GLIN IPA

Pharmacy Factor

Anticoagulation & Antiplatelet Update: a Review of Triple Therapy Recommendations

Anticoagulation & Antiplatelet Update

Question of the Month

Did You Know...Generic Dabigatran is Available?

In November of 2022, the generic formulation of Pradaxa (dabigatran) became available for patient use for indications of treatment to reduce the risk of blood clots and strokes in adults with non-valvular atrial fibrillation as well as to treat deep vein thrombosis and pulmonary embolism. The patient still must receive a parenteral anticoagulant such as heparin or enoxaparin for treatment for the first 5 days at minimum prior to initiating dabigatran therapy.

Dabigatran is available in capsules in the strengths of 75 mg and 150 mg.

Generic dabigatran may be an option for patients who have cost concerns with using Eliquis or Xarelto, especially if they have traditionally been managed on warfarin with difficulty maintaining a therapeutic INR. Unfortunately, the landscape of DOAC coverage has not changed much with the generic release of dabigatran as prices for the generic formulation remain high. With Highmark/BCBS formularies, dabigatran is typically non-formulary and not covered. With the NYRX Medicaid Prescription Program, dabigatran is not covered and a prior authorization would be needed, whereas Eliquis is covered without the need of a prior authorization. IHA formularies typically have dabigatran listed as a tier two (2) copay, with other brand names DOACs such as Xarelto and Eliquis as tier three (3) copays. It is expected to gain wider formulary coverage across Medicare plans in the latter half of 2023.

The cash price of this medication is less than the cash price of the brand name DOACS. For example, through GoodRx, a 30-day supply of dabigatran 150 mg capsules is about $200, whereas a 30-day supply of Eliquis is about $600. For patients who do not have insurance and cannot utilize coupons or patient assistance programs through manufacturers, generic dabigatran may provide a less expensive option versus brand name DOACS, albeit with still a costly price.

References

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Anticoagulant & Antiplatelet Therapy (APT)

The following are some key points and clinical pathways from the ***2020 American College of Cardiology Expert Consensus Decision Pathway for Anticoagulant and Antiplatelet Therapy (APT) in patients with Atrial Fibrillation (AF) or Venous Thromboembolism (VTE) Undergoing Percutaneous Coronary Intervention (PCI) or with Atherosclerotic Cardiovascular Disease (ASCVD)***

In general, the use of "triple therapy" (dual antiplatelet therapy plus anticoagulation) is not recommended for most patients due to an increased risk of bleeding. If triple therapy is needed, a short duration (e.g., no more than 30 days) is recommended. When combined with an anticoagulant, clopidogrel is the recommended antiplatelet agent for most patients. If aspirin is being used, it should be limited to <100 mg daily dosing.

- Clopidogrel was used in most of the relevant randomized trials of patients who were taking oral anticoagulation

For patients on ≥ 2 antithrombotic agents, it is recommended to start or continue a proton pump inhibitor (or histamine H2-receptor antagonist in select cases). Proton pump inhibitor (or histamine H2-receptor antagonist) should be discontinued when the regimen returns to oral anticoagulant (OAC) therapy alone unless there are other indications for use (eg. Barrett's esophagus, Zollinger-Ellison syndrome, idiopathic chronic ulcer, etc.).

Clinical pathways are suggested for four potential clinical situations:

(1) prior AF on anticoagulation and the need for PCI

(2) new-onset AF requiring anticoagulation in a patient already on antiplatelet therapy for coronary artery disease (CAD)

