A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS OF PHARMACOLOGICAL TREATMENT OF HEART FAILURE WITH REDUCED EJECTION FRACTION (TROMP J, 2022)

جست‌وجو در منابع و تهیه اسلاید: دکتر امیرعلی برخورداریون (اینترن قلب)

ارائه: دکتر مریم فلسفی (اینترن قلب)

استاد راهنما: جناب آقای دکتر سخاوتی

بیمارستان ضیاییان- فروردین ۱۴۰۳

JACC: HEART FAILURE VOL. 10, NO. 2, 2022

PUBLISHED BY ELSEVIER

MINI-FOCUS ISSUE: DRUG THERAPY

CLINICAL RESEARCH

A Systematic Review and Network Meta-Analysis of Pharmacological Treatment of Heart Failure With Reduced Ejection Fraction

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INTRODUCTION

- Heart failure (HF) remains a major cause of mortality and hospitalization globally, despite advances in pharmacological treatment.
- In the last decade, treatment options for HFrEF increased with the addition of sacubitril/valsartan (ARNi) and ivabradine.
- Results of trials published in the past year showed that treatment with sodium-glucose cotransporter 2 inhibitors (SGLT2i) empagliflozin and dapagliflozin soluble guanylase cyclase stimulator vericiguat and cardiac-specific myosin activator omecamtiv-mecarbil can further improve outcomes in HFrEF.

INTRODUCTION

- Earlier trials were performed largely sequentially showing incremental benefit of novel pharmacological therapy on top of existing treatment but recent trials were performed in parallel Results of more recent trials cannot guide sequencing of therapy or determine the most beneficial combination of pharmacotherapy.
- Therefore, we conducted a systematic review and network meta-analysis to estimate and compare the aggregate treatment benefit of pharmacological therapy for HFrEF.

METHODS

- STUDY DESIGN- A systematic review and network meta-analysis was performed with a frequentist statistical approach, based on a prespecified study protocol. (A systematic search of MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials for randomized controlled trials published between 1987 and January 1, 2021.)
- Pharmacological agents considered included digoxin, isosorbide dinitrate and hydralazine (H-ISDN), ACEi, ARB, BB, MRA, ivabradine, ARNi, SGLT2i, vericiguat, and omecamtiv-mecarbil.

METHODS

- Target studies were limited to adult populations (aged >18 years) with HFrEF, enrolled in the outpatient setting or after stabilization following hospitalization for HF.
- Studies were excluded when the entire population included patients with a concomitant diagnosis that likely had a major effect on outcome (eg, patients with left ventricular dysfunction postmyocardial infarction, or trials only including patients with diabetes). Studies for treating patients in the acute phase of HF or comparing drugs within the same drug group were excluded.

RESULTS: STUDY SELECTION

- A total of 9,328 records after exclusion of duplicates.
- After screening, 75 full-text papers were included.
- In total, these studies included 95,444 patients (23% women), and 199,978 participant years of follow-up. (The median follow-up duration was 11 months.)
- The majority of patients were in New York Heart Association (NYHA) functional class II across studies, except for patients in 3 studies who were predominantlyin NYHA functional class III and IV.
- Overall risk of bias was low.

