Received: 17 May 2022 | Accepted: 23 May 2022

DOI: 10.1111/ene.15431

european journal of neurology
the official journal of the european academy of neurology

ORIGINAL ARTICLE

Levels and dynamics of estimated glomerular filtration rate and recurrent vascular events and death in patients with minor stroke or transient ischemic attack

Serdar Tütüncü[1] | Manuel C. Olma[1,2] | Claudia Kunze[1] | Michael Krämer[1,3] | Joanna Dietzel[1] | Johannes Schurig[1] | Paula Filser[1] | Waltraud Pfeilschifter[4] | Gerhard F. Hamann[5] | Thomas Büttner[6] | Peter U. Heuschmann[7,8] | Paulus Kirchhof[9,10,11,12] | Ulrich Laufs[13] | Darius G. Nabavi[14] | Joachim Röther[15] | Götz Thomalla[16] | Roland Veltkamp[17,18] | Kai-Uwe Eckardt[19] | Karl Georg Haeusler[20] | Matthias Endres[1,2,3,21,22,23] | MonDAFIS Investigators

[1]Center for Stroke Research Berlin, Charité–Universitätsmedizin Berlin, Berlin, Germany

[2]Department of Neurology with Experimental Neurology, Charité - Universitätsmedizin Berlin, Berlin, Germany

[3]Berlin Institute of Health, Berlin, Germany

[4]Department of Neurology, University Hospital Frankfurt, Frankfurt am Main, Germany

[5]Department of Neurology, BKH Günzburg, Günzburg, Germany

[6]Department of Neurology, Hans-Susemihl Hospital, Emden, Germany

[7]Institute of Clinical Epidemiology and Biometry, University of Würzburg, Würzburg, Germany

[8]Comprehensive Heart Failure Center and Clinical Trial Center Würzburg, University Hospital Würzburg, Würzburg, Germany

[9]German Atrial Fibrillation Network, Münster, Germany

[10]Institute of Cardiovascular Sciences, College of Medical and Dental Sciences, Medical School, University of Birmingham, Birmingham, UK

[11]Departments of Cardiology, UHB and SWBH National Health Service Trusts, Birmingham, UK

[12]University Heart and Vascular Center Hamburg, Hamburg, Germany

[13]Department of Cardiology, University Hospital of Leipzi, Leipzig, Germany

[14]Department of Neurology, Vivantes Hospital Neukölln, Berlin, Germany

[15]Department of Neurology, Asklepios Clinic Altona, Hamburg, Germany

[16]Department of Neurology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

[17]Department of Neurology, Alfried Krupp Hospital, Essen, Germany

[18]Department of Brain Sciences, Imperial College London, London, UK

[19]Department of Nephrology and Medical Intensive Care, Charité-Universitätsmedizin Berlin, Berlin, Germany

[20]Department of Neurology, University Hospital Würzburg, Würzburg, Germany

[21]German Center for Neurodegenerative Diseases, Partner Site Berlin, Berlin, Germany

[22]German Center for Cardiovascular Diseases, Partner Site Berlin, Berlin, Germany

[23]Excellence Cluster NeuroCure, Berlin, Germany

Trial registration number Clinicaltrials.gov NCT02204267.

Correspondence
Serdar Tütüncü, Center for Stroke Research Berlin, Charité–Universitätsmedizin Berlin, Charitéplatz 1, Berlin 10117, Germany.
Email: serdar.tuetuencue@charite.de

Funding information
The MonDAFIS study was an investigator-initiated, prospective, randomized, multicenter study sponsored by Charité–Universitätsmedizin Berlin, Germany and supported by an unrestricted research grant from Bayer Vital, Leverkusen, Germany to Charité–Universitätsmedizin Berlin, Germany

Abstract

Background and purpose: Impaired kidney function is associated with an increased risk of vascular events in acute stroke patients, when assessed by single measurements of estimated glomerular filtration rate (eGFR). It is unknown whether repeated measurements provide additional information for risk prediction.

Methods: The MonDAFIS (Systematic Monitoring for Detection of Atrial Fibrillation in Patients with Acute Ischemic Stroke) study randomly assigned 3465 acute ischemic stroke patients to either standard procedures or an additive Holter electrocardiogram. Baseline eGFR (CKD-EPI formula) were dichotomized into values of < versus ≥60 ml/min/1.73 m^2. eGFR dynamics were classified based on two in-hospital values as "stable normal" (≥60 ml/min/1.73 m^2), "increasing" (by at least 15% from baseline, second value ≥ 60 ml/min/1.73 m^2), "decreasing" (by at least 15% from baseline of ≥60 ml/min/1.73 m^2), and "stable decreased" (<60 ml/min/1.73 m^2). The composite endpoint (stroke, major bleeding, myocardial infarction, all-cause death) was assessed after 24 months. We estimated hazard ratios in confounder-adjusted models.

Results: Estimated glomerular filtration rate at baseline was available in 2947 and a second value in 1623 patients. After adjusting for age, stroke severity, cardiovascular risk factors, and randomization, eGFR < 60 ml/min/1.73 m^2 at baseline (hazard ratio [HR] = 2.2, 95% confidence interval [CI] = 1.40–3.54) as well as decreasing (HR = 1.79, 95% CI = 1.07–2.99) and stable decreased eGFR (HR = 1.64, 95% CI = 1.20–2.24) were independently associated with the composite endpoint. In addition, eGFR < 60 ml/min/1.73^2 at baseline (HR = 3.02, 95% CI = 1.51–6.10) and decreasing eGFR were associated with all-cause death (HR = 3.12, 95% CI = 1.63–5.98).

