USING OF DUAL ANTIPLATELET THERAPY IN POST PCI PATIENTS TO REDUCE CORONARY STENT THROMBOSIS: A REVIEW OF GENETIC TEST AND TEG

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ABSTRACT

Dual antiplatelet therapy with aspirin and clopidogrel is constantly given for the prevention of recurrent ischemic events. Despite well-documented efficacy, recurrent coronary thrombotic event occurrences, especially stent thrombosis, have been repeatedly demonstrated in stented patients treated with DAPT. Therefore, it is crucial to reliably identify patients with a high ischemic risk. Various laboratory methods are used to detect the effect of aspirin and clopidogrel administered. A lot of studies were conducted in order to suggest a better method, which could help identify these patients. Most researchers showed that low on-treatment platelet reactivity (LTPR), as estimated by few platelet function tests, and the carriage of CYP2C19*2 and CYP2C19*3 allele were independent risk factors for ischemia episodes. Few investigations identified thromboelastogram platelet mapping assay as an effective method to assess clopidogrel resistance in the setting of acute stent thrombosis. Numerous patient characteristics were also identified as independent predictors of ischemic, such as older age, diabetic mellitus, male sex and liver failure. This review discusses studies about genetic test and TEG analysis as useful tools to estimate the risk of stent thrombosis among post-PCI patients treated with DAPT.

Keywords: coronary thrombotic event, dual antiplatelet therapy, CYP2C19 genetic test, TEG analysis, stent thrombosis, percutaneous coronary intervention

INTRODUCTION

Percutaneous coronary intervention (PCI) with stent placement has become the standard of treatment for myocardial revascularization, especially in the setting of unstable coronary artery disease .[1]. Dual antiplatelet therapy (DAPT ;ie ,aspirin and clopidogrel) is necessitated to prevent stent thrombosis following coronary stent insertion .[2]. Interruption of DAPT is the essential etiology underlying stent thrombosis in the early months following coronary stent implantation .[3]. Given the serious clinical consequences of stent thrombosis, antiplatelet therapy following stenting has been the subject of intense clinical research over the last two decades.

The greater part of stent thrombosis happen in the first month and are defined as early stent thrombosis. It is a severe complication, with a mortality rate up to 40% and massive myocardial infarction in approximately 80% of survivors who remain exposed to frequent recurrence.[4, 5]. Lately much consideration has been focused on patient response to clopidogrel, with a strong affinity between high on-clopidogrel platelet reactivity and stent thrombosis despite rigorous adhesion to DAPT [6].

Clopidogrel is indeed a prodrug that converts to active metabolite through CY2C19 enzyme in the cytochrome P450 (CYP450) enzyme family in the liver. As a result of *CYP2C19* gene polymorphism, the transformation of clopidogrel to active metabolite reduces [7] P2Y12 receptors are found in the platelet layers and play a function in adenosine diphosphate (ADP)-induced platelet aggregation [8]. The goal of the active clopidogrel metabolite is the ADP platelet receptor P2Y12, therefore irreversibly inhibiting ADP linkage to platelets. As a result platelet activation and aggregation is inhibited [9].

Stent thrombosis: definitions and classification:

A modern description of stent thrombosis was recently proposed by an Academic Research Consortium (ARC) in order to make it possible to compare the true rates of stent thrombosis across different trials and registries [10] The ARC is composed of clinical investigators, industry representatives and regulators including the Food and Drug Administration, and the definition classify stent thrombosis according to the level of documentation and timing:

❖ Definite or confirmed event (symptoms suggestive of an acute coronary –syndrome and angiographic or pathologic confirmation of stent thrombosis) Probable event (unexplained death within 30 days or target vessel myocardial infarction without angiographic confirmation of stent thrombosis)

❖ Possible event (any unexplained death after 30 days) Based on the elapsed time since stent implantation stent thrombosis can be classified as:I)Early (0-30 days post stent implantation); II)Late (>30 days); III)Very late (>12 months);

Often,early stent thrombosis is further subdivided into acute (<24 hours) and subacute (1-30 days) events.

