Medication-Induced Coagulopathy

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Coagulopathy can be caused by congenital or acquired platelet or factor deficiencies. Acquired deficiencies can be due to various medications, due to interruption in platelet function, or interruption in the coagulation cascade. When medication-induced coagulopathy occurs, it is vital to know the offending agent if possible, various tools to measure or assess the degree or coagulopathy or dysfunction, and options for correcting the coagulopathy.

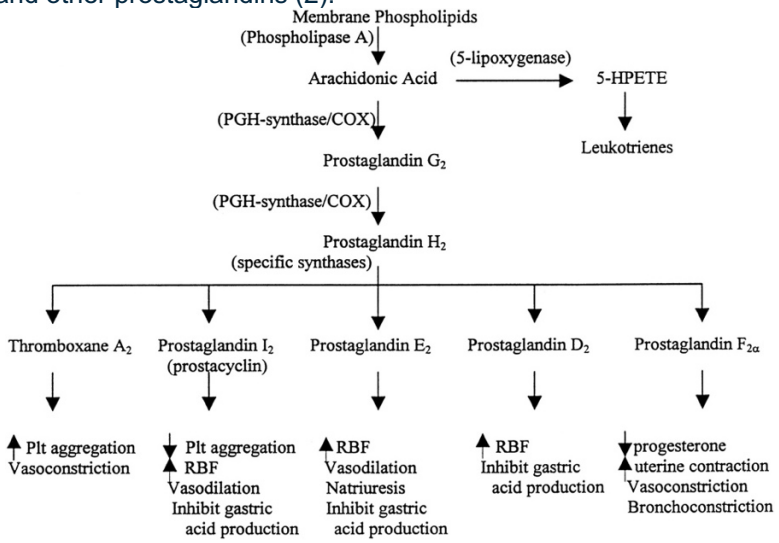
Antiplatelets

Antiplatelet agents are used for various medical reasons, such as reduction in cardiovascular disease and stroke (1). The main anti-platelet agents encountered are aspirin and the class of medications known as P2Y12 inhibitors.

Aspirin

Mechanism of Action

Aspirin exerts its effect primarily by interfering with the biosynthesis of cyclic prostanoids, ie, thromboxane A_2 (TXA_2), prostacyclin, and other prostaglandins (2).



Testing

Testing for aspirin effect includes platelet function assays.

- Options include Thromboelastography-platelet mapping (TEG-PM), platelet mapping, and VerifyNow (reports platelet functions in terms of aspirin-reaction units (ARU)).
    - TEG Platelet Mapping Assay is able to provide a semiquantitative analysis of platelet function through evaluation of the contribution of the ADP or thromboxane A2 (TxA2) receptors.
    - VerifyNow was created to determine if patients taking aspirin had adequate platelet inhibition, and therefore were not aspirin resistant. Although this test was created to evaluate aspirin resistance and compliance, this test has been used pre-operatively to determine bleeding risk as well (11).

Treatment

Aspirin irreversibly inhibits cyclooxygenase, and therefore there is no reversal agent. The minimum time from drug interruption to platelet restoration is 4 days (4). Treatment would therefore include support care and transfusion of platelets to aid in hemostasis.

P2Y12 Inhibitors

Mechanism of Action

P2Y12 inhibitors work by binding to the P2Y12 receptor on platelets, and therefore prevent activation and aggregation. P2Y12 inhibitors may be used as dual anti-platelet therapy along with aspirin in patients with acute coronary syndromes or those who undergo percutaneous coronary intervention.

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Medications

The medications within the class of P2Y12 inhibitors include clopidogrel, ticagrelor, prasugrel and cangrelor (3)

