5th IHEF CARD

The 5th Indonesian Symposium on Heart Failure and Cardiometabolic Disease

Indonesian Working Group on Heart Failure and Cardiometabolic Disease

WHFS World Heart Failure Society

HEART FAILURE SOCIETY (SINGAPORE)

ARNI as Fundamental Building Block in GDMT

Nana Maya Suryana
Persahabatan Hospital, Jakarta

June, 12-14 2025

Sheraton Grand Jakarta Gandaria City, Jakarta, Indonesia

0811-1900-8855 | scientific_ihefcard@inahfcarmet.org | @ina.hf | ihefcard.com

Disclosure

- Supported by Novartis

There is significant unmet need in Heart Failure

~64M
Estimated **HFrEF** patients globally[1,2]

50% mortality at **5 years** in EU and US[3]

Survival is worse than for breast, prostate or bowel **cancer**[4]

More than
1 million
Hospitalization for HF occur each year in the US and Europe alone[4]

>50% patients are **rehospitalized** for heart failure within **6** months of discharge

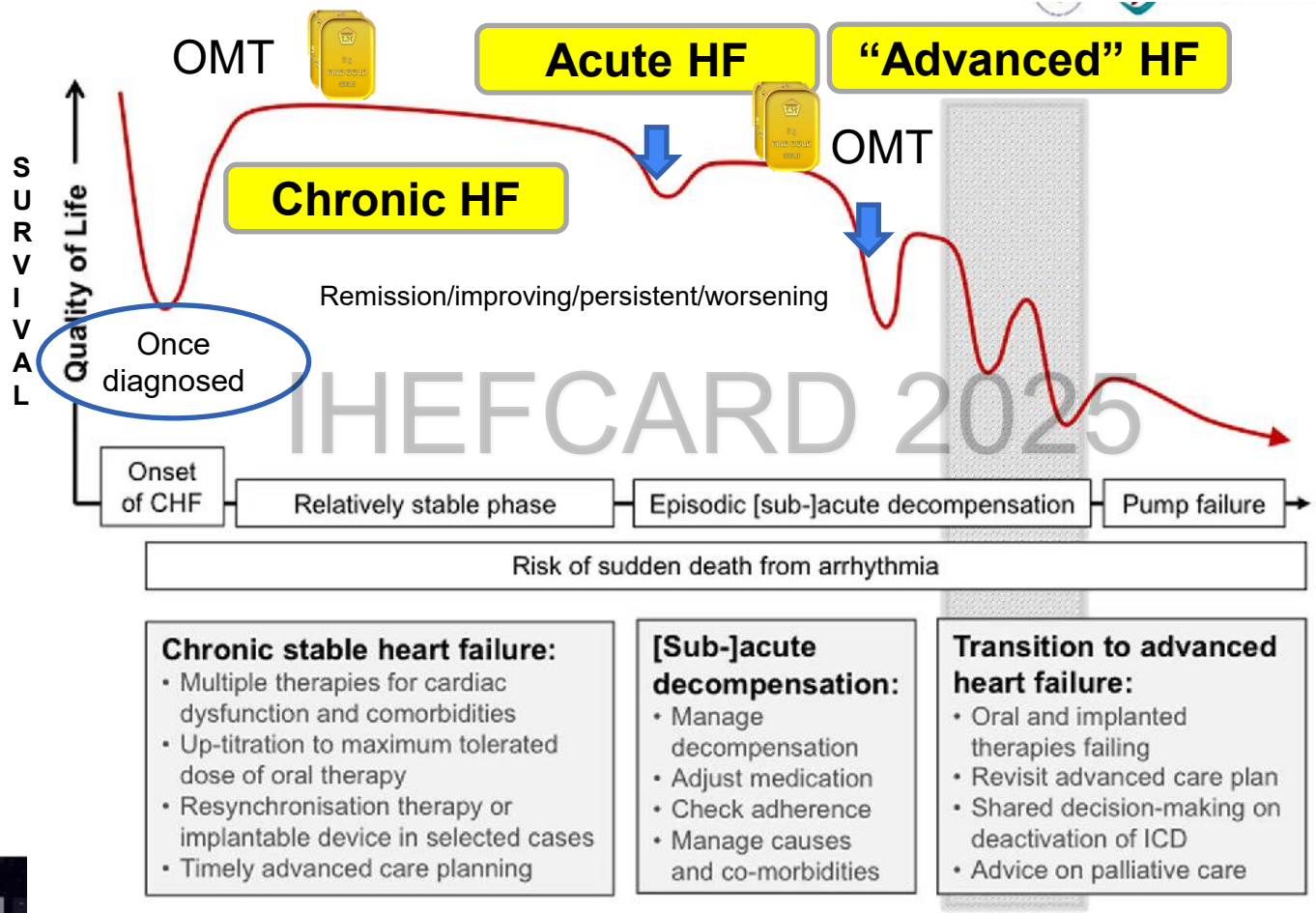
HF imposes a huge **Global economic burden**, estimated at **$108 billion** per annum[5].

BP, renal function, serum potassium, low HR are main physiological factors **limiting uptitration of SoC therapies**

9 out of **10**
patients, even with standard of care, **remain symptomatic**[6]

1. James et al. *Lancet*. 2018;392:1789-1858. 2. Savarese and Lund. *Card Fail Rev*. 2017;3:7-11) 3. Jones NR et al. Eur J Heart Fail. 2019;21(11):1306-1325
4. World Heart Failure Alliance. 2014. 5. Cook et al. *Int J Cardiol. 2014;171(3):368-376.6. Komajda M et al. Eur J Heart Fail 2019; 21, 921–929*

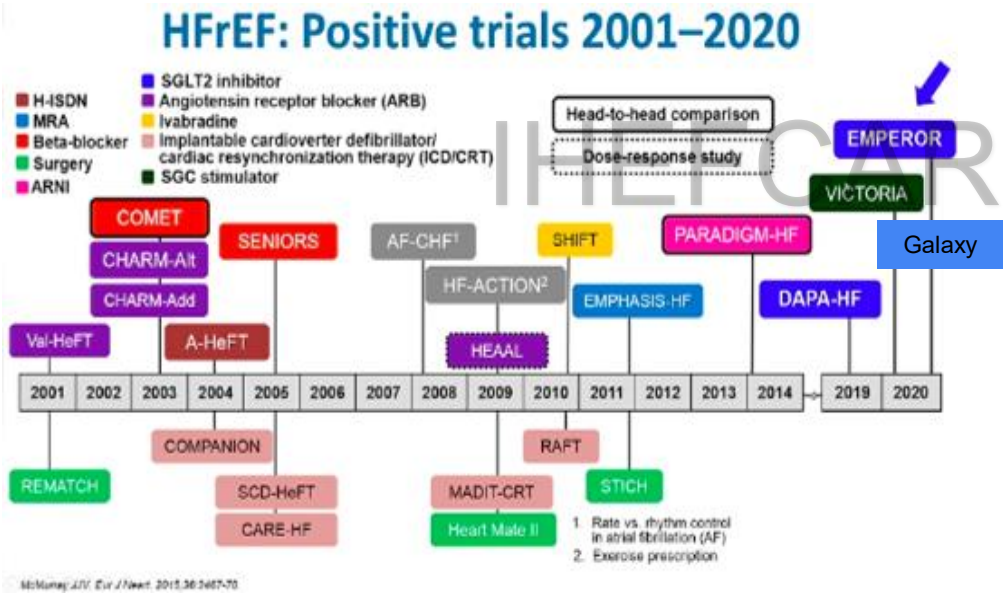
Heart Failure Trajectory – Progressing in Time



Hollenberg SM, et al.
J Am Coll Cardiol. 2019

What's the problem?

DESPITE these tremendous studies result …



Patient related factors (30%)

Physician related factors (50%)

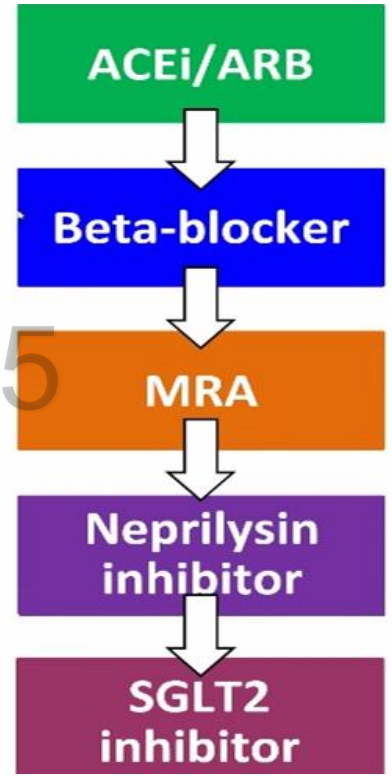
System related factors (20%)

Clinical inertia Underutilized GDMT

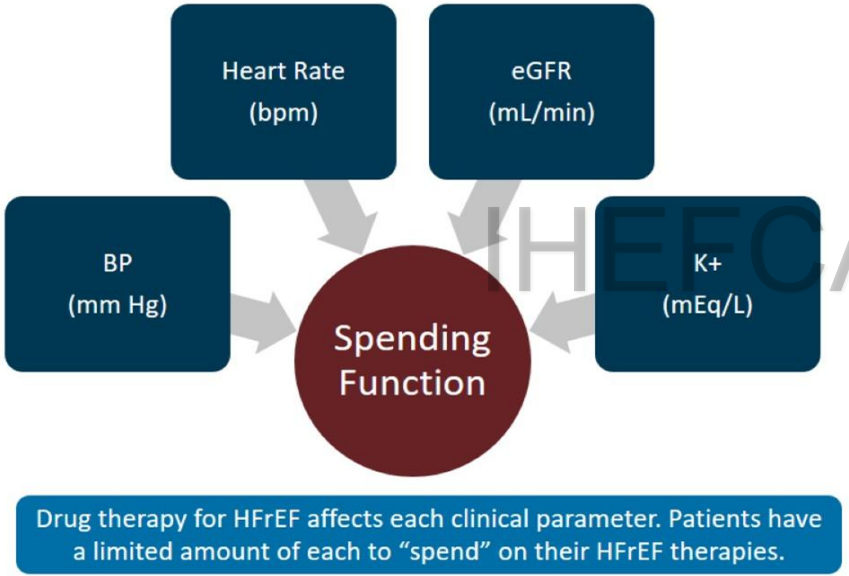
Sequencing is not important in optimizing HF treatment

