Updates in Outpatient Heart Failure Management

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Conflicts

None…but gladly accepting offers

Learning Objectives

1. Recognize the role of SGLT-2 inhibitors in the management of heart failure with preserved ejection fraction
2. Review the prevalence and management of iron deficiency in heart failure
3. Discuss new strategies for titrating heart failure medications

Heart Failure with Preserved EF

HFpEF Basics

Clinical diagnosis supported by:

- S/S of CHF (DOE, PND, orthopnea), LVEF >50, diastolic dysfunction
- Clinical or chemical evidence (BNP) of volume overload
- Clinical prediction tools = H2FPEF score
  - Age, BMI, e/e', PA systolic pressure, Afib

HFpEF Risk Factors

HTN

DM

Obesity

Age > 60

Atrial Fibrillation

CKD

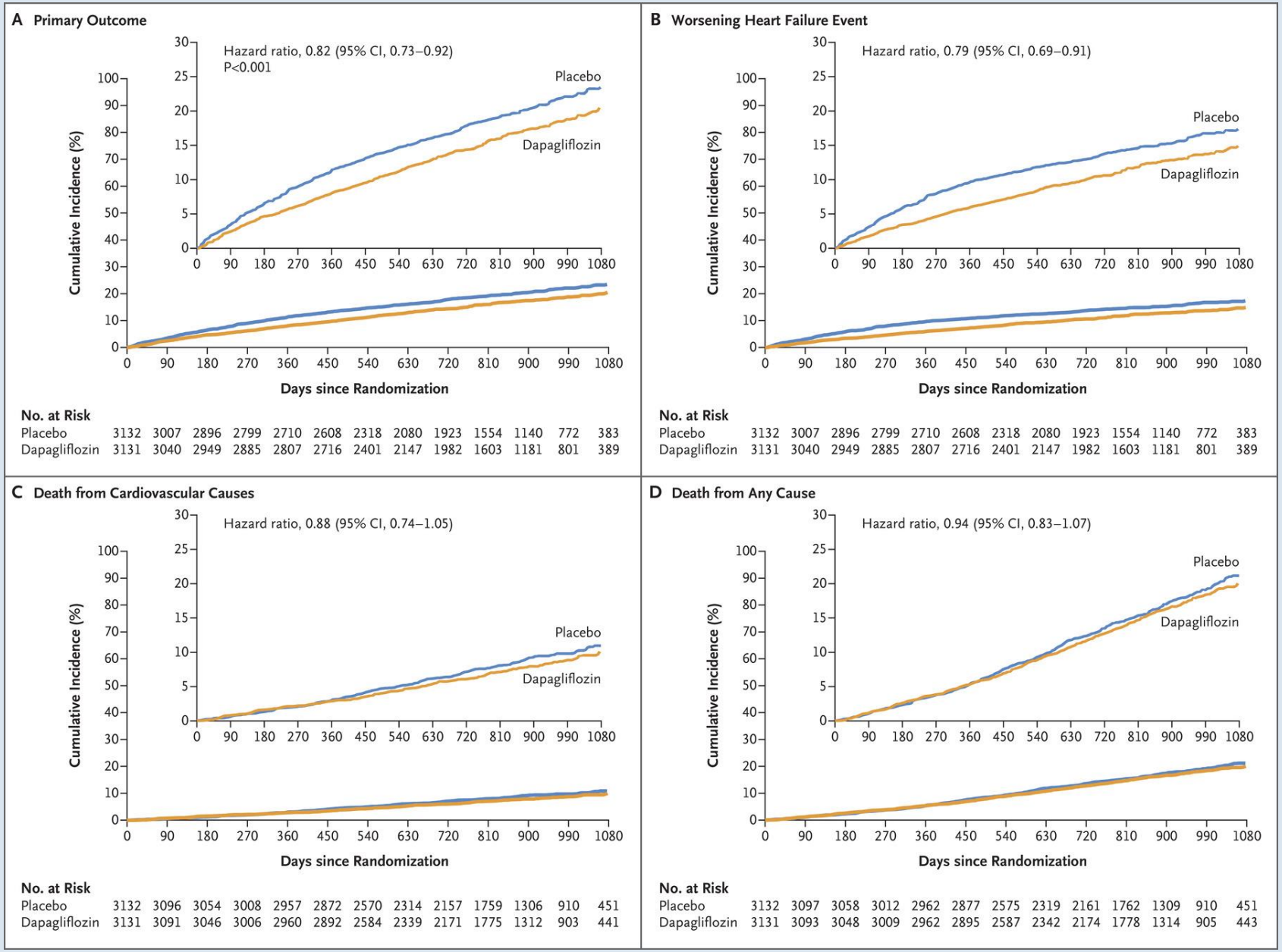
CAD

SGLT-2 Inhibitors in HF

- Empagliflozin (Jardiance), canagliflozin (Invokana), dapagliflozin (Farxiga)
  - Bexagliflozin, ertugliflozin approved in US for DM only
- Recommended for NYHA class II-IV with elevated BNP >100 or NT-proBNP > 300
- Independent indication from DM

Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction (DELIVER)

- Multicenter, double-blind, randomized control
- Dapagliflozin (3131) vs Placebo (3132)
- Notable inclusion criteria
  - LVEF > 40%, BMI < 50
  - No MI, revascularization, ablation, or valve repair within 12 weeks
- Primary outcome: CV death, HF hospitalization/urgent visit
  - 16.4% vs 19.5 %, NNT 32


A Primary Outcome
Hazard ratio, 0.82 (95% CI, 0.73–0.92)
