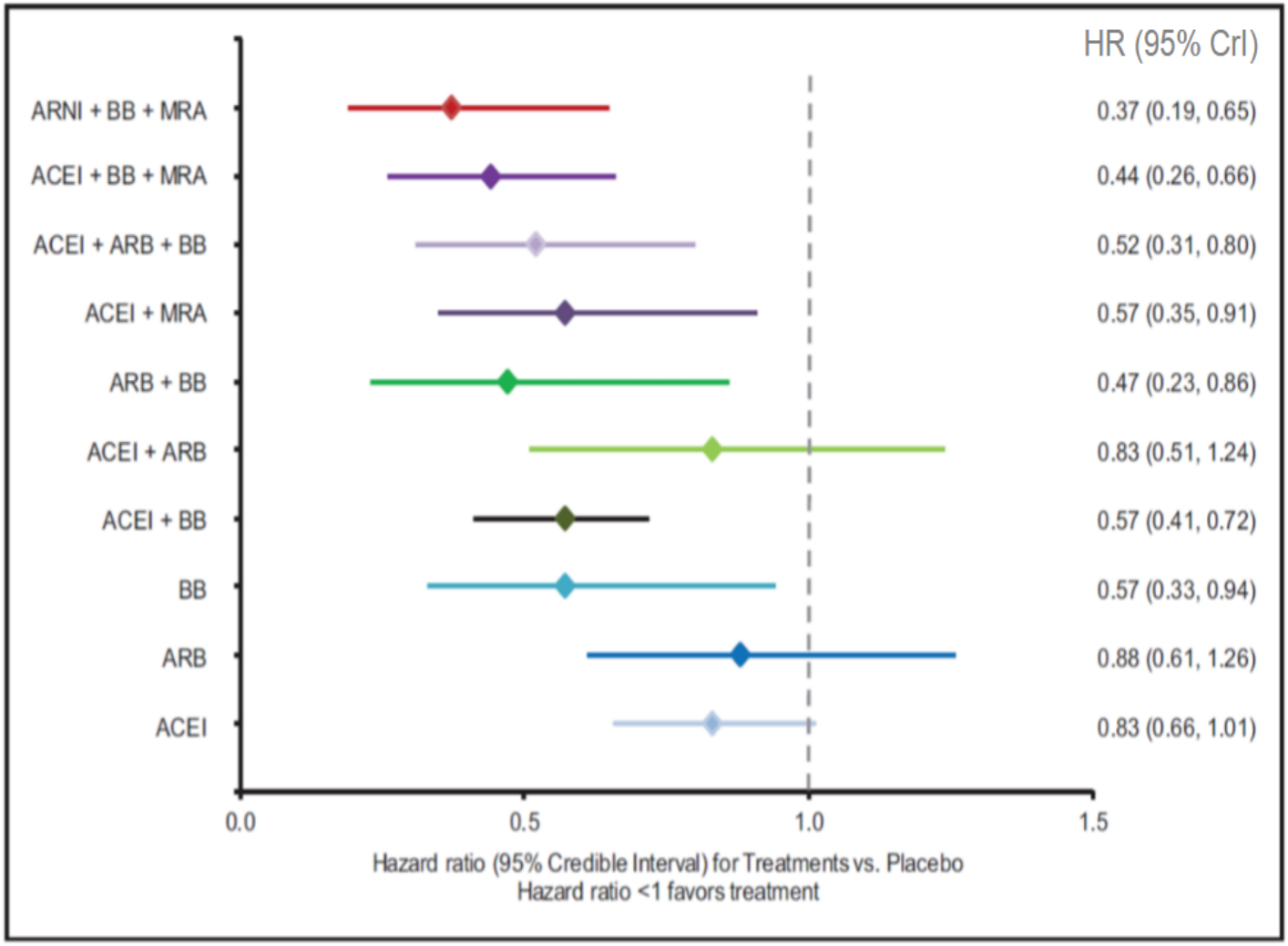
Tối Ưu Hóa Điều Trị Thuốc Trong Suy Tim Mạn EF Giảm Đồng Thuận HFA-ESC 2019

Optimising Medications In EFrHF Therapies. An Expert Consensus of HFA-ESC 2019

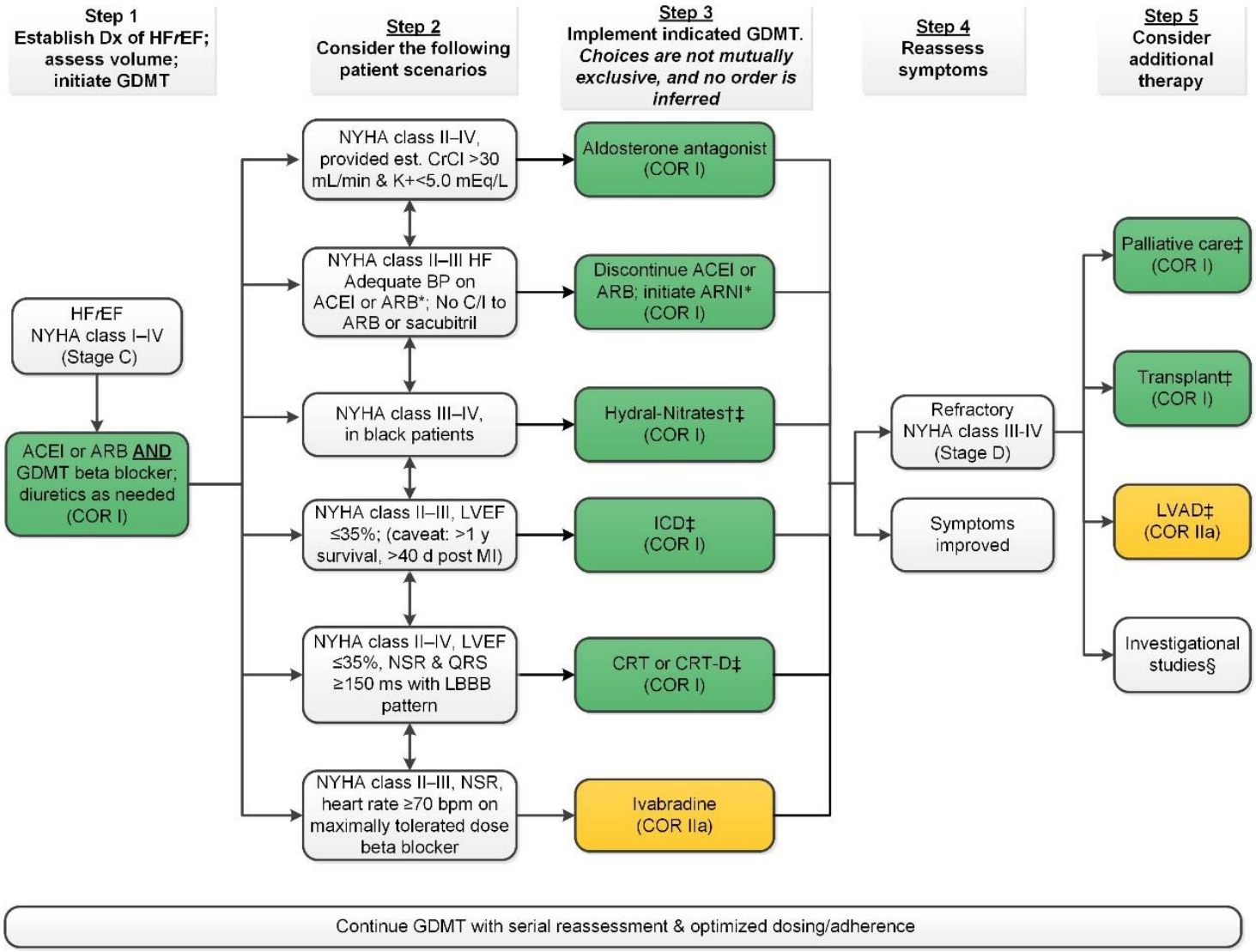
PGS TS BS TRẦN VĂN HUY FACC FESC
Phó Chủ Tịch Phân Hội THA Việt Nam
Chủ Tịch Hội Tim Mạch Khánh Hòa

