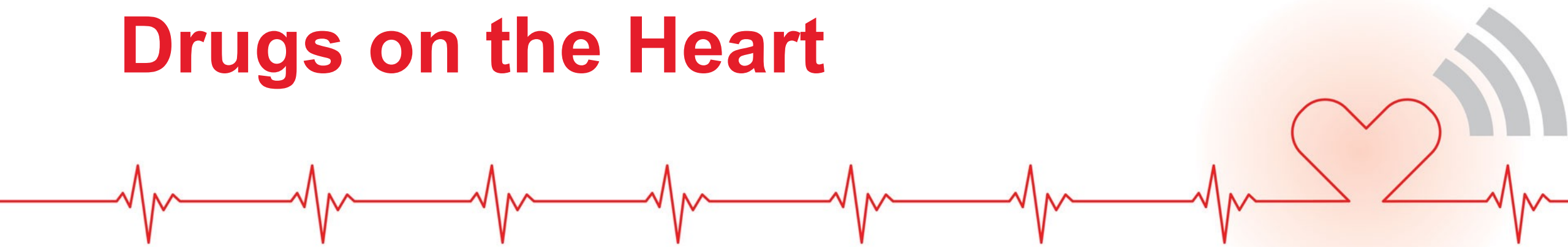
Effects of Non-Cardiovascular Drugs on the Heart



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- **Speaker fees**: None.
- **Other**: None.

Learning objectives

1. Describe non-cardiovascular (CV) drugs that can cause or exacerbate heart failure (HF), and summarize the best-available evidence
2. Recognize common, serious, and emerging interactions with HF drugs, and summarize the best-available evidence
3. Consider treatment alternatives to mitigate drug safety issues in patients with HF

Polypharmacy in HF

What is polypharmacy?

- Most commonly defined as ≥5 meds (some definitions also classify appropriateness)
- #1 predictor of polypharmacy: Number of comorbidities

Polypharmacy is the rule rather than the exception in HF patients

- Average 6-7 Rx meds (+ OTCs & naturopathics)
  - 75-95% receiving ≥5 meds
  - 20-40% receiving ≥10 meds ("hyperpolypharmacy")
- Usual composition:
  - HF meds ~25-30%, non-HF CV meds: ~25%
  - **Non-CV meds ~50%**

Am J Med 2011;124:136-43
BMC Cardiovasc Dis 2019;19:76
BMC Geriatrics 2017;17:230
Br J Gen Pract 2017;67:e314-e320
Br J Gen Pract 2021;71:e62-e70
Circulation HF 2020;13:e006977
Clin Interv Aging 2017;12:679-86

Polypharmacy in HF

“Mo’ Money Mo’ Problems”

– The Notorious B.I.G.

Polypharmacy in HF

“Mo’ Meds Mo’ Potential Med-Related Problems”

– All pharmacists everywhere

AHA SCIENTIFIC STATEMENT

Drugs That May Cause or Exacerbate Heart Failure

Consensus-based list of **77 medications & 8 naturopathic products** that can cause/exacerbate HF

Level of Evidenc (LOE)	Definition	
A	≥2 randomized controlled trials (RCTs)	**25%**
B	Single RCT or non-randomized studies	**40%**
C	Case reports, opinion	**35%**

Circulation 2016;134:e32-e69
Other lists: Arch Intern Med 2004;164:709-20 , Eur J Heart Fail 2014;16:915-22

Non-CV Drugs That Can Cause or Exacerbate HF
Prevalence

- ~25-50% of patients with HF taking med on AHA list
- Most common:
    1. NSAIDs/COX-2 inhibitors
    2. Diltiazem/verapamil/nifedipine
    3. Diabetes medications
    4. Alpha-blocker
- Risk factors: Women, ↑ comorbidities, ↑ prescribers, ↑ pharmacies

Am J Cardiol 2019;123:1458-63
Am J Cardiovasc Drugs 2020;20:603-10
J Am Coll Cardiol HF 2020;8:25-34

