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A DISPROPORTIONALITY ANALYSIS OF ANGIOEDEMA WITH TISSUE PLASMINOGEN ACTIVATORS (ALTEPLASE, RETEPLASE AND TENECTEPLASE) BASED ON FAERS DATABASE

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ABSTRACT

Background: Tissue plasminogen activator (tPAs) biochemically a serine protease (enzymes that cleave peptide bonds in proteins). It is considered as essential component for the dissolution of blood clots. It has its catalysing ability in the full conversion of plasminogen to plasmin, the primary enzyme involved in dissolving blood clots. Ischemic stroke, Myocardial infarction, Pulmonary embolism, Deep Vein Thrombosis are the main indications of tPAs. However, these medications have been associated with increased occurrence of angioedema. The objective of this study is to investigate potential safety signals for tPAs with angioedema using disproportionality analysis enscripted in the FDA Adverse Even Reporting System (FAERS) database. **Research design and methods:** The study retrospectively investigated case/non-case analysis using Openvigil 2.1-MedDRA-v24 (2004Q1 to 2022Q4). The preferred term used was 'angioedema' and the drugs included were Alteplase, Tenecteplase and Reteplase. Reporting Odds Ratio (ROR), Proportional Reporting Ratio (PRR), and Information Component (IC) were used to quantify the disproportionality and measure its signal strength. **Results:** Overall 19676 AE reports related to tPAs were identified, of which 790 reports (alteplase − 761, tenecteplase − 33, and reteplase − 0) associated with angioedema were obtained from FAERS. On analysis, alteplase had greater signal strength for age group of 65–100 years while tenecteplase had greater signal strength for age group of 0-18 years. In gender

categorization, alteplase showed greater signal strength for females while tenecteplase showed greater signal strength for males. Conclusions: Our study identified signals for angioedema with alteplase and tenecteplase.

KEYWORDS: Disproportionality Analysis, OpenVigil, tPAs, Angioedema, FAERS.

1. INTRODUCTION

Pharmacovigilance is the method of watching over and assessing the safety of drugs, which include prescription drugs, vaccines, and medical devices, once they are approved and marketed. As defined by the World Health Organization (WHO), pharmacovigilance is "the science and activities associated with the detection, assessment, understanding, and prevention of adverse effects or any other drug related problem."[1] Data mining may assist pharmaceutical companies evaluate drug safety, adhere to risk management policies, and obtain real-world information to supplement clinical trial data.[2] Disproportionality analysis is basically an approach for developing hypotheses about possible causative relationships between medications and adverse effects, which will be followed by clinical evaluation of the underlying particular case reports.[3] Open vigil2.1-MedDRA-v24 is a web-based pharmacovigilance analysis application that uses the FDA's open web interface to retrieve validated and normalized data.[4,5] The international pharmacovigilance data is acquired from the FDA Adverse Event Reporting System Database (FAERS) using Open vigil FDA, a unique pharmacovigilance analysis database with an online interface. Open FDA is an easily accessible platform that links pharmacovigilance data to real-life clinical issues.[6]

Tissue plasminogen activator (tPA) is a serine protease, an enzyme that splits peptide links in proteins. Thus, it plays a crucial role in the disintegration of blood clots. Its main function is to catalyze the transformation of plasminogen into plasmin, which is the main enzyme that dissolves blood clots. Tenecteplase, reteplase, and alteplase are some of these drugs. The use of tPA is indicated for ischemic stroke in patients who arrive at the treatment facility within three hours of the onset of symptoms; cardiac infarction if percutaneous transluminal coronary angioplasty is delayed by more than one or two hours; pulmonary embolism in major pulmonary embolisms, which result in significant instability due to elevated heart pressure; and thrombolysis.[7] Activating plasminogen causes active platelets to aggregate into fibrin meshes, which is how tPA dissolves blood clots. More precisely, it creates plasmin, a serine protease, by cleaving the zymogen plasminogen at its Arg561-Val562 peptide bond. The short-lived natural fibrinolytic enzyme plasmin destroys the cross-links

between fibrin molecules, which provide structural support for the blood clot. This brief period of time is caused by alpha 2-antiplasmin, a common plasmin inhibitor that rapidly deactivates plasmin and limits its activity to the area around the clot.[7,8]

tPAs include Alteplase, Urokinase, Reteplase, Anistreplase, Tenecteplase, Streptokinase, Lanoteplase, Amediplase and Saruplase. Alteplase, Reteplase and Tenecteplase are the commonly used tPAs worldwide. In November 1987, Alteplase was licensed for medical use in the United States to treat myocardial infarction following the findings of two more trials. Intravenous alteplase is the only authorized therapy for acute ischemic stroke. Tenecteplase, a genetically modified mutant tissue plasminogen activator, is a substitute thrombolytic agent.[9,10,11]