Table 1. Pharmacological Properties of $P2Y_{12}$ Receptor Inhibitors

	Clopidogrel	Prasugrel	Ticagrelor	Cangrelor
Receptor blockade	Irreversible	Irreversible	Reversible	Reversible
Prodrug	Yes	Yes	No	No
Half-life of parent drug	≈6 h	<5 min	6–12 h	3–6 min
Half-life of active metabolite	30 mins	Distribution half-life, 30–60 mins	8–12 h	NA
		Elimination half-life, 2–15 h		
Binding site	ADP-binding site	ADP-binding site	Allosteric binding site	Undetermined*
Administration route	Oral	Oral	Oral	Intravenous
Frequency	Once daily	Once daily	Twice daily	Bolus plus infusion
Onset of action†	2–8 h	30 min–4 h	30 min–4 h	≈2 min
Offset of action	5–10 d	7–10 d	3–5 d	60 min
CYP drug interaction‡	CYP2C19	No	CYP3A	No
Approved settings	ACS (invasive and noninvasively managed), stable CAD, PCI, PAD, and ischemic stroke	ACS undergoing PCI	ACS (invasive or noninvasively managed) or history of MI	PCI in patients with or without ACS

ACS indicates acute coronary syndrome; CAD, coronary artery disease; CYP, cytochrome P450; MI, myocardial infarction; PAD, peripheral arterial disease; and PCI, percutaneous coronary intervention.

**The binding site of cangrelor at the $P2Y_{12}$ receptor level is not clearly defined; nevertheless, cangrelor is associated with high levels of receptor occupancy, preventing ADP signaling.*

†Indicates times after loading dose and bolus administration for oral and intravenous agents, respectively. Times for oral agents refer to clinically stable subjects and may be prolonged in patients with ST-segment–elevation myocardial infarction or treated with opioids.

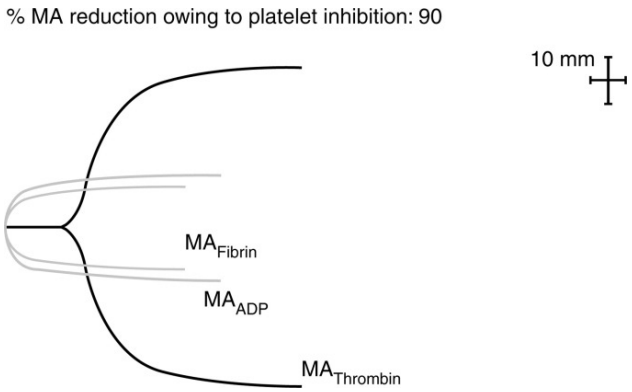
‡Indicates clinically significant drug interactions.

- Clopidogrel is a prodrug and therefore must be metabolized to its active form to work.
- Cangrelor is unique as it is an intravenous P2Y12 inhibitor, with a rapid onset and offset of approximately 3 minutes. The rapid off-set is due to metabolism of the medication by plasma esterases, which makes it a useful anti-platelet agent medication in those who are at high risk of bleeding or in need or procedures or surgeries.

Testing

Similar to aspirin, platelet function assays can be utilized to assess for responsiveness or nonadherence to P2Y12 inhibitors. Additionally, platelet function testing may help determine timing of surgery following withdrawal of P2Y12 inhibitors, such as for cardiac surgery. TEG-PM and VerifyNow may be used.

- Example of TEG-PM:



  - This is a patient with 90% inhibition, who was recently on clopidogrel

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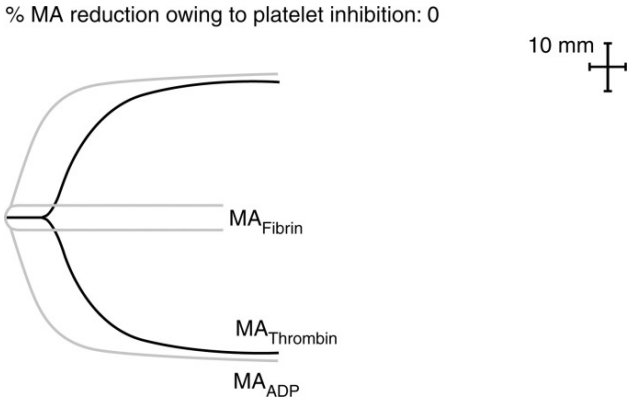

- This is a patient who was not taking any anti-platelets, with 0% inhibition (13).

VerifyNow may be used, and reports in terms of P2Y12 reaction units (PRU)
- Low response or nonresponse is indicated by high platelet reactivity.

