OPTIMAL MEDICAL MANAGEMENT OF CHRONIC HEART FAILURE

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Optimal Medical Management of Chronic Heart Failure

ESC Levels of evidence

Level of Evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of Evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of Evidence C	Consensus of opinion of the experts and/ or small studies, retrospective studies, registries.

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ESC Classes of recommendations

Classes of recommendations	Definition	Suggested wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended/ is indicated.
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	*Weight of evidence/opinion is in favour of usefulness/efficacy.*	Should be considered.
Class IIb	*Usefulness/efficacy is less well established by evidence/opinion.*	May be considered.
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended.

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Definition of Heart Failure

The pathophysiological state in which heart is unable to pump blood at a rate commensurate with the requirements of metabolizing tissue, or can do so only from an elevated filling pressure

(Braunwald,1994)

Definition of heart failure

With preserved (HFpEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF)

Type of HF		HFrEF	HFmrEF	PFpEF
CRITERIA	1	Symptoms ± Signs	Symptoms ± Signs	Symptoms ± Signs
	2	LVEF <40%	LVEF 40–49%	LVEF ≥50%
	3	–	1. Elevated levels of natriuretic peptides. 2. At least one additional criterion: a. relevant structural heart disease (LVF and/or LAE); b. diastolic dysfunction (for details see Section 4.3.2.).	1. Elevated levels of natriuretic peptides. 2. At least one additional criterion: a. relevant structural heart disease (LVF and/or LAE); b. diastolic dysfunction (for details see Section 4.3.2.).

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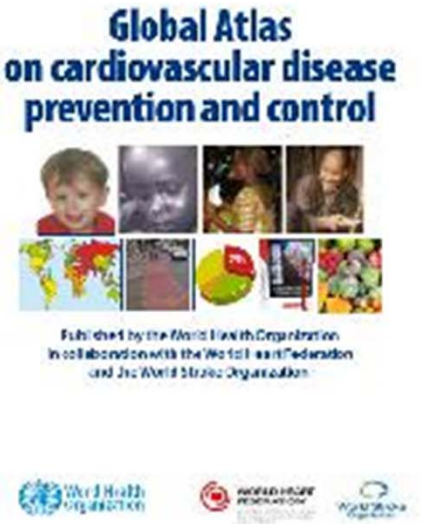
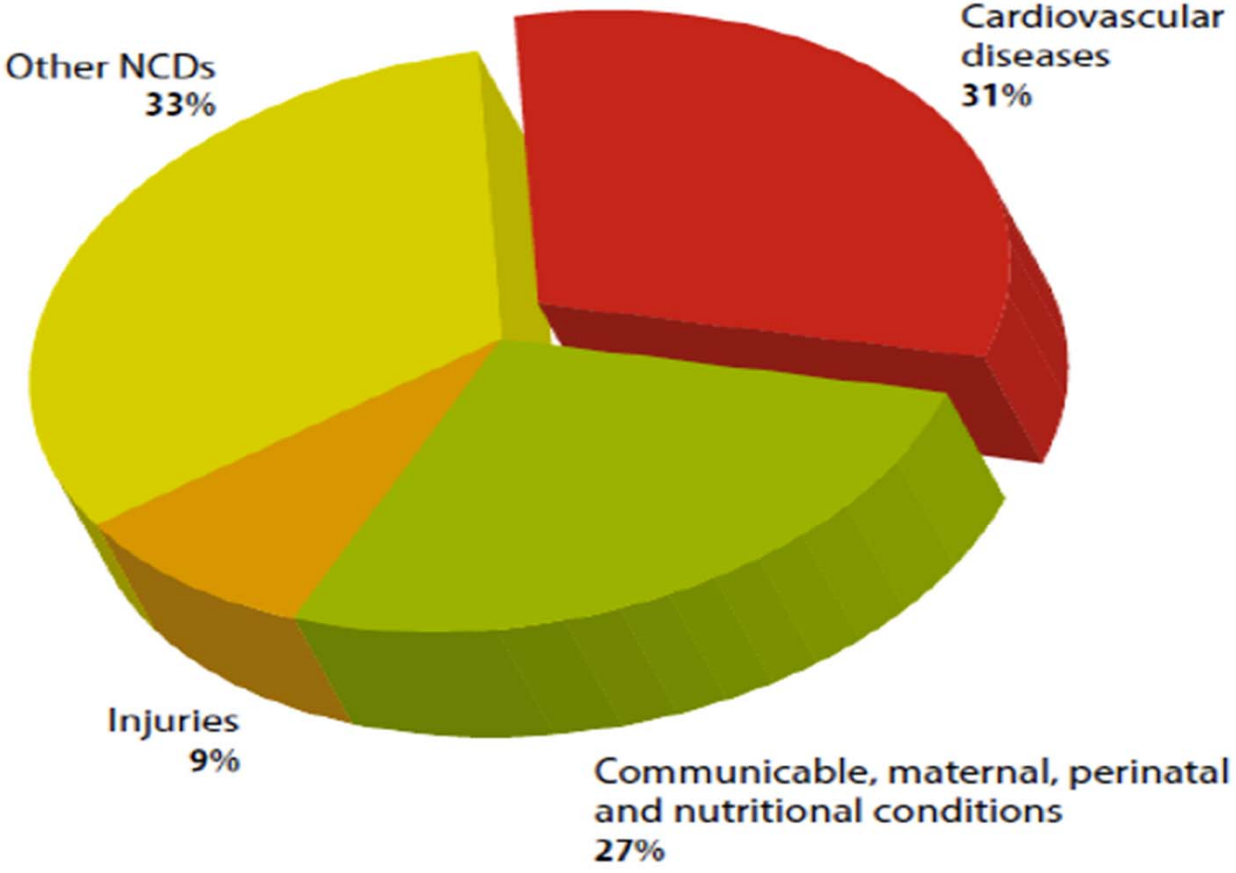
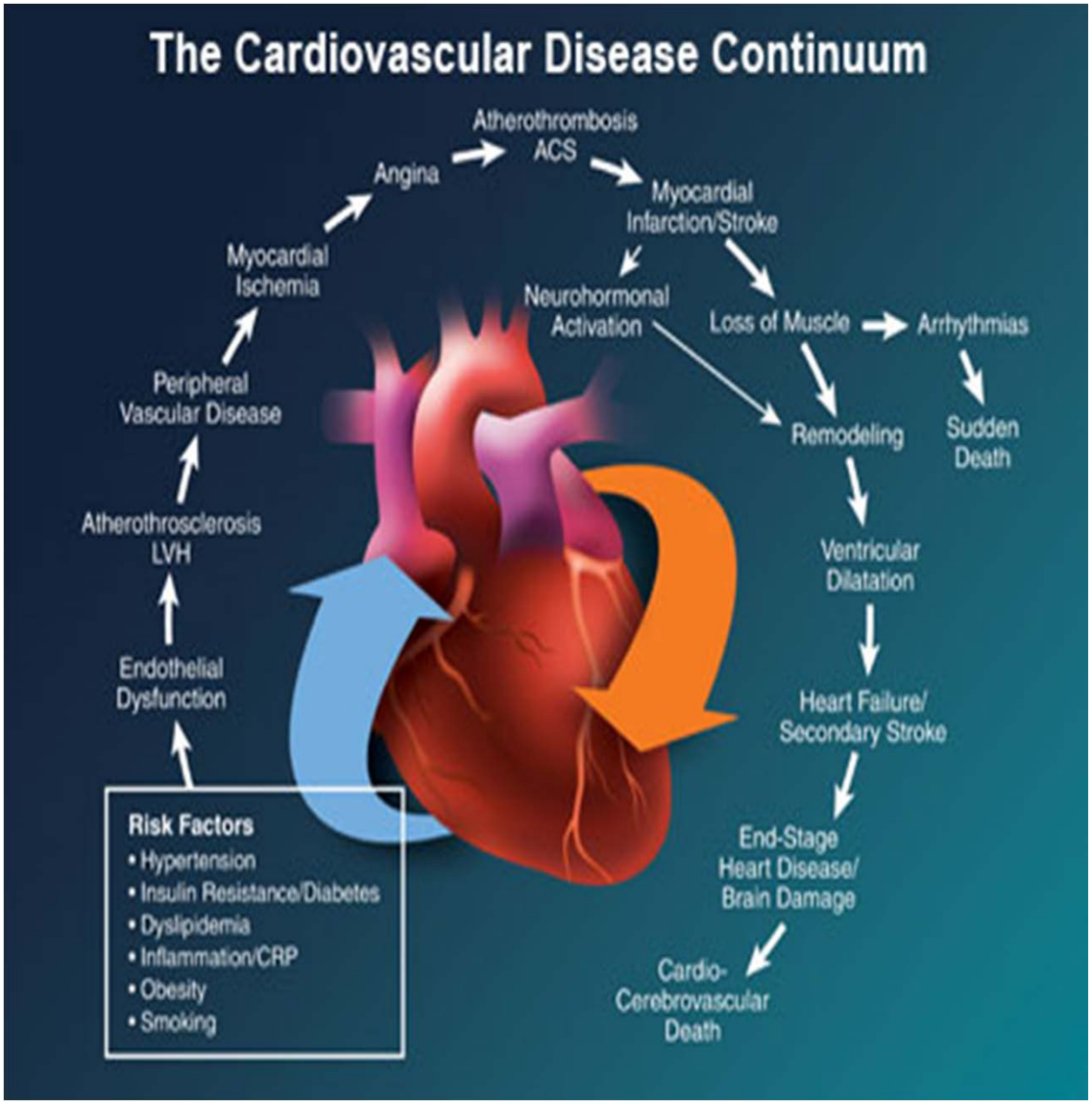
Global Causes of Death

