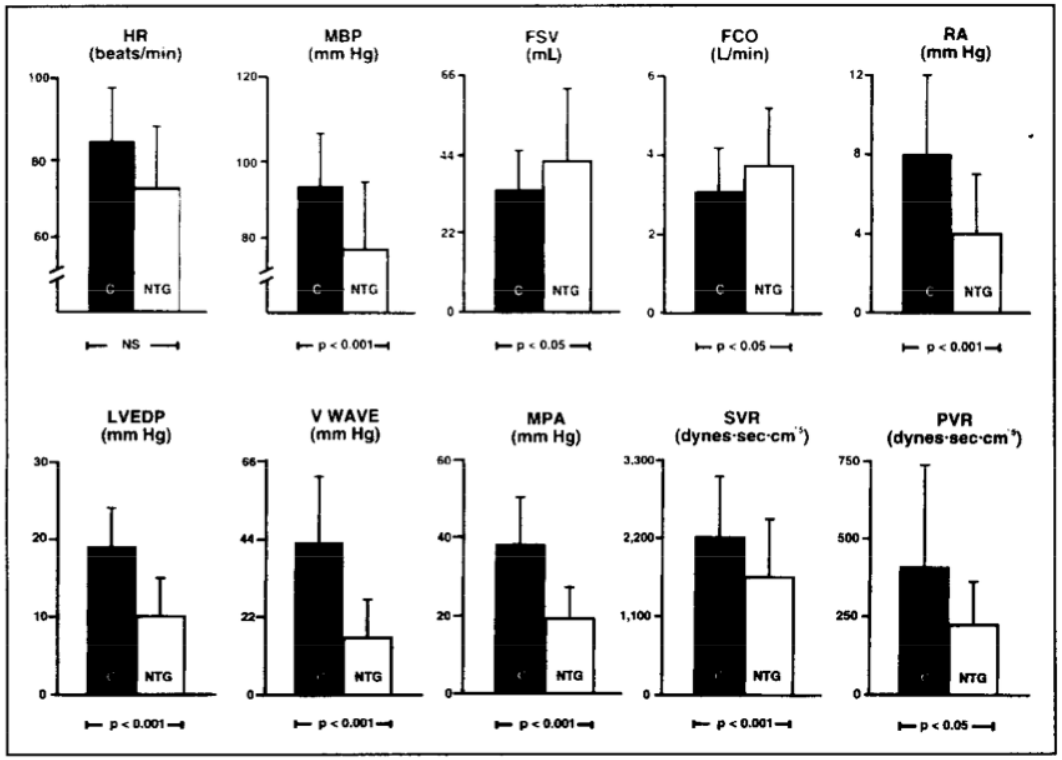
GIUSEPPE ZUCCALA'

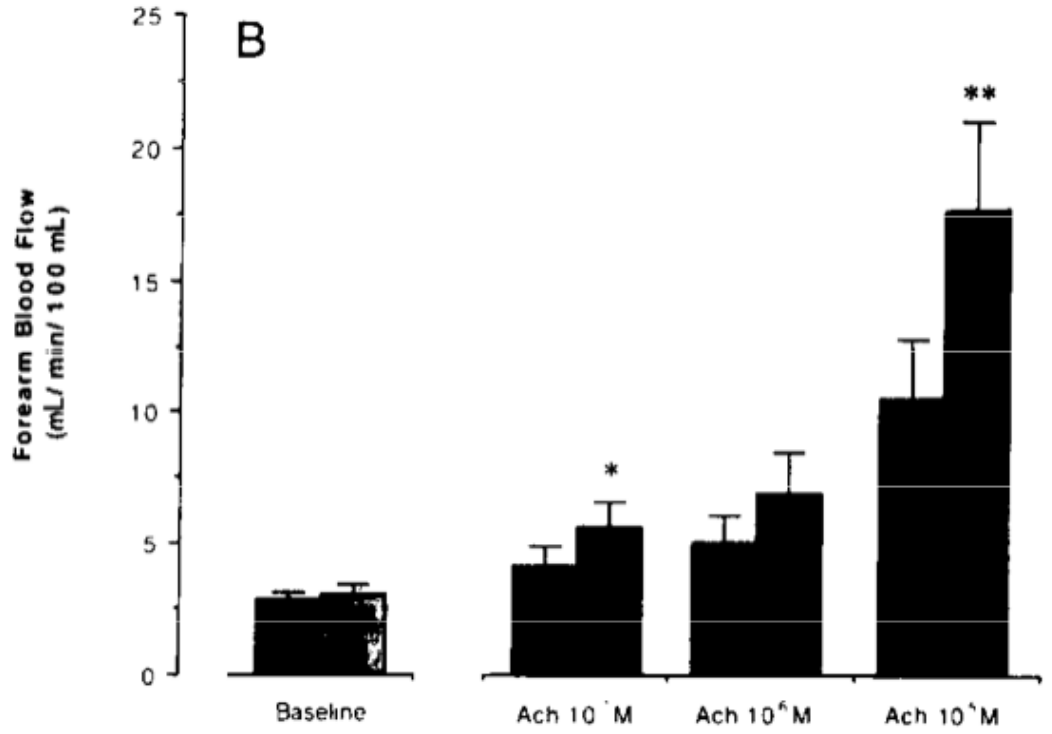
Il ruolo della guanilato ciclasi solubile in pazienti con riacutizzazione di scompenso cardiaco

SOCIETÀ ITALIANA
DI GERONTOLOGIA
E GERIATRIA

Roma, 30 novembre - 3 dicembre 2022
UNIVERSITÀ CATTOLICA DEL SACRO CUORE

Nitrates in the treatment of congestive heart failure





Elkayam U. Am J Cardiol 1996;77:41C-51C

ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012

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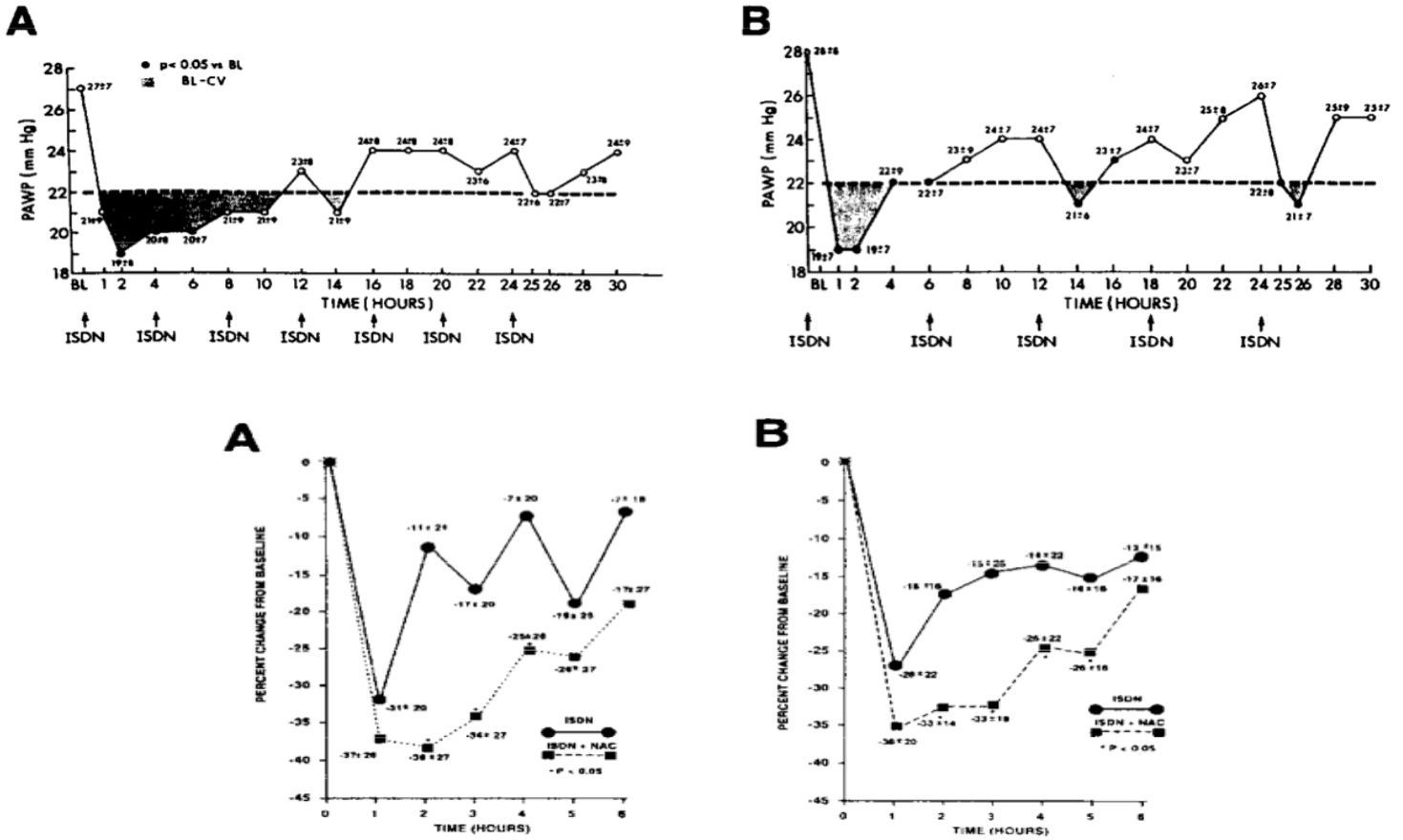
Recommendations for the treatment of patients with acute heart failure