Amediplase is a hybrid plasminogen activator that combines the catalytic protease domain of single chain urokinase-type plasminogen activator with the kringle-2 domain of tissue-type plasminogen activator. It has been shown that the first-generation fibrinolytic drugs streptokinase and urokinase are also useful in thrombolysis.[12] Saruplase is a recombinant form of Urokinase.[13] The human tissue-type plasminogen activator's protease and kringle 2 domains combine to form the recombinant peptide known as Retiplase.[14] Anistreplase is a second-generation thrombolytic agent with a lengthy half-life that is simple to use.[9,15] Recombinant plasminogen activator lanoteplase has thrombolytic action when given intravenously as a single bolus infusion.[10,16]

The fibrinolytic drugs streptokinase, anistreplase, alteplase, reteplase, and tenecteplase are utilized in AMI. Less is utilized of streptokinase and anistreplase than other medications because of hypotension and allergic reaction.[17] The only medication approved to treat acute ischemic stroke (AIS) is alteplase.[18] Even though it raises the risk of intracerebral hemorrhage, thrombolytic therapy with intravenous alteplase at a dose of 0.9 mg per kilogram of body weight is an effective treatment for acute ischemic stroke.[19] Tenecteplase is given for stroke at a dose of 0.25 mg/kg upto 25 mg.[20] A 10-unit IV bolus administered over two minutes is the recommended dosage of Reteplase for treating acute myocardial infarction; this should be repeated in thirty minutes.[21]

Angioedema is the swelling caused by the passage of fluid from blood arteries into the skin and tissues. Angioedema can affect any part of the body; however it is most commonly seen around the eyes, lips, mouth, tongue, extremities, and genitalia. The swelling might be

accompanied by superficial hives; however angioedema affects deeper layers of the skin. It can be divided into hereditary and acquired forms. Hereditary angioedema is a rare condition that is inherited as an autosomal dominant trait and is caused by a lack of Cl-esterase inhibitor. Nonhereditary Cl-esterase inhibitor deficiency; idiopathic, allergy, and drug-induced variants; angioedema linked with lupus erythematosus and hypereosinophilia; and angioedema triggered by physical stimuli are all examples of acquired angioedema.[22,23]

Thrombolytic-induced angioedema is a known consequence of alteplase or tenecteplase treatment, affecting 0.9-5.1% of patients who received thrombolytics for ischemic stroke. These medications' hazards have not been sufficiently assessed because their safety has not been thoroughly examined in clinical trials. Given these safety concerns, the goal of our work is to use disproportionality analysis with the FAERS database and Openvigil2.1-MedDRA-v−24 to discover potential safety signals of tPAs linked to angioedema.

Thrombolytic-induced angioedema is a recognized side effect of Alteplase or Tenecteplase treatment, affecting 0.9-5.1% of patients receiving thrombolytics for ischemic stroke. The safety of these medications has not been thoroughly assessed in clinical trials, raising concerns about their potential risks. Given these safety concerns, the objective of our study is to utilize disproportionality analysis with the FAERS database and OpenVigil 2.1-MedDRA-v24 to identify potential safety signals of tPAs associated with angioedema.

2. METHODOLOGY

2.1 DATA SOURCE

A publicly accessible FAERS database, which is a component of the Med Watch public-access database that enables patients, consumers, healthcare providers, and pharmaceutical companies to record adverse events globally, was used to conduct the case/non-case retrospective disproportionality study. Our study was based on all reports of angioedema associated with tPAs received by the Food and Drug Administration from First Quarter of 2013 to 3rd Quarter of 2023.

