How to Sell Deprescribing of CNS-active Medications & Antithrombotics

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Learning Objectives:

- 1. Demonstrate one approach to determining which CNS active medication to taper first based on specific patient characteristics or responses.
- 2. Discuss family/patient barriers to deprescribing.
- 3. Determine which antithrombotic medication to GDR first.

Antiepileptics, Antipsychotics, Benzos/hypnotics, Opioids, SSRI, SNRI, TCA

Table POLY-CNS-A: CNS-Active Medications

Antiepileptics		
brivaracetam	lacosamide	pimavanserin
cannabidiol	lamotrigine	rufinamide
carbamazepine	levetiracetam	stiripentol
divalproex sodium	methsuximide	tiagabine
eslicarbazepine	oxcarbazepine	topiramate
ethosuximide	perampanel	valproic acid
ethotoin	phenobarbital	vigabatrin
felbamate	phenytoin	ziparasidone
gabapentin	pregabalin	
Antipsychotics		
aripiprazole	iloperidone	pimavanserin
asenapine	loxapine	pimozide
brexpiprazole	lumateperone	quetiapine
cariprazine	lurasidone	risperidone
chlorpromazine	molindone	thioridazine
clozapine	olanzapine	thiothixine
fluphenazine	paliperidone	trifluoperazine
haloperidol	perphenazine	ziparasidone
Benzodiazepines and Nonbenzodiazepine Sedative/Hypnotics		
alprazolam	estazolam	quazepam
chlordiazepoxide	eszopiclone	temazepam
clobazam	flurazepam	triazolam
clonazepam	lorazepam	zaleplon
clorazepate	midazolam	zolpidem
diazepam	oxazepam	

Opioids -		
benzhydrocodone	hydrocodone	opium
buprenorphine [b]	hydromorphone	oxycodone
butorphanol (includes nasal spray)	levorphanol	oxymorphone
codeine	meperidine	tapentadol
dihydrocodeine	methadone	tramadol
fentanyl (includes nasal spray)	morphine	
Antidepressants: SNRIs, SSRIs, & TCAs		
amitriptyline	duloxetine	nortriptyline
amoxapine	escitalopram	paroxetine
citalopram	fluoxetine	protriptyline
clomipramine	fluvoxamine	sertraline
desipramine	imipramine	trimipramine
desvenlafaxine	levomilnacipram	venlafaxine
doxepin	milnacipram	

Case 1

- 69 y/o male DNR/DNI/DNH with goal of comfort
- PMH: s/p CVA with hemiplegia, dysphagia, RLS, low Vitamin D & B12, recurrent falls, orthostatic hypotension, DVT 2 months ago, constipation, COPD, anxiety/depression, hyperlipidemia, peripheral vascular disease, OA, bilateral carotid stenosis, h/o alcohol abuse, iron deficiency anemia
- PHQ9 4
- Meds:
- iron 325 daily
- baclofen 5mg 3x's daily
- Ropinirole 1mg 4x's daily
- Vitamin D 50,000 wkly
- Vitamin B12 1000 daily
- Midodrine 2.5 BID

Apixaban 5mg BID
Docusate 100mg HS
Sertraline 50mg daily
APAP 650mg q6 hours
Tramadol 50mg q6 hrs.
Lidocaine patch

Which of the following medications would you deprescribe first?

- 1. Baclofen - 5mg 3x's daily
- 2. Ropinirole – 1mg 4x's daily
- 3. Sertraline – 50mg daily
- 4. Tramadol - 50 mg q 6 hrs.

Determining which medicine to GDR first

1. **What is the indication?**
   - anxiety, depression, insomnia, migraine prophylaxis, fibromyalgia, etc.
- **2. Is it effective?**
   - GAD7 <5, PHQ9 <5, less migraines, improved sleep
- **3. Is there a safer alternative?**
   - Melatonin instead of quetiapine for insomnia

- **<u>If start with the lowest dose first, can get a quick “win”</u>**
- **<u>Can also start with one lacking appropriate indication, one that isn’t effective, one with safer alternative, one with side effects</u>**

Indication, Efficacy, Alternatives

	Indication	Efficacy	Alternative
Baclofen	hemiplegia	poor	ROM, splinting
Ropinirole	RLS	Poor w/ IDA	Address anemia, dose at HS only
Sertraline	depression	Good at doses >100mg	Other SSRIs, SNRIs w/ same risk
Tramadol	osteoarthritis	No improved function, more side effects	APAP, cream, patch, ROM

Case 1, cont.

- RLS could be caused by iron deficiency anemia
- Ropinirole could be contributing to orthostatic hypotension
- Baclofen not appropriate unless truly has spasticity related to h/o CVA.
- Sertraline at subtherapeutic dose and PHQ9 <5.
- Docusate generally ineffective, particularly with opioid
- Vitamin D 50,000 weekly risks of toxicity outweigh benefit

Case 1, cont.

- Options:
  - Reduce ropinirole to 0.5 4x's daily, then 3x's daily, then 2x's daily, then HS, then stop (4 wks.)
    - Repeat orthostatics, wean midodrine
  - Reduce baclofen to 5 BID, then daily, then stop (3 wks.)
  - Reduce tramadol to 3 x's daily, then 2x's daily, then daily, then stop (continue APAP) (3 wks.)
    - Stop docusate, use senna if needed
  - Reduce sertraline to 25mg daily, then stop (2 wks.)

12 Medications to 5

- Iron 325 daily
- ~~baclofen 5mg 3x's daily~~
- ~~Ropinirole 1mg 4x's daily~~
- ~~Vitamin D 50,000 weekly~~
- Vitamin B12 1000 daily
- ~~Midodrine 2.5 BID~~
- Apixaban 5mg BID
- ~~Docusate 100mg HS~~
- ~~Sertraline 50mg daily~~
- APAP 650mg q6 hours
- ~~Tramadol 50mg q6 hours~~
- Lidocaine patch

Summary of CNS Meds

- All are CNS active medications: Antiepileptics, antipsychotics, benzos, opioids, SSRIs, SNRIs, TCAs, and Z meds
- Deprescribing CNS meds must be an individualized decision based on goals of care, previous GDR attempts, current symptoms, etc.
- Do not automatically substitute one medication for another; consider if the medication is still needed and if the alternative medication is also a CNS active medication
- Consider indication, efficacy, and available alternatives when deciding which category of medicine to address first.
- Tapering should be individualized based on indication, efficacy, alternatives, previous GDR, dose, frequency, duration, specific category of medicine, etc.
- Generally, use next lowest available dose for 4 weeks until at lowest dose, then 2 weeks duration and discontinue

Patient/Family Barriers to Depprescribing

- **Inconsistent info** from health care providers causing lack of trust
  - “My cardiologist told me I had to take it forever.”
- **Feeling of abandonment**
  - Stopping medication(s) equates to stopping care
- **Fear of complications** if med stopped
  - Stroke, heart attack, blood clot if taken off antiplatelet and/or OAC
- **Confronted with mortality**
  - “I was told I had to take this until I die. Are you saying I’m going to die?”

Stevenson J, Abernethy AP, Miller C0, Currow DC. Managing comorbidities in patients at the end of life *BMJ* 2004; 329 :909.

