


Thrombolytic therapy in older acute ischemic stroke patients with gastrointestinal malignancy or recent bleeding

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Abstract

Background: There are limited data on the safety of intravenous recombinant tissue plasminogen activator (rtPA) for treating acute ischemic stroke in patients with gastrointestinal malignancy or recent gastrointestinal bleeding within 21 days of their index stroke.

Aims: To evaluate clinical outcomes in patients treated with rtPA for acute ischemic stroke who had gastrointestinal malignancy or recent gastrointestinal bleeding

Methods: We identified patients who were treated with rtPA for acute ischemic stroke between 2/2009 and 12/2015 from the Get With The Guidelines-Stroke linked to Medicare claims data. Gastrointestinal malignancy and recent gastrointestinal bleeding were defined as any gastrointestinal malignancy hospitalisation within one year prior to acute ischemic stroke and gastrointestinal bleeding hospitalisation within 21 days prior to acute ischemic stroke, respectively. Outcomes of interest included in-hospital mortality and bleeding complications.

Results: Among 40,396 patients aged 65 years or older treated with rtPA for acute ischemic stroke from 1522 sites (mean age [SD] 81.0 [8.1] years; 41.9% women), 136 (0.3%) had gastrointestinal malignancy ($n = 96$) or recent gastrointestinal bleeding ($n = 43$). Patients with gastrointestinal malignancy or bleeding had more severe stroke than those without (median NIHSS [interquartile range]: 14.0 [8.0–19.0] vs. 11.0 [6.0–18.0]). The rates of in-hospital mortality and life-threatening systemic haemorrhage were not significantly different between those with and without gastrointestinal malignancy or bleeding (mortality: 10.3% vs. 9.0%, adjusted odds ratio [aOR] 1.01, 95%CI 0.58–1.75; bleeding: 2.3% vs. 1.2%, aOR 1.72, 95%CI 0.58–5.11).

Conclusions: In this observational cohort, we did not find increased risk of in-hospital mortality and bleeding in rtPA-treated patients with gastrointestinal malignancy or recent gastrointestinal bleeding.

Keywords

Recombinant tissue plasminogen activator, thrombolysis, stroke, contraindication, eligibility criteria

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Introduction

The clinical benefit of thrombolysis therapy with intravenous recombinant tissue plasminogen activator (rtPA) for patients with a diagnosis of acute ischemic stroke (AIS) has been established. Yet, owing to the concern for exacerbating risk of bleeding, use of rtPA in AIS patients with structural gastrointestinal (GI) malignancy or recent history of GI bleeding event within 21 days of the indexed stroke event is

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contraindicated in the 2018 American Heart Association (AHA)/American Stroke Association (ASA) guideline based on consensus of expert opinion.¹ However, there are limited data to support or refute the safety of rtPA for this specific population.²

To address the sparse evidence, the goals of the study were to evaluate the characteristics and clinical outcomes in patients treated with rtPA for AIS who had GI malignancy or recent history of GI bleeding event compared with those treated with rtPA but have no medical history of GI malignancy or bleeding.

Methods

Data source

The cohort for this analysis was derived from the AHA/ASA Get With The Guidelines-Stroke (GWTG-Stroke). The GWTG-Stroke registry is an ongoing, voluntary, continuous registry sponsored by the AHA/ASA.³ The in-hospital data from the GWTG-Stroke registry were linked to the Centers for Medicare & Medicaid Services (CMS) claims data to identify structural GI malignancy or recent GI bleeding prior to the index stroke event. Because GWTG-Stroke is an inpatient registry, we link the GWTG-Stroke to CMS claims among Medicare fee-for-services patients

65 years or older and determine the timing of the previous GI malignancy or bleeding event. This probabilistic linkage has previously been validated and was done by matching on a series of indirect identifiers, including admission date, discharge date, patient age or date of birth, and sex.⁴ Prior work has shown that patients in the linked GWTG-Stroke/CMS database are representative of the national Medicare AIS population.^{5,6} IQVIA serves as the data collection and coordination centre for GWTG-Stroke.

