CSHP AB-Branch Symposium (CABS) 2021

Spill the Tea:

Notable (Non-COVID) News of 2020-2021

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October 2, 2021

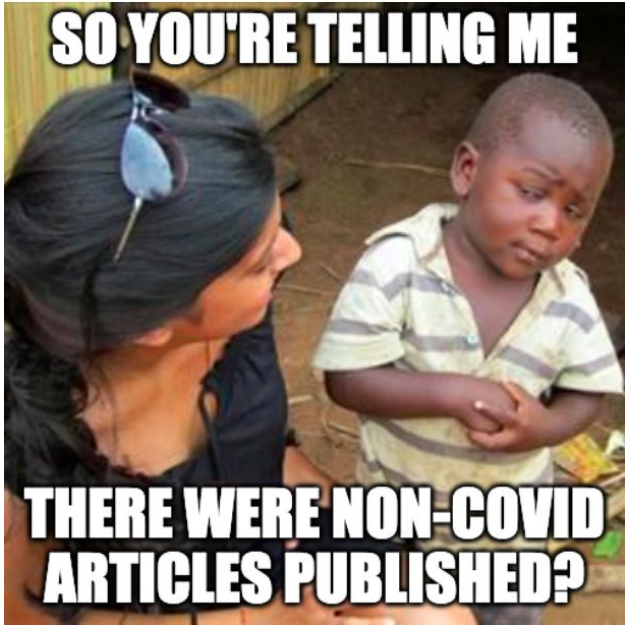
Presenter Disclosures

- I have no current or past relationship with commercial entities
- I have not received a speaker's fee for this learning activity

Objectives

To “spill the tea” (i.e., share the news) on noteworthy, **non-COVID** evidence updates that may influence your practice

- Reviewed major journals and guidelines from **Oct 1, 2020 to Oct 1, 2021**
- Topics include:
  - Atrial fibrillation, cirrhosis, infectious diseases, heart failure



RIVER

ORIGINAL ARTICLE

Rivaroxaban in Patients with Atrial Fibrillation and a Bioprosthetic Mitral Valve

H.P. Guimarães, R.D. Lopes, P.G.M. de Barros e Silva, I.L. Liporace, R.O. Sampaio, F. Tarasoutchi, C.R. Hoffmann-Filho, R. de Lemos Soares Patriota, T.L.L. Leiria, D. Lamprea, D.B. Precoma, F.A. Atik, F.S. Silveira, F.R. Farias, D.O. Barreto, A.P. Almeida, A.C. Zilli, J.D. de Souza Neto, M.A. Cavalcante, F.A.M.S. Figueira, F.C.S. Kojima, L. Damiani, R.H.N. Santos, N. Valeis, V.B. Campos, J.F.K. Saraiva, F.H. Fonseca, I.M. Pinto, C.C. Magalhães, J.F.M. Ferreira, J.H. Alexander, R. Pavanello, A.B. Cavalcanti, and O. Berwanger, for the RIVER Trial Investigators*

N Engl J Med 2020; 383:2117-2126

RIVER

DESIGN:

- Open-label, MC, NI-RCT x12mo
- NI margin of -8 days for RMST
- Funded by Bayer + Brazilian Ministry of Health

PATIENTS: ~1000 patients with

- AFib/AFL
- Bioprosthetic mitral valve replacement (MVR)
- >48hrs post mitral valve surgery
- Notably Excluded:
  - "Extremely high risk of bleeding", transient post-op AFib, mechanical AVR, intracardiac thrombus, use of 3A4 inh/ind.

