Guideline-directed medical therapy in heart failure & heart failure clinic

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HFSA 2010 Guideline Executive Summary

Executive Summary: HFSA 2010 Comprehensive Heart Failure Practice Guideline

HEART FAILURE SOCIETY OF AMERICA

St. Paul, Minnesota

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

ACCF/AHA Practice Guideline

2013 ACCF/AHA Guideline for the Management of Heart Failure

A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

Developed in Collaboration With the American College of Chest Physicians, Heart Rhythm Society and International Society for Heart and Lung Transplantation

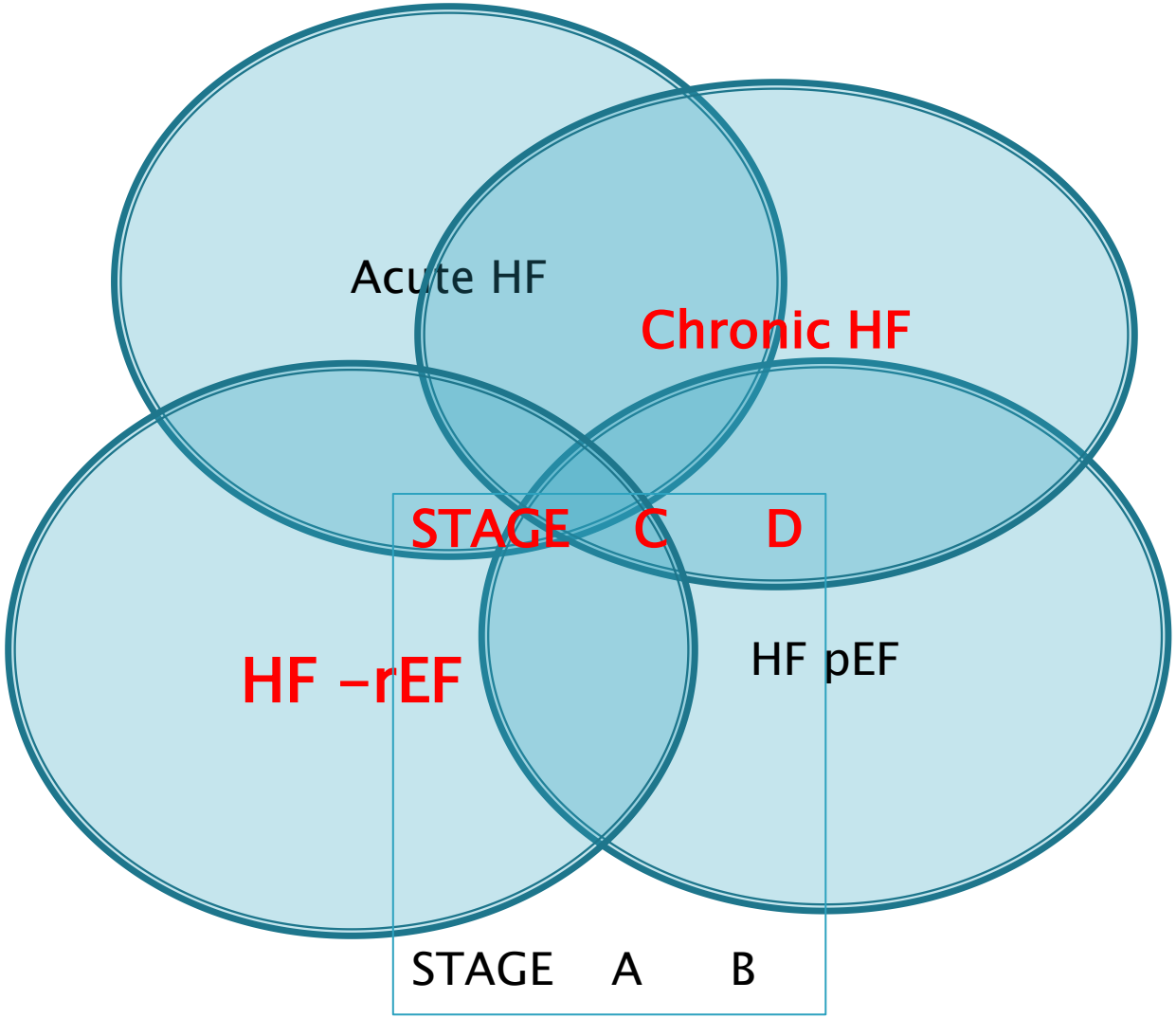
Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation

Yancy, CW, et al.
Heart Failure Focused Update on Pharmacological Therapy

2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure

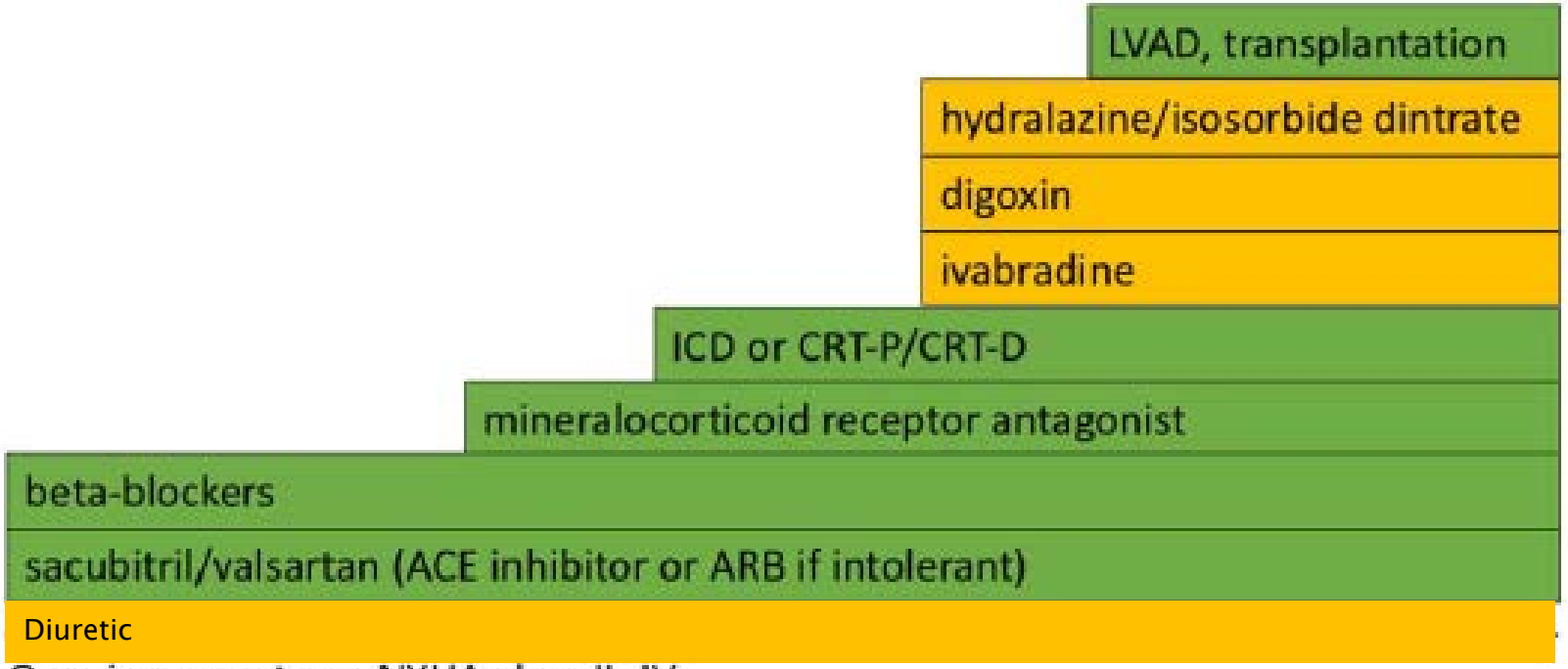
A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America

Developed in Collaboration With the International Society for Heart and Lung Transplantation


Acute HF
Chronic HF
STAGE C D
HF -rEF
HF pEF
STAGE A B

Philosophy of Medical Treatment in HF

- Live Better (Stronger): Improve
  - Clinical status
  - Functional capacity
  - QOL
  - Prevent HF hospital admission
- Live Longer
  - Reduce mortality

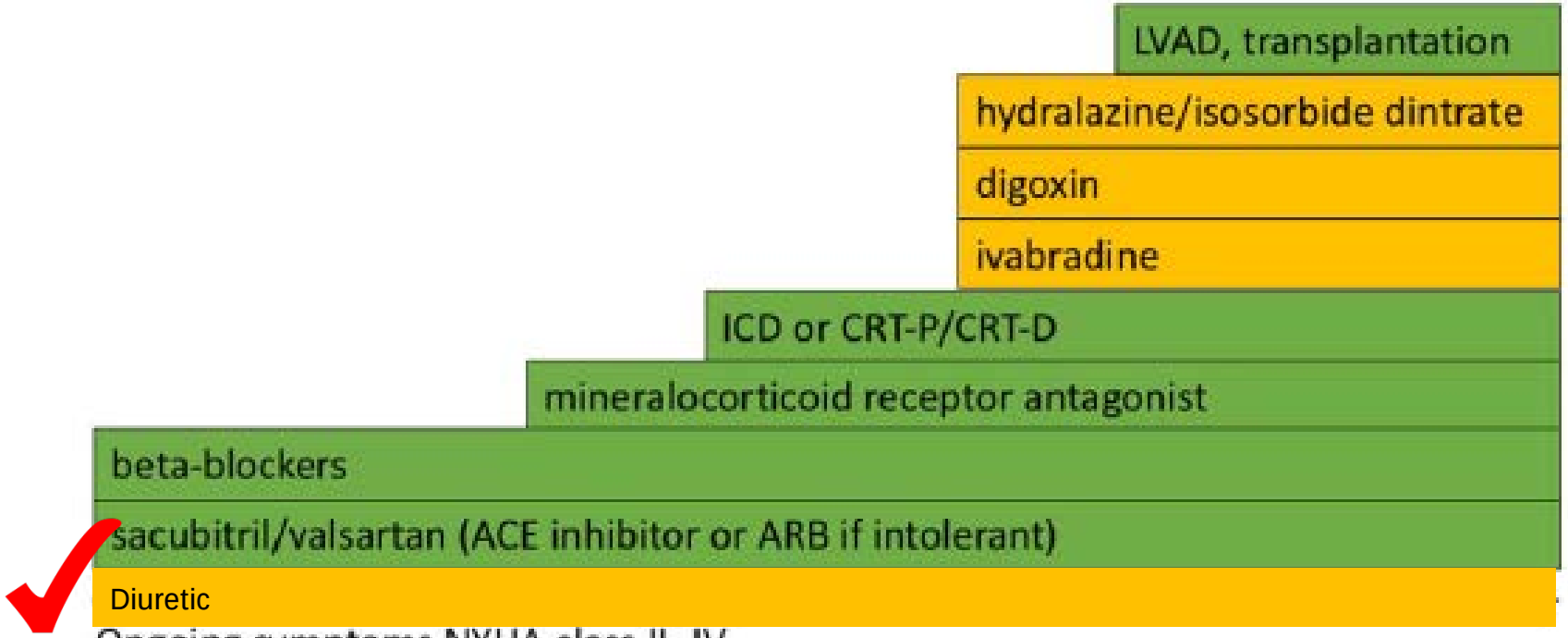


Ongoing symptoms NYHA class II- IV

Legend

Improves mortality +/- morbidity

Improves morbidity



Ongoing symptoms NYHA class II- IV

Legend

Improves mortality +/- morbidity

Improves morbidity

Diuretics

- Only when fluid retention
- Invisible fluid
- Back off when NYHA improved

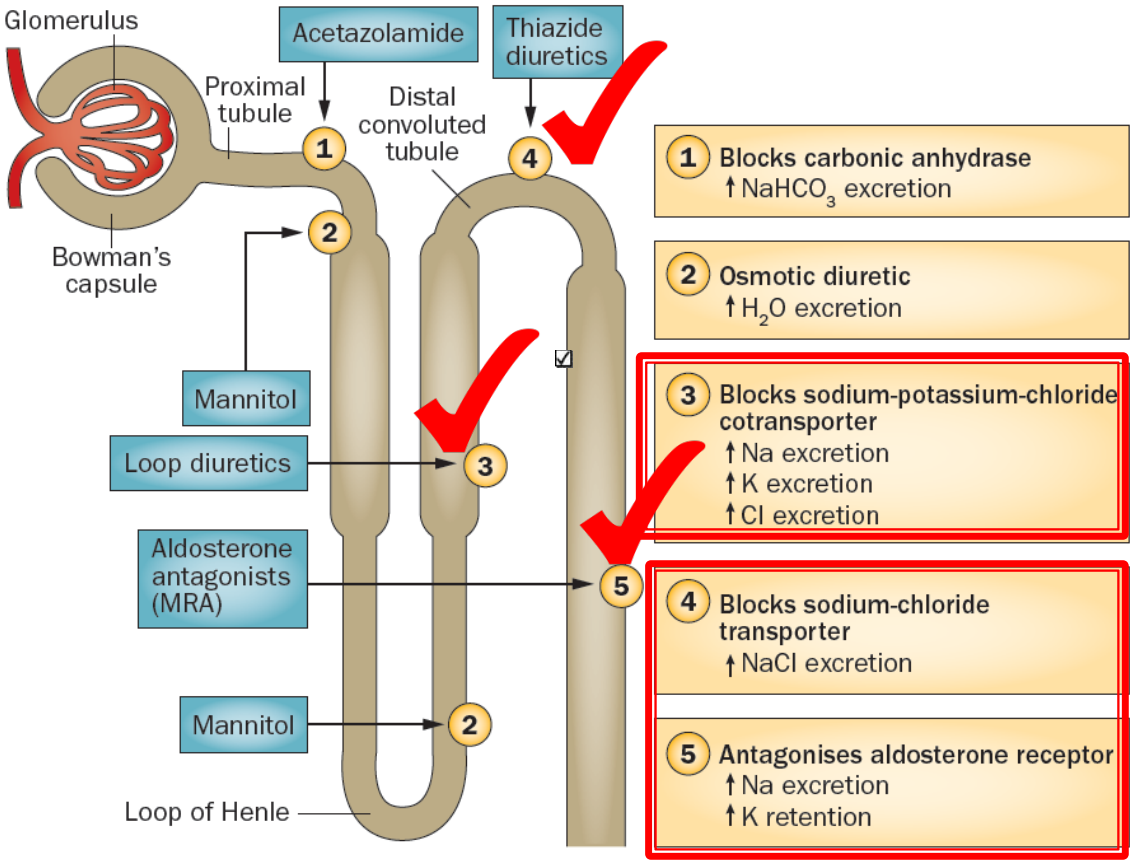
Recommendations	Class [a]	Level [b]
Diuretics		
Diuretics are recommended in order to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion.	I	B
Diuretics should be considered to reduce the risk of HF hospitalization in patients with signs and/or symptoms of congestion.	IIa	B

7.3.2.1. Diuretics: Recommendation

Class I

1. **Diuretics are recommended in patients with HF*r*EF who have evidence of fluid retention, unless contraindicated, to improve symptoms.** ***(Level of Evidence: C)***

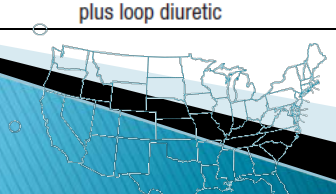
Diuretics


Glomerulus
Acetazolamide
Thiazide diuretics
Proximal tubule
Distal convoluted tubule
Bowman's capsule
Mannitol
Loop diuretics
Aldosterone antagonists (MRA)
Mannitol
Loop of Henle
1 Blocks carbonic anhydrase
↑ $NaHCO_3$ excretion
2 Osmotic diuretic
↑ H_2O excretion
3 Blocks sodium-potassium-chloride cotransporter
↑ Na excretion
↑ K excretion
↑ Cl excretion
4 Blocks sodium-chloride transporter
↑ NaCl excretion
5 Antagonises aldosterone receptor
↑ Na excretion
↑ K retention

Diuretics

Drug	Initial Daily Dose(s)	Maximum Total Daily Dose	Duration of Action
Loop diuretics			
Bumetanide	0.5 to 1.0 mg once or twice	10 mg	4 to 6 h
Furosemide	20 to 40 mg once or twice	600 mg	6 to 8 h
Torsemide	10 to 20 mg once	200 mg	12 to 16 h
Thiazide diuretics			
Chlorothiazide	250 to 500 mg once or twice	1000 mg	6 to 12 h
Chlorthalidone	12.5 to 25.0 mg once	100 mg	24 to 72 h
Hydrochlorothiazide	25 mg once or twice	200 mg	6 to 12 h
Indapamide	2.5 mg once	5 mg	36 h
Metolazone	2.5 mg once	20 mg	12 to 24 h
Potassium-sparing diuretics*			
Amiloride	5 mg once	20 mg	24 h
Spironolactone	12.5 to 25.0 mg once	50 mg†	1 to 3 h
Triamterene	50 to 75 mg twice	200 mg	7 to 9 h
Sequential nephron blockade			
Metolazone‡	2.5 to 10.0 mg once plus loop diuretic	N/A	N/A
Hydrochlorothiazide	25 to 100 mg once or twice plus loop diuretic	N/A	N/A
Chlorothiazide (IV)	500 to 1000 mg once plus loop diuretic	N/A	N/A

