Which drug when?
How to sequence heart failure drugs in 2021

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My employer, Glasgow University, is paid for my participation in clinical trials (and for other industry-related activities) and I have received personal payments for lectures and advisory boards: Relevant to this presentation AstraZeneca, Boehringer Ingelheim, and Novartis.

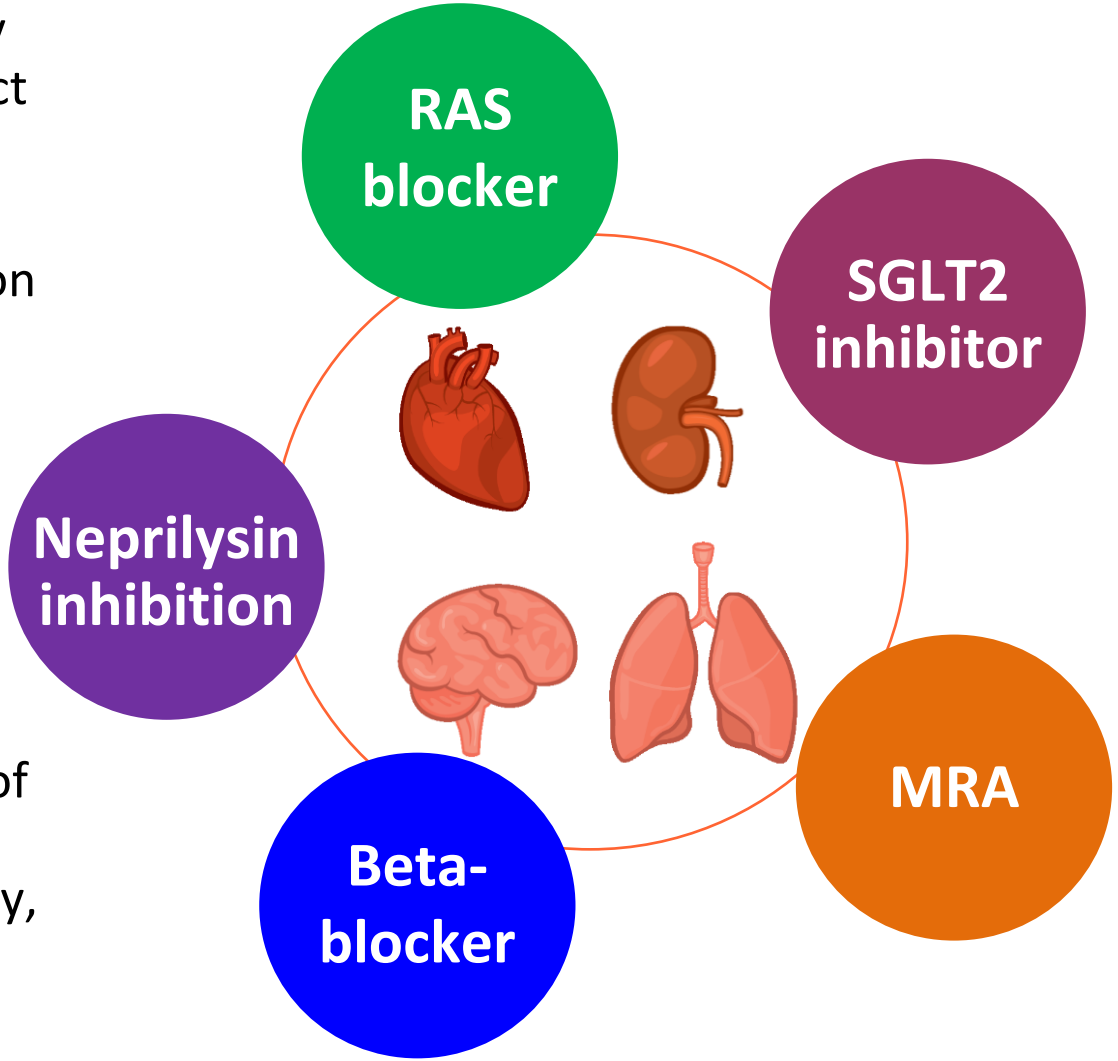
University of Glasgow

British Heart Foundation

NHS Greater Glasgow and Clyde

