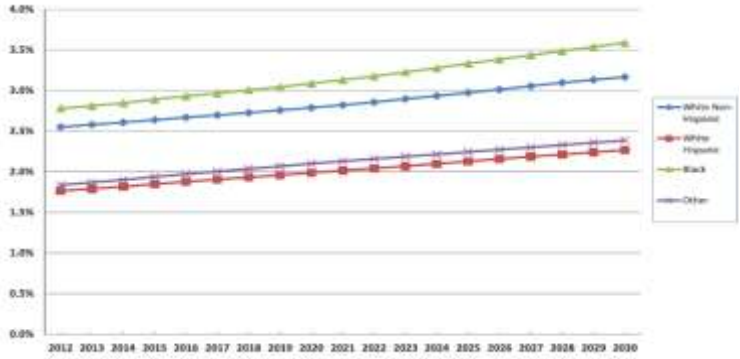
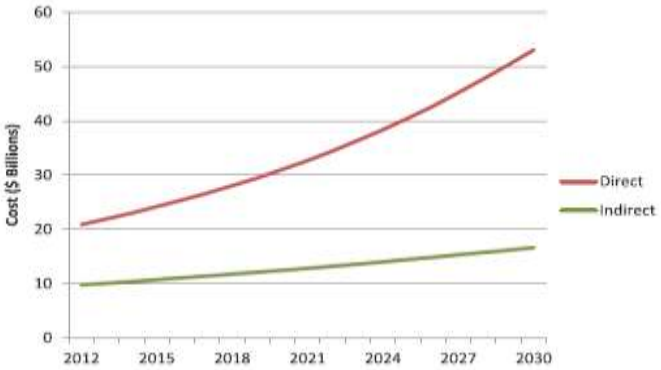
La Prevalenza dello Scompenso Cardiaco nel Futuro





Heidenreich PA, Circ Heart Fail 2013

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

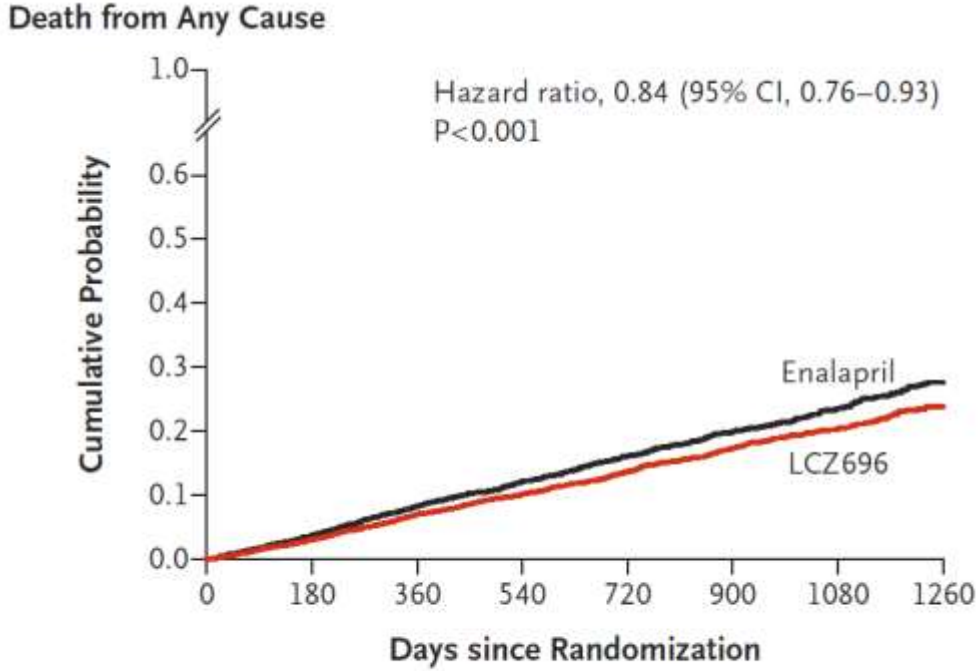
Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

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*

McMurray, et al. N Engl J Med 2014; 10.1056/NEJMoa1409077.

RESULTS:
Secondary endpoint:

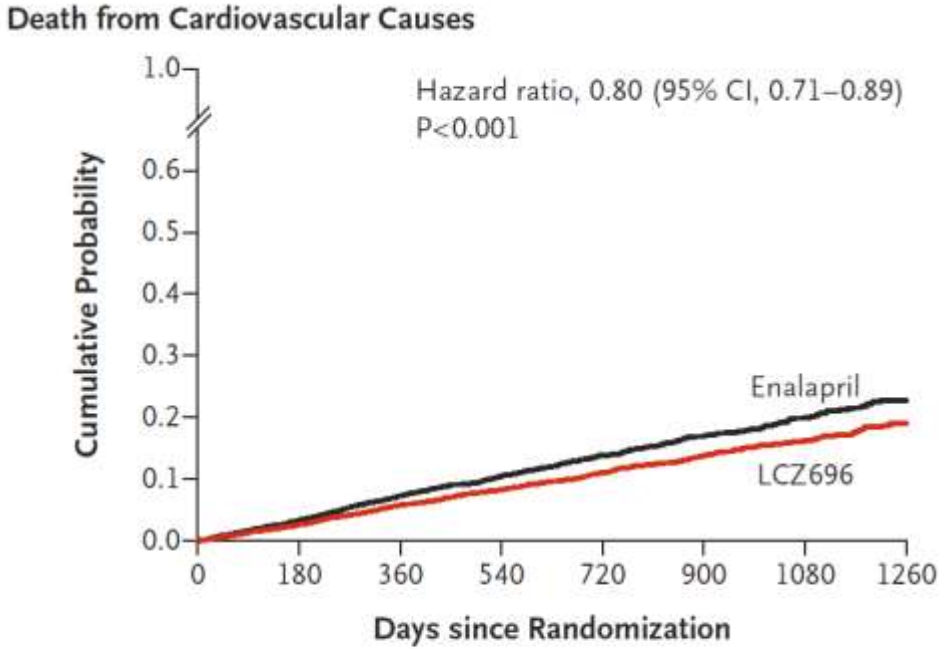
Death from any cause



McMurray, et al. N Engl J Med 2014; 10.1056/NEJMoa1409077.

RESULTS:
Components of primary endpoint:

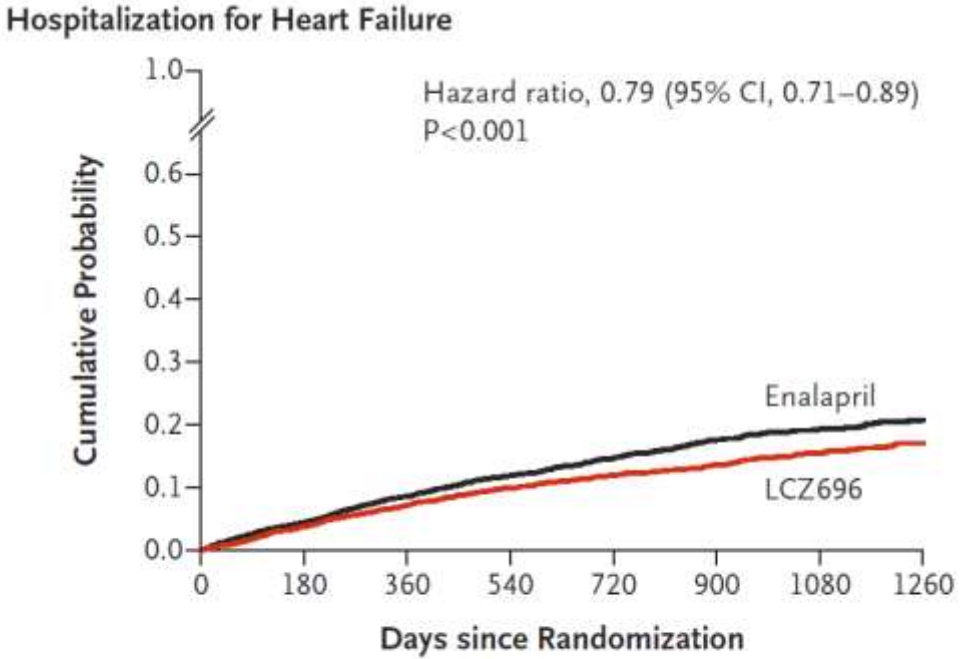
Death from CV causes



McMurray, et al. N Engl J Med 2014; 10.1056/NEJMoa1409077.

RESULTS:
Components of primary endpoint:

Hospitalization for HF



McMurray, et al. N Engl J Med 2014; 10.1056/NEJMoa1409077.