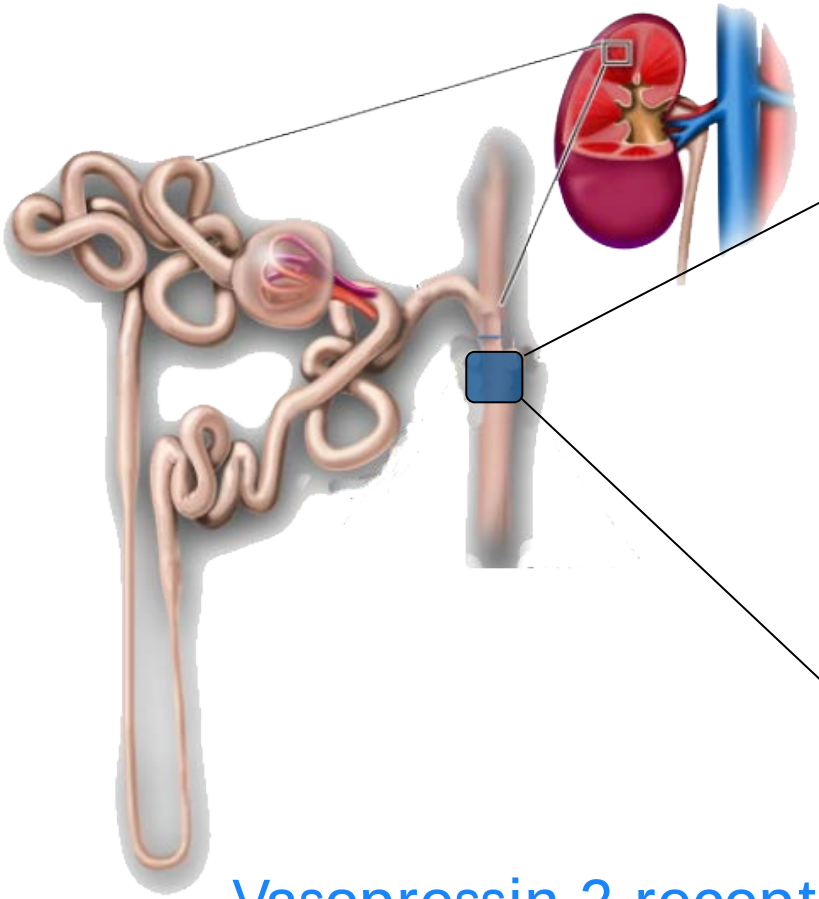
Diuretics	Initial dose (mg)		Usual daily dose (mg)	
Loop diuretics[a]				
Furosemide	20–40		40–240	
Bumetanide	0.5–1.0		1–5	
Torasemide	5–10		10–20	
Thiazides[b]				
Bendroflumethiazide	2.5		2.5–10	
Hydrochlorothiazide	25		12.5–100	
Metolazone	2.5		2.5–10	
Indapamide[c]	2.5		2.5–5	
Potassium-sparing diuretics[d]				
	+ACE-I/ ARB	-ACE-I/ ARB	+ACE-I/ ARB	-ACE-I/ ARB
Spironolactone/ eplerenone	12.5–25	50	50	100–200
Amiloride	2.5	5	5–10	10–20
Triamterene	25	50	100	200

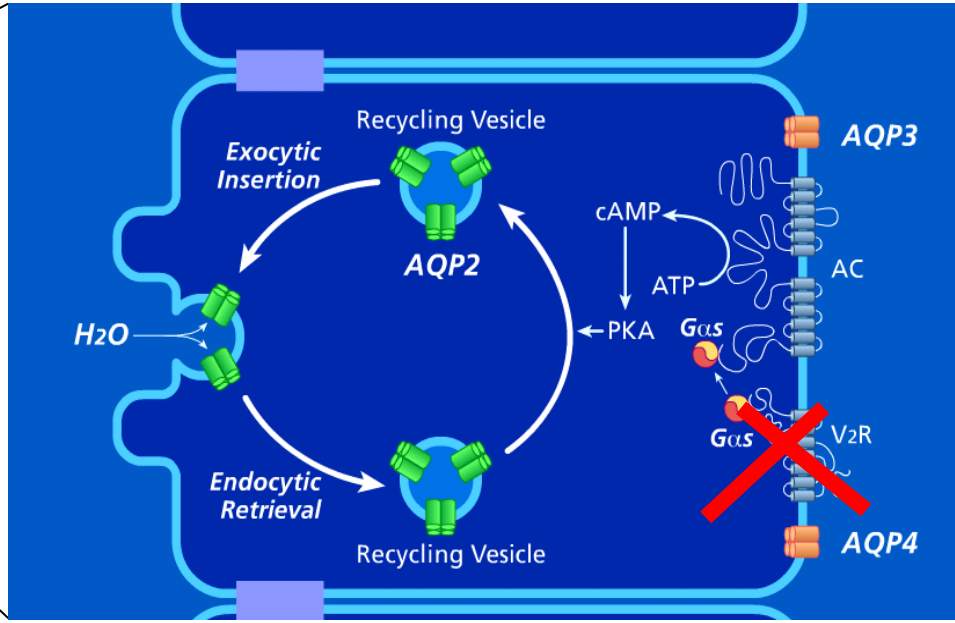


Diuretic-Side effect

- Hypo K, Hypo Mg
- Renal dysfunction
- Dyslipidemia
- Hyperuricemia
- Hearing
- Allergy

Aquaretics





Vasopressin 2 receptor antagonist = Free water re-absorption at renal collecting duct

Aquaretics

8.8. Arginine Vasopressin Antagonists: Recommendation

Class IIb

1. **In patients hospitalized with volume overload, including HF, who have persistent severe hyponatremia and are at risk for or having active cognitive symptoms despite water restriction and maximization of GDMT, vasopressin antagonists may be considered in the short term to improve serum sodium concentration in hypervolemic, hyponatremic states with either a V_2 receptor selective or a nonselective vasopressin antagonist.[787,788] *(Level of Evidence: B)***

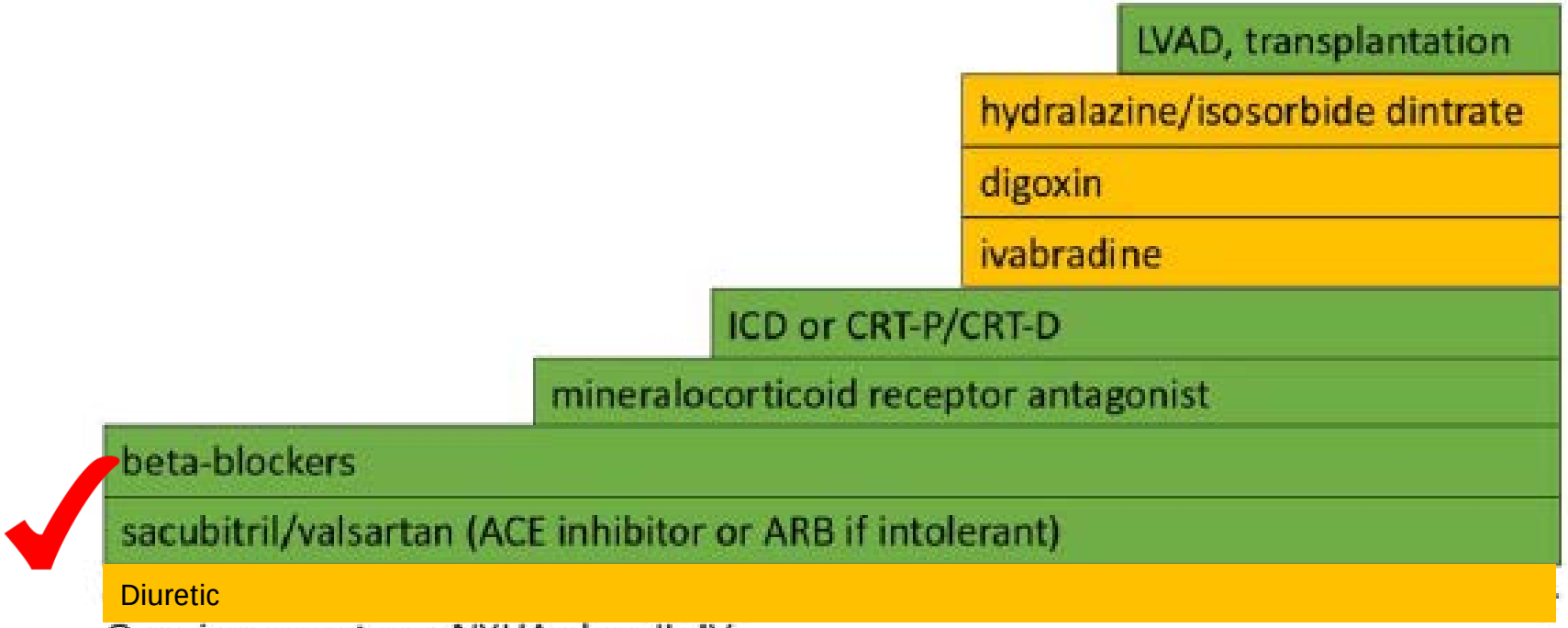
2013 ACC AHA

Vasopressin antagonists

Vasopressin antagonists such as tolvaptan block the action of arginine vasopressin (AVP) at the V_2 receptor in renal tubules and promote aquaresis. Tolvaptan may be used to treat patients with volume overload and resistant hyponatraemia (thirst and dehydration are recognized adverse effects).[577]

Not in the table anymore

2016 ESC



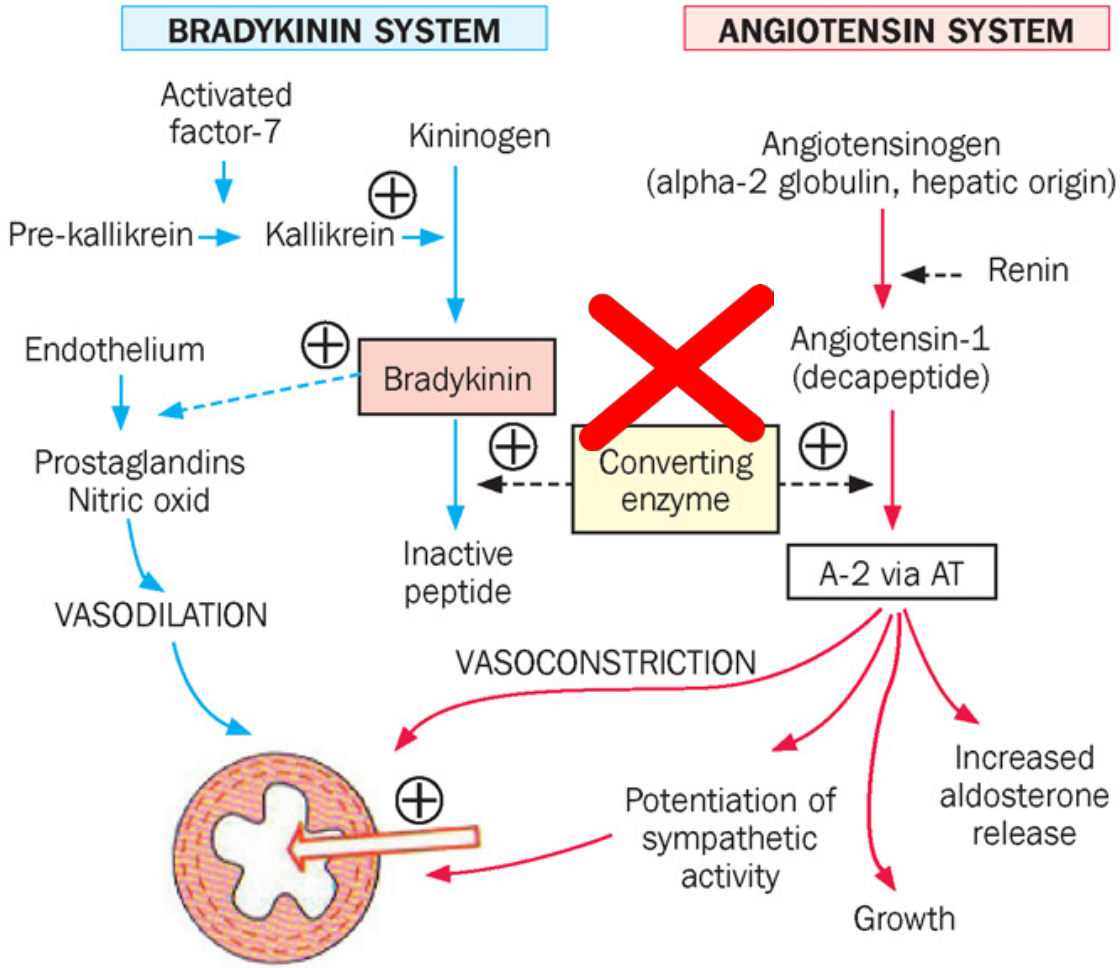
Ongoing symptoms NYHA class II- IV

Legend

Improves mortality +/- morbidity

Improves morbidity

ACE–I


BRADYKININ SYSTEM
ANGIOTENSIN SYSTEM
Activated factor-7
Kininogen
Angiotensinogen (alpha-2 globulin, hepatic origin)
Pre-kallikrein
Kallikrein
Renin
Endothelium
Bradykinin
Angiotensin-1 (decapeptide)
Prostaglandins Nitric oxid
Converting enzyme
Inactive peptide
A-2 via AT
VASODILATION
VASOCONSTRICTION
Potentiation of sympathetic activity
Increased aldosterone release
Growth

COR	LOE	Recommendations
I	ACE: A ARB: A ARNI: B-R	The clinical strategy of inhibition of the renin-angiotensin system with ACE inhibitors *(Level of Evidence: A)* (9-14), OR ARBs *(Level of Evidence: A)* (15-18), OR ARNI *(Level of Evidence: B-R)* (19) in conjunction with evidence-based beta blockers (20-22), and aldosterone antagonists in selected patients (23, 24), is recommended for patients with chronic HF*r*EF to reduce morbidity and mortality.

I	ACE: A	The use of ACE inhibitors is beneficial for patients with prior or current symptoms of chronic HF*r*EF to reduce morbidity and mortality (9-14, 25).

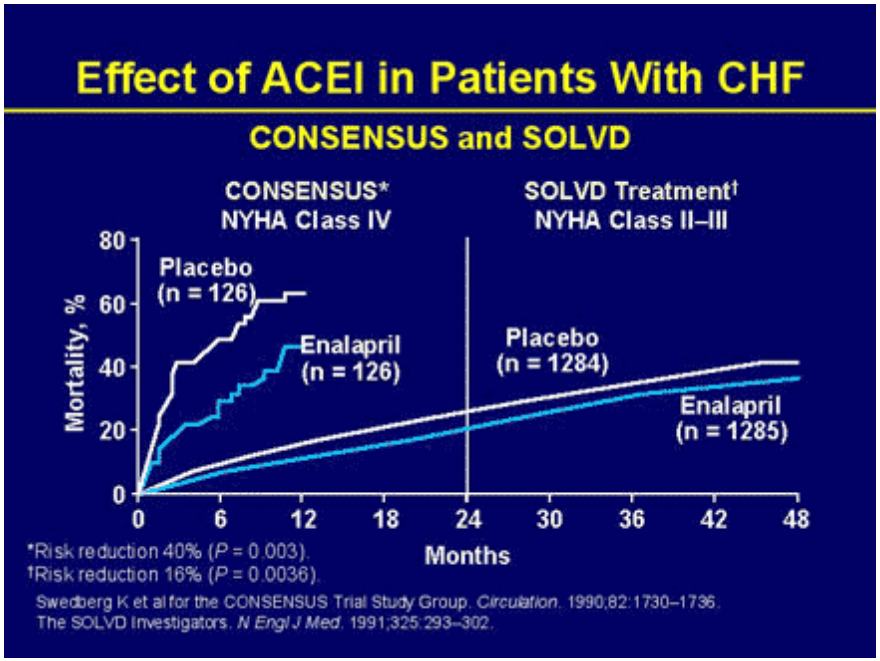
Recommendations	Class [a]	Level [b]
An ACE-I[d] is recommended, in addition to a beta-blocker, for symptomatic patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A
A beta-blocker is recommended, in addition an ACE-I[d], for patients with stable, symptomatic HFrEF to reduce the risk of HF hospitalization and death.	I	A
An MRA is recommended for patients with HFrEF, who remain symptomatic despite treatment with an ACE-I[d] and a beta-blocker, to reduce the risk of HF hospitalization and death.	I	A

