroke. Stroke physicians and neurologists should be mindful of kidney disease after stroke, as impaired kidney function identifies a high-risk group in need of careful risk-factor management, to prevent CKD progression and optimise vascular outcomes. Further research is needed to understand the mechanisms behind this increased risk and to optimise prevention strategies.

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