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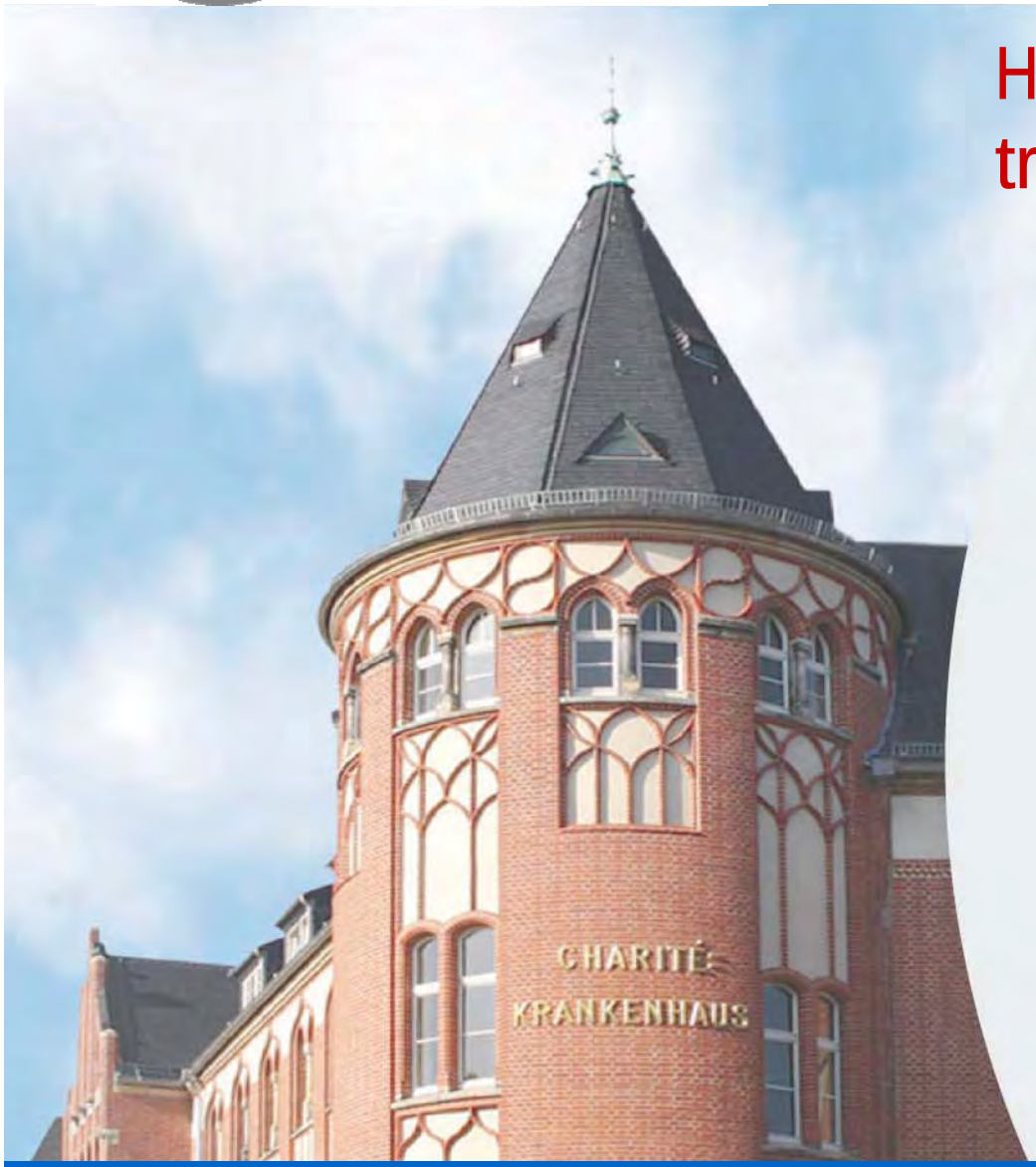


# Heart Failure and Arrhythmia - treatment

Prof. Vera Regitz-Zagrosek

Director, Institute of Gender in Medicine (GiM),

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Charité

# Topics

- **Chronic Heart Failure**
  - Relevance
  - Guideline based treatment:
    - **Life style changes, Drugs, HTX, devices (defibrillators, resynchronization, assist devices, )**
  - Novel developments

- **Arryhthmia**
  - Guideline based treatment
    - **Drugs**
    - **Catheter based ablation therapy**
  - Novel developments

# Clinical Relevance of HF

- High prevalence
  - **US: 5 mill people with HF in 2005**
  - **Medicare: higher spending than for any other disease,**
  - **total cost of 27.9 billion USD in 2005; 2.7 billion on drugs**
  - **ESC member states (900 mill people):**
  - **10 mill with symptomatic HF**
  - **10 mill with asymptomatic cardiac dysfunction“**
  - **Lifetime risk at age 55: 29 and 33 % for wo/men***
- Broad spectrum of conventionel, novel and hich tech diagnostic and therapeutic strategies available
- Guidelines (ESC 1995, 2001, 2005, AHA and ACC, 1995, 2001; 2005, DGK) and observational data available

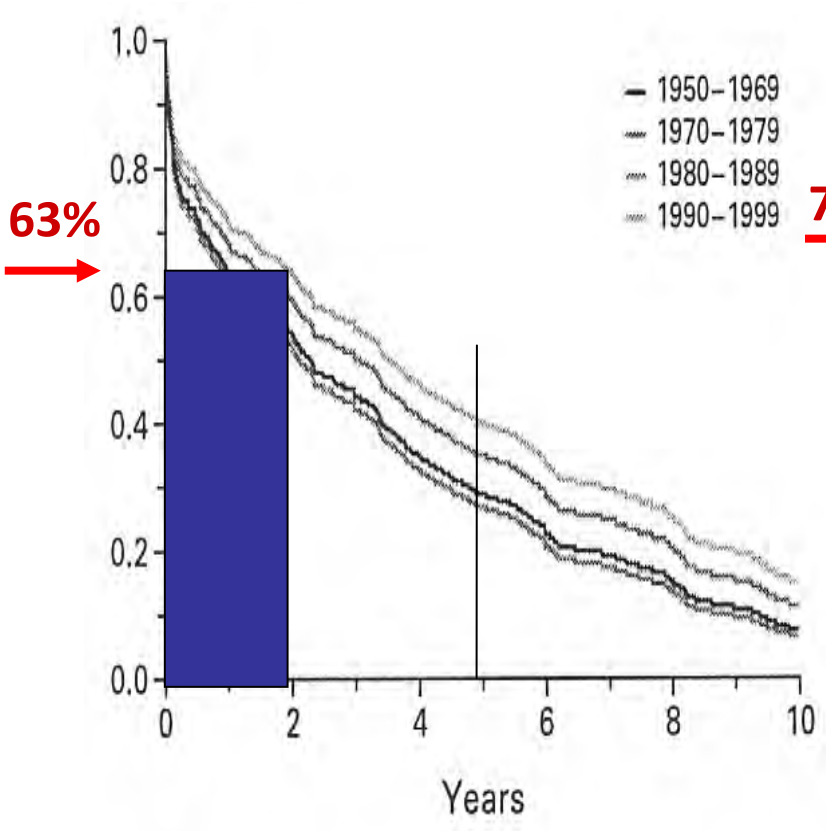
*Bleumink G S, Rotterdam Study, EHJ 2004

“ESC guidelines EHJ 2005

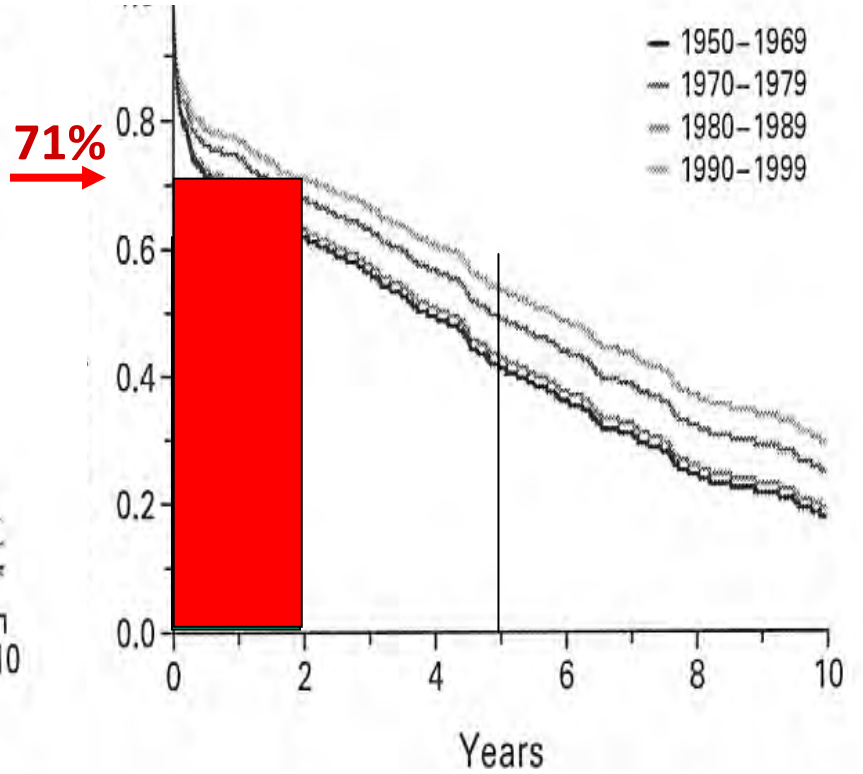
# Age and gender adjusted survival after onset of HF is improving

Framingham cohort  2- year survival  is 71 % in women and 63 % in men

**Men**




**Women, 2 years mortality 29 %**




Levy, NEJM 2002

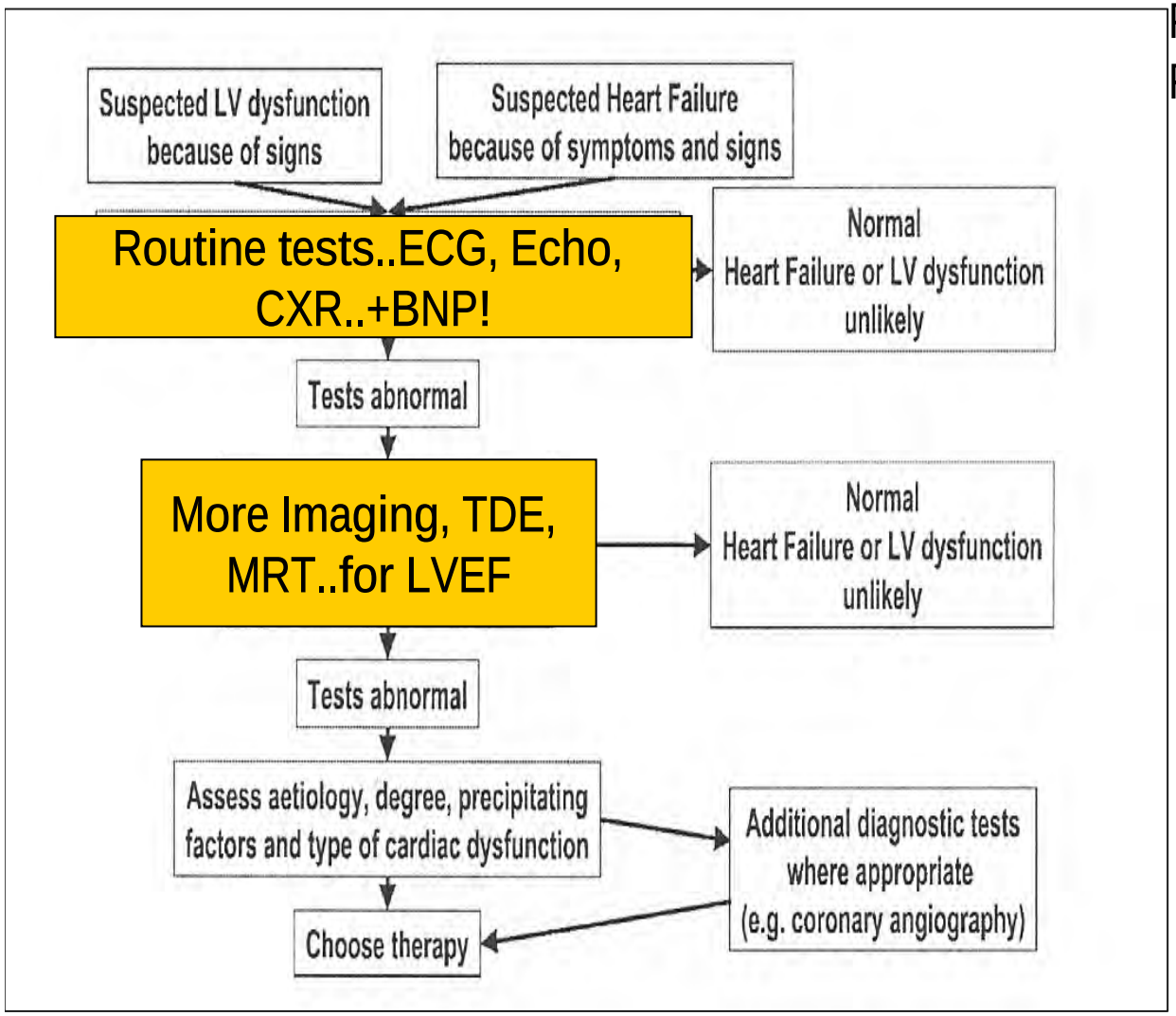
# Guideline based Treatment: Classes of recommendation and levels of evidence

