Antiplatelet Therapy: Essential Questions

GREGORY C HADLOCK, PHARMD, PHD, BCPS

1

Objectives for pharmacists

- Identify appropriate indications for antiplatelet (AP) therapy
- Evaluate bleeding risks of patients on AP therapy
- Develop guideline-based recommendations for dual and triple antithrombotic therapy

2

Objectives for technicians

- Identify OTC and prescription AP medications
- Recognize OTC medications that can increase bleeding risk
- Provide resources for patients to obtain further information regarding AP therapy

3

Disclosures

- None

4

Prevalence of ASA use

- Aspirin (acetylsalicylic acid; ASA) is the most commonly used AP and has numerous uses including for:
  - peripheral artery disease, cardiovascular disease (CVD), venous thromboembolism, preeclampsia, colon cancer risk reduction, polycythemia vera, valvular heart disease, and ischemic stroke
- In 2012-2015, nearly 22% of Americans self-reported taking ASA for primary CVD prevention[1]
- Over 30% reported taking ASA for primary and secondary CVD prevention in 2015[1]

1. Stuntz and Bernstein, 2017, Prev Med Reports 5: 183-186

5

Balance of benefits and risks

- Platelets are vital for hemostasis[1]
- Excessive platelet activation has been implicated in the formation of atherothromboses[1]
- AP therapy reduces the risk of vascular mortality (15%) and non-fatal myocardial infarction (MI; 34%) in high risk patients[2]
- AP therapy increases bleeding risk[1]
- AP therapy has similar major bleeding risk as oral anticoagulation (OAC)[3]

1. Eikelboom et al., CHEST 2012; 141: e89S-e119S
2. Antithrombotic Trialists, BMJ 2002; 324: 71-86
3. Mellonian et al., J Thromb Haem 2017; 15: 1500-1510

6

Balance of bleeding and clotting risks

7

7

Essential questions for patients on antiplatelet therapy

- What is the indication?
- What is the patient's thrombotic risk?
- What is the patient's bleeding risk?
- What is the duration of therapy?

8

8

Case 1

SB is a 69 year old male presenting to your clinic for comprehensive medication review. He has a past medical history significant for NSTEMI 2016 with 1 stent, HTN, and depression. He started citalopram 20 mg about 4 months ago with good response, but has been experiencing nose bleeds frequently.

Home medications: losartan 50 mg daily, carvedilol 12.5 mg twice daily, ASA 81 mg daily, clopidogrel 75 mg daily, atorvastatin 20 mg daily, citalopram 20 mg daily

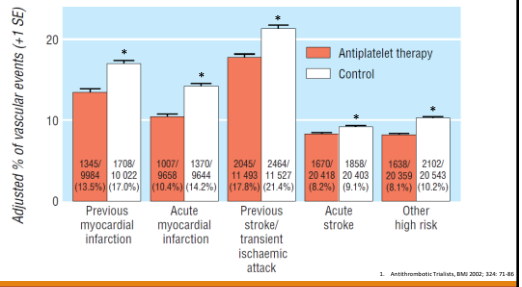
What is the most appropriate next step?

A. Increase his carvedilol to 25 mg twice daily
B. Refer him to an otolaryngologist
C. Recommend consider discontinue clopidogrel to his cardiologist
D. Decrease the citalopram to 10 mg daily

9

9

Secondary prevention of CVD events



1. Antithrombotic Trialists, BMJ 2002; 324: 71-86

10

10

Secondary prevention of CVD events

- Indefinite AP therapy is recommended for the secondary prevention of CVD, including after:
  - Acute ischemic stroke[1]
  - Coronary artery bypass graft (CABG)[2]
  - Non-ST elevated MI or unstable angina[3]
  - ST-elevated MI[4]
- Following percutaneous coronary intervention (PCI), dual-AP therapy (DAPT) is used to prevent stent thrombosis and CV events for typically 1 year[5]

1. AHA/ASA guidelines, 2018, Stroke; 49: e46-e110
2. Kulik et al., 2015, Circulation; 131: 927-964
3. AHA/ACC guidelines, 2014, J Am Coll Cardiol; 64: e139-e228
4. AHA/ACC guidelines, 2013, Circulation; 127: e362-425
5. Piccini and Jones, 2017, NEJM; 377: 1580-1582

11

11

Case 2

AG is a 69 year old female presenting to the pharmacy asking where she can find the "baby aspirin" that her friend told her that she should take to protect her heart. AG has a past medical history significant for hypertension, hyperlipidemia, depression, and a history of breast cancer.