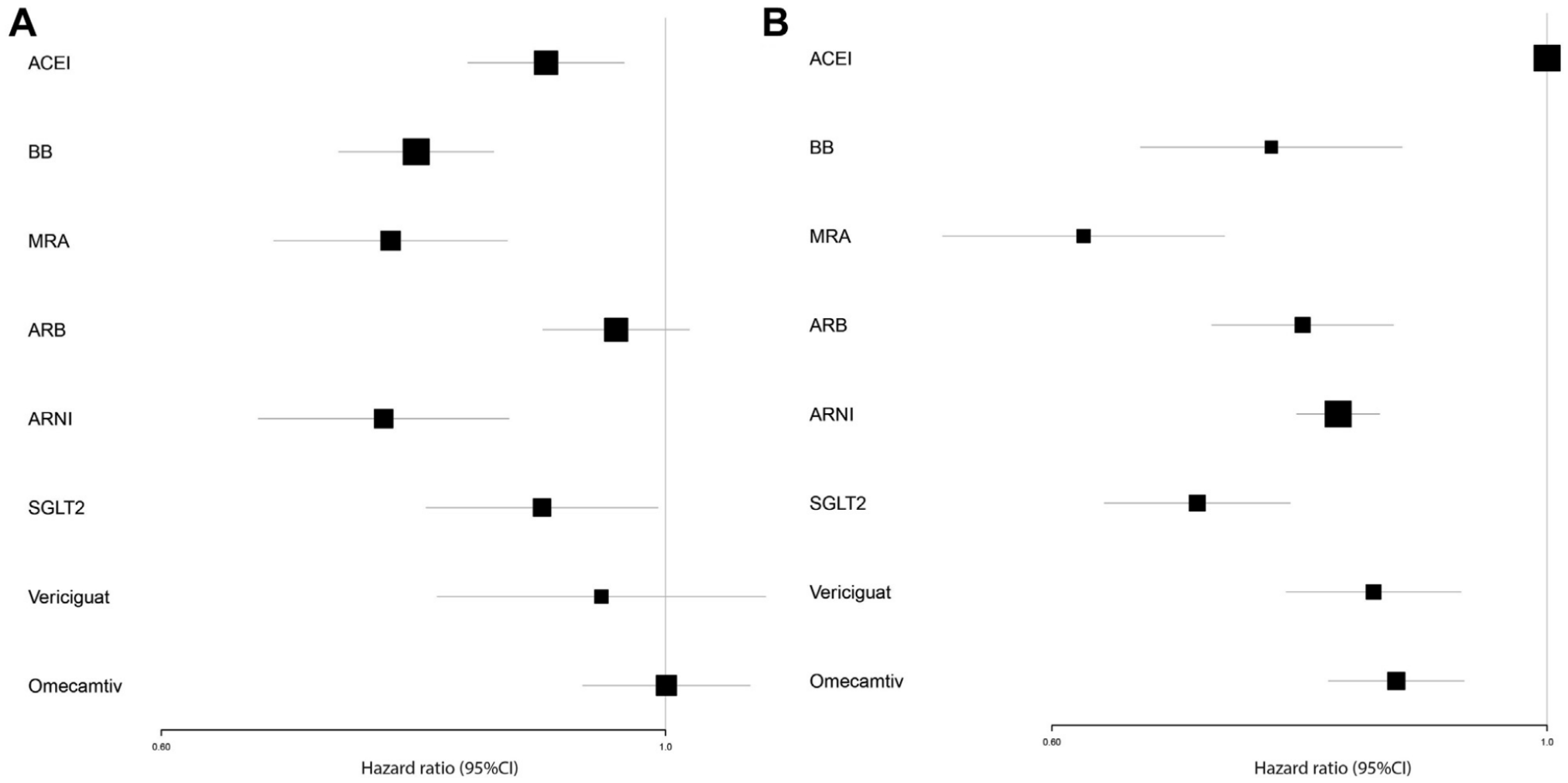
RESULTS: OUTCOMES

- All-cause mortality was reported a combined total of 17,684 events.
- ARNi (HR: 0.75; 95% CI: 0.66-0.85) and MRA (HR: 0.76; 95% CI: 0.67-0.85) was associated with the **largest reduction** in **all-cause death**, followed by BB (HR: 0.78; 95% CI: 0.72-0.84), ACEi (HR: 0.89; 95% CI: 0.82-0.96), SGLT2i (HR: 0.88; 95% CI: 0.78-0.99), and ARB (HR: 0.95; 95% CI: 0.88-1.02). Vericiguat (HR: 0.94; 95% CI: 0.79-1.11) and omecamtiv-mecarbil (HR: 1.0; 95% CI: 0.92-1.09) did reduce the risk of all-cause death.
- MRA (HR: 0.62; 95% CI: 0.54-0.72) was associated with the **largest reduction** in the **composite outcome**, followed by SGLT2i (HR: 0.70; 95% CI: 0.63-0.77).

