ARCHIVES OF THE TURKISH SOCIETY OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Cangrelor Monotherapy Bridging for Cardiac and Non-Cardiac Surgery Following Percutaneous Coronary Intervention

Perkütan Koroner Girişim Sonrasında Kalp ve Kalp Dışı Cerrahi için Köprü Oluşturan Cangrelor Monoterapisi

ABSTRACT

Managing dual antiplatelet therapy (DAPT) perioperatively is challenging, especially in patients who have recently undergone percutaneous coronary intervention (PCI). Intravenous antiplatelet agents are recommended in these cases. This case series describes the perioperative management of two high bleeding risk patients with recent PCI undergoing cardiac and non-cardiac surgeries using cangrelor monotherapy.

Keywords: Bridging therapy, cangrelor, DAPT, surgery

ÖZET

İkili antiplatelet tedavinin perioperatif yönetimi, özellikle yakın zamanda perkütan koroner girişim (PKG) yapılan hastalarda zordur. Bu senaryoda intravenöz antiplatelet ajanlar önerilmektedir. Bu vaka serisinde, kardiyak ve non-kardiyak cerrahi geçiren ve yakın zamanda PKG yapılan yüksek kanama riskli iki hastanın cangrelor monoterapisi kullanılarak perioperatif yönetimi anlatılmaktadır.

Anahtar Kelimeler: Köprüleme tedavisi, kangrelor, ikili antiplatelet tedavi, cerrahi

CASE REPORT
OLGU SUNUMU

Spyridon-Filippos Papadopoulos[1]
Emmanouela Peteinidou[1]
Konstantinos C. Theodoropoulos[1]
Matthaios Didagelos[1]
Athanasios Samaras[2]
Aristi Boulmpou[3]
Thomas Gossios[1]
Antonios Kouparanis[1]
George Kassimis[2]
Antonios Ziakas[1]

[1]*First Cardiology Department, AHEPA General University Hospital, Aristotle University of Thessaloniki, Greece*
[2]*Second Cardiology Department, Hippokration University Hospital of Thessaloniki, Thessaloniki, Greece*
[3]*Third Cardiology Department, Hippokration University Hospital of Thessaloniki, Thessaloniki, Greece*

Corresponding author:
Konstantinos C. Theodoropoulos
✉ ktheod2005@hotmail.com

Received: February 24, 2024
Accepted: April 01, 2024

Cite this article as: Papadopoulos SF, Peteinidou E, Theodoropoulos KC, et al. Cangrelor monotherapy bridging for cardiac and non-cardiac surgery following percutaneous coronary intervention. *Turk Kardiyol Dern Ars.* 2025;53(2):143-147.

DOI:10.5543/tkda.2024.86987

Dual antiplatelet therapy (DAPT), comprising aspirin and a $P2Y_{12}$ inhibitor, is the standard treatment for preventing atherothrombotic events in patients with acute coronary syndromes (ACS) and/or those undergoing percutaneous coronary intervention (PCI) for at least 6-12 months.[1] While on DAPT, a significant number of patients who have previously undergone PCI may require urgent or time-sensitive surgery. The cumulative incidence rates of non-cardiac surgery post-PCI at 30 days, 6 months, and 1 year have been reported to be 1%, 5%, and 9%, respectively. Additionally, 7-14% of patients with prior PCI may need to interrupt DAPT for surgery in the first 12 months following PCI.[2,3]

