HFrEF:Update – SGLT2 inhibitors – are we better at treating heart failure?

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1

NO DISCLOSURES for this presentation

Use of Brand name products within context

2

Learning Objectives

At the conclusion of this presentation, pharmacists will be able to:

1. Explain the Guideline Directed Medical Therapy, Class I, Level of Evidence A (i.e., first-line drugs) to manage heart failure with reduced ejection fraction (HFrEF) patients in the outpatient setting
2. Develop a medication treatment plan and optimize the titration of the heart failure medications discussed in patients with a diagnosis of HFrEF

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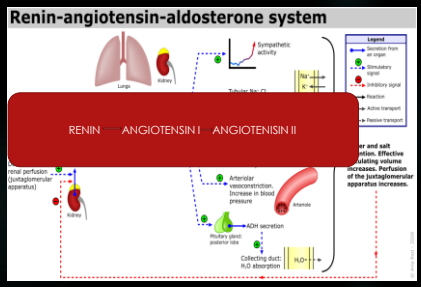

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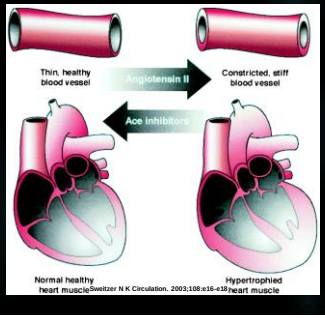

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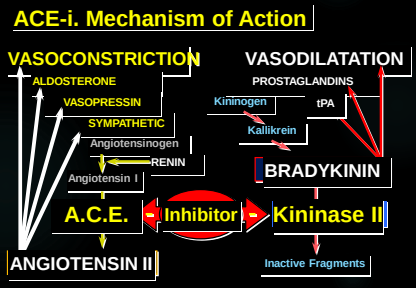

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Renin-Angiotensin System Inhibition With ACEi or ARB or ARNi

Recommendations for Renin-Angiotensin System Inhibition With ACEi or ARB or ARNi

COR	LOE	Recommendations
1	A	1. In patients with HFrEF and NYHA class II to III symptoms, the use of ARNi is recommended to reduce morbidity and mortality.
1	A	2. In patients with previous or current symptoms of chronic HFrEF, the use of ACEi is beneficial to reduce morbidity and mortality when the use of ARNi is not feasible.

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Renin-Angiotensin System Inhibition With ACEi or ARB or ARNi (con't.)

1	A
Value Statement: High Value (A)	
1	B-R

3. In patients with previous or current symptoms of chronic HFrEF who are intolerant to ACEi because of cough or angioedema and when the use of ARNi is not feasible, the use of ARB is recommended to reduce morbidity and mortality.
4. In patients with previous or current symptoms of chronic HFrEF, in whom ARNi is not feasible, treatment with an ACEi or ARB provides high economic value.
5. In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACEi or ARB, replacement by an ARNi is recommended to further reduce morbidity and mortality.

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Renin-Angiotensin System Inhibition With ACEi or ARB or ARNi (con't.)

Value Statement: High Value (A)	
3: Harm	B-R
3: Harm	C-LD
3: Harm	C-LD

6. In patients with chronic symptomatic HFrEF, treatment with an ARNi instead of an ACEi provides high economic value.
7. ARNi should not be administered concomitantly with ACEi or within 36 hours of the last dose of an ACEi.
8. ARNi should not be administered to patients with any history of angioedema.
9. ACEi should not be administered to patients with any history of angioedema.

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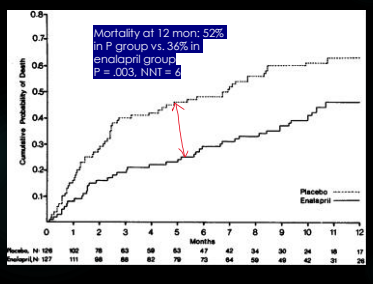

CONSENSUS TRIAL
NEJM 1987;316:1429

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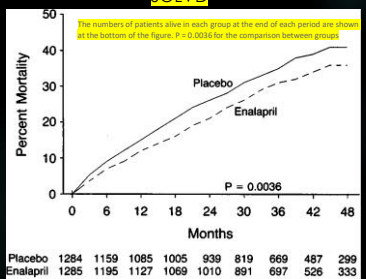
SOLVD



N Engl J Med 1991; 325:293-302
DOI: 10.1056/NEJM199108013250501

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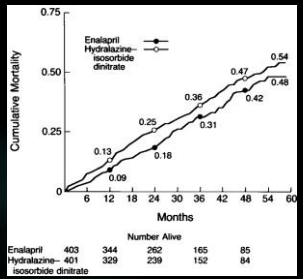

Vasodilator-Heart Failure Trial (V-HEFT)

N Engl J Med 1991; 325:303-310
DOI: 10.1056/NEJM199108013250502

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ACE-I. Contraindications

- Intolerance (angioedema, anuric renal fail.)
- Bilateral renal artery stenosis
- Pregnancy
- Renal insufficiency (creatinine > 3 mg/dl)
- Hyperkalemia (> 5.5 mmol/l)
- Severe hypotension

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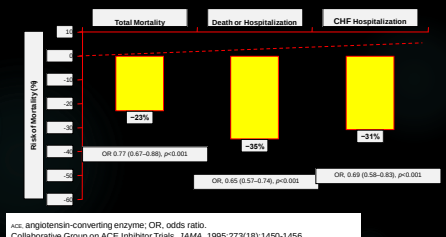
ACE Inhibitors Reduce Mortality and Hospitalizations in Patients With HF



ACE, angiotensin-converting enzyme; OR, odds ratio.
Collaborative Group on ACE Inhibitor Trials. *JAMA*. 1995;273(18):1450-1456.

32 Trials of ACE Inhibitors in Heart Failure: ACEI (n=3670) vs Placebo (n=3235)

14

Original Article

Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

John J.V. McMurray, M.D., Milton Packer, M.D., Akshay S. Desai, M.D., M.P.H., Jianjian Gong, Ph.D., Martin P. Lefkowitz, M.D., Adel R. Rizkala, Pharm.D., Jean L. Rouleau, M.D., Victor C. Shi, M.D., Scott D. Solomon, M.D., Karl Swedberg, M.D., Ph.D., Michael R. Zile, M.D., for the PARADIGM-HF Investigators and Committees

Neprilysin is an enzyme that contributes to the breakdown of the natriuretic peptides.