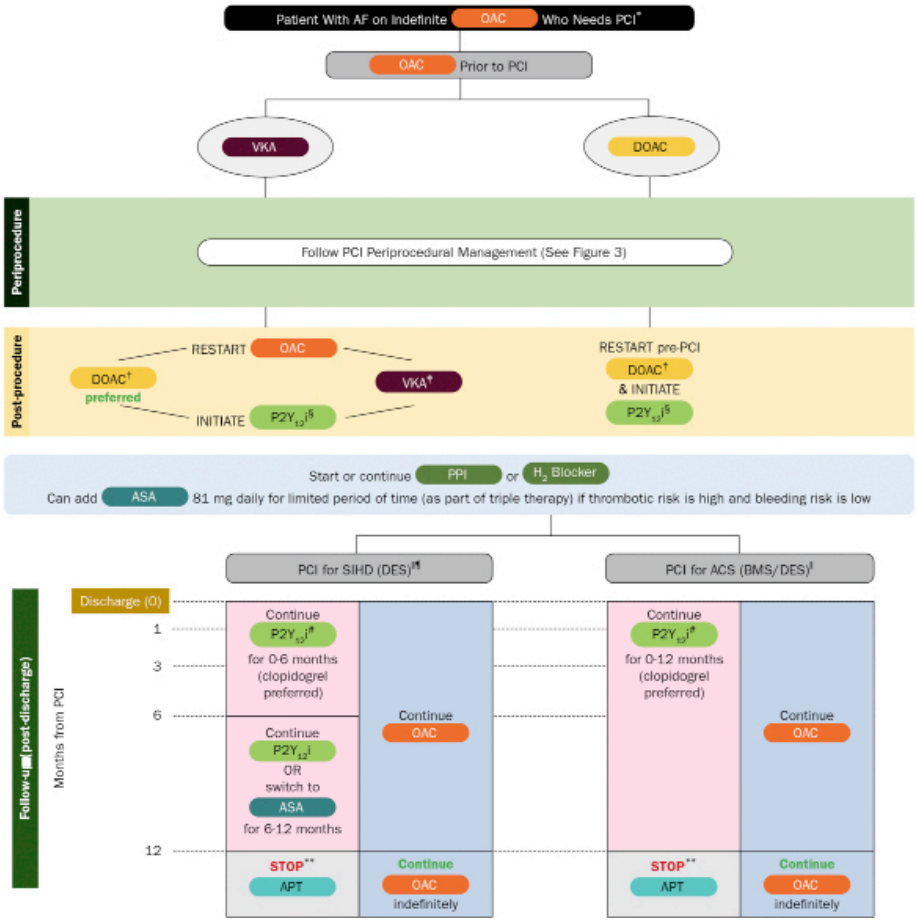
(3) prior VTE on anticoagulation and the need for PCI

(4) new or recurrent VTE requiring anticoagulation in a patient already on antiplatelet therapy for CAD

Clinical Pathways

Scenario 1

Patient with atrial fibrillation receiving an OAC who now needs PCI and APT



Medication Key

Antiplatelet therapy

- APT = Antiplatelet therapy
- ASA = Aspirin
- $P2Y_{12}i$ = $P2Y_{12}$ inhibitor

Anticoagulant therapy

- OAC = Oral anticoagulant
- DOAC = Direct oral anticoagulant
- VKA = Vitamin K antagonist

Acid Blockers

- H_2 Blocker = Histamine H2-receptor antagonist
- PPI = Proton pump inhibitor

APT refers to a P2Y12 inhibitor OR aspirin therapy

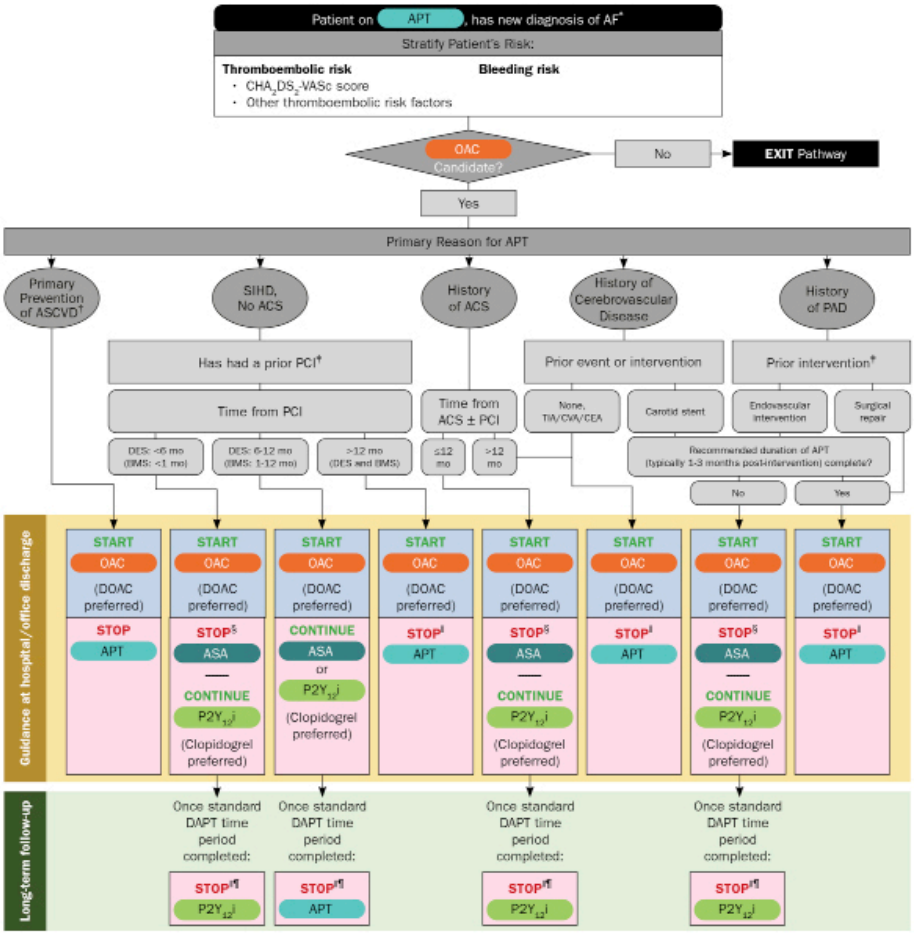
* See Table : Dosing Table for Atrial Fibrillation.
† See text for DOAC dosing.
‡ For those on a VKA, aspirin (81 mg daily) should be continued until the INR is in the therapeutic range.
§ Clopidogrel preferred over prasugrel/ticagrelor to th extent possible.
‖ If BMS, duration of P2Y12i is 1 month.
¶ The time frames listed here represent treatment durations post-PCI.
# Early discontinuation in those at high risk of bleedi is reasonable (after 3 months for SIHD and after 6 months for ACS).
** If perceived thrombotic risk is high and bleeding risk is low, continuation of SAPT (ASA 81 mg daily or clopidogrel 75 mg daily) beyond 12 months is reasonable.

