Towards Holistic & Comprehensive Cardiac Care

Beyond ARNI: Newer Pharmacotherapy in Heart Failure

Dr.Rajagopal Jambunathan

Avant BKG Hospital

Mysore, India

4 Pillars of Heart Failure Manag t

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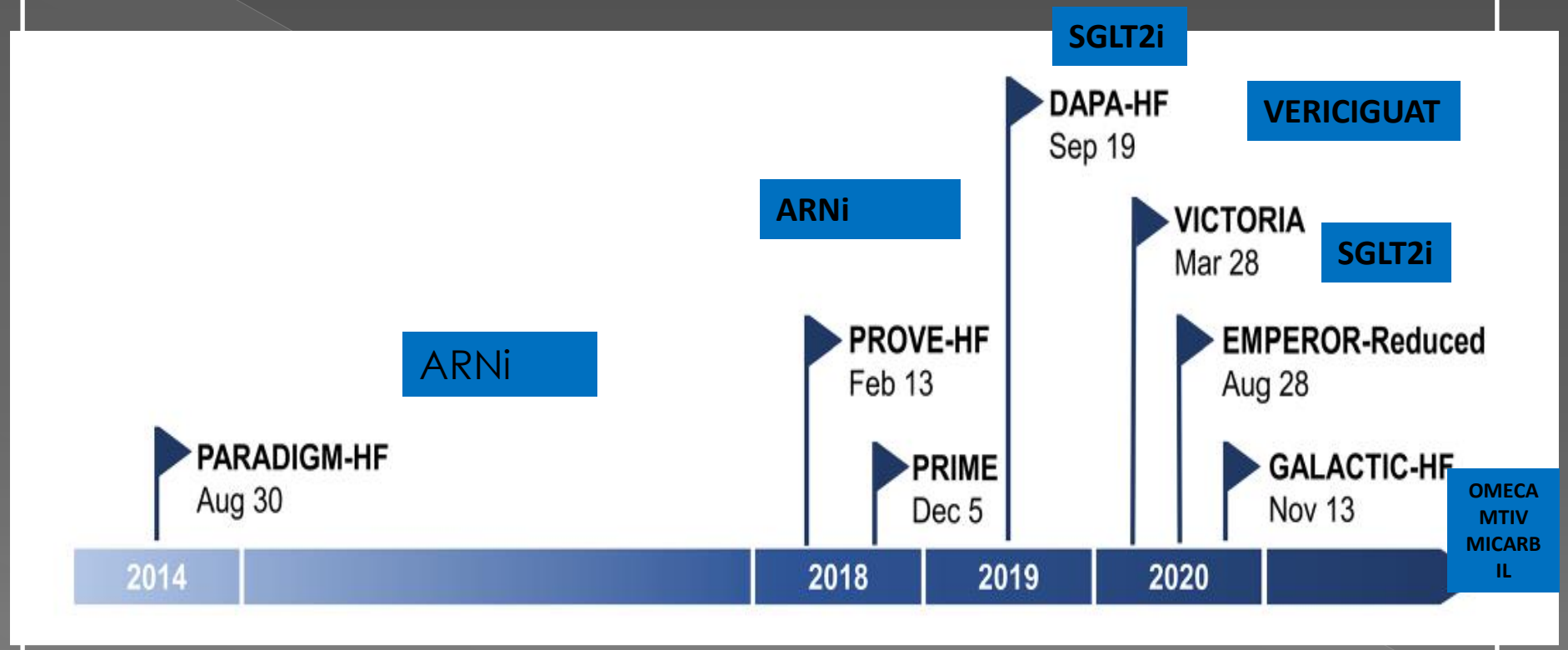

75 year old male

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- Diabetic and Hypertensive
- Post MI 8 years back – PTCA done
- LVEF=30% ⟶ 35%
- Stable for past 7 years
- Class III dyspnea at present
- LVEF=32%. HBA1C = 9.0%, Creatinine=1.4
- CAG – Patent stents, No De-novo disease

Next Step:

- Add SGLT2 inhibitors –

- Dapagliflozin:
  - **DAPA-HF**
  - **DETERMINE-Reduced and DETERMINE-Preserved**
  - **DELIVER**

- Empagliflozin:
  - EMPA-REG
  - EMPEROR – Reduced
  - EMPACT-MI

5th Pillar of management- SGLT2 inhibitors

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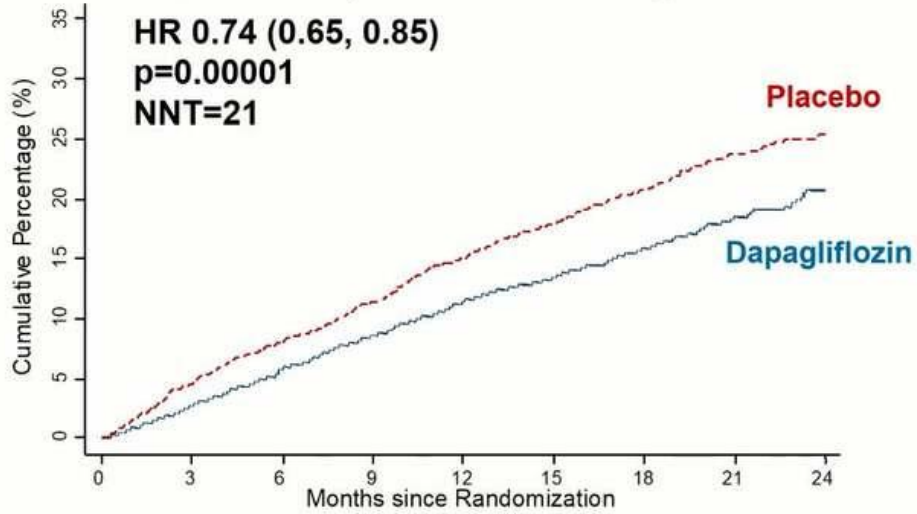
15:54 DAPA HF - The Dapagliflozin And Prevention Of Adverse-outcomes In Heart Failure Trial — Paris

Primary composite outcome

CV Death/HF hospitalization/Urgent HF visit



Number at Risk

Dapagliflozin	2373	2305	2221	2147	2002	1560	1146	612	210
Placebo	2371	2258	2163	2075	1917	1478	1096	593	210

6th Myanmar Cardiology Conference

5th Pillar of management-

50 year old male

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- Non-Diabetic and Non-Hypertensive
- Dilated Cardiomyopathy, Normal CAG
- Class III-IV ~~dysp~~nea,
- Admitted with Acute LVF
- LVEF=28%. HBA1C = 5.4%, Creatinine=1.0
- On good doses of Diuretic, ARNI and Betablockers

Can we add SGLT2 Inhibitors?

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- Both Empa and Dapa have no significant hypoglycemic effects on non-diabetics treated for heart failure
- Ensure adequate hydration and timely food intake

SOTAGLIFLOZIN:

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SOLOIST - WHF TRIAL

Bhatt DL et al. Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure. N Engl J Med. 2021;384(2):117-128.

SOTAGLIFLOZIN
inhibits

SGLT-2 ↓ increases urinary glucose excretion

SGLT-1 ↓ delays intestinal glucose absorption

QUESTION
In patients with diabetes and recently worsening HF, does SOTAGLIFLOZIN:
↓ CV mortality?
↓ HF urgent visits?
↓ HF hospitalizations?

