Лечение на ХСН при възрастни пациенти

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Структура на населението по възраст

Класификации на възрастта

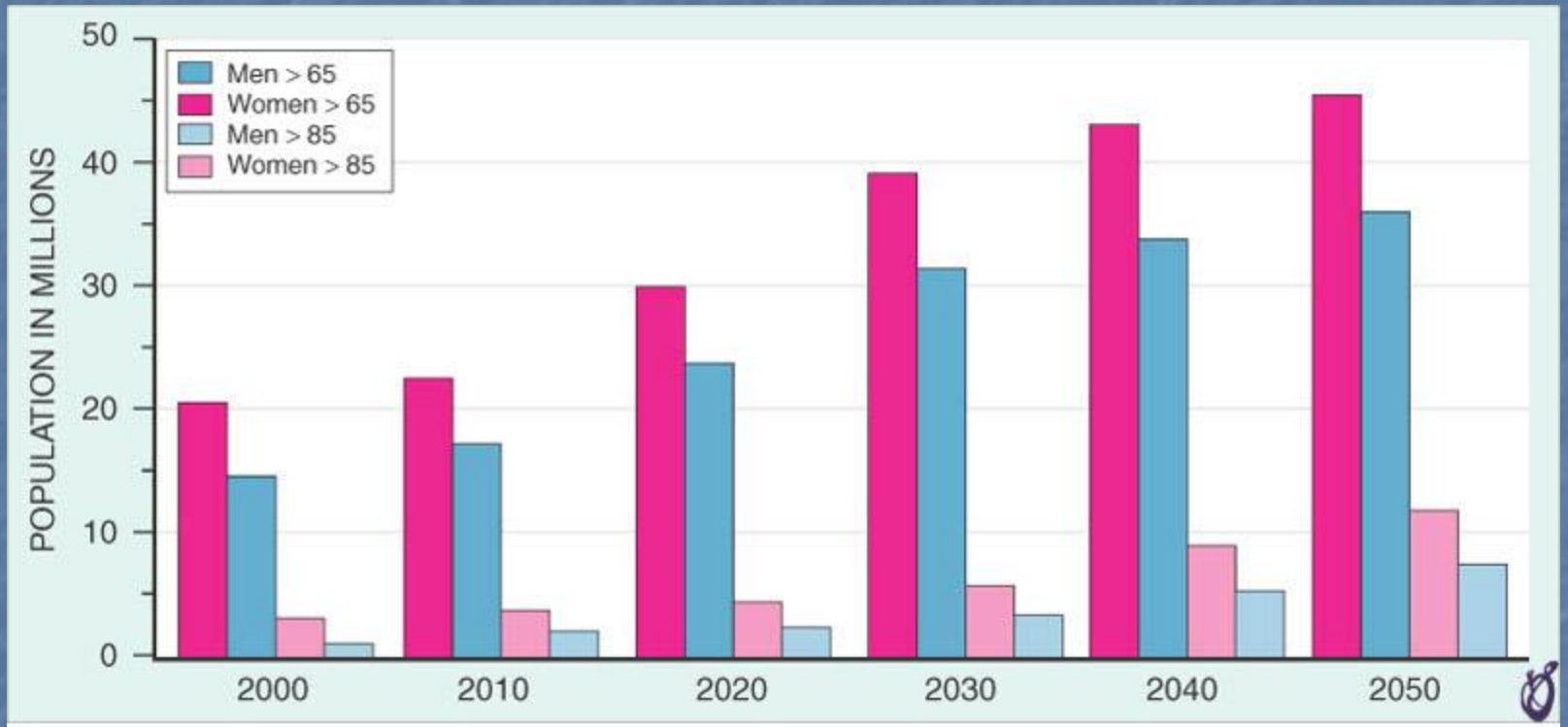
- *Класификация според СЗО*
  - 0-14 г. – детска възраст
  - 15-44 г. – млада възраст
  - 45-59 г. – средна (зряла) възраст
  - 60-74 г. – възрастни хора
  - 75-89 г. – стари хора (старческа възраст)
  - Над 90 г. – дълголетие

- *Класификация за нуждите на образованието и здравеопазването*
  - До 1 г. – кърмаческа възраст
  - 1-3 г. – ранна детска възраст
  - 4-6 г. – предучилищна възраст
  - 7-14 г. – училищна възраст

“Възрастта не е порок”

“Няма точно определение или сигурни биомаркери за понятието възрастен пациент”

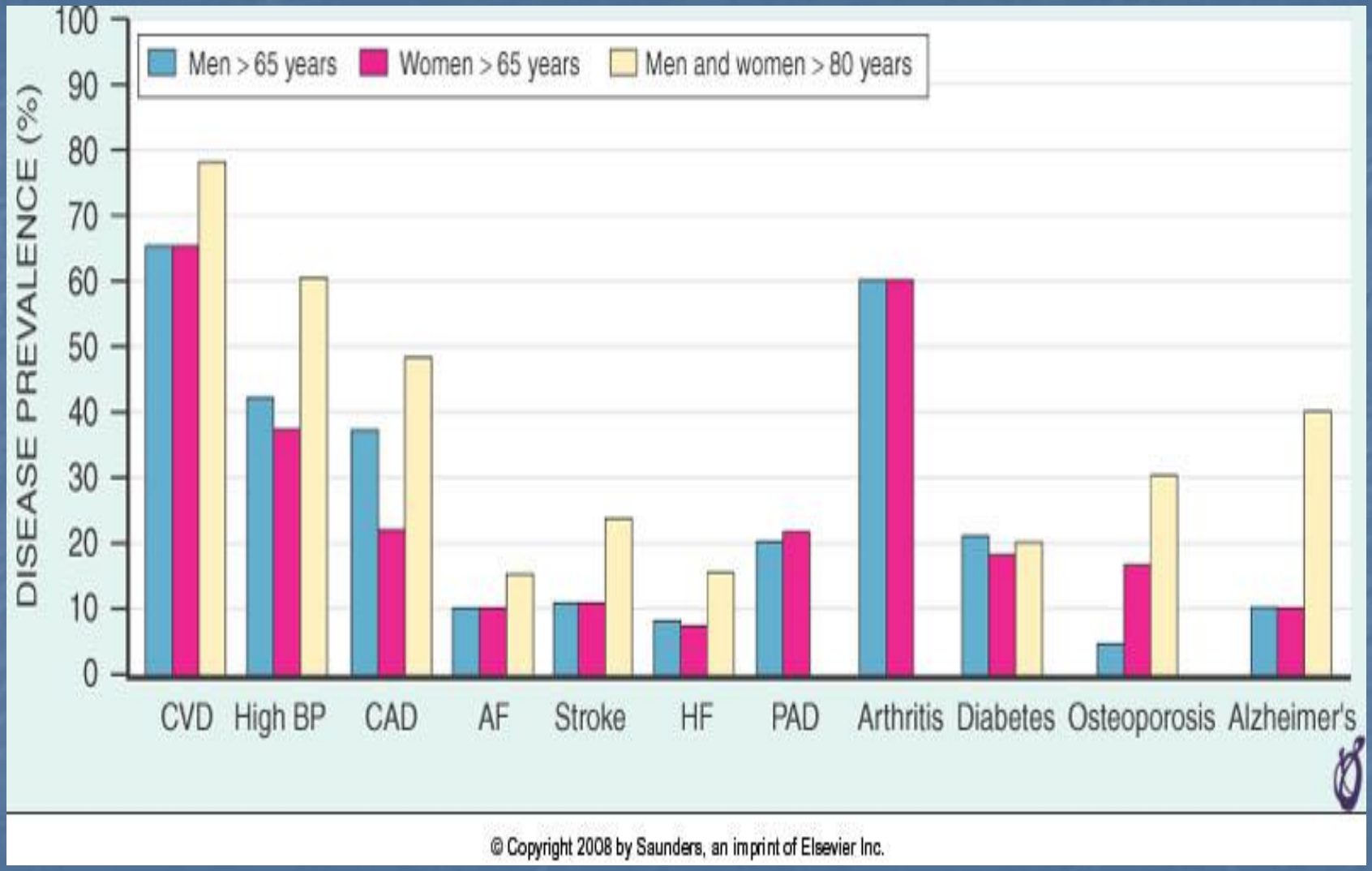
Епидемиологични данни



(From the U.S. Census Bureau.)