AC = anticoagulant; ACS = acute coronary syndrome; AF = atrial fibrillation; BMS = bare metal stent; DES = drug-eluting stent; INR = international normalized ratio; PCI = percutaneous coronary intervention; SIHD = stab ischemic heart disease.

Clinical Pathways

Scenario 2

Patient on APT for ASCVD with new-onset atrial fibrillation requiring OAC



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Anticoagulant therapy

- OAC = Oral anticoagulant

APT refers to a P2Y12 inhibitor OR aspirin therapy

* See Table 2: Dosing Table for AF.
† ASCVD indicates coronary artery disease cerebrovascular disease/peripheral artery disease.
‡ As discussed in the text, for SIHD patients who have undergone prior CABG surgery, time since CABG surgery should be considered once the patient has an indication for an OAC. Continue aspirin (<100 mg daily) if <1 year post-CABG surgery and stop aspirin if >1 year post-CABG surgery. For patients with PAD or SIHD that is medically managed, APT can be stopped once the OAC is started.
§ If thrombotic risk is high and bleeding risk is low, can continue ASA 81 mg daily (as part of triple therapy) for up to 30 days.
‖ Occasionally, in patients felt to be at high thrombotic risk/low bleeding risk who have completed the standard duration of APT, continuation of SAPT with an OAC may be considered.
¶ Resume standard dosing OAC.

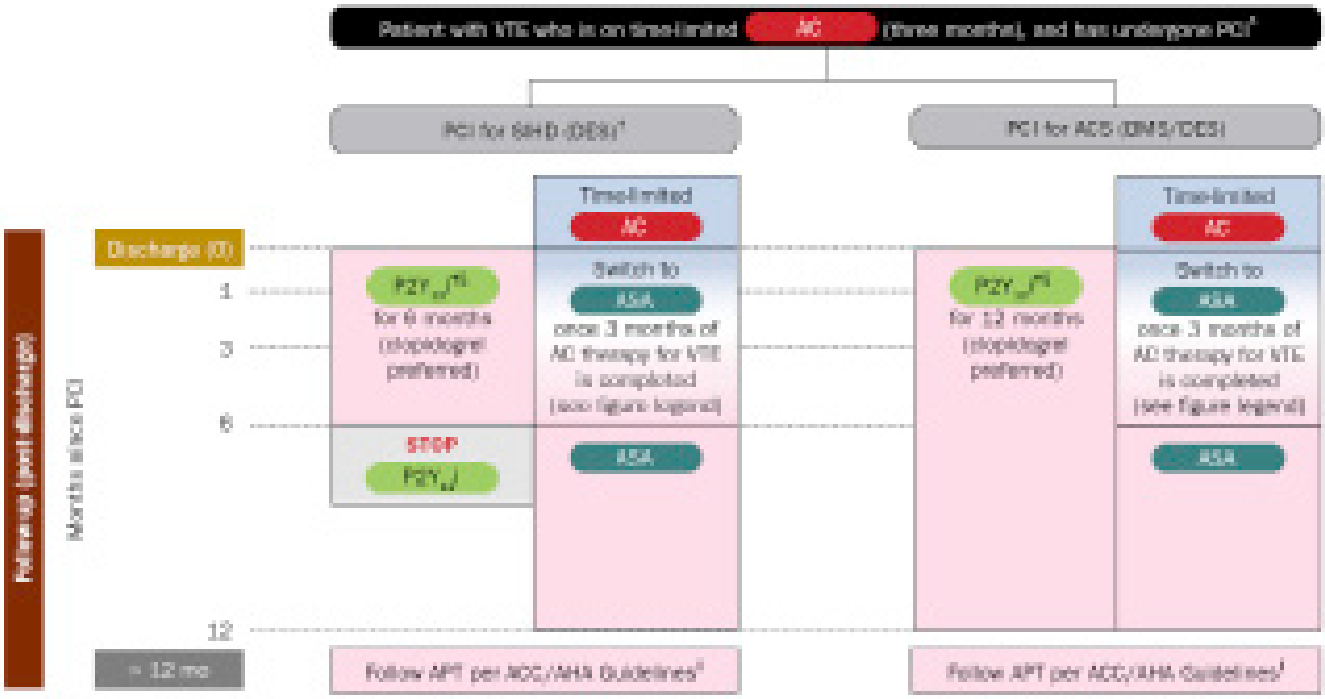
AF = atrial fibrillation; ACS = acute coronary syndrome; ASCVD = atherosclerotic cardiovascular disease; BMS = bare metal stent; CEA = carotid endarterectomy; CVA = cerebrovascular accident; DES = drug-eluting stent; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; SIHD = stable ischemic heart disease; TIA = transient ischemic attack.

