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Letters

TO THE EDITOR

Stent Fracture and Hypersensitivity

What Happens First?

Mori el al. (1) hypothesized that stent fracture accelerates release of metal ions leading to a focal hypersensitivity reaction and stent thrombosis. Although reasonable, we propose an opposite theory regarding the relationship between stent fracture and hypersensitivity.

Kounis syndrome (KS) is an allergic acute coronary syndrome induced by exposure to drugs, food, stent metallic components, and other triggers. Three major variants of KS have been described: types I, II, and III. KS type III (the least common, at 5.1%) includes patients with stent thrombosis/restenosis secondary to an allergy, possibly to the metallic ions. Mast cell degranulation and inflammatory mediators release is triggered by antigen-antibody reaction on the surface of the mast and basophil cells, and activation of the complement system. This stimulates a coagulation cascade with platelet aggregation and collagen fibers deposition around the implant to form a dense, acellular, and neointimal hyperplasia causing stent thrombosis/restenosis (2). Although unproven pathologically, KS had been previously reported with bare-metal stents (3).

Hoshi et al. (4) reported a patient with KS caused by metal allergy and resulting in coronary aneurysm. Coronary angioscopy and optical coherence tomography showed malapposed stent struts at the sites of positive remodeling, whereas multiple interstrut hollows and neointimal hyperplasia covering stent struts were observed in multiple areas. This supports our theory that hypersensitivity happens first and if progressed may result in-stent cavitations and subsequent fracture.

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RESEARCH LETTER:

Cangrelor Use in Cardiogenic Shock

A Single-Center Real-World Experience

Cardiogenic shock complicates approximately 5% of contemporary cases of acute coronary syndrome and is associated with an adverse prognosis, especially early after percutaneous coronary intervention (PCI) (1). Perturbations in hemodynamics, together with impaired gut absorption of oral antiplatelet therapies, may contribute to excess risk of early stent thrombosis (ST) in cardiogenic shock. Cangrelor, a parenteral, fast-acting, reversible $P2Y_{12}$ inhibitor, may possess favorable pharmacological properties in this high-risk cohort. Although the 3 phase 3 CHAMPION (Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition) trials (2) supported cangrelor's regulatory approval for use across a spectrum of PCI, these experiences excluded patients in cardiogenic shock. As such, the relative safety and tolerability of cangrelor in these patients are presently unknown.

In this single-center experience from a large tertiary-care center, we report patterns of use and periprocedural outcomes in patients in clinical shock who received cangrelor. Shock was adjudicated by 2

investigators and defined as requiring vasopressors, inotropes, or mechanical circulatory support immediately before or during cangrelor administration. Incidence of ST at 48 h, GUSTO (Global Use of Strategies to Open Occluded Coronary Arteries)-defined bleeding at 48 h, and post-discharge mortality were ascertained by retrospective chart review. The study protocol was approved by the Institutional Review Board.

From November 2015 to April 2017, a total of 147 patients received cangrelor, of whom 38 (26%) were in clinical shock (Table 1). Thirty-seven presented in cardiogenic shock, and 1 presented in mixed/distributive shock. Median age was 66 years and 63% were men. Patients frequently presented with cardiac arrest (42%) and/or required mechanical circulatory support (42%). Cangrelor was used in 31 patients for PCI for acute coronary syndrome, in 5 bridging to surgery (2 for coronary artery bypass graft surgery, 2 for left ventricular assist device placement, and 1 for gastrointestinal surgery), 1 because of ileus, and 1 as an antiplatelet challenge given high potential for bleeding. Twenty-nine patients received the dose of cangrelor used in the CHAMPION trials (30 μg/kg bolus, followed by 4 μg/kg/min), whereas 7 received the lower maintenance dose used in the BRIDGE (Maintenance of Platelet Inhibition With Cangrelor After Discontinuation of Thienopyridines in Patients Undergoing Surgery) trial (0.75 μg/kg/min) (3), and 2 received both doses. The median duration of BRIDGE dosing was 34 h (range 13 to 233 h). Most patients transitioned to an oral $P2Y_{12}$ antagonist after PCI (n = 30) were treated with ticagrelor (80%). Oral loading doses were administered before PCI in 3 patients (1 prasugrel, 2 ticagrelor), during PCI in 5 patients (all ticagrelor), and after PCI in the remaining 22 patients (5 clopidogrel, 17 ticagrelor). No patients received concomitant glycoprotein IIb/IIIa inhibitors.

