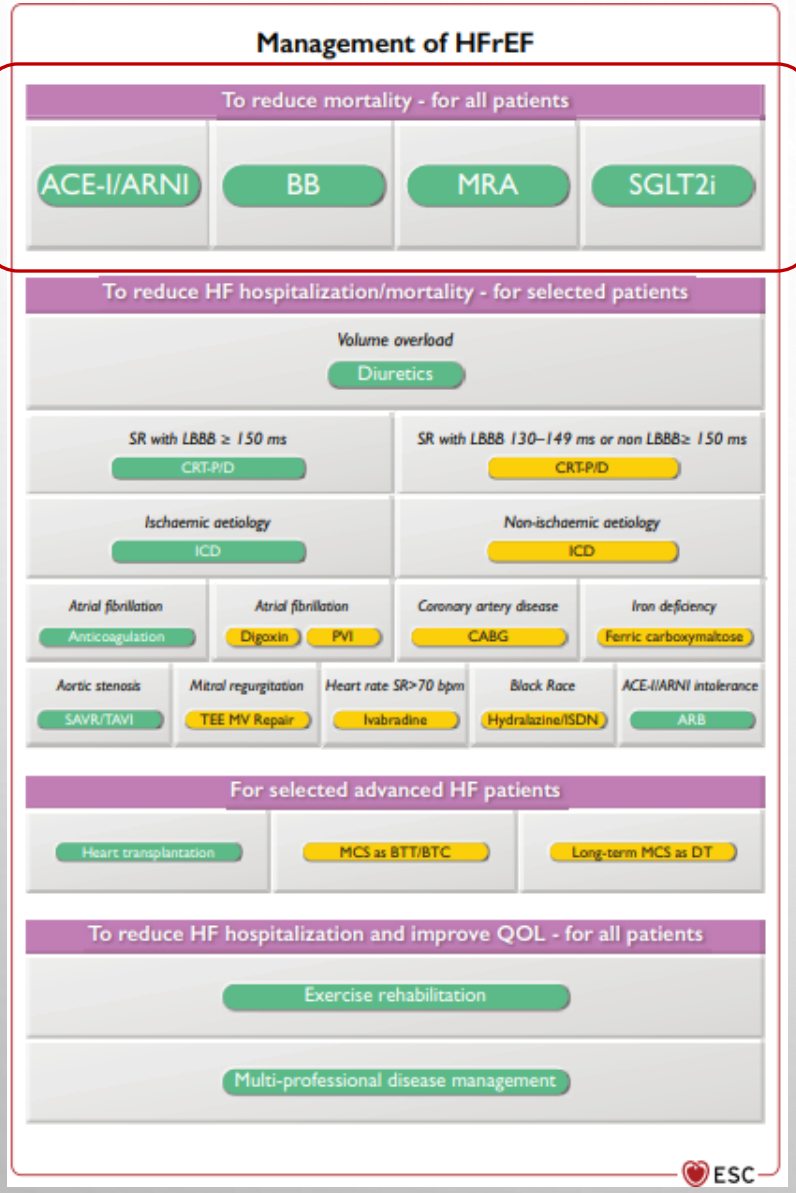
I sessione

Trattamento del Paziente Fragile con SCOMPENSO CARDIACO

La terapia farmacologica con i “fantastici quattro”

Dott.ssa Calcagnile Chiara

I “ FANTASTICI QUATTRO ”



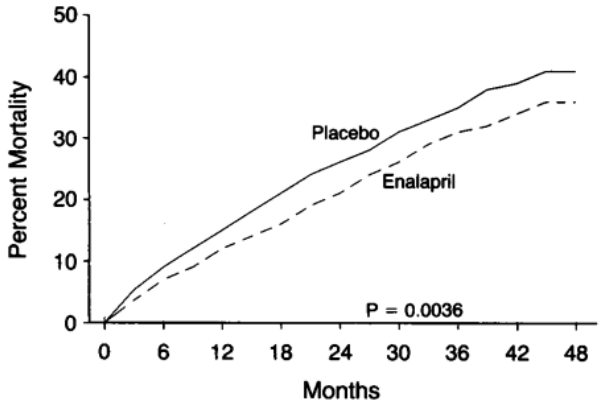
European Heart Journal (2021) 00, 1128 doi:10.1093/eurheartj/ehab368

ACE-I RAZIONALE

The New England
Journal of Medicine

Volume 325 AUGUST 1, 1991 Number 5

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



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.

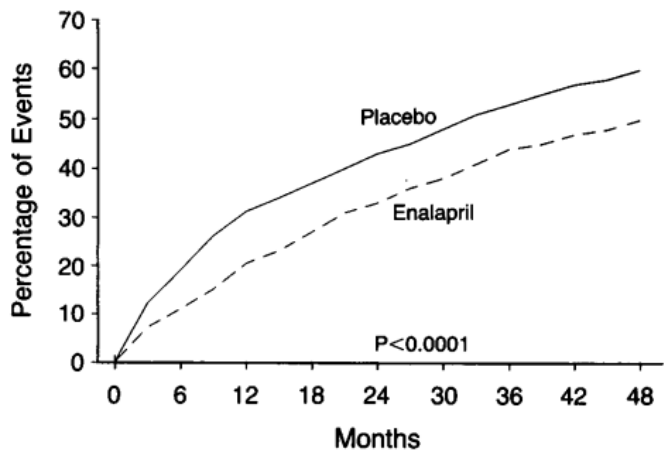


Figure 3. Percentage of Events, Defined as Death or Hospitalization for Congestive Heart Failure, Occurring in the Placebo and Enalapril Groups.