Clinical Pathways

Scenario 3

Patient with prior VTE receiving an OAC being considered for PCI

3a: Patient on time-limited OAC for provoked VTE and need for PCI



APT refers to a P2Y12 inhibitor OR aspirin therapy

The switch from an AC to ASA post-PCI only begins after discharge once a patient has completed 3 months of AC therapy for a VTE. The timing of the switch to ASA depends on how far out the patient is from their VTE. For example, if the VTE was 1 month ago, continue the AC for 2 more months to complete VTE treatment, then switch to ASA indefinitely. If the VTE was 10 weeks ago, continue the AC for 2 more weeks to complete VTE treatment and then switch to ASA indefinitely.

† If BMS, duration of P2Y12I is 1 month.

‡ Early discontinuation of APT in those at high risk of bleeding is reasonable (after 3 months for SIHD and after 6 months for ACS).

§ If perceived high thrombotic risk/low bleeding risk: can continue ASA 81 mg daily for up to 30 days post-intervention.

‖ Refer to 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease. ASA preferred over P2Y12I for secondary prevention of VTE, if SAPT is pursued.

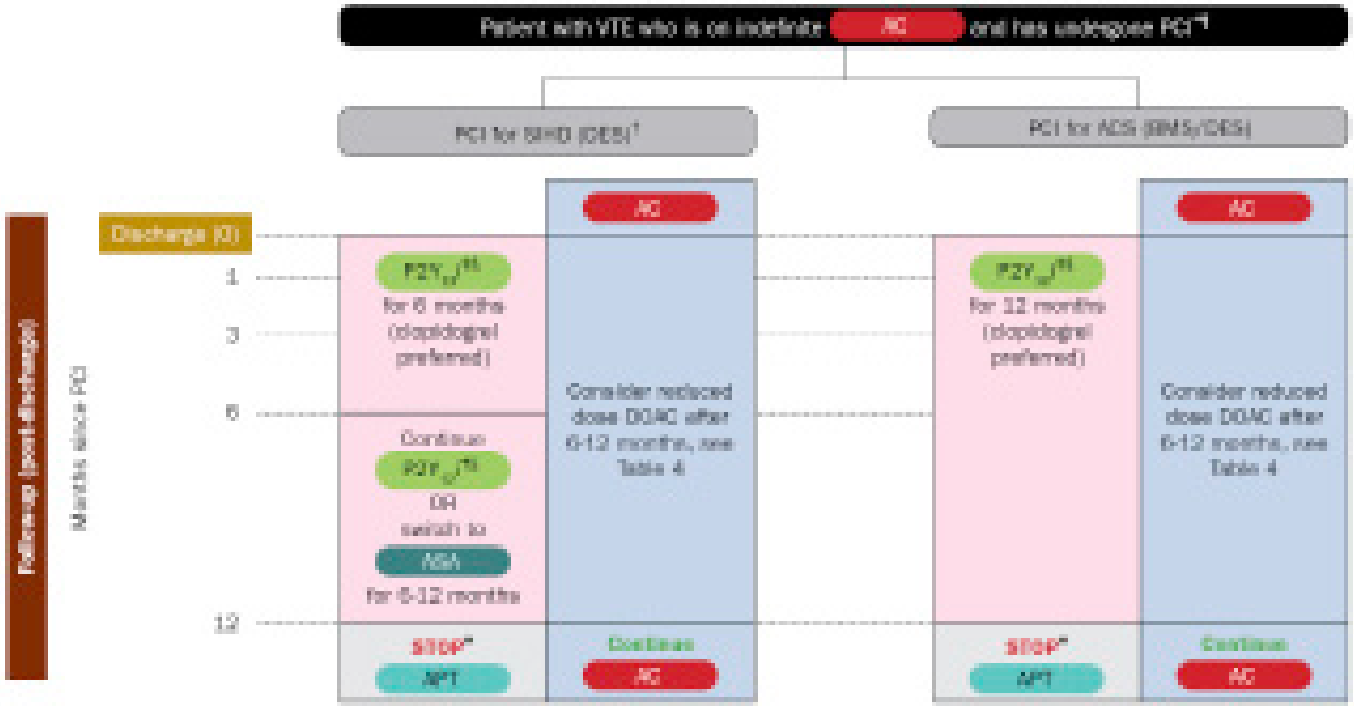
ACS = acute coronary syndrome; BMS = bare metal stent; DES = drug-eluting stent; OAC = oral AC; PCI = percutaneous coronary intervention; SAPT = single APT; SIHD = stable ischemic heart disease; VTE = venous thromboembolism.

