Lo scompenso cardiaco: nuove linee guida

Dott.ssa Gaia Cattadori
UO Cardiologia Riabilitativa
Scompenso Cardiaco
H San Giuseppe
Multimedica IRCCS
MILANO

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

Developed with the special contribution of the Heart Failure Association (HFA) of the ESC

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2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America

Developed in Collaboration With the International Society for Heart and Lung Transplantation

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CARDIOPULSE

What's new in the European Society of Cardiology 2016 Guidelines for the diagnosis and treatment of acute and chronic heart failure?

Ten commandments from the 2016 ESC Guidelines for diagnosis and treatment of acute and chronic heart failure:

(1) Three groups of HF patients can be identified: HFpEF (LVEF $\geq$ 50%), HFmrEF (LVEF 40–50%), and HFrEF (LVEF $<$ 40%).

(2) Definition of HFpEF and HFmrEF requires typical symptoms/signs, elevated levels of NPs and at least one of these two criteria: relevant structural heart disease (LV hypertrophy and/or left atrial enlargement [LAE]) or diastolic dysfunction. HFrEF requires typical symptoms/signs and a LVEF $<$ 40%.

(3) Delaying or preventing the onset of HF improves prognosis. Interventions are aimed to modify risk factors or treating asymptomatic LV systolic dysfunction.

(4) ACEIs and beta-blockers are recommended for all symptomatic patients with HFrEF. They should be up-titrated to the maximum tolerated dose. MRAs are recommended in patients with HFrEF, who are symptomatic despite ACEIs and beta-blockers.

(5) A new compound, LCZ696, which combines valsartan and a neprylisin inhibitor (sacubitril) is recommended as a replacement for the ACEIs in patients with HFrEF who remain symptomatic despite ACEIs, a beta-blocker and an MRA.

(6) Diuretics should be considered in all HFrEF symptomatic patients. ARBs are recommended in HFrEF symptomatic patients unable to receive ACEIs or MRAs. Ivabradine should be considered in sinus rhythm with a heart rate $\geq$ 70 bpm despite OMT or in patients who cannot receive beta-blockers.

(7) CRT is recommended in case of LBBB and a QRS duration $\geq$ 130 ms. In case of non-LBBB, it is recommended with a QRS duration $\geq$ 150 ms and should be considered with a QRS duration 130-150 ms. In patients with atrial fibrillation and NYHA class III-IV, considering CRT is conditioned to ensure bi-ventricular pacing.

(8) Implantable cardioverter-defibrillator (ICD) is recommended in secondary prevention in all patients who are expected to survive $>$ 1 year. An ICD is recommended in all patients with LVEF $\leq$ 35%, despite 3 months of OMT and NYHA class II-III in primary prevention.

(9) In patients presenting with acute heart failure, an early initiation of appropriate treatment is of key importance.

(10) For optimal management during the early phase of AHF, the algorithm based on clinical profiles evaluating the presence of congestion and peripheral hypoperfusion should be applied

HFmrEF

Table 3.1 Definition of heart failure with preserved (HFpEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF)

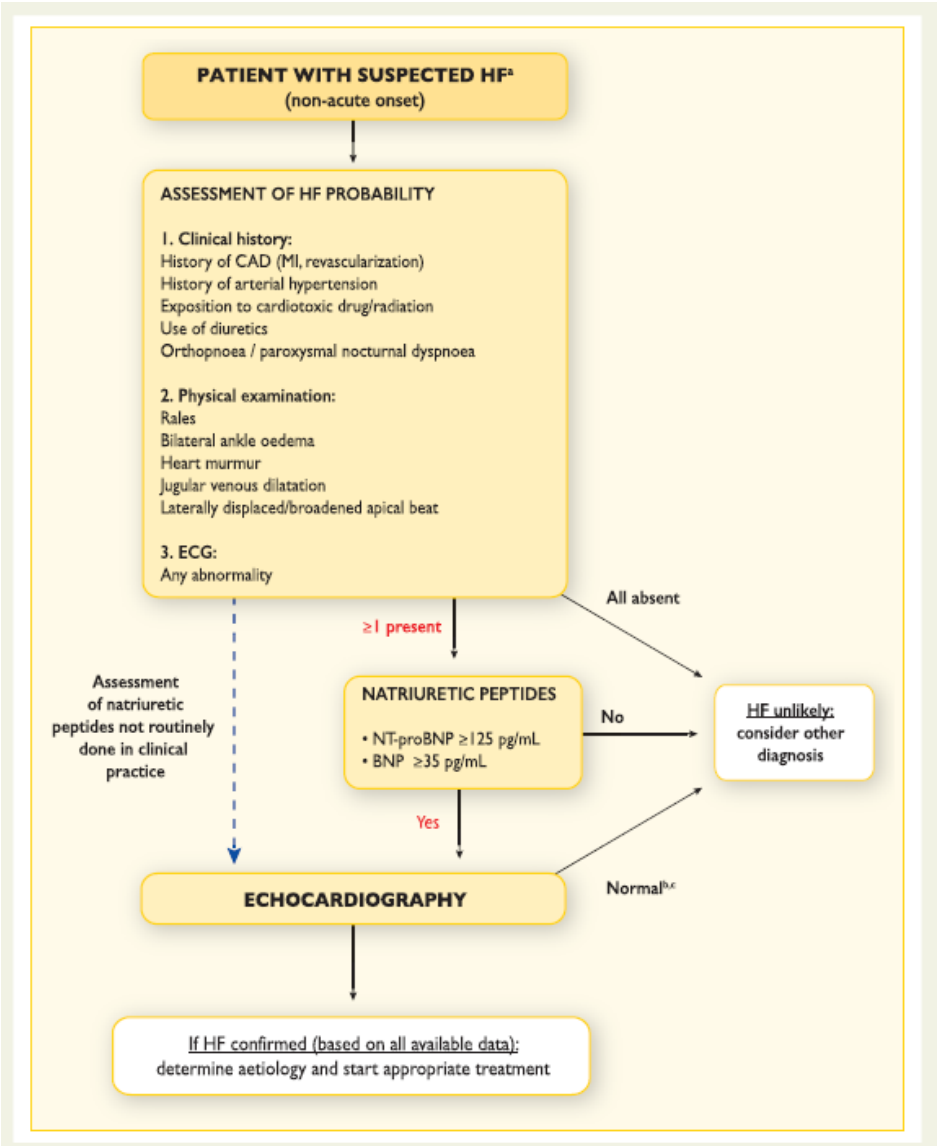
Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF <40%	LVEF 40–49%	LVEF ≥50%
	3	–	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).

BNP = B-type natriuretic peptide; HF = heart failure; HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LAE = left atrial enlargement; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; NT-proBNP = N-terminal pro-B type natriuretic peptide.

[a]Signs may not be present in the early stages of HF (especially in HFpEF) and in patients treated with diuretics.

[b]BNP > 35 pg/ml and/or NT-proBNP > 125 pg/mL.

Algoritmo diagnostico HF



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Prevenzione

Recommendations to prevent or delay the development of overt heart failure or prevent death before the onset of symptoms

Recommendations	Class[a]	Level[b]	Ref[c]
Treatment of hypertension is recommended to prevent or delay the onset of HF and prolong life.	I	A	126, 129, 150, 151
Treatment with statins is recommended in patients with or at high-risk of CAD whether or not they have LV systolic dysfunction, in order to prevent or delay the onset of HF and prolong life.	I	A	137–140, 152
Counselling and treatment for smoking cessation and alcohol intake reduction is recommended for people who smoke or who consume excess alcohol in order to prevent or delay the onset of HF.	I	C	131–134
Treating other risk factors of HF (e.g. obesity, dysglycaemia) should be considered in order to prevent or delay the onset of HF.	IIa	C	130, 141, 153–155
Empagliflozin should be considered in patients with type 2 diabetes in order to prevent or delay the onset of HF and prolong life.	IIa	B	130
ACE-I is recommended in patients with asymptomatic LV systolic dysfunction and a history of myocardial infarction in order to prevent or delay the onset of HF and prolong life.	I	A	5, 144, 145
ACE-I is recommended in patients with asymptomatic LV systolic dysfunction without a history of myocardial infarction, in order to prevent or delay the onset of HF.	I	B	5
ACE-I should be considered in patients with stable CAD even if they do not have LV systolic dysfunction, in order to prevent or delay the onset of HF.	IIa	A	142
Beta-blocker is recommended in patients with asymptomatic LV systolic dysfunction and a history of myocardial infarction, in order to prevent or delay the onset of HF or prolong life.	I	B	146
ICD is recommended in patients: a) with asymptomatic LV systolic dysfunction (LVEF ≤30%) of ischaemic origin, who are at least 40 days after acute myocardial infarction; b) with asymptomatic non-ischaemic dilated cardiomyopathy (LVEF ≤30%), who receive OMT therapy. In order to prevent sudden death and prolong life.	I	B	149, 156–158

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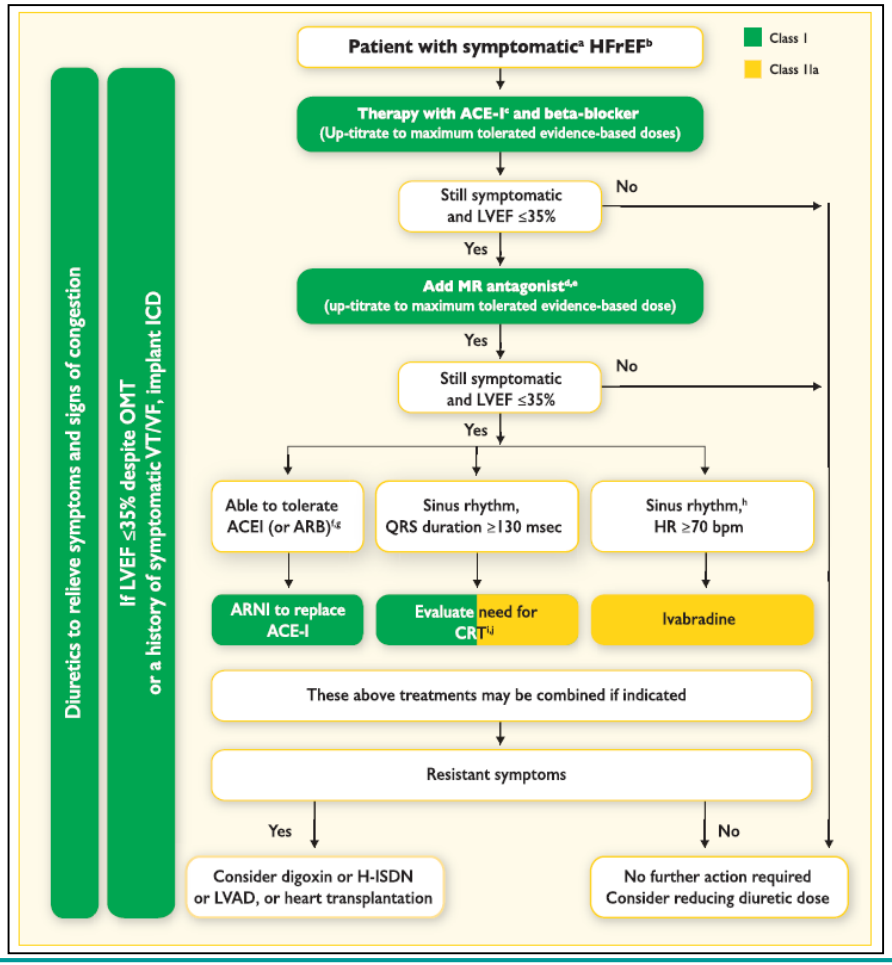
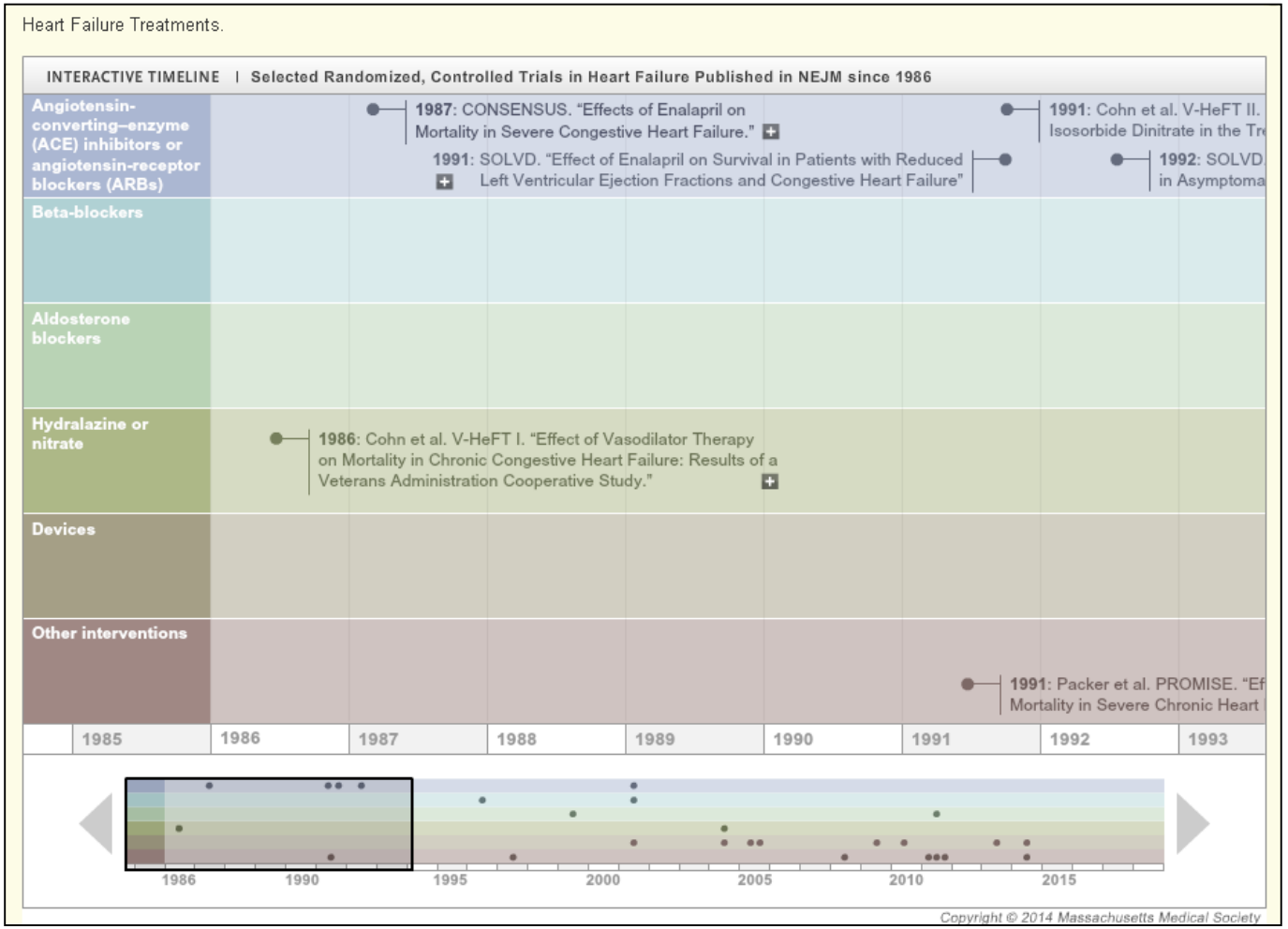


Paradigm Shifts in Heart-Failure Therapy — A Timeline

Chana A. Sacks, M.D., John A. Jarcho, M.D., and Gregory D. Curfman, M.D.

N ENGL J MED 371;11 NEJM.ORG SEPTEMBER 11, 2014

Heart Failure Treatments.



Heart Failure Treatments.

EFFECTS OF ENALAPRIL ON MORTALITY IN SEVERE CONGESTIVE HEART FAILURE

Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS)

THE CONSENSUS TRIAL STUDY GROUP*

Abstract To evaluate the influence of the angiotensin-converting-enzyme inhibitor enalapril (2.5 to 40 mg per day) on the prognosis of severe congestive heart failure (New York Heart Association [NYHA] functional class IV), we randomly assigned 253 patients in a double-blind study to receive either placebo (n = 126) or enalapril (n = 127). Conventional treatment for heart failure, including the use of other vasodilators, was continued in both groups. Follow-up averaged 188 days (range, 1 day to 20 months). The crude mortality at the end of six months (primary end point) was 26 percent in the enalapril group and 44 percent in the placebo group — a reduction of 40 percent (P = 0.002). Mortality was reduced by 31 percent at one year (P = 0.001). By the end of the study, there had been 68 deaths in the placebo group and 50 in the enalapril group — a reduction of 27 percent (P = 0.003). The entire reduction in total mortality was found to be among patients with progressive heart failure (a reduction of 50 percent), whereas no difference was seen in the incidence of sudden cardiac death.

A significant improvement in NYHA classification was observed in the enalapril group, together with a reduction in heart size and a reduced requirement for other medication for heart failure. The overall withdrawal rate was similar in both groups, but hypotension requiring withdrawal occurred in seven patients in the enalapril group and in no patients in the placebo group. After the initial dose of enalapril was reduced to 2.5 mg daily in high-risk patients, this side effect was less frequent.

We conclude that the addition of enalapril to conventional therapy in patients with severe congestive heart failure can reduce mortality and improve symptoms. The beneficial effect on mortality is due to a reduction in death from the progression of heart failure. (N Engl J Med 1987; 316:1429-35.)

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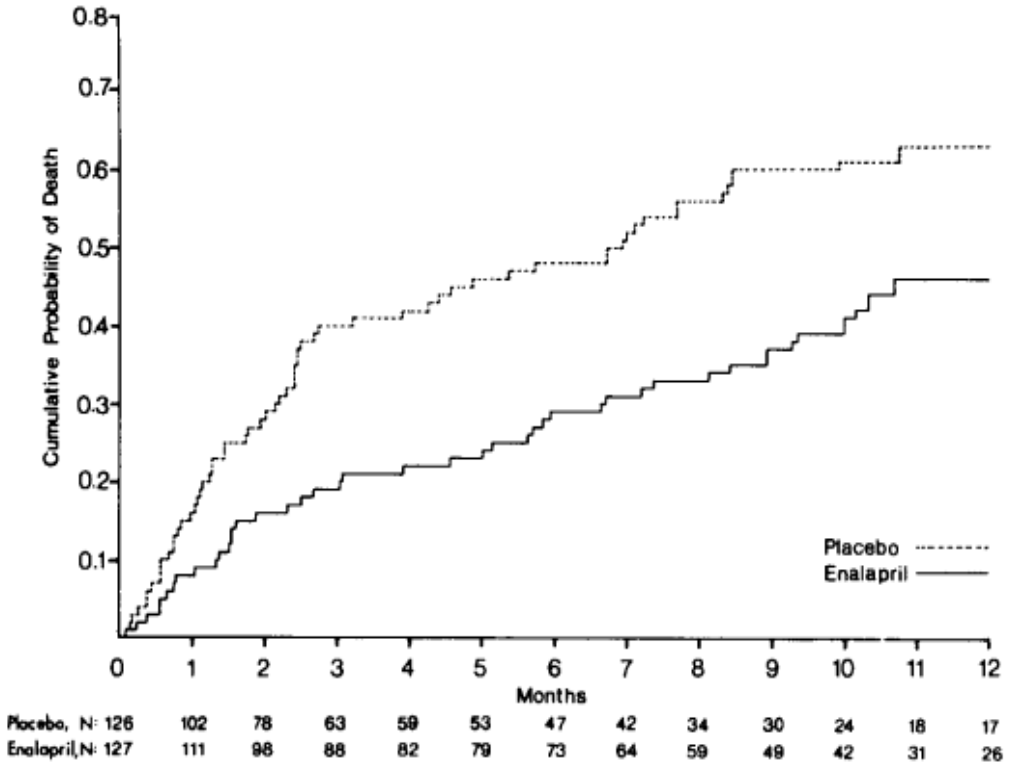


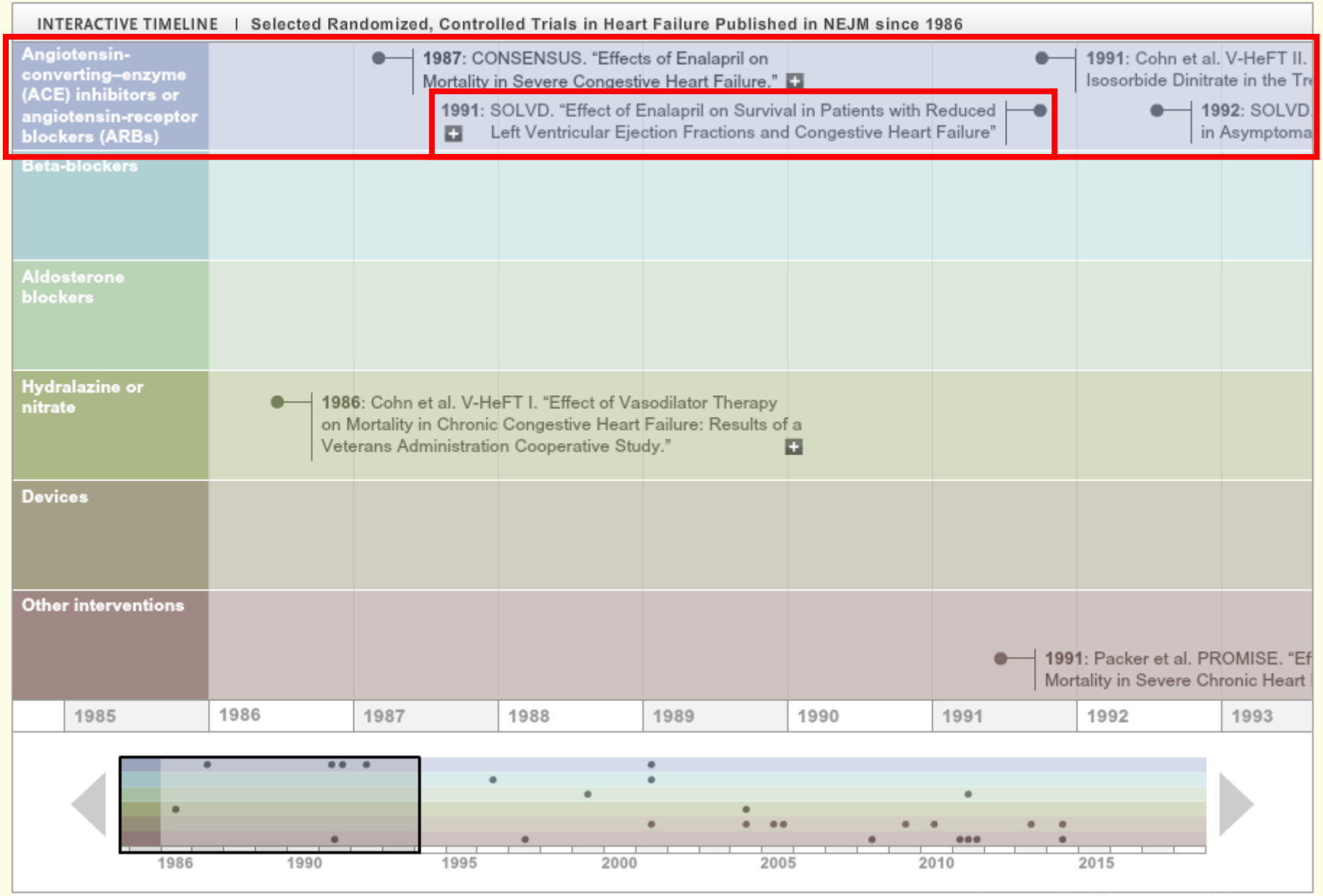
Figure 1. Cumulative Probability of Death in the Placebo and Enalapril Groups.

Table 2. Mortality from Any Cause in the Two Groups.*

	Treatment Group				Reduction in Relative Risk	P Value (Life-Table Analysis)
	Placebo (N = 126)		Enalapril (N = 127)			
	no.	%	no.	%	%	
Mortality at six months (180 days)	55	44	33	26	40	0.002
Mortality at one year (360 days)	66	52	46	36	31	0.001
Total mortality	68	54	50	39	27	0.003

*In the placebo group, the mean period of follow-up was 237 days among the 58 survivors and 93 days among the 68 patients who died, for an overall mean of 160 days. In the enalapril group, the mean period of follow-up was 260 days among the 77 survivors and 147 days among the 50 patients who died, for an overall mean of 215 days.

Heart Failure Treatments.



EFFECT OF ENALAPRIL ON SURVIVAL IN PATIENTS WITH REDUCED LEFT VENTRICULAR EJECTION FRACTIONS AND CONGESTIVE HEART FAILURE

THE SOLVD INVESTIGATORS*

Abstract *Background.* Patients with congestive heart failure have a high mortality rate and are also hospitalized frequently. We studied the effect of an angiotensin-converting–enzyme inhibitor, enalapril, on mortality and hospitalization in patients with chronic heart failure and ejection fractions ≤0.35.

