AASHP Annual Seminar Clinical Pearls

REBEKKA ADAMSON, PHARMD, BCCP; RYAN HADLEY, PHARMD, BCACP

LANE FARRELL, PHARMD, BCCCP; POOJA PATEL, PHARMD;

JOSIAH SMITH, PHARMD, BCCCP

Objectives

1. Discuss clinical scenarios that might not be widely observed or published
2. Describe medication management strategies in difficult or controversial patient care situations
3. Identify novel practice options for patient care in various health-system settings

End of an Aspirin Era? Alternative Antithrombotic Strategies for Chronic Coronary Syndrome (CCS)

Rebekka Adamson, PharmD, BCCP
Clinical Pharmacy Specialist
Dell Seton Medical Center
Austin, TX

Disclosure

No conflicts of interest to disclose.

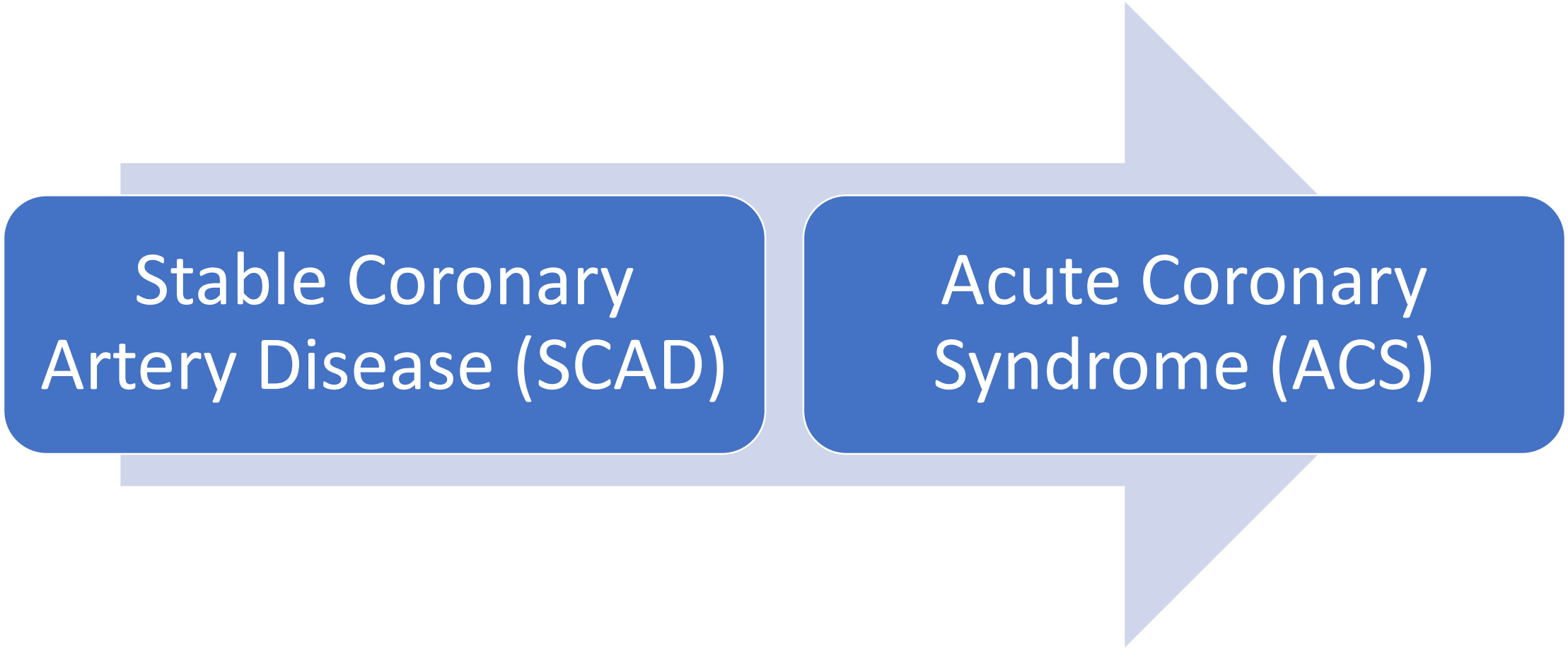
Learning Objectives: Pharmacist

1. Define chronic coronary syndrome (CCS)
2. Describe the outcomes of recent publications regarding the use of antithrombotics for the treatment and prevention of major cardiovascular events in patients with CCS
3. Evaluate the appropriateness of various pharmacotherapy regimens for CCS

Learning Objectives: Technicians

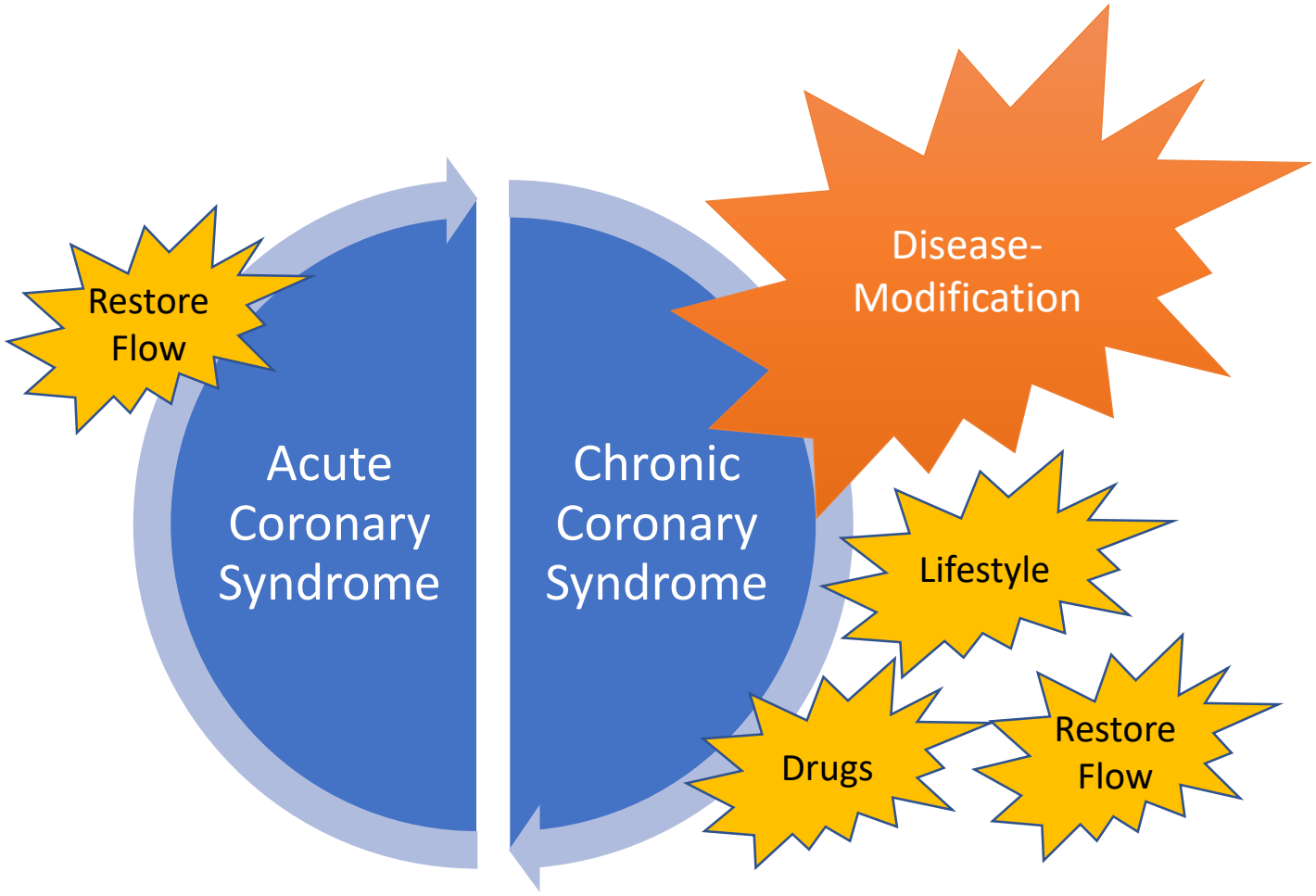
1. Explain the meaning of chronic coronary syndrome (CCS)
2. Compare and contrast antithrombotic agents used to prevent major cardiovascular events in patients with CCS
3. Describe the optimal antithrombotic strategy for the prevention of major cardiovascular events in patients with CCS

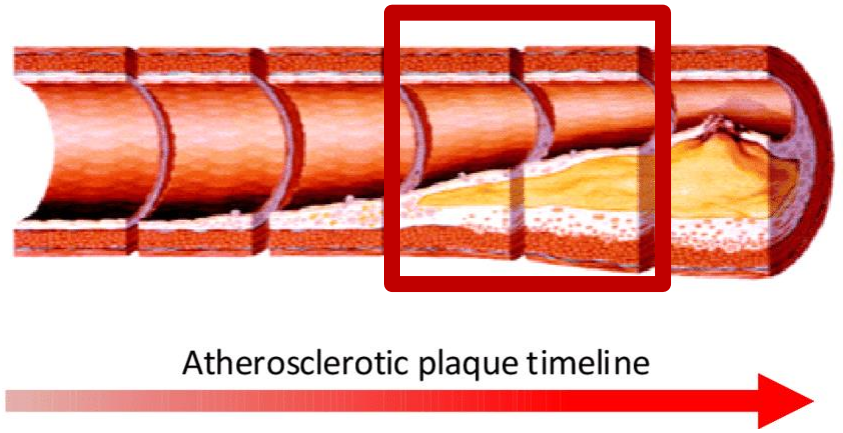
Previous State



ESC Scientific Group. Eur Heart J. 2019 Aug 31.

Redefined State

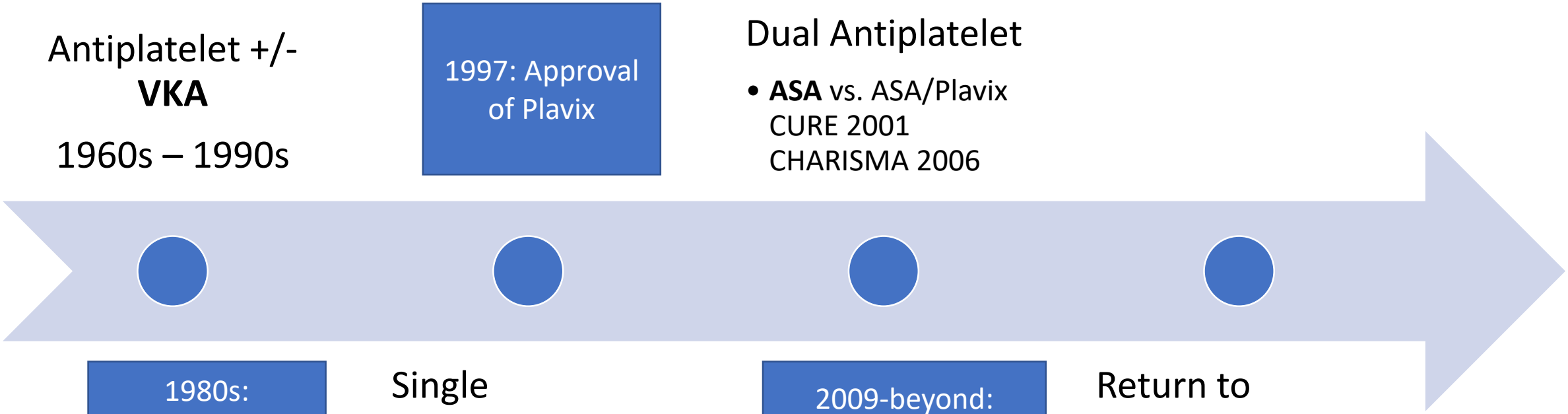




ESC Scientific Group. Eur Heart J. 2019 Aug 31.