N Engl J Med
Volume 371(11):993-1004
September 11, 2014

The NEW ENGLAND JOURNAL of MEDICINE

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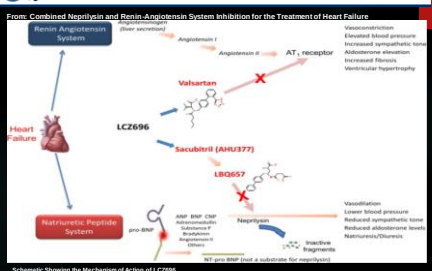
JACC Journals

From: Combined Neprilysin and Renin-Angiotensin System Inhibition for the Treatment of Heart Failure



Schematic Showing the Mechanism of Action of LCZ696

JCHF. 2014;2(6):640-670. doi:10.1016/j.jchf.2014.09.001

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*Neprilysin is a neutral endopeptidase that degrades some vasoactive peptides, including natriuretic peptides, bradykinin, and adrenomedullin.

*Inhibition of neprilysin by LBQ657, the active metabolite of sacubitril, increases the levels of these peptides, decreasing vasoconstriction, sodium retention, and maladaptive remodeling.

*Valsartan blocks the angiotensin II type-1 (AT_1) receptor, inhibiting angiotensin II and the release of aldosterone.

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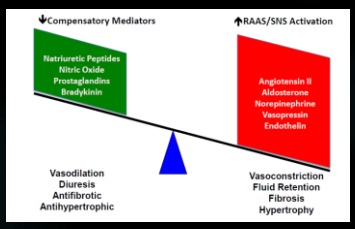
NEUROHORMONAL BALANCE IN HEART FAILURE



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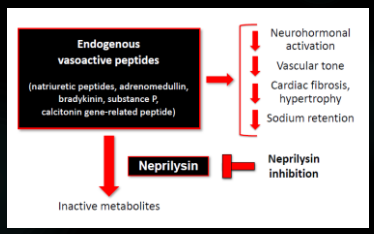
TARGETING NEPRILYSIN:



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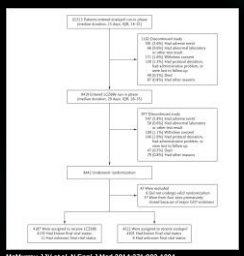
Screening Criteria, Run-in Periods, and Randomization.



McMurray JJV et al. N Engl J Med 2014;371:993-1004

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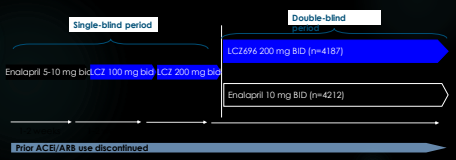
PARADIGM-HF

Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial

Age 64 yr. Female 22%. NYHA class II 70%, III 24%. LVEF 0.29. SBP 122 mmHg. BNP 253 pg/ml (NT pro BNP 1613 pg/ml). eGFR 68 ml/min/1.73m². AF 37%. Prior HF hosp. 62%. Diuretic 80%, digoxin 30%, β-blocker 93%, MRA 56%. ICD 15%. CRT 7%.



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PARADIGM-HF: Who was eligible?

Inclusion Criteria	Exclusion Criteria
• Chronic HF with LVEF ≤40% • NYHA II-IV symptoms • Elevated natriuretic peptides • On guideline-directed medical therapy for > 4 weeks including: – ACEI or ARB (enalapril 10 mg daily or equivalent) – β-blocker (unless intolerant) – MRA if appropriate	• History of angioedema • eGFR <30 mL/min/1.73 m² • Serum potassium >5.2 mmol/L • SBP <100 mmHg or symptomatic hypotension • Current Acute Decompensated HF

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PARADIGM-HF: Pre-specified endpoints

- Primary: Cardiovascular death or heart failure hospitalization
  - Cardiovascular death
  - Heart failure hospitalization
- Secondary:
  - **Death from any cause**
  - **KCCQ (CSS - symptoms and physical limitations)**
  - New onset atrial fibrillation
  - Decline in renal function

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- PARADIGM-HF Trial (Approval of sacubitril/valsartan [*Entresto®*]): double-blind trial in 8442 patients with class II-IV heart failure and a reduced ejection fraction.
- randomized to sacubitril 97 mg/valsartan 103 mg (*Entresto® 200mg)* twice daily or the ACE inhibitor enalapril (*Vasotec®*, and generics) 10 mg twice daily, both in addition to other HF drugs.
- The study was stopped early because a prespecified interim analysis showed lower cardiovascular mortality in patients randomized to sacubitril/valsartan arm

After a median follow-up of 27 months, the primary endpoint, a **composite** of first hospitalization for worsening heart failure or cardiovascular death, occurred in significantly fewer patients taking the combination product compared to those taking enalapril (21.8% vs 26.5%). The combination significantly reduced the risk of first hospitalization for worsening heart failure (12.8% vs 15.6%), death from cardiovascular causes (13.3% vs 16.5%), and all-cause mortality (17.0% vs 19.8%) It also slowed the progression of heart failure.

N Engl J Med 2014;371

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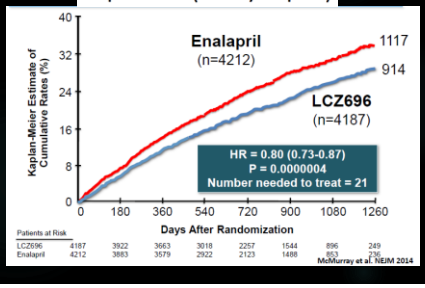
PARADIGM-HF: CV Death or HF Hospitalization (Primary Endpoint)



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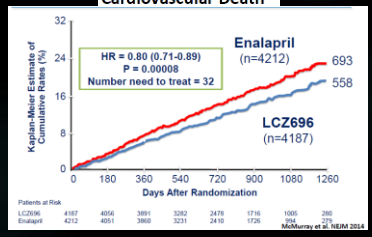
PARADIGM-HF: Cardiovascular Death



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PARADIGM-HF: Pre-specified endpoints

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  - New onset atrial fibrillation
  - Decline in renal function

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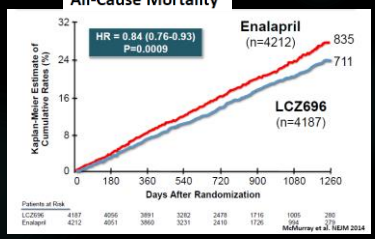
PARADIGM-HF: All-Cause Mortality



