JACC: Cardiovascular Interventions

Cangrelor in Patients With Coronary Artery Disease Pretreated With Ticagrelor

The Switching Antiplatelet (SWAP)-5 Study

Francesco Franchi, MD,[a] Luis Ortega-Paz, MD, PhD,[a] Fabiana Rollini, MD,[a] Mattia Galli, MD,[a,b] Latonya Been, AAS,[a] Ghussan Ghanem, MD,[a] Awss Shalhoub, MD,[a] Tiffany Ossi, MD,[a] Andrea Rivas, MD,[a] Xuan Zhou, MD,[a] Andres M. Pineda, MD,[a] Siva Suryadevara, MD,[a] Daniel Soffer, MD,[a] Martin M. Zenni, MD,[a] Birgit Reiter, PhD,[c] Bernd Jilma, MD,[d] Dominick J. Angiolillo, MD, PhD[a]

ABSTRACT

BACKGROUND There are no studies specifically designed to rule out a drug-drug interaction (DDI) when cangrelor is used among patients who have been pretreated with ticagrelor.

OBJECTIVES This study sought to rule out a DDI among cangrelor-treated patients who have been pretreated with ticagrelor.

METHODS In this prospective, randomized, double-blind, placebo-controlled, crossover, pharmacokinetic (PK) and pharmacodynamic (PD) study, patients with coronary artery disease (N = 20) were pretreated with a 180-mg ticagrelor loading dose and after 1 hour randomized to placebo or cangrelor (bolus and infusion for 2 hours). Patients crossed over after 1 to 4 weeks of washout. PK analysis included ticagrelor plasma levels and its active metabolite. PD assessments included VerifyNow $P2Y_{12}$ reaction units (PRU), light transmittance aggregometry, vasodilator-stimulated phosphoprotein, and Total Thrombus-Formation Analysis System. PK/PD assessments were performed at 7 time points.

RESULTS Compared with placebo, adding cangrelor to patients pretreated with ticagrelor resulted in a significant reduction in PRU at 30 minutes and 1 hour after starting infusion. At 2 hours after stopping cangrelor/placebo infusion, PRU were low and similar in both groups (16.9 vs 12.6; mean difference: 4.3; 95% CI: −28.6 to 37.3), meeting the noninferiority primary endpoint (predefined noninferiority margin 45 PRU). Consistent findings were shown with all PD assays. PK tracked PD findings with no differences between groups in plasma levels of ticagrelor and its metabolite.

CONCLUSIONS Compared with placebo, the use of cangrelor in patients pretreated with ticagrelor results in enhanced platelet inhibition with no differences in PK/PD profiles after discontinuation of drug infusion indicating the absence of a DDI. (PD and PK Profiles of Switching Between Cangrelor and Ticagrelor Following Ticagrelor Pre-treatment [SWAP-5]; NCT04634162) (J Am Coll Cardiol Intv 2023;16:36-46) © 2023 by the American College of Cardiology Foundation.

From the [a]Division of Cardiology, University of Florida College of Medicine - Jacksonville, Jacksonville, Florida, USA; [b]Maria Cecilia Hospital, GVM Care and Research, Cotignola, Italy; [c]Clinical Institute of Laboratory Medicine, Medical University of Vienna, Vienna, Austria; and the [d]Department of Clinical Pharmacology, Medical University of Vienna, Vienna, Austria.

