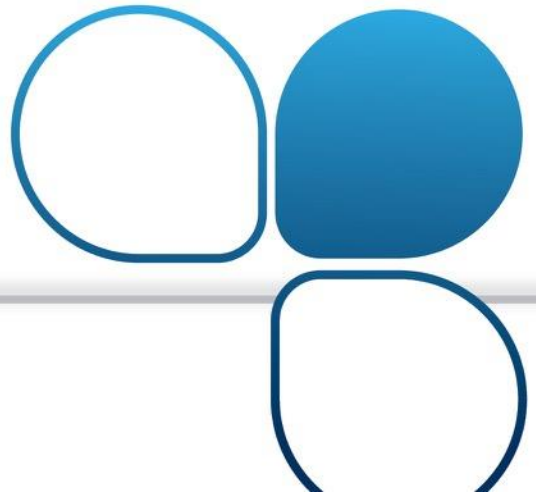
Incorporating the Use of Biosimilars into Clinical Practice: Opportunities for Pharmacists to Intervene



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Ali McBride, PharmD, MS, BCOP, FAzPA, FASHP, has the following relevant financial relationship with a commercial interest to disclose:

- Consultant: Pfizer
- Speaker's Bureau: Coherus

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Activity Type: Knowledge

Fee: Free

Law Credit

Educational Objectives

At the completion of this activity, participants will be able to:

- Review the approval process and required nomenclature for biosimilars as well as the differences between biosimilars and biologics
- Outline the safety, efficacy, and role of biosimilars in the treatment of inflammatory and oncology conditions compared with their corresponding biologic products
- Recognize the role of the pharmacist in augmenting the use of biosimilars via educating both prescribers and patients on the potential clinical and economic advantages of biosimilars

Select FDA-Approved Biosimilars

Reference product	Biosimilar	Approval date
Adalimumab	Adalimumab-adaz	October 2018
	Adalimumab-adbm	August 2017
	Adalimumab-afzb	November 2019
	Adalimumab-atto	September 2016
	Adalimumab-bwwd	July 2019
Bevacizumab	Bevacizumab-awwb*	September 2017
	Bevacizumab-bvzr	June 2019
Epoetin alfa	Epoetin alfa-epbx	May 2018
Etanercept	Etanercept-szzs	August 2016
	Etanercept-ykro	April 2019
Filgrastim	Filgrastim-sndz*	March 2015
	Filgrastim-aafi*	July 2018
Infliximab	Infliximab-abda	April 2017
	Infliximab-axxq	December 2019
	Infliximab-dyyb	April 2016
	Infliximab-qbtx	December 2017
Pegfilgrastim	Pegfilgrastim-jmdb*	June 2018
	Pegfilgrastim-cbqv*	November 2018
	Pegfilgrastim-bmez*	November 2019
Rituximab	Rituximab-abbs*	November 2018
	Rituximab-pvvr	July 2019
Trastuzumab	Trastuzumab-dkst*	December 2017
	Trastuzumab-pkrb	December 2018
	Trastuzumab-dttb	January 2019
	Trastuzumab-qyyp	March 2019
	Trastuzumab-anns*	June 2019

*Commercially marketed biosimilar.

Center for Drug Evaluation and Research. List of licensed biological products with (1) reference product exclusivity and (2) biosimilarity or interchangeability evaluations to date. US FDA. Published 2019. Accessed March 29, 2020. www.fda.gov/media/89589/download

Biologic Definitions

BIOLOGIC

- **A wide range of products such as vaccines, blood, and blood components and recombinant therapeutic proteins derived from living cells or organisms and intended to prevent, treat, or cure a disease.**

REFERENCE BIOLOGIC

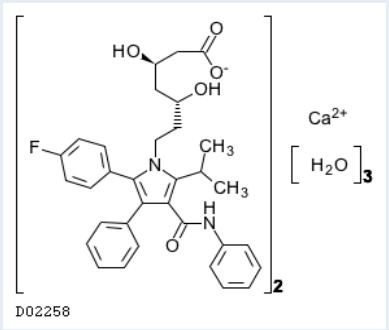
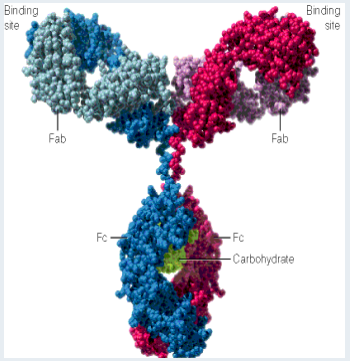
- **Originally licensed biologic product used for comparison.**

BIOSIMILAR

- **Biologic that is highly similar to the reference product with no clinically meaningful differences in terms of the safety, purity, and potency.**

Office of the Law Revision Counsel United States Code. 42 U.S.C. 262: Regulation of Biological Products. Accessed March 27, 2020. uscode.house.gov/view.xhtml?req=(title:42%20section:262%20edition:prelim; Weise M, et al. *Blood*. 2012;120(26):5111-5117.

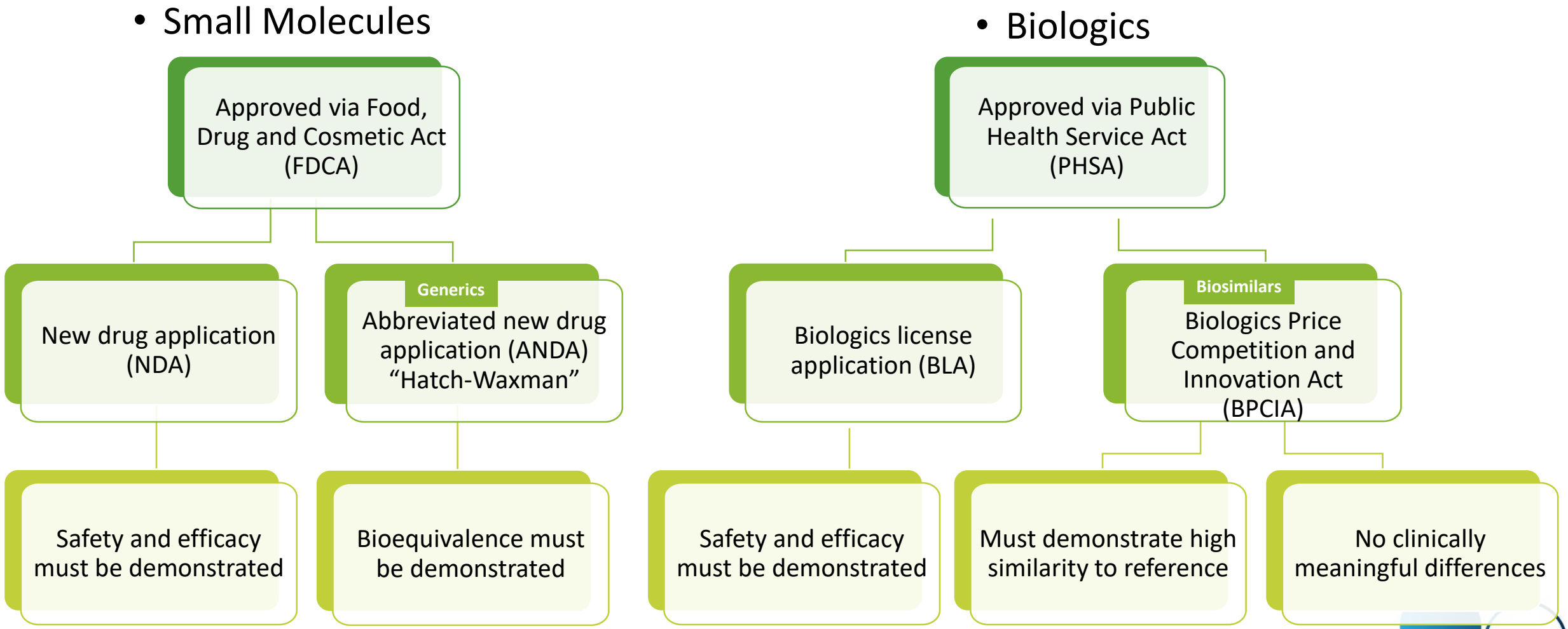
Small Molecules vs Biologics

	Small molecule drugs	Biologics
Size (MW)	Small (<1000 daltons)	Large (>10,000 daltons)
Source	Chemical synthesis	Cultures of living cells
Structure	Simple, well defined, independent of manufacturing process	Complex (heterogeneous), defined by the exact manufacturing process
Characterization	Easy to characterize	Cannot be characterized completely
Immunogenicity	Mostly nonimmunogenic	Immunogenic
Example	Atorvastatin  **Atorvastatin MW = 558.64**	Trastuzumab  **Trastuzumab MW = 185,000**

Declerck PJ. *GaBi J.* 2012;1(1):13-16.

MW, molecular weight.

FDA Approval Process Overview

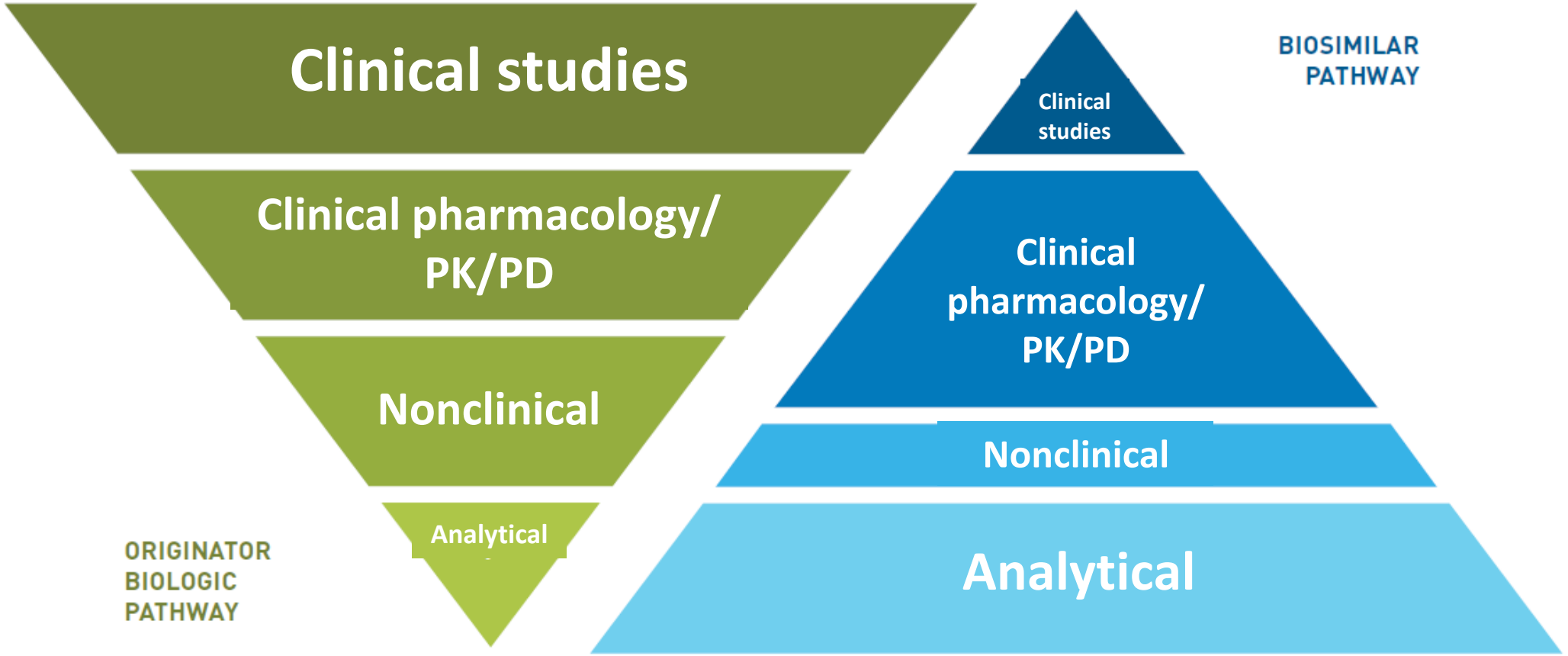


Biologics: A Regulatory Perspective

Characteristic	351(a) Originator	351(k) Biosimilar	351(k)(4) Interchangeable biosimilar	351(a) Nonoriginator biologic	351(a) Next-generation "biobetter"
Description	First-to-market biologic molecule; will likely be the reference product	"Highly similar" to reference product; approved via biosimilars pathway	A biosimilar that can be substituted for the reference without permission from prescriber	It is "another brand name" of an already approved biologic	Biologic that has been altered to achieve improved clinical outcomes
Depth of data submitted to the FDA	"Standard" data package: efficacy and safety	Abbreviated data package for comparability	More extensive data package for comparability supporting that the interchangeable biosimilar anticipated to produce same clinical effects for all the reference product's licensed conditions	"Standard" data package: efficacy and safety	"Standard" data package: efficacy and safety
Compared to originator?	N/A	Yes	Yes	Yes or no	Likely (standard of care)

Lucio SD, et al. *Am J Health Syst Pharm*. 2013;70(22):2004-2017; Considerations in demonstrating interchangeability with a reference product: guidance for industry. US FDA. Published May 2019. Accessed March 30, 2020. www.fda.gov/media/124907/download

Clinical Studies



Republished from Kirchhoff CF, Wang X-ZM, Conlon HD, Anderson S, Ryan AM, Bose A. Biosimilars: key regulatory considerations and similarity assessment tools. *Biotechnol Bioeng*. 2017;114(12):2696-2705. doi: 10.1002/bit.26438, under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium (https://creativecommons.org/licenses/by/4.0/).

Demonstrating Biosimilarity: General Principles

- Biosimilar must demonstrate no significant difference from its reference product
  - Robust analytical, toxicologic, pharmacokinetic/pharmacodynamic (PK/PD), and immunogenicity studies in comparison to reference product
  - Smaller comparative effectiveness clinical trial(s), which must be conducted in patients with a disease for which the reference product is licensed
  - No need to demonstrate efficacy in all indications
- No differences in safety or efficacy are expected between an approved biosimilar and its reference product
  - Same mechanism of action
  - Same route of administration
  - Same dosage form
  - Same strength

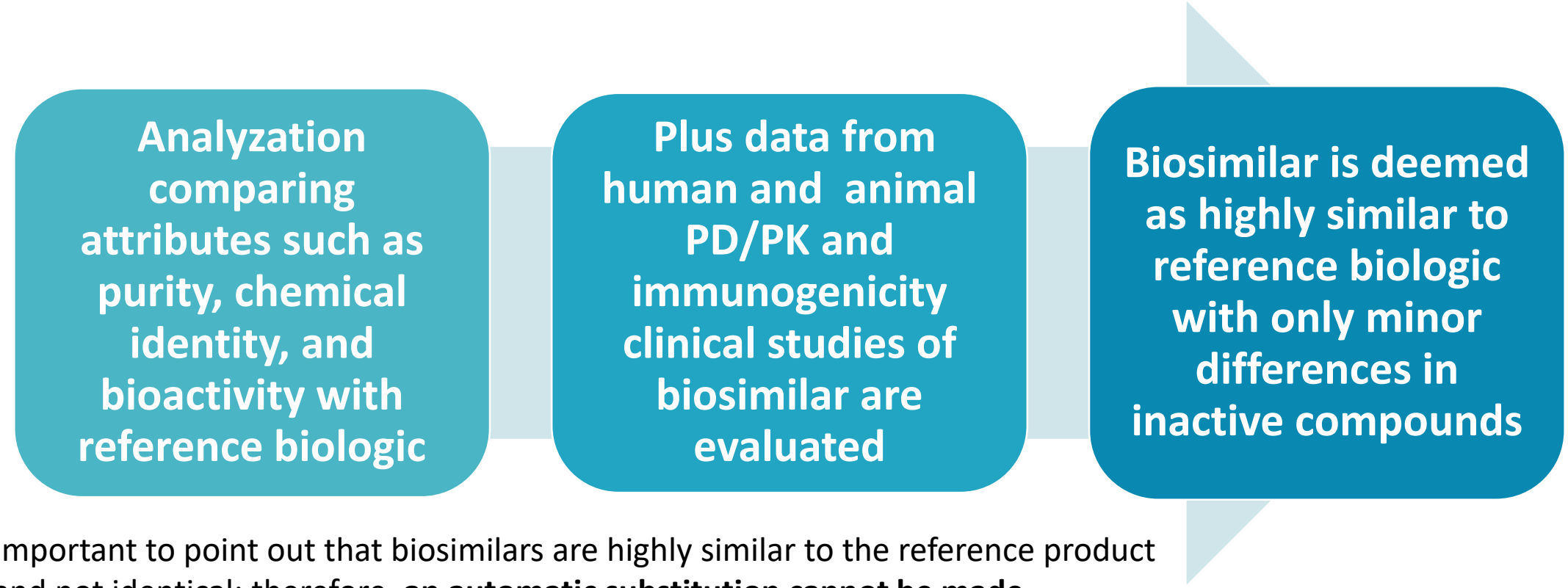
Scientific considerations in demonstrating biosimilarity to a reference product: guidance for industry. US FDA. Published April 2015. Accessed March 29, 2019. www.fda.gov/media/82647/download

Clinical Considerations in Demonstrating Biosimilarity

Patient population	• Most sensitive population to show clinically meaningful differences
Dose	• Based on dose-response curve • Chosen to sensitively detect any differences
End points	• Chosen to enable precise and meaningful comparison to the reference biologic
Design	• Noninferiority or equivalence margins • Parallel or crossover (depending on half-life)

Scientific considerations in demonstrating biosimilarity to a reference product: guidance for industry. US FDA. Published April 2015. Accessed March 29, 2020. www.fda.gov/media/82647/download

How Is a Biosimilar Different From the Reference Product and Why Is This Important?



Important to point out that biosimilars are highly similar to the reference product and not identical; therefore, **an automatic substitution cannot be made.**

Guidances (drugs). US FDA. Updated February 10, 2020. Accessed March 30, 2020. www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs; Kirchhoff CF, et al. *Biotechnol Bioeng*. 2017;114(12):2696-2705; Sandeep V, et al. *Int J Drug Regul Aff.* 2016;4(1):13-20.

The Purple Book

- Simple PDF; not a searchable database like the Orange Book
- Go-to list for biologic and biosimilar products approved by the FDA
- Information provided:
  - Date of approval
  - Approval pathway [351(a), 351(k)]
  - Interchangeability status (I)
  - Biosimilar status (B)
  - Exclusivity expiration date
- Updated “as resources permit”

Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations. US FDA. Updated March 25, 2020. Accessed March 27, 2020; www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/ucm411418.htm

Critical Concepts

Naming

Interchangeability

Extrapolation

Biosimilars and Biologics: FDA Naming Convention

Adalimumab-adbm
Adalimumab-atto
Bevacizumb-awwb
Etanercept-szzs
Filgrastim-sndz
Infliximab-abda
Infliximab-dyyb
Pegfilgrastim-cbqv

Core name

FDA-designated suffix must have: No recognizable meaning, 4 letters, and lowercase

Nonproprietary naming of biological products: guidance for industry. FDA.gov. March 2020.

Why Is Extrapolation Important?

- Bridges all the data collected from **1 indication** to **all indications originally approved** for the reference product

- Reduces/eliminates need for duplicative clinical studies in multiple indications
- Core to the concept of biosimilarity

Scientific considerations in demonstrating biosimilarity to a reference product: guidance for industry.
US FDA. Published April 2015. Accessed March 29, 2020. www.fda.gov/media/82647/download; European Medicines Agency (EMA), Committee for Medicinal Products For Human Use (CHMP). Guideline on similar biological medicinal products containing monoclonal antibodies—non-clinical and clinical issues. EMA; May 30, 2012. EMA/CHMP/BMWP/403543/201; www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128686.pdf; Zelenetz AD, et al. *J Natl Compr Canc Netw*. 2011;9(suppl 4):S1-S22.

FDA Extrapolation Considerations

- A biosimilar's indication may be extrapolated to additional indications of the reference biologic, beyond the indication in which it was studied
- Extrapolation must be justified regarding the following:
  - MOA(s) in each condition of use for which licensure is sought
    - Cannot extrapolate across indications in which reference product may have different MOAs (eg, rituximab in rheumatoid arthritis and lymphoma)
  - Product structure and target receptor interactions
  - Pharmacokinetics and biodistribution of the product in different patient populations
  - Immunogenicity of the product in different patient populations
  - Differences in expected toxicities in each condition of use and patient populations
  - Differences between conditions of use do not necessarily preclude extrapolation

MOA, mechanism of action.

Weise M, et al. *Blood*. 2014;124(22):3191-3196; Scientific considerations in demonstrating biosimilarity to a reference product: guidance for industry. US FDA. Published April 2015. Accessed March 29, 2020. www.fda.gov/media/82647/download

Introduction to Interchangeability

- Interchangeability definition
  - An interchangeable product may be substituted for the reference product without the involvement of the prescriber.
  - “Biosimilar to the US-licensed reference biological product and can be expected to produce the same clinical result as the reference product in any given patient”
  - “For a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product will not be greater than the risk of using the reference product without such alternation or switch”

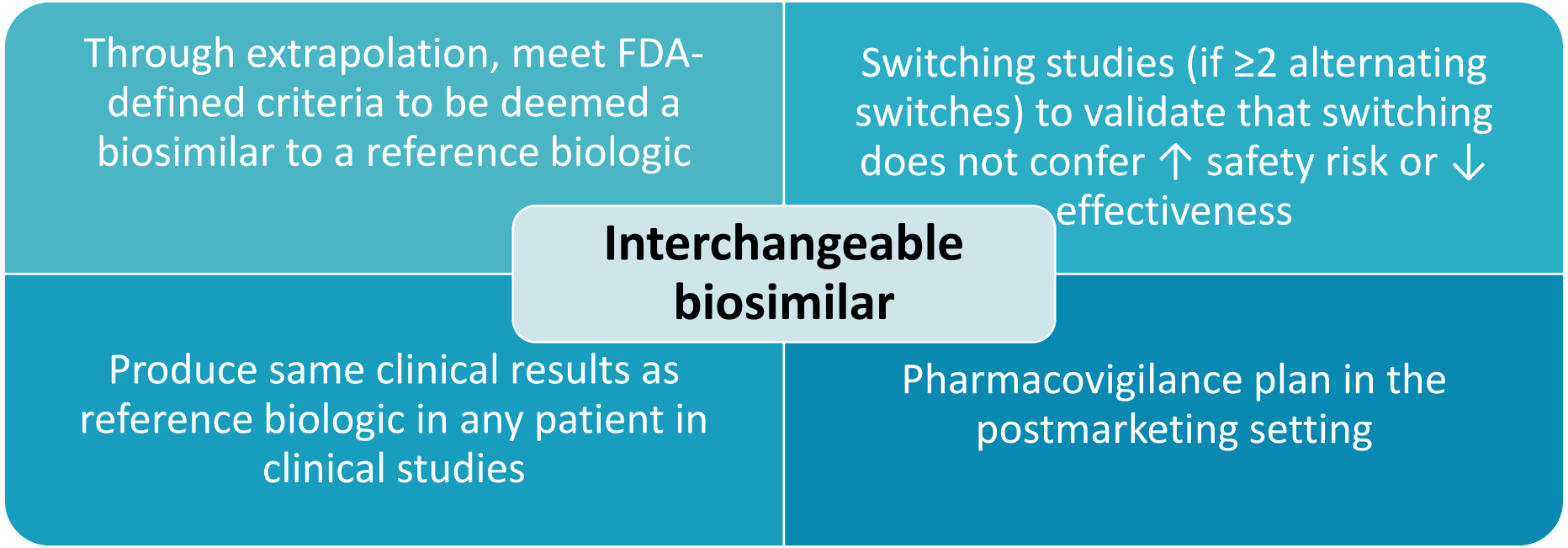
H.R.3590 Patient Protection and Affordable Care Act (Enrolled Bill [Final as Passed Both House and Senate]). US FDA. Accessed March 27, 2020. www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/ucm216146.pdf

Interchangeability

- Safety standards for determining interchangeability
  - Major risk is immunogenicity
  - Residual questions about diminished efficacy or increased immune-related reactions
- Will be “difficult” in the initial 351(k) application due to the sequential nature of the assessment
  - Immune reactions are highly variable and sensitive to many different factors
  - Data package to be submitted will generally not be sufficiently sensitive to detect rare/serious adverse effects

H.R.3590 Patient Protection and Affordable Care Act (Enrolled Bill [Final as Passed Both House and Senate]). US FDA. Accessed March 27, 2020. www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/ucm216146.pdf

Why Is Interchangeability Important From an Operational Standpoint?



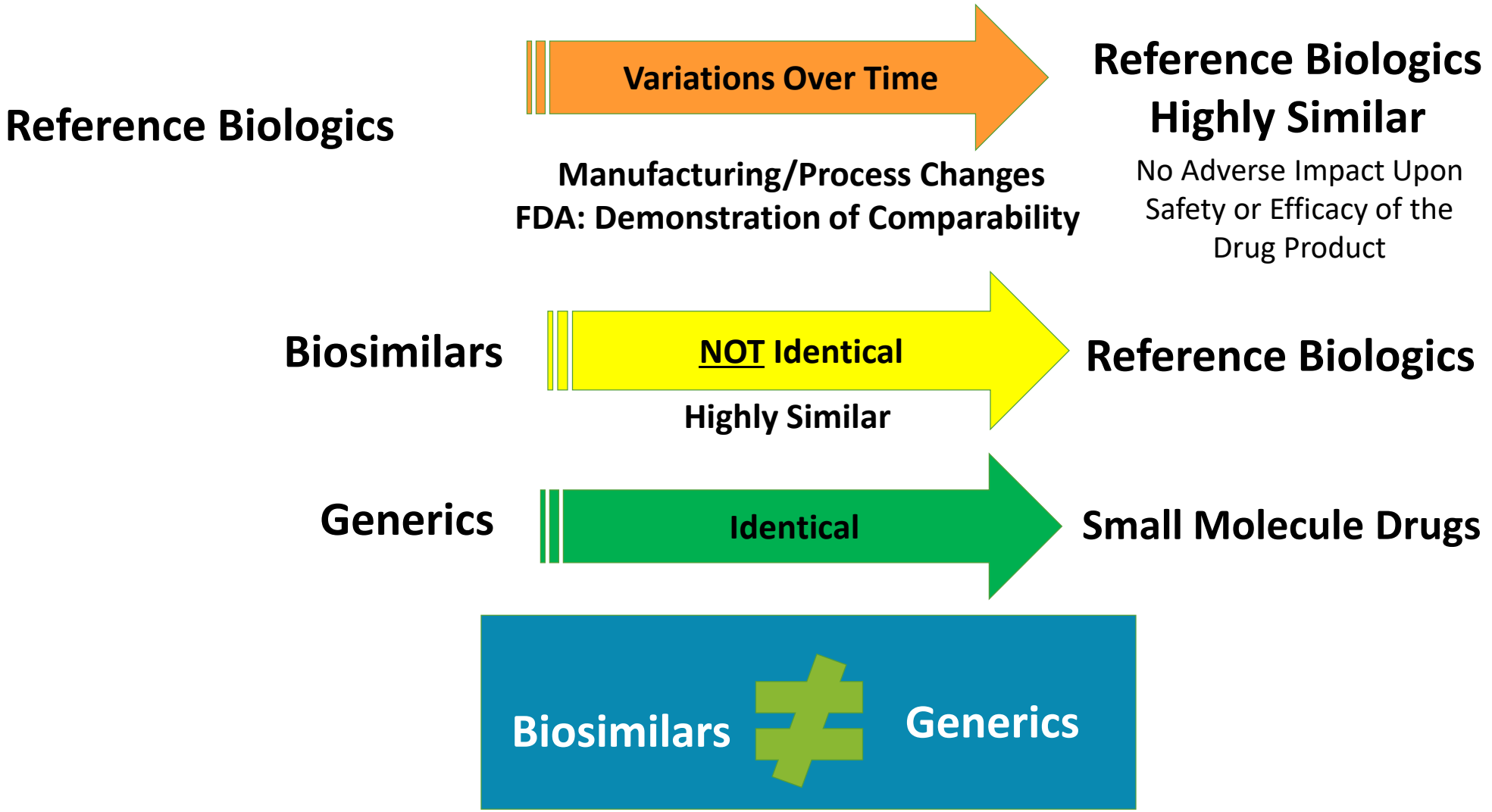
Currently there are no FDA-approved biologics in the United States that meet the criteria listed in the Biologics Price Competition and Innovation Act (BPCIA) for an interchangeable biosimilar; therefore, operationally a workflow needs to be created in institutions to allow for the substitution of biosimilars.

Biosimilar and interchangeable products. US FDA. Updated October 23, 2017. Accessed March 30, 2020. www.fda.gov/drugs/biosimilars/biosimilarand-interchangeable-products#biological; Endrenyi L, Markus R. *J Biopharm Stat*. 2019;29(6):1003-1010.

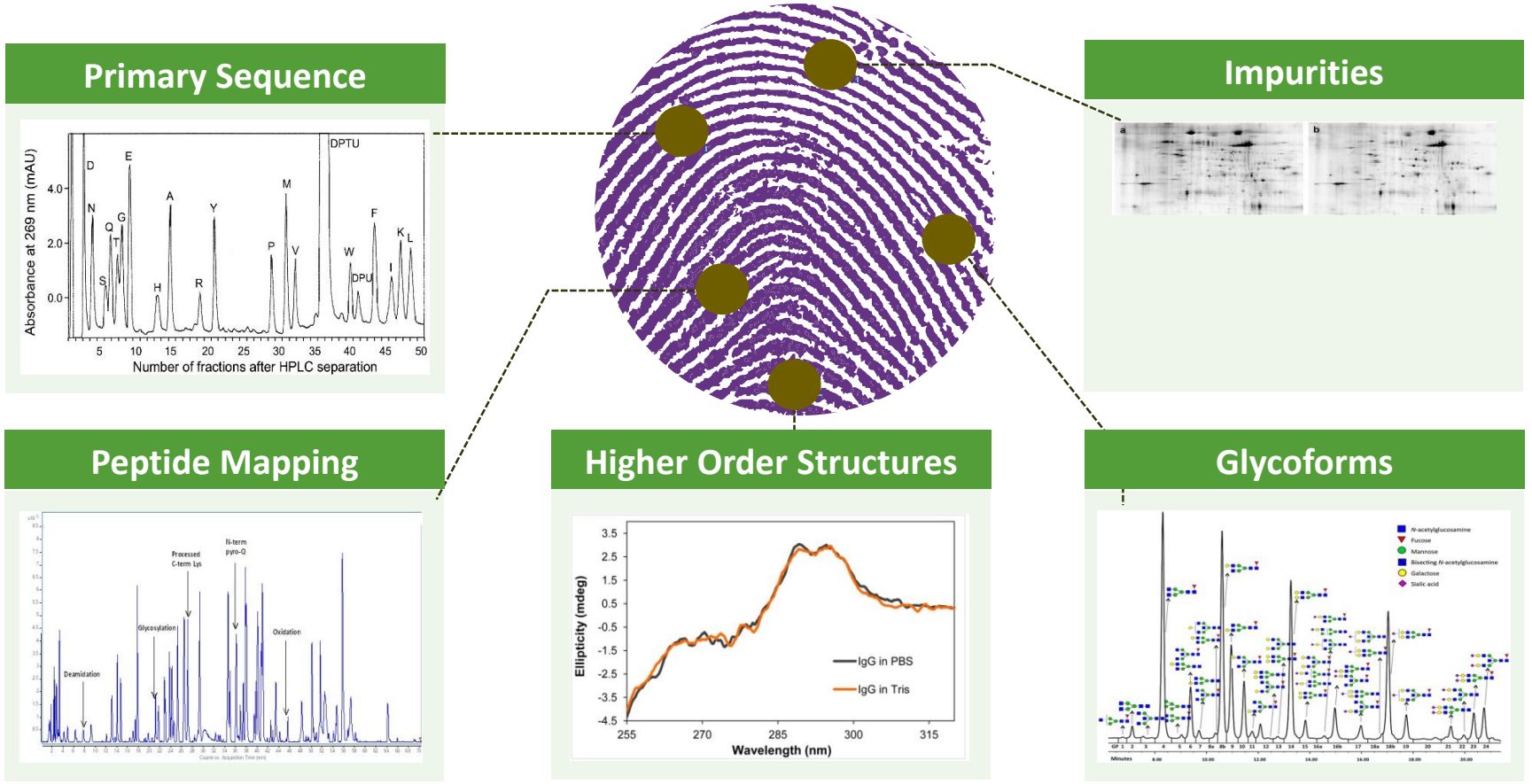
Challenges With Interchangeability

- No FDA-approved interchangeable biosimilars
- State laws on interchangeability
- Should be discussed at an institutional level
  - Different than formulary preferences or restrictions at the institution or payer level

Identical Copies of Biologics Cannot Be Made



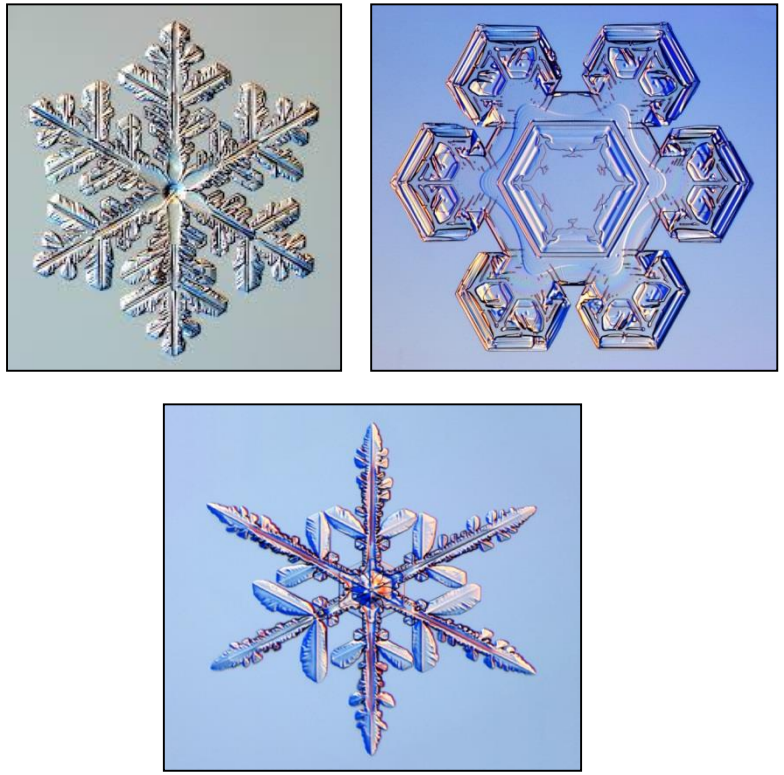
Establishing Fingerprint-like Similarity: Physiochemical Properties



Clinical pharmacology data to support a demonstration of biosimilarity to a reference product: guidance for industry. US FDA. Published December 2016. Accessed March 30, 2020. www.fda.gov/media/88622/download

Differences in Biologic Products

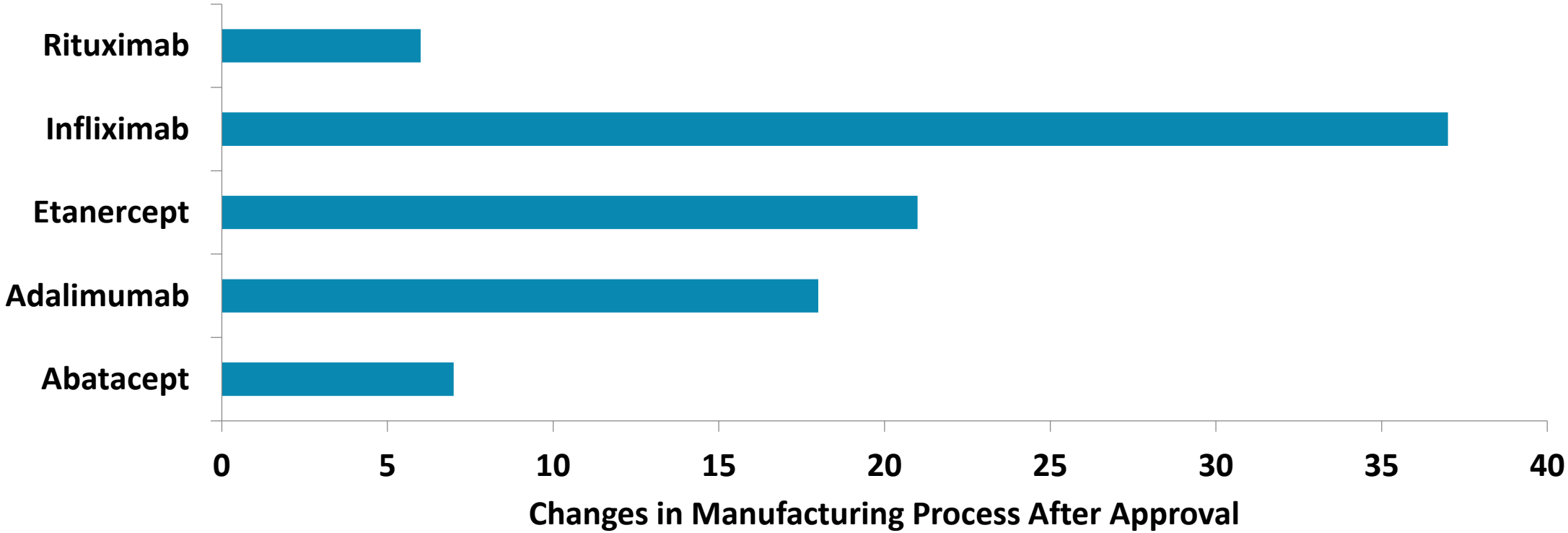
- Differences between proteins



- Post-translation modifications

- Amino acid substitution
- N- and C-terminal mods
- Mismatched S-S bonds
- Post-translation modifications folding
  - Carboxylation
  - Formylation
  - O-linked glycosylation
  - N-linked glycosylation
  - Methylation
  - Phosphorylation
  - Sulphation
- PEGylation

Reference Biologics and Post-approval "Life Cycle" Changes = Drift



Schneider CK. *Ann Rheum Dis*. 2013;72(3):315-318.

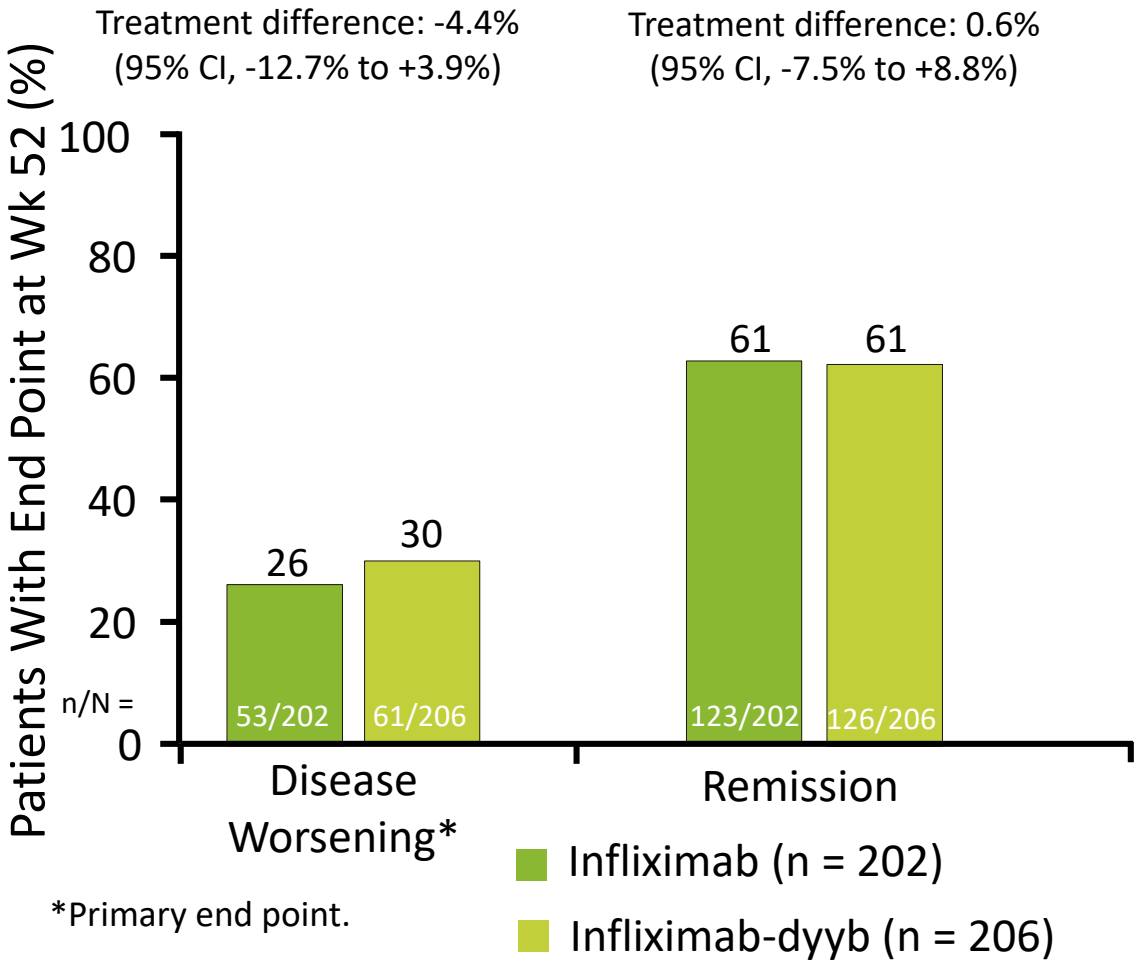
Switching

- Evaluates whether there are differences in efficacy or safety when patients are switched from a reference biologic to a biosimilar.
- Switching studies may look at multiple switches back and forth
- Outcomes are compared to patients who were continued on the reference biologic
- Meta-analysis evaluated 90 studies with more than 14,000 patients
  - Patients switched from a reference product to a biosimilar
  - Concluded that switching from reference product to biosimilar is not inherently dangerous, and patients and healthcare professionals should not be concerned about such switching
  - Pharmacovigilance is still important to monitor for rare safety events and for unexpected changes in efficacy or safety profiles

Cohen HP, et al. *Drugs.* 2018;78(4):463-478.

Examples of Biosimilars in Practice

NOR-SWITCH: Switch to Infliximab-dyyb for Multiple Indications



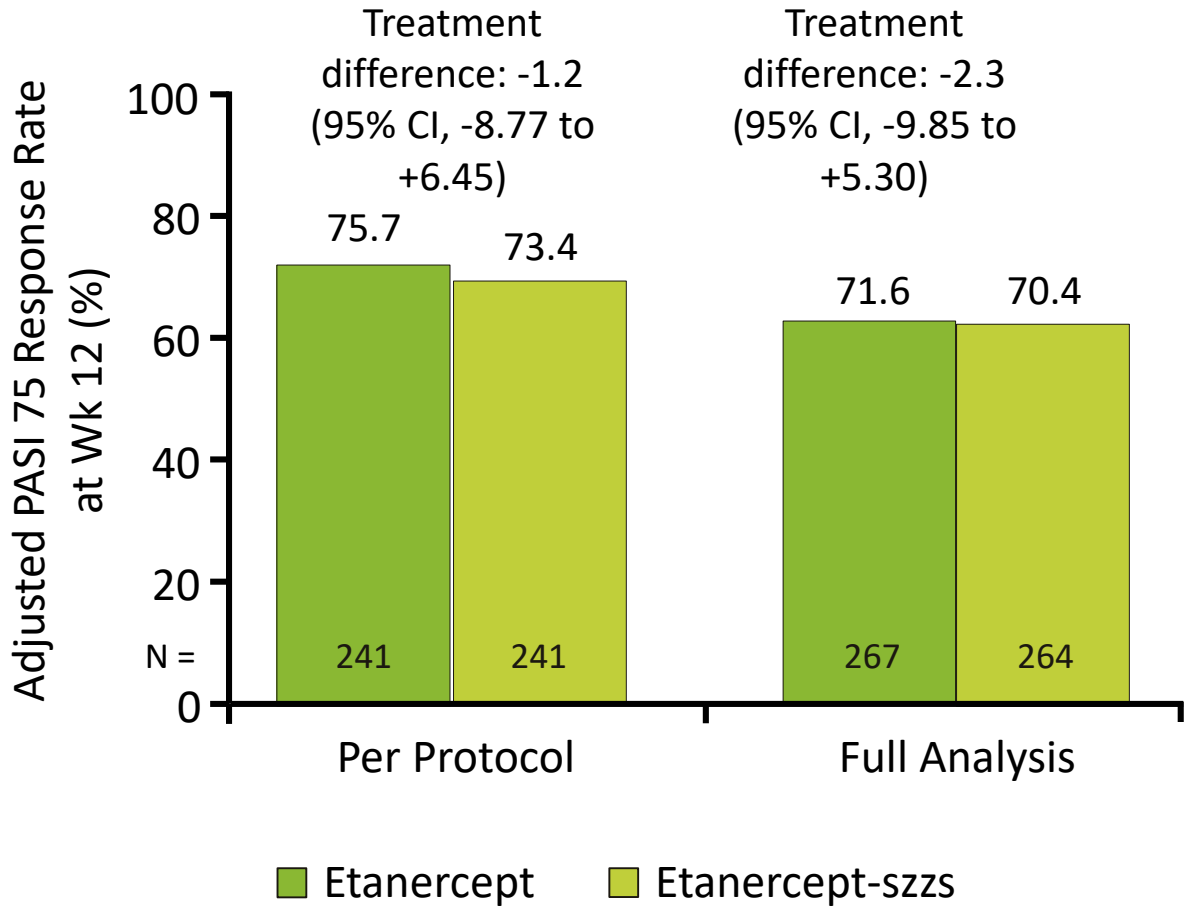
*Primary end point.

- 52-wk randomized, double-blind phase 4 trial in patients with RA, SpA, CD, Ps, PsA, or UC on stable infliximab for ≥6 mo
- Primary end point: disease worsening during 52-wk follow-up
  - Prespecified noninferiority margin: 15%
- Result: Switching from infliximab to infliximab-dyyb noninferior to continued treatment with infliximab

RA, rheumatoid arthritis; SpA, spondyloarthritis; CD, Crohn disease; Ps, plaque psoriasis, PsA, psoriatic arthritis; UC, ulcerative colitis.

Jørgensen KK, et al. *Lancet*. 2017;389(10086):2304-2316; Cohen HP, et al. *Drugs*. 2018;78(4):463-478.

EGALITY: Switch to Etanercept-szzs Equivalent to Remaining on Etanercept



- 12-week randomized double-blind trial in patients with PsA
- Week 12-30: patients switched therapies 3 times, then continued on same therapy to week 52

Griffiths CE, et al. *Br J Dermatol*. 2017;176(4):928-938; Cohen HP, et al. *Drugs*. 2018;78(4):463-478.

Biosimilars Currently in the Pipeline for Rheumatologic Conditions

Reference biologic	Drug class	≈ Patent exp. date	Indication	Biosimilars with phase 3 clinical trials
Adalimumab	TNF-α inhibitor	2022*	Autoimmune diseases	• BI695501 accepted for FDA review • Multiple others registered/under way
Infliximab	TNF-α inhibitor	2018*	Autoimmune diseases	• Multiple registered/under way

TNF, tumor necrosis factor.

Stevenson JG, et al. *Ann Pharmacother*. 2017;51(7):590-602; Panesar K. *US Pharm*. 2016;41:26-29; Goel N, et al. *Rheumatology*. 2017;56(2):187-197.

Growth Factors: Filgrastim and Pegfilgrastim

Medication	Approval	Indications
pegfilgrastim-cbqv	November 2018	FN prevention
pegfilgrastim-jmdb	June 2018	FN prevention
pegfilgrastim-bmez	November 2019	FN prevention
filgrastim-aafi	July 2018	FN prevention/treatment
filgrastim-sndz	March 2015	FN prevention/treatment

Biosimilar product information. US FDA. Updated February 24, 2020. Accessed March 31, 2020. www.fda.gov/drugs/biosimilars/biosimilar-product-information; Udenyca. Prescribing information. Amgen; 2020; Fulphila. Prescribing information. Mylan GmbH; 2019; Nivestym. Prescribing information. Hospira, Inc., a Pfizer Company; 2018; Zarxio. Prescribing information. Sandoz, Inc; 2019.

First FDA-Approved Biosimilar: Filgrastim-sndz—Analytics, PK/PD, Safety

- Approved March 6, 2015; first FDA-approved oncology-related biosimilar
- FDA approved use for all current FDA indications of filgrastim based on extrapolation
- Structural and functional studies demonstrated same amino acid sequence as US-licensed filgrastim
- Biological activity, receptor binding and physiochemical properties, product-related substances and impurities, and stability profile are highly similar to US-licensed filgrastim, notwithstanding minor differences in clinically inactive components
- 5 studies in healthy subjects evaluating ANC, C_{max}, and CD34+ cell counts demonstrated PK/PD similarity with US-licensed and EU-approved filgrastim
- Safety data in 204 healthy subjects and 214 pts with breast cancer were similar to US-licensed and EU-approved filgrastim

FDA. Oncologic Drugs Advisory Committee Meeting. 2015.

