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# A Review on Pharmacotherapy of P2Y12 Receptor Inhibitor (Ticagrelor)

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**Suganthi S*, Charumathi A, Babisha J, Sathish kumar R, Sankar C, Suresh Kumar R**

*Department of Pharmacy Practice, KMCH college of Pharmacy, Kovai Estate, Kalapatti Road, Coimbatore-641048, Tamil Nadu, India (Affiliated to The Tamil Nadu Dr. M.G.R. Medical University).*

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**ABSTRACT**

Ticagrelor is an antiplatelet agent with a mechanism of a direct and reversible competitive inhibition of P2Y12 receptor. According to European Cardiac society, Ticagrelor is used for prevention of thrombotic events in acute coronary syndromes. Until recently, a combination of clopidogrel and aspirin was acknowledged as a gold standard of the antiplatelet treatment. Now ticagrelor is preferred over clopidogrel, This review is mainly looking upon major aspects of ticagrelor. They are Pharmacokinetics, pharmacogenetics, drug-drug interactions, adverse effects, efficacy in specific patient populations and off-label properties of ticagrelor are discussed in this paper. Moreover, the results from pivotal clinical trials are presented.

## 1. INTRODUCTION

According to the recommendation of the European Society of Cardiology, an essential aspect of pharmacotherapy in ACS is the administration of antithrombotic drugs [1]. Their mechanism of action is based on inhibition of P2Y12 receptor located on the platelet surface. Until recently, a combination of clopidogrel and aspirin was acknowledged as a gold standard of the antiplatelet treatment. However, randomized clinical trials such as Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel Thrombolysis In Myocardial Infarction 38 (TRITON-TIMI 38) and Platelet Inhibition and Patient Outcomes (PLATO) showed that new generation antiplatelet drugs, ticagrelor, and prasugrel, are superior to treatment with clopidogrel [2,3]. The aim is to provide a comprehensive summary of ticagrelor.

## 2. METABOLISM AND MECHANISM OF ACTION

Contrary to thienopyridine derivatives (clopidogrel and prasugrel), which are prodrugs, ticagrelor does not require bioactivation to exert pharmacodynamic effect [4]. Structurally, ticagrelor very distinctly resembles ATP, which is a natural antagonist of P2Y12 and which served as a starting point in ticagrelor discovery[5]. It is the first drug of a new chemical class – cyclopentyltriazolopyrimidines. Its mechanism of action is a reversible, competitive binding to P2Y12 receptor and inhibition of ADP-induced signaling [6]. Approximately 30–40% of the absorbed dose of this drug is converted through demethylation to its main metabolite, labeled AR-C124910XX (Figure 1) [4]. Results of in vitro studies suggest that mainly CYP3A4, CYP3A5, and CYP2C9 are involved in this reaction [7]. Besides the main metabolite, nine other metabolites were successfully identified in plasma, urine, and feces [4]. Moreover, the main metabolite also exhibits antiplatelet activity similar to that of the parent drug [4]. Because metabolic activation is not essential, the pharmacodynamic effect of ticagrelor is rapid, with an onset of 2–4 h after oral administration [8].