Recommendations	Class[a]	Level[b]	Ref[c]
Patients with pulmonary congestion/oedema without shock			
An i.v. loop diuretic is recommended to improve breathlessness and relieve congestion. Symptoms, urine output, renal function, and electrolytes should be monitored regularly during use of i.v. diuretic.	I	B	213
High-flow oxygen is recommended in patients with a capillary oxygen saturation <90% or PaO_2 <60 mmHg (8.0 kPa) to correct hypoxaemia.	I	C	–
Thrombo-embolism prophylaxis (e.g. with LMWH) is recommended in patients not already anticoagulated and with no contraindication to anticoagulation, to reduce the risk of deep venous thrombosis and pulmonary embolism.	I	A	214–216
Non-invasive ventilation (e.g. CPAP) should be considered in dyspnoeic patients with pulmonary oedema and a respiratory rate >20 breaths/min to improve breathlessness and reduce hypercapnia and acidosis. Non-invasive ventilation can reduce blood pressure and should not generally be used in patients with a systolic blood pressure <85 mmHg (and blood pressure should be monitored regularly when this treatment is used).	IIa	B	217
An i.v. opiate (along with an antiemetic) should be considered in particularly anxious, restless, or distressed patients to relieve these symptoms and improve breathlessness. Alertness and ventilatory effort should be monitored frequently after administration because opiates can depress respiration.	IIa	C	–
An i.v. infusion of a nitrate should be considered in patients with pulmonary congestion/oedema and a systolic blood pressure >110 mmHg, who do not have severe mitral or aortic stenosis, to reduce pulmonary capillary wedge pressure and systemic vascular resistance. Nitrates may also relieve dyspnoea and congestion. Symptoms and blood pressure should be monitored frequently during administration of i.v. nitrates.	IIa	B	218, 219

McMurray JJV. Eur Heart J 2012; 33:1787–1847

Nitrates in the treatment of congestive heart failure



Elkayam U. Am J Cardiol 1996;77:41C-51C

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

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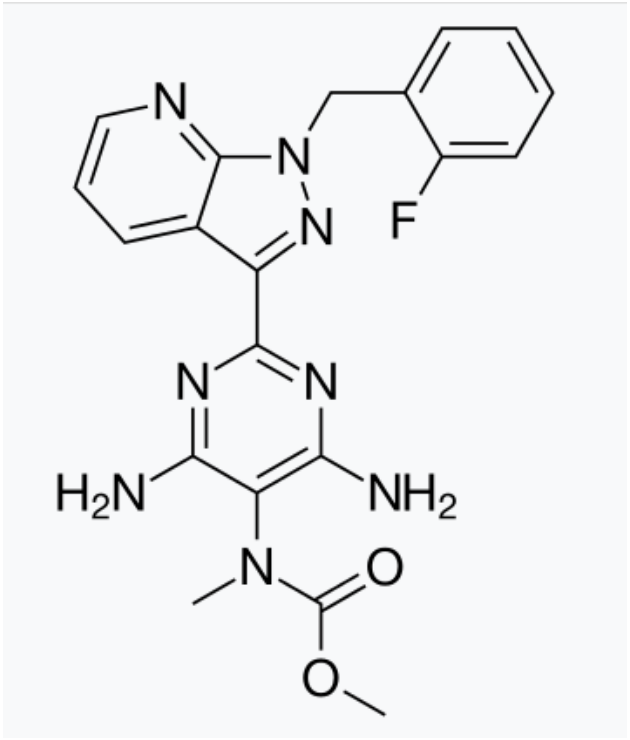
New recommendations

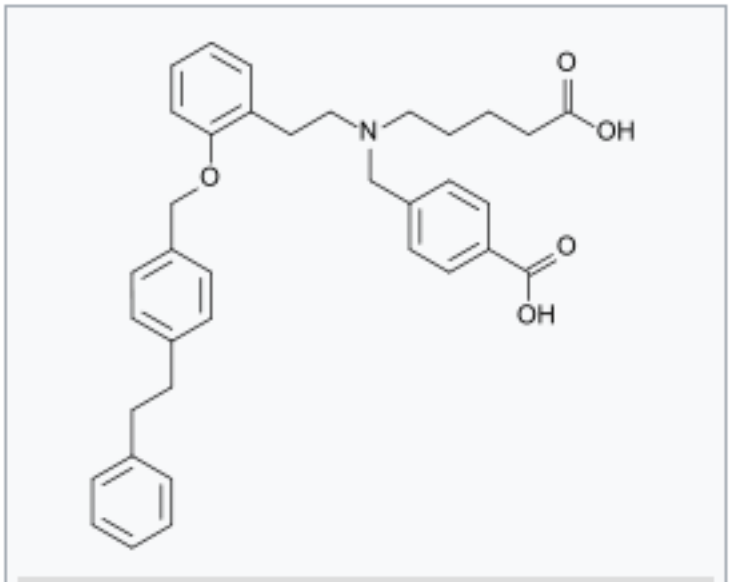
Recommendations	Class
Recommendations for the diagnosis of HF	
Right heart catheterization should be considered in patients where HF is thought to be due to constrictive pericarditis, restrictive cardiomyopathy, congenital heart disease, and high output states.	IIa
Right heart catheterization may be considered in selected patients with HFpEF to confirm the diagnosis.	IIb
Recommendations for treatment of chronic HF	
HFrEF	
Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	I
Vericiguat may be considered in patients in NYHA class II–IV who have had worsening HF despite treatment with an ACE-I (or ARNI), a beta-blocker and an MRA to reduce the risk of CV mortality or HF hospitalization.	IIb

McDonagh TA. Eur Heart J. 2021;42:3599-3726.