Alternating Biosimilar and Reference Filgrastim to Manage Severe Neutropenia in Breast Cancer

Adverse effect, %	Switched (alternating biosimilar and originator) N = 107	Reference only (n = 51)
Incidence of febrile neutropenia (FN)	3.4 95% CI: -9.65 to 4.96	0
Infections	9.3	9.9
Hospitalization due to FN	[1 patient in cycle 6]	0
Treatment-emergent AEs	42.1	39.2
Anti-drug antibodies	0	0

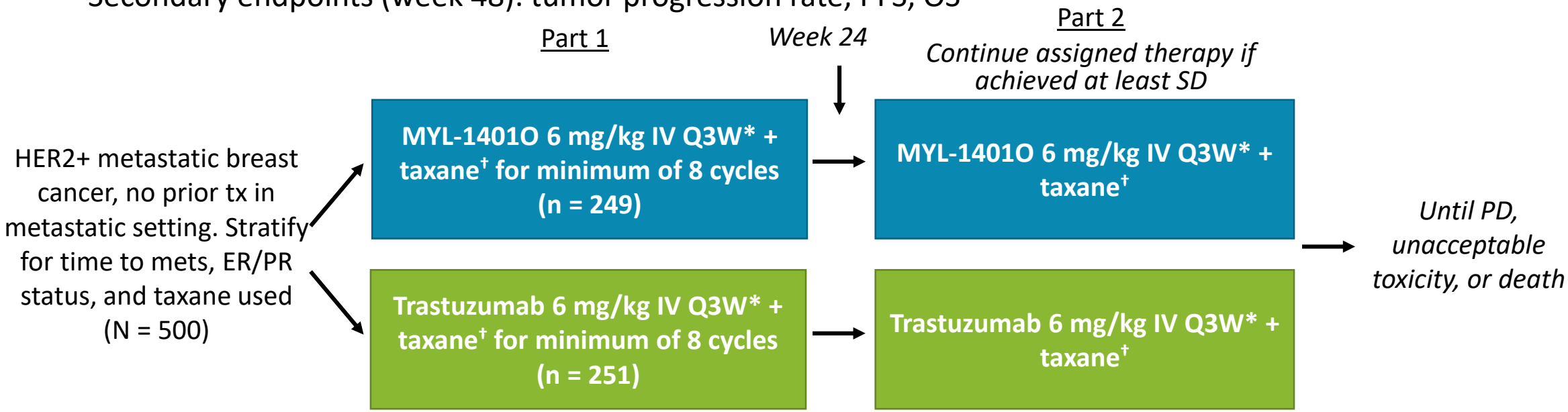
No evidence of clinically meaningful differences with switching.

Blackwell K, et al. *Ann Oncol*. 2018;29(1):244-249.

HERITAGE: First-line Trastuzumab vs Biosimilar MYL-1401O in HER2+ Metastatic Breast Cancer

Part 1 Results for Multicenter, Randomized, Double-blind Phase 3 Equivalence Study

- Primary end point (week 24): ORR
- Secondary endpoints (week 48): tumor progression rate, PFS, OS



*After usual loading dose.

†Physician choice of docetaxel or paclitaxel

Rugo HS, et al. *JAMA.* 2017;317:37-47.

HERITAGE: Safety Profile at Week 24

End point	MYL-1401O + taxane (n = 247)	Trastuzumab + taxane (n = 246)
Serious AE, % • ≥1 serious AE • Neutropenia • Neutropenia with fever • Leukopenia • Pneumonia	 38.1 27.5 4.5 1.6 1.6	 36.2 25.2 4.1 4.9 2.0
Deaths due to serious AEs, n	4	4
Median LFEV values, % (range) • Baseline • Wk 24 • Change from BL to wk 24	 64.0 (51-82) 63.5 (50-81) -1.0 (-13 to 21)	 63.0 (51-84) 63.0 (41-82) -1.0 (-19 to 13)

Rugo HS, et al. *JAMA.* 2017;317(1):37-47; Rugo HS, et al. *J Clin Oncol.* 34(suppl 18): Abstract LBA503.

HERITAGE Study Data in Clinical Perspective

	HERITAGE study		Historical data
End point	MYL-1401O	Herceptin	First-line HER2+ MBC
ORR 24 weeks (Primary)	70%	64%	55-69%
ORR ratio (90% CI): FDA requirement	1.09 (0.981, 1.218)		N/A
ORR difference (95% CI): EMA requirement	6.0% (-2.64%, 14.45%)		N/A
Time to progression (TTP) 48 weeks	11.1 months	11.1 months	11.3 -12.4 months
OS 48 weeks	89.1%	85.1%	75%-89%
Safety and toxicity	Comparable		Consistent
Immunogenicity	3.9%	4.4%	3.4%-7.1%
Exposure	Comparable		Consistent

Slamon DJ, et al. *N Engl J Med*. 2001;344(11):783-792; Mass RD, et al. *Clin Breast CA*. 2005;6(3):240-246; Marty M, et al. *J Clin Oncol*. 2005;23(19):4265-4274; Baselga J, et al. *N Engl J Med*. 2012;366(2):109-119; Swain SM, et al. *N Engl J Med.* 2015;372(8):724-734; Hegg R, et al. Presented at: 2012 *ESMO Congress*. Abstract 273P; Jackisch C, et al. *Annals of Oncology*. 2015;26(2):320-325.

Phase 3 Trastuzumab Biosimilars Trials Summary

	Trastuzumab-dttb (SB3)	Trastuzumab-anns (ABP 980)	Trastuzumab-pkrb (CT-P6)	Trastuzumab-dkst (MYL-14010)	Trastuzumab-qyyp (PF-05280014)
Trial	NCT02149524	NCT01901146	NCT02162667	NCT02472964	NCT01989676
Disease	EBC	EBC – both neoadjuvant and adjuvant	EBC – neo- and adjuvant/ metastatic	Metastatic	Neoadjuvant/ metastatic
# patients	800	696	549/475	500	226/707
Primary outcome	Equivalent rates of breast pathologic complete response	Similar rates of pathologic complete response	Similar rates of pathologic complete response, along with similar LVEF	Equivalent overall response rate at 24 weeks	Metastatic: Equivalent overall response rate at 25 and 33 weeks

EBC, early breast cancer.

Pivot X, et al. *J Clin Oncol*. 2018;36(10):968-974; Kolberg HC, et al. *Oncotarget.* 2018;10(1):8-9; Esteva FJ, et al. 2018 San Antonio Breast Cancer Symposium, Abstract P6-17-03; Im YH, et al. *J Clin Oncol*. 2013;31(15):629; Rugo HS, et al. *JAMA*. 2017;317(1):37-47; Lammers P, et al. *Br J Cancer*. 2018;119(3):266-273; Pegram MD, et al. *Br J Cancer*. 2019;120(2):172-182.

Oncology Biosimilars in Development

Medication	Approval Status	Number of Companies Developing
Bevacizumab	Approved; further approvals pending	>20 companies
Cetuximab biosimilars and biobetters	In development	7 companies
Denosumab	In development	3 companies
Rituximab	Approved; further approvals pending	>20 companies

Biosimilar product information. US FDA. Updated February 24, 2020. Accessed March 31, 2020. www.fda.gov/drugs/biosimilars/biosimilar-product-information

Key Considerations for Pharmacists

- Biosimilar product characteristics
  - Clinical Considerations
    - Analytical structure, function studies
  - Product Considerations
    - Naming convention
    - Packaging, labeling
  - Institutional Considerations
    - Storage needs

Cuellar S, et al. *Am J Health Syst Pharm.* 2019;76(21):1725-1738.

Considerations for P&T Committee Members Evaluating Biosimilars for Formulary Inclusion

Clinical considerations

- Indications
- Evaluation of efficacy and safety using available data
- Immunogenicity

Product considerations

- Nomenclature
- Manufacturing and supply chain considerations
- Packaging, labeling, and storage
- Look alike/sound alike

Institutional considerations

- Substitutions and interchangeability (therapeutic interchange)
- Transitions of care
- Pharmacovigilance
- Cost and reimbursement
- Third-party formulary requirements
- Provider and patient education
- Information technology
- Storage/space for various products (cost of medical-grade refrigerators)

Cuellar S, et al. *Am J Health Syst Pharm.* 2019;76(21):1725-1738.

P&T Conversations at the Coffee Table

Product characteristics	Are there any differences in formulation or excipients between the biosimilar under consideration versus the reference product?
	Are there any differences in compatibility (eg, injection pain, interference with laboratory assays) between the biosimilar under consideration and the reference product?
Medication availability	Are there any differences in clinic administration and/or retail availability between the biosimilar under consideration and reference product that may affect the overall availability of the products?
	Does the manufacturer have a process to ensure a reliable and uninterrupted supply of the product? Does the manufacturer maintain adequate levels of reserve product in stock?
Reimbursement	Will the biosimilar have all of the same indications as the originator?
Information technology support	Does the hospital have a robust information technology infrastructure to support the biosimilar? • Differentiating the biosimilar under consideration from the reference product during order entry? • Tracking which product was administered (biosimilar under consideration versus the reference product)?

Cuellar S, et al. *Am J Health Syst Pharm.* 2019;76(21):1725-1738.

Provider Education Tips From Pharmacists

- Provide education with easy access to current clinical information on biologic therapies, including therapeutic guidelines, clinical trial results, and adverse effects
- Discuss the following during:

Grand rounds	P&T committee meetings	1-on-1 discussions

• Development of biologics and biosimilars	• Formulary review
	  • Efficacy
	  • Outcomes
	  • Safety
	  • Extrapolation of data
	  • Cost
		• Biosimilar basics
		• Clinical studies
		• Current outcomes data

- Reinforce this information with advanced practitioners and nurses
- Educate local providers on the differences between biosimilars and generics
- Inform providers on the legal restrictions of pharmacies not being able to change prescriptions not covered to biosimilar counterparts that are covered

Biosimilars. US FDA. Updated February 3, 2020. Accessed March 30, 2020. www.fda.gov/drugs/therapeutic-biologics-applications-bla/biosimilars

Education Recommendations

ASCO recommendations:

- Call for health care professionals to educate patients
- Need for medical societies, government sources, and patient advocacy organizations to provide public awareness
- Develop education programs
- Establish as well as use standardized, publicly available materials

Lyman GH, et al. *J Clin Oncol.* 2018;36(12):1260-1265.

Pharmacists' Main Points for Educating Patients

Biosimilars are NOT generic drugs, but they are close

Biosimilars are just as safe and effective as the original biologic drug

Biosimilars will provide more treatment options

Biosimilars may help reduce overall health care costs

Lyman GH, et al. *J Clin Oncol.* 2018;36(12):1260-1265.

Additional Information to Share with Patients

- Use of biologic therapies in the specific disease
- Definition of a biosimilar
- Totality of evidence required for a biosimilar
- Efficacy similar to reference biologic
- Safety similar to reference biologic
- Delivery/administration of the agent
- Device use (if applicable)
- Access to treatment, insurance coverage, and out-of-pocket cost
- Services available to support the patient
- Clinical trials, including standard biosimilar trial design (active innovator comparator; no placebo arm)
- Manufacturer identity

Lyman GH, et al. *J Clin Oncol.* 2018;36(12):1260-1265.

Conclusion

- Biosimilars continue to change the current treatment paradigm of oncologic and nononcologic therapies.
- Institutions will need to continually evaluate biosimilars in practice coming onto the market and pricing and reimbursement conditions for utilization.
- Pharmacists can play a crucial role in helping to ease concerns and provide education to other healthcare providers and patients on biosimilars

Additional Resources

- FDA. Biosimilars. www.fda.gov/drugs/therapeutic-biologics-applications-bla/biosimilars
- FDA. Biosimilars Health Care Provider Materials. https://www.fda.gov/drugs/biosimilars/health-care-provider-materials
- Lyman GH, et al. American Society of Clinical Oncology Statement: Biosimilars in Oncology. *J Clin Oncol*. 2018;36(12):1260-1267

Influenza Vaccination: Opportunities for Pharmacists as Patient Advocates, Educators, and Administrators

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This activity is approved for 1.0 contact hour (0.10 CEU) under the ACPE universal activity number 0290-0000-20-083-L06-P. The activity is available for CE credit on May 16, 2020.

Activity Type: Application

Fee: Free

Immunization Credit

This activity is supported by an educational grant from Sanofi Pasteur Inc.

This activity is jointly sponsored by Rutgers University, Ernest Mario School of Pharmacy.

Educational Objectives

At the completion of this activity, participants will be able to:

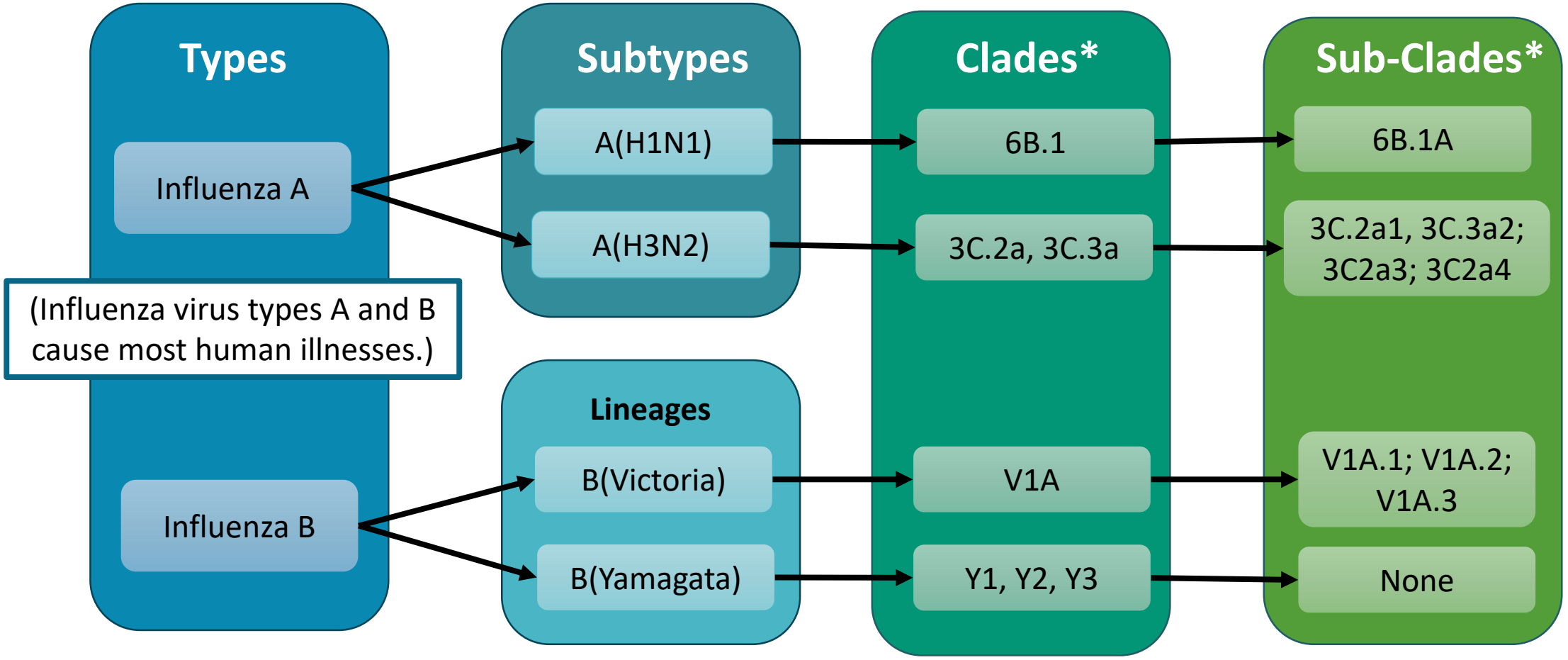
- Examine the etiology and transmission of the influenza virus
- Identify patient populations at risk for influenza-related complications and the critical nature of implementing ACIP recommendations regarding the annual influenza vaccination
- Analyze the safety, efficacy, and types of influenza vaccines available for the 2019-2020 influenza season
- Explore interventions that pharmacists can implement to dispel patient misconceptions regarding vaccinations

Influenza

- A viral, contagious respiratory illness that spreads through droplets
- Influenza can cause mild to severe illness and, at times, can lead to death
- Influenza usually comes on suddenly
- Most contagious in the first 3-4 days after the illness begins
- Patients can be contagious 1 day before symptoms develop and up to 5 to 7 days after becoming sick.
- Some people, especially young children and people with weakened immune systems, might be able to infect others with flu viruses for an even longer time.
- Symptoms can include fever (or feeling feverish), chills, cough, sore throat, runny nose, body aches, headache, and fatigue

Key facts about influenza (flu). Centers for Disease Control and Prevention (CDC). Reviewed September 13, 2019. Accessed May 11, 2020. cdc.gov/flu/about/keyfacts.htm

Influenza Nomenclature



Types of influenza viruses. CDC. Reviewed November 18, 2019. Accessed May 11, 2020. cdc.gov/flu/about/viruses/types.htm

*Select examples.

Composition

2019-2020

- A/Brisbane/02/2018 A(H1N1)pdm09-like virus (new)
- A/Kansas/14/2017 A(H3N2)-like virus (new)
- B/Colorado/06/2017-like (Victoria lineage) virus
- Quadrivalent (4-component) vaccines
  - B/Phuket/3073/2013-like (Yamagata lineage) virus

2020-2021

Egg-based Vaccines

- A/Guangdong-Maonan/SWL1536/2019 (H1N1)pdm09-like virus
- A/Hong Kong/2671/2019 (H3N2)-like virus
- B/Washington/02/2019 (B/Victoria lineage)-like virus
- B/Phuket/3073/2013 (B/Yamagata lineage)-like virus

Cell- or recombinant-based Vaccines

- A/Hawaii/70/2019 (H1N1)pdm09-like virus
- A/Hong Kong/45/2019 (H3N2)-like virus
- B/Washington/02/2019 (B/Victoria lineage)-like virus
- B/Phuket/3073/2013 (B/Yamagata lineage)-like virus

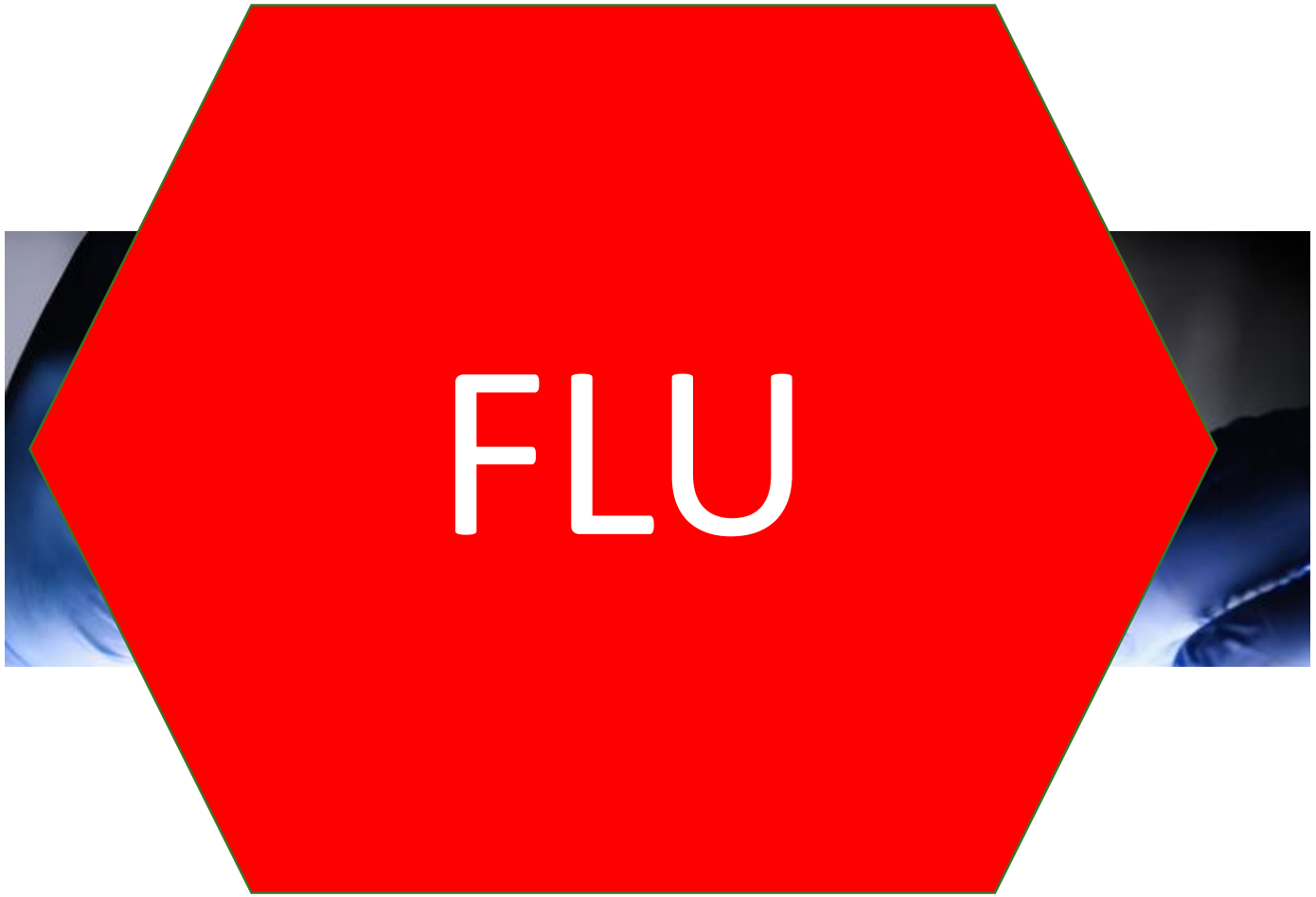
Frequently asked influenza (flu) questions: 2019-2020 season. CDC. Reviewed January 17, 2020. Accessed May 11, 2020. cdc.gov/flu/season/faq-flu-season-2019-2020.htm; Recommended composition of influenza virus vaccines for use in the 2020 - 2021 northern hemisphere influenza season. WHO. Accessed May 11, 2020. who.int/influenza/vaccines/virus/recommendations/2020-21_north/en/

Healthy People 2020 Objectives *We Are Here*!

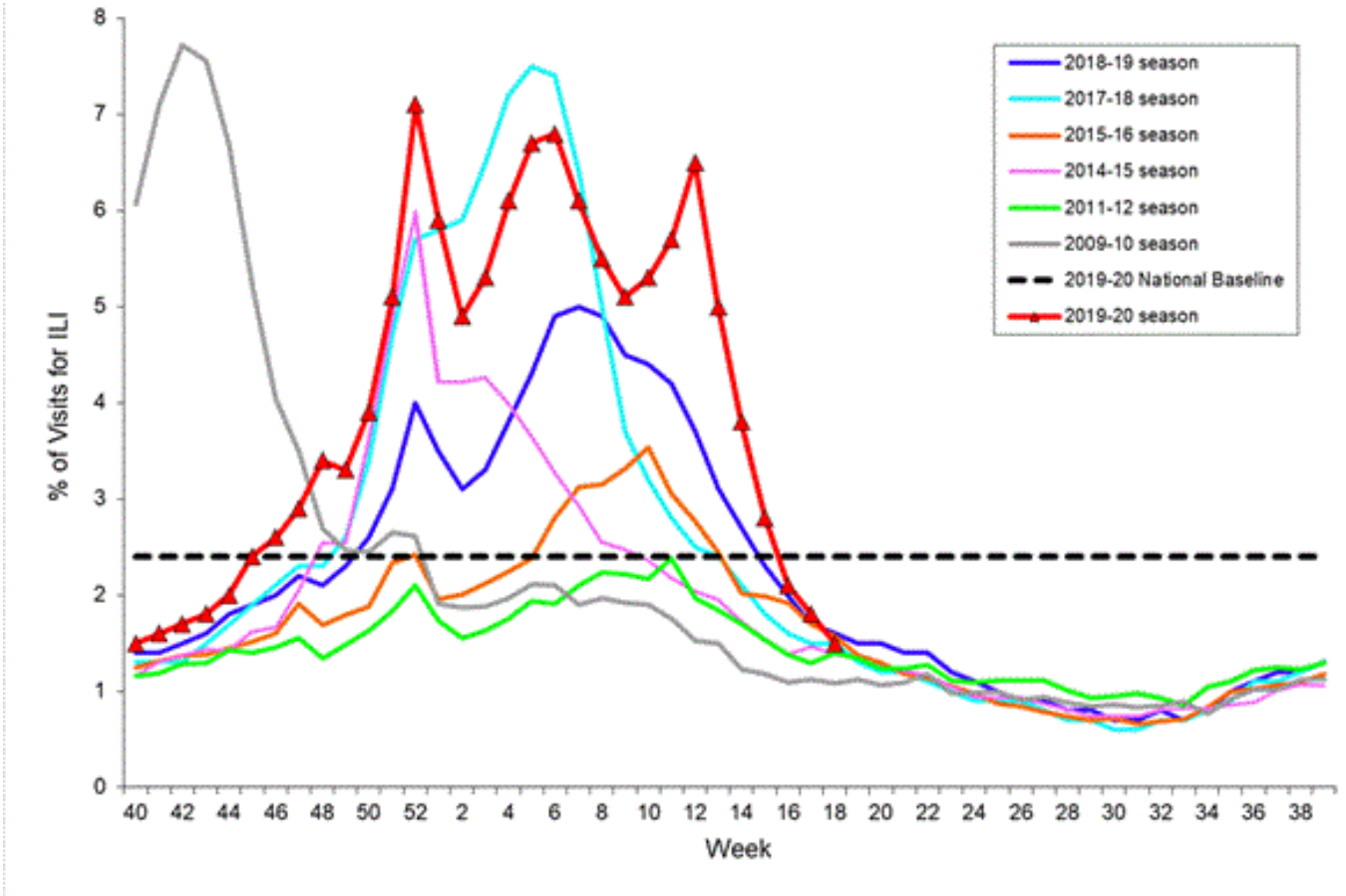
Category	Baseline (%)	2020 Goal (%)
Increase the percentage of children aged 6 months to ≤17 years who are vaccinated annually against seasonal influenza	46.9	70
Increase the percentage of adults ≥18 years who are vaccinated annually against seasonal influenza	38.1	70
Increase the percentage of health care personnel who are vaccinated annually against seasonal influenza	55.8	90
Increase the percentage of institutionalized adults aged ≥18 years in long-term or nursing homes who are vaccinated annually against seasonal influenza	71.4	90
Increase the percentage of pregnant women who are vaccinated against seasonal influenza	40.4	80

Immunization and infectious diseases: objectives. US Department of Health and Human Services. Accessed May 11, 2020. healthypeople.gov/2020/topics-objectives/topic/immunization-and-infectious-diseases/objectives

What Is Going on NOW?



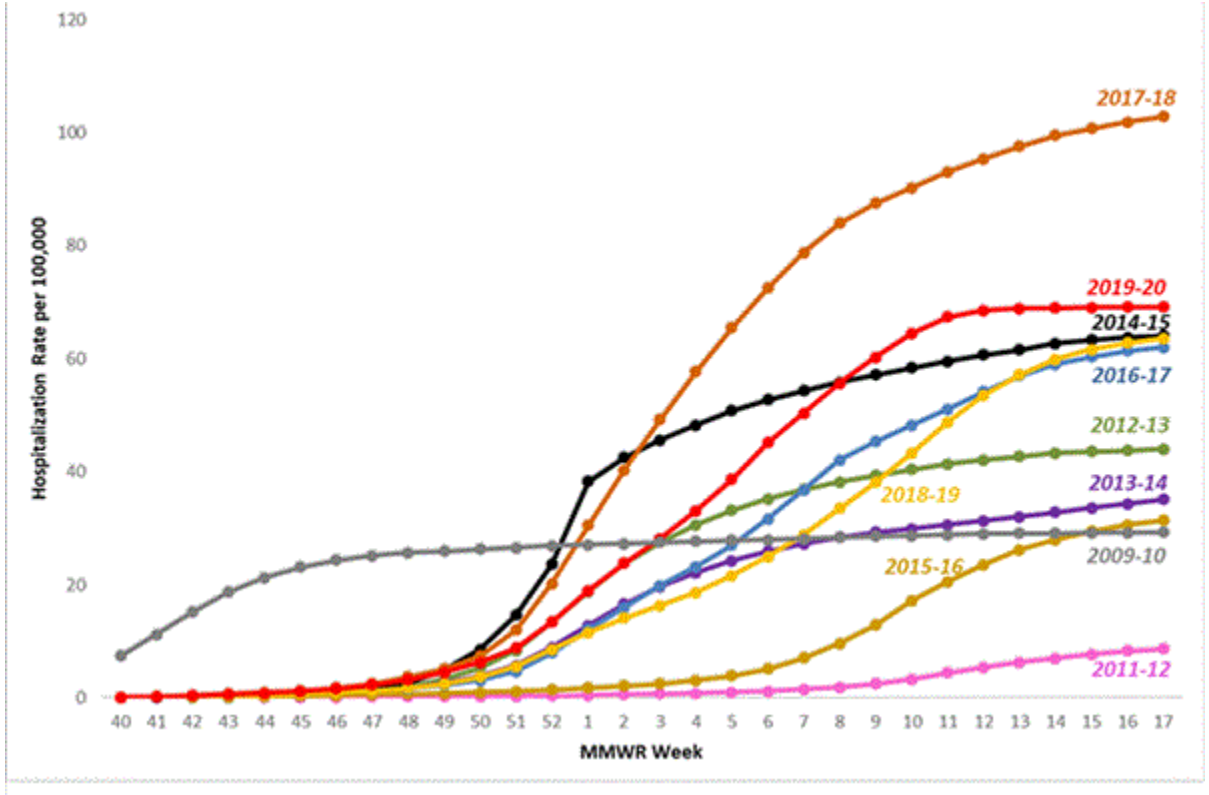
Percentage of Visits for Influenza-like Illness (ILI) Reported by the US Outpatient ILI Surveillance Network



Weekly National Summary, 2019-2020 and Selected Previous Seasons

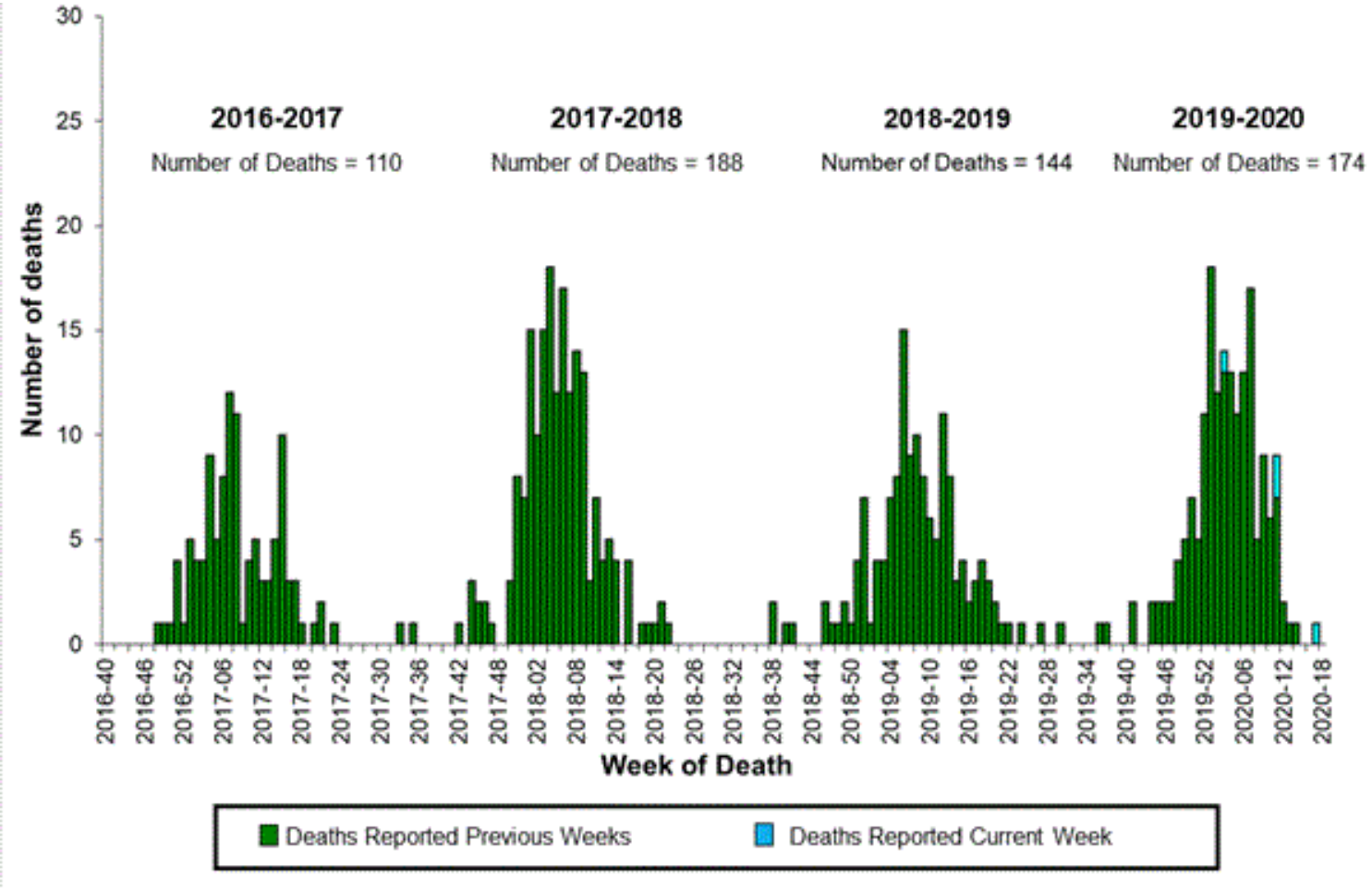
Weekly US influenza surveillance report. CDC. Reviewed May 8, 2020. Accessed May 11, 2020. cdc.gov/flu/weekly/index.htm

Cumulative Rate of Laboratory-confirmed Influenza Hospitalizations Among Cases of All Ages, 2011-2012 to 2019-2020



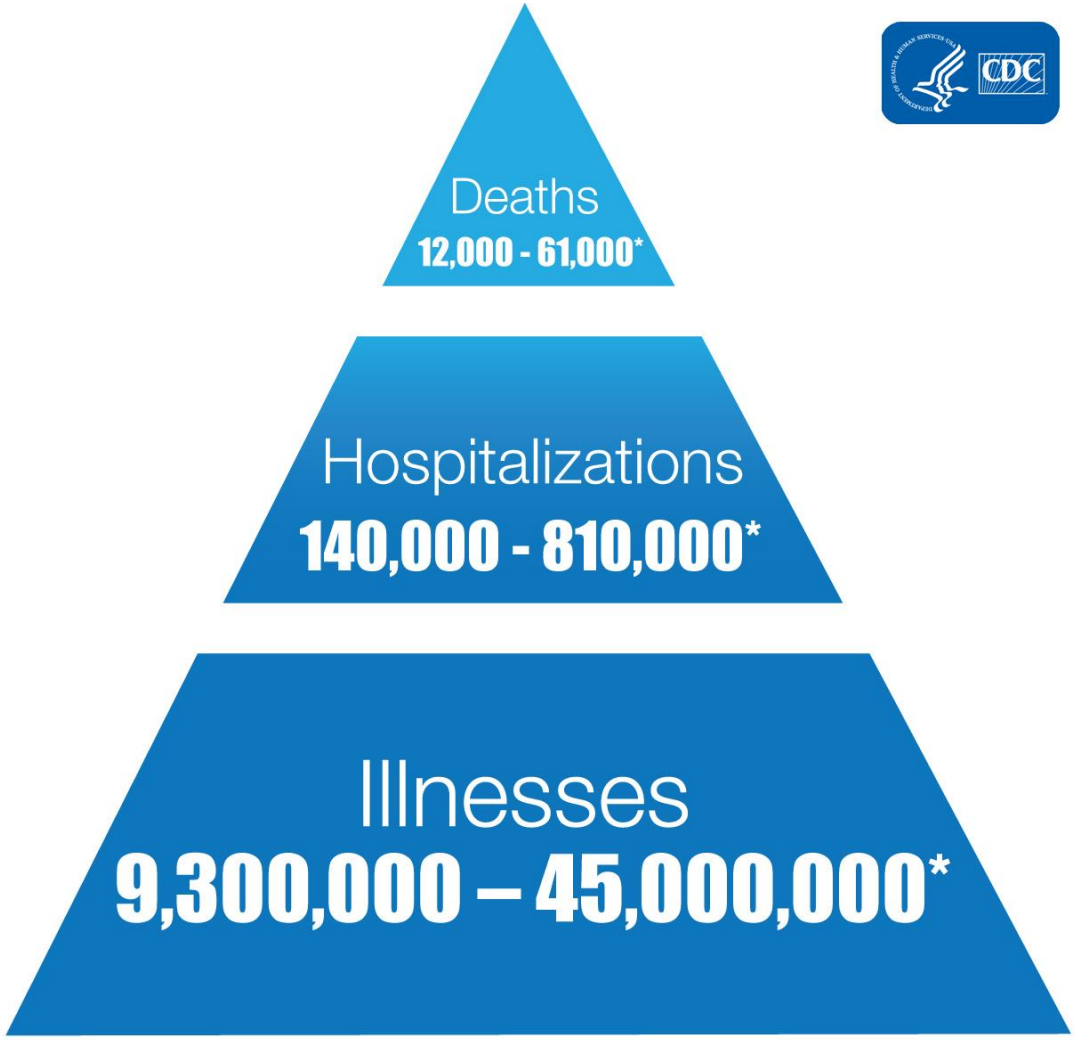
Weekly US influenza surveillance report. CDC. Reviewed May 8, 2020. Accessed May 11, 2020. cdc.gov/flu/weekly/index.htm

Influenza-associated Pediatric Deaths by Week of Death, 2016-2017 Season to 2019-2020 Season



Weekly US influenza surveillance report. CDC. Reviewed May 8, 2020. Accessed May 11, 2020. cdc.gov/flu/weekly/index.htm

Burden of Illness



*The top range of these burden estimates are from the 2017-2018 flu season. These are preliminary and may change as data are finalized.

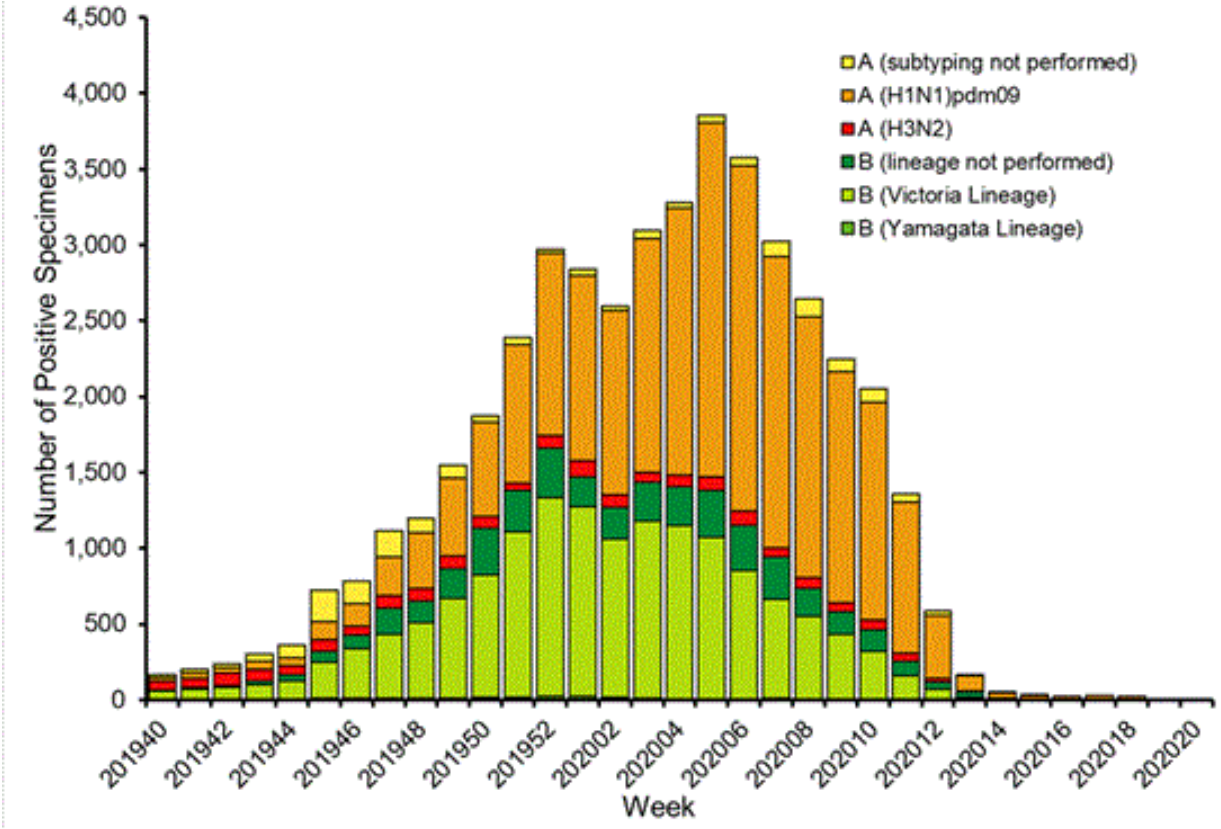
Disease burden of influenza. CDC. Reviewed January 10, 2020. Accessed May 11, 2020. cdc.gov/flu/about/burden/index.html

Weekly US Influenza Surveillance Report

	Week 11	Week 14	Data cumulative since September 29, 2019 (week 40)
No. of specimens tested	1374	356	81,392
No. of positive specimens	413	35	43,456
Positive specimens by type/subtype			
Influenza A	**333 (80.6%)**	**31 (88.6%)**	**24,822 (57.1%)**
(H1N1)pdm09	264 (93.0%)	28 (96.6%)	22,324 (92.6%)
H3N2	20 (7.0%)	1 (3.4%)	1780 (7.4%)
Subtyping not performed	49	2	718
Influenza B	**80 (19.4%)**	**4 (11.4%)**	**18,634 (42.9%)**
Yamagata lineage	0 (0.0%)	0 (0.0%)	238 (1.6%)
Victoria lineage	59 (100%)	0 (0.0%)	14,198 (98.4%)
Lineage not performed	21	4	4198

Weekly US influenza surveillance report. CDC. Reviewed May 8, 2020. Accessed May 11, 2020. cdc.gov/flu/weekly/index.htm

Influenza-positive Tests Reported to the CDC by US Public Health Laboratories, National Summary, 2019-2020 Season



Weekly US influenza surveillance report. CDC. Reviewed May 8, 2020. Accessed May 11, 2020. cdc.gov/flu/weekly/index.htm

2019-2020 Vaccine Efficacy (VE)

45%

overall (VE)

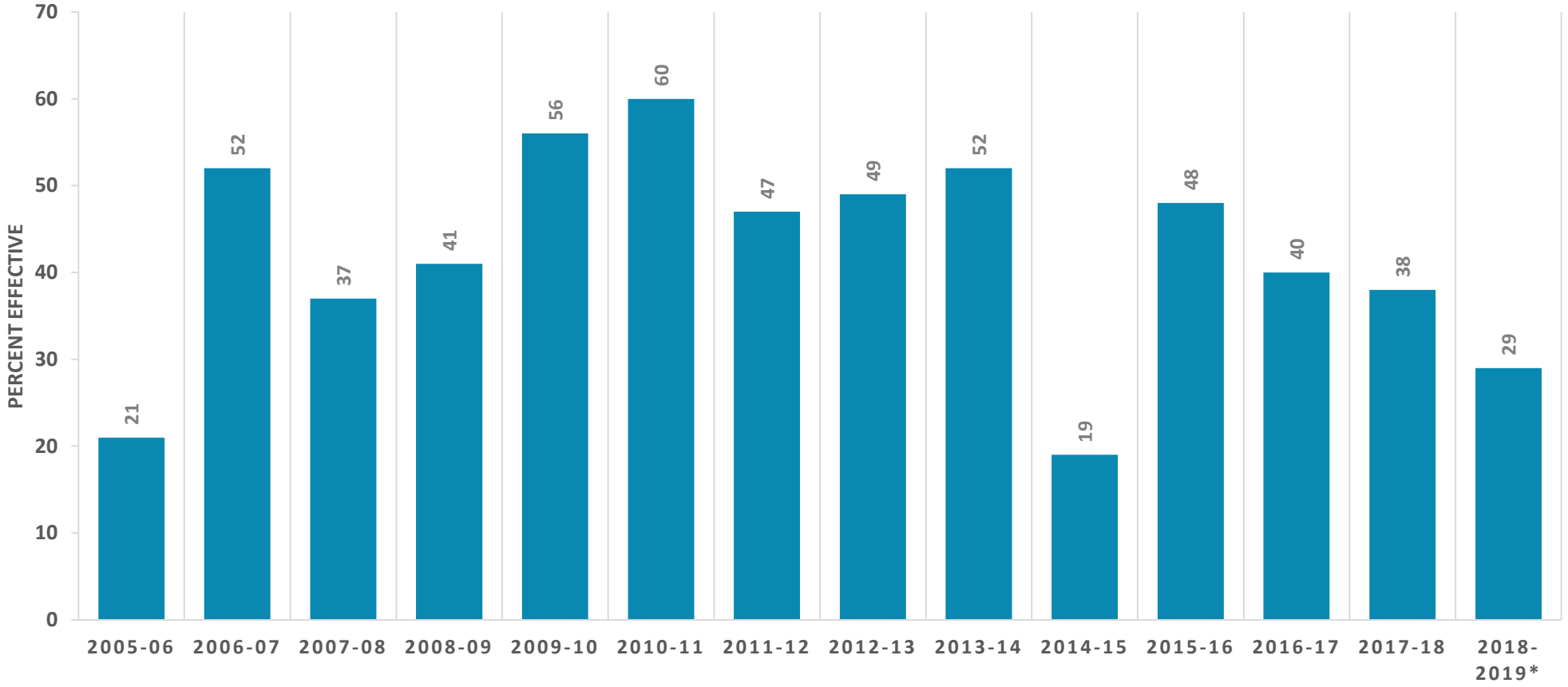
Protection by virus type and subtype was

37% against A(H1N1)

50% against influenza B viruses

Dawood FS, et al. *MMWR Morb Mortal Wkly Rep.* 2020;69(7):177-182.

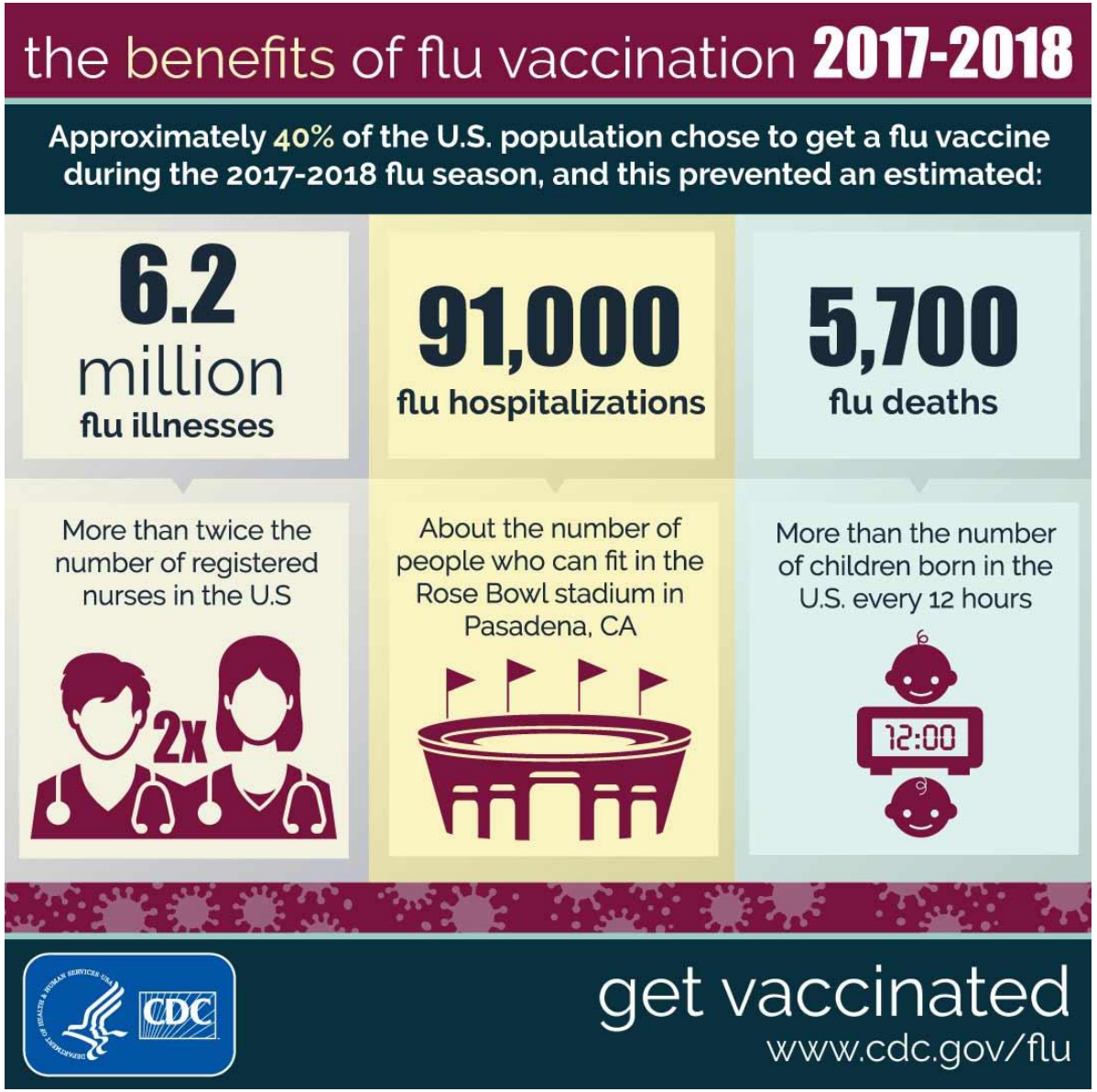
Effectiveness of Seasonal Influenza Vaccines from the 2005–2019 Influenza Seasons



*VE estimates for 2018-2019 were presented to the Advisory Committee on Immunization Practices (ACIP) on June 27, 2019.