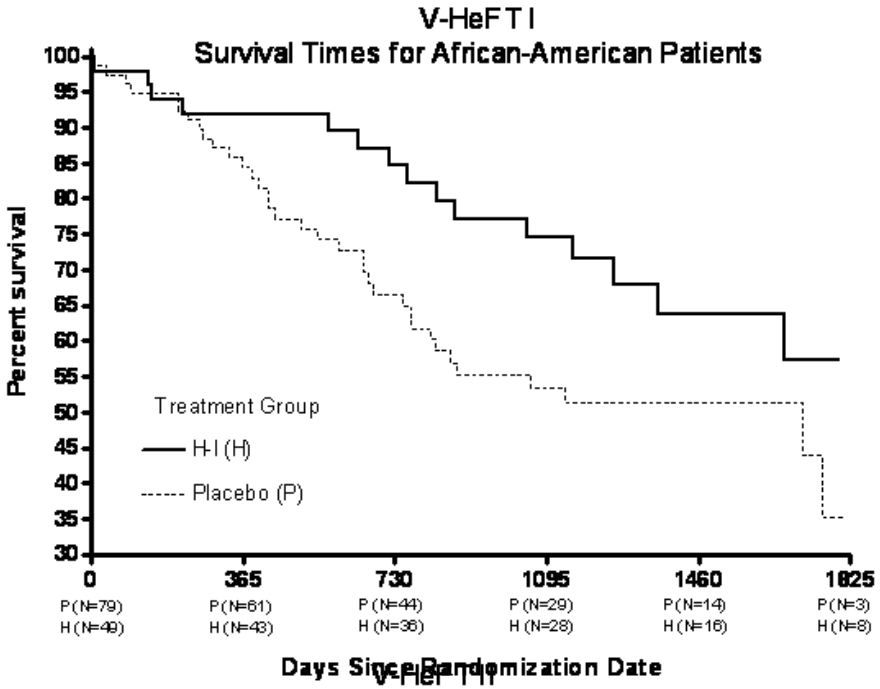
ACE–I

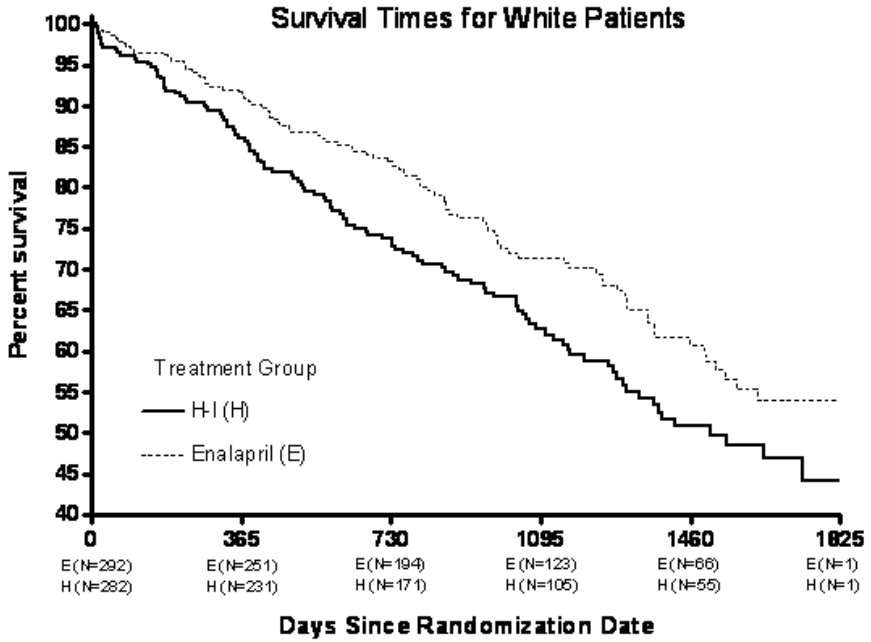
Drug	Initial Daily Dose(s)	Maximum Dose(s)	Mean Doses Achieved in Clinical Trials
ACE inhibitors			
Captopril	6.25 mg 3 times	50 mg 3 times	122.7 mg/d[422]
Enalapril	2.5 mg twice	10 to 20 mg twice	16.6 mg/d[413]
Fosinopril	5 to 10 mg once	40 mg once	N/A
Lisinopril	2.5 to 5 mg once	20 to 40 mg once	32.5 to 35.0 mg/d[445]
Perindopril	2 mg once	8 to 16 mg once	N/A
Quinapril	5 mg twice	20 mg twice	N/A
Ramipril	1.25 to 2.5 mg once	10 mg once	N/A
Trandolapril	1 mg once	4 mg once	N/A

	Starting dose (mg)	Target dose (mg)
ACE-I		
Captopril[a]	6.25 *t.i.d.*	50 *t.i.d.*
Enalapril	2.5 *b.i.d.*	10–20 *b.i.d.*
Lisinopril[b]	2.5–5.0 *o.d.*	20–35 *o.d.*
Ramipril	2.5 o.d.	10 *o.d.*
Trandolapril[a]	0.5 *o.d.*	4 *o.d.*

- Cr and K should be assessed within 1 to 2 weeks of initiation of therapy and periodically thereafter
- If target doses cannot be used or are poorly tolerated, intermediate doses should be used (likely to be only small differences in efficacy between low and high doses)
- Abrupt withdrawal of ACE I can lead to clinical deterioration and should be avoided.


Effect of ACEI in Patients With CHF
CONSENSUS and SOLVD
CONSENSUS*
NYHA Class IV
SOLVD Treatment†
NYHA Class II–III
Placebo
(n = 126)
Enalapril
(n = 126)
Placebo
(n = 1284)
Enalapril
(n = 1285)
Mortality, %
80
60
40
20
0
0
6
12
18
24
30
36
42
48
Months
*Risk reduction 40% (P = 0.003).
†Risk reduction 16% (P = 0.0036).
Swedberg K et al for the CONSENSUS Trial Study Group. Circulation. 1990;82:1730–1736.
The SOLVD Investigators. N Engl J Med. 1991;325:293–302.

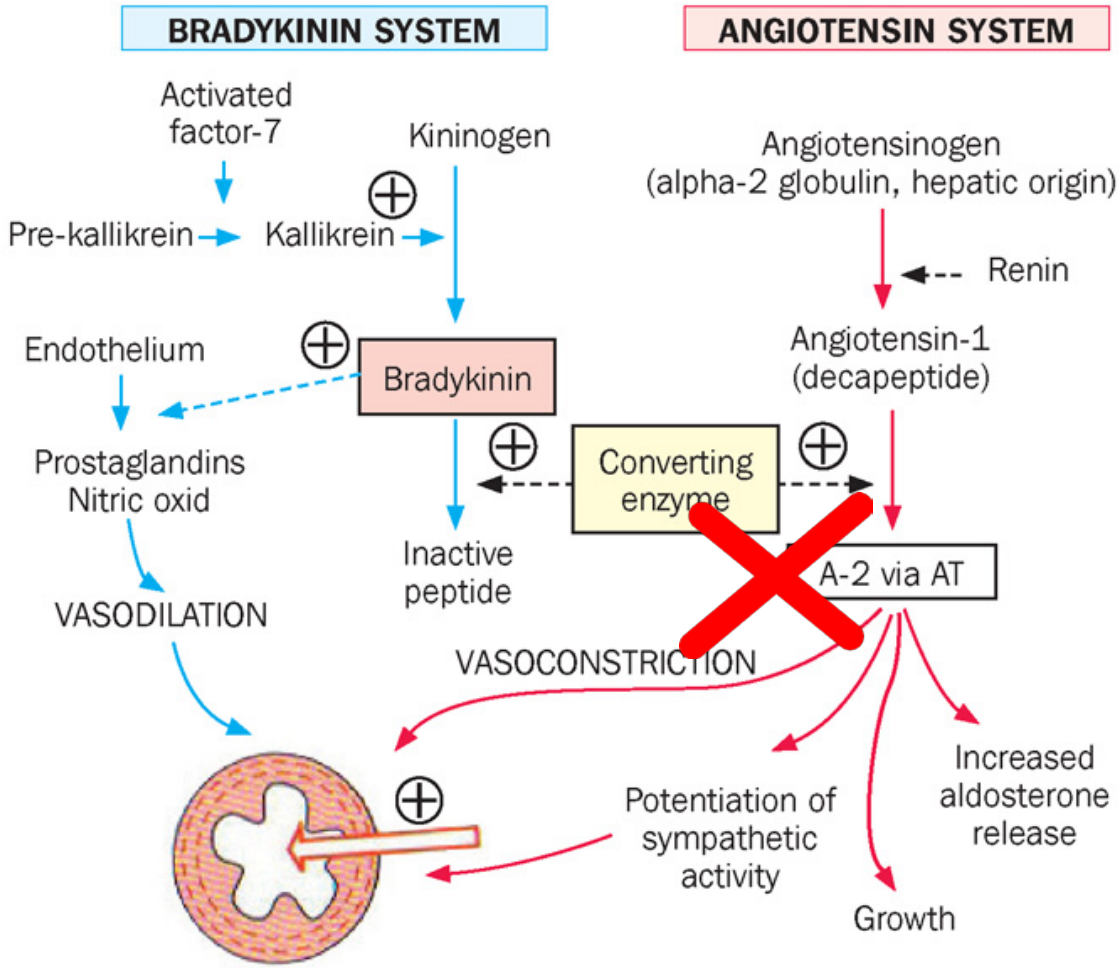

V-HeFT I
Survival Times for African-American Patients
Percent survival
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
Treatment Group
H-I (H)
Placebo (P)
0
365
730
1095
1460
1825
P(N=79)
H(N=49)
P(N=61)
H(N=43)
P(N=44)
H(N=36)
P(N=29)
H(N=28)
P(N=14)
H(N=16)
P(N=3)
H(N=8)
Days Since Randomization Date


Survival Times for White Patients
Percent survival
100
95
90
85
80
75
70
65
60
55
50
45
40
Treatment Group
H-I (H)
Enalapril (E)
0
365
730
1095
1460
1825
E(N=292)
H(N=282)
E(N=251)
H(N=231)
E(N=194)
H(N=171)
E(N=123)
H(N=105)
E(N=66)
H(N=55)
E(N=1)
H(N=1)
Days Since Randomization Date

ACE-I –Cautions

- very low systemic blood pressures (systolic blood pressure <80 mm Hg)
- creatinine >3 mg/dL
- bilateral renal artery stenosis,
- serum potassium >5.0 mEq/L.

ARB


BRADYKININ SYSTEM
ANGIOTENSIN SYSTEM
Activated factor-7
Kininogen
Angiotensinogen (alpha-2 globulin, hepatic origin)
Pre-kallikrein
Kallikrein
Renin
Endothelium
Bradykinin
Angiotensin-1 (decapeptide)
Prostaglandins Nitric oxid
Converting enzyme
Inactive peptide
A-2 via AT
VASODILATION
VASOCONSTRICTION
Potentiation of sympathetic activity
Increased aldosterone release
Growth

ARB

ARB		
An ARB is recommended to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients unable to tolerate an ACE-I (patients should also receive a beta-blocker and an MRA).	I	B
An ARB may be considered to reduce the risk of HF hospitalization and death in patients who are symptomatic despite treatment with a beta-blocker who are unable to tolerate an MRA.	IIb	C

Class I

1. ARBs are recommended in patients with HF*r*EF with current or prior symptoms who are ACE inhibitor intolerant, unless contraindicated, to reduce morbidity and mortality.[108,345,415,450] *(Level of Evidence: A)*

Class IIa

1. ARBs are reasonable to reduce morbidity and mortality as alternatives to ACE inhibitors as first-line therapy for patients with HF*r*EF, especially for patients already taking ARBs for other indications, unless contraindicated.[451–456] *(Level of Evidence: A)*

Class IIb

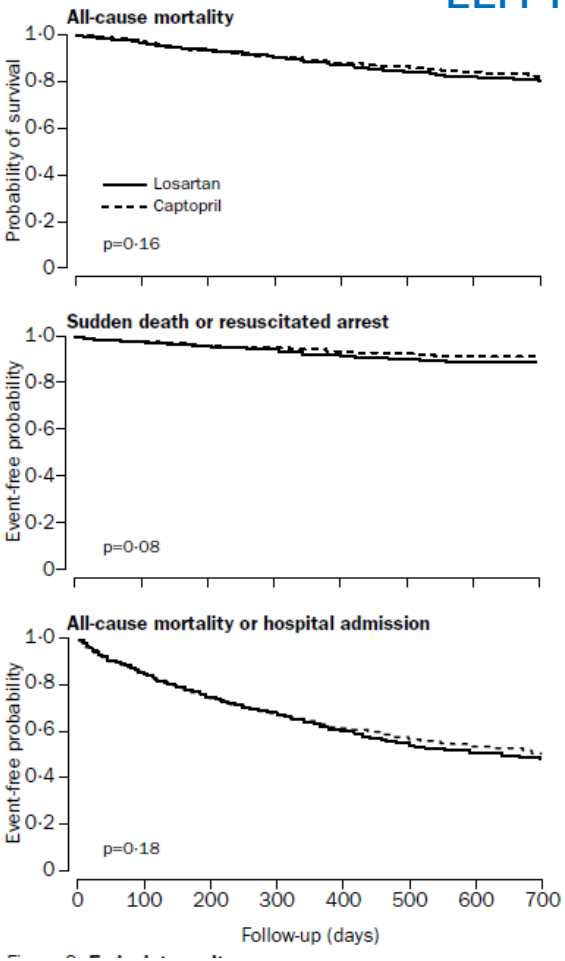
1. Addition of an ARB may be considered in persistently symptomatic patients with HF*r*EF who are already being treated with an ACE inhibitor and a beta blocker in whom an aldosterone antagonist is not indicated or tolerated.[420,457] *(Level of Evidence: A)*

Class III: Harm

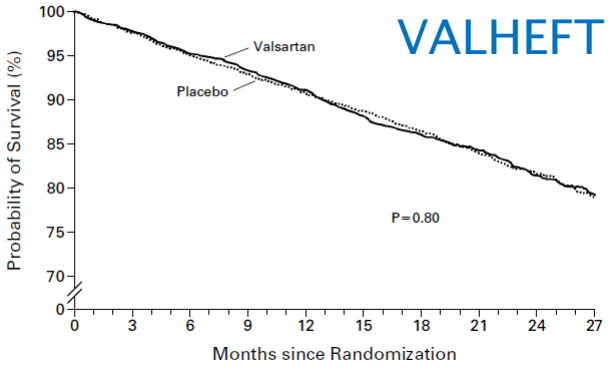
1. Routine *combined* use of an ACE inhibitor, ARB, and aldosterone antagonist is potentially harmful for patients with HF*r*EF. *(Level of Evidence: C)*

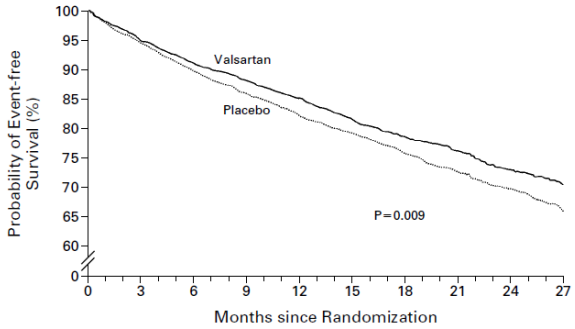
ARB

ELITTE II



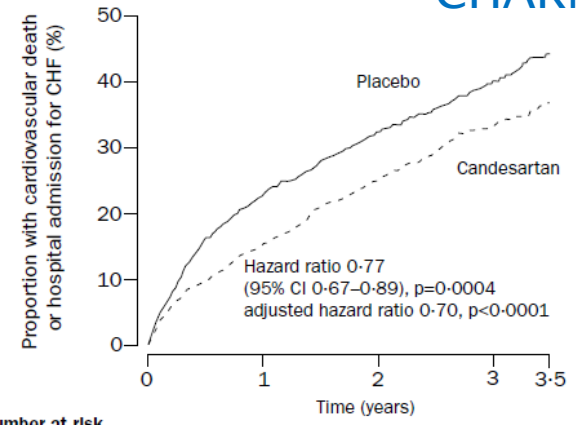
VALHEFT





Combined End Point (Death
from Any Cause, Cardiac Arrest with Resuscitation, Hospitalization for Worsening Heart Failure, or Therapy with Intravenous Inotropes or Vasodilators

