

ORIGINAL RESEARCH



Predictors of Hemorrhagic Transformation After IV Continuous Cangrelor Infusion Initiated During Mechanical Thrombectomy

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BACKGROUND: Cangrelor, a fast-acting intravenous P2Y₁₂ receptor inhibitor, is increasingly used during mechanical thrombectomy for acute ischemic stroke to treat or prevent thrombotic complications. While effective, its use may increase the risk of hemorrhagic transformation (HT). We investigated clinical, imaging, and procedural predictors of HT in this specific patient population.

METHODS: We performed a retrospective post hoc single-center study including 101 patients with acute ischemic stroke treated with intravenous cangrelor initiated directly after mechanical thrombectomy and continued for 12 hours between January 2021 and June 2024. Univariate and multivariable logistic regression models were used to assess associations between HT and clinical, radiological, and procedural factors.

RESULTS: Among the 101 patients included, 25 (24.7%) developed HT, and 9 (8.9%) experienced symptomatic intracerebral hemorrhage. In multivariable analysis, baseline blood glucose (adjusted odds ratio, 6.51 [95% CI, 1.35–31.4]; $P=0.02$), leukocytosis (adjusted odds ratio, 1.18 [95% CI, 1.00–1.38]; $P=0.047$), and subarachnoid hemorrhage on postmechanical thrombectomy cone-beam computed tomography (adjusted odds ratio, 16.60 [95% CI, 2.97–92.8]; $P=0.0014$) were independent predictors of HT. Contrast enhancement was associated with HT in univariate analysis but did not remain significant after adjustment.

CONCLUSIONS: Baseline blood glucose, leukocytosis, and isolated subarachnoid hemorrhage on postmechanical thrombectomy cone-beam computed tomography emerged as independent predictors of HT. Identifying high-risk patients using readily available clinical and imaging markers may support individualized antiplatelet strategies and help reduce hemorrhagic complications during cangrelor treatment.

REGISTRATION: URL: <https://www.clinicaltrials.gov>; Unique identifier: NCT03776877.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: blood glucose ■ cangrelor ■ humans ■ ischemic stroke ■ thrombectomy

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Nonstandard Abbreviations and Acronyms

AIS	acute ischemic stroke
ASPECTS	Alberta Stroke Program Early Computed Tomography Score
CBCT	cone-beam computed tomography
CE	contrast enhancement
CT	computed tomography
HT	hemorrhagic transformation
IQR	interquartile range
IVT	intravenous thrombolysis
mRS	modified Rankin Scale
MT	mechanical thrombectomy
mTICI	modified Thrombolysis in Cerebral Infarction
NIHSS	National Institutes of Health Stroke Scale
OR	odds ratio
SAH	subarachnoid hemorrhage
sICH	symptomatic intracerebral hemorrhage
TI	thrombo-inflammation

CLINICAL PERSPECTIVE

What Is New?

- In a consecutive cohort of 101 patients receiving continuous intravenous cangrelor immediately after mechanical thrombectomy, baseline hyperglycemia, leukocytosis, and isolated subarachnoid hemorrhage on postmechanical thrombectomy cone-beam computed tomography were identified as independent predictors of hemorrhagic transformation (HT), with hyperglycemia remaining the only consistent predictor across all HT subtypes, including parenchymal hematoma.
- Subarachnoid hemorrhage detected on postmechanical thrombectomy cone-beam computed tomography—a finding distinct from ECASS (European Cooperative Acute Stroke Study)-based HT on 24-hour imaging—independently predicts subsequent HT, potentially reflecting shared thrombo-inflammatory mechanisms rather than a direct causal pathway.

What Are the Clinical Implications?

- All 3 identified predictors are immediately available at the bedside after mechanical thrombectomy, enabling early HT risk stratification in patients for whom individualized decisions regarding cangrelor continuation, dose adjustment, or intensified post-procedural monitoring may be warranted.

Mechanical thrombectomy (MT) remains the cornerstone of treatment for acute ischemic stroke (AIS) related to large vessel occlusion, with success rates improving over the past decade.¹ However, achieving optimal recanalization outcomes may require adjunctive pharmacological strategies, particularly in cases of reocclusion,² resistant thrombus,³ or emergent stenting.⁴

Cangrelor (Kengrexal, Chiesi, Italy), an intravenous P2Y12-receptor inhibitor, has gained significant attention in the neurointerventional field due to its rapid onset and offset of action.⁵ This characteristic makes it particularly useful in managing high-risk endovascular procedures, including complex MT, where immediate and reversible platelet inhibition may be critical. Recent studies have reported improved reperfusion with cangrelor and demonstrated its efficacy across diverse patient populations.^{5,6}

Despite its clinical benefits, cangrelor use is associated with a delicate balance between the prevention of thrombotic events and the risk of hemorrhagic transformation (HT). To mitigate these risks, growing evidence has underscored the importance of individualized dosing strategies, particularly in patients at high risk of HT.⁷

As cangrelor use expands, there remains a need to identify predictors of HT and to inform individualized management in this setting. This study aims to contribute to this evolving field by identifying independent clinical, imaging, and procedural predictors of HT in a consecutive cohort of patients with AIS treated with standardized continuous intravenous cangrelor promptly after MT, with the goal of informing individualized risk stratification in the acute neurointerventional setting.