Antiplatelet vs Anticoagulant Medications

Antiplatelets

- Management of **ARTERIAL** blood clots (platelets/fibrin)
- Arterial blood clots cause: MI, TIA, Ischemic stroke, PVD, Stent thrombosis
- ADP inhibitors: Inhibits ADP resulting in decreased platelet activation and aggregation
  - **Aspirin *****
  - **Clopidogrel**
  - **Prasugrel**
  - **Ticagrelor**

Anticoagulants

- Management of **VENOUS** blood clots (erythrocytes/fibrin)
- Venous blood clots cause: DVT, PE, Thrombosis 2* to arrhythmias (low flow conditions)
  - **Apixaban**
  - Betrixaban
  - Dabigatran
  - Edoxaban
  - Rivaroxaban
  - Warfarin

Think of Antiplatelets for Arterial Clots and Anticoagulants for Venous Clots, Pharmacist's Letter, June 2018

Duration of Antiplatelet Therapy by Indication

* Clopidogrel most preferred ADP-I with a few exceptions.

Indication	Treatment & Duration
Cardiac Stent (Bare Metal Stent, Drug Eluting Stent)	BMS: Aspirin + ADP-I X 1 mo., then aspirin indefinitely DES: Aspirin + ADP-I X 6 mos., then aspirin indefinitely
Acute Coronary Syndrome (ACS)	DAPT(dual antiplatelet) x 12 mos., then aspirin indefinitely
Carotid Stent	DAPT(dual antiplatelet) x 1 mo., then aspirin indefinitely
Peripheral arterial stent	DAPT(dual antiplatelet) x 1-3 mos., then aspirin indefinitely
TIA/CVA/cerebrovascular disease	SAPT (single antiplatelet) indefinitely
Stable Ischemic cardiovascular disease	Aspirin indefinitely
Primary Prevention ASCVD (atherosclerotic cardiovascular disease)	New recommendation to individualize decision regarding aspirin

Therapeutic Research Center - February 2022 ~ Resource #380209 - Dual Antiplatelet Therapy for Coronary Artery Disease

Oral Anticoagulants for DVT/PE (CHEST guideline summary)

Embolic Event	Suggested Treatment
VTE (venous thromboembolism) without cancer	All DOACs are recommended over warfarin
VTE with cancer	LMWH is recommended over warfarin or DOACs
proximal DVT (provoked or unprovoked)	• **Treat for 3 months** • Provoked – immobility, surgery, trauma
Pulmonary Embolus	• Treat for 3 mos. if high risk of bleeding • **No scheduled stop date if low or moderate risk of bleeding**
For pts w/ unprovoked proximal DVT **or** PE who are stopping anticoagulant therapy	Use *aspirin* to prevent recurrent VTE if there are no contraindications

Stevens SM, Woller SC, Kreuziger LB, et al. Antithrombotic Therapy for VTE Disease: Second Update of the CHEST Guideline and Expert Panel Report. *Chest*. 2021 Dec;160(6):e545-e608.

Case 2 – OAC & DAPT

- 77 y/o female DNR/DNI with goal of function
- PMH: CKD3b, CAD, h/o falls, HLD, osteoarthritis, HTN, GAD/MDD, COPD, fibromyalgia, Rt BKA, h/o multiple LLE DVTs
- Meds: ASA 81 daily, ticagrelor/Brilinta 90mg BID, apixaban/Eliquis 2.5 BID, hydralazine 25 3x's daily, senna, pantoprazole 40 daily, atorvastatin 80, tizanidine 4mg q8 hrs., oxycodone 7.5mg 4x's daily, gabapentin 300 3x's daily, trazodone 100 HS, fluoxetine 40 daily
- Labs:
- Goes to hospital for angina, s/p LAD stent

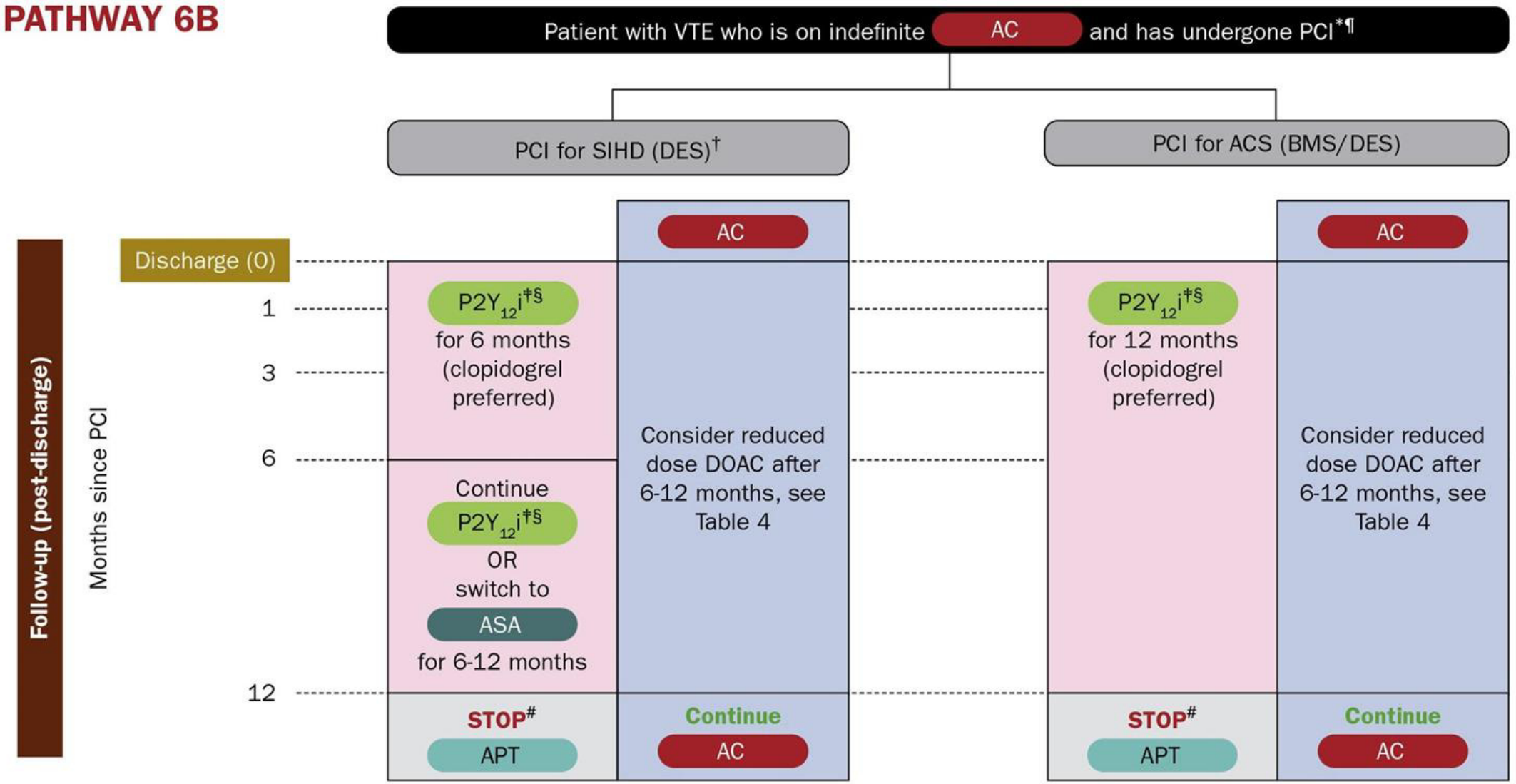
Evaluating Antiplatelet and Anticoagulant Medications

1. Which anti-platelet agents or anticoagulants is the patient taking?
   - Aspirin, clopidogrel, apixaban, rivaroxaban, warfarin, enoxaparin
2. What is the **indication** for each medication?
   - DVT/PE, a fib, mechanical heart valve, carotid stent, peripheral arterial stent, ACS, PCI, cardiac stent
3. When was the **inciting / last event** (3 months, 6 months, 12 months)?
   - ACS, PCI, stent placement
4. What is the **bleeding risk**?
   - Low, moderate, high
5. Is the treatment still appropriate/indicated based on treatment guidelines or could the med(s) be deprescribed?
   - 3 mos. duration anticoagulation for DVT, single antiplatelet indefinitely for stable ischemic heart disease

Indication, Last Event, Duration

	Indication	Last Event	Duration
Aspirin	CAD	Mar 2024	DAPT 6 mos. after stent
Ticagrelor/Brilinta	CAD	Mar 2024	DAPT 6 mos. after stent
Apixaban/Eliquis	Recurrent DVT	July 2023	lifelong

What is her Bleeding Risk?
How long should she be on triple therapy?