**Table I** Classes of recommendations

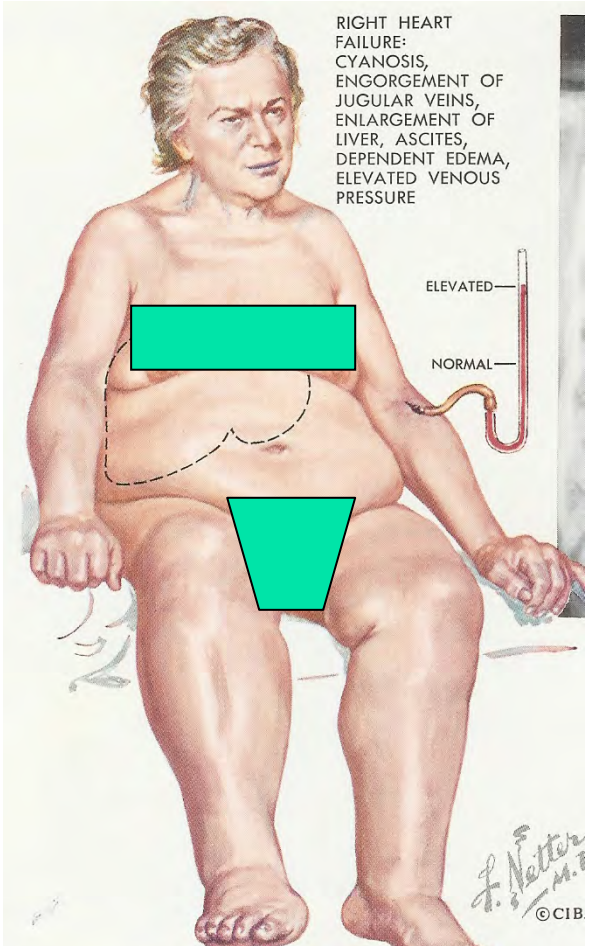
| Classes of Recommendations | Definition |
|---|---|
| Class I | Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective. |
| Class II | Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure. |
| *Class IIa* | Weight of evidence/opinion is in favour of usefulness/efficacy. |
| *Class IIb* | Usefulness/efficacy is less well established by evidence/opinion. |
| Class III | Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful. |

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

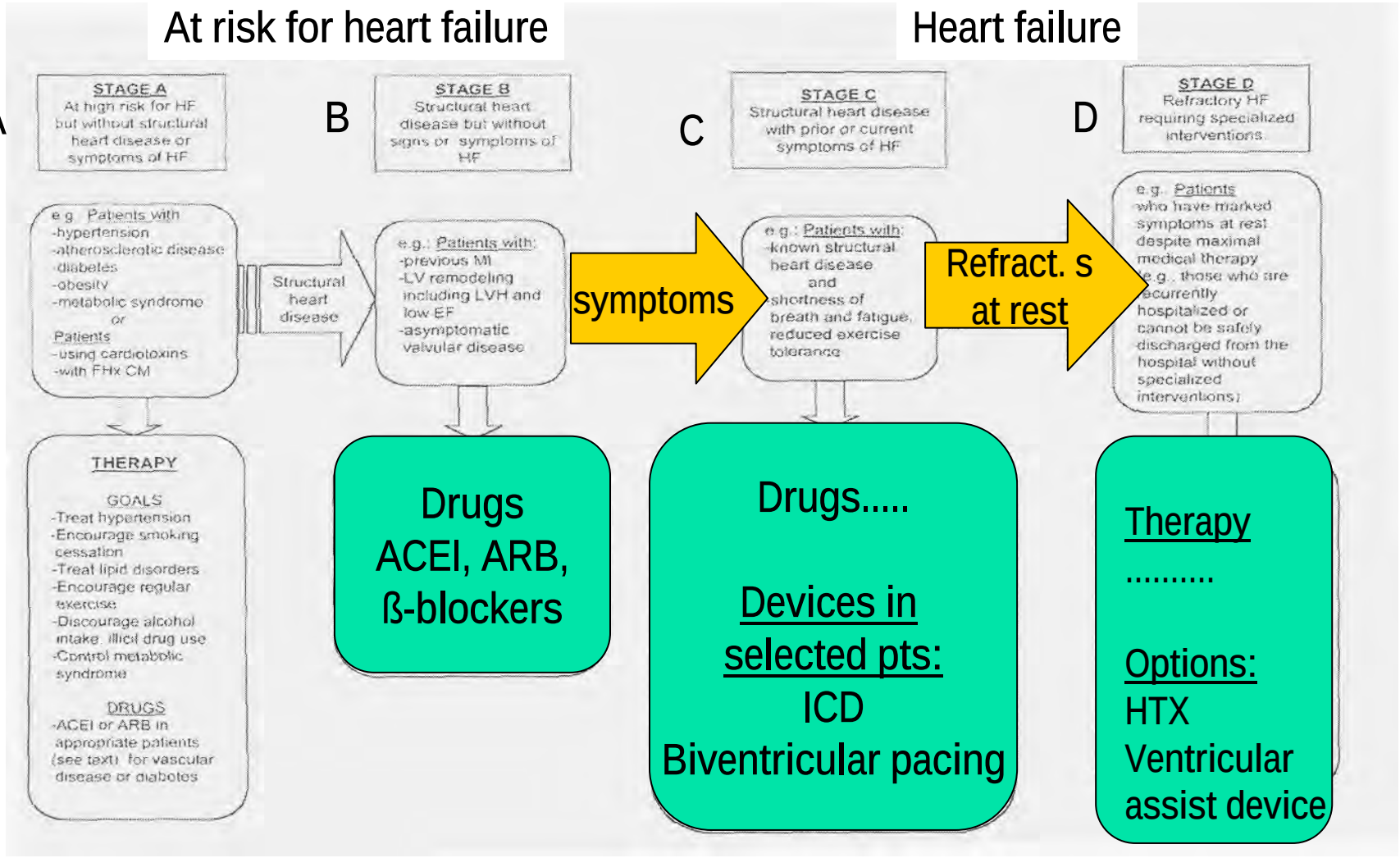
# Guidelines for diagnosis of HF – ESC, AHA, German cardiac society




Problem: impaired cardiac function
Fluid accumulation



# Guidelines for the diagnosis and therapy of HF: DGK, ESC, AHA

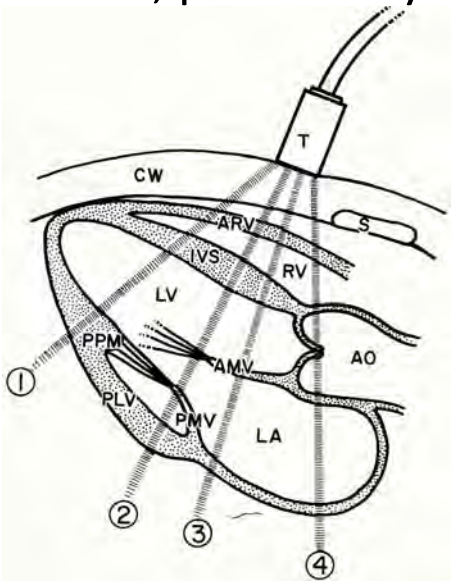


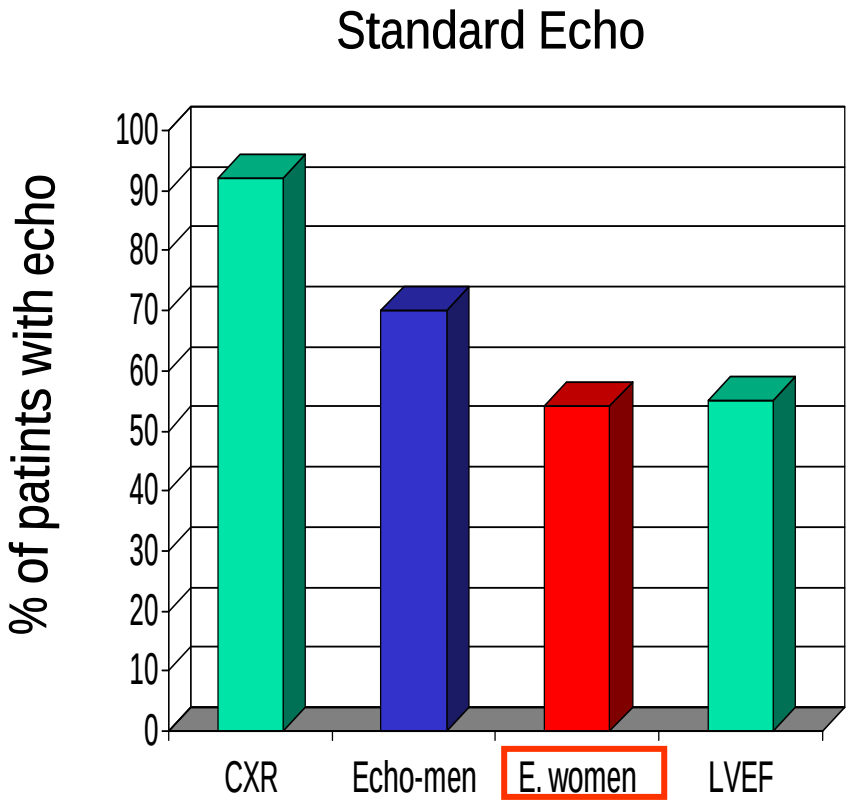

Circulation, 2005

# Euro Heart Failure Survey: Insufficient echocardiographic diagnosis: women >> Men

Cross sectional study in patients hospitalised for HF in Europe,
115 Hosp, 47600 Pat

- Underuse of standard echocardiography for diagnosis of HF, particularly in women




EHJ, Cleland 2003;
Agvall B, Scand Prim Health care, 2001

# (Why) is echocardiography and BNP underused? - EuroHeart Failure Survey

Facts: Standard echo: 66 % of men; 50 % of women
Tissue doppler and BNP: estimated < 10 % in women and men

**Reasons for underuse of Echo:**

- **Lack of adaequate equipment**
- **Lack of skills and knowledge of guidelines**

**Reasons for underdiagnosis in women:**

- **Lack of awareness of guidelines?**
- **Lack of trust in guidelines?**

**The second heavily underused technique**

- **BNP determinations - in special populations**
- **Lack of knowledge and availability, cost effectiveness**

# Treatment options

- Non-pharmacological management
  - General advice and measures
  - Exercise and exercise training
- Pharmacological therapy
  - ACE-inhibitors
  - Diuretics
  - Beta-adrenoceptor antagonists
  - Aldosterone receptor antagonists
  - Angiotensin receptor antagonists
  - Cardiac glycosides
  - Vasodilator agents (nitrates/hydralazine)
  - Positive inotropic agents
  - Anti-coagulation
  - Anti-arrhythmic agents
  - Oxygen
- Devices and surgery
  - Revascularization (catheter interventions and/or surgery),
  - Other forms of surgery (mitral valve repair)
  - Bi-ventricular (multi-site) pacing
  - Implantable cardioverter defibrillator (ICD)
  - Heart transplantation, ventricular assist devices, and artificial heart

# Treatment algorithms

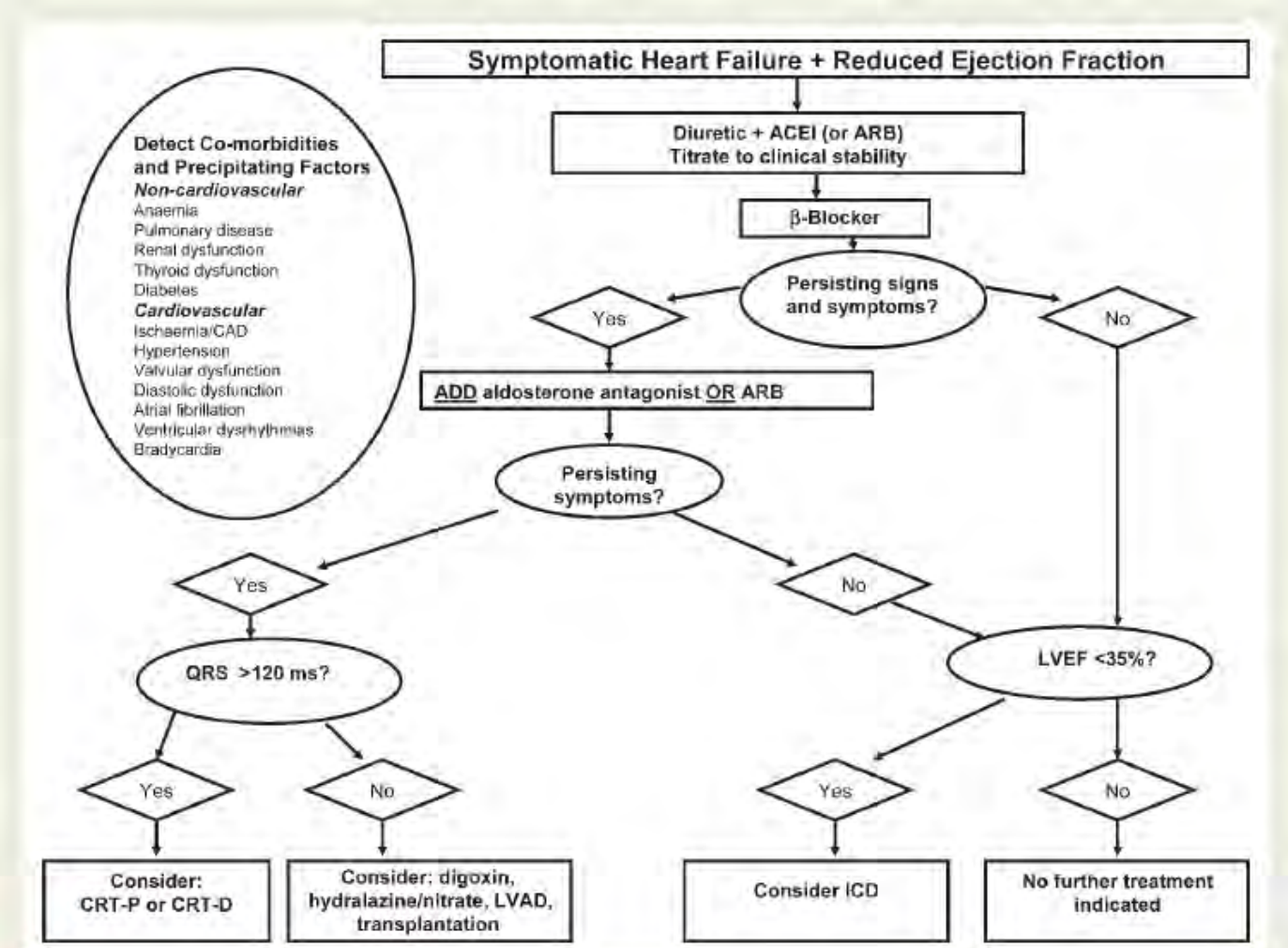



**Figure 2** A treatment algorithm for patients with symptomatic heart failure and reduced ejection fraction.

# Exercise training in HF

- **Evidence: mainly meta-analysis of trials.**
- **Mechanisms: reducing sympathetic activation, peripheral resistance and oxidative stress**
- **Animal model: Voluntary or forced exercise in mice/rats**