CDC seasonal flu vaccine effectiveness studies. CDC. Reviewed February 21, 2020. Accessed May 11, 2020. cdc.gov/flu/vaccines-work/effectiveness-studies.htm; Published June 27, 2019. Accessed May 11, 2020. cdc.gov/vaccines/acip/meetings/downloads/slides-2019-06/flu-3-flannery-508.pdf

Why should I get the influenza vaccine?



2017-2018 estimated influenza illnesses, medical visits, and hospitalizations averted by vaccination in the United States. CDC. Reviewed November 22, 2019. Accessed May 11, 2020. cdc.gov/flu/vaccines-work/averted-estimates.htm

High-risk Populations for Developing Influenza-related Complications

- Hospitalized
- Younger age (6-59 months)
- Older age (≥50 years)
- Chronic diseases
  - Pulmonary
  - Cardiovascular
  - Renal
  - Hepatic
  - Neurologic
  - Hematologic
  - Metabolic
- Immunocompromised
- Pregnant or postpartum
- <19 years of age receiving long-term aspirin therapy
- Long-term care facility residents
- American Indians/Alaska Natives
- Obese patients (BMI ≥40 kg/m^2)

Grohskopf LA, et al. *MMWR Recomm Rep*. 2019;678(3):1-21.

Influenza-related Complications

- Most people will recover in a few days to less than 2 weeks
- Complications include:
  - Pneumonia
  - Myocarditis
  - Encephalitis
  - Myositis, rhabdomyolysis
  - Multi-organ failure
  - Worsening of chronic medical conditions

Flu symptoms & complications. CDC. Reviewed September 18, 2019. Accessed May 11, 2020. cdc.gov/flu/symptoms/symptoms.htm

What's New With Influenza in 2019-2020?

- All regular-dose and recombinant vaccines will be quadrivalent
  - No trivalent regular-dose influenza shots will be available this season
- Baloxavir marboxil (Xofluza)
- CDC and ACIP recommend that vaccination be offered by the end of October

Frequently asked influenza (flu) questions: 2019-2020 season. CDC. Reviewed January 17, 2020. Accessed May 11, 2020. cdc.gov/flu/season/faq-flu-season-2019-2020.htm

Influenza Recommendations

- Routine annual influenza vaccination is recommended for all persons aged ≥6 months who do not have contraindications

Influenza (flu). CDC. Reviewed March 24, 2020. Accessed May 11, 2020. cdc.gov/flu

Types of Vaccines

- **Inactivated influenza vaccine (IIV)**
  - Inactivated influenza vaccines, quadrivalent (IIV4s), standard dose
  - Inactivated influenza vaccine, quadrivalent (ccIIV4), standard dose, cell culture-based
  - Adjuvanted inactivated influenza vaccine, trivalent (aIIV3), standard dose
  - Inactivated influenza vaccine, trivalent (IIV3), high dose
- **Recombinant influenza vaccine, quadrivalent (RIV4)**
- **Live attenuated influenza vaccine, quadrivalent (LAIV4)**

Influenza vaccines—United States, 2019-20 influenza season. CDC. Reviewed August 22, 2019. Accessed May 11, 2020. cdc.gov/flu/professionals/vaccines.htm

Dosing Recommendations

- 6 months to ≤8 years of age
  - 2 doses if never been previously immunized with seasonal influenza vaccine (spaced 4 weeks apart, minimum interval)
  - 1 dose only if previously immunized with seasonal influenza vaccine
- ≥9 years
  - 1 dose
- Dosing
  - 6-35 months
    - 0.25 mL or 0.5 mL, depending on manufacturer
  - ≥36 months (0.5 mL)

Frequently asked influenza (flu) questions: 2019-2020 season. CDC. Reviewed January 17, 2020. Accessed May 11, 2020. cdc.gov/flu/season/faq-flu-season-2019-2020.htm

Vaccines Licensed for Age ≥65 Years Only

- Trivalent, high-dose influenza vaccine
  - Contains 60 µg of hemagglutinin (HA) per virus (4x HA content of standard dose IIV3)
  - Fluzone HD-IIV3 licensed ≥65 years of age
  - Observed to provide stronger immune response and have greater efficacy in persons aged ≥65 years
- Adjuvanted inactivated influenza vaccine (aIIV3)
  - FLUAD
  - Contains MF59, an oil-in-water adjuvant
  - Intended to provide better immune response (noninferior compared with standard dose)

Fluzone High-Dose vaccine. Prescribing information. Sanofi Pasteur Inc; 2019;
FLUAD. Prescribing information. Seqirus; 2019.

History of High-dose Influenza Vaccine

2009: FDA licensure
2014: Relative VE; efficacy of IIV high-dose vaccine compared with IIV 24.2%; long-term care population
2015: Data published to support cardiorespiratory events, all-cause hospitalizations, and pneumonia
2017: Rate of death after an influenza admission across 2 influenza seasons; first randomized, controlled, prospective nursing home study
2018: Retrospective observational study of Veterans Health Administration patients; randomized, controlled in high-risk cardiovascular patients

Fluzone High-Dose (influenza vaccine) fact sheet. Sanofi Pasteur. Published March 2018. Accessed May 11, 2020; Shay DK, et al. *J Infect Dis*. 2017;215(4):510-517; Gravenstein S, et al. *Lancet Resp Med*. 2017;5(9):738-746; Young-Xu Y, et al. *J Infect Dis*. 2018;217(11):1718-1727; Vandeny O, et al. *Am Heart J*. 2018;202:97-103.

Adjuvanted Vaccine

FDA licensure: 2015

Post marketing data

- The relative VE for influenza hospital encounters was:
  - 10.7 (95% CI, 7.5-13.7) with cell-cultured quadrivalent
  - 8.4 (95% CI, 6.6-10.1) with egg-based high-dose trivalent
  - 3.3 with egg-based adjuvanted
  - –0.1 with egg-based standard-dose trivalent

FLUAD. Prescribing information. Seqirus; 2019.

Comparative Effectiveness of High-dose versus Adjuvanted Influenza Vaccine

- Adults 65 years and older
- Retrospective cohort study
- Patients received HD-IIV3 or aIIV3 during the 2016-2017 and 2017-2018 seasons
- Included
  - 842,282 HD-IIV3 and 34,157 aIIV3 recipients for the 2016-2017 season
  - 1,058,638 HD-IIV3 and 189,636 aIIV3 recipients for the 2017-2018 season

van Aalst R, et al. *Vaccine*. 2020;38(2):372-379.

Results

		No	Rate	RR	Relative VE
2016-2017					
Respiratory disease	aIIV3	513	248 (156, 362)	1.09 (0.68, 1.61)	15% (–4.3%, 34%)
	HD	15, 169	272 (106, 581)		
Cardio-respiratory disease	aIIV3	1584	767 (605, 947)	1.07 (0.84, 1.32)	14% (4.0%, 25%)
	HD	45,738	819 (508, 1255)		
2017-2018					
Respiratory disease	aIIV3	3293	265 (217, 318)	15 (0.93, 1.39)	11% (1.0%, 20%)
	HD	21,260	304 (201, 443)		
Cardio-respiratory disease	aIIV3	9918	797 (723, 876)	12 (1.00, 1.24)	5% (–0.1%, 10%)
	HD	62,269	891 (726, 1083)		

van Aalst R, et al. *Vaccine*. 2020;38(2):372-379.

Live Attenuated Influenza Vaccine (LAIV)

- Inhalation vaccine for healthy patients aged 2-49 years
- American Academy of Pediatrics (AAP) did not recommend the nasal spray during the 2016-2017 and 2017-2018 influenza seasons because it did not work as well against influenza A/H1N1 strain during the 2013-2014 and 2015-2016 influenza seasons
- 2019-2020 available to use per CDC and AAP

Live, intranasal influenza VIS. CDC. Reviewed August 15, 2019. Accessed May 11, 2020. cdc.gov/vaccines/hcp/vis/vis-statements/flulive.html; AAP updates vaccine recommendations for 2019-2020 flu season. American Academy of Pediatrics. Published March 14, 2019. Accessed May 11, 2020. aap.org/en-us/about-the-aap/aap-press-room/Pages/AAP-Updates-Vaccine-Recommendations-for-2019-2020-Flu-Season.aspx

Recombinant HA Influenza Vaccine

- Trivalent or quadrivalent influenza vaccine
- Approved for use in adults ≥18 years
- Produced differently and has a slightly shorter shelf-life than most influenza vaccines
- Contains no egg

Flublok. Prescribing information. Protein Sciences Corporation; 2019.

Efficacy of Recombinant Influenza Vaccine in Adults ≥50 Years

- Randomized, double-blind, multicenter trial
- RIV4 versus standard-dose IIV4
- 9003 participants ≥50 years were enrolled
- RIV4 recipients: attack rate was 2.2%
- IIV4 recipients: attack rate was 3.1%
- Influenza-like illness was 30% lower with RIV4 than with IIV4 ($P = 0.006$)

Dunkle LM, et al. *N Engl J Med*. 2017;376(25):2427-2436.

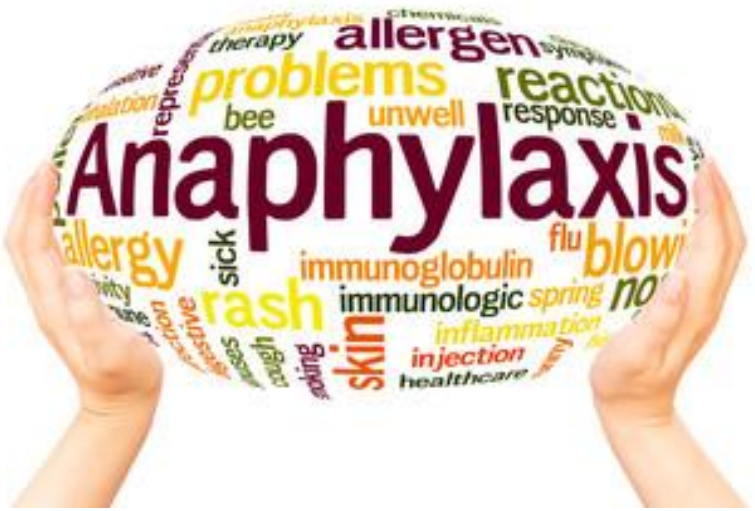
Differences Among Vaccines

Vaccine type	Live or inactivated	Age indication	Administer with other chronic diseases
Inactivated influenza vaccine	Inactivated	≥6 months, depending on manufacturer	Yes
High-dose inactivated influenza vaccine	Inactivated	≥65 years	Yes
Adjuvanted inactivated influenza vaccine	Inactivated	≥65 years	Yes
Recombinant HA influenza vaccine	Inactivated	≥18 years	Yes
Live-attenuated influenza vaccine	Live	2-49 years	No

Influenza vaccines—United States, 2019-20 influenza season. CDC. Reviewed August 22, 2019. Accessed May 11, 2020. cdc.gov/flu/professionals/vaccines.htm; Fluzone High-Dose vaccine. Prescribing information. Sanofi Pasteur Inc; 2019; Flublok. Prescribing information. Protein Sciences Corporation; 2019; FLUAD. Prescribing information. Seqirus; 2019.

Contraindications to IIV Administration

- **Contraindications**
  - Severe (life-threatening) allergies
    - To eggs*
    - To any vaccine component
    - To a previous dose of influenza vaccine



- **Precautions**
  - Patients experiencing moderate or severe acute illness (with or without fever)
  - GBS <6 weeks after a previous dose of influenza vaccine

*In prescribing information only.
GBS, Guillain-Barre syndrome.

Contraindications and precautions. CDC. Reviewed February 12, 2020. Accessed May 11, 2020. cdc.gov/vaccines/hcp/acip-recs/general-recs/contraindications.html

Egg Allergy

- Only hives: any licensed and recommended influenza vaccine that is otherwise appropriate for the recipient's age and health status may be used
- Reactions to egg involving symptoms other than hives, such as angioedema, respiratory distress, lightheadedness, or recurrent emesis; or who required epinephrine or another emergency medical intervention: any licensed and recommended influenza vaccine administered in an inpatient or outpatient medical setting
- A previous severe allergic reaction to influenza vaccine, regardless of the component suspected of being responsible for the reaction, is a contraindication to future receipt of the vaccine

A recent CDC study found the rate of anaphylaxis after all vaccines is 1.31 per 1 million vaccine doses given.

Flu vaccine and people with egg allergies. CDC. Reviewed November 19, 2020. Accessed May 11, 2020. cdc.gov/flu/prevent/egg-allergies.htm

Misconceptions About Influenza Vaccinations

Influenza is not serious, so I don’t need the vaccine.

The influenza vaccine can give me influenza.

The influenza vaccine can cause severe adverse effects.

I have had the vaccine and still gotten influenza, so it doesn’t work.

I am pregnant, so I shouldn’t get the influenza vaccine.

5 myths about the flu vaccine. WHO. Accessed May 11, 2020. who.int/influenza/spotlight/5-myths-about-the-flu-vaccine

Communication Is Key

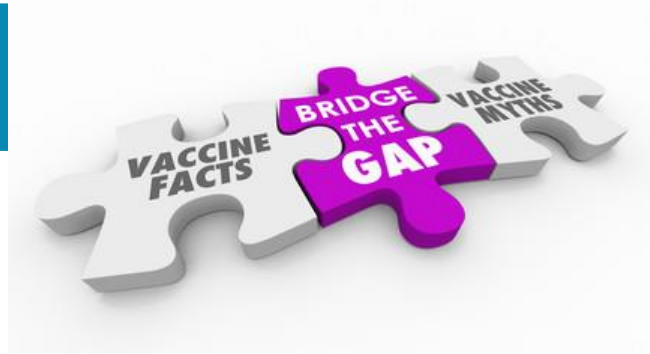
Listen to the patient's concerns and acknowledge them in a nonconfrontational manner

Discuss the benefits of vaccines and the possibility of adverse effects

Stress the number of lives saved by immunization as a positive approach rather than focusing on the number of deaths from not immunizing

Ask questions…

- "Do you have any cultural, religious, or personal belief regarding immunization?"
- "Has your child or any child you know had a serious adverse effect after an immunization?"
- "Do you have any vaccine safety concerns?"
- "What vaccine safety information can I provide?"



Addressing common concerns of vaccine-hesitant parents. American Academy of Pediatrics. Updated July 2013. Accessed May 11, 2020. aap.org/en-us/Documents/immunization_vaccine-hesitant%20parent_final.pdf

The Role of the Pharmacist

- Increasing patient education about vaccines: a strong recommendation is KEY!
- Encourage proper hygiene and infection prevention.
- Expanding immunization services with standing orders
- Reminder and recall interventions
- Increasing provider education to avoid missed opportunities
- Reducing out-of-pocket costs for adults for other vaccines
- Expanding access

Conclusion

- Pharmacists play an important role in identifying patients at high risk
- Pharmacists can assess adherence and identify barriers that may prevent patients from obtaining appropriate immunizations
- Pharmacists can increase adherence to immunization schedules via patient education
- Pharmacists can help bring awareness regarding the importance of obtaining annual influenza vaccine

Additional Resources

Review the websites below and stay current on information.

Resource	Website
Centers for Disease Control and Prevention	cdc.gov/vaccines/default.htm
Immunization Action Coalition	immunize.org
American Pharmacists Association Immunization Center	pharmacist.com/immunization-center
Morbidity and Mortality Weekly Report (MMWR)	cdc.gov/mmwr

Exploring the Clinical Benefits of Antiviral Therapies to Improve Patient Outcomes and Reduce Influenza-Related Complications

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This activity is approved for 0.75 contact hours (0.075 CEU) under the ACPE universal activity number 0290-0000-20-084-L01-P. The activity is available for CE credit on May 16, 2020.

Activity Type: Knowledge

Fee: Free

This activity is supported by an educational grant from Genentech.

Educational Objectives

At the completion of this activity, participants will be able to:

- Understand the pathophysiology, etiology, and epidemiology of the virus as well as patients who are at greater risk for influenza-related complications
- Recognize prevention and treatment strategies and guidelines for treating influenza including current and recently approved antivirals
- Discuss the role of the pharmacist in treating and preventing influenza

Influenza

About flu. Centers for Disease Control and Prevention (CDC). Reviewed September 5, 2019. Accessed May 11, 2020. cdc.gov/flu/about/index.html

Influenza

- A viral, contagious respiratory illness that spreads through droplets
- Influenza can cause mild to severe illness and at times can lead to death
- Influenza usually comes on suddenly
- Most contagious in the first 3-4 days after the illness begins
- Symptoms can include fever (or feeling feverish), chills, cough, sore throat, runny nose, body aches, headache, and fatigue

Key facts about influenza (flu). CDC. Reviewed September 13, 2019. Accessed May 11, 2020. cdc.gov/flu/about/keyfacts.htm

CDC estimates* that, from **October 1, 2019**, through **April 4, 2020**, there have been:

39,000,000 – 56,000,000
flu illnesses

18,000,000 – 26,000,000
flu medical visits

410,000 – 740,000
flu hospitalizations

24,000 – 62,000
flu deaths

*Because influenza surveillance does not capture all cases of flu that occur in the United States, the CDC provides these estimated ranges to better reflect the larger burden of influenza.

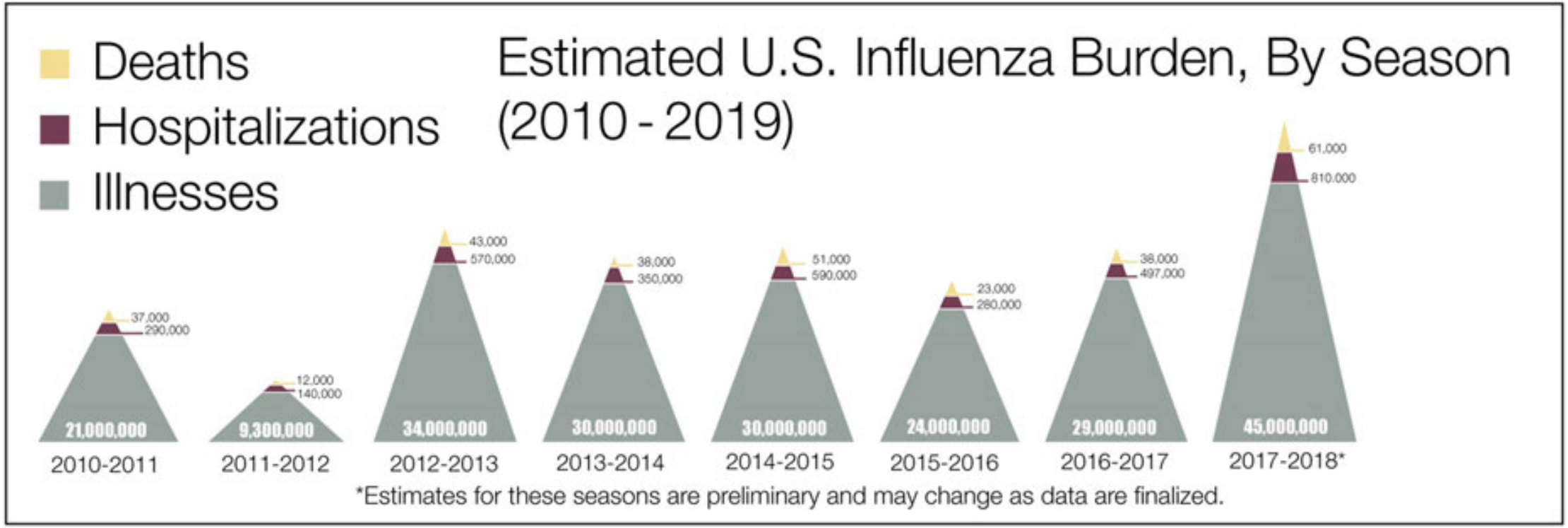
About flu. CDC. Reviewed September 5, 2019. Accessed May 11, 2020. cdc.gov/flu/about/index.html; 2019-2020 US flu season: preliminary burden estimates. Reviewed April 17, 2020. Accessed May 11, 2020. cdc.gov/flu/about/burden/preliminary-in-season-estimates.htm

Estimated Influenza Disease Burden 2018-2019 Influenza Season

Age group	Symptomatic illnesses	Medical visits	Hospitalizations	Deaths
0-4 y	3,633,104	2,434,180	25,328	266
5-17 y	7,663,310	3,984,921	21,012	211
18-49 y	11,913,203	4,407,885	66,869	2450
50-64 y	9,238,038	3,972,356	97,967	5676
≥65 y	3,073,227	1,721,007	279,384	25,555
All ages	35,520,883	16,520,350	490,561	34,157

Estimated influenza illnesses, medical visits, hospitalizations, and deaths in the United States—2018-2019 influenza season. CDC. Reviewed February 28, 2020. Accessed May 11, 2020. cdc.gov/flu/about/burden/2018-2019.html

Estimated US Influenza Burden, By Season



Disease burden of influenza. CDC. Reviewed January 10, 2020. Accessed May 11, 2020. cdc.gov/flu/about/burden/index.html

High-Risk Populations for Developing Flu-Related Complications

- Hospitalized
- Younger age (6-59 months)
- Older age (≥50 years)
- Chronic diseases
  - Pulmonary
  - Cardiovascular
  - Renal
  - Hepatic
  - Neurologic
  - Hematologic
  - Metabolic
- Immunocompromised
- Pregnant or postpartum
- <19 years of age receiving long-term aspirin therapy
- Long-term care facility residents
- Native Americans/Alaska Natives
- Obese patients (BMI ≥40 kg/m^2)

Grohskopf LA, et al. *MMWR Recomm Rep*. 2019;678(3):1-21.

CDC Says “Take 3” Actions to Fight Influenza

1. Take time to get an influenza vaccine.
2. Take everyday preventive actions to stop the spread of germs.
3. Take influenza antiviral drugs if your doctor prescribes them.

CDC says “take 3” actions to fight flu. CDC. Reviewed October 19, 2019. Accessed May 11, 2020. cdc.gov/flu/prevent/preventing.htm

Antiviral Treatment

Recommend early!

Do NOT wait for laboratory confirmation of influenza to start treatment!

Acute uncomplicated influenza outpatient = neuraminidase inhibitors or baloxavir

Hospitalized patients = oseltamivir

Influenza antiviral medications: summary for clinicians. CDC. Reviewed January 15, 2020. Accessed May 11, 2020. cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

Testing for Influenza

Advantages

Produces quick results in less than approximately 15 minutes; simple to perform

Some RIDTs are cleared for office/bedside use; RIDTs that have been CLIA waived can be used in settings that include point-of-care

Disadvantages

Suboptimal test sensitivity; false negative results are common, especially when influenza activity is high

Sensitivity of RIDTs to detect influenza B viral antigens is lower than for detection of influenza A viral antigens

Although specificity is high, false positive results can also occur, especially during times when influenza activity is low

CLIA, clinical laboratory improvement amendments; RIDT, rapid influenza diagnostic test.

Rapid influenza diagnostic tests. CDC. Reviewed October 25, 2016. Accessed May 11, 2020. cdc.gov/flu/professionals/diagnosis/clinician_guidance_ridt.htm

Accuracy and Minimizing False Results

- Many factors can influence the accuracy of RIDTs, including:
  - Clinical signs and symptoms consistent with influenza
  - Prevalence of influenza activity in the population tested
  - Time from illness onset to collection of respiratory specimens for testing
  - Type of respiratory specimen tested
  - Accuracy of the test compared to a reference test ("gold standard" = RT-PCR or viral culture)

- Collect specimens as early in the illness as possible (ideally <4 days from illness onset)
- Follow manufacturer's instructions
- Follow up negative results with confirmatory tests (RT-PCR or viral culture) if a laboratory-confirmed influenza diagnosis is desired or **TREAT**!

RT-PCR, reverse transcription-polymerase chain reaction.

Rapid influenza diagnostic tests. CDC. Reviewed October 25, 2016. Accessed May 11, 2020. cdc.gov/flu/professionals/diagnosis/clinician_guidance_ridt.htm

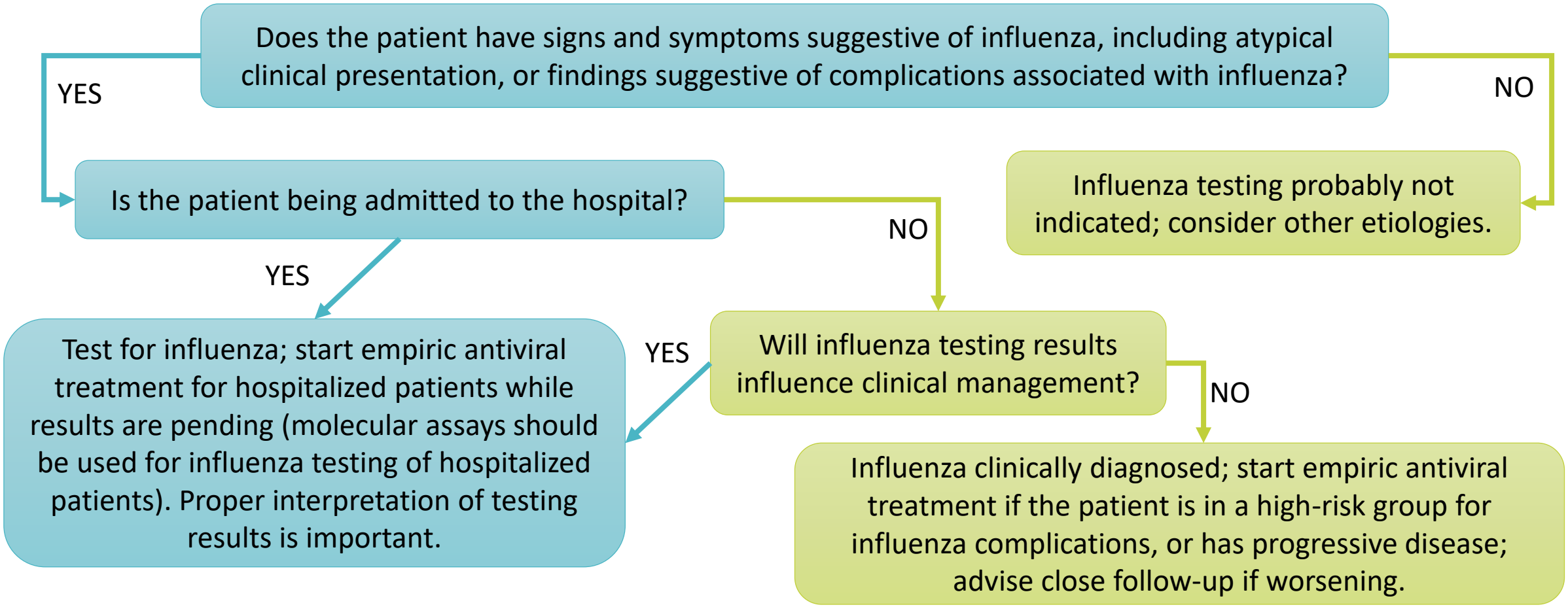
RIDTs

- Negative results do not exclude influenza virus infection in patients with signs and symptoms suggestive of influenza

- Therefore, if clinically indicated, antiviral treatment should not be withheld from patients with suspected influenza, even if they test negative!

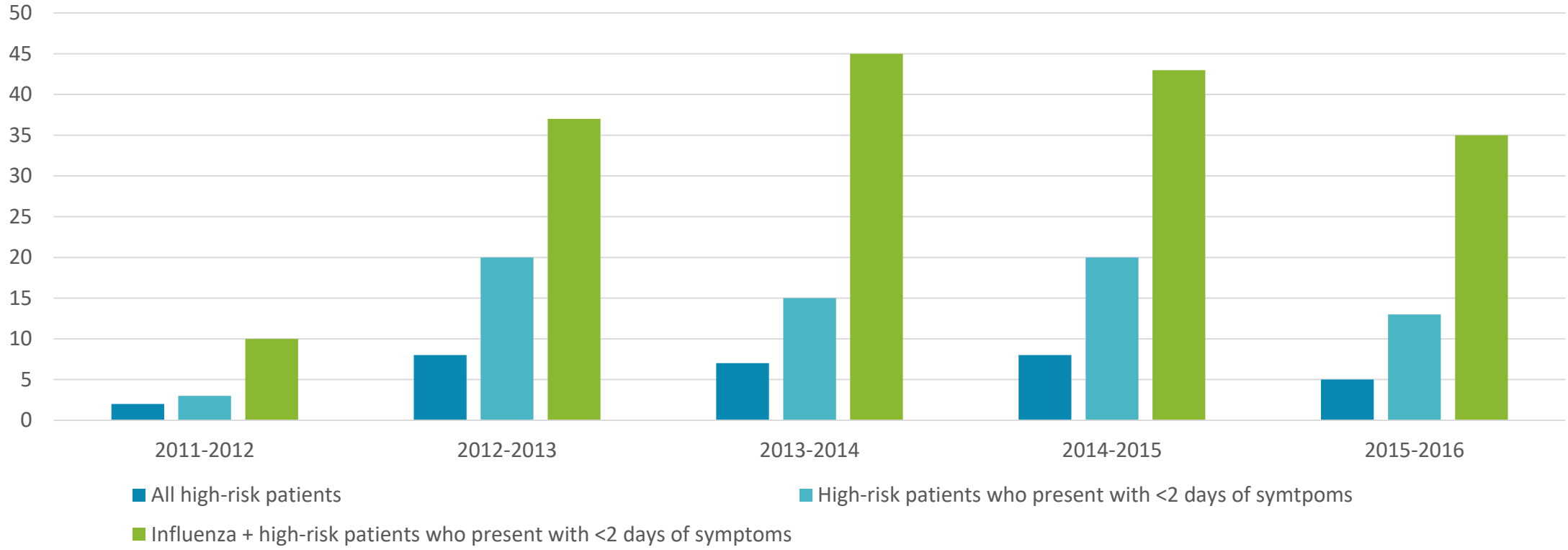
Rapid influenza diagnostic tests. CDC. Reviewed October 25, 2016. Accessed May 11, 2020. cdc.gov/flu/professionals/diagnosis/clinician_guidance_ridt.htm

Treatment Algorithm



Influenza antiviral medications: summary for clinicians. CDC. Reviewed January 15, 2020. Accessed May 11, 2020. cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

Proportion of High-Risk Outpatients With an Acute Respiratory Illness Prescribed Antiviral Treatment



Adapted from Stewart RJ, et al. *Clin Infect Dis.* 2018;66(7):1035-1041.

Remember the High-Risk Populations

- Hospitalized
- Younger age (6-59 months)
- Older age (≥50 years)
- Chronic diseases
  - Pulmonary
  - Cardiovascular
  - Renal
  - Hepatic
  - Neurologic
  - Hematologic
  - Metabolic
- Immunocompromised
- Pregnant or postpartum
- <19 years old receiving long-term aspirin therapy
- Long-term care facility residents
- American Indians/Alaska Natives
- Obese patients (BMI ≥40 kg/m^2)

Grohskopf LA, et al. *MMWR Recomm Rep*. 2019;678(3):1-21.

Antiviral Medications

Antiviral Medications

Depending on the medication, antivirals can be used to **prevent** or **treat** influenza

3 classes of medication are approved by the FDA:

1. **Adamantanes**
   - Amantadine and rimantadine
2. **Neuraminidase inhibitors**
   - Oral oseltamivir phosphate (Tamiflu), inhaled zanamivir (Relenza), and intravenous peramivir (Rapivab)
3. **Cap-dependent endonuclease inhibitor**
   - Oral baloxavir marboxil (Xofluza)

Influenza antiviral medications: summary for clinicians. CDC. Reviewed January 15, 2020. Accessed May 11, 2020. cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

Adamantanes

- Medication names: amantadine and rimantadine
- Mechanism of action (MOA): targets the M2 ion channel protein of the influenza A viruses
- They do not protect against influenza B
- There are high levels of resistance (>99%) to adamantanes among circulating influenza A(H3N2) and influenza A(H1N1)pdm09 (“2009 H1N1”) viruses
- Based on these data, CDC does not recommend amantadine and rimantadine for treatment or prevention for the 2019–2020 influenza season

Influenza antiviral medications: summary for clinicians. CDC. Reviewed January 15, 2020. Accessed May 11, 2020. cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

Neuraminidase Inhibitors

Medication names: oral oseltamivir phosphate, intravenous peramivir, and inhaled zanamivir

MOA: inhibitor of influenza virus neuraminidase affecting release of viral particles from the plasma membrane of infected cells

Tamiflu. Prescribing information. Genentech; 2019; Relenza. Prescribing information. GlaxoSmithKline; 2018; Rapivab. Prescribing information. BioCryst Pharmaceuticals; 2018.

Oral Oseltamivir Phosphate

Dose	Age	Adverse effects	Warnings and precautions

• Treatment: 75 mg twice daily (aged ≥13 years) or weight-based (pediatric) twice daily for 5 days
• Prevention: 75 mg once daily (aged ≥13 years) or weight-based (pediatric) once daily for 10 days
• Initiate treatment within 48 hours of symptom onset
• Requires dose adjustment for renal dysfunction
	• FDA approved
	  • Treatment: aged ≥2 weeks
	  • Prevention: aged ≥1 year
	• CDC and the American Academy of Pediatrics recommend
	  • Treatment: any age
	  • Prevention: aged ≥3 months
		• Nausea, vomiting, headache
		• Postmarketing reports of serious skin reactions and neuropsychiatric events
			• Serious skin/ hypersensitivity reactions
			• Neuropsychiatric events
			• Risk of bacterial infections
			• Fructose intolerance in patients with hereditary fructose intolerance

Tamiflu. Prescribing information. Genentech; 2019; Influenza antiviral medications: summary for clinicians. CDC. Reviewed January 15, 2020. Accessed May 11, 2020. cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

Intravenous Peramivir

Dose	Age	Adverse effects	Warnings and precautions
• Treatment: 600 mg intravenous infusion over 15-30 minutes as 1 dose (aged ≥13 years); pediatric based on weight • Prevention: not recommended • Initiate treatment within 48 hours of symptoms	• FDA approved • Treatment: aged ≥2 years	• Diarrhea • Postmarketing reports of serious skin reactions and neuropsychiatric events	• Skin reactions • Neuropsychiatric events • Risk of bacterial infections

Rapivab. Prescribing information. BioCryst Pharmaceuticals; 2017.

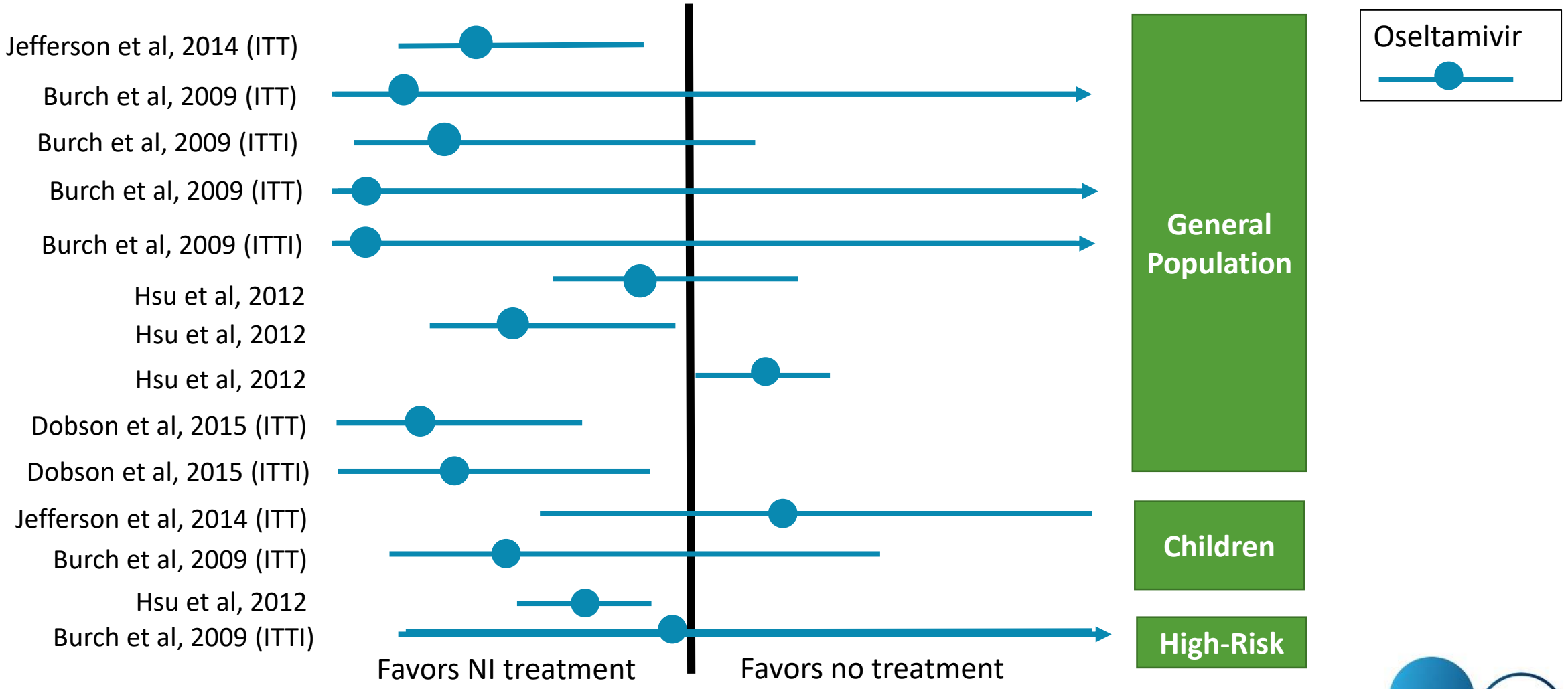
Inhaled Zanamivir

Dose	Age	Adverse effects	Warnings and precautions

• Treatment: 10 mg twice daily for 5 days
• Prevention: 10 mg once daily for 10 days (household setting) or 28 days (community outbreaks)
• Initiate treatment within 48 hours of symptoms
	• FDA approved
	  • Treatment: aged ≥7 years
	  • Prevention: aged ≥5 years
		• Sinusitis
		• Dizziness
		• Postmarketing reports of serious skin reactions, neuropsychiatric events, and respiratory and cardiac events
			• Bronchospasms: not recommended in airway disease
			• Neuropsychiatric events
			• High-risk underlying medical conditions: safety and efficacy were not established

Relenza. Prescribing information. GlaxoSmithKline; 2018.

The Odds or Risk of Pneumonia



Adapted from Doll MK, et al. *J Antimicrob Chemother*. 2017;72(1):2990-3007.

Cap-dependent Endonuclease Inhibitor

Medication name: baloxavir marboxil

MOA: inhibits the endonuclease activity of the polymerase acidic (PA) protein, preventing viral gene transcription and replication

Xofluza. Prescribing information. Genentech; 2019.

Oral Baloxavir Marboxil

Dose

- 40 kg - <80 kg: 40 mg once (2 tablets)
- ≥80 kg: 80 mg once (2 tablets)
- **Avoid dairy, calcium-fortified beverages, polyvalent cation-containing laxatives, antacids, and oral supplements**
- Initiate treatment within 48 hours of symptoms

Age

- Treatment: aged ≥12 years, NDA submitted for 1 to <12 years

Adverse effects

- Diarrhea, bronchitis, sinusitis, headache, and nausea

Warnings and precautions

- Risk of bacterial infections, hypersensitivity

Xofluza. Prescribing information. Genentech; 2019. Roche Investor Update. Accessed May 11, 2020. roche.com/investors/updates/inv-update-2020-03-27.htm

Baloxavir Marboxil for Uncomplicated Influenza in Adults and Adolescents (CAPSTONE-1)

1436 participants aged 12-64 years weighing ≤40 kg in the United States and Japan

Adults aged 20-64 years received:

- Baloxavir single oral dose
- Placebo single oral dose
- Oseltamivir twice daily

Placebo was given to match the oseltamivir group dosing in all groups

Regimen was 5 days

Adolescent participants aged 12 to <20 years received

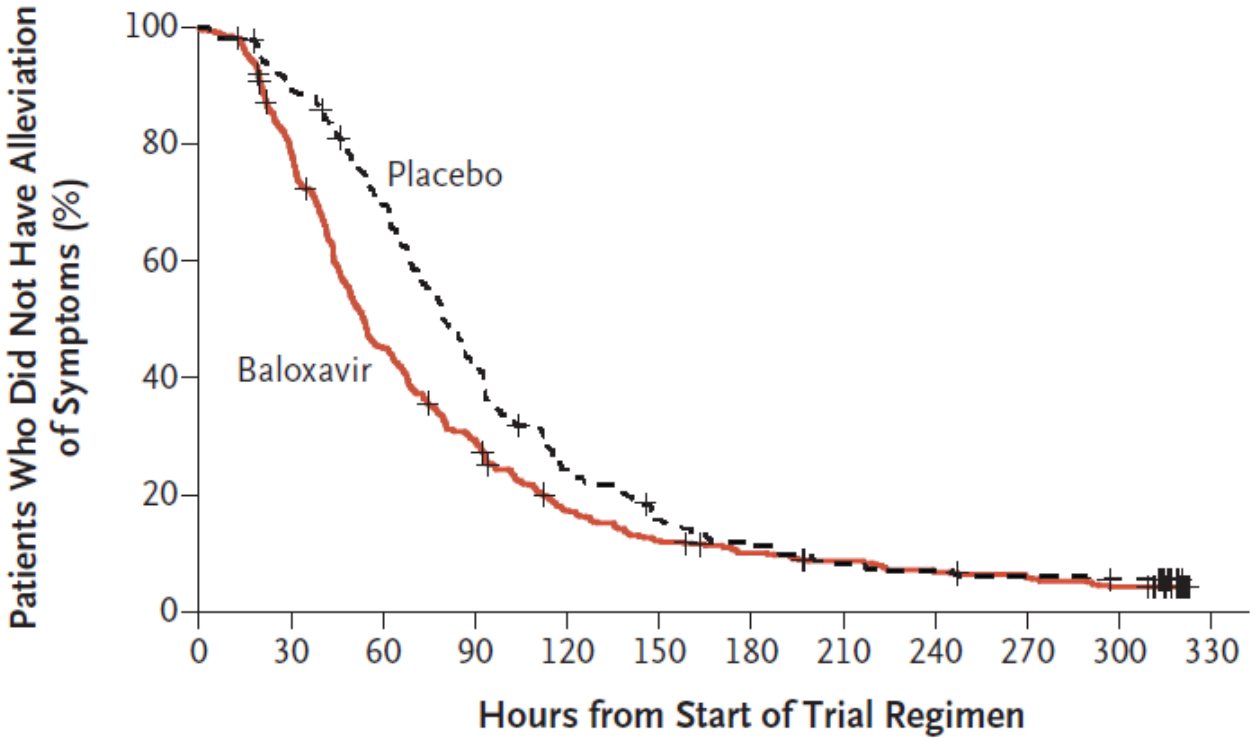
- Baloxavir single oral dose
- Placebo single oral dose

Influenza A/H3N2 was the predominant strain (90%), followed by influenza B (9%), and influenza A/H1N1 (2%)

Hayden FG, et al. *N Engl J Med*. 2018;379(10):913-923.

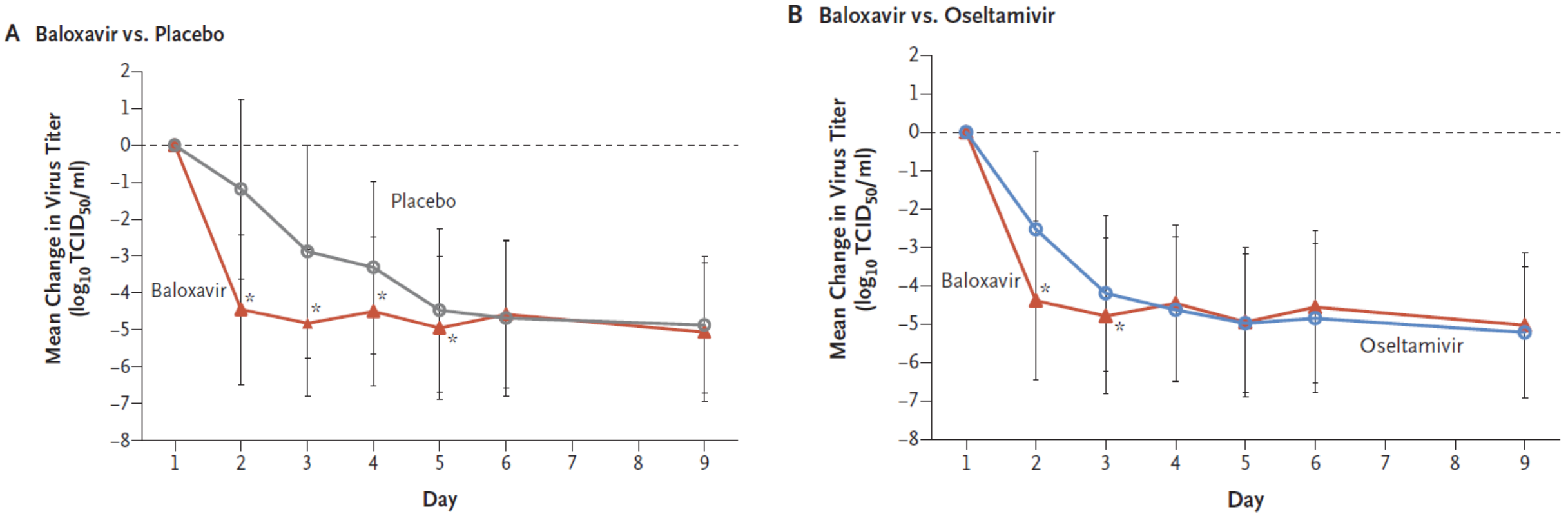
Baloxavir Marboxil for Uncomplicated Influenza in Adults and Adolescents

- Primary end point: time to alleviation of symptoms
- Time to alleviation of symptoms after single dose in subjects aged ≥12 years with acute uncomplicated influenza was 54 hours in the baloxavir group compared with 80 hours in the placebo group
- There was no difference in the time to alleviation of symptoms between subjects who received baloxavir (54 hours) and those who received oseltamivir (54 hours)



Hayden FG, et al. *N Engl J Med*. 2018;379(10):913-923; Reprinted from *New England Journal of Medicine*; Hayden FG, Sugaya N, Hirotsu N, et al; Baloxavir Marboxil for Uncomplicated Influenza in Adults and Adolescents; 379, 919 © 2019 Massachusetts Medical Society.