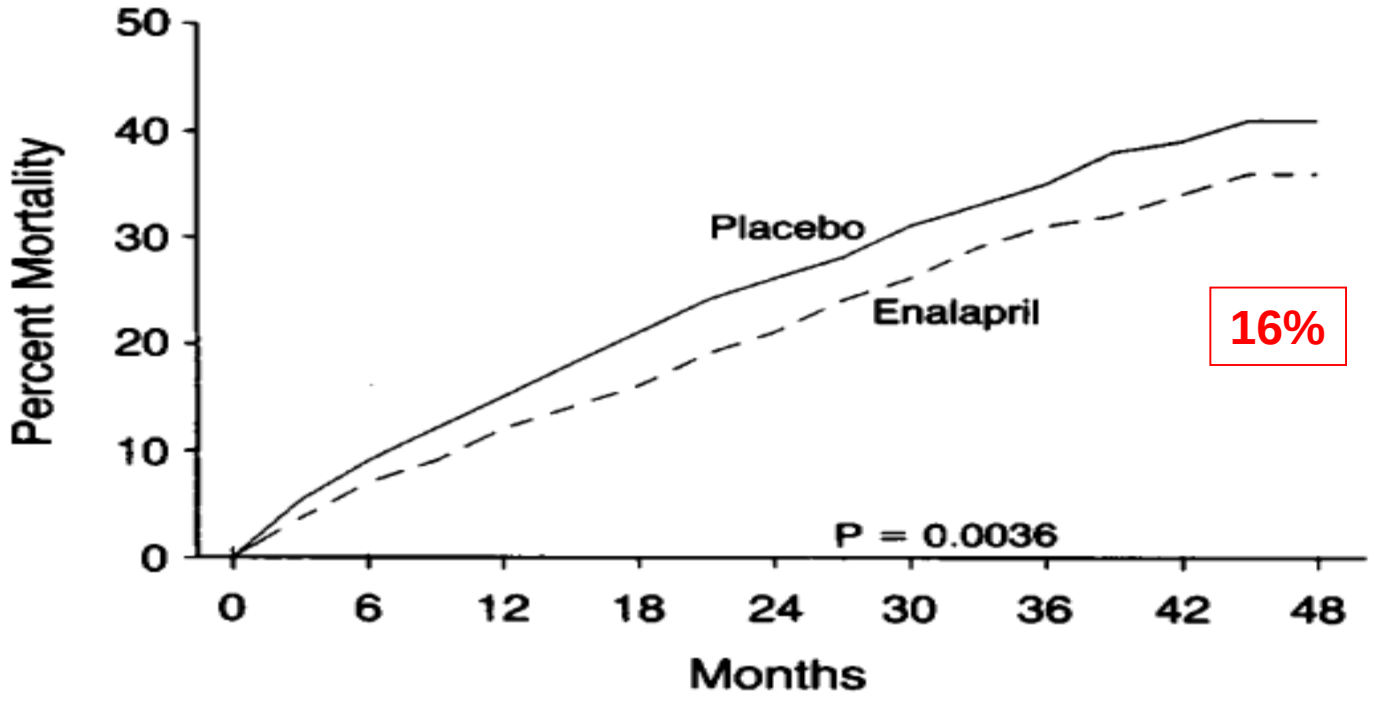
Methods. Patients receiving conventional treatment for heart failure were randomly assigned to receive either placebo (n = 1284) or enalapril (n = 1285) at doses of 2.5 to 20 mg per day in a double-blind trial. Approximately 90 percent of the patients were in New York Heart Association functional classes II and III. The follow-up averaged 41.4 months.

Results. There were 510 deaths in the placebo group (39.7 percent), as compared with 452 in the enalapril group (35.2 percent) (reduction in risk, 16 percent; 95 percent confidence interval, 5 to 26 percent; P = 0.0036). Although reductions in mortality were observed in several categories of cardiac deaths, the largest reduction occurred among the deaths attributed to progressive heart failure (251 in the placebo group vs. 209 in the enalapril group; reduction in risk, 22 percent; 95 percent confidence interval, 6 to 35 percent). There was little apparent effect of treatment on deaths classified as due to arrhythmia without pump failure. Fewer patients died or were hospitalized for worsening heart failure (736 in the placebo group and 613 in the enalapril group; risk reduction, 26 percent; 95 percent confidence interval, 18 to 34 percent; P<0.0001).

Conclusions. The addition of enalapril to conventional therapy significantly reduced mortality and hospitalizations for heart failure in patients with chronic congestive heart failure and low ejection fractions. (N Engl J Med 1991; 325:293-302.)

EFFECT OF ENALAPRIL ON SURVIVAL IN PATIENTS WITH REDUCED LEFT VENTRICULAR EJECTION FRACTIONS AND CONGESTIVE HEART FAILURE

THE SOLVD INVESTIGATORS*



Placebo	1284	1159	1085	1005	939	819	669	487	299
Enalapril	1285	1195	1127	1069	1010	891	697	526	333

Figure 1. Mortality Curves in the Placebo and Enalapril Groups.

Heart Failure Treatments.

EFFECT OF ENALAPRIL ON MORTALITY AND THE DEVELOPMENT OF HEART FAILURE IN ASYMPTOMATIC PATIENTS WITH REDUCED LEFT VENTRICULAR EJECTION FRACTIONS

THE SOLVD INVESTIGATORS*

Abstract *Background.* It is not known whether the treatment of patients with asymptomatic left ventricular dysfunction reduces mortality and morbidity. We studied the effect of an angiotensin-converting–enzyme inhibitor, enalapril, on total mortality and mortality from cardiovascular causes, the development of heart failure, and hospitalization for heart failure among patients with ejection fractions of 0.35 or less who were not receiving drug treatment for heart failure.

Methods. Patients were randomly assigned to receive either placebo (n = 2117) or enalapril (n = 2111) at doses of 2.5 to 20 mg per day in a double-blind trial. Follow-up averaged 37.4 months.

Results. There were 334 deaths in the placebo group, as compared with 313 in the enalapril group (reduction in risk, 8 percent by the log-rank test; 95 percent confidence interval, −8 percent [an increase of 8 percent] to 21 percent; P = 0.30). The reduction in mortality from cardiovascular causes was larger but was not statistically significant (298 deaths in the placebo group vs. 265 in the enalapril group; risk reduction, 12 percent; 95 percent confidence interval, −3 to 26 percent; P = 0.12). When we combined patients in whom heart failure developed and those who died, the total number of deaths and cases of heart failure was lower in the enalapril group than in the placebo group (630 vs. 818; risk reduction, 29 percent; 95 percent confidence interval, 21 to 36 percent; P<0.001). In addition, fewer patients given enalapril died or were hospitalized for heart failure (434 in the enalapril group vs. 518 in the placebo group; risk reduction, 20 percent; 95 percent confidence interval, 9 to 30 percent; P<0.001).

Conclusions. The angiotensin-converting–enzyme inhibitor enalapril significantly reduced the incidence of heart failure and the rate of related hospitalizations, as compared with the rates in the group given placebo, among patients with asymptomatic left ventricular dysfunction. There was also a trend toward fewer deaths due to cardiovascular causes among the patients who received enalapril. (N Engl J Med 1992;327:685-91.)

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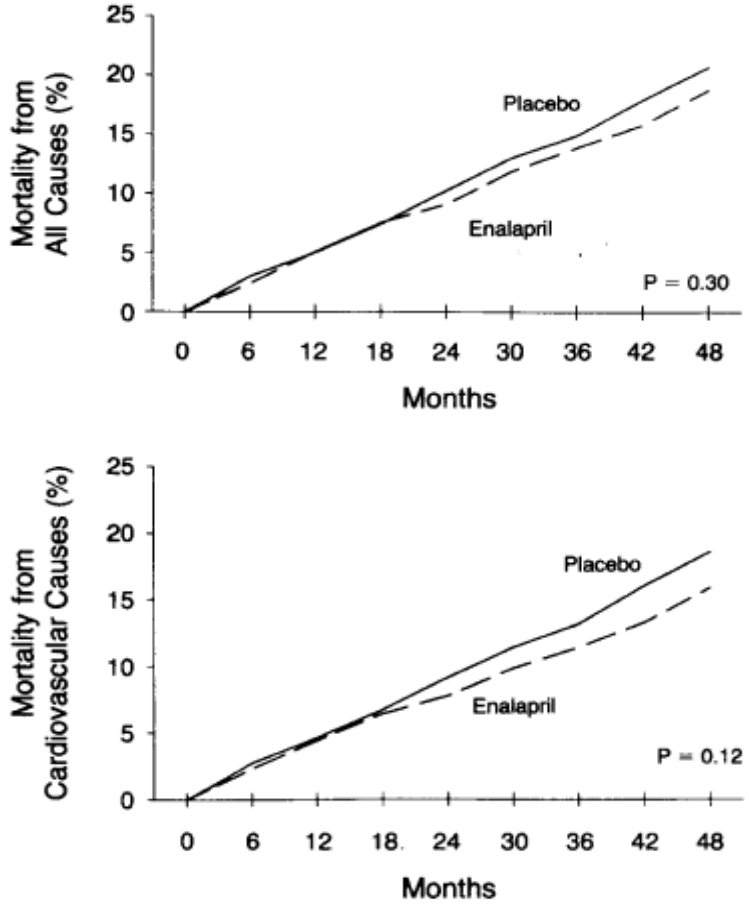

Figure 1. Total Mortality (Upper Panel) and Mortality from Cardiovascular Causes (Lower Panel) in the Prevention Trial.

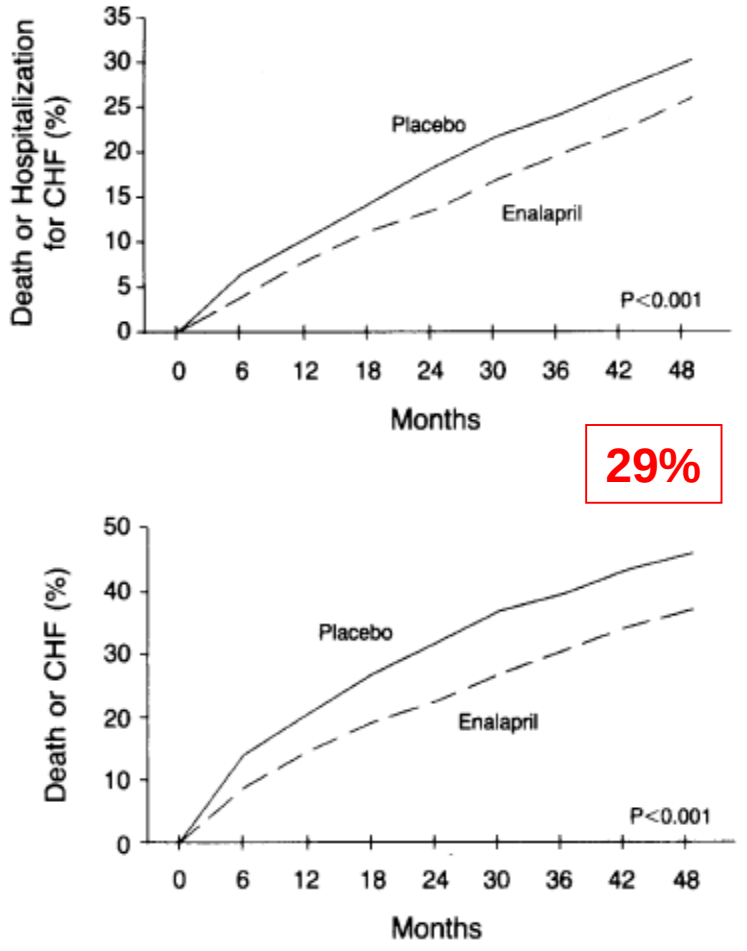

Figure 2. Death or Hospitalization for Congestive Heart Failure (CHF) and Death or Development of Heart Failure in the Prevention Trial.

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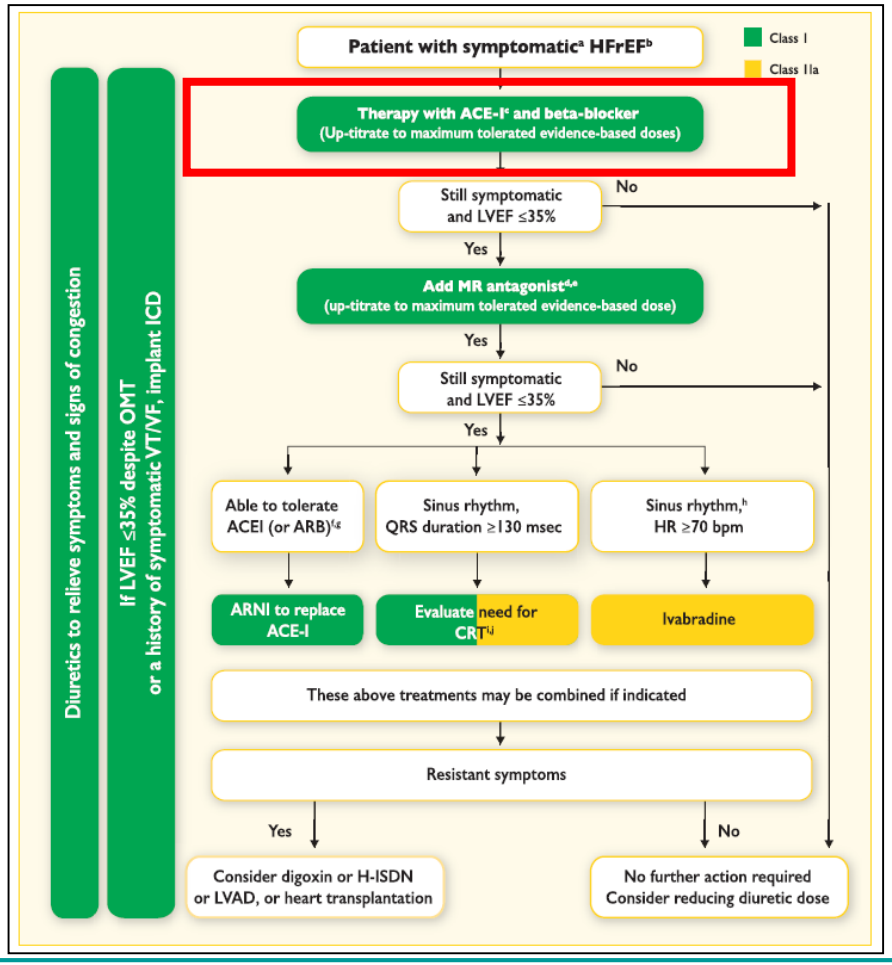

Heart Failure Treatments.

THE EFFECT OF CARVEDILOL ON MORBIDITY AND MORTALITY IN PATIENTS WITH CHRONIC HEART FAILURE

MILTON PACKER, M.D., MICHAEL R. BRISTOW, M.D., PH.D., JAY N. COHN, M.D., WILSON S. COLUCCI, M.D., MICHAEL B. FOWLER, M.B., B.S., EDWARD M. GILBERT, M.D., AND NEIL H. SHUSTERMAN, M.D., FOR THE U.S. CARVEDILOL HEART FAILURE STUDY GROUP*

Abstract *Background.* Controlled clinical trials have shown that beta-blockers can produce hemodynamic and symptomatic improvement in chronic heart failure, but the effect of these drugs on survival has not been determined.

Methods. We enrolled 1094 patients with chronic heart failure in a double-blind, placebo-controlled, stratified program, in which patients were assigned to one of four treatment protocols on the basis of their exercise capacity. Within each of the four protocols patients with mild, moderate, or severe heart failure with left ventricular ejection fractions ≤0.35 were randomly assigned to receive either placebo (n=398) or the beta-blocker carvedilol (n=696); background therapy with digoxin, diuretics, and an angiotensin-converting–enzyme inhibitor remained constant. Patients were observed for the occurrence of death or hospitalization for cardiovascular reasons during the following 6 months (12 months for the group with mild heart failure).

Results. The overall mortality rate was 7.8 percent in the placebo group and 3.2 percent in the carvedilol group; the reduction in risk attributable to carvedilol was 65 percent (95 percent confidence interval, 39 to 80 percent; $P<0.001$). This finding led the Data and Safety Monitoring Board to recommend termination of the study before its scheduled completion. In addition, as compared with placebo, carvedilol therapy was accompanied by a 27 percent reduction in the risk of hospitalization for cardiovascular causes (19.6 percent vs. 14.1 percent, $P=0.036$), as well as a 38 percent reduction in the combined risk of hospitalization or death (24.6 percent vs. 15.8 percent, $P<0.001$). Worsening heart failure as an adverse reaction during treatment was less frequent in the carvedilol group than in the placebo group.

Conclusions. Carvedilol reduces the risk of death as well as the risk of hospitalization for cardiovascular causes in patients with heart failure who are receiving treatment with digoxin, diuretics, and an angiotensin-converting–enzyme inhibitor. (N Engl J Med 1996;334:1349-55.)

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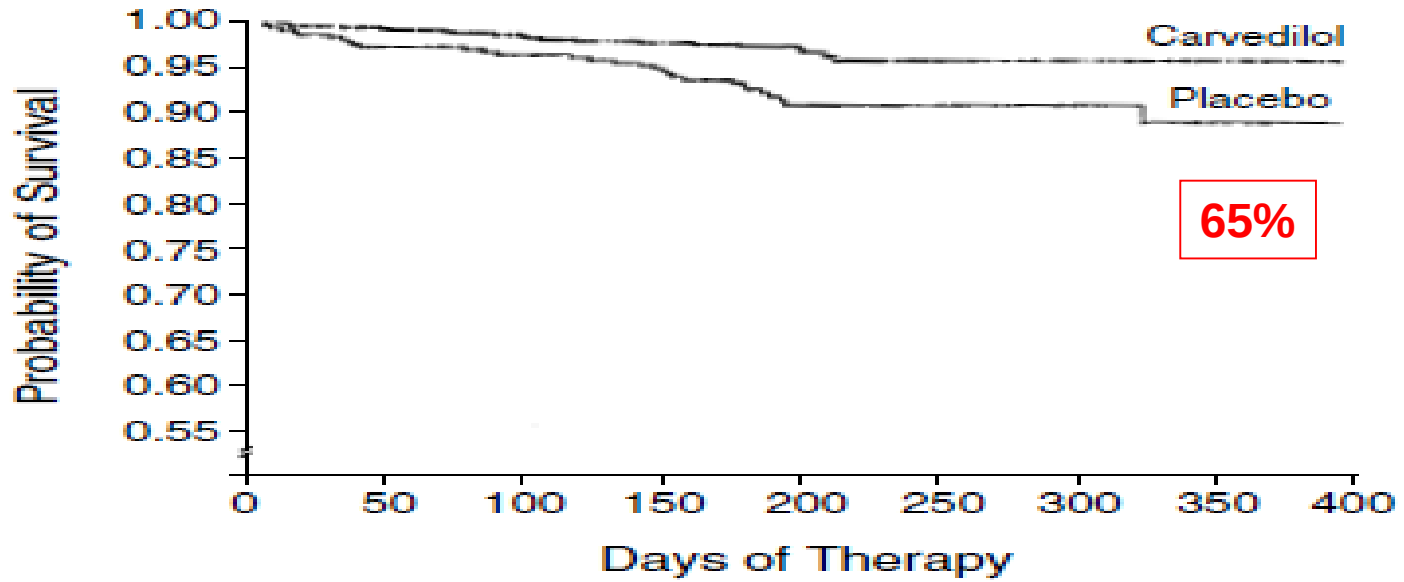
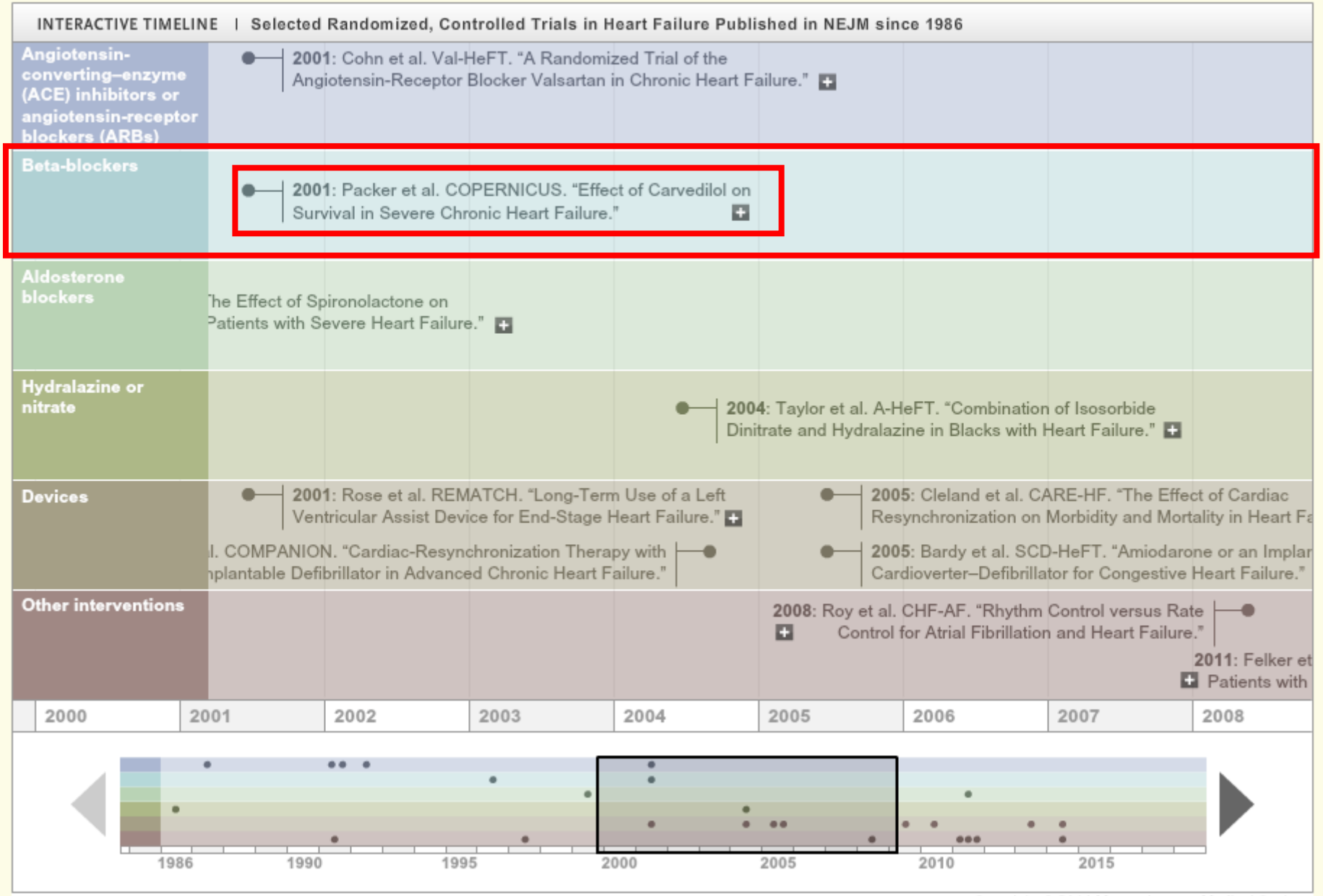


No. at Risk									
Placebo	398	353	329	305	163	71	55	43	3
Carvedilol	696	637	581	546	314	131	106	83	11

Figure 1. Kaplan–Meier Analysis of Survival among Patients with Chronic Heart Failure in the Placebo and Carvedilol Groups.

Patients in the carvedilol group had a 65 percent lower risk of death than patients in the placebo group ($P<0.001$).

Heart Failure Treatments.



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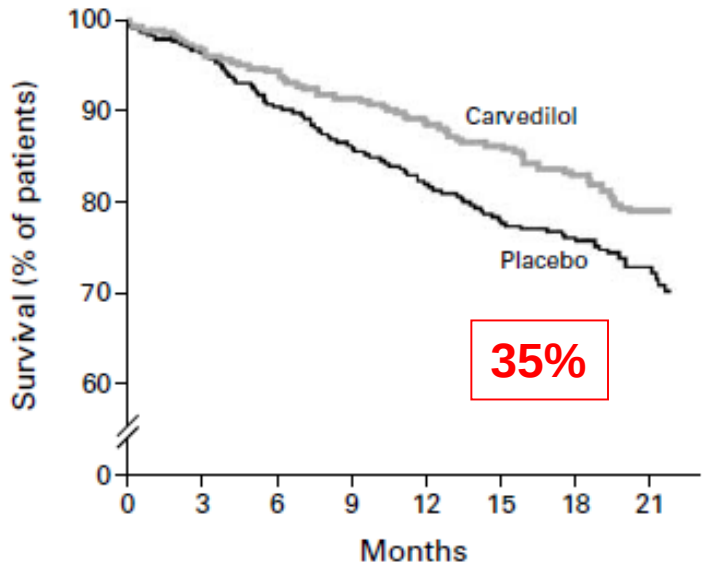
EFFECT OF CARVEDILOL ON SURVIVAL IN SEVERE CHRONIC HEART FAILURE

MILTON PACKER, M.D., ANDREW J.S. COATS, M.D., MICHAEL B. FOWLER, M.D., HUGO A. KATUS, M.D., HENRY KRUM, M.B., B.S., PH.D., PAUL MOHACSI, M.D., JEAN L. ROULEAU, M.D., MICHAL TENDERA, M.D., ALAIN CASTAIGNE, M.D., ELLEN B. ROECKER, PH.D., MELISSA K. SCHULTZ, M.S., AND DAVID L. DEMETS, PH.D., FOR THE CARVEDILOL PROSPECTIVE RANDOMIZED CUMULATIVE SURVIVAL STUDY GROUP*

The New England Journal of Medicine

VOLUME 344 MAY 31, 2001 NUMBER 22

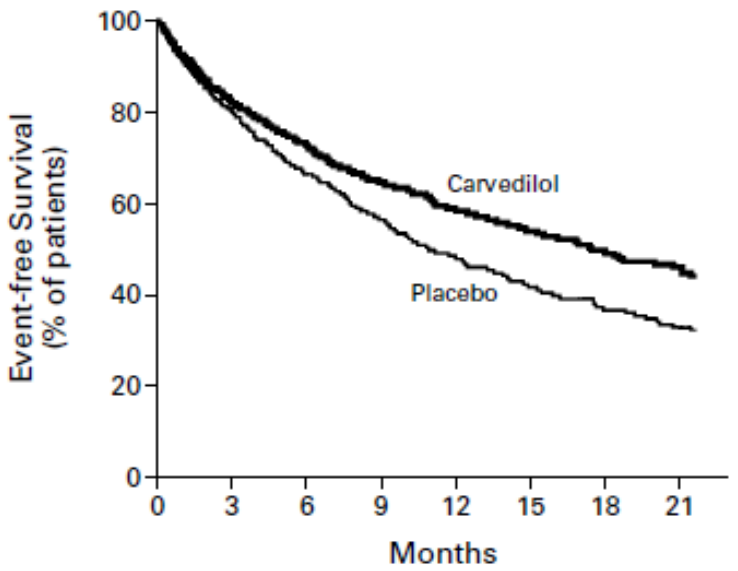


No. of Patients at Risk

Placebo	1133	937	703	580	446	286	183	114
Carvedilol	1156	947	733	620	479	321	208	142

Figure 1. Kaplan–Meier Analysis of Time to Death in the Placebo Group and the Carvedilol Group.

