The Side Effects of TICAGRELOR among Saudi Patients and comparison with conventional anti-platelet drug clopidogrel at Aseer Central Hospital, Southwest of Saudi Arabia

Dr Javed Iqbal Wani (1)
Dr Zia Ul Sabah (1),(2),(3)
Dr Mir Nadeem (1)
Mona Ali Hassan Alshehri (1)
Ahlam Muslih Al Ghamdi (1)
Nojoud Mohammed Alfarhan (1)
Haneen Ahmad Assiri (1)
Dr Adel Masswary (3)

(1) College of Medicine, King Khalid University Abha, Saudi Arabia.
(2) Aseer Central Hospital Abha
(3) Prince Faisal Bin Khalid Cardiac Center Abha

Corresponding author:
Mona Ali Hassan Alshehri
College of Medicine, King Khalid University Abha,
Saudi Arabia
Tel: +966547924161
Email: mona-ali.11@outlook.sa

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Abstract

Background: P2Y12 platelet receptor inhibitors (i.e., clopidogrel, prasugrel and ticagrelor) Ticagrelor are an oral, reversible, direct-acting inhibitor of the adenosine diphosphate receptor P2Y12 that has a more rapid onset and more pronounced platelet inhibition than clopidogrel. The P2Y12 platelet receptor inhibitors are the cornerstone of treatment of ACS patients. The common adverse effects include upper gastrointestinal (GI) bleeding, ecchymosis, haematuria, epistaxis, and possibility of ticagrelor-induced Thrombotic thrombocytopenia purpura (TTP).

Aim: This study was conducted to determine the incidence of dyspnoea and/or bleeding as side effects of ticagrelor and compare it with commonly used P2Y12 platelet receptor inhibitors, clopidogrel.

Methods: A record based retrospective cohort study was conducted including all patients using ticagrelor or clopidogrel for clinical indications attending The Cardiology Outpatient Clinics at Aseer Central Hospital. Patients were classified into cohorts based on type of drug received. Patients' files were prospectively reviewed to extract data. Data were extracted using pre-structured data extraction format to avoid errors, missing and inter rater bias.

Results: The study included 200 patients; 100 (50%) received PLAVIX (clopidogrel) medication (group 1) and 100 (50%) received BRILINTA (ticagrelor) medication (group 2). Exactly 38% of group 1 cases aged 60 years or more were compared to 39% of group 2 patients with no statistical significance. As for gender, 58 (58%) of group 1 cases were males in comparison to 89 (89%) of group 2 cases (P=.001). Also, 18% of group 1 cases were smokers compared to 32.1% of group 2 cases (P=.026). Hypertension was reported among 46% of group 1 cases compared to 56% of group 2 patients (P=.179). Also, hypercholesterolemia was detected among 29% of group 1 cases compared to 41.7% of group 2 (P=.072). Considering DM, it was diagnosed among 50% of group 1 patients in comparison to 51% of group 2 patients (P=.872). History of bleeding was reported among 9 cases of group 1 compared to 5 cases in group 2 (P=.437).

Conclusion: A significant number of patients who were started on ticagrelor develop dyspnoea but not compromising the therapeutic superiority of the drug as compared to clopidogrel and can be replaced as first line drug in the Saudi population. Other side effect profiles of ticagrelor are comparable to conventional anti platelet drugs with no significant statistical variability.

Key words: TICAGRELOR, P2Y12 platelet receptor inhibitors, side effects, adverse events, MI, ACS

