Presenter Disclosures

***Dr. Gordon Moe* – Presenter**

***Topic:* Management of HFrEF: the old and the new**

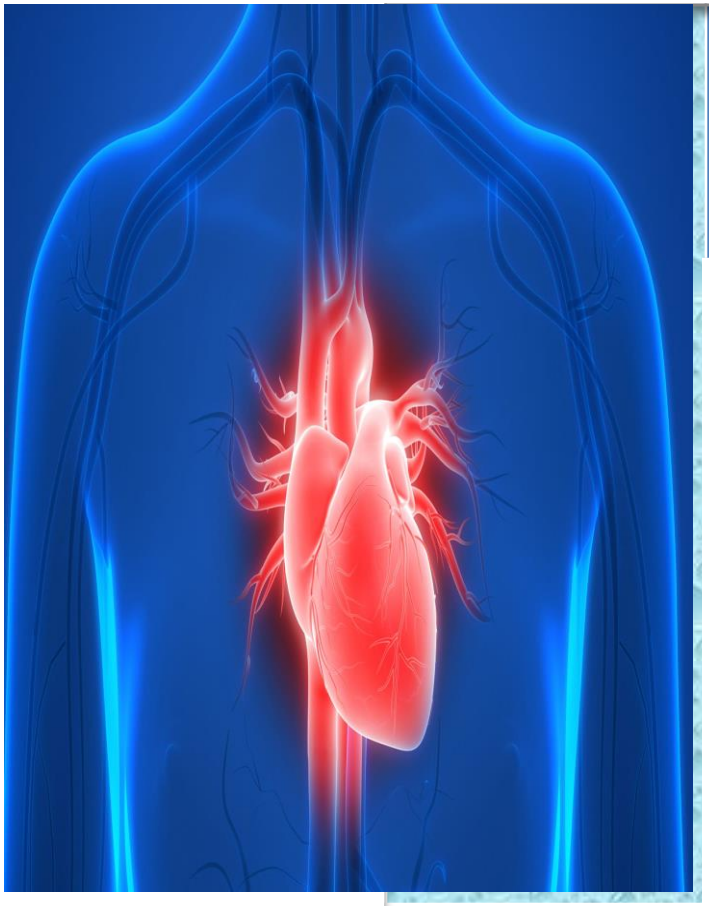
Relationships with financial sponsors:

- **Grants/Research Support:** Novartis, Servier, Merck
- **Speakers Bureau/Honoraria:** Novartis, Servier
- **Consulting Fees:** N/A
- **Patents:** N/A
- **Other:** N/A

Objectives

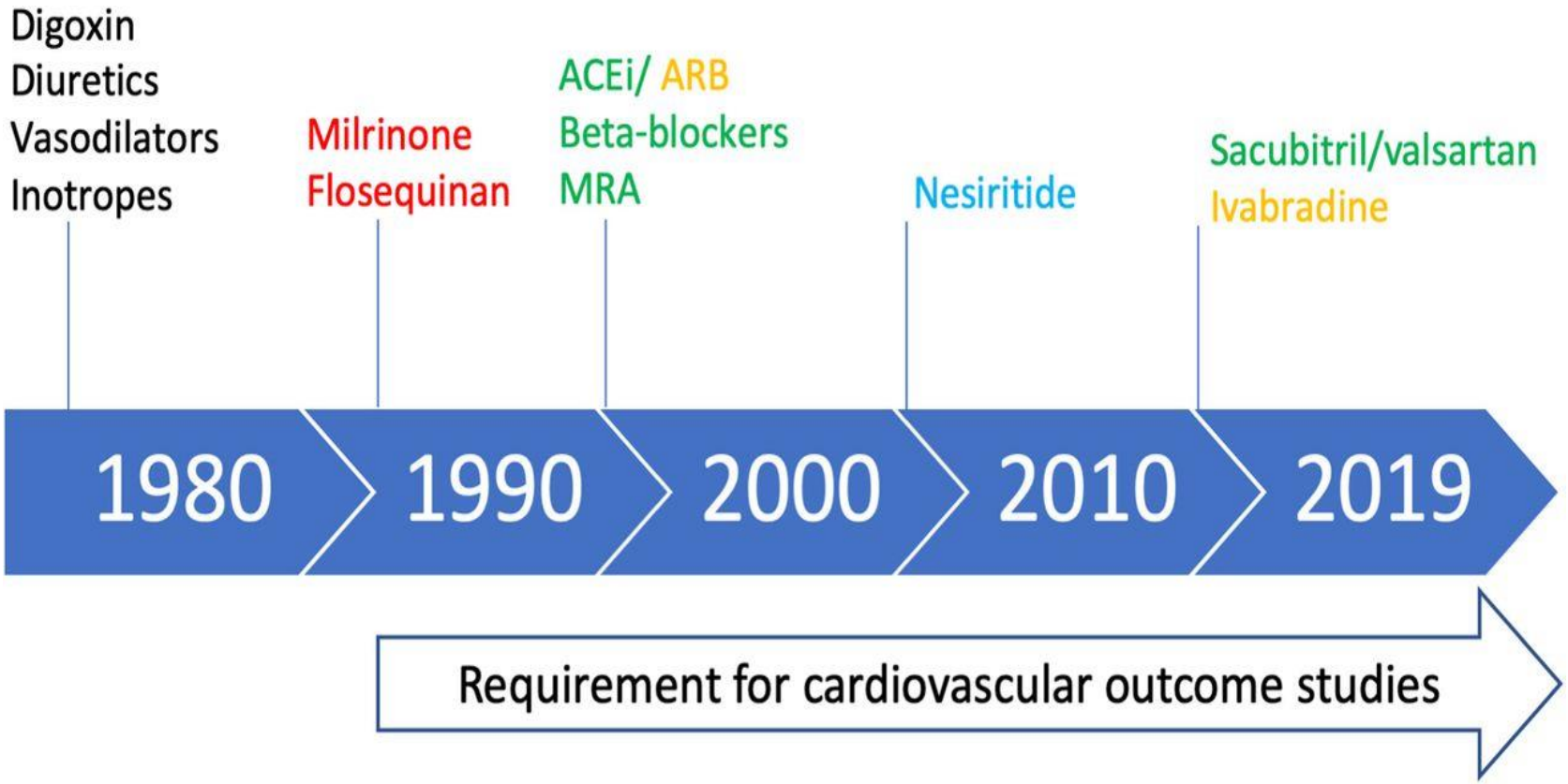
1. Define heart failure and reduced ejection fraction (HFrEF)
2. Review conventional pharmacologic treatments (“ the old”)
3. Review recent, late-breaking and future pharmacologic treatments (“the new”)