The perioperative management of DAPT in surgical patients is notably complex and fraught with ambiguity, given the increased risk for both thrombotic (such as stent thrombosis) and bleeding complications. Key risk factors for thrombotic complications due to $P2Y_{12}$ inhibitor interruption include the surgical 'stress-response,' timing of the surgery after PCI, type of implanted stent, and various clinical (PCI for ACS, diabetes, heart failure) and technical procedural factors (complex PCIs such as multivessel PCI, long lesions, bifurcations treated with a 2-stent strategy, chronic total occlusions, calcified lesions, or ostial lesions).[4] The risk of ischemic complications must be carefully balanced against the increased risk of bleeding if surgery is performed on DAPT. For urgent or time-sensitive operations that cannot be postponed, discontinuing the $P2Y_{12}$ inhibitor is generally required 5-7 days before surgery—7 days for prasugrel, 5 days for clopidogrel, and 3-5 days for ticagrelor—to minimize the risk of perioperative hemorrhage and transfusions, which are associated with higher morbidity and mortality.[5] The optimal antiplatelet therapy for patients requiring dual antiplatelet therapy before surgery is unclear due to the lack of randomized controlled data. Intravenous antiplatelet agents, such as glycoprotein IIb/IIIa inhibitors and the potent $P2Y_{12}$ inhibitor cangrelor, are used for bridging during the perioperative period, with a continuous low maintenance dose of aspirin.[4,5]

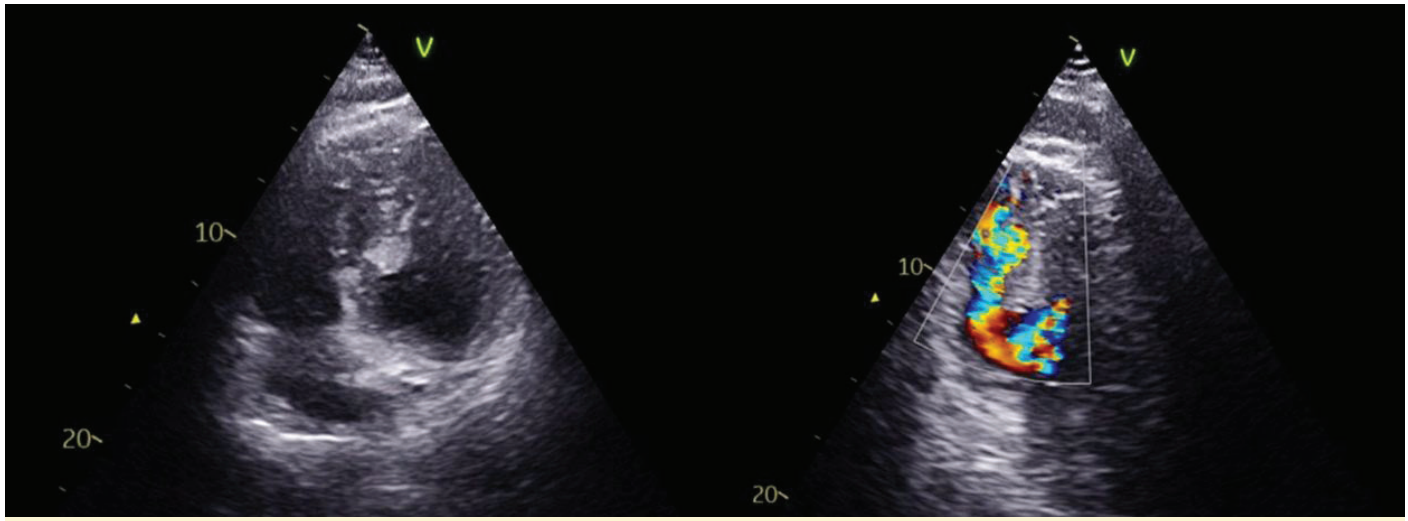

Figure 1. Transthoracic echocardiogram, 4-chamber view, showing the septal rupture in 2-D mode (left panel) and the left-to-right shunt with color Doppler (right panel).

Cangrelor is a potent parenteral $P2Y_{12}$ inhibitor with a reversible mechanism of action. It is a nonthienopyridine adenosine triphosphate analog with a rapid onset and offset of action.[6,7] Following intravenous bolus administration and a continuous infusion at 0.75 mg/kg/min, cangrelor achieves peak concentration (Cmax) within 2 minutes, maintaining a consistent concentration level throughout the infusion.[7] It has a half-life of 3-6 minutes due to rapid hydrolysis to its inactive metabolite, and platelet function returns to baseline within 60 minutes after infusion cessation.[8] The rapid onset and offset of action make cangrelor ideal for 'bridging' in patients who need to discontinue oral agents to undergo surgery.[9] We describe a cangrelor monotherapy perioperative bridging strategy in two patients at high bleeding and thrombotic risk requiring urgent surgery soon (8-10 days) after PCI.

