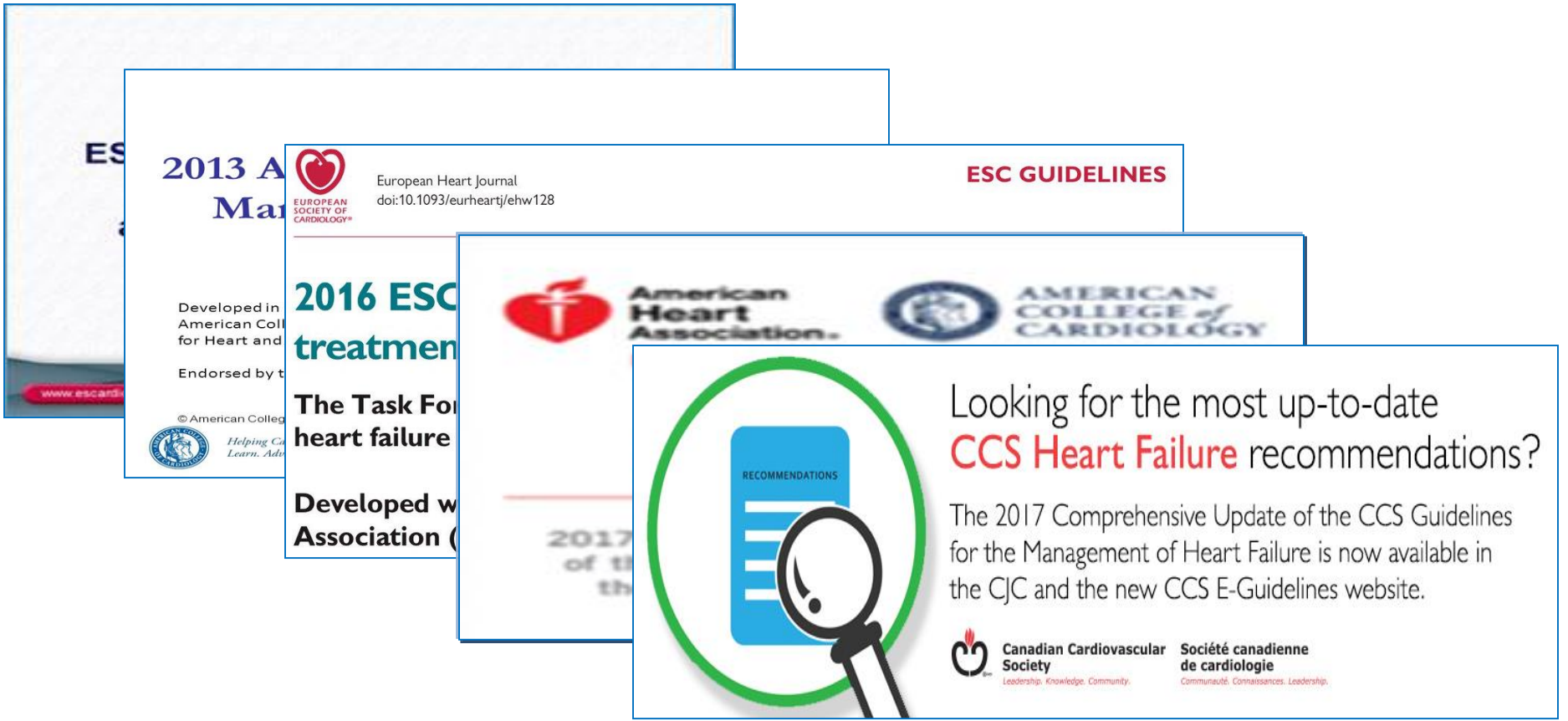
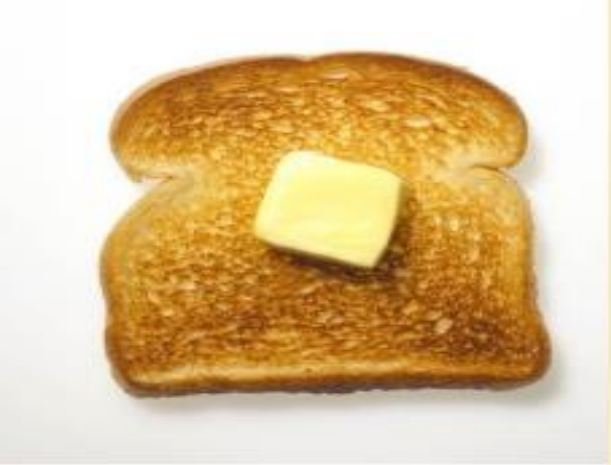
Cập nhật ESC 2019: NC DAPA – HF và KC mới của ESC thay đổi thực hành lâm sàng ra sao?

PGS. TS. Trương Quang Bình
ĐHYD TP. HCM

HF Guidelines 2012 - 2017





ESC 2016

Stage C HFrEF

Diuretics to relieve symptoms and signs of congestion

If LVEF ≤35% despite OMT or a history of symptomatic VT/VF, implant ICD

Class I

Class IIa

Patient with symptomatic[a] HFrEF[b]

↓

Therapy with ACE-I[c] and beta-blocker
(Up-titrate to maximum tolerated evidence-based doses)

↓

Still symptomatic and LVEF ≤35%? — No → →

↓ Yes

Add MR antagonist[d,e]
(up-titrate to maximum tolerated evidence-based dose)

↓

Still symptomatic and LVEF ≤35%? — No → →

↓ Yes

Able to tolerate ACEI (or ARB)[f,g]	Sinus rhythm, QRS duration ≥130 msec	Sinus rhythm,[h] HR ≥70 bpm
↓	↓	↓
ARNI to replace ACE-I	Evaluate need for CRT[i]	Ivabradine