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

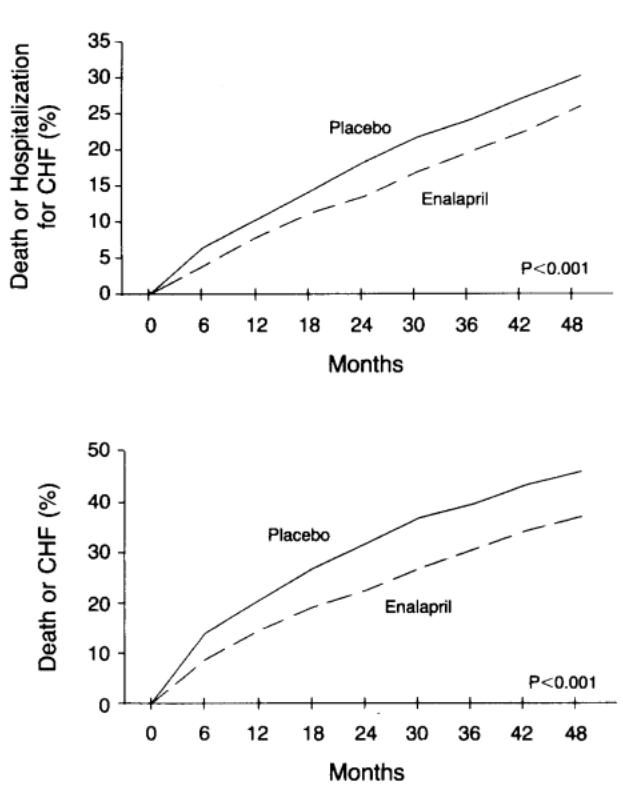


Figure 2. Death or Hospitalization for Congestive Heart Failure (CHF) and Death or Development of Heart Failure in the Prevention Trial.

ACE-I MECCANISMO D'AZIONE

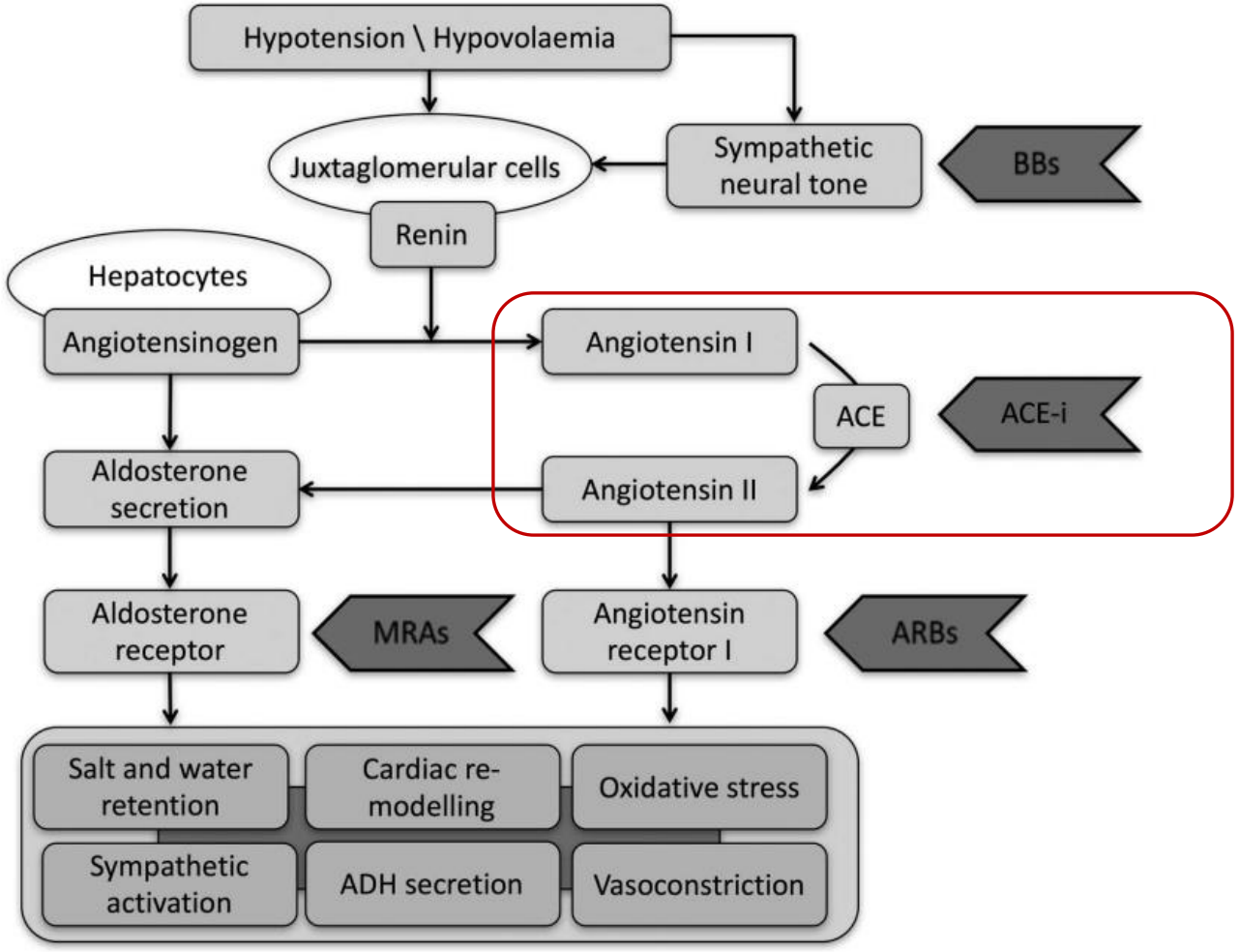


Figure 1 Schematic overview of the renin-angiotensin-aldosterone system and its manifestations in heart failure as well as the mechanism of action of currently recommended pharmacological agents. ADH, antidiuretic hormone; ACE-i, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonists; BB, β-blocker.

