Thrombolysis in Acute Ischaemic Stroke Patients with Chronic Kidney Disease

Running Title: Thrombolysis in Stroke with CKD

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ABSTRACT

Objective: We aimed to determine whether chronic kidney disease (CKD) is associated with adverse in-hospital outcomes after acute ischaemic stroke (AIS) and whether this association is dependent on thrombolysis administration.

Methods: 885,537 records representative of 4,283,086 AIS admissions were extracted from the US National Inpatient Sample (2005-2015) and categorised into 3 mutually exclusive groups: no CKD, CKD without end-stage renal disease (ESRD) and ESRD. Outcomes (mortality, prolonged hospitalisation >4 days and disability on discharge -derived using discharge destination as a proxy) were compared between groups using multivariable logistic regressions. Separate models containing interaction terms with thrombolysis were also computed.

Results: The median age (interquartile range) of the cohort was 73 (61-83) years and 47.32% were men. Compared to the no CKD group, both CKD/no ESRD group (odds ratio (99% confidence interval) = 1.04 (1.0003-1.09), P=0.009) and the ESRD groups (2.06 (1.90-2.25), P<0.001) had significantly increased odds of in-hospital mortality. Patients with CKD/No ESRD (1.03 (1.02-1.06), P<0.001) and ESRD (1.44 (1.37-1.51), P<0.001) were at higher odds of prolonged hospitalisation. Patients with CKD/No ESRD (1.13 (1.10-1.15), P<0.001) and ESRD (1.34 (1.26-1.41), P<0.001) were also at higher odds of moderate-to-severe disability on discharge. Interaction terms between thrombolysis and the CKD/ESRD groups were not statistically significant (P>0.01) for any outcome.

Conclusions: Renal dysfunction was independently associated with worse in-hospital outcomes in the acute phase of AIS. These associations were not influenced by the use of thrombolysis as emergency treatment for AIS. CKD/ESRD should not represent sole contraindications to thrombolysis for AIS.

Keywords: Ischaemic Stroke; Chronic Kidney Disease; Thrombolysis; In-hospital Mortality;

INTRODUCTION

Chronic kidney disease (CKD) affects more than 20 million Americans, of which over 500,000 have end-stage renal disease (ESRD) [1], while an estimated 795,000 people experience a new or recurrent stroke every year in the United States, of which an estimated 140,000 are fatal [2]. Current American Heart Association/American Stroke Association (AHA/ASA) guidelines recommend that thrombolysis should be given up to 4.5 hours following acute ischaemic stroke (AIS) as first line therapy, provided there are no contraindications [3,4]. Whilst CKD is not currently listed as either an absolute or relative contraindication for thrombolysis in the AHA/ASA guidelines, Japanese Guidelines from 2012 included "significant renal disorder" as a relative contraindication for thrombolysis [5]. CKD is known to increase the risk of bleeding, raising the question whether caution should be exercised when undertaking thrombolysis in patients with CKD [6].

While CKD has been previous established as a poor prognostic factor in AIS [7], previous studies evaluating the association between CKD and thrombolysis outcomes in patients with AIS have remained equivocal. Observational study findings are conflicting, with some studies concluding that renal dysfunction should not be a contraindication to thrombolysis [6,8–10], whilst others reporting the contrary [11–14]. A systematic review including 60,486 AIS patients undergoing thrombolysis concluded that moderate-to-severe CKD was independently associated with intracranial haemorrhage and worse functional outcomes [15]. Given that the clinical trials assessing the safety of thrombolysis in AIS have provided no subgroup analyses for renal disease [16–18], it remains unknown whether the association between CKD and adverse AIS outcomes differs based on thrombolysis administration. Furthermore, given the uncertainty regarding thrombolysis use in this patient subgroup, the real-world patterns of thrombolysis use in AIS patients with renal dysfunction remain unknown.

In this study, we aimed to determine (1) whether thrombolysis use for AIS was dependent on the level of renal dysfunction, (2) whether renal dysfunction was associated with adverse in-hospital outcomes (mortality, prolonged hospitalisation and moderate-to-severe disability on discharge) in this population and (3) whether the associations between renal dysfunction and adverse in-hospital outcomes were dependent on thrombolysis administration.

METHODS

This study was conducted in accordance with the principles of the Declaration of Helsinki (1975) and later amendments. As the National Inpatient Sample is a publicly available database with no patient identifiable information, ethical approval was not necessary for this project. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Data Source and Inclusion Criteria

The National Inpatient Sample (NIS) is a large publicly available database containing >7 million annual hospital admission records. The NIS contains admission records representing a 20% stratified sample of all community hospital admissions in the United States in a given timeframe. Hospital sampling strata in the NIS are defined by geographic regions, hospital location and teaching status, hospital ownership and hospital size[19]. Each record sampled in the NIS is assigned a sampling weight which is a measure inversely related to the probability of each hospital discharge being selected into the sample[20,21]. Using the provided sampling weights and information regarding NIS strata, this dataset can be used to provide national estimates for the sampling population, representative of ~95% of the US population[27,28]. Accounting for the complex stratified sample design of the NIS in this

manner is essential in order to provide accurate and unbiased results, as each record may be representative of a different number of admissions, depending on its assigned sampling weight[19]. Furthermore, this approach ensures equal representation of all sampling strata in analyses[19]

Prior to undertaking this project, all authors completed the online HCUP Data Use Agreement Training Tool. All authors also read and signed the Data Use Agreement for Nationwide Databases. Using data files containing annual admissions between 2005-2015, International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM) disease codes 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91 and 437.1 were used to identify all those admissions with a primary diagnosis of AIS [14,22], after the exclusion of elective admissions.

Figure 1 details the patient population flowchart: 934,638 records of ischaemic stroke admissions between January 2005-September 2015 were extracted. After the exclusion of 49,101 records either due to missing data, age <18 years or elective admissions, 885,537 records were included. Elective admissions were excluded to ensure that only admissions triggered by the acute stroke were included and not follow-up admissions. The *svy* survey data commands in Stata were employed in order to account for the complex survey design[23]. Strata containing only one sampling unit were identified using the *svydescribe* command and subsequently excluded from analyses using the *subpop* option, as their inclusion precludes the computation of variance estimates[23]. After the application of sampling weights as probability weights and stratifying for NIS stratum and year of admission [24] using the *svyset* command[23] as well as the exclusion of strata with single sampling units, included records were used to provide estimates for the population from which they were sampled: 4,283,086 admissions with a primary diagnosis of AIS.

Definition of Exposure, Grouping Variables, Confounders and Outcomes

Thrombolysis was defined using the procedural ICD-9 code 99.10. The included patient population was divided into three mutually exclusive groups: no CKD, CKD/no ESRD and ESRD. CKD was identified using ICD-9-CM codes 585.1, 585.3, 585.4, 585.5, 585.6 and 585.9, while ESRD was identified using the ICD-9-CM code 585.6. Patients with code 585.9 (Chronic Kidney Disease, unspecified) who also had ICD-9-CM codes for haemodialysis (39.95) or peritoneal dialysis (54.98) and did not have an Acute Kidney Injury (AKI) (584.5, 584.6, 584.7, 584.8 and 584.9) were also assigned to the ESRD group. All other patients from the "CKD, unspecified group" (585.9) were assigned to the CKD/no ESRD group. This method of patient selection has been used previously to accurately identify those patients with CKD and ESRD [25,26]. Comorbidities were determined using the HCUP Elixhauser comorbidity software [27] or using the ICD-9-CM codes detailed in Supplementary Table 1 and represent diagnoses assigned before or during the index acute ischaemic stroke hospitalisation.

The primary outcome of interest was all-cause in-hospital mortality. Secondary outcomes were length of hospital stay (LOS) greater than or equal to the median (4 days) and moderate-to-severe disability on discharge. The NIS discharge destination was employed as a proxy for discharge disability, using an approach that has been previously validated [28]. Briefly, all patients who died in hospital (n=206,893), those who were discharged alive to an unknown destination (n=4381) and those who were discharged against medical advice (n= 30,667 patients) were excluded and the discharge disability was dichotomised based on the discharge destination of the remainder, comprising of ~94.4% of the included sample. Thus, routine discharge was equated to none-or-minimal disability, whilst a moderate-to-severe disability status was assigned to all other discharge statuses: 'home health care', 'short-term hospital' and 'other facilities including intermediate care and skilled nursing home'. This

method has previously shown that discharge to a rehabilitation facility or nursing home to have a positive predictive value of 89% for a modified Rankin scale score of 2-6 at 3 months poststroke [28].

Intracranial haemorrhage (ICH) was defined using the ICD-9 comorbidity codes 430, 431, 432.0, 432.1; and 432.9 and was employed as outcome in secondary analyses including only AIS patients undergoing thrombolysis. While the ICD-9 comorbidity codes used in NIS do not allow differentiation between comorbidity diagnoses and in-hospital complications, it is reasonable to assume that the vast majority of ICH diagnoses recorded in patients undergoing thrombolysis most likely occurred during the index admission given that previous ICH is an absolute contraindication to thrombolytic therapy[4].