- I have nothing to declare

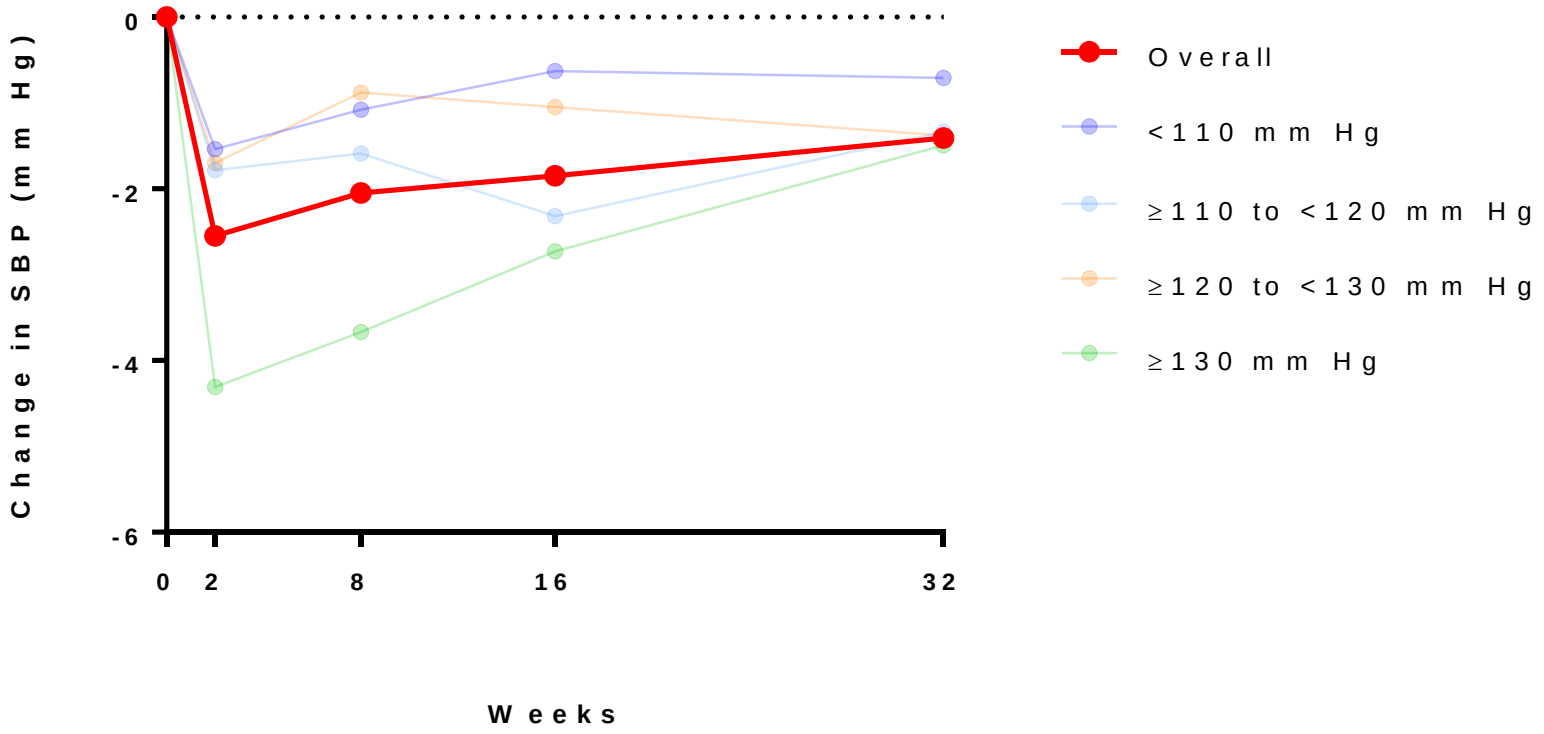
- These are complementary therapies acting on distinct patho-physiological pathways
- Their mechanisms of action are independent and additive
- The goal is to implement as many as possible as quickly as possible
- The order in which treatments are given should depend on speed of onset and size of benefit, ease of use and tolerability, and “synergy” with other treatments



Use a SGLT2 inhibitor early or even first?

