Fisiopatologia e clinica dello scompenso cardiaco

Andrea Di Lenarda

Centro Cardiovascolare, ASUI Trieste

ANMCO

Agenda

- Scompenso cardiaco e diabete: «a deadly intersection»
- La diagnosi di Scompenso Cardiaco
- Il trattamento (dal punto di vista cardiologico)

Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

Diabetes-Related Heart Failure

– Does Diabetic Cardiomyopathy Exist? –

- Difficile definire il rimodellamento cardiaco «diabetico» (mancanza di criteri diagnostici, biomarker, documenti di consenso
- Difficile stabilire il target glicemico dei pazienti scompensati
- La cardiomiopatia diabetica, inizialmente associata a HFrEF, include HFpEF?

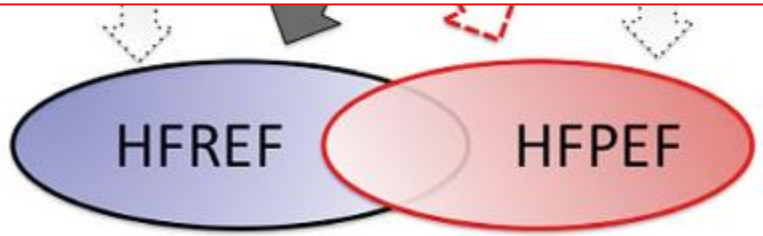
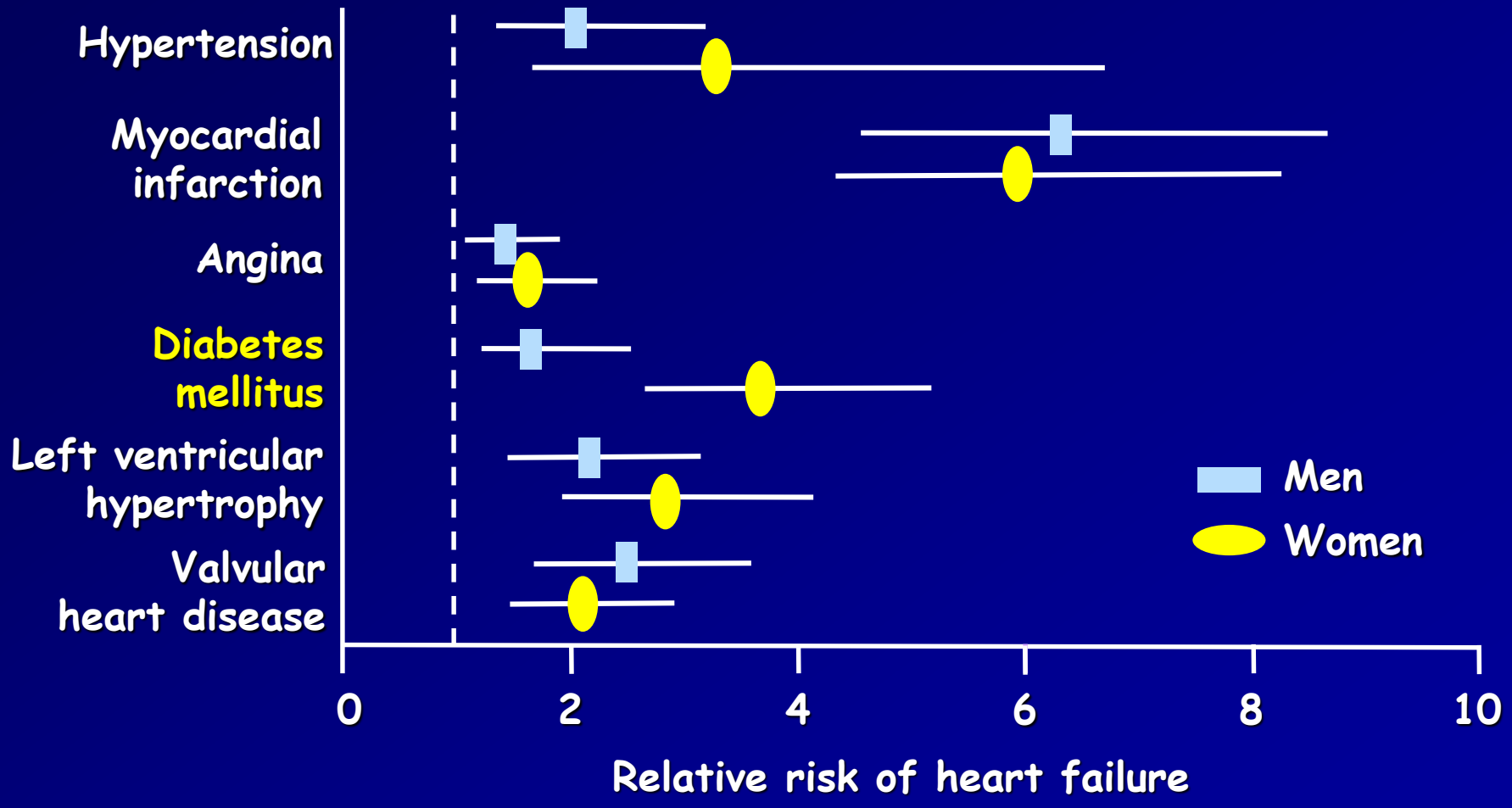


Figure 1. Overview of the clinical course of heart failure and its risk factors *: ref. 3 **ref. 4.

Relative risks for HF
Framingham Heart Study



Wilson PWF, *Am J Cardiol* 1997; 80(9B): 3J-8J

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REVIEW

Diabetes-Related Heart Failure

– Does Diabetic Cardiomyopathy Exist? –

Yasuko K. Bando, MD, PhD; Toyoaki Murohara, MD, PhD

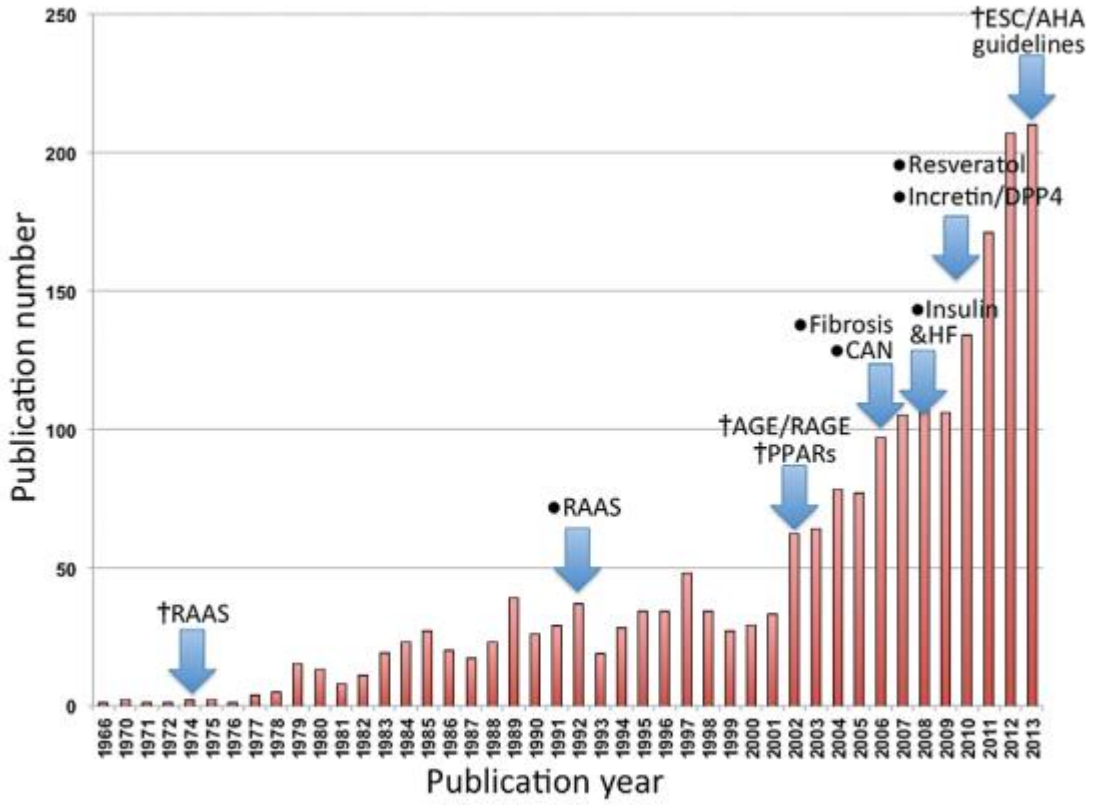

Figure 2. Exclusive increase in the number of publications on diabetic cardiomyopathy "DMC". Search engine powered by Pubmed. Notable events are indicated with arrows. †Year of the first report presenting the link to DMC.

