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Research Paper

Cangrelor in STEMI as a bridge to CABG- a mini-case series[☆]

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ABSTRACT

Background: Patients with STEMI receive dual antiplatelet therapy as soon as possible with aspirin and a P2Y₁₂ receptor antagonist prior to PCI. A fraction of these patients may have multi-vessel disease needing emergent CABG surgery. The choice of a P2Y₁₂ receptor antagonist plays a role in the timing of CABG surgery as it poses a bleeding risk until it is completely eliminated from the system. Oral P2Y₁₂ receptor antagonists have a long duration of platelet inhibition which is difficult to reverse. Cangrelor is an intravenous P2Y₁₂ receptor antagonist with a short half-life and rapid cessation of its effect after discontinuation.

Methods: Three patients who presented to our emergency department with STEMI were started on cangrelor infusion prior to cardiac catheterization instead of other P2Y₁₂ receptor antagonists like clopidogrel or ticagrelor. The study received ethical approval as it is part of the current standard of care for STEMI patients.

Results: All three patients were found to have multi-vessel disease during coronary angiography requiring CABG surgery. As cangrelor was used in these patients they were able to have their surgery within 24–48 h. Intravenous cangrelor was stopped about an hour before surgery. No bleeding complications occurred and all three patients made a speedy recovery in the ICU.

Conclusion: Cangrelor is a potent P2Y₁₂ receptor antagonist which can be used in patients presenting with STEMI as one of the two anti-platelet agents along with aspirin without any dilemma that it would cause a delay in CABG surgery if the patients need one.

1. Introduction

Multiple trials have shown primary percutaneous coronary intervention (PCI) to be more effective than thrombolytic therapy for ST-segment elevation myocardial infarction (STEMI) with improved survival and lower rate of hemorrhagic complications and recurrent MI [1]. A fraction of these patients require emergent coronary artery bypass graft (CABG) surgery [2–4]. Emergent surgery is recommended in patients with left main or triple vessel coronary disease who are hemodynamically unstable after successful or unsuccessful PCI of the culprit lesion and failed or unstable PCI result with ongoing ischemia [5].

It is recommended that patients with acute myocardial infarction receive dual antiplatelet therapy (DAPT) as soon as possible with aspirin and a P2Y₁₂ receptor antagonist [6]. The choice of P2Y₁₂ receptor blocking agent depends on if the patient is planned to receive PCI or fibrinolysis or an early CABG in which case it is not given. There are several P2Y₁₂ receptor blocking agents recommended in the

management of STEMI with ticlopidine and clopidogrel being first generation agents followed by prasugrel and ticagrelor [6]. While the pharmacokinetics of clopidogrel is highly variable [7–9] which may lead to variability in therapeutic response, the newer agents: prasugrel and ticagrelor have shown less variability and more potency [10,11]. All of these agents are oral with long duration of platelet inhibition and are difficult to reverse which becomes a barrier to emergent surgery.

Cangrelor is a non-thienopyridine adenosine triphosphate analogue that blocks adenosine diphosphate (ADP) receptor P2Y₁₂ which is equally effective as other agents but has reversible platelet inhibition [12,13]. It is an intravenous agent with a half-life ranging from 3 to 6 min and most importantly normalization of platelet function within in 30–60 min after discontinuation [12]. Its rapid onset and offset of action provides an important benefit over ticagrelor and prasugrel as studies have shown that the latter two needs loading dose while only one third to half of patients with STEMI have high platelet reactivity [14,15]. Several trials have shown that the use of cangrelor in patients awaiting

[☆] (Use of cangrelor in patients with STEMI who need CABG surgery) There are no conflicts of interest for any of the authors. There are no affiliations/grants to disclose.