Antiplatelets for Chronic Coronary Syndrome: Looking Beyond Aspirin

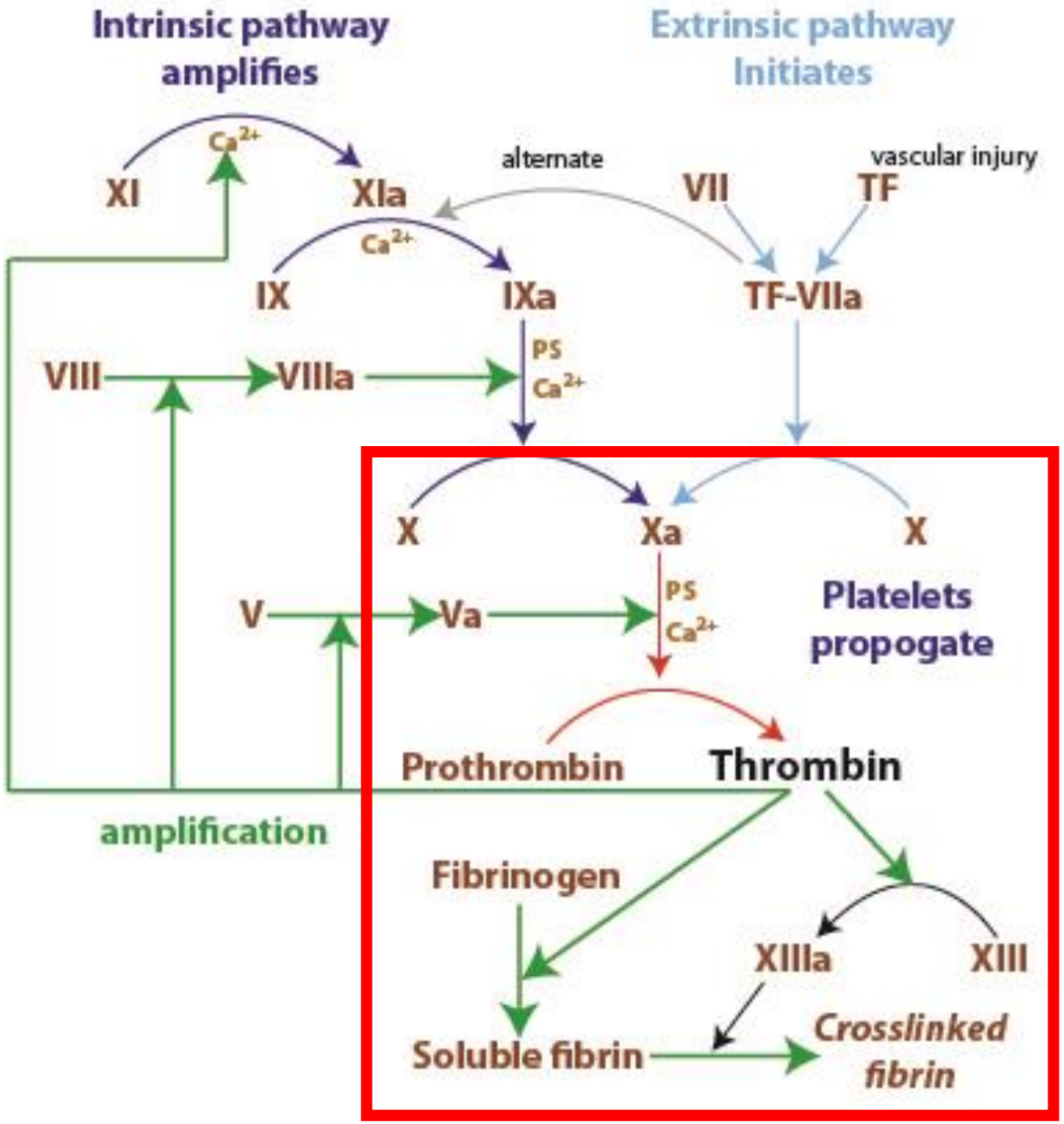
Evolution of Anticoagulation for CAD



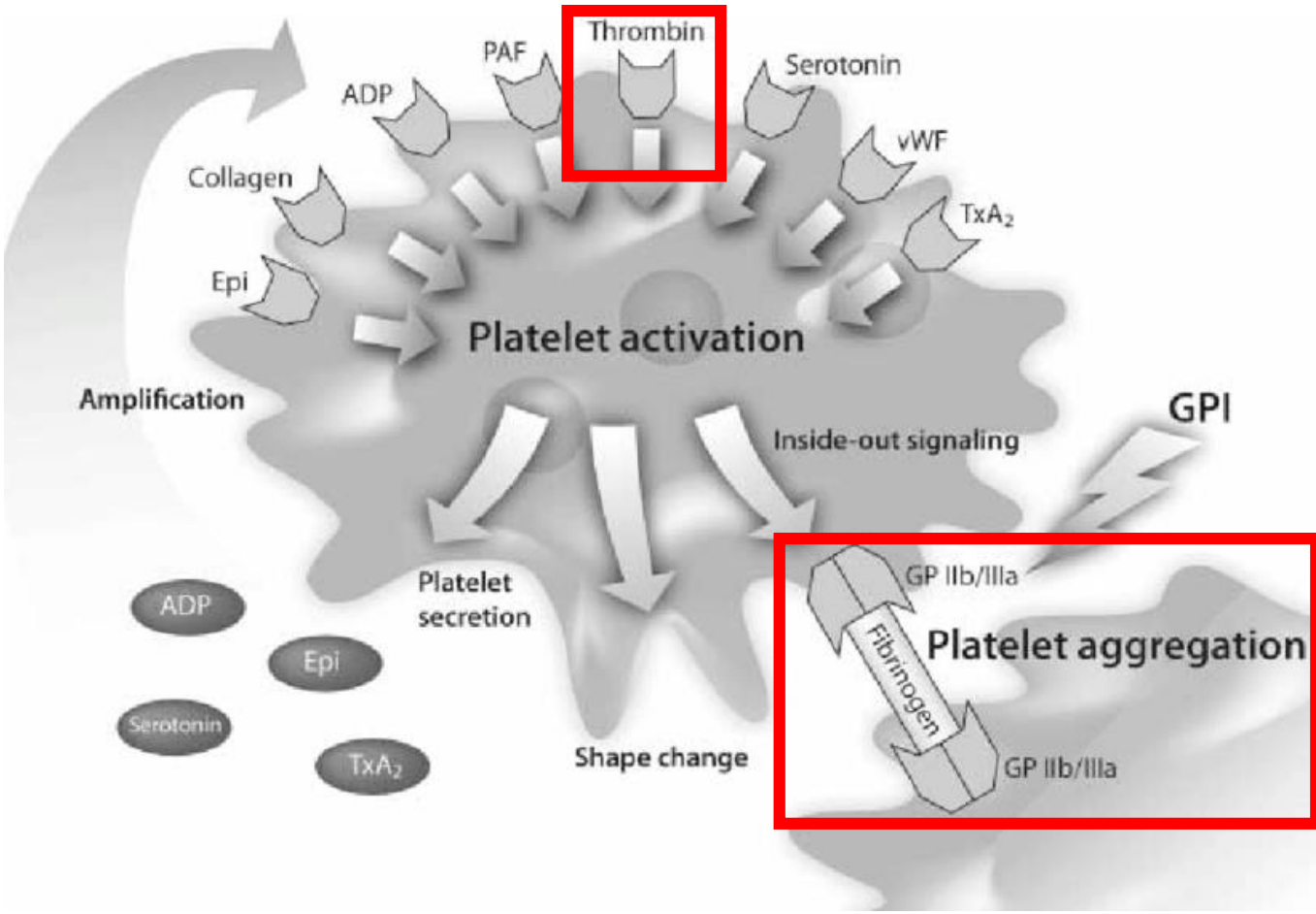
VKA: vitamin K antagonist
CVD: cardiovascular disease
AF: atrial fibrillation

J Am Coll Cardiol. 2003;41:62S-69S.

Coagulation Cascade

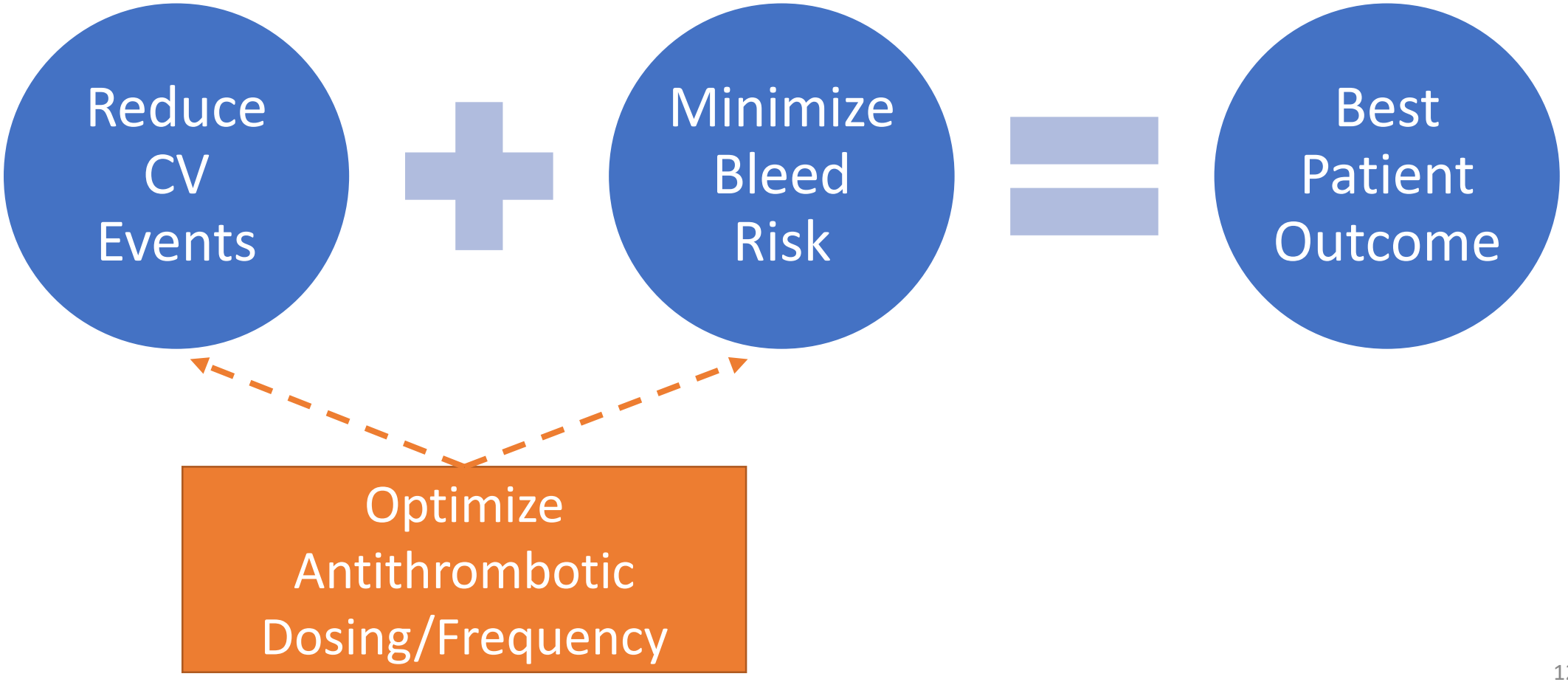


Platelet Function



Thrombosis and Haemostasis. 2012;107. 215-24.

Long-Term Secondary Prevention



CV: cardiovascular

2019 ESC CCS Guideline: Recommendations for Event Prevention

Antithrombotic therapy in patients with CCS and in sinus rhythm	Class/Level
Aspirin 75-100 mg daily is recommended in patients with a previous MI or revascularization.	I, A
Clopidogrel 75 mg daily is recommended as an alternative to aspirin in patients with aspirin intolerance.	I, B
Clopidogrel 75 mg daily may be considered in preference to aspirin in symptomatic or asymptomatic patients, with either PAD or a history of ischemic stroke or transient ischemic attack.	IIb, B
Aspirin 75-100 mg daily may be considered in patients without a history of MI or revascularization, but with definitive evidence of CAD on imaging.	IIb, C

ESC Scientific Group. Eur Heart J. 2019 Aug 31.