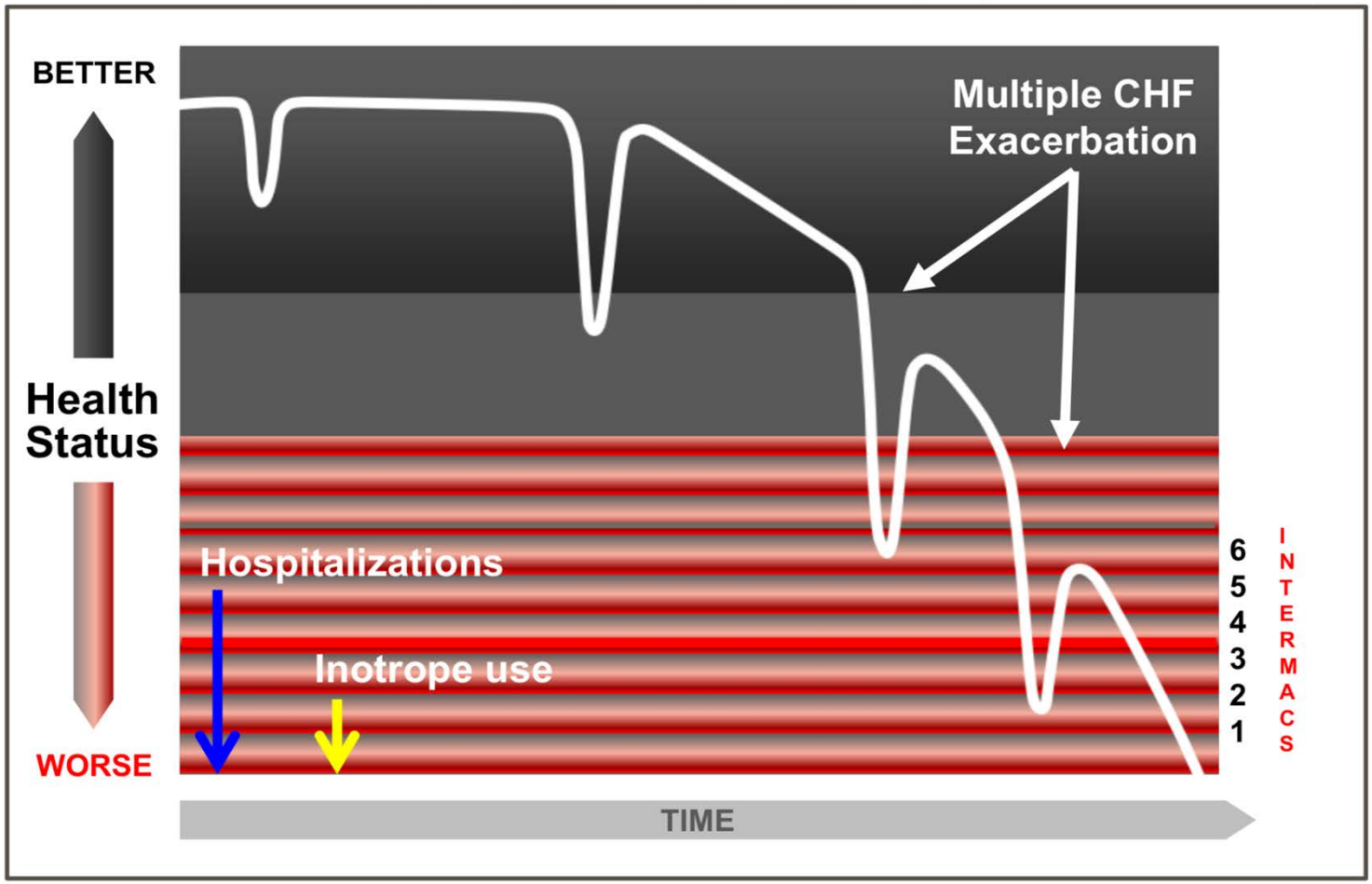




Ischemia + Heart Failure – sinister alliance



The progressive deterioration characteristic of chronic heart failure



Etiology

Coronary Artery Disease

HT

account for 70-85% of HF cases

Valvular and Congenital Heart Disease

Arrhythmias

Cardiomyopathy (dilated, hypertrophic/obstructive/oblilterative)

Alcohol and Drugs

Others (anemia, thyrotoxicosis, pulmonary HT, constrictive pericardit pericardial effusion)

Established and Hypothesized Risk Factors for Heart Failure

- Major Clinical Risk Factors
  - Age, male sex
  - Hypertension, LVH
  - Myocardial infarction
  - Diabetes Mellitus
  - Valvular heart disease
  - Obesity
- Minor Clinical Risk Factors
  - Smoking
  - Dyslipidemia
  - Sleep-disordered breathing
  - Chronic kidney disease
  - Albuminuria
  - Homocysteine
  - Immune activation, IGF1, TNFα, IL-6, CRP
  - Natriuretic peptides
  - Anemia
  - Dietary risk factors
  - Increased HR
  - Sedentary lifestyle
  - Low socioeconomic status
  - Psychological stress

Pharmacological treatments in patients with symptomatic (NYHA Class II-IV) heart failure with reduced ejection fraction

Recommendations	Class	Level
An ACE-I 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, 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 and a beta-blocker, to reduce the risk of HF hospitalization and death.	I	A

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Prevent or delay the development of overt heart failure or prevent death before the onset of symptoms (1)

Recommendations	Class	Level
Treatment of hypertension is recommended to prevent or delay the onset of HF and prolong life.	I	A
Treatment with statins is recommended in patients with or at high-risk of CAD whether or not they have LV systolic dysfunction, in order to prevent or delay the onset of HF and prolong life.	I	A
Counselling and treatment for smoking cessation and alcohol intake reduction is recommended for people who smoke or who consume excess alcohol in order to prevent or delay the onset of HF.	I	C
Treating other risk factors of HF (e.g. obesity, dysglycaemia) should be considered in order to prevent or delay the onset of HF.	IIa	C
Empagliflozin should be considered in patients with type 2 diabetes in order to prevent or delay the onset of HF and prolong life.	IIa	B
ACE-I is recommended in patients with asymptomatic LV systolic dysfunction and a history of myocardial infarction in order to prevent or delay the onset of HF and prolong life.	I	A

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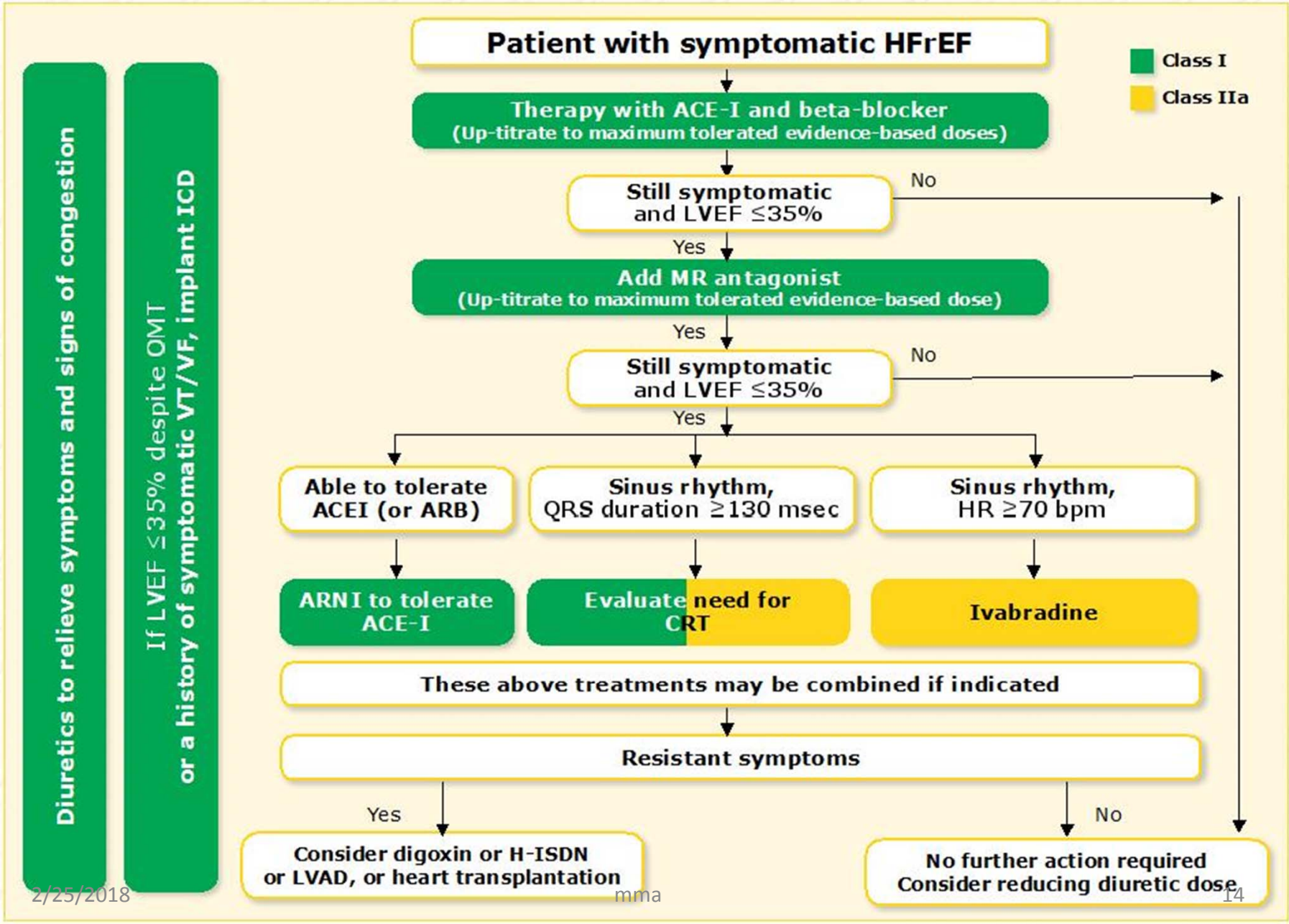
Therapeutic algorithm for a patient with symptomatic heart failure with reduced ejection fraction



ACEI trials in Chronic Heart Failure

Study	Population	Total (n)	ACEI	ACC Stage	Results
CONSENSUS 1	Clinical evidence of severe heart failure	253	Enalapril	D	40% RRR in mortality at 6 mo (1° endpoint) 50% RRR mortality from worsening heart failure
SOLVD Treatment	EF≤35%	2569	Enalapril	C	16% RR mortality (1° endpoint) 26% combined reduction mortality/hospitalization from progressive heart failure
SOLVD Prevention	EF≤35%	4228	Enalapril	B	Non-significant reduction in all-cause mortality(1° endpoint) 20% reduction in combined incidence of death or heart failure hospitalization
ATLAS	EF≤30%	3164	Lisinopril low dose (2.5-5mg) vs high dose (32.5-35mg)	C, likely D	8% non-significant RRR mortality (1° endpoint) 12% RRR mortality + hospitalization in higher dose group. 24% RRR heart failure hospitalization

CONSENSUS = Cooperative North Scandinavian Enalapril Survival Study; SOLVD = Studies Of left Ventricular Dysfunction trial:
ATLAS = Assessment of Treatment with Lisinopril an Survival trial; EF = ejection fraction; RRR = relative risk reduction; CV = cardiovascular