Conventional treatment approach

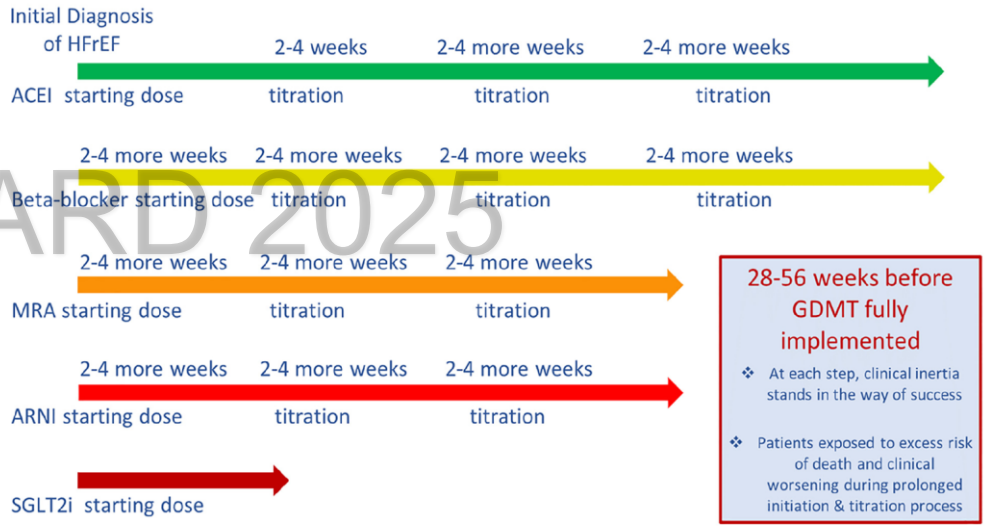
- Vertical, stepwise
- Titrate to full dose of each drug before adding next
- **Chronological approach – based on order completion of trials**
- **Not based on biological disorder approach**



Traditional HF treatment approach :
Concentrate on optimizing 1 or 2 meds before go to the next steps

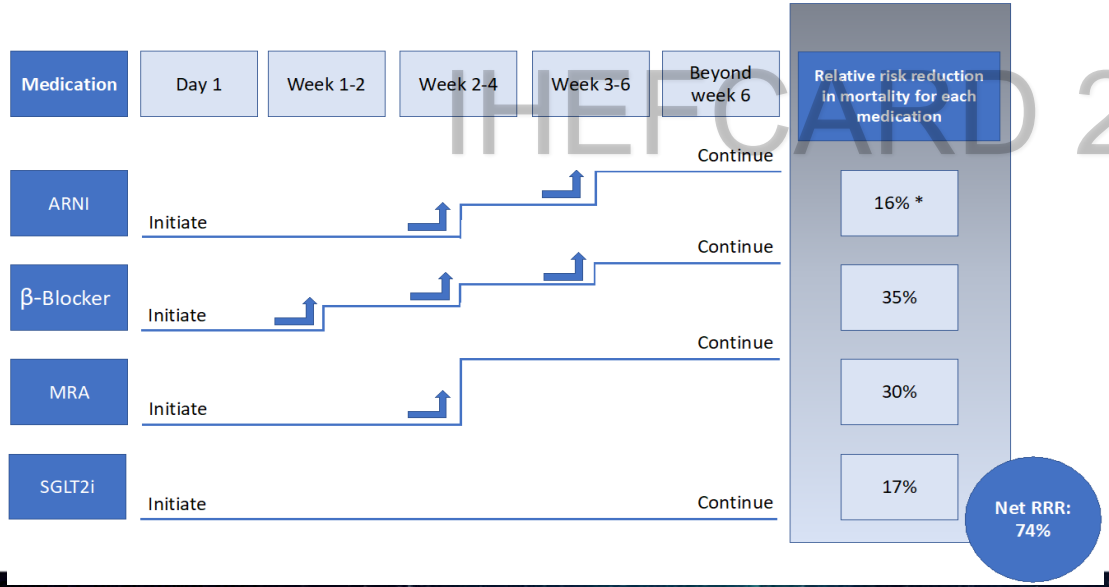


SPENDING TIME…



Can All 4 pillars drugs be started at the same time ?

Simultaneous or Rapid Sequence Initiation of Quadruple Medical Therapy for Heart Failure—Optimizing Therapy With the Need for Speed



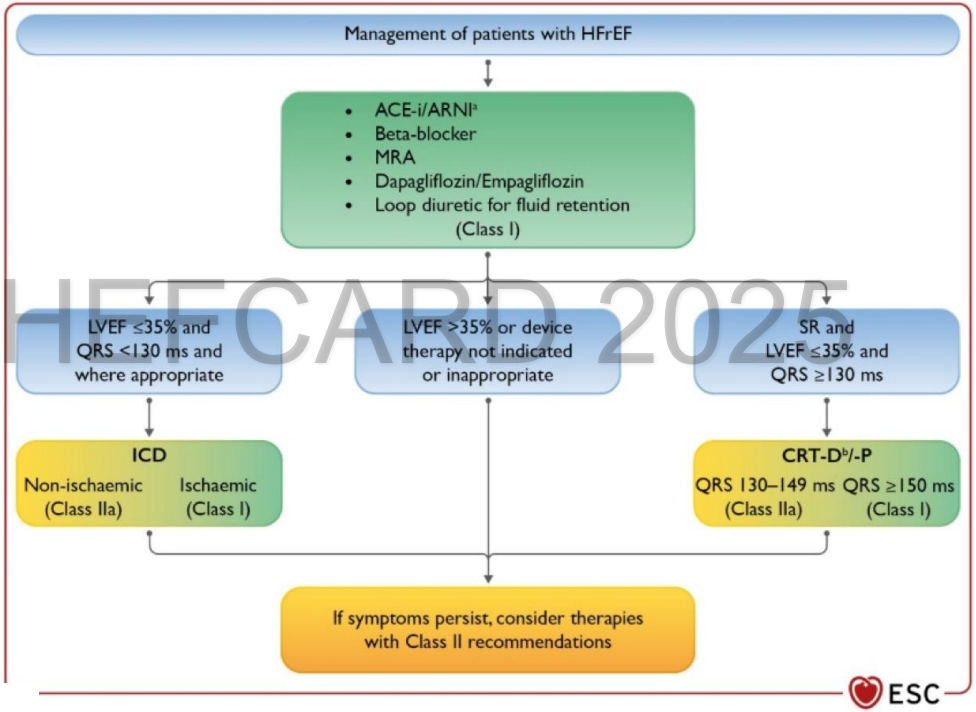
WHAT DO EXPERT SAY ?

- **Ensure All 4 drugs are started**
- **Minimize the possibility of clinical inertia**

Tolerability :

- **2 of 4 can affect BP**
- **Starting MRA and ARNI can increase hyper K**
- **Difficult to sort out an AE**

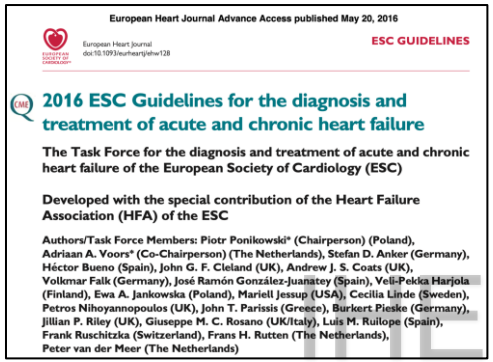
Heart Failure with Reduced EF



2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure, doi:10.1093/eurheartj/ehab368

The 5th Indonesian Symposium on Heart Failure and Cardiometabolic Disease

ARNI position on guideline recommendation



European Heart Journal Advance Access published May 20, 2016

European Heart Journal doi:10.1093/eurheartj/ehw128

ESC GUIDELINES

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

Developed with the special contribution of the Heart Failure Association (HFA) of the ESC

Authors/Task Force Members: Piotr Ponikowski* (Chairperson) (Poland), Adriaan A. Voors* (Co-Chairperson) (The Netherlands), Stefan D. Anker (Germany), Héctor Bueno (Spain), John G. F. Cleland (UK), Andrew J. S. Coats (UK), Volkmar Falk (Germany), José Ramón González-Juanatey (Spain), Veli-Pekka Harjola (Finland), Ewa A. Jankowska (Poland), Mariell Jessup (USA), Cecilia Linde (Sweden), Petros Nihoyannopoulos (UK), John T. Parissis (Greece), Burkert Pieske (Germany), Jillian P. Riley (UK), Giuseppe M. C. Rosano (UK/Italy), Luis M. Ruilope (Spain), Frank Ruschitzka (Switzerland), Frans H. Rutten (The Netherlands), Peter van der Meer (The Netherlands)

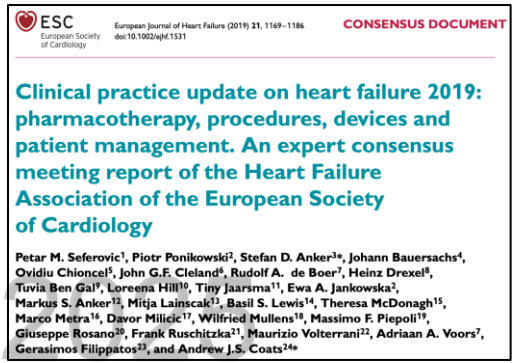
ELSEVIER

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,[g] 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,[r] Estrellita Estrella-Holder, RN,[o] Stephen Fremes, MD,[s] Lee Green, MD,[k] Haissam Haddad, MD,[t] Karen Harkness, RN,[r] Adrian F. Hernandez, MD,[c] Simon Kouz, MD,[u] Marie-Hélène LeBlanc, MD,[v] Frederick A. Masoudi, MD,[w] Heather J. Ross, MD,[x] Andre Roussin, MD,[y] and Bruce Sussex, MBBS[z]



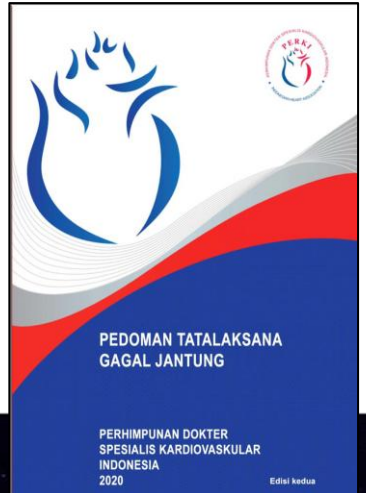
ESC European Society of Cardiology

European Journal of Heart Failure (2019) 21, 1169–1186 doi:10.1002/ejhf.1531

CONSENSUS DOCUMENT

Clinical practice update on heart failure 2019: pharmacotherapy, procedures, devices and patient management. An expert consensus meeting report of the Heart Failure Association of the European Society of Cardiology