The 35 percent lower risk in the carvedilol group was significant: P=0.00013 (unadjusted) and P=0.0014 (adjusted).



No. of Patients at Risk

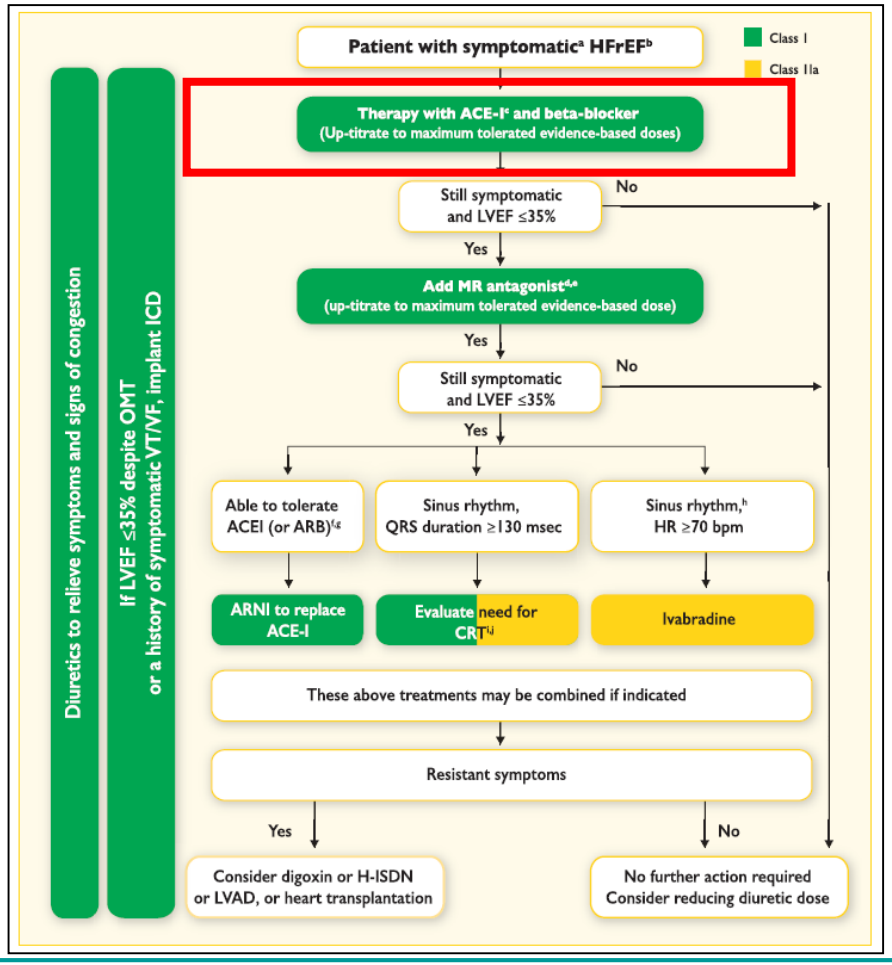
Placebo	1133	767	513	377	262	154	88	55
Carvedilol	1156	789	559	431	318	208	122	81

Figure 2. Kaplan–Meier Analysis of Time to Death or First Hospitalization for Any Reason in the Placebo Group and the Carvedilol Group.

The 24 percent lower risk in the carvedilol group was significant (P<0.001).

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)



11.14 Lung disease (including asthma and chronic obstructive pulmonary disease)

The diagnosis of COPD and asthma may be difficult in patients with HF, due to overlap in symptoms and signs, but also problems in the interpretation of spirometry, especially in HFpEF.[48,49,391] COPD (and asthma) in patients with HF may be overdiagnosed.[481] Spirometry should be performed when patients have been stable and euvolaemic for at least 3 months, to avoid the confounding effect of pulmonary congestion causing external obstruction of alveoli and bronchioles.[482] Both correctly and incorrectly labelled COPD are associated with worse functional status and a worse prognosis in HF.[48,49]

Beta-blockers are only relatively contraindicated in asthma, but not in COPD, although a more selective β1-adrenoceptor antagonist (i.e. bisoprolol, metoprolol succinate, or nebivolol) is preferred.[48,49,391] The contraindication to beta-blockers in asthma, as mentioned on pharmacy leaflets, is based on small case series published in the 1980s and late 1990s with very high initial dosages in young patients with severe asthma. In clinical practice, starting with low doses of cardioselective beta-blockers combined with close monitoring for signs of airway obstruction (wheezing, shortness of breath with lengthening of the expiration) may allow the use of profoundly effective beta-blockers in HFrEF, especially in older people where true severe asthma is uncommon. Therefore, according to the 2015 GINA global strategy report,[395,396] asthma is not an *absolute* contraindication, but these medications should only be used under close medical supervision by a specialist, with consideration of the risks for and against their use. The long-term safety of cardioactive inhaled pulmonary drugs is uncertain and the need for their use should be reconsidered in patients with HFrEF, especially as their benefit in asthma and COPD may be symptomatic only without a clear effect on mortality. Oral corticosteroids can cause sodium and water retention, potentially leading to worsening of HF, but this is not believed to be a problem with inhaled corticosteroids. Pulmonary hypertension can complicate severe long-standing COPD, which, as a result, makes right-sided HF and congestion more likely. Non-invasive ventilation, added to conventional therapy, improves the outcome of patients with acute respiratory failure due to hypercapnic exacerbation of COPD or HF in situations of acute pulmonary oedema.

Heart Failure Treatments.

The New England
Journal of Medicine

VOLUME 341 SEPTEMBER 2, 1999 NUMBER 10

THE EFFECT OF SPIRONOLACTONE ON MORBIDITY AND MORTALITY IN PATIENTS WITH SEVERE HEART FAILURE

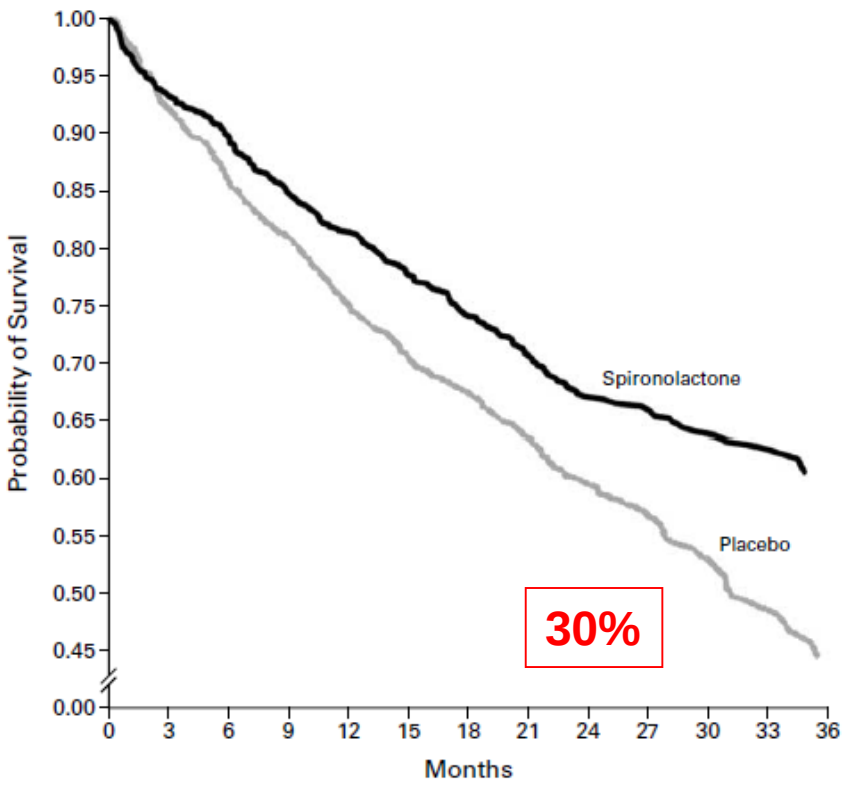
BERTRAM PITT, M.D., FAIEZ ZANNAD, M.D., WILLEM J. REMME, M.D., ROBERT CODY, M.D., ALAIN CASTAIGNE, M.D., ALFONSO PEREZ, M.D., JOLIE PALENSKY, M.S., AND JANET WITTES, PH.D., FOR THE RANDOMIZED ALDACTONE EVALUATION STUDY INVESTIGATORS*

The New England Journal of Medicine

VOLUME 341 SEPTEMBER 2, 1999 NUMBER 10

THE ITY

BERTRAM F GNE, M.D.,



No. at Risk

Placebo	841	775	723	678	628	592	565	483	379	280	179	92	36
Spironolactone	822	766	739	698	669	639	608	526	419	316	193	122	43

Figure 1. Kaplan–Meier Analysis of the Probability of Survival among Patients in the Placebo Group and Patients in the Spironolactone Group.

The risk of death was 30 percent lower among patients in the spironolactone group than among patients in the placebo group ($P<0.001$).

Gruppo MultiMedica

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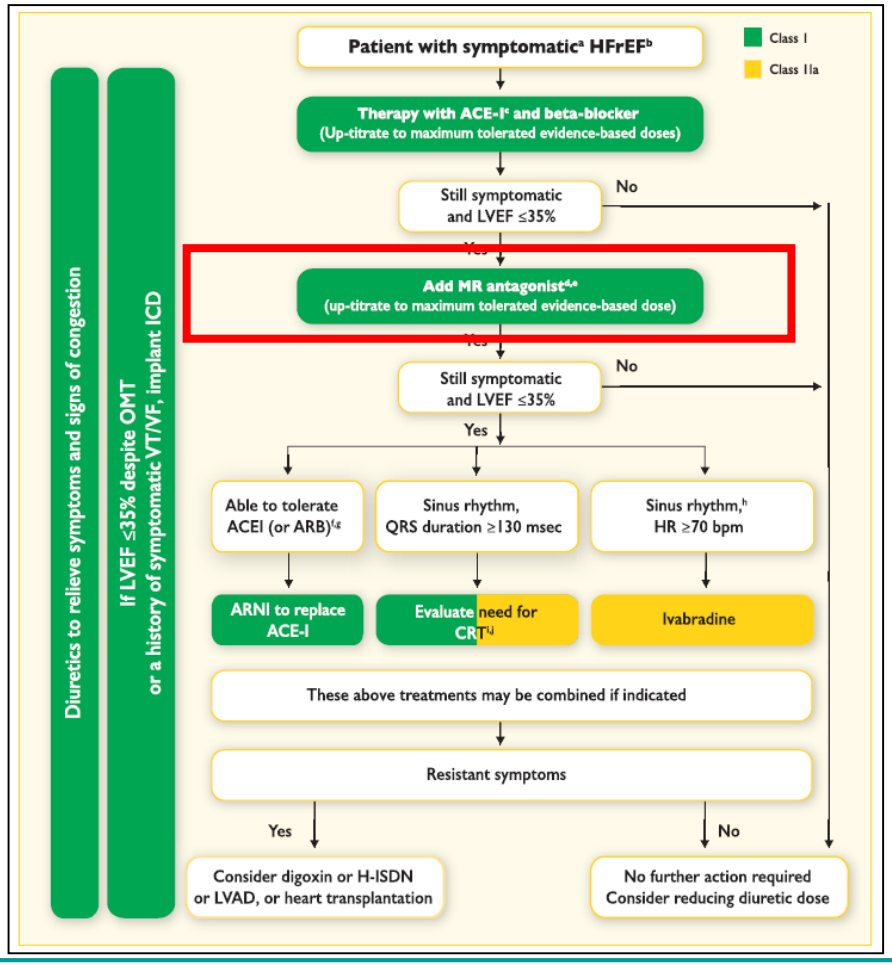
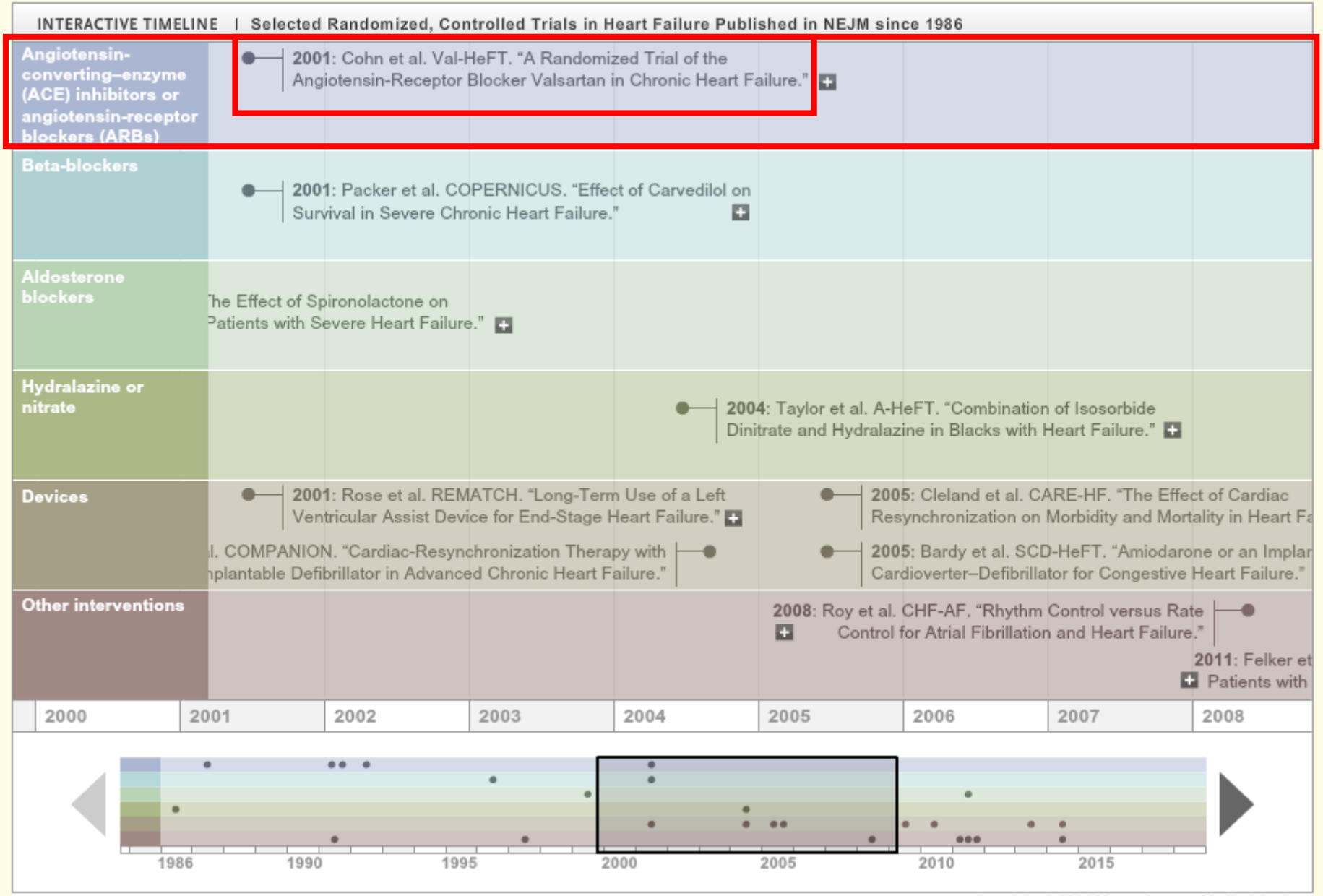
The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)



Heart Failure Treatments.



A RANDOMIZED TRIAL OF THE ANGIOTENSIN-RECEPTOR BLOCKER VALSARTAN IN CHRONIC HEART FAILURE

JAY N. COHN, M.D., AND GIANNI TOGNONI, M.D., FOR THE VALSARTAN HEART FAILURE TRIAL INVESTIGATORS*

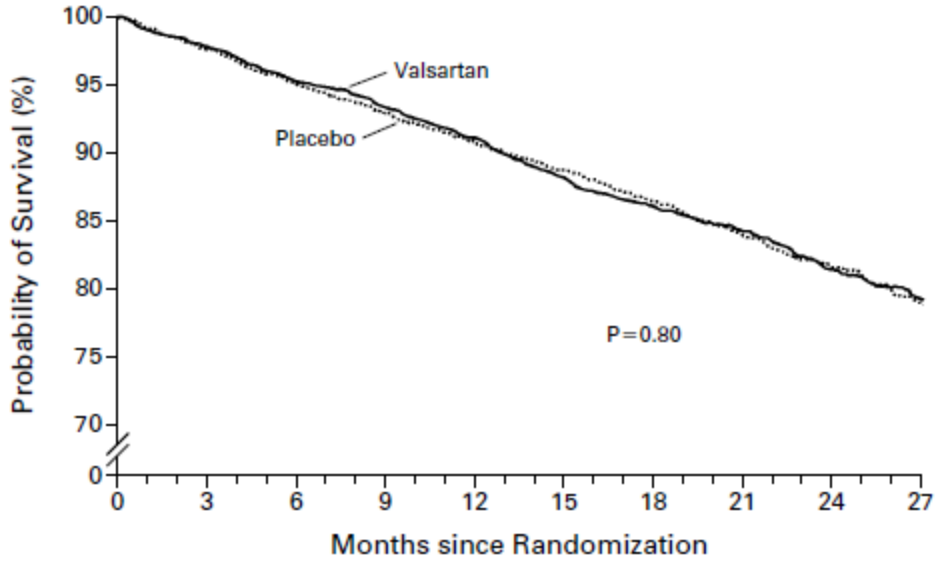
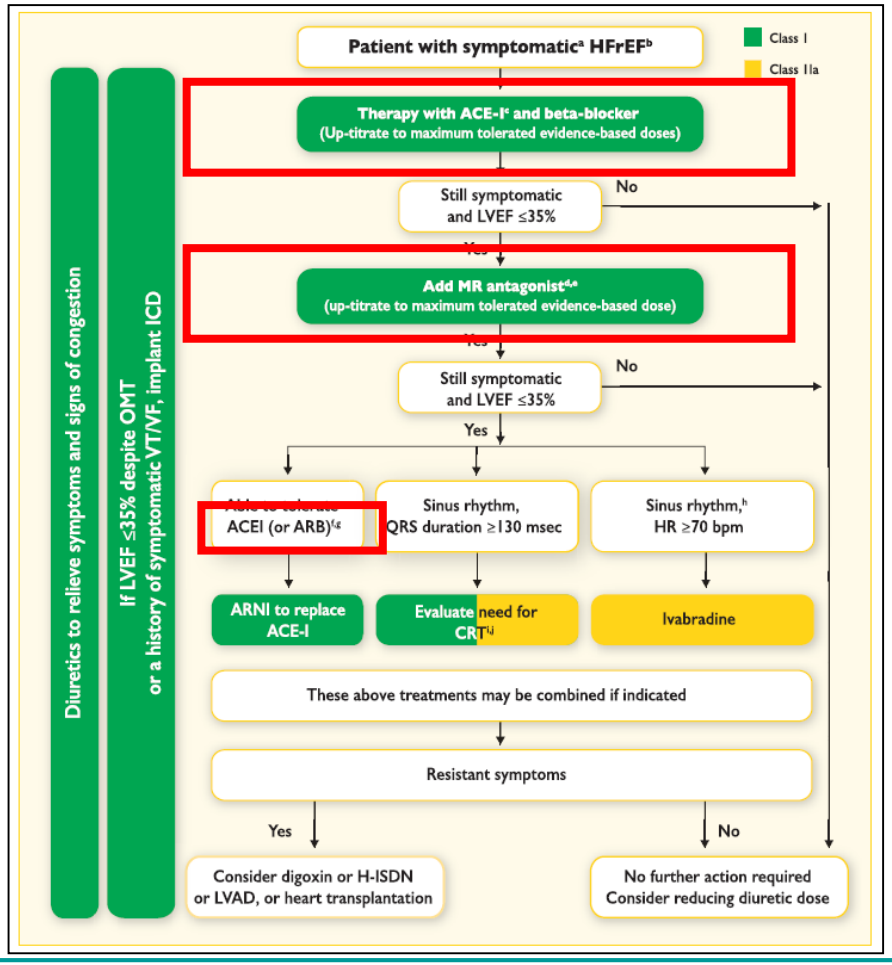


Figure 1. Kaplan–Meier Analysis of the Probability of Survival.

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)



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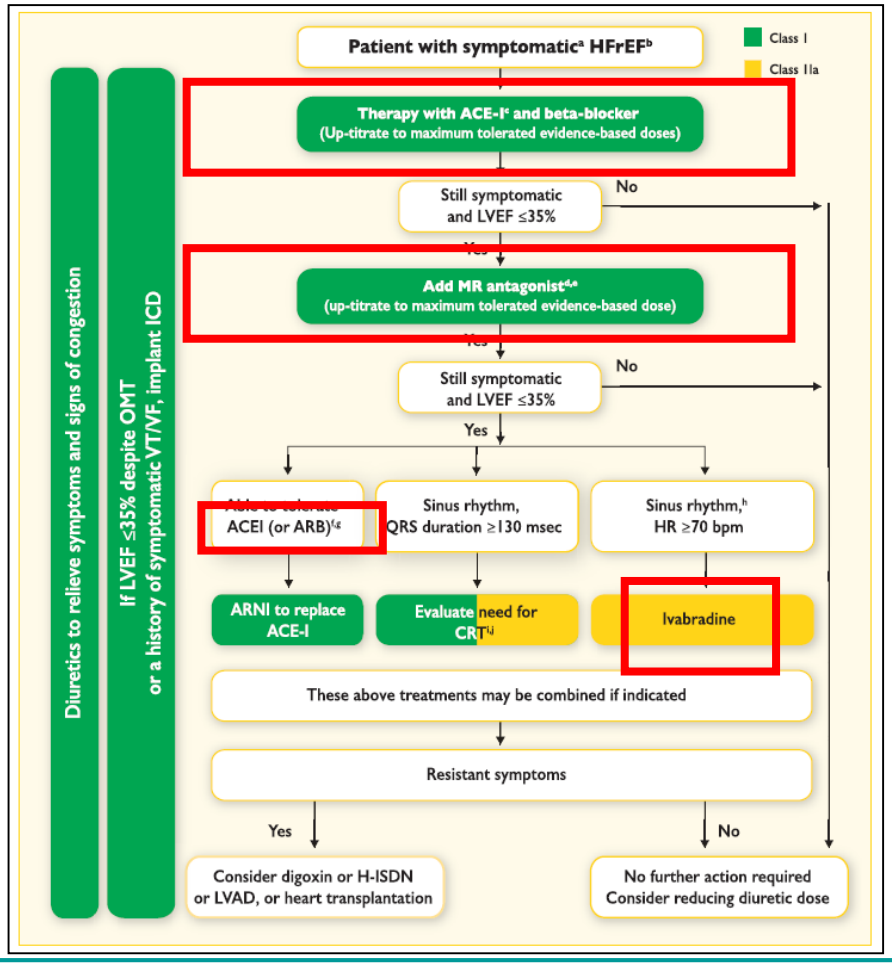

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2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