- **Single dose, no titration**
- **Can be started in hospital or in the community**
- **Benefit within <28 days**
- **Outstanding tolerability**
- **Negligible effect on blood pressure**
- **Preserves rather than worsens renal function**
  (do we even need to check blood chemistry?)
- **Reduces risk of hyperkalaemia with MRAs**
  (another concept: agents started earlier can enhance the safety of agents started later)

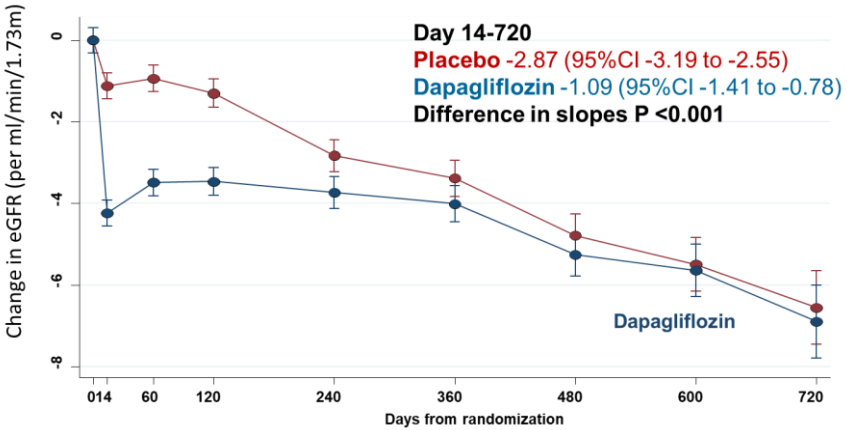
DAPA-HF: Placebo-corrected change in SBP



Serenelli et al Eur Heart J. 2020 Sep 21;41(36):3402-3418.