2.2 STUDY PROCEDURE

The OpenVigil 2.1-MedDRA-v24 web-based platform for pharmacovigilance data analysis from domestic and international sources was used for data mining, extraction, and filtration. Reporting Odds Ratio (ROR), Proportional Reporting Ratio (PRR), and Information Component (IC) were used to quantify the disproportionality. By eliminating the vast

majority of duplicates and reports with insufficient information, OpenVigil operates with clean data. We found reports of angioedema associated with tPAs, specifically Alteplase, Reteplase and Tenecteplase. Since there have been no reports of angioedema, other tPAs that are undergoing clinical trials were not included in the follow-up analysis. A number of filters were applied to the data to further refine it, including age, gender, reporter nation, and results.

2.3 STATISTICAL ANALYSIS

Strength of association between angioedema and tissue plasminogen activators using FAERS database with that of all other drugs were determined. To scrutinize the contrasting proportion of angioedema in targeted drugs through the use of ROR, PRR and IC values. We distinguish the proportion of angioedema of the target drug in the FAERS database with that of all other drugs to reveal the possible angioedema reporting risk.[24] According to Evans, PRR > 2, χ2Yates > 4 and drug exposed > 3 is considered as minimal criteria for a signal of disproportionality.[25] We exploited descriptive statistics to study the demographic characteristics of the targeted drug associated angioedema, including age, gender, outcome, and reporter country.

3. RESULT

The study examined the safety of tPAs, namely Alteplase, Tenecteplase and Reteplase, between 2013Q1 and 2023Q3 by analyzing 19676 adverse event (AE) reports related to these drugs. Out of these, 790 reports on angioedema were submitted to the FAERS database for analysis.

ALTEPLASE – ASSOCIATED ANGIOEDEMA

A total of 239 reports were found out from FAERS database for the drug Alteplase. Reports were grouped on the basis of different categories such as age, gender, outcome, and reporter country. Gender is subcategorized into male, female, and unknown. It estimated that female gender (n = 96) shown the greater signal strength of ROR 32.077, PRR 30.286, and IC 4.909 than male gender (n = 77) in which the ROR, PRR, and IC values are 11.453, 11.083, and 3.462, respectively. The age stratification was determined by dividing the study population into three groups: 0–18 years, 19–64 years, and 65–100 years. It estimated that the age group of 65–100 years (n = 88) had the greatest signal strength of ROR 20.729, PRR 19.473, and IC 4.266than other subset of age groups. The outcome-based analysis claimed that “death” (n = 16) had the greatest signal strength of ROR 21.036, PRR 20.875, and IC 4.332 than other

outcomes. Based on the reporter country analysis, Australia showed the greatest signal strength list with ROR value of 18.019, PRR17.074, and IC 6.662.

Table 1: Disproportionality of alteplase –associated angioedema; analysis based on gender, age, outcome and reporter country.

			ALTEPLASE	
GENDER BASED DATA	DE	ROR(95%CI)	PRR(95%CI)	IC(95%CI)
MALE	77	11.453 (9.117 -14.387)	11.083 (8.894 -13.811)	3.462
FEMALE	96	32.077 (26.082 - 39.448)	30.286 (24.919 -36.808)	4.909
AGE BASED DATA				
0-18 YRS	0	0	0	0.000
19-64 YRS	44	9.342 (6.915 -12.622)	9.073 (6.781 - 12.139)	3.177
65-100 YRS	88	20.729 (16.682 - 25.757)	19.473 (15.887 -23.868)	4.266
OUTCOME BASED				
CONGENITAL ANOMALY	0	0	0	0.000
DEATH	16	21.036 (12.744 - 34.725)	20.875 (12.695 -34.325)	4.332
DISABILITY	3	10.557 (3.357 - 33.196)	10.414 (3.369 - 32.192)	3.368
HOSPITALIZATION	60	11.378 (8.767 - 14.768)	10.826 (8.457 - 13.858)	3.429
LIFE THREATENING	51	9.349 (6.962 - 12.556)	8.313 (6.418 - 10.767)	3.040
OTHER	130	14.857 (12.445 -17.737)	14.153 (11.962 - 16.746)	3.812
REQUIRED INTERVENTION TO PREVENT PERMANENT IMPAIRMENT/DAMAGE	10	7.743 (3.859 - 15.534)	6.367 (3.656 - 11.088)	2.664