NSAIDs & COX-2 Inhibitors
Prototype for Drugs that Cause Fluid Retention

- Mechanism:
  - Inhibiting COX-2 leads to sodium & water retention, ↑ blood pressure (BP), blunting of diuretic effect
  - ↑ risk of myocardial infarction
- Class effect (ibuprofen ≈ naproxen ≈ celecoxib ≈ diclofenac)
- ↑ new HF risk by ~2x
- ↑ HF hospitalization by ~10x in patients with existing HF

Circulation 2016;134:e32-e69
Lancet 2013;382:769-79
Drug-Induced Diseases: Prevention, Detection, and Management. 2nd ed. Chapter 24: Heart failure

Other Medications that Cause Fluid Retention

- Corticosteroids
- Gabapentin & pregabalin LOE C
- Glitazones LOE A
- Licorice (pseudo-hyperaldosteronism)

Circulation 2016;134:e32-e69
Drug-Induced Diseases: Prevention, Detection, and Management. 2nd ed. Chapter 24: Heart failure

Beware "Hidden" Sodium in Medications

Medication	Sodium content
Oral	
Sodium polystyrene sulfonate (Kayexalate)	~500 mg Na absorbed/15 grams Kayexalate
PEG + electrolyte solutions (e.g. Golytely)	1.46 g/1 L
Intravenous	
Azithromycin	114 mg/500 mg vial
Metronidazole	790 mg/500 mg vial
Piperacillin/tazobactam	192 mg/3.375 g vial
Ranitidine	225 mg/50 mg vial

Circulation 2016;134:e32-e69

Calcium-Channel Blockers (CCBs) & HF
Prototypical Negative Inotropes

- Mechanism: ↓ myocardial contractility
  - Verapamil, nifedipine > diltiazem >>>> amlodipine, felodipine (minimal)
- **Verapamil, diltiazem, nifedipine**:
  - Do not *cause* HF, but can **exacerbate existing HF with reduced ejection fraction (HFrEF)** or asymptomatic left ventricular dysfunction
  - Immediate or delayed weeks-months: depends on baseline HF severity
- Amlodipine & felodipine can *mimic* worsening HF
  - Dose-dependent peripheral edema (~10%) & pulmonary edema (~4%)

Am J Cardiol 1990;65:1039-41 Circulation 1990;82:1954-61
Circulation 1991;83:52-60 Circulation 1997;96:856-63
J Am Coll Cardiol HF 2013;1:308-14

Other Medications That ↓ Contractility

- Antiarrhythmics
  - Disopyramide LOE B
  - Dronedarone LOE A
  - Flecainide & propafenone LOE B
- CNS drugs (rare)
  - Carbamazepine (overdose) LOE C
  - Tricyclic antidepressants LOE C
  - Propofol LOE B
- Itraconazole LOE C
- Topical beta-blockers LOE C

Circulation 2016;134:e32-e69
Drug-Induced Diseases: Prevention, Detection, and Management. 2nd ed. Chapter 24: Heart failure

Diabetes Medications – Overview

Drug or class	On AHA list?
Glitazones	**Yes (LOE A)**
Metformin	**Yes (LOE C)**
DPP-4 inhibitors	**Yes (LOE B)**
GLP-1 receptor agonists	
Insulin	
Secretagogues (meglitinides, sulfonylureas)	
SGLT2 inhibitors	
Sulfonylureas	

Circulation 2016;134:e32-e69

Diabetes Medications – Overview

Drug or class	On AHA list?	Causes/exacerbates HF?
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DPP-4 inhibitors	**Yes (LOE B)**	**Yes***
GLP-1 receptor agonists		No*
Insulin		No
Secretagogues (meglitinides, sulfonylureas)		No
SGLT2 inhibitors		No (the opposite!)
Sulfonylureas		No