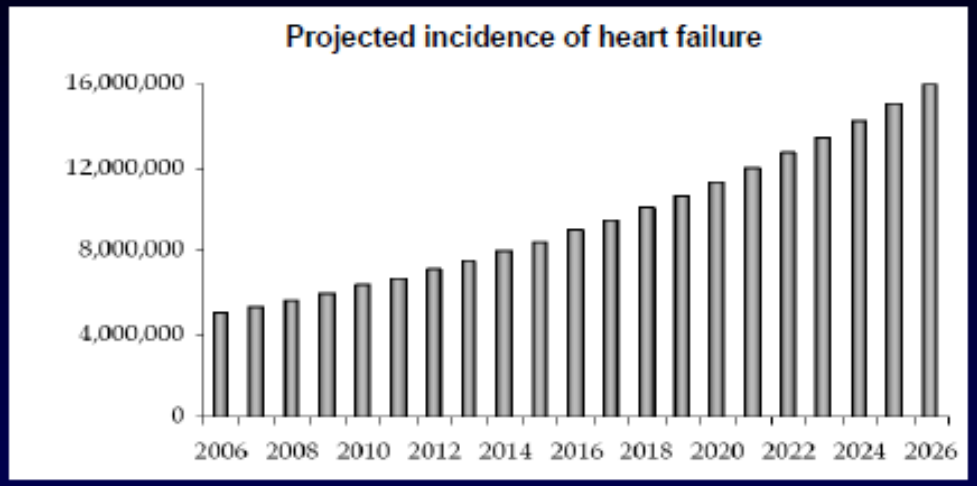
Структура на население под, във и над трудоспособна възраст

Години	Общо	Възрастови групи		
		Под трудоспособна възраст - %	В трудоспособна възраст - %	Над трудоспособна възраст - %
1990	100	21.6	55.5	22.9
1995	100	19.1	56.6	24.3
2000	100	16.8	58.3	24.9
2001	100	16.3	59.2	24.5
2002	100	15.9	60.1	24.0
2003	100	15.5	60.8	23.7
2004	100	15.1	61.6	23.3
2010				26.31 %



Heart Failure - Continued Unmet Need

- **Rising Patient Population**
  - > 5 million people in US
  - Age related diagnosis; aging will double incidence
  - > 500,000 new cases per year



- **Poor Prognosis**
  - 4-fold increased mortality at any age
  - Average survival < four years
  - Five-year survival rate of 25% in men and 38% in women with NYHA classes II to IV

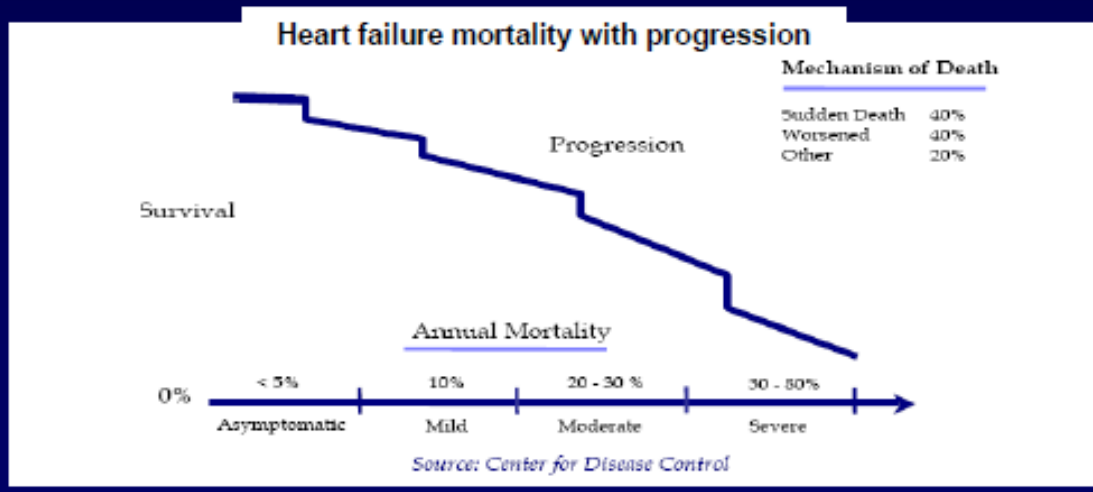


TABLE 75–4 Estimation of 4-Year Mortality in the Elderly Using Medical and Functional Information

		Points
Age (yr)	60-64	1
	65-69	2
	70-74	3
	75-79	4
	80-84	5
	>85	7
Male sex		2
Diabetes mellitus		1
Cancer		2
Lung disease		2
Heart failure		2
BMI < 25		1
Current smoker		2
Assistance needed for		
Bathing		2
Managing finances		2
Difficulty		
Walking several blocks		2
Pushing/pulling heavy objects		1

Score	4-Year Mortality (%)
0	0-1
1	1
2	1.5
3	3.5
4	5
5	5-8
6	9
7	12-15
8	19-20
9	20-24
10	27-28
11	43-45
12	44-48
13	54-59
≥14	64-67

BMI = body mass index.

Modified from Lee S, Lindquist K, Segal M, Covinsky K: Development and validation of a prognostic index for 4-year mortality in older adults. JAMA 295:801, 2006.

TABLE 75–4 Estimation of 4-Year Mortality in the Elderly Using Medical and Functional Information.

(Modified from Lee S, Lindquist K, Segal M, Covinsky K: Development and validation of a prognostic index for 4-year mortality in older adults. JAMA 295:801, 2006.)

Патофизиологични предпоставки за СН при възрастни

Δ Physiology




- ↓Cognitive function (memory problems, speed of thought, new learning)
- ↓ Renal function (↓ glomerular filtration)
- ↓ Heart rate and ↓ heart rate response to catecholamines
- ↑ Sympathetic nervous system activity
- ↓ Baroreflex function
- ↑ Orthostatic hypotension

TABLE 75–1	Differentiation Between Age-Associated Changes and Cardiovascular Disease in Older People

Organ	Age-Associated Changes	Cardiovascular Disease
Vasculature	Increased intimal thickness Arterial stiffening Increased pulse pressure Increased pulse wave velocity Early central wave reflections Decreased endothelial-mediated vasodilation	Systolic hypertension Coronary artery obstruction Peripheral artery obstruction Carotid artery obstruction
Atria	Increased left atrial size Atrial premature complexes	Atrial fibrillation
Sinus node	Decreased maximal heart rate Decreased heart rate variability	Sinus node dysfunction, sick sinus
Atrioventricular node	Increased conduction time	Type II block, third-degree block
Valves	Sclerosis, calcification	Stenosis, regurgitation
Ventricle	Increased left ventricular wall tension Prolonged myocardial contraction Prolonged early diastolic filling rate Decreased maximal cardiac output Right bundle branch block Ventricular premature complexes	Left ventricular hypertrophy Heart failure (with or without preserved systolic function) Ventricular tachycardia, fibrillation

TABLE 75–1 Differentiation Between Age-Associated Changes and Cardiovascular Disease in Older People.

TABLE 75–2 Estimated Glomerular Filtration Rate (eGFR) by Age, Sex, and Race

	Cr = 1					Cr = 1.2					Cr = 1.5				
Age (yr)	45	55	65	75	85	45	55	65	75	85	45	55	65	75	85
Caucasian men	86*	82	80	77	75	70	67	65	63	61	54	52	50	48	47
Caucasian women	64	61	59	57	56	52	50	48	47	45	40	38	37	36	35
African American men	104	100	97	94	91	84	81	78	76	74	65	63	61	59	57
African American women	77	74	72	70	68	63	60	58	56	55	48	46	45	44	43

*Data are average eGFR/1.73 m^2 for serum creatinine of 1 mg/dl (Cr = 1), 1.2 mg/dl (Cr = 1.2), and 1.5 mg/dl (Cr = 1.5) for Caucasian and African American men and women. Underscores indicate eGFR <60 ml/min/1.73 m^2 classified as moderate decreases in GFR or stage 3 chronic renal disease (ICD-9-CM code 585.3).

From Manjunath G, Sarnak M, Levey A: Prediction equations to estimate glomerular filtration rate: An update. Curr Opin Nephrol Hypertens 10:785-792, 2001 and Levey A, Bosch J, Lewis J, et al: A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. Ann Intern Med 130:461-470, 1999.

TABLE 75–2 Estimated Glomerular Filtration Rate (eGFR) by Age, Sex, and Race.