Conclusions: In addition to patients with low eGFR levels at baseline, also those with decreasing eGFR have increased risk for vascular events and death; hence, repeated estimates of eGFR might add relevant information to risk prediction.

KEYWORDS
kidney function, prognosis, stroke

INTRODUCTION

Patients with chronic kidney disease (CKD) are at higher risk for stroke than patients with normal kidney function, as patients with ischemic stroke and CKD share the same cardiovascular risk factors [1, 2]. Moreover, stroke patients with impaired kidney function have a higher risk of recurrent vascular events and death than patients with normal kidney function [3, 4], as atrial fibrillation [5], higher lipoprotein (a) levels [6], and symptomatic intracranial bleeding after intravenous thrombolysis for acute stroke [7] are observed more often in patients with CKD. However, the impact of reduced kidney function on recurrent vascular events goes beyond traditional risk factors [1, 8]. Nontraditional risk factors such as chronic inflammation, thrombogenic factors, and decreased klotho protein expression may contribute to a higher risk of incident and recurrent cardiovascular events in patients with CKD [8].

In stroke cohorts, kidney function has been defined primarily by single measurements of serum creatinine or estimated glomerular filtration rate (eGFR) [3, 9]. There are a limited number of studies examining the dynamics of kidney function after acute stroke. Lindner et al. examined the deterioration of kidney function by comparing serum creatinine levels at baseline and up to 1 year after stroke as a post hoc analysis of the ROCKET AF trial. The authors found a higher risk of cardiovascular death in stroke patients with a 20% decrease in serum creatinine, suggesting that an acute, reversible decline of eGFR is associated with poor prognosis [10]. A systematic review and meta-analysis showed an impact of acute kidney injury (AKI) on mortality in stroke patients [11].

Because kidney function may vary in the acute phase of stroke, we analyzed whether repeated measurements of serum creatinine levels or eGFR during the in-hospital stay of patients with acute ischemic stroke or transient ischemic attack (TIA) provide relevant additional information to risk prediction for recurrent vascular events or death.

METHODS

Study cohort

The Systematic Monitoring for Detection of Atrial Fibrillation in Patients with Acute Ischemic Stroke (MonDAFIS) study is an investigator-initiated, prospective, randomized, multicenter study sponsored by Charité–Universitätsmedizin Berlin, Berlin, Germany and supported by an unrestricted research grant from Bayer Vital, Leverkusen, Germany to Charité–Universitätsmedizin Berlin. The study rationale and design [12] as well as the primary and some secondary endpoints [13] were published previously. All study patients gave written informed consent. A critical event committee adjudicated all serious adverse events (including recurrent stroke, myocardial infarction, major bleeding, and all-cause death) blinded to study randomization.

Study population

Men or women ≥18 years of age were eligible for study enrollment if they had an ischemic stroke according to World Health Organization criteria [11], a TIA with new onset neurological deficit present and documented by a neurologist on hospital admission, or a TIA with documented corresponding acute ischemic lesion(s) on brain imaging. For detailed inclusion and exclusion criteria or the chosen diagnostic intervention procedure, see the previously published main analysis of the MonDAFIS trial [13]. Serum creatinine level at baseline, as well as a follow-up value, was available for a subset of the MonDAFIS complete randomized set. The eGFR was calculated using the creatinine-based CKD-EPI formula [14].

Outcomes and exposures

In line with the predefined secondary endpoint of the MonDAFIS study, we assessed the rate of recurrent stroke, myocardial infarction, major bleed, and all-cause death (composite endpoint) within 2 years after the index stroke in defined subgroups. Furthermore, all-cause death within 2 years was analyzed separately. The analyses were carried out in two parts. In the first part, the occurrence of the endpoints was analyzed using a single point estimate of GFR at baseline. Here, we used two different approaches. First, we analyzed eGFR as a dichotomized condition at baseline, considering patients with eGFR < 60 ml/min/1.73 m^2 as having impaired kidney function [2–4].

Second, patients were divided into four categories of normal or increased eGFR (≥90 ml/min/1.73 m^2), mildly reduced eGFR (60–89 ml/min/1.73 m^2), moderately reduced eGFR (30–59 ml/min/1.73 m^2), and severely reduced eGFR (<30 ml/min/1.73 m^2).

In the second part of the analyses, we examined the effects of eGFR dynamics on the occurrence of outcome values in those patients with a baseline and second eGFR during the in-hospital stay. Because the available data did not allow application of AKI criteria [11], we chose a change of at least 15% as a clinically relevant outcome value. This definition was chosen on the advice of an expert nephrologist (K.-U.E.) to exclude as much as possible a random decrease or increase in eGFR dynamics. In further explorative analyses, we also examined eGFR changes of at least 10% and 20%, respectively. Patients with a baseline and follow-up eGFR value were categorized into four groups: (i) "stable normal" (both eGFR values ≥ 60 ml/min/1.73 m^2), (ii) "increasing" (baseline eGFR value < 60 ml/min/1.73 m^2, increase of at least 15%, with a second value ≥ 60 ml/min/1.73 m^2), (iii) "decreasing" (decrease of at least 15% in patients with baseline eGFR ≥ 60 ml/min/1.73 m^2), and (iv) "stable decreased" (both eGFR values < 60 ml/min/1.73 m^2). For a further sensitivity analysis, we categorized patients with baseline and follow-up serum eGFR value as follows: (i) both eGFR values < 60 ml/min/1.73 m^2, (ii) baseline eGFR ≤ 60 ml/min and follow-up eGFR > 60 ml/min/1.73 m^2, (iii) baseline eGFR ≥ 60 ml/min and follow-up eGFR < 60 ml/min, and (iv) both eGFR values > 60 ml/min/1.73 m^2. Furthermore, we analyzed the dynamics of eGFR in-hospital using the delta value between both eGFR values (so-called "eGFR delta") as a continuous variable testing for linear association and squared eGFR delta for curvilinear association.