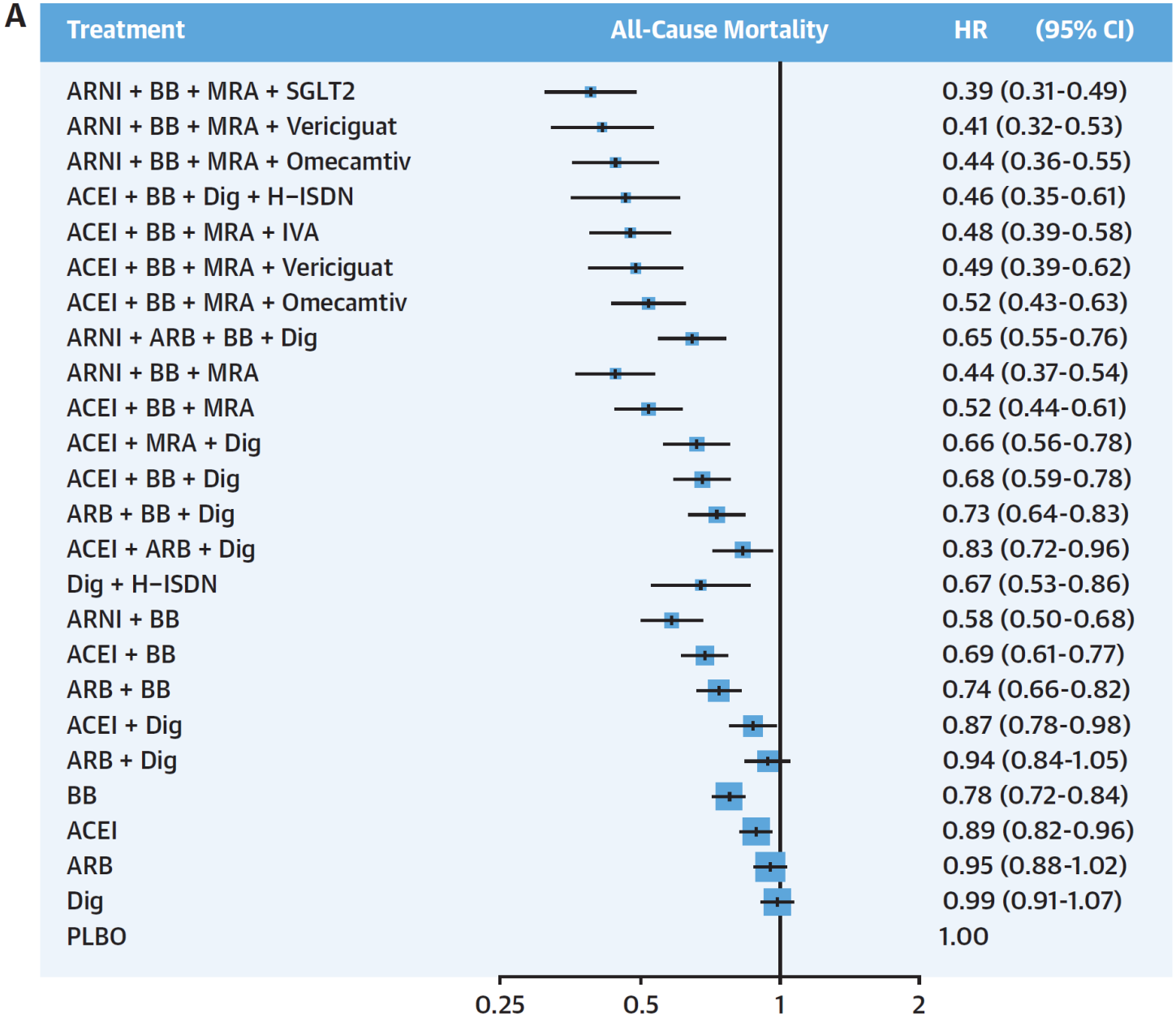
RESULTS: OUTCOMES

- The combination of ARNi, BB, MRA, and SGLT2i (HR: 0.39; 95% CI: 0.31-0.49) was **most effective in reducing all-cause death** relative to placebo.
- A combination of ARNi, BB, MRA, and SGLT2i was **most effective** in reducing the **composite outcome** compared with ACEi alone (HR: 0.36; 95% CI: 0.29-0.46), and compared with the second-best combination of ARNi, BB, MRA, and vericiguat (HR: 0.82; 95% CI: 0.66-0.1.01; P=0.061).
- The combination of ARNi, BB, MRA, and SGLT2i was **most effective** in reducing **CV death** (HR: 0.33; 95% CI: 0.26-0.43).

