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Antiplatelet drugs use situation for acute myocardial infarction patients in Vietnam

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Abstract. This study aims to evaluate antiplatelet drug use and possible interactions that can occur during acute myocardial infarction treatment. We establish a cross-sectional descriptive study with 380 acute myocardial infarction inpatient cases treated with antiplatelet drugs in Vietnam in 2021. In our study, the mean age is 69.3, and most patients are over sixty-five, accounting for 67.6%. Indicated antiplatelet drugs encompass aspirin (100%), clopidogrel (86.0%), and ticagrelor (42.6%). Dual antiplatelet therapy with aspirin-clopidogrel and aspirin-ticagrelor accounts for 86.0% and 42.6%, respectively. According to drugs.com and medscape.com, the results show three clinically significant combinations:aspirin-enalapril (37.4%), clopidogrel-esomeprazole (31.3%), and aspirin-captopril (20%). Of all discovered drug interactions, 28.1% are estimated as major and 38.8% as moderate (monitor closely). The results show that aspirin is considered the first-line drug, and the aspirin-clopidogrel combination is more common than aspirin-ticagrelor in the treatment of acute myocardial infarction patients. Aspirin-enalapril, clopidogrel-esomeprazole, and aspirin-captopril are clinically significant interactions avoided in indicating.

Keywords: *Acute myocardial infarction, antiplatelet drugs, medical records, and drug interactions.*

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1. Introduction

Nowadays, one of the foremost causes leading to mortality worldwide is cardiovascular disease, and myocardial infarction (MI) accounts for an essential proportion (Chatla & Obilineni, 2021; Tsao et al., 2022). In many developed countries, people over 75 usually suffer from myocardial infarction more than others. Nevertheless, it appears more commonly in people younger than forty-five living in South Asian countries (Chatla & Obilineni, 2021; Ly et al., 2022). Myocardial infarction is a potentially fatal disease that affects the entire global population. Researchers estimated that about 14% of patients died after experiencing it. In the United States, according to the National Health and Nutrition Examination Survey (NHANES), from 2015 to 2018, the rate of patients with myocardial infarction was 3.1%, and each forty-second, a case occurred (Tsao et al., 2022). Because of the severity and potential for dangerous to-life conditions, if not intervened promptly, the crucial principles of treating a myocardial infarction case include preventing complications and reducing the risk of death.

Dual antiplatelet therapy (DAPT) is the primary indication to relieve angina symptoms in acute myocardial infarction. In DAPT, the combination of aspirin and clopidogrel, a drug belonging to the P2Y12 receptor inhibitor group, has been widely indicated for a long time. As ticagrelor is gradually used, new P2Y12 receptor inhibitors are being developed. Compared to clopidogrel, patients treated with ticagrelor have lower ischemia and bleeding risks. In addition, the clopidogrel activity relates to the CYP2C19 isoenzyme, and it may influence some co-administered drugs' effectiveness through interaction events in the pharmacokinetic phase. Otherwise, ticagrelor does not have those interactions (Yasuda et al., 2019; Gragnano et al., 2021).

These medication characteristics affect the tendency and decision to choose a drug for treatment. However, information and data about using DAPT for acute myocardial infarction cases are still limited in Vietnam. Therefore, this study aims to evaluate the combination trends and antiplatelet drug interactions in acute myocardial infarction patients' treatment. It provides supplementary scientific evidence to optimize and ensure the safety and rationality of drug use.

2. Materials and Methods

2.1. Study design and patient population

We conducted a cross-sectional descriptive study based on medical records from a hospital in Vietnam (from January to December 2021). The medical records are collected appropriately by collating them according to the inclusion and exclusion criteria. Inclusion criteria include: (1) inpatient medical records with an acute myocardial infarction diagnosis; and (2) indicated antiplatelet therapy during the study period. Exclusion criteria encompass: (1) inter-hospital transfers of patients' medical records; (2) less than five days in the hospital; (3) pregnancy; or (4) death. Based on the sample size formula for determining/estimating a proportion in a population of unknown sample size, the required sample size is 374 medical records, and we collected 380 in reality. These 380 medical records were chosen from 780 others using systematic random sampling.

