بسم الله الرحمن الرحيم

New drugs for treatment of heart failure

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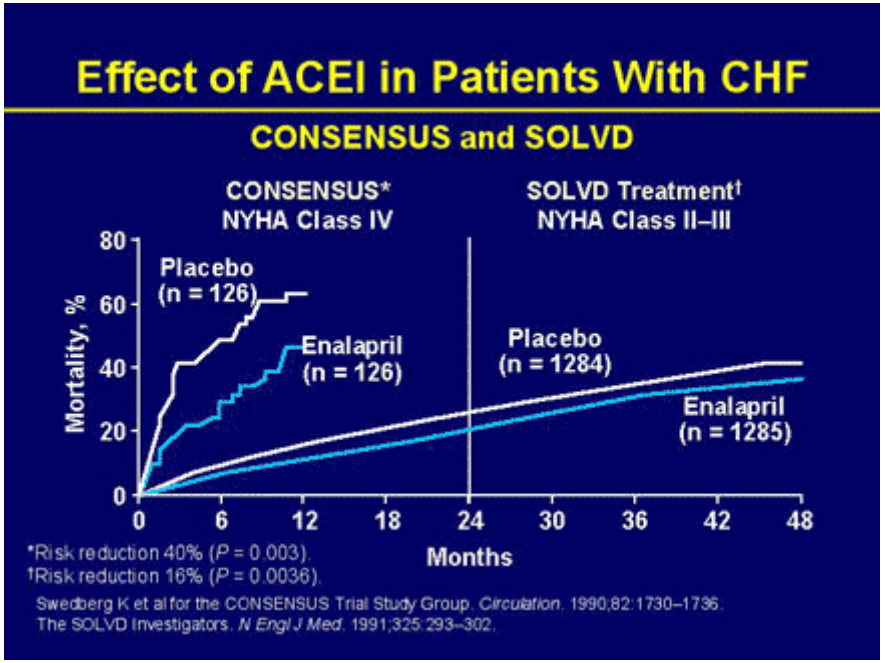
ESC GUIDELINES

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

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

With the special contribution of the Heart Failure Association (HFA) of the ESC

Angiotensin-converting enzyme inhibitors



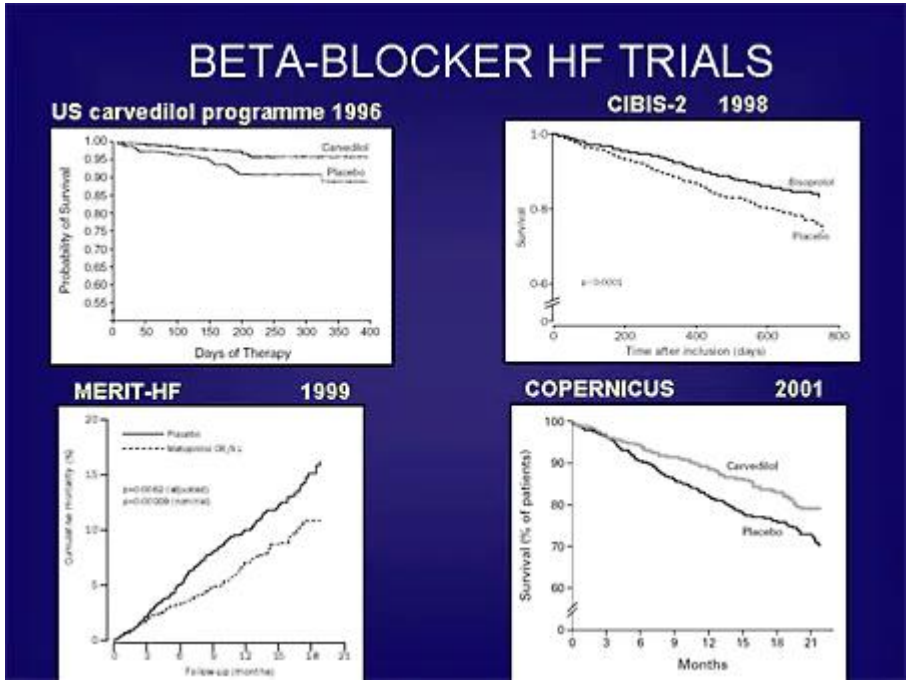
ACE-Is were the first class of drugs shown to reduce mortality and morbidity in patients with HFrEF

They have also been shown to improve symptoms

They are recommended in all patients unless contraindicated or not tolerated.

They should be uptitrated to the maximum tolerated recommended doses.