Heart Failure and Ejection Fraction



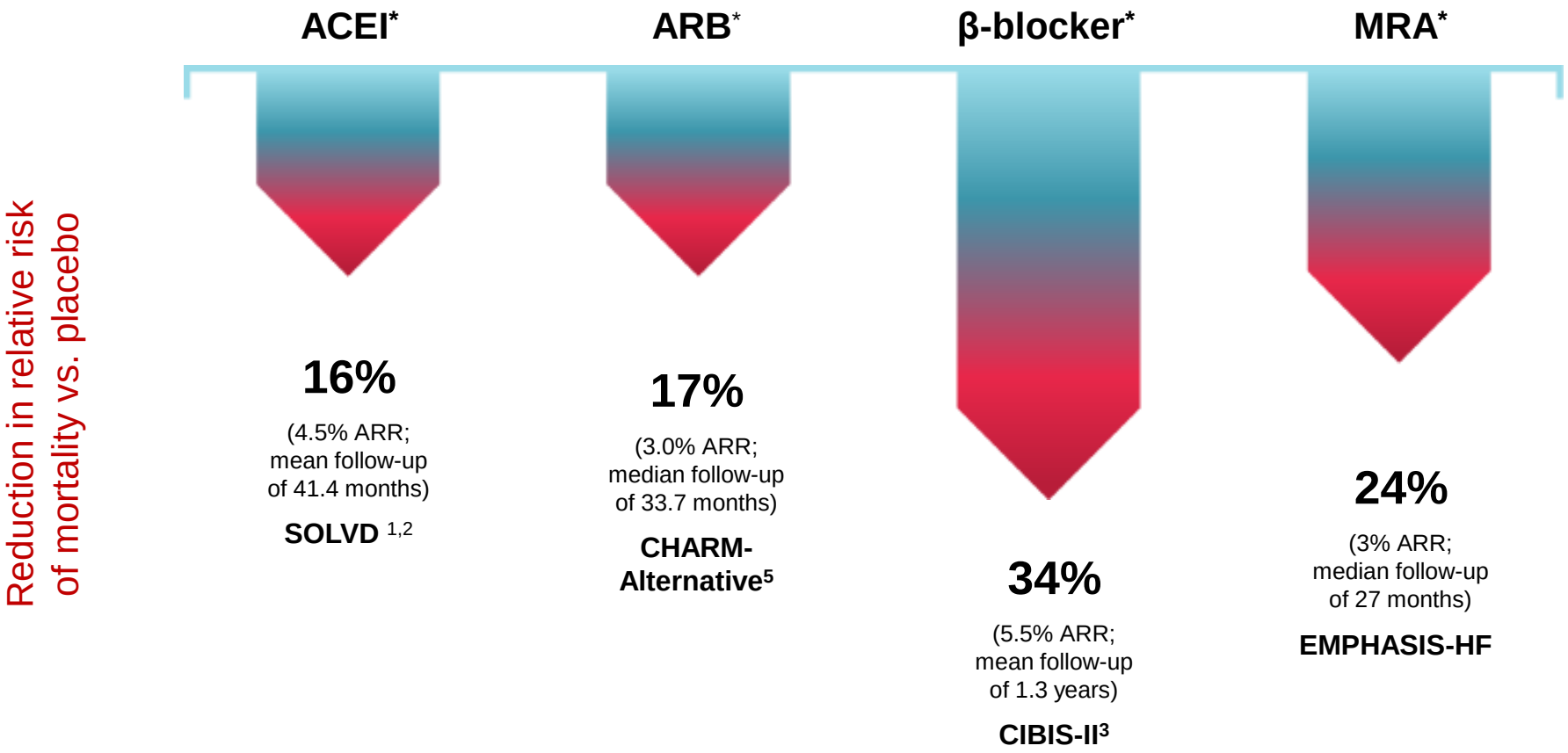
LVEF < 40%	*HFrEF*
LVEF = 40-50%	*HFmrEF*
LVEF > 50%	*HFpEF*

Timeline of Approved Drugs to Treat HF



Mona Fiuzat et al. J Am Coll Cardiol HF 2020;j.jchf.2019.12.011

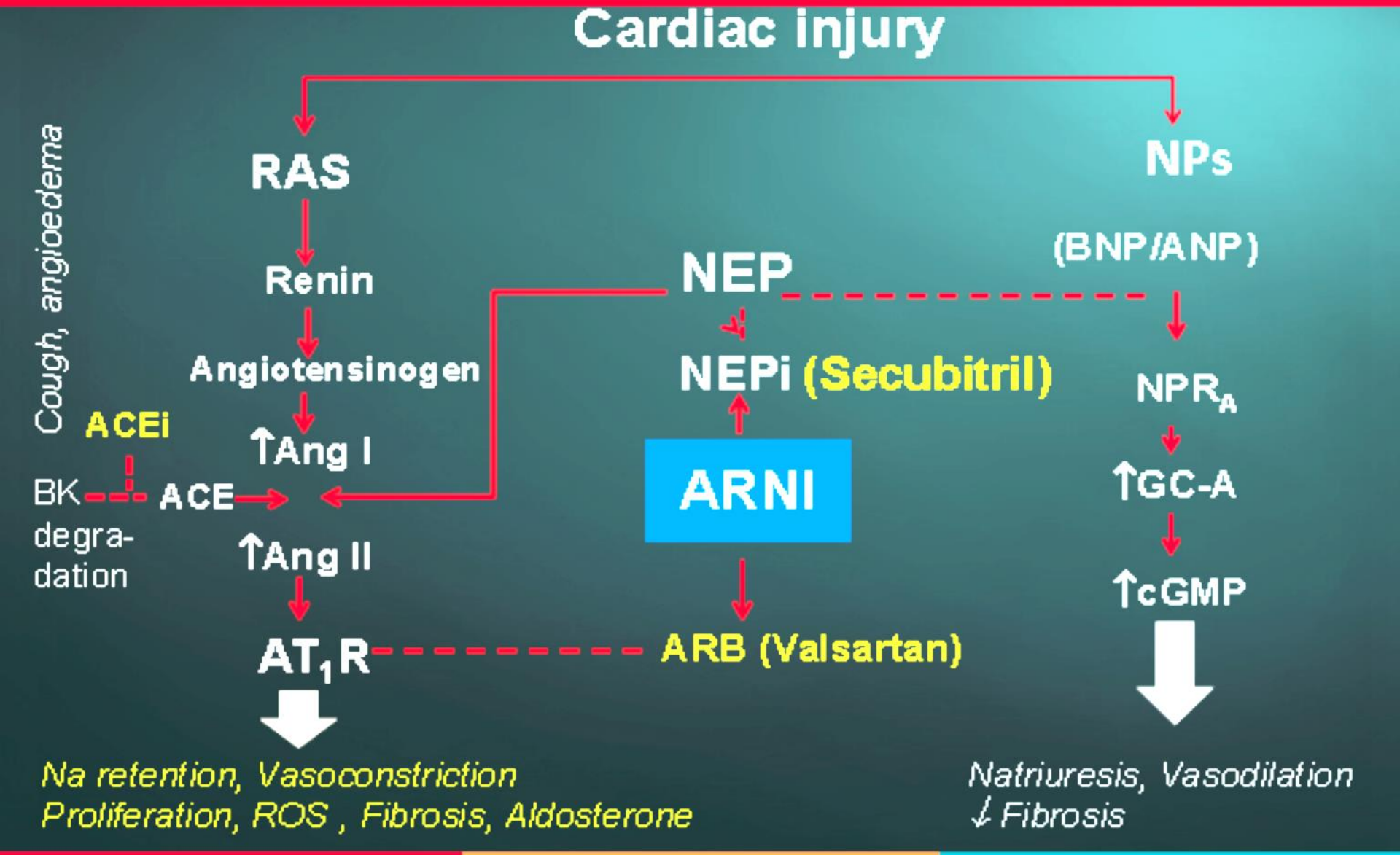
Approved Conventional Treatment of HFrEF: (the "Old")



