Myth or Real? The Potential Serious Side Effects of Ticagrelor

Wassam EL Din Hadad EL Shafey*

Cardiology Department, Menoufia University, Egypt

*** Corresponding author:** Wassam EL Din Hadad EL Shafey, Faculty of Medicine, Cardiology Department, Menoufia University, St Al Amin, Al Hayaa Pharmacy, Egypt, Tel: +201006420955; E-mail: dr_wesamhadad@yahoo.com

Abstract

Ticagrelor, a novel direct, reversibly binding P2Y12 antagonist, has better pharmacodynamics effects and improves clinical outcomes compared with clopidogrel in the setting of acute coronary syndromes (ACS). However, ticagrelor-related dyspnea and bradyarrhythmias have been observed in the PLATO trial, here in my case I will present a case of ticagrelor side effects and how it may burden the course of hospital stay.

Keywords: Ticagrelor, Side effects, ACS

Learning Objectives

Ticagrelor as a novel antiplatelet should be used in its on label use only as it may has some serious side effects that may add health and cost burdens.

Introduction

Ticagrelor is a novel, potent, direct-acting and reversible P2Y12-adenosine diphosphate (ADP) receptor blocker with rapid onset of action and intense, consistent platelet reactivity inhibition that has demonstrated higher biological efficacy superior to clopidogrel in decreasing major adverse cardiac events than clopidogrel.[1,2]

In the landmark PLATO trial ticagrelor was linked to increased incidence of ventricular pauses which were predominantly asymptomatic.[3] Here I report a case of ticagrelor-associated bradyarrhythmias, complete atrioventricular block and atrial fibrillation (AF) in a patient with ACS which necessitated resuscitation and insertion of temporary pacemaker.

Case Presentation

Male patient 59 years old, chronic heavy smoker, Insulin dependent diabetes militias, dyslipidaemic, hypertensive and ischemic heart disease with previous CABG 5 years ago, presented with typical chest pain, positive cardiac markers and ST segment depression, coronary angiography was done and revealed total occlusion of native LAD, OM and distal RCA, patent LIMA graft and venous grafts to both OM and PDA. While RCA proper showed high thrombus burden along its course, I decided to put the patient on GPIIb,IIIa infusion for 48 hours and redo control angiography ,loading dose of ticagrelor 180 mg was given and maintained doses 90 mg twice daily , patient was kept with no symptoms till the 3rd day where he developed chest pain again, I decided to do re-angiography where I find distal occlusion of large PL branch which was patent before

while RCA proper was cleared from thrombus , so I decided to do PCI to PL and distal RCA with 2 DES with good angiographic results (Figures 1a, 1b, 1c, 1d, 1e).

Chest pain was decreased dramatically after PCI, but in the first 24 h post PCI patient developed sinus bradycardia, he was on low dose bisoprolol 2.5mg which was stopped , along the patient CCU stay course he experienced different degrees of AV nodal block and finally degenerated into AF with slow ventricular rate (Figure 2).

Temporary Pacemaker was inserted on demand mode and elective DC shocks to revert sinus rhythm were applied then IV loading and maintaining doses of amiodarone were given in a trial to maintain sinus rhythm. Before this dysrhythmia time course patient developed remarkable dyspnea of unexplained cause as bed side echocardiographic study showed good ventricular function and chest X ray also where clear. Really it was the first time for me to use ticagrelor in daily practice and as if follow up cardiac markers were decreasing and improving and also chest pain totally vanished so I did not find any explanation for these serious side effects except they may be because of ticagrelor, so I started to switch the patient into clopidogrel and maintain follow up for more 2 days in the hospital, on the 3rd day before discharge sinus rhythm totally stabilized and dyspnea cleared totally and patient discharged home.

Discussion

In the recent ESC guidelines for the management of acute coronary syndromes in patients presenting with high risk non St segment elevation acute coronary syndrome (NSTE-ACS), with positive cardiac markers and also previous bypass surgery (CABG), I found it is wise able to start ticagrelor in my case as the optimal second antiplatelet superior to clopidogrel in addition to aspirin as in such cases the primary composite efficacy endpoint (death from CV causes, MI or stroke) was significantly reduced with ticagrelor compared with clopidogrel with similar reductions for CV death and all-cause mortality.[4]

Although the increased incidence of ventricular pauses associated with ticagrelor treatment has been previously reported, it is generally believed to be of no clinical importance.[3] Here I report a patient who developed severe symptomatic bradycardia with complete atrioventricular block and atrial fibrillation after receiving a recommended loading dose of ticagrelor. The patient was unresponsive to medical treatment and required invasive temporary pacing.