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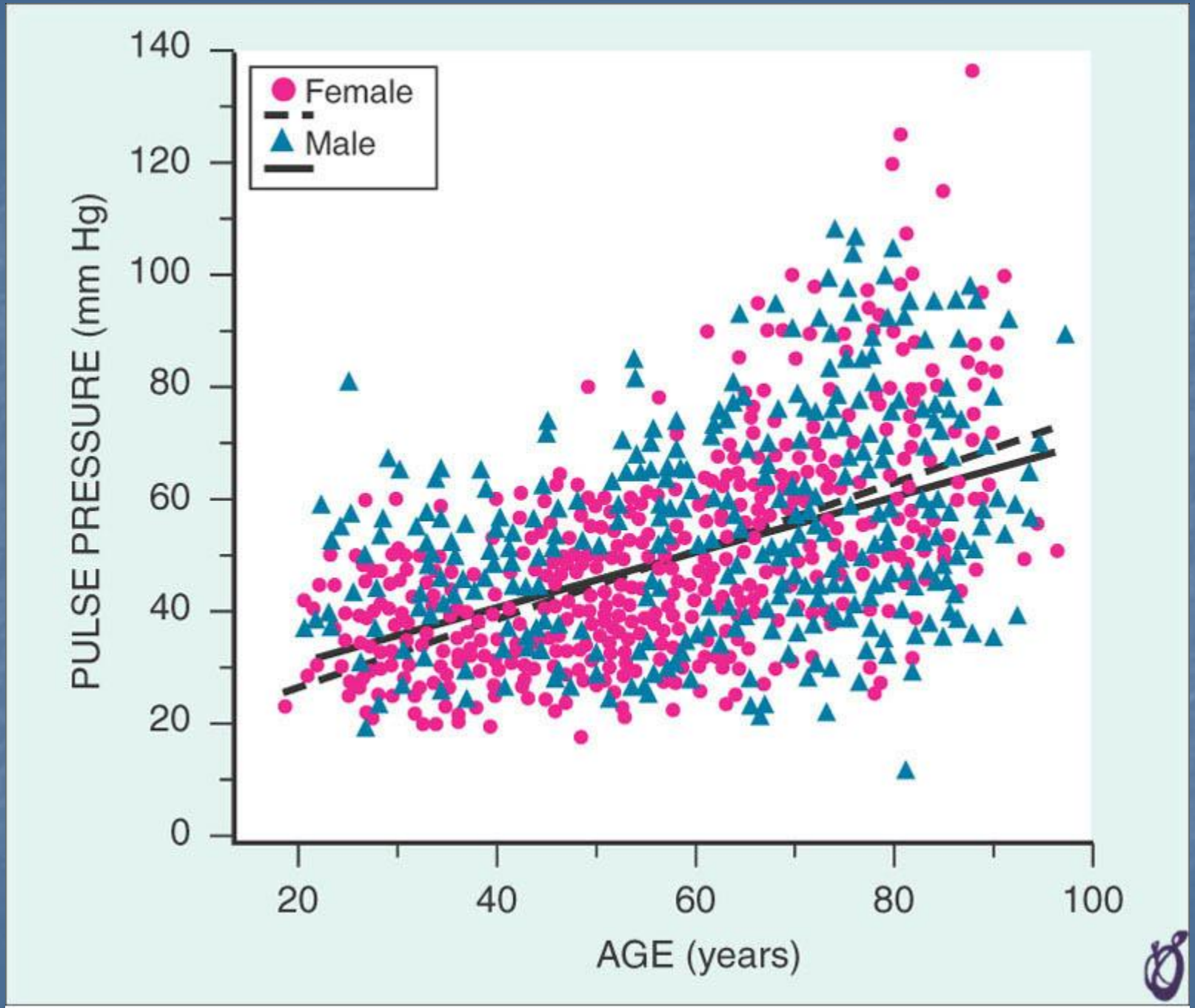

(Reprinted from Pearson JD, Morrell CH, Brant LJ, et al: J Gerontol Med Sci 53: M177-M183, 1997.)

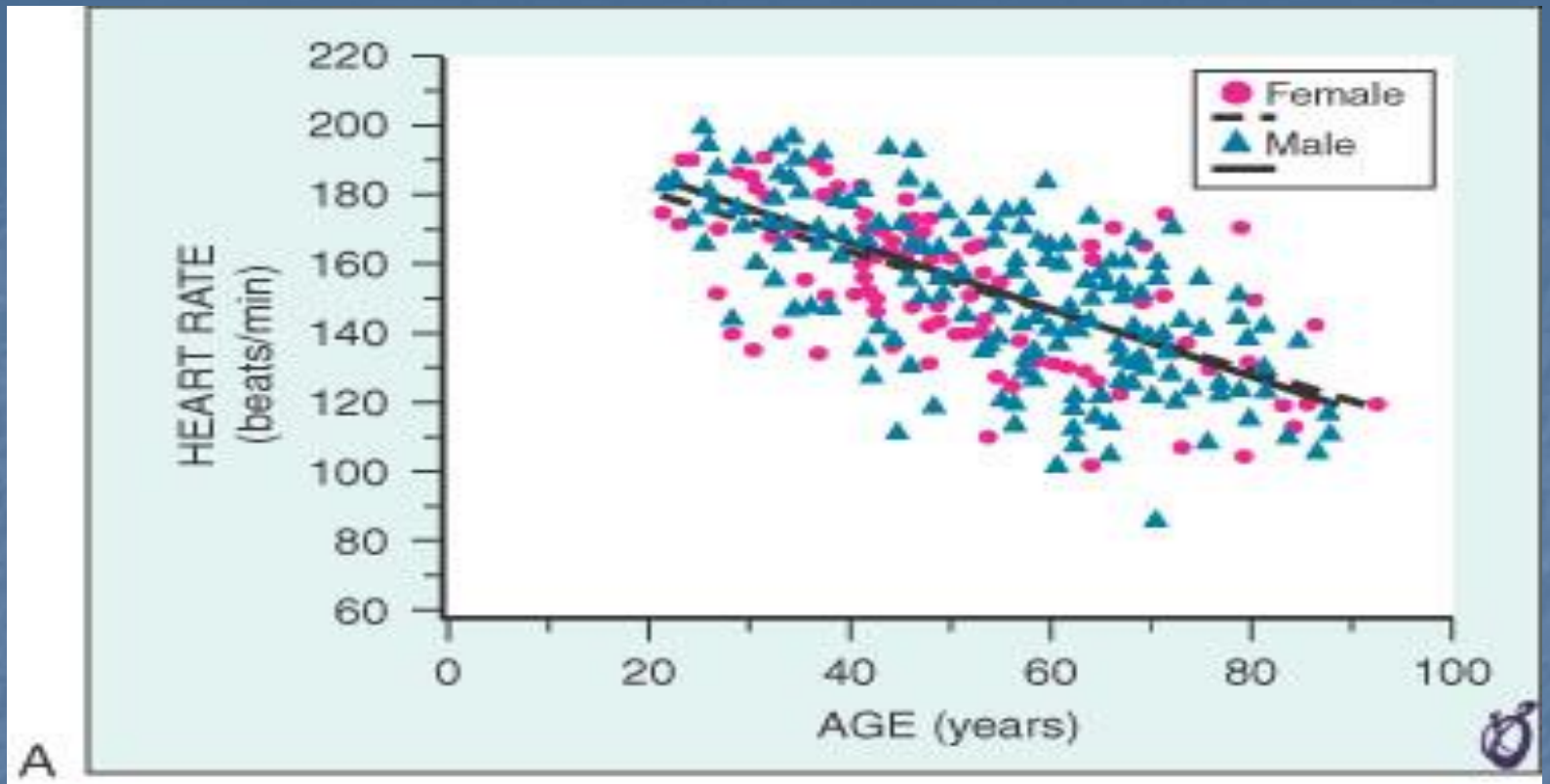

FIGURE 75–4A Maximum exercise heart rate **(A)**, cardiac index **(B)**, and left ventricular (LV) contractility index **(C)** in men and women in the Baltimore Longitudinal Study of Aging who had been prescreened to exclude clinical and occult cardiovascular disease.

(Reprinted from Fleg JL, O'Connor FC, Gerstenblith G, et al: Impact of age on the cardiovascular response to dynamic upright exercise in healthy men and women. J Appl Physiol 78:890-900, 1995.)