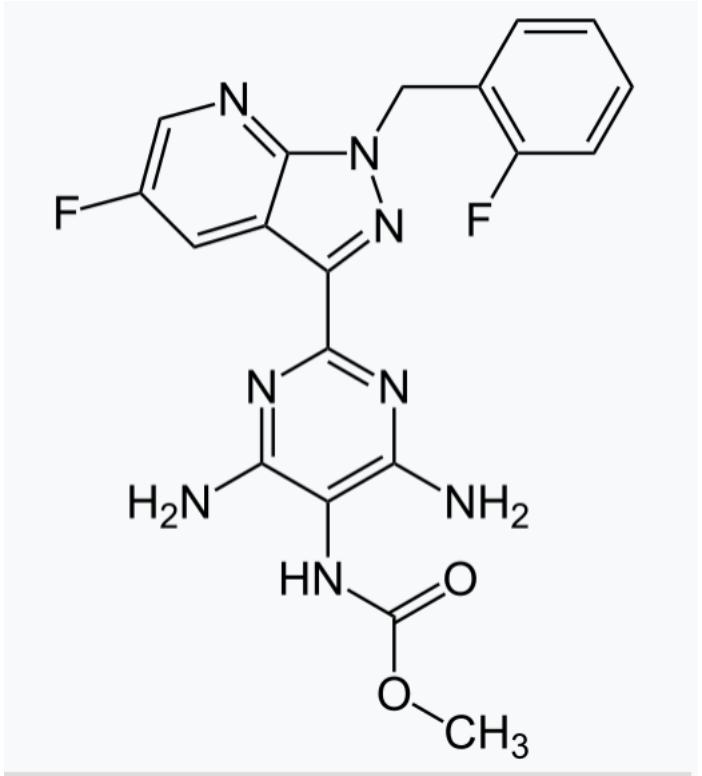
Riociguat

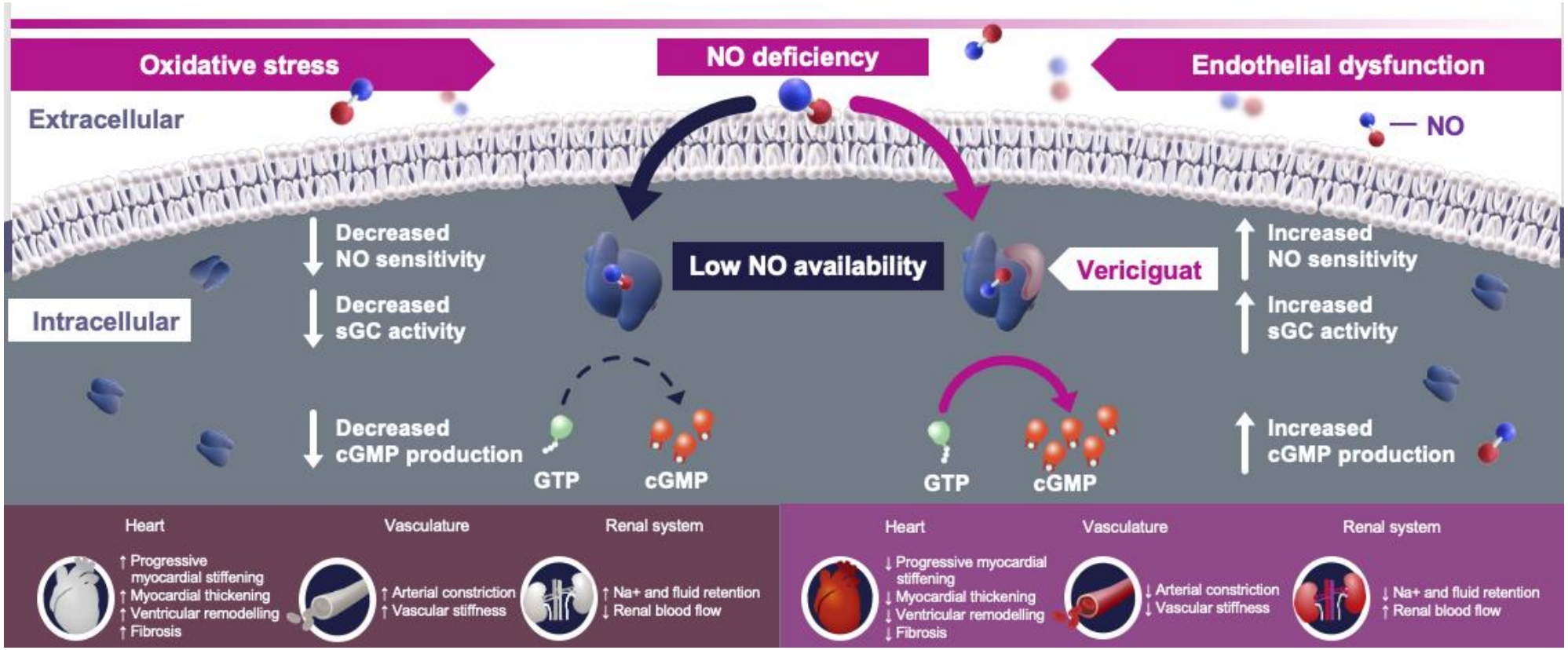


Cinaciguat



Vericiguat




Oxidative stress
NO deficiency
Endothelial dysfunction
Extracellular
NO
Intracellular
Decreased NO sensitivity
Decreased sGC activity
Decreased cGMP production
Low NO availability
Vericiguat
Increased NO sensitivity
Increased sGC activity
Increased cGMP production
GTP
cGMP
GTP
cGMP
Heart
↑ Progressive myocardial stiffening
↑ Myocardial thickening
↑ Ventricular remodelling
↑ Fibrosis
Vasculature
↑ Arterial constriction
↑ Vascular stiffness
Renal system
↑ Na+ and fluid retention
↓ Renal blood flow
Heart
↓ Progressive myocardial stiffening
↓ Myocardial thickening
↓ Ventricular remodelling
↓ Fibrosis
Vasculature
↓ Arterial constriction
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Renal system
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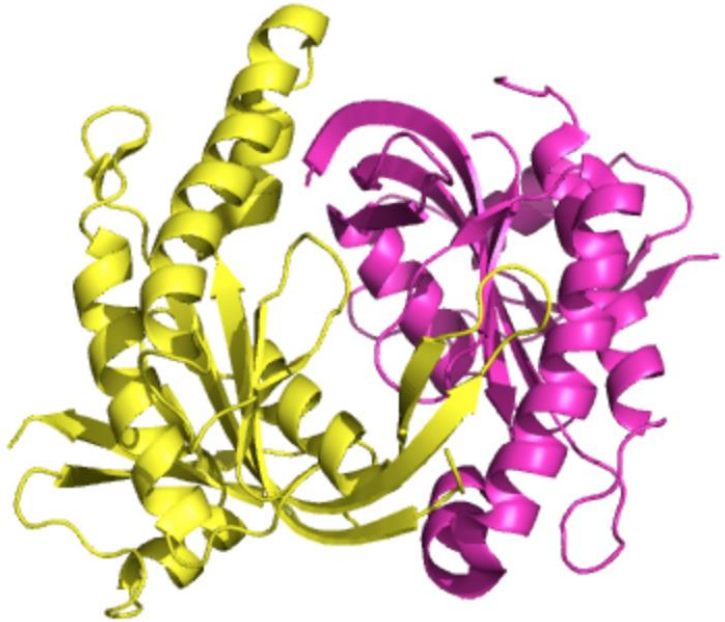
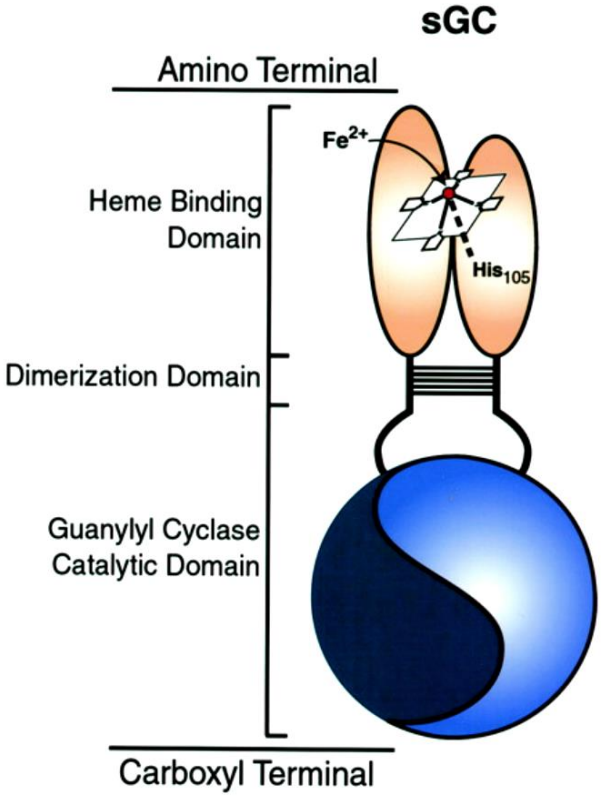
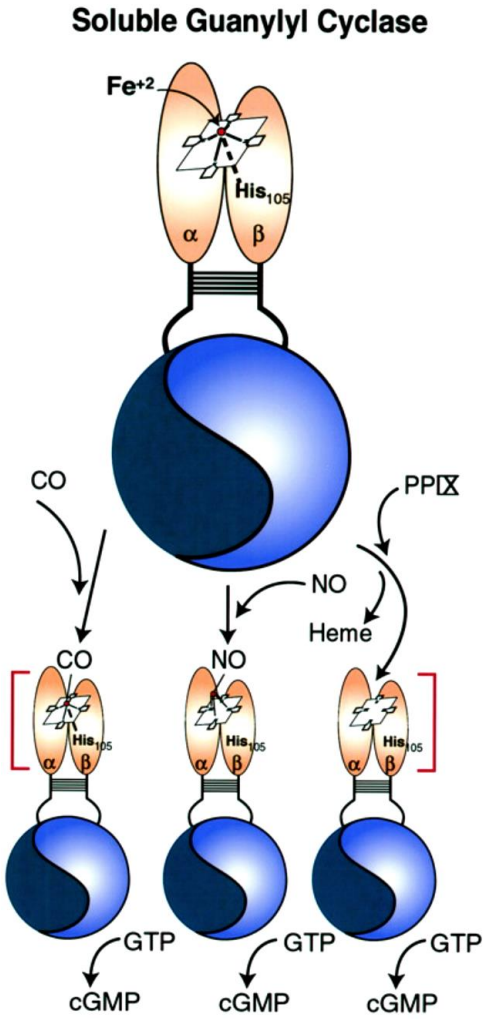
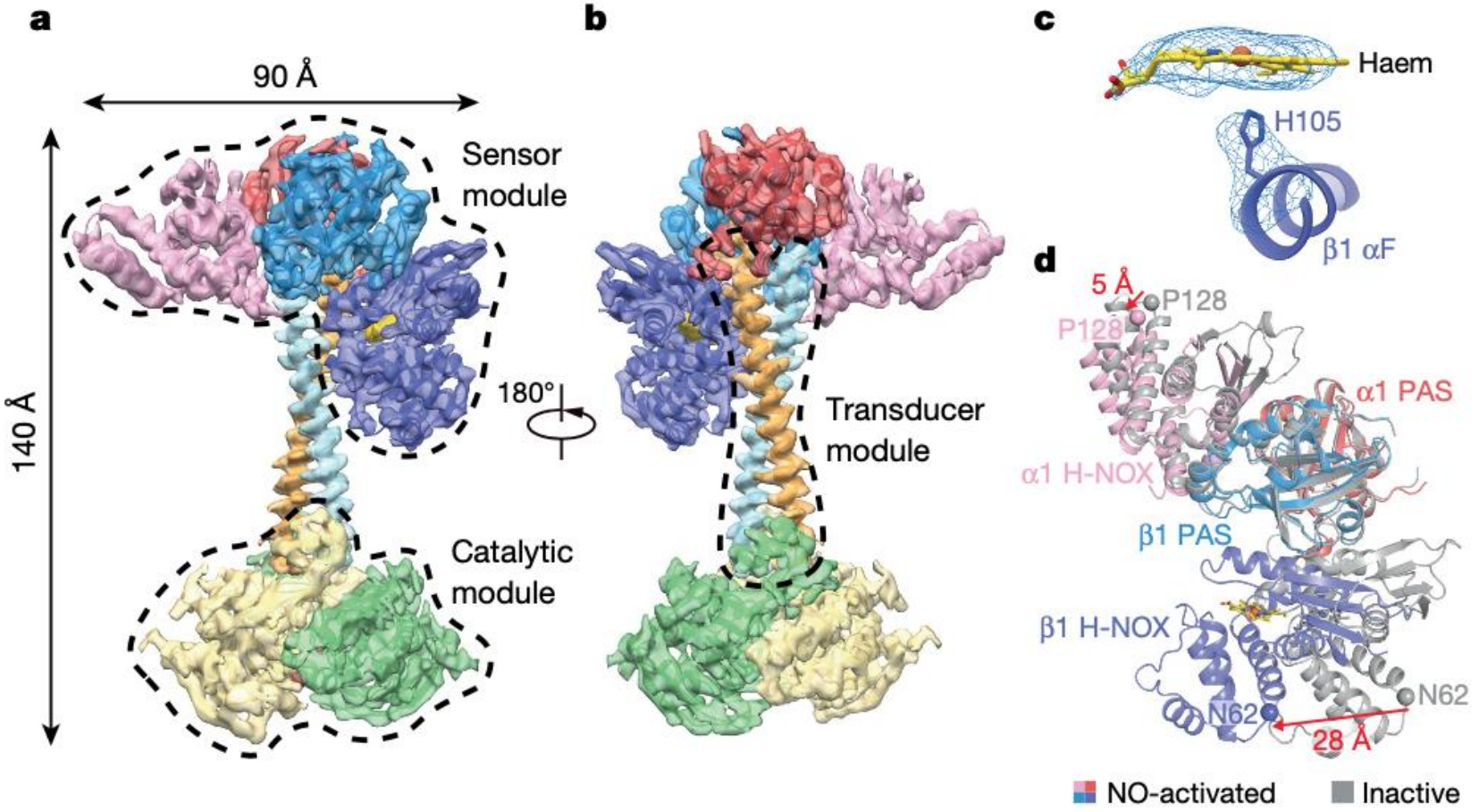
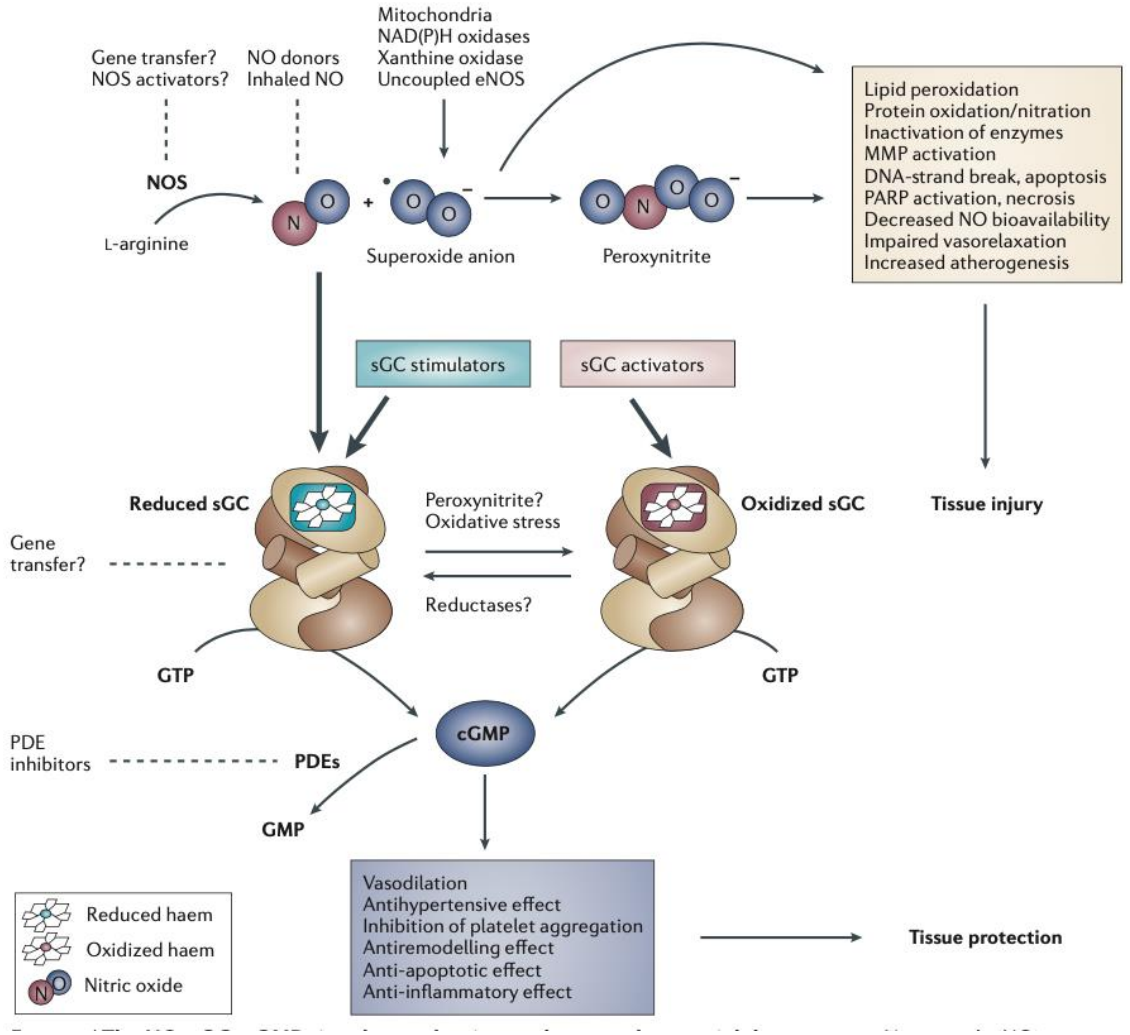
↑ Renal blood flow