PAD: peripheral arterial disease, MI: myocardial infarction, CAD: coronary artery disease

2019 ESC CCS Guideline: Recommendations for Event Prevention

Antithrombotic therapy in patients with CCS and in sinus rhythm	Class/Level
Addition of a **second antithrombotic** drug to aspirin for long-term secondary prevention should be considered in patients with a **high risk** of ischemic events and **without high bleeding risk.**	IIa, A
Addition of a **second antithrombotic** drug to aspirin for long-term secondary prevention should be considered in patients with a **moderately increased risk** (LOE: IIb) of ischemic events and **without high bleeding risk.**	IIb, A

ESC Scientific Group. Eur Heart J. 2019 Aug 31.

2019 ESC CCS Guideline: Recommendations for Event Prevention

Ischemic Risk Factors

- Diffuse multivessel disease
- DM requiring medication
- Recurrent MI
- Peripheral Arterial Disease (PAD)
- CKD (eGFR 15-59 mL/min)

Bleeding Risk Factors

- History of ICH or ischemic stroke
- Intracranial pathology
- Recent GI bleed or anemia due to GI bleed, other GI pathology with bleed risk
- Liver failure
- Extreme old age or frailty
- Renal failure requiring HD or eGFR <15 mL/min

DM: diabetes mellitus
CKD: chronic kidney disease
ICH: intracranial hemorrhage
GI: gastrointestinal
HD: hemodialysis
eGFR: estimated glomerular filtration rate

ESC Scientific Group. Eur Heart J. 2019 Aug 31.

Antithrombotics for Long-Term Secondary Event Prevention

Drug Option	Dose	Approved Indication	Post-MI Trial	CCS Trial
Antiplatelets				
Clopidogrel	75 mg	Post-MI, extended DAPT	DAPT Trial (2014)	CHARISMA (2006) DAPT Trial (2014)
Ticagrelor	**60 mg** BID	Post-MI, extended DAPT	PEGASUS-TIMI 54 (2016)	**THEMIS (2019)**
Prasugrel	10 mg QD or 5 mg* QD (*if <60 kg or >75 years)	Post-MI, extended DAPT	DAPT Trial (2014)	DAPT Trial (2014) Low-dose studies ongoing
Anticoagulants				
Rivaroxaban	2.5 mg BID	Post-MI >1 year or multivessel CAD	ATLAS ACS 2 – TIMI 51 (2012)	**COMPASS (2018)**

ESC Scientific Group. Eur Heart J. 2019 Aug 31.

THEMIS

Design	Placebo-controlled, double-blind, multicenter, RCT
Objective	Evaluate whether ticagrelor added to aspirin improves CV outcomes in patients with stable CAD and T2DM
Intervention	Ticagrelor 60 mg twice daily plus aspirin (75-150 mg) Placebo plus aspirin (75-150 mg)
Primary Endpoint	Composite of CV death, MI, or stroke
Patient Population	50 years of age or older with stable CAD and T2DM • **Established CAD:** previous PCI/CABG or documented angiographic stenosis of 50% in at least one coronary artery • **T2DM:** receipt of an antihyperglycemic medication for at least 6 months

N Engl J Med 2019. 381(14):1309-1320.

THEMIS Trial Results

	Ticagrelor	Placebo	P Value
Primary Outcome	**N = 9619**	**N = 9601**	
MI, stroke, CV death	736 (7.7)	818 (8.5)	0.04
Secondary Outcomes			
CV death	364 (3.8)	357 (3.7)	0.79
MI	274 (2.8)	328 (3.4)	
Stroke (ischemic)	152 (1.6)	191 (2)	
Safety Outcomes			
Major bleeding	206 (2.2)	100 (1)	< 0.01
Intracranial bleeding	70 (0.7)	46 (0.5)	0.005
Any bleeding	1446 (15.1)	595 (6.2)	< 0.01
Any bleeding leading to discontinuation of ticagrelor or placebo	466 (4.9)	125 (1.3)	< 0.01

N Engl J Med 2019. 381(14):1309-1320.

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Anticoagulants				
Rivaroxaban	2.5 mg BID	Post-MI >1 year or multivessel CAD	ATLAS ACS 2 – TIMI 51 (2012)	**COMPASS (2018)**

ESC Scientific Group. Eur Heart J. 2019 Aug 31.

COMPASS CAD

Design	Placebo-controlled, double-blind, multicenter, RCT
Objective	Evaluate whether rivaroxaban alone or in combination with aspirin would be more effective than aspirin alone for secondary cardiovascular protection
Intervention	• Rivaroxaban 2.5 mg twice daily + aspirin 100 mg daily • Rivaroxaban 5 mg twice daily alone • Aspirin 100 mg daily alone
Primary Endpoint	Composite of cardiovascular death, stroke, or myocardial infarction
Patient Population	Established **coronary artery disease + ischemic risk factors** • **Established CAD:** MI within last 20 years, or multivessel CAD (with symptoms or with history of stable or unstable angina or with previous intervention/PCI or CABG) • **Ischemic risk factors**: age ≥ 65 years, or age <65 and atherosclerosis in ≥2 vascular beds or two additional risk factors (current smoking, diabetes, renal insufficiency, heart failure, or nonlacunar ischemic stroke ≥1 month)

Lancet 2018;391:219-29.

COMPASS CAD Trial Results

	Low Dose Riv + ASA	Aspirin Alone	P Value
Primary Outcome	**N = 8313**	**N = 8261**	
MI, stroke, CV death	347 (4)	460 (6)	< 0.01
Secondary Outcomes			
MI	169 (2)	195 (2)	0.15
Stroke (ischemic)	60 (1)	130 (2)	< 0.01
Stroke (hemorrhagic)	14 (<1)	10 (<1)	0.43
CV death	139 (2)	184 (2)	0.010
Safety Outcomes			
Major bleeding	263 (3)	158 (2)	< 0.01
Fatal bleeding	14 (<1)	9 (<1)	0.30
GI bleeding	130 (2)	61 (1)	< 0.01
Intracranial bleeding	26 (<1)	23(<1)	0.69

Lancet 2018;391:219-29.

Assessment Question

- P.M. is a 55 year old male being seen by his outpatient cardiologist for a routine checkup. He has a PMH significant for HLD (controlled), type 2 DM (A1c: 7.2 % on insulin therapy), and remote history of MI (5 years ago). He is trying to stop smoking, but still smokes 1 pack per week. He does not have renal impairment.
- He takes the following medications daily: aspirin 81 mg, atorvastatin 80 mg, insulin glargine 20 units at bedtime, empagliflozin 25 mg, metformin 1000 mg twice daily

P.M. has a strong family history of premature CAD and asks if there are any medications he can add to his daily regimen to prevent another heart attack…

Assessment Question

Which of the following should NOT be recommended to further reduce PM's risk of future CV events?

a. Add nothing and continue aspirin 81 mg daily, as aspirin monotherapy is effective in preventing CV events.
b. Add rivaroxaban 2.5 mg BID, as low-dose anticoagulation has been shown to reduce CV events and PM is low risk for bleeding.
c. Add ticagrelor 60 mg BID, as low-dose P2Y12 therapy added to aspirin has been shown to reduce CV events and PM is low risk for bleeding.
d. Add clopidogrel 75 mg QD, as extended duration DAPT for secondary prevention has been shown to reduce CV events and PM is low risk for bleeding.

Conclusion

- Addition of long-term P2Y12 or low-dose OAC to low-dose aspirin may reduce CV events in patients with established coronary artery disease outside of the ACS window (1 year after event)
- More studies are needed to determine:
  - Optimal antithrombotic strategy (antiplatelet vs. OAC)
  - Patients most likely to benefit
  - Management of patients most at risk for bleeding (CKD, elderly)

End of an Aspirin Era? Alternative Antithrombotic Strategies for Chronic Coronary Syndrome (CCS)

Rebekka Adamson, PharmD, BCCP
Clinical Pharmacy Specialist
Dell Seton Medical Center
Austin, TX

STRATEGIES FOR MANAGING NEUROPATHIC PAIN

Ryan Hadley, PharmD, BCACP

Clinical Pharmacist CommUnityCare

LEARNING OBJECTIVES

Pharmacist

- Review the pathophysiology of neuropathic pain associated with DM
- Identify best practices for treatment of neuropathic pain (NP) associated with DM
- Analyze clinical trials comparing mono vs dual therapy

Technician

- Define the pathophysiology of neuropathic pain associated with DM
- Classify ADE of neuropathic medications
- Summarize benefits of different therapies used for treating neuropathic pain associated with DM

DISCLOSURES

- Nothing to disclose at this time

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NEUROPATHY REVIEW

NEUROPATHY

- Neuropathic pain (NP) – Pain that is caused by a lesion or disease affecting the nervous system
  - The exact mechanisms involved in the generation of diabetic NP is not fully established

- Clinical Presentation –descriptions of burning, pins and needles (paresthesia), tingling, numbness, electric shocks/shooting, crawling (formication), itching, intolerance to temperature and hyperalgesia

- Symptoms are more common and severe at night
  - Highest blood sugar of the day!!!
  - Glucose a "sharp" compound

Lancet Neurol. 2015;14(2):162–173
Exp Ther Med. 2019;17(3):1963-1976.

IMPACT

- Diabetic neuropathy is the most common complication of diabetes mellitus, becoming symptomatic after 14.5 years of chronic prolonged high blood glucose in type 1 diabetes, and after only 8.1 years in type 2 diabetes

- Impact:
  - Associated with a high economic burden on the individual and society
    - Over 45% need combination therapy
  - Painful diabetic neuropathy (PDN) affects 16% of patients with diabetes, and it is frequently unreported (12.5%) and more frequently untreated (39%)
  - Affects 30% of patients with diabetes who are hospitalized and 25% of those in the community

Pain Med. 2019;20:S2-S12.
Neurology. 2011;76(20):1758-65.
Exp Ther Med. 2019;17(3):1963-1976.

TYPES OF NEUROPATHY

Peripheral Neuropathy

- Affects nerves leading to the feet, legs, hands, and arms
- Symptoms
  - Burning, stabbing or electric-shock sensations
  - Muscle weakness
  - Poor coordination

Autonomic Neuropathy

- Affects nerves leading "involuntary" functions of your body such as:
  - Cardiovascular
  - Digestive
  - Genitourinary
- Symptoms
  - hypoglycemia unawareness