Orsborne C, et al. Postgrad Med J 2017;93:29–37. doi:10.1136/postgradmedj-2016-134045

ACE-I QUALI

Table 8 Evidence-based doses of disease-modifying drugs in key randomized trials in patients with heart failure with reduced ejection fraction

	Starting dose	Target dose
ACE-I		
Captopril[a]	6.25 mg *t.i.d.*	50 mg *t.i.d.*
Enalapril	2.5 mg *b.i.d.*	10–20 mg *b.i.d.*
Lisinopril[b]	2.5–5 mg *o.d.*	20–35 mg *o.d.*
Ramipril	2.5 mg *b.i.d.*	5 mg *b.i.d.*
Trandolapril[a]	0.5 mg *o.d.*	4 mg *o.d.*

European Heart Journal (2021) 00, 1128 doi:10.1093/eurheartj/ehab368

ARNI RAZIONALE

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 11, 2014 VOL. 371 NO. 11

Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

John J.V. McMurray, M.D., Milton Packer, M.D., Akshay S. Desai, M.D., M.P.H., Jianjian Gong, Ph.D., Martin P. Lefkowitz, M.D., Adel R. Rizkala, Pharm.D., Jean L. Rouleau, M.D., Victor C. Shi, M.D., Scott D. Solomon, M.D., Karl Swedberg, M.D., Ph.D., and Michael R. Zile, M.D., for the PARADIGM-HF Investigators and Committees*

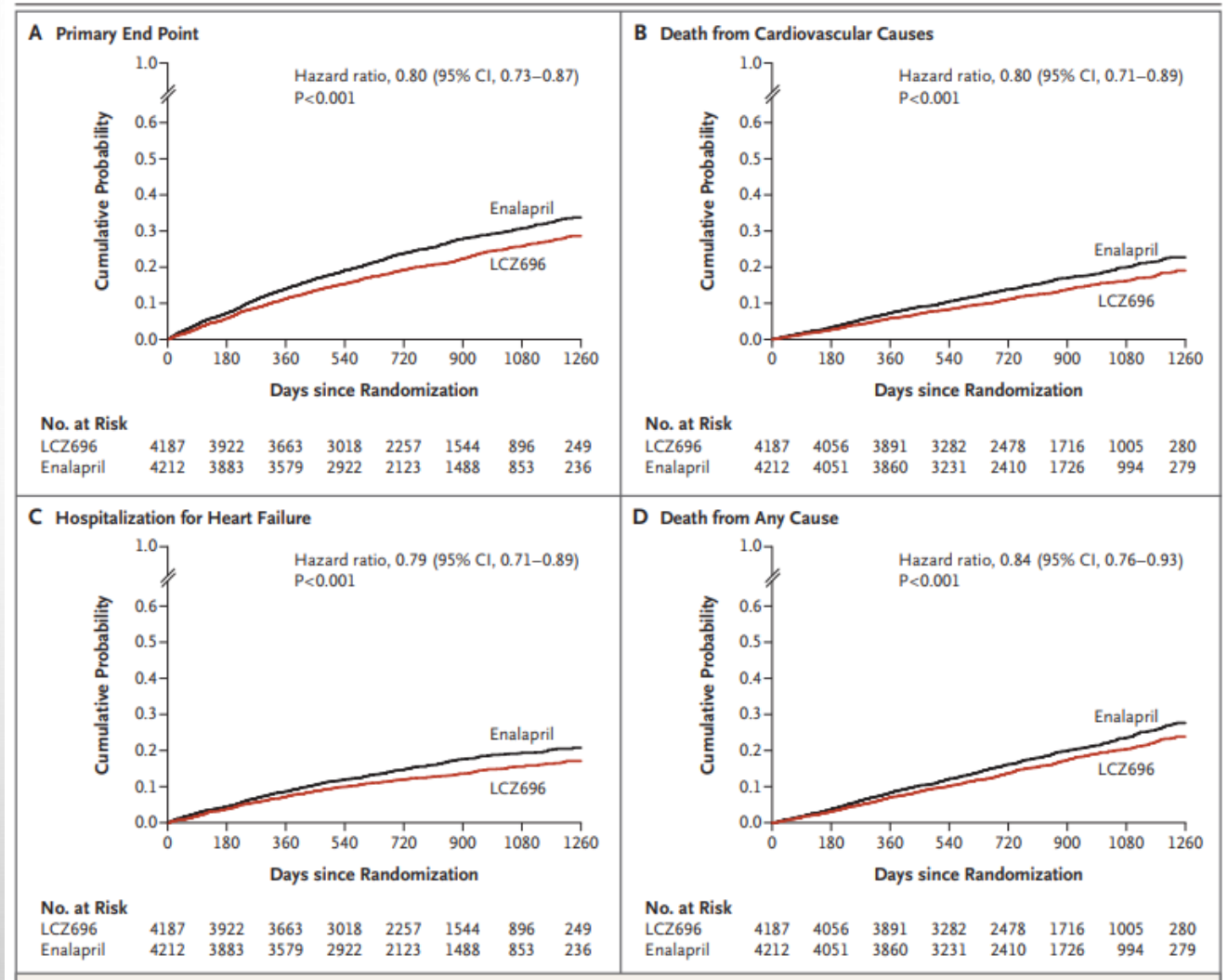


Figure 2. Kaplan–Meier Curves for Key Study Outcomes, According to Study Group.

Shown are estimates of the probability of the primary composite end point (death from cardiovascular causes or first hospitalization for heart failure) (Panel A), death from cardiovascular causes (Panel B), first hospitalization for heart failure (Panel C), and death from any cause (Panel D).