Circulation 2016;134:e32-e69

Metformin is Safe in HF

Included in AHA list based on historical concern (LOE C)

- HF was thought to increase risk of metformin-associated lactic acidosis
- Metformin not associated with causing/worsening HF

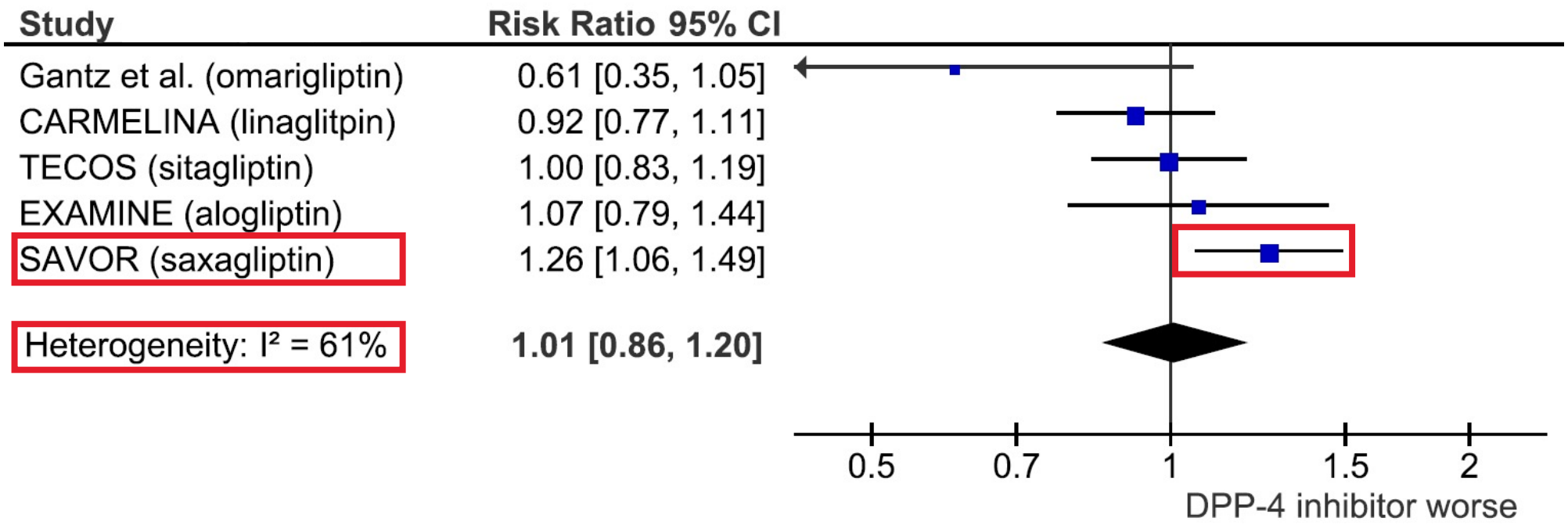
2 meta-analyses of large observational studies of metformin in type 2 diabetes + HF:

- ↔ risk of lactic acidosis
- ↓ HF hospitalization
- ↓ death

Ann Intern Med 2017;166:191-200
Circulation 2016;134:e32-e69
Circ Heart Fail 2013;6:395-402