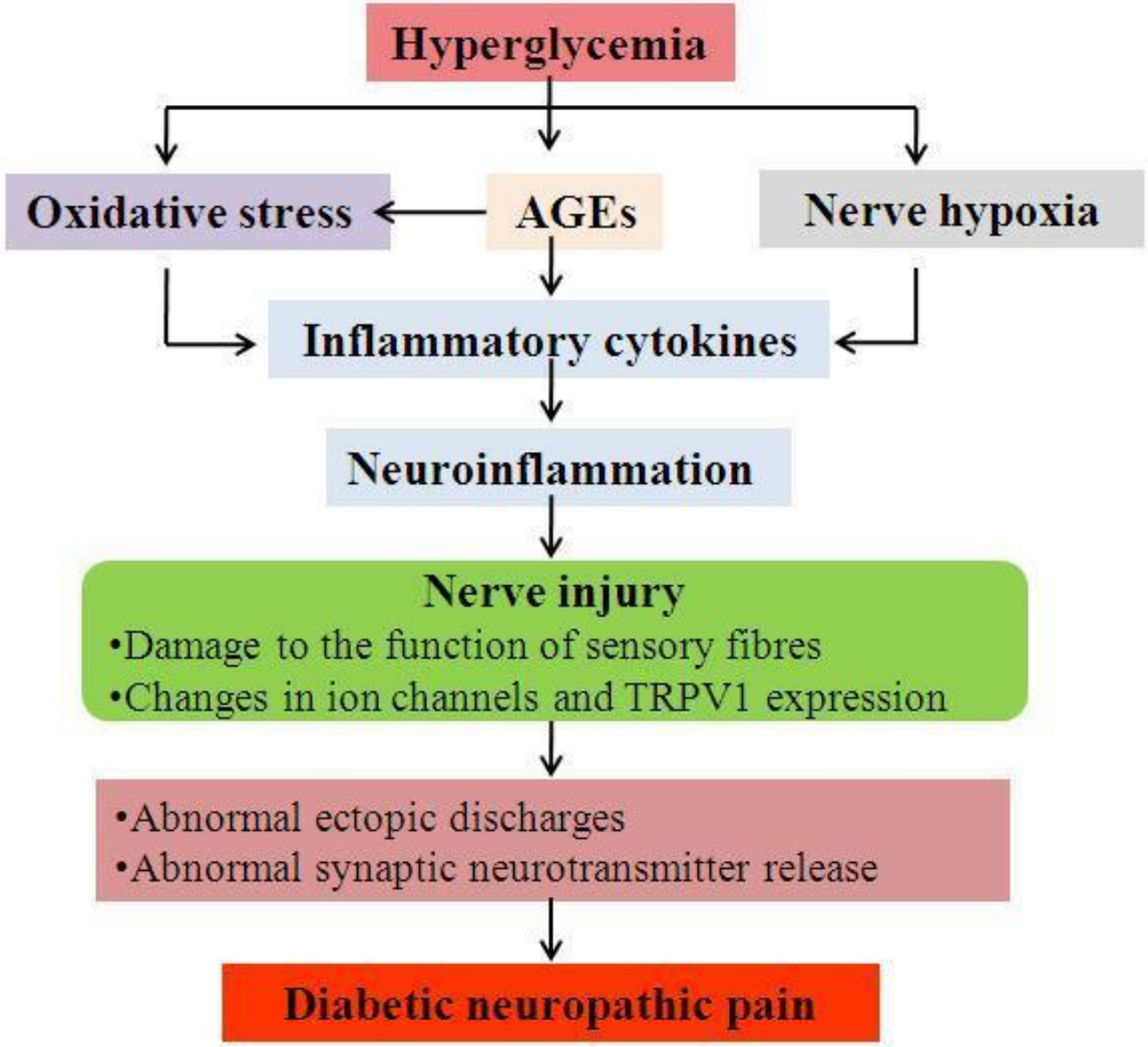
Proximal Neuropathy

- Affects nerves leading to the buttocks, hips, thighs, and legs
- Symptoms
  - Weakness in the legs
  - Pain or weakness in your arms/legs after symptoms in your legs start improving

Focal Neuropathy

- Comes on suddenly, and it usually affects nerves to the head, torso, or legs.
- Symptoms
  - Visual changes
  - Pain or weakness in chest, stomach, front of thigh and outside of shin

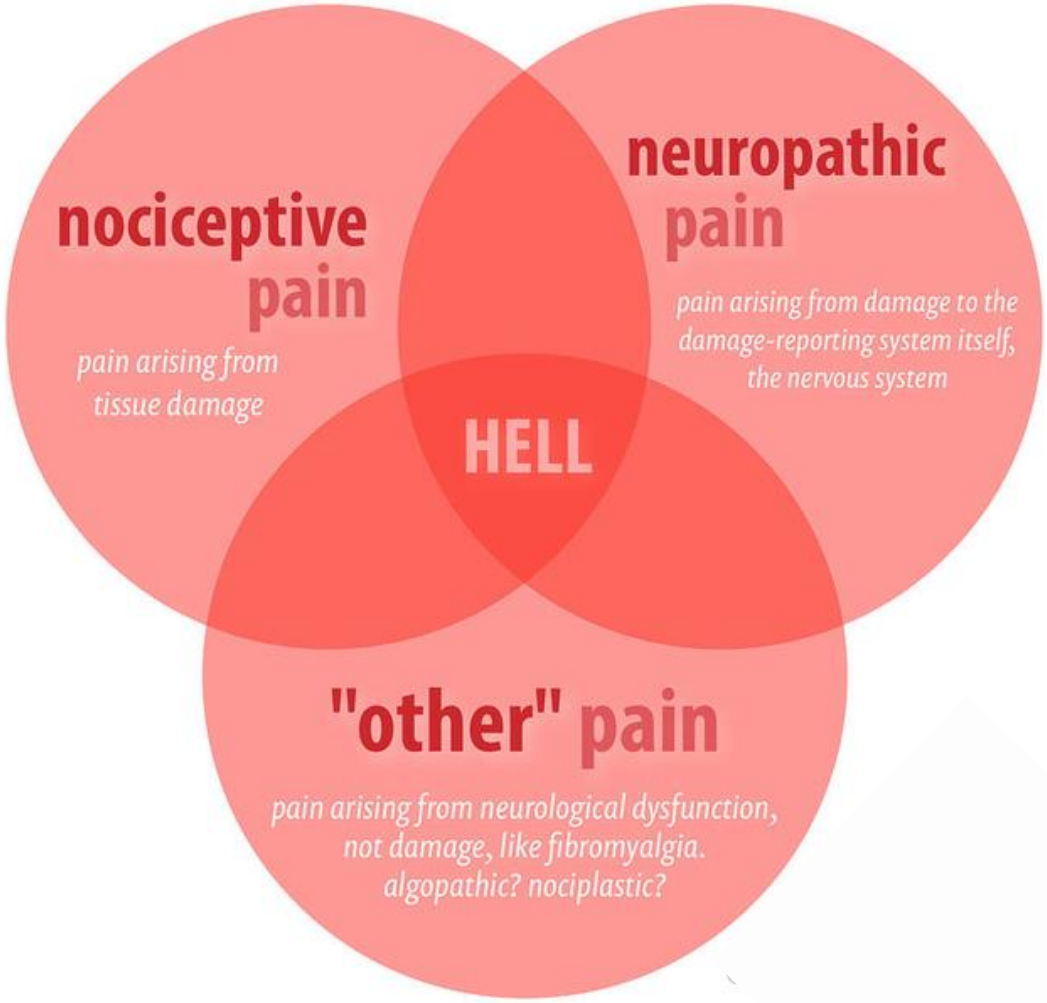
Neuroendocrinology 2013;98:267–280



Exp Ther Med. 2019;17(3):1963–1976

POSSIBLE MECHANISMS

- Hyperglycemia serves a crucial role in the development
- Increase in advanced glycation end-products production and a decrease in the regeneration of glutathione leads to accumulation of toxic compounds
- Impairment of intracellular glucose lead to oxidative stress the results in nerve injury



TYPES OF PAIN

- Pain as a homogeneous entity is an over simplification
- Several different types, each with distinct pathophysiological mechanisms
- This distinction is important because it not only reflects the cause of pain but also informs pharmacotherapy treatment.

BMJ. 2014;348:f7656.

MEDICATIONS AND GUIDELINES

BEST PRACTICE GUIDELINES

- Multidisciplinary care in chronic neuropathic pain has been shown to statistically significantly decrease pain and improve function, mood, catastrophizing, and pain acceptance

- Disease-specific treatment of neuropathy depends upon the underlying process.
  - Psychology, physiotherapy, exercise, and massage therapies can be used to assist the patient in chronic pain management

- Neither glycemic control or lifestyle management provide effective relief from NP and that pharmacotherapy is necessary to control symptoms

Clinical pharmacist 2017;9:12

Recommended Pharmacologic Agents for General Peripheral Neuropathic Pain from Major Guidelines

Therapy	National Institute for Health and Care Excellence (NICE)	Canadian Pain Society (CPS)	Neuropathic Pain Special Interest Group (NeuPSIG)	American Diabetes Association
	UK	Canada	International	United States
First-line pharmacotherapy	Amitriptyline Duloxetine Gabapentin (C-V) Pregabalin	Gabapentin (C-V) Pregabalin TCAs SNRIs	Gabapentin Gabapentin XR Pregabalin (C-V) SRNIs TCAs	Pregabalin (C-V) Duloxetine
Second-line pharmacotherapy	Capsaicin cream Short-term tramadol (C-IV) for acute rescue	Tramadol (C-IV) Controlled-release opioids	Tramadol (C-IV) Capsaicin 8% patch Lidocaine patch	Gabapentin TCAs
Third-line pharmacotherapy	Refer to specialist or use combination therapy	Cannabinoids		Refer to specialist or use combination therapy
Fourth-line pharmacotherapy		Topical lidocaine		

Doses and adverse effects of select medications used for the treatment of neuropathic pain (NP) in adults

Medication	Initial Dosing	Effective dosing	Common adverse effect(s)	Contraindications + precautions
Calcium channel α2-delta ligands				
Pregabalin	150mg/day, given in either two or three divided doses Dose may be increased to 300mg/day after an interval of three to seven days	300–600mg/day	Somnolence, peripheral oedema, weight gain	Caution in the elderly patients with cardiovascular disease. Caution with activities requiring mental alertness and at risk for falls due to CNS depression
Gabapentin	Day 1 — 300mg once daily Day 2 — 300mg twice daily Day 3 — 300mg three times daily	900–3,600mg/day	Sedation, peripheral oedema, weight gain	CNS depression (caution with activities requiring mental alertness and elderly at risk for falls)
Antidepressants – TCA				
Amitriptyline	10–25mg/day Dose can be increased 10–25mg every three to seven days as tolerated	25–150mg/day	Somnolence, xerostomia, urinary retention, constipation, blurred vision, mydriasis, fatigue, weight gain	Contraindicated in patients with recent myocardial infarction or cardiac rhythm disorders or severe liver disease Caution in patients with conditions that would be exacerbated by anticholinergic effects Do not use concurrently or within 14 days of discontinuation of an MAOI
Nortriptyline	25mg/day then gradually adjust levels to therapeutic benefit	75–100mg/day No evidence for does >150mg/day		
Imipramine	50mg at bedtime, then increase every three to seven days	100-200mg/day No evidence for doses >200mg/day		

Lancet Neurol. 2015;14(2):162-173
Pain Res Manag. 2014;19(6):328–335.

Doses and adverse effects of select medications used for the treatment of neuropathic pain (NP) in adults

Medication	Initial Dosing	Effective dosing	Common adverse effect(s)	Contraindications + precautions
Antidepressant – SNRI				
Duloxetine	30mg/day or 60mg/day	60–120mg/day in divided doses	Nausea, drowsiness, dizziness, constipation, dyspepsia, diarrhea, xerostomia, anorexia	Liver disease that results in hepatic impairment, renal impairment of CrCL <30mL/min, uncontrolled hypertension
Venlafaxine	37.5mg or 75mg each day.	75–225mg/day		
Topical/local treatment				
Lidocaine 5%	One to three patches for up to 12 hours applied to the painful area in a 24-hour period	One to three patches for up to 12 hours applied to the painful area in a 24-hour period	Local erythema, rash, itch at application site	Use only on intact skin, Caution in patients with cardiac, renal and/or hepatic impairment
Capsaicin 8%	Apply to the painful area 3-4 times daily	Apply to the painful area 3-4 times daily	Pain, erythema, dryness at application site	Use only on intact skin
Botulinum toxin type A	Individualise dosage according to response. May repeat every three months		Pain at injection site	Contraindicated if hypersensitivity or presence of infection at site
Opioids				
Tramadol	50mg/daily; increase weekly by 50mg/day	50–100mg four times daily or 100–400mg daily (controlled release)	Drowsiness, nausea, vomiting, constipation, light-headedness, dizziness, headache	

Lancet Neurol. 2015;14(2):162-173
Pain Res Manag. 2014;19(6):328–335.

CLINICAL TRIALS

CLINICAL TRIALS

Duloxetine + Pregabalin vs high dose monotherapy

- Outcomes:
  - Primary: Change in 24 hours average pain
  - Secondary: Response rate and severity item change
- Results:
  - Primary: No significant differences between combination and high-dose monotherapy (P= 0.370)
  - Secondary:
    - Response rates: 52.1% combination vs 39.3% monotherapy (P = 0.068)
    - Severity item change: No difference except in anxiety score (P = 0.049)

Imipramine + Pregabalin vs Monotherapy

- Outcomes:
  - Primary: Total pain intensity
  - Secondary: Pain relief and sleep disturbance
- Results:
  - Primary: Combination therapy lowered total pain intensity (P <0.001) compared to monotherapy
  - Secondary:
    - Combination therapy provided more pain relief (P=0.009)
    - Combination therapy had less sleep disturbances than monotherapy (P=0.011)

Pain. 2013;154(12):2616-25.
Pain. 2015;156(5):958-66.