SCC cronico

Registri ed Osservatorio-TS «community-based»

	Chronic HF (IN-HF Outcome)	Chronic HF (Long-term ESC Registry)	Chronic HF (Osservatorio Trieste)
Età	69 anni	66 anni	**76 anni**
Femmine	24%	29%	30%
NYHA 3-4	25%	25%	27%
Cardiopatia ischemica	46%	43%	**63%**
Ipertensione arteriosa	43%	58%	**79%**
FEVS	38%	35%	36%
Fibrillazione atriale	30%	38%	**48%**
IRC	21%	18%	**43%**
Diabete mellito	30%	32%	**35%**
BPCO	21%	14%	**22%**

22% >85 anni
2/3 HFpEF

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REVIEW

Diabetes-Related Heart Failure

– Does Diabetic Cardiomyopathy Exist? –

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advanced glycation end-products (AGEs)/interaction with the receptor RAGE
Link with DPP4 activity

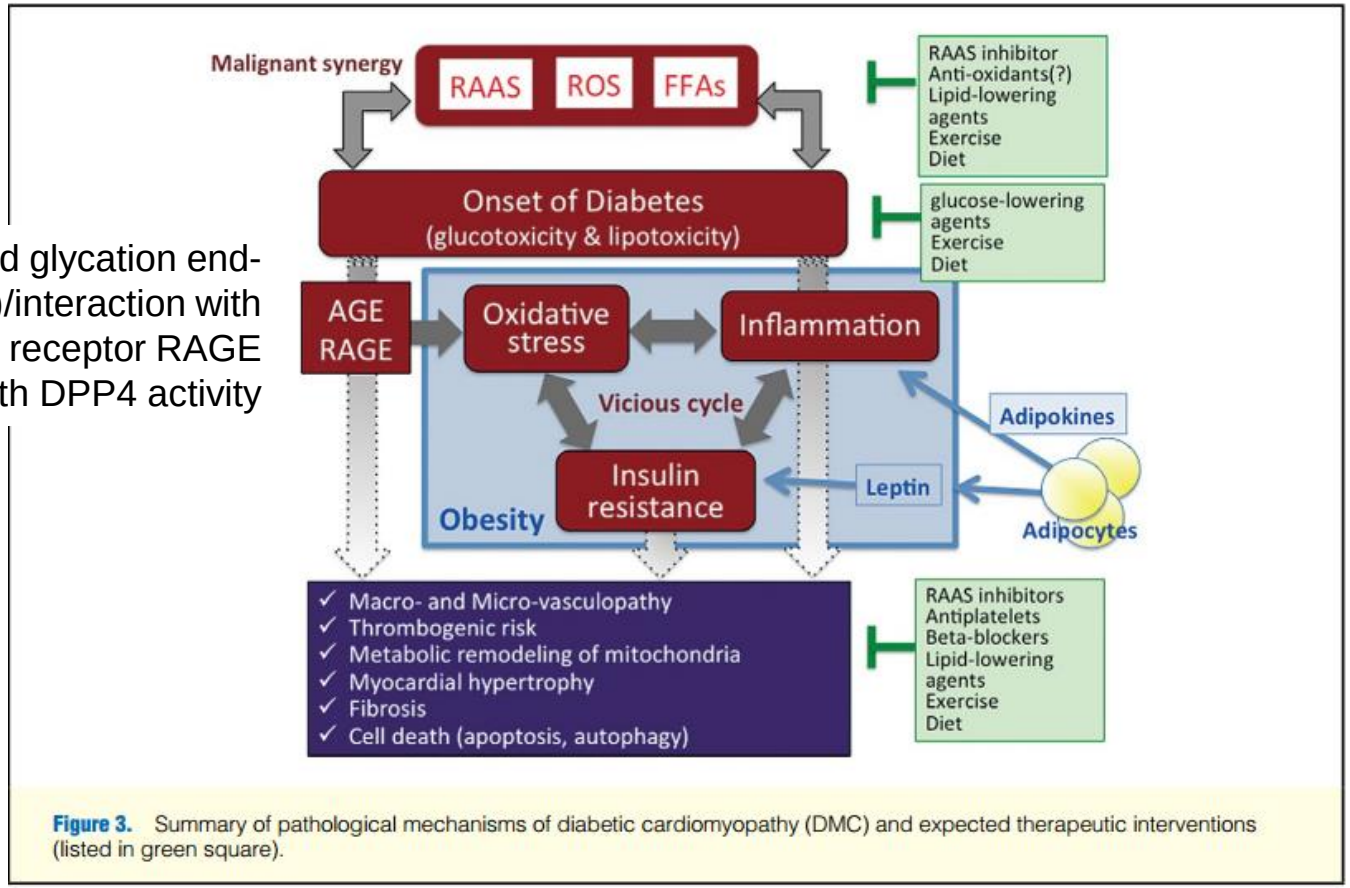

Figure 3. Summary of pathological mechanisms of diabetic cardiomyopathy (DMC) and expected therapeutic interventions (listed in green square).

Activation and Inhibition of Sodium-Hydrogen Exchanger Is a Mechanism That Links the Pathophysiology and Treatment of Diabetes Mellitus With That of Heart Failure

Packer M. Circulation. 2017;136:1548–1559

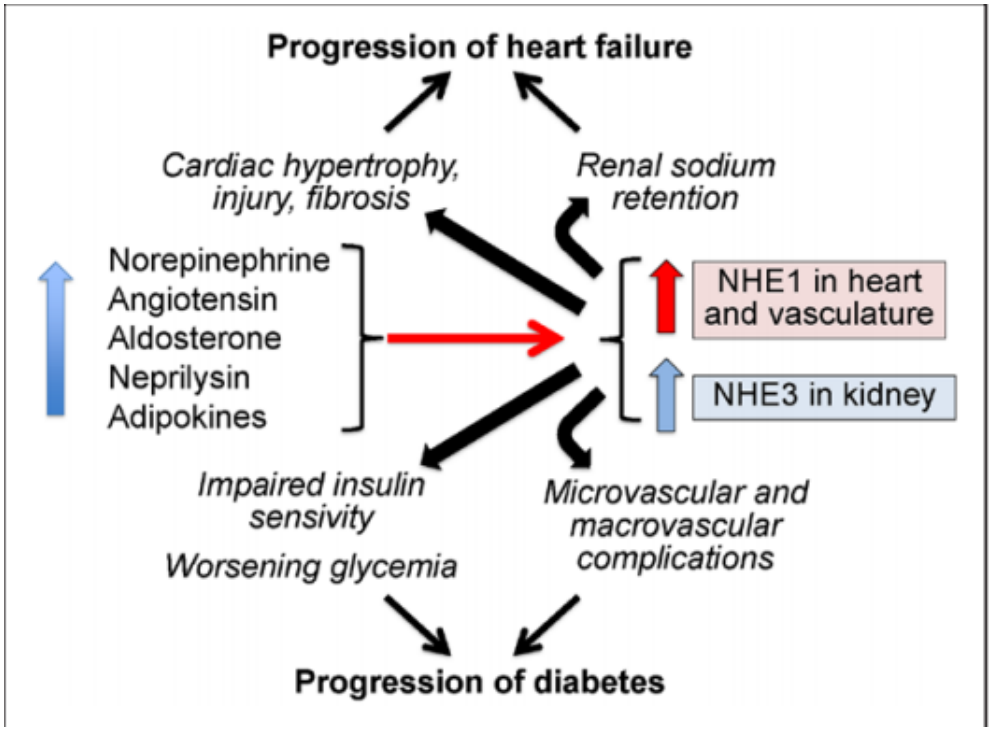

Figure 1. NHE-dependent pathways that may underlie the interplay of the pathogenesis of heart failure and diabetes.
Insulin and glucose (which are increased in type 2 diabetes mellitus) and neurohormonal mechanisms (which are activated in heart failure) stimulate the activity of NHE1 in the heart and vasculature and of NHE3 in the kidneys. The increase in these 2 NHE isoforms causes (1) sodium retention and cardiac hypertrophy, injury, and fibrosis (leading to the progression of heart failure); and (2) impaired insulin sensitivity and worsening glycemia, as well as microvascular and macrovascular complications (leading to the progression of diabetes mellitus). The deleterious effects of NHE1 upregulation in mesangial and tubular cells of the kidney in the pathogenesis of diabetic nephropathy are not shown. NHE indicates sodium-hydrogen exchanger.