METHODS

Data Availability Statement

The data underlying this article were derived from the ETIS registry (Endovascular Treatment in Ischemic Stroke) and are not publicly available due to French data protection regulations. Anonymized data may be made available upon reasonable request to the corresponding author, subject to ethics committee approval.

Study Design

We conducted a retrospective post hoc single-center analysis based on prospectively collected data extracted from the ETIS registry (URL: <https://www.clinicaltrials.gov>; Unique identifier: NCT03776877). Although ETIS is a nationwide prospective registry of patients with AIS treated with MT, only cases managed at the Rothschild Foundation Hospital were included in the present study.

The study protocol (Identifiant Recherche Biomédicale [French trial identifier]: 2017-A03457-46) was approved by the local institutional review board and complied with

national data protection regulations. In accordance with French law governing retrospective observational research (Loi Jardé, MR-004), patients were informed of their right to object to the use of their data, and no objection was raised. Written informed consent was therefore not required. Reporting followed the STROBE guidelines (Strengthening the Reporting of Observational Studies in Epidemiology).⁸

Study Population

We included all consecutive patients with AIS treated at a tertiary center (Hôpital Fondation Adolphe de Rothschild) between January 1, 2021, and June 30, 2024, who underwent MT for anterior or posterior large vessel occlusion and received standard-dose intravenous cangrelor. Only patients who received a continuous cangrelor infusion for 12 hours after the loading dose were eligible. To ensure homogeneous exposure across the cohort, we excluded patients enrolled in the REPERFUSE trial (Reperfusion With P2Y12 Inhibitors in Addition to Mechanical Thrombectomy for Perfusion Imaging Selected Acute Stroke Patients; NCT04667078), in whom cangrelor infusion was intentionally discontinued at the end of MT, resulting in a shorter and lower-dose regimen. During the study period, cangrelor was administered according to a standardized institutional protocol as adjunctive intravenous antiplatelet therapy in patients requiring pharmacological support during MT, including cases of intracranial or extracranial emergent stenting, early reocclusion or stenosis, and refractory thrombus despite multiple passes. Cangrelor was not used systematically in all MT cases but was indicated in the specific clinical and procedural scenarios above, reflecting the practice at a high-volume tertiary center.

Throughout this article, the phrase during MT refers to the overall angiographic procedural session—encompassing thrombectomy, post-MT cone-beam computed tomography (CBCT), and subsequent cangrelor initiation—rather than to the mechanical retrieval maneuvers themselves.

Data Collection

We retrospectively analyzed prospectively recorded ETIS data corresponding to patients treated at our center during the study period. Brain magnetic resonance imaging was the preferred admission modality. Computed tomography (CT) was used when magnetic resonance imaging was unavailable or contraindicated.

All procedures were performed by senior interventional neuroradiologists in dedicated biplane neuroangiography suites using contemporary devices. A follow-up CT or magnetic resonance imaging was systematically obtained 24 hours after MT.

Patient demographics, comorbidities, preadmission medications, National Institutes of Health Stroke Scale (NIHSS) score, laboratory data, large vessel occlusion

localization, Alberta Stroke Program Early Computed Tomography Score (ASPECTS), intravenous thrombolysis (IVT), contrast enhancement (CE), and isolated subarachnoid hemorrhage (SAH) on post-MT CBCT were collected. Procedural variables included first-pass effect (determined by a modified Thrombolysis in Cerebral Infarction [mTICI] score of 2C or 3 following a single pass⁹), number of passes, reperfusion classification using the mTICI score, time between symptom onset and recanalization, admission, imaging or cangrelor administration, CE, and isolated SAH on post-MT CBCT. Post-MT CBCT was acquired without dual-energy iodine suppression (virtual noncontrast) capability. The distinction between contrast staining and true hemorrhage therefore relied on qualitative assessment by the treating neuro-radiologist at the time of image review, based on lesion density, morphology, and distribution pattern, consistent with standard clinical practice at our institution. CE was defined as any hyperdense parenchymal, cortical, or deep enhancement pattern on CBCT. Isolated SAH on post-MT CBCT was defined as subarachnoid hyperdensity detected on the immediate post-MT CBCT, independently of and before the 24-hour follow-up CT used for ECASS (European Cooperative Acute Stroke Study) classification of HT.¹⁰ Given the known limitations of unenhanced CT in distinguishing contrast staining from true hemorrhage on immediate postprocedural imaging, CE and isolated SAH on CBCT were systematically recorded as distinct binary variables by the treating neuroradiologist at the time of the procedure, and were coded independently of the 24-hour ECASS-based HT classification. Periprocedural unfractionated heparin (50 IU/kg) was administered at the operator's discretion according to our institutional protocol, primarily in patients who had not received prior IVT. HT was classified according to the ECASS criteria.¹⁰ Symptomatic intracerebral hemorrhage (sICH) was defined as any HT associated with a ≥ 4 -point worsening in NIHSS score at 24 hours, consistent with the SITS-MOST (Safe Implementation of Thrombolysis in Stroke-Monitoring Study) definition.¹¹

Cangrelor Administration

Cangrelor was started immediately after the post-MT CBCT at a standardized dose consisting of a 30 $\mu\text{g/kg}$ bolus followed by a 4 $\mu\text{g/kg}$ per minute infusion for 12 hours.