H. Vernon "Skip" Anderson, MD, served as Guest Editor for this paper.

ISSN 1936-8798/$36.00

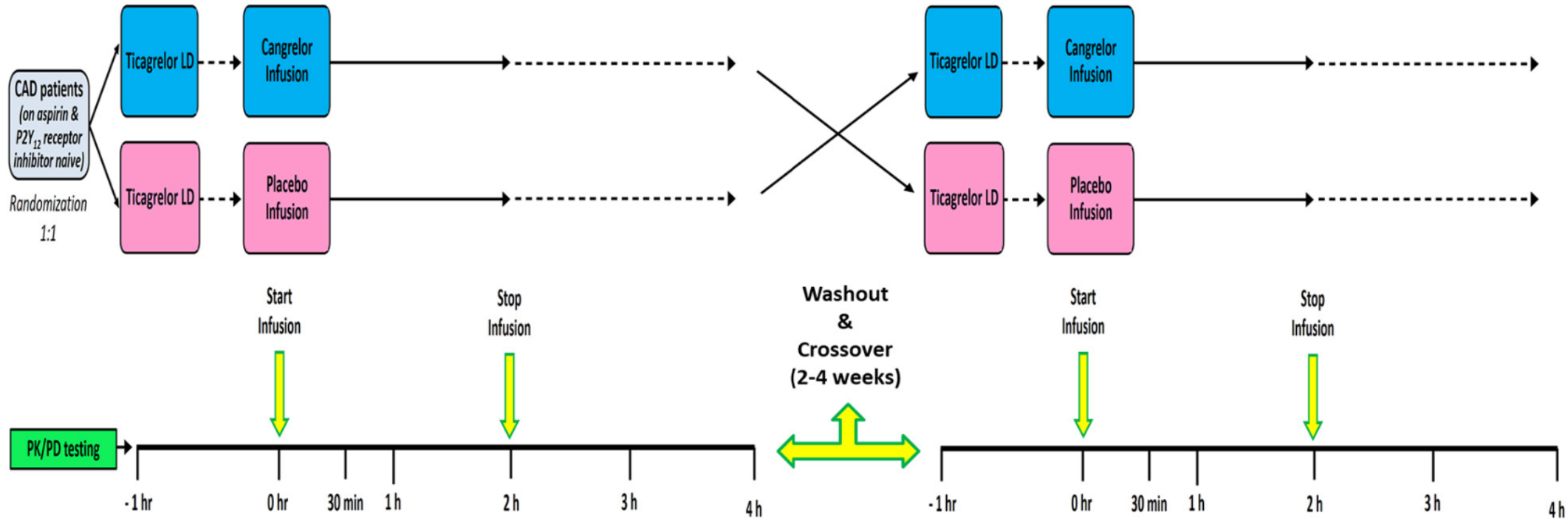
https://doi.org/10.1016/j.jcin.2022.10.034

JACC: Cardiovascular Interventions

Cangrelor in Patients With Coronary Artery Disease Pretreated With Ticagrelor

The Switching Antiplatelet (SWAP)-5 Study

FIGURE 1 SWAP-5 Study Design



Study design diagram. CAD = coronary artery disease; LD = loading dose; PD = pharmacodynamic; PK = pharmacokinetic; SWAP-5 = Switching Antiplatelet Therapy-5.

Cangrelor in Patients With Coronary Artery Disease Pretreated With Ticagrelor

The Switching Antiplatelet (SWAP)-5 Study

TABLE 1 Baseline Characteristics of the Pharmacodynamic Population (N = 20)

Age, y	68.4 ± 8.0
Female	11 (55.0)
Body mass index, kg/m^2	34.2 ± 6.6
Race	
Black	10 (50.0)
White	10 (50.0)
Current Smoking	2 (10.0)
Hypertension	20 (100.0)
Diabetes mellitus	18 (90.0)
Hyperlipidemia	17 (85.0)
Family history of premature CAD	7 (35.0)
PAD	1 (5.0)
Stroke	2 (10.0)
Prior MI	7 (35.0)
Prior PCI	13 (65.0)
Prior CABG	6 (30.0)
Congestive heart failure	7 (35.0)
Left ventricular ejection fraction, %	38.3 ± 15.1
Medications	
ASA	20 (100.0)
Statins	19 (95.0)
Beta-blockers	17 (85.0)
ACE inhibitors or ARBs	14 (70.0)
Nitrates	8 (40.0)
PPIs	7 (35.0)
Calcium-channel blockers	7 (35.0)
Oral antidiabetic drug	10 (50.0)
Insulin	8 (40.0)
Hemoglobin, g/dL	13.2 ± 1.8
Hematocrit, %	40.0 ± 8.2
Creatinine, mg/dL	1.1 ± 0.3
Platelet count, ×1,000/mm^3	235.0 ± 62.1