INCLUSION
18 - 85 yo patients with diabetes hospitalized for signs or symptoms of HF and treatment with IV diuretics

1222 patients

TOTAL NO. OF EVENTS (RATE PER 100 PATIENT YEARS)

	PRIMARY OUTCOME: HF urgent visits, HF hospitalizations, CV Death	SECONDARY OUTCOMES: HF urgent visits, HF hospitalizations	SECONDARY OUTCOMES: CV Death
Sotagliflozin n=608	245 (51)	194 (40)	51 (11)
	HR 0.67 95% CI 0.52-0.85 p<0.001	HR 0.64 95% CI 0.49-0.83 p<0.001	HR 0.84 95% CI 0.58-1.22 p=0.36
Placebo n=614	355 (76)	297 (64)	58 (13)

CONCLUSION
In patients with diabetes with worsening HF, sotagliflozin significantly decreased CV deaths, HF urgent visits, and HF hospitalizations

SCORED: Sotagliflozin Primary Efficacy in T2D and CKD—Total CV Death, HFH, and Urgent HF Visit

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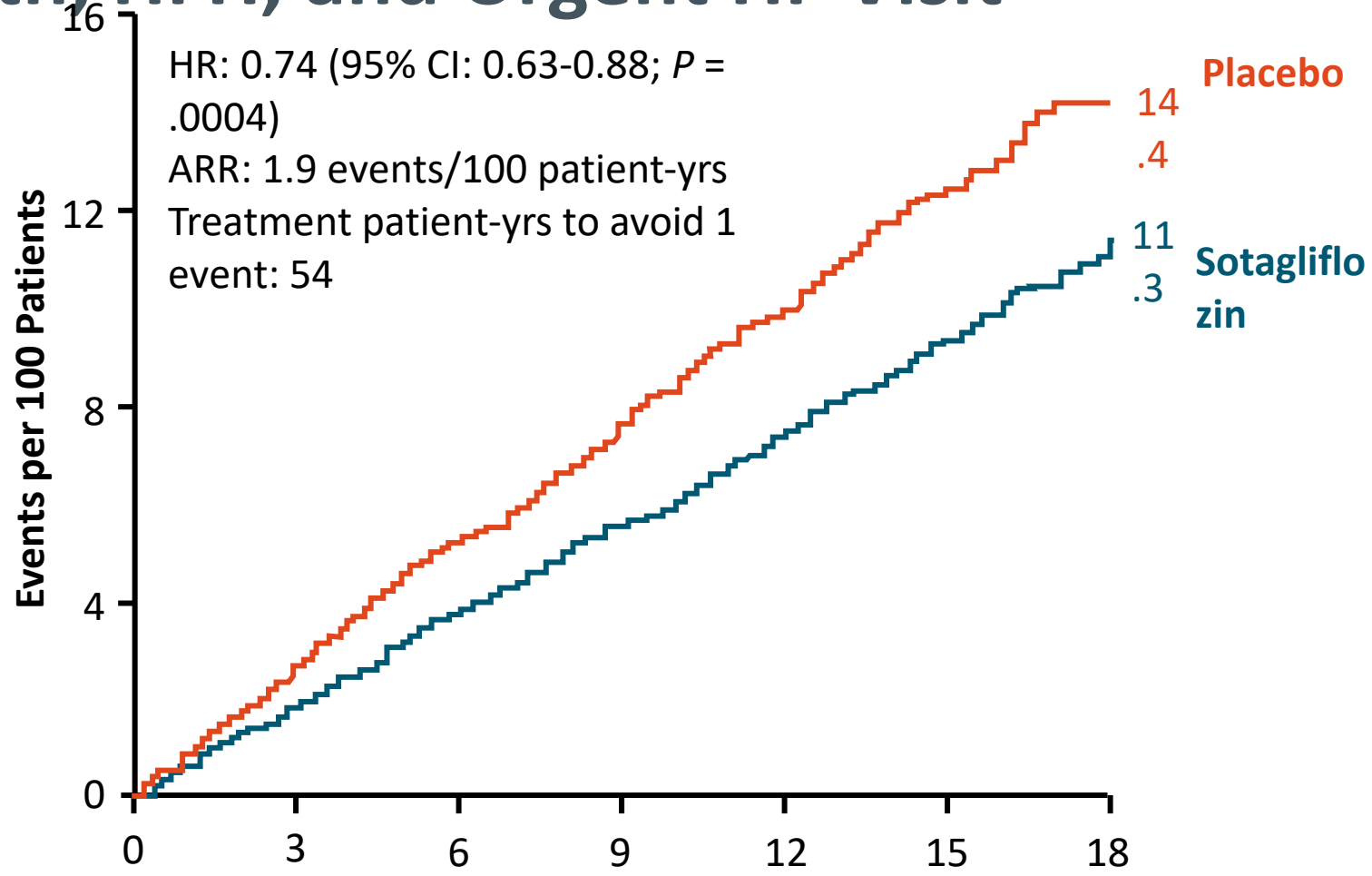

Case 3:

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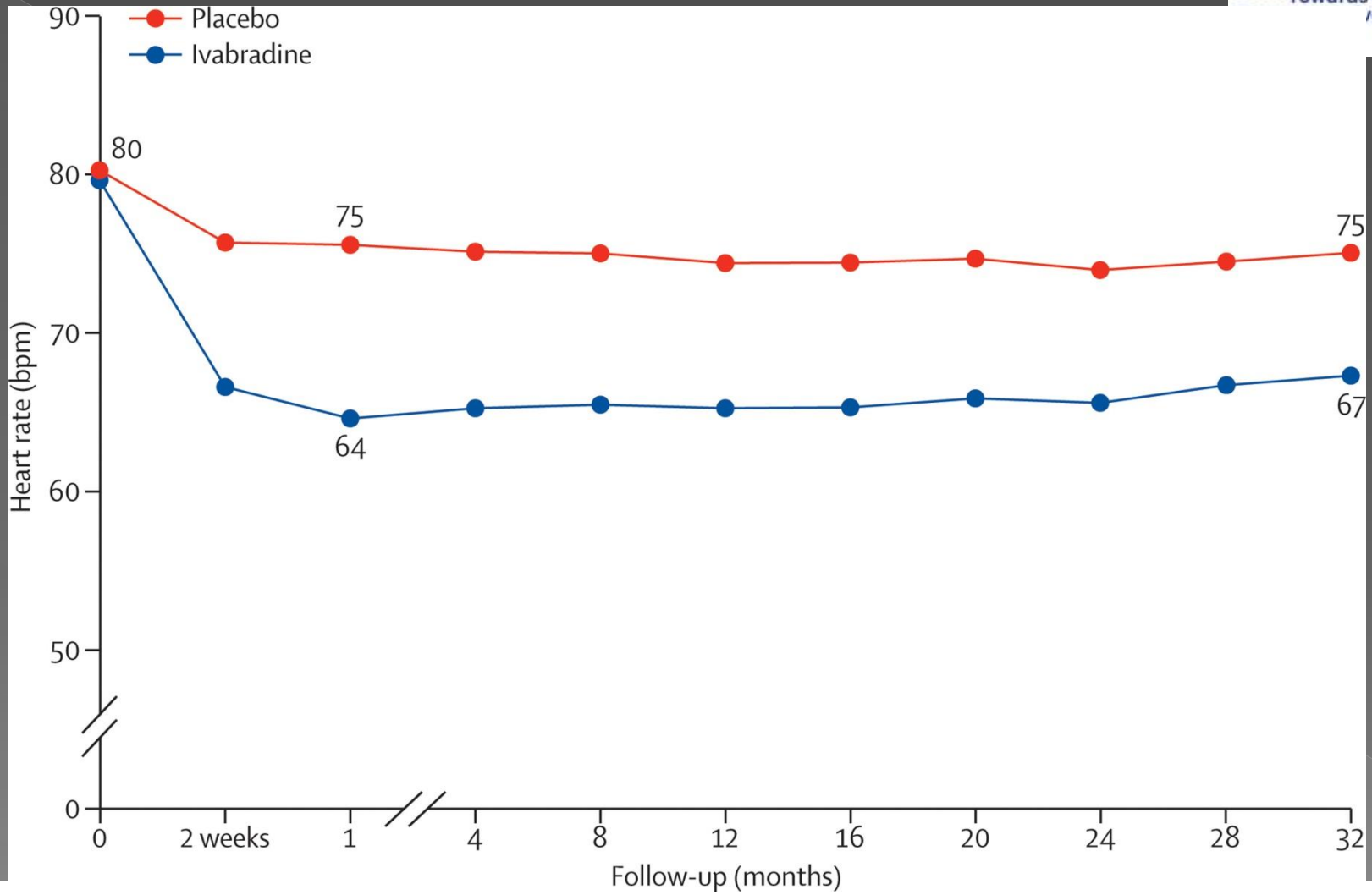
- 51 year old female, Diabetic and Post CABG
- On:
  - ARNI 100mg bd
  - Carvedilol 3.125 mg bd
  - Empa 25 mg od
  - Torsemide +aldactone
- BP – 90/60 mmHg
- Heart rate 110/min
- Recurrent admission with heart failure

