This article has been accepted for publication in NEURINTSURG following peer review.
The definitive copyedited, typeset version is available online at
10.1136/jnis-2025-024658

Ticagrelor vs Clopidogrel for Carotid Artery Stenting: Is There a Difference in Safety and Efficacy? A Propensity Score Matched Analysis

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Short Title: Ticagrelor vs Clopidogrel: CAS Outcomes

Word Count: 1673

Acknowledgement

This work was supported by the National Institutes of Health under award number 5U54GM104942-08. This manuscript is the result of funding in whole or in part by the National Institutes of Health (NIH). It is subject to the NIH Public Access Policy. Through acceptance of this federal funding, NIH has been given a right to make this manuscript publicly available in PubMed Central upon the Official Date of Publication, as defined by NIH.

Conflicting interests

Dhairya A. Lakhani and Vivek Yedavalli are consultants for iSchemaView, RapidAI. Dheeraj Gandhi receives research grants from the Focused Ultrasound Foundation, NIH, University of Maryland Medical Center, and Microvention, and is a consultant for Navigantis.

Funding

Research reported in this publication was supported by the National Institute of General Medical Sciences of the National Institutes of Health under Award Number 5U54GM104942-08. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Ethical approval

As the TriNetX lacks patient identifiers, this study was exempt from institutional review board approval and informed consent requirements.

Data availability statement

Study data are available upon reasonable request from the corresponding author.

Abstract

Background: Dual antiplatelet therapy (DAPT) is recommended around carotid artery stenting (CAS) to reduce periprocedural stroke risk. Clopidogrel is widely used, but response variability related to pharmacokinetics and CYP2C19 polymorphisms may limit its effectiveness. Ticagrelor is a more potent, direct-acting P2Y12 inhibitor; however, its comparative effectiveness in CAS remains uncertain.

Methods: We conducted a retrospective cohort study in the TriNetX database, identifying adults with carotid artery stenosis who underwent CAS between January 2016 and August 2025 and received either ticagrelor or clopidogrel. Primary outcomes at 180 days included ischemic stroke, major hemorrhage, intracranial hemorrhage, and all-cause mortality. Secondary outcomes included inpatient readmission and emergency department (ED) visits. Propensity score matching (1:1), Kaplan–Meier survival and Cox proportional hazards analysis were used.

Results: Among 6,996 patients, 378 received ticagrelor and 6,618 received clopidogrel; aspirin co-use was similar (89.7% vs 91.7%). After matching, 377 patients remained in each cohort. Ischemic stroke (2.7% vs 4.2%; HR 0.56, 95%CI 0.25–1.27; p=0.159) and major hemorrhage (2.9% vs 4.8%; HR 0.61, 95%CI 0.29–1.30; p=0.197) were numerically lower with ticagrelor. Rates of intracranial hemorrhage was similar (2.7% vs 2.7%; HR 0.61, 95%CI 0.14–2.53; p=0.488). Mortality was numerically higher with ticagrelor (3.4% vs 2.7%; HR 1.64, 95%CI 0.68–3.97; p=0.263). ED visits were similar (14.3% vs 14.6%; HR 0.97, 95%CI 0.67–1.42; p=0.895). Inpatient readmission was numerically lower with ticagrelor (15.9% vs 19.1%; HR 0.81, 95%CI 0.57–1.14; p=0.223).

Conclusion: Ticagrelor and clopidogrel showed comparable safety and effectiveness following CAS. Future prospective genotype-informed trials are warranted to confirm these findings.

Keywords

Carotid artery diseases; Carotid artery stenting; Dual antiplatelet therapy; Ticagrelor; Clopidogrel

Abbreviations

CAS – Carotid artery stenting; DAPT – Dual antiplatelet therapy; TICA – Ticagrelor; CLOP – Clopidogrel; ICH – Intracranial hemorrhage; SAH – Subarachnoid hemorrhage; IPH – Intraparenchymal hemorrhage; TCAR – Transcarotid artery revascularization; CEA – Carotid endarterectomy; HTPR – High on-treatment platelet reactivity; ACS – Acute coronary syndrome.