*On top of standard therapy except in CHARM-Alternative. SOLVD (Studies of Left Ventricular Dysfunction), CIBIS-II (Cardiac Insufficiency Bisoprolol Study II), and EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) enrolled chronic HF patients with LVEF ≤35%. CHARM-Alternative (Candesartan in Heart failure: Assessment of Reduction in Mortality and Morbidity) enrolled chronic HF patients with LVEF ≤40%.
ACEI = angiotensin-converting-enzyme inhibitor; ARB = angiotensin receptor blocker; MRA = mineralocorticoid receptor antagonist

McMurray et al. *Eur Heart J* 2012;33:1787–847; 2. SOLVD Investigators. *N Engl J Med* 1991;325:293–302; 3. CIBIS-II Investigators. *Lancet* 1999;353:9–13; 4. Zannad et al. *N Engl J Med* 2011;364:11-21; 5. Granger et al. *Lancet* 2003;362:772–6.

Angiotensin Receptor Neprilysin Inhibition (ARNI)



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 11, 2014 VOL. 371 NO. 11

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., and Michael R. Zile, M.D., for the PARADIGM-HF Investigators and Committees*

Sacubitril/Valsartan in Patients Hospitalized for HF

ORIGINAL ARTICLE

Angiotensin–Neprilysin Inhibition in Acute Decompensated Heart Failure

Eric J. Velazquez, M.D., David A. Morrow, M.D., M.P.H., Adam D. DeVore, M.D., M.H.S., Carol I. Duffy, D.O., Andrew P. Ambrosy, M.D., Kevin McCague, M.A., Ricardo Rocha, M.D., and Eugene Braunwald, M.D., for the PIONEER-HF Investigators*

Velazquez EJ et al. nejm.org/doi/full/10.1056/NEJMoa1812851

PIONEER-HF: Protocol and Outcome

PIONEER-HF

Study Design

Hospitalized with Acute Decompensated HF with Reduced EF

While hospitalized

Sacubitril/valsartan 97/103 mg twice daily*

vs

Enalapril 10 mg twice daily*

In-hospital initiation

Study Drug for 8 weeks

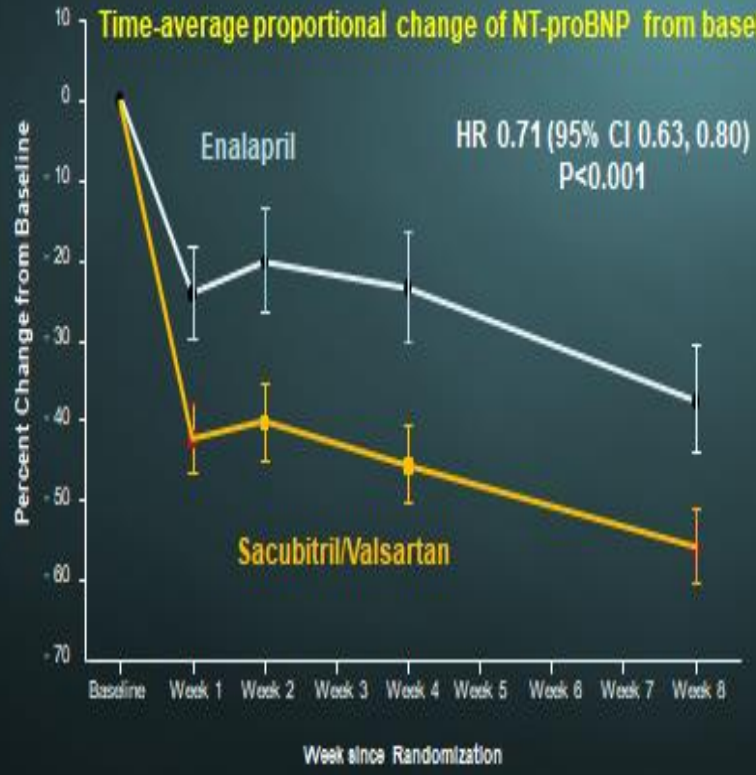
- Evaluate biomarker surrogates of efficacy
- Evaluate safety and tolerability
- Explore clinical outcomes

*Target Dose

Velazquez EJ et al. nejm.org/doi/full/10.1056/NEJMoa1812851

PIONEER-HF

Primary Endpoint



* Percentage (%) change from baseline to mean of weeks 4 and 8

Velazquez EJ et al. nejm.org/doi/full/10.1056/NEJMoa1812851

What does our CCS HF guideline say about ARNI?