DPP-4 Inhibitors – HF Risk Not a Class Effect

HF hospitalization

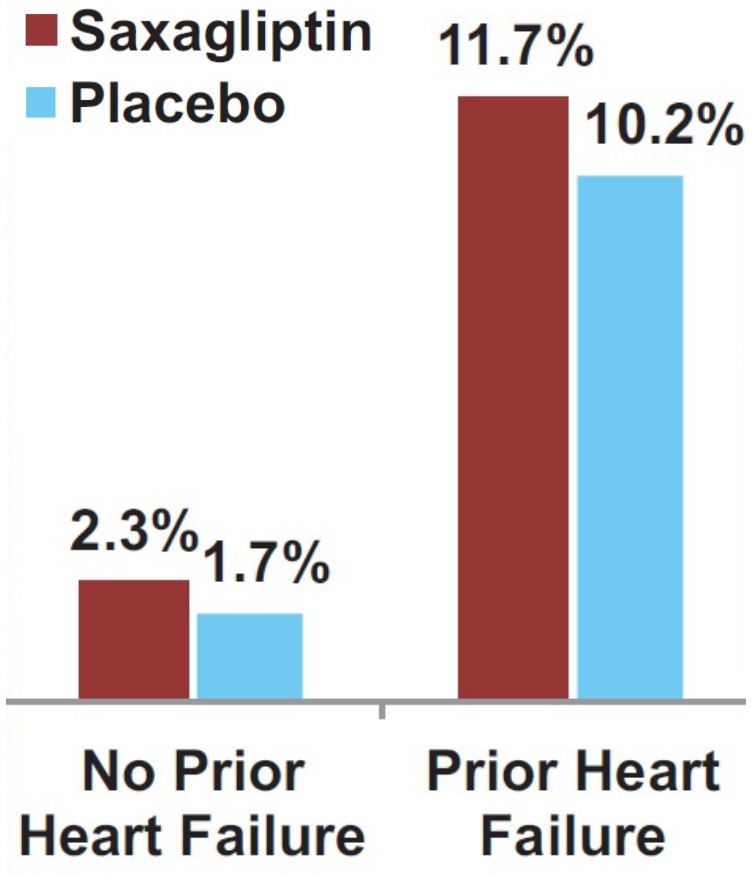


Can J Hosp Pharm 2019;72:385-7

Saxagliptin

SAVOR-TIMI-53 trial:

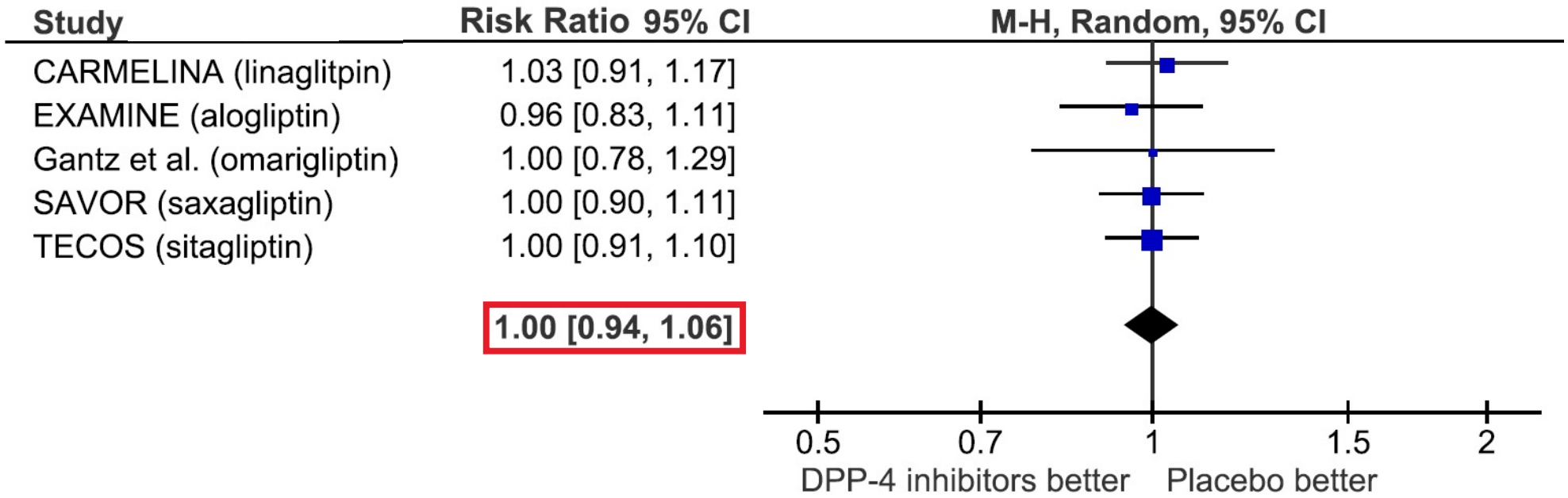
- Saxagliptin vs placebo: ~27% relative risk increase in HF hospitalization
- Absolute risk at 2 years:
  - No prior HF: +0.6%
    (number needed to harm [NNH]=167)
  - **Prior HF: +1.5% (NNH=67)**