A remarkable 30 years of progress in HFrEF:
Stepwise reduction in mortality



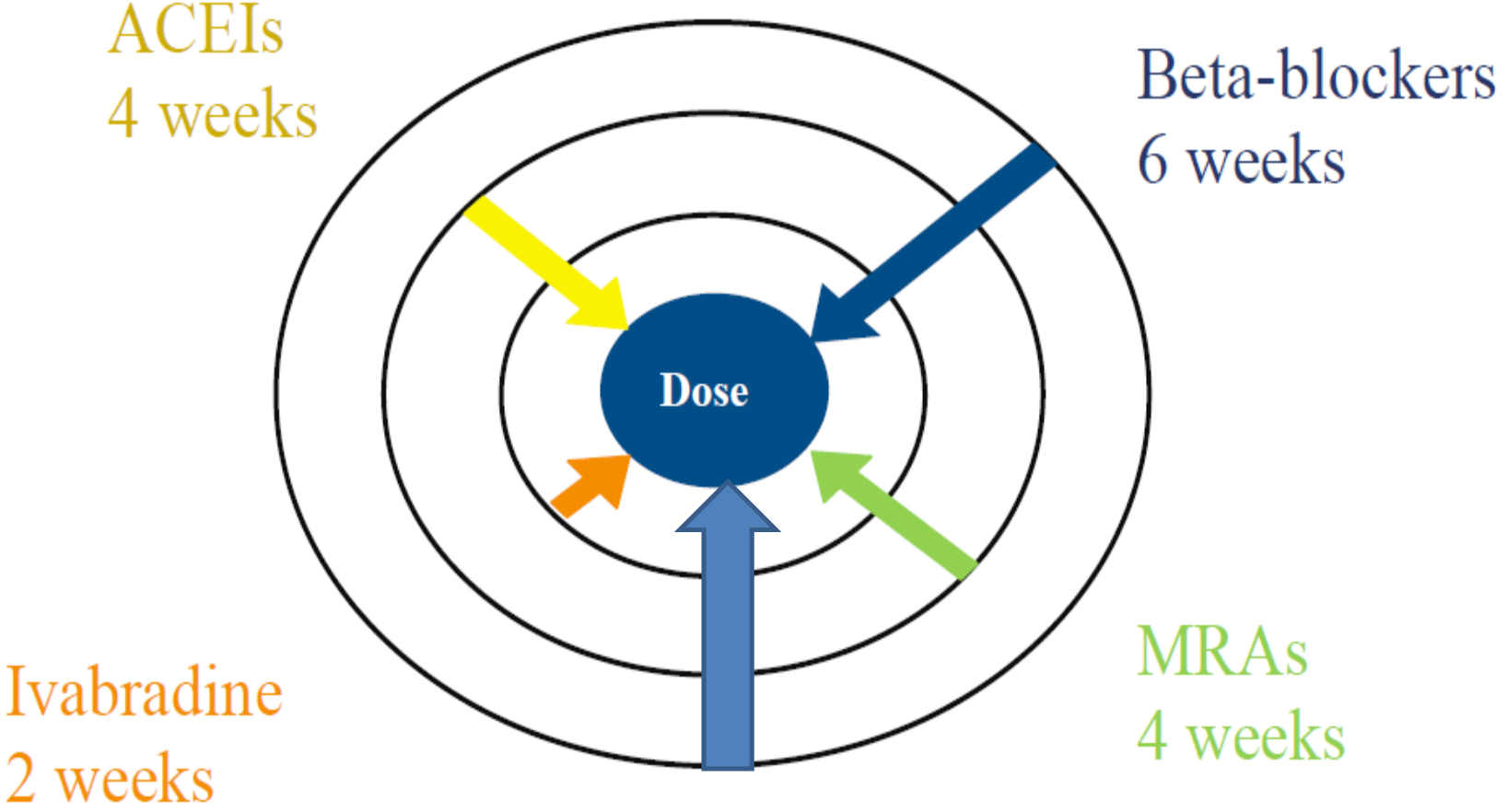
H Burnett et al. Circ Heart Fail. 2017;10:e003529

Treatment of HFrEF Stage C and D



Yancy, et. al. ACC/AHA/HFSA 2017 Heart Failure Focused Update

Uptitration target in stable HF patients



ARNI 5-8 weeks

ESC 2016 Guidelines for HF: Evidence-Based Disease Modifying Therapies With Recommended Doses

	Starting Dose (mg)	Target Dose (mg)
ACE inhibitors		
Captopril	6.25 tid	50 tid
Enalapril	2.5 bid	20 bid
Beta-blockers		
Bisoprolol	1.25 od	10 od
Carvedilol	3.125 bid	25 bid

	Starting Dose (mg)	Target Dose (mg)
ARBs		
Candesartan	4 to 8 od	32 od
Losartan	50 od	150 od
MRAs		
Eplerenone	25 od	50 od
Spironolactone	25 od	50 od
ARNI		
Sacubitril/valsartan	49/51 bid	97/103 bid

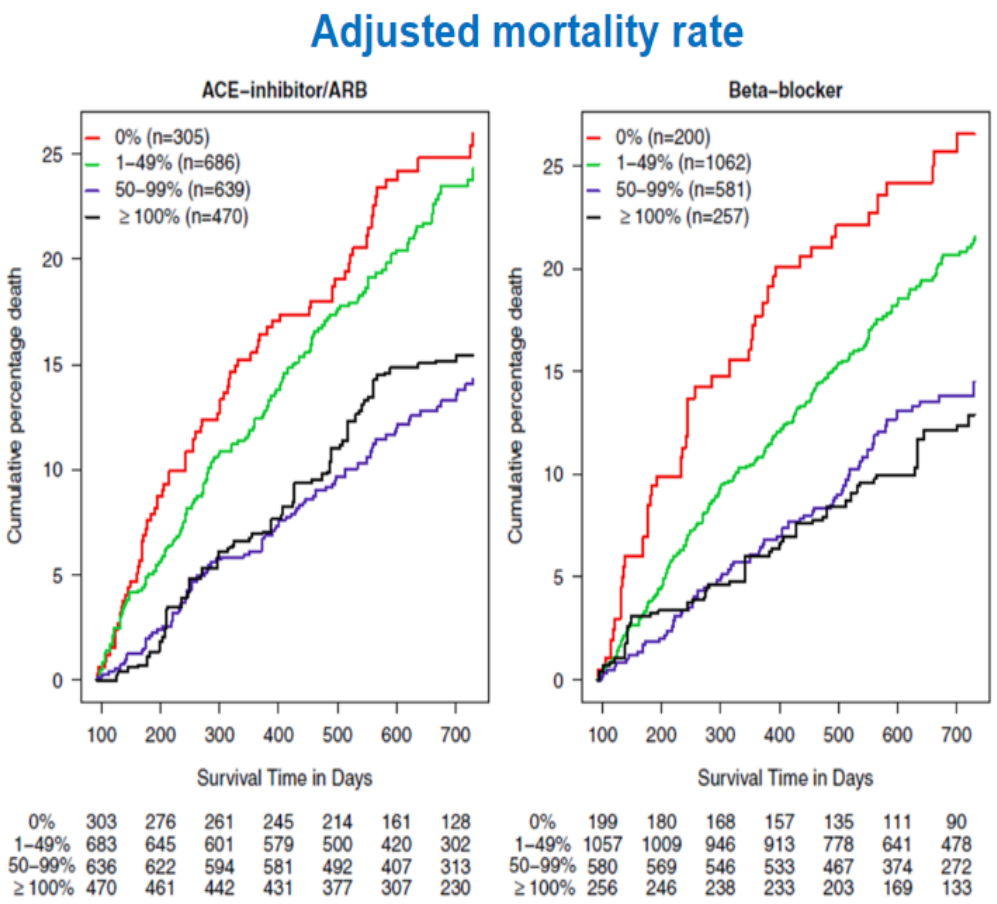
See published guidelines for additional recommendations

Ponikowski P, et al. *Eur Heart J*. 2016;18:891-975.