Baloxavir: Reduction in Viral Load



Reprinted from *New England Journal of Medicine*; Hayden FG, Sugaya N, Hirotsu N, et al; Baloxavir Marboxil for Uncomplicated Influenza in Adults and Adolescents; 379, 920 © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Phase 3 Trial of Baloxavir Marboxil in High-Risk Influenza Patients (CAPSTONE-2)

- 2184 participants
- Inclusion criteria:
  - Age ≥12 years, fever + influenza symptoms of ≤48-hour duration, and presence of ≥1 higher risk factor adapted from CDC criteria
- Baloxavir single oral dose, placebo single oral dose, or oseltamivir twice daily; matching placebos were also given
- Primary end point: time to improvement in influenza symptoms (TTIIS)
- Results: TTIIS was significantly shorter with baloxavir compared with placebo (median, 73.2 hours vs 102.3 hours; *P* <0.0001) and numerically shorter than oseltamivir (median, 81.0 hours; *P* = 0.8347)

Ison MG, et al. Phase 3 trial of baloxavir marboxil in high risk influenza patients (CAPSTONE-2 Study). Presented at: IDWeek 2018; October 3-7, 2018; San Francisco, CA. idsa.confex.com/idsa/2018/webprogram/Paper74204.html

1-dose Baloxavir in Children (MINISTONE-2)

- Phase 3, multicenter, randomized, double-blind study
- Evaluated the safety, pharmacokinetics, and efficacy of 1 dose of baloxavir compared with oseltamivir in otherwise healthy children aged 1 to ≤12 years with influenza
- Patients received 1 dose of baloxavir (2 mg/kg for patients <20 kg or 40 mg for patients ≥20 kg) or oseltamivir twice daily over 5 days
- Primary end point was the proportion of patients with adverse effects (AEs) or severe AEs up to study day 29
- Secondary end points included pharmacokinetics, time to alleviation of influenza signs and symptoms, and duration of symptoms, including fever

Roche presents positive phase III study results for one-dose Xofluza in children with flu. News release. Roche; September 2, 2019. Accessed May 11, 2020. www.roche.com/media/releases/med-cor-2019-09-02.htm

1-dose Baloxavir in Children (MINISTONE-2)

- In baloxavir-treated participants, 46.1% experienced ≥1 treatment-emergent AE compared with 53.4% in the oseltamivir arm
- Efficacy of baloxavir is comparable to oseltamivir
- Baloxavir reduced the length of time of viral shedding by ≥2 days compared with oseltamivir (median time of 24.2 hours vs 75.8 hours, respectively)

Roche presents positive phase III study results for one-dose Xofluza in children with flu. News release. Roche; September 2, 2019. Accessed May 11, 2020. www.roche.com/media/releases/med-cor-2019-09-02.htm

Baloxavir in Prevention (BLOCKSTONE)

- Phase 3, randomized, placebo-controlled, postexposure prophylaxis study
- Single dose of baloxavir compared with placebo in household members (adults and children) in Japan living with someone with an influenza infection confirmed by a RIDT during the 2018-2019 flu season in Japan
- Received a single dose of baloxavir (dose according to body weight) or placebo
- Primary end point of the study was to evaluate the proportion of participants who tested positive for the influenza virus and had fever as well as ≥1 respiratory symptom(s) between days 1 and 10
- The proportion of household members who became infected with influenza was significantly lower in the baloxavir group (1.9% vs 13.6%; *P* <0.0001)
- AEs were 22.2% in the baloxavir group compared with 20.5% in the placebo group

Roche presents positive phase III study results for one-dose Xofluza in children with flu. News release. Roche; September 2, 2019. Accessed May 11, 2020. www.roche.com/media/releases/med-cor-2019-09-02.htm

Baloxavir Safety

- Institute for Safe Medication Practices (ISMP) 2019
  - 50 cases of anaphylactic shock, 7 fatal
    - Company confirmed that it has also seen a safety signal for hypersensitivity, including anaphylaxis, and has been closely monitoring these events
  - CNS symptoms similar to oseltamivir (eg, altered consciousness, delirium, abnormal behavior, loss of consciousness, seizures)
  - GI symptoms (eg, colitis, blood in the stool, vomiting, diarrhea)

CAPSTONE-2 AEs (%)
Diarrhea (3%)
Bronchitis (3%)
Nausea (2%)
Sinusitis (2%)
Headache (1%)

QuarterWatch (includes new data from Quarter 4, 2018 and Quarter 1, 2019) focus on four new drugs: Xofluza, Aimovig, Ajovy, and Emgality. News release. ISMP; August 15, 2019. Accessed May 11, 2020. ismp.org/resources/quarterwatchtm-includes-new-data-quarter-4-2018-and-quarter-1-2019-focus-four-new-drugs; Roche announces FDA approval of Xofluza (baloxavir marboxil) for people at high risk of developing influenza-related complications. News release. Roche; October 18, 2019. Accessed May 11, 2020. roche.com/media/releases/med-cor-2019-10-18.htm

Summary

Antiviral agent	Use	CDC-recommended age	Not recommended for use in
Oral oseltamivir	Treatment	Any age	N/A
	Prophylaxis	≥3 mo	N/A
Inhaled zanamivir	Treatment	≥7 yrs	People with underlying respiratory disease (eg, asthma, COPD)
	Prophylaxis	≥5 yrs	People with underlying respiratory disease (eg, asthma, COPD)
Intravenous peramivir	Treatment	≥2 yrs	N/A
	Prophylaxis	Not recommended	N/A
Oral baloxavir	Treatment	≥12 yrs	N/A
	Prophylaxis	Not recommended	N/A

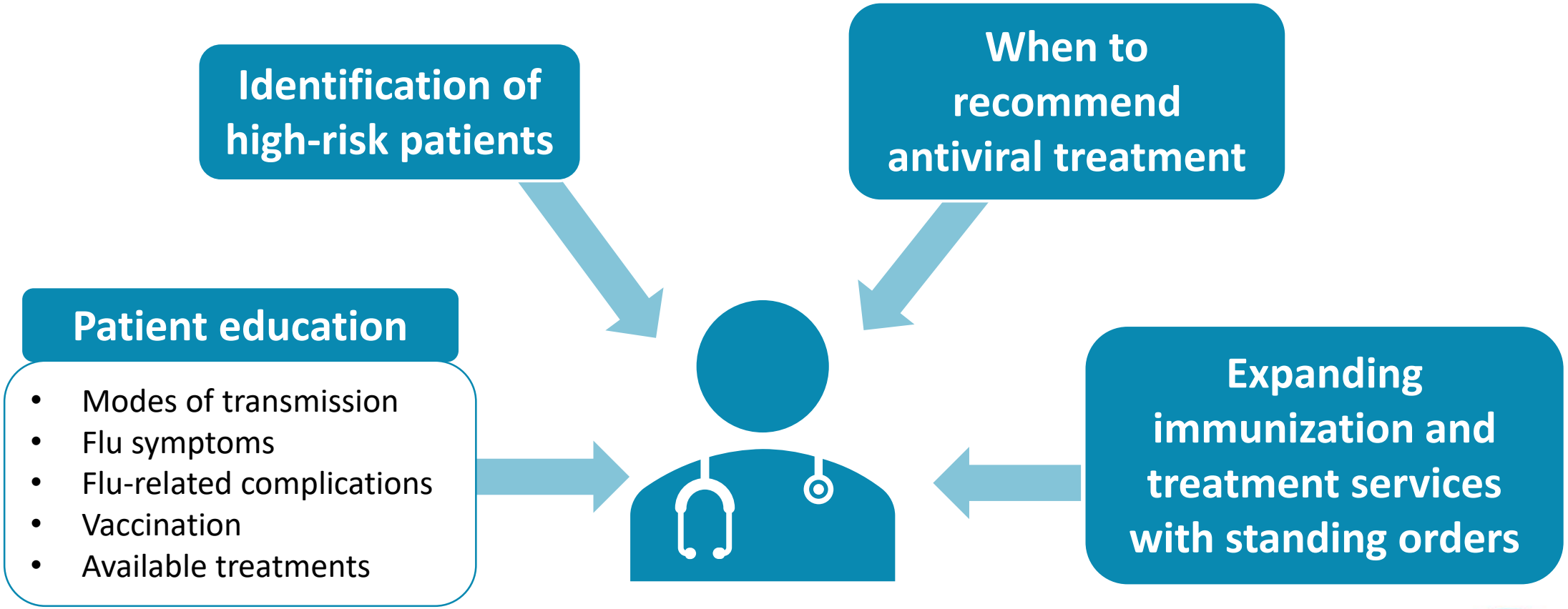
Influenza antiviral medications: summary for clinicians. CDC. Reviewed January 15, 2020. Accessed May 11, 2020. cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

Treatment Recommendations

	Neuraminidase inhibitors	Baloxavir	Not recommended
Outpatient, acute uncomplicated influenza	X	X	
Pregnant or breastfeeding	Oseltamivir		
Outpatient, severe or complicated illness with suspected or confirmed influenza	Oseltamivir		
Hospitalized patients with suspected or confirmed influenza	Oseltamivir		Baloxavir Inhaled zanamivir
Gastric stasis, malabsorption, or GI bleeding	Intravenous peramivir		

Influenza antiviral medications: summary for clinicians. CDC. Reviewed January 15, 2020. Accessed May 11, 2020. cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

The Role of the Pharmacist



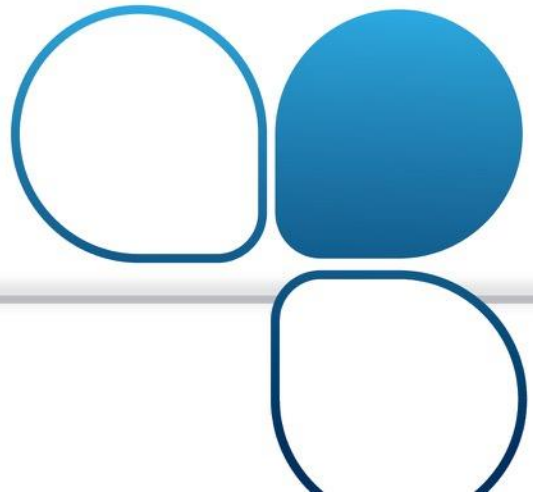
Conclusion

- Inpatient and outpatient pharmacists can identify high-risk patients
- Pharmacists can reduce complications of influenza by making a recommendation to vaccinate against influenza
- Pharmacists can encourage seeking antiviral therapy, especially in high-risk patients
- Pharmacists can counsel on AEs when taking antiviral therapies

Additional Resources

Centers for Disease Control and Prevention	cdc.gov/flu
Infectious Diseases Society of America	idsociety.org/practice-guideline/influenza
***Morbidity and Mortality Weekly Report* (MMWR)**	cdc.gov/mmwr/index.html
Immunization Action Coalition	immunize.org
American Pharmacists Association (APhA) Immunization Center	pharmacist.com/immunization-center

Use of Fixed-Ratio GLP-1 Receptor Agonist and Basal Insulin Combination Therapies to Safely and Effectively Meet Glycemic Targets



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Activity Type: Knowledge

Fee: Free

Educational Objectives

At the completion of this activity, participants will be able to:

- Review factors that may contribute to clinical inertia in patients with type 2 diabetes (T2D) and the negative impact clinical inertia may have on postponement of treatment intensification when warranted
- Recognize the most recent clinical data, the complementary mechanisms of action, the expanded indications, and essential safety and efficacy data associated with fixed-ratio combinations of basal insulin and glucagon-like peptide-1 receptor agonists in patients with T2D
- Detail the role of the pharmacist in recognizing and addressing clinical inertia and in recommending novel combination therapies to improve patient outcomes

The Latest Incidence Report

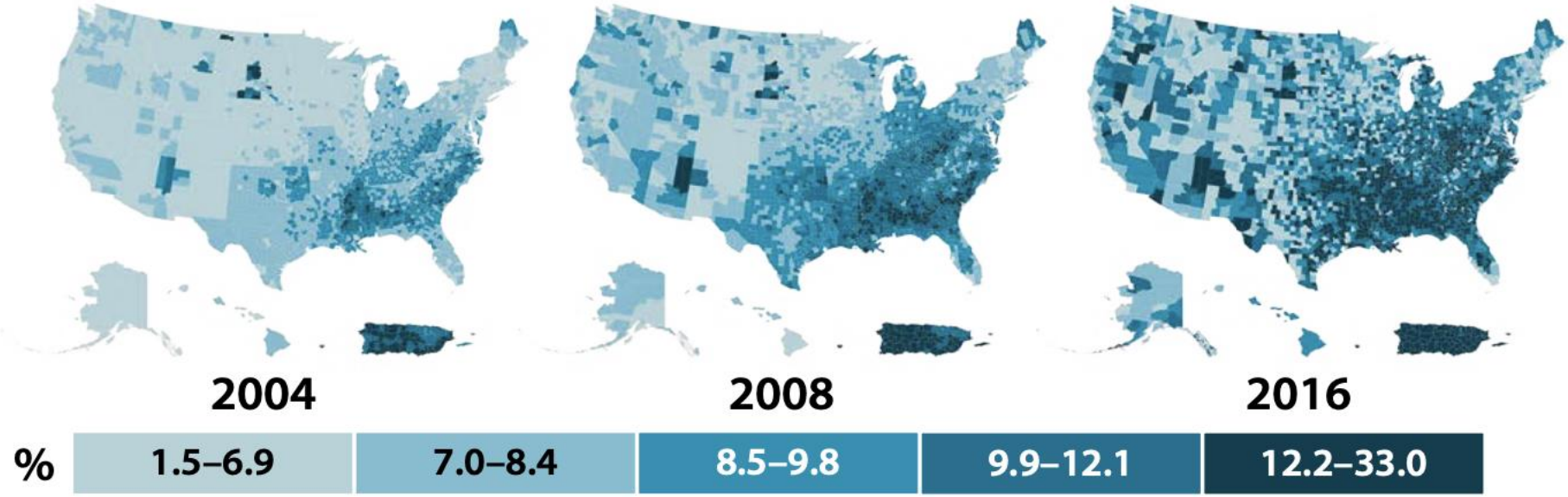
34.2 million

people have diabetes...

...which is about **1** in **10** people...

...and **1** in **5** people don't know they have diabetes.

Age-adjusted, county-level prevalence of diagnosed diabetes among adults aged ≥20 years, United States, 2004, 2008, and 2016



Centers for Disease Control and Prevention (CDC). National Diabetes Statistics Report, 2020. CDC, U.S. Dept of Health and Human Services; 2020; A snapshot of diabetes in the United States. CDC infographic. Accessed March 18, 2020. cdc.gov/diabetes/pdfs/library/socialmedia/diabetes-infographic.pdf

The Latest Cost Report

$327 billion in total medical costs and lost work and wages for people diagnosed with diabetes.

60% higher

risk of early death for adults with diabetes compared with adults without diabetes.

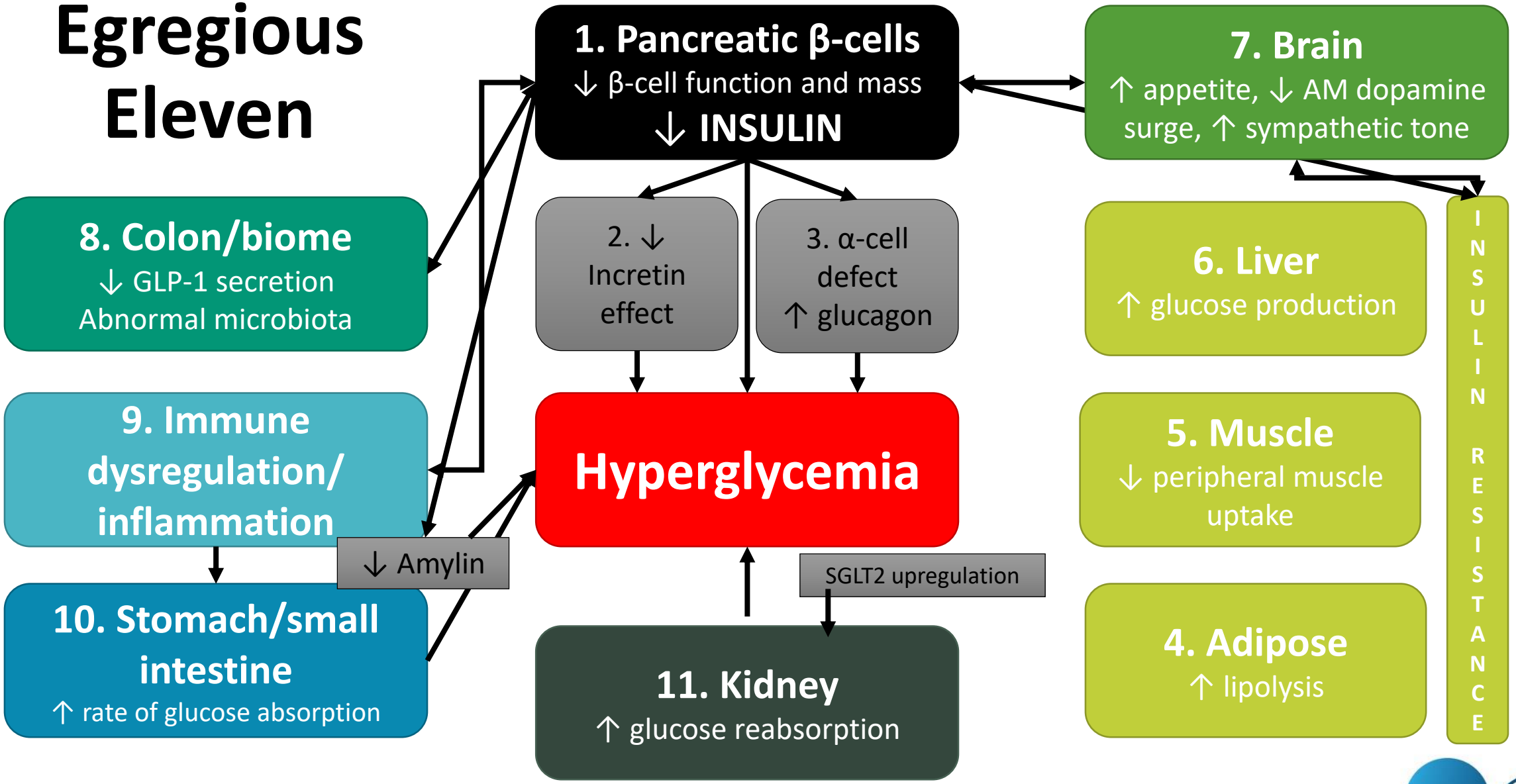
Medical costs for people with diabetes are more than **2x as high** as for people without diabetes.

People who have diabetes are at higher risk of serious health complications, including:

- Retinopathy
- Nephropathy
- Heart disease
- Stroke
- Neuropathy

Centers for Disease Control and Prevention (CDC). National Diabetes Statistics Report, 2020. CDC, U.S. Dept of Health and Human Services; 2020; A snapshot of diabetes in the United States. CDC infographic. Accessed March 18, 2020. cdc.gov/diabetes/pdfs/library/socialmedia/diabetes-infographic.pdf

Egregious Eleven



Adapted from Schwartz SS, et al. *Diabetes Care.* 2016;39(2):179-186.

Available Antihyperglycemic Therapies (First- or Second-line)*

Metformin

(Glucophage, Fortamet, Glumetza)

Sulfonylureas

Glyburide (Diabeta, Glynase)

Glipizide (Glucotrol)

Glimepiride (Amaryl)

Thiazolidinediones

Pioglitazone (Actos)

Rosiglitazone (Avandia)

SGLT2 Inhibitors

Canagliflozin (Invokana)

Dapagliflozin (Farxiga)

Empagliflozin (Jardiance)

Ertugliflozin (Steglatro)

DPP-4 Inhibitors

Sitagliptin (Januvia)

Saxagliptin (Onglyza)

Linagliptin (Tradjenta)

Alogliptin (Nesina)

GLP-1 RAs

Exenatide (Byetta, Bydureon BCise)

Liraglutide (Victoza)

Lixisenatide (Adlyxin)

Dulaglutide (Trulicity)

Semaglutide (Ozempic, Rybelsus)

Insulin

Rapid, short, intermediate, long-acting, ultra long-acting, concentrated, premixed, inhaled

GLP-1 RA + Basal Insulin

Insulin degludec and liraglutide (Xultophy)

Insulin glargine and lixisenatide (Soliqua)

*Brand names are not all inclusive as there are various formulations and combinations.

American Diabetes Association. 2. Pharmacologic approaches to glycemic treatment: *Standards of Medical Care in Diabetes—2020*. *Diabetes Care.* 2020;43(suppl 1):S98-S110.

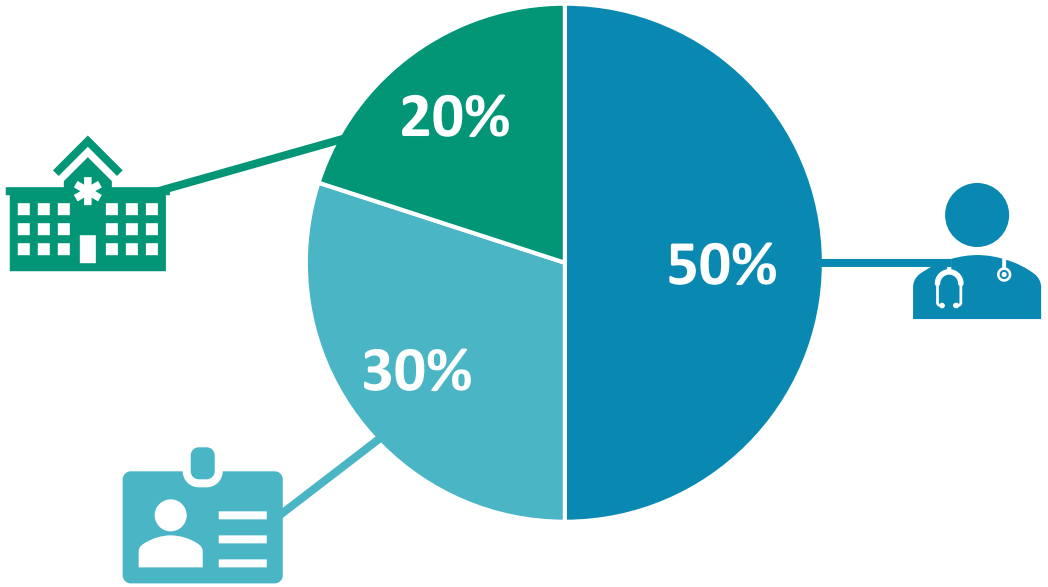
Glycemic Goals

Parameter	ADA	AACE
A1C	≤7% <6.5%: if it can be achieved without significant hypoglycemia or adverse drug events <8%: if history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, and those with long-standing diabetes in whom the general goal is difficult to attain	≤6.5% Individualize based on life expectancy, duration of diabetes, microvascular/ macrovascular complications status, comorbid conditions, CVD risk factors, risk of developing consequences from severe hypoglycemia, and patient's social, psychological, and economic status
Preprandial plasma glucose	80-130 mg/dL	<110 mg/dL
Postprandial plasma glucose	<180 mg/dL 1-2 hours after the start of a meal	<140 mg/dL

American Diabetes Association (ADA). Standards of Medical Care in Diabetes—2020. *Diabetes Care.* 2020;43(suppl 1); Garber AJ, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm—2017 executive summary. *Endocr Pract.* 2017;23(1):207-238.

Clinical Inertia

Office System Factors
- No clinical guideline
- No disease registry
- No visit planning
- No active outreach
- No decision support
- No team approach to care
- Poor communication between physician and staff



Physician Factors
- Goal setting
- Failure to initiate or titrate treatment
- Failure to identify and manage comorbid conditions
- Allowing patient to lead clinical encounter
- Insufficient time
- Reactive rather than proactive care

Patient Factors
- Deny having the disease
- Believe the disease is not serious
- Low health literacy
- Cost of medication

- Polypharmacy
- Medication AEs
- Poor communication with physician
- Do not trust the physician
- Depression, substance abuse

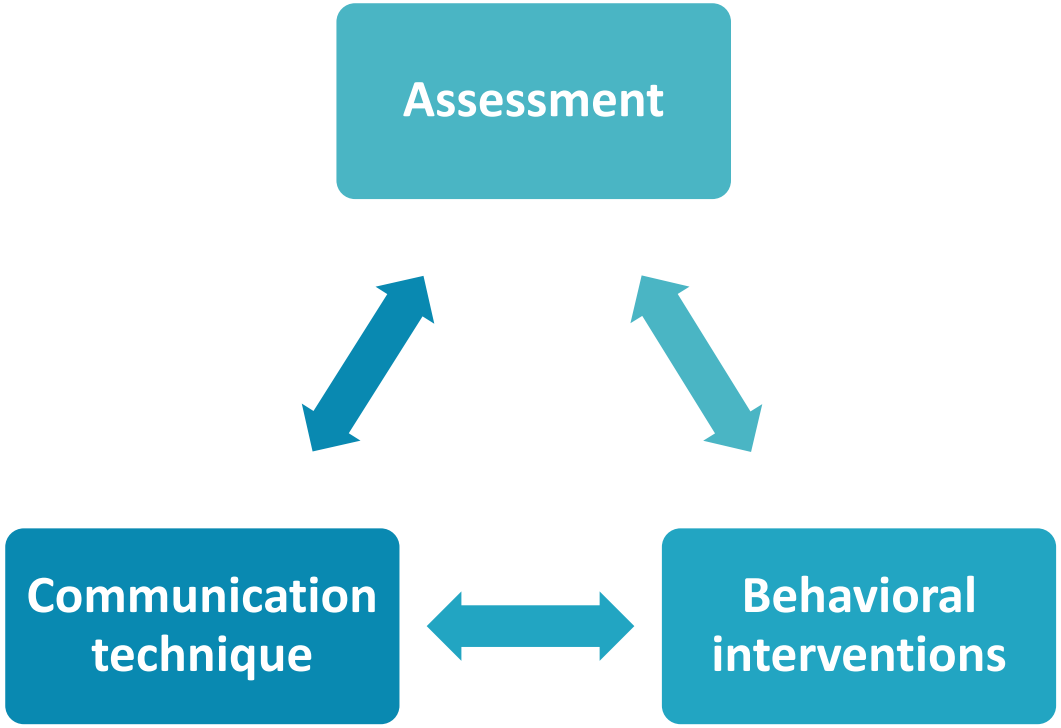
Adapted from O'Connor PJ, et al. *Advances in Patient Safety: From Research to Implementation,* Volume 2: Concepts and Methodology. Agency for Healthcare Research and Quality; 2005. Accessed March 18, 2020. ncbi.nlm.nih.gov/books/NBK20513/

Fear of Injectable Medications

What influences the initiation of injectable therapies?

- Negative baseline assumptions from clinician
- Negative connotation with insulin that then is associated with GLP-1 RA
- Patient's perception of feeling like a "failure"
- Patient's association of injectables leading to complication/death in family/friends
- Anticipation of pain

Strategies to Address Fear



Kruger DF, et al. *Diabetes Metab Syndr Obes*. 2015;8:49-56.

Open-ended Questions to Assess Barriers

- How satisfied are you with your current diabetes therapy?
- How do you think injectable therapy can help with your diabetes?
- Who do you know who has taken injectable therapy and what was their experience?
- What is your past experience with taking injectable medications?
- What is your greatest concern about starting injectable therapy?
- How confident are you that you can take injectable therapy on a regular basis?
- What obstacles do you think will keep you from taking injectable therapy?
- What information/support do you need to have to be willing to take injectable therapy?

Kruger DF, et al. *Diabetes Metab Syndr Obes*. 2015;8:49-56.

Strategies to Address Fear of Injectables

- Up-to-date knowledge
- Change perceptions about "controlled" and "time between intensification"
- Make changes when we can
- Empower patients to be change agent
- Shared decision making
- Establish relationships with prescribers
- Advocate and empower

Appropriate needle selection

Patient education

Empathy

Injection technique

Behavioral interventions

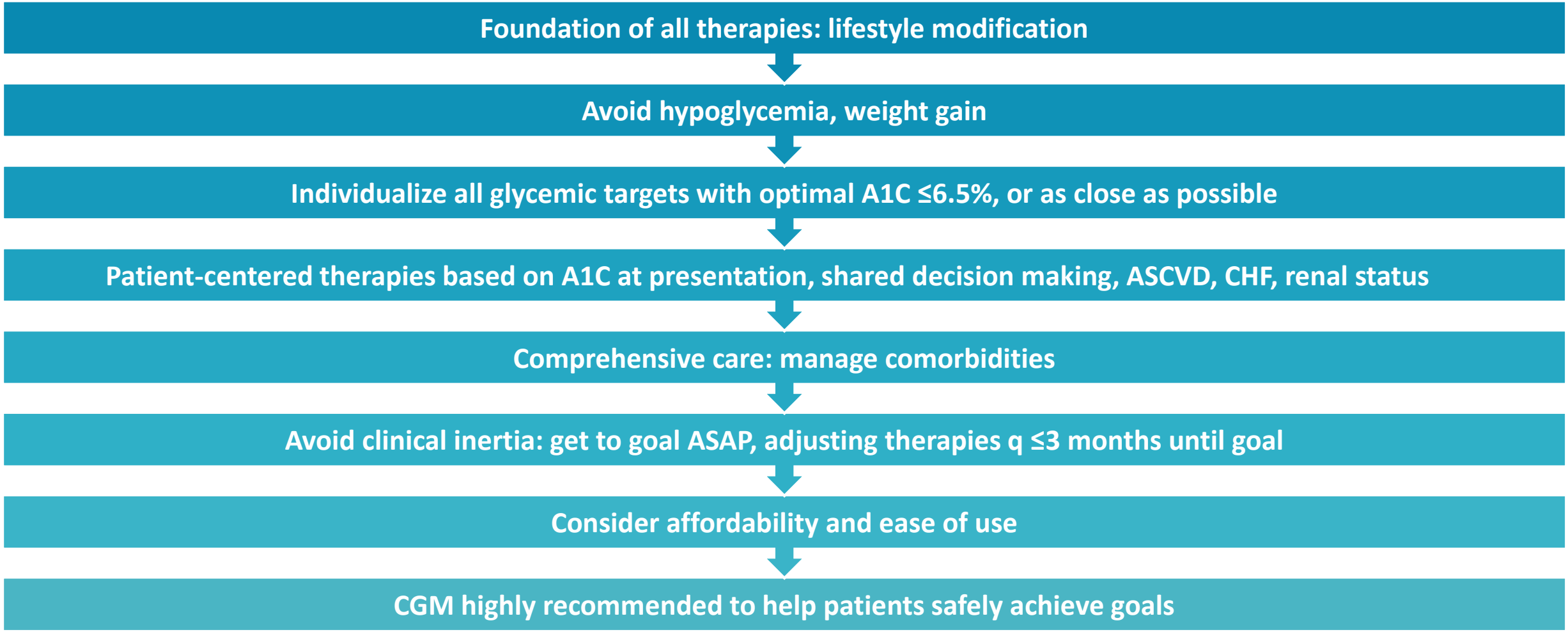
Mindfulness, deep breathing

Monitoring

Follow-up, discuss issues and experiences

Kruger DF, et al. *Diabetes Metab Syndr Obes*. 2015;8:49-56.

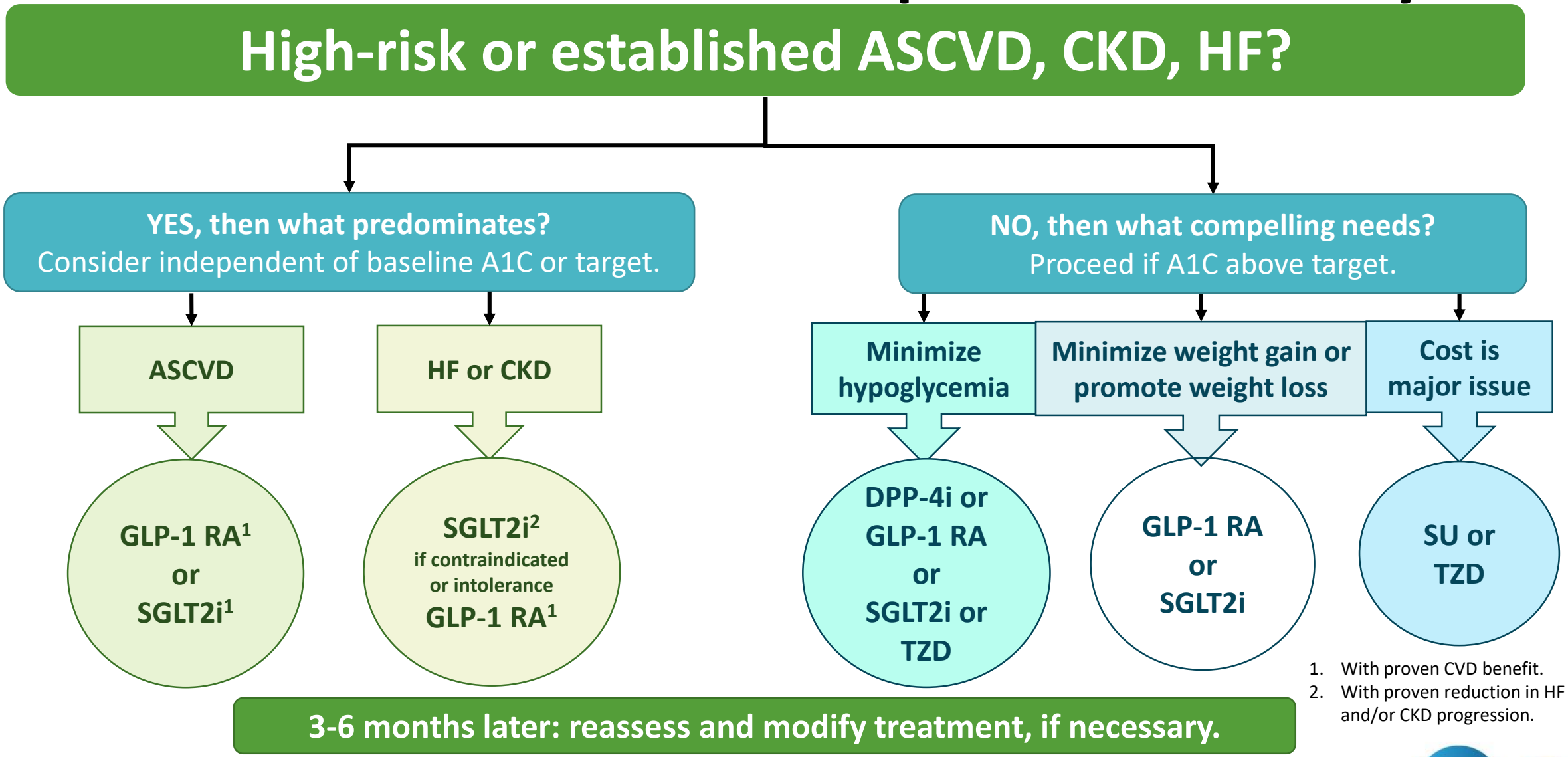
AACE/ACE: Principles of T2D Algorithm



Adapted from Garber AJ, et al. Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm – 2020 Executive Summary. *Endocr Pract.* 2020;26(1).

Treatment Algorithm Based on Patient and Drug Factors From ADA *Standards of Care 2020*

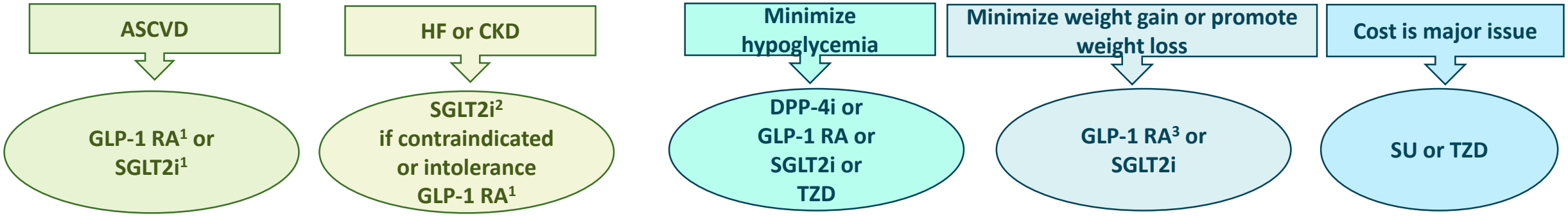
First Line*: Metformin + Comprehensive Lifestyle



1. With proven CVD benefit.
2. With proven reduction in HF and/or CKD progression.

American Diabetes Association. 2. Pharmacologic approaches to glycemic treatment: *Standards of Medical Care in Diabetes—2020*. *Diabetes Care*. 2020;43(suppl 1):S98-S110.

*May need to initiate insulin in certain patients.



3-6 months later: if A1C still above individualized target, then…

Choose agents with CV safety
- Add GLP-1 RA[1] if on SGLT2i[1]
- Add SGLT2i[1] if on GLP-1 RA[1]
- Add DPP-4i if not on GLP-1 RA
- Basal insulin
- TZD
- SU

Choose agents with CV safety
- Add GLP-1RA[1] if on SGLT2i[1]
- If HF, add DPP-4i only if not taking GLP-1 RA (but not saxagliptin)
- Basal insulin
- SU
- If HF, avoid TZD

- Add SGLT2i or TZD if on DPP-4i
- Add SGL2Ti or TZD if on GLP-1 RA
- Add GLP-1 RA or DPP-4i or TZD, if on SGLT2i
- Add SGLT2i or DPP-4i or GLP-1 RA if on SGLT2i

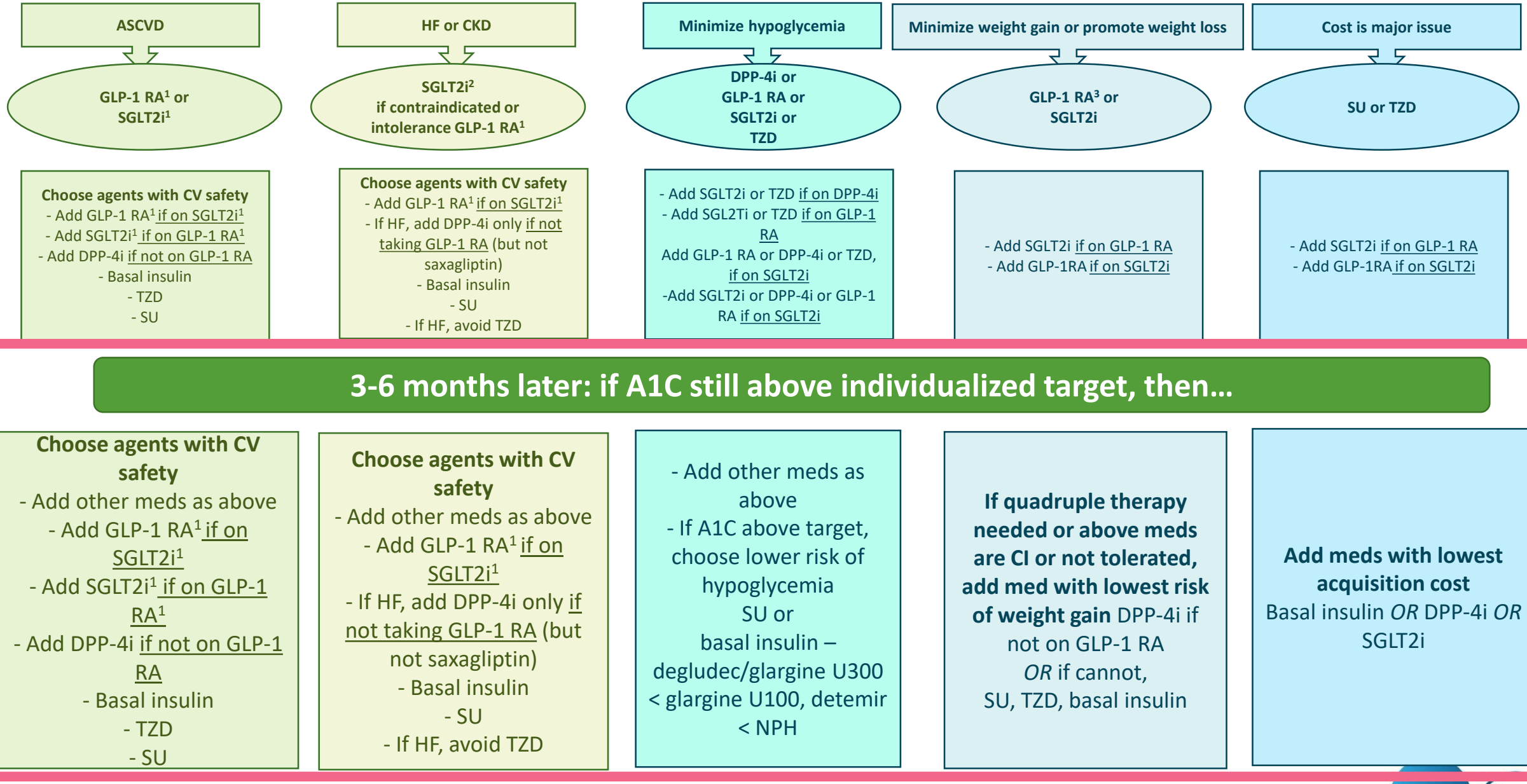
- Add SGLT2i if on GLP-1 RA
- Add GLP-1 RA if on SGLT2i

- Add SGLT2i if on GLP-1 RA
- Add GLP-1 RA if on SGLT2i

3-6 months later: if A1C still above individualized target, then…

American Diabetes Association. 2. Pharmacologic approaches to glycemic treatment: *Standards of Medical Care in Diabetes—2020*. *Diabetes Care.* 2020;43(suppl 1):S98-S110.

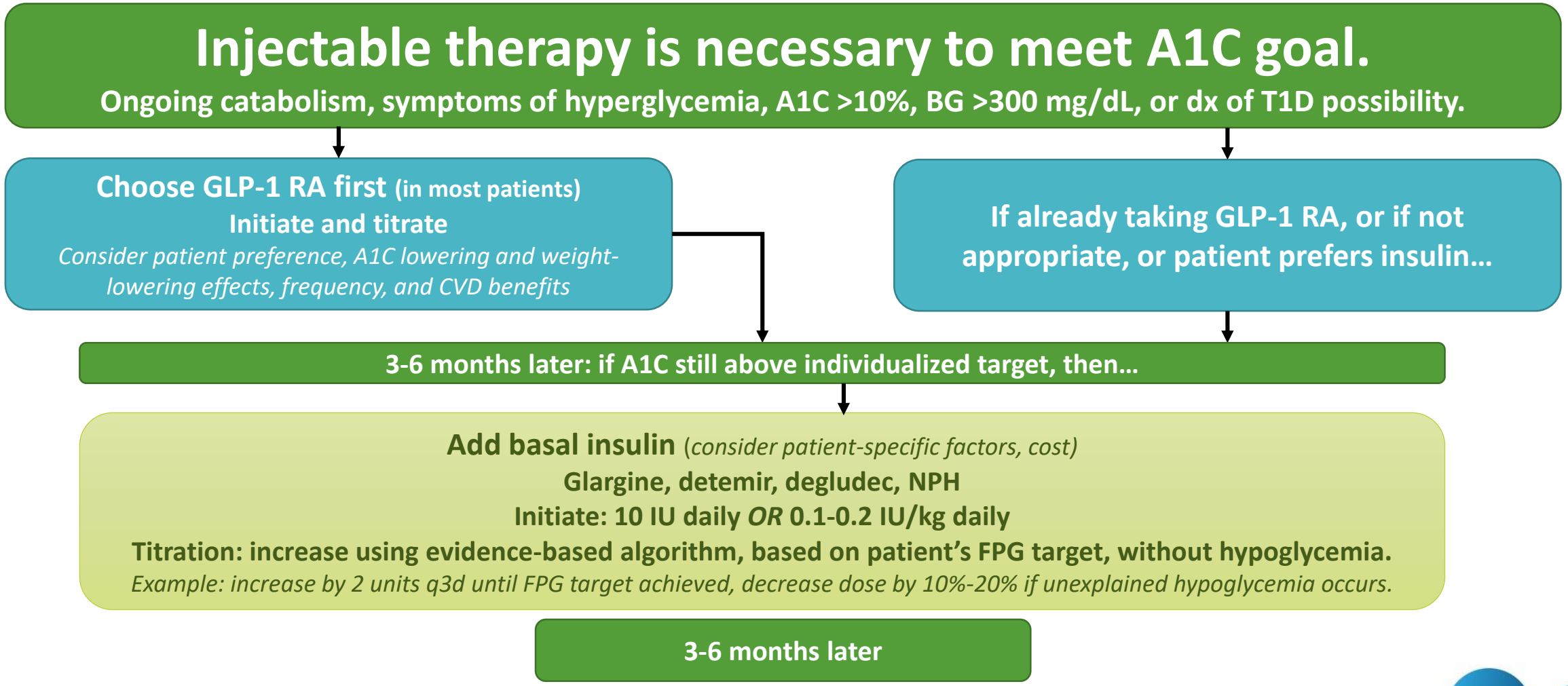
1. With proven CVD benefit; 2. With proven reduction in HF and/or CKD progression; 3. With good efficacy for weight loss



American Diabetes Association. 2. Pharmacologic approaches to glycemic treatment: *Standards of Medical Care in Diabetes—2020. Diabetes Care*. 2020;43(suppl 1):S98-S110.

1. With proven CVD benefit; 2. With proven reduction in HF and/or CKD progression; 3. With good efficacy for weight loss

Intensifying Injectable Therapies Algorithm



American Diabetes Association. 2. Pharmacologic approaches to glycemic treatment: *Standards of Medical Care in Diabetes—2020*. *Diabetes Care*. 2020;43(suppl 1):S98-S110.

Intensifying Injectable Therapies Algorithm

A1C still above individualized target with adequately titrated basal insulin *OR* basal dose >0.5 IU/kg *OR* FPG at target

Add prandial insulin to 1 meal with highest PPG excursion
Initiate: 4 IU/day or 10% of basal insulin
May decrease basal insulin by 4 IU or 10% if A1C <8%
Titration: 1-2 IU or 10%-15% increase 2x weekly
Decrease effected prandial dose by 10%-20% if unexplained hypoglycemia

Stepwise additions of prandial
Add a 2nd and/or 3rd additional prandial insulin

Full basal/bolus regimen

If taking bedtime NPH – convert to BID NPH
Initiate: 80% of total bedtime dose divided 2/3 qAM and 1/3 qHS

If A1C above target

Self-mixed or split insulin
Initiate 80% of current NPH dose, divided 2/3 AC breakfast and 1/3 AC dinner + 4 IU (or 10% of reduced NPH dose) short/rapid-acting to each injection
Titrate: each component based on individual needs

Twice-daily premix insulin
Initiate: unit per unit at same total daily dose, based on individual needs
Titrate: based on individual needs

American Diabetes Association. 2. Pharmacologic approaches to glycemic treatment: *Standards of Medical Care in Diabetes—2020*. *Diabetes Care*. 2020;43(suppl 1):S98-S110.

Available Basal Insulins

Basal insulin	Classification of insulin	Interesting properties
NPH U-100 (Humulin N, Novolin N)	Intermediate-acting	First basal insulin—protamine–insulin complex diffuses slowly from subcutaneous tissue
Glargine U-100 (Lantus, Basaglar)	Long-acting	Basaglar is a follow-on insulin, similar to Lantus
Glargine U-300 (Toujeo)	Ultra–long-acting	1/3 volume of liquid than glargine U-100; longer and flatter PK profile; less hypoglycemia and weight gain than long-acting
Detemir U-100 (Levemir)	Long-acting	Less acidic; make cause less stinging
Degludec U-100, U-200 (Tresiba)	Ultra–long-acting	Longer and flatter PK profile; less hypoglycemia and weight gain than long-acting
Regular U-500 (Humulin R U-500)	Basal/bolus combination	Concentrated insulin for use in patients taking >200 units of insulin/day without achieving goal glycemic levels

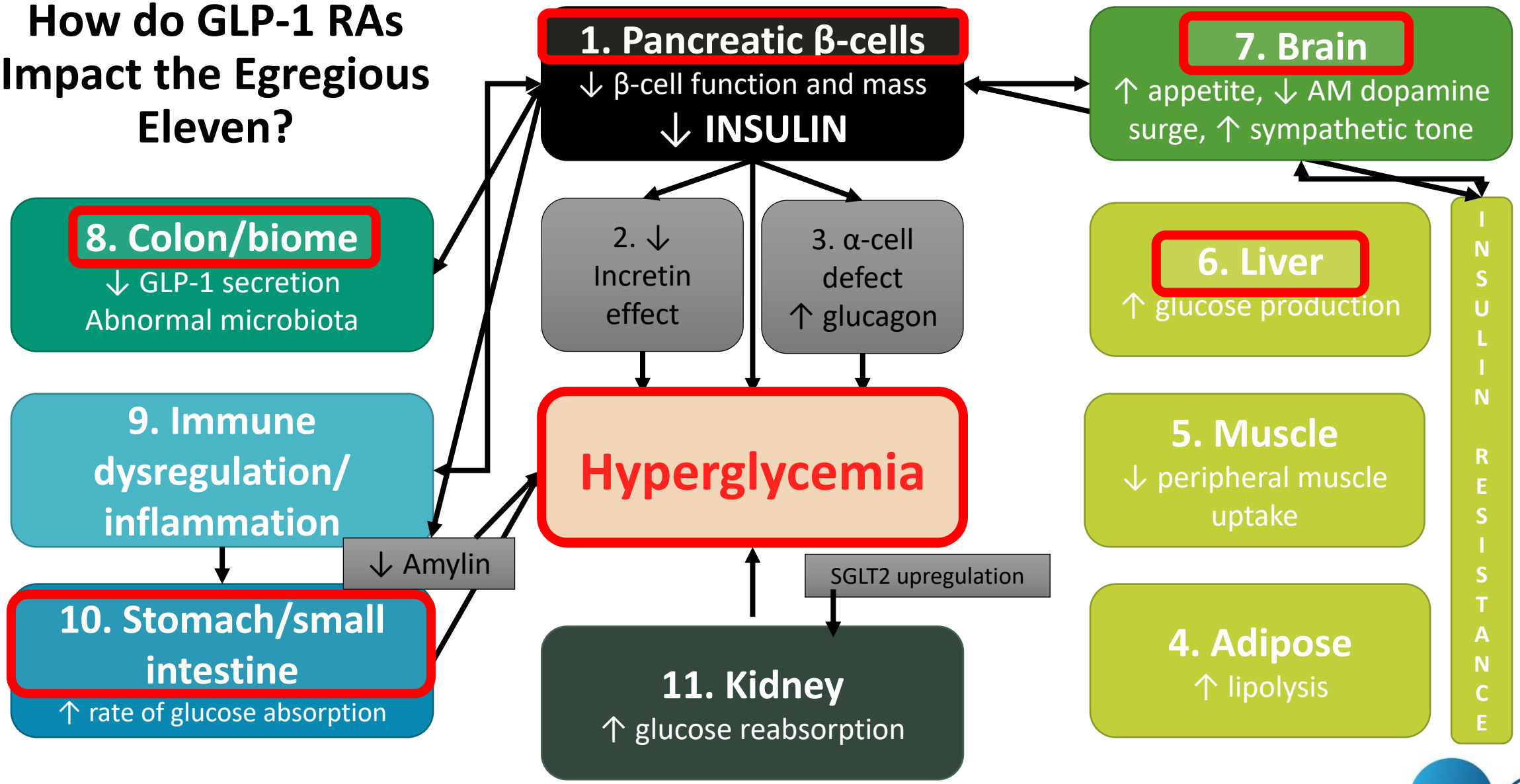
American Diabetes Association. 2. Pharmacologic approaches to glycemic treatment: *Standards of Medical Care in Diabetes—2020*. *Diabetes Care*. 2020;43(suppl 1):S98-S110.

Available GLP-1 RA Medications

GLP-1 receptor agonist	Duration of action	Dosing frequency	CV benefit	Renal dosing
Dulaglutide (Trulicity)	Long-acting	Once weekly	Yes (REWIND)	No adjustment
Exenatide BID (Byetta)	Short-acting	Twice daily	Neutral	Not recommended if eGFR <30 mL/min/1.73m^2
Exenatide qwk (Bydureon BCise)	Long-acting	Once weekly	Neutral (EXSCEL)	Not recommended if eGFR <30 mL/min/1.73m^2
Lixisenatide (Adlyxin)	Short-acting	Daily	Neutral (ELIXA)	Not recommended if eGFR <15 mL/min/1.73m^2, caution if eGFR 15-59 mL/min/1.73m^2
Liraglutide (Victoza)	Long-acting	Daily	Yes (LEADER)	No adjustment
Semaglutide (Ozempic)	Long-acting	Once weekly	Yes (SUSTAIN)	No adjustment
Semaglutide (Rybelsus)	Short-acting	Daily	Neutral (PIONEER-6)	No adjustment

American Diabetes Association. 2. Pharmacologic approaches to glycemic treatment: *Standards of Medical Care in Diabetes—2020*. *Diabetes Care*. 2020;43(suppl 1):S98-S110.