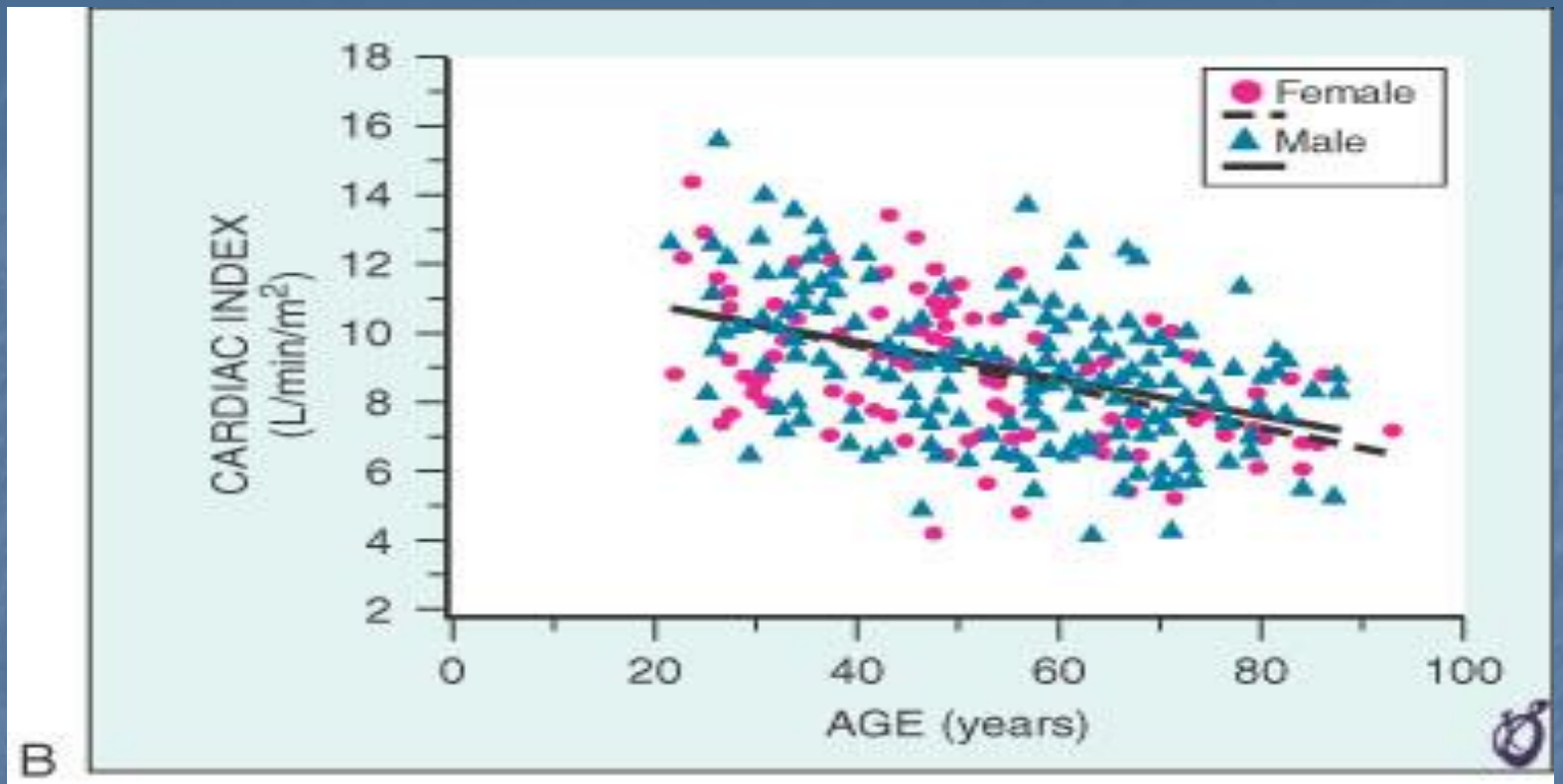

FIGURE 75–4B Maximum exercise heart rate **(A)**, cardiac index **(B)**, and left ventricular (LV) contractility index **(C)** in men and women in the Baltimore Longitudinal Study of Aging who had been prescreened to exclude clinical and occult cardiovascular disease.

(Reprinted from Fleg JL, O'Connor FC, Gerstenblith G, et al: Impact of age on the cardiovascular response to dynamic upright exercise in healthy men and women. J Appl Physiol 78:890-900, 1995.)

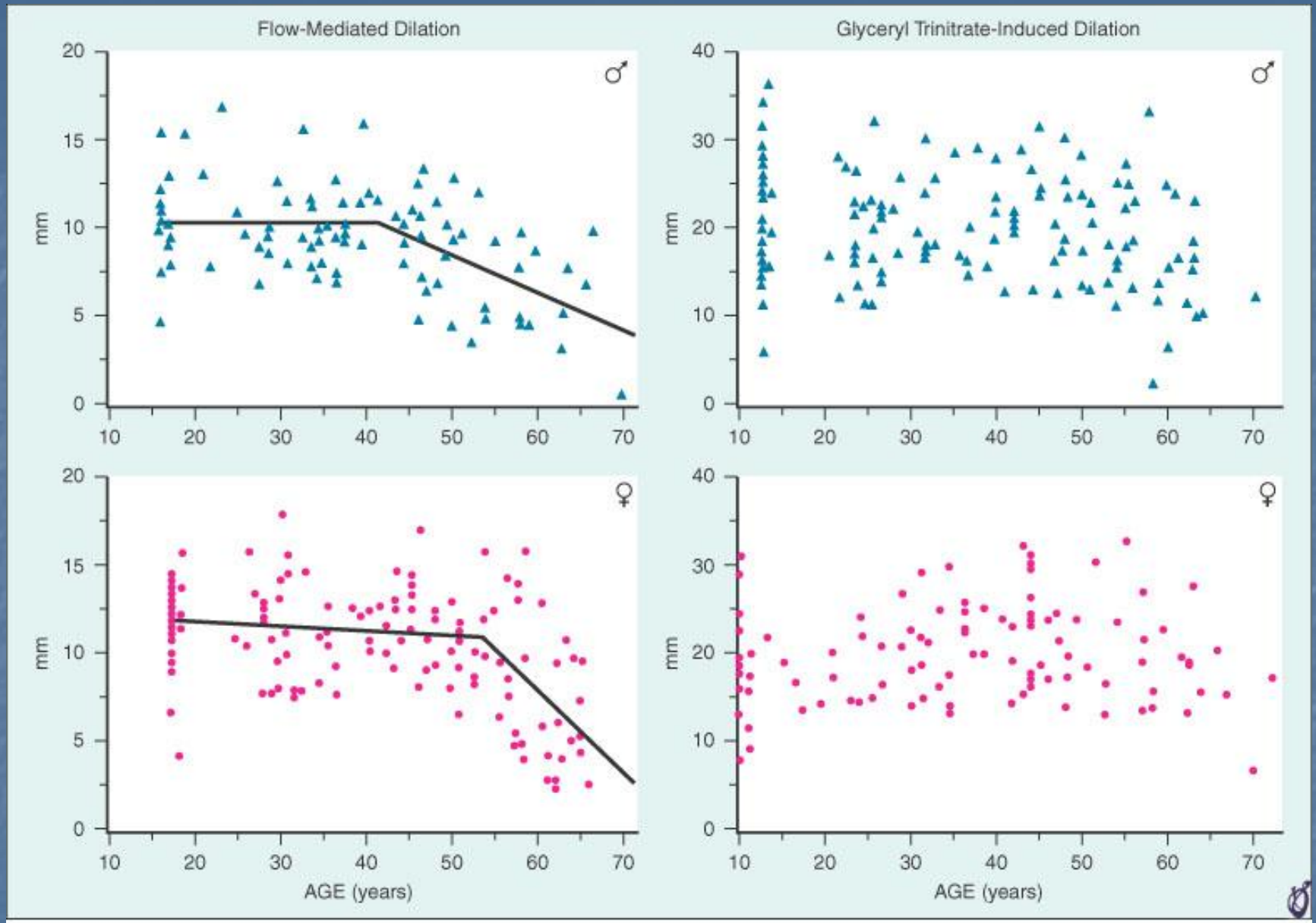

FIGURE 75–5 Endothelial (flow)-mediated and nonendothelial (glyceryl trinitrate)-induced arterial dilation in apparently healthy men and women. Age-associated declines are seen in flow-mediated dilation but not in glyceryl trinitrate–induced dilation. Age-related changes occur earlier in men compared with women.

(Reprinted from Celermajer DS, Sorensen KE, Spiegelhalter DJ, et al: J Am Coll Cardiol 24:471-476, 1994.)

Диагноза

- Несигурни анамнестични данни/коморбидност, ментални отклонения/
- Затруднено физикално изследване
- Акцент на инструменталните и лабораторни методи:

- Рентген
- Ехокардиография
- BNP

Optimal NT-proBNP Cut-points

"Rule in"

Age strata	Optimal cut-point	Sensitivity	Specificity	PPV	NPV	Accuracy
All <50 years (n=183)	450 pg/ml	97%	93%	76%	99%	95%
All 50-75 years (n=554)	900 pg/ml	90%	82%	82%	88%	85%
All >75 years (n=519)	1600 pg/ml	85%	73%	92%	55%	83%
Overall average		92%	84%	88%	66%	93%

Predictive value of plasma galectin-3 levels in heart failure with reduced and preserved ejection fraction

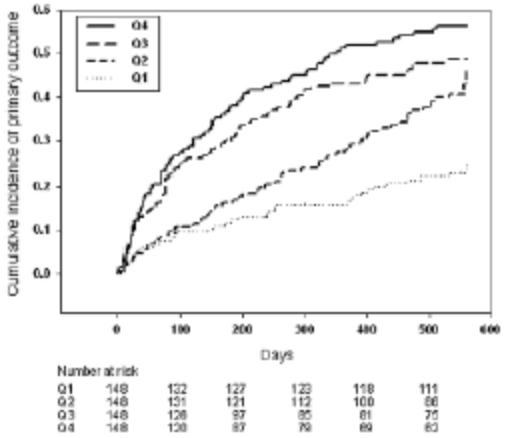

Figure 1. Adjusted Cox regression curves for quartiles of plasma galectin-3 showing the cumulative risk for the combined end-point all-cause mortality and hospitalization for HF.

