Comparison between the Incidence of Coronary No-Reflow in Patients with Acute ST-Elevation Myocardial Infarction Receiving Ticagrelor versus Clopidogrel Loading Doses

Thesis

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Dedication

Words can never express my sincere thanks to ***My Family and My Wife*** *for their generous emotional support and continuous encouragement; which brought the best out of me. I owe them all every achievement throughout my life.*

I would like to express my everlasting gratitude to all ***My Professors; Colleagues and Friends;*** *so many of them influenced; encouraged and inspired me throughout the years. I wish them the best of all.*

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List of Contents

List of Tables

List of Figures

List of Abbreviations

Abb.	Full term

ACC.....*American college of cardiology*
ACS.....*Acute coronary syndrome*
ADP.....*Adenosine diphosphate*
AHA.....*American heart association*
ARBs.....*Angiotensin receptor blockers*
ATP.....*Adenosine triphosphate*
AUC.....*Area under the curve*
BMS.....*Bare-metal stents*
CABG.....*Coronary artery bypass graft*
CAD.....*Coronary artery diseases*
CBC.....*Complete blood count*
CCB.....*Calcium-channel blocker*
CFR.....*Coronary flow reserve*
CHF.....*Congestive heart failure*
CI.....*Confidence interval*
CK.....*Creatine Kinase*
CNR.....*Coronary artery no-reflow*
CV.....*Cardiovascular*
CYP3A.....*Cytochrome P3A*
CYP450.....*Cytochrome P450*
DAPT.....*Dual anti-platelet therapy*
DES.....*Drug-eluting stents*
ECG.....*12-lead surface electrocardiography*
EF.....*Ejection Fraction*
EMS.....*Emergency medical services*
ENT-1.....*Equilibrative nucleoside transporter 1*
FFR.....*Fractional flow reserve*
GLP-1.....*Glucagon-like peptide 1*
GP.....*Glycoprotein*

List of Abbreviations (Cont...)

Abb.	Full term

HDL-C .....High density lipoprotein cholesterol
HR.....Hazard ratio
HS.....Highly significant
IABP .....Intra-aortic balloon pump
IHD .....Ischemic heart disease
IMR.....Index of microvascular resistance
IRA.....Infarct-related artery
IVUS .....Intravascular ultrasound
LAD.....Left anterior descending artery
LBBB .....Left bundle branch block
LCX.....Left circumflex artery
LDL-C.....Low density lipoprotein cholesterol
LGE.....Late Gadolinium enhancement
LV .....Left ventricular
LVEF .....Left ventricular ejection fraction
MACE .....Major adverse cardiac event
MBG.....Myocardial blush grade
MI.....Myocardial Infarction
MMP-9.....Matrix metalloproteinase 9
MRI.....Magnetic resonance imaging
MVO.....Microvascular obstruction
NADPH……..Nicotinamide adenine dinucleotide phosphate hydrogen
NOX-2.....NADPH oxidase 2
NS.....Non-significant
NSTE-ACS .....Non ST elevation acute coronary syndrome
NSTEMI .....Non ST elevation myocardial infarction
OM .....Obtuse marginal branch
PCI.....Percutaneous coronary intervention

List of Abbreviations (Cont...)

Abb.	Full term
PET	*Positron emission tomography*
PTCA	*Percutaneous trans-luminal coronary angioplasty*
RBCs	*Red blood cells*
RCA	*Right coronary artery*
RV	*Right ventricle*
S	*Significant*
SCAD	*Stable coronary artery disease*
SCAI	*Society for cardiovascular angiography and interventions*
SCUBE-1	*Signal peptide-CUB (complement C1r/C1s)-EGF-like domain-containing protein 1*
SD	*Standard deviation*
SPECT	*Single photon emission computed tomography*
SPSS	*Statistical program for social science*
STEMI	*ST segment elevation myocardial infarction*
SVG	*Saphenous vein graft*
SWMA	*Segmental wall motion abnormality*
TIMI	*Thrombolysis in Myocardial Infarction*
TTG	*Thrombolysis in myocardial infarction thrombus grade*

Abstract

The primary endpoint of no reflow occurred in 17 (34%) patients in the clopidogrel group versus 12 (24%) patients in the ticagrelor group. This difference was not statistically significant.