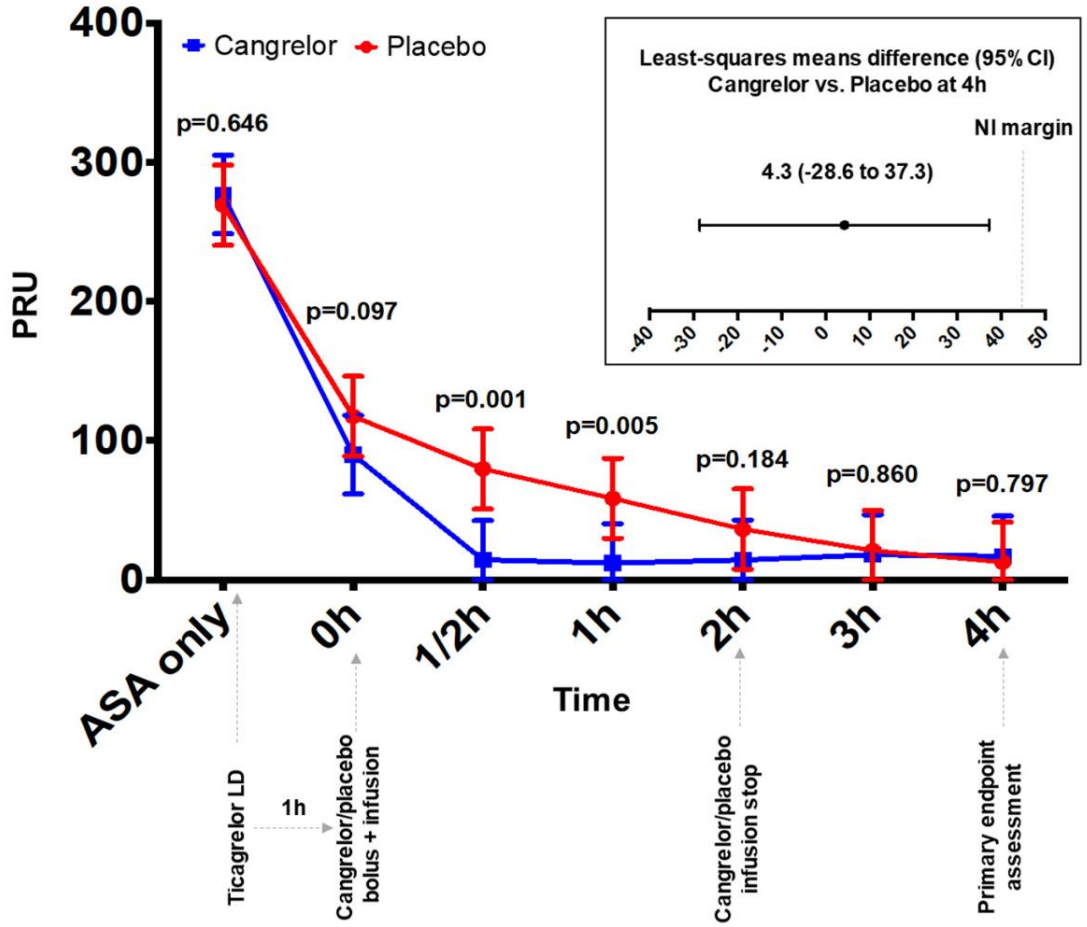
Values are mean ± SD or n (%).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ASA = acetylsalicylic acid; CABG = coronary artery bypass grafting; CAD = coronary artery disease; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; PPI = proton pump inhibitor.

