Unmet needs in Chronic Heart Failure

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Unmet needs in chronic HF

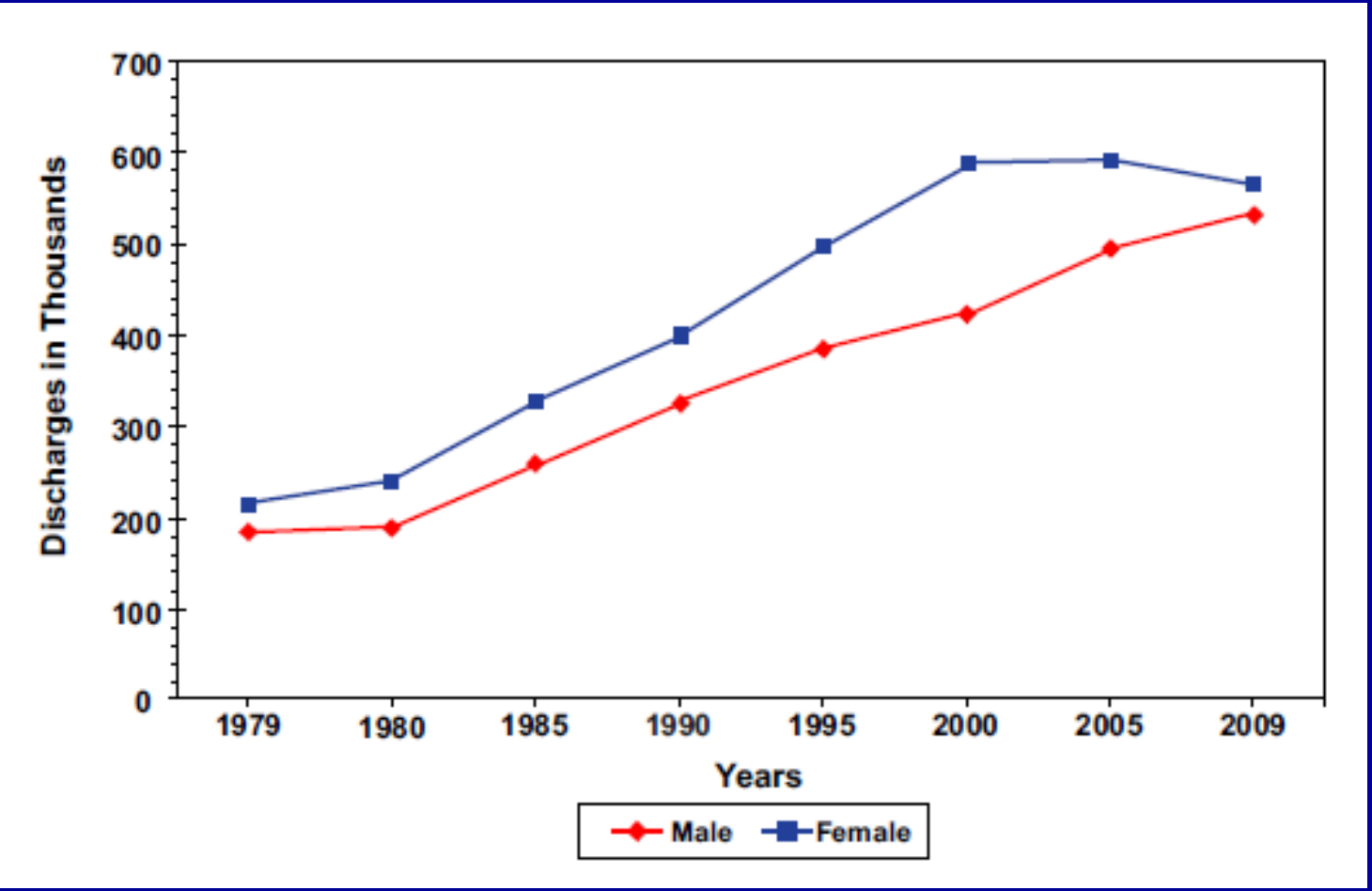
- Prevention of HF
- Comorbidities
- HF with preserved LV Ejection Fraction
- Appropriate use of drugs
- Appropriate use of devices
- Cardiac Valve dysfunction in elderly
- Prognostic modelling
- HF patient journey, Remote monitoring

The new “Heart Failure Paradox”

- “Striking improvements in the prognosis of individual cardiac conditions (ACS, severe hypertension, valvular and congenital heart disease) but ***growing prevalence*** *of heart failure”.*

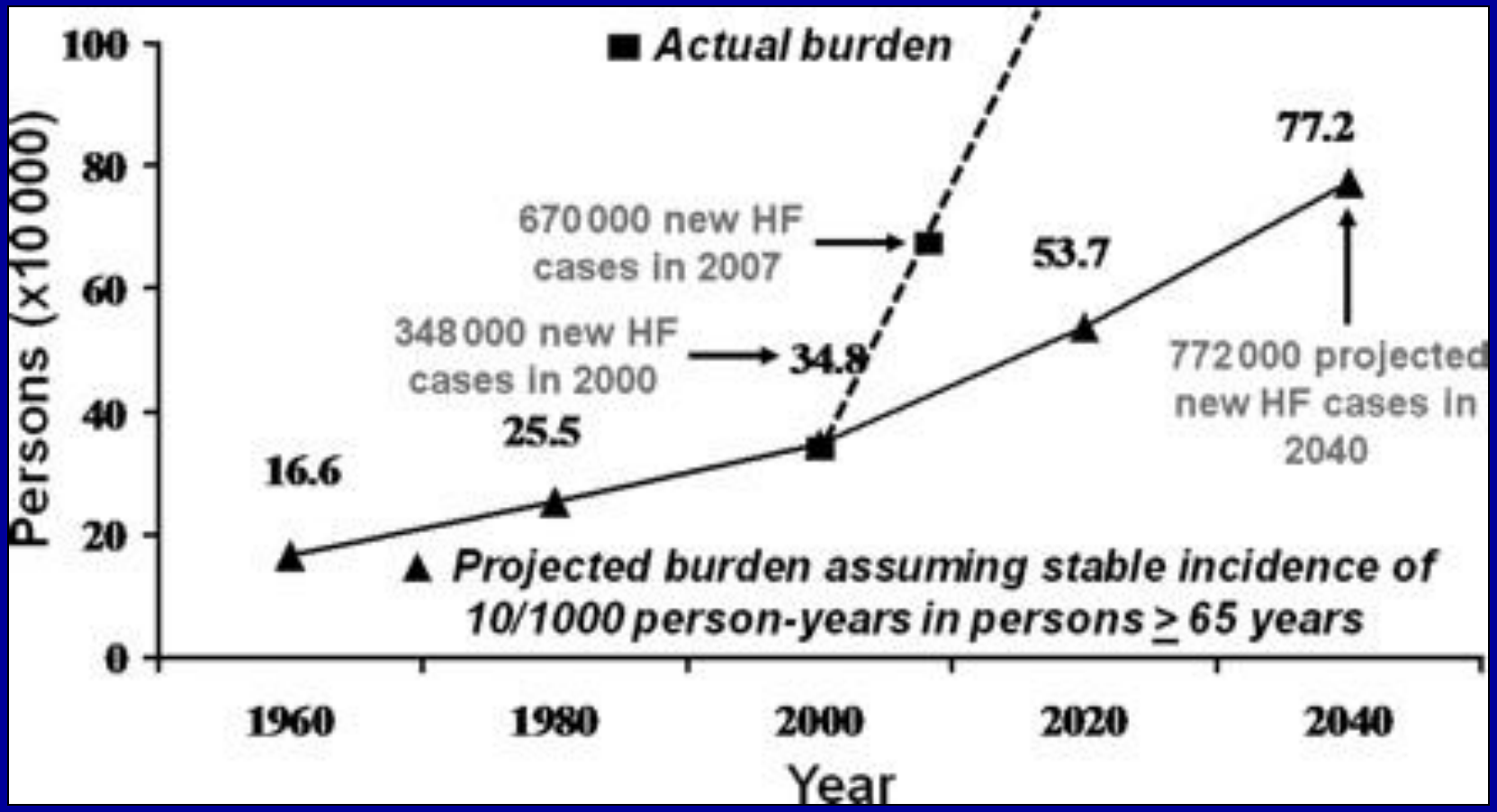
Braunwald E. JACC Heart Failure 2013: 1: 1-20

