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Recombinant Tissue Plasminogen Activator Therapy for Acute Ischemic Stroke in Patients with Chronic Kidney Disease

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Abstract

The outcomes of recombinant tissue plasminogen activator (rt-PA) for acute ischemic stroke among patients with reduced kidney function are uncertain. We conducted a retrospective cohort study between 2002-2013 to describe rt-PA use and the risk of secondary intracranial hemorrhage (ICH) and disability at discharge. In an overlap weighted cohort of rt-PA eligible patients (1,354), the relative risk (RR) of secondary ICH among those who received rt-PA (vs. no rt-PA) was 2.56 (99% confidence interval (CI) 1.77-3.69) in those with an estimated glomerular filtration rate (eGFR) ≥60, and 2.67 (2.17-6.20) in those with an eGFR 30-59 mL/min/1.73m^2. Those treated with rt-PA were more likely to be discharged alive and independent compared no rt-PA (RR ≥60: 1.34 (1.17-1.53), 30-59: 1.53 (1.21-1.93) and, <30/chronic dialysis: 2.13 (0.80-5.67)). rt-PA treated patients versus no rt-PA have a higher risk of bleeding but also have a greater chance of leaving hospital alive and independent.

Keywords

Ischemic stroke, tissue plasminogen activator, thrombolysis, chronic kidney disease, secondary intracranial hemorrhage, disability at discharge

Summary for Lay Audience

A commonly used drug to treat a stroke from a blood clot, tissue plasminogen activator, may be harmful to those whose kidneys do not work properly. We designed a study to understand how this drug treatment is used in people with different levels of kidney function and whether it is safe and works well. Among adults living in Ontario, Canada who had an acute ischemic stroke, we found that this drug treatment is given to people at all levels of kidney function. In a smaller group of people who met the criteria for receiving this treatment, we found that patients with normal and reduced kidney function who received the treatment were 3 times more likely to bleed into their brains than those who did not receive the treatment. At the same time, those who received the treatment were up to 2 times more likely to leave the hospital alive with independent function than those who did not receive the treatment. Across all levels of kidney function, we conclude that those who did versus did not receive treatment are more likely to bleed but also are more likely to leave the hospital alive with independent function.

Co-Authorship Statement

This thesis was primarily authored by Sarah E. Bota. Contributions to the study design, data analysis, interpretation and manuscript were provided by the supervisory committee and collaborators.

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Chapter 1

1 Introduction

1.1 What is chronic kidney disease?

Chronic kidney disease (CKD) describes a persistent reduction in kidney function[1] and affects approximately 13% of the adult Canadian population[2]. The kidneys are responsible for filtering blood of uremic toxins, and a reduction in kidney function results in high toxin concentrations in the blood. The level of kidney function is assessed by measuring the concentration of serum creatinine (SCr) in the blood and is often described as categories of function after converting SCr to an estimated glomerular filtration rate (eGFR). These categories range from high or normal (eGFR ≥90 mL/min/1.73m^2) to kidney failure or end-stage kidney disease (ESKD) (eGFR <15 mL/min/1.73m^2).[1] To put these categories into context, half or more of a patient's kidney function is lost when their GFR is <60 mL/min/1.73m^2.[3] ESKD is marked by the need for kidney replacement therapy (KRT) to sustain life. Current replacement therapies come in the form of chronic dialysis treatment (hemodialysis or peritoneal dialysis) or kidney transplantation.

1.2 Patients with CKD have different vascular risk factors than the general population

Declining kidney function is associated with a high risk of cardiovascular disease and can be explained, in part, by traditional risk factors that are common in both cardiovascular disease and CKD populations, such as older age, male sex, hypertension and diabetes.[4] The age-standardized rate of cardiovascular events per 100 person-years across categories of kidney function is estimated to range from 2.1 among those with an eGFR ≥60 mL/min/1.73m^2 to 36.6 among those with an eGFR <15 mL/min/1.73m^2.[5] The CKD population exhibits a strikingly high risk of stroke. Compared to patients with preserved kidney function, in relative terms the risk is 1.5 to 3 times higher across eGFR categories and 4 to 10 times higher in patients receiving dialysis.[6–10] Evidence suggests the risk of stroke increases as kidney function declines across categories of eGFR.[11,12] Furthermore, studies have estimated that one third or more of the stroke population will have CKD as a

comorbid condition[13,14] and CKD has been found to be an independent predictor of poor outcomes among patients with an acute stroke.[13,15–17]

1.3 What is a stroke?

A stroke is marked by acute neurological dysfunction based on evidence (pathological, imaging or other) or clinical evidence of cerebral injury that persists for at least 24 hours.[18] Strokes may be ischemic or hemorrhagic in etiology. Approximately 80% of stroke events in the general population are ischemic[19–22] and are the result of an occlusion in the central nervous system vasculature (either thrombotic or embolic) which obstructs the flow of blood and may result in brain cell death. This can lead to a variety of cognitive and physical deficits, depending on where the flow of blood is restricted and the length of time of the restriction. Hemorrhagic strokes lead to brain tissue death, where the bleeding occurs inside the brain itself or just outside in the subarachnoid space. Similar to an ischemic stroke, a hemorrhagic stroke can also lead to a variety of deficits depending on which part(s) of the brain are affected.[18] Both ischemic and hemorrhagic strokes present as acute neurological dysfunction with symptoms such as speech disturbance, weakness, ataxia (loss of body movement control) and/or headache.

The risk of death after stroke in the general population is high. The case fatality rate for all strokes in Ontario, Canada is 12.6% at 30 days and 22.4% at one-year, and is higher among those with an intracranial hemorrhage compared to ischemic stroke.[23] In-hospital stroke case-fatality is estimated to be 5%, of which 50% is caused by complications from stroke.[24]

1.4 Risk of ischemic stroke among patients with CKD including those receiving dialysis

Analogous to the general population, there is a higher incidence of ischemic stroke than hemorrhagic stroke among patients with CKD. For example, Nickolas et al. found that there was a higher percentage of ischemic compared to hemorrhagic (5.8% versus 0.8%) stroke among those with reduced kidney function established using SCr laboratory values in a multi-ethnic cohort over a follow-up period of 6.5 years.[25] Between 1993 and 1998, Seliger et al. used the United States Renal Data System to assess stroke type among

dialysis patients with a stroke; only 15% were hemorrhagic.[7] This trend has also been shown in other studies among subgroups of patients receiving dialysis.[7,26,27] A study of 539,287 Swedish residents 30 years of age or older found that declining kidney function was associated with an increased hazard of ischemic stroke, with an adjusted hazard rate of 1.09 (95% confidence interval (CI)1.04 to 1.14, eGFR 60 to 90), 1.24 (95% CI 1.10 to 1.34, eGFR 30 to 60), and 2.27 (95% CI 1.63 to 3.17, eGFR 15 to 30) compared to an eGFR >90 mL/min/1.73m^2.[28] Similar results were found in a Dutch study among patients over 55 years of age.[29] A graded increase in the relative risk of hemorrhagic stroke as kidney function declines has also been established.[28,30]

One study estimated the one-year rates of death after ischemic stroke to be 11%, 15%, and 37% among those with CKD, >60, 45 to 60 and 15 to 44 mL/min/1.73m^2, respectively. Corresponding estimates after a hemorrhagic stroke were 46%, 36% and 86%.[31] It is important to note that patients with a low eGFR would have a higher 1-year risk of death than those with a higher eGFR because they have more comorbidities. However, Hoj Fabjan et al. found that after multivariable adjustment eGFR was a significant predictor of in-hospital death after ischemic stroke.[32] Among the dialysis population, the one-year rate of death after dialysis initiation was 18% among those without a history of stroke and 40% among those with a prior history of stroke.[33]

Combined, these studies demonstrate a trend of higher stroke and stroke-related death risks as kidney function declines.

1.5 Tissue plasminogen activator for the treatment of ischemic stroke

Patients who present to the emergency department with an acute ischemic stroke may be eligible for a thrombolytic agent, known as recombinant tissue plasminogen activator (rt-PA), for treatment of their occlusion.

1.5.1 What is rt-PA?

Tissue plasminogen activator is an enzyme involved in the breakdown of blood clots. [34,35] The manufactured biosynthetic version of this enzyme, rt-PA,[34–37] is commonly referred

to as alteplase (generic drug name). rt-PA is cleared through the liver.[35,38] Multiple randomized controlled trails (RCTs) have tested the safety and efficacy of rt-PA versus placebo for acute ischemic stroke in the general population, and a Cochrane review and meta-analysis of these controlled trials (total n = 7,012) found a significant reduction in morbidity with the use of rt-PA.[39,40] The odds ratio of being alive and independent at final follow-up (4 weeks to 6 months) among those who were given rt-PA up to six hours after symptom onset in 12 trials was 1.17 (95% CI 1.06 to 1.29) compared to those who did not receive rt-PA therapy. The magnitude of benefit increased in a subgroup of patients who received rt-PA within three hours of symptom onset [odds ratio of 1.53 (95% CI 1.26 to 1.86)]. The odds ratio of death in the rt-PA treatment group compared to placebo seven days after symptom onset was 1.44 (95% CI 1.18 to 1.76), but this effect was attenuated and no longer significant at the end of follow-up (1.06, 95% CI 0.94 to 1.20) (range from four to six months).[40] However, rt-PA also comes with a risk of intracranial hemorrhage. An ICH manifests similarly to a hemorrhagic stroke but etiologically it is a hemorrhagic conversion of the cerebral infarct resulting from rt-PA therapy.[41] Clinical presentation can be marked by rapid deterioration of a patient's clinical state but not all are symptomatic. It is estimated that up to 40% of patients with symptomatic ICH may have poor outcomes, such as disability and death, as a result of continued bleeding post rt-PA therapy.[42] Wardlaw et al. (2012) found that the odds ratio of symptomatic intracranial hemorrhage (hemorrhagic conversion of the infarct that manifests symptoms) was 3.72 (95% CI 2.98 to 4.64) in the rt-PA treatment group (up to 6 hours after the stroke) compared to control at 7 days from symptom onset. The odds ratios were amplified when looking at the subgroup of patients who received rt-PA therapy vs. control within 3 hours of the stroke to 4.55 (95% CI 2.92 to 7.09). Acknowledging the high odds ratio of symptomatic intracranial hemorrhage, the conclusion of the Cochrane review was that there is an overall net benefit in independence and mortality among those who receive thrombolytic therapy in highly selected patients.[40] One of the major limitations of the trial data is that the safety and efficacy of rt-PA was assessed in a narrow range of patients who had a limited number of comorbidities.[39]

The Canadian Alteplase for Stroke Effectiveness Study (CASES) was essential for the licensure of rt-PA for the treatment of acute ischemic stroke in Canada.[43] Sixty centres

across the country including 1,135 patients participated in the study. Investigators found that 37% of patients experienced a return to their pre-stroke functioning with rt-PA treatment and 22% (95% CI 20.0 to 25.0) died within 90 days. These outcome frequencies aligned with the NINDS rt-PA Stroke Study.[44] Symptomatic ICH occurred in 5% (95% CI 3% to 6%) of the participants who received rt-PA, of which 75% died in hospital. This rate of symptomatic ICH was lower than that seen in clinical trials.[43]

rt-PA is the standard of care in Canada for the treatment of acute ischemic stroke in patients who meet inclusion criteria[45] and it is the only approved thrombolytic treatment for acute ischemic stroke available in the United States [40] and Canada[45]. In order to minimize the risk of secondary ICH, criteria have been established to guide physicians in determining which patients will most benefit from receiving rt-PA therapy.

1.5.2 Who can receive rt-PA as a treatment for ischemic stroke?

The Canadian Stroke Best Practices Recommendations for Acute Ischemic Stroke Treatment outline the criteria for acute thrombolytic therapy; listing the inclusion and exclusion criteria for receiving rt-PA including age, time from stroke symptom onset and hemorrhage on brain imaging (a full list of the criteria can be found in Appendix A).[46,47] The recommendations are developed using Practice Guideline Evaluation and Adaptation methodology[48,49] by a multi-disciplinary group of leaders and experts.[50] Front-line physicians who treat patients with ischemic stroke can use these recommendations to guide acute management of ischemic stroke. The acute thrombolytic therapy recommendations were first published in 2006 and have gone through minor updates over the years.

Reduced kidney function is not listed as a contraindication for rt-PA therapy as it was not an exclusion criterion in any of the clinical trials of rt-PA.[51,52] Furthermore, the *Canadian Stroke Best Practice Recommendations for Hyperacute Stroke Care* does not provide a recommendation based on kidney function in the guidelines.[50] In light of this, it is not clear whether patients with reduced levels of kidney function are treated with rt-PA similarly to those with normal kidney function. One particularly broad exclusion, “Any source of active hemorrhage or any condition that could increase the risk of major

hemorrhage after rt-PA administration" in the Canadian guidelines, may impact a physician's decision to treat a patient with CKD.[46] This is predicated on the notion that physicians who treat patients with ischemic stroke are aware of the general bleeding risks associated with decreased kidney function.[28,53–62] The three-year cumulative incidence of major hemorrhage, defined as a hospitalization for intracranial or gastrointestinal hemorrhage, was significantly higher (4.6 %) among those with moderate kidney function to kidney failure compared to those with high to mildly decreased kidney function (1.0 %). Furthermore, there was a dose response relationship, as kidney function declined the incidence of major hemorrhage increased, with a cumulative incidence ranging from 0.7% among those with high to normal function to 12% among those with ESKD.[53] In a study of patients initiating chronic dialysis, the three-year cumulative incidence of major hemorrhage was 14%[55] and continued to persist among those who received a kidney transplant, 4%, although the incidence was attenuated[63].

In stratified analysis of the three-year risk of major hemorrhage in patients in Ontario, investigators found an increased crude relative risk of hemorrhagic stroke across all categories of eGFR when compared to those with high to normal kidney function, ranging from 2.2 (95 % CI 2.0 to 2.5) to 13.5 (95% CI 11.5 to 15.8).[53] The high risk of major hemorrhage in the kidney disease population has been replicated in many studies across geographical areas.[54,57–62,64]

Based on this evidence, there is reason to hypothesize that patients with reduced kidney function may also have different bleeding risks after rt-PA therapy than the general population that participated in the original rt-PA RCTs. This makes the overall benefit – risk considerations for the use of rt-PA in patients with reduced kidney function uncertain.

1.5.3 The real-world use of rt-PA across categories of CKD

The use of rt-PA may differ among the general population and those with CKD. In two separate surveys of opinion among nephrologists and experts in thrombolytic therapy for acute stroke, both groups reported concern over the bleeding risk after rt-PA therapy among patients with reduced kidney function.[65,66] The utilization of rt-PA and the reasons

for withholding treatment across stages of real function have not been described previously.

The real-world safety and effectiveness of rt-PA in the CKD and dialysis population who received rt-PA therapy have been investigated in several international observational studies[3,51,52,67–76], some of which have been pooled in a meta-analysis[77]. The largest and most comprehensive study is that done by Ovbiagele et al. who estimated the odds ratio of serious systemic hemorrhage, in-hospital mortality and functional status (no independent ambulation at discharge) across categories of kidney function in 44,410 patients who suffered ischemic stroke and received rt-PA.[78] Compared to patients without CKD, those with CKD did not exhibit an increased adjusted odds ratio of symptomatic ICH (adjusted OR 1.0, 95% CI 0.91 to 1.10). In other words, the incidence of symptomatic ICH within 36-hours after rt-PA did not vary by kidney function category. Patients with ischemic stroke who received rt-PA and had CKD, compared to those who received rt-PA and did not have CKD, were more likely to have an unfavourable functional status at discharge (adjusted OR 1.13, 95% CI 1.07 to 1.19) and die in-hospital (adjusted OR 1.22, 95% CI 1.14 to 1.32). In the adjusted analyses, both functional outcomes and in-hospital death showed statistically higher odds ratio in those with reduced kidney function (eGFR <30) compared to those with normal or high kidney function (eGFR ≥90).[78]

The remainder of the observational studies show mixed estimates of the odds ratio of secondary intracranial hemorrhage, poor outcome, and death among those who received rt-PA therapy comparing those with an eGFR <60 mL/min/1.73m^2 to those with an eGFR ≥60 mL/min/1.73m^2.[3,67,70,73–77,79–85] To-date, no RCT assigning treatment to rt-PA therapy versus placebo has been done in the CKD population to understand the risk and benefit of therapy. Furthermore, a comparison of the risks and benefits of rt-PA exposure in a real-world setting (observational study) in the CKD population has not been done.

Chapter 2

2 Objectives and hypotheses

Our first objective was to describe acute ischemic stroke characteristics comparing those who received rt-PA therapy to no therapy within categories of eGFR, and to describe the variation of these characteristics across eGFR categories. Additionally, we sought to describe the treatment characteristics among patients who received rt-PA across eGFR categories. We hypothesized that those who received rt-PA therapy compared to those who did not, would present to the hospital earlier and would have more severe strokes. As eGFR declined, time from symptom onset to hospital arrival would decrease and stroke severity would increase.

Our second objective was to determine rt-PA therapy eligibility among patients who had an acute ischemic stroke by eGFR category using administrative and research databases. We hypothesized that most patients would be ineligible for rt-PA therapy, and ineligibility would increase as kidney function declined.

Our third objective was to estimate the absolute and relative risk of secondary intracranial hemorrhage (ICH) and disability at hospital discharge among those eligible to receive rt-PA therapy after they suffered an acute ischemic stroke, comparing patients who received rt-PA therapy to no therapy within categories of eGFR. Furthermore, we wanted to determine if the relative risk of our outcomes were modified across eGFR categories in absolute and relative terms. We hypothesized that those who received rt-PA compared to those who did not would have a higher relative risk of bleeding but a lower relative risk of disability at discharge within all categories of eGFR. Furthermore, across categories of declining baseline kidney function, there would be a graded absolute increase in the relative risk of secondary ICH with vs. without rt-PA (a harm of treatment), accompanied by a graded absolute increase in the chance of being discharged alive from hospital with independent function (a benefit of treatment).

Chapter 3

3 Methods

3.1 Study design and setting

We designed a retrospective cohort of adults (≥18 years of age) with ischemic stroke in Ontario, Canada. We included patients who had an acute hospital admission for an ischemic stroke between April 1, 2002 and March 31, 2013. Patients were followed from their hospital arrival for one-year. To capture episodes of ischemic stroke care, we used linked administrative and research databases held at ICES. The use of data in this project was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a Research Ethics Board. The reporting of this observational study adheres to Reporting of studies conducted using observational routinely-collected health data (RECORD) guidelines (Appendix B).[86]

3.2 Patients

Patients were eligible if they had a discharge diagnosis of ischemic stroke in the Ontario Stroke Registry (OSR) database. The OSR is a registry designed for the measurement and monitoring of stroke care in Ontario and consists of two overlapping data collection methods. The Ontario Stroke Audit (OSA) is a population-based retrospective chart extraction project that collected a sample of cases approximately every two years between 2002 and 2013. The Regional Stroke Centre (RSC) data was a combination of prospective and retrospective ascertainment of cases at the regional stroke centres between 2001 and 2012. The registry is made up of a population-based sample of patients with suspected stroke and transient ischemic attack seen in an emergency department or admitted to an acute hospital in the province (see Appendix C for detailed sampling strategies). The OSR is a database held at ICES and is linked to other administrative datasets including the Registered Persons Database, the Canadian Institute for Health Information Discharge Abstract Database, the Ontario Health Insurance Plan, and the Canadian Organ Replacement Register (CORR). These datasets were linked using unique encoded identifiers and analyzed at ICES. Patients were excluded from our study based on the following criteria: 1) missing age, sex, ICES unique identifier, or were not an

Ontario resident (data cleaning), 2) evidence of death before the index date (suggesting data entry error), 3) missing baseline serum creatinine measurement (which is needed to determine baseline kidney function), 4) missing international normalized ratio (INR) measurement at admission (key covariate), 5) missing glucose measurement at admission (key covariate), 6) missing time from hospital arrival to imaging (key covariate), 7) history of hemi, para or quadriplegia (as this impacts their access to rt-PA), 8) received stroke care at a non-designated hospital (as this impacts their access to rt-PA therapy), evidence of an in-hospital stroke (as we are unable to determine their baseline kidney function). If patients had multiple events, we restricted to the first event available in the OSR. The index date was the date of arrival to hospital.

3.3 Exposure

The exposure was treatment with rt-PA therapy (yes/no) as recorded in the OSR. Results were reported by baseline kidney function estimated using the first serum creatinine documented at the time of hospital presentation for the stroke (usually done in the emergency department) and converted to an estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Appendix D).[87] We tested the stability of this laboratory value in a subgroup of patients with a prior pre-hospitalization outpatient serum creatinine laboratory measurement and found to it had substantial agreement within eGFR categories (see Appendix E for details). eGFR was categorized, as normal, high or mildly decreased, ≥60 mL/min/1.73m^2, moderately decreased, 30-59 mL/min/1.73m^2, severely decreased and kidney failure, <30 mL/min/1.73m^2, using modified cut-points of eGFR described in the Kidney Disease Improving Global Outcomes (KDIGO) guidelines.[1] Chronic dialysis was defined using CORR and these patients were grouped within the KDIGO severely decreased and kidney failure category (eGFR <30 mL/min/1.73m^2).

3.4 Outcomes

The primary outcomes were secondary ICH and disability at discharge. Secondary ICH could occur at any time within the hospital admission for stroke and was captured by subsequent neuroimaging after the initial admission brain scan. The definition includes

both symptomatic and asymptomatic secondary ICH and was captured using the OSR and supplemented with the Discharge Abstract Database. Disability was measured using the modified Rankin scale (mRS) at discharge in the OSR. The mRS is a scale for the measurement of the degree of disability (0 to 6) based on daily activities after stroke.[88] For the purposes of our analyses, we made the mRS binary (categorized as 0-2 yes/no) which captures those who were alive and independent at discharge. Our secondary outcomes were death in-hospital, at 30 days and 1-year from the time last seen normal, and systemic hemorrhage. The administrative codes used to define each of the exposure and outcome variables can be found in Table 1.

3.5 Statistical methods

3.5.1 rt-PA and ischemic stroke characteristics

Baseline characteristics are reported by those who received rt-PA and those who did not (control) within three categories of eGFR. Continuous variables were reported as medians and interquartile ranges (25^{th}, 75^{th} percentiles) and categorical variables are reported as frequencies and percentages. Standardized differences were used to estimate between-group differences in baseline characteristics, where a difference ≥10% is considered statistically significant.[89,90] The concept definitions for the baseline variables can be found in Appendix F. An exploratory analysis was conducted to estimate the percentage of patients with ischemic stroke presenting to the hospital with a concurrent acute kidney injury (AKI) (details of these analyses can be found in Appendix G).