↓

These above treatments may be combined if indicated

↓

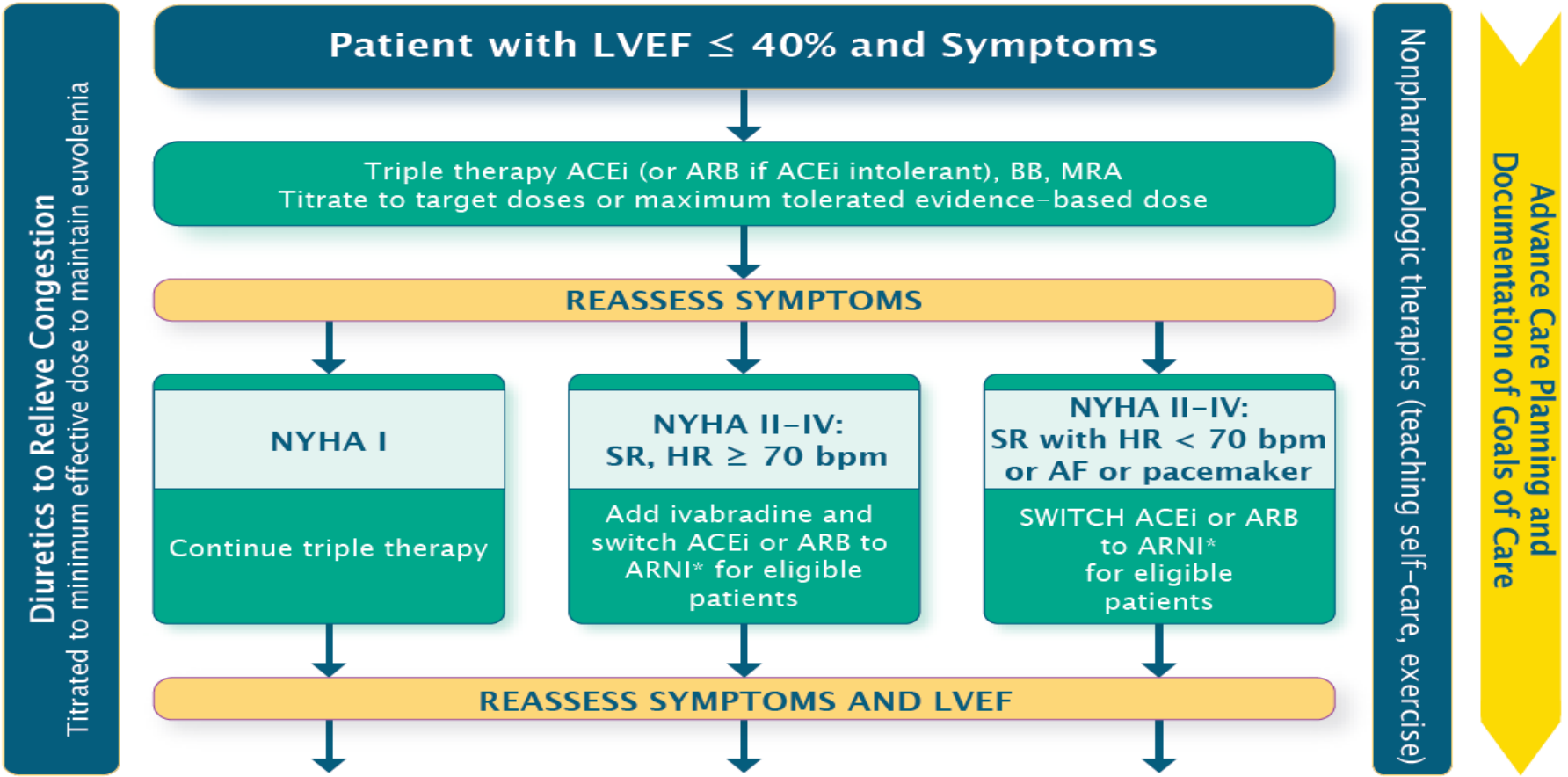
Resistant symptoms

Yes ↓ — No ↓

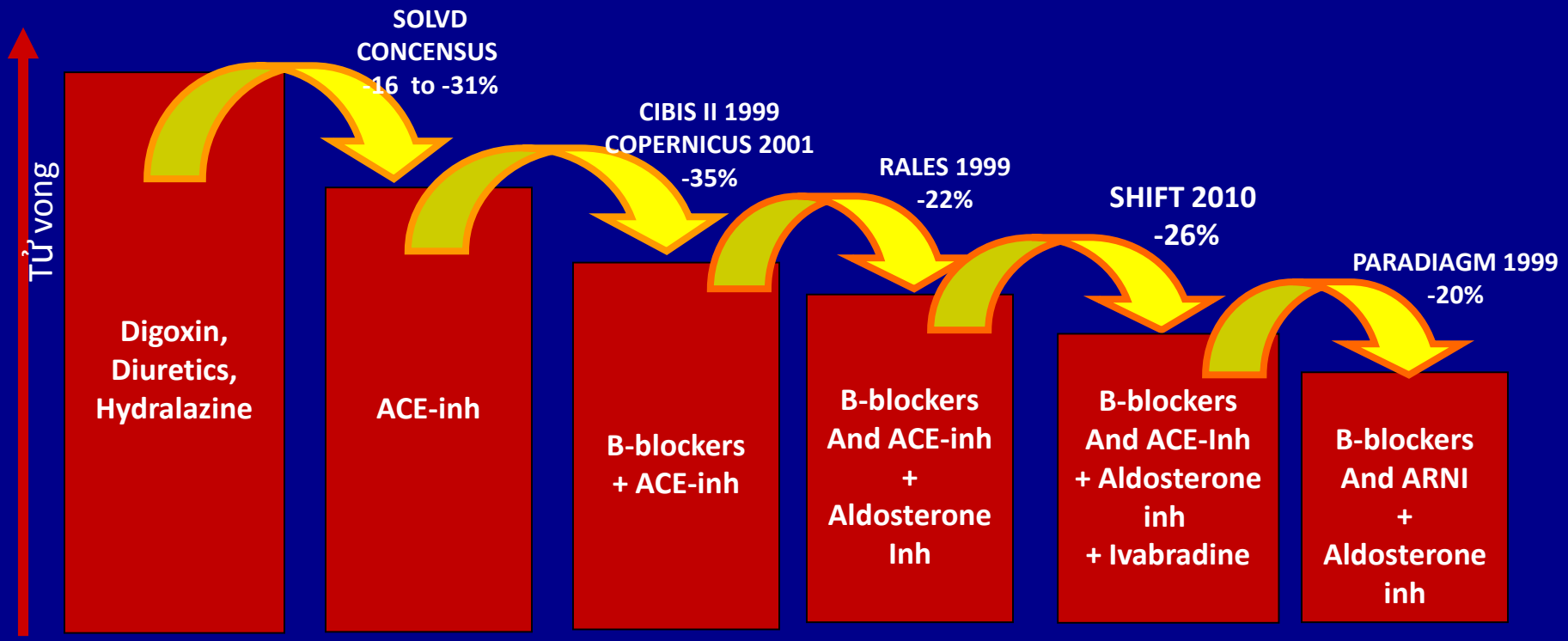
Consider digoxin or H-ISDN or LVAD, or heart transplantation