CLINICAL TRIALS (CONT'D)

Duloxetine + Pregabalin vs high dose monotherapy

- Observed ADE frequencies and response rates were higher during initial therapy than during combination/high-dose therapy regardless of initial therapy
- Adverse Events leading to discontinuation: no statistical differences between groups
  - Dizziness
  - Nausea
  - Somnolence
  - Headache

Imipramine + Pregabalin vs Monotherapy

- Drop-outs were more common during combination therapy and almost only because of side effects
- Similar ADEs occurred during the monotherapies and highest ADEs was seen during the combination therapy
  - Dry mouth
  - Dizziness
  - Sweating
  - Nausea

Pain. 2013;154(12):2616-25.
Pain. 2015;156(5):958-66.

PEARLS AND SUMMARY

- Neuropathic pain is highly debilitating, difficult to diagnose, and only partially responsive to nearly all treatment.
- Neuropathic pain and its physical, psychological, and social consequences for the patient are variable throughout the course of the condition.
- No one drug is effective for all patients, pain relief is usually partial and is limited due to side effects tolerability
  - 45% of those with neuropathic pain utilize two or more medications for their pain.
- Combination therapy can be effective, but is often times limited due to ADEs

J Med Econ. 2006;9(1–4):55–68.
Exp Ther Med. 2019;17(3):1963-1976.

QUESTION #1

- Neuropathic pain is experienced in both type 1 and type 2 diabetics and is associated with a higher economic burden. Patients with type 2 diabetics experience neuropathic pain before type 1 diabetics do.

  - True
  - False

QUESTION #2

- FM is a 48yo female type 2 diabetic with HTN, HLD the reports to your pharmacotherapy clinic for neuropathic management. According to the American Diabetes association, what is an appropriate first line treatment to be prescribed today for the neuropathic pain?

A. Amitriptyline
B. Gabapentin
C. Duloxetine
D. Pregabalin

QUESTION #3

- When compared directly to monotherapy, which following combination is more effective in decreasing total pain intensity according to ?

A. Duloxetine + imipramine
B. Pregabalin + gabapentin
C. Duloxetine + tramadol
D. Pregabalin + imipramine

THANK YOU FOR LISTENING

Emergent Reversal of Factor Xa Inhibitors

Lane B. Farrell, PharmD, BCCCP
Austin-Round Rock Regional Clinical Coordinator
Lane.Farrell@BSWHealth.org

Baylor Scott & White HEALTH

Disclosures

- No conflicts of interest relative to this presentation
- The views expressed in this presentation are those of the presenter and do not represent those of Baylor Scott & White
- Off-label Use
  - 4 Factor Prothrombin Complex Concentrate (4FPCC- KCentra®)
  - Activated Prothrombin Complex Concentrate(aPCC- FEIBA®)

Objective

Following this section, the audience member will be able to:

- Compare and contrast reversal agents for factor Xa (FXa) inhibitors

Indication for Reversal

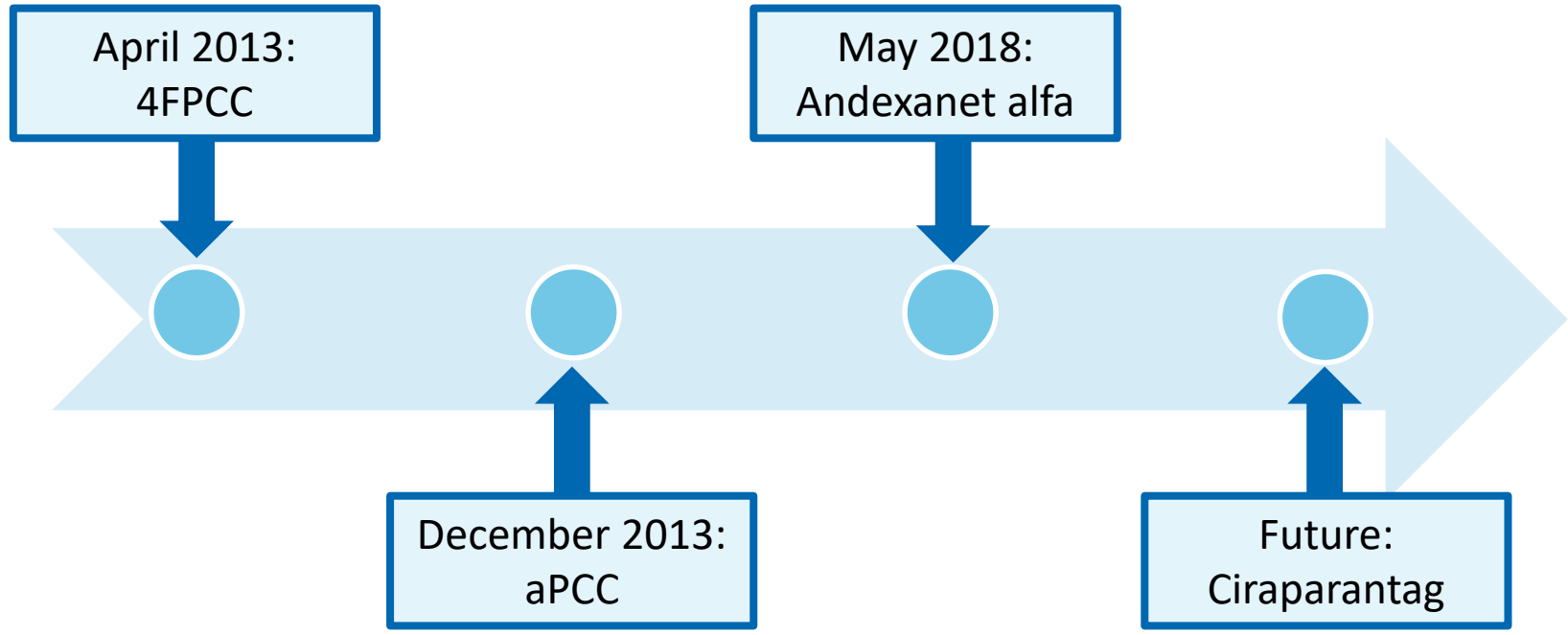
"We suggest administration of a reversal agent only if bleeding is life-threatening, into a critical organ, or is not controlled with maximal supportive measures and there is demonstration or reasonable expectation that the patient has clinically relevant plasma DOAC levels"

– Anticoagulation Forum, 2019

Assessing Need for Reversal

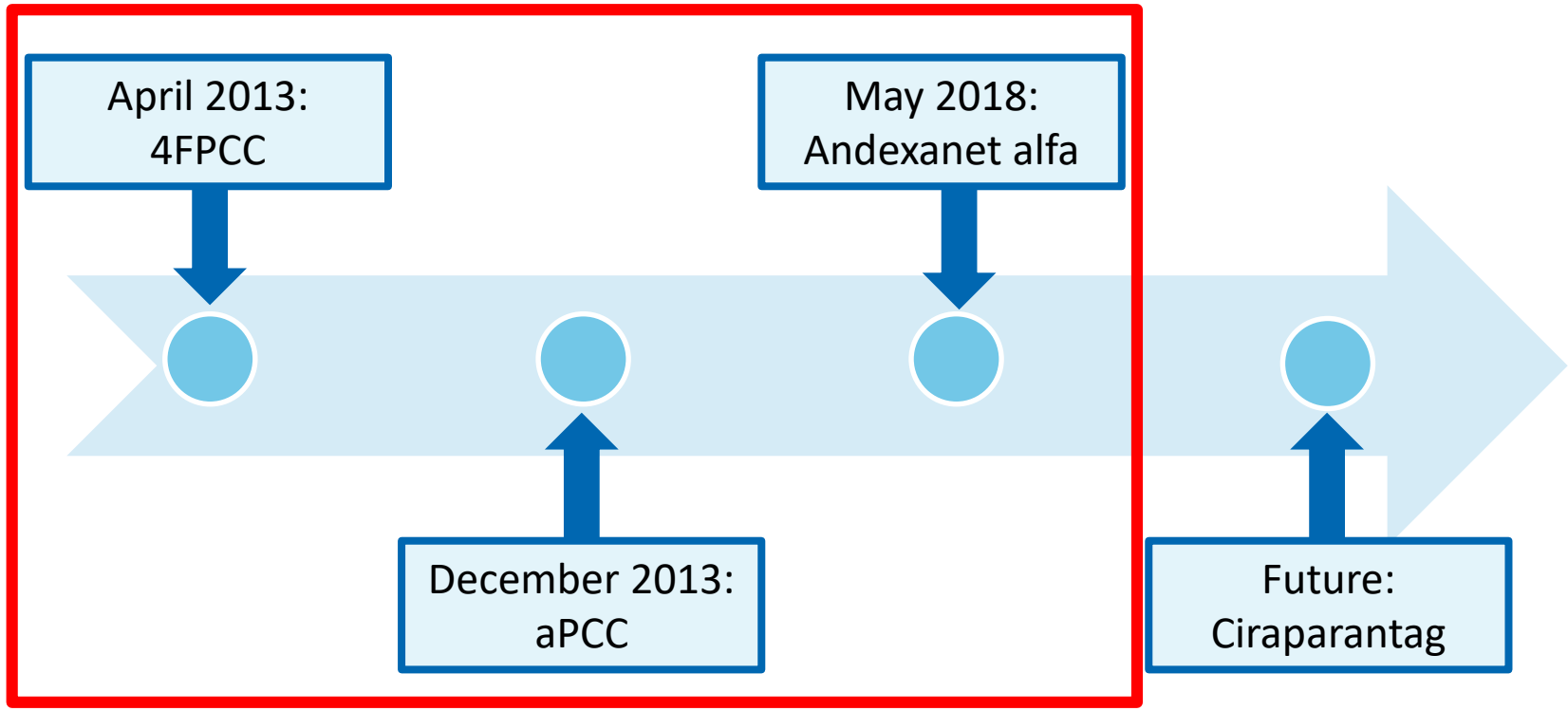
Factor	Considerations
Degree of Urgency	**Degree of Bleed** • Major vs. Minor • Acute vs. Subacute **Time frame for action** • Emergency surgery vs. routine procedure
Timing of Last Administration	**Estimate level of FXa inhibitor activity in absence of assay** • Half-life: ranges from 8 – 14 hours (longer in renal dysfunction). Considered cleared in 4-5 half-lives
Weigh Risk/Benefit of Reversal	**Indication for anticoagulation** • Example: remote venous thromboembolism vs. presence of mechanical valve

Timeline for Reversal Agents



4FPCC: Four factor prothrombin complex concentrate
aPCC: Activated prothrombin complex concentrate

Timeline for Reversal Agents



4FPCC: Four factor prothrombin complex concentrate
aPCC: Activated prothrombin complex concentrate

Reversal Agents- PCCs

Product	4FPCC (KCentra®)	aPCC (FEIBA®)
Mechanism	• Contains factors II, VII, IX, X as well as anti-thrombotic protein C&S	• Contains factors II, VIIa, IX, and X
Dosing	Variable • 25 – 50 units/kg (max 5000u) • 2000 units fixed dose	Variable • 20 – 50 units/kg (max 4000 u) • 2000 units fixed dose
Kinetics	Onset • Rapid, within 10 minutes Duration • ~6 to 8 hours	Onset • 15 to 30 minutes • Duration 8 to 12 hours
Pricing	~$2.90/ unit ($5800 - $14,500)	~$2.70/unit ($5400 - $10,800)
Comparison	• Higher quality of evidence (prospective and retrospective data) • Low thrombosis risk (%3.6)	• Evidence largely retrospective pooled case reports • Higher thrombotic risk

Reversal Agents- Andexanet

- **Brand name**: Andexxa®
- **Mechanism:**
  - Acts as decoy to bind and sequester the FXa inhibitors. Inhibits activity of tissue factor pathway inhibitor increasing thrombin generation
- **Dosing**
  - High dose/low dose administered as bolus followed by 2 hour infusion
- **Pricing**
  - $3300 per 100mg vial ($29,700 - $59, 400)
  - CMS NTAP reimbursement

Baylor Scott & White HEALTH

CMS: Centers for Medicare and Medicaid services
NTAP: New technology add-on payment

Andexanet alfa

- **Critical reviews**
  - **"I Have Issues with Andexanet"** –EMCrit, Kristina Kipp
  - **"I Have Andexanet Issues, 2: A formulary toolkit"** -EMPharmD, Zahra Nasrazadani
  - **"Andexanet alfa: More garbage science in the New England Journal of Medicine"** -First10EM blog, Justin Morgenstern

- **Criticisms**
  - Pricing
  - Surrogate outcomes leading to unconfirmed safety and efficacy
  - Lack of scientific method

Guidance

"In patients with rivaroxaban or apixaban-associated major bleeding...we suggest treatment with andexanet alfa. If andexanet alfa is not available, we suggest treatment with 4FPCC 2000 units"

-Anticoagulation Forum, 2019

Factor		4FPCC (UPRATE Trial)	Andexanet alfa (ANNEXA-4)
Outcomes	Hemostasis	**69%** (clinical outcomes)	**82%** (anti-FXa activity*)
	Thrombosis	**3.6%** (30 days)	**10%** (30 days)
	Mortality	**32%** (30 days)	**14%** (30 days)
Pricing/Cost		$5800 - $14,000	$29,700 - $59,400[†]
Duration of Action		6 – 8 hours	~1 hour after infusion

Baylor Scott & White HEALTH

*No correlation between anti-FXa activity and hemostasis

[†]NTAP reimbursement

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Assessment

A 52 yo male presents to the emergency department with a new intracranial hemorrhage while on apixaban (taken 6 hours prior). Which of the following is **NOT** a treatment option?

a) 4FPCC 2000 units x1 stat
b) Andexanet alfa (High dose)
c) 4FPCC 25 units/kg x1
d) Idarucizumab

Assessment

A 52 yo male presents to the emergency department with a new intracranial hemorrhage while on apixaban (taken 6 hours prior). Which of the following is **NOT** a treatment option?

