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Frequency of dyspnea related to intake of ticagrelor or clopidogrel in patients with chronic coronary syndrome undergoing coronary intervention

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In patients with chronic coronary syndrome, ticagrelor decreases cardiovascular events more efficiently than clopidogrel. In several studies investigating novel $P2Y_{12}$ inhibitors dyspnea has been detected. A rise of adenosine blood levels is supposed to be one of cases of dyspnea induced by ticagrelor. Dyspnea is a prevalent and complex symptom. It is associated with deterioration of the quality of life and hospital readmission.

Aim. To determine the frequency of dyspnea related with ticagrelor or clopidogrel intake in patients with stable coronary artery disease undergoing coronary intervention. Also, to determine which patients could continue ticagrelor intake and which patients couldn't, and show the causes of ticagrelor discontinuation.

Material and methods. Between October 2023 and January 2024, an observational prospective comparative case-control study was conducted at Baghdad Heart Center in Baghdad Teaching Hospital in Medical City. In this study, individuals with stable coronary artery disease who just had therapeutic catheterization and dual antiplatelet therapy were included. The patients from group 1 received aspirin and ticagrelor, while those from group 2 received aspirin and clopidogrel.

Results. A total of 120 patients were included. With the ticagrelor intake, the severity of dyspnea was classified as mild 64.2% (77 [120]) and moderate 19.1% (23 [120]). About 16.7% (20 [120]) had no dyspnea at all. The difference between patients who continued ticagrelor intake (16%) and those who stopped using it (84%) was significant. With clopidogrel intake no dyspnea was recorded.

Conclusions. According to our findings, the risk or occurrence of dyspnea is only evident in patients who received ticagrelor. When compared to irreversible $P2Y_{12}$ inhibitors like clopidogrel, the reversible $P2Y_{12}$ antagonist ticagrelor has a higher incidence of dyspnea in increasing order.

Keywords: dyspnea, ticagrelor, clopidogrel, chronic coronary syndrome, coronary intervention.

Relationships and Activities: none.

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Частота одышки, связанной с приемом тикагрелора или клопидогрела, у пациентов с хроническим коронарным синдромом, перенесших коронарное вмешательство

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У пациентов с хроническим коронарным синдромом тикагрелор снижает частоту сердечно-сосудистых событий более эффективно, чем клопидогрел. Ряд исследований продемонстрировал появление одышки у пациентов, получающих новые блокаторы $P2Y_{12}$-рецепторов. Предполагается, что при приеме тикагрелора это связано с повышением уровня аденозина в крови. Важно отметить, что одышка является распространенным и многогранным симптомом, ухудшающим качество жизни пациента и повышающим риск повторных госпитализаций.

Цель. Определить частоту развития одышки, связанной с приемом тикагрелора или клопидогреля, у пациентов со стабильной ишемической болезнью сердца (ИБС), перенесших коронарное вмешательство. Также определить когорты пациентов, которым необходимо продолжать или прекращать прием тикагрелора, и показать причины отмены тикагрелора.

Материал и методы. В период с октября 2023г по январь 2024г в Багдадском кардиологическом центре было проведено наблюдательное проспективное сравнительное исследование "случай-

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контроль". В него были включены лица со стабильной ИБС, которым была проведена коронарная ангиопластика с последующим назначением двойной антиагрегантной терапии. Больные 1-й группы получали аспирин и тикагрелор, 2-й группы — аспирин и клопидогрел.

Результаты. Всего было включено 120 пациентов. При приеме тикагрелора в 64,2% (77 [120]) и 19,1% (23 [120]) выявлялась легкая и умеренная одышка, соответсвтенно. Около 16,7% (20 [120]) не имели одышки. Разница между пациентами, продолжавшими прием тикагрелора (16%), и теми, кто прекратил его прием (84%), была значительной. При приеме клопидогрела появление одышки не была зафиксировано.

Заключение. По нашим данным, возникновение одышки доказано только у пациентов, получавших тикагрелор. По сравнению с необратимыми ингибиторами $P2Y_{12}$, такими как клопидогрел, обратимый антагонист $P2Y_{12}$ тикагрелор имеет более высокую частоту возникновения одышки.

Ключевые слова: одышка, тикагрелор, клопидогрел, хронический коронарный синдром, коронарное вмешательство.

Отношения и деятельность: нет.

