Miocardiopatia Diabetica

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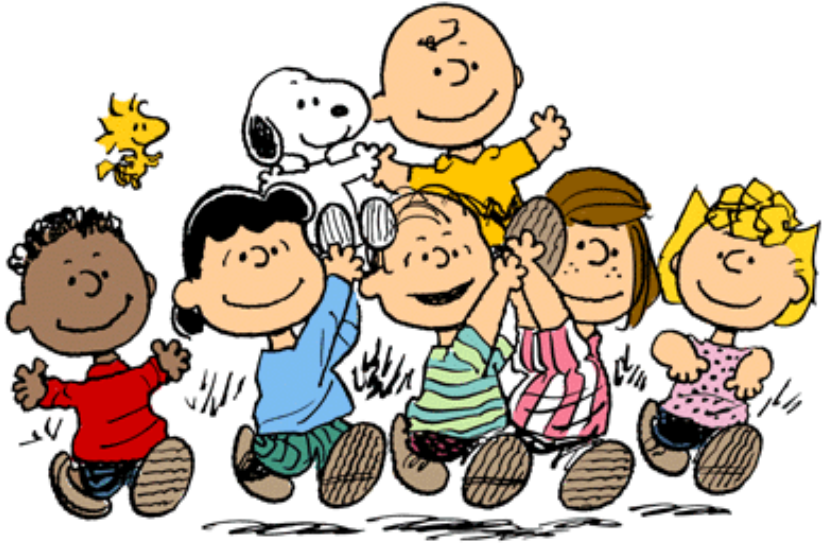


Conflitti di interesse

M. Nizzoli

Ai sensi dell'art. 3.3 sul conflitto di interessi, pag 17 del Regolamento Applicativo Stato-Regioni del 5/11/2009, dichiaro che negli ultimi 2 anni **NON** ho avuto rapporti diretti di finanziamento con soggetti portatori di interessi commerciali in campo sanitario

Conflitti di interesse

M. Iacoviello

Ai sensi dell'art. 3.3 sul conflitto di interessi, pag 17 del Regolamento Applicativo Stato-Regioni del 5/11/2009, dichiaro che negli ultimi 2 anni ho avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

Speaker Honorarium: Alere SpA

CASO CLINICO: MARA 67 anni

- Diabete mellito di tipo 2 dall'età di 60 anni
- Familiarità per diabete e cardiopatia ischemica (padre IMA a 57 anni)
- Regolarmente seguita dal servizio di diabetologia da circa 3 anni
- Terapia in corso:
  - Metformina 1000 mg x 2 al dì
  - Gliclazide RM 30 mg 1 cp al dì
  - Simvastatina 20 mg 1 cp al dì
  - Cardioaspirina 1 cp al dì
  - Ramipril 2.5 mg 1 cp al dì

MARA 67 anni: dati

- BMI 29.5 Kg/mq
- PA 130/85 mmHg, polso ritmico 84 min.
- HbA1c 8.2 % (66 mmol/mol)
- Creatinina 1.13
- Filtrato 68 ml/min
- Col LDL 103
- Microalbuminuria 26 mg/g creat

MARA 67 anni: Dati

- Polsi periferici presenti
- Obiettività cardiopolmonare negativa
- ABI nella norma
- Iporiflessia arti inferiori
- Biotesiometria e test monofilamento compatibili con polineuropatia sensitiva
- Piede neuropatico
- Retinopatia non proliferante di grado lieve
- Ecolor doppler carotideo di due anni prima: negativo

MARA 67 anni

- Riferisce dispnea da sforzo: ha sempre fatto le 3 rampe di scala di casa senza problemi, nonostante la vita sedentaria
- Ultimamente deve fermarsi dopo le prime due
- Di recente dopo un episodio simil-influenzale, ha presentato un lieve edema agli arti inferiori serale, che il mattino seguente era scomparso

Che significato dareste a questa dispnea ?

1. Dispnea come equivalente coronarico (cardiopatia ischemica silente)
2. Dispnea di origine polmonare
3. Dispnea di altra natura

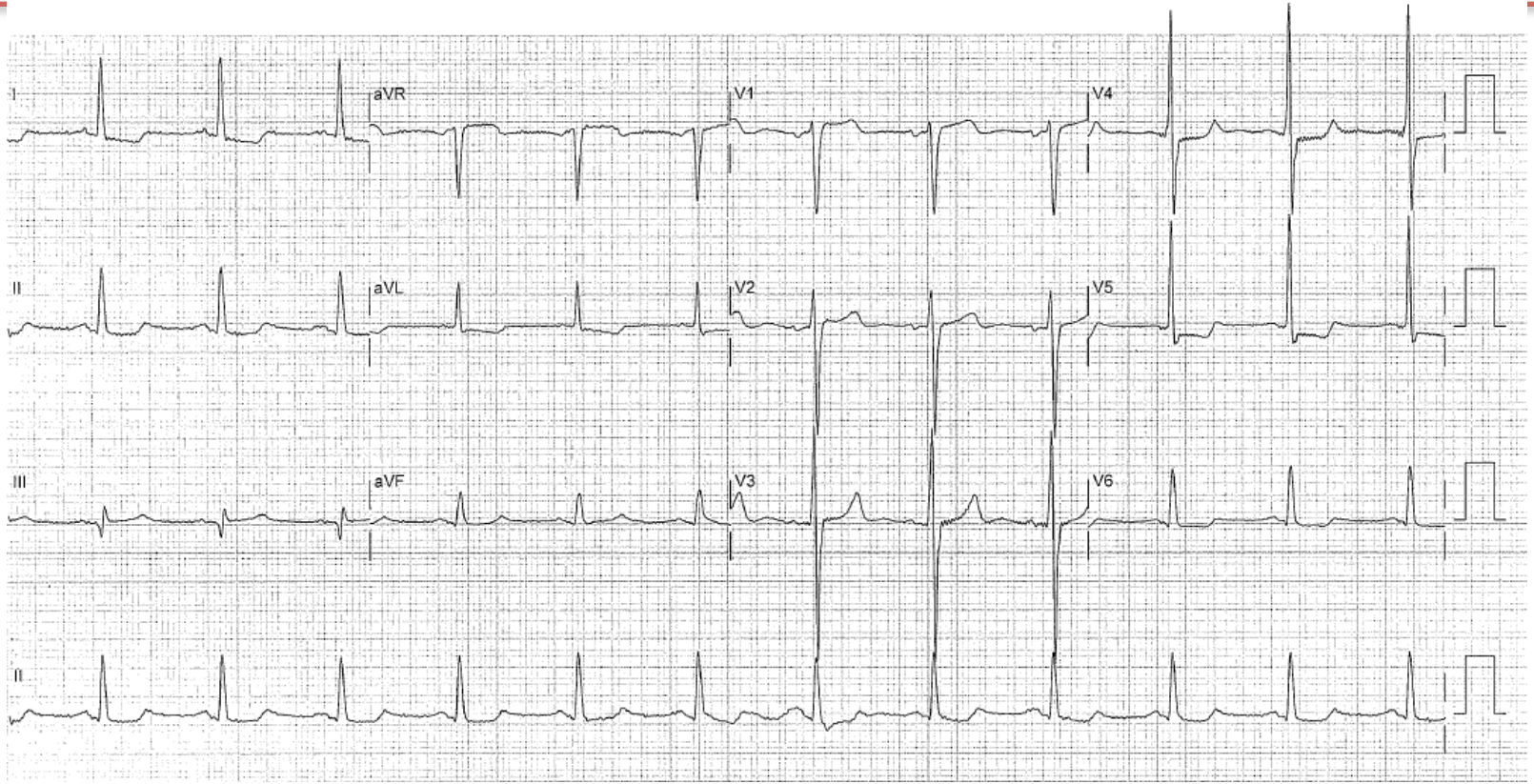
Che esami fareste ?

1. ECG + Rx Torace
2. ECG + Ecocardiografia
3. ECG + Test da sforzo
4. ECG + RX torace + PFR
5. ECG + NT-proBNP

ESAMI

- Rx torace: negativo
- PFR: FEV1 92%
- ECG: r.s., IVS, alterazioni della RV a tipo sovraccarico - ischemia

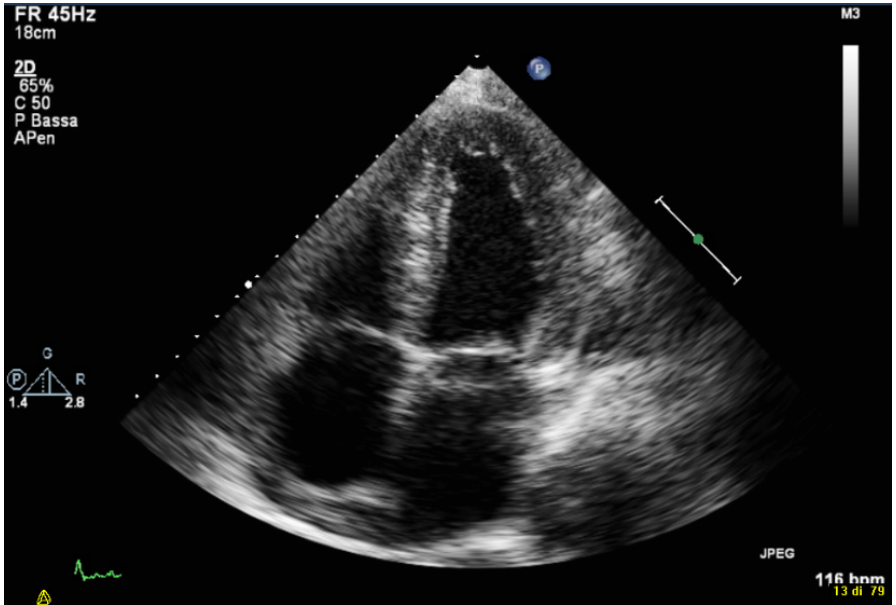
ECG

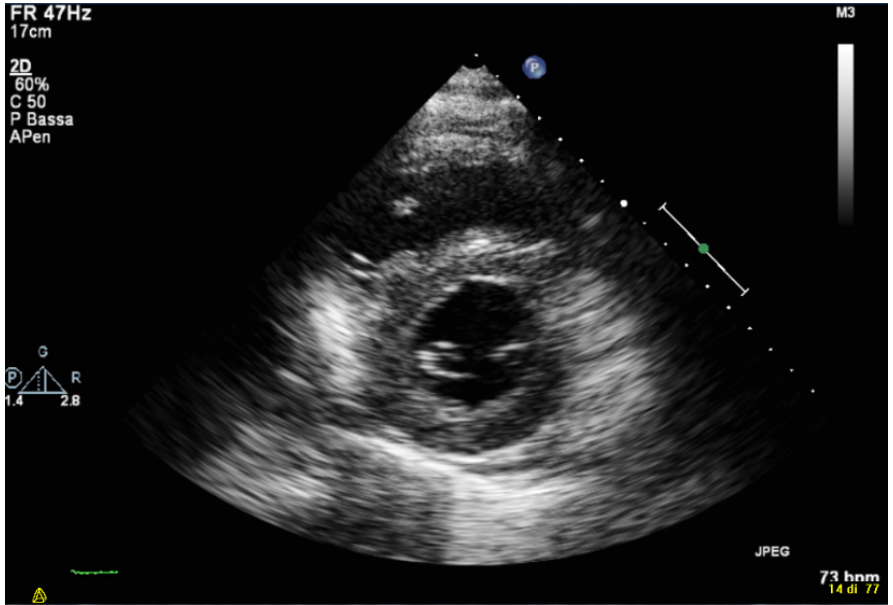


r.s., IVS, alterazioni della RV a tipo sovraccarico - ischemia

ECOCARDIOGRAMMA

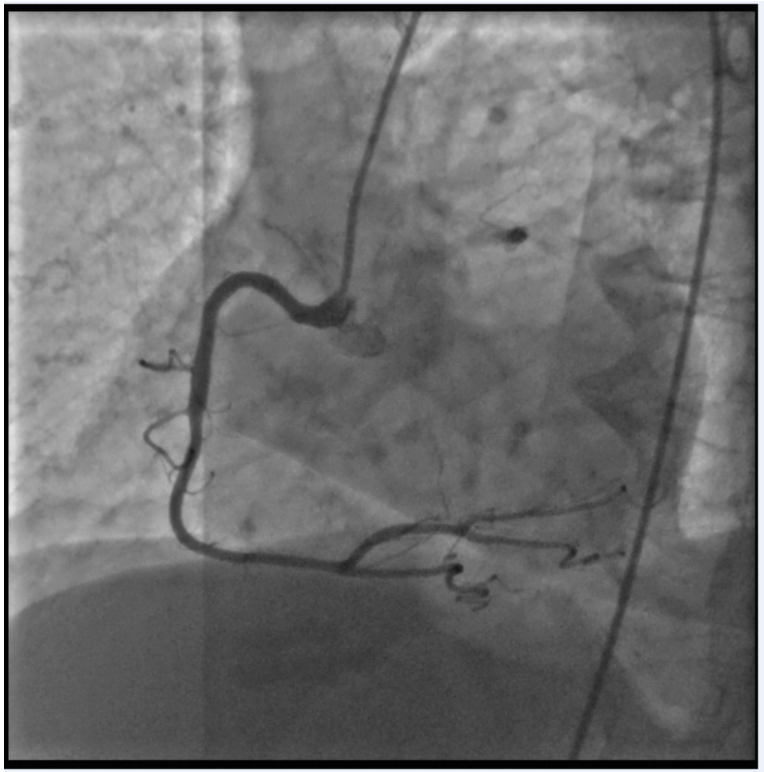
Ventricolo sinistro di dimensioni ai limiti superiori, ipertrofia parietale, funzione sistolica lievemente depressa, FE 47 %, disfunzione diastolica di II grado

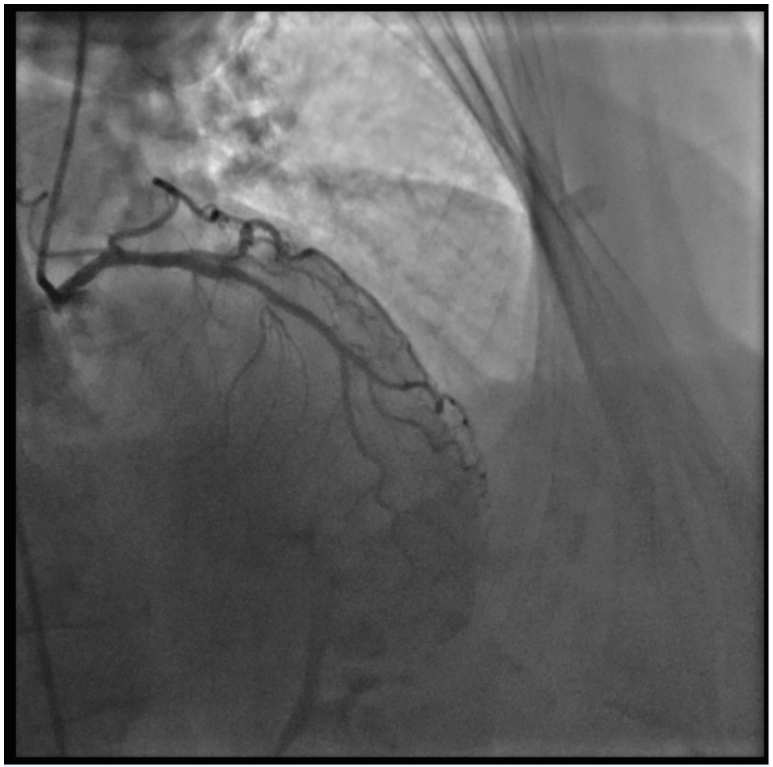




CORONAGRAFIA

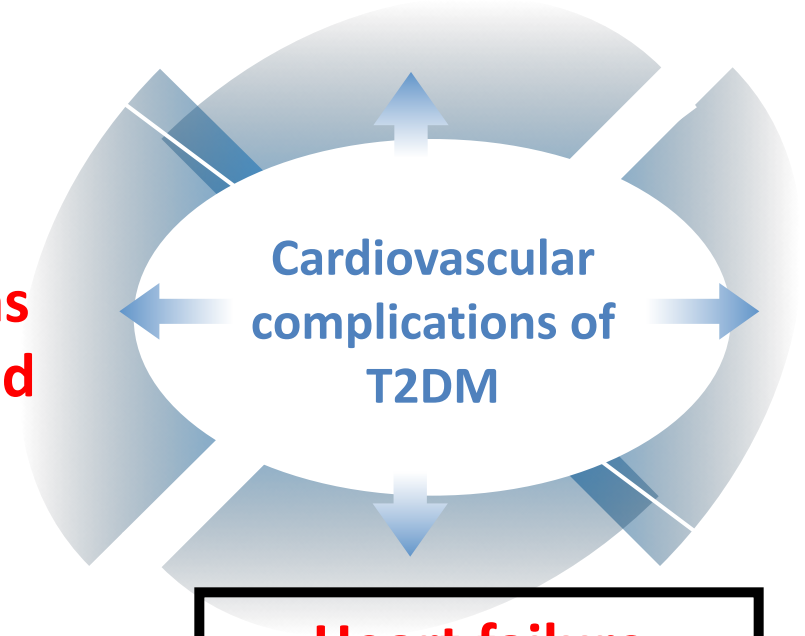
CORONARIE INDENNI





Cardiovascular disease and diabetes

~ 65% of deaths are due to CVD



CHD deaths
↑ 2 to 4 fold

Stroke
↑ 2 to 4 fold

Indipendentemente da ipertensione arteriosa e coronaropatia

Heart failure
↑ 2 M to 5 F fold

Prognostic Impact of Diabetes on Long-term Survival Outcomes in Patients With Heart Failure: A Meta-analysis

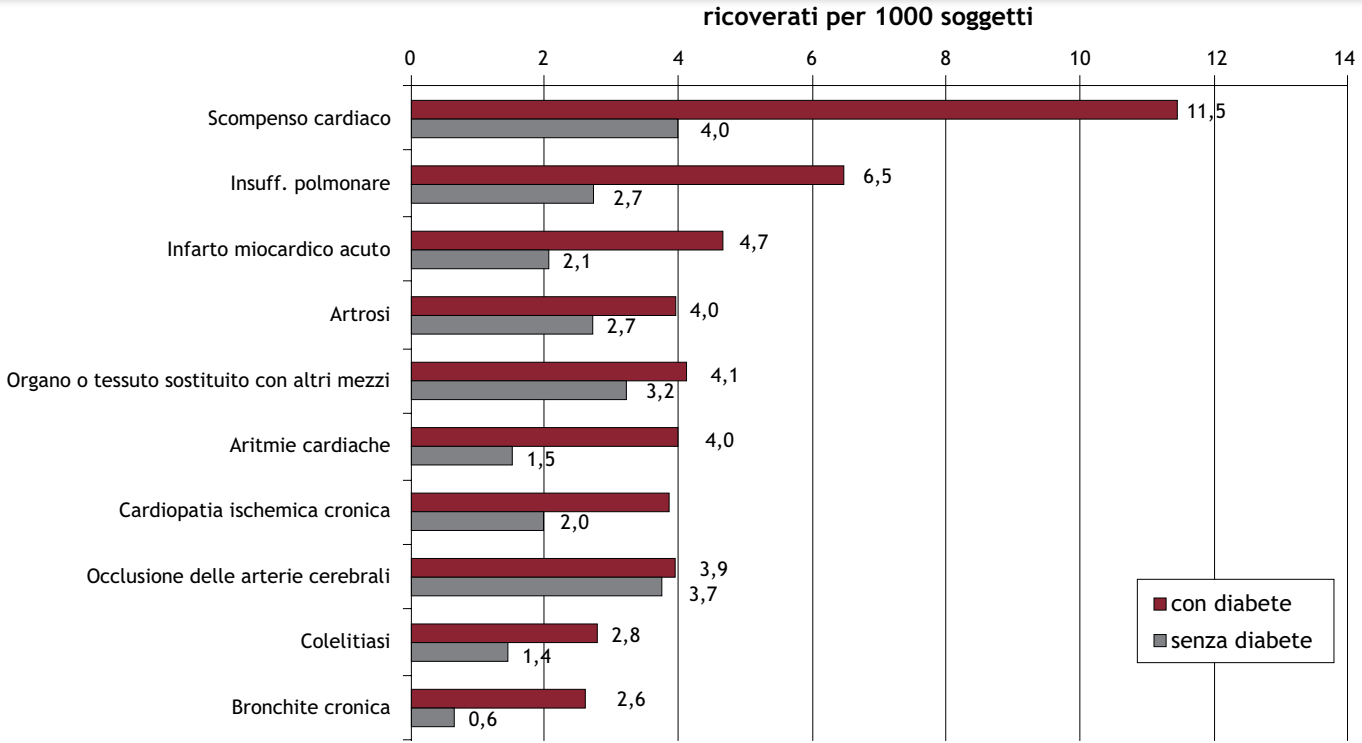
Diabetes Care 2017;40:1597–1605 | https://doi.org/10.2337/dc17-0697

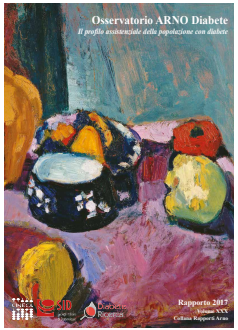
- 31 registri e 12 trials
- 381725 pz (26.1% diabetici: 99720 pz)
- Età media: 68,9 anni, 56 % M
- Follow up medio: 3 anni
- 199832 per Acuto HF (23.8% diabetici: 47495 pz)
- 181893 per Cronico HF (28.7% diabetici: 52225 pz)

END POINT	HR
Mortalità per tutte le cause	1.28 (CI 1.21 – 1.35)
Morte cardiovascolare	1.34 (CI 1.20 – 1.49)
Ospedalizzazione	1.35 (CI 1.20 – 1.50)
Morte per tutte le cause + ospedalizzazione	1.41 (CI 1.29 – 1.53)

- Il rischio di mortalità e ospedalizzazione era maggiore per pz. diabetici con scompenso cronico rispetto a quelli con scompenso acuto (maggiore morbilità)
- Nessuna differenza tra LVEF ≤ 35% vs > 35% di partenza