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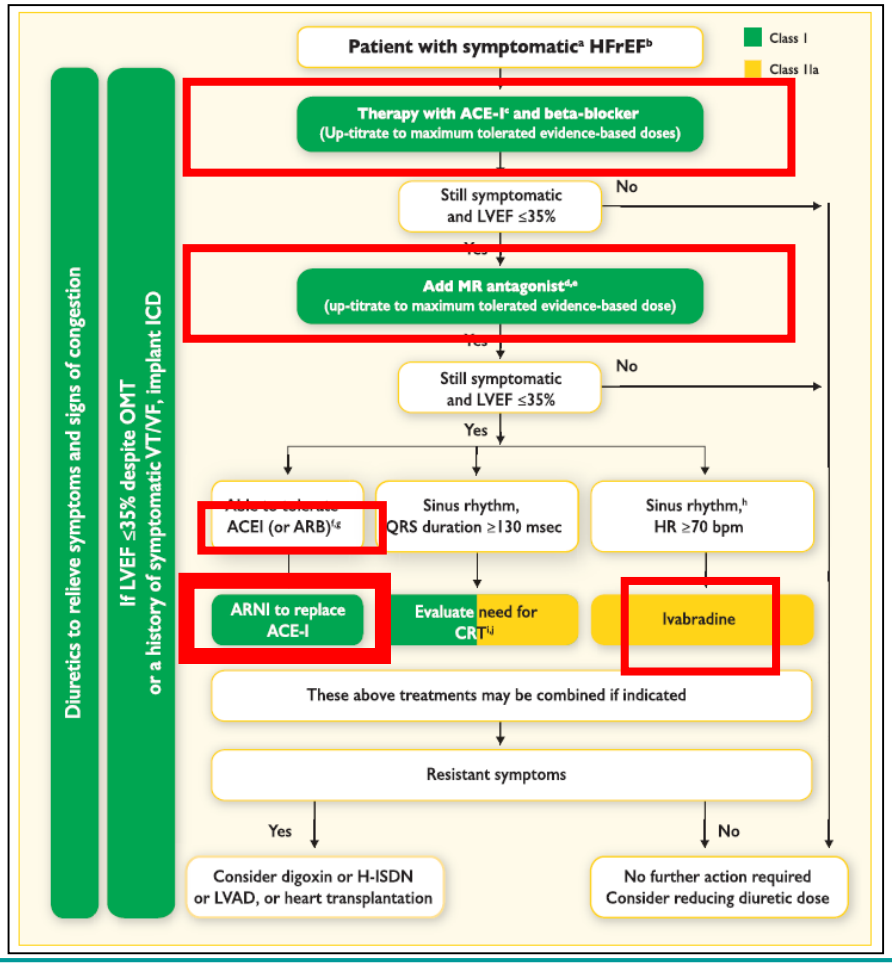
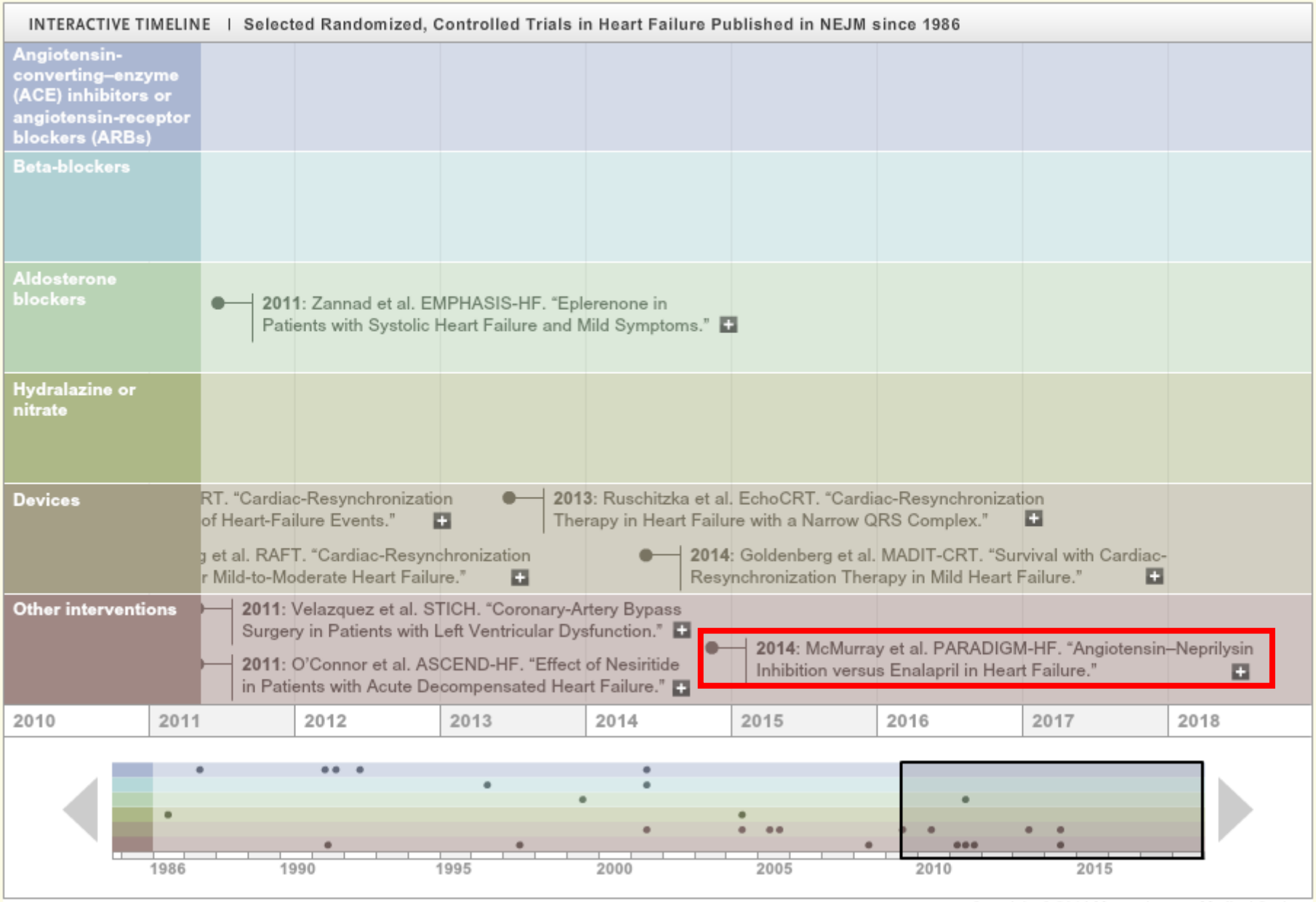
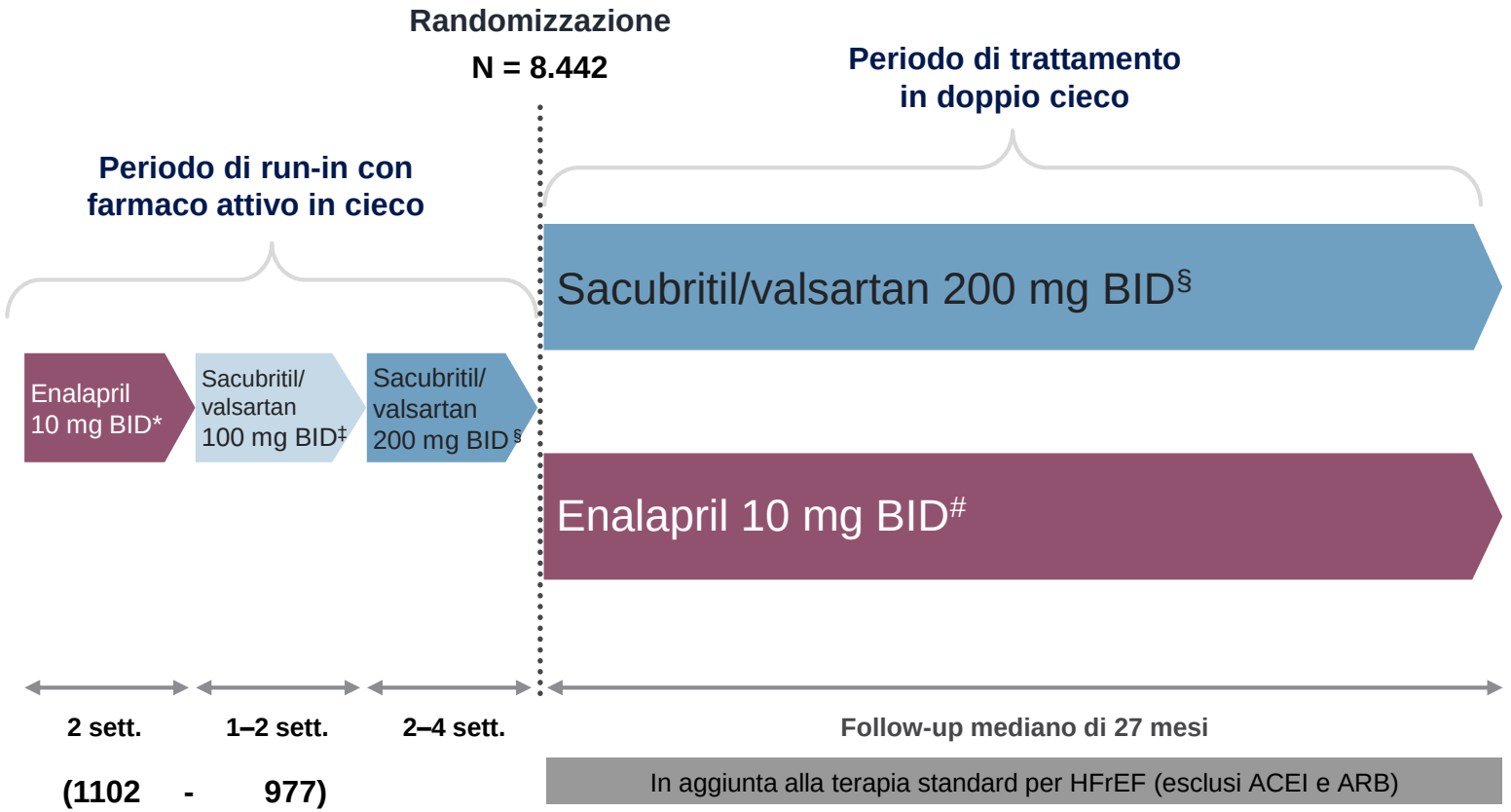


Gruppo MultiMedica

Heart Failure Treatments.



PARADIGM-HF: disegno dello studio



*Enalapril 5 mg BID (10 mg TDD) per 1–2 settimane seguito da enalapril 10 mg BID (20 mg TDD) come dose ottimale di partenza del run-in per quei pazienti trattati con ARB o ACEI a bassa dose; ‡200 mg TDD; §400 mg TDD; #20 mg TDD

McMurray et al. Eur J Heart Fail. 2013;15:1062–73; McMurray et al. Eur J Heart Fail 2014;16:817–25; McMurray et al. N Engl J Med 2014;371:993–1004

Studio PARADIGM-HF
Criteri chiave di inclusione

- HF cronico di classe funzionale NYHA II–IV con LVEF ≤35%*
- Livelli di BNP (o NT-proBNP) come segue:
  - ≥150 (o ≥600 pg/ml), oppure
  - ≥100 (o ≥400 pg/ml) e un'ospedalizzazione per HFrEF entro gli ultimi 12 mesi
- Trattamento stabile per ≥4 settimane con un ACEI o un ARB# e un β-bloccante
- Per tutti i pazienti si deve considerare un antagonista dell'aldosterone (con un trattamento con una dose stabile per ≥4 settimane, se somministrato)

*Nel protocollo originale il criterio di inclusione della frazione d'eiezione era ≤40%; #Dosaggio equivalente a ≥10 mg/die di enalapril.

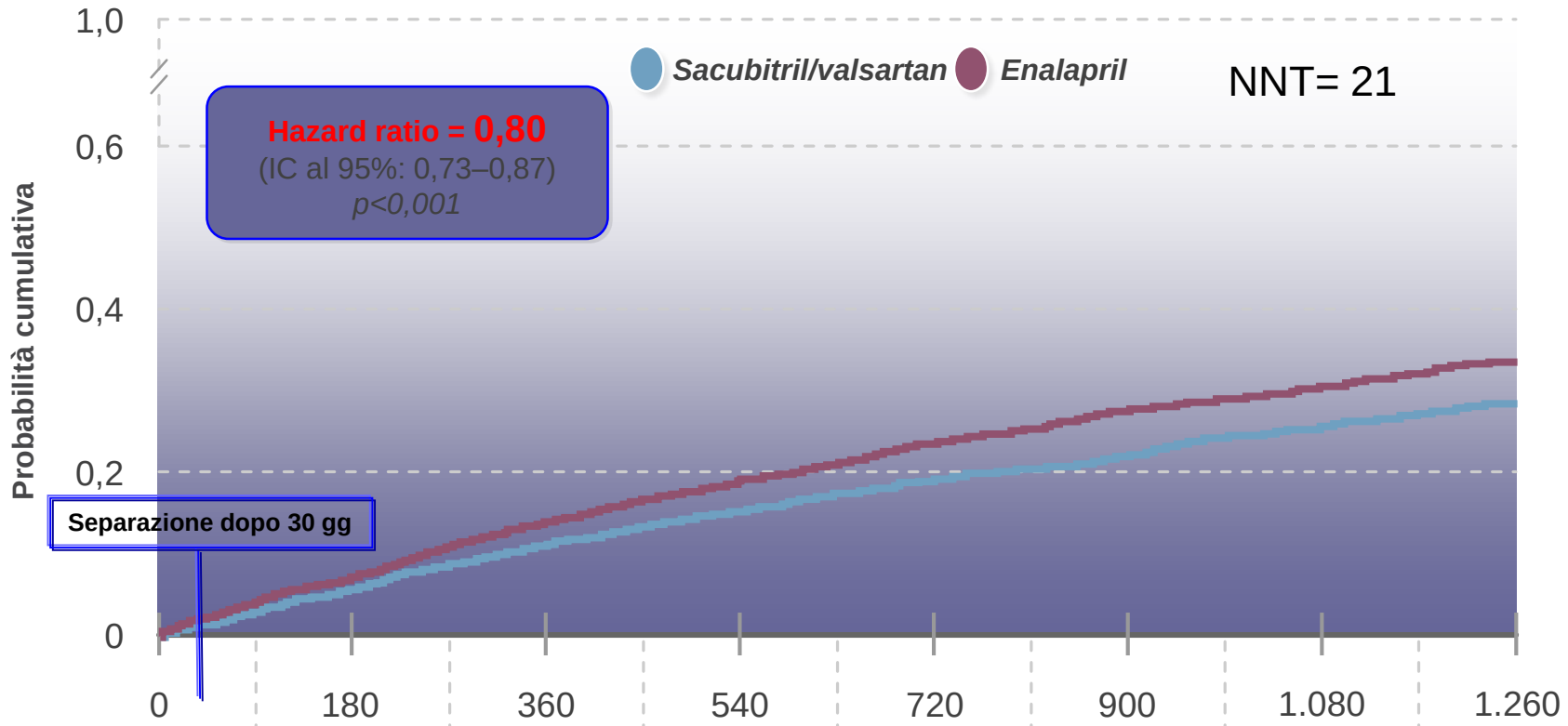
McMurray et al. Eur J Heart Fail. 2013;15:1062–73

Studio PARADIGM-HF
Criteri chiave di esclusione

- **eGFR <30 ml/min/1,73 m^2** allo screening, alla fine del run-in con enalapril o alla randomizzazione, oppure una riduzione >35% della eGFR tra lo screening e la fine del run-in con enalapril oppure tra lo screening e la randomizzazione
- **Potassio sierico >5,2 mmol/l** allo screening OPPURE **>5,4 mmol/l** alla fine del run-in con enalapril o alla fine del run-in con sacubitril/valsartan
- Necessità di trattamento con ACEI e/o ARB
- **Ipotensione sintomatica, PAS <100 mmHg** allo screening, OPPURE **PAS <95 mmHg** alla fine del run-in con enalapril o alla randomizzazione
- **Anamnesi positiva per angioedema**
- HF scompensato acuto in atto
- Anamnesi positiva per **grave pneumopatia**
- Sindrome coronarica acuta, ictus, attacco ischemico transitorio, intervento chirurgico cardiaco, alla carotide o altro intervento di chirurgia maggiore, PCI o angioplastica carotidea **entro i 3 mesi precedenti lo screening**

McMurray et al. Eur J Heart Fail. 2013;15:1062–73

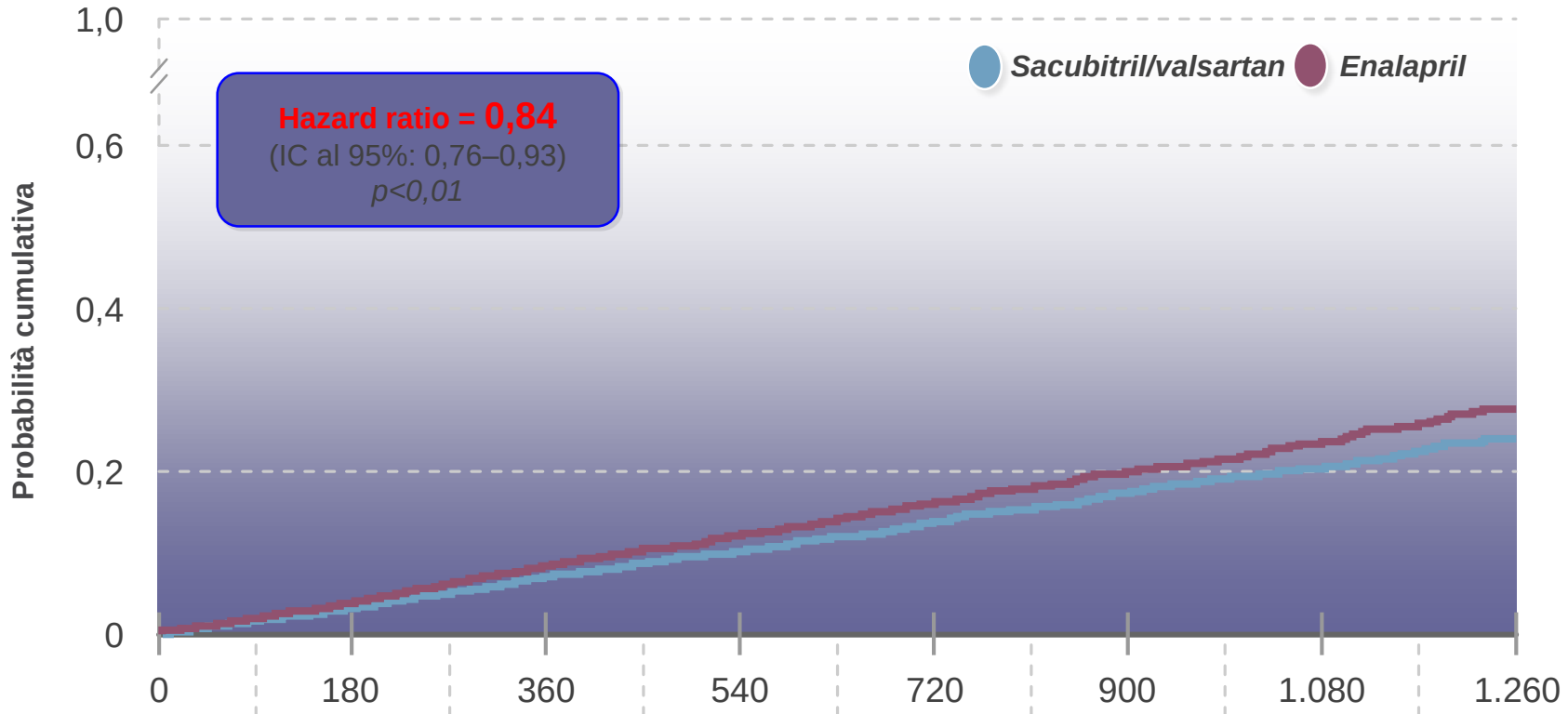
End point primario
Decesso per cause CV o prima ospedalizzazione per HF



N° a rischio								
Sacubitril/valsartan	4.187	3.922	3.663	3.018	2.257	1.544	896	249
Enalapril	4.212	3.883	3.579	2.922	2.123	1.488	853	236

McMurray et al. N Engl Med 2014;371:993–1004.

End point secondario
Mortalità per qualsiasi causa



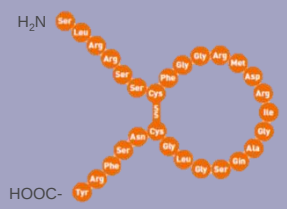
N° a rischio								
Sacubitril/valsartan	4.187	4.056	3.891	3.282	2.478	1.716	1.005	280
Enalapril	4.212	4.051	3.860	3.231	2.410	1.726	994	279

McMurray et al. N Engl Med 2014;371:993–1004.

Il sistema dei peptidi natriuretici (NP)

Il cuore è un organo endocrino che rilascia NP in risposta allo stiramento meccanico

Peptide natriuretico atriale (ANP)



- Espresso negli **atri**
- Misurabile nel plasma

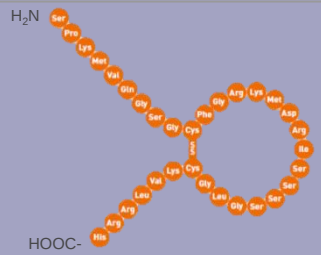
Effetti:
- Vasorilassamento
- ↑ Diuresi/natriuresi
- ↓ Proliferazione
- ↓ Ipertrofia
- ↓ Aldosterone
- ↓ Tono simpatico
- ↓ Precarico cardiaco
- ↑ Compliance venosa

Peptide natriuretico di tipo C (CNP)

- Espresso nelle **cellule endoteliali vascolari** e nel **sistema venoso centrale**
- Non rilevabile nel plasma – principalmente sintetizzato nel sistema vascolare, agisce localmente nei tessuti

Effetti:
- Vasorilassamento
- Dilatazione venosa più potente di ANP e BNP
- ↓ Proliferazione
- Regolazione della crescita ossea

Peptide natriuretico di tipo b (BNP)

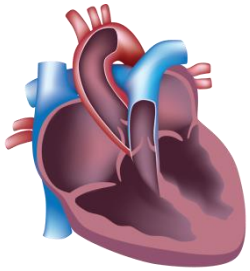


- Espresso nel tessuto **atriale** e **ventricolare**
- Misurabile nel plasma

Effetti:
- Vasorilassamento
- ↑ Diuresi/natriuresi
- ↓ Aldosterone
- ↓ Tono simpatico

Levin et al. N Engl J Med 1998;339;321–8; Gardner et al. Hypertension 2007;49:419–26; Pandey. J Am Soc Hypertens 2008;2:210–16; Von Lueder et al. Pharmacol Ther 2014;144:41–9; Potter. FEBS J 2011;278:1808–17; Lumsden et al. Curr Pharm Des 2010;16:4080–8; Mangiafico et al. Eur Heart J 2013;34:886–93; Volpe. Int J Cardiol 2014;176:630–9

Effetti del sistema NP

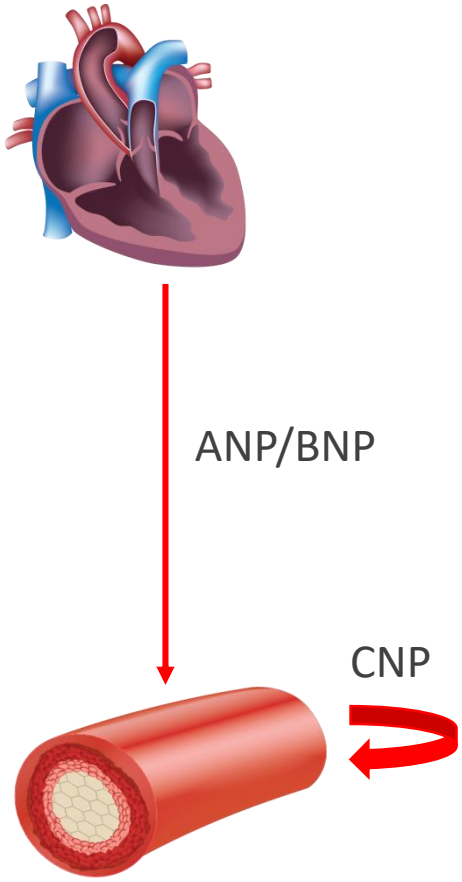


ANP/BNP

Inibizione della fibrosi
e della proliferazione

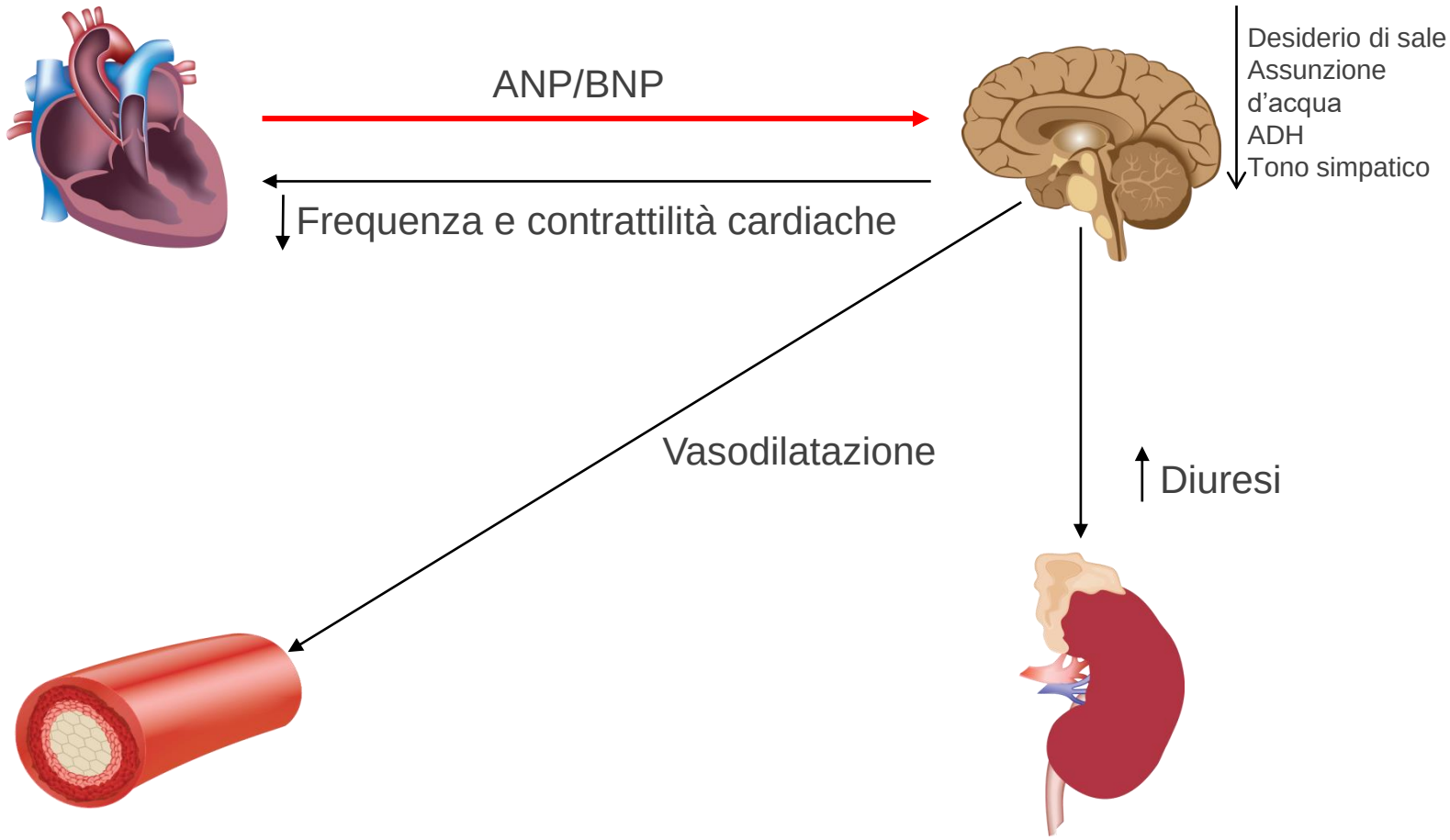
Adattato da Levin et al. N Engl J Med 1998;339;321–8

