

Ticagrelor, a molecular breakthrough to modulate cytokine network in the treatment of acute myocardial infarction “perspective and prospective”.

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Abstract

Current knowledge on the pharmacotherapy of acute myocardial infarction (AMI) has been limited with various cellular factors. The present research perspectives are mainly focusing on the efficacy of different antiplatelet therapy to treat the AMI. Ticagrelor has been proved as a better therapeutic choice for treating AMI when compared to clopidogrel and prasugrel. Proinflammatory cytokines like TNF- α , IL-1 β and IL-6 are released during infarction and plays pleiotropic mode of action that induces cell damage and also involved in cell protection. However, the available data on the cytokine network during antiplatelet therapy is inadequate. This review method is based on the search of various search engines such as PubMed Central, PubMed, Scopus, Medline, Research Gate to capture many articles and we examined the importance of cellular factors and ticagrelor in AMI. Thus, the present review analyses the role of cytokine network during the treatment of AMI which is an important key factor to understand the essential cellular mechanism of cardiomyocytes and the effect of ticagrelor on pro-inflammatory cytokine network during the therapeutic phase of AMI.

Keywords: Acute myocardial infarction, Cytokine network, Antiplatelet therapy, Ticagrelor.

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Introduction

Worldwide acute myocardial infarction (AMI) remains significant cause of morbidity and mortality [1]. The recent focus of coronary artery diseases has been believed that the occurrence of cardiovascular diseases (CVD) is due to the modern stressful life style [2]. The pathogenesis of myocardial infarction was authenticating that myocardial infarction is caused by coronary thrombosis [3]. Later in years, the pathogenicity was first reported by Herrick, remarkable Chicago physician published in 1912 in the Western medical literature [4]. The global burden of CVD mortality for the next decades is expected to increase predominantly. This has been reported by the World Health Organization (WHO) and therefore, United Nations is initiating a global action targeting 25% reduction in the probability of disease occurrence in the year 2025 [5]. In the year 2016, American Heart Association (AHA) has reported that 15.5 million persons developed myocardial infarction above the age of 20 year. The prevalence of coronary artery diseases (CAD) was reported to be 5.5% in Saudi Arabia in 2015. Recently, AMI occur due to the

decreased blood supply to the heart muscle due to the stenosed vessel, atherosclerosis [6-10].

Generally, the diagnosis of myocardial infarction is relying on the presence of chest pain; ST segment and T wave abnormality of electrocardiogram (ECG) furthermore rise and fall in cardiac enzymes specifically troponins after cardiac muscle damage is a highly specific marker of myocardial infarction [3]. The prospective of pharmacotherapy is on the utilization of a wide range of various drugs for the treatment and management of AMI. Anti-platelets drugs play a significant role in the treatment of cardiovascular diseases. These drugs either inhibit the platelet activation, aggregation or other signaling pathways, thereby inhibiting the clot formation. The prescribed drugs for AMI are aspirin, nitroglycerin, β -blockers, ACE inhibitors, calcium channel inhibitors, and thrombolytic therapy, heparin and P2Y₁₂ receptor antagonists [11,12]. Although various drugs and treatment aspects are practiced, P2Y₁₂ receptor inhibitors therapy was found to be better and more promising in the management of AMI. Clopidogrel and Prasugrel are the thienopyridine class of drugs which are eliciting action by inhibiting P2Y₁₂ receptors. Their

usage has been experienced several limiting factors because of drug metabolism and irreversible binding with P2Y₁₂ receptor causing the prolonged recovery of platelet activation. Furthermore, the efficacy of drug also influenced by the genotypes of individual patients [12].

The immune system plays a key role in the development of AMI, healing and remodelling after AMI. The progenitors and cellular systems of both innate and adaptive immunity equally balanced in pathogenic and healing of AMI. The effector cells are communicated by messenger called cytokines which has a prominent role in the effector mechanism of developing AMI and also has pleiotropic effect in healing after reperfusion of AMI [13].

The risk of MI is highly influenced by genetic factors (Table 1). Genome-wide associated studies (GWAS) have been identified for single nucleotide polymorphism in genes that are associated with coronary heart disease.