Canadian Journal of Cardiology 33 (2017) 1342–1433

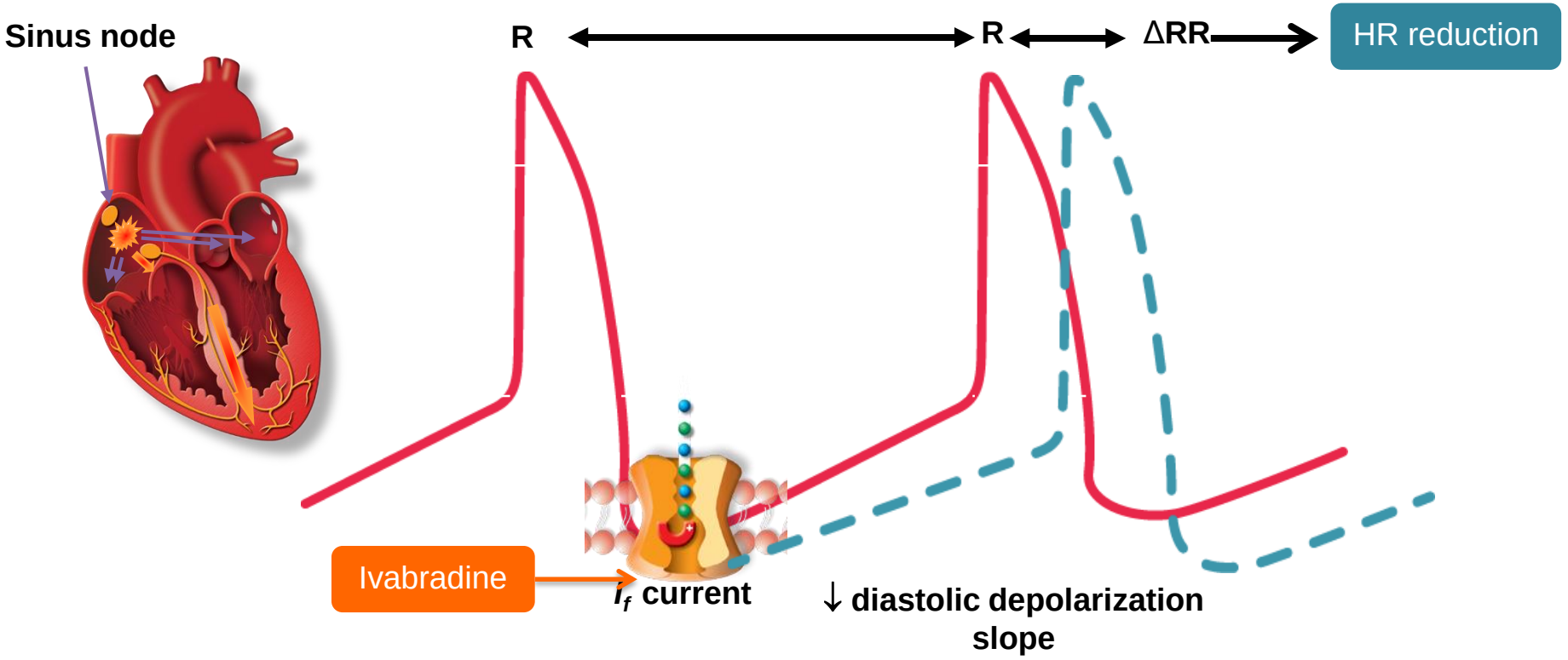
Society Guidelines

2017 Comprehensive Update of the Canadian Cardiovascular Society Guidelines for the Management of Heart Failure

Primary Panel: Justin A. Ezekowitz, MBBCh (Chair),[a] Eileen O'Meara, MD (Co-chair),[b] Michael A. McDonald, MD,[c] Howard Abrams, MD,[c] Michael Chan, MBBS,[d] Anique Ducharme, MD,[b] Nadia Giannetti, MD,[e] Adam Grzeslo, MD,[f] Peter G. Hamilton, MBBCh,[a] George A. Heckman, MD,[g] Jonathan G. Howlett, MD,[h] Sheri L. Koshman, Pharm D,[a] Serge Lepage, MD,[i] Robert S. McKelvie, MD,[j] Gordon W. Moe, MD,[k] Miroslaw Rajda, MD,[l] Elizabeth Swiggum, MD,[m] Sean A. Virani, MD,[n] Shelley Zieroth, MD,[o] **Secondary Panel:** Abdul Al-Hesayen, MD,[k] Alain Cohen-Solal, MD,[p] Michel D'Astous, MD,[q] Sabe De, MD,[j] Estrellita Estrella-Holder, RN,[o] Stephen Fremes, MD,[r] Lee Green, MD,[a] Haissam Haddad, MD,[s] Karen Harkness, RN,[f] Adrian F. Hernandez, MD,[t] Simon Kouz, MD,[u] Marie-Hélène LeBlanc, MD,[v] Frederick A. Masoudi, MD,[w] Heather J. Ross, MD,[c] Andre Roussin, MD,[x] and Bruce Sussex, MBBS[y]

Ivabradine selectively inhibits the I_f current

I_f is the main current of diastolic depolarization that leads to the generation of a new potential action



DiFrancesco & Camm. Drugs 2004; 64 (16): 1757-65

SHIFT Trial: Protocol and Outcomes

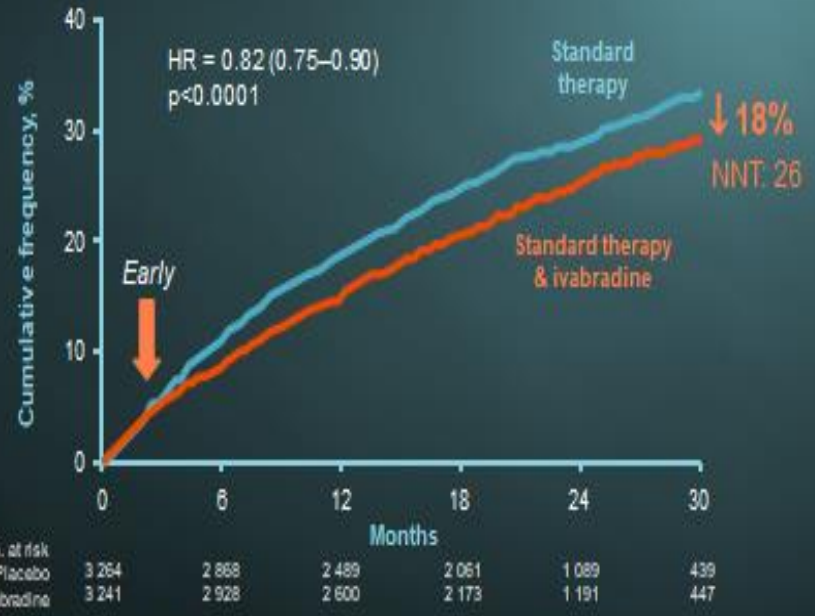
Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial — SHIFT

In 6,505 patients with

- Chronic HFrEF
- Moderate to severe chronic HF symptoms
  - NYHA class II-IV
- Left ventricular ejection fraction ≤ 35%
- HR ≥ 70 bpm
- Sinus rhythm
- Optimal standard therapy

Ivabradine dose: 7.5 mg twice daily
Median study duration: 23 months
Median HR: 77 bpm

CV mortality and HF hospitalization (Primary Endpoint) — SHIFT



- *The curves begin to diverge at 3 months, and the difference is statistically significant at 6 months*

Swedberg et al. Lancet 2010; 376: 875-85.

Swedberg et al. Lancet 2010; 376: 875-85

What does our CCS HF guideline say about Ivabradine?

RECOMMENDATION

We recommend that ivabradine be considered in patients with HFrEF, who remain symptomatic despite treatment with appropriate doses of GDMT, with a resting heart rate > 70 beats per minute (bpm), in sinus rhythm, and a previous HF hospitalization within 12 months, for the prevention of cardiovascular death and HF hospitalization (Strong Recommendation; Moderate-Quality Evidence).