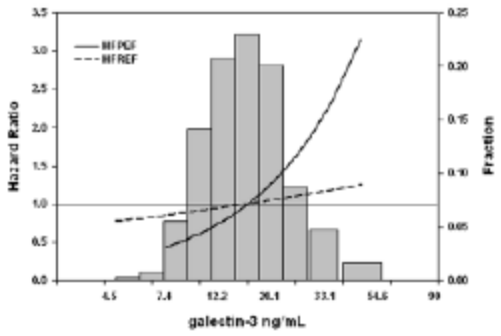

Figure 2. Graphical depiction of the risk estimates for experiencing the primary outcome in patients with HFPEF and HFREF with increasing levels of plasma galectin-3. The distribution of (log-transformed) galectin-3 is depicted in the background in brown bars. A similar increase in galectin-3 causes a much more pronounced increase in risk in patients with HFPEF compared to patients with HFREF.

RUDOLF A. DE BOER[1], DIRK J. A. LOK[2], TINY JAARSMA[1], PETER VAN DER MEER[1], ADRIAAN A. VOORS[1], HANS L. HILLEGE[1] & DIRK J. VAN VELDHUISEN[1]

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The novel biomarker growth differentiation factor 15 in heart failure with normal ejection fraction

Raoul Stahrenberg[1†], Frank Edelmann[1†], Meinhard Mende[2], Anke Kockskämper[3], Hans-Dirk Düngen[4], Claus Lüers[1], Lutz Binder[5], Christoph Herrmann-Lingen[6], Götz Gelbrich[2], Gerd Hasenfuß[1], Burkert Pieske[3], and Rolf Wachter[1*]

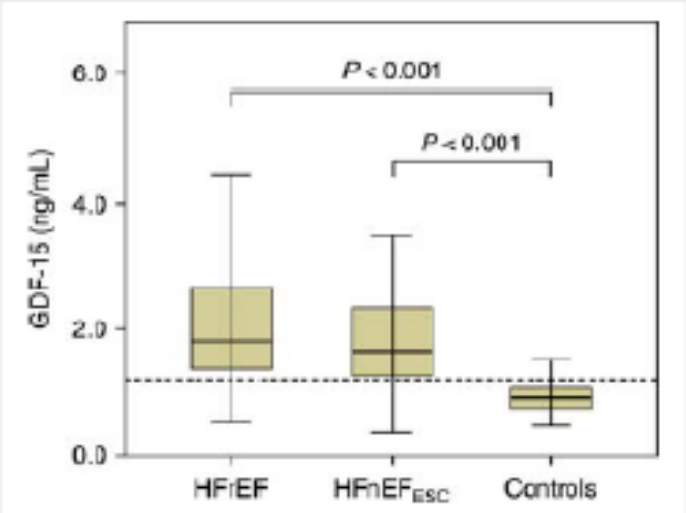


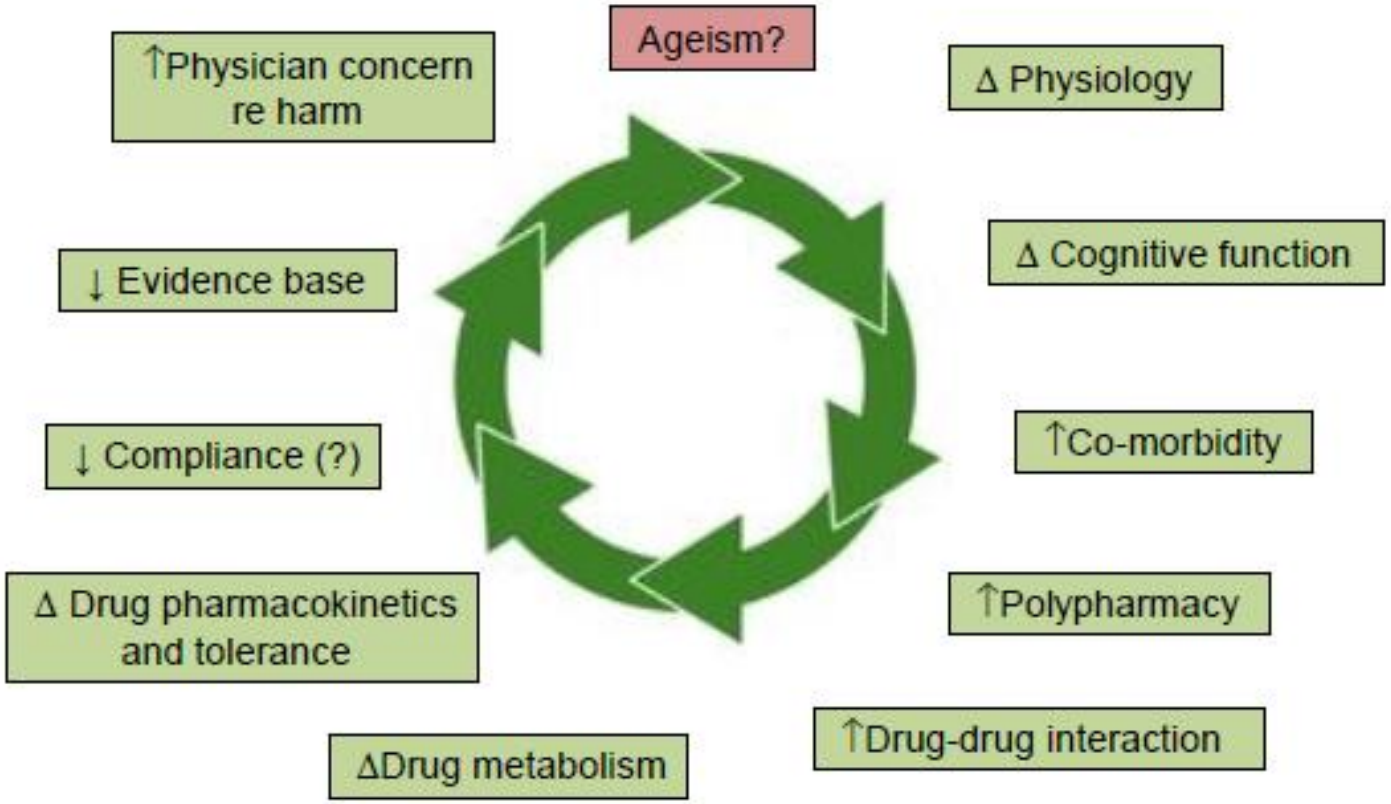
Figure 1 Growth differentiation factor 15 levels in systolic heart failure, HFnEF$_{ESC}$ and controls. Broken line denotes recommended cut-off of 1.20 ng/mL.

Table 2 Comparative diagnostic properties of growth differentiation factor 15 and NT-proBNP for HFnEF$_{New}$

	NT-proBNP	GDF-15
Specificity fixed		
Cut-off value	220 ng/L[a]	1.51 ng/mL
Sensitivity (%)	55	61
Specificity (%)	97	97
Precision (%)	84	86
Odds ratio	36.7	47.8
Sensitivity fixed		
Cut-off value	110 ng/L[a]	1.28 ng/mL
Sensitivity (%)	74	74
Specificity (%)	80	90
Precision (%)	78	86
Odds ratio	10.9	27.6

[a]Recommended by ESC guidelines[4] to rule in or out HFnEF$_{ESC}$.

Age



Jugdutt BI. Expert Rev CV Therap 2010; 8: 695 – 715

Лечение

- Контингента на големите клинични проучвания обхваща пациенти на средна възраст
- Ограничен брой проучвания при възрастни.
- Популацията възрастни пациенти е различна и трудно се естраполират данните за лечението при тях.