Guidelines for Cessation Prior to Surgery or Procedures
When anticipating invasive procedures or surgeries, P2Y12 inhibitors need to be held to minimize bleeding risks. The 2024 ACC/AHA guidelines recommend the management of anti-platelet therapy be determined by a multi-disciplinary team to weigh the risks of bleeding, thrombosis, and consequences of delay of surgery (4).

Recommendations for Antiplatelet Therapy and Timing of Noncardiac Surgery in Patients With Coronary Artery Disease
Referenced studies that support the recommendations are summarized in the Online Data Supplement.

COR	LOE	Recommendations
1	B-NR	1. For patients with CAD undergoing elective NCS, management of perioperative antiplatelet therapy and timing of surgery should be determined by a multidisciplinary team with shared decision-making to weigh the risks of bleeding, thrombosis, and consequences of delayed surgery.[1–7]

Treatment
Supportive care with cessation of the medication and platelet transfusions may be necessary if a bleeding patient was on a P2Y12 inhibitor.

Anticoagulants
Anticoagulants are varying classes of medications that are used to prevent or treat thrombosis. Vitamin K antagonists were the traditional medications used, followed by direct oral anticoagulants. These medications may be used in situations such as atrial fibrillation for stroke prevention, treatment or prevention of venous thromboembolism, or other states in which there is a high risk of thrombosis.

Vitamin K Antagonists (VKA)
Mechanism of Action
VKAs work by inhibiting the enzyme vitamin K epoxide reductase, and therefore prevent the synthesis of vitamin K dependent clotting factors, such as factors II, VII, IX, and X.

Medications
Warfarin is the most commonly used oral VKA.

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Testing
International normalized ratio (INR) is used to determine the effect of VKAs. Elevated INR levels have been associated with bleeding.

Guidelines for cessation prior to surgery or procedures
VKAs should be held for 5 days prior to surgery or an invasive procedure (4). In patients with high thromboembolic risks, bridging with heparin may be utilized.

Treatment
Treatment options include vitamin K supplementation, prothrombin complex concentrates (PCCs), and plasma administration.

- Vitamin K Supplementation
  - Vitamin K reverses the effects of VKAs. In bleeding patients, or prior to surgery or an invasive procedure, IV vitamin K may be given. The onset is approximately 2 hours. Subcutaneous vitamin K can also be given, but its absorption and response is less predictable.
  - In non-bleeding patients with an elevated INR of 4.5-10, the recommendation is not to administered vitamin K to these patients. A 2019 systematic review supported this recommendation (5).
- Prothrombin complex concentrates (PCCs)
  - PCCs include 3-factor (3F), 4-factor (4F), or activated PCCs. 3F-PCCs include factors II, IX,and X, 4F-PCCs include II, VII, IX, and X, and aPCCs include II, IX, X, and activated VII.
  - Sarode et al (6) found that 4F-PCC were noninferior to plasma in terms of efficacy, and superior with respect to safety. Guidelines therefore support 4F-PCC over plasma in bleeding patients taking VKAs.
  - PCCs have several advantages to plasma including faster reversal, no need for blood matching, reduced viral transmission, and reduced risk of volume overload.
- Plasma
  - Plasma contains clotting factors amongst others components, and can also therefore reverse the effects of VKAs.

Table. Available Treatments for Reversal of Vitamin K Antagonist–Associated Coagulopathy

Characteristic	Vitamin K	Fresh Frozen Plasma	3-Factor PCC	4-Factor PCC
Constituents	Vitamin K	All vitamin K–dependent clotting factors	Factor II, IX, X, proteins C and S*	Factor II, VII, IX, X, proteins C and S*
Route of administration	Oral or intravenous	Intravenous	Intravenous	Intravenous
Dose	5–10 mg	10–15 mL/kg	25–50 IU of factor IX/kg	25–50 IU of factor IX/kg
Onset of effect	6–8 h	Duration of infusion†	15–30 min†	15–30 min†
Adverse effects	Rare anaphylaxis	Fluid overload; febrile and allergic reactions; viral transmission; transfusion-related acute lung injury	Possible increase in thromboembolic complications	Possible increase in thromboembolic complications
Cost	Minimal	Moderate	High	High
Other	Intravenous administration produces more rapid reversal	Requires coadministration of vitamin K to sustain reversal	Requires coadministration of vitamin K to sustain reversal; may require coadministration of plasma or recombinant factor VIIa as a source of factor VII	Requires coadministration of vitamin K to sustain reversal

PCC indicates prothrombin complex concentrate.
*Some preparations also contain antithrombin and small amounts of heparin.
†Onset can also be affected by the dose administered.