Statistical Analysis

Data were analysed using Stata 15.1 SE (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC). All analyses were performed according to the Healthcare Cost and Utilisation Project (HCUP) guidelines [29], utilising the provided discharge weights as probability weights and survey data analysis techniques stratifying by NIS stratum and year of admission [24] in order to account for patient clustering within hospitals and produce US-wide estimates [30]. Given the large sample size, a 1% threshold for statistical significance (P <0.01) was used in all analyses to minimise the type I error rate.

Descriptive Statistics

The Pearson χ^2 test, the independent sample t-test and the Mann-Whitney U tests were used to compare differences between patients receiving thrombolysis and those who did not amongst each group of renal dysfunction, for categorical, normally distributed continuous and non-normally distributed continuous variables, respectively. Whether a continuous

variable was normally distributed was ascertained by visual inspection of the corresponding histogram. The yearly (2005-2015) rates of thrombolysis usage were computed for each level of renal dysfunction.

Associations between renal dysfunction and receipt of thrombolysis

Multivariable logistic regressions were performed modelling the association between the levels of renal dysfunction and the odds of receiving IVT or ET therapy, using the no CKD group as a reference category. The models were adjusted for the covariates listed below.

Associations between renal dysfunction and adverse outcomes as a function of receipt of thrombolysis

Multivariable logistic regressions were performed modelling the associations between the level of renal dysfunction (no CKD – reference; CKD/no ESRD; ESRD) and in-hospital outcomes. Separate models containing an interaction term between the level of renal dysfunction and receipt of thrombolytic therapy were constructed in order to ascertain whether the relationship between renal dysfunction and in-hospital outcomes varies depending on receipt of thrombolysis. All models were adjusted for the covariates listed below.

Association between renal dysfunction and intracranial haemorrhage in patients receiving thrombolysis

A further multivariable logistic regression model was employed to analyse the association between renal dysfunction (no CKD – reference; CKD/no ESRD; ESRD) and intracranial haemorrhage amongst AIS patients receiving thrombolysis.

Post-hoc analyses

Given the observed increases in thrombolysis use with time, a secondary *post-hoc* analysis was performed in order to explore any differences in the associations between renal dysfunction and adverse in-hospital outcomes with time. Similarly, given the marked differences in thrombolysis use by hospital location and teaching status, a *post-hoc* analysis was also performed to explore differences the associations between renal dysfunction and adverse in-hospital outcomes with hospital location and teaching status. Separate multivariable logistic regressions were therefore performed adding interaction terms between the levels of renal dysfunction and (i) a variable indicating whether an admission occurred either before 2011 or from 2011 onwards as well as (ii) the hospital location/status (urban teaching vs. urban nonteaching vs. rural).

Adjusting co-variates

All models were adjusted for age, sex, ethnicity, hospital region, location and teaching status and a wide range of comorbidities. These included the Elixhauser comorbidities (HIV/AIDS, alcohol abuse, deficiency anaemia, collagen vascular disease, chronic blood loss anaemia, congestive heart failure, chronic pulmonary disease, coagulopathy, depression, diabetes mellitus, drug abuse, hypertension, hypothyroidism, liver disease, lymphoma, fluid and electrolyte disorders, metastatic cancer, other neurological disorders, obesity, paralysis, peripheral vascular disease, psychosis, pulmonary circulation disorders, solid tumour without metastasis, peptic ulcer disease, valvular disease, weight loss) as well as additional comorbidities which were considered important confounders of the relationship between renal disease and stroke in-hospital outcomes (atrial fibrillation, previous stroke, coronary heart disease, smoking, dyslipidaemia and dementia). The

Elixhauser comorbidity index is a well-established list of important predictors of in-hospital outcomes and has been developed[31] and validated[32] on large administrative datasets, including the NIS[33]. Adjusting variables other than Elixhauser comorbidities were identified as potential confounders based on previous literature[12,22,34] and clinical judgement.

RESULTS

Descriptive Statistics

A total sample representative of 4,283,086 AIS admissions was included in the study: 47.32% were men, with a median (inter-quartile range) age of 73 (61-83) years. There were 3,755,784 (87.69%) admissions with no CKD, 452,802 (10.57%) admissions with CKD but no ESRD, and 74,499 (1.74%) admissions with ESRD. Table 1 and Supplementary Table 2 show the baseline characteristics and outcome measures of the entire cohort, stratified by receipt of thrombolysis and level of renal dysfunction. There were fewer patients receiving thrombolysis treatment with increasing severity of renal dysfunction: 5.36% for no CKD, 4.91% for CKD/no ESRD and 3.70% for ESRD. Patients receiving thrombolysis had a significantly lower proportion of female patients than those not receiving thrombolysis amongst the no CKD group (50.44% versus 53.53%, $P<0.001$), but not amongst the CKD/no ESRD (45.91% versus 46.82%, $P=0.233$) or ESRD group (52.30% versus 54.53%, $P=0.307$). A significantly higher proportion of white patients received thrombolysis across all levels of renal dysfunction: 64.93% versus 61.10%, $P<0.001$ amongst the no CKD group, 63.24% versus 59.10%, $P<0.001$ amongst the CKD/no ESRD group and 45.15% versus 39.42%, $P=0.005$ amongst the ESRD group. The proportion of patients with hypertension (78.28% for no CKD, 91.87% for CKD/no ESRD and 95.50% for ESRD), diabetes mellitus (28.02% for no CKD, 32.30% for CKD/no ESRD and 32.79% for ESRD), congestive heart failure (12.18% for no CKD, 28.21% for CKD/no ESRD and 29.61% for ESRD) and coagulopathy

(2.62% for no CKD, 4.50% for CKD/no ESRD and 6.33% for ESRD) increased with declining renal function. The percentage of patients that were current smokers (16.66% for no CKD, 10.24% for CKD/no ESRD and 7.32% for ESRD) decreased with declining renal function. The groups receiving thrombolysis had higher prevalence of atrial fibrillation than the groups not receiving thrombolysis, across all levels of renal function: 31.81% versus 22.13% for no CKD, 42.45% versus 29.49% for CKD/no ESRD and 33.89% versus 21.71% for ESRD. The groups receiving thrombolysis had a higher proportion of patients treated at urban teaching hospitals than the groups not receiving thrombolysis, across all levels of renal function: 63.98% versus 47.24% for no CKD, 63.48% versus 49.48% for CKD/no ESRD and 69.096% versus 52.56% for ESRD.

Figure 2 details the yearly trends in thrombolysis use between 2005-2015, stratified by level of renal dysfunction. Since 2005, thrombolysis use has increased from 1.96% (99% CI 1.58-2.43) to 8.54% (99% CI 8.17-8.93) in 2014 in the no CKD group. Over the same time frame, thrombolysis use has increased from 2.40% (99% CI 1.37-4.17) to 7.11% (99% CI 6.45-7.83) in the CKD/no ESRD group and from 2.94% (99% CI 1.24-6.84) to 5.34% (99% CI 3.94-7.21) in the ESRD group.

Association between renal dysfunction and odds of receiving thrombolysis

Supplementary Table 3 details the adjusted odds of receiving thrombolysis treatment stratified by level of renal dysfunction. Compared to the no CKD group, CKD/no ESRD was not significantly associated with the odds of receiving thrombolysis: OR (99% CI) = 1.01 (0.95-1.06). Nevertheless, ESRD was associated with significantly decreased odds of receiving thrombolysis: 0.81 (0.70-0.94).

Association between thrombolysis and adverse outcomes as a function of renal dysfunction

Table 2 details the adjusted odds ratios underlying the association between renal dysfunction and the outcome measures. Compared to the no CKD group, both CKD/no ESRD group (1.04 (1.0003-1.09)) and the ESRD groups (2.06 (1.90-2.25)) had significantly increased odds of in-hospital mortality. Similarly, patients with CKD/No ESRD (1.03 (1.02-1.06)) and ESRD (1.44 (1.37-1.51)) were at higher odds of prolonged hospitalisation. Finally, patients with CKD/No ESRD (1.13 (1.10-1.15)) and ESRD (1.34 (1.26-1.41)) were also at higher odds of moderate-to-severe disability on discharge. Table 3 details the separate models containing interaction terms between thrombolysis treatment and the level of renal dysfunction, which revealed that these associations were independent of receipt of thrombolysis.

Association between renal dysfunction and intracranial haemorrhage in patients receiving thrombolysis

Table 4 details the associations between renal dysfunction and ICH amongst patients receiving thrombolysis. The number of ICH events was 18,028 (8.95%) in those with no CKD, 2218 (9.97%) in those with CKD/no ESRD and 233 (8.47%) in those with ESRD. The logistic regression models revealed no statistically significant differences in this outcome between the different levels of renal dysfunction upon confounder adjustment.