Effetti del sistema NP



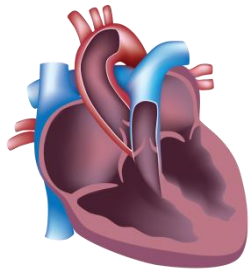
Adattato da Levin et al. N Engl J Med 1998;339;321–8

Effetti del sistema NP

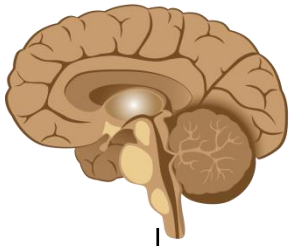


Adattato da Levin et al. N Engl J Med 1998;339;321–8

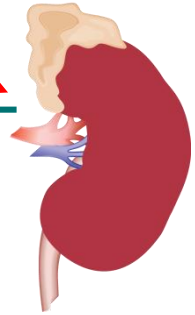
Effetti del sistema NP



ANP/BNP

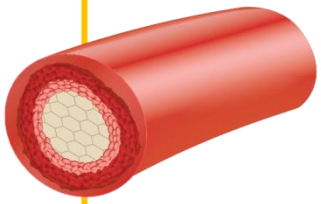


↓ Renina



↑ GFR

↓ Vasodilatazione

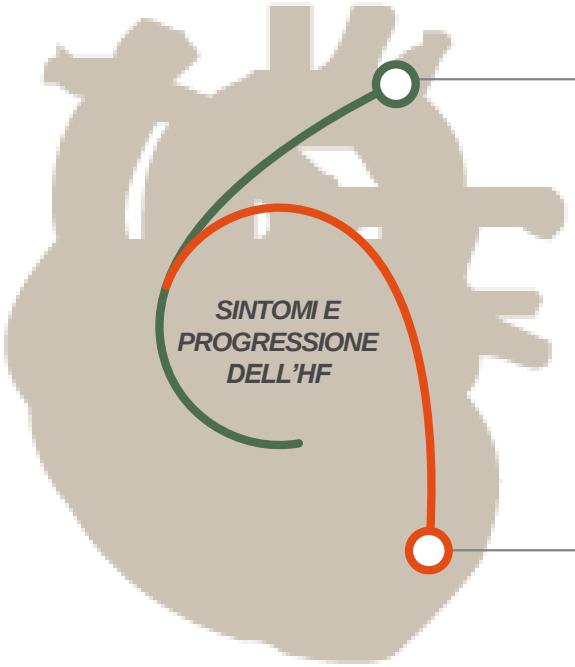


↓ Ang-II ↓ Aldosterone

↑ Natriuresi
Diuresi

Vasodilatazione

Adattato da Levin et al. N Engl J Med 1998;339;321–8



SNS

Adrenalina
Noradrenalina → Recettori α_1, β_1, β_2

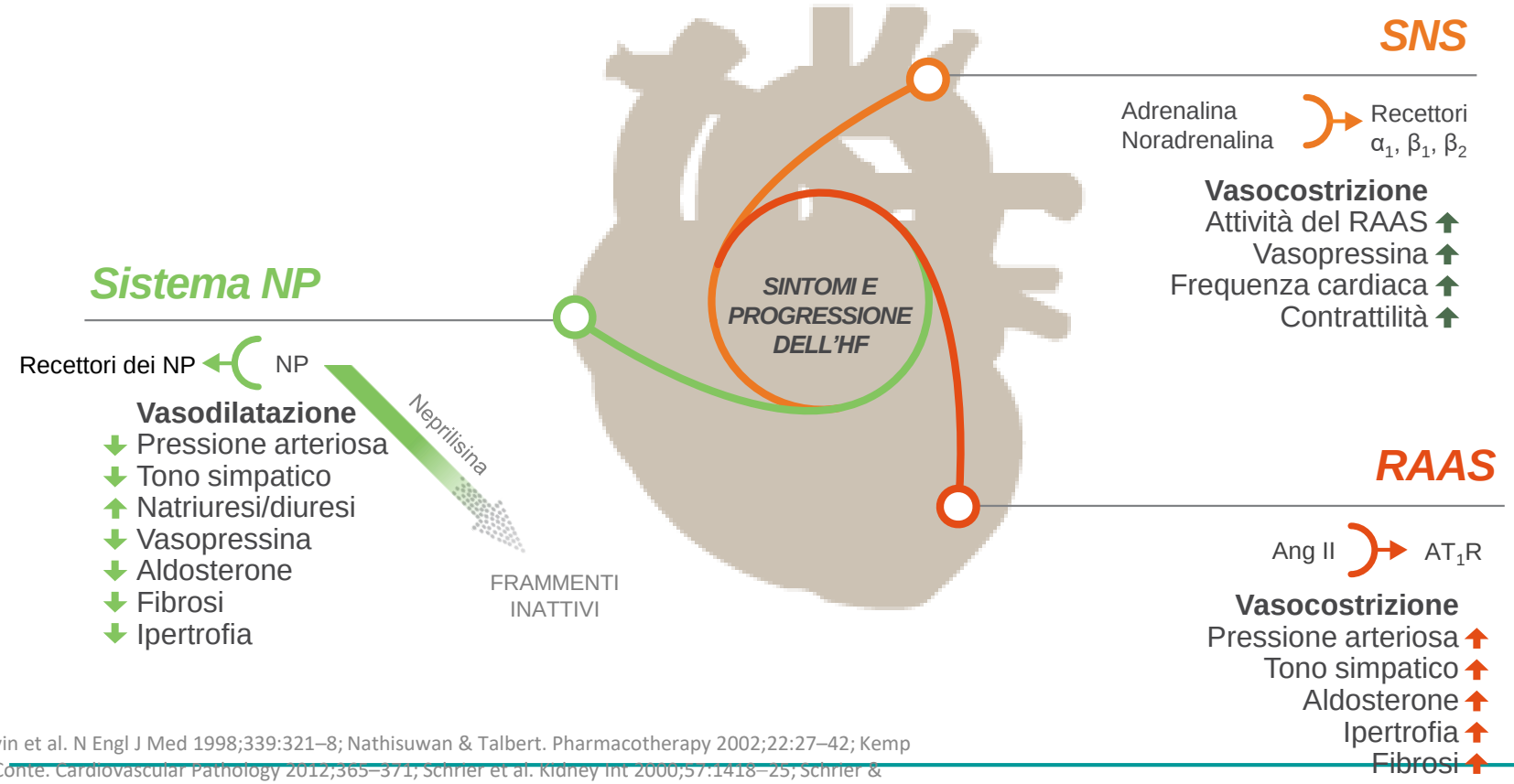
Vasocostrizione
Attività del RAAS ↑
Vasopressina ↑
Frequenza cardiaca ↑
Contrattilità ↑

RAAS

Ang II → Recettori AT_1

Vasocostrizione
Pressione arteriosa ↑
Tono simpatico ↑
Aldosterone ↑
Ipertrofia ↑
Fibrosi ↑

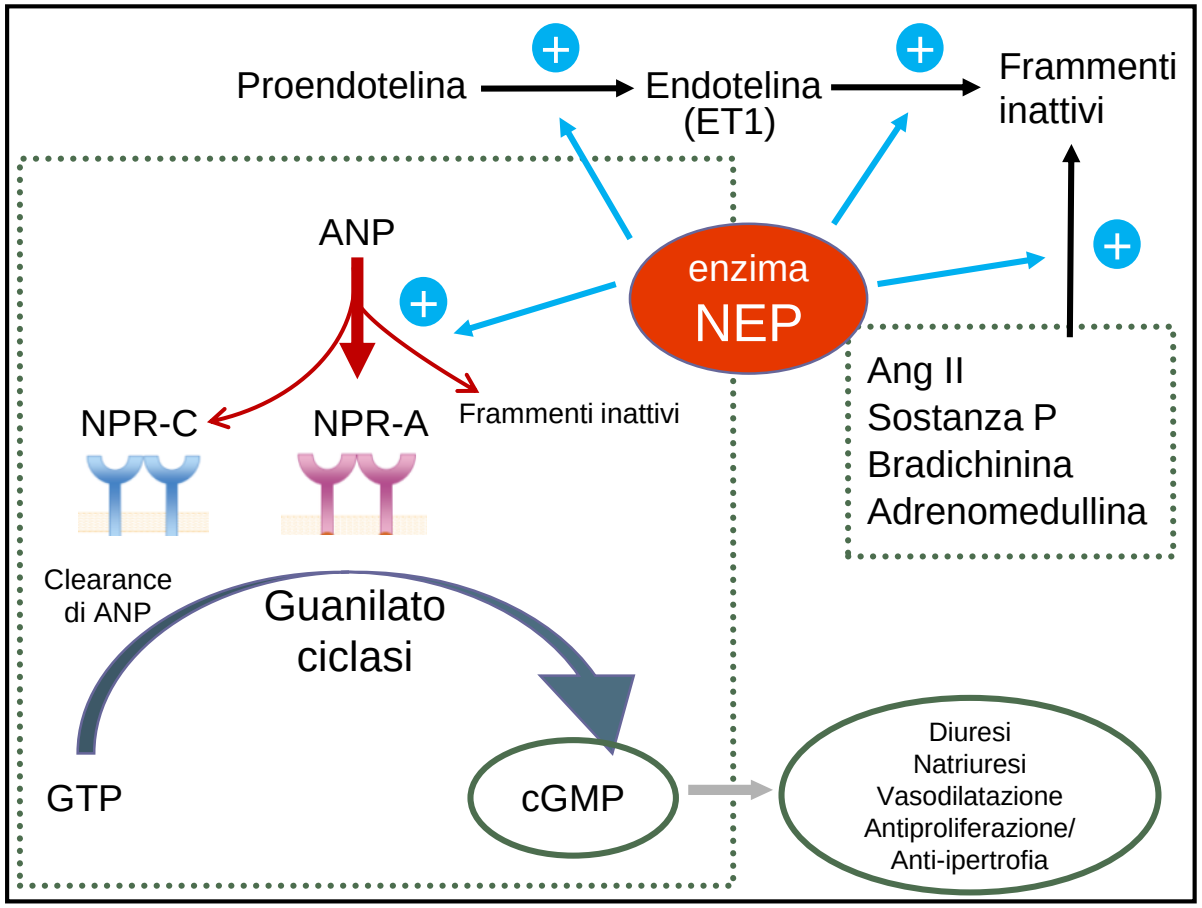
Levin et al. N Engl J Med 1998;339:321–8; Nathisuwan & Talbert. Pharmacotherapy 2002;22:27–42; Kemp & Conte. Cardiovascular Pathology 2012;365–371; Schrier et al. Kidney Int 2000;57:1418–25; Schrier & Abraham N Engl J Med 2009;341:577–85



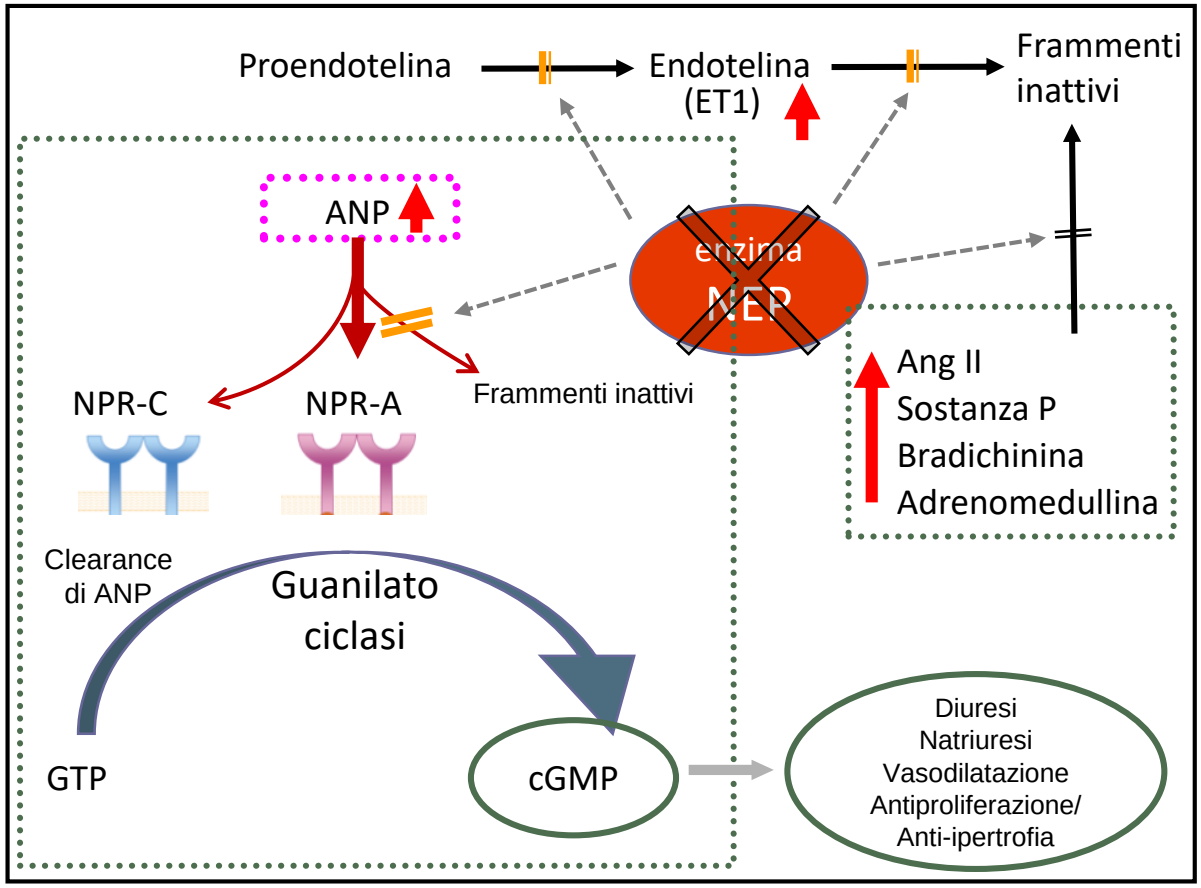
Levin et al. N Engl J Med 1998;339:321–8; Nathisuwan & Talbert. Pharmacotherapy 2002;22:27–42; Kemp & Conte. Cardiovascular Pathology 2012;365–371; Schrier et al. Kidney Int 2000;57:1418–25; Schrier & Abraham N Engl J Med 2009;341:577–85; Boerrigter & Burnett. Expert Opin Invest Drugs 2004;13:643–52; Ferro et al. Circulation 1998;97:2323–30; Brewster et al. Am J Med Sci 2003;326:15–24

La neprilisina è responsabile della degradazione degli NP

Non è specifica per gli NP, ma catalizza anche la degradazione di peptidi vasocostrittori, come Ang II

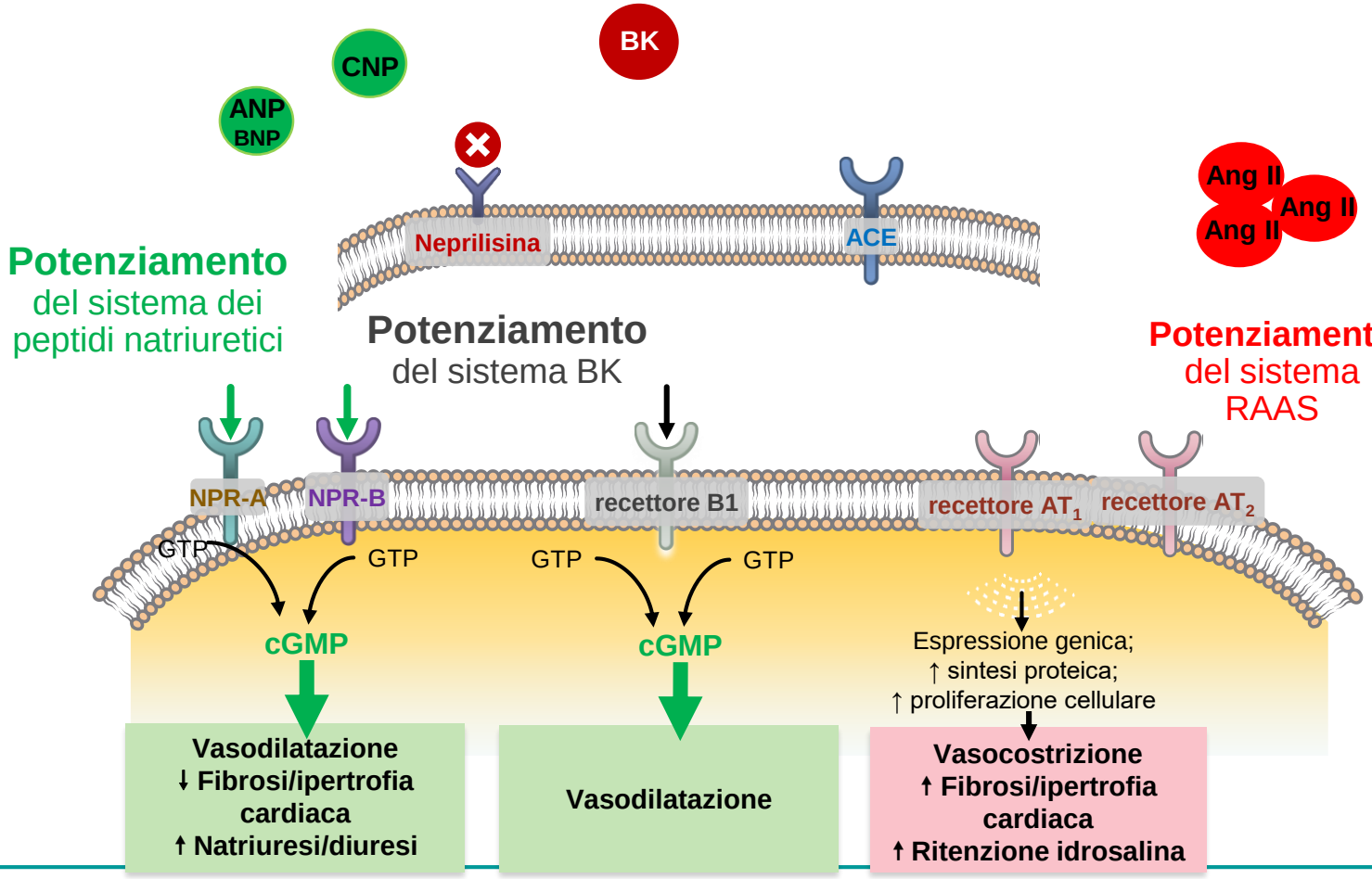


L’inibizione della neprilisina potenzia gli effetti degli NP, di Ang II, endotelina 1 e altri peptidi vasoattivi



L'inibizione della solo neprilisina

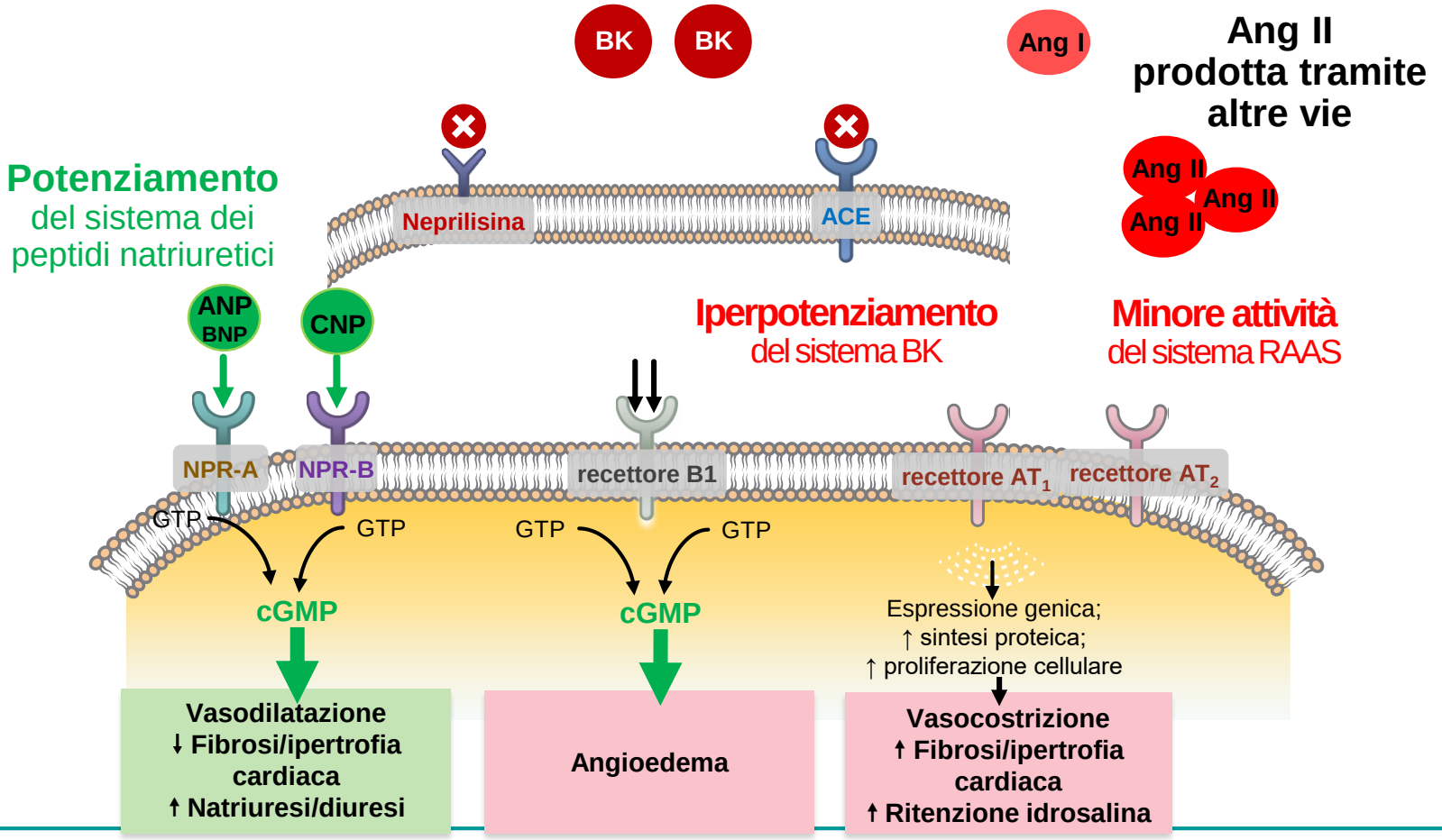
è associata a un aumento dei livelli di Ang II, che controbilancia i potenziali benefici dell'inibizione della neprilisina



Volpe, Carnovali et. Clinical Science (2016) 130, 57–77 doi: 10.1042/CS20150469 Langenickel and Dole. Drug Discov Today: Ther Strateg 2012;9:e131–9.