No further action required
Consider reducing diuretic dose

Therapeutic Approach to Patients With HFrEF



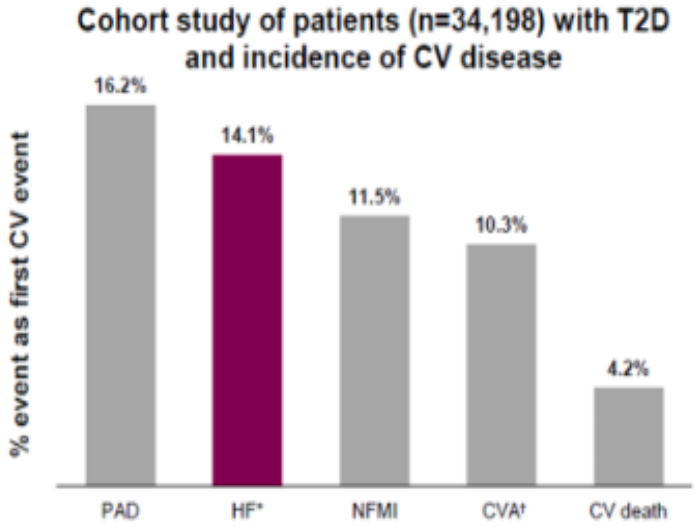
Vai trò của các thuốc điều trị suy tim kinh điển



Swedberg K, et al. *Eur J Heart Fail.* 2010;12:75-81

Suy tim ở bệnh nhân Đái tháo đường

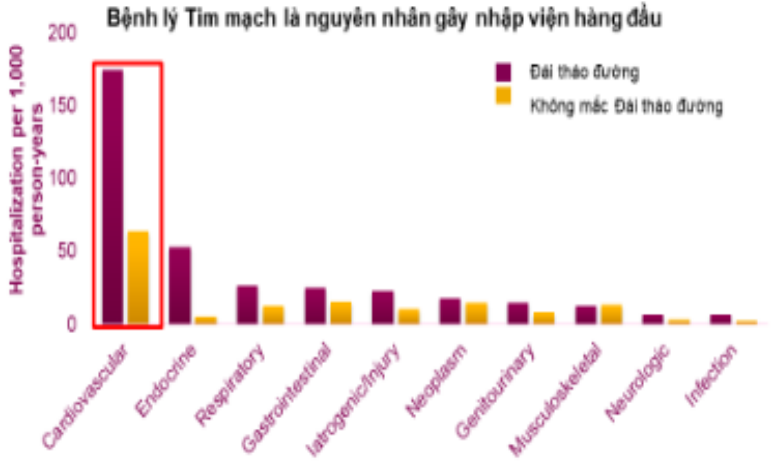
Biến cố thường gặp và xuất hiện SỚM



*Heart failure post-MI was not included in this definition of HF.
† 'Stroke not further specified' included ischaemic stroke.

CV, cardiovascular; CVA, cerebrovascular accident; HF, heart failure; MACE, major adverse cardiovascular events; NFMI, nonfatal myocardial infarction; PAD, peripheral arterial disease; T2D, type 2 diabetes.
Shah AD, et al. *Lancet Diabetes Endocrinol.* 2015;3(2):105-113, Appendix.

Nguyên nhân gây nhập viện hàng đầu



- Bệnh nhân có Đái tháo đường thường nhập viện suy tim sung huyết
- Bệnh nhân không đái tháo đường thường nhập viện vì bệnh lý động mạch vành

CI, confidence interval; CV, cardiovascular; HbA_{1c}, glycated haemoglobin; T2D, type 2 diabetes
Schernthaner AL, et al. *Diabetes Care* 2016;39:772–779

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.

Expert consensus on HF January 2019

Petar M. [illegible], 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], Andrew J. S. Coats[24]

1. SGLT2 inhibitors

January 2019

Consensus recommendation.

- The 2016 Guideline indicated that empagliflozin **should be considered** in patients with T2DM "in order to prevent or delay the onset of heart failure or prolong life"[8].

- The 2019 expert consensus was that canagliflozin and dapagliflozin **should** also **be considered** for patients with T2DM and either established CV disease or at high CV risk in order to prevent or delay the onset of and hospitalisations for HF.