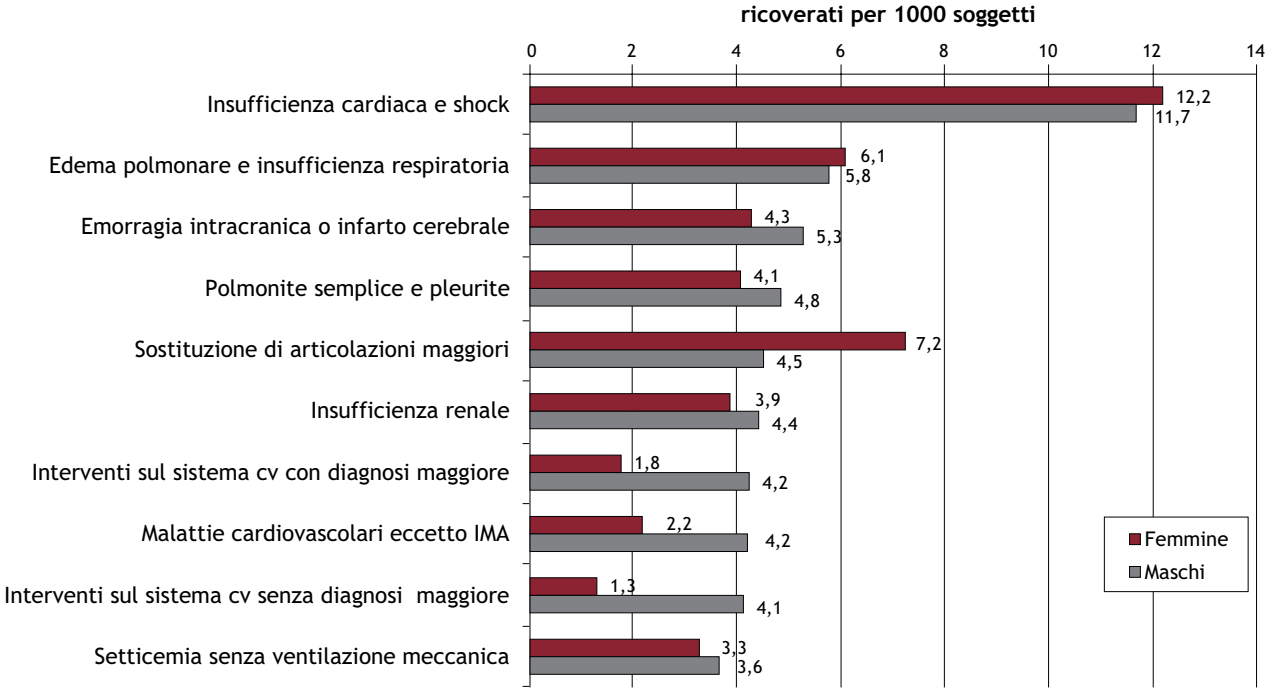
Osservatorio ARNO Diabete 2017

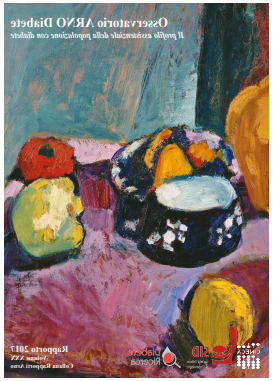




Prime 10 diagnosi principali in corso di ricovero ordinario in soggetti con e senza diabete

Osservatorio ARNO DIABETE 2017





10 DRG più frequenti nei diabetici ricoverati in regime ordinario in funzione del sesso

DIABETICI

Trial	Prevalence of HF at baseline
Glucose-lowering trials	
UKPDS 33[11]	NR (severe concurrent illness excluded)
ADVANCE[12,13]	NR
ACCORD[14]	4.3%
VADT[15]	NR
DPP4 inhibitor trials	
SAVOR-TIMI 53[16,17]	13%
TECOS[18]	18%
EXAMINE[19]	28%
SGLT2 inhibitor trials	
EMPA-REG OUTCOME[20]	10%
CANVAS[21]	14–15%
GLP-1 receptor agonist trials	
LEADER[22]	14%
ELIXA[23]	22%
EXSCEL[24]	16%

10 – 30 %

CARDIOPATICI

Trial	Prevalence of T2DM
Trials of HFrEF	
PARADIGM-HF[31]	35%
SHIFT[32]	30%
EchoCRT[33]	41%
HF-ACTION[34]	32%
SENIORS[35]	26%
SOLVD[36]	15%
MERIT-HF[37]	25%
CHARM-Added[38]	29%
DIG-REF[39]	28%
Trials of HFpEF	
I-Preserve[40]	27%
PEP-CHF[41]	21%
DIG-PEF[42]	29%
CHARM-Preserved[43]	28%
TOPCAT[44]	33%
Trials of acute HF	
EVEREST[45]	39%
TRUE-AHF[46]	39%
ASCEND-HF[47]	42.6%
RELAX-AHF-2[48]	47%

Trials: 30%

Ospedalizzati: 40 – 45%

ITALIAN CHAPTER

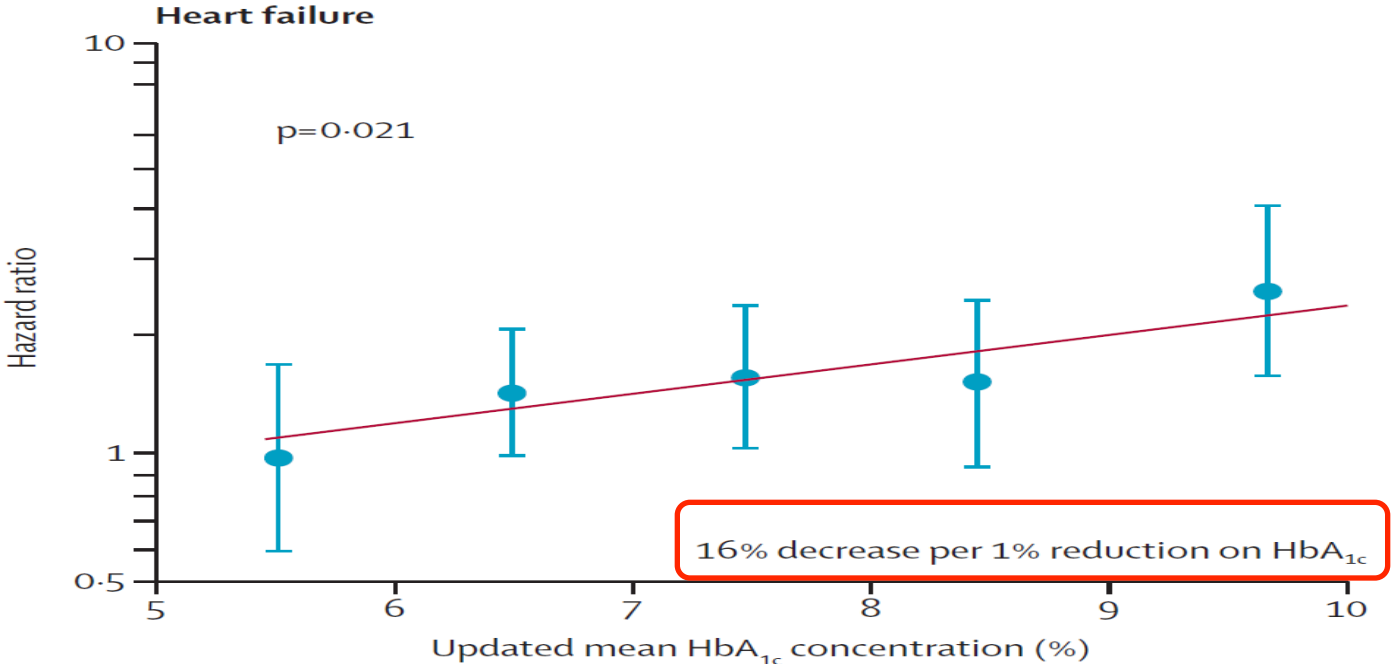
Prevalenza del diabete di tipo 2 in pazienti con scompenso cardiaco negli studi di popolazione

Study	Year of publication	Age (years)	Prevalence of T2DM in HF	Prevalence of T2DM without HF
England[25]	2001	>45	24%	3%
Rotterdam[26]	2001	55–94	18%	10%
Italy[27]	1997	>65	30%	13%
Reykjavik[9]	2005	33–84	12%	3%
Copenhagen[28]	2005	Mean 69	25%	NA
USA, Olmsted County[29]	2006	Mean 77	20%	NA

Trials randomizzati in pazienti con diabete di tipo 2 nei quali lo scompenso cardiaco è riportato come outcome

OUTCOME	UKPDS	ADVANCE	ACCORD	VADT	RENAAL	IDNT	ALTITUDE
Morte CV	-	5 %	2 %	4 %	11 %	8 %	5 %
IMA	15 %	6 %	5 %	8 %	8 %	7 %	3 %
Stroke	5 %	4 %	5 %	4 %	6 %	4 %	3 %
HF	**3 %**	**4 %**	**3 %**	**9 %**	**13 %**	**13 %**	**5 %**

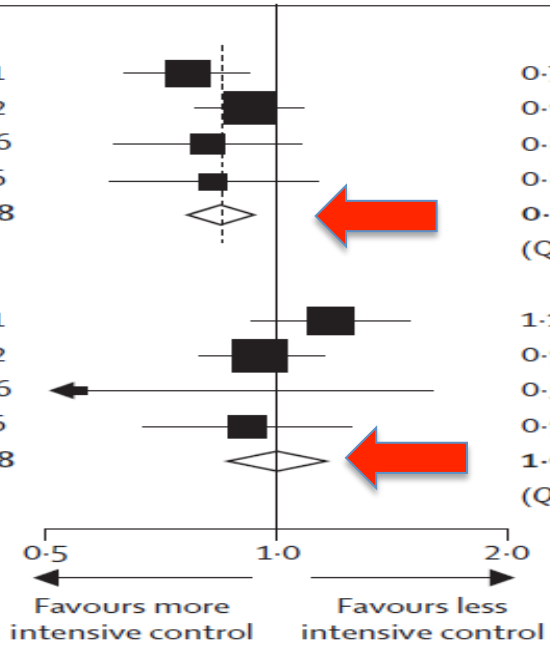
Rapporto tra controllo glicemico ed HF
Osservazione epidemiologica



Stratton (**UKPDS** 35) *BMJ* 2000; **321:** 405–12

Rapporto tra controllo glicemico ed HF nei Trial d'intervento

	Number of events (yearly event rate, %)		ΔHbA_{1c} (%)	HR (95% CI)
	More intensive	Less intensive		
Myocardial infarction				
ACCORD	198 (1·18)	245 (1·51)	−1·01	0·77 (0·64–0·93)
ADVANCE	310 (1·18)	337 (1·28)	−0·72	0·92 (0·79–1·07)
UKPDS	150 (1·20)	76 (1·40)	−0·66	0·81 (0·62–1·07)
VADT	72 (1·65)	87 (1·99)	−1·16	0·83 (0·61–1·13)
Overall	**730**	**745**	**−0·88**	**0·85 (0·76–0·94)**
				(Q=2·25, p=0·52, I^2=0·0%)
Admission to hospital/fatal heart failure				
ACCORD	152 (0·90)	124 (0·75)	−1·01	1·18 (0·93–1·49)
ADVANCE	220 (0·83)	231 (0·88)	−0·72	0·95 (0·79–1·14)
UKPDS	8 (0·06)	6 (0·11)	−0·66	0·55 (0·19–1·60)
VADT	79 (1·80)	85 (1·94)	−1·16	0·92 (0·68–1·25)
Overall	**459**	**446**	**−0·88**	**1·00 (0·86–1·16)**
				(Q=3·59, p=0·31, I^2=16·4%)



Diabetologia 2009; **52:** 2288–98.

European Journal of Heart Failure (2018) **20**, 853–872
doi:10.1002/ejhf.1170

HFA POSITION STATEMENT

Type 2 diabetes mellitus and heart failure: a position statement from the Heart Failure Association of the European Society of Cardiology

Petar M. Seferović[1]*, Mark C. Petrie[2], Gerasimos S. Filippatos[3], Stefan D. Anker[4], Giuseppe Rosano[5], Johann Bauersachs[6], Walter J. Paulus[7], Michel Komajda[8], Francesco Cosentino[9], Rudolf A. de Boer[10], Dimitrios Farmakis[2], Wolfram Doehner[11], Ekaterini Lambrinou[12], Yuri Lopatin[13], Massimo F. Piepoli[14], Michael J. Theodorakis[15], Henrik Wiggers[16], John Lekakis[2], Alexandre Mebazaa[17], Mamas A. Mamas[18], Carsten Tschöpe[19], Arno W. Hoes[20], Jelena P. Seferović[21], Jennifer Logue[22], Theresa McDonagh[23], Jillian P. Riley[24], Ivan Milinković[1], Marija Polovina[1], Dirk J. van Veldhuisen[25], Mitja Lainscak[26], Aldo P. Maggioni[27], Frank Ruschitzka[28], and John J.V. McMurray[29]

Diabete mellito ⇄ Scompenso cardiaco

Cause di scompenso nel diabete mellito →

Cardiopatia ischemica (CAD)
Cardiopatia ipertensiva
Cardiomiopatia Diabetica

Danno cardiaco che insorge nel paziente con diabete mellito indipendentemente da una coronaropatia, ipertensione arteriosa e patologia valvolare e che evolve verso lo scompenso cardiaco

Cardiomiopatia diabetica: concetto non nuovo

1954 Lunbaek K. "Diabetic angiopathy: a specific disease". Lancet 1954; 263:377-379: osservava che la disfunzione miocardica fosse una complicanza correlata al diabete e presente in 2/3 dei pazienti anziani diabetici; avanzò l'ipotesi che potesse esservi una cardiomiopatia correlata al diabete ***Diabetes mellitus-related cardiomyopathy***

1972 Rubler S. and Coll. "a new type of cardiomiopathy associated with diabetic glomerosclerosis". Am J Cardiol 1972; 30:595 - 602: descrisse 4 casi di pazienti diabetici complicati con nefropatia e deceduti per scompenso cardiaco, nei quali le coronarie erano indenni da malattia aterosclerotica, non vi era valvulopatia, anamnesi negativa per abuso alcolico; avanzò l'ipotesi di una miocardiopatia microangiopatica ***Cardiomiopathy dysfunction***

1977 Regan TJ and All. "Evidence for cardiomyopathy in familial diabetes mellitus". J Clin Invest. 1977; 60: 884-99

2012 L. Ernade, G. Deremeaux: ***Diabetic cardiomyopathy: myth or reality***

MECCANISMI NOTI CHE PROMUOVONO IL DANNO MIOCARDICO

- Glicazione
- Disfunzione endoteliale
- ***Alterazione del sistema nervoso autonomo***
- ***Attivazione del sistema renina-angiotensina***
- Stress ossidativo
- Disfunzione mitocondriale
- Infiammazione e cascata infiammatoria
- Insulino-resistenza
- Glucotossicità
- Lipotossicità

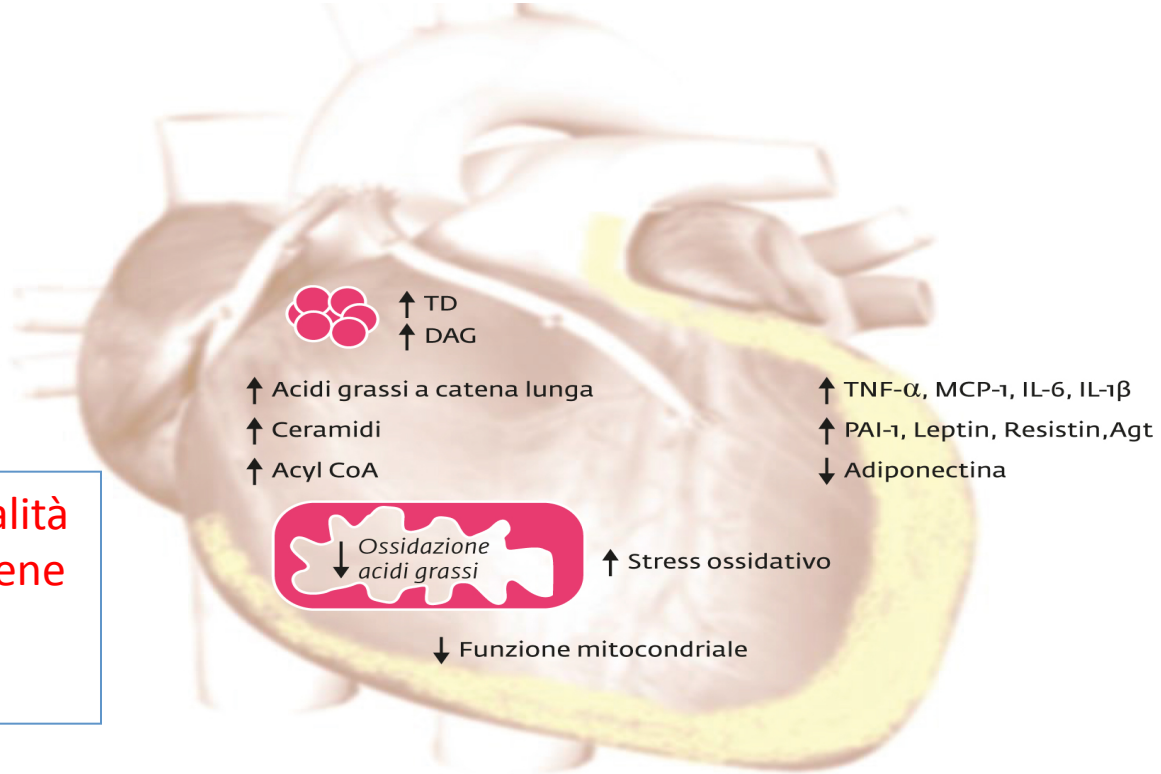
CARDIOMIOPATIA DIABETICA

DUE ATTORI PRINCIPALI:

GRASSO: epicardico, extrapericardico, intramiocardico

MUSCOLO CARDIACO

LIPOTOSSICITA'



In condizioni di normalità 60 – 90% di ATP proviene da FFA e 10 – 40% dal glucosio

La cardiomiopatia diabetica. Il Diabete Vol. 27 n° 2 giugno 2015

- ACIDI GRASSI NON ESTERIFICATI
- IPERGLICEMIA
- IPERINSULINEMIA

Disfunzione dei cardiomiociti e delle CSC

Apoptosi
Autofagia
Stress del reticolo endoplasmatico
microRNA
Meccanismi epigenetici
Attivazione di fattori di trascrizione
Modifiche post-traslazionali

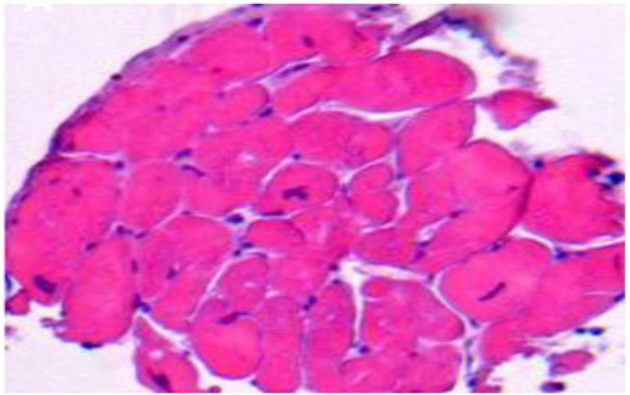
Alterazione dei processi omeostatici

Danni strutturali e funzionali a carico dei cardiomiociti e delle cellule staminali

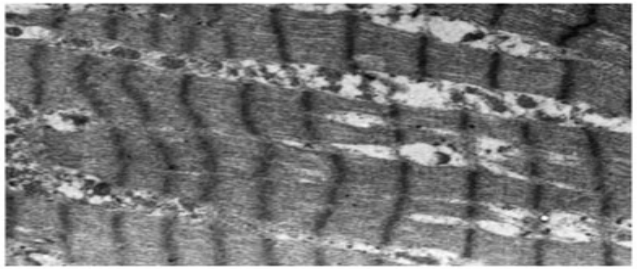
Ipertrofia dei cardiomiociti
Fibrosi miocardica

La cardiomiopatia diabetica. Il Diabete Vol. 27 n° 2 giugno 2015

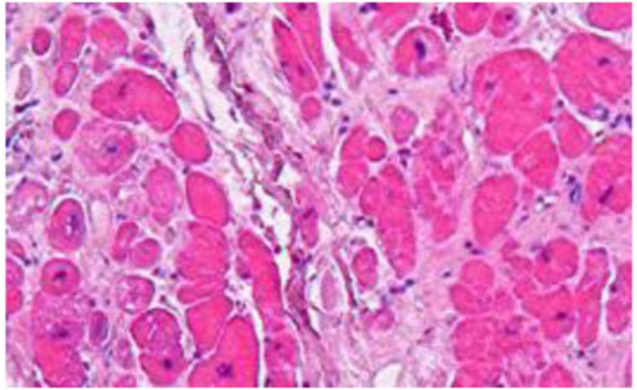
Restrictive/HFPEF phenotype



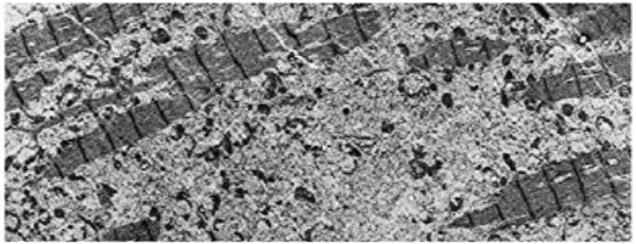
HFpEF



Dilated/HFREF phenotype



HFrEF



Clinical diabetic cardiomyopathy: a two-faced disease with restrictive and dilated phenotypes

European Heart Journal (2015) **36**, 1718–1727
doi:10.1093/eurheartj/ehv134

Quando dobbiamo pensare a una cardiomiopatia diabetica ?

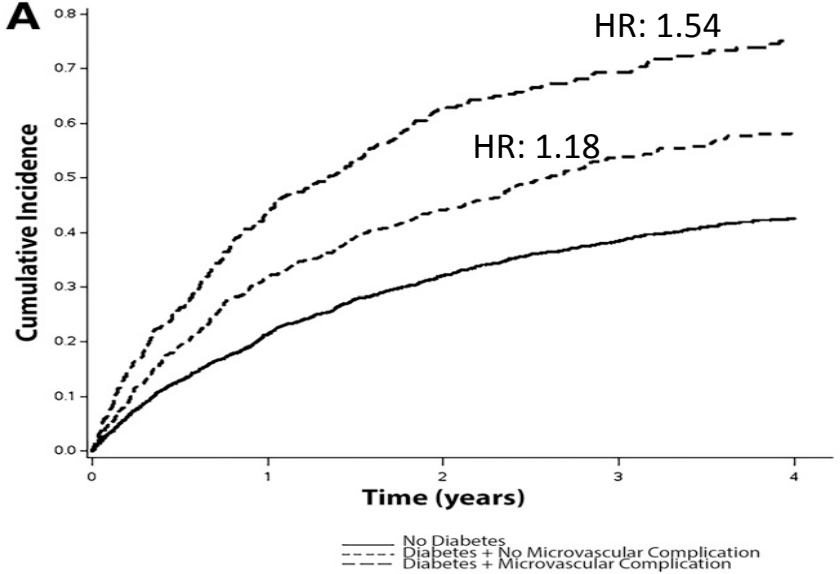
Quale è il paziente diabetico che può rappresentare il fenotipo più a rischio di cardiomiopatia diabetica ?