The NEW ENGLAND JOURNAL of MEDICINE

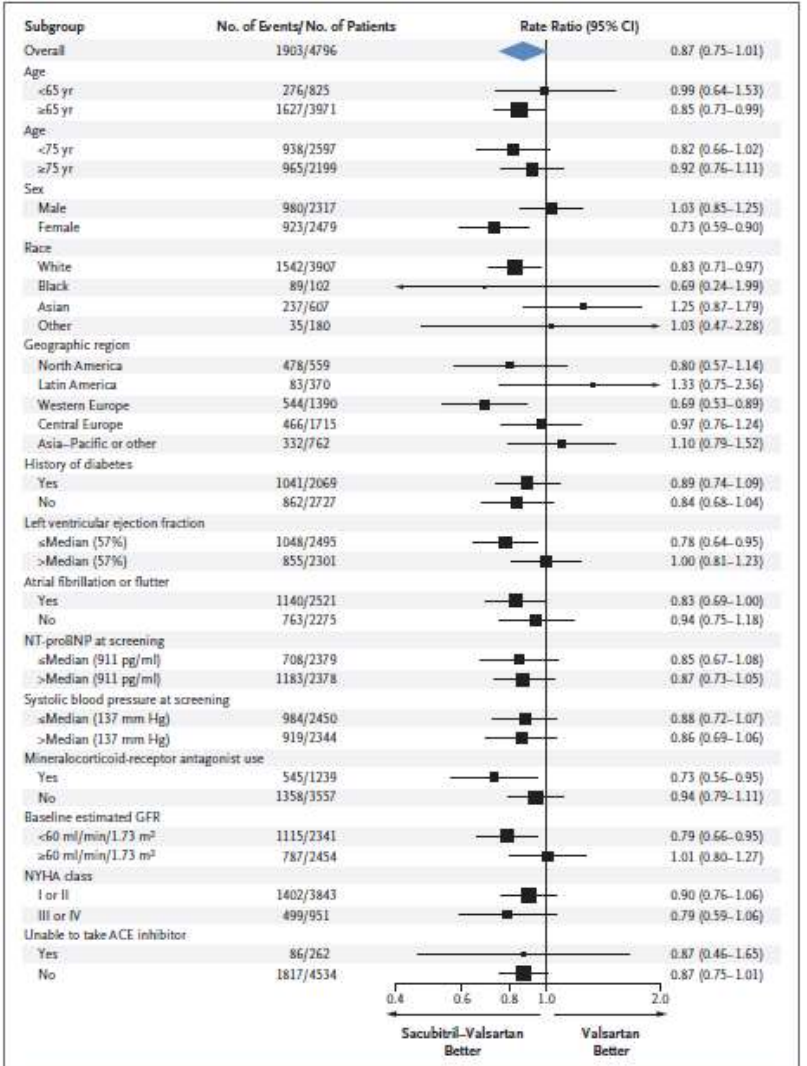
ORIGINAL ARTICLE

Angiotensin–Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction

S.D. Solomon, J.J.V. McMurray, I.S. Anand, J. Ge, C.S.P. Lam, A.P. Maggioni, F. Martinez, M. Packer, M.A. Pfeffer, B. Pieske, M.M. Redfield, J.L. Rouleau, D.J. van Veldhuisen, F. Zannad, M.R. Zile, A.S. Desai, B. Claggett, P.S. Jhund, S.A. Boytsov, J. Comin-Colet, J. Cleland, H.-D. Düngen, E. Goncalvesova, T. Katova, J.F. Kerr Saraiva, M. Lelonek, B. Merkely, M. Senni, S.J. Shah, J. Zhou, A.R. Rizkala, J. Gong, V.C. Shi, and M.P. Lefkowitz, for the PARAGON-HF Investigators and Committees

Table 2. Primary and Secondary Outcomes.*

Outcome	Sacubitril–Valsartan (N=2407)	Valsartan (N=2389)	Ratio or Difference (95% CI)
Primary composite outcome and components			
Total hospitalizations for heart failure and death from cardiovascular causes†			RR, 0.87 (0.75–1.01)
Total no. of events	894	1009	
Rate per 100 patient-yr	12.8	14.6	
Total no. of hospitalizations for heart failure	690	797	RR, 0.85 (0.72–1.00)
Death from cardiovascular causes — no. (%)	204 (8.5)	212 (8.9)	HR, 0.95 (0.79–1.16)
Secondary outcomes			
Change in NYHA class from baseline to 8 mo — no./total no. (%)			OR, 1.45 (1.13–1.86)
Improved	347/2316 (15.0)	289/2302 (12.6)	
Unchanged	1767/2316 (76.3)	1792/2302 (77.8)	
Worsened	202/2316 (8.7)	221/2302 (9.6)	
Change in KCCQ clinical summary score at 8 mo‡	−1.6±0.4	−2.6±0.4	Difference, 1.0 (0.0–2.1)
Renal composite outcome — no. (%)§	33 (1.4)	64 (2.7)	HR, 0.50 (0.33–0.77)
Death from any cause — no. (%)	342 (14.2)	349 (14.6)	HR, 0.97 (0.84–1.13)


Subgroup
No. of Events/No. of Patients
Rate Ratio (95% CI)
Overall 1903/4796 0.87 (0.75–1.01)
Age
<65 yr 276/825 0.99 (0.64–1.53)
≥65 yr 1627/3971 0.85 (0.73–0.99)
Age
<75 yr 938/2597 0.82 (0.66–1.02)
≥75 yr 965/2199 0.92 (0.76–1.11)
Sex
Male 980/2317 1.03 (0.85–1.25)
Female 923/2479 0.73 (0.59–0.90)
Race
White 1542/3907 0.83 (0.71–0.97)
Black 89/102 0.69 (0.24–1.99)
Asian 237/607 1.25 (0.87–1.79)
Other 35/180 1.03 (0.47–2.28)
Geographic region
North America 478/559 0.80 (0.57–1.14)
Latin America 83/370 1.33 (0.75–2.36)
Western Europe 544/1390 0.69 (0.53–0.89)
Central Europe 466/1715 0.97 (0.76–1.24)
Asia–Pacific or other 332/762 1.10 (0.79–1.52)
History of diabetes
Yes 1041/2069 0.89 (0.74–1.09)
No 862/2727 0.84 (0.68–1.04)
Left ventricular ejection fraction
≤Median (57%) 1048/2495 0.78 (0.64–0.95)
>Median (57%) 855/2301 1.00 (0.81–1.23)
Atrial fibrillation or flutter
Yes 1140/2521 0.83 (0.69–1.00)
No 763/2275 0.94 (0.75–1.18)
NT-proBNP at screening
≤Median (911 pg/ml) 708/2379 0.85 (0.67–1.08)
>Median (911 pg/ml) 1183/2378 0.87 (0.73–1.05)
Systolic blood pressure at screening
≤Median (137 mm Hg) 984/2450 0.88 (0.72–1.07)
>Median (137 mm Hg) 919/2344 0.86 (0.69–1.06)
Mineralocorticoid-receptor antagonist use
Yes 545/1239 0.73 (0.56–0.95)
No 1358/3557 0.94 (0.79–1.11)
Baseline estimated GFR
<60 ml/min/1.73 m² 1115/2341 0.79 (0.66–0.95)
≥60 ml/min/1.73 m² 787/2454 1.01 (0.80–1.27)
NYHA class
I or II 1402/3843 0.90 (0.76–1.06)
III or IV 499/951 0.79 (0.59–1.06)
Unable to take ACE inhibitor
Yes 86/262 0.87 (0.46–1.65)
No 1817/4534 0.87 (0.75–1.01)
0.4
0.6
0.8
1.0
2.0
Sacubitril–Valsartan Better
Valsartan Better

GRUPPO CARDIOLOGICO ITALIANO
(III° RIUNIONE - MILANO, 25 APRILE 1937 - XV)

RELAZIONE

LE MIOCARDITI CRONICHE

(parte clinica)

Prof. LUIGI CONDORELLI

Estratto dagli Atti del Gruppo Cardiologico Italiano

La parte più appassionata e più promettente dello studio clinico delle miocarditi è quella che tende a crearci la possibilità di scoprire la lesione miocardica prima ancora che insorgano i chiari sintomi d'insufficienza cardiaca, nel momento in cui una appropriata terapia possa riuscire ad arrestare o ad attenuare la progressione della lesione, o almeno ad impedire o a ritardare con opportune norme igieniche la comparsa di fenomeni d'insufficienza di circolo.

In altri termini i nostri sforzi debbono essere indirizzati alla diagnosi del « danno miocardico » prima ancora che appaiano i fenomeni d'insufficienza di circolo: il quadro clinico della miocardite non deve essere identificato,

Depressed myocardial energetic efficiency is associated with increased cardiovascular risk in hypertensive left ventricular hypertrophy

Giovanni de Simone[a,b], Raffaele Izzo[a,b], Maria Angela Losi[a,c], Eugenio Stabile[a,c], Francesco Rozza[a,c], Grazia Canciello[a,b], Costantino Mancusi[a,b], Valentina Trimarco[a,d], Nicola De Luca[a,b], and Bruno Trimarco[a,c]

Background and purpose: Myocardial mechano-energetic efficiency (MEE) can be easily approximated by the ratio of stroke work [i.e. SBP times stroke volume (SV)] to a rough estimate of energy consumption, the 'double product' [SBP times heart rate (HR)], which can be simplified as SV/HR. We evaluated whether MEE is associated with adverse prognosis in relation to the presence of left ventricular hypertrophy (LVH).

Methods: Hypertensive participants of the Campania Salute Network ($n = 12\,353$) without prevalent coronary or cerebrovascular disease and with ejection fraction more than 50% were cross-sectionally and longitudinally analyzed, over a median follow-up of 31 months. MEE was estimated by echocardiographic SV (z-derived)/(HR × 0.6).

Results: Due to the close relation with left ventricular mass (LVM) ($P < 0.0001$), MEE was normalized for LVM (MEEi) and divided into quartiles. The lowest quartile of MEEi (<0.29 ml/s per g) was considered 'low MEEi'. MEEi was greater in women than in men ($P < 0.0001$). Progressively lower MEEi was associated with older age, male sex, obesity, diabetes, LVH, concentric geometry, inappropriate LVM and diastolic dysfunction, more use of antihypertensive therapy, and higher BP (all $P < 0.002$). In Cox regression, after controlling for LVH, age, sex, and average follow-up SBP, low MEEi exhibited increased hazard of composite fatal and nonfatal cardiovascular end-points ($P < 0.01$), independently of antihypertensive therapy and associated cardiovascular risk factors.

Conclusion: A simple estimate of low myocardial mechano-energetic efficiency is associated with altered metabolic profile, LVH, concentric left ventricular geometry, and diastolic dysfunction and predicts cardiovascular end-points, independently of age, sex, LVH antihypertensive therapy, and cardiovascular risk factors.

Keywords: cardiovascular risk, hypertension, left ventricular hypertrophy, myocardial energetic efficiency

myocardial oxygen consumption; SPSS, Statistical Package for Social Science; SV, stroke volume; SW, stroke work

BACKGROUND

Arterial hypertension (AH) causes different types of left ventricular (LV) adaptation, depending on the type of hemodynamic overload [1]. The interaction between LV mass (LVM), chamber dimension, and relative wall thickness determines each specific geometric pattern of adaptation, associated with different degrees of cardiovascular risk [1–3]. Paralleling magnitude of LV chamber dimension, for similar and normal values of ejection fraction (i.e. LV systolic function), critical differences are reported in the magnitude of stroke volume (SV, i.e. LV pump performance), heart rate (HR) and blood pressure (BP) [3]. One unexplored aspect of these differences is whether myocardial mechano-energetic efficiency (MEE) could help explaining the risk of adverse cardiovascular outcome in the context of hemodynamic overload inducing cardiovascular remodeling.