ESC
European Society of Cardiology
European Heart Journal (2019) **00**, 1–69
doi:10.1093/eurheartj/ehz486

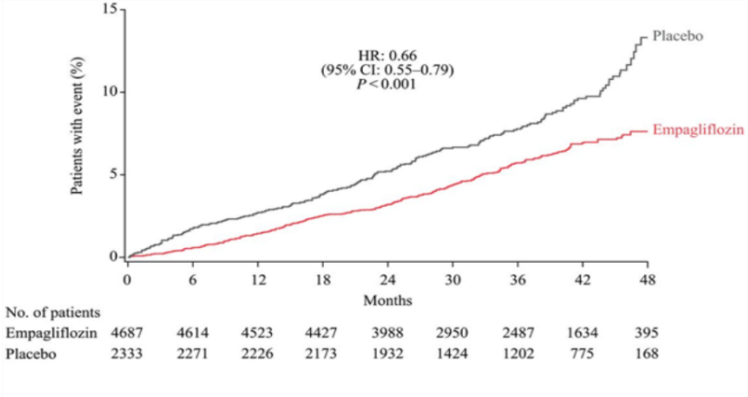
ESC GUIDELINES

2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD

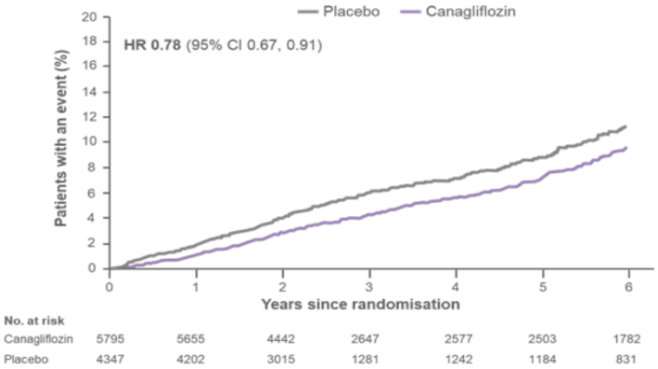
The Task Force for diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD)

CVOTs with SGLT2 inhibitors II
Heart failure hospitalisation or CV death

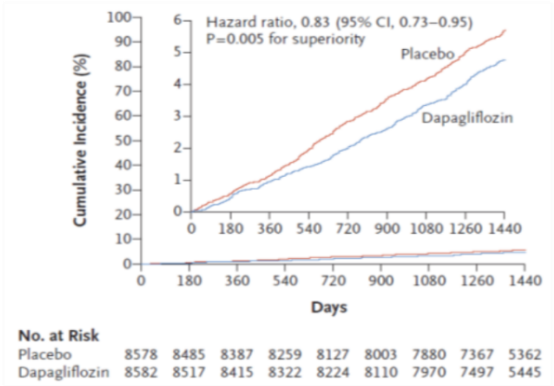
EMPA-REG Outcome[1]



Canvas program[2]



DECLARE[3]



1. Zinman B et al. N Engl J Med. 2015; 373:2117-2128
2. Neal B et al. N Engl J Med 2017; 377:644-656
3. Wiviott SD et al. N Engl J Med 2018;380:347-357

Sept 2019, ESC guideline

Recommendations for the treatment of patients with diabetes to reduce heart failure risk

Recommendations	Class[a]	Level[b]
SGLT2 inhibitors (empagliflozin, canagliflozin, and dapagliflozin) are recommended to lower risk of HF hospitalization in patients with DM.[306,311,496]	I	A

