From Bench to Launch

The sGC stimulator vericiguat: A new mode of action for treating chronic heart failure

Annual Congress of the Czech Society of Cardiology

Brno, May 13-16th 2023

Peter Sandner
BAYER AG, Cardiology & sGC Research

PP-VER-CZ-0159-1, 05/2023

Nitric Oxide (NO) an effective treatment for Angina Pectoris

THE LANCET,] [JULY 27, 1867. 97

ON THE

USE OF NITRITE OF AMYL IN ANGINA PECTORIS.

BY T. LAUDER BRUNTON, B.Sc., M.B.,
SENIOR PRESIDENT OF THE ROYAL MEDICAL SOCIETY, AND RESIDENT PHYSICIAN TO THE CLINICAL WARDS OF THE ROYAL INFIRMARY, EDINBURGH.

80 THE LANCET,] [JAN. 18, 1879.

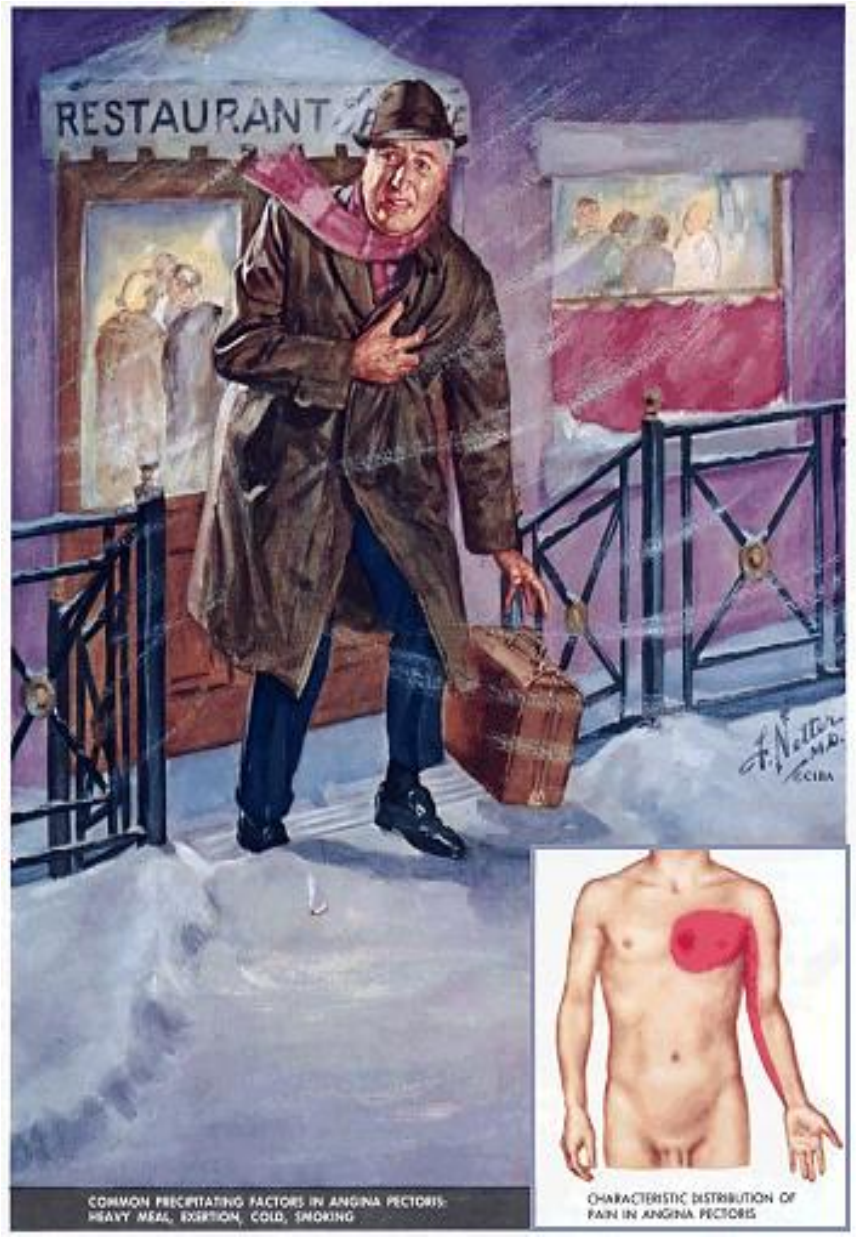
NITRO-GLYCERINE AS A REMEDY FOR ANGINA PECTORIS.

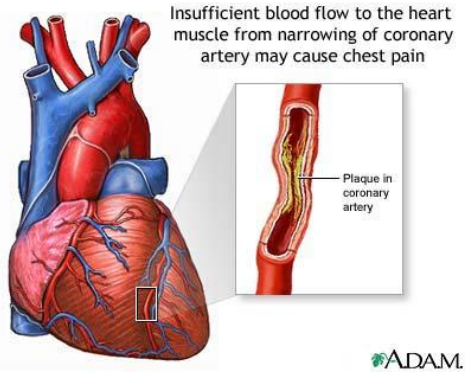
BY WILLIAM MURRELL, M.R.C.P.,
LECTURER ON PRACTICAL PHYSIOLOGY AT WESTMINSTER HOSPITAL, AND ASSISTANT-PHYSICIAN TO THE ROYAL HOSPITAL FOR DISEASES OF THE CHEST.

(Continued from p. 115.)

DURING the last nine months I have treated three cases of undoubted angina pectoris with nitro-glycerine, with what success the cases themselves will show.

Fye et al. Circulation 1986;74:222-229





Impairment of NO/sGC signaling is associated with CAD and MI

LETTER 432 | NATURE | VOL 504 | 19/26 DECEMBER 2013
doi:10.1038/nature12722

Dysfunctional nitric oxide signalling increases risk of myocardial infarction

Jeanette Erdmann[1,2]*, Klaus Stark[3,4]*, Ulrike B. Esslinger[3,5]*, Philipp Moritz Rumpf[6,7]*, Doris Koesling[8], Cor de Wit[2,9], Frank J. Kaiser[2,10], Diana Braunholz[10], Anja Medack[1], Marcus Fischer[3], Martina E. Zimmermann[3], Stephanie Tennstedt[1], Elisabeth Graf[11,12], Sebastian Eck[11,12], Zouhair Aherrahrou[1,2], Janja Nahrstaedt[1], Christina Willenborg[1,2], Petra Bruse[1], Ingrid Brænne[1], Markus M. Nöthen[13,14], Per Hofmann[13,15], Peter S. Braund[16,17], Evanthia Mergia[8], Wibke Reinhard[6,7], Christof Burgdorf[6], Stefan Schreiber[18], Anthony J. Balmforth[19], Alistair S. Hall[20], Lars Bertram[21], Elisabeth Steinhagen-Thiessen[22], Shu-Chen Li[23,24], Winfried März[25,26,27], Muredach Reilly[28], Sekar Kathiresan[29,30,31], Ruth McPherson[32], Ulrich Walter[33,34], CARDIoGRAM†, Jurg Ott[35,36], Nilesh J. Samani[16,17], Tim M. Strom[11,12], Thomas Meitinger[6,11,12], Christian Hengstenberg[6,7] & Heribert Schunkert[6,7]

Myocardial infarction, a leading cause of death in the Western world[1], usually occurs when the fibrous cap overlying an atherosclerotic plaque in a coronary artery ruptures. The resulting exposure of blood to the atherosclerotic material then triggers thrombus formation, which occludes the artery[2]. The importance of genetic predisposition to coronary artery disease and myocardial infarction is best documented by the predictive value of a positive family history[3]. Next-generation sequencing in families with several affected individuals has revolutionized mutation identification[4]. Here we report the segregation of two private, heterozygous mutations in two functionally related genes, *GUCY1A3* (p.Leu163Phefs*24) and *CCT7* (p.Ser525Leu), in an extended myocardial infarction family. *GUCY1A3* encodes the α1 subunit of soluble guanylyl cyclase (α1-sGC)[5], and *CCT7* encodes CCTη, a member of the tailless complex polypeptide 1 ring complex[6], which, among other functions, stabilizes soluble guanylyl cyclase. After stimulation with nitric oxide, soluble guanylyl cyclase generates cGMP, which induces vasodilation and inhibits platelet activation[7]. We demonstrate *in vitro* that mutations in both *GUCY1A3* and *CCT7* severely reduce α1-sGC as well as β1-sGC protein content, and impair soluble guanylyl cyclase activity. Moreover, platelets from digenic mutation carriers contained less soluble guanylyl cyclase protein and consequently displayed reduced nitric-oxide-induced cGMP formation. Mice deficient in α1-sGC protein displayed accelerated thrombus formation in the microcirculation after local trauma. Starting with a severely affected family, we have identified a link between impaired soluble-guanylyl-cyclase-dependent nitric oxide signalling and myocardial infarction risk, possibly through accelerated thrombus formation. Reversing this defect may provide a new therapeutic target for reducing the risk of myocardial infarction.

LETTERS

nature genetics

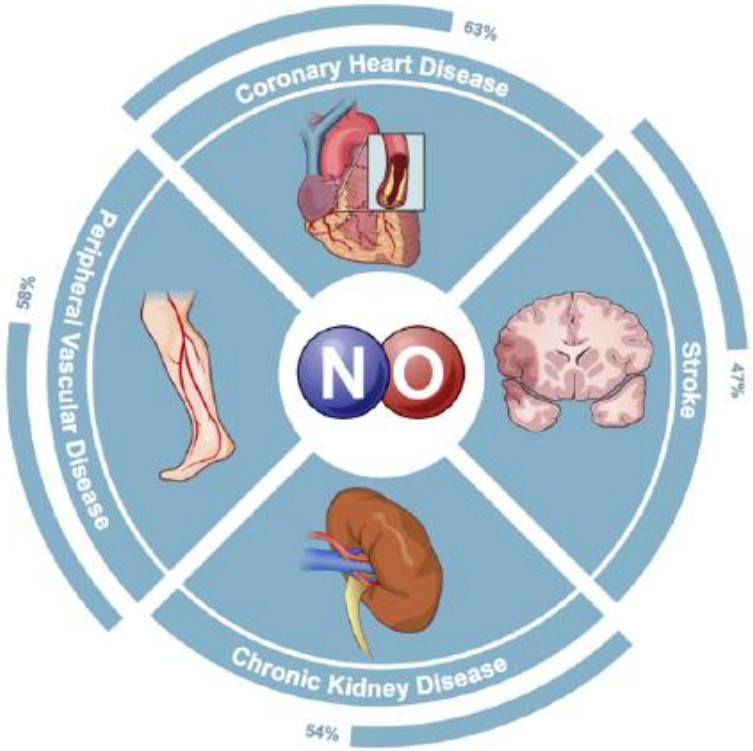
VOLUME 44 | NUMBER 8 | AUGUST 2012 NATURE GENETICS

Genome-wide association study in Han Chinese identifies four new susceptibility loci for coronary artery disease