P<0.001
Placebo
Dapagliflozin
Cumulative Incidence (%)
Days since Randomization
No. at Risk
Placebo 3132 3007 2896 2799 2710 2608 2318 2080 1923 1554 1140 772 383
Dapagliflozin 3131 3040 2949 2885 2807 2716 2401 2147 1982 1603 1181 801 389
B Worsening Heart Failure Event
Hazard ratio, 0.79 (95% CI, 0.69–0.91)
Placebo
Dapagliflozin
Cumulative Incidence (%)
Days since Randomization
No. at Risk
Placebo 3132 3007 2896 2799 2710 2608 2318 2080 1923 1554 1140 772 383
Dapagliflozin 3131 3040 2949 2885 2807 2716 2401 2147 1982 1603 1181 801 389
C Death from Cardiovascular Causes
Hazard ratio, 0.88 (95% CI, 0.74–1.05)
Placebo
Dapagliflozin
Cumulative Incidence (%)
Days since Randomization
No. at Risk
Placebo 3132 3096 3054 3008 2957 2872 2570 2314 2157 1759 1306 910 451
Dapagliflozin 3131 3091 3046 3006 2960 2892 2584 2339 2171 1775 1312 903 441
D Death from Any Cause
Hazard ratio, 0.94 (95% CI, 0.83–1.07)
Placebo
Dapagliflozin
Cumulative Incidence (%)
Days since Randomization
No. at Risk
Placebo 3132 3097 3058 3012 2962 2877 2575 2319 2161 1762 1309 910 451
Dapagliflozin 3131 3093 3048 3009 2962 2895 2587 2342 2174 1778 1314 905 443

Empagliflozin in Heart Failure with a Preserved Ejection Fraction (EMPEROR-preserved)

- Multicenter, double-blind, randomized controlled
- Empagliflozin (2997) vs Standard (2991)
- Notable inclusion criteria
  - BMI < 45, LVEF > 40%
  - No history of valvular disease, MI/CV surgery/CVA/TIA within 90 days
- Primary outcome: CV death or HF hospitalization
  - 13.8% vs 17.1%, NNT of 30