Case Report

Case 1

A 62-year-old man with an inferior ST-segment elevation myocardial infarction underwent primary PCI (PPCI) of the right coronary artery (RCA). DAPT with aspirin and ticagrelor was initiated. The following day, while in the coronary care unit, he became hemodynamically unstable. A bedside transthoracic echocardiogram revealed an interventricular septum (IVS) rupture as the cause of his deterioration (Figure 1).

Stabilization was achieved with the insertion of an intra-aortic balloon pump (IABP) and intravenous inotropes infusion. Following a discussion with the cardiac surgeons (Heart team), the patient was scheduled for surgical treatment within the next 7-10 days. Delayed surgery (more than 7 days) may be associated with better survival.[10] Considering the risks of early stent thrombosis and perioperative bleeding (and also taking into account the fragility of the infarcted tissue), the treatment was switched from aspirin and ticagrelor to the potent intravenous $P2Y_{12}$ inhibitor cangrelor. Cangrelor was initiated 24 hours after the last dose of aspirin and ticagrelor. A continuous infusion of cangrelor (0.75 mcg/kg/min), without a bolus, was maintained for 8 days and stopped two hours before surgery (Figure 2). The patient also received enoxaparin 100 mg twice daily (1 mg/kg every 12 hours) as anticoagulation treatment for the IABP to reduce the likelihood of catheter-related thrombosis and embolism. Compared to unfractionated heparin, low molecular-weight heparin (LMWH) appears to reduce the risk of major bleeding in patients receiving IABP.[11] The patient was transferred to the operation theater where was he underwent ventricular septal rupture (VSR) closure using the sandwich patch technique. Cangrelor was restarted 6 hours after the cardiac surgery. Unfortunately, the patient was in refractory cardiogenic shock post-surgery and, despite support with venoarterial extracorporeal membrane oxygenation (VA-ECMO), he died 48 hours later due to multi-organ failure.

Case 2

A 72-year-old man presented with an inferior ST-elevation myocardial infarction (STEMI). After loading with aspirin and clopidogrel, he was transferred to the hemodynamic laboratory. The RCA was occluded, and PPCI with implantation of a drug-eluting stent was performed. Several hours later, while the patient was recovering, he suffered significant hematuria due to pulling out the urinary catheter. He was transfused with a total of 2 units of packed red blood cells. Given that three days of

ABBREVIATIONS

ACS	Acute coronary syndromes
BRIDGE	Bridging Antiplatelet Therapy with Cangrelor in Patients Undergoing Cardiac Surgery
COX	Cyclooxygenase
DAPT	Dual antiplatelet therapy
DVT	Deep vein thrombosis
IABP	Intra-aortic balloon pump
IVS	Interventricular septum
LMWH	Low molecular-weight heparin
PCI	Percutaneous coronary intervention
RCA	Right coronary artery
STEMI	ST-elevation myocardial infarction
VA-ECMO	Venoarterial extracorporeal membrane oxygenation
VSR	Ventricular septal rupture