***Post-hoc* analyses**

Supplementary Tables 4 and 5 detail the results of the secondary post-hoc analyses. There were no significant interactions between renal dysfunction and either (i) year of admission (before 2011 vs. 2011 onwards) or (ii) the hospital location/status and the association in terms of adverse in-hospital outcomes.

DISCUSSION

In this study including a sample representative of ~4.3 million AIS admissions between 2005-2015, we determined that while compared to the no CKD group, CKD without ESRD was not associated with decreased odds of receiving thrombolysis for AIS, ESRD was associated with 19% lower odds of receiving thrombolysis. Furthermore, our analyses also showed that CKD was associated with increased odds of in-hospital mortality, prolonged hospitalisation and moderate-to-severe disability on discharge. Patients with ESRD were at even higher odds of all adverse in-hospital outcomes than those with CKD without ESRD. Our results nevertheless show that thrombolysis was not associated with any increases in the CKD/ESRD-associated excess odds of adverse outcomes. Furthermore, we found no association between the different levels of renal dysfunction and intracranial haemorrhage in AIS patients undergoing thrombolysis.

The results of our study are consistent with previous literature highlighting the association between CKD and adverse AIS in-hospital outcomes [7]. Furthermore, our results highlight that CKD patients without ESRD exhibited relatively small increases (4-13%) in the odds of adverse outcomes, while ESRD was associated with higher increases (34-106%), consistent with the previously reported dose-response relationship between decreasing glomerular filtration rate and adverse AIS outcomes [7]. In terms of thrombolysis for AIS, previous investigations found that CKD was associated with adverse outcomes amongst AIS patients receiving thrombolysis [11–13,22,35,36], thus highlighting CKD as a potential contraindication to thrombolysis for stroke. Nevertheless, other investigations have not found an association between CKD and adverse AIS outcomes, including intracranial haemorrhage, in patients undergoing thrombolysis [6,8–10]. Including a large, representative sample of AIS patients across the United States, our study brings further clarification to these conflicting results. Our results underline for the first time that the association between CKD, ESRD and

adverse AIS outcomes does not differ based on whether thrombolytic therapy was administered, suggesting that the safety of thrombolysis treatment remains constant across levels of renal dysfunction. Furthermore, in a secondary analysis only including AIS patients undergoing thrombolysis, we found no association between renal dysfunction and intracranial haemorrhage, an important acute complication of thrombolytic therapy.

The conflicting evidence regarding thrombolysis use in CKD, accompanied by divided expert opinion [37,38], may also result in lower overall utilisation of thrombolysis in AIS patients with renal dysfunction. Our results highlight that in the United States, patients with CKD and ESRD had lower raw rates of thrombolysis than those without CKD, trend which persisted despite the constant yearly increase in thrombolysis utilisation between 2005 and 2015. Nevertheless, our multivariable analyses adjusting for a wide range of confounders including age, sex, ethnicity and a wide range of comorbidities, showed that CKD without ESRD was not independently associated with lower odds of receiving thrombolysis for AIS, while ESRD was associated with 19% lower odds of receiving thrombolysis.

Our study is powered by several strengths such as including a large sample representative of ~4.3 million AIS admissions across the United States between 2005 and 2015. Thus, the results of our study may have several implications for clinical practice. Our results suggest that whilst CKD and ESRD were associated with increased odds of in-hospital mortality, prolonged hospitalisation and increased disability on discharge, these associations were not influenced by thrombolysis use. Therefore, our study suggests that renal dysfunction should not represent a contraindication to emergency thrombolytic therapy for AIS in itself. Furthermore, these results further underline that patients with renal dysfunction, especially those with end-stage disease, are at significantly higher odds of mortality and complications in the acute phase of AIS. These results not only warrant caution in the acute management of

AIS in patients with renal dysfunction, but also highlight the importance of appropriate stroke prevention in this particularly vulnerable patient population.

These clinical implications should nevertheless be interpreted in the light of the limitations of our study. As a study of administrative data, we based the ascertainment of CKD/ESRD, comorbidities and thrombolysis on ICD-9 codes. Furthermore, we lacked data quantifying stroke severity, such as the National Institutes of Health Stroke Scale, and we were thus unable to stratify our analyses by stroke severity. We were also unable to evaluate any changes in neurological disability associated with thrombolysis in patients with renal dysfunction. However, we used the patient discharge destination (discharges to 'home health care', 'short-term hospital' and 'other facilities including intermediate care and skilled nursing home') as a proxy for moderate-to-severity disability on discharge, which has been previously validated [28]. Nevertheless, this approach may bias the results as the discharge destination in the US setting is also dependent on health insurance status and not only clinical need. Furthermore, given the administrative nature of our data source, it was not possible to establish the temporal relationship between bleeding events coded using ICD-9 codes and the incident AIS event. Nevertheless, given that previous ICH is an absolute contraindication to thrombolytic therapy, we performed a secondary analysis of ICH events post-thrombolysis assuming that the majority of AIS patients receiving thrombolysis would not have a history of ICH. The results of this analysis should therefore be interpreted in the light of this assumption and further research ascertaining ICH occurring only after the index AIS event is needed in order to further clarify the relationship between renal dysfunction and this outcome. We also lacked laboratory data quantifying renal dysfunction, such as creatinine clearance or the estimated glomerular filtration rate. Nevertheless, we employed ICD-9 codes to classify admissions into 3 mutually exclusive categories: no CKD, CKD without ESRD and ESRD, as previously described [25,26]. We were thus able to draw differentiate between

admissions with ESRD and those with less severe CKD in all our analyses. Finally, our administrative data source did not provide any information on certain contraindications to thrombolysis such as time from stroke onset to first medical contact, blood pressure on admission and laboratory data such as platelet count or coagulation studies. We were thus unable to determine whether the reduced odds of receiving thrombolysis associated with ESRD were driven by a higher prevalence of such contraindications amongst this group.

In conclusion, in this study of real-world data representative of ~95% of AIS admissions in the United States between 2005-2015, renal dysfunction was independently associated with higher in-hospital mortality, prolonged hospitalisation and moderate-to-severe disability on discharge in the acute phase of AIS. These associations were not influenced by the use of thrombolysis as emergency treatment for AIS, thus suggesting that previous findings of increases in the risk of adverse outcomes after thrombolysis in patients with CKD/ESRD were mainly driven by renal dysfunction and were comparable to those recorded amongst their counterparts not undergoing thrombolysis. In conjunction with previous findings suggesting that the higher rates of haemorrhagic complications recorded in patients with renal dysfunction after thrombolysis were driven by non-CKD related factors [9], the results of this study suggest that renal dysfunction in itself should not represent a contraindication to thrombolysis for AIS.

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CONFLICT OF INTEREST

There are no conflicts of interest.

AUTHORS' CONTRIBUTIONS

TAP, JQ and PKM conceived the study. Data were analysed by JQ and TAP under the supervision of MOM and PKM. TAP, JQ and PKM drafted the article, and all the authors contributed to writing the article. PKM is the guarantor.

REFERENCES

1. Drawz P, Rahman M. Chronic kidney disease. *Ann Intern Med* 2015;162:ITC1–ITC14.

2. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Das SR, Delling FN, Djousse L, Elkind MSV, Ferguson JF, Fornage M, Jordan LC, Khan SS, Kissela BM, Knutson KL, Kwan TW, Lackland DT, Lewis TT, Lichtman JH, Longenecker CT, Loop MS, Lutsey PL, Martin SS, Matsushita K, Moran AE, Mussolino ME, O'Flaherty M, Pandey A, Perak AM, Rosamond WD, Roth GA, Sampson UKA, Satou GM, Schroeder EB, Shah SH, Spartano NL, Stokes A, Tirschwell DL, Tsao CW, Turakhia MP, VanWagner LB, Wilkins JT, Wong SS, Virani SS. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. *Circulation* 2019;139:e56–e66.

3. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, Jauch EC, Kidwell CS, Leslie-Mazwi TM, Ovbiagele B, Scott PA, Sheth KN, Southerland AM, Summers D V, Tirschwell DL. 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke* 2018;49:e46–e110.

4. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, Jauch EC, Kidwell CS, Leslie-Mazwi TM, Ovbiagele B, Scott PA, Sheth KN, Southerland AM, Summers D V, Tirschwell DL. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke . *Stroke* 2019;50:e344–e418.

5. Minematsu K, Toyoda K, Hirano T, Kimura K, Kondo R, Mori E, Nakagawara J, Sakai N,

Shiokawa Y, Tanahashi N, Yasaka M, Katayama Y, Miyamoto S, Ogawa A, Sasaki M, Suga S, Yamaguchi T. Guidelines for the Intravenous Application of Recombinant Tissue-type Plasminogen Activator (Alteplase), the Second Edition, October 2012: A Guideline from the Japan Stroke Society. *J Stroke Cerebrovasc Dis* 2013;22:571–600.

6. Sobolewski P, Kozera G, Kaźmierski R, Michalak S, Szczuchniak W, Śledzińska-Dźwigał M, Nyka WM. Intravenous rt-PA in patients with ischaemic stroke and renal dysfunction. *Clin Neurol Neurosurg* 2013;115:1770–4.