Cangrelor in Patients With Coronary Artery Disease Pretreated With Ticagrelor

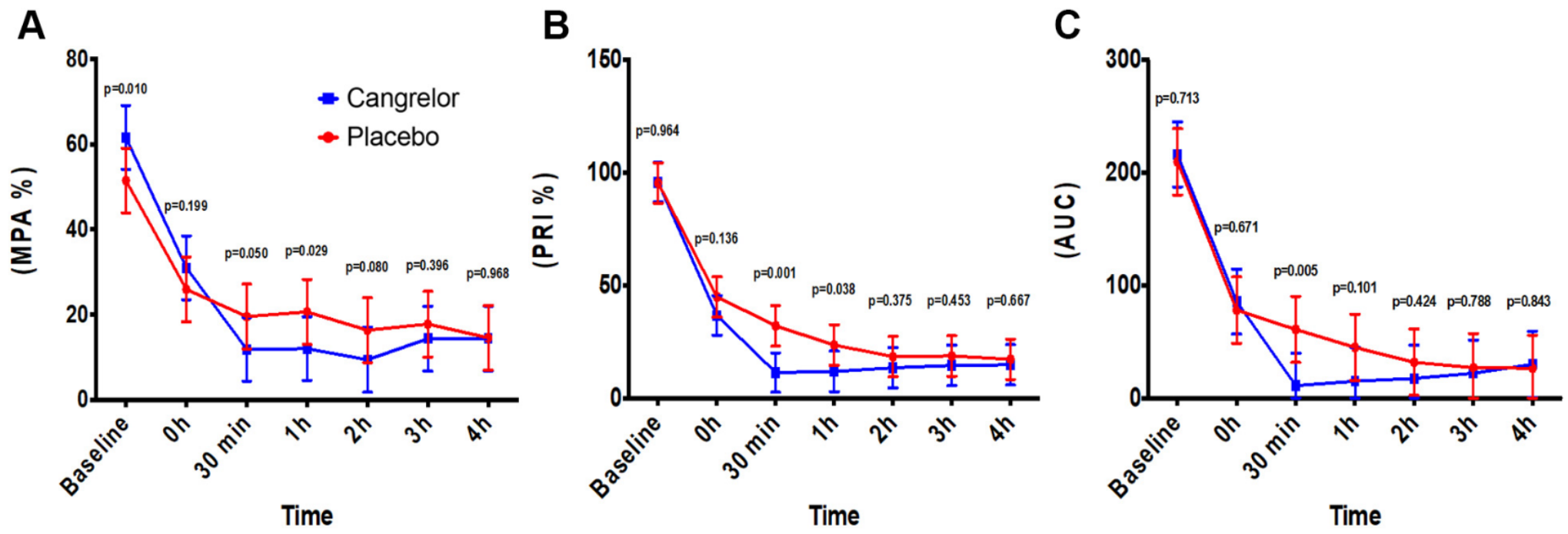
The Switching Antiplatelet (SWAP)-5 Study

FIGURE 2 Pharmacodynamic Profile of Cangrelor vs Placebo Assessed by VerifyNow PRU



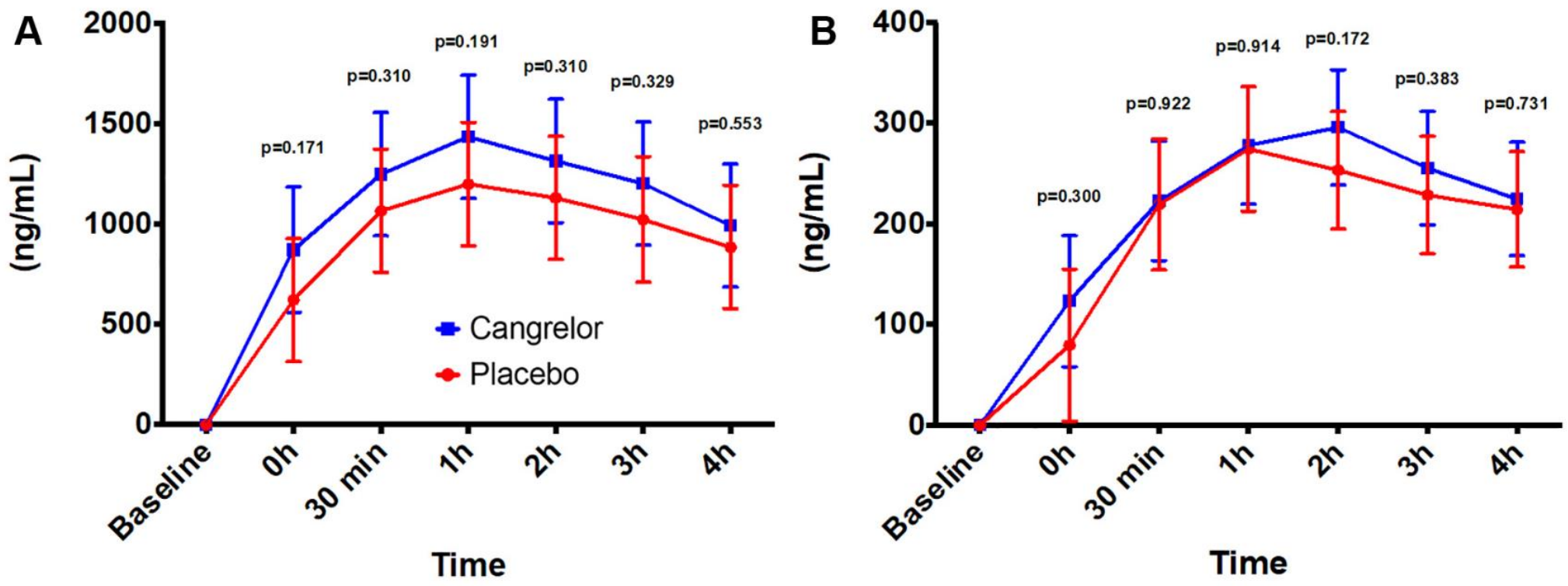
$P2Y_{12}$ reaction units (PRU) measured by the VerifyNow $P2Y_{12}$ assay. Values are expressed as least-squares means. **Error bars** indicate 95% CIs. *P* values indicate comparisons between groups at each time point. ASA = acetylsalicylic acid; LD = loading dose; NI = noninferiority.