Circulation 2014;130:1579-88

DPP-4 Inhibitors – Best-Case Scenario
No CV Benefit

Major adverse cardiovascular events



Can J Hosp Pharm 2019;72:385-7

GLP-1 Receptor Agonists & HF

- In type 2 diabetes without HF:
  - ↓ Death, myocardial infarction & stroke
  - ↔ HF hospitalizations
- **Conflicting evidence in patients with HF**
  - ↑ serious adverse cardiac events in 2 small HFrEF RCTs (FIGHT, LIVE)
  - ↔ HF events in HF subgroup (n=~800) of LEADER trial
- GLP-1 receptor agonists **increase heart rate (by up to 10 bpm)** by direct stimulation of sinoatrial node
  - Possible mechanism for ↑ cardiac events in HFrEF patients

Ann Intern Med 2020;173:278-86 Cardiovasc Diabetol 2017;16:6
Diabetes Care 2016;39:e22-e23 Eur J Heart Fail 2017;19:69-77
J Am Coll Cardiol 2020;75:1128-41 JAMA 2016;316:500-8
Scand Cardiovasc J 2020;54:294-9

Diabetes Medications & HF
Bottom Line

- Use metformin & SGLT2 inhibitors as 1st line agents
- **Avoid glitazones & saxagliptin**
- **Don't use** other DPP-4 inhibitors (no CV benefit)
- **Use caution with** GLP-1 receptor agonists in HFrEF
    - Monitor heart rate & optimize β-blockers +/- ivabradine

Alpha Blockers & HF

- On AHA list due to ↑ **HF with doxazosin vs chlorthalidone in ALLHAT trial**
  - However, inconclusive effect on HF vs placebo in network meta-analysis of hypertension RCTs
- Most alpha-blockers used now are “uroselective” (e.g. tamsulosin), with minimal effect on vascular α_{1B} receptors responsible for vasodilation & ↓ BP
- **Likely safe in patients with existing HF**
  - V-HeFT trial: No difference in death with prazosin vs placebo
  - Cohort (n=388): ↔ death/HF admission with alpha-blockers
  - Larger cohort (n=71,426): Small/no difference in HF hospitalization/death

Arch Intern Med 2011;171:384-94 , Am J Cardiol 2009;104:270-5 , Circulation 2016;134:e32-e69
Hypertension 2003;42:239-46 , J Am Coll Cardiol HF 2018;6:917-25 , NEJM 1986;314:1547-52

Medications That Cause
Direct Myocardial Toxicity

Class	Drug
Anti-cancer drugs	• Anthracyclines LOE A (e.g. doxorubicin) • Antimetabolite (e.g. 5-FU LOE B) • Alkylating agents (e.g. cyclophosphamide LOE B) • Anti-HER2 (e.g. trastuzumab LOE A) • Interferon, interleukin-2 LOE C • Taxanes (e.g. paclitaxel) LOE B
Anti-infectives	• Amphotericin B LOE C
CNS drugs	• Bromocriptine LOE B • Clozapine LOE C • Lithium LOE C • Stimulants LOE B (e.g. amphetamine)
Rheumatologic drugs	• Hydroxychloroquine LOE C • Anti-TNF-alpha (e.g. infliximab LOE A)

Circulation 2016;134:e32-e69

Drug-Induced Diseases: Prevention, Detection, and Management. 2nd ed. Chapter 24: Heart failure