Can J Cardiol 2017;33:1342-1433

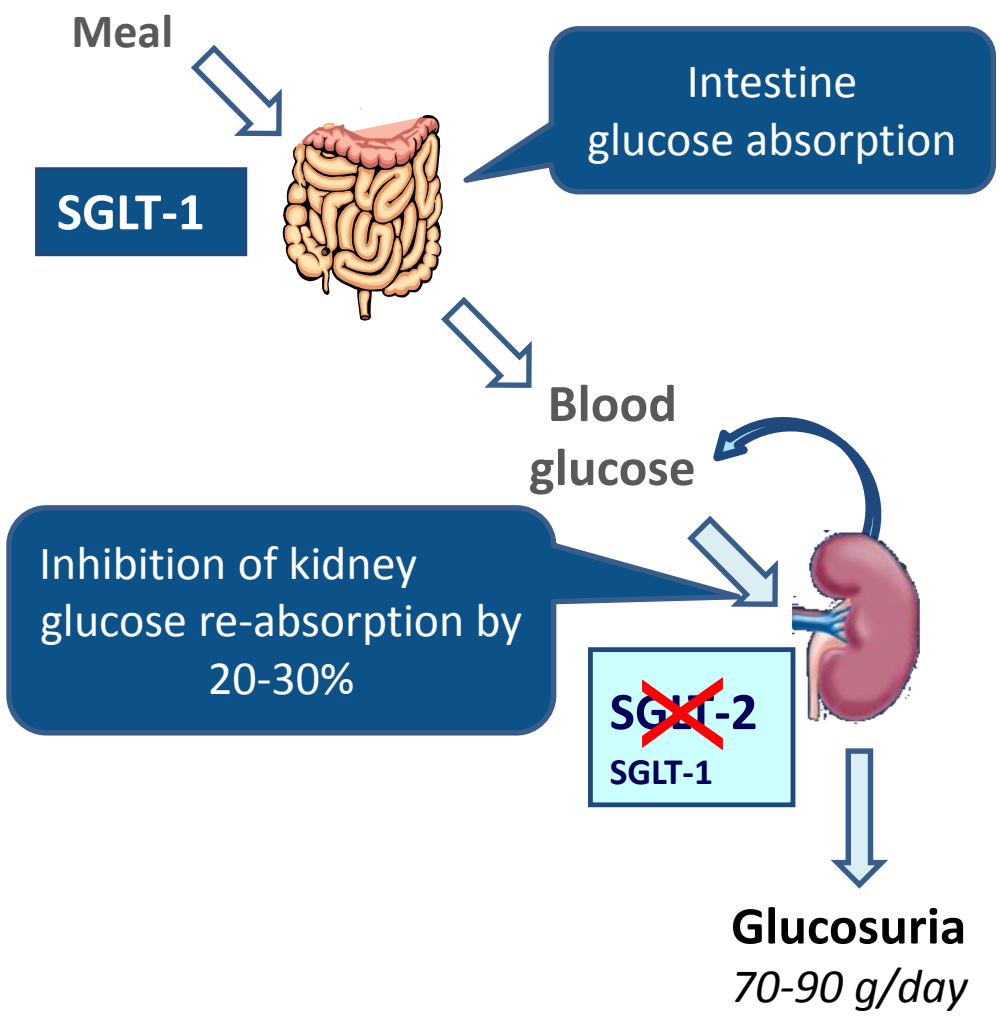
SGLT2 inhibitors

Inhibiting SGLT-2 in the proximal convoluted tubule:

- increases glucosuria
- inhibits renal glucose reabsorption

- causes weight loss
- does not induce hypoglycemia
- reduces blood pressure
- gives CV benefits
- may have renal benefits

- causes osmotic diuresis
- can induce genital mycotic infection
- leads to DKA if insulin too low



Bailey CJ, Day C. Br J Diabetes Vasc Dis 2010; 10: 193-9

Trials of SGLT2 inhibitors on HF Events: "Primary Prevention"

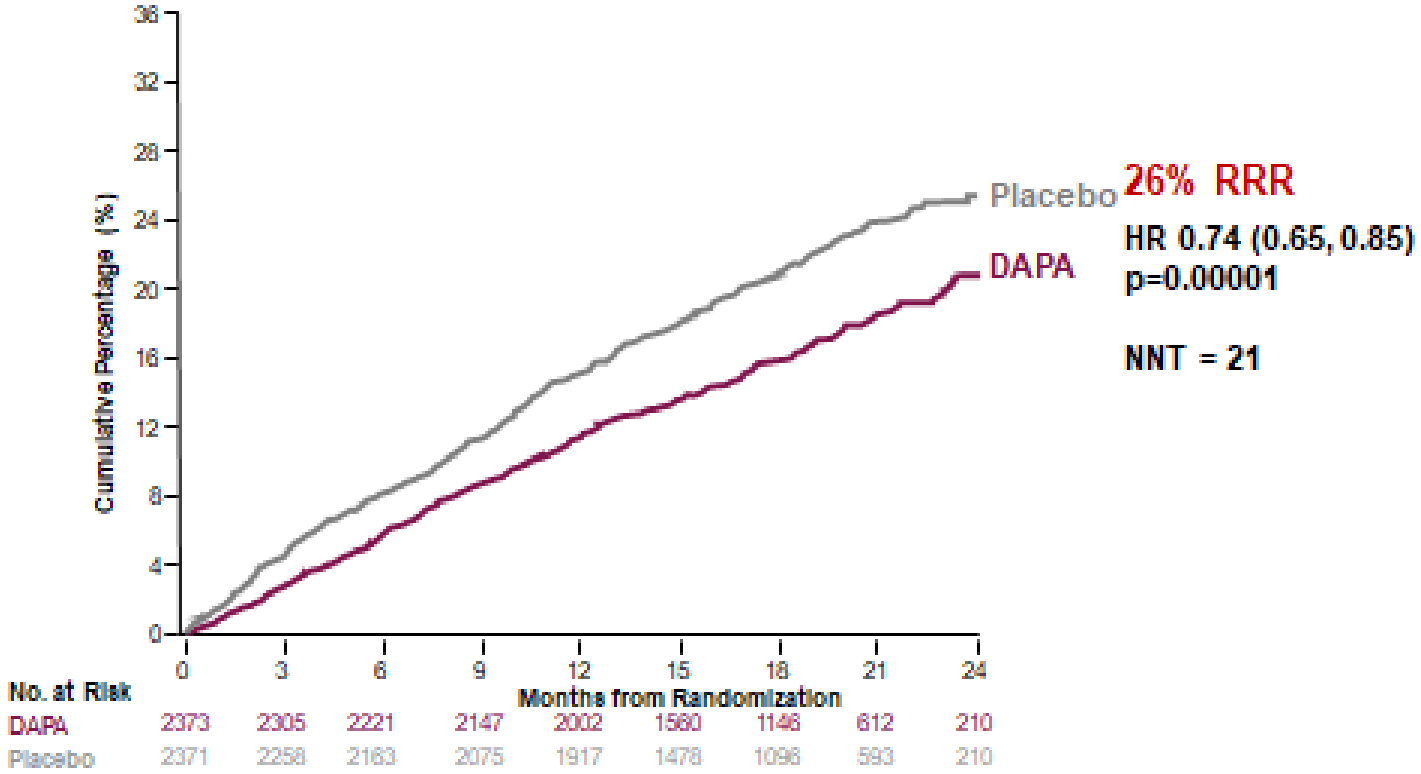
Clinical trials	Patient numbers	HF hospitalization
DM2, multiple risk factors, **no known CVD** EMPA-REG OUTCOME, CANVAS-R, DECLARE-TIMI 58	13,672	0.64 (0.48-0.85)
DM2, **known CVD** Trials as above	20,650	0.71 (0.62-0.82)
DM2 and albuminuric CKD CREDENCE	4,401	0.61 (0.47-0.8)

EMPA -REG OUTCOME, Empagliflozin cardiovascular outcome event trial
CANVAS-R, Canagliflozin cardiovascular assessment study-Renal
DECLARE-TIMI 58, Dapagliflozin effect on cardiovascular event
CREDENCE, Canagliflozin and renal events in diabetes with established nephropathy clinical evaluation