Key Message

What is already known on this topic

Clopidogrel remains the standard P2Y12 inhibitor for dual antiplatelet therapy during carotid artery stenting, but ticagrelor is increasingly used as an alternative; however, its comparative efficacy and safety in this setting remain uncertain.

What this study adds

This propensity matched real-world analysis demonstrates comparable safety and efficacy between ticagrelor and clopidogrel for patients undergoing carotid artery stenting.

How this study might affect research, practice, or policy

These findings suggest clopidogrel is non-inferior to ticagrelor for most patients, supporting continued use of clopidogrel as standard therapy, while highlighting the need for prospective studies in patients with clopidogrel resistance to guide individualized antiplatelet strategies.

Introduction

The global prevalence of carotid plaque and carotid artery stenosis is estimated at 21% and 1.5–5%, respectively,[1,2] and carotid artery stenting (CAS) is a mainstay treatment for patients with severe or symptomatic stenosis. While CAS, including both transfemoral approaches or transcarotid artery revascularization (TCAR) with flow reversal, may have advantages over carotid endarterectomy (CEA) given that it is a minimally invasive procedure that may be better tolerated for those with high anatomical or surgical risks due to medical comorbidities, perioperative and post-operative stroke were potential complications[3]. To mitigate this risk, current guidelines generally recommend dual antiplatelet therapy (DAPT) for at least 3 days before and up to 30 days after CAS.[4–8] Conventionally, DAPT regimen consists of aspirin and a P2Y12 inhibitor, most commonly clopidogrel.[4,5] However, clopidogrel is known to be limited by slow therapeutic onset and variable antiplatelet effect due to genetic polymorphism, with up to two-thirds of patients exhibiting high on-treatment platelet reactivity (HTPR) with clopidogrel after CAS procedures, which can increase the risks of thromboembolic complications.[9–11]

Recently, ticagrelor, a reversible P2Y12 inhibitor, has been shown to be a rapidly acting agent than clopidogrel, with meta-analyses in the cardio- and cerebrovascular literature demonstrating its potential superiority over clopidogrel[12,13], particularly in the setting of acute ischemic events. While there is mounting evidence in support of ticagrelor use in acute ischemia, its safety and efficacy in the setting of elective endovascular procedures is lesser known. To date, several studies have investigated the efficacy and safety of ticagrelor compared to clopidogrel in the setting of CAS, but results have been inconsistent.[14–19] Most studies found no significant adverse events with comparable efficacy, while a few reported superior outcomes with ticagrelor in patients with clopidogrel resistance.[15,16]

In this study, we analyzed a large multicenter database to compare clinical outcomes between ticagrelor and clopidogrel in patients undergoing CAS.

Methods

Study Design and Data Source

We conducted a retrospective cohort study using the TriNetX platform, a federated research network comprising more than 120 healthcare organizations and over 275 million patients. The platform enables real-time, privacy-compliant data access with standardized terminologies including ICD-10-CM codes. All study variables were extracted using ICD-10 codes and RxNorm codes (Supplemental **Table 1**).

Study Population

We identified patients aged 18 years or older with a diagnosis of occlusion and stenosis of either carotid artery (ICD-10 code I65.21/ I65.22) who underwent carotid stenting procedures between January 2016 and August 2025. Patients were included if they were initiated on either ticagrelor or clopidogrel immediately after carotid stenting (2 weeks before and 3 days after carotid stenting). The broad time window is to allow margins for reporting errors. Patients with a history of ischemic stroke, intracranial hemorrhage, or other major bleeding events prior to the CAS were excluded.

Exposure and Outcomes

The primary exposure is ticagrelor versus clopidogrel. Primary outcomes of interest included ischemic stroke, major hemorrhage (defined as any intracranial hemorrhage or any

hospitalization requiring blood transfusions), any intracranial hemorrhage (ICH), and all-cause mortality within 180 days post-procedure. Additional endpoints included major adverse events needing emergency department visits (ED visits) and inpatient readmissions.