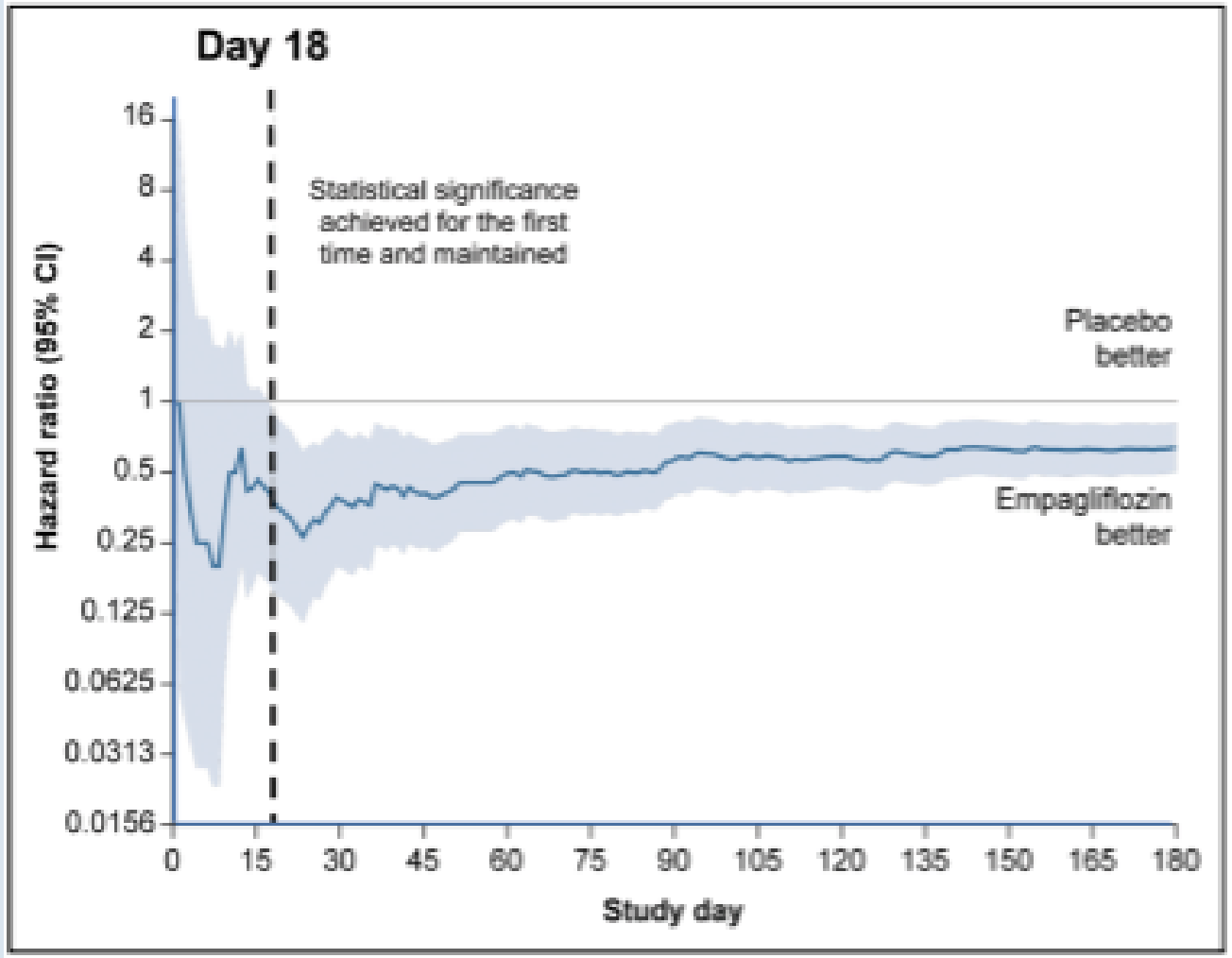


Figure 3. Time of first statistical significance in time-to-first-event analysis of cardiovascular death, hospitalization for heart failure, or emergency or urgent heart failure visit requiring intravenous treatment for worsening heart failure.
To determine the time point when statistical significance was reached and maintained for the first time, Cox regression models were fitted and sequentially censored at increasing number of days since randomization, yielding a continuous display of hazard ratios with confidence bands.