US: Discharges from HF hospitalization

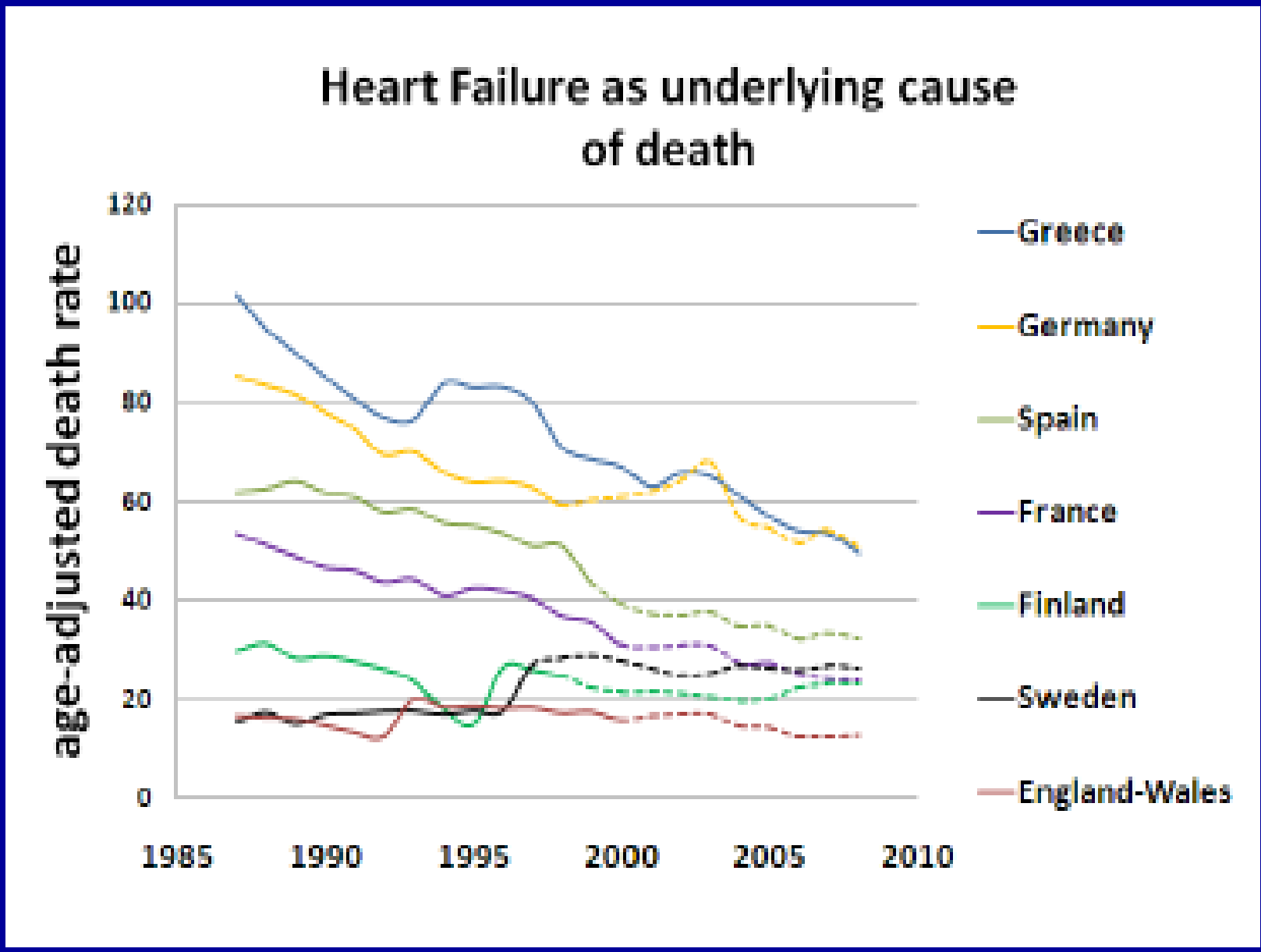


Braunwald E. JACC Heart Failure 2013: 1: 1-20

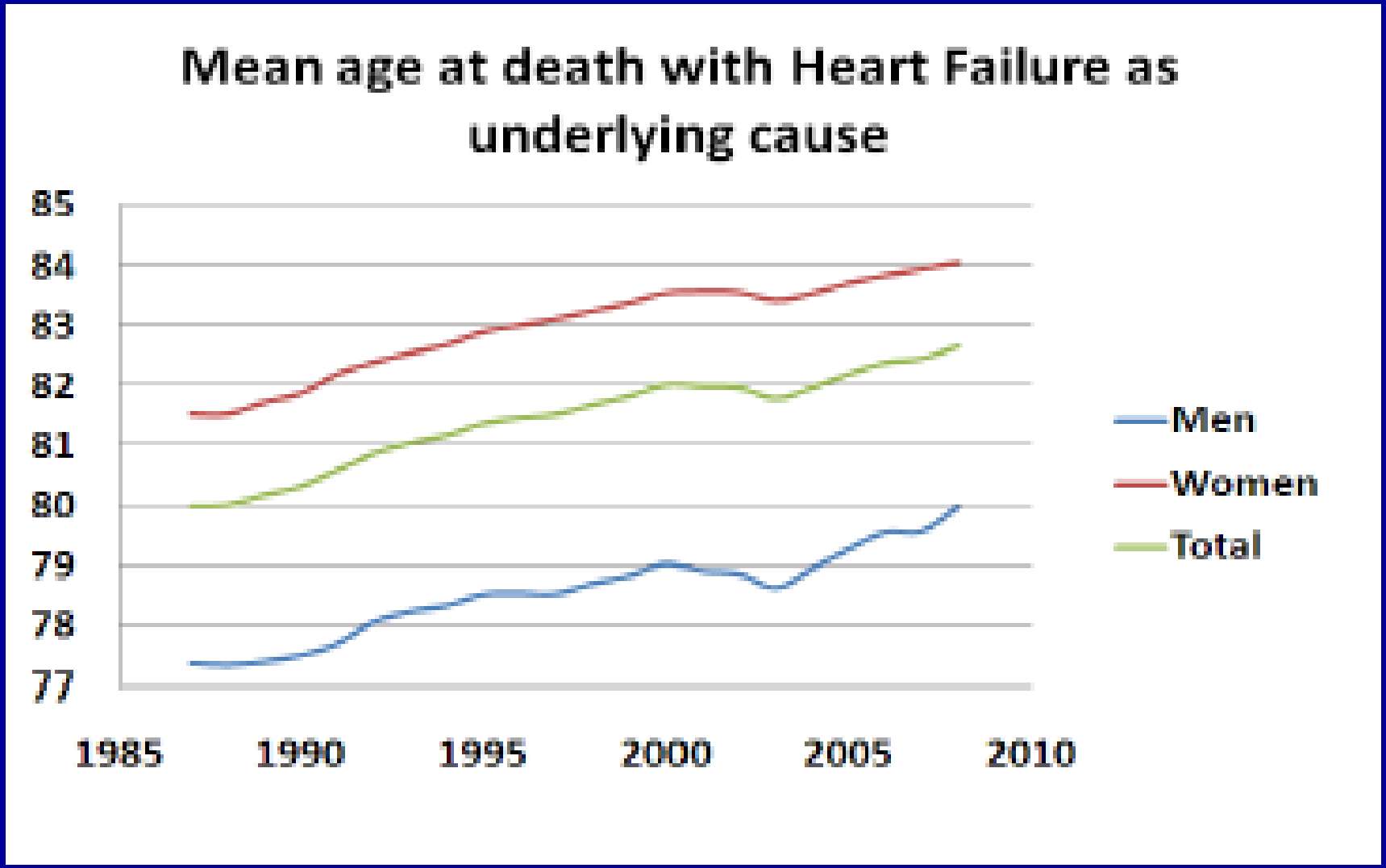
US:Projected and actual burden of heart failure