This sequence—recanalization, post-MT CBCT, then cangrelor initiation—was standardized across all 101 patients, ensuring that isolated SAH on CBCT was systematically available before cangrelor initiation in every case.

Outcome Measures

The primary objective of this study was to identify clinical, radiological, and procedural predictors of HT within

24 hours after MT in patients treated with intravenous cangrelor.

The primary outcome was the occurrence of any HT within 24 hours post-MT.

Secondary outcomes included (1) sICH, (2) the ordinal classification of HT according to the ECASS criteria, and (3) functional independence at 90 days postintervention, defined as a modified Rankin Scale (mRS) score of 0 to 2, according to the occurrence of a HT.

Statistical Analysis

Categorical variables were summarized as frequencies and percentages, while continuous variables were described using means and SDs or medians and interquartile ranges (IQRs; Q1–Q3), based on the symmetry of their distribution.

Potential risk factors for HT were evaluated by comparing patients with HT ($n=25$) with those without HT ($n=76$), using simple and multivariable logistic regression models. Odds ratios (ORs), 95% CIs, and P values were provided for each model.

In the multivariable model, prespecified confounders were considered (age, NIHSS score at admission (H0), ASPECTS at H0, IVT, and prior antiplatelet treatment), as well as all baseline characteristics associated with HT in univariate analysis ($P<0.10$). Blood glucose values were log-transformed in logistic regressions. Periprocedural heparin use was evaluated as a candidate variable; however, given its near-complete cooccurrence with the absence of IVT in this cohort (93.8% of heparin-treated patients had not received IVT, $P<0.001$), its inclusion in the multivariable model—which already adjusted for IVT—would have introduced collinearity, and it was therefore not retained. The multivariable model included 8 candidate variables for 25 events, corresponding to an events-per-variable ratio of 3.1, below the commonly recommended threshold of 10. A backward stepwise selection yielded the same final multivariable model; forward selection additionally retained CE without altering the core findings.

The mRS at 90 days was compared across patient groups defined by the occurrence or the absence of HT and the hemorrhage categories following the ECASS scale. The mRS values were analyzed in multiple ways: binary (presence or absence of hemorrhage), grouped hemorrhagic infarction type 1 or 2 (H1/H2) versus parenchymal hemorrhage type 1 or 2 (PH1/PH2), detailed (5 specific hemorrhage categories), and among hemorrhagic cases only.

Statistical testing was conducted at the 2-tailed α -level of 0.05. No multiple-testing correction was applied, as this was an exploratory analysis, and results should be interpreted with caution. All statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC), and graphics were generated using R software (version 4.3.1). Model discrimination was

assessed using the area under the receiver operating characteristic curve.

RESULTS

Between January 1, 2021, and June 30, 2024, 101 patients received a standardized dose of intravenous cangrelor and were included in the present study (Figure S1).

Baseline Characteristics and Clinical Outcome According to 24-Hour HT

As presented in Table S1, the mean age was 59.8 ± 12.5 years, and females represented 33.7% of the cohort ($N=101$). Hypertension was present in 46 (45.5%) patients, diabetes in 20 (19.8%), and active smoking in 27 (26.7%). In addition, 18 (17.8%) patients had received previous antithrombotic treatment (6.9% single antiplatelet therapy, 6.9% dual antiplatelet therapy, 1.0% vitamin K antagonist, and 3.0% direct-acting oral anticoagulant). Intravenous thrombolysis was administered in 58 (57.4%) patients. The median baseline NIHSS was 14 (IQR, 9–18). Target occlusions were anterior in 85/101 (84.2%) and posterior in 16/101 (15.8%). The mean anterior circulation ASPECTS was 7.5 ± 1.8 , while the mean posterior circulation ASPECTS was 7.2 ± 2.2 . Baseline systolic blood pressure averaged 148 ± 29 mmHg, and the mean leukocyte count was $10.2\pm 3.5\times 10^3/\mu\text{L}$. The median baseline blood glucose was 7.1 mmol/L (IQR, 6.3–9.0). First-pass effect (mTICI 2C–3 after a single pass) occurred in 5/101 (5.0%) patients. Periprocedural heparin was given to 32/101 (31.7%) patients at a dose of 50 IU/kg. Of these, 30 (93.8%) had not received prior IVT; heparin use was strongly associated with the absence of IVT ($P<0.001$) and was not independently associated with HT in univariate analysis ($P>0.05$; Table 1). Angioplasty alone was performed in 11 (10.9%) patients, stenting without angioplasty in 13 (12.9%) cases, and combined stenting and angioplasty in 18 (17.8%) cases, for an overall 31 (30.7%) cases with any stent placement. Early stenosis or reocclusion occurred in 60 (59.4%) patients. The median time from symptom onset to cangrelor administration was 364 minutes (IQR, 300–463), from symptom onset to femoral puncture was 292 minutes (IQR, 226–420), and recanalization was achieved 404 minutes from symptom onset (IQR, 336–551). Successful recanalization (defined as mTICI $\geq 2B$) was achieved in 78.2% of patients, with complete or near-complete recanalization (mTICI 2C–3) in 50.5%. This cohort was characterized by a low first-pass effect rate (5.0%), a high rate of early stenosis or reocclusion (59.4%), frequent stenting (30.7%), a mean of 4.6 ± 2.9 thrombectomy passes, and a prolonged median onset to cangrelor time of 364 minutes (IQR, 300–463).