The Prognostic Significance of Diabetes and Microvascular Complications in Patients With Heart Failure With Preserved Ejection Fraction

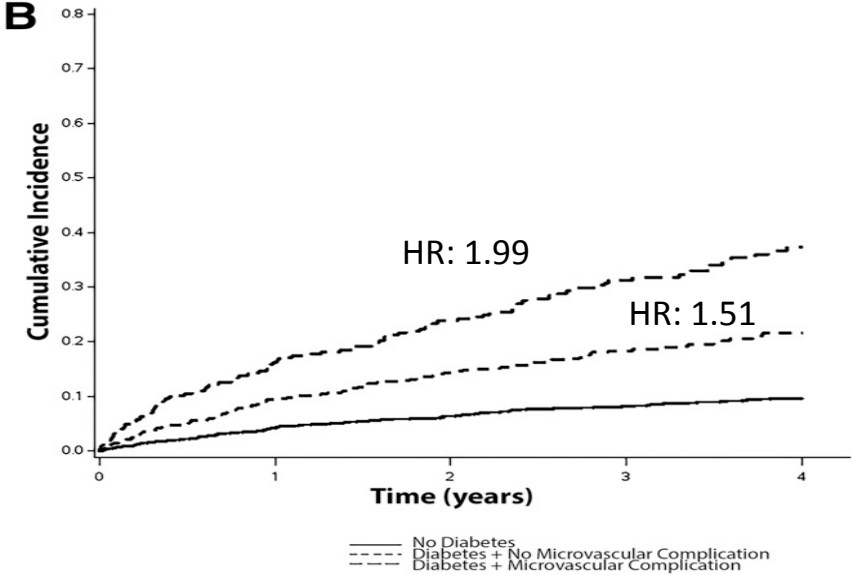
Diabetes Care 2018;41:150–155 | https://doi.org/10.2337/dc17-0755

Trial TOPCAT

3.385 pz di cui 32% diabetici e di questi il 32% aveva almeno una complicanza microangiopatica



Ospedalizzazione per tutte le cause

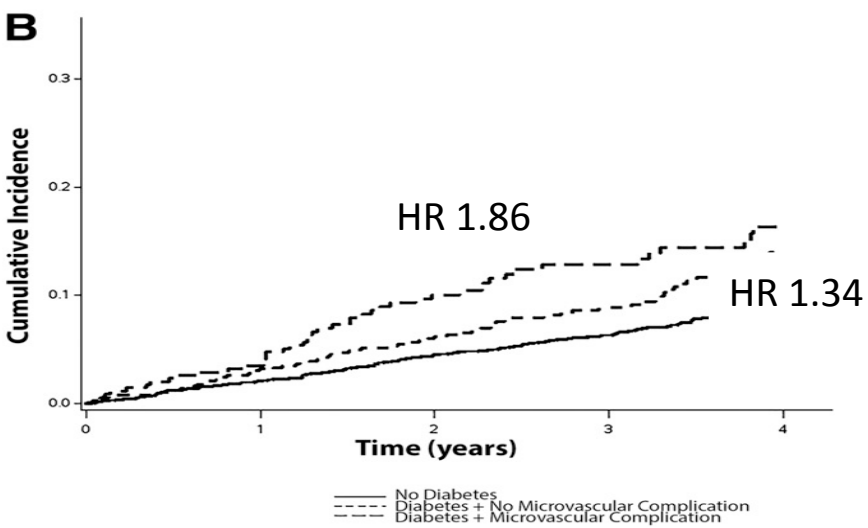


Ospedalizzazione per scompenso cardiaco

The Prognostic Significance of Diabetes and Microvascular Complications in Patients With Heart Failure With Preserved Ejection Fraction

Diabetes Care 2018;41:150–155 | https://doi.org/10.2337/dc17-0755

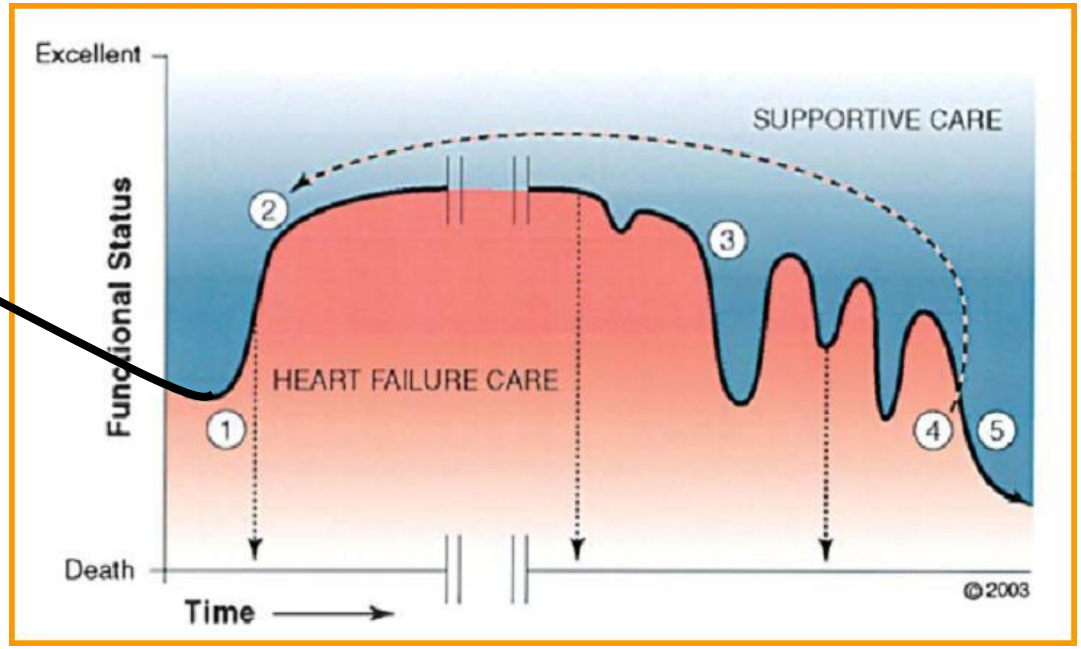
Morte per tutte le cause



Morte cardiovascolare

Miocardiopatia diabetica e scompenso cardiaco: Storia naturale

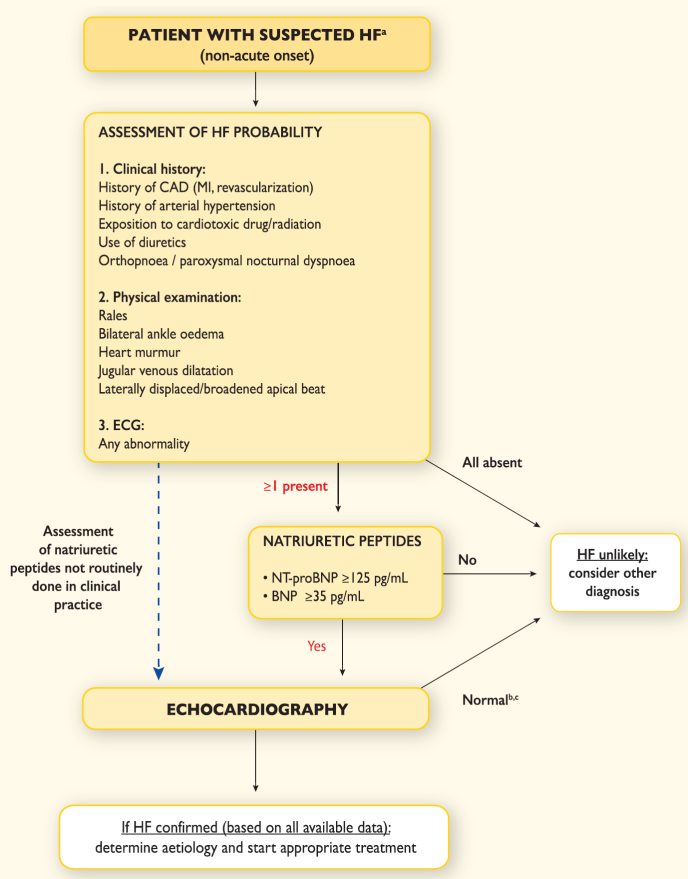
Diagnosi di scompenso

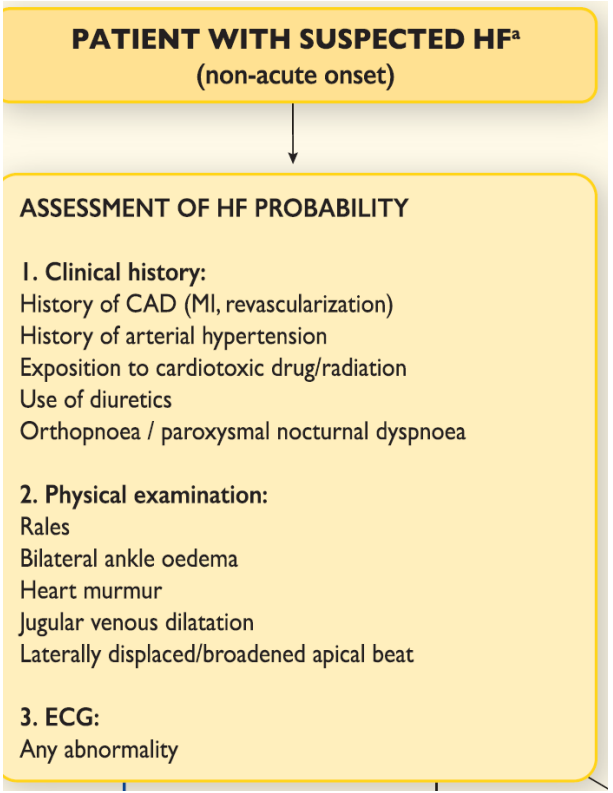


A **B** → **C** → **D**

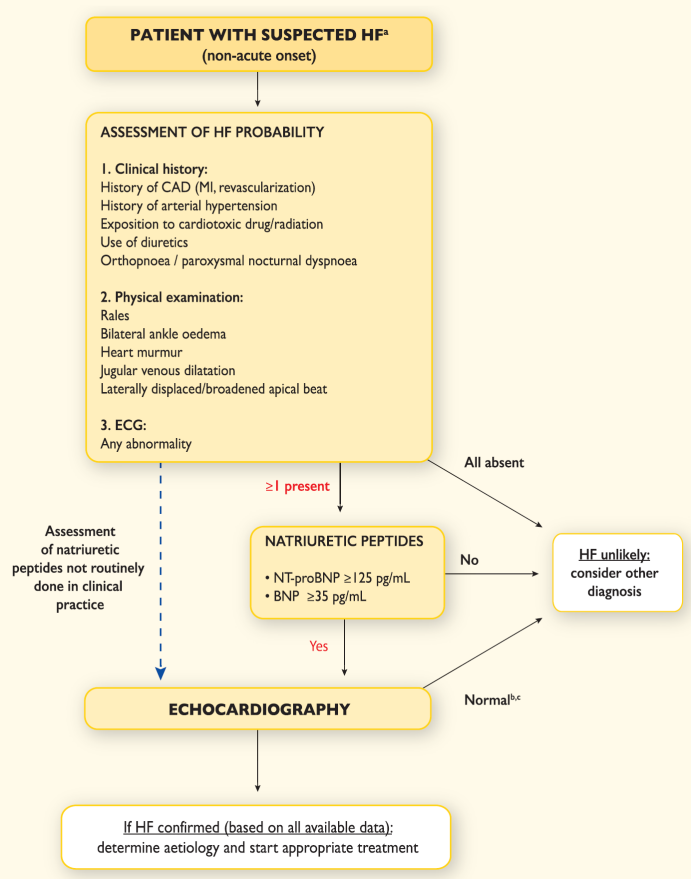
Goodlin, Journal of Cardiac Failure 2004

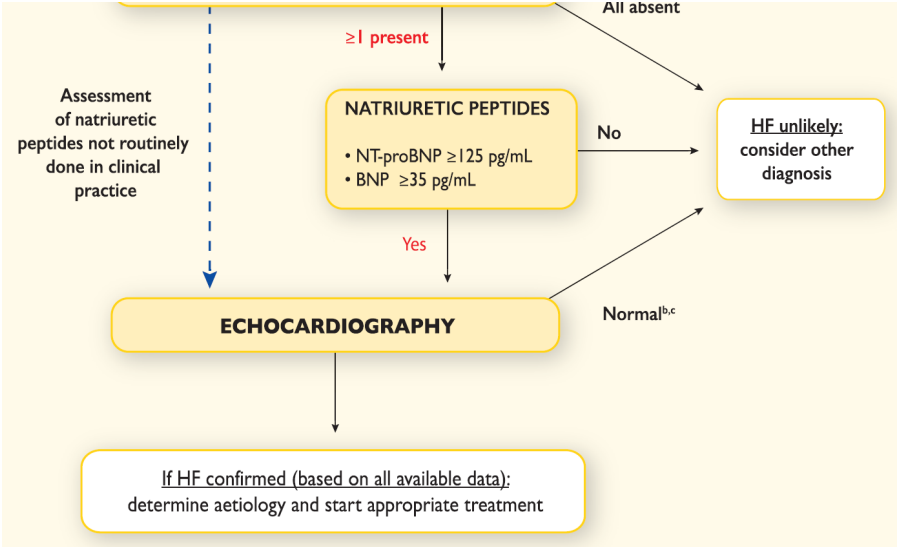
Miocardiopatia diabetica e scompenso cardiaco: aspetti diagnostici



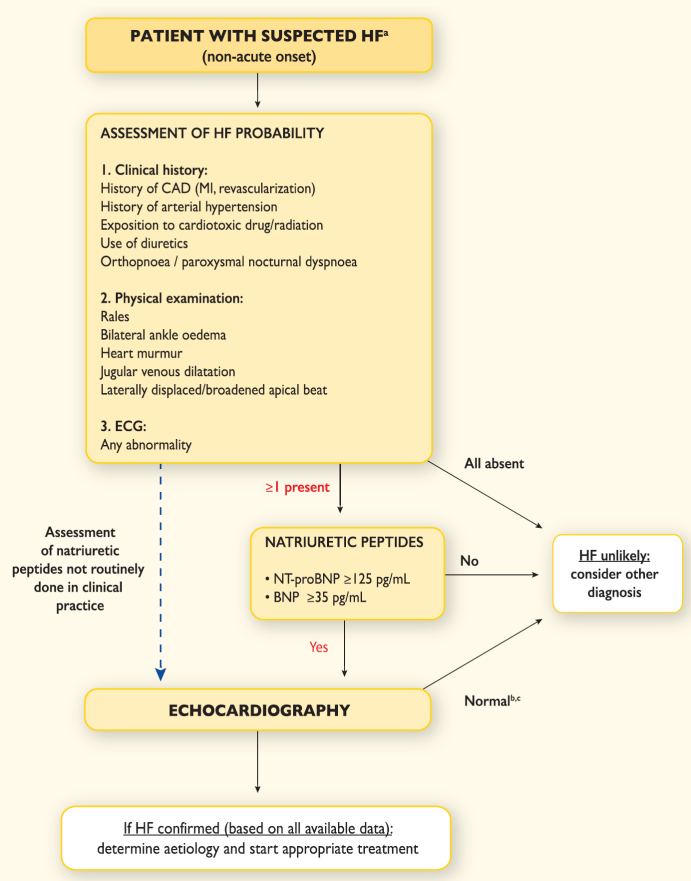


Miocardiopatia diabetica e scompenso cardiaco: aspetti diagnostici





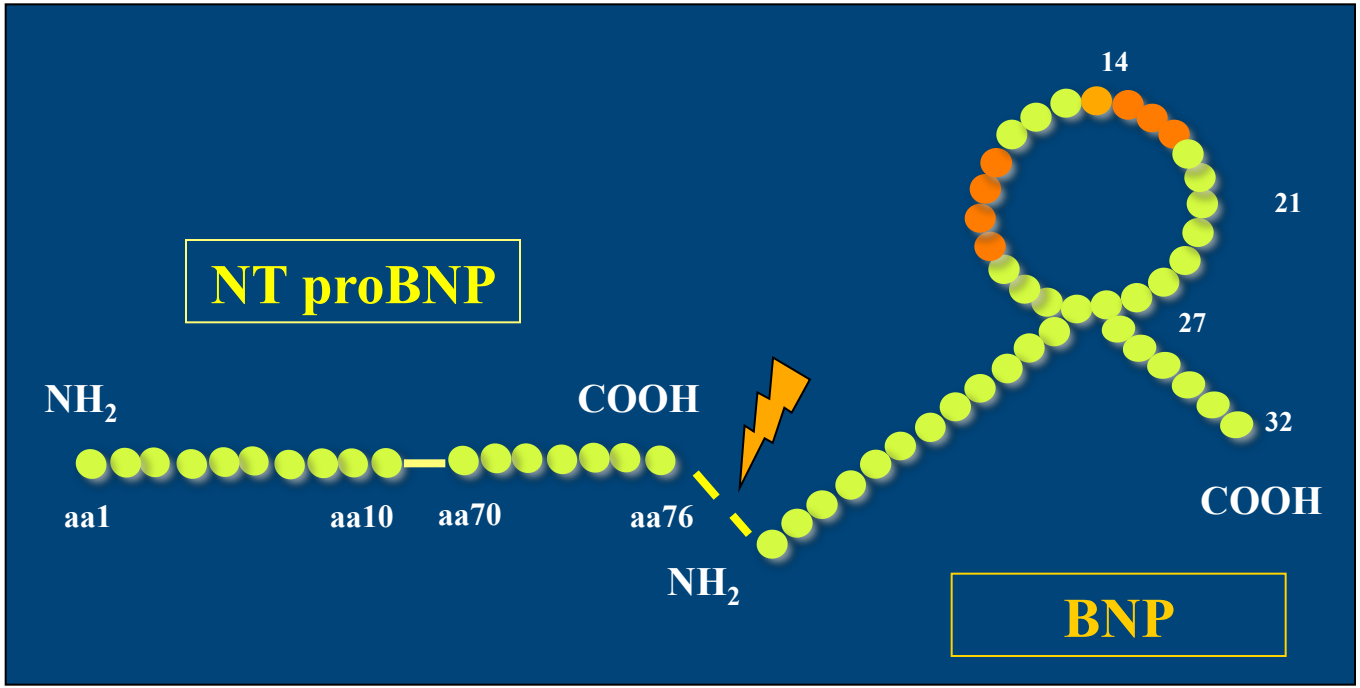
Miocardiopatia diabetica e scompenso cardiaco: aspetti diagnostici



NATRIURETIC PEPTIDES

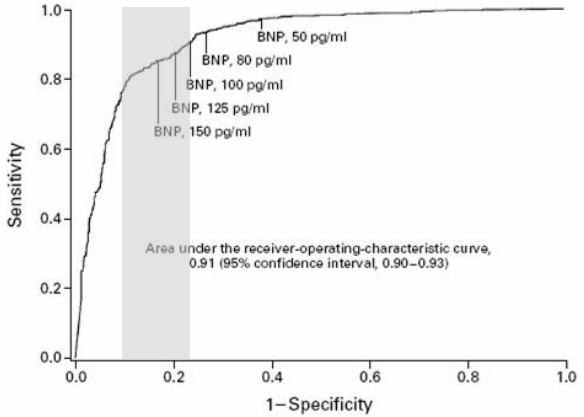
- NT-proBNP ≥125 pg/mL
- BNP ≥35 pg/mL

Peptide natriuretico cerebrale (BNP)



Miocardiopatia diabetica e scompenso cardiaco: aspetti diagnostici

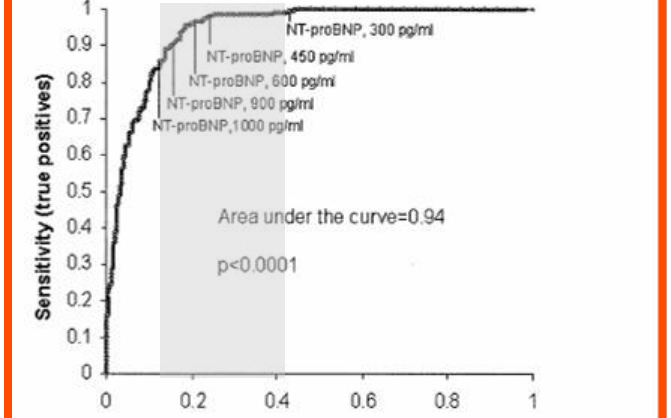
BNP



BNP pg/ml	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy
	(95 percent confidence interval)				
50	97 (96–98)	62 (59–66)	71 (68–74)	96 (94–97)	79
80	93 (91–95)	74 (70–77)	77 (75–80)	92 (89–94)	83
100	90 (88–92)	76 (73–79)	79 (76–81)	89 (87–91)	83
125	87 (85–90)	79 (76–82)	80 (78–83)	87 (84–89)	83
150	85 (82–88)	83 (80–85)	83 (80–85)	85 (83–88)	84

Maisel AS N Eng J Med 2002;347:161

NTproBNP



Cut Point	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy
300 pg/ml	99%	68%	82%	99%	79%
450 pg/ml	98%	76%	88%	99%	83%
600 pg/ml	96%	81%	73%	97%	86%
900 pg/ml	90%	85%	76%	94%	87%
1000 pg/ml	87%	88%	78%	91%	87%

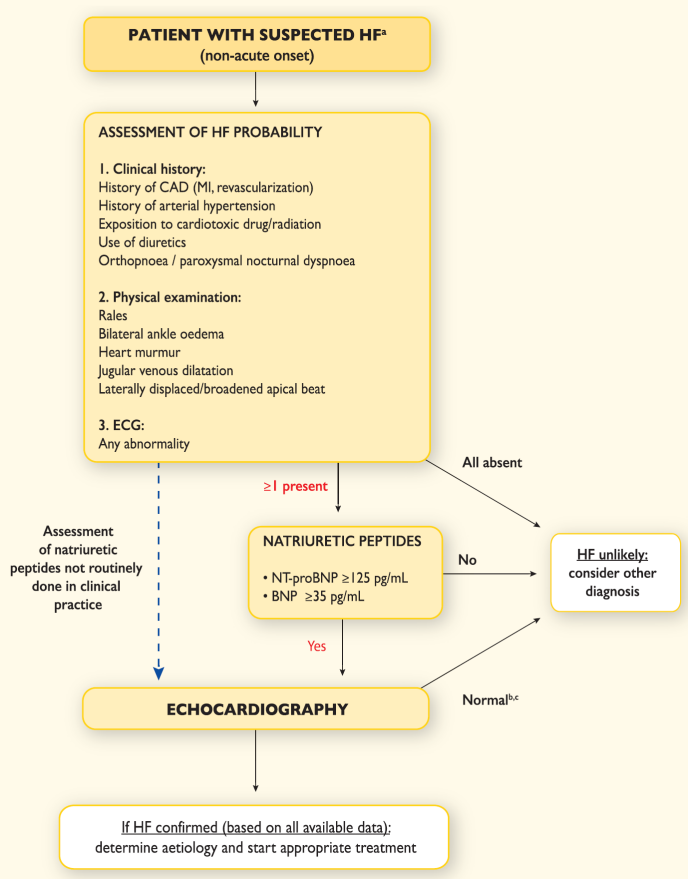
Jannuzzi JL Am J Cardiol 2005;95:948

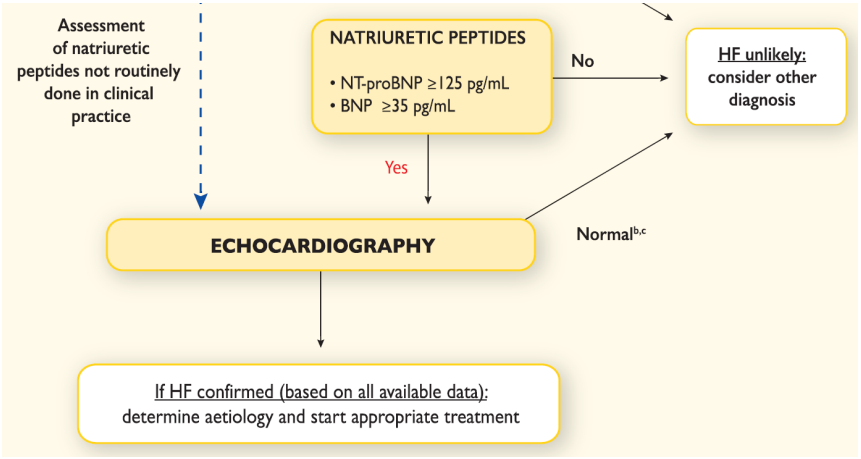
Miocardiopatia diabetica e scompenso cardiaco: aspetti diagnostici

Characteristic	BNP	NT-proBNP
Components	BNP molecule	NT fragment (1–76)
Molecular Weight	4 kilodaltons	8.5 kilodaltons
Genesis	Cleavage from proBNP	Cleavage from proBNP
Half-life	20 minutes	120 minutes
Clearance Mechanism	Neutral endopeptidase Clearance receptors	Renal clearance
Increases with Normal Aging	+	++++
Correlation GFR	–0.20	–0.60
Negative correlation BMI	+++	++
Approved cutoff(s) for CHF Diagnosis	100 pg/mL	Age < 75: 125 pg/mL Age ≥ 75: 450 pg/mL

Modif da McCullough PA, Rev Cardiovasc Med. 2003.