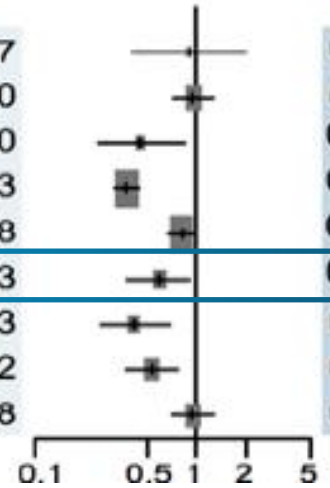
Xiangfeng Lu[1,45], Laiyuan Wang[1,2,45], Shufeng Chen[1], Lin He[3], Xueli Yang[1], Yongyong Shi[3], Jing Cheng[4,5], Liang Zhang[4], C Charles Gu[6], Jianfeng Huang[1], Tangchun Wu[7], Yitong Ma[8], Jianxin Li[1], Jie Cao[1], Jichun Chen[1], Dongliang Ge[1], Zhongjie Fan[9], Ying Li[1], Liancheng Zhao[1], Hongfan Li[2], Xiaoyang Zhou[10], Lanying Chen[1], Donghua Liu[1], Jingping Chen[1], Xiufang Duan[1], Yongchen Hao[1], Ligui Wang[7], Fanghong Lu[11], Zhendong Liu[11], Cailiang Yao[12], Chong Shen[12], Xiaodong Pu[13], Lin Yu[13], Xianghua Fang[14], Lihua Xu[15], Jianjun Mu[16], Xianping Wu[17], Runping Zheng[18], Naqiong Wu[19], Qi Zhao[1], Yun Li[20], Xiaoli Liu[21], Mengqin Wang[22], Dahai Yu[1], Dongsheng Hu[23,24], Xu Ji[25], Dongshuang Guo[26], Dongling Sun[27], Qianqian Wang[1], Ying Yang[1], Fangchao Liu[1], Qunxia Mao[1], Xiaohua Liang[1], Jingfeng Ji[1], Panpan Chen[28], Xingbo Mo[1], Dianjiang Li[1], Guoping Chai[1], Yida Tang[19], Xiangdong Li[1], Zhenhan Du[1], Xuehui Liu[2], Chenlong Dou[2], Zili Yang[29], Qingjie Meng[30], Dong Wang[31], Renping Wang[32], Jun Yang[33], Heribert Schunkert[34,35], Nilesh J Samani[36,37], Sekar Kathiresan[38–40], Muredach P Reilly[41], Jeanette Erdmann[34,35], The Coronary ARtery DIsease Genome-Wide Replication And Meta-Analysis (CARDIoGRAM) Consortium[42], Xiaozhong Peng[43], Xigui Wu[1], Depei Liu[43], Yuejin Yang[19], Runsheng Chen[44], Boqin Qiang[43] & Dongfeng Gu[1]

We performed a meta-analysis of 2 genome-wide association studies of coronary artery disease comprising 1,515 cases and 5,019 controls followed by replication studies in 15,460 cases and 11,472 controls, all of Chinese Han ancestry. We identify four new loci for coronary artery disease that reached the threshold of genome-wide significance ($P < 5 \times 10^{-8}$). These loci mapped in or near *TTC32-WDR35*, *GUCY1A3*, *C6orf10-BTNL2* and *ATP2B1*. We also replicated four loci previously identified in European populations (in or near *PHACTR1*, *TCF21*, *CDKN2A-CDKN2B* and *C12orf51*). These findings provide new insights into pathways contributing to the susceptibility for coronary artery disease in the Chinese Han population.

Enhanced NO/sGC signaling is associated with better outcome of various cardiovascular diseased including heart failure



Outcome	Cases	Controls	OR per 5 mmHg MAP	p –value
Cardiometabolic disease (Primary)				
Aortic Stenosis	1577	333887	0.90 [0.41; 2.00]	0.8
Atrial Fibrillation	12764	322700	0.96 [0.72; 1.28]	0.78
Chronic Kidney Disease	12385	104780	0.46 [0.25; 0.83]	0.011
Coronary Heart Disease	73246	446523	0.37 [0.31; 0.45]	5.5*10^-26
Diabetes	50567	434718	0.81 [0.67; 0.99]	0.037
Heart Failure	5051	330413	0.59 [0.38; 0.92]	0.021
Peripheral Arterial Disease	4011	331453	0.42 [0.26; 0.68]	0.00046
Stroke	7772	327692	0.53 [0.37; 0.76]	0.00058
Venous Thromboembolism	11346	324118	0.95 [0.70; 1.29]	0.75
PheWAS (Secondary)				



Circulation

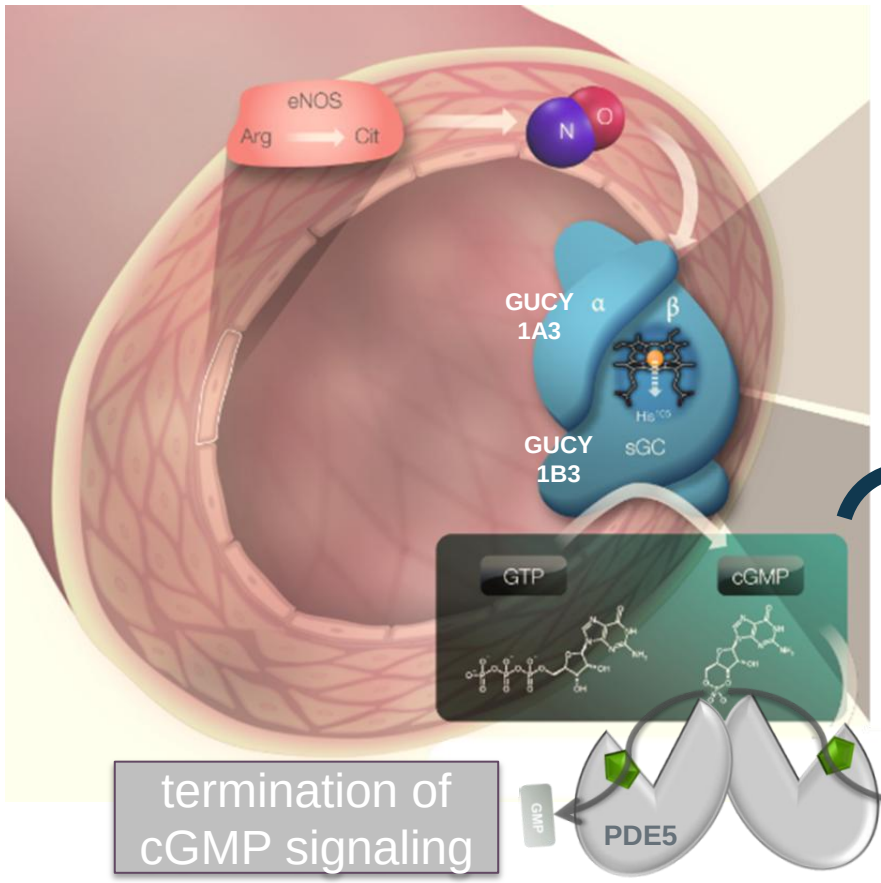
Circulation. 2018;137:222–232. DOI: 10.1161/CIRCULATIONAHA.117.028021

American Heart Association.

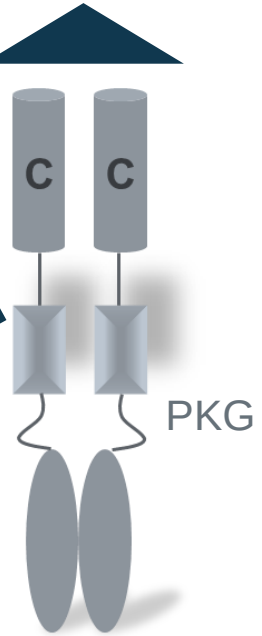
Phenotypic Consequences of a Genetic Predisposition to Enhanced Nitric Oxide Signaling
Connor A. Emdin, Amit V. Khera, Derek Klarin, Pradeep Natarajan, Seyedeh M. Zekavat, Akihiro Nomura, Mary Haas, Krishna Aragam, Diego Ardissino, James G. Wilson, Heribert Schunkert, Ruth McPherson, Hugh Watkins, Roberto Elosua, Matthew J. Bown, Nilesh J. Samani, Usman Baber, Jeanette Erdmann, Padhraig Gormley, Aarno Palotie, Nathan O. Stitziel, Namrata Gupta, John Danesh, Danish Saleheen, Stacey Gabriel and Sekar Kathiresan

A genetic predisposition to enhanced NO signalling is associated with a reduced risk of CHD, stroke, chronic kidney disease, diabetes mellitus and heart failure

The NO/sGC/cGMP signalling pathway



potassium channels / L-type calcium channels, IRAG, phospholamban, MLCK/MLCP, titin, …



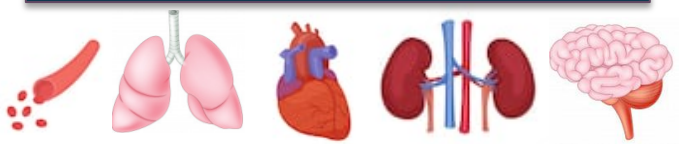
- vascular smooth muscle cells

- endothelial cells
- smooth muscle cells
- cardiomyocytes
- fibroblasts/myofibroblasts
- platelets

