DISCUSSANT
DAPA-HF: Effects on KCCQ and according to age

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Disclosures

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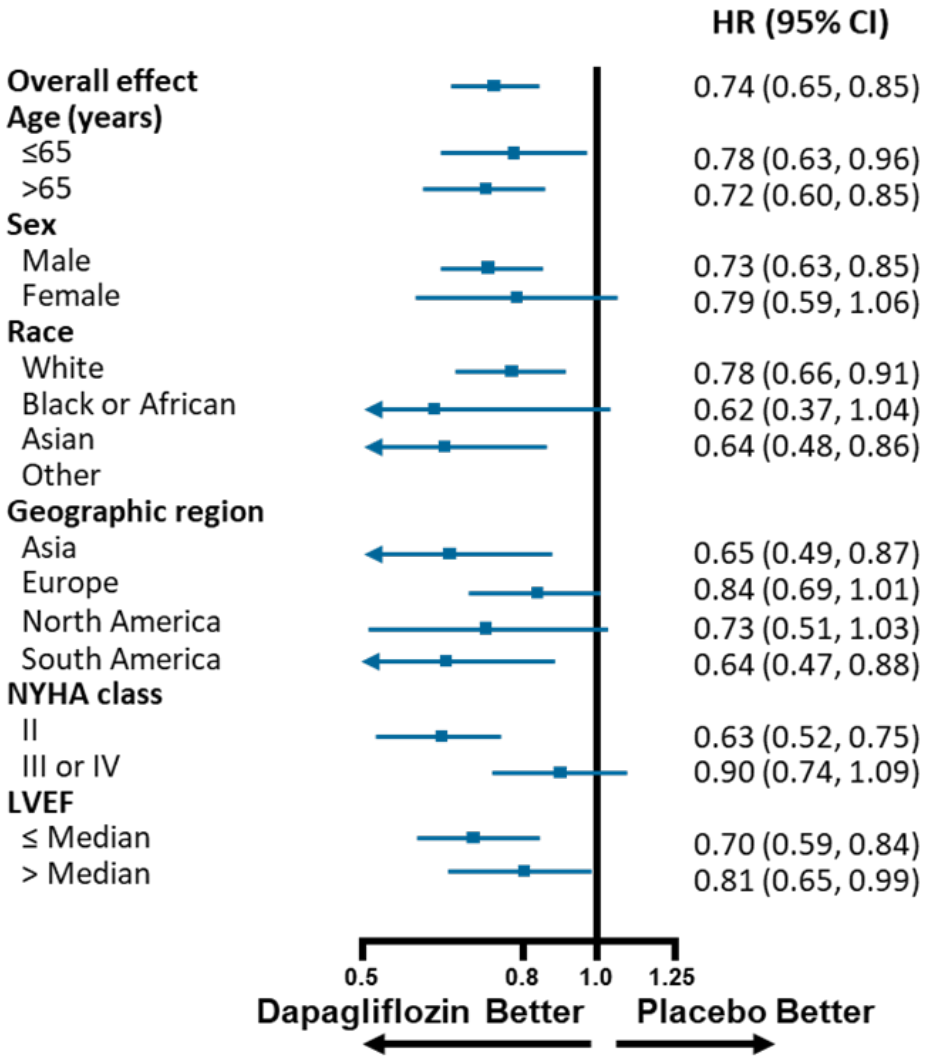
DAPA-HF Pre-specified subgroups & Secondary outcomes



- What about efficacy and safety in the elderly (>75y)? Age-related comorbidities, frailty and polypharmacy may alter the benefit/risk ratio in the elderly

McMurray JJV, et al. *N Engl J Med* 2019, DOI: 10.1056/NEJMoa1911303; *Calculated from win ratio, incorporating death.