Drug Interactions with HF Medications
Principles

- Drug interactions fall broadly in 2 categories
  - Pharmacodynamic: One drug alters how another affects the body
  - Pharmacokinetic: One drug alters how the body affects another drug
- Most clinically relevant interactions with HF medications are pharmacodynamic (additive or synergistic ↑ adverse events)
  - Exception: Digoxin (many pharmacokinetic interactions)

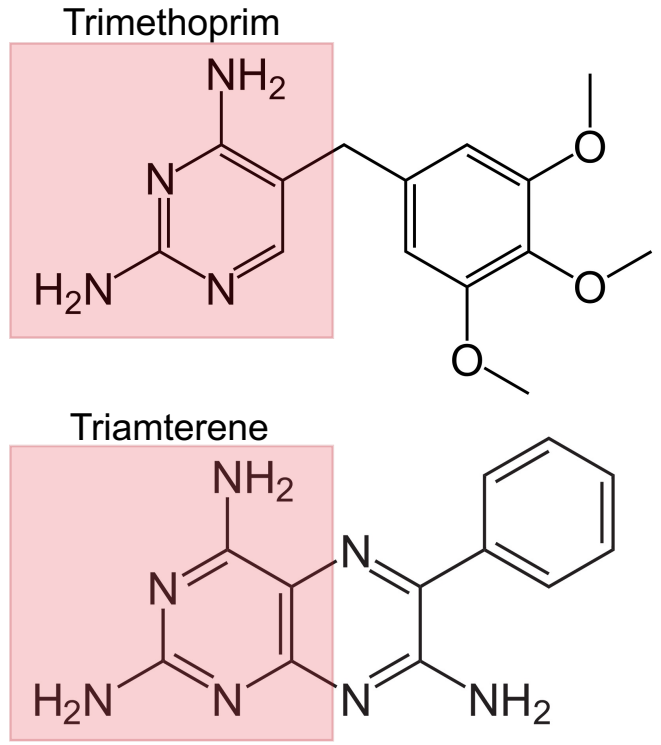
ref

Key Interactions with HF Medications

Adverse event	Key interacting drugs
↓ **blood pressure**	• Antipsychotics • CCBs • Clonidine • Levodopa & dopamine agonists • **Trazodone** • **Tricyclic antidepressants** • **Antipsychotics**
Hyperkalemia	• **Potassium supplements** • **Trimethoprim** +/- sulfamethoxazole (co-trimoxazole, Septra) • NSAIDs & COX-2 inhibitors • Tacrolimus/cyclosporine • Drospirenone (contraceptive: e.g. Yasmin, Yaz)

Trimethoprim/Co-Trimoxazole & Hyperkalemia

- Commonly used to treat urinary tract infections
- Structurally similar to the **potassium-sparing** diuretic triamterene
  - Inhibits potassium excretion in distal tubule
- In patients taking ACEI, ARB or MRA, trimethoprim/co-trimoxazole (even 3-5 day course) associated with:
  - 2-12x ↑ **hospitalization for hyperkalemia**
  - 1.5-2.5x ↑ **sudden death**