ACEI trials in Post-MI

Study	Population	Total (n)	ACEI	Results
AIRE	3-10 days post-MI. Clinical evidence of heart failure	1986	Ramipril	23% RRR overall mortality (1° endpoint) 19% RRR combined death, AMI, worsening heart failure, Stroke
SAVE	EF≤ 40%	2231	Captopril	19% RRR overall mortality (1° endpoint) 25% RR recurrent MI 21% RRR CV mortality
TRACE	EF≤ 35% 3-7 days post-MI	1749	Trandopril	22% RRR all-cause mortality (1° endpoint) 29% reduction in progression of heart failure
GISSI-3	Within 24 hrs of AMI	18895	Lisinopril	11% decrease in mortality at 6 weeks (1° endpoint)
ISIS-4	Within 24 hrs of AMI	58050	Captopril	7% reduction in mortality at 5 weeks (1° endpoint)
CONSENSUS II	Within 24 hrs of AMI	6090	Enalapril (Intravenous followed by oral enalapril)	No improvement in survival 6 months post-MI (1° endpoint)
SMILE	Within 24 hrs of AMI	1556	Zofenopril	33% RRR in combined death or progression to severe heart faillure at 6 weeks (1° endpoint) 29% RRR mortality at 1 year

SAVE = Survival and Ventricular Enlargement; TRACE = Trandopril Cardiac Evaluation Study; GISSI-3 = Gruppo Italian per lo Studio della Sopravvivenza nell'Infarto Miocardico; ISIS-4 = International Study of Infarct Survival; AIRE – Acute Infarction Ramipril Efficacy tri
SMILE = Survival of Myocardial Infarction Long-Term Evaluation;
AMI = Acute Myocardial Infarct; EF = ejection fraction; RRR = relative risk reduction; CV= cardiovascular

ACEI in Heart Failure

- ACC/AHA guidelines for management of patients after an ST elevation MI (STEMI) give a class I recommendation for initiation of ACEI therapy within 24 hours of AMI.

- ACC/AHA also give a Class I recommendation for initiating early ACEI therapy in patients with non-STEMI (NSTEMI) or unstable angina who have concomitant persistent hypertension, symptoms of heart failure, LV dysfunction, or diabetes.

ARB trials in Heart Failure (1)

Study	Population	Total (n)	ARB	ACC stage	Results
OPTIMAAL	Acute-MI and clinical evidence of heart failure EF<35%	5477	Losartan (losartan vs captopril)	B, C, D	NS superiority in captopril group for all-cause mortality (1° endpoint) Losartan better tolerated than captopril
VALIANT	EF≤35% and/or clinical evidence of heart failure. 0.5-10 days post-MI	9818	Valsartan (valsartan vs valsartan + captopril vs captopril)	B, C, D	NS for mortality (1° endpoint); SCD; hospitalization).
CHARM-Alternative	EF≤40% Intolerant of ACEI	2028	Candesartan (candesartan vs placebo)	C, D	23% RRR CV death or HF hospitalization (1° endpoint)
ELITE II	EF≤40% Age≥60 yr old	3152	Losartan (losartan vs captopril)	C, D	NS difference in mortality (1° endpoint) or SCD

OPTIMAAL = Optimal trial in Myocardial Infarction with Angiotensin II Antagonist Losartan; VALIANT = Valsartan in Acute Myocardial In
CHARM = Candesartan in Heart Failure; ELITE = Evaluation of Losartan in the Elderly; NS = non-significant; SCD = sudden cardiac de

Beta-blocker trials in HF

Study	Population	Total (n)	Beta-blocker	ACC stage	Results
U.S.Carvedilol	EF ≤ 40%	1,094	Carvedilol	C, D	48% RR heart failure progression (1° endpoint) 65% RRR overall mortality 27% reduction CV hospitalization
COPERNICUS	EF < 25%	2,289	Carvedilol	D	35% RRR overall mortality (1° endpoint)
MERIT-HF	EF ≤ 40%	3,991	Metoprolol	C, D	34% RRR overall mortality (1° endpoint) 41% reduction in SCD
CIBIS II	EF ≤ 35%	2,647	Bisoprolol	C, D	34% RRR overall mortality (1° endpoint) 32% RRR death/hospitalization 42% RRR sudden cardiac death
REVERT	EF < 40%	149	Metoprolol XL	B	200mg dose: LVEF ↑ 6% LVESVI ↓ 14 ml/m² (1° endpoint) 50mg dose: LVEF ↑ 4%
CAPRICORN	EF ≤ 40% 3-21 days post-MI	1,959	Carvedilol	B, C, D	23% reduction all-cause mortality (1° endpoint) 59% reduction atrial arrhythmias 70% fewer ventricular arrhythmias

COPERNICUS = Carvedilol Prospective Randomized Cumulative Survival trial; MERIT-HF = Metoprolol CR/XL Randomized Trial in Congestive Heart Failure; CIBIS – II = Cardiac Insufficiency Bisoprolol Study II; REVERT = Reversal of Ventricular R with Toprol-XL; CAPRICORN = Carvedilol Post-Infarct Survival Control in LV Dysfunction;

Evidence-based doses of disease-modifying drugs in key randomized trials in HF with reduced ejection fraction (or after myocardial infarction)

	Starting dose (mg)	Target dose (mg)
ACE-I		
Captopril	6.25 *t.i.d.*	50 *t.i.d.*
Enalapril	2.5 *b.i.d.*	10–20 *b.i.d.*
Lisinopril	2.5–5.0 *o.d.*	20–35 *o.d.*
Ramipril	2.5 *o.d.*	10 *o.d.*
Trandolapril	0.5 *o.d.*	4 *o.d.*
Beta-blockers		
Bisoprolol	1.25 *o.d.*	10 *o.d.*
Carvedilol	3.125 *b.i.d.*	25 *b.i.d.*
Metoprolol succinate (CR/XL)	12.5–25 *o.d.*	200 *o.d.*
Nebivolol	1.25 *o.d.*	10 *o.d.*
ARBs		
Candesartan	4–8 *o.d.*	32 *o.d.*
Valsartan	40 *b.i.d.*	160 *b.i.d.*
Losartan	50 *o.d.*	150 *o.d.*
MRAs		
Eplerenone	25 *o.d.*	50 *o.d.*
Spironolactone	25 *o.d.*	50 *o.d.*
ARNI		
Sacubitril/valsartan	49/51 *b.i.d.*	97/103 *b.i.d.*
If -channel blocker		
Ivabradine	5 *b.i.d.*	7.5 *b.i.d.*

Other pharmacological treatments recommended in selected patients with symptomatic (NYHA Class II-IV) HF with reduced ejection fraction (1)

Recommendations	Class	Level
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
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.	I	B
***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 betablocker (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

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Other pharmacological treatments recommended in selected patients with symptomatic (NYHA Class II-IV) HF with reduced ejection fraction (2)

Recommendations	Class	Level
ARB		
An ARB is recommended to reduce the risk of HF hospitalization and cardio-vascular 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
Hydralazine and isosorbide dinitrate		
Hydralazine and isosorbide dinitrate should be considered in self-identified black patients with LVEF ≤35% or withan 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
Other treatments with less-certain benefits		
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
N-3 PUFA		
An n-3 PUFA preparation may be considered in symptomatic HF patients to reduce the risk of cardiovascular hospitalization and cardiovascular death.	IIb	B

ACEI/ARB/B B

	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.*	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.*
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[c]	1.25 *o.d.*	10 *o.d.*
ARBs		
Candesartan	4–8 *o.d.*	32 *o.d.*
Valsartan	40 *b.i.d.*	160 *b.i.d.*
Losartan[b,c]	50 *o.d.*	
MRAs		
Eplerenone	25 *o.d.*	
Spironolactone	25 *o.d.*	
ARNI		
Sacubitril/valsartan	49/51 *b.i.d.*	
If-channel blocker		
Ivabradine	5 *b.i.d.*	7.5 *b.i.d.*

Disease-modifying drugs in HF with reduced EF: Angiotensin Receptor Neprilysin-Inhibitor (ARNI)

Sacubitril/Valsartan is very useful in patients with mild-moderate symptoms who did tolerate higher dosages of ACE-inhibitors and have still elevated NT-pro BNP