Lam CSP, et al. Eur J Heart Fail 2011;13:18-28

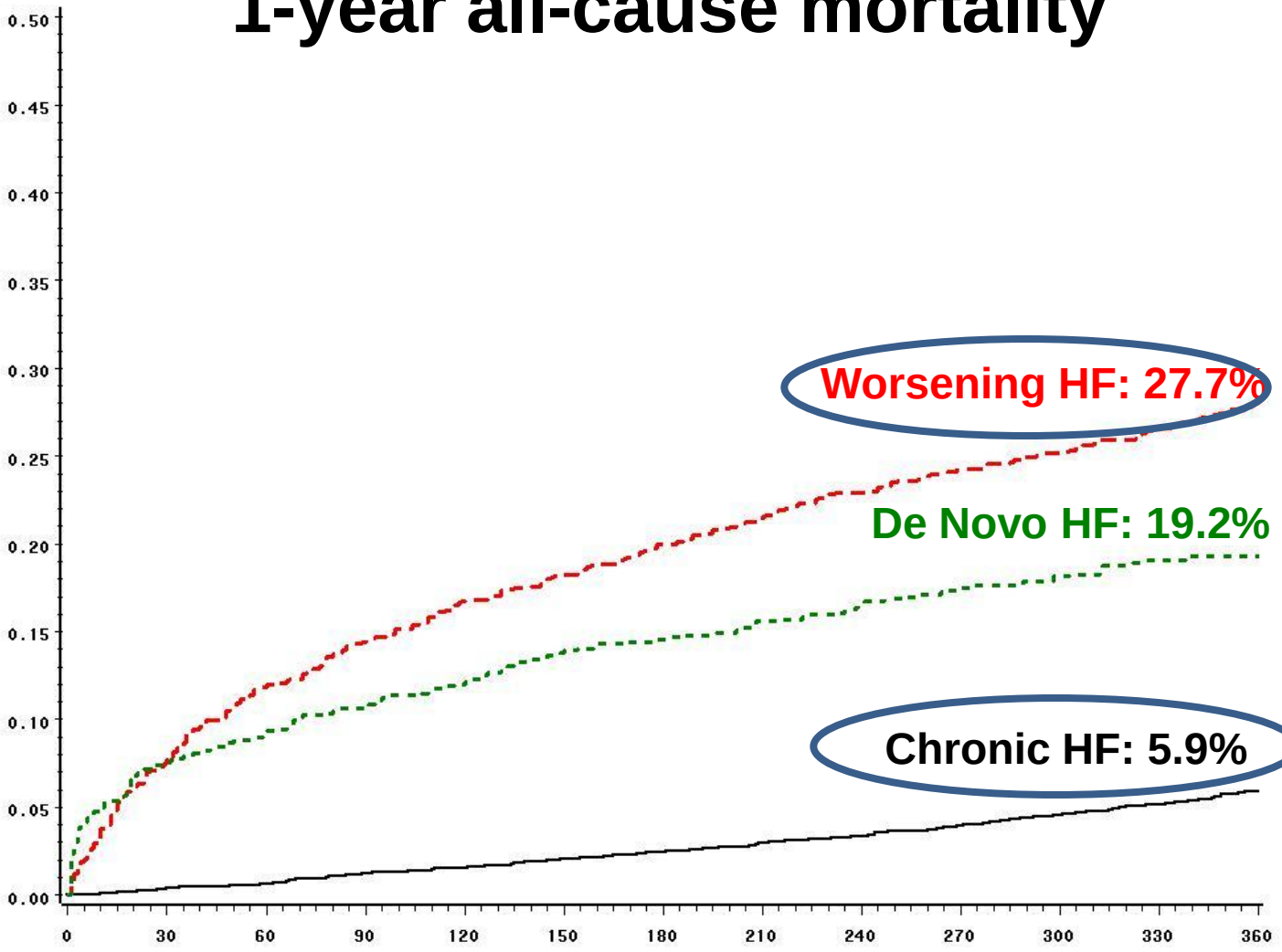


Laribi S, et al. Eur J Heart Fail 2012;14:234-9



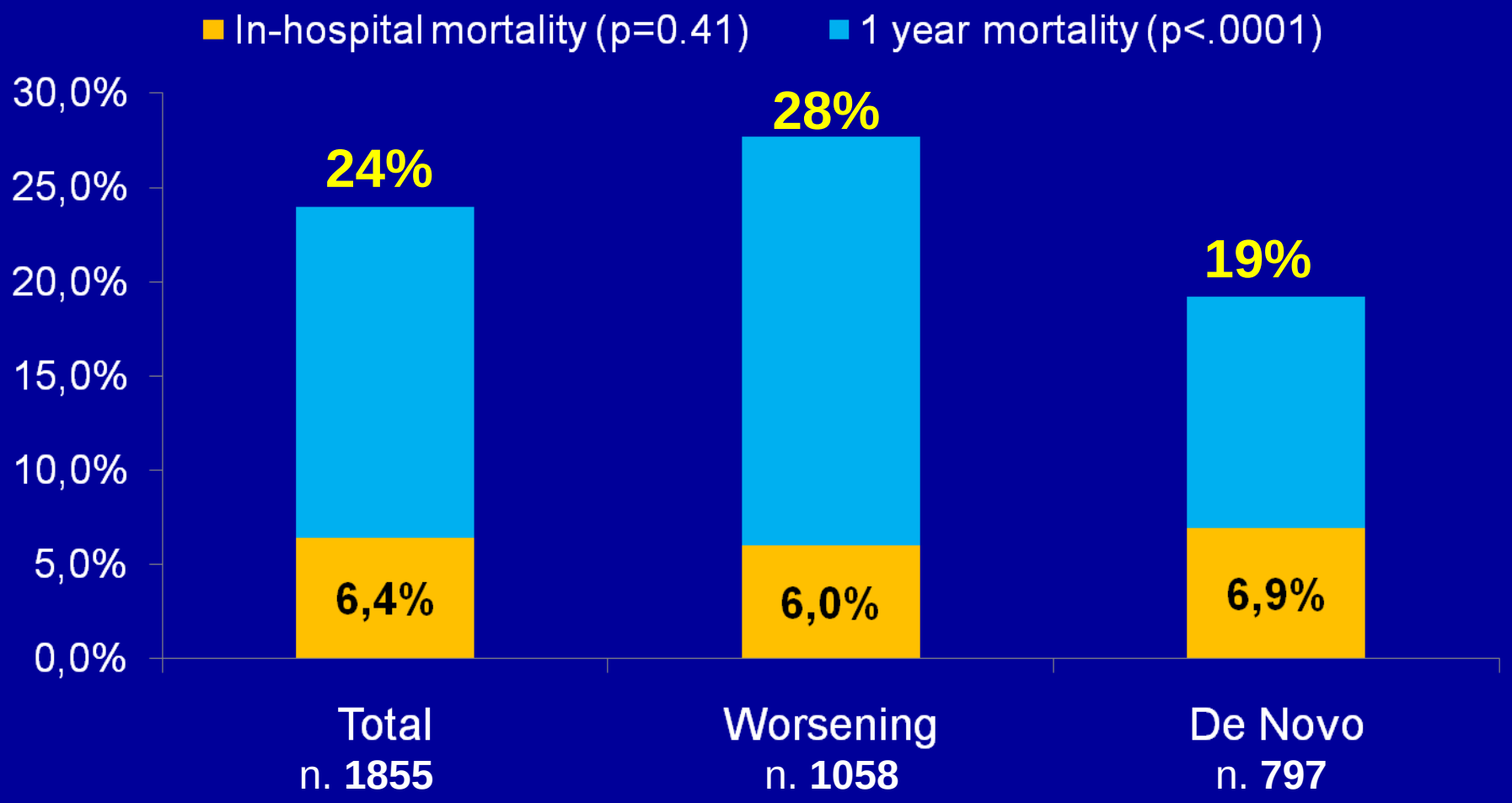
Laribi S, et al. Eur J Heart Fail 2012;14:234-9

1-year all-cause mortality



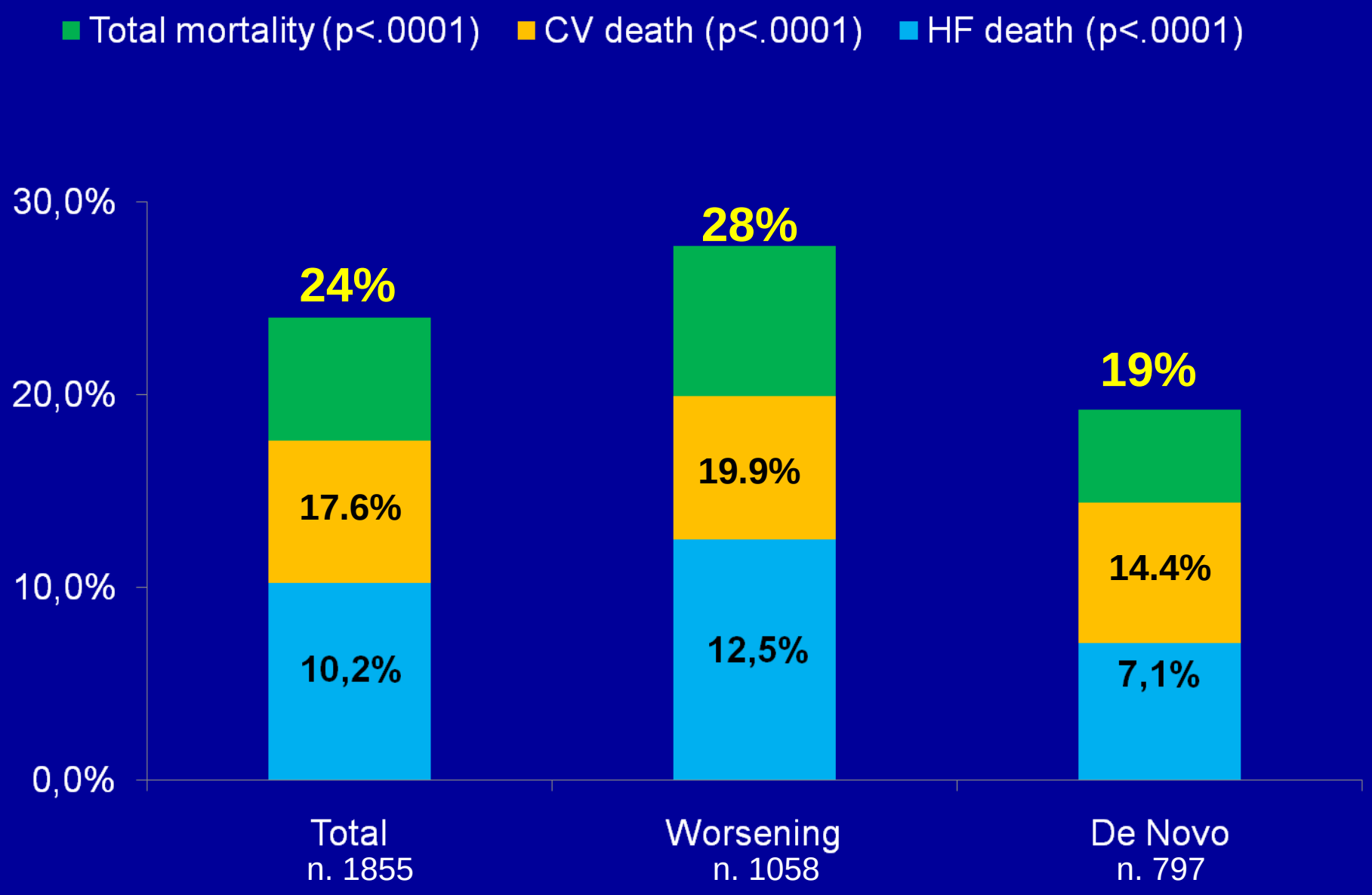
Tavazzi L, et al Circ Heart Fail. 2013;6:473-481.