How do GLP-1 RAs Impact the Egregious Eleven?



Adapted from Schwartz SS, et al. *Diabetes Care.* 2016;39(2):179-186.

GLP-1 RAs: Are They Created Equally?

<u>Short Acting</u>: > PPG

Exenatide BID, lixisenatide

<u>Long Acting</u>: > FPG

Exenatide qwk, liraglutide, dulaglutide, semaglutide

Timing of dose
Missed dose
Changing day of dose
Storage
Needles (included or not)
Do not combine any with DPP-4 inhibitors
Combination with basal insulin
FDA indications
Injectable versus oral

Newest GLP-1 RA: PO Semaglutide

- Dose initiation
  - Dose titration
    - Initiate 3 mg daily → 30 days → increase to 7 mg daily → 30 days → increase, if necessary, to 14 mg daily
  - Changing dosage forms
    - From PO 14 mg → change to SC 0.5 mg, starting day after last dose of PO
    - From SC 0.5 mg → change to PO 7 mg or 14 mg 7 days after last dose of SC
- Dose administration
  - 30 minutes prior to food with sip of water (maximum = 4 ounces)
  - Push out from blister pack when ready for dose
  - Swallow whole

- Adverse effects
  - Nausea, vomiting, abdominal pain, diarrhea, decreased appetite, constipation

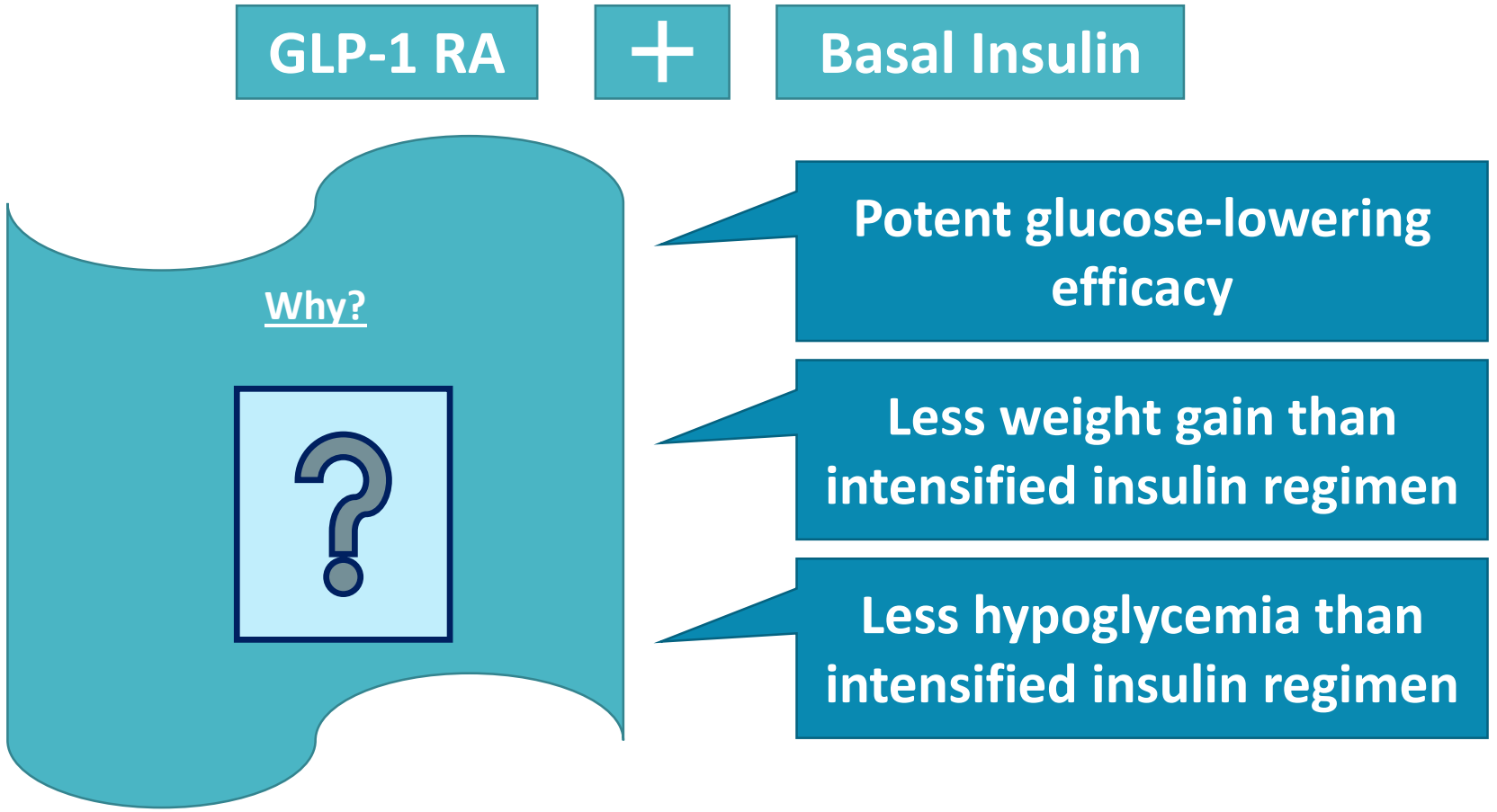
Rybelsus. Prescribing information. Novo Nordisk Inc; 2019.

GLP-1 RA Medications and CV Benefit: FDA Indications

- **All have an indication as** "as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus"
- **Dulaglutide (Trulicity) injection 0.75 mg or 1.5 mg** "to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with type 2 diabetes mellitus who have established cardiovascular disease or multiple cardiovascular risk factors"
- **Liraglutide (Victoza) injection 1.2 mg or 1.8 mg** "to reduce the risk of major adverse cardiovascular (CV) events (CV death, non-fatal myocardial infarction, or non-fatal stroke) in adults with type 2 diabetes mellitus and established CV disease"
- **Semaglutide (Ozempic) injection 0.5 mg or 1 mg** "to reduce the risk of major adverse cardiovascular (CV) events (CV death, nonfatal myocardial infarction or nonfatal stroke) in adults with type 2 diabetes mellitus and established CV disease"

American Diabetes Association. 2. Pharmacologic approaches to glycemic treatment: *Standards of Medical Care in Diabetes—2020*. *Diabetes Care*. 2020;43(suppl 1):S98-S110.

Combination Injectable Therapy for T2D



Insulin Glargine/Lixisenatide

Insulin Glargine/Lixisenatide

Availability	• Soliqua 100/33 (100 units glargine/mL and 33 mcg lixisenatide/mL) • Prefilled 3-mL pen with a clear, colorless solution in 1-unit increments, delivering 15-60 units in single injection
Naïve to basal insulin or GLP-1 RA, on a GLP-1 RA, or on <30 units/day of basal insulin	• Initiate 15 units daily (15 units insulin glargine/5 mcg lixisenatide)
Currently taking 30-60 units of basal insulin daily +/- GLP-1 RA	• Initiate 30 units daily (30 units insulin glargine/10 mcg lixisenatide)
Dosing information	• Discontinue basal insulin and/or GLP-1 RA • SC injection once daily within 1 hour prior to first meal of day • Missed doses: inject next scheduled dose
Titration	• ↓ or ↑ by 2-4 units qwk based on individual patient needs: ○ until goal fasting plasma glucose is reached ***or*** ○ if hypoglycemia occurs ***or*** ○ fasting glucose is below target range

Soliqua. Prescribing information. Sanofi-Aventis; 2019.

Insulin Glargine/Lixisenatide

- Hypoglycemia
- GI symptoms
  - Nausea, vomiting, constipation, dyspepsia, gastritis, abdominal pain, flatulence, gastroesophageal reflux disease, abdominal distension, decreased appetite
- Nasopharyngitis (7%)
- Diarrhea (7%)
- Upper respiratory tract infection (5.5%)
- Headache (5.4%)
- Pancreatitis
- Injection-site reaction

Soliqua. Prescribing information. Sanofi-Aventis; 2019.

iGlarLixi vs iGlar

Trial (n)	Background therapy	Baseline characteristics	Primary outcome change in A1C (%)	Secondary outcomes
Proof of Concept **iGlarLIxi (n = 161)** **iGlar (n = 162)**	Insulin-naïve on metformin	Average age = 56.8 y Duration of T2D = 6.7 y BMI = 32.1 A1C = 8.1 v 8	-1.82% vs -1.64% Treatment difference: -0.17%, 95%CI (-0.31 to -0.04), *P* <0.01	1. % achieving A1C <7%: 84% vs 78% 2. Mean bodyweight change -1.16 kg vs + 0.39 kg
LixiLan O **iGlarLIxi (n = 467)** **iGlar (n = 467)** **Lixi (n = 233)**	Metformin +/- other OAD	Average age = 58.4 y Duration of T2D = 8.8 y BMI = 31.8 A1C = 8.1	-1.63% vs -1.34% vs Lixi -0.85% Treatment difference with Lixi: -0.80% 95%CI (-0.9% to -0.7%), *P* <0.0001 Treatment difference with iGlar: -0.30% 95%CI (-0.4% to -0.2%]) *P* <.0001	1. % achieving A1C <7%: 73.7% vs 59.4% vs 33% 2. Mean bodyweight change -0.36 kg vs + 1.1 kg vs -2.3 kg
LixiLan L **iGlarLIxi (n = 367)** **iGlar (n = 369)**	Basal insulin +/- 2 OADs	Average age = 60 y Duration of T2D = 12.05 y BMI = 31.2 A1C = 8.1	-1.1% vs -0.60% Treatment difference with iGlar: -0.50% 95%CI(-0.6% to -0.4%) *P* <0.0001	1. % achieving A1C <7%: 54.9% vs 29.6% 2. Mean bodyweight change -0.7 kg vs + 0.7 kg

Nuffer W, et al. *Ther Adv Endocrinol Metab*. 2018;9(3):69-79; Rosenstock J, et al. *Diabetes Care*. 2016;39:1579-1586; Rosenstock J, et al. *Diabetes Care*. 2016;39:2026-2035; Aroda VR, et al. *Diabetes Care*. 2016;9:1972-1980.

Insulin Degludec/Liraglutide

Insulin Degludec/Liraglutide

Availability
- Xultophy 100/3.6 (100 units degludec/mL and 3.6 mg liraglutide/mL)
- Prefilled 3-mL pen with a clear, colorless solution in 1-unit increments, delivering 16-50 units in single injection

Naïve to basal insulin or GLP-1 RA
- Initiate 10 units daily (10 units insulin glargine/0.36 mg liraglutide)

Currently on basal insulin or GLP-1 RA
- Initiate 16 units daily (16 units insulin glargine/0.58 mg liraglutide)

Dosing information
- Discontinue basal insulin and/or GLP-1 RA
- SC injection once daily at the same time +/- food
- Missed doses: inject next scheduled dose, if >3 days since last dose, initiate at starting dose

Titration
- ↓ or ↑ by 2 units qwk or twice weekly based on individual patient needs
  - until goal FPG is reached ***or***
  - if hypoglycemia occurs ***or***
  - fasting glucose is below target range

Xultophy. Prescribing information. Novo Nordisk; 2019.

Insulin Degludec/Liraglutide

- Hypoglycemia
- GI symptoms
  - Nausea (7.8%), diarrhea (7.5%), vomiting, constipation, dyspepsia, gastritis, abdominal pain, flatulence, gastroesophageal reflux disease, abdominal distension, decreased appetite
- Nasopharyngitis (9.6%)
- Upper respiratory tract infection (5.7%)
- Headache (9.1%)
- Increased lipase (6.7%)
- Pancreatitis
- Injection-site reaction

Xultophy. Prescribing information. Novo Nordisk; 2019.

Dual Action of Liraglutide and iDeg (DUAL) Trials

Trial (n)	Background therapy	Baseline characteristics (mean)	Primary outcome change in A1C (%) after 26 wks	Secondary outcomes
DUAL I: open-label **iDegLira (n = 833) vs iDeg (n = 413) vs Lira (n = 414)** Titration twice a week, fasting target 72-90 mg/dL and Lira qwk to 1.8-mg dose	Metformin +/- pioglitazone	Age = 55 y Duration of T2D = 6.9 y BMI = 31.2 A1C = 8.3%	-1.9 vs -1.4 vs -1.3% Noninferiority to iDeg – treatment difference -0.47%, 95% CI (-0.58 to -0.36), *P* <0.0001 Superiority to Lira - treatment difference -0.64%, 95% CI (-0.75 to -0.53), *P* <0.0001	1. % achieving A1C <7%: 81% vs 65% vs 60% 2. Mean bodyweight change -0.5 kg vs + 1.6 kg vs -3 kg 3. Nausea: 8.8% iDegLira vs 19.7% Lira 4. Hypoglycemia: 1.8 events/pt yr iDegLira vs 2.6 events/pt yr Lira
DUAL II: double-blind **iDegLira (n = 199) vs iDeg (n = 199)** Titration twice weekly, fasting target 72-90 mg/dL	Basal insulin + metformin +/- sulfonylurea or glinides	Age = 57.5 y Duration of T2D = 10.5 y BMI = 33.7 A1C = 8.7 v 8.8%	-1.9 vs -0.9% Superiority for iDegLira vs iDeg: end of treatment difference: -1.1% 95% CI (-1.3 to -0.80), *P* <0.0001	1. % achieving A1C <7%: 60% vs 23% 2. Mean bodyweight change -2.7 kg vs 0 kg 3. Nausea: 6.5% iDegLira vs 3.5% Lira 4. Hypoglycemia: 24% iDegLira vs 25% iDeg
DUAL III: **iDegLira (n = 292) vs unchanged, max dose GLP-1 RA (n = 146)** Titration twice a week, fasting target 72-90 mg/dL	Metformin ± pioglitazone ± sulfonylurea	Age = 58.4 y Duration of T2D = 10.4 y BMI = 32.95 kg A1C = 7.8 vs 7.7%	-1.3% versus -0.3% Superiority, treatment difference -0.94%, 95% CI (-1.11 to -0.78), *P* <0.001	1. % achieving A1C <7%: 75% vs 36% 2. Mean bodyweight change +2 kg vs – 0.8 kg 3. Nausea: 3.1% iDegLira vs 4.1% unchanged GLP-1 RA 4. Hypoglycemia: 2.82 PYE iDegLira vs 0.12 PYE unchanged GLP-1 RA

Nuffer W, et al. *Ther Adv Endocrinol Metab*. 2018;9(3):69-79; Gough SC, et al. *Lancet Diabetes Endocrinol.* 2014;2:885-893; Linjawi S, et al. *Diabetes Ther.* 2017;8:101-114.

Dual Action of Liraglutide and iDeg (DUAL) Trials

Trial (n)	Background therapy	Baseline characteristics (mean)	Primary outcome change in A1C (%) after 26 wks	Secondary outcomes
DUAL IV **iDegLira (n = 289) vs Placebo (n = 146)** Titration twice a week, fasting target 72-108 mg/dL	Sulfonylurea +/- metformin	Age = 59.7 y Duration of T2D = 9.15 y BMI = 31.6 kg A1C = 7.9%	-1.15% vs -0.5% *superiority – treatment difference -1.02%, 95% CI (-1.18 to -0.87), *P* <0.001	1. % achieving A1C <7%: 79.2% vs 28.8% 2. Mean bodyweight change +0.5 kg vs – 1 kg 3. Nausea: 4.5% iDegLira vs 3.4% 4. Hypoglycemia: 41.7% vs 17.1%
DUAL V **iDegLira (n=278) vs iGlar (n=279)** Titration twice a week, fasting target 72-90 mg/dL	Metformin (PWD previously taking iGlar + metformin)	Age = 58.8 y Duration of T2D = 11.5 y BMI = 31.7 kg A1C = 8.4 % vs 8.2%	-1.81% vs -1.13%; noninferiority, then superiority with treatment difference: -0.59%, 95% CI (-0.74;-0.45), *P* <0.001	1. % achieving A1C <7%: 71.6% vs 47% 2. Mean bodyweight change -1.4 kg vs + 1.8 kg 3. Nausea: 9.4% iDegLira vs 1.1% iGlar 4. Hypoglycemia: 2.23 PYE vs 5.05 PYE

Nuffer W, et al. *Ther Adv Endocrinol Metab*. 2018;9(3):69-79; Rodbard HW, et al. *Diabet Med*. 2017;34:189-196; Lingvay I, et al. *JAMA*. 2016;315:898-907.

Specific Considerations With Fixed-Ratio GLP-1 RA/Basal Insulin Combination Medications

Differences in Dosing and Administration

Degludec/Liraglutide

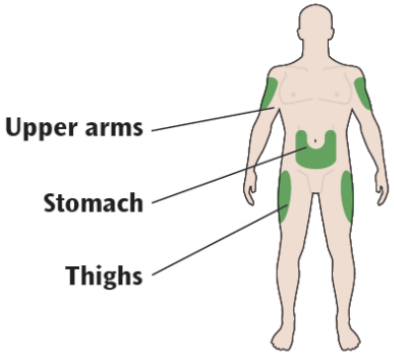
- Initiate 10 units daily if:
  - Basal insulin or GLP-1 RA-naïve
- Initiate 16 units daily if:
  - Taking basal insulin or GLP-1 RA: 16 units daily
- Titrate by 2 units **q3-4d** as needed to goal
- If **missed 3 days** of doses, **start back** at 16 units
- **Once daily**, same time, **with or without food**
- Maximum = 50 units of degludec and 1.8 mg liraglutide/day
- Black box warning

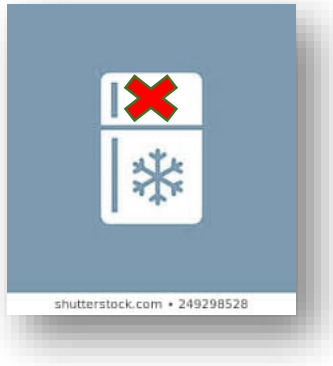
Glargine/Lixisenatide

- Initiate 15 units daily if:
  - Basal insulin-naïve or GLP-1 RA-naïve
  - Currently taking GLP-1 RA
  - Currently on <30 units/day of basal insulin
- Initiate 30 units daily if:
  - Currently on 30-60 units/day of basal insulin
  - +/- GLP-1 RA
- Titrate by 2-4 units **qwk** as needed to goal
- If **missed,** take **dose next day as scheduled**
- Take within **1 h prior to first meal** of day
- Maximum = 60 units of glargine and 20 mcg of lixisenatide/day

Soliqua. Prescribing information. Sanofi-Aventis; 2019; Xultophy. Prescribing information. Novo Nordisk; 2019.

Summary of Patient Education





Patient education

- Injection technique
- Adverse reactions
- Storage
- Dosing/missed doses

Differences in Patient Education

Degludec/Liraglutide

- Prime by dialing to prime symbol with each dose
- After injection, keep needle in skin for **6 seconds**
- Unused pens, keep in fridge at 36° to 46°F
- **In-use pens, keep at room** temperature (59°-86°F) **or fridge** (36°-46°F)
- Discard after **21 days**

Glargine/Lixisenatide

- Safety test with 2 units with each dose
- After injection, keep needle in skin for **10 seconds**
- Unused pens, keep in fridge at 36° to 46°F
- **In-use pens, keep at room** temperature (<77° F)
- Discard after **28 days**

Soliqua. Prescribing information. Sanofi-Aventis; 2019; Xultophy. Prescribing information. Novo Nordisk; 2019.

Addressing Adverse Drug Events

Titrate dose

- Based on patient's experience

Relieve/lessen nausea

- Eat smaller meals
- Stop eating when full
- Lessens over time

Injection-site reactions

- Rotate sites

Weight loss

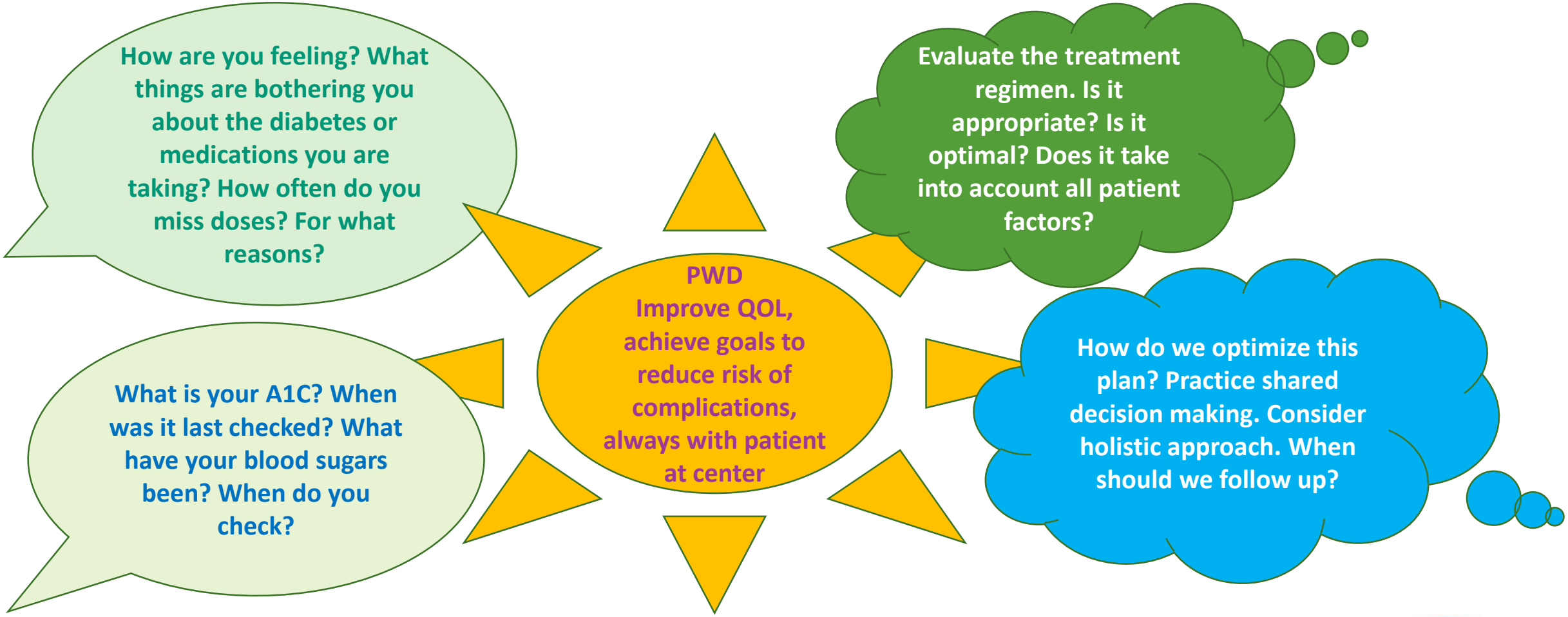
- Set realistic expectations

Hypoglycemia

- Fear of hypoglycemia
- Prevention is key
- 15-15 rule

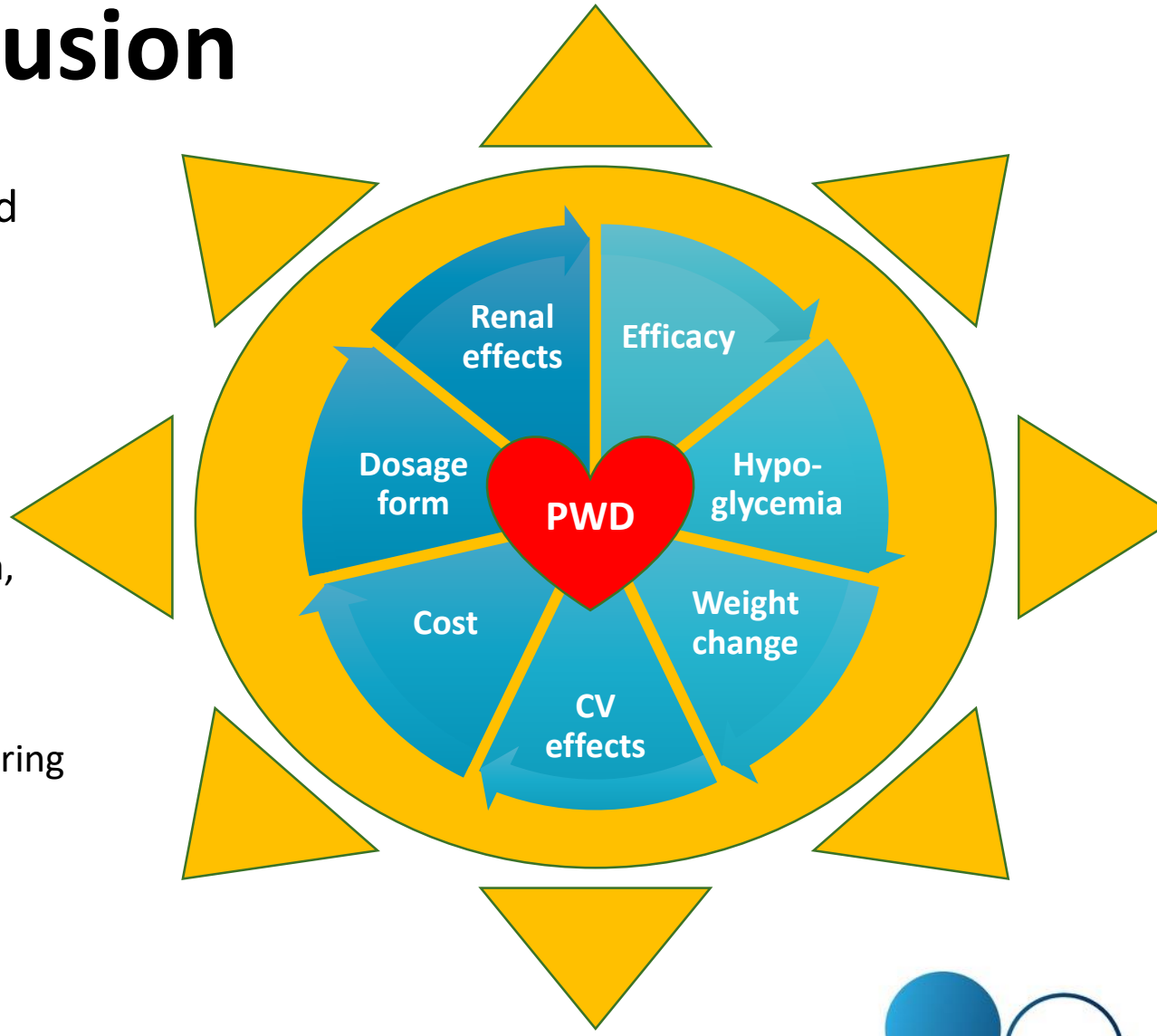
Hinnen D. *Diabetes Spectrum.* 2017;30(3):202-210.

Addressing Clinical Inertia: Engaging Patients and Assessing Information



Conclusion

- Metformin is first-line for T2D unless contraindicated or not tolerated
- Next step is to determine significant comorbidities:
  - ASCVD or high-risk for ASCVD
  - CKD
  - HF
- Other patient factors:
  - Compelling need to minimize weight gain, hypoglycemia, cost
- Combination injectable therapies
  - Help achieve A1C goals
  - Mitigate weight gain and hypoglycemia in patients requiring insulin
  - Improve adherence
- Recognizing and address clinical inertia to optimally help patients achieve goals in a safe, effective, and timely way



Additional Resources

- American Diabetes Association Standards of Care 2020—care.diabetesjournals.org/content/43/Supplement_1
- American Association of Clinical Endocrinologists Diabetes Resource Center—www.aace.com/disease-state-resources/diabetes
- Product websites
  - soliqua100-33.com/hcp
  - xultophy10036pro.com

COVID-19 Essentials for Pharmacists and What You Need to Know Right Now

PTce
www.pharmacytimes.org

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This activity is approved for 1.0 contact hour (0.10 CEU) under the ACPE universal activity number 0290-0000-20-117-L01-P. The activity is available for CE credit on May 16, 2020.

Fee: Free

Activity Type: Knowledge

This activity is supported by MJH Life Sciences, the parent company of *Pharmacy Times* and *PT*CE.

Educational Objectives

At the completion of this activity, participants will be able to:

- Discuss the epidemiology and severity of the emerging COVID-19 disease
- Describe the evidence of agents under investigation for treatment
- Review frequently asked questions from patients and caregivers

COVID-19 Questions

What is COVID-19?
How does it spread?
What does the epidemiology of the virus tell us?

Have there been any updates on symptoms?

What should I advise patients if they suspect a COVID-19 infection?

What are the recommendations from the CDC regarding face masks?

What are the disparities?

Who is at highest risk for COVID-19?

What about complications?

Can you update us on viral assays and antibody testing?

What future needs remain?

What is the role of community pharmacists in testing for COVID-19?

naspa.us/resource/covid-19-information-from-the-states

www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations#covid19ivd

There are reports of people still testing positive weeks after infection.

Do we know anything new about the course of the virus?

Treatment Updates:

Hydroxychloroquine +/- azithromycin

Immunomodulators

Convalescent Plasma

Others

What does the FDA's Emergency Use Authorization (EUA) for remdesivir mean?

Any guidance or updates on managing hypercoagulability in patients with COVID-19?

Are there any updates on the use of vitamins and minerals for treatment or prevention of COVID-19?

ftc.gov/news-events/press-releases/2020/04/ftc-sends-21-letters-warning-marketers-stop-making-unsupported

Any update on famotidine?

At what stage of development is a COVID-19 vaccine?

Are there any updates for providing routine adult vaccinations?

Are there any updates regarding ibuprofen and ACEIs/ARBs in the management of patients with COVID-19?

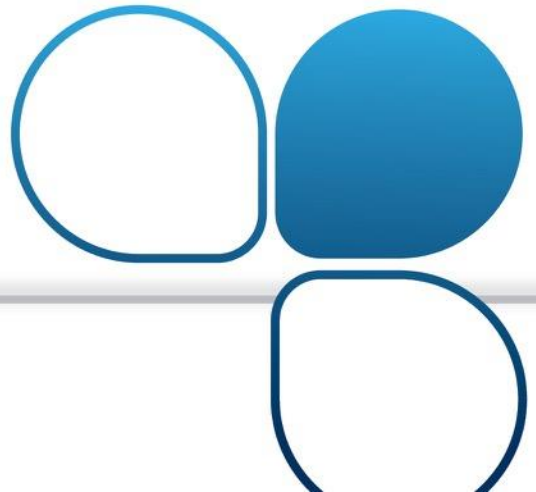
Additional Resources

Centers for Disease Control and Prevention	cdc.gov/coronavirus/2019-ncov/index.html
World Health Organization	who.int/emergencies/diseases/novel-coronavirus-2019
Infectious Diseases Society of America	idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management
National Institutes of Health	covid19treatmentguidelines.nih.gov
American Pharmacists Association	pharmacist.com/coronavirus
National Alliance of State Pharmacy Associations	naspa.us/resource/covid-19-information-from-the-states
Contagion	contagionlive.com

Thank You!

PTce
www.pharmacytimes.org

Managing Therapy in Heart Failure: Updates for Pharmacists



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This activity is approved for 0.75 contact hour (0.075 CEU) under the ACPE universal activity number 0290-0000-19-080-L01-P. The activity is available for CE credit on May 16, 2020.

Activity Type: Knowledge

Fee: Free

This activity is supported by an educational grant from Novartis Pharmaceuticals Corporation.

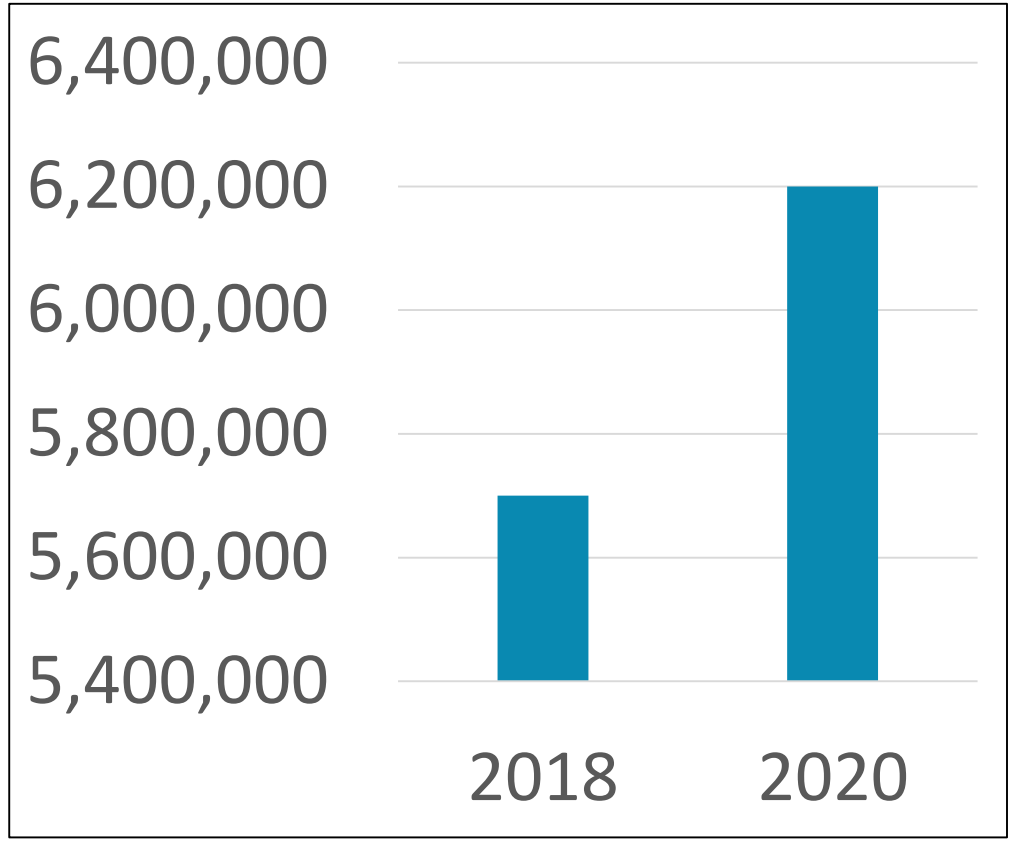
Educational Objectives

At the completion of this activity, participants will be able to:

- Review dosing and titration requirements for new and emerging agents used for heart failure (HF) management
- Outline safety and efficacy of emerging treatment strategies for HF
- Recognize the pharmacist's role with addressing barriers to optimal transitions of care and improving adherence in patients with HF

Heart Failure (HF) in 2020

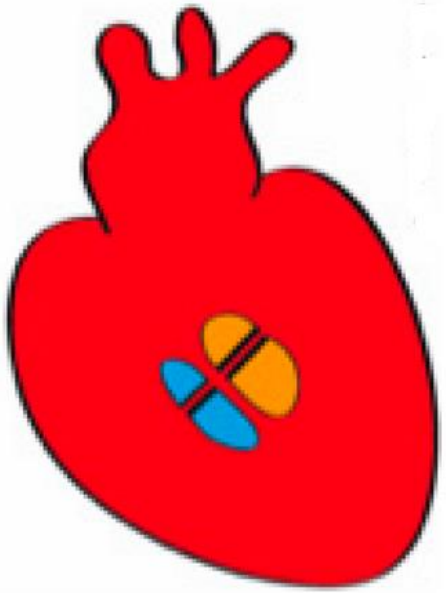
- Project 46% increase from 2012 to 2030
- Annualized mortality rate in 2017 was 80,480 (up from 75,251 from previous year)
- ≈1,000,000 admissions annually



Virani SS, et al. *Circulation.* 2020;141(9):e139-e596; Benjamin EJ, et al. *Circulation*. 2018;137(12):e67-492.

HF Types

Heart Failure with Preserved Ejection Fraction (HF*p*EF)



Ejection Fraction (EF)

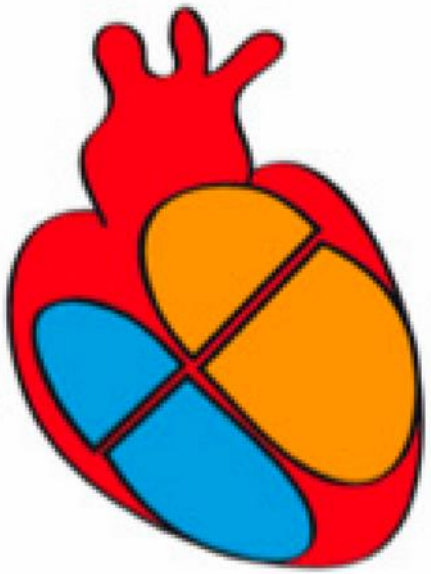
>50%

Heart Failure with Mid-Range Ejection Fraction (HF*m*EF)

EF

40%-50%

Heart Failure with Reduced Ejection Fraction (HF*r*EF)



EF

<40%

Yancy CW, et al. *J Am Coll Cardiol.* 2013;62(16):e147-e239; Hsu JJ, Ziaeian B, Fonarow GC. *JACC Heart Fail*. 2017;5(11):763-771.

Guideline-Directed Medical Therapy (GDMT) for HFrEF

American Heart Association (AHA) HF Stages

A
- High-risk for HF but without structural heart disease or symptoms of HF

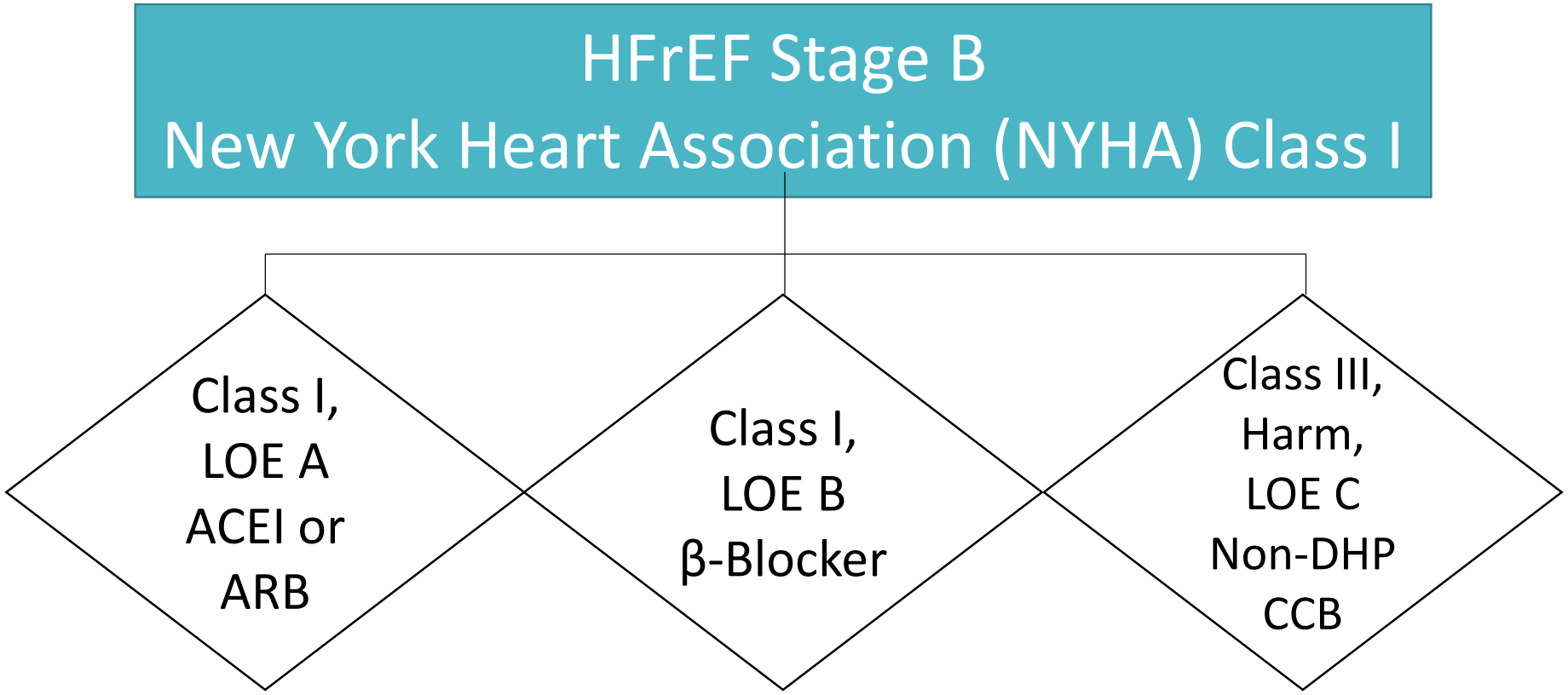
B
- Structural heart disease but without signs and symptoms of HF

C
- Structural heart disease with prior or current symptoms of HF

D
- Refractory HF requiring specialized interventions

Yancy CW, et al. *J Am Coll Cardiol.* 2013;62(16):e147-e239.

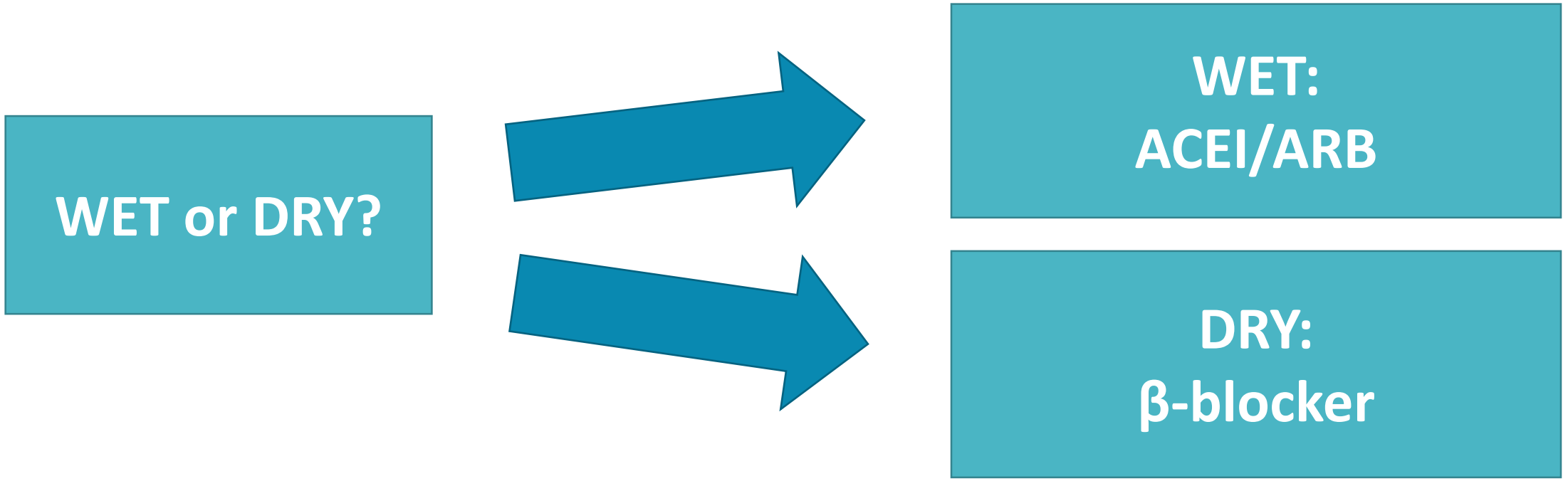
Pharmacotherapy in Stage B HFrEF



ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; Non-DHP CCB, non-dihydropyridine calcium channel blocker.

Yancy CW, et al. *J Am Coll Cardiol.* 2013;62(16):e147-e239; Yancy CW et al. *J Am Coll Cardiol*. 2016;70(6):776-803.

ACEI/ARB versus β-Blocker?



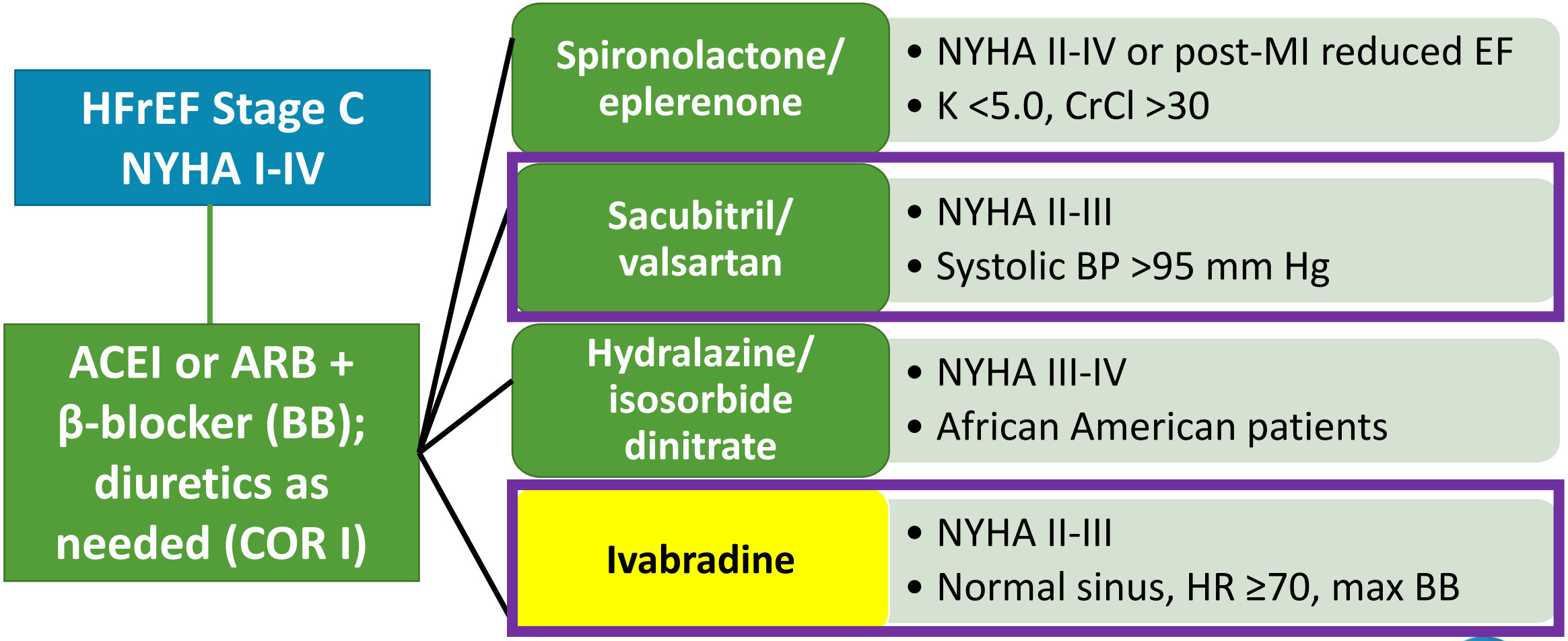
- 1010 patients with mild-moderate HFrEF not on any background therapy in CIBIS-III trial
- Noninferiority between bisoprolol or enalapril as first treatment in intent-to-treat arm

Yancy CW, et al. *J Am Coll Cardiol.* 2013;62(16): e147-e239; Willenheimer R, et al. *Circulation.* 2005;112(16): 2426-2435.

Which β-Blocker to Pick?

	Carvedilol	Metoprolol succinate	Bisoprolol
Adherence		★	★
Low BP		★	★
High BP	★		
Diabetes	★		
Chronic lung disease	★	★	★

Pharmacotherapy in Stage C HFrEF



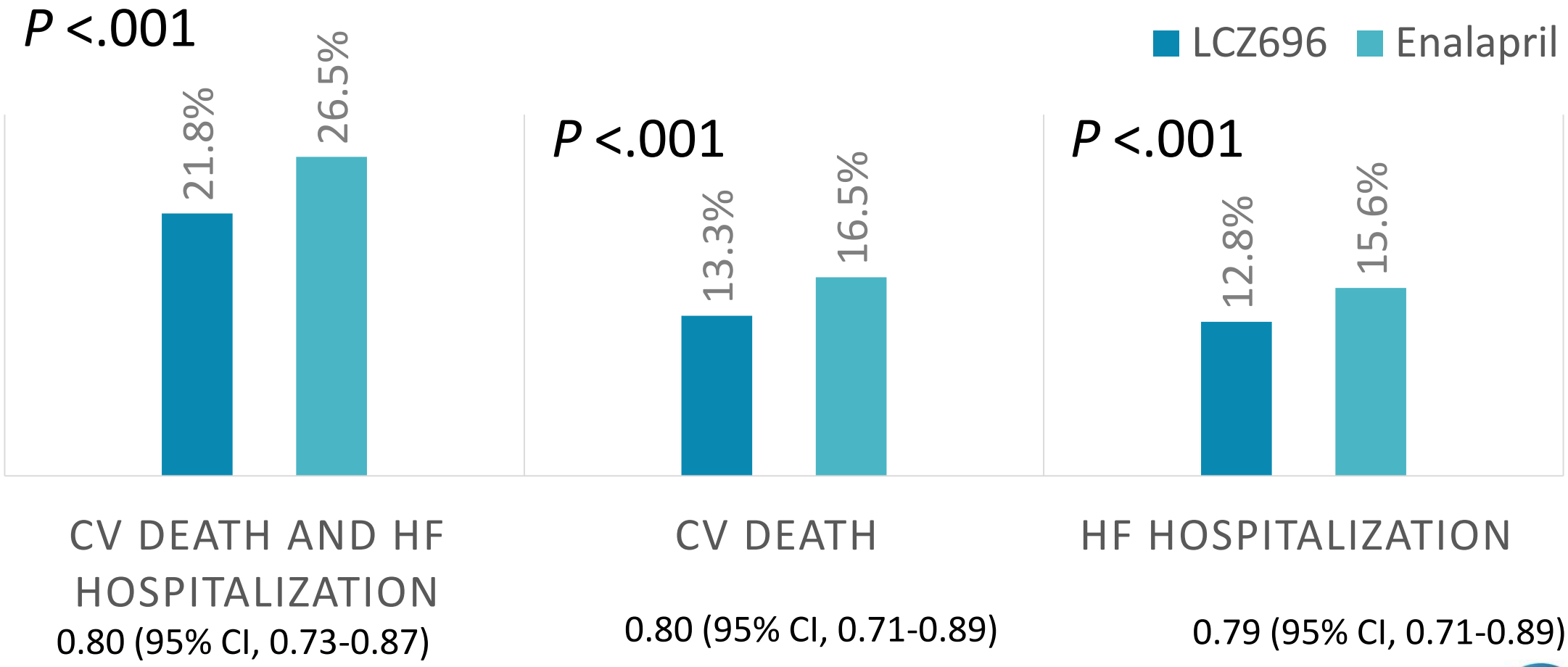
Yancy CW, et al. *J Am Coll Cardiol.* 2013;62(16):e147-e239; Yancy CW, et al. *J Am Coll Cardiol*. 2016;70(6):776-803.