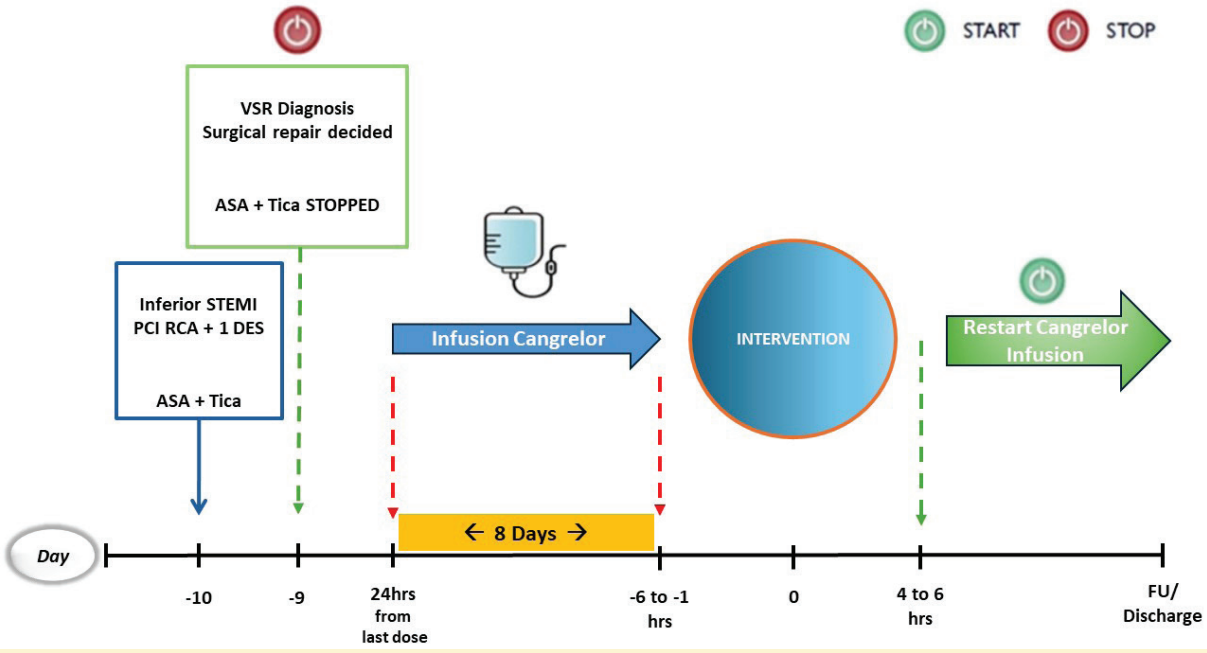

Figure 2. Timeline for Case 1. Cardiac surgery was conducted 10 days post-primary percutaneous coronary intervention (PPCI) and 8 days after discontinuation of dual antiplatelet therapy (DAPT). Bridging therapy included intravenous cangrelor at 0.75 mcg/kg/min for 8 days, continuing until 2 hours before surgery.