Clinical importance of DAPT in the prevention of Stent thrombosis:

DAPT is an essential component of stent thrombosis prevention. The efficacy of DAPT has been demonstrated in numerous randomized controlled trials (RCTs) by comparing DAPT with single antiplatelet or anticoagulation therapy [11, 12]. Most Bare metal stents(BMSs) are almost completely endothelialized after 1 month, and are completely endothelialized after 3 to 6 months [13, 14] but delayed and incomplete endothelialization is common even 6 to 12 months after Drug eluting stents(DES) implantation [15-17]. Thus, 6- to 12-month DAPT is recommended by major interventional societies, yet the recommendations are based generally on observational studies or expert opinions in the early period of DES. Subsequently, several medium-to-large sized RCTs have been performed to evaluate the optimal duration of DAPT after DES implantation.

CYP2C19 genetic testing as a method to determine the risk of stent thrombosis:

Hepatic bioactivation of clopidogrel is accomplished via a number of different CYP isoenzymes, essentially the *CYP2C19* isoenzyme.Current evidence suggests that there are 4 major variants of *CYP2C19* [18, 19].

Reaction to clopidogrel differ generally with nonresponse rates ranging from 4% to 30% at 24 hours[20]. Clopidogrel is a second-generation thienopyridine that can inhibit platelet aggregation, is a mainstay, along with aspirin, in the treatment of patients with coronary artery disease, with acute coronary syndromes (ACS), and/or after percutaneous coronary interventions (PCI) .[21]. However, a remarkable amount of patients remains at the threat for subsequent death, myocardial infarction (MI), stent thrombosis, and stroke because of inadequate clopidogrel-induced platelet inhibition. The active metabolite of clopidogrel irreversibly inhibits the platelet ADP receptor, P2Y12. A number of diverse alleles of CYP2C19 have been distinguished; depending on the allele display, research facility showings of the enzymatic action of CYP2C19 can be ordinary, diminished, or expanded [22-24]. The *1 ("star 1") allele is the ordinary or normal copy that has full enzymatic activity. The *2 ("star 2") and *3 ("star 3") alleles are the most common variants and result in complete loss of enzymatic activity. [22]. Consequently, carriers of the *2 and *3 alleles have reduced formation of clopidogrel's active metabolite and show reduced clopidogrel-induced platelet inhibition[25, 26] The prevalence of the *2 and *3 alleles vary by ethnicity. In Caucasians, Blacks, and Asians, the proportion of patients who carry at least one copy of *2 is 25%, 30%, and 40-50% respectively, while the proportion for *3 is < 1%, < 1%, and 7%, respectively. Additional variants, *4 and *5, also result in no enzymatic activity, but these variants are rare in all ethnicities (< 1%) and their effect on laboratory outcomes has not been fully documented. Finally, the variant *17 is present in nearly 40% of Caucasians, Blacks, and Asians, and results in *increased* CYP2C19 activity, higher production of active metabolite, and improved clopidogrel-induced platelet inhibition.[24, 27]
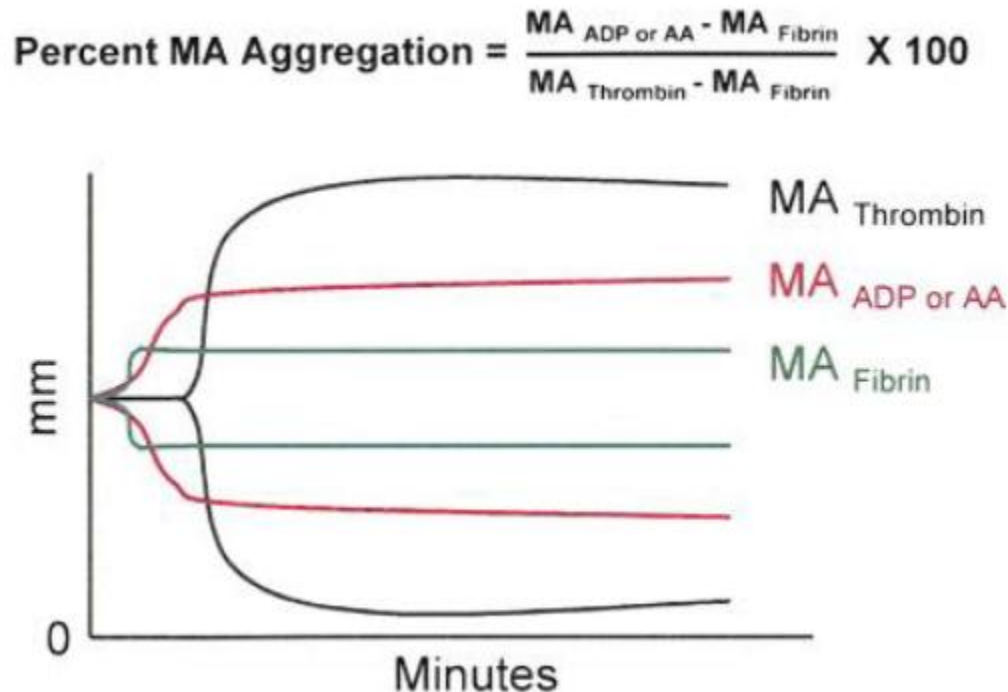
The CYP2C19 loss-of-function (LOF) alleles (*2 and *3 alleles) result in less formation of functional thiol metabolite, causing absence of platelet aggregation inhibition, which restate into a higher rate of rate