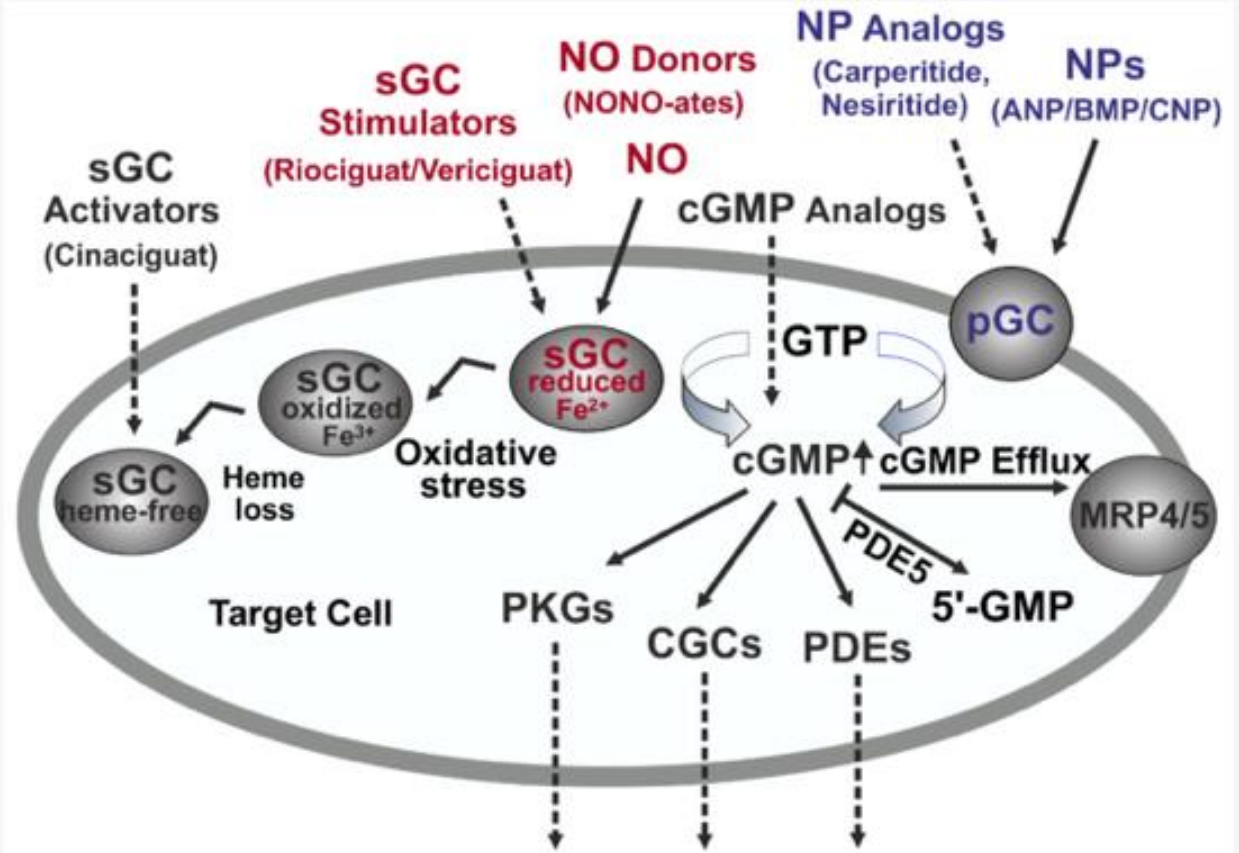


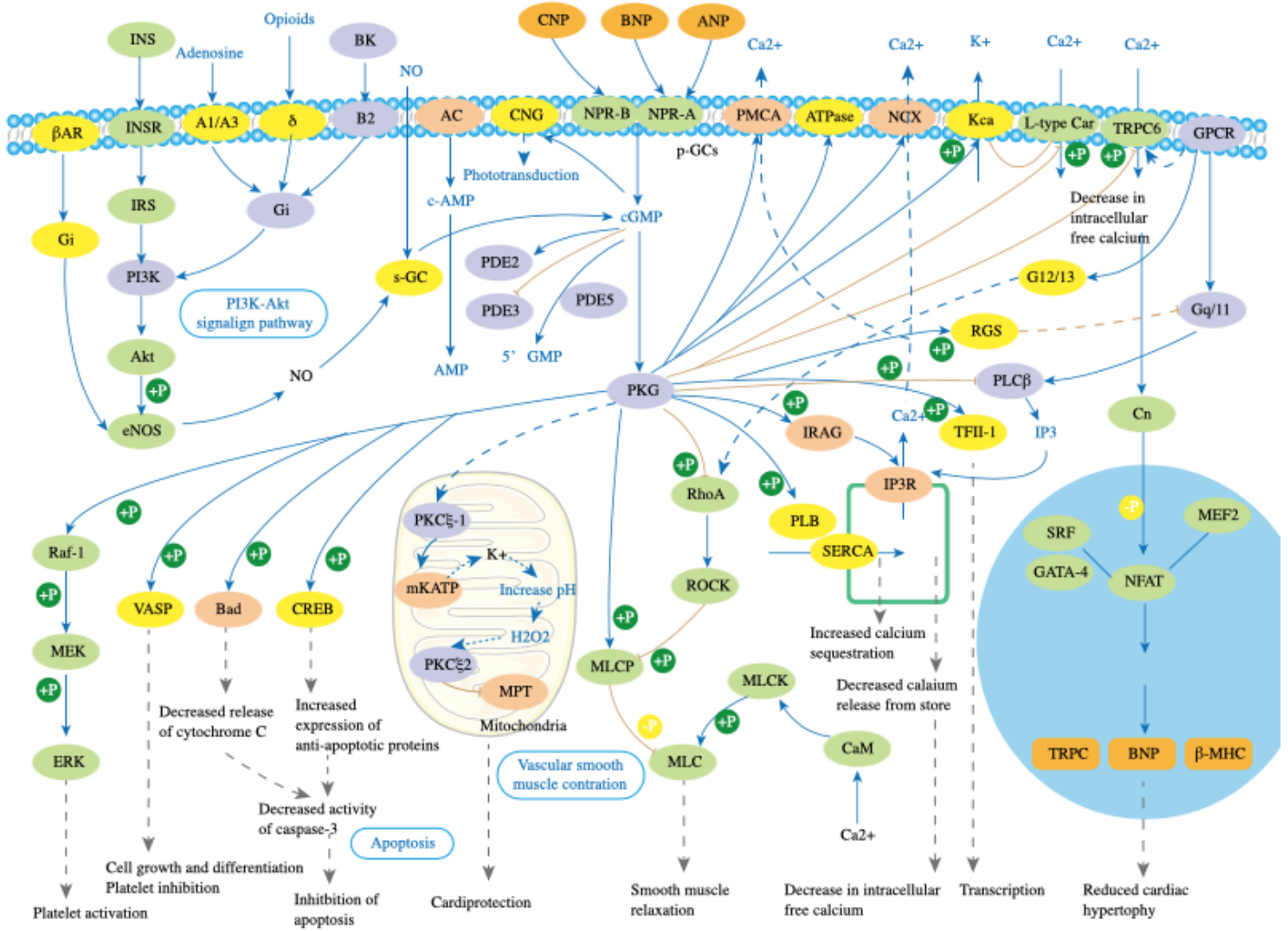

sGC
Amino Terminal
Heme Binding Domain
Dimerization Domain
Guanylyl Cyclase Catalytic Domain
Carboxyl Terminal
Fe2+
His105