MEE is the ratio between the produced external work (measurable as stroke work) and the amount of oxygen consumed during contraction [4]. Under normal conditions, this ratio is 25%, and the residual energy mainly dissipates as heat [5]. At a given external work, increased energetic expenditure results in lower values of MEE. Thus, low MEE might contribute to progression of overt cardiovascular disease [6,7]. Hypertensive patients with low MEE have a more severe cardiovascular profile than those with normal MEE [8].

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$$\mathrm{MEE} = \frac{\mathrm{SW}}{\mathrm{DP}} \approx \frac{\mathrm{BPs} \times \mathrm{SV}}{\mathrm{BPs} \times \mathrm{HR}} = \frac{\mathrm{SV}}{\mathrm{HR}}$$

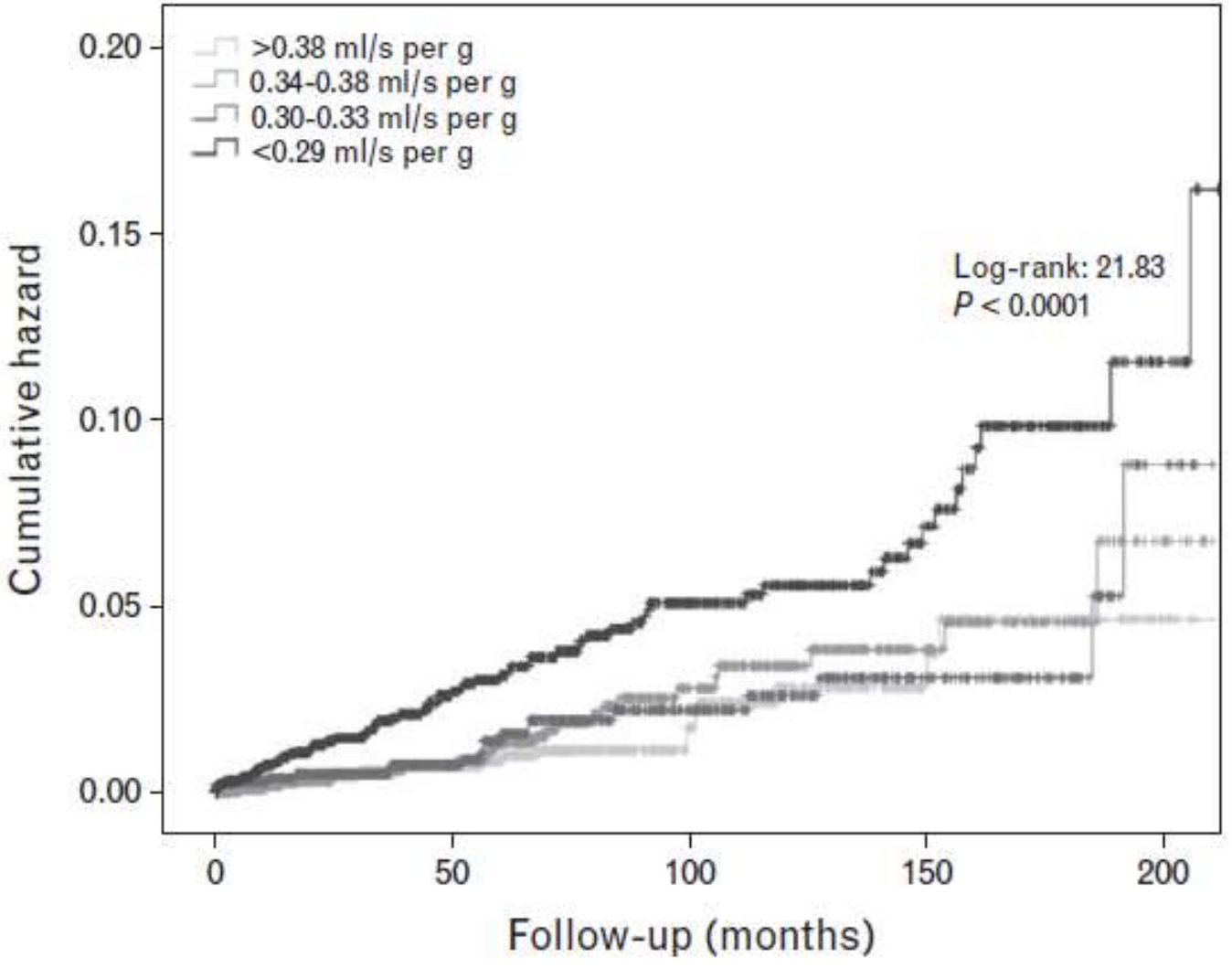
>0.38 ml/s per g
0.34-0.38 ml/s per g
0.30-0.33 ml/s per g
<0.29 ml/s per g
Log-rank: 21.83
P < 0.0001
Cumulative hazard
0.20
0.15
0.10
0.05
0.00
0
50
100
150
200
Follow-up (months)

TABLE 4. Sequential models of proportional hazard analysis for major cardiovascular events (MACE: death, myocardial infarction and stroke), adjusting for groups of covariates. Significant predictors are highlighted in italic

	Model 1			Model 2			Model 3			Model 4			
	Sig.	HR	95.0% CI	Sig.	HR	95.0% CI	Sig.	HR	95.0% CI	Sig.	HR	95.0% CI	
Predictors			Lower–upper			Lower–upper			Lower–upper			Lower–upper	VIF
Age (years)	*0.0001*	1.06	1.05–1.08	*0.0001*	1.06	1.04–1.07	*0.0001*	1.06	1.04–1.08	*0.0001*	1.06	1.04–1.08	1.38
Female sex	*0.0001*	0.45	0.31–0.64	*0.0001*	0.41	0.29–0.59	*0.0001*	0.42	0.29–0.60	*0.0001*	0.42	0.29–0.61	1.10
Low MEEi (<0.29 ml/s per g)	*0.001*	1.82	1.30–2.55	*0.007*	1.60	1.14–2.29	*0.007*	1.61	1.14–2.27	*0.009*	1.58	1.12–2.22	1.19
LVH (n/y)				0.01	1.55	1.10–2.18	*0.005*	1.65	1.17–2.33	*0.005*	1.66	1.16–2.37	1.32
Follow-up SBP (×5 mmHg)				0.09	1.01	1.00–1.03	0.07	1.01	1.00–1.03	0.15	1.06	0.98–1.14	1.70
Follow-up DBP (×5 mmHg)				0.91	1.00	0.97–1.03	0.84	1.00	0.97–1.03	0.89	1.01	0.84–1.16	1.72
B-blockers (n/y)							0.78	0.94	0.64–1.37	0.73	0.93	0.64–1.37	1.06
Anti-RAS (n/y)							0.19	0.79	0.55–1.13	0.15	0.77	0.54–1.10	1.27
Diuretics (n/y)							0.14	0.77	0.55–1.09	0.16	0.781	0.55–1.10	1.24
Ca^{++}-channel blockers (n/y)							0.64	0.92	0.65–1.31	0.53	0.89	0.63–1.30	1.06
Obesity (n/y)										0.58	0.90	0.62–1.31	1.11
Diabetes (n/y)										0.02	1.70	1.10–2.62	1.09

Journal of
Clinical Medicine

MDPI

Article

Depressed Myocardial Energetic Efficiency Increases Risk of Incident Heart Failure: The Strong Heart Study

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Abstract: An estimation of myocardial mechano-energetic efficiency (MEE) per unit of left ventricular (LV) mass (MEEi) can significantly predict composite cardiovascular (CV) events in treated hypertensive patients with normal ejection fraction (EF), after adjustment for LV hypertrophy (LVH). We have tested whether MEEi predicts incident heart failure (HF), after adjustment for LVH, in the population-based cohort of a "Strong Heart Study" (SHS) with normal EF. We included 1912 SHS participants (age 59 ± 8 years; 64% women) with preserved EF (≥50%) and without prevalent CV disease. MEE was estimated as the ratio of stroke work to the "double product" of heart rate times systolic blood pressure. MEEi was calculated as MEE/LV mass, and analyzed in quartiles. During a follow-up study of 9.2 ± 2.3 years, 126 participants developed HF (7%). HF was preceded by acute myocardial infarction (AMI) in 94 participants. A Kaplan-Meier plot, in quartiles of MEEi, demonstrated significant differences, substantially due to the deviation of the lowest quartile ($p < 0.0001$). Using AMI as a competing risk event, sequential models of Cox regression for incident HF (including significant confounders), demonstrated that low MEEi predicted incident HF not due to AMI ($p = 0.026$), after adjustment for significant effect of age, LVH, prolonged LV relaxation, diabetes, and smoking habits with negligible effects for sex, hypertension, antihypertensive therapy, obesity, and hyperlipemia. Low LV mechano-energetic efficiency per unit of LVM, is a predictor of incident, non-AMI related, HF in subjects with initially normal EF.

Table 1. Characteristics of quartiles of LV mass-normalized myocardial mechano-energetic efficiency (MEEi).

