«Πρακτικά διλήμματα και δυσκολίες στην κλινική αντιμετώπιση των ασθενών με καρδιακή ανεπάρκεια»

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ΆΓΙΟΣ ΛΟΥΚΆΣ

&

ΙΑΤΡΕΊΟ ΚΑΡΔΙΑΚΗΣ ΑΝΕΠΑΡΚΕΙΑΣ, Γ ΠΑΝΕΠΙΣΤΗΜΙΑΚΗ ΚΛΙΝΙΚΗ ΑΠΘ, ΙΠΠΟΚΡΑΤΕΙΟ ΝΟΣΟΚΟΜΕΙΟ ΘΕΣΣΑΛΟΝΙΚΗΣ

ΟΞΥΓΟΝΟ ΣΤΗΝ ΚΑΡΔΙΑΚΗ ΑΝΕΠΑΡΚΕΙΑ

Oxygen in Cardiac Patients: Friend or Foe?

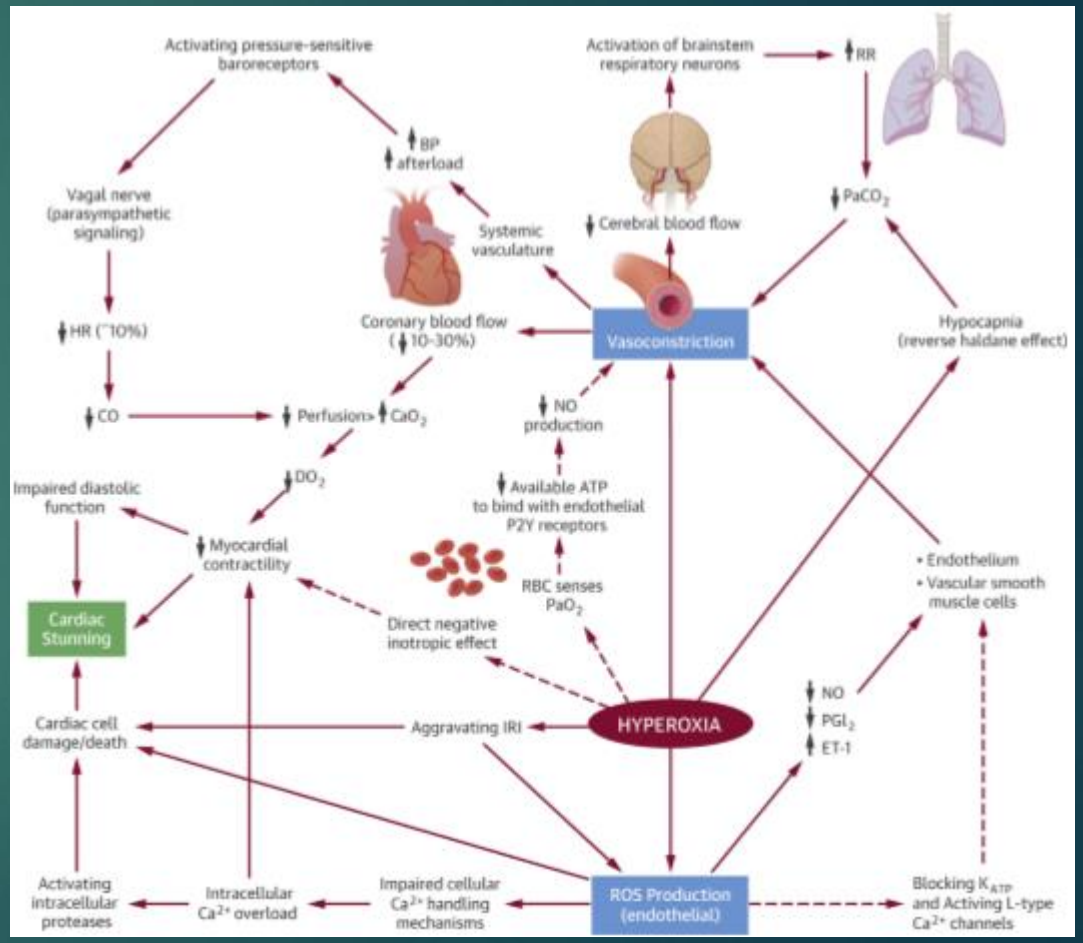
FIGURE 1 Forest Plot of Oxygen Versus Room Air Comparison for the Outcome of In-Hospital Death in Patients With Acute Myocardial Infarction

Study or Subgroup	Oxygen Events	Oxygen Total	Room Air Events	Room Air Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Rawles 1976	9	80	3	77	19.9%	2.89 [0.81, 10.27]	1976
Ukholkina 2005	1	58	0	79	2.8%	4.07 [0.17, 98.10]	2005
Ranchord 2012	1	68	2	68	13.0%	0.50 [0.05, 5.39]	2012
Stub 2015	4	218	10	223	64.3%	0.41 [0.13, 1.29]	2015
Total (95% CI)		**424**		**447**	**100.0%**	**1.02 [0.51, 2.03]**	
Total events	15		15				

Heterogeneity: Chi² = 6.10, df = 3 (P = 0.11); I² = 51%
Test for overall effect: Z = 0.04 (P = 0.97)

Risk Ratio M-H, Fixed, 95% CI

0.01 0.1 1 10 100
Favors Oxygen Favors Room Air

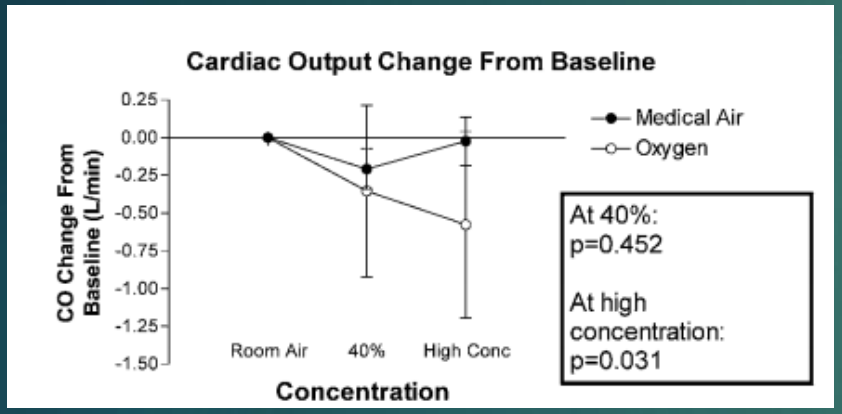


Oxygen is indicated in hypoxic patients with arterial oxygen saturation (SaO_2) < 90%. There is some evidence suggesting that hyperoxia may be harmful in patients with uncomplicated MI, presumably due to increased myocardial injury. Thus, routine oxygen is not recommended when SaO_2 is ≥ 90%.

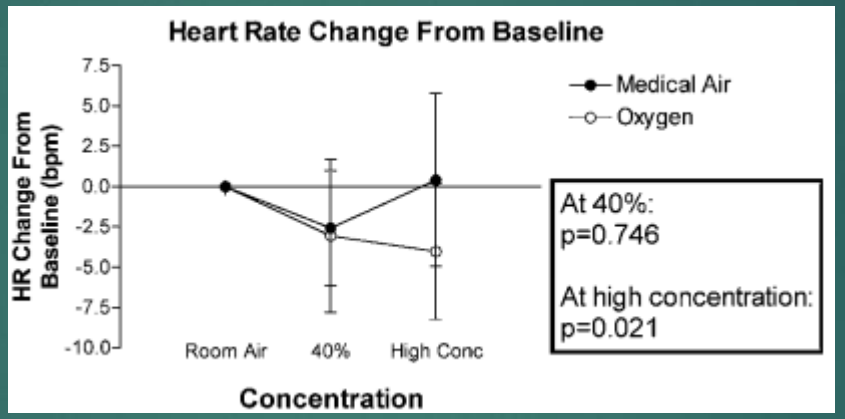
ESC STEMI Guidelines 2017

N Sepehrvand et al JACC 2016

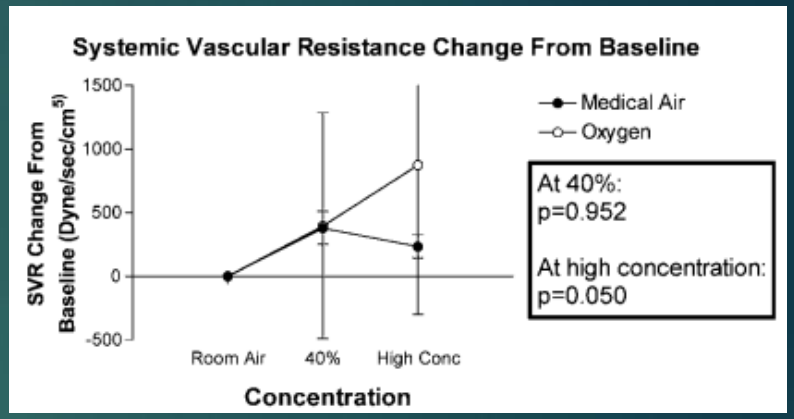
Potentially detrimental cardiovascular effects of oxygen in patients with chronic left ventricular systolic dysfunction



Cardiac Output



Heart Rate



Vascular Resistance

High-concentration inhaled oxygen has significant haemodynamic effects in patients with LVSD and mild HF. Such effects may be **detrimental** in patients with decompensated HF.

JH Park Heart 2009

Oxygen therapy and ventilatory support

Recommendations	Class [a]	Level [b]	Ref [c]
Monitoring of transcutaneous arterial oxygen saturation (SpO_2) is recommended.	I	C	
Measurement of blood pH and carbon dioxide tension (possibly including lactate) should be considered, especially in patients with acute pulmonary oedema or previous history of COPD using venous blood. In patients with cardiogenic shock arterial blood is preferable.	IIa	C	
Oxygen therapy is recommended in patients with AHF and SpO_2 <90% or PaO_2 <60 mmHg (8.0 kPa) to correct hypoxaemia.	I	C	
Non-invasive positive pressure ventilation (CPAP, BiPAP) should be considered in patients with respiratory distress (respiratory rate >25 breaths/min, SpO_2 <90%) and started as soon as possible in order to decrease respiratory distress and reduce the rate of mechanical endotracheal intubation. Non-invasive positive pressure ventilation can reduce blood pressure and should be used with caution in hypotensive patients. Blood pressure should be monitored regularly when this treatment is used.	IIa	B	541–545
Intubation is recommended, if respiratory failure, leading to hypoxaemia (PaO_2 <60 mmHg (8.0 kPa)), hypercapnia ($PaCO_2$ >50 mmHg (6.65 kPa)) and acidosis (pH <7.35), cannot be managed non-invasively.	I	C	

Oxygen should not be used routinely in non-hypoxaemic patients, as it causes vasoconstriction and a reduction in cardiac output

ΥΠΟΤΑΣΗ ΚΑΙ ΚΑΡΔΙΑΚΗ ΑΝΕΠΑΡΚΕΙΑ

"Symptomatic hypotension is the Achilles' heel of heart failure management"

- ❑ **A sign of advanced pump failure.**
- ❑ **A side effect of the HF treatment.**

Questions that frequently arise are, among patients with low blood pressure at baseline:

1. which medication should be initiated first?
2. whether 1 agent should be increased to a target dose before initiation of another,?
3. which drug should be decreased in the setting of hypotension?

Table. Strategies in Management of HF Patients With Hypotension

General approaches for most HF patients with low BP
Avoid overuse of medications that cause hypotension, such as α-blockers, calcium-channel blockers, nitrates, PDE-5 inhibitors
Avoid inappropriate overdosing of diuretics
Separate timing of medications that cause hypotension apart from each other
Assess and treat possible noncardiac causes of hypotension
Avoid abrupt withdrawal of ACEI or β-blocker without a compelling clinical indication
Approaches for HF patients with asymptomatic low BP before initiation of HF medications
Initial occasional low BP is usually transient and most patients tolerate HF medications
It is not unreasonable to start β-blockers after intermediate doses of ACEI are achieved
Initiate and uptitrate GDMT slowly and cautiously with close follow-up
Approaches for patients with HF with asymptomatic low BP after initiation of HF medications
Do not reduce or discontinue ACEI or β-blockers for asymptomatic low BP measurements
With improvement of HF status with GDMT and/or CRT, BP profile usually improves
HF patients with symptomatic hypotension
Hypotension may be because of advanced systolic HF and/or noncardiac causes
Initial occasional hypotension or dizziness usually resolves as HF improves with GDMT and/or CRT
Additional HF medications may need to be adjusted before consideration of any changes in ACEI or β-blockers

B Bozkurt Circ Heart Fail. 2012

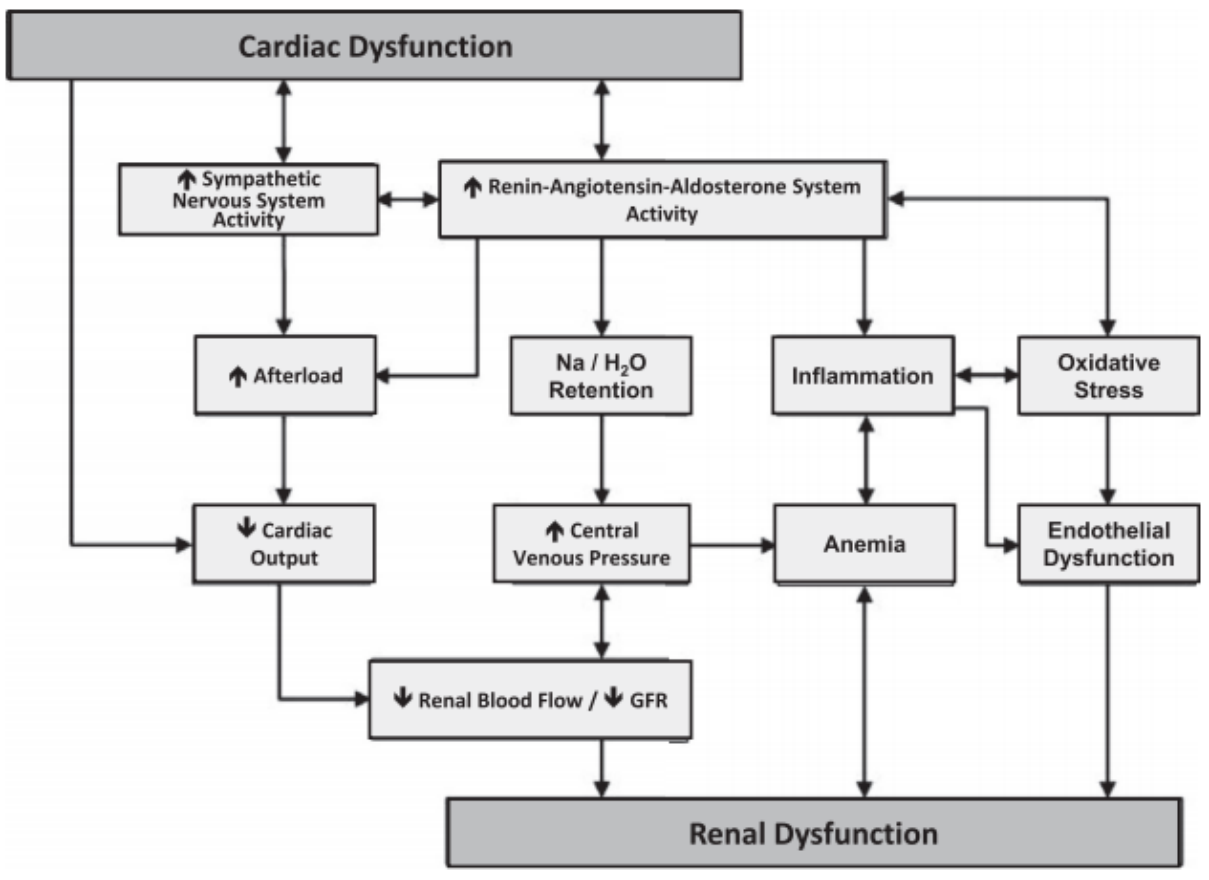
Practical recommendations in Hypotensive CHF

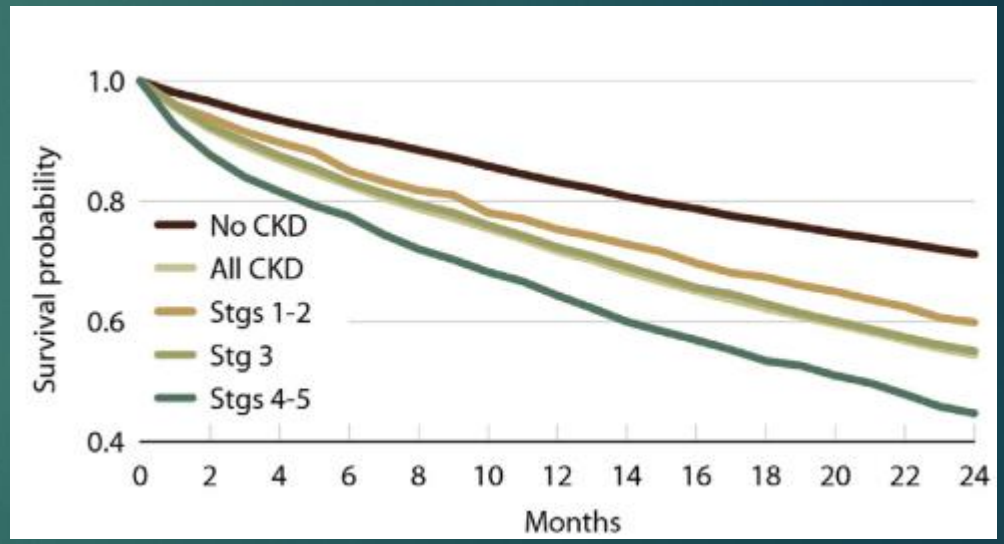
- If a patient is able to tolerate without functionally limiting dizziness, light headedness or other significant side effects, **it is beneficial to up-titrate HF medications to target doses**.
- This is achievable even if the systolic **BP (SBP) is <100 mmHg, but >80 mmHg**.
- In patients with baseline **SBP <80mm Hg**, initiation of GDMT with ACEI and/or β-blockers usually are not feasible.
- If the patient has **bradycardia along with hypotension**, β-blockers need to be avoided until bradycardia is evaluated and treated.
- In real-world patients with chronic HF, the prevalence of hypotension seems to be in the range of **5% to 10%**.
- β-blockers with **vasodilatory or a-blocking properties**, such as carvedilol, may have slightly more BP lowering effect than bisoprolol.
- shorter acting ACEI, such as **captopril** may allow smaller, but more frequent doses for up-titration, than long-acting ACEI in patients with low BP.