Soluble Guanylyl Cyclase
Fe+2
His105
α
β
CO
NO
Heme
GTP
cGMP

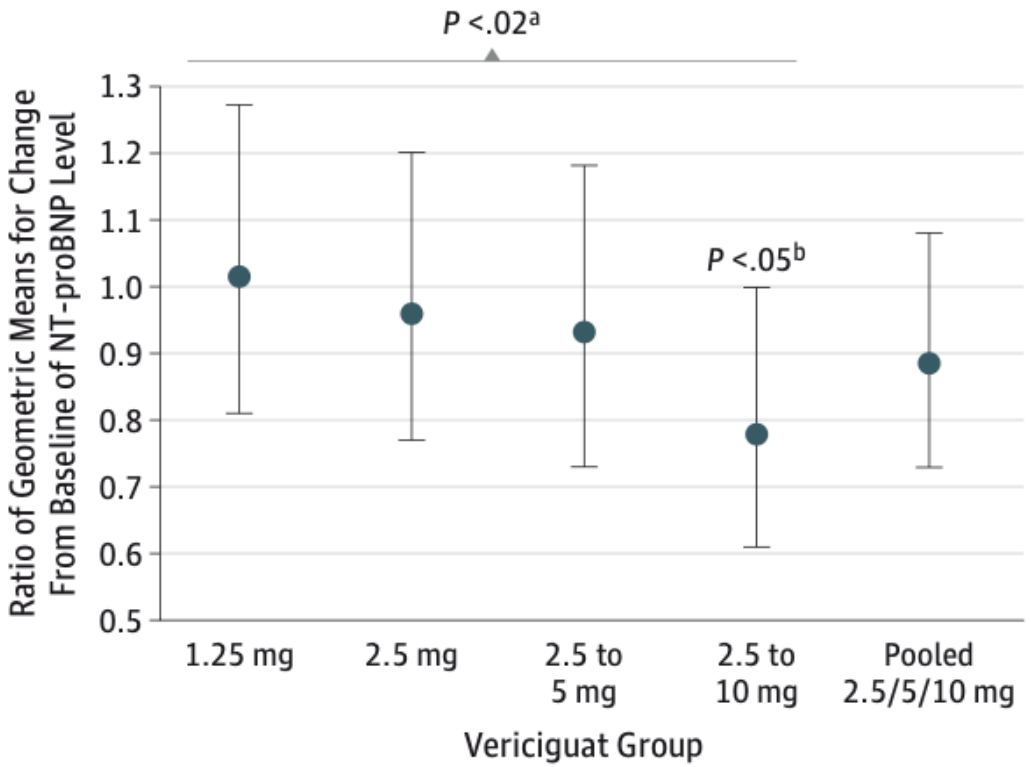

a
90 Å
140 Å
Sensor module
180°
Catalytic module
b
Transducer module
c
Haem
H105
β1 αF
d
5 Å
P128
P128
α1 PAS
α1 H-NOX
β1 PAS
β1 H-NOX
N62
N62
28 Å
NO-activated
Inactive


Mitochondria
NAD(P)H oxidases
Xanthine oxidase
Uncoupled eNOS
Gene transfer?
NOS activators?
NO donors
Inhaled NO
NOS
L-arginine
Superoxide anion
Peroxynitrite
Lipid peroxidation
Protein oxidation/nitration
Inactivation of enzymes
MMP activation
DNA-strand break, apoptosis
PARP activation, necrosis
Decreased NO bioavailability
Impaired vasorelaxation
Increased atherogenesis
sGC stimulators
sGC activators
Reduced sGC
Oxidized sGC
Peroxynitrite?
Oxidative stress
Reductases?
Tissue injury
Gene transfer?
GTP
GTP
cGMP
PDE inhibitors
PDEs
GMP
Reduced haem
Oxidized haem
Nitric oxide
Vasodilation
Antihypertensive effect
Inhibition of platelet aggregation
Antiremodelling effect
Anti-apoptotic effect
Anti-inflammatory effect
Tissue protection


NP Analogs
(Carperitide, Nesiritide)
NPs
(ANP/BMP/CNP)
NO Donors
(NONO-ates)
sGC
Stimulators
(Riociguat/Vericiguat)
NO
sGC
Activators
(Cinaciguat)
cGMP Analogs
pGC
GTP
sGC
reduced
Fe2+
sGC
oxidized
Fe3+
sGC
heme-free
Heme
loss
Oxidative
stress
cGMP
cGMP Efflux
MRP4/5
PDE5
5'-GMP
Target Cell
PKGs
CGCs
PDEs
sGC: Cardiac Protection, Antifibrotic, Smooth Muscle Relaxation,
Neuronal Plasticity, Endothelial Permeability, Lower Urinary Tract Functions
and Gene Transcription
pGC: Diuresis, Natriuresis, Anti-inflammatory, Antifibrosis, Antiapotosis,
Vasodilation and Mesangial Relaxation


INS
Adenosine
Opioids
BK
NO
CNP
BNP
ANP
Ca2+
Ca2+
K+
Ca2+
Ca2+
βAR
INSR
A1/A3
δ
B2
AC
CNG
NPR-B
NPR-A
PMCA
ATPase
NCX
Kca
L-type Car
TRPC6
GPCR
p-GCs
+P
Phototransduction
c-AMP
cGMP
Decrease in intracellular free calcium
IRS
Gi
Gi
PI3K
PI3K-Akt signalign pathway
s-GC
PDE2
PDE3
PDE5
5' GMP
AMP
G12/13
Gq/11
RGS
Akt
+P
NO
eNOS
PKG
PLCβ
IRAG
Ca2+
TFII-1
IP3
Cn
+P
RhoA
IP3R
PLB
SERCA
Raf-1
+P
VASP
Bad
CREB
PKCξ-1
K+
mKATP
Increase pH
H2O2
PKCξ2
MPT
Mitochondria
ROCK
MLCP
MLCK
MLC
CaM
Ca2+
Increased calcium sequestration
Decreased calaium release from store
SRF
GATA-4
MEF2
NFAT
-P
TRPC
BNP
β-MHC
MEK
ERK
Decreased release of cytochrome C
Increased expression of anti-apoptotic proteins
Decreased activity of caspase-3
Apoptosis
Vascular smooth muscle contration
Platelet activation
Cell growth and differentiation
Platelet inhibition
Inhitbition of apoptosis
Cardiprotection
Smooth muscle relaxation
Decrease in intracellular free calcium
Transcription
Reduced cardiac hypertophy

Effect of vericiguat, a soluble guanylate cyclase stimulator, on natriuretic peptide levels in patients with worsening chronic heart failure and reduced ejection fraction - The SOCRATES-REDUCED randomized trial



Gheorghiade M et al. JAMA. 2015;314:2251-62.

Effect of vericiguat, a soluble guanylate cyclase stimulator, on natriuretic peptide levels in patients with worsening chronic heart failure and reduced ejection fraction - The SOCRATES-REDUCED randomized trial

