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AJNR Am J Neuroradiol 2022, 43 (3) 381-387
doi: https://doi.org/10.3174/ajnr.A7412
http://www.ajnr.org/content/43/3/381

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ABSTRACT

BACKGROUND AND PURPOSE: Hemorrhagic transformation is a critical complication associated with ischemic stroke and has been associated with contrast media administration. The objective of our study was to use real-world in-hospital data to evaluate the correlation between contrast media type and transformation from ischemic to hemorrhagic stroke.

MATERIALS AND METHODS: We obtained data on inpatient admissions with a diagnosis of ischemic stroke and a record of either iso-osmolar or low-osmolar iodinated contrast media for a stroke-related diagnostic test and a treatment procedure (thrombectomy, thrombolysis, or angioplasty). We performed multivariable regression analysis to assess the relationship between contrast media type and the development of hemorrhagic transformation during hospitalization, adjusting for patient characteristics, comorbid conditions, procedure type, a threshold for contrast media volume, and differences across hospitals.

RESULTS: Inpatient visits with exclusive use of either low-osmolar ($n = 38,130$) or iso-osmolar contrast media ($n = 4042$) were included. We observed an overall risk reduction in hemorrhagic transformation among patients who received iso-osmolar compared with low-osmolar contrast media, with an absolute risk reduction of 1.4% ($P = .032$), relative risk reduction of 12.5%, and number needed to prevent harm of 70. This outcome was driven primarily by patients undergoing endovascular thrombectomy ($n = 9211$), in which iso-osmolar contrast media was associated with an absolute risk reduction of 4.6% ($P = .028$), a relative risk reduction of 20.8%, and number needed to prevent harm of 22, compared with low-osmolar contrast media.

CONCLUSIONS: Iso-osmolar contrast media was associated with a lower rate of hemorrhagic transformation compared with low-osmolar contrast media in patients with ischemic stroke.

ABBREVIATIONS: CM = contrast media; HT = hemorrhagic transformation; IOCM = iso-osmolar contrast media; LOCM = low-osmolar contrast media

According to the World Health Organization, stroke is among the leading causes of death worldwide.[1] In the United States, the prevalence of stroke in adults is 2.9% and increases with age in both sexes.[2] An estimated 795,000 adults experience a stroke each year, most of these ($n = 610,000$) are first events.[2] That is approximately 1 stroke every 40 seconds, which contributes to the status of stroke as a leading cause of serious long-term disability. Among all strokes, 87% are classified as ischemic; 10%, as intracerebral hemorrhage; and 3%, as subarachnoid hemorrhage.[2]

Imaging procedures, specifically CT, CTA, and CTP, provide important information in the management of patients with stroke. Accordingly, the 2018 American Heart Association/American Stroke Association Guideline recommends noncontrast CT for the evaluation of initial brain imaging and CTA for vessel evaluation if patients are suspected of having intracranial large-vessel occlusion.[3] 3D reformats of contrast-enhanced CTAs provide clear images of cerebral blood vessels,[4] which support a diagnosis before the initiation of systemic, surgical, or endovascular therapy.

The transformation from ischemic to hemorrhagic stroke, also referred to as hemorrhagic transformation (HT), is a potential complication following acute ischemic stroke. Permeability of the blood-brain barrier[5-9] due to tissue and vessel wall injury from severe ischemia[9,10] allows blood[11] as well as contrast media (CM) leakage[11-13] across the barrier and has been hypothesized to be associated with HT. The risk of HT has been demonstrated

Received May 3, 2021; accepted after revision November 21.

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This study was sponsored by GE Healthcare.

