Newer Antiplatelet Drugs

Washington Archive Report

Washington P&T Committee

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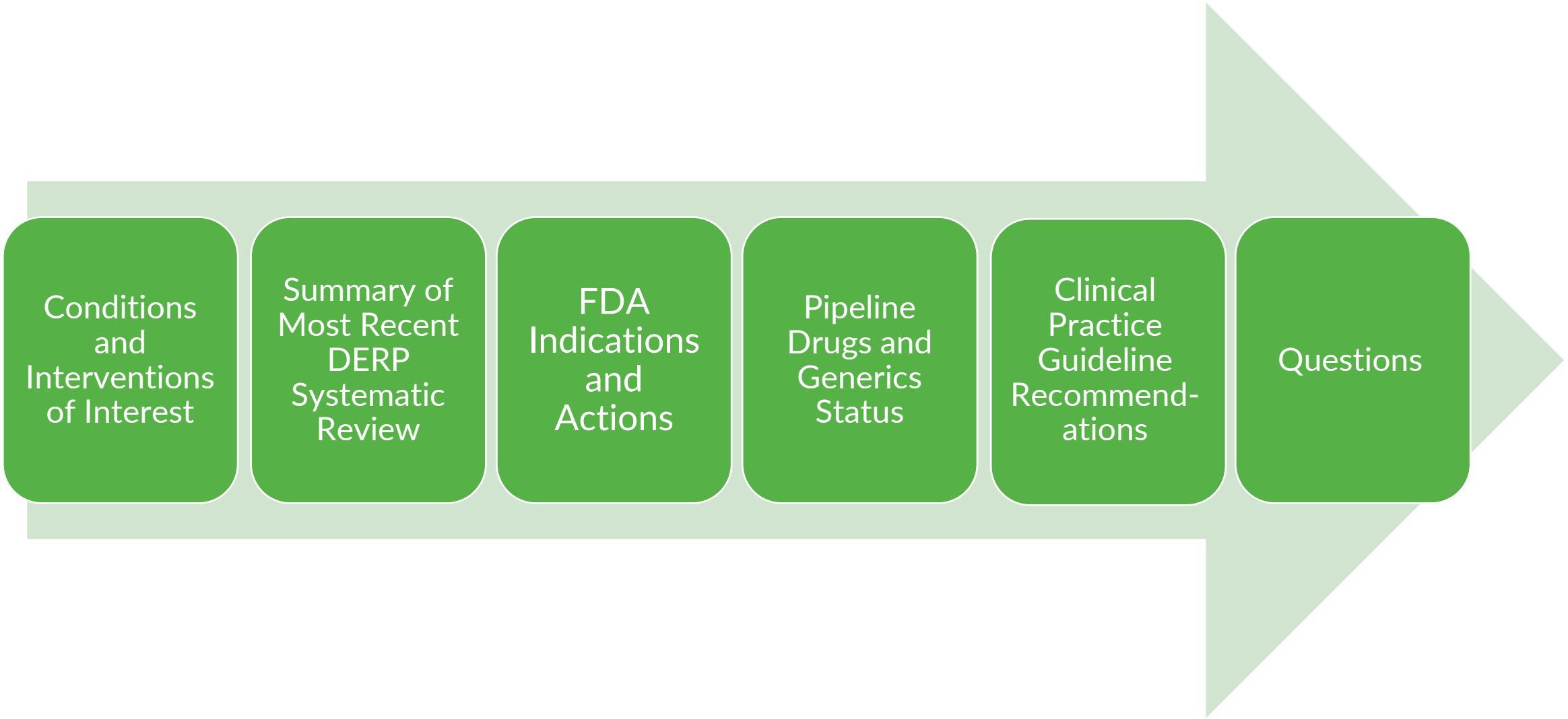
OHSU

Aim of Project

- The Drug Effectiveness Review Project (DERP) aims to present information to the Washington State Pharmacy and Therapeutics (P&T) Committee with topic reports on 9 drug classes that are candidates to be archived from active review by the Committee
- The 9 drug classes identified by the Washington Health Care Authority (HCA) as archive candidates are:
    - Anticoagulants
    - Antiemetics
    - **Antiplatelets**
    - Asthma controllers
    - Asthma quick relief drugs
    - Long-acting opioids
    - Overactive bladder drugs
    - PCSK9 inhibitors
    - Statins

*Drug class in **green** is presented in this report*

Overview


Conditions and Interventions of Interest
Summary of Most Recent DERP Systematic Review
FDA Indications and Actions
Pipeline Drugs and Generics Status
Clinical Practice Guideline Recommend-ations
Questions