3.5.2 rt-PA eligibility criteria

Based on Canadian stroke guidelines and previous RCT eligibility criteria, patients were assessed on their eligibility to receive rt-PA based on 15 criteria using baseline administrative and registry data. The detailed criteria used to assess eligibility can be found in Appendix H. There were some stroke eligibility criteria that could not be estimated using available datasets. These criteria, based on best practice guidelines, were (1) “Any other condition that could increase the risk of hemorrhage after rt-PA administration”, (2) “Elevated partial thromboplastin time”, (3) “CT showing early signs of extensive infarction, represented by a score of less than five on the Alberta Stroke

Program Early CT Score (ASPECTS), or MRI showing an infarct volume greater than 150 cc on diffusion-weighted imaging", (4) "Arterial puncture at a non-compressible site in last 7 days" and (5) "Rapidly improving symptoms".[46]

rt-PA eligibility criteria were applied to all the patients in our cohort. Patients were categorized as either eligible or ineligible for rt-PA therapy based on these criteria. We calculated the frequency and percentage of patients in each eligibility group within categories of eGFR to understand if eligibility changed by kidney function category. We also estimated the reliability of our administrative-based eligibility criteria compared to the real-world frequency of rt-PA administration based on chart review, i.e. patients who received rt-PA in the OSR. We calculated percent agreement, Cohen's simple kappa, p-values and 95% confidence intervals. We also reported the reasons rt-PA was not given among those who did not receive rt-PA using the OSR data. For secondary ICH and disability risk analyses (objective 3), we restricted the cohort to those who were eligible to receive rt-PA.

3.5.3 Primary and secondary outcomes

To estimate the relative risk of secondary ICH and disability at discharge by rt-PA exposure we estimated a patient's propensity score for receiving rt-PA using logistic regression. This was done separately for each eGFR category by rt-PA exposure. Propensity score is a statistical method that balances baseline characteristics between two groups in an effort to reduce systematic differences and mimic the conditions of a RCT. The propensity score is the predicted probability that each patient will receive the exposure given their measured covariates. Using a logistic regression model, treatment status is regressed on baseline characteristics to create similar distributions among patients with the same propensity score.[91] Baseline characteristics that were unbalanced were included in our propensity score model. The characteristics used in each propensity score model varied across eGFR categories and the exact variables included in each model are outlined in Appendix I. Simple imputation was used for baseline characteristics with <10% missing. The distribution of propensity scores (Appendix J) showed a large number of patients with extreme values in the tails. In light of this, we applied overlap weighting which estimates the probability of being assigned to the

opposite exposure group. This method reduces the influence of individuals in the tails of the propensity score distribution without excluding them and up-weights individuals with a higher likelihood of receiving either treatment.[92] Subsequently, the overlap weighted propensity score exposure group distributions looked similar between rt-PA exposure groups (Appendix J). Within each category of eGFR, exposure groups were weighted such that 50% of the patients were in each group. To assess the overlap weighting balance, baseline characteristics were compared between the weighted exposure groups within each category of eGFR. The frequency, percentages and standardized differences reported were weighted and rounded for ease of interpretation. The relative risk of secondary ICH, being alive and independent and our secondary outcomes within eGFR categories were estimated using modified Poisson regression.[93] Some patients (13%) were removed from the mRS analysis due to missing data or because they died in-hospital.

Ninety-nine percent confidence intervals (α= 0.01) were used to account for multiple comparisons across eGFR categories. We estimated the risk difference and number needed to treat/harm (NNT/NNH) for all outcomes. All results were estimated within the modified version of the KDIGO eGFR categories (≥60 mL/min/1.73m^2, 30-59 mL/min/1.73m^2 and <30 mL/min/1.73m^2 or on chronic dialysis) due to small sample size among those with kidney failure. Often the percentages of our outcome were >10% so we also estimated the odds ratio (OR) for comparison with the literature. We estimated the multiplicative and additive interaction across eGFR categories, where an eGFR ≥60 mL/min/1.73m^2 was the reference group. Multiplicative interaction was estimated using the log of the relative risk point estimates for each outcome,[94] and additive interaction was estimated using the proportion of outcomes by rt-PA exposure.[95] The E-value was also estimated in a sensitivity analysis for each outcome to better understand residual confounding. The E-value is the minimum strength of association that an unmeasured confounder would need to explain away the observed effect estimate.[96]

A sensitivity analysis was done to account for pre-event independence in the mRS outcome. We created a subgroup of patients who were independent or had a slight

disability prior to the ischemic stroke event and repeated the RR analysis within eGFR categories.

Analyses for our systemic hemorrhage secondary outcome were abandoned after we found a small number of events within all categories of eGFR. Due to ICES privacy policies, the results are not reported.

Table 1. Exposure and outcome concept definitions

Variable	**ICES Database**	**Definition**
Tissue plasminogen therapy (rt-PA) administration	Ontario Stroke Registry (OSR)	EI_THROMBOLYSIS Documentation in the patient chart regarding the receipt of thrombolytic therapy
Serum Creatinine (µmol/L) on hospital arrival	OSR	EI_CREAT Serum creatinine converted to estimated glomerular filtration rate (eGFR) and categorized by modified Kidney Disease Improving Global Outcomes (KDIGO): ≥60 mL/min/1.73m^2, 45-59 mL/min/1.73m^2, 30-44 mL/min/1.73m^2, <30 mL/min/1.73m^2
Chronic dialysis	Canadian Organ Replacement Register (CORR)	RECIPIENT_TREATMENT dataset TREATMENT_CODE ≠ 171, 181 TRANSFER_CODE ≠ "W" Patients with chronic dialysis were categorized with patients in the KDIGO kidney failure category (<30 mL/min/1.73m^2).
Secondary Intracranial Hemorrhage (ICH)	OSR Discharge Abstract Database (DAD)	Either: a. rt-PA administered to patient EI_HEMTRANSFORMTYPE (Any Hem) *If first scan normal:* IV2_NEWLESION= new hemorrhage *If first scan is ischemic:* IV2_INFARCTIONSECONDARY IV2_SECONDARY ICD10: I60 (except I60.8) & I61 <u>OR</u> b. rt-PA not administered to patient *If first scan normal:* IV2_NEWLESION=new hemorrhage *If first scan ischemic:* IV2_INFARCTIONSECONDARY IV2_SECONDARY

		OR c. ICD10: I60 (except I60.8) & I61
Modified Rankin Scale (mRS) assessed at hospital discharge	OSR	D_RANKIN Categorized as 0-2 (alive and independent) (Yes/No). Patients with a mRS of 6 (which meant they died) were removed from this analysis.
Death within ischemic stroke hospitalization	OSR Registered Persons Database (RPDB)	D_STATUS
Death within 30-days of the date last seen normal	OSR RPDB	DEATH_30D
Death within 1-year from the date last seen normal	OSR RPDB	DEATH_1YR

Chapter 4

4 Results

There were 44,659 patients with an acute ischemic stroke in the OSR. Based on pre-specified criteria, we excluded 22,250 patients (see Figure 1 flow diagram), leaving 22,409 patients in the study cohort.

4.1 Acute ischemic stroke characteristics according to rt-PA therapy by eGFR category

In our cohort of 22,409 patients, 4,013 (18%) were treated with rt-PA. Across eGFR categories, the proportion who received rt-PA was 18% with an eGFR ≥60 mL/min/1.73m^2, 19% with an eGFR 30-59 mL/min/1.73m^2, and 14% with an eGFR <30 mL/min/1.73m^2 or on chronic dialysis (Table 2). The documented reasons that rt-PA was not given to patients can be found in Appendix K.

Most patients (51%) arrived at the hospital within 4.5 hours of ischemic stroke symptom onset. Within this group, 34% received rt-PA, compared to 1% of those who presented to hospital beyond 4.5 hours. Among those who arrived at the hospital within 4.5 hours across the eGFR categories, the proportion who received rt-PA declined as eGFR declined.

Most patients (81%) presented with weakness, but less than 22% of those with weakness received rt-PA. Across eGFR categories, the proportion of patients with weakness who received rt-PA was slightly lower in those with an eGFR <30 or on chronic dialysis (17%) compared to the other eGFR categories (21%).

The National Institute for Stroke Scale (NIHSS) is an assessment tool that quantifies a patient's level of stroke impairment. rt-PA was administered more frequently to those with moderate to severe strokes (NIHSS ≥5) compared to those with no symptoms or minor strokes (NIHSS <5). However, most patients (80%) in all NIHSS categories did not receive rt-PA therapy. Across eGFR categories, among those with moderate to severe

strokes (NIHSS ≥5) rt-PA administration declined as eGFR declined. This is despite evidence that the median stroke severity score increased across lower eGFR categories.

Most patients (80%) had a brain scan within 3.5 hours of hospital arrival and within this group, 22% received rt-PA. Across eGFR categories, the proportion of patients who received a brain scan and rt-PA was slightly lower in those with an eGFR <30 or on chronic dialysis (18%) compared to the other eGFR categories (22%).

Of those who received rt-PA therapy (4,013), most (>96%) received this therapy within 3.5 hours from stroke symptom onset. The time between stroke symptom onset and receipt of rt-PA therapy was similar as eGFR category declined (Table 3).

Most patients were administered rt-PA therapy intravenously (compared to intra-arterially) and the percentage of patients who received intravenous vs. intra-arterial rt-PA increased as eGFR category declined (from 93% to 97%). Among those who received intravenous rt-PA, the median dose was higher in those with an eGFR ≥60 ml/min/1.73m^2 compared to the other two eGFR categories (68 mg vs. 63 mg).

4.2 The proportion of patients with ischemic stroke who were eligible to receive rt-PA treatment by eGFR category

Using eligibility criteria established in the RCTs testing rt-PA vs. placebo and the Canadian Stroke Best Practice Recommendations, we assessed eligibility for rt-PA of each patient with an ischemic stroke event in our cohort (22,409). Eligibility was assessed according to characteristics recorded within our administrative and research databases. In Table 4, we report the frequency and percentage of patients who were eligible or ineligible for each criterion when assessed independently (i.e. not unique). A large number of patients were found to be ineligible based on the following criteria: hospital arrival time >4.5 hours after symptom onset (49%), blood pressure >185/110 mm/Hg (19%), and mild stroke (NIHSS ≤4) (34%).

When we accounted for all the eligibility criteria, 4,632 of 22,409 patients (21%) were eligible for rt-PA therapy. The percentage of patients who were rt-PA eligible was consistent across eGFR categories: 2,711 of 13,214 (21%) with an eGFR ≥60 mL/min/1.73m^2 were rt-PA eligible, and corresponding proportions in those with an eGFR between 30 and 60, and <30 mL/min/1.73m^2 including those receiving dialysis were 1,629 of 7,735 (21%), and 292 or 1,460 (20%), respectively.

We measured the reliability of our eligibility criteria definition using administrative and research databases by comparing it to those who received rt-PA therapy in the real-world. The percent agreement between the two measures was 89.9% (95% CI 85.5 to 86.4). When we estimated Cohen's simple kappa, we found a coefficient of 0.55 (95% CI, 0.54 to 0.56) suggesting moderate agreement. For the remainder of the study analyses, we excluded all patients who did not meet all the eligibility criteria outlined above leaving 4,632 patients eligible to receive rt-PA.

4.3 Characteristics of ischemic stroke in patients eligible to receive rt-PA by rt-PA treatment status and eGFR category

In patients eligible to receive rt-PA (4,632), rt-PA therapy was administered to 39% (1,049 of 2,711) of those with a baseline eGFR ≥60 mL/min/1.73m^2, 41% (670 of 1,629) in those with an eGFR of 30-59, and 55% (161 of 292) in those with an eGFR of <30 or on chronic dialysis.

In patients eligible to receive rt-PA, patient characteristics according to whether they received rt-PA or not and by eGFR category is presented in Table 5. We initially focused on examining the characteristics of those who did and did not receive rt-PA within categories of eGFR, and then compared those who did and did not receive rt-PA across eGFR categories.

The median age of patients who received rt-PA was 71, 80 and 81 in eGFR categories ≥60, 30-59 and <30 mL/min/1.73m^2 or on chronic dialysis, respectively. The median age

of those who did not receive rt-PA therapy was 67, 82 and 84, respectively. Most patients who received rt-PA with normal to high kidney function (eGFR ≥60) were male (59%), whereas most patients with decreased kidney function were female (57% with an eGFR 30-59, and 63% with an eGFR <30 or on chronic dialysis). Similar results were found among those who did not receive rt-PA; there were more males among those with an eGFR ≥60 (59%) and more females with an eGFR 30-59 (59%) and <30 or on chronic dialysis (57%).

Of those with pre-event independence data (2,642), 36%, 44% and 17% of the rt-PA group were independent prior to their stroke event by eGFR ≥60, 30-59 and <30 or on chronic dialysis category, respectively. In the group who did not receive rt-PA therapy, 55%, 24% and 36% were independent. Pre-event independence missingness ranged from 36% to 52% of the rt-PA eligible cohort.

The median NIHSS of patients who received rt-PA was 7, 12 and 14 in eGFR categories ≥60, 30-59 and <30 or on chronic dialysis, respectively. The median NIHSS of those who did not receive rt-PA therapy was 11, 8 and 10, respectively.

Of those who received rt-PA and those who did not, most patients (>65%) had a Charlson Comorbidity Index of 0-1 in eGFR categories ≥60 and 30-59. However, the majority of patients with an eGFR <30 or on chronic dialysis had a Charlson score ≥2 in both rt-PA therapy groups (>59%). Comorbidities such as diabetes, hyperlipidemia, coronary artery disease and stroke were high in rt-PA eligible cohort and were more frequent among those who did not receive rt-PA therapy compared the rt-PA therapy group in those whose eGFR was <60 mL/min/1.73m^2.

Most patients with an eGFR ≤60 mL/min/1.73m^2 or on chronic dialysis had a high risk of bleeding score (HASBLED ≥3) in both rt-PA and no rt-PA groups at baseline (>52%).

Across eGFR categories, both age and the percentage of females increased as eGFR deceased in those who received rt-PA and those who did not. Diabetes, hyperlipidemia, coronary artery disease and a high risk of bleeding score (HASBLED ≥3) also increased as eGFR declined in both exposure groups (rt-PA and no rt-PA). Both rt-PA therapy

groups showed an increase in slight to severe pre-event disability as eGFR declined. In those who received rt-PA therapy, the median NIHSS increased as eGFR declined but among those who did not receive rt-PA these scores decreased with declining eGFR. Additional baseline characteristic results can be found in Appendix L.

4.4 Weighted baseline characteristics by rt-PA therapy exposure and eGFR category

After overlap weighting on the propensity score, there was a total of 1,354 patients in our cohort, with 804 (59%), 492 (36%) and <64 (<5%) patients in eGFR categories ≥60, 30-59 and <30 or on chronic dialysis, respectively (Table 6). After overlap weighting, those who received rt-PA vs. those who did not were well balanced within categories of eGFR on all baseline characteristics. A table of all the weighted baseline characteristics can be found in Appendix M.

4.5 Risk of secondary ICH by rt-PA exposure within categories of eGFR

Secondary ICH occurred in 14% of patients with an eGFR ≥60, 15% with an eGFR 30-59, and 16% with an eGFR <15mL/min/1.73m^2 or on chronic dialysis who received rt-PA therapy (weighted) (Figure 2a). The percentage of secondary ICH was higher in those treated with rt-PA vs. those who did not receive rt-PA. The weighted absolute risk increase of secondary ICH with rt-PA vs. no rt-PA was 9% in those with an eGFR ≥60 mL/min/1.73m^2 (number needed to harm (NNH) 12 patients treated with rt-PA), 11% (NNH 10 patients), and 16% (NNH 6 patients) in those with an eGFR 30-59 mL/min/1.73m^2 and <30 mL/min/1.73m^2 or on chronic dialysis, respectively (positive additive interaction p-value=0.02). In a descriptive subgroup analysis, we estimated the weighted frequency of secondary ICHs that were symptomatic (clinically detectible neurological deterioration). We found 47% of ICHs among those with an eGFR of ≥60 were symptomatic. Corresponding numbers for an eGFR 30-59, and <30 or on chronic dialysis, were 44% and 25%, respectively.

In relative terms, receiving rt-PA therapy (vs. no therapy) was associated with a higher relative risk of secondary ICH among patients with an eGFR ≥60 (weighted relative risk (RR_w) 2.56, 99% confidence interval (CI) 1.77 to 3.69) and those with an eGFR 30-59 (RR_w 3.67, 99% CI 2.17 to 6.20). The magnitude of this risk did not significantly differ between the groups (p-value for interaction 0.42) (Figure 3). We were unable to fit the weighted relative risk model within the eGFR <30 or on chronic dialysis category due to a small number of events. In addition to relative risk we also estimated the weighted odds ratio of secondary ICH by eGFR category and these results can be found in Appendix N.

We assessed the robustness of this association and found the E-values estimating the strength of the weighted relative risk association that an unmeasured confounder would need to explain the effect of rt-PA on secondary ICH were 4.56 and 4.78 (≥60 and 30-59, respectively) (see Appendix O for E-value figures).

4.6 Disability at hospital discharge

In those who received rt-PA, the chance of leaving the hospital alive with independent function (mRS 0-2) was 45% in those with an eGFR ≥60, 33% with an eGFR 30-59, and 16% with an eGFR <15mL/min/1.73m^2 or on chronic dialysis (weighted) (Figure 2b). In those who did not receive rt-PA, the chance of leaving hospital alive with independent function was 34% in those with an eGFR ≥60, and 22% and 8% in those with an eGFR 30 to 59 and <30 or on chronic dialysis, respectively.

Receipt of rt-PA (vs. no rt-PA) resulted in a better chance of leaving hospital alive with independent function across all eGFR categories. The weighted absolute risk differences were 11% (NNT 9 patients treated with rt-PA) among patients with an eGFR ≥60, 12% (NNT 9 patients) among patients with an eGFR 30-59, and 9% (NNT 12 patient) for those with an eGFR <30 or on chronic dialysis. A positive additive interaction (p-value=0.001) was found comparing disability at discharge among patients who received rt-PA vs. those who did not with eGFRs ≥60 to 30-59 mL/min/1.73m^2, and a negative interaction (p-value= -0.03) among patients with eGFRs ≥60 to <30 mL/min/1.73m^2 or on chronic dialysis.

Receiving rt-PA therapy was associated with a weighted relative risk of being discharged alive and independent of 1.34 (99% CI 1.17 to 1.53) in those with an eGFR ≥60, 1.53 (99% CI 1.21 to 1.93) in those with an eGFR 30-59, and 2.13 (99% CI 0.80 to 5.67) in those with an eGFR <30 or on chronic dialysis, compared to those who did not receive rt-PA therapy (Figure 3). When we compared the weighted relative risk of being discharged alive and independent comparing patients on their use of rt-PA therapy by eGFR category (≥60 vs. 30-59, ≥60 vs. <30 or chronic dialysis), we did not find a significant interaction effect.

When we assessed the robustness of this association, the E-values estimating the strength of the weighted relative risk association that an unmeasured confounder would need to explain the effect of rt-PA on disability are 2.01, 2.43 and 3.68 (≥60, 30-59 and <30 or on chronic dialysis, respectively) (see Appendix O for E-value figures).

In a sensitivity analysis, we estimated the weighted relative risk in a subgroup of patients who were independent or had a slight disability prior to their stroke event and found that being discharged alive and independent was 1.16 (99% CI 0.98 to 1.36) times higher among those who received rt-PA and had an eGFR ≥60. Among those with an eGFR <30 or on chronic dialysis, the relative risk of being discharged alive and independent was 0.87 (99% CI 0.19 to 4.06) times lower for those who received rt-PA therapy. There was no difference in the relative risk among patients with an eGFR 30-59 (1.01, 99% CI 0.77 to 1.33).

4.7 Death in-hospital, 30 days and one-year

Death in-hospital occurred in 9% of those with an eGFR ≥60, 15% with an eGFR 30-59, and 18% with an eGFR <30 or on chronic dialysis who received rt-PA therapy (weighted) (Figure 2c). In those who did not receive rt-PA, death occurred in 12% in those with an eGFR ≥60, and 14% and 23% in those with an eGFR 30 to 59 and <30 or on chronic dialysis, respectively.

The weighted absolute risk difference was 2% (NNT 44 patients treated with rt-PA), 1% (NNT 112 patients) and 5% (NNT 20 patients) among eGFR categories ≥60, 30-59 and

<30 or on chronic dialysis, respectively. A positive additive interaction (p-value=0.03) was found comparing in-hospital death among patients who received rt-PA vs. those who did not with eGFRs ≥60 to 30-59, and a negative interaction (p-value= -0.03) among patients with eGFRs ≥60 to <30 or on chronic dialysis.

Receiving rt-PA therapy was associated with a weighted relative risk of 0.81 (99% CI 0.61 to 1.08) in eGFR ≥60, 1.07 (99% CI 0.78 to 1.45) in eGFR 30-59, and 0.78 (99% CI 0.38 to 1.58) in eGFR <30 or on chronic dialysis compared to those who did not receive rt-PA therapy (Figure 3). When we compared the weighted relative risk of dying in-hospital comparing patients on their use of rt-PA therapy by eGFR category ≥60 vs. 30-59 and vs. <30 or chronic dialysis, we did not find significant interaction.

The percentage of death at 30 days and 1-year among those who received rt-PA were higher than the in-hospital findings but the trend across eGFR categories was similar (Figure 2d-e). Compared to those with an eGFR ≥60 who received rt-PA, patients with an eGFR 30-59 and <30 or on chronic dialysis and received rt-PA had statistically higher frequency of 30 day and 10-year death (standardized difference >21%). Positive additive interaction was found comparing death among those with an eGFR ≥60 vs. 30-59 and negative additive interaction was found comparing eGFR ≥60 vs. <30 or on chronic dialysis at 30 days and 1-year.

Receiving rt-PA therapy was associated with similar weighted relative risks of death compared to those who did not receive rt-PA at 30 days and 1-year to the in-hospital risks estimates (Figure 3). When we estimated the weighted relative risk of death at 30 days and 1-year comparing patients on their use of rt-PA therapy by eGFR category (≥60 vs. 30-59, ≥60 vs. <30 or chronic dialysis), we did not find a significant interaction. The exception was the relative risk of 1-year death comparing rt-PA usage among patients with an eGFR ≥60 to 30-59 (interaction p-value 0.01). The E-values estimating the strength of the relative risk association that an unmeasured confounder would need to explain the effect of rt-PA on death are available in Appendix O.