CHARM



Number at risk

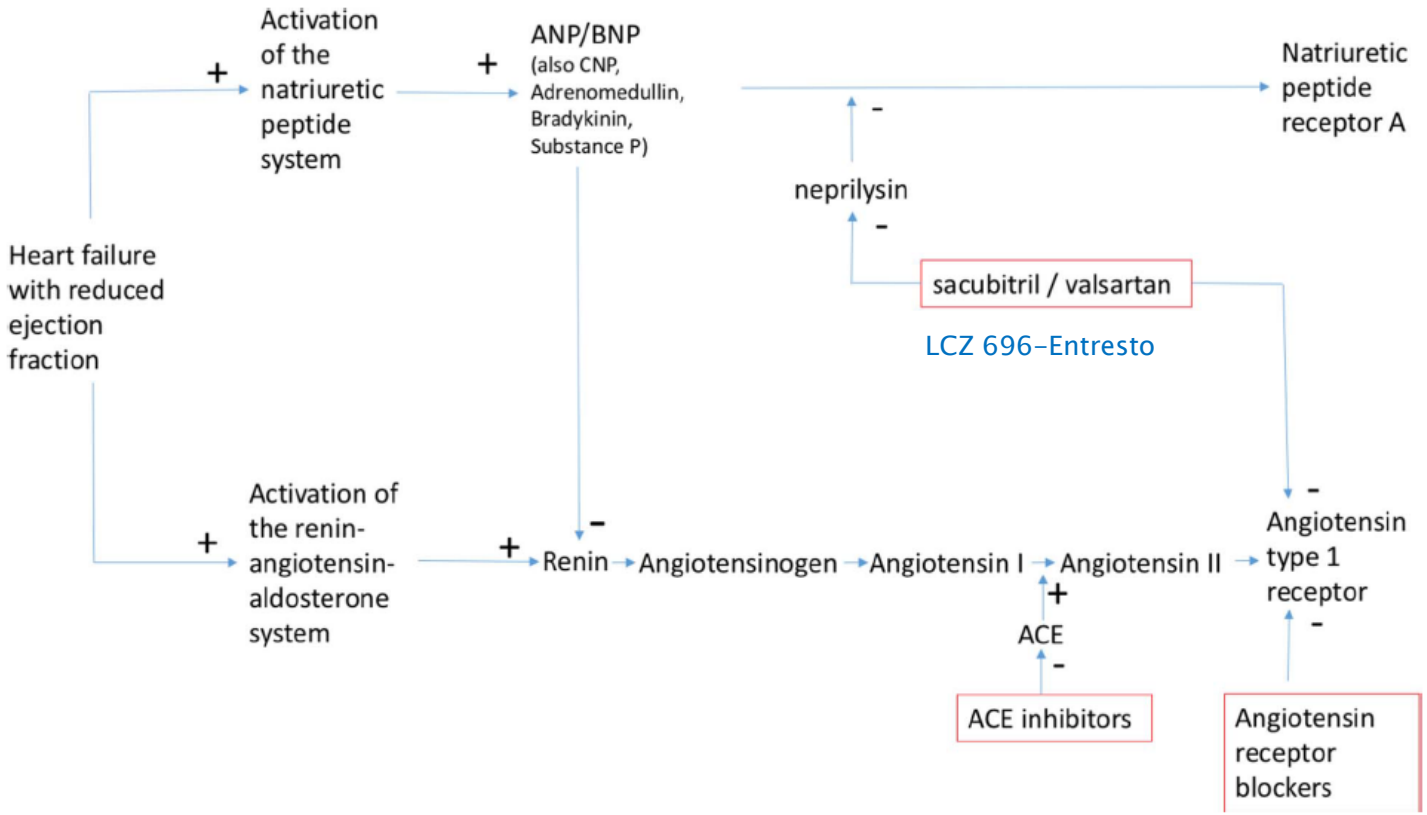
ARB

ARBs		
Candesartan	4–8 *o.d.*	32 *o.d.*
Valsartan	40 *b.i.d.*	160 *b.i.d.*
Losartan[b,c]	50 *o.d.*	150 *o.d.*

Drug	Initial Daily Dose(s)	Maximum Dose(s)	Mean Doses Achieved in Clinical Trials
ARBs			
Candesartan	4 to 8 mg once	32 mg once	24 mg/d[420]
Losartan	25 to 50 mg once	50 to 150 mg once	129 mg/d[421]
Valsartan	20 to 40 mg twice	160 mg twice	254 mg/d[108]

- Titration–double dose q 2 weeks
- Caution similar to ACE-I

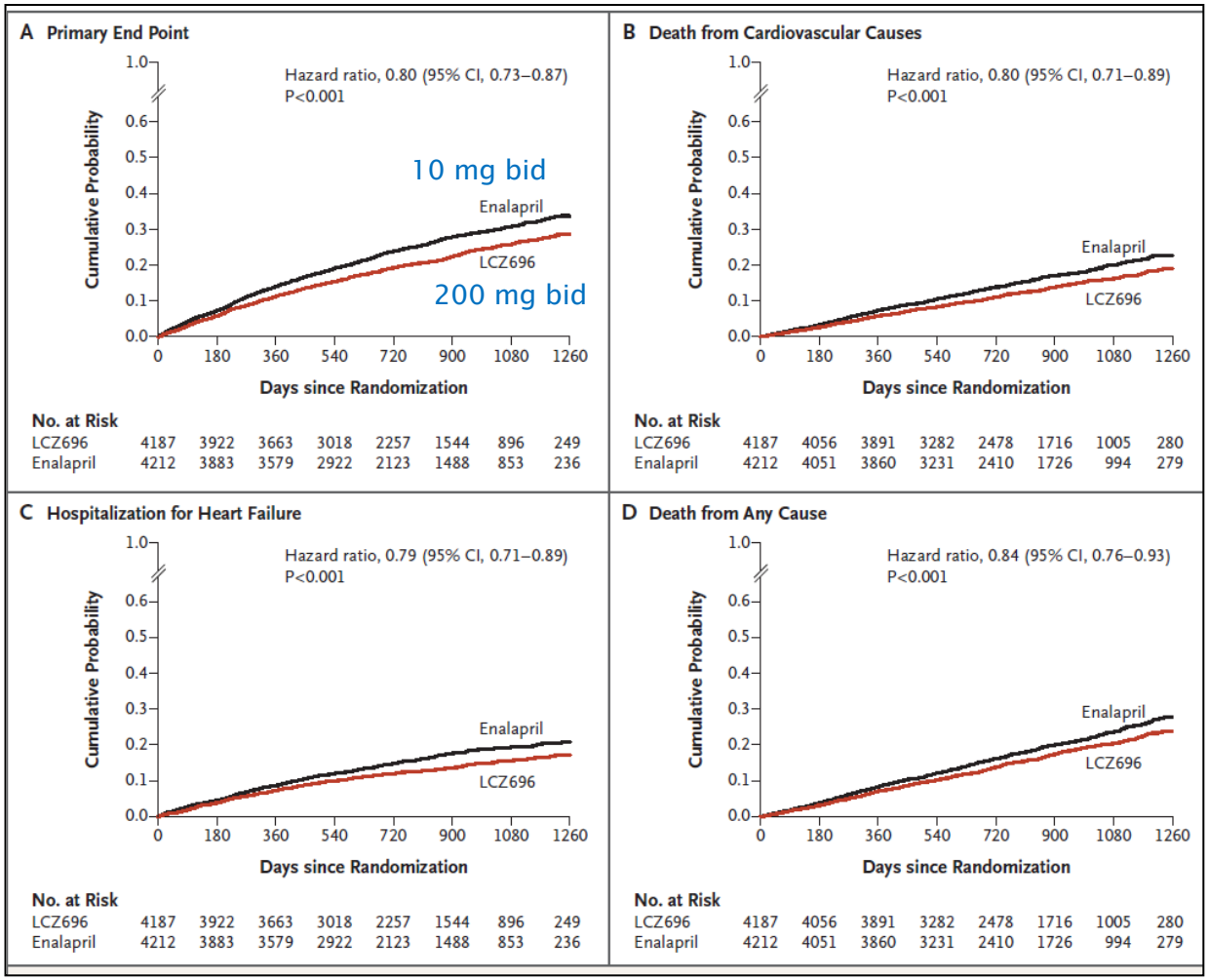
ARNI– angiotensin receptor neprilysin inhibitor



The NEW ENGLAND JOURNAL of MEDICINE

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

Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure



- NYHA II–IV
- LVEF ≤40%
- on a β-blocker and MRA,
- On ACE-I /ARB (20/5000 naïve)
- SBP of ≥100 mm Hg
- eGFR ≥30 mL/min/1.73 m2
- potassium ≤5.2 mmol/L

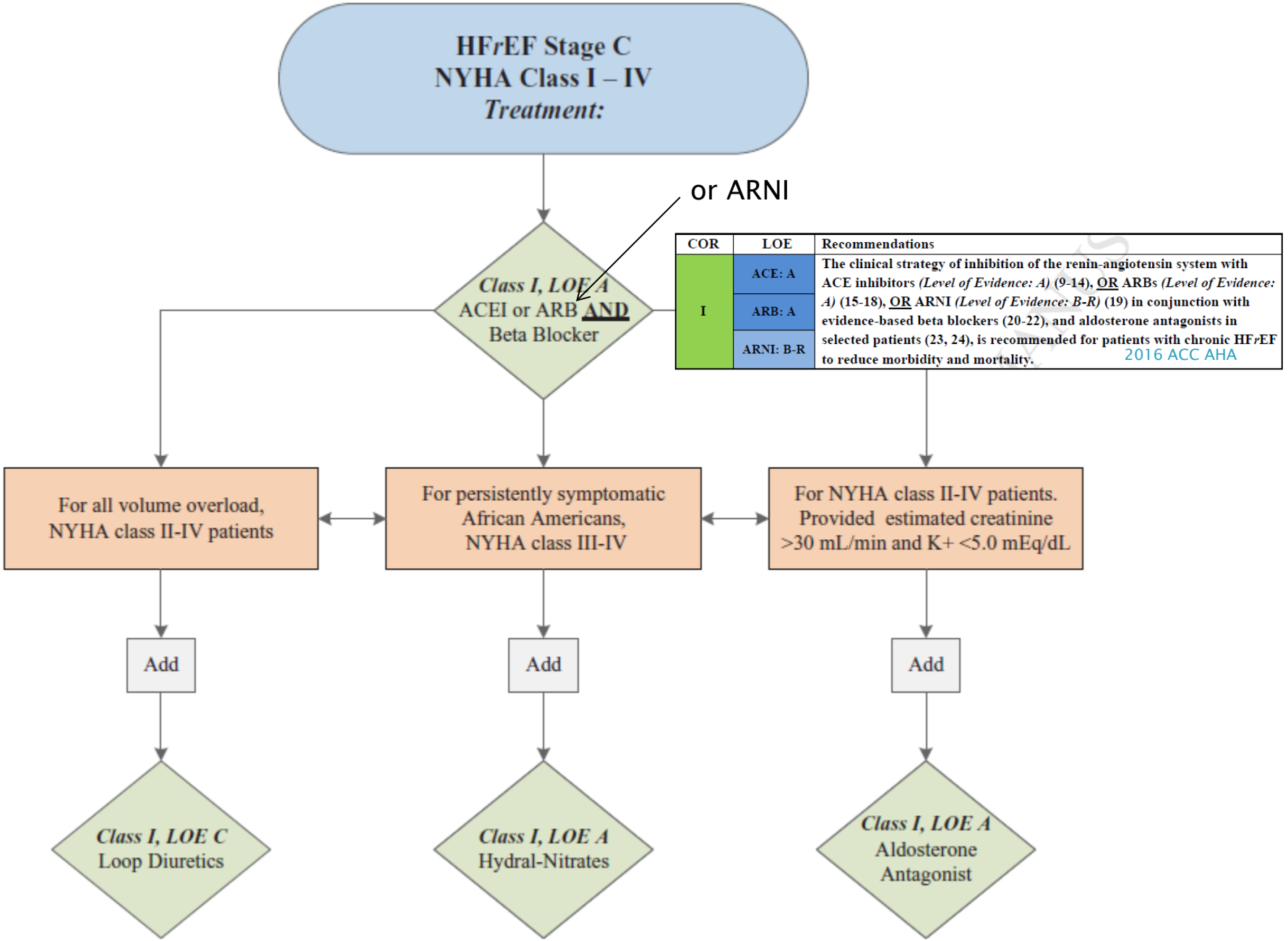
- BNP ≥150 pg/mL (NTpro-BNP ≥600 pg/mL) or
- if hospitalised with HF a BNP ≥100 pg/mL (NTpro-BNP ≥400 pg/mL))
- these are not part of the FDA or EMA prescribing information,

Lack of evidence

- Newly diagnosed HF-rEF
- Naïve ACE-I and ARB

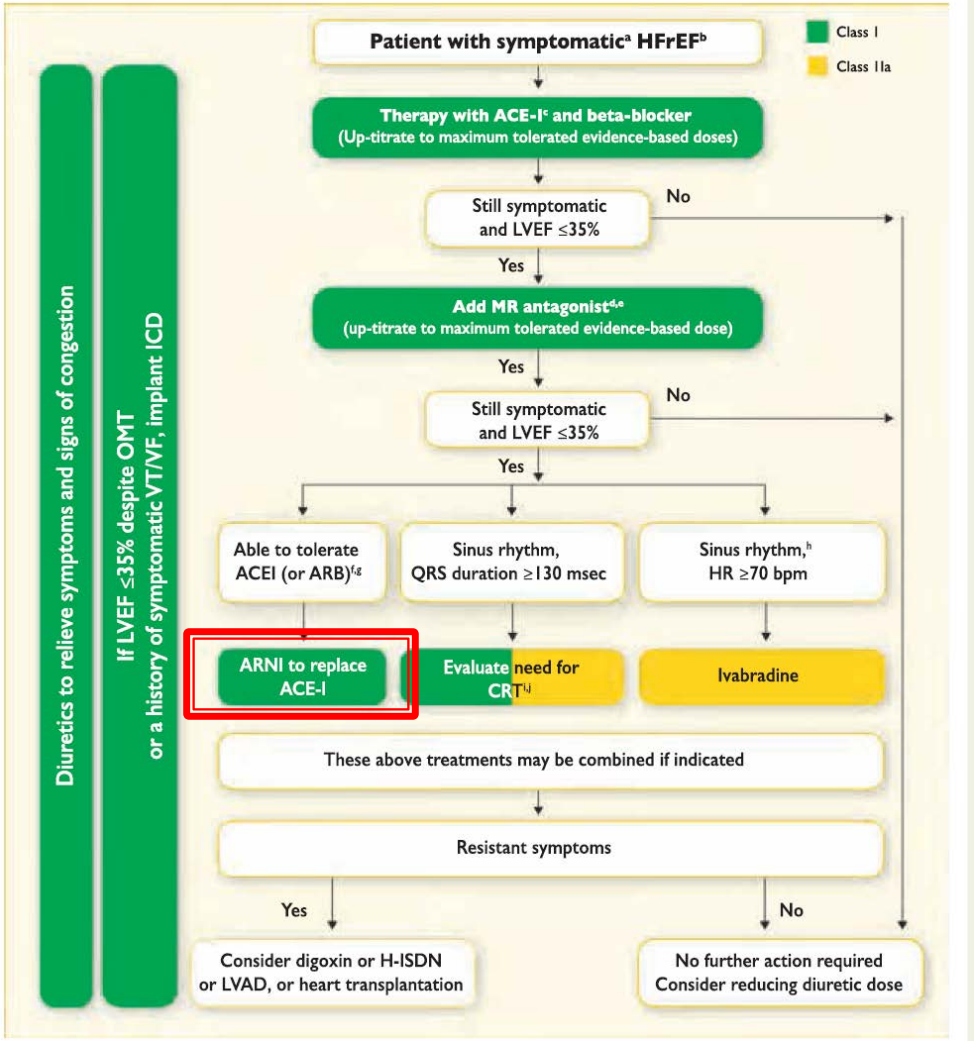
Should they be established on an ACE inhibitor (or ARB) for at least 1 month
after which time they would have been eligible for PARADIGM-HF then switch to ARNI?

- logical (if not entirely evidence-based) to start
  - lower risks of renal dysfunction and hyperkalaemia with sacubitril/valsartan
  - may enable more patients to achieve optimal RAAS inhibition.
- Conducting a trial in ACE inhibitor/ARB-naïve patients would be nearly impossible
  - recruitment would be slow (much smaller number of patients with incident heart failure)
  - cross-over from the ACE inhibitor group to the sacubitril/valsartan group is likely to be very high, confounding interpretation of outcomes.