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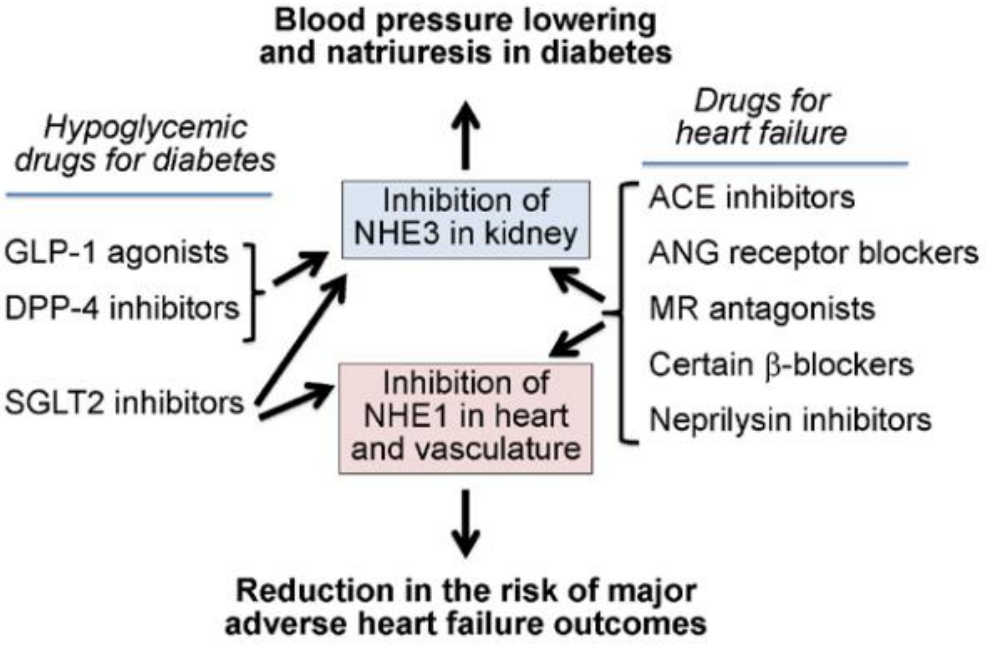
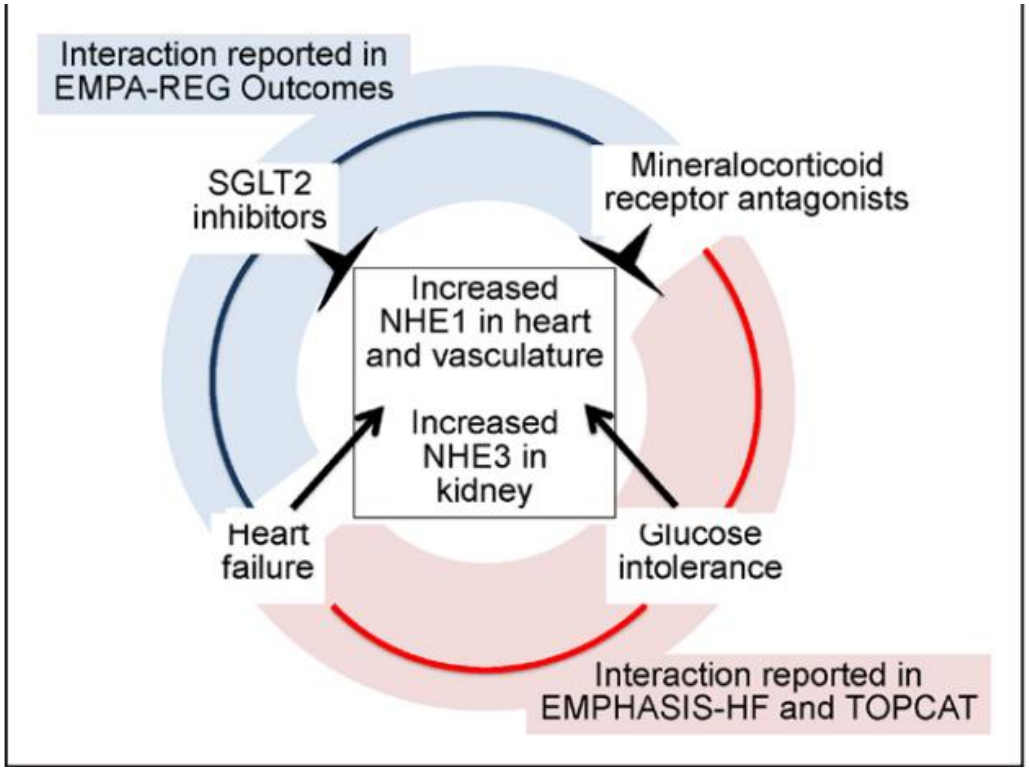


Figure 2. NHE-dependent pathways that may underlie the interplay of treatments of heart failure and diabetes mellitus.
Drugs conventionally used for the treatment of heart failure and drugs typically prescribed to lower blood glucose in diabetes mellitus can inhibit the activity of both NHE1 in the heart and vasculature and NHE3 in the kidneys. The suppression of NHE3 leads to the inhibition of proximal tubular reabsorption of sodium (and thereby a lowering of blood pressure and natriuresis in diabetes mellitus), whereas the suppression of NHE1 leads to the amelioration of cardiac hypertrophy, injury, and fibrosis and thereby a reduction in the risk of cardiovascular death and hospitalization for heart failure, the 2 major end points in heart failure trials. The potential role of NHE1 in the kidneys is not shown. ACE indicates angiotensin converting-enzyme; ANG, angiotensin; DPP, dipeptidyl peptidase; GLP, glucagon-like peptide; MR, mineralocorticoid receptor; NHE, sodium-hydrogen exchanger; and SGLT, sodium-glucose cotransporter.

Activation and Inhibition of Sodium-Hydrogen Exchanger Is a Mechanism That Links the Pathophysiology and Treatment of Diabetes Mellitus With That of Heart Failure

Packer M. Circulation. 2017;136:1548–1559

Figure 3. Drug–drug and drug–disease interactions influencing the risk of cardiovascular events after NHE-1 and NHE-3 inhibition in patients with heart failure and glucose intolerance.
NHE modulation is central to the pathogenesis and treatment of both diabetes mellitus and heart failure, and both SGLT2 inhibitors and mineralocorticoid receptor antagonists may exert clinical benefits by NHE1 and NHE3 suppression. (Interference with the actions of aldosterone on NHE1 in the kidney may also attenuate the pathogenesis of diabetic nephropathy.) In both the EMPHASIS-HF trial (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) of eplerenone in heart failure and a reduced ejection fraction and the TOPCAT trial (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) of spironolactone in heart failure and a preserved ejection fraction, patients with glucose intolerance (as evidenced by obesity or diabetes mellitus) were particularly likely to respond favorably to mineralocorticoid receptor antagonism (red-shaded semicircle). Similarly, in the EMPA-REG Outcomes trial (*Empagliflozin, Cardiovascular Outcomes*, and *Mortality* in Type 2 *Diabetes*), the beneficial effect of SGLT2 inhibition with empagliflozin on heart failure outcomes was attenuated in patients concomitantly treated with spironolactone (blue-shaded semicircle). NHE indicates sodium hydrogen exchanger; and SGLT, sodium-glucose cotransporter.