Beta-blockers



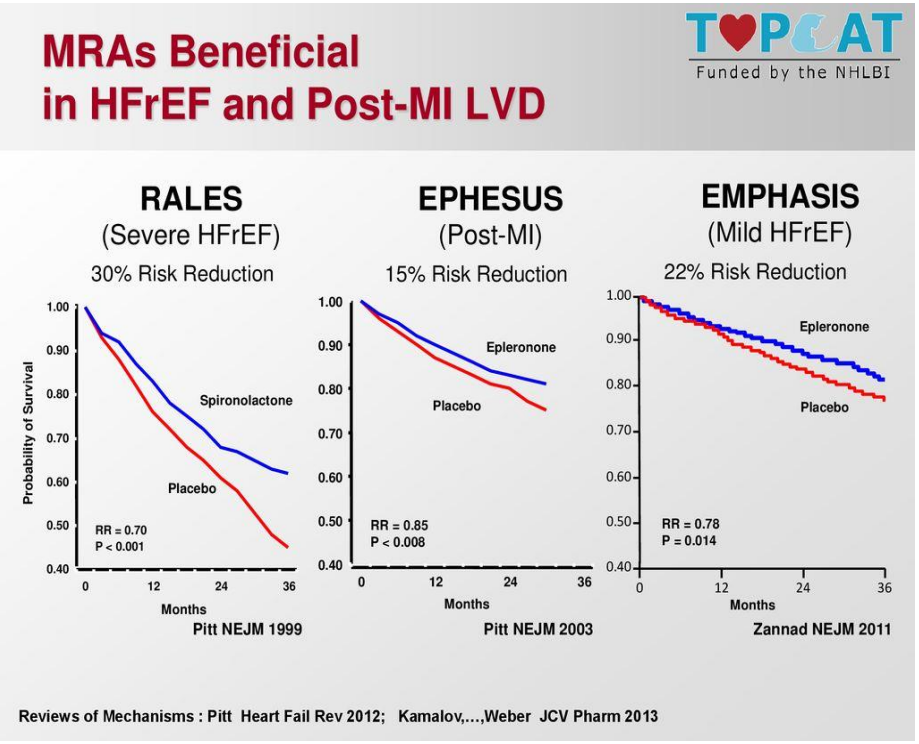
Beta-blockers have been shown to reduce mortality and morbidity in patients with HFrEF, in addition to treatment with an ACE-I and diuretic.

They also improve symptoms

There is consensus that ACE-I and beta-blockers can be commenced together as soon as the diagnosis of symptomatic HFrEF is established.

Beta-blockers should be initiated in clinically stable, euvolaemic, patients at a low dose and gradually uptitrated to the maximum tolerated dose.

Mineralocorticoid receptor antagonists



MRAs (spironolactone or eplerenone) are recommended, in addition to an ACE-I and a beta-blocker, in all patients with HFrEF to reduce mortality and the risk of HF hospitalization.

They also improve symptoms.

Caution should be exercised when MRAs are used in patients with impaired renal function and in those with serum potassium concentrations >5.0mmol/L.

Diuretics

- Loop diuretics are recommended to reduce the signs and/or symptoms of congestion in patients with HFrEF. The quality of the evidence regarding diuretics is poor and their effects on morbidity and mortality have not been studied in RCTs.

Angiotensin II type I receptor blockers

- The place of ARBs in the management of HFrEF has changed over the last few years. They are now recommended for patients who cannot tolerate ACE-I or ARNI because of serious side effects.
- However, no ARB has reduced all-cause mortality in any trial.

Combination of hydralazine and isosorbide dinitrate

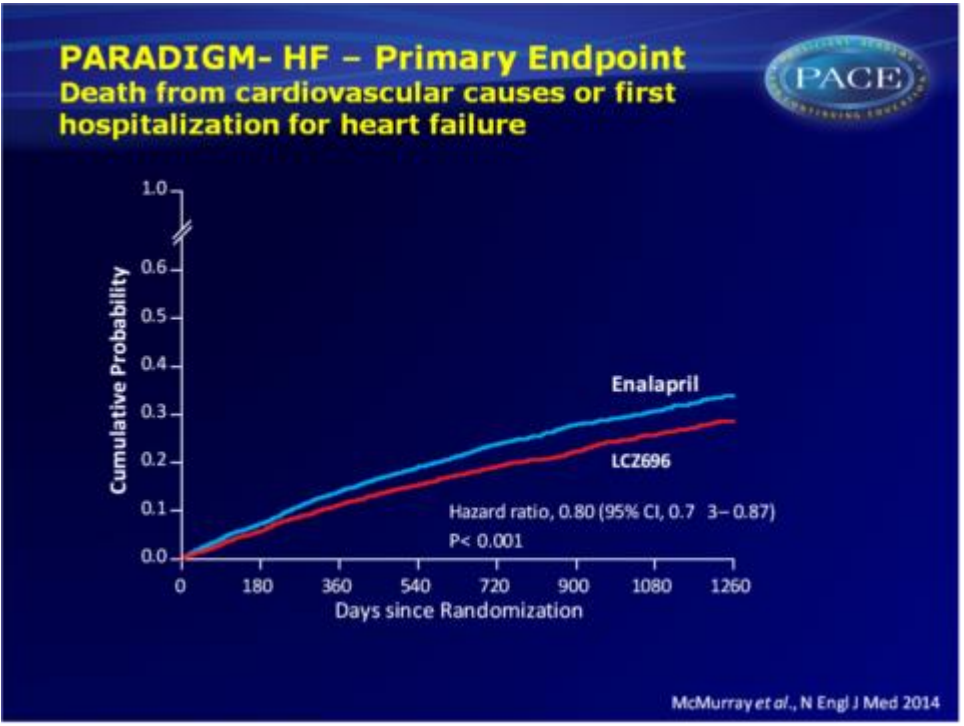
- A small RCT conducted in self-identified black patients showed that an addition of the combination of hydralazine and isosorbide dinitrate to conventional therapy (an ACE-I, a beta-blocker, and an MRA) reduced mortality and HF hospitalizations in patients with HFrEF and NYHA classes III-IV.
- These results are difficult to translate to patients of other racial or ethnic origins.

- A combination of hydralazine and isosorbide dinitrate may be considered in symptomatic patients with HFrEF who cannot tolerate any of an ACE-I, ARNI, or an ARB (or if they are contraindicated) to reduce mortality. However, this recommendation is based on the results of the relatively small Veterans Administration Cooperative Study, which included only male patients with symptomatic HFrEF who were treated with digoxin and diuretics.