2020 ACC Expert Consensus Decision Pathway for Anticoagulant and Antiplatelet Therapy in Patients With Atrial Fibrillation or Venous Thromboembolism Undergoing Percutaneous Coronary Intervention or With Atherosclerotic Cardiovascular Disease: A Report of the American College of Cardiology Solution Set Oversight Committee.

Discussion with Cardiologist

Reasons for Resistance

1. **Unfamiliar with guidelines** or accepted NH practice
2. **Need to be in control**: “my way or the highway”
3. **Lack of trust**: Unfamiliar with PCP skills/knowledge
4. **Fear** of litigation
5. **Unaware of** patient/family **goals** for treatment (longevity vs. function vs. comfort)

Suggested Approaches

- Refer to the JACC article from 2020 & algorithms
- Emphasize NH patient, multimorbidity, prognosis, and patient/family goal for treatment

Take Home Messages

- No advantage to aspirin dosing >81 mg.
- Clopidogrel is generally preferred ADPi.
- Dual antiplatelet (DAPT) for stents are time-limited (1-3 or 6 mos. based on location), 12 mos. for ACS
- Patients on oral anticoagulant (a fib, PE) who require PCI
  - If bleeding risk is high and ischemic risk is low, long-term DOAC monotherapy
  - If high ischemic risk and low bleeding risk, DOAC plus single antiplatelet therapy

Take Home Messages

- For A fib: OAC recommended for CHA2DS2-VASc >2 and HAS-BLED score <3
- For DVT: OAC x3 mos., recurrent DVT or PE: OAC indefinite if low/moderate bleeding risk
- DOACs are generally preferred to warfarin unless mechanical heart valve, previous failure of DOAC therapy, or moderate to severe mitral stenosis then warfarin is recommended
- Falls alone are not a reason to avoid OAC
- Anticoagulation is individualized decision based on goals of care and risk vs. benefit
- Use of “triple therapy” (DAPT plus anticoagulation) is NOT recommended for most patients due to an increased risk of bleeding.

Appendix

Tramadol: Dosing

Mechanism of Action

- Centrally acting synthetic opioid analgesic
- For management of moderate to moderately severe pain in adults

- **Background**
  - Approved as a non-controlled analgesic in 1995
  - Reclassified as schedule IV in 2014

- **Dosing**
  - 50 mg, 100mg tablets
  - Max dose 400mg/day
  - Max dose for pts >75 y/o 300mg/day (due to prolonged half-life)
  - For CrCl < 30 mL/min, dosing interval increased to 12 hours, with maximum daily dose of 200 mg.

Tramadol: Drug-Drug & Drug-Disease Interactions

- **Drug-Drug Interactions**

- Serotonin syndrome
- Do not use with carbamazepine
- Caution with quinidine, fluoxetine, paroxetine, amitriptyline as well as ketoconazole and erythromycin (increased risk of seizures)
- Caution with SSRIs, MAOIs, triptans, linezolid, lithium, or St. John's Wort (serotonin syndrome)

- **Drug-Disease Interactions**

- Can increase risk of seizures
- Can cause CNS & respiratory depression – use lower doses in combination with CNS depressants such as alcohol, opioids, anesthetic agents, phenothiazines, tranquilizers or sedative hypnotics.
- Neurotoxicity

Tramadol: Monitoring

- **Withdrawal symptoms**
- anxiety, sweating, insomnia, rigors, pain, nausea, tremors, diarrhea, upper respiratory symptoms, piloerection, and rarely hallucinations.

- **How to Taper**
  - By dose – 100 mg to 50mg
  - By frequency – q4, 6, 8, 12 hours
  - Longer durations of use mean longer duration of taper
  - If pain increases, consider scheduling APAP between doses of tramadol, ice/heat, PT/OT, topical agents (diclofenac, menthol, etc.) BEFORE automatically resuming previous dose

Tramadol Efficacy for Osteoarthritis

- **Cochrane Review published 2019**

Osteoarthritis

- 22 studies involving 3871 people taking tramadol and 2625 people in a comparator group
- Moderate quality evidence showed that taking tramadol for up to 3 months had no important benefit on mean pain or function, although slightly more people in the tramadol group reported an important improvement (defined as 20% or more).
- Tramadol group had more side effects: nausea, vomiting, dizziness, constipation, tiredness and headache.
- https://www.cochrane.org/CD005522/MUSKEL_tramadol-osteoarthritis

Toupin April K, Bisaillon J, Welch V, Maxwell LJ, Jüni P, Rutjes AWS, Husni M, Vincent J, El Hindi T, Wells GA, Tugwell P. Tramadol for osteoarthritis. Cochrane Database of Systematic Reviews 2019, Issue 5. Art. No.: CD005522. DOI: 10.1002/14651858.CD005522.pub3

Tramadol Efficacy for Neuropathic Pain

- **Cochrane Review published 2019**

Neuropathic Pain

- 6 trials with 438 participants, duration 4-6 weeks
- Small, largely inadequate studies with potential risk of bias.
- Evidence of benefit from tramadol was of low or very low quality,
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6481580/

Duehmke RM, Derry S, Wiffen PJ, Bell RF, Aldington D, Moore RA. Tramadol for neuropathic pain in adults. Cochrane Database Syst Rev. 2017;6(6):CD003726. Published 2017 Jun 15. doi:10.1002/14651858.CD003726.pub4

Sertraline: Dosing & Mechanism of Action

Mechanism of Action:
SSRI (selective serotonin reuptake inhibitor)

Serotonin regulates mood, low levels correlate with depression

- **Dosing**
- 25, 50, 100 mg tabs; 20mg/ml solution
- **Starting dose** 25-50mg, adjust weekly, maximum 200mg per day
- 100mg generally **optimal dose** for effectiveness

- **Discontinuation Syndrome**
- nausea, sweating, dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesia), tremor, anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures.

Sertraline: Tapering

- **Tapering**
- GDR is generally **NOT recommended** for OCD, recurrent or severe depression, or GAD (generalized anxiety disorder)
- Taper **gradually** over weeks to months depending on dose and duration
- **Discontinuation syndrome** can occur within 1-3 days of dose reduction
- **Recurrence of previous symptoms** (depression/anxiety) can occur within 1-2 weeks of GDR

GDR Example: sertraline 100mg daily for 6 months, PHQ9 is 0

1. Decrease to 50mg daily for 4 wks.,
2. Then 25mg daily for 2 wks.

- Monitor for symptoms of depression, PHQ9
- If symptoms reoccur at 25mg dose, resume 50mg dose and consider GDR in 3-6 mos.