Statistical methods

This is an explorative analysis of the MonDAFIS study dataset using predefined outcomes. Baseline characteristics are reported as frequencies, and data are presented as percentages for categorical variables or median and limits of the interquartile range (IQR; 25th and 75th percentile) for metric variables. For the outcomes of interest, we conducted event-free survival analyses comparing cumulative hazards between patient groups. Event-free survival time as well as survival was measured in person-days until one of the events of the composite endpoint or death occurred, the study ended, or the participant was lost to follow-up. These dropouts are censored at time of last contact. We used Kaplan–Meier curves and the log-rank test to compare crude cumulative hazard distributions. Cox proportional hazard models, crude and adjusted for cardiovascular risk factors and group randomization (Adjusted Model 1) and additionally stroke subtype (ischemic stroke, TIA) and medical secondary prevention (Adjusted Model 2), were used to estimate hazard ratios (HRs) for the composite endpoint or separately for all-cause death risk within 2 years after index ischemic stroke or TIA. Cox proportional hazard assumption was checked. Data preparation was done using the software IBM SPSS Statistics 24.

RESULTS

Of 3470 patients recruited into the MonDAFIS study, 39 patients were excluded from analysis due to violation of main inclusion or exclusion criteria. The remaining cohort of 3431 patients was defined

as the "MonDAFIS complete randomized set" [13]. Figure S1 shows the derivation of the study population of this subanalysis.

Single point estimate of GFR at hospital admission and outcomes

A serum creatinine value at baseline was available in 2947 (85.9%) MonDAFIS patients. Baseline characteristics of patients with or without impaired kidney function (eGFR </≥ 60 ml/min/1.73 m^2) are shown in Table S1. Median age was 68 (IQR = 58–77) years; 39.0% were female. Median National Institutes of Health Stroke Scale (NIHSS) score in admission was 2 points [IQR=1-4]. Within 2 years after stroke, the predefined composite endpoint occurred in 439 (14.9%) patients (recurrent stroke in 198 [6.7%], myocardial infarction in 41 [1.4%], major bleeding in 48 [1.6%], and all-cause death in 152 [5.2%]). All-cause death occurred in 162 (5.5%) participants within 2 years (for explanation, 10 patients had other events of the combined endpoint before death). Decreased eGFR of <60 ml/min/1.73 m^2 was present in 625 (21.2%) of 2947 patients.

All-cause death occurred in 68 (11%) of 625 patients with decreased eGFR of <60 ml/min/1.73 m^2. We had no additional information on four of these deaths. Vascular death occurred in 46 (56.3%) of 64 deaths. In patients with normal eGFR of ≥60 ml/min/1.73 m^2 (n = 2322), all-cause death occurred in 94 (4.1%) patients. We had no additional information on six of these deaths. Vascular death occurred in 45 (51.1%) of 88 deaths.

As shown in Table 1 and Figure 1, risk for the composite endpoint or all-cause death was higher in patients with eGFR < 60 ml/min/1.73 m^2 than for patients with eGFR ≥ 60 ml/min/1.73 m^2 at baseline. The HR in the Adjusted Model 1 analysis was 1.36 (95% confidence interval [CI] = 1.09–1.67) for the composite endpoint and 1.65 (95% CI = 1.17–2.31) for all-cause death. The results of the Adjusted Model 2 analysis, also including stroke subtype (ischemic stroke, TIA) and medical secondary prevention (oral anticoagulation, antiplatelet) were similar and are shown in Table 1. For comparability and sensitivity analysis, we performed the abovementioned analyses in those who had repeated measurements of eGFR value (n = 1623). The results of these sensitivity analyses yielded similar results (Table S2).

Of 2947 patients, 855 (29.0%) had normal or increased eGFR (≥90 ml/min/1.73 m^2), 1467 (49.8%) had slightly reduced eGFR (60–89 ml/min/1.73 m^2), 558 (18.9%) had moderately reduced eGFR (30–59 ml/min/1.73 m^2), and 67 (2.3%) had severely reduced eGFR (<30 ml/min/1.73m^2). Results for this analysis are shown in Table S3.

In-hospital dynamics of eGFR and outcomes

A second serum creatinine value was available in 1623 (47.3%) MonDAFIS patients, with a median interval between baseline and follow-up measurement of 2 days [IQR=1-5]; the time period between both measurements ranged from 1 to 29 days. Baseline characteristics of patients stratified by dynamics of eGFR are shown in Table S4. Median age of patients was 69 [59–77] years; 39.7% were female. Median NIHSS score on admission was 2 (IQR = 1–4) points. Overall, 1001 (61.5%) of 1623 patients had stable normal eGFR, 231 of 1623 (14.2%) had increasing eGFR, 74 of 1623 (4.6%) had decreasing eGFR, and 317 of 1623 (19.5%) had stable decreased eGFR.