FIGURE 2 **Forest Plots Showing the Relative Risk Reduction Against Placebo**



Forest plots showing the relative risk reduction for all-cause mortality **(A)**, and CV death or hospitalization for HF vs ACEi **(B)**. ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNi = angiotensin receptor-neprilysin inhibitor; BB = beta-blocker; MRA = mineralocorticoid receptor antagonist; SGLT2 = sodium glucose cotransporter-2.



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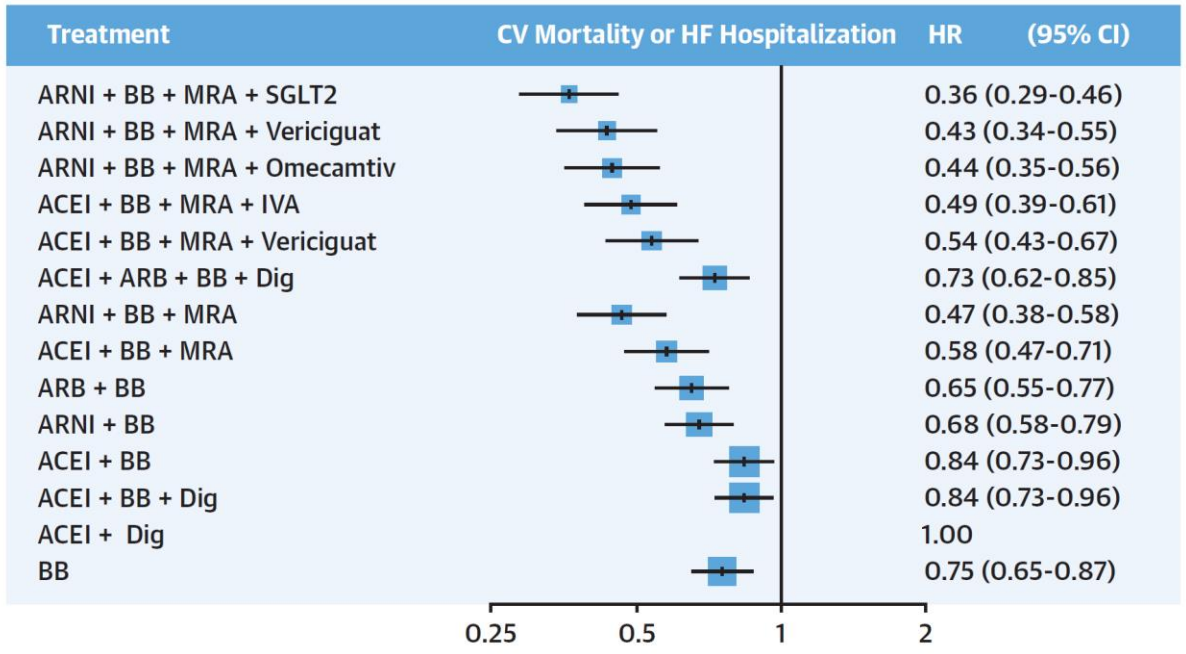
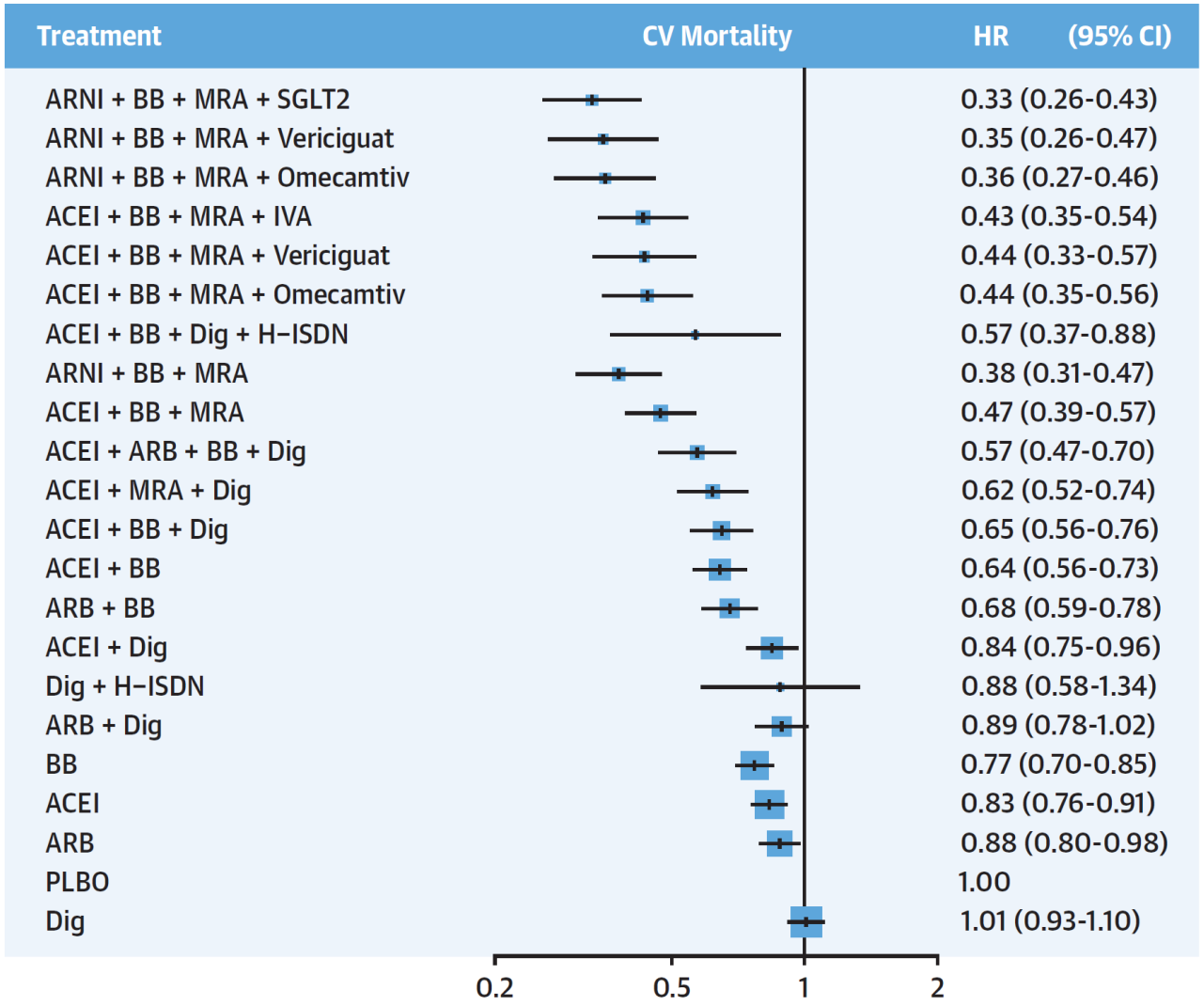
B