Under-representation of the very elderly in RCTs

Table 1. Composite mean age distribution in the research studies used as evidence for recommendations in the clinical practice guidelines

CLINICAL PRACTICE GUIDELINES	TOTAL NO. OF STUDIES REVIEWED	NO. OF STUDIES PROVIDING MEAN AGE*	COMPOSITE MEAN AGE, Y	NO. OF STUDIES PROVIDING SD FOR MEAN AGE	NO. OF STUDIES WITH MEAN AGE PLUS 1 SD OF ≥ 80 Y (%)	NO. OF STUDIES WITH MEAN AGE ≥80 Y (%)	NO. OF STUDIES PROVIDING AGE RANGE	NO. OF STUDIES WITH AGE RANGE CROSSING 80 Y (%)
Diabetes[1]	1363	1206	52.0	917	22 (2.4)	4 (0.3)	582	116 (19.9)
Heart failure[2-5]	500	458	68.1	356	96 (27.0)	10 (2.2)	213	116 (54.5)
Hypertension[6-13]	168	136	58.3	106	5 (4.7)	3 (2.2)	96	43 (44.7)
Osteoporosis[14-16]	473	425	64.5	354	47 (13.3)	14 (3.3)	230	118 (51.3)
Stroke[17,18]	55	47	61.6	28	7 (25.0)	0 (0.0)	21	18 (85.7)

*This represents the number of studies that were included in the calculation of the composite mean age.

Most RCTs look for effect-modification by age – but usually take a cut-point of 65 years!

Cox L et al. Can Fam Physician 2011; 57: e263 – 9

Do guidelines help?

- ESC 2012 guideline:
  - No specific mention of the elderly in therapy section
- NICE 2010 guideline:
  - "The management of HF should be determined by clinical criteria, irrespective of the age of the patient"
  - "Tolerance of drugs may be lower and side-effects require closer and more frequent monitoring in older patients"

- ACC/AHA 2005 guideline:
  - 3 paragraphs
  - HF in elderly patients is inadequately recognised and treated
  - Some reports suggest elderly patients may have diminished response to diuretics, ACE inhibitors, and positive inotropes, and a higher risk of adverse events
  - Risk-benefit uncertainties exacerbated by poor representation of very elderly in large-scale clinical trials on efficacy and safety of new treatments in HF

TABLE 75–14	Approach to the Older Patient with Heart Failure (HF)
Symptoms may be nonspecific in the older patient—suspect HF. Consider HF diagnosis in patients with fatigue, dyspnea, exercise intolerance, or low activity.	
Diagnosis may be assisted by use of echocardiography or serum markers of HF.	
HF may be present in the older patient with preserved systolic function (ejection fraction), especially older women.	
Aggressive treatment of hypertension or diabetes when present may improve HF outcomes.	
Treat symptoms with a goal of improving quality of life and morbidity: Control blood pressure-systolic and diastolic. Treat ischemia. Control atrial fibrillation rate. Promote physical activity. Adjust medications for age and disease-related changes in kinetics and dynamics.	
Educate and involve patients, family members, or caregivers in management of HF: Monitor weight. Consider use of multidisciplinary team approaches.	

TABLE 75–3	Guidelines for Medication Prescribing in Older Patients
In general, loading doses should be reduced—weight (or body surface area) can be used to estimate loading dose requirements; doses in women are usually less than in men.	
Use estimates of glomerular filtration to guide dosing of renally cleared medications and contrast administration; reduce doses of metabolically or hepatically cleared drugs.	
Time between dosage adjustments and evaluation of dosing changes should be longer in older patients than younger patients.	
Routine use of strategies to avoid drug interactions is essential—incorporating reference materials, a team approach, and quality improvement initiatives are effective strategies.	
Knowledge of effects of noncardiac medications is necessary.	
Assessment of adherence and attention to factors contributing to nonadherence should be part of the prescribing process.	
Physicians must be familiar with the patient's source of prescription medication coverage including Medicare D legislation and provide patient education and assistance with obtaining critical medications.	
Multidisciplinary approaches to monitoring medication therapy may increase successful outcomes of medication therapy.	

TABLE 75–3 Guidelines for Medication Prescribing in Older Patients.

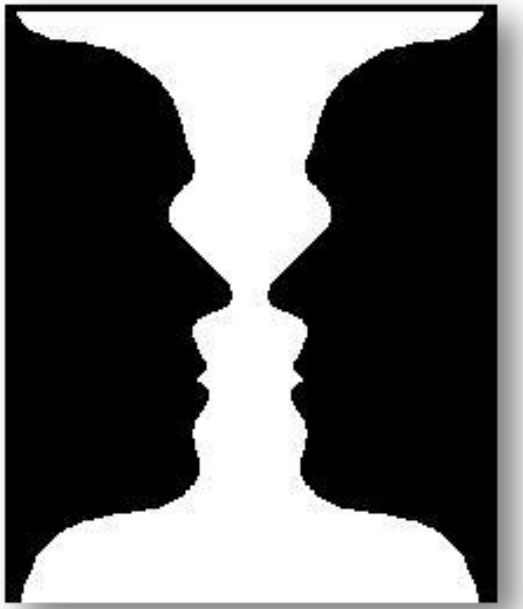
What is a ‘co’-morbidity?

Heart failure

Hypertension

Chronic lung disease

Peripheral arterial disease



Osteoarthritis

Dementia

Depression

Renal failure

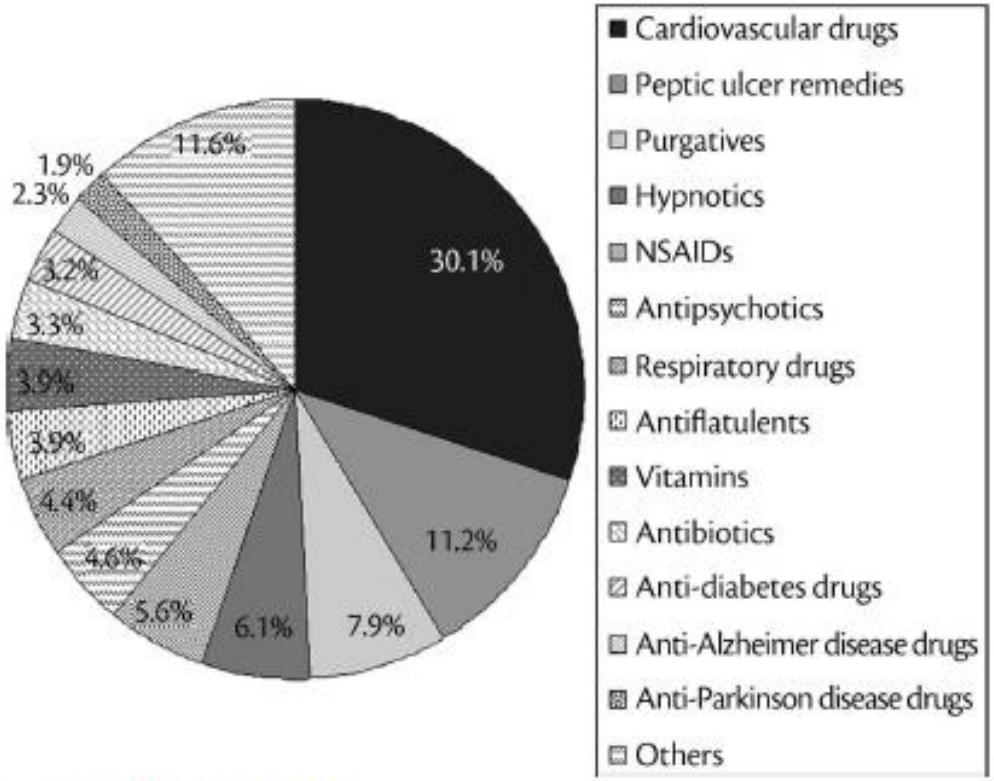
A ‘person-centred’ approach is likely to be much more appropriate than a ‘disease-centred’ approach

Polypharmacy

- *Nobili A et al. Eur J Int Med 2011; 22: 597-602*
- REPOSI Study in Italian Hospitals
- HF patients - average of 7.3 [6.5-8.2] drugs
- Odds ratio for polypharmacy (≥ 5 drugs) was 3.6

- *Mizokami F et al. Am J Geriatric Pharm 2012; 10: 123-8*
- USA hospitals
- HF patients - average of 6.1 drugs (SD 4)
- 60% of HF patients were on ≥ 5 drugs

Polypharmacy: which drugs?