Home medications: lisinopril 10 mg daily, atorvastatin 20 mg daily, escitalopram 10 mg daily

What is the most appropriate next step?

A. Tell her where to find the ASA 81 mg tablets
B. Calculate an ASCVD risk score and recommend ASA if >10%
C. Ask her if she discussed ASA use with her doctor
D. Tell her that she does not have an indication for ASA use and it can be dangerous

12

12

U.S. Preventive Service Task Force 2016

Population	Recommendation	Grade (What's This?)
Adults aged 50 to 59 years with a ≥10% 10-year CVD risk	The USPSTF recommends initiating low-dose aspirin use for the primary prevention of cardiovascular disease (CVD) and colorectal cancer (CRC) in adults aged 50 to 59 years who have a 10% or greater 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years.	B
Adults aged 60 to 69 years with a ≥10% 10-year CVD risk	The decision to initiate low-dose aspirin use for the primary prevention of CVD and CRC in adults aged 60 to 69 years who have a 10% or greater 10-year CVD risk should be an individual one. Persons who are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years are more likely to benefit. Persons who place a higher value on the potential benefits than the potential harms may choose to initiate low-dose aspirin.	C
Adults younger than 50 years	The current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin use for the primary prevention of CVD and CRC in adults younger than 50 years.	I
Adults aged 70 years or older	The current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin use for the primary prevention of CVD and CRC in adults aged 70 years or older.	I

1. USPTF Task Force, 2016, Ann Int Med; 12: 804-813

13

13

ASA for primary prevention of CVD events

- Prior studies showed minimal benefit of ASA for primary prevention
- 2016 USPTF recommendations based on meta-analysis of numerous older studies
  - Varying baseline CVD risks
  - Some older studies in patients who may not have been standard therapies shown to reduce CVD risk (e.g., statins and optimal blood pressure control)
- What truly qualifies as "high risk"? What about patients >70 year old? What about patients younger than 50 years old with other risk factors like diabetes?

1. USPTF Task Force, 2016, Ann Int Med; 12: 804-813

14

14

New primary prevention evidence

- Three large, multicenter, double-blind, placebo controlled trials in 2018
- **ASCEND**[1]
  - Patients with >40 years old with diabetes (~63 years old; n=15,480); 7.4 years; 12% reduction in CVD events (NNT=91); 28% increase in major bleeds (NNT=112)
- **ARRIVE**[2]
  - Patients ~64 years old with moderate CVD risk (avg ASCVD 17.3%; n=12,546); 5.0 years; no difference in CVD events; doubled risk of GI bleeds
- **ASPREE**[3]
  - Patients ~74 years without CVD (n=19,114); 4.7 years; 14% increased risk of mortality (primarily driven by cancer related deaths); no difference in CVD related mortality

1. ASCEND, 2018, NEJM; 379: 1529-1539
2. ARRIVE, 2018, Lancet; 392: 1036-1046
3. ASPREE, 2018, NEJM; 379: 1519-1528

15

15

2019 ACC/AHA primary CVD prevention guidelines

4.6. Aspirin Use

Recommendations for Aspirin Use

Referenced studies that support recommendations are summarized in Online Data Supplements 17 and 18.

COR	LOE	Recommendations
IIb	A	1. Low-dose aspirin (75-100 mg orally daily) might be considered for the primary prevention of ASCVD among select adults 40 to 70 years of age who are at higher ASCVD risk but not at increased bleeding risk (S4.6-1–S4.6-8).
III: Harm	B-R	2. Low-dose aspirin (75-100 mg orally daily) should not be administered on a routine basis for the primary prevention of ASCVD among adults >70 years of age (S4.6-9).
III: Harm	C-LD	3. Low-dose aspirin (75-100 mg orally daily) should not be administered for the primary prevention of ASCVD among adults of any age who are at increased risk of bleeding (S4.6-10).