7. Vart P, Barlas RS, Bettencourt-Silva JH, Metcalf AK, Bowles KM, Potter JF, Myint PK. Estimated glomerular filtration rate and risk of poor outcomes after stroke. *Eur J Neurol* 2019;26:1455–1463.

8. Hsieh C-Y, Lin H-J, Sung S-F, Yang Y-HK, Lai EC-C, Hsieh H-C, Chen C-H. Does renal dysfunction modify the effect of intravenous thrombolysis for acute ischemic stroke within 4.5 hours of onset? A multicenter observational study. *J Stroke Cerebrovasc Dis* 2015;24:673–9.

9. Ovbiagele B, Smith EE, Schwamm LH, Grau-Sepulveda M V, Saver JL, Bhatt DL, Hernandez AF, Peterson ED, Fonarow GC. Chronic kidney disease and bleeding complications after intravenous thrombolytic therapy for acute ischemic stroke. *Circ Cardiovasc Qual Outcomes* 2014;7:929–35.

10. Hao Z, Yang C, Liu M, Wu B. Renal dysfunction and thrombolytic therapy in patients with acute ischemic stroke: a systematic review and meta-analysis. *Medicine (Baltimore)* 2014;93:e286.

11. Carr SJ, Wang X, Olavarria V V., Lavados PM, Rodriguez JA, Kim JS, Lee TH, Lindley RI, Pontes-Neto OM, Ricci S, Sato S, Sharma VK, Woodward M, Chalmers J, Anderson CS, Robinson TG. Influence of Renal Impairment on Outcome for Thrombolysis-Treated Acute Ischemic Stroke: ENCHANTED (Enhanced Control of Hypertension and Thrombolysis

Stroke Study) Post Hoc Analysis. *Stroke* 2017;48:2605–2609.

12. Sadeghi-Hokmabadi E, Baş DF, Farhoudi M, Taheraghdam A, Savadi Oskouei D, Yazdchi M, Hashemilar M, Uzuner N, Mirnour R, Colak E, Özdemir AÖ. Renal Dysfunction Is an Independent Risk Factor for Poor Outcome in Acute Ischemic Stroke Patients Treated with Intravenous Thrombolysis: A New Cutoff Value. *Stroke Res Treat* 2017;2017:2371956.

13. Jung J-M, Kim HJ, Ahn H, Ahn IM, Do Y, Choi J-Y, Seo W-K, Oh K, Cho K-H, Yu S. Chronic kidney disease and intravenous thrombolysis in acute stroke: A systematic review and meta-analysis. *J Neurol Sci* 2015;358:345–50.

14. Alqahtani F, Berzingi CO, Aljohani S, Hajji M Al, Diab A, Alvi M, Boobes K, Alkhouli M. Temporal Trends in the Outcomes of Dialysis Patients Admitted With Acute Ischemic Stroke. *J Am Heart Assoc* 2018;7.

15. Malhotra K, Katsanos AH, Goyal N, Tayal A, Gensicke H, Mitsias PD, Marchis GM De, Berge E, Alexandrov AW, Alexandrov A V, Tsivgoulis G. Intravenous thrombolysis in patients with chronic kidney disease: A systematic review and meta-analysis. *Neurology* 2020;95:e121–e130.

16. ECASS III: Guidetti D, Larrue V, Lees KR, Medeghri Z, Machnig T, Schneider D, Kummer R Von, Wahlgren N, Toni D, Investigators E. Thrombolysis with Ateplase 3 to 4.5 Hours after Acte Ischemic Stroke (ECASS III). *N Engl J Med* 2008:1317–1329.

17. Wahlgren N, Ahmed N, Dávalos A, Ford GA, Grond M, Hacke W, Hennerici MG, Kaste M, Kuelkens S, Larrue V, Lees KR, Roine RO, Soinne L, Toni D, Vanhooren G, SITS-MOST investigators. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. *Lancet (London, England)* 2007;369:275–82.

18. Sandercock P, Wardlaw JM, Lindley RI, Dennis M, Cohen G, Murray G, Innes K, Venables G, Czlonkowska A, Kobayashi A, Ricci S, Murray V, Berge E, Slot KB, Hankey

GJ, Correia M, Peeters A, Matz K, Lyrer P, Gubitz G, Phillips SJ, Arauz A. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial. *Lancet (London, England)* 2012;379:2352–2363.

19. Houchens R, Ross D, Elixhauser A, Jiang J. *Nationwide Inpatient Sample (NIS) Redesign Final Report Report # 2014-04. HCUP Methods Series.*; 2014. Available at: http://www.hcup-us.ahrq.gov/reports/methods/methods.jsp.HCUP. Accessed June 4, 2021.

20. (HCUP) Healthcare Cost and Utilization Project. HCUP NIS Description of Data Elements. *Agency Healthc Res Qual Rockville, MD* 2008. Available at: https://hcup-us.ahrq.gov/db/vars/discwt/nisnote.jsp.

21. Bell BA, Onwuegbuzie AJ, Ferron JM, Jiao QG, Hibbard ST, Kromrey JD. Use of design effects and sample weights in complex health survey data: a review of published articles using data from 3 commonly used adolescent health surveys. *Am J Public Health* 2012;102:1399–1405.

22. Tariq N, Adil MM, Saeed F, Chaudhry SA, Qureshi AI. Outcomes of thrombolytic treatment for acute ischemic stroke in dialysis-dependent patients in the United States. *J Stroke Cerebrovasc Dis* 2013;22:e354-9.

23. StataCorp. *Stata 15 Survey Data Reference Manual*. College Station, TX; 2017. Available at: https://www.stata.com/manuals15/svy.pdf. Accessed June 4, 2021.

24. (HCUP) Healthcare Cost and Utilization Project. HCUP NIS Description of Data Elements. *Agency Healthc Res Qual Rockville, MD* 2008. Available at: www.hcup-us.ahrq.gov/db/vars/dispuniform/nisnote.jsp. Accessed April 28, 2020.

25. Gupta T, Paul N, Kolte D, Harikrishnan P, Khera S, Aronow WS, Mujib M, Palaniswamy C, Sule S, Jain D, Ahmed A, Cooper HA, Frishman WH, Bhatt DL, Fonarow GC, Panza JA. Association of chronic renal insufficiency with in-hospital outcomes after percutaneous

coronary intervention. *J Am Heart Assoc* 2015;4:e002069.

26. Kumar G, Sakhuja A, Taneja A, Majumdar T, Patel J, Whittle J, Nanchal R. Pulmonary embolism in patients with CKD and ESRD. *Clin J Am Soc Nephrol* 2012;7:1584–1590.

27. (HCUP) Healthcare Cost and Utilization Project. HCUP Elixhauser Comorbidity Software. *Agency Healthc Res Qual Rockville, MD* 2017. Available at: www.hcup-us.ahrq.gov. Accessed April 28, 2020.

28. Qureshi AI, Chaudhry SA, Sapkota BL, Rodriguez GJ, Suri MFK. Discharge destination as a surrogate for Modified Rankin Scale defined outcomes at 3- and 12-months poststroke among stroke survivors. *Arch Phys Med Rehabil* 2012;93:1408-1413.e1.

29. (HCUP) Healthcare Cost and Utilization Project. Checklist for Working with the NIS. *Agency Healthc Res Qual Rockville, MD* 2017. Available at: www.hcup-us.ahrq.gov/db/nation/nis/nischecklist.jsp. Accessed April 28, 2020.

30. Houchens R, Ross D, Elixhauser A. Final Report on Calculating National Inpatient Sample (NIS) Variances for Data Years 2012 and Later. 2015.

31. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. *Med Care* 1998;36:8–27.

32. Tang J, Wan JY, Bailey JE. Performance of comorbidity measures to predict stroke and death in a community-dwelling, hypertensive Medicaid population. *Stroke* 2008;39:1938–1944.

33. Potts J, Nagaraja V, Suwaidi J Al, Brugaletta S, Martinez SC, Alraies C, Fischman D, Kwok CS, Nolan J, Mylotte D, Mamas MA. The influence of Elixhauser comorbidity index on percutaneous coronary intervention outcomes. *Catheter Cardiovasc Interv Off J Soc Card Angiogr Interv* 2019;94:195–203.

34. Pana TA, Mohamed MO, Clark AB, Fahy E, Mamas MA, Myint PK. Revascularisation therapies improve the outcomes of ischemic stroke patients with atrial fibrillation and heart

failure. *Int J Cardiol* 2020.

35. Rao Z-Z, Gu H-Q, Wang X-W, Xie X-W, Yang X, Wang C-J, Zhao X, Xian Y, Wang Y-L, Li Z-X, Xiao R-P, Wang Y-J. Renal Dysfunction and In-Hospital Outcomes in Patients With Acute Ischemic Stroke After Intravenous Thrombolytic Therapy. *J Am Heart Assoc* 2019;8:e012052.