Post-MT CE on CBCT was observed in 61 (60.4%) patients. SAH was detected in 12 (11.9%) patients. Of

Table 1. Baseline Characteristics, Procedural Variables and Early Postprocedural Findings According to the Occurrence of HT

Variable	All (N=101)	No HT (n=76)	HT (n=25)	P value
Demographics and risk factors				
Age, y	59.8±12.5	58.7±12.1	62.9±13.3	0.15
Female sex	34 (33.7)	25 (32.9)	9 (36.0)	0.78
Hypertension	46 (45.5)	34 (44.7)	12 (48.0)	0.78
Diabetes	20 (19.8)	14 (18.4)	6 (24.0)	0.54
Smoking	27 (26.7)	22 (28.9)	5 (20.0)	0.38
Previous antithrombotic treatment	18 (17.8)	16 (21.1)	2 (8.0)	0.16
SAPT	7 (6.9)	7 (9.2)	0 (0.0)	
DAPT	7 (6.9)	6 (7.9)	1 (4.0)	
VKA	1 (1.0)	1 (1.3)	0 (0.0)	
DOAC	3 (3.0)	2 (2.6)	1 (4.0)	
Baseline stroke characteristics				
NIHSS	14 (9–18)	14 (9–18)	14 (10–18)	0.93
SBP, mm Hg	148±29	145±29	158±28	0.065
Blood glucose level, mmol/L	7.1 (6.3–9.0)	7.0 (5.9–8.5)	8.0 (7.0–12.8)	0.0052*
Leukocytes, 103/μL	10.2±3.5	9.8±3.4	11.3±3.8	0.079
ASPECTS overall	7.4±1.8	7.6±1.9	7.3±1.9	0.53
Treatment and procedure				
IVT	58 (57.4)	42 (55.3)	16 (64.0)	0.44
Periprocedural heparin (50 IU/Kg)	32 (31.7)	24 (31.6)	8 (32.0)	0.97
Occlusion site				0.23
Anterior	85 (84.2)	62 (81.6)	23 (92.0)	
Posterior	16 (15.8)	14 (18.4)	2 (8.0)	
Final mTICI ≥2B	79 (78.2)	61 (80.3)	18 (72.0)	0.39
No. of passes	4.6±2.9	4.3±3.0	5.5±2.4	0.065
First-pass effect	5 (5.0)	5 (6.6)	0 (0.0)	0.40
Timing				
Unknown moment of onset	8 (7.9)	5 (6.6)	3 (12.0)	0.39
Time between onset and cangrelor, min	364 (300–463)	354 (293–498)	385 (335–416)	0.31
Time between onset and first image, min	140 (90–220)	147 (80–230)	132 (105–200)	0.46
Time between onset and femoral puncture, min	292 (226–420)	294 (219–422)	292 (253–359)	0.38
Time between onset and recanalization, min	404 (336–551)	390 (333–558)	417 (357–453)	0.34
Post-MT CBCT				
CE	61 (60.4)	41 (53.9)	20 (80.0)	0.026*
Isolated SAH	12 (11.9)	3 (3.9)	9 (36.0)	<0.001*

Values are mean ± SD, median (IQR), or n (%). Variables expressed as median (IQR)—including all timing variables (time from symptom onset to cangrelor administration, first imaging, femoral puncture, and recanalization) and baseline blood glucose—were log-transformed for regression analyses. No missing data unless otherwise specified. ASPECTS indicates Alberta Stroke Program Early Computed Tomography Score; CBCT, cone-beam computed tomography; CE, contrast enhancement; DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulant; HT, hemorrhagic transformation; MT, mechanical thrombectomy; mTICI, modified Thrombolysis in Cerebral Infarction; NIHSS, National Institutes of Health Stroke Scale; SAH, isolated subarachnoid hemorrhage; SAPT, single antiplatelet therapy; SBP, systolic blood pressure; and VKA, vitamin K antagonist.