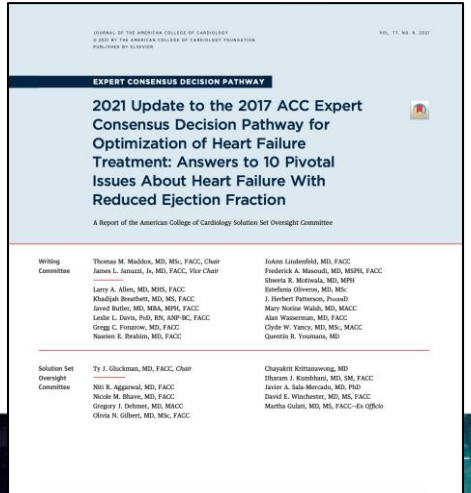
Petar M. Seferovic[1], Piotr Ponikowski[2], Stefan D. Anker[3]*, Johann Bauersachs[4], Ovidiu Chioncel[5], John G.F. Cleland[6], Rudolf A. de Boer[7], Heinz Drexel[8], Tuvia Ben Gal[9], Loreena Hill[10], Tiny Jaarsma[11], Ewa A. Jankowska[2], Markus S. Anker[12], Mitja Lainscak[13], Basil S. Lewis[14], Theresa McDonagh[15], Marco Metra[16], Davor Milicic[17], Wilfried Mullens[18], Massimo F. Piepoli[19], Giuseppe Rosano[20], Frank Ruschitzka[21], Maurizio Volterrani[22], Adriaan A. Voors[7], Gerasimos Filippatos[23], and Andrew J.S. Coats[24]*



PEDOMAN TATALAKSANA GAGAL JANTUNG

PERHIMPUNAN DOKTER SPESIALIS KARDIOVASKULAR INDONESIA 2020

Edisi kedua



JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 77, NO. 6, 2021

EXPERT CONSENSUS DECISION PATHWAY

2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure With Reduced Ejection Fraction

A Report of the American College of Cardiology Solution Set Oversight Committee

Writing Committee: Thomas M. Maddox, MD, MSc, FACC, *Chair*; James L. Januzzi, Jr, MD, FACC, *Vice Chair*; Larry A. Allen, MD, MHS, FACC; Khadijah Breathett, MD, MS, FACC; Javed Butler, MD, MBA, MPH, FACC; Leslie L. Davis, PsD, RN, ANP-BC, FACC; Gregg C. Fonarow, MD, FACC; Nasrien E. Ibrahim, MD, FACC; JoAnn Lindenfeld, MD, FACC; Frederick A. Masoudi, MD, MSPH, FACC; Shweta R. Motiwala, MD, MPH; Estefanía Oliveros, MD, MSc; J. Herbert Patterson, PharmD; Mary Norine Walsh, MD, MACC; Alan Wasserman, MD, FACC; Clyde W. Yancy, MD, MSc, MACC; Quentin R. Youmans, MD

Solution Set Oversight Committee: Ty J. Gluckman, MD, FACC, *Chair*; Niti R. Aggarwal, MD, FACC; Nicole M. Bhave, MD, FACC; Gregory J. Dehmer, MD, MACC; Olivia N. Gilbert, MD, MSc, FACC; Chayakrit Krittanawong, MD; Dharam J. Kumbhani, MD, SM, FACC; Javier A. Sala-Mercado, MD, PhD; David E. Winchester, MD, MS, FACC; Martha Gulati, MD, MS, FACC–*Ex Officio*

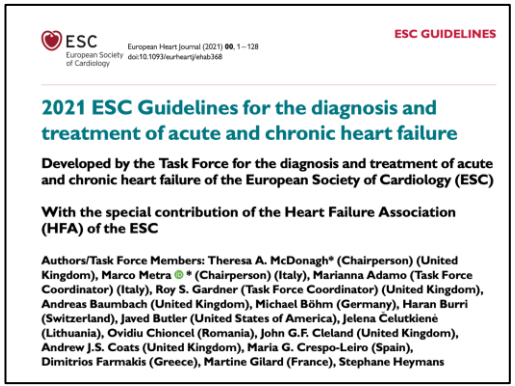
ELSEVIER

Canadian Journal of Cardiology 37 (2021) 531–546

Society Guidelines

CCS/CHFS Heart Failure Guidelines Update: Defining a New Pharmacologic Standard of Care for Heart Failure With Reduced Ejection Fraction

Primary Panel: Michael McDonald, MD (Co-chair),[a] Sean Virani, MD (Co-chair),[b] Michael Chan, MBBS,[c] Anique Ducharme, MD,[d] Justin A. Ezekowitz, MBBCh,[e] Nadia Giannetti, MD,[f] George A. Heckman, MD,[g] Jonathan G. Howlett, MD,[h] Sheri L. Koshman, Pharm D,[e] Serge Lepage, MD,[i] Lisa Mielniczuk, MD,[j] Gordon W. Moe, MD,[k] Eileen O'Meara, MD,[d] Elizabeth Swiggum, MD,[l] Mustafa Toma, MD,[h] Shelley Zieroth, MD,[m] **Secondary Panel:** Kim Anderson, MD,[n] Sharon A. Bray, EdD,[a] Brian Clarke, MD,[h] Alain Cohen-Solal, MD,[o] Michel D'Astous, MD,[p] Margot Davis, MD,[h] Sabe De, MD,[q] Andrew D.M. Grant, MD,[h] Adam Grzeslo, MD,[f] Jodi Heshka, MD,[r] Sabina Keen, MD,[r] Simon Kouz, MD,[s] Douglas Lee, MD, PhD,[g] Frederick A. Masoudi, MD MSPH,[w] Robert McKelvie, MD,[x] Marie-Claude Parent, MD,[d] Stephanie Poon, MD,[w] Miroslaw Rajda, MD,[n] Abhinav Sharma, MD,[f] Kyla Siatecki, MN, NP,[m] Kate Storm, NP,[n] Bruce Sussex, MBBS,[a] Harriette Van Spall, MD MPH,[f] and Amelia Ming Ching Yip, MD[y]



ESC European Society of Cardiology

European Heart Journal (2021) 00, 1–128 doi:10.1093/eurheartj/ehab368

ESC GUIDELINES

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Authors/Task Force Members: Theresa A. McDonagh* (Chairperson) (United Kingdom), Marco Metra * (Chairperson) (Italy), Marianna Adamo (Task Force Coordinator) (Italy), Roy S. Gardner (Task Force Coordinator) (United Kingdom), Andreas Baumbach (United Kingdom), Michael Böhm (Germany), Haran Burri (Switzerland), Javed Butler (United States of America), Jelena Čelutkienė (Lithuania), Ovidiu Chioncel (Romania), John G.F. Cleland (United Kingdom), Andrew J.S. Coats (United Kingdom), Maria G. Crespo-Leiro (Spain), Dimitrios Farmakis (Greece), Martine Gilard (France), Stephane Heymans

EXPERT CONSENSUS DECISION PATHWAY

2024 ACC Expert Consensus Decision Pathway for Treatment of Heart Failure With Reduced Ejection Fraction

A Report of the American College of Cardiology Solution Set Oversight Committee

FIGURE 1 Ten Pivotal Issues About HFrEF

Ten Pivotal Issues About HFrEF

How to implement GDMT...

Issue 1. Initiate & Switch
Treatment algorithm for GDMT, including novel therapies (*Figures 2 and 3*)

Issue 2. Titration
Target doses, indications, contraindications, and other considerations of select GDMT for HFrEF (*Tables 1, 2, 3, 4, 5*)

Considerations for monitoring

How to address challenges with...

Issue 3. Referral
Triggers for referral to HF specialist (*Table 6*)

Issue 4. Care Coordination
Essential skills for a HF team (*Table 7*)

Infrastructure for team-based HF care (*Table 8*)

Issue 5. Adherence
Causes of non-adherence (*Table 9*)

Considerations to improve adherence (*Table 10*)

Issue 6. Specific Patient Cohorts
Evidence based recommendations and assessment of risk for special cohorts: African-American patients, older adults, and patients with frailty (*Table 11*)

Issue 7. Medication Cost and Access
Strategies to reduce patients' cost of care (*Table 12*)
Helpful information for completion of prior authorization forms (*Table 13* and Online Supplemental Appendix)

How to manage...

Issue 8. Increasing Complexity
Ten pathophysiologic targets in HFrEF and treatments (*Table 14*)

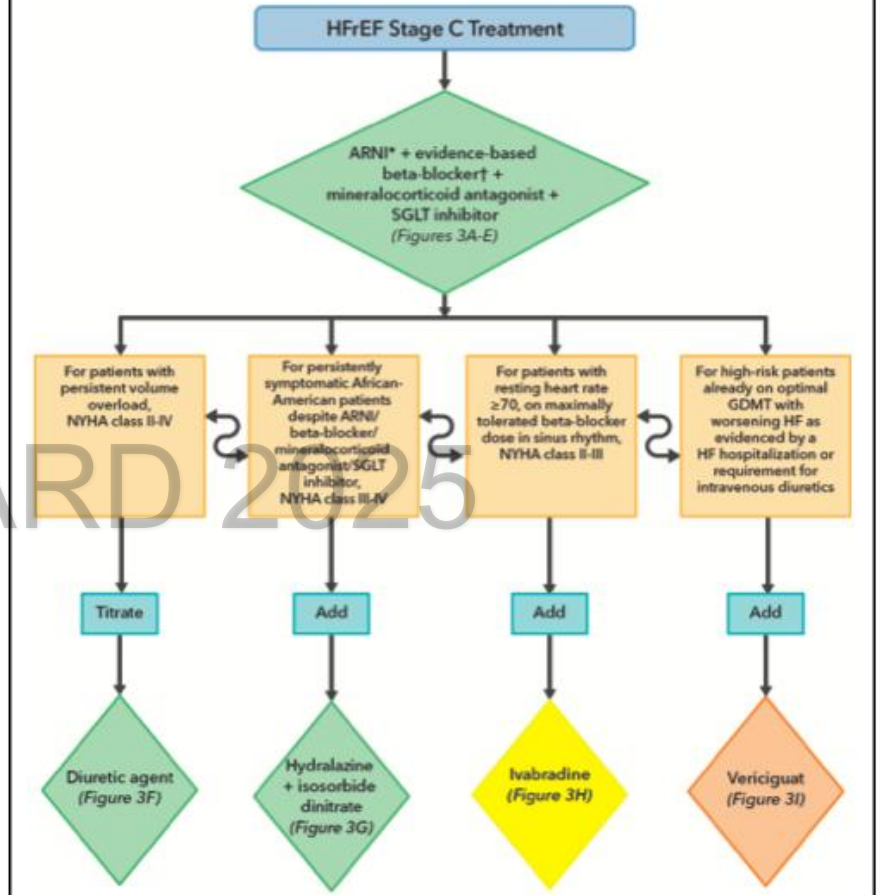
Ten principles and actions to guide optimal therapy