Condition of Interest: Complications of Atherosclerosis

- Cardiac and cerebral vascular events due to atherosclerosis (the narrowing or hardening of the arteries due to plaque build-up)
  - Ischemic coronary artery disease (CAD) → ***Heart attack***
  - Cerebrovascular disease → ***Stroke***
  - Peripheral arterial disease (PAD) → ***Injury to arms or legs***
- Risk factors include:
  - Unhealthy lifestyle behaviors
    - Poor diet, physical inactivity, smoking, poor sleep
  - Medical conditions
    - Hypertension, dyslipidemia, diabetes, overweight or obesity, inflammatory diseases, PCOS, endometriosis
  - Genetics
    - Family history of atherosclerosis and related conditions
  - Advanced age

Cardiovascular Disease Epidemiology

- Prevalence of cardiovascular disease (CVD) in adults is 48.6% in the US (NHANES 2017 to March 2020), and increases with age
  - 207 in 100,000 people died of heart disease and stroke in 2020
- Deaths caused by heart disease:
  - CVD remains as the leading cause of death in the US
  - Is highest among Black (22.6%) and Asian (18.6%) populations in the US (vs. 18% in White and 11.9% in Hispanic populations)
    - The MESA study found Black participants had a 34% higher mortality hazard compared with white participants in the US
  - Affects about 1 in every 4 male deaths, and about 1 in every 5 female deaths in the US

Treatment and Prevention of Atherosclerosis-Related Events

- Pharmacological treatments
  - Agents to treat and prevent complications (cardiovascular events) of atherosclerosis
    - Nitrates (to dilate arteries and relieve or prevent angina)
    - Intravenous antiplatelet agents (more commonly used as initiation to treatment)
    - Aspirin (older antiplatelet agent)
    - Newer antiplatelet agents (alone or with aspirin [dual antiplatelet therapy, or DAPT])
      - Adenosine reuptake inhibitors
      - P2Y12 receptor inhibitors
      - Protease-activated receptor (PAR-1) antagonists

- ***Out of scope for this presentation***:
  - Treatments/recommendations to **reduce risk** of atherosclerosis (e.g., agents to reduce blood pressure, cholesterol levels, control blood sugar levels, and healthy lifestyle behaviors

Summary of Most Recent DERP Products

Last Report	**2017**
Date Presented	August 2017
Report Title	*Newer Antiplatelet Drugs: A Targeted Update Report*
Search Dates	December 2010 through April 18, 2017
Authors	Pacific Northwest Evidence-based Practice Center and CEbP authors
Scan/Surveillance Since Last Report	
July 2018	*Newer Antiplatelet Drugs* • Search Dates: January 2017 through June 22, 2018

PICOS of Most Recent DERP Report

- *Population*
  - Adults (at least 18 years) with one of the following:
    - Acute coronary syndrome (ACS)
    - Recent or ongoing coronary revascularization by stenting or coronary artery bypass graft (CABG)
    - Previous ischemic stroke or transient ischemic attack (TIA)
    - Symptomatic PAD
- *Comparators*
  - Antiplatelet drugs compared with each other (head-to-head)
  - Placebo or aspirin (for included drugs with no head-to-head evidence)
- *Study Designs*
  - Randomized controlled trials, retrospective observational studies, and systematic reviews

PICOS of Most Recent DERP Report

- *Interventions*[a]

Name	Brand Name	FDA Approval Date	Generics Status	Mechanism
Clopidogrel[b]	Plavix	November 17, 1997		P2Y12 inhibitor
Dipyridamole[c]	Persantine	September 1998	Available	Adenosine reuptake inhibitor
Dipyridamole ER/aspirin	Aggrenox	November 11, 1999		COX inhibitor, adenosine reuptake inhibitor
Prasugrel	Effient	July 10, 2009		P2Y12 inhibitor
Ticagrelor[d]	Brilinta	July 20, 2011	Applications submitted	P2Y12 inhibitor
Vorapaxar[d]	Zontivity	May 8, 2014		Reversible antagonist of PAR-1

Notes. [a] *Intravenous drugs ticlopidine and cangrelor were excluded;* [b] *Alone or in combination with aspirin;* [c] *In combination with aspirin;* [d] *New with this report.*

PICOS of Most Recent DERP Report

- *Outcomes*

Efficacy and Effectiveness

- All-cause mortality
- Cardiovascular mortality
- Myocardial infarction (MI)
- Stroke
- Failure of an invasive vascular procedure

Safety

- Overall adverse effects
- Withdrawals due to adverse effects
- Serious adverse events, such as neutropenia or major hemorrhage
- Specific adverse events, such as diarrhea or rash
- Withdrawals due to specific adverse events

Key Questions in Most Recent DERP Report

- For adults with ACS, coronary revascularization via stenting or CABG, previous ischemic stroke or TIA, or symptomatic PAD:
  1. Do antiplatelet agents differ in efficacy or effectiveness?
  2. Do antiplatelet agents differ in harms?
  3. Are there subgroups of patients based on demographics, socioeconomic status, other medications, comorbidities, or pregnancy for which one antiplatelet agent is more effective or associated with fewer harms?
  4. Do antiplatelet agents differ in effects when therapy duration varies?