FIGURE 3 **Pharmacodynamic Profiles of Cangrelor vs Placebo Assessed by Light Transmittance Aggregometry, Vasodilator-Stimulated Phosphoprotein, and Total Thrombus-Formation Analysis System**



(A) Light transmittance aggregometry following adenosine diphosphate (20 μM) stimuli results reported as maximum platelet aggregation (MPA%). **(B)** Vasodilator-stimulated phosphoprotein results reported as platelet reactivity index (PRI%). **(C)** Total Thrombus-Formation Analysis System with results reported as the area under the curve (AUC). Values are expressed as least-squares means. **Error bars** indicate 95% CIs. *P* values indicate comparisons between groups at each time point.

FIGURE 4 Plasma Concentrations of Ticagrelor and AR-C124910XX



Ticagrelor loading dose (180-mg orally) was administered at baseline 1 hour before the beginning of cangrelor bolus and infusion at time 0 hours. Plasma levels of **(A)** ticagrelor and **(B)** its major active metabolite AR-C124910XX during the 5 hours following the administration of ticagrelor loading dose. Values are expressed as means. **Error bars** indicate 95% CIs.

TABLE 2 Pharmacokinetic Profiles of Ticagrelor and AR-C124910XX

	Cangrelor	Placebo	*P* Value
Ticagrelor			
T_{max}, h	2.00 (1.00-5.00)	2.00 (1.00-5.00)	0.158
C_{max}, ng/mL	1,695.3 (862.9-3,477.69)	1,410.8 (195.8-2,866.9)	0.259
$AUC_{0\text{-}2h}$, ng·h/mL	2,429.0 (242.8-5,468.1)	1,450.5 (63.4-5,141.5)	0.156
$AUC_{0\text{-}last}$, ng·h/mL	5,025.8 (1,998.0-8,846.8)	3,487.7 (247.4-8,599.7)	0.047
AR-C124910XX			
T_{max}, h	3.00 (1.50-5.00)	3.00 (1.50-5.00)	0.422
C_{max}, ng/mL	312.3 (177.4-492.7)	301.6 (124.1-701.8)	0.731
$AUC_{0\text{-}2h}$, ng·h/mL	443.0 (44.4-979.3)	324.4 (44.5-1,078.5)	0.274
$AUC_{0\text{-}last}$, ng·h/mL	944.0 (214.3-1,762.7)	815.4 (205.6-2,340.9)	0.281

T_{max} is reported as median (range). C_{max} and $AUC_{0\text{-}last}$ are reported as geometric mean (range).