Issue 9. Comorbidities
Common CV and non-CV comorbidities with suggested actions (*Table 15*)

Issue 10. Palliative/ Hospice Care
Seven principles and actions to consider regarding palliative care

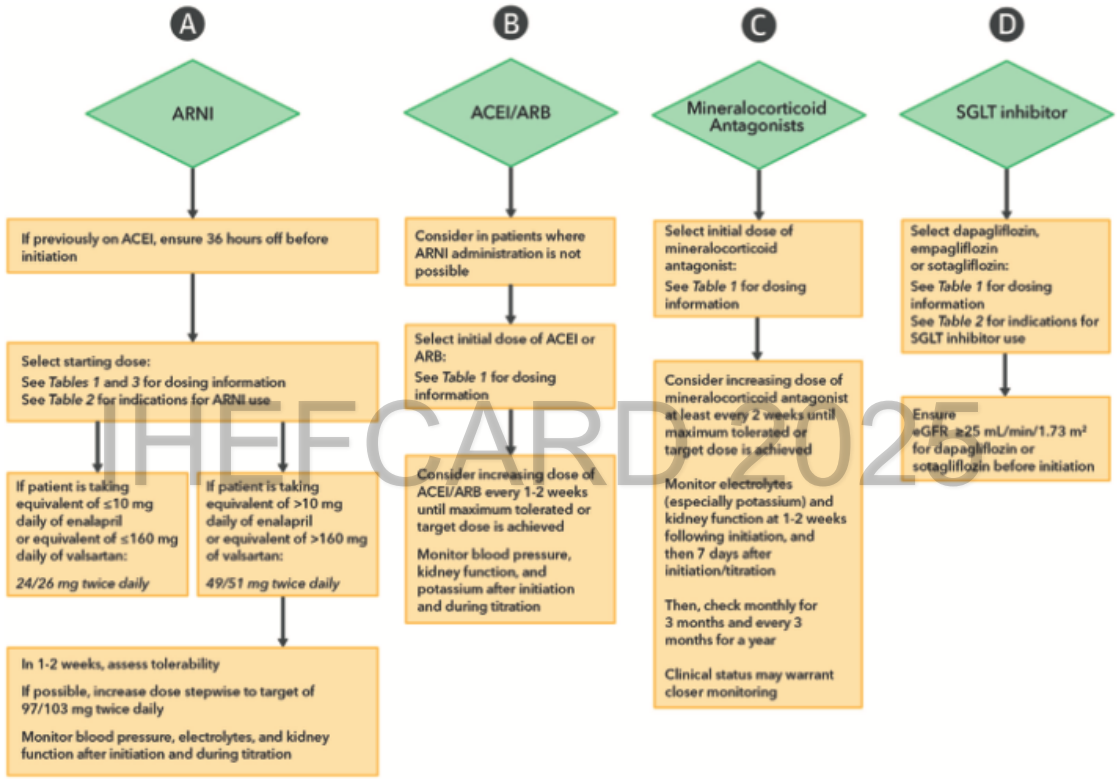
CV = cardiovascular; GDMT, guideline-directed medical treatment; HF = heart failure; HFrEF = heart failure with reduced ejection fraction.

FIGURE 2 Treatment Algorithm for Guideline-Directed Medical Therapy



*ACE inhibitors/ARBs should only be considered in patients with contraindications, intolerance, or inaccessibility to ARNI. In those instances, please consult Figure 3 and the text for guidance on initiation. †Carvedilol, metoprolol succinate, or bisoprolol. Colors correspond to ACC/AHA Class of Recommendation. Green = Class 1 (strong); Yellow = Class 2a (moderate); Orange = Class 2b (weak). ARNI = angiotensin receptor/neprilysin inhibitors; ACC = American College of Cardiology; AHA = American Heart Association; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; NYHA = New York Heart Association; SGLT = sodium-glucose cotransporter.

FIGURE 3 GDMT, Including Newer Therapies, in the ECDP for Chronic HF

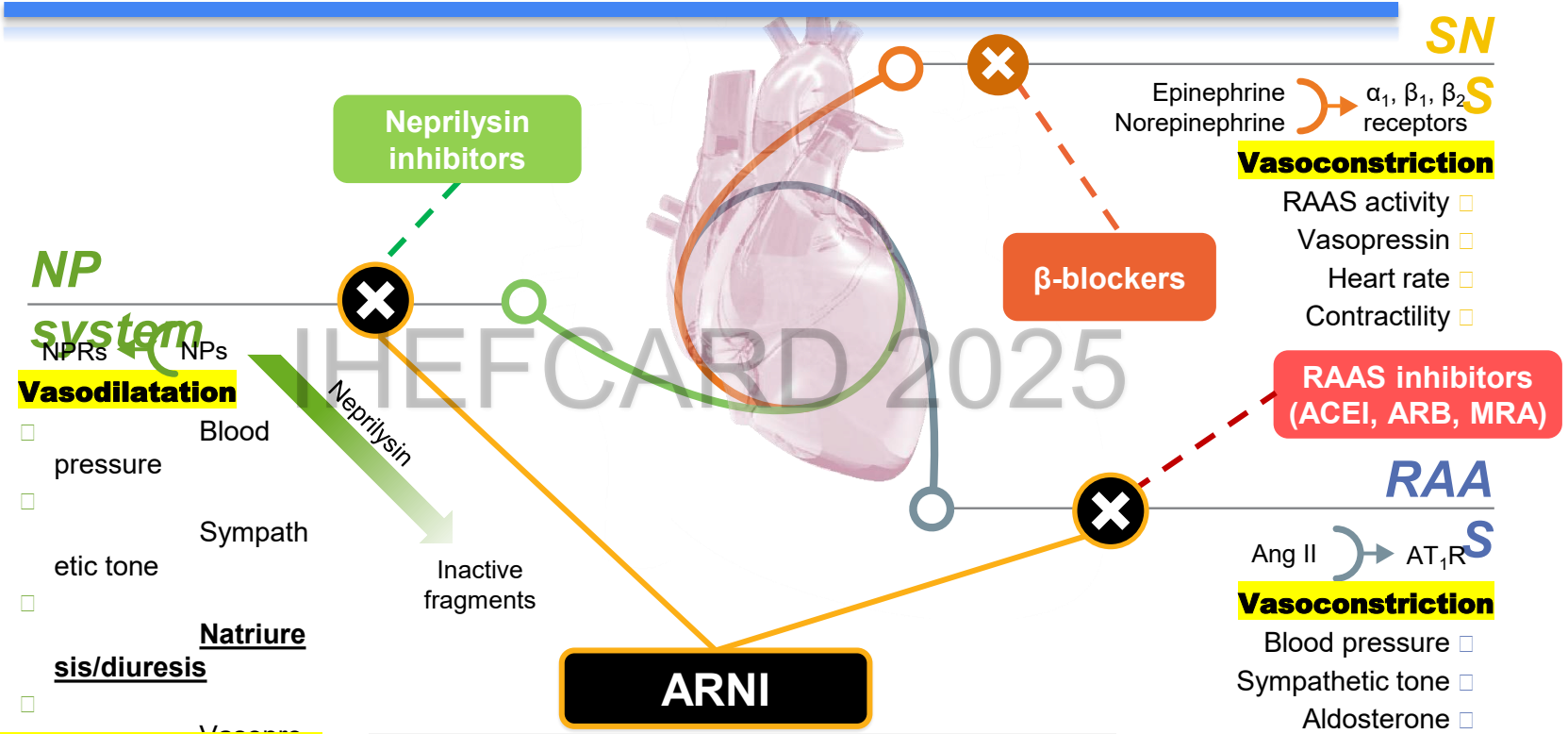


ARNIs are the preferred renin-angiotensin system inhibitor and should be used as first-line therapy whenever possible. For patients in whom ARNI administration is not possible, an ACE inhibitor/ARB is recommended. *Carvedilol, metoprolol succinate, or bisoprolol. ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor/neprilysin inhibitors; CBC = complete blood count; eGFR = estimated glomerular filtration rate; SGLT = sodium-glucose cotransporter.

Continued on the next page

EVOLUTION OF PHARMACOLOGIC APPROACHES IN HF:

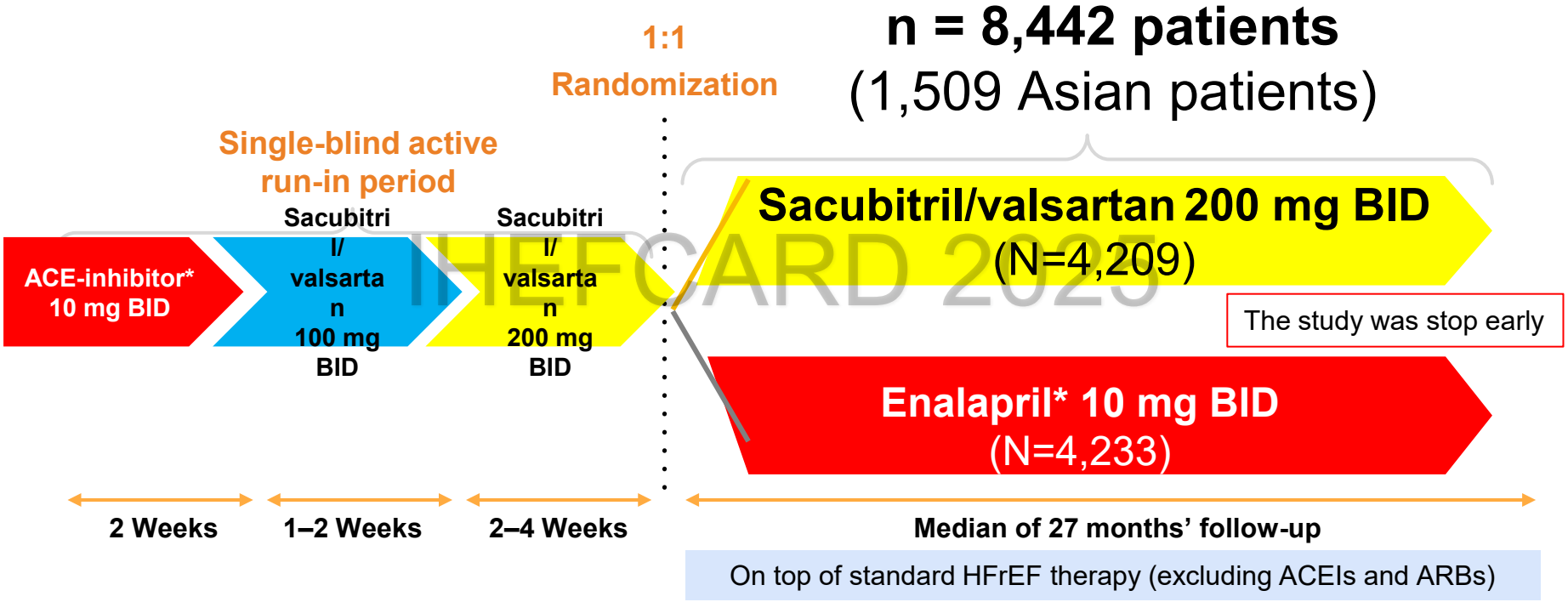
ARNI AS A NEW ALTERNATIVE TO AN ACE-I OR ARBS IN PATIENTS WITH HFREF[1]