BIOSTAT-HF

Sự tuân thủ chuẩn liều theo khuyến cáo là gắn liền với tiên lượng tốt hơn ở bệnh nhân HFrEF ngoại trú

Một nghiên cứu tiến cứu 2.516 bn HFrEF đánh giá chuẩn liều ACEs, BB ở 11 QG Châu Âu



Ouwerkerk W et al Eur Heart J. 2017;38(24):1883-1890

Azienda Ospedaliera Papa Giovanni XXIII Bergamo

Sự Khác Biệt Trong Các Bước Chuẩn Liều Thuốc Để Đạt Liều Tối Ưu

- MRA use may require only 2 steps[a,b]
- BB use may require multiple steps -- "usually start low and go slow"[a,b,c]
- ACE inhibitor and ARNI (sacubitril/valsartan) use -- can take 3 steps[a,b,d]

a. Ponikowski P, et al. *Eur Heart J.* 2016;18:891-975.
b. Ponikowsk P, et al. *Eur Heart J.* 2016. Web Addenda.
c. Atherton JJ, et al. *Card Fail Rev.* 2017;3:25-32.
d. Entresto SmPC 2015.

ESC HF Long-Term Registry

Patients at Target Dose With Recommended Drug Therapies

	At target, n (%)	Not at target, n (%)
ACE inhibitors (4710 patients)	1380 (29.3)	3330 (70.7)
ARBs (1500 patients)	362 (24.1)	1138 (75.9)
Beta-blockers (6468 patients)	1130 (17.5)	5338 (82.5)
MRAs (4226 patients)	1290 (30.5)	2936 (69.5)

Maggioni A, et al. *Eur J Heart Fail*. 2013;15:1173-1184.

ARNI Khởi Trị Lúc Nào & Tăng Chuẩn Liều như thế nào cho tốt nhất và có chỉ định trong suy tim nội viện?

Recent Trials With Sacubitril/Valsartan

Angiotensin-Neprilysin Inhibition in Acute Decompensated Heart Failure[a]

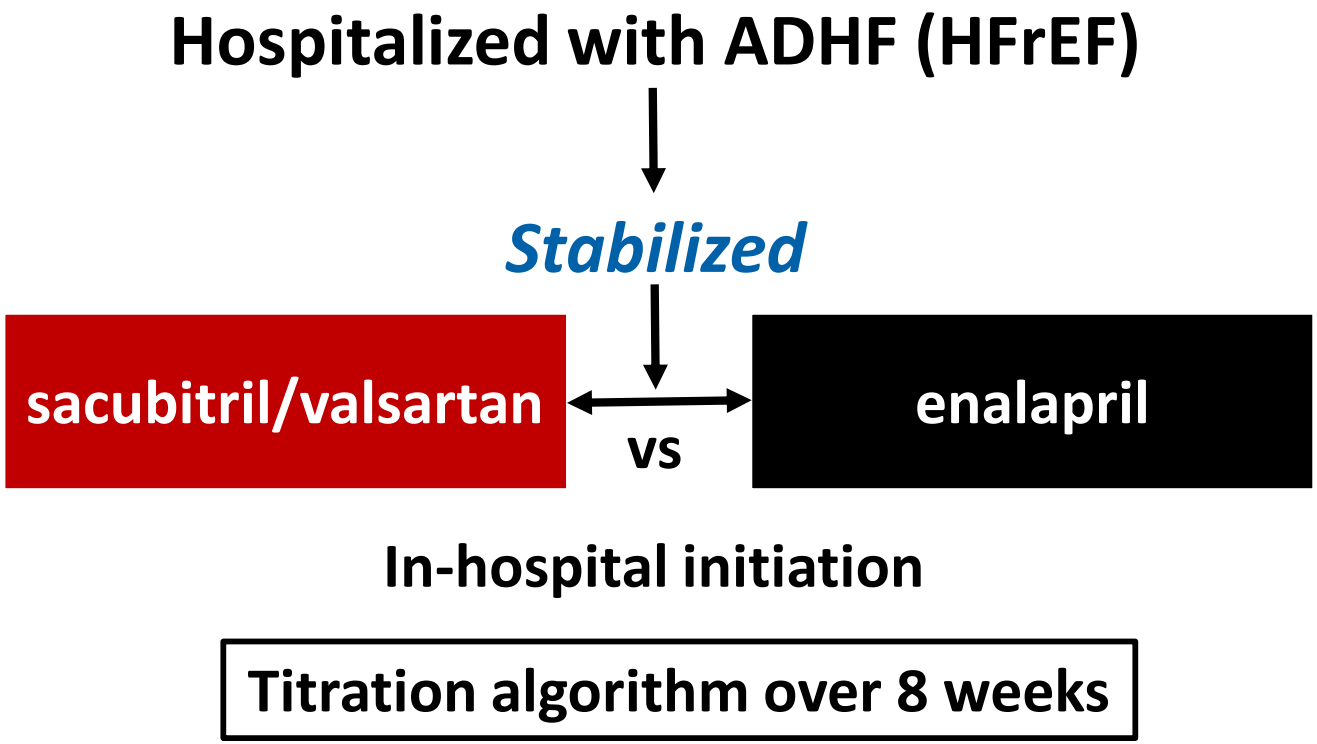
Eric J. Velazquez, MD, David A. Morrow, MD, MPH, Adam D. DeVore, MD, MHS, Carol I. Duffy D.O., Andrew P. Ambrosy, MD, Kevin McCague, M.A., Ricardo Rocha, MD, and Eugene Braunwald, MD, for the PIONEER-HF Investigators

Sacubitril/Valsartan initiated in hospitalized patients with heart failure with reduced ejection fraction after hemodynamic stabilization. Primary results of the TRANSITION study[b]

Rolf Wachter, MD, Michele Senni, MD, Jan Belohlavek, MD, Dmytro Butylin, MD, Adele Noe, MD, Domingo Pascual-Figal, MD for the TRANSITION Study Investigators

a. Velazquez EJ, et al. *N Engl J Med.* 2018;380:539-548.
b. Wachter R, et al. *J Cardiac Failure*. 2018;24:S15.

Study Design



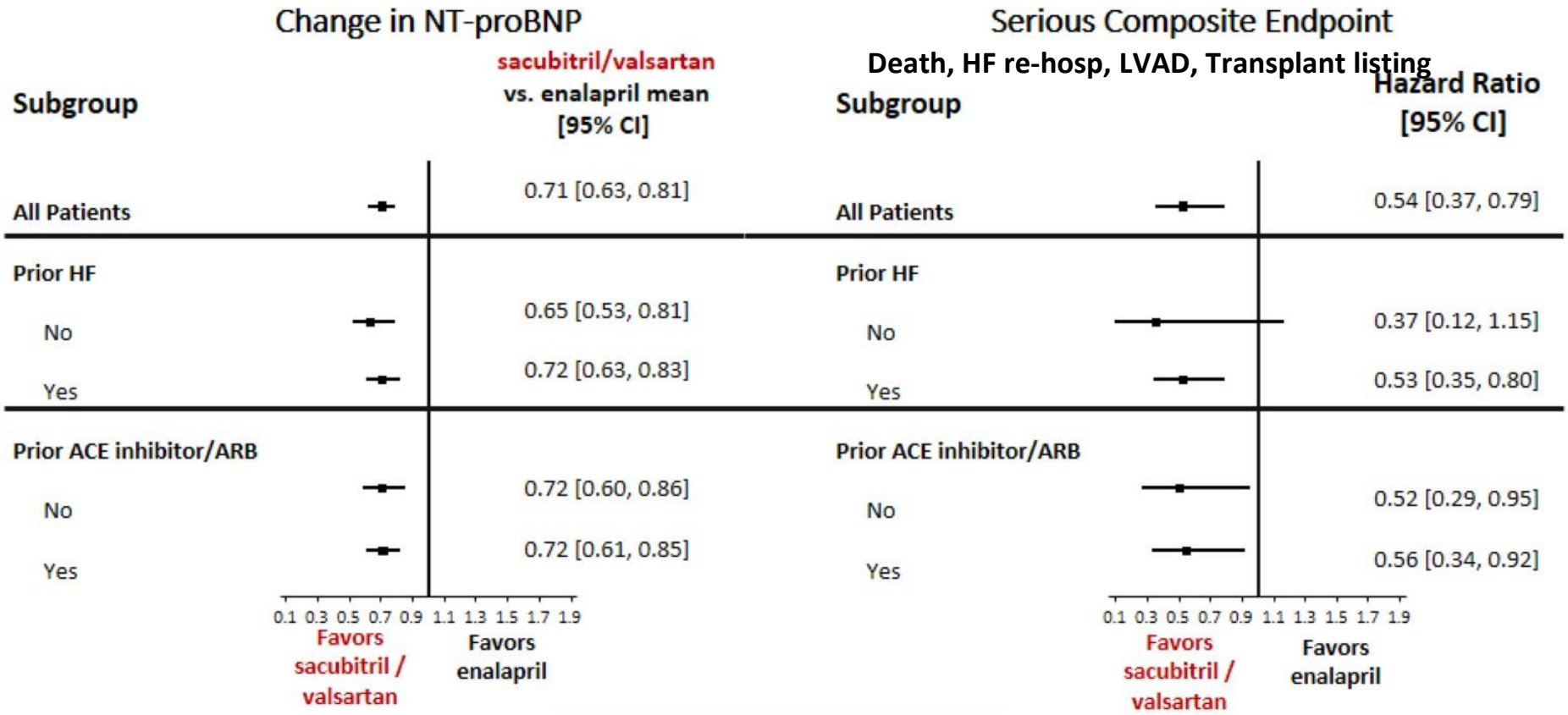
In-hospital initiation

Titration algorithm over 8 weeks

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

Velazquez EJ et al . N Engl J Med. 2018;380:539-548

PIONEER HF: Key Subgroup Analyses



P value (interaction) = NS

Velazquez EJ, et al. *N Engl J Med.* 2018;380:539-548.