SGLT2i slow the rate of decline in eGFR in HFrEF

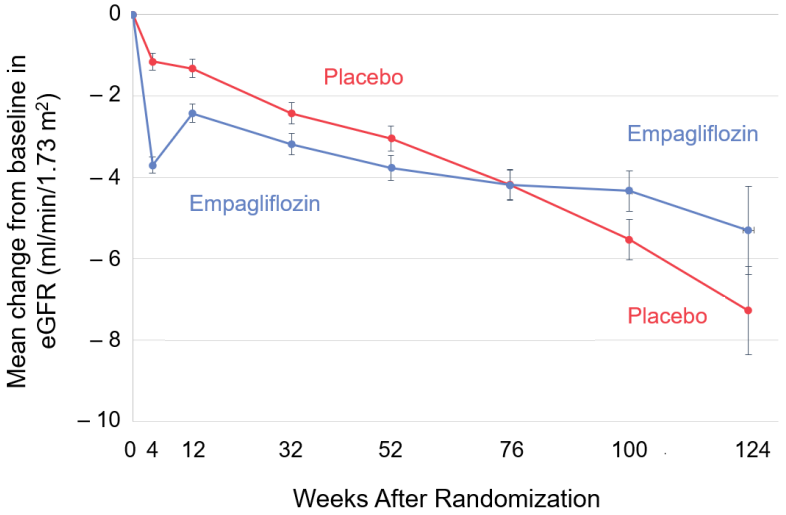
DAPA-HF



Difference = 1.78 ml/min/yr

Jhund P et al. Circulation. 2020 Oct 12.
doi: 10.1161/CIRCULATIONAHA.120.050391

EMPEROR-Reduced

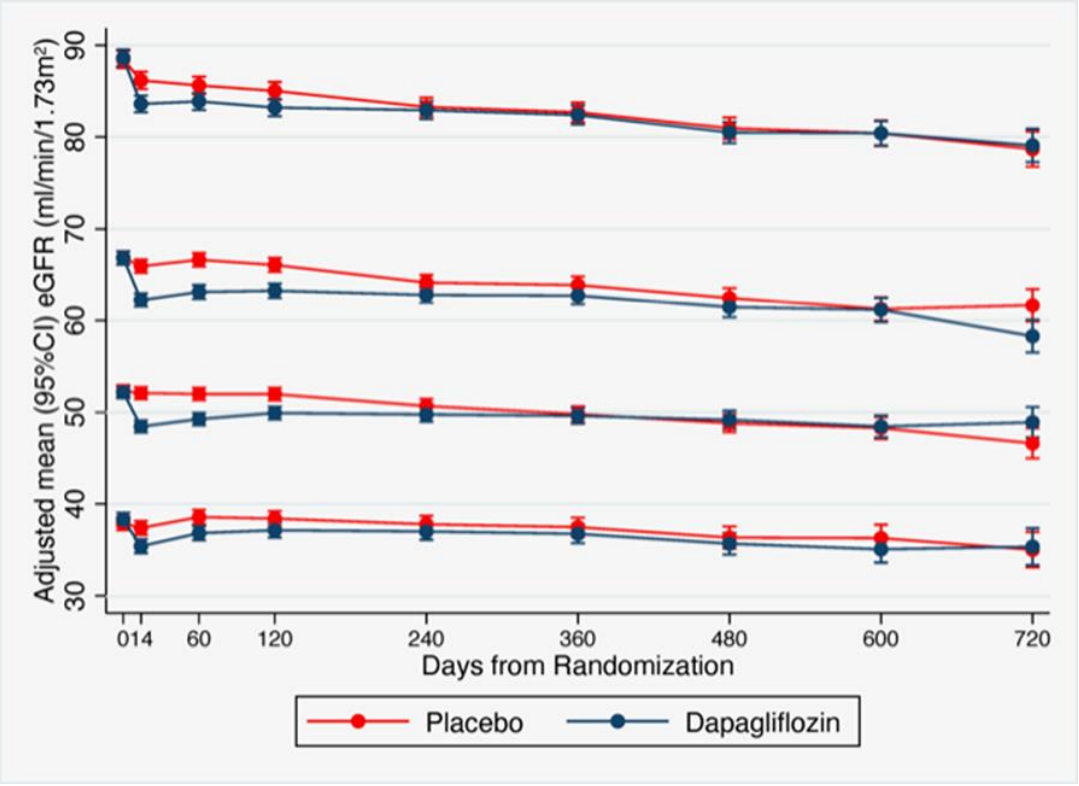


Difference = 1.73 ml/min/yr

Zannad F et al. Circulation. 2020 Oct 23.
doi: 10.1161/CIRCULATIONAHA.120.051685

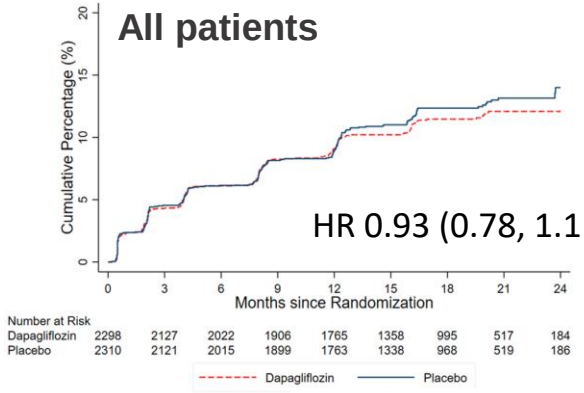
DAPA-HF: Mean eGFR over time according to baseline eGFR category and randomised treatment assignment (both dapagliflozin and placebo groups shown)

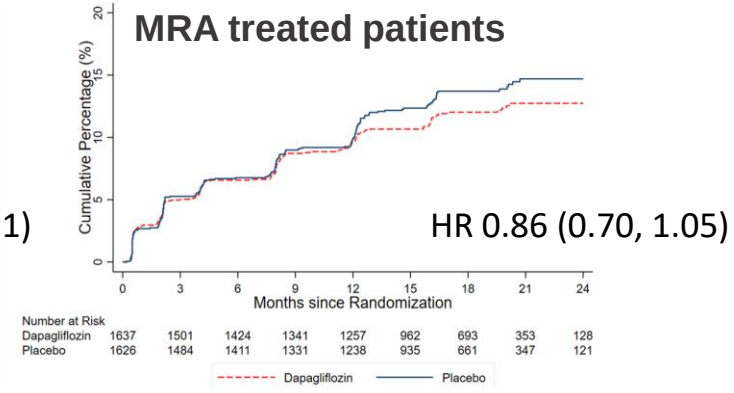
eGFR categories: >75, <75- ≥60-, <60- ≥45, <45, and ml/min/1.73 m^2