Neprilysin inhibitors : enhance natriuretic peptide (NP) bioavailability

Enhancement of natriuretic and other vasoactive peptides, with simultaneous RAAS suppression

PARADIGM-HF: Study design ARNI vs ACEI

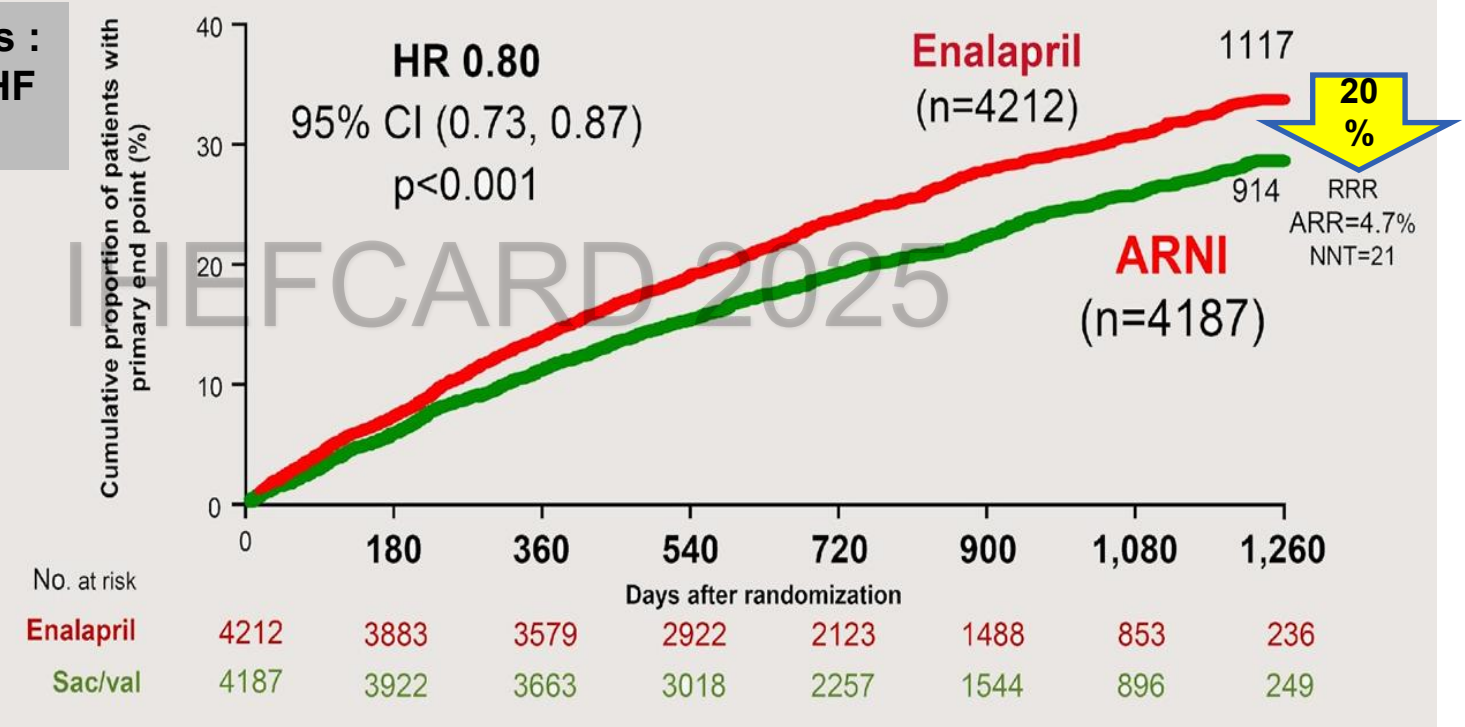


*Enalapril 5 mg BID (10 mg TDD) for 1–2 weeks followed by enalapril 10 mg BID (20 mg TDD) as an optional starting run-in dose for those patients who are treated with ARBs or with a low dose of ACEI; †200 mg TDD; ‡400 mg TDD; §20 mg TDD.

McMurray et al. Eur J Heart Fail. 2013;15:1062–73; McMurray et al. Eur J Heart Fail. 2014;16:817–25;
McMurray, et al. N Engl J Med 2014; ePub ahead of print: DOI: 10.1056/NEJMoa1409077.

Summary from Paradigm-HF trials: Sacubitril valsartan was proven superiority over enalapril

Primary Endpoints : CV death or first HF hospitalization



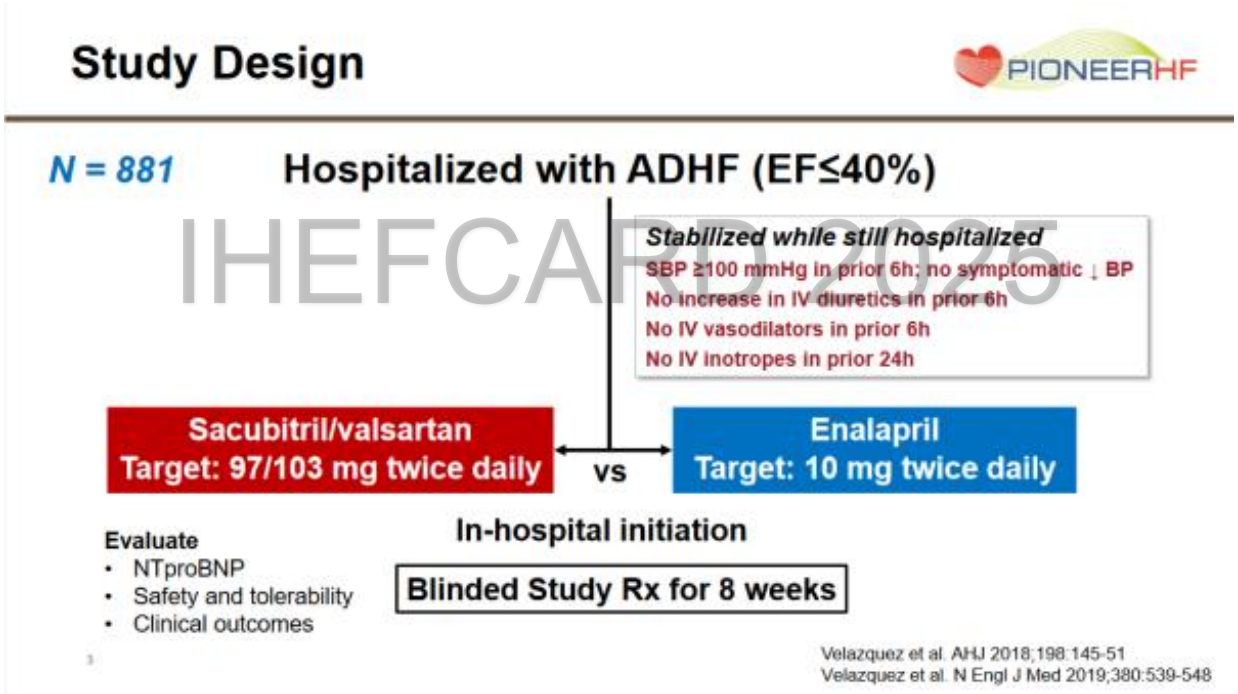
ARR, absolute risk reduction; CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; NNT, number needed to treat; RRR, relative risk reduction; Sac/val, sacubitril valsartan

1. McMurray JJV, et al. N Engl J Med 2014;371(11):993-1004; 2. Desai AS, et al. Eur Heart J 2015;36(30):1990-7; 3. Packer M, et al. Circulation 2015;131(1):54-61

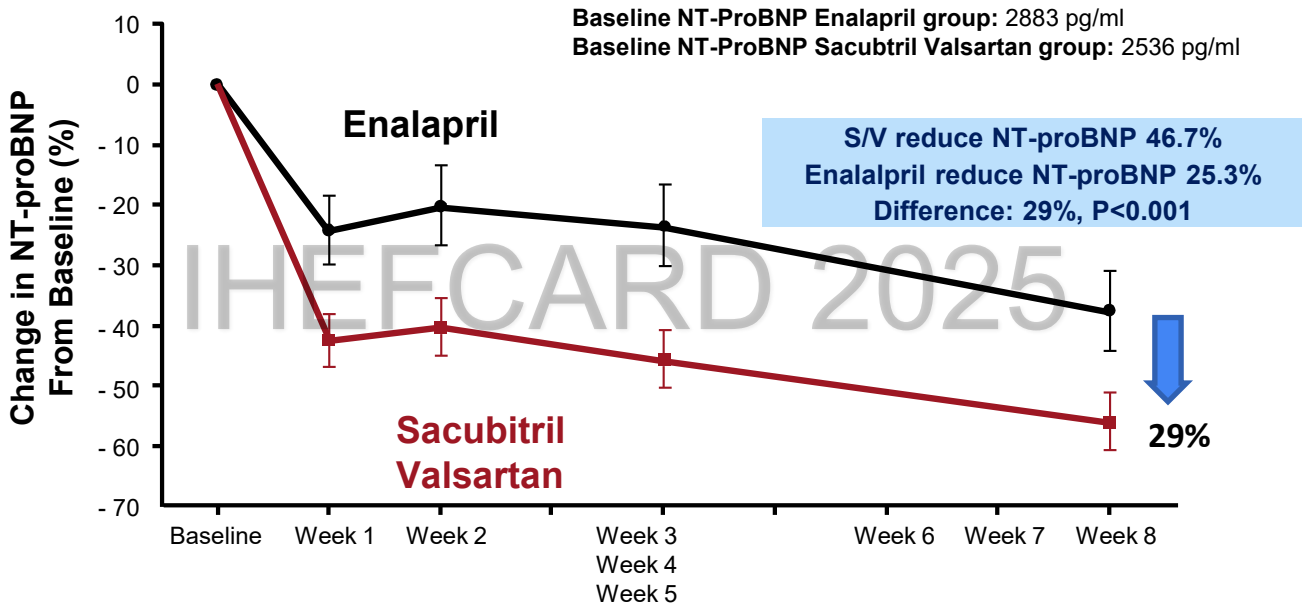
Table 2. Primary and Secondary Outcomes.*