ARNI MECCANISMO D'AZIONE

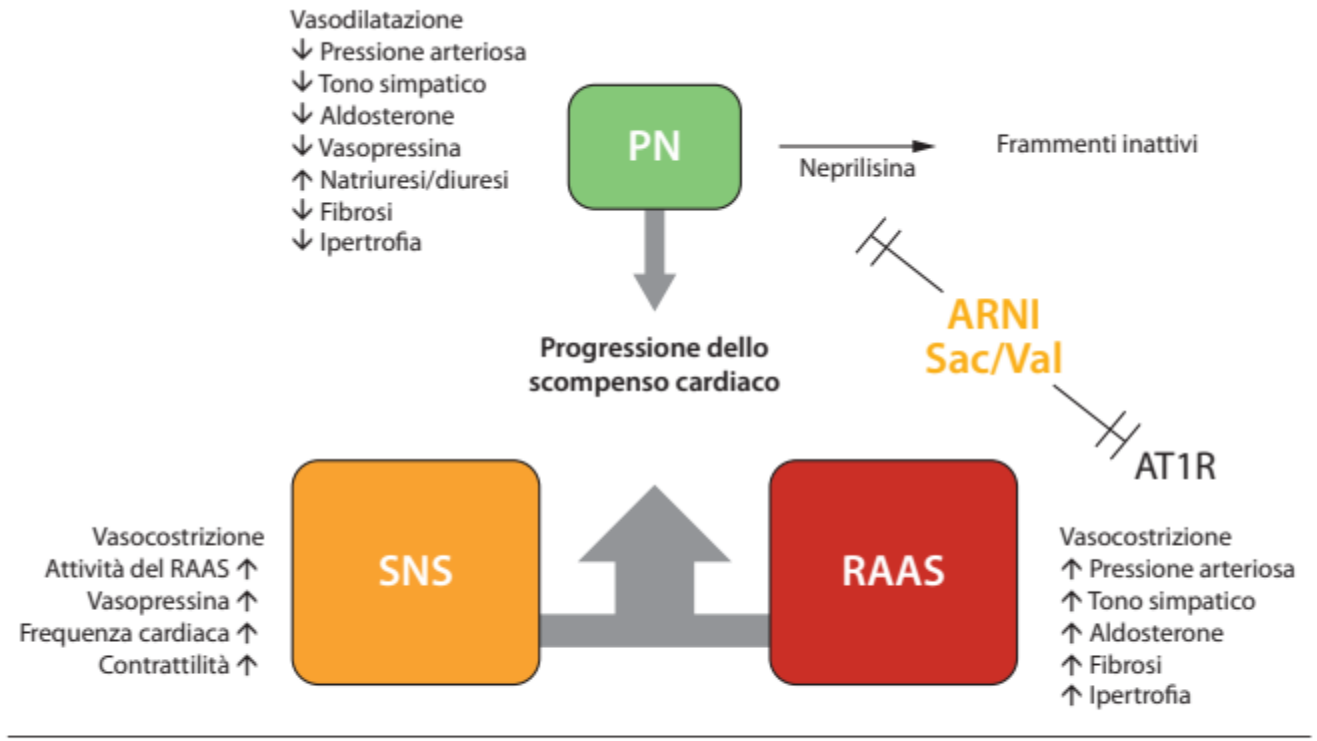


Figura 3. Meccanismo d'azione degli inibitori del recettore dell'angiotensina e della neprilisina (ARNI). AT1R, recettore per l'angiotensina II di tipo 1; PN, peptidi natriuretici; RAAS, sistema renina-angiotensina-aldosterone; Sac/Val, sacubitril/valsartan; SNS, sistema nervoso simpatico.

G Ital Cardiol 2022;23(3):217-228

ARNI DOSAGGIO

	Bassa dose	Dose intermedia	Dose target
Sacubitril/Valsartan	24/26 mg x 2	49/51 mg x 2	97/103 mg x 2
Enalapril	2,5 mg x 2	5 mg x 2	10 mg x 2
Ramipril	2,5 mg/die	5 mg/die	10 mg/die
Valsartan	80 mg/die	80 mg x 2	160 mg x 2
…			

BETA BLOCCANTI RAZIONALE

Table 2 | Summary of main clinical trials reported in the text investigating the efficacy of BB in HF.

Study name (reference)	No patients	BB used	Description	Main findings	Additional findings and comments
MDC (Waagstein et al., 1993)	383	Metoprolol	HF secondary to Dilated Cardiomyopathy (EF <40%)	34% decrease in mortality or need for transplantation	No significant difference in mortality alone
MERIT-HF (Hjalmarson et al., 2000)	3991	Metoprolol succinate	Mild-moderate HF (EF <40%) NYHA II-IV	<34% decrease in all cause mortality	<39% decrease in cardiac death and non-fatal MI
CIBIS (CIBIS Investigators and Committees, 1994)	641	Bisoprolol	Moderate HF (EF <40%) NYHA III-IV	No significant difference in mortality	Significant improvement of functional status of the patients
CIBIS II (CIBIS-II Investigators, 1999)	2647	Bisoprolol	Moderate HF (EF <35%) NYHA III-IV	32% decrease risk of mortality and hospitalization for HF	Greatest effects in patients with ischaemic HF and NYHA III at baseline
CIBIS III (Willenheimer et al., 2005)	1010	Bisoprolol (vs. enalapril)	Mild moderate HF (EF <35%) NYHA II-III	Non-inferiority of bisoprolol vs enalapril in reducing mortality as first treatment in ITT	Non-inferiority of bisoprolol was not proven in *per-protocol* analysis
US Carvedilol study (Packer et al., 1996)	1094	Carvedilol	Mild moderate HF NYHA II-IV	65% mortality reduction	38% reduction in death or hospitalization for cardiovascular reasons
COPERNICUS (Packer et al., 2002)	2289	Carvedilol	Severe HF (EF <25%) NYHA III-IV	35% in risk of death	27% decrease death or hospitalization for a cardiovascular reason
CAPRICORN (The CAPRICORN Investigators, 2001)	1959	Carvedilol	Patients with recent MI and left ventricular dysfunction (EF <40%)	23% reduction in mortality	No significant difference in primary endpoint (all-cause mortality or hospitalization for cardiovascular problems)
COMET (Poole-Wilson et al., 2003)	3029	Carvedilol vs. Metoprolol tartrate	Mild moderate HF (EF <35%) NYHA II-IV	17% decrease in carvedilol- vs. metoprolol- arm	Concerns about metoprolol formulation
BEST (BEST Investigators, 2001)	2708	Bucindolol	Mild moderate HF (EF <35%) NYHA III-IV	No significant overall survival benefit	Reduction in mortality in patients homozygous for Arg389 (subsequent pharmacogenetic analysis)
SENIORS (Flather et al., 2005)	2128	Nebivolol	Mild moderate HF (EF <35% in last 6-months) Age >70yrs	14% reduction mortality and hospitalizations	Significant increase of LVEF and decrease in end-systolic volume