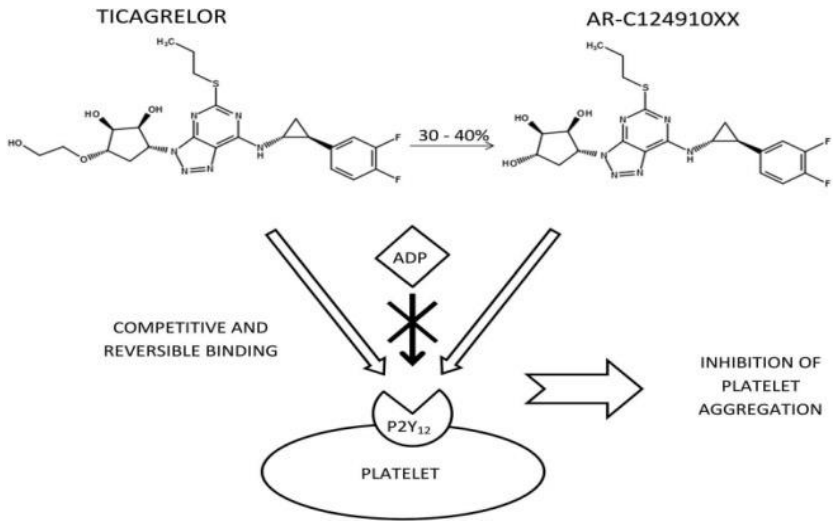


**Figure No. 1. Metabolism of ticagrelor to its main active metabolite and mechanism of action.**

## 3. PHARMACOKINETICS

A pilot study involving patients with the atherosclerotic disease showed that pharmacokinetics of both ticagrelor and AR- C124910XX are linear over the range of 50–400 mg bid, after the first dose and in the steady-state [9]. However, at greater doses (200 mg bid and 400 mg bid), the exposure to ticagrelor after 28 days of the therapy was greater than dose-proportional. Exposure to the main metabolite was noted to be approximately 35% of exposure to the parent drug. Maximal concentrations of the drug are observed 1.5–3 h after administration and a steady state is achieved after three days of the therapy [8]. The effect of food on maximum concentration and area under time concentration curve of ticagrelor and its main metabolite is considered to be of minimal clinical significance [10]. The elimination half-life for ticagrelor is approximately 8 h, while a longer half-life of 11.5 h was noted for AR-C124910XX [4]. It was found that several other factors might significantly affect the systemic clearance of ticagrelor. Cl/F was higher in obese patients (>110 kg) and lower in patients with small body- weight (<50 kg). Also, sex, age, and smoking might influence Cl/F of both ticagrelor and its main metabolite. Habitual smoking appears to lower Cl/F of ticagrelor even by 22% [11]. Since CYP3A participates in the metabolism of ticagrelor, concomitant administration of inducers or inhibitors of this isoenzyme also significantly impacts Cl/F of the drug [11]. As observed in the population analysis, the differences in the bioavailability of the drug might be influenced by ethnic differences. Compared to patients of Caucasian origin, bioavailability was 39% higher in Asian subjects and 18% lower in Black patients [11].

## 4. CURRENT RECOMMENDATIONS OF EUROPEAN CARDIAC SOCIETY AND AMERICAN COLLEGE OF CARDIOLOGY

According to the recommendations issued by the European Cardiac Society and European Association of Cardio-Thoracic Surgery (ECS/EACTS), ticagrelor, along with prasugrel, is recommended for prevention of stent thrombosis in patients undergoing myocardial revascularization as a part of dual antiplatelet therapy in combination with aspirin [12]. The guidelines indicate that ticagrelor is preferred over clopidogrel for patients with non- ST-segment elevation acute coronary syndromes (NSTE-ACS) and STEMI (Class I, level of evidence B). However, the addition of ticagrelor as a part of triple antiplatelet therapy with an oral anticoagulant is not recommended. Newest guidelines update of the American College of Cardiology and American Heart Association (ACC/AHA) likewise suggests that the use of ticagrelor in dual antiplatelet therapy is more reasonable than clopidogrel in patients with NSTEMI or STEMI who are managed with medical therapy alone (moderate recommendation with the B-R level of evidence) [13]. Also, according to the guidelines, the therapy should be continued for at least 12 months in patients who were treated with bare-metal stents or drug-eluting stents. Additionally, a continuation of antiplatelet treatment past the 12- month threshold might be possible in patients who well tolerated the drug and are not at high risk of bleeding [13]. However, discontinuation of treatment with P2Y12 inhibitor after 6 months might be reasonable in patients who are at high risk of severe bleeding complications (e.g. major surgery), who develop a high risk of bleeding (e.g. concomitant oral anticoagulant therapy) or develop significant bleeding. Another important issue is pretreatment with P2Y12 inhibitors, which assumes initiation of the treatment at the time of diagnosis in patients with ACS. The concept of pre-treatment was introduced, when the administration of aspirin and clopidogrel before PCI resulted in a significant reduction of the composite endpoint of cardiovascular death, myocardial infarction or urgent revascularization[14]. Recent studies showed that in NSTE-ACS patients pretreatment with ticagrelor may result in >1% increase in net clinical benefit assessed on a basis of mortality, myocardial infarction, and major bleeding when the ischemic risk exceeds 11% [15]. Also, in NSTE-ACS patients, administration of a loading dose of ticagrelor as soon as possible before PCI is superior in prevention of periprocedural myonecrosis to the administration of prasugrel at time of the procedure [16]. As for pretreatment with ticagrelor in STEMI patients, the treatment is considered as generally safe [17]. Additionally, some studies suggest that

