

Heart Failure 2005

The octogenarian failing heart

Lisbon, 14 June 2005

**Pharmacological Treatment: is There
Any Evidence-based Medicine for
the Very Old?**

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**No, not even for the
slightly old !**

Mean Age of the Patients with Heart Failure in Epidemiological Studies

| Author (year) | No. of patients | Age (years), M \pm SD |
|-----------------------------|-----------------|-------------------------|
| Chae (1999) | 221 | 77.9 \pm 5 |
| EPICA, Portugal (2000) | 551 | 70 \pm 11 |
| Ghali (1997) | 1133 | 77.6 \pm 7.9 |
| Lowe (1998) | 579 | 77 |
| MacIntyre (2000) | 66 547 | ♀: 78; ♂: 72 |
| McCulloch (2002) | 29 686 | ♀: 73.7; ♂: 69.2 |
| Mosterd, Netherlands (2000) | 24 868 | ♀: 77.7; ♂: 72.9 |
| Senni, Minnesota (1998) | 216 | 77.3 \pm 12.1 |
| SEOSI (1997) | 3 921 | 67 \pm 12 |
| EuroHeart Failure (2003) | 46 788 | 71 |

Mean Age and Proportions of Elderly Patients in Multicenter Trials

| Trial | No. of patients | Mean Age | % > 70 years |
|-----------------|------------------------|-----------------|------------------------|
| CONSENSUS I | 253 | 71 | 50% |
| SOLVD-T | 6 797 | 61 | 15% |
| DIG | 7 788 | 63 | 27% |
| MERIT-HF | 3 991 | 64 | 32% |
| CIBIS-II | 2 647 | 61 | ... |
| COPERNICUS | 2 289 | 63 | ... |
| RALES | 1 633 | 61 | ... |
| EPHESUS | 6 642 | 64 | |
| ELITE-II | 3 152 | 71 | 58% |
| Val-HeFT | 5 010 | 62 | ... |
| CHARM | 7 601 | 66 | 23% (>75) |

Factors Distinguishing HF in the Elderly from HF at Middle Age

| | Middle age | Elderly |
|-------------------|-------------------|----------------|
| Prevalence | <1% | ~ 10% |
| Sex | Men > women | Women > men |
| Etiology | CAD | Hypertension |
| Clinical features | Typical | Atypical |
| LVEF | Reduced | Normal |
| Comorbidities | Few | Multiple |
| Physician | Cardiologist | Primary care |
| RCTs | Many | Few |
| Therapy | Evidence-based | Empiric |

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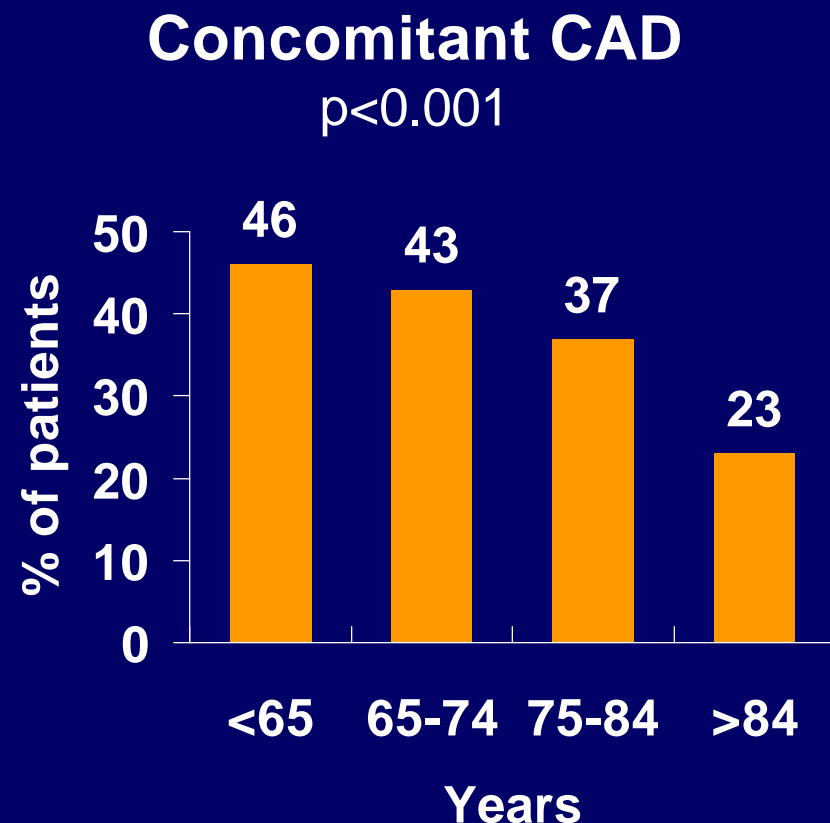
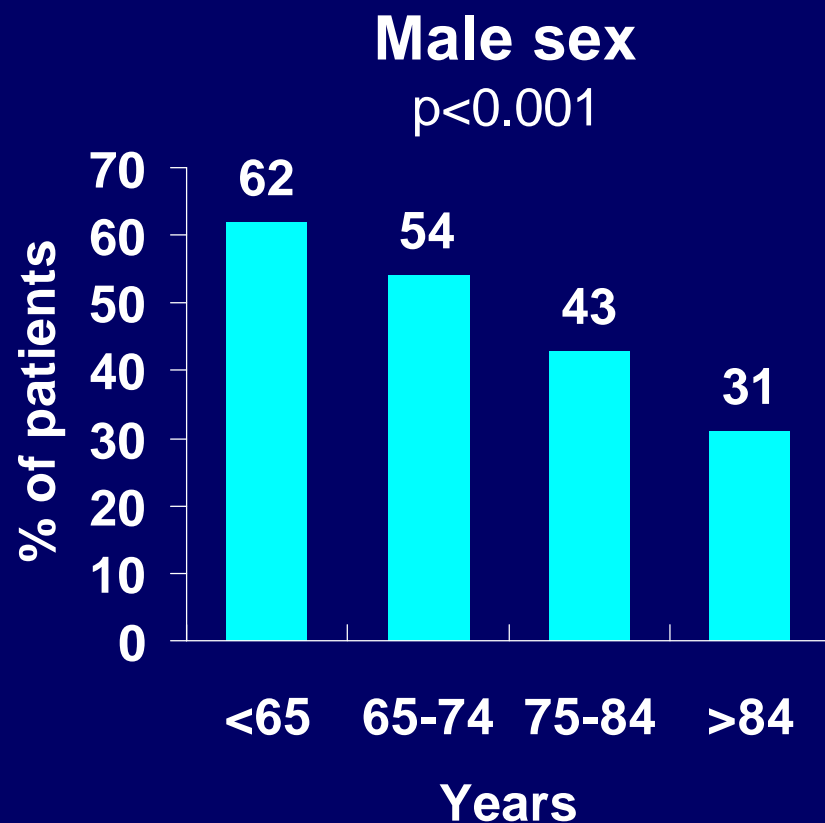
Baseline Characteristics of Patients Recruited in COMET Subdivided According to Age (mean, 62 ys.; range, 18-90)

| | < 60 years (n = 1171) | 60-70 years (n = 1119) | > 70 years (n = 739) |
|----------------------------|-------------------------------------|-----------------------------------|------------------------------------|
| Female, % | 17% | 19% | 26% |
| BMI, m \pm sd | 28 \pm 5 | 27 \pm 4 | 25 \pm 4 |
| Dyspnoea score \geq 4, % | 13% | 18% | 27% |
| Fatigue score \geq 4, % | 13% | 16% | 26% |
| NT-ProBNP, median | 804 | 1314 | 1826 |
| Creatinine, median | 92 | 102 | 114 |
| Diabetes, % | 20% | 29% | 25% |
| Atrial fibrillation, % | 15% | 20% | 27% |
| Paced rhythm, % | 2% | 7% | 12% |

All these variables were significantly different between the different age subgroups

Clinical Characteristics of the Patients with HF According to Age: IMPROVEMENT Study

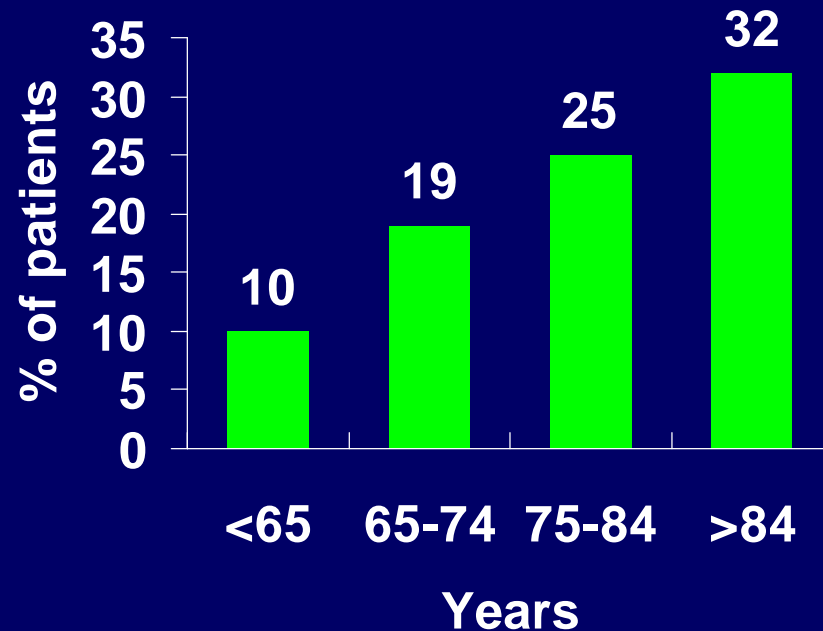
8256 patients in 15 countries, 1999-2000



Concomitant Diseases of the Patients with HF According to Age: IMPROVEMENT Study 8256 patients in 15 countries, 1999-2000

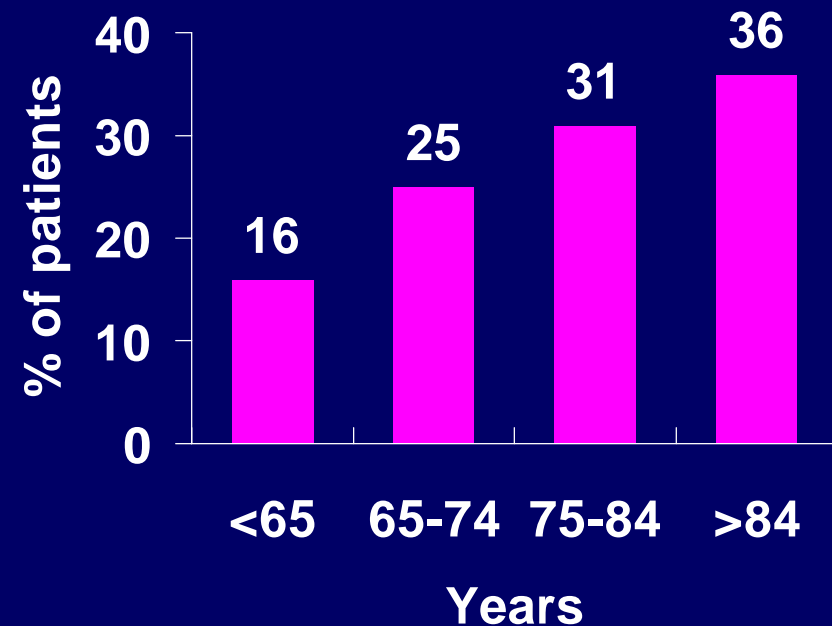
Renal dysfunction

$p < 0.001$



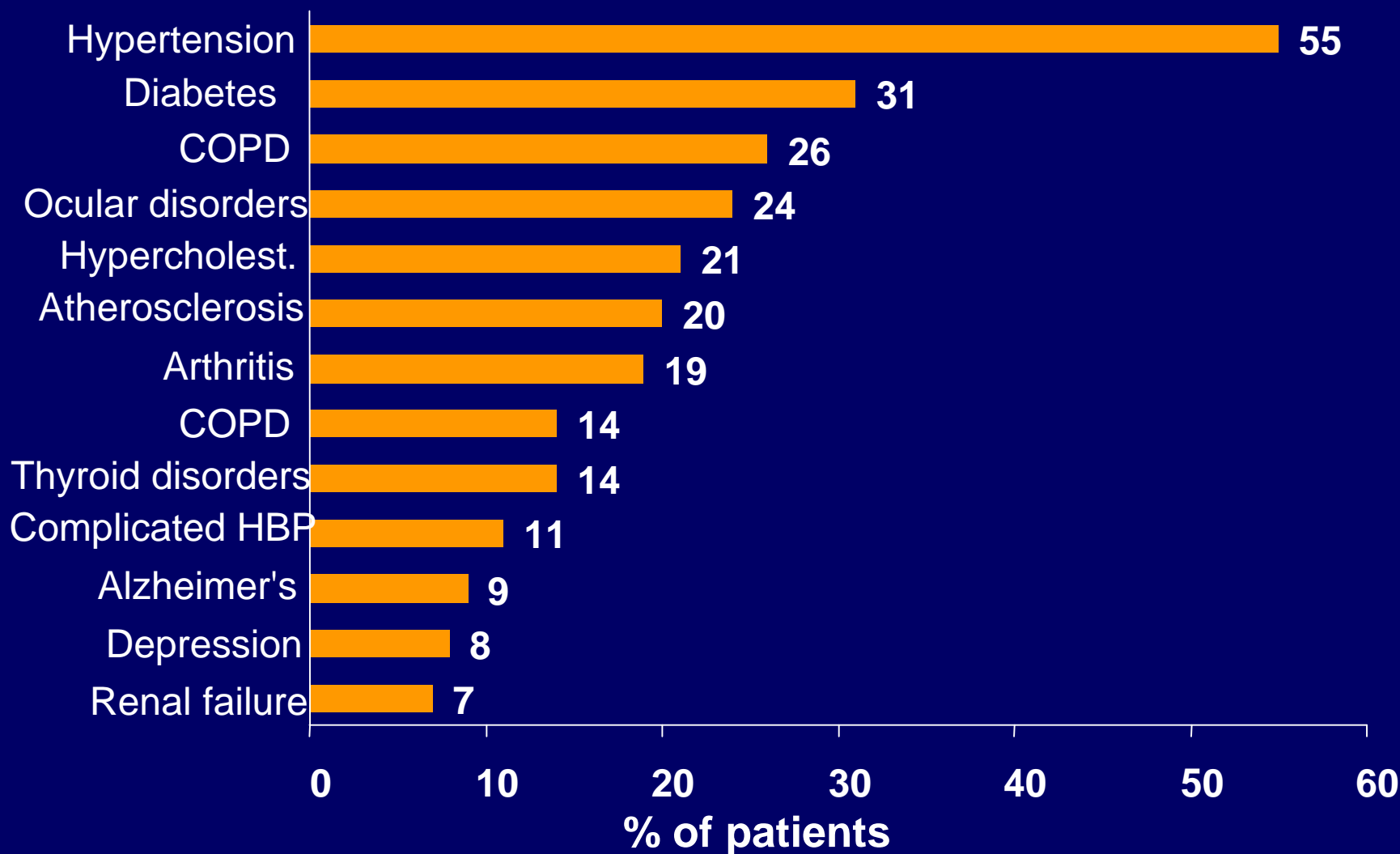
Atrial Fibrillation

$p < 0.001$



~ prevalence of hypertension and pulmonary disease
↓ prevalence of diabetes and ↑ prevalence of stroke with ↑ age