Sertraline: Warnings

Black box warning:

For children and young adults; suicidal thoughts and behaviors

- **Drug-Disease Interactions**
- **Seizures:** Use with caution in patients with seizure disorders
- Risk of **Hyponatremia** with all SSRIs and SNRIs – especially geriatric patients

- **Drug-Drug Interactions**
- **Serotonin Syndrome:** Increased risk when co-administered with other serotonergic agents (e.g., SSRI, SNRI, triptans), but also when taken alone.
- **Increased risk of bleeding** especially with concomitant use of aspirin, NSAIDs, other antiplatelet drugs, warfarin, and other anticoagulants.
- Do **not combine** with MAOI (within 14 days) or pimozide

Sertraline: Efficacy

- Cochrane Review 2010

Depression	Generalized Anxiety Disorder (GAD)
59 studies, mostly of low quality, were included in the review, involving multiple treatment comparisons between sertraline and other antidepressant agents. • Sertraline favored for the acute phase treatment of major depression for efficacy (fluoxetine) and acceptability/tolerability (amitriptyline, imipramine, paroxetine and mirtazapine). • Sertraline was generally associated with a higher rate of diarrhea. • Cipriani A, La Ferla T, Furukawa TA, et al. Sertraline versus other antidepressive agents for depression. *Cochrane Database of Systematic Reviews* 2010	• Adult outpatients, improvement in anxiety, well-tolerated • Allgulander C, Dahl AA, Austin C, et al. Efficacy of Sertraline in a 12-Week Trial for Generalized Anxiety Disorder. *American Journal of Psychiatry*. 2004; 61(9): 1642-1649

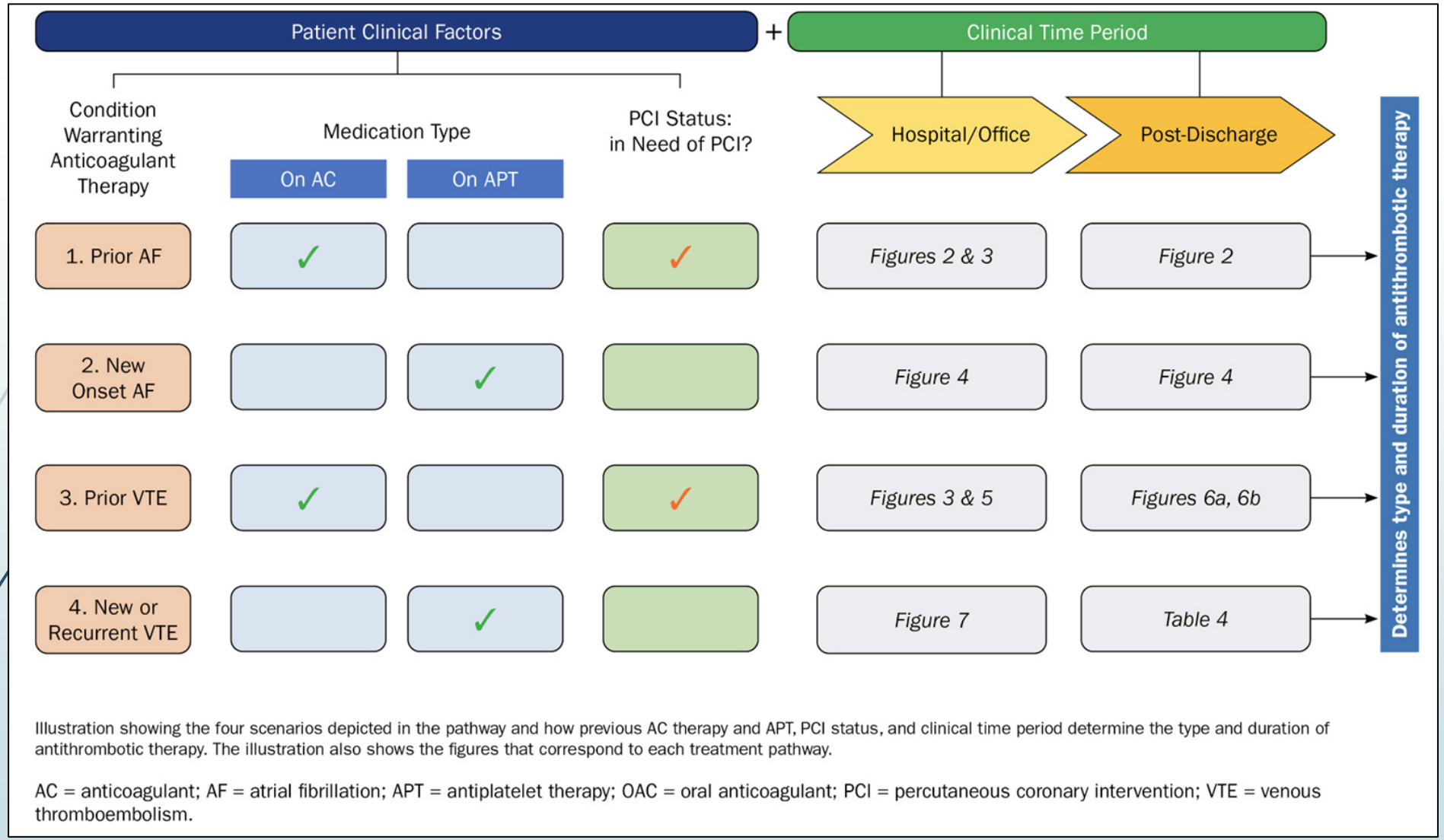


Illustration showing the four scenarios depicted in the pathway and how previous AC therapy and APT, PCI status, and clinical time period determine the type and duration of antithrombotic therapy. The illustration also shows the figures that correspond to each treatment pathway.

AC = anticoagulant; AF = atrial fibrillation; APT = antiplatelet therapy; OAC = oral anticoagulant; PCI = percutaneous coronary intervention; VTE = venous thromboembolism.

JACC

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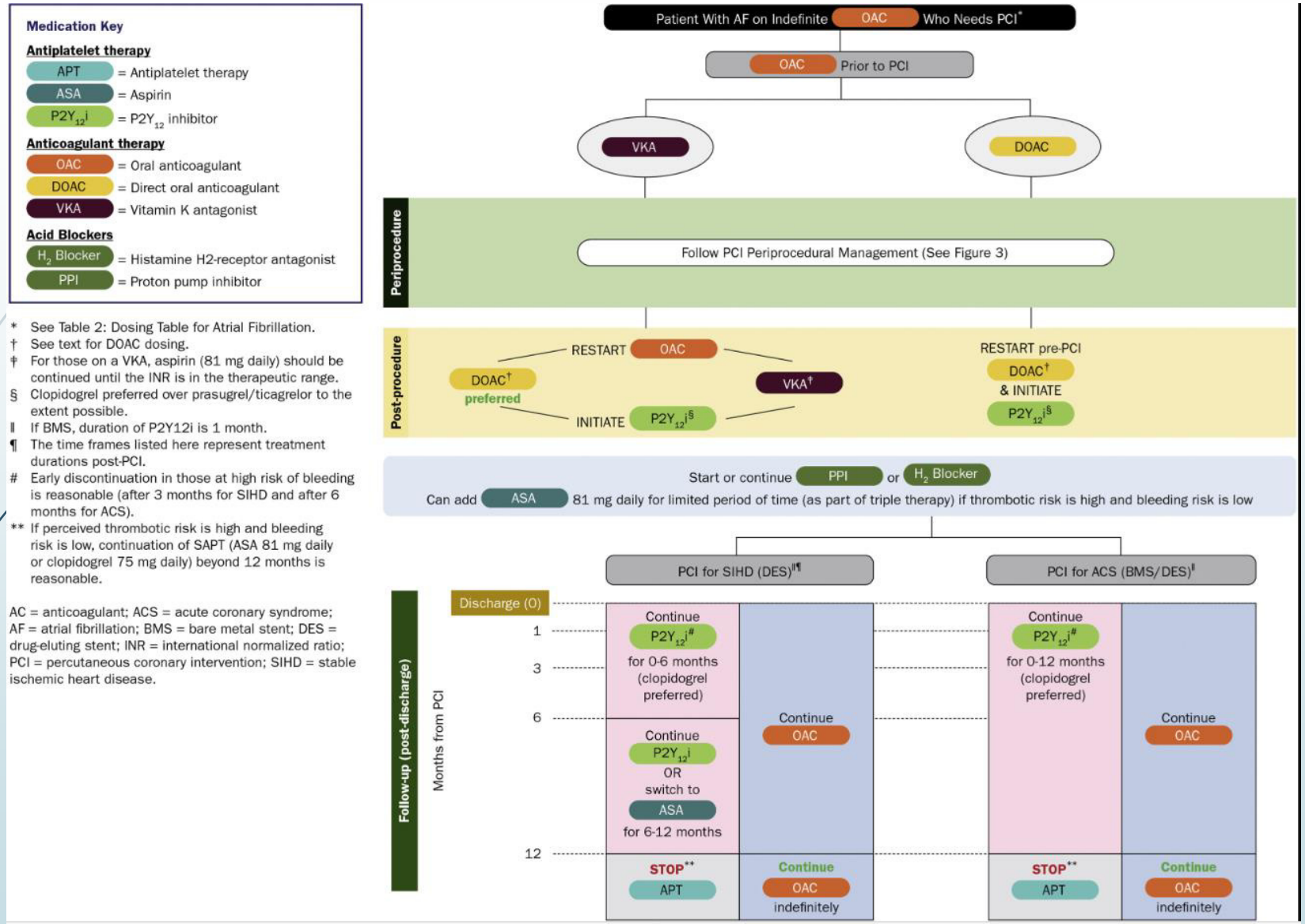
Patient With AF on OAC Who Now Needs PCI: Post-Procedure and Long-Term Management of Antithrombotic Therapy