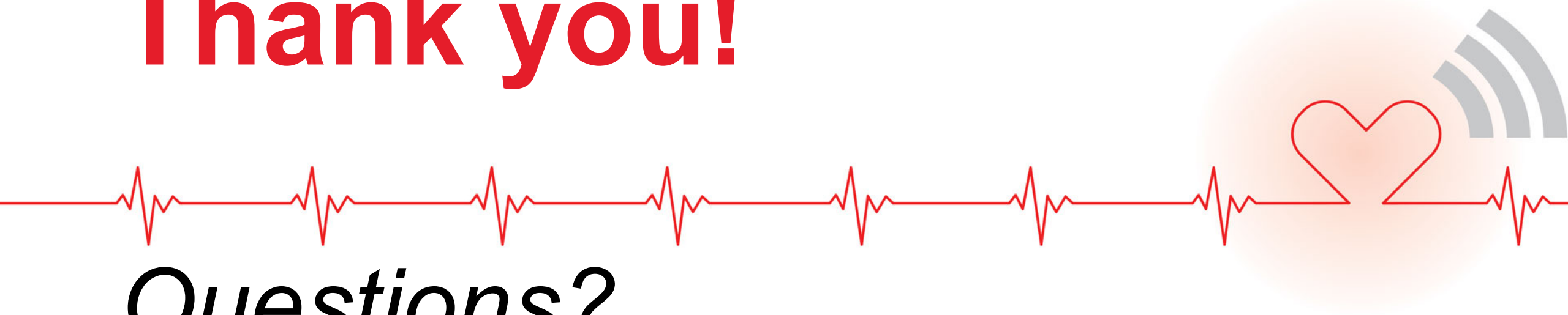


Arch Intern Med 2010;170:1045-9
BMJ 2011;343:d5228
BMJ 2014;349:g6196
BMJ 2018;360:k341
CMAJ 2015. DOI:10.1503/cmaj.140826

Summary

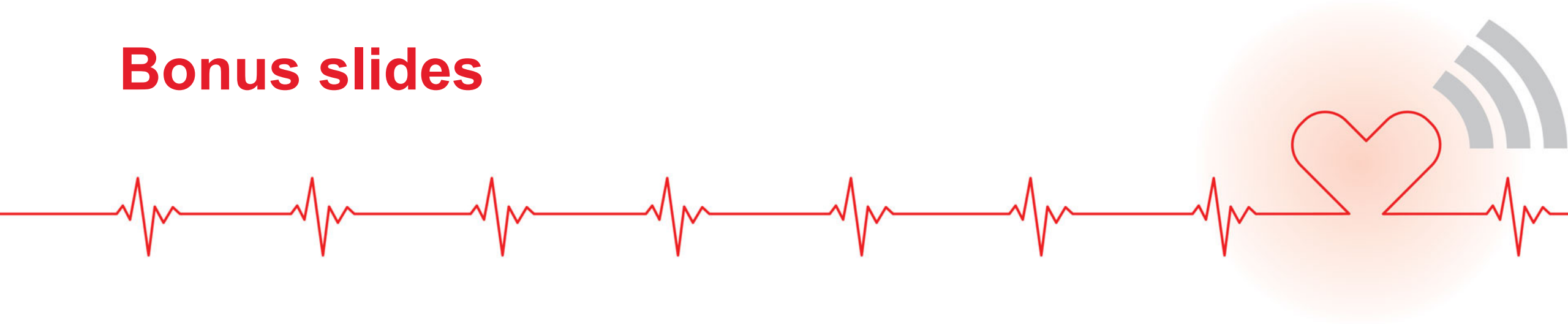
- 25-50% of HF patients take a prescription medication that may worsen HF
  - Most common culprits:
    1. NSAIDs (& COX-2 inhibitors)
    2. CCBs (diltiazem, nifedipine, verapamil)
    3. Saxagliptin, glitazones
  - Though on AHA list, metformin & tamsulosin appear safe in HF
- Many non-CV medications can ↑ adverse effects of HF medications
  - New/worsening side-effect or lab abnormality → Review the **whole** med list (including OTCs, supplements & natural products)

Thank you!



Questions?