*If $P<0.05$.

these 12 patients, 9 presented with isolated SAH on post-MT CBCT without parenchymal hemorrhage on 24-hour imaging; among the 25 patients who developed HT, 7 were classified as isolated SAH according to ECASS criteria on follow-up CT. At 90 days, the median mRS score was 3 (IQR, 2–5).

Factors Associated With HT

Among 101 patients, 25 (24.7%) developed HT. In the univariate analysis, baseline blood glucose level was significantly associated with HT, with an OR of 6.66 (95% CI, 1.76–25.2; $P=0.0052$; Table 2; Figure). Age, initial

Table 2. Univariate and Multivariable Logistic Regression Analysis for Predictors of Hemorrhagic Transformation

Variable	Simple models			Multivariable model		
	OR	95% CI	P value	Adjusted OR	95% CI	P value
Adjusted variables						
Age, y	1.03	0.99–1.07	0.15	1.04	0.99–1.09	0.14
Previous antithrombotic treatment (yes vs no)	0.33	0.07–1.53	0.16	0.41	0.08–2.21	0.30
NIHSS	1.00	0.92–1.08	0.93	0.94	0.85–1.04	0.24
ASPECTS	0.93	0.73–1.17	0.53	1.02	0.75–1.40	0.88
IVT	1.44	0.57–3.66	0.44	1.58	0.51–4.95	0.43
Separately associated variables						
SBP, mm Hg	1.01	1.00–1.03	0.065			
Blood glucose level, mmol/L	6.66	1.76–25.2	0.0052*	6.51	1.35–31.4	0.020*
Leukocytes, 103/μL	1.12	0.99–1.27	0.079	1.18	1.00–1.38	0.047*
CE	3.41	1.16–10.40	0.026*			
No. of passes	1.16	0.99–1.35	0.065			
Isolated SAH	13.70	3.33–56.3	<0.001*	16.60	2.97–92.8	0.0014*

No missing data unless specified. ASPECTS indicates Alberta Stroke Program Early Computed Tomography Score; CE, contrast enhancement; IVT, intravenous thrombolysis; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; SAH, subarachnoid hemorrhage; and SBP, systolic blood pressure.
*If $P<0.05$.

NIHSS score, ASPECTS, prior antithrombotic treatment, and IVT were not associated with HT in univariate analysis (all $P>0.05$; Table 1).
In addition, CE and isolated SAH on post-MT CBCT were also significant predictors of HT occurrence (OR, 3.41 [95% CI, 1.16–10.04]; $P=0.026$ and OR, 13.70 [95% CI, 3.33–56.3]; $P<0.001$, respectively), as presented in Table 2. In the multivariable model, adjusted for age, previous antithrombotic treatment, baseline NIHSS, baseline ASPECTS, and IVT, the baseline blood glucose level remained a significant predictor, with an adjusted OR of 6.51 (95% CI, 1.35–31.4; $P=0.020$). Leukocyte count also remained statistically significant in the adjusted model (adjusted OR, 1.18 [95% CI, 1.00–1.38]; $P=0.047$), as did SAH (adjusted OR, 16.60 [95% CI, 2.97–92.8]; $P=0.0014$; Table 2). CE, while significant in univariate analysis, did not retain significance

after multivariable adjustment. The multivariable model included 8 variables for 25 events (events-per-variable ratio=3.1). Age, baseline NIHSS, ASPECTS, prior antithrombotic treatment, and IVT were not independently associated with HT in univariate or multivariable analysis (all $P>0.05$; Tables 1 and 2).

Sensitivity Analysis Excluding Isolated SAH on CBCT

Because post-MT SAH may represent a significant confounder rather than an independent predictor, we repeated the stepwise selection excluding it from the candidate variable list. Blood glucose (adjusted OR, 11.70 [95% CI, 2.19–62.52]; $P=0.0040$) and leukocyte count (adjusted OR, 1.19 [95% CI, 1.02–1.38]; $P=0.030$) remained independently predictive, and CE emerged as an additional independent predictor (adjusted OR, 5.09 [95% CI, 1.35–19.24];