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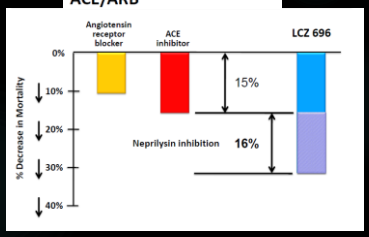
Doubling of Survival over ACE/ARB



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Caveats

- Patients with low blood pressure, CKD, and more severe HF were less likely to complete the run-in period and be randomized
- Tolerability in unselected populations in practice may be less
- No data to support use in:
  - New-Onset Heart Failure
  - Post-MI patients with Heart Failure
  - Acute Decompensated Heart failure
  - Advanced CKD
- Be mindful of eligibility criteria

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Using Sacubitril/Valsartan in practice

- For most patients, initial recommended dose sacubitril/valsartan 49/51 mg bid (equivalent to LCZ696 100 bid).
- Initiation at lower dose (24/26 mg bid) may be appropriate for patients in whom tolerability is a concern.
- Must interrupt ACE-inhibitor for 36 hours prior to initiation of sacubitril/valsartan to avoid overlap and risk of angioedema
- Since BNP levels rise with neprilysin inhibition, use of serum BNP to monitor HF severity or response to therapy not appropriate
- Serum NT-proBNP is still a useful marker on treatment

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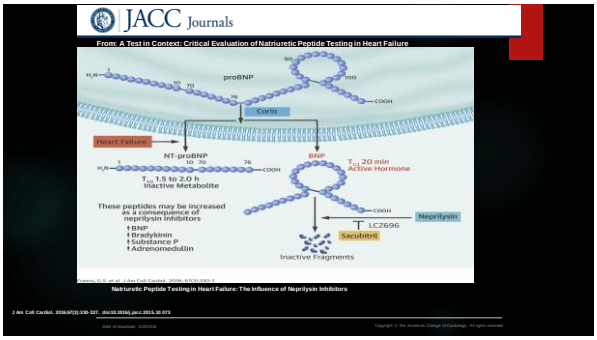

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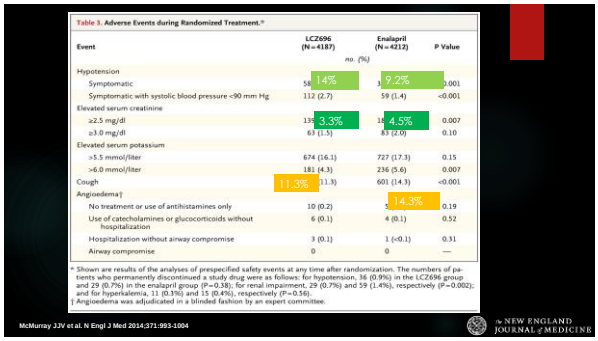
Table 3. Adverse Events during Randomized Treatment.*

Event	LCZ696 (N=4187)	Enalapril (N=4212)	P Value
	no. (%)		
Hypotension			
Symptomatic	588 (14.0)	388 (9.2)	<0.001
Symptomatic with systolic blood pressure <90 mm Hg	112 (2.7)	59 (1.4)	<0.001
Elevated serum creatinine			
≥2.5 mg/dl	139 (3.3%)	189 (4.5%)	0.007
≥3.0 mg/dl	63 (1.5)	87 (2.0)	0.10
Elevated serum potassium			
>5.5 mmol/liter	674 (16.1)	727 (17.3)	0.15
>6.0 mmol/liter	181 (4.3)	236 (5.6)	0.007
Cough	1175 (11.3%)	601 (14.3)	<0.001
Angioedema†			
No treatment or use of antihistamines only	10 (0.2)	5 (0.1)	0.19
Use of catecholamines or glucocorticoids without hospitalization	6 (0.1)	4 (0.1)	0.52
Hospitalization without airway compromise	3 (0.1)	1 (<0.1)	0.31
Airway compromise	0	0	—

* Shown are results of the analyses of prespecified safety events at any time after randomization. The numbers of patients who permanently discontinued a study drug were as follows: for hypotension, 36 (0.9%) in the LCZ696 group and 29 (0.7%) in the enalapril group (P=0.38); for renal impairment, 29 (0.7%) and 59 (1.4%), respectively (P=0.002); and for hyperkalemia, 11 (0.3%) and 15 (0.4%), respectively (P=0.56).
† Angioedema was adjudicated in a blinded fashion by an expert committee.

McMurray JJV et al. N Engl J Med 2014;371:993-1004

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- The valsartan salt in sacubitril/valartan (S/V) approved product is different from the one in the brand *Diovan®*; 103 mg of valsartan in the *Entresto®* marketed product is equivalent to 160 mg of valsartan in the *Diovan®* product.
- The recommended starting dosage of the S/V approved product is 49/51 mg twice daily. The dose should be titrated after 2-4 weeks as tolerated to reach the target maintenance dosage of 97/103 mg twice daily.
- ACE inhibitor treatment should be stopped for 36 hours before starting treatment S/V.
- For patients not currently taking an ACE inhibitor or an ARB, or for those with severe renal impairment (eGFR <30 mL/min/1.73 m^2) or moderate hepatic impairment, the starting dosage of S/V is 24/26 mg twice daily.
- The approved S/V product is not recommended for patients with severe hepatic impairment.

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Sodium-Glucose Cotransporter 2 Inhibitors

Recommendation for SGLT2i

COR	LOE	Recommendation
1	A	1. In patients with symptomatic chronic HFrEF, SGLT2i are recommended to reduce hospitalization for HF and cardiovascular mortality, irrespective of the presence of type 2 diabetes.
Value Statement: Intermediate Value (A)		2. In patients with symptomatic chronic HFrEF, SGLT2i therapy provides intermediate economic value.