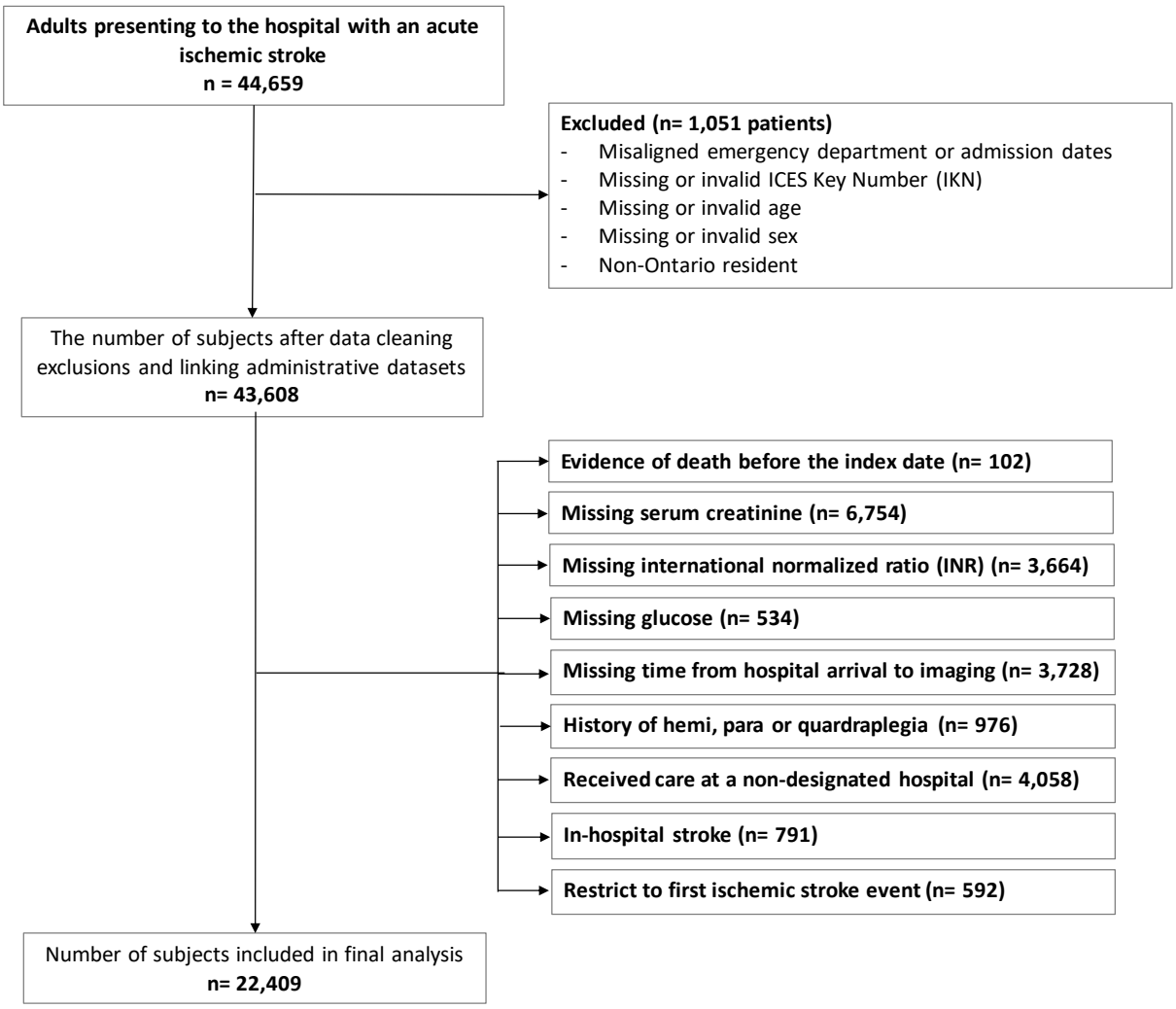


Figure 1. Cohort build flow diagram

Table 2. Acute ischemic stroke characteristics according to recombinant tissue plasminogen activator (rt-PA) therapy by estimated glomerular filtration rate (eGFR) category

	eGFR ≥60 mL/min/1.73m^2			**eGFR 30-59 mL/min/1.73m^2**			**eGFR <30 mL/min/1.73m^2 or chronic dialysis**		
	Total	**rt-PA**	**No rt-PA**	**Total**	**rt-PA**	**No rt-PA**	**Total**	**rt-PA**	**No rt-PA**
	N	N (%)	N (%)	**N**	N (%)	N (%)	**N**	N (%)	N (%)
rt-PA therapy status	**13,214**	2,374 (18.0%)	10,840 (82.0%)	**7,735**	1,429 (18.5%)	6,306 (81.5%)	**1,460**	210 (14.4%)	1,250 (85.6%)
Acute stroke characteristics and healthcare utilization									
Presented to Regional Stoke Centre[†]	**10,569**	1,857 (17.6%)	8,712 (82.4%)	**6,317**	1,175 (18.6%)	5,142 (81.4%)	**1,162**	174 (15.0%)	988 (85.0%)
Presented to District Stroke Centre[†]	**2,645**	517 (19.5%)	2,128 (80.5%)	**1,418**	254 (17.9%)	1,164 (82.1%)	**298**	36 (12.1%)	262 (87.9%)
Stroke symptoms at hospital presentation									
Weakness	**10,529**	2,233 (21.2%)	8,296 (78.8%)	**6,406**	1,373 (21.4%)	5,033 (78.6%)	**1,187**	204 (17.2%)	983 (82.8%)
Speech disturbance	**1,853**	432 (23.3%)	1,421 (76.7%)	**1,495**	338 (22.6%)	1,157 (77.4%)	**271**	48 (17.7%)	223 (82.3%)
Sensory symptoms	**3,741**	642 (17.2%)	3,099 (82.8%)	**1,590**	325 (20.4%)	1,265 (79.6%)	**275**	48 (74.5%)	227 (82.5%)
Dysphagia	**1,041**	212 (20.4%)	829 (79.6%)	**774**	166 (21.4%)	608 (78.6%)	**134**	16 (11.9%)	118 (88.1%)
Monocular blindness	**288**	56 (19.4%)	232 (80.6%)	**157**	45 (28.7%)	112 (71.3%)	**24**	6 (25.0%)	18 (75.0%)
Field defect	**1,421**	452 (31.8%)	969 (68.2%)	**932**	292 (31.3%)	640 (68.7%)	**185**	55 (29.7%)	130 (70.3%)
Other cognitive symptoms[‡]	**2,089**	326 (15.6%)	1,763 (84.4%)	**1,494**	228 (15.3%)	1,266 (84.7%)	**320**	30 (9.4%)	290 (90.6%)
Brainstem or cerebellar signs	**3,159**	407 (12.9%)	2,752 (87.1%)	**1,481**	182 (12.3%)	1,299 (87.7%)	**265**	25 (9.4%)	240 (90.6%)
Headache or seizure	**2,272**	274 (12.1%)	1,998 (87.9%)	**842**	79 (9.4%)	763 (90.6%)	**141**	15 (10.6%)	126 (89.4%)
Time from symptom onset to hospital arrival (hours)									
Median (25th, 75th percentiles)	**5 (1-17)**	1 (1-2)	8 (2-22)	**3 (1-14)**	1 (1-2)	6 (2-17)	**4 (1-15)**	1 (1-2)	6 (2-18)

<4.5 hours	**6,483**	2,293 (35.4%)	4,190 (64.6%)	**4204**	1,389 (33.0%)	2,815 (67.0%)	**751**	208 (27.7%)	543 (72.3%)
≥4.5 hours	**6,582**	47 (0.7%)	6,535 (99.3%)	**3,429**	21 (0.6%)	3,408 (99.4%)	**682**	0 (0.0%)	682 (100.0%)
Time of day									
12am-<8am	**1,584**	262 (16.5%)	1,322 (83.5%)	**828**	117 (14.1%)	711 (85.9%)	**139**	17 (12.2%)	122 (87.8%)
8am-<5pm	**8,000**	1,342 (16.8%)	6,658 (83.2%)	**4,519**	764 (16.9%)	3,755 (83.1%)	**851**	111 (13.0%)	740 (87.0%)
5pm-<12am	**3,629**	770 (21.2%)	2,859 (78.8%)	**2,388**	548 (22.9%)	1,840 (77.1%)	**470**	82 (17.4%)	388 (82.6%)
Time from hospital arrival to imaging									
Median (25th, 75th percentiles) (minutes)	**74 (30-178)**	24 (14-36)	100 (42-206)	**65 (28-163)**	25 (16-37)	90 (37-190)	**72 (30-180)**	25 (15-32)	89 (37-204)
<3.5 hours	**10,533**	2,336 (22.2%)	8,197 (77.8%)	**6,306**	1,408 (22.3%)	4,898 (77.7%)	**1,153**	207 (18.0%)	946 (82.0%)
National Institutes of Health Stroke Scale (NIHSS)[§]									
Median (25th, 75th percentiles)	**5 (2-10)**	11 (7-16)	4 (1-8)	**6 (2-13)**	13 (8-18)	5 (2-11)	**7 (3-14)**	15 (9-19)	6 (2-12)
Uncaptured stroke signs/symptoms (0)	**1887**	16 (0.8%)	1,871 (99.2%)	**792**	8 (1.0%)	784 (99.9%)	**118**	0 (0.0%)	118 (100.0%)
Minor stroke (1-4)	**4338**	232 (5.3%)	4,106 (94.7%)	**2238**	98 (4.4%)	2,140 (95.6%)	**394**	13 (3.3%)	381 (96.7%)
Moderate stroke (5-15)	**5153**	1,405 (27.3%)	3,748 (72.7%)	**3080**	778 (25.3%)	2,302 (74.7%)	**591**	98 (16.6%)	493 (83.4%)
Moderate to severe stroke (16-20)	**1140**	490 (43.0%)	650 (57.0%)	**988**	347 (35.1%)	641 (64.9%)	**198**	59 (29.8%)	139 (70.2%)
Severe stroke (21-42)	**416**	199 (47.8%)	217 (52.2%)	**407**	187 (45.9%)	220 (54.1%)	**85**	39 (45.9%)	46 (54.1%)
Laboratory measurements, median (25th, 75th percentiles)									
Systolic blood pressure	**154 (137-176)**	151 (135-171)	155 (138-177)	**156 (138-178)**	156 (136-177)	156 (138-178)	**150 (130-173)**	150 (132-175)	150 (130-172)
Diastolic blood pressure	**84 (74-95)**	84 (74-95)	84 (74-95)	**80 (70-92)**	81 (70-92)	80 (70-92)	**76 (64-88)**	77 (64-90)	75 (63-87)

International normalized ratio	**1 (1-1)**	1 (1-1)	1 (1-1)	**1 (1-1)**	1 (1-1)	1 (1-1)	**1 (1-1)**	1 (1-1)	1 (1-1)

† Institution types include 1) District stroke centre: A facility that has written stroke protocols for emergency services, emergency department and acute care including: transport and triage protocols; ability to offer thrombolytic therapy, timely computed tomography scanning and expert interpretation; clinicians with stroke expertise; and linkages to rehabilitation and secondary prevention; and 2) Regional stroke centre: A facility that has all the requirements of a district stroke centre, plus neurosurgical facilities and interventional radiology; non-designated hospital: An acute hospital that does not fit the definition or a district or regional stroke centre.
‡ Other cognitive symptoms refer to any deficits in memory, judgment, attention, or reasoning, and include personality changes.
§ National Institutes of Health Stroke Scale (NIHSS) is a measure of stroke-related neurological deficit and severity is categorized as 0: No stroke symptoms, 1-4: Minor stroke, 5-15: Moderate stroke, 16-20: Moderate to severe stroke or 21-42: Severe stroke.

Missingness was not reported for weakness, dysphagia, monocular blindness, other cognitive symptoms, seizure, headache, sensory symptoms, rt-PA route of administration. time of day, time from hospital arrival to imaging, and time from hospital arrival to rt-PA due to cells less than or equal to five. In accordance with ICES privacy policies, cell sizes less than or equal to five cannot be reported.
Standardized differences were calculated comparing rt-PA therapy to no rt-PA therapy for each baseline characteristic across all eGFR categories but are not reported.

Table 3. Recombinant tissue plasminogen activator (rt-PA) therapy characteristics by estimated glomerular filtration rate (eGFR) category

	eGFR ≥60 mL/min/1.73m^2		**eGFR 30-59 mL/min/1.73m^2**		**eGFR <30/chronic dialysis mL/min/1.73m^2**	
	2,374		**1,429**		**210**	
	N	**%**	**N**	**%**	**N**	**%**
Time from hospital arrival to rt-PA						
Median (IQR) (minutes)	68	(51-92)	70	(53-92)	75	(56-96)
<3.5 hours	2,288	96.4%	1,390	97.3%	203	96.7%
≥3.5 to ≤4.5 hours	68	2.9%	34	2.4%	6	2.9%
rt-PA Route of administration						
Intravenous (IV)	2,211	93.1%	1,379	96.5%	204	97.1%
Intravenous (IV) dose, mg						
Median (25th, 75th percentile)	68	(58-79)	63	(54-73)	63	(54-72)
Intra-arterial (IA) dose, mg						
Median (25th, 75th percentile)	8	(5-15)	14	(6-20)	5	(5-12)

Table 4. Tissue plasminogen activator (rt-PA) therapy eligibility assessment based on ICES research and administrative databases

		Exclusion present		Exclusion absent	
rt-PA treatment exclusions		**N**	**%**	**N**	**%**
1	Symptom onset to rt-PA therapy >4.5 hours	10,971	49.0%	11,438	51.0%
2	History of intracranial hemorrhage in previous 6 months	17	0.1%	22,392	99.9%
3	Stroke or serious head trauma or spinal trauma in last 3 months	95	0.4%	22,314	99.6%
4	Recent major surgery, such as cardiac, thoracic abdominal or orthopedic	1,064	4.7%	21,345	95.3%
5	Stroke symptoms due to another non-ischemic acute neurological condition such as seizures with post-ictal Todd's paralysis or focal neurological signs due to severe hypo- or hyperglycemia	0	0.0%	22,409	100.0%
6	Hypertension (blood pressure >185/110)	4,265	19.0%	18,144	81.0%
7	Blood glucose concentration below 2.7 mmol/L or above 22.22 mmol/L	227	1.0%	22,182	99.0%
8	International Normalized Ratio (INR) > 1.7	1,134	5.1%	21,275	94.9%
9	Platelet count <100,000 per cubic millimeter	6	0.0%	22,403	100.0%
10	Any hemorrhage on computerized tomography (CT) or magnetic resonance imaging (MRI)	158	0.7%	22,251	99.3%
11	Mild stroke	7,593	33.9%	14,816	66.1%
12	Severe stroke	1,373	6.1%	21,036	93.9%
13	Anticoagulant 14 days prior to stroke onset	1,779	7.9%	20,630	92.1%
14	Gastrointestinal bleed or urologist visit in previous 21 days	375	1.7%	22,034	98.3%
15	Pregnant or has delivered within 6 weeks of symptom onset	14	0.1%	22,395	99.9%

(1) Exclusions were based on eligibility criteria from the original tissue plasminogen activator randomized control trails[36,40] and the Canadian Stroke Best Practice Recommendations[46] for acute thrombolytic therapy.
(2) Exclusions defined using the Ontario Stroke Registry with "unable to determine" or missing answer types were coded as ineligible.
(3) Patients with missing laboratory values for platelets in the Gamma Dynacare dataset were coded as eligible.
(4) Patients across criteria are not unique, that is, an individual can contribute to >1 criterion.
(5) The following criteria could not be captured using ICES databases: a) Any other condition that could increase the risk of hemorrhage after tPA administration; b) Elevated partial thromboplastin time; c) CT showing early signs of extensive infarction, represented by a score of less than five on the Alberta Stroke Program Early CT Score [ASPECTS], or MRI showing an infarct volume greater than 150 cc on diffusion-weighted imaging; d) Arterial puncture at a non-compressible site in last 7 days; e) Rapidly improving symptoms; f) Symptoms suggestive of subarachnoid hemorrhage (SAH) (Note: symptoms of SAH were not captured because evidence to support this is contested).

Table 5. Crude baseline patient characteristics by recombinant tissue plasminogen activator (rt-PA) treatment status and estimated glomerular filtration rate (eGFR) among a subgroup of patients eligible for rt-PA therapy (N=4,632).

	eGFR ≥60 mL/min/1.73m^2					eGFR 30-59 mL/min/1.73m^2					eGFR <30 mL/min/1.73m^2 or on chronic dialysis				
	rt-PA 1,049		No rt-PA 1,662		Std Diff*	rt-PA 670		No rt-PA 959		Std Diff*	rt-PA 161		No rt-PA 131		Std Diff*
Characteristic	N	%	N	%	%	N	%	N	%	%	N	%	N	%	%
Demographics & characteristics at index															
Age															
Median (25th, 75th percentile)	71	(59-80)	67	(57-77)		80	(73-86)	82	(75-88)		81	(74-87)	84	(78-89)	
18-59	269	25.6%	516	31.0%	**12%**	35	3.6%	19	2.8%	5%	7	5.3%	6	3.7%	8%
60-79	497	47.4%	810	48.7%	3%	435	45.4%	238	35.5%	**20%**	53	40.5%	46	28.6%	**25%**
80+	283	27.0%	336	20.2%	**16%**	487	50.8%	413	61.6%	**22%**	70	53.4%	109	67.7%	**30%**
Sex, female	426	40.6%	690	41.5%	2%	542	56.5%	398	59.4%	6%	83	63.4%	91	56.5%	**14%**
Income quintile															
1 - Lowest	266	25.4%	353	21.2%	**10%**	200	20.9%	177	26.4%	**13%**	28	21.4%	40	24.8%	8%
2	201	19.2%	352	21.2%	5%	196	20.4%	139	20.7%	1%	27	20.6%	36	22.4%	4%
3	207	19.7%	339	20.4%	2%	173	18.0%	114	17.0%	3%	24	18.3%	22	13.7%	**13%**
4	175	16.7%	317	19.1%	6%	187	19.5%	131	19.6%	0%	25	19.1%	34	21.1%	5%
5 - Highest	196	18.7%	297	17.9%	2%	203	21.2%	104	15.5%	**15%**	26	19.8%	27	16.8%	8%
Rural residence	117	11.2%	205	12.3%	3%	109	11.4%	68	10.1%	4%	11	8.4%	16	9.9%	5%
Pre-event residence															
Home	798	76.1%	1343	80.8%	**11%**	767	80.0%	469	70.0%	**23%**	100	76.3%	109	67.7%	**19%**
Other†	25	2.4%	17	1.0%	11%	17	1.8%	39	5.8%	21%	9	6.9%	8	5.0%	8%
Pre-event independence‡															

Independent	381	36.3%	919	55.3%	**39%**	424	44.2%	161	24.0%	**44%**	27	16.8%	47	35.9%	**44%**
Slight to severe disability	145	13.8%	142	8.5%	**17%**	149	15.5%	161	24.0%	**21%**	50	38.2%	36	22.4%	35%
Missing	523	49.9%	601	36.2%	**28%**	386	40.3%	348	51.9%	**23%**	48	36.6%	84	52.2%	**32%**
National Institutes of Health Stroke Scale (NIHSS)[§], Median (25^{th}, 75^{th} percentile)	7	(4-12)	11	(7-16)		12	(8-17)	8	(4-14)		14	(8-19)	10	(5-15)	
Comorbidities															
Estimated glomerular filtration rate	79	(69-91)	80	(69-91)		48	(41-54)	48	(40-54)		24	(20-28)	23	(18-27)	
Charlson Comorbidity Index															
0	423	40.3%	899	54.1%	**28%**	337	35.1%	163	24.3%	**24%**	28	21.4%	21	13.0%	**22%**
1	263	25.1%	452	27.2%	5%	289	30.1%	195	29.1%	2%	26	19.8%	24	14.9%	**13%**
2	153	14.6%	164	9.9%	**14%**	149	15.5%	145	21.6%	**16%**	23	17.6%	37	23.0%	**13%**
≥3	210	20.0%	147	8.8%	**32%**	184	19.2%	167	24.9%	**14%**	54	41.2%	79	49.1%	**16%**
HASBLED Score															
Median (25^{th}, 75^{th} percentile)	2	(1-3)	2	(1-2)		3	(2-3)	3	(2-4)		3	(3-4)	3	(3-4)	
High bleeding risk ≥3	278	26.5%	295	17.7%	**21%**	506	52.8%	373	55.7%	6%	113	86.3%	147	91.3%	**16%**
Chronic dialysis	0	0.0%	0	0.0%	0%	0	0.0%	0	0.0%	0%	11	8.4%	20	12.4%	**13%**
Stroke	201	19.2%	207	12.5%	**18%**	163	17.0%	165	24.6%	**19%**	27	20.6%	36	22.4%	4%
Transient ischemic attack	136	13.0%	143	8.6%	**14%**	111	11.6%	125	18.7%	**20%**	16	12.2%	25	15.5%	**10%**
Atrial fibrillation	147	14.0%	237	14.3%	1%	218	22.7%	164	24.5%	4%	30	22.9%	44	27.3%	**10%**
Coronary artery disease	237	22.6%	323	19.4%	8%	289	30.1%	208	31.0%	2%	44	33.6%	63	39.1%	**11%**
Congestive heart failure	55	5.2%	61	3.7%	7%	94	9.8%	112	16.7%	**20%**	29	22.1%	32	19.9%	5%
Diabetes mellitus	234	22.3%	263	15.8%	**17%**	215	22.4%	183	27.3%	**11%**	48	36.6%	65	40.4%	8%
Hypertension	626	59.7%	936	56.3%	7%	763	79.6%	531	79.3%	1%	112	85.5%	136	84.5%	3%
Venous thromboembolism	24	2.3%	27	1.6%	5%	20	2.1%	10	1.5%	5%	≤5	3.8%	6	3.7%	**14%**

Gastrointestinal bleed	38	3.6%	15	0.9%	**18%**	22	2.3%	29	4.3%	**11%**	≤5	3.8%	10	6.2%	**19%**
Hyperlipidemia	361	34.4%	636	38.3%	8%	437	45.6%	290	43.3%	5%	120	91.6%	141	87.6%	**13%**
Liver disease	22	2.1%	34	2.0%	1%	16	1.7%	12	1.8%	1%	≤5	3.8%	≤5	0.6%	**14%**
Peripheral vascular disease	52	5.0%	36	2.2%	**15%**	53	5.5%	44	6.6%	5%	11	8.4%	16	9.9%	5%
Current smoker	225	21.4%	382	23.0%	4%	96	10.0%	70	10.4%	1%	17	13.0%	7	4.3%	**31%**
Valvular heart disease	38	3.6%	61	3.7%	1%	49	5.1%	29	4.3%	4%	10	7.6%	22	13.7%	**20%**
Valve replacement	18	1.7%	28	1.7%	0%	16	1.7%	14	2.1%	3%	≤5	3.8%	6	3.7%	8%
Pre-event medications (14 days prior to stroke event)															
Antiplatelets	285	27.2%	366	22.0%	**12%**	278	29.0%	242	36.1%	**15%**	46	35.1%	64	39.8%	**10%**

* Standardized difference (Std Diff) ≥10% representing a statistically significant result when comparing rt-PA exposure groups. Statistically significant values are bolded.
† Other pre-event residence includes nursing home, long-term care, retirement home, in-patient rehabilitation, complex continuing care, other acute, other emergency department and other (e.g. homeless).
‡ The level of dependence definition in the Ontario Stroke Registry is based on the patient's ability to manage activities of daily living (ADL) prior to their stroke event. Independence: Patient is fully independent in all ADLs and instrumental ADLs (IADL); Slight Disability: Patient is fully independent in all ADLs but is unable to carry out all IADLs; Moderate Disability: Patient requires help for some ADLs but remains ambulatory (with or without a cane or walker) without the assistance of another person; Moderately Severe Disability: Patient is unable to perform some of their ADLs, is unable to walk but can be left alone for several hours without supervision; Severe Disability: Patient is bedridden, incontinent and requires constant nursing care.
§ National Institutes of Health Stroke Scale (NIHSS) is a measure of stroke-related neurological deficit and severity is categorized as 0: No stroke symptoms, 1-4: Minor stroke, 5-15: Moderate stroke, 16-20: Moderate to severe stroke, or 21-42: Severe stroke.
Missingness was not reported for income quintile, rural residence, pre-event residence, weakness, dysphagia, monocular blindness, other cognitive symptoms, seizure, and headache due to cells less than or equal to five. In accordance with ICES privacy policies, cell sizes less than or equal to five cannot be reported.