The Table re-elaborates and integrates the data reported in Table I of Kubon et al., 2011.

REVIEW ARTICLE
published: 14 November 2013
doi: 10.3389/fphys.2013.00323

BETA BLOCCANTI MECCANISMO D'AZIONE

- *ANTAGONIZZANO L'EFFETTO CARDIOTOSSICO DELLE CATECOLAMINE DERIVANTE DALLA PERSISTENTE ATTIVAZIONE DEL SISTEMA NERVOSO SIMPATICO*
- *PROLUNGANO LA FASE DIASTOLICA → MIGLIORAMENTO DEL FLUSSO CORONARICO*
- *RIDUCONO LA FREQUENZA CARDIACA E LA PRESSIONE ARTERIOSA*
- *EFFETTO ANTIARITMICO*

J. *Cardiovasc. Dev. Dis. 2021, 8, 101. https://doi.org/10.3390/jcdd8090101*

BETA BLOCCANTI QUALI

Table 8 Evidence-based doses of disease-modifying drugs in key randomized trials in patients with heart failure with reduced ejection fraction

Beta-blockers		
Bisoprolol	1.25 mg *o.d.*	10 mg *o.d.*
Carvedilol	3.125 mg *b.i.d.*	25 mg *b.i.d.*[e]
Metoprolol succinate (CR/XL)	12.5–25 mg *o.d.*	200 mg *o.d.*
Nebivolol[d]	1.25 mg *o.d.*	10 mg *o.d.*

European Heart Journal (2021) 00, 1128 doi:10.1093/eurheartj/ehab368

MRA RAZIONALE

The New England Journal of Medicine

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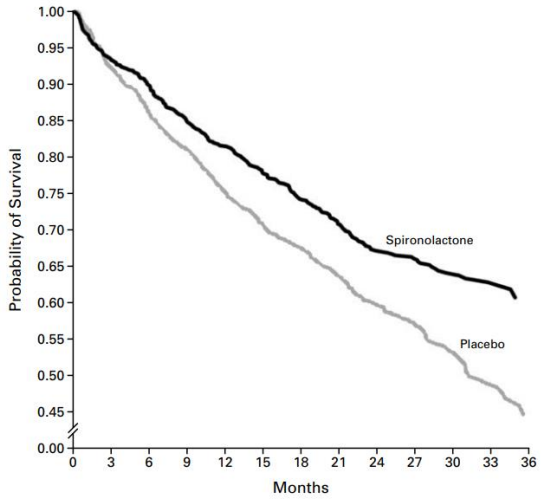
VOLUME 341 SEPTEMBER 2, 1999 NUMBER 10

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*



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).

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 6, 2011 VOL. 364 NO. 1

Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms

Faiez Zannad, M.D., Ph.D., John J.V. McMurray, M.D., Henry Krum, M.B., Ph.D., Dirk J. van Veldhuisen, M.D., Ph.D., Karl Swedberg, M.D., Ph.D., Harry Shi, M.S., John Vincent, M.B., Ph.D., Stuart J. Pocock, Ph.D., and Bertram Pitt, M.D., for the EMPHASIS-HF Study Group*

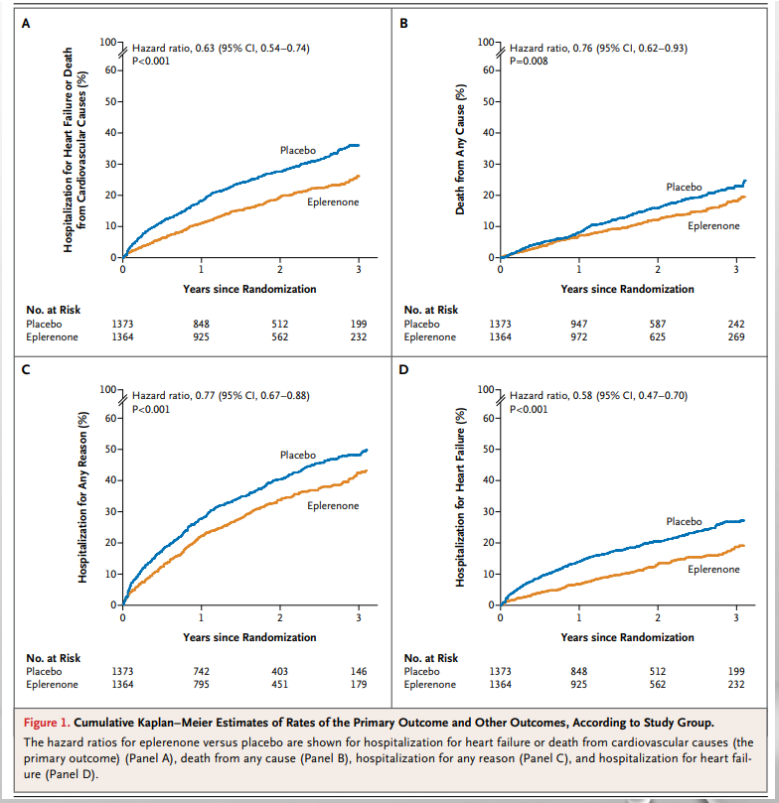


Figure 1. Cumulative Kaplan–Meier Estimates of Rates of the Primary Outcome and Other Outcomes, According to Study Group.