Recently, many researchers have reported that gene analysis study has identified several loci on the chromosomes whose variants are positively linked with CVD. However, the genetic influences also vary with the country and region [14-18].

Table 1. Genotyping and MI prevalence in various countries.

Type of gene	SNP	Chromosomal locus	Country/region	Reference
KIF6	Trp719Arg	6p21	European	15
CDKN2A/B	rs10757278	9p21	USA	16
QK1	rs6941513	9p21	European	16
MTHFR	C677T	1p36.22	Japan	17
K1F6	Trp719Arg	6p21.2	Saudi Arabia	18
CDKN2BAS1	rs564398	9p21.3	Saudi Arabia	19

Ticagrelor is a classical anti-platelet therapeutic agent, chemically a cyclopentyl triazolo pyrimidine having molecular formula C₂₃H₂₈F₂N₆O₄, and its molecular weight is 522.57. Ticagrelor exerting its action by binding reversibly on P2Y₁₂ receptor which does not require metabolic activation, unlike clopidogrel and prasugrel.

The drug molecule inhibits the platelet activation and aggregation by blocking signal transduction [19]. Recent evidence-based therapies across the world including in Saudi Arabia are proving that ticagrelor a unique molecule and an ultimate choice of drug for the treatment and management of AMI.

Thus, this review is focusing on various aspects of AMI and treatment aspects to understand why ticagrelor is a versatile drug moiety to manage and recover from AMI.

Molecular Aspects of Oxidative Stress and Cytokine Network

Oxidative stress as the predominant factor of MI

Oxidative stress of cardiomyocytes during myocardial infarction (MI) is characterized by reperfusion injuries that result in the accumulation of oxygen free radicals called reactive oxygen species (ROS) that initiates lipid peroxidation, oxidation of proteins and DNA damage [19] inside myocardial cells. Thus, oxidative stress is an invasive condition due to the induction of cellular toxicity by oxidant metabolite that modulating the altered cellular metabolic mechanisms. During cardiac ischemia, the cellular respiration becomes anaerobiosis where the need for more ATP to get the energy to the cells but ATPs are insufficient and also break down into hypoxanthine and xanthine [19-21]. In the meantime, cardiac myocytes develop acidosis as a result of oxidative stress caused by anaerobic respiration of the cells [19]. Thus, the proteolysis of hypoxanthine takes place and lead to the production of xanthine oxidase. The xanthine oxidase binds with molecular oxygen as a substrate that produces oxy free radicals. On the other side, reperfusion increases the aerobic respiration in mitochondria of cardiac myocytes and electron diffuse out from mitochondria is also generated free radicals. The generated free oxygen radicals with cellular nitrous oxide (NO) leads to the development of free radicals called reactive nitrogen species (RNS). RNS is an alternative group of free radicals which includes NO, nitrogen dioxide (NO₂) and peroxynitrite (ONOO⁻) which has specific oxidant property in the normal cellular respiration. The molecular oxygen available in cell undergo reduction to yield superoxide molecule, an anion plays an important role in the formation of OH free radicals since it acts on hydrogen peroxidase (H₂O₂) of the cells. H₂O₂ is not a free radical molecule but considered as predominant ROS because of high reactive in nature that can easily be disassociated as OH⁻ and OH⁺ radicals. However, strong oxidants pursuing the action through the Fenton type of reactions with metal complexes and happens due to the acceptance of an electron by H₂O₂ from the metal ions such as Fe²⁺ [19].

Cytokines as an orchestral mechanism of MI

In the sequence of cellular mechanism of MI, cytokines are the lower molecular glycoproteins that are the classical messenger induced by ROS, and interestingly cytokines also induce ROS, a reversible induction mechanism. In ischemic cardiac cells, H₂O₂ can induce a proinflammatory marker cytokine tumor necrosis factor- α (TNF- α) via p38 mitogen-associated protein kinases (p38 MAPK) molecules pathway that elicits a potent action that leads to myocardial dysfunction and also apoptosis [22]. Generally, TNF- α is not expressed in normal cardiomyocytes but the expression of TNF- α is observed after the development of ischemia and infarction. The hypoxic state of cardiac myocytes leads to the activation of mononuclear macrophages which are localized in infarcted area as well as infarcted border zone that causes myocardial cells to release