All-cause death occurred in 46 (4.6%) patients with stable normal eGFR. We had no additional information on two of these deaths. Vascular death occurred in 23 (52.3%) of 44 deaths. In patients with increasing eGFR, all-cause death occurred in 13 (5.6%) patients. We had no additional information on one of these deaths. Vascular death occurred in four (33.3%) of 12 deaths. In patients with decreasing eGFR, all-cause death occurred in 12 (16.2%) patients; five (41.7%) deaths were categorized as vascular deaths. In patients with stable

TABLE 1 Adjusted survival analyses, Cox regression, results for the composite endpoint (recurrent stroke, myocardial infarction, major bleeding, all-cause death) and all-cause death within 24 months of the MonDAFIS trial in patients with impaired kidney function at baseline (eGFR < 60 ml/min/1.73 m^2; n = 2947)

Model	eGFR, ml/min/1.73 m^2	n	Composite endpoint		All-cause death	
			HR (95% CI)	p	HR (95% CI)	p
Crude	≥60	2322	1		1	
	<60	625	1.79 (1.46–2.19)	<0.001	2.76 (2.02–3.77)	<0.001
Adjusted Model 1[a]	≥60	2322	1		1	
	<60	625	1.36 (1.09–1.67)	0.006	1.65 (1.17–2.31)	0.004
Adjusted Model 2[b]	≥60	2322	1		1	
	<60	625	1.35 (1.08–1.68)	0.007	1.62 (1.15–2.27)	0.006

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MonDAFIS, Systematic Monitoring for Detection of Atrial Fibrillation in Patients with Acute Ischemic Stroke.

[a]Adjusted for age, stroke severity on admission (National Institutes of Health Stroke Scale score), diabetes mellitus, arterial hypertension, coronary heart disease, detection of atrial fibrillation in-hospital, and randomization.

[b]Adjusted for all variables of Adjusted Model 1 and for medication at discharge (anticoagulation, antiplatelet) and stroke type (ischemic stroke, transient ischemic attack).

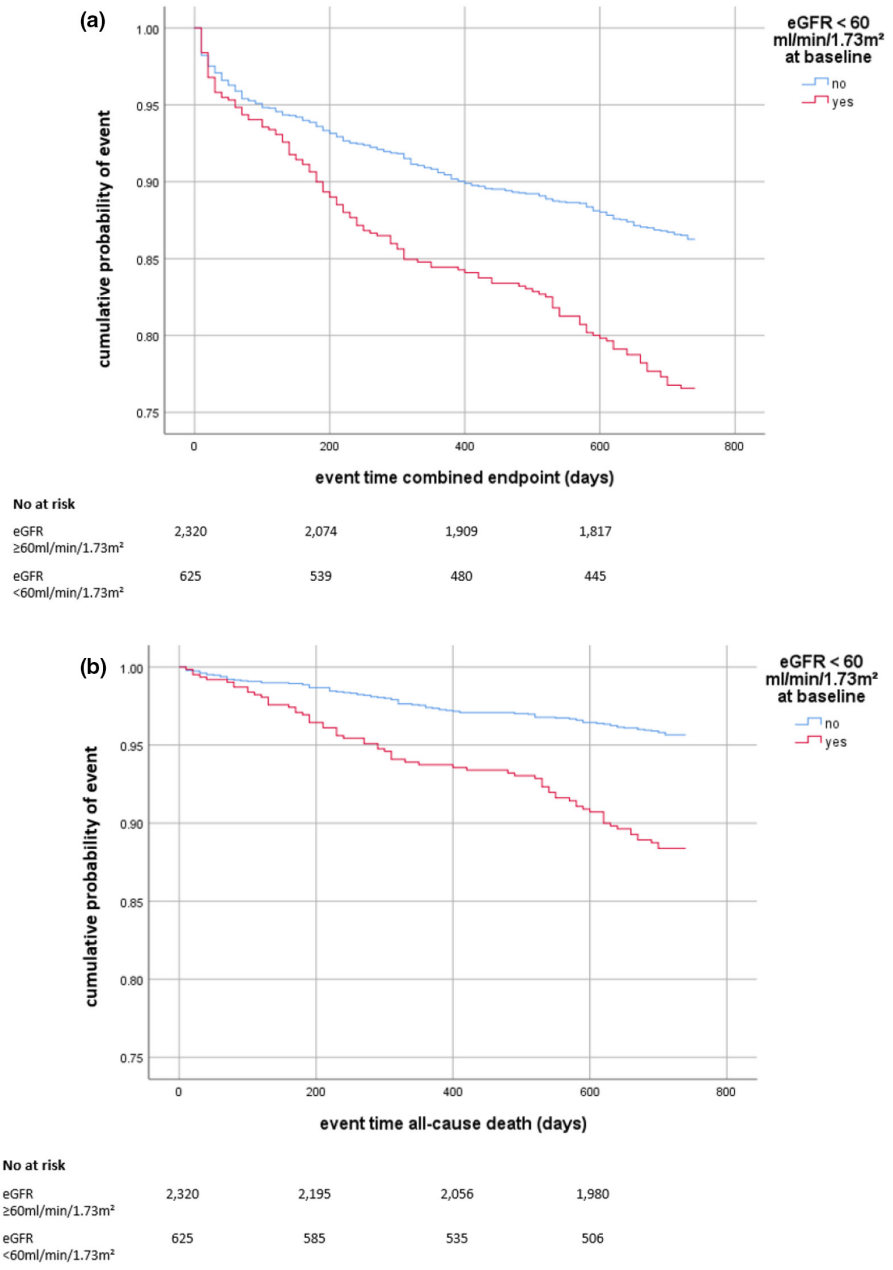

FIGURE 1 Time to event analysis of the MonDAFIS (Systematic Monitoring for Detection of Atrial Fibrillation in Patients with Acute Ischemic Stroke) study according to kidney function at baseline. Occurrence of the composite endpoint (recurrent stroke…all-cause death) (a) or all-cause death (b) within 24 months after the index stroke/transient ischemic attack is shown. eGFR, estimated glomerular filtration rate [Colour figure can be viewed at wileyonlinelibrary.com]

decreased eGFR, all-cause death occurred in 39 (12.3%) patients. We had no additional information on three of these deaths. Vascular death occurred in 22 (61.1%) of 36 deaths.