The hazard ratios for eplerenone versus placebo are shown for hospitalization for heart failure or death from cardiovascular causes (the primary outcome) (Panel A), death from any cause (Panel B), hospitalization for any reason (Panel C), and hospitalization for heart failure (Panel D).

MRA MECCANISMO D'AZIONE

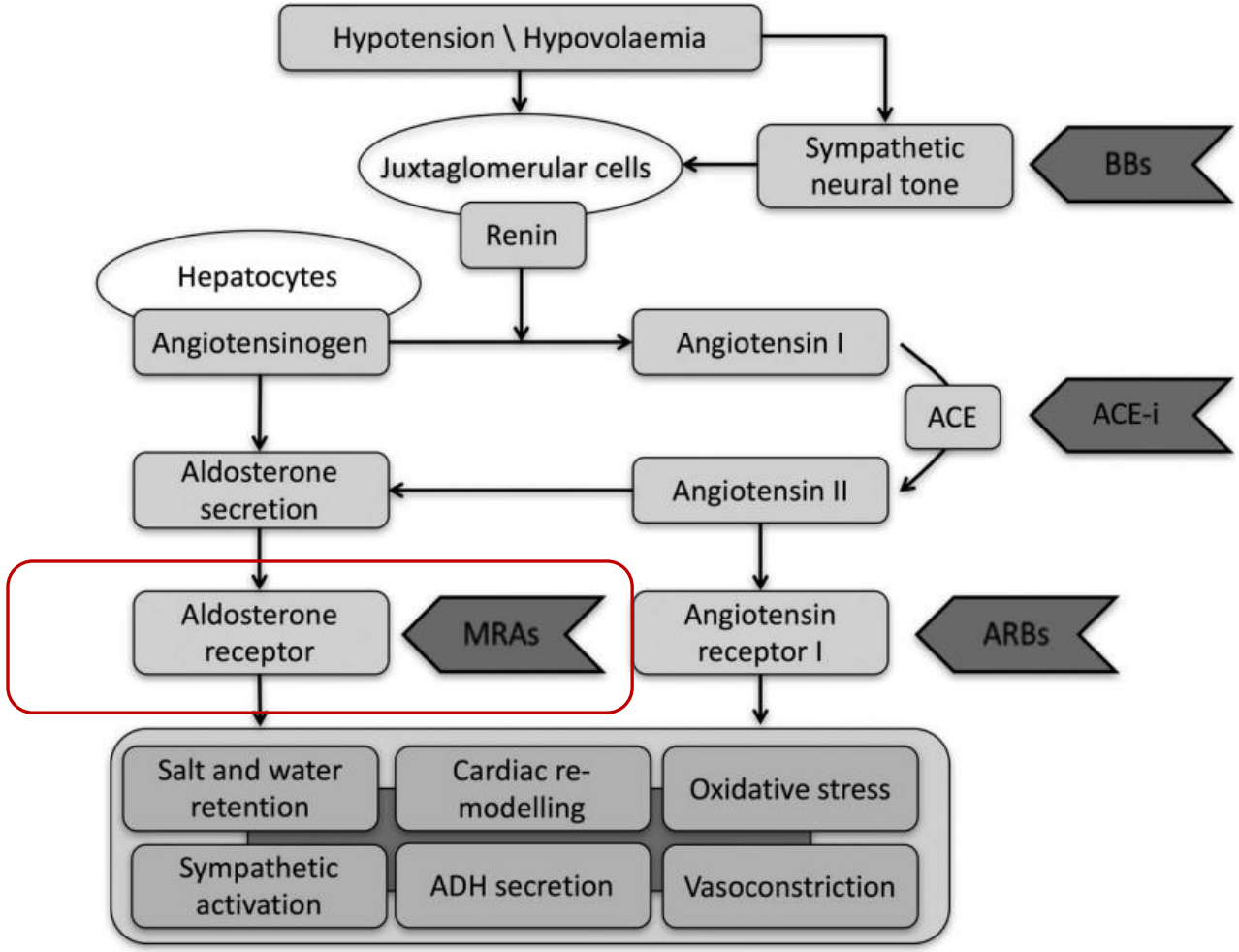


Figure 1 Schematic overview of the renin-angiotensin-aldosterone system and its manifestations in heart failure as well as the mechanism of action of currently recommended pharmacological agents. ADH, antidiuretic hormone; ACE-i, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonists; BB, β-blocker.

Orsborne C, et al. Postgrad Med J 2017;93:29–37. doi:10.1136/postgradmedj-2016-134045

MRA QUALI

Table 8 Evidence-based doses of disease-modifying drugs in key randomized trials in patients with heart failure with reduced ejection fraction

MRA		
Eplerenone	25 mg *o.d.*	50 mg *o.d.*
Spironolactone	25 mg *o.d.*[f]	50 mg *o.d.*