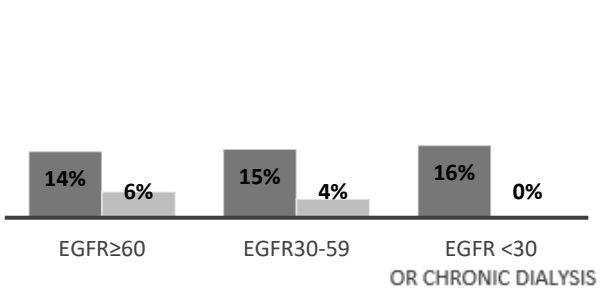
Table 6. Among patients eligible to receive recombinant tissue plasminogen activator (rt-PA), weighted baseline characteristics for those who did and did not receive rt-PA by estimated glomerular filtration rate (eGFR) category (N=1,354)

	eGFR ≥60 mL/min/1.73m^2					eGFR 30-59 mL/min/1.73m^2					eGFR <30 mL/min/1.73m^2 or on chronic dialysis				
	rt-PA 402		No rt-PA 402		Std Diff*	rt-PA 246		No rt-PA 246		Std Diff*	rt-PA <32		No rt-PA <32		Std Diff*
Characteristic	N	%	N	%	%	N	%	N	%	%	N	%	N	%	%
Demographics & characteristics at index															
Age															
Median (25th, 75th percentile)	69	(57-79)	69	(57-79)		81	(74-87)	81	(73-87)		83	(77-89)	84	(76-90)	
60-79	189	47.1%	189	47.1%	0%	101	41.1%	101	41.1%	0%	9	30.6%	9	30.6%	0%
80+	93	23.1%	93	23.1%	0%	137	55.5%	137	55.5%	0%	19	65.0%	19	65.0%	0%
Sex, female	172	42.9%	166	41.3%	3%	140	56.9%	143	58.3%	3%	18	62.8%	18	62.8%	0%
Income quintile															
1 - Lowest	91	22.7%	91	22.7%	0%	60	24.3%	60	24.3%	0%	≤5	17.9%	≤5	17.9%	0%
2	77	19.3%	77	19.3%	0%	52	20.9%	52	20.9%	0%	7	24.9%	7	24.9%	0%
3	83	20.7%	83	20.7%	0%	43	17.3%	43	17.3%	0%	≤5	16.0%	≤5	16.0%	0%
4	73	18.3%	73	18.3%	0%	48	19.6%	48	19.6%	0%	≤5	17.8%	≤5	17.8%	0%
5 - Highest	76	18.8%	76	18.8%	0%	44	17.9%	44	17.9%	0%	6	22.2%	6	22.2%	0%
Rural residence	57	14.3%	51	12.7%	5%	31	12.6%	27	10.9%	5%	≤5	11.8%	≤5	11.8%	0%
Pre-event residence															
Home	305	76.0%	305	76.0%	0%	186	75.4%	186	75.4%	0%	21	72.8%	21	72.8%	0%
Other†	94	23.3%	94	23.3%	0%	60	24.2%	60	24.2%	0%	6	20.7%	6	20.7%	0%
Pre-event independence‡															
Independent	178	44.3%	178	44.3%	0%	80	32.5%	80	32.5%	0%	7	25.1%	7	25.1%	0%

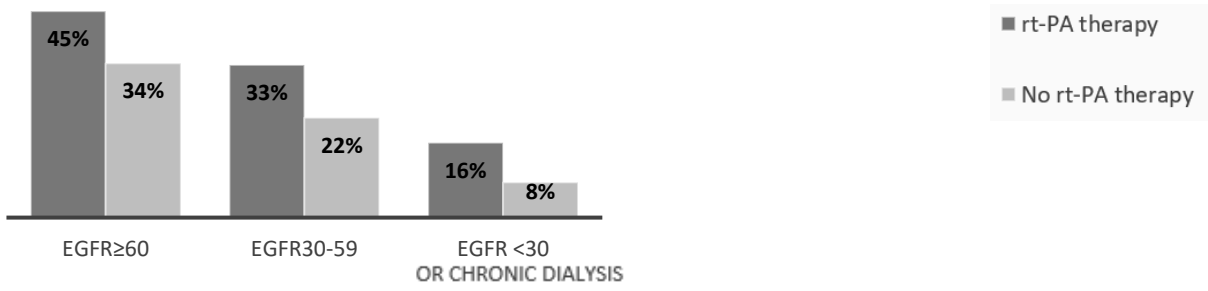
Slight to severe disability	51	12.7%	51	12.7%	0%	55	22.3%	55	22.3%	0%	10	34.5%	10	34.5%	0%
Missing	172	42.9%	172	42.9%	0%	112	45.4%	112	45.4%	0%	12	40.2%	12	40.2%	0%
National Institutes of Health Stroke Scale (NIHSS)[§], Median (25th, 75th percentile)	9	(6-13)	9	(5-15)		10	(7-15)	11	(5-16)		10	(7-17)	11	(7-16)	
Comorbidities															
Estimated glomerular filtration rate	80	(70-91)	79	(69-92)		48	(41-55)	49	(41-54)		23	(20-27)	24	(18-27)	
Charlson Comorbidity Index															
≤2	340	84.6%	340	84.6%	0%	185	75.2%	188	76.4%	3%	16	55.2%	16	55.2%	0%
≥3	61	15.3%	61	15.3%	0%	61	24.8%	57	23.2%	4%	13	44.7%	13	44.7%	0%
HASBLED Score															
Median (25th, 75th percentile)	2	(1-2)	2	(1-2)		3	(2-3)	3	(2-3)		3	(3-4)	3	(3-4)	
High bleeding risk ≥3	88	21.9%	86	21.4%	1%	130	52.8%	130	52.8%	0%	26	89.4%	26	89.4%	0%
Chronic dialysis	0	0%	0	0%	0%	0	0%	0	0%	0%	≤5	6.9%	≤5	6.9%	0%
Stroke	64	15.8%	64	15.8%	0%	52	21.1%	52	21.1%	0%	≤5	18.6%	≤5	18.6%	8%
Transient ischemic attack	47	11.8%	47	11.8%	0%	39	15.8%	39	15.8%	0%	≤5	12.6%	≤5	12.6%	0%
Atrial fibrillation	56	13.9%	59	14.7%	2%	55	22.3%	61	24.8%	6%	7	23.1%	7	23.1%	0%
Coronary artery disease	80	20.0%	92	22.8%	7%	71	29.0%	71	29.0%	0%	11	36.3%	11	36.3%	0%
Congestive heart failure	16	4.0%	15	3.8%	1%	34	13.8%	34	13.8%	0%	7	22.6%	7	22.6%	0%
Diabetes mellitus	80	19.8%	80	19.8%	0%	64	26.0%	64	26.0%	0%	10	35.4%	10	35.4%	0%
Hypertension	232	57.8%	235	58.4%	1%	194	78.9%	199	80.6%	4%	24	83.8%	24	83.8%	0%
Venous thromboembolism	8	2.1%	11	2.7%	4%	≤5	1.9%	≤5	1.9%	0%	≤5	2.9%	≤5	2.9%	0%
Gastrointestinal bleed	8	2.0%	8	2.0%	0%	8	3.4%	8	3.4%	0%	≤5	4.7%	≤5	4.7%	0%
Hyperlipidemia	139	34.7%	139	34.7%	0%	111	45.1%	119	48.4%	7%	14	47.5%	14	47.5%	0%
Liver disease	11	2.7%	8	1.9%	5%	≤5	1.8%	≤5	1.3%	4%	0	1.4%	0	1.4%	0%

Peripheral vascular disease	13	3.2%	13	3.2%	0%	16	6.4%	13	5.4%	4%	≤5	4.4%	≤5	4.4%	0%
Current smoker	92	22.8%	92	22.8%	0%	25	10.3%	25	10.3%	0%	≤5	5.5%	≤5	5.5%	0%
Valvular heart disease	16	4.0%	14	3.5%	3%	14	5.8%	11	4.5%	6%	≤5	9.6%	≤5	9.6%	0%
Valve replacement	7	1.8%	10	2.4%	4%	≤5	1.5%	≤5	2.2%	5%	≤5	4.1%	≤5	4.1%	0%
Pre-event medications (14 days prior to stroke event)															
Antiplatelets	99	24.7%	99	24.7%	0%	81	32.8%	81	32.8%	0%	10	34.4%	10	34.4%	0%

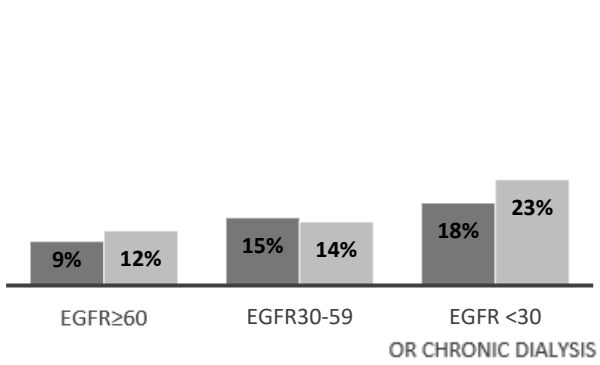
* Standardized difference (Std Diff) ≥10% representing a statistically significant result when comparing rt-PA exposure groups. Statistically significant values are bolded.
† Other pre-event residence includes nursing home, long-term care, retirement home, in-patient rehabilitation, complex continuing care, other acute, other emergency department and other (e.g. homeless).
‡ The level of dependence definition in the Ontario Stroke Registry is based on the patient's ability to manage activities of daily living (ADL) prior to their stroke event. Independence: Patient is fully independent in all ADLs and instrumental ADLs (IADL); Slight Disability: Patient is fully independent in all ADLs but is unable to carry out all IADLs; Moderate Disability: Patient requires help for some ADLs but remains ambulatory (with or without a cane or walker) without the assistance of another person; Moderately Severe Disability: Patient is unable to perform some of their ADLs, is unable to walk but can be left alone for several hours without supervision; Severe Disability: Patient is bedridden, incontinent and requires constant nursing care.
§ National Institutes of Health Stroke Scale (NIHSS) is a measure of stroke-related neurological deficit and severity is categorized as 0: No stroke symptoms, 1-4: Minor stroke, 5-15: Moderate stroke, 16-20: Moderate to severe stroke or 21-42: Severe stroke.
Missingness was not reported for income quintile, rural residence, pre-event residence, weakness, dysphagia, monocular blindness, other cognitive symptoms, seizure and headache due to cells less than or equal to five. In accordance with ICES privacy policies, cell sizes less than or equal to five cannot be reported



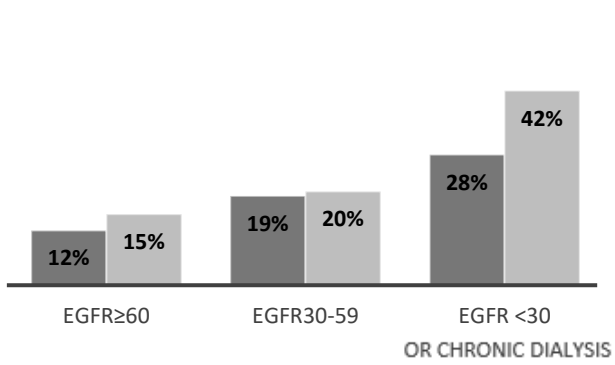
a. Secondary intracranial hemorrhage



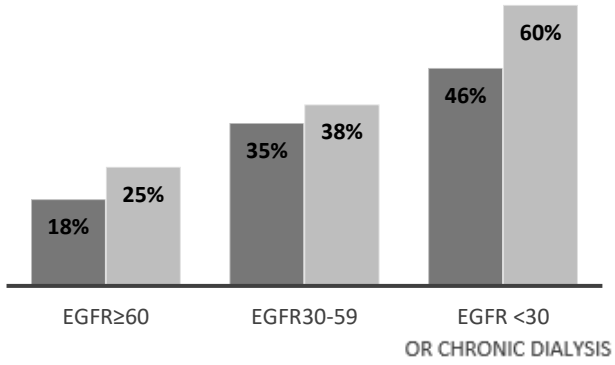
b. Alive and independent (modified Rankin Score 0-2)



c. In-hospital death



d. Death, 30 days



e. Death, 1-year

Figure 2a-e. Weighted percentage of outcomes by recombinant tissue plasminogen activator (rt-PA) therapy and estimated glomerular filtration rate (eGFR) categories

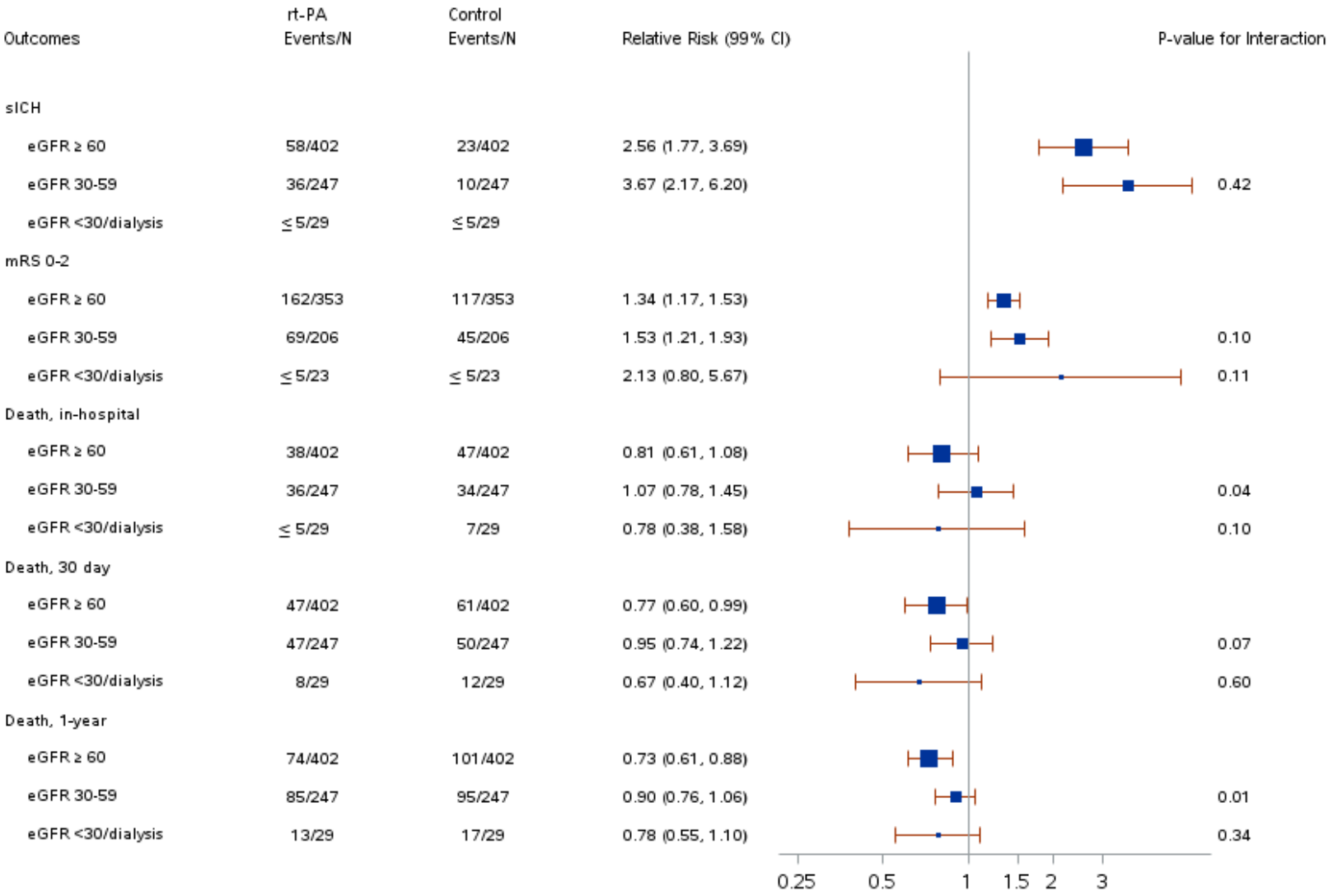


Figure 3. Weighted effects of recombinant tissue plasminogen activator (rt-PA) within categories of estimated glomerular filtration rate (eGFR) (N=1,354)

* Ninety-nine percent confidence intervals were used to account for multiplicity, therefore p-values ≤ 0.01 are considered statistically significant.
† Patients who died prior to hospital discharge were removed from the modified Rankin Scale (mRS) analyses.

Chapter 5

5 Discussion

5.1 Ischemic stroke characteristics according to rt-PA therapy, treatment characteristics and the variation by eGFR category

In our cohort of 22,409 patients presenting to the hospital with ischemic stroke we found that patients were treated with rt-PA similarly across eGFR categories ≥60 and 30-59 (18% to 19%), but only 14% of those with an eGFR <30 mL/min/1.73m^2 or on chronic dialysis received rt-PA therapy. Greater than 82% of the ischemic stroke population across categories of eGFR did not receive rt-PA therapy. At first glance it would appear that those with an eGFR <30 or on chronic dialysis do not receive rt-PA similarly to other eGFR categories. However, these data do not consider rt-PA eligibility. When we assessed each patient's eligibility and restricted the cohort to only those eligible to receive rt-PA, we found that the proportion of those receiving rt-PA increased as eGFR declined from 39% in those ≥60 to 55% in those <30 or on chronic dialysis. Therefore, the declining usage of rt-PA therapy in the total acute ischemic cohort is misleading.

Among those who received rt-PA, most (>96%) were treated within 3.5 hours of stroke symptom onset and there were no significant differences in the medians across eGFR categories. Of those who received rt-PA, a patient's kidney function did not seem to be a barrier to their time to receiving therapy even though patients with severely decreased kidney function or kidney failure can be medically complex. Furthermore, those with reduced renal function exhibited higher NIHSS scores indicating a more severe presentation of stroke symptoms. Unsurprisingly, patients who received rt-PA had a higher median NIHSS score than controls.

5.2 rt-PA eligibility among patients with ischemic stroke

We used research and administrative data to quantify a patient's eligibility to receive rt-PA therapy at the time of hospital presentation for an ischemic stroke in order to limit bias when comparing patients who did and did not receive rt-PA. Many patients were found to be ineligible for rt-PA therapy based on hospital arrival time >4.5 hours after symptom onset and this aligns with the documented reason rt-PA was not administered in the patient hospital medical record. Additionally, unmanaged blood pressure and anticoagulant use was frequently a criterion that indicated ineligibility. Other studies have attempted to estimate a patient's eligibility to receive rt-PA using retrospective data with the intent of understanding how rt-PA treatment could be increased in the ischemic stroke population.[97–100] Delay in arrival time was also found to be the most common avoidable exclusion across these studies.

We found that 21% of ischemic stroke patients were potentially eligible to receive rt-PA and the frequency of therapy was similar across eGFR categories (range 20% to 21%). International estimates show an increased rate of rt-PA therapy use for all patients with ischemic stroke over time ranging from 1% to 7% between 2003 and 2010.[101–103] One reason the frequency of rt-PA treatment is much higher in our study is because we excluded non-designated stroke centres. When included, the percentage of patients with ischemic stroke administered therapy in Ontario was 4% in 2004/05 and 12% in 2012/13.[104] This suggests that the eligibility criteria we used is missing some factor(s) that drive real-world rt-PA utilization in the province.

When we compared those who were eligible for rt-PA using the database-based definition with those who received rt-PA therapy in the real-world we found moderate agreement (reliability). This is likely due, in part, to the subjective nature of clinical decision making despite having the best practice recommendations as guidelines. A physician and patient weigh multiple factors into their decision to treat with rt-PA and this is difficult to capture in a comprehensive manner. Additionally, there were several criteria that we could not capture in ICES databases and this may have contributed to the performance. Most notably is "…any condition that could increase the risk of hemorrhage after rt-PA

administration" which is highly subjective. These findings may suggest that the real-world decision-making process relies on additional factors outside of the eligibility criteria which are likely patient- and physician-centered.