Hospitalized HF patients: in-hospital and 1-year all-cause mortality



Tavazzi L, et alCirc Heart Fail. 2013;6:473-481.

Acute HF:causes of 1-year mortality



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ESC Heart Failure Guide Lines (2008) Gaps in evidence: comorbidities

Does any specific treatment of these co-morbidities reduce morbidity and mortality in HF patients?

- diabetes
- COPD
- renal dysfunction
- anaemia
- depression
- disordered breathing during sleep

Prevalence of diabetes in Heart Failure

- Chronic Heart Failure: 20-30%
- Acute Heart Failure: 30-40%

Prevalence of diabetes in heart failure according to left ventricular EF

	Reduced LVEF	Preserved LVEF
ADHERE	40%	45%
EURO HF Survey	28%	26%
CHARM	28%	28%
GISSI-HF	27%	28%
I-PRESERVE	-	28%

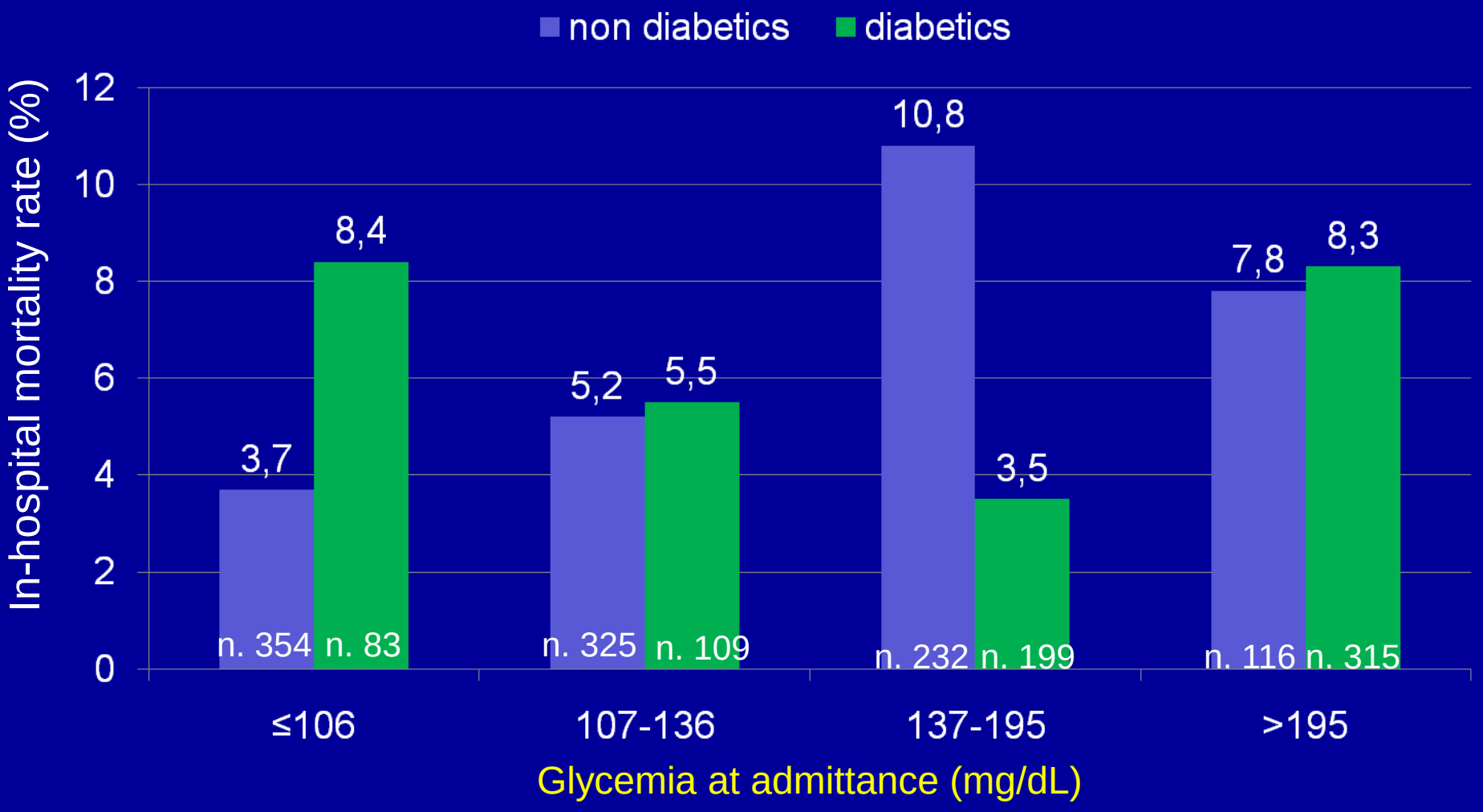
Treatment of Diabetes in Heart Failure

Treatment of Heart Failure in Diabetes

Treatment of diabetes in Heart Failure

- METFORMIN: firts-line, insulin sensitizer. Still Inconsistent results in HF.
- SULFONYLUREAS: not attractive as insulin- releasing agent. Should only be considered if metformin is contraindicated or in association.
- Thiazolidinediones: not recommended
- Incretin modulators α-glucosidase inhibitors: not tested in heart failure
- Insulin: Prescribed in Diabetes type II when oral treatment fails, and in acute conditions. Caution recommended (hypoglycemia)

Acute HF: in-hospital mortality by glycemia and diabetes



DPP-4 inhibitors in cardiovascular outcome trials *(Clinicaltrials.gov)*

Study	Drug/ Expected end	No. of pts	Design	Population	Primary outcome: Time to any event in composite

SAVOR	Saxagliptin (2013)	16500	Superiority vs placebo	• Age > 40 years
				• High CV risk
				  • Atherosclerotic disease
				  • Risk factors
					CV death, non-fatal MI, stroke

TECOS	Sitagliptin (2014)	14000	NI* vs placebo	• Age ≥ 50 years • History of CV disease	CV death, non-fatal MI, stroke, angina requiring hospitalisation
EXAMINE	Alogliptin (2015)	5 400	NI vs placebo (if NI met, then test for superiority)	• Age ≥ 18 years • Acute coronary syndrome within previous 15–90 days	CV death, non-fatal MI, stroke
CAROLNA	Linagliptin vs Glimeperide (2018)	6 000	NI vs glimepiride (if NI met, then test for superiority)	• Age > 40 < 85 years • Pre-existing CV disease OR • Specified diabetes end organ damage OR • age > 70 years OR • ≥ 2 risk factors	CV death, non-fatal MI, stroke, angina requiring hospitalization

GLP-1 receptor agonists in cardiovascular outcome trials *(Clinicaltrials.gov)*

Study	Drug/ Expected end	No. of pts	Design	Population	Primary outcome: Time to any event in composite
ELIXA	Lixisenatide 1/day (2014)	6000	Superiority vs placebo	≥ 30 years HbA1c >5.5 < 11% < 180 days after ACS event	CV death, non-fatal MI, stroke, hospitalization for unstable angina
LEADER	Liraglutide 1/day (2016)	9341	Superiority vs placebo	> 50 years with CV, PAD or RI >60 years with CV risk factors HbA1c ≥ 7 % Drug-naïve or any combination	CV death, non-fatal MI, stroke
EXSCEL	Exenatide 1/weekly (2017)	9500	Superiority vs placebo	≥ 18 years HbA1c >7 < 10% On ≤ 3 oral agents < 60% prior CV event	CV death, non-fatal MI, stroke

Other antidiabetis agents in cardiovascular outcome trials *(Clinicaltrials.gov)*

Study	Drug	Population
ACE	Acarbose vs. usual care	T2D at high CV risk
ALLECARDIO	Aleglitazar vs. placebo	T2D, recent ACS
CANVAS	Canagliflozin vs. placebo	T2D at high CV risk
DECLARE – TIMI 58	Dapagliflozin vs. placebo	T2D at high CV risk
IRIS	Pioglitazone vs. placebo	Insulin resistant, non diabetic, recent stroke or TIA
LOOKAHEAD	Intensive lifestyle vs. diabetes support and education	T2D

http://clinicaltrials.gov/

Treatment of Heart Failure in Diabetics

- *Diuretics:* Increase insulin-resistence
- *RAAS Axis*
  - *Anti-renin (Alkiskiren):* neutral or detrimental
  - *Anti-angiotensine, Anti-aldosterone:* beneficial
- *Beta-blockade:* beneficial (?)
- *Statines:* neutral

All by subgroup analyses of trials

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HF with preserved LVEF in summary

- Multi-factorial disease, related to an abnormal response of both heart and vessels to common *CV risk factors* (age, hypertension, obesity, physical inactivity) and *comorbidities* (COPD, diabetes, chronic kidney disese, anemia) lasting decades in *vulnerable subjects*

HFpEF : an inflammatory disease?