Treatment
CV Mortality or HF Hospitalization
HR
(95% CI)
ARNI + BB + MRA + SGLT2
0.36 (0.29-0.46)
ARNI + BB + MRA + Vericiguat
0.43 (0.34-0.55)
ARNI + BB + MRA + Omecamtiv
0.44 (0.35-0.56)
ACEI + BB + MRA + IVA
0.49 (0.39-0.61)
ACEI + BB + MRA + Vericiguat
0.54 (0.43-0.67)
ACEI + ARB + BB + Dig
0.73 (0.62-0.85)
ARNI + BB + MRA
0.47 (0.38-0.58)
ACEI + BB + MRA
0.58 (0.47-0.71)
ARB + BB
0.65 (0.55-0.77)
ARNI + BB
0.68 (0.58-0.79)
ACEI + BB
0.84 (0.73-0.96)
ACEI + BB + Dig
0.84 (0.73-0.96)
ACEI + Dig
1.00
BB
0.75 (0.65-0.87)
0.25
0.5
1
2

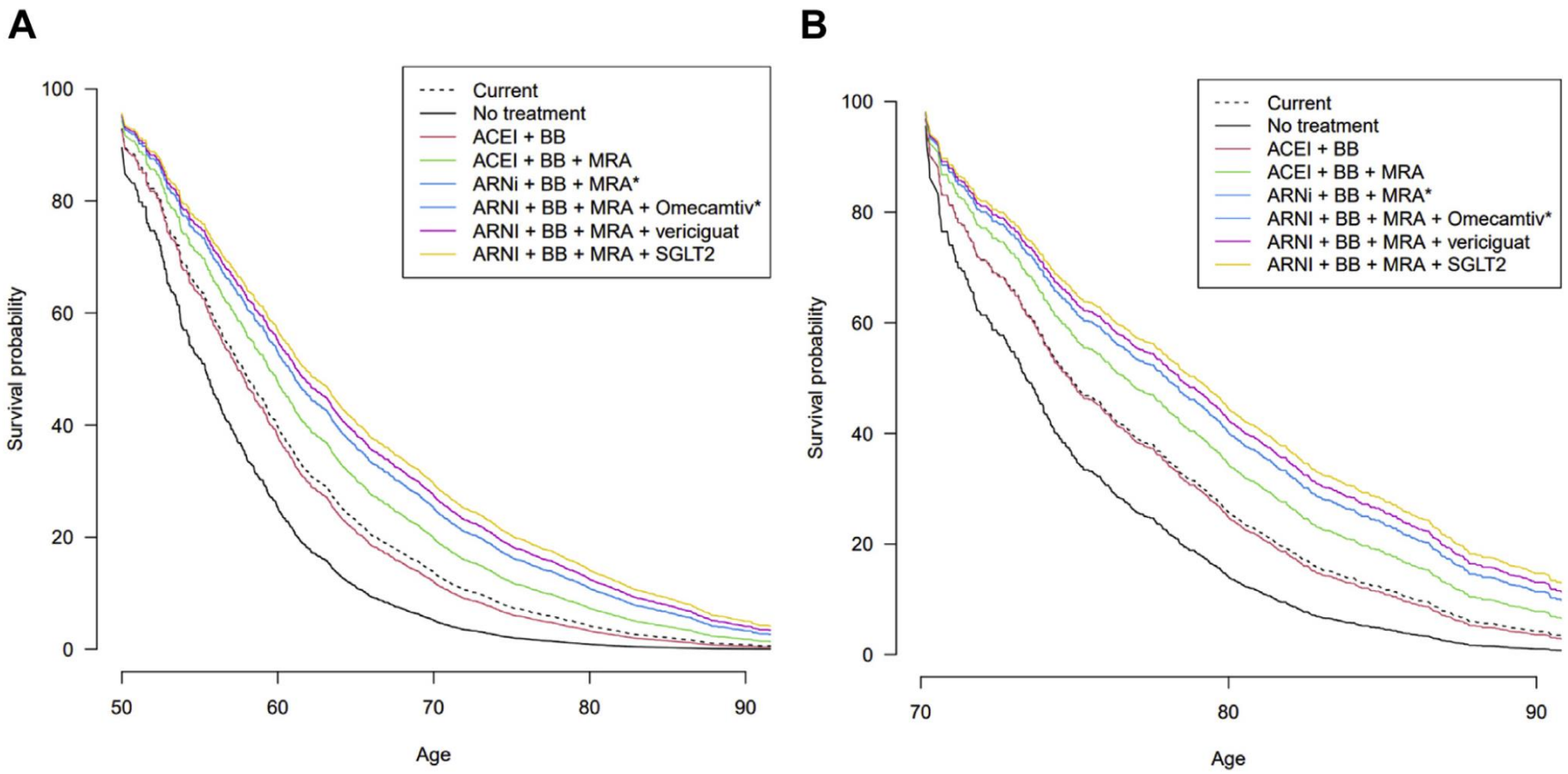
C


Treatment
CV Mortality
HR
(95% CI)
ARNI + BB + MRA + SGLT2
0.33 (0.26-0.43)
ARNI + BB + MRA + Vericiguat
0.35 (0.26-0.47)
ARNI + BB + MRA + Omecamtiv
0.36 (0.27-0.46)
ACEI + BB + MRA + IVA
0.43 (0.35-0.54)
ACEI + BB + MRA + Vericiguat
0.44 (0.33-0.57)
ACEI + BB + MRA + Omecamtiv
0.44 (0.35-0.56)
ACEI + BB + Dig + H–ISDN
0.57 (0.37-0.88)
ARNI + BB + MRA
0.38 (0.31-0.47)
ACEI + BB + MRA
0.47 (0.39-0.57)
ACEI + ARB + BB + Dig
0.57 (0.47-0.70)
ACEI + MRA + Dig
0.62 (0.52-0.74)
ACEI + BB + Dig
0.65 (0.56-0.76)
ACEI + BB
0.64 (0.56-0.73)
ARB + BB
0.68 (0.59-0.78)
ACEI + Dig
0.84 (0.75-0.96)
Dig + H–ISDN
0.88 (0.58-1.34)
ARB + Dig
0.89 (0.78-1.02)
BB
0.77 (0.70-0.85)
ACEI
0.83 (0.76-0.91)
ARB
0.88 (0.80-0.98)
PLBO
1.00
Dig
1.01 (0.93-1.10)
0.2
0.5
1
2

RESULTS

- **SENSITIVITY ANALYSES-** ACEi, BB, MRA, and SGLT2i was numerically more effective in reducing all-cause death (HR: 0.44; 95% CI: 0.37-0.54), than ACEi, BB, MRA, and vericiguat (HR: 0.49; 95% CI: 0.39-0.62) and ACEi, BB, MRA, and omecamtivmecarbil (HR: 0.52; 95% CI: 0.43-0.63).
- **ESTIMATED LIFE-YEARS GAINED-** Median age was 63 years (IQR: 54-72 years), 1,664 (23%) were women, 2,904 (43%) were NYHA functional class III/IV. Over a median follow-up of 22 months (IQR: 12-25 months), 1,287 (19%) participants died.
- Compared with estimated placebo (no treatment), the aggregate treatment effect of ARNi, BB, MRA, and SGLT2i was 7.9 life-years (95% CI: 4.7-11.2 life-years) gained for a 50-year-old and 5.0 life-years (95% CI: 2.5-7.5 life-years) gained for a 70 year-old.