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c) 4FPCC 25 units/kg x1
d) Idarucizumab

Emergent Reversal of Factor Xa Inhibitors

Lane B. Farrell, PharmD, BCCCP
Austin-Round Rock Regional Clinical Coordinator
Lane.Farrell@BSWHealth.org

Baylor Scott & White HEALTH

Basic Biosimilars

Pooja Patel, PharmD

Clinical Oncology Pharmacist – Baylor Scott & White

October 26th, 2019

Pharmacist Objectives

- Compare and contrast definitions of biosimilars and generic products
- Investigate growth of biosimilar approvals and recognize the role of biosimilars in the specialty market
- Assess potential issues and barriers associated with biosimilars

Technician Objectives

- Differentiate between biosimilar products and generic drugs
- Recognize three biosimilar products that have been approved and are available in market

FDA News Release

FDA approves first biosimilar for the treatment cancer

Mvasi, a biosimilar to the cancer drug Avastin, is approved for certain colorectal, lung, brain, kid and cervical cancers

FDA News Release

FDA approves Inflectra, a biosimilar to Remicade

SHARE TWEET LINKEDIN PIN IT EMAIL PRINT

FDA News Release

FDA approves first epoetin alfa biosimilar for the treatment of anemia

SHARE TWEET LINKEDIN PIN IT EMAIL PRINT

iate April 5, 2016

For Immediate Release May 15, 2018

Sandoz launches Zarxio™ (filgrastim-sndz), the first biosimilar in the United States

- *Launch follows March 6, 2015 FDA approval*

Consensus-based recommendations for the use of biosimilars to treat rheumatological diseases

Jonathan Kay[1], Monika M Schoels[2], Thomas Dörner[3], Paul Emery[4], Tore K Kvien[5], Josef S Smolen[2, 6], Ferdinand C Breedveld[7] on behalf of the Task Force on the Use of Biosimilars to Treat Rheumatological Diseases

t of Cancer: A Systematic Review

Ira Jacobs' · Reginald Ewesuedo[c] · Sadiq Lula[3] · Charles Zacharchuk[2]

Table Of Contents

WHAT IS A BIOSIMILAR?

Biologics

Purpose	Description	Growth
Medical products used to diagnose, prevent, treat, and cure diseases and medical conditions	Generally large, complex molecules produced through biotechnology in a living system Monoclonal antibodies & vaccines	Biological products are the fastest-growing class of therapeutic products in the US

U.S. FDA. Biosimilar and Interchangeable Products. 2017

Biosimilars

- A biologic product
- Highly similar to a reference product
- No clinically meaningful differences from a reference product
- Approved by FDA after rigorous evaluation and testing

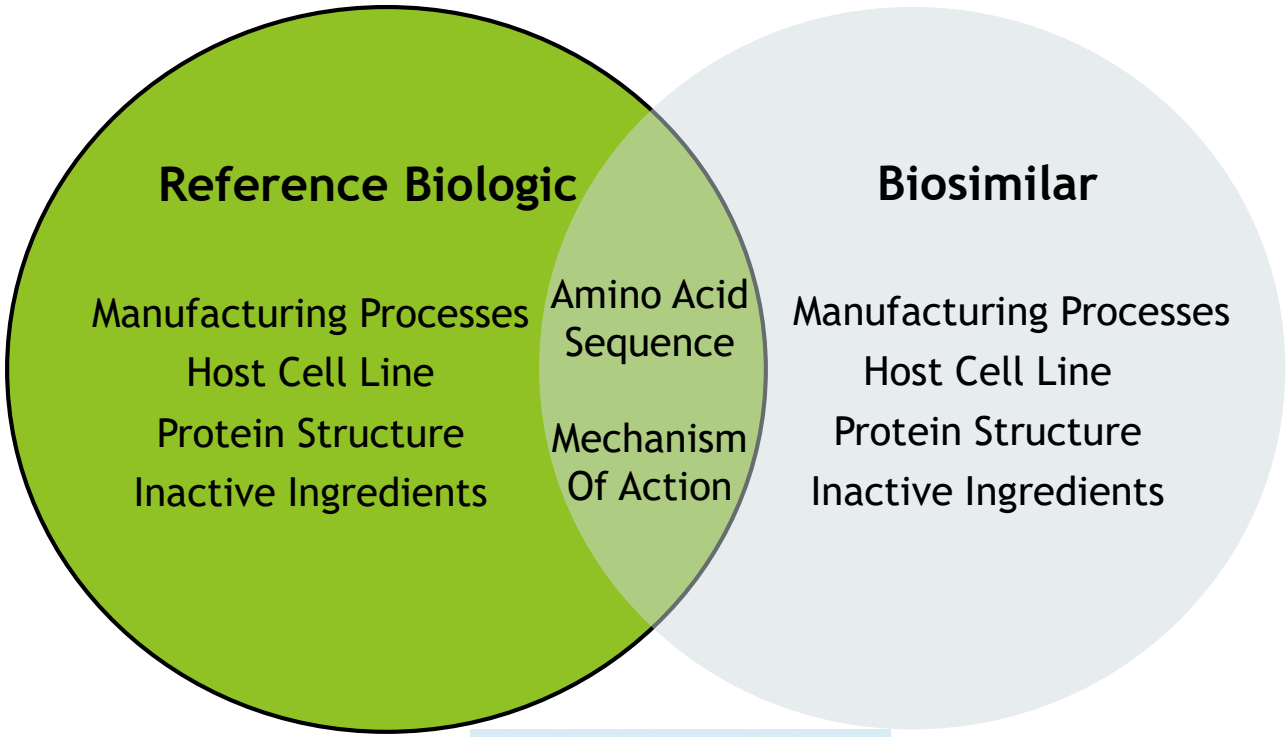
U.S. FDA. Biosimilar and Interchangeable Products. 2017

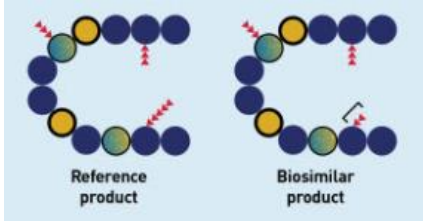
“Highly Similar”

Extensive analysis	Structure and function of both reference product and biosimilar
Comparison	Purity, chemical identity, bioactivity
Anticipation	Slight differences are expected during manufacturing process of biological products
Accepted	Minor differences in clinically inactive components are acceptable Minor differences in stabilizer or buffer

U.S. FDA. Biosimilar and Interchangeable Products. 2017

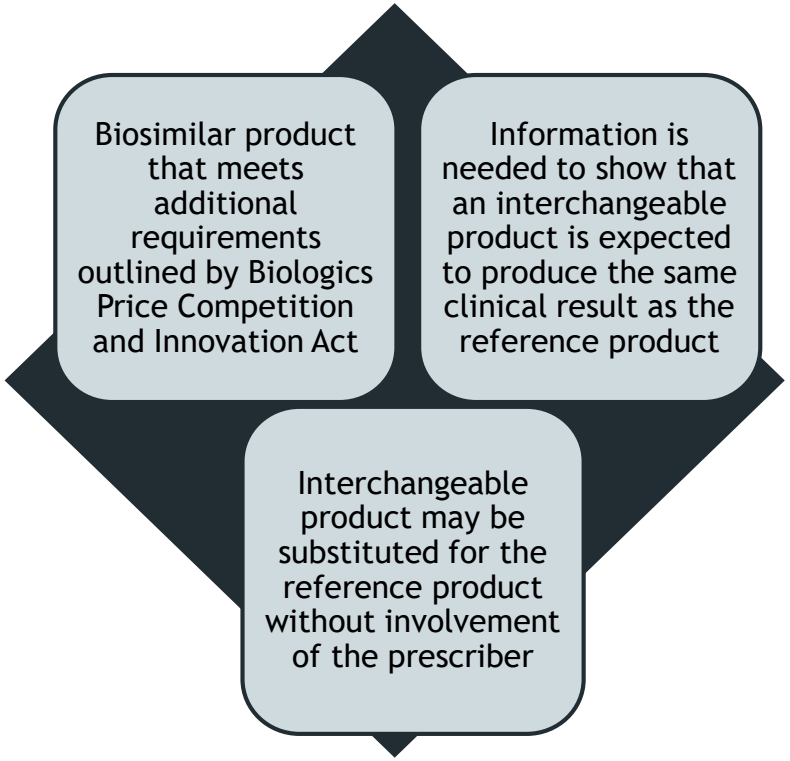
Features





Li E et al. J Manag Care Spec Pharm. 2015

Interchangeable Products



U.S. FDA. Biosimilar and Interchangeable Products. 2017

Just Fancy Generics?

Versions of brand name drugs

- Offer more affordable treatment options
- Approved via different abbreviated pathways that avoid duplicating costly clinical trials

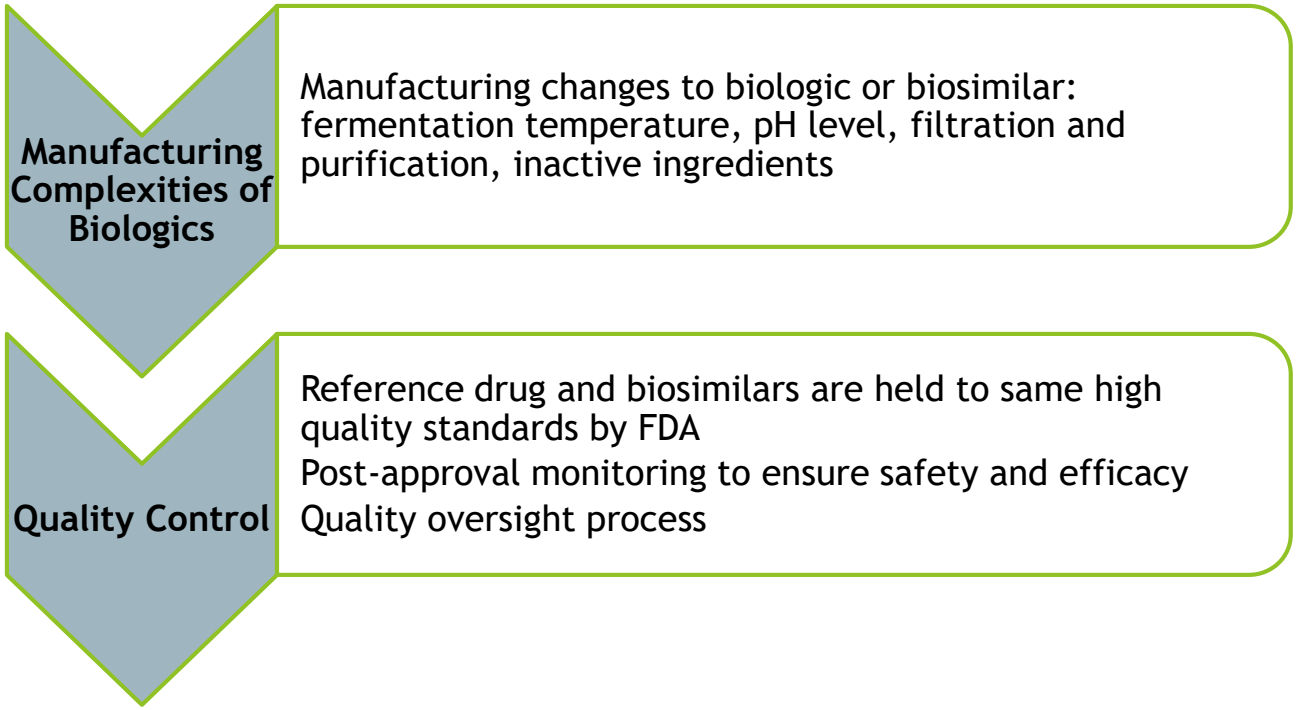
Biosimilars are NOT the same as generics