DAPA-HF - A global trial

4,744 patients 20 countries

North America

Canada	223
USA	454

Western Europe

Denmark	99
Germany	186
Netherlands	135
Sweden	68
UK	62

Central/Eastern Europe

Bulgaria	266
Czech Rep.	210
Hungary	250
Poland	290
Slovakia	166
Russia	422

Latin America

Argentina	297
Brazil	520

Asia-Pacific

China	237
India	237
Japan	343
Taiwan	141
Vietnam	138

Background

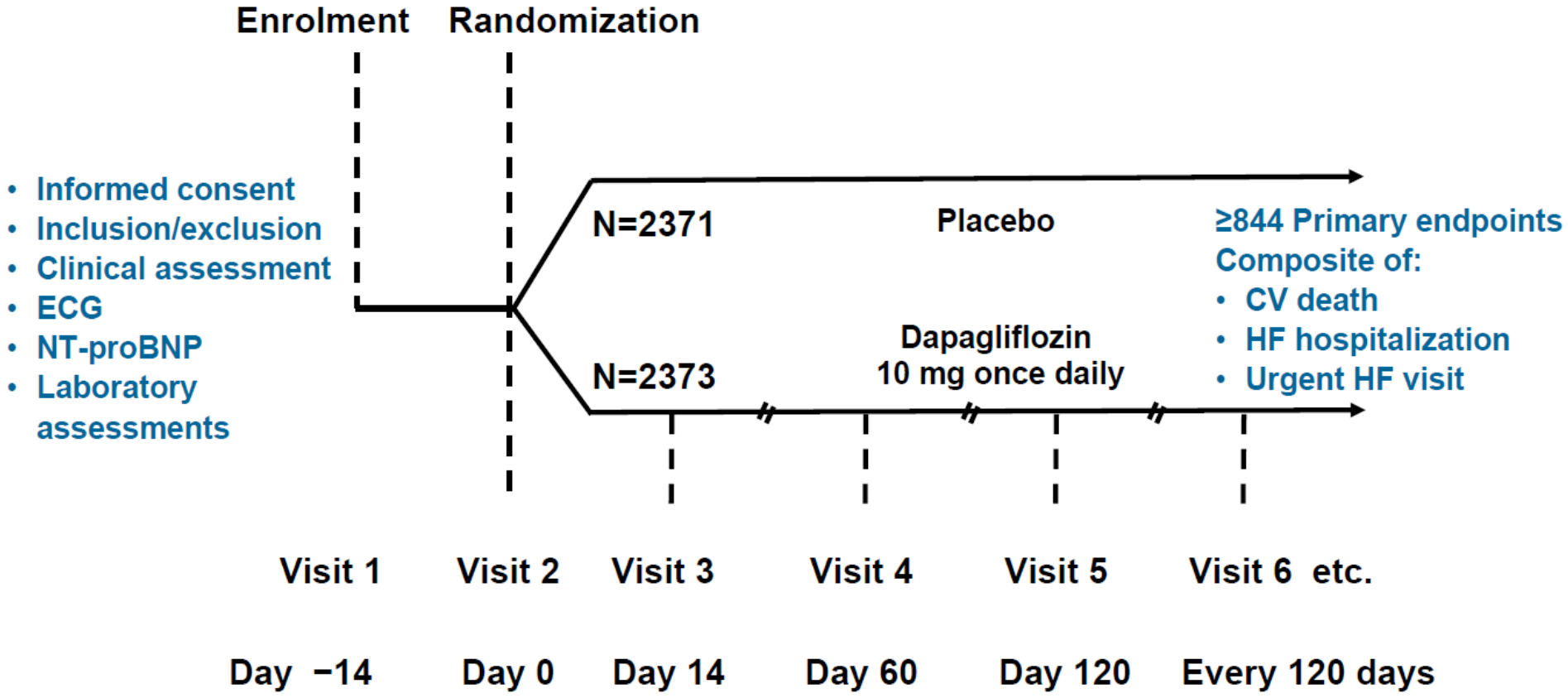
- Sodium-glucose co-transporter 2 (SGLT2) inhibitors ***prevent*** the development of heart failure in patients with type 2 diabetes (T2D). Can they be used to ***treat*** patients with established heart failure?
- The benefits of SGLT2 inhibitors may be glucose-independent. Can SGLT2 inhibitors be used to treat patients ***without*** T2D?
- We tested the SGLT2 inhibitor dapagliflozin,10 mg once daily, added to standard therapy, in patients with heart failure and reduced ejection fraction (HFrEF) both ***with and without*** T2D

Trial Design

- **Key inclusion criteria:** Symptomatic HF; EF ≤40%; NT-proBNP ≥600 pg/ml (if hospitalized for HF within last 12 months ≥400 pg/mL; if atrial fibrillation/flutter ≥900 pg/mL)
- **Key exclusion criteria:** eGFR <30 ml/min/1.73 m^2; symptomatic hypotension or SBP <95 mmHg; type 1 diabetes mellitus
- **Primary endpoint:** Worsening HF event or cardiovascular death (worsening HF event = unplanned HF hospitalization or an urgent heart failure visit requiring intravenous therapy)

For full details see McMurray JJV et al Eur J Heart Fail. 2019;21:665-675

DAPA-HF Design



Baseline treatment

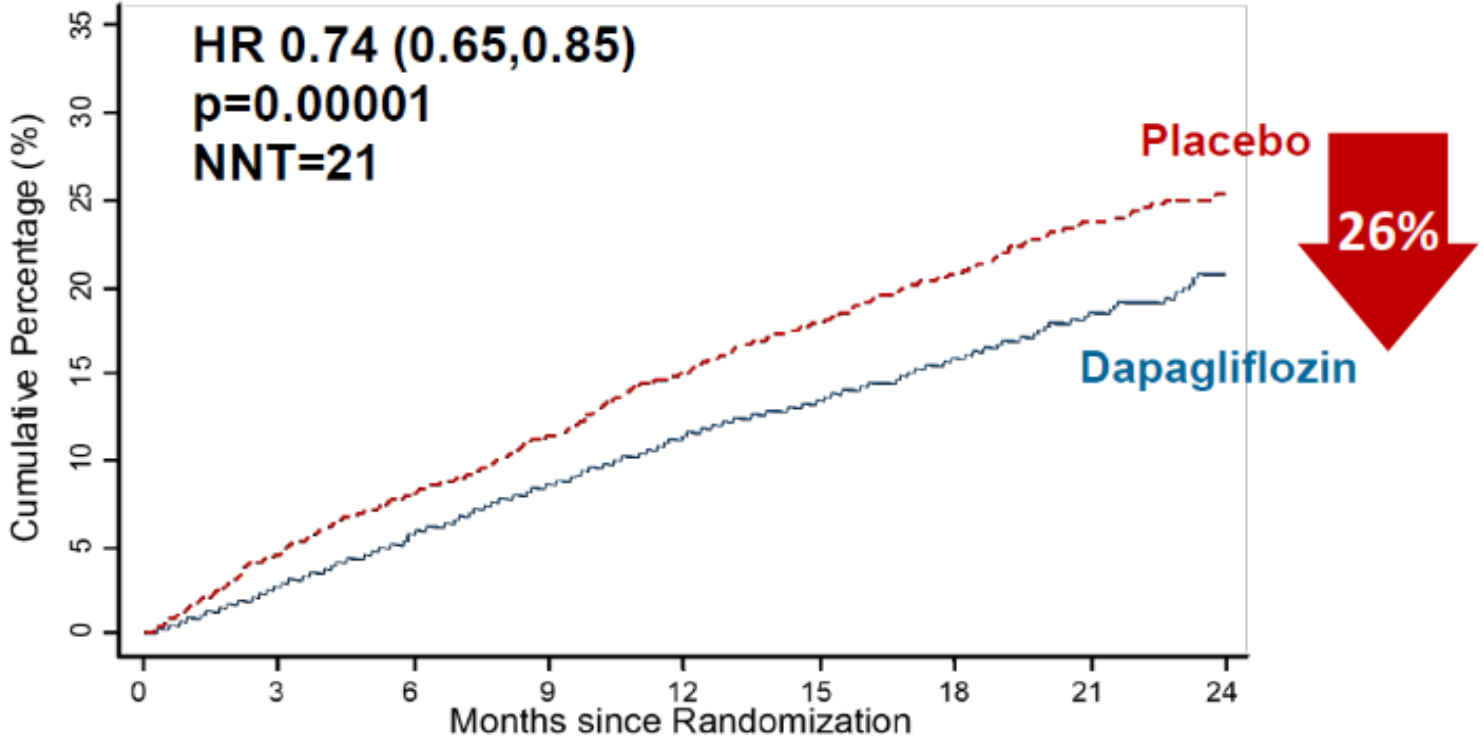
Treatment (%)	Dapagliflozin (n=2373)	Placebo (n=2371)
Diuretic	93	94
ACE-inhibitor/ARB/ARNI⁺	94	93
ACE inhibitor	56	56
ARB	28	27
Sacubitril/valsartan	11	11
Beta-blocker	96	96
MRA	71	71
ICD*	26	26
CRT**	8	7