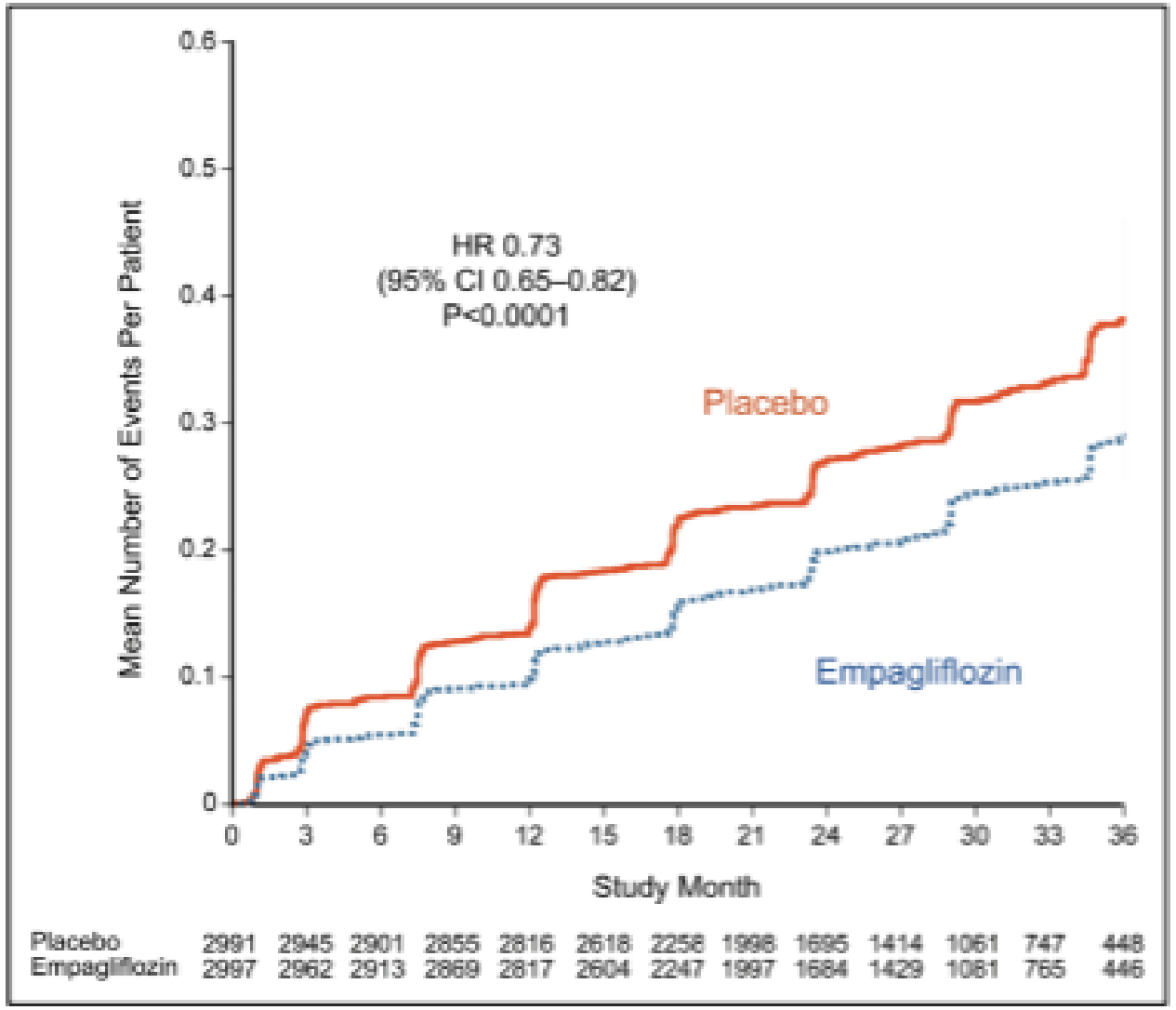


Figure 4. Total number of outpatient visits reporting interval intensification of diuretics for worsening heart failure.
Shown are mean cumulative function curves for placebo (shown in red) and for empagliflozin (shown in blue). HR indicates hazard ratio.

