Characterization of $P2Y_{12}$ Assay Response in Cangrelor Bridge Therapy

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Introduction

- Cangrelor is an intravenous $P2Y_{12}$ inhibitor FDA approved for use in percutaneous coronary intervention (PCI) at a dose of 4 mcg/kg/min following a 30 mcg/kg IV bolus[1]
- In the BRIDGE Trial's stage 1, dose-finding study (n=11), patients who received cangrelor 0.75 mcg/kg/min (n=6) achieved adequate platelet inhibition in bridge to cardiac surgery[2]
- In the stage 2, randomized, controlled trial (n=210), cangrelor 0.75 mcg/kg/min achieved higher maintenance platelet inhibition (<240 $P2Y_{12}$ Reaction Units [PRUs]) compared to placebo (98.8% versus 19.0%; p<0.001)[2]
- $P2Y_{12}$ assays can be utilized to measure the $P2Y_{12}$ receptor blockade
- Expert consensus proposed PRU cutoff values >208 and <85 may be associated with an increased risk of recurrent ischemic and bleeding events, respectively[3]
- There is limited literature on alternative cangrelor dosing strategies and the use of $P2Y_{12}$ assays to guide dose adjustments

Methods

- Single-center, retrospective, observational cohort study of adult patients initiated on cangrelor infusion for maintenance platelet inhibition from October 1, 2015 to July 31, 2021
- Study approved by VCUHS Institutional Review Board

Inclusion Criteria

- 18 – 89 years of age
- Cangrelor infusion ≤0.75 mcg/kg/min for ≥24 hours
- ≥1 VerifyNow® $P2Y_{12}$ level while on cangrelor infusion

Exclusion Criteria

- Pregnancy or prisoners
- Received abciximab within 14 days of $P2Y_{12}$ sample
- Received eptifibatide or tirofiban within 48 hours of $P2Y_{12}$ sample

Primary Outcome

- Characterize initial cangrelor dosing strategies based on level of platelet inhibition and need for subsequent dose adjustments

Secondary Outcomes

- Compare cangrelor dosing strategies and level of platelet inhibition for patients initiated on standard cangrelor dose (0.75 mcg/kg/min) versus a reduced dose (<0.75 mcg/kg/min)
- Characterize all $P2Y_{12}$ levels with their corresponding cangrelor dose
- Incidence of stent thrombosis or recurrent myocardial infarction (MI)
- Incidence of bleeding (as with Bleeding Academic Research Consortium [BARC] criteria)
- Hospital & intensive care unit (ICU) length of stay
- Hospital mortality

Results

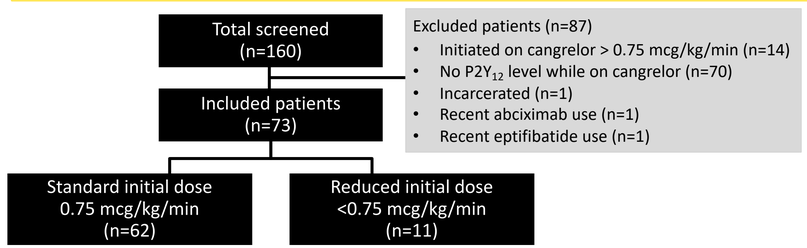

Table 1. Baseline Characteristics

Variable	All patients (n=73)	Standard dose (n=62)	Reduced dose (n=11)
Age (years), mean (SD)	62.2 (10.3)	62.7 (9.4)	59.8 (14.7)
Male sex, n (%)	56 (76.7)	47 (75.8)	9 (81.8)
Weight (kg), mean (SD)	89.1 (22.6)	87.7 (19.7)	97.0 (34.7)
Reason for presentation – ACS, n (%)	34 (46.6)	29 (46.8)	5 (45.5)
Cardiac stent placed <1 month ago[1]	63 (88.7)	55 (91.7)	8 (72.7)
Reason for cangrelor therapy, n (%)			
Bridge to/from procedure	21 (28.8)	18 (29.0)	3 (27.3)
Recent/active bleed	22 (30.1)	18 (29.0)	4 (36.4)
Concomitant ECMO	16 (21.9)	13 (21.0)	3 (27.3)
Baseline $P2Y_{12}$ level[2] (PRU), mean (SD)	214.6 (57.6)	214.7 (54.5)	214.3 (68.4)
Oral $P2Y_{12}$ agent prior to cangrelor, n (%)	40 (54.8)	32 (51.6)	8 (72.7)
Last dose if known[3] (h), mean (SD)	41.7 (57.9)	29.0 (24.1)	89.9 (113.9)
Concomitant medications during cangrelor therapy, n (%)			
Aspirin	61 (83.6)	52 (83.9)	9 (81.8)
Unfractionated heparin infusion	27 (37.0)	23 (37.1)	4 (36.4)
Bivalirudin	16 (21.9)	13 (21.0)	3 (27.3)

[1]n=71 for all patients; n=60 for standard initial dose
[2]n=36 for all patients; n=26 for standard initial dose; n=10 for reduced initial dose
[3]n=24 for all patients; n=19 for standard initial dose; n=5 for reduce initial dose