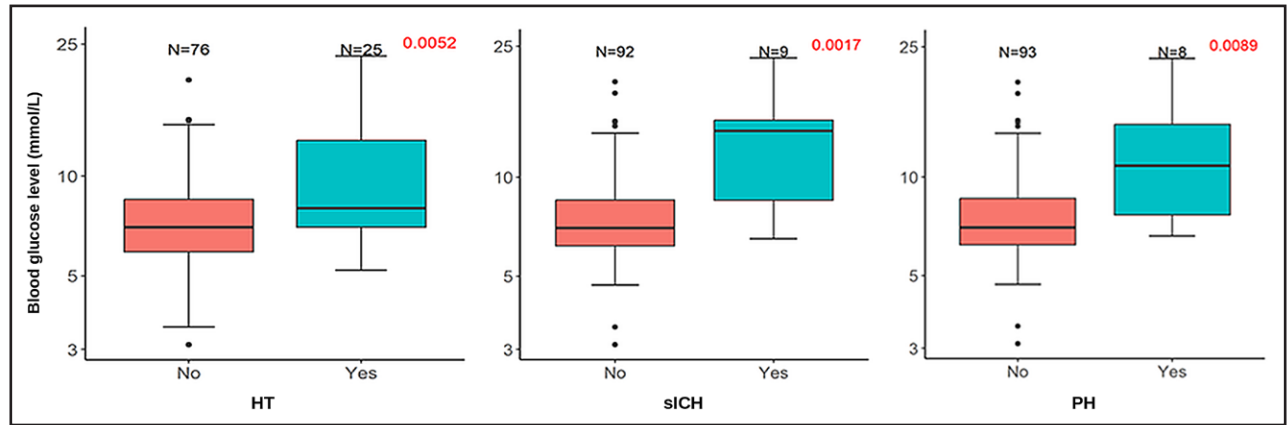


Figure. Baseline blood glucose (mmol/L) according to hemorrhage outcome. Boxplots show median and interquartile range. Blood glucose levels were higher in patients with hemorrhagic transformation (HT), symptomatic intracerebral hemorrhage (sICH), and parenchymal hemorrhage (PH; $P=0.0052$, 0.0017 , and 0.0089 , respectively).

$P=0.017$; Table S5). In the subgroup of patients without isolated SAH ($n=89$), hyperglycemia remained the sole independent predictor (adjusted OR, 5.76 [95% CI, 1.07–30.90]; $P=0.041$); no predictor reached significance in the small subgroup with SAH ($n=12$).

Sensitivity Analysis Using Dichotomized Variables

To address potential nonlinearity across covariate intervals, continuous variables were dichotomized using clinically prespecified thresholds (age $>70/80$ years, NIHSS >6 , ASPECTS >6 , leukocytes $>10\,000/\mu\text{L}$) and Youden index-derived cut points. For systolic blood pressure, blood glucose, and number of passes, the clinically prespecified threshold coincided exactly with the Youden-optimal cut point identified in this cohort (>140 mmHg, >6.5 mmol/L, and >4 passes, respectively; Tables S6 through S8). Hyperglycemia remained an independent predictor in all models tested (adjusted OR, 20.95 [95% CI, 2.46–178.40]; $P=0.0054$ with SAH; adjusted OR, 17.40 [95% CI, 2.55–118.66]; $P=0.0035$ without SAH), whereas dichotomized leukocytosis ($>10\,000/\mu\text{L}$) lost statistical significance. Elevated systolic blood pressure and isolated SAH emerged as additional predictors in the model including SAH; systolic blood pressure, number of passes, and CE emerged as predictors when SAH was excluded.

Factors Associated With Symptomatic Intracerebral Hemorrhage

Among the 101 included patients, 9 (8.9%) developed sICH (Table S2). Baseline clinical characteristics were similar between patients with and without sICH, with no significant differences in age, sex, vascular risk factors, prior antithrombotic treatment, NIHSS at admission, ASPECTS, or IVT administration (all $P>0.05$). Procedural characteristics, including occlusion site, number of passes, final reperfusion status (mTICI $\geq 2\text{B}$), and all timing variables, were also comparable between groups. In contrast, baseline blood glucose level was significantly higher in patients with sICH (median, 13.8 mmol/L [IQR, 8.5–14.9] versus 7.0 mmol/L [IQR, 6.2–8.6]; $P=0.0017$). Regarding postprocedural imaging, isolated SAH on post-MT CBCT was more frequent in patients with sICH (33.3% versus 9.8%; $P=0.053$), while CE occurred at similar rates (59.8% versus 66.7%; $P=0.69$). Given the small number of sICH events ($n=9$), these analyses should be interpreted as descriptive and hypothesis-generating only, with insufficient power for formal statistical inference.

Impact of HT on Outcome

Patients with any type of hemorrhage (SAH, H1, H2, PH1, or PH2) exhibited significantly worse 90-day outcomes than those without hemorrhage (median mRS, 4 versus 3; $P=0.009$; Table S4). When hemorrhages were grouped into SAH, HI (H1–H2), and PH (PH1–PH2),

functional status differed significantly across categories ($P=0.039$). Patients with PH had the worst outcomes (median mRS, 6; IQR, 3.5–6.0; $n=8$), followed by those with H1–H2 (median, 4.5; IQR, 3.0–5.0; $n=10$) and SAH (median, 4; IQR, 4–6; $n=7$).

Detailed analysis of each hemorrhage subtype confirmed this gradient. PH2 ($n=6$) demonstrated the highest disability burden (median mRS, 6; IQR, 4.0–6.0), followed by H2 (median, 5.5; IQR, 4.5–6.0; $n=4$) and PH1 (median, 4.5; IQR, 3.0–6.0; $n=2$). Patients with SAH had intermediate outcomes (median, 4; IQR, 4.0–6.0; $n=7$), while those with H1 had the most favorable profile among hemorrhagic subtypes (median, 3; IQR, 0.0–5.0; $n=6$). When all 6 groups—including the no-hemorrhage category—were compared, mRS distributions differed significantly ($P=0.024$). However, restricting the comparison to hemorrhagic groups alone yielded no statistically significant difference ($P=0.19$).