administration of this agent 1.5 h before PCI improves pre-angiographic coronary reperfusion in comparison with administration immediately before the procedure [18].

## 5. PIVOTAL CLINICAL TRIALS

The guidelines issued by renowned medical associations are based on the results from large multicenter clinical trials. Table 1 presents the main conclusions from the most important clinical trials involving ticagrelor. Overall, the drug is mostly well tolerated. The main advantage of ticagrelor over clopidogrel is a greater and more consistent antiplatelet effect [19]. This finding was confirmed by the most widely used assays for measuring platelet aggregation or platelet reactivity, including light transmittance aggregometry (LTA), VerifyNow P2Y12 or vasodilator-stimulated phosphoprotein phosphoryl a- tion (VASP) [20]. The onset of action is faster in patients taking ticagrelor than in those taking clopidogrel [21]. Moreover, the patients that are found to be resistant to clopidogrel respond well to ticagrelor [20]. Also, it was found that ticagrelor is more efficient in preventing death from vascular causes, myocardial infarction or stroke in patients with ACS and noncardioembolic, nonsevere ischemic stroke or high-risk transient ischemic attack [3,22]. Long-term therapy (>12 months) was also found to be beneficial for reducing the incidence of cardiovascular death or stroke [23]. However, the findings from newest Examining Use Of Ticagrelor In Pad Trial (EUCLID), which aimed at comparing cardiovascular events of ticagrelor and clopidogrel in patients with peripheral artery disease, show that in this group of patients the benefits are similar for both clopidogrel and ticagrelor [24].Some studies were aimed at comparison of safety and efficacy of ticagrelor and prasugrel. Obtained results suggest that ticagrelor does not appear to be superior to prasugrel in STEMI patients in the first 24 h of treatment [26]. Also, the efficacy in preventing death, reinfarction, urgent revascularization or stroke of both drugs seems to be similar, as well as the safety of use [27].Although ticagrelor was successfully approved by the US Food and Drug Administration (FDA), some authors point out, that the approval was questionable. The main issues were concerning some inconsistencies within the results of the PLATO trial, different outcomes in the USA-based sites, incomplete follow-up, skewed exclusion of adjudicated death and problems with blinding[28].