Bonus slides



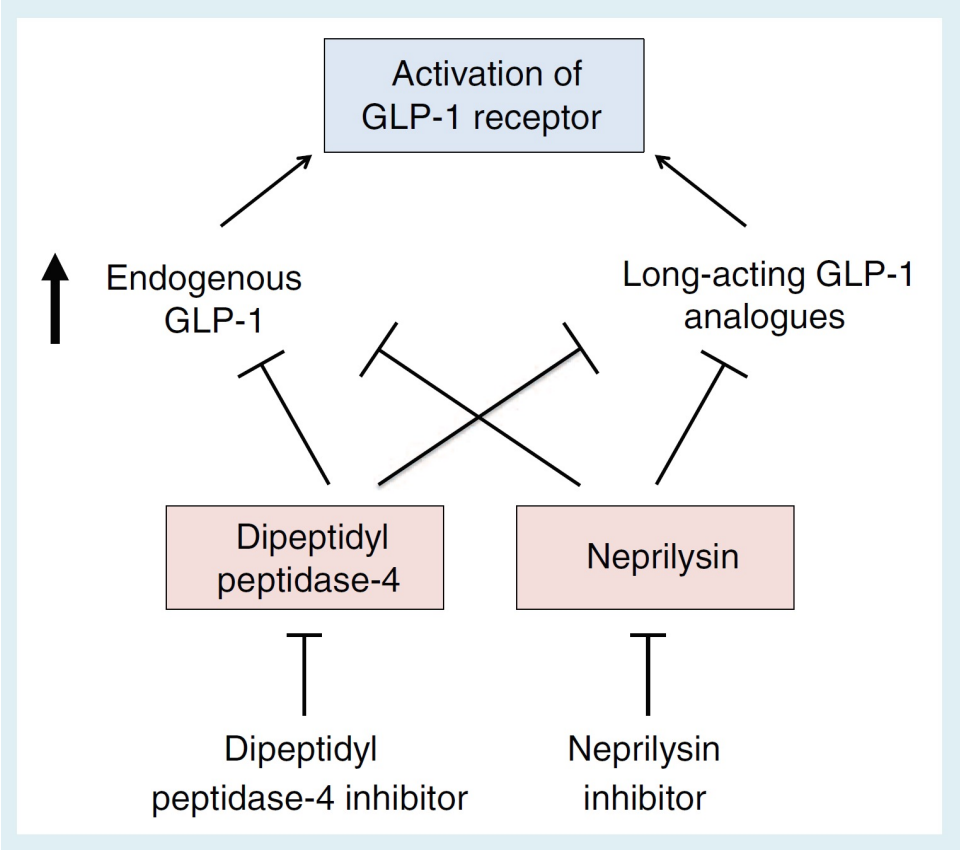
HF Medications & Hypoglycemia

HF medication	Key interacting drugs
• ACEI (data conflicting) • ARNI • SGLT2 inhibitor	• Insulin • Oral antihyperglycemics • Sulfamethoxazole • Tramadol • Selective serotonin reuptake inhibitors (SSRIs) • Hydroxychloroquine

Clin Ther 1999;21:1387-400
Diabetes Care 1997;20:1363-7
JAMA 1997;278:40-3

ARNI & Hypoglycemia

- Modest ↓ hypoglycemic effect (hemoglobin A1c ↓0.1%) vs ACE I in diabetes subgroup of PARADIGM-HF
  - Hypoglycemia common & differences inconclusive (HR 1.18, 95% CI 0.79-1.76)
  - 20% taking insulin
  - <1% with type 1 diabetes



Eur J Heart Fail 2018;20:973-7
Lancet Diabetes Endocrinol 2017;5:333-40

ARNI & Hypoglycemia

- Emerging case reports of clinically important ↓ blood glucose with ARNI
  - Case 1: T1DM with insulin pump with 2 episodes of severe hypoglycemia after switch to ARNI
    - Required ~10% reduction in basal insulin rate
  - Case 2: Type 2 diabetes on insulin pump
    - Progressive ↓22% in daily insulin after switch to ARNI
  - 8 other cases reported to Canada Vigilance as of April 2021

Bottom Line: When starting ARNI in patients with diabetes, monitor for hypoglycemia (especially if on insulin or prior hypoglycemia)

Can J Cardiol Open 2020;2:176-8
J Diabetes Sci Technol 2018;12:1254-5