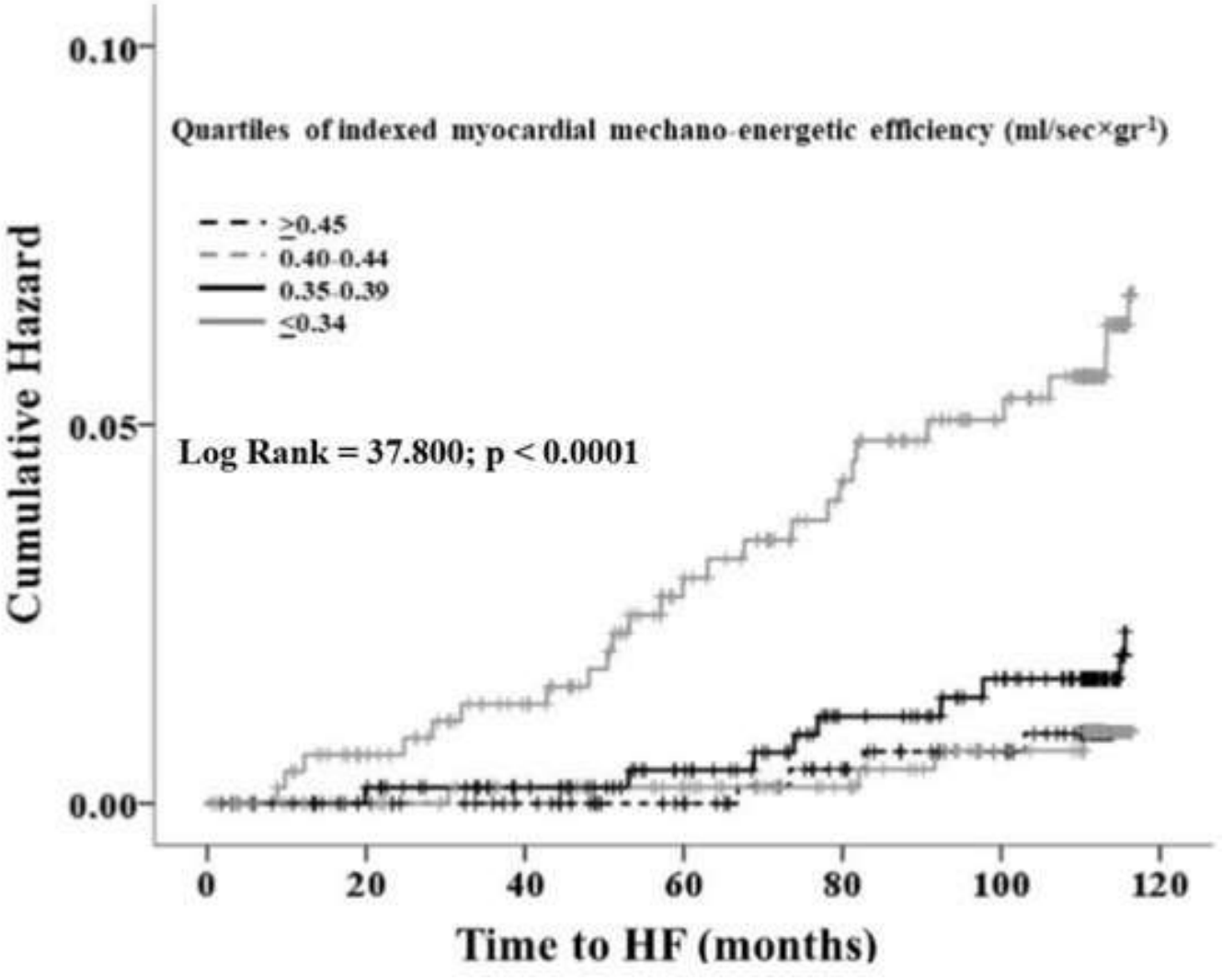
		Quartiles of Indexed Myocardial Mechano-Energetic Efficiency			
	Whole Population (n = 1912)	**≥0.45 (n = 478)**	**0.40–0.44 (n = 477)**	**0.35–0.39 (n = 479)**	**≤0.34 (n = 478)**
Age (years)	59 ± 8	59 ± 8	60 ± 8	59 ± 8	60 ± 8
Hypertension (%) [a]	27%	22%	25%	29%	34%
Proportion of women (%) [a]	64%	68%	69%	65%	55%
Concentric LV geometry (%) [a]	4%	0.2 %	1%	2%	11%
LV Hypertrophy (%) [a]	23%	9%	18%	23%	40%
Mitral E/A ratio <0.6 (%) [a]	4.1	2.1	2.5	1.3	10.5
Mitral E/A ratio >1.5 (%) [a]	2.6	4.5	3.4	1.5	1.1
Obesity (%) [a]	51%	40%	51%	57%	58%
Diabetes (%) [a]	40%	25%	37%	41%	57%
Hyperlipemia (%)	58	57	55	59	62
Former smoker (%)	35	33	34	36	38
Current smoker	36	39	35	34	35

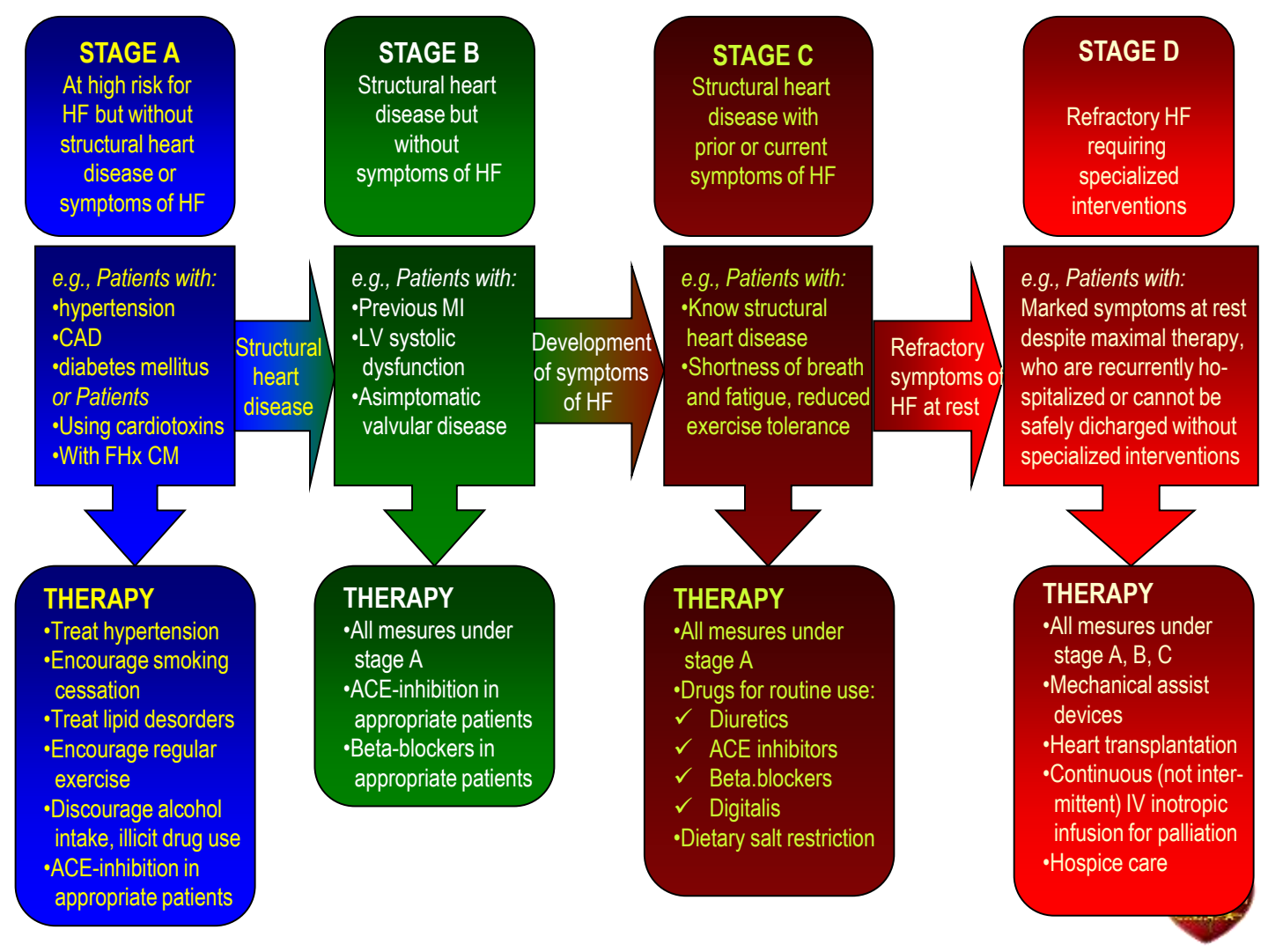
LV = left ventricular; [a] Kendall's τ-b: all $p < 0.0001$.

Table 2. Sequential models of proportional hazard analysis of incident heart failure (HF) in relation to low MEEi.

Predictors	Model 1			Model 2			Model 3		
	p	HR	95%CI	*p*	HR	95%CI	*p*	HR	95%CI
Age (years)	0.004	1.04	1.01–1.06	0.007	1.04	1.01–1.06	0.001	1.05	1.02–1.08
Female sex	0.666	0.93	0.62–1.38	0.846	0.96	0.63–1.46	0.833	1.05	0.68–1.61
LV Hypertrophy	<0.0001	2.51	1.70–3.73	0.001	2.01	1.37–3.10	0.004	1.89	1.23–2.91
E/A <0.6	<0.0001	3.72	1.99–6.98	0.002	2.85	1.48–5.51	0.004	2.60	1.35–5.05
E/A >1.5	0.612	0.60	0.08–4.33	0.629	0.61	0.09–4.43	0.800	0.77	0.11–5.60
Low MEEi				0.005	1.83	1.21–2.79	0.026	1.61	1.06–2.44
Hypertension				0.484	1.27	0.66–2.45	0.672	1.15	0.60–2.23
Anti-hypertensive therapy (y/n)				0.012	2.28	1.20–4.35	0.094	1.75	0.91–3.35
Diabetes							<0.0001	3.11	2.01–4.80
Obesity							0.191	0.76	0.50–1.15
Hyperlipemia							0.832	0.96	0.64–1.43
Former smoker							0.006	2.11	1.24–3.60
Current Smoker							0.003	2.38	1.35–4.17

LV = left ventricular; MEEi = indexed myocardial mechano-energetic efficiency; HR = hazard ratio.