Digoxin

- in patients with symptomatic HF and AF, digoxin may be useful for the treatment of patients with HFrEF and AF with rapid ventricular rate, when other therapeutic options cannot be pursued

Angiotensin receptor-neprilysin inhibitor

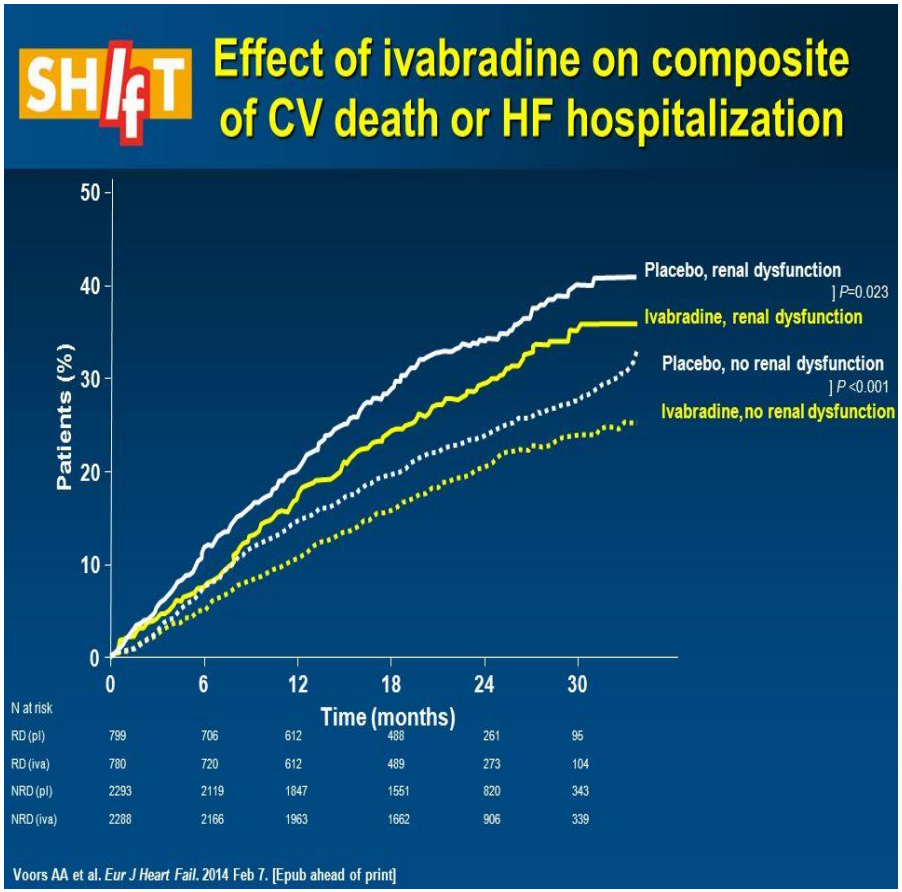


Additional benefits of sacubitril/ valsartan included an improvement in symptoms and QOL, a reduction in the incidence of diabetes requiring insulin treatment, and a reduction in the decline in eGFR, as well as a reduced rate of hyperkalaemia

Practical points in ARNI use

- It is recommended that an ACE-I or ARB is replaced by sacubitril/valsartan in ambulatory patients with HFrEF, who remain symptomatic despite optimal treatment outlined above.
- Patients being commenced on sacubitril/valsartan should have an adequate blood pressure (BP), and an eGFR >_30 mL/min/1.73 m2.
- A washout period of at least 36 h after ACE-I therapy is required in order to minimize the risk of angioedema.

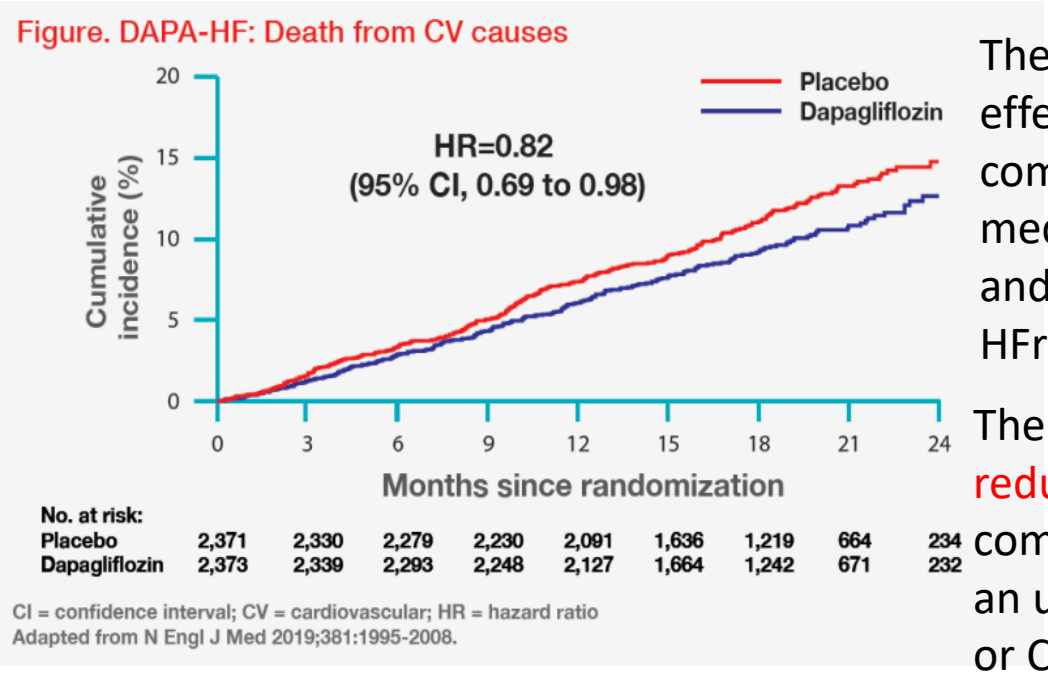
If -channel inhibitor



Ivabradine slows heart rate by inhibition of the If channel in the sinus node and is therefore only effective in patients in SR.