more TNF- α . Simultaneously, the expression of TNF R1 and R2 also increases significantly [23]. The apoptosis signal usually initiated by the action of TNF- α directly on the mitochondria of cardiac myocytes, which enhances the function of ROS that releases cytochrome C and Ca²⁺ flux also involved in the development of apoptosis of cardiac myocytes. This is related to the activation of calpain, a calcium-dependent protein which is a proteolytic enzyme called cysteine proteases [24,25]. Studies are suggesting that TNF- α is having the pleiotropic mode of action which elicit action on cardiomyocytes that involve both cardiac damages as well as cardiac protective action. This effective mechanism is executed by binding with soluble receptor molecules. In this way, there are two kinds of TNF receptors namely the membrane-bound death receptor TNFR1 and the expression of TNFR2 on the surface of endothelial cells of infarcted area and hematopoietic cells that regulates a wide range of biological action. However, the efficacy of effect of TNF- α on myocardial cell is highly influenced by the combination of these receptors. In this regard, TNF- α combines with TNFR1 increases the apoptosis-related proteins and inflammatory mediators that lead to cellular aggregation, platelet-leukocyte interaction and thrombus formation. TNF- α : TNFR1 complex will induce the nitrous oxide (NO) synthesis that activates the enzyme sphingomyelinase reducing the release of Ca²⁺ that leads to depletion of ventricular systolic function. Besides, TNF- α : TNFR2 complex activates and increase the expression of IL-6 and IL-1 β . The progressive combination of TNF- α either with TNFR1 or TNFR2 can induce ROS production that can damage DNA in cardiomyocytes and T lymphocytes through the stimulation of NF kB pathway. However, NF kB inhibitors and IL-10 can prevent the DNA damage. Excessive expression of TNF- α may enhance the transcription of hypertrophic genes NF kB and p38 MAPK pathways that cause hypertrophy of cardiomyocytes that occurs after the development of MI [23]. Thus, excessive secretion can be balanced by targeting and inhibiting TNF- α expression which will be an important target for the treatment.

Interleukin-6 (IL-6) is a pro-inflammatory cytokine of the innate immune system which is a key mediator of inflammation meticulously associated with AMI [26-28]. The involvement of IL-6 in AMI through reperfusion injury was reported by Frangogiannis et al. [29]. IL-6 stimulates the production of C-reactive proteins (CRP) during hypoxic conditions and venous congestion [30]. The biological action of IL-6 is determined by binding with the soluble IL-6 receptor (sIL-6R). The sIL-6R is a membrane-bound receptor present on the surface of cardiomyocytes [31]. After binding of IL-6 with IL-6R, an active complex is directly associating with glycoprotein 130 (gp130) receptor which is a common signal transducing receptor on the cell membrane of cardiomyocytes, mononuclear cells and thus activates the intracellular molecular pathway to induce inflammatory effects [32]; reports suggesting that sIL-6R levels were high in AMI when compared to other stable coronary artery diseases (CAD). In 2016, Vibeke et al. suggested the casual association of IL-6 with atherosclerosis [33]. However, the present scientific

reports on signaling pathways of IL-6 on soluble gp130 and soluble IL-6 are few to determine the mechanism in the development of atherosclerosis associated STEMI [34]. An earlier report on age factor and IL-6 level depicting that the level of IL-6 is very high in elderly patients and found to be a risk in developing cardiovascular diseases. Besides, the dysregulation of the production of IL-6 has been observed in elderly person. Thus, it is very difficult to map age factor and IL-6 level in the development of CAD [35-38]. The earlier studies suggesting that the trans-signaling pathway of IL-6 is very important to exert the proinflammatory effects. The activation of IL-6: gp130 receptor complex induces mitogen-activated protein kinases (MAPK) and Janus kinase (JAK)/Signal Transducer and Activator of Transcription (STAT) pathways. Nevertheless, STAT3 is a chief pathway in the hemodynamics and physiological mechanisms in myocardial ischemia [38]. The trans-signaling pathway of IL-6 plays an important role in STEMI. In contrast the soluble gp130 protein also exerts an inhibitory action of trans-signaling of gp130. Therefore, IL-6 is a pleiotropic type cytokine having both proinflammatory and anti-inflammatory mode of action.