(7)

Direct Oral Anticoagulants (DOACs)

Mechanism of Action
DOACs are classified into two major categories based on mechanism of action. Direct thrombin inhibitors (DTIs) are one class, and Xa inhibitors are another class.

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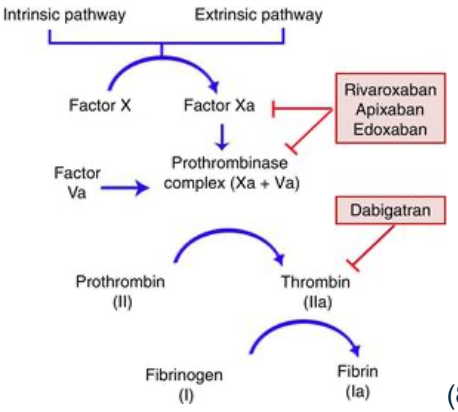

(8)

Medications

- DTIs include the oral agent, dabigatran, and intravenous agents, argatroban and bivalrudin.
- Xa Inhibitors include the oral agents apixaban, rivaroxaban, and edoxaban.
- XI inhibitors are emerging as potential anticoagulants with the same goal of preventing thromboembolism while minimizing bleeding risks.

Testing

- Global coagulation testing (such as prothrombin time (PT) and activated partial thromboplastin time (aPTT)) has not been proven to be beneficial in assessing the coagulant effect of DOACs; and therefore, are not recommended to assess relevant DOAC concentrations.
- The one exception is using dilute thrombin time for dabigatran, where a normal thrombin time represents no residual dabigatran effect.
- Drug-specific calibrated anti-Xa assays are regarded as the “gold standard” method for monitoring direct anti-Xa inhibitors. If drug-specific anti-Xa assays are not available, chromogenic anti-Xa assays calibrated for unfractionated heparin can be utilized with sufficient accuracy.

Guidelines for Cessation Prior to Surgery or Procedures

The 2024 ACC/AHA guidelines recommend the management of oral anticoagulants be determined by a multi-disciplinary team with time-based interruption to balance the competing risks of thromboembolism and bleeding (4).

Table 13. Perioperative Management of Direct Oral Anticoagulants and Vitamin K Antagonists

Preoperative DOAC Schedule												
		Preoperative Interruption						Surgery/ Procedure	Postoperative Resumption			
	Procedure Bleeding Risk	Day -6	Day -5	Day -4	Day -3	Day -2	Day -1	Day 0	Day +1	Day +2	Day +3	Day +4
Apixaban, edoxaban, rivaroxaban	High	*	*	*	*	†	†	†	†	†	*	*
	Low/Moderate	*	*	*	*	*	†	†	*	*	*	*
	Minimal	*	*	*	*	*	*	*	*	*	*	*
Apixaban, edoxaban, rivaroxaban with renal impairment (CrCl <30 mL/min)	High	*	*	*	†	†	†	†	†	†	*	*
	Low/Moderate	*	*	*	*	†	†	†	*	*	*	*
	Minimal	*	*	*	*	*	*	*	*	*	*	*
Dabigatran CrCl ≥50 mL/min	High	*	*	*	*	†	†	†	†	†	*	*
	Low/Moderate	*	*	*	*	*	†	†	*	*	*	*
	Minimal	*	*	*	*	*	*	*	*	*	*	*
Dabigatran CrCl <50 mL/min	High	*	*	†	†	†	†	†	†	†	*	*
	Low/Moderate	*	*	*	*	†	†	†	*	*	*	*
	Minimal	*	*	*	*	*	*	*	*	*	*	*