0.10
0.05
0.00
Cumulative Hazard
Quartiles of indexed myocardial mechano-energetic efficiency (ml/sec×gr-1)
≥0.45
0.40-0.44
0.35-0.39
≤0.34
Log Rank = 37.800; p < 0.0001
0
20
40
60
80
100
120
Time to HF (months)


STAGE A
At high risk for HF but without structural heart disease or symptoms of HF
STAGE B
Structural heart disease but without symptoms of HF
STAGE C
Structural heart disease with prior or current symptoms of HF
STAGE D
Refractory HF requiring specialized interventions
e.g., Patients with:
•hypertension
•CAD
•diabetes mellitus
or Patients
•Using cardiotoxins
•With FHx CM
Structural heart disease
e.g., Patients with:
•Previous MI
•LV systolic dysfunction
•Asimptomatic valvular disease
Development of symptoms of HF
e.g., Patients with:
•Know structural heart disease
•Shortness of breath and fatigue, reduced exercise tolerance
Refractory symptoms of HF at rest
e.g., Patients with:
Marked symptoms at rest despite maximal therapy, who are recurrently hospitalized or cannot be safely dicharged without specialized interventions
THERAPY
•Treat hypertension
•Encourage smoking cessation
•Treat lipid desorders
•Encourage regular exercise
•Discourage alcohol intake, illicit drug use
•ACE-inhibition in appropriate patients
THERAPY
•All mesures under stage A
•ACE-inhibition in appropriate patients
•Beta-blockers in appropriate patients
THERAPY
•All mesures under stage A
•Drugs for routine use:
✓ Diuretics
✓ ACE inhibitors
✓ Beta.blockers
✓ Digitalis
•Dietary salt restriction
THERAPY
•All mesures under stage A, B, C
•Mechanical assist devices
•Heart transplantation
•Continuous (not intermittent) IV inotropic infusion for palliation
•Hospice care

Circulation

Decreased Activity of the L-Arginine–Nitric Oxide Metabolic Pathway in Patients With Congestive Heart Failure

Stuart D. Katz, Tehreen Khan, Guillermo A. Zeballos, Leena Mathew, Prathibha Potharlanka, Mathias Knecht, and James Whelan

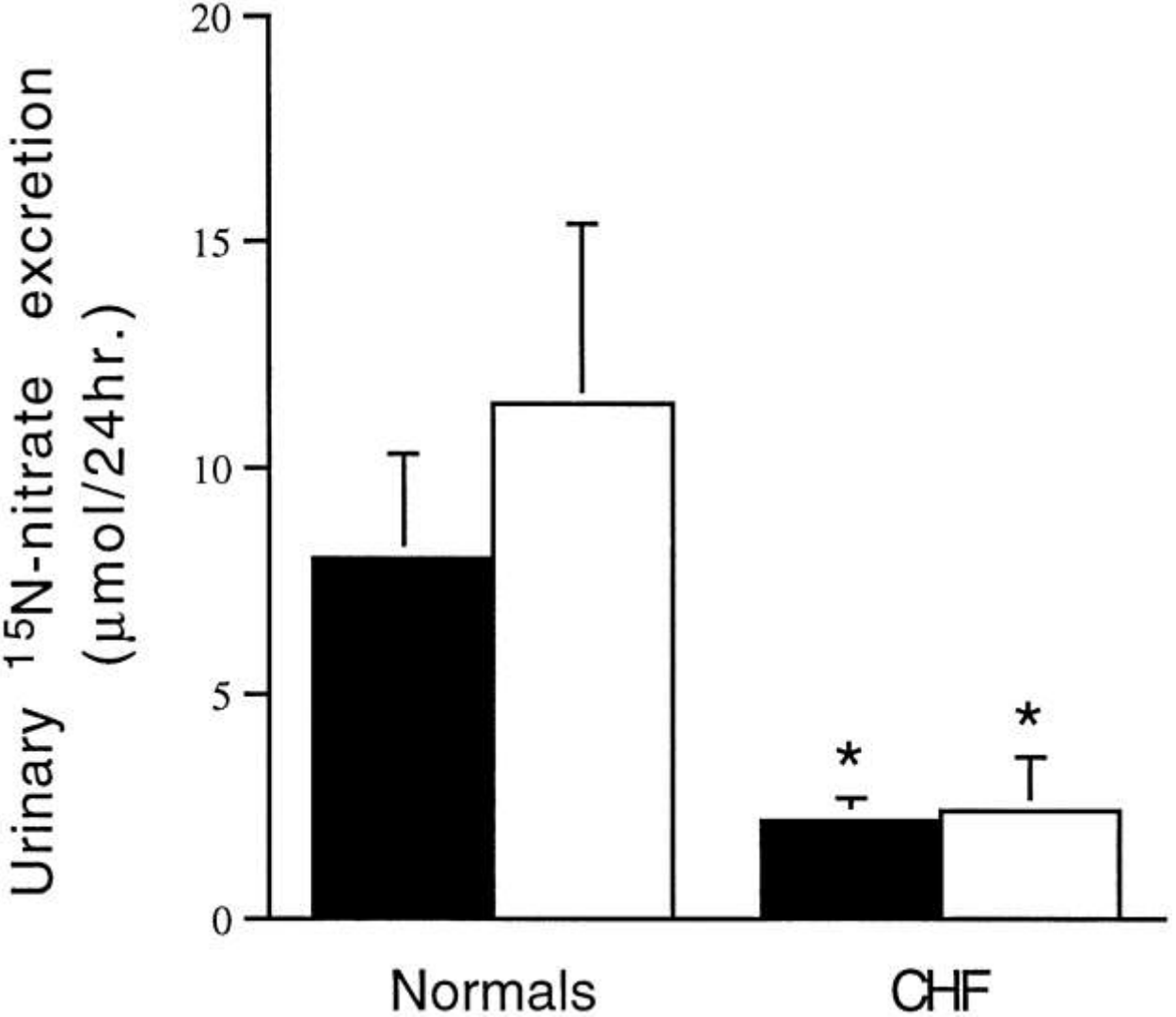
Originally published 27 Apr 1999 | https://doi.org/10.1161/01.CIR.99.16.2113 | Circulation. 1999;99:2113–2117

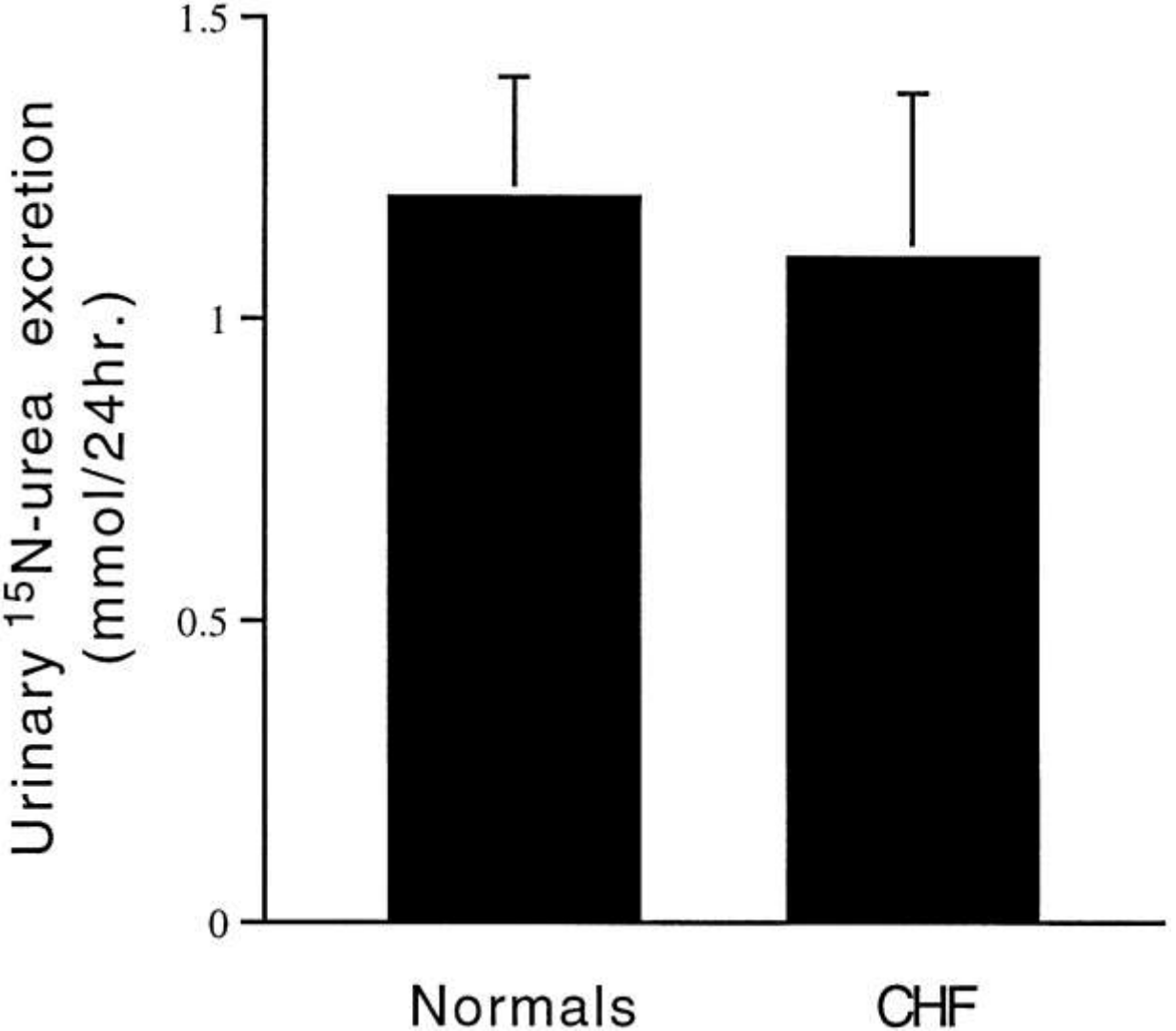
Abstract

Background—Impaired endothelium-dependent, nitric oxide (NO)–mediated vasodilation may contribute to increased vasomotor tone in patients with heart failure. Whether decreased endothelium-dependent, NO-mediated vasodilation in patients with heart failure is due to decreased synthesis or increased degradation of NO is unknown.

Methods and Results—To specifically assess the synthetic activity of the L-arginine–NO metabolic pathway, urinary excretion of [^{15}N]nitrates and [^{15}N]urea was determined after a primed continuous intravenous infusion of L-[^{15}N]arginine (40 μmol/kg) in 16 patients with congestive heart failure and 9 age-matched normal control subjects at rest and during submaximal treadmill exercise. After infusion of L-[^{15}N]arginine, 24-hour urinary excretion of [^{15}N]nitrates was decreased in patients with congestive heart failure at rest (2.2±0.5 versus 8.0±2.3 μmol/24 h) and during submaximal exercise (2.4±1.2 versus 11.4±4.0 μmol/24 h) compared with control subjects (both $P<0.01$). After infusion of L-[^{15}N]arginine, 24-hour urinary excretions of [^{15}N]urea at rest in patients with congestive heart failure and control subjects were not different (1.1±0.3 versus 1.2±0.2 mmol/24 h, $P>0.20$).