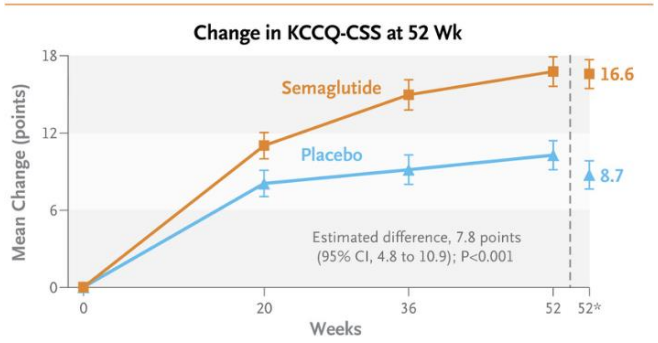
Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity (STEP-HFpEF)

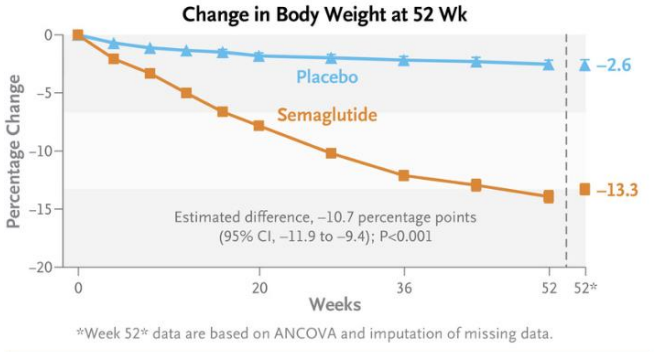
- Multicenter, double-blind, randomized controlled
- 2.4 mg semaglutide weekly vs placebo x 52 weeks
- Notable inclusion criteria
  - BMI > 30, LVEF > 45%, NYHA II-IV
  - No history of DM
- Primary outcome: KCCQ-CSS and body weight
  - KCCQ-CSS increased 16.6 vs 8.7 (P<0.001)
  - Body weight -13.3% vs -2.6% (P<0.002)

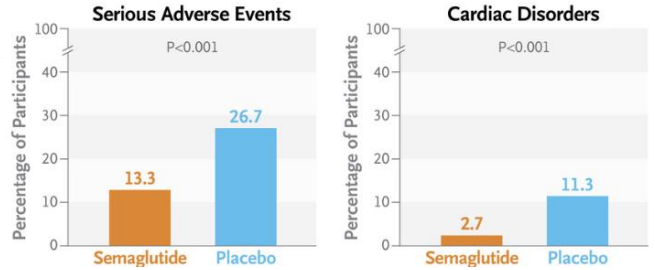
STEP-HFpEF Continued

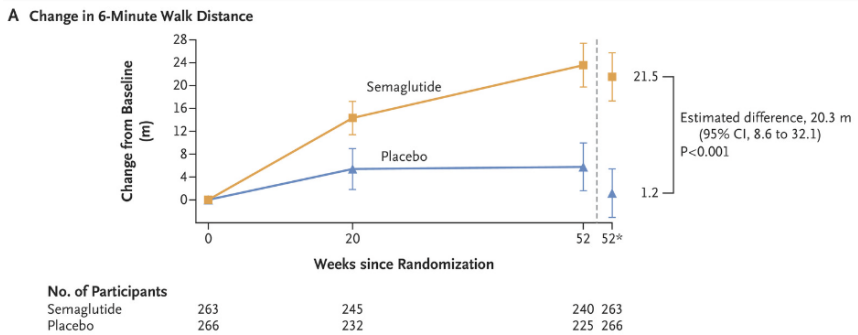
Secondary outcomes:

- CRP -43.5% vs -7.3%
- Serious adverse events 13.3% vs 26.7%
- 6min walk change from baseline +21.5 m vs +1.2









Iron Replacement in Heart Failure

Iron Deficiency in Heart Failure - Summary

- Affects up to 50% of patients with HFrEF
- Decreased exercise capacity, reduced quality of life
- Cutoff values for ID in HF: ferritin <100mg/l, or ferritin, 100 to 300 µg/l, with transferrin saturation of <20%
- Oral <<< IV iron
- Treatment of ID in HF yields:
  - Reduction in hospitalization rates for HF
  - Reduction in cardiovascular mortality
  - Improvement in HF symptoms (NYHA) and improvement of quality of life

Diagnosing Iron Deficiency in Heart Failure

- Ferritin and transferrin saturation should be part of routine baseline assessment of HF
- Ferritin cut-off for patients without chronic inflammation: <30 µg/L
- Ferritin cut-off for patients with HFrEF: <100µg/L or 100-300µg/L if TSAT <20%.
- Iron deficiency in HF is independent of anemia status and should not factor in decision to treat.

Risk factors for ID in HF:

- Female sex
- ↑ NYHA classification
- ↑ pro-BNP levels.

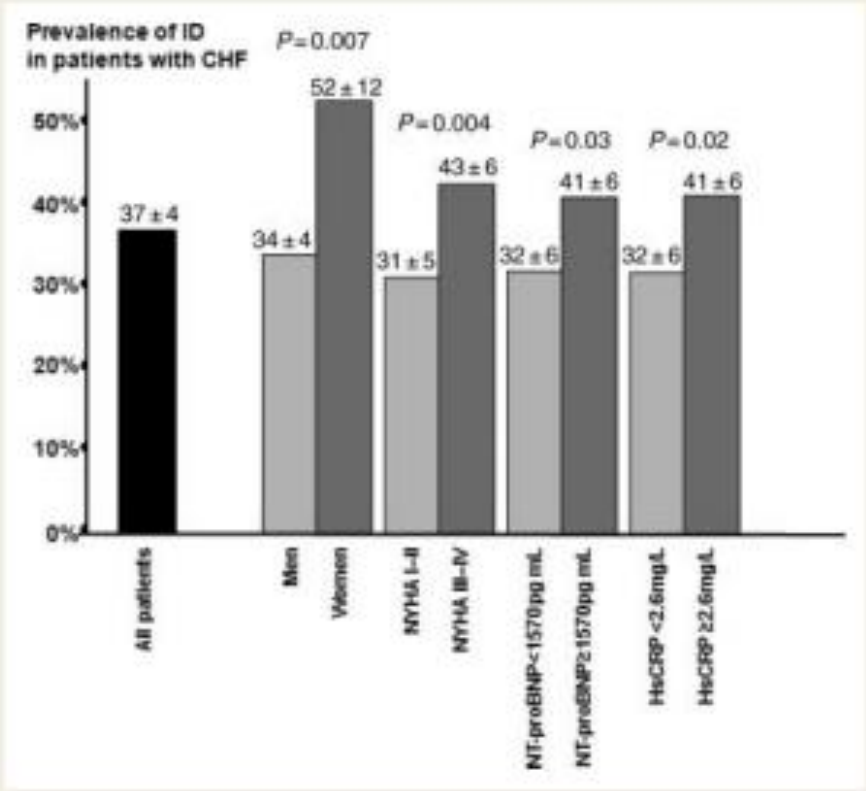


Figure 1 Prevalence of iron deficiency in patients with chronic heart failure (CHF), also in clinical subgroups (percentages ± 95% confidence intervals). In the case of plasma N-terminal pro-type B natriuretic peptide (NT-proBNP) and serum high-sensitivity C-reactive protein (hs-C-reactive protein), medians were used as cut-off values.

