Targeting Cyclic Guanylate Monophosphate in Resistant Hypertension and Heart Failure: Are Sacubitril/Valsartan and Vericiguat Synergistic and Effective in Both Conditions?

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1 Current Therapeutic Scenario of Hypertension Management

The achievement of adequate levels of “blood pressure” (BP) still remains an unmet target in the management of hypertension. Only 40 to 65% of hypertensive patients achieve a BP level lower of 140/90 mmHg even in the most recent reports [1]. Moreover, it has been shown that drug-resistant hypertension accounts for up to 17% of patients uncontrolled on treatment, this represents a relevant clinical challenge in view of the higher risk of hypertension-mediated organ damage (HMOD) including left ventricular hypertrophy (LVH), and heart failure (HF) in this condition [2]. The current definition of resistant hypertension is the failure to achieve the recommended BP targets despite appropriate lifestyle measures and treatment with optimal or best-tolerated doses of three or more drugs which should include a diuretic and typically an angiotensin-converting enzyme inhibitors (ACEi) or an angiotensin receptor blocker (ARB) and a calcium channel blocker (CCB) as recommended by the international guidelines [3, 4]. This suggests that even with the combination therapy with the available and recommended drugs there is room for searching for other therapeutic tools to achieve a better control of high BP.

2 New Therapeutic Avenues: The Appealing Evidence with ARNi

In a recent post-hoc analysis of data from the PARAGON-HF (Prospective Comparison of ARNi With ARB Global Outcomes in Heart Failure With Preserved Ejection Fraction) trial, which compared the efficacy of sacubitril/valsartan (Sac/Val), a type 1 angiotensin receptor/neprilysin inhibitor (ARNi), with the ARB valsartan (320 mg) in patients with HF with preserved ejection fraction (HFpEF) [5], Jackson and colleagues showed that individuals with resistant hypertension had a greater risk of the primary composite of hospitalization for HF and CV death and of the prespecified exploratory composite of hospitalization for HF, myocardial infarction, stroke, and CV death [6]. In this study Sac/Val was associated with a significantly larger reduction of systolic BP (SBP) compared to valsartan in subjects with resistant hypertension (−4.8 mmHg vs −3.8 mmHg, respectively) and increased the proportion of patients who achieved BP goals and were satisfactorily controlled (47.9% vs 34.3%, respectively) [6]. In view of these results, Sac/Val may be considered as an additional reasonable therapeutic strategy in the management of resistant hypertension, potentially delaying or even preventing the development of HMOD and the progression to HF [7].

Apart from the PARAGON-HF trial, other studies evaluating the administration of ARNi in HF patients support the use of this combination treatment to control BP. In the phase II PARAMOUNT (Prospective comparison of ARNi with ARB on Management Of heart failUre with preserved ejection fracTion) trial, the 12-week SBP reduction was significantly greater in the Sac/Val compared with the valsartan group (29.3 vs. 22.9 mmHg, respectively) [8].

Moreover, previous studies had already investigated the potential efficacy of Sac/Val as an antihypertensive agent with very encouraging results. Ruilope and colleagues demonstrated the superiority of Sac/Val compared to valsartan in

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reducing 8-week mean sitting diastolic BP (DBP) and SBP and 24-h mean ambulatory SBP [9]. A study performed in an Asian population also showed a significant effect on BP reduction with Sac/Val [10].

3 ARNi, ANP and Cyclic GMP Signaling: A Potentially Beneficial Mechanism in Hypertension

The marked BP reduction obtained with Sac/Val compared to valsartan may be explained by the neprilysin inhibition-dependent increase of biologically active natriuretic peptides (NPs), mainly the carboxy terminal ANP [11, 12], and their binding with particulate guanylate cyclase (GC)/cyclic guanylate monophosphate (cGMP)-coupled receptors, resulting in vasodilation, diuresis, natriuresis, counterbalancing of the renin–angiotensin–aldosterone system (RAAS), the sympathetic nervous system (SNS), endothelin, and vasopressin [13, 14]. Interestingly, experimental studies demonstrated a significant protective effect of ARNi toward HMOD development [15, 16]. Some evidence is also available in human hypertension [17].

However, there is currently no indication for ARNi in the treatment of hypertension, being HF_{rEF} the only indication for their clinical use.