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Treatment

- Treatment options include PCCs, plasma, or direct reversal agents. For rivaroxaban and apixaban, andexanet alfa is a Xa decoy molecule that binds the medication making it relatively inactive in a matter a minutes. The Anexxa-4 trial (9) looked at patients taking Xa inhibitors with major bleeds, majority were gastrointestinal and intracranial hemorrhages. Xa activity level decreased by 89% and 93% in patients taking rivaroxaban and apixaban respectively. Additionally, hemostasis was excellent or good in 79% of patients, with thrombotic events occurring in 18% of patients at a 30-day follow-up. This to approval of andexanet alfa for major bleeding associated with rivaroxaban or apixaban.
- The Anexxa-I was a follow-up trial looking solely at patients with intra-cranial hemorrhage who were taking Xa inhibitors. Patients either received andexanet alfa, or usual care. The patients who received andexanet alfa 67% had hemostatic efficacy compared to 53.1% in the usual carer group. Additionally, Xa activity level decreased 94.5% in the andexanet group compared to 26.9% in the usual care group. Thrombotic events occurred in 10.3% in the andexanet group compared to 5.6% in the usual care group. Of note, 85.5% of patients in the usual care group received PCCs.
- Although andexanet alfa has been used in major bleeding with good results, the use in cardiac surgery should be carefully considered as many case reports and series document inability to appropriate heparinize for cardiopulmonary bypass or even the formation pump thrombosis. Therefore, this specific population has many risks associated with andexanet alfa use.
- Idarucizumab is an antibody fragment and directly reverses the effect of dabigatran within minutes (12).

References

1. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;140(11):e596-e646
2. Awtry, EH, Loscalzo, J. Aspirin. Circulation. 2000;101(10)
3. Angiolillo DJ, Rollini F, Storey RF, Bhatt DL, James S, et al. International Expert Consensus on Switching Platelet P2Y12 Receptor-Inhibiting Therapies. Circulation. 2017;136(20).
4. Thompson A, Fleischmann KE, Smilowitz NR, de las Fuentes L, Mukherjee D, et al. 2024 AHA/ACC/ACS/ASNC/HRS/SCA/SCCT/SCMR/SVM Guideline for Perioperative Cardiovascular Management for Noncardiac Surgery: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2024;15(19)
5. Khatib R, Ludwikowska M, Witt DM, Ansell J, Clark NP, et al. Vitamin K for reversal of excessive vitamin K antagonist anticoagulation: a systematic reviewe and meta-analysis. Blood Adv. 2019;3(5):789-796
6. Sarode R, Milling TJ Jr, Refaai MA, et al. Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting with major bleeding: a randomized, plasma-controlled, phase IIIb study. Circulation 2013;128:1234-1243.
7. Quinlan DJ, Eikelboom JW, eitz JI. Four-factor prothrombin complex concentrate for urgent reversal of vitamin K antagonists in patients with major bleeding. Circulation;2013(128):1179-1181.
8. Cabezas-Calderon V, Bassas Freixas P, Garcia-Patos B. Direct-acting Oral Anticoagulants in Dermatologic Surgery. Practical Dermatology 2020;111(5):357-363.
9. Connolly SJ, Truman MJ, Eikelboom JW, Gibson CM, Curnutte JT, et al. Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors. NEJM 2016;375(12).
10. Connolly SJ, Sharma M, Cohen AT, Demchuk AM, Czlonkowska A, et al. Andexanet for Factor Xa Inhibitor-Associated Acute Intracerebral Hemorrhage. NEJM 2024;390:174-1755.
11. Welsh KJ, Dasgupta A, Nguyen AND, Wahed A. Utility of VerifyNow for Point-of-Care Identification of an Aspirin Effect Prior to Emergency Cardiac Surgery. Ann Clin Lab Sci 2015;45(4):377-81.
12. Pollack CV, Reilly. PA, Eikelboom J, Glund S, Verhamme P, et al. Idarucizumab for Dabigatran Reversal. NEJM 2015;373:511-520.
13. Collyer TC, Gray DJ, Sandhu R, Berridge J, Lyons G. Assessmemnt of platelet inhibition secondary to clopidogrel and aspirin therapy in preoperative acute surgical patients measured by Thromboelastography Platelet Mapping. BJA 2009;102(4):492-498.

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