# Guideline based HF treatment - drugs

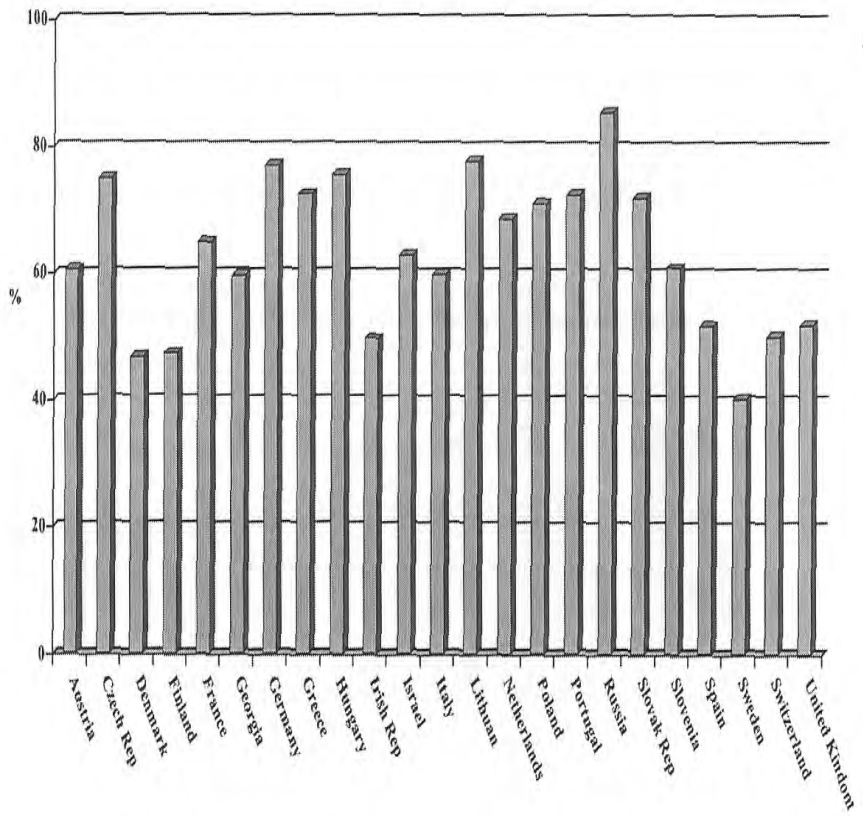
**Level I**

- **Diuretics (and salt retention) if fluid retention**
- **ACE Inhibitors, ARB**
- **ß-blockers**
- **Withdrawal of NSAR, most anti-arrhythmic agents, most Ca-blockers**
- **Exercise training**
- **ICD in selected patients**
- **Cardiac resynchronization therapy in selected patients**
- **MR antagonists in selected patients**

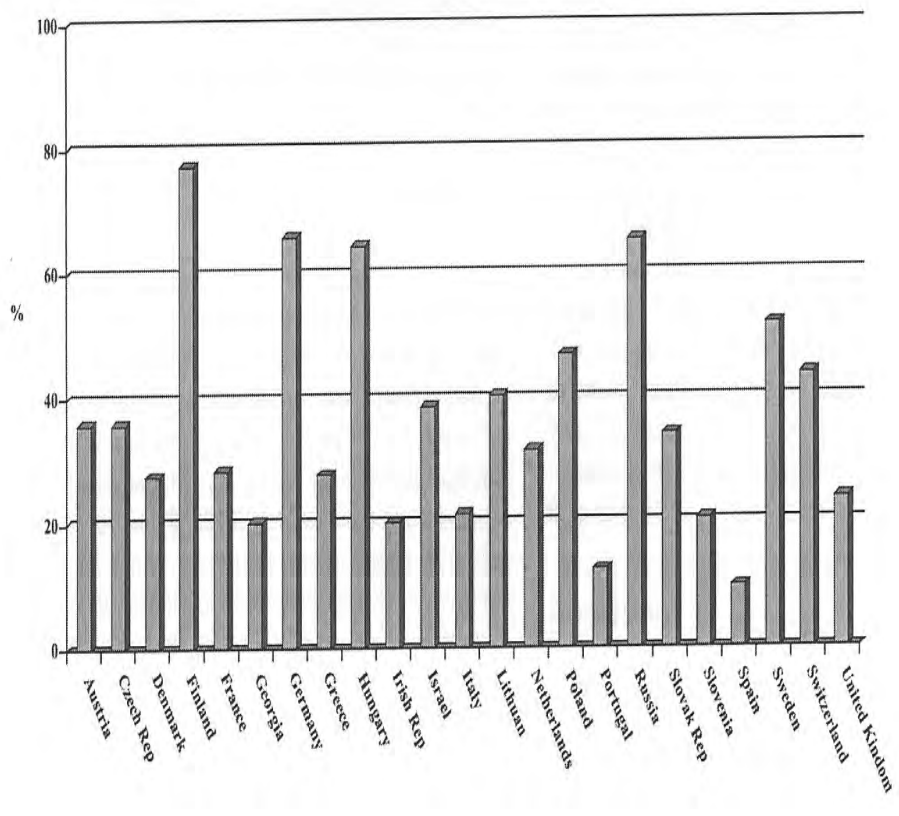
# HF treatment in Europe depends on the country….

100%

ACE-inhibitors

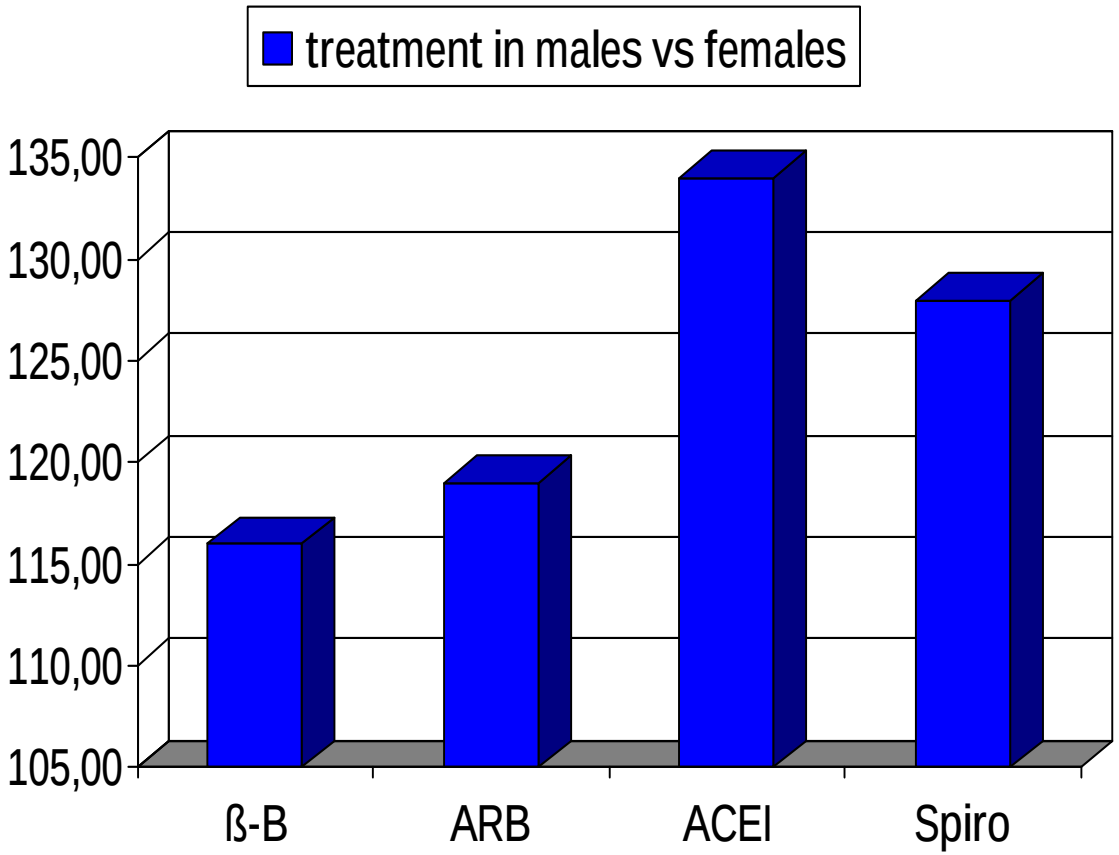



ß-Blockers




EHJ, 2003, 24: 464, study group on HF

# …..and HF-treatment differs by sex




Male gender increases likelihood of adaequate therapy in multivariate analysis – and female gender decreases it.

EHJ, 2003, 24: 464, study group on HF

# Pharmacological therapy - example

**Table 3. Cardiovascular Medications Useful for Treatment of Various Stages* of Heart Failure**

| Drug | Stage A | Stage B | Stage C |
|---|---|---|---|
| **ACE Inhibitors** | | | |
| Benazepril | H | — | — |
| Captopril | H, DN | Post MI | HF |
| Enalapril | H, DN | HF | HF |
| Fosinopril | H | — | HF |
| Lisinopril | H, DN | Post MI | HF |
| Moexipril | H | — | — |
| Perindopril | H, CV Risk | — | — |
| Quinapril | H | — | HF |
| Ramipril | H, CV Risk | Post MI | Post MI |
| Trandolapril | H | Post MI | Post MI |
| **Angiotensin Receptor Blockers** | | | |
| Candesartan | H | — | HF |
| Eprosartan | H | — | — |
| Irbesartan | H, DN | — | — |
| Losartan | H, DN | CV Risk | — |
| Olmesartan | H | — | — |
| Telmisartan | H | — | — |
| Valsartan | H, DN | Post MI | Post MI, HF |
| **Aldosterone Blockers** | | | |
| Eplerenone | H | Post MI | Post MI |
| Spironolactone | H | — | HF |
| **Beta Blockers** | | | |
| Acebutolol | H | — | — |
| Atenolol | H | Post MI | — |
| Betaxolol | H | — | — |
| Bisoprolol | H | — | HF |
| Carteolol | H | — | — |
| Carvedilol | H | Post MI | HF, Post MI |
| Labetalol | H | — | — |
| Metoprolol succinate | H | — | HF |
| Metoprolol tartrate | H | Post MI | — |
| Nadolol | H | — | — |
| Penbutolol | H | — | — |
| Pindolol | H | — | — |
| Propranolol | H | Post MI | — |
| Timolol | H | Post MI | — |
| **Digoxin** | — | — | HF |

Asymptomatic CV Risk indicates reduction in future cardiovascular events; DN, diabetic nephropathy; H, hypertension; HF, heart failure; LVSD, asymptomatic left ventricular systolic dysfunction; and Post MI, reduction in heart failure or other cardiac events following myocardial infarction.

*See Figure 1 for explanation of stages of heart failure.

# Novel developments in HF treatment

- Novel MR antagonists
- V1a/V2 Vasopressin Rezeptor Antagonisten
- Soluble Guanylate cyclase activators
- MMP inhibitors

# MR antagonist

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## A New Mode of Mineralocorticoid Receptor Antagonism by a Potent and Selective Nonsteroidal Molecule*[S]

Received for publication, April 7, 2010, and in revised form, July 22, 2010 Published, JBC Papers in Press, July 22, 2010, DOI 10.1074/jbc.M110.131342

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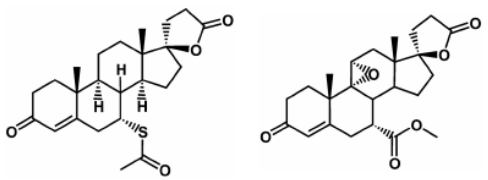

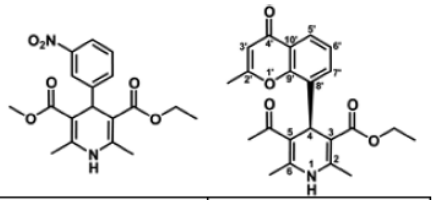

| | Spironolactone | Eplerenone | Nitrendipine | BR-4628 |
|---|---|---|---|---|
| MR ($IC_{50}$) | 24 ± 1 | 990 ± 40 | 1996 ± 170 | 28 ± 2 |
| GR ($IC_{50}$) | 2410 ± 260 | 21980 ± 1890 | 25760 ± 4240 | 5470 ± 470 |
| AR ($IC_{50}$) | 77 ± 4 | 21240 ± 2340 | 10050 ± 760 | 4440 ± 590 |
| PR ($IC_{50}$/*$EC_{50}$) | 740 ± 60* | 31210 ± 3190 | 9730 ± 1720 | 9020 ± 550 |
| L-type $Ca^{2+}$ Channel ($IC_{50}$) | | | 0.26 ± 0.004 | 1990 ± 170 |

- *BAYER has discovered potent and selective, non-steroidal Dihydropyridine-based MR antagonists*

# Cardiac and Renal Protection by a New Mineralocorticoid Receptor Antagonist in Salt-Sensitive Arterial Hypertension

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World Congress of Cardiology 2006, Barcelona
Eur. Heart J. 2006, 27 (Suppl1), 110

## PURPOSE

Activation of the mineralocorticoid receptor (MR) via aldosterone may contribute to hypertension, end-organ damage and mortality in salt sensitive individuals. We therefore investigated the effect of specific MR blockade on blood-pressure, renal and cardiac impairment, and mortality in two animal models of salt sensitive hypertension.