Statistical Analysis

Patient characteristics were presented as mean with standard deviation (SD), or percentages. Baseline characteristics were compared using chi-square tests for categorical variables and t-tests for continuous variables. To address potential confounding, propensity score matching (PSM) was performed using a 1:1 nearest neighbor matching algorithm without replacement. Standardized mean differences (SMD) were calculated to assess balance, with SMD <0.10 considered acceptable. For outcome comparisons, Kaplan-Meier analyses were used to estimate event probabilities at 180 days, log-rank tests were used to compare survival curves between groups, and Cox proportional hazards regression was employed to calculate hazard ratios (HR) with 95% confidence intervals (CI) among PSM cohorts. All statistical analyses were performed on the TriNetX analysis platform, and p-values <0.05 were considered statistically significant.

Results

Baseline Characteristics

The study included 6,996 patients, with 378 receiving ticagrelor and 6,618 receiving clopidogrel. Before matching, several baseline characteristics differed significantly between groups. Ticagrelor patients were slightly younger (69.7 ± 11.3 vs 72.0 ± 9.1 years, $p<0.001$, **Table 1**) and had different racial distributions, with fewer white patients (77.2% vs 84.3%, $p<0.001$, **Table 1**). Clopidogrel patients had higher rates of atrial fibrillation and flutter, while ticagrelor patients had

higher rates of various medical comorbidities including hemolytic anemia, and bone marrow failure syndromes including aplastic and other anemias (all p<0.05, **Table 1**). Finally, a majority of both ticagrelor and clopidogrel patients received concomitant aspirin, consistent with the current standard of care (89.7% and 91.7%, respectively; **Table 1**).

After PSM, 377 patients remained in each group with well-balanced baseline characteristics (all SMD <0.10).

Study outcomes

Ischemic stroke rates were numerically lower among patients treated with ticagrelor compared to those treated with clopidogrel (2.6% vs 4.2%; HR 0.56, 95% CI 0.25–1.27; p = 0.159). Similarly, rates of major hemorrhage (2.9% vs 4.8%; HR 0.61, 95% CI 0.29–1.30; p = 0.197) were also numerically lower in the ticagrelor group. Intracranial hemorrhage rates were similar between the two groups (2.7% vs 2.7%; HR 0.61, 95% CI 0.14–2.53; p = 0.488) In contrast, mortality was numerically higher among ticagrelor patients compared to clopidogrel patients (3.4% vs 2.7%; HR 1.64, 95% CI 0.68–3.97; p = 0.263).

Emergency department visits were similar between the two groups (14.3% vs 14.6%; HR 0.97, 95% CI 0.67–1.42; p = 0.895), while inpatient readmission rates were numerically lower in the ticagrelor group as compared to clopidogrel group (15.9% vs 19.1%; HR 0.81, 95% CI 0.57–1.14; p = 0.223).

All outcomes are summarized in **Table 2**, and the corresponding hazard ratios are illustrated in **Figure 1** as a forest plot.

Discussion

In this large-scale, real-world analysis of patients with carotid artery disease undergoing CAS, no significant differences were observed between ticagrelor and clopidogrel in post-procedural ischemic stroke, major hemorrhage, intracranial hemorrhage, mortality, inpatient readmission, and emergency department visits, and, consistent with findings from prior studies.[14,17] These results provide additional data to suggest therapeutic equivalence between clopidogrel and ticagrelor in the setting of CAS.