In a case like that of Ünlü et al.[5] they also experienced persistent atrioventricular block which necessitated to insert permanent pacemaker in a patient presented with ACS and stent revascularization in circumflex coronary artery, while in my case it was only temporary pacemaker then after, the patient resolved after stopping and switching to clopidogrel.

My patient was on chronic beta-blocker therapy that could potentiate the influence of ticagrelor on cardiac conduction; although none of these is considered contraindication to ticagrelor therapy. Also, many patients with acute coronary syndrome receive beta blockers and conduction disturbances are not rare in this population. The mechanism of bradyarrhythmic effect of ticagrelor is poorly understood.[3] One possibility is a direct effect of ticagrelor on cardiac automaticity and conduction. The other one implicates an adenosine mediated effect. Ticagrelor inhibits cellular uptake and increases plasma concentration of adenosine,[6] which has a potent atrioventricular blocking effect. As such, adenosine is widely used as a diagnostic and therapeutic agent (e.g., in patients with supraventricular tachycardia).Therefore, increase in adenosine levels in patient treated with ticagrelor could be a plausible explanation for its effect on cardiac conduction.

Finally the brady arrhythmic effects of ticagrelor can have important (although rare) clinical consequences. I would advise caution and careful observation of patients after initiating of ticagrelor therapy, especially in patients with already compromised conduction system or treated with medications with atrioventricular blocking properties.

Conflict of Interest

No

References

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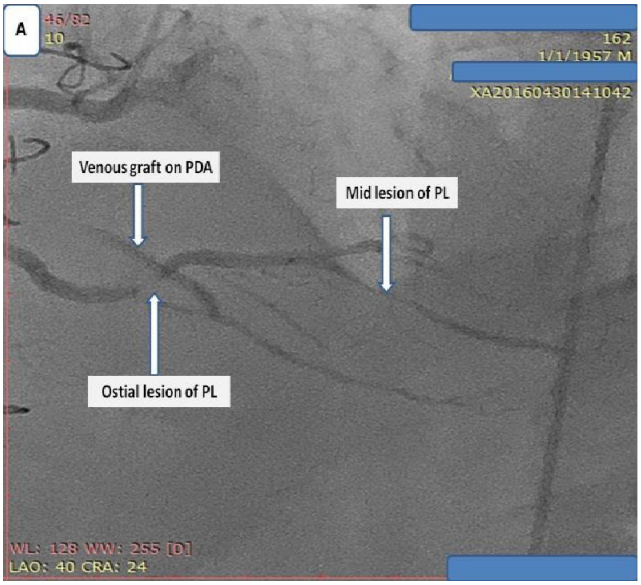

Figure 1a: Coronary angiography of RCA shows occlusion of distal RCA and mid PL branch, patent venous graft to PDA.

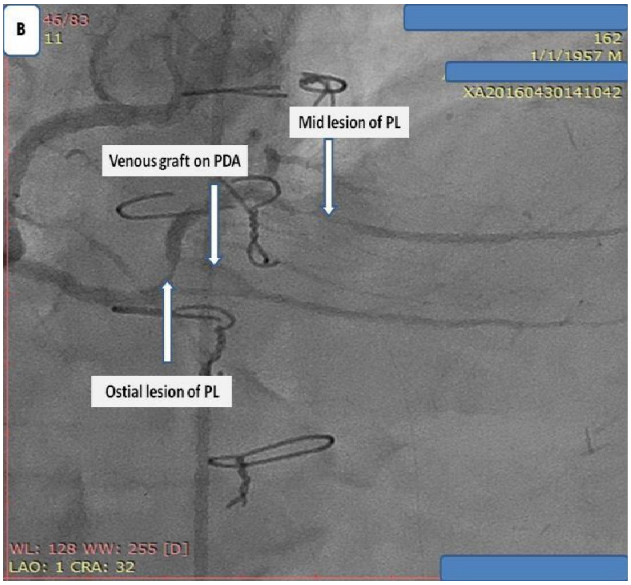

Figure 1b: Coronary angiography of RCA shows occlusion of distal RCA and mid PL branch, patent venous graft to PDA.