5.3 Risk of secondary ICH by rt-PA exposure within categories of eGFR

Using overlap weighting on the propensity score, we found that the weighted relative risk of secondary ICH was almost four times higher among those who received rt-PA compared to those who did not within eGFR categories ≥60 or 30-59 mL/min/1.73m^2 (relative risk and odds ratio estimates). In a meta-analysis of the rt-PA RCTs, Wardlaw et al. found that the odds ratio of symptomatic ICH within 7 days of rt-PA administration was 3.72 (95% CI 2.98 to 4.64) in the group who received rt-PA up to 6 hours after hospital arrival compared to controls.[40] However, in the group of patients who received rt-PA within 3 hours of arrival, the pooled odds ratio of symptomatic ICH was 4.55 (95% CI 2.92 to 7.09). The smaller magnitude of secondary ICH risk found in our study could be due to differences in case mix which occurs frequently when comparing observational studies to RCTs; usually the general population includes a more diverse and complicated profile of baseline comorbidities but we restricted our analysis to those eligible for rt-PA therapy based on the trials and the best practice recommendations. These criteria are quite comprehensive and more stringent than what was included in the original trials. This potentially gives some indication that the guidelines may reduce the risk of secondary ICH in the eGFR ≥60 population, and perhaps among those with an eGFR <60. An additional consideration is that we were unable to distinguish symptomatic secondary ICH in both exposure groups which resulted in including asymptomatic secondary ICH in our definition. These hemorrhages are clinically less relevant and could contribute to the difference in estimates between studies.

The rt-PA trials and our study sample sizes are relatively small and therefore it is difficult to estimate the true strength of secondary ICH risk, particularly among those with an eGFR <30. In a secondary analysis, Gensicke et al. compared a subgroup of their observational cohort (N= 1,427) by rt-PA exposure and eGFR. They found a higher odds

ratio of symptomatic ICH treated with rt-PA compared to those without rt-PA treatment among those with normal (≥60 mL/min/1.73m^2) and low (<60 mL/min/1.73m^2) eGFR, 5.31 (95% CI 2.3 to 12.1) and 21.3 (95% CI 4.9 to 99.0), respectively, when adjusting for age and NIHSS.[75] This analysis did not account for a patients eligibility to receive rt-PA, i.e. excluding those who, in the real-world would not likely receive rt-PA from the control group. To our knowledge, other data stratifying the rt-PA-secondary ICH association by eGFR category is not available elsewhere.

We found that compared to those who did not receive rt-PA therapy, those who did had a significantly higher relative risk of secondary ICH and the magnitude of this relative risk was higher among those with an eGFR 30-59. From a biological standpoint, there is evidence to suggest that the coagulant gradient is modified by eGFR, although the mechanism behind it is not well established.[52,105,106] There have been a number of hypotheses regarding the mechanisms that could contribute to an increased risk of secondary ICH including platelet dysfunction, other thrombus mechanics[80,106], and endothelial dysfunction such as white matter disease.[73,77] To date, there is no published data investigating the biological factors associated with rt-PA activity in the CKD population.[52] Observational studies have shown an overall increased systemic bleeding risk by eGFR category compared to those with normal to high eGFR, among patients on chronic dialysis, and in kidney transplant recipients.[53,55,63] When we look at the trend in the weighted percentage of secondary ICH comparing rt-PA therapy to controls across eGFR categories it is not significant and the frequency of bleeds is relatively stable (14% to 15%). We tested the weighted relative risk estimates across eGFR categories for interaction, i.e. a difference in weighted relative bleeding risk by rt-PA therapy status at different levels of kidney function, and did not find a statistically significant difference when comparing those with an eGFR ≥60 to those 30-59 mL/min/1.73m^2. Put differently, the weighted relative risk of secondary ICH between those who received rt-PA therapy compared to controls is not statistically different across the eGFR categories reported. This finding is interesting in light of the observational literature on symptomatic ICH in the CKD population who received rt-PA. A meta-analysis of symptomatic ICH among those who received rt-PA and had CKD (eGFR ≥60 vs. <60) found the pooled OR to be 1.56 (95% CI 1.05 to 2.33).[77] The largest observational study to date (n= 44,410), which

was not included in the meta-analysis, found an adjusted odds ratio estimate of 1.0 (95% CI 0.91 to 1.10) comparing those with and without reduced kidney function.[78] Therefore, the estimates of secondary ICH after rt-PA therapy in the observational literature is conflicting among those with CKD. Our study also did not find a significant difference in the relative risk of rt-PA therapy compared to control between those with high to mildly decreased (≥60 mL/min/1.73m^2) and moderately to severely decreased (30-59 mL/min/1.73m^2) kidney function and the E-value for these estimates were quite high (>4.6). Unfortunately, we are lacking the power to show the relative risk among those with an eGFR <30 or on chronic dialysis.

5.4 Disability at hospital discharge

We found that the weighted relative risk of being discharged alive and independent was up to two times higher among patients who received rt-PA therapy compared to controls (relative risk and odds ratio estimates). This protective relative effect increased as eGFR declined, recognizing that there are a low number of events in the lowest eGFR category. In the rt-PA RCT meta-analysis they also observed that use of rt-PA vs. control was associated with a greater chance of leaving the hospital alive and independent (OR 1.17, 95% CI 1.06 to 2.38) up to 6 hours after receiving rt-PA, and 1.56 (95% CI 1.28 to 1.90) up to 3 hours after receiving rt-PA.[40] Compared to our eGFR ≥60 group (OR_w 1.62, 99% CI 1.08 to 2.41), this study provides additional evidence of a benefit in receiving rt-PA therapy in terms of functional status at discharge, which increases as eGFR declines. Furthermore, our E-value estimate would suggest an unmeasured confounder would need a relative risk of 2.01 to completely explain away our estimated effect (eGFR ≥60 category). The most benefit appears to be among the eGFR <30 or on chronic dialysis (RR_w 2.11) even though the NIHSS scores in the weighted cohort were similar across all rt-PA and control groups (scores ranging from 9 to 11, i.e. moderate stroke severity). Gensicke et al. estimated the odds ratio of a poor outcome defined as mRS 3-6 at 3 months in a subgroup analysis in an observational study. When comparing those by tr-PA status with low eGFR (<60 mL/min/1.73m^2), they found that the adjusted odds ratio of poor outcome were higher (1.79, 95% CI 1.41 to 2.25) among those who received rt-PA than controls. Those with normal eGFR (60 to 120 mL/min/1.73m^2) who received rt-PA

had lower adjusted odds ratio of a poor outcome (0.77, 95% CI 0.63 to 0.94) than controls.[75] As mentioned previously, these results were only adjusted for age and NIHSS and a patient's eligibility for rt-PA was not considered.

In the interaction analysis comparing the weighted relative risk across eGFR categories we found no statistically significant differences in the relative risk estimates. However, among those who received rt-PA it is clear that the risk of being discharged alive and independent is different for someone within an eGFR ≥60 compared to <30 or on chronic dialysis.–There is a dose response relationship; as eGFR declined the weighted rt-PA therapy groups less frequently observed a good outcome when comparing patients with similar exposure status. Obviagele et al. found a similar trend across eGFR categories among those who received rt-PA; as kidney function declined, the percentage of disability at discharge increased.[78] This graded relationship is not unique to stroke and has also been shown in studies estimating the risk of major hemorrhage, death, and cardiovascular disease.[53,56,107,108] The pooled estimate of poor outcome in Jung et al. found no difference between those with an eGFR ≥60 compared to <60 (OR 1.16, 95% CI 0.95 to 1.43) but noted that there was significant heterogeneity across studies.[77] The remainder of the observational studies report disability by kidney function (eGFR ≥60 vs. <60) in the rt-PA population and provide conflicting estimates of the odds ratio of a poor outcome (mRS 2-6 or 3-6).[68,70,75,76,82,109]

5.5 Death in-hospital, 30 days and 1-year

We found that 9%, 15% and 18% of patients with an eGFR of ≥60, 30-59 and <30 mL/min/1.73m^2 or on chronic dialysis, respectively, died in-hospital after rt-PA treatment compared to 12%, 14% and 23% of those who did not receive rt-PA (weighted). Within eGFR categories, there was no difference in the relative risk of in-hospital death between those who received rt-PA therapy and those who did not. In the meta-analysis of the rt-PA clinical trials, they found the odds ratio of death after 7 days from rt-PA therapy to be 0.93 (95% CI, 0.73 to 1.18) among those treated with rt-PA within 3 hours compared to controls.[40] Our weighted odds ratio estimate (0.79, 99% CI 0.44 to 1.43) shows a comparable odds ratio of death. Patients with ischemic stroke in our weighted cohort had

a similar median hospital length of stay across eGFR categories, 7 to 8 days, and most were treated within 3.5 hours of symptom onset. We found the magnitude of benefit to be greater, but our weighted estimates produced a low number of events which may be a contributing factor to this difference. It should be noted that Wardlaw et al. cited significant heterogeneity across RCTs for the death outcomes.[40] As previously mentioned, our study eligibility criteria are more extensive than the trails and this may also contribute to the lower death estimates.

As the number of events increased in our 30 day and 1-year death estimates, most eGFR categories exhibited no difference in the relative risk of death in these extended time intervals across eGFR categories. Wardlaw et al.'s meta-analysis results for long-term death (trials ranged from 4 weeks to 6 months) found a pooled odds ratio of 1.06 (95% CI 0.94 to 1.20).[40] Most of our results were not statistically significant, though most were in favour of rt-PA therapy within categories of eGFR, i.e. the relative risk and odds ratio of death was lower among those who received rt-PA and had comparable kidney function.

For all death endpoints, our interaction estimates of the differences in relative risk between exposure groups suggest that, for the most part, those that receive rt-PA therapy, and those that do not, do similarly across eGFR categories. However, the overall risk of death is not the same for someone who received rt-PA with an eGFR ≥60 to an eGFR <30 mL/min/1.73m^2 or on chronic dialysis. Obviagele et al. found that the adjusted odds ratio of in-hospital death among those that received rt-PA by eGFR category increased as kidney function declined, ranging from 1.09 (95% CI 0.97 to 1.22) (eGFR ≥60) and 2.07 (95% CI 1.59 to 2.69) (eGFR <15).[78] Observational data comparing those who received rt-PA therapy by their kidney function (≥60 vs. <60 mL/min/1.73m^2) found mixed results on the odds ratio of death (in-hospital and 3 months). In a meta-analysis comparing patients with eGFR ≥60 vs. <60, the pooled odds ratio of death (in-hospital and 3 month) among those who received rt-PA was 1.70 (95% CI 1.03 to 2.81) but they reported significant heterogeneity (p=0.00001).[77]

5.6 Limitations

We recognize that there are some study limitations. First, the gold standard for estimating the safety and efficacy of rt-PA by kidney function should be done using an RCT design but this is unlikely due to costs for a relatively small population and ethical considerations in light of the potential benefit. Instead we used propensity score and the overlap weighting method to mimic aspects of an RCT design and to adjust for confounding due to extreme differences between exposure groups. Despite this, there is still some level of residual confounding in our estimates. We used the E-value to assess the degree of confounding to which the results would be altered and most of our estimates were robust.

Second, some of the ICES databases we used were not created for the purposes of research, e.g. the Discharge Abstract Database and the Registered Persons Database, and this may result in residual and unmeasured confounding as administrative data is limited by the information collected. That said, the Ontario Stroke Registry, of which most of our study was based, was created with the intent of enriching the administrative stroke care data in Ontario for the purpose of research and monitoring and should reduce the amount of information bias and residual confounding.

Third, attempting to estimate a patient's eligibility to receive rt-PA proved to be challenging and restricted our sample size. Although many of the eligibility criteria, from RCTs and the Canadian Stroke Best Practice Guidelines, were quantifiable using research and administrative data, the reliability of database-based eligibility was moderate when compared against real-world use of rt-PA therapy. Therefore, misclassification bias may be present when attempting to categorize rt-PA eligibility. There were six eligibility criteria that we were not able define using administrative data. This could result in some misclassification for the propensity to receive rt-PA therapy and alter our estimates of the outcomes of rt-PA vs. no rt-PA.

We cannot make inferences about the entire ischemic stroke population in Ontario because our cohort does not include those who received care at a non-designated

(community) hospital or those not included in the in the Ontario Stroke Audit sample. Furthermore, our sample size declines with eGFR as does the precision of our estimates and this impacts the strength of understanding of the outcomes among patients with severely decreased function and kidney failure.

5.7 Interpretation

We found a high relative risk of secondary ICH among those who received rt-PA compared to those who did not in eGFR categories ≥60 and 30-59 mL/min/1.73m^2. However, those who received rt-PA were more likely to be alive and independent compared to controls within all eGFR categories. This benefit increased as eGFR declined. Compared to those who received rt-PA within eGFR categories, the relative risk of death was almost always higher for who did not. Recognizing that we had a small sample/events in the eGFR <30 or on chronic dialysis group which impacts the precision of these estimates for all outcomes. Generally, the benefits (less disability and death) and risks (secondary ICH) of rt-PA therapy compared to controls are similar when comparing those with an eGFR ≥60 to other categories of eGFR except death at 1-year where eGFR is 30-59 mL/min/1.73m^2. Therefore, a patient's kidney function may not impact how rt-PA therapy performs compared to controls with similar kidney function. However, the frequency of an outcome across eGFR categories appears to be markedly different when comparing those with normal kidney function (≥60 mL/min/1.73m^2) to those with reduced kidney function (<60 mL/min/1.73m^2) with the same exposure (i.e. received rt-PA therapy). Differences in the risk of our outcomes across eGFR may be more strongly associated with kidney function than rt-PA therapy; additional research to understand this relationship is necessary. A large multi-centre RCT to further investigate the safety and efficacy of rt-PA in the chronic kidney disease population who suffer an ischemic stroke would provide better estimates of treatment effects but may never be done.

5.8 Generalizability

We restricted our analysis to those who received care at a Regional or District Stroke Centre in Ontario so our findings may not be applicable to those that receive care in non-

designated facilities. However, the majority of patients with an acute stroke in the province access care at either a Regional or District Stroke Centre. The multivariable analysis was restricted to those who were eligible to receive rt-PA based on research and administrative databases which was found to have moderate agreement. Furthermore, these findings would not extend to those who do not meet the recommended criteria for receiving rt-PA. These findings may not be generalizable to other ischemic stroke populations in other regions due differences in populations.

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Appendices

Appendix A. Canadian Stroke Best Practice Recommendations for Acute Thrombotic Therapy with Intravenous Alteplase (recombinant tissue plasminogen activator)

Box 5B Criteria for Acute Thrombolytic Therapy with Intravenous Alteplase

Refer to Section 4.2 and Box 4A for detailed recommendations on neuroimaging-based selection criteria

These criteria are designed to guide clinical decision-making; however, the decision to use alteplase in these situations should be based on the clinical judgment of the treating physician. The relative benefits of alteplase therapy versus any potential risks or contraindications should be weighed on an individual basis.

IV alteplase Treatment Inclusion Criteria

- ❑ Diagnosis of ischemic stroke causing disabling neurologic deficit in a patient who is 18 years of age or older.
  - For adolescents, decision to administer alteplase should be based on clinical judgment, presenting symptoms, and patient age; and, if possible, consultation with a pediatric stroke specialist.
- ❑ Time from last known well (onset of stroke symptoms) less than 4.5 hours before alteplase administration. * For patients beyond 4.5 hours refer to Section 5.1 Clinical considerations for more information..

Absolute Exclusion Criteria

- ❑ Any source of active hemorrhage or any condition that could increase the risk of major hemorrhage after alteplase administration.
- ❑ Any hemorrhage on brain imaging.

Relative Exclusion Criteria (requiring clinical judgement based upon the specific situation)

Historical

- ❑ History of intracranial hemorrhage.
- ❑ Stroke or serious head or spinal trauma in the preceding three months.
- ❑ Major surgery, such as cardiac, thoracic, abdominal, or orthopedic in the preceding 14 days. Risk varies according to the procedure.
- ❑ Arterial puncture at a non-compressible site in the previous seven days.

Clinical

- ❑ Symptoms suggestive of subarachnoid hemorrhage.
- ❑ Stroke symptoms due to another non-ischemic acute neurological condition such as seizure with post-ictal Todd's paralysis or focal neurological signs due to severe hypo- or hyperglycemia.
- ❑ Hypertension refractory to aggressive hyperacute antihypertensive treatment such that target blood pressure less than 180/105 cannot be achieved or maintained. Blood pressure should be treated rapidly and aggressively in order to minimize delays to thrombolysis.
- ❑ Patient currently prescribed and taking a direct non-vitamin K oral anticoagulant (DOAC). *Refer to Section 5.2 clinical considerations for additional information.*

CT or MRI Findings

- ❑ CT showing early signs of extensive infarction

Laboratory

- ❑ Blood glucose concentration below 2.7 mmol/L or above 22.2 mmol/L.
- ❑ Elevated activated partial-thromboplastin time.
- ❑ International Normalized Ratio greater than 1.7.
- ❑ Platelet count below 100,000 per cubic millimetre.

Footnote: The clinical criterion on the use of a direct non-vitamin K oral anticoagulant (DOAC) was not part of the eligibility criteria during the study period (April 1, 2002 to March 31, 2013) and was not included in this study.

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And to: Emily Sternberg, General Counsel
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HEART AND STROKE FOUNDATION OF CANADA

[redacted]

Name: Dominique Mongeon
Title: Intellectual Property Manager

SARAH BOTA

[redacted]

Name: Sarah Bota (Meyer)
Title: Student, MSc candidate

Appendix B. Checklist of recommendations for reporting of observation studies using the Reporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement

	Item No	STROBE items	RECORD items	Reported
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract. (b) Provide in the abstract an informative and balanced summary of what was done and what was found.	(1.1) The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. (1.2) If applicable, the geographic region and time frame within which the study took place should be reported in the title or abstract. (1.3) If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Title page
Introduction				
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported.		Introduction
Objectives	3	State specific objectives, including any prespecified hypotheses.		Objectives

Methods				
Study design	4	Present key elements of study design early in the paper.		Methods
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection.		Methods
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up. (b) For matched studies, give matching criteria and number of exposed and unexposed.	(6.1) The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. (6.2) Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. (6.3) If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	Methods

Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	(7.1) A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Methods
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group.		Methods
Bias	9	Describe any efforts to address potential sources of bias.		Methods
Study size	10	Explain how the study size was arrived at.		Methods
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why.		Methods
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding. (b) Describe any methods used to examine subgroups and interactions.		Methods

		(c) Explain how missing data were addressed. (d) If applicable, explain how loss to follow-up was addressed. (e) Describe any sensitivity analyses.		
Data access and cleaning methods		N/A	(12.1) Authors should describe the extent to which the investigators had access to the database population used to create the study population. (12.2) Authors should provide information on the data cleaning methods used in the study.	Methods
Linkage		N/A	(12.3) State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	Methods
Results				
Participants	13	(a) Report numbers of individuals at each stage of study--e.g. numbers potentially eligible, examined for eligibility, confirmed	(13.1) Describe in detail the selection of the persons included in the study (i.e., study population selection), including	Results

		eligible, included in the study, completing follow-up, and analyzed. (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram.	filtering based on data quality, data availability, and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	
Descriptive data	14	(a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders. (b) Indicate number of participants with missing data for each variable of interest. (c) Summarize follow-up time (e.g. average and total amount).		Results
Outcome data	15	Report numbers of outcome events or summary measures over time.		Results
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g. 95% confidence interval). Make clear which confounders were adjusted for and why they were included.		Results

		(b) Report category boundaries when continuous variables were categorized. (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period.		
Other analyses	17	Report other analyses done (e.g. analyses of subgroups and interactions, and sensitivity analyses).		Results
Key results	18	Summarize key results with reference to study objectives.		Discussion
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	(19.1) Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Discussion
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.		Discussion

Generalizability	21	Discuss the generalizability (external validity) of the study results.		Discussion
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based.		Discussion
Accessibility of protocol, raw data, and programming code		N/A	(22.1) Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Appendices

*Benchimol et al. [87]

Appendix C. Ontario Stroke Registry sampling strategies

The Ontario Stroke Audit (OSA) is a population-based chart abstraction project that occurs approximately every two years that started in 2002 and continued until 2013. Each audit year, a random sample of patients visiting an emergency department or who are admitted with a suspected stroke or transient ischemic attack are generated at ICES based on International Classification of Disease 10th version Canadian edition (ICD-10-CA) codes and each patient's medical record is audited based on this case list. The Regional Stroke Centre data consisted of prospective and retrospective data collection at the regional facilities between 2001 and 2012. One hundred percent the suspected stroke and TIA cases were captured at participating centres.

The sampling strategies for each audit and stroke centre data collection year are as follows:

Fiscal Year	Regional Stroke Centre Sampling Strategy	Ontario Stroke Audit Sampling Strategy
2001/2002	Prospective chart abstraction at 21 sites. Random sample of eligible patients (N=1,372). Consent required	No OSA data collection
2002/03	Prospective chart abstraction at 24 sites. 20 stroke centres and 4 Telestroke sites.	All Ontario hospitals with >10 stroke admissions in a year. Pediatric and psychiatric hospitals were excluded

	Random sample of eligible patients (N=1,652). Consent required	20% random sample selected from all eligible cases N=3,534
2004/05	Hybrid of prospective and retrospective chart abstraction. 10 stroke centres and 3 Telestroke sites. All suspected stroke and transient ischemic attack events.	All Ontario hospitals with >10 stroke admissions in a year. Pediatric and psychiatric hospitals were excluded 20% random sample selected from all eligible cases N=5,032
2008/09	Hybrid of prospective and retrospective chart abstraction. 10 stroke centres and 3 Telestroke sites. All suspected stroke and transient ischemic attack events.	All Ontario hospitals with >10 stroke admissions in a year. Pediatric and psychiatric hospitals were excluded 20% random sample selected from all eligible cases N=4,363
2010/11	Hybrid of prospective and retrospective chart abstraction.	All Ontario acute care hospitals with >10 stroke admissions per year.

	10 stroke centres and 3 Telestroke sites. All suspected stroke and transient ischemic attack events.	Psychiatric hospitals were excluded. 100% of eligible events at designated stroke centres and Telestroke sites, and a 30% random sample of eligible cases at all other non-designated sites. N=14,540
2012/13	Hybrid of prospective and retrospective chart abstraction. 10 stroke centres and 3 Telestroke sites. All suspected stroke and transient ischemic attack events.	All Ontario hospitals with >30 stroke admissions in a year. Pediatric and psychiatric hospitals were excluded. 100% of eligible events at designated stroke centres and Telestroke sites, and a 50% random sample at high-volume non-designated sites (>100 cases per year) and 30% random sample at low-volume non-designated sites (<100 cases per year) N=14,439

Appendix D. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Equation

The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation[88] for converting serum creatinine to estimated glomerular filtration rate:

$$\text{CKD-EPI} = 141 \times \min(\text{Scr}/\kappa, 1)^{\alpha} \times \max(\text{Scr}/\kappa, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018\ [\text{if Female}] \times 1.159\ [\text{if African American}]$$

Where:

κ = 0.7 for females and 0.9 for males,

α = -0.329 for females and -0.411 for males,

min = the minimum of Scr/κ or 1,

max = the maximum of Scr/κ or 1.