Figure 2



Dharam J. Kumbhani et al. *J Am Coll Cardiol* 2020; 77:629-658.

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Patient With AF on OAC Who Now Needs PCI: Long-Term Management of Antithrombotic Therapy
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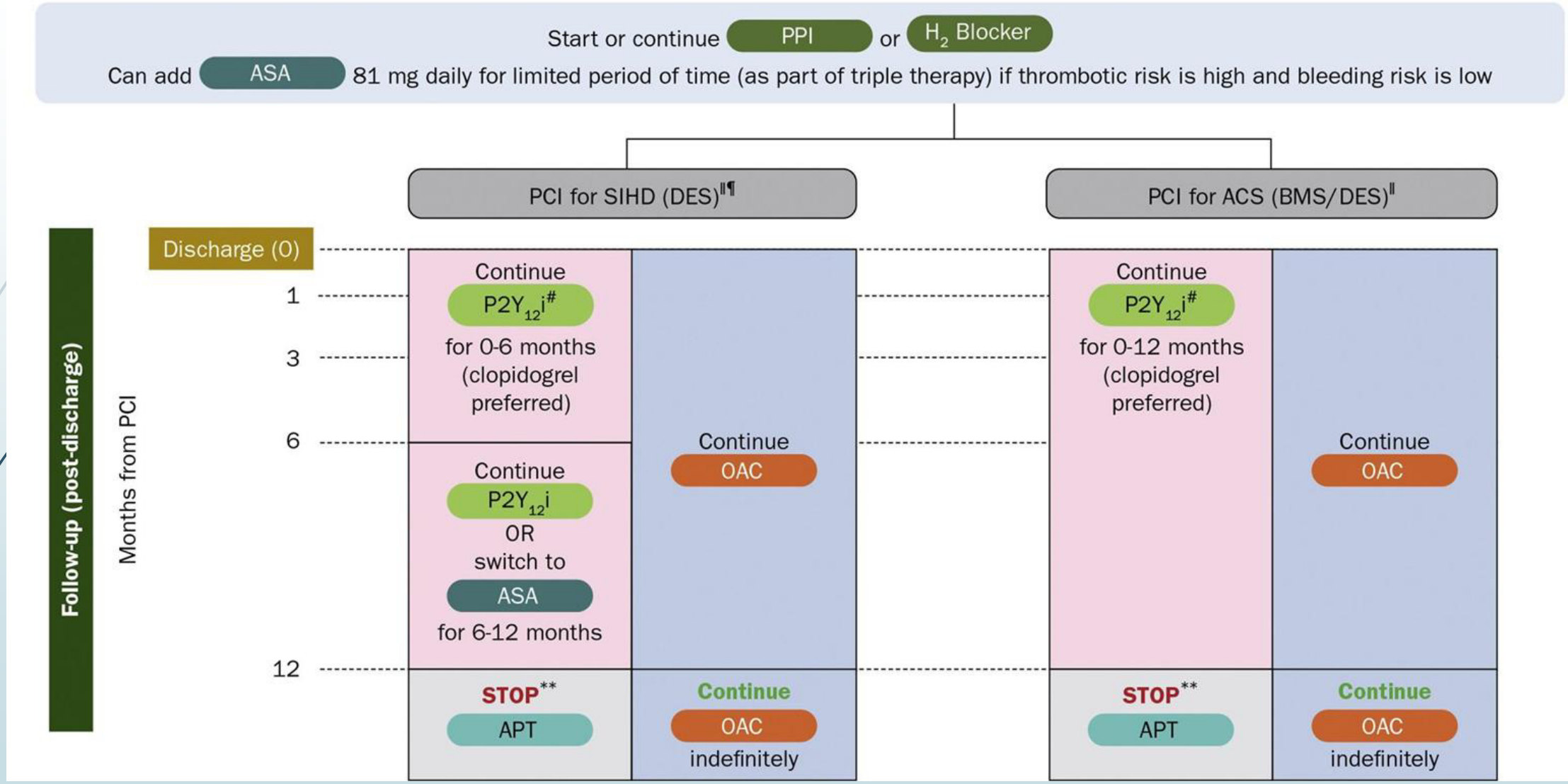