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ACC — American College of Cardiology, ACS — acute coronary syndrome, AHA — American Heart Association, CAD — coronary artery disease, MI — myocardial infarction, $P2Y_{12}$ — chemoreceptor for adenosine diphosphate (antiplatlate inhibitor), PCI — percutaneous coronary intervention, SCAI — Society for Cardiovascular Angiography & Interventions.

Key messages

What is already known about the subject?

- Ischemic heart disease is associated with an inadequate blood supply to the myocardium due to closure of the arteries by atherosclerotic plaques.
- The mechanism of adenosine diphosphate $P2Y_{12}$ receptor antagonists by their receptor binding activity that activates the G-protein inhibitor secondary messenger system, mediates the completion and amplification of the aggregatory responses.

What might this study add?

- Dyspnea is evident in patients who received ticagrelor.
- Clopidogrel (irreversible $P2Y_{12}$ inhibitor) is superior to the ticagrelor (reversible $P2Y_{12}$ antagonist).
- In Iraqi patients, the cost is the major issue that led to ticagrelor discontinuation.

Ключевые моменты

Что известно о предмете исследования?

- В основе ишемической болезни сердца лежит недостаточное кровоснабжение миокарда вследствие атеросклеротического поражения артерий.
- Механизм действия антагонистов $P2Y_{12}$ рецепторов связан с активацией системы ингибирования G-белка вторичными мессенджерами.

Что добавляют результаты исследования?

- Одышка наблюдается у пациентов, получающих тикагрелор.
- Клопидогрел (необратимый ингибитор $P2Y_{12}$) превосходит тикагрелор (обратимый антагонист $P2Y_{12}$).
- У иракских пациентов финансовая составляющая является основной проблемой, которая приводит к отмене приема тикагрелора.

Introduction

Ischemic heart disease, also referred to as coronary heart disease (CAD), is the term associated with an inadequate supply of blood to the myocardium due to obstruction of the coronary arteries, usually due to atherosclerosis. Patients may have chronic (stable) or acute (unstable) disease. Most of the patients with chronic coronary syndrome, also referred to a stable ischemic heart disease, based on a classic history of angina pectoris and the presence of either risk factors or already known atherosclerotic cardiovascular disease [1]. The prevalence of stable CAD increases with age in both sexes. Women aged 45-64 years have a prevalence of 5-7%, whilst men in the same age range have a prevalence of 4-7%. This increases to a prevalence of 10-12% in women aged 65-84 years and 12-14% in similarly aged men [2].

An adequate supply of oxygen to the myocardium requires a satisfactory level of oxygen-carrying capacity of the blood (determined by the inspired level of oxygen, pulmonary function, and haemoglobin concentration and function) and an adequate level of coronary blood flow. By reducing the lumen of the coronary arteries, atherosclerotic plaques limit appropriate increases in perfusion when the demand for flow is augmented, as occurs during exertion or excitement. When the

luminal reduction is severe, myocardial perfusion in the basal state is reduced. Coronary blood flow also can be limited by spasm, blood clots, and, rarely, coronary embolism as well as by ostial thinning due to aortitis. Myocardial ischemia also can occur if myocardial oxygen demands are markedly increased and particularly when coronary blood flow may be limited, as occurs in severe left ventricular hypertrophy due to aortic stenosis[1].

Evaluation for CAD usually begins with a functional study such as stress testing with electrocardiography, imaging or pharmacologic stress testing with imaging. The choice of test may be influenced by the patient's resting electrocardiogram, the patient's physical ability to perform exercise, local clinician expertise, and available technologies [3]. In patients with chronic coronary syndrome, there are two primary indications to identify patients likely to benefit from coronary angiography followed by revascularization. First, angina significantly interferes with a patient's lifestyle despite maximal tolerable medical therapy. Second, patients with clinical characteristics and results of noninvasive testing that indicate a high likelihood of severe CAD (eg, imaging or strongly positive treadmill test suggesting a large amount of viable myocardium at risk) [4, 5].

Revascularization is performed in appropriate patients in whom angiography reveals anatomy for which revascularization has a proven benefit or in whom medical therapy has failed. Patients with anatomy for which revascularization has a proven survival benefit such as significant left main CAD (>50% luminal narrowing) or multivessel CAD with a reduction of left ventricular ejection fraction and a large area of potentially ischemic myocardium [4, 5].