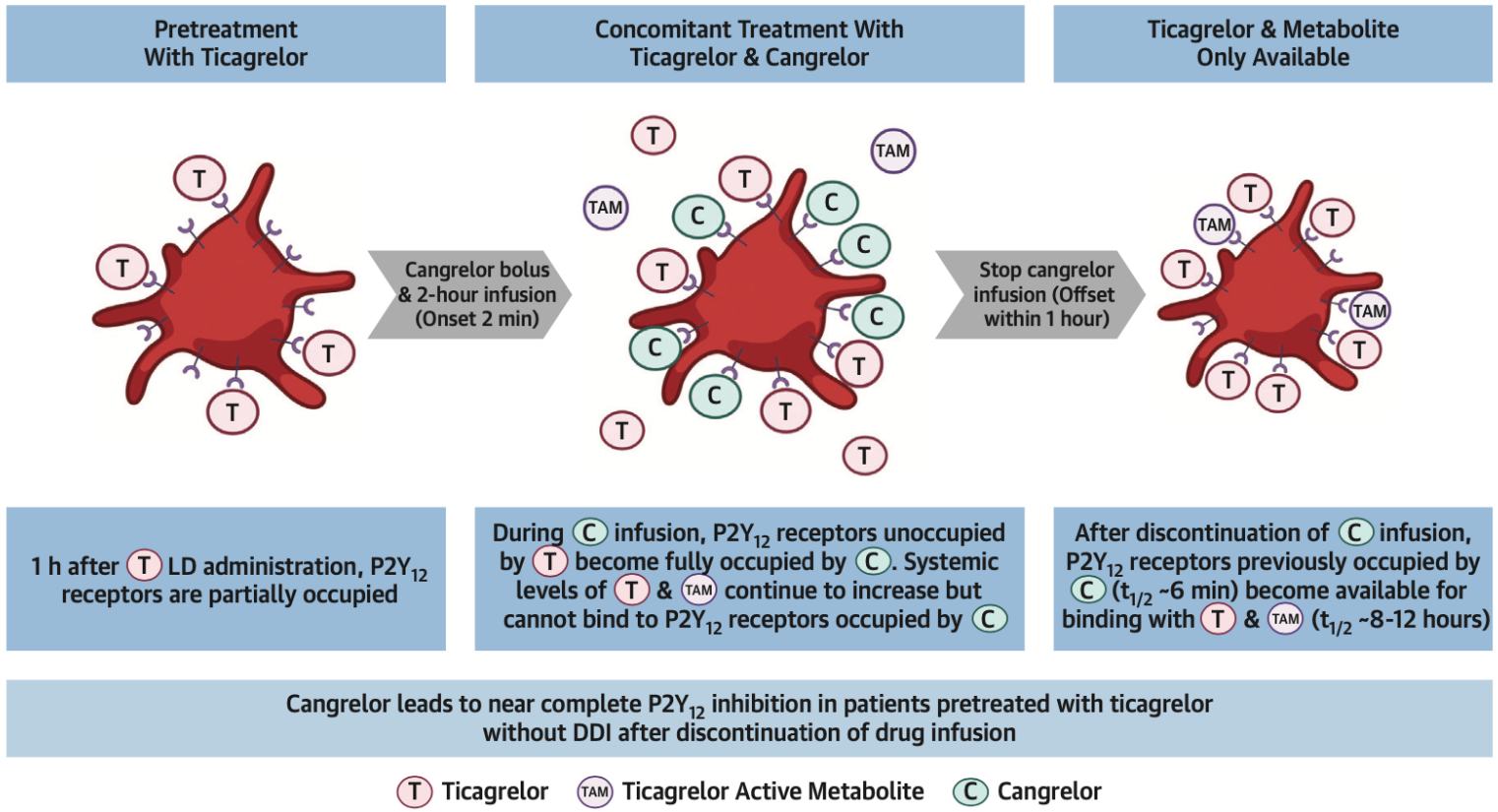
$AUC_{0\text{-}last}$ = AUC to the last measurable concentration; $AUC_{0\text{-}2h}$ = area under the curve from time 0 to 2 hours; C_{max} = maximum observed plasma concentration; T_{max} = time to maximum observed plasma concentration.

JACC: Cardiovascular Interventions

Cangrelor in Patients With Coronary Artery Disease Pretreated With Ticagrelor

The Switching Antiplatelet (SWAP)-5 Study

CENTRAL ILLUSTRATION **Pharmacokinetic and Pharmacodynamic Profiles Associated With the Use of Cangrelor in Patients With Coronary Artery Disease Pretreated With Ticagrelor**



Franchi F, et al. J Am Coll Cardiol Intv. 2023;16(1):36-46.

The ticagrelor active metabolite is AR-C124910XX. DDI = drug-drug interaction; LD = loading dose; $t_{1/2}$ = half-life.

Cangrelor in Patients With Coronary Artery Disease Pretreated With Ticagrelor

The Switching Antiplatelet (SWAP)-5 Study

PERSPECTIVES

WHAT IS KNOWN? The lack of a DDI between ticagrelor and cangrelor was demonstrated in studies in which ticagrelor was given at the time of initiation or during cangrelor infusion.

WHAT IS NEW? Adding cangrelor to patients pretreated with ticagrelor results in enhanced platelet inhibition, thus bridging the gap in platelet imbibition observed with the use of oral $P2Y_{12}$ inhibitors, with no differences in PK/PD profiles after discontinuation of drug infusion, indicating the absence of a DDI.

WHAT IS NEXT? The clinical implications of these PK/PD findings warrant investigation in dedicated trials of patients with ACS.

JACC: CARDIOVASCULAR INTERVENTIONS

PUBLISHED BY ELSEVIER