Our findings were largely in line with prior reports. Ghamraoui and Ricotta et al.[18], found that ticagrelor had similar efficacy and safety compared to clopidogrel. Experimental studies in a rabbit model also demonstrated comparable outcomes post CAS involving restenosis and thrombosis of stent.[20] Furthermore, in a case series of patients who switched from clopidogrel to ticagrelor after CAS, no ischemic or hemorrhagic complications were found,[19] further supporting the safety and efficacy of ticagrelor. While ticagrelor may be safe, its efficacy is less clear. In a propensity-matched large database study,[14] ticagrelor was not found to be associated with differences in perioperative outcomes compared to clopidogrel, though there may be the presence of effect modification by protamine use, where ticagrelor may be associated with better outcomes only when protamine was used as well as an association with higher rates of bleeding when protamine was not used. Similarly, another analysis using the Society for Vascular Surgery Vascular Quality Initiative registry, revealed comparable outcomes between ticagrelor and clopidogrel DAPT groups underwent transcarotid artery revascularization (TCAR) procedures.[17]

One possible explanation for the lack of difference between clopidogrel and ticagrelor patients in the prior literature and our study may be that, unlike patients with ACS or acute ischemic stroke who require immediate platelet inhibition, CAS patients typically begin antiplatelet therapy prior

to intervention, which may allow drug levels to reach steady state and mitigate any potential advantage of ticagrelor's more rapid onset of action.[5,7]. Current vascular and stroke guidelines continue to endorse dual antiplatelet therapy (DAPT) with aspirin and clopidogrel around CAS, without recommending ticagrelor as superior.[5,8]

While prior studies and our current data suggest that ticagrelor may not confer a significant advantage over clopidogrel for patients undergoing CAS, it is worth noting that personalizing antiplatelet choice based on individual pharmacokinetics may be reasonable. Clopidogrel resistance may be a significant predictor of new cerebral ischemic lesions following CAS.[9] Mazzaccaro et al.[15] showed switching from clopidogrel to ticagrelor in resistant patients led to improved platelet reactivity profiles and favorable clinical outcomes without increased risk of cardiovascular adverse event. Kreiberg et al.[16] also showed superior outcomes of ticagrelor in clopidogrel resistance patients. Although variability in clopidogrel response is well described in the literature, rigorous clinical trials have not shown a definitive association with adverse outcomes such as stent thrombosis, leading to heterogeneity in clopidogrel resistance testing across the neurovascular community. Validated tools such as the ABCD-GENE score (incorporating Age, Body Mass Index, Chronic Kidney Disease, Diabetes Mellitus, and Genotyping) may help stratify patients at higher risk for clopidogrel resistance.[21] Thus, based on the currently available data, antiplatelet selection should remain individualized, taking into account bleeding risk, CYP2C19 genotype (where available), medication adherence, and economic factors.

Efficacy at the cost of safety with ticagrelor is still an area of active debate, as existing literature reports heterogeneous bleeding outcomes compared with conventional anti-platelet clopidogrel. Some studies including PLATO trial[22] have reported higher rates of ICH or major bleeding in

ticagrelor arm as compared to clopidogrel.[23] Similarly, Huang et al. also demonstrated higher rates of ICH in high risk patients treated with ticagrelor as compared Plavix.[24]In contrast, recent CHANCE-2 trial[25] and few other studies showed no significant difference in ICH rates between two agents.[26] Furthermore, pooled analysis from larger meta-analysis including multiple randomized clinical trials have shown that ticagrelor does not confer a statistically higher risk of ICH relative to clopidogrel.[27,28] Consistent with these more contemporary data, our analysis also demonstrated comparable rates of major bleeding, including ICH, between patients receiving ticagrelor and those receiving clopidogrel. Future prospective and randomized studies are needed to further determine the comparative effectiveness of these two antiplatelet agents in the context of CAS and to develop optimized treatment decision protocols.