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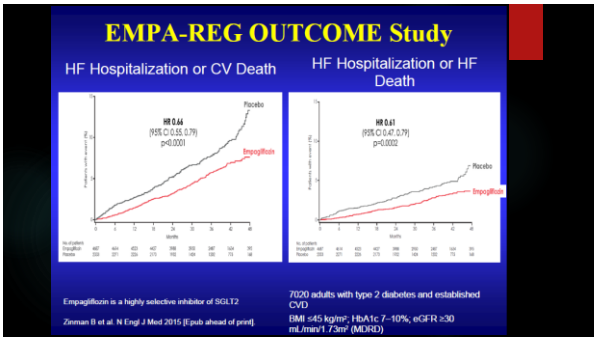

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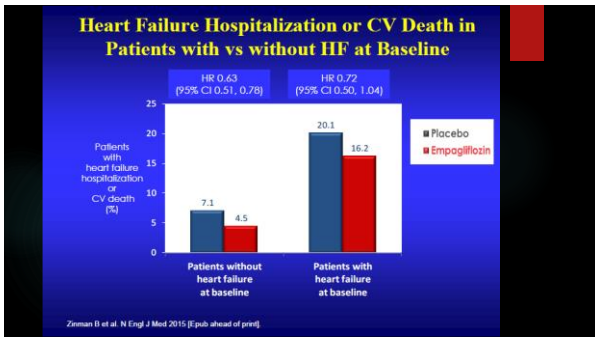

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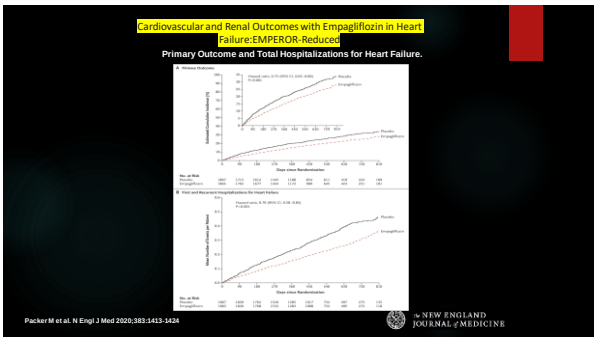

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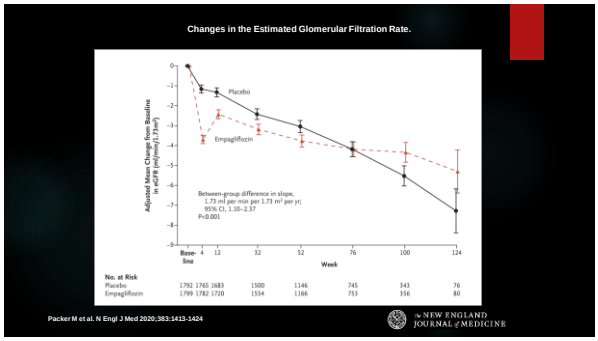

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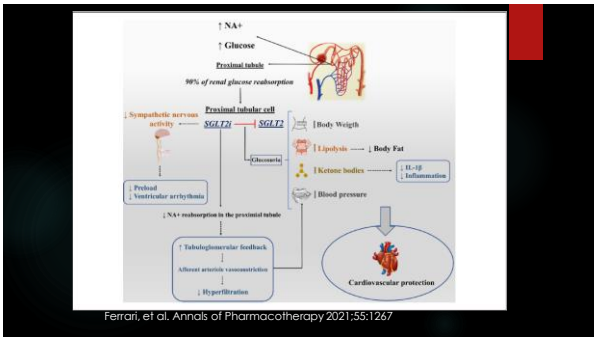

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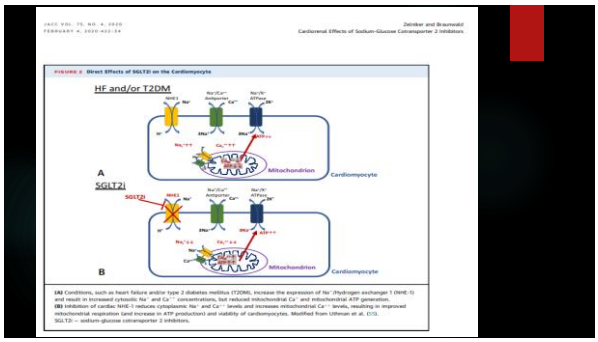

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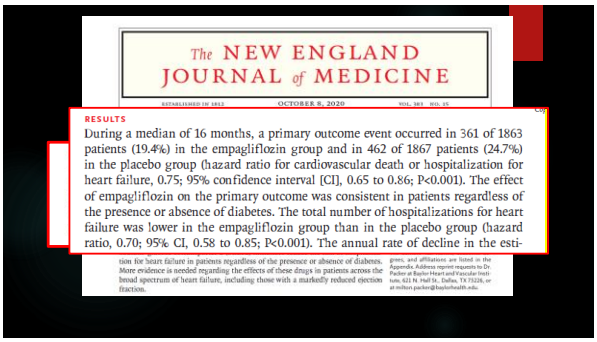

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Original Article

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

John J.V. McMurray, M.D., Scott D. Solomon, M.D., Silvio E. Inzucchi, M.D., Lars Køber, M.D., D.M.Sc., Mikhail N. Kosiborod, M.D., Felipe A. Martinez, M.D., Piotr Ponikowski, M.D., Ph.D., Marc S. Sabatine, M.D., M.P.H., Inder S. Anand, M.D., Jan Bělohlávek, M.D., Ph.D., Michael Böhm, M.D., Ph.D., Chern-En Chiang, M.D., Ph.D., Vijay K. Chopra, M.D., Rudolf A. de Boer, M.D., Ph.D., Akshay S. Desai, M.D., M.P.H., Mirta Diez, M.D., Jaroslaw Drozdz, M.D., Ph.D., Andrej Dukát, M.D., Ph.D., Junbo Ge, M.D., Jonathan G. Howlett, M.D., Tzvetana Katova, M.D., Ph.D., Masafumi Kitakaze, M.D., Ph.D., Charlotta E.A. Ljungman, M.D., Ph.D., Béla Merkely, M.D., Ph.D., Jose C. Nicolau, M.D., Ph.D., Eileen O'Meara, M.D., Mark C. Petrie, M.B., Ch.B., Pham N. Vinh, M.D., Ph.D., Morten Schou, M.D., Ph.D., Sergey Tereshchenko, M.D., Ph.D., Subodh Verma, M.D., Ph.D., Claes Held, M.D., Ph.D., David L. DeMets, Ph.D., Kieran F. Docherty, M.B., Ch.B., Pardeep S. Jhund, M.B., Ch.B., Ph.D., Olof Bengtsson, Ph. Lic., Mikaela Sjöstrand, M.D., Ph.D., Anna-Maria Langkilde, M.D., Ph.D., for the DAPA-HF Trial Committees and Investigators

N Engl J Med
Volume 381(21):1995-2008
November 21, 2019

NEW ENGLAND JOURNAL of MEDICINE

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Study Overview

- In this randomized, placebo-controlled trial, investigators evaluated the effects of the sodium–glucose cotransporter 2 inhibitor dapagliflozin in patients with heart failure and a reduced ejection fraction with or without type 2 diabetes.
- The risk of worsening heart failure or cardiovascular death was lower among those who received dapagliflozin, regardless of the presence or absence of diabetes.