1. Arnett et al., 2019, Circulation, DOI: 10.1161/CIR.0000000000000678

16

16

Weighing risks and benefits

- **Primary prevention benefit:**
  - Strong family history of premature MI (female <65 and male <55 years old)
  - Inability to achieve lipid, BP, or glucose lowering targets
  - Significant elevated coronary artery calcium scoring
  - Likely to be able to take ASA for 5-10 years
- Patient-specific bleeding risk factors
  - Age>70, prior stroke, prior bleeding, renal dysfunction, anemia, uncontrolled hypertension, malignancy, thrombocytopenia, liver dysfunction, EtOH abuse, excessive fall risk

17

17

Case 3

CG is a 81 year old female who presented to your hospital with atrial fibrillation. She has a past medical history significant for STEMI with 2 stents 8 months ago, hypertension, diabetes.

Home medications: lisinopril 10 mg daily, atorvastatin 40 mg daily, metformin 1000 mg twice daily, metoprolol 25 mg twice daily, ASA 81 mg daily, ticagrelor 90 mg twice daily

Apixaban is selected for OAC. What is most appropriate plan for her AP therapy?

A. Discontinue aspirin, change ticagrelor to clopidogrel, and continue AP until 1 year post-MI
B. Change ticagrelor to clopidogrel and continue DAPT until 1 year post-MI
C. Continue DAPT until 1 month after apixaban initiated then discontinue the ASA
D. Make no changes

18

18

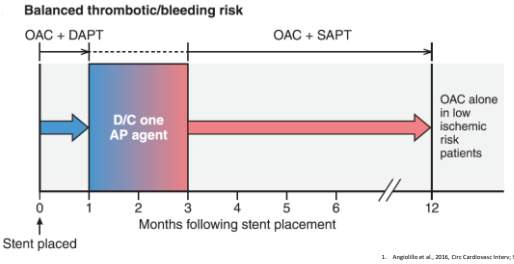
AP therapy in patients on OAC

- OAC is often used for patients with atrial fibrillation (AF) and is used in the treatment of venous thromboembolism
- In patients older than 55 years old, 1 in 5 will develop AF[1]
- Following PCI, DAPT is used to prevent stent thrombosis and CV events for typically 1 year[2]
- Use of DAPT in patients on OAC (triple antithrombotic therapy; TT) nearly quadruples the risk of major and non-major bleeding[3]
- Approximately 25% of patients with AF and have a PCI were discharged on TT[4]

1. Staerk et al., 2018, BMJ; k1453
2. Piccini and Jones, 2017, NEJM; 377: 1580-1582
3. Hansen et al., 2010, Arch Int Med; 170: 1433-1441
4. Hess et al., 2015, JACC; 66:616-627

19

AP therapy in patients on OAC



1. Angiolillo et al., 2016, Circ Cardiovasc Interv; 9: e004305

20

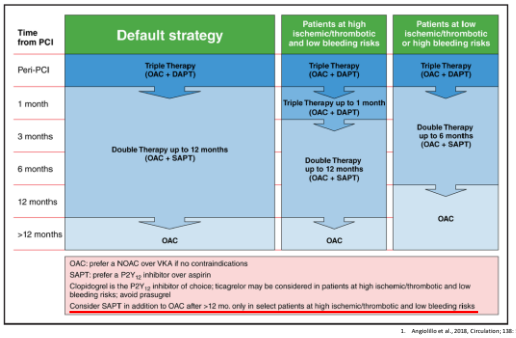
Evolving practice in patients with AF and undergoing PCI

- **WOEST**[1]
  - TT vs warfarin+clopidogrel (DT); 1 year; 64% less bleeding in DT and no difference in thrombotic events
- **PIONEER AF-PCI**[2]
  - TT vs rivaroxaban (15 mg)+P2Y$_{12}$ (DT); 1 year; 41% less bleeding in DT and no difference in CV events and death
- **RE-DUAL PCI**[3]
  - TT vs dabigatran (standard dose)+P2Y$_{12}$ (DT); 14 months; 28% less bleeding in DT and DT was non-inferior to TT for thrombotic events
- **AUGUSTUS**[4]
  - TT vs apixaban (standard dose)+clopidogrel (DT) in patients with AF and undergoing PCI (n=4614); 6 months; less bleeding in DT (47%) but numerically more thrombotic events (7.3% vs 6.5%)