**Table No. 1: Pivotal Clinical Trials Involving Ticagrelor**

| STUDY GROUP | DRUGS | OUTCOME | REFERENCES |
|---|---|---|---|
| 200 patients with atherosclerosis (DISPERSE trial) | Ticagrelor 50, 100, or 200 mg bid or 400 mg vs. 75 mg clopidogrel daily | Higher antiplatelet efficacy of ticagrelor 100 and 200 mg bid as compared to clopidogrel. Good tolerability of ticagrelor, however, the incidence of bleeding events was higher than in the clopidogrel group | 9 |
| 990 patients with NSTE-ACS (DISPERSE-2 trial) | Clopidogrel (300 mg LD and 75 mg MD)vs. ticagrelor (90 mg bid or 180 bid) | No difference in major bleeding but increase in minor bleeding after higher doses of ticagrelor | 29 |
| 91 patients with ACS (DISPERSE-2 trial substudy) | Clopidogrel (300 mg LD and 75 mg MD)vs. ticagrelor (90 mg bid or 180 bid) | Greater and more consistent inhibition of platelet aggregation in the ticagrelor group as compared with clopidogrel | 19 |
| 18,624 with ACS, with and without ST-segment elevation (PLATO trial) | Clopidogrel (300–600 mg LD and75 mg LD) vs. ticagrelor (180 mg LD and 90 mg bid MD) | Lower incidence of death from vascular causes, MI or stroke in ticagrelor group (9.8% vs. 11.7%). No significant differences in major bleeding rates, but a higher rate of major bleeding not related to coronary-artery bypass grafting, including fatal intracranial bleeding | 3 |
| 98 patients with stable CAD, divided into clopidogrel responders and non-responders (RESPOND trial) | Clopidogrel(600mgLDand75mgMD) vs. ticagrelor (180 mg LD and 90 mg bidMD) | Better response to treatment in the ticagrelor group, as measured with LTA, VerifyNow and VASP assays. Lower platelet aggregation after switching from clopidogrel to ticagrelor. The antiplatelet effect of ticagrelor was the same in responders and non-responders to Clopidogrel | 20 |
| 123 patients with stable CAD (ONSET/OFFSET trial) | Clopidogrel (600 mg LD and 75 mg MD) vs. ticagrelor (180 mg LD and 90 mg bid MD) vs. placebo | Faster onset of the antiplatelet effect of ticagrelor, as well as greater inhibition of platelet aggregation than in the clopidogrel group. The faster offset of the inhibition of platelet aggregation after discontinuation of treatment with ticagrelor | 21 |
| 21,162 patients with a history of myocardial infarction and taking 75–150 mg aspirin daily (PEGASUS-TIMI 54 trial) | Ticagrelor 90 mg bid vs. ticagrelor 60 mg bid vs. placebo | Long-term (>1 year) treatment with ticagrelor + aspirin reduces the incidence of cardiovascular death, myocardial infarction or stroke. Risk of major bleeding events was higher when ticagrelor was administered | 23 |

| | | | |
|---|---|---|---|
| 13,199 patients witch noncardioembolic, nonsevereischemic strokeorhigh-risk transient ischemic attack (SOCRATES trial) | Aspirin(300mgLD and100mgMD)vs. ticagrelor (180 mg and 90 bidMD) | Lower incidence of stroke, myocardial infarction or death ticagrelor-treated patients (6.7% vs. 7.5%) with the similar occurrence of major bleeding | 22 |
| 13,885 patients with symptomatic peripheral artery disease (EUCLID trial) | Clopidogrel (75 mg MD) vs. ticagrelor (90 mg bid MD) | Reduction of the occurrence of cardiovascular death, myocardial infarction or ischemic stroke was similar in both study groups, as well as the rates of major bleeding. No differences in the reduction of acute limb events | 24, 25 |

ACS: acute coronary syndromes; CAD: coronary artery disease; LD: loading dose; LTA: light transmission aggregometry; MD: maintenance dose; MI: myocardial infarction; NSTE: no-ST-elevation, VASP: vasodilator-stimulated phosphoprotein.

## 6. TOLERABILITY AND SAFETY

In general, ticagrelor is thought to be well-tolerated and the rate of adverse effects is similar to clopidogrel. Following adverse events were reported: dizziness, headache, chest pain, nausea, dyspepsia, insomnia, hypotension and incidence of ventricular pauses [9,26]. However, most frequently reported and most pronounced events are bleeding and dyspnea, which may even lead to early drug discontinuation [27].

### 6.1. Bleeding

Bleeding is the most common adverse event treatment. According to the results from PLATO trial that took into consideration different bleeding scales, ticagrelor was similar to clopidogrel in PLATO major bleeding (11.6% vs. 11.2%), TIMI major bleeding (7.9% vs. 7.7%), and GUSTO severe bleeding (2.9% vs. 3.1%) [28].