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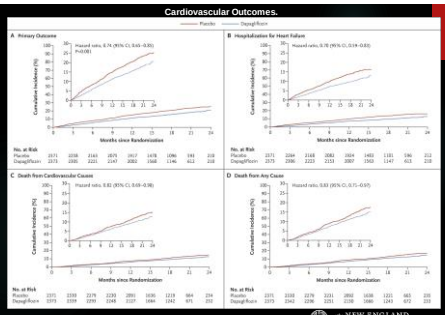
Cardiovascular Outcomes.



McMurray JJV et al. N Engl J Med 2019;381:1995-2008

NEW ENGLAND JOURNAL of MEDICINE

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Original Article

Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure

- Patients with diabetes and recent worsening heart failure that had led to hospitalization were randomly assigned to receive sotagliflozin or placebo.
- At a median of 9 months, the total number of deaths from cardiovascular causes and hospitalizations and urgent visits for heart failure was significantly lower with sotagliflozin than with placebo.

Volume 384(2):117-128
January 14, 2021

NEW ENGLAND JOURNAL of MEDICINE

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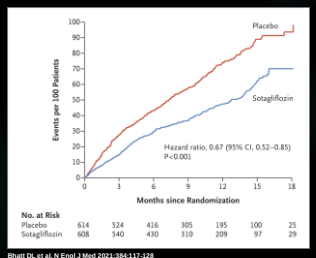
Primary Efficacy End-Point Events.



Bhatt DL et al. N Engl J Med 2021;384:117-128

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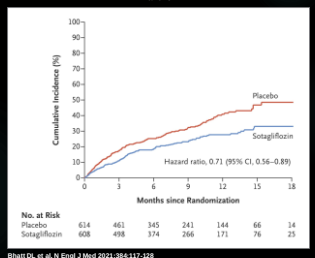
First Occurrence of Either Death from Cardiovascular Causes or Hospitalization for Heart Failure.



Bhatt DL et al. N Engl J Med 2021;384:117-128

NEW ENGLAND JOURNAL of MEDICINE

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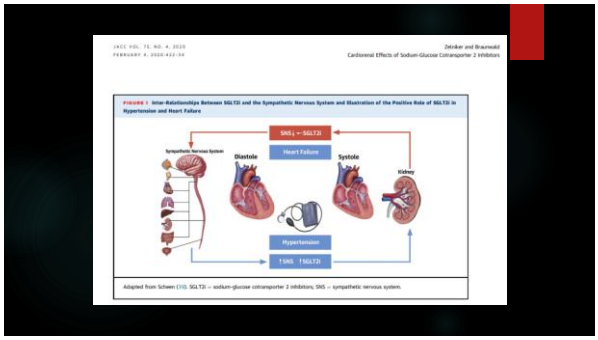

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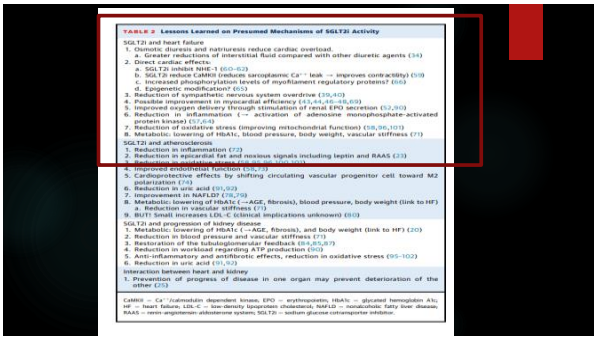

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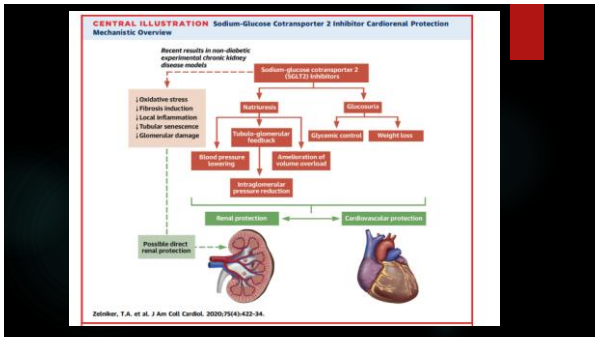

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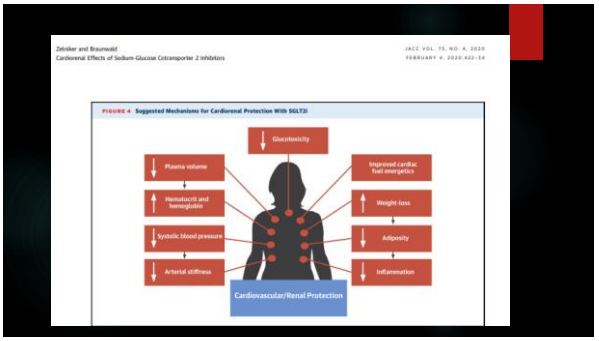

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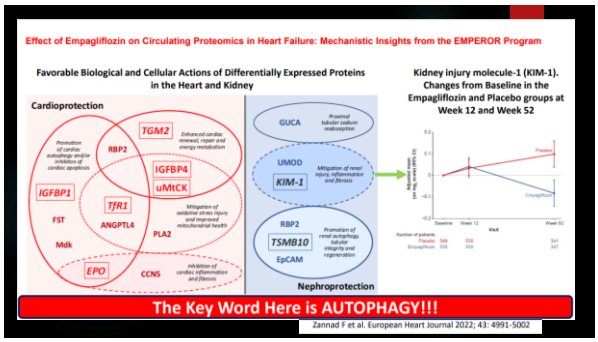

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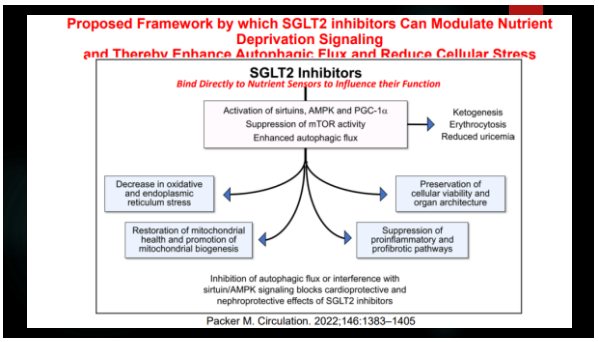