European Heart Journal (2021) 00, 1128 doi:10.1093/eurheartj/ehab368

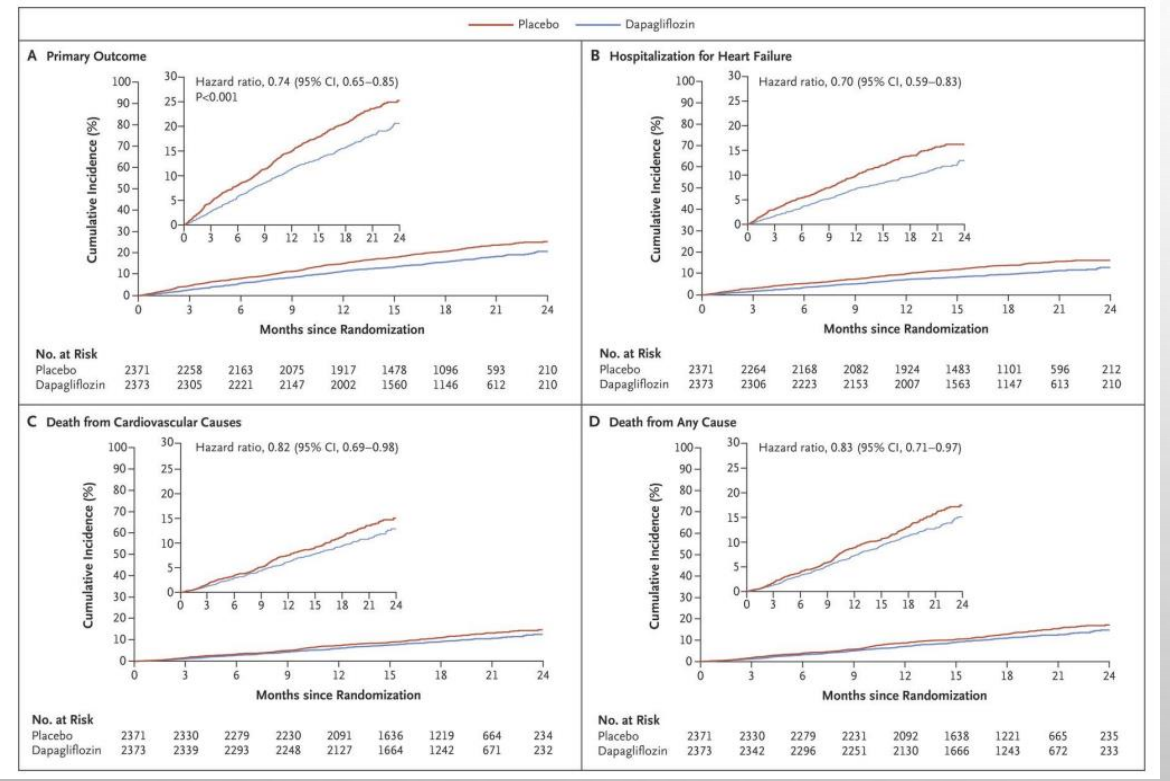
SGLT2i RAZIONALE

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 21, 2019 VOL. 381 NO. 21

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

J.J.V. McMurray, S.D. Solomon, S.E. Inzucchi, L. Køber, M.N. Kosiborod, F.A. Martinez, P. Ponikowski, M.S. Sabatine, I.S. Anand, J. Bělohlávek, M. Böhm, C.-E. Chiang, V.K. Chopra, R.A. de Boer, A.S. Desai, M. Diez, J. Drozdz, A. Dukát, J. Ge, J.G. Howlett, T. Katova, M. Kitakaze, C.E.A. Ljungman, B. Merkely, J.C. Nicolau, E. O'Meara, M.C. Petrie, P.N. Vinh, M. Schou, S. Tereshchenko, S. Verma, C. Held, D.L. DeMets, K.F. Docherty, P.S. Jhund, O. Bengtsson, M. Sjöstrand, and A.-M. Langkilde, for the DAPA-HF Trial Committees and Investigators*

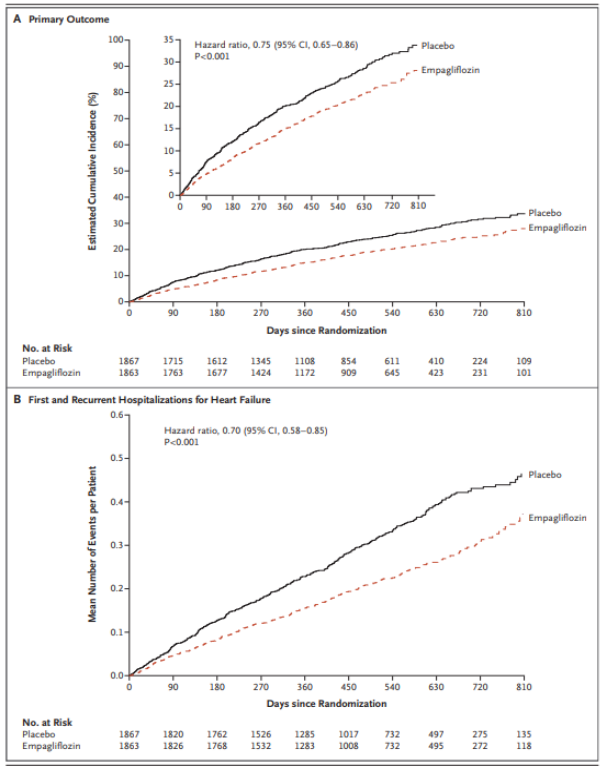


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 8, 2020 VOL. 383 NO. 15

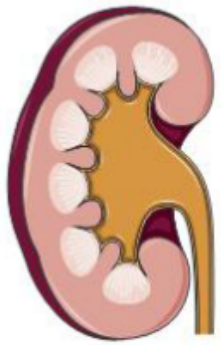
Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

M. Packer, S.D. Anker, J. Butler, G. Filippatos, S.J. Pocock, P. Carson, J. Januzzi, S. Verma, H. Tsutsui, M. Brueckmann, W. Jamal, K. Kimura, J. Schnee, C. Zeller, D. Cotton, E. Bocchi, M. Böhm, D.-J. Choi, V. Chopra, E. Chuquiure, N. Giannetti, S. Janssens, J. Zhang, J.R. Gonzalez Juanatey, S. Kaul, H.-P. Brunner-La Rocca, B. Merkely, S.J. Nicholls, S. Perrone, I. Pina, P. Ponikowski, N. Sattar, M. Senni, M.-F. Seronde, J. Spinar, I. Squire, S. Taddei, C. Wanner, and F. Zannad, for the EMPEROR-Reduced Trial Investigators*



SGLT2I MECCANISMO D'AZIONE

Figura 1 ◆ Meccanismo d'azione degli inibitori di SGLT2



Aumento dell'escrezione di glucosio

Riduzione glicemica → ↓ HbA_{1c}

Perdita di calorie → ↓ Peso corporeo

Aumento diuresi Natriuresi → Ridotto carico di sodio → ↓ Pressione arteriosa

COME FARE?

