Clopidogrel in ischemic heart disease: A critical appraisal

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ABSTRACT

Aspirin and clopidogrel are the commonest dual antiplatelet agents being used in the secondary prevention of cardiovascular disease. In high risk patients with coronary heart disease, the use of aspirin was associated with a significant risk reduction of myocardial infarction, stroke and vascular death. The use of clopidogrel alone was slightly superior to aspirin, and associated with reduced risk of vascular death, ischemic stroke and myocardial infarction. Dual antiplatelet therapy has been well studied in patients with acute coronary syndrome and those undergoing percutaneous coronary intervention (PCI). In patients with stable coronary heart disease or multiple risk factors the combination of clopidogrel plus aspirin was not significantly more effective than aspirin alone in reducing MI, stroke or death from cardiovascular causes.

Keywords: Clopidogrel; Ischemic Heart Disease; Thienopyridine; Platelets Inhibition

1. INTRODUCTION

Clopidogrel, a potent antiplatelet agent is a thienopyridine agent inhibits platelet function by the irreversible modification of the P2Y12 adenosine diphosphate (ADP) receptor [1].

It has been a decade since clopidogrel approved for the treatment of ischemic heart disease (IHD), particularly non ST-elevation acute coronary syndrome since 2001 [2]. During this 12 year period, plenty of trials conducted to examine the role of this agent at different stages and in different presentations of ischemic heart disease.

This review will look with a criticizing eye to examine benefits of clopidogrel as a medical treatment of ischemic heart disease.

2. IN PATIENTS AT RISK OF ISCHEMIC EVENTS

CAPRIE was the first trial to compare this drug to ASA (325 mg) in reducing events in these patients. The primary end point of this trial was based on the incidence of the first occurrence of ischemic stroke, myocardial infarction, or vascular death, but the inclusion criteria insisted on stroke, MI or peripheral arterial disease. This fact makes the primary end point of the trial actually as the incidence of re-stroke and re myocardial infarction. If further analyzed, it shows that only these with peripheral arterial disease benefited as clearly if these patients were not included, the weak positivity of CAPRIE Trial would have not been shown. The incidence of the first stroke or MI is not tested by CAPRIE trial. It is important to remember that event rate of vascular death per year was the same in Clopidogrel and ASA group and was roughly around 2%. To translate the results of CA-PRIE into clinical practice, you need to treat one thousand patients for one year with Clopidogrel to prevent five extra nonfatal events more than aspirin [3].

CHARISMA study enrolled stable patient population with either established other thrombotic disease or multiple risk factors for atherothrombotic events. The result of this trial showed a non-significant difference in the primary end point of CV death, MI, or stroke over a median of 26 months between dual anti platelets versus aspirin alone. Further analysis of this study showed that with stable cardiovascular disease without documented thrombotic event which constituted around 25% of the study population, did not drive any benefit (rate was 5.5 for ASA and 4.7% for dual therapy P = 0. 38) [4]. Even the attempt of Bhatt D, *et al.*, to study the CAPRIE like Cohort, *i.e.* those patients with documented stroke, MI, or peripheral artery disease showed that primary end point which included both same primary end point of CA-PRIE trail added to the primary safety end point which was defined as severe bleeding as per GUSTO trial criteria, was just significant (P = 0.051) in favor of dual antiplatelet over ASA only after excluding moderate bleeding which was significantly high in dual antiplatelet arm [5].

3. ST-ELEVATION MYOCARDIAL INFARCTION

CLARITY-TIMI 28 included 3491 ST Elevation MI

patients who presented within 12 hours. These patients were randomized to either clopidogrel or placebo. The placebo arm received ASA, thrombolytic therapy and heparin. High risk patients, age more than 75 years, previous CABG, Cardiogenic shock, and any planned Coronary angiogram within 48 hours were excluded.

The primary end point of the study was the composite of occluded artery (TIMI 0 - 1), death before angiography, or recurrent MI before angiography. Those who had no angiography, the time were day 8 or discharge whichever came first. The primary end point happened in 21.7% of the placebo compared to 15% of clopidogrel with absolute risk reduction of 6.7%. This benefit is only due to the reduction of occluded artery. In fact death was higher in clopidogrel group but did not reach clinical significance [6].

The other trial which studied clopidogrel in ST-Elevation MI was COMMIT Trial [7]. The following are important facts challenging the result of this trial. Firstly, it was co-funded by the manufacturer of clopidogrel and done in China. Secondly, low rate of revascularization where only 54% received thrombolytic mainly urokinase and only 3% had elective PCI. Thirdly, the primary end point was 9.2% vs. 10.1% with an absolute risk reduction of less than one. The fact that P value was significant is easily explained by the huge number of participants > 45,000. Fourthly, the claim of survival benefit of clopidogrel in this trial is easily challenged by the fact that the absolute reduction in death was only 0.4 and by the fact that for elderly patients who received loading dose of clopidogrel, no safety data available [7]. Lastly, the mortality rate of clopidogrel in this trial was 7.7%, which is higher than the old thrombolytic therapy trials done decades ago.