The main findings in our study are the following:

- There was no significant difference between the 2 groups in terms of epicardial coronary flow defined by TIMI flow.
- There was no significant difference between the 2 groups in terms of myocardial perfusion defined by MBG.
- There was no significant difference between the 2 groups as regards the primary endpoint of CNR defined as a TIMI flow<3 and/or an MBG of 0-1.
- There was no significant difference between the 2 groups in terms of short term clinical outcomes of death, non-fatal MI, myocardial contractility, repeat revascularization and stroke.

Our study concluded that the incidence of no reflow does not seem to be affected by the type of P2Y12 inhibitor loading received in the setting of STEMI. Further large-scale multi-center studies are required to prove or disprove the current evidence on the superiority of ticagrelor over clopidogrel in STEMI patients.

Keywords: Hazard ratio - Stable coronary artery disease - Right coronary artery

INTRODUCTION

Atherosclerotic coronary artery disease (CAD) has become a major cause of death worldwide ***(Schunemann et al., 2008).*** Epidemiological studies suggest that morbidity and mortality from CAD are rising, especially in young adults ***(Ford and Capewell, 2007).***

At percutaneous coronary intervention (PCI) - capable hospitals, PCI is the preferred reperfusion strategy for ST segment elevation myocardial infarction (STEMI), because it offers prompt and complete recanalization of an occluded infarct-related artery (IRA). However, in spite of successfully restored (Thrombolysis in Myocardial Infarction [TIMI] grade 3) epicardial blood flow, myocardial reperfusion is not regained in some patients. This phenomenon is referred to as coronary no reflow (CNR). Its incidence is high, about 32% ***(Rezkalla et al., 2017).*** Such patients with CNR have higher incidence of resting segmental wall motion abnormalities (SWMA), myocardial free wall rupture, and death ***(Morishima et al., 1995).***

No definite etiology of CNR is known. Mostly, it's multifactorial. Possible mechanisms are endothelial dysfunction, micro-vascular arteriolar spasm and distal embolization of thrombus fragments ***(Kloner et al., 1974 and Bouleti et al., 2015).***

Platelets have a significant role during occlusion and reperfusion periods of myocardial infarction. Also, they contribute to micro-vascular obstruction, maintenance of vessel patency and tissue perfusion ***(Davi and Patrono, 2007).*** This may explain the role of anti-platelets in the prevention and treatment of no reflow. In ***2010, Niccoli and his colleagues*** showed the benefit of chronic aspirin administration, in patients presented with their first acute myocardial infarction (MI), to reduce angiographic thrombus grade.

By relieving thrombus burden and minimizing distal embolization, Glycoprotein IIb/IIIa inhibitors improve microcirculation ***(Gibson et al., 2001 and Deibele et al., 2010).*** P2Y12 inhibitors, having antiplatelet effect, may prevent CNR as well. Clopidogrel loading dose of 600 mg decreased the incidence of angiographic CNR in acute MI patients, more than 300 mg did ***(Mangiacapra et al., 2010).*** But, there is little evidence about the benefit of loading doses of the more potent P2Y12 inhibitors, ticagrelor and prasugrel in comparison to clopidogrel.

AIM OF THE WORK

So, the aim of this work was to compare the effect of 180 mg ticagrelor versus 600 mg clopidogrel loading doses, on the incidence of no-reflow in acute ST segment elevation myocardial infarction (STEMI) patients.

Chapter 1
S-T Segment Elevation Myocardial Infarction (STEMI)

Ischemic heart disease (IHD) is the most common cause of mortality worldwide and its frequency is rising, accounting for 20% of all deaths in Europe ***(Townsend et al., 2016).*** Acute myocardial infarction (MI) is the term used when there is evidence of myocardial injury (defined as elevated cardiac troponins with at least one value more than 99th percentile upper reference limit), with clinical manifestations of myocardial ischemia ***(Thygesen et al., 2012).***

For the sake of reperfusion therapy, patients with persistent chest pain or other symptoms suggestive of ischemia, with ST-segment elevation, at least in 2 contiguous leads, are diagnosed as ST-segment elevation MI (STEMI). Meanwhile, patients without ST-segment elevation are considered to have non-ST-segment elevation MI (NSTEMI) ***(Roffi et al., 2016).***

Epidemiology of ST-segment elevation myocardial infarction

The incidence of STEMI is decreasing and NSTEMI is relatively increasing. It seems that STEMI is more common in younger than older people and in males than females ***(McManus et al., 2011).*** Mortality in STEMI patients is affected by many factors, including advanced age, history of