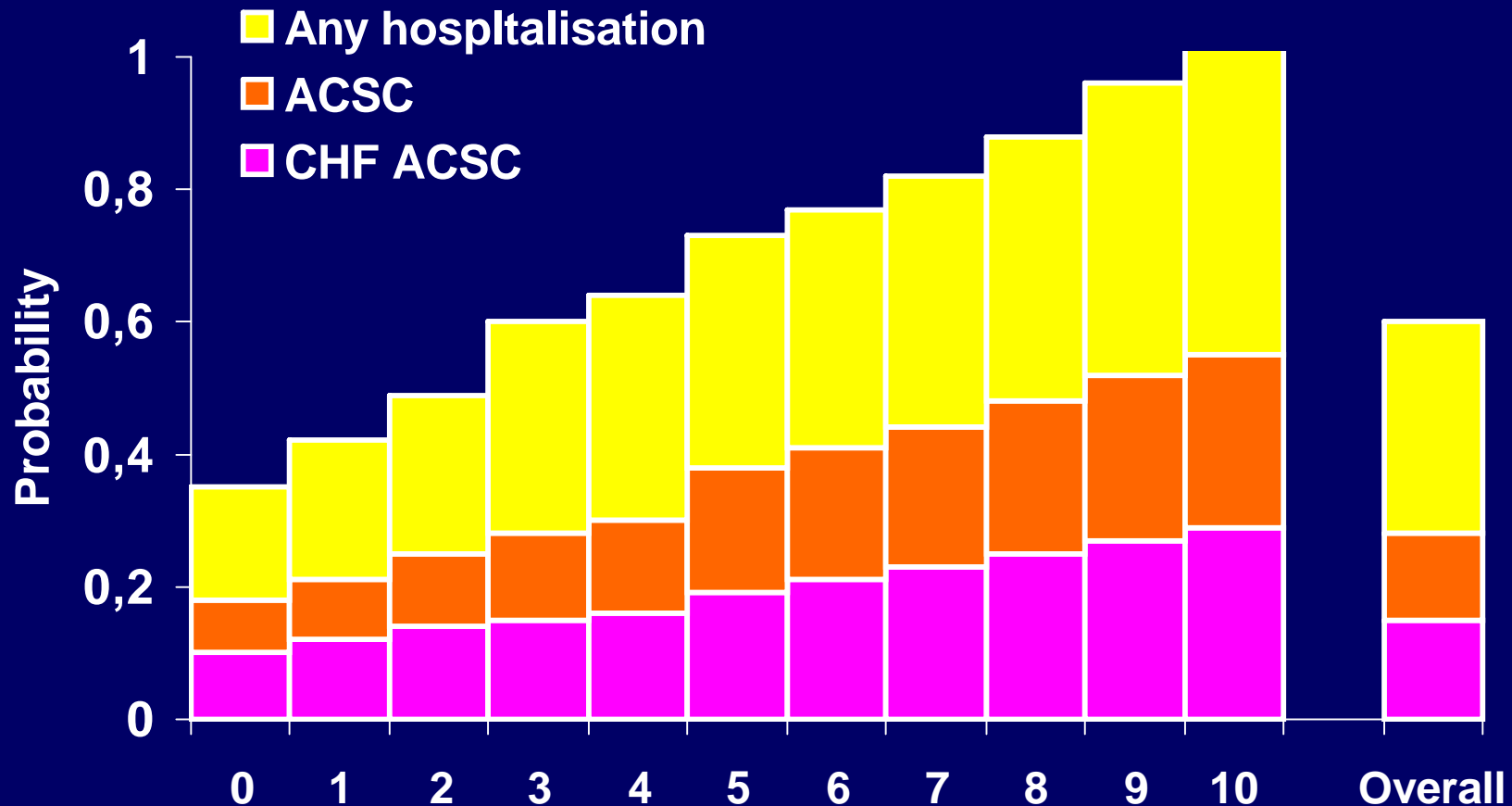
Most Common Non-cardiac Diseases for Patients \geq 65 years with CHF: An analysis of 122 630 subjects



Braunstein et al., J Am Coll Cardiol 2003;42:1226

Non-cardiac Comorbidity Increases Preventable Hospitalizations among Medicare Beneficiaries with CHF

A survey of 122 630 Subjects Aged ≥ 65 years

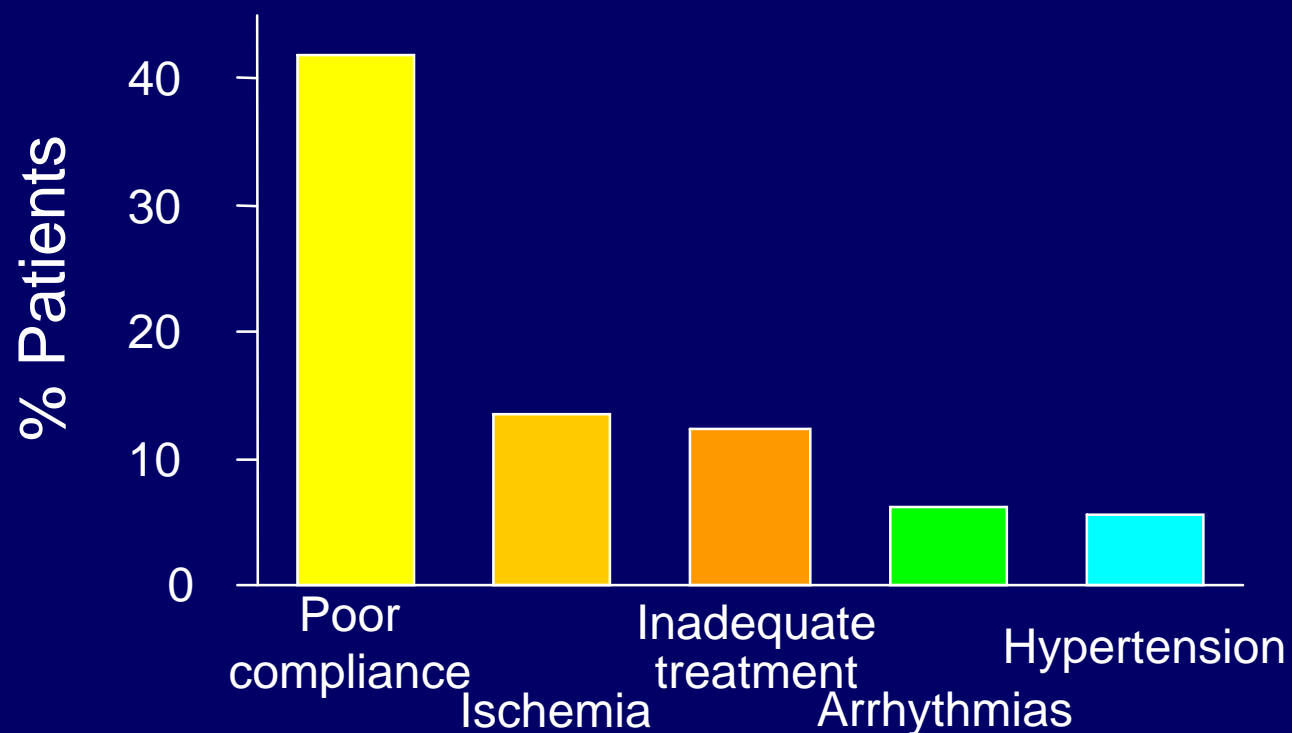


ACSC = Ambulatory Care Sensitive
(e.g. preventable) Condition

Braunstein et al., JACC 2003;42:1226

Incidence of Precipitating Factors as Causes of Hospital Admissions in Patients with Heart Failure

Causes of hospitalizations
(179 pts.; age, 75±10 years)



Michaelsen et al., Heart 1998;80:437

Management of HF in the Elderly: General Measures

- Educate the patients and their family → ↑ compliance!
- Limit sodium intake (< 1.5 Gm/day)
- Monitor body weight daily
- Avoid smoking
- Only moderate alcohol consumption (e.g. < 1-2 drinks/day)
- Low-intensity aerobic exercise (3-5 times/week)
- Treat concomitant diseases
 - Hypertension, and/or diabetes, CAD...
 - anemia, thyroid disease, sleep disorders, depression...
- Minimize use of NSAIDs

Effect of Antihypertensive Therapy in the Primary Prevention of HF in Older Adults

| Trial (year) | No. | Age, ys | Risk reduction for HF |
|-------------------|------|---------|-----------------------|
| EWPHE (1985) | 840 | >60 | ↓22% |
| Coope (1986) | 884 | 60-79 | ↓ 32% |
| STOP-HTN (1991) | 1627 | 70-84 | ↓ 51% |
| SHEP (1991) | 4736 | ≥60 | ↓ 55% |
| STONE (1996) | 1632 | 60-79 | ↓ 68% |
| Syst-Eur (1997) | 4695 | ≥60 | ↓ 36% |
| Syst-China (1998) | 2934 | ≥60 | ↓ 38% |

Pharmacological therapy of heart failure due to Left Ventricular Systolic Dysfunction

For Survival/Morbidity
mandatory therapy

For Symptoms

NYHA I

Cont. ACE inhibitor/ARB if ACE inhibitor intolerant, continue aldosterone antagonist if post-MI
add beta-blocker if post-MI

reduce / stop diuretic

NYHA II

ACE inhibitor as first-line treatment/ARB if ACE inhibitor intolerant
add beta-blocker
and aldosterone antagonist if post MI

+/- diuretic
depending on fluid retention

NYHA III

ACE inhibitor plus ARB or ARB alone if ACE intolerant
beta-blocker
add aldosterone antagonist

+ diuretics + digitalis
If still symptomatic

NYHA IV

Continue ACE inhibitor/ARB
beta-blocker
Aldosterone antagonist

+diuretics + digitalis
+ consider temporary inotropic support

Treatment of HF in the Elderly: What Do the Guidelines Say

| Drug | | Efficacy | Side effects | Tolerance |
|-------------------------|-----|----------|--------------|-----------|
| ACEi | (+) | + | ↑ | ↓ |
| Loop diuretics | | + | ↑ | ↓ |
| Beta-blockers | + | + | ↑ | ↓ |
| Aldosterone antagonists | | + | ↑↑ | ↓ |
| ARBs | + | + | ↑ | ↓ |
| Digoxin | | + | ↑ | ↓ |

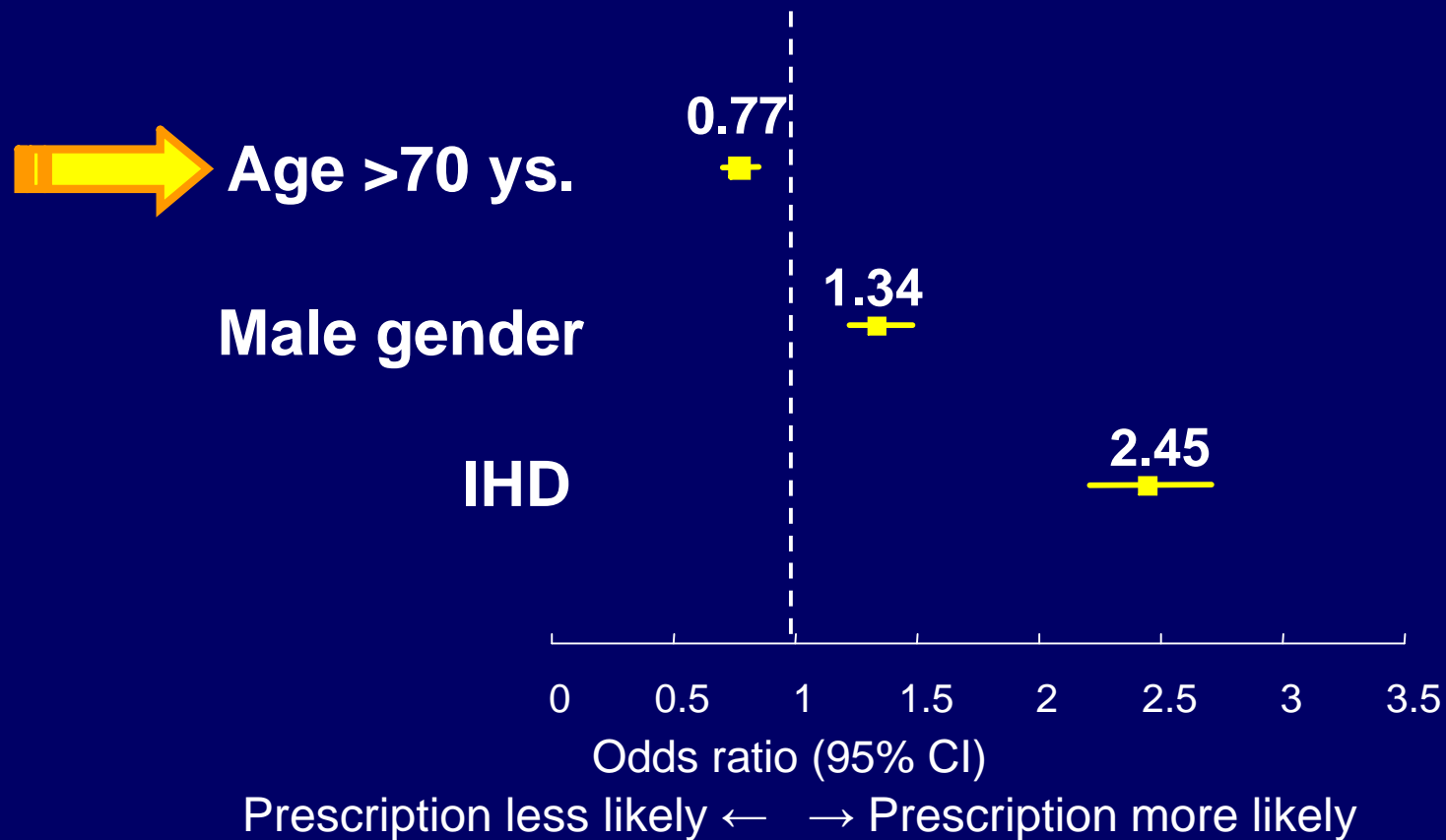
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| Aldosterone antagonists | (+) | + | ↑↑ | ↓ |
| ARBs | + | + | ↑ | ↓ |
| Digoxin | (+) | + | ↑ | ↓ |