### 6.2. Dyspnea

Dyspnea might be a result of the stimulation of pulmonary C fibers through activation of A1 receptors by adenosine [27]. The rate of dyspnea reported in several clinical trials ranges from 10% to 15% of patients receiving ticagrelor and is significantly higher than in other P2Y12 inhibitors, however, according to some studies even nearly 40% of patients might report it

[29,30]. Even though the shortness of breath was frequently reported, no effect of ticagrelor on pulmonary function (lung volumes, spirometry, pulse oximetry) was seen in ticagrelor patients as compared to clopidogrel [30,31]. Also, dyspnea was not related to patient's elderly age and overall safety and efficacy of ticagrelor were not associated with this adverse effect [29,32]. The occurrence of dyspnea might lead to discontinuation of the treatment. In PEGASUS-TIMI 54 trial 6.5% of patients taking 90 mg ticagrelor bid and 4.6% taking 60 mg bid, decided to cease the therapy due to dyspnea [33].

## 7. PHARMACOGENETICS

Ticagrelor appears to be an important alternative to treatment with clopidogrel in carriers of CYP2C19 loss-of-function alleles. As shown in clinical trials, ticagrelor efficacy in reducing platelet aggregation and ischemic events was unaffected by the presence of the aforementioned alleles, contrary to clopidogrel [34,35]. This finding is an understandable consequence of the lack of involvement of CYP2C19 in ticagrelor's metabolism. Also, ticagrelor is a direct-acting P2Y12 inhibitor and does not require transformation into a pharmacologically active entity. However, other genetic polymorphisms might influence the pharmacodynamic or pharmacokinetic properties of this drug. Several studies indicated that single nucleotide polymorphisms in P2RY12, P2RY1, and ITGB3 genes or common haplotypes did not affect the antiplatelet effect of ticagrelor [36-38]. Other common polymorphisms, such as rs5911 G>T mutation in the ITGBA2B gene, were shown to have an association with decreased activity of ticagrelor, but the effect was shown ex-vivo only [37]. Newer findings from genome-wide association study revealed, that potentially SLCO1B1, CYP3A4, and UGT2B7 loci might be of the most importance on ticagrelor [39]. It was shown that rs62471956 and rs56324128 variants in the CYP3A4 gene influence the metabolic rate of ticagrelor, resulting in higher concentrations of the active metabolite. Also, an rs113681054 variant in the SLCO1B1 gene influenced concentrations of both ticagrelor and its active metabolite, while rs61361928 variant in UGT2B7 gene was associated with higher levels of the active metabolite. However, these alleles were mostly of minor frequency (<5%), and their impact was limited. Moreover, the presence of candidate polymorphisms had no impact on the clinical outcomes of clopidogrel treatment, such as risk reduction of cardiovascular death, myocardial infarction, smoke or bleeding. Similar results were reported in a recently published study by Li et al. [40]. None of the studied polymorphisms (SLCO1B1 rs113681054,

SLCO1B1*5, CYP3A4*1G, and CYP3A5*3) affected neither pharmacokinetics nor pharmacodynamics of ticagrelor.