			ALTEPLASE	
REPORTED COUNTRY	DE	ROR(95%CI)	PRR(95%CI)	IC(95%CI)
AFRICA	0	0	0	0.000
ASIA	8	2.692 (1.34 -5.408)	2.676 (1.341 - 5.34)	1.417
EUROPE	25	3.438 (2.313 - 5.111)	3.391 (2.299 - 5.003)	1.759
NORTH AMERICA	196	31.21 (27.009 - 36.066)	29.682 (25.872 - 34.052)	4.873
OCEANIA	24	18.019 (6.534 - 49.694)	17.074 (6.546 - 44.535)	6.662
SOUTH AMERICA	0	0	0	0.000

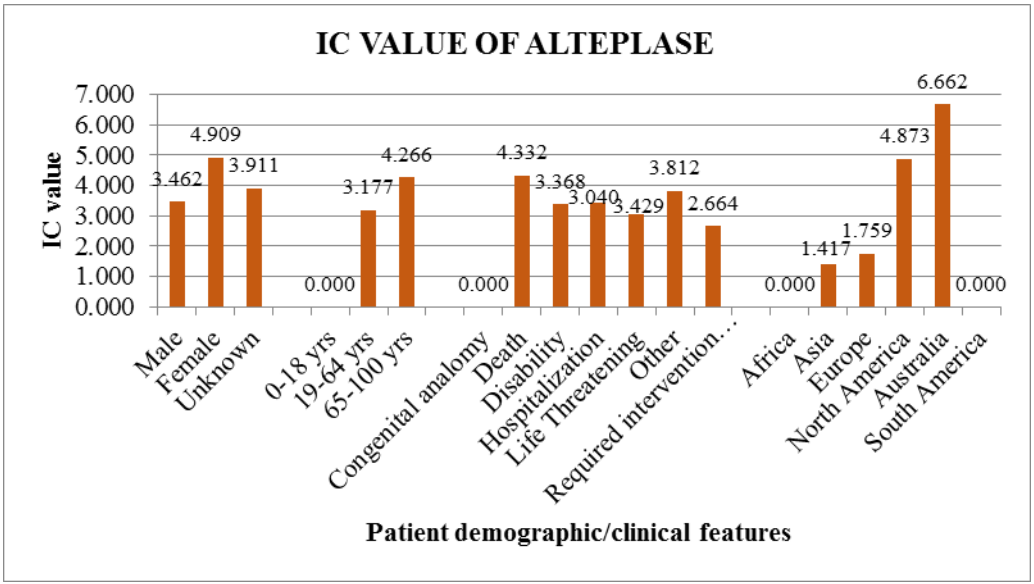

Figure 1: Graphical representation of alteplase illustrate IC value related to the patient demographics. The vertical axis represents the IC value, and horizontal axis represents the patient clinical features.

TENECTEPLASE – ASSOCIATED ANGIOEDEMA

A total of 10 reports were identified from FAERS database for Tenecteplase. Reports were grouped on the basis of different categories such as age, gender, and outcome and reporter country. Gender is subcategorized into male, female, and unknown. It estimated that "unknown" category (n = 4) shown the greater signal strength of ROR 11.829, PRR 11.619, and IC 3.536 than other subset of gender outcomes. The age stratification was determined by dividing the study population into three groups: 0–18 years, 19–64 years, and 65–100 years. It is estimated that the age group of 0-18 years (n = 1) had the greatest signal strength of ROR 85.463, PRR 64.347, and IC 6.007 than other subset of age groups. The outcome-based analysis claimed that "death" (n = 1) had the greatest signal strength of ROR 9.959, PRR 9.923, and IC 3.308 than other outcomes. Based on the reporter country analysis, North America (n=9) showed the greatest signal strength list with ROR value of 15.68, PRR15.292, and IC 3.934.

Table 2: Disproportionality of Tenecteplase –associated angioedema; analysis based on gender, age, outcome and reporter country.