Safety

Safety Events (%)	sacubitril/ valsartan (n=440)	enalapril (n=441)	RR (95% CI)
Worsening renal function*	13.6	14.7	0.93 (0.67-1.28)
Hyperkalemia†	11.6	9.3	1.25 (0.84-1.84)
Symptomatic hypotension	15.0	12.7	1.18 (0.85-1.64)
Angioedema event	1 (0.2%)	6 (1.4%)	0.17 (0.02-1.38)

P = NS for all safety events

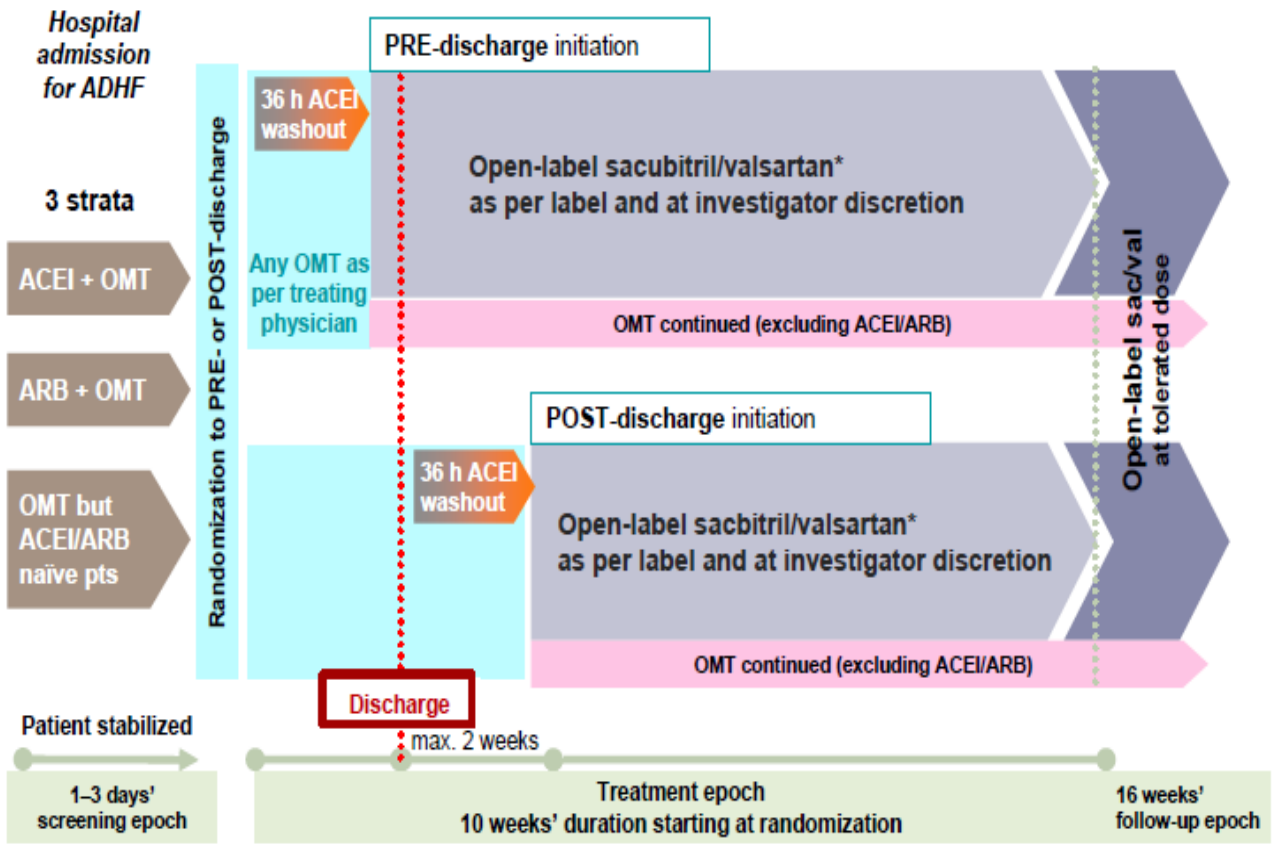
*Cr ≥0.5 with simultaneous reduction in eGFR of ≥25%

†K+ >5.5 mg/dl

Velazquez EJ et al . N Engl J Med. 2018;380:539-548

TRANSITION study design

- 10 weeks
- 1002 patients
- EF≤40%
- BP ≥110 mmHg
- Stable therapy (oral diuretics from 24h)



*Sacubitril/valsartan starting dose (24/26 mg or 49/51 mg bid) was decided by the investigator and up-titration was based on label recommendations and on tolerability, allowing the dose to be doubled every 2–4 weeks at the treating physician's discretion up to the target dose of 97/103 mg bid

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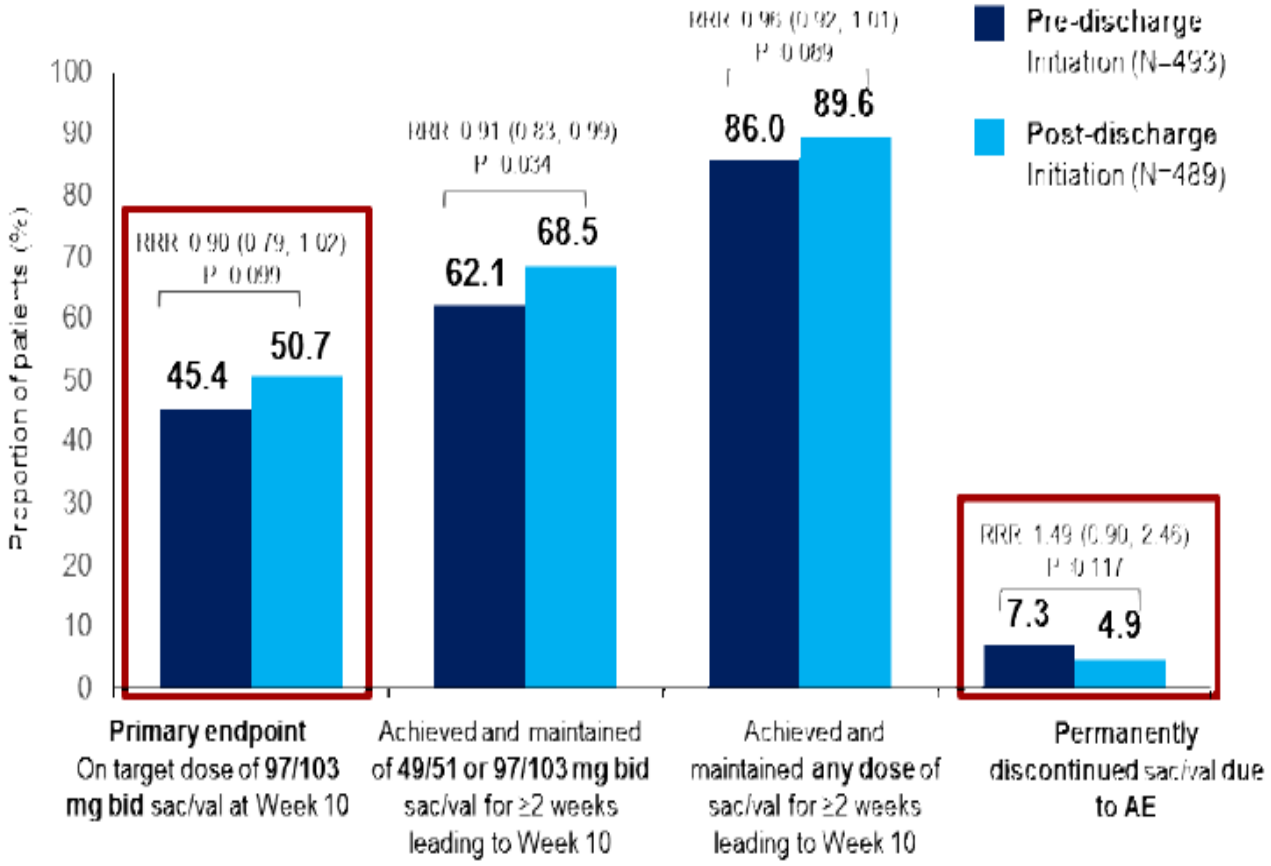
Pascual-Figal D, et al. ESC Heart Fail 2018;5(2):327–368