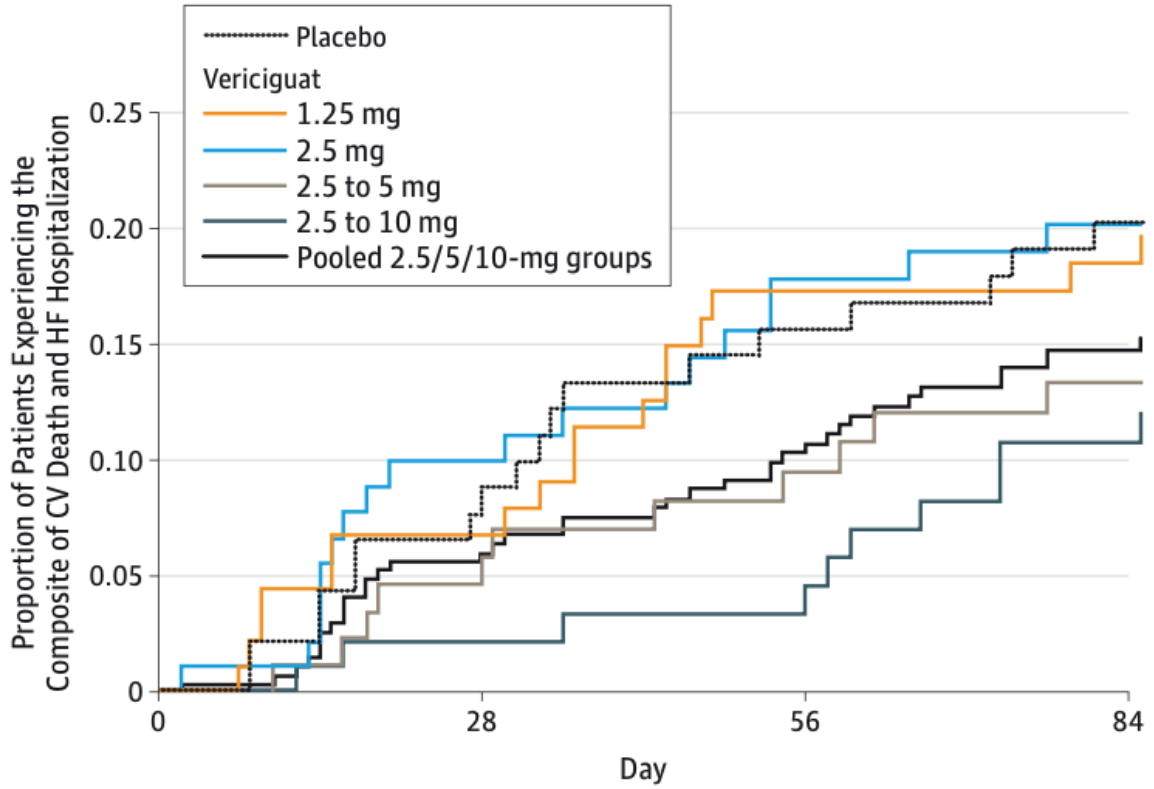


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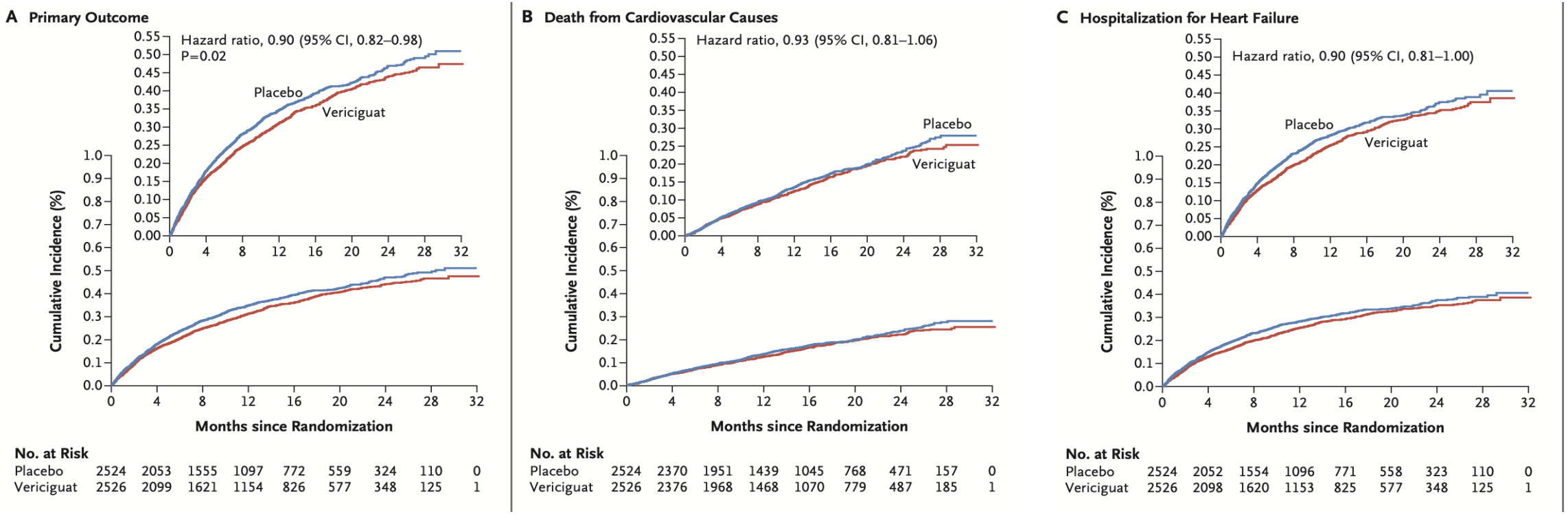
Table 5. Adverse Events (Safety Analysis Set)

	No. of Patients (%)				
		Vericiguat			
	Placebo (n = 92)	1.25 mg (n = 91)	2.5 mg (n = 90)	2.5 to 5 mg (n = 91)	2.5 to 10 mg (n = 91)
Any AE	71 (77.2)	64 (70.3)	71 (78.9)	67 (73.6)	65 (71.4)
Any study drug-related AE	13 (14.1)	10 (11.0)	13 (14.4)	12 (13.2)	15 (16.5)
AE with outcome death	5 (5.4)	6 (6.6)	4 (4.4)	2 (2.2)	4 (4.4)
Any SAE	36 (39.1)	31 (34.1)	35 (38.9)	24 (26.4)	29 (31.9)
Any study drug-related SAE	3 (3.3)	1 (1.1)	1 (1.1)	1 (1.1)	4 (4.4)
Discontinuation of study drug due to AE	7 (7.6)	10 (11.0)	9 (10.0)	8 (8.8)	8 (8.8)
Discontinuation of study drug due to SAE	5 (5.4)	6 (6.6)	2 (2.2)	5 (5.5)	7 (7.7)
Treatment-emergent AEs of interest					
Hypotension[a,b]	6 (6.5)	5 (5.5)	6 (6.7)	4 (4.4)	14 (15.4)[b]
Asymptomatic	1 (1.1)	2 (2.2)	3 (3.3)	2 (2.2)	5 (5.5)
Symptomatic	5 (5.4)	3 (3.3)	3 (3.3)	2 (2.2)	10 (11.0)
Syncope	1 (1.1)	0	2 (2.2)	1 (1.1)	4 (4.4)
Acute kidney injury	3 (3.3)	5 (5.5)	2 (2.2)	1 (1.1)	3 (3.3)

Gheorghiade M et al. JAMA. 2015;314:2251-62.

Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction



Armstrong PW et al. N Engl J Med. 2020;382:1883-1893.

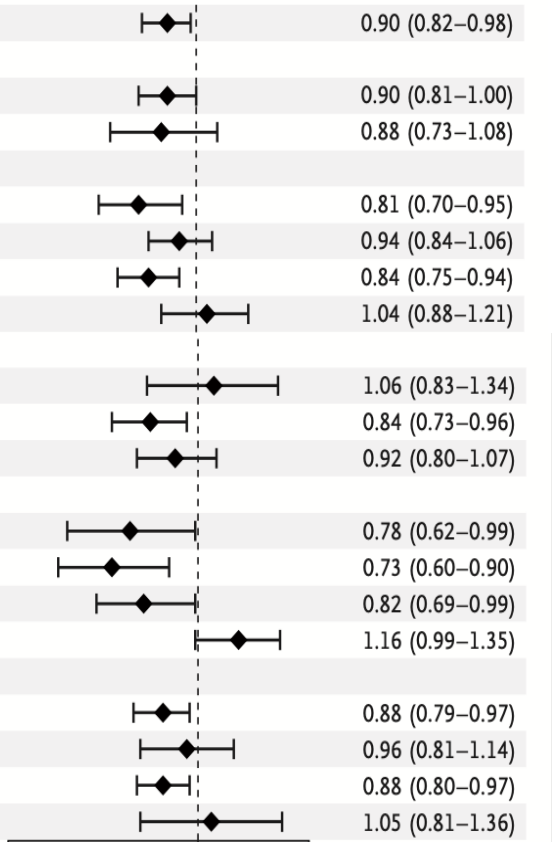
Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction

Characteristic	Vericiguat (N=2526)	Placebo (N=2524)	Total (N=5050)
Mean age — yr	67.5±12.2	67.2±12.2	67.3±12.2
Sex — no. (%)			
Male	1921 (76.0)	1921 (76.1)	3842 (76.1)
Female	605 (24.0)	603 (23.9)	1208 (23.9)
Mean body-mass index‡	27.7±5.8	27.9±6.1	27.8±5.9
Mean ejection fraction at screening — %	29.0±8.3	28.8±8.3	28.9±8.3
Ejection fraction <40% — no. (%)	2158 (85.8)	2158 (85.6)	4316 (85.7)

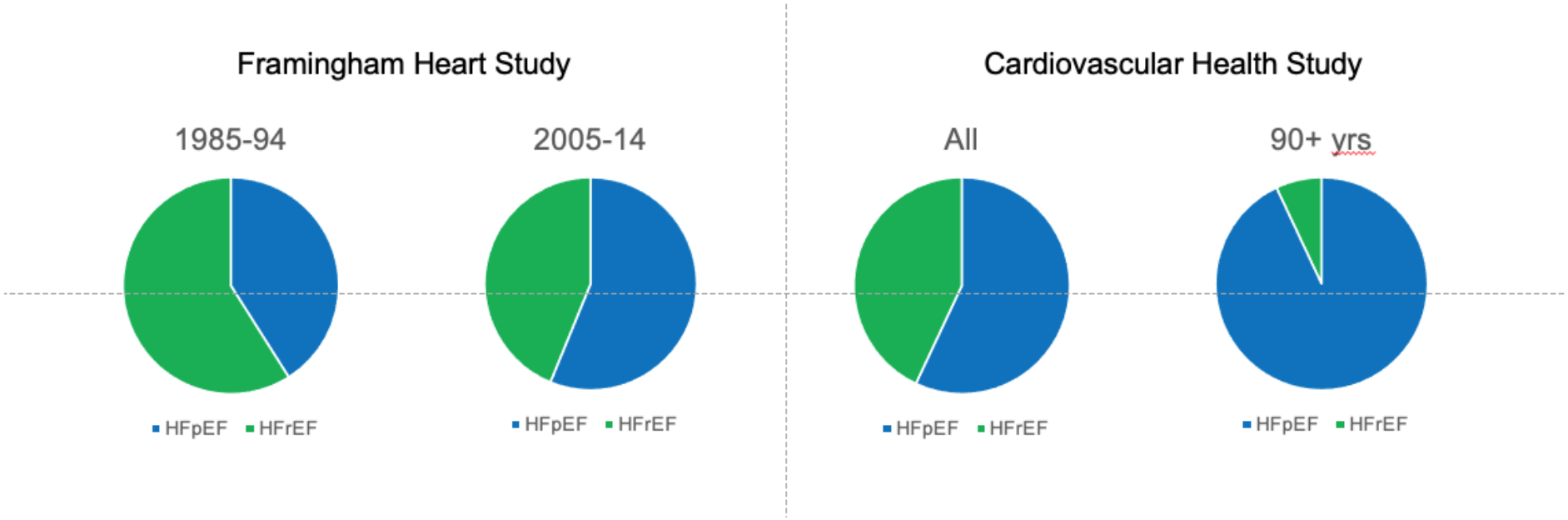
Armstrong PW et al. N Engl J Med. 2020;382:1883-1893.

Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction

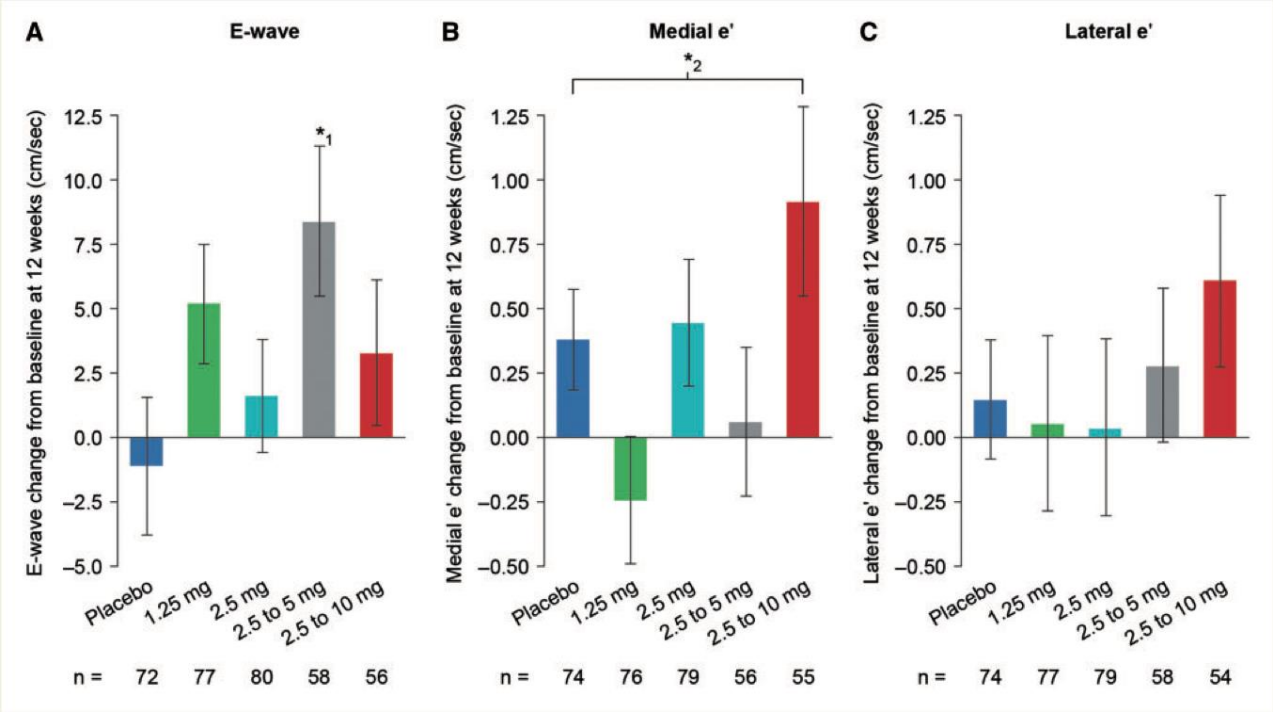
Subgroup	Vericiguat	Placebo	Hazard Ratio (95% CI)
	no. of events		
All patients	897	972	0.90 (0.82–0.98)
Sex			
Male	704	762	0.90 (0.81–1.00)
Female	193	210	0.88 (0.73–1.08)
Age			
<65 yr	290	348	0.81 (0.70–0.95)
≥65 yr	607	624	0.94 (0.84–1.06)
<75 yr	579	669	0.84 (0.75–0.94)
≥75 yr	318	303	1.04 (0.88–1.21)
Estimated GFR			
≤30 ml/min/1.73 m^2	143	128	1.06 (0.83–1.34)
>30 to ≤60 ml/min/1.73 m^2	392	455	0.84 (0.73–0.96)
>60 ml/min/1.73 m^2	346	372	0.92 (0.80–1.07)
NT-proBNP level			
Quartile 1 (≤1556.0 pg/ml)	128	161	0.78 (0.62–0.99)
Quartile 2 (>1556.0 to ≤2816.0 pg/ml)	165	201	0.73 (0.60–0.90)
Quartile 3 (>2816.0 to ≤5314.0 pg/ml)	213	257	0.82 (0.69–0.99)
Quartile 4 (>5314.0 pg/ml)	355	302	1.16 (0.99–1.35)
Ejection fraction			
<35%	637	703	0.88 (0.79–0.97)
≥35%	255	265	0.96 (0.81–1.14)
<40%	773	851	0.88 (0.80–0.97)
≥40%	119	117	1.05 (0.81–1.36)



Armstrong PW et al. N Engl J Med. 2020;382:1883-1893.


Framingham Heart Study
1985-94
2005-14
HFpEF
HFrEF
HFpEF
HFrEF
Cardiovascular Health Study
All
90+ yrs
HFpEF
HFrEF
HFpEF
HFrEF

Vericiguat in patients with worsening chronic heart failure and preserved ejection fraction: results of the soluble guanylate cyclase stimulator in heart failure patients with preserved EF (Socrates-preserved) study



Pieske B et al. Eur Heart J. 2017;38:1119-1127.

Vericiguat in patients with worsening chronic heart failure and preserved ejection fraction: results of the soluble guanylate cyclase stimulator in heart failure patients with preserved EF (Socrates-preserved) study

Primary analysis[a]			Baseline	12 weeks (Visit 5)	Treatment comparison			
		n	Mean (SD)	Mean change from baseline (SD)	Difference (Treat-Plac) [Back-transformed[b]]	90% Confidence interval [Back-transformed[b]]	*P*-value[c] One-sided	*P*-value[c] Two-sided
LAV (mL)	Placebo	67	89.075 (51.059)	-3.361 (12.654)				
	Pooled 2.5/5/10 mg	194	87.083 (30.204)	-1.732 (12.808)	1.6291	-1.36 to 4.62	0.8156	0.3688
log(NT-proBNP) [log(pg/mL)]	Placebo	73	6.897 (1.203)	-0.098 (0.778)				
	Pooled 2.5/5/10 mg	195	6.945 (1.297)	0.038 (0.782)	0.1372 [1.147]	-0.04 to 0.31 [0.96–1.37]	0.8991	0.2017

Pieske B et al. Eur Heart J. 2017;38:1119-1127.

Vericiguat in patients with worsening chronic heart failure and preserved ejection fraction: results of the soluble guanylate cyclase stimulator in heart failure patients with preserved EF (Socrates-preserved) study

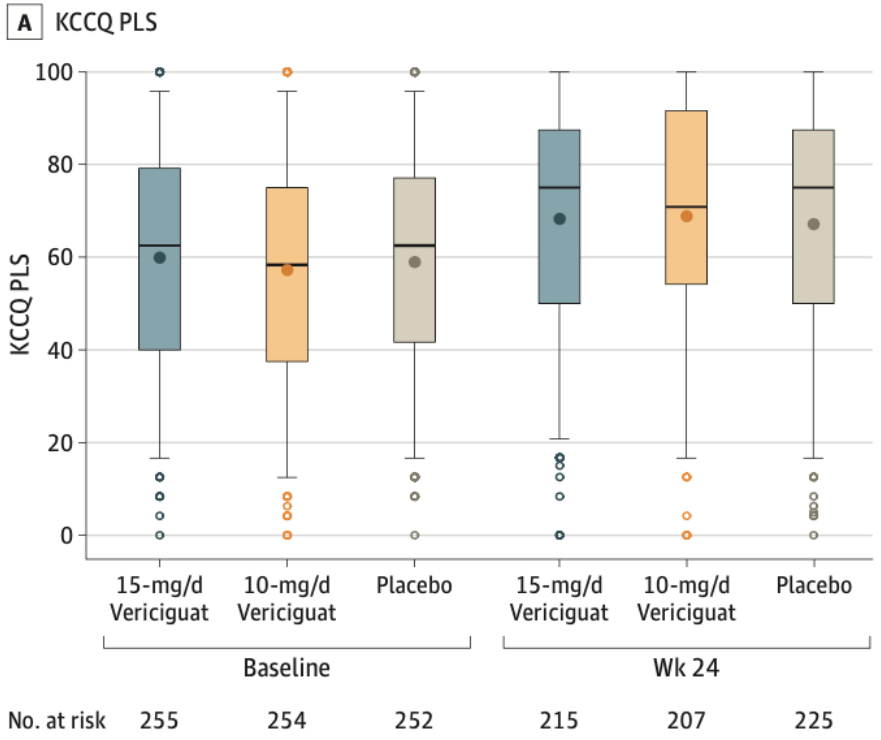
Table 3 Kansas City cardiomyopathy questionnaire-clinical summary score (full analysis set excluding patients with incorrectly assigned doses)

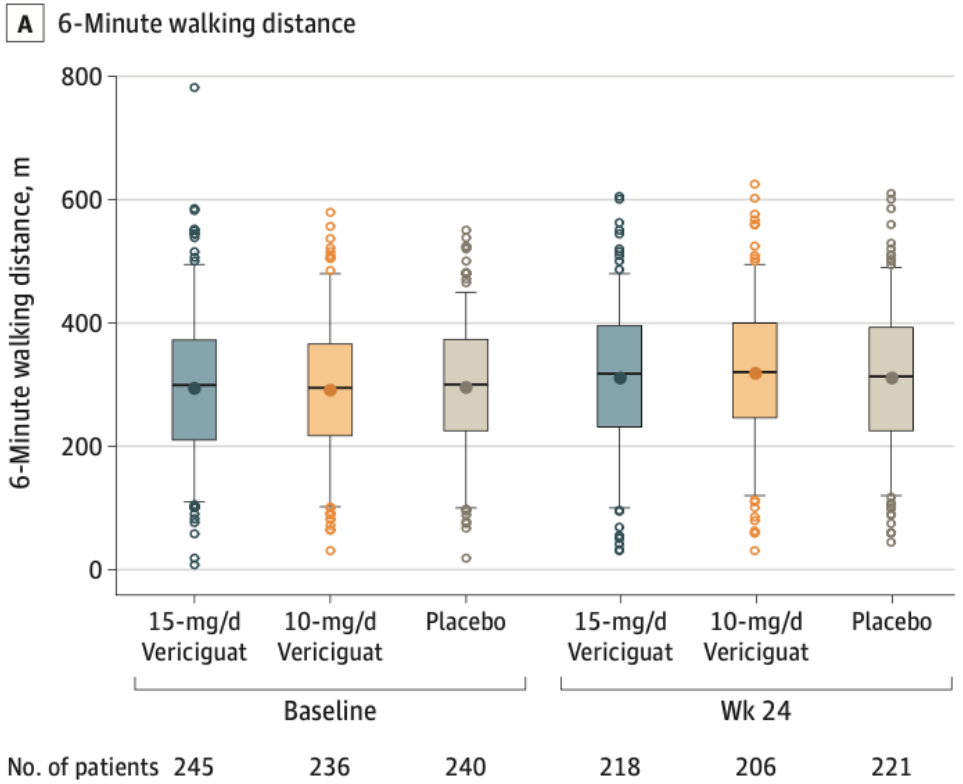
	Baseline		12 weeks (Visit 5)				Treatment comparison				Regression
	Mean (SD)		Mean change from baseline (SD)		Mean change from Week 4 (SD)		Change at 12 weeks from baseline		Change between 4 and 12 weeks		Slope (SD), *P*-value[b]
	n		*n*		*n*		Difference (Treat-Plac)	*P*-value[a]	Difference (Treat-Plac)	*P*-value[a]	
2.5–10 mg	68	52.3 (20.4)	61	19.3 (16.3)	60	6.2 (15.7)	9.2	0.016	5.7	0.0465	0.92 (0.29),
2.5–5 mg	75	52.9 (24.0)	61	12.3 (18.9)	60	7.4 (13.6)	2.1	0.5065	6.9	0.0046	*P*=0.0017
2.5 mg	95	57.3 (22.3)	83	8.7 (18.4)	83	2.6 (15.7)	-1.4	0.2897	2.1	0.4468	
1.25 mg	96	56.0 (22.5)	82	11.4 (19.1)	81	3.4 (15.8)	1.3	0.5802	2.9	0.2445	
Placebo	92	54.1 (23.0)	78	10.2 (20.0)	79	0.5 (14.1)					

SD, standard deviation.
[a]Non-parametric Wilcoxon rank-sum test.
[b]Linear regression with dose group as explanatory variable.