B Bozkurt Circ Heart Fail. 2012

ΑΝΤΙΜΕΤΩΠΙΣΗ ΚΑΡΔΙΑΚΗΣ ΑΝΕΠΑΡΚΕΙΑΣ ΣΕ ΑΣΘΕΝΕΙΣ ΜΕ ΝΕΦΡΙΚΗ ΑΝΕΠΑΡΚΕΙΑ

Cardiorenal Syndrome

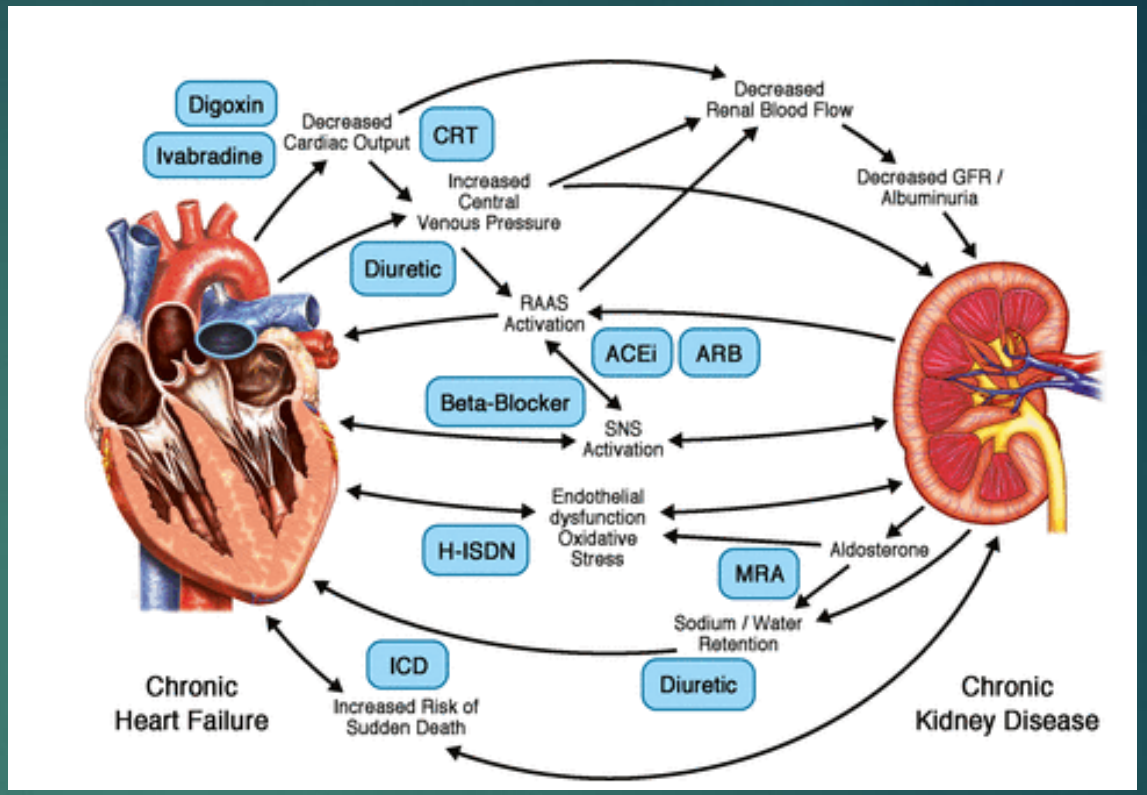




AA House AJKD 2018

Medicines in Heart Failure patients with Renal Failure (ACEi & ARBs)

- Unfortunately, many of the pivotal studies of HF management excluded patients with advanced CKD.
- **SOLVD trial**: **enalapril** significantly reduced hospitalizations for cardiovascular events in patients with eGFRs < 60 mL/min/1.73 m2 , although the effect on all-cause, cardiovascular, and HF mortality was not improved to a statistically significant degree.
- **SAVE trial**: Study outcomes worsened with each incremental decline in kidney function, but the efficacy of **captopril** was maintained in the group with CKD stage 3 or greater.
- **CONSENSUS trial**: serum creatinine concentrations of individuals in the **enalapril** group were found to increase to about 10% to 15% above baseline (commonly within the first several weeks), consistent with the recognized hemodynamic effects of ACE inhibition on GFRs.
- **Val-HeFT trial**: the group with CKD randomly assigned to **valsartan** treatment experienced a rate of first morbid event (including death or HF hospitalization or intravenous vasoactive drug administration) that was statistically significantly lower.



Stages of CKD		Prevalence			Levels of Kidney Dysfunction	Distribution		
Stage	Description	General Population	HFREF*	HFPEF	GFR (ml/min/1.73 m^2)	General Population	HFREF	HFPEF
1	Kidney damage with normal or ↑ GFR	3.3	2.8	NA	≥90	64.3	8.2	8.2
2	Kidney damage with mild ↓ GFR	3.0	10.6	NA	60–89	31.2	37.2	34.9
3	Moderate ↓ GFR	4.3	45.5	46.1	30–59	4.3	45.5	46.1
4	Severe ↓ GFR	0.2	7.8	8.1	15–29	0.2	7.8	8.1
5	Kidney failure	0.2	1.3	2.7	<15 (or dialysis)	0.2	1.3	2.7

K. Damman et al JACC 2014

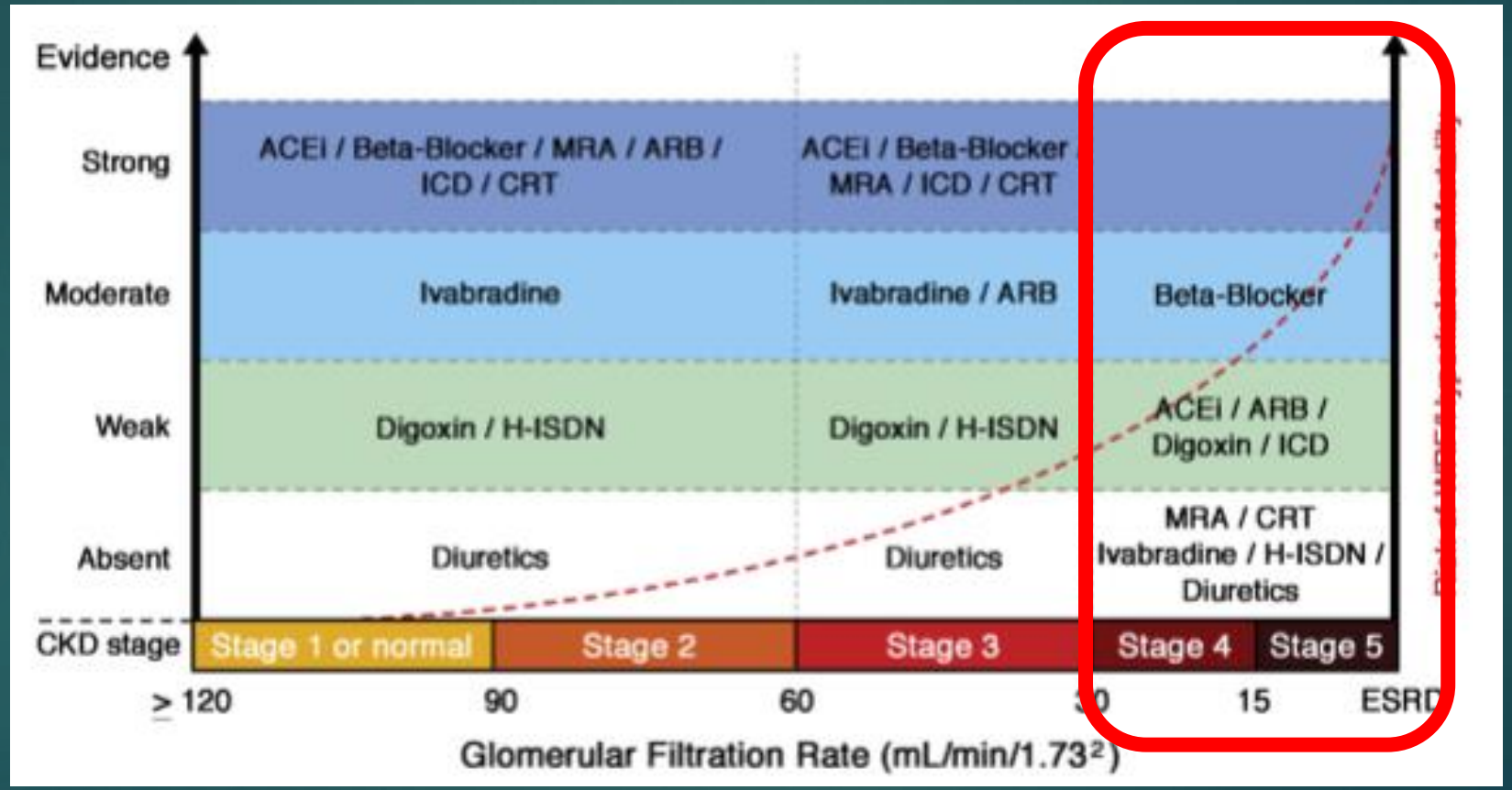
Pharmacological Treatments in HF Patients with Stage 3-5 CKD

Table 3 Pharmacological Treatments Indicated in Patients With HF and Stage 3–5 CKD

Practical Considerations	Stage 3 CKD eGFR 30–59 ml/min/1.73 m^2) Evidence*	Ref. #	Stage 4–5 CKD eGFR <30 ml/min/1.73 m^2) Evidence*	Ref. #
ACEi				
An ACEi is recommended in all patients with EF ≤40% and stage 3 CKD and might be considered in stage 4–5 CKD with careful monitoring of renal function and electrolytes.	Strong	(18–21)	Weak	(18,21)
BBL				
A BBL is recommended in all patients with EF ≤40% and stage 3 CKD and should be considered in stage 4–5 CKD.	Strong	(34–37)	Moderate	(34–36,38)
MRA				
An MRA is recommended in all patients with EF ≤35%, persisting symptoms despite ACEi and BBL therapy, and stage 3 CKD. In stage 4–5 CKD, MRA should not be given.	Strong	(7,31,33)	Absent	—
ARB				
An ARB is recommended in patients with EF ≤40% and intolerance to ACEi or having symptoms despite ACEi and BBL and intolerant of a MRA and stage 3 CKD. Add-on ARB might be considered in stage 4–5 CKD with careful monitoring of renal function and electrolytes.	Moderate	(27,78)	Weak	(30)
Digoxin				
Might be considered in patients with sinus rhythm, EF ≤35%, who do not tolerate BBL, or on top of BBL, ACEi, and/or ARB/MRA and stage 3–5 CKD with careful monitoring of electrolytes and digoxin levels (stage 4–5 CKD).	Weak	(40)	Weak	(40)
Ivabradine				
Should be considered in patients in sinus rhythm with an EF ≤35%, a heart rate ≥70 beats/min, and persisting symptoms despite treatment with BBL (or intolerance), ACEi and an MRA (or ARB), and stage 3 CKD.	Moderate	(41,42)	Absent	—
Diuretics				
Diuretics should be considered in any patient with signs and symptoms of congestion and volume overload and stage 3–5 CKD with careful monitoring of renal function and electrolytes.	Absent	—	Absent	—
ICD				
Secondary prevention An ICD is indicated in a patient with a history of ventricular arrhythmia and hemodynamic instability or survivors of cardiac arrest, and stage 3 CKD, and might be considered in stage 4–5 CKD.	Strong	(53,55,56)	Absent	—
Primary prevention An ICD is indicated in ischemic and nonischemic etiology of patients with EF ≤35%, symptomatic HF, and stage 3 CKD, and might be considered in stage 4–5 CKD.	Strong	(49,52)	Weak	(57)
CRT				
CRT is indicated in symptomatic patients (NYHA II–IV), on optimal medical therapy, in SR, with QRS duration >120 ms, LBBB QRS morphology and EF ≤35% (or QRS >130 ms and EF ≤30%) and stage 3 CKD, and might be considered in stage 4–5 CKD.	Strong	(58,59,79,80)	Absent	—
CRT should be considered in symptomatic patients (NYHA II–IV), on optimal medical therapy, in SR, with QRS duration >150 ms, irrespective of QRS morphology and EF ≤35% and stage 3 CKD, and might be considered in stage 4–5 CKD.	Moderate	(59,80)	Absent	—

K. Damman et al JACC 2014

Strength of Evidence of Improvement in Clinical Outcome for Each Treatment Group According to CKD Stages



K. Damman et al JACC 2014

ΑΝΤΙΣΤΑΣΗ ΣΤΑ ΔΙΟΥΡΗΤΙΚΑ

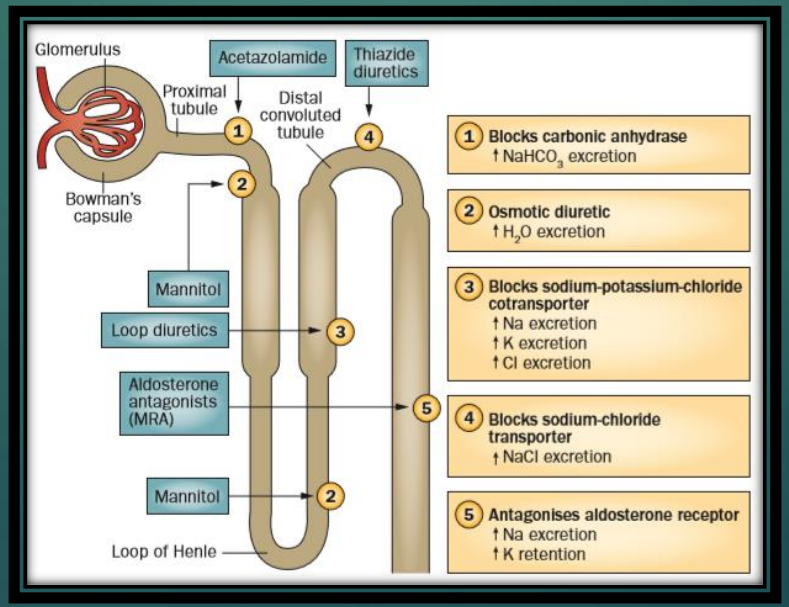
Diuretic Resistance: Definition, Epidemiology

- It can simply be defined as either a **loss of response or reduction in the response to loop diuretics**.
- Generally, failure to reduce the volume of extracellular fluid despite using diuretics appropriately can be termed as '**diuretic resistance**".
- Diuretic resistance can be expressed as **a fractional excretion of sodium (FENa+) of <0.2%** that represents the amount of sodium excreted (mmol/time) as a percentage of the filtered sodium load.
- It can develop in one out of every three HF patients.