Limitations

This study has several limitations inherent to its retrospective observational design. Although propensity score matching was employed, residual confounding cannot be excluded. Important clinical variables that substantially influence CAS outcomes—such as carotid stenosis severity, plaque morphology, comorbidities, collateral circulation, and procedural factors—were not fully captured in our dataset and may confound the observed treatment effects[29] Emergency department visits and inpatient readmissions were recorded as all-cause events and could not be linked to specific diagnoses, preventing determination of whether these encounters were directly related to CAS-associated complications. TriNetX is subject to coding variability and potential misclassification, making it less precise than prospectively curated stroke registries. Given the complexity of evaluating CAS-related outcomes, our findings should be interpreted as associational rather than definitive despite the large sample size. Clinicians may have preferentially prescribed ticagrelor for more urgent or symptomatic patients to avoid potential

clopidogrel nonresponse, introducing selection bias that could favor the clopidogrel group and influence observed ischemic outcomes, although this would not be expected to affect hemorrhagic events. Additionally, variations in antiplatelet testing practices, dosing regimens, and therapy duration across institutions could not be assessed, and these factors may also influence outcomes. The extent and severity of complications such as hemorrhage or infarction could not be evaluated due to the absence of imaging data. Finally, CYP2C19 genotyping information was unavailable, meaning our clopidogrel cohort likely included both responders and nonresponders. This is relevant given that clopidogrel resistance has been reported in up to 30% of the general population and as high as 66% among CAS patients, which may influence drug response and comparative effectiveness.[9,10,30,31]

Conclusion

In this large real-world comparative analysis of ticagrelor and clopidogrel in CAS, we found no significant differences in ischemic stroke, hemorrhage, mortality, and major adverse health events needing inpatient readmissions and emergency department visits. Overall, these findings suggest that ticagrelor does not confer a significant advantage over clopidogrel in terms of efficacy and safety for most CAS patients. Future randomized studies were needed to refine patient selection and optimize periprocedural antiplatelet strategies in CAS.

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Table 1: Patient characteristics before and after propensity score matching.