			TENECTEPLASE	
GENDER BASED DATA	DE	ROR(95%CI)	PRR(95%CI)	IC(95%CI)
MALE	5	5.329 (2.201 - 12.903)	5.256 (2.204 -12.537)	2.394
FEMALE	1	11.829 (4.394 - 31.849)	11.619 (4.399 - 30.687)	1.584
AGE BASED DATA				
0-18 YRS	1	85.463 (8.884- 822.115)	64.347 (11.777 - 351.594)	6.007
19-64 YRS	2	3.062 (0.76 - 12.336)	3.039 (0.766 - 12.062)	1.604
65-100 YRS	4	6.481 (2.407 - 17.456)	6.366 (2.413 - 16.792)	2.670
OUTCOME BASED				
CONGENITAL ANOMALY	0	0	0	0.000
DEATH	1	9.959 (1.394 - 71.136)	9.923 (1.4 - 70.335)	3.308
DISABILITY	0	0	0	0.000
HOSPITALIZATION	1	1.22 (0.171 -8.714)	1.219 (0.173 - 8.602)	0.286
LIFE THREATENING	1	0.687 (0.096 -4.929)	0.69 (0.098 - 4.851)	-0.535
OTHER	5	6.32 (2.604 - 15.338)	6.2 (2.606 - 14.752)	2.632
REQUIRED INTERVENTION TO PREVENT PERMANENT IMPAIRMENT/DAMAGE	2	8.595 (1.784 - 41.403)	6.907 (2.033 - 23.469)	2.787

			TENECTEPLASE	
REPORTER COUNTRY	DE	ROR(95%CI)	PRR(95%CI)	IC(95%CI)
AFRICA	0	0	0	0.000
ASIA	0	0	0	0.000
EUROPE	1	1.565 (0.219 -11.213)	1.56 (0.222 -10.982)	0.642
NORTH AMERICA	9	15.68 (8.085 - 30.408)	15.292 (8.025 -29.143)	3.934
OCEANIA	0	0	0	0.000
SOUTH AMERICA	0	0	0	0.000

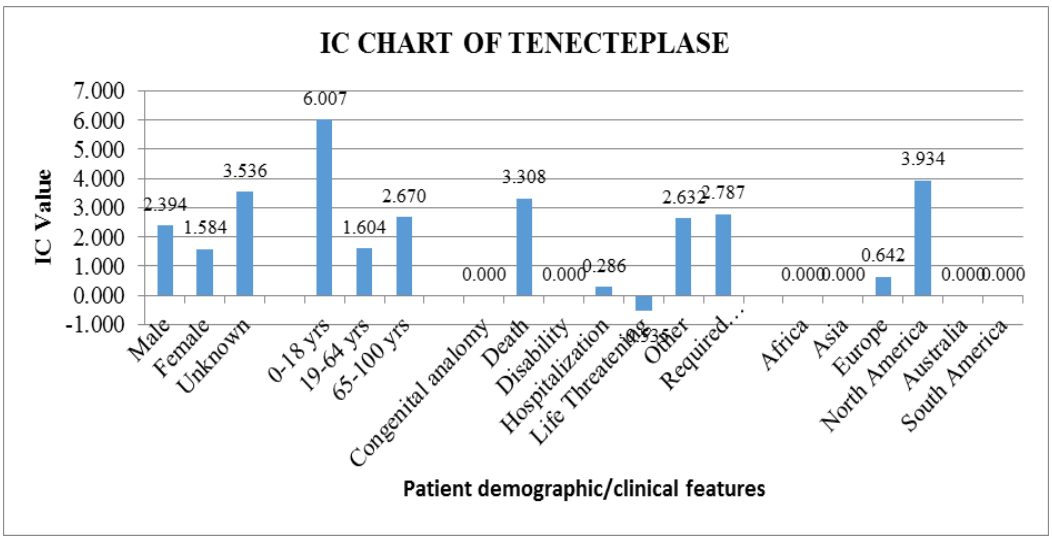

Figure 2: Graphical representation of tenecteplase illustrate IC value related to the patient demographics. The vertical axis represents the IC value, and horizontal axis represents the patient clinical features.

RETEPLASE- ASSOCIATED ANGIOEDEMA

Reteplase associated angioedema was not reported in patients until 31st December 2023.

4. DISCUSSION

Spontaneous reporting system (SRS) is a universally accepted system to report adverse events by health care professionals, drug manufacturers, or patients to the national authorities synchronizing PV activities around the whole country. This reporting system paves way for revamping the safety profile of a targeted drug by identifying and reporting ADRs that had not been detected during premarketing clinical trials or during post marketing surveillance. Therefore, it could be claimed as a process entailed for seeking new, rare, or serious ADR events. One of the significant element of SRS is that it can be applied all drugs during its course of life and not finite to a period of study.[26]

A number of limitations of the present study could muddle up the depicted results. First, the FAERS database which has been proclaimed as a fully-fledged spontaneous reporting adverse event database, is restricted by the initiative, precision, and timeliness of reporting adverse events by general practitioners, patients, and other healthcare professionals; therefore, chances of under-reporting and misreporting is irrevocable. Second, the obstacles intertwined with non-standard reports and missing data in FAERS, such as age and sex is always rectified. Third, reporters from the United States, the United Kingdom, are more dwelling than other countries, contributing to drawbacks in the generalization of conclusions among Asians. Fourth, the causality between fibrinolytics and angioedema is too difficult to detect and needs to be rectified in further prospective clinical trials.