TRANSITION:

Primary and secondary endpoints

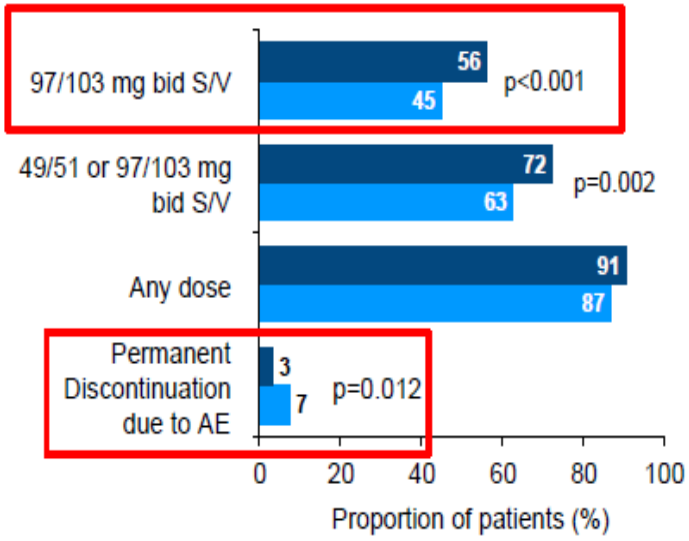


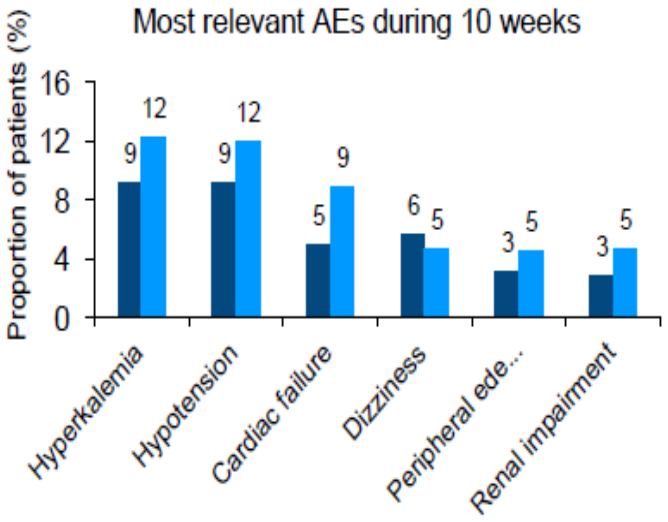
Azienda Ospedaliera
Papa Giovanni XXIII
Bergamo

Wachter R, et al. accepted Eur J Heart Fail

TRANSITION: *De novo* patients

Endpoints & safety





de novo HF (n=286) Prior CHF (n=705)

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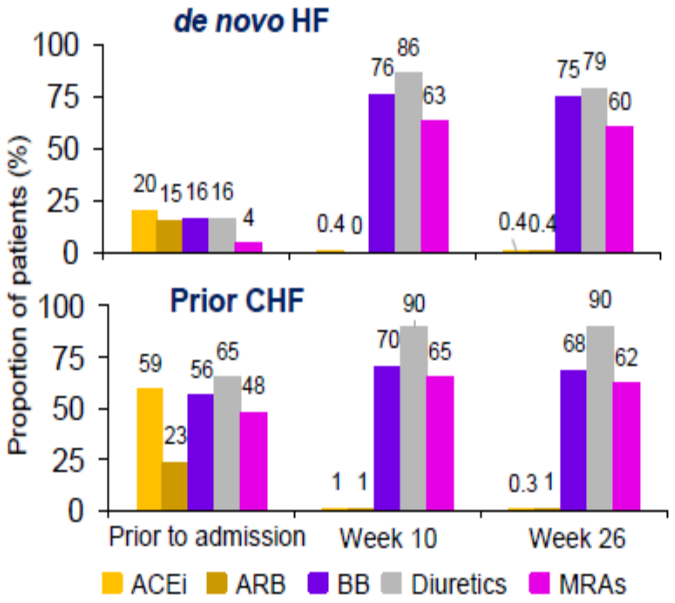
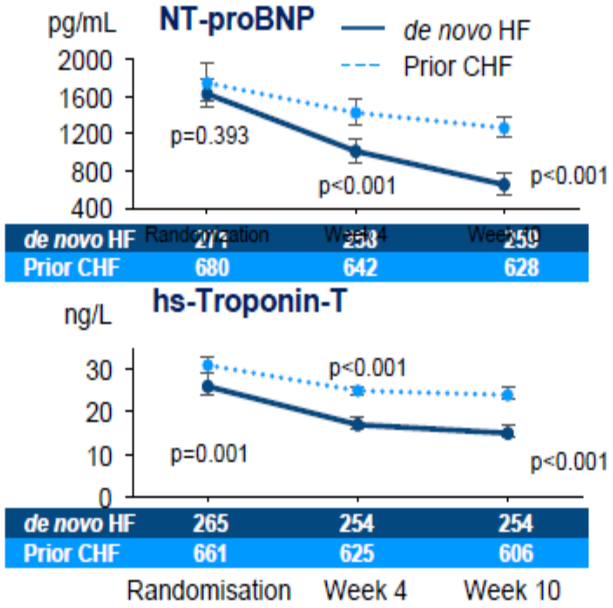
Senni M et al. Presented at HFA Congress Athens, 2019

TRANSITION: De novo patients

HF-meds optimization & biomarkers





Azienda Ospedaliera
Papa Giovanni XXIII
Bergamo

Senni M et al. Presented at HFA Congress Athens, 2019

Use of Sacubitril/Valsartan: 2019 ESC Clinical Practice Update

2019 ESC Clinical Practice Update

Sacubitril/valsartan is recommended as a replacement for an ACEI to further reduce the risk of HHF and death in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with an ACEI, BB, and MRA

Initiation of sacubitril/valsartan rather than an ACEI or an ARB may be considered for patients hospitalized with new-onset HF or decompensated HF to reduce the short-term risk of AEs and to simplify management

Seferovic PM, et al. *Eur J Heart Fail*. 2019 May 26 [Epub ahead of print]

2019 ACC Expert Consensus Decision Management, and Clinical Trajectory of Patients Hospitalized With Heart Failure

- ƯCMC, CTTAII, ARNI xem xét sau khi tình trạng Suy Tim Cấp ổn định
- Có thể xem xét cho ARNI nội viện theo tình trạng HA, chức năng thận, điều kiện tuân thủ sau khi xuất viện của bệnh nhân..