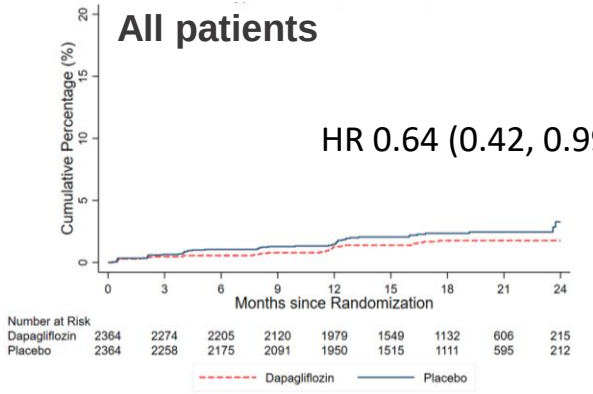
DAPA-HF: Incidence of hyperkalaemia

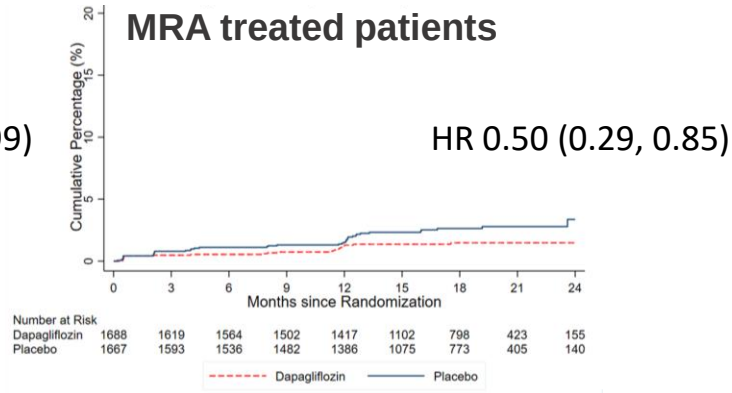
Incidence of hyperkalemia (>5.5 mmol/l)





Incidence of hyperkalemia (>6.0 mmol/l)





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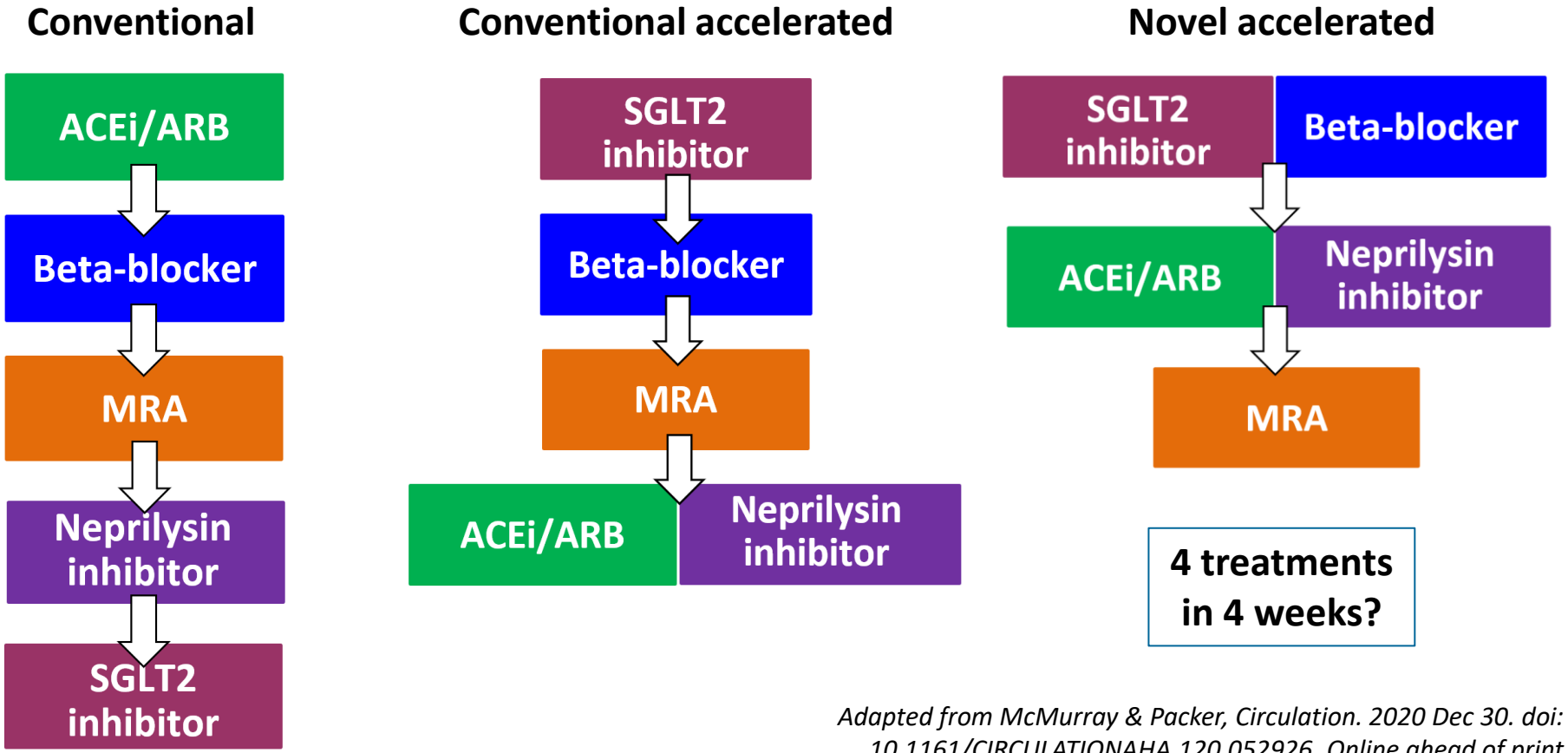
Should we do it differently? The debate for 2021