HFpEF: pathophysiologic phenotype approach

Targeted therapies for heart failure phenotypes, instead of the "one-size-fits-all" approach.

Senni M et al. Eur Heart J 2014

Analysis of midwall shortening reveals high prevalence of left ventricular myocardial dysfunction in patients with diabetes mellitus: the DYDA study

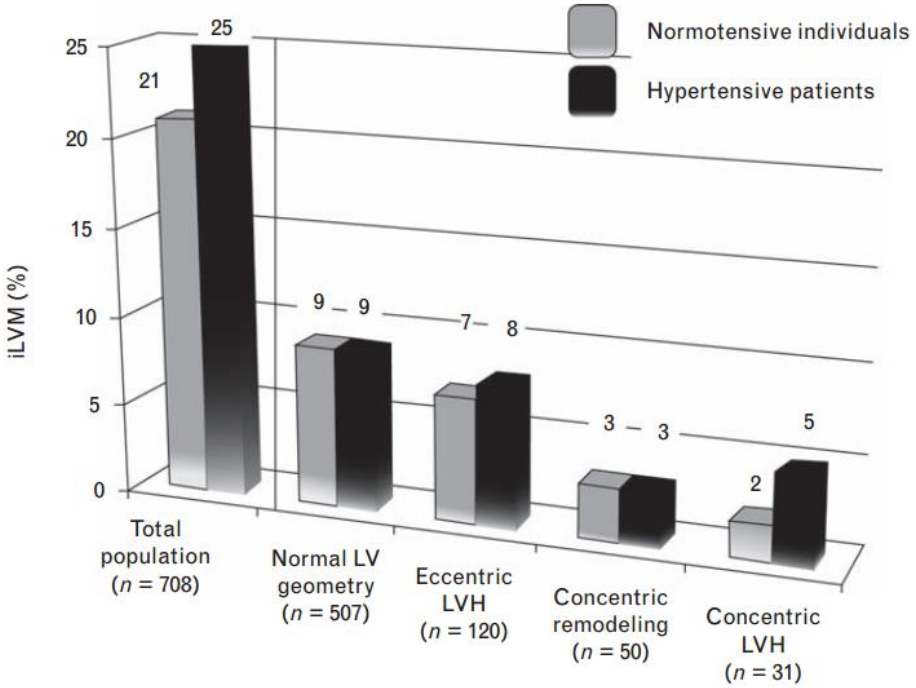
FR correlati al riscontro di disfunzione VS diast/sist

Età
Hb glicata
Sindrome metabolica

Cioffi et al. Eur J Prev Cardiol. 2012;19: 935-43

Inappropriately high left ventricular mass in patients with type 2 diabetes mellitus and no overt cardiac disease. The DYDA study

Giovanni Cioffi[a], Pompilio Faggiano[b], Donata Lucci[c], Andrea Di Lenarda[d], Gian Francesco Mureddu[e], Luigi Tarantini[f], Paolo Verdecchia[g], Marco Comaschi[h], Carlo B. Giorda[i], Mario Velussi[j], Marcello Chinali[k], Roberto Latini[l], Serge Masson[l], Giovanni De Simone[k], on behalf of DYDA Investigators

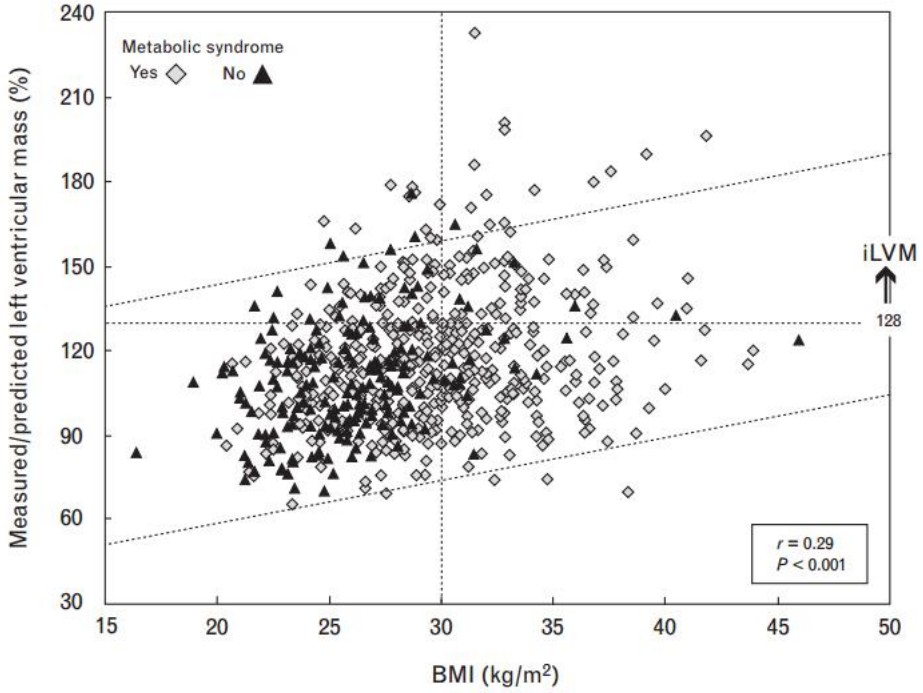


Massa inappropriata 23%

Prevalence (%) of inappropriately high left ventricular mass (iLVM) in hypertensive and normotensive diabetic patients divided according to left ventricular geometric patterns. LVH, left ventricular hypertrophy.

Inappropriately high left ventricular mass in patients with type 2 diabetes mellitus and no overt cardiac disease. The DYDA study

Giovanni Cioffi[a], Pompilio Faggiano[b], Donata Lucci[c], Andrea Di Lenarda[d], Gian Francesco Mureddu[e], Luigi Tarantini[f], Paolo Verdecchia[g], Marco Comaschi[h], Carlo B. Giorda[i], Mario Velussi[j], Marcello Chinali[k], Roberto Latini[l], Serge Masson[l], Giovanni De Simone[k], on behalf of DYDA Investigators



Relationship between appropriateness of left ventricular mass (defined as measured/predicted left ventricular mass ratio %) and BMI. Scatter plot of linear correlation and 95% confidence limits of the total population (dotted lines) are shown. Gray diamonds and black triangles identify patients with or without metabolic syndrome, respectively. iLVM, inappropriately high left ventricular mass.