Study population

For the purpose of this analysis, we identified all patients aged 65 years or older with a diagnosis of AIS treated with rtPA within 4.5 h from the symptom onset from the GWTG-Stroke/CMS linked dataset between February 2009 and December 2015. In this study, only patients aged 65 years or older were included to enable to link to Medicare database, since it provides health insurance for Americans aged 65 and older. We excluded (1) inpatient onset of AIS, (2) patients transferred in, (3) patients treated with experimental rtPA, (4) discharge status missing, not documented, or discharge against medical advice, and transfer out, and (5) patients who underwent catheter-based treatment (Figure 1). Patients treated with experimental rtPA refer to those participating in

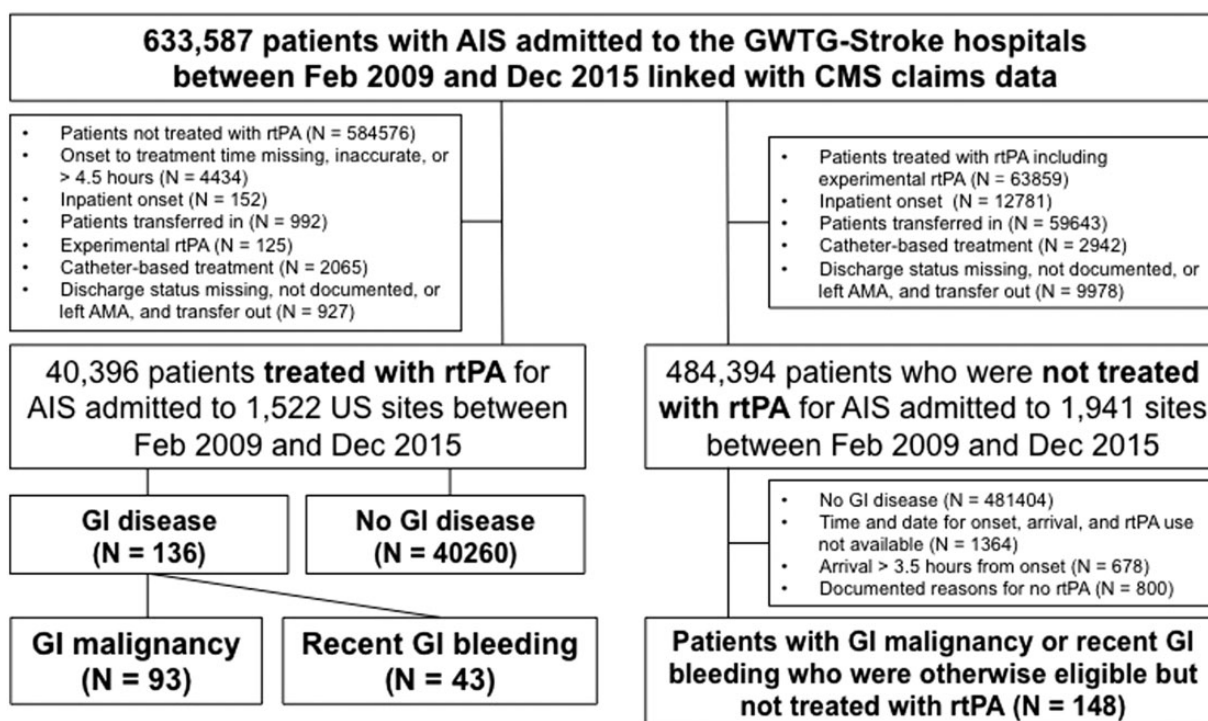


Figure 1. Study cohort creation.

AIS: acute ischemic stroke; CMS: Centers for Medicare & Medicaid Services; FFS: fee-for-service; rtPA: recombinant tissue plasminogen activator; AMA: against medical advice; GI: gastrointestinal.

clinical trials. Then, we classified patients according to the presence or absence of either GI malignancy or recent GI bleeding or both. GI malignancy and recent GI bleeding were identified using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9 CM) primary diagnosis codes (eAppendix in the Supplement). GI malignancy was defined as any GI malignancy

hospitalisation within one year prior to AIS. Recent GI bleeding was defined as GI bleeding hospitalisation within 21 days prior to AIS.

To evaluate potential treatment selection in patients with GI malignancy or bleeding who received rtPA and those not received rtPA, we also identified a separate cohort of AIS patients with GI malignancy or recent GI bleeding who were otherwise eligible but not treated

Table 1. Baseline characteristics between AIS patients treated with rtPA with vs. without GI malignancy or recent GI bleeding.