Conclusions—A specific decrease in synthetic activity of the L-arginine–NO metabolic pathway contributes to decreased endothelium-dependent vasodilation in patients with congestive heart failure.


Urinary ^{15}N-nitrate excretion (µmol/24hr.)
20
15
10
5
0
*
*
Normals
CHF


Urinary ^{15}N-urea excretion
(mmol/24hr.)
1.5
1
0.5
0
Normals
CHF

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Metabolism

www.metabolismjournal.com

Basic Science

Effects of L-arginine supplementation associated with continuous or interval aerobic training on chronic heart failure rats

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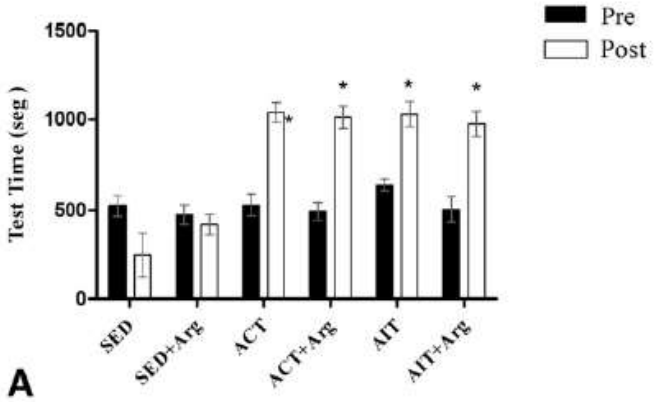
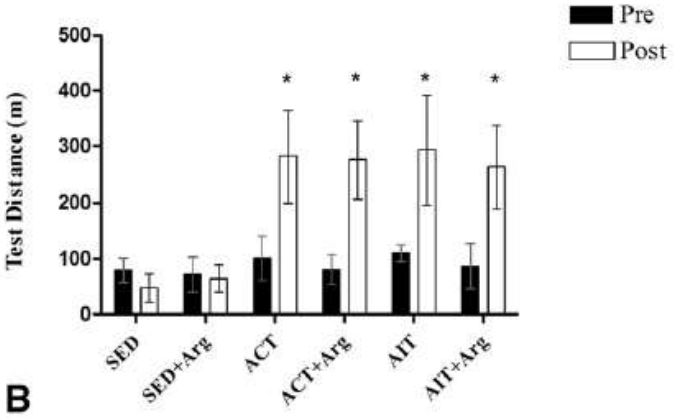

Pre
Post
1500
1000
500
0
Test Time (seg)
SED
SED+Arg
ACT
ACT+Arg
AIT
AIT+Arg
A


Pre
Post
500
400
300
200
100
0
Test Distance (m)
SED
SED+Arg
ACT
ACT+Arg
AIT
AIT+Arg
B

Circulation

Randomized, Double-Blind, Placebo-Controlled Study of Supplemental Oral L-Arginine in Patients With Heart Failure

Thomas S. Rector, Alan J. Bank, Kathleen A. Mullen, Linda K. Tschumperlin, Ronald Sih, Kamalesh Pillai, and Spencer H. Kubo

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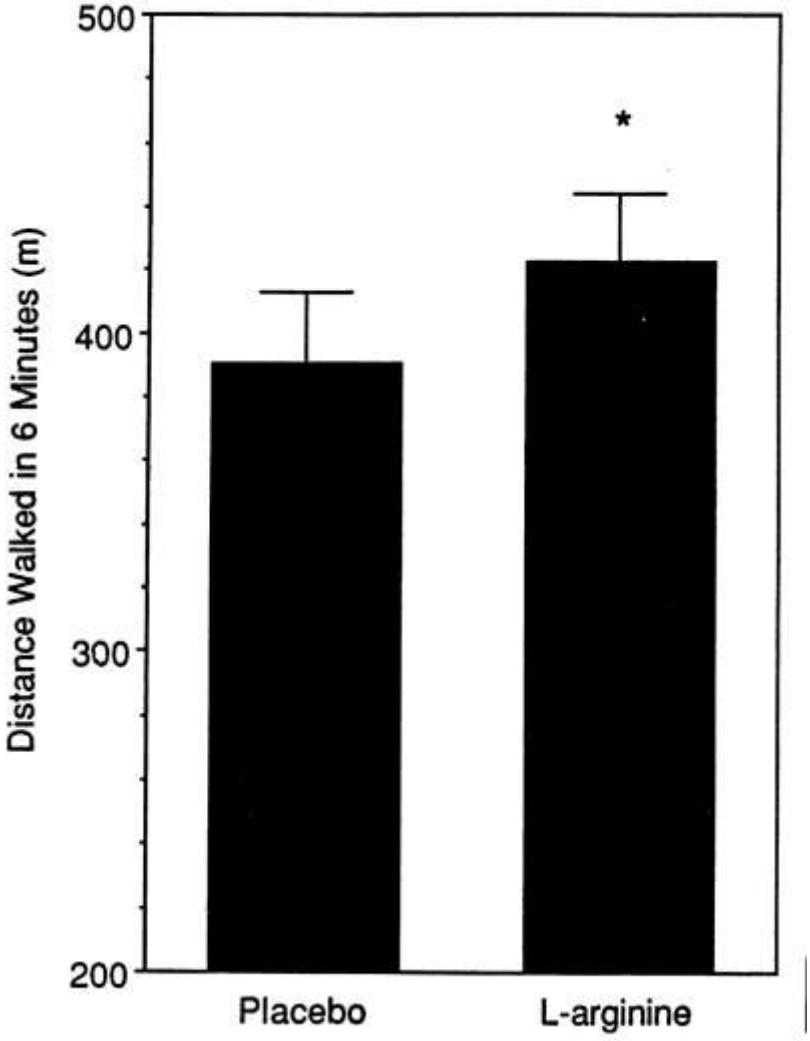
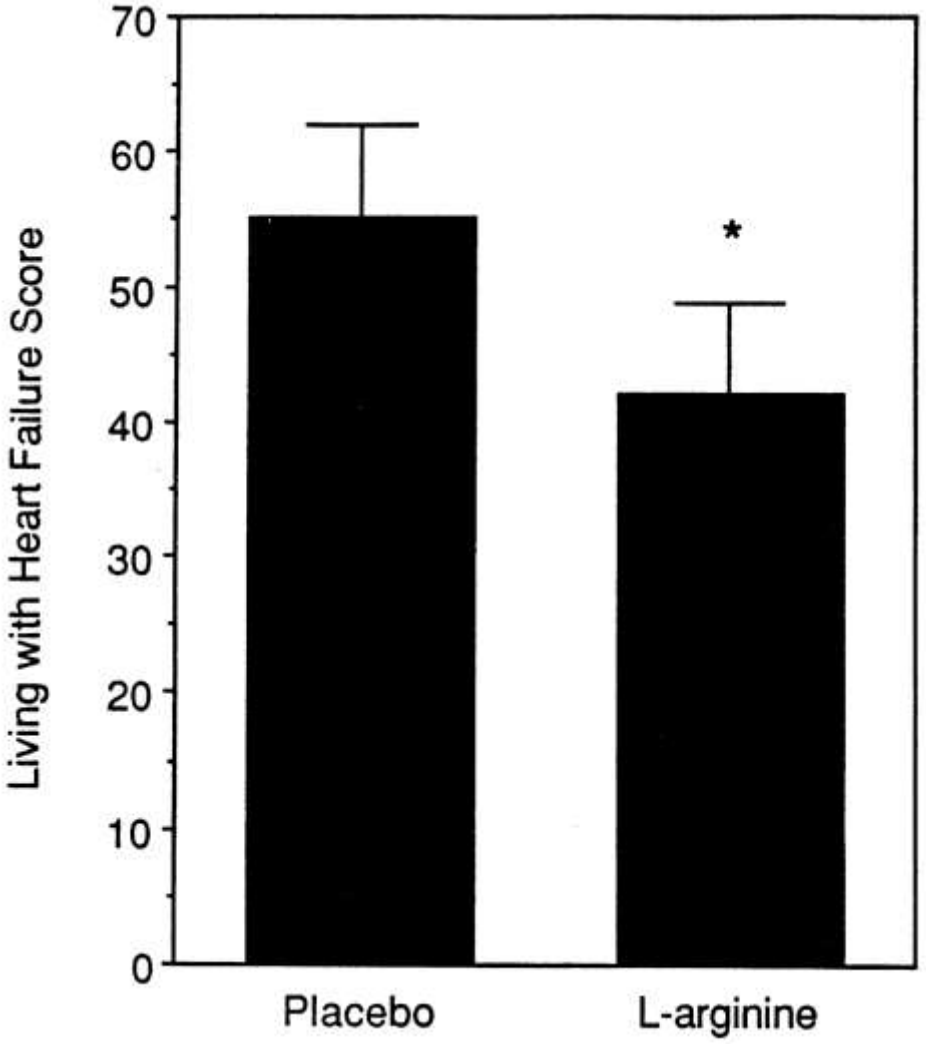
Abstract