Adapted from McMurray & Packer, Circulation. 2020 Dec 30. doi: 10.1161/CIRCULATIONAHA.120.052926. Online ahead of print

Can we predict what might work best?

- Model the effects of introducing therapies in an “treatment-naïve” cohort (placebo arm of SOLVD-Treatment and CHARM-Alternative not receiving beta-blocker or MRA – used to calculate event rates and events avoided)
- Estimate effect of treatments based on results of RCTs (SOLVD-T, MERIT-HF, EMPHASIS-HF, PARADIGM-HF, DAPA-HF).
- Main model – assumes full effect of treatment obtained half-way through dose up-titration

Shen et al submitted

Can we predict what might work best?

What did we model?

- i) Conventional sequence of treatments (ESC guidelines 2016)
- ii) An accelerated approach to up-titration of the conventional sequence of treatments
- iii) Start with an ARNI (sacubitril/valsartan), rather than a RASi, and up-titrate all drugs rapidly as in ii)
- iv) Test alternative sequences of introducing the four life-saving treatments, up-titrating all drugs rapidly, as in ii) and iii)

Shen et al submitted

Modelling the difference

Applying results of trials to patients with HFrEF: CV death/HF hospitalization prevented per 1000 patients over 1 year

1. Conventional

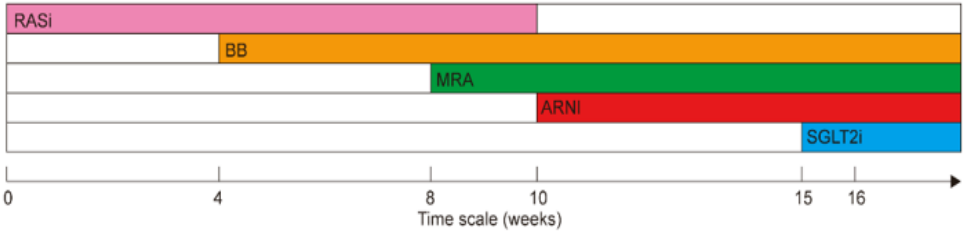
Potentially avoid 161 events

Modelling the difference

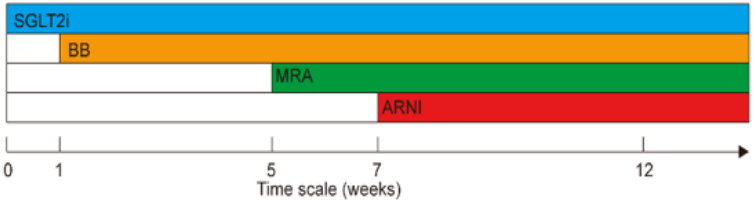
Applying results of trials to patients with HFrEF: CV death/HF hospitalization prevented per 1000 patients over 1 year