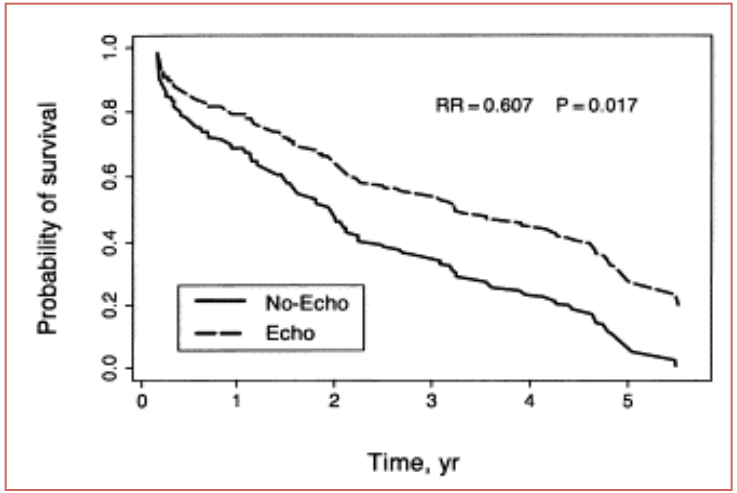
Miocardiopatia diabetica e scompenso cardiaco: aspetti diagnostici





Miocardiopatia diabetica e scompenso cardiaco: aspetti diagnostici

Ruolo dell'ecocardiogramma



Senni M. et al. J Am Coll Cardiol. 1999;33:164-70.

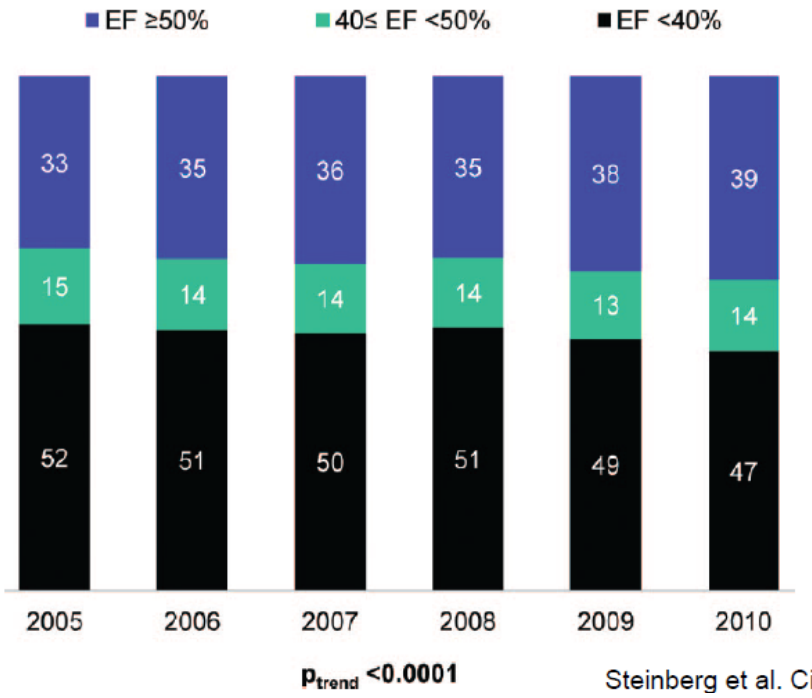
- Dimensioni ventricolo sinistro
- Funzione sisto-diastolica
- Massa ventricolo sinistro
- Dimensioni atriali
- Dimensione e funzione del ventricolo destro
- Funzione valvolare
- Patologia pericardica
- Pressione polmonare
- Trombi
- Vitalità
- Difetti settali

Miocardiopatia diabetica e scompenso cardiaco: aspetti diagnostici

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.).

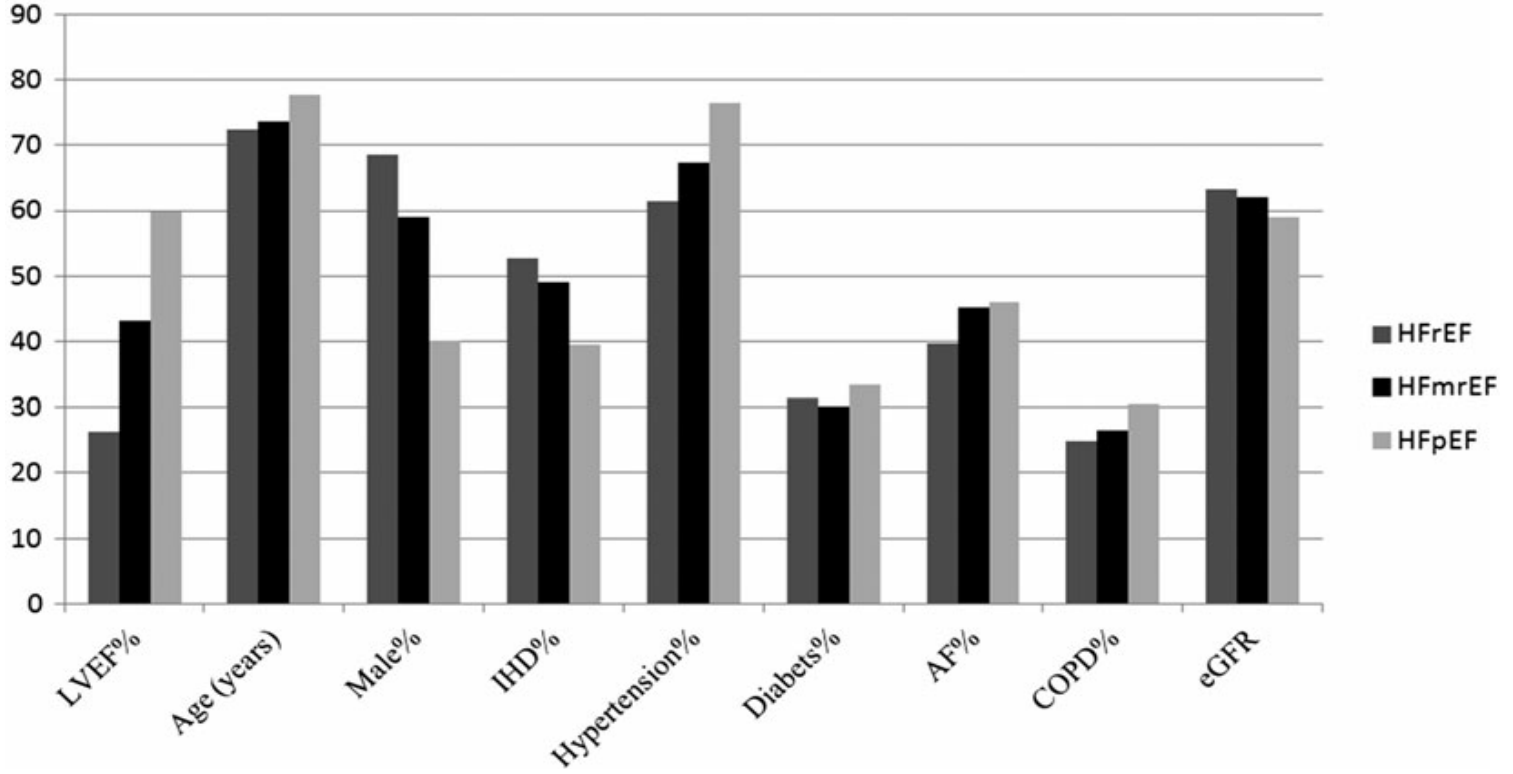
ESC Guidelines 2016

Miocardiopatia diabetica e scompenso cardiaco: aspetti epidemiologici



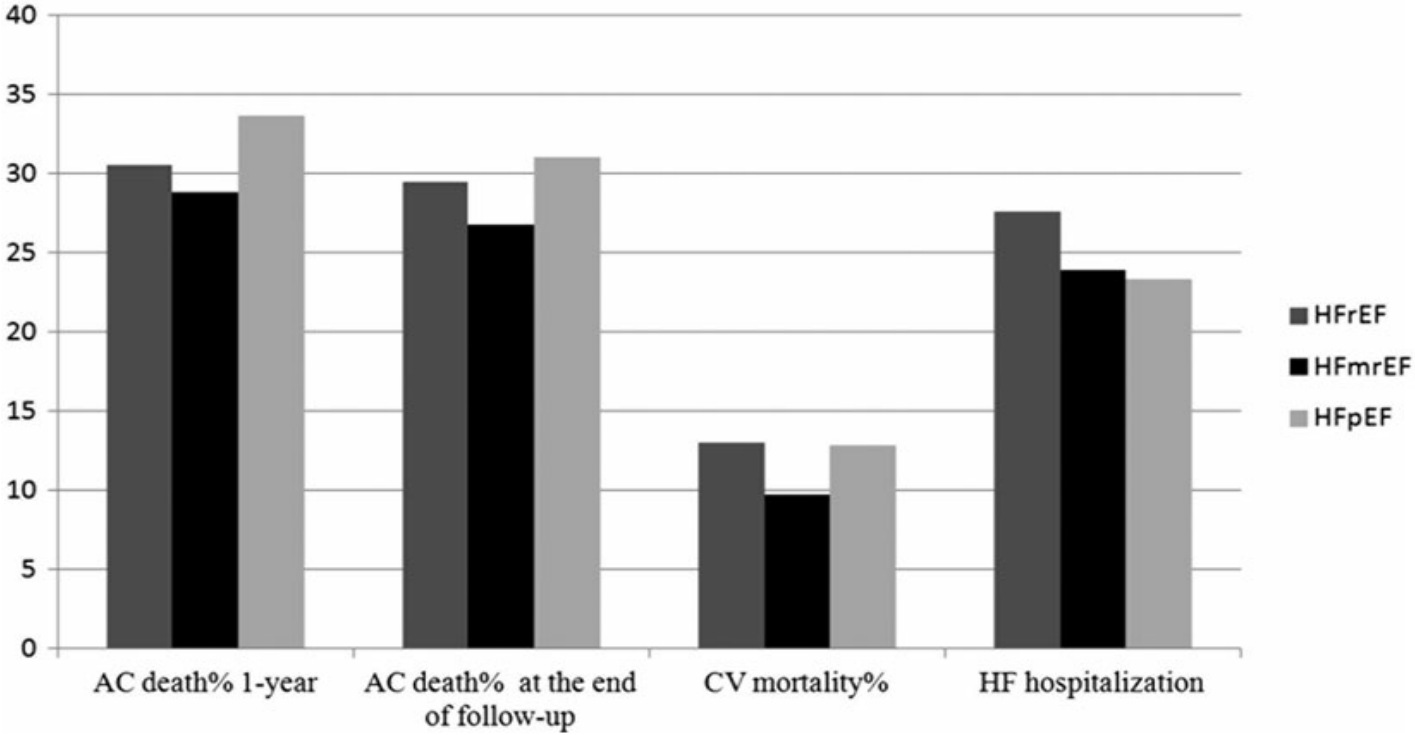
Steinberg et al. Circulation 2012

Miocardiopatia diabetica e scompenso cardiaco: aspetti epidemiologici



Lauritsen et al. ESC Heart Failure 2018; 5: 685–694

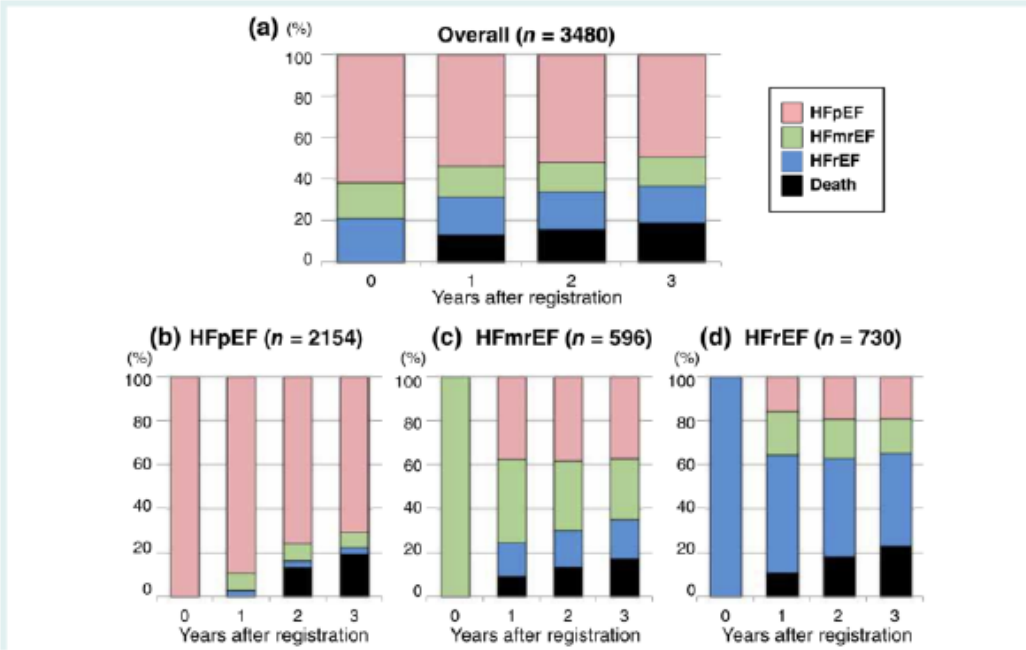
Miocardiopatia diabetica e scompenso cardiaco: aspetti epidemiologici



Lauritsen et al. ESC Heart Failure 2018; 5: 685–694

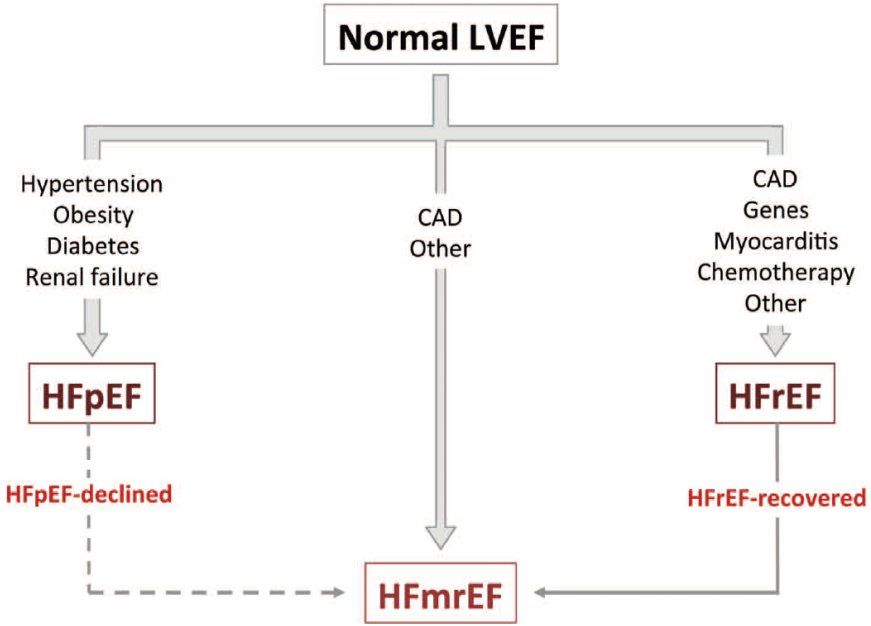
Miocardiopatia diabetica e scompenso cardiaco: aspetti diagnostici

Frazione d'eiezione del ventricolo sinistro



Tsuji K Eur J Heart Fail 2017

Miocardiopatia diabetica e scompenso cardiaco: aspetti diagnostici



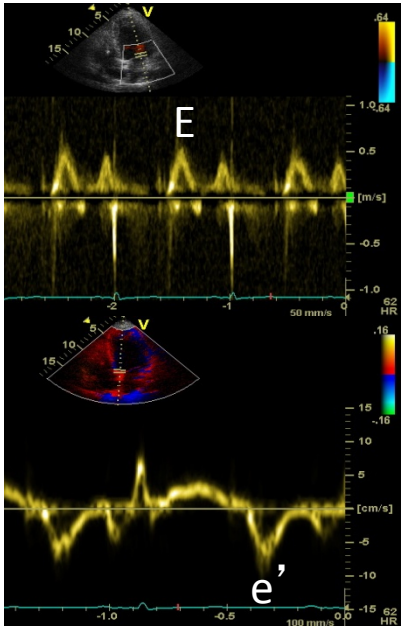
Bayés-Genìs Eur J Heart Fail 2017

Miocardiopatia diabetica e scompenso cardiaco: aspetti diagnostici

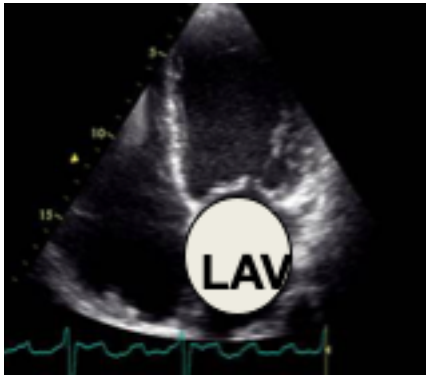
Type of HF		HFrEF	HFmrEF	PFpEF
CRITERIA	1	Symptoms ± Signs	Symptoms ± Signs	Symptoms ± Signs
	2	LVEF <40%	LVEF 40-49%	LVEF ≥50%
	3	–	1. Elevated levels of natriuretic peptides. 2. At least one additional criterion: a. relevant structural heart disease (LVF and/or LAE); b. diastolic dysfunction (for details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

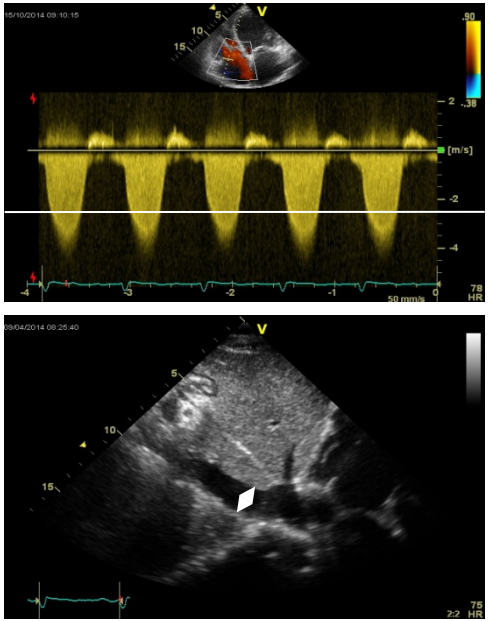
ESC Guidelines 2016

Miocardiopatia diabetica e scompenso cardiaco: aspetti diagnostici



Studio funzione diastolica





- Rapporto E/e'
- Volume atriale sinistro
- Massa ventricolare sinistra
- Pressioni polmonari

Miocardiopatia diabetica e scompenso cardiaco: aspetti diagnostici

- Key structural alterations are
  - A left atrial volume index (LAVI) >34 mL/m2
  - a left ventricular mass index (LVMI) ≥115 g/m2 for males and ≥95 g/m2 for females.
- Key functional alterations are
  - an E/e′ ≥13
  - mean e' septal and lateral wall <9 cm/s.
- Other (indirect) echocardiographically derived measurements are longitudinal strain or tricuspid regurgitation velocity (TRV).

Miocardiopatia diabetica e scompenso cardiaco: aspetti diagnostici

Indicazioni alla coronarografia

European Heart Journal (2013) **34**, 2949–3003
doi:10.1093/eurheartj/eht296

ESC GUIDELINES

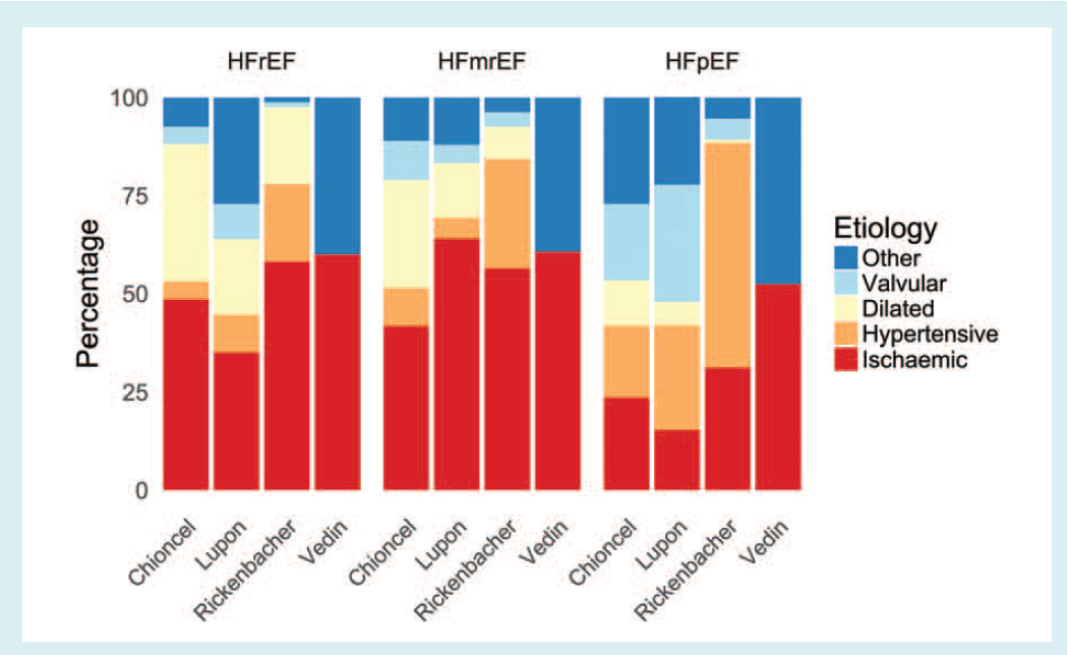
2013 ESC guidelines on the management of stable coronary artery disease

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

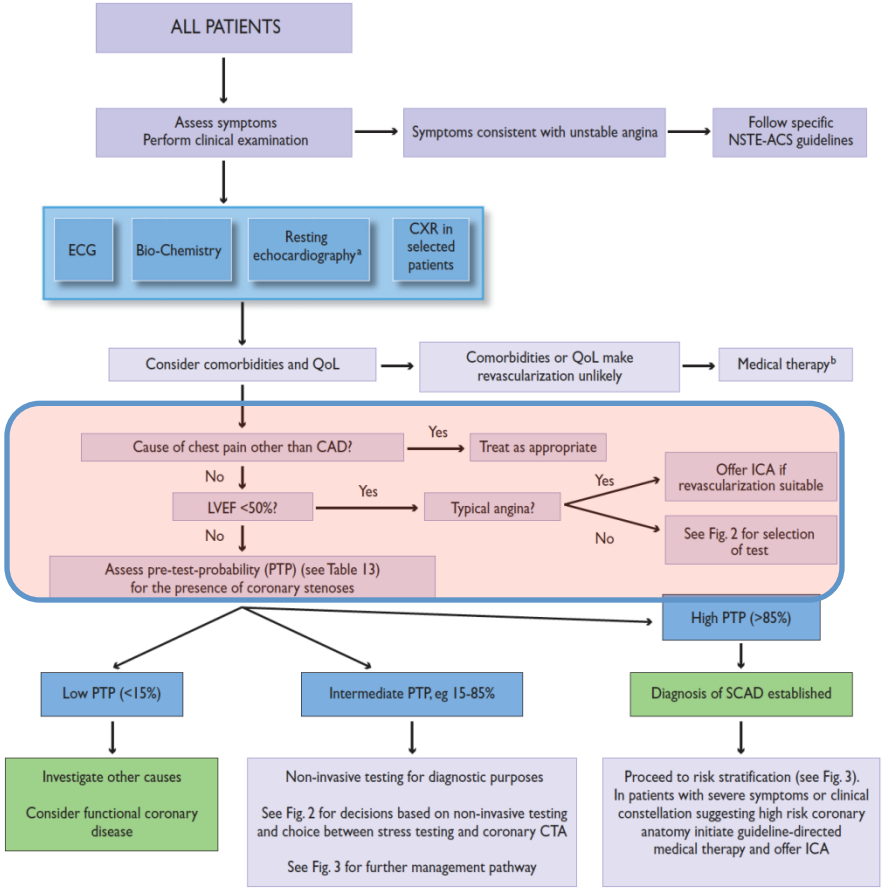
Recommendations	Class [a]	Level [b]
Invasive coronary angiography is recommended in patients with HF and angina pectoris recalcitrant to pharmacological therapy or symptomatic ventricular arrhythmias or aborted cardiac arrest (who are considered suitable for potential coronary revascularization) in order to establish the diagnosis of CAD and its severity.	I	C
Invasive coronary angiography should be considered in patients with HF and intermediate to high pre-test probability of CAD and the presence of ischaemia in non-invasive stress tests (who are considered suitable for potential coronary revascularization) in order to establish the diagnosis of CAD and its severity.	IIa	C

ESC GUIDELINES 2016

Miocardiopatia diabetica e scompenso cardiaco: aspetti epidemiologici



Nauta et al. Eur J Heart Fail. doi:10.1002/ejhf.1058



ESC GUIDELINES 2013

Indicazioni alla coronarografia

Table 4 Traditional clinical classification of chest pain

Typical angina (definite)	Meets all three of the following characteristics: • substernal chest discomfort of characteristic quality and duration; • provoked by exertion or emotional stress; • relieved by rest and/or nitrates within minutes.
Atypical angina (probable)	Meets two of these characteristics.
Non-anginal chest pain	Lacks or meets only one or none of the characteristics.