In this research, we scrutinized the aptitude of this strategy and the analysis showcased, alteplase to have a greater ROR, PRR, and IC values, whereas Reteplase showed the lesser value with respect to angioedema. Consequently, Reteplase appears to have a minimal chance of causing angioedema compared to other drugs in the class specified. Throughout the analysis, it depicted delineated results where males have greater signal strength for angioedema with respect to ROR, PRR, and IC than females in case of alteplase while females showed a stronger signal strength for Tenecteplase. Age-based stratification claimed that alteplase has greater signal strength in age group of 65– 100, whereas Tenecteplase showed greater signal strength in age group of 0-18.Alteplase and Tenecteplase reported enormous amount of death cases when outcome stratification was enacted. The drug

Reteplase showed no ADR -event reports suggesting that it may be least associated with corresponding adverse reaction.

There were numerous studies based on these fibrinolytics carried out for their appropriate analysis. A systematic review and meta-analysis of randomized controlled trials comparing anticoagulation plus systemic thrombolysis with anticoagulation alone for patients with acute PE, they also sought to identify potential subgroups of patients with a favourable risk–benefit ratio and planned to separately analyse studies according to their criteria of PE severity, in addition to this, they also found that Thrombolytic therapy reduces total mortality, PE recurrence, and PE-related mortality in patients with acute PE. But while comparing with our study, our study was based on signal strength (ROR,PRR,RRR,IC) and included outcome based studies which had greater audacity than the later.[27]

Another systematic review to assess the incidence of seizures and the association of recombinant tissue plasminogen activator with seizure occurrence was reported had too its limitations in comparison with our study, as our study clearly depicted the incidence rate of the adr-event pair. And also were able to categorise the given data based on age, gender, outcome and reported country.[28]

In a disproportionality analysis by Fang-E Shi, four data mining algorithms (ROR, PRR, BCPNN, and EBGM) were used to detect signals of AEs and to evaluate the disproportionality of AEs associated with Tenecteplase and alteplase in real-world data. Subsequently, Breslow-Day statistical analysis was incorporated to distinguish the RORs belonging to the main system organ classes (SOCs) and key preferred terms (PTs) between Tenecteplase and alteplase. Here IC values were not used, in addition to that only 2 drugs were taken into consideration.[29]

A comparative study was conducted as there is increasing interest in replacing alteplase with Tenecteplase as the preferred thrombolytic treatment for patients with acute ischaemic stroke. The study aimed to establish the non-inferiority of Tenecteplase to alteplase for these patients. This study was not on focus as they didn’t consider data mining algorithms in their studies like ROR, PRR, and IC Values and lacked categorization based on reported country. A Randomised Control Trial was done by Dana Barequetto to evaluate the safety and the adjunctive effect of intracameral tissue plasminogen activator (tPA) in trabeculectomy for

patients with primary open-angle glaucoma (POAG) which didn't include datamining algorithms.[30]

However, our study had constraints while interpreting the results. Under-reporting and misreporting could be irrevocable and unexpected incident while using pharmacovigilance database. Also, the association between a drug–reaction pair cannot be firmed out via disproportionality alone and signal detection is purport for exploratory, hypothesis generating purposes. So disproportionality analysis has more potential to hypothesize on the existence of newly identified drug–reaction associations.

5. CONCLUSION

Our analysis used the FAERS database to determine the relationship between tPAs and angioedema. The risk-benefit profile of the medicine was identified and reevaluated using a disproportionality study, which employed the data mining algorithms ROR, PRR, and IC to identify any relevant signals. The purpose of this study is to alert medical practitioners to the risk of angioedema associated with tPAs and the importance of closely monitoring and caring for these individuals.

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7. AUTHORS CONTRIBUTION

All authors have contributed equally.

8. CONFLICT OF INTEREST

NIL.

9. CONSENT FOR PUBLICATION

All authors have consented for the publication of their work.

10. COMPETING INTEREST

All authors declare that they have no competing interests.

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