cardiovascular incidents than noncarriers.[28].

TEG analysis as method to evaluate stent thrombosis:

Thromboelastogram (TEG) is characterized as an index that can comprehensively reflect dynamic changes of blood coagulation [29]. The detection of TEG could help to understand the whole process of the fibrin formation and dissolution in blood sample, which makes the analysis of platelet aggregation, fibrin cross connection and the blood clot dissolution process possible [29]. Usually, the maximum amplitude (MA) of the TEG expressing the clot strength has been used to distinguish the result of antiplatelet therapy. Previous studies have shown that TEG MA is a predictive parameter for ischemic episodes after PCI in patients on antiplatelet agents [30, 31].

A standard empirical definition has been mostly used in different studies, in which the aspirin and clopidogrel, as well as platelet aggregation rate were determined using TEG method, when AA-induced platelet inhibition rate is less than or equal to 50% [32] For aspirin resistance, ADP-induced platelet inhibition rate is <30% in clopidogrel or ticagrelor resistance [32] TEG can precisely show the coagulation status and platelet aggregation in advanced fram, direct the clinical treatment and give early caution for ischemic episodes [29] several studies illustrated that high thrombin-induced platelet-fibrin clot strength (MATHROMBIN) measured by TEG and high LTAADP were risk factors for 6-month post-PCI ischemic events. In that study MATHROMBIN was a better risk discriminator[30].

$$\text{Percent MA Aggregation} = \frac{MA_{\text{ADP or AA}} - MA_{\text{Fibrin}}}{MA_{\text{Thrombin}} - MA_{\text{Fibrin}}} \times 100$$

Thrombelastograh plateletMapping Analysis parameters

MAThrombin= measure of maximum thrombin-induced platelet-fibrin clot strength;

MAFibrin= contribution of fibrin to clot strength; MAADP or AA = represents clot strength after adenosine diphosphate (ADP) or arachidonic acid (AA) stimulation.

DISCUSSION

The existence of a high level of individual variability in platelet responsiveness to antiplatelet therapy and on-treatment platelet reactivity have been confirmed in the majority of clinical studies examining antiplatelet therapy efficacy in PCI patients.[33] John Morton showed that usage of a TEG Platelet Mapping assay diagnosed clopidogrel resistance in the setting of acute stent thrombosis.[34] Gurbel PA's study was the first to show the demonstration of the prognostic usefulness of MA(ADP) in predicting long-term event occurrence after stenting. The quantitative appraisal of ADP-stimulated platelet-fibrin clot quality measured by thrombelastography could serve as a future device in examinations of individualized antiplatelet treatment outlined to diminish ischemic episodes and bleeding, according to Gurbel PA's study TEG measures secondary aggregation, though all other point-of-care tests measure primary aggregation, overlooking the contribution of fibrin and platelet contractility in the method. This may clarify the expanded capacity of the TEG to risk stratify. An appraisal of platelet-fibrin interactions by TEG, particularly by estimation of MAADP, may facilitate future research of personalized antiplatelet treatment outlined to decrease post-stenting ischemic events, manage bleeding risk, and determine appropriate cessation of therapy [31]. Xu L's study shows that antiplatelet treatment guided by TEG checked platelet profile could not improve clinical efficacy in coronary artery disease patients treated with high-risk complex PCI.[35]. The results of the PREPARE POST-STENTING study[30],also indicated that increased ADP-induced aggregation measured by TEG in patients with ischaemic events, compared with patients without events. Furthermore, Gurbel *et al* reported that MAADP>47 mm had the best predictive value of long-term ischemic events compared with other measurements. Each of these studies supported the important role of modified TEG in optimising antiplatelet treatment and reducing adverse events.[31] One study identified TEG as a fast, good strategy for assessing the time-dependent impacts of antiplatelet therapy on clotting utilizing a novel parameter of area of the TEG trace, which could have a substantial clinical application as a point of care test of viability, especially in the setting of acute coronary syndrome and percutaneous coronary intervention.[36]. To summarize the majority of these studies identified TEG analysis as an important method to evaluate the risk of ischemic events among post-PCI patients, however still further investigations are needed to choose TEG analysis as a predictive tool to evaluate the risk of stent thrombosis.