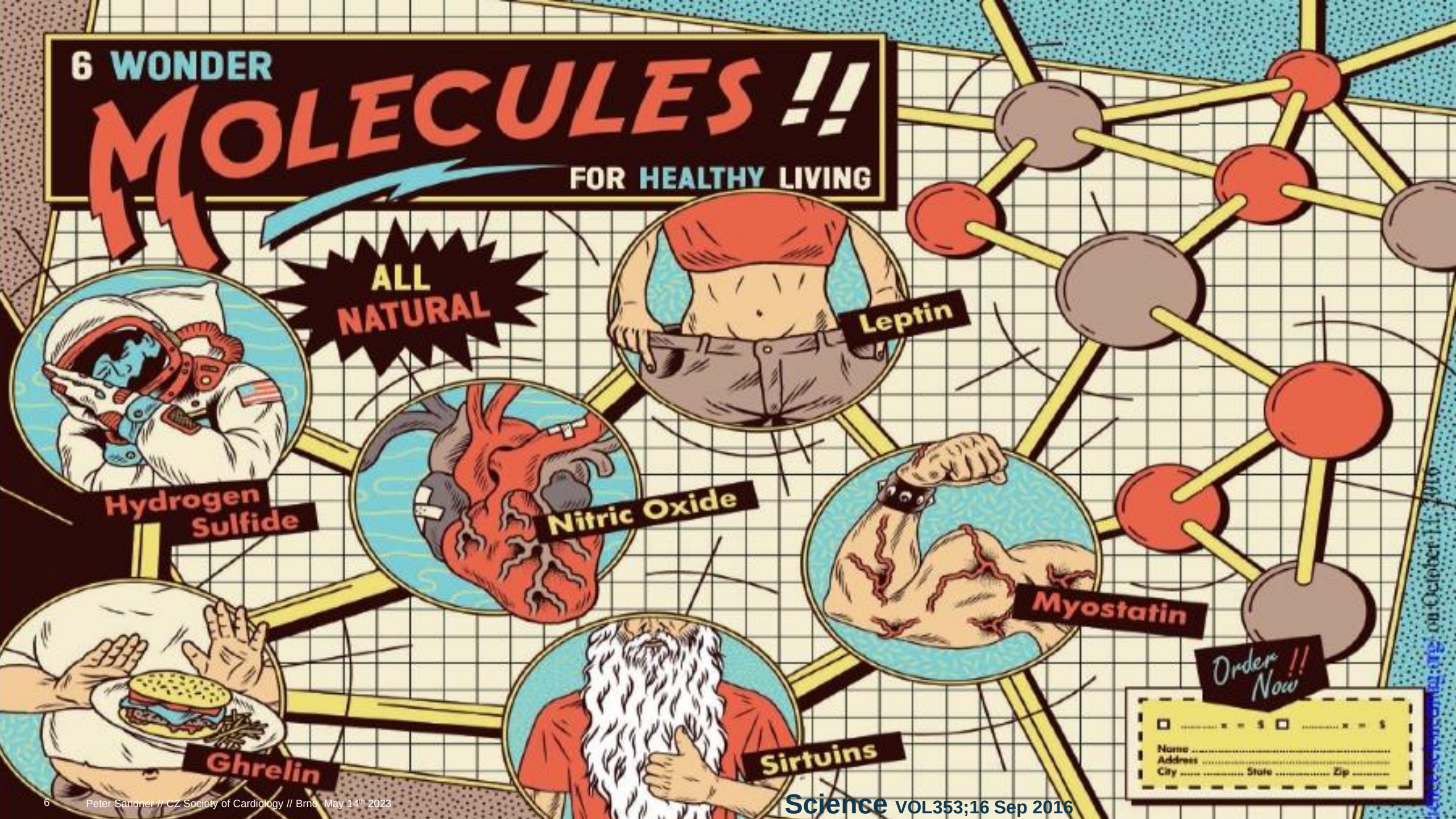
- vasodilation

- endothelial protection
- decrease of vascular stiffness
- antifibrosis
- antihypertrophy
- antiinflammation

vasodilation & tissue protection



Stasch & Hobbs, Handb Exptl Pharmacol 2009; Sandner, Neuser & Bischoff . Handb Exp Pharmacol. 2009;(191):507-31; Follmann et al., Angew. Chem. Int. Ed. 2013;52:9442-9462; Sandner, Biol Chem. 2018 Jun 27;399(7):679-690; Sandner et al.; Handb Exp Pharmacol. 2021;264:355-394; Sandner et al. Br J Pharmacol. 2021 Oct 2. Epub ahead of print



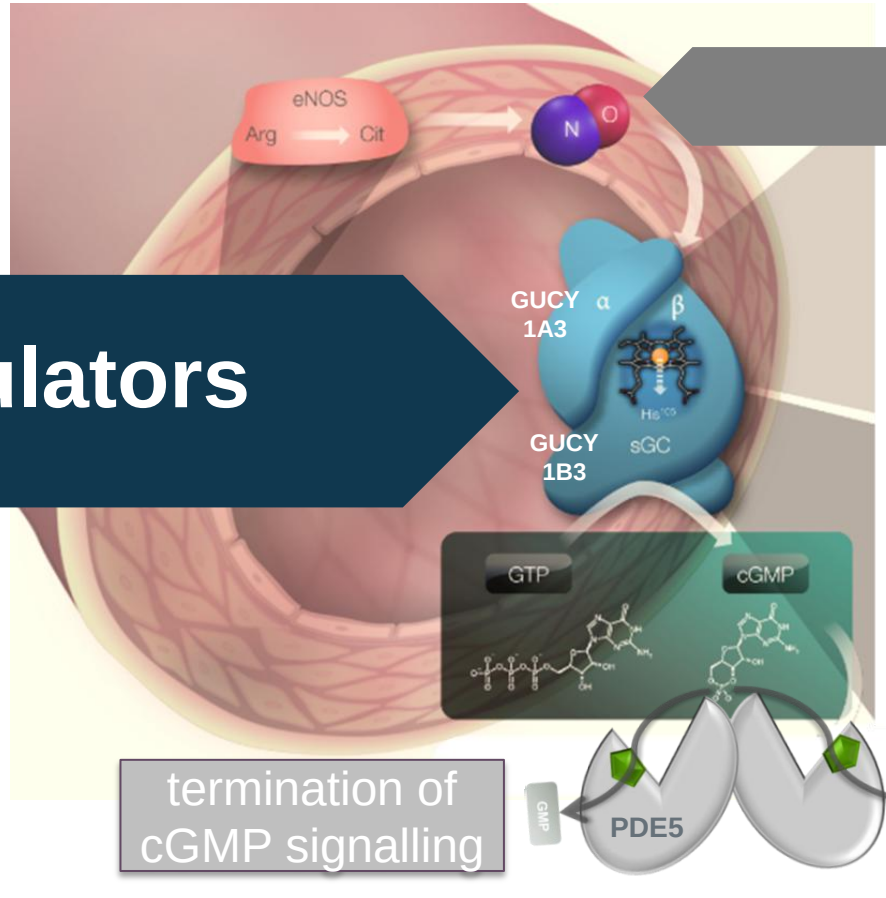
Science VOL353;16 Sep 2016

Pharmacological targets in the NO/cGMP pathway

limitations and new concepts

NO-donors (Nitrates)

sGC stimulators



Restore dysfunctional sGC cGMP signalling

vasodillation, and lung, heart, kidney protection

termination of cGMP signalling

PDE5 Inhibitors

Stasch & Hobbs, Handb Exptl Pharmacol 2009; Sandner, Neuser & Bischoff . Handb Exp Pharmacol. 2009;(191):507-31; Follmann et al., Angew. Chem. Int. Ed. 2013;52:9442-9462; Sandner, Biol Chem. 2018 Jun 27;399(7):679-690; Sandner et al.; Handb Exp Pharmacol. 2021;264:355-394

The discovery of sGC stimulators

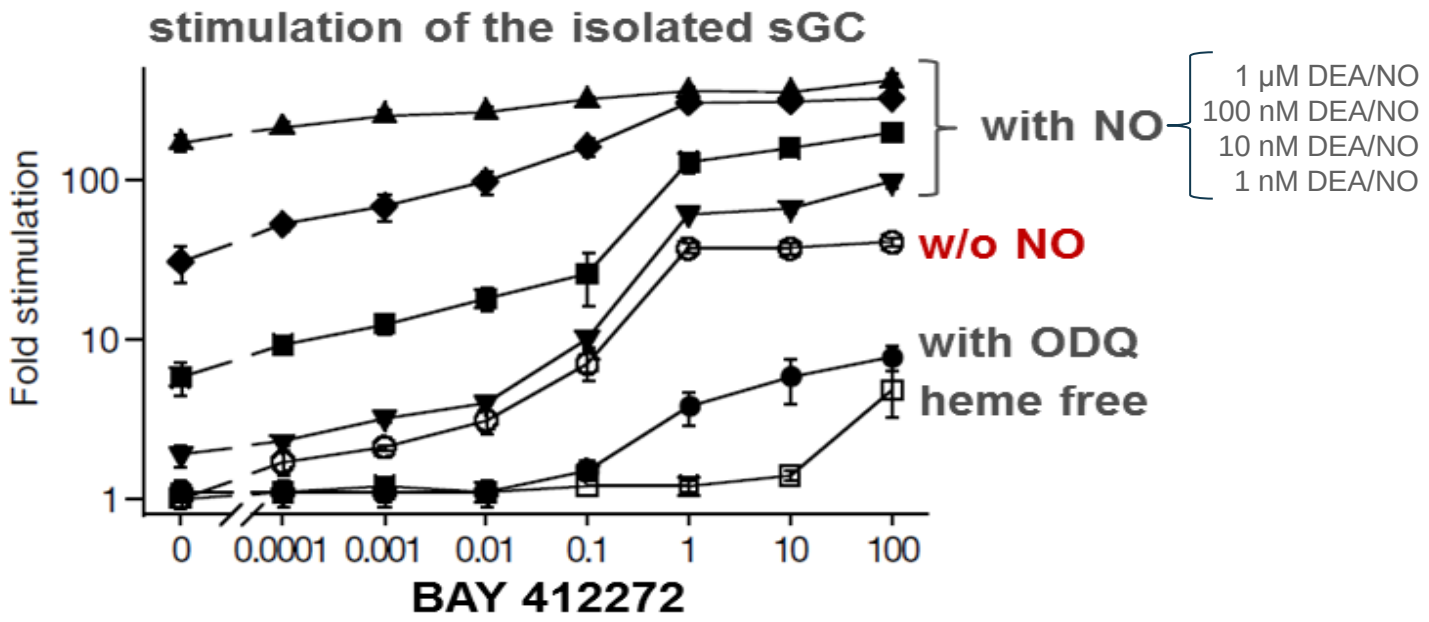
BAY 41-2272 and BAY 41-8543

NO-independent regulatory site on soluble guanylate cyclase

Johannes-Peter Stasch*, Eva Maria Becker*, Cristina Alonso-Alija*, Heiner Apeler*, Klaus Dembowsky*, Achim Feurer*, Rupert Gerzer‡, Torsten Minuth*, Elisabeth Perzborn*, Ulrich Pleiß*, Henning Schröder†, Werner Schroeder*, Elke Stahl*, Wolfram Steinke*, Alexander Straub* & Matthias Schramm*

** Pharma Research Center, Bayer AG, Aprather Wey 18a, D-42096 Wuppertal, Germany*
† Martin Luther University, School of Pharmacy, Wolfgang-Langenbeck-Strasse 4, D-06099 Halle, Germany
‡ DLR, Institute of Aerospace Medicine, Linder Höhe, D-51147 Köln, Germany