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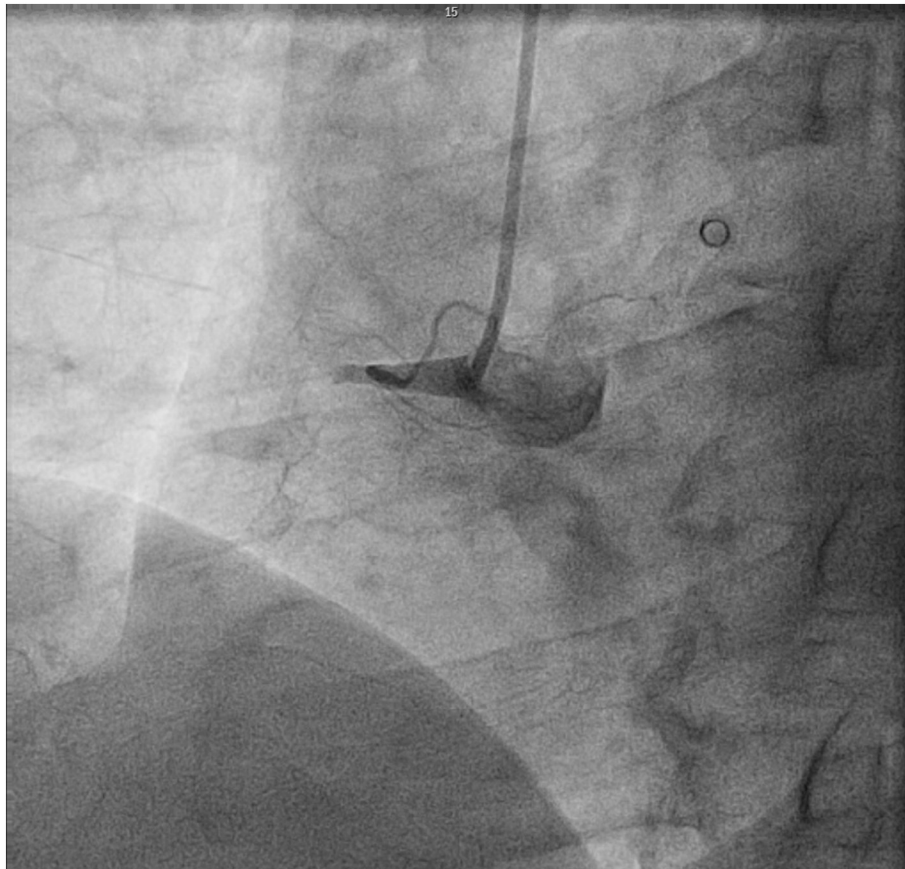


Fig. 1. Coronary angiogram showing proximal right coronary artery disease on left anterior oblique and caudal projection.

cardiac surgery have a higher rate of maintenance of platelet inhibition with significant reduction in the rate of ischemic events, including stent thrombosis during PCI without increasing bleeding risk [16,17]. We present a case series of 3 patients with STEMI who had coronary artery disease requiring CABG surgery where we used cangrelor bridging with excellent outcomes.

2. Case presentation

2.1. Case 1

An 86-year-old male presented to an outside emergency department with intermittent chest pain for 2 days. He also had some nausea and shortness of breath. His medical history was significant for congestive heart failure, paroxysmal atrial fibrillation on dofetilide and dabigatran and had an automatic implantable cardioverter-defibrillator (AICD). An electrocardiogram (ECG) showed ST elevations in leads V5–6, II, III and aVF with depression in V1–3. Patient was given aspirin, sublingual nitroglycerine and started on unfractionated heparin infusion. He was then transferred to our facility for PCI. His emergent coronary angiography showed left main, circumflex, left anterior descending (LAD) and right coronary artery (RCA) disease with occluded circumflex artery being the infarct-related vessel. He underwent successful balloon angioplasty of the circumflex artery with restoration of TIMI 3 flow. An intra-aortic balloon pump was inserted. Cangrelor infusion ($0.75 \mu\text{g}/\text{kg}/\text{min}$) was also started and cardiothoracic surgery was consulted for CABG. Surgery had to be delayed due to patient's last dose of dabigatran. Subsequent ECG showed resolution of ST-elevations and T-wave inversions in leads V3–6, II, III and aVF. Post PCI echocardiogram showed severe concentric left ventricular hypertrophy, moderately reduced systolic function with an ejection fraction of 35–40% and grade

II diastolic dysfunction. About 48 h later he underwent CABG surgery with left internal mammary artery graft to obtuse marginal and right internal mammary artery graft to left anterior descending artery and also ligation of left atrial appendage. Cangrelor infusion was stopped one hour prior to surgery. Patient was extubated on post-operative day 1 and discharged to rehab facility on post-operative day 9. On follow up visit 3 months later the patient was doing well. He still had RCA residual disease with plans for PCI in the future.