Hollenberg et al. JACC Sept. 2019

Liều ARNI khởi đầu cần phải giảm trong một số nhóm bệnh cảnh sau:

- ACEi/ARB naive or on low dose
- SBP 100-110 mm Hg
- eGFR 30-60 ml/min/m^2
- Moderate hepatic impairment
- Elderly according to renal function

→ Sacubitril/valsartan 24 mg/26 mg twice daily should be considered

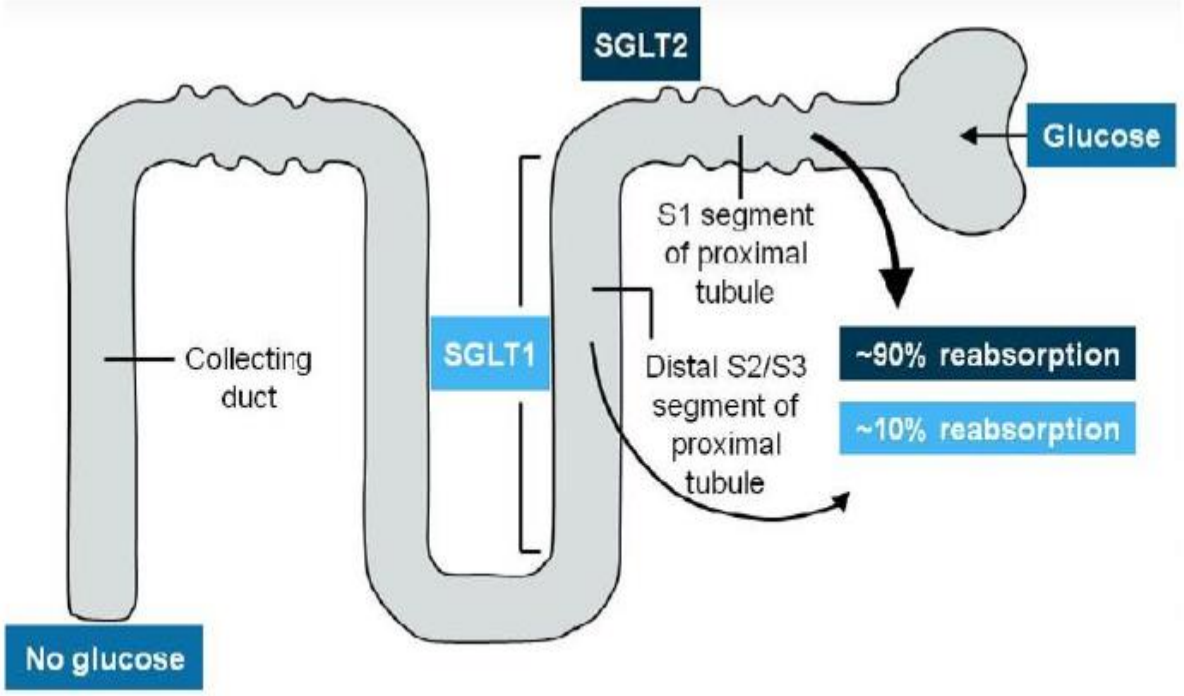
Chuẩn liều tăng dần với từng bước đi chậm (start low & go low) để đến đích và duy trì đích sacubitril/valsartan 97/103mg 2 lần /ngày

Senni M et al. Eur J Heart Fail 2016;18:1193-202; Wachter R, et al. Eur J Heart Fail *accepted*; Velazquez EJ, et al. N Engl J Med 2019;380:539–548

Thuốc ức chế SGLT2 có chỉ định trong điều trị suy tim không?

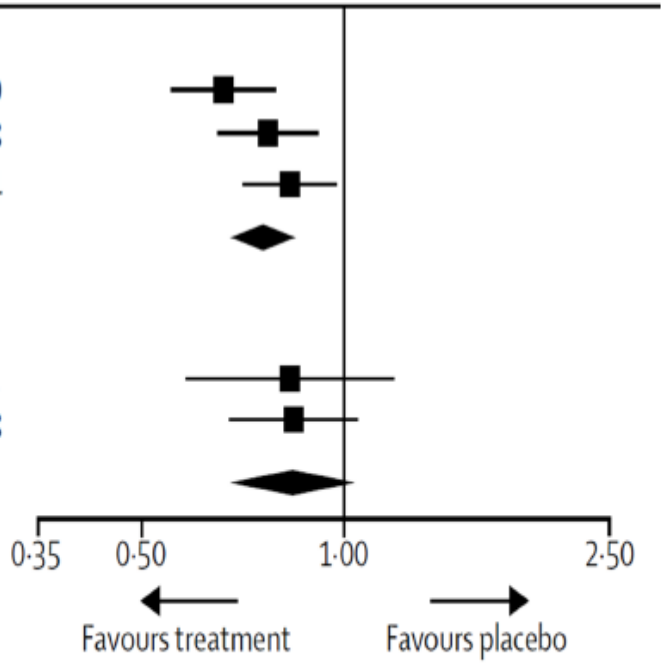
SGLT-2 inhibitors

Inhibit proximal tubular glucose reabsorption, cause diuresis and natriuresis, lower BP and reduce weight.
Also renoprotective (in diabetes)?



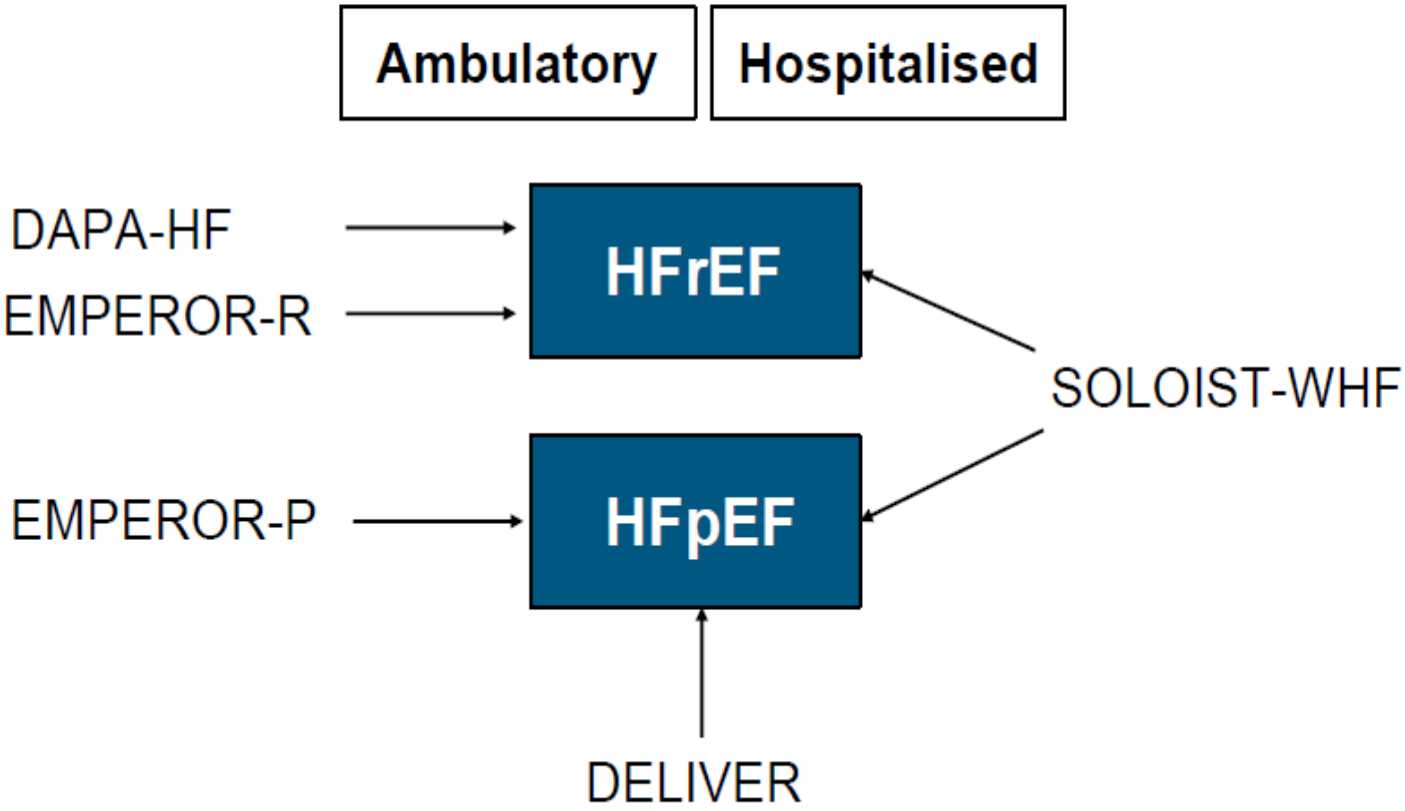
Large SGTLT2 inhibitor RCTs: Effect on heart failure hospitalization