Background

Anti-platelet therapy is a cornerstone component of treatment of acute coronary syndrome (ACS). It has been well acknowledged that development of ACS has a strong link to platelet aggregation, hence standard treatment has been established with the use of dual anti-platelet therapy (DAPT) with P2Y12 receptor inhibitor and aspirin for ACS patients regardless of previous treatments such as medical management or percutaneous coronary intervention (PCI) [1,2]. The management strategies of ACS have evolved over recent decades with the development of more potent anti-platelet agents. Trials on ACS have shown the newer anti-platelets can more effectively reduce cardiovascular events. However, a narrow window between safety and efficacy, beyond which the risk of bleeding and other adverse effects can outweigh the benefits of anti-platelet therapy remains the major challenge and striking a balance between them remains a concern for clinicians. The common adverse effects of anti-platelet therapy include upper gastrointestinal bleeding, ecchymosis, haematuria, epistaxis and dyspnea. Aspirin and clopidogrel have been the mainstay of treatment for ACS for many years, however, a substantial number of ACS patients continue to experience recurrent ischemic events during DAPT with aspirin and clopidogrel. It has been reported that the platelet inhibitory effect of clopidogrel is diminished in patients who carry a genetic variant, loss-of-function CYP2C19 allele, due to significantly lower levels of the active metabolite of clopidogrel [3], leading to developing more potent anti-platelet agents for ACS. Currently, a new generation P2Y12 inhibitors including ticagrelor and prasugrel have replaced clopidogrel as first-line anti-platelet agents for ACS treatment, but the risks of bleeding and other adverse effects have been reported with more potent anti-platelet agents, especially in elderly patients [4]. And these adverse effects need a detailed clinical review and research to make sure the benefit and adverse effect balance is equalized for a better outcome. The common adverse effects include upper gastrointestinal (GI) bleeding, ecchymosis, haematuria, epistaxis and dyspnea. Among the newer anti platelets ticagrelor is a direct-acting oral antagonist of P2Y12-adenosine diphosphate (ADP) receptor blocker, does not have catabolite activation pathway and has reversibility as compared to clopidogrel making its action faster and with greater platelet inhibition than clopidogrel [5,6]. Ticagrelor proved to have more beneficial outcomes in reversible long-term P2Y12 inhibition than clopidogrel in the total death, cardiovascular prevention, stent thrombosis as well as myocardial infarction without increasing the major bleeding rates in a wide ACS patient population, according to the Phase III PLATO (Platelet Inhibition and Patient Outcomes) trial [7]. Based on these outcomes several trials and cardiological associations suggest that ticagrelor could be a valid replacement and associated with superior effects over clopidogrel for P2Y12 inhibition in ACS patients [8,9]. Earlier studies have been published for the assessment of safety and efficacy of ticagrelor versus clopidogrel in ACS patients Nevertheless, given the differences of genetic backgrounds, comorbidities, disease patterns, and demographics, patients tend to show various prognostic results with uncertain bleed-ing risk [10,11]. Keeping these things in mind and along with previous scarce data on safety profile of these anti platelet drugs in the Saudi population a lot of inpatient based and population based studies need to be done especially after a few studies show a high rate of clopidogrel in-vitro nonresponse among the Saudi population undergoing coronary angiography as shown by a population based study showing two-thirds of our patients undergoing coronary angiography were clopidogrel non-responders [12].

Aims and Objectives

1- Determine the incidence of major side effects bleeding and dyspnea of ticagrelor and compare it with commonly used P2Y12 platelet receptor inhibitors, clopidogrel.
2- To compare our findings with the internationally published data.
3- To assess knowledge towards the side effects of ticagrelor among Saudi patient users of ticagrelor in Abha city, Saudi Arabia.

Methodology

A record based retrospective cohort study was conducted including all patients using ticagrelor or clopidogrel for clinical indications attending the Cardiology Outpatient Clinics at Aseer Central Hospital, southwest of Saudi Arabia during the period from Dec 2019 to June 2020. Patients were classified into cohorts based on type of drug received with initial collection of personal data, clinical data, and drug use indications. Then, files for each cohort were explored retrospectively to assess reported side effects and laboratory findings. Data were extracted using pre-structured data extraction format to avoid errors, missing, and interrater bias. An oral consent from all participants was taken before being included in the study either directly or using mobile phone calls after confirming their data confidentiality.

INCLUSION CRITERIA:
Patients using ticagrelor or clopidogrel for clinical indications attending the Cardiology inpatient and Outpatient departments.

EXCLUSION CRITERIA:
Patients with history of recent surgery (major) and trauma (major), LVEF <45%, Significant valve lesions, Chronic lung diseases, Chronic liver disease, Chronic kidney disease (creatinine >2.0mg/dl) were excluded from the study.

Data analysis
After data were extracted, it was revised, coded, and fed to statistical software IBM SPSS version 22 (SPSS, Inc. Chicago, IL). All statistical analysis was done using two tailed tests. P value less than 0.05 was statistically significant. Comparative analysis between study cohorts was done for all variables including patient's

bio-demographic data, drug indications, and complications and was used based on cross tabulation. Significance of relations in cross tabulation was tested using Pearson chi-square test for categorical parameters while scale variables (laboratory investigations and ECHO) were compared using independent samples t-test. To control for smoking as confounder for relation between type of drug and developing shortness of breath, stratified analysis was done with estimating magnitude of relation with each stratum (smokers and non-smokers) based on Odds ratio with 95% confidence interval.