Characteristics - mean ± SD or % (n)	Before matching				After matching			
	Ticagrelor N = 378	Clopidogrel N = 6618	p-Value*	SMD	Ticagrelor N = 377	Clopidogrel N = 377	p-Value*	SMD
Demographics								
Age at Index	69.7 ± 11.3	72.0 ± 9.1	**<0.001**	0.224	69.7 +/- 11.4	70.4 +/- 10.4	0.418	0.059
Female	41.0% (155)	36.1% (2390)	0.055	0.101	40.8% (154)	37.9% (143)	0.412	0.06
Race								
White	77.2% (292)	84.3% (5581)	**<0.001**	0.18	77.2% (291)	78.0% (294)	0.793	0.019
Black or African American	4.8% (18)	4.7% (314)	0.988	0.001	4.8% (18)	4.8% (18)	1	<0.001
Asian	2.6% (10)	0% (0)	0.333	0.048	2.7% (10)	2.7% (10)	1	<0.001
Comorbidities								
Atrial fibrillation and flutter	12.7% (48)	18.1% (1199)	**0.007**	0.151	12.7% (48)	11.7% (44)	0.656	0.032
Essential (primary) hypertension	78.6% (297)	81.1% (5366)	0.227	0.063	78.5% (296)	76.1% (287)	0.434	0.057
Hyperlipidemia	66.9% (253)	71.3% (4716)	0.071	0.094	67.1% (253)	63.4% (239)	0.284	0.078
Diabetes mellitus	39.2% (148)	38.1% (2520)	0.675	0.022	39.0% (147)	36.1% (136)	0.408	0.06
Smoking	23.8% (90)	21.8% (1444)	0.363	0.047	23.9% (90)	22.8% (86)	0.731	0.025
Heart failure	22.5% (85)	20.9% (1386)	0.474	0.037	22.5% (85)	23.1% (87)	0.862	0.013
Cerebral atherosclerosis	5.8% (22)	4.5% (301)	0.252	0.057	5.8% (22)	5.6% (21)	0.875	0.011
Obesity	20.1% (76)	19.8% (1312)	0.894	0.007	20.2% (76)	17.5% (66)	0.352	0.068
Peripheral vascular diseases	26.5% (100)	34.7% (2296)	**0.001**	0.18	26.5% (100)	24.7% (93)	0.559	0.043
Ischemic heart diseases	64.3% (243)	59.5% (3940)	0.067	0.098	64.2% (242)	63.9% (241)	0.94	0.006
Headache	13.0% (49)	10.4% (691)	0.121	0.079	12.7% (48)	10.3% (39)	0.305	0.075
Anxiety disorders	21.4% (81)	21.9% (1452)	0.815	0.012	21.5% (81)	19.1% (72)	0.415	0.059
Mood disorders	19.0% (72)	18.0% (1192)	0.611	0.027	18.8% (71)	17.2% (65)	0.57	0.041
Substance use disorders	33.1% (125)	33.0% (2182)	0.969	0.002	32.9% (124)	30.8% (116)	0.532	0.046
Aplastic and other anemias, bone marrow failure syndromes	32.3% (122)	27.2% (1797)	**0.03**	0.112	32.1% (121)	31.8% (120)	0.938	0.006
Disorders of blood and blood-forming organs	14.0% (53)	12.3% (812)	0.314	0.052	14.1% (53)	13.3% (50)	0.75	0.023
Nutritional anemias	11.4% (43)	10.0% (665)	0.405	0.043	11.1% (42)	9.8% (37)	0.552	0.043
Hemolytic anemias	2.6% (10)	0.6% (43)	**<0.001**	0.157	2.7% (10)	2.7% (10)	1	<0.001
Alcohol related disorders	5.6% (21)	5.8% (382)	0.86	0.009	5.6% (21)	5.8% (22)	0.875	0.011
Diseases of liver	8.7% (33)	8.4% (556)	0.823	0.012	8.8% (33)	6.9% (26)	0.343	0.069
Chronic kidney disease	21.4% (81)	23.5% (1555)	0.356	0.05	21.5% (81)	21.8% (82)	0.93	0.006
Coagulopathy	9.8% (37)	9.2% (611)	0.717	0.019	9.8% (37)	8.0% (30)	0.37	0.065
Antithrombotic (prior use)								
Warfarin	5.6% (21)	5.4% (357)	0.893	0.007	5.6% (21)	4.8% (18)	0.622	0.036
Rivaroxaban	5.3% (20)	4.5% (295)	0.447	0.039	5.3% (20)	5.6% (21)	0.872	0.012
Apixaban	9.8% (37)	9.5% (632)	0.878	0.008	9.8% (37)	9.5% (36)	0.902	0.009
Aspirin	89.7% (339)	91.7% (6071)	0.161	0.071	89.7% (338)	92.0% (347)	0.256	0.083

*Bolded p value indicates significant difference.

Table 2: Study outcomes at 6-months following propensity score matching

*Outcomes^*	Ticagrelor N = 377	Clopidogrel N = 377	p-value	HR [95%CI]
Ischemic Stroke	2.7% (<11)	4.2% (16)	0.159	0.56 [0.25-1.27]
Major hemorrhage	2.9% (11)	4.8% (18)	0.197	0.61 [0.29-1.30]
Intracranial hemorrhage	2.7% (<11)	2.7% (<11)	0.488	0.61 [0.14-2.53]
All-cause mortality	3.4% (13)	2.7% (<11)	0.263	1.64 [0.68-3.97]
Inpatient readmission	15.9% (60)	19.1% (72)	0.223	0.81 [0.57-1.14]
Emergency Department Visit	14.3% (54)	14.6% (55)	0.895	0.97 [0.67-1.42]

^Outcomes were reported as event probability at 180 days per Kaplan Meier analysis and event counts, p-values were derived from log-rank tests of Kaplan Meier curves, and hazard ratios (HR) represent risk associated with ticagrelor versus clopidogrel calculated using Cox proportional hazards models. Outcomes with less than 11 events were reported as such per data use agreement with ANONYMIZED DATABASE; having counts <11 did not impact the exact calculation of true event probabilities, p-values, or hazards ratios.

Figure Legends

Figure 1: Hazard Ratio of ticagrelor vs clopidogrel for outcomes following Carotid artery stenting