4. UNSTABLE ANGINA/NON-ST ELEVATION MYOCARDIAL INFARCTION

CURE trial enrolled 12,562 patients within 24 hrs of symptoms to either combination of clopidogrel and ASA or aspirin alone [8]. The median follow up period was 9 months, it is important to remember that those who received IIb/IIIa inhibitors in the previous 3 days were excluded.

It is also important to know that the inclusion criteria have changed after the initial 3000 patients and this could have led to over estimation of benefits in low risk patients [9].

The primary end point of death/nonfatal MI and stroke occurred in 9.3% in clopidogrel group as compared to 11.4% in the placebo group with 2.1% absolute reduction. This 2.1% difference reached statistical significance because of exceptionally large study size which has been

changed from 9000 to more than 12,000 patients. Yet this was largely due to 1.5% absolute reduction in myocardial infarction. The individual end points of death/MI showed no significant reduction. In fact even the combination of death and stroke showed no significance. It should be documented that CURE used a strange definition of myocardial infarction which included even patients with only elevated troponins.

The most concerning complication in CURE trial was major bleeding which was significantly higher by an absolute risk of 1% in clopidogrel group. Almost 50% of major bleeds were defined as life threatening [10,11]. The minor bleeds were also higher in clopidogrel significantly, importantly the definition of minor bleeding has been revised many times during the study with changing incidence of 15.3% when study initially presented to 5.1% in the final manuscript. This certainly makes clopidogrel looks safer than it really is.

PCI-CURE is a pre-specified sub study of the original CURE which tested the hypothesis whether pretreatment with a loading dose of clopidogrel followed by long term therapy after PCI is superior to strategy of no pretreatment and short term therapy for only 4 weeks after PCI [12].

A total of 2658 patients of the cure trial population presenting with ACS and need for PCI were pre-treated with ASA and clopidogrel or placebo for a median of 6 days after enrollment. After PCI, 911 patients received an open-label thienopyridine (clopidogrel or ticlopidine) in combination with ASA for 2 - 4 weeks. Thereafter, study medication (clopidogrel or placebo) was restarted and continued for a mean of 8 months. The primary end point was the composite of CV death, MI, or urgent target vessel revascularization (TVR) within 30 days of PCI. The primary end point occurred in 4.5% in clopidogrel versus 6.4% in placebo. This was due to reduction of MI. In fact there was one extra death in clopidogrel group. It is important to remember that PCI-CURE is rather an observations study within the main CURE, and that the median time to PCI was 10 days. The CURE and PCI-CURE rather favor a conservative approach to ACS which contradicts the results of multiple large scale trials.

To translate the results of CURE into numbers if clopidogrel is given to one thousand patients with ACS, it will prevent 15 MI but 10 additional patients will develop major bleeding, 69 additional patients have minor bleeding and 200 patients will have surgical intervention complicating clopidogrel use. These bleeding complications occurred, in addition to the fact that those 978 patients taking clopidogrel received no significant benefit from these drugs and all of these occur without saving one life [11].

CREDO was designed to evaluate: The benefit of long

term treatment (12 months) with clopidogrel after PCI and to test safety and efficiency of 300 mg loading dose. In spite of the fact that 52.8% of the Credo trial population presented with unstable angina, the 28 day end points of death, MI, and target lesion revascularization was not significantly reduced by the drug, even in those who received the loading dose 12 - 24 hours before PCI [13]. At one year, the incidence of primary end point of death, MI, and stroke was significantly reduced in the group having continuously received clopidogrel up to one year. The absolute risk reduction was only 3%. Due to the fact that patients were not re-randomized after 28 days of therapy, it is not completely possible to separate treatment benefit of long term from that of pretreatment. The treatment effect from day 29 till the end of follow-up was not a pre specified analysis.

5. THE ISSUE OF HYPO-RESPONSIVENESS OF CLOPIDOGREL

The hypo-responsiveness to CYP450 genetic polymorphism in the activation of clopidogrel prodrug is well documented. This may leads to 30% incidence of poor metabolizers [14]. It has been suggested by multiple studies that usage of clopidogrel in those poor metabolizers with ACS is associated with increased cardiovascular events [15-17]. No firm data is currently available on benefit of genotyping.

6. THE ISSUE OF BLEEDING WITH CLOPIDOGREL

Data from cure, match, and charisma studies provide confirmatory evidence that combined Aspirin and clopidogrel therapy is associated with significantly increased incidence of upper gastrointestinal tract (GIT) bleeding when compared to either drug alone [18,19]. In fact in a hospital base care control study of 2777 patients with major upper GIT bleeding, it was found that clopidogrel had a similar risk of upper GIT bleeding to a 100 mg of aspirin [20]. Few studies support ASA cotherapy with once daily PPI rather than clopidogrel alone to reduce risk of upper GIT bleeding [21].

7. CONCLUSION

It is clear from this review that clopidogrel is yet to prove itself as a lifesaving drug. If used in genetically poor metabolizer it might increase mortality. The risk of bleeding is increased with its usage.

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