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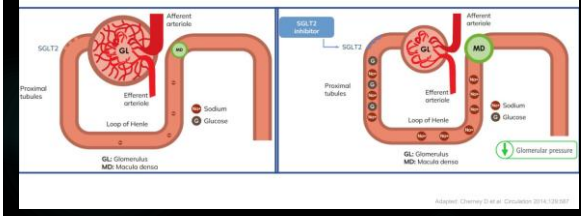
Effect of SGLT2 inhibition on the kidney



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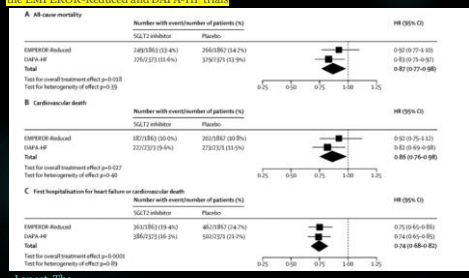
SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials



Lancet, The
Volume 396, Issue 10254

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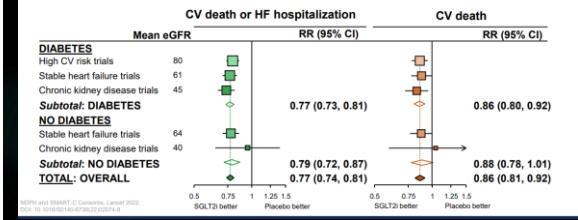
Cardiovascular outcomes



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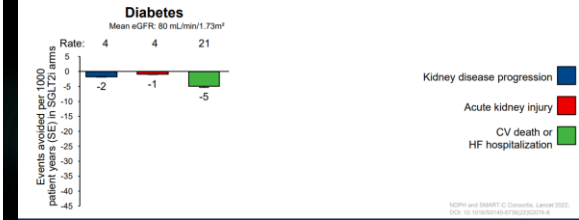
Absolute benefits: (i) T2DM + CV disease



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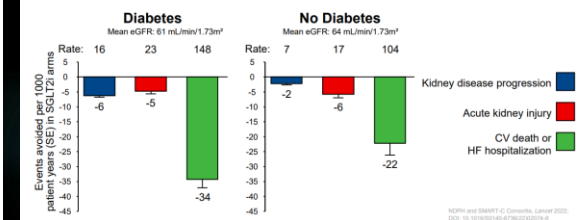
Absolute benefits: (ii) Heart failure



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3. DAPA-MI Trial Design

Phase 3 multicenter, parallel-group, registry-based, randomized, double-blind, placebo-controlled trial to evaluate the safety and efficacy of dapagliflozin vs. placebo in patients without known diabetes or established HF, presenting with MI and impaired left ventricular systolic function or Q-wave MI, in addition to SOC

- MI within 7(+3) days
- Impaired LV systolic function or Q-wave
- No known T1DM or T2DM or established HF and no clear indication for SGLT2i treatment

R 1:1

Dapagliflozin (10 mg OD) + SOC

Placebo (OD) + SOC

N=~4000

Randomization stratified by country (Sweden and the UK)

PRIMARY COMPOSITE OUTCOME
The hierarchical composite outcome of:
1. Death (first CV death, followed by non-CV death)
2. HHF
3. Non-fatal MI
4. AF/flutter event
5. New onset of T2DM
6. NYHA Functional Classification at last visit
7. Body weight decrease ≥5% at last visit

SECONDARY OUTCOMES
- Key outcome consists of same composite as primary, excluding body weight reduction
- Other secondary outcomes include time-to-event outcomes

AF, atrial fibrillation; HHF, hospitalization for heart failure; HF, heart failure; LV, left ventricular; MI, myocardial infarction; NYHA, New York Heart Association; OD, once daily; R, randomization; SGLT2, sodium-glucose co-transporter-2; SOC, standard of care; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

James S, Erlinge D, Storey RF, et al. *Am Heart J*. 2023;266:188-197.

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DAPA-MI – dapagliflozin post MI (Registry trial)

- Key eligibility criteria
  - Recent MI
  - LV impairment or Q waves
  - No diabetes
  - No known chronic HF with hospitalization in last yr
- Randomized to dapagliflozin 10mg or placebo
- 4017 participants
- Mean FU 1 year
- Primary outcome: *hierarchical* composite
  1) Death
  2) Hospitalization for HF
  3) Non-fatal MI
  4) Atrial fibrillation/flutter event
  5) New-onset T2DM
  6) NYHA status
  7) Body weight decrease of ≥5%

win ratio

Characteristic	Value
Age (yr)	63
Sex (female)	20%
LVEF ≥30%	88%
STEMI	72%

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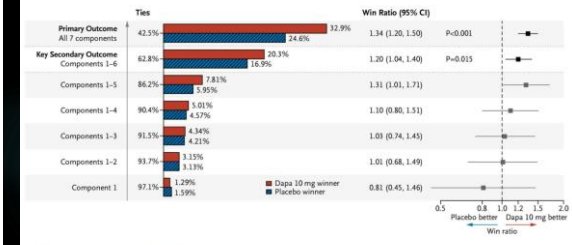
DAPA-MI Primary and Key Secondary Hierarchical Composite Outcome



James S, Erlinge D, Storey RF, et al. *NEJM Evidence*. 2023.