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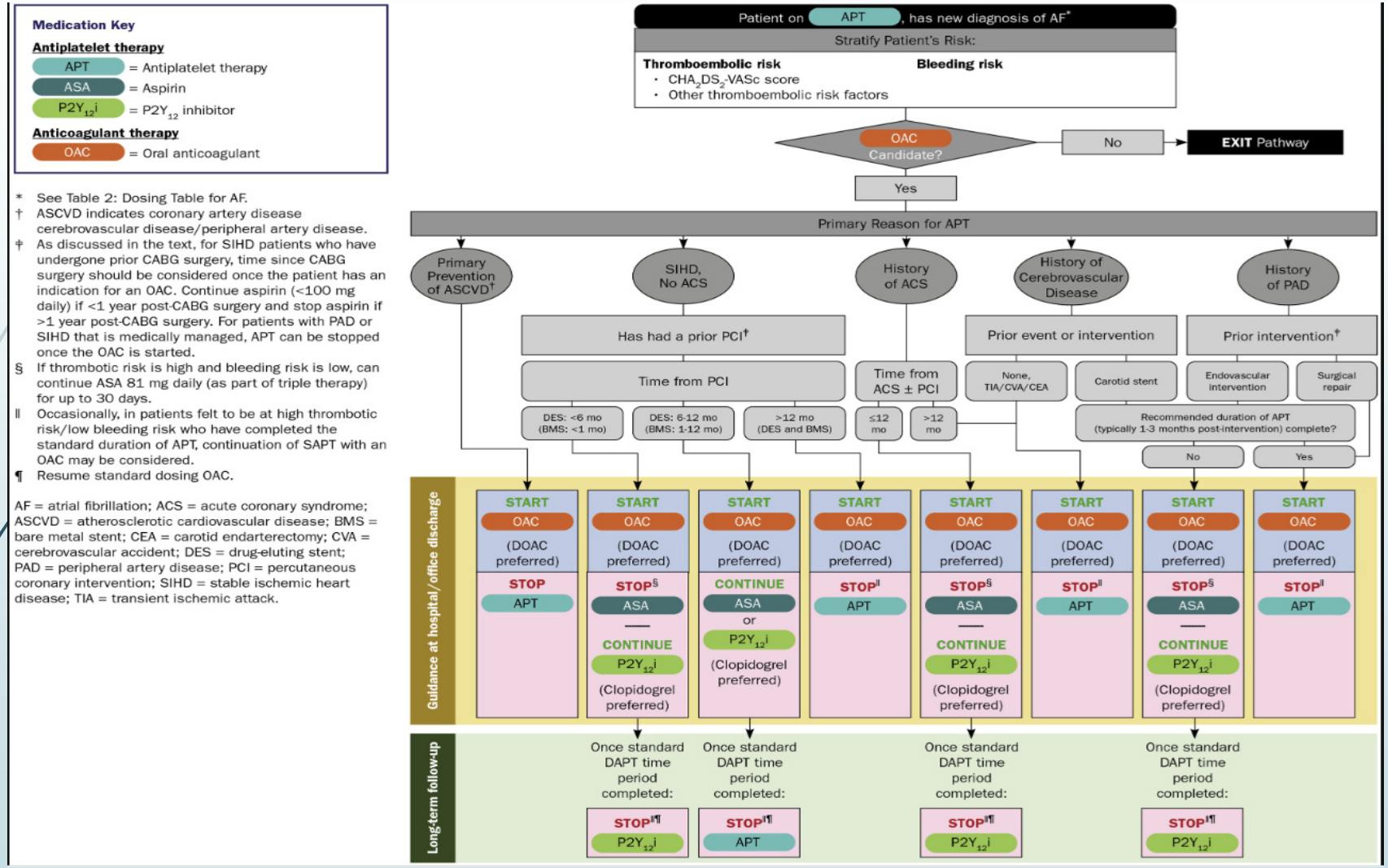
Patient on APT With a New Diagnosis of AF: Discharge and Long-Term Management of Antithrombotic Therapy

Figure 4



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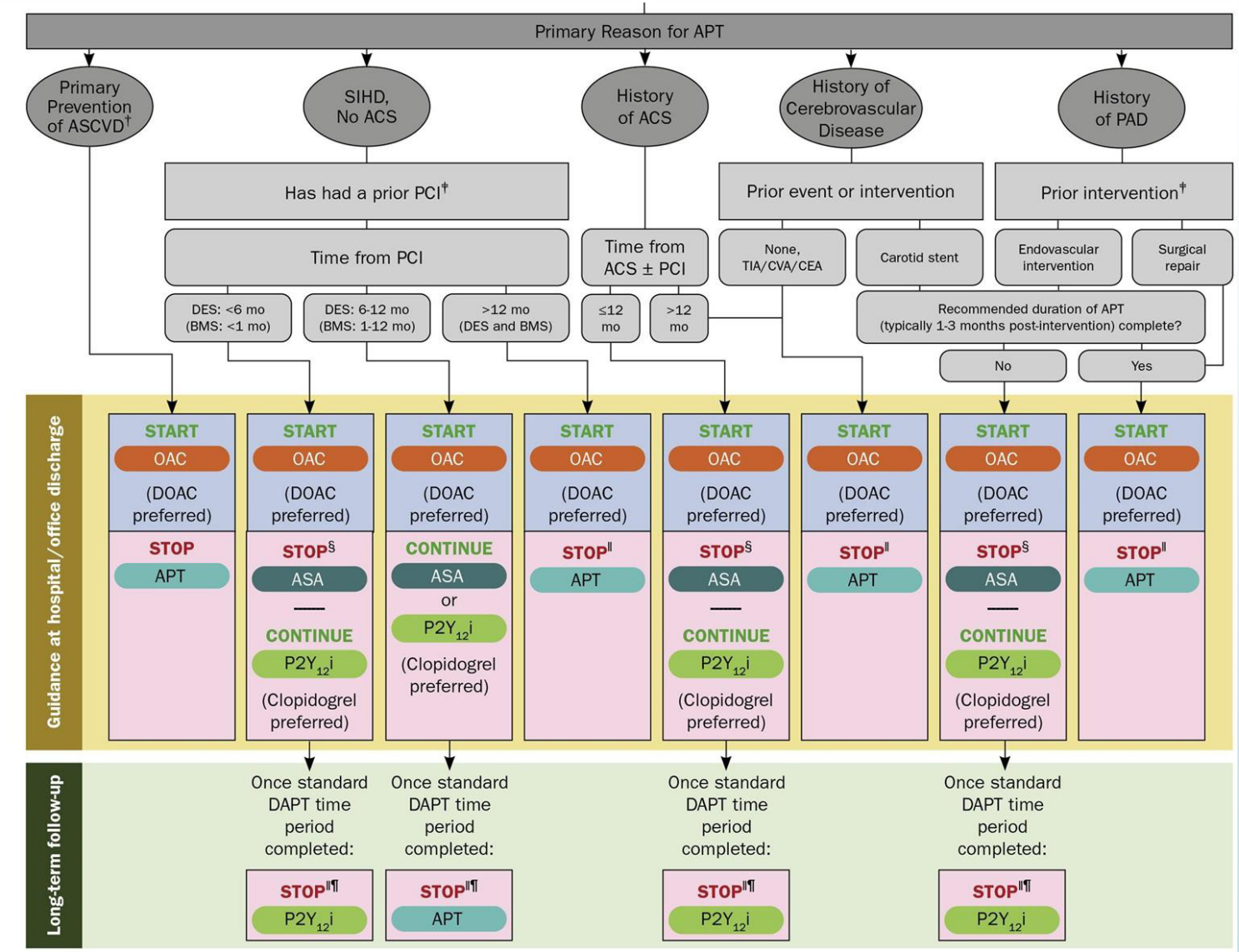

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Patient With VTE on AC Who Has Undergone PCI

(6A: Time-Limited AC; 6B: Indefinite AC): Long-Term Post-Discharge Management of Antithrombotic Therapy