FIGURE 3 Estimated Average Lifetime Graphs



Estimated average lifetime benefit for selected treatment combinations in BIOSTAT-CHF and ASIAN-HF at age 50 years **(A)** and age 70 years **(B)**. Survival curves overlap for combinations with a *. Abbreviations as in Figure 2.

DISCUSSION

- Current guidelines for HF recommend starting with ACEi/ARB as first-line treatment. In this analyses, ARNi showed a smaller HR for all-cause mortality than ACEi/ARB and a lower risk for discontinuation compared with placebo. Therefore, our results support starting with ARNi as first-line therapy rather than ACEi or ARB.
- A combination of ARNi, BB, MRA, and SGLT2i demonstrated the greatest reduction in risk for all-cause death and composite of CV death or HHF compared with the same combination replacing SGLT2i by vericiguat or omecamtiv-mecarbil.

DISCUSSION

- The substantial combined survival benefit of comprehensive therapy for HFrEF compared with single pharmacological agents advocates for early initiation of comprehensive treatment over sequencing of single agents with titration to target dosages.
- comprehensive pharmacological therapy (ARNi, BB, MRA, and SGLT2i) can collectively extend life-expectancy in HFrEF by 7.9 years in a 50-year-old and by 5.0 years in a 70-year-old patient compared with no treatment.

CONCLUSIONS

- Together, results of this comprehensive network meta-analysis support treatment of patients with HFrEF with a combination of ARNi, BB, MRA, and SGLT2i. The expected number of life-years gained with this and other combinations is considerable.


thank you
merci
gracias
danke
謝謝
شكراً جزيلاً
ngiyabonga
teşekkür ederim
спасибо
рахмат
Баярлалаа
faafetai lava
vinaka
спасибі
blagodaram
dank je
misaotra
matondo
paldies
grazzi
mahalo
tapadh leat
хвала
asante
manana
obrigada
tenki
kiitos
dankie
nanni
nandri
dhanyavad
bedankt
bayarlalaa
gràcie
hvala
mauruuru
köszönöm
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তোমাকে ধন্যবাদ
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