Ivabradine: SHIFT study



Ivabradine:

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SHIFT: Results

- Significant 18% reduction in HR for CV death or hospitalization for worsening HF with ivabradine vs control group—driven by significant 26% HR reductions for the individual secondary end points of death from HF and hospitalization for worsening HF

Primary and secondary end points[a]

Outcomes	Ivabradine (n=3241), %	Placebo (n=3264), %	HR (95% CI)	p
Primary end point	24	29	0.82 (0.75–0.90)	<0.001
Death from HF	3	5	0.74 (0.58–0.94)	0.014
HF hospitalization	16	21	0.74 (0.66–0.83)	<0.001
CV death, HF hospitalization, or admission for nonfatal MI	25	30	0.82 (0.74–0.89)	<0.001

Ivabradine:

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- An invaluable addition to heart failure management
- Readmissions and Mortality benefit
- Heart rate control even in Hypotension and while on ionotropes
- Use in acute heart failure is proposed

Case 4:

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- Known hypertensive, non diabetic
- CKD – creat-3.2 mg/dL
- On and off Hyperkalemia
- Post PTCA status, EF 32%
- On Beta blockers, Ivabradine, Hydrallazine-Isosorbide, Empagliflozin and diuretics.
- Class II – III at present

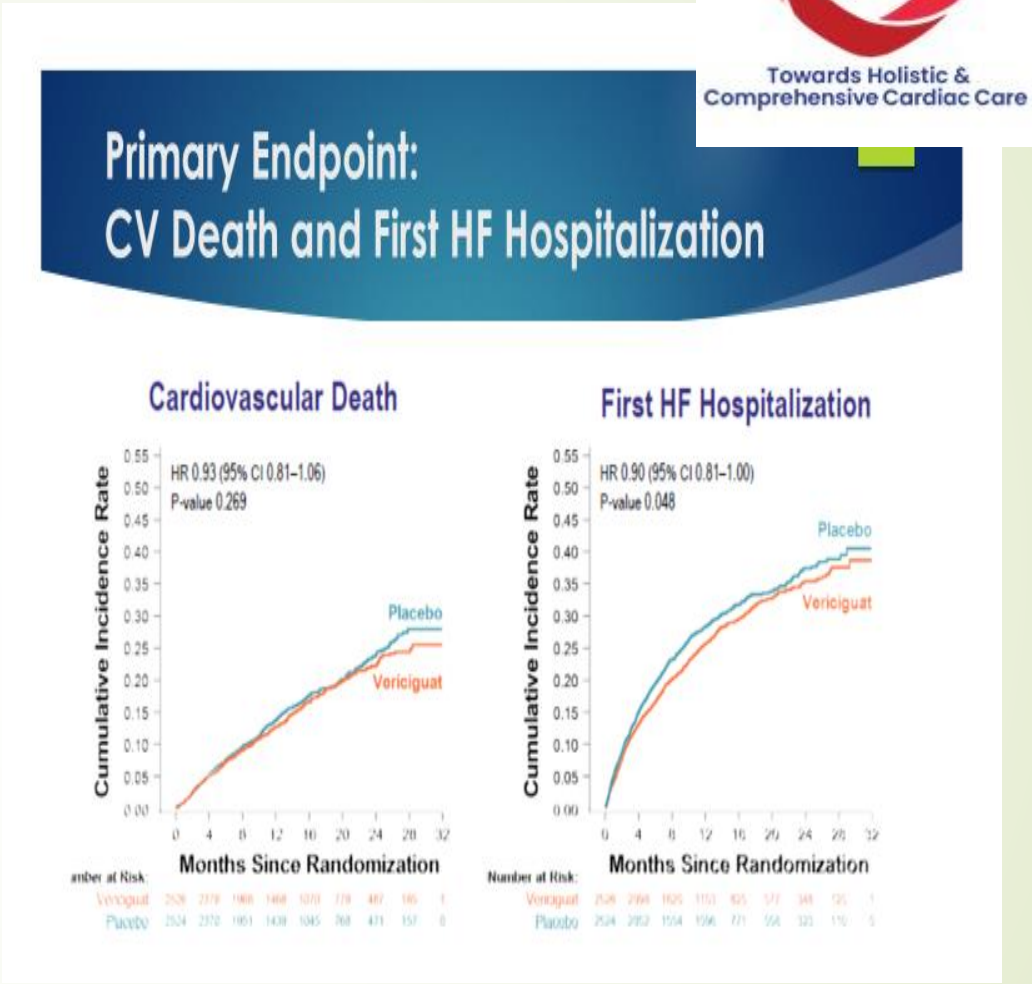
VERICIGUAT:

- Shown to reduce composite rate of CV death or HF hospitalizations after median 10.8 mos of follow-up

- 35.5% with vericiguat vs 38.5% with placebo

VICTORIA Study:

To evaluate the safety and tolerability of vericiguat in this high-risk population with HF with reduced EF (HFrEF)