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Indicates article with online supplemental data.

http://dx.doi.org/10.3174/ajnr.A7412

to increase with the use of fibrinolytic agents, which may increase potent fibrinolytic activity, and with endovascular treatment, which may result in mechanical damage to the blood vessel endothelium.[14] The association of CM properties with HT has been studied in an occlusion and reperfusion rat model by Morales et al,[15] who showed a statistically significant reduction in cortical intracranial hemorrhage with the iso-osmolar CM (IOCM) iodixanol in comparison with the low-osmolar CM (LOCM) iopamidol. This difference in outcome might be related to the known differences in physicochemical properties that exist between LOCM and IOCM.[16] The Interventional Management of Stroke III trial[17] assessed 5 efficacy and safety end points, including asymptomatic and symptomatic intracranial hemorrhage, and mortality between iodixanol and LOCM among patients with stroke treated with endovascular therapy. The study found that unadjusted and adjusted results for efficacy and safety end points favored the use of iodixanol and concluded that it contributed less endothelial cytotoxic effect to the thrombotic process. In a subsequent MCA occlusion/reperfusion model in rats, Morales et al[18] confirmed their previous results and hypothesized that the presence of HT may represent a direct/indirect effect of radiographic CM in the brain parenchyma, with less impact of IOCM iodixanol compared with LOCM iopamidol. These promising prior investigations have not yet been extended to larger patient cohorts in the real-world setting.

The objective of this study was, therefore, to use real-world hospital data to evaluate the correlation between the type of iodinated CM used in the diagnosis and treatment of acute ischemic stroke and HT of ischemic stroke during inpatient visits.

MATERIALS AND METHODS

Data Source

We obtained data from the Premier Healthcare Database,[19] which is a large, all-payer data base containing records from hospitals around the United States, primarily nonprofit, nongovernmental, community, teaching hospitals, and health care systems from rural and urban areas. The data base represents approximately 25% of annual inpatient discharges in the United States, including >6 million visits per year since 2012. All data used to perform this analysis were de-identified and accessed in compliance with the Health Insurance Portability and Accountability Act. As a retrospective analysis of a de-identified data base, the research was exempt from institutional review board review under Department of Health and Human Services regulations for the protection of human subjects, 45 CFR 46.101(b)(4).

Inclusion/Exclusion Criteria

We analyzed records from the Premier Healthcare Database from July 1, 2012, through December 31, 2018, and included those with a diagnosis of ischemic stroke on admission or as an admitting diagnosis. Patients were also required to have a record of both a diagnostic test (CT, MR imaging, sonography, or angiography) and a treatment procedure (endovascular or open thrombectomy, systemic or catheter thrombolysis, or angioplasty) (Online Supplemental Data). Patients were excluded if they had documented end-stage kidney disease, chronic kidney disease stage 5, or a prior history of stroke (Online Supplemental Data).

Predictors and Outcome Variables

Patients who met the above inclusion criteria were placed into cohorts based on CM usage: IOCM or LOCM. CM usage was determined using Premier's standard charge master (which is a comprehensive table of items billable to a patient or health insurance provider), within which we identified IOCM (iodixanol) and LOCM (iohexol, ioversol, iopamidol, and other) contrast media. IOCM (versus LOCM) was the main exposure variable of interest. Patients with evidence of both LOCM and IOCM use, unknown contrast, or no contrast were excluded to allow a true comparison of CM.

Independent variables of interest included patient demographics, comorbid conditions, admission status, and CM volume. Patient demographics for this analysis included age, race, sex, and year of admission. Admission source, admission type, and hospital characteristics including bed size, location (urban or rural), teaching status, and United States census region were also characterized. Comorbid conditions were measured via the Elixhauser Comorbidity Index score.[20] The Elixhauser Comorbidity Index score includes 31 categories of comorbidities such as congestive heart failure, liver and renal disease, diabetes, neurologic disorders, peripheral vascular disorders, and others that are associated with mortality. These comorbidities were identified using diagnosis codes from the admission for ischemic stroke. A composite score was calculated from the comorbidity categories (Online Supplemental Data). Additional comorbid conditions were considered, including chronic kidney disease status and prior acute kidney injury. Patients with stage 5 chronic kidney disease or end-stage renal disease were excluded.