	Typical angina		Atypical angina		Non-anginal pain	
Age	Men	Women	Men	Women	Men	Women
30–39	59	28	29	10	18	5
40–49	69	37	38	14	25	8
50–59	77	47	49	20	34	12
60–69	84	58	59	28	44	17
70–79	89	68	69	37	54	24
>80	93	76	78	47	65	32

Shortness of breath may be the sole symptom of SCAD and it may be difficult to differentiate this from shortness of breath caused by bronchopulmonary disease.

ESC GUIDELINES 2013

TERAPIA

Dell'Endocrinologo

- Insulina Glargine 10 U serale (secondo schema treat to target)
- Metformina 1000 mg a colazione + 1000 mg a cena

Del Cardiologo

- Ramipril 5 mg, ½ cp x 2 al dì
- Lasix 1 cp al dì
- Bisoprololo 1.25 mg, 1 cp x 2 al dì
- Cardioaspirin 100 mg, 1 cp al dì
- Atorvastatina 20 mg, 1 cp al dì

Siete d'accordo con la terapia del cardiologo ?
Siete d'accordo con la terapia dell'endocrinologo ?

Comparative Safety and Effectiveness of Metformin in Patients With Diabetes Mellitus and Heart Failure

Systematic Review of Observational Studies Involving 34 000 Patients

(*Circ Heart Fail.* 2013;6:395-402.)

METFORMINA VS CONTROLLI	
	RR
Mortalità	0.80 (0.74 – 0.87)
HFrEF	0.91 (0.72 – 1.14)
HF + CKD	0.81 (0.64 – 1.02)
Ospedalizzazione	0.93 (0.89 – 0.98)
nessun rischio di acidosi lattica	

Diabetes			
Metformin should be considered as a first-line treatment of glycaemic control in patients with diabetes and HF, unless contra-indicated.	IIa	C	440 ,441

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

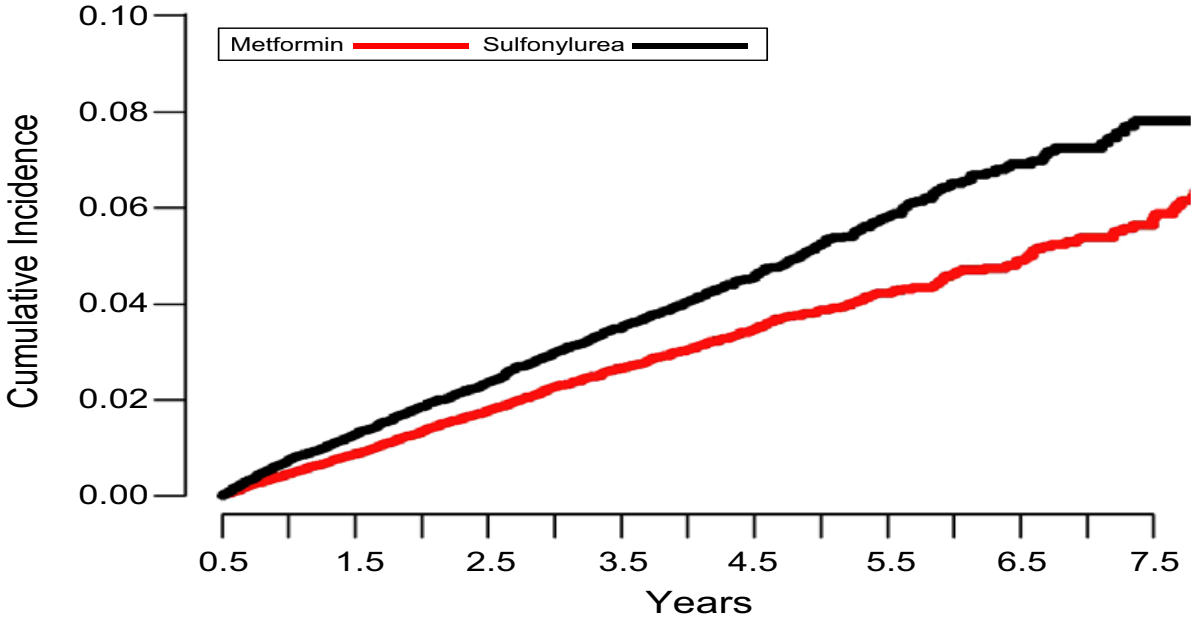
METFORMINA

Effects of acarbose on cardiovascular and diabetes outcomes in patients with coronary heart disease and impaired glucose tolerance (ACE): a randomised, double-blind, placebo-controlled trial

Lancet Diabetes Endocrinol 2017; 5: 877–86

	Acarbose group (n=3272)		Placebo group (n=3250)		Hazard ratio (95% CI)	p value
	n (%)	Number per 100 person-years	n (%)	Number per 100 person-years		
Primary outcome						
Five-point MACE*	470 (14·4%)	3·33	479 (14·7%)	3·41	0·98 (0·86–1·11)	0·73
Secondary outcomes						
Three-point MACE†	285 (8·7%)	1·93	299 (9·2%)	2·04	0·95 (0·81–1·11)	0·51
Death from any cause	216 (6·6%)	1·42	219 (6·7%)	1·45	0·98 (0·81–1·19)	0·85
Cardiovascular death	145 (4·4%)	0·96	163 (5·0%)	1·03	0·89 (0·71–1·11)	0·29
Fatal or non-fatal myocardial infarction	122 (3·7%)	0·82	108 (3·3%)	0·73	1·12 (0·87–1·46)	0·38
Fatal or non-fatal stroke	75 (2·3%)	0·50	77 (2·4%)	0·52	0·97 (0·70–1·33)	0·83
Hospital admission for unstable angina	174 (5·3%)	1·19	170 (5·2%)	1·17	1·02 (0·82–1·26)	0·87
Hospital admission for heart failure	65 (2·0%)	0·43	73 (2·2%)	0·49	0·89 (0·63–1·24)	0·48
Developed diabetes	436 (13·3%)	3·17	513 (15·8%)	3·84	0·82 (0·71–0·94)‡	0·005
Developed impaired kidney function§	41 (1·3%)	0·33	50 (1·5%)	0·41	0·81 (0·54–1·23)‡	0·33

ACARBOSIO



	6 months	1.5 years	2.5 years	3.5 years	4.5 years	5.5 years	6.5 years	7.5 years
Metformin								
N at Risk	65986	35388	22232	14861	9863	5514	2736	1187
N events		436	256	164	103	60	28	17
Sulfonylurea								
N at Risk	65986	31225	17633	10529	6230	3264	1531	665
N events		613	262	164	91	61	28	10

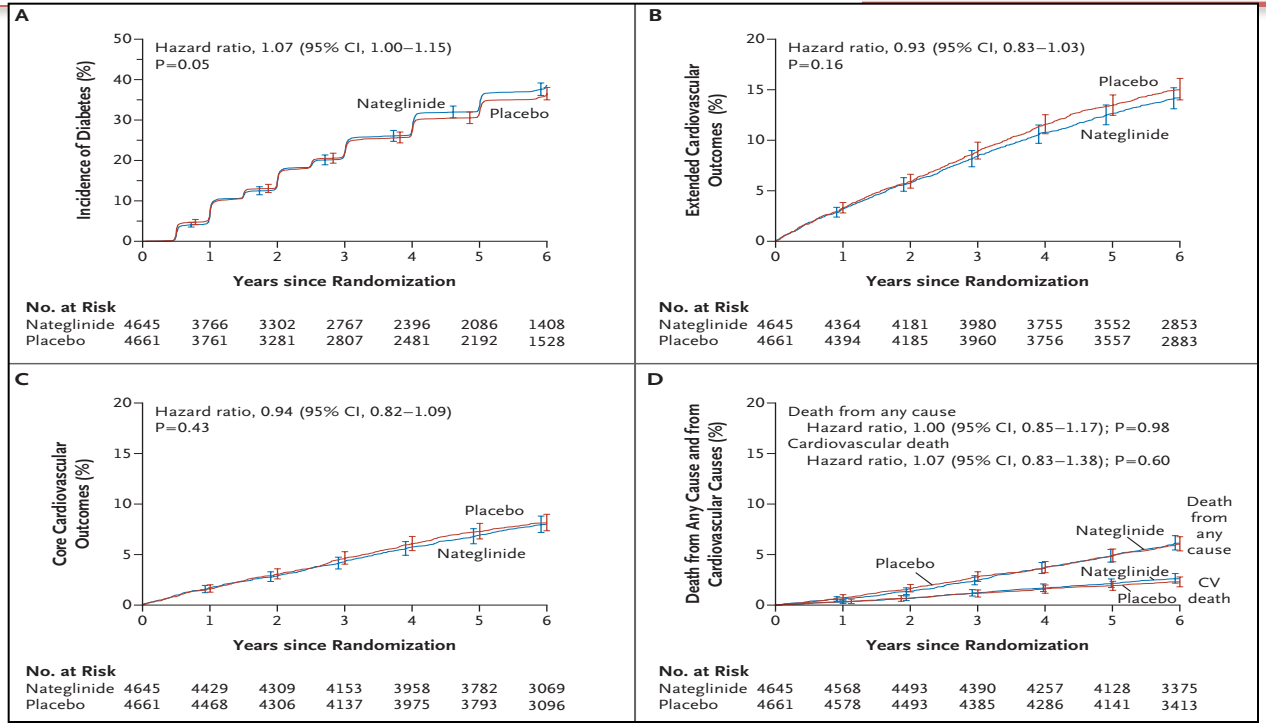
Cumulative incidence of heart failure hospitalization or cardiovascular death over time

Effect of Nateglinide on the Incidence of Diabetes and Cardiovascular Events

The NAVIGATOR Study Group*

The NEW ENGLAND JOURNAL of MEDICINE
N ENGL J MED 362;2 NEJM.ORG APRIL 22, 2010

ITALIAN CHAPTER



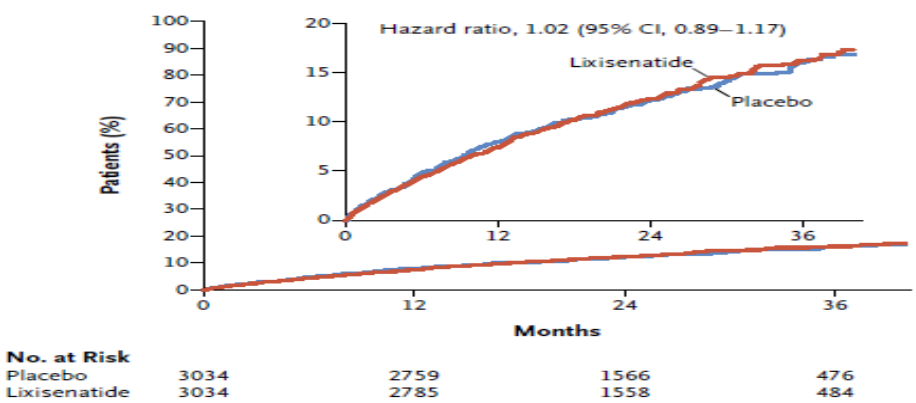
Rischio di ospedalizzazione per scompenso cardiaco Nateglinide vs placebo: 3.1 vs 3.6 eventi per 100 pazienti anno

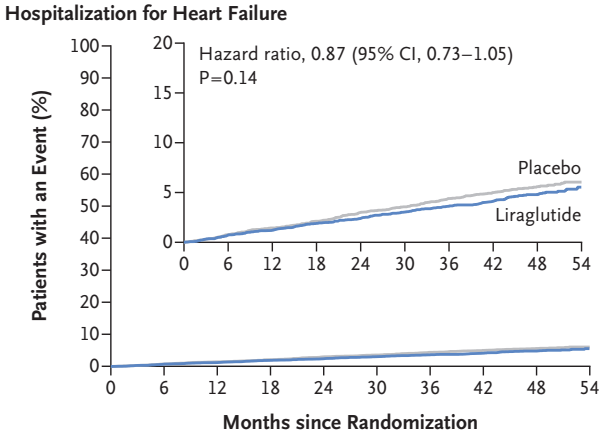
TIAZOLIDINEDIONI

PROACTIVE: pioglitazone comporta un maggior numero di ospedalizzazioni per HF, 6% vs 4% nell'arco di un follow up di 3 anni; nessuna differenza di mortalità per HF, 1% in entrambi i bracci
IRIS: pazienti insulinoresistenti con pregresso stroke, non diabetici, pioglitazone vs placebo HF 3.8% vs 3.7% e ospedalizzazioni per HF 2.6% vs 2.2%

RECORD: rosiglitazone vs metformina e sulfonilurea comporta un maggior rischio di ospedalizzazioni per HF o morti correlate al HF (2.7% vs 1.3%, HR 2.10, CI 1.35 – 3.27)
DREAM: rosiglitazone vs placebo in pazienti in prevenzione primaria con alterata tolleranza al glucosio HF 0.5% vs 0.1% (HR 7.03, CI 1.6 -30.09)

- Questi farmaci non sono raccomandati nei pazienti con scompenso cardiaco e controindicati nei pazienti con NYHA classe III/IV
- Metanalisi di 7 studi con pioglitazone o rosiglitazone indicano un rischio di HF (HR 1.71, CI 1.21 – 2.4)





GLUCAGON – LIKE PEPTIDE 1 RECEPTOR AGONISTS

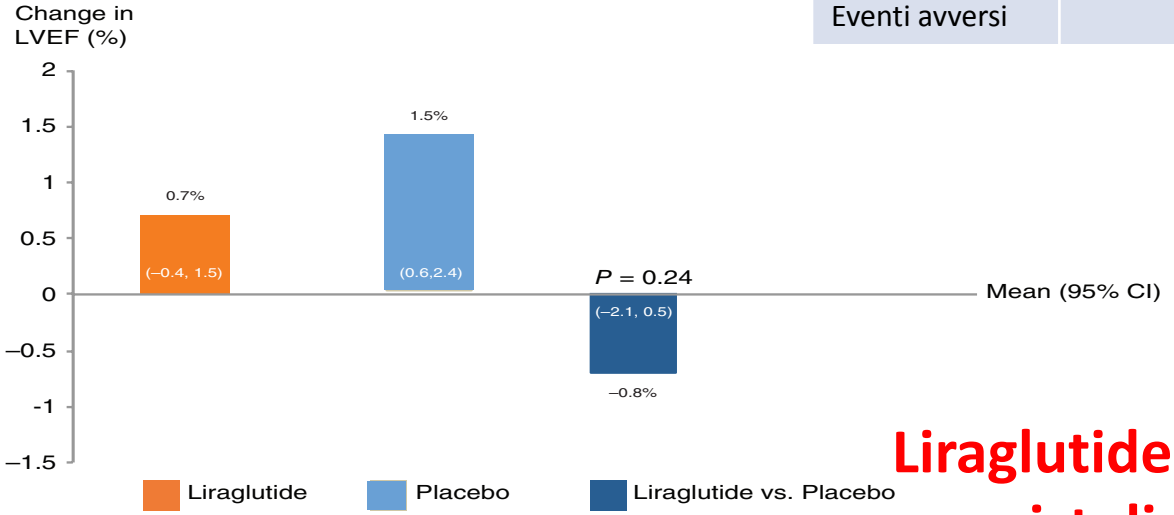
Trial	MACE	% pz con HF all'ingresso	HR ospedalizzazioni per HF
ELIXA (lixisenatide)	NS	22.3 %	0.96 (0.75 – 1.23)
LEADER (liraglutide)	- 13 %	17.8 %	0.87 (0.73 – 1.05)
SUSTAIN 6 (Semaglutide)	- 26 %	23.6 %	1.11 (0.77 – 1.61)

Effect of liraglutide, a glucagon-like peptide-1 analogue, on left ventricular function in stable chronic heart failure patients with and without diabetes (LIVE)—a multicentre, double-blind, randomised, placebo-controlled trial

European Journal of Heart Failure (2017) **19**, 69–77
doi:10.1002/ejhf.657

ITALIAN CHAPTER

	LIRAGLUTIDE 122 pz	PLACEBO 119 pz
LVEF %	33.7 %	35.4 %
Diabete	32 %	29 %
Eventi avversi	10 %	3 %

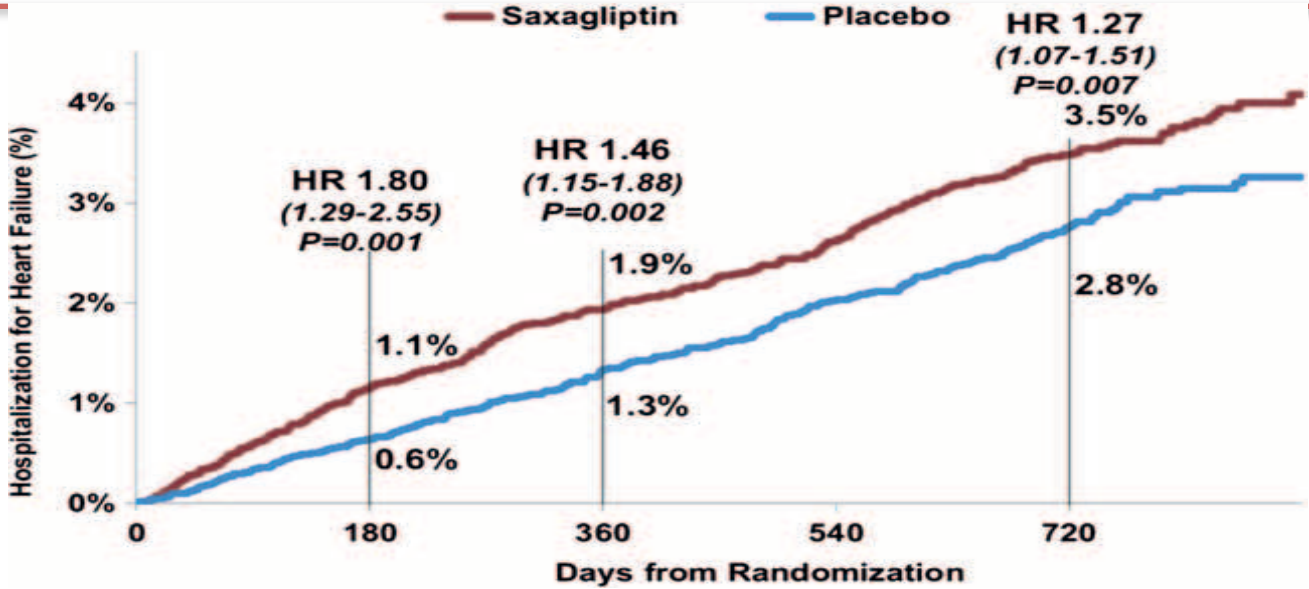


Liraglutide non modifica la funzione sistolica nei pazienti con HF

Effetto dei DPP-IV inibitori sul rischio di ospedalizzazione per HF

Trials	% HF	terapia	Ospedalizzazione per HF	Ospedalizzazione per HF (sottogruppo di pz senza HF all'entrata)
TECOS	18 %	METF. 81.6 % INS. 23.2 % TZD 2.7 %	**1 (0.83 – 1.19)**	**no**
SAVOR TIMI 53	12.8 %	METF. 69.5 % INS. 41.1 % TZD 6 %	**1.27 (1.77 – 1.51)**	**1.30 (2.03 – 2.65)**
EXAMINE	27.9 %	METF. 66.2 % INS. 29.9 % TZD 2.4 %	**1.19 (0.90 – 1.58)**	**1.76 (1.07 – 2.9)**

SAVOR TIMI 18



Saxagliptin incrementa del 81 % (HR 1.81, CI 1.21 – 2.76) il rischio di scompenso cardiaco nei pazienti che non assumono β bloccanti, ma solo del 18 % (HR 1.18, CI 0.97 – 1.43) in coloro che li assumono

Dipeptidyl peptidase-4 inhibitors and risk of heart failure in type 2 diabetes: systematic review and meta-analysis of randomised and observational studies

the bmj | BMJ 2016;352:i610

Evidence-Based Medicine Online First, published on April 21, 2016 as 10.1136/ebmed-2016-110436