- Two hypotheses

  - HFpEF simply reflects the cumulative expression of risk factors/comorbidities,

  or

  - all are united by a common thread consisting in a systemic inflammatory state, leading to endothelial dysfunction and driving the clinical syndrome

(Paulus WJ, Tschope C, doi.10.1016/j.jacc.2013.02.092)

HF with preserved LV Ejection Fraction

- Needs:
  - Understanding (research)
  - Prevention (control of risk gactors and comorbidities)
  - Therapy (no specific therapy available)

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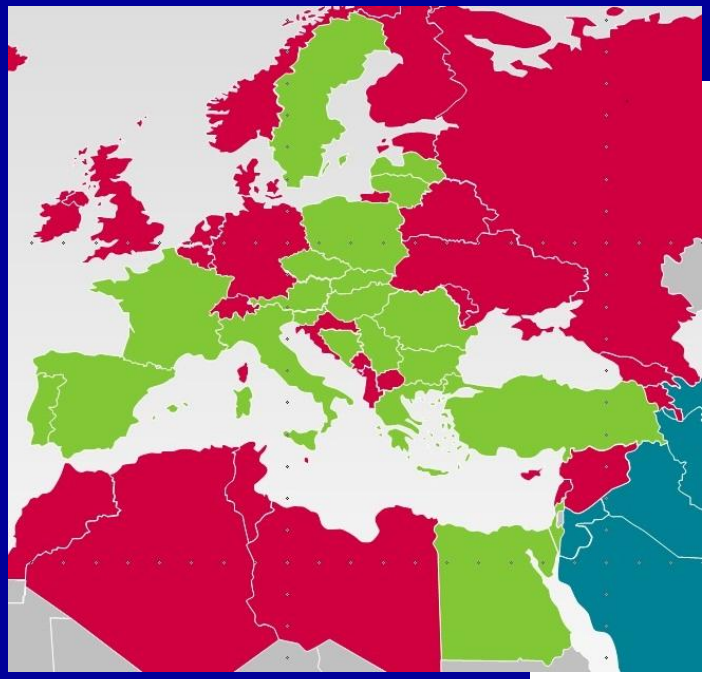
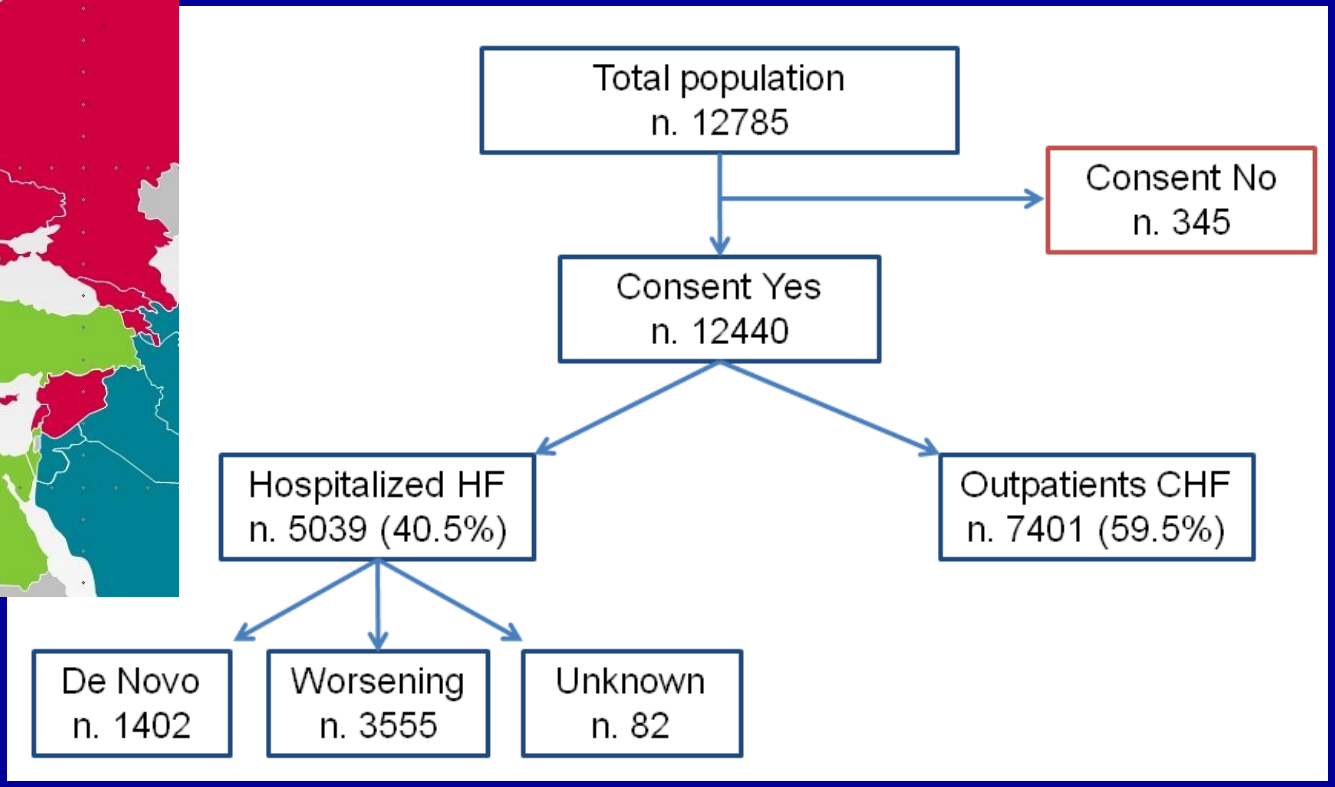
ESC – HF Registry
12,440 patients, 211 centres of 21 ESC Countries

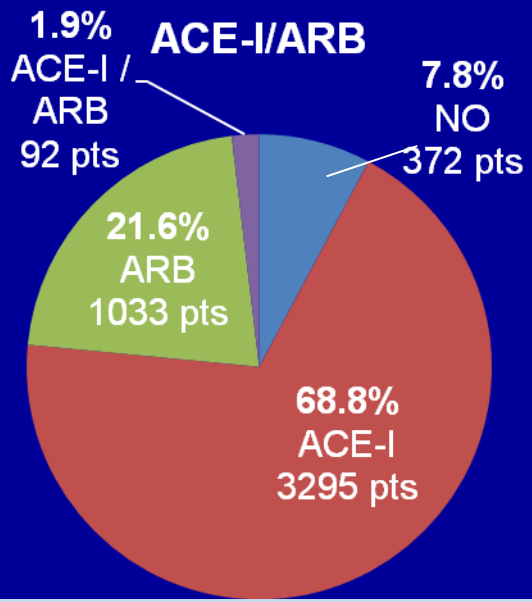


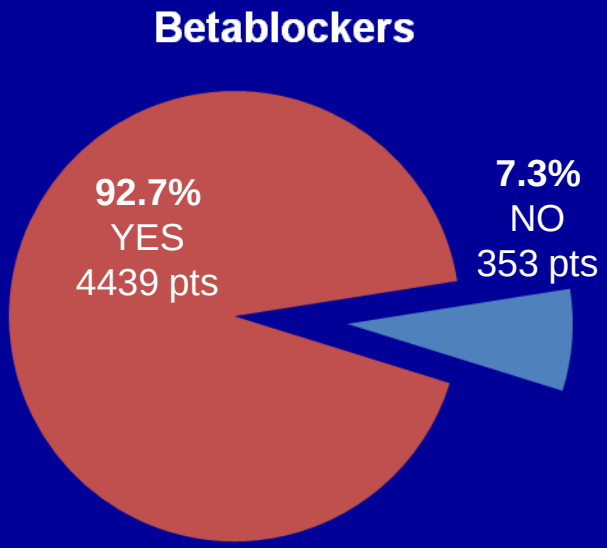
Patient disposition

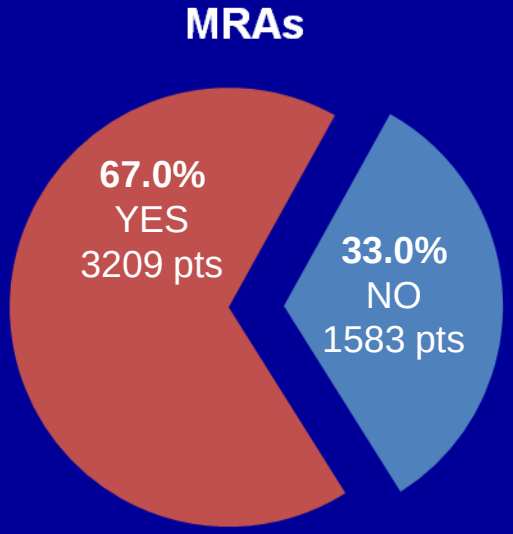


Aim: To evaluate how recommendations of European guidelines regarding pharmacological and non-pharmacological treatments for HF are adopted in clinical practice