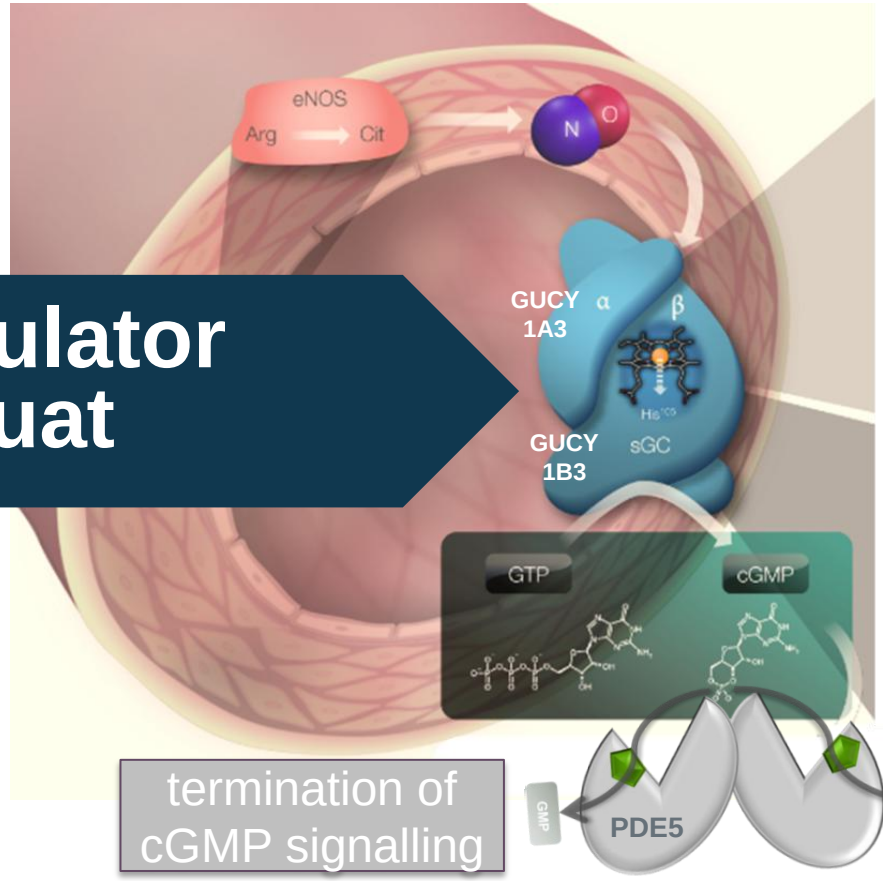
NATURE | VOL 410 | 8 MARCH 2001 |



Pharmacological targets in the NO/cGMP pathway

mode of action of sGC stimulators

sGC stimulator Riociguat



bind allosterically to the heme-NO-binding (H-NOX) domain

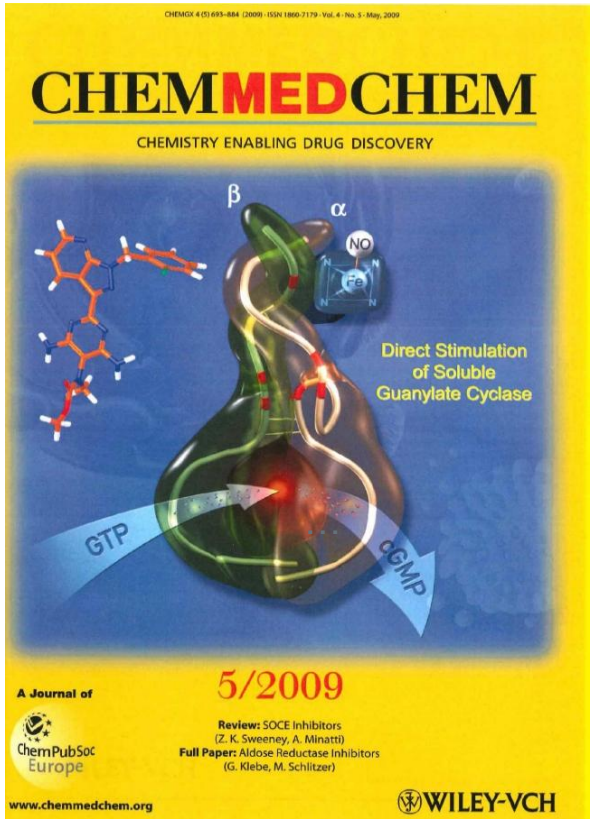
stimulate sGC

- **independent from endogenous NO**
- **synergistically with endogenous NO**

Restore dysfunctional sGC cGMP signalling

Stasch & Hobbs, Handb Exptl Pharmacol 2009; Sandner, Neuser & Bischoff . Handb Exp Pharmacol. 2009;(191):507-31; Follmann et al., Angew. Chem. Int. Ed. 2013;52:9442-9462; Sandner, Biol Chem. 2018 Jun 27;399(7):679-690; Sandner et al.; Handb Exp Pharmacol. 2021;264:355-394

The sGC stimulator Riociguat



Discovery of Riociguat (BAY 63-2521): A Potent, Oral Stimulator of Soluble Guanylate Cyclase for the Treatment of Pulmonary Hypertension

Joachim Mittendorf,[a] Stefan Weigand,[a, d] Cristina Alonso-Alija,[a] Erwin Bischoff,[b] Achim Feurer,[a, e] Michael Gerisch,[c] Armin Kern,[c] Andreas Knorr,[b] Dieter Lang,[c] Klaus Muenter,[b] Martin Radtke,[c] Hartmut Schirok,[a] Karl-Heinz Schlemmer,[c] Elke Stahl,[c] Alexander Straub,[a] Frank Wunder,[b] and Johannes-Peter Stasch[b]

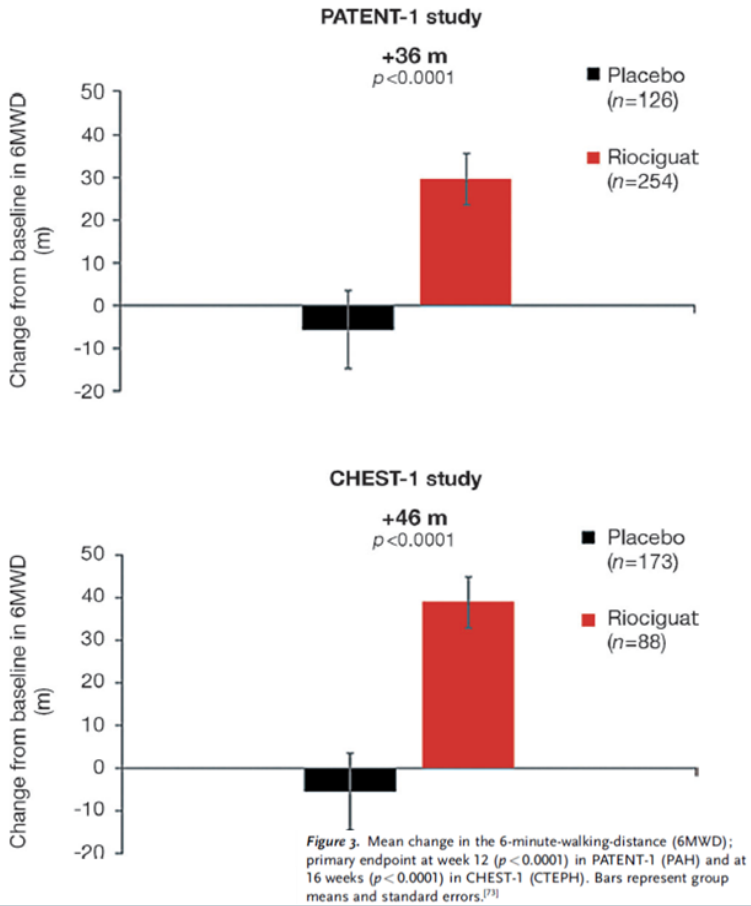


Figure 3. Mean change in the 6-minute-walking-distance (6MWD); primary endpoint at week 12 ($p < 0.0001$) in PATENT-1 (PAH) and at 16 weeks ($p < 0.0001$) in CHEST-1 (CTEPH). Bars represent group means and standard errors.[73]

The NEW ENGLAND JOURNAL of MEDICINE
N Engl J Med 2013;369:330-40.

ORIGINAL ARTICLE

Riociguat for the Treatment of Pulmonary Arterial Hypertension

Hossein-Ardeschir Ghofrani, M.D., Nazzareno Galiè, M.D., Friedrich Grimminger, M.D., Ekkehard Grünig, M.D., Marc Humbert, M.D., Zhi-Cheng Jing, M.D., Anne M. Keogh, M.D., David Langleben, M.D., Michael Ochan Kilama, M.D., Arno Fritsch, Ph.D., Dieter Neuser, M.D., and Lewis J. Rubin, M.D., for the PATENT-1 Study Group*

The NEW ENGLAND JOURNAL of MEDICINE
N Engl J Med 2013;369:319-29.

ORIGINAL ARTICLE

Riociguat for the Treatment of Chronic Thromboembolic Pulmonary Hypertension

Hossein-Ardeschir Ghofrani, M.D., Andrea M. D'Armini, M.D., Friedrich Grimminger, M.D., Marius M. Hoeper, M.D., Pavel Jansa, M.D., Nick H. Kim, M.D., Eckhard Mayer, M.D., Gerald Simonneau, M.D., Martin R. Wilkins, M.D., Arno Fritsch, Ph.D., Dieter Neuser, M.D., Gerrit Weimann, M.D., and Chen Wang, M.D., for the CHEST-1 Study Group*

Clinical Efficacy of riociguat in patients with PAH and CTEPH

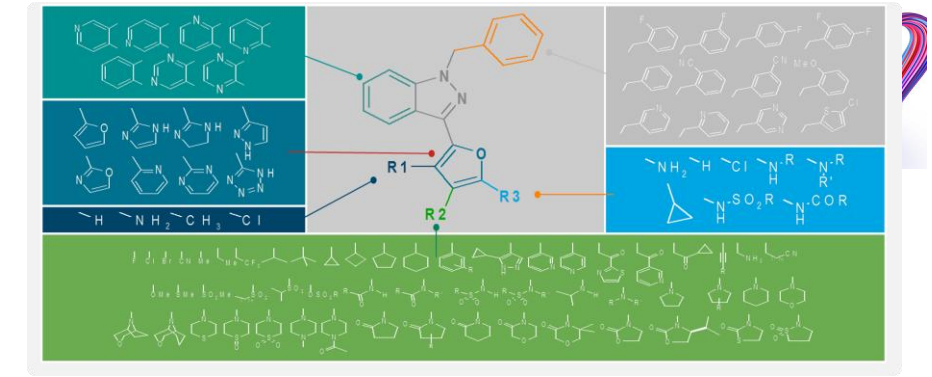
Approval of riociguat (Adempas™) as first in class sGC stimulator for the treatment for both forms of PH in 2013

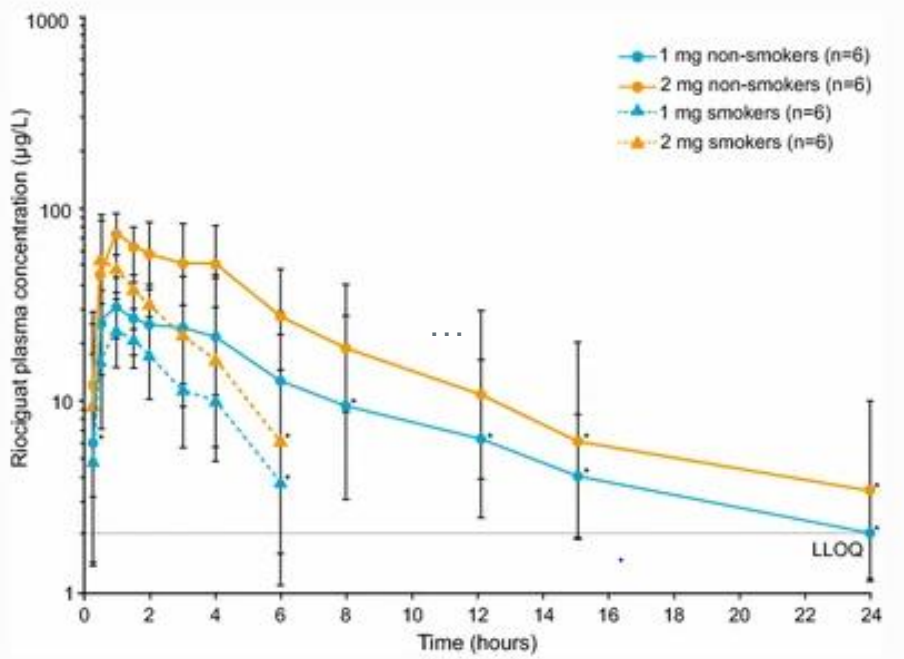
Mittendorf et al.; ChemMedChem. 2009 May;4(5):853-865
Stasch & Evgenov, Handb Exp Pharmacol. 2013;218:279-313
Ghofrani et al.; Chest. 2017 Feb;151(2):468-480
Sandner et al., Nitric Oxide. 2018 Jul 1;77:88-95