NOTE: Race component of the formula was not used for the analyses, as race is not available in all years of the OSR datasets or in other administrative databases held at ICES.

Appendix E. Precision of kidney function measurements

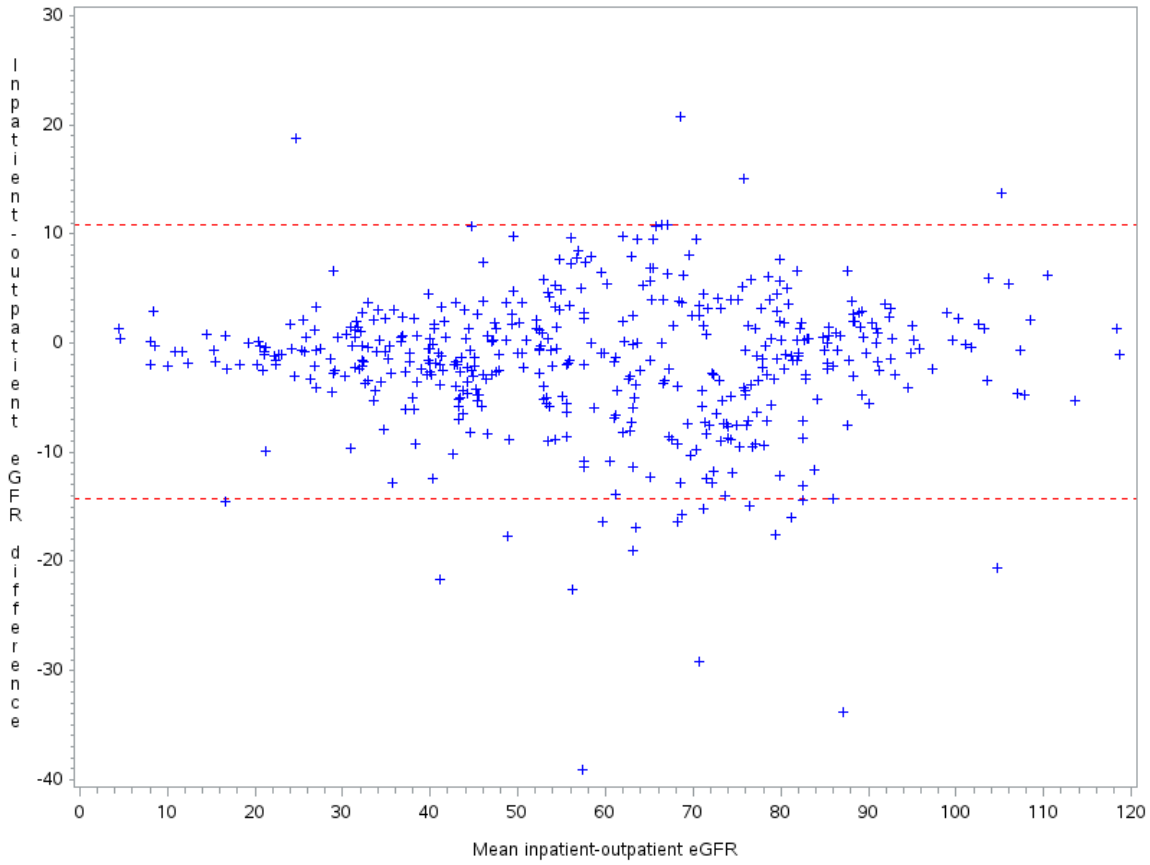
We tested the agreement of baseline estimated glomerular filtration rate (eGFR) found in the OSR at the time of the acute ischemic stroke to outpatient eGFR found in other laboratory sources (Gamma Dynacare Medical Laboratories) to determine whether acute eGFR after an ischemic stroke is a good approximation of stable eGFR. First, serum creatinine (SCr) from both databases were converted to eGFR using the CKD-EPI equation (Appendix C). We established stable kidney function in the outpatient population by requiring evidence of at least two outpatient eGFR values for each patient separated by ≥3 months to <1 year and within 5 mL/min/1.73m^2 or ≤5% of each other.[1,110] The mean value of these two results was used to represent stable outpatient kidney function. We then found the first hospital-based eGFR value done at the time of the acute stroke, within 7 and 365 days of the most recent prior outpatient eGFR value. The distribution of eGFRs was calculated by inpatient and outpatient status. All the eGFRs were then sorted into KIDGO kidney function categories. We calculated percent agreement, Cohen's kappa statistic, and p-values, along with corresponding 95% confidence intervals. A Bland-Altman plot was also generated to assess agreement between to two groups within eGFR categories.

Results

Of the 20,409 patients with ischemic stroke in our cohort, 478 had evidence of kidney function defined as two outpatient SCr laboratory values separated by ≥3 months to 1 year, within 5 mL/min/1.73m^2 or ≤ 5% of each other. The median (25th, 75th percentiles) eGFR among those with an inpatient and median of mean outpatient eGFR was 56 (39,75) and 59 (43,81), respectively. There were 384 instances of agreement and 94 instances of disagreement within eGFR categories. Agreement was defined as both eGFR measurements in the same KIDGO category (≥60, 30-59, <30 mL/min/1.73m^2). When we calculated the percent agreement of mean outpatient versus inpatient eGFR, we found that 80% (95% CI 77 to 84) of laboratory tests agreed within categories of KDIGO eGFR. When we calculated the weighted kappa, we found substantial agreement between inpatient and mean outpatient eGFR values (0.71, 95% CI 0.66 to 0.77). Finally, we assessed the two methods of eGFR measurement using the Pearson's correlation

coefficient and a Bland-Altman correlation plot. We found that inpatient and mean outpatient eGFR are equally precise (Pearson's correlation coefficient= -0.03, p-value= 0.49) and reasonable agreement based on visual inspection of the Bland-Altman correlation plot (Figure E1).

Figure E1. Bland-Altman correlation plot testing the agreement between inpatient and mean outpatient estimated glomerular filtration rate



Appendix F. Baseline characteristic concept definitions

Variable	Database	Variable/Codes
Age	Ontario Stroke Registry (OSR)	AGE
Sex	OSR	SEX
Residential status	RPDB	PSTLYEAR
Residence type	OSR	ER_REGISTRYARRFROM
Index year	OSR	FYEAR
Institution type	OSR	OSACLASS
Time from symptom onset to hospital arrival (mins)	OSR	ER_HOSPARRIVAL
Arrival time	OSR	ER_AFRHTIME
Time from hospital arrival to first brain scan (min)	OSR	DOOR2SCAN_MIN

Serum creatinine (SCr) (µmol/L) on hospital arrival	OSR	EI_CREAT
Glucose (mmol/L) on hospital arrival	OSR	EI_GLUCOSE
rt-PA therapy status	OSR	EI_THROMBOLYSIS
Reason rt-PA not given	OSR	EI_NOTPAREASONCONTRAINDICATION EI_NOTPAREASONDELAYEDDECISION EI_NOTPAREASONMDDECISION EI_NOTPAREASONREFUSED EI_NOTPAREASONTOOLATE EI_NOTPAREASONTOOMILD EI_NOTPAREASONTOOSEVERE EI_NOTPAREASONOTHER
Door to needle time (minutes)	OSR	DOOR2TPA_MIN
Route	OSR	EI_ROUTE

Dose (mg)		OSR	EI_IVDOSE EI_IADOSE
Initial symptoms		OSR	SD_WEAKNESS SD_APHASIA SD_DYSARTHRIA SD_DYSPHAGIA SD_MONOCBLIND SD_FIELDDEFECT SD_COGNITIVE SD_BRAINSTEM SD_SEIZURE SD_HEADACHE
Stroke Severity (at admission)	Canadian Neurological Scale (CNS)	OSR	SD_CNSSCORE
	National Institutes of Health Stroke Scale (NIHSS)	OSR	SD_NIHSCORE
Systolic blood pressure (SBP) (mm HG)		OSR	EI_SBP

Diastolic BP (DBP) (mm HG)	OSR	EI_DBP
International Normalized Ratio (INR)	OSR	EI_INR
Pre-event independence	OSR	PMH_PREEVENTINDEPEND
Diabetes	OSR	PMH_DIABETES
Hypertension	OSR	PMH_HYPERTENSION
Hyperlipidemia	OSR	PMH_HYPERLIPIDEMIA
Smoking history	OSR	PMH_SMOKERTYPE
History of stroke	OSR	PMH_STROKE
History of TIA	OSR	PMH_TIA
Congestive heart failure/pulmonary edema	OSR	PMH_PULMEDEMA

Peripheral vascular disease	OSR	PMH_PERIPHERALDISEASE
Atrial fibrillation or flutter	OSR	PMH_ATRIALFIB
Valvular heart disease	OSR	PMH_VALVULAR
Valve replacement	OSR	PMH_VALVE
Venous thromboembolism	OSR	PMH_DEEPVEIN
Coronary artery disease	OSR	PMH_CAD
GI bleed	OSR	PMH_GIBLEED
Chronic liver disease	CIHI-DAD Source ☒ All Institution types ☒ Acute care	International Classification of Disease (ICD) 9th version: 4561, 4562, 070, 5722, 5723, 5724, 5728, 573, 7824, V026, 571, 2750, 2751, 7891, 7895

	Include suspected/questionable diagnoses? ☒ No NACRS Source ☒ Emergency Department visits Include planned visits ☒ No OHIP Claim Type ☒ NONLAB	ICD10: B16, B17, B18, B19, I85, R17, R18, R160 R162, B942, Z225, E831, E830, K70, K713, K714, K715, K717, K721, K729, K73, K74, K753, K754, K758, K759, K76, K77 Ontario Health Insurance Plan (OHIP) fee: Z551, Z554 OHIPdx: 571, 573, 070
HAS BLED bleeding risk score	OSR	HASBLED
Charlson Comorbidity Index (CCI)	OSR	CHARLSON

Anticoagulant prior to stroke event	OSR Ontario Drug Benefit Database (ODB)	MPR_ANTICOAG
Antiplatelet	OSR ODB	MPR_ANTIPLT
Warfarin	OSR ODB	MPR_WARFARIN

Appendix G. Determining the presence of acute kidney injury at admission

To estimate the proportion of acute kidney injury (AKI) in our acute stroke inpatient population we captured patient's inpatient SCr for their acute stroke event and an outpatient SCr within 7 and 365 days prior.[111,112] A single outpatient SCr was used because we found the SCr laboratory measurements to be a stable measure of kidney function in our cohort. Patients with an eGFR <15 mL/min/1.73m^2 or on chronic dialysis were removed from this analysis. Patients were classified into KIDGO categories of AKI, which groups patients into three stages (1 to 3) or no AKI based on a change from their outpatient to inpatient SCr.[113]

Results

Starting with the kidney function precision cohort (n=478) we excluded 12 patients based on kidney function <15 mL/min/1.73m^2 or on chronic dialysis. We found that most patients with stroke (87%) did not have any evidence of AKI when presenting to their stroke hospitalization. Among those with AKI, 13% were classified as having stage 1-3, 2% as 2-3 and less than 1% as stage 3.

Appendix H. Recombinant tissue plasminogen activator therapy eligibility criteria definitions

The eligibility criteria we used was gathered based on a compilation of the Canadian Stroke Best Practice Recommendations Hyper-acute ischemic stroke treatment and criteria used in the randomized controlled trials (RCT) of recombinant tissue plasminogen activator (rt-PA) versus control. All the criteria in the Canadian Stroke Best Practice Recommendations were incorporated if it was feasible to define within ICES databases. Criteria obtained from the RCTs was included if it was used in two or more trials.

Study Criteria	Sources
Symptom onset to rt-PA therapy >4.5 hours	Canadian Stroke Best Practice Recommendations (CSBPR)[46], [114–116]
History of intracranial hemorrhage in previous 6 months	CSBPR[46]
Stroke or serious head trauma or spinal trauma in last 3 months	CSBPR[46] RCT[114–120]
Recent major surgery, such as cardiac, thoracic, abdominal or orthopedic	CSBPR[46] RCT[114–120]
Stroke symptoms due to another non-ischemic acute neurological condition such as seizures with post-ictal Todd's paralysis or focal neurological signs due to severe hypo- or hyperglycemia	CSBPR[46]
Hypertension (blood pressure <185/110)	CSBPR[46] RCT[114–120]

Blood glucose concentration below 2.7 mmol/L or above 22.22 mmol/L	CSBPR[46]
International Normalized Ratio (INR) > 1.7	CSBPR[46]
Platelet count <100,000 per cubic millimeter	CSBPR[46]
Any hemorrhage on computerized tomography (CT) or magnetic resonance imaging (MRI)	CSBPR[46]
Mild stroke	RCT[114–120]
Severe stroke	RCT[114–120]
Anticoagulant prior to stroke onset	RCT[115,116,119,120]
Gastrointestinal bleed or urologist visit in previous 21 days	RCT[114–120]
Pregnant or has delivered within 6 weeks of symptom onset	RCT[114,116]

Canadian Stroke Best Practice recommendations that could not be measured using ICES data holdings:

(1) “Any other condition that could increase the risk of hemorrhage after rt-PA administration”;

(2) “Elevated partial thromboplastin time”;

(3) “CT showing early signs of extensive infarction, represented by a score of less than five on the Alberta Stroke Program Early CT Score [ASPECTS], or MRI showing an infarct volume greater than 150 cc on diffusion-weighted imaging”;

(4) “Arterial puncture at a non-compressible site in last 7 days”; and

(5) “Rapidly improving symptoms”

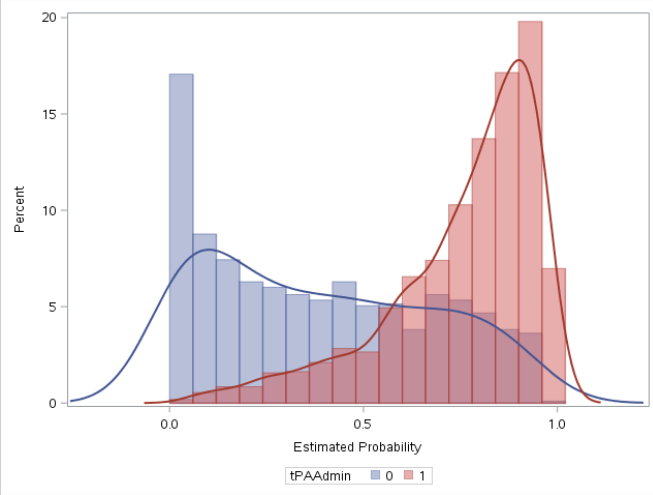
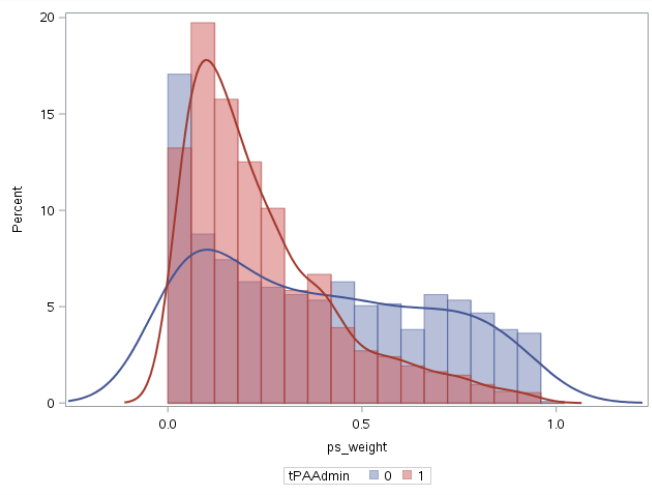
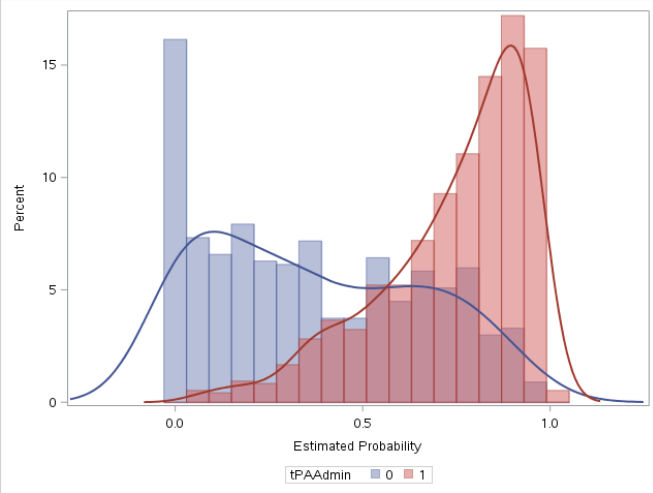
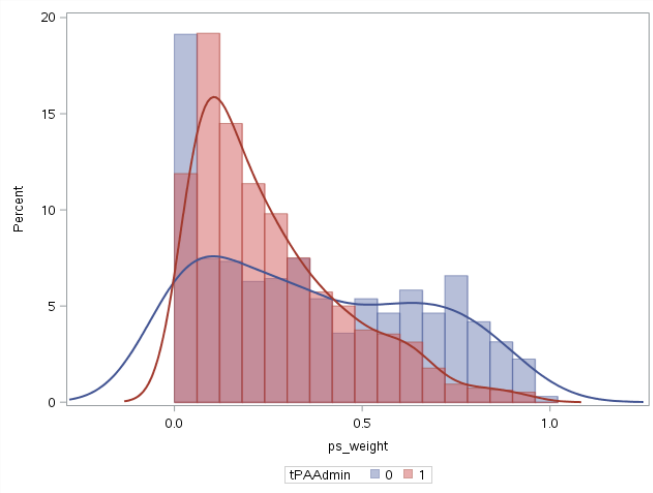
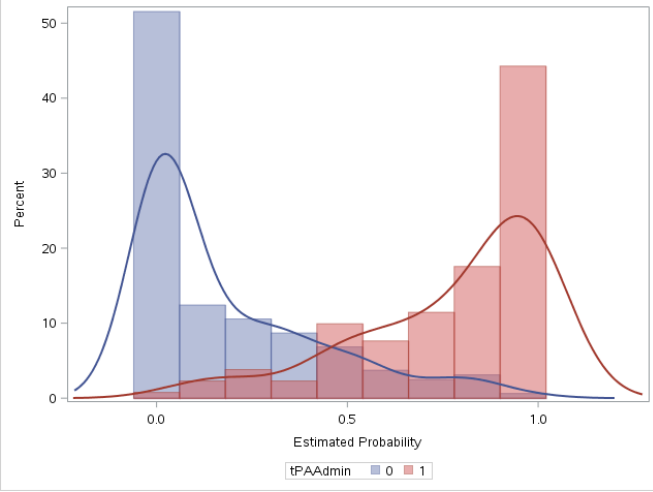
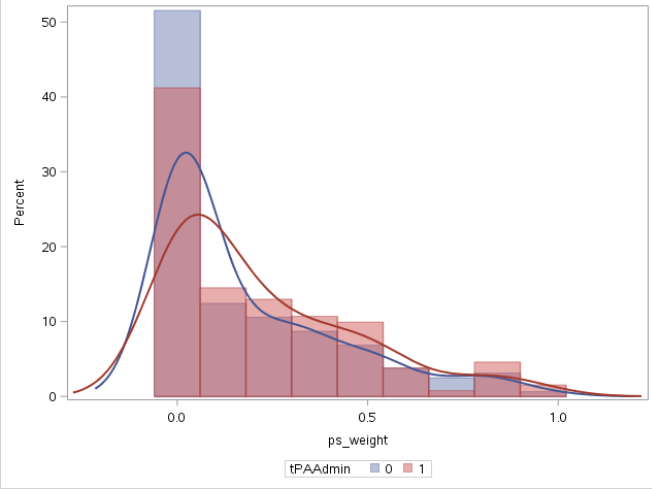
Appendix I. Covariates included in each Propensity Score model by estimated glomerular filtration rate (eGFR) category
Covariates were included in the propensity score if the difference between tPA exposure groups was ≥10%

≥60 mL/min/1.73m^2	**30-59 mL/min/1.73m^2**	**eGFR <30 mL/min/1.73m^2 or chronic dialysis**
Age (Continuous/Categorical)	Age (Continuous/Categorical)	Age (Continuous/Categorical)
Antiplatelet prescription	CCI (Continuous)	CCI (Continuous/Categorical)
Charlson Comorbidity Score (CCI) (Continuous/Categorical)	Cognitive (initial stroke symptoms)	Diabetes Mellitus
Diabetes Mellitus	Diabetes Mellitus	DBP
International normalized ratio (INR)	HAS-BLED bleeding risk score (Continuous/Categorical)	INR
Systolic blood pressure (SBP)	NIHSS	Index year
Index year	Time from hospital arrival to first imaging (Continuous/Categorical)	GI bleed
HAS-BLED bleeding risk score (Continuous, quadratic)	Speech (initial stroke symptoms)	HAS-BLED bleeding risk score (Continuous/Categorical)
Headache	Stroke	Hypertension
Time from symptom onset to hospital arrival (Continuous)	TIA	Dialysis
National Institute for Health Stroke Scale (NIHSS)	Field defect (initial stroke symptoms)	Time from symptom onset to hospital arrival (Continuous/Categorical)

Time from hospital arrival to first imaging (Continuous/Categorical)	Pre-event dependence	NIHSS
Smoking status	Monocular blindness (initial stroke symptoms)	PVD
Stroke	Pre-event residence	Time from hospital arrival to first imaging (Continuous/Categorical)
Field defect (initial stroke symptoms)	Seizure (initial stroke symptoms)	Smoking status
Pre-event dependence	Weakness (initial stroke symptoms)	Speech (initial stroke symptoms)
Pre-event residence	Arrival time (time of day)	Brain symptoms (initial stroke symptoms)
Weakness (initial stroke symptoms)	Antiplatelet prescription	Income
Cognitive symptoms (initial stroke symptoms)	Congestive heart failure (CHF)	Pre-event dependence
Diastolic blood pressure (DBP)	Index year	Pre-event residence
Gastrointestinal (GI) bleed	GI bleed	Weakness (initial stroke symptoms)
Hyperlipidemia	Time from symptom onset to hospital arrival (Continuous/Categorical)	Arrival time (time of day)
Arrival time (time of day)	Smoking status	Atrial fibrillation
Income	Income	CHF
Seizure (initial stroke symptoms)	Coronary artery disease (CAD)	Venous thromboembolism (VTE)
Peripheral vascular disease (PVD)	DBP	Glucose

Transient ischemic attack (TIA)	Glucose	Hyperlipidemia
	Institution type	TIA
	Sensory (initial stroke symptoms)	Field defect (initial stroke symptoms)
		Sex
		Monocular blindness (initial stroke symptoms)
		Valve replacement
		Valvular heart disease
		Antiplatelet prescription
		Liver disease
		SBP
		Rural residence
		Seizure (initial stroke symptoms)
		Coronary artery disease
		Cognitive (initial stroke symptoms)
		Dysphagia (initial stroke symptoms)
		Headache (initial stroke symptoms)
		Sensory (initial stroke symptoms)

Appendix J. Distribution of propensity scores pre- and post-overlap weighting across categories of estimated glomerular filtration rate

Pre-overlap weighting	Post-overlap weighting
≥60 mL/min/1.73m^2	
	
30-59 mL/min/1.73m^2	
	
<30 mL/min/1.73m^2 or chronic dialysis	
	

Appendix K. Reasons recombinant tissue plasminogen activator (rt-PA) was not given

When analyzing the documented reasons that patients did not receive rt-PA (N=18,396), the top reason was that the patient arrived at the hospital too late after onset of symptoms (>55%), their ischemic stroke was too mild (>23%), followed by patient decision (<16%) (Table K1). Approximately 6.1% of patients who did not receive rt-PA did not have a reason documented. There were some significant differences across eGFR categories, reasons such as patient's stroke too severe, contraindication to thrombolysis and physician decision were more frequent as eGFR declined.