ESC Registries 2013 - Rate of use and reasons for non use of recommended treatments in HF patients with reduced EF







Contraindicated	**n. 94 (2.0%)**
Severe renal dysfunction	*n. 61 (64.9%)*
Symptomatic hypotension	*n. 13 (13.8%)*
Hyperkalemia	*n. 8 (8.5%)*
Other	*n. 12 (12.8%)*
Not tolerated	**n. 123 (2.6%)**
Worsening renal function	*n. 22 (17.9%)*
Symptomatic hypotension	*n. 83 (67.5%)*
Hyperkalemia	*n. 6 (4.9%)*
Angioedema	*n. 2 (1.6%)*
Other	*n. 10 (8.1%)*
Real undertreatment	**n. 155 (3.2%)**

Contraindicated	**n. 78 (1.6%)**
Asthma/COPD	*n. 28 (35.9%)*
Bradyarrhythmia	*n. 11 (14.1%)*
Symptomatic hypotension	*n. 11 (14.1%)*
PAD	*n. 3 (3.8%)*
Other	*n. 25 (32.1%)*
Not tolerated	**n. 165 (3.4%)**
Bronchospasm	*n. 39 (23.6%)*
Symptomatic hypotension	*n. 46 (27.9%)*
Bradyarrhythmia	*n. 22 (13.3%)*
Worsening HF	*n. 36 (21.8%)*
Other	*n. 22 (13.3%)*
Real undertreatment	**n. 110 (2.3%)**

Contraindicated	**n. 268 (5.6%)**
Hyperkalemia	*n. 94 (35.1%)*
Renal dysfunction	*n. 153 (57.1%)*
Other	*n. 21 (7.8%)*
Not tolerated	**n. 147 (3.1%)**
Hyperkalemia	*n. 53 (36.1%)*
Worsening renal function	*n. 34 (23.1%)*
Gynecomastia	*n. 34 (23.1%)*
Other	*n. 26 (17.7%)*
Not indicated	**n. 908 (18.9%)**
Real undertreatment	**n. 260 (5.4%)**

Maggioni APM, et al. Eur J Heart Fail 2013 15: 808-817

ESC registries 2013 - Rate of HF patients at target dosage of recommended treatments

	At target n. (%)	Not at target and *Reason for not at target,* n. (%)	
ACE-I (4710 pts)	**1380 (29%)**	**3330 (70.7)**	
		1123 (33.7) Still in uptitration	*85 (2.6) Hyperkalemia*
		866 (26.0) Symptomatic hypotension	*29 (0.9) Cough*
		264 (7.9) Worsening renal function	*5 (0.2) Angioedema*
		958 (28.8) Other/Unknown	
ARBs (1500 pts)	**362 (24%)**	**1138 (75.9)**	
		369 (32.4) Still in uptitration	*25 (2.2) Hyperkalemia*
		295 (25.9) Symptomatic hypotension	*1 (0.1) Angioedema*
		115 (10.1) Worsening renal function	***333 (29.3) Other/Unknown***
Betablockers (6468 pts)	**1130 (17%)**	**5338 (82.5)**	
		1871 (35.1) Still in uptitration	*185 (3.5) Worsening HF*
		904 (16.9) Symptomatic hypotension	*146 (2.7) Bronchospasm*
		586 (11.0) Bradyarrhythmia	*56 (1.1) Worsening PAD*
		1557 (29.2) Other/Unknown	*33 (0.6) Sexual dysfunction*
MRAs (4226 pts)	**1290 (30%)**	**2936 (69.5)**	
		864 (29.4) Still in uptitration	*284 (9.7) Worsening renal function*
		350 (11.9) Hyperkalemia	*60 (2.0) Gynecomastia*
		1378 (46.9) Other/Unknown	

Maggioni APM, et al. Eur J Heart Fail 2013 15: 808-817

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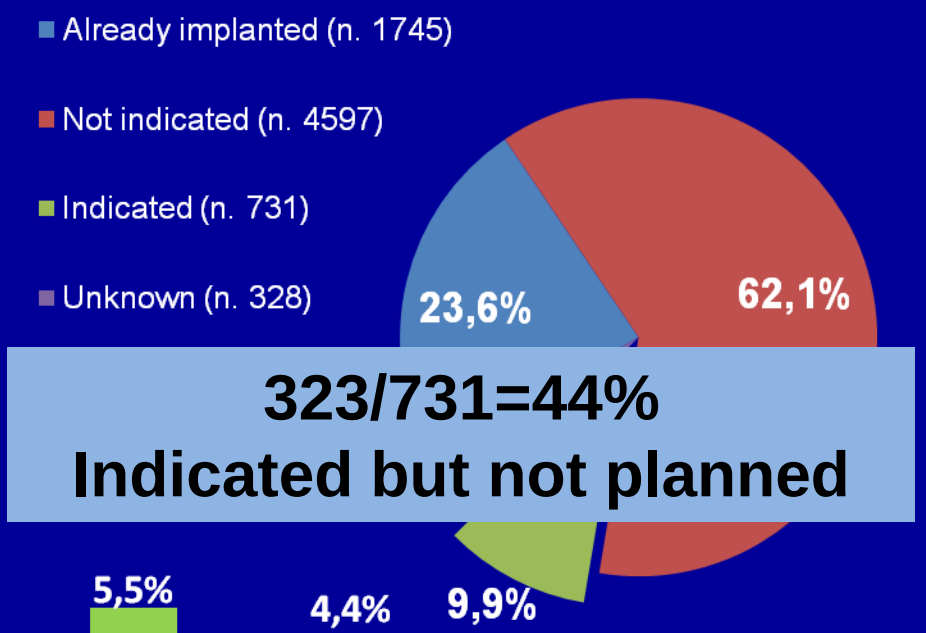
ESC-HF Registry, 2013 - Rate of implantation of devices and reasons for non implantation

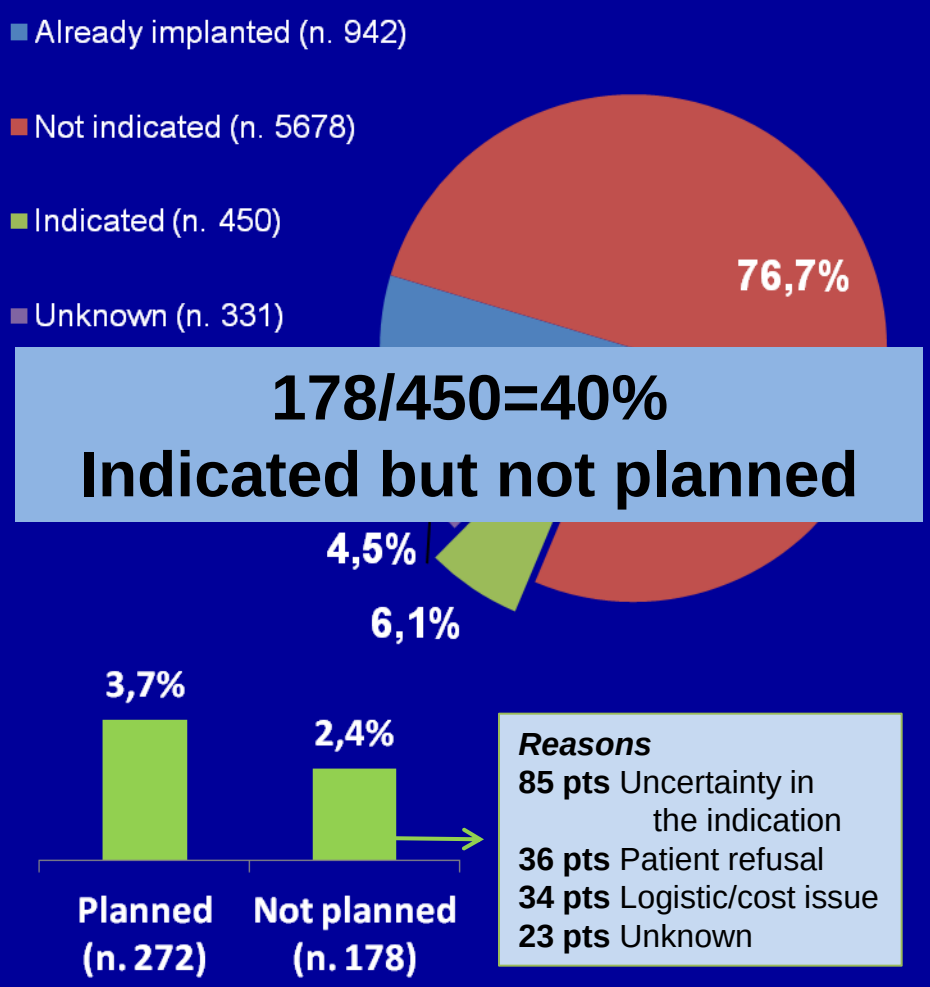
ICD (7401 pts)