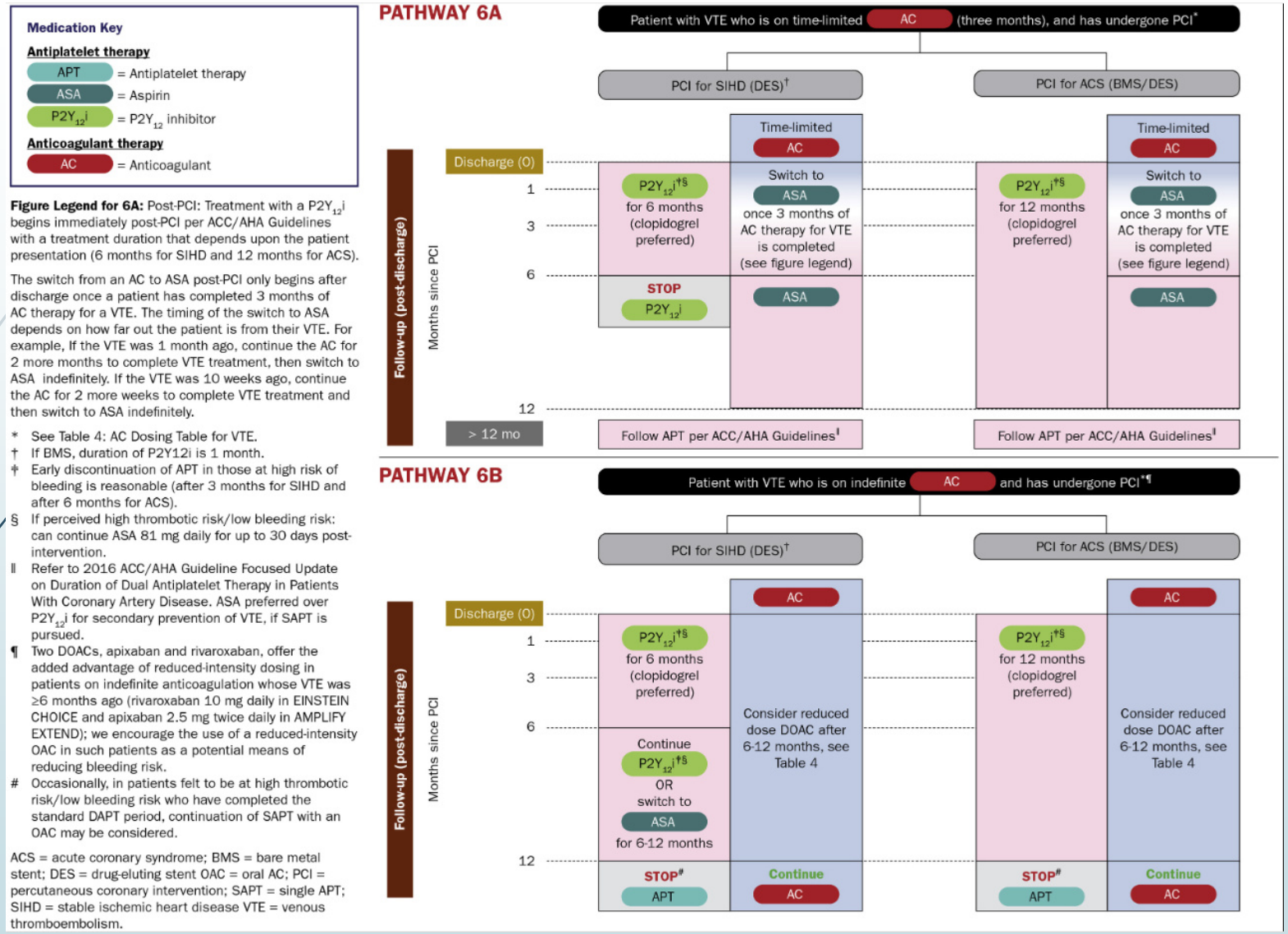

Figure Legend for 6A: Post-PCI: Treatment with a $P2Y_{12}i$ begins immediately post-PCI per ACC/AHA Guidelines with a treatment duration that depends upon the patient presentation (6 months for SIHD and 12 months for ACS).

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.

* See Table 4: AC Dosing Table for VTE.
† If BMS, duration of P2Y12i is 1 month.
ǂ 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 $P2Y_{12}i$ for secondary prevention of VTE, if SAPT is pursued.
¶ 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.

Dharam J. Kumbhani et al. *J Am Coll Cardiol* 2020; 77:629-658.