2.2. Case 2

A 71-year-old male smoker presented to our hospital with chest pain that started during sexual intercourse few hours earlier. He initially dismissed his symptoms attributing it to indigestion and tried antacids with no relief. He had a history of cerebrovascular disease in the past with left carotid endarterectomy, hyperlipidemia and Barrett's esophagus. As the pain got worse he called EMS. The on-site ECG showed ST segment elevation in anterolateral leads with reciprocal changes in inferior leads. He was then transferred to our facility for PCI. His coronary angiography showed proximal LAD occlusion, the culprit lesion, which was revascularized with a drug eluting stent, and disease in left main, first diagonal branch and right coronary arteries. As critical stenosis in other territories was noted, cardiothoracic surgery was consulted for CABG. Cangrelor infusion ($0.75 \mu\text{g}/\text{kg}/\text{min}$) was also started. 48 h later patient underwent CABG with left internal mammary artery (LIMA) to LAD, saphenous venous graft (SVG) to diagonal, SVG to lateral circumflex, and SVG to right PDA. Patient was then extubated on post-operative day 1 and discharged to home in a week.

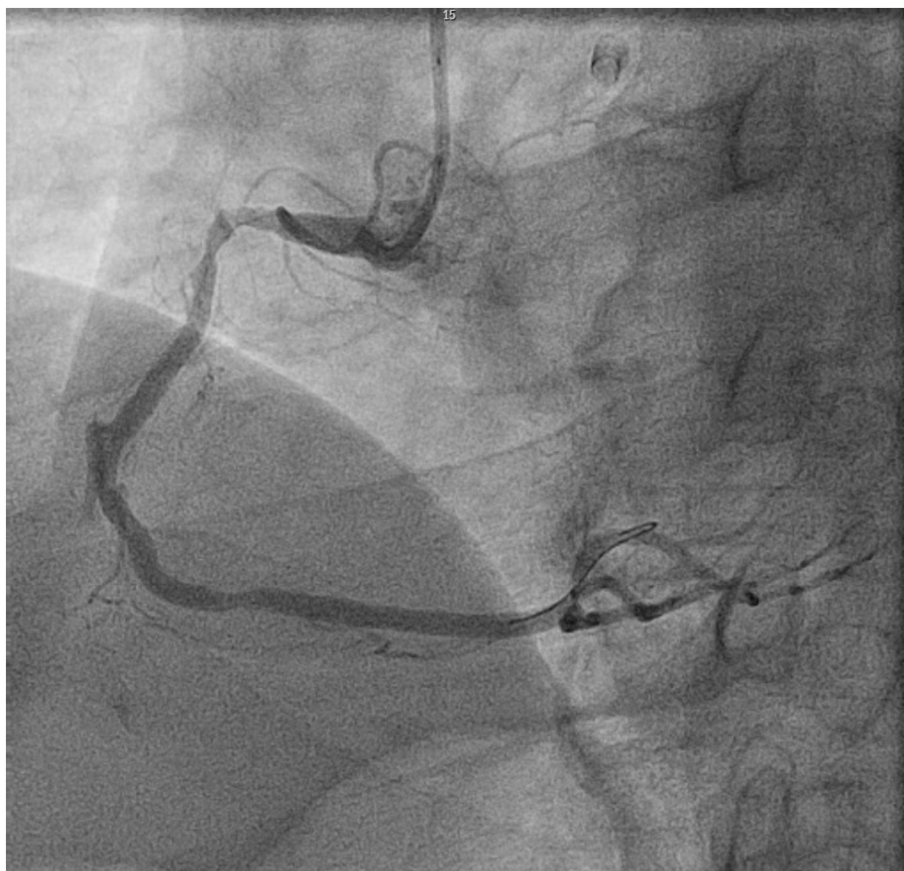


Fig. 2. Coronary angiogram showing right coronary artery post bare metal stent placement on left anterior oblique and caudal projection.

2.3. Case 3

An 88-year-old man presented to the hospital with chest pain that started when he was working outside his house. He had known coronary artery disease with PCI of his LAD and RCA in the past. He also had a history of hypertension, diabetes and hyperlipidemia. On-site ECG showed infero-lateral STEMI so the patient was rushed to the cardiac catheterization lab. He was found to have proximal RCA occlusion, the infarct-related lesion, which was stented with a bare metal stent (Figs. 1 and 2). He also had residual left main, distal LAD and diagonal artery disease (Figs. 3 and 4). Patient was started on cangrelor infusion (0.75 $\mu\text{g}/\text{kg}/\text{min}$) and cardiothoracic surgery was consulted for CABG. He underwent surgery the next day with left internal mammary artery graft to left anterior descending and saphenous vein graft to lateral circumflex and diagonal. Patient was extubated on post-operative day 1. His postoperative course was complicated by paroxysmal A. fib with several episodes of sinus bradycardia intervening period due to which he was started on amiodarone and metoprolol. A dual-chamber pacemaker had to be placed. He was then discharged to rehabilitation facility on post-operative day 20. Upon one month follow up in clinic patient was doing well in terms of physical activity.