Clinical Pathways

Scenario 3

Patient with prior VTE receiving an OAC being considered for PCI

3b: Patient on indefinite OAC for unprovoked VTE or event provoked by active cancer and need for PCI



Medication Key

Antiplatelet therapy

- APT = Antiplatelet therapy
- ASA = Aspirin
- $P2Y_{12}I$ = $P2Y_{12}$ inhibitor

Anticoagulant therapy

- AC = Anticoagulant

APT refers to a P2Y12 inhibitor OR aspirin therapy

† If BMS, duration of P2Y12i is 1 month.

‡ Early discontinuation of APT in those at high risk of bleeding is reasonable (after 3 months for SIHD and after 6 months for ACS).

§ If perceived high thrombotic risk/low bleeding risk: can continue ASA 81 mg daily for up to 30 days post-intervention.

¶ Two DOACs, apixaban and rivaroxaban, offer the added advantage of reduced-intensity dosing in patients on indefinite anticoagulation whose VTE was ≥6 months ago (rivaroxaban 10 mg daily in EINSTEIN CHOICE and apixaban 2.5 mg twice daily in AMPLIFY EXTEND); we encourage the use of a reduced-intensity OAC in such patients as a potential means of reducing bleeding risk.

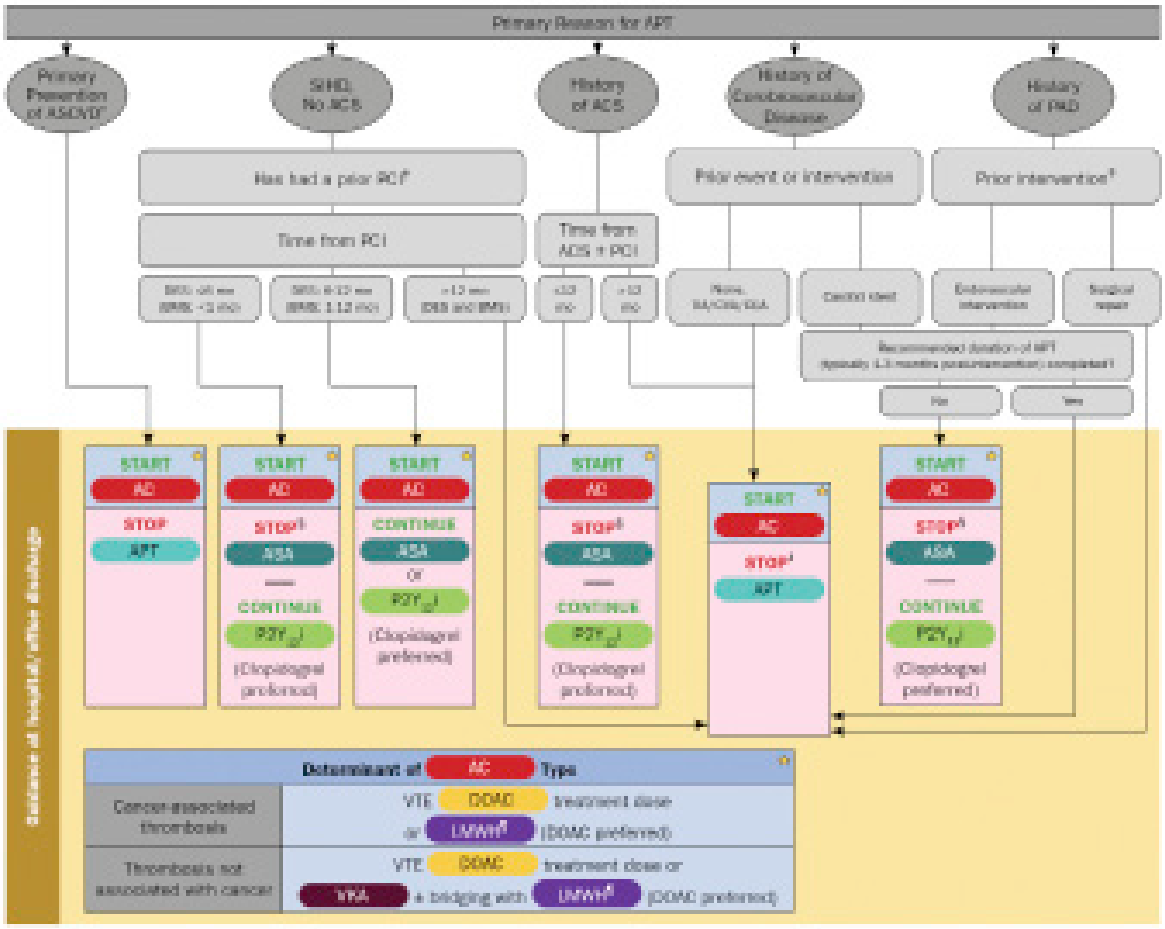
Occasionally, in patients felt to be at high thrombotic risk/low bleeding risk who have completed the standard DAPT period, continuation of SAPT with an OAC may be considered.