## METHODS

***DOCA-salt loaded rat:***
Uninephrectomized male Sprague Dawley rats (n 38) were exposed to DOCA (30 mg/kg/wk s.c.) and NaCl (1% in drinking water) and treated for five weeks with either vehicle control, BAY (10 & 30mg/kg/d), or Eplerenone (100 mg/kg/d). Blood pressure was measured by the tail cuff method, total protein was determined in urine collected over 24 hours, and hearts and kidneys were weighed after 36 days of treatment.

***Stroke-prone spontaneously hypertensive rat (SHRSP):***
37 salt loaded (2% in drinking water) SHRSPs (age 16-20 weeks) were treated with vehicle control, BAY, Eplerenone or Spironolactone (all 30 mg/kg/d) for 8 weeks. The experiment was terminated when 6 of 10 vehicle animals had died. Aortas, hearts and kidneys were fixed in 10% neutral buffered formalin and embedded in Paraplast. Sections were prepared and stained with haematoxylin and eosin and analysed by semi-quantitative scoring (grade 1–3).

## RESULTS

***DOCA-salt loaded rat:***
The novel non steroidal MR antagonist BAY and Eplerenone reduced systolic blood pressure to a similar extent (Figure 1A). BAY substantially reduced heart weight as well as proteinuria in this model of arterial hypertension (Figure 1B C). Similarly, kidney weights were reduced by BAY, but not by Eplerenone.

***Stroke-prone spontaneously hypertensive rat (SHRSP):***
After a treatment period of 8 weeks mortality was significantly decreased in the BAY treated group (0/9) versus placebo treated animals (6/10). Protection by Eplerenone and Spironolactone was moderate (3/9 deaths in both groups, Figure 2). Histopathological evaluation of the kidneys demonstrated significant reduced hypertensive lesions (i.e.vasculopathy, glomerulopathy, and tubular degeneration) in the BAY treated animals in comparison to all other groups.

## CONCLUSIONS

We have discovered a novel selective, non steroidal MR antagonist which:
- reduces blood pressure
- prevents end organ damage
- improves survival

in salt sensitive hypertension.

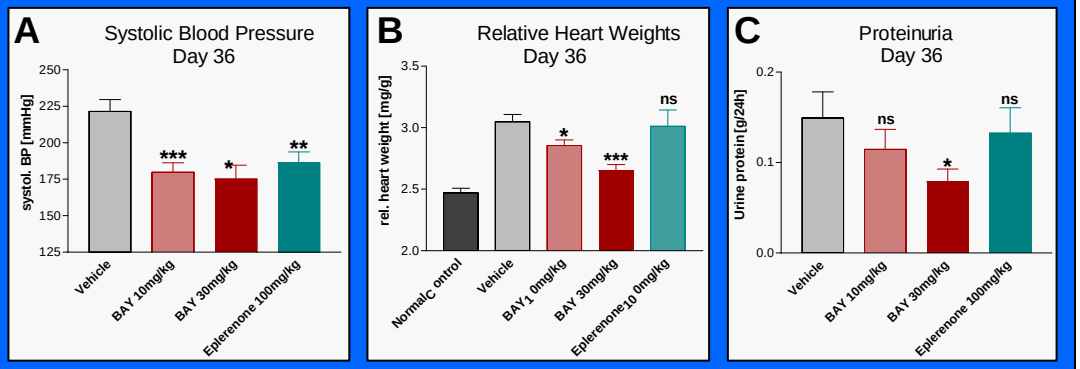



Figure 1 : Changes in A) systolic blood pressure, B) relative heart weights and C) urinary protein excretion after 36 days of treatment with either vehicle, BAY or Eplerenone. *p≤0.05, **p≤0.01, ***p≤0.005, ns not significant.

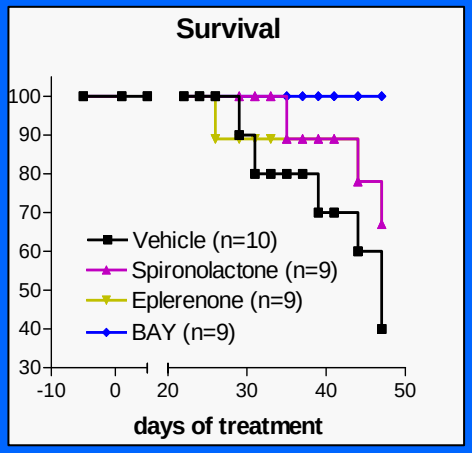



Figure 2: Survival benefit from different MR Antagonists in salt loaded SHRSPs.

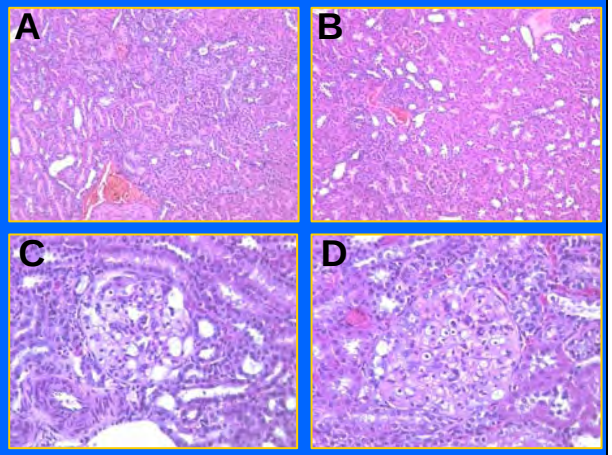



Figure 3: Histopathological kidney lesions.
Vehicle group, grade 3 (A), BAY group, grade 1 (B).
Representative sections at higher magnifications showing glomerulopathy in BAY group, grade 1 (C), and Eplerenone group, grade 2 (D).

# Pharmacological Characterization of a Mutant Mineralocorticoid Receptor Responsible for Severe, Early-Onset Hypertension

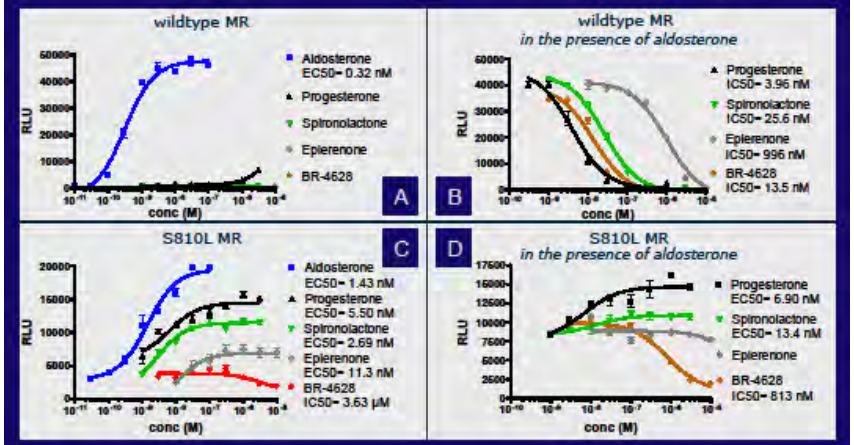
Peter Kolkhof, Verena Jilg and Stefan Schäfer
BAYER HealthCare AG, Global Drug Discovery, Wuppertal, Germany
Institute for Cardiovascular Research

## PURPOSE

Increased aldosterone levels and, consequently, overactivation of the mineralocorticoid receptor (MR) can lead to refractory arterial hypertension and end organ damage. Recently, a gain-of function mutation of the MR has been identified, which is characterized by a leucine for serine mutation (S810L), leading to paradoxical activation, rather than blockade, of the receptor by its natural steroidal antagonist progesterone. Clinically, the mutation is linked to early-onset hypertension in men and gestational hypertension in women.
We have recently discovered a selective, non-steroidal MR antagonist (BR-4628) which potently blocks wildtype MR.
In the present study, we investigated the characteristics of the traditional, steroidal MR antagonists (spironolactone, eplerenone) in comparison to BR-4628 at the wildtype and mutant receptor.

## RESULTS

- Progesterone ($IC_{50}$ 3.9 nM), spironolactone ($IC_{50}$ 25.6 nM), eplerenone ($IC_{50}$ 996 nM) and BR-4628 ($IC_{50}$ 14 nM) were all potent and competitive aldosterone antagonists at wildtype MR (A and B).
- S810L MR cells are characterized by a constitutive receptor activity (five-fold increase over baseline luciferase signal in wildtype cells, ).
- The luciferase signal in S810L MR cells was dose dependently increased by progesterone (5.2-fold, $EC_{50}$ 5.5 nM), spironolactone (4-fold, $EC_{50}$ 2.7 nM), and eplerenone (1.7-fold, $EC_{50}$ 11.3 nM), compared to aldosterone (6.9-fold, $EC_{50}$ 1.4 nM, C).
- Moreover, there was an additive activation of the mutant receptor by progesterone and spironolactone in the presence of 1 nM aldosterone ($EC_{50}$ 6.9 and 13.4 nM, D).
- In contrast, the non-steroidal MR antagonist BR-4628 was a strong inhibitor of the luciferase signal in the absence and presence of aldosterone ($IC_{50}$ 3.6 and 0.81 µM, respectively, C and D).




## METHODS

We developed a stable functional cell based assay for both wildtype and mutant S810L MR. The mutant MR was generated by site-directed mutagenesis of the wildtype MR cDNA. Gene activation by wildtype or mutant MR upon ligand binding was detected by a luciferase reporter detection system in these stable cell lines. Compounds were given in eight dilutions in triplicates to the cells and luciferase activity (expressed in relative light units, RLUs) was determined with a video camera system after an incubation time of five to six hours. Antagonistic function was tested in the presence of the natural ligand aldosterone (1 nM).

## CONCLUSIONS

The steroidal MR antagonists progesterone, spironolactone and eplerenone paradoxically activate the S810L mutant form of the mineralocorticoid receptor, potentially leading to exacerbation of arterial hypertension in affected patients. In strong contrast to the steroidal MR antagonist, a novel potent and selective, non-steroidal MR antagonist, BR-4628 blocks both wild-type and S810L MR. This compound offers a potential for causal treatment of aldosterone-related hypertension and end organ damage in a broad hypertensive population including patients with rare genetic forms of hypertension where other drugs are even contraindicated.

# Aldosterone Receptor Blockade in salt-sensitive Hypertension: End-organ protection and role of Monocyte chemoattractant protein

P. Kolkhof[1], A. Kretschmer[2], P. Ammelung[1], D. Chodor[1], A. Götte[3], I. Hutmacher[3], E. Hartmann[3], and S. Schäfer[1]
BAYER Schering Pharma, Global Drug Discovery, Wuppertal, Germany
Institute for [1]Cardiovascular Research, [2]Target Discovery, [3]Toxicology

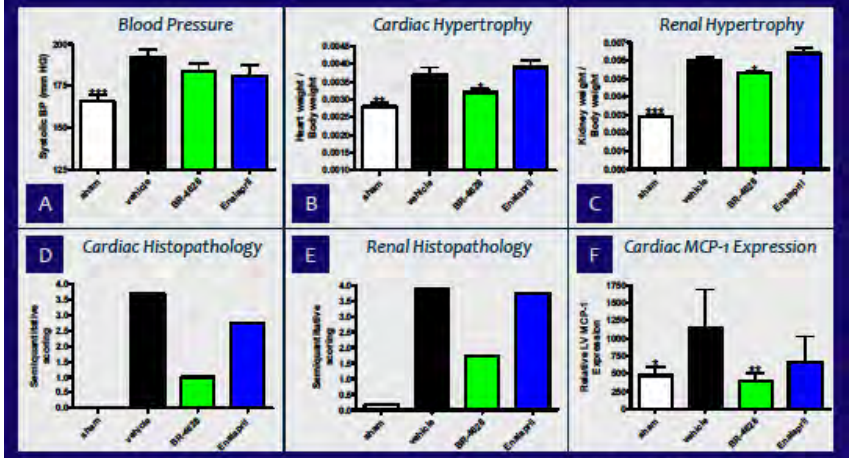
## PURPOSE

Aldosterone concentrations inappropriate for salt status may lead to cardiac and vascular inflammation and fibrosis and are associated with increased cardiovascular event rates including target organ damage. Monocyte chemoattractant protein-1 (MCP-1) is a key factor in initiation of inflammatory processes and has been shown to provide independent prognostic value in patients with acute coronary syndrome that is complementary to standard clinical biomarkers.
We investigated in a model of salt-sensitive hypertension, heart failure and target organ damage:

1.) end-organ protection as a consequence of pharmacological blockade of either mineralocorticoid receptor (MR) or angiotensin converting enzyme (ACE) action at dosages without major blood pressure effects
2.) whether cardiac MCP-1 expression can be influenced by pharmacological intervention.

## RESULTS

- BR-4628 and enalapril reduced systolic blood pressure (A, tail cuff method) not significantly but to the same extent after 6 weeks (placebo: 192.3±4.7, BR-4628: 183.4±4.9, Enalapril: 180.8±6.3 mmHg)
- However, BR-4628, but not enalapril, substantially reduced heart (B) and kidney weight (C) determined after 6 weeks of treatment.
- Proteinuria was found to be reduced by both pharmacological interventions, but only aldosterone blockade revealed significant activity.
- Histopathological analysis (semiquantitative scoring) of cardiac (D) and kidney tissue (E) revealed substantial reduction of myocardial degeneration, vasculopathy, glomerular and tubulo-interstitial damage in the BR-4628 group (mean grades for cardiac lesions 1.0 and kidney lesions 1.71), compared to placebo (mean grades 3.71 and 3.86, respectively), whereas enalapril was less effective (mean grades 2.75 and 3.75, respectively).
- Corresponding to the superior cardioprotection, BR-4628 afforded a substantial reduction in left ventricular MCP-1 expression (F).