3. Discussion

Antiplatelet therapy is vital in the management of acute myocardial infarction as an adjunct to percutaneous coronary intervention. Most patients receive aspirin and an additional antiplatelet agent. Majority of time the second antiplatelet agent is clopidogrel with ticagrelor and prasugrel gaining popularity. The problem with these agents is that the

platelet inhibitory effect lasts long and is irreversible which delays surgery if needed. Cangrelor is an adenosine triphosphate (ADP) receptor blocker with rapid onset of action and quick cessation of platelet inhibitory effect once discontinued. This comes in handy in patients needing surgery due to the complexity of coronary artery disease on angiogram as they do not have to wait for days to wear off antiplatelet effect as with other agents.

This case series showcases a common cardiology scenario where a patient who presents with STEMI undergoes cardiac catheterization and needs CABG due to left main coronary artery or multivessel disease. The use of cangrelor as the second antiplatelet agent prevented the delay for CABG. In all three cases we achieved excellent outcomes without any peri-procedural ischemic or bleeding complications. This highlights the potential for Cangrelor Bridge to facilitate urgent CABG without an oral P2Y₁₂ receptor inhibitor, even in patients treated with a stent for the infarct-related artery.

The CHAMPION (Cangrelor Versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition) trial program was a series of three trials compared cangrelor with clopidogrel and concluded decrease in peri-procedural ischemic complications but with mildly increased bleeding risk [18–21]. The relative risk reduction for composite of death from any cause, myocardial infarction, or ischemia-driven revascularization at 48 h was found to be significant for STEMI population in the study, which consisted about 19% of the sample size. These results make cangrelor ideal for patients with STEMI where there is very short time to pretreat the patient as they are rushed emergently to the PCI laboratory. In addition, as mentioned earlier, there is always the advantage of rapid reversal of platelet function if patients need surgery.

However as the newer antiplatelet agents are becoming more



Fig. 3. Coronary angiogram showing severe left main disease on left anterior oblique and caudal projection.

popular we do not have much data on combining cangrelor with these agents. The CANTIC study (Platelet Inhibition with Cangrelor and Crushed Ticagrelor in STEMI Patients Undergoing Primary Percutaneous Coronary Intervention) was a prospective, randomized, double-blinded, placebo-controlled study that looked at the pharmacodynamics of cangrelor in patients with STEMI treated with crushed ticagrelor [22]. After coronary angiography all patients received ticagrelor as crushed tablets at the time of cangrelor or placebo infusion and pharmacodynamic analysis was performed. Cangrelor was found to have markedly reduced platelet reactivity measured by VerifyNow P2Y12 test (Accriva, San Diego, CA) as early as 5 min after the infusion was started and the effect persisted during the infusion.

Another phase II clinical trial, the BRIDGE (Maintenance of Platelet Inhibition With Cangrelor After Discontinuation of Thienopyridines in Patients Undergoing Surgery) trial, was a double-blinded study that randomized 210 patients awaiting CABG [23]. These patients had either ACS or received coronary stents who were treated with a thienopyridine. Patients were randomized to receive cangrelor infusion as a ‘bridge to surgery’ or placebo. The study looked at the percentage of patients who maintained platelet reactivity of <240 platelet reactivity units with safety outcome being excessive CABG-related bleeding. Patients treated with cangrelor had lower levels of platelet reactivity throughout the treatment period (98.8 vs. 19.0%; $p < 0.001$) when compared to placebo without any significantly different CABG-related bleeding. The study was underpowered to measure outcomes like death, MI or stent

thrombosis.

The role of cangrelor as bridging therapy to reduce the risk of thrombotic events after cessation of antiplatelet agent and surgery in patients who receive drug-eluting stents is an important application of this medication even though it is not currently considered standard of care. When oral P2Y12 inhibitors are used, they have to be discontinued at least 5 days prior to surgery to reduce the risk of bleeding during the procedure [24,25]. GPIIb/IIIa inhibitors have been used as a bridging antiplatelet agent in patients awaiting surgery, but its safety and efficacy have not been demonstrated in this application [26,27]. The three cases that we have presented in this series received only cangrelor that was started prior to PCI and continued until one hour before surgery. None of our patients suffered thrombotic event or any bleeding complication. We conclude that in STEMI patients cangrelor has the potential to substitute for oral P2Y12 inhibitors with an advantage of quick reversal of platelet inhibitory effect (Table 1).