Ivabradine reduced the combined endpoint of CV mortality and HF hospitalization in patients with symptomatic HFrEF with an LVEF <_35%, with HF hospitalization in recent 12 months, in sinus rhythm (SR) and with a heart rate >_70 b.p.m. who were on evidence-based therapy including an ACE-I (or ARB), a beta-blocker, and an MRA.

Sodium-glucose co-transporter 2 inhibitors



The DAPA-HF trial investigated the long-term effects of dapagliflozin (SGLT2 inhibitor) compared to placebo in addition to optimal medical therapy (OMT), on morbidity andmortality in patients with ambulatory HFrEF

Therapy with dapagliflozin resulted in a 26% reduction in the primary endpoint: a composite of worsening HF (hospitalization or an urgent visit resulting in i.v. therapy for HF) or CV death. Both of these components were significantly reduced. Moreover, dapagliflozin reduced all-cause mortality, alleviated HF symptoms, improved physical function and QOL in patients with symptomatic HFrEF.

Sodium-glucose co-transporter 2 inhibitors

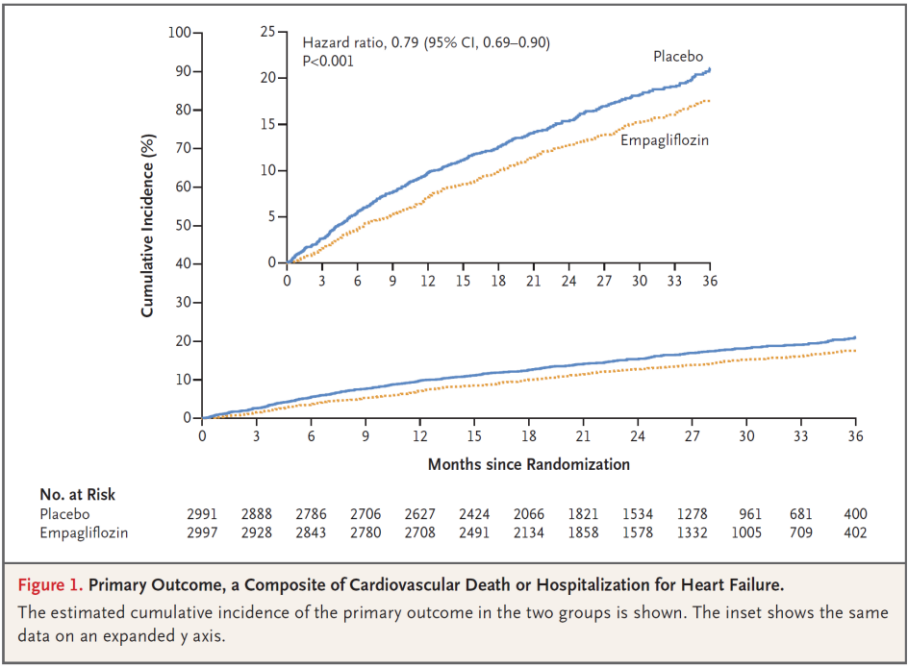


Figure 1. Primary Outcome, a Composite of Cardiovascular Death or Hospitalization for Heart Failure.
The estimated cumulative incidence of the primary outcome in the two groups is shown. The inset shows the same data on an expanded y axis.

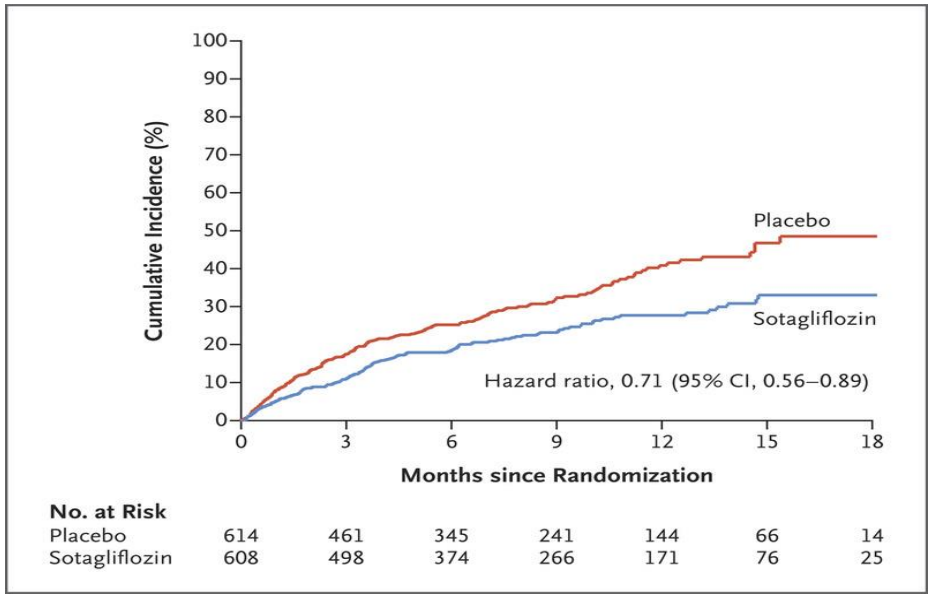
Subsequently, the EMPEROR-Reduced trial found that empagliflozin reduced the combined primary endpoint of CV death or HF hospitalization by 25% in patients with NYHA class III-V symptoms, and an LVEF <_40% despite OMT.