Mizokami F et al. Am J Geriatric Pharm 2012; 10: 123-8

TABLE 75–6	Considerations for Pharmacological Therapy of Older Patients with Hypertension and Other Disorders

Hypertension +	Efficacy Considerations	Toxicity/Adverse Effect Considerations
Arthritis	–	ACE, ARB, aldosterone antagonist interactions with NSAIDs
Atrial fibrillation	Beta blocker,* calcium channel blocker (non-DHP),* amiodarone	Interactions with warfarin
Atrioventricular block	–	Beta blockers, non-DHP calcium channel blockers
Carotid disease/stroke	Calcium channel blocker,* ACEI†	
Constipation	–	Verapamil
Coronary artery disease	Beta blocker,*† calcium channel blocker*†	Nitrates and postural hypotension
Dementia	Clonidine‡	
Depression	–	SSRIs and hyponatremia
Diabetes	ACE,*† ARB,*† calcium channel blocker (non-DHP),† beta blocker†	Chlorpropamide and hyponatremia
Gout		Diuretics
Heart failure	ACE,*† ARB*† + loop diuretic,*† ± beta blocker*† ± aldosterone antagonist*†§	Calcium channel blockers (possible) ACE, ARB, aldosterone antagonist and hyperkalemia
Hyponatremia	–	Diuretic (especially with SSRI)
Incontinence	–	Diuretic
Myocardial infarction	Beta blocker,*† ± ACE,*† ± aldosterone antagonist†	ACE, ARB, aldosterone antagonist and hyperkalemia
Osteoporosis	–	Thiazides and bone loss
Peripheral artery disease	Calcium channel blocker (DHP)*	Beta blocker (if severe)
Postural hypotension	Thiazide¶	Alpha blocker, calcium channel blocker (DHP)
Prostatic hypertrophy	Alpha blocker*	
Renal failure	ACE,*† ARB,*† ACE + ARB; loop diuretic*	Aldosterone antagonists
Ventricular arrhythmias	Beta blocker*	Thiazide, loop diuretics, and hypokalemia

*Recommendations for first-line therapy from the European Society of Cardiology guidelines for the management of arterial hypertension.[101]
†Recommendations for second-line agents usually added to thiazide diuretics from The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.[97]
‡Only available transdermal formulation for patients unable to swallow or who refuse oral medications.
§Systolic heart failure only.
¶Nursing home patients.
ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocking inhibitor; DHP = dihydropyridine; NSAIDs = nonsteroidal antiinflammatory drugs; SSRIs = selective serotonin reuptake inhibitors.

TABLE 75–6 Considerations for Pharmacological Therapy of Older Patients with Hypertension and Other Disorders.

Бета - блокери за лечение на сърдечна недостатъчност

- Карведилол
- Бизопролол
- Метопролол сукцинат с бавно освобождаване
- Небиволол

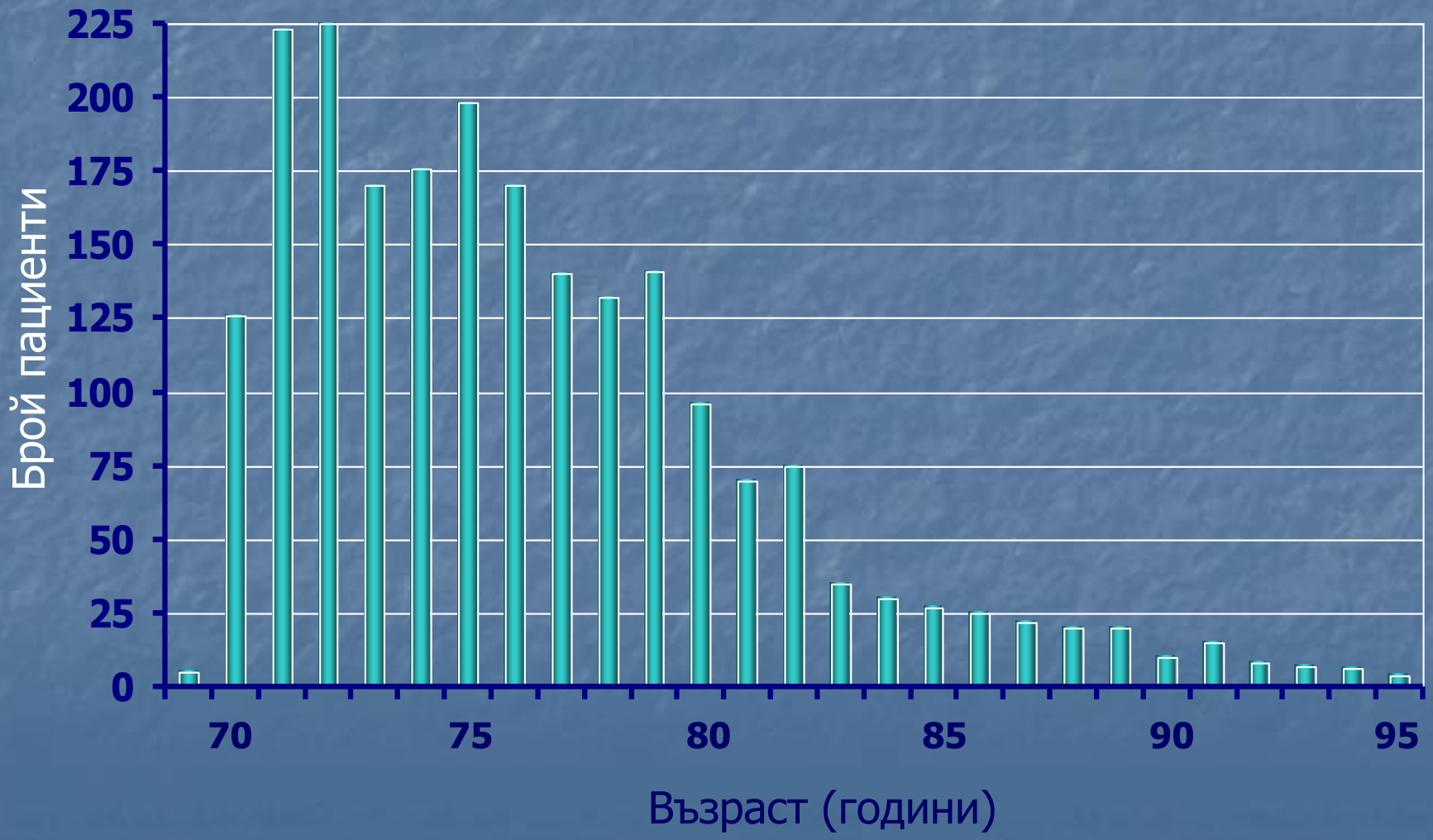
ESC Guidelines for CHF. Eur Heart J 2005; 26:1127

SENIORS

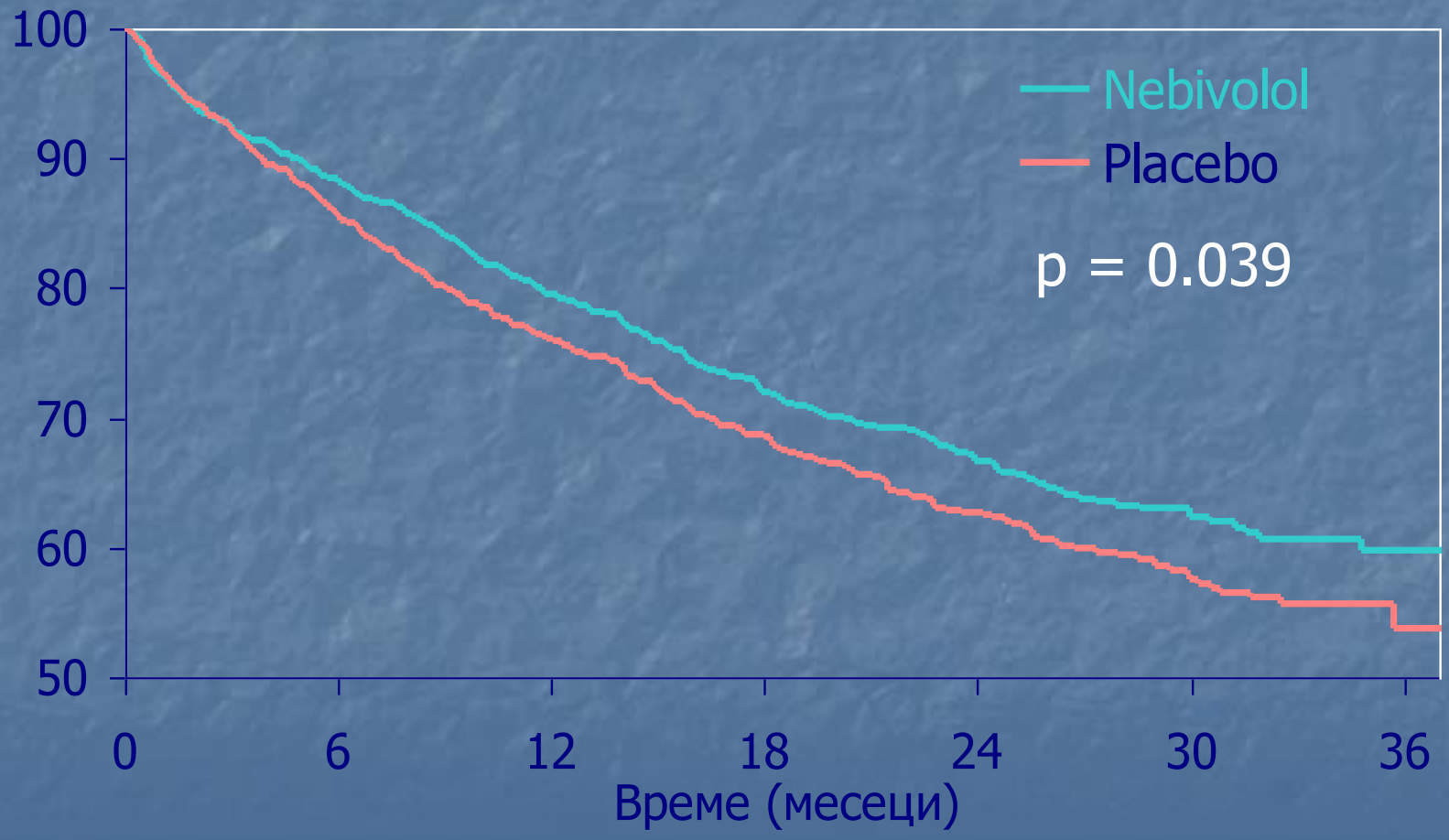
Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure

Рандомизирано, двойно-сляпо, плацебо-контролирано проучване, целящо да установи ефекта на Nebivolol върху заболеваемостта, смъртността и честотата на хоспитализациите при пациенти в напреднала възраст със СН.