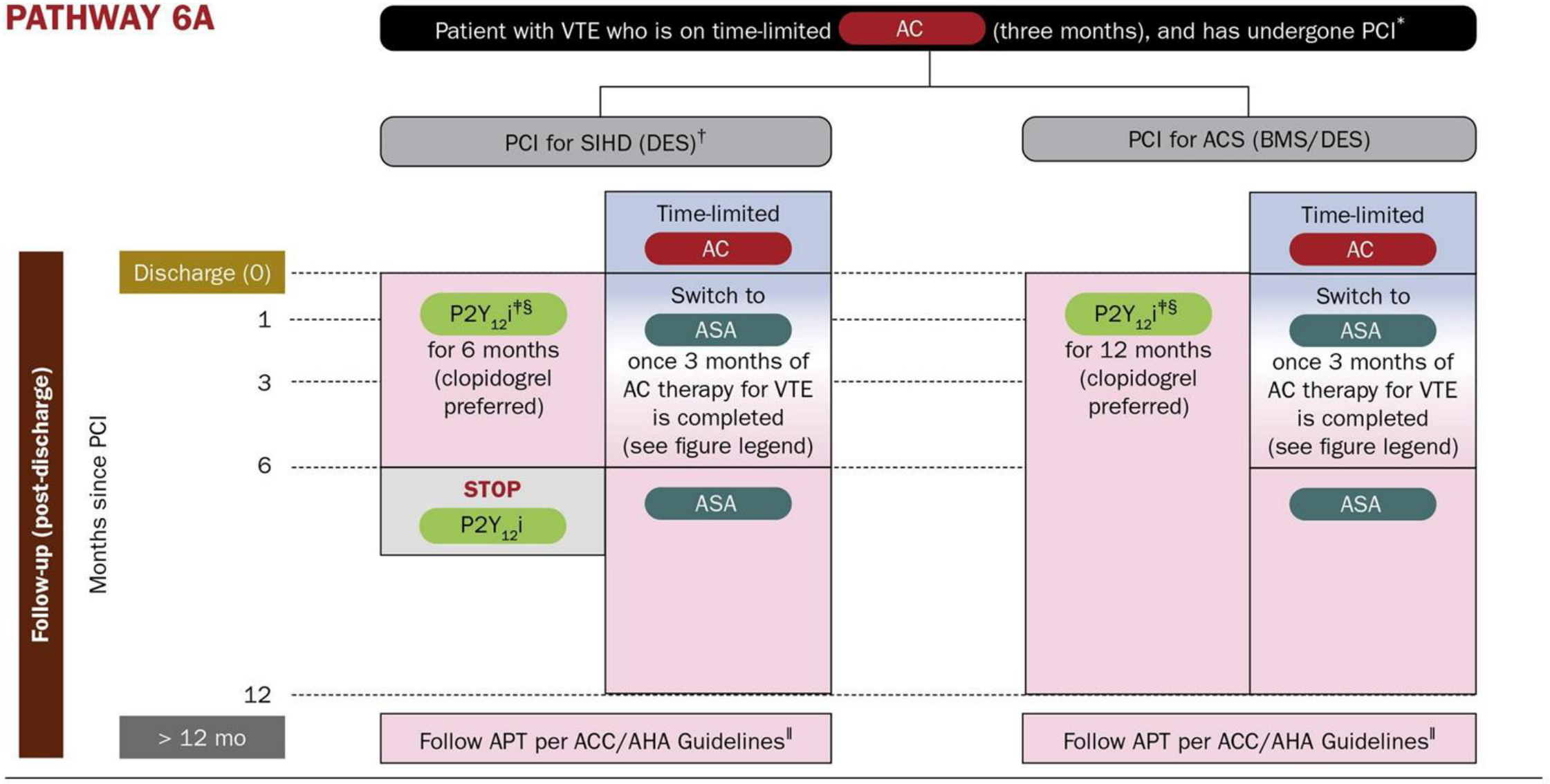

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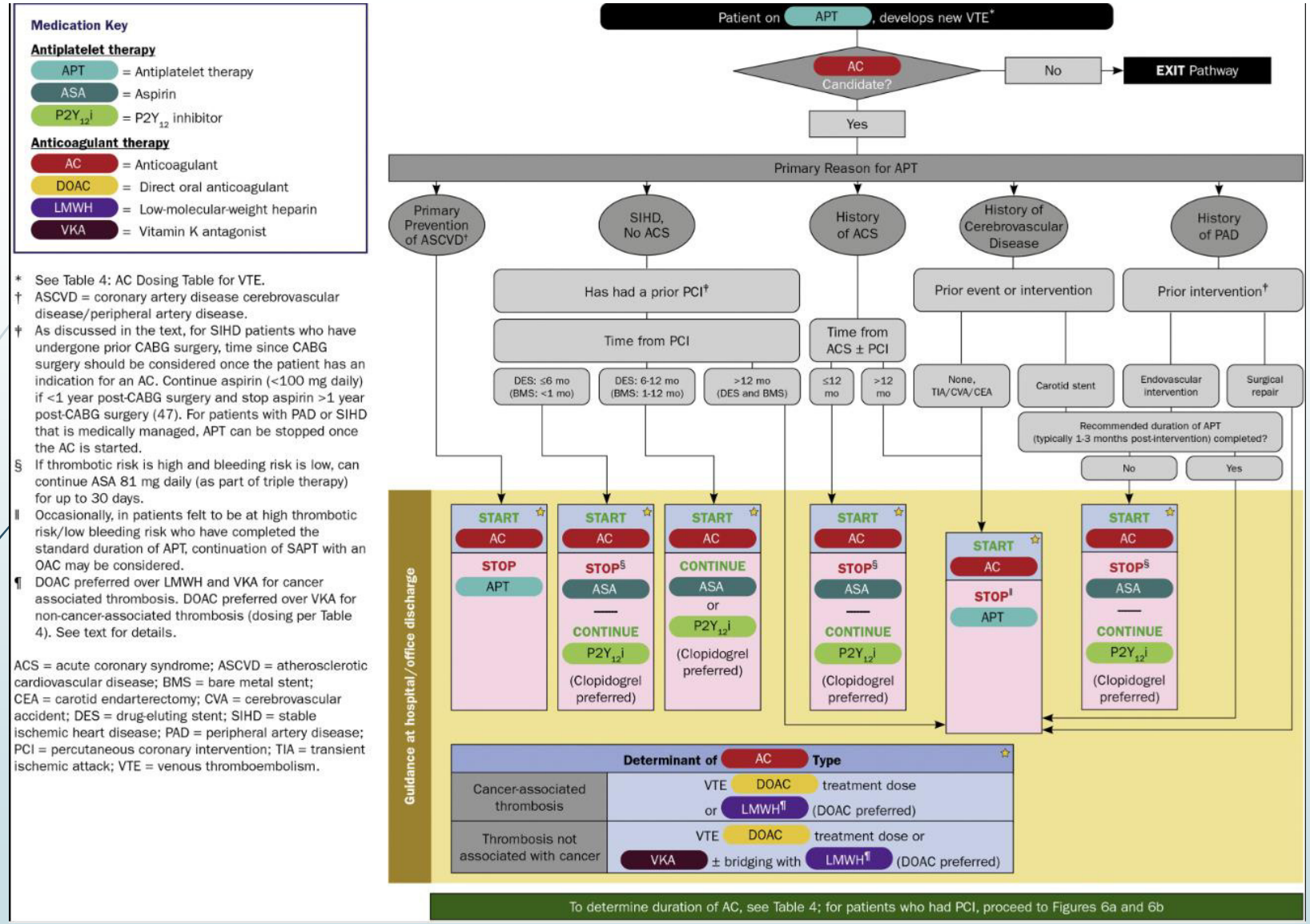
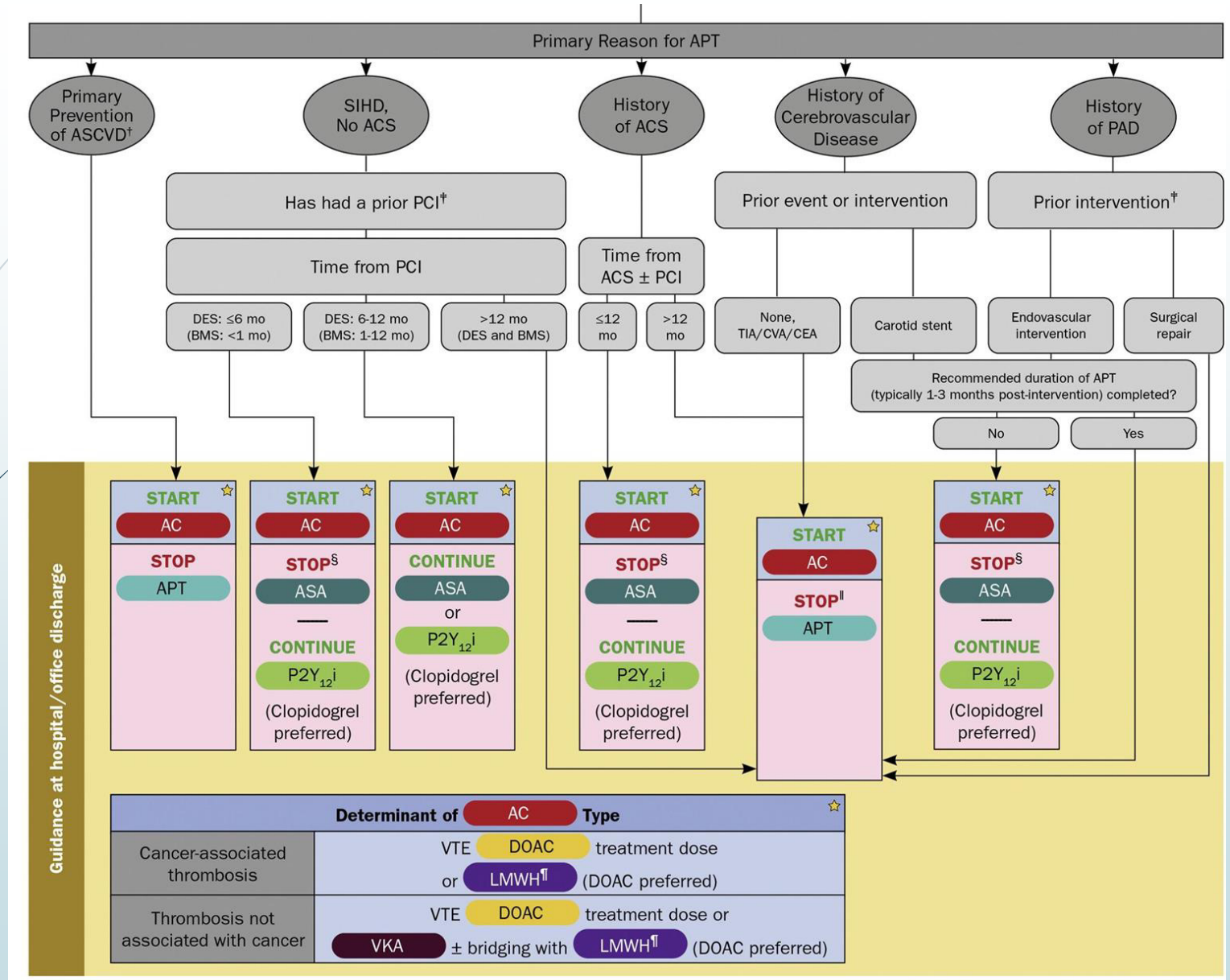
Figure 7



Dharam J. Kumbhani et al. *J Am Coll Cardiol* 2020; 77:629-658.

Patient on APT With New VTE: Management of Initial Antithrombotic Therapy at Discharge

Figure 7



2020 ACC Expert Consensus Decision Pathway for Anticoagulant and Antiplatelet Therapy in Patients With Atrial Fibrillation or Venous Thromboembolism Undergoing Percutaneous Coronary Intervention or With Atherosclerotic Cardiovascular Disease: A Report of the American College of Cardiology Solution Set Oversight Committee.