It was also associated with an improvement in QOL.

Sodium-glucose co-transporter 2 inhibitors

- Therefore, dapagliflozin or empagliflozin are recommended, in addition to OMT with an ACE-I/ARNI, a beta-blocker and an MRA, for patients with HFrEF regardless of diabetes status.
- The diuretic/ natriuretic properties of SGLT2 inhibitors may offer additional benefits in reducing congestion and may allow a reduction in loop diuretic requirement.
- Therapy with SGLT2 inhibitors may increase the risk of recurrent genital fungal infections.
- A small reduction in eGFR following initiation is expected and is reversible and should not lead to premature discontinuation of the drug.

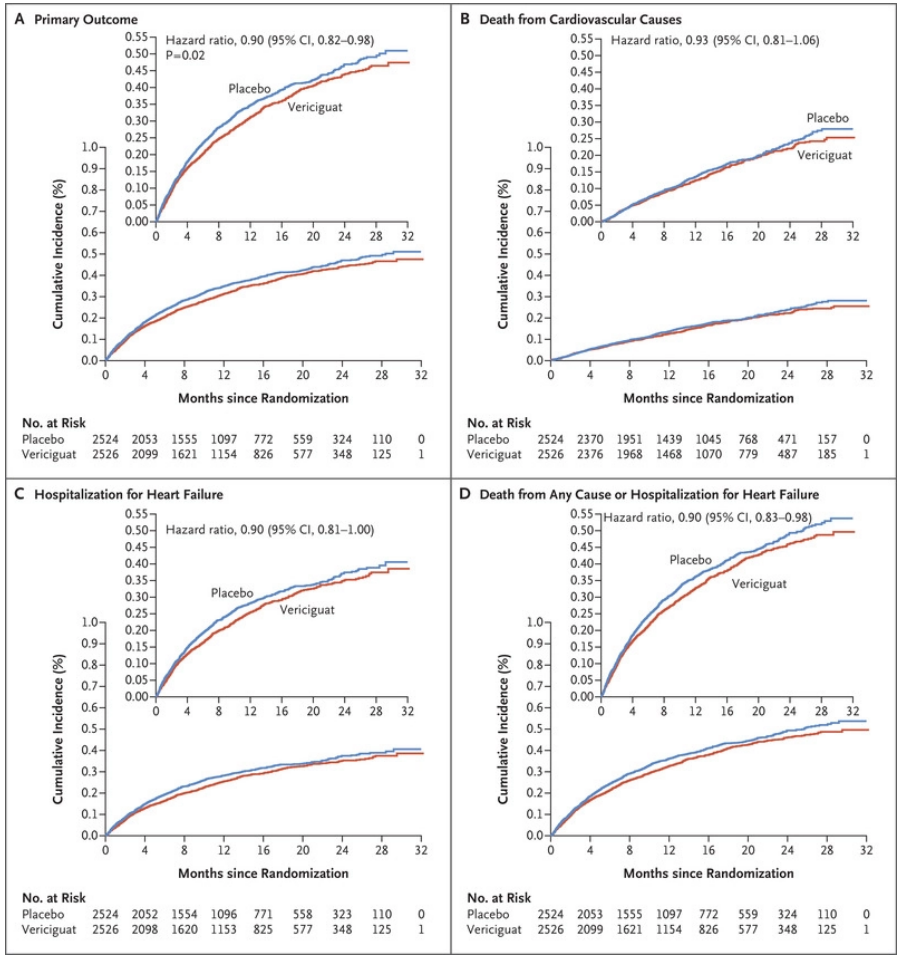
The combined SGLT-1 and 2 inhibitor



Sotagliflozin, has also been studied in patients with diabetes who were hospitalized with HF. The drug reduced CV death and hospitalization for HF.

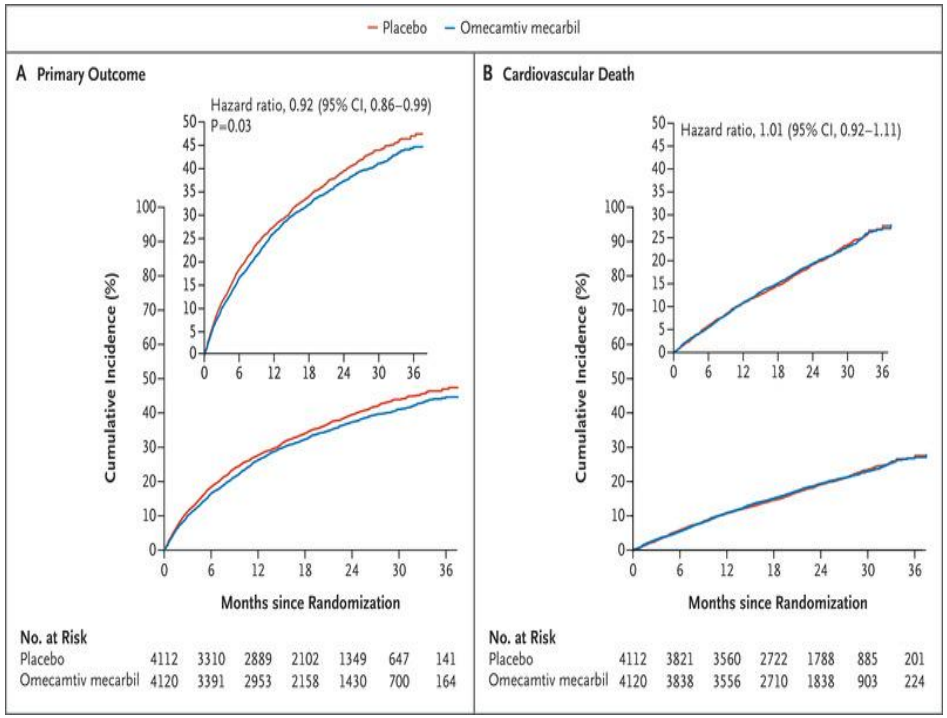
Recently reported advances from trials in heart failure with reduced ejection fraction