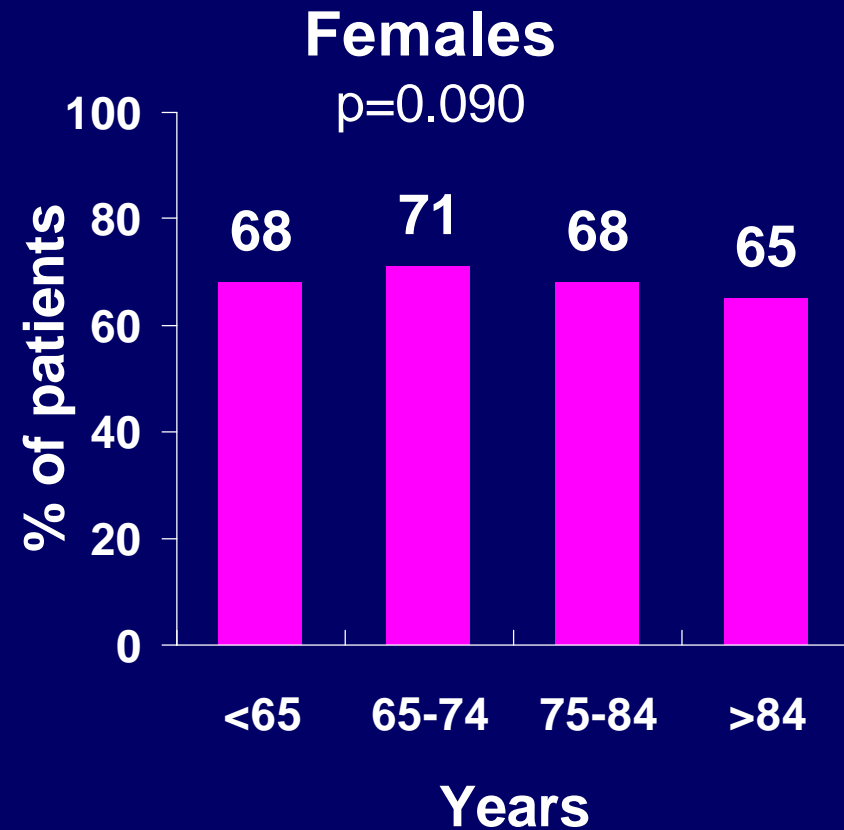
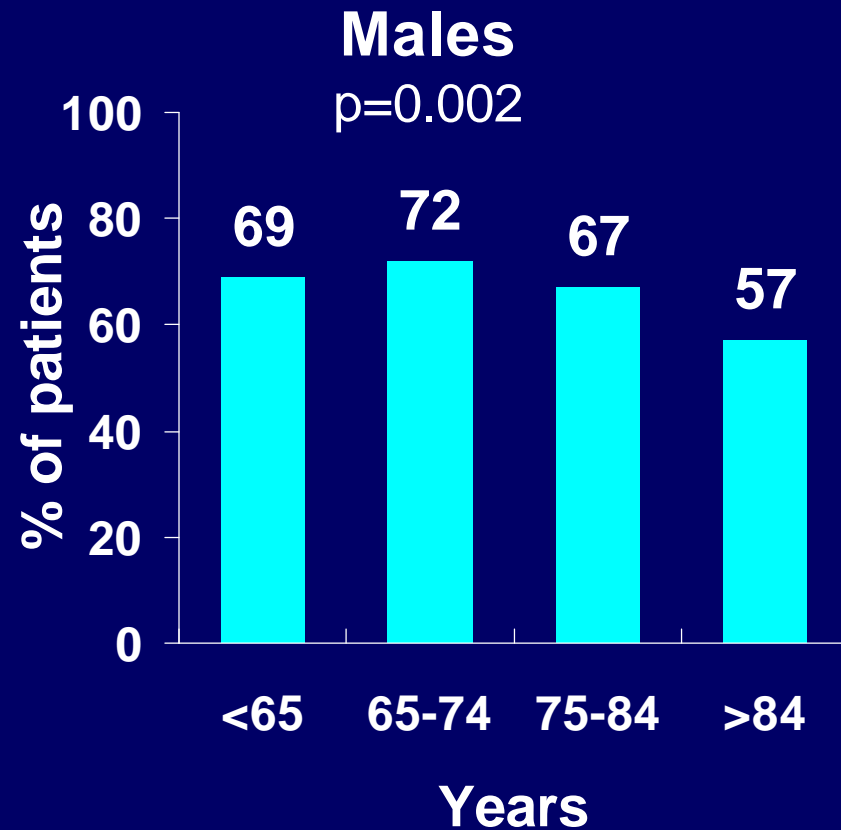
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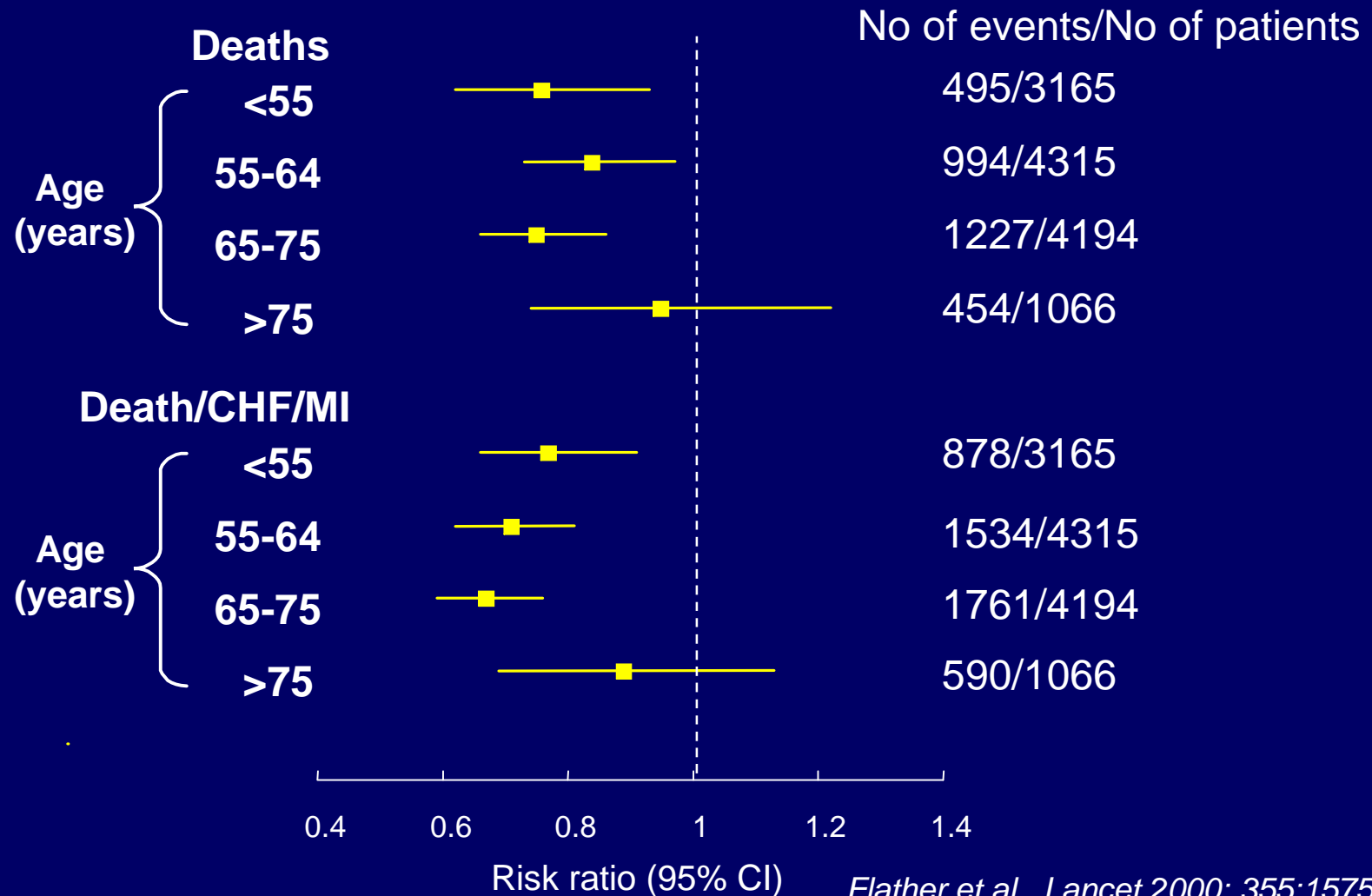
Elderly Age is an Independent Predictor of Lack of Prescription of ACE Inhibitors: Results from the EuroHeart Failure Survey



ACEi/ARBs Prescriptions in the Patients with HF According to Age: IMPROVEMENT Study 8256 patients in 15 countries, 1999-2000



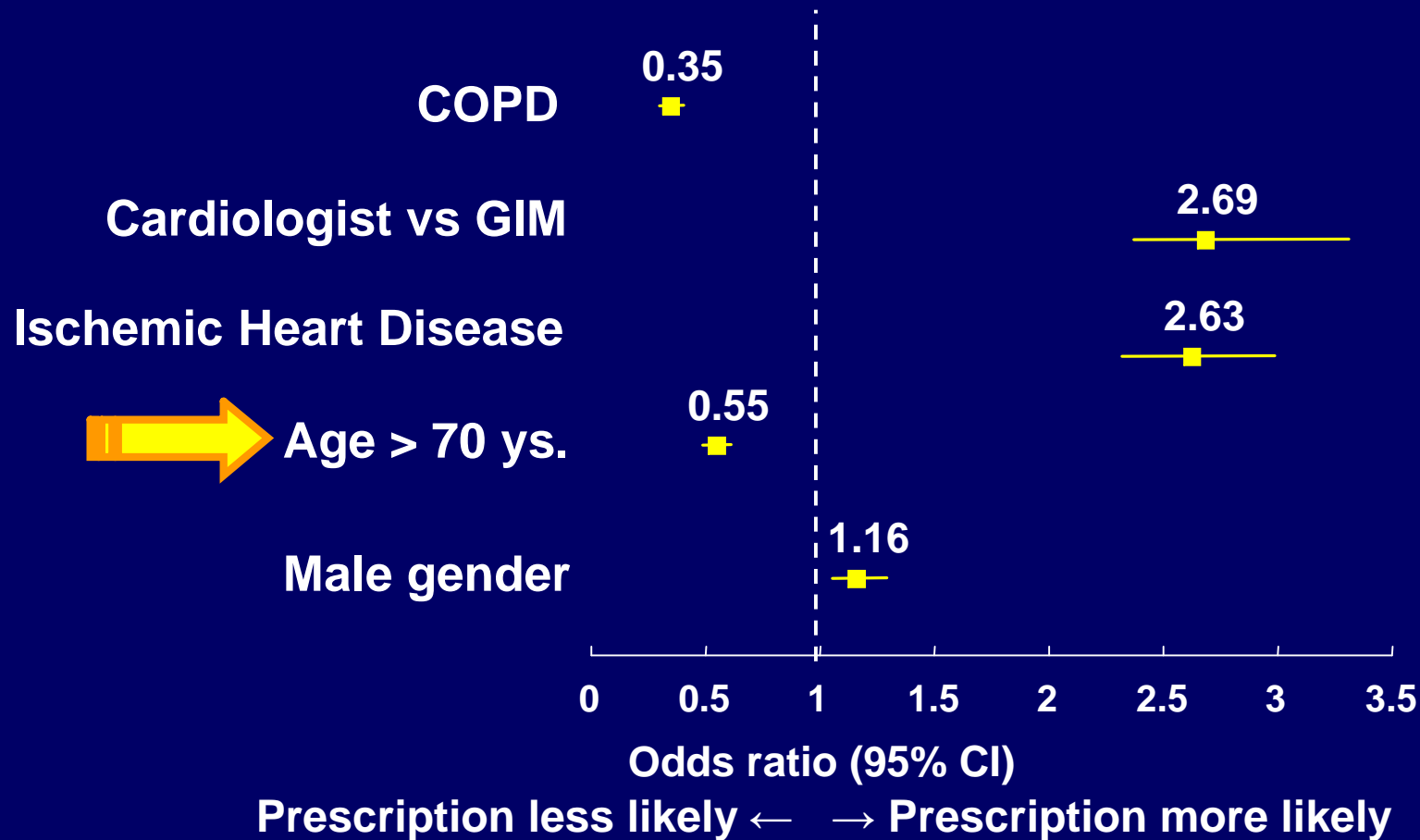
Effects of ACE inhibitors on outcome in patients subdivided on the basis of their age: Meta-analysis of the SOLVD, SAVE, AIRE and TRACE trials