## METHODS

Uninephrectomized male Sprague Dawley rats were exposed to DOCA (30 mg/kg/wk s.c.) and NaCl (1% in drinking water) and were treated for six weeks with the angiotensin converting enzyme (ACE) inhibitor enalapril (10 mg/kg/d), a novel selective, non-steroidal MR antagonist (BR-4628, 10 mg/kg/d) or placebo. Blood pressure was measured by the tail cuff m
neutral but
prepared a
semi-quanti

## CONCLUSIONS

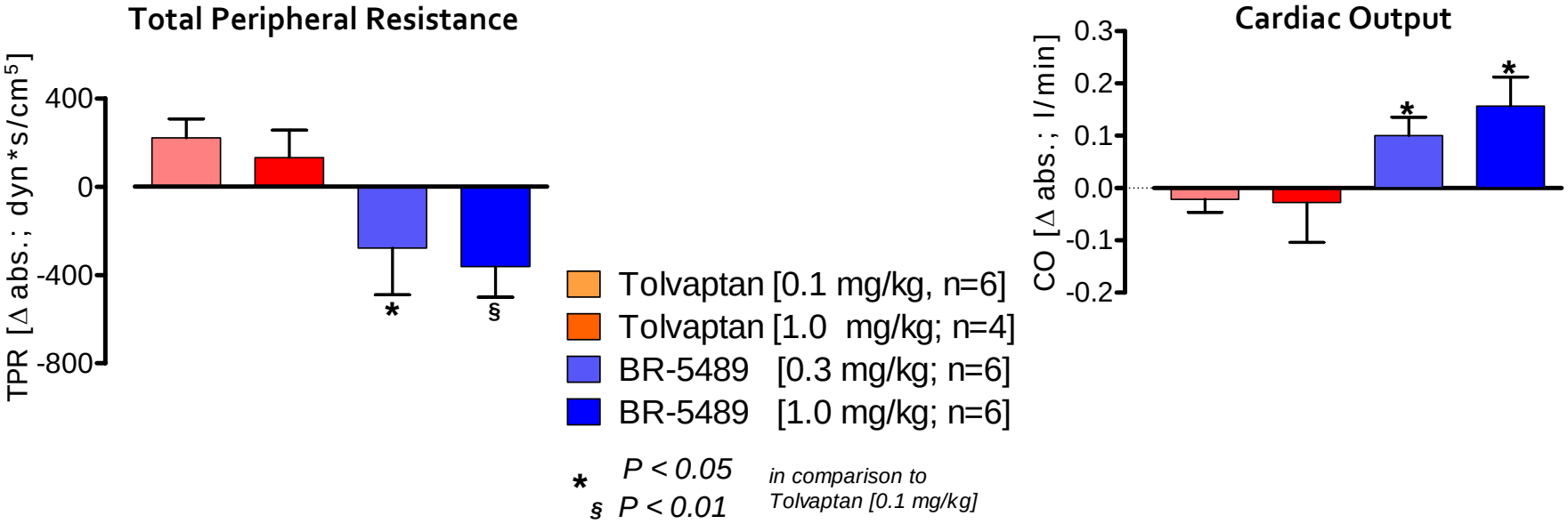
Pharmacological blockade of the mineralocorticoid receptor prevents cardiac and renal end organ damage more effectively than ACE inhibition in a model of salt sensitive hypertension. Reduction of the mediator of inflammation, MCP-1, may contribute to this beneficial effect.

73th Annual Meeting of the German Cardiac Society
Clin. Res. Cardiol. 2007, 96(Suppl 1).

## HF induced by tachypacing in adult mongrels

- Determination of hemodynamic effects in anaesthetized dogs with heart failure induced by prolonged tachypacing
- AVP was infused (up to 4mU/kg/min) in order to achieve constant pathophysiological levels of AVP
- CO recording via Swan Ganz catheter


Parameters at 20 minutes post application




- BR-5489 decreases total peripheral resistance while Tolvaptan slightly increases TPR
- BR-5489 increases cardiac output while Tolvaptan is without effects

# Additional aspects in HF treatment

- Special populations
  - **Women,**
  - **Ethnic subgroups,**
  - **Elderly**
  - **Cancer patients**
- Anticoagulation
- Management of cardiac arrhythmias
- Device therapy
  - **Resynchronization**
  - **ICD**

# Acute Hemodynamic Effects of Atrio-Biventricular Pacing in Humans

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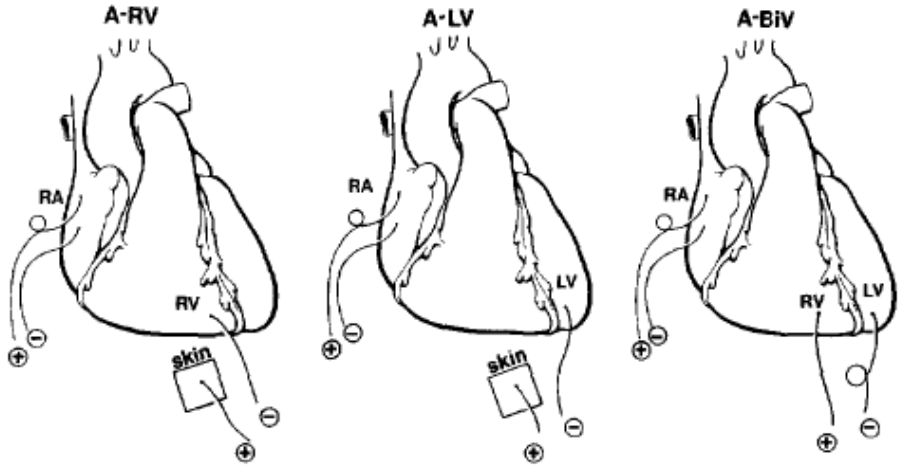
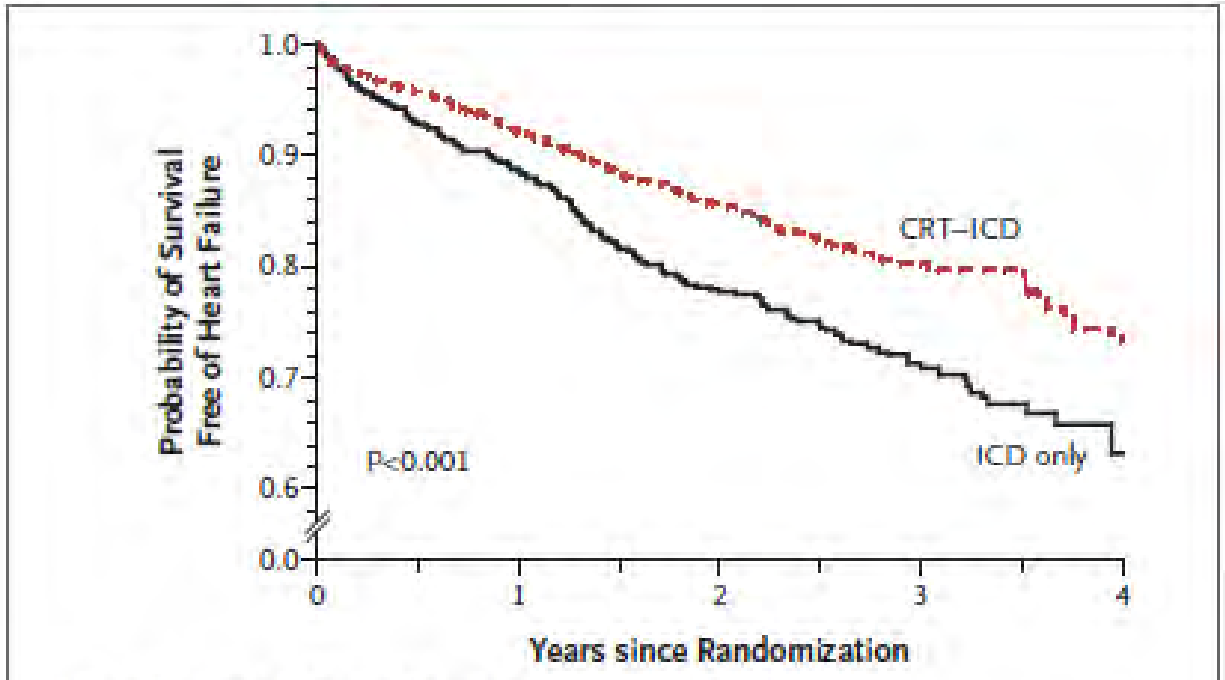


# Resynchronization therapy

**Table 1. Baseline Demographic and Clinical Characteristics of the Patients.***

| Variable | ICD-Only Group (N=731) | CRT-ICD Group (N=1089) |
|---|---|---|
| Age — yr | 64±11 | 65±11 |
| Male sex — no. (%) | 553 (75.6) | 814 (74.7) |
| Race — no./total no. (%)† | | |
| White | 657/724 (90.7) | 979/1083 (90.4) |
| Black | 56/724 (7.7) | 87/1083 (8.0) |
| Other | 11/724 (1.5) | 17/1083 (1.6) |
| Cardiac history — no. (%) | | |
| Ischemic heart disease | | |
| NYHA class I | 113 (15.5) | 152 (14.0) |
| NYHA class II | 288 (39.4) | 446 (41.0) |
| Nonischemic heart disease | | |
| NYHA class II | 330 (45.1) | 491 (45.1) |
| NYHA class III or IV >3 mo before enrollment — no. (%) | 73 (10.0) | 109 (10.0) |

Moss, NEJM 2009

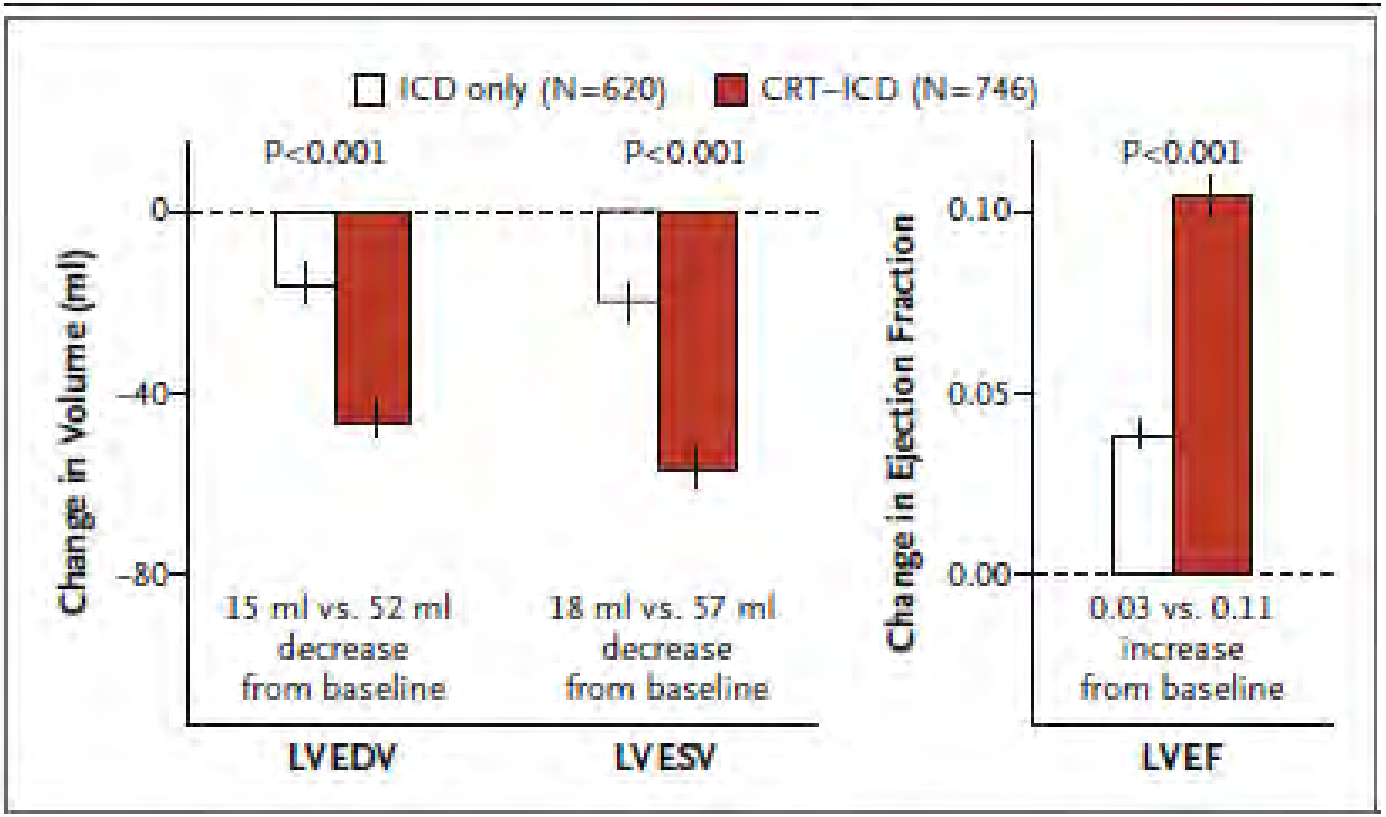



| No. at Risk (Probability of Survival) | | | | | |
|---|---|---|---|---|---|
| ICD only | 731 | 621 (0.89) | 379 (0.78) | 173 (0.71) | 43 (0.63) |
| CRT–ICD | 1089 | 985 (0.92) | 651 (0.86) | 279 (0.80) | 58 (0.73) |

**Figure 2. Kaplan–Meier Estimates of the Probability of Survival Free of Heart Failure.**

There was a significant difference in the estimate of survival free of heart failure between the group that received cardiac-resynchronization therapy plus an implantable cardioverter–defibrillator (CRT–ICD) and the group that received an ICD only (unadjusted P<0.001 by the log-rank test).