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- Scompenso cardiaco e diabete: «a deadly intersection»
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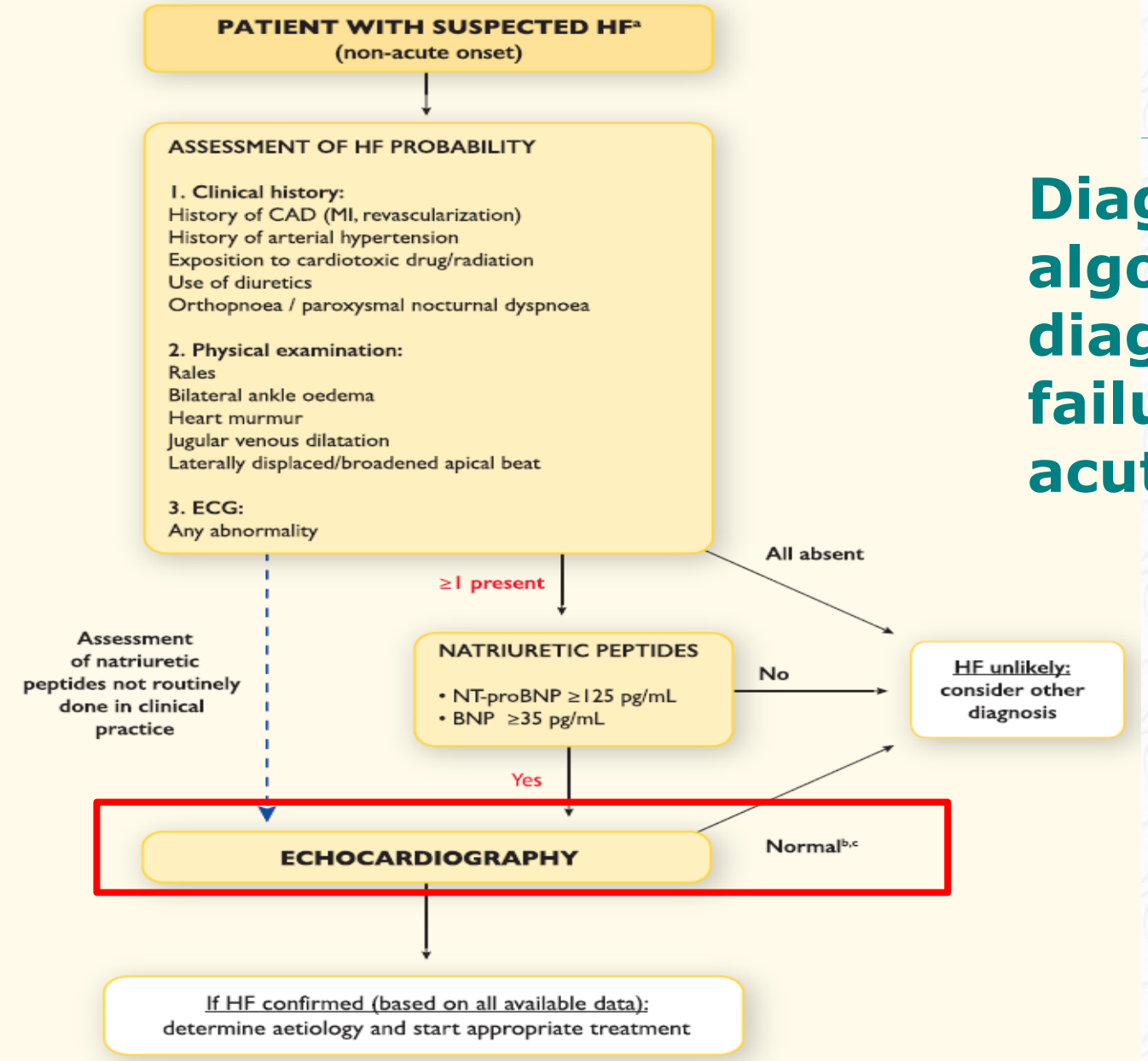
Diagnostic algorithm for a diagnosis of heart failure of non-acute onset



www.escardio.org/guidelines

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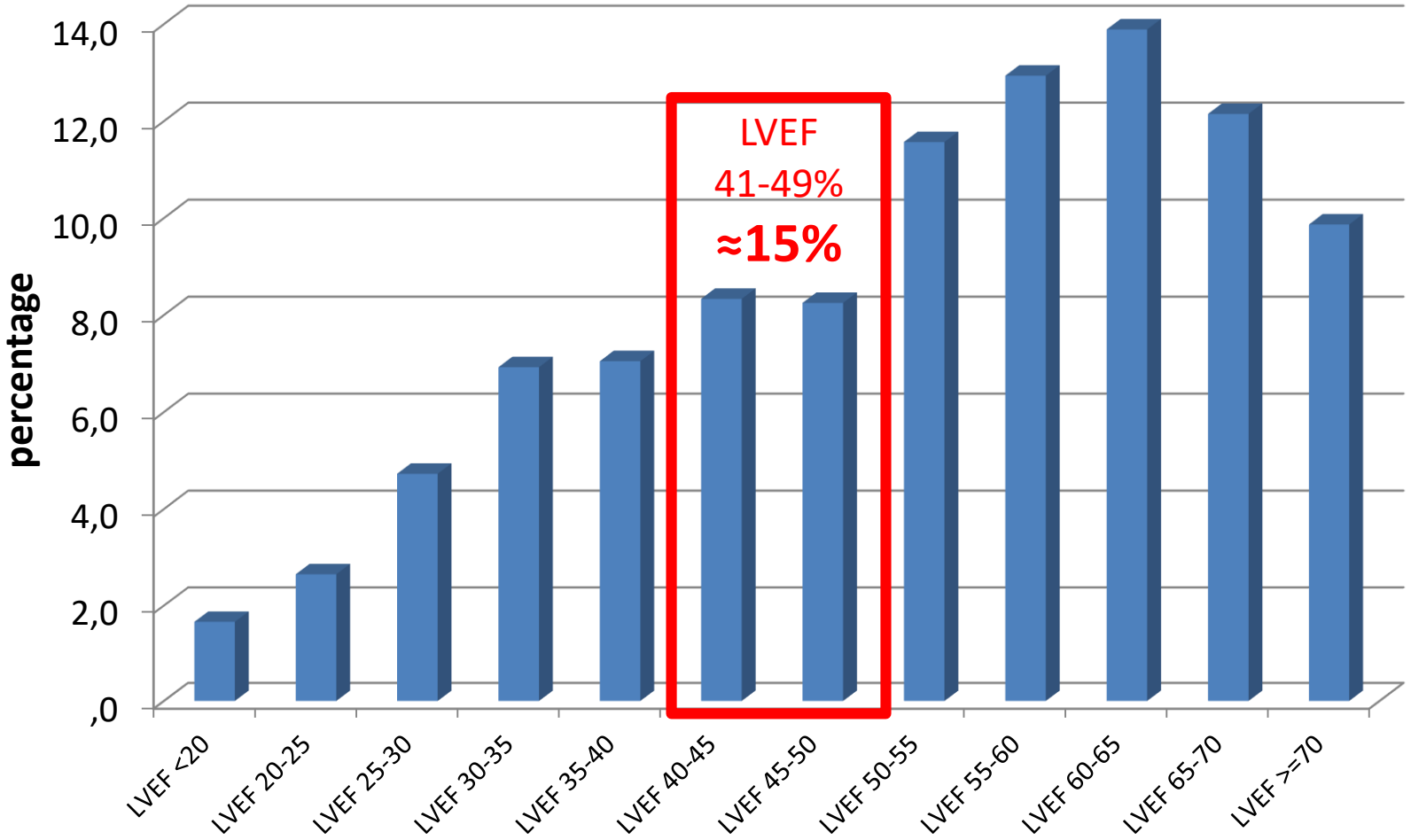
Recommendations for cardiac imaging in patients with suspected or established heart failure

Recommendations	Class [a]	Level [b]
TTE is recommended for the assessment of myocardial structure and function in subjects with suspected HF in order to establish a diagnosis of either HFrEF, HFmrEF or HFpEF.	I	C
TTE is recommended to assess LVEF in order to identify patients with HF who would be suitable for evidence-based pharmacological and device (ICD, CRT) treatment recommended for HFrEF.	I	C
TTE is recommended for the assessment of valve disease, right ventricular function and pulmonary arterial pressure in patients with an already established diagnosis of either HFrEF, HFmrEF or HFpEF in order to identify those suitable for correction of valve disease.	I	C
TTE is recommended for the assessment of myocardial structure and function in subjects to be exposed to treatment which potentially can damage myocardium (e.g. chemotherapy).	I	C
Other techniques (including systolic tissue Doppler velocities and deformation indices, i.e. strain and strain rate), should be considered in a TTE protocol in subjects at risk of developing HF in order to identify myocardial dysfunction at the preclinical stage.	IIa	C
CMR is recommended for the assessment of myocardial structure and function (including right heart) in subjects with poor acoustic window and patients with complex congenital heart diseases (taking account of cautions/contra-indications to CMR).	I	C
CMR with LGE should be considered in patients with dilated cardiomyopathy in order to distinguish between ischaemic and non-ischaemic myocardial damage in case of equivocal clinical and other imaging data (taking account of cautions/contra-indications to CMR).	IIa	C
CMR is recommended for the characterization of myocardial tissue in case of suspected myocarditis, amyloidosis, sarcoidosis, Chagas disease, Fabry disease non-compaction cardiomyopathy, and haemochromatosis (taking account of cautions/contra-indications to CMR).	I	C