Be careful
In patients with very low blood pressure during ACE inhibition

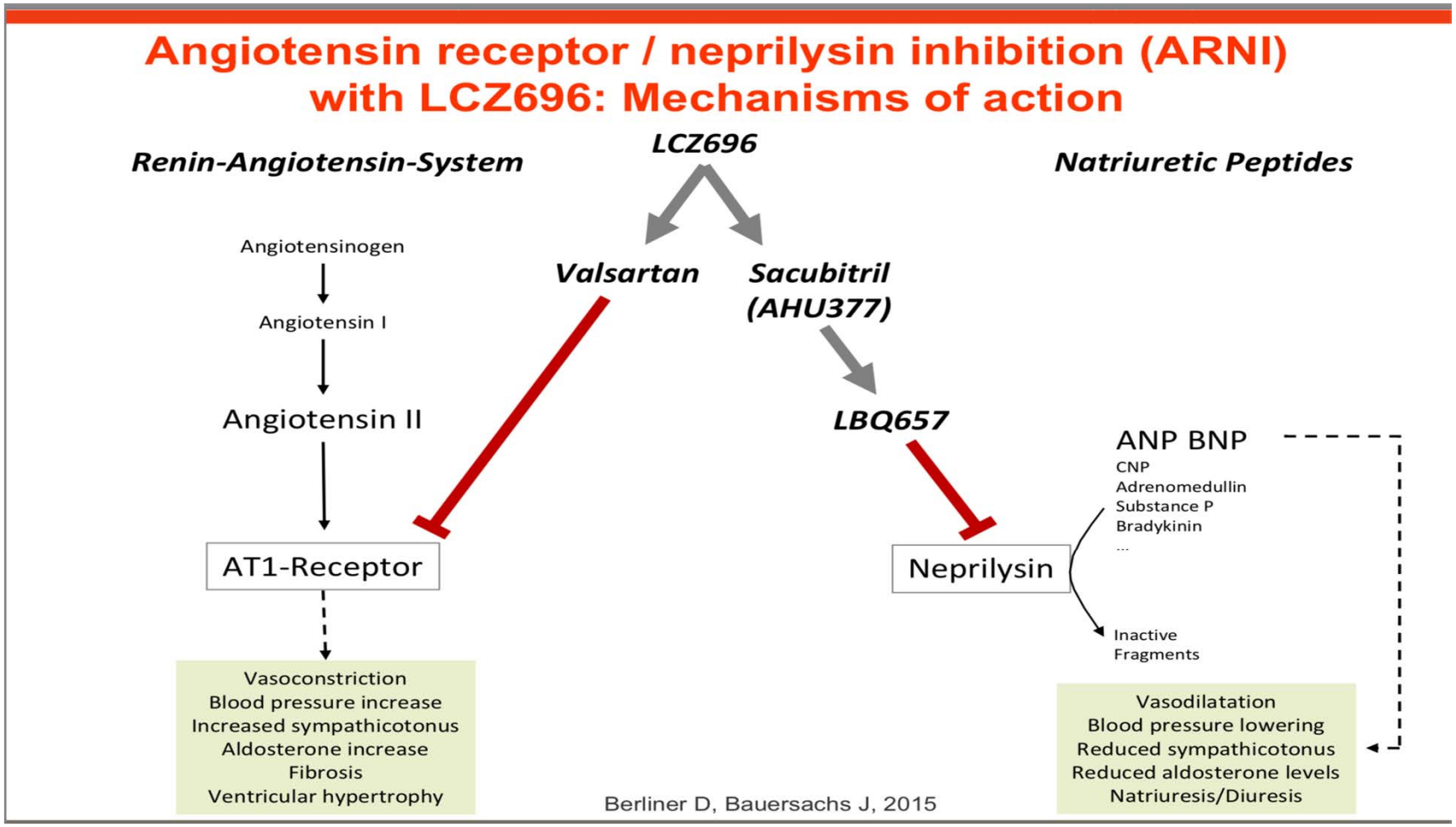
Sacubitril/Valsartan

Start 49/51 mg

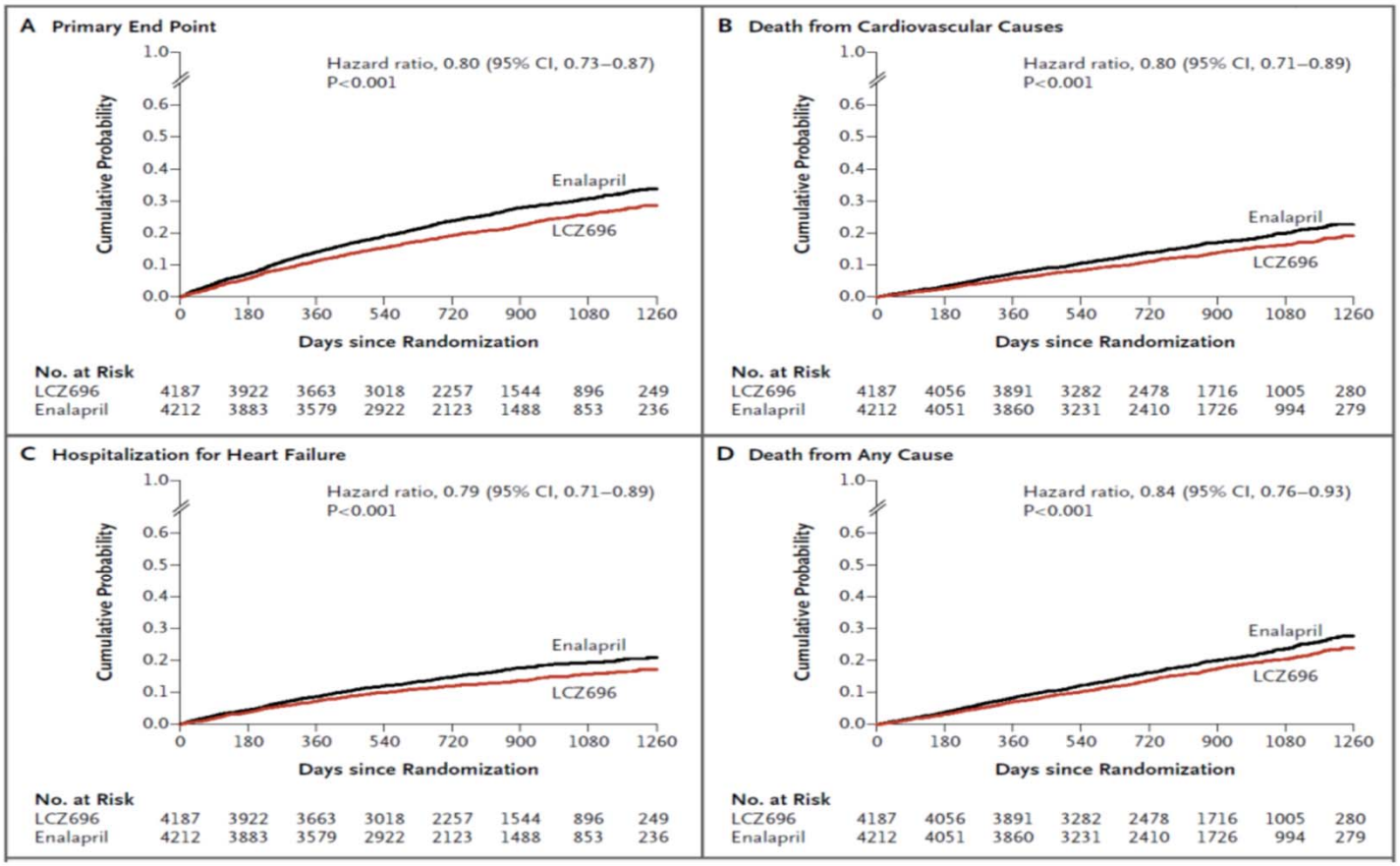
Target dose 97/103 mg

MHH Medizinische Hochschule

ARNI

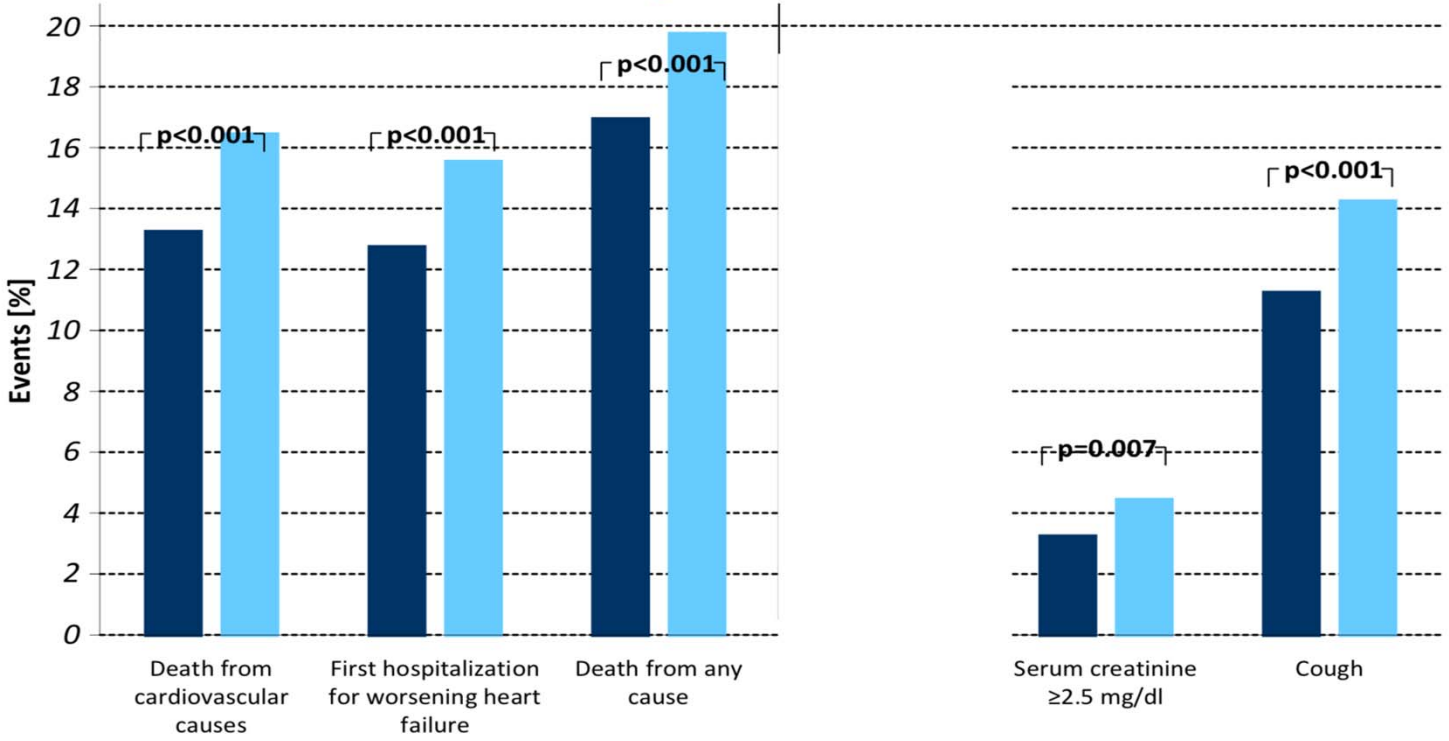

Angiotensin receptor / neprilysin inhibition (ARNI)
with LCZ696: Mechanisms of action
Renin-Angiotensin-System
LCZ696
Natriuretic Peptides
Angiotensinogen
Angiotensin I
Angiotensin II
Valsartan
Sacubitril
(AHU377)
LBQ657
AT1-Receptor
Neprilysin
ANP BNP
CNP
Adrenomedullin
Substance P
Bradykinin
...
Inactive
Fragments
Vasoconstriction
Blood pressure increase
Increased sympathicotonus
Aldosterone increase
Fibrosis
Ventricular hypertrophy
Vasodilatation
Blood pressure lowering
Reduced sympathicotonus
Reduced aldosterone levels
Natriuresis/Diuresis
Berliner D, Bauersachs J, 2015

PARADIGM-HF: Important endpoints



McMurray et al., N Engl J Med 2014

PARADIGM-HF: ARNI vs. ACE inhibitor
- summary of the results -



Berliner D, Bauersachs J, 2015

DIGITALIS

ESC Guideline 2016 – Digitalis in patients with advanced systolic heart failure (HFrEF)

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

7.4.1 Digoxin and other digitalis glycosides

Digoxin may be considered in patients in sinus rhythm with symptomatic HFrEF to reduce the risk of hospitalization (both all-cause and HF hospitalizations),[185] although its effect on top of beta-blockers has never been tested. The effects of digoxin in patients with HFrEF and AF have not been studied in RCTs, and recent studies have suggested potentially higher risk of events (mortality and HF hospitalization) in patients with AF receiving digoxin.[195,196] However, this remains controversial, as another recent meta-analysis concluded on the basis of non-RCTs that digoxin has no deleterious effect on mortality in patients with AF and concomitant HF, most of whom had HFrEF.[197]

Digitalis should always be prescribed under specialist supervision. Given its distribution and clearance, caution should be exerted in females, in the elderly and in patients with reduced renal function. In the latter patients, digitoxin should be preferred.

the prevailing evidence suggests that strict rate control might be deleterious. A resting ventricular rate in the range of 70–90 bpm is recommended based on current opinion, although one trial suggested that a resting ventricular rate of up to 110 bpm might still be acceptable.[202] This should be tested and refined by further research.