Interleukin-1 (IL-1) is a typical proinflammatory cytokine family induced to exert a diversity of secondary inflammatory mediators [39,40]. IL-1 plays an important role in maintaining both innate and adaptive immunity. It is a central mediator of host cell inflammatory response. IL-1 is secreted due to the activation of mononuclear phagocytic cells, dendritic cells. B cells, large granular lymphocytes, fibroblasts and endothelial cells. IL-1 predominantly involved in the inflammatory process that is responsible for coronary syndromes since IL-1 induces IL-6 and enhances the gene expression of clotting factor [41]. IL-1 is expressed by activated macrophages as a biomolecule which is responsible for inflammatory mediated ACS [42,43]. There are two forms of IL-1, IL-1 α and IL-1 β . IL-1 α is a key marker of pro infarction stage of MI since it is released from necrotic cardiomyocytes. The activation of inflammasome after tissue injury induces and amplifies the expression of IL-1 β . Activated platelets releases IL-1 β and mainly found in circulation produced by precursor IL-1 β (Pro IL-1 β) which cleaves caspase-1 in the site of inflammasome [44-49]. The spectrum of the release of active IL-1 β is highly dependent on ATP facilitated P₂X₂ membrane receptor mediation process [43]. The release of IL-1 α and IL-1 β during myocardial ischemia also enhances the apoptosis signaling pathway of cardiomyocytes. Interleukin 18 (IL-18) is a proinflammatory cytokine belongs to the IL-1 family that has been implicated in the regulation of cardiomyocyte hypertrophy and causing cardiac contractile dysfunction and extracellular matrix remodeling [44]. Thus, MI is characterized by triggering inflammatory reactions to necrotic cardiomyocytes that signals activated proinflammatory cytokine network (Figure 1). However, the biological action of cytokines is the pleiotropic mode of action with a predominant proinflammatory effect and to a lesser extent as an anti-inflammatory. Furthermore, the anti-inflammatory cytokine IL-10 is highly elevated in reperfused myocardium that downregulates the concentrations of TNF- α and IL-6, which can be useful as a marker that

hypothesizes the transit state from proinflammatory to anti-inflammatory conditions in AMI [45]. Interleukin-18 (IL-18) is also the member of the IL-1 cytokine family which has structural similarities with IL-1 β and reported as an important biomarker relating in AMI. It has been reported that IL-18 has the pro-inflammatory action that induces apoptosis of cardiac myocytes and excites nitric oxide production. Furthermore, IL-18 stimulates the action of cytotoxic T-lymphocytes (CTL) i.e. CD8⁺ cells. It is involved in the synthesis of intercellular adhesion molecule (ICAM)-1. Both CD8⁺ and ICAM-1 have been reported to be related with the development of cardiac dysfunction [46].

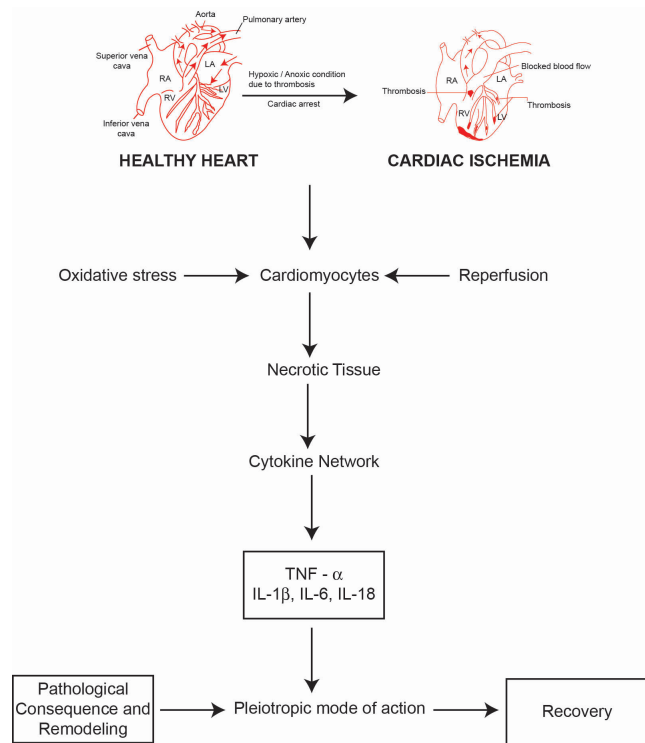


Figure 1. Cytokine network.