During the first 48 h, there was no ST in the 38 patients in clinical shock and 1 ST in the 109 hemodynamically stable patients. In the shock subset, all 11 GUSTO-defined bleeding events (29%) were classified as mild or moderate. Five required ≥1 blood transfusion. Two were access site-related, 2 were gastrointestinal, 2 were genitourinary, 4 were from multiple sites, 1 was presumed with an unidentified source, and none were intracranial. Two critically ill patients required temporary disruption in cangrelor because of excess bleeding. In the hemodynamically stable subset, there were 16 GUSTO-defined mild or moderate bleeding events (15%) of which 6 were access site-related, 4 gastrointestinal, 1 retroperitoneal, 1 genitourinary, and 4 were from other or unidentified sources. There was no intracranial bleeding. Four

TABLE 1 Clinical Profiles and Outcomes of Patients in Clinical Shock Receiving Cangrelor in a Single-Center Real-World Experience (n = 38)

Demographic characteristics	
Age, yrs	65.5 (55.5–75.5)
Male	24 (63.2)
Medical history	
Diabetes mellitus	13 (34.2)
Hypertension	23 (60.5)
Prior stroke or transient ischemic attack	3 (7.9)
Prior myocardial infarction	12 (31.6)
Prior percutaneous coronary intervention	10 (26.3)
Prior coronary artery bypass graft surgery	4 (10.5)
History of heart failure	7 (18.4)
History of peripheral artery disease	3 (7.9)
Chronic kidney disease	5 (13.2)
Shock presentation	
Left ventricular ejection fraction, %	43 (30–55)
Cardiac arrest	16 (42.1)
Ventricular tachycardia/fibrillation	12 (31.6)
Pulseless electrical activity/asystole	4 (10.5)
Therapeutic hypothermia	9 (23.7)
Mechanical ventilation	16 (42.1)
Renal-replacement therapy	3 (7.9)
Pulmonary artery catheter	18 (47.4)
Mechanical circulatory support	16 (42.1)
Intra-aortic balloon pump	13 (34.2)
Extracorporeal membrane oxygenation	4 (10.5)
Impella	2 (5.3)
Ventricular assist device	2 (5.3)
Periprocedural medications, %*	
Glycoprotein IIb/IIIa inhibitor	0
Bivalirudin	9.7 (3/31)
Unfractionated heparin	90.3 (28/31)
Procedural characteristics*	
Culprit vessels, %	
Left main	9.7 (3/31)
Left anterior descending	16.1 (5/31)
Left circumflex	19.4 (6/31)
Ramus intermedius	0 (0/31)
Right coronary artery	41.9 (13/31)
Saphenous vein graft	6.5 (2/31)
>1 vessel†	6.5 (2/31)
Radial access, %	51.6 (16/31)
Drug-eluting stents implanted, %	80.6 (25/31)
Bare-metal stents implanted, %	9.7 (3/31)
Balloon angioplasty, %	3.2 (1/31)
Unsuccessful or no PCI performed, %	6.5 (2/31)
Aspiration thrombectomy, %	16.1 (5/31)
Duration of PCI, min	72.5 (53–129.3)
Timing and transition to oral $P2Y_{12}$ inhibitors, %‡	
Clopidogrel	16.7 (5/30)
Prasugrel	3.3 (1/30)
Ticagrelor	80 (24/30)
Oral loading dose before PCI	10 (3/30)
Oral loading dose during PCI	16.7 (5/30)
Oral loading dose after PCI	73.3 (22/30)

Values are median (interquartile range) or n (%). *Patients who underwent coronary angiography with intent of PCI. †More than 1 culprit vessel requiring PCI identified by the primary operator. ‡Patients who were transitioned from intravenous cangrelor to an oral $P2Y_{12}$ inhibitor after PCI.
PCI = percutaneous coronary intervention.

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required ≥1 blood transfusion. In both subsets, adverse effects of cangrelor infusion (dyspnea or bradyarrhythmias) were not observed. There were 5 deaths and 1 terminally ill patient in each of the clinical shock and hemodynamically stable cohorts at median 12-months post-discharge follow-up.

We present the largest real-world experience of cangrelor use in cardiogenic shock, a cohort excluded from the CHAMPION trial program. In this single-center series (4), more than one-quarter of patients receiving cangrelor were in clinical shock. Mild/moderate bleeding and short-term mortality occurred at approximately twice the rate observed in hemodynamically stable patients. Despite their high-risk presentations, there was no observed ST or severe/life-threatening bleeding at 48 h, and no patients required bailout glycoprotein IIb/IIIa inhibitors.

Our clinical series is limited to a single-center experience with a small sample size. Critically ill patients in cardiogenic shock at risk for gut malabsorption are well-suited for rapidly acting and reversible intravenous antiplatelet therapies, but are at high risk of attendant bleeding complications. Augmenting use of radial access, considering bivalirudin instead of heparin, and avoiding concurrent administration of glycoprotein IIb/IIIa inhibitors (5) may further improve the bleeding profile of cangrelor. The optimization of ischemic and bleeding risks in patients in cardiogenic shock represents an unmet clinical need. Our initial data suggest that cangrelor may offer a potent, parenteral strategy in patients in cardiogenic shock and seems to be well-tolerated with low rates of clinically significant ischemic or bleeding events.

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