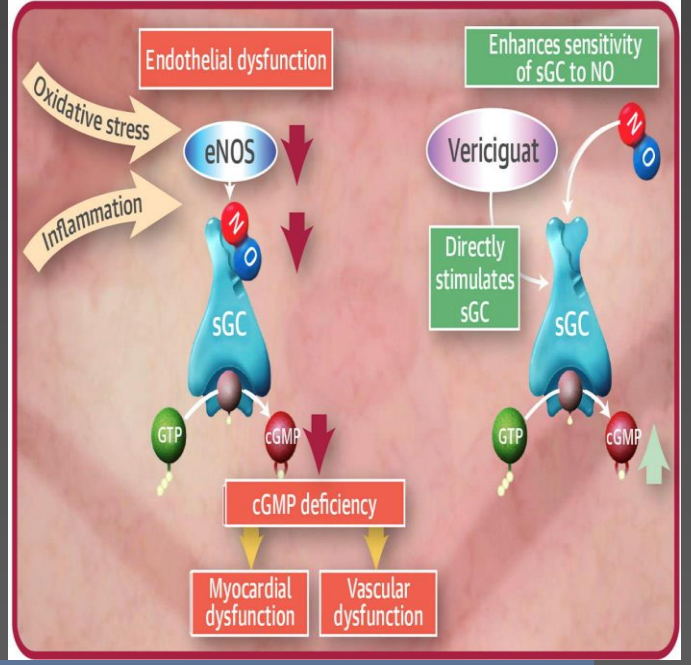


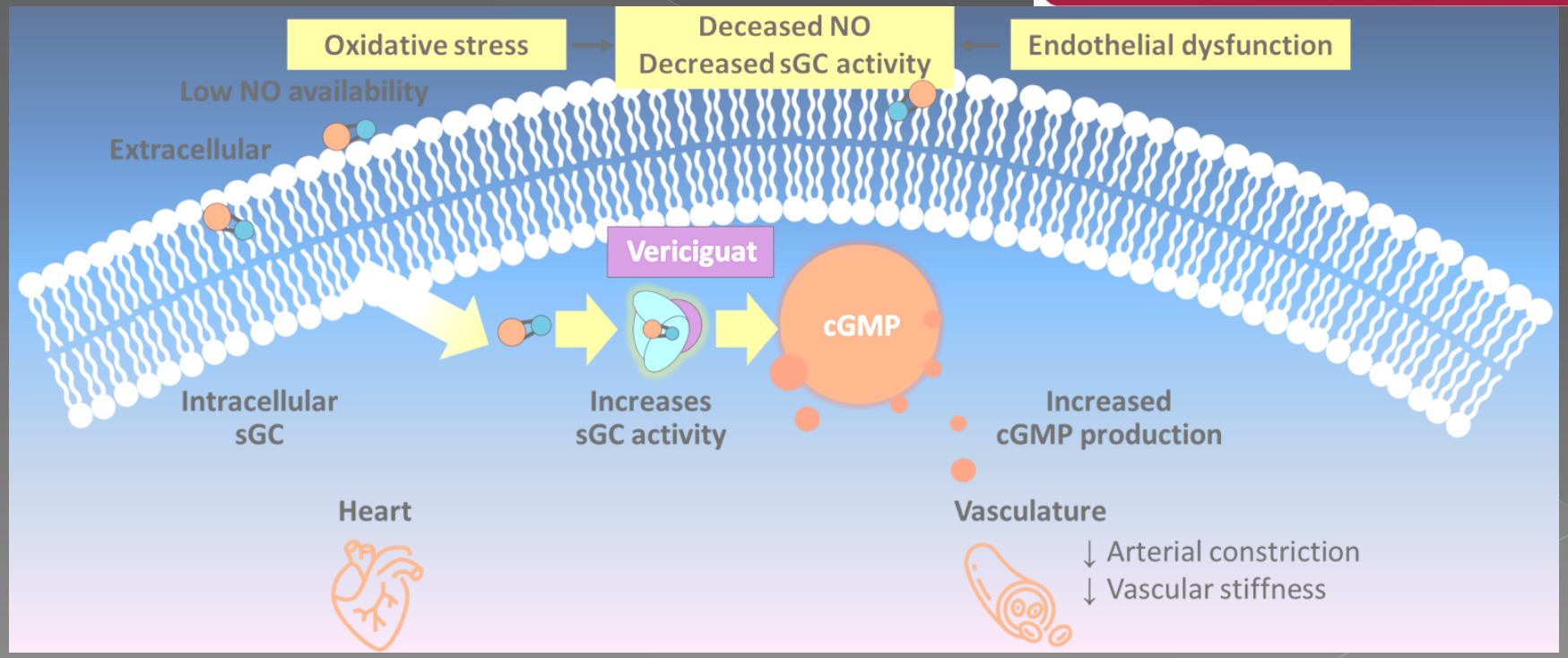
7 %

10 %

Vericiguat:

- Oral soluble guanylate cyclase stimulator – Myocardial and vascular function





VERICIGUAT:

- Start with 2.5 mg and can titrate to 10 mg OD
- Irrespective of renal status
- Watch for hypotension in first few weeks
- Do not use with Riociguat (For PAH)

Case 5:

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- 18 year old young adult male
- Diagnosed with Hypertrophic Cardiomyopathy on calaptin
- IVS – 2.3cm.
- LVOT gradient – 14 mmHg. LVEF- 78%
- Class III dyspnea , not tolerating diuretics or beta blockers

MAVACAMTEN:

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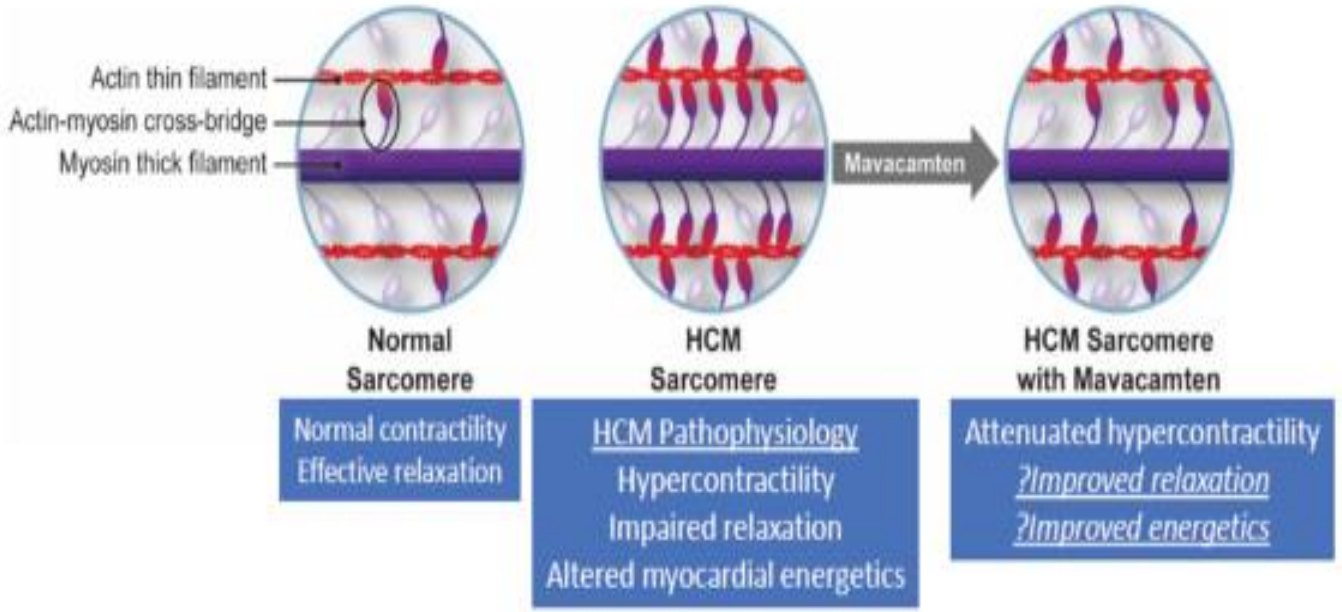
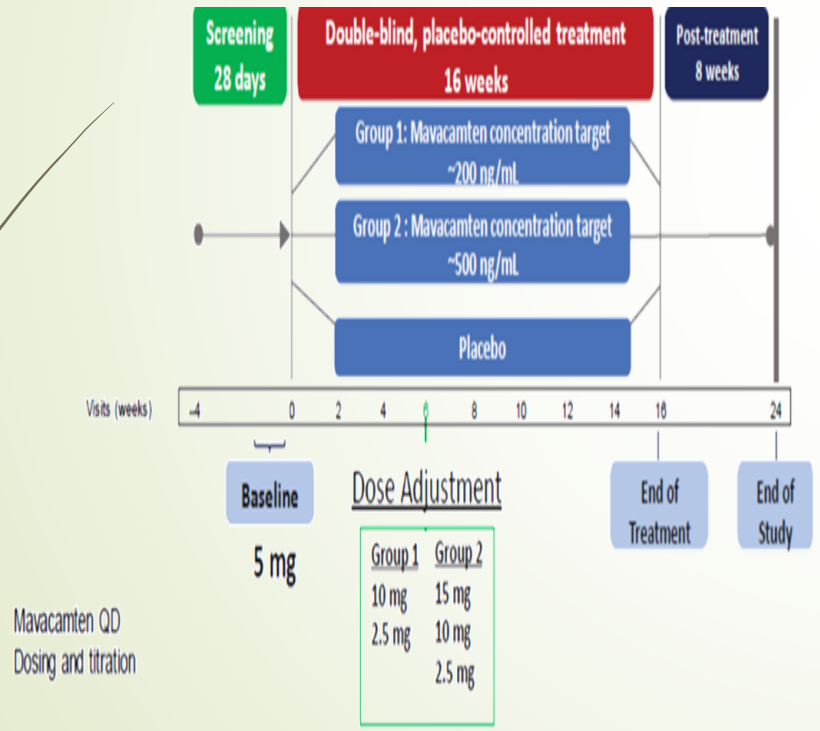