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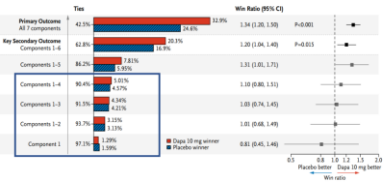
DAPA-MI – dapagliflozin post MI (Registry trial)



	Dapa N=2019	Placebo N=1998
Death	41	33
HF hospitalized	27	32
MI	44	39
AF / flutter	16	18
New-onset DM	42	78

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EMPACT-MI Trial Design

Phase 3 multinational, randomized, double-blind, placebo-controlled trial to evaluate the safety and efficacy of empagliflozin vs. placebo in patients hospitalized for MI with or at high risk of new onset HF, in addition to SOC

- Diagnosis of spontaneous* acute MI WITH
  Symptoms or signs of HF requiring treatment†
  OR
  Newly developed LVEF<45%
  AND
  ±1 enrichment criterion‡ (e.g. age, CKD or biomarker levels)
- Hospital admission within past 14 days before randomization
- No history of HF or LVSD

R 1:1

N=~5000

Empagliflozin (10 mg OD) + SOC

Placebo (OD) + SOC

PRIMARY COMPOSITE ENDPOINT
- Time to first HHF or all-cause mortality

SECONDARY ENDPOINTS
Total number of:
- HHF or all-cause mortality
- Non-elective CV hospitalizations or all-cause mortality
- Non-elective all-cause hospitalizations or all-cause mortality
- Hospitalizations for MI or all-cause mortality

Randomization stratified by diabetes status and geographical region

*Spontaneous MI: defined as MI with a primary etiology of acute CAD pathology (e.g., plaque rupture/erosion, in-stent restenosis or thrombosis).
†Symptoms: e.g., dyspnea; decreased exercise tolerance; fatigue; Signs: e.g. pulmonary rales, crackles or crepitations; elevated jugular venous pressure; congestion on chest X-ray); Treatment: e.g. augmentation or initiation of oral diuretic therapy; IV diuretic therapy; IV vasoactive agent; mechanical intervention etc. ‡Age ≥65 years; newly developed LVEF <35%; prior MI; eGFR < 60 ml/min/1.73m2; AF; T2DM; NT-proBNP ≥1,400 pg/mL for patients in sinus rhythm ≥2,800 pg/mL if AF; BNP ≥350 pg/mL for patients in sinus rhythm, ≥700 pg/mL if AF; uric acid ≥7.5 mg/dL (≥446 µmol/L); PASP (or RVSP) ≥40 mmHg; patient not revascularized (and no planned revascularization) for the index MI; 3-vessel CAD at time of index MI; diagnosis of PAD.

Harrington J, Udell JA, Jones W, et al. *Am Heart J*. 2022;253:86–98.

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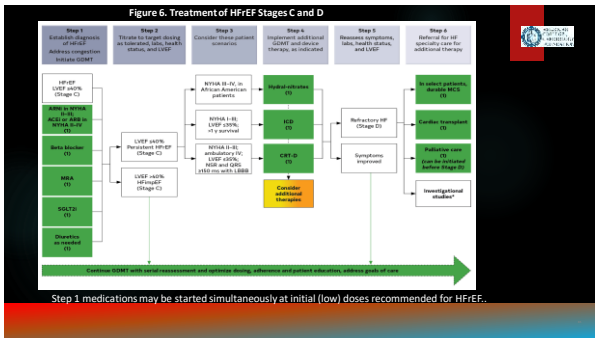

Step 1 medications may be started simultaneously at initial (low) doses recommended for HFrEF..

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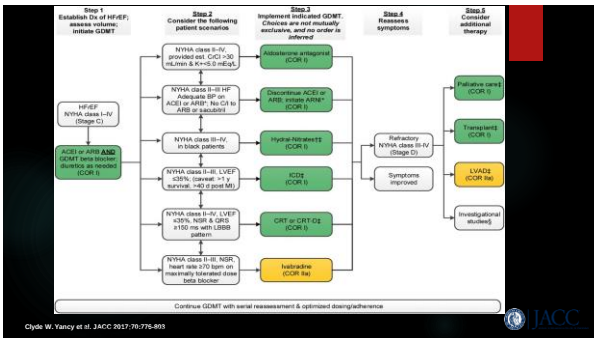

Clyde W. Yancy et al. JACC 2017;70:776-803

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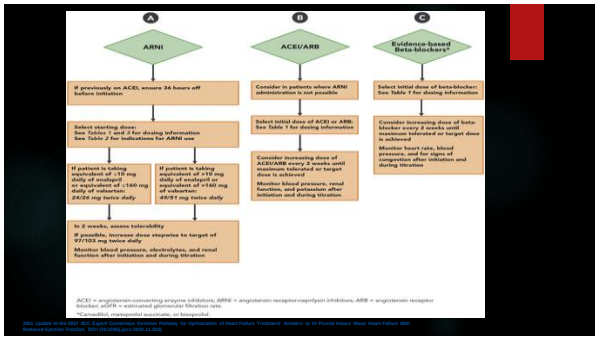

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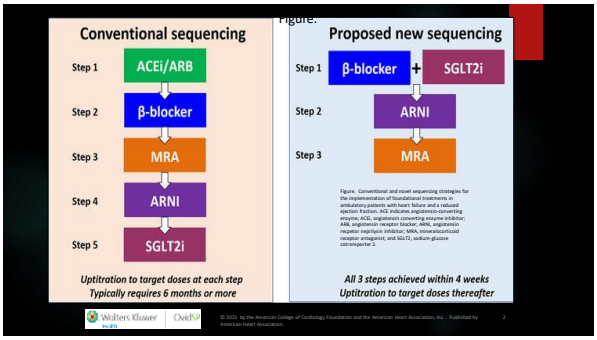

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- New sequencing assumes the traditional sequencing was based on concept that the most effective therapies were discovered first and then the next and so on, such that they must be added in that order
- Getting the GDMT on board is MORE important that reaching the target dosing – low doses of drugs for HFrEF yield sig benefits to morbidity and mortality
- (new) Drugs tested in trials were not tested in patients who were receiving background therapy at target doses of approved agents; most were either not on the full complement of GDMT or were subtarget in doses
- Current approach has been criticized in needing to achieve target dosing and prioritizing each agent added, thus, adding significant length of time before all mortality-reducing agents are on board -- note that each of the "foundational drugs has been shown to reduce morbidity and mortality within 30 days of initiating treatment

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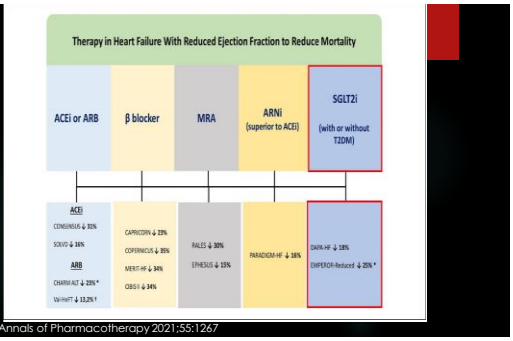