Results

The study included 200 patients; 100 (50%) received PLAVIX (clopidogrel) medication (group 1) and 100 (50%) received BRILINTA (ticagrelor) medication (group 2). Exactly 38% of group 1 cases aged 60 years or more were compared to 39% of group 2 patients with no statistical significance. As for gender, 58 (58%) of group 1 cases were males in comparison to 89 (89%) of group 2 cases (P=.001). Also, 18% of group 1 cases were smokers compared to 32.1% of group 2 cases (P=.026). Hypertension was reported among 46% of group 1 cases compared to 56% of group 2 patients (P=.179). Also, hypercholesteremia was detected among 29% of group 1 cases compared to 41.7% of group 2 (P=.072). Considering DM, it was diagnosed among 50% of group 1 patients in comparison to 51% of group 2 patients (P=.872). History of bleeding was reported among 9 cases of group 1 compared to 5 cases in group 2 (P=.437). Considering indications of drug use, the most reported among group 1 patients who received PLAVIX were MI (51%), ACS (22%), and unstable angina (11%). The most reported indications among group 2 patients who received BRILINTA were MI (53.6%) followed by ACS (17.9%), and HF (8.3%) (Table 1).

Table 2 illustrates drug use associated complications among study groups. Exactly 5 patients (5%) of group 1 had bleeding in comparison to 3 cases (3%) of group 2 patients with no recorded statistical significance (P=.355). The most reported source of bleeding among group 1 cases were epistaxis (3 cases), hemoptysis (1 case), and wound (1 case). The most reported among group 2 patients were epistaxis (1 case) and punctured wound (1 case). Shortness in breath was reported among 10 patients in group 1 (10%) compared to 22 (22%) of group 2 patients with recorded statiscal significance (P=0.032). Orthopnea was diagnosed among 9 cases of group 1 compared to 6 cases in group 2 (P=.674) while 7 cases in group 1 had PND compared to 6 cases in group 2 (P=.447).

Table 3 demonstrates association of shortness of breath by study groups according to smoking status. Among smokers, BRILINTA drug intake was significantly associated with 4 fold more likelihood for developing shortness of breath compared to PLAVIX drug (OR=4.1; 95% CI: 1.1-30.6; P=.046). Among non-smokers, the likelihood was decreased to twice fold with no statistical significance (OR=2.1; 95% CI: 0.53-26.7; P=.219).

Table 4 shows laboratory findings among study groups. LDL was insignificantly higher among group 2 patients compared to group 1 (126.2 vs. 114.8, respectively; P=.425). HDL was insignificantly higher among group 1 patients compared to group 2 (41.7 vs. 38.1, respectively; P=.307). Magnesium level was nearly the same among the two groups (mean value of 2 for both). Random blood sugar (RBS) was insignificantly higher among group 1 than group 2 (190.3 and 144.3, respectively; P=.116).

Discussion

Our study was performed with a purpose of data collection and population based formulation of anti-platelet drug therapy in acute coronary syndrome and confirming the drug profile of ticagrelor along with the adverse effects of the drug on the Saudi population as was needed because of documentation of higher clopidogrel non responders in the Saudi population Haitham I. Sakr et al [12]. Since the PLATO trial [7] has clearly shown treatment with ticagrelor as compared to clopidogrel in patients of acute coronary syndrome significantly reduced the rate of death from vascular causes, MI, and these therapeutic effects were achieved without increase in the rate of major bleeding as was demonstrated in our study we documented the incidence of bleeding in our study group was around 3% of patients who had bleeding diathesis as compared to 5% in clopidogrel, with no statistically significance most reported source of bleeding being epistaxis in both groups , our results were in accordance with the PLATO trial as well as seen by Husted S, et al [7]. In our study we also concentrated on the much discussed adverse effect of Ticagrelor associated dyspnoea which was seen in 22% of patients taking ticagrelor as compared to clopidogrel where only 10% the findings were statistically significant and usually patients developed dyspnea in the first week of starting the drug our findings coincided with findings by Cannon CP et al [13]. While drug substitution and discontinuation of ticagrelor because of drug associated dyspnea was seen in 1% of patients, as the adverse effect is pronounced further therapeutic monitoring and relation of dyspnoea with the drug plasma concentration needs to be done in the Saudi population. Ruling out other causes of dyspnoea in these patients vis a vis heart failure, respiratory causes and other systemic disease was done and we went a step further and close review demonstrated the incidence of dyspnoea increased four fold in smokers taking ticagrelor as compared to smokers taking clopidogrel with an odds ratio of 4.1 and statistically significant p value as also seen by Parodi G et al [14]. Our study had a par-allel relation with the PLATO trial hence giving a complementary data to further validate the trial especially in the Saudi Arabian population regarding the adverse effect comparison arm of the original trials. Further studies are still needed at tertiary care level to find the risk factors associated with a slightly higher percentage of dyspnoea in the Saudi population on ticagrelor.