Mortality at 90 days, inferred from mRS=6, was highest in patients with parenchymal hematomas. In particular, PH2 showed the strongest mortality signal (IQR, 4–6), with similarly elevated fatality rates in H2 (IQR, 4.5–6.0) and PH1 (IQR, 3–6). SAH displayed occasional fatal outcomes (IQR, 4–6), while no deaths were observed in patients with H1 (IQR, 0–5). Overall, parenchymal hematomas—especially PH2—were associated with the greatest fatality risk (Figure S2).

DISCUSSION

Our analysis identified baseline blood glucose level, baseline leukocytosis, and post-MT isolated SAH on CBCT as independent predictors of HT in patients with AIS treated with continuous intravenous cangrelor infusion in addition to MT. Blood glucose level was the only variable that remained significantly associated with HT across all models and hemorrhage subtypes, including when PH was assessed separately. Notably, baseline leukocyte count was also independently associated with HT in the fully adjusted model, together with SAH and blood glucose level. CE, while significant in univariate analysis, did not retain significance after adjustment, likely reflecting collinearity with isolated SAH on post-MT CBCT, as both variables capture postprocedural microvascular injury on the same imaging modality. It should be noted, however, that post-MT SAH on CBCT and subsequent HT on 24-hour imaging share temporal and pathophysiological proximity; whether isolated SAH on CBCT represents a true antecedent of HT or an early marker of the same microvascular injury cannot be established from this retrospective analysis.

In this highly selected cohort of patients treated with cangrelor, conventional predictors of HT¹² did not retain significant associations with HT. Given the limited sample size and the restricted variability of clinical and imaging characteristics in this setting, these findings likely reflect

limited statistical power rather than a true absence of effect. Of note, the prolonged median time from symptom onset to cangrelor administration (364 minutes; IQR, 300–463) likely reflects the procedural complexity of this cohort, which included a high proportion of cases requiring emergent stenting (30.7%), multiple thrombectomy passes (mean 4.6), and management of early stenosis or reocclusion (59.4%), rather than representing a standard thrombectomy population. This context is important when interpreting both the hemorrhagic risk profile and the generalizability of these findings.

A notably high rate of hemorrhagic events was observed in this cohort: any HT in 24.7% of cases, sICH in 8.9%, and PH in 7.9%. While broadly consistent with prior cangrelor series—Marnat et al¹³ reported any HT in ≈20% of patients treated for refractory occlusions, and Pop et al¹⁶ observed similar rates in carotid stenting procedures—these rates remain substantially higher than the 0% sICH reported with intravenous tirofiban in the OPTIMISTIC trial (One Pass Tirofiban in Management of Ischemic Stroke Thrombectomy in China),¹⁴ suggesting that continuous cangrelor infusion may be associated with a different hemorrhagic risk profile than tirofiban; however, direct comparisons are substantially limited by differences in patient complexity, procedural indications, treatment duration, and dosing regimens across studies. Furthermore, the functional impact of these events differed markedly across hemorrhage subtypes. While parenchymal hematomas—particularly PH2—were associated with the worst 90-day outcomes and the strongest mortality signal, H1 had a comparatively modest functional impact. This gradient indicates that the clinical consequences of HT under cangrelor are not uniform and depend critically on the severity and extent of the bleeding.

This discrepancy between tirofiban and cangrelor safety profiles may reflect either differential bleeding phenotypes or differences in patient complexity. In either case, these findings underscore the importance of patient selection and procedural context when interpreting bleeding risk estimates across studies, and highlight the need for randomized trials such as REPERFUSE (NCT04667078) to clarify the safety profile of cangrelor in this setting.

Of note, a recent comparative analysis of cangrelor versus glycoprotein IIb/IIIa inhibitors during endovascular thrombectomy found cangrelor to be associated with decreased odds of hemorrhagic conversion and improved functional outcomes at 90 days,¹⁵ suggesting that differences in patient selection, dosing protocols, and procedural indications may substantially influence the hemorrhagic risk profile observed across studies.

In this context, our analysis identified a link between both leukocytosis and hyperglycemia and the occurrence of HT after MT. A plausible pathophysiological explanation lies in the implications of both biological markers as mediators of thrombo-inflammation (TI), a phenomenon closely related to HT.¹⁶

Although the magnitude of association was modest (adjusted OR per 103/ μ L, 1.18), the biological plausibility of leukocytosis as a mediator of thrombo-inflammation is well established.¹⁷ In particular, enzymes and neutrophil extracellular traps released by activated neutrophils contribute to blood-brain barrier breakdown,¹⁸ promoting intravascular¹⁹ and parenchymal inflammation²⁰ or amplifying coagulation pathways.²¹

These processes are further reinforced by a complex and potent amplification loop with platelets,^{22,23} ultimately leading to microvascular obstruction²⁴ and an increased risk of HT.²⁵

Baseline hyperglycemia is an established predictor of HT in the general stroke population.¹² The present study extends this observation to patients receiving continuous intravenous cangrelor, a setting in which potent and sustained P2Y12 inhibition may lower the threshold for HT in a context already primed by hyperglycemia-driven TI. Whether cangrelor exposure amplifies the hemorrhagic risk associated with hyperglycemia beyond what is observed in nonantiplatelet-treated patients cannot be determined from this observational analysis.