Mavacamten is a first-in-class, selective allosteric inhibitor of cardiac myosin

→ Reduces the number of myosin-actin cross-bridges and thus decreases excessive

MAVERICK-HCM: Phase 2, placebo-controlled, dose-ranging study in symptomatic non-obstructive HCM



Primary objective: Safety and Tolerability

Key safety endpoint:

- Frequency and severity of treatment-emergent adverse events (TEAEs), AEs of special interest, and serious adverse events (SAEs)

Exploratory Efficacy Objectives

- Change from baseline to Week 16 in:
  - N-terminal pro b-type natriuretic peptide (NT-proBNP)
  - Peak oxygen uptake (pVO_2) measured by cardiopulmonary exercise testing (CPET)
  - New York Heart Association (NYHA) Functional Class
  - Echocardiographic measures of LVEF and parameters of diastolic function (eg, E/e')
  - Composite functional endpoint:
    1) ≥1.5 mL/kg/min increase in pVO_2 and ≥1 NYHA Class improvement; **OR**
    2) ≥ 3.0 mL/kg/min increase in pVO_2 with no worsening in NYHA Class

Ho, C. Y., Mealiffe, M. E., Bach, R. G., Bhattacharya, M., Choudhury, L., Edelberg, J. M., ... & Heitner, S. B. (2020). Evaluation of mavacamten in symptomatic patients with nonobstructive hypertrophic cardiomyopathy. *Journal of the American College of Cardiology*, *75*(21), 2649-2660.

MAVERICK-HCM:

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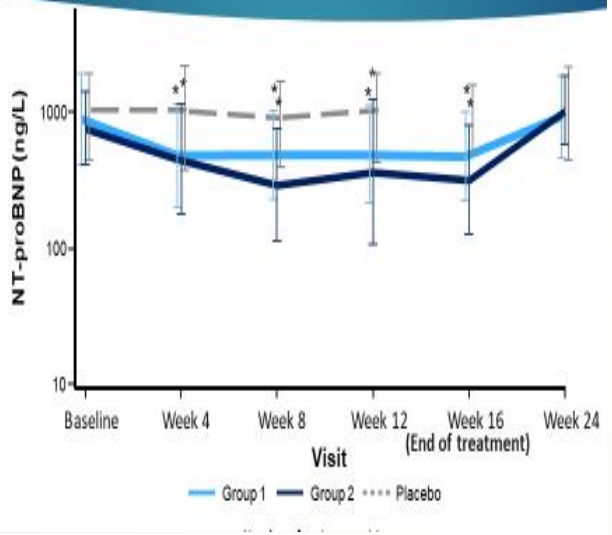
Reduction in NT-proBNP

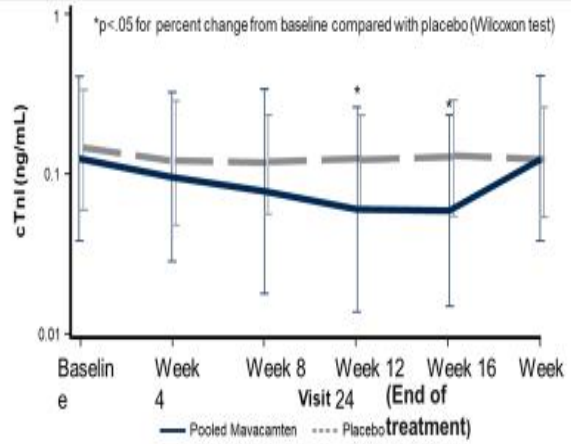


*p<.05 for percent change from baseline compared with placebo (Wilcoxon test)

Group 1 mavacamten ~200 ng/mL (n = 19)	Group 2 mavacamten ~500 ng/mL (n = 21)	Placebo (n = 19)

Reduction in cTnI

cTnI Geometric Mean: Baseline to End of Washout
Subpopulation with Baseline cTnI >99th Percentile



WHAT ABOUT OBSTRUCTIVE HCM?