Ponikowski et al., Eur Heart J 2016

Positive functional / symptomatic effects of Digitalis in heart failure

	with ACE Inhibitor/ Diuretics
Treadmill time	improved
6-minutes walking test	improved
Frequency of treatment failure	reduced
Signs and symptomes for heart failure	improved
Live quality (Minnesota Living with Heart Failure Questionnaire)	improved
CHF Score	improved
LVEF	improved
Heart rate	reduced
Body weight	reduced

Mod. from Gheorghiade et al., Circulation 2006

DIURETICS

Diuretics in the treatment of heart failure

- Indispensable in acute decompensations
- Indispensable for chronic treatment in moderate to severe heart failure
- Symptomatic therapy
- No proven benefit on prognosis

→ Aim for the lowest achievable dose to maintain euvolemia (dry weight) in stable patients

Doses of diuretics commonly used in patients with heart failure

Diuretics	Initial dose (mg)		Usual daily dose (mg)	
Loop diuretics				
Furosemide	20–40		40–240	
Bumetanide	2.5–1.0		1–5	
Torasemide	5–10		10–20	
Thiazides				
Bendroflumethiazide	2.5		2.5–10	
Hydrochlorothiazide	25		12.5–100	
Metolazone	2.5		2.5–10	
Indapamidec	2.5		2.5–5	
Potassium-sparing diuretics				
	+ACE-1/ARB	-ACE-1/ARB	+ACE-1/ARB	-ACE-1/ARB
Spironolactone/eplerenone	12.5–25	*50*	50	100–200
Amiloride	2.5	5	5–10	10–20
Triamterene	25	50	100	200

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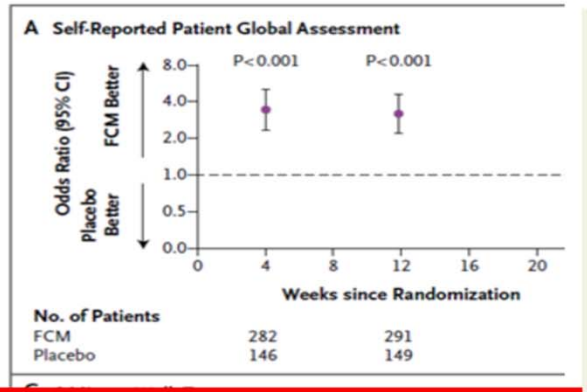
CO MOBIDITIES

Iron substitution with ferric carboxymaltose improves symptoms in HFrEF and iron deficiency



Recommendations	Class [a]	Level [b]	Ref [c]
Iron deficiency			
Intravenous FCM should be considered in symptomatic patients with HFrEF and iron deficiency (serum ferritin <100 µg/L, or ferritin between 100–299 µg/L and transferrin saturation <20%) in order to alleviate HF symptoms, and improve exercise capacity and quality of life.	IIa	A	469, 470

Anker et al., New Engl. J Med 2009

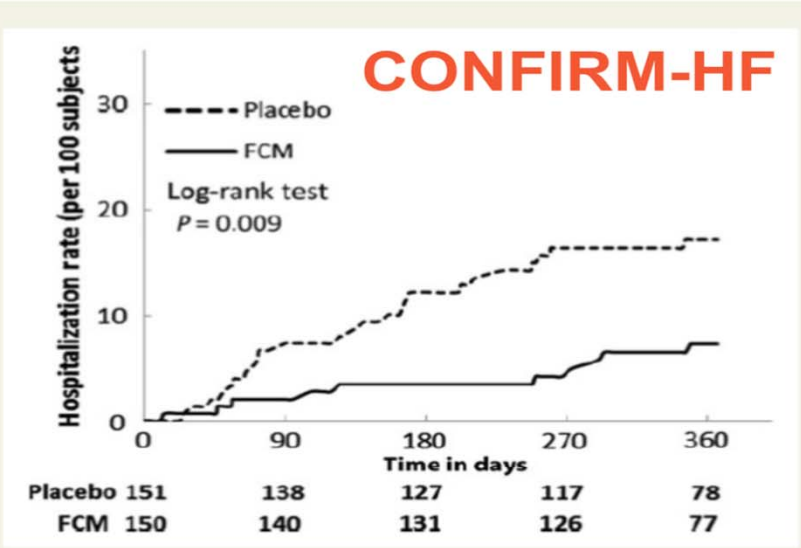


Figure 4 Time to first hospitalization due to worsening heart failure. The time to first hospitalization due to worsening heart failure was estimated using the Kaplan–Meier method, on the full-analysis set. Subjects were censored at their death, study completion, or withdrawal date. Ponikowski et al, Eur Heart J 2014

Heart failure and co-morbidities

- co-morbidities may affect the use of treatments for heart failure
- the drugs used to treat co-morbidities may cause worsening of heart failure (e.g. NSAIDs given for arthritis)
- the drugs used to treat heart failure and those used to treat co-morbidities may also interact with one another
- most co-morbidities are associated with worse clinical status and are predictors of poor prognosis in heart failure (e.g. depression, diabetes, COPD, cachexia)
- **Management of co-morbidities is a key component of the holistic care of patients with heart failure.**

Importance of co-morbidities in patients with heart failure

1. Interfere with the diagnostic process of HF (e.g. COPD as a potentially confounding cause of dyspnoea).
2. Aggravate HF symptoms and further impair quality of life.
3. Contribute to the burden of hospitalizations and mortality, as the main cause of readmissions at 1 and 3 months.
4. May affect the use of treatments for HF (e.g. renin–angiotensin system inhibitors contra-indicated in some patients with severe renal dysfunction or beta-blockers relatively contra-indicated in asthma).
5. Evidence base for HF treatment is more limited as co-morbidities were mostly an exclusion criterion in trials; efficacy and safety of interventions is therefore often lacking in the presence of co-morbidities.
6. Drugs used to treat co-morbidities may cause worsening HF (e.g. NSAIDs given for arthritis, some anti-cancer drugs).
7. Interaction between drugs used to treat HF and those used to treat co-morbidities, resulting in lower efficacy, poorer safety, and the occurrence of side effects (e.g. beta-blockers for HFrEF and beta-agonists for COPD and asthma).

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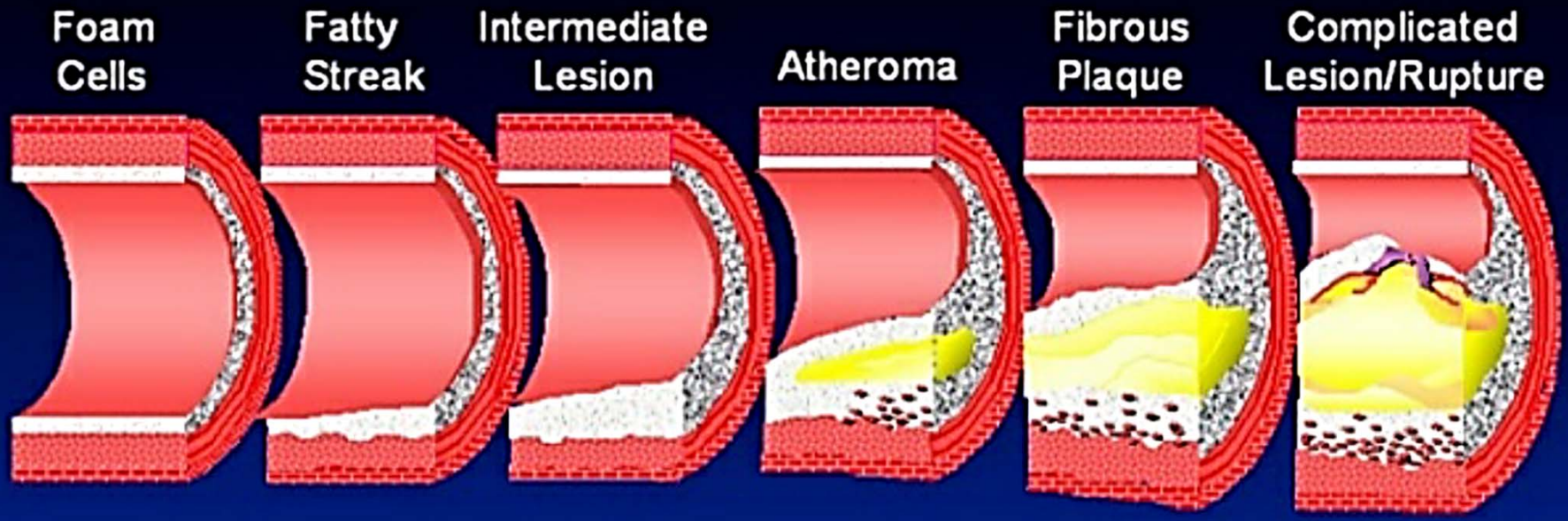
ANGINA

The Evolution of Atherosclerosis



From 1st Decade | From 3rd Decade | From 4th Decade

Growth Mainly by Lipid Accumulation | Smooth Muscle & Collagen | Thrombosis, Hematoma

Adapted From Stary HC et al. *Circulation*. 1995;92:1355-1374

The treatment of stable angina pectoris with symptomatic (NYHA Class II-IV) heart failure with reduced ejection fraction (1)

Recommendations	Class	Level
Step 1		
A beta-blocker (in an evidence-based dose or maximum tolerated) is recommended as the preferred first-line treatment to relieve angina because of the associated benefits of this treatment (reducing the risk of HF hospitalization and the risk of premature death).	I	A
Step 2: On top of beta-blocker or if a beta-blocker is not tolerated		
Ivabradine should be considered as an anti-anginal drug in suitable HFrEF patients (sinus rhythm and HR ≥70 bpm) as per recommended HFrEF management.	IIa	B
Step 3: For additional angina symptom relief - except from any combination not recommended		
A short-acting oral or transcutaneous nitrate should be considered (effective anti-anginal treatment, safe in HF).	IIa	A
A long acting oral or transcutaneous nitrate should be considered (effective anti-anginal treatment, not extensively studied in HF).	IIa	B
Trimetazidine may be considered when angina persists despite treatment with a beta-blocker (or alternative) to relieve angina (effective anti-anginal treatment, safe in HF).	IIb	A
Amlodipine may be considered in patients unable to tolerate a beta-blocker to relieve angina (effective anti-anginal treatment, safe in HF).	IIb	B