Outcome	LCZ696 (N=4187)	Enalapril (N=4212)	Hazard Ratio or Difference (95% CI)	P Value
Primary composite outcome — no. (%)				
Death from cardiovascular causes or first hospitalization for worsening heart failure	914 (21.8)	1117 (26.5)	0.80 (0.73–0.87)	<0.001
Death from cardiovascular causes	558 (13.3)	693 (16.5)	0.80 (0.71–0.89)	<0.001
First hospitalization for worsening heart failure	537 (12.8)	658 (15.6)	0.79 (0.71–0.89)	<0.001
Secondary outcomes — no. (%)				
Death from any cause	711 (17.0)	835 (19.8)	0.84 (0.76–0.93)	<0.001
Change in KCCQ clinical summary score at 8 mo†	–2.99±0.36	–4.63±0.36	1.64 (0.63–2.65)	0.001
New-onset atrial fibrillation‡	84 (3.1)	83 (3.1)	0.97 (0.72–1.31)	0.83
Decline in renal function§	94 (2.2)	108 (2.6)	0.86 (0.65–1.13)	0.28

Angiotensin–Neprilysin Inhibition in Acute Decompensated Heart Failure



Primary Endpoint: Time-averaged proportional **change of NT-proBNP from baseline**



In-hospital initiation of Sacubitril/Valsartan reduce NT-pro BNP sigificantly vs. enalapril

Percentage (%) change from baseline to mean of weeks 4 and 8
Velazquez E, Morrow D, DeVore, A, et al., N Engl J Med. 2018. doi: 10.1056/NEJMoa1812851.

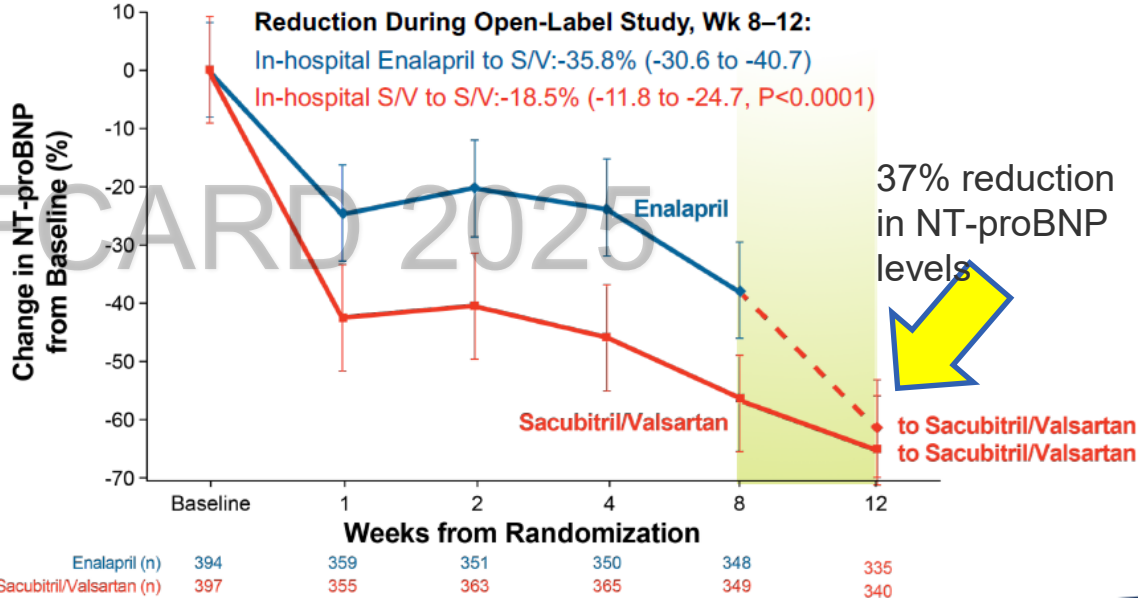
Open Label Extension Study of PIONEER-HF

Change from Baseline in NT-proBNP

In PIONEER-HF, 8 weeks after randomization patients continued in a 4-week, open-label study with all patients receiving sacubitril-valsartan

Objective:

- **Describe changes in NT-proBNP among patients with HFrEF who were recently hospitalized for ADHF switching from enalapril to sacubitril/valsartan**
- **Compare the totality of clinical events during the 12-week study period by randomized treatment arm**

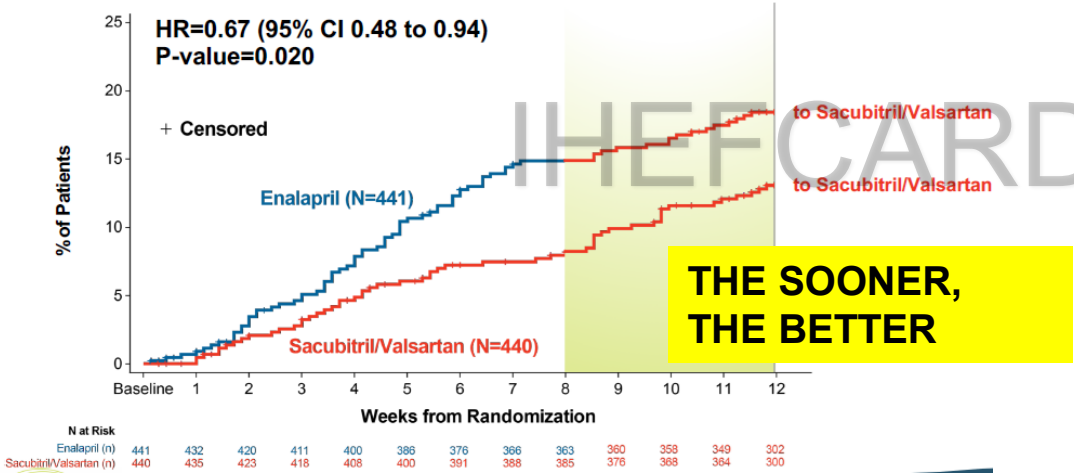


37% reduction in NT-proBNP levels

DeVore A, Braunwald E, Morrow D, et al. Initiation of Angiotensin-Neprilysin Inhibition after Acute Decompensated Heart Failure: Results of the Open-Label Extension of the PIONEER-HF Trial. Data presented at: American College of Cardiology's 68th Annual Scientific Session, March 16-18; New Orleans, United States.

Open Label Extension Study of PIONEER-HF

Death, HF Hospitalization, or LVAD Implantation

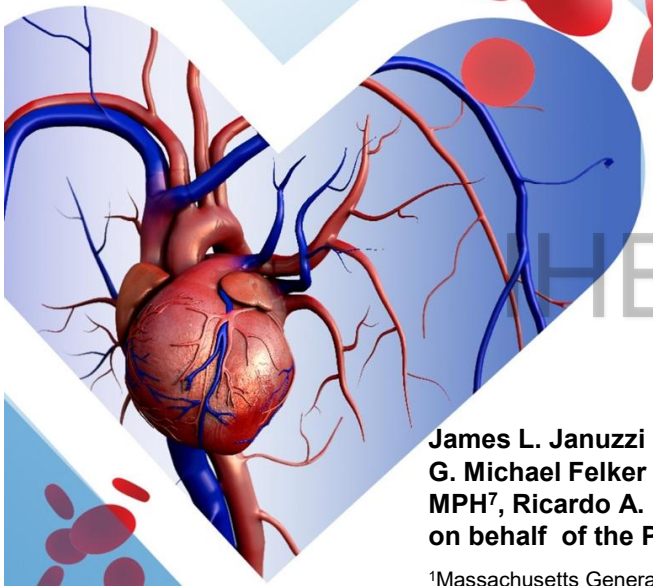


THE SOONER, THE BETTER

Over the entire 12 weeks of follow-up, patients that began taking sacubitril/valsartan in the hospital had a lower hazard for the composite outcome compared with patients that initiated enalapril in the hospital and then had a delayed initiation of sacubitril/valsartan 8 weeks later (hazard ratio, 0.69; 95% CI 0.49-0.97).

DeVore A, Braunwald E, Morrow D, et al. Initiation of Angiotensin-Neprilysin Inhibition after Acute Decompensated Heart Failure: Results of the Open-Label Extension of the PIONEER-HF Trial. Data presented at: American College of Cardiology's 68th Annual Scientific Session, March 16-18; New Orleans, United States.

PROVE-HF



Prospective Study of Biomarkers, Symptom Improvement and Ventricular Remodeling During Entresto Therapy for Heart Failure

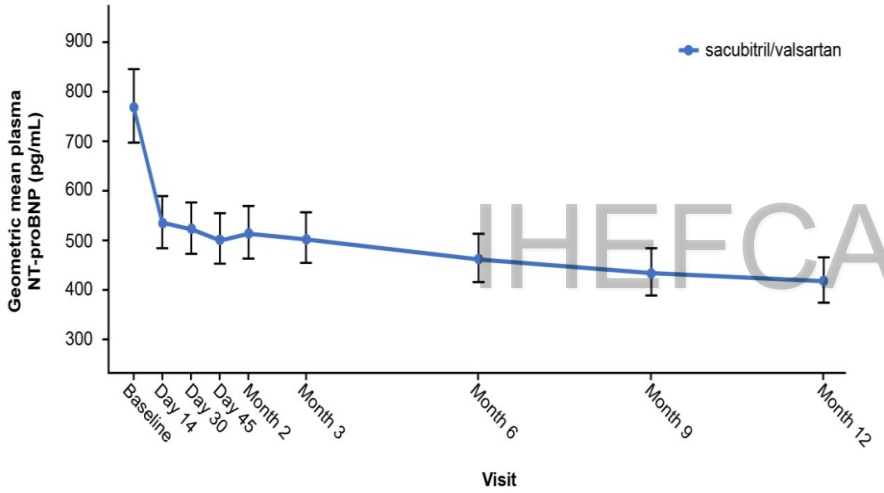
(PROVE-HF; NCT02887183)

James L. Januzzi MD[1,2], Margaret F. Prescott PhD[3], Javed Butler MD MPH MBA[4], G. Michael Felker MD MHS[5], Alan S. Maisel MD[6], Kevin McCague MA[3], Alexander Camacho PhD[1], Ileana L. Piña MD MPH[7], Ricardo A. Rocha MD[3], Amil M. Shah MD MPH[8], Kristin M. Williamson PharmD[3], and Scott D. Solomon MD[8] on behalf of the PROVE-HF Investigators