Niel Shah et al Therapeutic Advances in Cardiovascular Disease 11(10)

Mechanism of Action of Diuretic Classes

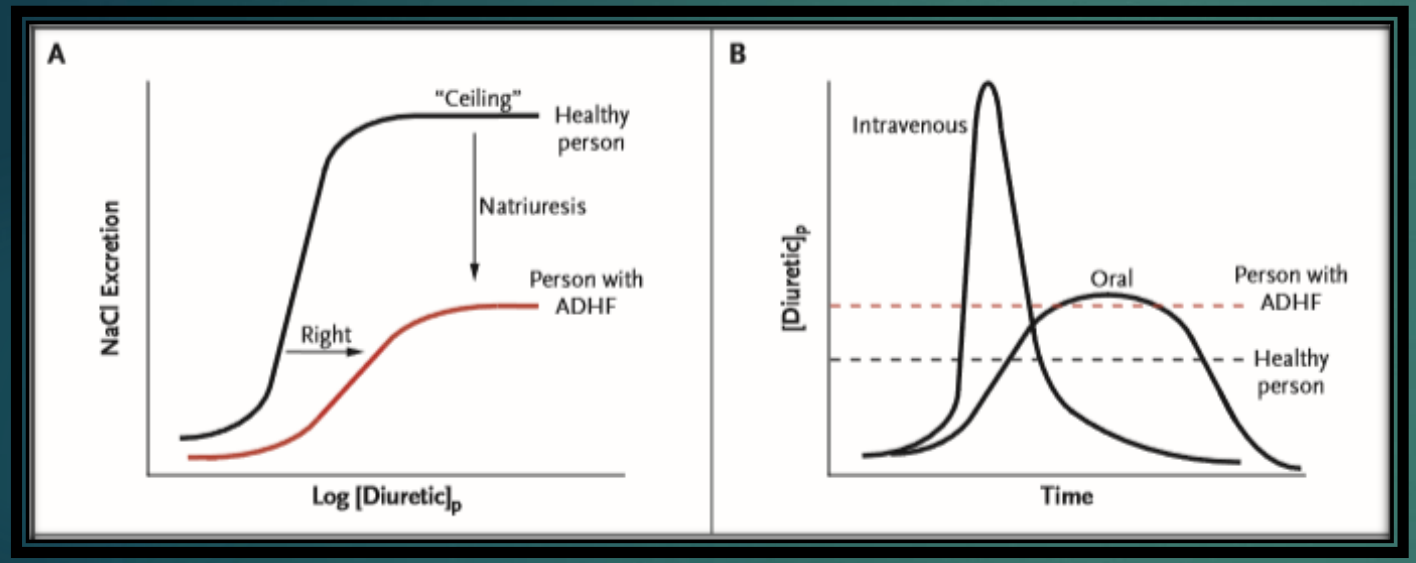
Drug Class	Examples	Mechanism of Action
Carbonic anhydrase inhibitors	Acetazolamide	Inhibition of proximal convoluted tubule sodium bicarbonate reabsorption
Loop diuretics	Furosemide Bumetanide Torsemide	Inhibition of Na/K/2Cl cotransporter in thick ascending loop of Henle
Thiazide-type diuretics	Hydrochlorothiazide Metolazone	Inhibition of Na/Cl cotransporter in distal convoluted tubule
Potassium-sparing diuretics	Amiloride Triamterene	Inhibition of aldosterone-responsive epithelial Na channel (ENaC) in distal nephron + collecting tubule
Aldosterone antagonists	Spironolactone Eplerenone	Inhibition of aldosterone receptors in distal nephron + collecting tubule, reducing Na channel and Na/K ATPase
Vasopressin antagonists	Conivaptan* Tolvaptan	Inhibition of V_2 receptors in distal nephron + collecting tubule, reducing aquaporin (water) channel density

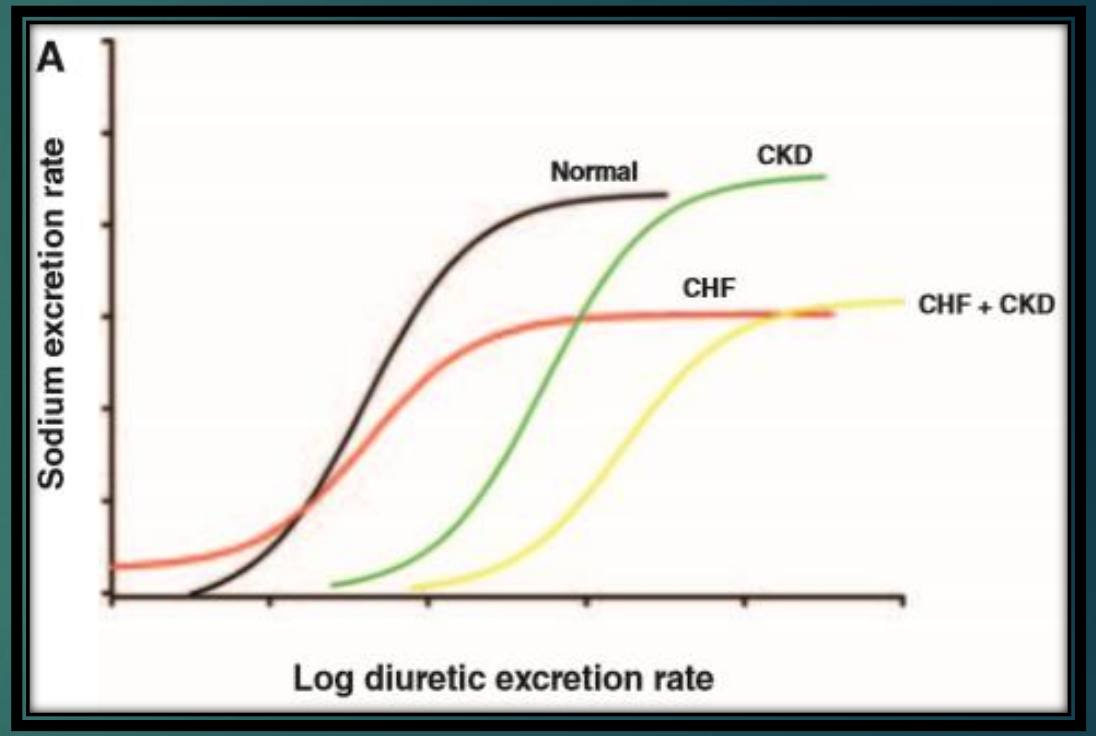


J. Maaten et al Nat Rev Card 2015

Jentzer et a JACC, 2010

Pharmacokinetic &Pharmacodynamic Properties of Loop Diuretics





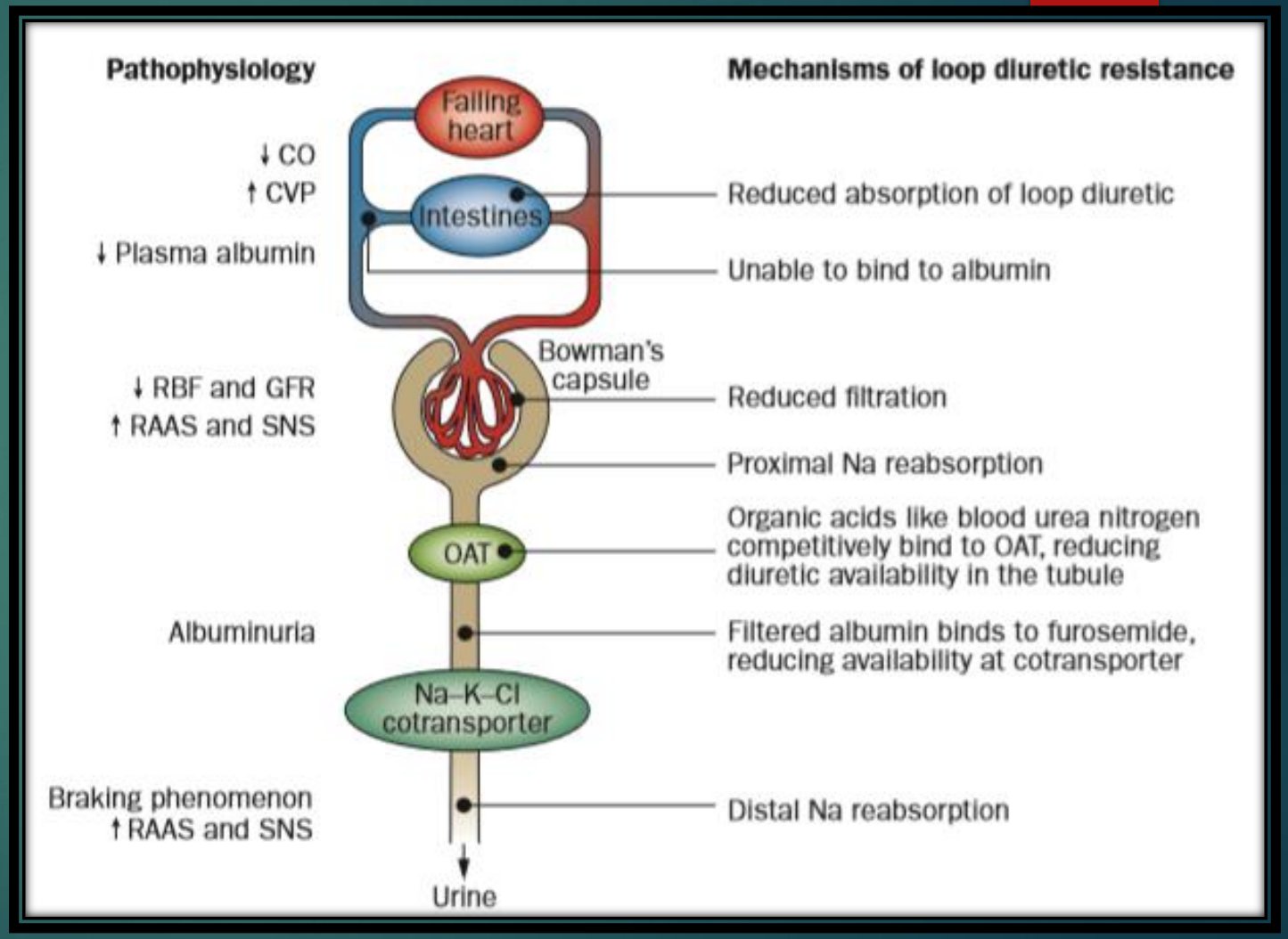
DH. Ellison et al N Engl J Med 377;20: 2017

D Aronson European Journal of Heart Failure 2017

Causes and Pathophysiology of Diuretic Resistance

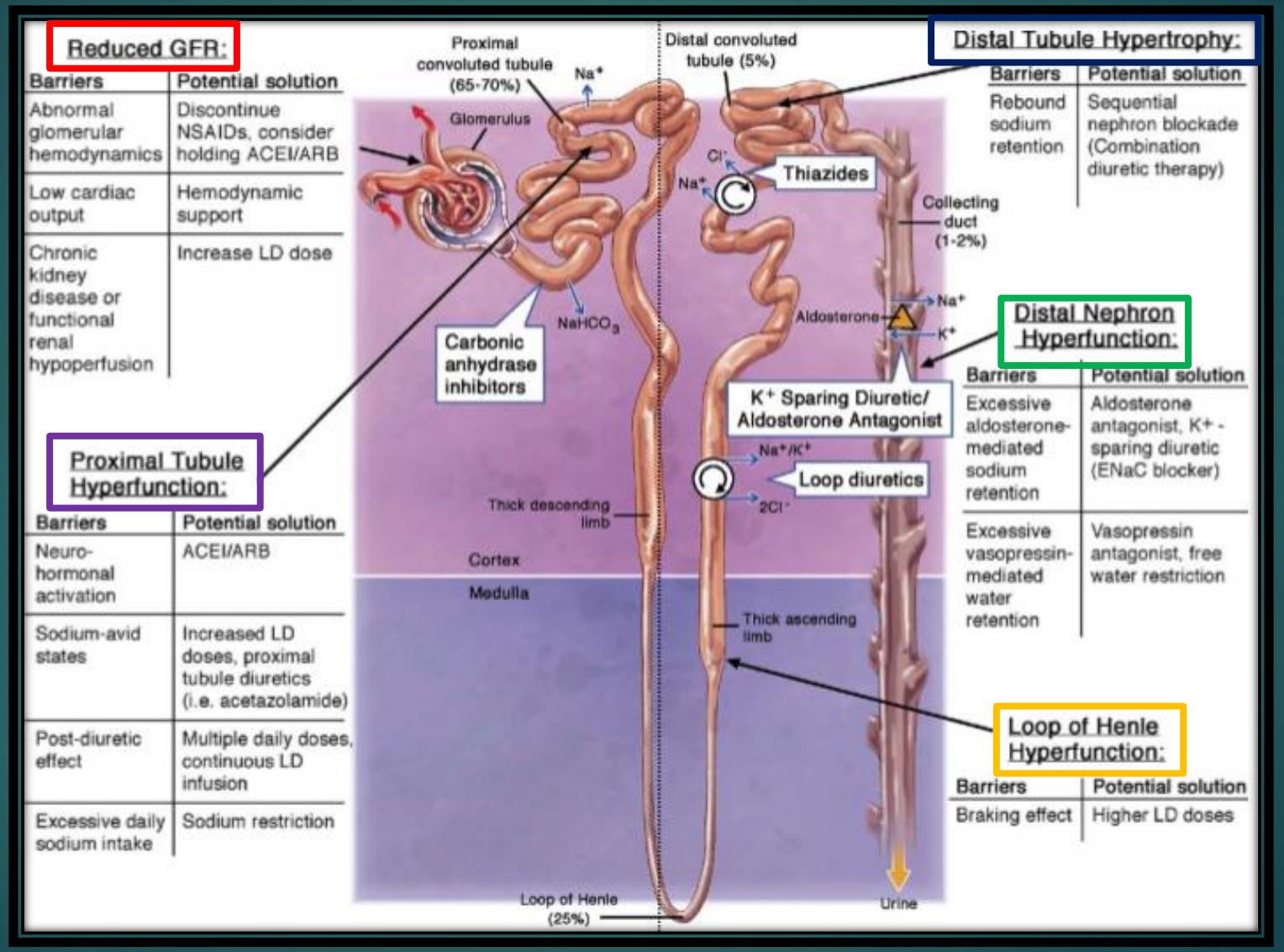
Table 1. Causes of Diuretic Resistance.