Moss, NEJM 2009




Moss, NEJM 2009

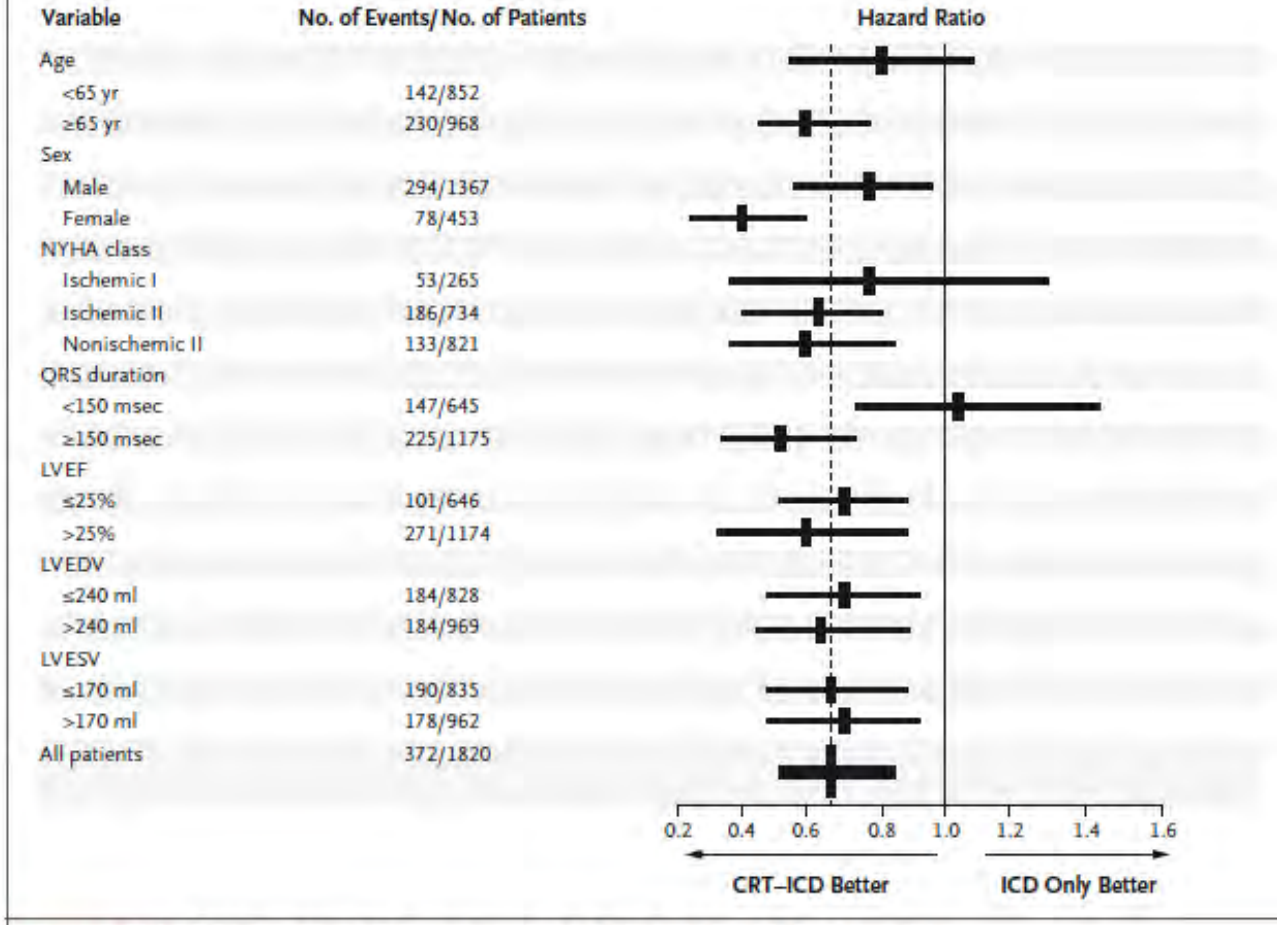



**Figure 3. Risk of Death or Heart Failure, According to Selected Clinical Characteristics.**

The hazard ratios for death or nonfatal heart failure (whichever came first) are shown for various subgroups among patients who received cardiac-resynchronization therapy plus an implantable cardioverter–defibrillator (CRT–ICD) and those who received an ICD only. The dashed vertical line represents the results for the entire study (hazard ratio in the CRT–ICD group, 0.66), and the horizontal lines indicate 95% confidence intervals. LVEDV denotes left ventricular end-diastolic volume, LVEF left ventricular ejection fraction, LVESV left ventricular end-systolic volume, and NYHA New York Heart Association. Two subgroup treatment interactions were identified, for sex (P=0.01) and QRS duration (P=0.001). All other interaction P values exceeded 0.10.

Moss, NEJM 2009

# Update ESC guidelines - 2009

**Recommendation in patients with heart failure in New York Heart Association function class III/IV**

| Recommendation | Patient population | Class[a] | Level[b] | Ref.[c] |
|---|---|---|---|---|
| CRT-P/CRT-D is recommended to reduce morbidity and mortality[d] | NYHA function class III/IV<br>LVEF ≤35%, QRS ≥120 ms, SR<br>Optimal medical therapy<br>Class IV patients should be ambulatory[e] | I | A | 5–19 |

**Recommendation in patients with heart failure in New York Heart Association function class II**

| Recommendation | Patient population | Class[a] | Level[b] | Ref.[c] |
|---|---|---|---|---|
| CRT preferentially by CRT-D is recommended to reduce morbidity or to prevent disease progression[d] | NYHA function class II<br>LVEF ≤35%, QRS ≥150 ms, SR<br>Optimal medical therapy | I | A | 9, 20–22 |

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
[d]The guideline indication has been restricted to patients with HF in NYHA function class II with a QRS width ≥150 ms, a population with a high likelihood of a favourable response.
CRT = cardiac resynchronization therapy; CRT-D = CRT with defibrillator function; HF = heart failure; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SR = sinus rhythm.

EHJ, 2010, 31:2677

**Recommendation in patients with severe heart failure ineligible for transplant**

| Recommendations | Patient population | Class[a] | Level[b] | Ref.[c] |
|---|---|---|---|---|
| LVAD may be considered as destination treatment to reduce mortality | NYHA function class IIIB/IV<br>LVEF ≤25%<br>peak $VO_2$<14 mL/kg/min[d] | IIb | B | 49–53 |

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
[d]If obtainable.
LVAD = left ventricular assist device; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

EHJ, 2010, 31:2677

# Diastolic Dysfunction

**Evidence based**

- **Control of hypertension**
- **Control of ventricular rate in a fib**
- **Use of diuretics**

**Treatment of comorbidities**

# Heart Failure - Treatment of comorbidities

**Table 24 Management of patients with heart failure and atrial fibrillation**

**General recommendations**

- Precipitating factors and co-morbidities should be identified
- HF treatment should be optimized

**Rhythm control**

- Immediate electrical cardioversion is recommended for patients with new-onset AF and myocardial ischaemia, symptomatic hypotension or symptoms of pulmonary congestion or rapid ventricular response not controlled by appropriate pharmacological measures

**Rate control**

- Digoxin alone or in combination with β-blocker is recommended

**Prevention of thromboembolism**

- Antithrombotic therapy is recommended, unless contraindicated
- Optimal approach should be based on risk stratification: in patients at highest risk of stroke [prior stroke, transient ischaemic attack (TIA), or systemic embolism] oral anticoagulant therapy with a vitamin K antagonist is recommended

EHJ, 2008; 29:2388

# Guidelines for end stage HF

**Level I**

- **Meticulous fluid control**
- **HTX**
- **Specialized Management programs**
- **End of life care**

**II a**

- **Ventricular assist Devices (VAD)**

**IIb**

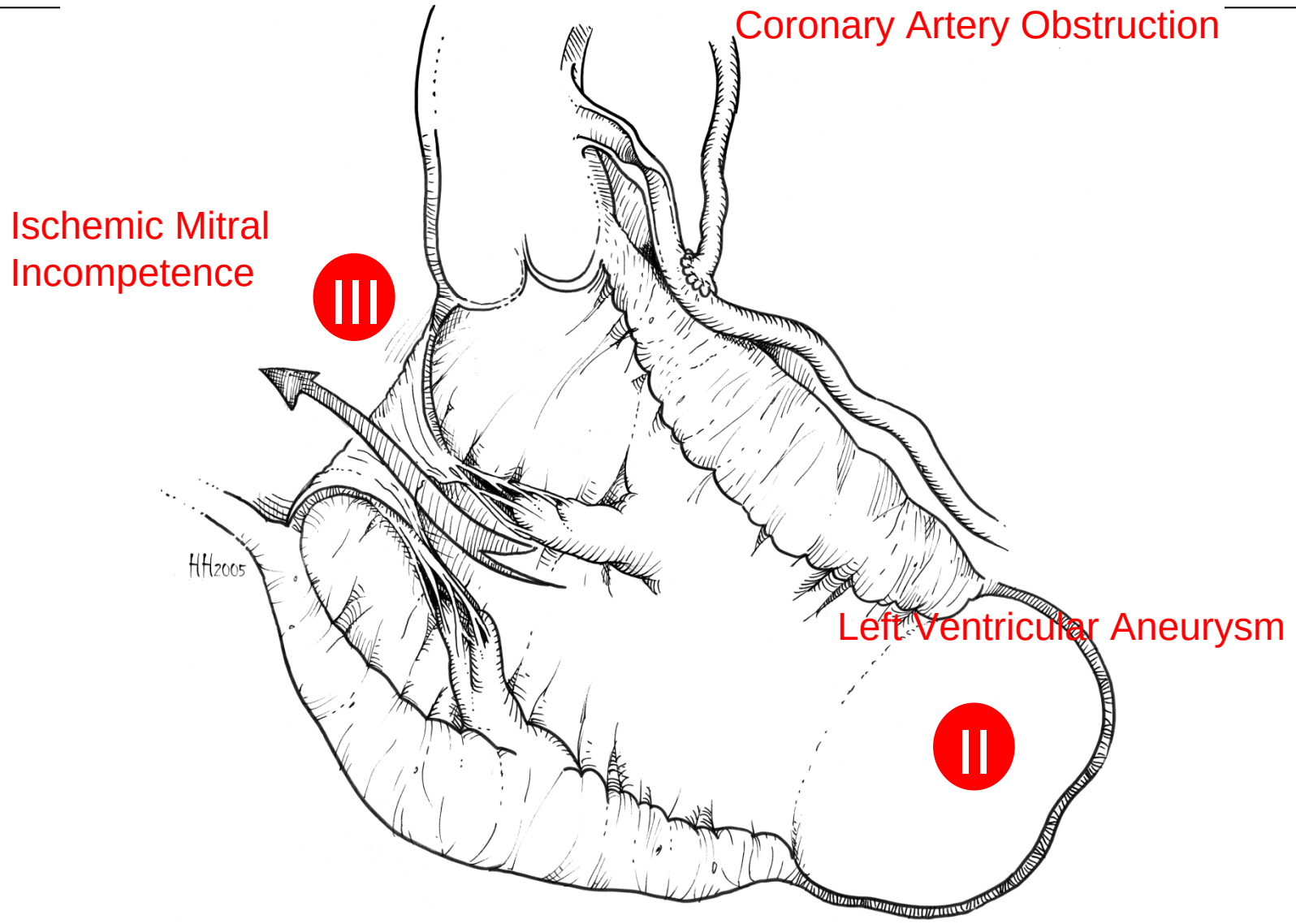
**Mitral valve repair……**

**others**

# L O C I M A N

- **L**eft ventricular failure
- **O**bstruction of **C**oronary arteries
- **I**schemic **M**itral incompetence
- Left ventricular **AN**eurysm

# LOCIMAN


Coronary Artery Obstruction
Ischemic Mitral Incompetence
III
HH2005
Left Ventricular Aneurysm
II

# L O C I M A N

## Questions

- **What is the relative contribution to left ventricular failure of**
  - **hibernating myocardium**
  - **ischemic mitral incompetence**
  - **left ventricular aneurysm / akinesia**

- **What is the relative benefit of**
  - **coronary bypass**
  - **mitral repair**
  - **ventricular restoration / aneurysmectomy**