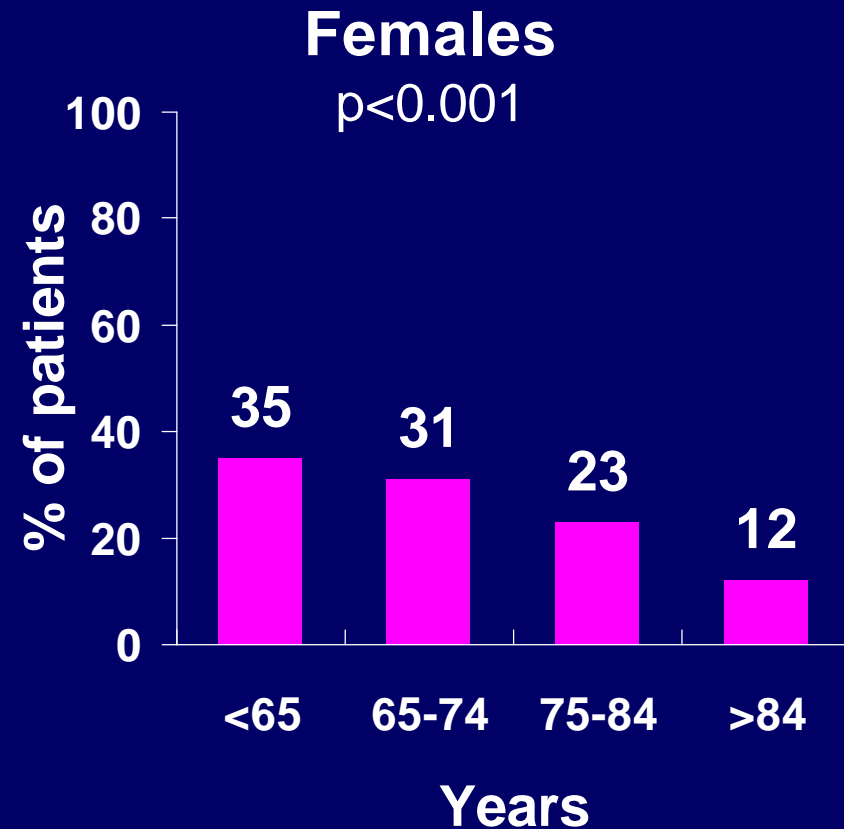
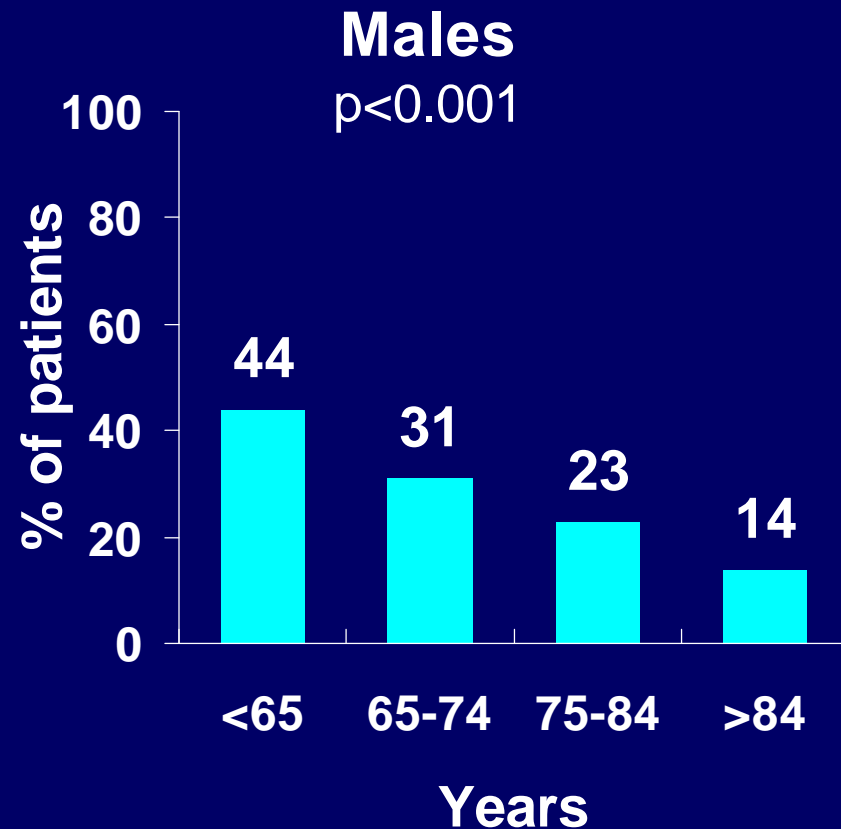
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| Beta-blockers | + | + | ↑ | ↓ |
| | | | | |
| | | | | |
| | | | | |
| | | | | |

Elderly Age is an Independent Predictor of Lack of Prescription of Beta-blockers: Results from the EuroHeart Failure Survey



Beta-blockers Prescriptions in the Patients with HF According to Age: IMPROVEMENT Study 8256 patients in 15 countries, 1999-2000



BRING UP

Reasons for Not Commencing β -Blockade

| | On β blockers (n = 771) | β blockers started (n = 865) | No β blockers (n = 1455) | P value |
|---------------------|-------------------------------------|------------------------------------------|--------------------------------------|---------|
| Age \geq 70 years | 24% | 25% | 43% | 0.001 |
| NYHA III-IV | 26% | 29% | 42% | 0.001 |
| Pulmonary rales | 10% | 20% | 26% | 0.001 |
| Periph. oedema | 12% | 13% | 21% | 0.001 |
| Atrial fibrillation | 14% | 17% | 21% | 0.001 |
| EF not available | 5% | 3% | 6% | 0.008 |
| EF $<$ 30% | 30% | 30% | 35% | 0.017 |

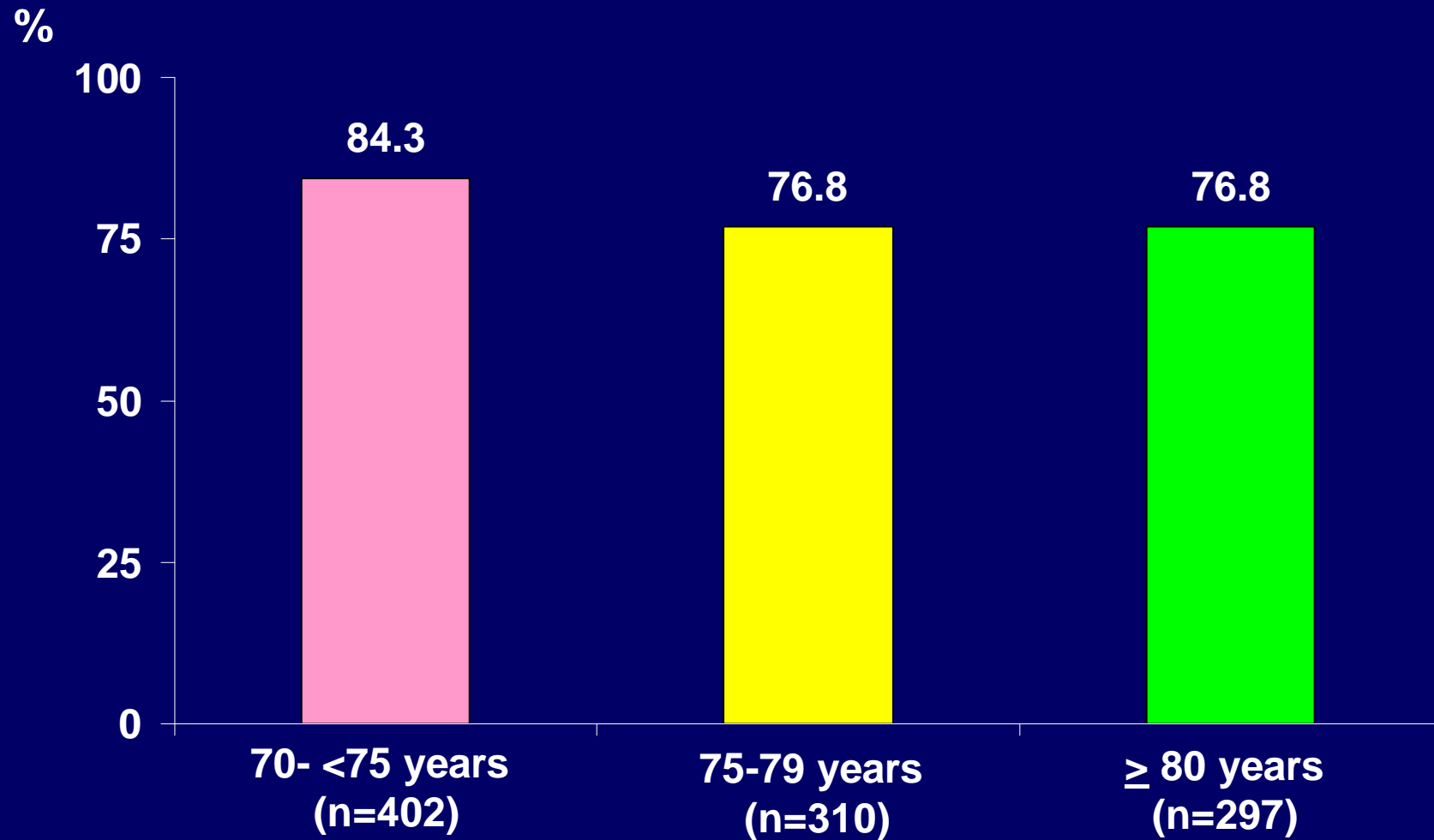
BRING UP

Independent Predictors of β Blocker Tolerability

| | OR | 95% CI | P value |
|-------------------------------------------------------|------|-------------|---------|
| Age (as a continuous variable) | 0.97 | 0.96 - 0.97 | 0.0001 |
| NYHA class (III-IV v I-II) | 0.62 | 0.51 - 0.75 | 0.0001 |
| Systolic blood pressure (as a continuous variable) | 1.02 | 1.01 - 1.02 | 0.0001 |
| Heart rate (as a continuous variable) | 1.01 | 1.01 - 1.02 | 0.0001 |
| Ejection fraction (not available v available) | 0.46 | 0.28 - 0.76 | 0.0022 |