From Riociguat to Vericiguat

Years of intense profiling

T1/2 requires TID dosing in PAH
- ✓ once daily
- ✓ long acting
- ✓ no variability



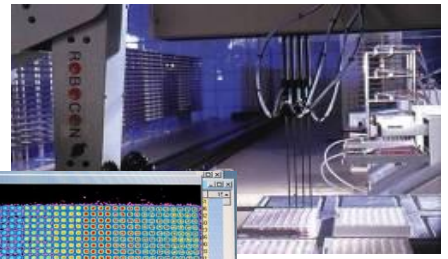


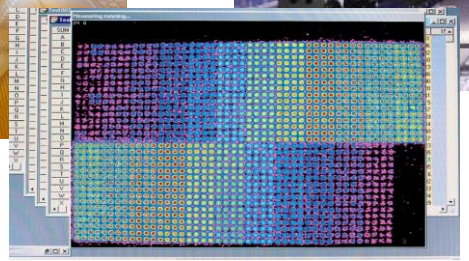
Clin Pharmacokinet (2016) 55:615–624
DOI 10.1007/s40262-015-0337-4

ORIGINAL RESEARCH ARTICLE

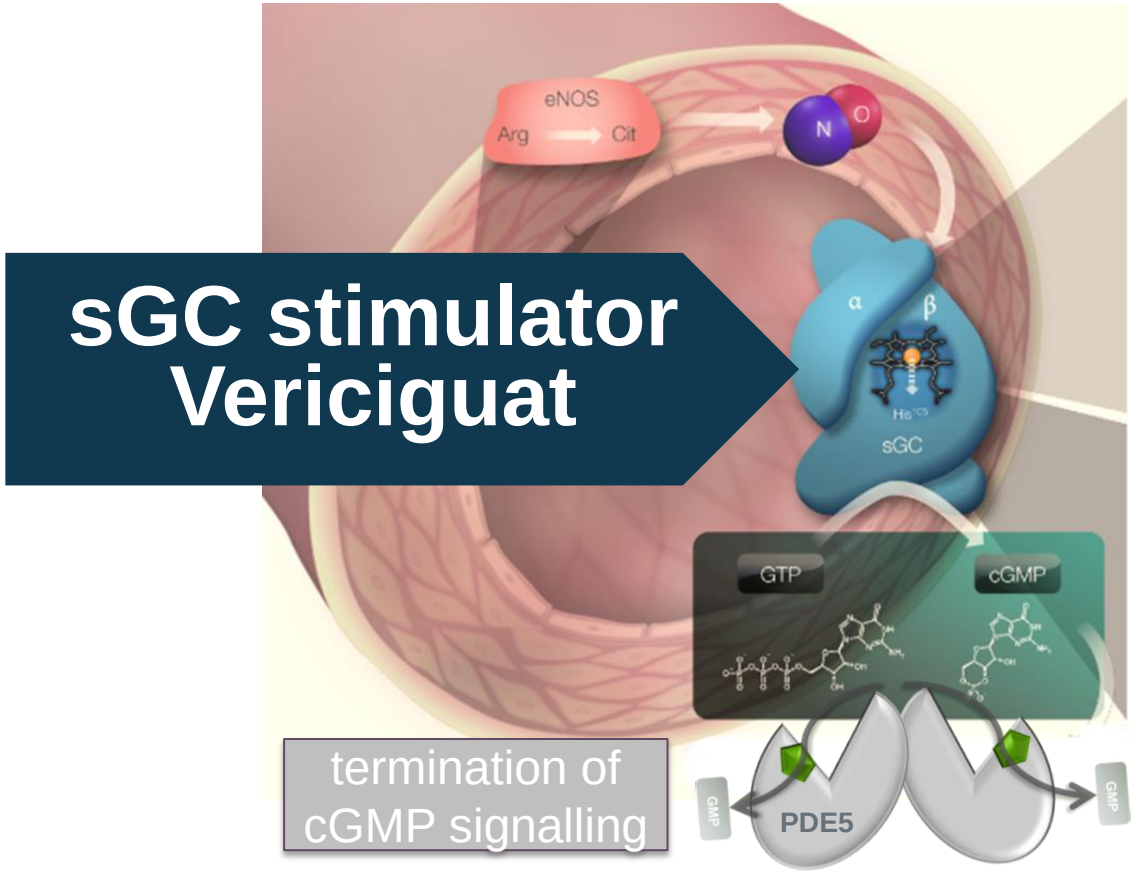
Pharmacokinetics of the Soluble Guanylate Cyclase Stimulator Riociguat in Healthy Young Chinese Male Non-Smokers and Smokers: Results of a Randomized, Double-Blind, Placebo-Controlled Study

Xia Zhao[1] · Zining Wang[1] · Yukun Wang[2] · Hong Zhang[2] · Hartmut Blode[2] · Kenichi Yoshikawa[3] · Corina Becker[4] · Sigrun Unger[5] · Reiner Frey[4] · Yimin Cui[1]

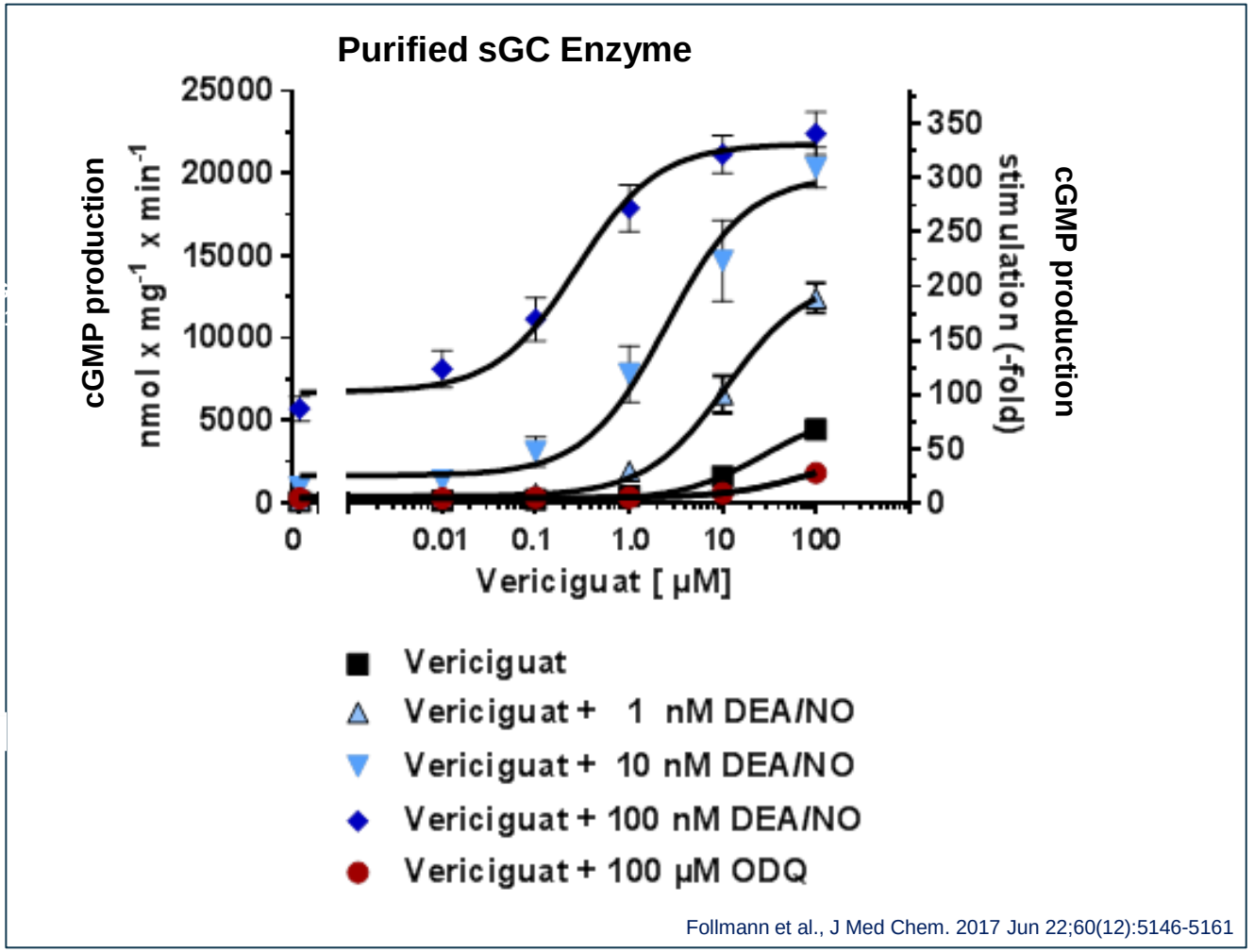




Vericiguat
in vitro pharmacology



Stasch & Hobbs, Handb Exptl Pharmacol 2009; Sandner, Neuser & Bischoff . Handb Exp Pharmacol. 2009;(191):507-31; Follmann et al., Angew. Chem. Int. Ed. 2013;52:9442-9462; Sandner, Biol Chem. 2018 Jun 27;399(7):679-690; Sandner et al.; Handb Exp Pharmacol. 2021;264:355-394



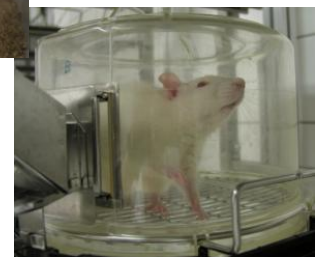
Follmann et al., J Med Chem. 2017 Jun 22;60(12):5146-5161

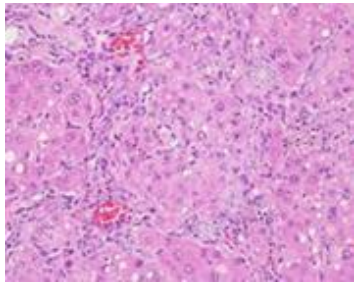
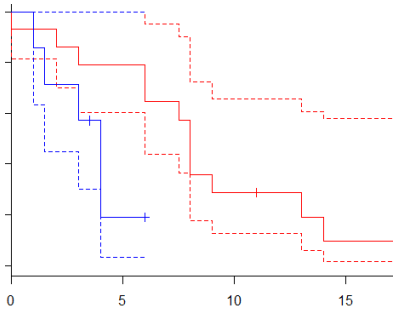
The sGC stimulator vericiguat
Preclinical studies in CV-diseases and Heart Failure