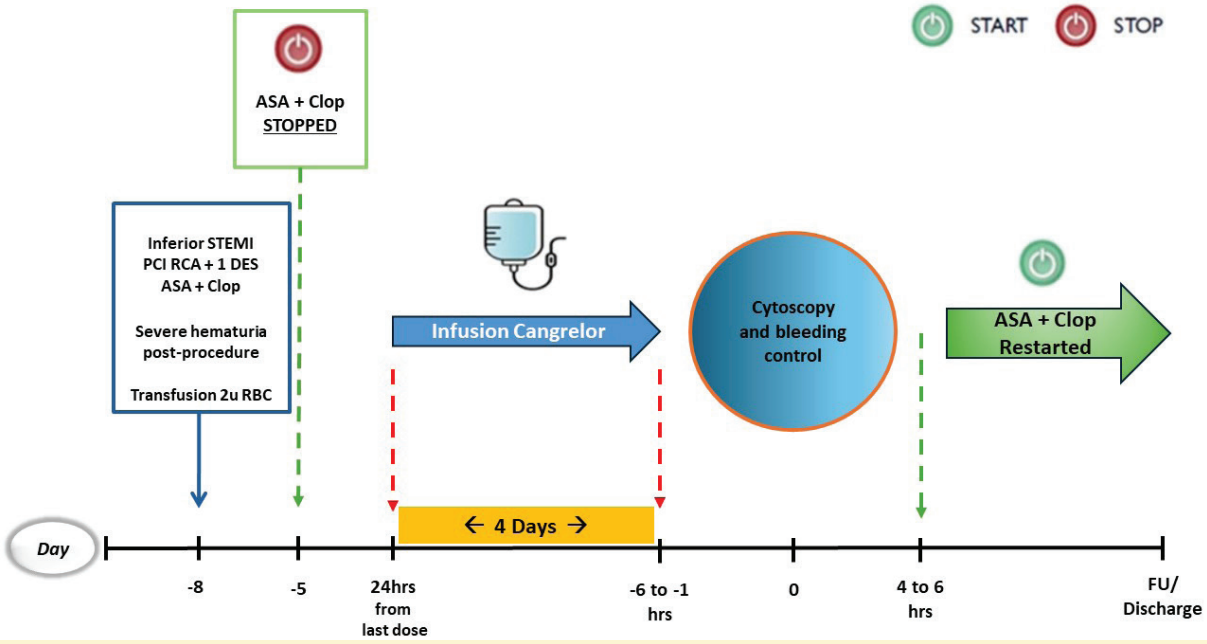

Figure 3. Timeline for Case 2. Cystoscopy was performed 8 days post-PPCI and 5 days after DAPT interruption. Bridging therapy involved intravenous cangrelor at 0.75 mcg/kg/min for 4 days, ending 2 hours before the procedure.

bladder irrigation with normal saline solutions failed to arrest the hematuria, we consulted the urology team to rule out other causes of hematuria such as neoplasm. The urologists recommended a cystoscopy and advised stopping antiplatelet agents for at least five days due to the potential need for spinal anesthesia. We discontinued DAPT and bridged the gap with a continuous intravenous dose of cangrelor at 0.75 mcg/kg/min for four days (Figure 3). The patient also received a prophylactic dose of enoxaparin (1 mg/kg once daily) for deep vein thrombosis (DVT) prevention during this time.

The cystoscopy was performed on the fifth day after DAPT discontinuation and two hours after stopping cangrelor. Neoplastic

disease was ruled out, and the hematuria was successfully controlled. Oral administration of aspirin and clopidogrel was resumed six hours after the procedure, with only clopidogrel given as a loading dose. The patient was discharged four days later without further thrombotic or bleeding complications.

Discussion

To our knowledge, this case series is the first to report the use of cangrelor monotherapy as a bridging therapy in patients who have recently undergone PCI, need urgent surgery, and require continuous DAPT. A theoretical bridging algorithm using cangrelor monotherapy for perioperative management in patients undergoing spine surgery shortly after PCI has been previously proposed.[12]

It is well known that perioperative discontinuation of antiplatelet therapy is a significant cause of major adverse cardiovascular events (MACEs).[13,14] To date, the only antiplatelet agents used for bridging when DAPT discontinuation is necessary have been cangrelor and glycoprotein IIb/IIIa inhibitors. However, cangrelor is preferred due to its favorable pharmacokinetic and pharmacodynamic profile, characterized by a short half-life (3-6 minutes) and rapid restoration of platelet function (within 60 minutes). Furthermore, there is no need for dose adjustments based on renal function, and the dosing regimen for bridging is fixed (0.75 mg/kg/min intravenously), unlike glycoprotein IIb/IIIa inhibitors. These inhibitors have a longer half-life and shorter offset of action (4-6 hours), require dosing adjustments in chronic kidney disease, and lack a standard bridging dose.[15] Glycoprotein IIb/IIIa inhibitors also carry an increased risk of thrombocytopenia and have never been tested as bridging therapy in a randomized trial.[16] On the other hand, cangrelor was evaluated in a randomized trial (Bridging Antiplatelet Therapy with Cangrelor in Patients Undergoing Cardiac Surgery (BRIDGE) trial), where the primary efficacy endpoint (platelet reactivity) was significantly lower in the cangrelor group compared to placebo throughout the entire treatment period, with no significant differences in bleeding outcomes.[9] Bridging with intravenous cangrelor infusion, along with low-dose aspirin throughout the period, has been reported in a variety of cardiac and non-cardiac operations such as lobectomy, prostatectomy, gastrectomy, and nephrectomy. Additionally, there have been recent reports of perioperative cangrelor use in two liver transplantation cases.[16, 17]