Inibizione della neprilisina + ACEI (omapatrilat)

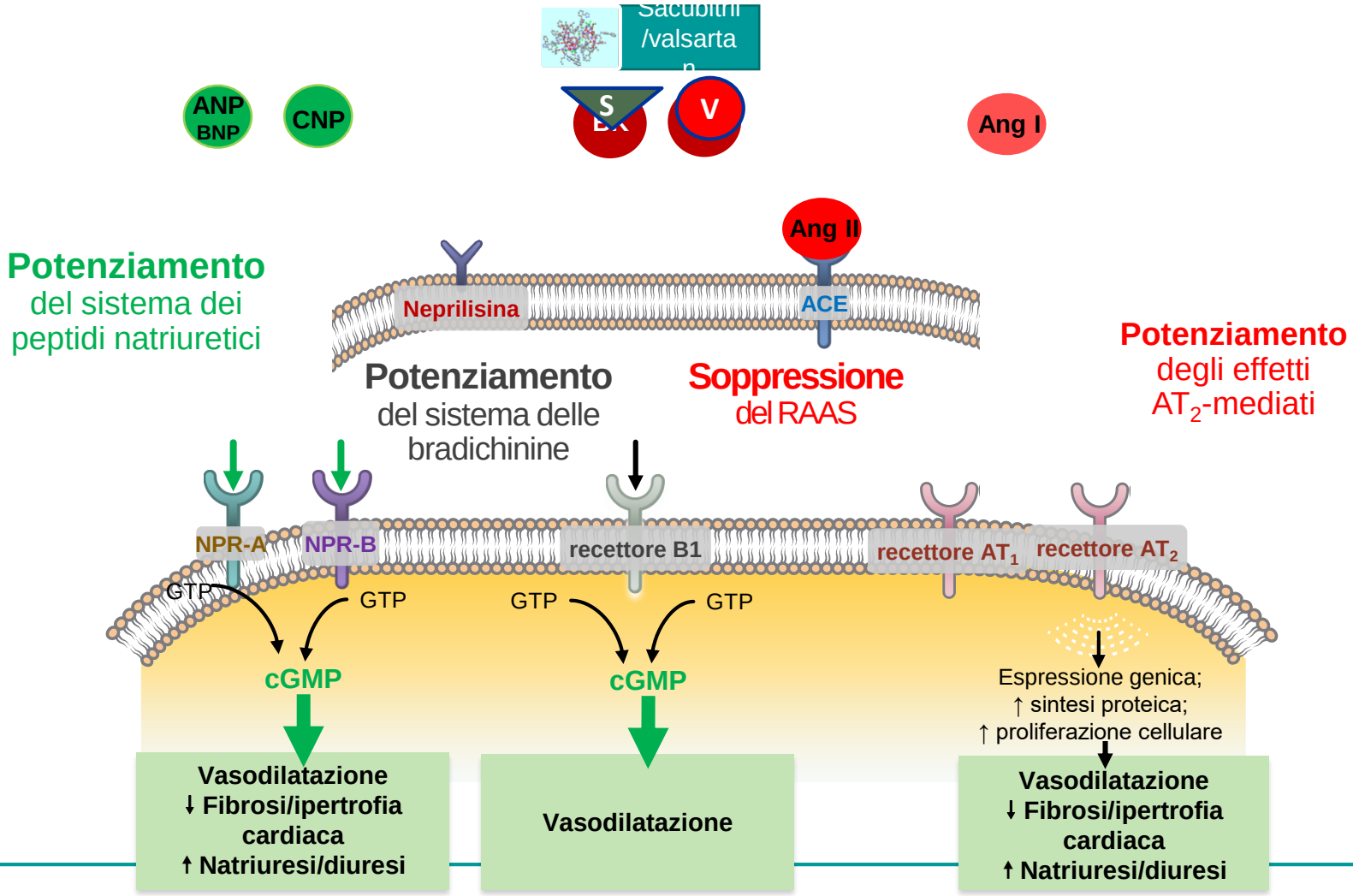
Nell'HFrEF dimostra un trend verso una ridotta morbilità e mortalità, ma è stata interrotta per un'aumentata frequenza di angioedema



Adattato da Volpe, Carnovali et. Clinical Science (2016) 130, 57–77 doi: 10.1042/CS20150469

Inibizione della neprilisina + ARB (sacubitril/valsartan)

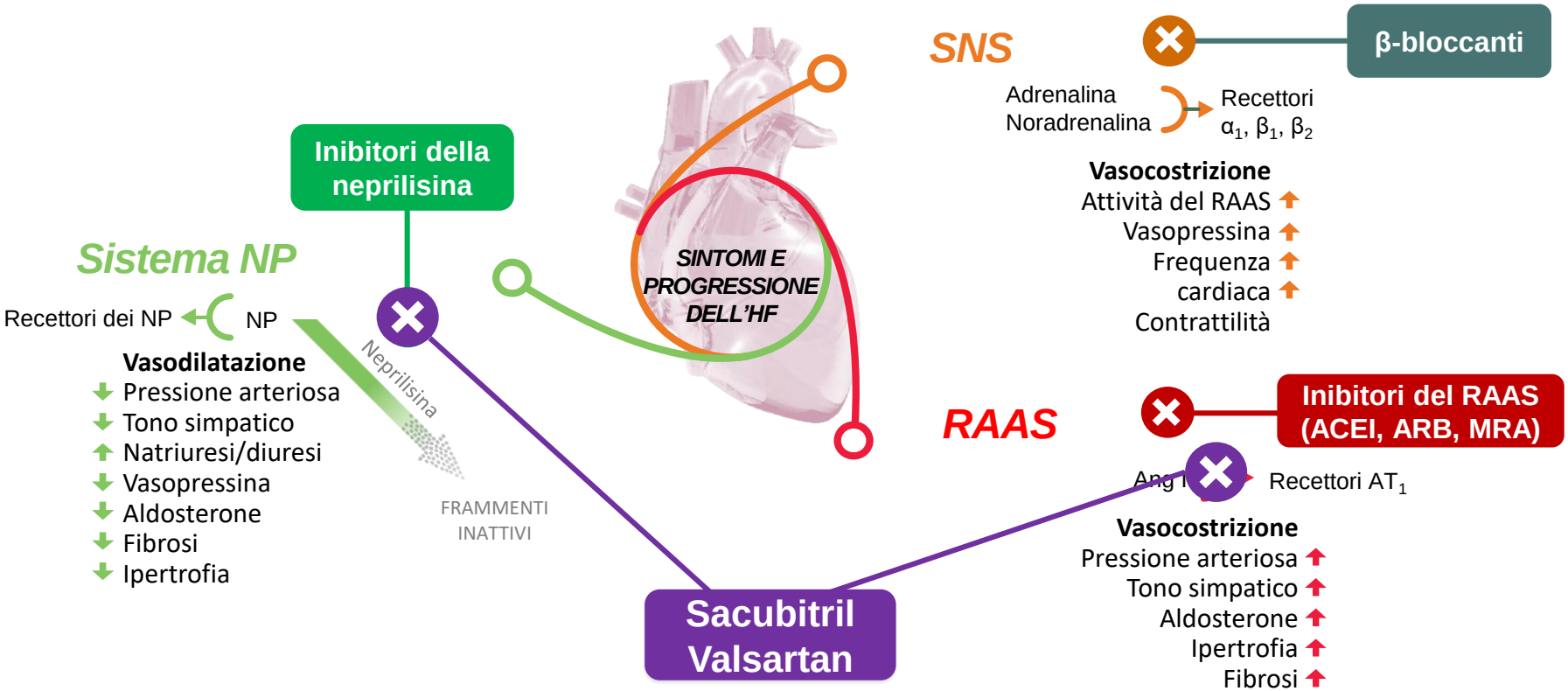
Il meccanismo d'azione di sacubitril/valsartan consente un trattamento efficace e ben tollerato del CHF



Adattato da Volpe, Carnovali et. Clinical Science (2016) 130, 57–77 doi: 10.1042/CS20150469

Sacubritil/valsartan

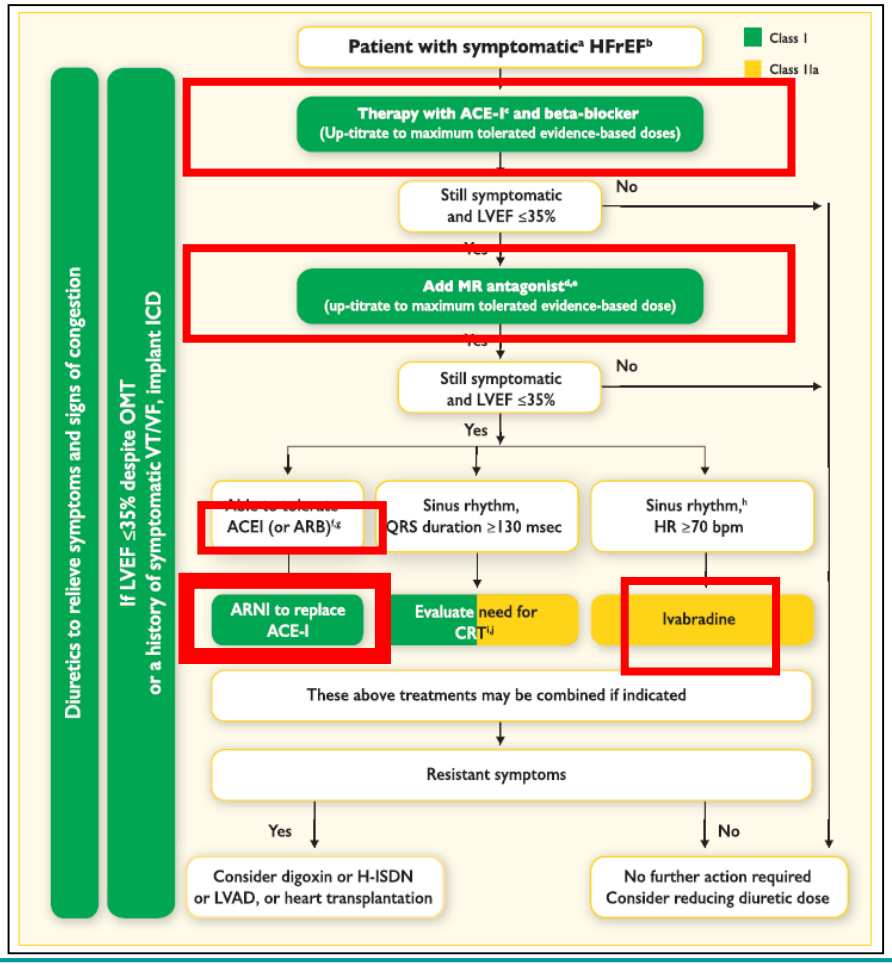
Potenziamento dei peptidi natriuretici e di altri peptidi vasoattivi, con simultanea soppressione del RAAS



1. McMurray et al. Eur J Heart Fail. 2013;15:1062–73;
Rif. Figura: Levin et al. N Engl J Med 1998;339:321–8; Nathisuwan & Talbert. Pharmacotherapy 2002;22:27–42;
Kemp & Conte. Cardiovascular Pathology 2012;365–371; Schrier & Abraham N Engl J Med 2009;341:577–85

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)



Gruppo MultiMedica

2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America

Developed in Collaboration With the International Society for Heart and Lung Transplantation

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Cheryl Westlake, PhD, RN, ACNS-BC, FHFSA¶

Recommendations for Renin-Angiotensin System Inhibition With ACE Inhibitor or ARB or ARNI		
COR	**LOE**	**Recommendations**
I	ACE: A ARB: A ARNI: B-R	The clinical strategy of inhibition of the renin-angiotensin system with ACE inhibitors *(Level of Evidence: A)* (9-14), OR ARBs *(Level of Evidence: A)* (15-18), OR ARNI *(Level of Evidence: B-R)* (19) in conjunction with evidence-based beta blockers (20-22), and aldosterone antagonists in selected patients (23, 24), is recommended for patients with chronic HF*r*EF to reduce morbidity and mortality.
I	ARNI: B-R	In patients with chronic symptomatic HF*r*EF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality (19).
III: Harm	B-R	ARNI should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor (31, 32).
III: Harm	C-EO	ARNI should not be administered to patients with a history of angioedema.

European Heart Journal (2016) **37**, 3121–3129
doi:10.1093/eurheartj/ehw421

CARDIOPULSE

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(5) A new compound, LCZ696, which combines valsartan and a neprylisin inhibitor (sacubitril) is recommended as a replacement for the ACEIs in patients with HFrEF who remain symptomatic despite ACEIs, a beta-blocker and an MRA.

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(9) In patients presenting with acute heart failure, an early initiation of appropriate treatment is of key importance.

(10) For optimal management during the early phase of AHF, the algorithm based on clinical profiles evaluating the presence of congestion and peripheral hypoperfusion should be applied

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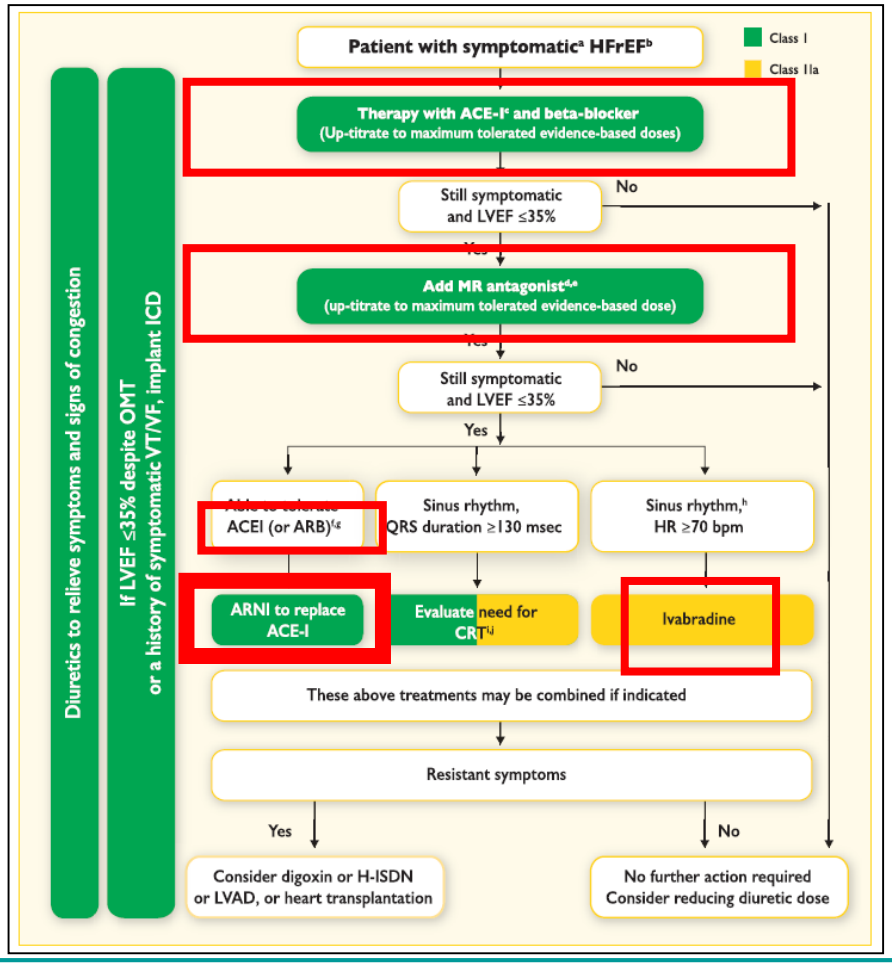
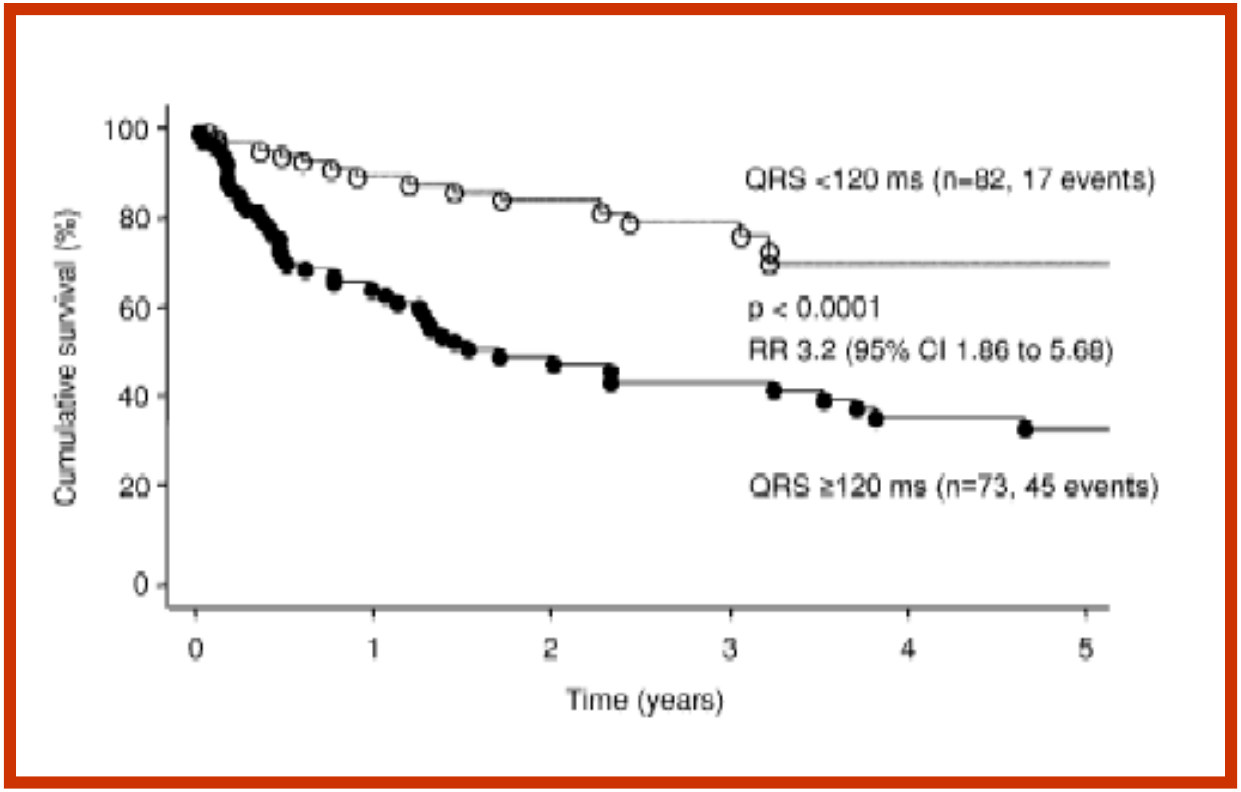


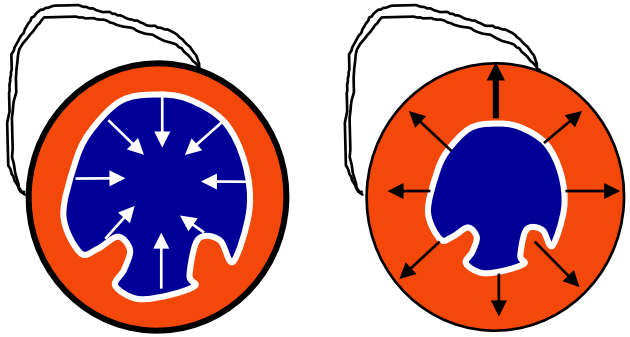
Gruppo MultiMedica

Prolungamento QRS → 30% CHF



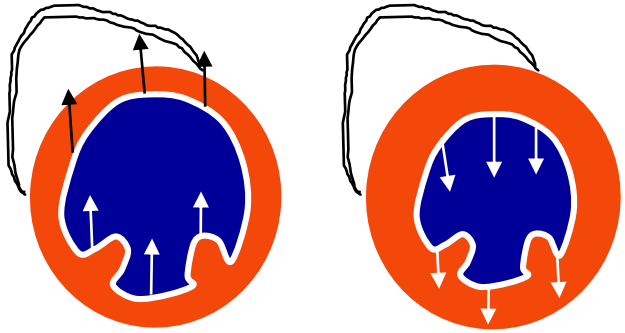
Karla et al. *Clinical characteristics and survival of patients with chronic heart failure and prolonged QRS duration.* International Journal of Cardiology, 2002

NORMAL Synchrony

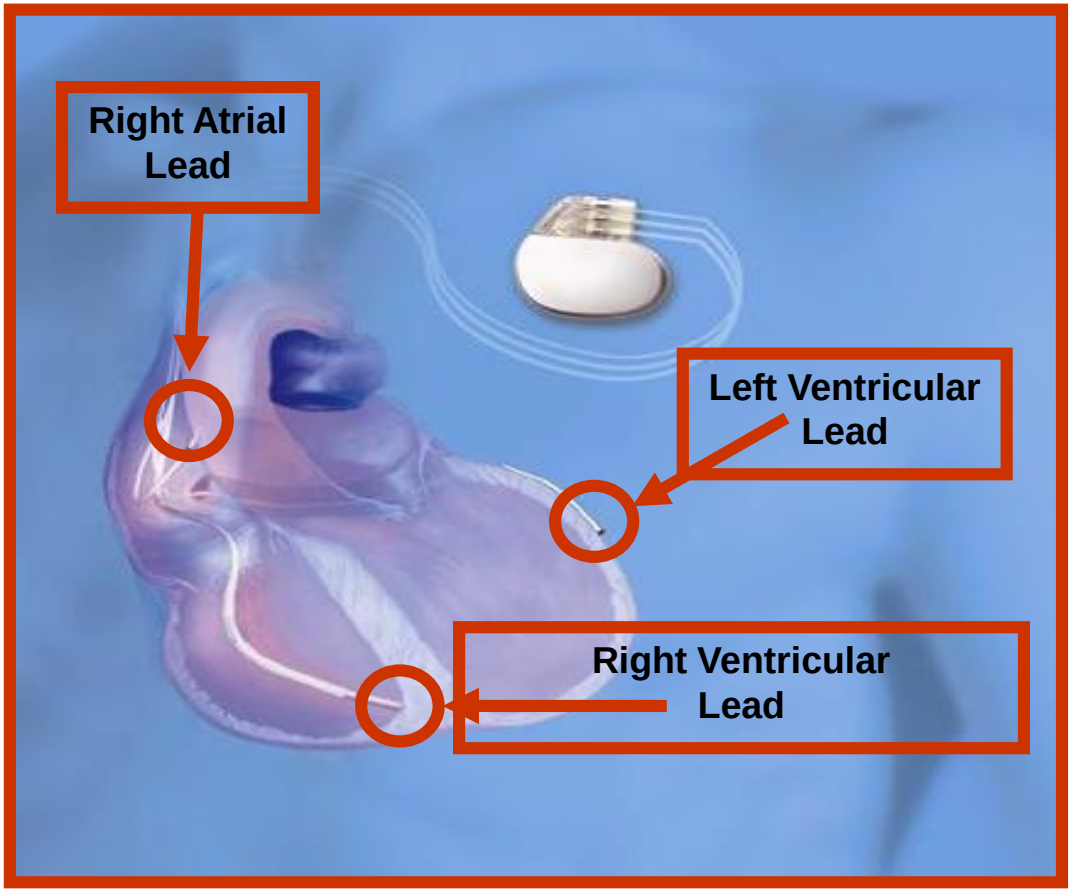


Systole Diastole

LBBB Dyssynchrony



Systole Diastole


Right Atrial Lead
Left Ventricular Lead
Right Ventricular Lead

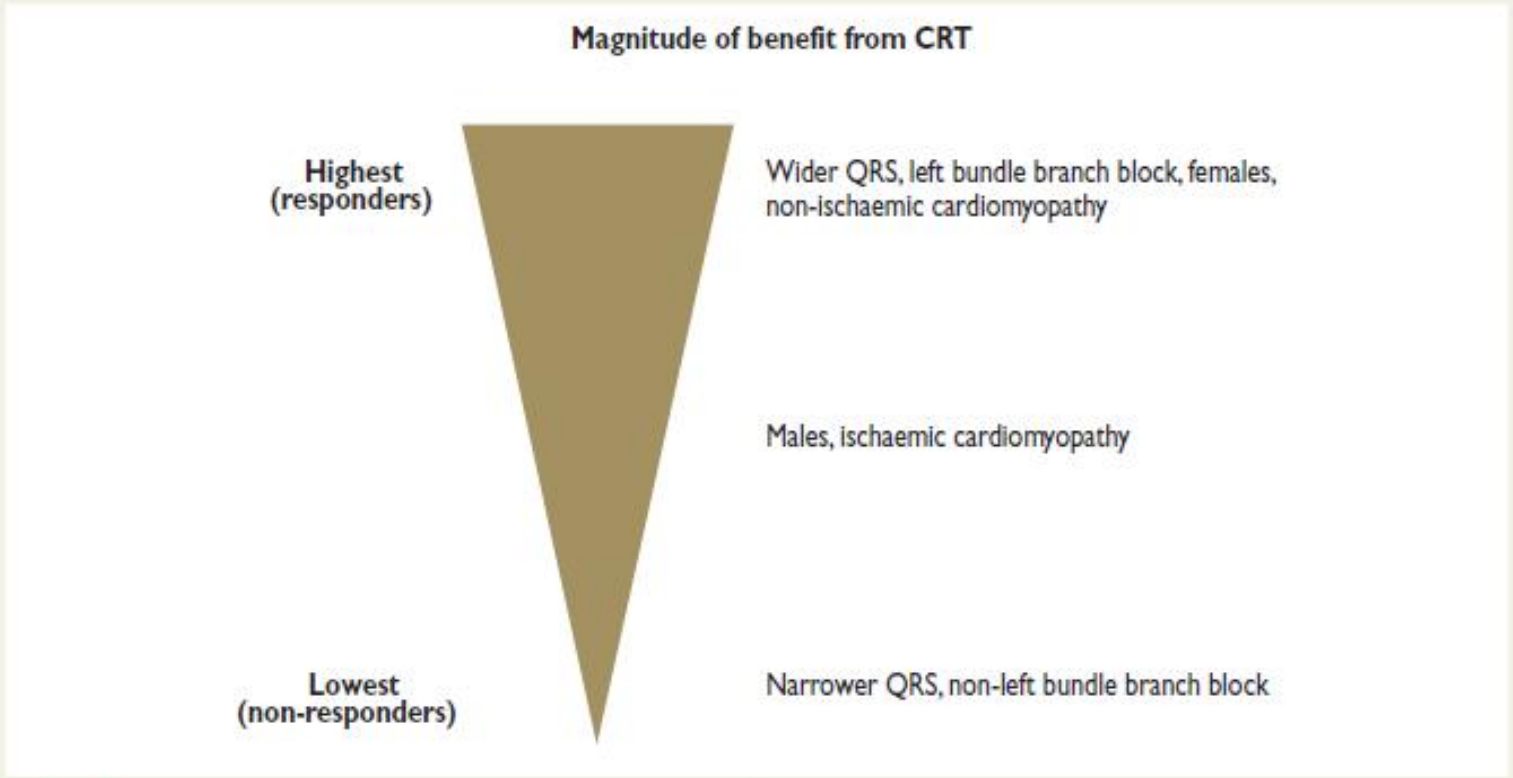


Figure 8 Clinical factors influencing the likelihood to respond to CRT.