36. Zhu J, Shen X, Han C, Mei C, Zhou Y, Wang H, Kong Y, Jiang Y, Fang Q, Cai X. Renal Dysfunction Associated with Symptomatic Intracranial Hemorrhage after Intravenous Thrombolysis. *J stroke Cerebrovasc Dis Off J Natl Stroke Assoc* 2019;28:104363.

37. Power A, Fogarty D, Wheeler DC. Acute stroke thrombolysis in end-stage renal disease: A national survey of nephrologist opinion. *Nephron - Clin Pract* 2013;124:167–172.

38. Palacio S, Gonzales NR, Sangha NS, Birnbaum LA, Hart RG. Thrombolysis for acute stroke in hemodialysis: International survey of expert opinion. *Clin J Am Soc Nephrol* 2011;6:1089–1093.

TABLES

Table 1. Baseline characteristics and outcomes of AIS patients receiving/not receiving thrombolysis, stratified by level of renal dysfunction. Further descriptive statistics are detailed in Supplementary Table 2.

	No CKD			**CKD/No ESRD**			**ESRD**		
	No IVT	IVT	*P* value	No IVT	IVT	*P* value	No IVT	IVT	*P* value
N	3554367	201417		430548	22254		71743	2757	
Age, median (IQR) †	70.00 (58.00-81.00)	72.00 (60.00-82.00)	**<0.001**	78.00 (69.00-86.00)	77.00 (67.00-85.00)	**<0.001**	69.00 (59.00-78.00)	68.00 (58.00-77.00)	0.078
Length-of-stay, median (IQR) †	4.00 (3.00-7.00)	4.00 (2.00-6.00)	**<0.001**	5.00 (3.00-8.00)	4.00 (3.00-7.00)	**<0.001**	7.00 (4.00-11.00)	5.00 (3.00-9.00)	**<0.001**
Sex Female, N (%)‡	1902492 (53.53)	101601 (50.44)	**<0.001**	201573 (46.82)	10217 (45.91)	0.233	39124 (54.53)	1442 (52.30)	0.307
Ethnicity ‡			**<0.001**			**<0.001**			**0.005**
White	2171771 (61.10)	130770 (64.93)		254440 (59.10)	14073 (63.24)		28278 (39.42)	1245 (45.15)	
Black	476284 (13.40)	24653 (12.24)		82799 (19.23)	3566 (16.02)		21769 (30.34)	820 (29.74)	
Hispanic	228607 (6.43)	13532 (6.72)		26227 (6.09)	1224 (5.50)		8799 (12.26)	366 (13.26)	
Asian or Pacific Islander	79531 (2.24)	5070 (2.52)		11207 (2.60)	744 (3.34)		2422 (3.38)	79 (2.88)	
Native American	14565 (0.41)	602 (0.30)		1603 (0.37)	84 (0.38)		619 (0.86)	<11	
Other	77518 (2.18)	5529 (2.75)		8585 (1.99)	580 (2.60)		1468 (2.05)	55 (2.01)	
Comorbidities ‡									
Congestive heart failure	429186 (12.07)	28305 (14.05)	**<0.001**	120089 (27.89)	7639 (34.32)	**<0.001**	21127 (29.45)	933 (33.83)	0.028
Chronic Pulmonary Disease	515690 (14.51)	28983 (14.39)	0.523	78057 (18.13)	4129 (18.55)	0.472	11593 (16.16)	488 (17.69)	0.346

Diabetes Mellitus, Uncomplicated	1004763 (28.27)	47538 (23.60)	**<0.001**	139424 (32.38)	6819 (30.64)	0.015	23582 (32.87)	850 (30.85)	0.306
Diabetes Mellitus, Chronic Complications	155582 (4.38)	5451 (2.71)	**<0.001**	68198 (15.84)	2749 (12.35)	**<0.001**	22456 (31.30)	782 (28.36)	0.138
Hypertension	2785066 (78.36)	155103 (77.01)	**<0.001**	395230 (91.80)	20742 (93.21)	**<0.001**	68466 (95.43)	2678 (97.17)	0.050
Liver Disease	36920 (1.04)	1882 (0.93)	0.044	6310 (1.47)	293 (1.31)	0.414	1854 (2.58)	64 (2.33)	0.702
Metastatic Cancer	53273 (1.50)	1507 (0.75)	**<0.001**	5075 (1.18)	201 (0.90)	0.095	571 (0.80)	28 (1.02)	0.555
Peripheral Vascular Disease	289670 (8.15)	16011 (7.95)	0.166	62305 (14.47)	3164 (14.22)	0.648	12637 (17.61)	437 (15.84)	0.269
Solid Tumour (without metastasis)	60175 (1.69)	2739 (1.36)	**<0.001**	8438 (1.96)	322 (1.45)	0.017	877 (1.22)	20 (0.74)	0.310
Valvular Disease	346070 (9.74)	21152 (10.50)	**<0.001**	56180 (13.05)	3216 (14.45)	**0.007**	7969 (11.11)	307 (11.15)	0.975
Atrial Fibrillation	786723 (22.13)	64062 (31.81)	**<0.001**	126988 (29.49)	9447 (42.45)	**<0.001**	15572 (21.71)	934 (33.89)	**<0.001**
Previous stroke	316791 (8.91)	19227 (9.55)	**<0.001**	55461 (12.88)	2630 (11.82)	0.042	6722 (9.37)	253 (9.19)	0.890
Coronary Heart Disease	864809 (24.33)	51025 (25.33)	**<0.001**	163496 (37.97)	8999 (40.44)	**<0.001**	27197 (37.91)	1156 (41.94)	0.049
Smoking	589646 (16.59)	36044 (17.90)	**<0.001**	44143 (10.25)	2216 (9.96)	0.526	5237 (7.30)	219 (7.95)	0.556
Dyslipidaemia	1730383 (48.68)	104613 (51.94)	**<0.001**	236190 (54.86)	13000 (58.42)	**<0.001**	28513 (39.74)	1134 (41.16)	0.516
Outcomes, N (%)‡									
In-hospital mortality	159265 (4.48)	16160 (8.02)	**<0.001**	22843 (5.31)	2361 (10.61)	**<0.001**	5899 (8.22)	365 (13.23)	**<0.001**
Length-of-stay >4 days	1331502 (37.46)	99953 (49.63)	**<0.001**	193216 (44.88)	12482 (56.09)	**<0.001**	41104 (57.29)	1924 (69.81)	**<0.001**
Moderate-to-severe disability on discharge	2047841 (60.86)	119378 (65.01)	**<0.001**	291493 (71.91)	15134 (76.52)	**<0.001**	46417 (71.37)	1788 (75.41)	0.049

CKD – Chronic Kidney Disease; ESRD – End Stage Renal Disease; IVT – intravenous thrombolysis, SD – Standard Deviation; IQR – Interquartile Range; Statistically significant differences (P <0.01) highlighted in **bold.**

† The Mann-Whitney U test was used to compare differences between patients receiving thrombolysis and those who did not amongst each group of renal dysfunction for this variable.

‡ The Pearson χ^2 test was used to compare differences between patients receiving thrombolysis and those who did not amongst each group of renal dysfunction for this variable.

1

Table 2. Results of multivariable logistic regressions evaluating the association between levels of renal dysfunction and adverse acute ischaemic stroke in-hospital outcomes.

	In-hospital mortality		**Prolonged hospitalisation**		**Moderate-to-severe disability on discharge**	
	OR (99% CI)	***P* value**	**OR (99% CI)**	***P* value**	**OR (99% CI)**	***P* value**
No CKD (n= 3,755,784)	Reference	-	Reference	-	Reference	-
CKD/No ESRD (n= 452,802)	**1.04 (1.0003-1.09)**	**0.009**	**1.03 (1.02-1.06)**	**<0.001**	**1.13 (1.10-1.15)**	**<0.001**
ESRD (n= 74,499)	**2.06 (1.90-2.25)**	**<0.001**	**1.44 (1.37-1.51)**	**<0.001**	**1.34 (1.26-1.41)**	**<0.001**

Models adjusted for age, sex, ethnicity, hospital region, location and teaching status and a wide range of comorbidities (HIV/AIDS, alcohol abuse, deficiency anaemia, collagen vascular disease, chronic blood loss anaemia, congestive heart failure, chronic pulmonary disease, coagulopathy, depression, diabetes mellitus, drug abuse, hypertension, hypothyroidism, liver disease, lymphoma, fluid and electrolyte disorders, metastatic cancer, other neurological disorders, obesity, paralysis, peripheral vascular disease, psychosis, pulmonary circulation disorders, solid tumour without metastasis, peptic ulcer disease, valvular disease, weight loss, atrial fibrillation, previous stroke, coronary heart disease, smoking, dyslipidaemia and dementia).

OR – Odds Ratio; CI – Confidence Interval;

Statistically significant differences (P <0.01) highlighted in **bold**.

Table 3. Results of multivariable logistic regressions evaluating the association between levels of renal dysfunction and adverse acute ischaemic stroke in-hospital outcomes including interaction terms with use of thrombolysis.