INTERVENTION/COMPARATOR:

- Rivaroxaban 20mg po daily (15mg if CrCl <50)
- Warfarin (INR target 2-3)

OUTCOMES: composite of

- Death
- MACE (stroke/systemic embolism, TIA, valve thrombosis, HF hospitalization)
- Major bleeding

RIVER

Typical Patient: 59/F with mitral valve replacement >1yr

- HTN, DLP, CHF, permanent AFib
- CHA_2DS_2-VASc 3, HASBLED 2 | CrCl ~78mL/min

Table S4. Primary end point (death due to any cause, major cardiovascular events, or major bleeding)

Analysis	Rixaroxaban	Warfain	RMST Difference,† Days (95% CI)	P value	
			Rivaroxaban – Warfarin	Noninferiority§	Superiority
Intention-to-treat					
Total, no.	500	505			
RMST*, days	347.5	340.1	7.4 (-1.4 to 16.3)	<0.001	0.101
As-treated					
Total, no.	482	514			
RMST*, days	350.1	339.6	10.5 (1.9 to 19.1)	<0.001	0.016
Per-protocol					
Total, no.	434	459			
RMST*, days	356.7	347.1	9.6 (2.2 to 16.9)	< 0.001	0.01

CI denotes confidence interval; RMST, restricted mean survival time.
*RMSTs are calculated to 365 days
†For the difference measures, a negative value indicates an increased risk of rivaroxaban treatment.
§Non-inferiority margin set at - 8 days

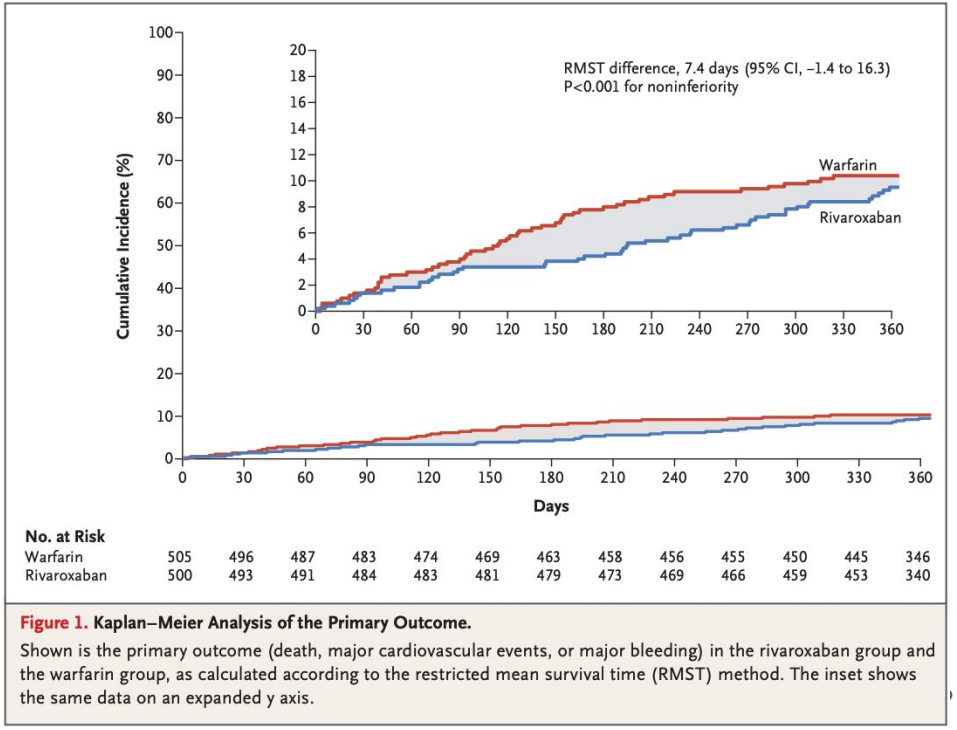


Figure 1. Kaplan–Meier Analysis of the Primary Outcome.
Shown is the primary outcome (death, major cardiovascular events, or major bleeding) in the rivaroxaban group and the warfarin group, as calculated according to the restricted mean survival time (RMST) method. The inset shows the same data on an expanded y axis.

cshp scph

RIVER

Quali-TEA: ☕☕☕☕☕

Applicabili-TEA: ☕☕☕☕☕

SAFETY (rivaroxaban vs. warfarin):

- Any bleeding: 13% vs. 15.4% (HR 0.83; 0.59-1.15)

CAVEATS & APPLICATION:

- Open-label design; concurrent PPI use not reported
- Restricted mean survival time (RMST) → reflects how many days of average life the treatment prolongs/reduces
  - "Over 1 year, rivaroxaban would add ~7 days of event-free survival time vs. warfarin"

BOTTOM LINE: In patients with AFib + bioprosthetic MVR, **rivaroxaban is non-inferior for death/MACE/major bleeding** vs. warfarin

ATTIRE

ORIGINAL ARTICLE

A Randomized Trial of Albumin Infusions in Hospitalized Patients with Cirrhosis

Louise China, Ph.D., Nick Freemantle, Ph.D., Ewan Forrest, M.D., Yiannis Kallis, Ph.D., Stephen D. Ryder, D.M., Gavin Wright, Ph.D., Andrew J. Portal, M.D., Natalia Becares Salles, Ph.D., Derek W. Gilroy, Ph.D., and Alastair O'Brien, Ph.D., for the ATTIRE Trial Investigators*

ATTIRE

DESIGN:

- Open-label, MC, parallel, RCT
- Follow-up x 6mo
- Non-industry funded

PATIENTS: 777 hospitalized pts with

- Acute decompensated cirrhosis
- Albumin <30g/L within 72h of admission
- Anticipated LOS ≥5 days
- Notably Excluded:
  - Advanced HCC, palliative care, severe cardiac dysfxn, "**any condition which the investigator considers would make the patient unsuitable**"

INTERVENTION/COMPARATOR:

- Daily albumin 20% (target Alb >35g/L) vs.
- Standard medical care (incl. albumin for LVP, SBP, HRS)

OUTCOMES: [infection, kidney dysfxn, and death at 3-15d, 28d, 3mo, 6mo]

N Engl J Med 2021; 384:808-817

ATTIRE

Typical Patient: 54/M with alcoholic cirrhosis &
- New-onset/worsening ascites
- Albumin 20-25g/L

Table 2. End Points.*

Variable	Albumin Group (N=380)	Standard-Care Group (N=397)	Adjusted Odds Ratio (95% CI)†	P Value
Composite primary end point — no. (%)	113 (29.7)	120 (30.2)	0.98 (0.71–1.33)	0.87
Components of composite primary end point — no. (%)‡				
Incidence of new infection	79 (20.8)	71 (17.9)	1.22 (0.85–1.75)	
Incidence of kidney dysfunction	40 (10.5)	57 (14.4)	0.68 (0.44–1.11)	
Incidence of death	30 (7.9)	33 (8.3)	0.95 (0.56–1.59)	
Death at 28 days	53 (14.0)	62 (15.6)	0.86 (0.57–1.30)	
Death at 3 mo	92 (24.2)	93 (23.4)	1.05 (0.74–1.48)	
Death at 6 mo	132 (34.7)	119 (30.0)	1.27 (0.93–1.73)	
Total median albumin infused per patient (IQR) — g	200 (140–280)	20 (0–120)	143 (127–158)§	

* Unless stated, the time of the end point is during the trial treatment period (15 days after randomization).
† Odds ratios are adjusted for stratification variables, with sites as random intercept terms.
‡ The end points are defined in the original trial protocol.[26]
§ This is the adjusted mean difference between the groups.

ATTIRE

Quali-TEA: ☕☕☕

Applicabili-TEA: ☕☕☕☕

SAFETY (albumin vs. standard care):

- Serious AE: 28 events vs. 11 events
- Any pulmonary edema or fluid overload: 23 events vs. 8 events

CAVEATS & APPLICATION:

- Possible selection bias with investigators ability to exclude patients
- "Nail-in-the-coffin" against the routine use of albumin for acute decomp. cirrhosis + hypoalbuminemia (outside of LVP, SBP, HRS)

BOTTOM LINE: In patients hospitalized for acute decomp. cirrhosis + albumin <30, **daily albumin 20% did NOT improve clinically important outcomes** vs. standard care

Effect of ciprofloxacin vs levofloxacin on QTc-interval and dysglycemia in diabetic and non-diabetic patients