1. Dewilde et al., 2013, Lancet; 381: 1107-1115
2. Gibson et al., 2016, NEJM; 375: 2423-2434
3. Cannon et al., 2017, NEJM; 377: 1513-1524
4. Lopes et al., 2019, NEJM; DOI: 10.1056/NEJMoa1817083

21

AP in patients on OAC



1. Angiolillo et al., 2018, Circulation; 138: 527-536

22

Assessing bleeding risk

- Numerous bleeding risk scoring systems
  - HAS-BLED, ORBIT, HEMORR$_2$HAGES, RIETE, ATRIA
- Generally validated for AF or VTE
- Bleeding risk factors
  - Age >70
  - Prior stroke
  - Prior bleeding
  - Renal dysfunction
  - Anemia
  - Uncontrolled hypertension
  - Malignancy
  - Thrombocytopenia
  - Liver dysfunction
  - EtOH abuse
  - Excessive fall risk

1. Staerk et al., 2018, BMJ; k1453
2. Piccini and Jones, 2017, NEJM; 377: 1580-1582
3. Hansen et al., 2010, Arch Int Med; 170: 1433-1441

23

Medications associated with increased bleeding risk

- NSAIDs
- Other AP therapies
- OAC
- SSRI antidepressants
- Fish oil
- Some herbals supplements (gingko, ginseng, garlic, turmeric etc.)

24

Important counseling points for patients on AP therapies

- Signs and symptoms of major bleeding
  - Dark tarry stools, coffee ground-like substance in vomit, blood in stool or vomit
- If you are having a surgical procedure done, be sure to tell the providers
- Sudden dizziness or faintness
- Stroke or heart attack symptoms

25

25

Balance of bleeding and clotting risks

26

26

Essential questions for patients on antiplatelet therapy

- What is the indication?
- What is the patient's thrombotic risk?
- What is the patient's bleeding risk?
- What is the duration of therapy?

27

27

Conclusions

- AP therapy is recommended to be used indefinitely for secondary prevention after a CV events
- ASA should be used for primary preventions for patients at particularly high CVD risk
- Concomitant OAC and AP therapy is associated with significant bleeding risk and often is appropriate for a specific duration after major CV events

28

28

Case 1

SB is a 69 year old male presenting to your clinic for comprehensive medication review. He has a past medical history significant for NSTEMI 2016 with 1 stent, HTN, and depression. He started citalopram 20 mg about 4 months ago with good response, but has been experiencing nose bleeds frequently.

Home medications: losartan 50 mg daily, carvedilol 12.5 mg twice daily, ASA 81 mg daily, clopidogrel 75 mg daily, atorvastatin 20 mg daily, citalopram 20 mg daily

What is the most appropriate next step?

A. Increase his carvedilol to 25 mg twice daily
B. Refer him to an otolaryngologist
C. Recommend consider discontinue clopidogrel to his cardiologist
D. Decrease the citalopram to 10 mg daily

29

29

Case 2

AG is a 69 year old female presenting to the pharmacy asking where she can find the "baby aspirin" that her friend told her that she should take to protect her heart. AG has a past medical history significant for hypertension, hyperlipidemia, depression, and a history of breast cancer.

Home medications: lisinopril 10 mg daily, atorvastatin 20 mg daily, escitalopram 10 mg daily

What is the most appropriate next step?

A. Tell her where to find the ASA 81 mg tablets
B. Calculate an ASCVD risk score and recommend ASA if >10%
C. Ask her if she discussed ASA use with her doctor
D. Tell her that she does not have an indication for ASA use and it can be dangerous

30

30

Case 3

CG is a 81 year old female who presented to your hospital with atrial fibrillation. She has a past medical history significant for STEMI with 2 stents 8 months ago, hypertension, diabetes.

Home medications: lisinopril 10 mg daily, atorvastatin 40 mg daily, metformin 1000 mg twice daily, metoprolol 25 mg twice daily, ASA 81 mg daily, ticagrelor 90 mg twice daily

Apixaban is selected for OAC. What is most appropriate plan for her AP therapy?

A. Discontinue aspirin, change ticagrelor to clopidogrel, and continue AP until 1 year post-MI
B. Change ticagrelor to clopidogrel and continue DAPT until 1 year post-MI
C. Continue DAPT until 1 month after apixaban initiated then discontinue the ASA
D. Make no changes

31

31

Thank you

Questions?

32

32