Replacement – Oral Iron

- Oral iron:
  - Limited gut absorption
  - Side effects of nausea, abdominal pain, diarrhea, etc.
- IRON-HF (2013):
  - IV iron was superior to oral iron in increasing functional capacity in HF
- IRONOUT-HF (2017):
  - Failed to support use of oral iron supplementation in HFrEF
    - No significant change in peak oxygen uptake, 6-minute walk tests, NT-proBNP

Replacement – IV Iron

- FAIR-HF (2009):
  - Improved NYHA class, 6-min walk distance, KCCQ-CSS
- CONFIRM-HF (2015):
  - Improved 6-minute walk test
- EFFECT-HF (2017):
  - IV iron improved patient peak O2 consumption
- Meta-analyses (2016/2017):
  - Decreased rates of recurrent CV hospitalizations and CV mortality
  - Reduction in recurrent HF hospitalizations and CV mortality.
  - Reduced all-cause mortality and cardiovascular hospitalization
  - Reduced worsening of HF

Guidelines/Further Research

1. European Society of Cardiology guidelines only advocates for the use of IV ferric carboxymaltose, US guidelines do not differentiate between IV iron formulations
2. IV iron should be administered regardless of anemia status
3. No current data showing IV iron shows improvement in patients with HFpEF, trials currently are underway

Heart Failure Medication Titration

Background

- Guideline-directed medical therapy (GDMT) is the cornerstone of HFrEF treatment
- Consists of:
  - Beta blockers, ACE/ARB/ARNi, MRA, SGLT-2 inhibitor
- Titrating multiple meds is a clinical challenge

Safety, tolerability, and efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF)

- Multi-center, open label, randomized controlled
- High intensity GDMT vs usual care
  - High intensity = half-maximal BB, RAASi, MRA at discharge, full dose 2 weeks post discharge q 2 week follow up
  - Usual care = standard local practice, 90 day follow up
- Notable inclusion criteria
  - Admitted w/ HF exacerbation in previous 72 hrs
  - Not on maximal GDMT
  - Any EF