ACS = acute coronary syndrome; BMS = bare metal stent; DES = drug-eluting stent OAC = oral AC; PCI = percutaneous coronary intervention; SAPT = single APT; SIHD = stable ischemic heart disease VTE = venous thromboembolism.

Clinical Pathways

Scenario 4

Patient on APT for ASCVD with a new VTE requiring an OAC



Medication Key

Antiplatelet therapy

- APT = Antiplatelet therapy
- ASA = Aspirin
- $P2Y_{12}$ = $P2Y_{12}$ inhibitor

Anticoagulant therapy

- AC = Anticoagulant
- DOAC = Direct oral anticoagulant
- LMWH = Low-molecular-weight heparin
- VKA = Vitamin K antagonist

APT refers to a P2Y12 inhibitor OR aspirin therapy

† ASCVD = coronary artery disease cerebrovascular disease/peripheral artery disease.

‡ As discussed in the text, for SIHD patients who have undergone prior CABG surgery, time since CABG surgery should be considered once the patient has an indication for an AC. Continue aspirin (<100 mg daily) if <1 year post-CABG surgery and stop aspirin >1 year post CABG surgery (47). For patients with PAD or SIHD that is medically managed, APT can be stopped once the AC is started.

§ If thrombotic risk is high and bleeding risk is low, can continue ASA 81 mg daily (as part of triple therapy) for up to 30 days.

‖ Occasionally in patients felt to be at high thrombotic risk/low bleeding risk who have completed the standard duration of APT, continuation of SAPT with an OAC may be considered.

¶ DOAC preferred over LMWH and VKA for cancer associated thrombosis. DOAC preferred over VKA for non-cancer-associated thrombosis (dosing per Table 4). See text for details.

ACS = acute coronary syndrome; ASCVD = atherosclerotic cardiovascular disease; BMS = bare metal stent; CEA = carotid endarterectomy; CVA = cerebrovascular accident; DES = drug-eluting stent; SIHD = stable ischemic heart disease; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; TIA = transient ischemic attack; VTE = venous thromboembolism.

Other Considerations

Patients with heart valves

- In patients with mechanical heart valves: all patients must be treated with vitamin K antagonists
- In patients with surgical bioprosthetic heart valves, a DOAC is a reasonable choice

Non-stented ACS patients with indication for anticoagulation

- Optimal antithrombotic approach in these patients is not known
- Recommend these patients to be discharged on oral anticoagulants plus P2Y12 inhibitor and treat for 1 year
- In patients at very-high thrombotic risk who are not at high bleeding risk, consider adding aspirin 81 mg by mouth once daily for 1 month
- Oral anticoagulant plus aspirin 81 mg by mouth once daily for 1 year is reasonable alternative to oral anticoagulant plus P2Y12 inhibitor
- After 12 months recommendations are similar to stented ACS patients

Aspirin for Primary Prevention

Below are recommendations from the USPSTF regarding aspirin use to prevent cardiovascular disease (CVD):

Population	Recommendation
Adults aged 40 to 59 years with a 10% or greater 10-year CVD risk	The decision to initiate low-dose aspirin use for the primary prevention of CVD in adults aged 40 to 59 years who have 10% or greater 10-year CVD risk should be an individual one. Evidence indicates that the net benefit of aspirin use in this group is small. Persons who are not at increased risk for bleeding and are willing to take low-dose aspirin daily are more likely to benefit.
Adults 60 years or older	The USPSTF recommends against initiating low-dose aspirin use for the primary prevention of CVD in adults 60 years or older