Definition of heart failure with preserved (HFpEF), mid-range (HFmrEF) & reduced ejection fraction (HFrEF)

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

La distribuzione della FEVS (Osservatorio CV Trieste: n=2412)



Recommendations to prevent or delay the development of overt heart failure or prevent death before the onset of symptoms

Recommendations	Class [a]	Level [b]
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
ACE-I is recommended in patients with asymptomatic LV systolic dysfunction without a history of myocardial infarction, in order to prevent or delay the onset of HF.	I	B
ACE-I should be considered in patients with stable CAD even if they do not have LV systolic dysfunction, in order to prevent or delay the onset of HF.	IIa	A
Beta-blocker 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 or prolong life.	I	B
ICD is recommended in patients: a) with asymptomatic LV systolic dysfunction (LVEF ≤30%) of ischaemic origin, who are at least 40 days after acute myocardial infarction, b) with asymptomatic non-ischaemic dilated cardiomyopathy (LVEF ≤30%), who receive OMT therapy, in order to prevent sudden death and prolong life.	I	B

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Il documento nazionale intersocietario di consenso "Il percorso assistenziale del paziente con scompenso cardiaco"

Epidemiology of Heart Failure			Management models	
ALVD screening	The stable HF patient	AHF admissions	The patient with severe HF	The frail elderly With HF

ma anche…

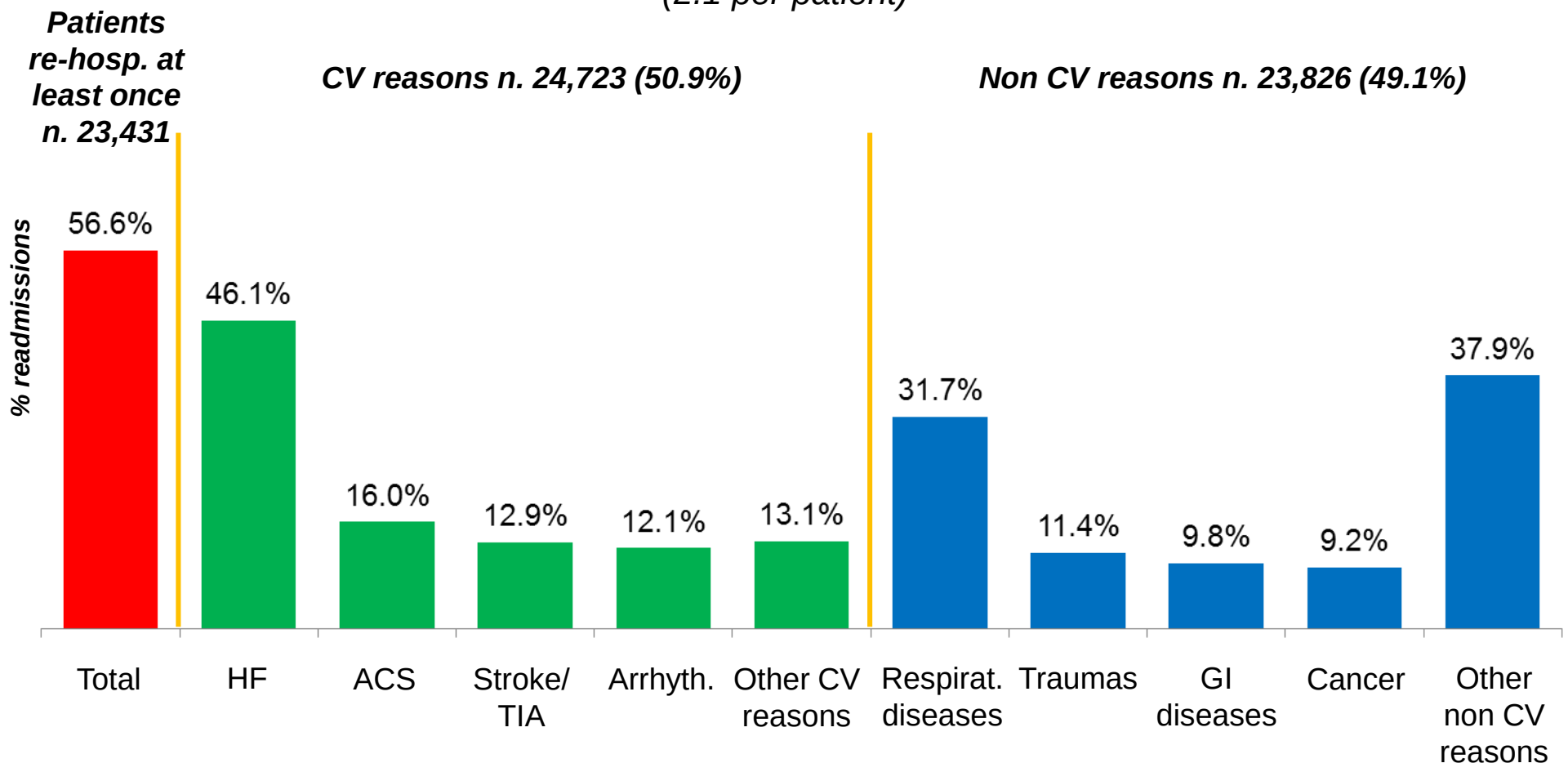
- Fenotipo (ESC/AHA/ACC: FEVS ≤40%/41-49%/≥50%)
- SCC de novo/Caratterizzazione eziologica (non solo ischemica vs no!) e stratificazione del rischio
- Fasi cliniche (acuta vs cronica con ricorrenti instabilizzazioni)
- Comorbidità, politerapia
- Servizi assistenziali e contesto socio-assistenziale (non solo età!)
- …

Di Lenarda A et al, Consensus GIC 2006

Rate and causes of 1-year hospital re-admissions

Total number of re-admissions = 48,549

(2.1 per patient)



HF=heart failure; ACS=acute coronary syndrome; TIA=transient ischemic attack; CV=cardiovascular; GI=gastrointestinal

Courtesy of A. Maggioni

Quali esigenze ha il cardiopatico cronico complesso (e specificatamente il paziente con scompenso)?

Multidisciplinarietà

Multidimensionalità

Multiprofessionalità

Recommendations for exercise, multidisciplinary management and monitoring of patients with heart failure

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	622–625
Referral to primary care for long-term 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	626, 627
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	628, 629
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	630

Table 14.1 Characteristics and components of management programmes for patients with heart failure

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.