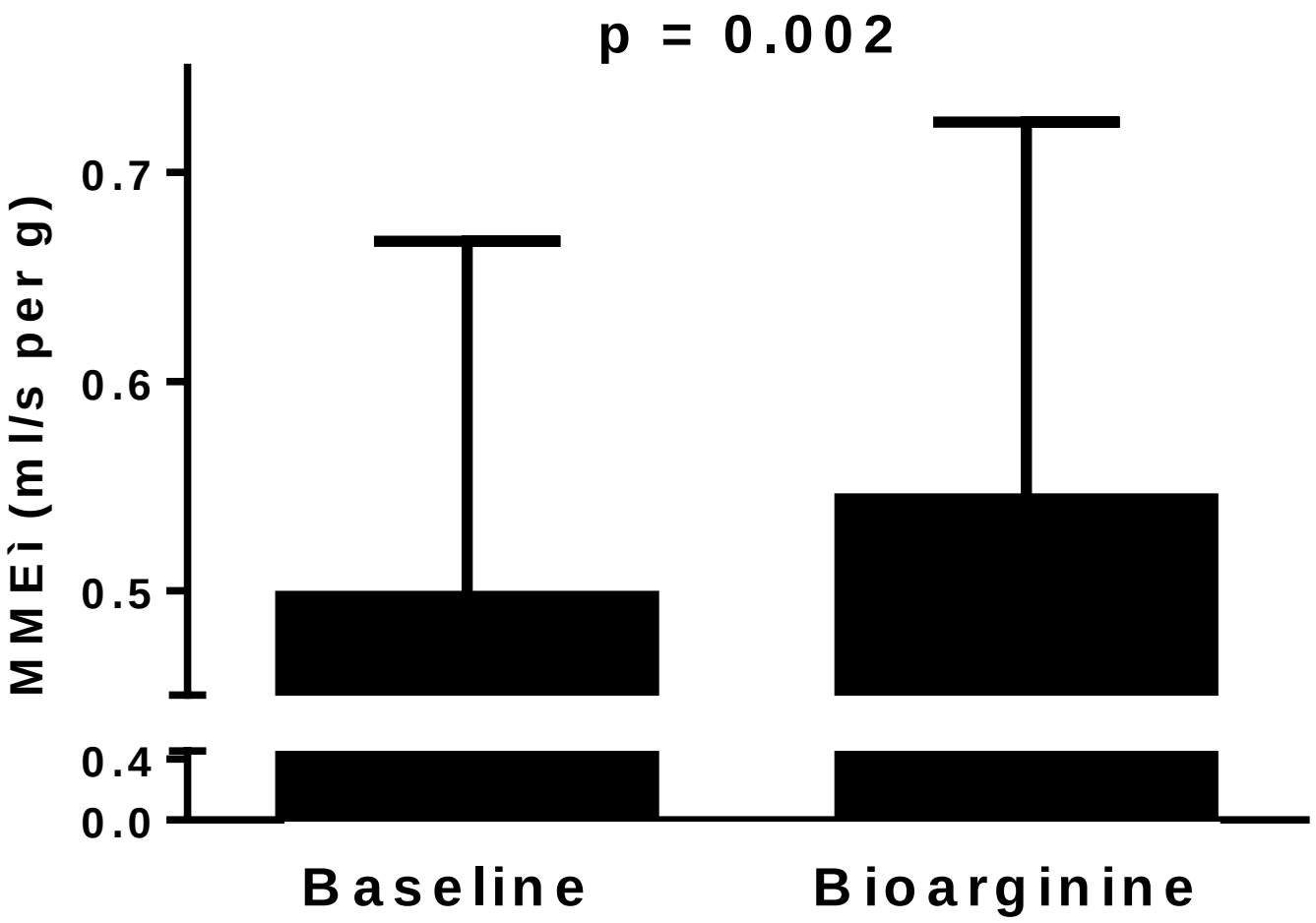
Background Patients with heart failure have reduced peripheral blood flow at rest, during exercise, and in response to endothelium-dependent vasodilators. Nitric oxide formed from L-arginine metabolism in endothelial cells contributes to regulation of blood flow under these conditions. A randomized, double-blind crossover study design was used to determine whether supplemental oral L-arginine can augment peripheral blood flow and improve functional status in patients with moderate to severe heart failure.

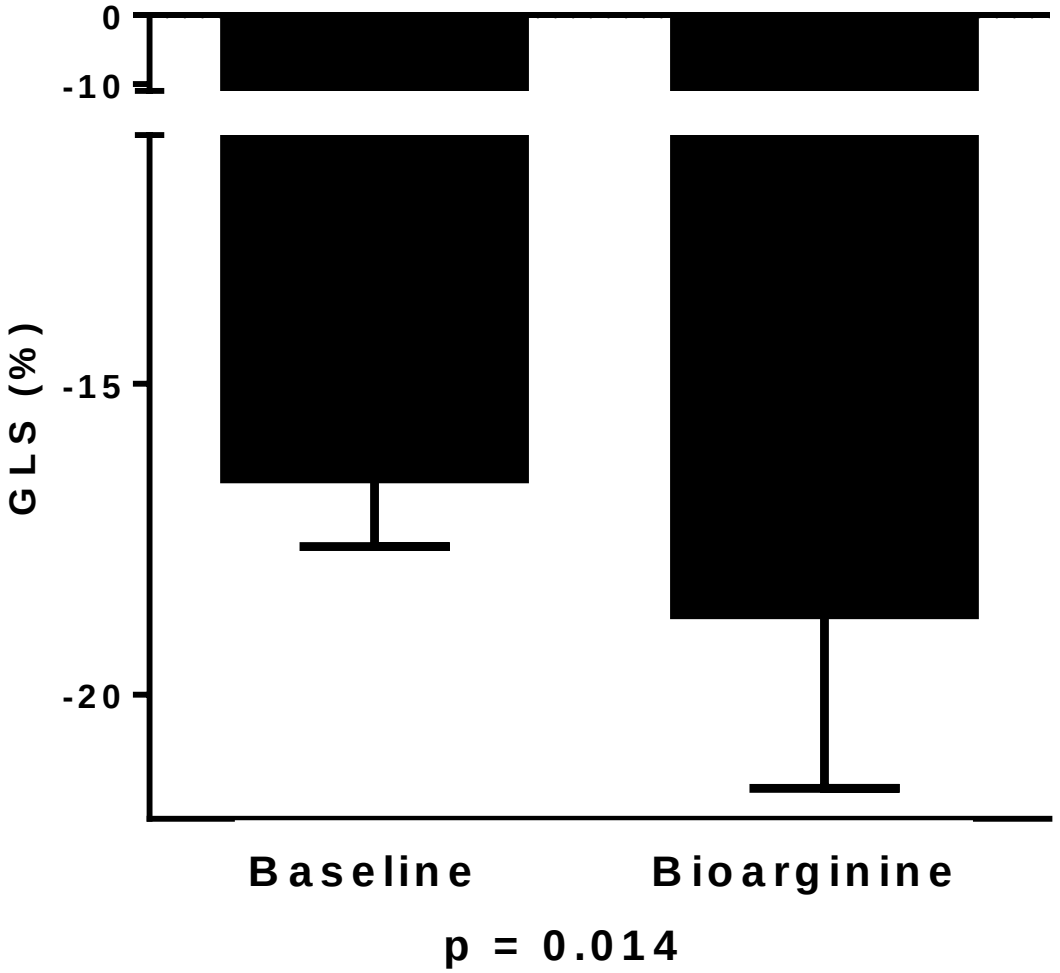
Methods and Results Fifteen subjects were given 6 weeks of oral L-arginine hydrochloride (5.6 to 12.6 g/d) and 6 weeks of matched placebo capsules in random sequence. Compared with placebo, supplemental oral L-arginine significantly increased forearm blood flow during forearm exercise, on average from 5.1±2.8 to 6.6±3.4 mL·min^{-1}·dL^{-1} (P<.05). Furthermore, functional status was significantly better on L-arginine compared with placebo, as indicated by increased distances during a 6-minute walk test (390±91 versus 422±86 m, P<.05) and lower scores on the Living With Heart Failure questionnaire (55±28 versus 42±26, P<.05). Oral L-arginine also improved arterial compliance from 1.99±0.38 to 2.36±0.30 mL/mm Hg (P<.001) and reduced circulating levels of endothelin from 1.9±1.1 to 1.5±1.1 pmol/L (P<.05).

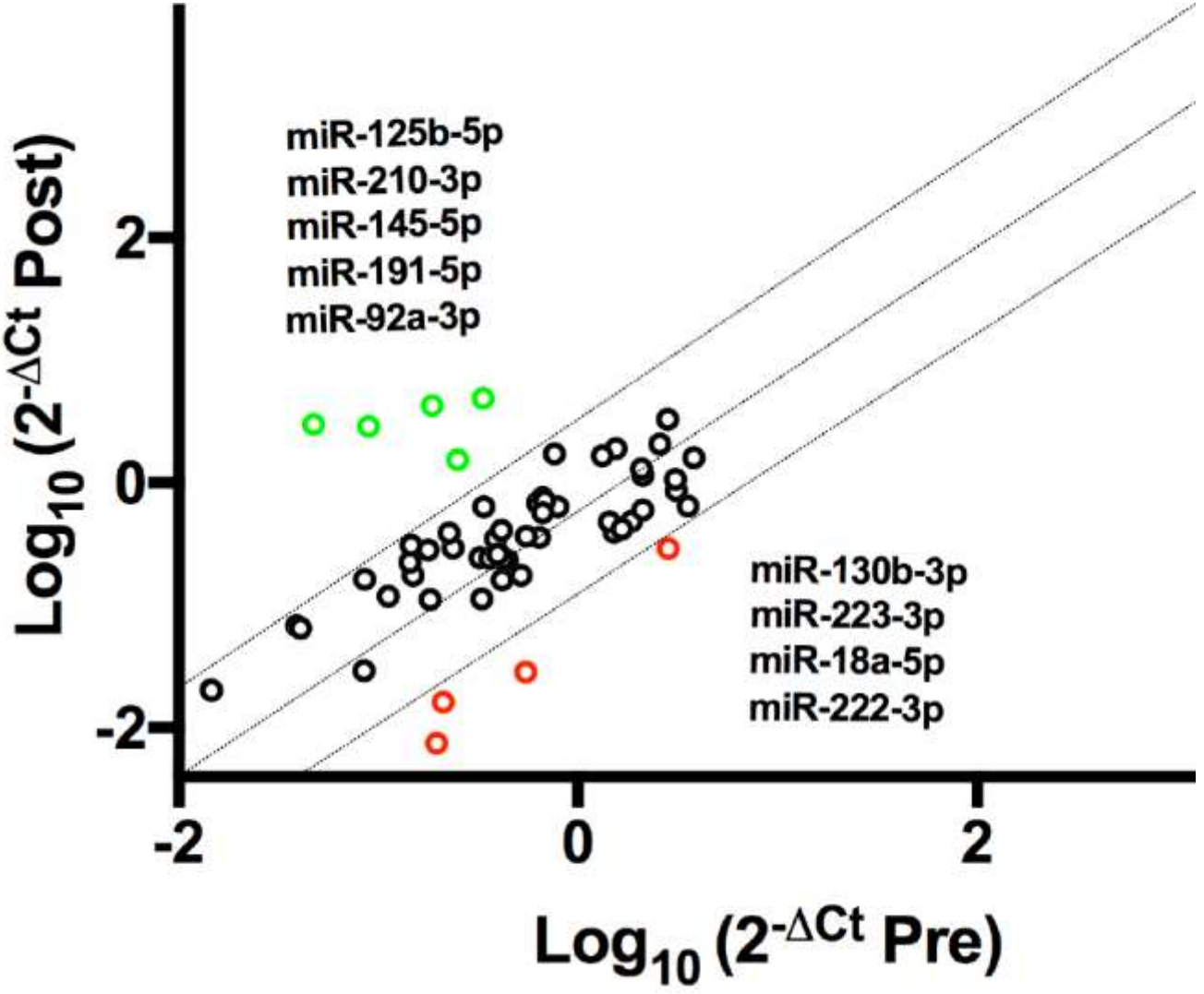
Conclusions Supplemental oral L-arginine had beneficial effects in patients with heart failure. Further studies are needed to confirm the therapeutic potential of supplemental oral L-arginine and to identify mechanisms of action in patients with heart failure.