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- EXPLORER HCM trial

EXPLORER-HCM

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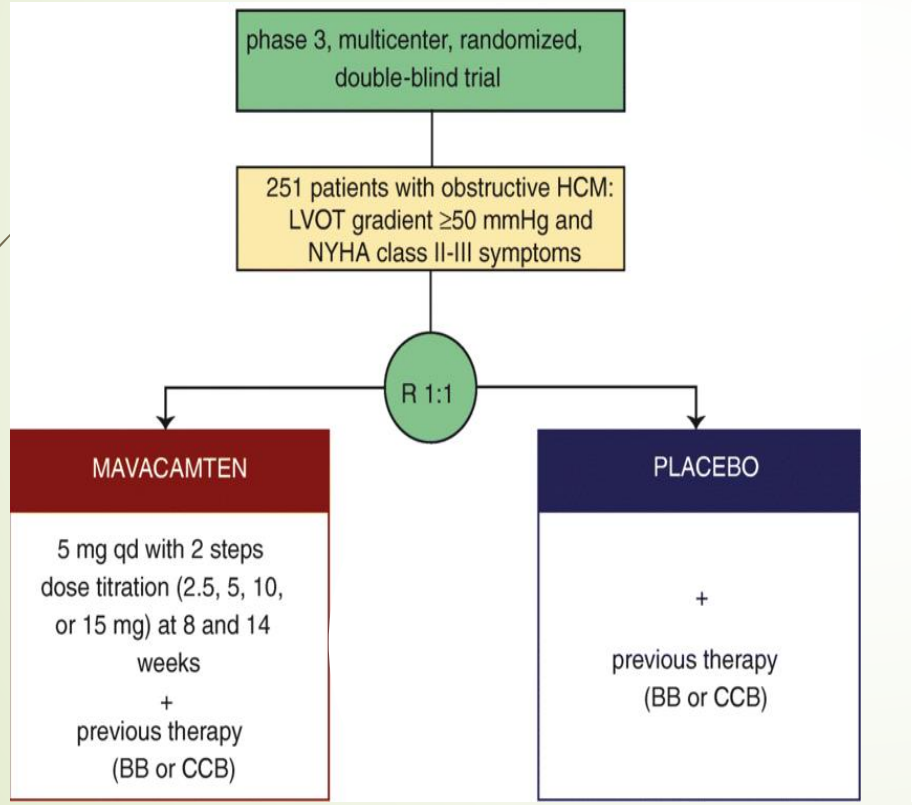
STUDY DESIGN



RESULT

Endpoints	MAVACAMTEN	PLACEBO	P value
≥1.5 ml/kg/min increase in pVO_2 with ≥1 NYHA class improvement OR ≥3.0 ml/kg/min increase in pVO_2 with no worsening of NYHA class	37%	17%	0.0005
Post-exercise LVOT gradient	- 47mmHg	-10mmHg	<0.0001
pVO_2 (ml/kg/min)	+1.40	- 0.05	0.0006
≥1 NYHA class improvement	+ 65%	+31%	<0.0001
KCCQ-CSS (n)	+14	+ 4	<0.0001

Case 6:

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- 56 year old Female
- Well controlled Diabetic
- Poorly controlled Hypertensive
- Class III dyspnea,
- Admitted with Acute LVF
- HBA1C = 5.4%, Creatinine=1.0
- LVEF=60%. Grade 2 Diastolic dysfunction
- Normal CAG
- On Telmisartan, Diuretics and Betablockers

HF with PEF?

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- SGLT2 Inhibitors –
  - -Emperor Preserved
  - - DELIVER
- Beta Blockers – only Nebivolol _(SENIORS Study) has evidence of benfit
- No role for ARNI or ACEI or Digoxin

NEWER DRUGS in the pipeline:

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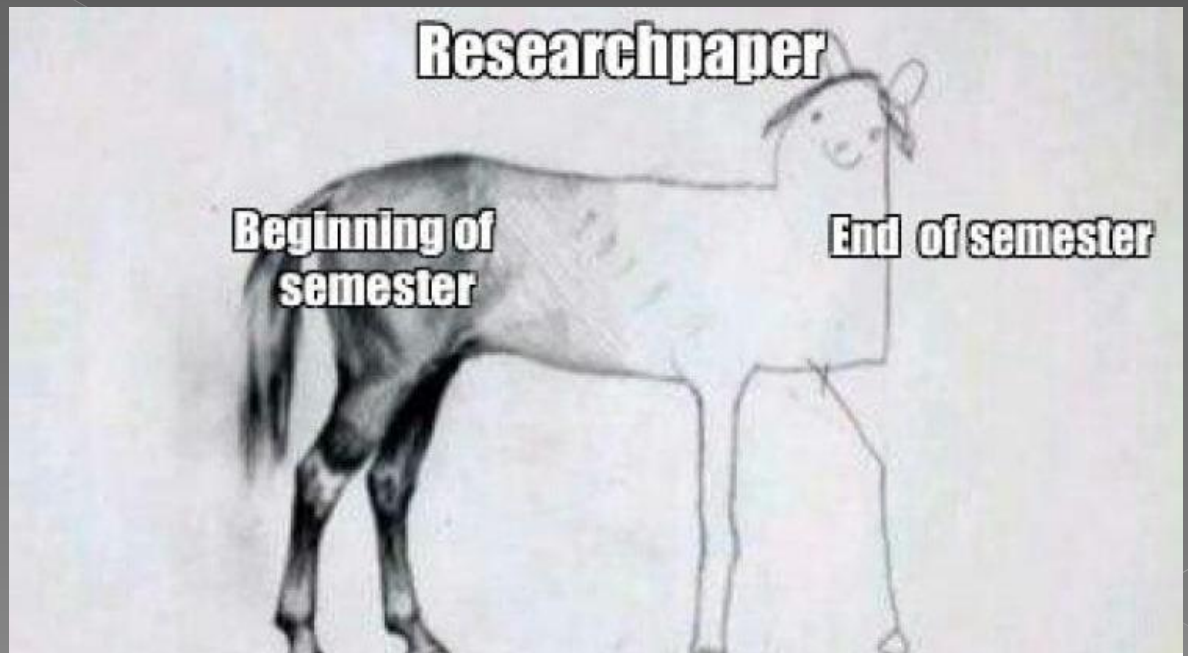
- Omecativ Mecarbil



Omecativ Mecarbil

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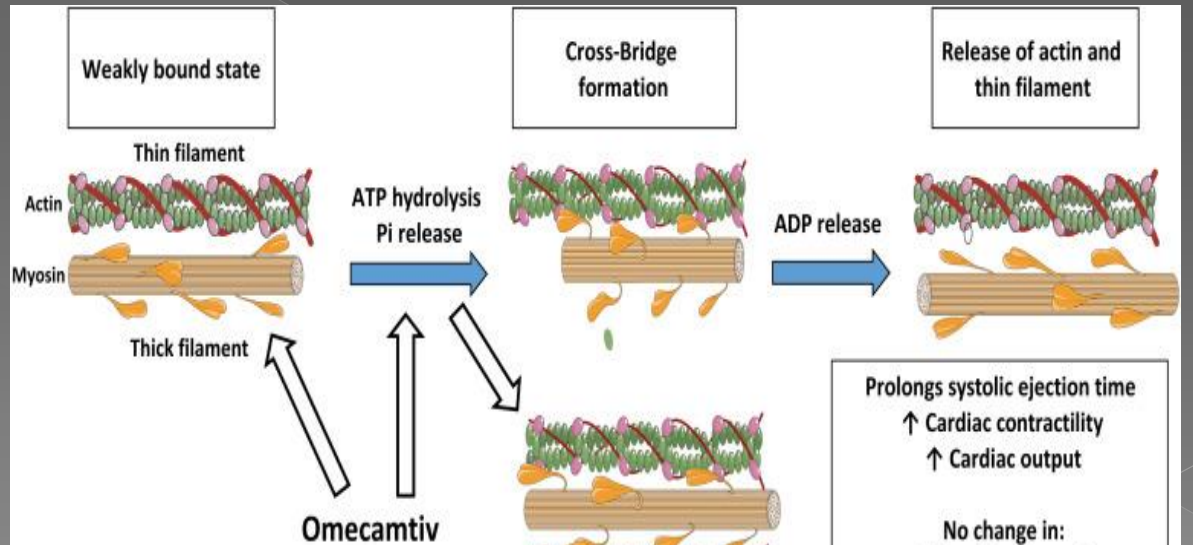
- activates myocardial ATPase and improves energy utilization.
- Enhances effective myosin cross-bridge formation and duration,
- Velocity of contraction remains the same.