CRedit authorship contribution statement

Bishesh Shrestha: Chart review and manuscript writing.
 Daniel Katz: Patient care and manuscript review.
 John Kelley: Patient care and manuscript review.
 Dhananjai Menzies: Patient care and manuscript review.
 Mun K. Hong: Patient care and manuscript writing, principle investigator.

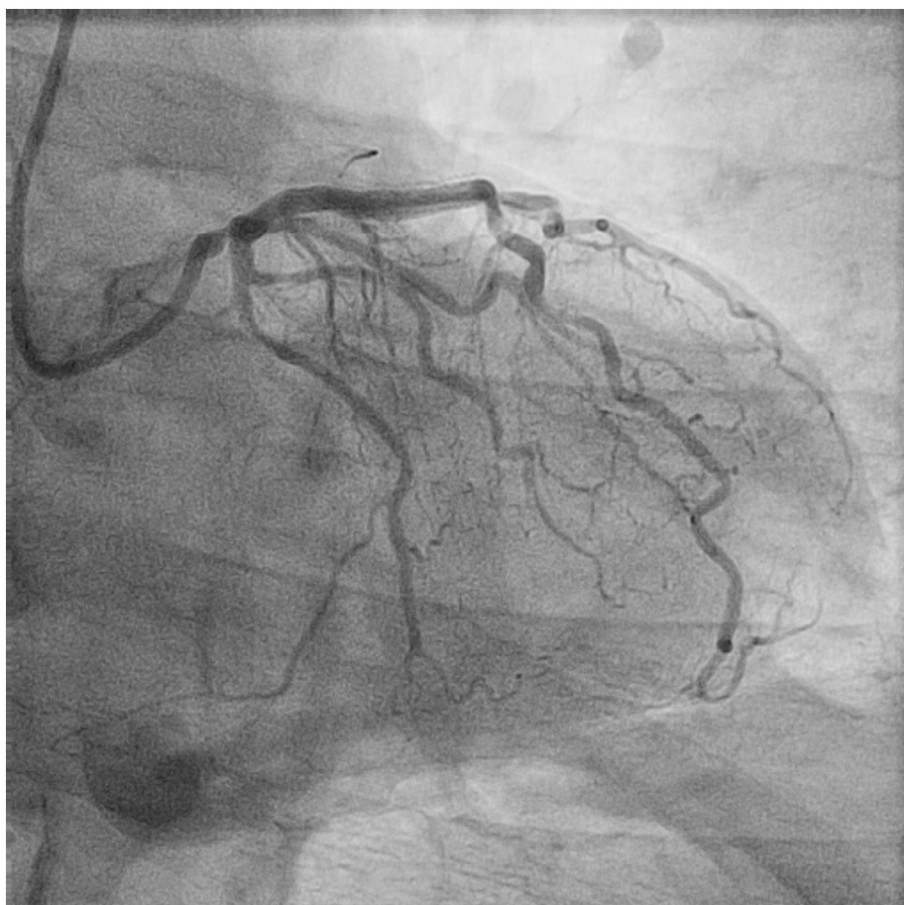


Fig. 4. Coronary angiogram showing severe left main artery, distal left anterior descending artery; ostial diagonal 1 artery lesions on right anterior oblique and caudal projection.

Table 1

Laboratory values of patients at the time of presentation.

High sensitivity troponin on presentation (pg/mL)	1094.8	1456.8	1153.8
Hemoglobin (g/dL)	18.7	19.2	15.3
Hematocrit (%)	54.3	55.5	46.3
White Blood Cell Count ($\times 10^3$ cells/uL)	7.0	13.8	12.3
Platelet Count ($\times 10^3$ cells/uL)	184	260	186
Blood urea nitrogen (mg/dL)	19	14	36
Serum creatinine (mg/dL)	1.1	1.1	1.8
Potassium (mmol/L)	3.5	4.6	3.3
Magnesium (mmol/L)	2.1	1.7	2.2
INR	1.2	1.1	1.4

pg/dL: pictogram per deciliter; g/dL: gram per deciliter; %: percentage; cells/uL: cells per unit liter; mg/dL: milligram per deciliter; mmol/L: milimol per liter.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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