Characteristics	GI malignancy or Recent GI bleeding (N = 136)	No GI disease (N = 40,260)	Absolute standardised difference (%)
Age, median (IQR), y	80 (76–86)	81 (74–87)	5.67
Women, no. (%)	72 (52.9)	23,370 (58.1)	10.3
Race, no. (%)			21.6
Non-Hispanic white	120 (88.2)	33,205 (82.6)	
Non-Hispanic black	8 (5.9)	3337 (8.3)	
Hispanic	3 (2.2)	1526 (3.8)	
Asian	4 (2.9)	829 (2.1)	
Other	1 (0.7)	1298 (3.2)	
Medical history, No. (%)			
AF or atrial flutter	69 (51.5)	12,227 (30.6)	43.6
Previous stroke	26 (19.4)	8123 (20.3)	2.3
Previous transient ischemic attack	14 (10.5)	4122 (10.3)	0.5
Carotid stenosis	8 (6.0)	1394 (3.5)	11.7
CAD including prior myocardial infarction	45 (33.6)	12,078 (30.2)	7.3
Diabetes mellitus	41 (30.6)	10,429 (26.1)	10.1
Peripheral vascular disease	7 (5.2)	1787 (4.5)	3.5
Hypertension	105 (78.4)	31,803 (79.5)	2.8
Smoker	9 (6.7)	3052 (7.6)	3.5
Dyslipidaemia	69 (51.5)	18,775 (46.9)	9.1
Heart failure	20 (14.9)	4803 (12.1)	8.6
Laboratory data			
Creatinine, median (IQR), mg/dL	1.0 (0.9–1.4)	1.0 (0.8–1.3)	1.5
Arrival and admission information, No. (%)			
EMS arrival	109 (89.3)	32,914 (87.3)	6.3
Arrived off-hours	72 (52.9)	19,019 (47.2)	11.4
NIHSS at presentation, median (IQR)	14 (8–19)	11 (6–18)	23.2
Preadmission medication, no. (%)			
Antiplatelet	46 (37.4)	20,382 (54.2)	34.1
Anticoagulant	16 (13.1)	3105 (8.3)	15.8
Antihypertensive	94 (82.5)	26,306 (76.8)	14.1
Cholesterol reducer	58 (43.9)	19,063 (47.6)	7.3
Diabetic medications	22 (19.6)	6711 (20.1)	1.11
Vital signs			
Heart rate, median (IQR), bpm	79 (69–92)	78 (68–90)	6.5
sBP, median (IQR), mmHg	154 (136–171)	157 (140–177)	18.1
dBP, median (IQR), mmHg	79 (67–89)	81 (70–93)	24.3
Hospital characteristics			
Bed size, median (IQR), No.	361 (260–538)	378 (258–585)	8
Academic centre, No. (%)	105 (79.0)	30,794 (77.5)	3.5
Primary stroke centre, No. (%)	29 (21.3)	9253 (23.0)	4
Rural hospital, No. (%)	5 (3.7)	1251 (3.1)	3.1
Annual IV rtPA cases, median (IQR)	23.0 (16.6–38.2)	26.0 (15.9–38.6)	8.6

GI: gastrointestinal; IQR: interquartile range; EMS: emergency medical services; sBP: systolic blood pressure; dBP: diastolic blood pressure; rtPA: recombinant tissue plasminogen activator.

with rtPA. Along with our primary study population, baseline characteristics as well as outcomes of AIS patients with GI malignancy or bleeding who were treated with rtPA were compared with those of AIS patients with GI malignancy or bleeding who were otherwise eligible but not treated with tPA. Patients were considered eligible if they arrived within 3.5 h from symptom onset (potentially eligible for the 0–4.5 h treatment window) without any documented reasons for no rtPA use except for GI malignancy or recent GI bleeding (Figure 1).

Outcome measures

The primary outcomes were in-hospital mortality and life-threatening or serious systemic haemorrhage within 36 h after rtPA use (yes vs. no). Other outcomes included discharge disposition (home vs. other), in-hospital mortality or discharge to hospice, ambulatory status at discharge (able to ambulate independently vs. not), and modified Rankin Scale (mRS) at discharge (range of 0 [no symptoms] to 6 [death], with 0–2 as functional independence) and complications related to rtPA, including symptomatic intracranial haemorrhage within 36 h and any serious complications.

Statistical analysis

We reported the medians with interquartile ranges (IQRs) for continuous and counts with percentages for categorical variables. An absolute standardised difference was used to compare baseline differences among groups. An absolute standardised difference greater than 10 indicates significant imbalance. Multivariable logistic regression models were performed to assess the relationship between a history of GI malignancy or bleeding with each clinical outcome. These analyses adjusted for all variables are listed in Table 1. Generalised estimation equations modelling approach was used to account for within-hospital clustering of patients. As a sub-group analysis, GI malignancy or recent GI bleeding was separately analysed. All variables in the multivariable analyses had less than 5% missingness except for arrival via EMS (6%), pre-admission medications (6% for antiplatelet and anticoagulation, 15% for antihypertensive and diabetic medications), and systolic blood pressure (11%). Given that missing data were uncommon, single imputation methods were used for multivariable analyses; female for sex, non-Hispanic white for race/ethnicity, and “No” for others.