ORIGINAL PAPER
INFECTIOUS DISEASES

THE INTERNATIONAL JOURNAL OF CLINICAL PRACTICE WILEY

Effect of ciprofloxacin vs levofloxacin on QTc-interval and dysglycemia in diabetic and non-diabetic patients

Nada A. Saad[1] | Ahmed A. Elberry[2] | Hazem Samy Matar[3] | Raghda R. S. Hussein[1]

Effect of ciprofloxacin vs levofloxacin on QTc-interval and dysglycemia in diabetic and non-diabetic patients

DESIGN:

- Single-centre, RCT x6mo
- Unclear if blinded

PATIENTS: 100 patients aged 18-70

- Admitted to intermediate care unit
- Sub-divided into DM and non-DM
- Notably Excluded:
  - Hx of QTc prolongation (>450ms in men, >470ms in women), cardiac disease, received class IA/III AAD or macrolides

INTERVENTION/COMPARATOR:

- Levofloxacin 750mg IV q24h
- Ciprofloxacin 400mg IV q12h

OUTCOMES: QTc and FBG prior to Abx, 72h from first dose, and 72h from Abx cessation

- Hyperglycemia: >5.6 (non-DM) and >7.2 (DM)
- Hypoglycemia: <3.9

Int J Clin Pract. 2021 May;75(5):e14072

Effect of ciprofloxacin vs levofloxacin on QTc-interval and dysglycemia in diabetic and non-diabetic patients

Typical Patient: 50/M with

- CrCl ~97mL/min + normal hepatic function
- K^+ 4.3mmol/L, Mg^{2+} 0.75mmol/L

TABLE 2 Comparison of QT interval between each group regarding times

Drug	Time DM Or non	Baseline	24 h after the 1st dose	72 h after the 1st dose	72 h after cessation
Ciprofloxacin	Diabetic	402 ± 31.4	417 ± 26.7*	416 ± 26.4*	419.8 ± 19.7*
	Non diabetic	404 ± 52.6	417 ± 32	428 ± 31.9*	418.7 ± 20.4*
Levofloxacin	Diabetic	414 ± 29.5	427.4 ± 38.3*	436 ± 26*	425 ± 21.7*
	Non diabetic	411 ± 32.8	426 ± 30.5*	434 ± 35*	422 ± 30.5*

Note: Data are presented as mean QTc (ms) ± SD.
*Considered significant at $P < .05$ compared to baseline value.

- **Cipro**: ~15-20ms increase
- **Levo**: ~20-25ms increase
- Levofloxacin more likely to cause dysglycemia than cipro (especially in DM)

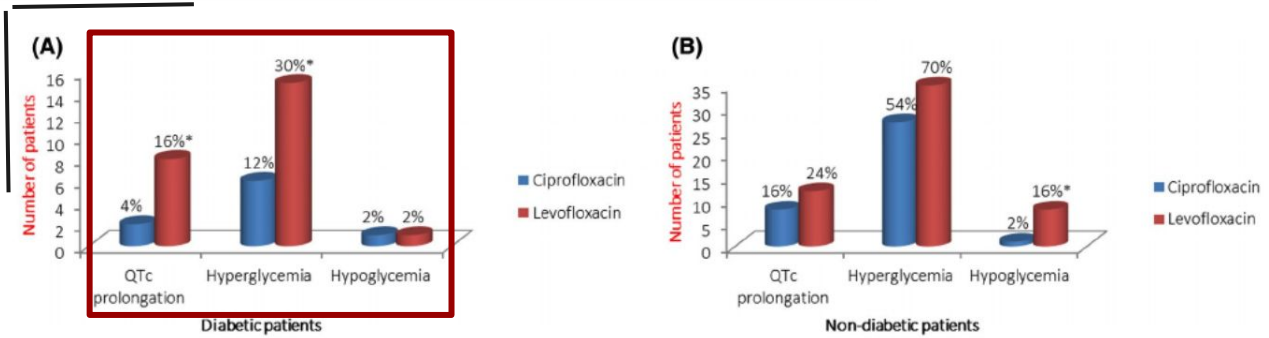


FIGURE 3 The relative risk for QTc prolongation, hyperglycemia, and hypoglycemia in diabetic and non-diabetic patients after the administration of ciprofloxacin and levofloxacin. *Considered significant at $P < .05$ compared to ciprofloxacin

cshp scph

Effect of ciprofloxacin vs levofloxacin on QTc-interval and dysglycemia in diabetic and non-diabetic patients