- Active ingredients of generic drugs are the same as those of brand name drugs
- Manufacturer of generic drug must demonstrate bioequivalence to brand name drug
- Biosimilar manufacturers must demonstrate that biosimilar is highly similar to reference products

U.S. FDA. Biosimilar and Interchangeable Products. 2017

Manufacturing Process

Complex Manufacturing



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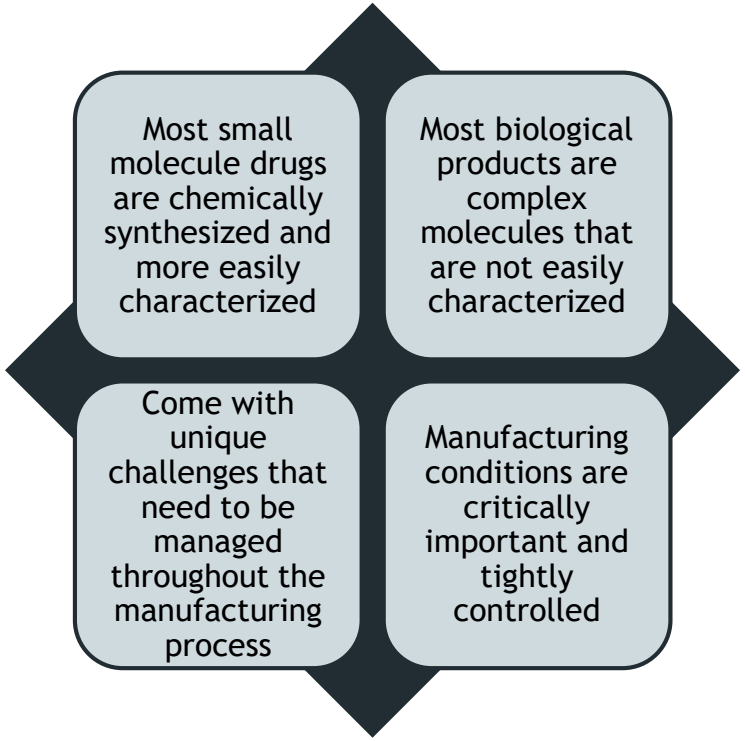
Unique Challenges



U.S. FDA. Biosimilar and Interchangeable Products. 2017

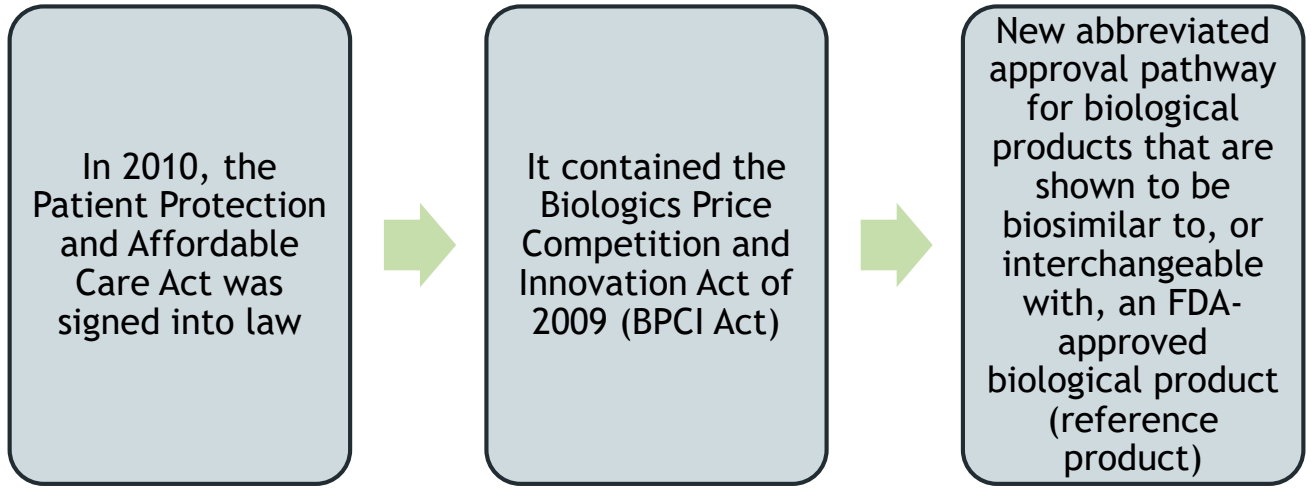
Biologics and Biosimilars Manufacturing

Production	Sensitive to changes in manufacturing conditions Consistency is founded on rigorous design and control
Minor changes	Small changes in any component could lead to product drift, evolution, and divergence Impacts the quality, safety, efficacy and/or interchangeability of biologics

Ramanan S et al. Bio Drugs. 2014

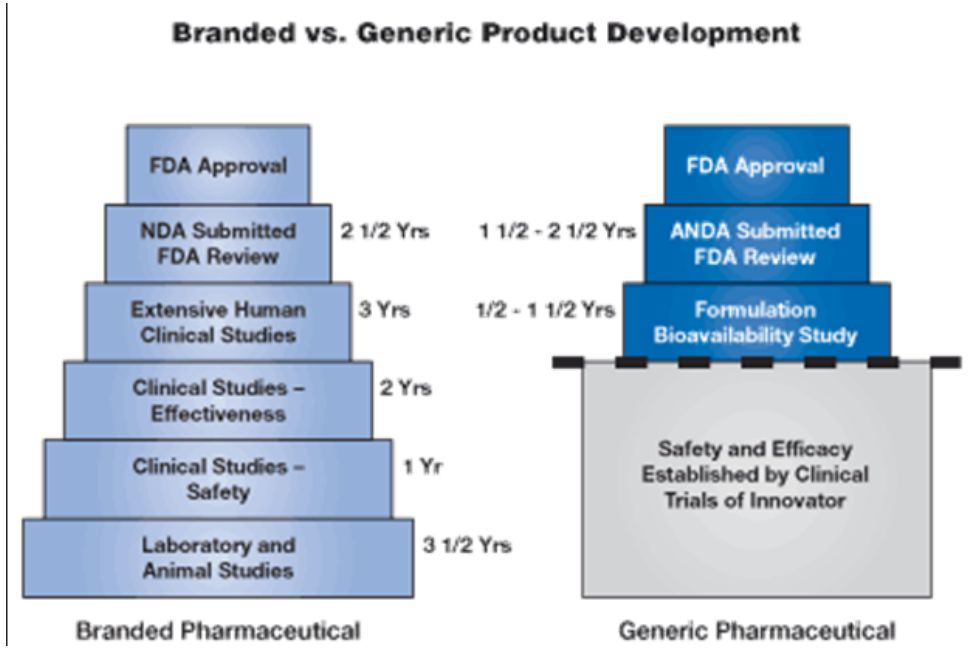
Approval Process

A New Pathway



U.S. FDA. Biosimilar and Interchangeable Products. 2017

Regulatory Requirements



Christi L et al. Overview of Regulatory Pathway and FDA's Guidance for the Development and Approval of Biosimilar Products in the US. 2016

Nonproper Names

FDA's guidance for the industry on nonproprietary naming of biological products

January 2017 (updated in March 2019)

- Smooth the pathway to uptake for biosimilars
- Intended to be applied to interchangeable products
- Features a core name and a suffix included in the proper name
- FDA designates a distinguishing suffix devoid of meaning, and comprised of 4 lowercase letters in the nonproprietary names of reference biological products

U.S. FDA. Nonproprietary Naming of Biological Products: Update. 2019

Assessment Question

Which of the following is **FALSE** regarding biosimilars and generic drugs?

A. There is a designated distinguishing suffix comprised of 4 lowercase letters in the nonproprietary names of biosimilars

B. Compared with chemically synthesized small-molecule drugs (i.e. generics), biologics are more sensitive to changes in manufacturing conditions

C. Active ingredients of generic drugs and biosimilars are the same as those of brand name drugs and reference biologics, respectively

D. Both are approved via different abbreviated pathways that avoid duplicating costly clinical trials

Biosimilar Products

They Are Not That New

Experience	Biosimilars are a fairly new concept in the United States Other countries have had longer biosimilar experience
European Union	First biosimilar approval in 2006 Safety surveillance system has not recognized any differences in the rate, as well as the severity, of adverse events between biosimilars and their reference products
Price	Price reductions have ranged from 30% for anti-tumor necrosis factor drugs, 60% for granulocyte colony-stimulating factor drugs, and up to 66% for erythropoietin Lead to increased patient access to these biologics

Hung A et al. JMCP. 2017

The Market

Although the BPCI was signed in 2010, it was not until 2015 that the FDA granted its first biosimilar approval.

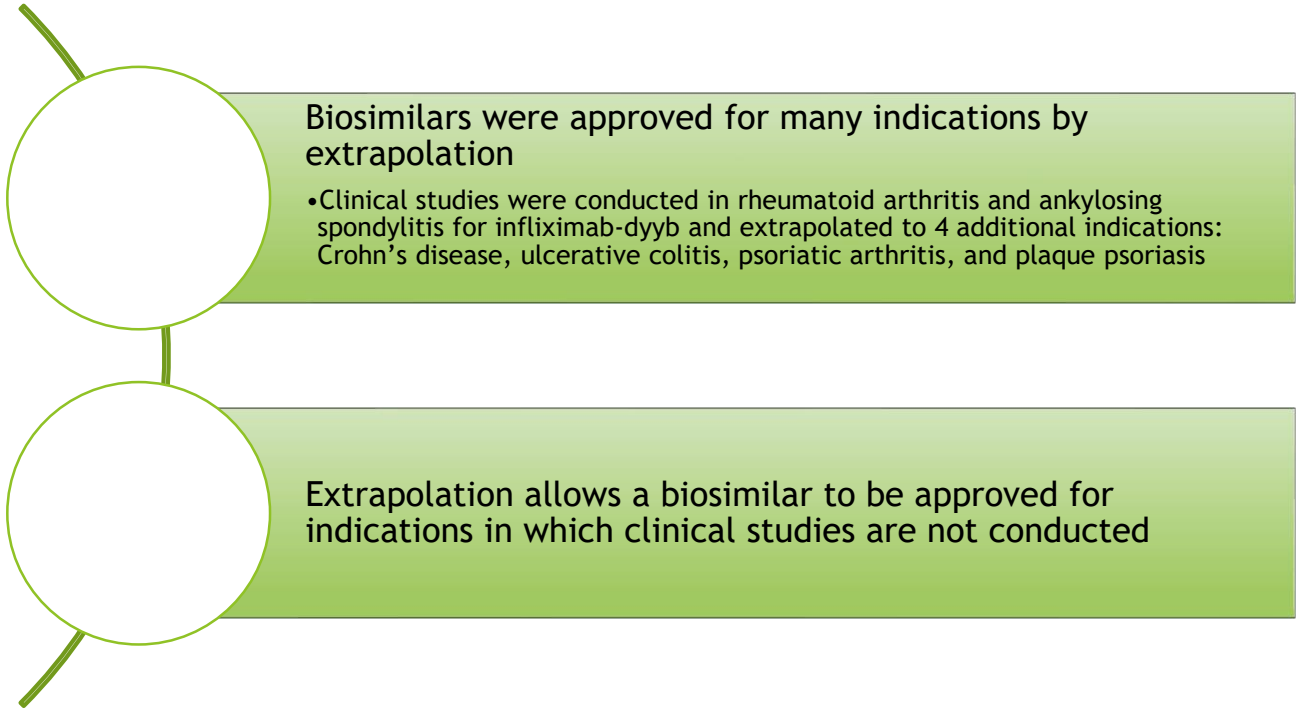
Biosimilar	Approval Date
***Zarxio (filgrastim-sndz)**	**March 2015**
***Inflectra (infliximab-dyyb)**	**April 2016**
Erelzi (etanercept-szzs)	August 2016
Amjevita (adalimumab-atto)	September 2016
***Renflexis (infliximab-abda)**	**May 2017**
Cyltezo (adalimumab-adbm)	August 2017
Mvasi (bevacizumab-awwb)	September 2017
Ogivri (trastuzumab-dkst)	December 2017
Ixifi (infliximab-qbtx)	December 2017
***Retacrit (epoetin alfa-epbx)**	**May 2018**
***Fulphila (pegfilgrastim-jmdb)**	**June 2018**