- Inadequate dose of diuretic
- Nonadherence
  - Not taking drug
  - High sodium intake
- Pharmacokinetic factors
  - Slow absorption of diuretic because of gut edema
  - Impaired secretion of diuretic into the tubule lumen
    - Chronic kidney disease
    - Aging
    - Drugs
      - Nonsteroidal antiinflammatory drugs*
      - Probenecid
- Hypoproteinemia
- Hypotension
- Nephrotic syndrome
- Antinatriuretic drugs
  - Nonsteroidal antiinflammatory drugs*
  - Antihypertensive agents
- Low renal blood flow
- Nephron remodeling
- Neurohormonal activation



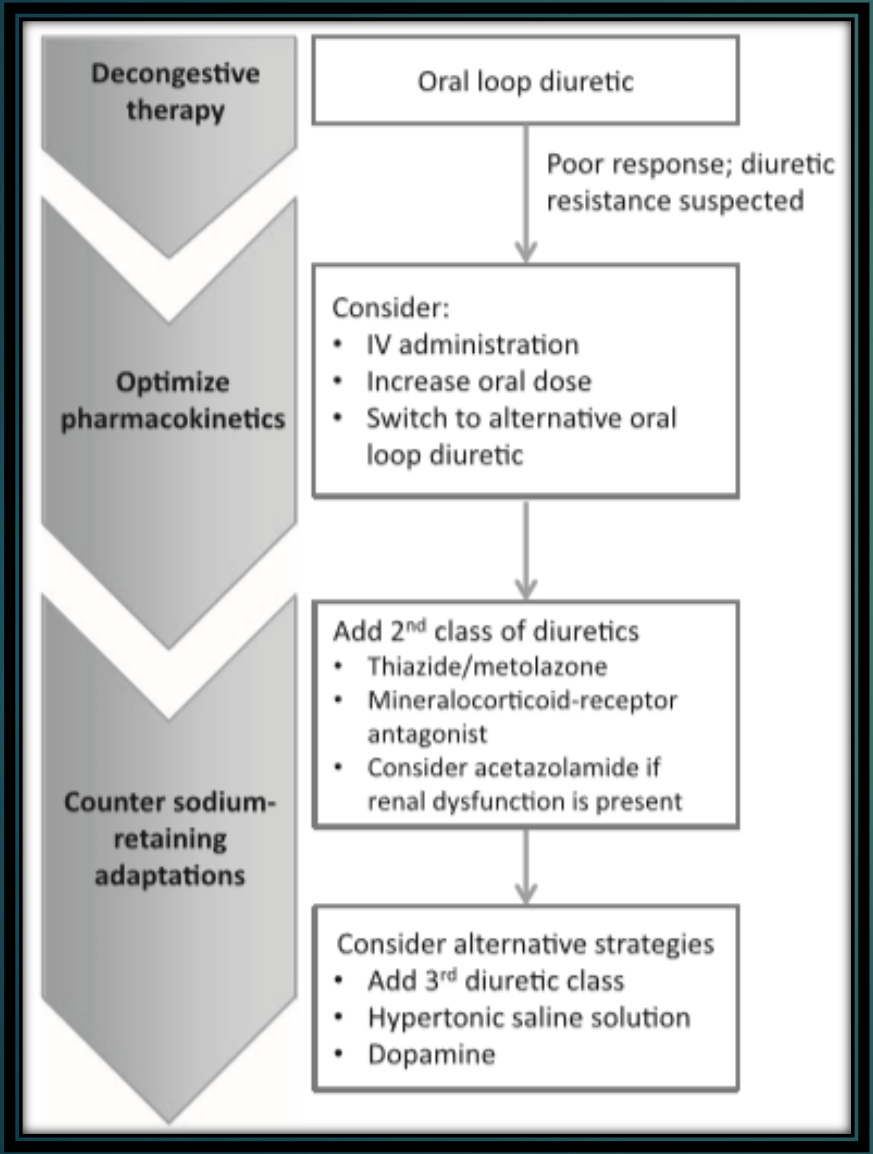
JM. ter Maaten et al Nature Reviews Cardiology 2015

Pathophysiology of Diuretic Resistance



Jentzer et a JACC Vol. 56, No. 19, 2010

How to Overcome Diuretic Resistance?



- **IV administration** of diuretic therapy.
- **High doses** (ie, up to 2.5 times the patient's dose before admission)
- **Continuous infusion** of diuretic therapy.
- **Change** the Loop Diuretic (**Torsemide**).
- **Sequential nephron blockade**: Drugs that block sodium chloride reabsorption there (e.g., metolazone or other thiazide-type drugs).
- **Carbonic anhydrase inhibitors**, which inhibit the chloride bicarbonate exchanger pendrin, may be especially useful when metabolic alkalosis occurs.
- **Extracorporeal ultrafiltration** is a theoretically attractive method with which to remove sodium chloride and water, with less stimulation of the renin–angiotensin–aldosterone system and a lower risk of rehospitalization than the risk associated with the use of diuretics
- **Subcutaneous furosemide** may allow delivery of "intravenous-like" diuretics outside the hospital setting, with potentially important implications for care delivery and cost.

BN. Bowman Cardiology in Review 2016

Η ΔΙΓΟΞΙΝΗ ΣΗΜΕΡΑ

The demonization of Digitalis

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI	Year
Hallberg 2007 (no heart failure)	0.3507	0.049	7.4%	1.42 [1.29, 1.56]	2007
Hallberg 2007 (heart failure)	0	0.0316	8.4%	1.00 [0.94, 1.06]	2007
Gjesdal 2008	0.4574	0.1035	4.3%	1.58 [1.29, 1.94]	2008
Fauchier 2009	-0.1054	0.1582	2.5%	0.90 [0.66, 1.23]	2009
Friberg 2010	0.0953	0.0802	5.5%	1.10 [0.94, 1.29]	2010
Whitbeck 2013	0.3436	0.0866	5.2%	1.41 [1.19, 1.67]	2013
Rodriguez-Manero 2014	0.3507	0.3123	0.8%	1.42 [0.77, 2.62]	2014
Chao 2014	0.1906	0.0922	4.9%	1.21 [1.01, 1.45]	2014
Gamst 2014	0.1484	0.046	7.6%	1.16 [1.06, 1.27]	2014
Turakhia 2014	0.1906	0.0172	9.0%	1.21 [1.17, 1.25]	2014
Shah 2014 (heart failure)	0.131	0.0182	9.0%	1.14 [1.10, 1.18]	2014
Shah 2014 (no heart failure)	0.157	0.0133	9.1%	1.17 [1.14, 1.20]	2014
Mulder 2014	-0.8916	0.3924	0.5%	0.41 [0.19, 0.88]	2014
Allen 2015 (heart failure)	0.0392	0.097	4.6%	1.04 [0.86, 1.26]	2015
Pastori 2015	0.729	0.328	0.7%	2.07 [1.09, 3.94]	2015
Okin 2015	0.0392	0.1806	2.1%	1.04 [0.73, 1.48]	2015
Washam 2015	0.131	0.0618	6.6%	1.14 [1.01, 1.29]	2015
Allen 2015 (no heart failure)	0.1989	0.1277	3.4%	1.22 [0.95, 1.57]	2015
Al-Zakwani 2015 (no heart failure)	1.4398	0.3254	0.8%	4.22 [2.23, 7.99]	2015
Al-Zakwani 2015 (heart failure)	0.3148	0.3142	0.8%	1.37 [0.74, 2.54]	2015
Freeman 2015	0.5365	0.0601	6.7%	1.71 [1.52, 1.92]	2015
Total (95% CI)			**100.0%**	**1.22 [1.15, 1.30]**	

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 130.63$, df = 20 ($P < 0.00001$); $I^2 = 85\%$

Test for overall effect: $Z = 6.79$ ($P < 0.00001$)

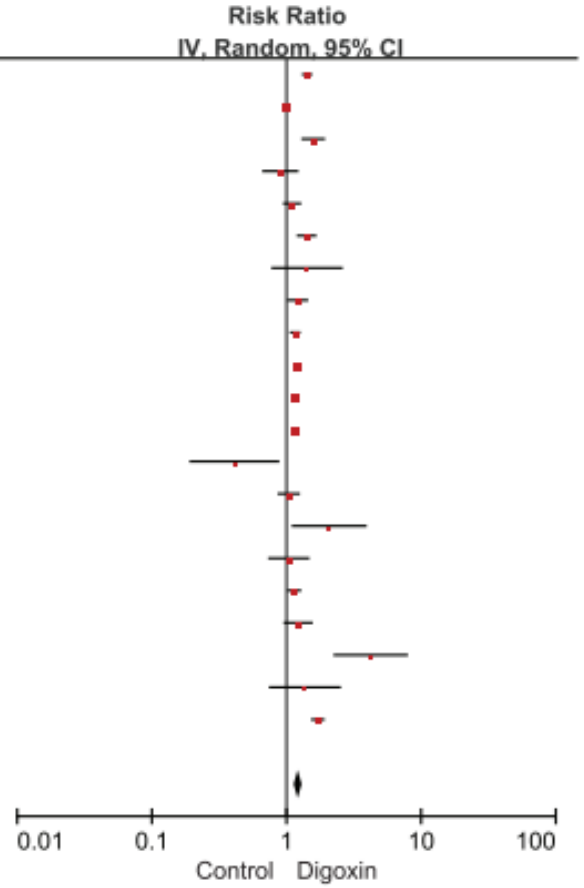
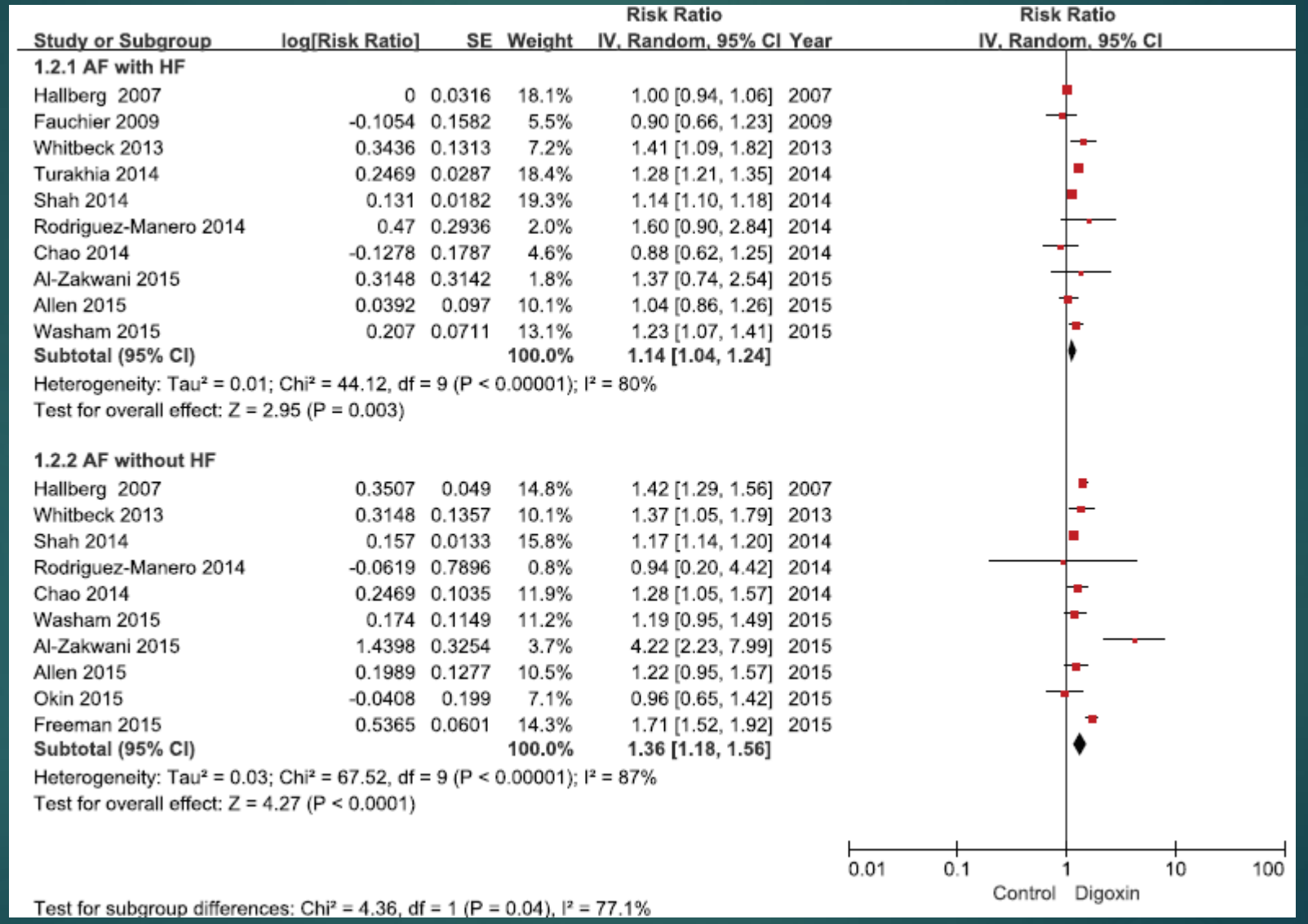


FIGURE 2. Forest plot of the comparison: digoxin therapy versus no digoxin therapy, outcome: all-cause mortality in atrial fibrillation (AF) patients.

Y. Chen et al. Medicine 94, 52, 2015

Digitalis: AF with or without HF



Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI	Year
1.2.1 AF with HF					
Hallberg 2007	0	0.0316	18.1%	1.00 [0.94, 1.06]	2007
Fauchier 2009	-0.1054	0.1582	5.5%	0.90 [0.66, 1.23]	2009
Whitbeck 2013	0.3436	0.1313	7.2%	1.41 [1.09, 1.82]	2013
Turakhia 2014	0.2469	0.0287	18.4%	1.28 [1.21, 1.35]	2014
Shah 2014	0.131	0.0182	19.3%	1.14 [1.10, 1.18]	2014
Rodriguez-Manero 2014	0.47	0.2936	2.0%	1.60 [0.90, 2.84]	2014
Chao 2014	-0.1278	0.1787	4.6%	0.88 [0.62, 1.25]	2014
Al-Zakwani 2015	0.3148	0.3142	1.8%	1.37 [0.74, 2.54]	2015
Allen 2015	0.0392	0.097	10.1%	1.04 [0.86, 1.26]	2015
Washam 2015	0.207	0.0711	13.1%	1.23 [1.07, 1.41]	2015
Subtotal (95% CI)			**100.0%**	**1.14 [1.04, 1.24]**	
Heterogeneity: Tau² = 0.01; Chi² = 44.12, df = 9 (P < 0.00001); I² = 80%					
Test for overall effect: Z = 2.95 (P = 0.003)					
1.2.2 AF without HF					
Hallberg 2007	0.3507	0.049	14.8%	1.42 [1.29, 1.56]	2007
Whitbeck 2013	0.3148	0.1357	10.1%	1.37 [1.05, 1.79]	2013
Shah 2014	0.157	0.0133	15.8%	1.17 [1.14, 1.20]	2014
Rodriguez-Manero 2014	-0.0619	0.7896	0.8%	0.94 [0.20, 4.42]	2014
Chao 2014	0.2469	0.1035	11.9%	1.28 [1.05, 1.57]	2014
Washam 2015	0.174	0.1149	11.2%	1.19 [0.95, 1.49]	2015
Al-Zakwani 2015	1.4398	0.3254	3.7%	4.22 [2.23, 7.99]	2015
Allen 2015	0.1989	0.1277	10.5%	1.22 [0.95, 1.57]	2015
Okin 2015	-0.0408	0.199	7.1%	0.96 [0.65, 1.42]	2015
Freeman 2015	0.5365	0.0601	14.3%	1.71 [1.52, 1.92]	2015
Subtotal (95% CI)			**100.0%**	**1.36 [1.18, 1.56]**	
Heterogeneity: Tau² = 0.03; Chi² = 67.52, df = 9 (P < 0.00001); I² = 87%					
Test for overall effect: Z = 4.27 (P < 0.0001)					
Test for subgroup differences: Chi² = 4.36, df = 1 (P = 0.04), I² = 77.1%					

Y. Chen et al. Medicine 94, 52, 2015

Digitalis indication in HF

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	185

❖Digoxin may be considered in patients ***in sinus rhythm*** with symptomatic HFrEF to reduce the risk of hospitalization (both all-cause and HF hospitalizations)

❖In patients with symptomatic HF and ***AF***, digoxin may be useful to slow a rapid ventricular rate, but it is only recommended for the treatment of patients with HFrEF and **AF with rapid ventricular rate** when other therapeutic options cannot be pursued.