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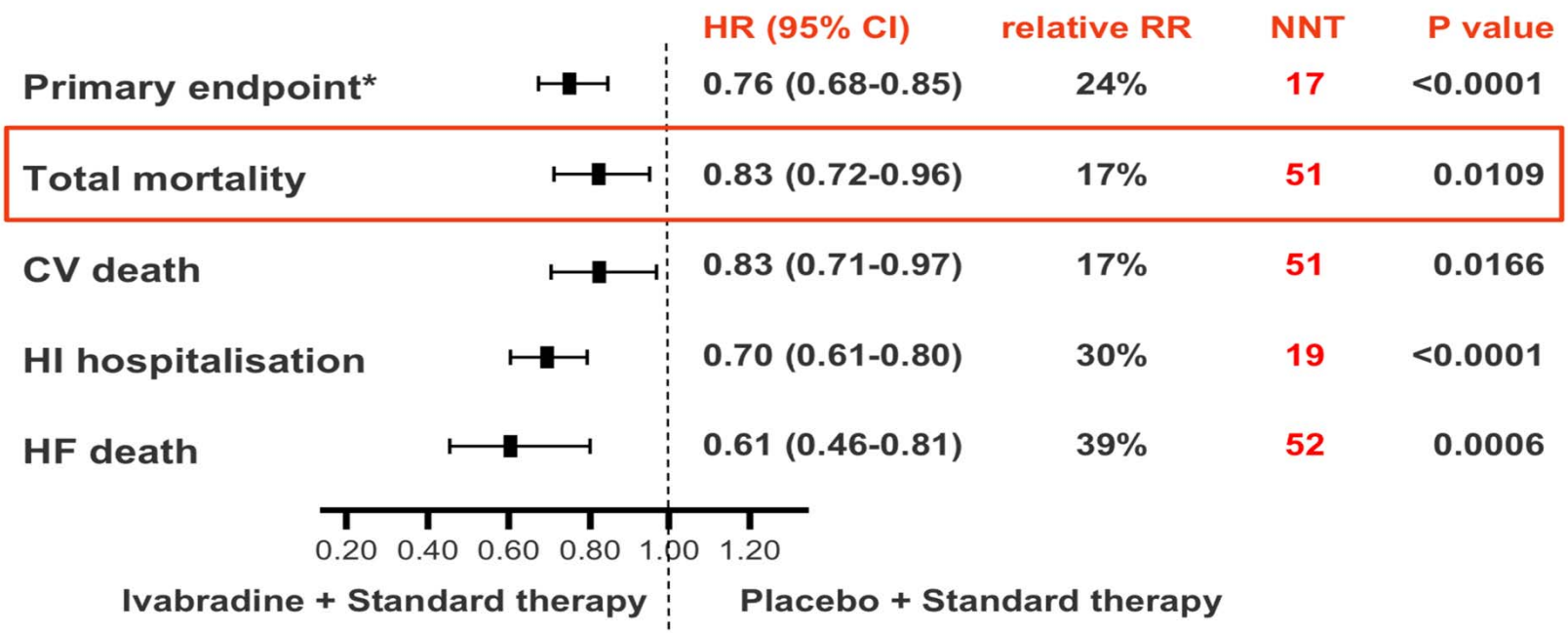
IVABRADINE

SHIFT – Patients with heart rate ≥75/min: Significant improvement of all endpoints by Ivabradine

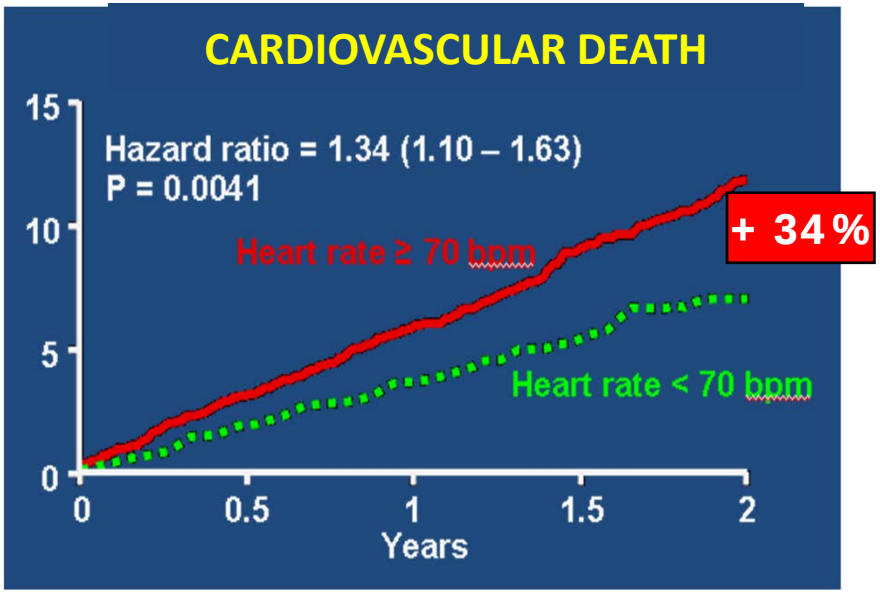


Böhm et al., Clin Res Cardiol., 2012

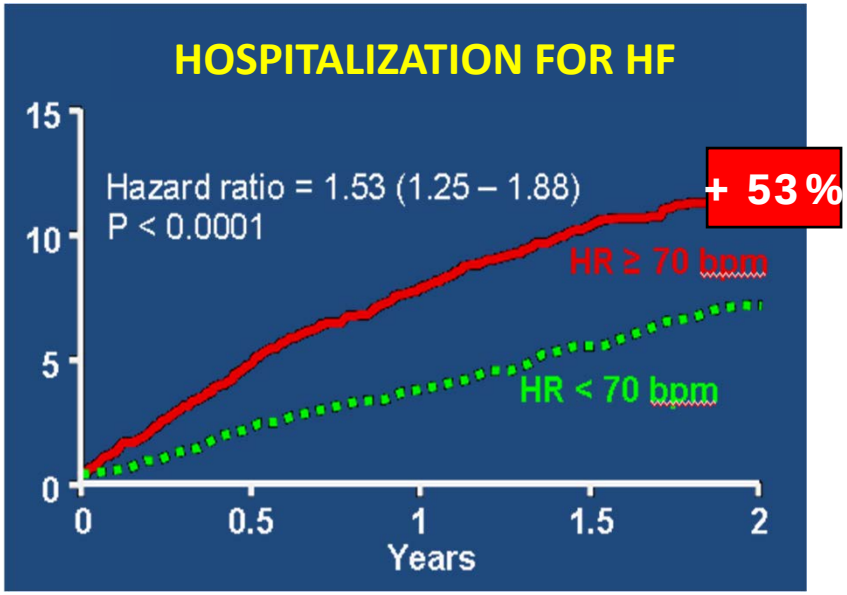
BEAUTIFUL

Heart rate as a predictor of

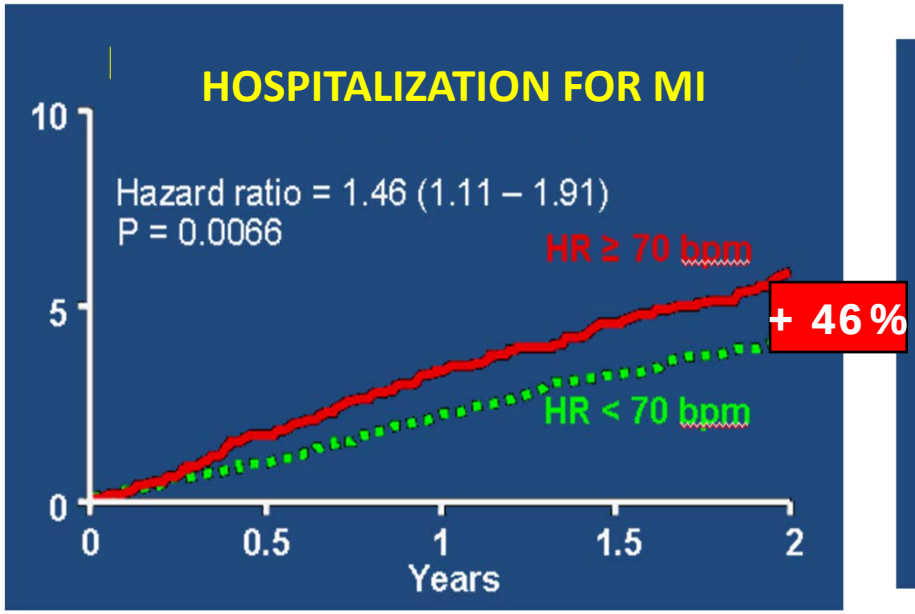
CARDIOVASCULAR DEATH



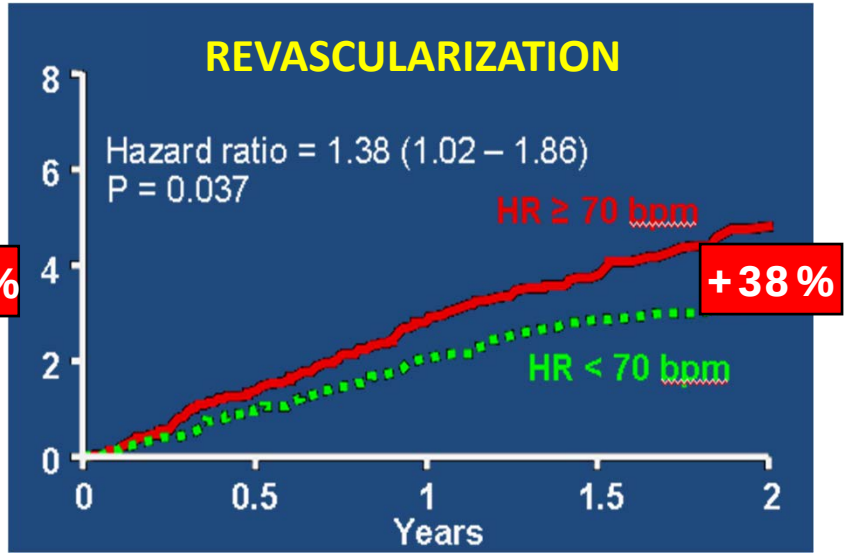
HOSPITALIZATION FOR HF



HOSPITALIZATION FOR MI



REVASCULARIZATION



Ivabradine - the only antianginal treatment to reduce myocardial infarction in stable coronary patients

	Improved total exercise duration	Improved time to onset of ST-segment depression	Decrease in anginal episodes	Reduced revascularization	Prevention of MI	Improved survival
β-Blockers	+	+	+	–	–	–
Calcium antag.	+	+	+	+	–	–
Nitrates	+	+	+	–	–	–
Trimetazidine	+	+	+	–	–	–
Ranolazine	+	+	+	NA	NA	NA
Nicorandil	+	+	+	NA	–	–
Ivabradine	**+**	**+**	**+**	**+**	**+**	**–**