1. Conventional

2. Conventional accelerated



3. Novel accelerated



Potential benefit of new approaches

Approach 2 vs. Approach 1

14 fewer events

3 vs. 1

26 fewer events

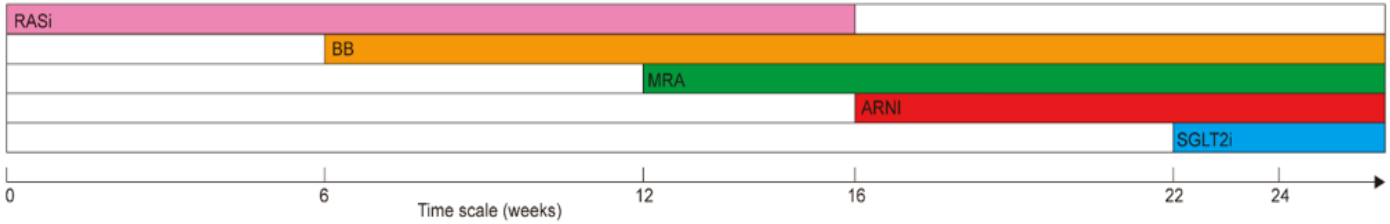
3 vs. 2

11 fewer events

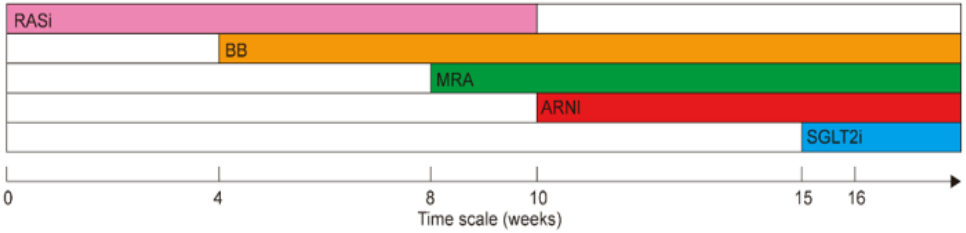
Modelling the difference

Applying results of trials to patients with HFrEF: CV death/HF hospitalization prevented per 1000 patients over 1 year

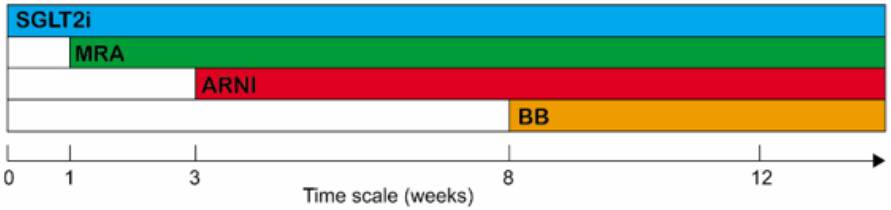
1. Conventional



2. Conventional accelerated



3. Novel accelerated (best)



Potential benefit of new approaches

Approach 2 vs. Approach 1

14 fewer events

3 vs. 1

29 fewer events

3 vs. 2

15 fewer events

Caveats – it's a modelling exercise

- Assumes all patients tolerate all treatments
- Assumes all patients are titrated to target dose of each treatment
- Assumes all patients need all treatments
- Does not take account of cost (all the best scenarios include sacubitril valsartan)
- For simplicity, only one treatment started at a time

Tolerability and synergy considerations with other treatments

“Synergies”

- **Neprilysin inhibition:** Slows rate of decline in eGFR (with RAS blockers) and reduces risk of hyperkalaemia (with an MRA)

Tolerability

- **MRA:** Negligible effect on blood pressure
- **Beta-blocker:** No effect on eGFR

Tailoring treatment to the patient: Main considerations

- **Congestion** – SGLT2 inhibitors are diuretics; MRAs also?
- **Blood pressure** – Less blood pressure reduction with SGLT2 inhibition and an MRA than with sacubitril/valsartan (most BP reduction)
- **Potassium** – Neprilysin inhibition and SGLT2 inhibition do not increase potassium and may reduce the risk of MRA induced hyperkalaemia (but remember sac/val includes an ARB)
- **Renal function** – Key issues are volume status and BP, especially in context of RAS blockade. Switching to sac/val should not worsen renal function if intensity of RAS blockade the same (may improve kidney function or slow rate of decline) – better to start sac/val earlier than later. Small decline in eGFR on starting SGLT2 inhibitor (as with a RAS blocker); thereafter, slower rate of decline in eGFR.

Pharmacological therapy for HFrEF: Summary and conclusions

- These are complementary therapies acting on distinct patho-physiological pathways
- Their mechanisms of action are independent and additive
- The goal is to implement as many as possible as quickly as possible – because they work quickly
- The order in which treatments are given should depend on speed of onset and size of benefit, ease of use and tolerability, and “synergy” with other treatments – and not on the history of clinical trials