❖A resting **ventricular rate in the range of 70– 90 bpm** is recommended based on current opinion,

ESC Heart Failure Guidelines 2016

Non SVT στην Καρδιακή Ανεπάρκεια

Incidence of ventricular arrhythmias in HF

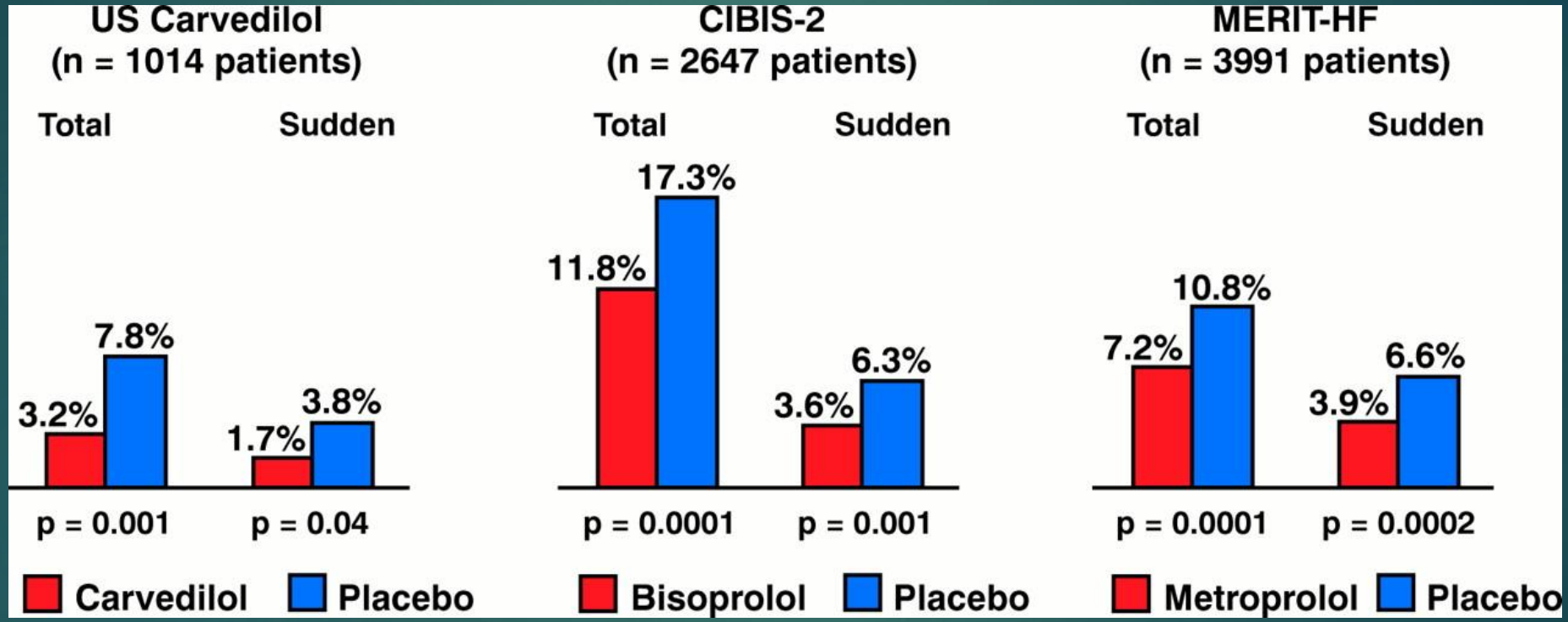
Table 1 **Studies of the natural history of ventricular arrhythmias in chronic heart failure: some examples**

Author	Description	N	Prevalence/incidence
Studies of ventricular tachyarrhythmias in HF-rEF			
Podrid *et al.*[55]	Review of 13 case series baseline prevalences	1322	VPBs = 87%, NSVT = 45%
Cleland *et al.*[56]	Review of six CHF RCTs baseline	516–1080	Couplets or VPBs > 30/h = 60–80% NSVT = 30–60%
Liao *et al.*[57]	Sampling of national insurance data	7894	Incidence of VT/VF/SCD = 1.95% per year
Baldassero *et al.*[58]	Registry baseline	5517	Prevalence NSVT = 28.7%
Packer *et al.*[59]	SCD-HeFT trial FU	2521	Incidence of VT-related death 1.2% in the ICD group, 2.4% on amiodarone, and 3.0% on placebo
Studies of ventricular bradyarrhythmias in HF-rEF			
Cleland *et al.*[60]	Registry	11 016	Prevalence bradyarrhythmia = 6.0%
Studies of ventricular tachyarrhythmias in HF-pEF			
McMurray *et al.*[61]	I-Preserve trial baseline	4133	Prevalence of ICD use = 0.3%

CHF, chronic heart failure; HF-rEF, heart failure with reduced ejection fraction; HF-pEF, heart failure with preserved ejection fraction; ICD, implanted cardioverter defibrillator; NSVT, non-sustained ventricular tachycardia; RCT, randomized controlled trial; VPB, ventricular premature beats; VF, ventricular fibrillation; VT, ventricular tachycardia.

EHRA/HFA joint consensus document on arrhythmias in heart failure, 2015

β Blockers in patients with heart failure: effects on total mortality and SCD



A. Maggioni Heart 2001;85:97-103

Beta-blockers in HF

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

A beta-blocker is recommended, in addition an ACE-I[d], for patients with stable, symptomatic HFrEF to reduce the risk of HF hospitalization and death.	I	A	167–173

Beta-blocker		
Bisoprolol	1.25 o.d.	10 o.d.
Carvedilol	3.125 b.i.d.	25–50 b.i.d.
Metoprolol succinate (CR/XL)	12.5/25 o.d.	200 o.d.
Nebivolol[c]	1.25 o.d.	10 o.d.

ESC Heart Failure Guidelines 2016

Management of Non-SVT in HF

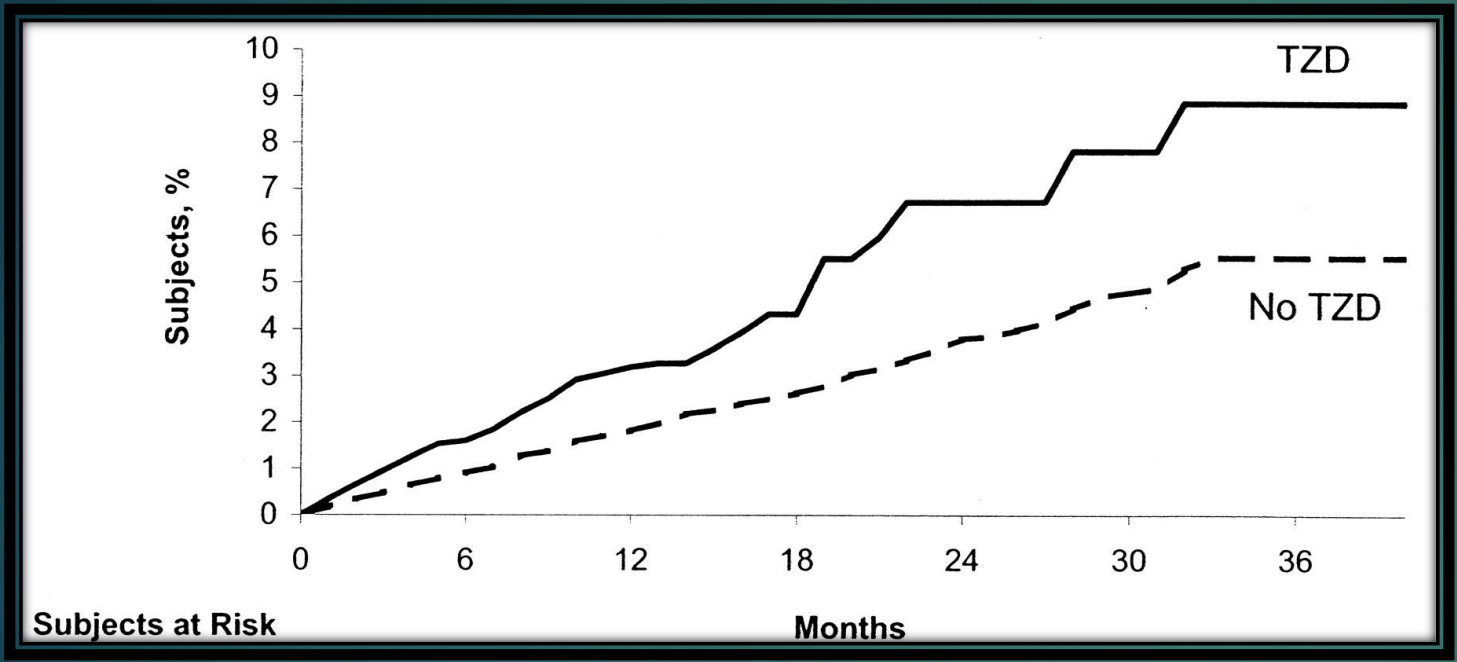
Recommendations for the management of ventricular tachyarrhythmias in heart failure

Several strategies should be considered to reduce recurrent symptomatic arrhythmias in patients with an ICD (or in those who are not eligible for ICD), including attention to risk factors and optimal pharmacological treatment of HF, amiodarone, catheter ablation and CRT.	IIa	C	
Routine use of antiarrhythmic agents is not recommended in patients with HF and asymptomatic ventricular arrhythmias because of safety concerns (worsening HF, proarrhythmia, and death).	III	A	247, 248, 364, 365
Treatment with beta-blocker, MRA and sacubitril/valsartan reduces the risk of sudden death and is recommended for patients with HFrEF and ventricular arrhythmias (as for other patients)(see Section 7).	I	A	162, 170–175
Implantation of an ICD or CRT-D device is recommended for selected patients with HFrEF (see Section 8).	I	A	223–226, 388

ESC Heart Failure Guidelines 2016

Αντιδιαβητικά στην Καρδιακή Ανεπάρκεια

The bad experience of Glitazones in HF



FDA places "black box" warning on antidiabetes drugs

Janice Hopkins Tanne NEW YORK

The US Food and Drug Administration has asked the makers of two antidiabetes drugs—rosiglitazone (marketed as Avandia), made by GlaxoSmithKline, and pioglitazone (Actos), made by Takeda—to place "black box" warnings, the most serious kind, on their labels.

The new labels warn of an increased risk of congestive heart failure. Andrew von Eschenbach, the FDA's commissioner, announced the warning at a hearing of the US House of Representatives' Committee on Oversight and Government Reform last week to examine the FDA's role in evaluating the safety of rosiglitazone.

The new labels do not address the question of whether these drugs pose an increased risk of heart attacks and strokes.

The cardiovascular risk was raised last month by an article and accompanying editorial in the *New England Journal of Medicine* (doi: 10.1056/NEJMoa072761).

John Buse, of the University of North Carolina, and the incoming president of the American Diabetes Association, told the hearing that SmithKlineBeecham (now part of GlaxoSmithKline) had tried to intimidate him when he spoke out with his concerns about rosiglitazone's cardiovascular safety.

Dr Buse said that he had spoken at least twice in June 1999 about "a trend toward increases in serious cardiovascular events and cardiovascular deaths with Avandia as compared to active comparators."

He said that employees of SmithKlineBeecham had told him in telephone calls that "there were some in the company who felt that my actions were scurrilous enough to attempt to hold me liable for a loss in market capitalisation [share value]."

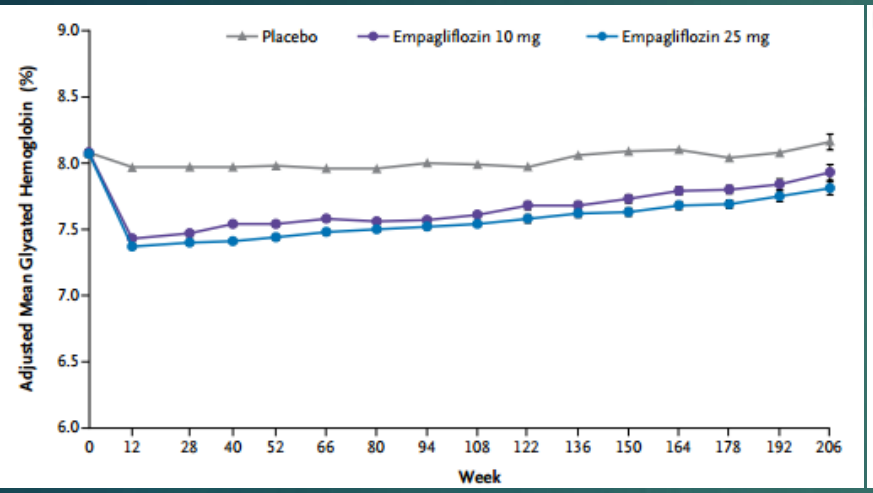
See Editorial, p 1233

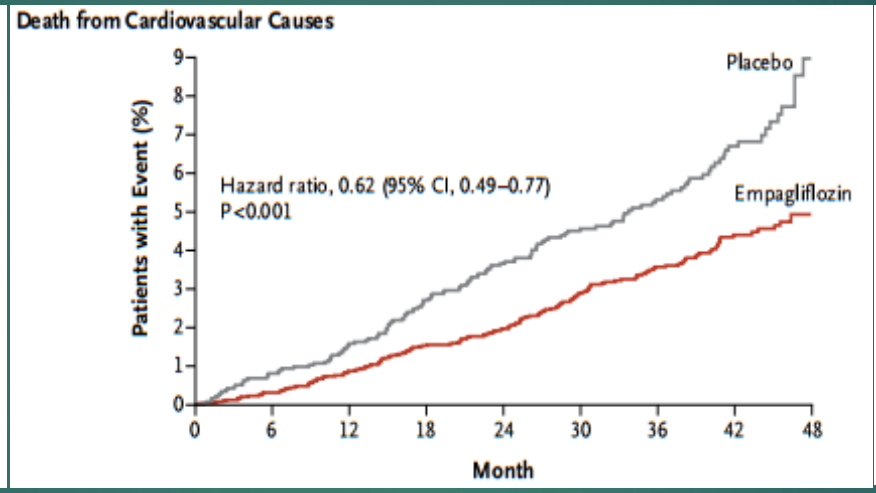
The new labels warn of an increased risk of congestive heart failure, because rosiglitazone and related drugs can cause fluid retention.

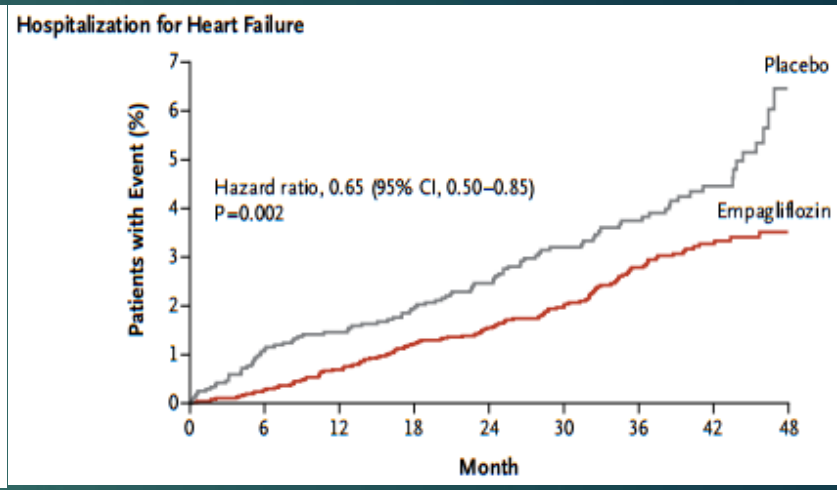
TE. Delea et al Diabetes Care 2006

Empagliflozin- diabetes type 2

- Inhibitors of sodium–glucose cotransporter 2 **decreases renal glucose reabsorption**, thereby increasing urinary glucose excretion







- **Empagliflozin reduced hospitalization for HF and mortality**, but not myocardial infarction or stroke, **in patients with diabetes at high cardiovascular risk**.
- EMPEROR HF (HFRF + HFPF) clinical trial programme will evaluate the efficacy and safety of empagliflozin in patients with chronic heart failure, including those with and without type 2 diabetes. Estimated completion: 2020

EMPA-REG Trial NEJM 2015

Αντιδιαβητικά Φάρμακα σε ασθενείς με Κ/Α

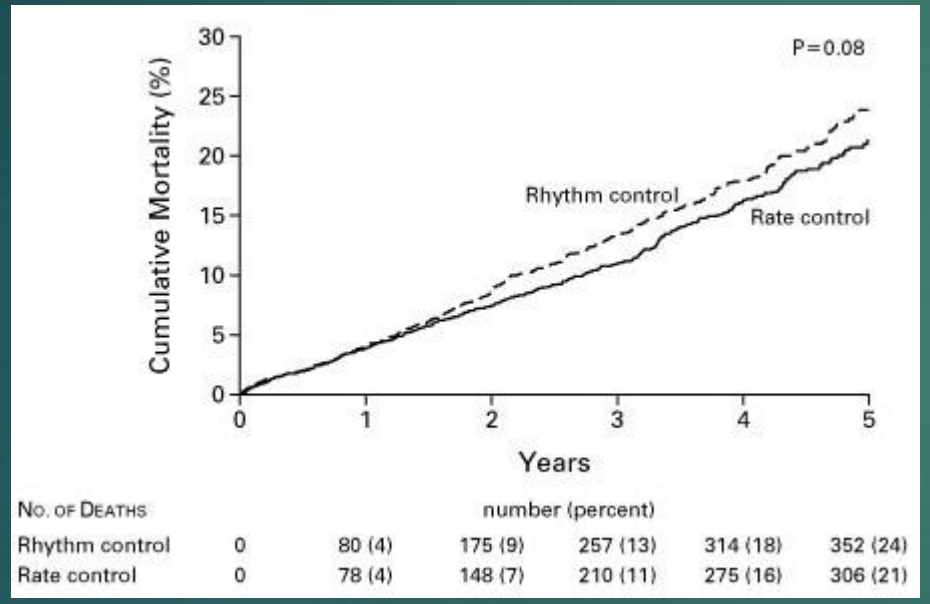
	CVD	HF	Hypoglycemia	Others
Metformin	😊 (UKPDS/DIGAMI 2)	Indicated	Low risk	…
Acarbose	😊 (MERIA, STOP-NIDDM), ACE ongoing	Can be used	Low risk	…
Pioglitazone	😊 (PROactive)	Contraindicated >NYHA I	Low risk	Fluid retention
DPP4-inhibitors	😐 No CV harm	Increase in HF? (not sitagliptin 😊)	Low risk	…
GLP1 receptor agonists	Emerging CVOT data (😐 ELIXA, 😊 LEADER)	Can be used?	Low risk	↑ Heart rate
SGLT2 inhibitors	😊 EMPA-REG OUTCOME	Can/should be used	Low risk	↑ LDL-C, ↑ genitourinary infections
Sulfonylureas	😊 (UKPDS) 😐 Neutral (DIGAMI 2)	(Not recommended)?	↑↑ Risk (↑ related CV risk in ORIGIN)	Inhibit ischemic preconditioning (?)
Insulin	😊 (UKPDS) ☹ Some adverse effects (DIGAMI 2)	?, but neutral with insulin glargine	↑↑ Risk (low-related CV risk in ORIGIN)	Potential fluid retention