Editorial

Clinicians should think twice before prescribing DPP-4 inhibitors for diabetes

Joshua J Fenton

VIVID 2014	NR	253	52	63	NR	7.8	NR
Laakso 2015	III	235	52	66.6	NR	8.1	NR
Savor-Timi 53 2013	IV	16492	109	65	31.1	NR	10.2
Examine 2015	III	5380	76	60.9	29.5	NR	9.2

controlli	DPP-IV	Rischio Relativo	Rischio per controllo	Rischio per DPP-IV
552/18474 3%	622/18554 3.4%	1.13 (1-1.26)	60 x 1000	+ 8

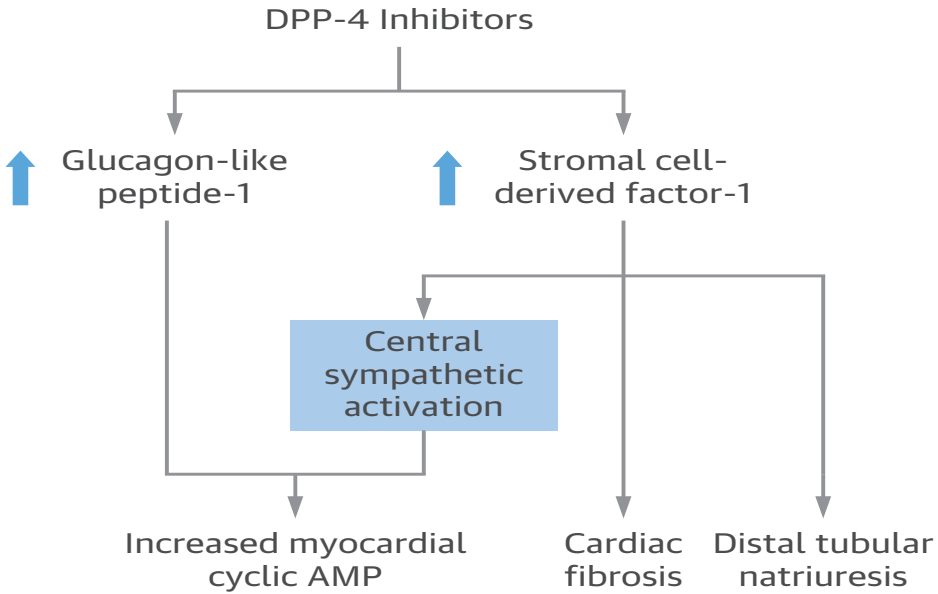
Qualità dell' evidenza: ⊕ ⊕ ⊕ ◯

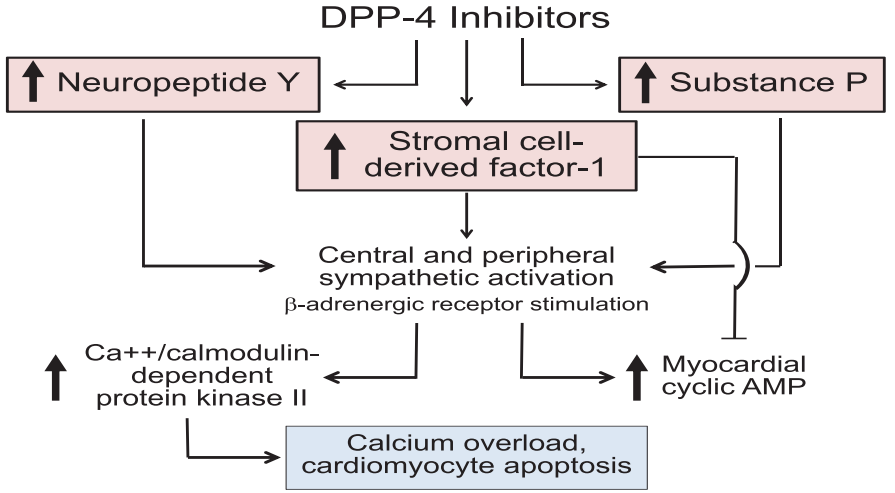
Worsening Heart Failure During the Use of DPP-4 Inhibitors
VOL. 6, NO. 6, 2018
JACC: HEART FAILURE
Pathophysiological Mechanisms, Clinical Risks, and Potential Influence of Concomitant Antidiabetic Medications

Do DPP-4 Inhibitors Cause Heart Failure Events by Promoting Adrenergically Mediated Cardiotoxicity? Clues From Laboratory Models and Clinical Trials

Circ Res. 2018;122:928-932.

ITALIAN CHAPTER

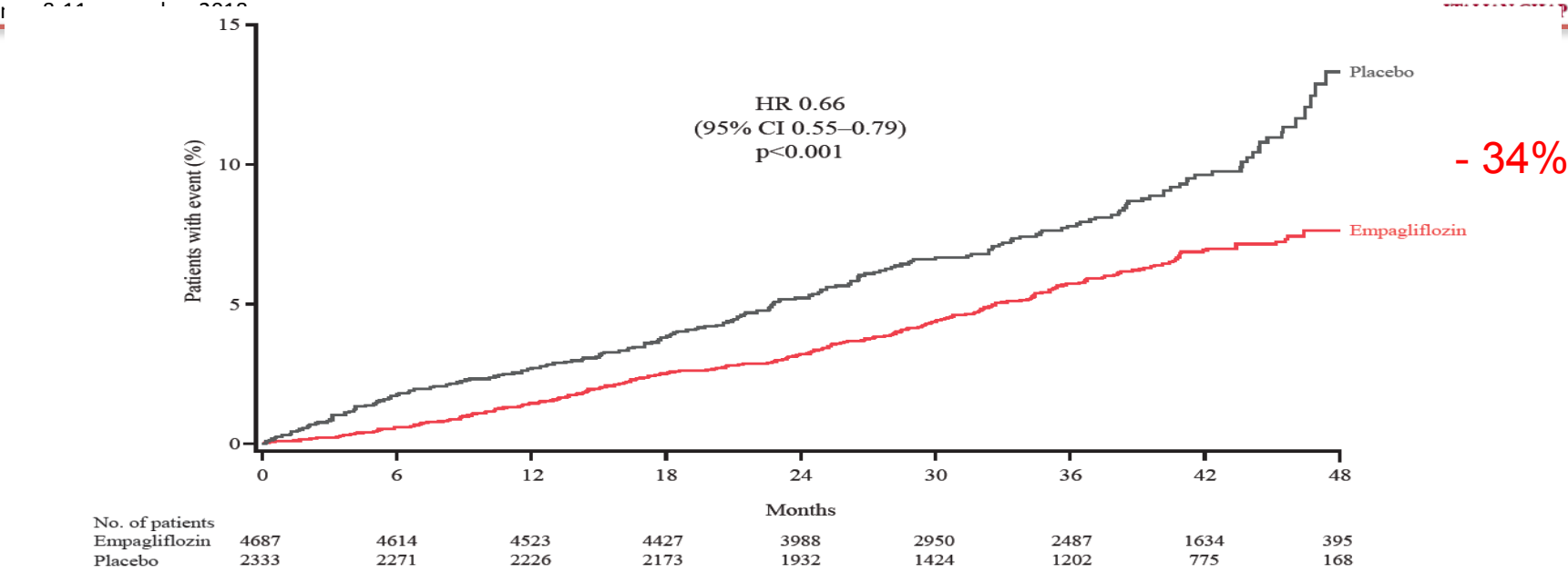




Attivazione del sistema Simpatico
Alterazione della struttura e funzione del cuore

Milton Parker

Heart failure hospitalisation or CV death



- 34%

-14% 3 point MACE

-34% di ospedalizzazione per scompenso cardiaco

-32% della mortalità per tutte le cause

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

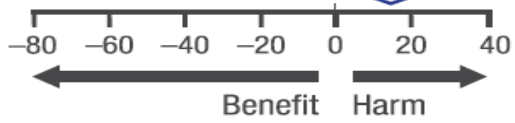
Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

Canagliflozin for Primary and Secondary Prevention of Cardiovascular Events

Results From the CANVAS Program (Canagliflozin Cardiovascular Assessment Study)

● Secondary prevention ▭ Primary prevention ◇ Overall population

	Number of participants	Patients per 1000 patient-years: Canagliflozin	Patients per 1000 patient-years: Placebo	Excess number of active patients experiencing the event in 1000 patients over 5 years (95% CI)*
CV death, nonfatal MI, or nonfatal stroke	796	34.1	41.3	−36 (−63, −9)
	215	15.8	15.5	2 (−20, 23)
	1011	26.9	31.5	−23 (−42, −4)
Hospitalization for heart failure	198	7.3	11.3	−20 (−33, −7)
	45	2.6	4.2	−8 (−18, 2)
	243	5.5	8.7	−16 (−25, −7)
40% reduction in eGFR renal replacement therapy, or renal death	179	6.4	10.5	−21 (−33, −8)
	70	4.1	6.6	−13 (−25, 0.5)
	249	5.5	9.0	−18 (−27, −8)
Lower extremity amputation	154	8.6	4.4	21 (11, 31)
	33	2.8	1.7	5 (−3, 13)
	187	6.3	3.4	15 (8, 22)



Cardiovascular outcome

	SGLT-2 I	Follow up	MACE	Mortalità cardiovascolare	Mortalità per tutte le cause	Scompenso cardiaco	IMA non fatale	Stroke non fatale
CVD-REAL Nordik	Dapagliflozin 94%	0.9	0.78 (0.69 – 0.87)	0.53 (0.40 – 0.71)	0.51 (0.45 – 0.58)	**0.70 (0.61 – 0.81)**	0.87 (0.73 – 1.03)	0.86 (0.72 – 1.04)
CVD-REAL US	Canagliflozin 75 – 76% Dapagliflozin 19%	0.5	NA	NA	0.38 (0.29 – 0.50)	**0.55 (0.44 – 0.69)**	NA	NA
EASEL		1.6	0.67 (0.60 – 0.75)		0.57 (0.49 – 0.66)	**0.57 (0.45 – 0.73)**	0.81 (0.64 – 1.03)	0.85 (0.66 – 1.1)
EMPA-REG	Empagliflozin 100%	3.1	0.86 (0.74 – 0.99)	0.62 (0.49 – 0.77)	0.68 (0.57 – 0.82)	**0.65 (0.50 – 0.85)**	0.87 (0.70 – 1.09)	1.24 (0.92 – 1.67)
CANVAS	Canagliflozin 100%	3.6	0.86 (0.75 – 0.97)	0.87 (0.72 – 1.06)	0.87 (0.74 – 1.01)	**0.67 (0.32 – 0.87)**	0.85 (0.69 – 1.05)	0.90 (0.71 – 1.15)

Heart failure outcomes in clinical trials of glucose-lowering agents in patients with diabetes

David H. Fitchett[1]*, Jacob A. Udell[2], and Silvio E. Inzucchi[3]

European Journal of Heart Failure (2016)
doi:10.1002/ejhf.633

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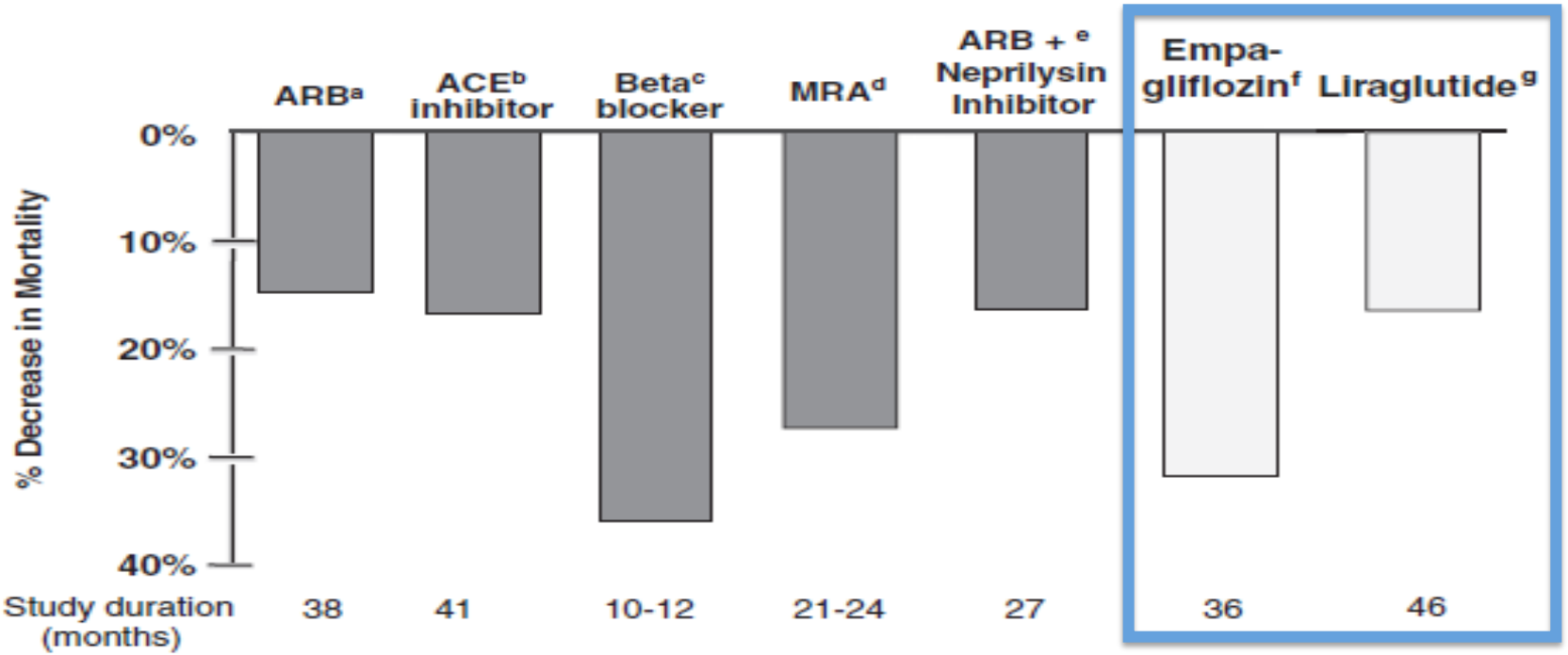

Comparison of all-cause mortality reduction observed in heart failure trials

Heart failure outcomes in clinical trials of glucose-lowering agents in patients with diabetes

David H. Fitchett[1]*, Jacob A. Udell[2], and Silvio E. Inzucchi[3]

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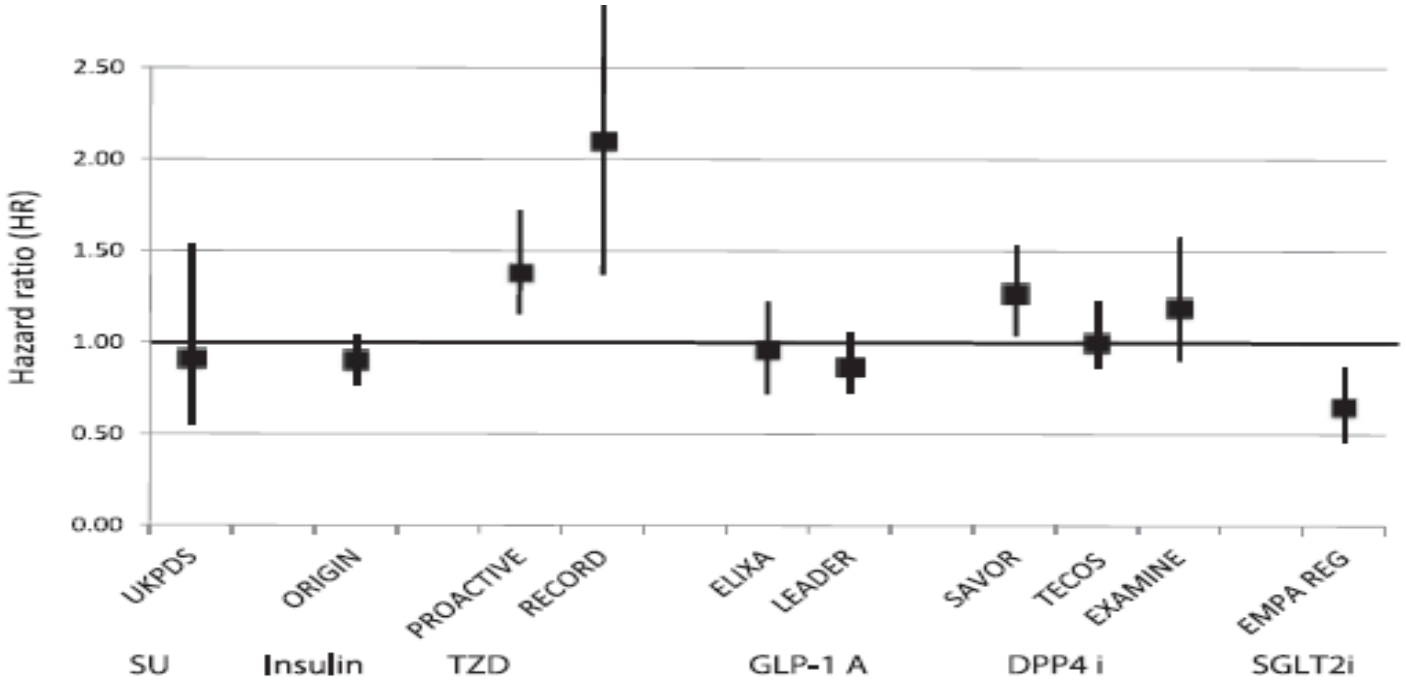
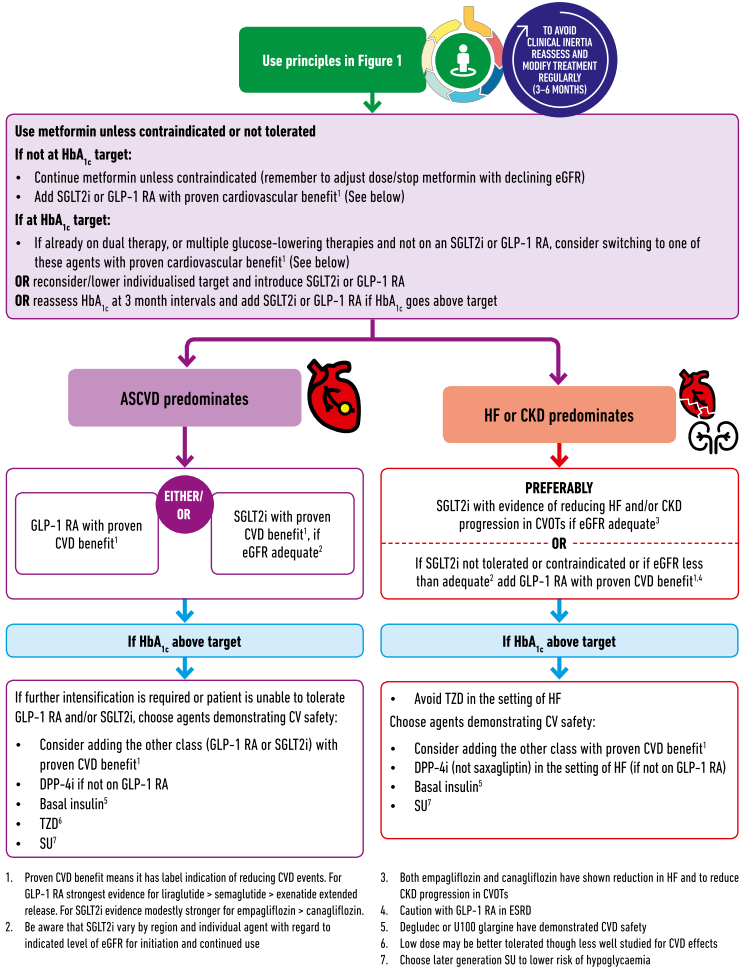


Impact of glucose-lowering drugs on incidence of hospitalization for heart failure

	Metformina	Acarbose	GLP1RA	Gliflozine	Gliptine	Pioglitazone	SU/glinidi	Insulina ba-sale	Insulina ba-sal-bolus
Interazioni con altri farmaci	-	-	-	-	-	+	++	-	-
Ipoglicemia	-	-	-	-	-	-	++	+++	+++
Aumento di peso	-	-	-	-	-	++	+	+++	+++
Pancreatiti	-	-	+/-	-	+	-	-	-	-
Fratture ossee	-	-	-	+/-[a]	-	+++	-	-	-
Scompenso cardiaco	-	-	-	-	+/-[b]	++	+	-	-
Disturbi gastrointestinali	++	+++	++	+/-	-	-	-	-	-
Infezioni genitali	-	-	-	+	-	-	-	-	-
Acidosi lattica	+	-	-	-	-	-	-	-	-
Chetoacidosi	-	-	-	+	-	-	-	-	-
Amputazioni minori	-	-	-	+/-[a]	-	-	-	-	-

EFFETTI COLLATERALI E RISCHI DEI FARMACI PER IL DIABETE DI TIPO 2

CHOOSING GLUCOSE-LOWERING MEDICATION IN THOSE WITH ESTABLISHED ATHEROSCLEROTIC CARDIOVASCULAR DISEASE (ASCVD) OR CHRONIC KIDNEY DISEASE (CKD)



1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Both empagliflozin and canagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs
4. Caution with GLP-1 RA in ESRD
5. Degludec or U100 glargine have demonstrated CVD safety
6. Low dose may be better tolerated though less well studied for CVD effects
7. Choose later generation SU to lower risk of hypoglycaemia

Miocardiopatia diabetica e scompenso cardiaco:

Aspetti terapeutici

Trattamento dello scompenso cardiaco cronico

HF-rEF

FE ≤ 40%

SOPRAVVIVENZA

Beta-bloccanti
ACE – inibitori / AT1R antagonisti
ARNi
Spironolattone
PCD e/o CRT

SINTOMI

Digitale
Diuretici
Vasodilatatori

HF-pEF
HF-mrEF

FE > 40%

PATOLOGIA SOTTOSTANTE

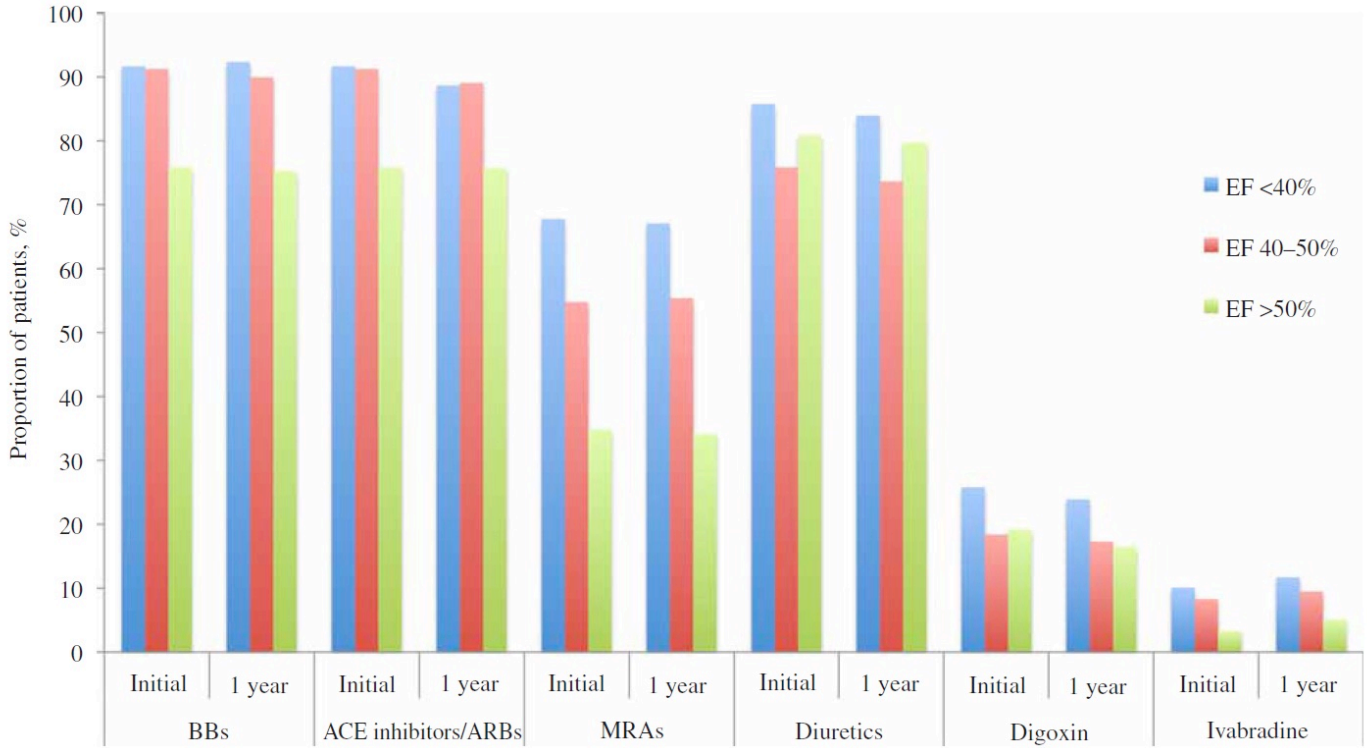
Ipertensione arteriosa
Ischemia miocardica
Aritmia atriale