Angiotensin Receptor and Neprilysin Inhibitor (ARNI)

- Sacubitril inhibits neprilysin to increase peptides, specifically natriuretic peptide (eg, vasodilation/natriuresis)
- Valsartan antagonizes the effect of angiotensin II
- PARADIGM-HF trial

McMurray JJ, et al. *N Engl J Med.* 2014;371(11):993-1004.

PARADIGM-HF Results



McMurray JJ, et al. *N Engl J Med.* 2014;371(11):993-1004.

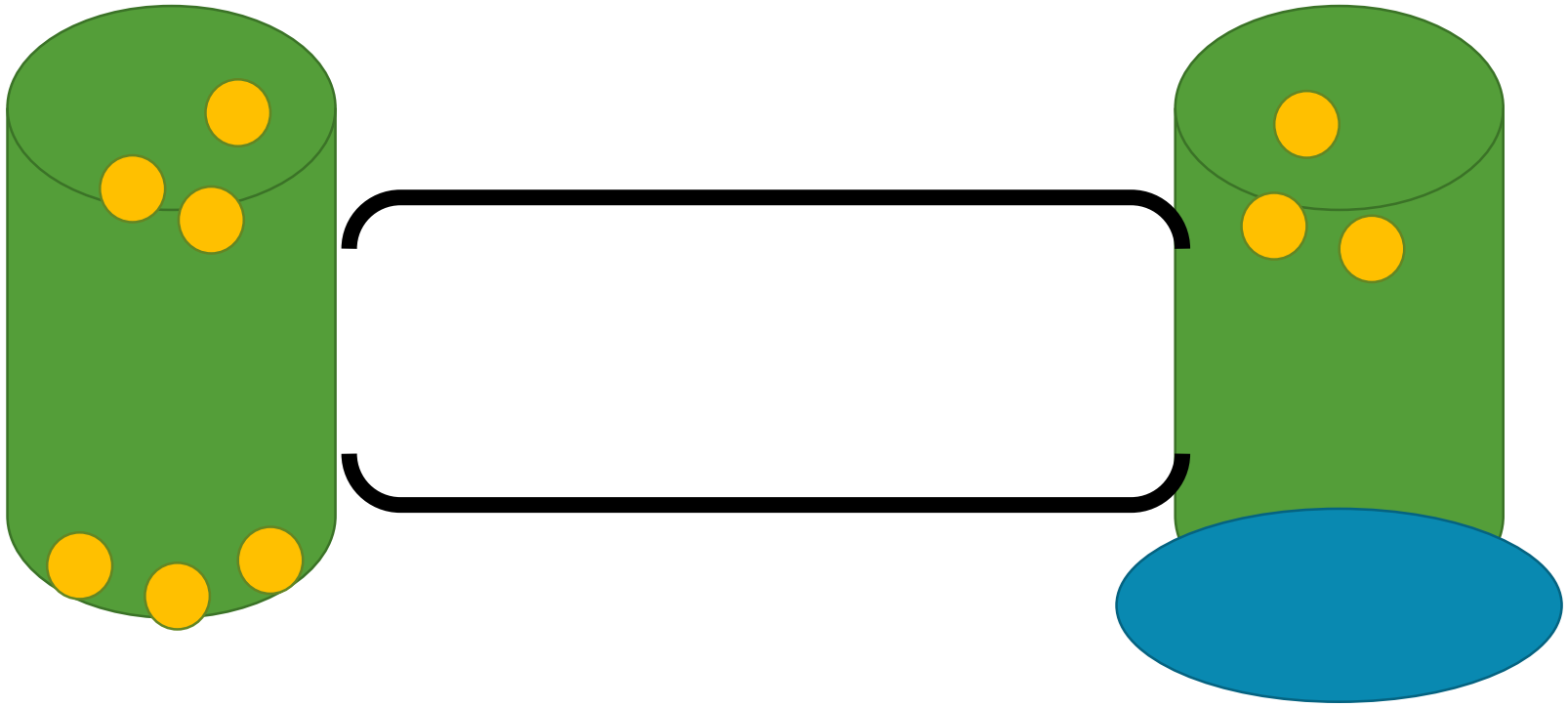
Sacubitril-Valsartan Considerations

- Should **NOT** be administered concomitantly with ACEIs or within 36 hours of the last dose of an ACEI (COR III, B-R)
- Should **NOT** be administered to patients with a history of angioedema (COR III, C-EO)
- Monitor for hypotension, elevated SCr, or elevated potassium
- PIONEER-HF = safety in hospitalized patients for acute HF with stable hemodynamics

Yancy CW, et al. *J Am Coll Cardiol.* 2013;62(16):e147-e239; Yancy CW, et al. *J Am Coll Cardiol*. 2016;70(6):776-803.

Ivabradine

Antagonist of the I*f* current
(hyperpolarization-activated cyclic nucleotide-gated [HCN] channel blocker)



- Reduce sinoatrial node automaticity and, subsequently, HR
- No appreciable effect on contractility or BP

Swedberg K, et al. *Lancet*. 2010;376(9744):875-885.

Systolic HF Treatment With *If* Inhibitor Ivabradine (SHIFT) Trial

- 6558 adult patients with HF with EF ≤35% in normal sinus rhythm (NSR), stable NYHA II-IV symptoms, hospitalization within 1 year, maximal guideline-directed medical therapy (GDMT)

Outcomes	Ivabradine	Placebo	Hazard ratio (95% CI)
CV death/HF hospitalization	24%	29%	0.82 (0.75-0.90)
All-cause mortality	16%	17%	0.90 (0.80-1.02)
CV death	14%	15%	0.91 (0.80-1.03)
HF hospitalization	**16%**	**21%**	**0.74 (0.66-0.83)**

Swedberg K, et al. *Lancet*. 2010;376(9744):875-885.

Ivabradine

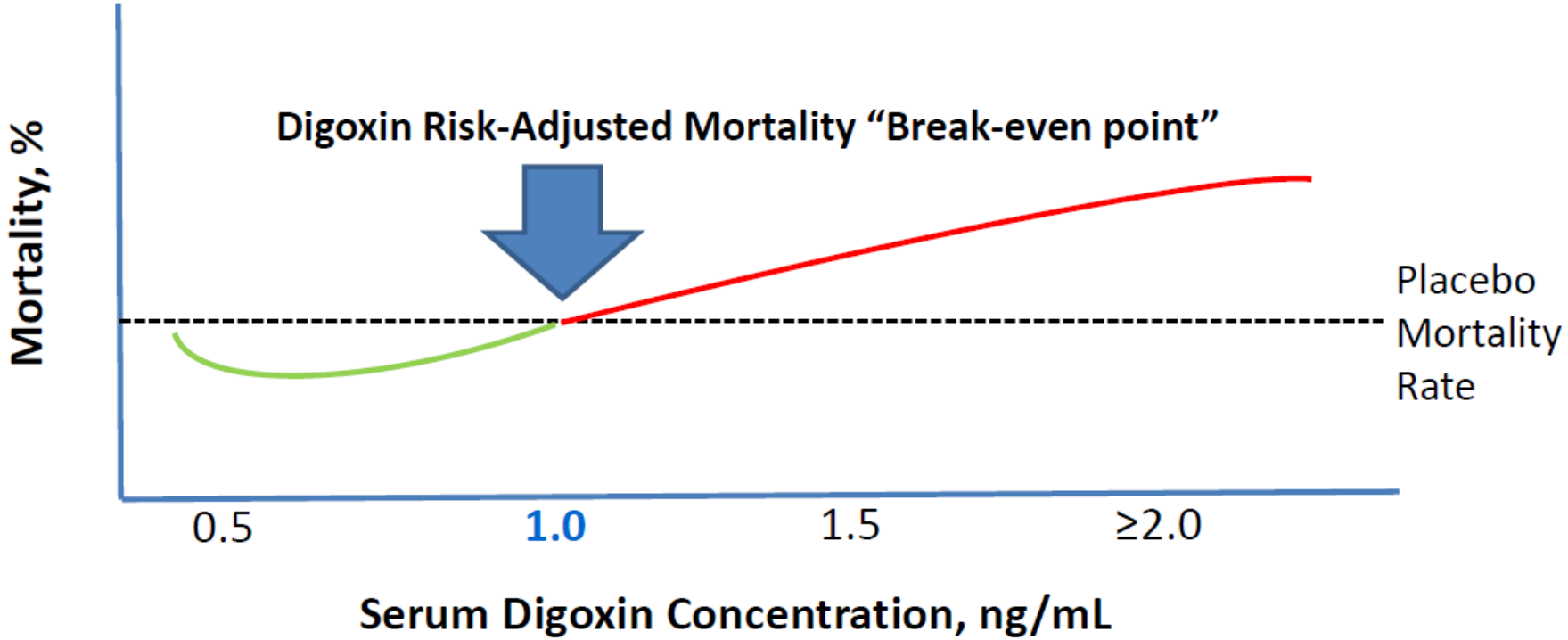
- Phosphenes can occur
  - Generally in first 2 months of therapy
  - Resolve upon stopping

Phosphenes can include transient enhanced brightness in a limited area of the visual field, halos, image decomposition, colored bright lights, or multiple images.

Corlanor. Prescribing information. Amgen Inc; 2019.

What About Digoxin?

- Can be beneficial in patients with HFrEF, unless contraindicated, to decrease hospitalization for HF (COR IIa, LOE B)



Yancy CW, et al. *J Am Coll Cardiol.* 2013;62(16):e147-e239; Digitalis Investigation Group. *N Engl J Med*. 1997;336(8):525-533.

Digoxin Considerations

- Once thou start digoxin, thou shalt keep digoxin at all cost (RADIANCE, PROVED, and Malik analysis)
- Debate about digoxin in atrial fibrillation and HF and mortality (mixed results), use as adjunct
- Thou shalt review kidney function:
  - 0.125 mg daily for 61-80 kg with CrCl ≥30 mL/min
  - 0.0625 mg daily for 61-80 kg with CrCl <30 mL/min

Malik A, et al. *J Am Coll Cardiol.* 2019;74(5):617-627.

Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors in HFrEF

- Evaluation of the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients with Chronic Heart Failure (DAPA-HF) Trial
- Reduced composite HF hospitalizations, HF urgent visits, or CV death by 26% relative to placebo (*P* <.001)
- Favorable safety and no treatment heterogeneity with/without diabetes

McMurray JJ, et al. *N Engl J Med.* 2019;381(21):1995-2008.

Important Numbers of DAPA-HF Trial

51%

of patients with diabetes were taking metformin at baseline.

11%

were on background sacubitril/valsartan.

Do not share same mechanism, adverse drug profile, or drug-drug interactions.

7%

of patients had volume depletion.

No loop adjustment protocol, not different from placebo.

McMurray JJ, et al. *N Engl J Med.* 2019;381(21):1995-2008.

SGLT2 Considerations in HFrEF

- Similar outcomes with all other agents (canagliflozin, empagliflozin)
  - *HFrEF with or without diabetes*
  - *Diabetes with kidney disease, HF, or atherosclerotic CVD*
  - *Diabetes high risk for CVD*
- Discontinue non–evidence-based HF therapy
- Decrease/stop other non-CV favorable antidiabetes agents and/or insulin

Honigberg MC, et al. *Circ Heart Fail.* 2020;13(2):e006623.

What About GDMT Dosing?

Generally, consider titrating dose of GDMT every 2 weeks.

	Starting dose	Maximum dose
Bisoprolol Carvedilol Metoprolol succinate	1.25 mg daily 3.125 mg daily 12.5-25 mg daily	10 mg daily 25-50 mg twice daily 200 mg daily
Sacubitril/valsartan	24/26 mg-49/51 mg twice daily	97/103 mg twice daily
Captopril Enalapril Lisinopril	6.25 mg three times daily 2.5 mg twice daily 2.5-5 mg daily	50 mg three times daily 10-20 mg twice daily 20-40 mg daily
Candesartan Losartan Valsartan	4-8 mg daily 25-50 mg daily 20-40 mg twice daily	32 mg daily 150 mg daily 160 mg twice daily
Spironolactone Eplerenone	12.5-25 mg daily 25 mg daily	25-50 mg daily 50 mg daily
Hydralazine/isosorbide dinitrate	25-50/20-30 mg three times daily	75/40 mg three times daily
Ivabradine	5 mg twice daily (2.5 mg if HR history)	7.5 mg twice daily

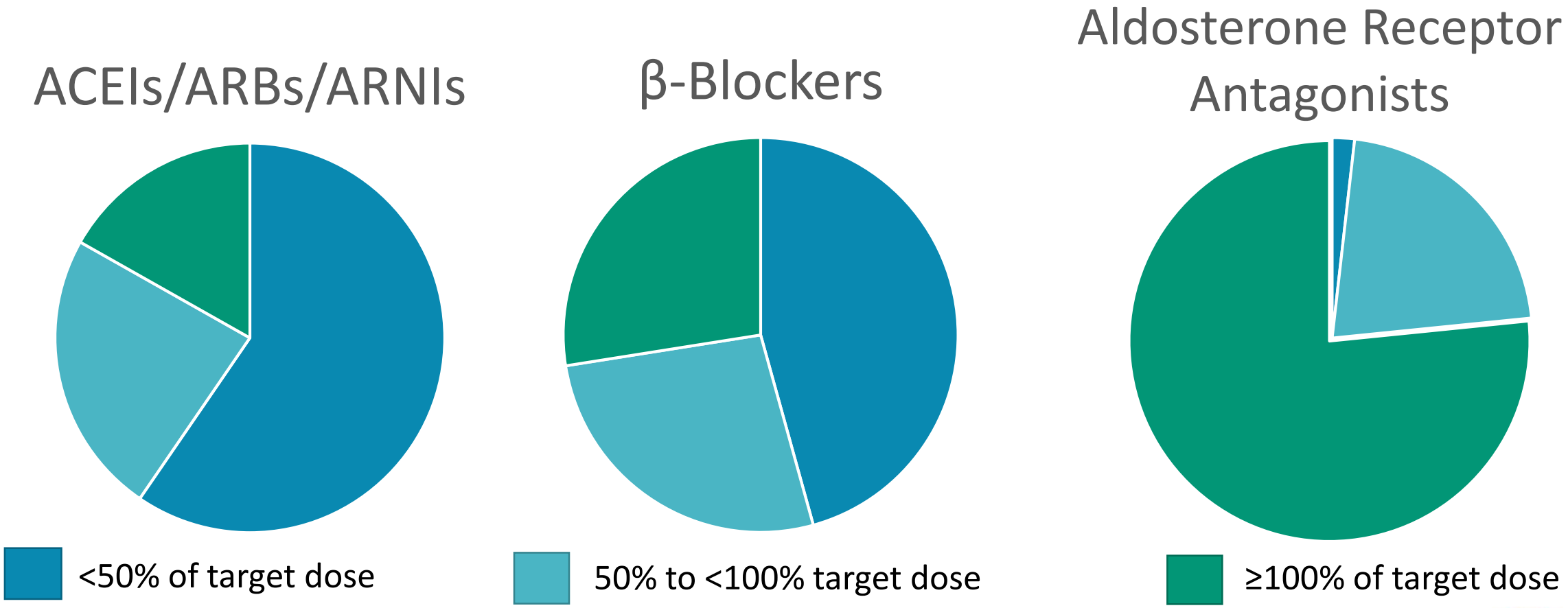
Yancy CW, et al. *J Am Coll Cardiol.* 2013;62(16):e147-e239; Yancy CW, et al. *J Am Coll Cardiol*. 2016;70(6):776-803.

GDMT Dose Does Matter

Trial	HR for death and HF hospitalization	95% CI
ACEI/ARB trials		
ATLAS (lisinopril)	0.85	0.78-0.93
HEAAL (losartan)	0.90	0.82-0.99
Egiziano et al	ACEI: 0.91 ARB: 0.85	0.87-0.95 0.77-0.95
β-blockers		
HF-ACTION	0.96 per 10-mg dose	0.93-0.99

Packer M. *Circulation.* 1999;100(23):2312-2318; Konstam MA, et al. *Lancet*. 2009;374(9704):1840-1848; Egiziano G, et al. *Arch Intern Med*. 2012;172(16):1263-1265; Fiuzat M, et al. *J Am Coll Cardiol*. 2012;60(3):208-215.

How Are We Doing With GDMT Dosing? CHAMP-HF Registry



Greene SJ. *J Am Coll Cardiol.* 2018;72(4):351-356.

Pipeline

Vericiguat

- Soluble guanylate cyclase (sGC) stimulator
- VICTORIA trial to be presented at ACC.20, appears potentially positive result in preliminary analysis

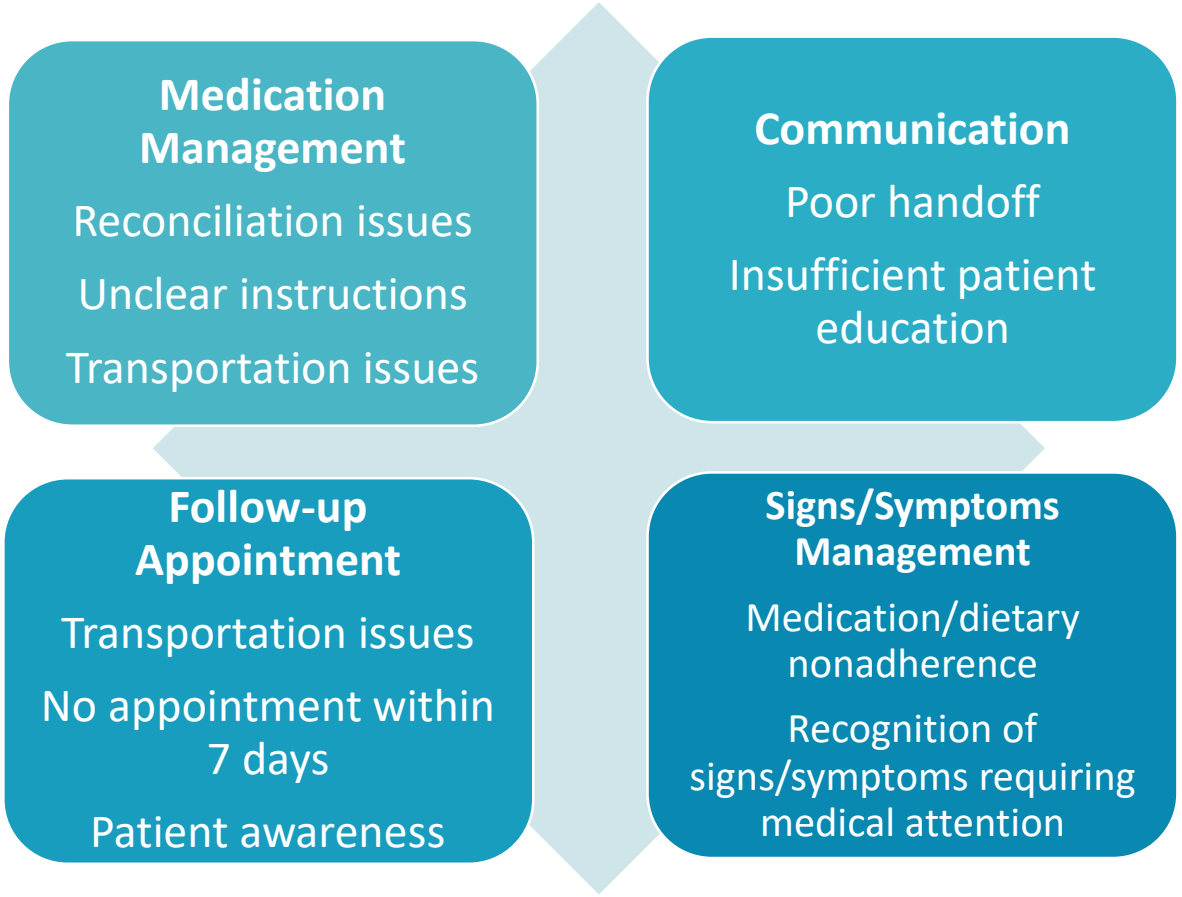
Omecamtiv mecarbil

- Cardiac myosin activator
- Oral agent
- GALACTIC-HF trial underway

Cytokinetics news release. February 6, 2020.biospace.com/article/releases/cytokinetics-announces-publication-relating-to-design-of-galactic-hf-a-phase-3-clinical-trial-of-omecamtiv-mecarbil-in-patients-with-heart-failure-. Accessed March 24, 2020; www.ajmc.com/newsroom/victoria-results-to-headline-accs-firstever-virtual-meeting. Accessed March 30, 2020.

How Can We as Pharmacists Help?

Factors Impeding Transitions of Care and/or Predictors of Readmissions



Albert NM, et al. *Circ Heart Fail*. 2015;8(2):384-409.

Education and Discharge Counseling for Patients With HF

- ✓ Address barriers
- ✓ Perform medication review
- ✓ Engage caregivers and other team members
- ✓ Optimize written materials
- ✓ Employ teach back
- ✓ Identify and follow up on drug-related problems
- ✓ Emphasize self-care
- ✓ Assess patient resources
- ✓ Vary teaching methods
- ✓ Use inpatient and outpatient settings
- ✓ Ensure plan communicated to all providers

Wiggins B, et al. *Pharmacotherapy*. 2013;33(5):558-580.

The Pharmacist's Role in Improving Transitions of Care

- Perform medication reconciliation
- Identify and follow up on drug-related problems
- Assess and address adherence issues
- Educate patient and caregiver
- Engage with community/ambulatory care pharmacists

Hume Al, et al. *Pharmacotherapy*. 2012;32:e326-e337.

Medication History and Reconciliation

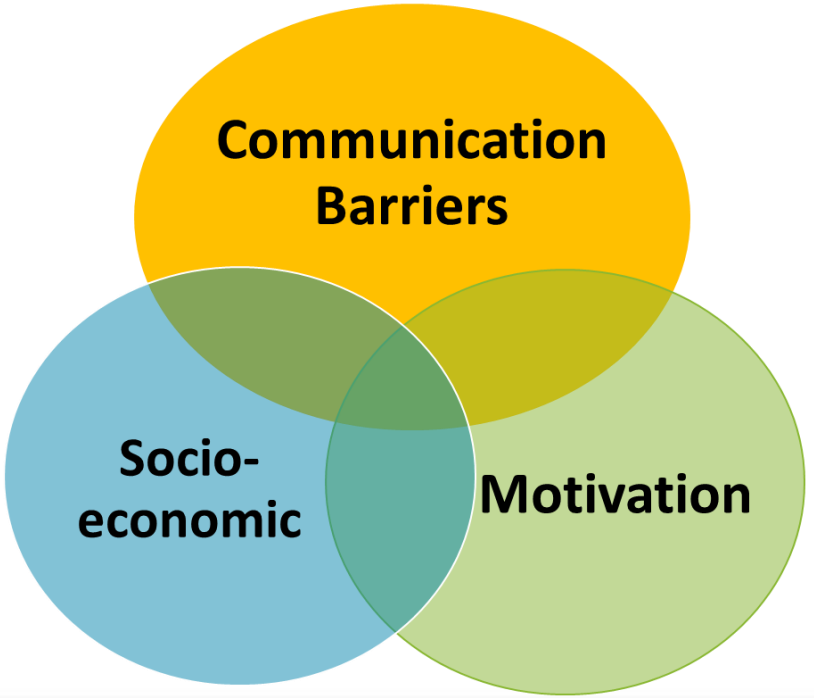
- Should occur at each entry and exit point for every patient (inpatient or outpatient)

- Why is this critical?

Bond CA, Raehl CL. *Pharmacotherapy*. 2007;27(4):481-493; Mueller S. *Arch Intern Med*. 2012;172(14):1057-1069.

Addressing Nonadherence

- Screen patients during interaction for nonadherence
  - Morisky Medication Adherence ($$)
  - Heart Failure Compliance Questionnaire-Modified
  - Simply ask leading questions
    - “How often do you miss medications/not follow diet?”
    - “How do you obtain medications?”
- Motivations of non-adherence:



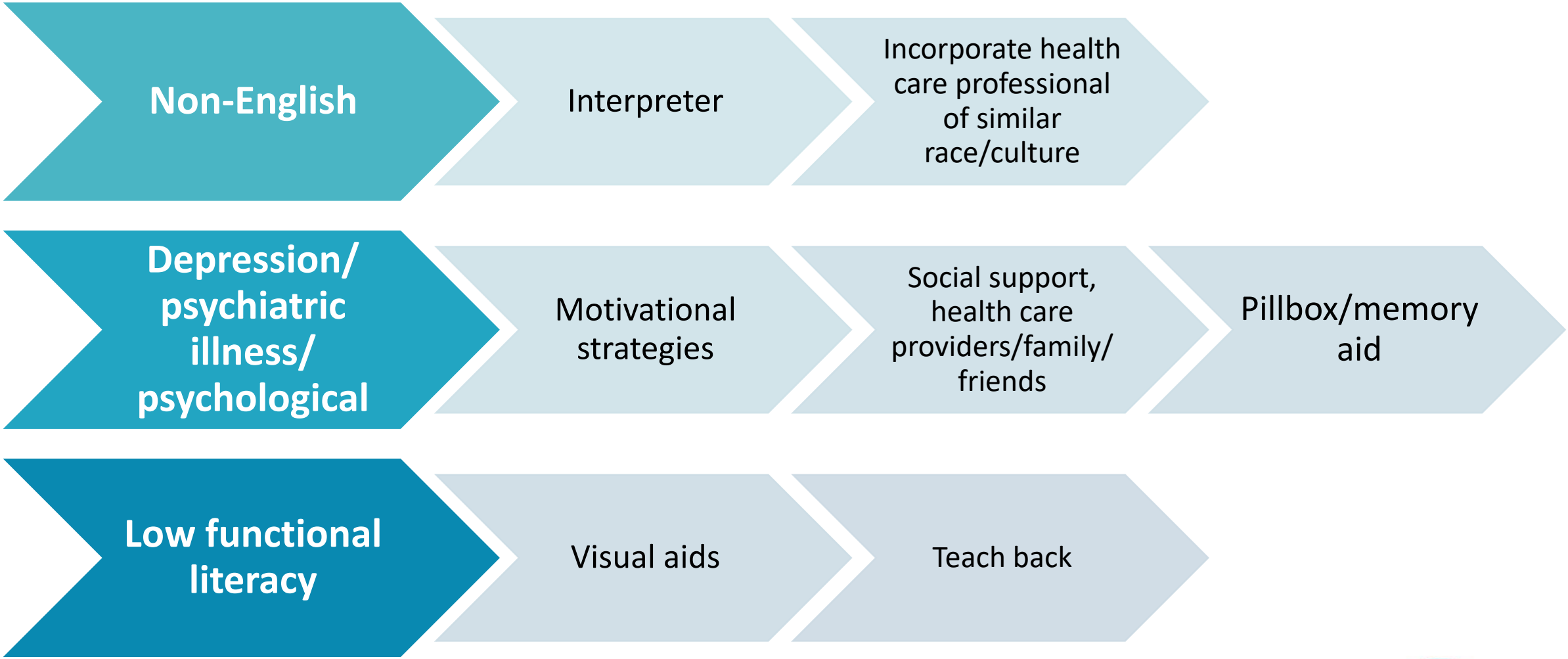
Baroletta S, Dell’Orfano H. *Circulation*. 2010;121(12):1455-1458.

Socioeconomic

Health care coverage	Cost concerns	Complexity
• Work with social worker • Explore drug discount programs	• Generics • Mail order (if transportation issues) • Discount drug programs	• Once-daily dosing • Poly pill

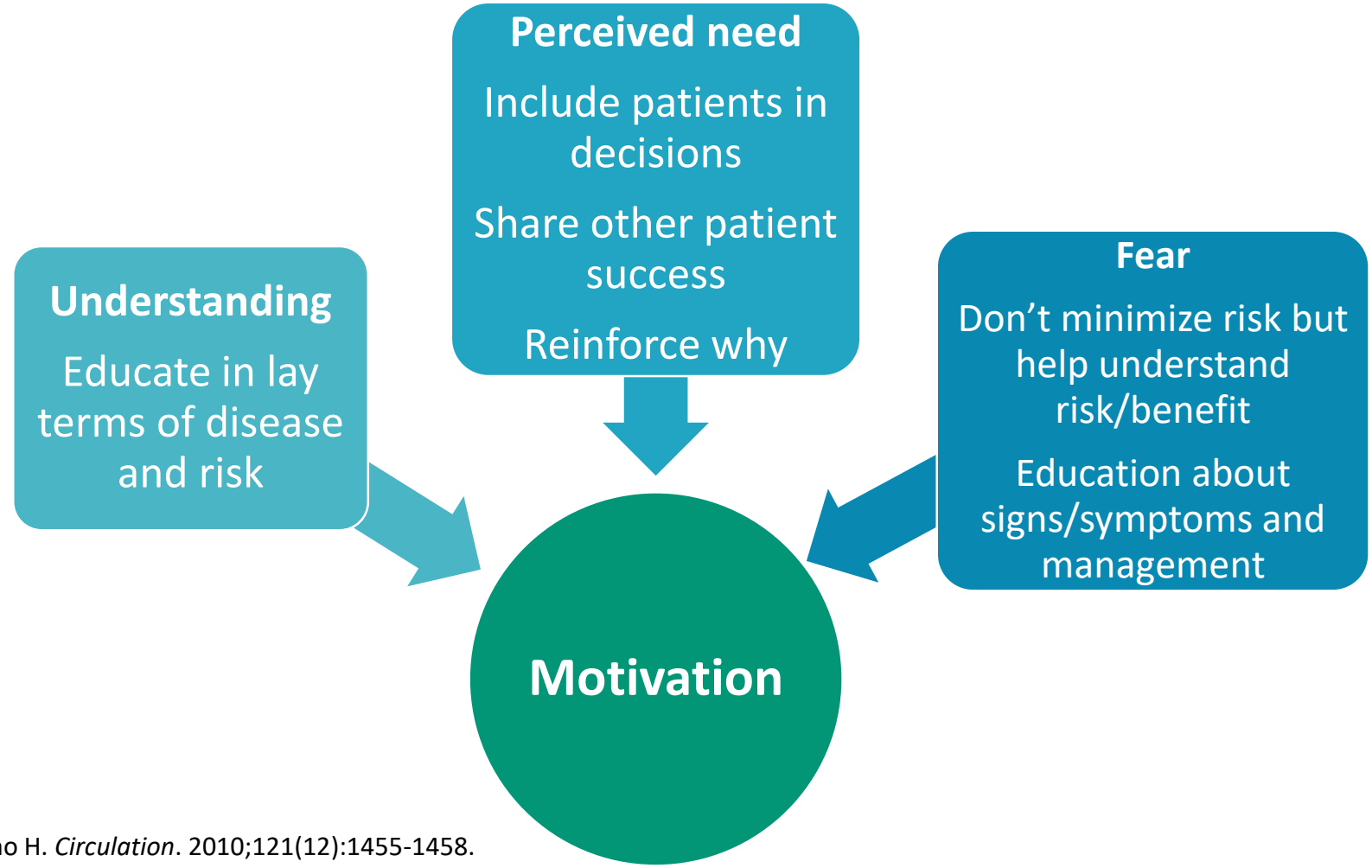
Baroletta S, Dell'Orfano H. *Circulation*. 2010;121(12):1455-1458.

Communication Barriers



Baroletta S, Dell'Orfano H. *Circulation*. 2010;121(12):1455-1458.

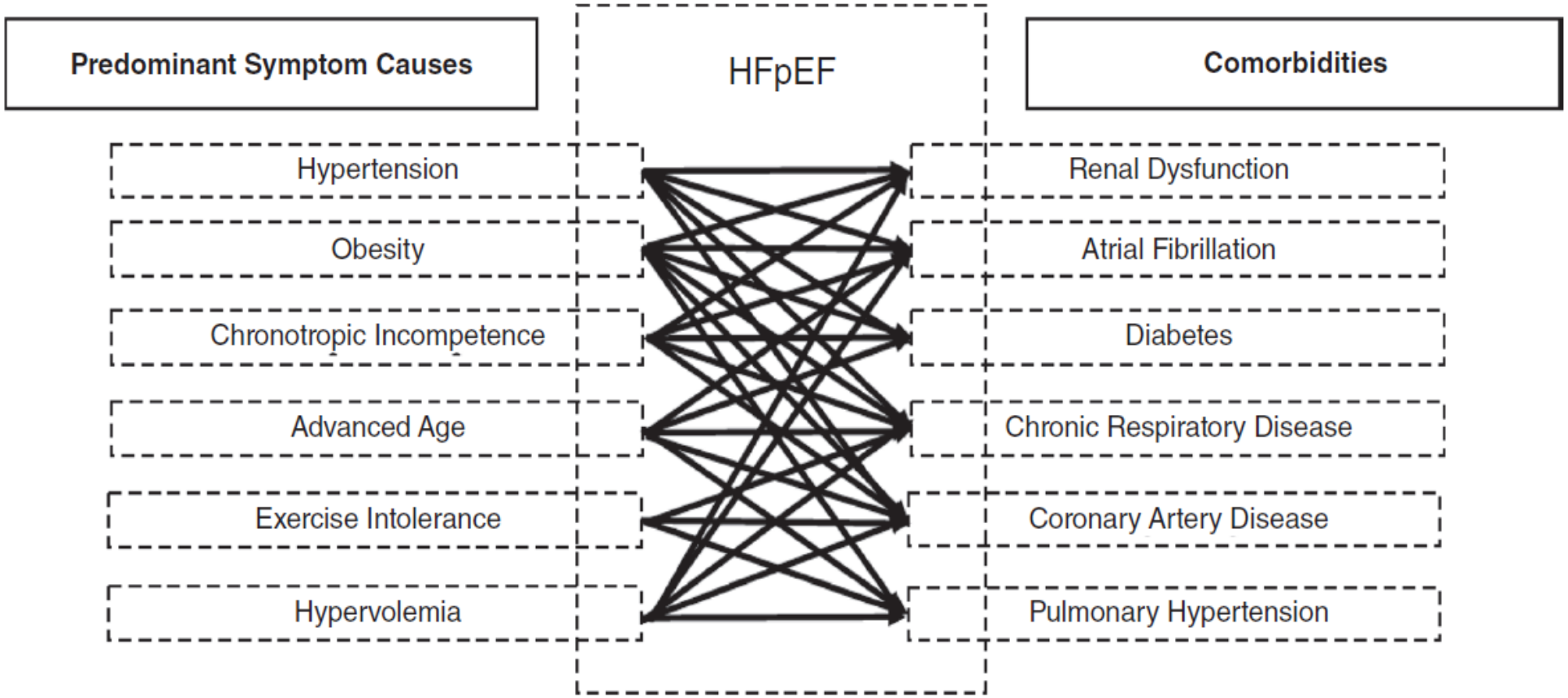
Motivation



Baroletta S, Dell'Orfano H. *Circulation*. 2010;121(12):1455-1458.

Heart Failure With Preserved Ejection Fraction (HFpEF)

HFpEF


Predominant Symptom Causes
HFpEF
Comorbidities
Hypertension
Obesity
Chronotropic Incompetence
Advanced Age
Exercise Intolerance
Hypervolemia
Renal Dysfunction
Atrial Fibrillation
Diabetes
Chronic Respiratory Disease
Coronary Artery Disease
Pulmonary Hypertension

Comorbidities Induce Systemic Proinflammatory State Leading to LV Dysfunction

Coronary microvascular endothelial inflammation	
Theoretical Intervention	Statins

↓

↓ nitric oxide, cyclic GMP, protein kinase G in myocytes	
Theoretical Intervention	Nitrates, PDE5-inhibitors, soluble guanylate cyclase inhibitors

↓

Fibrosis and collagen deposits	
Theoretical Intervention	ACEI/ARB/ARNI/Antifibrotic agents

Lam CS, et al. *Euro Heart J*. 2018;39(30):2780-2792.

HFpEF Pharmacotherapy: HR Agents

Drug/drug class	Pathophysiologic effects	Outcomes	ACC/AHA recommendations
β-Blockers	↓ HR, ventricular response rate, BP, and ↑LV relaxation, blood flow, ↑ diastolic filling	Mixed	Class IIa C for HTN
Verapamil and diltiazem		No benefit	No recommendation
Ivabradine	↓ HR	No improvements any measure	No recommendation
Digoxin	↓ HR, ventricular response rate	No benefit	No recommendation

Yancy CW, et al. *J Am Coll Cardiol.* 2013;62(16):e147-e239; Yancy CW, et al. *J Am Coll Cardiol*. 2016;70(6):776-803.

HFpEF Pharmacotherapy: ACEI/ARB/ARNI

Drug/ drug class	Pathophysiologic effects	Outcomes	ACC/AHA recommendations
ACEI	↓ BP, ↓ LV hypertrophy	↓ hospitalizations 1 year out	Class IIa C for HTN
ARB		↓ hospitalizations	Class IIa C for HTN Class IIb B for hospitalizations
ARNI	↓ BP, ↓ LV hypertrophy, ↓ fibrosis, ↑ natriuresis	↓ NT-pro BNP and wall stress	No recommendations

Yancy CW, et al. *J Am Coll Cardiol.* 2013;62(16):e147-e239.

PARAGON-HF
NYHA II-IV, EF ≥45%, ↑ NT-proBNP

- Primary outcome: total hospitalizations for HF and CV death
  - Death from CV causes: HR, 0.95; 95% CI, 0.79-1.16
  - No benefit individual components of primary outcome

Solomon SD, et al. *N Engl J Med.* 2019;381(17):1609-1620.

HFpEF Pharmacotherapy
Aldosterone Receptor Antagonist

Drug/ drug class	Pathophysiologic effects	Outcomes	ACC/AHA recommendations
ARNI	↓ LV hypertrophy, ↓ fibrosis, ↑ diastolic function	↓ hospitalizations	Class IIb B-R for hospitalizations

- TOPCAT trial
- Primary outcome: death from CV causes, aborted arrest, hospitalizations
  - HR, 0.89; 95% CI, 0.77-1.04
- Hospitalizations: HR, 0.83; 95% CI, 0.69-0.99

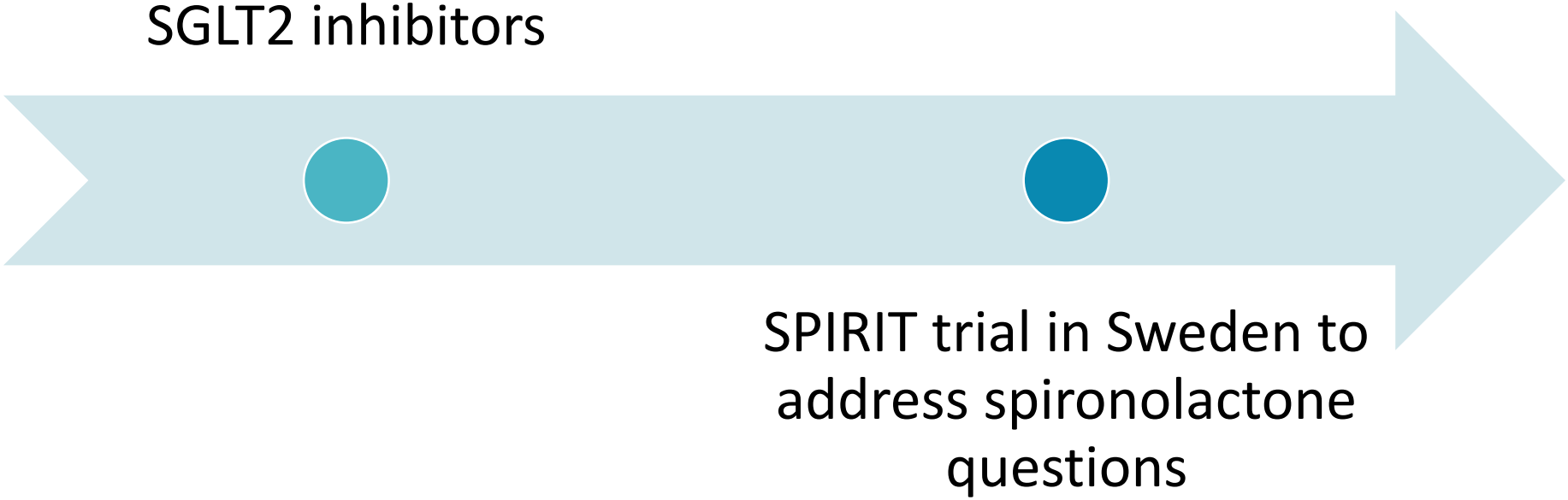
Yancy CW, et al. *J Am Coll Cardiol.* 2013;62(16):e147-e239; Pitt B, et al. *N Engl J Med.* 2014;370(15):1382-1392.

HFpEF Pharmacotherapy: Nitrates/PDE5-Is

Drug/ drug class	Pathophysiologic effects	Outcomes	ACC/AHA recommendations
Nitrates	↓ vascular resistance ↑ myocardial flood flow ↑ endothelial function	No improvement in activity or quality of life	Class III B-R
PDE5-Is	↓ vascular resistance ↓ pulmonary pressure ↑ myocardial flood flow ↑ endothelial function	No improvement in peak VO2 or 6-minute walk	Class III B-R

Yancy CW, et al. *J Am Coll Cardiol.* 2013;62(16):e147-e239.

Pipeline


SGLT2 inhibitors
SPIRIT trial in Sweden to address spironolactone questions

What About Comorbidities in HF?

- Chronic obstructive pulmonary disease
  - Emphasis on prevention (smoking cessation, vaccinations)
  - Consider preferential use of inhaled anticholinergics over β-agonists
  - Early intervention in exacerbations of either disease
  - Volume optimization

Mentz RJ, et al. *J Am Coll Card*. 2014;64(21):2281-2293.

What About Comorbidities in HF?

- Anemia
  - Thorough evaluation and treatment of underlying cause(s) of anemia
  - Iron deficiency anemia common; intravenous iron only proven agent
  - Management of contributing factors, such as diabetes and kidney disease
  - Erythropoietin-stimulating agents are harmful (RED-HF)

Mentz RJ, et al. *J Am Coll Card*. 2014;64(21):2281-2293.

What About Comorbidities in HF?

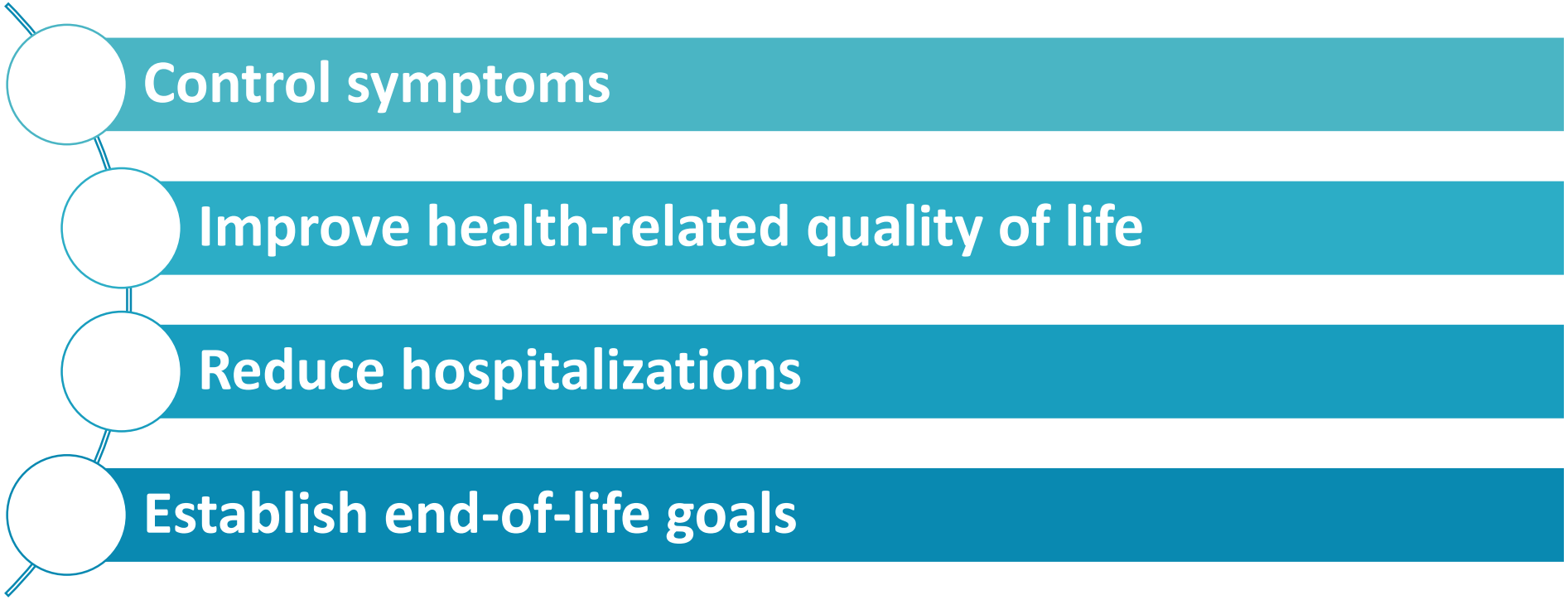
- Kidney dysfunction
  - Appropriate initiation of ACEIs/ARBs/ARNIs with careful monitoring
  - Expect an increased SCr with these agents 0.3-0.5
  - Monitor volume status

Mentz RJ, et al. *J Am Coll Card*. 2014;64(21):2281-2293.

End-of-Life Care in HF

Stage D: Refractory HF

(Marked HF symptoms at rest and/or recurrent hospitalizations despite optimal GDMT)



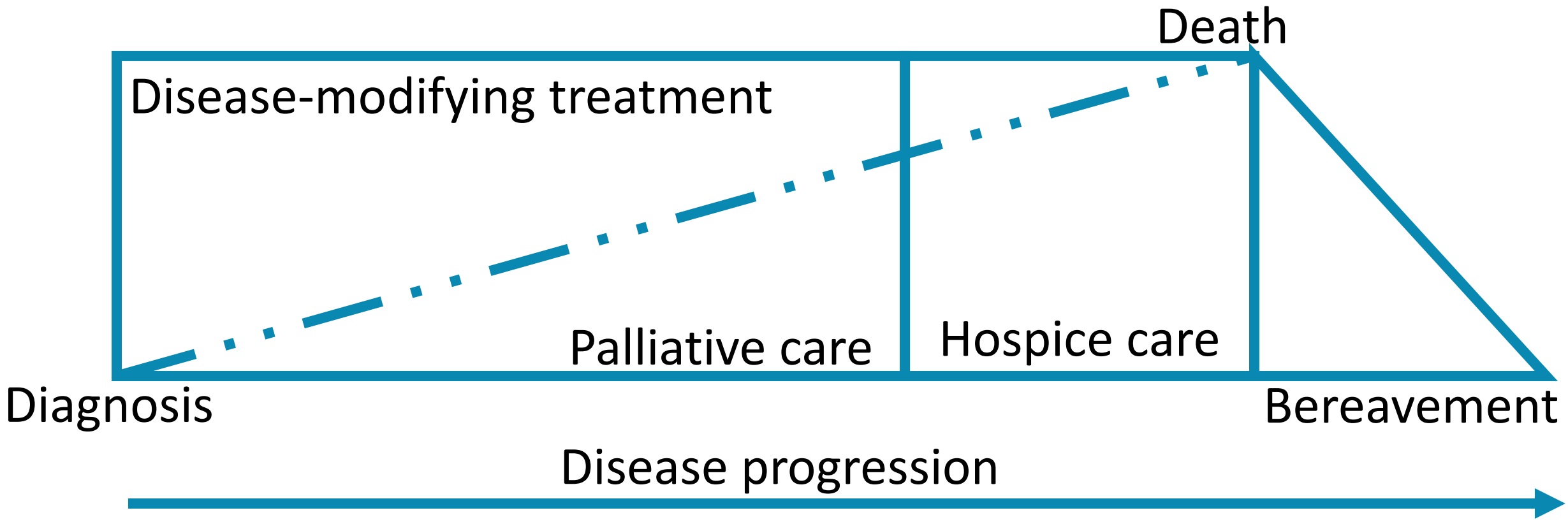
Yancy CW, et al. *J Am Coll Cardiol.* 2013;62(16):e147-e239.

Stage D: Options

- Advanced care measures
- *Heart transplantation*
- *Chronic inotropes*
- *Temporary or permanent mechanical circulatory support*
- Experimental drugs or surgery
- Palliative care or hospice

Yancy CW, et al. *J Am Coll Cardiol.* 2013;62(16):e147-e239.

Palliative Care



Aspects of Palliative Care

Manage cardiac and noncardiac symptoms
Support caregivers/loved ones
Advanced care planning
Goals of care discussions
Determine needs for a palliative care specialist

Hollenberg SM, et al. *J Am Coll Card*. 2019;74(15):1966-2001.