- For patients initiating aspirin use, it would be reasonable to use a dose of 81 mg per day
- For patients who are eligible and chose to start taking aspirin, the benefits become smaller with advancing age, and data suggest clinicians and patients should consider stopping aspirin use around age 75 years

Oral P2Y12 Inhibitor Chart

Drug Name	Typical Dosing Based on Indication (not all indications may be listed)	Dose Adjustment for Renal Dysfunction	Dose Adjustment for Hepatic Dysfunction	Clinical Pearls
Clopidogrel (Plavix™)	For MI prophylaxis and stroke prophylaxis in persons with established peripheral arterial disease or CAD: 75 mg PO daily For MI prophylaxis and stroke prophylaxis in persons with unstable angina or acute MI: 300 mg PO loading dose, following by 75 mg PO daily For MI prophylaxis in persons with ACS undergoing PCI: 300 or 600 mg loading dose followed by 75 mg PO daily For MI prophylaxis and stroke prophylaxis in persons with stable ischemic heart disease undergoing PCI: 300 or 600 mg PO loading dose, followed by 75 mg PO daily	Specific guidelines are not available	Specific guidelines are not available	Patients identified as CYP2C19 poor metabolizers have a diminished antiplatelet response to clopidogrel
Prasugrel (Effient™)	For arterial thromboembolism prophylaxis (including stent thrombosis) in persons with ACS (i.e., unstable angina, acute MI, NSTEMI, or acute MI, STEMI) who are to be managed with PCI: For adults weighing 60 kg or more: 60 mg PO loading dose, then 10 mg PO once daily in combination with aspirin. For adults weighing less than 60 kg: 60 mg PO loading dose, then 5 mg PO once daily in combination with aspirin	Limited experience in patients with end-stage renal disease. Of note, patients with moderate to severe renal impairment are at increased risk of bleeding	Specific guidelines are not available Of note, use with caution as patients with severe hepatic disease may be at increased risk of bleeding	• May be administered with or without food • Tablets are not scored; avoid breaking or crushing tablets in an attempt to administer a smaller dose, as split-tab dosing accuracy cannot be assured
Ticagrelor (Brilinta™)	For arterial thromboembolism prophylaxis in persons with ACS (unstable angina, acute MI), including those undergoing PCI: 180 mg PO loading dose, then 90 mg PO twice daily in combination with low-dose aspirin. Reduce dose to 60 mg PO twice daily in combination with low-dose aspirin after 1 year For the reduction in risk of first MI or stroke in patients with CAD at high risk for these events: 60 mg PO twice daily plus aspirin 75-100 mg PO daily For stroke prophylaxis in patients with acute ischemic stroke (NIH scale score 5 or less) or high risk transient ischemic attack: 180 mg PO loading dose plus aspirin (300 to 325 mg PO) then 90 mg PO twice daily plus aspirin (75-100mg PO once daily) for up to 30 days	Specific guidelines are not available	Moderate hepatic impairment → use with caution (increase in exposure to ticagrelor) Severe impairment → contraindicated	May be administered with or without food

ACS: acute coronary syndrome; CAD: coronary artery disease; MI: myocardial infarction