Standl et al Circ Res. 2016

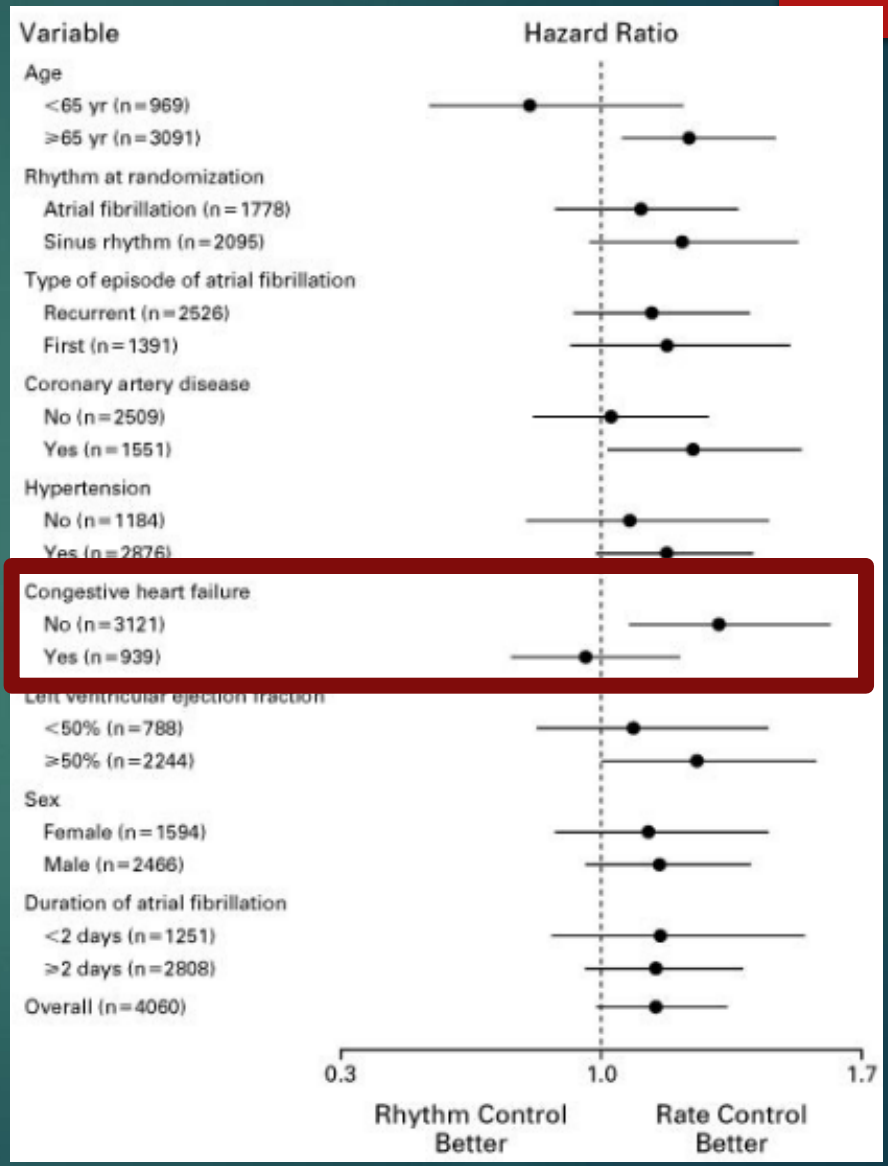
Κολπική Μαρμαρυγή και Καρδιακή Ανεπάρκεια: Rate ή Rhythm Control?

AF in HF: Rate or Rhythm Control?

Cumulative Mortality from Any Cause in the Rhythm-Control Group and the Rate-Control Group.

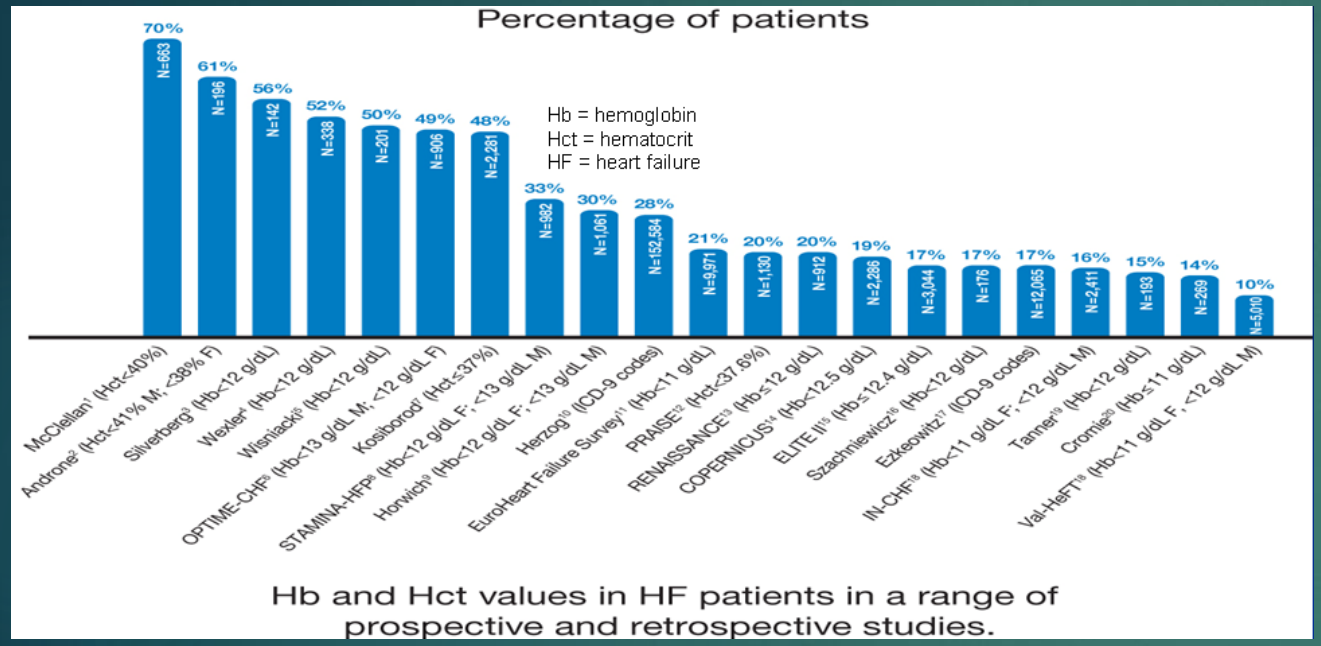


No. of Deaths		number (percent)				
Rhythm control	0	80 (4)	175 (9)	257 (13)	314 (18)	352 (24)
Rate control	0	78 (4)	148 (7)	210 (11)	275 (16)	306 (21)

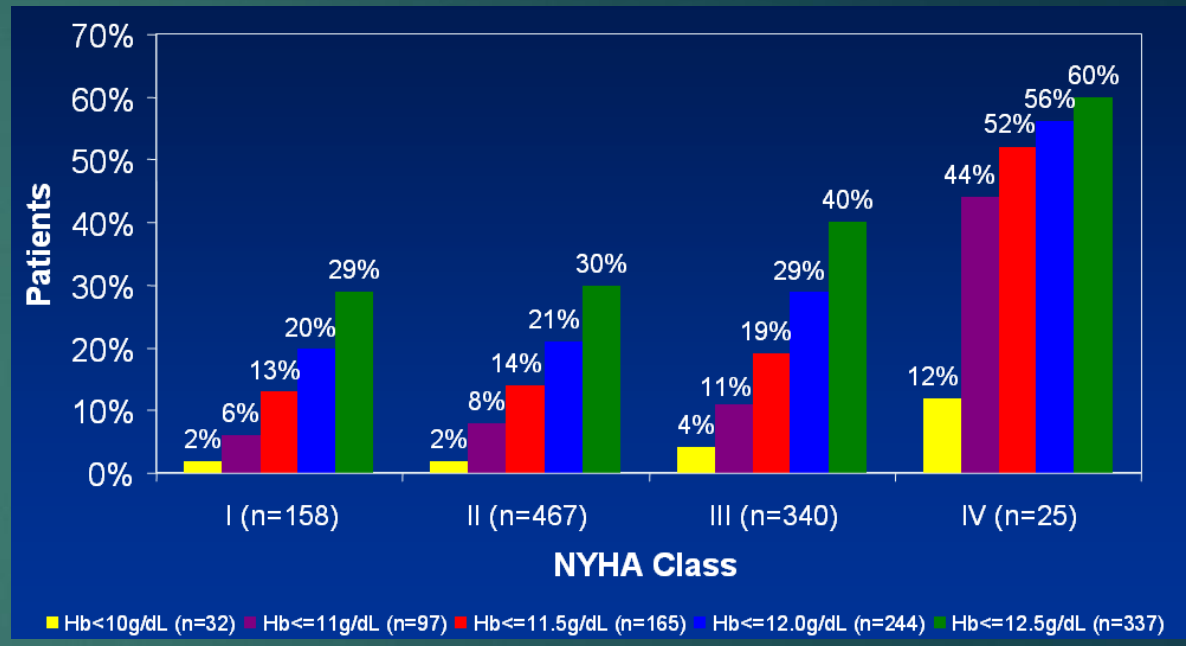


AFFRIM Study, N Engl J Med 2002

Anemia in Heart Failure



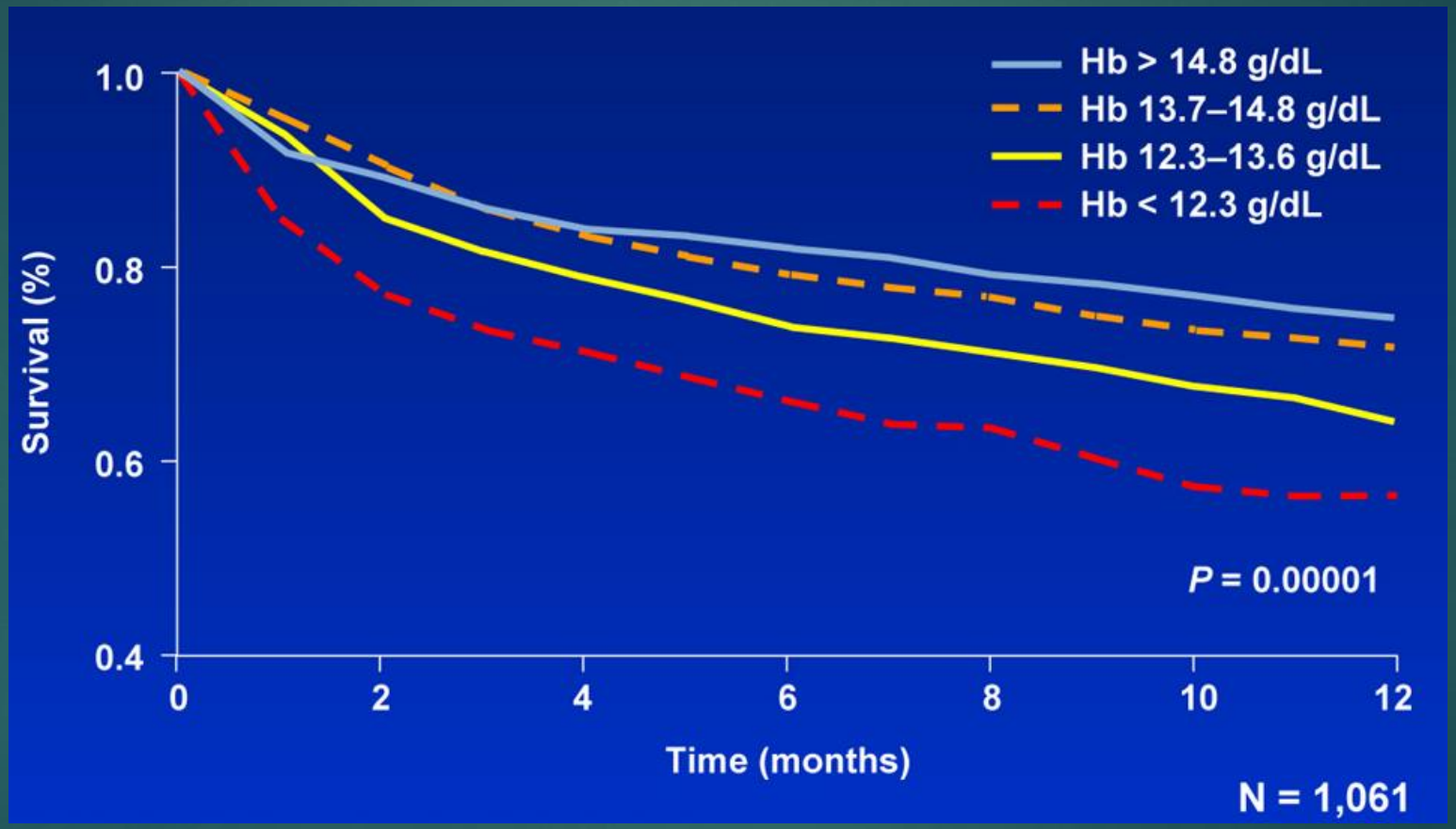
Hb and Hct values in HF patients in a range of prospective and retrospective studies.