Ethical approval for this study was obtained from the institutional review board of Duke University. Each participating hospital received either human research approval to enrol patients without individual

patient consent under the Common Rule or a waiver of authorisation and exemption from subsequent review by their institutional review board. All statistical analyses were performed by the Duke Clinical Research Institute using SAS software version 9.4 (SAS Institute, Inc., Cary, NC). All *P*-values are two-sided, and $P < 0.05$ was considered statistically significant and 95% confidence interval was reported.

Results

Baseline characteristics

Our study included a total of 40,396 AIS patients who were treated with rtPA (mean age [SD] 81.0 [8.1] years; 41.9% women) at 1522 US sites between February 2009 and December 2015 (Figure 1). Of these, 136 patients (0.3%) had GI malignancy ($n = 93$) within one year or recent GI bleeding ($n = 43$) within 21 days. The median time interval from recent GI bleeding event to stroke onset was 15 days (25–75 percentiles 10–18) with a minimum of 3 days and maximum of 21 days. Baseline characteristics by GI conditions are shown in Table 1. Patients with GI malignancy or bleeding were more likely to be male and non-Hispanic white, and have a higher prevalence of atrial fibrillation or flutter and diabetes. The severity of AIS at admission as measured by NIHSS was greater in patients with GI malignancy or bleeding than those without (median [IQR]: 14.0 [8.0–19.0] vs. 11.0 [6.0–18.0]).

Among AIS patients with GI malignancy or bleeding who arrived within the 3.5 h time window, 148 were otherwise eligible but did not receive rtPA (Figure 1). Therefore, in the GWTG-Stroke/CMS linked dataset between February 2009 and December 2015, there were a total of 284 AIS patients with GI malignancy or bleeding otherwise eligible for rtPA, and of these, 47.9% ($n = 136$) was actually treated with rtPA. When compared with those treated with rtPA, patients not receiving rtPA were more likely to be older and female, have a higher prevalence of comorbidities, arrive later (median [IQR] onset to arrival time: 65.5 [41.5–94.0] min vs. 55.0 [35.0–89.0] min), be on oral anticoagulants prior to AIS, have less severe AIS (median [IQR]: 10.0 [4.0–18.0] vs. 14.0 [8.0–19.0]), and be treated in less experienced institutes for rtPA use (eTable 1 in the Supplement).

Clinical outcomes

Clinical outcomes by the presence or absence of GI malignancy or bleeding are summarised in Figure 2. The unadjusted in-hospital mortality rates were 10.3% for those with GI malignancy or bleeding and 9.0% for those without. After the adjustment for