The primary outcome was the transformation from ischemic to hemorrhagic stroke during an inpatient hospitalization. Hemorrhagic transformation was defined as any patient visit that had an admitting International Classification of Diseases version 9 or 10 diagnosis of ischemic stroke without hemorrhagic stroke being present on admission in combination with a primary or secondary diagnosis code or outcome of hemorrhagic stroke that developed during the hospital visit. Success of a given treatment was not considered because the purpose of the study was to compare the 2 contrast classes.

Statistical Analysis

Descriptive analysis included summarizing categoric variables with counts and percentages, while continuous variables were summarized with means and SDs.

The association of the IOCM (versus LOCM) use with the end point of transformation to hemorrhagic stroke was examined using multivariable regression analysis. We modeled all patient visits including the following procedures: catheter thrombolysis, systemic thrombolysis, open thrombectomy, and endovascular thrombectomy. Endovascular thrombectomy was also modeled separately as a subanalysis. Hospital sites were used as fixed effects to control for observable and unobservable differences in the severity of patients' conditions and all other hospital factors (such as surgical practices, treatments, staffing patterns, physician skill, and so forth) across hospitals that may be associated with not only outcomes but also choice of CM. The multivariable regression model adjusted for year, patient demographics (age, sex, admission status, and race), the Elixhauser Comorbidity

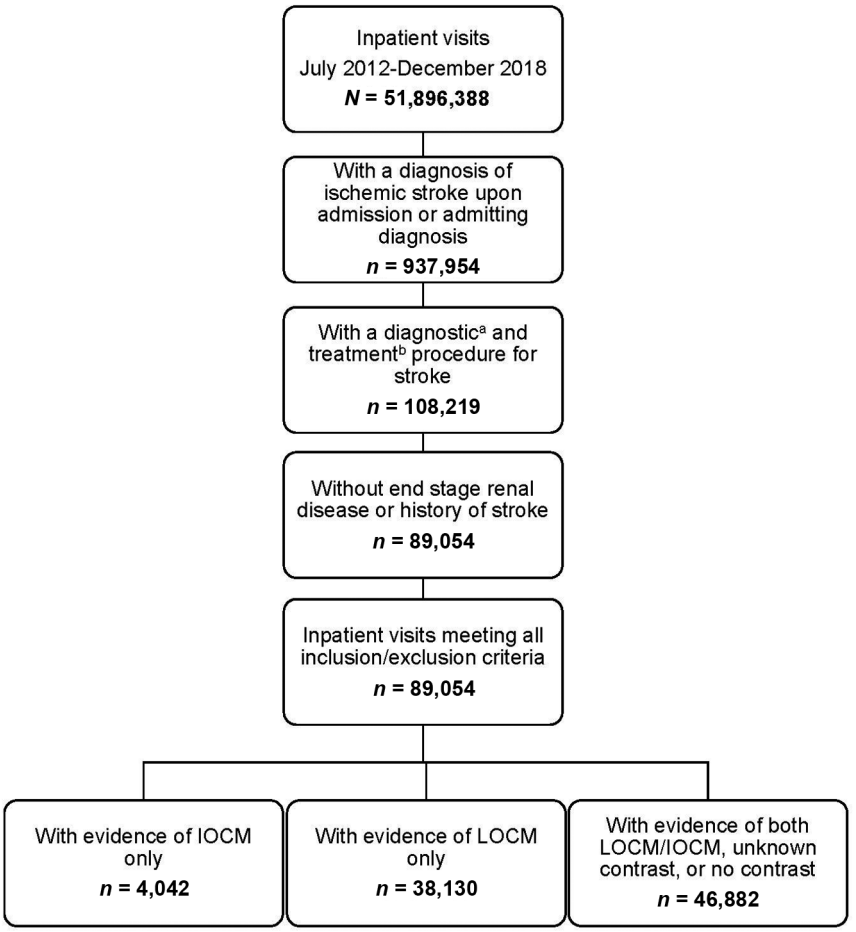

FIG 1. Attrition diagram. Diagnostic procedures[a]: CT, MRI, ultrasound, angiography. Treatment procedures[b]: endovascular and open thrombectomy, systemic or catheter thrombolysis, angioplasty

Index score, chronic kidney disease status, and history of acute kidney injury, and a threshold flag for CM volume used was set at ≥200 mL. All statistical analyses in this study were performed using SAS software, Version 9.4 (SAS Institute).