	Patients		Events	Events per 1000 patient-years		Weight (%)
	Treatment (n/N)	Placebo (n/N)		Treatment	Placebo	
Patients with atherosclerotic CV disease						
EMPA-REG OUTCOME	4687/7020	2333/7020	463	19·7	30·1	30·9
CANVAS Program	3756/6656	2900/6656	524	21·0	27·4	32·8
DECLARE-TIMI 58	3474/6974	3500/6974	597	19·9	23·9	36·4
Fixed effects model for atherosclerotic cardiovascular disease (p<0·0001)						
Patients with multiple risk factors						
CANVAS Program	2039/3486	1447/3486	128	8·9	9·8	30·2
DECLARE-TIMI 58	5108/10 186	5078/10 186	316	7·0	8·4	69·8
Fixed effects model for multiple risk factors (p=0·0634)						



Sabatine M et al Lancet 2019: 393:31-39

Large Phase III mortality/morbidity outcome trials with SGLT2 (or SGLT1/2) inhibitors in heart failure



SGLT2 inhibitors Consensus Recommendation

- Ngoài empagliflozin đã được khuyến cáo năm 2016 chỉ định phải được xem xét cho ở bệnh nhân ĐTĐ T 2 “để dự phòng hoặc làm chậm khởi phát suy tim và kéo dài tuổi thọ” .
- Đồng thuận 2019 canagliflozin và dapagliflozin cũng phải được xem xét ở bệnh nhân ĐTĐ T2 có bệnh TM hoặc nguy cơ cao để ngăn ngừa hoặc làm chậm khởi phát và nhập viện do suy tim .
- Đến lúc nầy, chưa có khuyến cáo dùng ức chế SGLT2 cho bệnh nhân suy tim

European Journal of Heart Failure. May 2019

Recommendations for SGLT-2 inhibitors in reducing heart failure risk

Recommendations	Class	Level
SGLT2 inhibitors (empagliflozin, canagliflozin, dapagliflozin) are associated with a lower risk of HF hospitalization in patients with DM, and are recommended if the eGFR is stable and >30mL/min/1.73m^2.	I	A
Metformin should be considered for DM treatment in patients with HF, if the eGFR is stable and >30 mL/min/1.73 m^2.	IIa	C
GLP1-RAs (lixisenatide, liraglutide, semaglutide, exenatide, dulaglutide) have a neutral effect on the risk of HF hospitalization, and may be considered for DM treatment in patients with HF.	IIb	A

2019 ESC Guidelines on Diabetes, pre-diabetes and cardiovascular diseases (European Heart Journal; 2019 - doi/10.1093/eurheartj/ehz486)

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

John McMurray
BHF Cardiovascular Research Centre,
University of Glasgow & Queen Elizabeth
University Hospital, Glasgow

University of Glasgow

DAPAHF

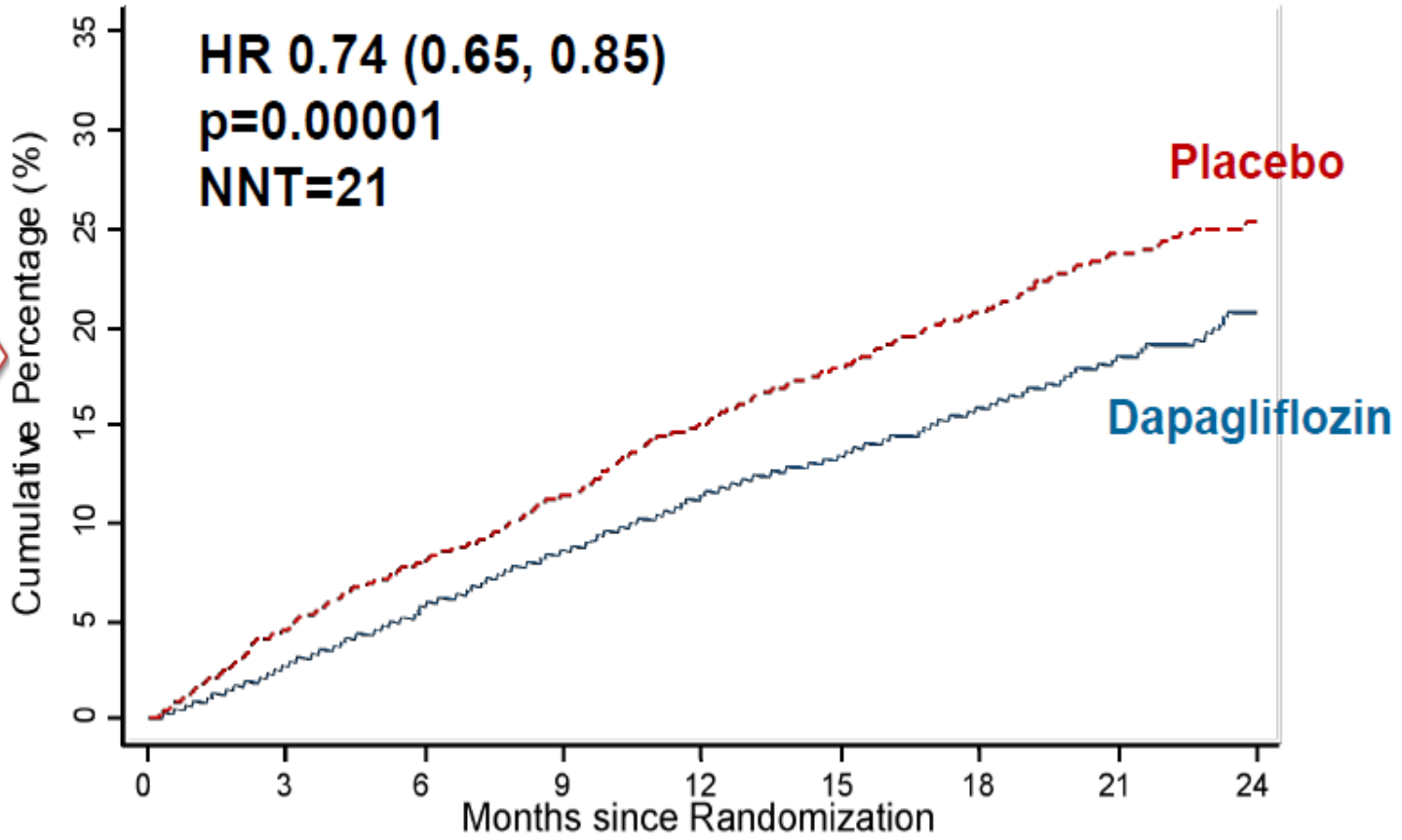
AstraZeneca

N Engl J Med 2019. DOI: 10.1056/NEJMoa1911303.

Primary composite outcome

CV Death/HF hospitalization/Urgent HF visit

DAPA-HF
dapagliflozin 10 mg/5 mg
vs.
placebo
In patients with
HFrEF (LVEF <40%)



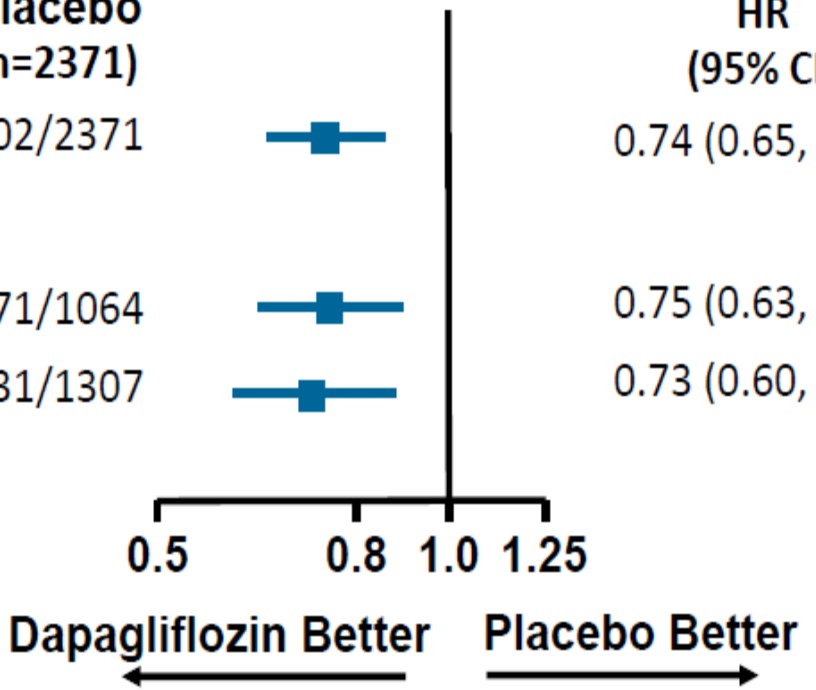
Number at Risk

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

N Engl J Med 2019. DOI: 10.1056/NEJMoa1911303.