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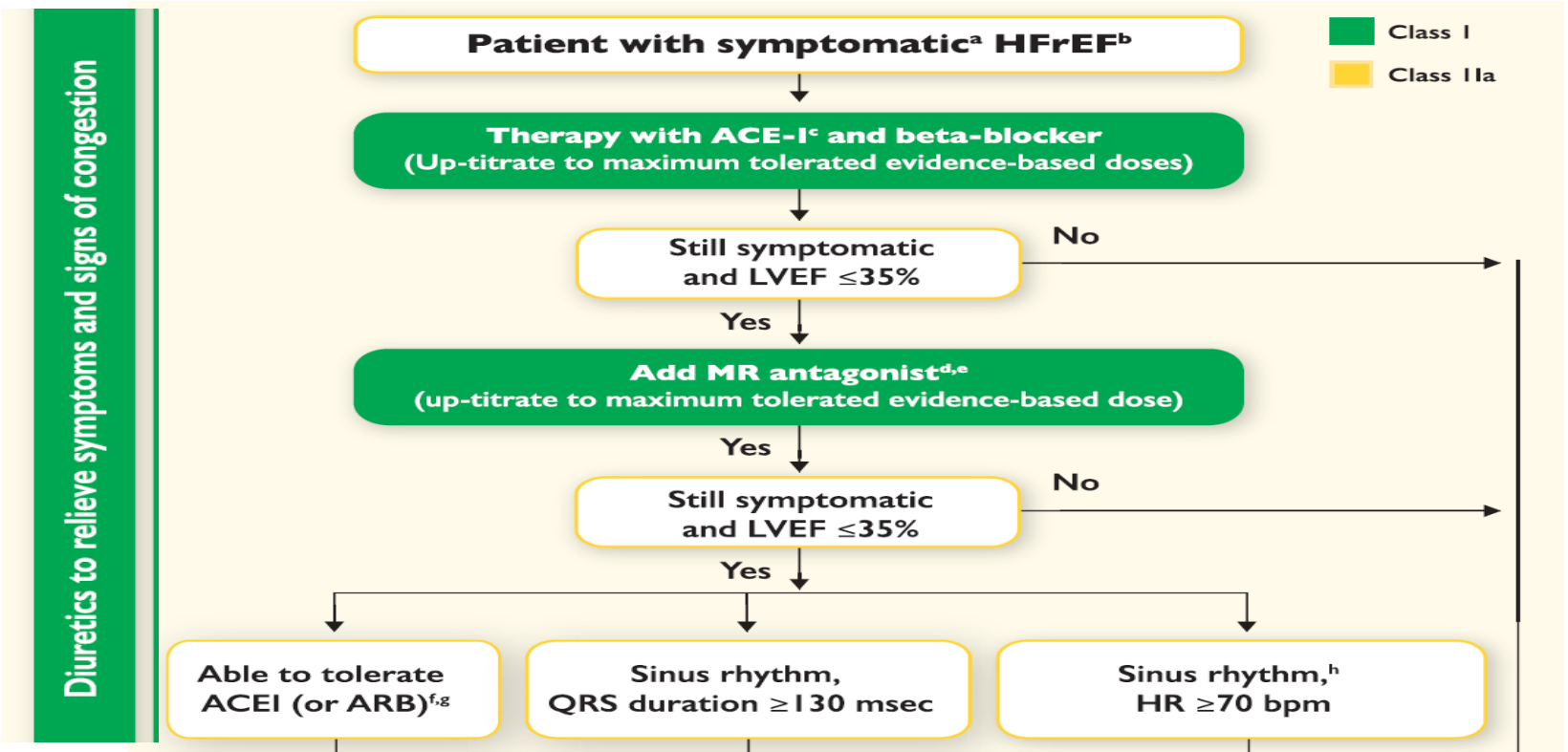
2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

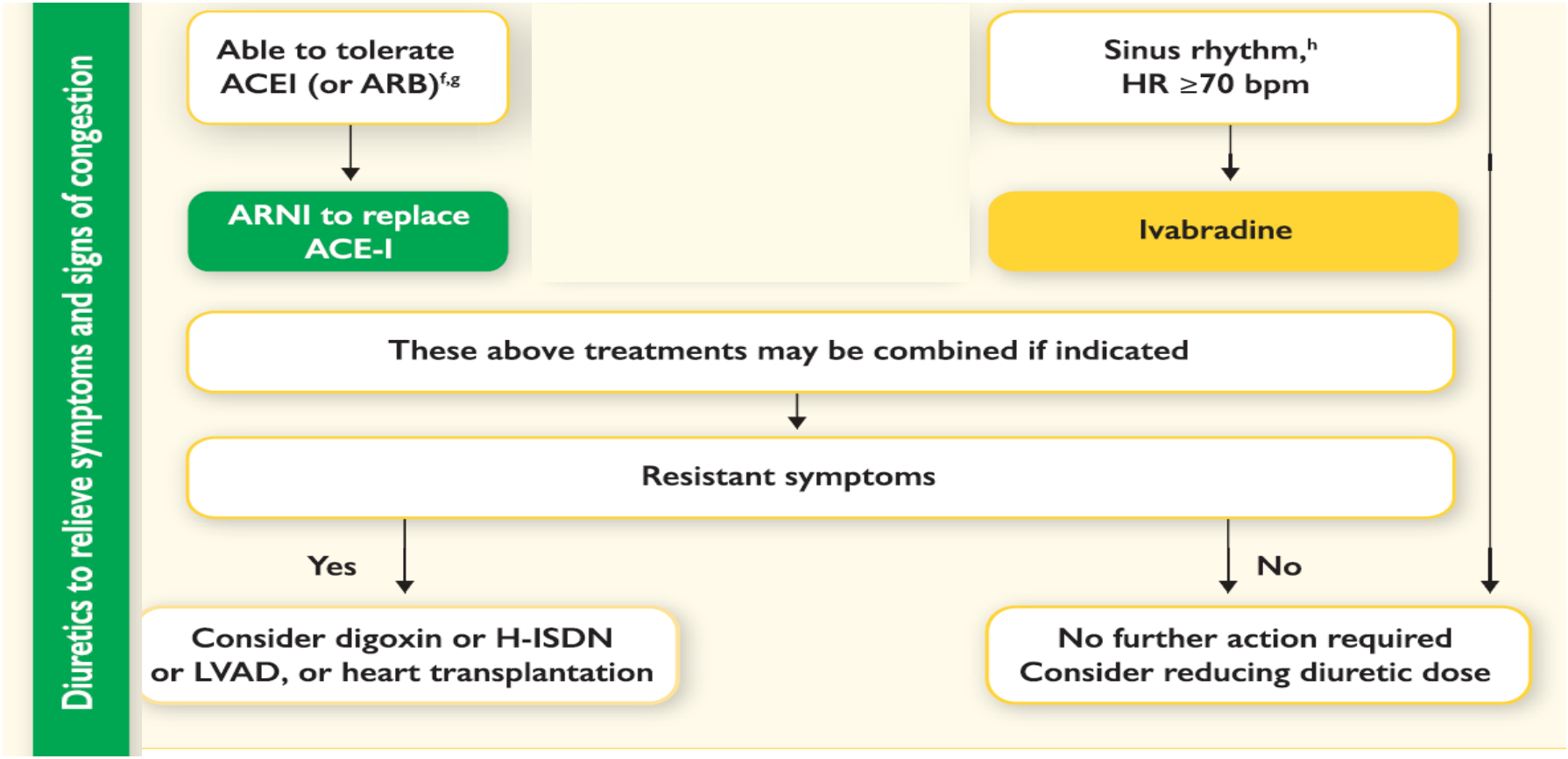
The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

Developed with the special contribution of the Heart Failure Association (HFA) of the ESC

Therapeutic algorithm for a patient with symptomatic HF with reduced ejection fraction.



Therapeutic algorithm for a patient with symptomatic HF with reduced ejection fraction. (cont..)