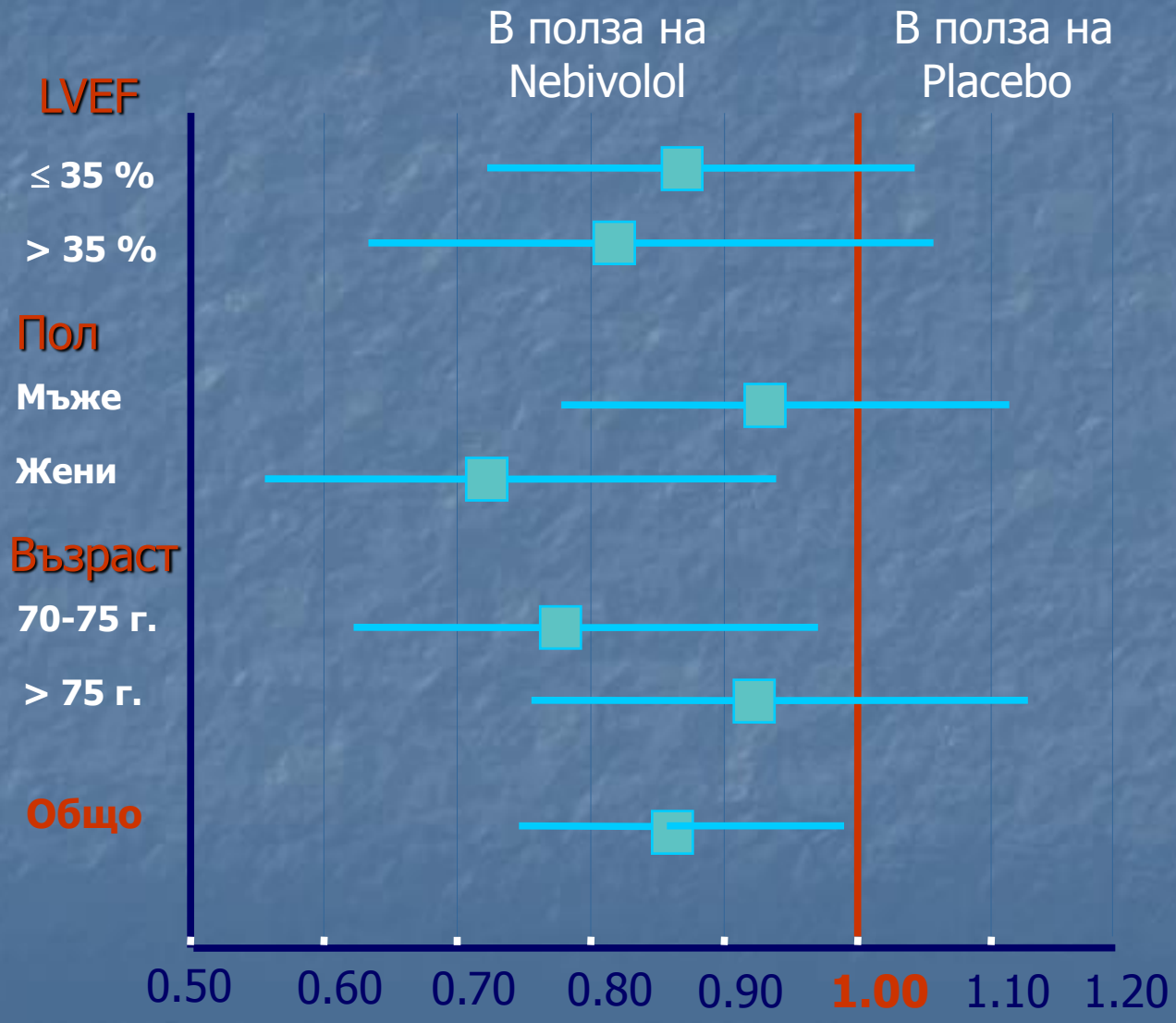
Разпределение на пациентите по възраст



Обща смъртност или хоспитализации по повод ССЗ



Смъртност или хоспитализации по повод ССЗ в подгрупите



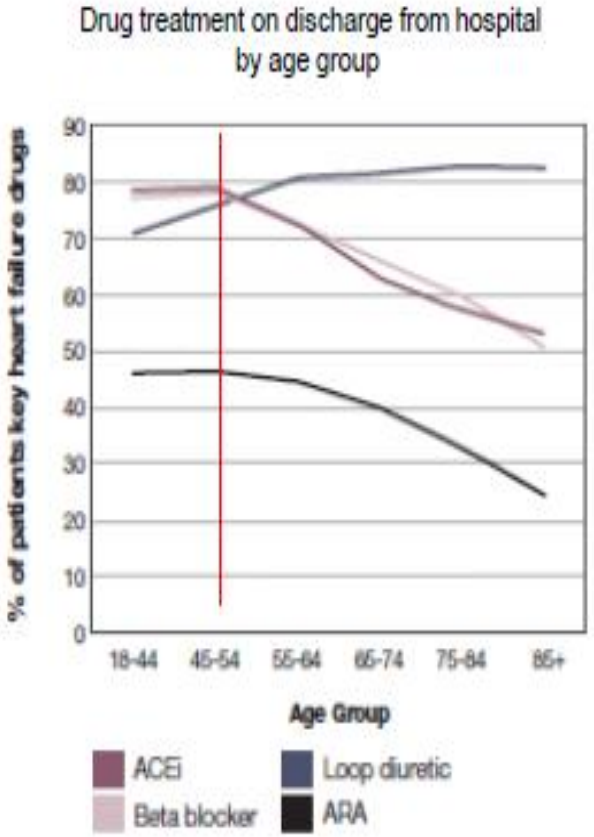
Пациенти, достигнали таргентна доз

	Patients reaching target dose
SENIORS (10 mg o.d.)	**68 %**
MERIT HF (200 mg o.d.) [1]	**64 %**
COPERNICUS (25 mg bid) [2]	**65.1%**

1 . MERIT HF Study group, Lancet 1999; 353: 2001-07;
2. Packer M et al. N Eng J Med 2001;344(22):1651-1658

NEBIVOLOL отвъд β_1-блокадата: специфични благоприятни ефекти при ХСН

- повишава УО
- намалява системното и пулмоналното съдово съпротивление
- без изразена редукция на сърдечната честота
- повишава коронарния резерв
- не нарушава вентилацията



National Heart Failure Audit 2010/11. NICOR, UCL, London 2012.

Drug issues: beware!

- Beware polypharmacy:
  - are all the other drugs necessary?
- Avoid NSAIDs if at all possible:
  - ↓renal function, fluid retention, ↓ACEI efficacy
- Beware orthostatic hypotension:
  - always do sitting and standing BP
- Beware excessive diuresis:
  - hypotension, confusion, incontinence
- May be more sensitive to BB and other HR lowering medication
- Digoxin tolerance lower than in younger patients
- Watch renal function closely, particularly with new medication or intercurrent illness:
  - Use eGFR, not just serum creatinine

ЗАКЛЮЧЕНИЕ

- В световен мащаб нараства процента на възрастните пациенти със СН
- Акцент в диагнозата са инструменталните и лабораторни методи.
- Липсват достатъчно клинични проучвания относно лечението на възрастни пациенти.
- Медикаментите прилагани за лечението на СН при възрастни са подобни на общоприетите, като в съображение влизат – намаления толеранс, редукция на дозата, бъбречна функция, коморбидност , комплексен подход.