McDonald M, et al. Can J Cardiol 2020;36:159-69

SGLT2 Inhibition in Established HFrEF
DAPA-HF trial: Primary Endpoint

Primary Endpoint: CV Death/HF Hospitalization/Urgent HF Visit

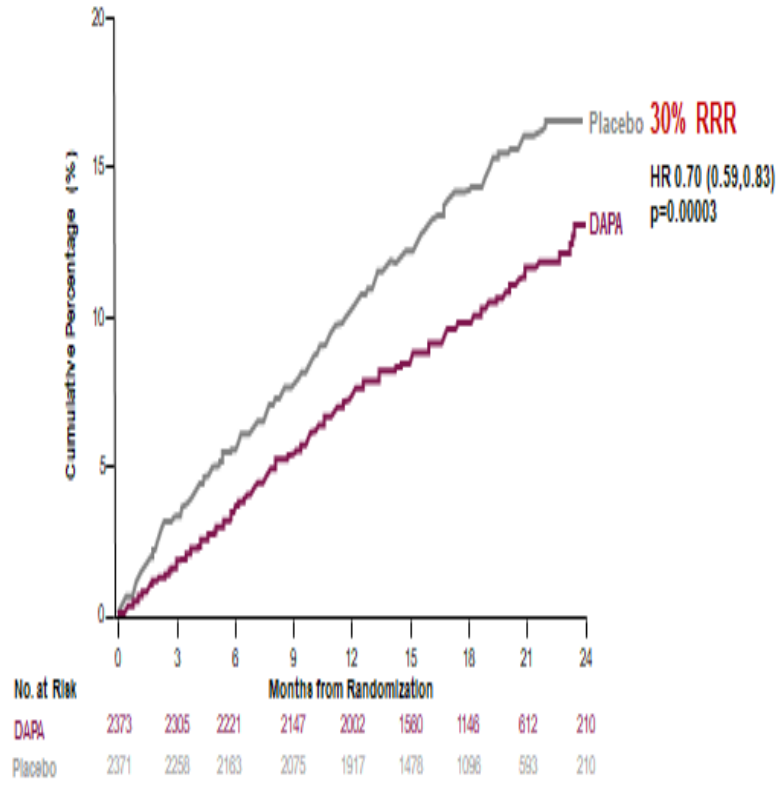


DAPA = dapagliflozin; HF = heart failure; HR = hazard ratio; NNT = number needed to treat.

McMurray J. Presentation at: European Society of Cardiology Congress. September 1, 2019; Paris, France.

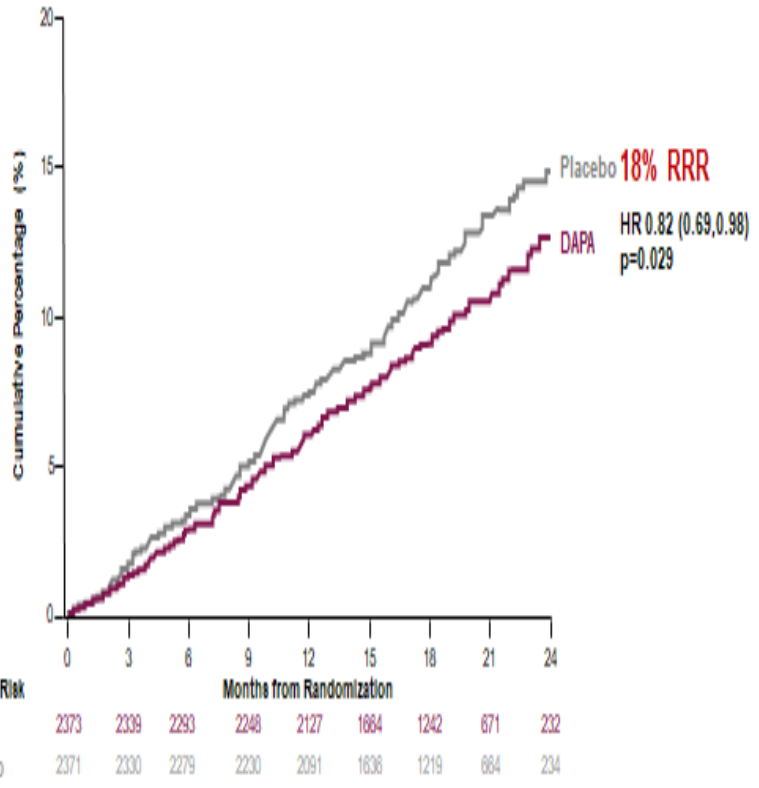
Primary Endpoint Components

Component of Primary Endpoint: Worsening HF Event



DAPA = Dapagliflozin; HF = Heart failure; HR = Hazard ratio.

Component of Primary Endpoint: Cardiovascular Death



DAPA = Dapagliflozin; HR = Hazard ratio.

McMurray J. Presentation at: European Society of Cardiology Congress. September 1, 2019; Paris, France.

What does our CCS HF guideline say about SGLT2 inhibitors?

Canadian Journal of Cardiology 36 (2020) 159–169

Society Guidelines

CCS/CHFS Heart Failure Guidelines: Clinical Trial Update on Functional Mitral Regurgitation, SGLT2 Inhibitors, ARNI in HFpEF, and Tafamidis in Amyloidosis

Primary Panel and Secondary Panel Writing Members: Eileen O'Meara, MD,[a,*] Michael McDonald, MD,[b,*] Michael Chan, MBBS,[c] Anique Ducharme, MD,[a] Justin A. Ezekowitz, MBBCh,[d] Nadia Giannetti, MD,[e] Adam Grzeslo, MD,[f] George A. Heckman, MD,[g] Jonathan G. Howlett, MD,[h] Sheri L. Koshman, PharmD,[d] Serge Lepage, MD,[i] Lisa M. Mielniczuk, MD,[j] Gordon W. Moe, MD,[k] Elizabeth Swiggum, MD,[l] Mustafa Toma, MD,[m] Sean A. Virani, MD,[m] Shelley Zieroth, MD,[n] Sabe De, MD,[o] Sylvain Marteau, MD,[j,p] Marie-Claude Parent, MD,[a] **External Reviewers and Co-authors:** Anita W. Asgar, MD,[a] Gideon Cohen, MD,[q] Nowell Fine, MD,[r] Margot Davis, MD,[m] Subodh Verma, MD,[s] David Cherney, MD,[t] **Secondary Panel:** Howard Abrams, MD,[u] Abdul Al-Hesayen, MD,[k] Alain Cohen-Solal, MD,[v] Michel D'Astous, MD,[w] Diego H. Delgado, MD,[u] Olivier Desplantie, MD,[x] Estrellita Estrella-Holder, RN,[y] Lee Green, MD,[d] Haissam Haddad, MD,[z] Karen Harkness, RN,[aa] Adrian F. Hernandez, MD,[bb] Simon Kouz, MD,[cc] Marie-Hélène LeBlanc, MD,[dd] Douglas Lee, MD,[u] Frederick A. Masoudi, MD,[ee] Robert S. McKelvie, MD,[ff] Miroslaw Rajda, MD,[gg] Heather J. Ross, MD,[b] and Bruce Sussex, MBBS[hh]

CCS HF guideline recommendations on SGLT2 inhibitors?

5. **Updated.** We recommend SGLT2 inhibitors, such as empagliflozin, canagliflozin or dapagliflozin, be used for treatment of patients with type 2 diabetes and atherosclerotic cardiovascular disease to reduce the risk of HF hospitalization and death (Strong Recommendation, High-Quality Evidence).

6**. New.** We recommend SGLT2 inhibitors, such as dapagliflozin be used in patients with type 2 diabetes aged > 50 years with additional risk factors for atherosclerotic cardiovascular disease to reduce the risk of HHF (Strong High-Quality).