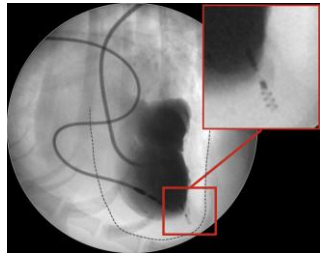
Vericiguat

- stimulated cGMP production of purified sGC
- stimulated cGMP production in biochemical luminometric assay, cGMP reporter cell line and vascular endothelial cells
- relaxed isolated blood vessels
- relaxed nitrate-tolerant blood vessels
- reduced coronary perfusion pressure in rat Langendorff heart
- increased survival of hypertensive rats
- reduced mortality with moderate/no blood pressure lowering in hypertensive rats with endothelial dysfunction
- protected from cardiac and renal damage in rats
- reduced afterload in tachypaced dogs
- reduced augmentation index in hypertensive dogs
- had a favorable PK profile





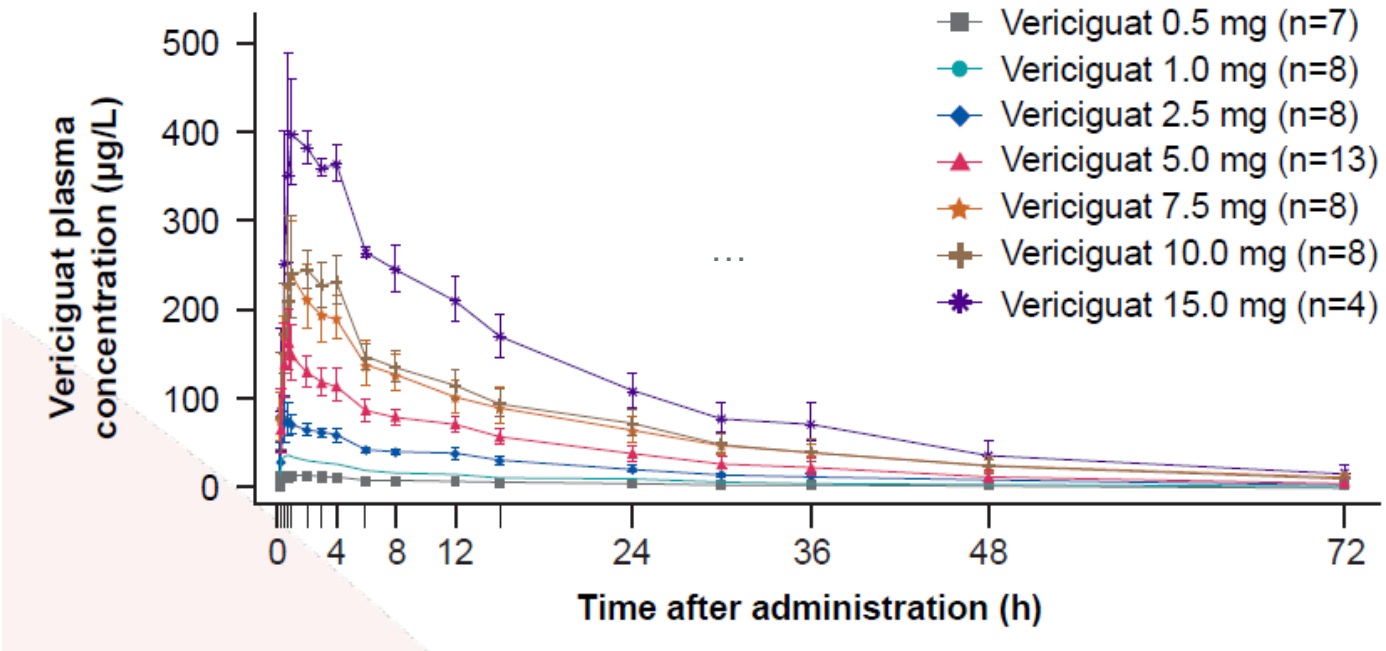



Broad preclinical evidence that vericiguat has treatment potential in chronic heart failure

Follmann et al., J Med Chem. 2017 Jun 22;60(12):5146-5161
Breitenstein et al., Handb Exp Pharmacol. 2017;243:225-247
Mathar et al. Circulation. 2018;138 Suppl-1:A15553
Mondritzki et al. JAAC 03/2020; 75(11):795
Sandner et al.; Handb Exp Pharmacol 2021;264:355-394.
Boden et al. Circ Heart Fail. 2022;15:e008735

Vericiguat
Phase 1 profiling

Figure 1. Mean vericiguat plasma concentrations following SD administration of vericiguat 0.5–15 mg (solution form)



European Journal of Clinical Pharmacology (2021) 77:527–537
https://doi.org/10.1007/s00228-020-03023-7

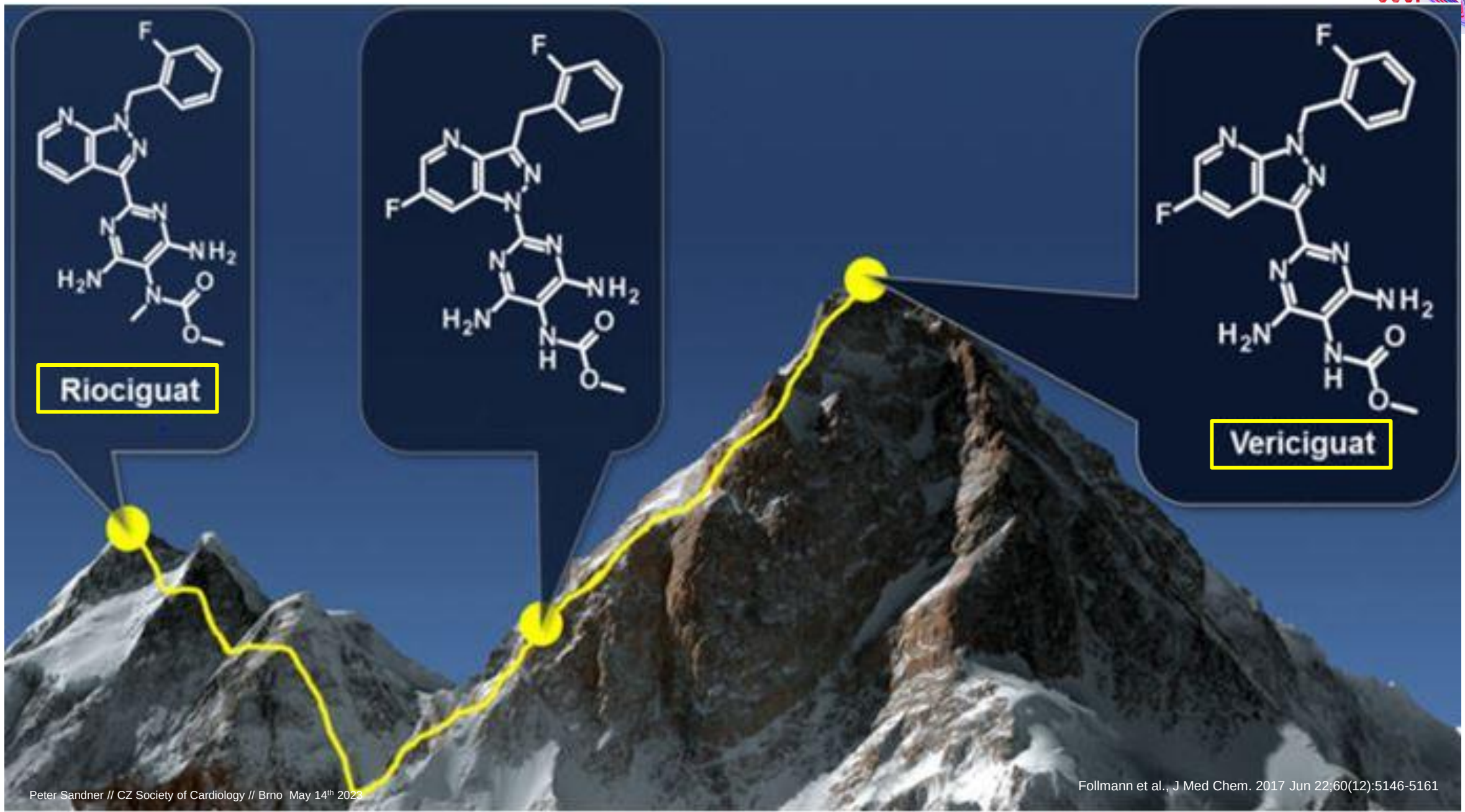
CLINICAL TRIAL

Check for updates

Safety, pharmacodynamic, and pharmacokinetic characterization of vericiguat: results from six phase I studies in healthy subjects

Michael Boettcher[1] · Dirk Thomas[2] · Wolfgang Mueck[3] · Stephanie Loewen[4] · Erich Arens[1,5] · Kenichi Yoshikawa[6] · Corina Becker[1,3]

From Riociguat to Vericiguat - *Years of intense profiling*



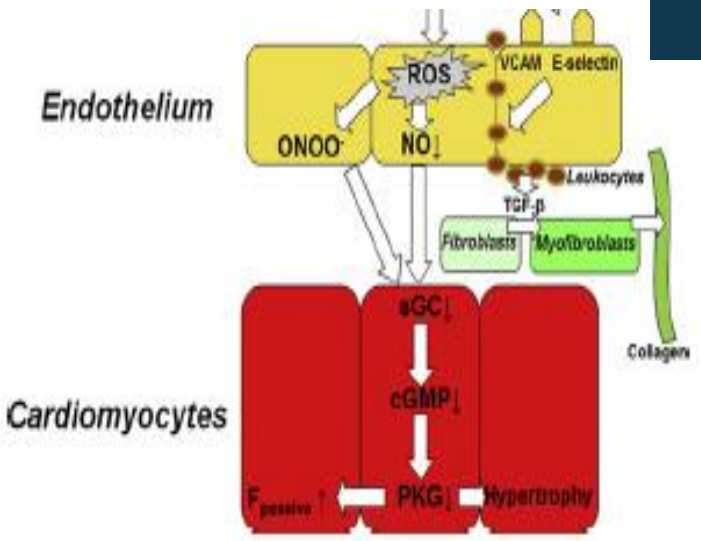
Follmann et al., J Med Chem. 2017 Jun 22;60(12):5146-5161