GE Healthcare provided financial support for the study performed by CTI Clinical Trial & Consulting Services, with the design and interpretation input of clinicians. Although the funding for the project was provided by GE Healthcare, the authors had freedom of investigation and full control of the design of the study, methods used, outcome parameters and results, analysis of data, and production of the written report.

RESULTS

During the study period of July 2012 to December 2018, there were 51,896,388 inpatient visits included in the data base of a total of 563 unique hospital identifications. Of these visits, 937,954 had a diagnosis of ischemic stroke at admission. Eleven percent of those ($n = 108,219$) received a diagnostic test and treatment procedure for stroke. Patients with chronic kidney disease stage 5, end-stage renal disease, or a history of stroke were excluded, leaving 89,054 inpatient visits. Of those, 4042 patients had a record of IOCM use and 38,130 had a record of LOCM use. An additional 46,882 had evidence of both LOCM and IOCM, unknown CM, or no CM; these patients were not analyzed further (Fig 1).

Patients receiving IOCM were slightly older (mean age, 69.1 [SD, 13.8] years versus 67.2 [SD, 14.6] years for patients receiving LOCM) with Medicare usage in 64.8% of the IOCM and 58.6% of the LOCM cohort (Table 1). Patients receiving IOCM had higher rates of chronic kidney disease stage 3 or 4 (stage 3 IOCM, 9.0%, versus LOCM, 5.4%; stage 4 IOCM, 2.0%, versus LOCM, 0.8%) and of acute kidney injury on admission (10.0% IOCM versus 7.7% LOCM). Nearly all patients underwent CT (91.6% IOCM versus 98.3% LOCM), and nearly 70% of each cohort underwent MR imaging (Table 2). The use of sonography was 5.2% in the IOCM and 7.9% in the LOCM cohort. The use of angiography varied between the groups with 47.1% of those receiving IOCM having angiography in comparison with only 21.3% of those receiving LOCM. The rate of thrombectomy was higher in patients receiving IOCM at 43.5% in comparison with patients receiving LOCM at 30.2% (Table 2). The rate of endovascular procedures was higher in patients receiving IOCM in comparison with patients receiving LOCM. Thrombolysis was performed more often in patients receiving LOCM, with 76.2% of these patients undergoing a systemic thrombolysis procedure in comparison with 56.8% of patients receiving IOCM.

In unadjusted analysis, there were 516 HTs (12.8%) in the IOCM cohort and 4354 (11.4%) in the LOCM cohort. On multivariable regression analysis, a significant reduction in the incidence of transformation from ischemic to hemorrhagic stroke was seen in patients receiving IOCM versus LOCM (Fig 2). Compared with LOCM, the absolute risk reduction of HT associated with IOCM was 1.4% (95% CI, 2.7%–0.1%; $P = .032$), the relative risk reduction was 12.5%, and the number needed to prevent harm was 70. This outcome following the multivariable regression analysis was driven by age, race, the Elixhauser Comorbidity Index score, and the high CM volume threshold of 200 mL.

When therapeutic procedures were modeled individually, patients undergoing endovascular thrombectomy ($n = 1439$ receiving IOCM, $n = 7772$ receiving LOCM) showed significant risk reduction associated with IOCM (HT rate 20.6% after IOCM versus 22.2% after LOCM, ie, absolute risk reduction, 4.66%; 95% CI, 8.7%–0.5%; $P = .028$; relative risk reduction, 20.8%; and