Summary of Findings in Most Recent DERP Report (slide 1 of 2)

- 2017 report[a]
  - Cumulative from original report (2005): 44 RCTs, 3 cohort studies, 1 pooled analysis
- Summary of key findings
  - Few differences in cardiovascular benefits were found between competing antiplatelet drugs, and benefits were small if existed (about 1% to 2%)
  - Vorapaxar as add-on treatment to existing antiplatelet therapy compared with placebo, demonstrated no benefit with atherosclerosis and small benefits in patients with prior MI or CAD, but increased major bleeding in all studied populations

Notes: [a]Reporting of methods and included studies has changed since the preparation of this report (please see final 2017 report for complete references list)

Summary of Findings in Most Recent DERP Report (slide 2 of 2)

- Summary of key findings (cont.)
  - In ACS or prior MI
    - Compared with ticagrelor, there were no differences in effectiveness or harms with prasugrel, more CV events but fewer AE withdrawals with clopidogrel, and more CV events but less bleeding and fewer AE withdrawals with aspirin
    - Compared with prasugrel, clopidogrel resulted in more major CV events but fewer major bleeding events
  - In PAD, clopidogrel with more strokes and fewer withdrawal AEs compared with ticagrelor
  - In stroke or TIA
    - Compared with clopidogrel, no differences in effectiveness or major bleeding but more overall AEs compared with dipyridamole ER/ASA
    - Compared with aspirin, no differences in effectiveness and major bleeding, but more overall AEs with ticagrelor

Summary of Findings in Most Recent Scans/Surveillance

- 2018 Scan (searched through June 22, 2018)
  - No new drugs, formulations, indications, or serious harms
  - 1 new systematic review of ticagrelor compared with other antiplatelet agents or placebo for stroke prevention
  - 4 new head-to-head trials
    - 3 trials of ticagrelor vs. clopidogrel
      - 2 trials in patients undergoing percutaneous coronary intervention
      - 1 trial in patients with CAD
    - 1 trial of ticagrelor vs. prasugrel in persons with MI

New FDA Drugs and Indications Since Most Recent DERP Report

- **New drugs (oral delivery)**
  - Yosprala (aspirin + omeprazole) approved in 2106, discontinued in 2018
- **New indications**
  - Ticagrelor (Brilinta)
    - Expanded to use for the reduction in risk of a first MI or stroke in patients with CAD at high risk for such events (May 2020)
    - Expanded to use for the reduction in risk of stroke in patients with acute ischemic stroke or high-risk TIA (November 2020)

FDA-Approved Indications

- Indications as of November 1, 2023

	To Reduce Risk For:						Use with aspirin (dual therapy)
Generic Name (Brand Name)	MI, stroke and/or CV death in patients with ACS	MI, stroke, and/or CV death, or thrombotic events in patients with history of MI, stroke, or PAD	Postoperative thromboembolic complications of cardiac valve replacement	Stroke in patients with history of TIA or stroke	Thrombotic CV events in patients managed with PCI (stent)	First MI or stroke in patients with high-risk CAD	
Clopidogrel (Plavix)	√	√					√ for ACS
Dipyridamole (Persantine[a])			√				No specifics
Dipyridamole ER and aspirin (Aggrenox[a])				√			Dual agent
Prasugrel (Effient)					√		√
Ticagrelor (Brilinta)	√	√		√		√	√
Vorapaxar (Zontivity)		√			√		√

Note. [a] *Brand discontinued since last report.*
Abbreviations. ACS: acute coronary syndrome; CV: cardiovascular; MI: myocardial infarction; PAD: peripheral artery disease; PCI: percutaneous coronary intervention.

New FDA Warnings and Pipeline Agents Since Most Recent DERP Report

- **New boxed warnings**
  - No new boxed warnings
- **New warnings/precautions/contraindications**
  - Ticagrelor
    - Not recommended in people who are breastfeeding (April 2019)
  - Vorapaxar
    - Not recommended in people who are pregnant or breastfeeding (November 2019)
- **Pipeline Agents**
  - No new oral antiplatelet pipeline agents

Generic Drug Status

Name	Generic Availability	Status
Clopidogrel	**Yes**	***Newly available as generic since last report***
Dipyridamole	Yes	Generic reported as available in last report
Dipyridamole ER/aspirin	**Yes**	***Newly available as generic since last report***
Prasugrel	**Yes**	***Newly available as generic since last report***
Ticagrelor	No	Estimated date of earliest possible generic launch, May 2025
Vorapaxar	No	Estimated loss of exclusivity, December 2027