	In-hospital mortality		**Prolonged hospitalisation**		**Moderate-to-severe disability on discharge**	
	OR (99% CI)	***P* value**	**OR (99% CI)**	***P* value**	**OR (99% CI)**	***P* value**
No CKD (n= 3,755,784)	Reference	-	Reference	-	Reference	-
CKD/No ESRD (n= 452,802)	1.04 (0.99-1.09)	0.020	**1.04 (1.02-1.07)**	**<0.001**	**1.13 (1.10-1.16)**	**<0.001**
Interaction term: Thrombolysis use	1.02 (0.88-1.19)	0.701	0.91 (0.82-1.00)	0.010	0.91 (0.81-1.02)	0.028
ESRD (n= 74,499)	**2.09 (1.91-2.28)**	**<0.001**	**1.43 (1.36-1.51)**	**<0.001**	**1.34 (1.26-1.42)**	**<0.001**
Interaction term: Thrombolysis use	0.84 (0.59-1.21)	0.223	1.12 (0.84-1.47)	0.328	0.95 (0.69-1.30)	0.647

Models adjusted for age, sex, ethnicity, hospital region, location and teaching status and a wide range of comorbidities (HIV/AIDS, alcohol abuse, deficiency anaemia, collagen vascular disease, chronic blood loss anaemia, congestive heart failure, chronic pulmonary disease, coagulopathy, depression, diabetes mellitus, drug abuse, hypertension, hypothyroidism, liver disease, lymphoma, fluid and electrolyte disorders, metastatic cancer, other neurological disorders, obesity, paralysis, peripheral vascular disease, psychosis, pulmonary circulation disorders, solid tumour without metastasis, peptic ulcer disease, valvular disease, weight loss, atrial fibrillation, previous stroke, coronary heart disease, smoking, dyslipidaemia and dementia).

OR – Odds Ratio; CI – Confidence Interval;

Statistically significant differences (*P* <0.01) highlighted in **bold**.**Table 4.** Results of multivariable logistic regressions evaluating the association between levels of renal dysfunction and intracranial haemorrhage amongst acute ischaemic stroke patients undergoing thrombolysis.

AIS admissions undergoing thrombolysis			
	ICH* events N (%)	**OR (99% CI)**	***P* value**
No CKD (n=201,417)	18,028 (8.95)	Reference	-
CKD/No ESRD (n=22,254)	22,254 (9.97)	0.93 (0.80-1.08)	0.215
ESRD (n=2757)	233 (8.47)	0.88 (0.57-1.35)	0.430

*defined using ICD-9 comorbidity codes 430; 431; 432.0; 432.1; 432.9. While the ICD-9 comorbidity codes used in the National Inpatient Sample do not allow differentiation between comorbidity diagnoses and in-hospital complications, this model assumes that ICH diagnoses recorded in patients undergoing thrombolysis occurred during the index admission as a complication of thrombolysis given that previous intracranial haemorrhage (ICH) is an absolute contraindication to thrombolytic therapy.

Models adjusted for age, sex, ethnicity, hospital region, location and teaching status and a wide range of comorbidities (HIV/AIDS, alcohol abuse, deficiency anaemia, collagen vascular disease, chronic blood loss anaemia, congestive heart failure, chronic pulmonary disease, coagulopathy, depression, diabetes mellitus, drug abuse, hypertension, hypothyroidism, liver disease, lymphoma, fluid and electrolyte disorders, metastatic cancer, other neurological disorders, obesity, paralysis, peripheral vascular disease, psychosis, pulmonary circulation disorders, solid tumour without metastasis, peptic ulcer disease, valvular disease, weight loss, atrial fibrillation, previous stroke, coronary heart disease, smoking, dyslipidaemia and dementia).

ICH – intracranial haemorrhage; OR – Odds Ratio; CI – Confidence Interval;

FIGURE LEGENDS

Figure 1. Patient population flowchart.

Figure 2. Yearly trends in thrombolysis use in acute ischaemic stroke patients included in the National Inpatient Sample between 2005-2015 over time, stratified by renal function.

CKD – Chronic Kidney Disease; ESRD – End Stage Renal Disease;

Supplementary Material

Supplementary Tables

Supplementary Table 1. International Classification of Disease – ninth edition (ICD9) codes used to extract co-morbidities, procedures and in-hospital outcomes.

Comorbidities	**ICD 9 codes (Diagnosis)**
Atrial Fibrillation	427.31; 427.32
Previous cerebrovascular disease	V125.4
Coronary Heart Disease	411.1; 411.81; 411.89; 412; 413.1; 413.9; 414.00; 414.01; 414.02; 414.04; 414.05; 414.8; 414.9
Smoking	305.1; V158.2
Dyslipidaemia	272.0; 272.1; 272.2; 272.4
Dementia	290.0; 290.10; 290.40; 290.41; 290.42; 290.43; 290.9; 294.10; 294.11; 294.20; 294.21; 331.0; 331.19; 331.2; 331.82
Outcomes	
Intracranial haemorrhage	430; 431; 432.0; 432.1; 432.9;
Procedures	**ICD 9 codes (Procedural)**
Thrombolysis	99.10

ICD 9 - International Classification of Disease – ninth edition

Supplementary Table 2. Baseline characteristics and outcomes of AIS patients receiving/not receiving thrombolysis, stratified by level of renal dysfunction.

	No CKD			**CKD/No ESRD**			**ESRD**		
	No IVT	IVT	*P* value	No IVT	IVT	*P* value	No IVT	IVT	*P* value
N	3554367	201417		430548	22254		71743	2757	
Age, median (IQR)	70.00 (58.00-81.00)	72.00 (60.00-82.00)	**<0.001**	78.00 (69.00-86.00)	77.00 (67.00-85.00)	**<0.001**	69.00 (59.00-78.00)	68.00 (58.00-77.00)	0.078
Length-of-stay, median (IQR)	4.00 (3.00-7.00)	4.00 (2.00-6.00)	**<0.001**	5.00 (3.00-8.00)	4.00 (3.00-7.00)	**<0.001**	7.00 (4.00-11.00)	5.00 (3.00-9.00)	**<0.001**
Sex Female, N (%)	1902492 (53.53)	101601 (50.44)	**<0.001**	201573 (46.82)	10217 (45.91)	0.233	39124 (54.53)	1442 (52.30)	0.307
Ethnicity			**<0.001**			**<0.001**			**0.005**
White	2171771 (61.10)	130770 (64.93)		254440 (59.10)	14073 (63.24)		28278 (39.42)	1245 (45.15)	
Black	476284 (13.40)	24653 (12.24)		82799 (19.23)	3566 (16.02)		21769 (30.34)	820 (29.74)	
Hispanic	228607 (6.43)	13532 (6.72)		26227 (6.09)	1224 (5.50)		8799 (12.26)	366 (13.26)	
Asian or Pacific Islander	79531 (2.24)	5070 (2.52)		11207 (2.60)	744 (3.34)		2422 (3.38)	79 (2.88)	
Native American	14565 (0.41)	602 (0.30)		1603 (0.37)	84 (0.38)		619 (0.86)	<11	
Other	77518 (2.18)	5529 (2.75)		8585 (1.99)	580 (2.60)		1468 (2.05)	55 (2.01)	
Elixhauser Comorbidities									
HIV/AIDS	6332 (0.18)	273 (0.14)	0.044	897 (0.21)	65 (0.29)	0.239	370 (0.52)	<11	0.273
Alcohol abuse	149622 (4.21)	9179 (4.56)	**<0.001**	10677 (2.48)	526 (2.37)	0.624	768 (1.07)	45 (1.62)	0.222
Deficiency anaemia	330090 (9.29)	19326 (9.60)	0.059	107698 (25.01)	5492 (24.68)	0.615	35324 (49.24)	1480 (53.68)	0.042
Rheumatoid arthritis/ Collagen vascular disease	85050 (2.39)	4883 (2.42)	0.695	11968 (2.78)	661 (2.97)	0.447	1648 (2.30)	81 (2.94)	0.321