COSMIC-HF – Phase 2

- Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure trial
- The role of 20 weeks of and omecamtiv mecarbil (OM) in patients with stable HF
- 448 outpatients with chronic symptomatic class II or III), LVEF <40%, and elevated natriuretic peptides.
- Patients were randomized 1:1 to placebo or an oral OM pharmacokinetic (PK)-guided dose titration group (initial 25 mg twice daily dose increased to 50 mg.

COSMIC HF:

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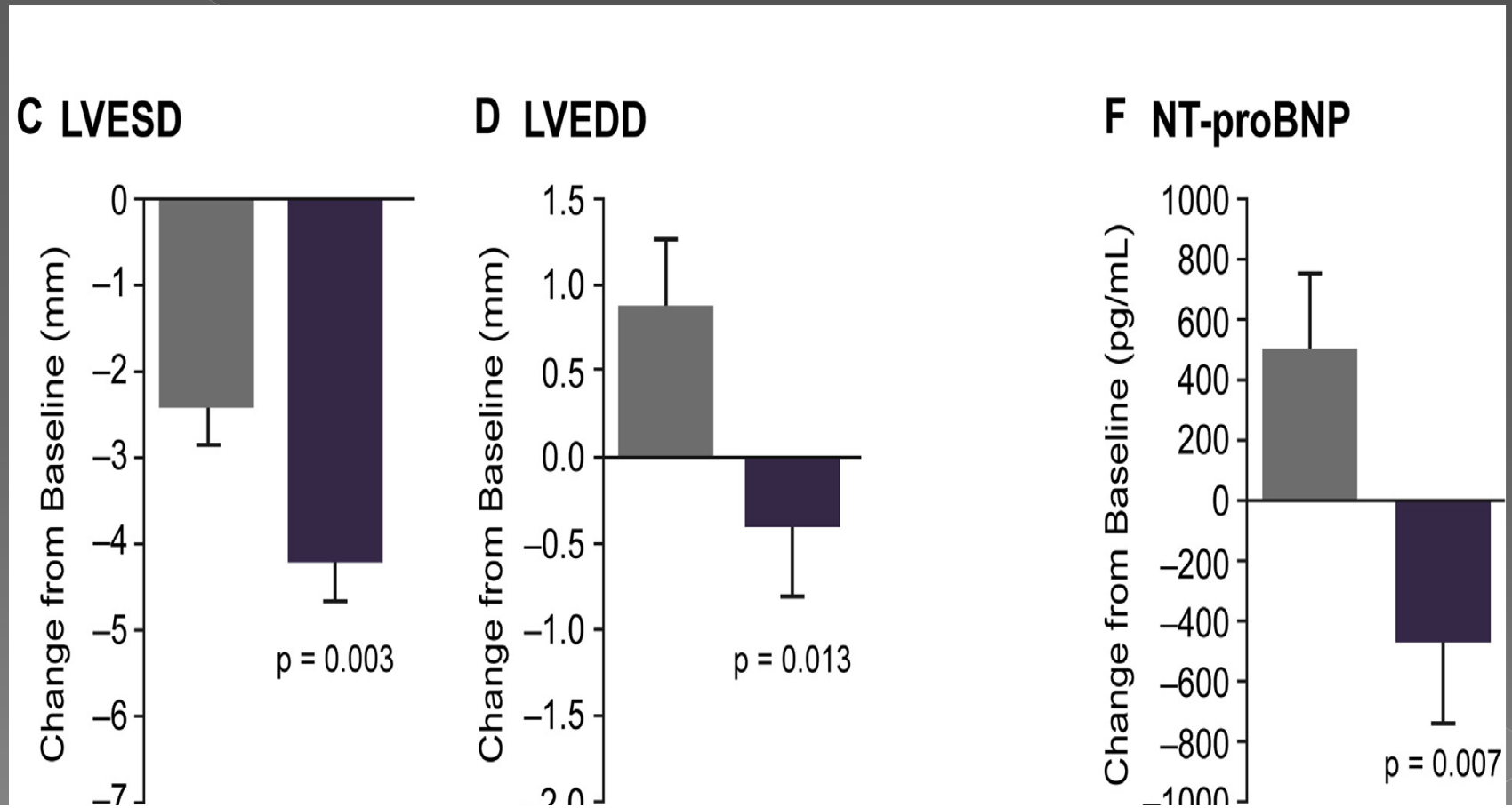
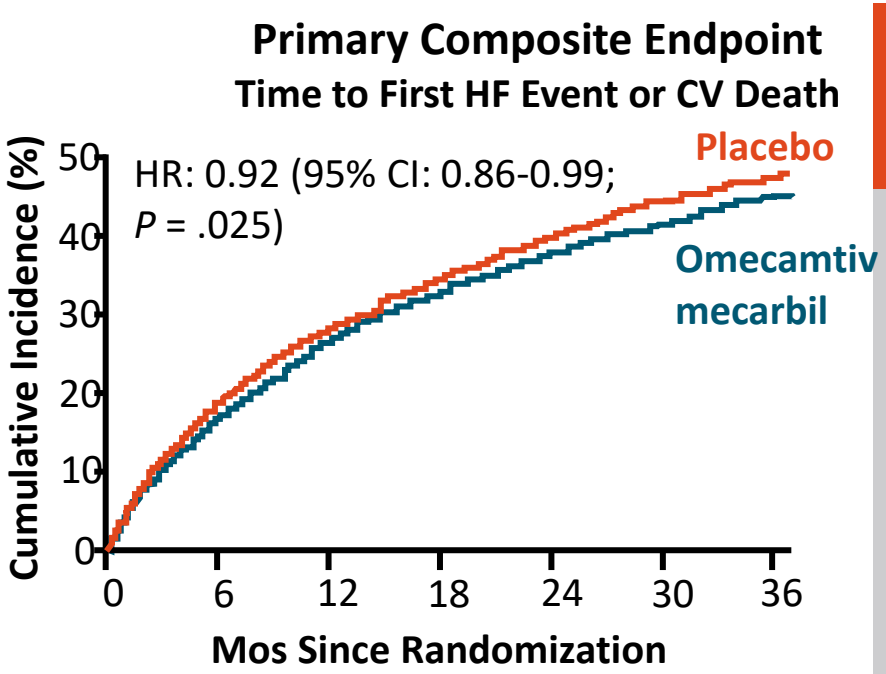


GALACTIC-HF: Omecamtiv Mecarbil in HFrEF



Outcome	HR (95% CI)	*P* Value
Time to first HF event or CV death (primary outcome)	0.92 (0.86-0.99)	.025
▪ Subgroup with baseline LVEF ≤ 28%	0.84 (0.77-0.92)	$P_{interaction} = .003$
▪ Subgroup with baseline LVEF > 28%	1.04 (0.94-1.16)	
Time to first HF event	0.93 (0.86-1.00)	.06
Time to CV death	1.01 (0.92-1.11)	.86

GALACTIC HF – Phase 3

- Reduced composite risk of first HF or CV death
  - However, no significant reduction in components of primary endpoint
- KCCQ symptom score change from BL to Wk 24 with omecamtiv mecarbil did not reach multiplicity controlled significance threshold of *P* = .002