Table 1: Patient demographics and comorbidities

Patient Characteristics (No.) (%)[a]	IOCM (n = 4042)		LOCM (n = 38,130)	
Age (yr)				
Mean (SD)	69.1	(13.8)	67.2	(14.6)
Sex				
Male	2083	(51.5)	20,140	(52.8)
Female	1959	(48.5)	17,988	(47.2)
Race				
White	3058	(75.7)	28,995	(76.0)
Black	501	(12.4)	4652	(12.2)
Other	483	(11.9)	4483	(11.8)
Insurance				
Commercial	174	(4.3)	2020	(5.3)
Medicare	2619	(64.8)	22,347	(58.6)
Medicaid	334	(8.3)	3907	(10.2)
Managed care	670	(16.6)	6726	(17.6)
Other	245	(6.1)	3130	(8.2)
Elixhauser Comorbidity Index score[b]				
Mean (SD)	4.6	(2.2)	4.5	(2.2)
Chronic kidney disease				
Stage 1	6	(0.1)	34	(0.1)
Stage 2	33	(0.8)	319	(0.8)
Stage 3	363	(9.0)	2067	(5.4)
Stage 4	81	(2.0)	293	(0.8)
Unspecified	274	(6.8)	1574	(4.1)
Record of acute kidney injury				
On admission	405	(10.0)	2929	(7.7)
In previous admission	37	(0.9)	321	(0.8)

[a] All values reported as No. (%) unless otherwise noted.
[b] The Elixhauser Comorbidity Index score is calculated using 31 categories of comorbidities associated with mortality and is based on International Classification of Diseases 9 and 10 codes. Each comorbidity category is dichotomous and includes heart failure, cardiac arrhythmia, hypertension, diabetes mellitus, obesity, and so forth.

Table 2: Diagnostic and treatment procedures

Procedures[a]	IOCM (n = 4042)		LOCM (n = 38,130)	
Diagnostic procedures				
CT	3704	(91.6)	37,497	(98.3)
MR imaging	2812	(69.6)	27,652	(72.5)
Sonography	211	(5.2)	2997	(7.9)
Angiography	1904	(47.1)	8105	(21.3)
Treatment procedures				
Thrombectomy	1759	(43.5)	11,501	(30.2)
Endovascular thrombectomy	1439	(35.6)	7772	(20.4)
Open thrombectomy	325	(8.0)	3761	(9.9)
Thrombolysis	2296	(56.8)	29,073	(76.2)
Catheter thrombolysis	392	(9.7)	2656	(7.0)
Systemic thrombolysis	1904	(47.1)	26,417	(69.3)
Angioplasty	780	(19.3)	2718	(7.1)

[a] Data are No. (%).

number needed to prevent harm, 22). There were no significant differences in absolute risk between IOCM and LOCM in patients undergoing catheter thrombolysis, systemic thrombolysis, and open thrombectomy.

DISCUSSION

Cerebral infarction is an important clinical problem by itself. Because it primarily affects elderly populations, its prevalence is expected to increase as populations age.[2] There is also increased recognition that stroke is now occurring in younger populations.[2] Additionally, the coronavirus disease 2019 (COVID-19) pandemic has added a new group of patients with stroke needing treatment.[21] Iodinated intravascular contrast media have long been a staple of radiographic diagnosis and interventions. The safety of contrast agents continues to be carefully studied with largely familiar adverse events, including renal,[22-24] cardiovascular,[23,25] hemodynamic,[26] injection site discomfort,[27] and acute allergic reactions.[28] Given that many patients undergoing interventional procedures are in at-risk categories, the reduction of complications from contrast becomes even more important and the choice of an appropriate agent is an important consideration along with other frequently used periprocedural mitigation measures such as patient risk assessments, optimal periprocedural hydration, contrast volume management, and necessary premedication or withholding of medications.