In preclinical settings, hyperglycemia triggers all actors of TI as it increases proinflammatory cytokines²⁶ and neutrophil extracellular traps²⁷ secretion by activated neutrophils, platelet activation, and tissue factor secretion.²⁸ The many processes triggered by hyperglycemia may indeed explain the absence of correlation between leukocytosis and hyperglycemia in our series. Ultimately, hyperglycemia impairs microvascular reperfusion despite successful macrovascular recanalization and increases the risk of HT.²⁹

Although the evidence is less direct, it is conceivable that the impact of SAH on the occurrence of HT may reflect similar underlying TI mechanisms. Indeed, preclinical data highlight the fact that platelets and neutrophils adhere to the microvessel endothelium within minutes³⁰ after SAH, provoking a persistent³¹ microvascular thrombosis observed at autopsy³² and a parenchymal TI³³ responsible for microstructural injury.³⁴ These phenomena, closely resembling those observed in TI following AIS, could exacerbate them during the acute phase and thereby contribute to increased risk of HT.³⁵ It is also conceivable that potent P2Y12 inhibition by cangrelor may amplify this thrombo-inflammatory cascade by impairing platelet-mediated microvascular sealing, thereby lowering the threshold for hemorrhagic conversion in an already vulnerable blood-brain barrier.

This study has several limitations. Its retrospective, single-center design may introduce selection bias. The sample size was moderate, and hemorrhagic events were relatively infrequent; accordingly, some associations may have been underpowered to reach statistical significance. HT evaluation relied on CT, a modality for which the ECASS classification demonstrates only fair-to-moderate interrater agreement, and differentiating contrast staining from

true hemorrhage remains challenging.³⁶ Furthermore, with 25 HT events and several variables included in the multivariable model, the events-per-variable ratio falls below the commonly recommended threshold of 10, which may limit the stability of the regression estimates. Sensitivity analyses excluding isolated SAH on CBCT and using dichotomized covariates (Tables S5 through S8) confirmed the robustness of the hyperglycemia association in particular, while indicating that the leukocyte-HT relationship may be better captured as a continuous rather than threshold effect. To address this concern, a sensitivity analysis using Firth's penalized logistic regression confirmed that baseline blood glucose (adjusted OR, 5.33 [95% CI, 1.07–26.55]; $P=0.041$) and post-MT SAH on CBCT (adjusted OR, 15.20 [95% CI, 2.37–97.41]; $P=0.004$) remained statistically significant, while leukocyte count showed a consistent direction of effect; the multivariable findings should nonetheless be interpreted as exploratory and hypothesis-generating rather than confirmatory. It should be acknowledged that the causal relationship between post-MT SAH on CBCT and subsequent HT on 24-hour imaging may reflect shared microvascular pathophysiology rather than an independent predictive pathway. Whether isolated SAH on CBCT represents a true antecedent of HT or an early marker of the same microvascular injury remains to be clarified. Nonetheless, the single-center design ensured a high degree of protocol homogeneity, as all patients received the same standardized cangrelor regimen (30 µg/kg bolus followed by 4 µg/kg per minute for 12 hours) administered under consistent procedural conditions. Furthermore, with 101 consecutive patients treated with this specific agent, this cohort represents one of the largest single-center series reported to date for cangrelor use during MT, lending credibility to the observed associations despite the inherent limitations of the design.

Recent comparative work has shown substantial discrepancies in HT detection and grading across CT, dual-energy CT, and magnetic resonance imaging, yet DECT was not available in our cohort.³⁷

Nevertheless, our study identifies 3 readily assessable risk factors for HT—baseline blood glucose, leukocytosis, and post-MT SAH—which may reflect TI-related mechanisms and should prompt cautious reconsideration of cangrelor use in emergency settings.

It also highlights the need for randomized controlled trials, such as REPERFUSE (NCT04667078), which evaluates adjunctive cangrelor therapy in patients with AIS selected by perfusion imaging and will provide more definitive evidence regarding its safety.

CONCLUSIONS

In this single-center study, baseline blood glucose level, leukocytosis, and isolated SAH on post-MT CBCT emerged as independent predictors of HT in patients receiving cangrelor, with hyperglycemia being the only

consistent marker across all HT subtypes. These findings identify 3 readily available clinical and imaging markers that may guide individualized antiplatelet risk stratification during cangrelor administration and inform patient selection for ongoing randomized trials such as REPERFUSE (NCT04667078).

ARTICLE INFORMATION

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Disclosures

Dr Olivot is a consultant for Boehringer Ingelheim. The other authors report no conflicts.

Supplemental Material

Tables S1–S8
Figures S1–S2
Major Resources Table
STROBE Checklist

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