Table 1. Bio-demographic data of study groups

Bio-demographic data		Group				P-value
		PLAVIX		BRILINTA		
		No	%	No	%	
Age in years	< 50 Yrs.	23	23.0%	22	22%	.984
	50-60	39	39.0%	38	38%	
	> 60 Yrs.	38	38.0%	39	39%	
Gender	Male	58	58.0%	89	89%	.001*
	Female	42	42.0%	11	11%	
Smoking	Yes	18	18.0%	32	32%	.026*
	No	82	82.0%	68	68%	
Hypertension	Yes	46	46.0%	56	56.0%	.179
	No	54	54.0%	44	44.0%	
Hypercholesterolemia	Yes	29	29.0%	42	42%	.072
	No	71	71.0%	58	58%	
DM	Yes	50	50.0%	51	51%	.872
	No	50	50.0%	49	49%	
History of chronic lung disease	Yes	0	0.0%	2	2%	.121
	No	100	100.0%	97	97%	
History of bleeding	Yes	9	9.0%	6	6.0%	.437
	No	91	91.0%	94	94.0%	
Indications of use	ACS	22	22.0%	18	18%	.061#
	HF	5	5.0%	8	8%	
	IHD	2	2.0%	7	7.%	
	MI	51	51.0%	54	54%	
	No	3	3.0%	2	2%	
	NSTEMI	0	0.0%	4	4%	
	S/P PCI TO LAD	3	3.0%	0	0.0%	
	STABLE ANGINA	2	2.0%	0	0.0%	
	STEMI	1	1.0%	2	2%	
	UNSTABLE ANGINA	11	11.0%	3	3%	

P: Pearson X^2 test; #: P: Exact probability test; * P < 0.05 (significant)

Table 2: Drug use associated complications among study groups

Associated Complications	Group				P-value
	PLAVIX		BRILINTA		
	No	%	No	%	
Suffered bleeding	5	5.0%	3	3%	.355
Source of bleeding					
HEMOPTYSIS	1	20.0%	0	0.0%	
EPIXTAXIS	3	60.0%	1	50.0%	.344
PUNCTURED WOUND	0	0.0%	1	50.0%	
WOUND	1	20.0%	0	0.0%	
Shortness in breath	10	10%	22	22%	.032*
Orthopnea	9	9.0%	7	7%	.674
PND	7	7.0%	6	6.0%	.447
ECHO (Mean ± SD)	43.6 ± 12.0		47.1 ± 12.6		.066 $

P: Exact probability test; $: independent t-test; * P < 0.05 (significant)

Table 3. Association of shortness of breath by study groups according to smoking statu

Group	Shortness in breath				OR (95% CI)
	Yes		No		
	No	%	No	%	
PLAVIX	1	1.0%	18	100.0 %	ref
BRILINTA	7	18.5%	22	81.5%	4.1 (1.1-30.6) *
PLAVIX	9	12.2%	72	87.8%	ref
BRILINTA	13	22.8%	44	77.2%	2.1 (0.53-26.7)

OR: Odds ratio CI: Confidence interval * P < 0.05 (significant)

Table 4. Laboratory findings among study groups

Group	Shortness in breath				OR (95% CI)
	Yes		No		
	No	%	No	%	
PLAVIX	1	1.0%	18	100.0 %	ref
BRILINTA	7	18.5%	22	81.5%	4.1 (1.1-30.6) *
PLAVIX	9	12.2%	72	87.8%	ref
BRILINTA	13	22.8%	44	77.2%	2.1 (0.53-26.7)

P: independent t-test

Conclusion

At the end of this retrospective registry-based study we came to a conclusion that

1. A significant number of patients who are started on ticagrelor develop Dyspnoea but not com-promising the therapeutic superiority of the drug as compared to clopidogrel and can be replaced as first line drug in the Saudi population
2. Our study gives a complimentary validation of the PLATO trial regarding adverse effects of the drug in comparison with clopidrogel in the Saudi population
3. Further studies need to be commenced in various tertiary care settings in the Kingdom of Saudi Arabia to formulate the risk factors in development of adverse effects of Ticagrelor in patients.
4. Other side effect profiles of ticagrelor are comparable to conventional anti platelet drugs with no significant statistical variability.

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