[1]Massachusetts General Hospital, [2]Baim Institute for Clinical Research, Boston, MA, USA; [3]Novartis Pharmaceuticals, East Hanover, NJ, USA; [4]University of Mississippi Medical Center, Jackson, MS, USA; [5]Duke University Medical Center and Duke Clinical Research Institute, Durham, NC, USA; [6]University of California, San Diego School of Medicine, San Diego, CA, USA; [7]Detroit Medical Center, Detroit, MI, USA; [8]Brigham and Women's Hospital, Boston, MA, USA

PROVE-HF Primary Endpoint

Correlation between change in NT-proBNP and remodeling parameters



Parameter	Pearson r (IQR)	P value
NT-proBNP (pg/mL) / LVEF (%)	-0.381 (-0.448, -0.310)	<.0001
NT-proBNP (pg/mL) / LVEDVi (mL/m^2)	0.320 (0.246, 0.391)	<.0001
NT-proBNP (pg/mL) / LVESVi (mL/m^2)	0.405 (0.335, 0.470)	<.0001
NT-proBNP (pg/mL) / LAVi (mL/m^2)	0.263 (0.186, 0.338)	<.0001
NT-proBNP (pg/mL) / E/E'	0.269 (0.182, 0.353)	<.0001

Rapid and significant reduction of NT-proBNP, with majority of reduction within the first 2 weeks

Reduction in NT-proBNP following treatment with ARNI was significantly associated with reverse cardiac remodeling

PROVE-HF: Change in Cardiac Remodeling Measurements from Baseline to 12 Months After Initiation of Sacubitril-Valsartan

ALL PATIENTS

	Baseline Value, Median (25th to 75th Percentile)	12-mo Value, Median (25th to 75th Percentile)	LS Mean Change From Baseline at 12 mo (95% CI)
LVEF, %	n = 757 28.2 (24.5 to 32.7)	n = 648 37.8 (32.3 to 45.2)	9.4 (8.8 to 9.9)
LVEDVI, mL/m²	n = 756 86.93 (76.17 to 100.43)	n = 648 74.15 (63.46 to 86.30)	−12.25 (−12.92 to −11.58)
LVESVI, mL/m²	n = 756 61.68 (51.95 to 75.00)	n = 648 45.46 (34.84 to 57.56)	−15.29 (−16.03 to −14.55)
LAVI, mL/m²	n = 747 37.76 (31.63 to 46.09)	n = 639 29.31 (24.40 to 35.85)	−7.57 (−7.98 to −7.15)

LVEDVI: left ventricular end-diastolic volume index; LVESVI: left ventricular end-systolic volume index; LAVI: left atrial volume index

Adapted from Januzzi J et al. As presented during ESC Congress 2019, Abstract 3007.

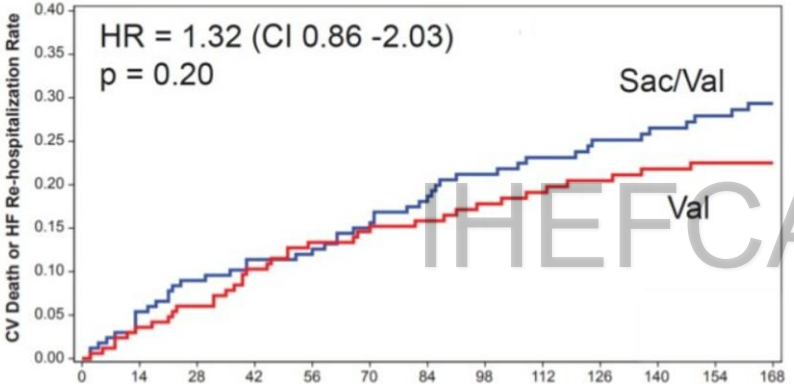
LIFE Trial
Sac/Val in Advanced Heart Failure with Reduced Ejection Fraction

- Primary End Point : AUC for the proportional change in NT-proBNP levels from baseline through 24 weeks
- Secondary End Point : Efficacy – Days alive, out of hospital and free from HF events (listing/cardiac transplantation/LVAD, continuous inotropic therapy for ≥ 7 days, hospitalization for HF on ≥ 2 occasions)
- Secondary End Point : Tolerability – Drug tolerability, hypotension, worsening renal function, hyperkalemia

Mann D.L et al. J Am Coll Cardiol HF.

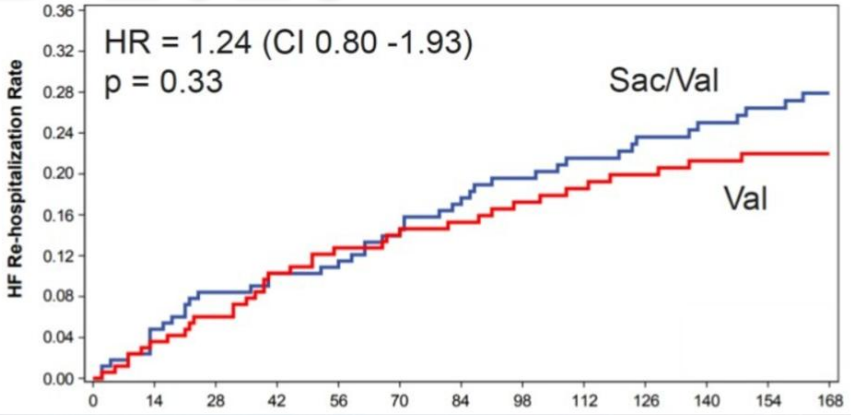
HEART FAILURE NETWORK

CV Death or Heart Failure Hospitalization



HEART FAILURE NETWORK

Heart Failure Hospitalizations



Practical guidance on the use of ARNI in HFrEF

IN WHOM AND WHEN?

Indications:

1. Patients with HFrEF as a replacement for ACE-I/ARB.
2. It may be considered in patients with HFrEF in those who are ACE-I/ARB naïve (*de novo* use).

NEW!

Contraindications:

1. History of angioedema.[a]
2. Known bilateral renal artery stenosis.
3. Pregnancy/risk of pregnancy and breastfeeding period.
4. Known allergic reaction/other adverse reaction (drug-specific).
5. eGFR <30 mL/min/1.73 m^2.
6. Symptoms of hypotension or a SBP <90 mmHg (PARADIGM-HF enrolled patients with SBP >95 mmHg at randomization)

Cautions/seek specialist advice:

1. A washout period of at least 36 h after ACE-I therapy is required in order to minimize the risk of angioedema.
2. Significant hyperkalaemia (K^+ >5.0 mmol/L).

McDonagh TA, et al. Eur Heart J. 2021;42:3599-3726.

TABLE 3 Dose Adjustments of Sacubitril/Valsartan for Specific Patient Populations

Population	Initial Dose
High-dose ACE inhibitor *>10-mg total daily dose of enalapril or therapeutically equivalent dose of another ACE inhibitor* *High-dose ARB* *>160-mg total daily dose of valsartan or therapeutically equivalent dose of another ARB*	**49/51 mg twice daily**
De novo initiation of ARNI *Low- or medium-dose ACE inhibitor* *≤10-mg total daily dose of enalapril or therapeutically equivalent dose of another ACE inhibitor* *Low- or medium-dose ARB* *≤160-mg total daily dose of valsartan or therapeutically equivalent dose of another ARB* *ACE inhibitor/ARB-naive* *Severe kidney impairment* (eGFR <30 mL/min/1.73 m²)* *Moderate hepatic impairment (Child-Pugh class B)* *Elderly patients (age ≥75 y)*	**24/26 mg twice daily**

*This population was not studied in the PARADIGM-HF trial. The statement is consistent with U.S. Food and Drug Administration-approved labeling indications.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor/neprilysin inhibitor; eGFR = estimated glomerular filtration rate; PARADIGM-HF = Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in HF.

TABLE 4 Contraindications and Cautions for Sacubitril/Valsartan

Contraindications

A. Sacubitril/Valsartan

- Within 36 h of ACE inhibitor use
- Any history of angioedema
- Pregnancy
- Lactation (no data)
- Severe hepatic impairment (Child-Pugh class C)
- Concomitant aliskiren use in patients with diabetes
- Known hypersensitivity to either ARBs or ARNIs

Cautions

- Kidney impairment:
  - Mild-to-moderate (eGFR 30-59 mL/min/1.73 m²): no starting dose adjustment required
  - Severe* (eGFR <30 mL/min/1.73 m²): reduce starting dose to 24 mg/26 mg twice daily; double the dose every 2-4 weeks to target maintenance dose of 97 mg/103 mg twice daily, as tolerated
- Hepatic impairment:
  - Mild (Child-Pugh class A): No starting dose adjustment required
  - Moderate (Child-Pugh class B): Reduce starting dose to 24/26 mg twice daily; double the dose every 2-4 weeks to target maintenance dose of 97/103 mg twice daily, as tolerated
- Renal artery stenosis
- Systolic blood pressure <100 mm Hg
- Volume depletion

Summary

- ARNI therapy is recognised as a critical component of guideline-directed medical therapy GDMT for heart failure with reduced ejection fraction (HFrEF).
- Patients with both acute and chronic HF benefit from early GDMT initiation.
- 4 pillars at low doses is better than < 4 at higher doses
- Evolution of ARNI position in guidelines due to positive result except in advance HF (**the sooner the better**) □ can be given in naive HF patients without contraindication

Thank You

WORKING GROUP ON HEART FAILURE AND CARDIOMETABOLIC DISEASE
INDONESIAN HEART ASSOCIATION
Kelompok Kerja Gagal Jantung dan Penyakit Kardiometabolik
Pengurus Pusat Perhimpunan Dokter Spesialis Kardiovaskular Indonesia
National Cardiovascular Center Harapan Kita Hospital
Jl. Letjen S Parman Kav 87 Jakarta, 11420 – INDONESIA
Phone : +6221-5684085, 5684093, 5684111 (Ext 2409) Fax : +6221- 5684130, 5684230
E-mail : pokjahf@gmail.com, website : www.inahfcarmet.org