Consequently, pro-inflammatory cytokines interleukin (IL)-1 β , TNF- α , IL-6 and IL-18 are involved in AMI including reperfusion injury and cardiac hypertrophy. Thus, it is essential to study the cytokine network process in order to understand the pathological consequence of myocardial infarction. On the other hand, the pro-inflammatory cytokines are having the pleiotropic mode of action showing anti-inflammatory action. Cytokines in the myocardium initiate the wound repair process which includes phagocytosis of necrotic tissue of infarcted area, hypertrophy of myocytes, synthesis of collagen, integrins, the proliferation of myofibroblasts, and initiation of angiogenesis as well vasculogenesis and progenitor cell proliferation. Interleukin-10 (IL-10) is a potent anti-inflammatory cytokine that plays a key role to heal the cardiac wounds after AMI. This is mainly due to the pleiotropic effects that regulate the inflammatory response and involves in the regeneration of tissue by regulating the extracellular matrix, endothelial progenitors and fibroblast cellular function [47-49].

The balance between pro and anti-inflammatory cytokines is essential for appraising the genuine effect of different cytokines and the characteristics of the cytokine network; the cytokine network also influenced by disease condition like diabetes mellitus, renal failure, COPD, allergic bronchitis and asthma; patients under immunosuppressive treatments.

Pharmacotherapy of MI

The treatment of AMI has progressed a long way since 1912 and there are various methods employed in the management of AMI one among that is drug therapy [3]. The platelet aggregation is dependent on the activation of 2G protein-coupled receptors P2Y₁ and P2Y₁₂. The pharmacotherapy of AMI has been recently more successful due to the development of novel drug molecules that elicit their action through specific receptor P2Y₁₂ based action. P2Y₁₂ receptor is a member of P2Y receptor family which can couple with G proteins and termed as G proteins coupled purinergic receptor, a chemoreceptor for ADP [50,51]. ATP's are master molecular energy source of the human cellular system. ATP's are involved in the transmission and storage of energy inside the cell. It is also involved in the synthesis of sugar, protein, fats and nucleotides. Upon neural stimulation ATP's are released in extracellular space in autocrine or paracrine fashion. ATP's are involved in platelet aggregation a predominant factor for MI [52,53]. P2Y₁₂ receptor is distributed on the cells of the brain, spinal cord and platelets. P2Y₁₂ receptor has a key role in the activation of platelet during ischemic damage and leads to AMI. Due to this functionality of P2Y₁₂ receptor, a significant attention was attributed by pharmaceutical researchers to develop novel drug molecules that block the action of P2Y₁₂ receptor mode of action. Thus, blocking the P2Y₁₂ receptor activation has opened a new lane that has significant therapeutic outcome [54-56]. A comparative oral antiplatelet therapy in the treatment of AMI has been tabulated (Table 2). The mechanism of antiplatelet therapy is highly accomplished by binding with P2Y₁₂ receptor and blocking the platelet aggregation.

Thienopyridines therapy

Thienopyridine molecules were first introduced as platelet adenosine diphosphate (ADP) receptor blocks. Ticlopidine was the first drug molecule accepted for clinical use. The drug was proving 46% of the reduction in the risk of death due to MI at 6 months of treatment. However, the usage of ticlopidine becomes limited due to the development of severe hematological toxic neutropenia [55]. Clopidogrel and prasugrel are the most successful thienopyridines that are selective in action which inhibits ADP mediated platelet activation irreversibly. Clopidogrel is a prodrug that needs cytochrome P 450 (CYP) 3A4 and 3A5 enzymes of the liver, with contributions from 2C19, 2C9, and 1A2 enzymes [56-59] to convert to active drug molecule that inhibits platelet aggregation through P2Y₁₂ receptor action. Since it depends on CYP system the efficacy also varies with individual patients

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due to the variability of enzyme activity developed by genetic polymorphism.