Bridging patients in need of DAPT prior to surgery with intravenous antiplatelet agents has been applied and recommended only in conjunction with low-dose aspirin.[5,18] Aspirin (acetylsalicylic acid) has been a cornerstone antiplatelet agent for primary and secondary prevention in atherothrombotic cardiovascular disease for more than 60-70 years. It acts as a non-reversible cyclooxygenase (COX) inhibitor, particularly as a COX-1 inhibitor. As such, aspirin irreversibly inhibits thromboxane-A2 synthesis, and this inhibition lasts for the lifespan of platelets (8 to 10 days). An aspirin loading dose achieves maximum platelet inhibition within 2 hours and can inhibit up to 50% of platelet aggregation for five days. Given that only 10% of the platelet pool is replenished daily, aspirin maintains COX-1 inhibition with repeated low maintenance dosing.[19,20]

Both patients in this case series underwent either a cardiac or a non-cardiac surgery/intervention within 8-10 days post-PPCI. Consequently, they had to discontinue the guideline-recommended antiplatelet treatment, which includes loading and maintenance doses of aspirin and a $P2Y_{12}$ inhibitor. Specifically, the first patient underwent surgery 10 days post-PPCI and 8 days after discontinuing DAPT, proceeding to surgery on cangrelor monotherapy as a bridging strategy. The second patient underwent a urological procedure 8 days post-PPCI and 5 days post-DAPT discontinuation. It is understood that during these time frames, the antiplatelet effect of aspirin is diminished but not entirely absent, considering its pharmacodynamics. The potential of cangrelor monotherapy as a viable bridging therapy in patients needing surgery shortly after PCI warrants further investigation in a randomized manner.

Conclusion

The management of patients on DAPT in the perioperative period is challenging, and current practice favors the use of intravenous antiplatelet agents with a short duration of action, along with a low maintenance dose of aspirin. The efficacy of cangrelor monotherapy as a bridging therapy in these circumstances should be explored in a large-scale trial.

Informed Consent: Written informed consent was obtained from the patient's family (Case 1) and from the patient (Case 2) for the publication of this case report and any accompanying images.

Peer-review: Externally/Internally peer-reviewed.

Author Contributions: Concept – S.F.P., K.C.T., E.P., M.D.; Design – S.F.P., K.C.T., E.P., M.D.; Supervision – A.K., G.K., A.Z.; Resource – M.D., A.S., A.B., T.G.; Data Collection and/or Processing – M.D., A.S., A.B., T.G.; Literature Review – E.P., M.D., A.S., A.B., T.G.; Writing – S.F.P., K.C.T.; Critical Review – T.G., G.K., A.K., A.Z.

Use of AI for Writing Assistance: The authors confirm that artificial intelligence (AI)-assisted technologies, such as Large Language Models (LLMs), chatbots, or image creators, were not used in the production of this work.

Conflict of Interest: The authors have no conflicts of interest to declare.

Funding: The authors declared that this study received no financial support.

References

1. Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J.* 2018;39(3):213–260. [CrossRef]
2. Saia F, Belotti LM, Guastaroba P, et al. Risk of adverse cardiac and bleeding events following cardiac and noncardiac surgery in patients with coronary stent: How important is the interplay between stent type and time from stenting to surgery? *Circ Cardiovasc Qual Outcomes.* 2016;9(1):39–47. [CrossRef]
3. Banerjee S, Angiolillo DJ, Boden WE, et al. Use of antiplatelet therapy/DAPT for Post-PCI patients undergoing noncardiac surgery. *J Am Coll Cardiol.* 2017;69(14):1861–1870. [CrossRef]
4. Sullivan AE, Nanna MG, Wang TY, et al. Bridging antiplatelet therapy after percutaneous coronary intervention: JACC review topic of the week. *J Am Coll Cardiol.* 2021;78(15):1550–1563. [CrossRef]