323/731=44%
Indicated but not planned

Reasons
161 pts Uncertainty in the indication
81 pts Patient refusal
51 pts Logistic/cost issue
30 pts Unknown

CRT (7401 pts)



178/450=40%
Indicated but not planned

Reasons
85 pts Uncertainty in the indication
36 pts Patient refusal
34 pts Logistic/cost issue
23 pts Unknown

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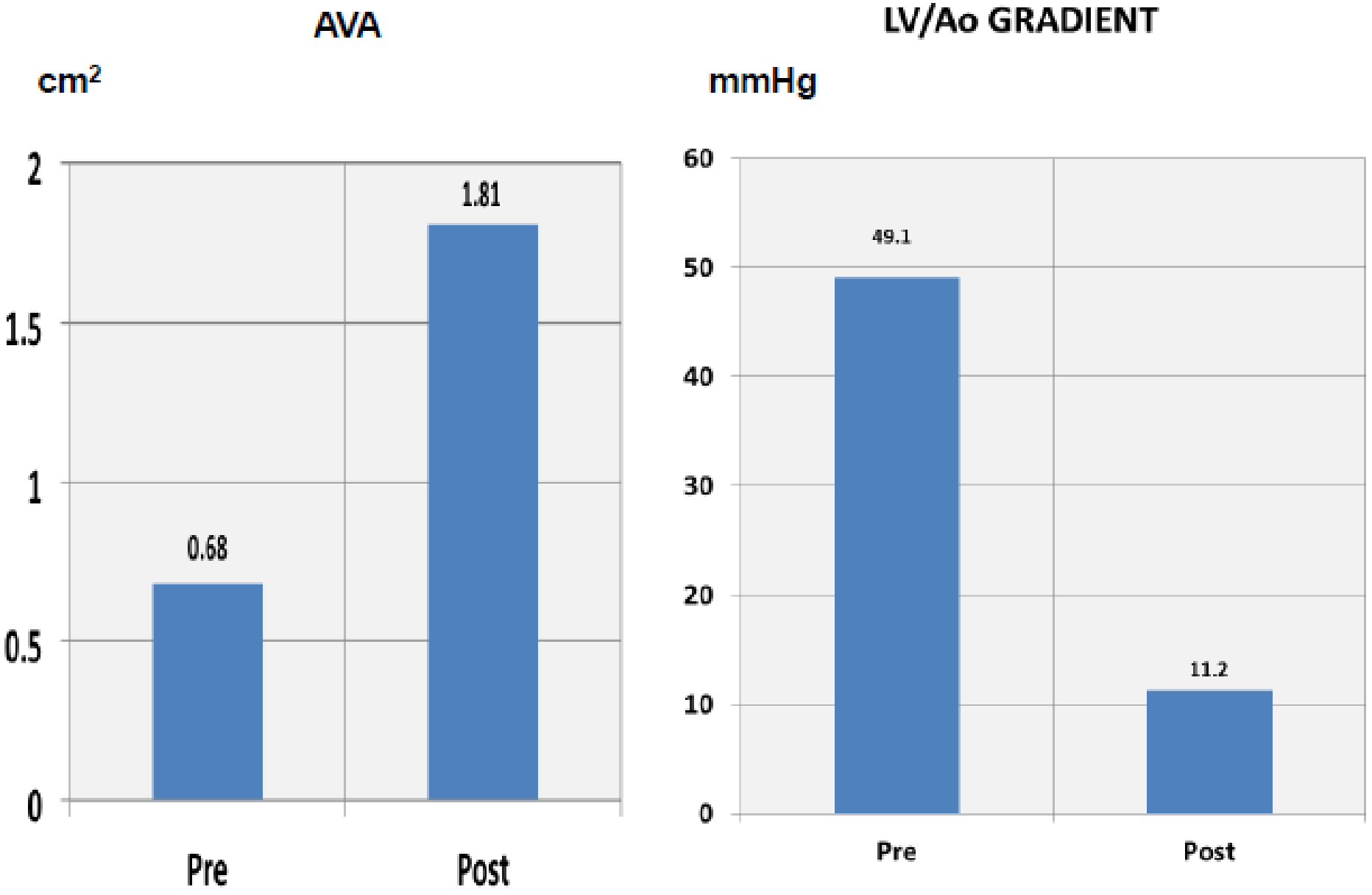
EUR *Observational* Research Programme

TransCatheter Valve Treatment, Pilot

- 12 Countries participating
- **Patients:** - **TAVI : 5140**
  - **Mitral : 769**