Table 2. Antiplatelet drugs and their properties.

Drug name	Chemical name	Type receptor	of	Type of drug	Mode of action	Spectrum of activity
Ticlopidine	Thienopyridines	ADP Receptor		Prodrug requires metabolism to convert as metabolite	Irreversible	Effect is variable
Clopidogrel	Thienopyridines	P2Y ₁₂		Prodrug requires metabolism to convert as metabolite	Irreversible	Effect is variable
Prasugrel	Thienopyridines	P2Y ₁₂		Prodrug requires metabolism to convert as metabolite	Irreversible	Effect is variable
Ticagrelor	Cyclopentyl triazolo pyrimidine	P2Y ₁₂		Active drug molecule	Reversible	Effect is variable

Table 3. Benefits of Ticagrelor therapy when compared to thienopyridines therapy.

Does not require liver metabolic activity and has fast onset of action
The rate of MI is reduced
The death rate is reduced
No interactions with proton pump inhibitors
Lower rates of stent thrombosis
Drug resistance is usually not observed. Very few have been reported

The development of genetic polymorphisms resulting in a reduced function CYP2C19 allele is more susceptible to clopidogrel resistance. Patients with ACS and clopidogrel resistance are at high risk for the development of serious ischemic and cardiovascular complications. Due to this enzyme dependence, clopidogrel is having many drug-drug interactions [60-62]. Furthermore, it has been reported that patients with poor response to the clopidogrel drug therapy had developed coronary thrombosis [63,64]. Studies suggesting that the clopidogrel affects CRP as like aspirin over 6 months treatment of MI [65]. Furthermore, clopidogrel has shown interaction with proton pump inhibitors such as omeprazole. Thus, US FDA has strictly framed a guideline that the combined use of clopidogrel as well as omeprazole or esomeprazole must be avoided [64]. Prasugrel is superior to ticlopidine and clopidogrel since it has been reported that the onset of action is faster and the spectrum of activity is strong than the clopidogrel. However, prasugrel also requires hepatic CYP3A4 enzyme metabolic activation [62]. Prasugrel has been reported as successful molecule in reducing 50% stent thrombosis. Conversely, the major drawbacks of prasugrel are highly associated with bleeding risk especially patients undergoing coronary artery bypass graft (CABG) and patients above the age of 75 y old having the history of stroke or ischemic attack. Due to the bleeding problem the usage of prasugrel has been limited; however, the prasugrel shown a better effect in patients with MI complicated with diabetes mellitus when compared to clopidogrel. The absorption of clopidogrel and prasugrel is highly regulated by membrane-bound p-glycoprotein which is an efflux pump-mediated by ATP that exchanges various

molecules from the intracellular environment to extracellular membrane. Besides, the drug molecules clopidogrel and prasugrel are irreversible blockers of P2Y₁₂ receptor having the modest spectrum of activity with more limited efficacy. Furthermore, both the drugs are producing the increased risk of adverse clinical outcomes [66-70].

Ticagrelor, a breakthrough in the pharmacotherapy of AMI

Ticagrelor is a unique drug molecule that belongs to the class cyclopentyl triazolo pyrimidine which is the first reversible binding P2Y₁₂ receptor antagonist that inhibits ADP induced platelet aggregation [68]. The ticagrelor does not require metabolic activation like thienopyridine derivatives since it is not a prodrug that offers a better potency in platelet inhibition during the treatment of AMI/MI and has potential advantages when compared to thienopyridine molecules (Table 3). Constantly, ticagrelor has much faster antiplatelet effects than clopidogrel in patients with acute coronary syndrome (ACS). Since the onset of action is quick ticagrelor provokes a strong platelet reactivity inhibition in patients with ACS and has a very low inter-patient inconsistency. Ticagrelor is a reversible P2Y₁₂-ADP receptor antagonist that permits a quicker rejuvenation of platelet function than thienopyridines. Ticagrelor inhibits platelet aggregation within 30 min of administration with a loading dose of 180 mg. The ticagrelor is significantly reducing the incidence of MI in PLATO (Platelet inhibition and platelet outcome) research study [69-74]. Interestingly the PLATO study demonstrated that 16% risk reduction in MI without increase of bleeding risk even in CABG when compared to clopidogrel [69]. Ticagrelor is a CYP450 substrate which is susceptible to limited drug-drug interactions. It has been shown that ticagrelor strongly inhibits CYP3A5, inhibits CYP2C9 and CYP2D6 moderately, and it is a weak inhibitor of CYP3A4. Furthermore, ticagrelor and its active metabolite molecules are the inhibitors of P-glycoprotein. Ticagrelor concentration significantly increased in plasma while interacting with drug molecules that include the CYP3A inhibitors ketoconazole and diltiazem. However, a significant reduction of ticagrelor concentration in plasma was observed when interacting with the strong CYP3A inducer