Conclusion

- ARNIs are in for patients who meet criteria
- Consider SGLT2 for patients with HFrEF with and without diabetes
- Optimize therapy, optimize therapy, optimize therapy
- Proper comorbidity management is best for HFpEF
- Pharmacists are critical in the management of patients with HF across all spectrums of the disease

Additional Resources

- 2019 ACC Expert Consensus Document on Patients Hospitalized with Heart Failure
  - *J Am Coll Cardiol*. 2019;74(15):1967-2001. doi: 10.1016/j.jack.2019.08.001

- 2018 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment
  - *J Am Coll Cardiol*. 2018;71(2):202-230. doi: 10.1016/j.jack.2018.09.020

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A Pharmacist's Perspective in Hyperkalemia: Improving Clinical Outcomes With Safe and Effective Treatment Options

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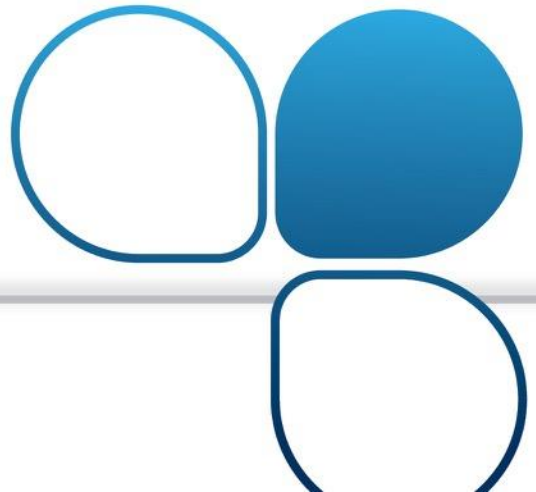
A Pharmacist's Perspective in Hyperkalemia: Improving Clinical Outcomes With Safe and Effective Treatment Options

Todd Brothers, PharmD, BCCCP, BCPS



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Educational Objectives

At the completion of this activity, participants will be able to:

- Review the etiology, risk factors, and health-related complications associated with hyperkalemia
- Outline the challenges associated with traditional therapies, such as SPS, for hyperkalemia
- Recognize the mechanisms of action, dosing, and adverse effect profiles of novel FDA-approved agents for the management and treatment of chronic hyperkalemia
- Express the role of the pharmacist in recognizing patients at risk for hyperkalemia and in making clinical recommendations for the safe and effective treatment of hyperkalemia

Pretest Questions

Pretest Question 1

Before participating in the activity, how confident are you in identifying patients at risk for hyperkalemia?

A. Not at all
B. Somewhat
C. Moderately
D. Very
E. Extremely

Pretest Question 2

Which patient is at highest risk for developing hyperkalemia?

A. A 62-year-old with chronic kidney disease (CKD) Stage III
B. A 75-year-old with controlled type 2 diabetes on valsartan
C. A 51-year-old with HFrEF (35%) and CKD Stage III on lisinopril and metoprolol
D. A 70-year-old with end-stage renal disease (ESRD) receiving dialysis Monday, Wednesday, and Friday

HFrEF, heart failure with reduced ejection fraction.

Pretest Question 3

Prior to 2015, sodium polystyrene sulfonate (SPS) was the only oral potassium binder available on the US market.

Which of the following is/are <u>TRUE</u> regarding SPS?

A. Predictable onset of action
B. Lacks drug–drug interactions
C. Limited clinical trial data to support its use
D. Selectively exchanges K^+ for Na^+ in the colon

Pretest Question 4

Which of the following correctly corresponds to the important counseling points to discuss when a patient begins oral potassium-binding therapy?

A. Patiromer: refrigerate product; if stored at room temperature, use within 3 months
B. Sodium zirconium cyclosilicate (SZC): take 15 grams once daily for the first 72 hours for the initial (acute) treatment
C. Patiromer: separate other oral medications by at least an hour before or after patiromer
D. SZC: may cause hypomagnesemia

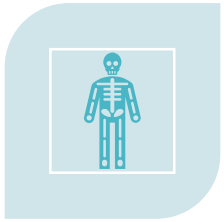
Pretest Question 5

A 59-year-old woman with HFrEF (35%) and CKD Stage III receives guideline-directed medication therapy including: lisinopril 40 mg PO daily, metoprolol XL 50 mg PO daily, and furosemide 40 mg PO daily. Her electrolytes are within normal limits and her cardiologist has recently added spironolactone due to continuing HF symptoms. Two weeks later, a basic metabolic panel revealed a serum potassium level = 5.2 mEq/L of which the patient is asymptomatic.

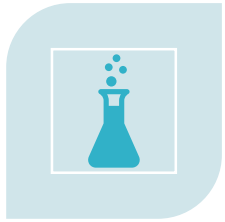
Which of the following actions would be <u>MOST</u> appropriate to take?

A. Discontinue spironolactone
B. Decrease lisinopril to 20 mg PO daily
C. Increase furosemide to 40 mg PO BID
D. Add SZC 10 grams 3x/day x 48 hours

Potassium Physiology

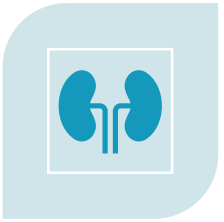


Can be a life-threatening condition and is associated with increased risk of all-cause mortality as well as malignant arrhythmias

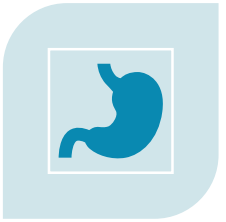


K^+ is primarily an intracellular cation (98%)

Homeostasis is maintained in a narrow range (3.5-5.0 mEq/L)



K^+ homeostasis is primarily managed by the kidneys (90%) matching intake with excretion

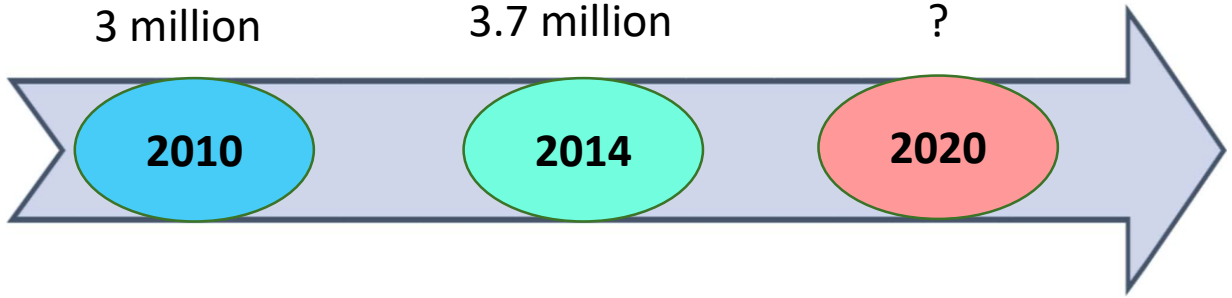


GI tract/sweat removes the remaining potassium excess (10%)

Kovesdy CP. *Kidney Int Suppl (2011)*. 2016;6(1):3-6; Dépret F, et al. *Ann Intensive Care*. 2019;9(1):32; Udensi UK, Tchounwou PB. *Int J Clin Exp Physiol.* 2017;4(3):111-122.

Prevalence

- Incidence of new cases in the general population has been estimated between 2% and 3% and up to 10% in hospitalized patients
- Chronic disease states (CKD, HF, DM) contribute to the development of both acute and chronic hyperkalemia (HK)



- 2018 study identified a 4-fold increase (6.35% vs 1.57%) in the prevalence of HK in patients with CKD and/or HF
- ≈73% of patients with advanced CKD and 40% of patients with chronic HF may be at risk of HK

CKD, chronic kidney disease;
DM, diabetes mellitus;
HF, heart failure.

Betts KA, et al. *Curr Med Res Opin.* 2018;34(6):971-978; Kovesdy CP. *Nat Rev Nephrol.* 2014;10(11):653-662; Acker C, et al. *Arch Intern Med.* 1998;158(8):917-924; Collins A, et al. *Am J Nephrol* 2017;46:213-221; Rosano G, et al. *Eur Heart.* 2018;4:180-188.

Burden of Hyperkalemia

Clinical

- Mortality rates were **more than double** in the Medicare hyperkalemic cohorts (24.9% vs 10.4%) regardless of CKD staging

Economic

- Per-patient-per-month cost was substantially **higher in both** the Medicare ($4945 vs $2137) and commercial ($7247 vs $2879) hyperkalemia cohorts
- 2014: Agency for Healthcare Research and Quality (AHRQ), estimated **$1.2 billion** in total annual hospital charges for patients admitted with a primary diagnosis of HK, with an average **LOS of 3.3 days** and mean charges of **$29,181 per stay**

LOS, length of stay.

Fitch K, et al. *Am Health Drug Benefits.* 2017;10(4):202-210; Polson M, et al. *J Manag Care Spec Pharm*. 2017;23(4-a):S2-S9.

Etiology

1

Acute K^+ intake/load

- Dietary
- Blood transfusion

2

Altered transfer intracellularly

- Acidosis
- Insulin deficit
- β-adrenergic blockers

3

Release from the intracellular space

- Hemolysis
- Tissue injury

4

Altered renal clearance

- CKD
- AKI
- RAAS inhibition

5

Acute changes: AKI on CKD

- Hypovolemia
- Sepsis

Dépret F, et al. *Ann Intensive Care*. 2019;9(1):32; Sarafidis P, et al. *Expert Opin Pharmacother*. 2015;16(14):2205-2215.

AKI, acute kidney injury;
RAAS, renin-angiotensin-aldosterone system.

Clinical Manifestations

- Often there are no warning signs/asymptomatic
  - Mild hyperkalemia (5.5 mEq/L–6.0 mEq/L)
- Symptoms usually develop at higher levels (6.5 mEq/L–7 mEq/L)
  - Rate of change is more important than the absolute laboratory value
- Clinical manifestations associated with HK primarily are related to the muscular and cardiac systems
  - Muscular symptoms include dyspnea, muscle weakness, and paralysis
  - Cardiac symptoms include ventricular arrhythmias, asystole, and mortality

Lewis JL. Hyperkalemia. Merck Manual Professional Version. Reviewed March 2018. Accessed December 28, 2019. www.merckmanuals.com/professional/endocrine-and-metabolic-disorders/electrolyte-disorders/hyperkalemia; Dépret F, et al. *Ann Intensive Care*. 2019;9(1):32; Kovesdy CP. *Kidney Int Suppl (2011)*. 2016;6(1):3-6.

Risk Factors + Comorbidities

- CKD/renal insufficiency (GFR <15 mL/min)*
- HF
- DM
- Hypertension
- Advanced age: ≥65 years
- Medication use
  - RAAS inhibitors, MRAs

*Highest risk factor.

GFR, glomerular filtration rate;
MRA, mineralocorticoid receptor antagonist;
RAAS, renin-angiotensin-aldosterone system.

Rosano GC, et al. *Eur Heart J.* 2018;4:180-188; Kovesdy CP. *Kidney Int Suppl (2011)*. 2016;6(1):3-6; Khanagavi J, et al. *Arch Med Sci*. 2014;10(2):251-257; Betts KA, et al. *Kidney Int Rep.* 2018;3(2):285-393; Luo J, et al. *Clin J Am Soc Nephrol*. 2016;11(1):90-100; Raebel M. *Cardiovasc Therap.* 2012;30:e156-166. Desai A, et al. *J Am Coll Cardiol.* 2007;50(20):1959-1966; Epstein M, et al. *Am J Manag Care*. 2015;21:S212-S220; Palmer B. *N Engl J Med.* 2004;351:585-592.

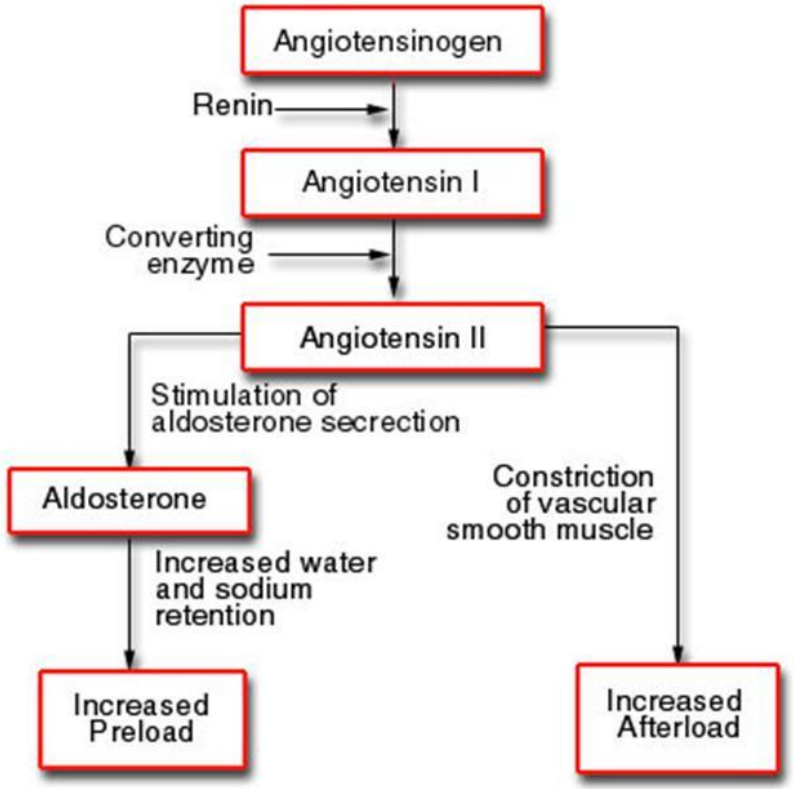
United States: Adult Statistics

- 37 million living with CKD
- 6.5 million living with HF
- In 2015, 30.3 million Americans, or 9.4% of the population, had diabetes
  - 84.1 million had prediabetes
- Patients with at-risk comorbidities especially when combined are **2 to 5x** more likely to experience chronic HK

Kidney disease: the basics. National Kidney Foundation. kidney.org/news/newsroom/factsheets/KidneyDiseaseBasics; CDC. cdc.gov/heartdisease/heart_failure.htm; New CDC report: more than 100 million Americans have diabetes or prediabetes. News release. CDC. Published July 18, 2017. Accessed April 1, 2020. cdc.gov/media/releases/2017/p0718-diabetes-report.html; Rafique Z, et al. *J Manag Care Spec Pharm* 2017;23(4-a suppl):S10-S19.

Medication-Induced HK + RAASi Therapy

- RAAS plays a key role in the regulation of blood volume, blood pressure, and cardiovascular function
- RAAS inhibitors reduce morbidity and mortality risk in patients with HF**r**EF and possibly reduce HF hospitalization risk in patients with HF**p**EF
- Development of hyperkalemia often leads to dose-reduction or discontinuation and denies patients of therapeutic benefits and can worsen clinical and economic outcomes

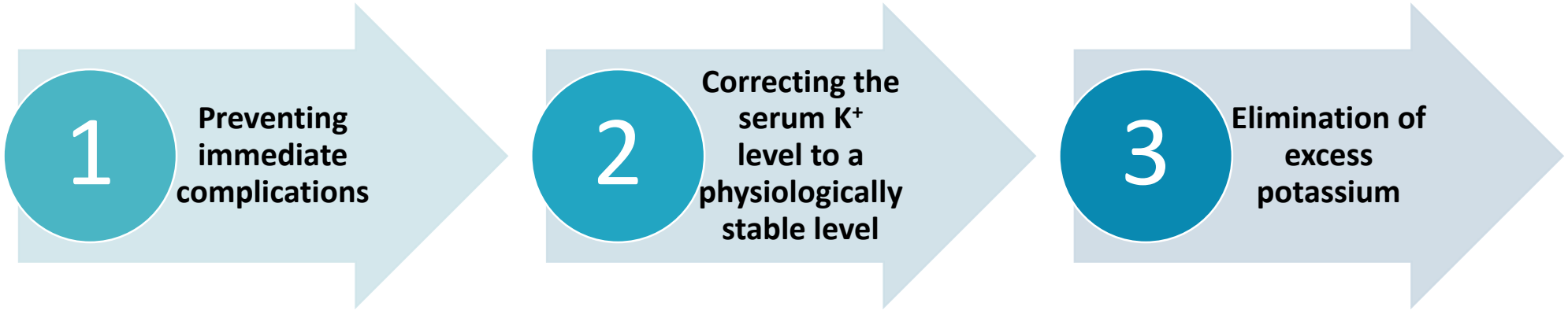


RAASi, renin-angiotensin-aldosterone system inhibitor; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction.

Palmer B. *N Engl J Med.* 2004;351:585-592; Collins A, et al. *Am J Nephrol.* 2017;46:213-221; Jain N, et al. *Am J Cardiol.* 2012;109:1510-1513; Yildirim T, et al. *Ren Fail* 2012;34:1095-1099; Pitt B, et al. *N Engl J Med* 1999;341:709-717; Pitt B, et al. *N Engl J Med.* 2003;348:1309-1321; Zannad F, et al. *N Engl J Med.* 2011;364:11-21; Khan MS, et al. *ESC Heart Fail.* 2017;4:402-408; De Vecchis R, et al. *ESC Heart Fail.* 2018;5:649-650; Linde C, et al. *J Amer Heart Assoc.* 2019;8:e012655.

Management of HK

- Management involves addressing 3 measures



- Treatment is dependent on the extent of increase in the plasma potassium concentration and the presence or absence of electrocardiographic changes or neuromuscular symptoms
- In-hospital mortality rate can be as high as 30% if severe HK is not treated rapidly

Karmacharya P, et al. *J Comm Hosp Intern Med Perspect*. 2015;5(3):10; Betts KA, et al. *Curr Med Res Opin.* 2018;34(6):971-978; Palmer BF, et al. *N Engl J Med.* 2004;351(6):585-592; An JN, et al. *Crit Care*. 2012;16(6):R225.

Acute Treatment Algorithm

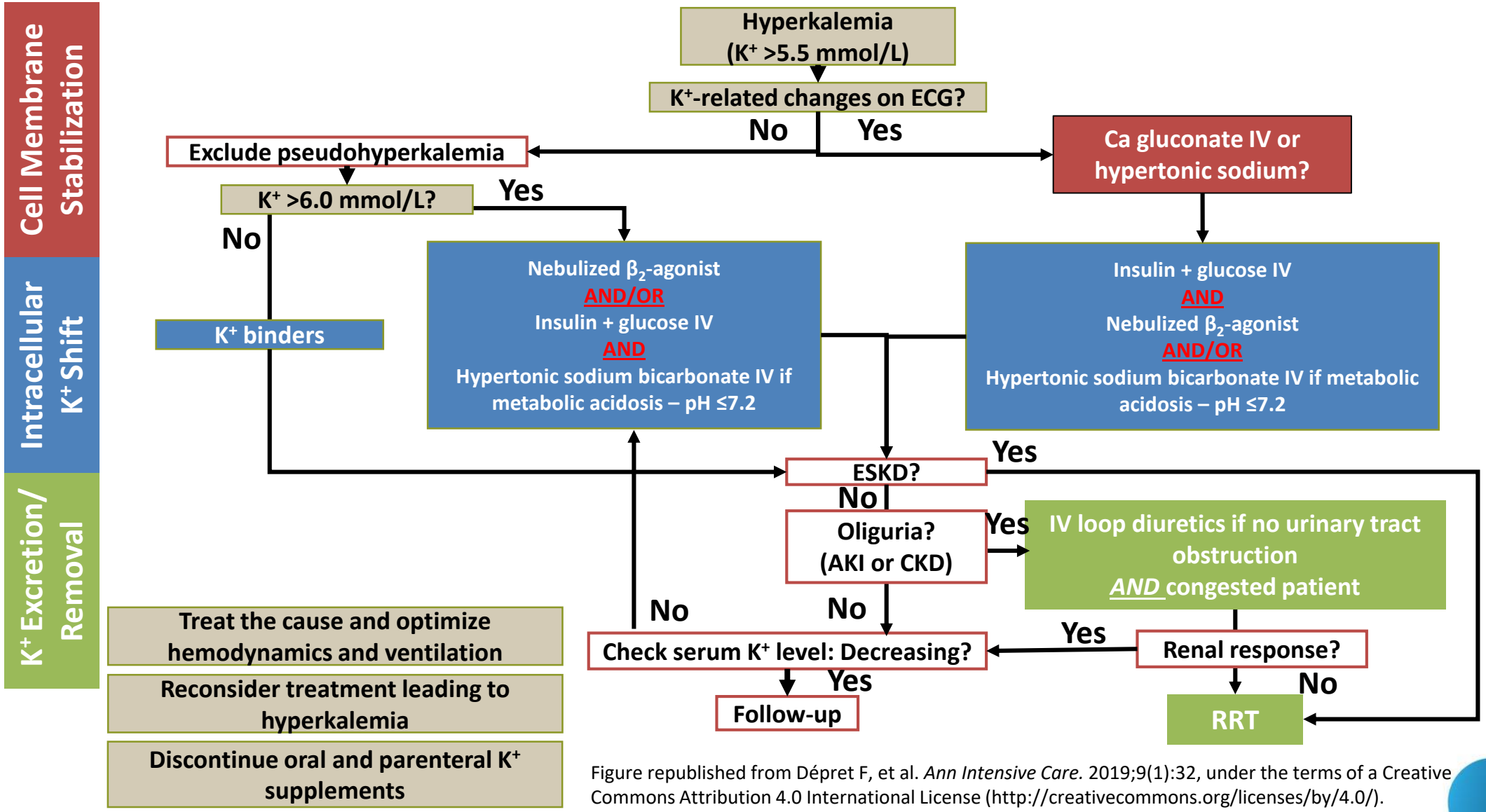


Figure republished from Dépret F, et al. *Ann Intensive Care.* 2019;9(1):32, under the terms of a Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

Historical Treatment and Warnings

- 1958-2015: sodium polystyrene sulfonate (SPS)
- Frequently prescribed with an estimated 5 million doses administered in the United States per year
- Despite its long-standing and widespread use, lacking clinical evidence on efficacy
- There have been several case reports of serious and fatal gastrointestinal (GI) injury associated with SPS

FDA Black Box Warning

- **2009:** released warning and discontinuation of 70% sorbitol–sodium polystyrene sulfonate due to case reports of intestinal injury and colonic necrosis

- **2017:** warned patients not to take any other oral medications for at least 3 hours before or after administration
  - 6 hours for patients with gastroparesis/other conditions that delay the passage of food from the stomach to the small intestine

Sterns RH. *J Am Soc Nephrol*. 2010;21(5):733-735; Harel Z. *Am J Med*. 2013;126(3):264.e9-264.e24; McGowan CE, et al. *South Med J.* 2009;102(5):493-497; Chaitman M, et al. *P T*. 2016;41:43-50; Batterink J, et al. *Can J Hosp Pharm.* 2015;68:296-303; Abraham SC, et al. *Am J Surg Pathol*. 2001;25:637-644; Epstein M, Pitt B*. Expert Opin Pharmacother*. 2016;17:1435-1448; Kayexalate. Prescribing information. Sanofi-Aventis; 2018.

SPS Limitations

- SPS mechanism of action: **non-selectively** exchanges K^+ for Na^+ in the colon
  - Has led to volume retention, hypertension, hypomagnesemia, and hypocalcemia
- Variable time to onset of effect: considered a poor choice in acute HK management
- Drug interactions: separate dosing from other medications
- Poor taste; promoting nonadherence; potentiating recurrence; poorer clinical and economic outcomes

Chaitman M, et al. *Pharm Therap.* 2016;41(1):43-50; Rafique Z, et. al. *J Manag Care Spec Pharm.* 2017;23(4-a):S10-S19.

Risk of Hospitalization for Serious Adverse GI Effects Associated With SPS Use

- 2019: population-based, retrospective, cohort study of 20,020 matched adult patients (age ≥ 66) were dispensed SPS and the risk of hospitalization for serious adverse GI effects from 2003-2015 were analyzed
- Findings: SPS use was associated with a 1.9-fold higher risk of hospitalization within 30 days of initial prescription for adverse gastrointestinal events compared with nonuse
- When examining the subtypes of GI injury, the hazard ratio was highest for intestinal ischemia/thrombosis (HR, 4.92), whereas no association was detected for GI ulceration/perforation (HR, 1.75) or resection/ostomy (HR, 1.34)

With unknown efficacy and noted safety concerns,
clinicians have struggled for years to safely and effectively manage HK with SPS.

Noel JA, et al. *JAMA Intern Med*. 2019;179(8):1025-1033; Sterns RH, et al. *J Am Soc Nephrol.* 2010;21(5):733-735.

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Newer Oral Potassium-Binding Agents

Patiromer (Veltassa)

Sodium Zirconium Cyclosilicate (Lokelma)

Chronic and Recurrent Treatment Options

	Sodium polystyrene sulfonate (SPS)	Patiromer	Sodium zirconium cyclosilicate (SZC)
FDA approval	1958	2015	2018
Properties and mechanism of action	Cation exchange resin; exchanges Na^+ for K^+ in gut	Nonabsorbable polymer; exchanges Ca^{++} for K^+ in the colon	Nonabsorbable polymer; exchanges H^+ and Na^+ for K^+ in the colon
Sorbitol content	20 grams in each 15-g dose	2 grams in each 4.2-g dose	None
Site of action	Primarily large intestine	Distal colon	Entire GI tract
Dosing	15-60 g daily (oral) 30-50 g daily (enema)	8.4-25.2 g daily (oral) titrated weekly	Acute: 10 g 3x/day x up to 48 h Chronic: 10 g once daily (can range from 5 g every other day to 15 g daily; adjust as needed (oral))
Onset of action/duration (h)	Onset: 1-2 up to 12 h Duration: 4-6 h	Onset: 7 h Duration: 24 h	Onset: 1 h (after 10-g dose) Duration: 12-24 h
ADEs	Constipation, hypomagnesemia, hypocalcemia, colonic necrosis	Constipation/diarrhea, hypomagnesemia	Mild to moderate edema

Savarese G, et al. *Card Fail Rev*. 2017;3(1):33-39; Mikrut M. *Hosp Pharm.* 2004;39(8):765-771; Sodium polystyrene sulfonate. Prescribing information. Sanofi-Aventis; 2010; Veltassa. Prescribing information. Relypsa, Inc; 2018; Lokelma. Prescribing information. AstraZeneca; 2018.

Patiromer Trial Summaries

Study design	Patient population	Primary end point(s)	Treatment + duration	Conclusion
AMETHYST-DN Phase 2, prospective, randomized, open-label, dose ranging	n = 306 Outpatients with HK; DM II + CKD receiving ACE-I, ARB or both	Mean change in K^+ from baseline to week 4 or prior dose titration	4.2 g, 8.4 g, 12.6 g twice daily [mild HK] or 8.4 g, 12.6 g, 16.8 g twice daily [moderate HK] x 52 weeks	All doses of patiromer decreased K^+ at 4 weeks, which was maintained at 52 weeks
PEARL-HF Phase 2, prospective, randomized, double-blind, placebo controlled, parallel group	n = 105 HF + HK with indication for initiation of aldosterone-antagonist treatment	Mean change in K^+ from baseline to end of study (28 days)	15g oral twice daily vs placebo	At 28 days, serum potassium was significantly lower in the patiromer group compared with placebo
OPAL-HK Phase 3, prospective, single group/single blind initial tx phase and a randomized single blind, placebo-controlled withdrawal phase	Initial phase: n = 243 Randomized phase: n = 107 Initial 4-week phase: CKD III or IV + HK on RAASi Randomized 8-week phase: Patients with K^+ 3.8-5 mEq/L at end of initial phase who had K^+ ≥5.5 mEq/L at baseline	Initial: Mean change in K^+ from baseline to week 4 Randomized: between group difference in median change in K^+ over the first 4 weeks or earliest visit when K^+ <3.8 or >5.5 mEq/L	Initial: 4.2 g mild (5.1-5.4 mEq/L); 8.4 g moderate to severe (5.5-6.4 mEq/L); twice daily x 4 weeks Randomized: continued same dose at week 4 or switched to placebo x 8 weeks	Initial phase: K^+ reduction of 1.01 ± 0.03 mEq/L Randomized phase: median K^+ increase 0.72 mEq/L in placebo group and no change in patiromer group

Bakris GL, et al. *JAMA.* 2015;314 (2):151-161; Pitt B, et al. *Eur Heart J.* 2011;32(7):820-828; Weir MR, et al. *N Engl J Med.* 2015;372(3):211-221; Beccari M. *Core Evidence.* 2017;12:11-24.

Phase 3b DIAMOND Trial

- Patiromer use to improve outcomes by enabling patients with HF +/- CKD to be treated with RAASi therapy in accordance with HF treatment guidelines
- Study design: global, multicenter, double-blind, placebo-controlled trial aiming to study approximately 2400 patients in more than 400 sites
- Eligible patients will have HF +/- CKD with either current HK at screening or a history of HK in the past year that led to a reduction or discontinuation of RAASi therapy
- The primary end point: the time to first occurrence of cardiovascular death or cardiovascular hospitalization
- Results are expected in 2022

First patient treated in DIAMOND study to evaluate if Veltassa (patiromer) improves outcomes by establishing long-term use of essential RAASi therapy. News release. Relypsa. Published May 21, 2019. Accessed January 11, 2020. relypsa.com/newsroom/press-releases/052119

SZC Trial Summaries

Study design	Patient population	Primary end point(s)	Treatment + duration	Conclusion
HARMONIZE Phase 3, prospective, randomized, double-blind, placebo-controlled trial	n = 258 Open-label phase: (outpatients with HK)	Open-label: Change in K^+ over 48 hours	Open-label: SZC 10 g oral 3 times daily x 2 days	Open-label: by 48 hours; mean rate of K^+ reduction/h = 0.3%; mean absolute reduction = 1.1 mEq/L
	n = 237 Randomized phase: (outpatient with normal K^+) at hour 48 of initial phase	Randomized: Mean K^+ in each SZC group compared to placebo during days 8-29	Randomized: SZC 5g, 10g, 15g oral daily or placebo x 28 days	Randomized: Mean K^+ 5 g = 4.8 mEq/L 10 g = 4.5 mEq/L 15 g = 4.4 mEq/L Placebo = 5.1 mEq/L
Subgroup analysis of HARMONIZE trial, 11-month, open-label extension phase	n = 87 Patients with HF at baseline + evidence of hyperkalemia (60 of 87 receiving RAASi therapy)	Mean serum K^+ and proportion maintaining normokalemia during days 8-29 post-randomization	Randomized: SZC 5 g, 10 g, 15 g oral daily or placebo x 28 days	1. 98% of patients achieved normokalemia within 48 hours 2. Proportions of SZC (83%, 89%, 92%) maintained normokalemia vs placebo (40%) 3. RAASi doses remained unchanged: 5 g, 10 g, and 15 g = 4.7, 4.5, and 4.4 mmol/L) vs placebo (5.2 mmol/L)

Kosiborod M, et al. *JAMA.* 2014;312(21):2223-2233; Anker S, et al. *Eur J Heart Fail.* 2015;17:1050-1056; Beccari M. *Core Evidence.* 2017;12:11-24.

DIALIZE Trial

- The DIALIZE study evaluated SZC in the management of hyperkalemia in hemodialysis patients
  - DIALIZE is the first randomized, placebo-controlled trial to evaluate a potassium binder in patients on stable hemodialysis
- Patients with ESRD have minimal renal potassium excretion and despite hemodialysis, often have persistent pre-dialysis hyperkalemia
- Study design: phase 3b, randomized, double-blind, placebo controlled trial
- Participants were randomized to receive SZC or placebo once daily on non-dialysis days
- The primary outcome: proportion of patients who maintained serum potassium between 4 and 5 mEq/L during at least 3 of 4 dialysis treatments and did not require rescue therapy for hyperkalemia

Fishbane S, et al. *J Am Soc Nephrol.* 2019;30(9):1723-1733.

SZC in ESRD-HD + HK: DIALIZE Trial

Methods	Outcomes
196 patients with ESRD	SZC cohort maintained pre-HD K^+ levels between 4-5 mmol/L during ≥3 months of 4 HD treatments (41.2%) vs placebo (1.0%)
Managed ≥3 months by HD 3x/weekly with persistent HK (despite adequate HD)	Need for rescue therapy to reduce serum K^+ during the treatment period: 5.1% placebo cohort vs 2.1% SZC cohort
Randomized 1:1 to SZC 5 g daily vs placebo	**Conclusion**
4-week dose-titration period to establish normokalemia	SZC is effective and well tolerated treatment for pre-dialysis HK in patients with ESRD undergoing adequate dialysis sessions
Titrated in 5-g increments; max 15 g/day on non-HD days only; 4-week evaluation period with the stable dose maintained	

Fishbane S, et al. *J Am Soc Nephrol.* 2019;30(9):1723-1733.

HD, hemodialysis.

Additional Trials

- **Sodium Zirconium Cyclosilicate in Hyperkalemia,** *NEJM* 2015**:** Evaluated the use of SZC and found the mean reduction of serum potassium by 0.7 mEq/L within 4 hours after receiving a 10-gram dose.
- **Hyperkalemia Randomized Intervention Multidose ZS-9 Maintenance (HARMONIZE) Study,** *JAMA* 2014**:** Examined a subgroup of 45 patients with severe hyperkalemia (>6 mmol/L) who received a 10-gram dose of SZC and had a median time to serum potassium level less than 6.0 mmol/L within 1.1 hours and a median time to a level of less than 5.5 mmol/L at 4 hours.
- **A Study to Evaluate a Potassium Normalization Treatment Regimen Including Sodium Zirconium Cyclosilicate [ZS] Among Patients With S-K ≥5.8 (ENERGIZE),** *Acad Emerg Med* 2020**:** Phase 2, parallel-group, multicenter, randomized, double-blind, placebo-controlled pilot study - evaluated the effect of SZC versus placebo when added to standard of care (insulin and glucose) on the reduction of serum potassium at 4 hours after administration
  - 70 patients randomized (SZC n = 33, placebo n = 37) with mean initial serum K^+ similar between groups
  - SZC: Least squares mean (±SD) serum K^+ change from baseline to 4 hours was -0.41 (±0.11) mmol/L;

    Placebo: -0.27 (±0.10) mmol/L
  - Greater reduction in mean (±SD) serum K^+ from baseline occurred with SZC compared with placebo at 2 hours: -0.72 (±0.12) versus -0.36 (±0.11) mmol/L
  - Adverse events were similar in both the SZC and placebo groups at 0 to 24 hours
  - Concluded: Study demonstrated that SZC in combination with insulin and glucose may provide an incremental benefit in the emergency treatment of hyperkalemia over insulin and glucose alone

Packham DK, et al. *N Engl J Med*. 2015;372(3):222-231. Kosiborod M, et al. *JAMA.* 2014;312(21):2223-2233; Peacock WF, et al. *Acad Emerg Med* .2020; Epub ahead of print; https://clinicaltrials.gov/ct2/show/NCT03337477

Advantages: Newer Agents

Better clinical trial data to support efficacy and safety

Better tolerability and adverse effect profiles

High-risk populations: Continuation of RAASi therapy at optimal doses

Medication Use and Counseling

Patiromer

- Tasteless powder for suspension
- Storage: refrigerate at 2°-8 °C [36° -46 °F]
  - If room temperature, must be used within 3 months
- Preparation:
  - Empty entire contents of packet into 30 mL of water, stir well (do not add to heated drinks)
  - Add an additional 60 mL of water, stir well; mixture will be cloudy
- Administration: Drink immediately
  - If powder remains in the glass, add water, stir, and drink contents; repeat until no powder remains
- Drug Interactions: Separate other oral medications by at least 3 hours before or after patiromer
- AE: Avoid with severe constipation, bowel obstruction
  - Diarrhea, nausea, abdominal discomfort, flatulence
  - Hypomagnesemia

SZC

- Tasteless powder for suspension
- Storage: in foil packets at room temperature 15°-30 °C [59°-86 °F]
- Preparation:
  - Empty entire contents of packet into a drinking glass with 3 tablespoons of water or more if desired and stir well
- Administration: Drink immediately
  - If powder remains in the glass, add water, stir, and drink contents; repeat until no powder remains
- Drug Interactions: Separate other oral medications by at least 2 hours before or after SZC
- AE: Avoid with severe constipation, bowel obstruction
  - Edema: Every 5 grams of SZC = 400 mg of Na^+

Veltassa. Prescribing information. Relypsa, Inc; 2018; Lokelma. Prescribing information. AstraZeneca LP; 2018.

The Role of the Pharmacist

Inpatient → Transitions of Care → Outpatient

Clinician

- Involvement and therapeutic recommendations, monitoring patient response, guideline development
- Identification of medication-induced HK
- Proactive screening for high-risk patient populations (prevention)

Educator

- Clinician: key differences in therapeutic options (place in therapy, onset, dosing, anticipated response)
- Patient: signs and symptoms of HK, dietary intake, proper administration, adherence, provider follow-up

Patient Advocate

- Improve quality of life
- Minimize poor clinical outcomes (reduction in RAASi therapy, disease-related mortality)
- Improve health-system economic burden (reduction in emergency department visits/hospitalizations)

Conclusion

- Hyperkalemia presents numerous challenges that influence both clinical and economical outcomes
- Prevention of the disturbance requires the practitioner to
  - Proactively identify at-risk populations
  - Evaluate potential dietary and medication-induced causes
  - Provide routine monitoring and follow-up
  - Ensure access and adherence to pharmacotherapeutic agents
- Clinical trial data have supported the use of newer oral potassium-binding agents, patiromer and SZC, with favorable adverse effect profiles and tolerability
- Utilization of the agents can allow for optimization of RAASi therapies in high-risk populations
- Pharmacists are uniquely positioned within the health care system to provide consultation both on the acute and chronic management of hyperkalemia to both providers and patients

Additional Resources

- Dépret F, et al. Management of hyperkalemia in the acutely ill patient. *Ann Intensive Care.* 2019;9(1):32.
- National Kidney Foundation. Best practices in managing hyperkalemia in chronic kidney disease. www.kidney.org/sites/default/files/02-10-7259_DBH_Best-Practices-in-Managing-Hyperkalemia-in-CKD.pdf
- National Kidney Foundation. Educate your patients about hyperkalemia and kidney disease. www.kidney.org/sites/default/files/02-10-7271_ABG_Hyperkalemia_Card_P11b.pdf
- Your kidneys and high potassium (hyperkalemia). www.kidney.org/sites/default/files/01-10-7269_ABG_PatBro_Hyperkalemiap7.pdf
- Hyperkalemia Clinical Insights. www.hyperkalemiainsights.com/resources

Posttest Questions

Posttest Question 1

After participating in the activity, how confident are you in identifying patients at risk for hyperkalemia?

A. Not at all
B. Somewhat
C. Moderately
D. Very
E. Extremely

Posttest Question 2

Which patient is at highest risk for developing hyperkalemia?

A. A 62-year-old with chronic kidney disease (CKD) Stage III
B. A 75-year-old with controlled type 2 diabetes on valsartan
C. A 51-year-old with HFrEF (35%) and CKD Stage III on lisinopril and metoprolol
D. A 70-year-old with end-stage renal disease (ESRD) receiving dialysis Monday, Wednesday, and Friday

HFrEF, heart failure with reduced ejection fraction.

Posttest Question 3

Prior to 2015, sodium polystyrene sulfonate (SPS) was the only oral potassium binder available on the US market.

Which of the following is/are <u>TRUE</u> regarding SPS?

A. Predictable onset of action
B. Lacks drug–drug interactions
C. Limited clinical trial data to support its use
D. Selectively exchanges K^+ for Na^+ in the colon

Posttest Question 4

Which of the following correctly corresponds to the important counseling points to discuss when a patient begins oral potassium-binding therapy?

A. Patiromer: refrigerate product; if stored at room temperature, use within 3 months
B. Sodium zirconium cyclosilicate (SZC): take 15 grams once daily for the first 72 hours for the initial (acute) treatment
C. Patiromer: separate other oral medications by at least an hour before or after patiromer
D. SZC: may cause hypomagnesemia

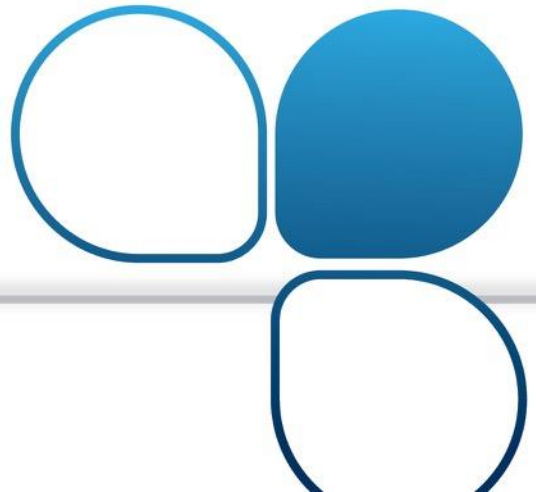
Posttest Question 5

A 59-year-old woman with HFrEF (35%) and CKD Stage III receives guideline-directed medication therapy including: lisinopril 40 mg PO daily, metoprolol XL 50 mg PO daily, and furosemide 40 mg PO daily. Her electrolytes are within normal limits and her cardiologist has recently added spironolactone due to continuing HF symptoms. Two weeks later, a basic metabolic panel revealed a serum potassium level = 5.2 mEq/L of which the patient is asymptomatic.

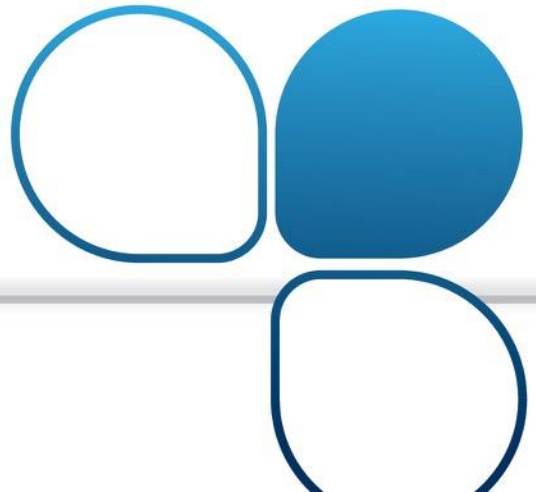
Which of the following actions would be <u>MOST</u> appropriate to take?

A. Discontinue spironolactone
B. Decrease lisinopril to 20 mg PO daily
C. Increase furosemide to 40 mg PO BID
D. Add SZC 10 grams 3x/day x 48 hours

Question and Answer Session



Thank You!



THE NEXT SESSION WILL BEGIN **MOMENTARILY**

Identifying and Managing Immune-Related Adverse Effects Associated With Immune Checkpoint Inhibitor Therapies

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Faculty and Staff Disclosures

Jacob Kettle, PharmD, BCOP, has the following relevant financial relationships with commercial interests to disclose:

- Speakers Bureau: Amgen, Genentech, Merck
- Advisory Board: Merck, Pfizer

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Activity Type: Application

Fee: Free

Patient Safety Credit

This activity is supported by an educational grant from Merck Sharp & Dohme Corp.

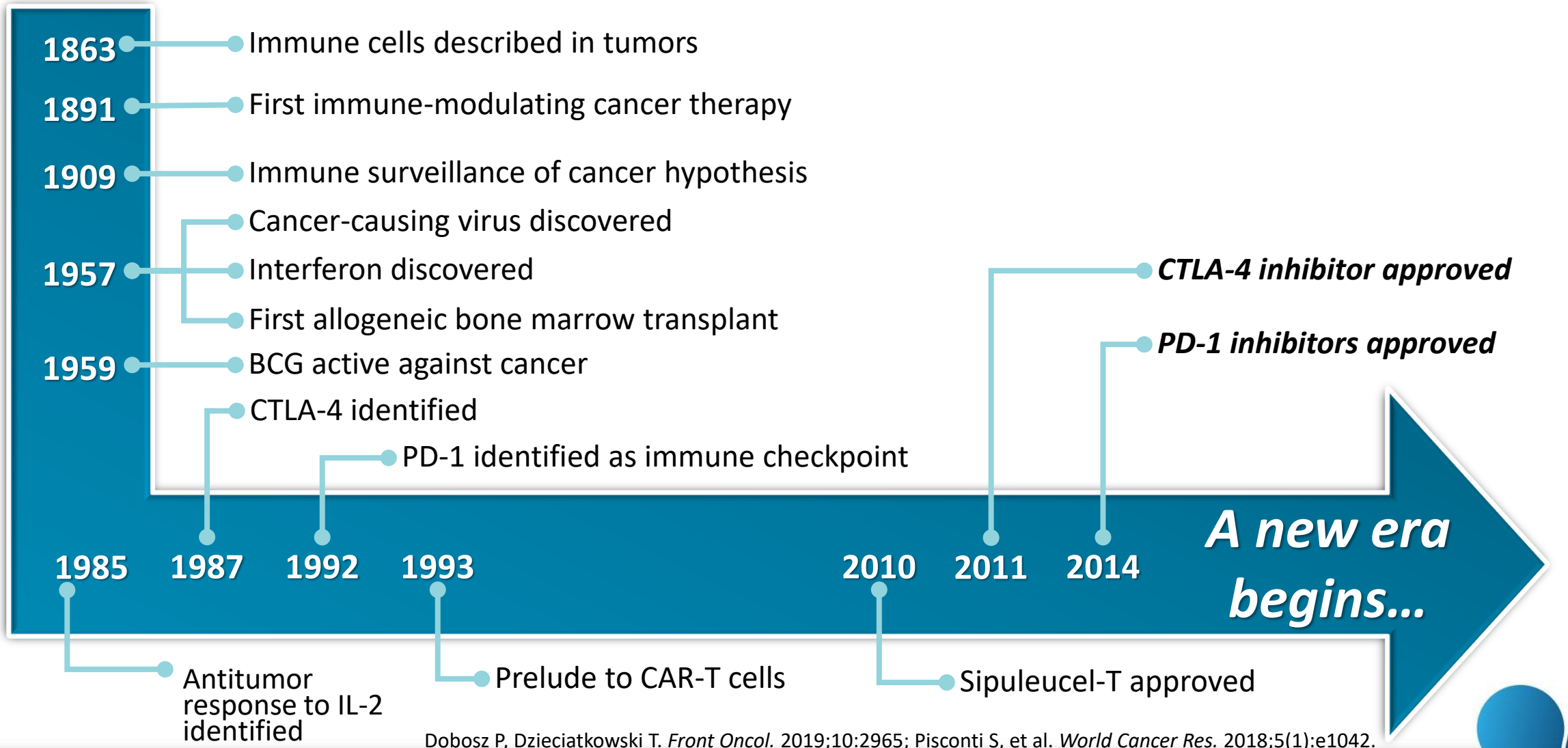
Educational Objectives

At the completion of this activity, participants will be able to:

- Examine the role of the immune system in fighting cancer and the development of immuno-oncology agents for the treatment of several types of cancer
- Compare the mechanisms of action, indications, and safety and efficacy data associated with immune checkpoint inhibitors in the treatment of numerous types of cancer
- Explore the various immune-related adverse effects (irAEs) that are associated with the use of immune checkpoint inhibitors
- Demonstrate the role of the pharmacist in identifying and managing irAEs in those patients treated with immuno-oncology agents, such as immune checkpoint inhibitors

Overview of Immuno-Oncology

An Overnight Success Decades in the Making



Dobosz P, Dzieciatkowski T. *Front Oncol.* 2019;10:2965; Pisconti S, et al. *World Cancer Res.* 2018;5(1):e1042.