## Further Questions

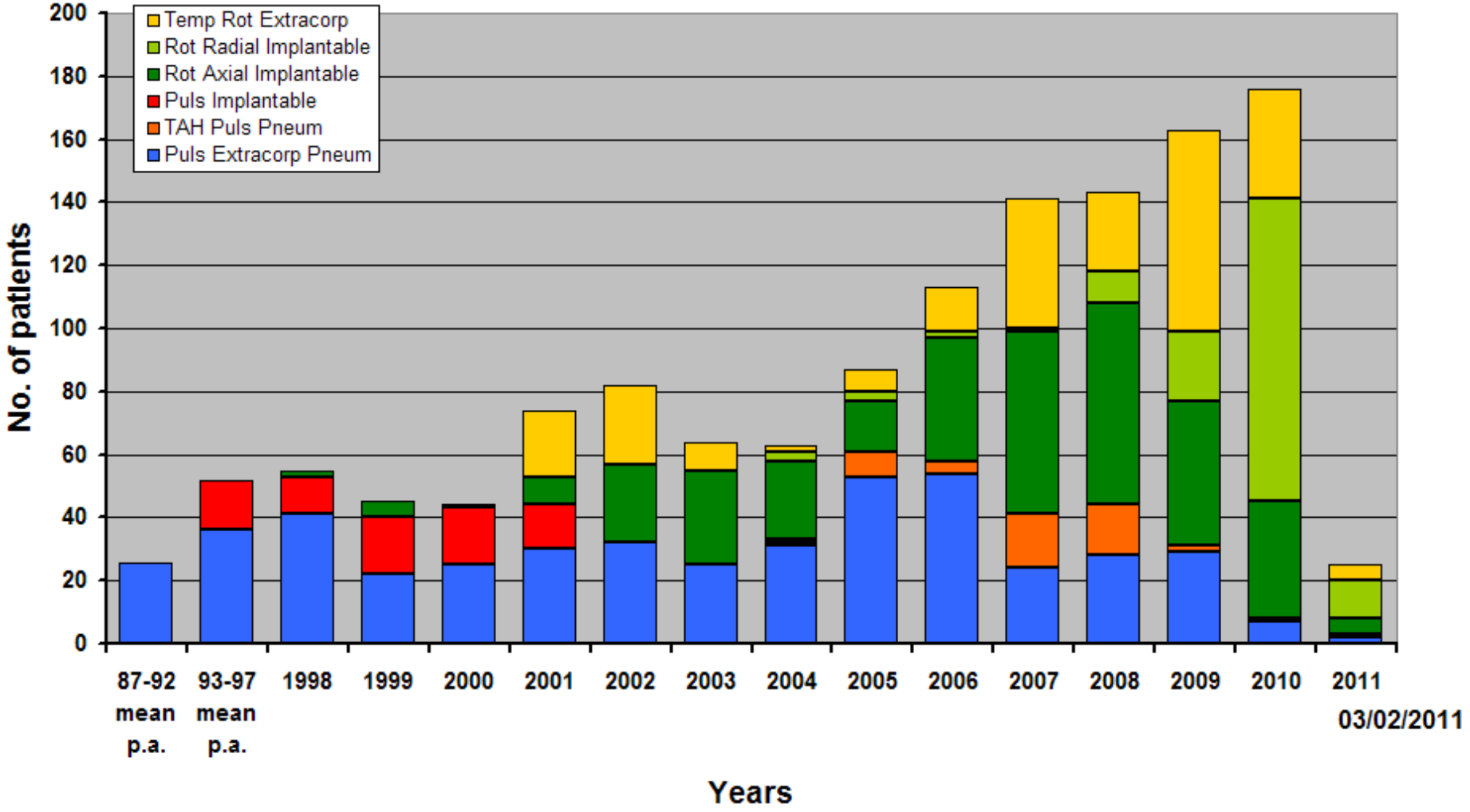
- When is an implantable VAD indicated for temporary use and ventricular recovery ?

- When is a permanent VAD or TAH indicated ?

# 78 year-old male iCMP (LOCIMAN)

- CABG and Aneurysmectomy 1991
- Implantation of ICD in 1997 and CRT in 2001
- REDO CABG and Aneurysmectomy 2002
- PTCA and Stenting 2003
- PTCA and Stenting 2004
- Hypertension, chronic renal failure, pulmonary hypertension
- July 29, 2009 progessive heart failure and implantation of HeartMate II via left lateral thoracotomy for permanent support
- July 2010: Patient well at home

Support ongoing at 357 days



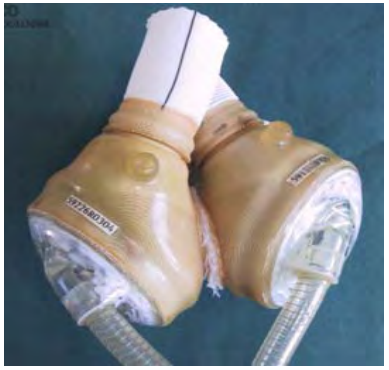

**DHZB 2009** Hennig

## pulsatile

Paracorporeal

implanted

CardioWest



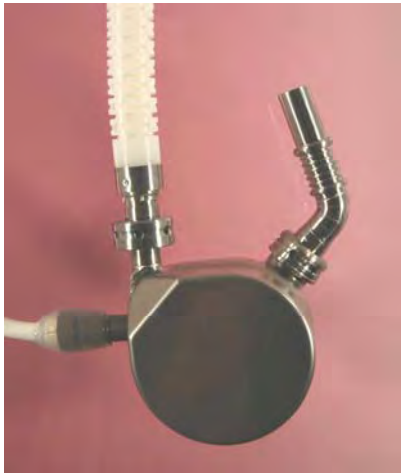
Total Artificial Heart

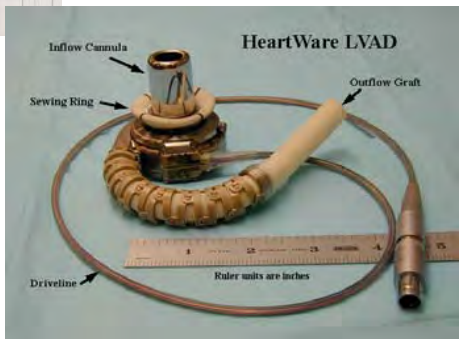
EXCOR® VAD


## axial flow


## rotational

radial flow



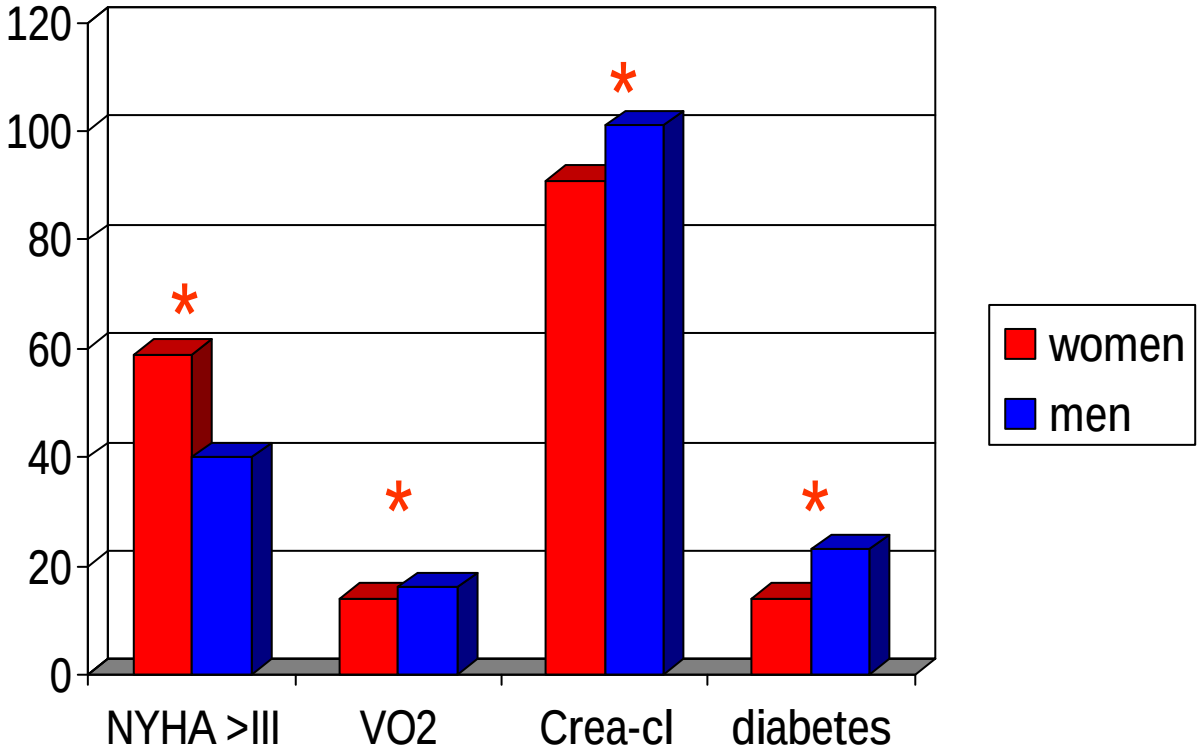
# Women are less frequently/later referred for heart transplantation than men

Women are more rarely presented for HTX, 110/704 DCM

Prospective DHZB Study:

Women

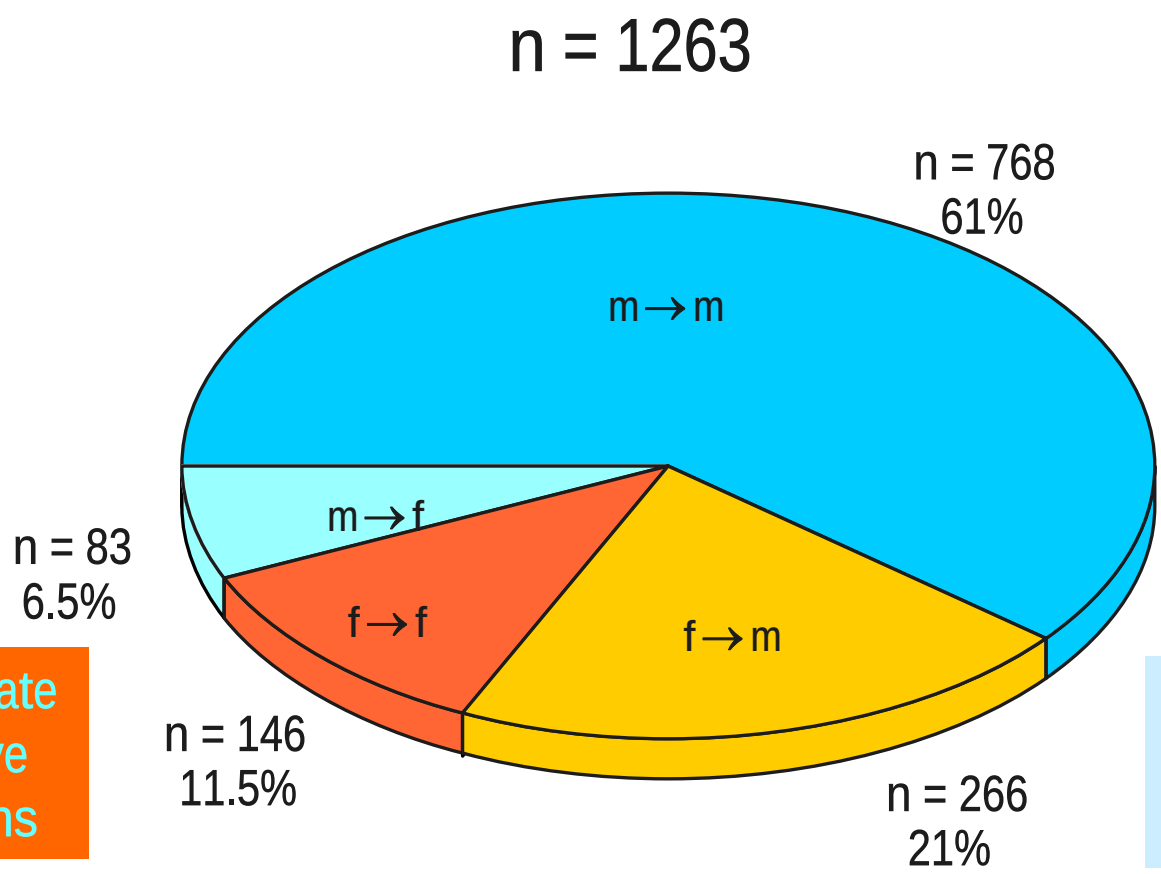
- were underrepresented
- had more severe disease
  - Higher NYHA stage
  - Lower exerc tolerance
  - Lower kidney function
- Less relative contra-indications - diabetes




* P<0.05

Transplantation, 2009

# Heart Transplantation: Women are more frequent donors and men recipients

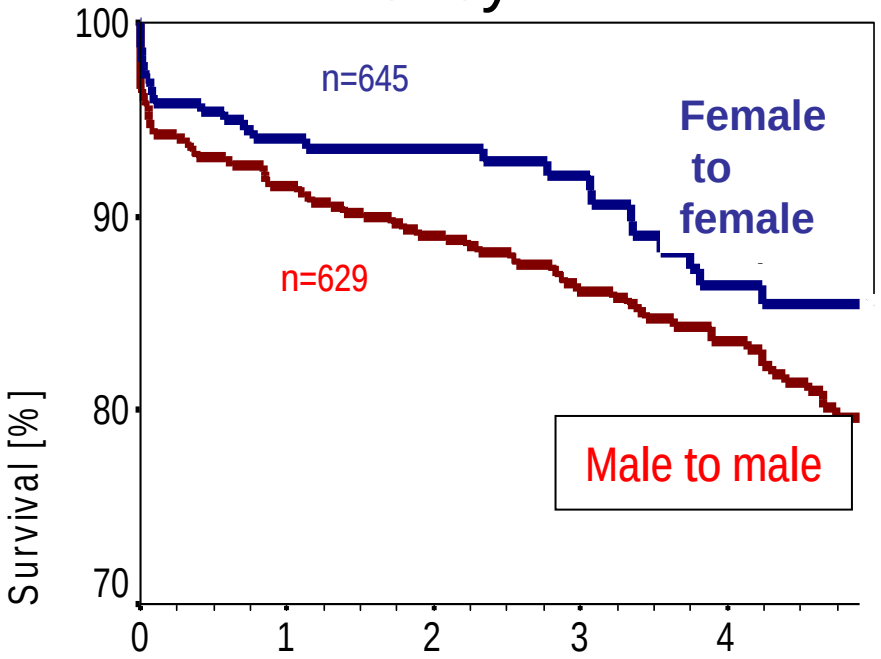



Females donate
32 and receive
18 % of organs

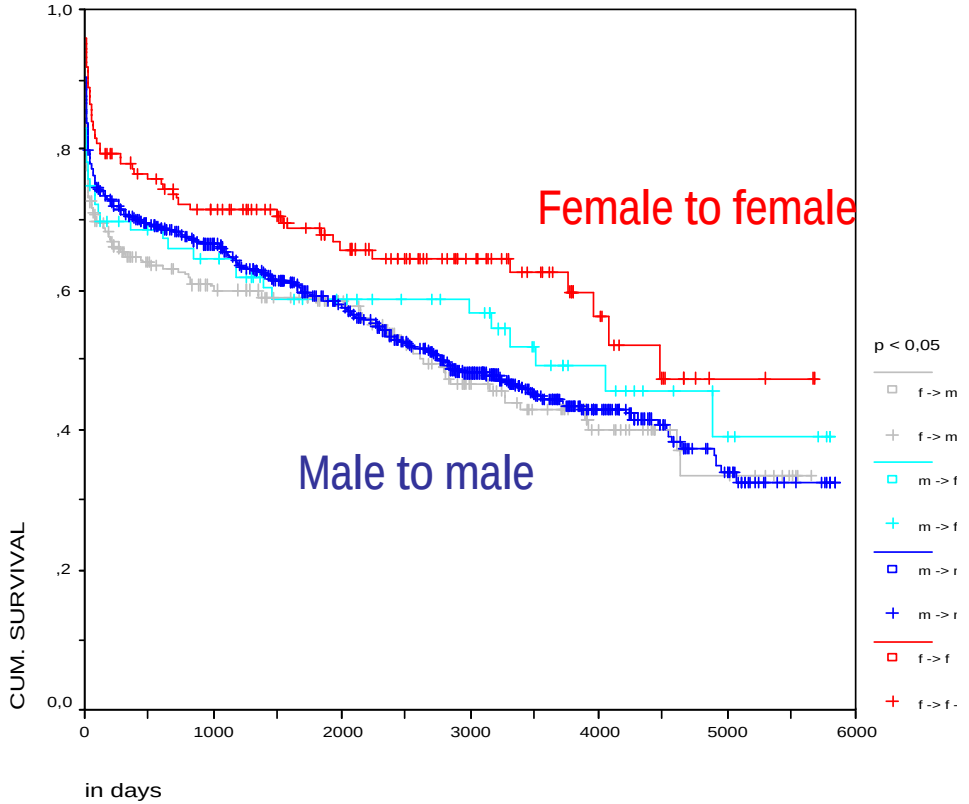
Males donate
68 and receive
82 % of organs