Quali-TEA: ☕☕☕☕☕

Applicabili-TEA: ☕☕☕☕☕

CAVEATS & APPLICATION:

- No information on baseline characteristics of other potential QTc-prolonging or antihyperglycemic agents in each group
- Alternative definitions of hyperglycemia used compared to acute inpatient
- Provides some guidance to the degree of QTc-prolongation/incidence of dysglycemia with fluoroquinolones

BOTTOM LINE: In hospitalized patients without CVD, **levofloxacin IV is associated with higher rates of QTc-prolongation and dysglycemia (notably hyperglycemia with DM)** vs. cipro IV

Rapid evidence-based sequencing of foundational drugs for HFrEF

ESC European Society of Cardiology

European Journal of Heart Failure (2021) **23**, 882–894
doi:10.1002/ejhf.2149

Rapid evidence-based sequencing of foundational drugs for heart failure and a reduced ejection fraction

Milton Packer[1,2]* and John J.V. McMurray[3]

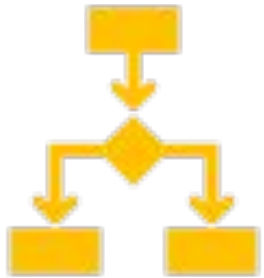
Rapid evidence-based sequencing of foundational drugs for HFrEF

DESIGN:

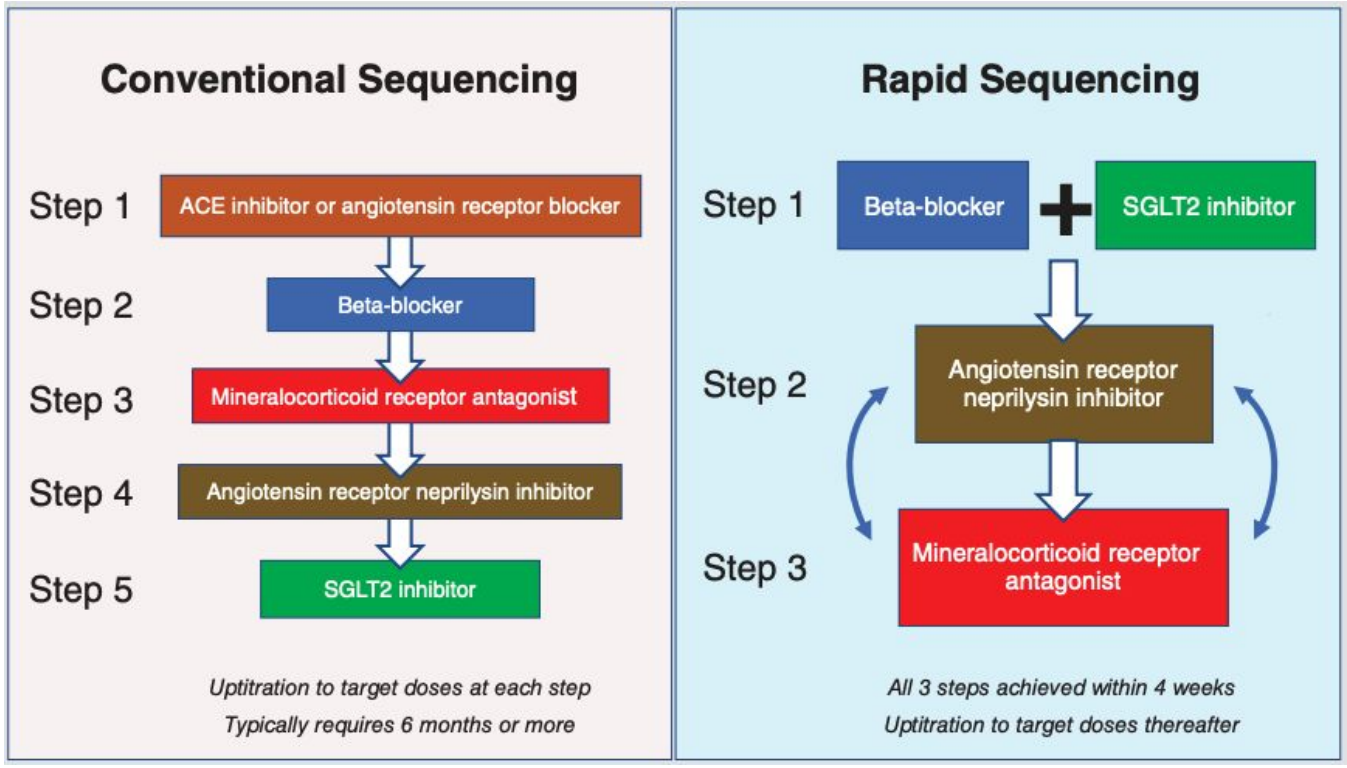
- Narrative review article
- Discusses evidence for **rapid sequencing strategies** for foundational HFrEF medications
- Includes large-scale RCTs that reduce CV death, all-cause mortality, or HF hospitalizations