COLA II

Tolerability according to Age

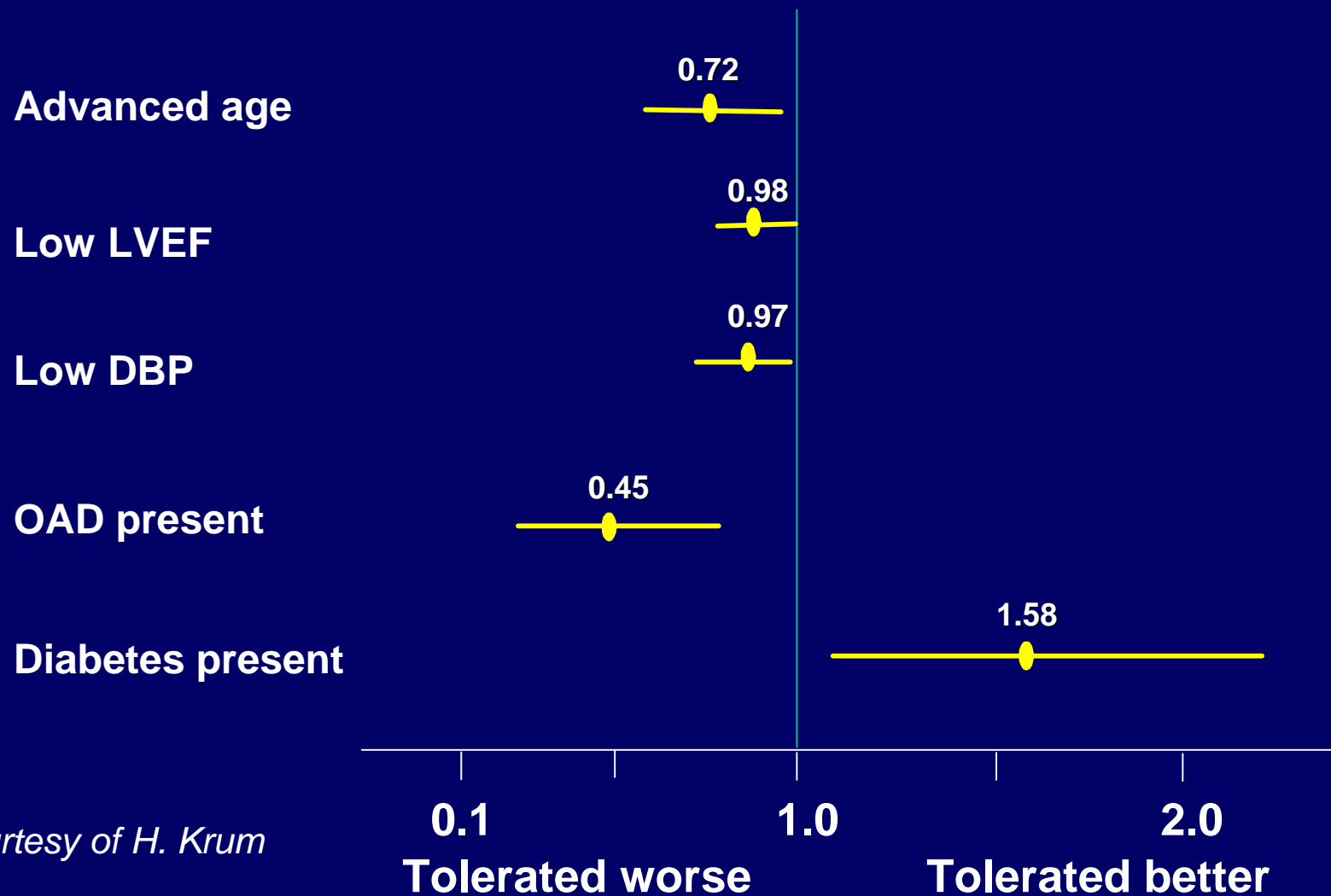


Courtesy of Henry Krum

P<0.05 by ANOVA

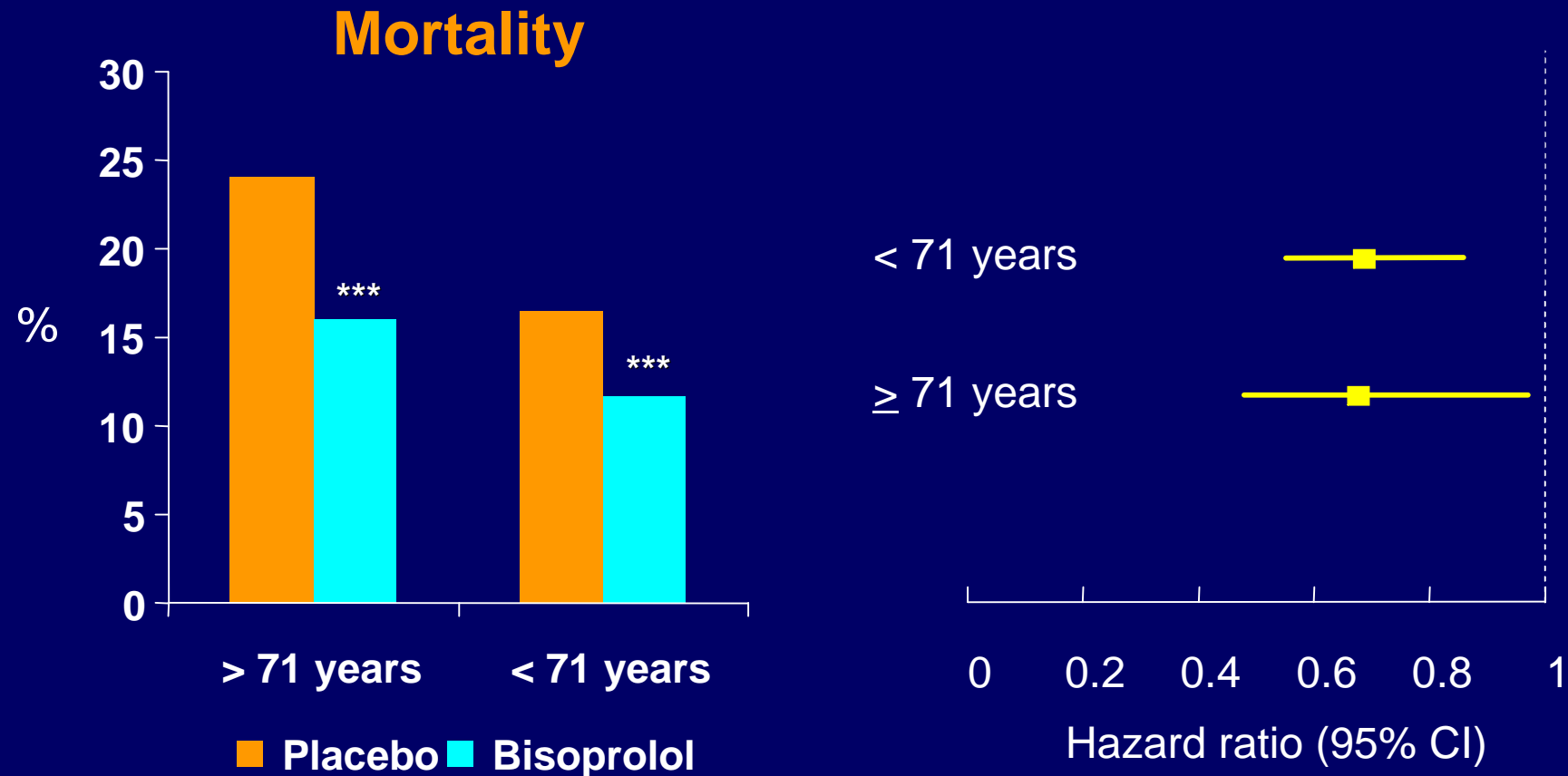
COLA II

Multivariate predictors of tolerability

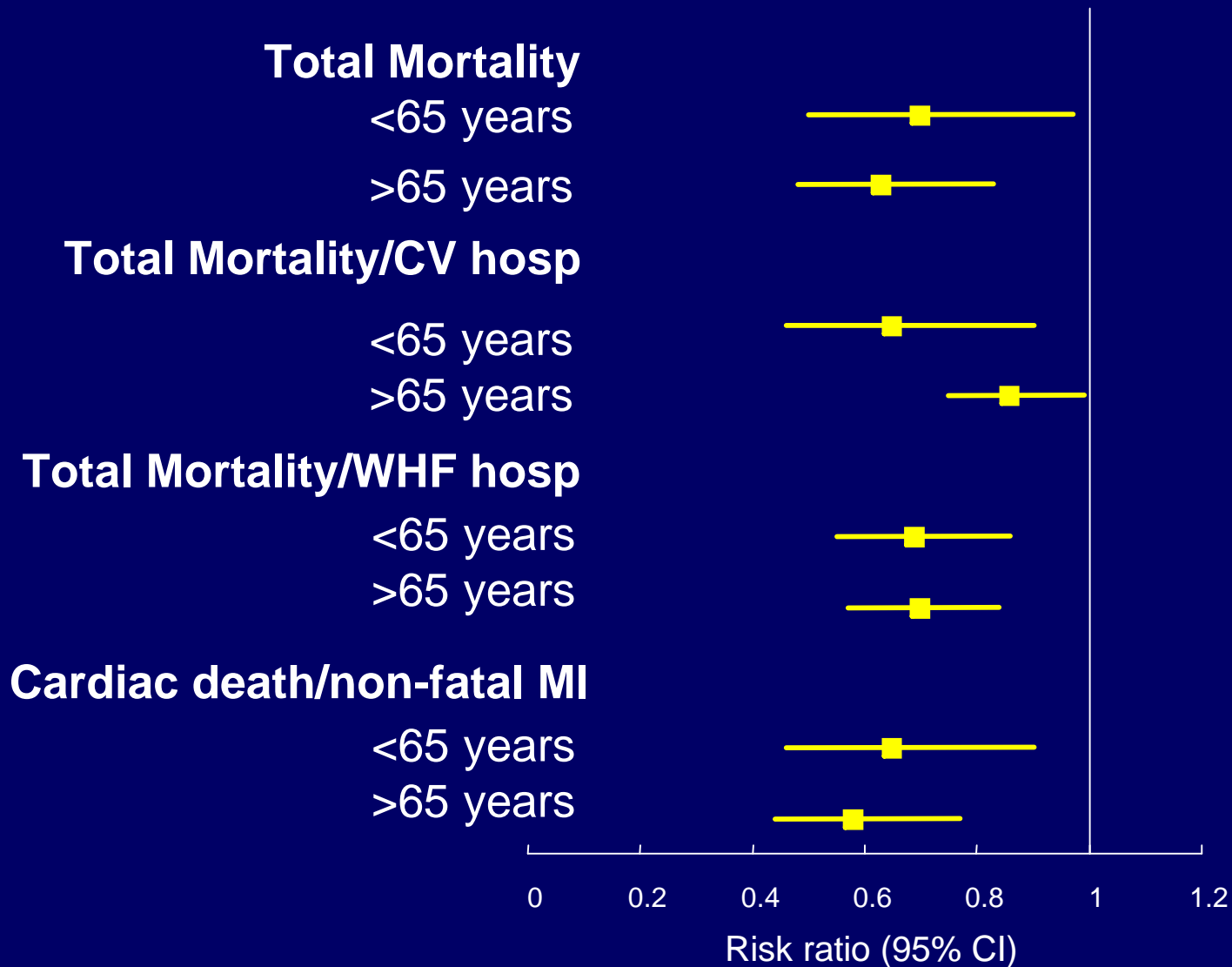


Courtesy of H. Krum

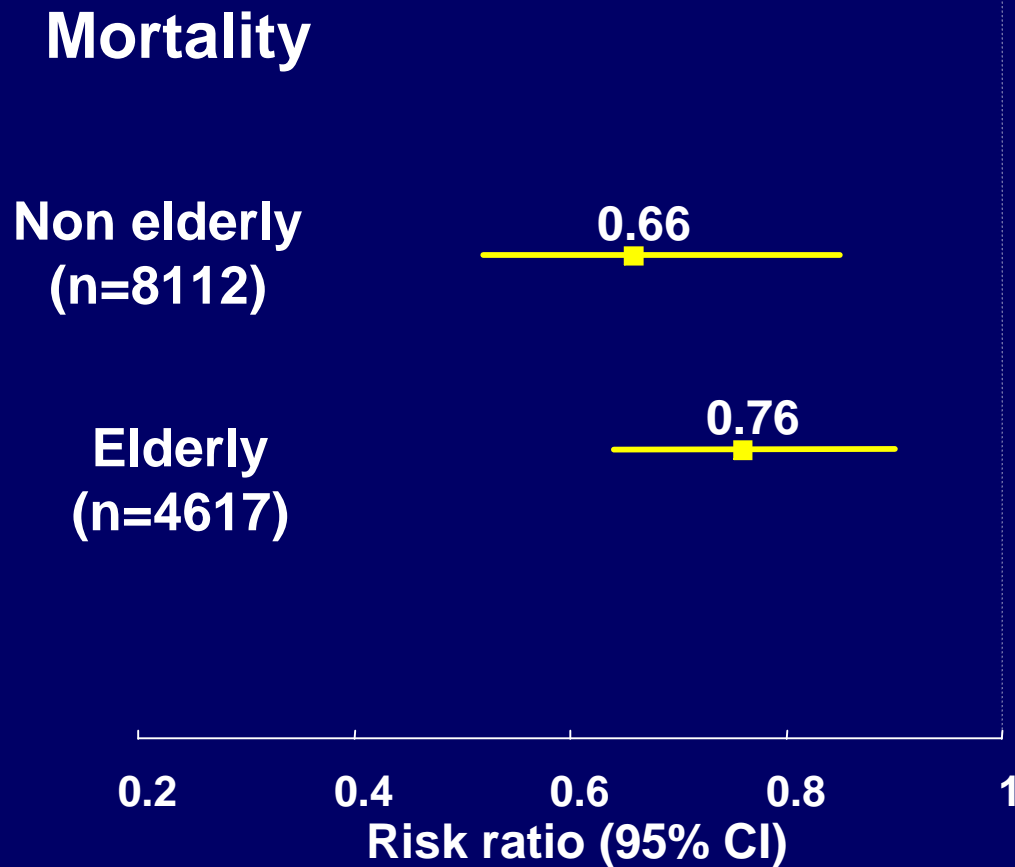
Effect of Bisoprolol on Mortality in Different Age Subgroups



Efficacy of Metoprolol CR/XL in Elderly Patients with Heart Failure: the MERIT-HF Study



Beta-blockers Reduce Mortality also in Elderly Patients: Meta-analysis of >12,000 Patients in Large-scale Trials (BEST, Carvedilol US, CIBIS-II, COPERNICUS, MERIT-HF)



SENIORS Trial: Inclusion Criteria

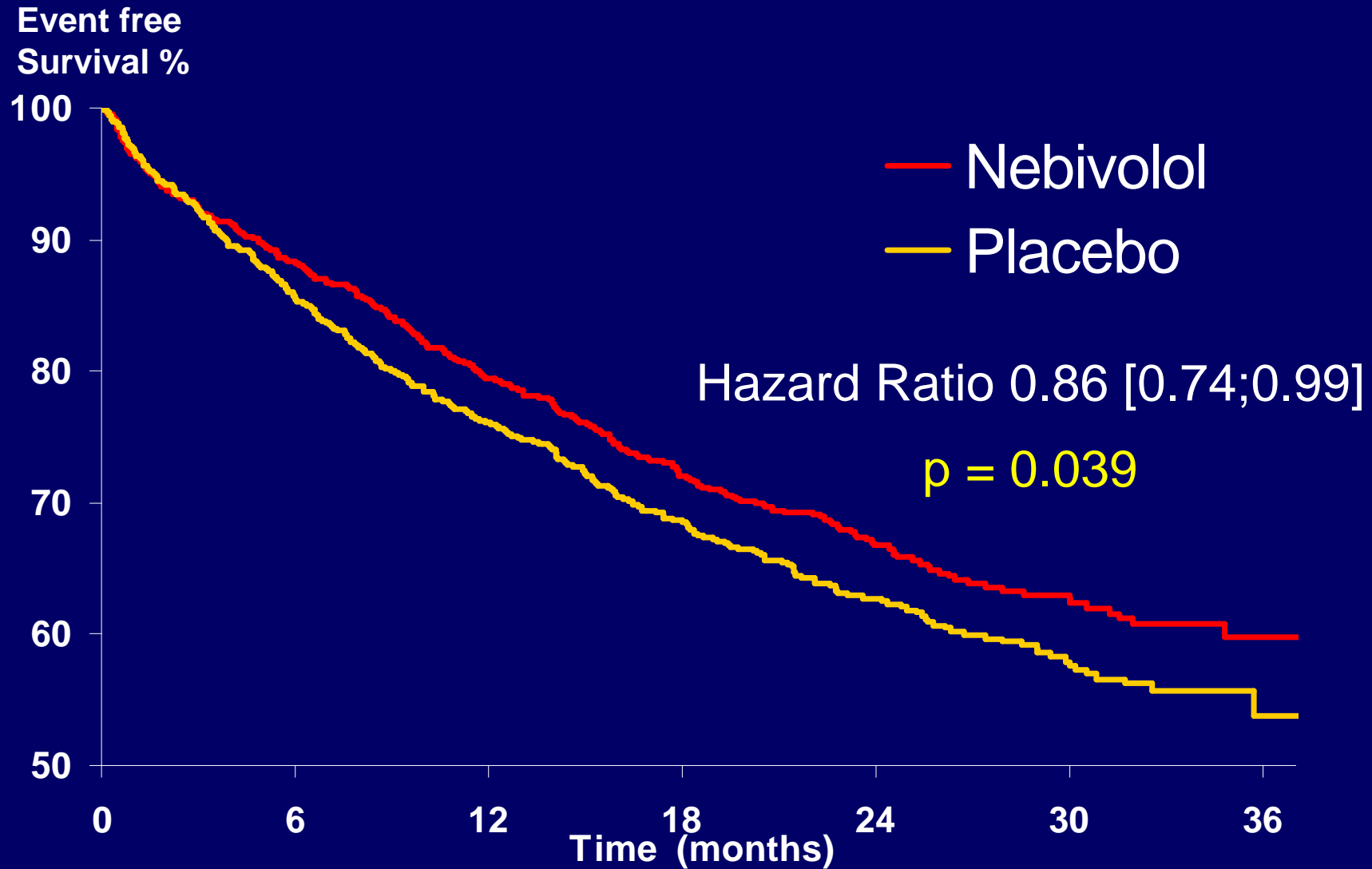
- **Age \geq 70 years**
- A clinical diagnosis of chronic heart failure (HF) and either of:
 - a) documented LVEF \leq 35% within previous 6 months
 - or
 - b) hospital admission within previous 1 year for congestive HF
- Written consent prior to enrolment into the study