With regard to the soluble GC (sGC)/cGMP pathway, its impairment and the consequent reduction of nitric oxide (NO) bioavailability has been extensively described as one of the most relevant pathophysiological mechanisms involved in the development and progression of HF [18, 19]. Indeed, the protein kinase G1 α (PKG1 α), the primary direct effector of cGMP, plays an important role in the inhibition of inflammation and leukocyte recruitment, platelet aggregation, smooth muscle proliferation, vasoconstriction, coronary microvascular impairment, fibrosis and hypertrophy through several downstream mechanisms, such as the SR Ca²⁺-ATPase (SERCA)-mediated increased re-uptake of Ca²⁺ into the sarcoplasmic reticulum and the blockade of mitochondrial permeability transition pore [20, 21].

Although the substitution of exogenous NO by nitrates and the inhibition of cGMP degradation by phosphodiesterase inhibitors have shown some potential benefits in the treatment of HF, a long-term effect has not been demonstrated [18]. On the other hand, the stimulation of sGC has attracted increasing interest as a therapeutic strategy. Two possible mechanisms of direct action on sGC have been developed: sGC stimulation and activation. Soluble GC stimulation may occur with a dual mode of action: sensitizing sGC to lower levels of NO by a stabilization of the nitrosylheme complex which results in a long-lasting active configuration of the enzyme; increasing of sGC activity by a NO-independent binding to the enzyme, this mechanism

being possible only in the presence of a reduced (ferrous) prosthetic heme [22]. On the other hand, sGC activators can trigger oxidized sGC in an NO-independent manner when the heme moiety is oxidized or missing [23].

4 Soluble Guanylate Cyclase Stimulators: Another Area of Investigation in the Therapy of Heart Failure and Hypertension

In experimental models of HF, sGC stimulators normalized endothelial function, improved sensitivity to NO, reduced systemic BP, pulmonary arterial pressure and pulmonary capillary wedge pressure, producing an increase in cardiac output [24].

On the basis of the beneficial effects achieved with the sGC stimulator riociguat in patients with HF with reduced ejection fraction (HF_{rEF}) and pulmonary hypertension [25], vericiguat, another stimulator with a once daily posology has been developed and tested [26].

The VICTORIA (the Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction) study, a phase 3, randomized, double-blind, placebo-controlled trial, has investigated the effects of vericiguat on top of standard therapy (target dose 10 mg) in a population of 5050 patients with worsening HF, LVEF < 45% and NYHA (New York Heart Association) class II–IV, who experienced hospitalization for HF within 6 months before randomization or needed intravenous diuretic therapy, without hospitalization, within the previous 3 months [27]. In the overall population, compared to placebo, vericiguat was able to significantly reduce the primary composite outcome of death from CV causes or first hospitalization for HF (hazard ratio [HR], 0.90; 95% confidence interval [CI] 0.82 to 0.98) and the secondary end-points of total hospitalizations for HF (HR 0.91; 95% CI 0.84–0.99) and death from any cause or first hospitalization for HF (HR 0.90; 95% CI 0.83–0.98) [19]. During the first 16 weeks of treatment, SBP was lowered by about 4 mmHg in the vericiguat group [27].

5 Combined Use of ARNi and sGC Stimulators: Available Evidence and Perspectives

An issue of particular interest is represented by the lack of benefits obtained with vericiguat in the subgroup of patients who received Sac/Val, that accounted for the 15% of the study-population [27]. This finding may indeed appear somewhat controversial, due to the available and increasingly robust evidence of the benefits of a Sac/

Fig. 1 Biological mechanism of the interaction between Sacubitril/valsartan and vericiguat underlying BP control and cardioprotection. ANP atrial natriuretic peptide, cGMP cyclic guanosine monophosphate, CNG gated-ion channel, ERK extracellular-signal-regulated kinase, HMOD hypertension mediated organ damage, JAK Janus kinase, JNK c-JUN N-terminal kinase, MAPK p38 mitogen-activated protein kinase, MEK mitogen-activated protein kinase, NEP neprilysin, NO nitric oxide, NPRA type A natriuretic peptide receptor, NP natriuretic peptide, p70S6K ribosomal protein S6 kinase beta-1, PIK3 phosphatidylinositol 3-kinase, PDE phosphodiesterase, pGC particulate guanylate cyclase, PKC protein kinase C, PKG protein kinase G, PyK2 proline-rich tyrosine kinase 2, Rac1 Ras-related C3 botulinum toxin substrate, RO reactive oxygen species, sGC soluble guanylate cyclase, STAT3 signal transducer and activator of transcription 3

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Val-based approach as first therapeutic strategy in patients with HFrEF [28].