⁺ARNI = angiotensin receptor neprilysin inhibitor
*ICD or CRT-D **CRT-P or CRT-D

For full details see McMurray JJV et al
Eur J Heart Fail.2019 Jul 15. doi: 10.1002/ejhf.1548

Primary composite outcome

CV Death/HF hospitalization/Urgent HF visit

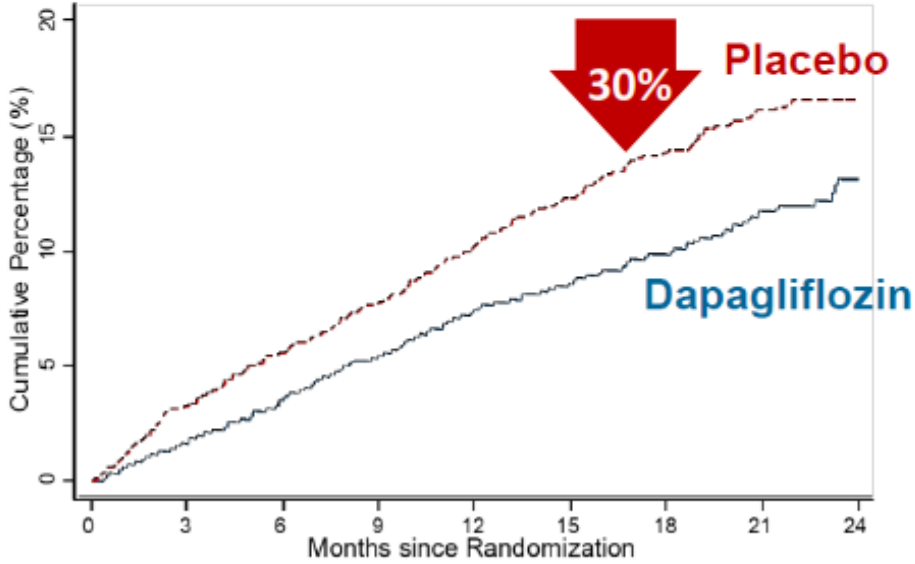


Number at Risk									
Dapagliflozin	2373	2305	2221	2147	2002	1560	1146	612	210
Placebo	2371	2258	2163	2075	1917	1478	1096	593	210