20% των εξωνοσοκομειακών και 30% των νοσηλευομένων ασθενών έχουν αναιμία

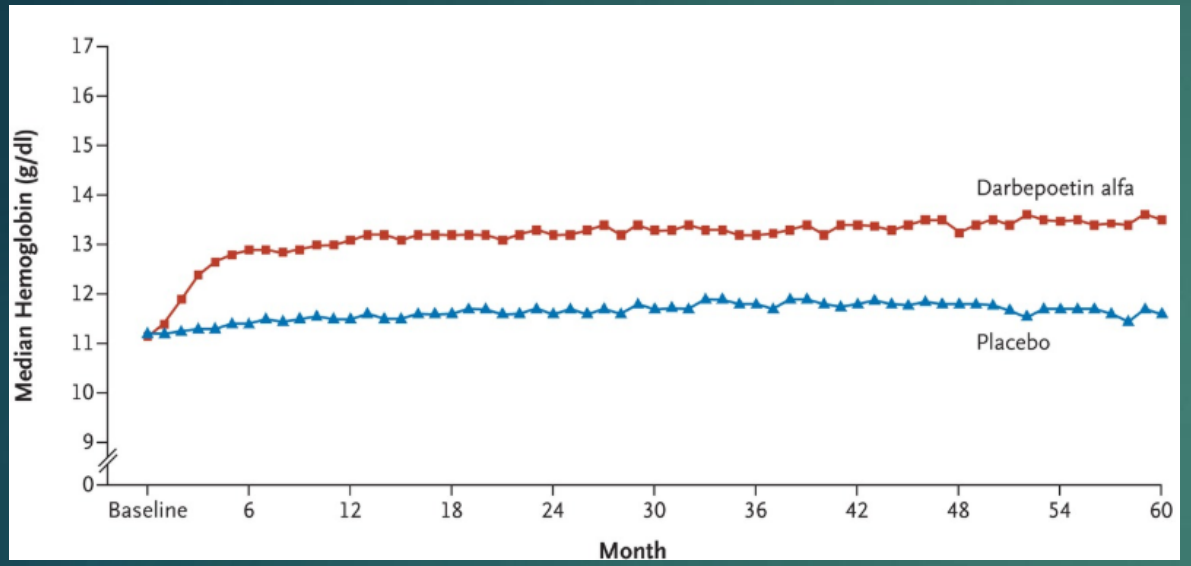
STAMINA-HFP, J Cardiac Failure, 2003

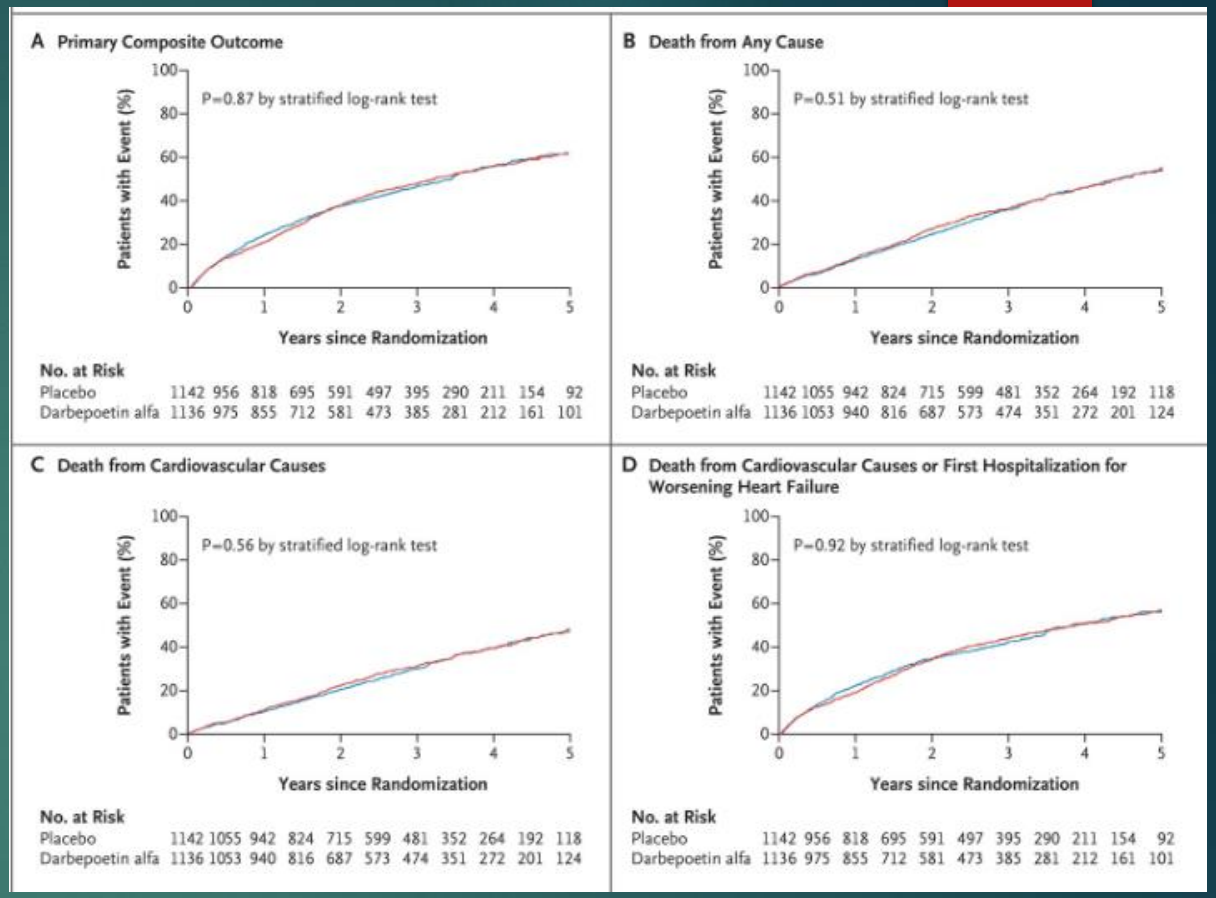
Survival of Heart Failure Patients



TB. Horwich et al, JACC 2002

Erythropoietin in Heart Failure Anemia

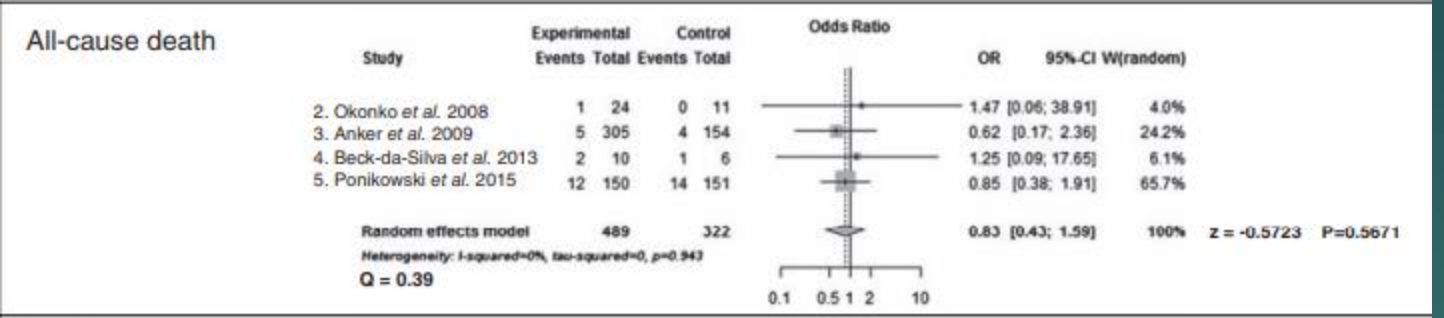


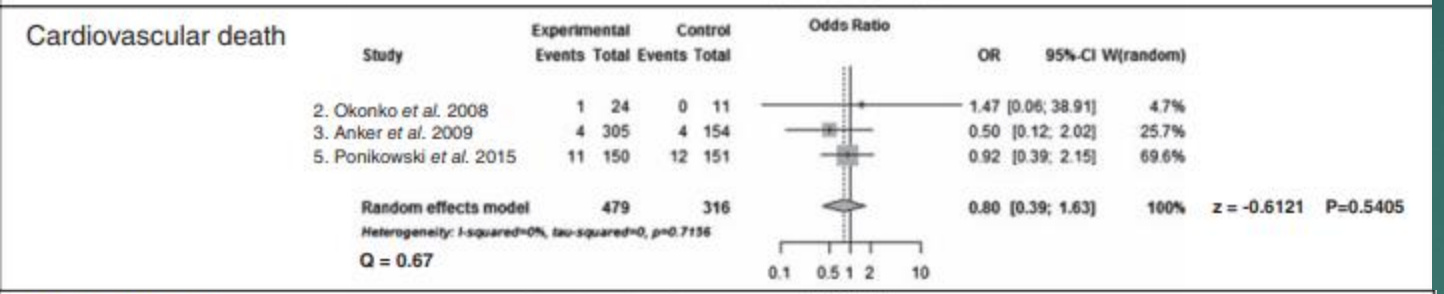


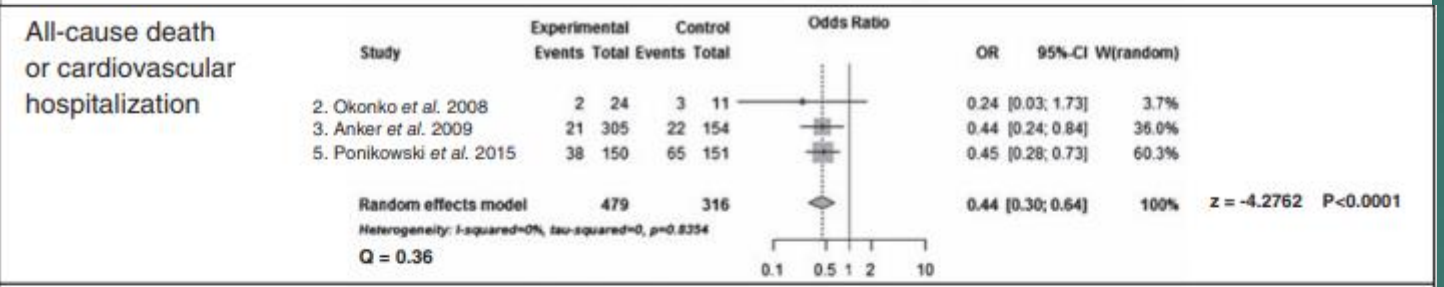
The correction of anemia with the use of darbepoetin alfa **did not reduce the rate of death or hospitalization** among patients with systolic heart failure who were receiving contemporary treatment. Moreover, there was a significant **increase in the risk of thromboembolic events** among patients receiving darbepoetin alfa.

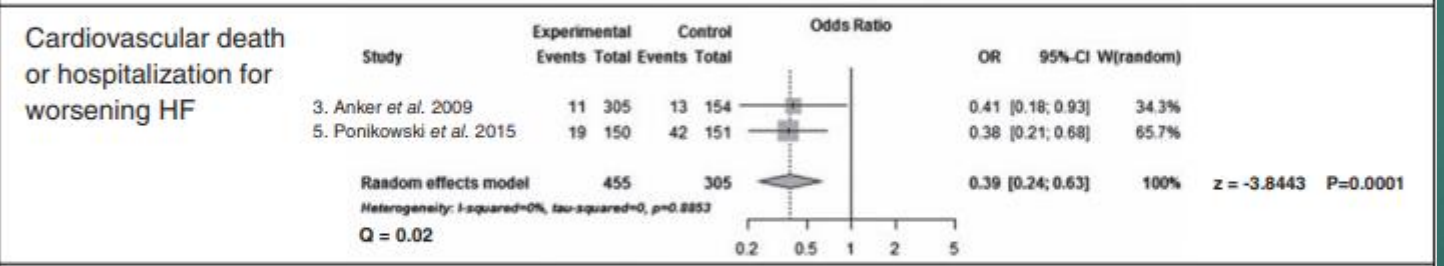
K Swedberg et al NEJM 2013

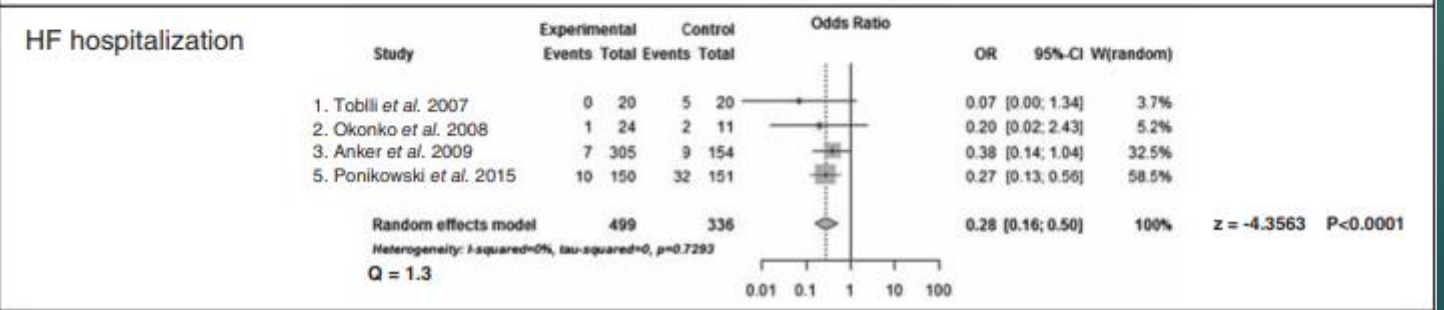
Intravenous iron therapy in HFrEF











FAIR-HF trial
CONFIRM-HF trial

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

- Serum Ferritin<100 µg/L
- Serum Ferritin=100-300 µg/L και Transferin Saturation<20%

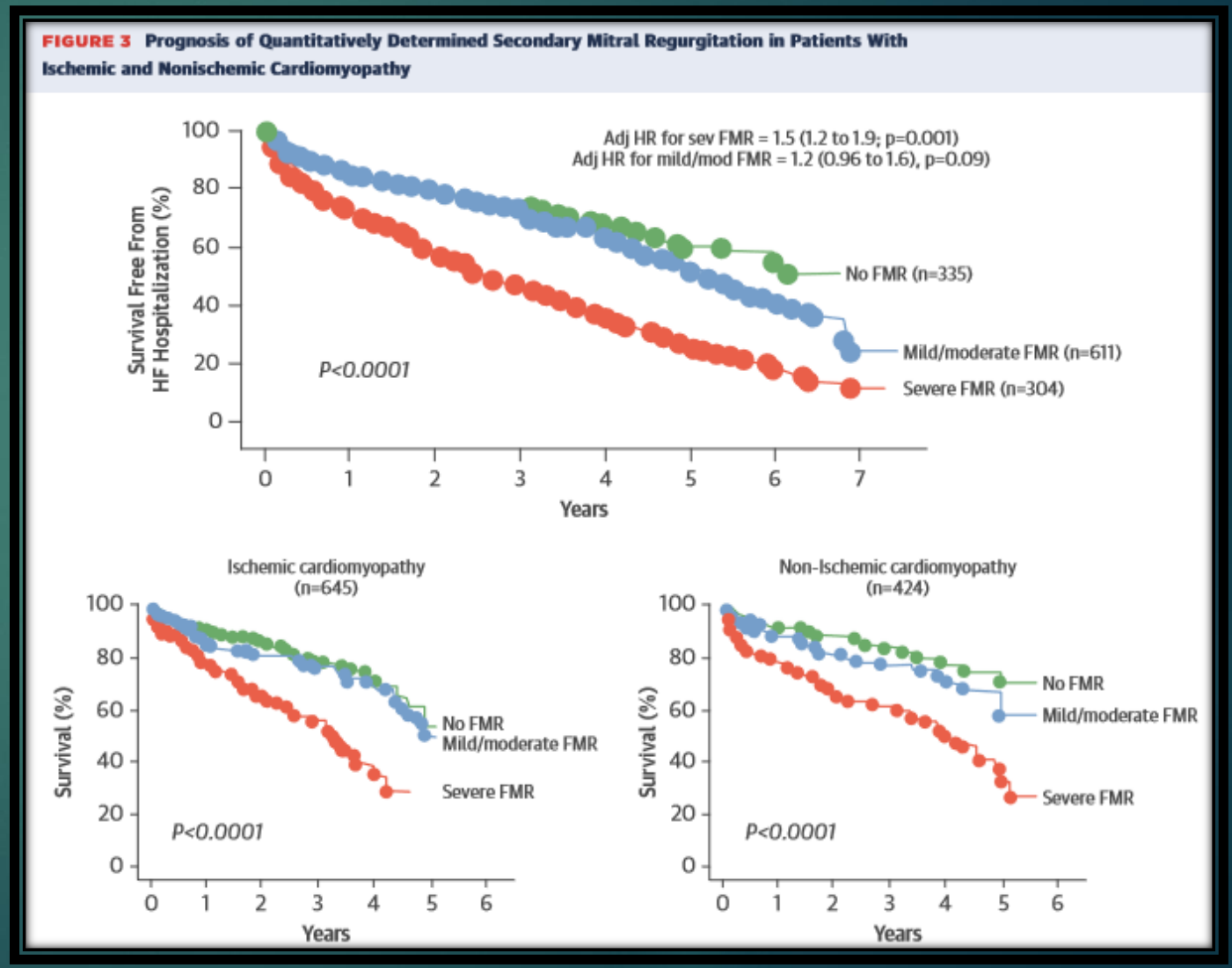
EA. Jankowska et al Eur J Heart Fail 2016

ΛΕΙΤΟΥΡΓΙΚΗ ΑΝΕΠΑΡΚΕΙΑ ΜΙΤΡΟΕΙΔΟΥΣ

Survival and Hospitalization in Heart Failure according to the degree of FMR

FMR is not a primary organic valve disease but rather is secondary to continued left ventricular remodeling

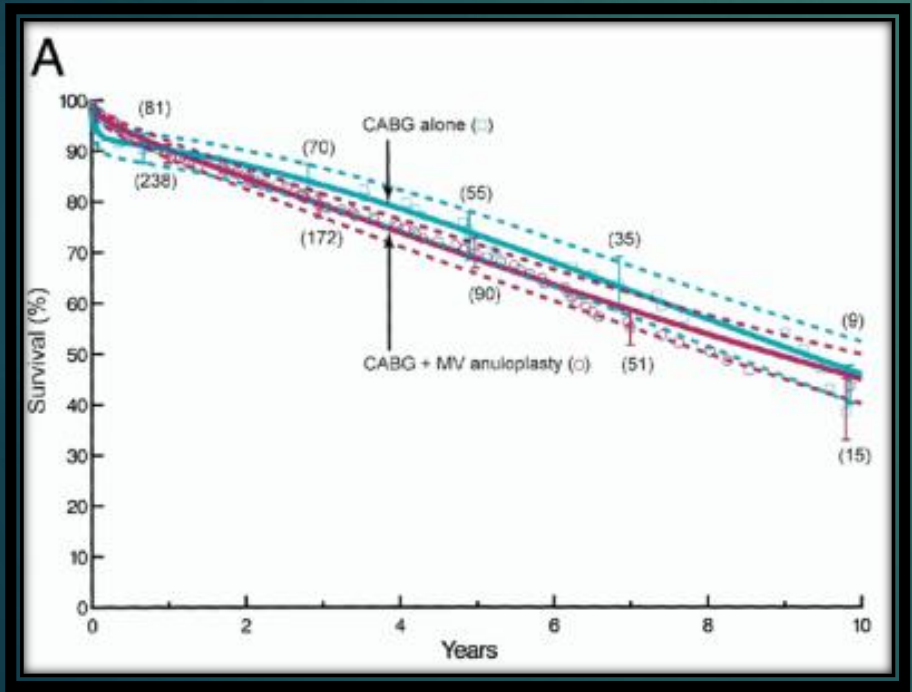
- ❑ It is more common than primary MR,
- ❑ It is associated with a worse prognosis (compounded by the underlying cardiomyopathy),
- ❑ and (in contrast to primary MR) the benefits of MV surgery are uncertain.