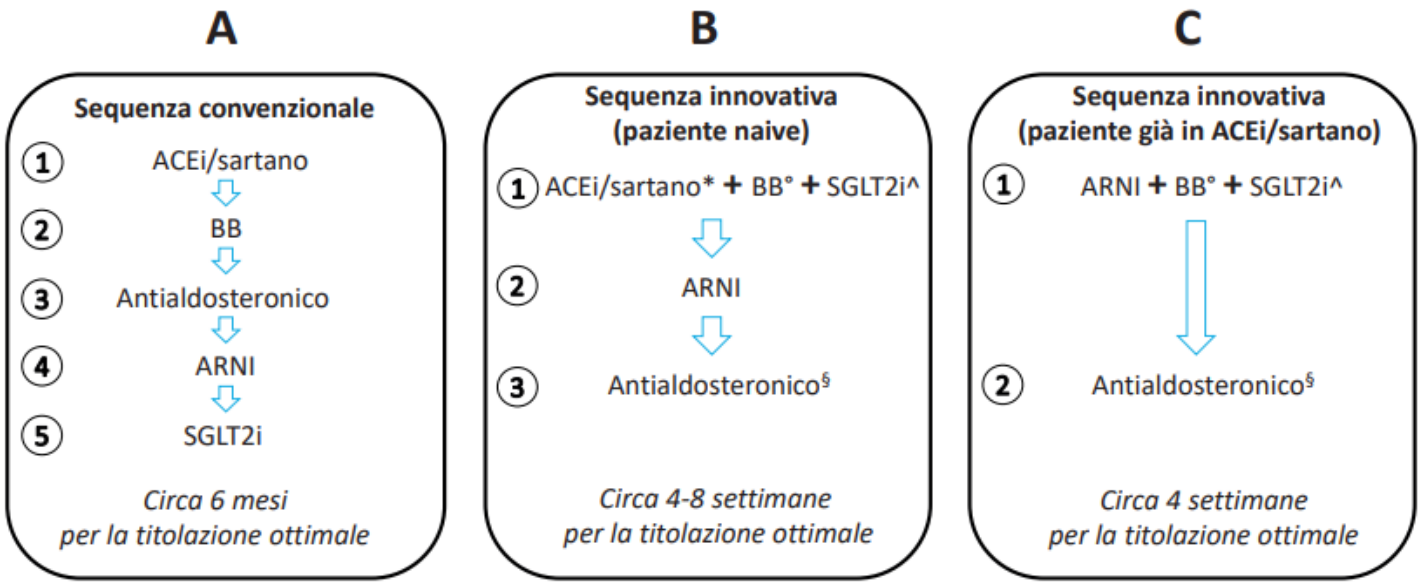


Figura 2. Schema di sequenza di inizio della terapia nel paziente con scompenso sistolico convenzionale (*A*) ed esempi di sequenze innovative in pazienti naive (*B*) o già in terapia con inibitori dell'enzima di conversione dell'angiotensina (ACEi) o sartano (*C*).
ARNI, inibitori del recettore dell'angiotensina e della neprilisina (sacubitril/valsartan); BB, betabloccante; SGLT2i, inibitore del co-trasportatore sodio-glucosio di tipo 2.
*In caso di compatibilità con il Piano Terapeutico AIFA l'inizio dell'ARNI in pazienti non ipotesi può essere anticipato.
°In pazienti con scompenso cardiaco avanzato l'inizio del BB può seguire la stabilizzazione con inibitori del sistema renina-angiotensina e diuretici.
^In pazienti ospedalizzati l'inizio degli SGLT2i dovrebbe essere posticipato alla fase post-dimissione.
§In pazienti significativamente ipotesi l'inizio dell'antialdosteronico può essere anticipato rispetto ad ARNI.

G Ital Cardiol 2021;22(10):861-868

CONCLUSIONI

- *LE LINEE GUIDA EUROPEE RACCOMANDANO 4 CLASSI DI FARMACI PER IL TRATTAMENTO DEI PAZIENTI CON HFrEF*
- *LA TRIADE ACE-I/ARNI – BETA BLOCCANTI – MRA E' RACCOMANDATA COME TERAPIA DI BASE RICORDANDO CHE QUESTI FARMACI ANDREBBERO TITOLATI ALLA MASSIMA DOSE TOLLERATA DAL PAZIENTE*
- *GLI ARNI VANNO CONSIDERATI IN SOSTITUZIONE DEGLI ACE-I (NEI PAZIENTI ANCORA SINTOMATICI) O IMPOSTATI COME TERAPIA DI PRIMA LINEA AL POSTO DEGLI ACE-I*
- *GLI SGLT2i DEVONO ESSERE AGGIUNTI ALLA TERAPIA CON ACE-I/ARNI-BETA BLOCCANTI-MRA AL FINE DI RIDURRE IL RISCHIO DI MORTE CARDIOVASCOLARE E DI PEGGIORAMENTO DELLO SCOMPENSO CARDIACO*
- *E' DA PREFERIRE UN APPROCCIO MULTIFARMACO A STEP RAPIDI RISPETTO A UNA CLASSICA STRATEGIA SEQUENZIALE*

GRAZIE PER L'ATTENZIONE