The composite endpoint occurred in 263 (16.2%) patients (recurrent stroke in 109 [6.7%], myocardial infarction in 29 [1.8%], major bleeding in 30 [1.8%], and all-cause death in 95 [5.9%]). All-cause death occurred in 110 (6.8%) participants within 2 years (for explanation, 15 patients had other events of the composite endpoint before death).

After adjusting for cardiovascular risk factors and randomization (Adjusted Model 1), the risk for the composite endpoint was higher in patients with stable decreased eGFR (HR = 1.64, 95% CI = 1.20–2.24) and in patients with decreasing eGFR (HR = 1.79, 95% CI = 1.07–2.99), if compared to patients with stable normal eGFR. Risk for all-cause death was also higher for patients with decreasing eGFR (HR = 3.12, 95% CI = 1.63–5.98), but not for those with stable decreased eGFR (HR = 1.54, 95% CI = 0.97–2.45), if compared to patients with stable normal eGFR, as shown in Figure 2 and Table 2. Adding stroke subtype (ischemic stroke, TIA) and medical secondary prevention (oral anticoagulation, antiplatelet) to the model (Adjusted Model 2) revealed similar results, as shown in Table 2. Analyses for at least 10% or 20% changes of eGFR revealed similar results (Tables S5 and S6). A further sensitivity analysis examining dynamics of eGFR, using a strict limit at 60 ml/min/1.73^2 (<60 vs. ≥60) at baseline and follow-up measurement to assess whether kidney function is normal, decreased, increasing, or decreasing, showed that patients with baseline eGFR ≥ 60 ml/min/1.73 m^2 and follow-up eGFR < 60 ml/min/1.73 m^2 (n = 49/1623, 3.0%) had higher risk for the composite endpoint and all-cause death (Table S7). In addition, eGFR delta (as a continuous variable) was significantly linearly associated

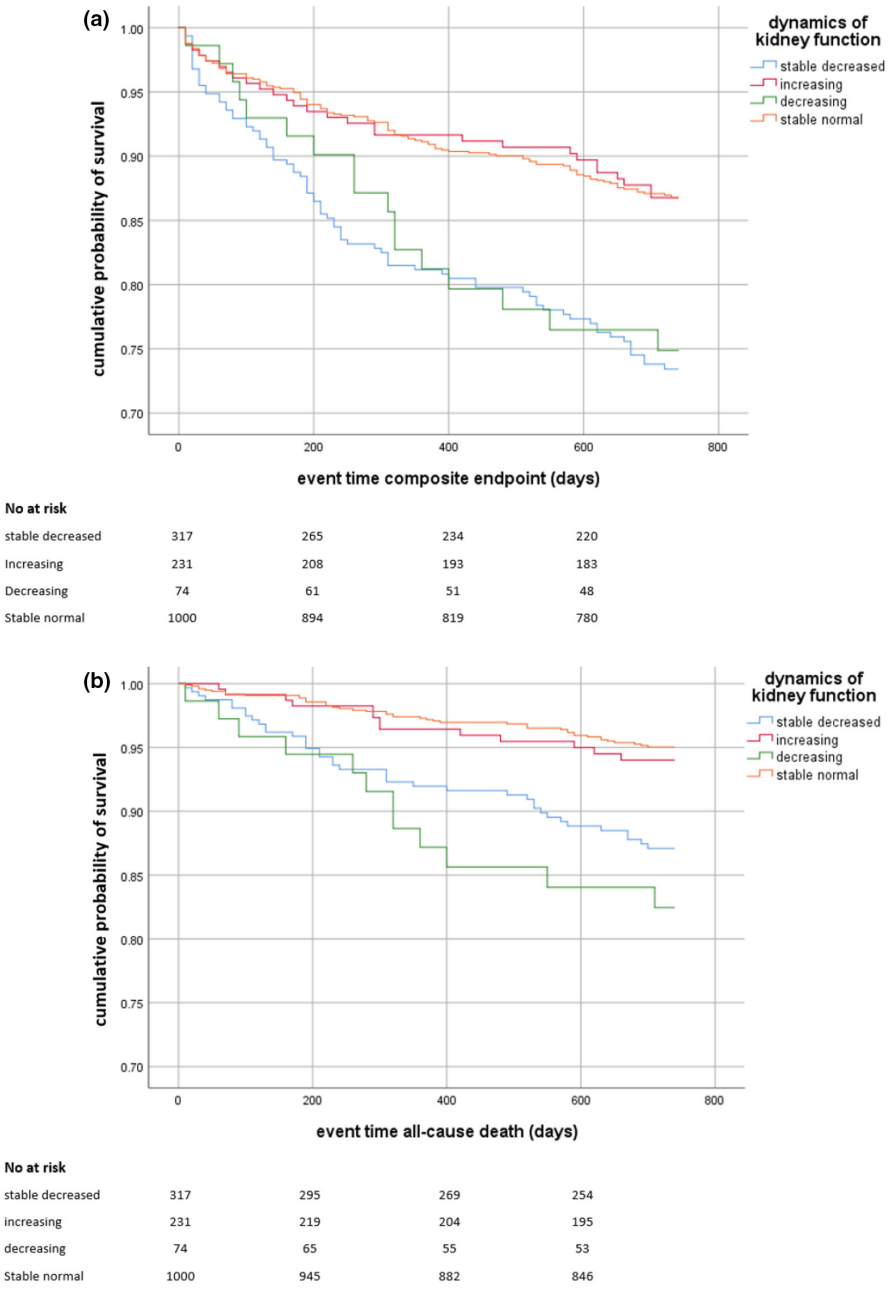

FIGURE 2 Time to event analysis of the MonDAFIS (Systematic Monitoring for Detection of Atrial Fibrillation in Patients with Acute Ischemic Stroke) study according to dynamics of kidney function (of at least 15%) during the in-hospital stay. Occurrence of the composite endpoint (recurrent stroke…all-cause death) (a) or all-cause death (b) within 24 months is shown [Colour figure can be viewed at wileyonlinelibrary.com]