SINTOMI

Diuretici

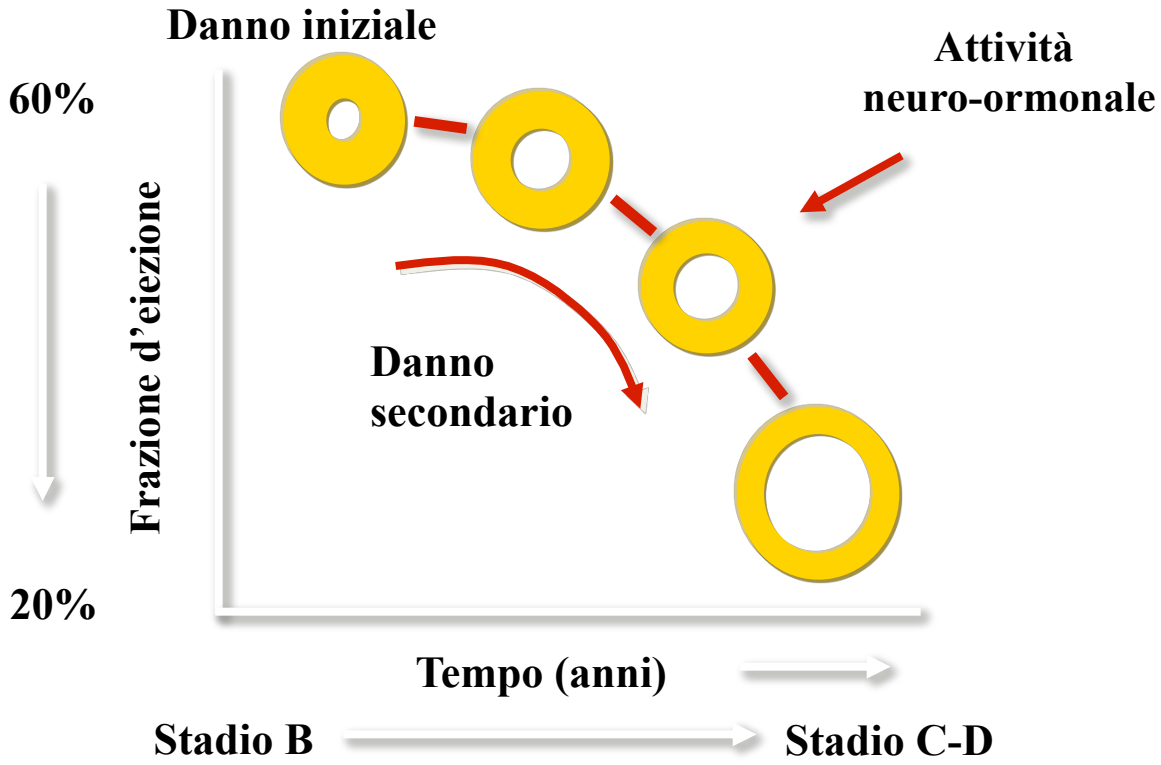
SOPRAVVIVENZA

Beta-bloccanti?
ACE – inibitori?

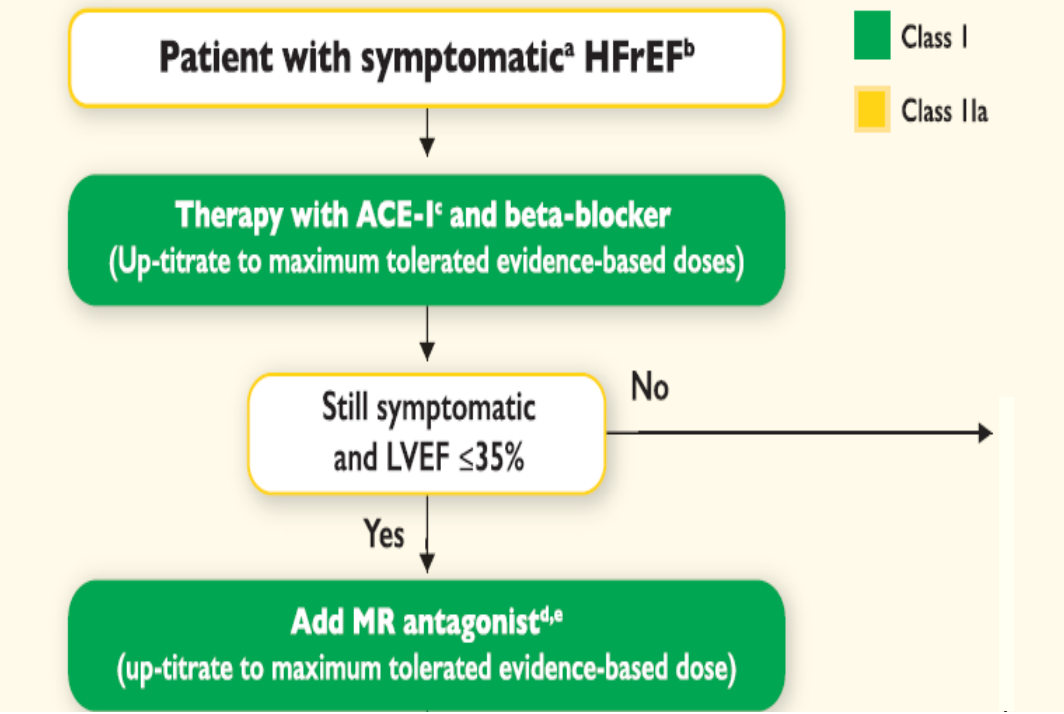


Chioncel O Eur J Heart Fail. 2017
doi: 10.1002/ejhf.813.

HF-rEF

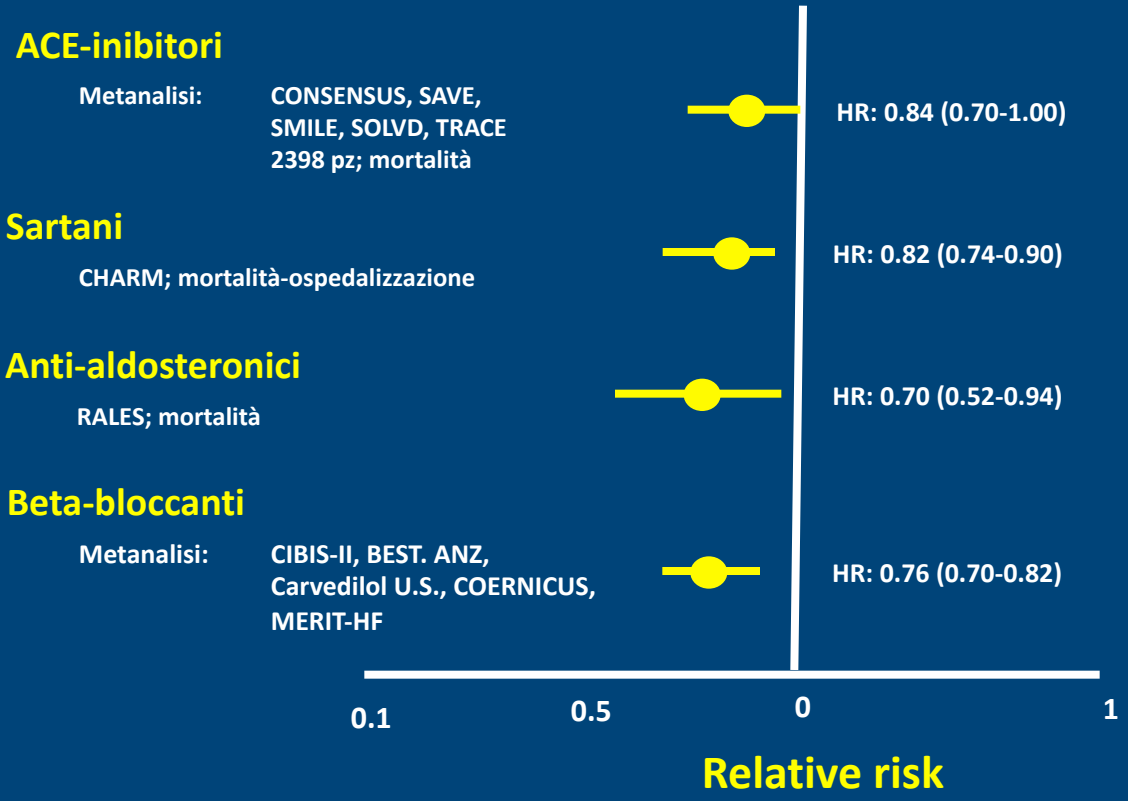


Mann DM, Circulation 1999



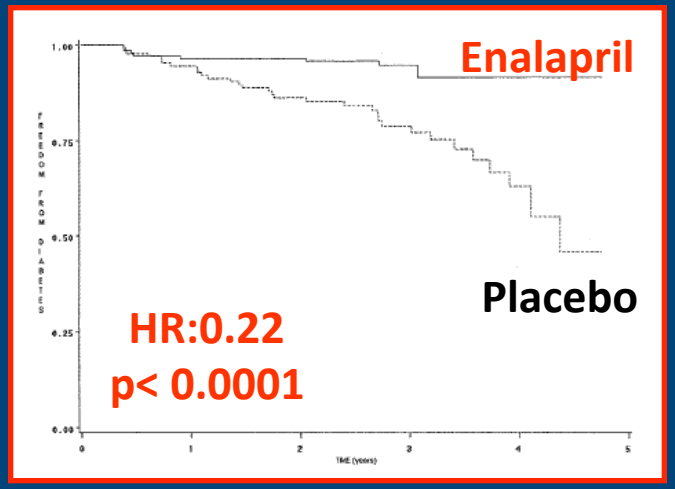
ESC Guidelines 2016

Riduzione della morbilità e mortalità nel paziente diabetico

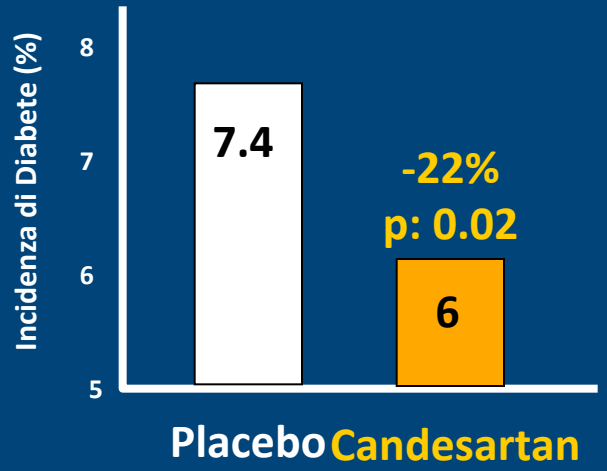


ACE-inibitori e Sartani

SOLVD



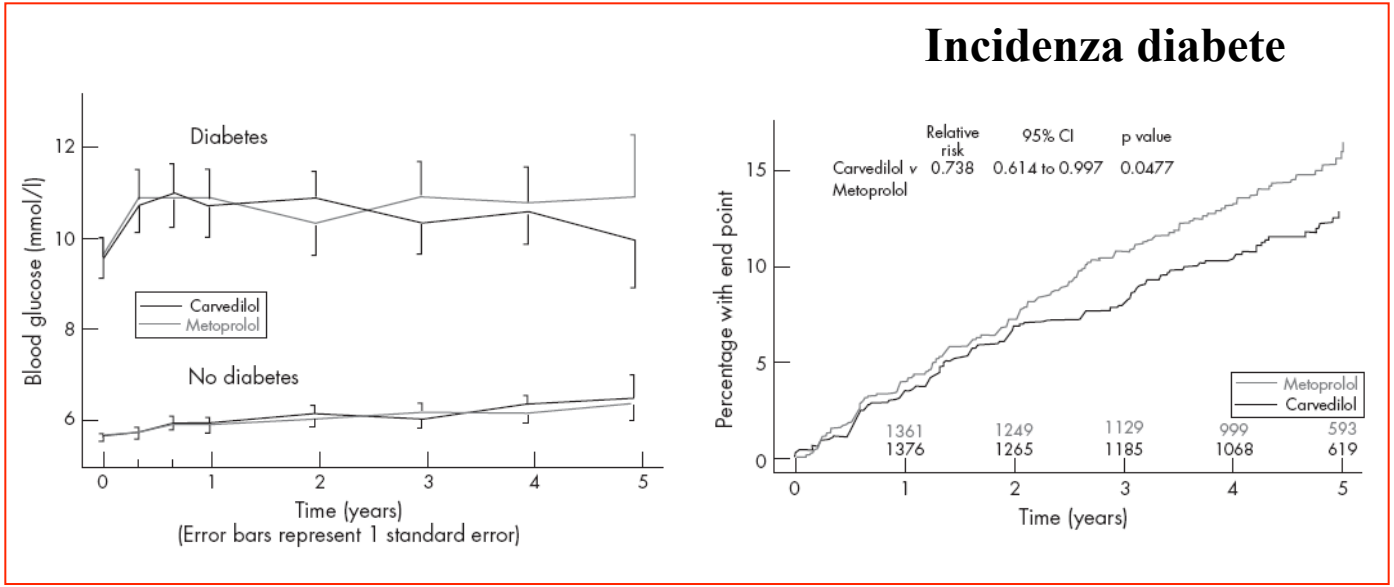
CHARM



Vermes E et al, Circulation 2003;107:1291

Yusuf S et al, Circulation 2005;112:48

Uso dei beta-bloccanti nel paziente diabetico con scompenso (Studio COMET)



Top Pedersen et al. Heart 2007;93:968.

Modello cardiorenale

- Diuretici

Modello cardiocircolatorio

- Inotropi
- Vasodilatatori

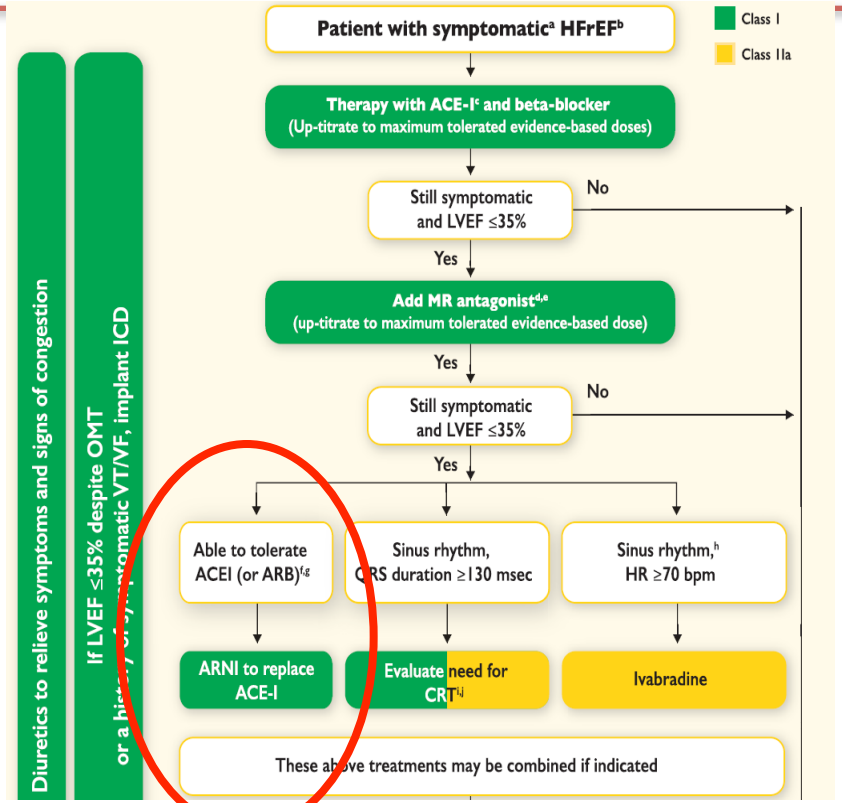
Modello neurormonale

- ACE inibitori
- β-bloccanti
- ARB
- ARNi
- Antag. aldosterone

Altre strategie

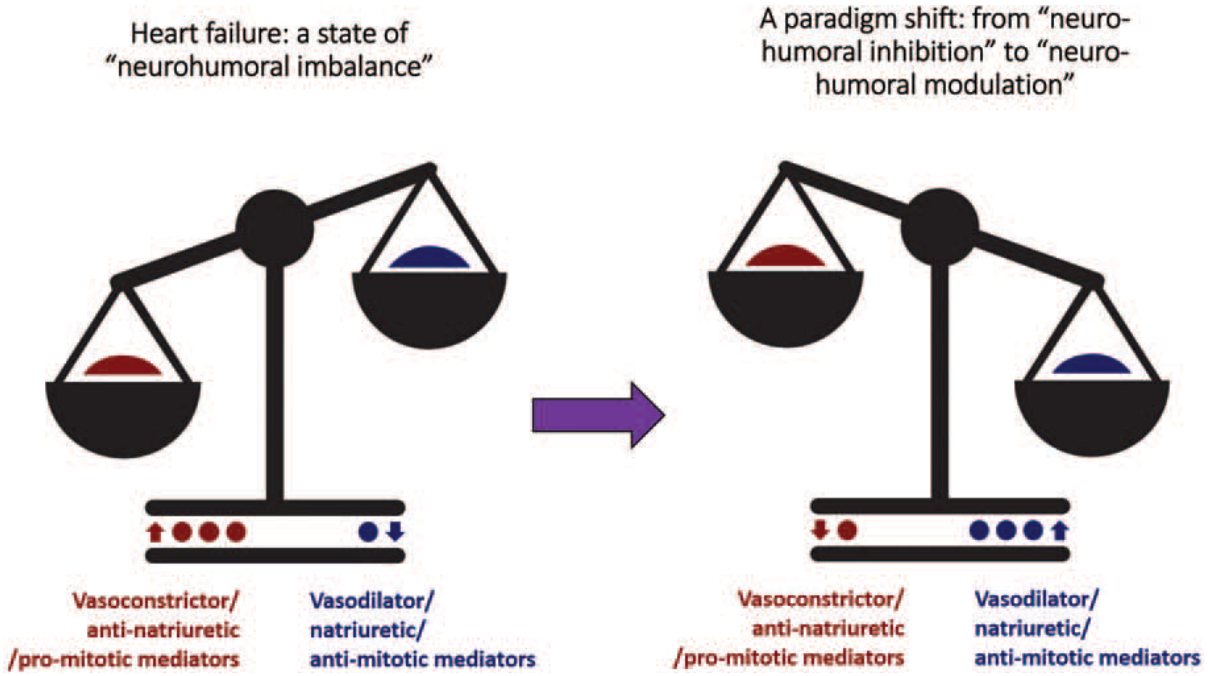
- Modulazione neurormonale
- CRT
- Ivabradina