The treatment of stable angina pectoris with symptomatic (NYHA Class II-IV) heart failure with reduced ejection fraction (1)

Recommendations	Class	Level
Step 1		
A beta-blocker (in an evidence-based dose or maximum tolerated) is recommended as the preferred first-line treatment to relieve angina because of the associated benefits of this treatment (reducing the risk of HF hospitalization and the risk of premature death).	I	A
Step 2: On top of beta-blocker or if a beta-blocker is not tolerated		
Ivabradine should be considered as an anti-anginal drug in suitable HFrEF patients (sinus rhythm and HR ≥70 bpm) as per recommended HFrEF management.	IIa	B
Step 3: For additional angina symptom relief - except from any combination not recommended		
A short-acting oral or transcutaneous nitrate should be considered (effective anti-anginal treatment, safe in HF).	IIa	A
A long acting oral or transcutaneous nitrate should be considered (effective anti-anginal treatment, not extensively studied in HF).	IIa	B
Trimetazidine may be considered when angina persists despite treatment with a beta-blocker (or alternative) to relieve angina (effective anti-anginal treatment, safe in HF).	IIb	A
Amlodipine may be considered in patients unable to tolerate a beta-blocker to relieve angina (effective anti-anginal treatment, safe in HF).	IIb	B

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The treatment of stable angina pectoris with symptomatic (NYHA Class II-IV) heart failure with reduced ejection fraction (2)

Recommendations	Class	Level
Step 3: For additional angina symptom relief - except from any combination not recommended *(cont'd)*		
Nicorandil may be considered in patients unable to tolerate a beta-blocker to relieve angina (effective anti-anginal treatment, but safety in HF uncertain).	IIb	C
Ranolazine may be considered in patients unable to tolerate a beta-blocker to relieve angina (effective anti-anginal treatment, but safety in HF uncertain).	IIb	C
Step 4: Myocardial revascularization		
Myocardial revascularization is recommended when angina persists despite treatment with anti-angina drugs.	I	A
Alternatives to myocardial revascularization: combination of ≥3 antianginal drugs (from those listed above) may be considered when angina persists despite treatment with beta-blocker, ivabradine and an extra anti-angina drug (excluding the combinations not recommended below).	IIb	C
The following are NOT recommended:		
(1) Combination of any of ivabradine, ranolazine, and nicorandil because of unknown safety.	III	C
(2) Combination of nicorandil and a nitrate (because of lack of additional efficacy).	III	C
Diltiazem and verapamil are not recommended because of their negative inotropic action and risk of worsening HF.	III	C

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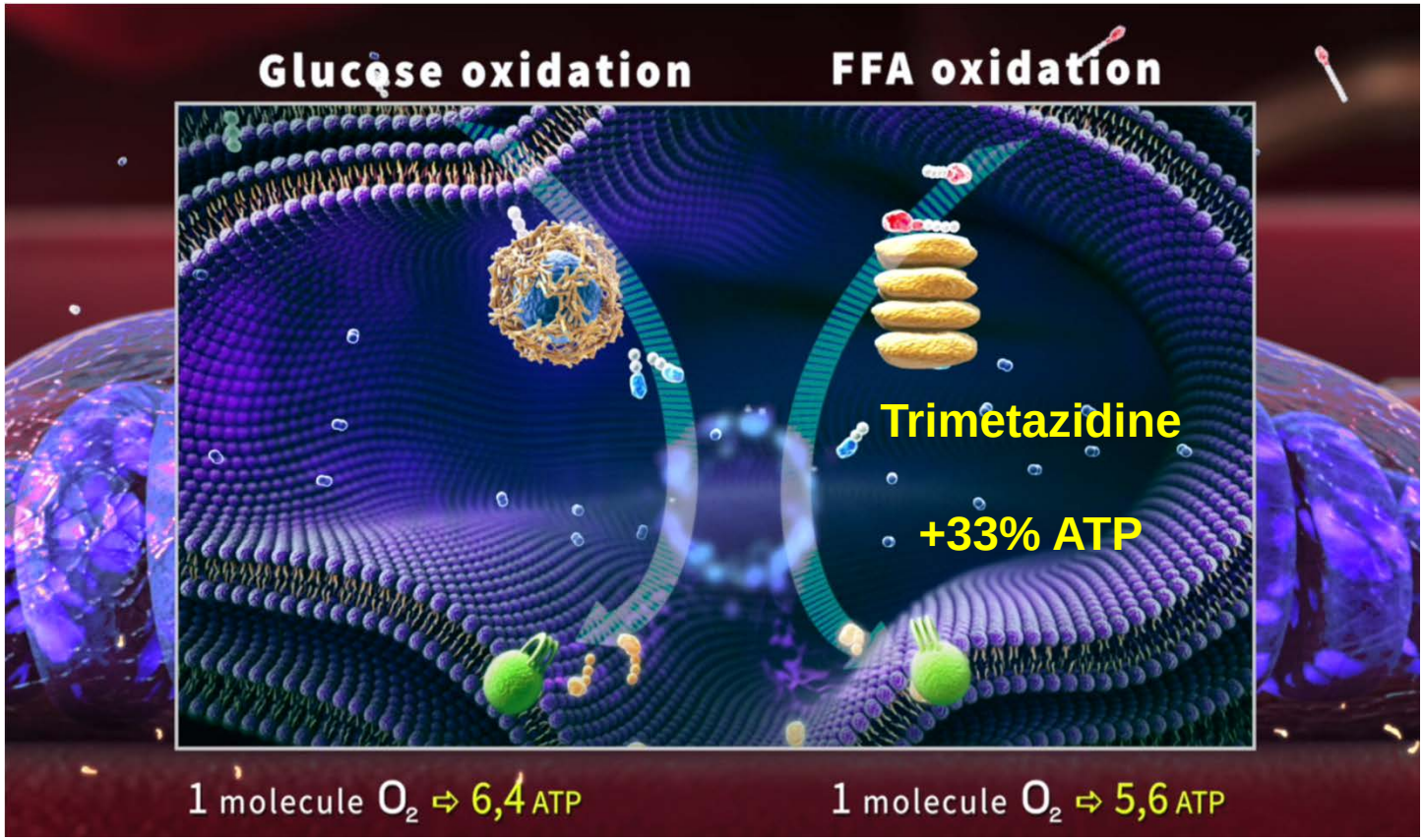
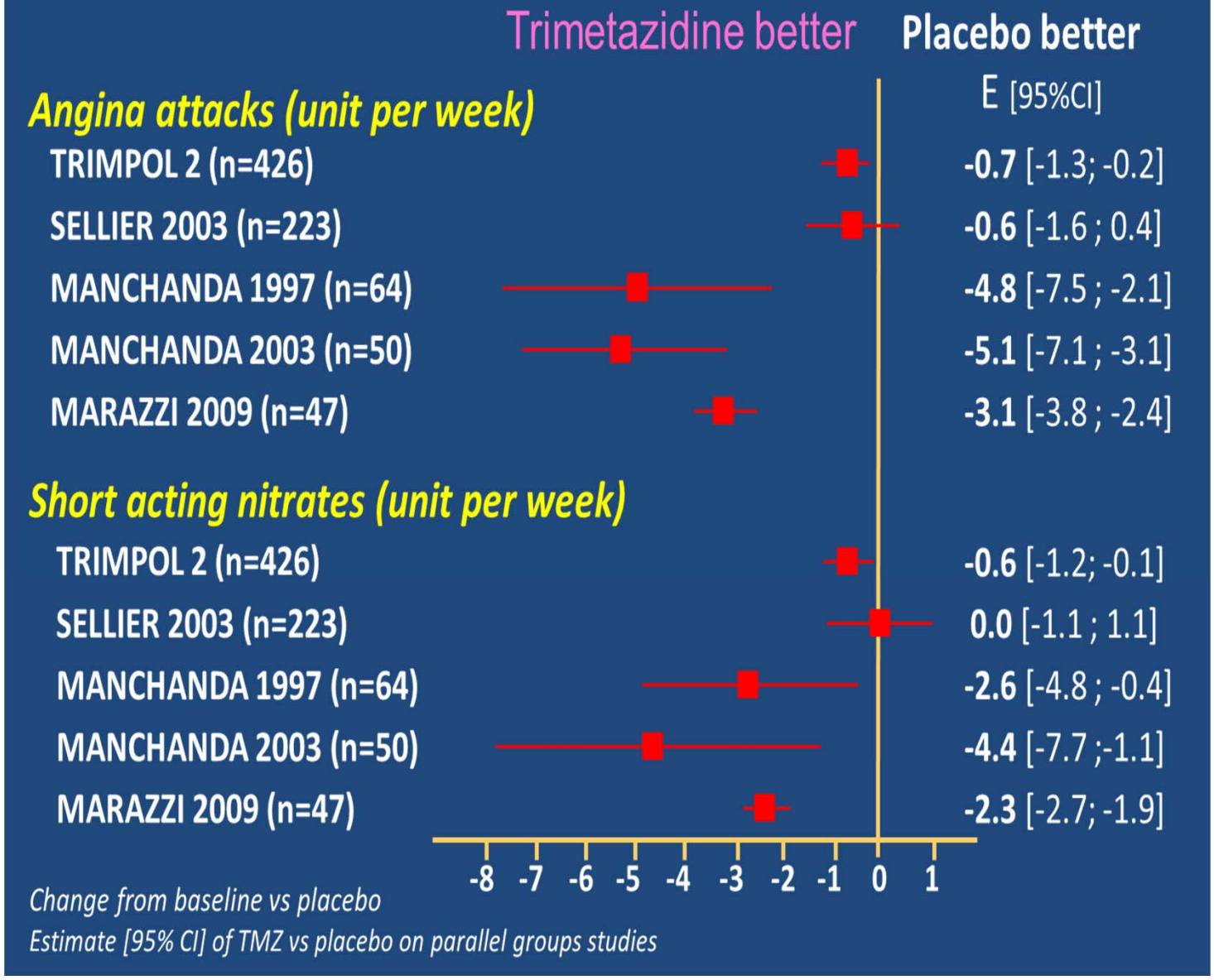
Metabolic Modulation of Ischaemia



By shifting cardiac energy metabolism, from FFA to glucose, metabolic agents provide +33%more ATP

Most relevant studies on clinical benefit of Trimetazidine as an add-on therapy



Trimetazidine is part of recommendations in various guidelines

ESC GUIDELINES

2013 ESC guidelines on the management of stable coronary artery disease

The Task Force on the management of stable coronary artery disease of the European Society of Cardiology

Angina relief

1st line

Short-acting Nitrates, plus

- Beta-blockers or CCB-heart rate
- Consider CCB-DHP if low heart rate or intolerance/contraindications
- Consider Beta-blockers + CCB-DHP if CCS Angina > 2

2nd line

May add or switch (1st line for some cases)

Ivabradine
Long-acting nitrates
Nicorandil
Ranolazine
Trimetazidine

+ Consider Angio → PCI – Stenting or CABG

Event prevention

- Lifestyle management
- Control of risk factors

+ Educate the patient

- Aspirin
- Statins
- Consider ACEI or ARBs

Circulation

American Heart Association

2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease : A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons

Stephan D. Fihn, Julius M. Gardin, Jonathan Abrams, Kathleen Berra, James C. Blankenship, Apostolos P. Dallas, Pamela S. Douglas, JoAnne M. Foody, Thomas C. Gerber, Alan L. Hinderliter, Spencer B. King III, Paul D. Kligfield, Harlan M. Krumholz, Raymond Y.K. Kwong, Michael J. Lim, Jane A. Linderbaum, Michael J. Mack, Mark A. Munger, Richard L. Prager, Joseph F. Sabik, Leslee J. Shaw, Joanna D. Sikkema, Craig R. Smith, Jr, Sidney C. Smith, Jr, John A. Spertus and Sankey V. Williams

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In patients with chronic stable angina, trimetazidine "delays the onset of ischemia associated with exercise and reducing the number of weekly angina episodes and weekly nitroglycerin consumption."