No diabetes/diabetes subgroup: Primary endpoint

	Dapagliflozin (n=2373)	Placebo (n=2371)	HR (95% CI)
All patients	386/2373	502/2371	0.74 (0.65, 0.85)
Type 2 diabetes at baseline*			
Yes	215/1075	271/1064	0.75 (0.63, 0.90)
No	171/1298	231/1307	0.73 (0.60, 0.88)

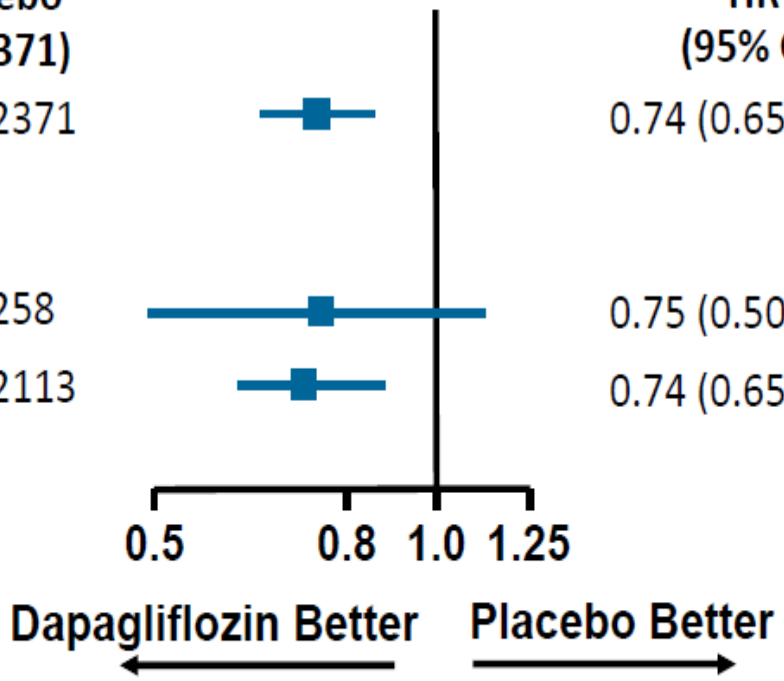


*Defined as history of type 2 diabetes or HbA1c ≥6.5% at both enrollment and randomization visits.

N Engl J Med 2019. DOI: 10.1056/NEJMoa1911303.

ARNI/no ARNI *post hoc* subgroup: Primary endpoint

	Dapagliflozin (n=2373)	Placebo (n=2371)	HR (95% CI)
All patients	386/2373	502/2371	0.74 (0.65, 0.85)
Angiotensin Receptor Neprilysin Inhibitor (ARNI)			
Yes	41/250	56/258	0.75 (0.50, 1.13)
No	345/2123	446/2113	0.74 (0.65, 0.86)



N Engl J Med 2019. DOI: 10.1056/NEJMoa1911303.

Summary and conclusions

- Dapagliflozin reduced the risk of worsening heart failure events and cardiovascular death, and improved symptoms, in patients with HFrEF, when added to standard therapy
- The relative and absolute risk reductions in death and hospitalization were substantial, clinically important, and consistent across important subgroups, including patients ***without*** T2D
- Dapagliflozin was well tolerated and the rate of treatment discontinuation was low
- Dapagliflozin offers a new approach to the treatment of HFrEF

N Engl J Med 2019. DOI: 10.1056/NEJMoa1911303.

Heart-Failure Therapy — New Drugs but Old Habits?

- Will clinicians incorporate this new class of heart failure medications into their daily practice?
- That remains to be seen, since there are barriers to the use of additional drugs in patients with heart failure, despite the evidence of benefit

James C. Fan. N Engl J Med. DOI: 10.1056/NEJMoa1911303.

Phòng Chống Suy Thận Và Tăng Kali Máu Khi Tăng Chuẩn Liều Hệ RAS Trong Điều Trị Suy Tim

- **read (and implement) heart failure guidelines web adenda**
- laboratory and clinical follow-up essential
  - RAASi initiated/titrated: check K/creatinine at W1
  - ACEi/ARB acceptable changes
    - K 5.5 mmol/L
    - Creatinine 50% increase/266 µmol/L
  - Halve dose: K >5.5 mmol/L / Creatinine >221 µmol/L
  - STOP: K >6.0 mmol/L / Creatinine >310 µmol/L
- new agents available for potassium binding: efficacy and safety tested

Patiromer:

OPAL

GFR 15-59; K 5.1-6.4; RAASi; 42-49% HF

4w; 74% normoK

8w randomized withdrawal → 15% vs 60% recurrence

PEARL-HF

HF + ([K requiring d/c RAASi] or [eGFR<60]) +

K 4.3-5.1 → init. Patiromer + Spiro

4w → hyperK in 7% vs 24%;

91% vs 74% on Spiro 50 mg/d

ZS-9:

HARMONIZE - HF sub-group

K≥5.1

48h→ 93% normoK

28d→ 83-92% vs. 40% maintained normoK

Patiromer in Patients with Kidney Disease and Hyperkalemia Receiving RAAS Inhibitors

Matthew R. Weir, M.D., George L. Bakris, M.D., David A. Bushinsky, M.D., Martha R. Mayo, Pharm.D., Dahlia Garza, M.D., Yuri Stasiv, Ph.D., Janet Wittes, Ph.D., Heidi Christ-Schmidt, M.S.E., Lance Berman, M.D., and Bertram Pitt, M.D., for the OPAL-HK Investigators*

European Heart Journal (2011) 32, 820–828
doi:10.1093/eurheartj/ehq502

FASTTRACK CLINICAL

Evaluation of the efficacy and safety of RLY5016, a polymeric potassium binder, in a double-blind, placebo-controlled study in patients with chronic heart failure (the PEARL-HF) trial

Bertram Pitt[1]*, Stefan D. Anker[2,3], David A. Bushinsky[4], Dalane W. Kitzman[5], Faiez Zannad[6], and I-Zu Huang[7], on behalf of the PEARL-HF Investigators

European Journal of Heart Failure (2015) 17, 1050–1056
doi:10.1002/ejhf.300

Maintenance of serum potassium with sodium zirconium cyclosilicate (ZS-9) in heart failure patients: results from a phase 3 randomized, double-blind, placebo-controlled trial

Stefan D. Anker[1]*, Mikhail Kosiborod[2], Faiez Zannad[3], Ileana L. Piña[4],

Clinical practice update on heart failure 2019. An expert consensus meeting report of HFA of the ESCc

- Patiromer và ZS-9 **có thể được xem xét ở bệnh nhân suy tim với hay không có Bệnh Thận Mạn để phòng chống tăng kali máu**. Trong những bệnh nhân chọn lọc, liệu pháp nầy có thể dùng để chuẩn liều MRA và ức chế RAS cao hơn.

European Journal of Heart Failure. May 2019

Kết Luận

- Qua 30 năm tiến bộ điều trị suy tim EF giảm các thuốc đã chứng minh (UCM/CTTAII, ARNI, BB, MRA) có hiệu quả cần bắt đầu và chuẩn liều đạt đến đích và duy trì liều đích sau khi tình trạng suy tim cấp ổn định và theo dõi sát các tác dụng phụ.
- Đồng thuận điều trị suy tim 2019 của ESC 2019

  - ARNI có thể nên dùng ngay từ nội viện khi tình trạng suy tim cấp ổn định

  - Có thể xem xét thuốc hạ kali khi chuẩn liều hệ RASi, MRA

  - Ức chế SGLT2 cần cho BN ĐTĐ có BTM hoặc nguy cơ cao chứ chưa có chỉ định chung cho BN suy tim. Tuy nhiên DAPA-HF đang mở ra nhiều hứa hẹn cho bệnh nhân suy tim