STRONG-HF Continued

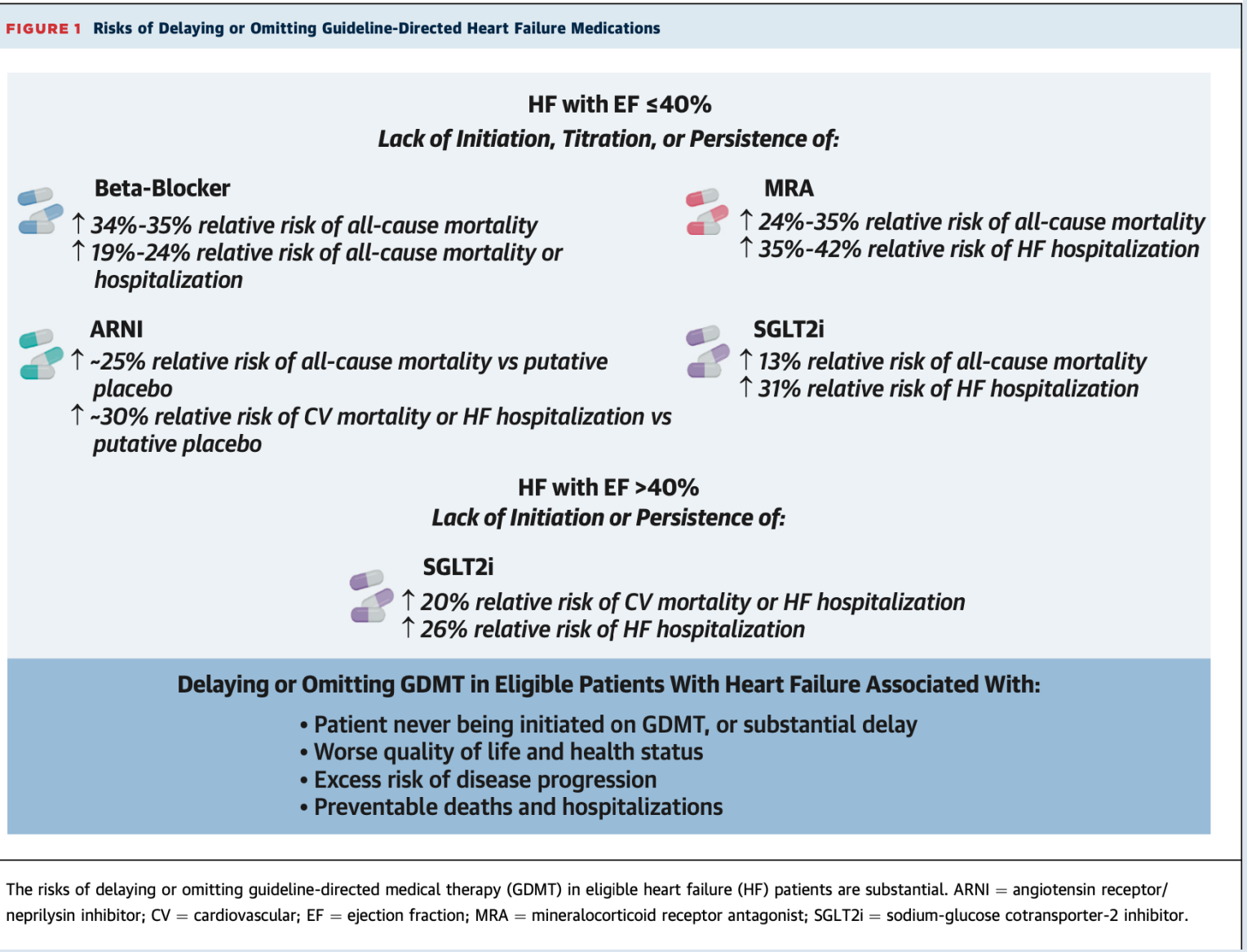
- Primary outcome: all cause death or HF admission at 6 mo
  - 15.2% vs 23.3% (NNT 13)
- Adverse events:
  - 41% vs 29% (NNH 9)
- Serious (16% vs 17%) and fatal (5% vs 6%) adverse events similar

STRONG-HF Interpretation

- Rapid up-titration of GDMT is safe and effective at preventing death or HF rehospitalization at 180 days
- Results cannot be attributed to close follow up alone (ECAD-HF, Pact-HF, COACH, CONNECT-HF)
- Open label study may confound results, particularly with regards to QoL rating
- Studied before SGLT-2 inhibitors and IV iron approved for use in HF
- No EF requirement was specified, results could be applied to large HF spectrum

- <25% HFrEF patients on RAASi, BB, MRA
- Average regimen cost <$160/yr
- No proven medical benefit or increased tolerance w/ delayed initiation of GDMT

FIGURE 1 Risks of Delaying or Omitting Guideline-Directed Heart Failure Medications



The risks of delaying or omitting guideline-directed medical therapy (GDMT) in eligible heart failure (HF) patients are substantial. ARNI = angiotensin receptor/neprilysin inhibitor; CV = cardiovascular; EF = ejection fraction; MRA = mineralocorticoid receptor antagonist; SGLT2i = sodium-glucose cotransporter-2 inhibitor.

Key Points

- SGLT-2 inhibitors have mortality benefit in HFpEF
- Iron deficiency is common in HF, treatment improves outcomes
- IV iron superior to oral iron, treatment should be initiated regardless of anemia
- Rapid titration of GDMT is safe and effective in HF
- Failure to titrate GDMT results in adverse outcomes

Questions?

Special thanks to our mentor Kang Zhang, MD, FACP, and STHC Primary Care Track Director, Caitlin Allen, MD!