Direct Acting Oral Anticoagulant

Drug Name	Typical Dosing Based on Indication	Dose Adjustment for Renal Dysfunction	Dose Adjustment for Hepatic Dysfunction	Clinical Pearls
Apixaban (Eliquis™)	Stroke and systemic embolism prevention in NVAF: 5 mg PO BID DVT/PE: 10 mg PO BID x 7 days followed by 5 mg BID For reduction in the risk of recurrent DVT/PE after completion of DVT/PE treatment: 2.5 mg PO BID after at least 6 months of treatment For DVT/PE prophylaxis in patients undergoing knee or hip replacement surgery: 2.5 mg PO BID for 12 days after knee replacement surgery or for 35 days after hip replacement surgery	No dose adjustment is required when used for treatment or prevention of DVT/PE For NVAF, dose should be adjusted to 2.5 mg PO BID if 2 of the 3 criteria are met: Serum creatinine of ≥1.5 mg/dl Age of 80 years or older Weight of 60 kg or less In patients with NVAF and ESRD maintained or intermittent HD, the recommended dose is 5 mg PO BID; reduce the dose to 2.5 mg PO BID if patient is 80 years or older OR weighs 60 kg or less.	In patients with: mild impairment → no dosage adjustments warranted moderate impairment → limited dosing experience in this population Severe impairment → use not recommended	• May be taken with or without food • Tablet may be crushed and suspended in water, 5% dextrose or apple juice for prompt administration • Tablets may be crushed and suspended in 60 mL of 5% dextrose or water and promptly delivered through a NG tube
Dabigatran (Pradaxa™)	Stroke and systemic embolism prevention in NVAF: 150 mg PO BID DVT/PE AFTER 5 days of initial parenteral anticoagulation: 150 mg PO BID For reduction in the risk of recurrent DVT/PE after completion of treatment: 150 mg PO BID For DVT/PE prophylaxis in patients undergoing hip replacement surgery: 110 mg PO daily 1-4 hours after surgery for 1 dose, then 220 mg PO daily for 28-35 days	For NVAF: CrCl 15-30 ml/min: 75 mg PO BID CrCl < 15 ml/min: No specific dosing recommendations per manufacturer For HD patients: dabigatran is removed by dialysis, use is not recommended	Specific guidelines are not available	• If co-administered with Pgp inhibitors dronedarone or ketoconazole and Crcl is 30-50 ml/min, dose should be adjusted to 75 mg PO BID, if Crcl is < 30 ml/min, use is not recommended • Capsules must be stored by patients in the original manufacturer bottle due to the potential for breakdown from moisture and loss of potency
Edoxaban (Savaysa™)	Stroke and systemic embolism prophylaxis in NVAF: 60 mg PO daily DVT/PE AFTER 5 days of initial parenteral anticoagulation (adults weighing >60 kg): 60 mg PO daily for at least 3 months DVT/PE AFTER 5 days of initial parenteral anticoagulation (adults weighing ≤60 kg): 30 mg PO daily for at least 3 months	For NVAF: CrCl > than 95 ml/min: use is NOT recommended CrCl 15 -50 ml/min: 30 mg PO daily CrCl < 15 ml/min: use not recommended DVT/PE: CrCl 15-50 ml/min: 30 mg PO daily CrCl < 15 ml/min: use not recommended	Mild impairment (Child-Pugh Class A) → no dose adjustment needed Moderate impairment (Child-Pugh Class B) → use not recommended Severe impairment (Child-Pugh Class C) → use not recommended	• When using for NVAF, edoxaban should not be used when CrCl > 95 ml/min (as renal function improves, edoxaban concentrations decrease increasing risk for ischemic stroke) • May be taken with or without food • For patients unable to swallow the tablet whole, tablets may be crushed and mixed with 2 to 3 oz of water and immediately administered by mouth or gastric tube
Rivaroxaban (Xarelto™)	Stroke and systemic embolism prophylaxis in NVAF: 20 mg PO daily with evening meal DVT/PE: 15 mg PO BID for 21 days, then 20 mg PO daily for at least 3 months For reduction in risk of recurrence of DVT and/or PE in adult patients at continued risk for DVT and/or PE: 10 mg PO daily after at least 6 months of standard anticoagulation For DVT/PE prophylaxis in patients undergoing knee or hip replacement surgery: 10 mg PO daily for 12 days after knee replacement surgery or for 35 days after hip replacement surgery For the reduction of cardiovascular mortality to reduce the risk of major thrombotic events in patients with CAD or PVD including those with PVD who have recently undergone a lower extremity revascularization procedure: 2.5 mg PO BID	CrCl 15-79 ml/min: do not administer in patients receiving a combined Pgp and moderate CYP3A4 inhibitor unless the potential benefit justifies the potential risk For NVAF: CrCl ≤ 50 ml/min: 15 mg PO daily with evening meal Treatment and prophylaxis of VTE (e.g. after hip or knee replacement surgery) CrCl < 15 ml/min: avoid use CAD and peripheral artery/vascular disease No dose adjustment based on CrCl For HD patients: systemic concentrations in patients with ESRD receiving intermittent dialysis were similar to those in moderate renal impairment; HD had no significant impact on rivaroxaban exposure	Mild impairment (Child-Pugh Class A) → no dose adjustment needed, but avoidance is recommended for any degree of hepatic disease associated with coagulopathy Moderate impairment (Child-Pugh Class B) → avoid use Severe impairment (Child-Pugh Class C) → avoid use	• Doses of 15 mg or 20 mg should be taken WITH FOOD to increase absorption. Doses of 10 mg or less do not need to be taken with food to ensure adequate absorption • For adult patients unable to swallow whole tablets, tablets may be crushed and mixed with applesauce • May be administered via NG or gastric feeding tube – the tablets should be crush and suspended in 50 mL of water

CAD: coronary artery disease; ESRD: end-stage renal disease; HD: hemodialysis; NG: nasogastric; NVAF: non-valvular atrial fibrillation; Pgp: P-glycoprotein; PVD: peripheral vascular disease; VTE: venous thromboembolism

For additional questions, please reach out to your assigned Practice Transformation Consultant.

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