SENIORS: Baseline Characteristics

| | Nebivolol | Placebo |
|---------------------------|------------|------------|
| Age (mean, yrs) | 76.1 | 76.1 |
| Male (n, %) | 657 (61.6) | 686 (64.7) |
| LVEF \leq 35 % (n, %) * | 683 (64.3) | 686 (64.8) |
| LVEF (mean, %) | 36.0 | 36.0 |
| NYHA Class (n, %) | | |
| I | 32 (3.0) | 29 (2.7) |
| II | 603 (56.5) | 597 (56.3) |
| III | 413 (38.7) | 411 (38.7) |
| IV | 19 (1.8) | 24 (2.3) |

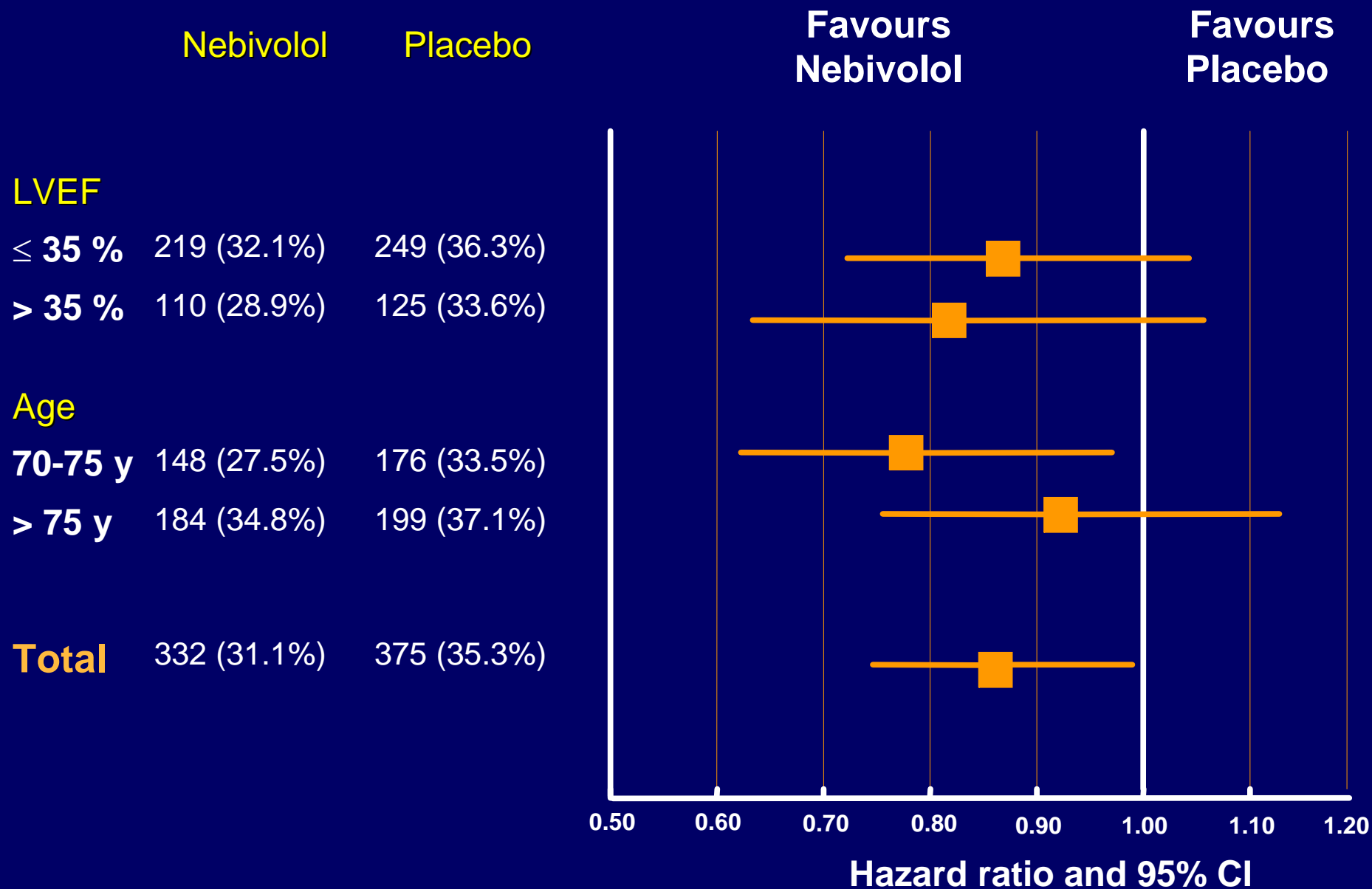
* 7 patients with missing LVEF at baseline

SENIORS Trial: All Cause Mortality or CV Hospital Admission (Primary Outcome)



No. of events: Nebivolol 332 (31.1%); Placebo 375 (35.3%)

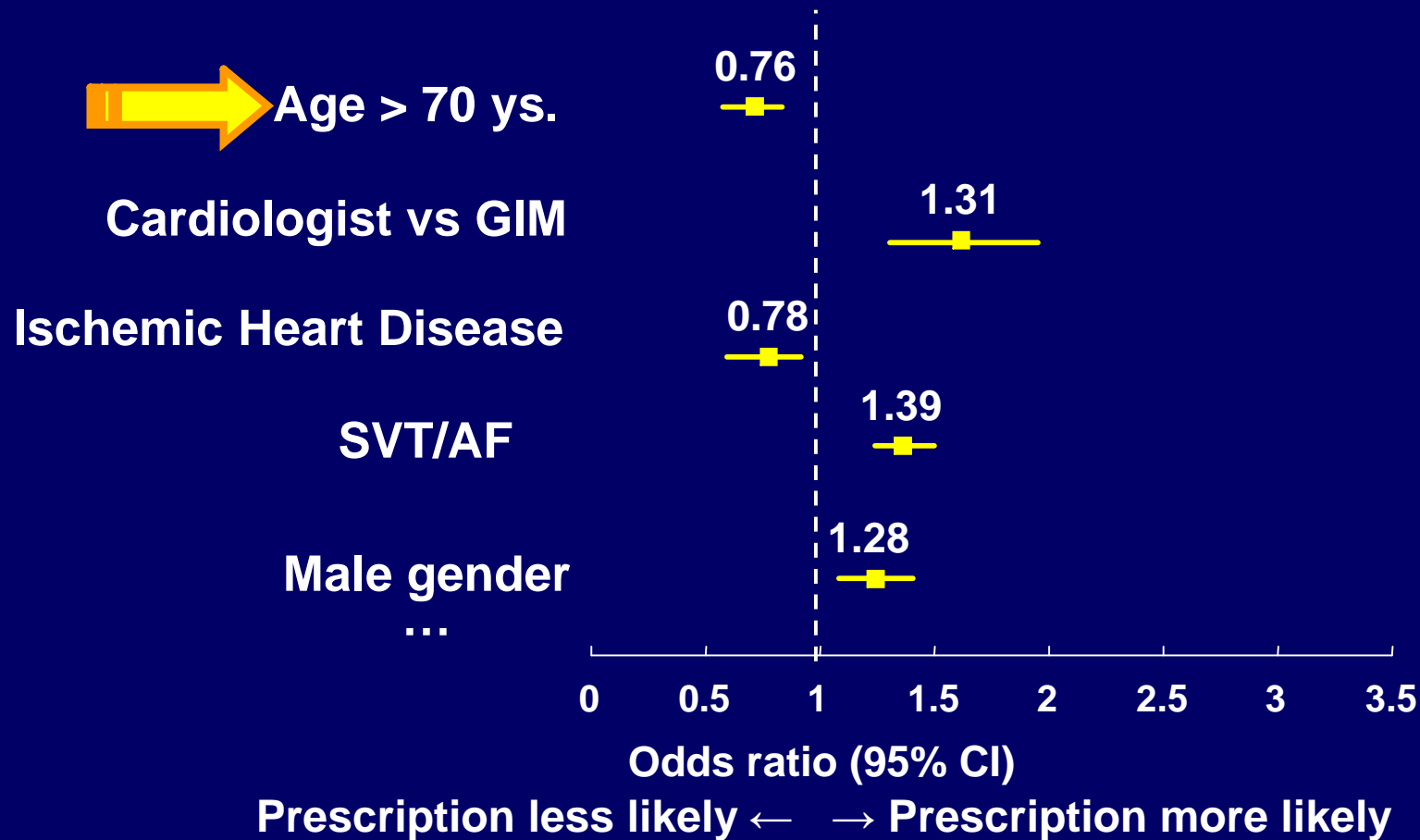
Death or CV Hospitalisation by Subgroup



Treatment of HF in the Elderly: What Do the Guidelines Say

| Drug | Evidence | Efficacy | Side effects | Tolerance |
|-------------------------|----------|----------|--------------|-----------|
| ACEi | (+) | + | ↑ | ↓ |
| Loop diuretics | 0 | + | ↑ | ↓ |
| Beta-blockers | + | + | ↑ | ↓ |
| Aldosterone antagonists | (+) | + | ↑↑ | ↓ |
| ARBs | + | + | ↑ | ↓ |
| Digoxin | (+) | + | ↑ | ↓ |

Elderly Age is an Independent Predictor of Lack of Prescription of Spironolactone: Results from the EuroHeart Failure Survey



Spironolactone-induced hyperkalemia and renal insufficiency in patients with heart failure

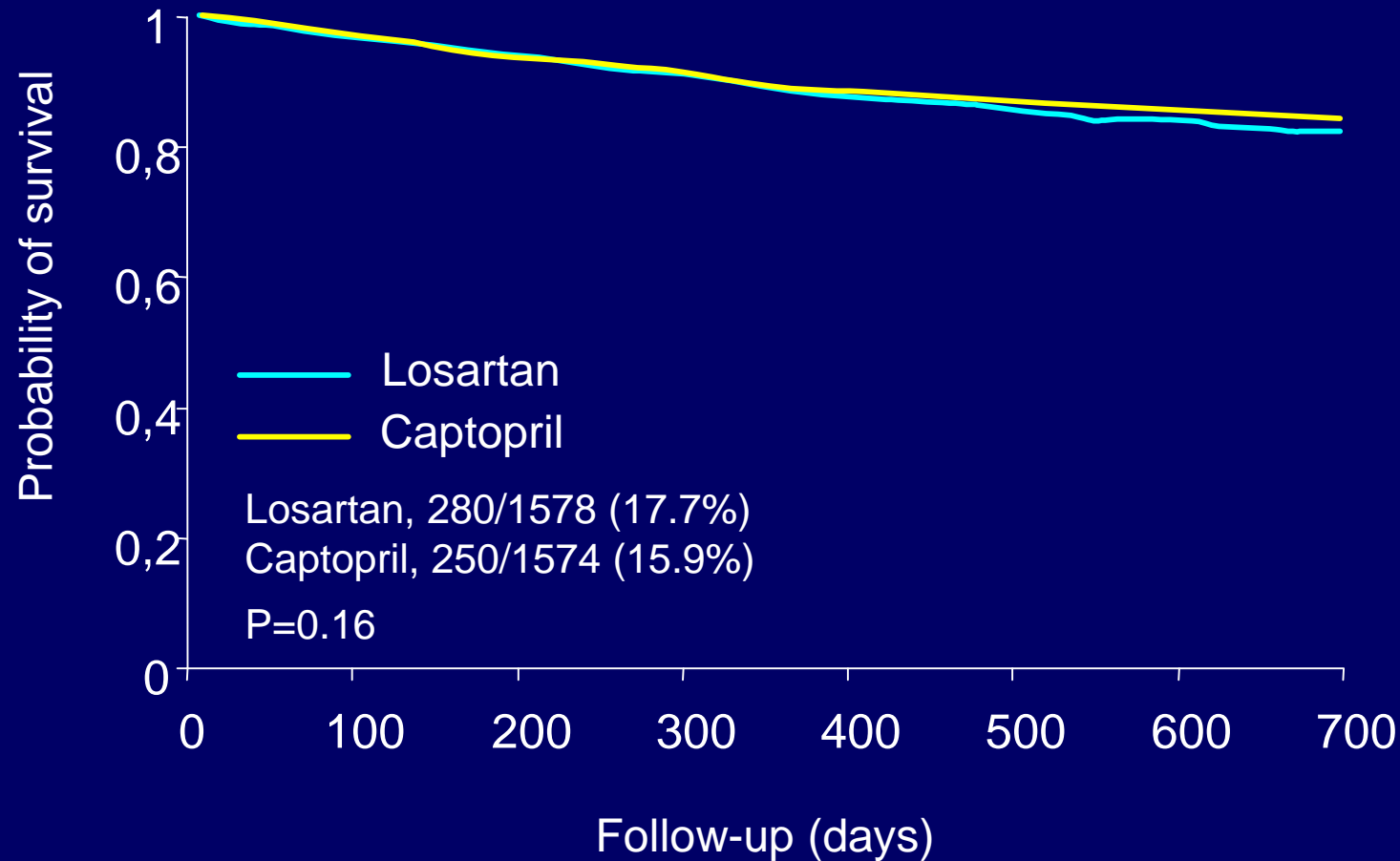
| Variable | <i>P</i> value |
|------------------------------------------|----------------|
| Predictors of changes in serum potassium | |
| Serum potassium (baseline) | <.001 |
| Age | .017 |
| Beta-blocker use | .019 |
| Predictors of change in serum creatinine | |
| Thiazide diuretic | .007 |

Treatment of HF in the Elderly: What Do the Guidelines Say

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| Beta-blockers | + | + | ↑ | ↓ |
| Aldosterone antagonists | (+) | + | ↑↑ | ↓ |
| ARBs | + | + | ↑ | ↓ |
| Digoxin | (+) | + | ↑ | ↓ |

Effects of Losartan Compared with Captopril on Mortality in Patients with Symptomatic Heart Failure: ELITE II Results