Recommendations for cardiac resynchronization therapy implantation in patients with heart failure

Recommendations	Class [a]	Level [b]	Ref [c]
CRT is recommended for symptomatic patients with HF in sinus rhythm with a QRS duration ≥150 msec and LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.	I	A	261–272
CRT should be considered for symptomatic patients with HF in sinus rhythm with a QRS duration ≥150 msec and non-LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.	IIa	B	261–272
CRT is recommended for symptomatic patients with HF in sinus rhythm with a QRS duration of 130–149 msec and LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.	I	B	266, 273
CRT may be considered for symptomatic patients with HF in sinus rhythm with a QRS duration of 130–149 msec and non-LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.	IIb	B	266, 273
CRT rather than RV pacing is recommended for patients with HFrEF regardless of NYHA class who have an indication for ventricular pacing and high degree AV block in order to reduce morbidity. This includes patients with AF (see Section 10.1).	I	A	274–277
CRT should be considered for patients with LVEF ≤35% in NYHA Class III–IV[d] despite OMT in order to improve symptoms and reduce morbidity and mortality, if they are in AF and have a QRS duration ≥130 msec provided a strategy to ensure bi-ventricular capture is in place or the patient is expected to return to sinus rhythm.	IIa	B	275, 278–281
Patients with HFrEF who have received a conventional pacemaker or an ICD and subsequently develop worsening HF despite OMT and who have a high proportion of RV pacing may be considered for upgrade to CRT. This does not apply to patients with stable HF.	IIb	B	282
CRT is contra-indicated in patients with a QRS duration < 130 msec.	III	A	266, 283–285

AF = atrial fibrillation; AV = atrio-ventricular; CRT = cardiac resynchronization therapy; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; ICD = implantable cardioverter-defibrillator; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; OMT = optimal medical therapy; QRS = Q, R and S waves (combination of three of the graphical deflections); RV = right ventricular.

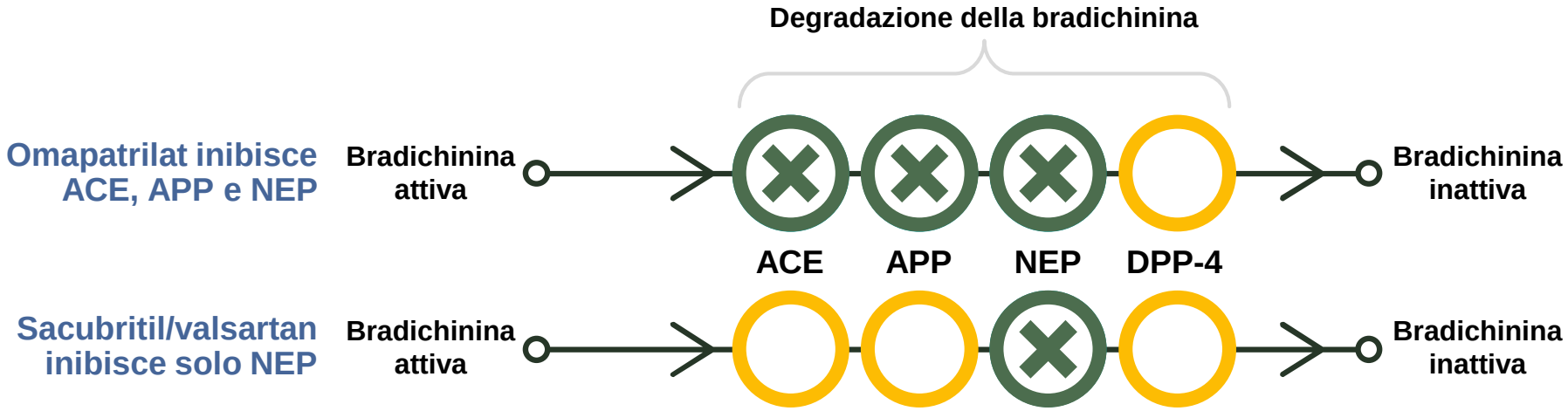
[a]Class of recommendation.

[b]Level of evidence.

[c]Reference(s) supporting recommendations.

[d]Use judgement for patients with end-stage HF who might be managed conservatively rather than with treatments to improve symptoms or prognosis.

Sacubritil/valsartan inibisce attivamente la neprilisina e il recettore AT_1, ma lascia attive la maggior parte delle vie di degradazione della bradichinina[1]

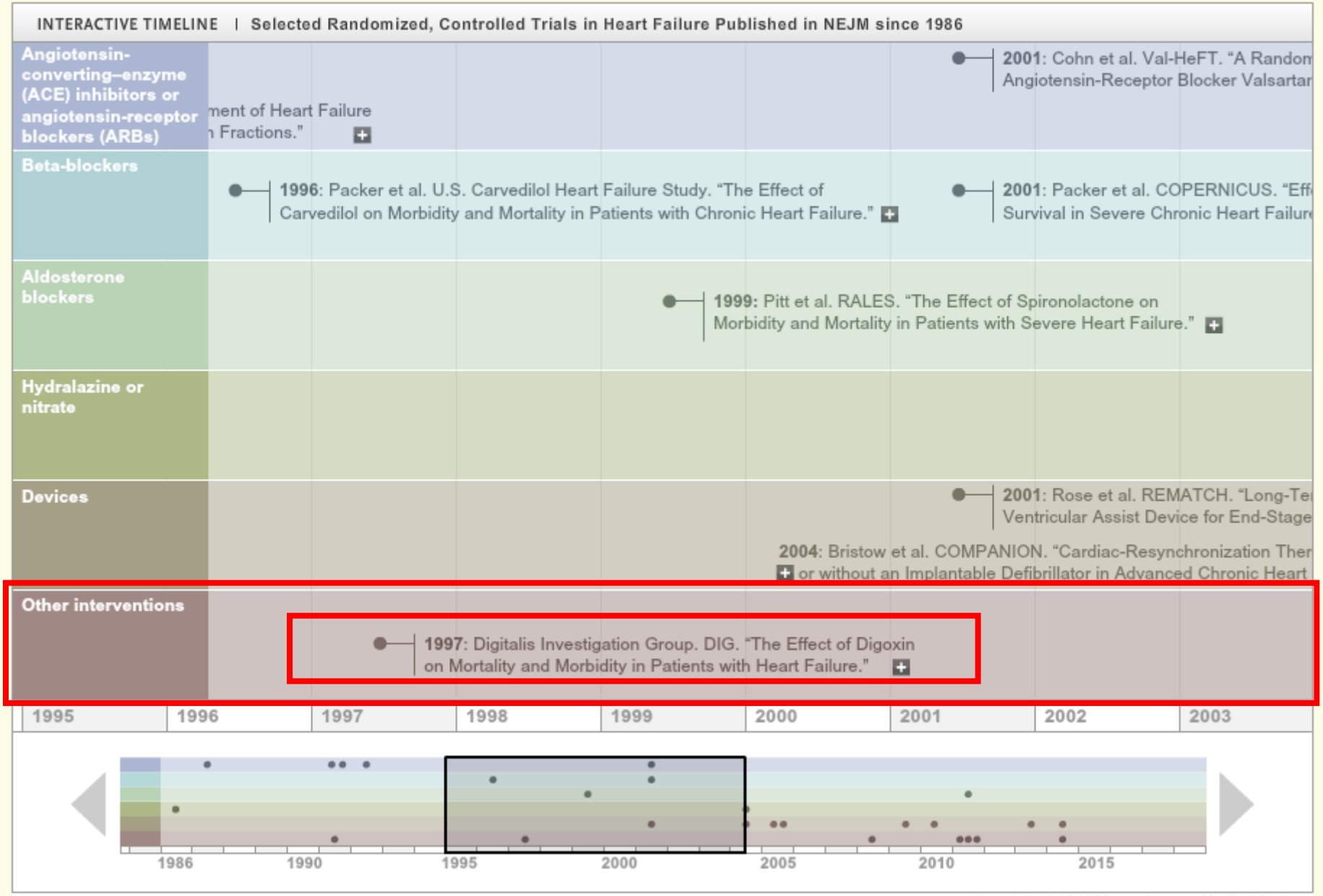


- La bradichinina è un substrato della neprilisina e di altre vasopeptidasi (ACE, APP, DPP-4); il suo rialzo è stato associato a tosse e angioedema[2,3]
- Omapatrilat inibisce tre enzimi (ACE, APP, NEP) coinvolti nella degradazione della bradichinina, che probabilmente è responsabile dello sviluppo di angioedema[2]

Le informazioni qui presentate sono dati pubblicamente disponibili e non tratti da sperimentazioni cliniche dirette.

1. McMurray et al. Eur J Heart Fail. 2014;16:817–25; 2. Fryer et al. Br J Pharmacol 2008;153:947–55; 3. Semple. J Hypertens Suppl 1995;13:S17–21; 4. Gu et al. J Clin Pharmacol 2010;50:401–14; 5. McMurray et al. Eur J Heart Fail. 2013;15:1062–73; 6. McMurray, et al. N Engl J Med 2014;371:993–1004

Heart Failure Treatments.



The New England
Journal of Medicine

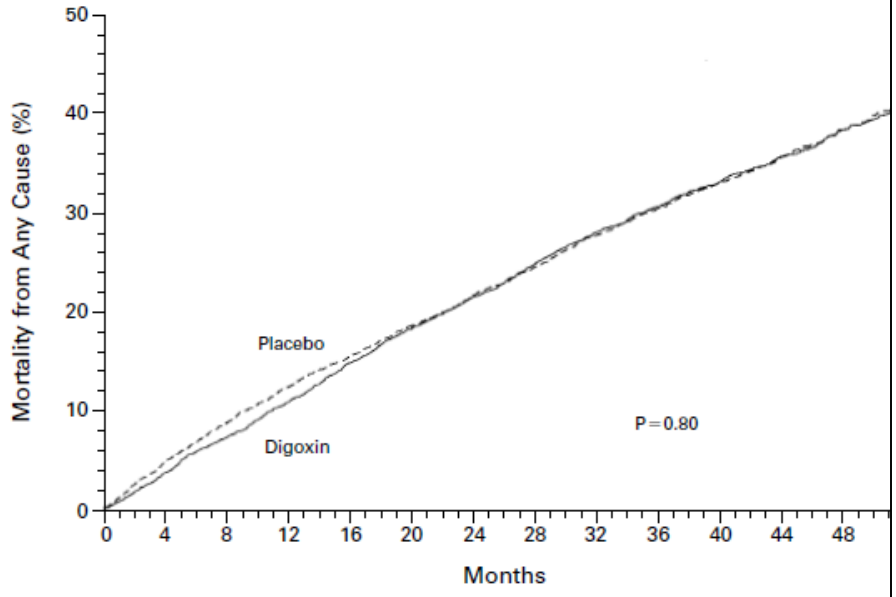
VOLUME 336 FEBRUARY 20, 1997 NUMBER 8

THE EFFECT OF DIGOXIN ON MORTALITY AND MORBIDITY IN PATIENTS WITH HEART FAILURE

THE DIGITALIS INVESTIGATION GROUP*

The New England Journal of Medicine

VOLUME 336 FEBRUARY 20, 1997 NUMBER 8



No. of Patients at Risk

Placebo	3403	3239	3105	2976	2868	2758	2652	2551	2205	1881	1506	1168	734
Digoxin	3397	3269	3144	3019	2882	2759	2644	2531	2184	1840	1475	1156	737

Figure 1. Mortality in the Digoxin and Placebo Groups.
The number of patients at risk at each four-month interval is shown below the figure.

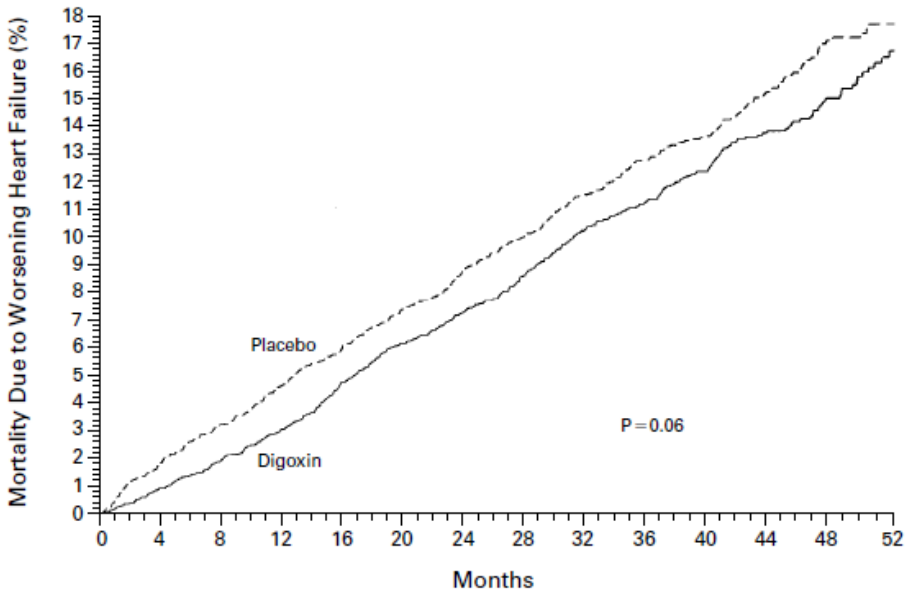


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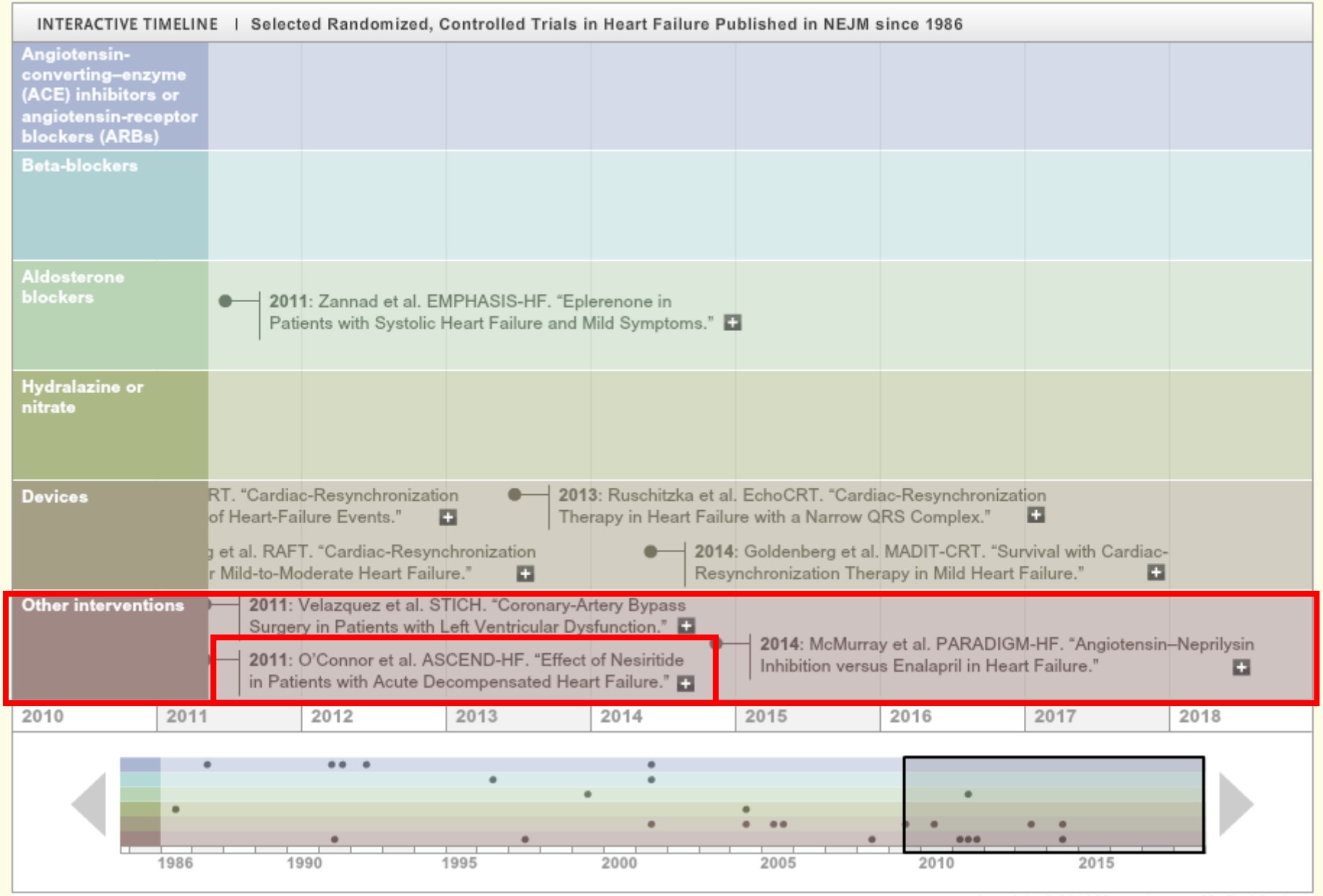
Figure 2. Mortality Due to Worsening Heart Failure in the Digoxin and Placebo Groups.
The number of patients at risk at each four-month interval is shown below the figure.

Heart Failure Treatments.



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of Nesiritide in Patients with Acute Decompensated Heart Failure

C.M. O'Connor, R.C. Starling, A.F. Hernandez, P.W. Armstrong, K. Dickstein, V. Hasselblad, G.M. Heizer, M. Komajda, B.M. Massie, J.J.V. McMurray, M.S. Nieminen, C.J. Reist, J.L. Rouleau, K. Swedberg, K.F. Adams, Jr., S.D. Anker, D. Atar, A. Battler, R. Botero, N.R. Bohidar, J. Butler, N. Clausell, R. Corbalán, M.R. Costanzo, U. Dahlstrom, L.I. Deckelbaum, R. Diaz, M.E. Dunlap, J.A. Ezekowitz, D. Feldman, G.M. Felker, G.C. Fonarow, D. Gennevois, S.S. Gottlieb, J.A. Hill, J.E. Hollander, J.G. Howlett, M.P. Hudson, R.D. Kociol, H. Krum, A. Laucevicius, W.C. Levy, G.F. Méndez, M. Metra, S. Mittal, B.-H. Oh, N.L. Pereira, P. Ponikowski, W.H.W. Tang, S. Tanomsup, J.R. Teerlink, F. Triposkiadis, R.W. Troughton, A.A. Voors, D.J. Whellan, F. Zannad, and R.M. Califf

ABSTRACT

BACKGROUND

Nesiritide is approved in the United States for early relief of dyspnea in patients with acute heart failure. Previous meta-analyses have raised questions regarding renal toxicity and the mortality associated with this agent.

METHODS

We randomly assigned 7141 patients who were hospitalized with acute heart failure to receive either nesiritide or placebo for 24 to 168 hours in addition to standard care. Coprimary end points were the change in dyspnea at 6 and 24 hours, as measured on a 7-point Likert scale, and the composite end point of rehospitalization for heart failure or death within 30 days.

RESULTS

Patients randomly assigned to nesiritide, as compared with those assigned to placebo, more frequently reported markedly or moderately improved dyspnea at 6 hours (44.5% vs. 42.1%, P=0.03) and 24 hours (68.2% vs. 66.1%, P=0.007), but the prespecified level for significance (P≤0.005 for both assessments or P≤0.0025 for either) was not met. The rate of rehospitalization for heart failure or death from any cause within 30 days was 9.4% in the nesiritide group versus 10.1% in the placebo group (absolute difference, −0.7 percentage points; 95% confidence interval [CI], −2.1 to 0.7; P=0.31). There were no significant differences in rates of death from any cause at 30 days (3.6% with nesiritide vs. 4.0% with placebo; absolute difference, −0.4 percentage points; 95% CI, −1.3 to 0.5) or rates of worsening renal function, defined by more than a 25% decrease in the estimated glomerular filtration rate (31.4% vs. 29.5%; odds ratio, 1.09; 95% CI, 0.98 to 1.21; P=0.11).

CONCLUSIONS

Nesiritide was not associated with an increase or a decrease in the rate of death and rehospitalization and had a small, nonsignificant effect on dyspnea when used in combination with other therapies. It was not associated with a worsening of renal function, but it was associated with an increase in rates of hypotension. On the basis of these results, nesiritide cannot be recommended for routine use in the broad population of patients with acute heart failure. (Funded by Scios; ClinicalTrials.gov number, NCT00475852.)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of Nesiritide in Patients with Acute Decompensated Heart Failure

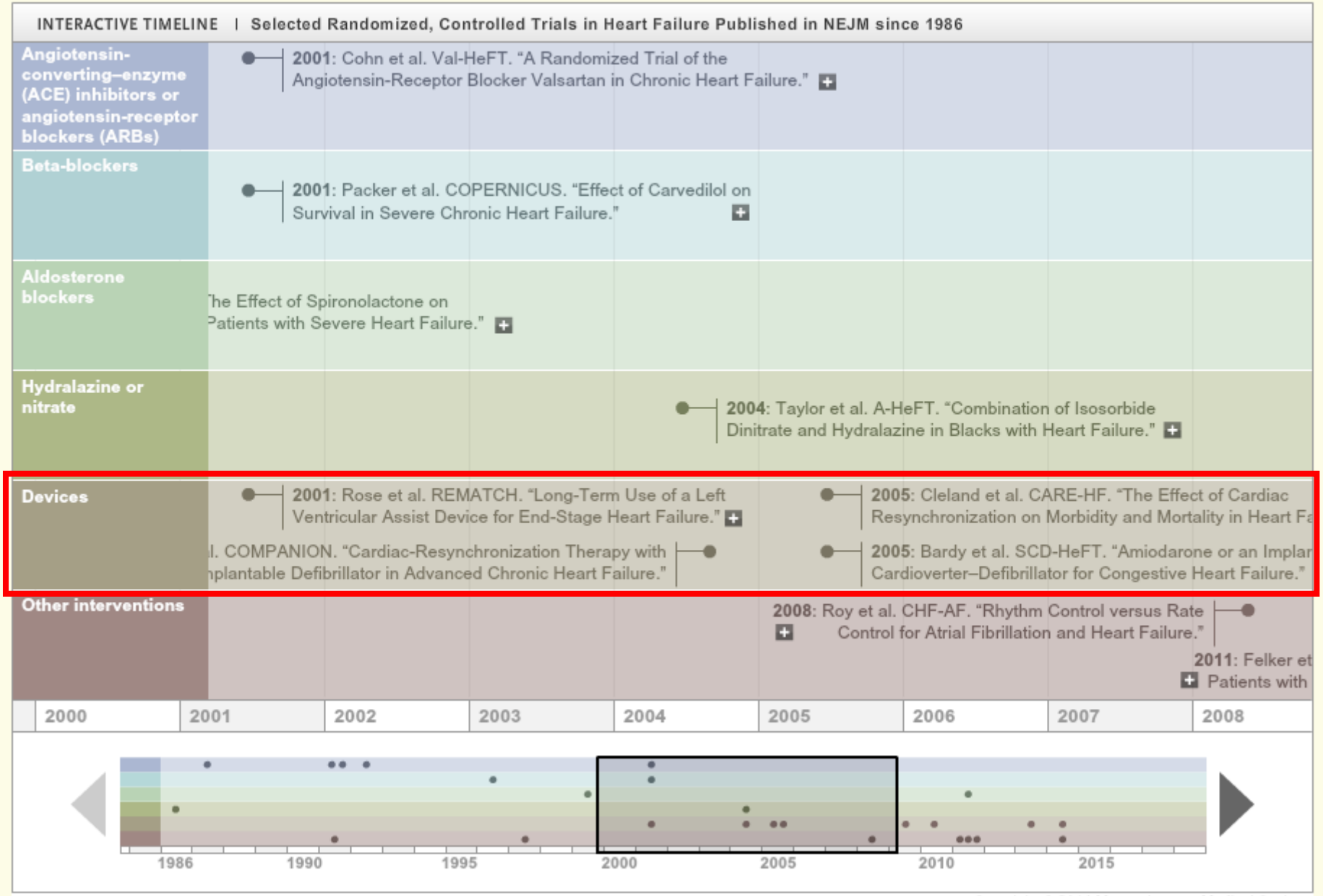
Table 2. Primary and Secondary Clinical End Points and Safety End Points through Day 30.*

End Point	Nesiritide (N=3496)	Placebo (N=3511)	Percentage-Point Difference or Odds Ratio (95% CI)†	P Value
Primary clinical end points				
Death from any cause or rehospitalization for heart failure — no./total no. (%)	321/3423 (9.4)	345/3413 (10.1)	−0.7 (−2.1 to 0.7)	0.31
Death from any cause	126/3490 (3.6)	141/3499 (4.0)	−0.4 (−1.3 to 0.5)	
Rehospitalization for heart failure	204/3422 (6.0)	208/3411 (6.1)	−0.1 (−1.2 to 1.0)	
Secondary clinical end points				
Persistent or worsening heart failure or death from any cause through hospital discharge — no./total no. (%)	147/3459 (4.2)	165/3462 (4.8)	−0.6 (−1.5 to 0.5)	0.30
Days alive and out of hospital through day 30	20.9±6.9	20.7±7.1	0.2 (−0.13 to 0.53)	0.16
Rehospitalization or death from cardiovascular causes — no./total no. (%)	372/3423 (10.9)	402/3415 (11.8)	−0.9 (−2.4 to 0.6)	0.24
Safety end points				
Death from cardiovascular causes — no./total no. (%)	112/3498 (3.2)	124/3509 (3.5)	−0.3 (−1.2 to 0.5)	0.44
Sudden death from cardiac causes — no./total no. (%)	19/3324 (0.6)	16/3327 (0.5)	0.1 (−0.3 to 0.4)	0.61
Hypotension — no./total no. (%)	930/3498 (26.6)	538/3509 (15.3)	11.3 (9.4 to 13.1)	<0.001
Asymptomatic	748/3498 (21.4)	436/3509 (12.4)	9.0 (7.2 to 10.7)	<0.001
Symptomatic	250/3496 (7.2)	141/3509 (4.0)	3.2 (2.1 to 4.2)	<0.001
>25% decrease in estimated GFR from study-drug initiation — no./total no. (%)	1032/3289 (31.4)	968/3278 (29.5)	1.09 (0.98 to 1.21)	0.11
Baseline estimated GFR <60 ml/min/1.73 m^2	484/1714 (28.2)	449/1717 (26.2)	1.11 (0.96 to 1.3)	0.16
Baseline estimated GFR ≥60 ml/min/1.73 m^2	548/1575 (34.8)	519/1561 (33.2)	1.07 (0.92 to 1.24)	0.38

* Plus–minus values are means ±SD. CI denotes confidence interval, and GFR glomerular filtration rate.
† Data shown are percentage-point differences, with the exception of data for >25% decrease in estimated GFR from study-drug initiation, for which the data shown are odds ratios.

combination with other therapies. It was not associated with a worsening of renal function, but it was associated with an increase in rates of hypotension. On the basis of these results, nesiritide cannot be recommended for routine use in the broad population of patients with acute heart failure. (Funded by Scios; ClinicalTrials.gov number, NCT00475852.)