Components of primary outcome

Worsening HF event

HR 0.70 (0.59, 0.83); p=0.00003

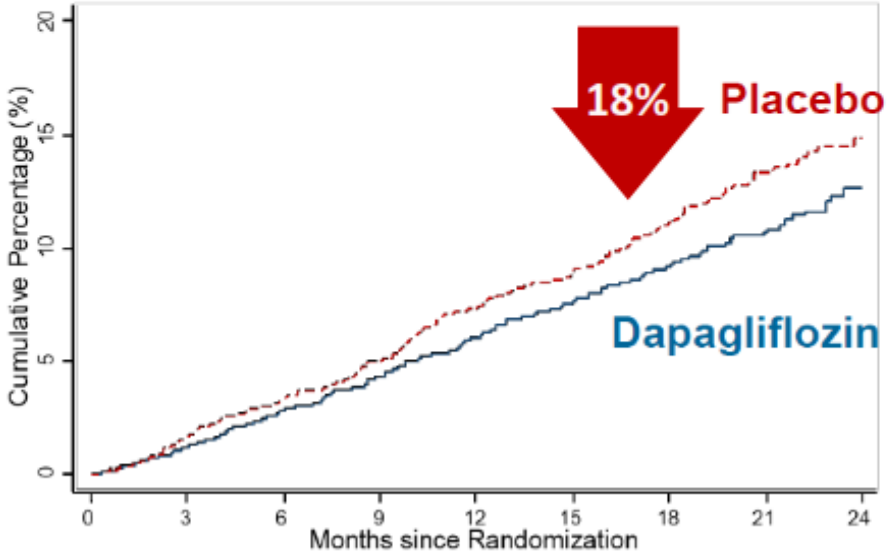


Number at Risk

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

Cardiovascular death

HR 0.82 (0.69, 0.98); p=0.029



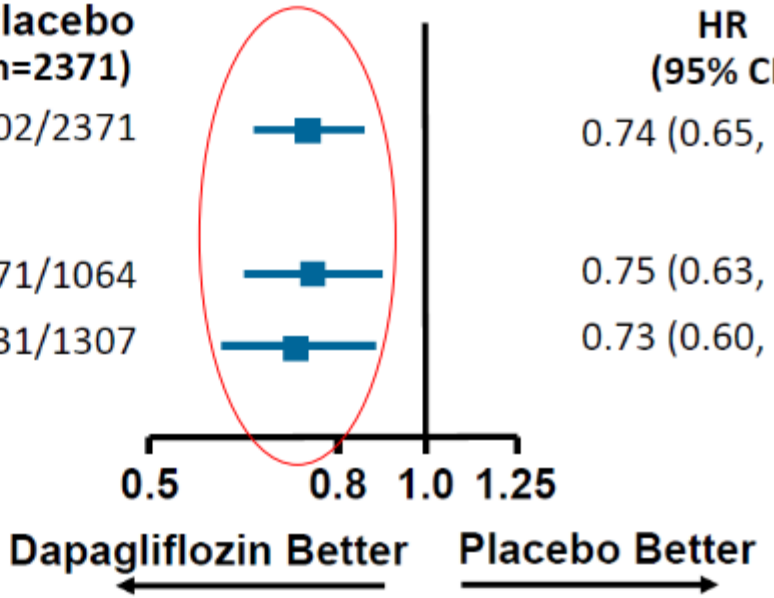
	2373	2339	2293	2248	2127	1664	1242	671	232
	2371	2330	2279	2230	2091	1636	1219	664	234

No diabetes/diabetes subgroup: Primary endpoint

Kết quả ĐỒNG NHẤT trên cả 2 phân nhóm:

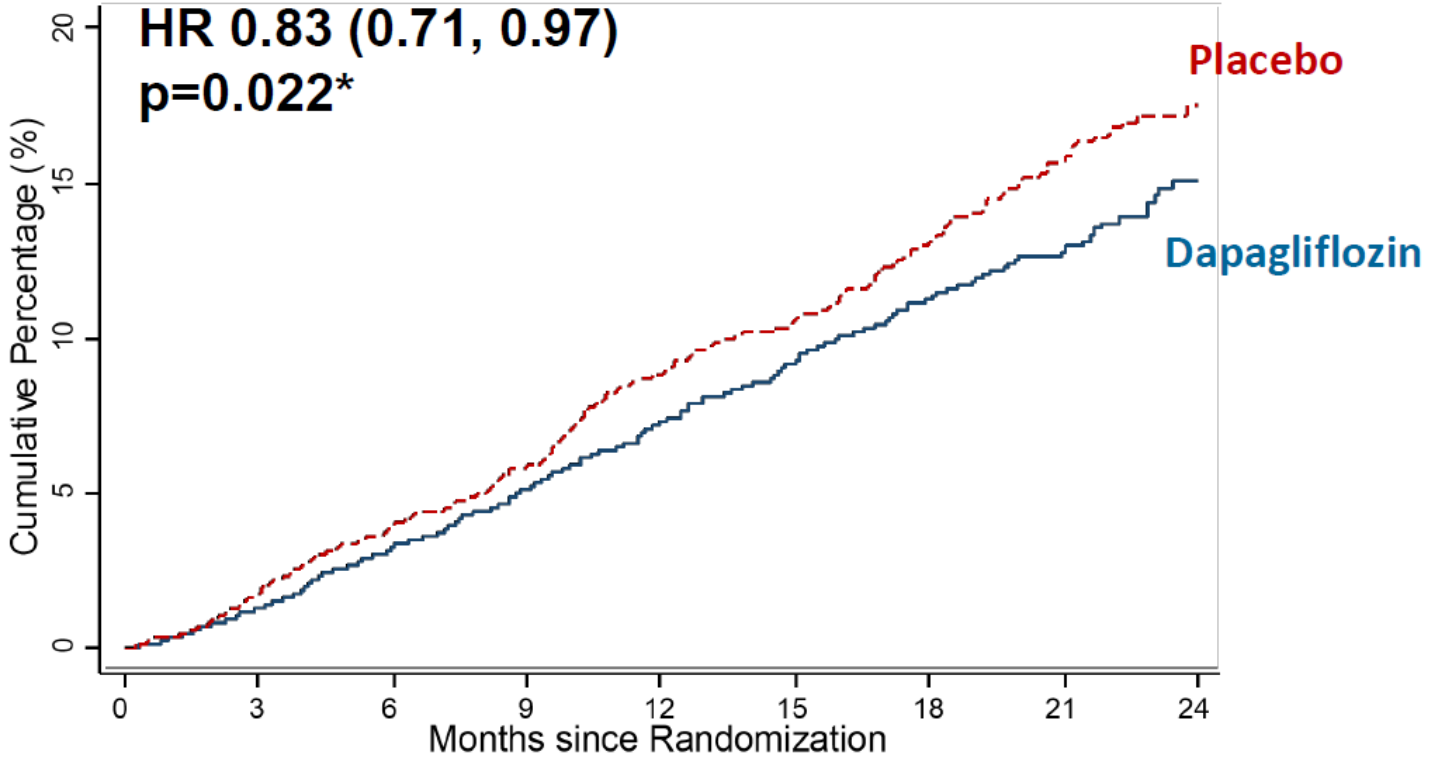
CÓ hoặc KHÔNG CÓ ĐÁI THÁO ĐƯỜNG

	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.