Soluble guanylate cyclase stimulator

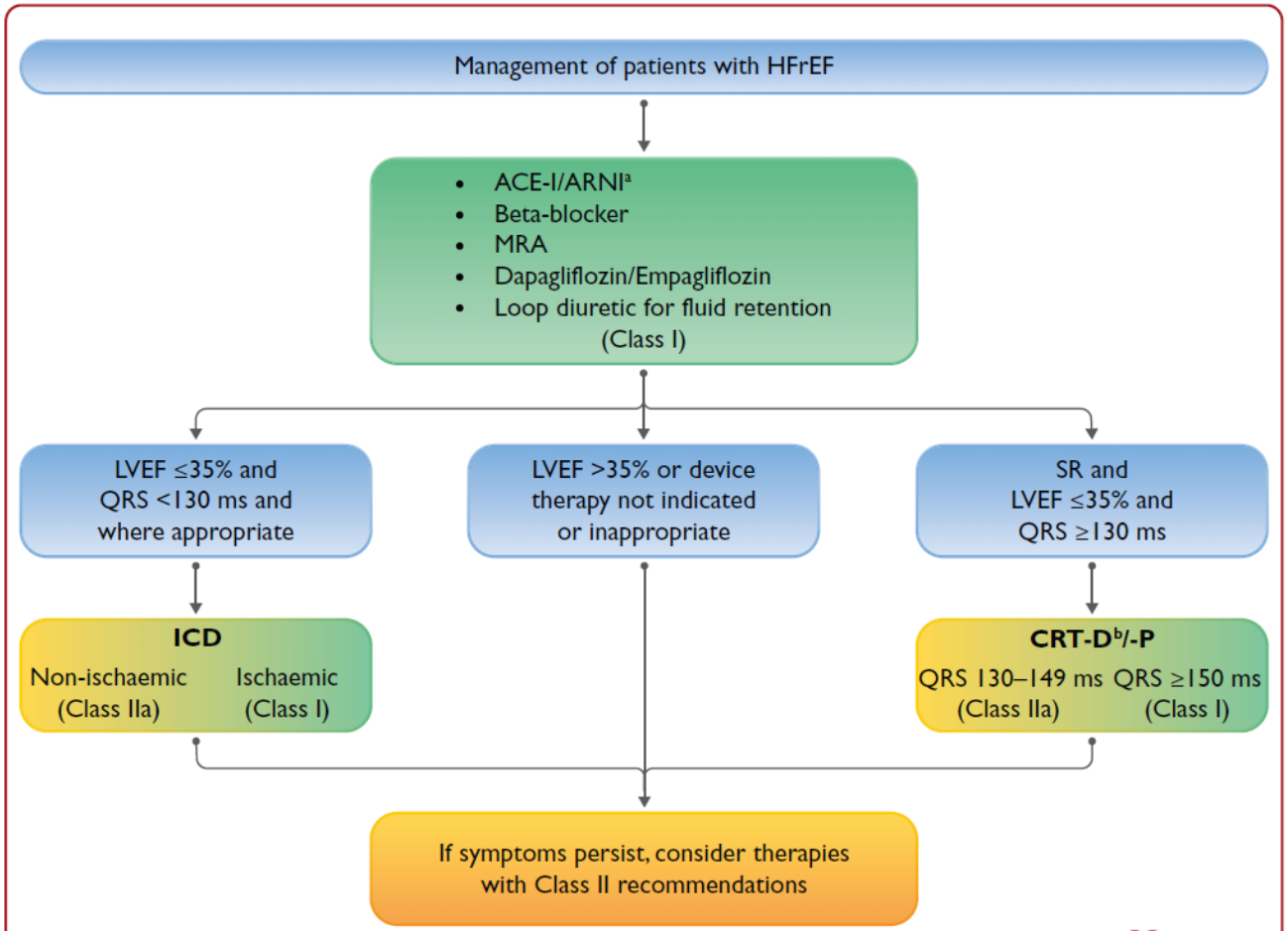


The VICTORIA study assessed the efficacy and safety of the oral soluble guanylate cyclase stimulator, vericiguat, in patients with a reduced EF and recently decompensated CHF. The incidence of the primary endpoint of death from CV causes or hospitalization for HF was lower among those who received vericiguat than among those who received placebo. There was no reduction in either all-cause or CV mortality. Thus, vericiguat may be considered, in addition to standard therapy for HFrEF, to reduce the risk of CV mortality and hospitalizations for HF.

Cardiacmyosin activator



The GALACTIC-HF study assessed the efficacy and safety of the cardiac myosin activator, omecamtiv mecarbil, in HFrEF patients, enrolling patients in both the inpatient and outpatient settings. The primary endpoint of a first HF event or CV death was reduced by 8%. There was no significant reduction in CV mortality. Currently, this drug is not licensed for use in HF. However, in the future it may be able to be considered, in addition to standard therapy for HFrEF to reduce the risk of CV mortality and hospitalization for HF.