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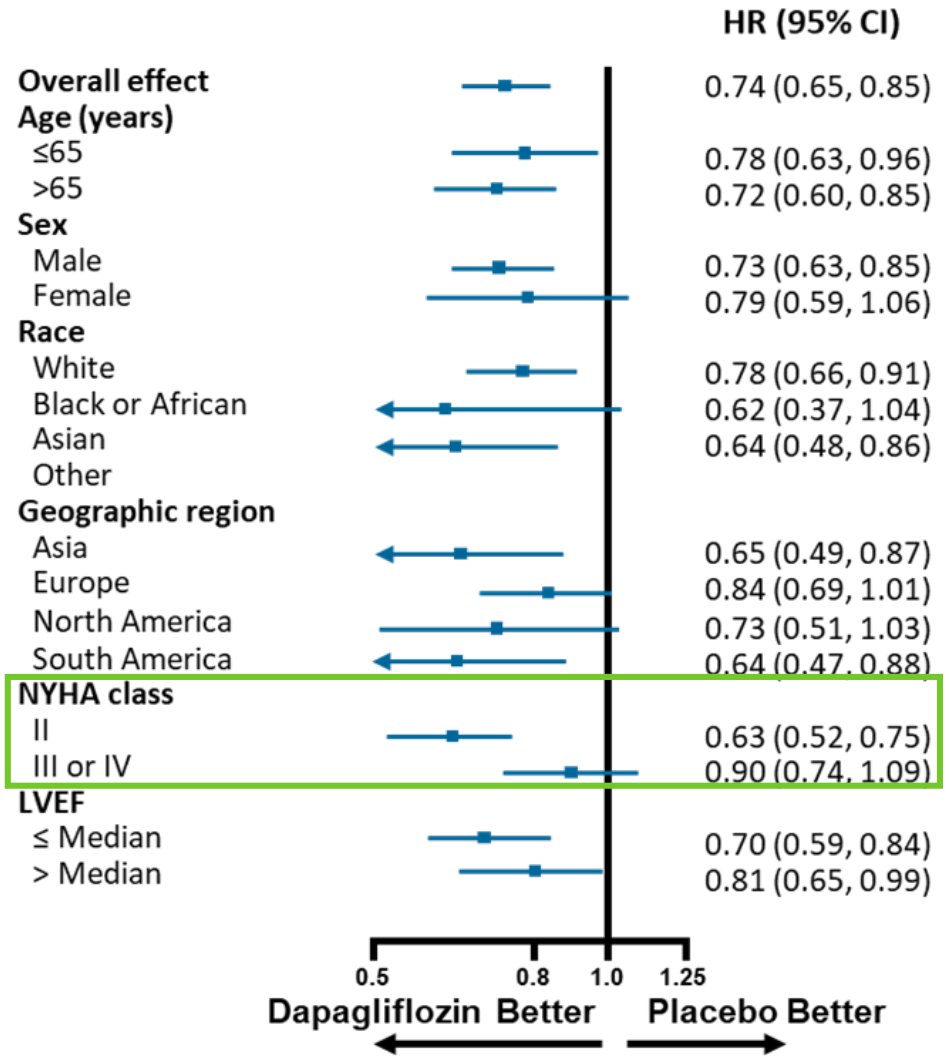

- What about efficacy and safety in the elderly (>75y)? Age-related comorbidities, frailty and polypharmacy may alter the benefit/risk ratio in the elderly
- No heterogeneity in benefit of dapagliflozin across subgroups of baseline KCCQ-TSS
- What about benefits beyond mortality and HF events? Improving patient-reported outcomes (PRO) is an important goal in HF

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Dapagliflozin, health status and age in HFrEF

- **Benefit/risk profile of dapagliflozin as favorable in older as in younger patients**
  - Relative risk reduction similar, absolute risk reduction greater in older patients
  - Adverse events more likely in older patients but no difference between dapagliflozin and placebo in any age group and generally well-tolerated
  - Older patients less likely to be aggressively treated with GDMT which may have amplified the benefit of dapagliflozin but also suggests therapeutic inertia

- **Dapagliflozin improved HF-related health status as measured by KCCQ**
  - Benefits emerged early and sustained over 8 month
  - Substantial proportions of patients experienced clinically meaningful improvements

Martinez FA, Serenelli M et al. Circulation 2019; Kosiborod M, Jhund P et al. Circulation 2019