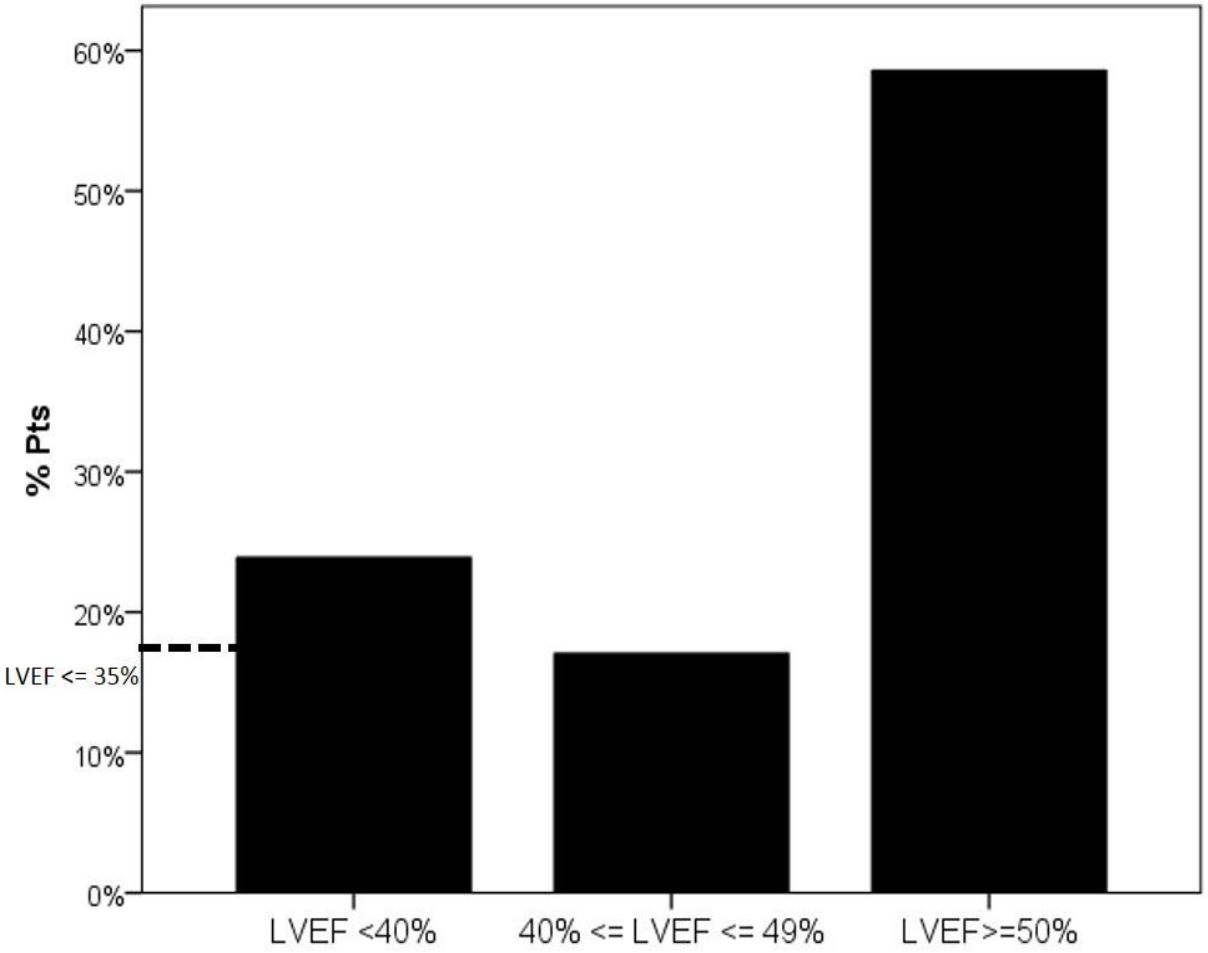


Available online on Eur J Heart Fail

Importance of co-morbidities in patients with HF

1. interfere with the diagnostic process of HF (e.g. COPD as a potentially confounding cause of dyspnoea).[390,391]
2. aggravate HF symptoms and further impair quality of life.[391,392]
3. contribute to the burden of hospitalizations and mortality,[393] as the main cause of readmissions at 1 and 3 months.[394]
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).[395,396]
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).[397]
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).[391,395,396]

Osservatorio Cardiovascolare Trieste
Scompenso cardiaco 2009-2015 (n=2528)



Osservatorio Cardiovascolare Trieste

Scompenso cardiaco 2009-2015 (n=2528)

	N (%)	With at least 50% of the target dosage
LVEF ≤ 35% (n=460)		
ACEs	333 (72.4%)	53.0
MRAs	787 (38.1%)	90.2

Solo in circa 2/3 dei pazienti è chiaro il motivo del sottotrattamento

ESC-adherence	LVEF ≤ 35%	LVEF > 35%
All 3 drugs	27.1%	22.2%

Osservatorio Cardiovascolare Trieste
Scompenso cardiaco 2009-2015 (n=2528)

Proportion of subjects with a PDC ≥ 75% by drug class during the first year of follow up among those with at least 50% of the target dosage

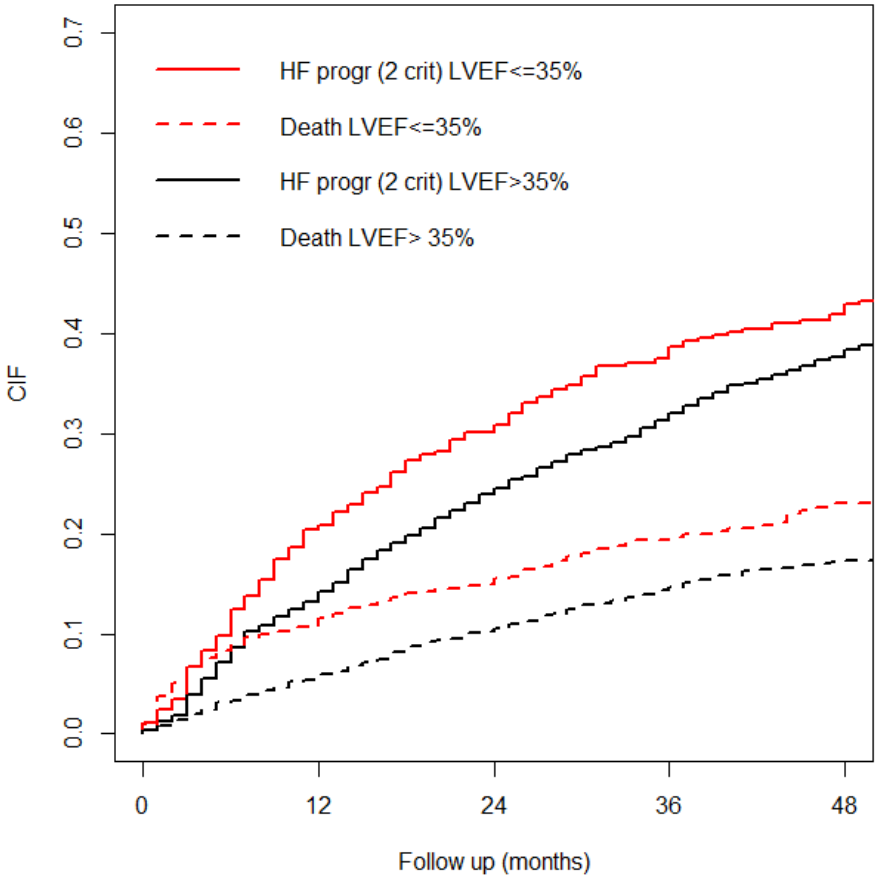
	LVEF ≤ 35%	LVEF > 35%
ACE/ARB	40.1%	44.9%
Beta-blockers	32.9%	42.0%
MRAs	19.8%	18.8%
All 3 drugs	4.8%	3.8%

Osservatorio Cardiovascolare Trieste
Scompenso cardiaco 2009-2015 (n=2528)

Cumulative incidence function of HF progression vs death (as a competing risk) stratified by LVEF

Definition of **HF progression** is the presence of at least 2 of the following criteria with respect to the index visit:

- Step up of ≥1 NYHA class;
- Absolute decrease LVEF ≥10%;
- Association of diuretics (thiazides + furosemide) or increase ≥50% of furosemide dosage (in any case >25 mg).



Osservatorio Cardiovascolare Trieste

Scompenso cardiaco 2009-2015 (n=2528)

Outcome: HF progression and/or deaths

Parameter	HR	95% CI		p-value
ESC-Guideline adherence	0.957	0.848	1.080	0.4753
Patient-adherence	0.805	0.704	0.922	0.0017
Age	1.036	1.028	1.044	<.0001
Sex (Male)	1.359	1.207	1.531	<.0001
Previous HF hospitalisation	1.317	1.167	1.486	<.0001
COPD	1.309	1.158	1.479	<.0001
Diabetes Mellitus	1.138	1.011	1.282	0.0323
Chronic Kidney disease	1.258	1.115	1.421	0.0002
Anemia	1.357	1.208	1.525	<.0001
LVEF ≤ 35%	1.347	1.168	1.553	<.0001
No. drugs ≥ 5	0.899	0.791	1.023	0.1056

Clinical progression of HF: a time-dependent covariate

KM «extended»

Did patients who developed “clinical” HF progression during follow up show a worse survival ?