2.2. Statistical analysis

All of the collected data were entered and analyzed using Microsoft Excel 2016 and SPSS 23.0 software.

2.3. Ethics

We conduct this research with adherence to ethical principles in medical research. The Ethics Committee in Biomedical Research and the City General Hospital Directors approved the research protocol. We collect data from the original medical records stored in the hospital's General Planning Department without affecting patients' health. During the research period, we committed to honesty and seriousness. All of the patients' private information is kept confidential. We only use this information to improve patients' health, limit errors in medication use, and restrict adverse drug interactions.

3. Results and Discussion

3.1. Study population characteristics

The results show that most patients in the research are over 65 (257 patients), accounting for 67.6%. The patients' mean age is 69.3, the oldest is 96, and the youngest is 25. Of all 380 patients, the male proportion (54.5%) is 1.2 times higher than the female proportion (45.5%) (Table 1).

Table 1. Age and gender characteristics of patient

Age group	Male	Female	Total (N = 380)
	n (%)	n (%)	n (%)
< 65 years old	93 (24.5%)	30 (7.9%)	123 (32.4%)
≥ 65 years old	114 (30%)	143 (37.6%)	257 (67.6%)
Total	207 (54.5%)	173 (45.5%)	380 (100%)
Mean age		69.3 ± 11.6	
The oldest patient		96 years old	
The youngest patient		25 years old	

3.2. Used antiplatelet drugs proportion in acute myocardial infarction treatment.

According to the study results, aspirin appears in all 380 medical records collected, accounting for 100%. Clopidogrel and ticagrelor are indicated for patients in 327 (86.0%) and 162 (42.6%) medical records, respectively (Table 2). However, according to Gorgis et al. (2022), aspirin accounts for 77.9%, clopidogrel is 12.2%, and ticagrelor is 41.9%. Prescribing a drug depends on the balance between its benefits and risks. Aspirin is an ordinary antiplatelet agent indicated in acute myocardial infarction treatment. Presently, combining aspirin with a P2Y12 receptor blocker as a dual antiplatelet therapy is widely used. Clopidogrel is the well-

studied P2Y12 inhibitor, but ticagrelor has a more potent and stable platelet inhibitory effect than clopidogrel. The choice of antiplatelet agent and treatment duration are crucial to improving cardiovascular events and mortality.

There is a higher antiplatelet drug use rate in the NSTEMIN group compared to the STEMI group. Therein, there are 135 (35.5%) ST-segment elevation myocardial infarction (STEMI) cases using aspirin, 103 (27.1%) cases using clopidogrel, and 85 (22.3%) cases using ticagrelor (Table 2). We also explore two dual antiplatelet therapies frequently used, including the aspirin-clopidogrel combination and the aspirin-ticagrelor combination. Much previous research has proposed various pieces of evidence to prove aspirin's effectiveness. It is readily available, reasonably priced, and convenient for patients because of its small size. As a result, aspirin has become more popular, and now it has become the first choice in acute MI treatment. Although the therapeutic efficacy of clopidogrel and ticagrelor is similar, clopidogrel is cheaper and more readily available. In addition, in some cases, the aspirin-clopidogrel combination is ineffective, so ticagrelor is substituted with clopidogrel, which aims to bring higher efficiency, avoid risks, and minimize cardiovascular death (Gulizia et al., 2018; Ahn et al., 2020). In our study, the aspirin-clopidogrel combination rate accounted for 86%, higher than aspirin-ticagrelor (42.6%). Similarly, about the DAPT, another study shows a superior aspirin combination with clopidogrel (46.8%) than with ticagrelor (6.6%) (Lam et al., 2020). The difference in medication choices might be because of drugs' availability, current legal recommendations or guidelines, drug effectiveness reports, and doctors' medication use experiences. In acute myocardial infarction treatment, using clopidogrel or ticagrelor in DAPT produces equivalently effective results, but more investigation needs to be established to determine ticagrelor safety (Guan et al., 2017).