Dapagliflozin, health status and age in HFrEF

Intervention	Study	KCCQ improvement	Citation
Dapagliflozin	**DAPA-HF**	**+2.8 (TSS), +2.5 (CSS), +2.3 (OSS) at 8 months ↑≥5 points (TSS) in 58% (vs 51% placebo)**	**Kosiborod 2019**
	DEFINE-HF	+3.7 (OSS), +4.6 (CSS) at 3 months ↑≥5 points (OSS) in 43% (vs 33% placebo)	Nassif 2019
Exercise	HF-ACTION	+1.9 (OSS) at 3 months	Flynn 2009
Ivabradine	SHIFT	+2.4 (OSS), +1.8 (CSS) at 12 months ↑≥5 points in 51%(OSS), 48%(CSS) (vs 48%, 44% placebo)	Ekman 2011

TSS, total symptom score; CSS, clinical summary score; OSS, overall summary score

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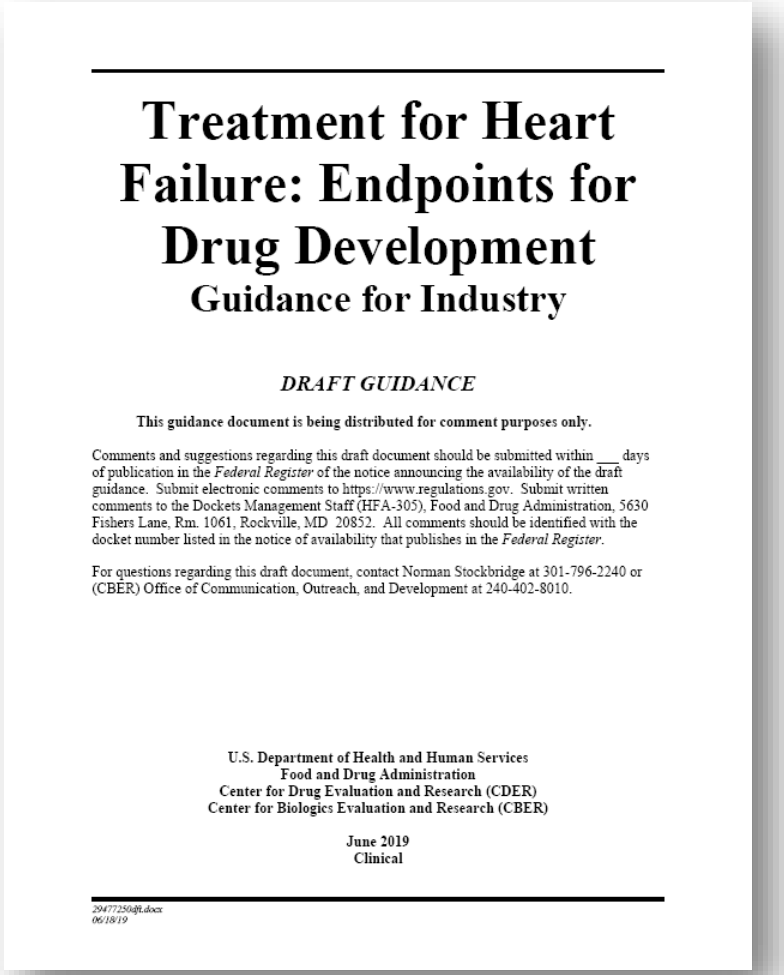
Sacubitril/ valsartan	PARADIGM-HF	+1.6 (CSS) at 8 months ↑≥5 points (OSS) in 35% (vs 33% enalapril)	McMurray 2014 Lewis 2017
	EVALUATE-HF	+4.2 (OSS) at 3 months ↑≥5 points (OSS) in 58% (vs 43% enalapril)	Desai 2019
	CHAMP-HF Registry	+2.9 (OSS, covariate-adj vs no ARNI) at median 57 days ↑≥5 points (OSS) in 44% (vs 40% no ARNI)	Khariton 2019

* Note placebo effect

TSS, total symptom score; CSS, clinical summary score; OSS, overall summary score

Remaining questions



Treatment for Heart Failure: Endpoints for Drug Development

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within ___ days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact Norman Stockbridge at 301-796-2240 or (CBER) Office of Communication, Outreach, and Development at 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