HF-rEF: Aspetti terapeutici



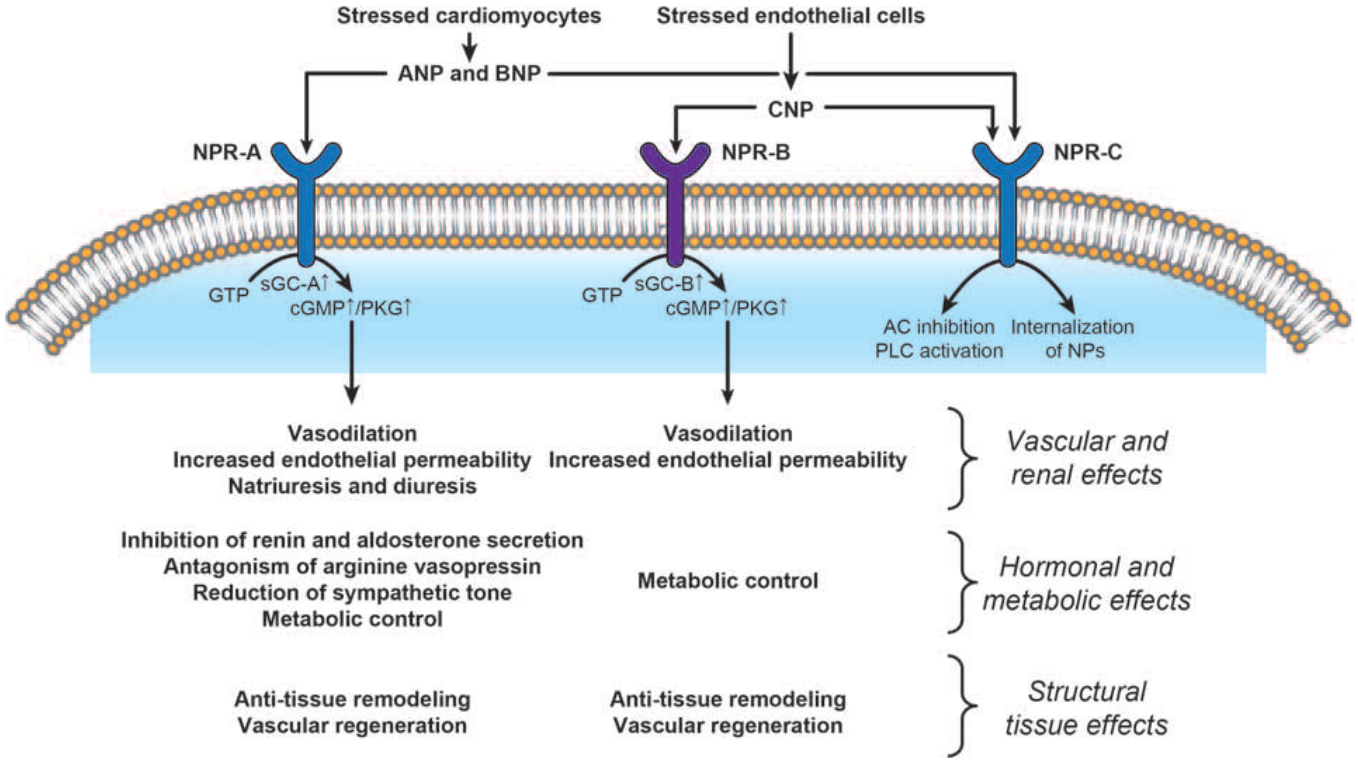
ESC Guidelines 2016

HF-rEF: Modulazione neurormonale



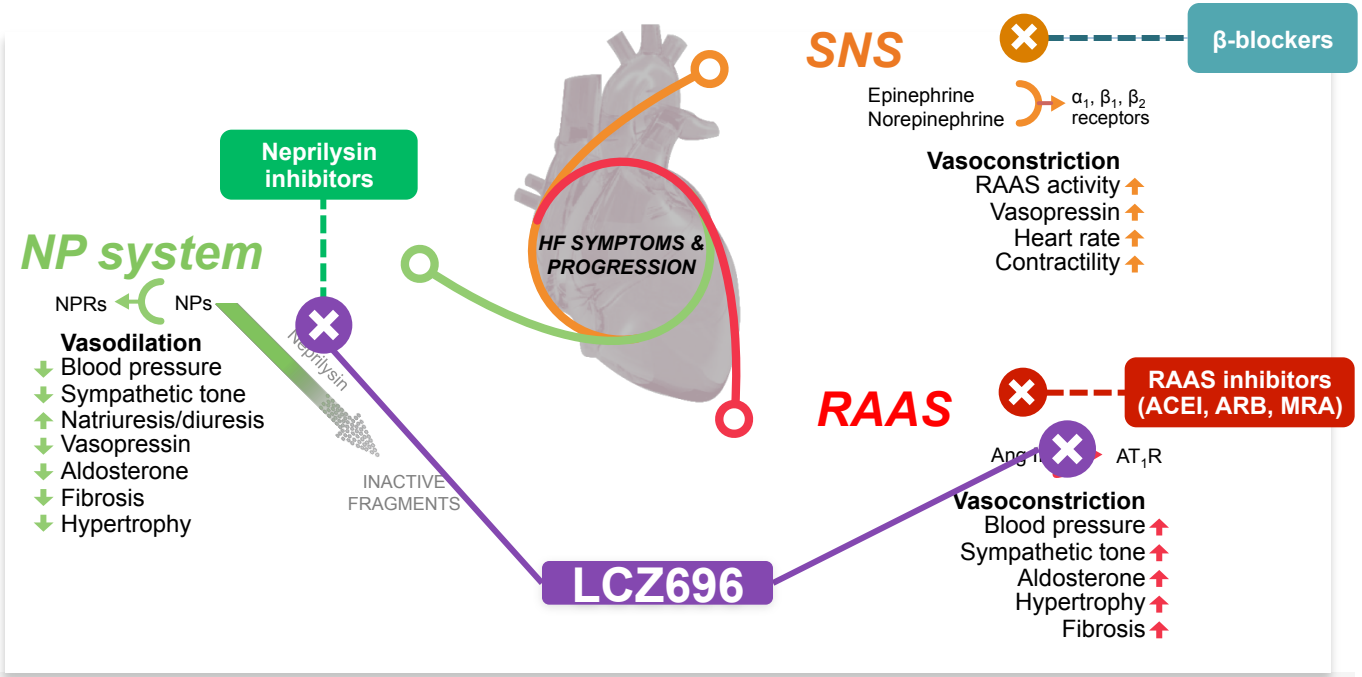
McMurray. European Journal of Heart Failure 2015

HF-rEF: Aspetti terapeutici



Diez G. European Journal of Heart Failure 2016

HF-rEF: Modulazione neurormonale



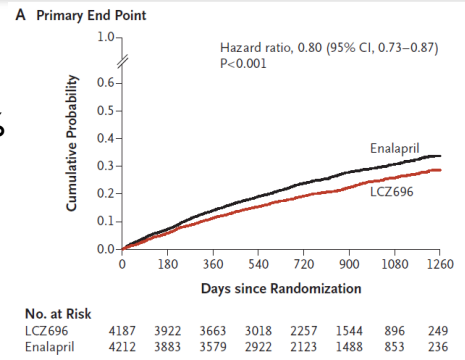
- LCZ696: enhancement of natriuretic and other vasoactive peptides, with simultaneous RAAS suppression

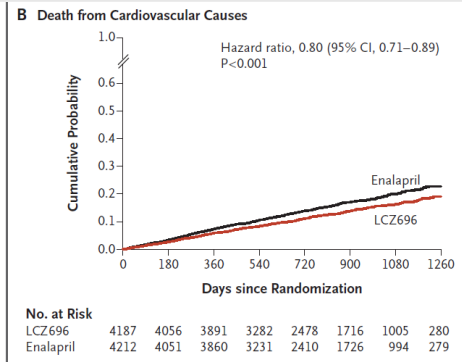
ACEI=angiotensin-converting- enzyme inhibitor; Ang=angiotensin; ARB=angiotensin receptor blocker; AT_1 = angiotensin II type 1; HF=heart failure; MRA=mineralocorticoid receptor antagonist; NEP=neprilysin; NP=natriuretic peptide; NPRs=natriuretic peptide receptors; RAAS=renin-angiotensin-aldosterone system; SNS=sympathetic nervous system

1. McMurray et al. Eur J Heart Fail. 2013;15:1062–73;
Figure references: Levin et al. N Engl J Med 1998;339:321–8; Nathisuwan & Talbert. Pharmacotherapy 2002;22:27–42; Kemp & Conte. Cardiovascular Pathology 2012;365–371; Schrier & Abraham N Engl J Med 2009;341:577–85

HF-rEF: Modulazione neurormonale

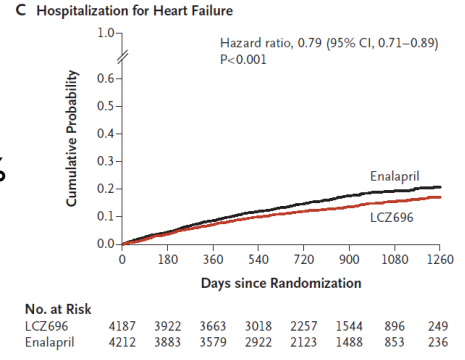
RRR: -20%
ARR: -4.7%
NNT: 21

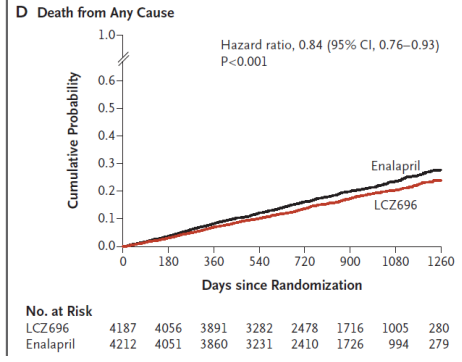




RRR: -20%
ARR: -3.2%
NNT: 32

RRR: -21%
ARR: -2.8%
NNT: 36

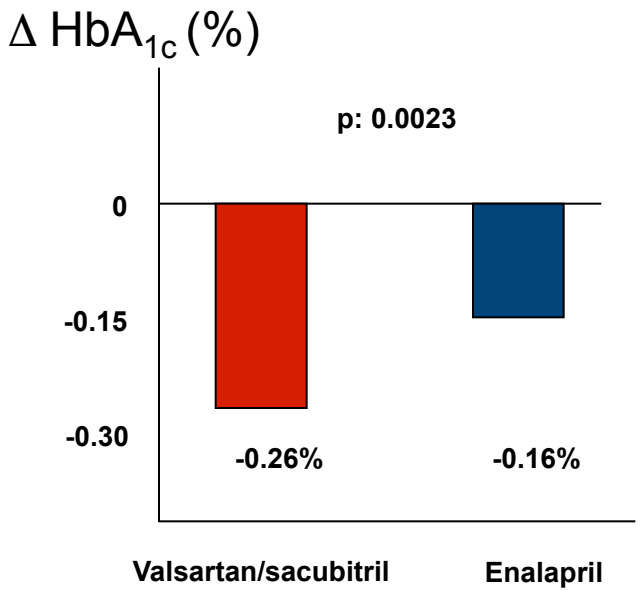


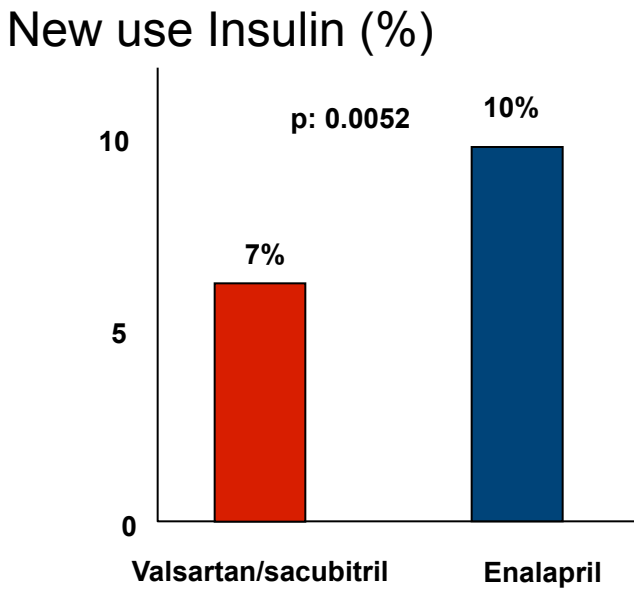


RRR: -16%
ARR: -2.8%
NNT: 36

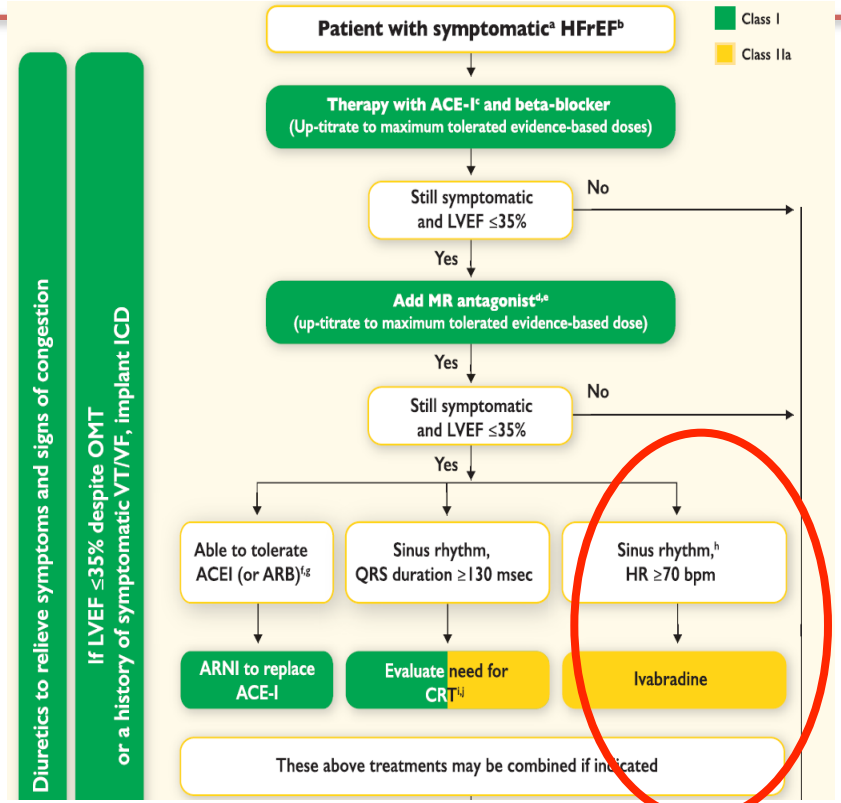
McMurray Eur J Heart Fail 2015

HF-rEF: Modulazione neurormonale e diabete



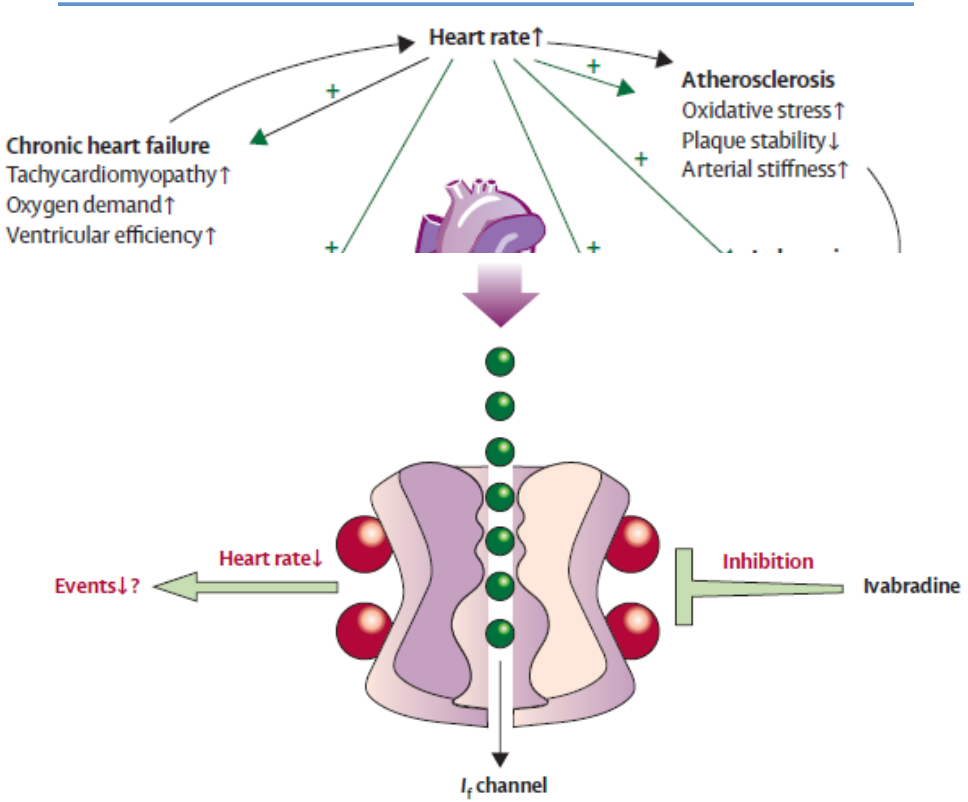


Seferovic et al. The Lancet Diab & End 2017



ESC Guidelines 2016

Controllo della frequenza cardiaca



Reil JC, Bohm M. Lancet 2008;372:779-80

Controllo della frequenza cardiaca

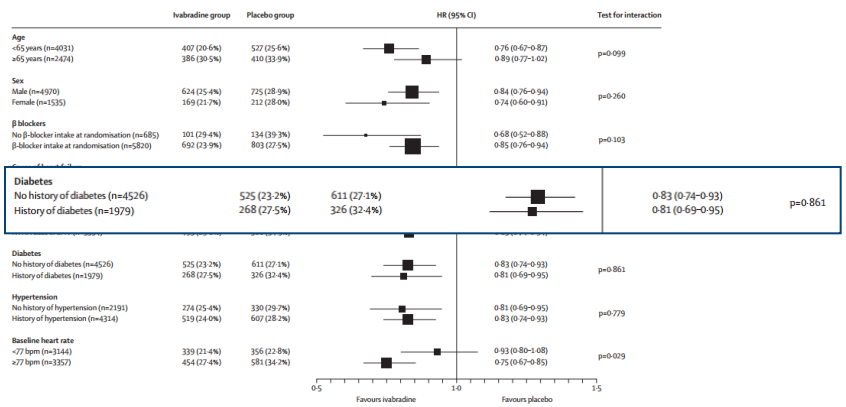
Studio Shift

Endpoints	HR	95% CI	RRR	p value	ARR	NTT
Endpoint primario composito	0.82	[0.75;0.90]	- 18%	*p*<0.0001	- 4,3%	23
Morte CV	0.91	[0.80;1.03]	- 9%	*p*=0.128	-1,4%	71
Mortalità Totale	0.90	[0.80;1.02]	- 10%	*p*=0.092	- 1,2%	83
Morte per scompenso	0.74	[0.58;0.94]	- 26%	*p*=0.014	- 1,2%	83
Ospedalizzazione Totale	0.89	[0.82;0.96]	- 11%	*p*=0.003	- 3,6%	28
Ospedalizzazione per CV	0.85	[0.78;0.92]	- 15%	*p*=0.0002	- 4,5%	22

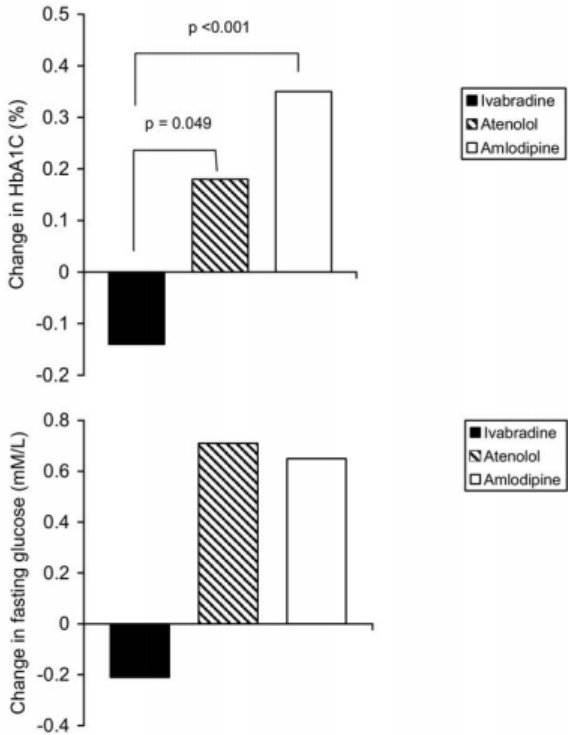
Follow-up mediano 22.9 mesi

Swedberg et al. Lancet 2010; 376:886-94

Controllo della frequenza cardiaca



Swedberg K et al. Lancet. 2010;376:875-85.



Borer JS Am J Cardiol. 2010;105:29-35.

Scompenso cardiaco e comorbilità

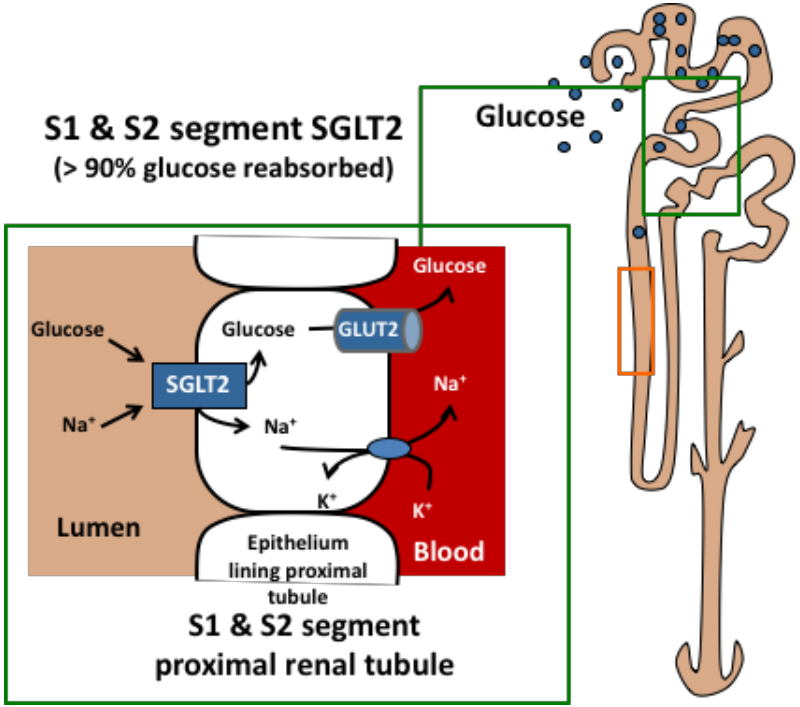
Recommendations for the treatment of other co-morbidities in patients with heart failure

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
Diabetes			
Metformin should be considered as a first-line treatment of glycaemic control in patients with diabetes and HF, unless contra-indicated.	IIa	C	440 ,441

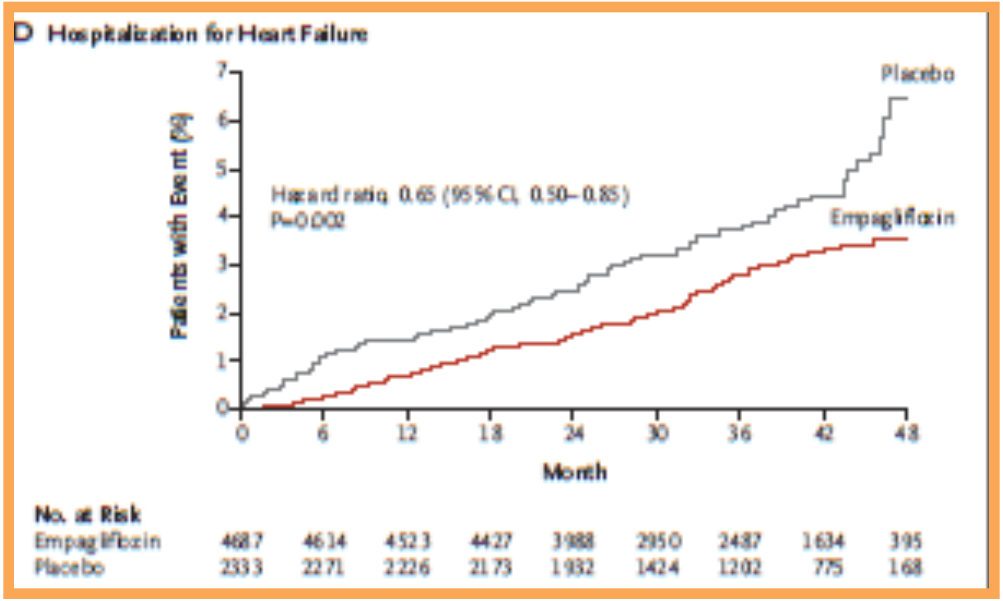
Treatments not recommended of other co-morbidities in patients with heart failure

Recommendations	Class [a]	Level [b]	Ref [c]
Sleep apnoea			
Adaptive servo-ventilation is not recommended in patients with HFrEF and a predominant central sleep apnoea because of an increased all-cause and cardiovascular mortality.	III	B	473
Diabetes			
Thiazolidinediones (glitazones) are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization.	III	A	209, 210
Arthritis			
NSAIDs or COX-2 inhibitors are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization.	III	B	211–213

Miocardiopatia diabetica



EMPA-REG OUTCOME Pooled Analysis (N=7020)



Take Home Message

- La coesistenza di diabete di tipo 2 e scompenso cardiaco è frequente nel 30 – 40% dei pazienti
- Le cause dello scompenso sono nell'ordine: la coronaropatia aterosclerotica, l'ipertensione arteriosa e la cardiomiopatia diabetica
- Il fenotipo HFpEF è il più frequente e nella cardiomiopatia diabetica precede sempre quello a HFrEF
- Non ci sono particolari limitazioni nel trattamento dello scompenso cardiaco nel paziente diabetico

Take Home Message

- Abbiamo limitazioni nella terapia del diabete di tipo 2 con scompenso cardiaco
- La metformina è secondo le linea guida il farmaco di prima scelta
- Tra i nuovi farmaci gli SGLT-2 inibitori hanno dimostrato, sia nei trial di sicurezza cadiovascolare, sia negli studi real world, una indubbia efficacia e superiorità nel ridurre le ospedalizzazioni per scompenso cardiaco