Biosimilar	Approval Date
***Nivestym (filgrastim-aafi)**	**July 2018**
Hyrimoz (adalimumab-adaz)	October 2018
***Udenyca (pegfilgrastim-cbqv)**	**November 2018**
Truxima (rituximab-abbs)	November 2018
Herzuma (trastuzumab-pkrb)	December 2018
Ontruzant (trastuzumab-dttb)	January 2019
Trazimera (trastuzumab-qyyp)	March 2019
Eticovo (enteracept-ykro)	April 2019
***Kanjinti (trastuzumab-anns)**	**June 2019**
Zirabev (bevacizumab-bvzr)	June 2019
Hadlima (adalimumab-bwwd)	July 2019
Ruxience (rituximab-pvvr)	July 2019

*Bolded biosimilars are currently available on the market

U.S. FDA. Biosimilar Product Information. 2019

Extrapolated Information



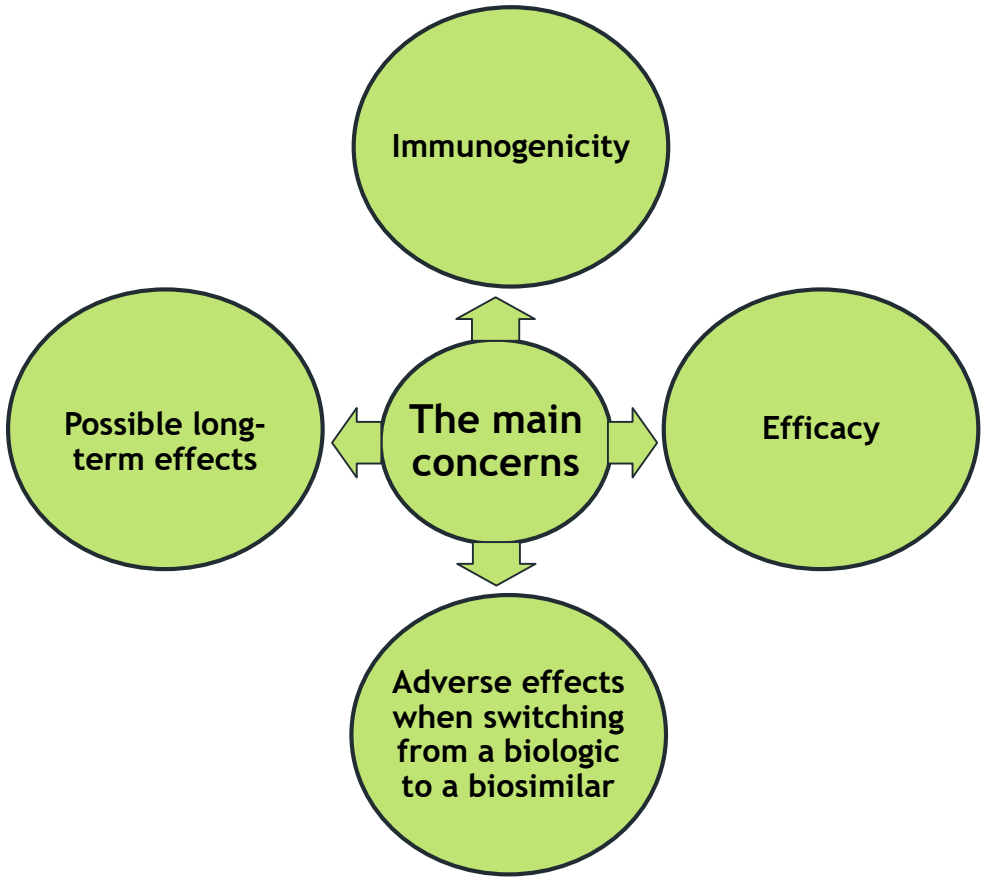
Hung A et al. JMCP. 2017

Assessment Question

Which of the following is **FALSE** with regards to use of biosimilars in patients?

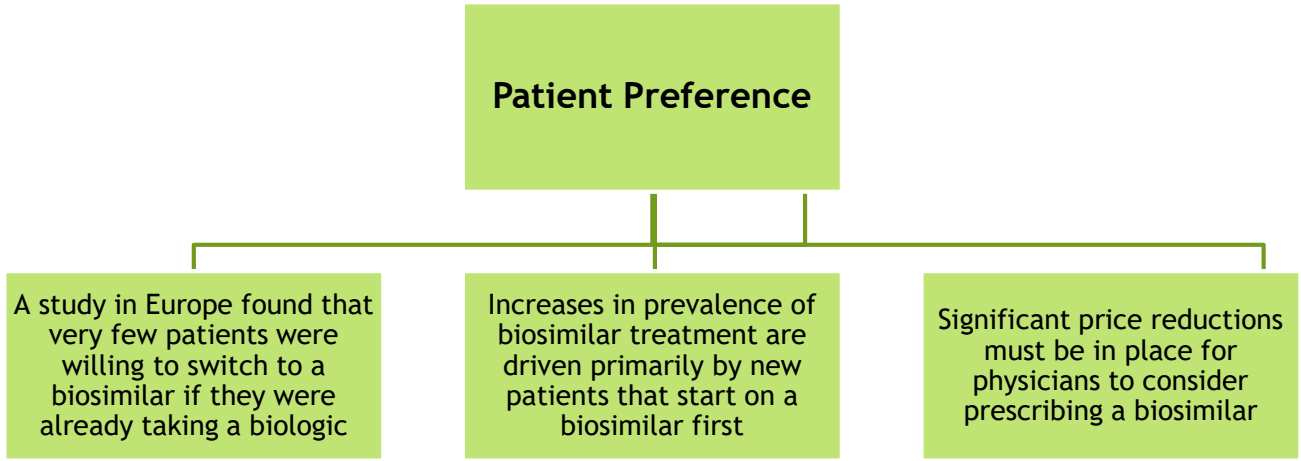
A. All biosimilars approved till date, are available on the market
B. Extrapolation allows for biosimilars to be approved for indications for which clinical studies are not conducted
C. The first FDA approved biosimilar was Zarzio which is used to boost ANC after chemotherapy

Barriers for use of biosimilars



Kaida-Yip F et al. World J Clin Cases. 2018

Are The Patients Ready To Switch?



Kaida-Yip F et al. World J Clin Cases. 2018

Assessment Question

Which of the factors listed below contribute to the biggest barrier for use of biosimilars?

A. Provider or patient uncertainty
B. Difficulty for manufacturers to prove equivalent efficacy
C. Logistics for switching between agents

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Basic Biosimilars

Pooja Patel, PharmD

Clinical Oncology Pharmacist – Baylor Scott & White

October 26th, 2019

St David's | South Austin Medical Center

What's New with MRSA and the Flu?

AASHP 2019 Annual Pharmacy Seminar

St David's HealthCare

Josiah P. Smith, PharmD., BCCCP
Critical Care Pharmacy Coordinator
St. David's South Austin Medical Center

Disclaimer

St David's | South Austin Medical Center

The views expressed in this presentation are those of the presenter and do not represent St. David's South Austin Medical Center

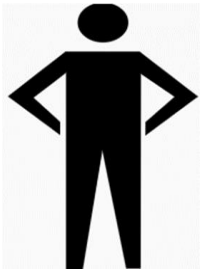
I do not have any relevant financial relationships to disclose

Baloxavir marboxil (Xofluza®)

- FDA-Approved on Oct 24th, 2018
- Indication
  - Uncomplicated influenza in patients ≥ 12 years of age who have been symptomatic for **no more** than 48 hours
- Mechanism of action
  - Interferes with viral RNA polymerase complex -> inhibiting virus replication

Dosing (weight-based)*

Weight: 40-79 kg	*Weight: ≥ 80 kg*
40 mg by mouth once	80 mg by mouth once



No Liver Adjustment

No Kidney Adjustment

*Only available in oral formulation

Baloxavir marboxil – CAPSTONE 1

- Time to symptom alleviation similar to oseltamivir (53.5 v 53.8 hrs)
- Quicker symptom alleviation if taken within 24 vs 48 hours of symptom onset (32.8 vs 46 hrs; p<0.001)
- Shorter median duration of infectious viral detection compared to oseltamivir (24 v 72 hrs; p<0.001)
- Adverse effects: diarrhea, bronchitis

Baloxavir marboxil – Points of Consideration

- Not studied in patients requiring admission to the hospital
- Transmission of influenza was not studied
- Patients under 40kg
- Oseltamivir – resistant strains
- Cost

Delafloxacin (Baxdela®)

- FDA-Approved on June 19th, 2017
- Indication
  - –Acute bacterial skin and skin structure infections
  - –Community-acquired bacterial pneumonia (sNDA pending)
- Mechanism of action
  - –Inhibits DNA gyrase and topoisomerase IV enzymes

Intravenous Dosing*

300 mg every 12 hrs

- eGFR 15-29+:
  - 200mg q q12hrs
- eGFR <15/HD+: ✖

Oral Dosing*

450 mg every 12 hrs

- eGFR 15-29+:
  - No adjustment
- eGFR <15/HD+: ✖

*No hepatic adjustments

sNDA = supplemental new drug application

+eGFR = estimated glomerular filtration rate (ml/min/1.73m^2)

Delafloxacin - PROCEED 1 and 2

- Response at 48-72 hours was non-inferior to vancomycin/aztreonam (78.2 vs 80.9%; 83.7 v 80.6%)
- Microbiological MRSA eradication was similar to vancomycin/aztreonam (100 vs 98.5%; 96 vs 97%)
- Follow-up and long term follow-up cure rates were similar among both groups
- Adverse Effects: Diarrhea, Nausea

MRSA = Methicillin-Resistant Staphylococcus Aureus)

Delafloxacin - Points of Consideration

St David's South Austin Medical Center

- Broad-spectrum: MRSA, *Pseudomonas aeruginosa*, anaerobes
- Similar fluoroquinolone side effect profile?
- Resistance
- Cost, formulation availability, and future FDA-approved indications

MRSA = Methicillin-Resistant Staphylococcus Aureus

Formulary Consideration

- Both baloxivir marboxil and delafloxacin should remain non-formulary and only orderable by an infectious disease physician.

Assessment Question

Which of the following statements is true regarding baloxivir marboxil?

A. It is superior to oseltamivir to time of alleviation of symptoms
B. It is dose adjusted for renal and liver impairment
C. It has not been studied in hospitalized patients
D. It inhibits DNA gyrase and topoisomerase IV enzymes

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St David's | South Austin Medical Center

What's New with MRSA and the Flu?

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AASHP Annual Seminar Clinical Pearls

REBEKKA ADAMSON, PHARMD, BCCP; RYAN HADLEY, PHARMD, BCACP

LANE FARRELL, PHARMD, BCCCP; POOJA PATEL, PHARMD;

JOSIAH SMITH, PHARMD, BCCCP