"Few data exist on the effect of trimetazidine on cardiovascular endpoints, mortality, or quality of life."

European Heart Journal Advance Access published May 20, 2016

ESC GUIDELINES

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

The Task Force for the diagnosis and treatment of acute and chronic

Recommendations for the treatment of stable angina pectoris with symptomatic (NYHA Class II-IV) heart failure with reduced ejection fraction[112,113]

Recommendations	Class[a]	Level[b]	Ref[c]
Step 1			
A beta-blocker (in an evidence-based dose or maximum tolerated) is recommended as the preferred first-line treatment to relieve angina because of the associated benefits of this treatment (reducing the risk of HF hospitalization and the risk of premature death).	I	A	167–173
Step 2: on top of beta-blocker or if a beta-blocker is not tolerated			
Ivabradine should be considered as an anti-anginal drug in suitable HFrEF patients (sinus rhythm and HR ≥70 bpm) as per recommended HFrEF management.	IIa	B	180, 410, 411
Trimetazidine may be considered when angina persists despite treatment with a beta-blocker (or alternative) to relieve angina (effective anti-anginal treatment, safe in HF).	IIb	A	400–403
Amlodipine may be considered in patients unable to tolerate a beta-blocker to relieve angina (effective anti-anginal treatment, safe in HF).	IIb	B	215, 407
Nicorandil may be considered in patients unable to tolerate a beta-blocker to relieve angina (effective anti-anginal treatment, but safety in HF uncertain).	IIb	C	
Ranolazine may be considered in patients unable to tolerate a beta-blocker to relieve angina (effective anti-anginal treatment, but safety in HF uncertain).	IIb	C	
Step 4: Myocardial revascularization			
Myocardial revascularization is recommended when angina persists despite treatment with anti-angina drugs.	I	A	385, 412, 413
Alternatives to myocardial revascularization: combination of ≥3 antianginal drugs (from those listed above) may be considered when angina persists despite treatment with beta-blocker, ivabradine and an extra anti-angina drug (excluding the combinations not recommended below).	IIb	C	
The following are NOT recommended:			
(1) Combination of any of ivabradine, ranolazine, and nicorandil because of unknown safety.	III	C	
(2) Combination of nicorandil and a nitrate (because of lack of additional efficacy).	III	C	
Diltiazem and verapamil are not recommended because of their negative inotropic action and risk of worsening HF.	III	C	214

Recommendations for treatment of patients with DHF

Recommendation	Class	Level of Evidence
Physicians should control systolic and diastolic hypertension, in accordance with published guidelines.	I	A
Physicians should control ventricular rate in patients with atrial fibrillation.	I	C
Physicians should use diuretics to control pulmonary congestion and peripheral edema.	I	C
Coronary revascularization is reasonable in patients with coronary artery disease in whom symptomatic or demonstrable myocardial ischemia is judged to be having an adverse effect on cardiac function.	IIa	C
Restoration and maintenance of sinus rhythm in patients with atrial fibrillation might be useful to improve symptoms.	IIa	C
The use of beta-adrenergic blocking agents, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, or calcium antagonists in patients with controlled hypertension might be effective to minimize symptoms of heart failure.	IIb	C
The use of digitalis to minimize symptoms of heart failure is not well established.	IIb	C

The treatment of hypertension in patients with symptomatic (NYHA- Class II-IV) heart failure reduced ejection fraction (1)

Recommendations	Class	Level
Step 1		
ACE-I (or ARB) a beta-blocker or an MRA (or a combination) is recommended to reduce blood pressure as first-, second- and third line-therapy, respectively, because of their associated benefits in HFrEF (reducing the risk of death and HF hospitalization). They are also safe in HFpEF.	I	A
Step 2		
A thiazide diuretic (or if the patient is being treated with a thiazide diuretic, switching to a loop diuretic) is recommended to reduce blood pressure when hypertension persists despite treatment with a combination of an ACE-I (or alternatively ARB but NOT together withan ACE-I), a beta-blocker and an MRA.	I	C
Step 3		
Amlodipine or hydralazine is recommended to reduce blood pressure when hypertension persists despite treatment with a combination of an ACE-I (or alternatively ARB but NOT together withan ACE-I), a beta-blocker, an MRA and a diuretic.	I	A

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Regarding management of patients with cardiogenic shock

Recommendations	Class	Level
In all patients with suspected cardiogenic shock, immediate ECG and echocardiography are recommended.	I	C
All patients with cardiogenic shock should be rapidly transferred to a tertiary care center which has a 24/7 service of cardiac catheterization, and a dedicated ICU/CCU with availability of short-term mechanical circulatory support.	I	C
In patients with cardiogenic shock complicating ACS an immediate coronary angiography is recommended (within 2 hours from hospital admission) with an intent to perform coronary revascularization.	I	C
Continous ECG and blood pressure monitoring are recommended.	I	C
Invasive monitoring with an arterial line is recommended.	I	C
Fluid challenge (saline or Ringer's lactate, >200 ml/15-30 min is recommended as the first-line treatment if there is no sign of overt fluid overload.	I	C
Intravenous inotropic agents (dobutamine) may be considered to increase cardiac output.	IIb	C
Vasopressors (norepinephrine preferable over dopamine) may be considered if there is a need to maintain SBP in the presence of persistent hypoperfusion.	IIb	B
IABP is not routinely recommended in cardiogenic shock.	III	B
Short-term mechanical circulatory support may be considered in refractory cardiogenic shock depending on patient age, co-morbidities and neurological function.	IIb	C

TEAM CARE

ESC Guideline Heart Failure 2016

Organisation of Care

It is recommended that patients with HF are enrolled in a multidisciplinary care management programme to reduce the risk of HF hospitalization and mortality.	I	A

Ponikowski et al., Eur Heart J 2016

Characteristics	Should employ a multidisciplinary approach (cardiologists, primary care physicians, nurses, pharmacists, physiotherapists, dieticians, social workers, surgeons, psychologists, etc.).
	Should target high-risk symptomatic patients.
	Should include competent and professionally educated staff.[617]
Components	Optimized medical and device management.
	Adequate patient education, with special emphasis on adherence and self-care.
	Patient involvement in symptom monitoring and flexible diuretic use.
	Follow-up after discharge (regular clinic and/or home-based visits; possibly telephone support or remote monitoring).
	Increased access to healthcare (through in-person follow-up and by telephone contact; possibly through remote monitoring).
	Facilitated access to care during episodes of decompensation.
	Assessment of (and appropriate intervention in response to) an unexplained change in weight, nutritional status, functional status, quality of life, or laboratory findings.
	Access to advanced treatment options.
	Provision of psychosocial support to patients and family and/or caregivers.

Prof. Dr. Johann Bauersachs
Klinik für Kardiologie und Angiologie
Medizinische Hochschule Hannover

Exercice, multidisciplinary management and monitoring of patients with heart failure

Recommendations	Class	Level
It is recommended that regular aerobic exercise is encouraged in patients with HF to improve functional capacity and symptoms.	I	A
It is recommended that regular aerobic exercise is encouraged in stable patients with HFrEF to reduce the risk of HF hospitalization.	I	A
It is recommended that patients with HF are enrolled in a multidisciplinary care management programme to reduce the risk of HF hospitalization and mortality.	I	A
Referral to primary care for longterm follow-up may be considered for stable HF patients who are on optimal therapy to monitor for effectiveness of treatment, disease progression and patient adherence.	IIb	B
Monitoring of pulmonary artery pressures using a wireless implantable haemodynamic monitoring system (CardioMems) may be considered in symptomatic patients with HF with previous HF hospitalization in order to reduce the risk of recurrent HF hospitalization.	IIb	B
Multiparameter monitoring based on ICD (IN-TIME approach) may be considered in symptomatic patients with HFrEF (LVEF ≤35%) in order to improve clinical outcomes.	IIb	B

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FOLLOW UP

Specific recommendations regarding monitoring and follow-up of the older adult with heart failure

Monitor frailty and seek and address reversible causes (cardiovascular and non-cardiovascular) of deterioration in frailty score.
Medication review: optimize doses of heart failure medication slowly and with frequent monitoring of clinical status. Reduce polypharmacy; number, doses and complexity of regime. Consider stopping medication without an immediate effect on symptom relief or quality of life (such as statin). Review the timing and dose of diuretic therapy to reduce risk of incontinence.
Consider need to refer to specialist care of the elderly team and to general practitioner and social worker, etc. for follow-up and support for the patient and his/her family.

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Patients with heart failure in whom end of life care should be considered

Progressive functional decline (physical and mental) and dependence in most activities of daily living.
Severe heart failure symptoms with poor quality of life despite optimal pharmacological and non-pharmacological therapies.
Frequent admissions to hospital or other serious episodes of decompensation despite optimal treatment.
Heart transplantation and mechanical circulatory support ruled out.
Cardiac cachexia.
Clinically judged to be close to end of life.

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Key components of palliative care service in patients with heart failure

Focus on improving or maintaining the quality of life of a patient and his/her family as well as possible until he/she dies.
Frequent assessment of symptoms (including dyspnoea and pain) resulting from advanced heart failure and other co-morbidities and focus on symptom relief.
Access for the patient and his/her family to psychological support and spiritual care according to need.
Advanced care planning, taking account of preferences for place of death and resuscitation (which may include deactivating devices, such as pacemaker and/or implantable cardioverter defibrillator).

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THANK YOU