Management of patients with HFrEF
ACE-I/ARNI[a]
Beta-blocker
MRA
Dapagliflozin/Empagliflozin
Loop diuretic for fluid retention
(Class I)
LVEF ≤35% and
QRS <130 ms and
where appropriate
LVEF >35% or device
therapy not indicated
or inappropriate
SR and
LVEF ≤35% and
QRS ≥130 ms
ICD
Non-ischaemic
(Class IIa)
Ischaemic
(Class I)
CRT-D[b]/-P
QRS 130–149 ms
(Class IIa)
QRS ≥150 ms
(Class I)
If symptoms persist, consider therapies
with Class II recommendations

Pharmacological treatments indicated in patients with (NYHA class II–IV) heart failure with reduced ejection fraction (LVEF ≤40%)

Recommendations	Class[a]	Level[b]
An ACE-I is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[110–113]	I	A
A beta-blocker is recommended for patients with stable HFrEF to reduce the risk of HF hospitalization and death.[114–120]	I	A
An MRA is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[121,122]	I	A
Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[108,109]	I	A
Sacubitril/valsartan is recommended as a replacement for an ACE-I in patients with HFrEF to reduce the risk of HF hospitalization and death.[105]	I	B

Other pharmacological treatments indicated in selected patients with NYHA class II–IV heart failure with reduced ejection fraction (LVEF ≤40%)

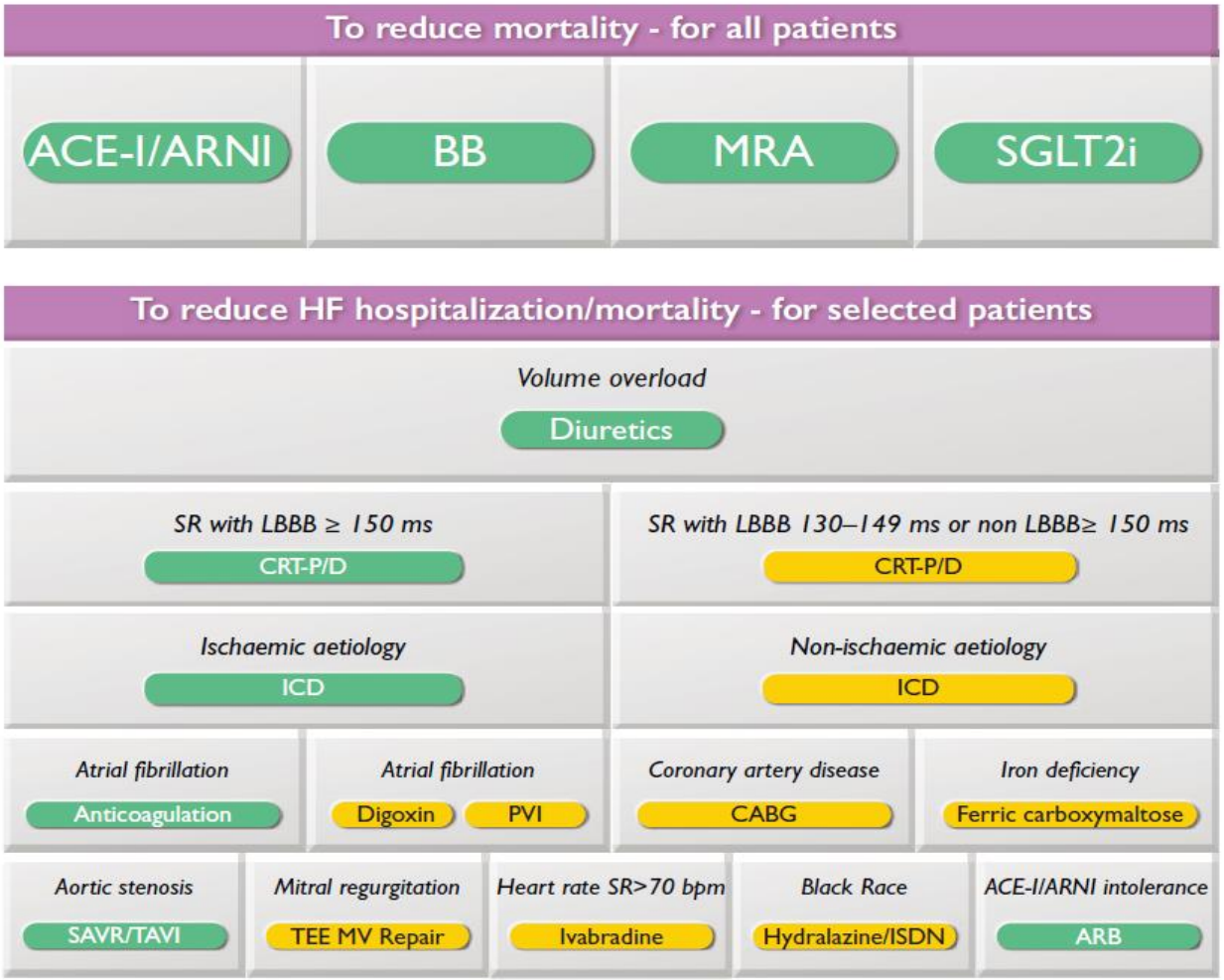
Recommendations	Class[a]	Level[b]
Loop diuretics		
Diuretics are recommended in patients with HFrEF with signs and/or symptoms of congestion to alleviate HF symptoms, improve exercise capacity, and reduce HF hospitalizations.[137]	I	C
ARB		
An ARB[c] is recommended to reduce the risk of HF hospitalization and CV death in symptomatic patients unable to tolerate an ACE-I or ARNI (patients should also receive a beta-blocker and an MRA).[138]	I	B
I_f-channel inhibitor		
Ivabradine should be considered in symptomatic patients with LVEF ≤35%, in SR and a resting heart rate ≥70 b.p.m. despite treatment with an evidence-based dose of beta-blocker (or maximum tolerated dose below that), ACE-I/(or ARNI), and an MRA, to reduce the risk of HF hospitalization and CV death.[139]	IIa	B
Ivabradine should be considered in symptomatic patients with LVEF ≤35%, in SR and a resting heart rate ≥70 b.p.m. who are unable to tolerate or have contraindications for a beta-blocker to reduce the risk of HF hospitalization and CV death. Patients should also receive an ACE-I (or ARNI) and an MRA.[140]	IIa	C