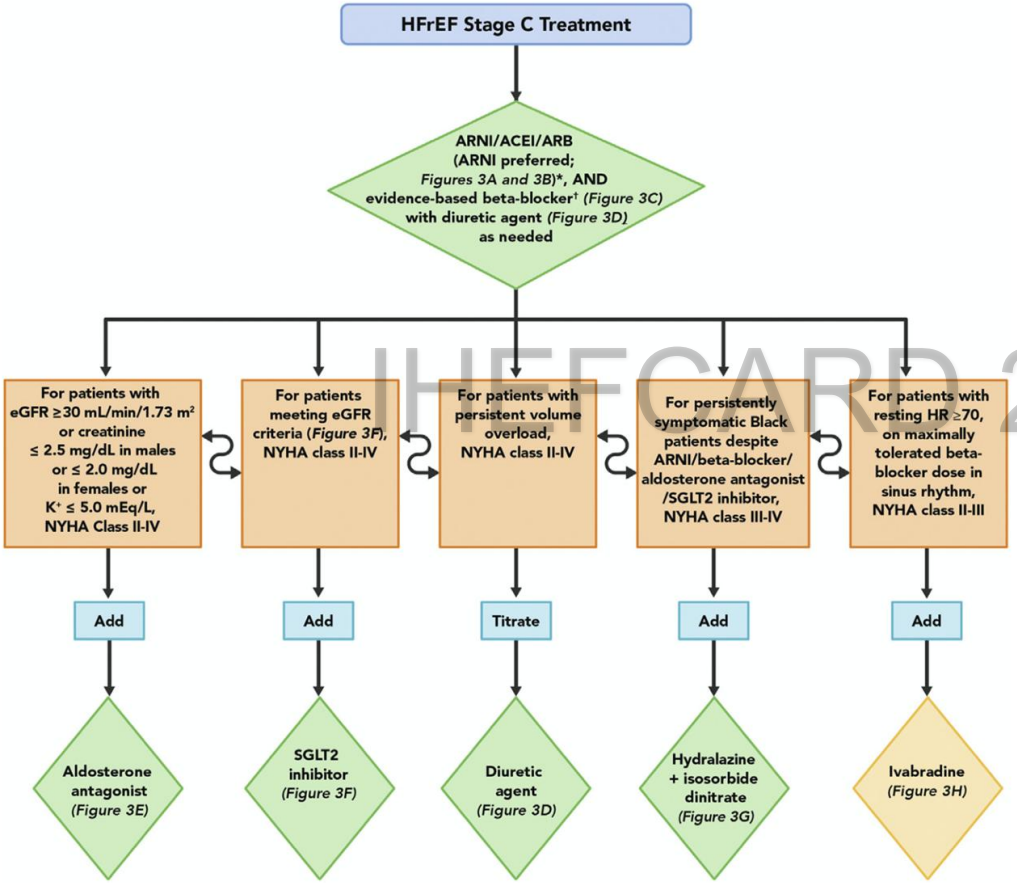
REKOMENDASI PENGGUNAAN ARNI (Sacubitril-Valsartan) 2022

Berdasarkan Rekomendasi Tatalaksana Gagal Jantung 2020 Perhimpunan Dokter Spesialis Kardiovaskular Indonesia (PERKI), salah satu pilihan terapi untuk pasien gagal jantung adalah *Angiotensin Receptor-Neprilysin Inhibitor* (ARNI) yang merupakan molekul tunggal Sacubitril-Valsartan yang telah terbukti dapat menurunkan morbiditas dan mortalitas pada gagal jantung dengan penurunan fraksi ejeksi ventrikel kiri (*HFrEF, Heart Failure reduced Ejection Fraction*, EF ≤ 40%).

Efisiensi dapat dilakukan melalui pembatasan penggunaan ARNI berdasarkan penerapan rekomendasi tersebut sehingga tidak akan terjadi utilisasi berlebih. Maka Kelompok Kerja Gagal Jantung PERKI memberikan usulan restriksi sebagai berikut:

a. ARNI dapat diinisiasi pada pasien gagal jantung fraksi ejeksi ventrikel kiri ≤ 40% dengan penggunaan ACEI/ARB yang telah mencapai dosis optimal sebelumnya, namun tetap bergejala (kelas fungsional) NYHA II-IV
b. Dosis inisial yang dianjurkan adalah 2x50 mg dan dapat ditingkatkan hingga dosis target 2x200 mg (yang merupakan dosis maksimal) sesuai studi PARADIGM
c. Dosis inisial yang lebih rendah yakni 2x25 mg dianjurkan untuk pasien dengan gangguan fungsi ginjal berat (eGFR < 30 ml/min/1.73 m^2), gangguan hepar derajat sedang (Kelas B Child-Pugh), serta pada tekanan darah sistolik < 100 mmHg. Naikkan dosisnya tiap 2-4 minggu hingga mencapai dosis target 2x200 mg bila pasien dapat mentoleransi
d. Evaluasi ekokardiografi dilakukan dalam 6 bulan pertama setelah inisiasi ARNI kemudian selanjutnya dilakukan setiap 1 tahun, kecuali jika pasien mengalami perburukan gejala atau penurunan kelas fungsional NYHA maka evaluasi ekokardiografi dapat dilakukan lebih cepat
e. Pada pasien dimana evaluasi ekokardiografi menunjukkan perbaikan fraksi ejeksi menjadi > 40%, dianjurkan untuk tetap memberikan ARNI (bila memungkinkan). Tetapi bila tidak memungkinkan (dimana ARNI harus diganti kembali menjadi ACEI/ARB), maka evaluasi ekokardiografi ulang dalam waktu minimal 6 bulan berikutnya atau jika pasien mengalami perburukan gejala atau penurunan kelas fungsional NYHA maka evaluasi ekokardiografi dapat dilakukan lebih cepat guna mengevaluasi apakah pasien memiliki rekomendasi yang kuat untuk mendapatkan ARNI kembali
f. Diberikan di fasilitas kesehatan (Faskes) tingkat 2 dan 3

The 2021 Update to the 2017 HF ECDP



ARNIs are now the preferred first-line renin angiotensin inhibitor for patients with NYHA class II-IV and EF < 40%

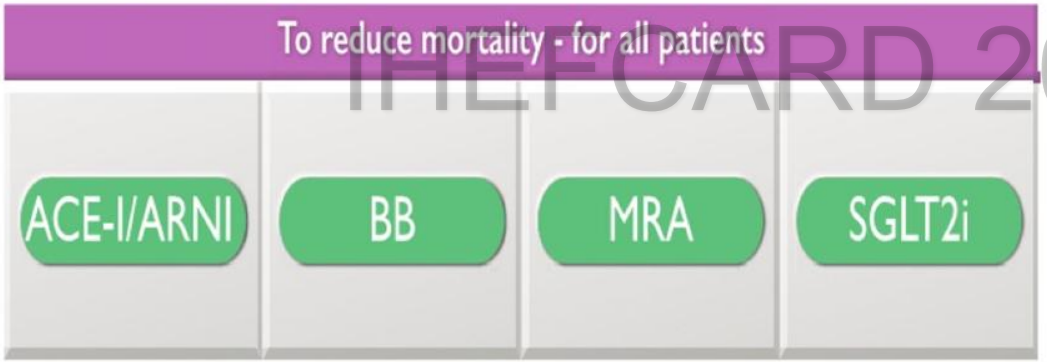
New recommendation

- We recommend that in the absence of contraindications, patients with HFrEF be treated with combination therapy including 1 evidence-based medication from each of the following categories:
  a. ARNI (or ACEI/ARB);
  b. Beta-blocker;
  c. MRA;
  d. SGLT2 inhibitor.

  Strong Recommendation, Moderate-Quality Evidence

McDonald M, Ezekowitz J, O'Meara E, et al. 2024 Update to the Canadian Cardiovascular Society/Canadian Heart Failure Society Guidelines for the Management of Heart Failure. Canadian Journal of Cardiology 37(2024): 531-546

2021 ESC Heart Failure Guidelines : Four Pillars Therapy



- All HFrEF patients should be on quadruple therapy unless there is an intolerance or contraindication as soon as possible
- SGLT 2 inhibitors are recommended at the same time as BB, MRA, ACE-inhibitors or ARNI.*
- Sacubitril/valsartan (ARNI) is recommended as a replacement for ACE-inhibitor therapy in the first-line setting. It may also be added as first line therapy in new onset HF

BB, beta blocker.

*ARBs may be used for patients intolerant to ACE-inhibitors or ARNI.

McDonagh TA, et al. Eur Heart J. 2021;42:3599-3726.

Management of HFrEF

To reduce mortality - for all patients

- ACE-I/ARNI
- BB
- MRA
- SGLT2i

To reduce HF hospitalization/mortality - for selected patients

Volume overload
- Diuretics

SR with LBBB ≥ 150 ms	*SR with LBBB 130–149 ms or non LBBB≥ 150 ms*
CRT-P/D	CRT-P/D
Ischaemic aetiology	*Non-ischaemic aetiology*
ICD	ICD
Atrial fibrillation	*Atrial fibrillation* / *Coronary artery disease* / *Iron deficiency*
Anticoagulation	Digoxin, PVI / CABG / Ferric carboxymaltose

Aortic stenosis	*Mitral regurgitation*	*Heart rate SR>70 bpm*	*Black Race*	*ACE-I/ARNI intolerance*
SAVR/TAVI	TEE MV Repair	Ivabradine	Hydralazine/ISDN	ARB

For selected advanced HF patients

- Heart transplantation
- MCS as BTT/BTC
- Long-term MCS as DT

To reduce HF hospitalization and improve QOL - for all patients

- Exercise rehabilitation
- Multi-professional disease management

INDONESIAN GUIDELINES

FRAKSI EJEKSI VENTRIKEL KIRI ≤40%

3 PILAR TERAPI UTAMA

ACEinhibitor (atau ARB bila tidak toleran dg ACEi), Beta blocker (BB), Mineraloreseptor antagonis (MRA)

Titrasi sampai dosis targer atau dosis maksima l yang dapat ditoleransi (berdasar buktii ilmiah)

Evaluasi gejala

NYHA I :
Lanjutkan terapi utama

NYHA II-IV :
Irama sinus, Nadi ≥ 70x/mnt
Tambah Ivabradine dan atau ganti ACEi atau ARB ke ARNI

NYHA II-IV
Irama sinus dg Nadi <70x/mnt
Ganti ACEi atau ARB ke ARNI

Diuretik untuk kongesti (Titrasi sampai dosis terkecil yang efektif untuk mencapai euvolemia)

NYHA I atau FEVK >40%
Lanjutkan terapi

Evaluasi ulang gejala dan FEVK

NYHA I-III dan FEVK ≤ 40% :
Pertimbangkan ICD dan atau CRT

NYHA IV
Pertimbangkan :
-Hidralazine/nitrat
-Rujuk untuk perawatan gagal jantung lanjut (bantuan mekanik atau transplantasi)
-Rujuk ke tempat rujukan gagal jantung lanjut

Evaluasi ulang tiap 1-3 tahun (tergantung dari kondisi klinis)

Evaluasi ulang ekokardiografi tiap 1-5 tahun

Evaluasi ulang ekokardiografi sesuai dengan kondisi klinis

McDonagh TA et al. European Heart Journal (2021) 00, 1–128.
Pedoman Tatalaksana Gagal Jantung PERKI 2020