HFrEF Stage C
NYHA Class I – IV
Treatment:
or ARNI
Class I, LOE A
ACEI or ARB AND
Beta Blocker
COR
LOE
Recommendations
I
ACE: A
ARB: A
ARNI: B-R
The clinical strategy of inhibition of the renin-angiotensin system with ACE inhibitors (Level of Evidence: A) (9-14), OR ARBs (Level of Evidence: A) (15-18), OR ARNI (Level of Evidence: B-R) (19) in conjunction with evidence-based beta blockers (20-22), and aldosterone antagonists in selected patients (23, 24), is recommended for patients with chronic HFrEF to reduce morbidity and mortality.
2016 ACC AHA
For all volume overload,
NYHA class II-IV patients
For persistently symptomatic
African Americans,
NYHA class III-IV
For NYHA class II-IV patients.
Provided estimated creatinine
>30 mL/min and K+ <5.0 mEq/dL
Add
Add
Add
Class I, LOE C
Loop Diuretics
Class I, LOE A
Hydral-Nitrates
Class I, LOE A
Aldosterone
Antagonist

2013 ACC AHA

Angiotensin receptor neprilysin inhibitor		
Sacubitril/valsartan is recommended as a replacement for an ACE-I to further reduce the risk of HF hospitalization and death in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with an ACE-I, a beta-blocker and an MRA[d]	I	B



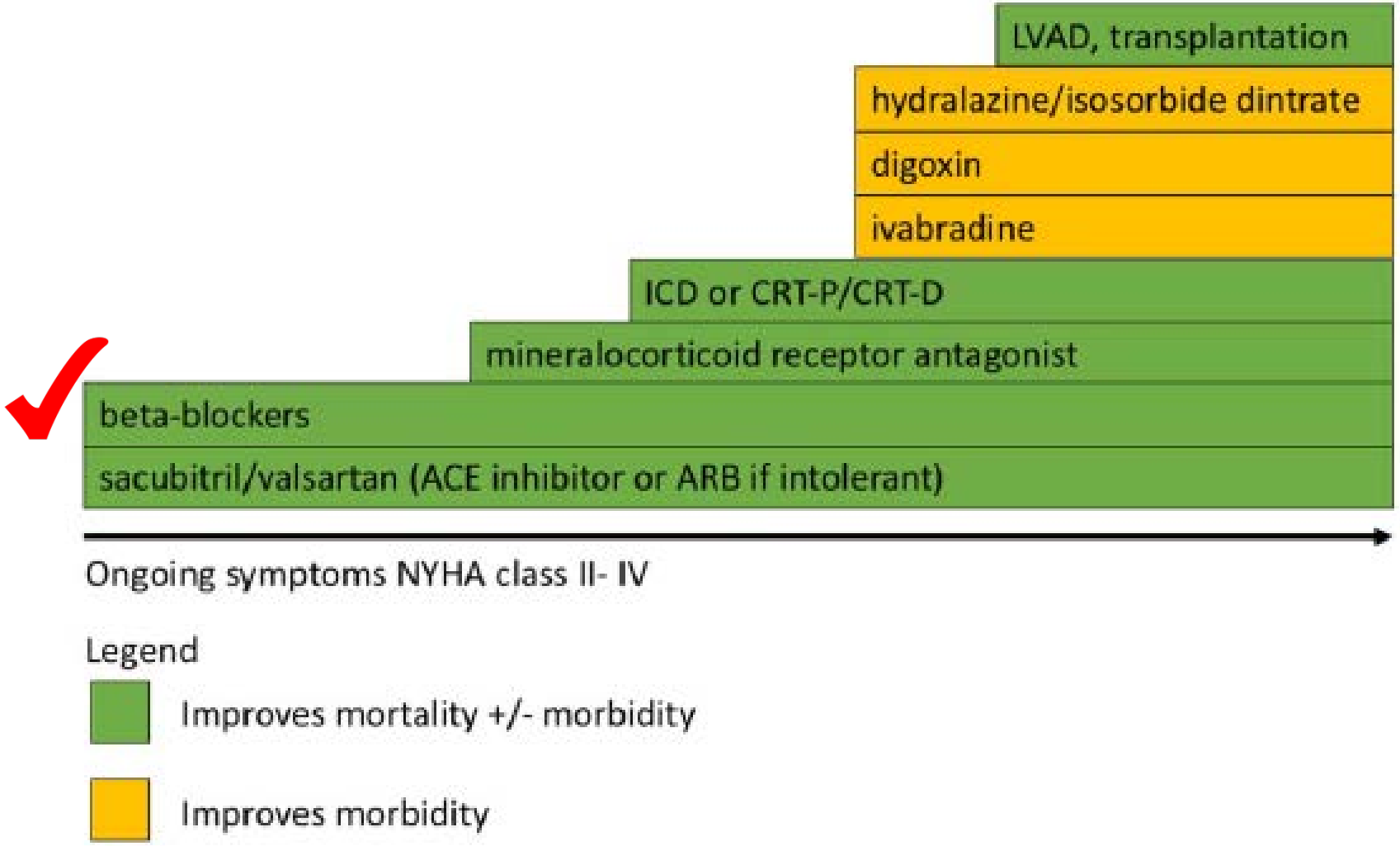
2016 ESC

How to start?

- 50 mg bid or lower
- ACE-I free 36 hrs
- No need for ARB free
- Double uptitration q 2-4 weeks

	Starting dose (mg)	Target dose (mg)
ARNI		
Sacubitril/valsartan	49/51 *b.i.d.*	97/103 *b.i.d.*

III: Harm	**B-R**	**ARNI should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor (31, 32).**
III: Harm	**C-EO**	**ARNI should not be administered to patients with a history of angioedema.**


LVAD, transplantation
hydralazine/isosorbide dintrate
digoxin
ivabradine
ICD or CRT-P/CRT-D
mineralocorticoid receptor antagonist
beta-blockers
sacubitril/valsartan (ACE inhibitor or ARB if intolerant)
Ongoing symptoms NYHA class II- IV
Legend
Improves mortality +/- morbidity
Improves morbidity

Beta-blocker

Recommendations	Class [a]	Level [b]
An ACE-I[d] is recommended, in addition to a beta-blocker, for symptomatic patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A
A beta-blocker is recommended, in addition an ACE-I[d], for patients with stable, symptomatic HFrEF to reduce the risk of HF hospitalization and death.	I	A
An MRA is recommended for patients with HFrEF, who remain symptomatic despite treatment with an ACE-I[d] and a beta-blocker, to reduce the risk of HF hospitalization and death.	I	A

Class I

1. **Use of 1 of the 3 beta blockers proven to reduce mortality (eg, bisoprolol, carvedilol, and sustained-release metoprolol succinate) is recommended for all patients with current or prior symptoms of HF*r*EF, unless contraindicated, to reduce morbidity and mortality.[346,416–419,448] *(Level of Evidence: A)***

Beta-Blocker

	Starting dose (mg)	Target dose (mg)
Beta-blockers		
Bisoprolol	1.25 *o.d.*	10 *o.d.*
Carvedilol	3.125 *b.i.d.*	25 *b.i.d.*[d]
Metoprolol succinate (CR/XL)	12.5–25 *o.d.*	200 o.d.
Nebivolol[e]	1.25 *o.d.*	10 *o.d.*

Drug	Initial Daily Dose(s)	Maximum Dose(s)	Mean Doses Achieved in Clinical Trials
Beta blockers			
Bisoprolol	1.25 mg once	10 mg once	8.6 mg/d[117]
Carvedilol	3.125 mg twice	50 mg twice	37 mg/d[447]
Carvedilol CR	10 mg once	80 mg once	N/A
Metoprolol succinate extended release (metoprolol CR/XL)	12.5 to 25 mg once	200 mg once	159 mg/d[448]

Slow Up titration
85% tolerant

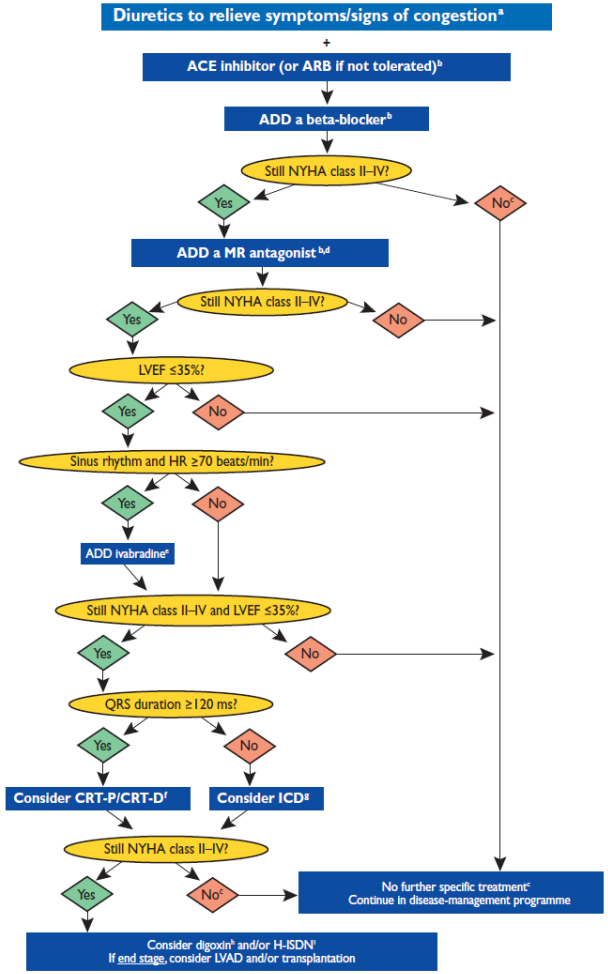
Beta-blocker: Risk of treatment

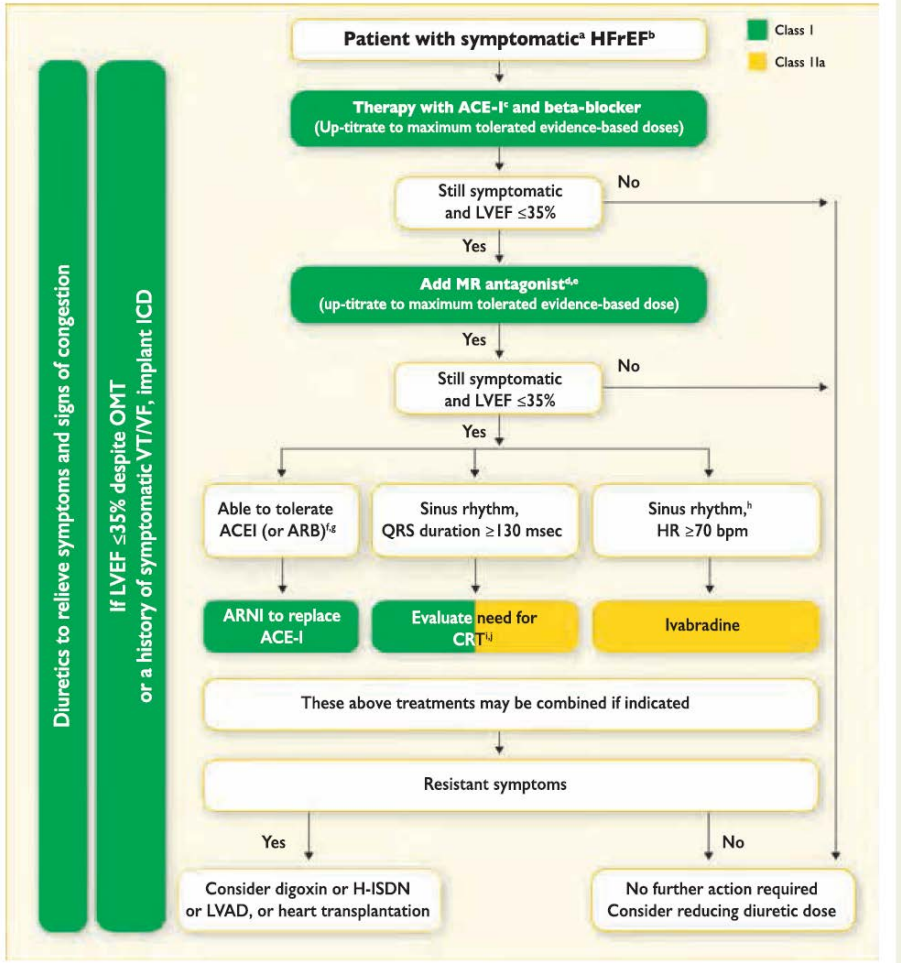
- fluid retention , worsening HF
- fatigue
- bradycardia or heart block
- Hypotension
- Bronchospasm
- PAD

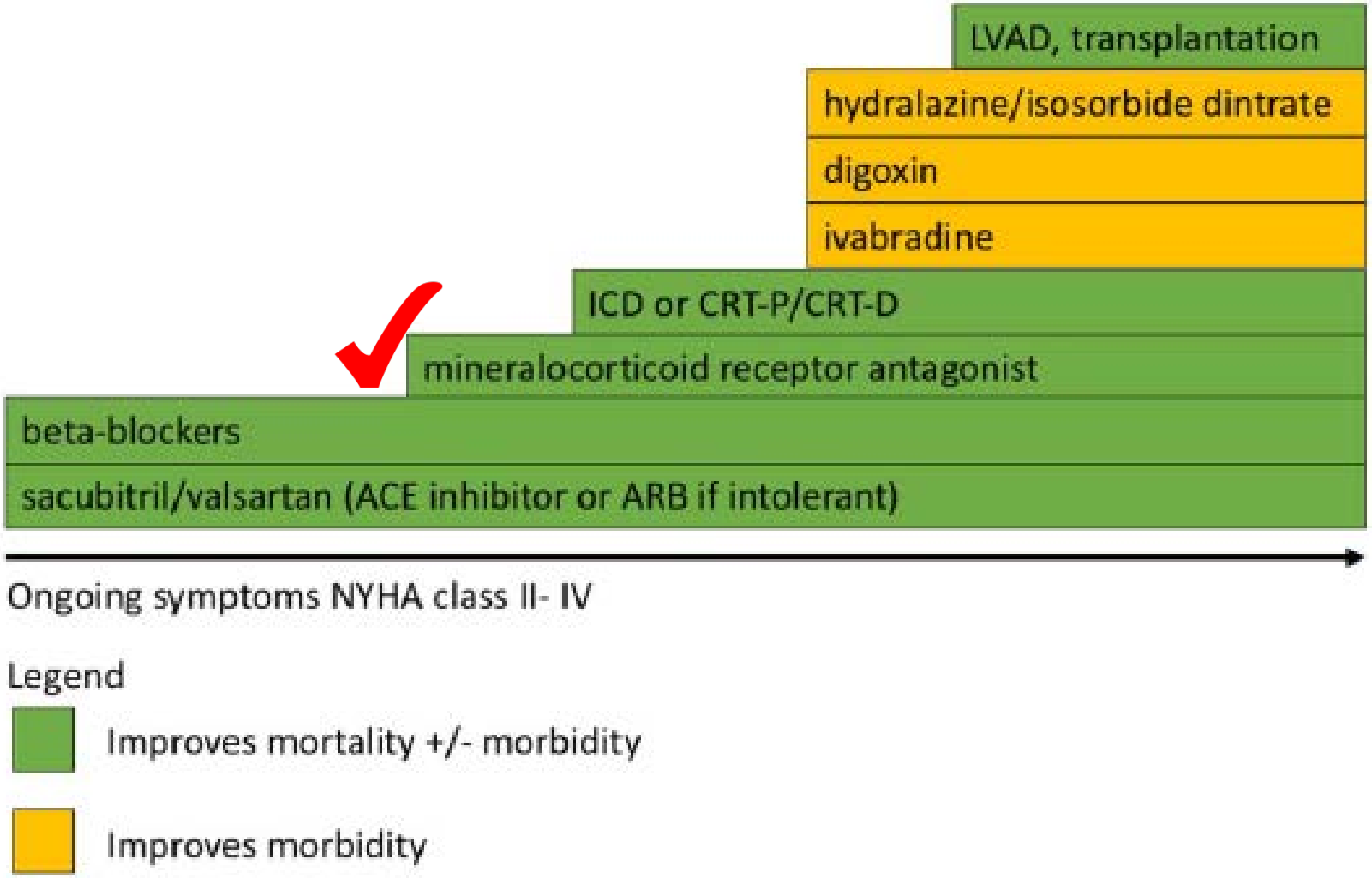
The occurrence of fluid retention or worsening HF is not generally a reason for the permanent withdrawal of BB

Table 18. Medical Therapy for Stage C HF*r*EF: Magnitude of Benefit Demonstrated in RCTs

GDMT	RR Reduction in Mortality (%)	NNT for Mortality Reduction (Standardized to 36 mo)	RR Reduction in HF Hospitalizations (%)
ACE inhibitor or ARB	17	26	31
Beta blocker	34	9	41
Aldosterone antagonist	30	6	35
Hydralazine/nitrate	43	7	33


Diuretics to relieve symptoms/signs of congestion[a]
+
ACE inhibitor (or ARB if not tolerated)[b]
ADD a beta-blocker[b]
Still NYHA class II–IV?
Yes
No[c]
ADD a MR antagonist[b,d]
Still NYHA class II–IV?
Yes
No
LVEF ≤35%?
Yes
No
Sinus rhythm and HR ≥70 beats/min?
Yes
No
ADD ivabradine[e]
Still NYHA class II–IV and LVEF ≤35%?
Yes
No
QRS duration ≥120 ms?
Yes
No
Consider CRT-P/CRT-D[f]
Consider ICD[g]
Still NYHA class II–IV?
Yes
No[c]
No further specific treatment[c]
Continue in disease-management programme
Consider digoxin[h] and/or H-ISDN[i]
If end stage, consider LVAD and/or transplantation


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)
Yes
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,j]
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
Diuretics to relieve symptoms and signs of congestion
If LVEF ≤35% despite OMT or a history of symptomatic VT/VF, implant ICD


LVAD, transplantation
hydralazine/isosorbide dintrate
digoxin
ivabradine
ICD or CRT-P/CRT-D
mineralocorticoid receptor antagonist
beta-blockers
sacubitril/valsartan (ACE inhibitor or ARB if intolerant)
Ongoing symptoms NYHA class II- IV
Legend
Improves mortality +/- morbidity
Improves morbidity

MRA

Drug	Initial Daily Dose(s)	Maximum Dose(s)	Mean Doses Achieved in Clinical Trials
Aldosterone antagonists			
Spironolactone	12.5 to 25.0 mg once	25 mg once or twice	26 mg/d[425]
Eplerenone	25 mg once	50 mg once	42.6 mg/d[446]

	Starting dose (mg)	Target dose (mg)
MRAs		
Eplerenone	25 *o.d.*	50 *o.d.*
Spironolactone	25 *o.d.*	50 *o.d.*

Class I

1. Aldosterone receptor antagonists (or mineralocorticoid receptor antagonists) are recommended in patients with NYHA class II–IV HF and who have LVEF of 35% or less, unless contraindicated, to reduce morbidity and mortality. Patients with NYHA class II HF should have a history of prior cardiovascular hospitalization or elevated plasma natriuretic peptide levels to be considered for aldosterone receptor antagonists. Creatinine should be 2.5 mg/dL or less in men or 2.0 mg/dL or less in women (or estimated glomerular filtration rate >30 mL/min/1.73 m^2), and potassium should be less than 5.0 mEq/L. Careful monitoring of potassium, renal function, and diuretic dosing should be performed at initiation and closely followed thereafter to minimize risk of hyperkalemia and renal insufficiency.[425,426,478] *(Level of Evidence: A)*
2. Aldosterone receptor antagonists are recommended to reduce morbidity and mortality following an acute MI in patients who have LVEF of 40% or less who develop symptoms of HF or who have a history of diabetes mellitus, unless contraindicated.[446] *(Level of Evidence: B)*

Table 16. Drug Dosing for Aldosterone Receptor Antagonists

	Eplerenone		Spironolactone	
eGFR (mL/min/1.73 m^2)	≥50	30 to –49	≥50	30 to 49
Initial dose (only if K^+ ≤5 mEq/L)	25 mg once daily	25 mg once every other day	12.5 to 25.0 mg once daily	12.5 mg once daily or every other day
Maintenance dose (after 4 wk for K^+ ≤5 mEq/L)*	50 mg once daily	25 mg once daily	25 mg once or twice daily	12.5 to 25.0 mg once daily

*After dose initiation for K^+, increase ≤6.0 mEq/L or worsening renal function, hold until K^+ <5.0 mEq/L. Consider restarting reduced dose after confirming resolution of hyperkalemia/renal insufficiency for at least 72 h.

eGFR indicates estimated glomerular filtration rate; and, K^+, potassium.