Soluble guanylate cyclase stimulator		
Vericiguat may be considered in patients in NYHA class II–IV who have had worsening HF despite treatment with an ACE-I (or ARNI), a beta-blocker and an MRA to reduce the risk of CV mortality or HF hospitalization.[141]	**IIb**	**B**
Hydralazine and isosorbide dinitrate		
Hydralazine and isosorbide dinitrate should be considered in self-identified black patients with LVEF ≤35% or with an LVEF <45% combined with a dilated left ventricle in NYHA class III–IV despite treatment with an ACE-I (or ARNI), a beta-blocker and an MRA to reduce the risk of HF hospitalization and death.[142]	**IIa**	**B**
Hydralazine and isosorbide dinitrate may be considered in patients with symptomatic HFrEF who cannot tolerate any of an ACE-I, an ARB, or ARNI (or they are contraindicated) to reduce the risk of death.[143]	**IIb**	**B**
Digoxin		
Digoxin may be considered in patients with symptomatic HFrEF in sinus rhythm despite treatment with an ACE-I (or ARNI), a beta-blocker and an MRA, to reduce the risk of hospitalization (both all-cause and HF hospitalizations).[144]	**IIb**	**B**

Table 8 **Evidence-based doses of disease-modifying drug in key randomized trials in patients with heart failure with reduced ejection fraction**

	Starting dose	Target dose
ACE-I		
Captopril[a]	6.25 mg *t.i.d.*	50 mg *t.i.d.*
Enalapril	2.5 mg *b.i.d.*	10—20 mg *b.i.d.*
Lisinopril[b]	2.5—5 mg *o.d.*	20—35 mg *o.d.*
Ramipril	2.5 mg *b.i.d.*	5 mg *b.i.d.*
Trandolapril[a]	0.5 mg *o.d.*	4 mg *o.d.*
ARNI		
Sacubitril/valsartan	49/51 mg *b.i.d.*[c]	97/103 mg *b.i.d.*
Beta-blockers		
Bisoprolol	1.25 mg *o.d.*	10 mg *o.d.*
Carvedilol	3.125 mg *b.i.d.*	25 mg *b.i.d.*[e]
Metoprolol succinate (CR/XL)	12.5—25 mg *o.d.*	200 mg *o.d.*
Nebivolol[d]	1.25 mg *o.d.*	10 mg *o.d.*
MRA		
Eplerenone	25 mg *o.d.*	50 mg *o.d.*
Spironolactone	25 mg *o.d.*[f]	50 mg *o.d.*
SGLT2 inhibitor		
Dapagliflozin	10 mg *o.d.*	10 mg *o.d.*
Empagliflozin	10 mg *o.d.*	10 mg *o.d.*
Other agents		
Candesartan	4 mg *o.d.*	32 mg *o.d.*
Losartan	50 mg *o.d.*	150 mg *o.d.*
Valsartan	40 mg *b.i.d.*	160 mg *b.i.d.*
Ivabradine	5 mg *b.i.d.*	7.5 mg *b.i.d.*
Vericiguat	2.5 mg *o.d.*	10 mg *o.d.*
Digoxin	62.5 µg *o.d.*	250 µg *o.d.*
Hydralazine/ Isosorbide dinitrate	37.5 mg *t.i.d.*/20 mg *t.i.d.*	75 mg *t.i.d.*/40 mg *t.i.d.*

Management of HFrEF



Recommendations for treatment of chronic HF	
HFrEF	
Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	I
Vericiguat may be considered in patients in NYHA class II—IV who have had worsening HF despite treatment with an ACE-I (or ARNI), a beta-blocker and an MRA to reduce the risk of CV mortality or HF hospitalization.	IIb
HFmrEF	
An ACE-I may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.	IIb
An ARB may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.	IIb
A beta-blocker may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.	IIb
An MRA may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.	IIb
Sacubitril/valsartan may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.	IIb
HFpEF	
Screening for, and treatment of, aetiologies, and CV and non-CV comorbidities are recommended in patients with HFpEF (see relevant sections of this document).	I

Pharmacological treatments to be considered in patients with (NYHA class II–IV) heart failure with mildly reduced ejection fraction

Recommendations	Class[a]	Level[b]
Diuretics are recommended in patients with congestion and HFmrEF in order to alleviate symptoms and signs.[137]	I	C
An ACE-I may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.[11]	IIb	C
An ARB may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.[245]	IIb	C
A beta-blocker may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.[12,119]	IIb	C
An MRA may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.[246]	IIb	C
Sacubitril/valsartan may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.[13,247]	IIb	C

Recommendations for the treatment of patients with heart failure with preserved ejection fraction

Recommendations	Class[a]	Level[b]
Screening for, and treatment of, aetiologies, and cardiovascular and non-cardiovascular comorbidities is recommended in patients with HFpEF (see relevant sections of this document).	I	C
Diuretics are recommended in congested patients with HFpEF in order to alleviate symptoms and signs.[137]	I	C

Thank you