Ferrari, et al. Annals of Pharmacotherapy 2021;55:1267

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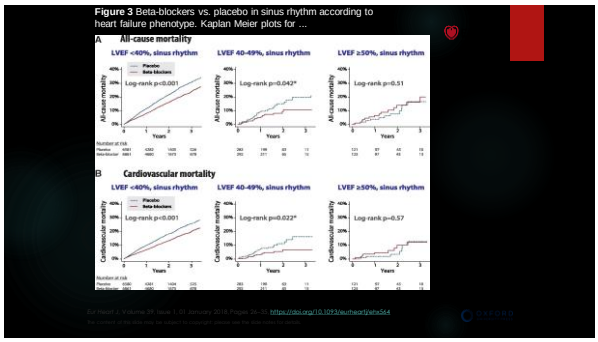

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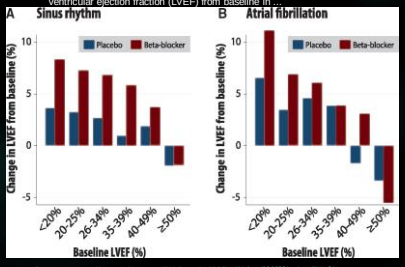

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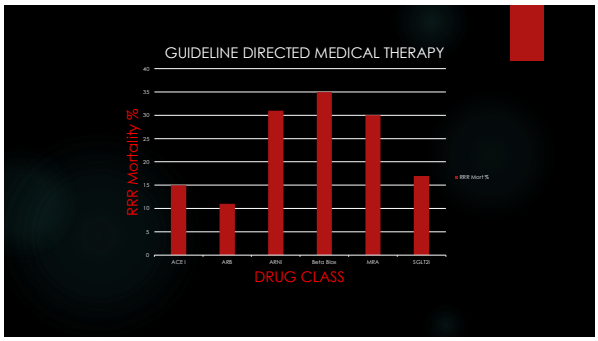

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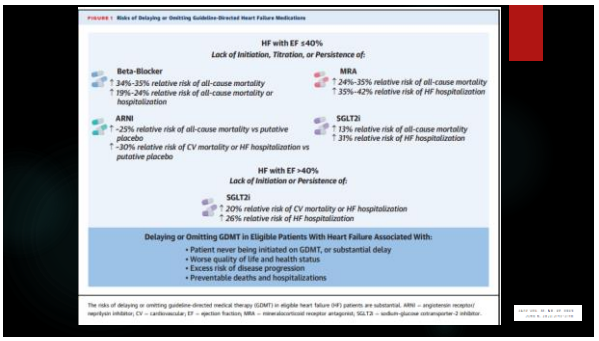

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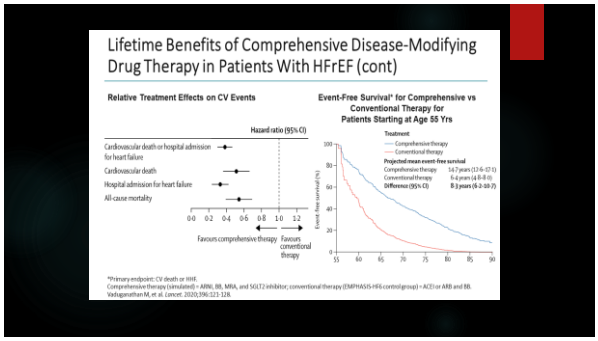

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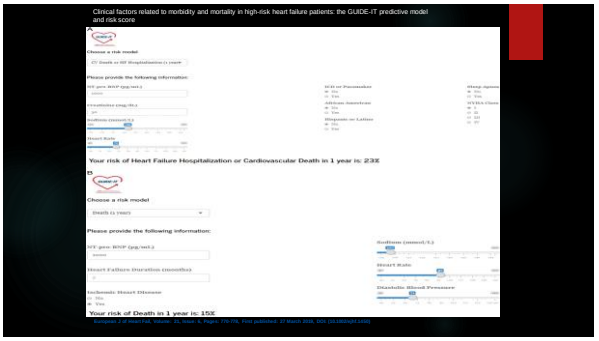

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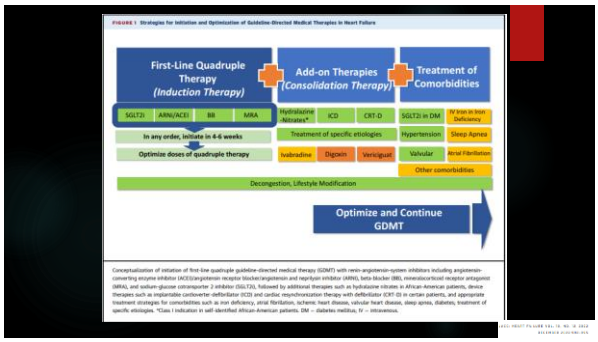

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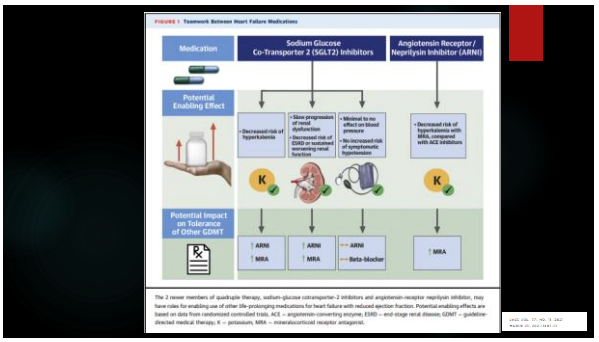

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Summary:

Three Fundamental Changes to the Approach to GDMT

1. Order and sequence of therapies
   There is no fixed order and no preference for the sequence used
2. Initiation vs dose titration
   Prioritize initiation over up-titration of dose
3. Speed matters
   We have been too slow in introducing life-saving therapies in the past

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1. When initiating pharmacotherapy for Heart Failure with reduced Ejection Fraction (HFrEF), the medications must be introduced into the patient in the correct order (e.g., ACEi/ARB/ARNi first, then beta- blocker, then aldosterone antagonist, then serum-glucose transporter-2 inhibitor to obtain the most effective outcomes. T F
2. Which of the following statements regarding serum-glucose transporter-2 inhibitors is true regarding their use in HFrEF patients?
   1. Their mortality reduction is considered to be a class effect, so all of the drugs in this class have a class I-A guideline recommendation
   2. Empagliflozin and Dapagliflozin both have shown effectiveness in cardiovascular outcomes in patient with OR without type -2 diabetes mellitus
   3. They are potent hypotensive agents so care must be used when adding to therapy
   4. They are nephrotoxic and are contraindicated in patients with eGFR < 50ml/min

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