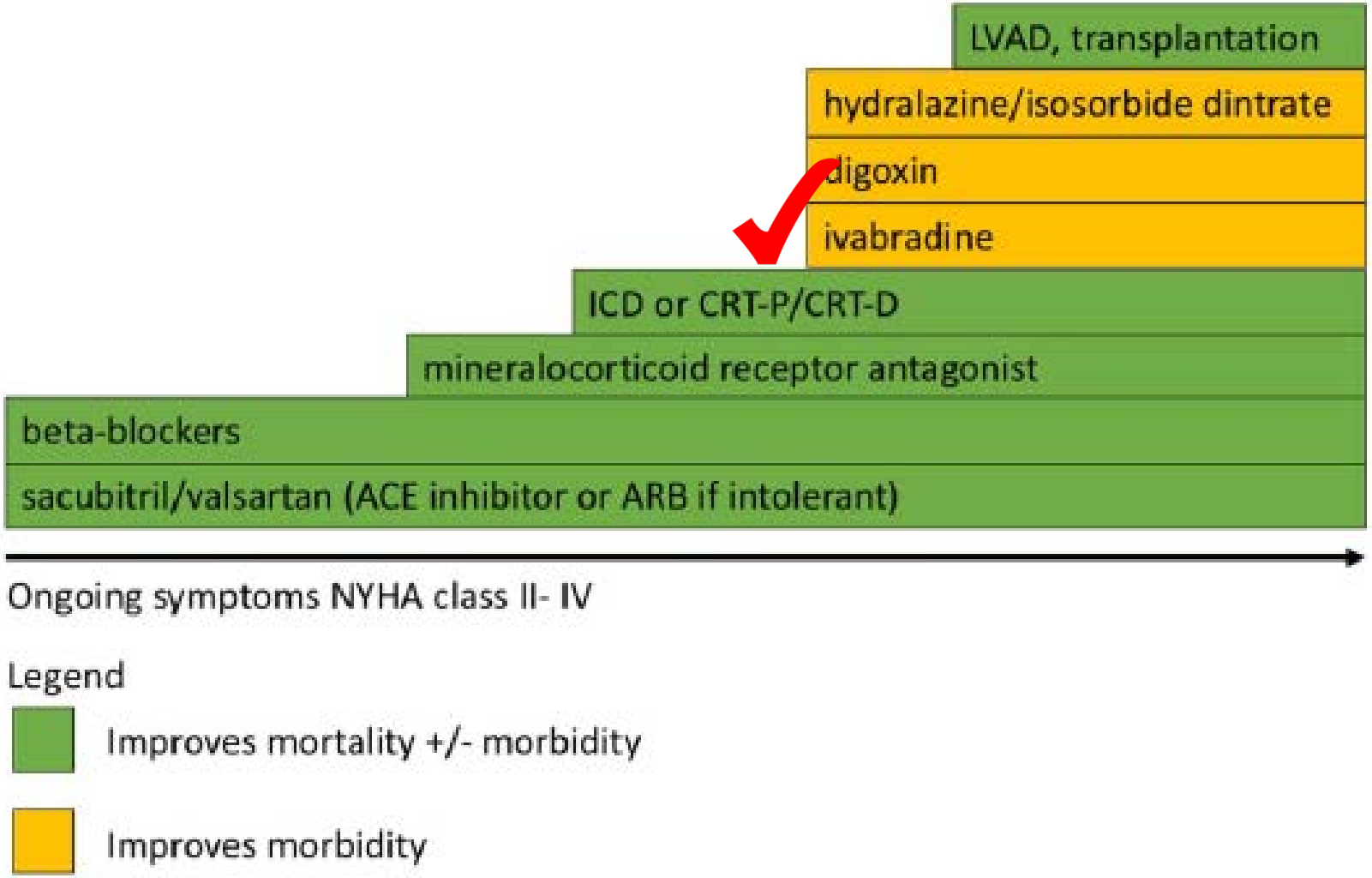
Adapted from Butler et al.[481]

Table 17. Strategies to Minimize the Risk of Hyperkalemia in Patients Treated With Aldosterone Antagonists

1. Impaired renal function is a risk factor for hyperkalemia during treatment with aldosterone antagonists. The risk of hyperkalemia increases progressively when serum creatinine is >1.6 mg/dL.* In elderly patients or others with low muscle mass in whom serum creatinine does not accurately reflect glomerular filtration rate, determination that glomerular filtration rate or creatinine clearance is >30 mL/min/1.73 m^2 is recommended.
2. Aldosterone antagonists would not ordinarily be initiated in patients with baseline serum potassium >5.0 mEq/L.
3. An initial dose of spironolactone of 12.5 mg or eplerenone 25 mg is typical, after which the dose may be increased to spironolactone 25 mg or eplerenone 50 mg if appropriate.
4. The risk of hyperkalemia is increased with concomitant use of higher doses of ACE inhibitors (captopril ≥75 mg daily; enalapril or lisinopril ≥10 mg daily).
5. In most circumstances, potassium supplements are discontinued or reduced when initiating aldosterone antagonists.
6. Close monitoring of serum potassium is required; potassium levels and renal function are most typically checked in 3 d and at 1 wk after initiating therapy and at least monthly for the first 3 mo.

*Although the entry criteria for the trials of aldosterone antagonists included creatinine <2.5 mg/dL, the majority of patients had much lower creatinine; in 1 trial,[425] 95% of patients had creatinine ≤1.7 mg/dL.

ACE indicates angiotensin-converting enzyme.


LVAD, transplantation
hydralazine/isosorbide dintrate
digoxin
ivabradine
ICD or CRT-P/CRT-D
mineralocorticoid receptor antagonist
beta-blockers
sacubitril/valsartan (ACE inhibitor or ARB if intolerant)
Ongoing symptoms NYHA class II- IV
Legend
Improves mortality +/- morbidity
Improves morbidity

Ivabradine

- If channel blocker
- Slow HR, no negative inotrope impact

If-channel inhibitor		
Ivabradine should be considered to reduce the risk of HF hospitalization or cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm despite treatment with an evidence-based dose of beta-blocker (or maximum tolerated dose below that), ACE-I (or ARB), and an MRA (or ARB).	IIa	B
Ivabradine should be considered to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm who are unable to tolerate or have contra-indications for a beta-blocker. Patients should also receive an ACE-I (or ARB) and an MRA (or ARB).	IIa	C

Recommendation for Ivabradine		
COR	**LOE**	**Recommendation**
IIa	**B-R**	**Ivabradine can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA class II-III) stable chronic HF*r*EF (LVEF ≤35%) who are receiving GDEM, including a beta blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of 70 bpm or greater at rest (37-40).**

	Starting dose (mg)	Target dose (mg)
If-channel blocker		
Ivabradine	5 *b.i.d.*	7.5 *b.i.d.*

Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study

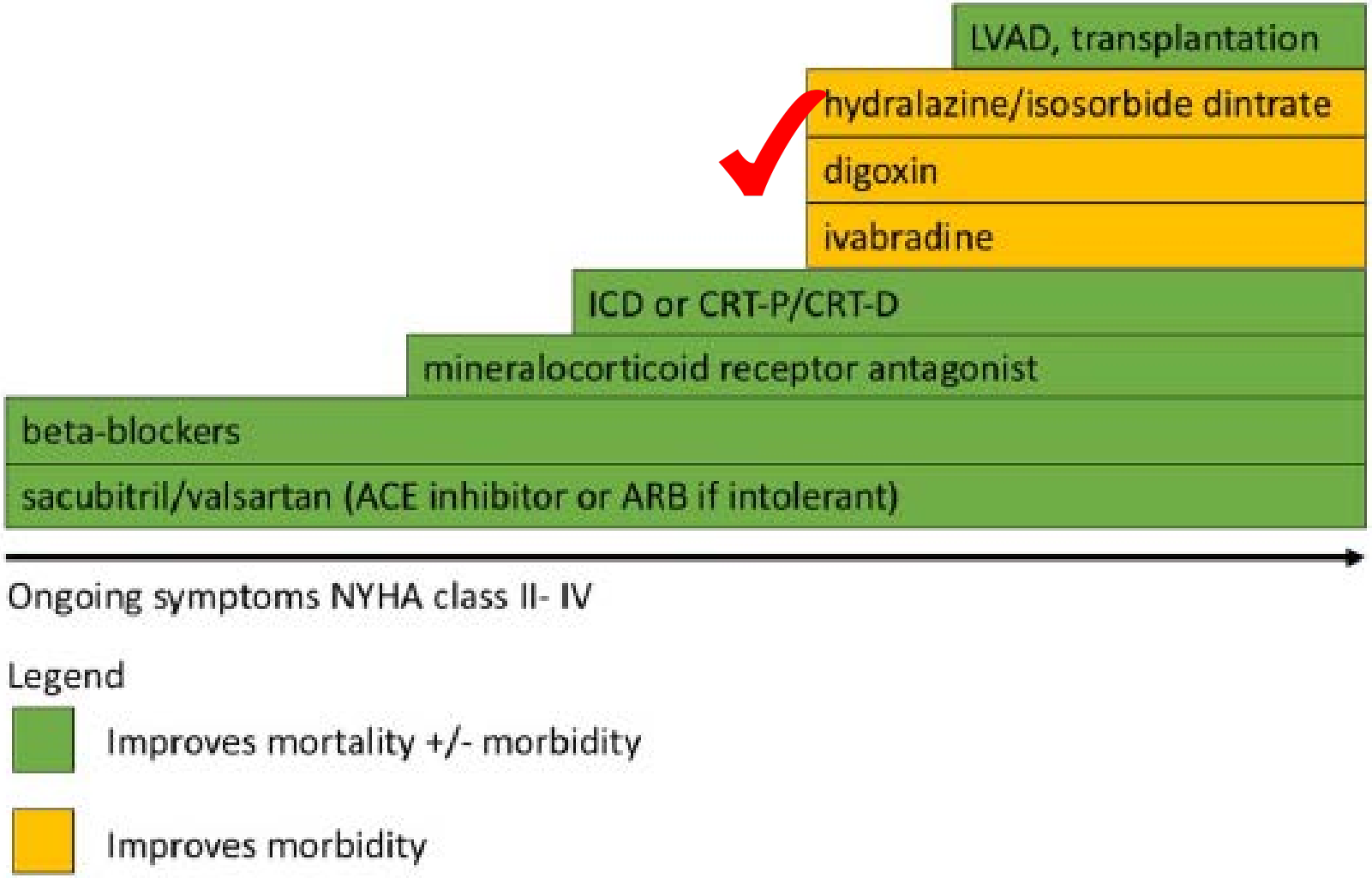
*Karl Swedberg, Michel Komajda, Michael Böhm, Jeffrey S Borer, Ian Ford, Ariane Dubost-Brama, Guy Lerebours, Luigi Tavazzi, on behalf of the SHIFT Investigators**

	Ivabradine group (n=3241)	Placebo group (n=3264)	HR (95% CI)	p value
Primary endpoint				
Cardiovascular death or hospital admission for worsening heart failure	793 (24%)	937 (29%)	0·82 (0·75–0·90)	<0·0001
Mortality endpoints				
All-cause mortality	503 (16%)	552 (17%)	0·90 (0·80–1·02)	0·092
Cardiovascular mortality	449 (14%)	491 (15%)	0·91 (0·80–1·03)	0·128
Death from heart failure	113 (3%)	151 (5%)	0·74 (0·58–0·94)	0·014
Other endpoints				
All-cause hospital admission	1231 (38%)	1356 (42%)	0·89 (0·82–0·96)	0·003
Hospital admission for worsening heart failure	514 (16%)	672 (21%)	0·74 (0·66–0·83)	<0·0001
Any cardiovascular hospital admission	977 (30%)	1122 (34%)	0·85 (0·78–0·92)	0·0002
Cardiovascular death, or hospital admission for worsening heart failure, or hospital admission for non-fatal myocardial infarction	825 (25%)	979 (30%)	0·82 (0·74–0·89)	<0·0001

Data are number of first events (%), hazard ratio (HR; 95% CI), and p values.

Table 3: **Effects on primary and major secondary endpoints**

Lancet Vol 376 September 11, 2010


LVAD, transplantation
hydralazine/isosorbide dintrate
digoxin
ivabradine
ICD or CRT-P/CRT-D
mineralocorticoid receptor antagonist
beta-blockers
sacubitril/valsartan (ACE inhibitor or ARB if intolerant)
Ongoing symptoms NYHA class II- IV
Legend
Improves mortality +/- morbidity
Improves morbidity

Digoxin

7.3.2.7. Digoxin: Recommendation

Class IIa

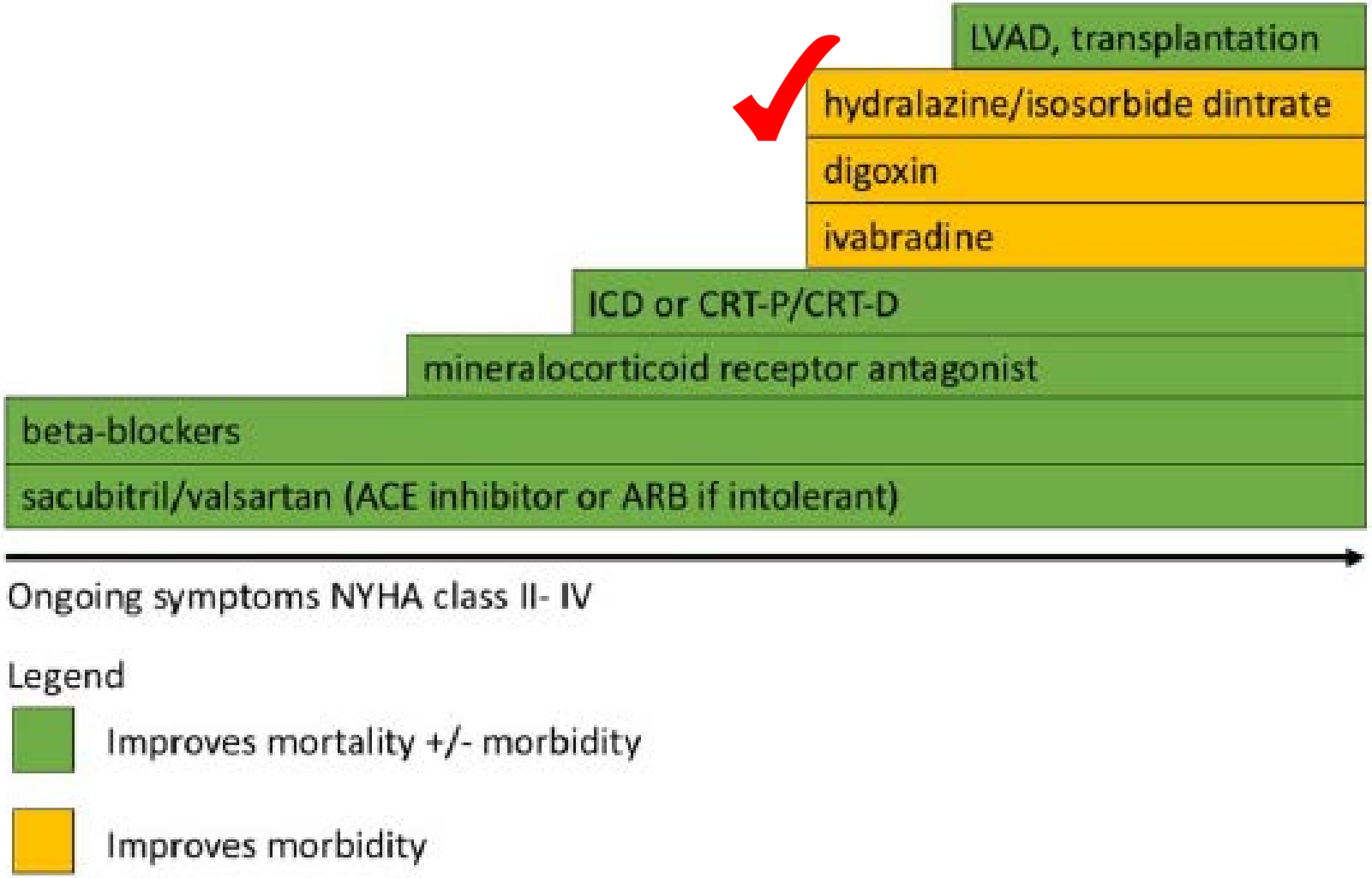
1. **Digoxin can be beneficial in patients with HF*r*EF, unless contraindicated, to decrease hospitalizations for HF.[484–491] *(Level of Evidence: B)***