This study used real-world, inpatient hospital data to evaluate the association between the type of contrast used and HT rates in patients hospitalized for ischemic stroke in the United States. Our analysis demonstrated a statistically significant risk reduction of HT between IOCM and LOCM use in a real-world cohort of >40,000 visits in patients presenting with ischemic stroke. This difference is most impressive among the subset of 9211 patients undergoing endovascular thrombectomy, indicating that overall HT differences were driven by this procedural cohort. The exact reason for this outcome is open to speculation. It is difficult to imagine that the physical effects of thrombectomy on the large vessels affect the endothelium in the distal vessels. Nevertheless, both groups would have had the same mechanical effects, with a similar impact on HT rates. Additionally, endothelial damage and HT arising from it are likely part of a broader set of conditions, including patient risk factors, anatomic location of ischemic stroke, and time to treatment. These may also introduce bias, expected to be the same for both cohorts. It is, therefore, likely that this outcome is a result of the contrast.

If the mechanical thrombectomy group had been removed from the overall analysis, it would have been difficult to demonstrate a positive effect of IOCM. The conundrum, however, is that at presentation with neurologic symptoms, it is not known

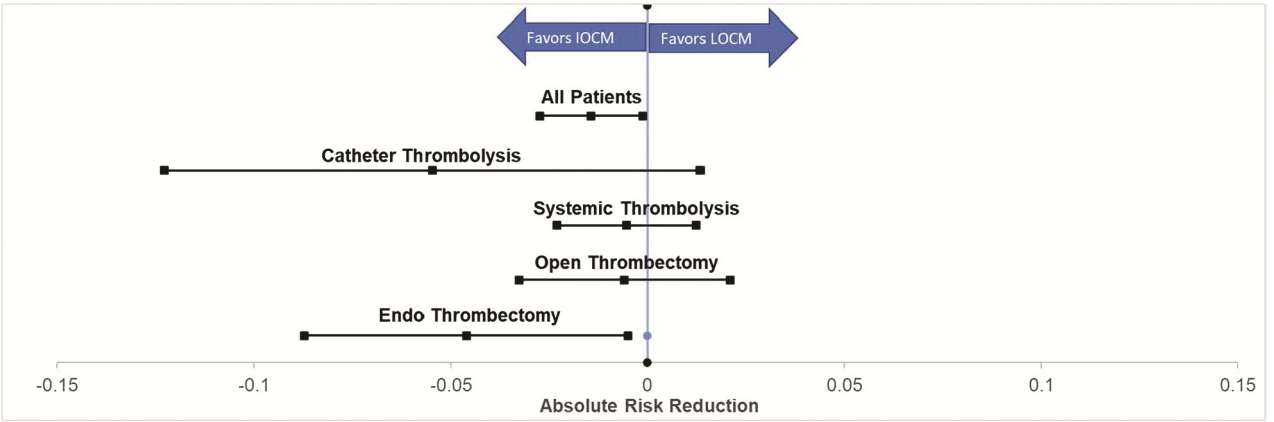

FIG 2. Multivariable model results. The all-patients model estimated a significant reduction in the incidence of transformation to hemorrhagic stroke in patients with ischemic stroke receiving IOCM versus LOCM. Only the endovascular thrombectomy subanalysis was statistically significant. Thrombolysis and open thrombectomy were not significant. Endo indicates endovascular.

whether the patient is going to undergo thrombectomy. On the basis of previously published preclinical and clinical studies,[13,15,17,18] it has been hypothesized that the presence of HT following a procedure with CM injection may represent a direct or indirect effect of the CM itself. This effect has been further hypothesized to be less after IOCM (iodixanol) administration compared with LOCM (iopamidol) administration and could be due to its larger molecular size or the reduced hydrodynamic effect of its more viscous macromolecular properties, resulting in less leakage across the blood-brain barrier.[18]

Despite these potential explanations for the observed differences in HT, the role of CM in this context is still not completely understood. In addition, it has been shown that 50% of patients with ischemic stroke undergoing endovascular treatment who also underwent contrast-enhanced CT developed HT.[29,30] With CTA/CTP techniques improving and their increasing use in the management of patients with stroke, the clinical relevance of these findings warrants further scrutiny. This is of particular importance because of the additional use of CM for endovascular procedures and has determined the inclusion criteria for this retrospective analysis of the Premier Hospital Database.