ULARITIDE

- Synthetic analog of urodilatin
- Inhibits Na+ reabsorption

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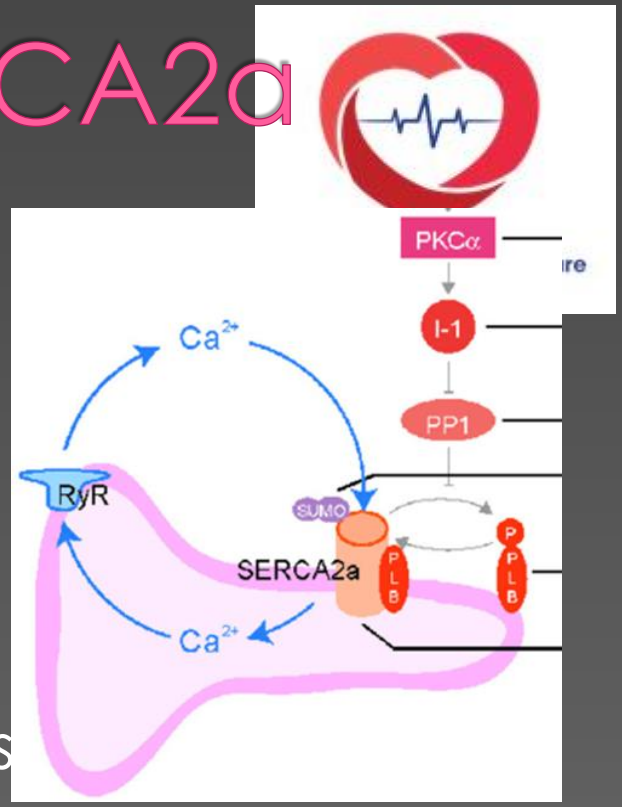
TRUE-AHF was a randomized double-blind parallel group placebo-controlled trial in 2,157 patients

- Effect of **ularitide** on CV mortality and 48-hour clinical status
- The drug produced satisfactory hemodynamic effects such as **reduced SBP and decreased NT-proBNP levels.**

It did not significantly impact any of the primary or secondary outcomes like CV Mortality.

Gene Therapy: SERCA2a

- SERCA2a, is a critical ATPase responsible for Ca2+ re-uptake during excitation–contraction coupling
- The regulation of calcium levels inside cardiomyocytes is often imbalanced in the heart of a person with LV dysfunction, therefore proteins that regulate calcium levels are the main targets of gene therapy
- Supplying a cell with genes for SERCA2a restores the intracellular calcium concentration in different phases of myocardial activity



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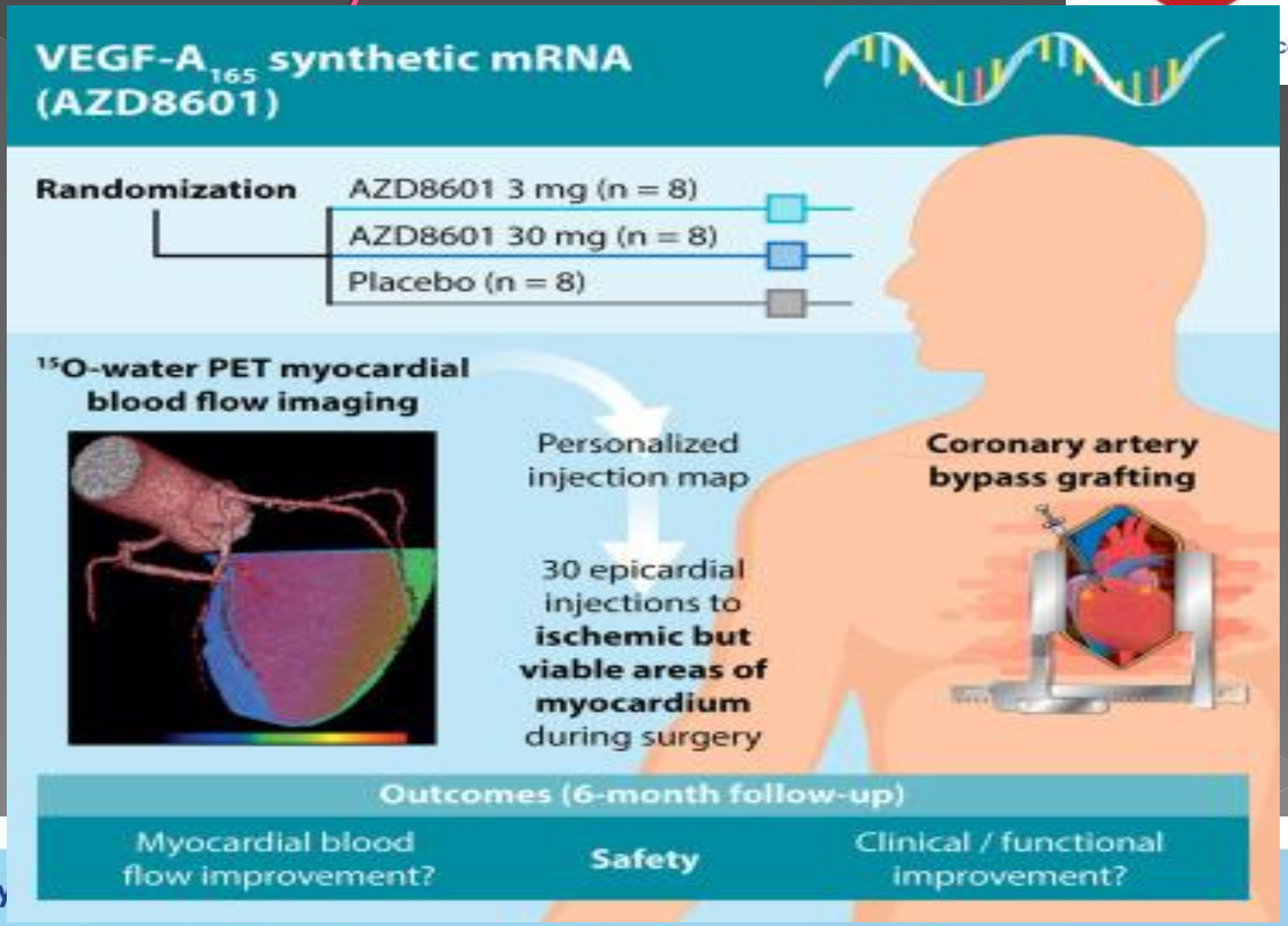
- 12-month observational study concluded that a high-dose treatment significantly decreases the risk of CV events (HR =0.12; P=0.003) and reduces the average time of hospitalization 11-fold vs a placebo (P=0.05).

- An additional 3-year experiment proved that this gene therapy is safe and reduces the risk of CV events.

VEGF synthetic m-RNA



EPICCURE STUDY

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- Preliminary data on adverse events, echocardiography and clinical laboratory findings indicate no safety signals of concern
- ACC November 2021 showed that the primary endpoint of safety and tolerability was met, and exploratory efficacy analyses support further clinical development of *VEGFA* mRNA.

CONCLUSION:

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- The four pillars of Heart Failure therapy are augmented by the SGLT2 inhibitors as the fifth pillar
- HFpEF has unique challenges – with promising results by the SGLT2i and newer drugs
- Vericiguat and Ivabradine are a very valuable addition in HFrEF

MESSAGE

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- Till newer drugs are proven, titrate the GDMT to as much target doses as possible

THANKS FOR YOUR KIND ATTENTION