Patients with chronic stable CAD who were treated with therapeutic catheterization (percutaneous coronary intervention (PCI) with bare metal stent) should receive dual antiplatelet therapy (aspirin and $P2Y_{12}$ receptor antagonists) for 3 months and after that should remain on one of them indefinitely [6]. Adenosine diphosphate $P2Y_{12}$ receptor antagonists are used by their activity of binding of the $P2Y_{12}$ receptor by its agonist, adenosine diphosphate, activate the G-protein inhibitor secondary messenger system through a complex series of events, mediate the completion and amplification of the aggregatory response [7]. According to the 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization, the Initial oral dose of clopidogrel is 600 mg once, administered ⩾2 hours before PCI, ideally ⩾24 hours before PCI; followed by 75 mg once daily [8]. The main indications of ticagrelor are acute coronary syndrome (ACS) (to reduce the risk of cardiovascular death, myocardial infarction (MI), and stroke in patients with the ACS or a history of MI). It also reduces the risk of stent thrombosis in patients who have been stented for treatment of ACS [9, 10].

This study aimed to determine the dyspnea frequency with ticagrelor or clopidogrel in patients with stable CAD undergoing coronary intervention and to determine in which cases patients could continue ticagrelor intake and in which couldn't.

Material and methods

Study design. An observational comparative case control study is accomplished at Baghdad Heart Center in Baghdad Teaching Hospital in Medical City/Baghdad between October 2023 and January 2024.

Patients. In this study, we observed the patients with stable CAD undergoing therapeutic catheterization and receiving dual antiplatelet (Group I: (120 patients received aspirin and ticagrelor) and Group II (120 cases received aspirin and clopidogrel)). Aspirin 300 mg as loading dose followed by 100 mg daily as maintenance dose. Ticagrelor 180 mg as loading dose followed by then 90 mg twice daily as maintenance dose. Clopidogrel 600 mg as loading dose (8 tablets of 75 mg-each tablet) followed by 75 mg daily as maintenance dose.

Inclusion and exclusion criteria. Patients were eligible if they were ⩾18 years old and had clinical evidence of CAD and were expected to have catheterization.

Exclusion criteria by determining the patients with the ACS, with chronic obstructive pulmonary diseseas and asthma. Also, cardiac ejection fraction is less than 35% of patients, need for oral anticoagulation therapy, concomitant therapy with strong cytochrome-450 3A4 (inhibitor or inducer), were excluded.

Ethical consideration. Approved by the Ethical Committee at Iraqi Board for Medical Specializations, Baghdad/Iraq.

Statistical analysis. Quantitative data were expressed as the mean and standard deviation, whereas qualitative date described as frequency and percentage using the statistical software for social sciences (SPSS) version 24 (BMI, US-NY). The non-dependent t-test and chi-square was used. p-value ⩽0.05 was selected as the significant criterium.

Results

Patient characteristics are shown in table 1. No dyspnea was recorded in group-II while 100 (41.7%) cases from group-I suffered from dyspnea.

About 64.2% of patients showed mild intensity of dyspnea. However, 19.2% of cases presented with moderate dyspnea and no case presented with severe dyspnea with a high significant difference (p=0.002).

Distribution of cases according to ticagrelor continuation showed that 20 cases (16.7%) were continued therapy while 100 (83.3%) of patients stopped ticagrelor. Although, 74 (74%) of patients whom stopped therapy due to cost of the drug.

Discussion

For the first time in Iraq, the current study showed the degree of dyspnea with ticagrelor intake compared

[1] Jameson JL, Fauci AS, Kasper DL, et al. In: Jameson J, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J. (eds). Harrison's Principles of Internal Medicine, 20e. McGraw-Hill Education; 2018. Accessed April 18, 2024. https://accessmedicine.mhmedical.com/content.aspx?bookid=2129&sectionid=191734545.

Table 1

Patient's characteristics

Character		Group I (TICAGRELOR) n (%)/mean±SD	Group II (CLOPIDOGREL) n (%)/mean±SD	p
Age (years)		60.2±7.3	61.7±6.4	0.105
Gender	Male	74 (61.7)	71 (59.2)	0.79
	Female	46 (38.3)	49 (40.8)	
Weight (Kg)		80.6±6.4	79.2±5.7	0.094
Height (cm)		151.4±12.7	152.8±11.6	0.08
Hypertension	Yes	22 (18.3)	29 (24.2)	0.066
	No	98 (81.7)	91 (75.8)	
Diabetes	Yes	16 (13.3)	27 (22.5)	0.07
	No	104 (86.7)	93 (77.5)	
Smoker	Yes	16 (13.3)	27 (22.5)	0.059
	No	104 (86.7)	93 (77.5)	

Note: SD — standard deviation.

with clopidogrel in patients undergone PCI. In this comprehensive study, we found that individuals taking reversible $P2Y_{12}$ inhibitors ticagrelor have a higher risk of dyspnea than those on irreversible medicines like clopidogrel who are not complaining of dyspnea.