It should be noted that both Sac/Val and vericiguat produce a significant decrease in BP and their association may result in the occurrence of symptomatic hypotension and of a premature interruption of the active treatment. This may have influenced the results of the study in the subgroup treated with ARNi [28].

Although this mechanism may appear counterproductive in the treatment of HF, the association of Sac/Val and vericiguat might be proposed for the treatment of resistant hypertension. In this condition, the anti-hypertensive action resulting from the combined effects of increased ANP level due to Sac/Val and from the vasodilation due to sGC stimulation may be more efficacious compared to that obtained with each single agent.

Moreover, the HMOD related to resistant hypertension may benefit of such combined therapeutic strategy. In this regard, it should be noted that both Sac/Val and vericiguat share the same intracellular downstream signaling, that is

the cGMP-PKG pathway, and probably have a synergistic complementary effect on cardiovascular protection. It is known that the increase of ANP and the stimulation of cGMP favor autocrine/paracrine effects within the cardiovascular system with anti-hypertrophic, anti-fibrotic, anti-inflammatory and anti-proliferative properties that counteract the cardiovascular remodelling process in hypertension [13]. In particular, ANP exerts its anti-hypertrophic and anti-fibrotic effects through the modulation of calcineurin/NFAT (Nuclear factor of activated T-cells), the sodium exchanger NHE-1 (sodium-hydrogen antiporter 1) and the TGFβ1 (Transforming growth factor β1)/Smad signaling pathways [29]. At the vascular level, ANP reduces inflammation by inhibiting the TNFα-induced expression of adhesion molecules, such as E-selectin and ICAM-1 [30].

The enhancement of the cardiovascular protective effects of NPs linked to cGMP activation could be enhanced in the long term with the sGC stimulator although this needs to be tested and proven. Besides, apart from the cGMP activation,

Sac/Val inhibits AT1R and the consequent deleterious signaling pathways involved in fibrosis, cellular proliferation, hypertrophy and vasoconstriction such as RAC1 (Ras-related C3 botulinum toxin substrate)/p38/MAPK (mitogen-activated protein kinase), which is involved in the activation of Akt, mTOR and its downstream target p70S6K, Ras/MEK (mitogen-activated protein kinase)/ERK (extracellular-signal-regulated kinase), which leads to an increased expression of c-fos mRNA and JNK (c-JUN N-terminal kinase), and c-Src, which stimulates JAK2 (Janus kinase 2)-STAT3 (signal transducer and activator of transcription 3) through PKC (protein kinase C) and PyK2 (proline-rich tyrosine kinase 2) (Fig. 1) [31].

As a result of all mechanisms discussed above, the combination of Sac/Val with sGC stimulation may represent an intriguing area of clinical investigation in hypertension and may be a promising approach to achieve a more pronounced hypotensive effect and a more robust protection toward HMOD and HF development in resistant hypertension.

Future studies are required to specifically evaluate the biological mechanisms underlying the interaction between Sac/Val and vericiguat and to investigate the potential efficacy and safety of their association in the challenging clinical field of resistant hypertension management.