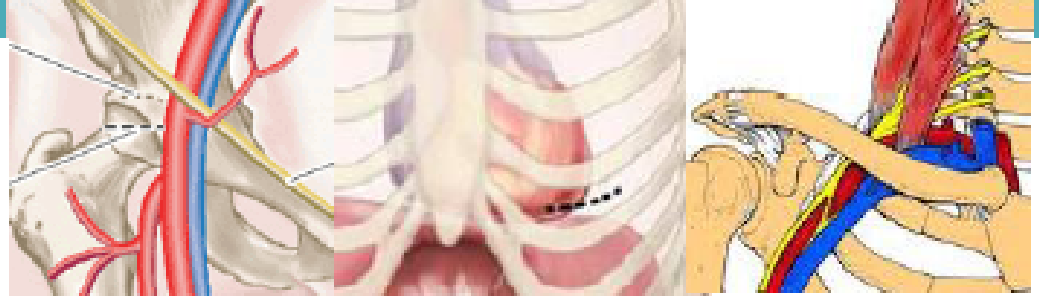
TCVT Pilot Registry

Haemodynamic Changes after TAVI



Courtesy of C. Di Mario

TCVT Registry
In-Hospital Complications by Access Site

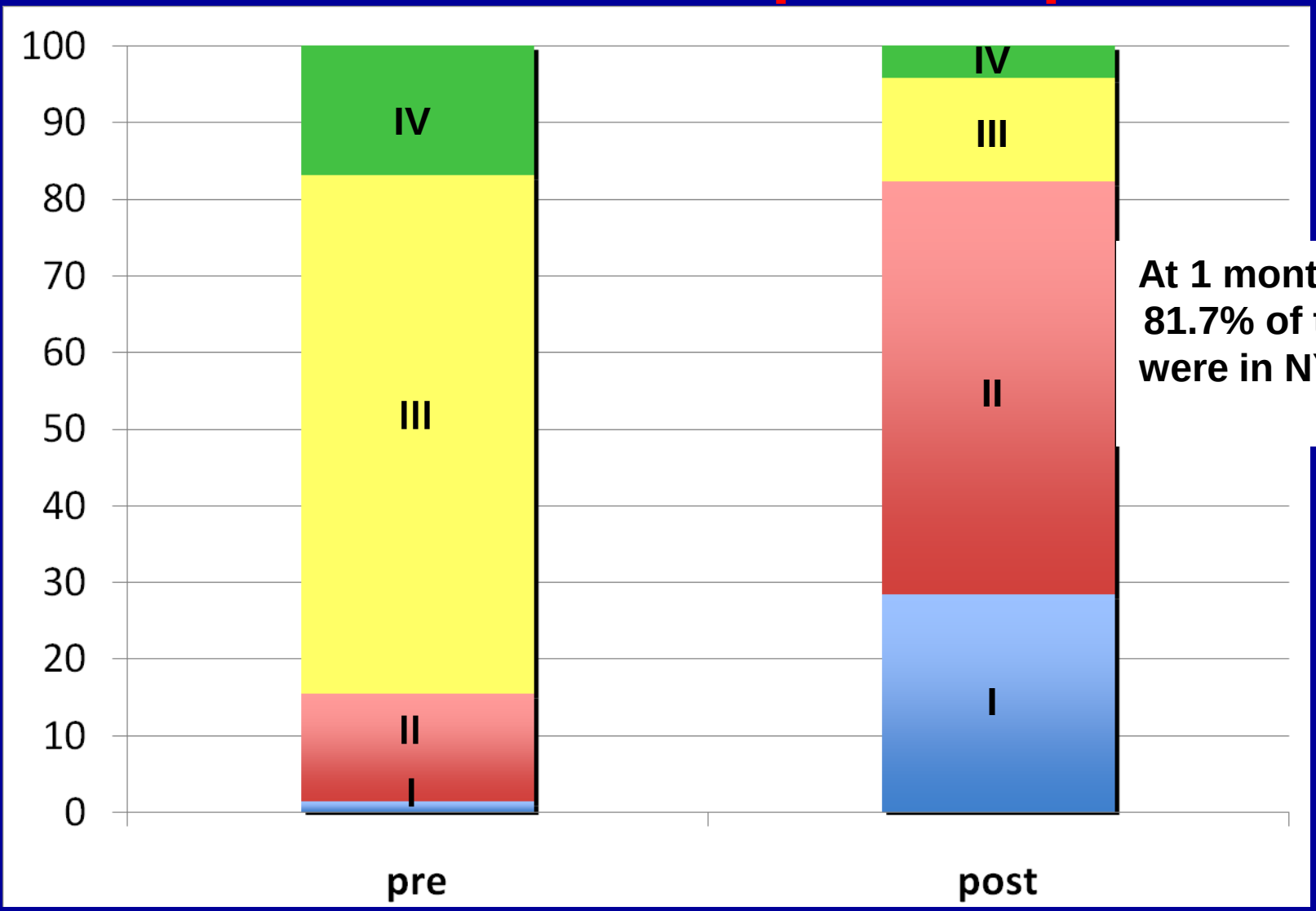


	Femoral	Apical	Other	
Death (Total 7.4%)	5.9	12.8	9.7	<0.01
Stroke (Total 1.8%)	1.9	1.6	1.4	0.68
MI (Total 0.9%)	0.9	0.7	1.9	0.09
PM implantation	15.5	4.5	10.7	<0.01
Haemodialysis	1.2	2.4	3.6	<0.01
Transfusion(s)	15	20.8	22.9	<0.01
New onset AF	5.1	9	6.5	<0.01
Hosp. stay >10 days	22	43.8	39.5	<0.01

Courtesy of C. Di Mario

TCVT Pilot Registry: TMVR @ 2012

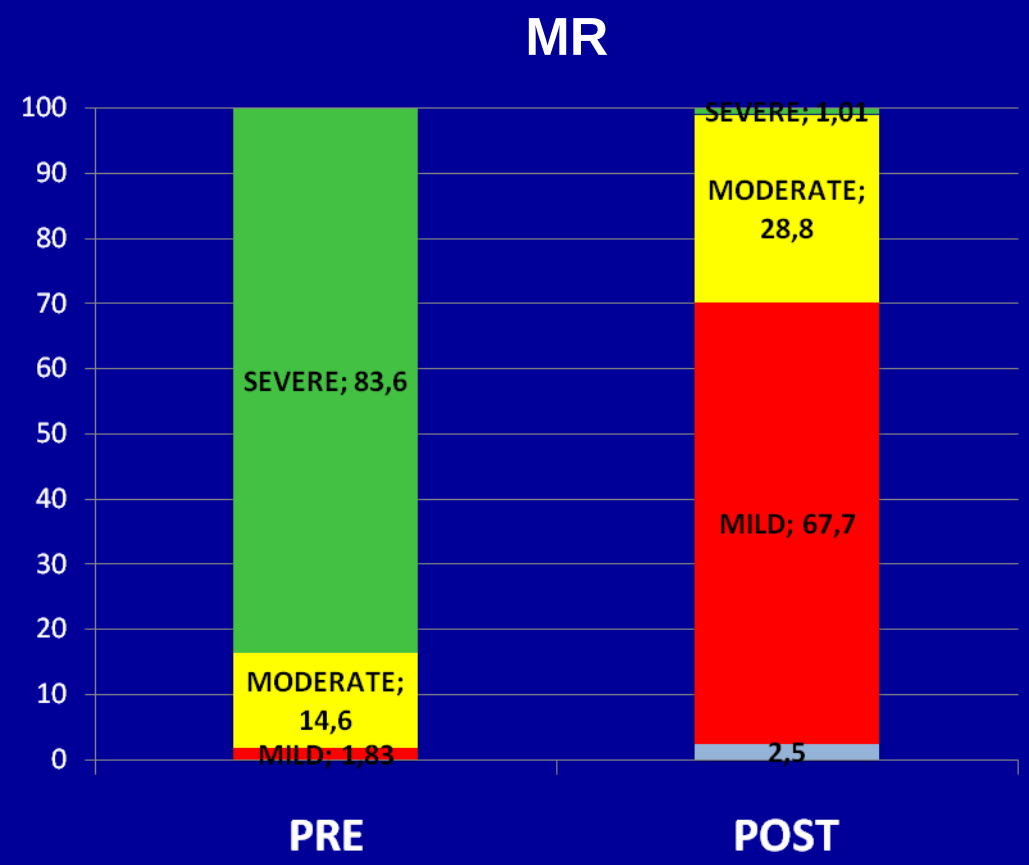
NYHA class pre and post

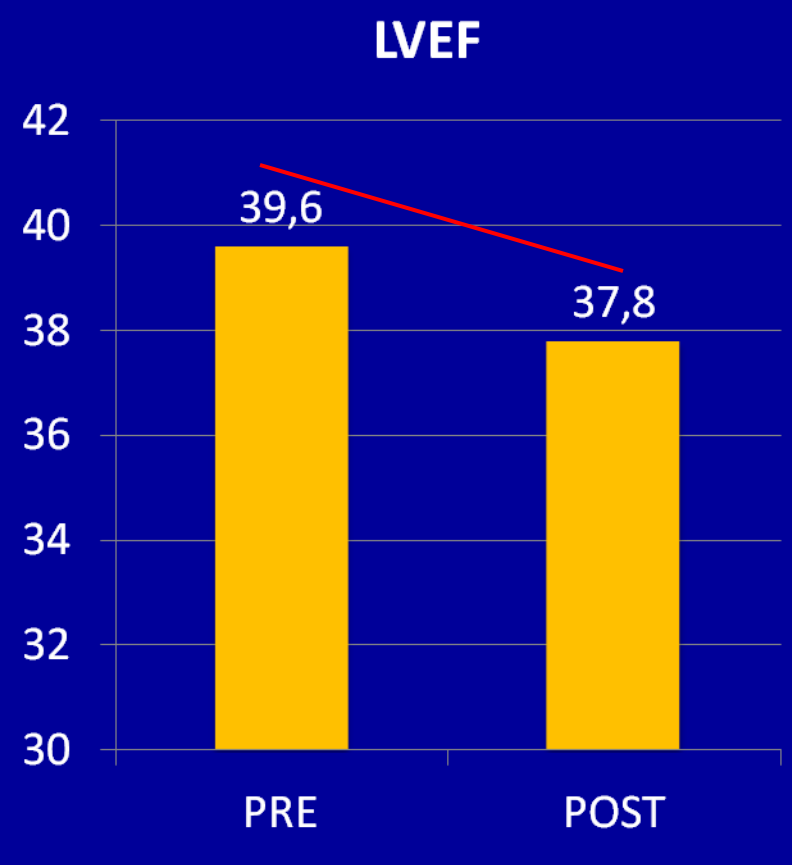


At 1 month follow-up, 81.7% of the patients were in NYHA class I-II

ESC-TCVT Pilot Registry: TMVR @ 2012

Mitral Regurgitation and Severity & LVEF





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Prognostic Modelling in Chronic Heart Failure

2012 ESC Heart Failure GuideLines PROGNOSTICATION

a list of 57 variables shown to be predictive of outcome

Risk Prediction Models for Mortality in Ambulatory Patients With Heart Failure. A Systematic Review

Alba AC et al. *Circ Heart Fail*. 2013;6:881-889

- **20 different risk models** developed for patients with heart failure.
- Only 5 with external validation, showing poor-to-modest discrimination (*c*-statistic, 0.56–0.79), being lower in more recent cohorts, and overall showing inconsistent performance.

Prognostic scores are not used in clinical practice. WHY?

- Non representative of real world (selected or undefined populations: age, comorbidities, HF severity, “once forever” assessment)
- Trials are disease-specific, but multimorbidity is the norm ≥65 years (2/3 of chronic HF pts)
- No sequential data and time-related analyses
- Not useful for decision making
- Lack of personalized therapy (same for all)

Predictive Models in Heart Failure. Who Cares?

Califf RM, Pencina MJ ***Circ Heart Fail*. 2013;6:877-878.**

- Currently, time to-event nature of the data are not taken into account.
- Models considering the inception point of patient observation and updated according to changes in the patient's condition are needed
- The new data electronic fabric will enable development of algorithms that can make predictions in real time about nearterm and long-term prognosis and enable evaluation of the comparative effectiveness of choices about diagnosis, prevention, and treatment

Predictive Models in Heart Failure. Who Cares?

Califf RM, Pencina MJ ***Circ Heart Fail*. 2013;6:877-878.)**

- Califf's dream:

  "personal mobile devices will record and feed physiological data to electronic health records.

  New data electronic fabric will enable development of algorithms that can make predictions in real time about nearterm and long-term prognosis and enable evaluation of the comparative effectiveness of choices about diagnosis, prevention, and treatment"

HF prognostic modelling in clinical practice
The ESC programme (EORP)

- All variables showed as indipendent prognostic indicators in large MM RCTs are included in the ongoing Long-term Heart Failure Registry for:
  - comparing the prognostic power of available risk scores in the same population
  - searching for new scores and algorithms
  - taking advantage from the large numbers availabile to test the validity of new scores in the overall populations and selected groups

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END