Relevance of NO/sGC/cGMP signaling in Heart Failure

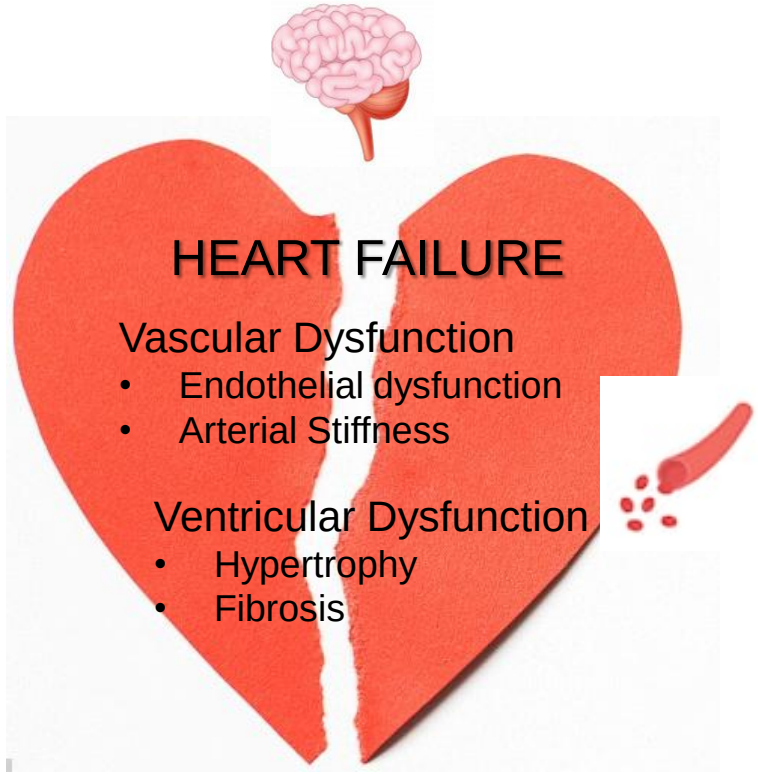
sGC stimulators effectively restore NO/cGMP deficiency

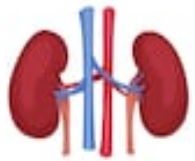
Gheorghiade M et al. 2013; Heart Fail Rev. 18:123-34
Greene S et al. 2013; J Am Heart Assoc. Dec 11;2(6):e000536

Ischemic heart disease, Myocardial Infarction
Cardiomyopathies, Hypertension
Overweight, Obesity
Atherosclerosis, Diabetes, …



NO inactivation & Low/No sGC activity
Low/No cGMP production





The sGC stimulator Vericiguat in Heart Failure

Phase II clinical programs with vericiguat in HFrEF and HFpEF

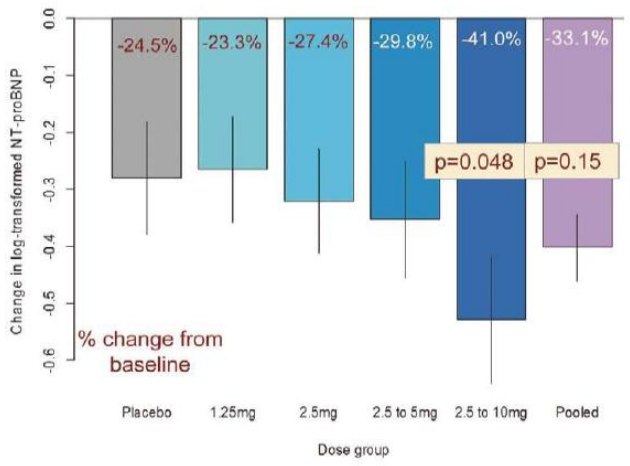
JAMA

Research

Original Investigation

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

Mihai Gheorghiade, MD; Stephen J. Greene, MD; Javed Butler, MD, MPH, MBA; Gerasimos Filippatos, MD; Carolyn S. P. Lam, MBBS; Aldo P. Maggioni, MD; Piotr Ponikowski, MD; Sanjiv J. Shah, MD; Scott D. Solomon, MD; Elisabeth Kraigher-Krainer, MD; Eliana T. Samano, MD; Katharina Müller, DiplStat; Lothar Roessig, MD; Burkert Pieske, MD; for the SOCRATES-REDUCED Investigators and Coordinators



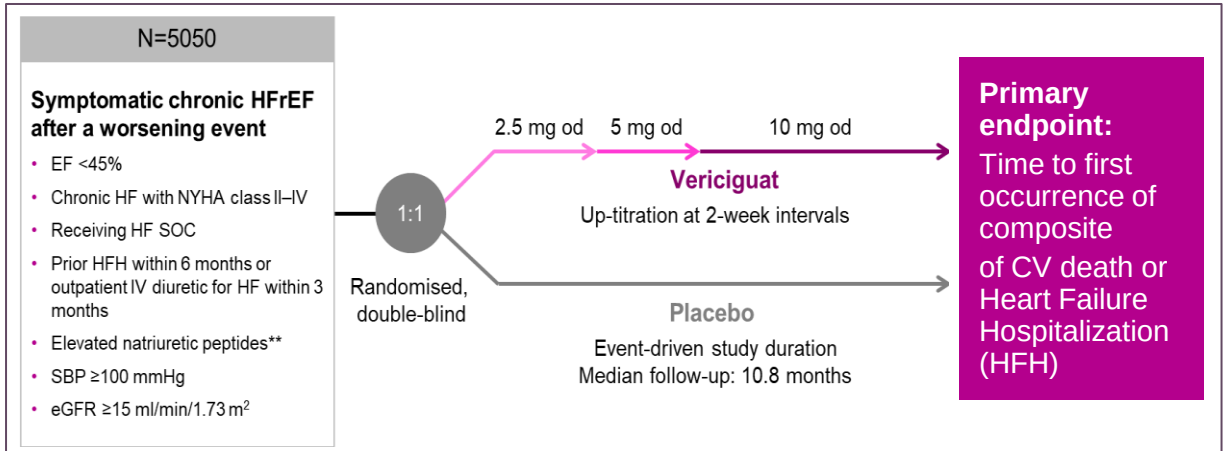
- SOCRATES Phase IIb trial in patients with HFrEF (N = 456)
- Primary endpoint (pooled analysis) not met
- 10 mg demonstrated greater reductions in log-transformed NT-proBNP than placebo at 12 weeks
- Patients randomized to 10 mg dose daily achieved:
  - Greater improvement in left ventricular ejection fraction
  - Numerically fewer cardiovascular deaths or HF hospitalizations
- Adverse events were not increased in the highest target dose arm of vericiguat compared to placebo

Gheorghiade et al. 2015; JAMA Dec 1;314(21):2251-2262

JACC: HEART FAILURE VOL. 6, NO. 2, 2018

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of the Efficacy and Safety of the Oral Soluble Guanylate Cyclase Stimulator
The VICTORIA Trial

Paul W. Armstrong, MD,[a] Lothar Roessig, MD,[b] Mahesh J. Patel, MD,[c] Kevin J. Anstrom, PhD,[d] Javed Butler, MD, MPH, MBA,[e] Adriaan A. Voors, MD, PhD,[f] Carolyn S.P. Lam, MBBS, PhD,[g,h] Piotr Ponikowski, MD,[i,j] Tracy Temple, BScN,[a] Burkert Pieske, MD,[k] Justin Ezekowitz, MBBCh, MSc,[a] Adrian F. Hernandez, MD,[d] Joerg Koglin, MD, PhD,[c] Christopher M. O'Connor, MD[d,l,m]



***VICTORIA: **V**er**IC**igua**T** gl**O**bal study in subjects with heart failure with **R**educed eject**I**on fr**a**ction

The sGC stimulator Vericiguat
clinical profiling: the pivotal phase 3 VICTORIA study*

Armstrong et al.; 2020 N Engl J Med. May 14;382(20):1883-1893

Study Chair: *Paul W. Armstrong (Canada)*

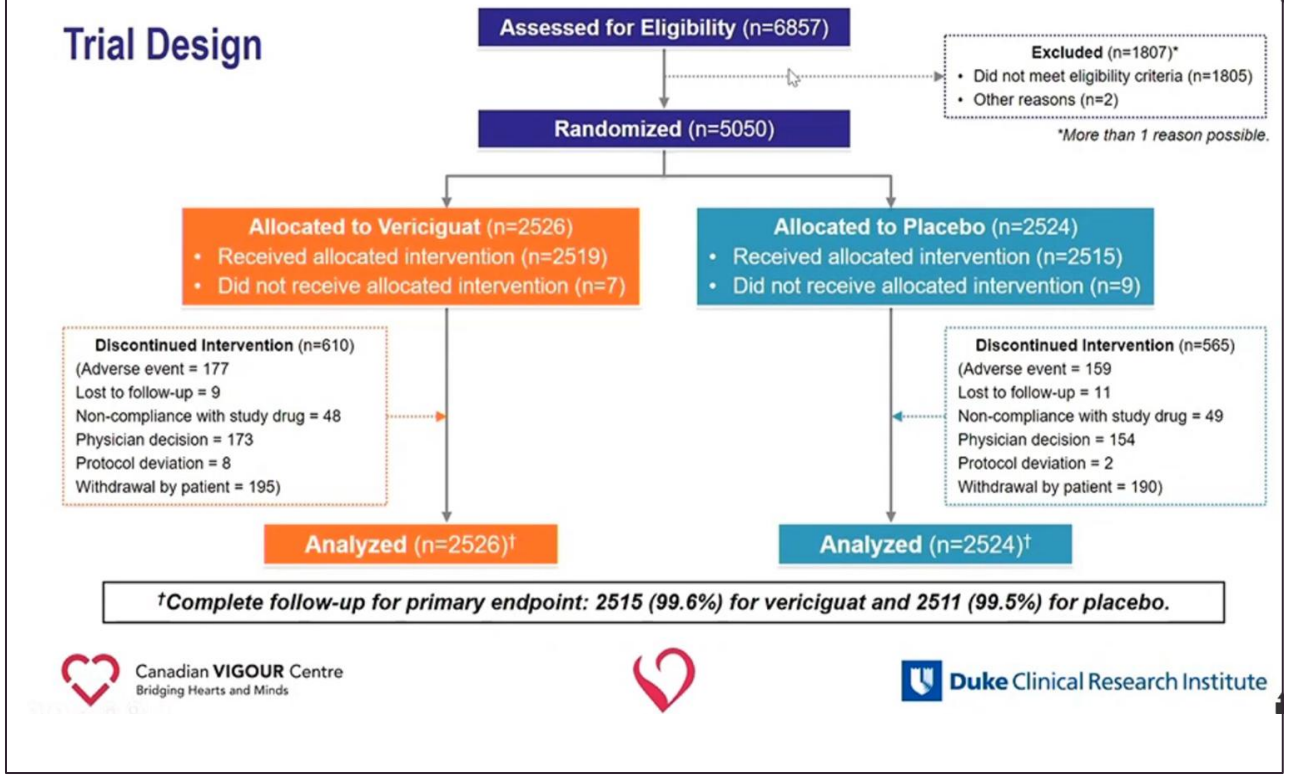
Principal Investigators: *Christopher M. O'Connor (USA) , Burkert Pieske (Germany)*

Executive Committee: *Kevin J. Anstrom (statistician), Javed Butler (USA), Justin A. Ezekowitz (Canada), Adrian F. Hernandez (USA), Joerg Koglin (Merck & Co), Carolyn Lam (Singapore), Piotr Pinokowski (Poland), Lothar Roessig (Bayer Healthcare), Adriaan Voors (Netherlands)*

Scientific Leadership: Canadian VIGOUR Centre – Bridging Hearts and Minds; Duke Clinical Research Institute – From Thought Leadership to Clinical Practice