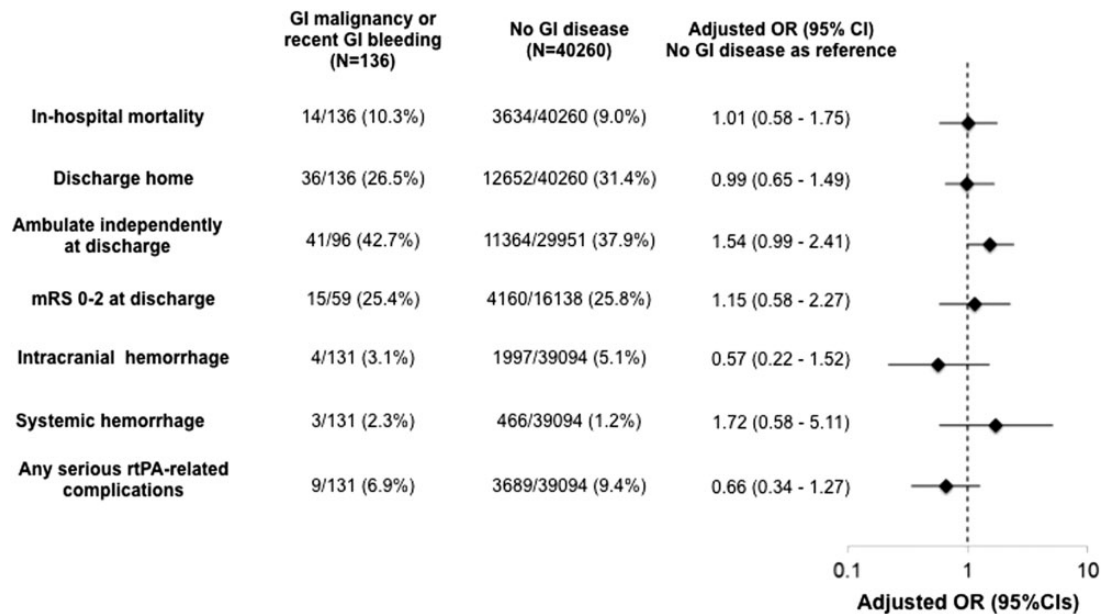


Figure 2. Clinical outcomes by the presence or absence of GI malignancy or recent GI bleeding.

GI: gastrointestinal; OR: odds ratio; CI: confidence interval; mRS: modified Rankin scale; rtPA: recombinant tissue plasminogen activator.

confounders, there was no difference in in-hospital mortality between groups (adjusted odds ratio [aOR] 1.01, 95%CI 0.58–1.75, $P=0.97$). Although the unadjusted rates of life-threatening systemic haemorrhage were numerically higher in those with GI malignancy or bleeding than those without, the difference was not significant after the risk adjustment (2.3% vs. 1.2%, aOR 1.72, 95%CI 0.58–5.11, $P=0.33$).

Sub-group analyses by GI condition

Among a total of 136 AIS patients with GI disease, 93 patients had GI malignancy and 43 patients had recent GI bleeding. Clinical outcomes by GI malignancy or recent GI bleeding are summarised in Table 2. Overall, even when GI malignancy or recent GI bleeding was separately analysed, findings were consistent with the main analysis.

Discussion

In this registry-based retrospective cohort study, among >40,000 AIS patients who were treated with rtPA, 0.3% of patients had GI malignancy or recent GI bleeding. After the risk adjustment, GI malignancy or recent GI bleeding was not associated with increased risks of in-hospital mortality and bleeding complications compared with no history of GI malignancy or bleeding.

Owing to the concern for exacerbating risk of bleeding, GI malignancy and recent GI bleeding were

excluded from the landmark clinical trials evaluating the efficacy and safety of rtPA in patients with a diagnosis of AIS, such as NINDS and ECASS 2 trials.^{7,8} As a result, these conditions are considered to be contraindicated for the use of rtPA in the AHA/ASA guidelines.¹ Reflecting the lack of evidence, the relevant statement in the 2018 guideline is not identical to that in the 2013 guideline. In the 2013 guideline, “active internal bleeding” is listed as a contraindication and differentiated from “recent GI haemorrhage within previous 21 days” that is considered as a warning,⁹ whereas, in the 2018 guideline, they are unified into “recent GI bleeding event within 21 days of their stroke event” and considered as a contraindication.¹ In addition, a structural GI malignancy is newly listed as a contraindication.¹ However, to date, there is no study to support or refute this statement. In our analysis, the rates of mortality and bleeding complications in patients with GI malignancy or recent GI bleeding were not significantly higher than those in patients without GI malignancy or bleeding, suggesting that use of rtPA for patients with GI malignancy or recent GI bleeding may be considered in carefully selected patients.

The safety of thrombolytic therapy for treating AIS in patients with cancer is still controversial;^{10–18} however, the majority of previous studies suggest that rtPA may be able to be used safely in selected patients. Murthy et al.¹⁰ reported the largest study from the US Nationwide Inpatient Sample evaluating

Table 2. Clinical outcomes in sub-group analyses.