AW Asgar et al JACC 2015

Impact of Mitral Valve Annuloplasty Combined With Revascularization in Patients With Functional Ischemic Mitral Regurgitation

- **Mitral valve annuloplasty benefits patients with moderate/severe functional ischemic mitral regurgitation who underwent CABG.**



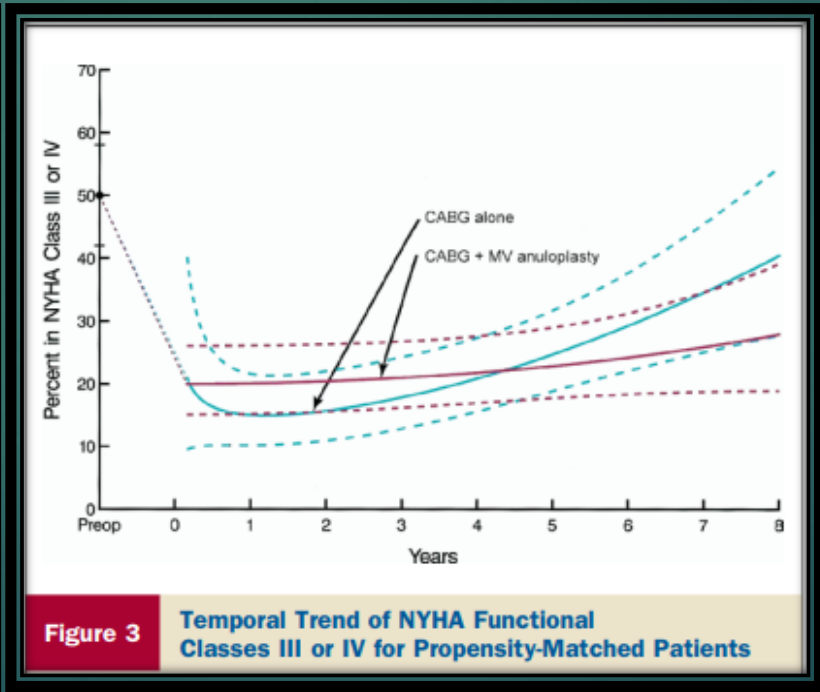


Figure 3 Temporal Trend of NYHA Functional Classes III or IV for Propensity-Matched Patients

Although CABG & MV annuloplasty reduces postoperative MR and improves early symptoms compared with CABG alone, it **does not improve long-term functional status or survival** in patients with severe functional ischemic MR.

T Mihaljevic et al JACC 2007

Indications for mitral valve intervention in chronic secondary mitral regurgitation

Surgery is indicated in patients with severe secondary mitral regurgitation undergoing CABG and LVEF >30%.	I	C
Surgery should be considered in symptomatic patients with severe secondary mitral regurgitation, LVEF <30% but with an option for revascularization and evidence of myocardial viability.	IIa	C
When revascularization is not indicated, surgery may be considered in patients with severe secondary mitral regurgitation and LVEF >30% who remain symptomatic despite optimal medical management (including CRT if indicated) and have a low surgical risk.	IIb	C
When revascularization is not indicated and surgical risk is not low, a percutaneous edge-to-edge procedure may be considered in patients with severe secondary mitral regurgitation and LVEF >30% who remain symptomatic despite optimal medical management (including CRT if indicated) and who have a suitable valve morphology by echocardiography, avoiding futility.	IIb	C
In patients with severe secondary mitral regurgitation and LVEF <30% who remain symptomatic despite optimal medical management (including CRT if indicated) and who have no option for revascularization, the Heart Team may consider a percutaneous edge-to-edge procedure or valve surgery after careful evaluation for a ventricular assist device or heart transplant according to individual patient characteristics.	IIb	C

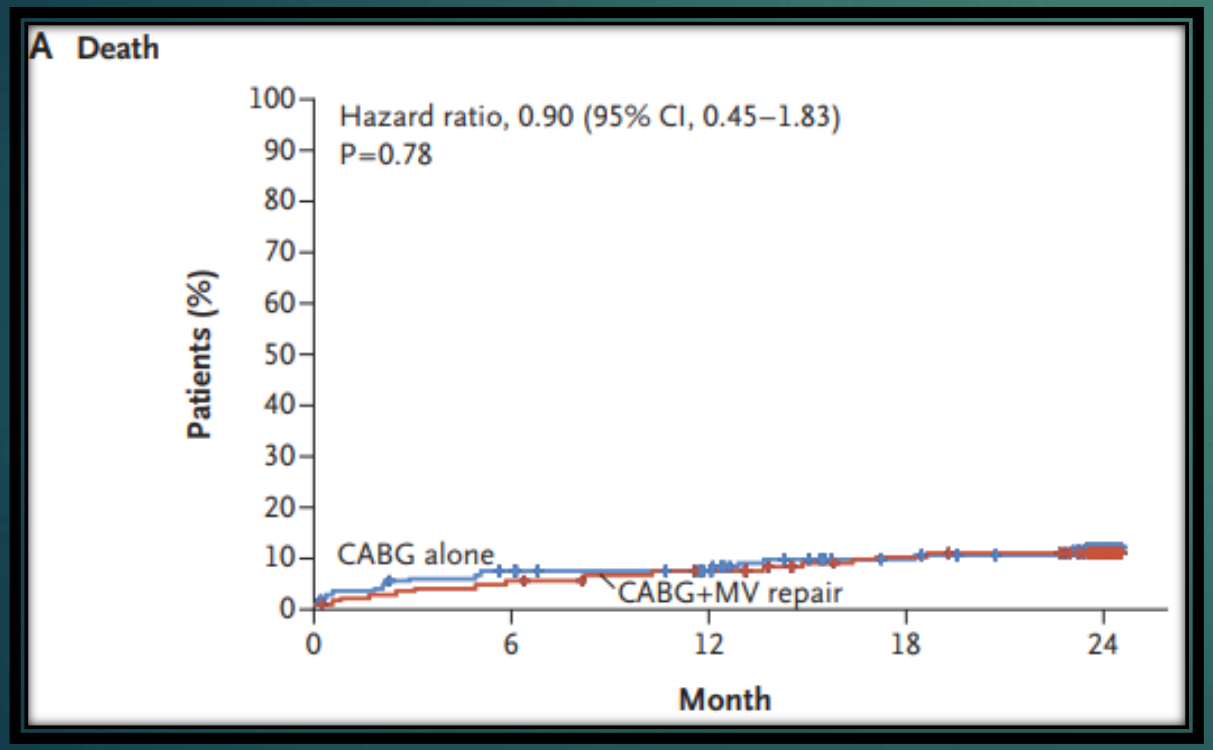
The presence of chronic secondary mitral regurgitation is associated with impaired prognosis.

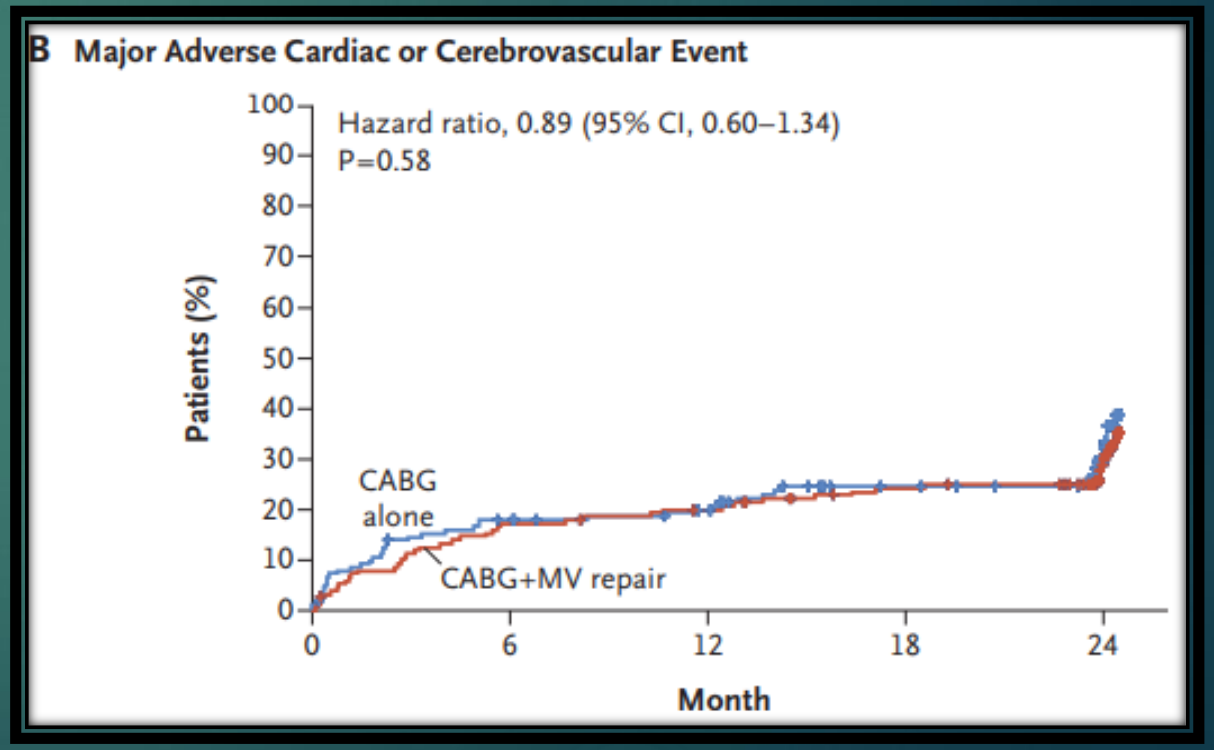
However, in contrast to primary mitral regurgitation, there is currently **no evidence that a reduction of secondary mitral regurgitation improves survival**

ESC Guidelines for Valvular Disease 2017

Two-Year Outcomes of Surgical Treatment of Moderate Ischemic Mitral

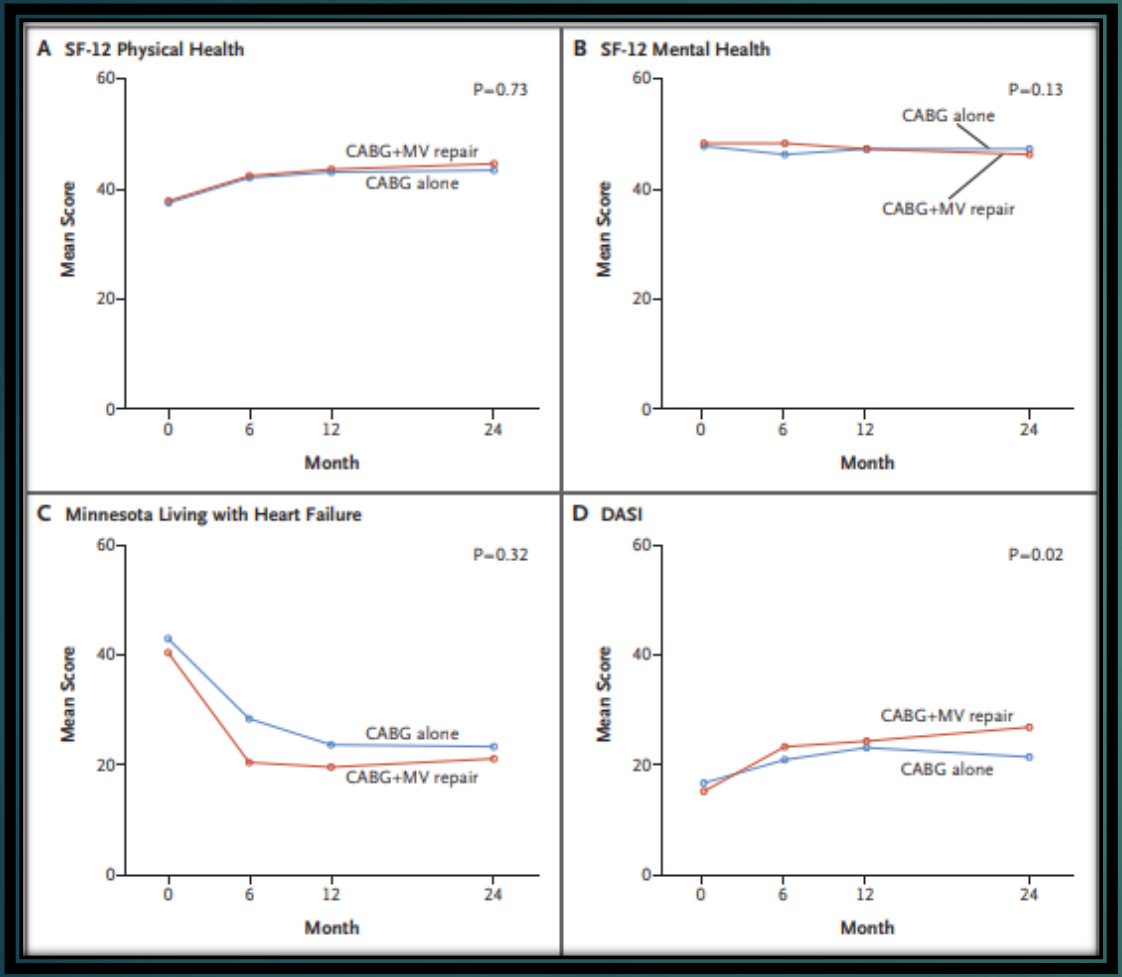
In a trial comparing CABG alone with CABG plus mitral-valve repair in patients with moderate ischemic mitral regurgitation





RE Michler et al NEJM 2016

Two-Year Outcomes of Surgical Treatment of Moderate Ischemic Mitral Regurgitation (II)



In patients with moderate ischemic mitral regurgitation undergoing CABG, the addition of mitral-valve repair:

1. did not lead to significant differences in left ventricular reverse remodeling at 2 years.
2. Mitral-valve repair provided a more durable correction of mitral regurgitation,
3. but did not significantly improve survival or reduce overall adverse events or readmissions and
4. was associated with an early hazard of increased neurologic and supraventricular arrhythmias.

Indications for mitral valve intervention in secondary mitral regurgitation	
2012	2017
IIa C Surgery should be considered in patients with moderate secondary mitral regurgitation undergoing CABG	Taken out

RE Michler et al NEJM 2106

ΦΑΡΜΑΚΑ ΠΟΥ ΑΝΤΕΝΔΕΙΚΝΥΝΤΑΙ ΣΤΗΝ Κ/Α

Treatments that may cause harm in patients heart failure with reduced EF

Recommendations	Class [a]	Level [b]	Ref [c]
Thiazolidinediones (glitazones) are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization.	III	A	209, 210
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
Diltiazem or verapamil are not recommended in patients with HFrEF, as they increase the risk of HF worsening and HF hospitalization.	III	C	214
The addition of an ARB (or renin inhibitor) to the combination of an ACE-I and an MRA is not recommended in patients with HF, because of the increased risk of renal dysfunction and hyperkalaemia.	III	C	