# Gender differences in kidney and heart transplant rejection

kidney




Heart




Hypotheses

Testosteron leads to stronger activation of vasoconstrictive and inflammatory pathways

Estradiol and 2-ME mediate counter regulation

# Arrhythmia treatment

**Table 9** Examples of drugs causing torsades de pointes[a]

Frequent (greater than 1%) (e.g., hospitalization for monitoring recommended during drug initiation in some circumstances)

- Disopyramide
- Dofetilide
- Ibutilide
- Procainamide
- Quinidine
- Sotalol
- Ajmaline

Less frequent

- Amiodarone
- Arsenic trioxide
- Bepridil
- Cisapride
- Anti-infectives: clarithromycin, erythromycin, halofantrine, pentamidine, sparfloxacin
- Antiemetics: domperidone, droperidol
- Antipsychotics: chlorpromazine, haloperidol, mesoridazine, thioridazine, pimozide
- Opioid dependence agents: methadone

[a]See www.torsades.org for up-to-date listing.

Adapted with permission from Roden DM. Drug-induced prolongation of the QT interval. *N Engl J Med* 2004;350:1013–1022. Copyright © 2004 Massachusetts Medical Society.[294]

**Table 10** Risk factors for drug-induced torsades de pointes

- Female gender
- Hypokalemia
- Bradycardia
- Recent conversion from atrial fibrillation
- Congestive heart failure
- Digitalis therapy
- High drug concentrations (*exception: quinidine*), often due to drug interactions
- Rapid rate of intravenous drug administration
- Baseline QT prolongation
- Ventricular arrhythmia
- Left ventricular hypertrophy
- Congenital long QT syndrome
- Certain DNA polymorphisms
- Severe hypomagnesemia
- Concomitant use of 2 or more drugs that prolong the QT interval
- Combination of QT-prolonging drug with its metabolic inhibitor

Adapted with permission from Roden DM. Drug-induced prolongation of the QT interval. *N Engl J Med* 2004;350:1013–1022. Copyright © 2004 Massachusetts Medical Society.[294]

DNA = deoxyribonucleic acid.

# Comparison: amiodarone and ICD

Table 1. Characteristics of the Patients at Baseline or at the Last Follow-up Visit.

| Characteristic | Amiodarone (N=845) | Placebo (N=847) | ICD Therapy (N=829) |
|---|---|---|---|
| Age — yr | | | |
| Median | 60.4 | 59.7 | 60.1 |
| Interquartile range | 51.7–68.3 | 51.2–67.8 | 51.9–69.2 |
| Female sex — no. (%) | 206 (24) | 192 (23) | 190 (23) |
| Nonwhite race — no. (%) | 196 (23) | 204 (24) | 189 (23) |
| Ejection fraction | | | |
| Median | 25.0 | 25.0 | 24.0 |
| Interquartile range | 20.0–30.0 | 20.0–30.0 | 19.0–30.0 |
| Diabetes — no. (%) | 243 (29) | 271 (32) | 253 (31) |
| Pulmonary disease — no. (%) | 147 (17) | 158 (19) | 175 (21) |
| Hypercholesterolemia — no. (%)* | 442 (52) | 456 (54) | 431 (52) |
| Hypertension — no. (%) | 469 (56) | 478 (56) | 453 (55) |
| Atrial fibrillation or flutter — no. (%) | 132 (16) | 117 (14) | 141 (17) |
| Nonsustained ventricular tachycardia — no. (%)† | 193 (23) | 180 (21) | 210 (25) |
| Syncope — no. (%) | 54 (6) | 56 (7) | 52 (6) |
| Electrophysiological study — no. (%) | 148 (18) | 130 (15) | 129 (16) |

Bardy, NEJM 2005

# Comparison: amiodarone and ICD

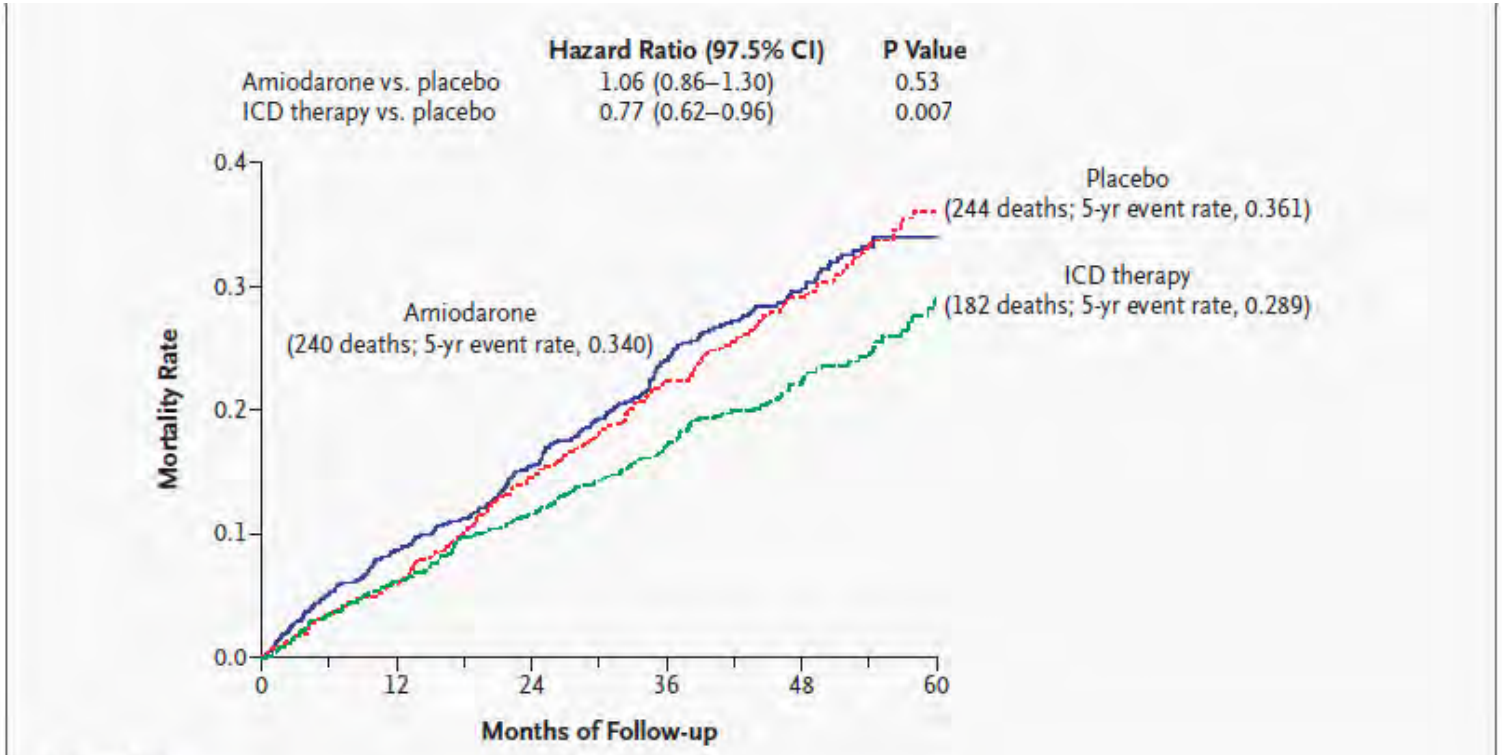



**Figure 1. Kaplan–Meier Estimates of Death from Any Cause.**
CI denotes confidence interval.

Bardy, NEJM 2005

# Ventricular arrhythmia – ICD – therapy

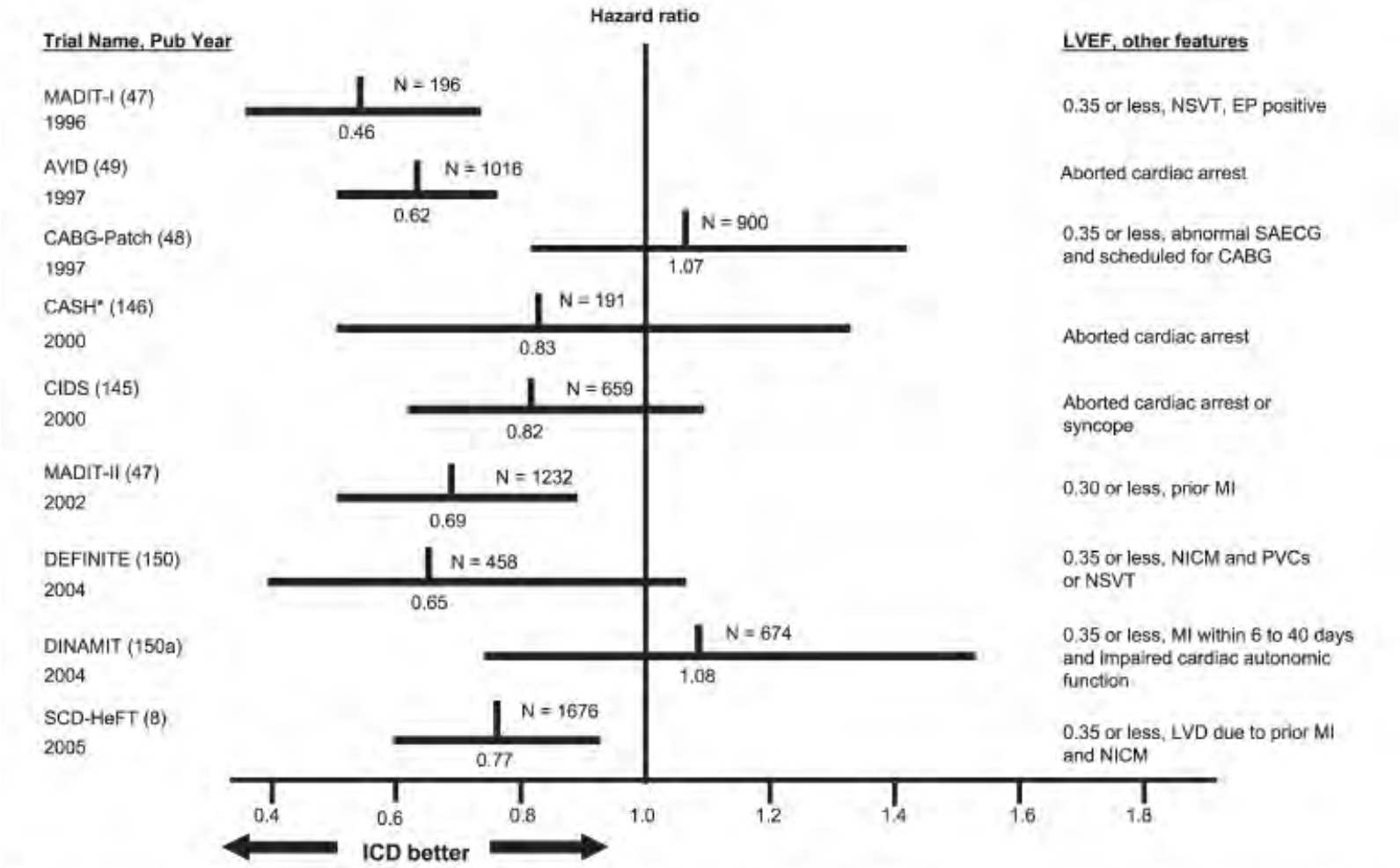



**Figure 2** Major implantable cardioverter-defibrillator (ICD) trials. Hazard ratios (vertical line) and 95% confidence intervals (horizontal lines) for death from any cause in the ICD group compared with the non-ICD group. *Includes only ICD and amiodarone patients from CASH. For expansion of trial names, see Appendix 3. CABG = coronary artery bypass graft surgery; EP = electrophysiological study; LVD = left ventricular dysfunction; LVEF = left ventricular ejection fraction; MI = myocardial infarction; N = number of patients; NICM = nonischemic cardiomyopathy; NSVT = nonsustained ventricular tachycardia; PVCs = premature ventricular complexes; SAECG = signal-averaged electrocardiogram.

# Summary

- Guidelines for diagnosis and therapy
- Novel drugs
- Use of CRT
- Use of conventional HF surgery, assist devices and Heart transplantation
- Antiarrhythmic treatment: ICD

# Thanks to the working group and to the sponsors

DFG Graduate training

EUGeneHeart

DFG Research Group 1054

EUGIM - EU