Table 2. Antiplatelet drugs use tendency

Antiplatelet drugs		STEMI	NSTEMI	Medical records (N=380)
		n (%)	n (%)	n (%)
Aspirin		135 (35.5%)	245 (64.5%)	380 (100%)
Clopidogrel		103 (27.1%)	224 (58.9%)	327 (86.0%)
Ticagrelor		85 (22.3%)	77 (20.3%)	162 (42.6%)
Dual antiplatelet therapy (DAPT)	Aspirin-Clopidogrel	103 (27.1%)	224 (58.9%)	327 (86.0%)
	Aspirin-Ticagrelor	85 (22.3%)	77 (20.3%)	162 (42.6%)

*STEMI: ST-segment elevation myocardial infarction; NSTEMI: Non-ST-segment elevation myocardial infarction.

In the research, we estimate that there are 146 cases (38.4%) of indicated aspirin with a 324 mg starting dose, encompassing 80 NSTEMI cases (21.0%) and 66 STMEMI cases (17.4%). Patients who used clopidogrel at the 300 mg starting dose are in 231 medical records (70.6%), including 165 NSTEMI patients (50.4%) and 66 STMEMI patients (20.2%). About ticagrelor, it appears in 133 medical records (82.1%) with a 180 mg starting dose, including 57 NSTEMI cases (35.2%) and 76 STMEMI cases (46.9%) (Table 3).

According to the European Society of Cardiology 2019 (ESC), in acute MI, patients should receive DAPT, including aspirin and a P2Y12 receptor antagonist (ticagrelor or clopidogrel) (Timmis et al., 2020). Based on these guidelines, the recommended aspirin starting dose is 150-300 mg, clopidogrel is 600 mg, and ticagrelor is 180 mg (Knuuti et al., 2019). It is partially distinct from our study results. Although there is no prospective evaluation of the minimum aspirin effective dose in percutaneous coronary intervention (PCI) in STEMI patients, the American Heart Association (AHA) and American College of Cardiology (ACC) recommend a 325 mg empiric dose as soon as possible before PCI, then continue to use the maintenance dose indefinitely (Lawton et al., 2021). In addition, doctors prefer using a 600 mg clopidogrel starting dose to a 300 mg dose due to more rapid and potent platelet inhibition at high doses and the beneficial effects reported in the Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events-Seventh Organization to Assess Strategies in Ischemic Syndromes (CURRENT-OASIS 7) analysis (Mehta et al., 2010). The Antiplatelet Therapy for Reduction of Myocardial Damage during Angioplasty-Myocardial Infarction (ARMYDA-6 MI) study also reported beneficial outcomes with higher clopidogrel starting doses (Patti et al., 2011).

Ticagrelor is a reversible P2Y12 receptor blocker with a relatively short plasma half-life (about 12 hours) and oral administration. Compared with clopidogrel, ticagrelor has a faster onset of action and is preferable because of its reversible binding and premature platelet function recovery. With a 180 mg starting dose, patients will use a 90 mg maintenance dose twice a day. In patients with NSTEMI, ticagrelor reduced composite mortality endpoints, including vascular causes, myocardial infarction, and stroke (decreased from 11.7% to 9.8%; hazard ratio, 0.84; P<0.001). Furthermore, the Platelet Inhibition and Patient Outcomes (PLATO)

study compares ticagrelor (initiating dose 180 mg, then 90 mg twice daily) with clopidogrel (initiating dose 300 mg or 600 mg, then 75 mg daily) for cardiovascular event prevention in 18,624 acute coronary syndrome patients (35% of them had an acute myocardial infarction). Its results demonstrate that in either NSTEMI or STEMI patients, treatment with ticagrelor significantly reduces vascular mortality, myocardial infarction, or stroke without increasing bleeding rates overall but increases nonprocedural bleeding rates versus clopidogrel (Wallentin et al., 2009).