Clinical Practice Guidelines (slide 1 of 6)

- Acute ST-elevation MI (STEMI)
  - Initial management is reperfusion and/or fibrinolysis
  - Initiate dual antiplatelet therapy (DAPT) as soon as possible (aspirin for all patients)
  - Type of $P2Y_{12}$ inhibitor can depend on reperfusion strategy
    - Start with ticagrelor or prasugrel with PCI
    - Loading dose of clopidogrel with fibrinolysis
    - None if preparing for CABG
    - No reperfusion, start with ticagrelor
  - Treat with DAPT for at least 12 months, unless high bleeding risk

Note. Primary source UpToDate; recommendations verified against key clinical practice guidelines (slide 24).

Clinical Practice Guidelines (slide 2 of 6)

- Acute non-ST-elevation ACS
  - Most patients should be treated with a DAPT
    - Invasive strategy
      - Pretreatment (if there is time): ticagrelor
      - Post-treatment: ticagrelor or prasugrel
    - Ischemia-guided: loading dose of ticagrelor as soon as possible
  - Continue DAPT for at least 12 months, depending on bleeding risk

Note. Primary source UpToDate; recommendations verified against key clinical practice guidelines (slide 24).

Clinical Practice Guidelines (slide 3 of 6)

- Elevated CV event risk with CAD who undergo percutaneous coronary intervention (PCI)
  - First year after PCI
    - Initiate triple therapy of oral anticoagulant, $P2Y_{12}$ inhibitor, and aspirin
      - Discontinue aspirin after 1 week (or longer if high thrombotic risk)
      - Clopidogrel recommended over prasugrel or ticagrelor for stable CAD
      - Clopidogrel or ticagrelor with acute coronary syndrome, but former if bleeding risk

Note. Primary source UpToDate; recommendations verified against key clinical practice guidelines (slide 24).

Clinical Practice Guidelines (slide 4 of 6)

- Elevated CV event risk with CAD who undergo percutaneous coronary intervention (PCI) (continued)
  - Long-term therapy
    - Treatment with oral anticoagulant with or without oral antiplatelet agents as needed, depending on bleeding risk
    - Clopidogrel is preferred over prasugrel or ticagrelor for most stable patients requiring DAPT
    - Prasugel or ticagrelor (more potent $P2Y_{12}$ inhibitor) preferred over clopidogrel in patients with ACS, but depends on bleed risk
    - Duration of DAPT is typically 6 to 12 months but depends on ischemic and bleeding risks

Note. Primary source UpToDate; recommendations verified against key clinical practice guidelines (slide 24).

Clinical Practice Guidelines (slide 5 of 6)

- Acute ischemic stroke treatment
  - Initiate aspirin alone or DAPT as soon as possible unless within 24 hours following treatment with IV thrombolysis
    - DAPT with clopidogrel generally indicated for first 21 days
- Ischemic stroke prevention
  - Long-term secondary prevention treatment with aspirin (alone), clopidogrel (alone), or dipyridamole ER + aspirin
    - Depends mostly on tolerance
    - DAPT generally not recommended given lack of greater efficiency and increased bleeding risk

Note. Primary source UpToDate; recommendations verified against key clinical practice guidelines (slide 24).

Clinical Practice Guidelines (slide 6 of 6)

- Prevention of secondary CV events with PAD[a]
  - Long-term antiplatelet therapy recommended (eg, aspirin, clopidogrel) for patients with symptomatic lower extremity PAD
- Vorapaxar typically reserved for use in very high-risk patients due to bleeding[b]
  - Either not mentioned in guidelines, or just as another option for oral antiplatelet agent

Note. [a]*Primary source UpToDate; recommendations verified against key clinical practice guidelines (slide 24);* [b]*Source. IPD Analytics.*

Key Clinical Practice Guidelines

Focus	Date	Title of Guideline
American Heart Association (AHA) / American College of Cardiology (ACC)		
Chronic coronary disease	2023	Management of Patients With Chronic Coronary Disease
Dual antiplatelet therapy	2016	Focused Update on Duration of Dual Antiplatelet Therapy in Patients With CAD
Peripheral artery disease	2016	Management of Patients With Lower Extremity Peripheral Artery Disease
Acute coronary syndromes	2014	Management of Patients With Non–ST-Elevation Acute Coronary Syndromes
American Heart Association (AHA) / American Stroke Association (ASA)		
Stroke	2021	Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack
European Society of Cardiology (ESC)		
Myocardial infarction	2017	Management of acute myocardial infarction in patients presenting with ST-segment elevation

Questions?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