Oncology Treatment Modalities

LOCALIZED

SURGERY

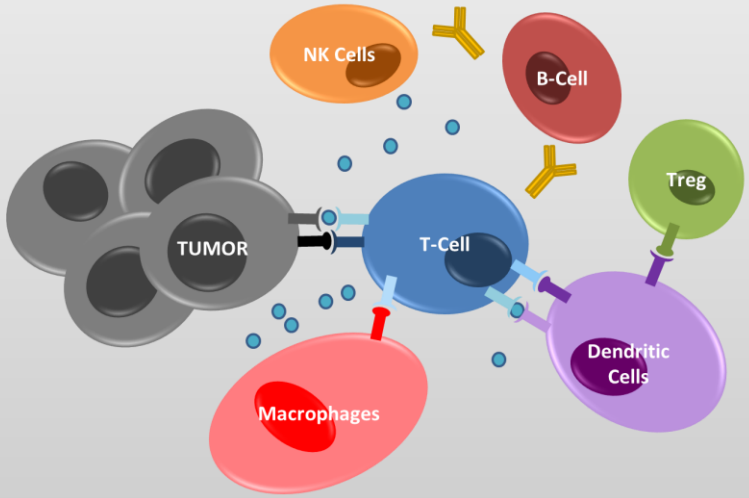
RADIATION

SYSTEMIC

CHEMOTHERAPY

TARGETED THERAPY

IMMUNOTHERAPY



Classification of Immunotherapy

Cytokines	Vaccines	Adoptive T Cell	Immune checkpoint inhibitors
			• CTLA-4 inhibitors • PD-1 inhibitors • PD-L1 inhibitors

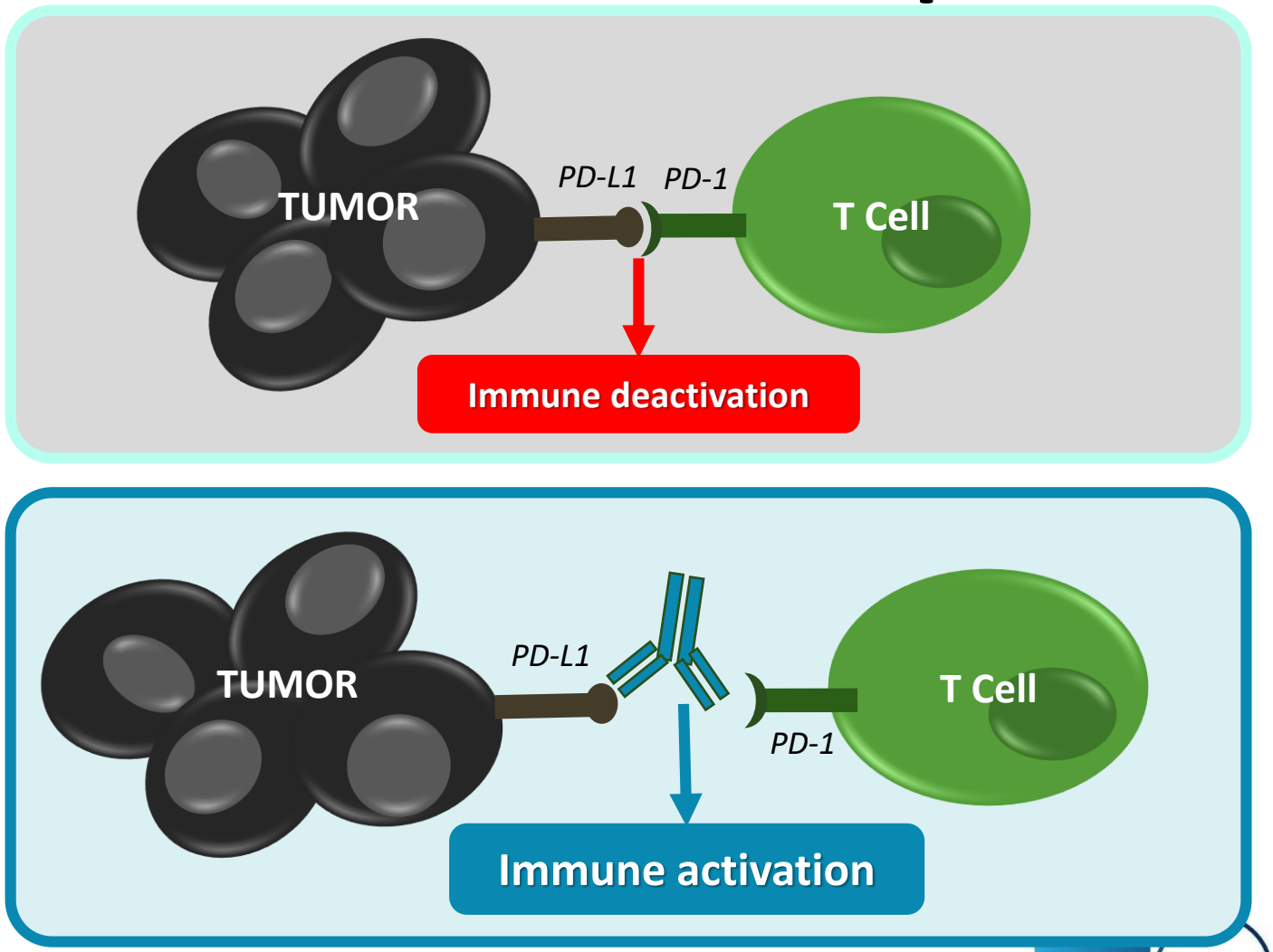
CTLA-4: Cytotoxic T-lymphocyte-associated protein 4; PD-1: Programmed death protein 1; PD-L1: Programmed death-ligand 1

Dobosz P, Dzieciatkowski T. *Front Oncol.* 2019;10:2965; Pisconti S, et al. *World Cancer Res.* 2018;5(1):e1042.

Review of Immune Checkpoint Inhibitors

Cancer Surveillance and Immune Checkpoints

- Cancer surveillance is a critical function of the immune system
- Immune checkpoints limit an ongoing immune response
- Tumors can evade immune action through similar mechanisms
- Binding of checkpoint inhibitors to various targets can restore an active immune response against the tumor



Chen DS, Mellman I. *Immunity.* 2013;39:1-10; Sharma P, et al. *Nat Rev Cancer.* 2011;11:805-812; De Mello RA, et al. *Oncol Targets Ther.* 2017;10:21-30.

Checkpoint Inhibitors

Agent	Proprietary name	Mechanism
Ipilimumab	Yervoy	CTLA-4 inhibitor
Pembrolizumab	Keytruda	PD-1 inhibitor
Nivolumab	Opdivo	PD-1 inhibitor
Atezolizumab	Tecentriq	PD-L1 inhibitor
Avelumab	Bavencio	PD-1 inhibitor
Durvalumab	Imfinzi	PD-L1 inhibitor
Cemiplimab-rwlc	Libtayo	PD-1 inhibitor

WHY?

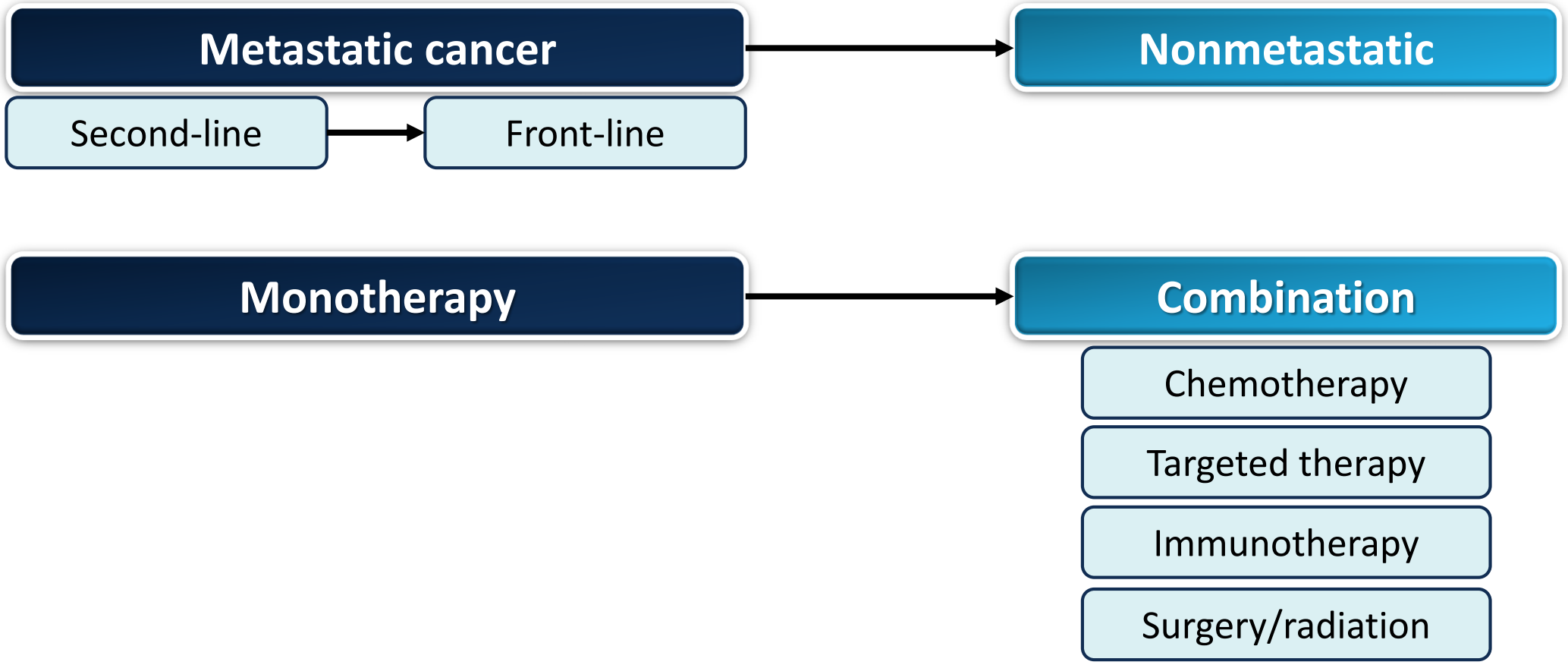
Why is this content relevant to the non-oncology practitioner?

Indications

Agent	Indications		
Ipilimumab	Melanoma	Renal cell cancer	
Pembrolizumab	Melanoma	Hodgkin lymphoma	MSI-H tumors
	Non-small cell lung cancer	Urothelial carcinoma	Gastric cancer
	Head and neck cancer	Large B-cell lymphoma	Cervical cancer
	Small cell lung cancer	Merkel cell carcinoma	Esophageal cancer
	Hepatocellular cancer	Renal cell cancer	
Nivolumab	Melanoma	Hodgkin lymphoma	Non-small cell lung cancer
	Head and neck cancer	Renal cell carcinoma	Urothelial carcinoma
	Hepatocellular carcinoma	Colorectal cancer	Small cell lung cancer
Atezolizumab	Non-small cell lung cancer	Small cell lung cancer	Breast cancer
		Urothelial carcinoma	
Avelumab	Merkel cell carcinoma	Urothelial carcinoma	Renal cell carcinoma
Durvalumab	Non-small cell lung cancer	Urothelial carcinoma	Small cell lung cancer
Cemiplimab-rwlc	Cutaneous squamous cell carcinoma		

The list above may not be comprehensive.

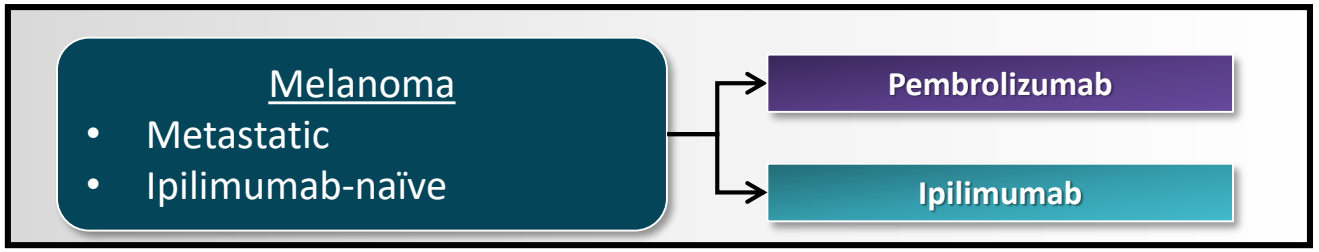
Indications



Improved Outcomes and Longer Survival

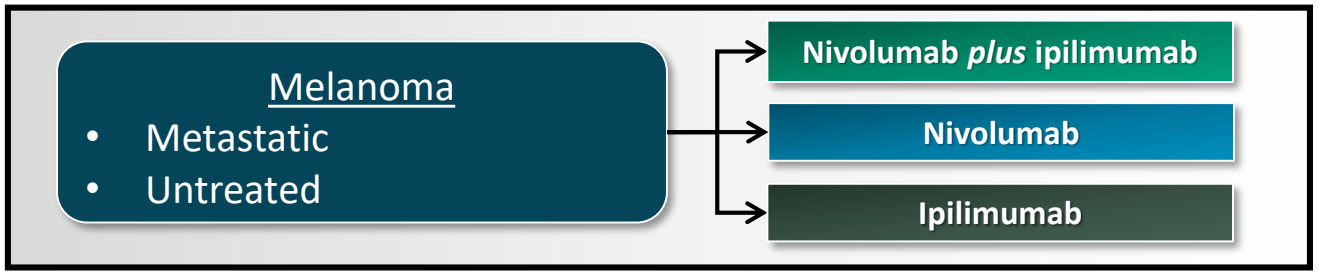
Keynote 006

Median OS 32.7 months with pembrolizumab



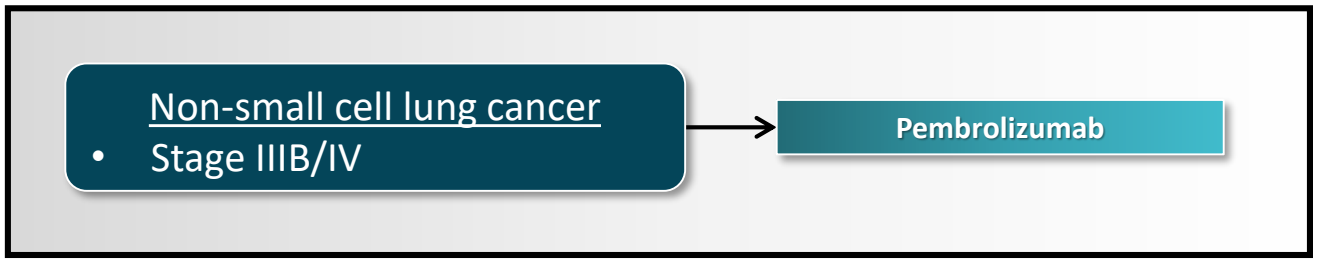
Checkmate 067

Median OS >60 with combination therapy



Keynote 001

5-year OS >25% in some subgroups

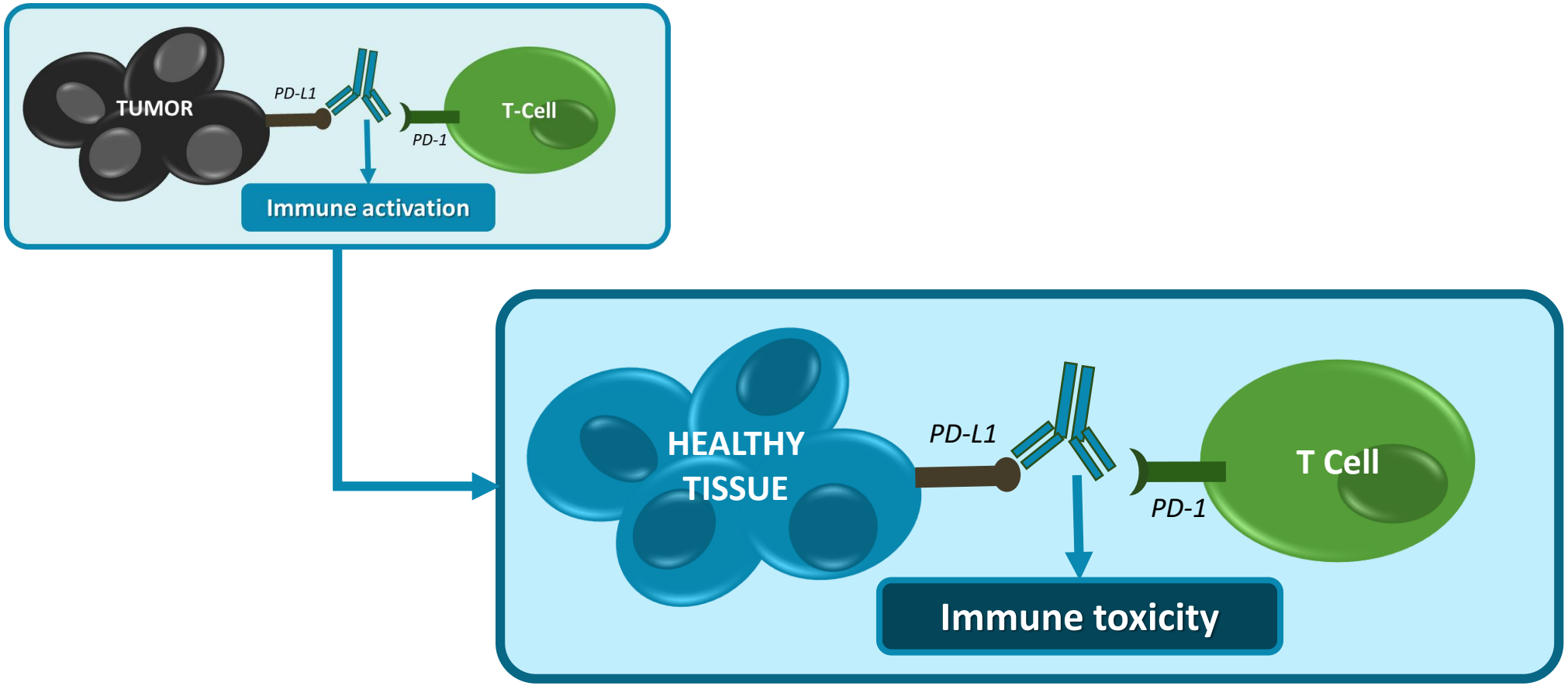


OS, overall survival.

Robert C, et al. *Lancet*. 2019;20(9):1239-1251; Larkin J, et al. *N Engl J Med*. 2019;381(16):1535-1546; Garon EB, et al. *J Clin Oncol*. 2019;37(28):2518-2527.

Management of Immune-Related Adverse Effects (irAEs)

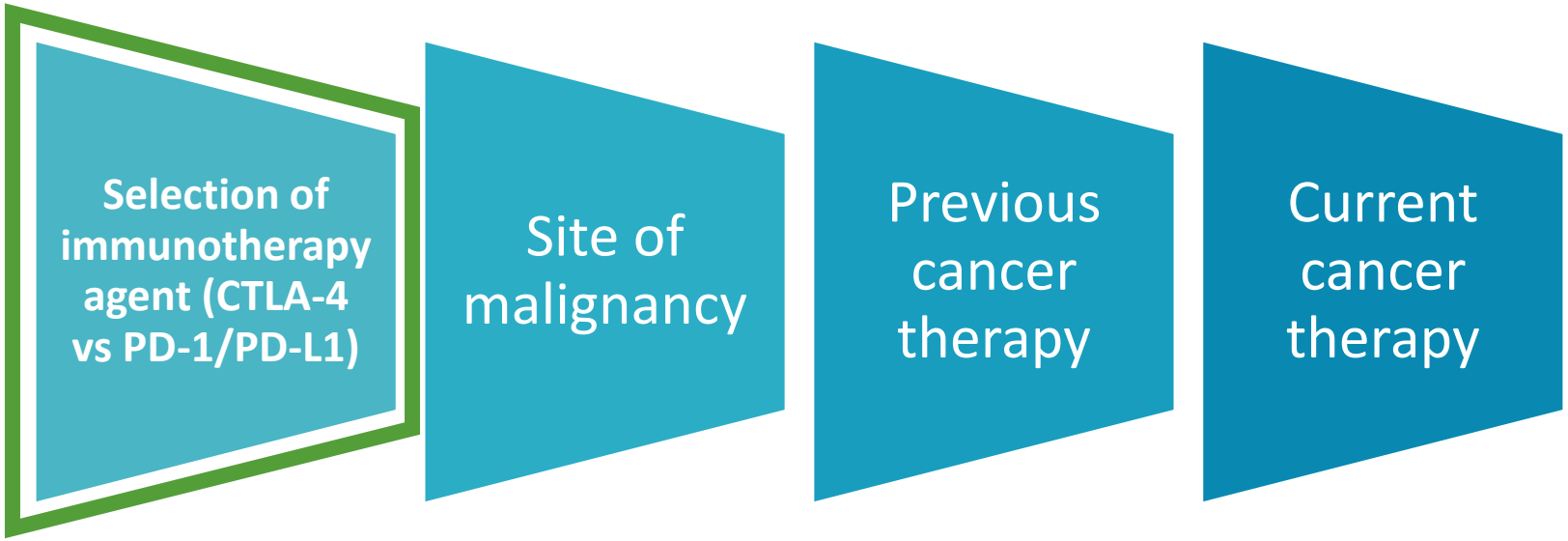
Mechanism of Adverse Effects (AEs)



Weinmann SC, Pisetsky DS. *Rheumatology.* 2019;58:vii59-vii67.

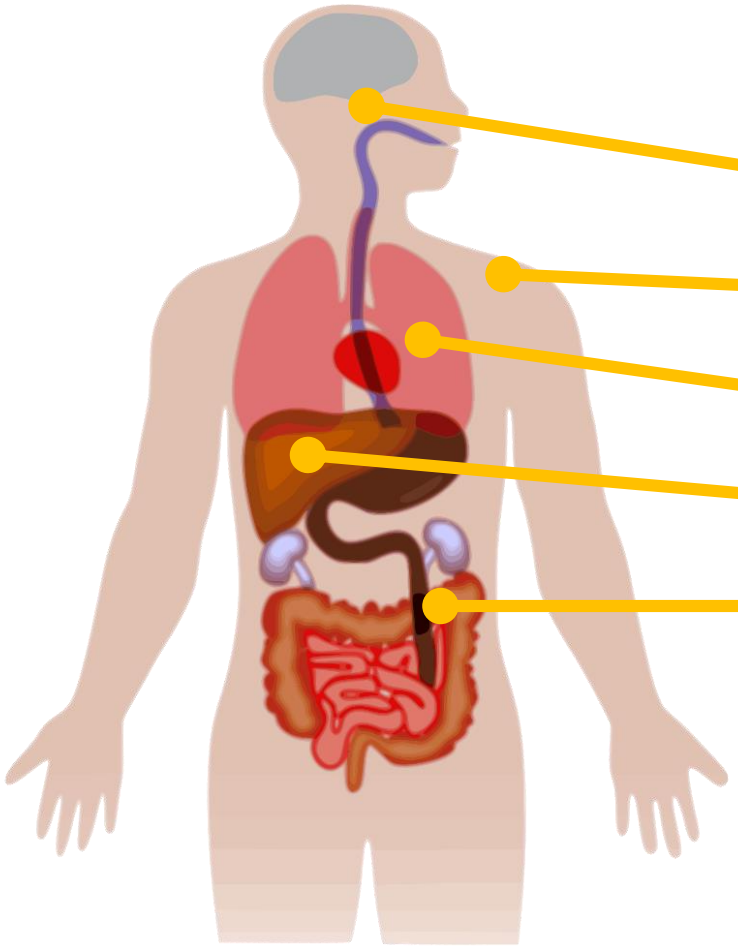
Mechanism of AEs

- Distinct mechanism of toxicity compared with conventional cytotoxic medications and targeted therapy
- Frequency of AEs varies, but can be impacted by:



NCCN Clinical Practice Guidelines in Oncology. Management of Immunotherapy-Related Toxicities. V1.2020.

Essential Clinical Pearls for Pharmacists



- Most common immune toxicities:
  - Endocrine
  - Dermal
  - Pulmonary
  - Hepatic
  - Gastrointestinal

BUT…any organ system can be impacted!

NCCN Clinical Practice Guidelines in Oncology. Management of Immunotherapy-Related Toxicities. V1.2020.

Essential Clinical Pearls for Pharmacists

- Many AEs have a broad spectrum of severity
- Severe events are uncommon
- **BUT…fatalities have been reported**

Organ system	Mild toxicity	Severe toxicity
Endocrine	Hypothyroidism	Diabetic ketoacidosis
Skin	Rash	Epidermal necrolysis
Liver	Transaminitis	Hepatic failure
Pulmonary	Pneumonitis	
Gastrointestinal	Diarrhea	Colitis

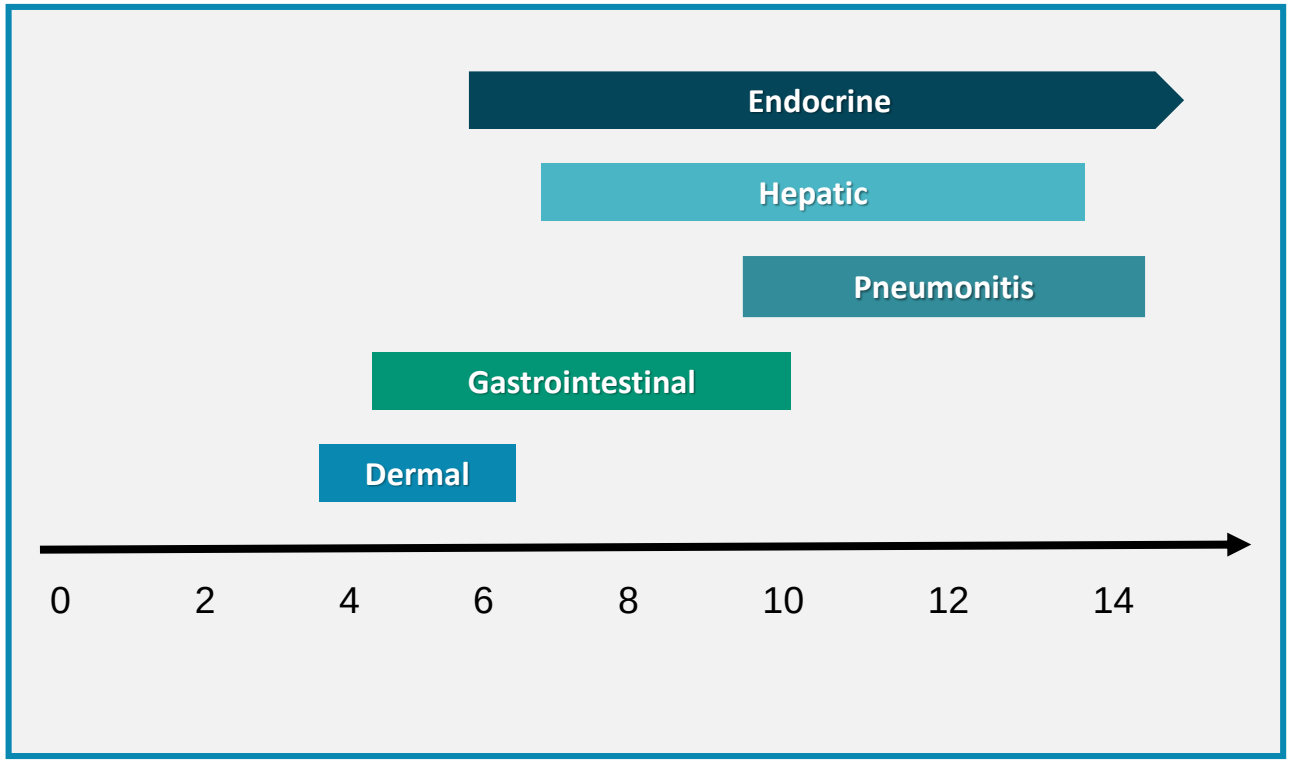
NCCN Clinical Practice Guidelines in Oncology. Management of Immunotherapy-Related Toxicities. V1.2020.

Essential Clinical Pearls for Pharmacists

- Most AEs occur 6-12 weeks after starting therapy
- There is a common chronological pattern to AEs

BUT…

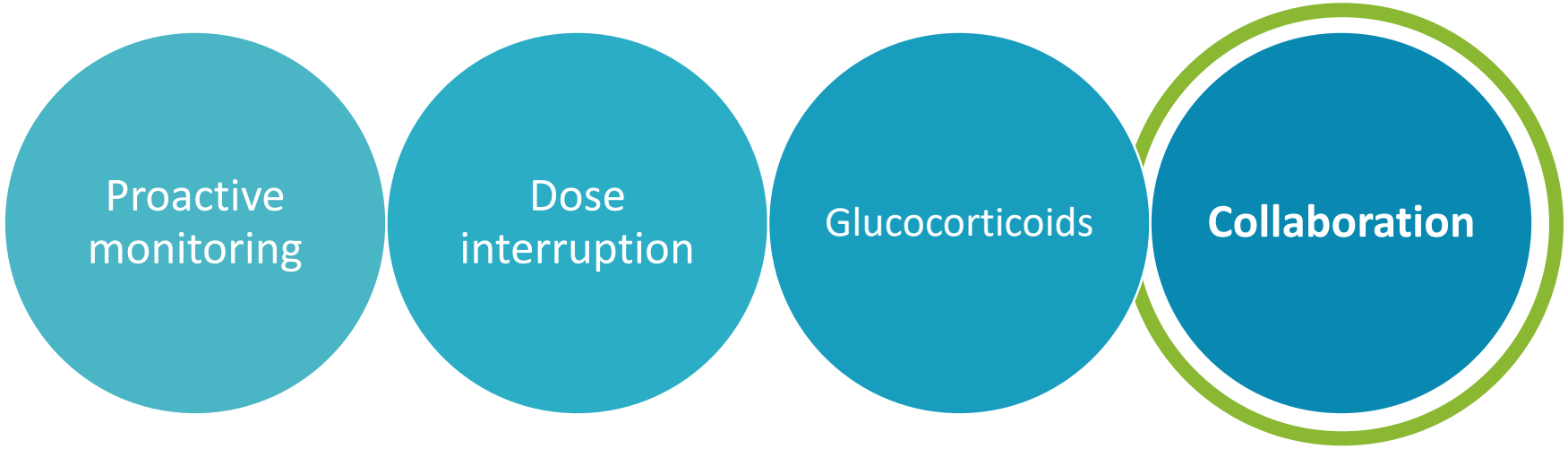
AEs can occur at any time!



Weber J, et al. *J Clin Oncol.* 2012;30(21):2691-2697.

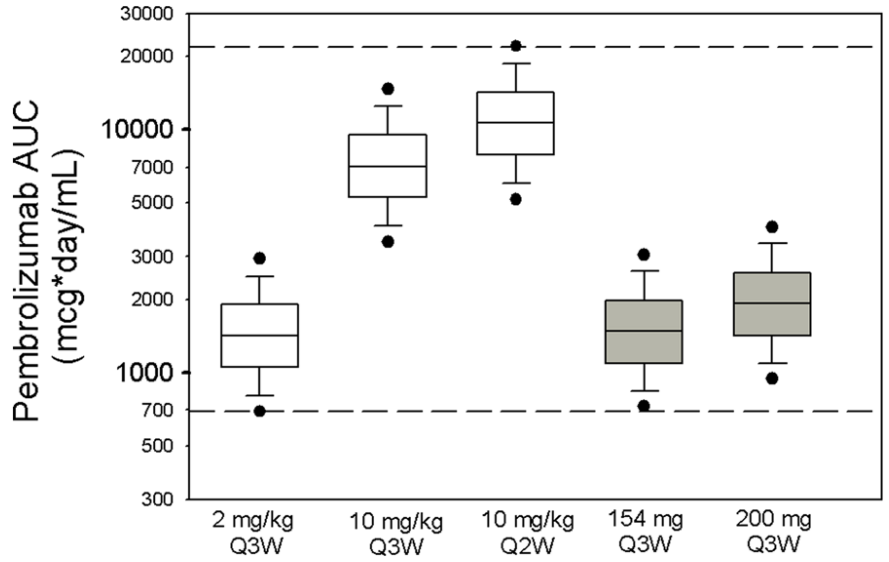
Essential Clinical Pearls for Pharmacists

- Most AEs are **reversible**
- Complex differential diagnosis
- Key components to management:



Essential Clinical Pearls: Dose Interruption

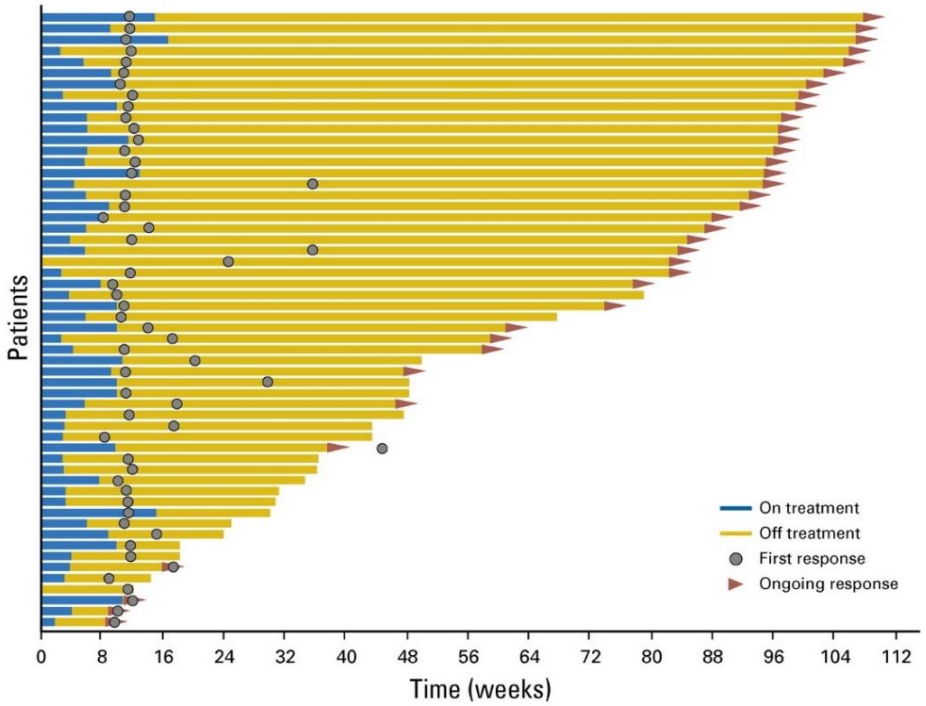
- Dose interruption **(not modification)**



- Re-challenge:
  - Mild-moderate toxicity → **Yes**
  - Severe/recurrent → **No**

Image republished from Freshwater T, et al. *J Immunother Cancer.* 2017;5:43, under the terms of the Creative Commons Attribution 4.0 International License (creativecommons.org/licenses/by/4.0/).

- Response may persist after discontinuation of therapy due to AEs



Schadendorf D, et al. *J Clin Oncol.* 2017;35(34):3807-3814. Reprinted with permission. © 2017 American Society of Clinical Oncology. All rights reserved.

Essential Clinical Pearls: Glucocorticoids

Corticosteroids are the MAINSTAY of treatment for immune toxicity

Chronic use of corticosteroids or immunosuppressants for other indications **does** appear to reduce response to immune checkpoint inhibitors

Treatment of irAEs with corticosteroids **does not** appear to reduce therapeutic response to immune checkpoint inhibitors

Arbour KC, et al. *J Clin Oncol.* 2018;36(28):2872-2878.

Essential Clinical Pearls: Glucocorticoids

DOSING

- Initial dosing depends on indication and severity
- Typically 0.5-2 mg/kg of prednisone or equivalent per day

DURATION

- A gradual taper over 4 weeks or longer may be required
- Pneumonitis and hepatitis may require 8 weeks or longer

Arbour KC, et al. *J Clin Oncol.* 2018;36(28):2872-2878.

Essential Clinical Pearls: Glucocorticoids

SUPPORTIVE CARE

Prevention of infection:

	Duration of corticosteroids	Daily dose of prednisone (or equivalent)
Pneumocystis jirovecii pneumonia (PJP)	4 or more weeks	20 mg
Antifungal	6 or more weeks	20 mg
Herpes zoster	Any	Any

Prevention of gastritis:

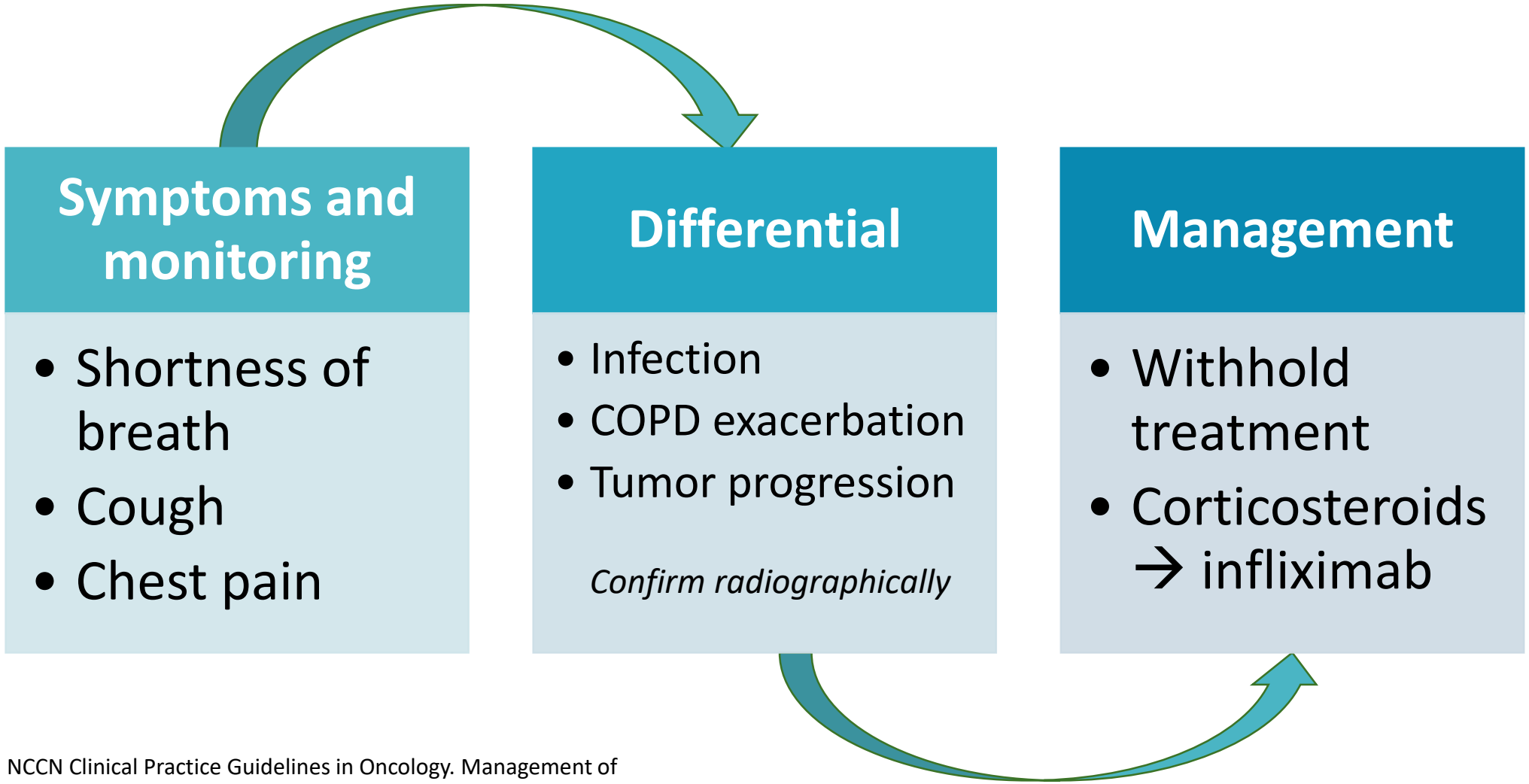
- Proton pump inhibitors (PPIs) or H2 blockers
- Continue throughout therapy if at high risk

Prevention of osteoporosis:

- Vitamin D and calcium
- Continue throughout therapy if on long-term steroid therapy

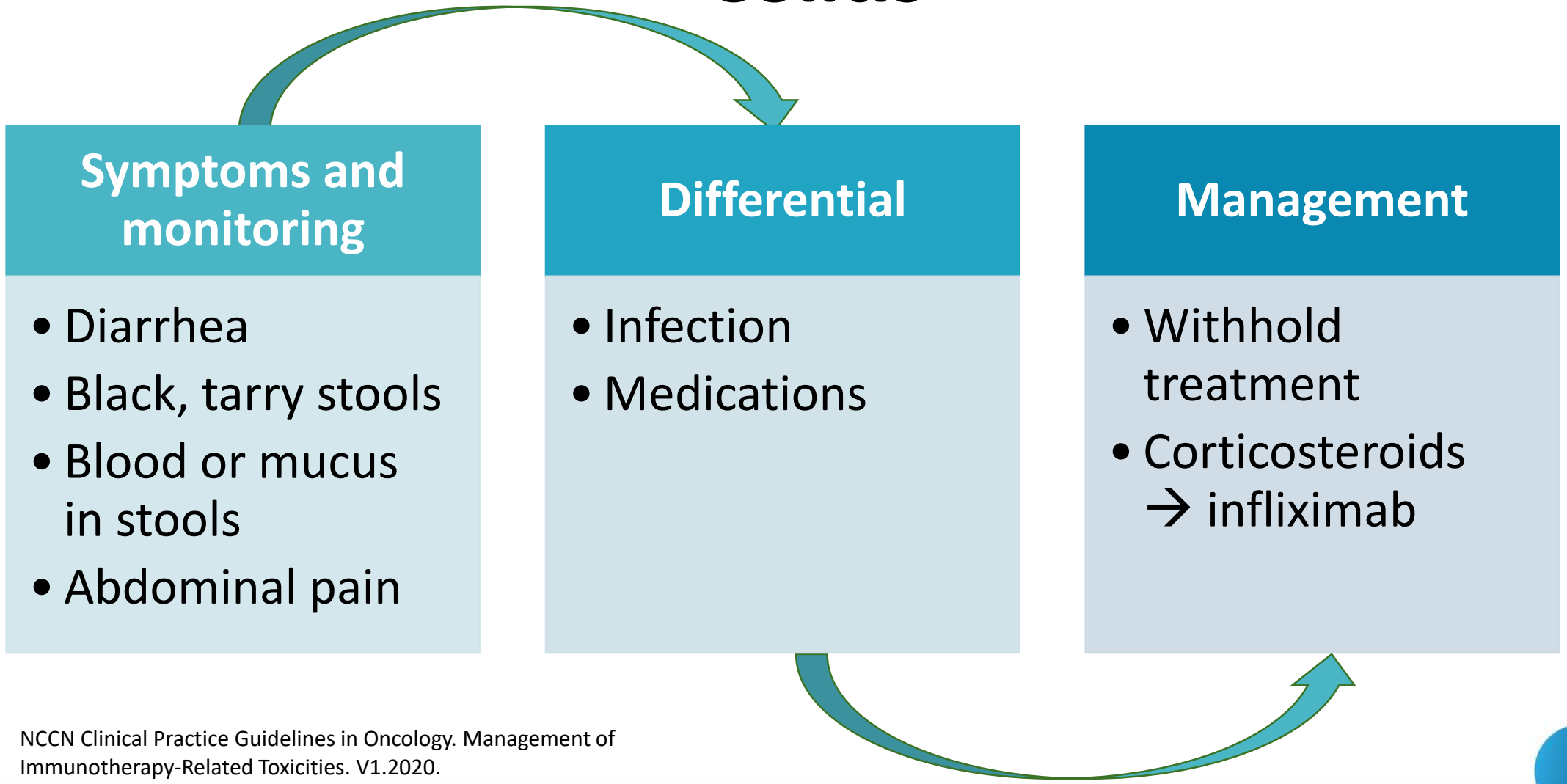
Arbour KC, et al. *J Clin Oncol.* 2018;36(28):2872-2878.

Pneumonitis



NCCN Clinical Practice Guidelines in Oncology. Management of Immunotherapy-Related Toxicities. V1.2020.

Colitis



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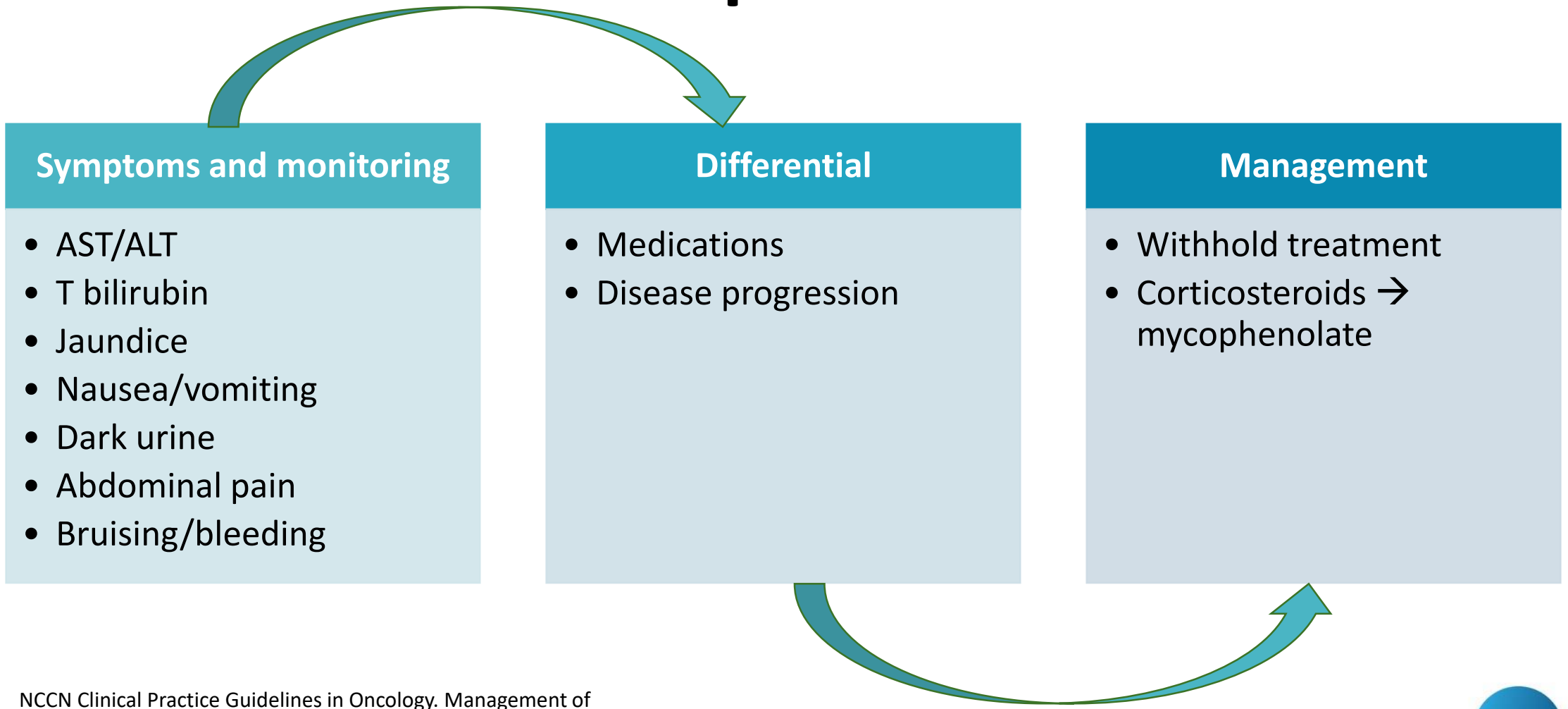
Hepatitis



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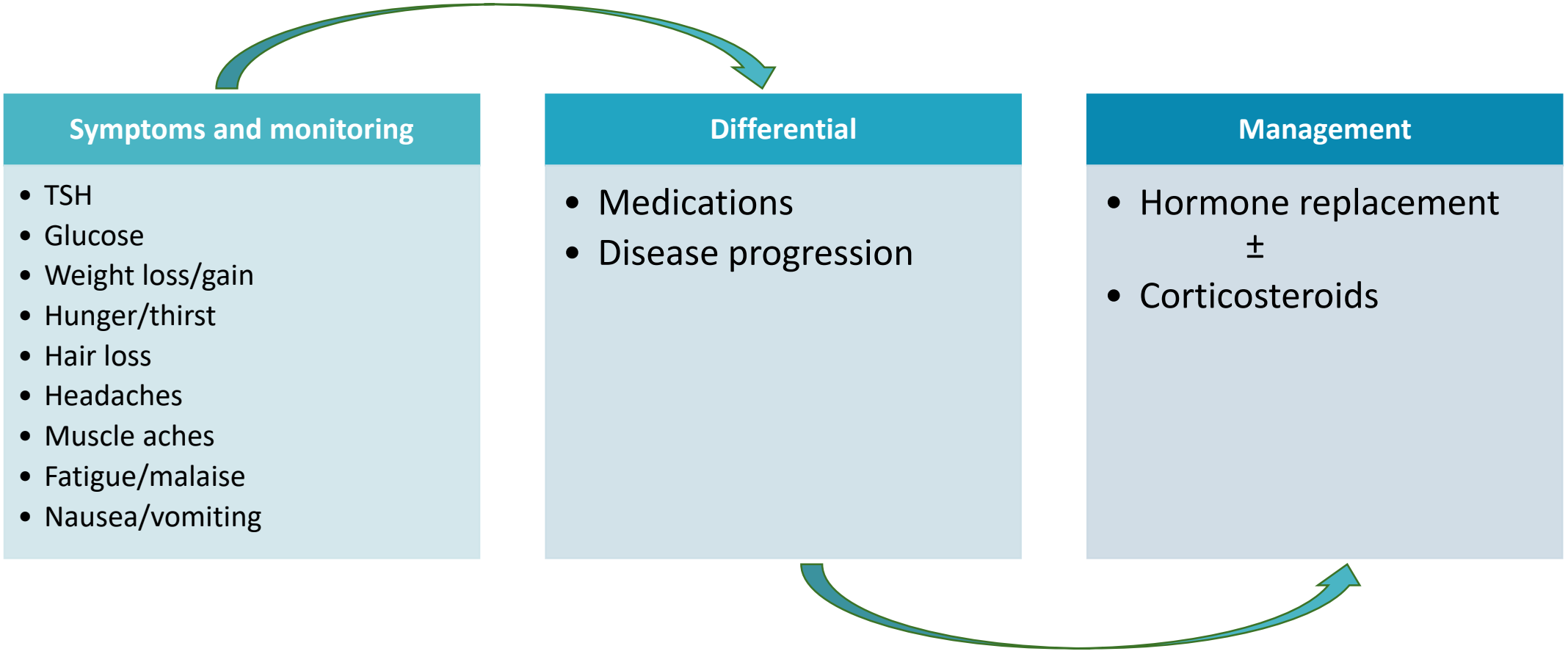
Endocrinopathies:

Hypophysitis, Thyroid Disorders, Type I Diabetes



NCCN Clinical Practice Guidelines in Oncology. Management of Immunotherapy-Related Toxicities. V1.2020.

Conclusion

- Deeper understanding of the link between oncology and immunology has delivered a substantial increase in available treatment
- Diversity of clinical application and improvement in treatment outcomes increase likelihood non-oncology practitioners will encounter these patients
- Effective identification and management of adverse effects is essential to ensuring optimum patient outcomes
- Pharmacists in all practice settings can play a crucial role in the care of patients with cancer receiving immunotherapy

Additional Resources

- ASCO Guidelines: Management of Immune-Related Adverse Events

  ascopubs.org/doi/10.1200/JCO.2017.77.6385
- NCCN Guidelines: Management of Immunotherapy-Related Toxicities

  nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf
- ESMO Patient Guide on Immunotherapy-Related Side Effects

  esmo.org/for-patients/patient-guides/immunotherapy-side-effects
- ONS Immunotherapy Wallet Card

  ons.org/sites/default/files/2019-01/IO%20Card%201-sided_Vertical.pdf
- Prescribing Information for Individual Agents