with the composite endpoint (HR per 1 ml/min/1.73^2 change = 0.98, 95% CI = 0.97–0.99) and all-cause death (HR per 1 ml/min/1.73^2 change = 0.98, 95% CI = 0.96–0.99).

According to multivariate logistic regression, increasing eGFR was independently associated with age (odds ratio [OR] per year = 1.05, 95% CI = 1.03–1.07) and eGFR on admission (OR per point = 0.85, 95% CI = 0.83–0.87) if compared to those with stable normal eGFR (Table S8).

DISCUSSION

This retrospective analysis of a prospective study confirms that impaired kidney function in acute stroke patients is associated with higher rates of vascular events and mortality [1, 2, 4, 8]. Patients with reduced kidney function (eGFR < 60 ml/min/1.73 m^2) at baseline had a higher rate of recurrent vascular events and death within 24 months compared to those with nonreduced kidney function (eGFR ≥ 60 ml/min/1.73 m^2). Our study further identifies patients with decreasing eGFR in-hospital (ie, with a 15% decrease from initially normal levels of ≥60 ml/min/1.73 m^2) as a high-risk group for both recurrent vascular events and death. These patients would have been falsely categorized into a low-risk group based on a single eGFR measurement. Of note, the observed eGFR decrease by at least 15% was not associated with administration of contrast medium for vessel imaging or acute endovascular thrombectomy (Table S4). Also, we would like to note that there are no known negative effects of intravenous thrombolysis on kidney function. Interestingly, an increase in eGFR during hospitalization, presumably reflecting the recovery from AKI occurring before admission,

TABLE 2 Adjusted survival analyses, Cox regression, results for the composite endpoint (recurrent stroke, myocardial infarction, major bleeding, all-cause death) and all-cause death within 24 months of the MonDAFIS study according to dynamics of kidney function (of at least 15%) during in-hospital stay ($n = 1623$)

			Composite endpoint[a]			All-cause death	
Model	**eGFR**	***n*[a]**	**HR (95% CI)**	***p***	***n***	**HR (95% CI)**	***p***
Crude	Stable normal	992	1		1001	1	
	Increasing	231	1.00 (0.67–1.50)	0.990	231	1.22 (0.66–2.25)	0.535
	Decreasing	73	2.02 (1.22–3.35)	0.007	74	3.86 (2.05–7.29)	<0.001
	Stable decreased	313	2.19 (1.65–2.90)	<0.001	317	2.74 (1.79–4.21)	<0.001
Adjusted Model 1[b]	Stable normal	992	1		1001	1	
	Increasing	231	0.91 (0.60–1.36)	0.633	231	1.00 (0.54–1.86)	0.994
	Decreasing	73	1.79 (1.07–2.99)	0.027	74	3.12 (1.63–5.98)	0.001
	Stable decreased	313	1.64 (1.20–2.24)	0.002	317	1.54 (0.97–2.45)	0.068
Adjusted Model 2[c]	Stable normal	992	1		1001	1	
	Increasing	231	1.35 (1.08–1.68)	0.007	231	0.98 (0.53–1.84)	0.959
	Decreasing	73	1.78 (1.07–2.99)	0.027	74	3.15 (1.64–6.03)	0.001
	Stable decreased	313	1.63 (1.20–2.23)	0.002	317	1.51 (0.95–2.41)	0.084

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MonDAFIS, Systematic Monitoring for Detection of Atrial Fibrillation in Patients with Acute Ischemic Stroke.

[a]In 14 patients the composite endpoint occurred before the second serum creatinine or eGFR value was measured; data of these 14 patients were excluded from the analysis for the composite endpoint only.

[b]Adjusted for age, stroke severity on admission (National Institutes of Health Stroke Scale score), diabetes mellitus, arterial hypertension, coronary heart disease, detection of atrial fibrillation in-hospital, and randomization.

[c]Adjusted 2 for all variables of Adjusted Model 1 and for medication at discharge (anticoagulation, antiplatelet) and stroke type (ischemic stroke, transient ischemic attack).

was not associated with adverse outcomes but with older age and lower eGFR levels at baseline. Therefore, our study provides important new information for clinical practice, as repeated measurements of eGFR may add relevant information to risk prediction for individual patients.

There are several limitations of our study. First, the MonDAFIS study was not designed to analyze the impact of eGFR level or its dynamics on recurrent vascular events or death, and values were only available when ordered as part of the routine care of patients, which may have introduced bias. A serum creatinine value at baseline was missing in 14%, and a second measurement during the in-hospital stay was missing in 52% of all patients. In particular, the patients who had a second creatinine value might represent a more severely ill group (Tables S8 and S9), and this may have led to a significant selection bias. Nevertheless, we observed associations between eGFR change and outcomes among those who had more than one measurement. Second, limited data availability did not allow application of diagnostic criteria for AKI. Third, estimating eGFR from serum creatinine requires steady state conditions, which were presumably not established in many patients. We therefore categorized patients rather than basing our analysis on individual numerical estimates and conducted a number of sensitivity analyses, which confirmed the conclusions. Fourth, urine albumin measurements were not available, and we refrained from applying diagnostic criteria for CKD and CKD staging, although the thresholds for eGFR categories were applied that are consistent with CKD stages. Fifth, the adjustments in the statistical analyses may be incomplete, because potentially relevant postrandomization variables were not measured. The strength of the study includes the large sample size, the adjudication of all endpoints, and the possibility of adjusting for a large number of clinical parameters according to the prospective study design.