rifampin. Since ticagrelor is a P-glycoprotein substrate inhibitor has been shown to significantly increase plasma digoxin concentrations. Unlike clopidogrel, ticagrelor has no interactions with proton pump inhibitors [64,75].

Diabetes mellitus is a major coexistence as a prehistoric disease development of MI. Studies suggesting that ticagrelor elicit a spectacular inhibitory action of platelets when compared to clopidogrel [76]. Ticagrelor treatment has been proved the reduced risk of ischemic events in patients suffering from coronary heart disease with diabetes mellitus [77]. Asthma and chronic obstructive pulmonary disease (COPD) are predominantly associated with developing ischemic events and AMI. Earlier reports suggesting that patients with COPD experiencing a high risk of developing the acute coronary syndromes (ACS); However, the study also reporting that treatment with ticagrelor decreased ischemic events in COPD condition without bleeding complications [78]. Furthermore, ticagrelor did not alter the pulmonary function of patients with asthma and COPD [79]. Studies on proinflammatory cytokines such as TNF- α , IL-1 β and IL-6 are increased in the MI after reperfusion which has been described in the earlier part of this article. Studies suggesting that ticagrelor inhibited the release of pro-inflammatory cytokines TNF- α and IL-6 in a human sepsis model. Ticagrelor significantly reduced the cytokine network during the treatment whereas clopidogrel did not modulate the cytokine network. The positive inhibitory effect of ticagrelor lay to develop of prevention of remodeling and fibrosis [80]. In 2011, Liao et al. reported the stimulation of the A1 receptor of adenosine suppresses the effect of TNF- α those inducing pro hypertrophic effects on cardiomyocytes [81]. However, ticagrelor treatment induces 15 epi-lipoxin A4; an eicosanoid mediator exerts a potent anti-inflammatory effect that inhibits the secretion of TNF- α and IL-1 β [82-84]. Beyond these positive effects, few negative effects also have been attributed. Ticagrelor also cause a fatal bleeding problem like other antiplatelet drugs but the spectrum of activity is lesser extent when compared to other platelet drugs. The usage of ticagrelor has been limited in patients with MI and severe hepatic impairment because ticagrelor is metabolized in the liver and enhance the liver impairment because of diminished synthesis of coagulation of proteins.

Conclusion

Acute myocardial infarction (AMI) is a cardiac event triggered by unstable ischemia due to lack of blood supply to the cardiac myocytes. Generally, the diagnosis of myocardial infarction has relied on the presence of chest pain. Improper diagnosis of patients with chest pain often leads to inappropriate hospital admission of patients without AMI which leads to more distress to the society. Diagnosing the biomarkers level in AMI condition is much more important to ascertain the disease condition. Cytokines are small molecular proteins function as cellular communicator released predominantly in the inflammatory and injury pathological sequences. The present review is analyzing various effects of antiplatelet drug therapy in AMI, among all ticagrelor found to be a better molecule

since it is not a prodrug having excellent pharmacokinetic and pharmacodynamic profile and showed the inhibitory effect on pro-inflammatory cytokines. However, the mechanistic study of drug molecule on cytokine network is very limited. Thus, a lot of opportunities are existing on the establishment of pro-inflammatory cytokine network during ticagrelor treatment which is opened to various researchers to find out wider mechanism.

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Conflict of Interest

Authors declare that there is no conflict of interest.

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