## 8. DRUG–DRUG INTERACTIONS

As ticagrelor is mostly metabolized by CYP3A4, most interactions arise from this metabolic pathway. Up to now, the most dangerous registered interaction is with CYP3A4-metabolized statins. According to pharmacokinetic data from healthy volunteers, concomitant administration of ticagrelor with simvastatin or atorvastatin significantly influences maximum concentrations of statins [41]. As a result, the risk of rhabdomyolysis is greater and several cases of ticagrelor-statin induced rhabdomyolysis have been reported [42-44]. At the same time, no influence on platelet reactivity or incidence of insufficient inhibition of platelet aggregation was reported. Nevertheless, co-administration of ticagrelor with high-dose statins, such as 80 mg atorvastatin, should be used with caution or avoided [41]. Ticagrelor can also influence the pharmacokinetics of other CYP3A4 substrates, such as midazolam, and therefore affect their efficacy [45]. On the other hand, CYP3A4 inducers, such as rifampicin or phenytoin, can have an impact on both pharmacokinetics and pharmacodynamics of ticagrelor. According to Teng et al. [46] the exposure to ticagrelor, as well as maximum concentration and elimination half-life significantly decreased when the drug was administered with rifampicin. Also, the offset of the antiplatelet effect was more rapid. Recently, a case study was reported, when ticagrelor was administered to a patient treated with phenytoin [47]. The authors noted, that the antiplatelet effect was also insufficient, but improved after discontinuation of phenytoin. On the other hand, grapefruit juice, a potent inhibitor of CYP3A4, increases the concentrations of ticagrelor and enhances inhibition of platelet aggregation [48].

## 9. PLEIOTROPIC EFFECTS OF TICAGRELOR

Early studies performed in animal models suggested that ticagrelor might have other, beneficial effect beside antiplatelet potency. According to the results from a rat model, the activation of the adenosine receptor by ticagrelor results in upregulation of nitric oxide synthase and an increase of cyclooxygenase-2 activity [49]. Further studies in human populations confirm the pleiotropic effects of ticagrelor. These effects are suggested to be related to an interaction with adenosine metabolism. In comparison to clopidogrel, adenosine plasma concentration is higher after administration of ticagrelor, which might be a result of

adenosine uptake inhibition [50]. However, some newer studies performed ex vivo and in vivo in healthy subjects suggest that at relevant plasma concentrations ticagrelor does not affect adenosine formation and transport [51]. Therefore, the exact mechanism of the pleiotropic properties of ticagrelor remains unknown. Newest studies show that in patients with STEMI or CAD ticagrelor, in contrast to clopidogrel or prasugrel, has a beneficial influence on factors directly correlated with inflammatory state and oxidative stress, such as higher levels of nitric oxide and lower concentrations of reactive oxygen species, high sensitivity C-reactive protein and cytokines (IL-6, TNF-α) [52-55]. Ticagrelor was also superior to clopidogrel in reducing microvascular injury in STEMI patients, defined by the index of microcirculatory resistance, wall motion score index and cardiac enzyme levels [55]. Overall, it appears that through these mechanisms ticagrelor might improve endothelial function in these groups of patients.

## 10. TICAGRELOR IN SPECIFIC POPULATIONS

### 10.1. Diabetes mellitus

Due to hyperglycemia, reduced platelet sensitivity, oxidative stress, and inflammation associated with endothelial dysfunction lead to increased platelet reactivity in diabetic patients [56]. This state of platelet hyperreactivity in diabetes is present despite ongoing dual antiplatelet therapy with P2Y12 inhibitors and aspirin and these patients are therefore more prone to thrombotic events [57,58]. Overall, large clinical trials and meta-analysis show that the addition of ticagrelor as an antiplatelet agent in diabetic patients with ACS reduces major events, such as cardiovascular death, myocardial infarction or stroke [59,60]. According to the recent results from the GRAPE (GReekAntiPlatElet) registry, diabetic patients with ACS undergoing PCI have a higher rate of major adverse cardiovascular events than nondiabetic patients [61]. Interestingly, a significant difference in the incidence rate was observed among clopidogrel-treated patients only, while newer agents such as prasugrel and ticagrelor, eliminated the negative influence of diabetes mellitus on the frequency of ischemic events. Several other studies also indicated that ticagrelor was superior to clopidogrel in inhibition of platelet aggregation in patients with diabetes mellitus, in terms of early onset of antiplatelet effect and its magnitude [56,62,63]. As shown in the CLOTILDIA (Clopidogrel High Dose Versus Ticagrelor for Antiplatelet Maintenance in Diabetic Patients) study, beneficial effects of treatment with ticagrelor over clopidogrel in patients with diabetes mellitus might result from the observed improvement in the endothelial function [64]. However, the comparison

between two new-generation P2Y12 inhibitors, ticagrelor, and prasugrel, results in more complex conclusions. Initial studies implicated, that diabetic patients with ACS undergoing PCI or with stable CAD, achieve greater inhibition of platelet reactivity after ticagrelor administration than with prasugrel [65-67].