At presentation, it is not known whether a patient with acute stroke symptoms will undergo mechanical thrombectomy or another treatment. The transformation of a bland infarction to a hemorrhagic infarction can result in increased morbidity and mortality as well as precluding the use of some treatments, ie, antiplatelet drugs. HT has been reported to occur in approximately 10% of patients with untreated ischemic stroke and increases with the use of intravenous/intra-arterial thrombolytic therapy.[6,31] Although the clinical significance of the additional impact of CM in this context is not clear, the results indicate that the IOCM iodixanol may be considered the CM of choice in the diagnosis and treatment of patients with ischemic stroke.

Limitations

The limitations of this study include those that are inherent to retrospective data base analyses. The data source for this study was the Premier Hospital Database, which represents 20% of all inpatient discharges in the United States; however, given its reliance on International Classification of Diseases codes 9 and 10, there is a potential risk of coding errors. A second limitation of this data source is that it does not track patients longitudinally. Thus, all patients that transformed from ischemic stroke to hemorrhagic stroke were captured only during their stroke hospitalization. Additionally, HT is commonly characterized as symptomatic or asymptomatic; however, because HT was determined on the basis of codes, this study did not have the detail available to include this characterization. It was not possible, given the nature of the study, to examine the individual scans. We were reliant on the radiologists, neurologists, and coders at each hospital for the outcomes reported as HT; coding errors, misdiagnoses, and discordant findings are, therefore, possible.[32,33]

This study was not able to track other factors that may impact HT rates or the severity of the HT, such as procedural factors (use of different catheters, catheter placement), heparin volume, and size of the infarct. It is also possible that there was a bias in the use of the contrast agents, depending on the initial evaluation of the patient, including imaging findings, large-core infarct area, and NIHSS scores. This information is also not recoverable from a claims-based data base. Also, because the study focused on the HT incidence correlated with the CM type, we did not evaluate HT outcomes correlated with other factors such as thrombolytic-versus-endovascular therapy. We acknowledge this omission is a possible limitation of this study.

CONCLUSIONS

In this large real-world analysis, IOCM use was associated with a lower rate of HT compared with LOCM in patients hospitalized with ischemic stroke. Our outcomes especially suggest that iso-osmolar contrast is associated with statistically significant lower rates of HT compared with low-osmolar contrast in patients undergoing endovascular thrombectomy to treat ischemic stroke. Additional controlled clinical trials may add to the evidence base on contrast-associated outcomes in the evaluation and treatment of patients with ischemic stroke in an acute care setting.

Disclosures: Franklin G. Moser—*RELATED*: *Consulting Fee or Honorarium*: GE Healthcare; *Support for Travel to Meetings for the Study or Other Purposes*: GE Healthcare; *Fees for Participation in Review Activities such as Data Monitoring Boards, Statistical Analysis, Endpoint Committees, and the Like*: GE Healthcare; *Payment for Writing or Reviewing the Manuscript*: GE Healthcare; *Provision of Writing Assistance, Medicines, Equipment, or Administrative Support*: GE Healthcare. Thomas M. Todoran—*UNRELATED*: *Consultancy*: GE Healthcare. Michael Ryan—*RELATED*: *Fees for Participation in Review Activities such as Data Monitoring Boards, Statistical Analysis, Endpoint Committees, and the Like*: GE Healthcare; *UNRELATED*: *Consultancy*: I work as a consultant. Erin Baker—*RELATED*: *Consulting Fee or Honorarium*: CTI Clinical Trial & Consulting Services, *Comments*: I am an employee of CTI Clinical Trial & Consulting Services, which is a consultant to GE Healthcare, the study sponsor.* Candace Gunnarsson—*RELATED*: *Consulting Fee or Honorarium*: GE Healthcare, *Comments*: I was a consultant for GE Healthcare; *UNRELATED*: *Consultancy*: Gunnarsson Consulting, *Comments*: I do outcomes research consulting for pharma and medical device companies. John A. Kellum—*RELATED*: *Consulting Fee or Honorarium*: GE Healthcare, *Comments*: paid consultant. *Money paid to the institution.

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