Pieske B et al. Eur Heart J. 2017;38:1119-1127.

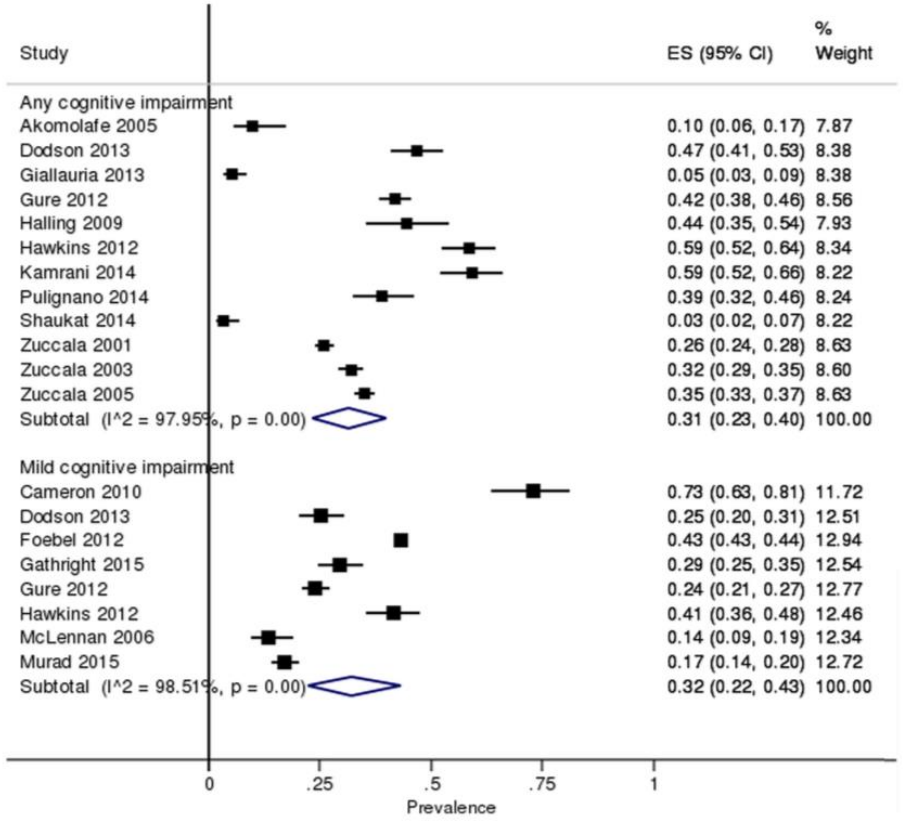
Effect of vericiguat vs placebo on quality of life in patients with heart failure and preserved ejection fraction - The VITALITY-HFpEF randomized clinical trial





Armstrong PW et al. JAMA. 2020;324:1512-1521.

Cognitive impairment in chronic obstructive pulmonary disease and chronic heart failure: a systematic review and meta-analysis of observational studies



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The effects of cognitive impairment on mortality among hospitalized patients with heart failure

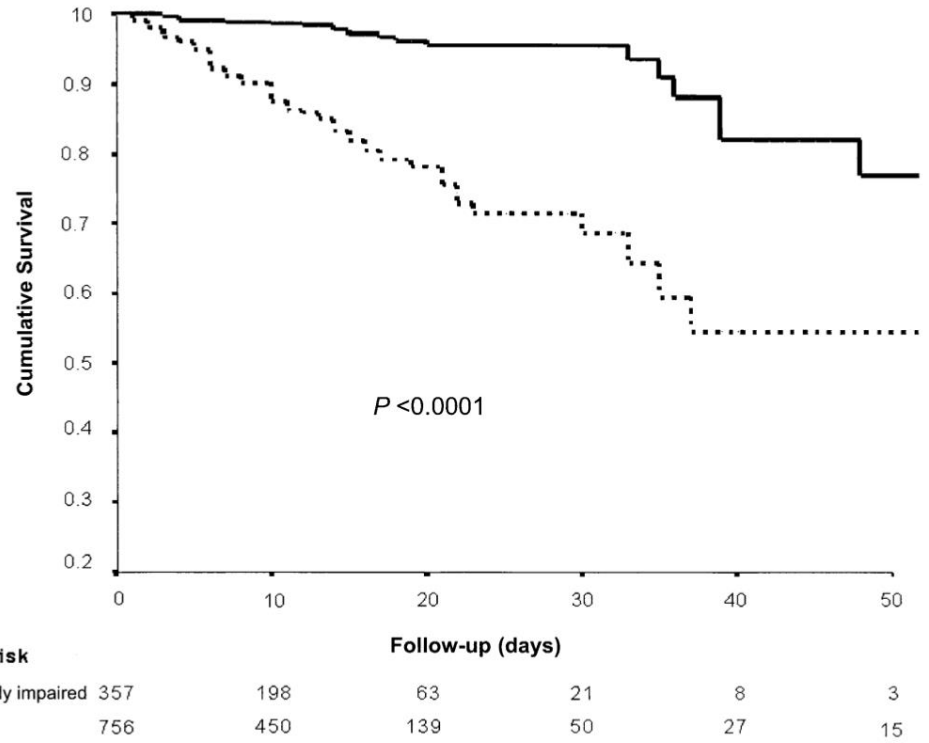

Figure 1. Kaplan-Meier analysis of in-hospital survival by the presence (dotted line) or absence (solid line) of cognitive impairment.

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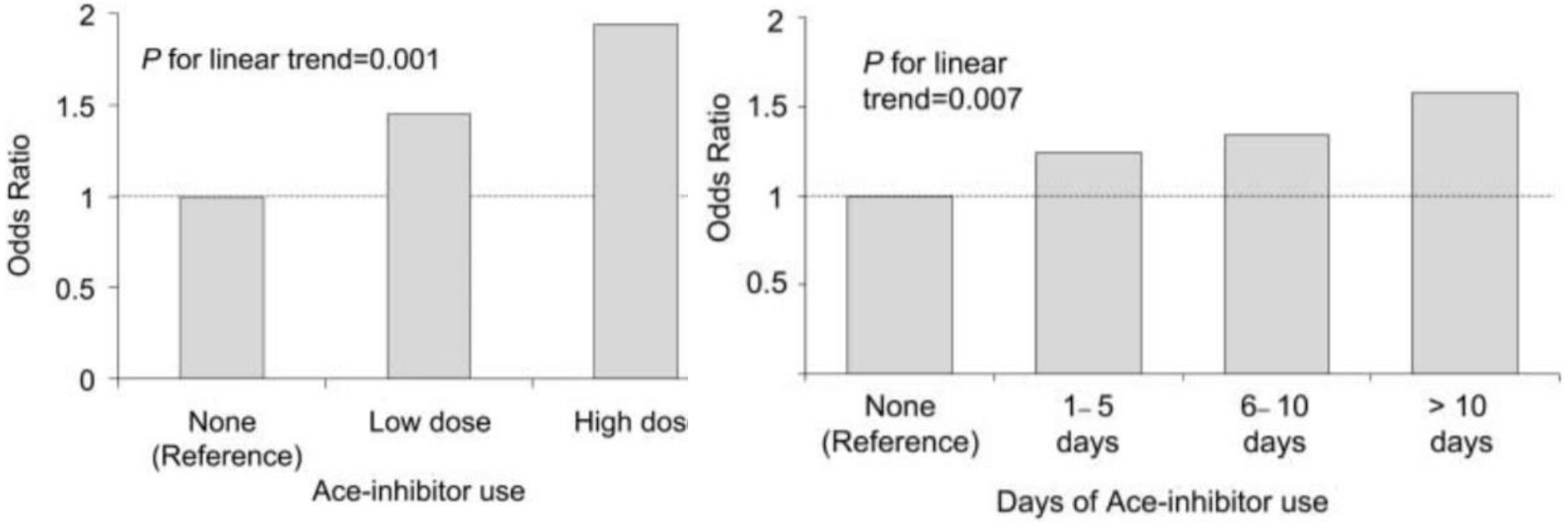
Use of angiotensin-converting enzyme inhibitors and variations in cognitive performance among patients with heart failure.



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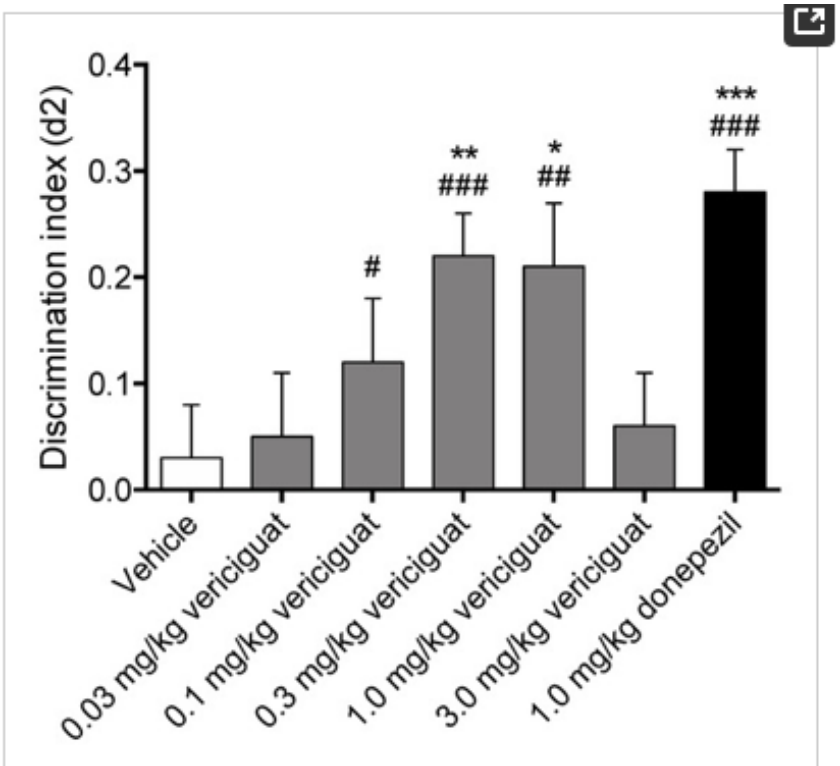
Soluble guanylate cyclase stimulator vericiguat enhances long-term memory in rats without altering cerebral blood volume



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