	GI malignancy in past 1 year N = 93	No GI malignancy in past 1 year N = 40,303	Adjusted OR (95% CI)	P	Recent GI bleeding N = 43	No GI bleeding in past 21 days N = 39,781	Adjusted OR (95% CI)	P
In-hospital outcomes								
In-hospital mortality	10/93 (10.8%)	3638/40,303 (9.0%)	1.14 (0.57, 2.30)	0.71	4/43 (9.3%)	3572/39,781 (9.0%)	0.79 (0.29, 2.12)	0.64
In-hospital death or discharge to hospice	21/93 (22.6%)	7141/40,303 (17.7%)	1.36 (0.76, 2.44)	0.3	7/43 (16.3%)	7011/39,781 (17.6%)	0.57 (0.26, 1.25)	0.16
Able to ambulate independently at discharge	30/65 (46.2%)	11,375/29,982 (37.9%)	1.49 (0.86, 2.57)	0.15	11/31 (35.5%)	11,273/29,621 (38.1%)	1.68 (0.82, 3.46)	0.16
Discharge home	27/93 (29.0%)	12,661/40,303 (31.4%)	0.95 (0.59, 1.50)	0.81	9/43 (20.9%)	12,539/39,781 (31.5%)	1.10 (0.46, 2.61)	0.83
Modified Rankin scale 0–2	13/41 (31.7%)	4162/16,156 (25.8%)	1.32 (0.61, 2.88)	0.48	2/18 (11.1%)	4137/15,937 (26.0%)	0.65 (0.11, 3.75)	0.63
rtPA related complication								
Symptomatic intracranial haemorrhage	4/89 (4.5%)	1997/39,136 (5.1%)	0.88 (0.32, 2.40)	0.81	0/42 (0%)	1968/39,628 (5.1%)	NA	NA
Life-threatening systemic haemorrhage	2/89 (2.3%)	467/39,136 (1.2%)	1.52 (0.42, 5.56)	0.52	1/42 (2.4%)	456/38,628 (1.2%)	2.33 (0.33, 16.3)	0.4
Any serious complication related to rtPA	8/89 (9.0%)	3690/39,136 (9.4%)	0.92 (0.44, 1.89)	0.81	1/42 (2.4%)	3632/38,628 (9.4%)	0.20 (0.03, 1.29)	0.09

GI: gastrointestinal; OR: odds ratio; rtPA: recombinant tissue plasminogen activator; NA: not applicable.

in-hospital outcomes after rtPA use in AIS patients with cancer ($n=807$) compared with non-cancer patients ($n=31,769$) and found that there was no difference in rates of in-hospital mortality and intracerebral hemorrhage.¹⁰ To the contrary, Nam et al.¹⁷ retrospectively reviewed 12 AIS patients with active cancer treated with rtPA and showed their poor clinical outcomes. These discrepancies may be due to the difference in the definition of malignancy and severity of the indexed stroke among studies. Importantly, none of these prior works were specific to GI malignancy. To our knowledge, our present study analysed the largest scale of AIS patients with GI malignancy and suggested the potential safety of rtPA use for this population.

No data are available with respect to the safety of rtPA use in patients with recent history of GI bleeding event within 21 days of the indexed stroke event. To date, two studies assessed the safety of off-label use of rtPA for treating AIS and showed the off-label thrombolysis therapy was not associated with poor clinical outcomes.^{19,20} In these two studies, a total of nine patients with “systemic disease with risk of bleeding” were included; however, there were no patients with recent GI bleeding. Given no difference in subsequent bleeding events after rtPA use, our study suggests that thrombolysis therapy may be considered, once a bleeding site is well controlled.

Limitation

There are several limitations in our study. First, our study does not have any information regarding the severity of underlying GI malignancy and recent GI bleeding, which may affect mortality and subsequent bleeding events. Second, despite the use of the largest stroke registry in the US, sample size may not be sufficient to analyse the safety of rtPA use in patients with GI malignancy or recent GI bleeding. However, we would like to emphasise that this is the first report to evaluate the safety of rtPA use in this specific population with this large-scale database. Third, rtPA was used only for selected subset in patients with GI malignancy or bleeding, which may have skewed the results. This selection bias may have resulted in either underestimated or overestimated risks in patients with GI malignancy or bleeding. Fourth, we were unable to evaluate the benefits of rtPA vs. no rtPA in patients with GI malignancy or bleeding because 90-day mRS and other post discharge functional outcomes are not collected in the registry. Fifth, we did not have data on concomitant use of proton pump inhibitors despite their potential effects on reducing the risk of GI bleeding.^{21,22} However, their use would likely be considered in patients at known high risk of upper GI bleeding.

Conclusions

In this observational cohort, we did not find statistically significant increased risk of mortality and bleeding complications in rtPA-treated patients with structural GI malignancy or recent GI bleeding within 21 days of their index stroke.

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Declaration of Conflicting Interests

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Informed consent

Each participating hospital received either human research approval to enrol patients without individual patient consent under the Common Rule or a waiver of authorisation and exemption from subsequent review by their institutional review board.

Ethical approval

Ethical approval for this study was obtained from the institutional review board of Duke University.

Guarantor

YX.

Trial registration

ClinicalTrials.gov Identifier: NCT02693223.

Authors' contributions

Dr. Taku Inohara and Dr. Ying Xian had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Supplemental material

Supplemental material for this article is available online.

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