ECMO: extracorporeal membrane oxygenation
ACS: acute coronary syndrome

Figure 1. Characterization of $P2Y_{12}$ Level & Cangrelor Dose

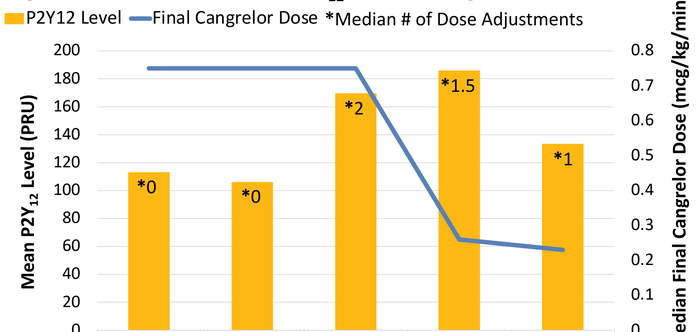

Table 2. Secondary Outcomes

Variable	Standard dose (n=62)	Reduced dose (n=11)	P value
$P2Y_{12}$ level (PRU), mean (SD)	106.1 (68.7)	152.9 (55.2)	**0.0361**
Number of dose adjustments, median (IQR)	0 (1)	1 (3)	**0.0066**
Final cangrelor dose (mcg/kg/min), median (IQR)	0.75 (0.25)	0.25 (0.4)	**0.0020**
Total duration of cangrelor (h), mean (SD)	137.8 (114.6)	90.6 (44.8)	0.1842

Figure 2. Characterization of $P2Y_{12}$ Response with Corresponding Cangrelor Dose

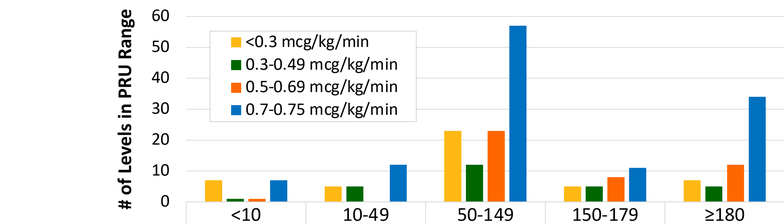

Table 3. Additional Secondary Outcomes

Variable	All patients (n=73)	Standard dose (n=62)	Reduced dose (n=11)	P value
Stent thrombosis or recurrent MI, n (%)	2 (2.7)	2 (3.2)	0 (0)	1.0000
Bleeding events, n (%)	27 (37.0)	21 (33.9)	6 (54.5)	0.3090
Hospital length of stay (d), mean (SD)	24.8 (25.0)	21.9 (15.0)	41.1 (52.7)	**0.0178**
ICU length of stay (d), mean (SD)	16.6 (13.8)	16.6 (14.2)	16.6 (12.2)	0.9959
Mortality, n (%)	17 (23.3)	16 (25.8)	1 (9.1)	0.2267

Table 4. Outcomes in Patients Initiated on Cangrelor for Concomitant ECMO

Variable	All patients (n=16)	Standard dose (n=13)	Reduced dose (n=3)
$P2Y_{12}$ level (PRU), mean (SD)	114.9 (67.5)	113.9 (69.1)	112.2 (75.3)
Number of dose adjustments, mean (SD)	0.9 (1.4)	0.7 (1.1)	1.9 (2.7)
Final cangrelor dose (mcg/kg/min), mean (SD)	0.60 (0.22)	0.61 (0.23)	0.56 (0.21)
Total duration of cangrelor (h), mean (SD)	129.5 (106.3)	137.7 (113.2)	93.1 (49.4)
Stent thrombosis or recurrent MI, n (%)	0 (0)	0 (0)	0 (0)
Bleeding events, n (%)	8 (50)	7 (53.8)	1 (33.3)

Hypothesis

- The results of this study will contribute to current literature on utilizing $P2Y_{12}$ levels to guide dose adjusted cangrelor therapy while minimizing risk for ischemic and hemorrhagic events

Conclusions

- Cangrelor administered at doses <0.75 mcg/kg/min maintained adequate platelet inhibition during bridge therapy as monitored through $P2Y_{12}$ assay response
- Reduced dose cangrelor in conjunction with the use of $P2Y_{12}$ assay monitoring to guide dose adjustments may represent an alternative dosing strategy for patients at high bleed risk
- Patients initiated on cangrelor for concomitant ECMO may benefit from cangrelor doses <0.75 mcg/kg/min to minimize bleed risk without an increased risk of stent thrombosis
- Larger studies are needed to further assess efficacy and safety of reduced cangrelor dosing strategies in specific patient populations

References:
1. Cangrelor [package insert]. Cary, MC: Chiesi USA, Inc.; 2015.
2. Angiolillo DJ, Firstenberg MS, Price MJ, et al. Bridging antiplatelet therapy with cangrelor in patients undergoing cardiac surgery: a randomized controlled trial. JAMA. 2012;307(3).
3. Tantry US, Bonello L, Aradi D, et al. Consensus and update on the definition of on-treatment platelet reactivity to adenosine diphosphate associated with ischemia and bleeding. *Journal of the American College of Cardiology*. 2013;62(24):2261-2273.