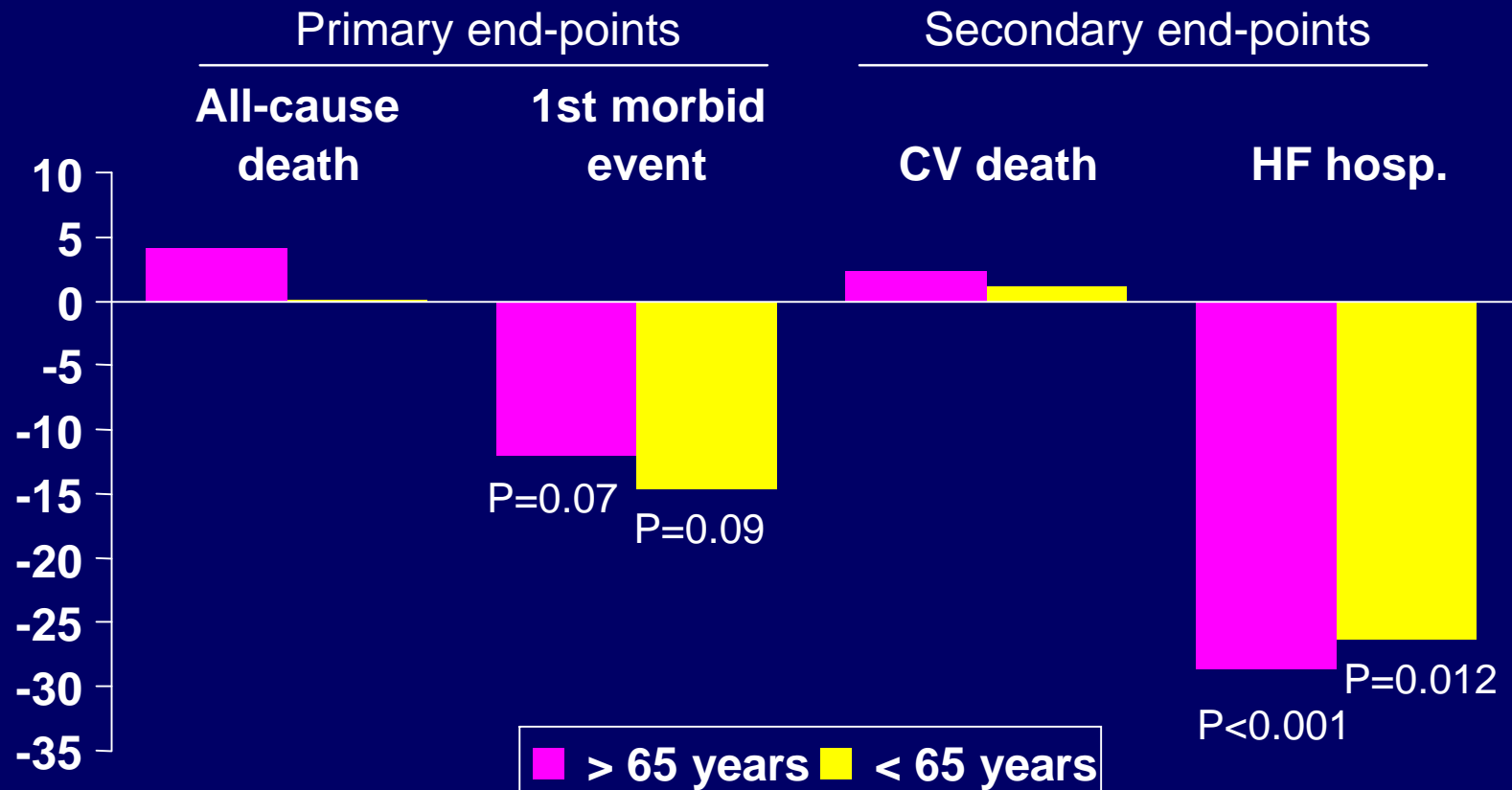
Total mortality



(Pitt et al., Lancet 2000; 355:1582)

Lack of Influence of Age on the Effects of Valsartan in Val-HeFT Trial

Risk Ratio Valsartan vs. Placebo



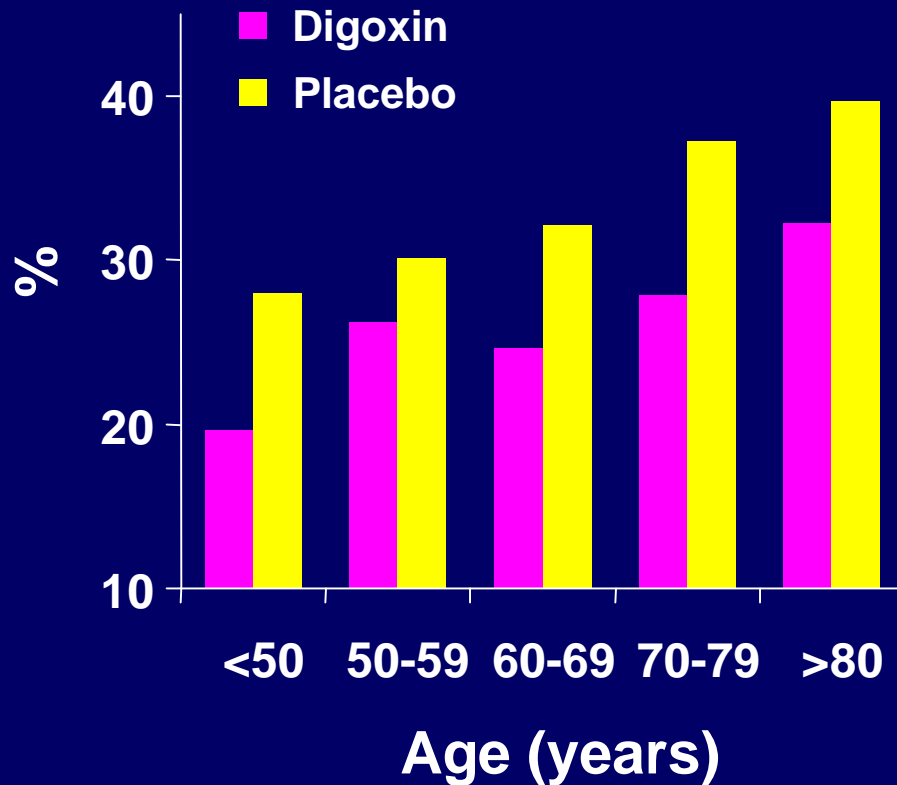
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| Beta-blockers | + | + | ↑ | ↓ |
| Aldosterone antagonists | (+) | + | ↑↑ | ↓ |
| ARBs | + | + | ↑ | ↓ |
| Digoxin | (+) | + | ↑ | ↓ |

Lack of effect of age on the effects on digoxin on outcome: Results from the DIG study

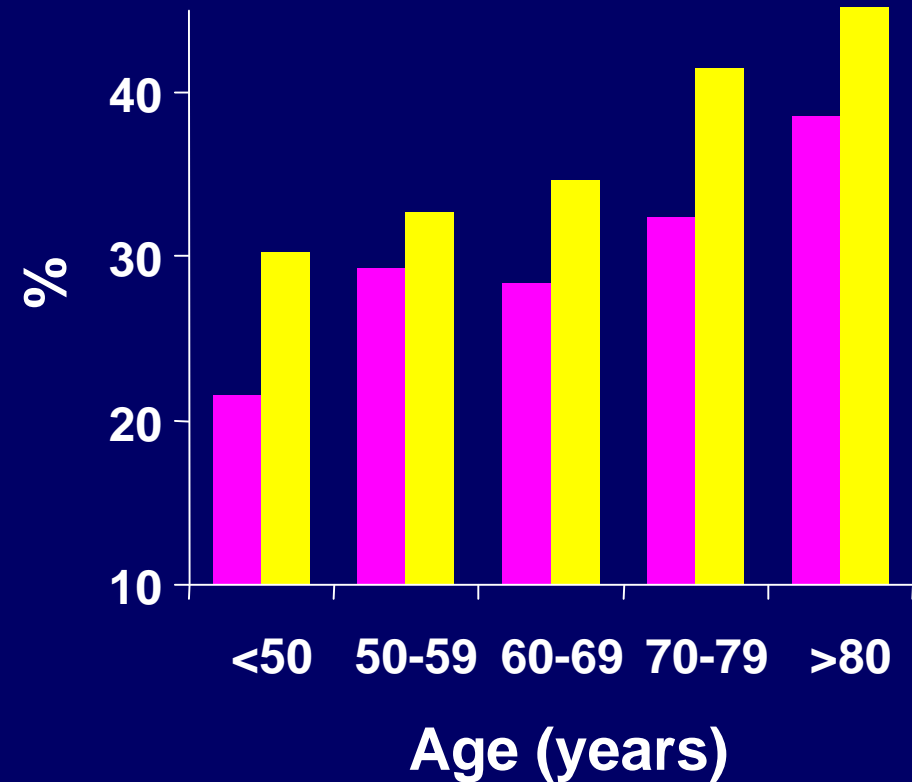
HF hospitalizations

P=0.0001

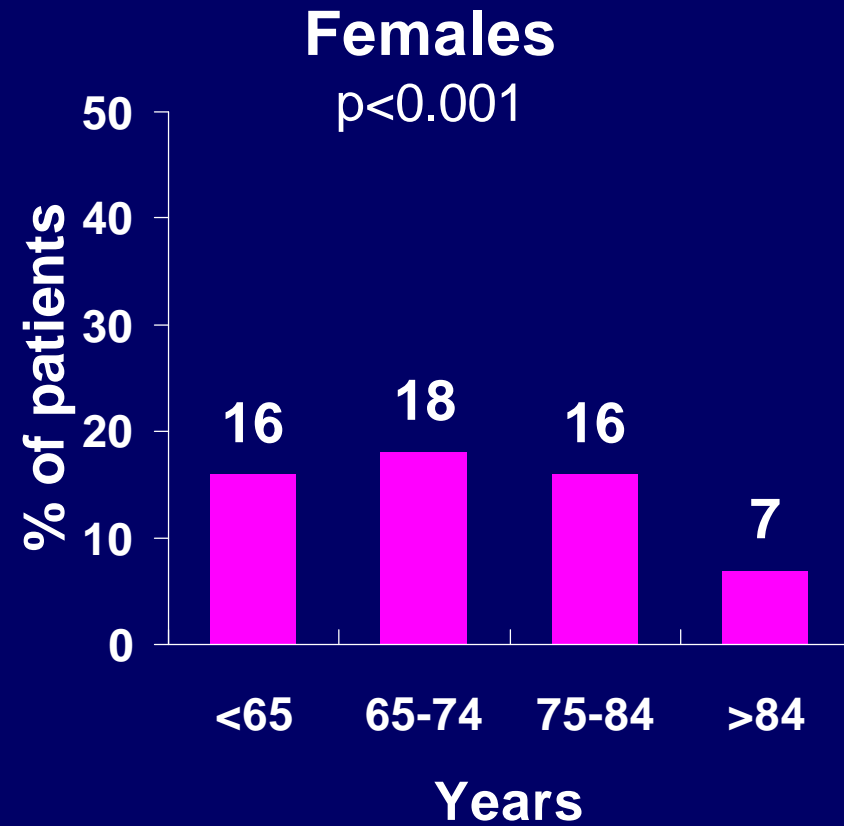
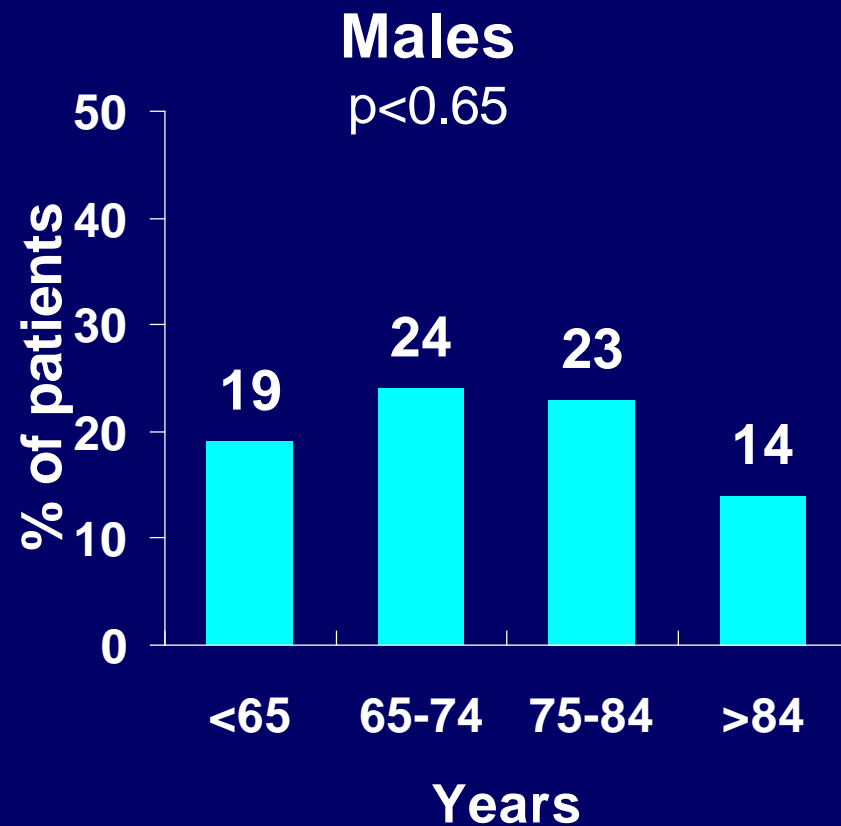


HF mortality or HF hospitalizations

P=0.0001



Oral Anticoagulant Prescriptions in the Patients with HF According to Age: IMPROVEMENT Study 8256 patients in 15 countries, 1999-2000