Corporate Sponsor: Bayer; MERCK

clinicaltrials.gov identifier: NCT02861534



VICTORIA National Leader for Czech Republic: Vojtěch Melenovský
VICTORIA Primary Site Investigators / Primary Study Coordinators for Czech Republic: Vojtech Melenovsky / Miroslava Krausova; Jan Malik; Martin Hajsl / Katerina Mala; Jan F Vojacek / Jana Fridrichova; Filip Malek / Dana Rihova; Vladimir Cech / Lenka Masarikova; Vilma Machova; Jindrich Spinar; Jan Macha; Libor Nechvatal

*VICTORIA: **V**er**IC**igua**T** gl**O**bal study in subjects with heart failure with **R**educed eject**I**on fr**a**ction

5050 patients in 42 countries across the globe at over 600 study sites and with 3 years of total study duration

The sGC stimulator Vericiguat

clinical profiling: the pivotal phase 3 VICTORIA study

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction

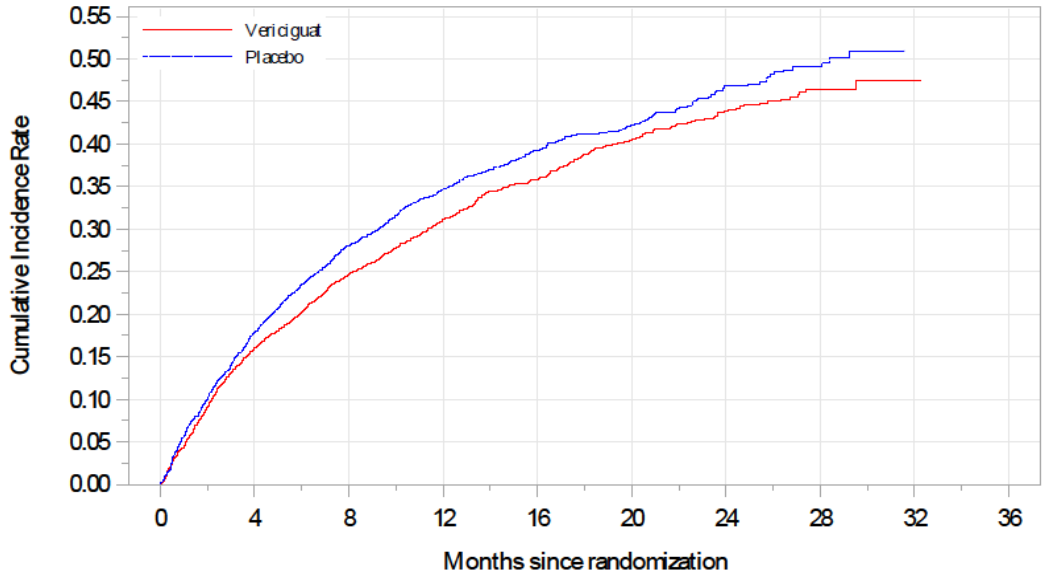
Paul W. Armstrong, M.D., Burkert Pieske, M.D., Kevin J. Anstrom, Ph.D., Justin Ezekowitz, M.B., B.Ch., Adrian F. Hernandez, M.D., M.H.S., Javed Butler, M.D., M.P.H., M.B.A., Carolyn S.P. Lam, M.B., B.S., Ph.D., Piotr Ponikowski, M.D., Adriaan A. Voors, M.D., Ph.D., Gang Jia, Ph.D., Steven E. McNulty, M.S., Mahesh J. Patel, M.D., Lothar Roessig, M.D., Joerg Koglin, M.D., Ph.D., and Christopher M. O'Connor, M.D., for the VICTORIA Study Group*

Summary prim. endpoint and components

	Vericiguat (N=2526)			Placebo (N=2524)			Treatment Comparison		
	n	(%)	Ann-ual %	n	(%)	Ann ual %	HR (95% CI)§	p-Value	ARR anual
Primary Composite Endpoint[1]	897	(35.5)	33.6	972	(38.5)	37.8	**0.90** (0.82, 0.98)	**0.019**	**4.2%**
Heart Failure Hospitalization	691	(27.4)		747	(29.6)				
Cardiovascular Death	206	(8.2)		225	(8.9)				
Cardiovascular Death[1]	414	(16.4)	12.9	441	(17.5)	13.9	**0.93** (0.81, 1.06)	**0.269**	**(1%)**
Heart Failure Hospitalization[1]	691	(27.4)	25.9	747	(29.6)	29.1	**0.90** (0.81, 1.00)	**0.048**	**3.2%**

Armstrong et al.; 2020 N Engl J Med. May 14;382(20):1883-1893

Kaplan-Meier plot for primary endpoint



Primary endpoint (time to composite of CV death or HF hospitalization) as secondary endpoint (time to HF hospitalization) demonstrated a significant benefit of Vericiguat in HFrEF patients

Acknowledgements

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Eva Becker-Pelster
Markus Follmann
Michael Hahn

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Thomas Mondritzki & team
Karoline Droebner, Qin Mao, Emanuel Haasbach, Shalini M. Krishnan

Nicola Wilck, Nadine Haase, Ralf Dechend, Dominik N. Müller & teams
Luděk Červenka
Vojtěch Melenovský
Olga Gawrys & teams

Institute for Clinical & Experimental Medicine

Robert & Susanne Feil & teams

Andreas Patzak & team
Frank Schweda, Jens Schlossmann & teams

Universität Regensburg

All Members
GRK 2381

Merck Sharp & Dohme Corp., NJ USA

Cardiology Research, Medicinal Chemistry, Early Development, Chemical Development, Pharmaceutical Development, Early Clinical Development, Project Management, Process Development, Analytics, Clinical Pharmacology, Clinical Development, Drug Safety, Strategic Marketing, Patents, Regulatory Affairs…

Thank you for your kind attention!

Zkrácené informace o léčivém přípravku

▼Tento léčivý přípravek podléhá dalšímu sledování. To umožní rychlé získání nových informací o bezpečnosti. Žádáme zdravotnické pracovníky, aby hlásili jakákoli podezření na nežádoucí účinky. Podrobnosti o hlášení nežádoucích účinků viz bod 4.8 SPC.

Název přípravku: Verquvo 2,5 mg potahované tablety, Verquvo 5 mg potahované tablety, Verquvo 10 mg potahované tablety.

Složení: Jedna potahovaná tableta obsahuje vericiguatum 2,5 mg, 5 mg nebo 10 mg.

Indikace: Léčba symptomatického chronického srdečního selhání u dospělých pacientů se sníženou ejekční frakcí, kteří jsou ve stabilizovaném stavu po nedávné epizodě dekompenzace vyžadující i.v. léčbu.

Dávkování a způsob podání: Vericigvát se podává současně s jinými přípravky k léčbě srdečního selhání. Doporučená zahajovací dávka je 2,5 mg vericigvátu jednou denně. Dávka by měla být zdvojnásobena přibližně každé 2 týdny do dosažení cílové udržovací dávky 10 mg jednou denně, podle tolerance pacienta. Přípravek Verquvo se má užívat spolu s jídlem. Pokud je vynechána dávka, má být užita, jakmile si pacient vzpomene, a to ve stejný den, kdy došlo k vynechání dávky. Pacienti nesmí užít dvě dávky vericigvátu v týž den.

Kontraindikace: Hypersenzitivita na léčivou látku nebo na kteroukoli pomocnou látku. Současné užívání spolu s jinými stimulátory solubilní guanylátcyklázy (sGC), jako je například riocigvát.

Zvláštní upozornění a opatření: Vericigvát může způsobovat symptomatickou hypotenzi. Pacienti s STK nižším než 100 mmHg nebo symptomatickou hypotenzí při zahájení léčby nebyli studováni. O možnosti rozvoje symptomatické hypotenze je třeba uvažovat u pacientů s hypovolémií, závažnou obstrukcí výtokového traktu levé komory, klidovou hypotenzí, dysfunkcí autonomního nervového systému, hypotenzí v anamnéze nebo souběžnou léčbou antihypertenzivy či organickými nitráty. Pokud se u pacientů objeví problémy s tolerancí (symptomatická hypotenze nebo STK nižší než 90 mmHg), doporučuje se přechodná titrace dávek vericigvátu směrem dolů nebo vysazení vericigvátu. Souběžné užívání vericigvátu a inhibitorů PDE5, jako je sildenafil, nebylo u pacientů se srdečním selháním studováno, a proto se nedoporučuje vzhledem k možnému zvýšenému riziku symptomatické hypotenze. Nebyly provedeny žádné studie u pacientů s eGFR <15 ml/min/1,73 m2 při zahájení léčby nebo na dialýze nebo u pacientů s těžkou poruchou funkce jater, a proto se léčba vericigvátem u těchto pacientů nedoporučuje. Tento léčivý přípravek obsahuje laktózu.

Fertilita, těhotenství a kojení: Údaje o podávání vericigvátu těhotným ženám nebo o přítomnosti vericigvátu v lidském mateřském mléku, účinku na kojené děti nebo účincích na tvorbu mléka nejsou k dispozici. Studie na zvířatech prokázaly reprodukční toxicitu v přítomnosti mateřské toxicity. Jako preventivní opatření se podávání vericigvátu v těhotenství a u žen v reprodukčním věku, které nepoužívají antikoncepci, nedoporučuje. Na základě posouzení prospěšnosti kojení pro dítě a prospěšnosti léčby pro matku je nutno rozhodnout, zda přerušit kojení nebo ukončit/přerušit podávání vericigvátu.

Interakce: Vericigvát je metabolizován prostřednictvím UGT1A9 a UGT1A1. Inhibitory těchto UGT mohou vést ke zvýšené expozici vericigvátu. Souběžná léčba léčivými přípravky, které zvyšují žaludeční pH, neměla vliv na expozici vericigvátu, pokud byl vericigvát pacienty se srdečním selháním užíván podle pokynů s jídlem. Současné podávání s léčivými přípravky, které ovlivňují jeden nebo více způsobů eliminace vericigvátu, nemá klinicky významný vliv na farmakokinetiku vericigvátu.

Nežádoucí účinky: Velmi časté: hypotenze. Časté: anemie, závrať, bolesti hlavy, nauzea, dyspepsie, zvracení, gastroezofageální reflux.

Podmínky uchovávání: Žádné zvláštní podmínky.

Držitel rozhodnutí o registraci: Bayer AG, 51368 Leverkusen, Německo.

Registrační čísla: Verquvo 2,5 mg: EU/1/21/1561/001–011.

Verquvo 5 mg: EU/1/21/1561/012–022. Verquvo 10 mg: EU/1/21/1561/023–033.

Datum poslední revize textu: 16. července 2021.

Výdej léčivého přípravku je vázán na lékařský předpis. Přípravek není hrazen z prostředků veřejného zdravotního pojištění. Aktuální výši a podmínky úhrady naleznete na www.sukl.cz. Před předepsáním léčivého přípravku si pečlivě přečtěte úplnou informaci o přípravku. Souhrn údajů o přípravku i s informacemi, jak hlásit nežádoucí účinky najdete na www.bayer.cz nebo obdržíte na adrese BAYER s.r.o., Siemensova 2717/4, 155 00 Praha 5, Česká republika.

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08/2021