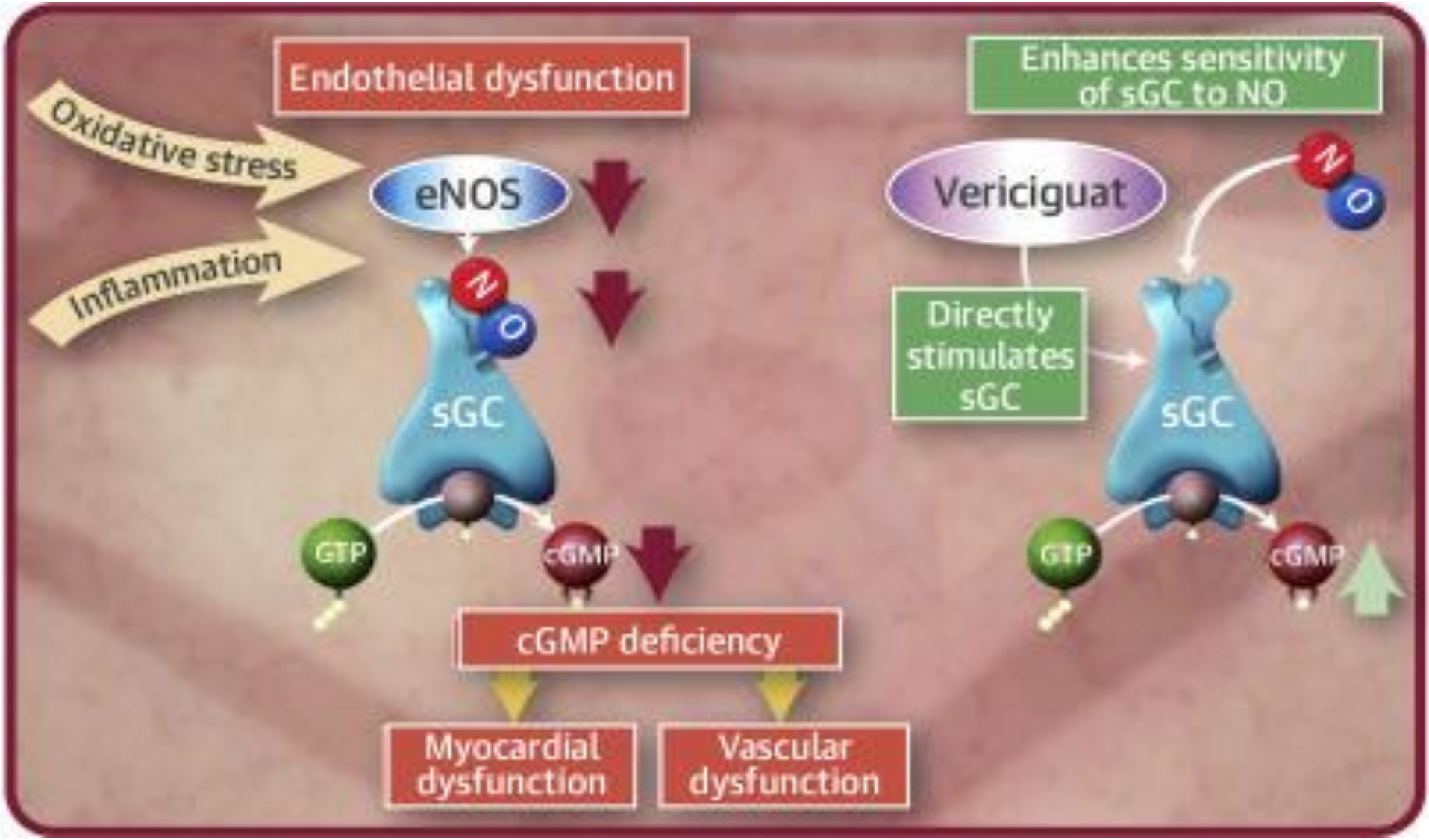
7. **New**. We recommend SGLT2 inhibitors, such as canagliflozin, be used in patients aged > 30 years with type 2 diabetes, and macroalbumineric renal disease, to reduce the risk of HF hospitalization and progression of renal disease (Strong, High-Quality).

8. **New.** We recommend SGLT2 inhibitors, such as dapagliflozin be used in patients with mild to moderate HF due to reduced LVEF (≤ 40%) and concomitant type 2 diabetes, to improve symptoms and quality of life and to reduce the risk of hospitalization and cardiovascular mortality (Strong, High-Quality).

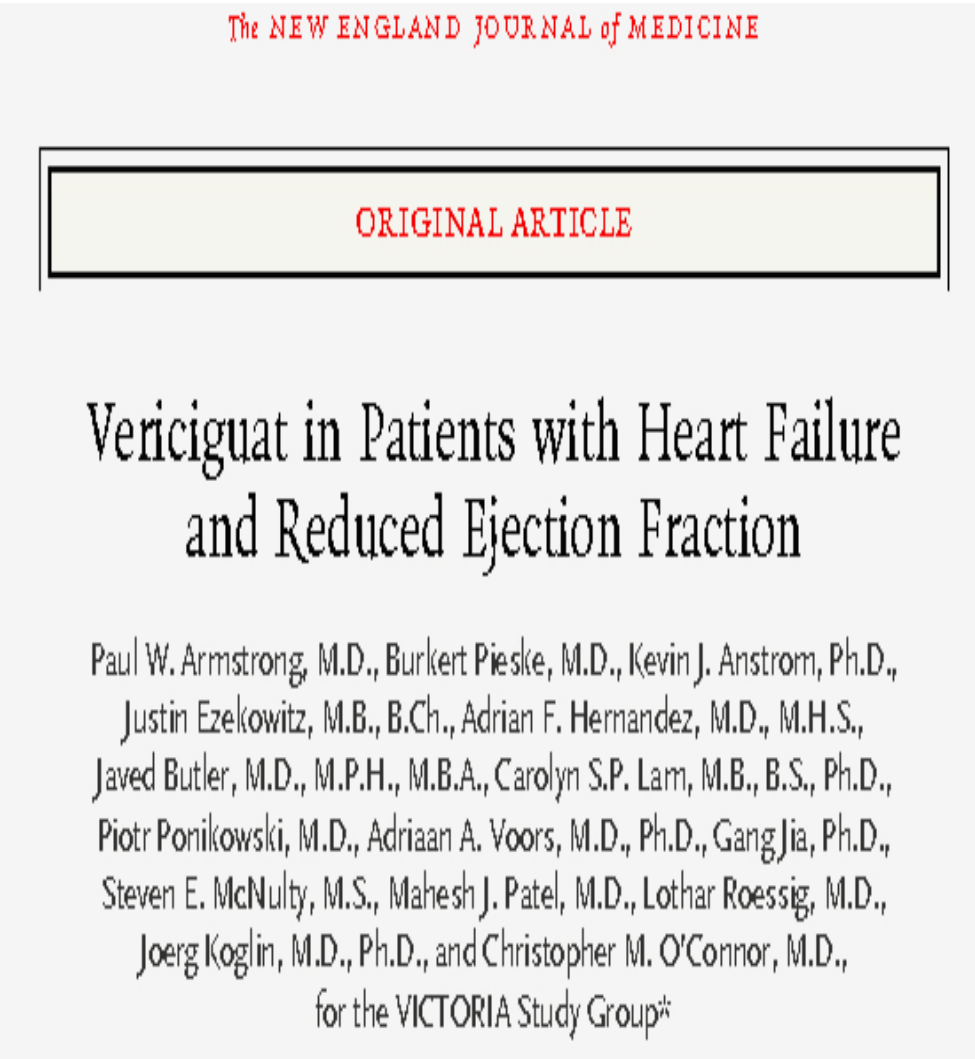
9. **New.** We recommend SGLT2 inhibitors, such as dapagliflozin be used in patients with mild to moderate HF due to reduced LVEF (40%) and without concomitant diabetes, to improve symptoms and quality of life and to reduce the risk of hospitalization and cardiovascular mortality (Conditional Recommendation, High-Quality Evidence).