All-cause death



Number at Risk									
Dapagliflozin	2373	2342	2296	2251	2130	1666	1243	672	233
Placebo	2371	2330	2279	2231	2092	1638	1221	665	235

*Nominal p value

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

Recent positive trials of pharmacological therapy in HFrEF

Trial	Background therapy	CV death/ HF hospital.	HF hospital.	CV death	All-cause death
SHIFT (n=6558) plac v. ivabradine	*ACE/ARB 93%* *BB 90%* *MRA 60%*	**0.82** *(0.75,0.90)*	**0.74** *(0.66,0.83)*	**0.91** *(0.80,1.03)*	**0.90** *(0.80,1.02)*
EMPHASIS-HF (n=2737) plac v. eplerenone	*ACE/ARB 94%* *BB 87%* ***MRA N/A***	**0.66** *(0.56,0.78)*	**0.61** *(0.50,0.75)*	**0.77** *(0.62,0.96)*	**0.78** *(0.64,0.95)*
PARADIGM-HF (n=8399) enalapril v. sac/val (control v. neprilysin inhib.)	*ACE/ARB 100%* *BB 93%* *MRA 56%*	**0.80** *(0.73,0.87)*	**0.79** *(0.71,0.89)*	**0.80** *(0.71,0.89)*	**0.84** *(0.76,0.93)*
DAPA-HF (n=4744) placebo v. dapagliflozin	*ACE/ARB* 94%* *BB 96%* *MRA 71%*	**0.75** *(0.65,0.85)*	**0.70** *(0.59,0.83)*	**0.82** *(0.69,0.98)*	**0.83** *(0.71,0.97)*

*including sacubitril/valsartan

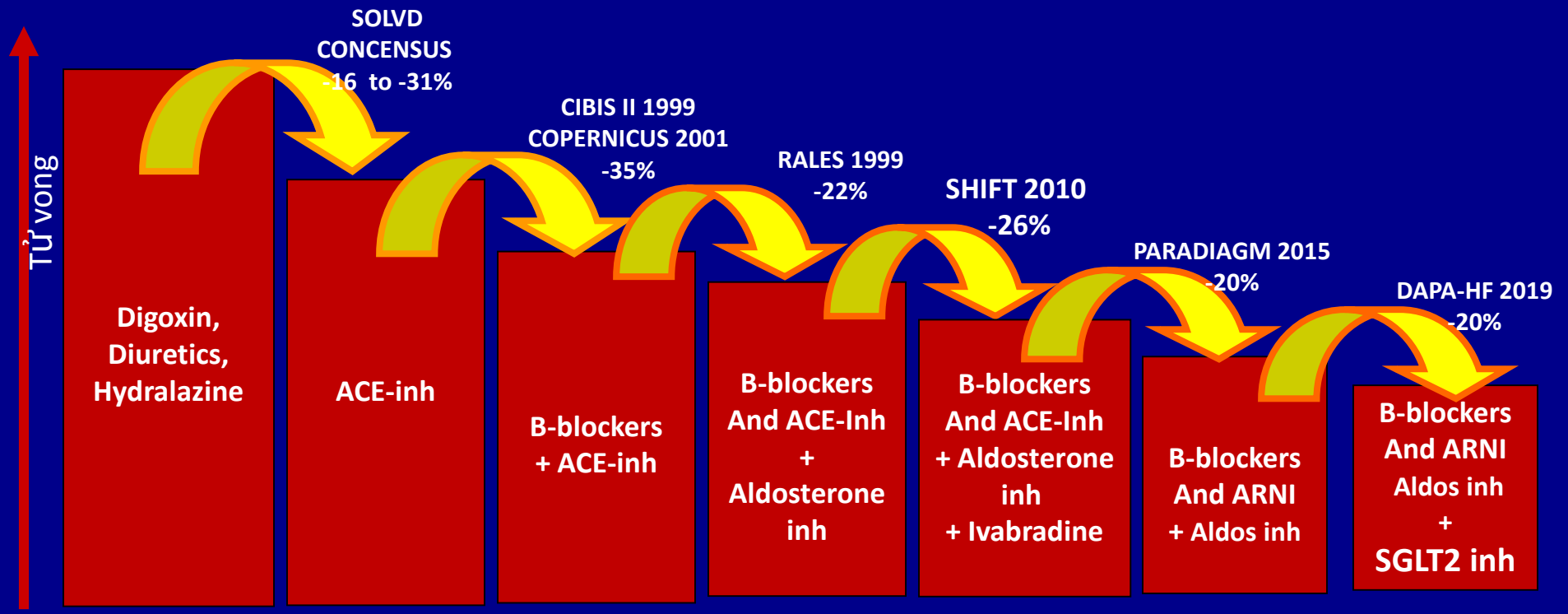
Absolute benefit of treatment

Reduction in events per 1000 person years

Trial	Background therapy	CV death/ HF hospital.	HF hospital.	CV death
PARADIGM-HF (n=8399) enalapril v. sac/val (control v. neprilysin inhib.)	*ACE/ARB 100%* *BB 93%* *MRA 56%*	**26.7**	**15.9**	**15.0**
DAPA-HF (n=4744) placebo v. dapagliflozin	*ACE/ARB* 94%* *BB 96%* *MRA 71%*	**38.7**	**29.2**	**14.0**

*including sacubitril/valsartan

Dùng thuốc điều trị suy tim trong thực hành LS



Swedberg K, et al. *Eur J Heart Fail.* 2010;12:75-81

Kết luận

- Tháng 1 – 2019, đồng thuận ESC: Empa, Cana, Dapa phòng ngừa suy tim và suy tim phải nhập viện cho BN ĐTĐ Type 2. **(CĐ nhóm IIa)**

- Tháng 9 – 2019, KC ESC: Empa, Cana, Dapa làm giảm nguy cơ nhập viện vì suy tim cho BN ĐTĐ type 2. **(chỉ định nhóm I)**

- NC DAPA-HF: Dapa làm giảm NC nhập viện vì suy tim
  Dapa làm giảm NC tử vong do tim mạch
  Dapa làm giảm NC tử vong do mọi NN
  (cho cả bn ĐTĐ lẫn bn KHÔNG ĐTĐ)

=> Một cách tiếp cận mới trong điều trị suy tim