5. Halvorsen S, Mehilli J, Cassese S, et al. 2022 ESC Guidelines on cardiovascular assessment and management of patients undergoing non-cardiac surgery. *Eur Heart J.* 2022;43(39):3826–3924. [CrossRef]
6. Alexopoulos D. p2y12 receptor inhibitors in acute coronary syndromes: From the research laboratory to the clinic and vice versa. *Cardiology.* 2014;127(4):211–219. [CrossRef]
7. Alexopoulos D, Pappas C, Sfantou D, Lekakis J. Cangrelor in percutaneous coronary intervention: Current status and perspectives. *J Cardiovasc Pharmacol Ther.* 2018;23(1):13–22. [CrossRef]
8. Akers WS, Oh JJ, Oestreich JH, Ferraris S, Wethington M, Steinhubl SR. Pharmacokinetics and pharmacodynamics of a bolus and infusion of cangrelor: A direct, parenteral P2Y12 receptor antagonist. *J Clin Pharmacol.* 2010;50(1):27–35. [CrossRef]
9. 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):265–274. [CrossRef]
10. Ronco D, Matteucci M, Kowalewski M, et al. Surgical treatment of postinfarction ventricular septal rupture. *JAMA Netw Open.* 2021;4(10):e2128309. [CrossRef]
11. Guan X, Chen M, Li Y, et al. Comparison of safety between different kinds of heparins in patients receiving ıntra-aortic balloon counterpulsation. *Thorac Cardiovasc Surg*. 2021;69(6):511–517. [CrossRef]
12. Peeters SM, Nagasawa D, Gaonkar B, et al. Perioperative dual antiplatelet therapy for patients undergoing spine surgery soon after drug eluting stent placement. *Surg Neurol Int.* 2021;12:302. [CrossRef]
13. Schouten O, van Domburg RT, Bax JJ, et al. Noncardiac surgery after coronary stenting: Early surgery and interruption of antiplatelet therapy are associated with an increase in major adverse cardiac events. *J Am Coll Cardiol.* 2007;49(1):122–124. [CrossRef]
14. Capodanno D, Angiolillo DJ. Management of antiplatelet therapy in patients with coronary artery disease requiring cardiac and noncardiac surgery. *Circulation.* 2013;128(25):2785–2798. [CrossRef]
15. Muñiz-Lozano A, Rollini F, Franchi F, Angiolillo DJ. Update on platelet glycoprotein IIb/IIIa inhibitors: Recommendations for clinical practice. *Ther Adv Cardiovasc Dis.* 2013;7(4):197–213. [CrossRef]
16. Rossini R, Masiero G, Fruttero C, et al. Antiplatelet therapy with cangrelor in patients undergoing surgery after coronary stent implantation: A real-world bridging protocol experience. *TH Open.* 2020;4(4):e437–e445. [CrossRef]
17. Succar L, Lopez CN, Victor DW 3rd, et al. Perioperative cangrelor in patients with recent percutaneous coronary intervention undergoing liver transplantation: A case series. *Pharmacotherapy.* 2022;42(3):263–267. [CrossRef]
18. Angiolillo DJ, Rollini F, Storey RF, et al. International expert consensus on switching platelet $P2Y_{12}$ receptor-inhibiting therapies. *Circulation.* 2017;136(20):1955–1975. [CrossRef]
19. Jneid H, Bhatt DL, Corti R, Badimon JJ, Fuster V, Francis GS. Aspirin and clopidogrel in acute coronary syndromes: Therapeutic insights from the CURE study. *Arch Intern Med.* 2003;163(10):1145–1153. [CrossRef]
20. Maree AO, Fitzgerald DJ. Variable platelet response to aspirin and clopidogrel in atherothrombotic disease. *Circulation.* 2007;115(16):2196–2207. [CrossRef]