Foundational HFrEF therapy:

- **BB** (CIBIS II, MERIT-HF, COPERNICUS)
- **ARNI** (PARADIGM-HF)
- **MRA** (RALES, EMPHASIS-HF)
- **SGLT2i** (EMPEROR-Reduced, DAPA-HF)



Rapid evidence-based sequencing of foundational drugs for HFrEF



Rapid evidence-based sequencing of foundational drugs for HFrEF

STEP 1: BB+SGLT2i

- Early BB = decreased sudden cardiac death (ensure euvolemic; titrate diuretics)
- SGLT2i may help mitigate BB-induced fluid retention + hyperK^{+} from ARNI/MRA; also at target dose already

STEP 2: ARNI (1-2 weeks later)

- Neprilysin inhibition may help mitigate hyperK^{+} from MRA/ARB
- Limiting factor is hypoTN; if intolerable, use low-dose valsartan alone then switch to ARNI or start MRA instead

STEP 3: MRA (1-2 weeks later)

- Minimal BP lowering; once-daily dosing, minimal up-titration

Eur J Heart Fail. 2021 Jun;23(6):882-894

Rapid evidence-based sequencing of foundational drugs for HFrEF

COMMON ASSUMPTIONS

"Efficacy/safety were seen on background therapy"

- RCTs suggest background therapy does NOT influence response to foundational therapies (e.g., ACEI: SOLVD and SAVE; MRA: RALES and EMPHASIS-HF)

ACE inhibitors (with or without beta-blockade)	SAVE (captopril)	Post-infarction patients with LV systolic dysfunction, 35-40% on beta-blockers	All-cause mortality	0.81 (0.68-0.97)
	SOLVD Treatment (enalapril)	Heart failure with LV systolic dysfunction, no use of beta-blockers		0.84 (0.74-0.95)
Mineralocorticoid receptor antagonists (with or without beta-blockade)	RALES (spironolactone)	≈10% on a beta-blocker	All-cause mortality	0.70 (0.60-0.82)
	EMPHASIS-HF (eplerenone)	>85% on a beta-blocker		0.76 (0.62-0.93)

Rapid evidence-based sequencing of foundational drugs for HFrEF

COMMON ASSUMPTIONS

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- RCTs suggest background therapy does NOT influence response to foundational therapies (e.g., ACEI: SOLVD and SAVE; MRA: RALES and EMPHASIS-HF)

- Historical order of medication testing ≠ order of implementation
  - E.g., majority of ACEi/BB trials were tested on background therapy of digoxin yet this is not widely implemented prior to starting ACEi/BB