In conclusion, repeated measurement of serum creatinine levels or eGFR during the in-hospital stay of acute stroke or TIA patients might add relevant information to the risk prediction of recurrent vascular events or death in patients with baseline eGFR of ≥60 ml/min/1.73 m^2. Our results need to be confirmed in further studies.

AUTHOR CONTRIBUTIONS

Serdar Tütüncü: Conceptualization (lead); formal analysis (lead); investigation (lead); methodology (lead); visualization (lead); writing – original draft (lead); writing – review and editing (lead). **Manuel Olma:** Formal analysis (supporting); methodology (supporting); writing – original draft (supporting); writing – review and editing (supporting). **Claudia Kunze:** Data curation (equal); funding acquisition (equal); project administration (lead); writing – original draft (supporting); writing – review and editing (supporting). **Michael Jens Krämer:** Data curation (equal); software (lead); writing – original draft (supporting); writing – review and editing (supporting). **Joanna Dietzel:** Data curation (equal); writing – original draft (supporting); writing – review and editing (supporting). **Johannes Schurig:** Data curation (equal); writing – original draft (supporting); writing – review and editing (supporting). **Paula Filser:** Validation (lead); writing – original draft

(supporting); writing – review and editing (supporting). **Waltraud Pfeilschifter:** Writing – original draft (supporting); writing – review and editing (supporting). **Gerhard F. Hamann:** Writing – original draft (supporting); writing – review and editing (supporting). **Thomas Büttner:** Writing – original draft (supporting); writing – review and editing (supporting). **Peter U. Heuschmann:** Conceptualization (supporting); writing – original draft (supporting); writing – review and editing (supporting). **Paulus Kirchhof:** Conceptualization (supporting); writing – original draft (supporting); writing – review and editing (supporting). **Ulrich Laufs:** Conceptualization (supporting); writing – original draft (supporting); writing – review and editing (supporting). **Darius G Nabavi:** Conceptualization (supporting); writing – original draft (supporting); writing – review and editing (supporting). **Joachim Röther:** Conceptualization (supporting); writing – original draft (supporting); writing – review and editing (supporting). **Götz Thomalla:** Conceptualization (supporting); writing – original draft (supporting); writing – review and editing (supporting). **Roland Veltkamp:** Conceptualization (supporting); writing – original draft (supporting); writing – review and editing (supporting). **Kai-Uwe Eckardt:** Methodology (equal); writing – original draft (equal); writing – review and editing (equal). **Karl Georg Haeusler:** "conceptualization", "funding acquisitation". Writing – original draft (equal); writing – review and editing (equal). **Matthias Endres:** methodology, Conceptualization (lead); funding acquisition (lead); supervision (lead); writing – original draft (equal); writing – review and editing (equal).

ACKNOWLDGEMENT

Open Access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST

P.K. is listed as inventor on two patents held by the University of Birmingham, Birmingham, UK (Atrial Fibrillation Therapy WO 2015140571, Markers for Atrial Fibrillation WO 2016012783). P.K. receives research support for basic, translational, and clinical research projects from the EU, British Heart Foundation, Leducq Foundation, UK Medical Research Council, and German Center for Cardiovascular Research, and from several drug and device companies active in atrial fibrillation, and has received honoraria from several such companies in the past. G.T. has received speaker's honoraria or consulting fees from Amarin, Daichi Sanyo, Acandis, Bayer Healthcare, Boehringer Ingelheim, Covidien, Bristol-Myers Squibb, Portola, Stryker, and Pfizer. D.G.N. has received speaker's honoraria and consulting fees from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Novartis, and Pfizer. J.R. has received speaker's honoraria and consulting fees from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer, and AstraZeneca. U.L. reports honoraria and reimbursements for lectures, participation in studies, scientific cooperation (with Saarland University, Saarland, Germany), consulting, travel, support of colleagues, or support of scientific meetings by Amgen, Bayer, Boehringer Ingelheim, Daiichi Sankyo, MSD, Sanofi, and Servier, outside the submitted work. R.V. reports grants and personal fees from and being a shareholder in Bayer; grants from Boehringer; grants and personal fees from Bristol-Myers Squibb and Pfizer; grants from Daiichi Sankyo, Medtronic, and Biogen; personal fees from Javelin, Abbott, and AstraZeneca; and holding shares in Novartis, outside the submitted work. R.V. is an investigator for the National Institute of Health Research Imperial Biomedical Research Centre and partially funded by the EU's Horizon 2020 research and innovation program (grant agreement 754,517 [PRESTIGE-AF]). P.U.H. reports grants from Charité–Universitätsmedizin Berlin during the conduct of the study (within MonDAFIS for biometry; member of the scientific board); research grants from the German Ministry of Research and Education, German Research Foundation, Bavarian State (Ministry for Science and the Arts; within STAAB COVID-19), EU, Berlin Chamber of Physicians, German Parkinson Society, University Hospital Würzburg, Robert Koch Institute, German Heart Foundation, Federal Joint Committee within the Innovation Fund, University Hospital Heidelberg (within RASUNOA-prime; supported by an unrestricted research grant to University Hospital Heidelberg from Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, and Daiichi Sankyo), and University of Göttingen (within FIND-AF[randomised]; supported by an unrestricted research grant to the University of Göttingen from Boehringer Ingelheim), outside the submitted work. K.G.H. reports speakers' honoraria, consulting fees, or lecture honoraria from Abbott, Alexion, AMARIN, AstraZeneca, Bayer Healthcare, Sanofi, Boehringer Ingelheim, Daiichi Sankyo, Pfizer, Bristol-Myers Squibb, Biotronik, Medtronic, Portola, Premier Research, SUN Pharma, WL Gore and Associates, and Edwards Lifesciences, as well as study support by Bayer and Getemed. M.E. reports grants from Bayer and fees paid to Charité–Universitätsmedizin Berlin from AstraZeneca, Amgen, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Covidien, Daiichi Sankyo, GlaxoSmithKline, Novartis, Pfizer, and Sanofi. None of the other authors has any conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