10.2. Renal dysfunction

Earliest results from the PLATO trial showed that the efficacy of ticagrelor in ACS patients with creatinine clearance <60 ml/ min was greater than that of clopidogrel [68]. Ticagrelorsuc- successfully reduced the occurrence of cardiovascular death, myocardial infarction or stroke within 12 months of the treatment (17.3% vs. 22.0%). Interestingly, the absolute risk reduction was more pronounced in patients with chronic kidney disease than in individuals with normal renal function. Similar results were obtained in the PEGASUS-TIMI 54 trial [69]. While the relative reduction in major adverse cardiovascular events with ticagrelor was similar in patients with normal and impaired renal function (estimated glomerular filtration rate <60 ml/min/1.73 m2), the absolute risk reduction was greater in the latter group. This observation was explained by the fact that patients with decreased renal function were generally at a greater risk of cardiovascular death, myocardial infarction or stroke. They were also more prone to minor bleeding events (1.93% vs. 0.69%). Even though renal failure might have a negative influence on the long-term survival of patients with ACS, the platelet reactivity in this group of patients appears to be similar to the reactivity reported in patients with normal renal function [70]. Likewise, the benefits of ticagrelor over clopidogrel and prasugrel, such as faster onset and offset of antiplatelet effect and greater reduction of platelet reactivity are also reported in patients with chronic kidney disease [71,72].

10.3. Elevated body mass index (BMI)

Even though clopidogrel efficacy was strongly affected by patient's BMI and the response to the drug was often inadequate in these patients, current evidence shows that effectiveness of ticagrelor seems to be independent of patient's body weight [3,63]. However, a meta-analysis by Alexopoulos et al. [73] suggests that 5 unit increase of BMI results in a 4.1% increase of platelet reactivity during maintenance therapy with ticagrelor, while 10 unit gain causes a 7.9% increase.

### 10.4. Smoking

Smokers' paradox, demonstrated by greater inhibition of platelet aggregation in smokers, is a phenomenon mostly associated with clopidogrel treatment [74]. The most probable explanation for this phenomenon is the increased activity of CYP1A2 in smokers. Since ticagrelor is a direct-acting P2Y12 inhibitor, it is expected that smoking should not significantly affect its properties. It was confirmed in the PLATO trial that the reduction in the study's composite endpoint was similar in habitual smokers and non-smokers [75]. However, the overall risk of stent thrombosis was higher when the patient was a smoker. Contrary to these findings, results from the meta-analysis showed that smoking hurt platelet reactivity and therefore smokers could be at a higher risk of bleeding [73]. Nevertheless, the clinical significance of the impact of smoking on the platelet reactivity during antiplatelet treatment is debatable. In a study by Patti et al. [76], it was shown that the interaction between smoking and several oral antiplatelet drugs was significant but very moderate in magnitude.

## 11. CONCLUSIONS

The present review shows that ticagrelor is a promising therapeutic choice for patients with ACS and CAD, especially for those with a risk of resistance to old-generation P2Y12 inhibitors. According to the results of research, ticagrelor is a more predictable antiplatelet agent with a fast onset and offset of action. The resistance to the drug is rarely observed and the number of factors that might significantly affect its efficacy is limited. Moreover, the pleiotropic effects of ticagrelor make it an interesting therapeutic option for patients with diabetes mellitus and metabolic syndromes. The use of ticagrelor is associated with a risk of non- procedure-related bleeding and a frequent occurrence of dyspnea. However, the benefits from treatment with this drug seem to equilibrate the potentially negative impact.

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