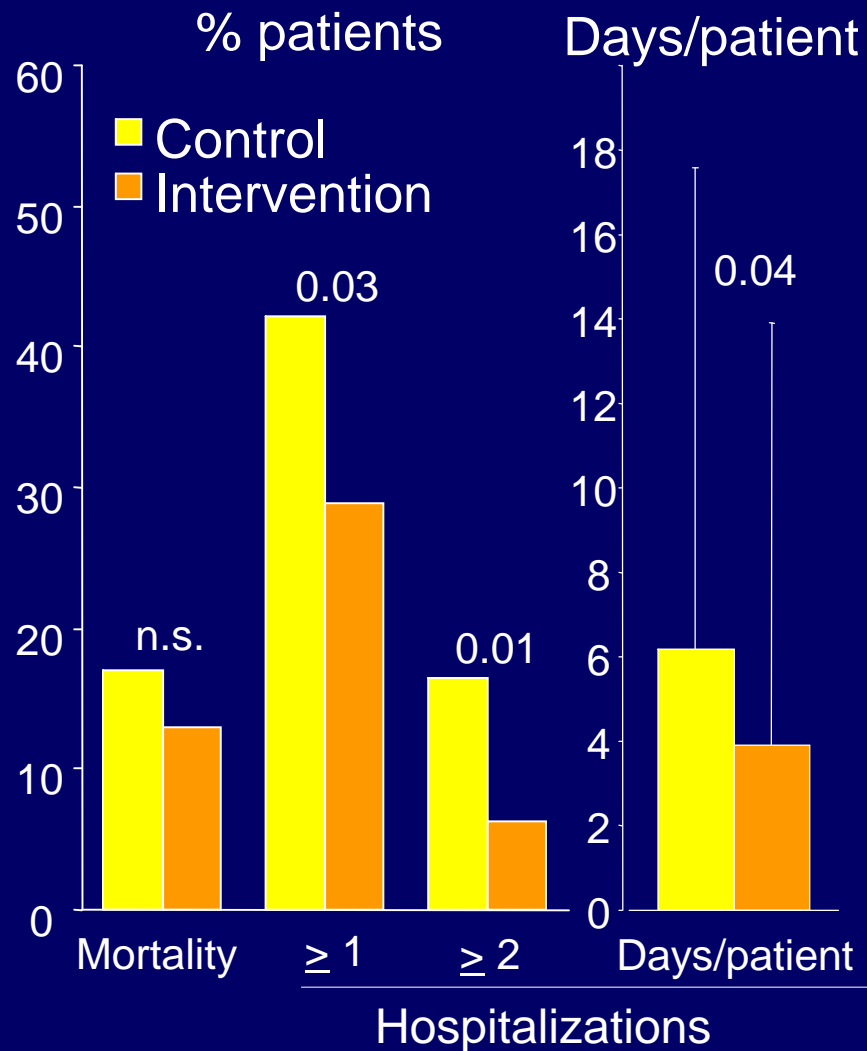
Randomised Controlled Trial of Cardiac Rehabilitation in Elderly Patients with HF

| | Control | | Rehabilitation | |
|---------------------------|------------|----------|----------------|----------|
| | Baseline | 24 weeks | Baseline | 24 weeks |
| Age, m \pm SD | 72 \pm 7 | | 72 \pm 6 | |
| 6-min walk distance, mts | 259 | 252 | 275 | 320*** |
| MLHF score | 44 | 37 | 41 | 23** |
| NYHA class | 2.53 | 2.48 | 2.21 | 2.01*** |
| Total hospital admissions | | 33 | | 11 |
| Days in hospital | | 187 | | 41 |
| Deaths | | 4 | | 5 |

Effects of a Multidisciplinary Intervention to Prevent the Readmission of Patients with Heart Failure

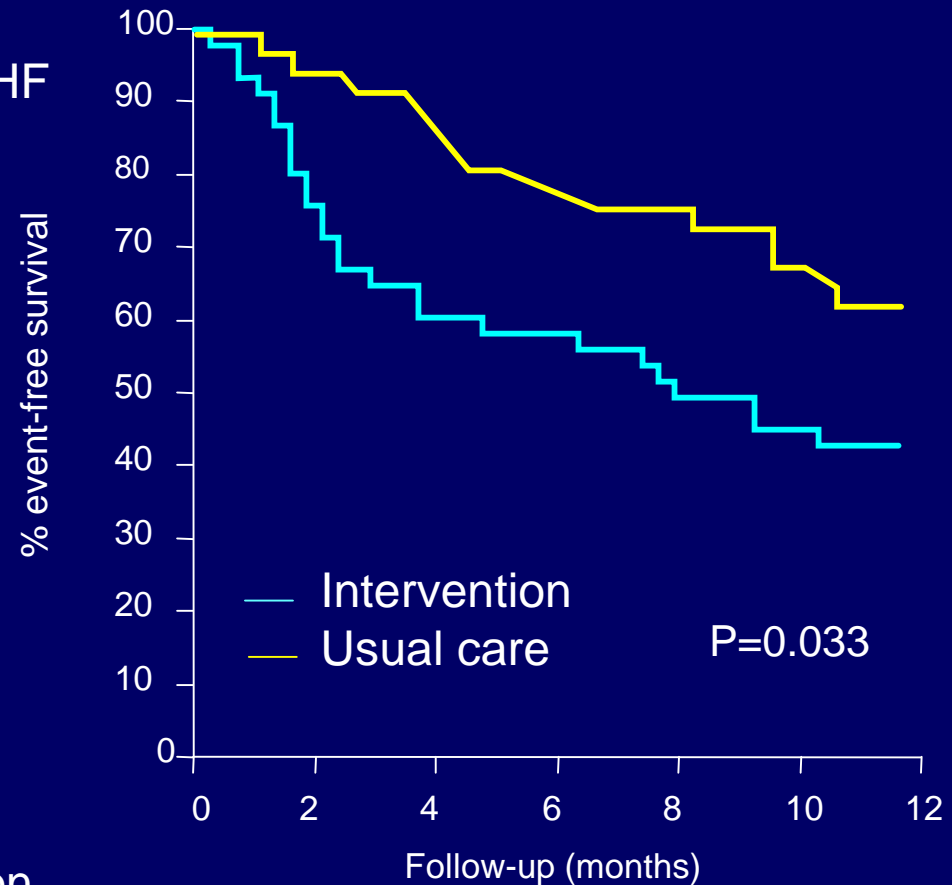
(Washington University HF disease management trial)

- Study group
 - 282 patients, selected among 1306
 - **Mean age 79 ys;** female, 65%
 - NYHA: 2.4 ± 1.1 ; EF: $41 \pm 13\%$
- Randomization
 - Intervention vs control groups
- Personnel
 - Nurse, dietician, social assistant, geriatrician, cardiologist
- Follow-up
 - 90 days
- Results
 - n.s. mortality
 - ↓ hospitalizations
 - ↓ costs (↓ \$153/month/pt.)
 - ↑ compliance and quality of life



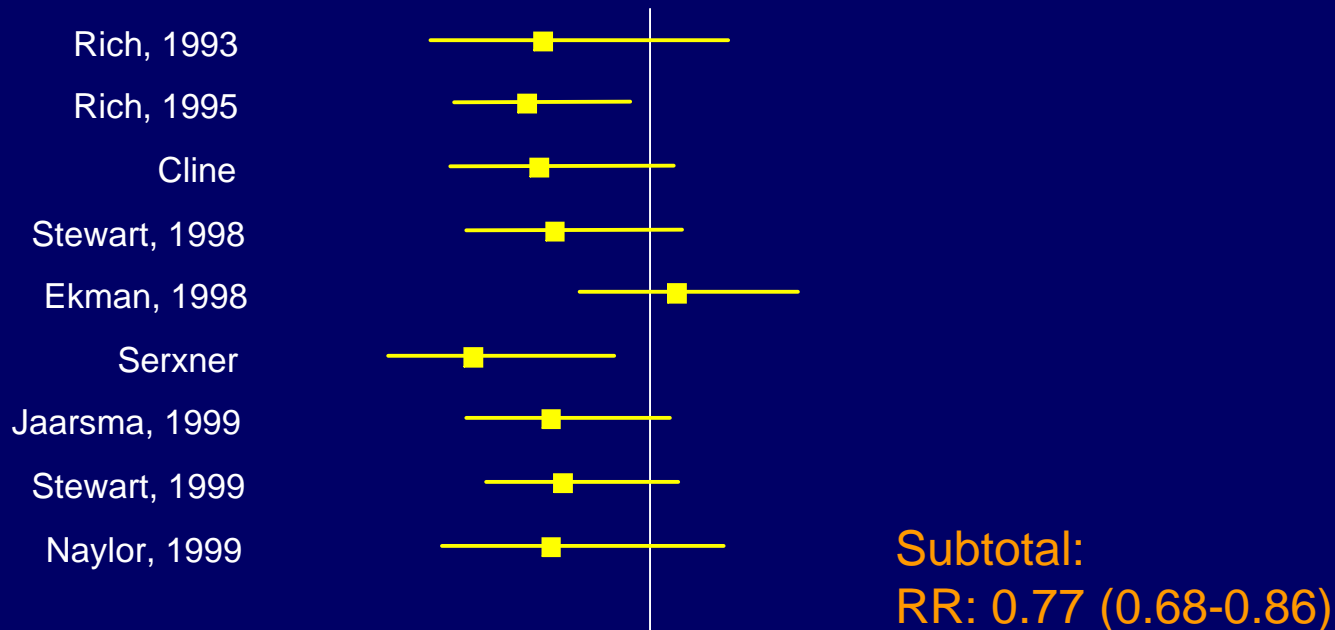
Randomized Controlled Trial of Specialist Nurse Intervention in Heart Failure

- Study group
 - 165 / 801 pts with an
 - **mean age: 75 ys,** female, 49%
 - Emergency admission for acute HF
 - Echo LV systolic dysfunction
 - NHYAII/III/IV, 43/76/81
- Randomization
 - Intervention vs control groups
- Personnel
 - Home visit by a nurse
 - Telephone contacts as needed
- Methods
 - Patient's education
 - Treatment optimization
 - Laboratory monitoring
- Results
 - Similar deaths (31% vs 30%)
 - ↓39% death or HF hospitalization
 - ↓ 28% death or all cause hospitalizations

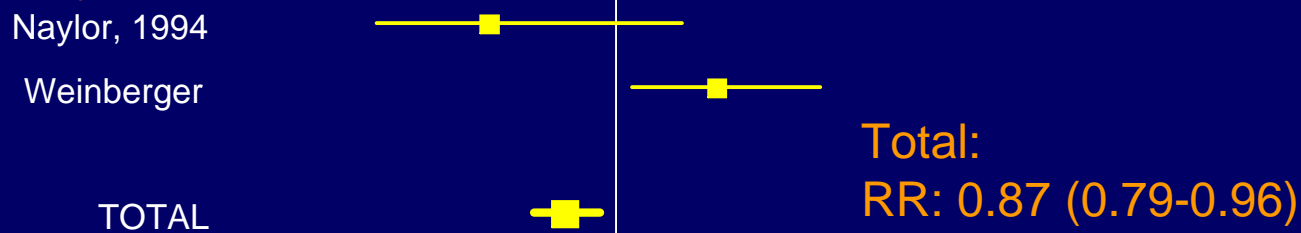


Effects of Disease Management Programs on Hospitalization Rates in Heart Failure

Multidisciplinary specialized team



Primary care



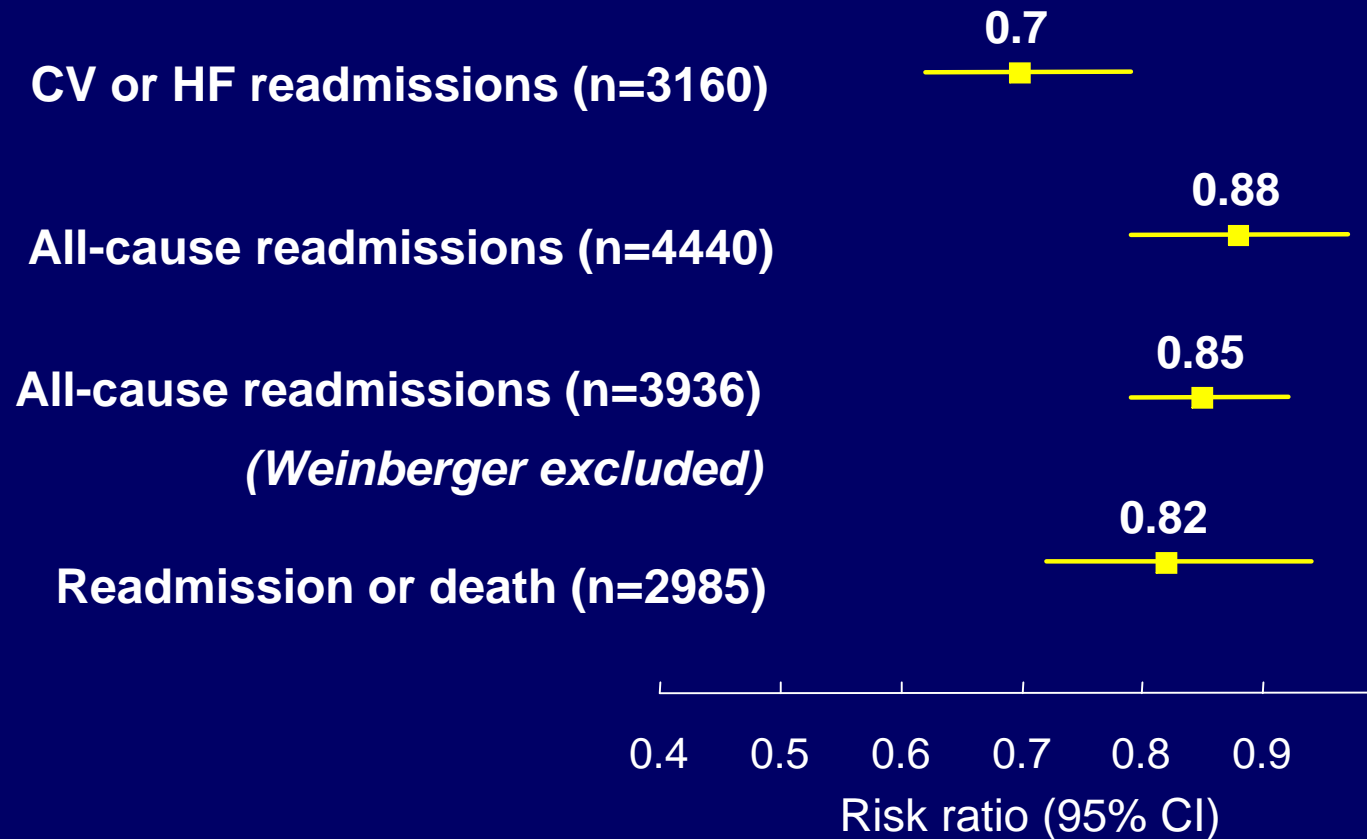
TOTAL

0 0,5 1 1,5 2

Risk ratio (95% CI)

Efficacy of Disease Management Programmes in Reducing Hospital readmissions in Older (>70 ys) Patients with HF

Randomised trials



Gonseth et al., *Eur Heart J* 2004; 25:1570