Table K1. Documented reasons recombinant tissue plasminogen activator (rt-PA) not given to patients with ischemic stroke by estimated glomerular filtration rate

	Estimated glomerular filtration rate mL/min per 1.73m^2			**Standardized difference***	
	≥60	**30 to 59**	**<30 or chronic dialysis**	**≥60 vs. 30 to 59**	**≥60 vs. <30/ chronic dialysis**
Number of patients with ischemic stroke who did not receive rt-PA	10,840	6,306	1,250		
Reasons	**N (%)**	**N (%)**	**N (%)**	**%**	**%**
Patient too mild	3,645 (33.6)	1,868 (29.6)	289 (23.1)	9%	**23%**
Patient too severe	357 (3.3)	403 (6.4)	103 (8.2)	**14%**	**21%**
Patient arrived too late (>4 hours)	6,657 (61.4)	3,558 (56.4)	694 (55.5)	**10%**	**12%**
Contraindication to thrombolysis	1,092 (10.1)	939 (14.9)	243 (19.4)	**15%**	**26%**
Physician decision	972 (9.0)	734 (11.6)	202 (16.2)	9%	**22%**
Patient decision	1,667 (15.4)	943 (15.0)	168 (13.4)	1%	6%

Delay in decision to treat despite (emergency department arrival <4 hours)	287 (2.6)	175 (2.8)	43 (3.4)	1%	5%
Other	1,079 (10.0)	725 (11.5)	170 (13.6)	5%	**11%**

*Standardized difference ≥10% representing a statistically significant result when compared to patients with an eGFR ≥60 mL/min/1.73m^2. Statistically significant values are bolded.

Other category includes age ≤18, not ischemic stroke or no reason documented.

Appendix L. Crude baseline characteristics by estimated glomerular filtration rate (eGFR) among a subgroup of patients eligible for recombinant tissue plasminogen activator (rt-PA) therapy (N=4,632)

	eGFR ≥60 mL/min/1.73m^2					eGFR 30-59 mL/min/1.73m^2					eGFR <30 mL/min/1.73m^2 or on chronic dialysis				
	rt-PA 1,049		No rt-PA 1,662		Std Diff*	rt-PA 670		No rt-PA 959		Std Diff*	rt-PA 161		No rt-PA 131		Std Diff*
Characteristic	N	%	N	%	%	N	%	N	%	%	N	%	N	%	%
Demographics															
Age															
Median (25th, 75th percentile)	71	(59-80)	67	(57-77)		80	(73-86)	82	(75-88)		81	(74-87)	84	(78-89)	
18-59	269	25.6%	516	31.0%	**12%**	35	3.6%	19	2.8%	5%	7	5.3%	6	3.7%	8%
60-79	497	47.4%	810	48.7%	3%	435	45.4%	238	35.5%	**20%**	53	40.5%	46	28.6%	**25%**
80+	283	27.0%	336	20.2%	**16%**	487	50.8%	413	61.6%	**22%**	70	53.4%	109	67.7%	**30%**
Sex, female	426	40.6%	690	41.5%	2%	542	56.5%	398	59.4%	6%	83	63.4%	91	56.5%	**14%**
Income quintile															
1 - Lowest	266	25.4%	353	21.2%	**10%**	200	20.9%	177	26.4%	**13%**	28	21.4%	40	24.8%	8%
2	201	19.2%	352	21.2%	5%	196	20.4%	139	20.7%	1%	27	20.6%	36	22.4%	4%
3	207	19.7%	339	20.4%	2%	173	18.0%	114	17.0%	3%	24	18.3%	22	13.7%	**13%**
4	175	16.7%	317	19.1%	6%	187	19.5%	131	19.6%	0%	25	19.1%	34	21.1%	5%
5 - Highest	196	18.7%	297	17.9%	2%	203	21.2%	104	15.5%	**15%**	26	19.8%	27	16.8%	8%
Rural residence	117	11.2%	205	12.3%	3%	109	11.4%	68	10.1%	4%	11	8.4%	16	9.9%	5%
Pre-event residence															
Home	798	76.1%	1343	80.8%	**11%**	767	80.0%	469	70.0%	**23%**	100	76.3%	109	67.7%	**19%**
Other†	25	2.4%	17	1.0%	11%	17	1.8%	39	5.8%	21%	9	6.9%	8	5.0%	8%
Pre-event independence‡															

Independent	381	36.3%	919	55.3%	**39%**	424	44.2%	161	24.0%	**44%**	27	16.8%	47	35.9%	**44%**
Slight to severe disability	145	13.8%	142	8.5%	**17%**	149	15.5%	161	24.0%	**21%**	50	38.2%	36	22.4%	35%
Missing	523	49.9%	601	36.2%	**28%**	386	40.3%	348	51.9%	**23%**	48	36.6%	84	52.2%	**32%**
Acute stroke characteristics and healthcare utilization															
Regional Stroke Centre	825	78.6%	1288	77.5%	3%	777	81.0%	533	79.6%	4%	103	78.6%	125	77.6%	2%
District Stroke Centre	224	21.4%	374	22.5%	3%	182	19.0%	137	20.4%	4%	28	21.4%	36	22.4%	2%
Stroke symptoms at hospital presentation															
Weakness	914	87.1%	1567	94.3%	**25%**	928	96.8%	615	91.8%	**22%**	126	96.2%	156	96.9%	4%
Speech disturbance	195	18.6%	295	17.7%	2%	207	21.6%	138	20.6%	2%	26	19.8%	33	20.5%	2%
Sensory Symptoms	461	27.7%	259	24.7%	7%	218	22.7%	112	16.7%	**15%**	30	22.9%	28	17.4%	**14%**
Dysphagia	97	9.2%	148	8.9%	1%	110	11.5%	83	12.4%	3%	12	9.2%	15	9.3%	0%
Monocular Blindness	13	1.2%	38	2.3%	8%	27	2.8%	7	1.0%	**13%**	≤5	3.8%	0	0.0%	**17%**
Field defect	96	9.2%	311	18.7%	**28%**	201	21.0%	72	10.7%	**28%**	32	24.4%	19	11.8%	**33%**
Other cognitive symptoms	177	16.9%	220	13.2%	**10%**	156	16.3%	151	22.5%	**16%**	19	14.5%	30	18.6%	**11%**
Brainstem or cerebellar signs	203	19.4%	277	16.7%	7%	123	12.8%	103	15.4%	7%	18	13.7%	21	13.0%	2%
Headache or seizure	165	15.7%	186	11.2%	**13%**	53	5.5%	53	7.9%	**10%**	3	2.3%	11	6.8%	**22%**
Time from symptom onset to hospital arrival (hours)															
Median (25^{th}, 75^{th} percentile)	2	(1-3)	1	(1-2)		1	(1-2)	2	(1-3)		1	(1-2)	2	(1-3)	
<3.5 hours	864	82.4%	1637	98.5%	**57%**	951	99.2%	563	84.0%	**57%**	130	99.2%	138	85.7%	**53%**
Time of day															
12am-<8am	139	13.3%	170	10.2%	**10%**	71	7.4%	76	11.3%	**13%**	11	8.4%	18	11.2%	9%
8am-<5pm	587	56.0%	946	56.9%	2%	520	54.2%	378	56.4%	4%	67	51.1%	87	54.0%	6%
5pm-<12am	323	30.8%	546	32.9%	5%	368	38.4%	216	32.2%	**13%**	53	40.5%	56	34.8%	**12%**

Time from hospital arrival to imaging Median (25th, 75th percentile) (minutes)	51	(26-124)	23	(13-35)		24	(15-36)	50	(24-109)		23	(15-31)	44	(27-96)	
<3.5 hours	889	84.7%	1649	99.2%	**55%**	953	99.4%	603	90.0%	**43%**	131	100.0%	144	89.4%	**49%**
National Institutes of Health Stroke Scale (NIHSS)§, Median (25th, 75th percentile)	7	(4-12)	11	(7-16)		12	(8-17)	8	(4-14)		14	(8-19)	10	(5-15)	
Laboratory measurements, Median (25th, 75th percentile)															
Estimated glomerular filtration rate	79	(69-91)	80	(69-91)		48	(41-54)	48	(40-54)		24	(20-28)	23	(18-27)	
Systolic blood pressure	147	(132-163)	147	(132-161)		150	(132-164)	150	(133-165)		144	(127-159)	145	(124-160)	
Diastolic blood pressure	80	(71-90)	81	(72-91)		78	(69-88)	77	(67-88)		74	(63-84)	72	(61-82)	
International normalized ratio	1	(1-1)	1	(1-1)		1	(1-1)	1	(1-1)		1	(1-1)	1	(1-1)	
Glucose	7	(6-8)	7	(6-8)		7	(6-8)	7	(6-8)		7	(6-10)	7	(6-9)	
Comorbidities															
Charlson Comorbidity Score															
0	423	40.3%	899	54.1%	**28%**	337	35.1%	163	24.3%	**24%**	28	21.4%	21	13.0%	**22%**
1	263	25.1%	452	27.2%	5%	289	30.1%	195	29.1%	2%	26	19.8%	24	14.9%	**13%**
2	153	14.6%	164	9.9%	**14%**	149	15.5%	145	21.6%	**16%**	23	17.6%	37	23.0%	**13%**
3	210	20.0%	147	8.8%	**32%**	184	19.2%	167	24.9%	**14%**	54	41.2%	79	49.1%	**16%**
HASBLED Score															
Median (25th, 75th percentile)	2	(1-3)	2	(1-2)		3	(2-3)	3	(2-4)		3	(3-4)	3	(3-4)	
High bleeding risk ≥3	278	26.5%	295	17.7%	**21%**	506	52.8%	373	55.7%	6%	113	86.3%	147	91.3%	**16%**
Chronic dialysis	0	0.0%	0	0.0%	0%	0	0.0%	0	0.0%	0%	11	8.4%	20	12.4%	**13%**
Stroke	201	19.2%	207	12.5%	**18%**	163	17.0%	165	24.6%	**19%**	27	20.6%	36	22.4%	4%
Transient ischemic attack	136	13.0%	143	8.6%	**14%**	111	11.6%	125	18.7%	**20%**	16	12.2%	25	15.5%	**10%**

Atrial fibrillation	147	14.0%	237	14.3%	1%	218	22.7%	164	24.5%	4%	30	22.9%	44	27.3%	**10%**
Coronary artery disease	237	22.6%	323	19.4%	8%	289	30.1%	208	31.0%	2%	44	33.6%	63	39.1%	**11%**
Congestive heart failure	55	5.2%	61	3.7%	7%	94	9.8%	112	16.7%	**20%**	29	22.1%	32	19.9%	5%
Diabetes mellitus	234	22.3%	263	15.8%	**17%**	215	22.4%	183	27.3%	**11%**	48	36.6%	65	40.4%	8%
Hypertension	626	59.7%	936	56.3%	7%	763	79.6%	531	79.3%	1%	112	85.5%	136	84.5%	3%
Venous thromboembolism	24	2.3%	27	1.6%	5%	20	2.1%	10	1.5%	5%	≤5	3.8%	6	3.7%	**14%**
Gastrointestinal Bleed	38	3.6%	15	0.9%	**18%**	22	2.3%	29	4.3%	**11%**	≤5	3.8%	10	6.2%	**19%**
Hyperlipidemia	361	34.4%	636	38.3%	8%	437	45.6%	290	43.3%	5%	120	91.6%	141	87.6%	**13%**
Liver disease	22	2.1%	34	2.0%	1%	16	1.7%	12	1.8%	1%	≤5	3.8%	≤5	0.6%	**14%**
Peripheral vascular disease	52	5.0%	36	2.2%	**15%**	53	5.5%	44	6.6%	5%	11	8.4%	16	9.9%	5%
Current smoker	225	21.4%	382	23.0%	4%	96	10.0%	70	10.4%	1%	17	13.0%	7	4.3%	**31%**
Valvular heart disease	38	3.6%	61	3.7%	1%	49	5.1%	29	4.3%	4%	10	7.6%	22	13.7%	**20%**
Valve replacement	18	1.7%	28	1.7%	0%	16	1.7%	14	2.1%	3%	≤5	3.8%	6	3.7%	8%
Pre-event medications (14 days prior to stroke event)															
Antiplatelets	285	27.2%	366	22.0%	**12%**	278	29.0%	242	36.1%	**15%**	46	35.1%	64	39.8%	**10%**

* Standardized difference (Std Diff) ≥10% representing a statistically significant result when comparing rt-PA exposure groups. Statistically significant values are bolded.
† Other pre-event residence includes nursing home, long-term care, retirement home, in-patient rehabilitation, complex continuing care, other acute, other emergency department and other (e.g. homeless).
‡ The level of dependence definition in the Ontario Stroke Registry is based on the patient's ability to manage activities of daily living (ADL) prior to their stroke event. Independence: Patient is fully independent in all ADLs and instrumental ADLs (IADL); Slight Disability: Patient is fully independent in all ADLs but is unable to carry out all IADLs; Moderate Disability: Patient requires help for some ADLs but remains ambulatory (with or without a cane or walker) without the assistance of another person; Moderately Severe Disability: Patient is unable to perform some of their ADLs, is unable to walk but can be left alone for several hours without supervision; Severe Disability: Patient is bedridden, incontinent and requires constant nursing care.
§ National Institutes of Health Stroke Scale (NIHSS) is a measure of stroke-related neurological deficit and severity is categorized as 0: No stroke symptoms, 1-4: Minor stroke, 5-15: Moderate stroke, 16-20: Moderate to severe stroke, or 21-42: Severe stroke.
Missingness was not reported for income quintile, rural residence, pre-event residence, weakness, dysphagia, monocular blindness, other cognitive symptoms, seizure, and headache due to cells less than or equal to five. In accordance with ICES privacy policies, cell sizes less than or equal to five cannot be reported.

Appendix M. Weighted baseline characteristics by estimated glomerular filtration rate (eGFR) among a subgroup of patients eligible for recombinant tissue plasminogen activator (rt-PA) therapy

	eGFR ≥60 mL/min/1.73m^2					eGFR 30-59 mL/min/1.73m^2					eGFR <30 mL/min/1.73m^2 or on chronic dialysis				
	rt-PA 402		Control 402		Std Diff*	rt-PA 246		Control 246		Std Diff*	rt-PA <32		Control <32		Std Diff*
Characteristic	N	%	N	%	%	N	%	N	%	%	N	%	N	%	%
Demographics															
Age															
Median (25th, 75th percentile)	69	(57-79)	69	(57-79)		81	(74-87)	81	(73-87)		83	(77-89)	84	(76-90)	
60-79	189	47.1%	189	47.1%	0%	101	41.1%	101	41.1%	0%	9	30.6%	9	30.6%	0%
80+	93	23.1%	93	23.1%	0%	137	55.5%	137	55.5%	0%	19	65.0%	19	65.0%	0%
Sex, female	172	42.9%	166	41.3%	3%	140	56.9%	143	58.3%	3%	18	62.8%	18	62.8%	0%
Income quintile															
1 - Lowest	91	22.7%	91	22.7%	0%	60	24.3%	60	24.3%	0%	≤5	17.9%	≤5	17.9%	0%
2	77	19.3%	77	19.3%	0%	52	20.9%	52	20.9%	0%	7	24.9%	7	24.9%	0%
3	83	20.7%	83	20.7%	0%	43	17.3%	43	17.3%	0%	≤5	16.0%	≤5	16.0%	0%
4	73	18.3%	73	18.3%	0%	48	19.6%	48	19.6%	0%	≤5	17.8%	≤5	17.8%	0%
5 - Highest	76	18.8%	76	18.8%	0%	44	17.9%	44	17.9%	0%	6	22.2%	6	22.2%	0%
Rural residence	57	14.3%	51	12.7%	5%	31	12.6%	27	10.9%	5%	≤5	11.8%	≤5	11.8%	0%
Pre-event residence															
Home	305	76.0%	305	76.0%	0%	186	75.4%	186	75.4%	0%	21	72.8%	21	72.8%	0%
Other†	94	23.3%	94	23.3%	0%	60	24.2%	60	24.2%	0%	6	20.7%	6	20.7%	0%
Pre-event independence‡															

Independent	178	44.3%	178	44.3%	0%	80	32.5%	80	32.5%	0%	7	25.1%	7	25.1%	0%
Slight to severe disability	51	12.7%	51	12.7%	0%	55	22.3%	55	22.3%	0%	10	34.5%	10	34.5%	0%
Missing	172	42.9%	172	42.9%	0%	112	45.4%	112	45.4%	0%	12	40.2%	12	40.2%	0%
Acute stroke characteristics and healthcare utilization															
Regional Stroke Centre	321	79.7%	308	76.5%	8%	198	80.5%	198	80.5%	0%	22	74.9%	22	74.3%	1%
District Stroke Centre	81	20.3%	94	23.5%	8%	48	19.5%	48	19.5%	0%	7	25.1%	7	25.7%	1%
Stroke symptoms at hospital presentation															
Weakness	367	91.3%	367	91.3%	0%	230	93.4%	230	93.4%	0%	28	97.4%	28	97.4%	0%
Speech disturbance	74	18.4%	78	19.4%	3%	53	21.4%	53	21.4%	0%	6	20.4%	6	20.4%	0%
Sensory Symptoms	113	28.0%	97	24.2%	9%	45	18.3%	45	18.3%	0%	≤5	16.7%	≤5	16.7%	0%
Dysphagia	35	8.8%	38	9.4%	2%	26	10.4%	29	11.8%	4%	≤5	8.9%	≤5	8.9%	0%
Monocular Blindness	7	1.7%	≤5	1.3%	3%	≤5	1.7%	≤5	1.7%	0%	0	0.0%	0	0.0%	0%
Field defect	51	12.7%	51	12.7%	0%	40	16.1%	40	16.1%	0%	≤5	18.9%	≤5	18.9%	0%
Other cognitive symptoms	60	14.9%	60	14.9%	0%	47	19.2%	47	19.2%	0%	6	19.2%	6	19.2%	0%
Brainstem or cerebellar signs	67	16.6%	72	17.9%	3%	32	13.2%	35	14.2%	3%	≤5	9.7%	≤5	9.7%	0%
Seizure	≤5	0.8%	≤5	0.8%	0%	≤5	0.4%	≤5	0.4%	0%	≤5	1.9%	≤5	1.9%	0%
Headache	52	12.9%	52	12.9%	0%	12	4.9%	16	6.6%	7%	≤5	2.7%	≤5	2.7%	0%
Time from symptom onset to hospital arrival (hours)															
Median (25^{th}, 75^{th} percentile)	1	(1-2)	1	(1-2)		1	(1-2)	1	(1-2)		1	(1-2)	1	(1-2)	
<3.5 hours	386	95.9%	378	94.1%	8%	241	97.7%	241	97.7%	0%	29	98.6%	29	98.6%	0%
≥3.5 to <4.0 hours	11	2.8%	17	4.1%	7%	6	2.3%	6	2.3%	0%	0	1.4%	0	1.4%	0%
≥4.0 to <4.5 hours	≤5	1.2%	7	1.8%	5%	0	0.0%	0	0.0%	0%	0	0.0%	0	0.0%	0%
Time of day[§]															

12am-<8am	46	11.6%	46	11.6%	0%	23	9.3%	23	9.3%	0%	-	-	-	-	-
8am-<5pm	225	55.9%	225	55.9%	0%	140	56.7%	140	56.7%	0%	-	-	-	-	-
5pm-<12am	131	32.5%	131	32.5%	0%	84	33.9%	84	33.9%	0%	-	-	-	-	-
Time from hospital arrival to imaging															
Median (25th, 75th percentile) (minutes)	25	(14-37)	35	(20-71)		25	(16-37)	38	(21-70)		26	(17-42)	30	(20-44)	
<3.5 hours	393	97.8%	393	97.8%	0%	243	98.7%	243	98.7%	0%	29	100.0%	29	100.0%	0%
National Institutes of Health Stroke Scale (NIHSS)‖, Median (25th, 75th percentile)	9	(6-13)	9	(5-15)		10	(7-15)	11	(5-16)		10	(7-17)	11	(7-16)	
Laboratory measurements, Median (25th, 75th percentile)															
Estimated glomerular filtration rate	80	(70-91)	79	(69-92)		48	(41-55)	49	(41-54)		23	(20-27)	24	(18-27)	
Systolic blood pressure	147	(132-162)	147	(133-162)		150	(133-164)	148	(132-164)		146	(123-160)	143	(126-160)	
Diastolic blood pressure	82	(73-91)	82	(73-91)		77	(68-88)	77	(68-89)		72	(61-84)	71	(60-83)	
International normalized ratio	1	(1-1)	1	(1-1)		1	(1-1)	1	(1-1)		1	(1-1)	1	(1-1)	
Glucose	7	(6-8)	7	(6-8)		7	(6-9)	7	(6-9)		7	(6-10)	7	(6-10)	
Comorbidities															
Charlson Comorbidity Score															
≤2	340	84.6%	340	84.6%	0%	185	75.2%	188	76.4%	3%	16	55.2%	16	55.2%	0%
≥3	61	15.3%	61	15.3%	0%	61	24.8%	57	23.2%	4%	13	44.7%	13	44.7%	0%
HASBLED Score															
Median (25th, 75th percentile)	2	(1-2)	2	(1-2)		3	(2-3)	3	(2-3)		3	(3-4)	3	(3-4)	
High bleeding risk ≥3	88	21.9%	86	21.4%	1%	130	52.8%	130	52.8%	0%	26	89.4%	26	89.4%	0%
Chronic dialysis	0	0%	0	0%	0%	0	0%	0	0%	0%	≤5	6.9%	≤5	6.9%	0%
Stroke	64	15.8%	64	15.8%	0%	52	21.1%	52	21.1%	0%	≤5	18.6%	≤5	18.6%	8%