Heart Failure Treatments.



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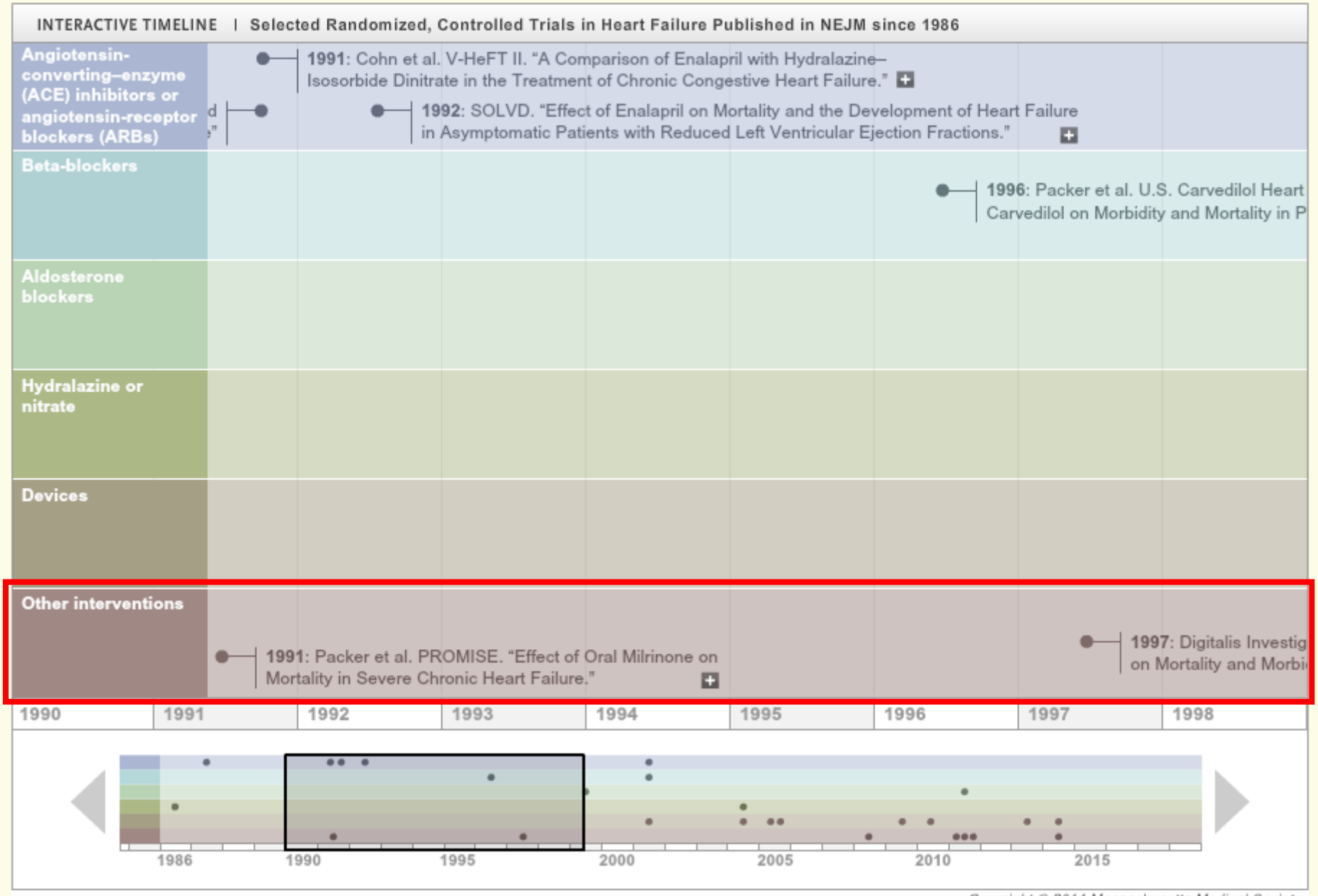

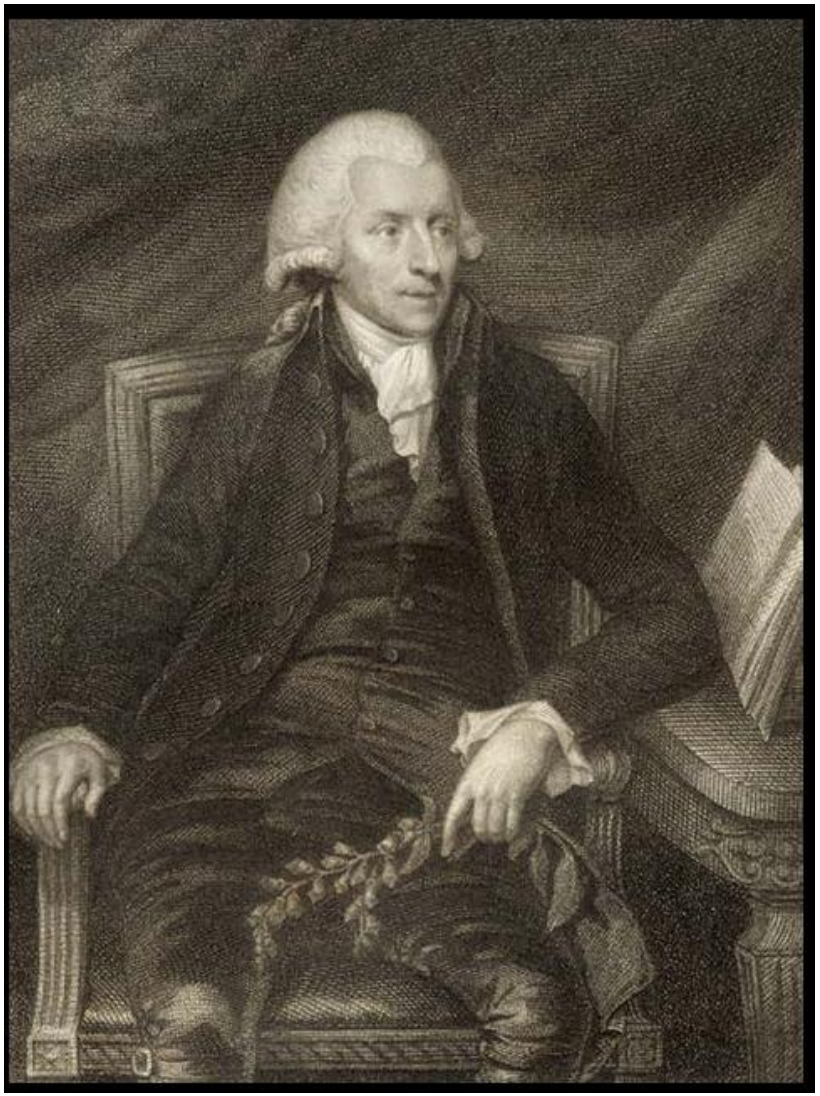

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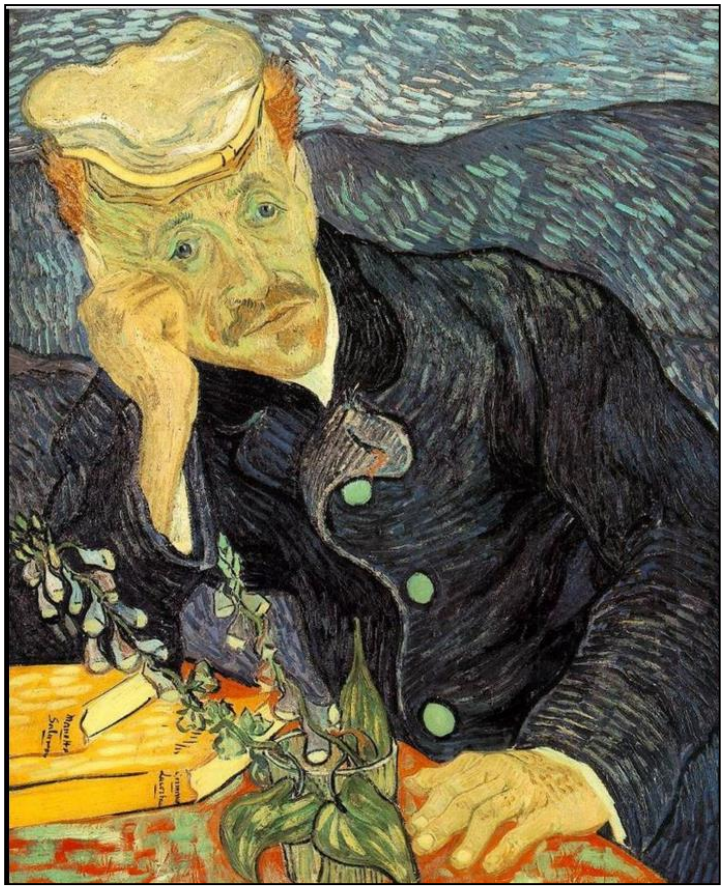

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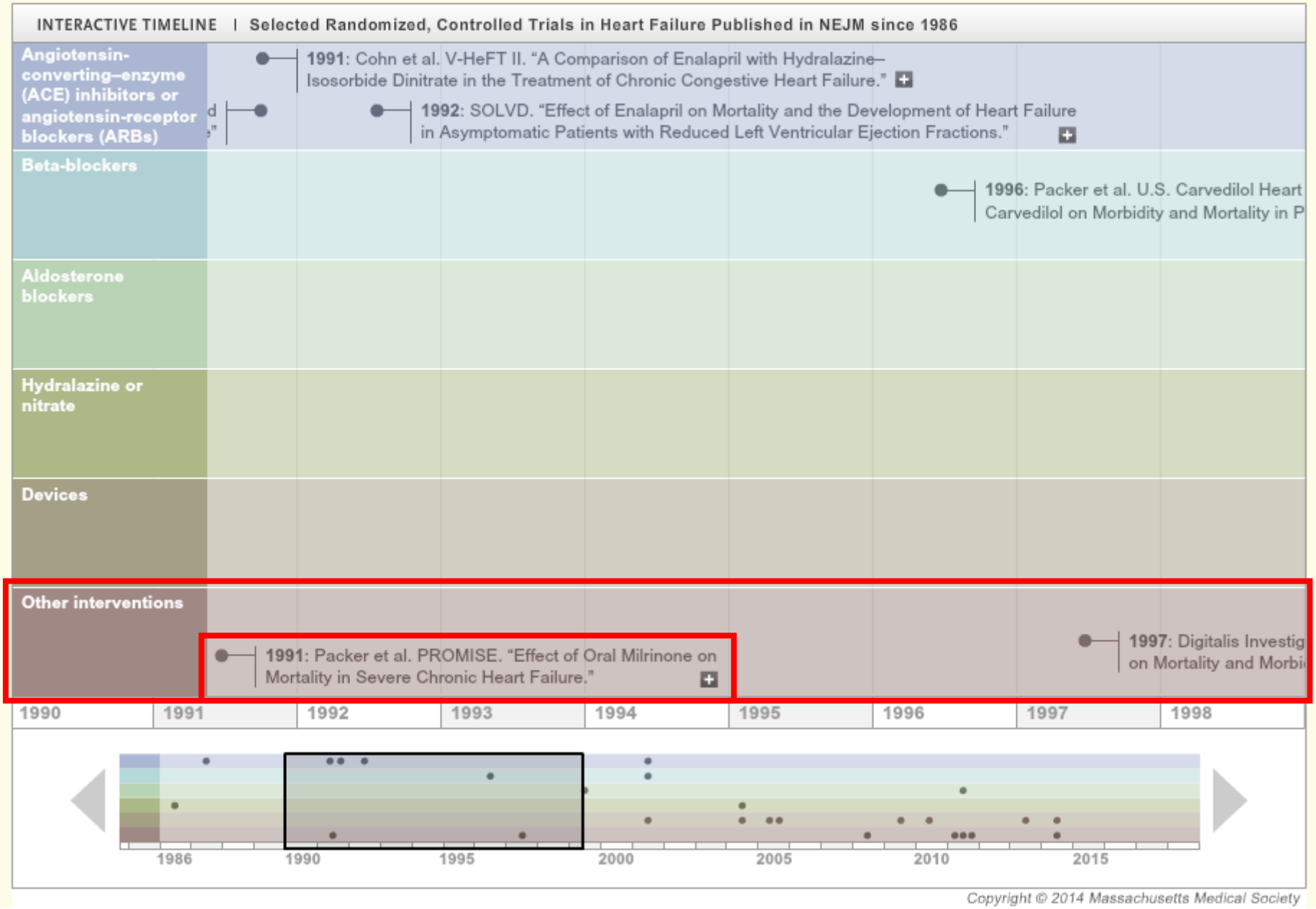

EFFECT OF ORAL MILRINONE ON MORTALITY IN SEVERE CHRONIC HEART FAILURE

MILTON PACKER, M.D., JOSEPH R. CARVER, M.D., RICHARD J. RODEHEFFER, M.D., RUSSELL J. IVANHOE, M.D., ROBERT DIBIANCO, M.D., STEVEN M. ZELDIS, M.D., GRADY H. HENDRIX, M.D., WILLIAM J. BOMMER, M.D., URI ELKAYAM, M.D., MARRICK L. KUKIN, M.D., GEORGE I. MALLIS, M.D., JOSEPHINE A. SOLLANO, R.N., JAMES SHANNON, M.D., P.K. TANDON, PH.D., AND DAVID L. DEMETS, PH.D., FOR THE PROMISE STUDY RESEARCH GROUP*

Abstract *Background.* Milrinone, a phosphodiesterase inhibitor, enhances cardiac contractility by increasing intracellular levels of cyclic AMP, but the long-term effect of this type of positive inotropic agent on the survival of patients with chronic heart failure has not been determined.

Methods. We randomly assigned 1088 patients with severe chronic heart failure (New York Heart Association class III or IV) and advanced left ventricular dysfunction to double-blind treatment with 40 mg of oral milrinone daily (561 patients) or placebo (527 patients). In addition, all patients received conventional therapy with digoxin, diuretics, and a converting-enzyme inhibitor throughout the trial. The median period of follow-up was 6.1 months (range, 1 day to 20 months).

Results. As compared with placebo, milrinone therapy was associated with a 28 percent increase in mortality from all causes (95 percent confidence interval, 1 to 61 percent; P = 0.038) and a 34 percent increase in cardiovascular mortality (95 percent confidence interval, 6 to 69 percent; P = 0.016). The adverse effect of milrinone was greatest in patients with the most severe symptoms (New York Heart Association class IV), who had a 53 percent increase in mortality (95 percent confidence interval, 13 to 107 percent; P = 0.006). Milrinone did not have a beneficial effect on the survival of any subgroup. Patients treated with milrinone had more hospitalizations (44 vs. 39 percent, P = 0.041), were withdrawn from double-blind therapy more frequently (12.7 vs. 8.7 percent, P = 0.041), and had serious adverse cardiovascular reactions, including hypotension (P = 0.006) and syncope (P = 0.002), more often than the patients given placebo.

Conclusions. Our findings indicate that despite its beneficial hemodynamic actions, long-term therapy with oral milrinone increases the morbidity and mortality of patients with severe chronic heart failure. The mechanism by which the drug exerts its deleterious effects is unknown.
(N Engl J Med 1991;325:1468-75.)

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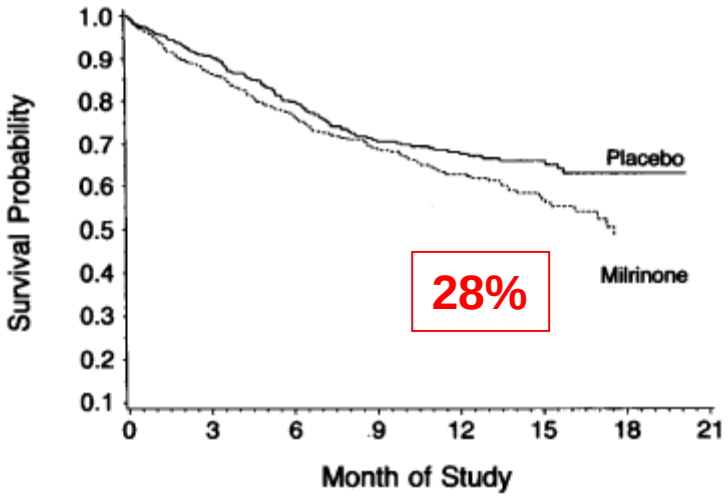
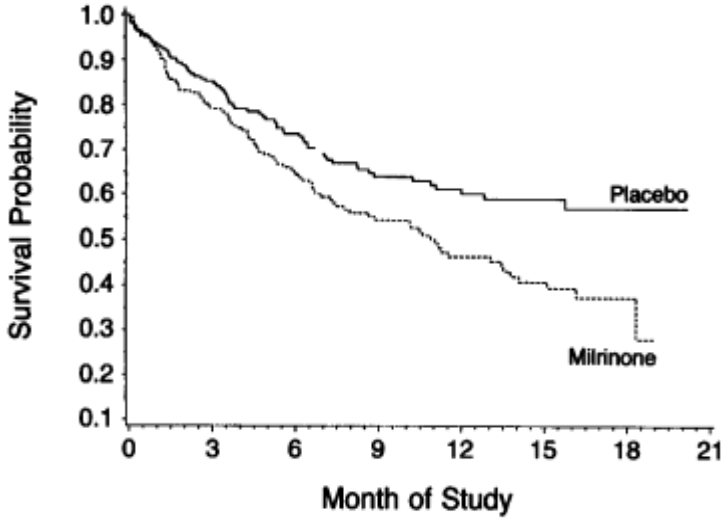


Placebo	527	375	270	185	137	77	21
Milrinone	561	395	284	184	132	74	14

Figure 1. Kaplan–Meier Analysis Showing Cumulative Rates of Survival in Patients with Chronic Heart Failure Treated with Milrinone or Placebo.

Mortality was 28 percent higher in the milrinone group than in the placebo group (P = 0.038). The numbers of patients at risk are shown at the bottom of the figure.



Placebo	224	159	116	78	59	35	12
Milrinone	233	155	109	69	49	30	6

Figure 2. Kaplan–Meier Analysis Showing Cumulative Rates of Survival in Patients with Class IV Heart Failure, According to Treatment Group.

Mortality was 53 percent higher in the milrinone group (P = 0.006).

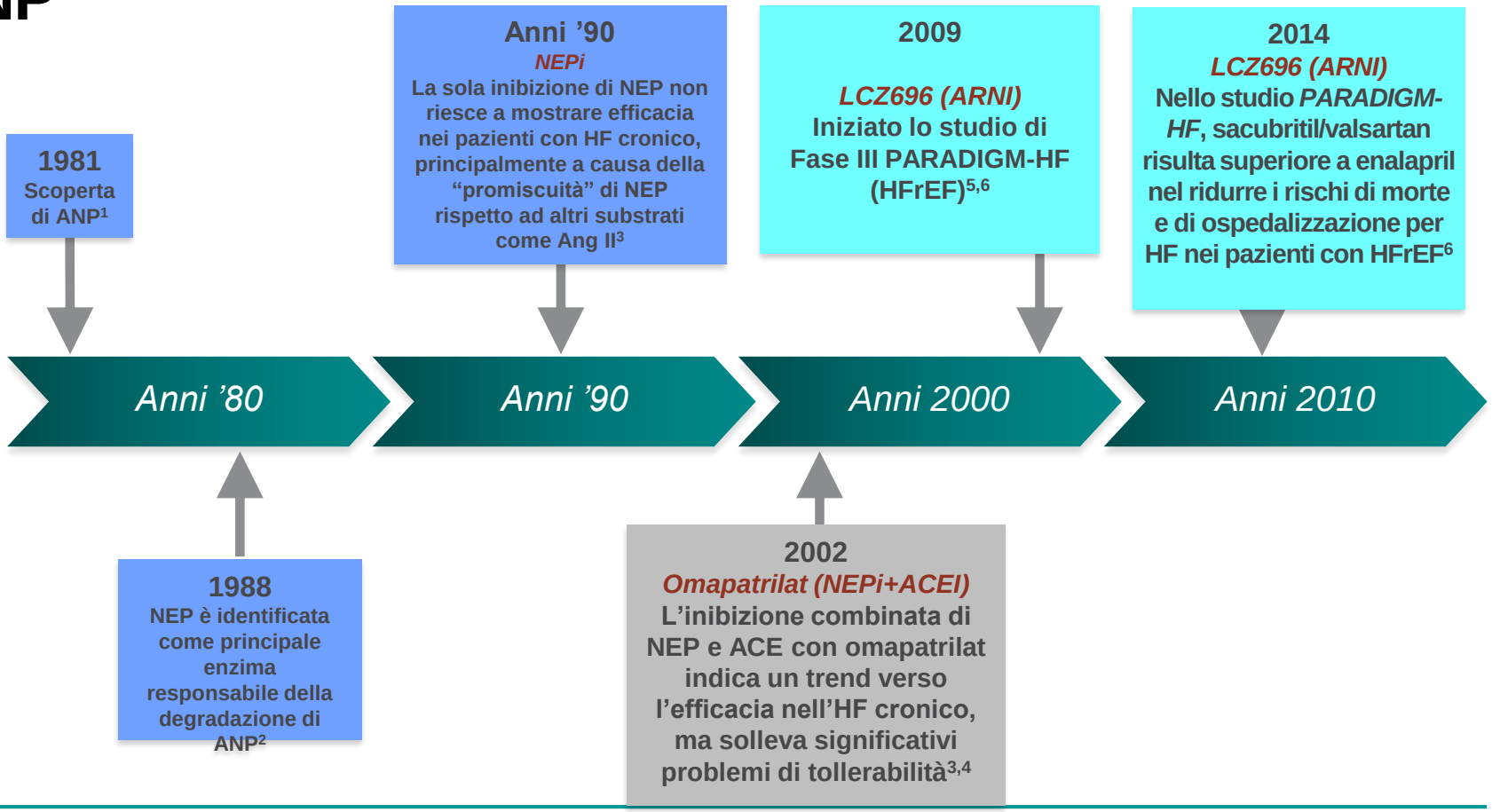
Studio PARADIGM-HF: riassunto delle caratteristiche al basale

Caratteristiche*	Sacubitril/valsartan (n=4.187)	Enalapril (n=4.212)
Età, anni	**63,8** ± 11,5	**63,8** ± 11,3
Donne, n (%)	879 (**21,0**)	953 (**22,6**)
Cardiomiopatia ischemica, n (%)	2.506 (59,9)	2.530 (60,1)
Frazione d'eiezione LV, %	**29,6** ± 6,1	**29,4** ± 6,3
Classe funzionale NYHA, n (%)		
II	2.998 (**71,6**)	2.921 (**69,3**)
III	969 (23,1)	1.049 (24,9)
PAS, mmHg	122 ± 15	121 ± 15
Frequenza cardiaca, bpm	72 ± 12	73 ± 12
NT-proBNP, pg/ml (IQR)	1.631 (885–3.154)	1.594 (886–3.305)
BNP, pg/ml (IQR)	255 (155–474)	251 (153–465)
Anamnesi positiva di diabete, n (%)	1.451 (34,7)	1.456 (34,6)
Trattamenti alla randomizzazione, n (%)		
Diuretici	3.363 (80,3)	3.375 (80,1)
Digitale	1.223 (29,2)	1.316 (31,2)
β-bloccanti	3.899 (**93,1**)	3.912 (**92,9**)
Antagonisti dei mineralcorticoidi	2.271 (**54,2**)	2.400 (**57,0**)
ICD	623 (14,9)	620 (14,7)
CRT	292 (7,0)	282 (6,7)

*Media ± deviazione standard, se non diversamente riportato

McMurray et al. N Engl Med 2014;371:993–1004

La combinazione sacubritil/valsartan è il primo farmaco che dimostra un significativo beneficio clinico nell'HFrEF mediante potenziamento del sistema NP



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