500
400
300
200
Distance Walked in 6 Minutes (m)
*
Placebo
L-arginine


70
60
50
40
30
20
10
0
Living with Heart Failure Score
*
Placebo
L-arginine


p = 0.002
MMEì (ml/s per g)
0.7
0.6
0.5
0.4
0.0
Baseline
Bioarginine


0
-10
-15
-20
GLS (%)
Baseline
Bioarginine
p = 0.014

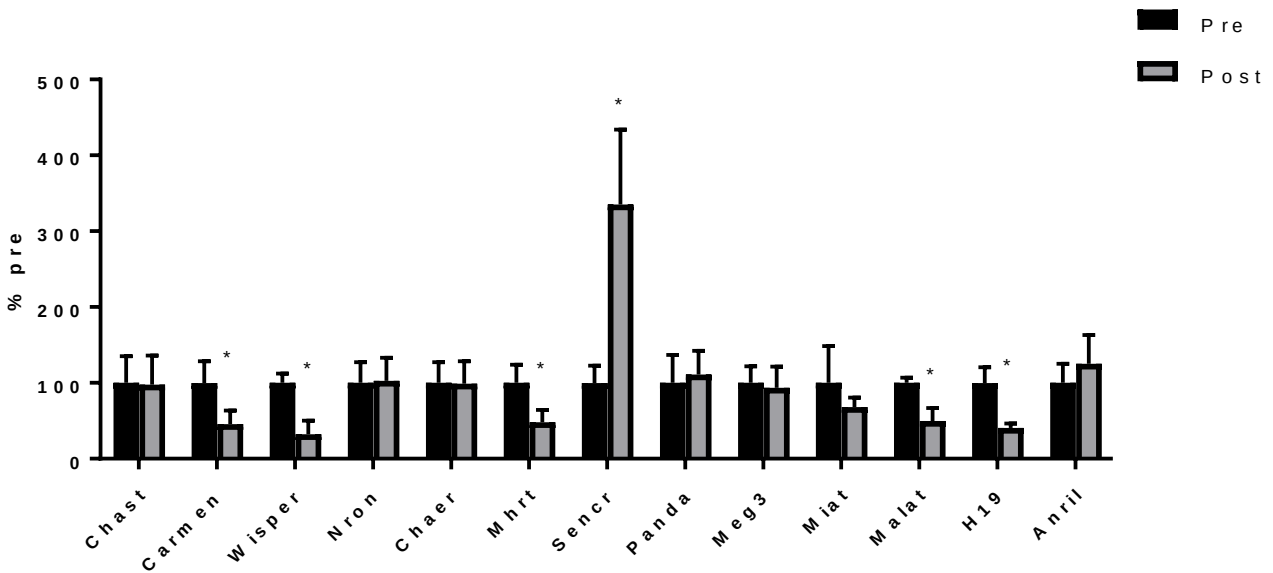

miR-125b-5p
miR-210-3p
miR-145-5p
miR-191-5p
miR-92a-3p
miR-130b-3p
miR-223-3p
miR-18a-5p
miR-222-3p
Log10 (2-ΔCt Post)
Log10 (2-ΔCt Pre)
2
0
-2
-2
0
2

-miR-92°-3p (tra quelli upregolati)

Questo miR ha come target NOX4, adrenergic receptor Bi (ADRB1), endothelin receptor B (EDNRB)

-miR-223-3p (tra quelli downregolati)

Questo miR è coinvolto nella regolazione del metabolismo e del potenziale d'azione nel cardiomiocita


Pre
Post
% pre
500
400
300
200
100
0
*
Chast
Carmen
Wisper
Nron
Chaer
Mhrt
Sencr
Panda
Meg3
Miat
Malat
H19
Anril

SENCR stabilizes vascular endothelial cell adherens junctions through interaction with CKAP4

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Edited by Michael A. Gimbrone, Harvard Medical School, Boston, MA, and approved November 26, 2018 (received for review June 22, 2018)

SENCR **is a human-specific, vascular cell-enriched long-noncoding RNA (lncRNA) that regulates vascular smooth muscle cell and endothelial cell (EC) phenotypes. The underlying mechanisms of action of *SENCR* in these and other cell types is unknown. Here, levels of *SENCR* RNA are shown to be elevated in several differentiated human EC lineages subjected to laminar shear stress. Increases in *SENCR* RNA are also observed in the laminar shear stress region of the adult aorta of humanized *SENCR*-expressing mice, but not in disturbed shear stress regions. *SENCR* loss-of-function studies disclose perturbations in EC membrane integrity resulting in increased EC permeability. Biotinylated RNA pull-down and mass spectrometry establish an abundant *SENCR*-binding protein, cytoskeletal-associated protein 4 (CKAP4); this ribonucleoprotein complex was further confirmed in an RNA immunoprecipitation experiment using an antibody to CKAP4. Structure–function studies demonstrate a noncanonical RNA-binding domain in CKAP4 that binds *SENCR*. Upon *SENCR* knockdown, increasing levels of CKAP4 protein are detected in the EC surface fraction. Furthermore, an interaction between CKAP4 and CDH5 is enhanced in *SENCR*-depleted EC. This heightened association appears to destabilize the CDH5/CTNND1 complex and augment CDH5 internalization, resulting in impaired adherens junctions. These findings support *SENCR* as a flow-responsive lncRNA that promotes EC adherens junction integrity through physical association with CKAP4, thereby stabilizing cell membrane-bound CDH5.**

tance of LSS in maintaining EC monolayer integrity and homeostasis through the stabilization of cell–cell junctions (14). One such junctional complex is the adherens junction, which forms cell–cell adhesive contacts through homophilic recognition of the extracellular domain of cadherin molecules (12, 16). CDH5 (also known as VE-cadherin) is an EC-restricted cadherin containing five extracellular calcium-dependent cadherin repeats, a transmembrane domain, and a conserved cytoplasmic domain (16). Several proteins have been shown to mediate CDH5 membrane localization and adherens junction integrity, including CTNND1 (catenin δ1, also known as p120-catenin), which regulates CDH5 internalization through binding of the juxtamembrane domain (JMD) of CDH5 (17). Although the mechanism of protein–protein interaction at adherens junctions has been well documented (16), the role of lncRNAs in this process is unknown.

Previous studies provided evidence for a role of *SENCR* in smooth muscle cell differentiation and the regulation of early EC commitment (18, 19). However, the mechanisms of action of *SENCR* in these or other cell types is unknown. Here, levels of *SENCR* are shown to be induced by LSS and *SENCR* knockdown disrupts EC membrane integrity and permeability. *SENCR* is

VIEWPOINT

Redefining Heart Failure With a Reduced Ejection Fraction

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The current management of patients with chronic heart failure depends on the noninvasive measurement of left ventricular ejection fraction (LVEF). In patients with an LVEF of 40% or lower, large-scale randomized clinical trials have demonstrated the benefits of inhibitors of the renin-angiotensin system, sympathetic nervous system, aldosterone, and neprilysin in reducing the risk of cardiovascular death and hospitalization for heart failure. Because these trials only enrolled patients with an LVEF of 40% or lower, a value of 40% has been used to define patients with heart failure and a reduced ejection fraction (HFrEF) for the past 30 years. Current guidelines strongly recommend the use of combination treatment with neurohormonal antagonists for patients with HFrEF.[1] By contrast, there are no evidence-based recommendations concerning the treatment of patients with LVEF greater than 40%, who have been conventionally referred to as having heart failure with a preserved ejection fraction (HFpEF). This lack of guidance is a concern because such patients now represent a majority of those with heart failure in the general community, particularly among women.[2]

How Should Patients With Impaired Systolic Function Be Identified?

ure with a mid-range ejection fraction."[5] The authors formulated this category to encourage further study of this intermediate group. However, this intent was widely misunderstood, and many physicians considered this mid-range group to represent a new distinct clinical entity.

Any classification of heart failure that relies on LVEF has inherent limitations. First, the measurement of LVEF is highly dependent on the method used for imaging, and even when the same method is used, there is considerable intraobserver and interobserver variability. Repeat measurements of LVEF in the same patients using the same methods by experts in echocardiography routinely vary by 7%; the variability is greater in clinical practice. When the echocardiograms of patients enrolled in clinical trials are reviewed using standardized criteria, differences between the values obtained by site investigators and the core laboratory routinely vary as much as 15% when reading the same images. Furthermore, the quality of images is highly operator-dependent, and the values for LVEF depend on loading conditions, ie, volume status and blood pressure. Hence, it is likely that a meaningful proportion of patients with an LVEF of 40% to 50% would be reclassified as having an LVEF of lower than 40% or higher than 50% if the measurement were repeated.

JAMA. 2019 Sep 13. doi: 10.1001/jama.2019.15600