Dyspnea is a common side effect of ticagrelor and can lead to drug discontinuation in roughly 1 in every 20 treated patients. Studies have suggested that ticagrelor inhibits the sodium-independent equilibrate nucleoside transporter-1, which may increase adenosine plasma levels and explain drug-related dyspnea [11].

Dyspnea was graded as mild (awareness of sign or symptom but easily tolerated), moderate (discomfort sufficient to cause interference with normal activities), or severe (incapacitating, with an inability to perform normal activities).

In the current study minor part of the patients had no dyspnea at all, two-thirds of all patients who experience dyspnea had mild symptoms, and the remaining one third experienced moderate dyspnea. No severe dyspnea was recorded. All recorded dyspnea cases were transient and occurred in the first week of therapy and did not limit exercise capacity. Twenty patients continued ticagrelor intake, they could afford the cost of treatment with no significant dyspnea occurred, it considered small population in compared to patients who discontinued ticagrelor. Patients received clopidogrel (120 patients) did not complain of dyspnea and continue with their medication.

These results are comparable to that found in study in which dyspnea is commonly associated with ticagrelor therapy, often arising during the first week of treatment, and is usually mild or moderate in severity and often transient despite continued treatment [12].

Also, Zhang N, et al. [13] found a higher risk of dyspnea in patients treated with ticagrelor as compared with clopidogrel.

In our study most of the patients discontinued ticagrelor either because of cost of the treatment or dyspnea, minor part of patients omitted their ticagrelor intake due to dyspnea intolerability while the high cost was the major cause of discontinuation. There is relatively high cost of ticagrelor in comparison with available generic clopidogrel due to the lack the health insurance programs in Iraq. However, in developed countries ticagrelor discontinuation occur for different causes, but the most significant is dyspnea, mild or moderate, that was showed in PREDATOR (PREvalence of DyspneA in patients treated with TicagrelOR) study. Study assesses the prevalence and treatment of ticagrelor-induced dyspnea in CAD. A disclosure of such information could provide medical practitioners with more effective tools preventing from consequences of therapy discontinuation due to mild adverse events [14].

Patient counseling by the researcher was done frequently about efficacy of ticagrelor and expected degrees of dyspnea that may occur this also observed by Bonaca MP, et al. in which when the treatment was initiated in stable patients with prior myocardial infarction, the rate of treatment discontinuation was significantly higher for patients who received ticagrelor than for patients who received placebo, particularly early after initiation. This early discontinuation of treatment was primarily driven by non serious adverse events, including mild to moderate dyspnea, illustrating the practical importance of such events. Moreover, for patients receiving the drug, there was a substantial benefit to ticagrelor. Data underscore the need for patient counseling when initiating treatment with ticagrelor, to optimize shared decision making and, when appropriate, maximize adherence and improve clinical efficacy [15].

Majority of group 1 patients experienced dyspnea while no dyspnea cases were reported in group 2 which is comparable to results that showed Storey RF, et al. (2010). The percentage of dyspnea occurrence in ticagrelor were higher than that occurred with clopidogrel [16].

A proposed cause of dyspnea induced by ticagrelor is an increase in adenosine blood levels. Caffeine is an adenosine antagonist, it can potentially improves drug tolerability regarding dyspnea. Van Giezen JJJ, et al. admits that initially adenosine may cause dyspnea by acting on the A1 vagal C fibers. Ticagrelor inhibits the absorption of adenosine in cells more than in platelets, and equilibrative nucleoside transporter 1 inhibited cellular adenosine uptake without directly acting on adenosine receptors [17].

Conclusion

According to our findings, the occurrence of dyspnea is evident only in patients who received ticagrelor. When compared to irreversible $P2Y_{12}$ inhibitors like clopidogrel, the reversible $P2Y_{12}$ antagonist ticagrelor has a higher incidence of dyspnea. All dyspnea recorded cases were mild to moderate and did not affect the quality of life. In respect to Iraqi patients included in the study, the cost was the major issue that led to drug discontinuation.

Relationships and Activities: none.

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