De-identified participant data with corresponding data dictionary of the data underlying the current manuscript will be made available on reasonable request to the corresponding author after publication of all secondary endpoints of the MonDAFIS study.

ETHICS STATEMENT

The MonDAFIS study received primary approval from the Ethics Committee of Charité–Universitätsmedizin Berlin, Germany. All 39 participating study centers provided approval from their respective ethics committees.

REFERENCES

1. Kelly DM, Ademi Z, Doehner W, et al. Chronic kidney disease and cerebrovascular disease: consensus and guidance from a KDIGO controversies conference. *Stroke*. 2021;52:e328-e346. doi:10.1161/STROKEAHA.120.029680
2. Kelly DM, Kelleher EM, Sood MM. Stroke and chronic kidney disease. *Contrib Nephrol*. 2021;199:1-11. doi:10.1159/000517698

3. Agarwal A, Cheung AK, Ma J, et al. Effect of baseline kidney function on the risk of recurrent stroke and on effects of intensive blood pressure control in patients with previous lacunar stroke: a post hoc analysis of the SPS3 trial (secondary prevention of small subcortical strokes). *J Am Heart Assoc*. 2019;8:e013098. doi:10.1161/JAHA.119.013098
4. Chang TH, Chiu PF, Tsai CC, et al. Favourable renal outcomes after intravenous thrombolytic therapy for acute ischemic stroke: clinical implication of kidney-brain axis. *Nephrology (Carlton)*. 2019;24:896-903. doi:10.1111/nep.13516
5. Bansal N, Xie D, Sha D, et al. Cardiovascular events after new-onset atrial fibrillation in adults with CKD: results from the chronic renal insufficiency cohort (CRIC) study. *J Am Soc Nephrol*. 2018;29:2859-2869. doi:10.1681/ASN.2018050514
6. Hopewell JC, Haynes R, Baigent C. The role of lipoprotein (a) in chronic kidney disease. *J Lipid Res*. 2018;59:577-585. doi:10.1194/jlr.R083626
7. Tutuncu S, Ziegler AM, Scheitz JF, et al. Severe renal impairment is associated with symptomatic intracerebral hemorrhage after thrombolysis for ischemic stroke. *Stroke*. 2013;44:3217-3219. doi:10.1161/STROKEAHA.113.002859
8. Toyoda K, Ninomiya T. Stroke and cerebrovascular diseases in patients with chronic kidney disease. *Lancet Neurol*. 2014;13:823-833. doi:10.1016/S1474-4422(14)70026-2
9. Kelly DM, Li L, Rothwell PM, et al. Etiological subtypes of transient ischemic attack and ischemic stroke in chronic kidney disease: population-based study. *Stroke*. 2020;51:2786-2794. doi:10.1161/STROKEAHA.120.030045
10. Lindner SM, Fordyce CB, Hellkamp AS, et al. Treatment consistency across levels of baseline renal function with rivaroxaban or warfarin: a ROCKET AF (rivaroxaban once-daily, Oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation) analysis. *Circulation*. 2017;135:1001-1003. doi:10.1161/CIRCULATIONAHA.116.024666
11. Arnold J, Ng KP, Sims D, et al. Incidence and impact on outcomes of acute kidney injury after a stroke: a systematic review and meta-analysis. *BMC Nephrol*. 2018;19:283. doi:10.1186/s12882-018-1085-0
12. Haeusler KG, Kirchhof P, Heuschmann PU, et al. Impact of standardized MONitoring for detection of atrial fibrillation in ischemic stroke (MonDAFIS): rationale and design of a prospective randomized multicenter study. *Am Heart J*. 2016;172:19-25. doi:10.1016/j.ahj.2015.10.010
13. Haeusler KG, Kirchhof P, Kunze C, et al. Systematic monitoring for detection of atrial fibrillation in patients with acute ischaemic stroke (MonDAFIS): a randomised, open-label, multicentre study. *Lancet Neurol*. 2021;20:426-436. doi:10.1016/S1474-4422(21)00067-3
14. AlFaleh HF, Alsuwaida AO, Ullah A, et al. Glomerular filtration rate estimated by the CKD-EPI formula is a powerful predictor of in-hospital adverse clinical outcomes after an acute coronary syndrome. *Angiology*. 2012;63:119-126. doi:10.1177/0003319711409565

ORCID

Serdar Tütüncü https://orcid.org/0000-0002-5057-7487
Waltraud Pfeilschifter https://orcid.org/0000-0001-6935-8842

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Tütüncü S, Olma MC, Kunze C, et al. Levels and dynamics of estimated glomerular filtration rate and recurrent vascular events and death in patients with minor stroke or transient ischemic attack. *Eur J Neurol*. 2022;29:2716-2724. doi: 10.1111/ene.15431