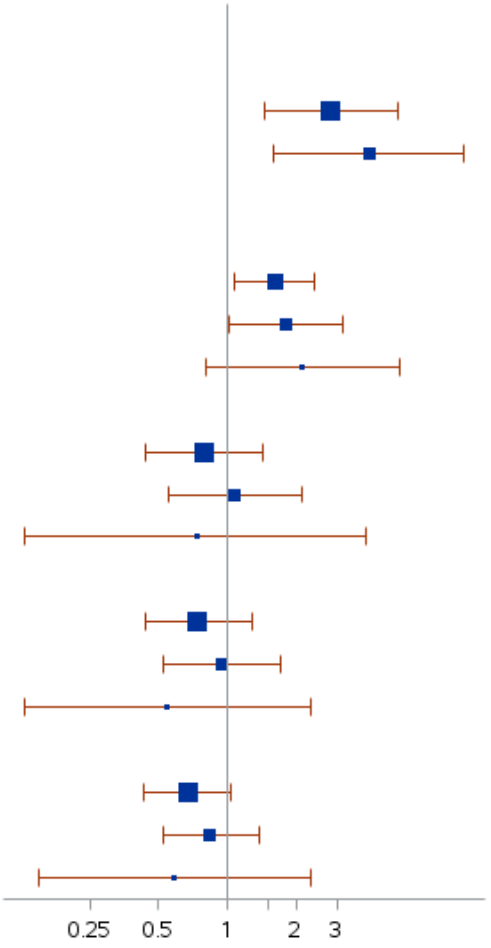
Transient ischemic attack	47	11.8%	47	11.8%	0%	39	15.8%	39	15.8%	0%	≤5	12.6%	≤5	12.6%	0%
Atrial fibrillation	56	13.9%	59	14.7%	2%	55	22.3%	61	24.8%	6%	7	23.1%	7	23.1%	0%
Coronary artery disease	80	20.0%	92	22.8%	7%	71	29.0%	71	29.0%	0%	11	36.3%	11	36.3%	0%
Congestive heart failure	16	4.0%	15	3.8%	1%	34	13.8%	34	13.8%	0%	7	22.6%	7	22.6%	0%
Diabetes mellitus	80	19.8%	80	19.8%	0%	64	26.0%	64	26.0%	0%	10	35.4%	10	35.4%	0%
Hypertension	232	57.8%	235	58.4%	1%	194	78.9%	199	80.6%	4%	24	83.8%	24	83.8%	0%
Venous thromboembolism	8	2.1%	11	2.7%	4%	≤5	1.9%	≤5	1.9%	0%	≤5	2.9%	≤5	2.9%	0%
Gastrointestinal bleed	8	2.0%	8	2.0%	0%	8	3.4%	8	3.4%	0%	≤5	4.7%	≤5	4.7%	0%
Hyperlipidemia	139	34.7%	139	34.7%	0%	111	45.1%	119	48.4%	7%	14	47.5%	14	47.5%	0%
Liver disease	11	2.7%	8	1.9%	5%	≤5	1.8%	≤5	1.3%	4%	0	1.4%	0	1.4%	0%
Peripheral vascular disease	13	3.2%	13	3.2%	0%	16	6.4%	13	5.4%	4%	≤5	4.4%	≤5	4.4%	0%
Current smoker	92	22.8%	92	22.8%	0%	25	10.3%	25	10.3%	0%	≤5	5.5%	≤5	5.5%	0%
Valvular heart disease	16	4.0%	14	3.5%	3%	14	5.8%	11	4.5%	6%	≤5	9.6%	≤5	9.6%	0%
Valve replacement	7	1.8%	10	2.4%	4%	≤5	1.5%	≤5	2.2%	5%	≤5	4.1%	≤5	4.1%	0%
Pre-event medications															
Antiplatelets	99	24.7%	99	24.7%	0%	81	32.8%	81	32.8%	0%	10	34.4%	10	34.4%	0%

[*] Standardized difference (Std Diff) ≥10% representing a statistically significant result when comparing rt-PA exposure groups. Statistically significant values are bolded.
[†] Other pre-event residence includes nursing home, long-term care, retirement home, in-patient rehabilitation, complex continuing care, other acute, other emergency department and other (e.g. homeless).
[‡] The level of dependence definition in the Ontario Stroke Registry is based on the patient's ability to manage activities of daily living (ADL) prior to their stroke event. Independence: Patient is fully independent in all ADLs and instrumental ADLs (IADLs) Slight Disability: Patient is fully independent in all ADLs but is unable to carry out all IADLs; Moderate Disability: Patient requires help for some ADLs but remains ambulatory (with or without a cane or walker) without the assistance of another person; Moderately Severe Disability: Patient is unable to perform some of their ADLs, is unable to walk but can be left alone for several hours without supervision; Severe Disability: Patient is bedridden, incontinent and requires constant nursing care.
[§] Time of day data were not reported for eGFR <30 or on chronic dialysis due to cells less than or equal to five. In accordance with ICES privacy policies, cell sizes less than or equal to five cannot be reported.
[l] National Institutes of Health Stroke Scale (NIHSS) is a measure of stroke-related neurological deficit and severity is categorized as 0: No stroke symptoms, 1-4: Minor stroke, 5-15: Moderate stroke, 16-20: Moderate to severe stroke or 21-42: Severe stroke.

Missingness was not reported for income quintile, rural residence, pre-event residence, weakness, dysphagia, monocular blindness, other cognitive symptoms, seizure, and headache due to cells less than or equal to five. In accordance with ICES privacy policies, cell sizes less than or equal to five cannot be reported.

Appendix N. Weighted effects of recombinant tissue plasminogen activator (rt-PA) within categories of estimated glomerular filtration rate (eGFR)

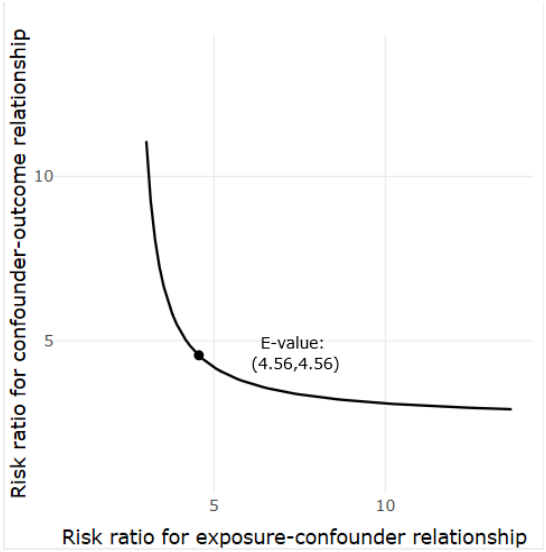
Outcomes	rt-PA Events/N	Control Events/N	Odds Ratio (99% CI)
sICH			
eGFR ≥ 60	58/402	23/402	2.82 (1.44, 5.50)
eGFR 30-59	36/247	10/247	4.14 (1.59, 10.7)
eGFR <30/dialysis	≤5/29	≤5/29	
mRS 0-2			
eGFR ≥ 60	162/353	117/353	1.62 (1.08, 2.41)
eGFR 30-59	69/206	45/206	1.80 (1.01, 3.20)
eGFR <30/dialysis	≤5/23	≤5/23	2.13 (0.80, 5.67)
Death, in-hospital			
eGFR ≥ 60	38/402	47/402	0.79 (0.44, 1.43)
eGFR 30-59	36/247	34/247	1.08 (0.55, 2.10)
eGFR <30/dialysis	≤5/29	7/29	0.73 (0.13, 3.99)
Death, 30 day			
eGFR ≥ 60	47/402	61/402	0.74 (0.44, 1.27)
eGFR 30-59	47/247	50/247	0.94 (0.52, 1.69)
eGFR <30/dialysis	8/29	12/29	0.54 (0.13, 2.29)
Death, 1-year			
eGFR ≥ 60	74/402	101/402	0.67 (0.43, 1.04)
eGFR 30-59	85/247	95/247	0.84 (0.52, 1.37)
eGFR <30/dialysis	13/29	17/29	0.58 (0.15, 2.29)



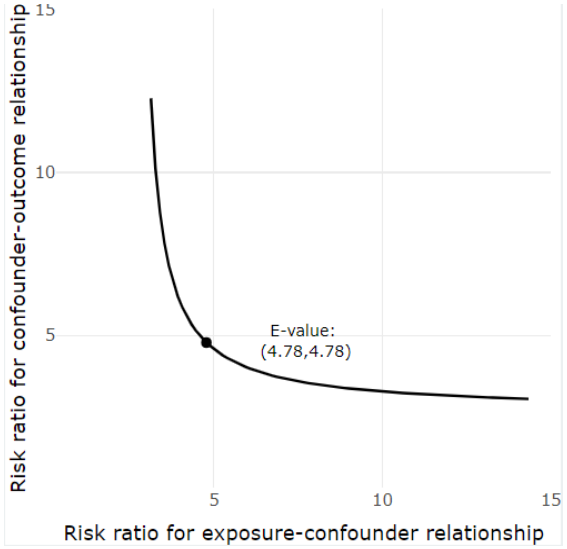
Appendix O. E-value figures for primary outcomes

a. Secondary intracranial hemorrhage

≥60 mL/min/1.73m^2

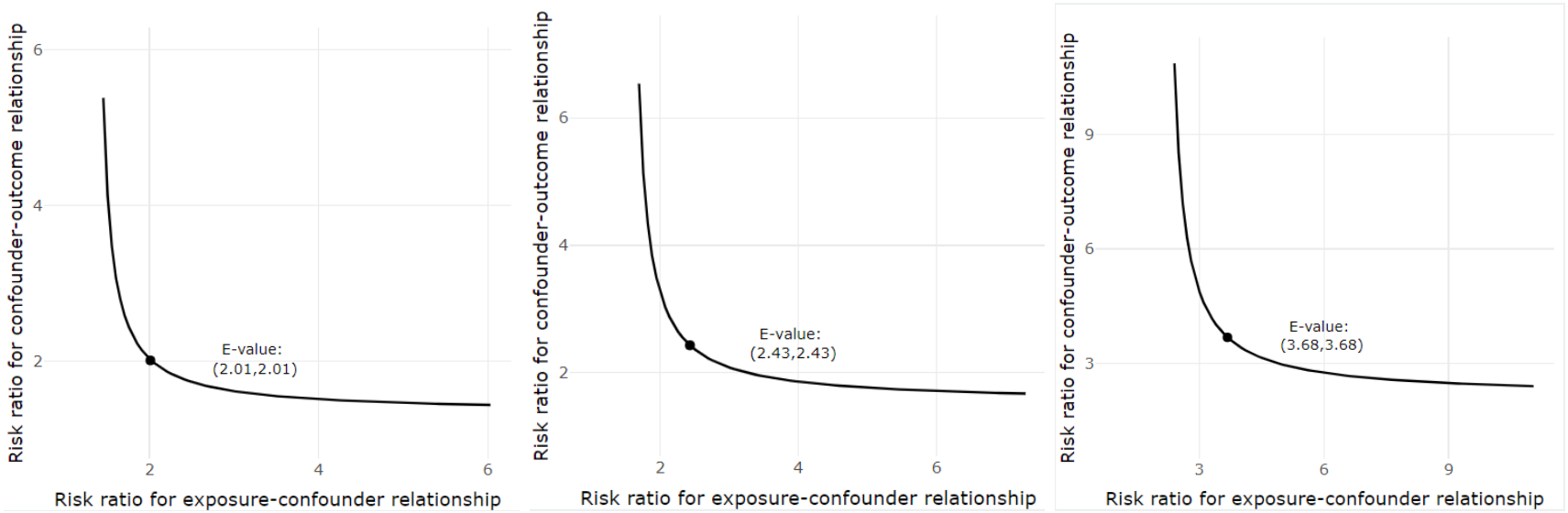


30-59 mL/min/1.73m^2



b. Modified Rankin Score (mRS) 0-2

≥60 mL/min/1.73m^2 | **30-59 mL/min/1.73m^2** | **<30 mL/min/1.73m^2 or chronic dialysis**



*Mathur et al.[121] and VanderWeele & Ding[122]

Curriculum Vitae

EDUCATION

Western University, London, ON – M.Sc. Epidemiology & Biostatistics, 2021

Université Laval, Quebec City, QC – Summer Enrichment Student, 2007

Simon Fraser University, Burnaby, BC – Bachelor of Arts, Psychology, 2007

Wilfrid Laurier University, Waterloo, ON – Undergrad, Psychology, 2004

AWARDS

Ontario Drug Policy Research Network (ODPRN) Student Training Program

2015-Present, $17,500

RESEARCH EXPERIENCE

Research Coordinator, ICES Western

London, ON – 2013-Present

- Senior coordinator for the provincial Kidney, Dialysis and Transplantation (KDT) program.
- Works with ICES Scientists and Knowledge Users to conduct observational research using linked administrative datasets.
- Duties include study conceptualization, design, analytic interpretation, and manuscript and grant writing.
- Deliver training and mentorship of new research coordinator and research assistant staff.

Project Manager, ICES

Toronto, ON – 2010-2012

- Responsible for the management of the primary data collection projects at the Ontario Stroke Registry (OSR), formerly the Registry of the Canadian Stroke Network, including the development and implementation of these clinical research projects and their validation strategies.

- Responsibilities included monitoring progress and completeness of incoming data, training abstractors, overseeing expenses, managing inquiries on privacy, security, technical, & clinical issues, and maintaining all research ethics board approvals.
- Worked with the Principal Investigators to develop the 2008/09 Ontario Stroke Audit Report which examined provincial trends in stroke care.

Research Assistant, ICES

Toronto, ON – 2009-2010

- Provided research support for the Ontario Stroke Registry (OSR) and partnering Stroke Evaluation Office, including managing ongoing requests for use of the OSR database and assisted the Publications Committee in processing these requests, provided administrative support to the Stroke Evaluation & Quality Committee (SEQC) and was the administrator and content writer on the OSR website.
- Worked with the Principal Investigators to develop two stroke evaluation reports which presented variations in stroke care and patient outcomes by stroke care sectors.

Research Assistant, The University of Waterloo

Waterloo, ON – 2008-2009

- Carried-out numerous tasks on a multitude of projects in the field of Gerontology and Health Informatics, including conducting literature searches, creating PowerPoint slides, editing reports, managing references, and synthesizing information into tables.
- Created a comprehensive table of 56 studies characterizing outcome measures in geriatric interventions that was published in the appendix of *Brocklehurst's Textbook of Geriatric Medicine and Gerontology, 7th Edition*.

Research Assistant, aestima Research

Waterloo, ON – 2008-2008

- Assisted in the development of a comprehensive report on best practices in elder abuse that required the use of French language skills and was completed for the department of Human Resources and Development Canada.
- Assisted in the third-year evaluation of the Senior Health Research Transfer Network (SHRTN) by creating and distributing surveys, conducting phone interviews, and performing data analysis (using SPSS), which was presented to SHRTN.

PRESENTATIONS

Sood MM, Garg AX, **Bota SE**, Marisiddappa L, McArthur E, Naylor K, Kapral MK, Kim SJ, Lam N, Molnar A, Harel Z, Perl J, Knoll G. Risk of hospitalization with major non-traumatic hemorrhage after kidney transplantation. Oral Presentation at the Kidney Clinical Research Unit Research Day, London, Ontario; 2014.

Sood MM, **Meyer SE**, McArthur E, Kapral MK, Tangri N, Knoll G, Zimmerman D & Garg A The three-year incidence of hospitalization with hemorrhage among older adults initiating chronic dialysis. Oral presentation at the Kidney Clinical Research Unit Research Day, London, Ontario; 2013.

Meyer S, Stamplecoski M, Hall R, Silver FL, Asllani E, Fang J, Richards J, O'Callaghan C, & Kapral MK. *Stroke Care in Ontario: Results from Three Consecutive Registry of the Canadian Stroke Network Audits*. Poster presentation at the Canadian Stroke Congress, Ottawa, Ontario; 2011.

Stamplecoski M, **Meyer S**, Hall R, Silver FL, Asllani E, Fang J, Richards J, O'Callaghan C, & Kapral MK. *Stroke Care in Different Institution Types in Ontario: Findings from the 2008/09 Ontario Stroke Audit*. Poster presentation at the Canadian Stroke Congress, Ottawa, Ontario; 2011.

Hall R, Bayley M, O'Callaghan C, Liu Y, **Meyer S**, Willems D, Lumsden J, Linkewich, B. *Stroke Rehabilitation Best Practices: How Does Ontario Measure Up?* Poster presentation at the Canadian Stroke Congress, Quebec City, Quebec; 2010.

PUBLICATIONS

Hundemer GL, Talarico R, Tangri N, Leon SJ, **Bota SE**, Rhodes E, Knoll GA, Sood MM. Ambulatory Treatments for RAAS Inhibitor-Related Hyperkalemia and the 1-Year Risk of Recurrence. *Clin J Am Soc Nephrol*. 2021;16(3):365-373.

Molnar AO, **Bota SE**, Garg AX, et al. Dialysis Modality and Mortality in Heart Failure: A Retrospective Study of Incident Dialysis Patients. *Cardiorenal Med*. 2020;10(6):452-461.

Silver SA, **Bota SE**, McArthur E, et al. Association of Primary Care Involvement with Death or Hospitalizations for Patients Starting Dialysis. *Clin J Am Soc Nephrol*. 2020;15(4):521-529.

Molnar AO, **Bota S**, Jeyakumar N, McArthur E, Battistella M, Garg AX, Sood MM, Brimble KS. Potentially inappropriate prescribing in older adults with advanced chronic kidney disease. *PLoS ONE*. 2020;15(8): e0237868.

Ashley J, McArthur E, **Bota SE**, Harel Z, Battistella M, Molnar AO, Jun M, Badve SV, Garg AX, Manuel D, Tanuseputro P, Wells P, Mavrakanas T, Rhodes E, Sood MM. Risk of cardiovascular events and mortality among elderly patients with reduced GFR receiving direct oral anticoagulants. American Journal of Kidney Diseases. 2020; 76(3): 311-320.

Hosseini-Moghaddam SM, Ouédraogo A, Naylor KL, **Bota SE**, Husain S, Nash SM, Paterson JM. Incidence and outcomes of invasive fungal infection among solid organ

transplant recipients: A population-based cohort study. *Transplant Infectious Disease*. 2020; 22(2): e13250.

Noel JA, **Bota SE**, Petrcich W, Garg AX, Carrero JJ, Harel Z, Tangri N, Clark EG, Komenda P, Sood MM. Risk of hospitalization for serious adverse gastrointestinal events associated with sodium polystyrene sulfonate use in patients of advanced age. *JAMA Internal Medicine*. 2019; 179(8): 1025-1033.

de Chickera SN, **Bota SE**, Kuwornu JP, Wijeysundera HC, Molnar AO, Lam NN, Silver SA, Clark EG, Sood MM. Albumin, reduced kidney function and the risk of ST- and non-ST-segment-elevation myocardial infarction. *Journal of the American Heart Association*. 2018; 7(20): e009995.

McArthur E, **Bota SE**, Sood MM, Nesrallah GE, Kim SJ, Garg AX, Dixon SN. Comparing five comorbidity indices to predict mortality in chronic kidney disease: A retrospective cohort study. 2018. *Canadian Journal of Kidney Health and Disease*. 2018; 5: 2054358118805418.

Nesrallah GE, Dixon SN, MacKinnon M, Jassal SV, **Bota SE,** Dirk JS, Arthurs E, Blake PG, Sood MM, Garg AX, Davison SN. Home palliative service utilization and care trajectory among Ontario residents dying on chronic dialysis. *Canadian Journal of Kidney Health and Disease*. 2018; 5: 2054358118783761.

Massicotte-Azarniouch D, Eddeen AB, LazoLanger A, Molnar AO, Lam NN, McCallum MK, **Bota SE**, Zemmerman D, Garg AX, Harel Z, Perl J, Wald R, Sood MM. Risk of venous thromboembolism in patients by albuminuria and estimated GFR. American *Journal of Kidney Diseases*. 2017; 70 (6): 826-833.

Molnar AO, **Bota SE**, McArthur E, Lam NN, Garg AX, Wald R, Zimmerman D, Sood MM. Risk and complications of venous thromboembolism in dialysis patients. *Nephrology Dialysis Transplantation*. 2017; 33(5): 874-880.

Keskar V, McArthur E, Wald R, Harel Z, Zimmerman D, Molnar AO, Garg AX, Lam NN, McCallum MK, **Bota SE**, Perl J, Sood MM. The association of anticoagulation, ischemic stroke, and hemorrhage in elderly adults with chronic kidney disease and atrial fibrillation. *Kidney International*. 2017; 9(4): 928-936.

Lam NN, Garg AX, Knoll GA, Kim SJ, Lentine KL, McArthur E, Naylor KL, **Bota SE**, Sood MM. Venous thromboembolism and the risk of death and graft loss in kidney transplant recipients. *American Journal of Nephrology*. 2017; 46(4): 343-354.

Molnar AO, **Bota SE**, Garg AX, Harel Z, Lam N, McArthur E, Nesrallah G, Perl J, Sood MM. The risk of major hemorrhage with CKD. *The Journal of the American Society of Nephrology*. 2016; 27(9): 2825-32.

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Sood MM, **Bota SE**, McArthur E, Kapral MK, Tangri N, Knoll G, Zimmerman D & Garg A. The three-year incidence of major hemorrhage among older adults initiating chronic dialysis. *Canadian Journal of Kidney Health and Disease*. 2014; 1:21.

REPORTS

Kapral MK, Hall R, Stamplecoski M, **Meyer S**, Asllani E, Fang J, Richards J, O'Callaghan C, Silver FL. Registry of the Canadian Stroke Network – Report on the 2008/09 Ontario Stroke Audit. Toronto: Institute for Clinical Evaluative Sciences; 2011.

Hall R, Khan F, O'Callaghan C, **Meyer S**, Fang J, Hodwitz K, Bayley M. Ontario Stroke Evaluation Report 2011: Improving System Efficiency by Implementing Stroke Best Practices. Toronto: Institute for Clinical Evaluative Sciences; 2011.

Hall R, O'Callaghan C, Bayley M, **Meyer S**, Khan F, Liu Y, Linkewich B, Lumsden J, Willems D. Ontario Stroke Evaluation Report 2010: Technical Report. Toronto: Institute for Clinical Evaluative Sciences; 2010.