June 2019
Clinical

2947725dft.docx
06/18/19

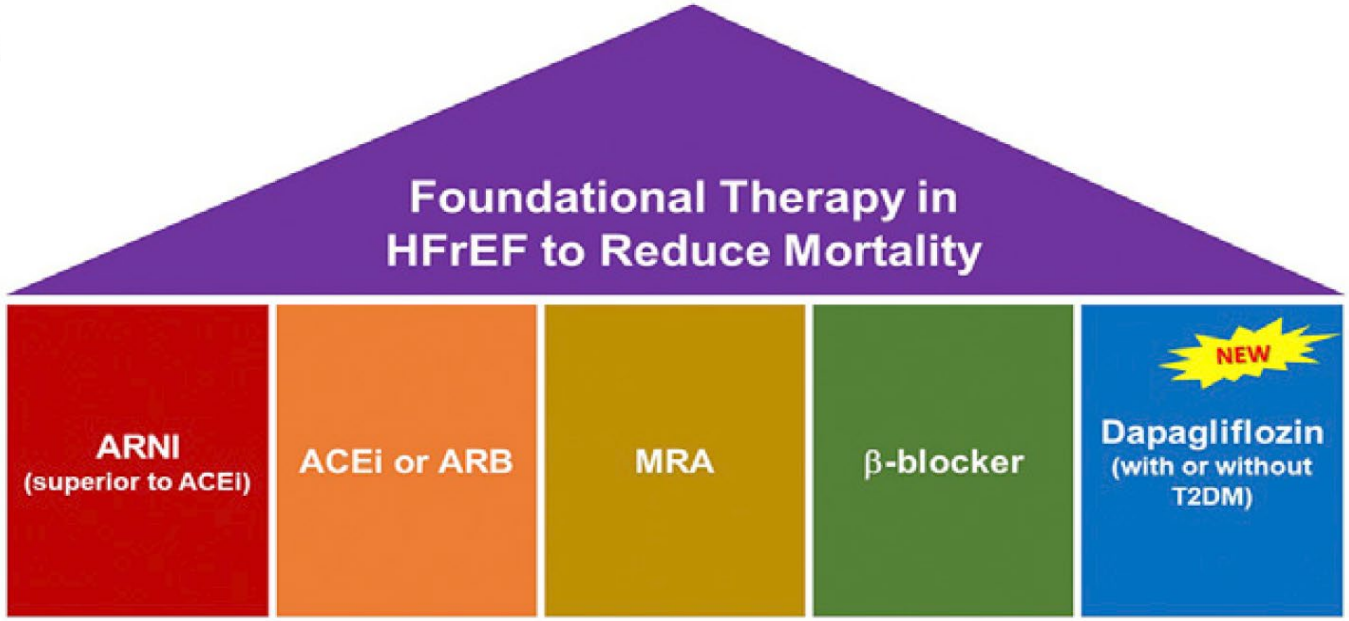
FDA, June 2019

FDA: "Evidence of effectiveness for a heart failure drug could be based on improvements in symptoms(e.g., dyspnea, fatigue, edema) and/or function (e.g., walking…"

- Post-hoc analyses of a single trial: Specific drug vs class effect? Generalizability to real world setting?
- Effect in combination with ARNI?
- Other patient groups e.g. hospitalized HF, higher risk patients, HFpEF?
- Specific mechanisms underlying observed benefits?
- Will PRO data help treatment sequencing and selection by patients, providers, payers, guidelines?
  - Which PRO tool? Which KCCQ domains? Regional differences?
- Challenges to implementation?

Conclusions

- Dapagliflozin meets the 3 critical goals in HF management: (1) reduced mortality, (2) reduced hospitalizations, (3) improved HF-related health status
- These studies provide further important data which, if confirmed in other trials of SGLT2i in HFrEF, support SGLT2 inhibition as the next foundational pillar of HFrEF treatment



"The knowledge gained needs to be translated into patient care – something we have done poorly with ARNIs… If we are to win the war against heart failure, science will need to be coupled with pragmatic and deliberate implementation approaches with the goal of overcoming inertia"

Bhatt DL, Verma S, Braundwald E. CELL METABOLISM. 2019;30:847-849