Table 3. Used antiplatelet drugs' starting dose proportion in acute myocardial infarction treatment

Antiplatelet drugs	Starting dose	STEMI	NSTEMI	Medical records
		n (%)	n (%)	n (%)
Aspirin	81mg	31 (8.2%)	71 (18.7%)	102 (26.9%)
	162 mg	18 (4.7%)	72 (18.9%)	90 (23.6%)
	243 mg	20 (5.3%)	22 (5.8%)	42 (11.1%)
	324 mg	66 (17.4%)	80 (21.0%)	146 (38.4%)
Clopidogrel	75 mg	16 (4.9%)	43 (13.1%)	59 (18.0%)
	150 mg	8 (2.4%)	9 (2.8%)	17 (5.2%)
	225 mg	7 (2.2%)	4 (1.2%)	11 (3.4%)
	300 mg	66 (20.2%)	165 (50.4%)	231 (70.6%)
	600 mg	6 (1.9%)	3 (0.9%)	9 (2.8%)
Ticagrelor	90 mg	9 (5.6%)	20 (12.3%)	29 (17.9%)
	180 mg	76 (46.9%)	57 (35.2%)	133 (82.1%)

*STEMI: ST-segment elevation myocardial infarction; NSTEMI: Non-ST-segment elevation myocardial infarction.

3.3. Drug-drug interactions in acute myocardial infarction treatment

Based on the drugs.com database, we estimate 820 drug-drug interactions in all 380 medical records. Clinically significant interaction levels include major (14.6%), minor (39.2%), and moderate extent, accounting for the highest rate (46.2%). In addition, when we check drug-drug interactions in the Medscape database, among 646 drug-drug interactions, there are minor (3.0%), serious (42.4%), and monitor-closely-affected, accounting for the most elevated proportion (54.6%). After combining information from two databases to evaluate clinically meaningful interactions, 977 drug-drug interactions appeared totally in the study population, including serious interactions (28.1%) and moderate or closely monitored interactions (38.8%) (Table 4).

Table 4. Clinically significant drug interaction levels are estimated in acute myocardial infarction patients' medical records

	Drugs interaction level	Frequency n (%)
Drugs.com	Major	120 (14.6%)
	Moderate	379 (46.2%)
	Minor	321 (39.2%)
	Total	820 (100%)
Medscape	Contraindication	0 (0.0%)
	Serious	274 (42.4%)
	Monitor closely	353 (54.6%)
	Minor	19 (3.0%)
	Total	646 (100%)
Drugs.com and Medscape combination	Serious	274 (28.1%)
	Moderate (Monitor closely)	379 (38.8%)
	Minor	324 (33.1%)
	Total	977 (100%)

According to the drugs.com database, clinically significant drug-drug interactions encompass clopidogrel-esomeprazole (31.3%) and ticagrelor-clarithromycin (0.3%).On the other hand, following the Medscape database, these interactions include aspirin-enalapril (37.4%), clopidogrel-esomeprazole (31.3%), aspirin-captopril (20%), ticagrelor-ivabradine (6.1%), and clopidogrel-clarithromycin (0.3%) (Table 5). Clopidogrel-esomeprazole is an interaction pair found in both databases to a clinically significant extent. In essence, clopidogrel-esomeprazole is an interaction pair found in both databases to a clinically meaningful extent. Clopidogrel is a prodrug, so when entering the plasma, it needs to undergo metabolism by the enzyme CYP2C19 to the active pharmacological sulfhydryl form. Consequently, it may have various potential adverse drug interactions when co-administered with CYP2C19 inhibitor drugs, for instance, proton pump inhibitors (PPI) (Ritter et al., 2018). Because clopidogrel is a prodrug, the clinical consequences of the interacting pair may be most pronounced. Using clopidogrel in dual antiplatelet therapy carries a gastrointestinal bleeding risk, so PPI indications (omeprazole, esomeprazole, dexlansoprazole, and pantoprazole) aim to reduce that risk. Nevertheless, as mentioned, PPIs will inhibit the clopidogrel metabolic enzyme; each PPI drug hinders CYP2C19 to another extent, so it may reduce the cardioprotective effect, raise cardiovascular events, and increase MI and stroke (Serbin et al., 2016; Rouby et al., 2018). If PPIs are extremely necessary for treatment, recommended drugs include dexlansoprazole, lansoprazole, and pantoprazole. In clinical practice, the pantoprazole/dexlansoprazole and clopidogrel combination has increased significantly, gradually replacing omeprazole/esomeprazole (Frelinger et al., 2012; Guérin et al., 2016). Alternatively, rabeprazole-clopidogrel co-administration may not affect the effectiveness of clopidogrel antiplatelet therapy (Wu et al., 2013). Besides that, we can also convert PPIs to H_2 receptor antagonists or antacids during treatment (Farhat et al., 2019).