Eur J Heart Fail. 2021 Jun;23(6):882-894

Rapid evidence-based sequencing of foundational drugs for HFrEF

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- Historical order of medication testing ≠ order of implementation
  - E.g., majority of ACEi/BB trials were tested on background therapy of digoxin yet this is not widely implemented prior to starting ACEi/BB

“Benefits were seen at target doses in trials”

- In RCTs, majority of benefit shown by 30d mark with starting doses
  - Incremental benefits (and increased AE risk) towards target dose

Eur J Heart Fail. 2021 Jun;23(6):882-894

Rapid evidence-based sequencing of foundational drugs for HFrEF

Quali-TEA: 

Applicabili-TEA: 

CAVEATS & APPLICATION:

- Proposed sequence has flexibility → individualize
- Some insurance companies may not cover SGLT2i or ARNI as initial agent (criteria-dependent)

BOTTOM LINE: In patients with HFrEF, **clinicians should aim to start all foundational agents (BB, ARNI, MRA, SGLT2i) at low doses within 4 weeks**, then titrate to target doses.

Eur J Heart Fail. 2021 Jun;23(6):882-894

EMPEROR-Preserved

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin in Heart Failure with a Preserved Ejection Fraction

S.D. Anker, J. Butler, G. Filippatos, J.P. Ferreira, E. Bocchi, M. Böhm, H.-P. Brunner–La Rocca, D.-J. Choi, V. Chopra, E. Chuquiure-Valenzuela, N. Giannetti, J.E. Gomez-Mesa, S. Janssens, J.L. Januzzi, J.R. Gonzalez-Juanatey, B. Merkely, S.J. Nicholls, S.V. Perrone, I.L. Piña, P. Ponikowski, M. Senni, D. Sim, J. Spinar, I. Squire, S. Taddei, H. Tsutsui, S. Verma, D. Vinereanu, J. Zhang, P. Carson, C.S.P. Lam, N. Marx, C. Zeller, N. Sattar, W. Jamal, S. Schnaidt, J.M. Schnee, M. Brueckmann, S.J. Pocock, F. Zannad, and M. Packer, for the EMPEROR-Preserved Trial Investigators*

N Engl J Med. 2021. doi: 10.1056/NEJMoa2107038.

EMPEROR-Preserved

DESIGN:

- DB, MC/international, RCT
- Median f/u ~2yrs
- Industry-funded (BI & Eli Lilly)

PATIENTS: ~6000 pts with

- NYHA class II-IV
- EF >40%
- Documented evidence of HF (i.e., structural heart disease or HF hosp. in last 12mo)
- NT-proBNP >300 (or >900 with AFib)
- Notably Excluded:
  - Recent acute decomp. HF, CRT, eGFR <20mL/min/1.73m^2, SBP <100 or symptomatic hypoTN

INTERVENTION/COMPARATOR:

- Empagliflozin 10 mg po daily vs. placebo

OUTCOMES: [CV death + HF hosp.]

N Engl J Med. 2021. doi: 10.1056/NEJMoa2107038.

EMPEROR-Preserved

Typical Patient: 72/M (Caucasian) with
- HFpEF (EF 54%, NYHA II, NT-proBNP 995)
- HTN, DM, AFib | eGFR ~61mL/min/1.73m^2