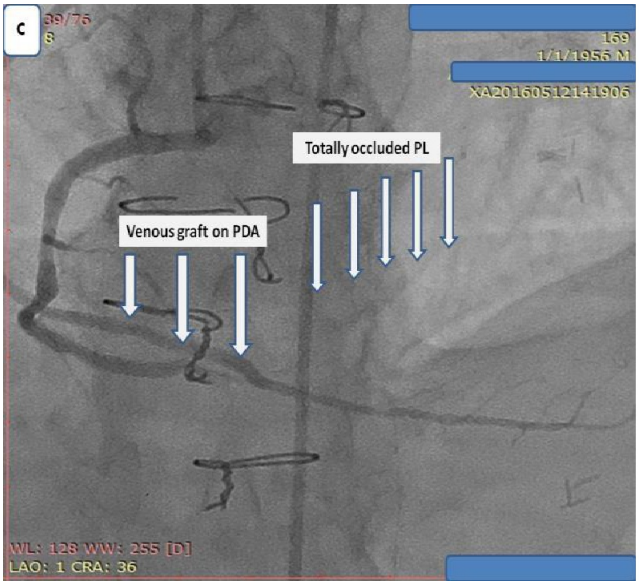

Figure 1c: Total occlusion of PL branch.

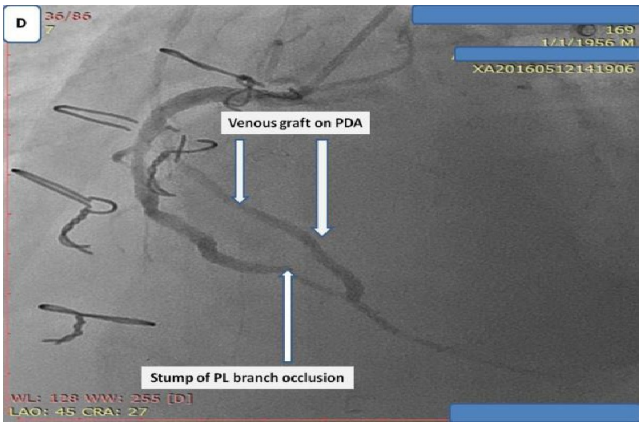

Figure 1d: Total occlusion of PL branch.

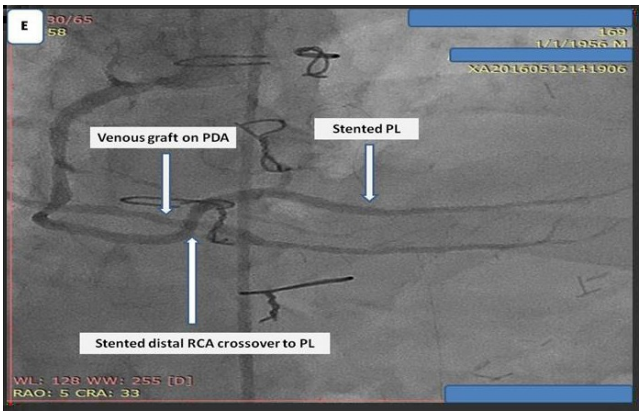

Figure 1e: 2DES in distal RCA crossover with PL stents with good distal runoff.

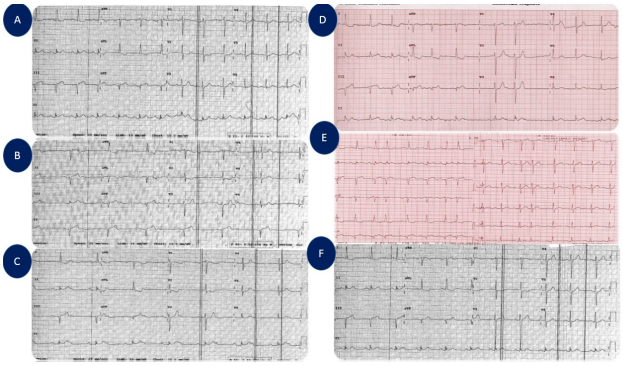

Figure 2: ECG follow-up A: sinus rhythm with ST segment depression. B: 2:1 AV nodal block. C: Complete heart block. D: AF with slow ventricular rate. E: AF with rapid ventricular rate. F: reverted sinus rhythm.