Following the study outcomes, although the ticagrelor-clarithromycin interaction pair accounts for a low proportion, it is essential to be concerned about. Ticagrelor is a weak CYP3A4 inhibitor, while clarithromycin is a potent inhibitor. Since isoenzymes are primarily responsible for ticagrelor's metabolism, concurrent administration may increase plasma concentrations of the drug (Siller-Matula et al., 2014). Thence, clarithromycin is contraindicated with ticagrelor, as it can significantly elevate drug exposure and expose patients to toxic effects such as bleeding (Dunn et al., 2012). In cases where macrolide antibiotics are compulsory, azithromycin is an appropriate choice.

Table 5. Drug-drug interactions proportion found in acute myocardial infarction patients' medical records

	Seriousdrugs interactions	**Medical records (N=380) n (%)**
Drugs.com	Clopidogrel – Esomeprazole	119 (31.3%)
	Ticagrelor - Clarithromycin	1 (0.3%)
Medscape	Aspirin - Enalapril	142 (37.4%)
	Aspirin - Captopril	76 (20.0%)
	Clopidogrel – Esomeprazole	119 (31.3%)
	Clopidogrel - Clarithromycin	1 (0.3%)
	Ticagrelor – Ivabradine	23 (6.1%)
Drugs.com and Medscape combination	Aspirin - Enalapril	142 (37.4%)
	Aspirin - Captopril	76 (20.0%)
	Clopidogrel – Esomeprazole	119 (31.3%)
	Clopidogrel - Clarithromycin	1 (0.3%)
	Ticagrelor – Ivabradine	23 (6.1%)
	Ticagrelor - Clarithromycin	1 (0.3%)

Next, regarding interactions estimated by Medscape databases, other notable pairs are aspirin-enalapril, aspirin-captopril, and ticagrelor-ivabradine. Aspirin will hinder the production of prostaglandins, reducing the angiotensin-converting enzyme inhibitor (ACEI) therapeutic effect in hypertension treatment (Subramanian et al., 2018). Besides, the ticagrelor-ivabradine interaction pair accounts for 6.1%, which also needs attention because ivabradine is also a CYP3A4 inhibitor, so these drugs' co-administration may increase the risk of excessive bradycardia and conduction disorders (Di Serafino et al., 2014).

In general, in the study population, six drug-drug interaction pairs were identified: aspirin-enalapril (37.4%), clopidogrel-esomeprazole (31.3%), aspirin-captopril (20%), ticagrelor-ivabradine (6.1%), clopidogrel-clarithromycin (0.3%), and ticagrelor-clarithromycin (0.3%) (Table 5). Each database has a system for classifying drug interactions, ranging from mild with no intervention necessary to severe requiring intervention or discontinuation. Not all drug interactions are clinically significant among the thousands of theoretically documented drug interactions. According to the European Medicines Agency (2012) guidelines, a drug interaction is clinically significant if it meets the following conditions: altering results in therapeutic efficacy or/and drug toxicity to an extent requiring a correction dose or other medical intervention. However, some interactions appear in this database but not in others, so the drugs.com and Medscape databases combined aim to have a general view and limit errors. After combining the two interaction lookup software, in our study, moderate drug interactions (close monitoring) appeared the most. Aspirin-enalapril interactions appeared with the highest frequency, followed by clopidogrel-esomeprazole interactions. Clarithromycin-ticagrelor and clarithromycin-clopidogrel are just determined one time.

4. Conclusions

In summary, in acute myocardial infarction treatment, the commonly used antiplatelet agents are aspirin, clopidogrel, and ticagrelor. Aspirin is considered a first-line drug in all cases. Alternatively, in DAPT, the aspirin-clopidogrel combination is preferable to aspirin-ticagrelor. Clinically significant drug interactions are serious to a moderate (close monitoring) extent, and two drug-drug interactions, including aspirin-enalapril and clopidogrel-esomeprazole, frequently occur.

Conflicts of interest. The authors mentioned that none of them have a conflict of interest when it comes to this article.

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