References

1. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 201 population-representative studies with 104 million participants. *Lancet*. 2021;398(10304):957–980.
2. Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, et al. 2020 international society of hypertension global hypertension practice guidelines. *Hypertension*. 2020;75(6):1334–57.
3. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, Kahan T, Mahfoud F, Redon J, Ruilope L, Zanchetti A, Kerins M, Kjeldsen SE, Kreutz R, Laurent S, Lip GYH, McManus R, Narkiewicz K, Ruschitzka F, Schmieder RE, Shlyakhto E, Tsioufis C, Aboyans V, Desormais I, ESC Scientific Document Group. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J*. 2018;39:3021–104.
4. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbiagele B, Smith SC Jr, Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA Sr, Williamson JD, Wright JT Jr. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*. 2018;71:e13–115.
5. Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, Martinez F, Packer M, Pfeffer MA, Pieske B, Redfield MM, Rouleau JL, van Veldhuisen DJ, Zannad F, Zile MR, Desai AS, Claggett B, Jhund PS, Boytsov SA, Comin-Colet J, Cleland J, Dünge H-D, Goncalvesova E, Katova T, Kerr Saraiva JF, Lelonek M, Merkely B, Senni M, Shah SJ, Zhou J, Rizkala AR, Gong J, Shi VC, Lefkowitz MP. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med*. 2019;381:1609–20.
6. Jackson AM, Jhund PS, Anand IS, Dünge HD, Lam CSP, Lefkowitz MP, Linssen G, Lund LH, Maggioni AP, Pfeffer MA, Rouleau JL, Saraiva JFK, Senni M, Vardeny O, Wijkman MO, Yilmaz MB, Saito Y, Zile MR, Solomon SD, McMurray JJV. Sacubitril-valsartan as a treatment for apparent resistant hypertension in patients with heart failure and preserved ejection fraction. *Eur Heart J*. 2021;42(36):3741–52.
7. Volpe M, Gallo G. Sacubitril/valsartan for heart failure with preserved ejection fraction and resistant hypertension: one shot for a double strike? *Eur Heart J*. 2021;42(36):3753–5.
8. Solomon SD, Zile M, Pieske B, Voors A, Shah A, Kraigher-Krainer E, Shi V, Bransford T, Takeuchi M, Gong J, Lefkowitz M, Packer M, McMurray JJ. Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectionN fracTion (PARAMOUNT) Investigators. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. *Lancet*. 2012;380:1387–95.
9. Ruilope LM, Dukat A, Böhm M, Lacourcière Y, Gong J, Lefkowitz MP. Blood-pressure reduction with LCZ696, a novel dual-acting inhibitor of the angiotensin II receptor and neprilysin: a randomised, double-blind, placebo-controlled, active comparator study. *Lancet*. 2010;375(9722):1255–66.
10. Wang TD, Tan RS, Lee HY, Ihm SH, Rhee MY, Tomlinson B, Pal P, Yang F, Hirschhorn E, Prescott MF, Hinder M, Langenickel TH. Effects of Sacubitril/valsartan (LCZ696) on natriuresis, diuresis, blood pressures, and NT-proBNP in salt-sensitive hypertension. *Hypertension*. 2017;69(1):32–41.
11. Ibrahim NE, McCarthy CP, Shrestha S, Gaggin HK, Mukai R, Szymonifka J, Apple FS, Burnett JC Jr, Iyer S, Januzzi JL Jr. Effect of neprilysin inhibition on various natriuretic peptide assays. *J Am Coll Cardiol*. 2019;73(11):1273–84.
12. Nougé H, Pezel T, Picard F, Sadoune M, Arrigo M, Beauvais F, Launay JM, Cohen-Solal A, Vodovar N, Logeart D. Effects of sacubitril/valsartan on neprilysin targets and the metabolism of natriuretic peptides in chronic heart failure: a mechanistic clinical study. *Eur J Heart Fail*. 2019;21(5):598–605.
13. Volpe M, Carnovali M, Mastromarino V. The natriuretic peptides system in the pathophysiology of heart failure: from molecular basis to treatment. *Clin Sci*. 2016;130:57–77.
14. Bavishi C, Messerli FH, Kadosh B, Ruilope LM, Kario K. Role of neprilysin inhibitor combinations in hypertension: insights from hypertension and heart failure trials. *Eur Heart J*. 2015;36:1967–73.
15. Pu Q, Brassard P, Javeshghani DM, Iglarz M, Webb RL, Amiri F, Schiffrin EL. Effects of combined AT1 receptor antagonist/NEP inhibitor on vascular remodeling and cardiac fibrosis in SHRSP. *J Hypertens*. 2008;26(2):322–33.
16. Rubattu S, Cotugno M, Forte M, Stanzione R, Bianchi F, Madonna M, Marchitti S, Volpe M. Effects of dual angiotensin type 1 receptor/neprilysin inhibition vs. angiotensin type 1 receptor inhibition on target organ injury in the stroke-prone spontaneously hypertensive rat. *J Hypertens*. 2018;36(9):1902–14.
17. Kato J. Natriuretic peptides and neprilysin inhibition in hypertension and hypertensive organ damage. *Peptides*. 2020;132:170352.
18. Tsai EJ, Kass DA. Cyclic GMP signaling in cardiovascular pathophysiology and therapeutics. *Pharmacol Ther*. 2009;122:216–38.