McDonald M et al. Can J Cardiol 2020;36:159-69

Vericiguat: Mechanisms of Actions



The VICTORIA Study



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

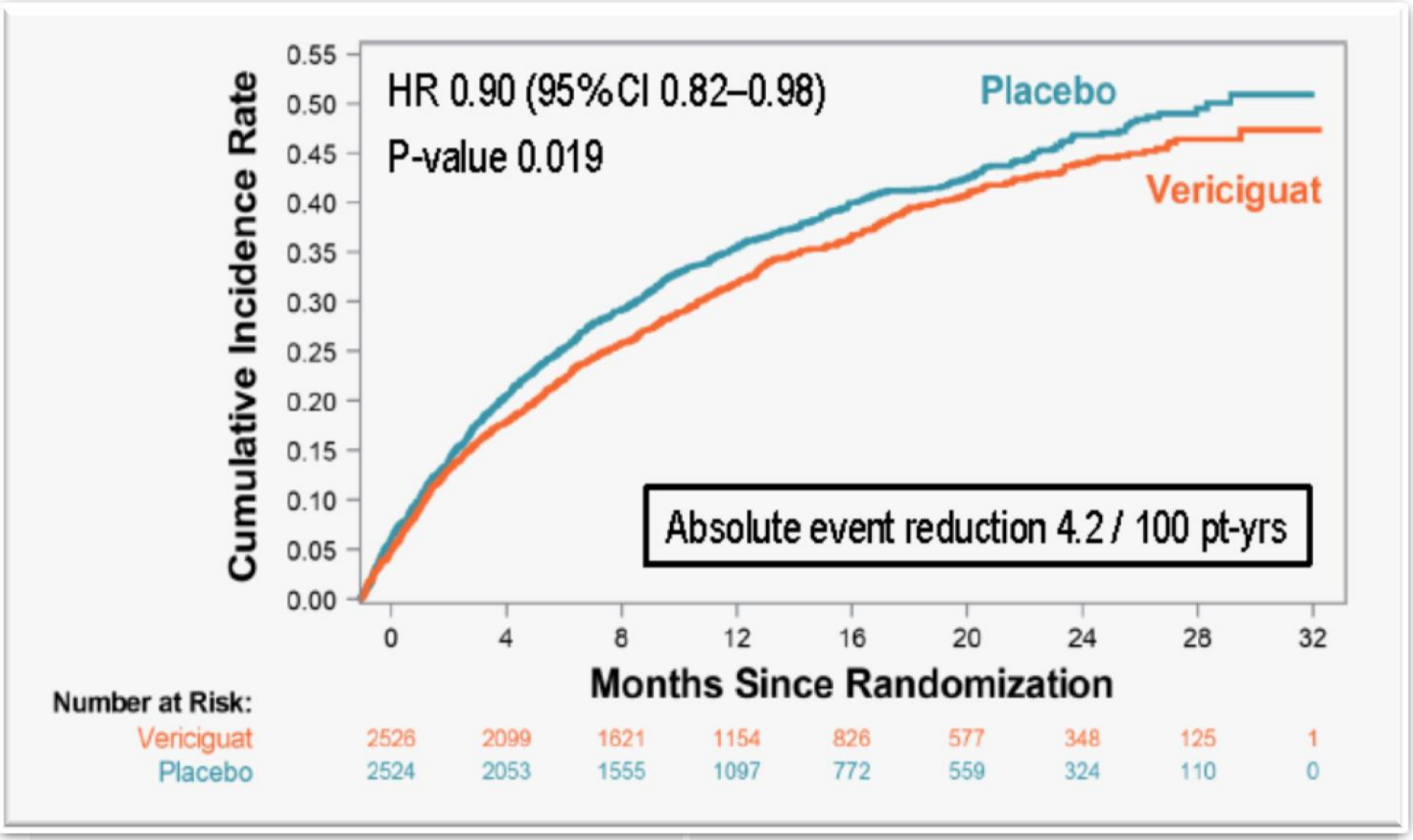
Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction

Paul W. Armstrong, M.D., Burkert Pieske, M.D., Kevin J. Anstrom, Ph.D., Justin Ezekowitz, M.B., B.Ch., Adrian F. Hernandez, M.D., M.H.S., Javed Butler, M.D., M.P.H., M.B.A., Carolyn S.P. Lam, M.B., B.S., Ph.D., Piotr Ponikowski, M.D., Adriaan A. Voors, M.D., Ph.D., Gang Jia, Ph.D., Steven E. McNulty, M.S., Mahesh J. Patel, M.D., Lothar Roessig, M.D., Joerg Koglin, M.D., Ph.D., and Christopher M. O'Connor, M.D., for the VICTORIA Study Group*

- Phase 3, RCT trial
- 5050 patients with chronic HF (NYHA class II, III, or IV)
- LVEF <45%
- HF hospitalization or IV diuretic Rx 3-6 months
- Vericiguat (target dose, 10 mg daily) or placebo, in addition to guideline-directed therapy
- 1° outcome CV death, 1st HF hospitalization

DOI: 10.1056/NEJMoa1915928

VICTORIA Study: Primary Endpoints



Ongoing Trials in HFrEF

GALACTIC-HF	Omecamtiv Mecarbil
EMPEROR-Reduced	Empagliflozin
HEART-FID	IV Ferric Carboxymaltose

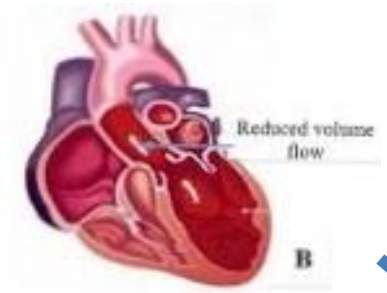
Cardiology for the Practitioner
Saturday, May 02, 2020

Management of HFrEF: The Old and the New

Summary and Conclusions

ST. MICHAEL'S
UNITY HEALTH TORONTO

Pharmacologic Management of HFrEF 2020



SGLT2 inhibitors

ACEI/ARB
Switch/Start ARNI

β-blockers

MRA

± Ivabradine

SGLT2 inhibitors

Tips, pitfalls and red flags for family physicians caring for patients with cardiovascular disease during the COVID-19 pandemic

Heart failure patients

Do not discontinue ACEI/ARB/Entresto in patients with heart failure in order to reduce the risk of contracting COVID-19, nor in people with confirmed/suspected COVID-19. There is no evidence to support this and doing so may lead to worsening heart failure. See the CCS RRT document on COVID-19 and cardiovascular medications.