NNT = 31 over ~2yrs

Table 2. Primary and Secondary Cardiovascular Outcomes.*

Variable	Empagliflozin (N=2997)	*events per 100 patient-yr*	Placebo (N=2991)	*events per 100 patient-yr*	Hazard Ratio or Difference (95% CI)	P Value
Primary composite outcome — no. (%)	415 (13.8)	6.9	511 (17.1)	8.7	0.79 (0.69–0.90)	<0.001
Hospitalization for heart failure	259 (8.6)	4.3	352 (11.8)	6.0	0.71 (0.60–0.83)	
Cardiovascular death	219 (7.3)	3.4	244 (8.2)	3.8	0.91 (0.76–1.09)	
Secondary outcomes specified in hierarchical testing procedure						
Total no. of hospitalizations for heart failure	407	—	541	—	0.73 (0.61–0.88)	<0.001
eGFR (CKD-EPI) mean slope change per year — ml/min/1.73 m^2†	−1.25±0.11	—	−2.62±0.11	—	1.36 (1.06–1.66)	<0.001
Other prespecified analyses						
Change in KCCQ clinical summary score at 52 wk‡	4.51±0.31	—	3.18±0.31	—	1.32 (0.45–2.19)	
Total no. of hospitalizations for any cause	2566	—	2769	—	0.93 (0.85–1.01)	
Composite renal outcome — no. (%)	108 (3.6)	2.1	112 (3.7)	2.2	0.95 (0.73–1.24)	
Onset of new diabetes in patients with prediabetes — no. (%)	120 (12.0)	6.1	137 (14.0)	7.4	0.84 (0.65–1.07)	
Death from any cause — no. (%)	422 (14.1)	6.6	427 (14.3)	6.7	1.00 (0.87–1.15)	

EMPEROR-Preserved

Quali-TEA: 

Applicabili-TEA: 

SAFETY (empa vs. placebo; any serious AE): 47.9% vs. 51.6%

- Uncomplicated UTI, genital infections, hypoTN more common with empagliflozin

CAVEATS & APPLICATION:

- Heavy industry involvement (methodology, statistical plan & analysis, recruitment)
- Important to have documented evidence of HF (not just a preserved EF)
- Some drug insurances may not cover SGLT2i without concurrent DM

BOTTOM LINE: In patients with HFpEF, **empagliflozin decreases CV death/HF hospitalizations** vs. placebo

N Engl J Med. 2021. doi: 10.1056/NEJMoa2107038.

Notable Mentions

GUIDELINE UPDATES

- **CCS**: AFib 2020 | HF 2020 | Lipid 2021
- **CSBPR**: 2' Stroke Prevention 2020 | sICH 2020
- **EHRA**: Practical Guide to NOAC use in AFib 2021

- **ADAPTABLE**: ASA 81mg vs. 325mg for 2' prevention of CVD
- **ELDERCARE-AF**: low-dose edoxaban vs. placebo for NVAF in elderly patients
- **QUARTET**: single polypill (four low-dose BP meds) vs. monotherapy for HTN
- **MASTER-DAPT**: DAPT x1mo vs. 3mo in patients post-PCI + high bleed risk
- **VALKYRIE**: rivaroxaban vs. warfarin for NVAF in hemodialysis
- **STRENGTH**: high dose omega-3 vs. corn oil for high-risk CVD
- **EAST-AFNET 4**: early rhythm control vs. usual therapy for early AFib (Dx <1yr)
- **STEP 1-4**: semaglutide vs. placebo in overweight/obese patients without DM (STEP 1), with T2DM (STEP 2), related comorbidities excl. T2DM (STEP 3), and related comorbidities excl. T2DM with withdrawal/extension of semaglutide (STEP 4)
- **Trial of Psilocybin vs. Escitalopram for Depression**

THANK YOU!

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(slides to be shared post-conference)

REFERENCES

1. **RIVER**. Guimarães HP et al. Rivaroxaban in Patients with Atrial Fibrillation and a Bioprosthetic Mitral Valve. N Engl J Med 2020; 383:2117-2126.
2. **ATTIRE**. China L et al. A Randomized Trial of Albumin Infusions in Hospitalized Patients with Cirrhosis. N Engl J Med 2021; 384:808-817.
3. Saad NA et al. Effect of ciprofloxacin vs levofloxacin on QTc-interval and dysglycemia in diabetic and non-diabetic patients. Int J Clin Pract. 2021 May;75(5):e14072
4. Packer M et al. Rapid evidence-based sequencing of foundational drugs for HFrEF. Eur J Heart Fail. 2021 Jun;23(6):882-894.
5. **EMPEROR-Preserved**. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. N Engl J Med. 2021. doi: 10.1056/NEJMoa2107038.