19. Murad F. Shattuck Lecture: nitric oxide and cyclic GMP in cell signaling and drug development. *N Engl J Med*. 2006;355:2003–11.
20. Greene SJ, Gheorghiade M, Borlaug BA, Pieske B, Vaduganathan M, Burnett JC Jr, Roessig L, Stasch JP, Solomon SD, Paulus WJ, Butler J. The cGMP signaling pathway as a therapeutic target in heart failure with preserved ejection fraction. *J Am Heart Assoc*. 2013;2: e000536. <https://doi.org/10.1161/JAHA.113.000536>.
21. Inserte J, Hernando V, Ruiz-Meana M, Poncelas-Nozal M, Fernandez C, Agullo L, Sartorio C, Vilardosa U, Garcia-Dorado D. Delayed phospholamban phosphorylation in post-conditioned heart favours Ca²⁺ normalization and contributes to protection. *Cardiovasc Res*. 2014;103:542–53.
22. Stasch JP, Becker EM, Alonso-Alija C, Apeler H, Dembowsky K, Feurer A, Gerzer R, Minuth T, Perzborn E, Pleiss U, Schroder H, Schroeder W, Stahl E, Steinke W, Straub A, Schramm M. NO-independent regulatory site on soluble guanylate cyclase. *Nature*. 2001;410:212–5.
23. Schmidt P, Schramm M, Schroder H, Stasch JP. Mechanisms of nitric oxide independent activation of soluble guanylyl cyclase. *Eur J Pharmacol*. 2003;468:167–74.
24. Boerrigter G, Costello-Boerrigter LC, Cataliotti A, Lapp H, Stasch JP, Burnett JC Jr. Targeting heme-oxidized soluble guanylate cyclase in experimental heart failure. *Hypertension*. 2007;49:1128–33.
25. Bonderman D, Ghio S, Felix SB, Ghofrani HA, Michelakis E, Mitrovic V, Oudiz RJ, Boateng F, Scalise AV, Roessig L, Semigran MJ, Left Ventricular Systolic Dysfunction Associated With Pulmonary Hypertension Riociguat Trial (LEPHT) Study Group. Riociguat for patients with pulmonary hypertension caused by systolic left ventricular dysfunction: a phase IIb double-blind, randomized, placebo-controlled, dose-ranging hemodynamic study. *Circulation*. 2013;128:502–11.
26. Gheorghiade M, Greene SJ, Butler J, Filippatos G, Lam CSP, Maggioni AP, Ponikowski P, Shah SJ, Solomon SD, Kraigher-Krainer E, Samano ET, Müller K, Roessig L, Pieske B. SOCRATES-REDUCED Investigators and Coordinators 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. *JAMA*. 2015;314:2251–62.
27. Armstrong PW, Pieske B, Anstrom KJ, Ezekowitz J, Hernandez AF, Butler J, Lam CSP, Ponikowski P, Voors AA, Jia G, McNulty SE, Patel MJ, Roessig L, Koglin J, O'Connor CM, VICTORIA Study Group. Vericiguat in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2020. <https://doi.org/10.1056/NEJMoa1915928>.
28. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR, PARADIGM-HF. Investigators and Committees Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371(11):993–1004.
29. Calvieri C, Rubattu S, Volpe M. Molecular mechanisms underlying cardiac antihypertrophic and antifibrotic effects of natriuretic peptides. *J Mol Med (Berl)*. 2012;90(1):5–13.
30. Kiemer AK, Weber NC, Vollmar AM. Induction of IkappaB: atrial natriuretic peptide as a regulator of the NF-kappaB pathway. *Biochem Biophys Res Commun*. 2002;295(5):1068–76.
31. Rubattu S, Gallo G, Volpe M. A Contemporary View of Natriuretic Peptides in the SARS-CoV-2 Era. *Front Physiol*. 2021;12:643721.