Some studies reported that carriage of the CYP2C19*2 allele is associated with an impaired pharmacodynamic reaction to nonidentical dosing regimens of clopidogrel, as determined with various platelet function assays[18, 37].Shen DL's investigation displayed the personal antiplatelet treatment supervised by CYP2C19 gene test significantly diminished the rate of major adverse cardiovascular events (MACE) without an increase in the rate of bleeding in the near term in the Chinese population[38]. Ankie M.et al. determined the impact of genetic variations related to the pharmacokinetics and pharmacodynamics of

clopidogrel on the occurrence of stent thrombosis in patients who were on clopidogrel and aspirin medications at the time of the event. ,their research found that carriers of the CYP2C19*2 and CYP2C9*3 loss-of-function alleles were at a 1.7- and 2.4-fold amplify risk of developing stent thrombosis, respectively; they also noticed that The influence of these genetic variants was most profound on the risk of subacute stent thrombosis; they did not observed a significant associations between the other investigated genetic variants and the occurrence of stent thrombosis, finally their research shows that the carriage of the loss-of-function alleles CYP2C19*2 and CYP2C9*3 increases the risk on stent thrombosis, the suggests Personalized therapy targeting patients who carry these genetic variants might help to improve the clinical outcome after coronary stent insertion[39]. Mega *et al.* investigated The affiliation between CYP2C19 genetic variants and stent thrombosis, they reported no associations of CYP2C19*3 and stent thrombosis. Dahabreh IJ and colleagues, found prove to affirm an association between loss-of-function CYP2C19 variations and expanded risk of adverse cardiovascular outcomes; they also found prove that high on-clopidogrel platelet reactivity is related to an increased risk of adverse cardiovascular outcomes, at least for some of the available assays. They noticed the strong evidence regarding these prognostic impacts was judged to be poor or diminish considering the matter toward selective outcome reporting and publication bias, and moreover the generally little number of studies reporting data on most clinical results. also The quality of prove regarding the application of gene test or platelet reactivity test to direct antiplatelet therapy choice was judged to be inadequate because investigations reporting on clinical effects were few, had different plans, and included heterogeneous populations. Comparative information on alternative test (genetic versus phenotypic) was missing[40]. To summarize most of these investigations have supported the hypothesis that CYP2C19 genetic test can be use as a better tool to evaluate the risk of coronary in-stent thrombosis among patients on DAPT medications, others researchers supported the Personalized dual antiplatelet therapy targeting patients who carry CYP2C19*2 and CYP2C9*3 genetic variants might help by providing a favorable clinical outcome after coronary stent insertion, also these studies have not demonstrated the accuracy of CYP2C19 genetic variants as a platelet function testing.

Conclusions and future directions:

The reactivity of platelets to agonists plays a central task in the genesis of post PCI thrombosis, DAPT has significantly reduced the occurrence of thrombotic events after PCI, including myocardial infarction and stent thrombosis. It is logical to investigate patients platelet aggregation response which could help in predicting stent thrombosis on post PCI patients. This review summarizes the use of TEG and CYP2C19 as useful method to evaluate the risk of stent thrombosis on post PCI patients on DAPT and suggests that the usage of TEG to guide antiplatelet medication can significantly reduce the incidence of ischemic events after PCI, also that antiplatelet treatment guided by TEG monitored platelet function could not improve clinical efficacy by predicting the patients at risk of stent thrombosis. The current review indicate that CYP2C19 genetic test in coronary stent thrombosis yield enormous potential to serve as a better clinical tool to predict

post PCI thombotic events, which has high application value for clinical treatment.

Thus, in future still needs further study to know and obtain knowledge about the accuracy of CYP2C19 gene test as a better predictive tool to identify the patients at risk of coronary stent thrombosis, new multi-center human studies with larger sample size, and longer follow-up times are needed to further identification of the better tool for post-PCI patients using DAPT, which will hopefully lead to further optimization of predicting the events of in coronary stents thrombus.

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