Chronic blood loss anaemia	14120 (0.40)	726 (0.36)	.246	2864 (0.67)	139 (0.62)	.743	419 (0.58)	11 (0.39)	.5640000000000001
Congestive heart failure	429186 (12.07)	28305 (14.05)	**<0.001**	120089 (27.89)	7639 (34.32)	**<0.001**	21127 (29.45)	933 (33.83)	0.028
Chronic Pulmonary Disease	515690 (14.51)	28983 (14.39)	0.523	78057 (18.13)	4129 (18.55)	0.472	11593 (16.16)	488 (17.69)	0.346
Coagulopathy	91964 (2.59)	6467 (3.21)	**<0.001**	19068 (4.43)	1289 (5.79)	**<0.001**	4554 (6.35)	161 (5.82)	0.615
Depression	340220 (9.57)	18145 (9.01)	**<0.001**	42476 (9.87)	2000 (8.99)	0.053	6475 (9.02)	208 (7.55)	0.229
Diabetes Mellitus, Uncomplicated	1004763 (28.27)	47538 (23.60)	**<0.001**	139424 (32.38)	6819 (30.64)	0.015	23582 (32.87)	850 (30.85)	0.306
Diabetes Mellitus, Chronic Complications	155582 (4.38)	5451 (2.71)	**<0.001**	68198 (15.84)	2749 (12.35)	**<0.001**	22456 (31.30)	782 (28.36)	0.138
Hypertension	2785066 (78.36)	155103 (77.01)	**<0.001**	395230 (91.80)	20742 (93.21)	**<0.001**	68466 (95.43)	2678 (97.17)	0.050
Hypothyroidism	439093 (12.35)	25588 (12.70)	0.046	68568 (15.93)	3946 (17.73)	**0.001**	9357 (13.04)	385 (13.95)	0.526
Liver Disease	36920 (1.04)	1882 (0.93)	0.044	6310 (1.47)	293 (1.31)	0.414	1854 (2.58)	64 (2.33)	0.702
Lymphoma	17286 (0.49)	955 (0.47)	0.732	3043 (0.71)	161 (0.72)	0.898	692 (0.96)	15 (0.54)	0.317
Fluid and electrolyte disorders	675617 (19.01)	39471 (19.60)	0.010	126870 (29.47)	6553 (29.45)	0.976	20724 (28.89)	970 (35.20)	**0.001**
Metastatic Cancer	53273 (1.50)	1507 (0.75)	**<0.001**	5075 (1.18)	201 (0.90)	0.095	571 (0.80)	28 (1.02)	0.555
Other neurological disorders	16135 (0.45)	2133 (1.06)	**<0.001**	2150 (0.50)	291 (1.31)	**<0.001**	892 (1.24)	43 (1.57)	0.491
Obesity	286120 (8.05)	19875 (9.87)	**<0.001**	46375 (10.77)	2595 (11.66)	0.067	6484 (9.04)	247 (8.97)	0.957
Paralysis	51156 (1.44)	109465 (54.35)	**<0.001**	5945 (1.38)	12764 (57.35)	**<0.001**	1677 (2.34)	1331 (48.28)	**<0.001**
Peripheral Vascular Disease	289670 (8.15)	16011 (7.95)	0.166	62305 (14.47)	3164 (14.22)	0.648	12637 (17.61)	437 (15.84)	0.269
Psychosis	110638 (3.11)	5252 (2.61)	**<0.001**	14678 (3.41)	637 (2.86)	0.057	2366 (3.30)	108 (3.91)	0.424

Pulmonary circulation disorders	94094 (2.65)	7368 (3.66)	**<0.001**	22564 (5.24)	1494 (6.72)	**<0.001**	3845 (5.36)	161 (5.85)	0.621
Solid Tumour (without metastasis)	60175 (1.69)	2739 (1.36)	**<0.001**	8438 (1.96)	322 (1.45)	0.017	877 (1.22)	20 (0.74)	0.310
Peptic ulcer disease (excluding bleeding)	1009 (0.03)	23 (0.01)	0.041	163 (0.04)	<11	0.204	46 (0.06)	<11	0.534
Valvular Disease	346070 (9.74)	21152 (10.50)	**<0.001**	56180 (13.05)	3216 (14.45)	**0.007**	7969 (11.11)	307 (11.15)	0.975
Weight loss	102205 (2.88)	6496 (3.23)	**0.002**	19994 (4.64)	1181 (5.31)	0.048	5257 (7.33)	264 (9.57)	0.050
Other Comorbidities									
Atrial Fibrillation	786723 (22.13)	64062 (31.81)	**<0.001**	126988 (29.49)	9447 (42.45)	**<0.001**	15572 (21.71)	934 (33.89)	**<0.001**
Previous stroke	316791 (8.91)	19227 (9.55)	**<0.001**	55461 (12.88)	2630 (11.82)	0.042	6722 (9.37)	253 (9.19)	0.890
Coronary Heart Disease	864809 (24.33)	51025 (25.33)	**<0.001**	163496 (37.97)	8999 (40.44)	**<0.001**	27197 (37.91)	1156 (41.94)	0.049
Smoking	589646 (16.59)	36044 (17.90)	**<0.001**	44143 (10.25)	2216 (9.96)	0.526	5237 (7.30)	219 (7.95)	0.556
Dyslipidaemia	1730383 (48.68)	104613 (51.94)	**<0.001**	236190 (54.86)	13000 (58.42)	**<0.001**	28513 (39.74)	1134 (41.16)	0.516
Dementia	285920 (8.04)	11064 (5.49)	**<0.001**	51474 (11.96)	2372 (10.66)	**0.008**	4376 (6.10)	115 (4.16)	0.070
Outcomes, N (%)									
In-hospital mortality	159265 (4.48)	16160 (8.02)	**<0.001**	22843 (5.31)	2361 (10.61)	**<0.001**	5899 (8.22)	365 (13.23)	**<0.001**
Length-of-stay >4 days	1331502 (37.46)	99953 (49.63)	**<0.001**	193216 (44.88)	12482 (56.09)	**<0.001**	41104 (57.29)	1924 (69.81)	**<0.001**
Moderate-to-severe disability on discharge	2047841 (60.86)	119378 (65.01)	**<0.001**	291493 (71.91)	15134 (76.52)	**<0.001**	46417 (71.37)	1788 (75.41)	0.049
Location/teaching status of hospital, N (%)			**<0.001**			**<0.001**			**<0.001**
Rural	435648 (12.26)	7658 (3.80)		46894 (10.89)	878 (3.95)		5197 (7.24)	71 (2.59)	

Urban non-teaching	1439645 (40.50)	66916 (33.22)		170612 (39.63)	7249 (32.57)		28834 (40.19)	781 (28.32)	
Urban teaching	1679073 (47.24)	126843 (62.98)		213042 (49.48)	14127 (63.48)		37711 (52.56)	1904 (69.09)	
Hospital Region, N (%)			**<0.001**			**<0.001**			**<0.001**
Northwest	664735 (18.70)	40348 (20.03)		71166 (16.53)	3898 (17.51)		12255 (17.08)	595 (21.57)	
Midwest	788129 (22.17)	42008 (20.86)		99652 (23.15)	5439 (24.44)		14818 (20.65)	521 (18.90)	
South	1450886 (40.82)	75198 (37.33)		171883 (39.92)	7602 (34.16)		30811 (42.95)	946 (34.33)	
West	650616 (18.30)	43863 (21.78)		87847 (20.40)	5315 (23.88)		13859 (19.32)	695 (25.20)	
Disposition of the patient at discharge, N (%)			**<0.001**			**<0.001**			**<0.001**
Routine	1317134 (37.06)	64243 (31.90)		113869 (26.45)	4643 (20.87)		18619 (25.95)	583 (21.16)	
Transfer to Short-term Hospital	105709 (2.97)	8244 (4.09)		10619 (2.47)	817 (3.67)		2280 (3.18)	120 (4.34)	
Transfer Other: Includes Skilled Nursing Facility (SNF), Intermediate Care Facility (ICF), Another Type of Facility	1495848 (42.08)	91866 (45.61)		214149 (49.74)	11677 (52.47)		32347 (45.09)	1297 (47.05)	
Home Health Care	446284 (12.56)	19268 (9.57)		66725 (15.50)	2641 (11.87)		11789 (16.43)	372 (13.48)	
Against Medical Advice (Ama)	26504 (0.75)	1493 (0.74)		1940 (0.45)	95 (0.43)		615 (0.86)	20 (0.73)	
Died	159265 (4.48)	16160 (8.02)		22843 (5.31)	2361 (10.61)		5899 (8.22)	365 (13.23)	
Discharged alive, destination unknown	3622 (0.10)	143 (0.07)		403 (0.09)	20 (0.09)		193 (0.27)	<11	

Supplementary Table 3. Results of multivariable logistic regressions evaluating the associations between level of renal dysfunction and the odds of receiving thrombolytic therapy for acute ischaemic stroke.

	Odds Ratio (99% Confidence Interval)	***P* value**
No CKD	Reference	-
CKD/No ESRD	1.01 (0.95-1.06)	0.720
ESRD	**0.81 (0.70-0.94)**	**<0.001**

Models adjusted for age, sex, ethnicity, hospital region, location and teaching status and a wide range of co-morbidities (HIV/AIDS, alcohol abuse, deficiency anaemia, collagen vascular disease, chronic blood loss anaemia, congestive heart failure, chronic pulmonary disease, coagulopathy, depression, diabetes mellitus, drug abuse, hypertension, hypothyroidism, liver disease, lymphoma, fluid and electrolyte disorders, metastatic cancer, other neurological disorders, obesity, paralysis, peripheral vascular disease, psychosis, pulmonary circulation disorders, solid tumour without metastasis, peptic ulcer disease, valvular disease, weight loss, atrial fibrillation, previous stroke, coronary heart disease, smoking, dyslipidaemia and dementia).

Statistically significant differences (P <0.01) highlighted in **bold**.