Digoxin		
Digoxin may be considered in symptomatic patients in sinus rhythm despite treatment with an ACE-I (or ARB), a beta-blocker and an MRA, to reduce the risk of hospitalization (both all-cause and HF-hospitalizations).	IIb	B

Digoxin

- Remain symptomatic despite GDMT
- 0.125 AD to 0.25 OD
- Dig level-no evidence-suggested 0.5-0.9 ng/dl
- Toxicity associated with level > 2 ng/dl or even lower if hypo K or Mg
- Cautions with
  - K, Mg
  - clarithromycin, dronedarone, erythromycin, amiodarone,itraconazole, cyclosporine, propafenone, verapamil, or quinidine
  - Renal dysfunction
  - Small BW
  - Elderly

Dig intoxication
- GI
- Yellow vison CNS
- Cardiac – heart block, VT


LVAD, transplantation
hydralazine/isosorbide dintrate
digoxin
ivabradine
ICD or CRT-P/CRT-D
mineralocorticoid receptor antagonist
beta-blockers
sacubitril/valsartan (ACE inhibitor or ARB if intolerant)
Ongoing symptoms NYHA class II- IV
Legend
Improves mortality +/- morbidity
Improves morbidity

Hydralazine–nitrate

7.3.2.6. Hydralazine and Isosorbide Dinitrate: Recommendations

Class I

1. **The combination of hydralazine and isosorbide dinitrate is recommended to reduce morbidity and mortality for patients self-described as African Americans with NYHA class III–IV HF*r*EF receiving optimal therapy with ACE inhibitors and beta blockers, unless contraindicated.[423,424] *(Level of Evidence: A)***

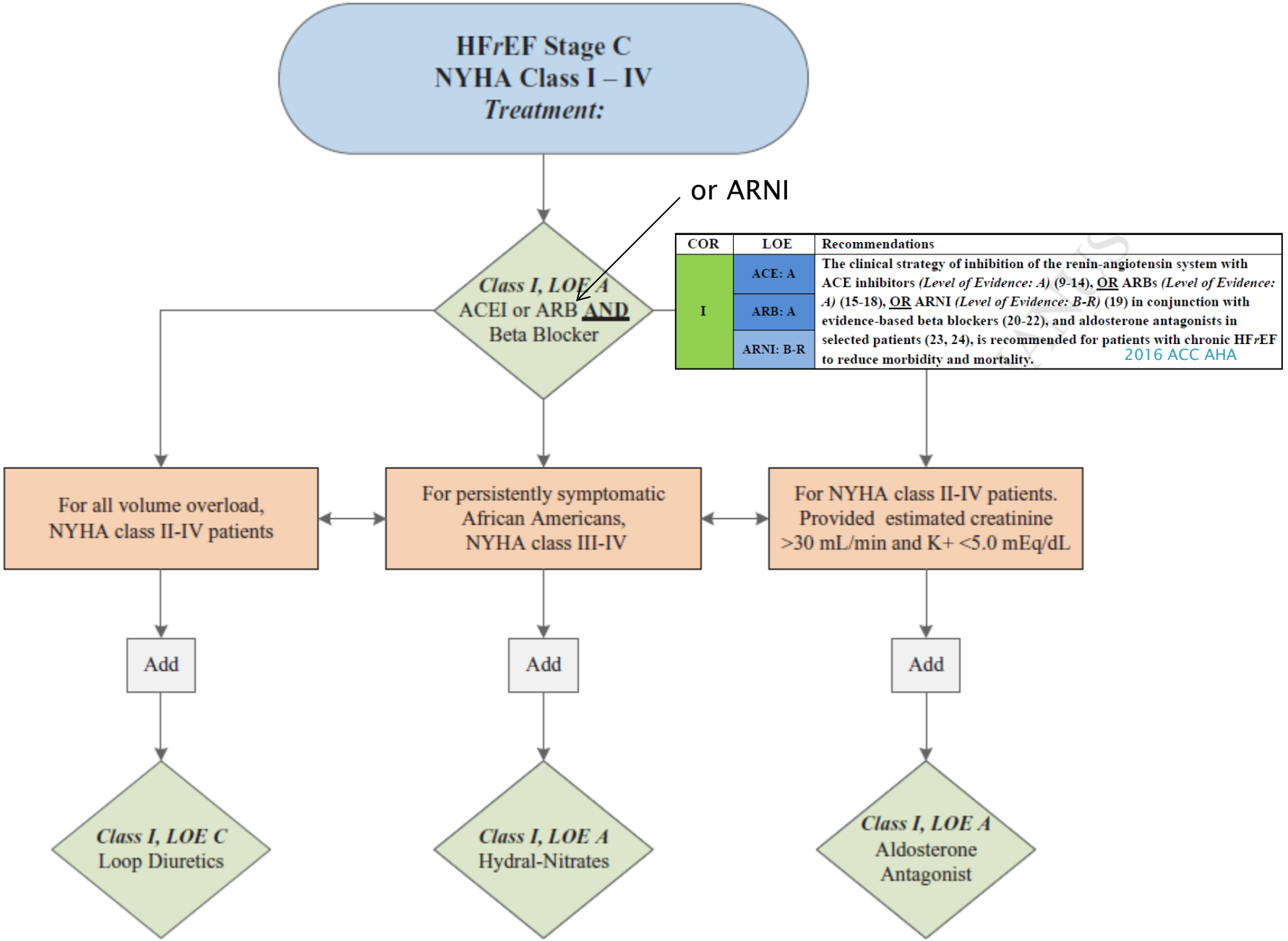
Class IIa

1. **A combination of hydralazine and isosorbide dinitrate can be useful to reduce morbidity or mortality in patients with current or prior symptomatic HF*r*EF who cannot be given an ACE inhibitor or ARB because of drug intolerance, hypotension, or renal insufficiency, unless contraindicated.[449] *(Level of Evidence: 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 LV in NYHA Class III–IV despite treatment with an ACE-I a beta-blocker and an MRA to reduce the risk of HF hospitalization and death.	IIa	B
Hydralazine and isosorbide dinitrate may be considered in symptomatic patients with HFrEF who can tolerate neither an ACE-I nor an ARB (or they are contra-indicated) to reduce the risk of death.	IIb	B

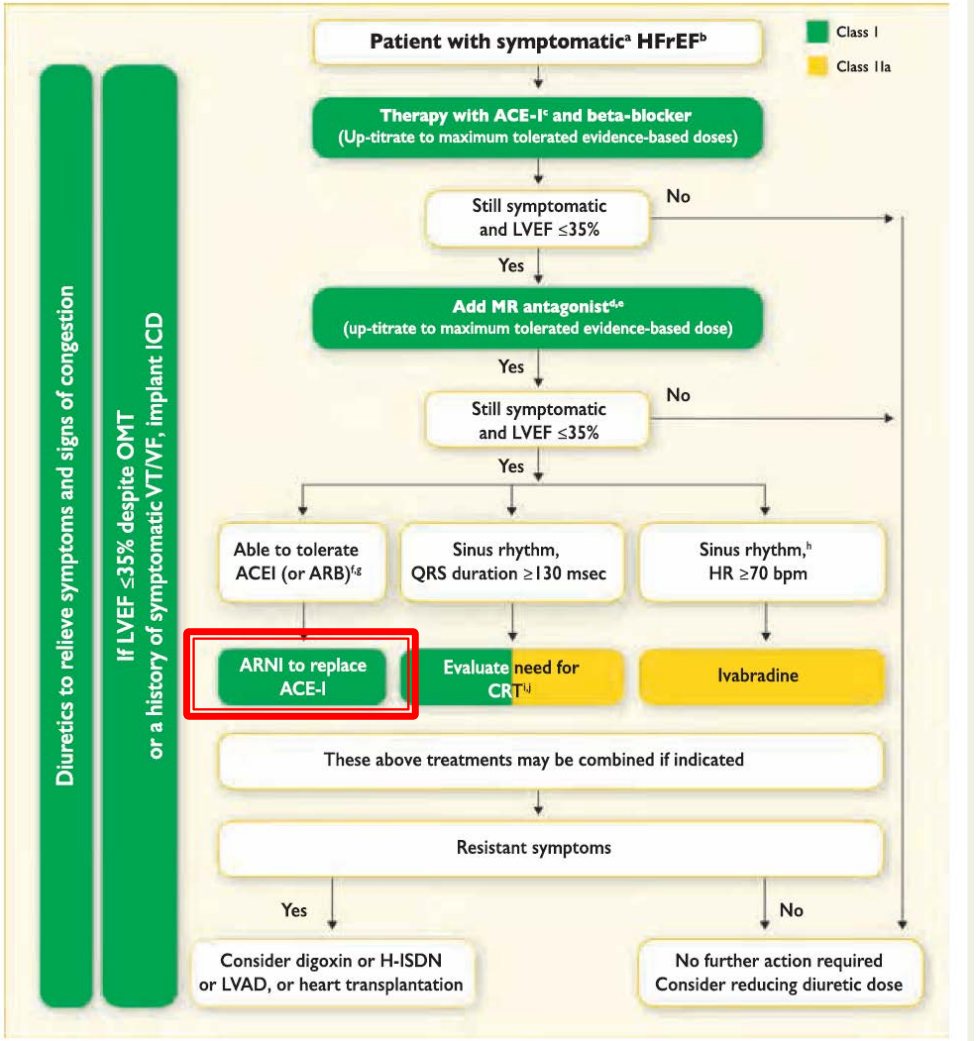
Hydralazine–nitrate

Drug	Initial Daily Dose(s)	Maximum Dose(s)	Mean Doses Achieved in Clinical Trials
Hydralazine and isosorbide dinitrate			
Fixed-dose combination[424]	37.5 mg hydralazine/20 mg isosorbide dinitrate 3 times daily	75 mg hydralazine/40 mg isosorbide dinitrate 3 times daily	~175 mg hydralazine/90 mg isosorbide dinitrate daily
Hydralazine and isosorbide dinitrate[449]	Hydralazine: 25 to 50 mg, 3 or 4 times daily and isosorbide dinitrate: 20 to 30 mg 3 or 4 times daily	Hydralazine: 300 mg daily in divided doses and isosorbide dinitrate: 120 mg daily in divided doses	N/A


HFrEF Stage C
NYHA Class I – IV
Treatment:
or ARNI
Class I, LOE A
ACEI or ARB AND
Beta Blocker
COR
LOE
Recommendations
I
ACE: A
ARB: A
ARNI: B-R
The clinical strategy of inhibition of the renin-angiotensin system with ACE inhibitors (Level of Evidence: A) (9-14), OR ARBs (Level of Evidence: A) (15-18), OR ARNI (Level of Evidence: B-R) (19) in conjunction with evidence-based beta blockers (20-22), and aldosterone antagonists in selected patients (23, 24), is recommended for patients with chronic HFrEF to reduce morbidity and mortality.
2016 ACC AHA
For all volume overload,
NYHA class II-IV patients
For persistently symptomatic
African Americans,
NYHA class III-IV
For NYHA class II-IV patients.
Provided estimated creatinine
>30 mL/min and K+ <5.0 mEq/dL
Add
Add
Add
Class I, LOE C
Loop Diuretics
Class I, LOE A
Hydral-Nitrates
Class I, LOE A
Aldosterone
Antagonist

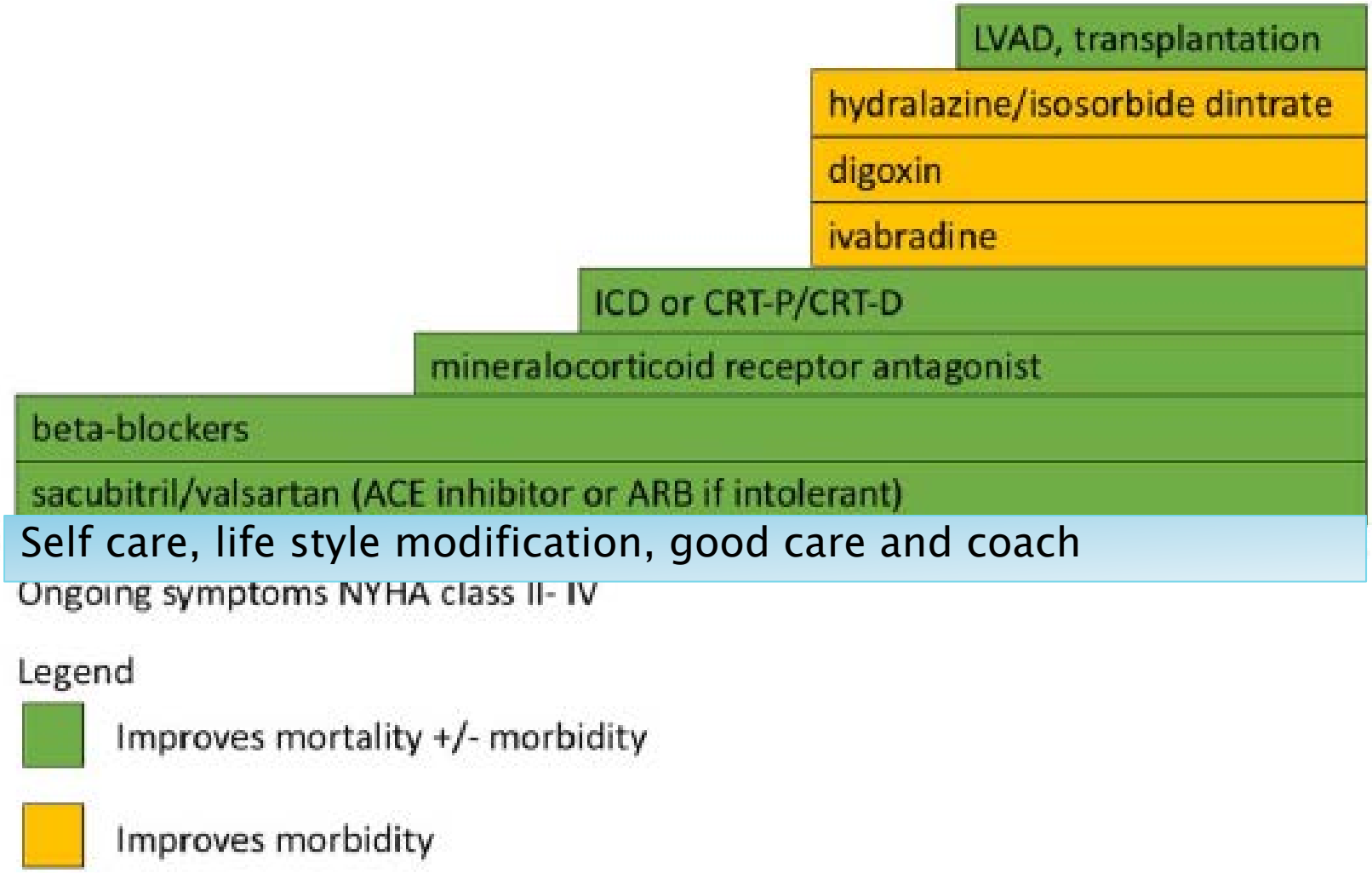
2013 ACC AHA

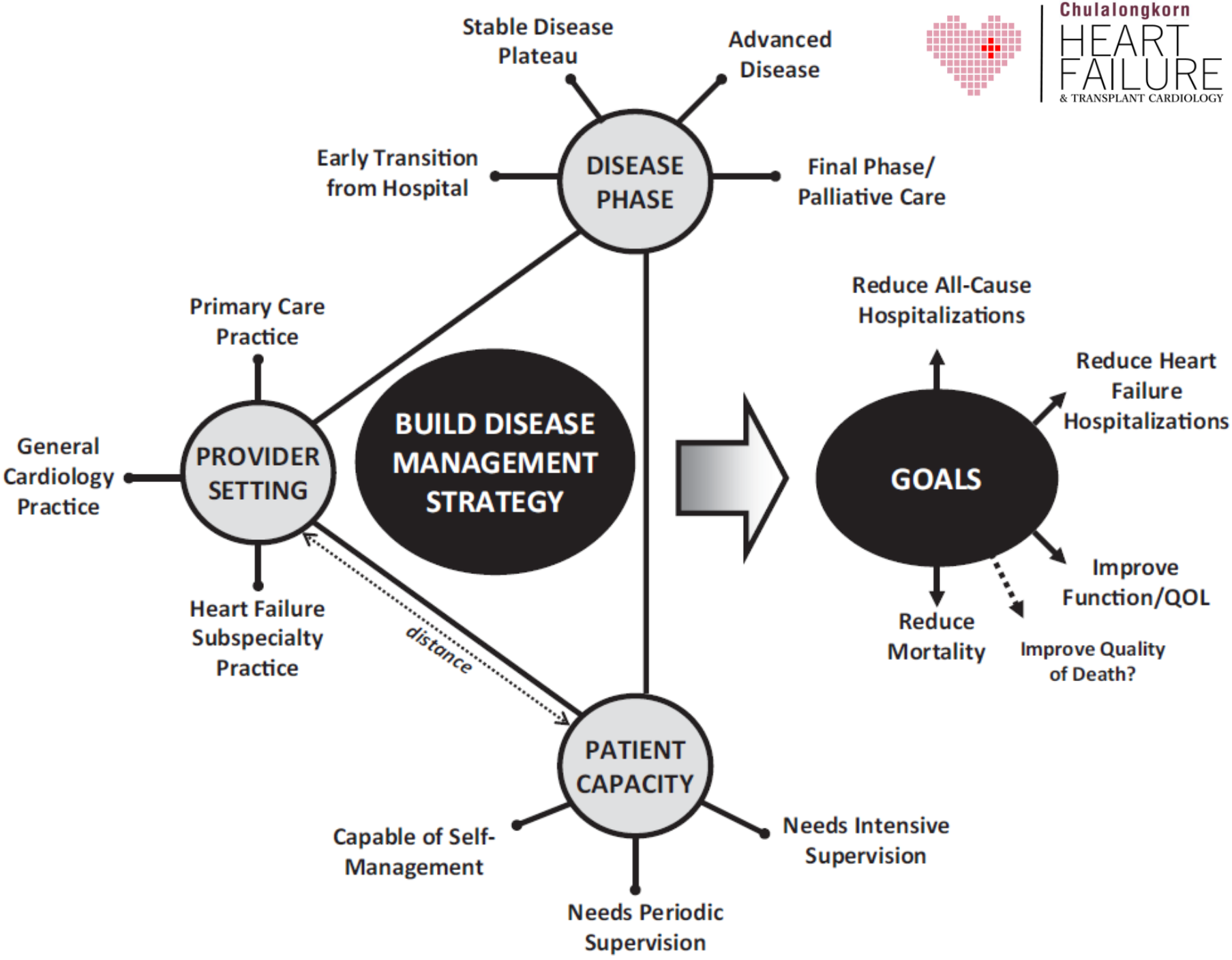
Angiotensin receptor neprilysin inhibitor		
Sacubitril/valsartan is recommended as a replacement for an ACE-I to further reduce the risk of HF hospitalization and death in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with an ACE-I, a beta-blocker and an MRA[d]	I	B



2016 ESC

What is lacking ?

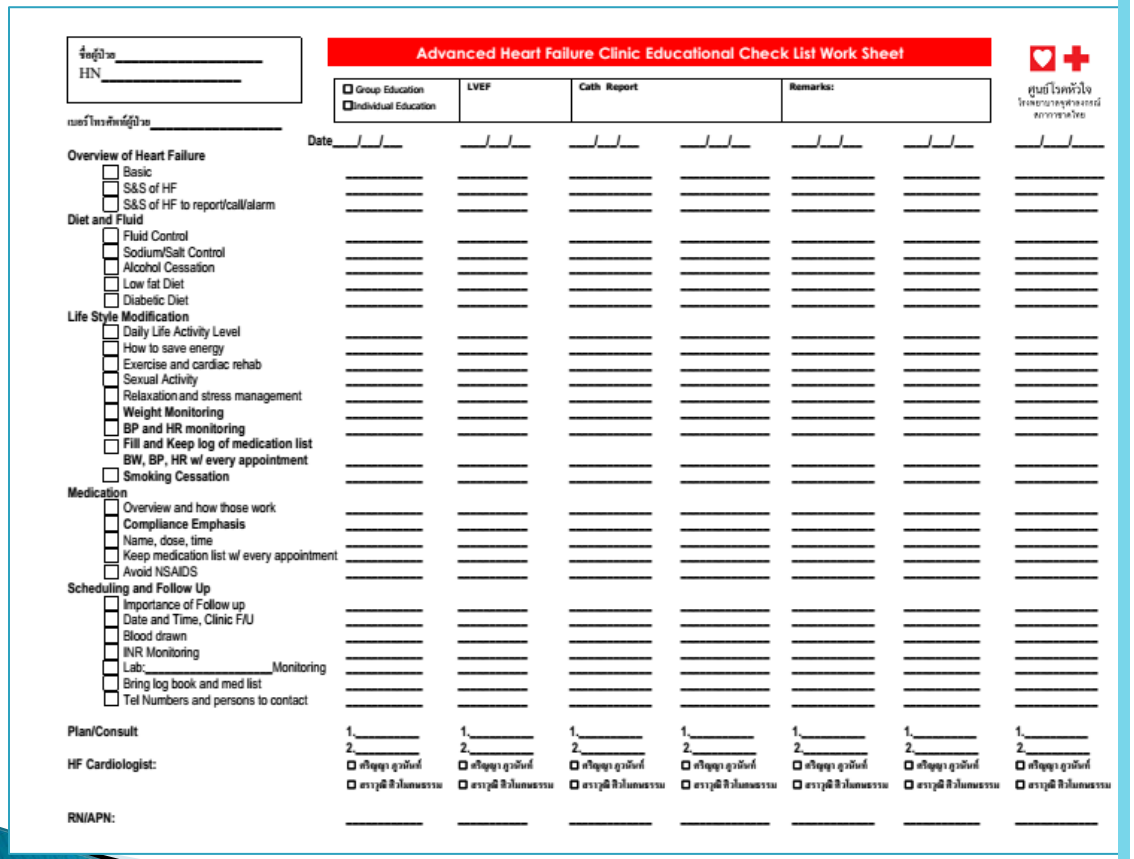



Chulalongkorn
HEART FAILURE
& TRANSPLANT CARDIOLOGY
Stable Disease Plateau
Advanced Disease
Early Transition from Hospital
DISEASE PHASE
Final Phase/ Palliative Care
Primary Care Practice
General Cardiology Practice
PROVIDER SETTING
Heart Failure Subspecialty Practice
BUILD DISEASE MANAGEMENT STRATEGY
distance
PATIENT CAPACITY
Capable of Self-Management
Needs Periodic Supervision
Needs Intensive Supervision
Reduce All-Cause Hospitalizations
Reduce Heart Failure Hospitalizations
GOALS
Improve Function/QOL
Reduce Mortality
Improve Quality of Death?

HF Clinic

- heart failure MD
- Well trained nurses
- pharmacists
- Dietician

RN:
Routine HF teaching



ชื่อผู้ป่วย_____
HN_____

เบอร์โทรศัพท์ผู้ป่วย_____

Advanced Heart Failure Clinic Educational Check List Work Sheet

ศูนย์โรคหัวใจ โรงพยาบาลจุฬาลงกรณ์ สภากาชาดไทย

☐ Group Education ☐ Individual Education	LVEF	Cath Report	Remarks:

Date___/___/___ ___/___/___ ___/___/___ ___/___/___ ___/___/___ ___/___/___ ___/___/___

Overview of Heart Failure
- ☐ Basic
- ☐ S&S of HF
- ☐ S&S of HF to report/call/alarm

Diet and Fluid
- ☐ Fluid Control
- ☐ Sodium/Salt Control
- ☐ Alcohol Cessation
- ☐ Low fat Diet
- ☐ Diabetic Diet

Life Style Modification
- ☐ Daily Life Activity Level
- ☐ How to save energy
- ☐ Exercise and cardiac rehab
- ☐ Sexual Activity
- ☐ Relaxation and stress management
- ☐ **Weight Monitoring**
- ☐ **BP and HR monitoring**
- ☐ **Fill and Keep log of medication list**
- **BW, BP, HR w/ every appointment**
- ☐ **Smoking Cessation**

Medication
- ☐ Overview and how those work
- ☐ **Compliance Emphasis**
- ☐ Name, dose, time
- ☐ Keep medication list w/ every appointment
- ☐ Avoid NSAIDS

Scheduling and Follow Up
- ☐ Importance of Follow up
- ☐ Date and Time, Clinic F/U
- ☐ Blood drawn
- ☐ INR Monitoring
- ☐ Lab:_____Monitoring
- ☐ Bring log book and med list
- ☐ Tel Numbers and persons to contact

Plan/Consult 1._____ 2._____

HF Cardiologist: ☐ เห็นสมควร ดูอาการ ☐ ตรวจผิดปกติ

RN/APN:

Date_

Overview of Heart Failure
- ☐ Basic
- ☑ S&S of HF
- ☐ S&S of HF to report/call/alarm

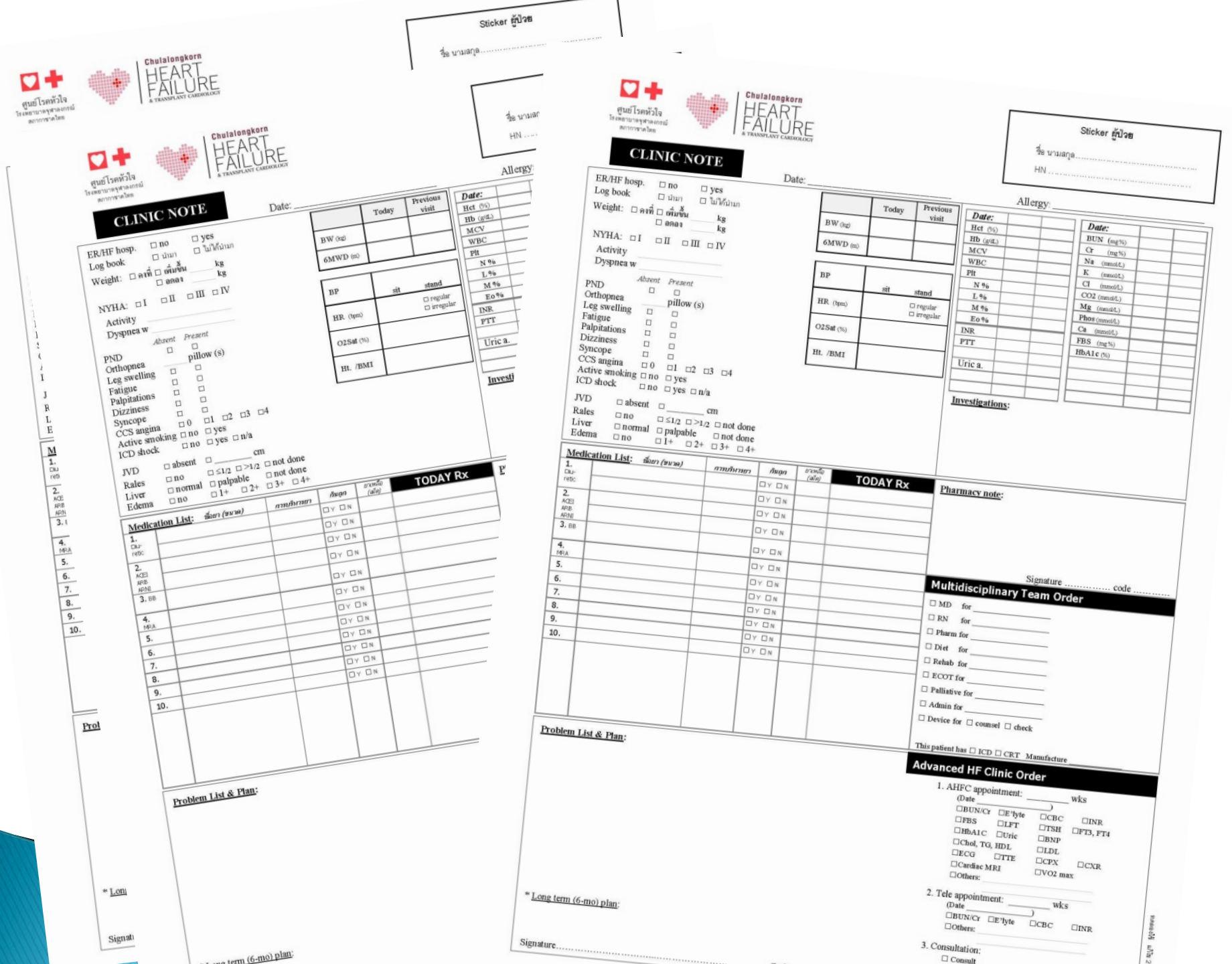
Diet and Fluid
- ☐ Fluid Control
- ☑ Sodium/Salt Control
- ☐ Alcohol Cessation
- ☐ Low fat Diet
- ☐ Diabetic Diet

Life Style Modification
- ☐ Daily Life Activity Level
- ☐ How to save energy
- ☐ Exercise and cardiac rehab
- ☐ Sexual Activity
- ☑ Relaxation and stress management
- ☐ Weight Monitoring
- ☐ BP and HR monitoring
- ☑ Fill and Keep log of medication list
- BW, BP, HR w/ every appointment
- ☐ Smoking Cessation

Medication
- ☐ Overview and how those work
- ☐ Compliance Emphasis
- ☐ Name, dose, time
- ☐ Keep medication list w/ every appointment
- ☑ Avoid NSAIDS

Scheduling and Follow Up
- ☐ Importance of Follow up
- ☐ Date and Time, Clinic F/U
- ☐ Blood drawn
- ☐ INR Monitoring
- ☐ Lab:_____Monitoring
- ☐ Bring log book and med list
- ☐ Tel Numbers and persons to contact

Best HF device



ศูนย์โรคหัวใจ โรงพยาบาลจุฬาลงกรณ์ สภากาชาดไทย

Chulalongkorn HEART FAILURE & TRANSPLANT CARDIOLOGY

Sticker ผู้ป่วย

ชื่อ นามสกุล.....

HN .....

CLINIC NOTE

Date: _____

Allergy: _____

ER/HF hosp. ☐ no ☐ yes
Log book ☐ มีมา ☐ ไม่ได้นำมา
Weight: ☐ คงที่ ☐ เพิ่มขึ้น _____ kg
☐ ลดลง _____ kg

NYHA: ☐ I ☐ II ☐ III ☐ IV
Activity
Dyspnea w

	Absent	Present
PND	☐	☐
Orthopnea	_____ pillow (s)	
Leg swelling	☐	☐
Fatigue	☐	☐
Palpitations	☐	☐
Dizziness	☐	☐
Syncope	☐	☐

CCS angina ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4
Active smoking ☐ no ☐ yes
ICD shock ☐ no ☐ yes ☐ n/a

JVD ☐ absent ☐ _____ cm
Rales ☐ no ☐ ≤1/2 ☐ >1/2 ☐ not done
Liver ☐ normal ☐ palpable ☐ not done
Edema ☐ no ☐ 1+ ☐ 2+ ☐ 3+ ☐ 4+

	Today	Previous visit
BW (kg)		
6MWD (m)		

BP	sit	stand
HR (bpm)		☐ regular ☐ irregular
O2Sat (%)		
Ht. /BMI		

Date:		
Hct (%)		
Hb (g/dL)		
MCV		
WBC		
Plt		
N %		
L %		
M %		
Eo %		
INR		
PTT		
Uric a.		

Investigations:

Date:		
BUN (mg%)		
Cr (mg%)		
Na (mmol/L)		
K (mmol/L)		
Cl (mmol/L)		
CO2 (mmol/L)		
Mg (mmol/L)		
Phos (mmol/L)		
Ca (mmol/L)		
FBS (mg%)		
HbA1c (%)		

Medication List: ชื่อยา (ขนาด) | การใช้ยา | กินอยู่ | ยาแพ้ (ผื่น)

1. Diu-retic			☐Y ☐N	
2. ACEI ARB ARNI			☐Y ☐N	
3. BB			☐Y ☐N	
4. MRA			☐Y ☐N	
5.			☐Y ☐N	
6.			☐Y ☐N	
7.			☐Y ☐N	
8.			☐Y ☐N	
9.			☐Y ☐N	
10.			☐Y ☐N	

TODAY Rx

Problem List & Plan:

* Long term (6-mo) plan:

Signature.....

Pharmacy note:

Signature ..... code .....

Multidisciplinary Team Order

☐ MD for _____
☐ RN for _____
☐ Pharm for _____
☐ Diet for _____
☐ Rehab for _____
☐ ECOT for _____
☐ Palliative for _____
☐ Admin for _____
☐ Device for ☐ counsel ☐ check

This patient has ☐ ICD ☐ CRT Manufacture _____

Advanced HF Clinic Order

1. AHFC appointment: _____ wks
(Date _____)
☐BUN/Cr ☐E'lyte ☐CBC ☐INR
☐FBS ☐LFT ☐TSH ☐FT3, FT4
☐HbA1C ☐Uric ☐BNP
☐Chol, TG, HDL ☐LDL
☐ECG ☐TTE ☐CPX ☐CXR
☐Cardiac MRI ☐VO2 max
☐Others: _____

2. Tele appointment: _____ wks
(Date _____)
☐BUN/Cr ☐E'lyte ☐CBC ☐INR
☐Others: _____

3. Consultation:
☐ Consult

Heart Failure Education –promote patient self care

Thank you

Chulalongkorn
HEART
FAILURE
& TRANSPLANT CARDIOLOGY