Supplementary Table 4. Results of multivariable logistic regressions evaluating the association between levels of renal dysfunction and adverse acute ischaemic stroke in-hospital outcomes including interaction terms with year of admission.

	In-hospital mortality		**Prolonged hospitalisation**		**Moderate-to-severe disability on discharge**	
	OR (99% CI)	***P* value**	**OR (99% CI)**	***P* value**	**OR (99% CI)**	***P* value**
No CKD (n= 3,755,784)	Reference		Reference		Reference	
CKD/No ESRD (n= 452,802)	**1.07 (1.00-1.13)**	**0.010**	**1.08 (1.04-1.12)**		**1.13 (1.09-1.18)**	**<0.001**
Interaction term: Admission year (2011 onwards vs. before 2011)	1.00 (0.92-1.09)	0.976	1.02 (0.97-1.07)	0.266	1.00 (0.95-1.05)	0.975
ESRD (n= 74,499)	**2.17 (1.94-2.42)**	**<0.001**	**1.49 (1.40-1.60)**	**<0.001**	**1.33 (1.23-1.44)**	**<0.001**
Interaction term: Admission year (2011 onwards vs. before 2011)	0.90 (0.77-1.06)	0.089	0.95 (0.86-1.05)	0.171	1.01 (0.90-1.13)	0.851

Models adjusted for age, sex, ethnicity, hospital region, location and teaching status and a wide range of co-morbidities (HIV/AIDS, alcohol abuse, deficiency anaemia, collagen vascular disease, chronic blood loss anaemia, congestive heart failure, chronic pulmonary disease, coagulopathy, depression, diabetes mellitus, drug abuse, hypertension, hypothyroidism, liver disease, lymphoma, fluid and electrolyte disorders, metastatic cancer, other neurological disorders, obesity, paralysis, peripheral vascular disease, psychosis, pulmonary circulation disorders, solid tumour without metastasis, peptic ulcer disease, valvular disease, weight loss, atrial fibrillation, previous stroke, coronary heart disease, smoking, dyslipidaemia and dementia).

OR – Odds Ratio; CI – Confidence Interval;

Statistically significant differences (P <0.01) highlighted in **bold**.

Supplementary Table 5. Results of multivariable logistic regressions evaluating the association between levels of renal dysfunction and adverse acute ischaemic stroke in-hospital outcomes including interaction terms with hospital location and teaching status.

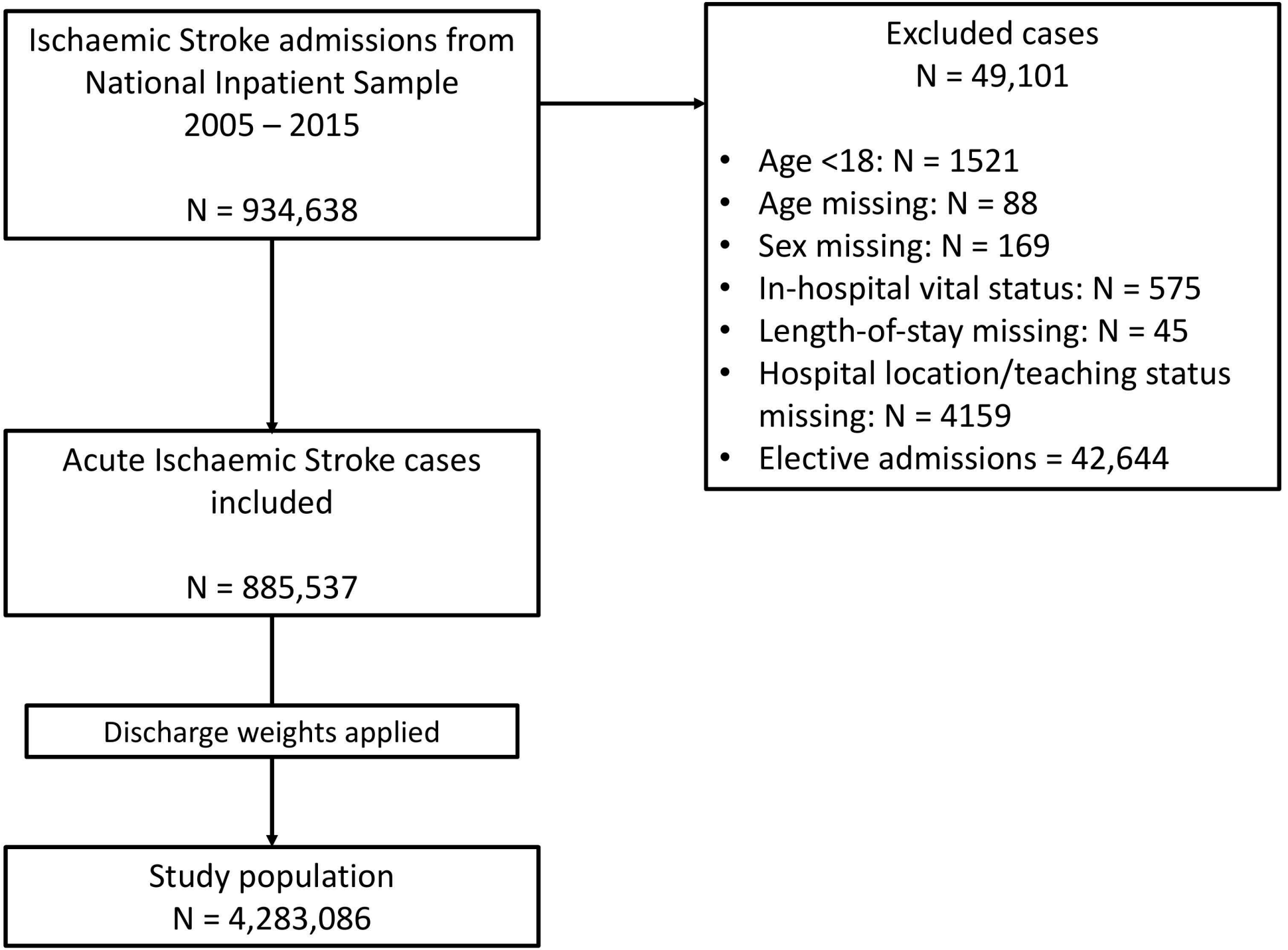
	In-hospital mortality		**Prolonged hospitalisation**		**Moderate-to-severe disability on discharge**	
	OR (99% CI)	***P* value**	**OR (99% CI)**	***P* value**	**OR (99% CI)**	***P* value**
No CKD (n= 3,755,784)	Reference		Reference		Reference	
CKD/No ESRD (n= 452,802)	1.06 (0.94-1.20)	0.188	1.00 (0.94-1.07)	0.907	**1.07 (1.00-1.15)**	**0.010**
Interaction term: Urban nonteaching vs. Rural	1.02 (0.89-1.17)	0.724	1.03 (0.96-1.11)	0.278	1.04 (0.96-1.13)	0.161
Interaction term: Urban teaching vs. Rural	0.95 (0.83-1.09)	0.341	1.05 (0.97-1.12)	0.112	1.07 (0.99-1.15)	0.032
ESRD (n= 74,499)	**2.08 (1.57-2.76)**	**<0.001**	**1.43 (1.19-1.71)**	**<0.001**	**1.41 (1.16-1.73)**	**<0.001**
Interaction term: Urban nonteaching vs. Rural	1.03 (0.75-1.40)	0.821	1.07 (0.87-1.30)	0.409	0.93 (0.75-1.16)	0.405
Interaction term: Urban teaching vs. Rural	0.97 (0.72-1.31)	0.813	0.96 (0.79-1.16)	0.589	0.94 (0.76-1.17)	0.476

Models adjusted for age, sex, ethnicity, hospital region, location and teaching status and a wide range of co-morbidities (HIV/AIDS, alcohol abuse, deficiency anaemia, collagen vascular disease, chronic blood loss anaemia, congestive heart failure, chronic pulmonary disease, coagulopathy, depression, diabetes mellitus, drug abuse, hypertension, hypothyroidism, liver disease, lymphoma, fluid and electrolyte disorders, metastatic cancer, other neurological disorders, obesity, paralysis, peripheral vascular disease, psychosis, pulmonary circulation disorders, solid

tumour without metastasis, peptic ulcer disease, valvular disease, weight loss, atrial fibrillation, previous stroke, coronary heart disease, smoking, dyslipidaemia and dementia).

OR – Odds Ratio; CI – Confidence Interval;

Statistically significant differences (P <0.01) highlighted in **bold**.


Ischaemic Stroke admissions from National Inpatient Sample 2005 – 2015
N = 934,638
Excluded cases
N = 49,101
Age <18: N = 1521
Age missing: N = 88
Sex missing: N = 169
In-hospital vital status: N = 575
Length-of-stay missing: N = 45
Hospital location/teaching status missing: N = 4159
Elective admissions = 42,644
Acute Ischaemic Stroke cases included
N = 885,537
Discharge weights applied
Study population
N = 4,283,086

Yearly Thrombolysis Rates