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Sacubitril/valsartan: A practical guide

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Experts opinion, endorsed by the Working Group on Heart Failure of the Portuguese Society of cardiology

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Abstract Renin-angiotensin-aldosterone system (RAAS) inhibitors are a cornerstone in the treatment of heart failure with reduced ejection fraction (HFrEF). Sacubitril/valsartan modulates the neurohormonal axis by inhibiting both angiotensin receptors and neprilysin, and improves neurohormonal balance more than blocking the RAAS alone.

The PARADIGM-HF trial validated this new treatment option for patients with HFrEF. Sacubitril/valsartan was also more effective than enalapril in slowing disease progression by decreasing the risk of worsening heart failure requiring hospitalization or emergency admission and the need for intensified therapy, heart failure devices or cardiac transplantation. More than 70% of patients included in PARADIGM-HF were in NYHA class II, and overall, the results indicate that sacubitril/valsartan should be started in the earliest symptomatic stages of the disease.

As PARADIGM-HF has excellent robustness for a cardiovascular trial, sacubitril/valsartan has been included as a new treatment option with a strong level of recommendation in the main international guidelines.

This expert task force proposes a practical guide to the use of this new drug that has been endorsed by the Working Group on Heart Failure of the Portuguese Society of Cardiology.

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Sacubitril/valsartan: um guia prático

Resumo Os inibidores do sistema renina-angiotensina-aldosterona são uma das pedras basilares no tratamento da insuficiência cardíaca com fração de ejeção reduzida. O sacubitril/valsartan promove a modulação neuro-hormonal, bloqueando os recetores da angiotensina e inibindo a neprilisina, e produz um maior equilíbrio neuro-hormonal, mais do que o bloqueio do sistema renina-angiotensina-aldosterona isoladamente. O estudo PARADIGM-HF validou essa nova opção para o tratamento de doentes com insuficiência cardíaca e fração de ejeção reduzida, em alternativa ao IECA/ARA.

O sacubitril/valsartan demonstrou ser mais eficaz do que o enalapril em retardar a progressão da doença, diminuindo o risco de agravamento da insuficiência cardíaca através da diminuição da necessidade de hospitalização e da menor necessidade de intensificação terapêutica, dispositivos ou transplante cardíaco. Mais de 70% dos doentes incluídos no estudo PARADIGM-HF estavam em classe II da NYHA, suportando a utilização do sacubitril/valsartan precocemente após o início dos sintomas.

Como o estudo PARADIGM-HF apresentou uma robustez sem precedentes para um estudo cardiovascular, o sacubitril/valsartan foi incluído como uma nova opção de tratamento nas Recomendações internacionais mais relevantes, com um elevado nível de evidência (I-B).

Este grupo de peritos em Insuficiência Cardíaca vem propor uma orientação prática para a utilização deste novo fármaco, subscrita pelo Grupo de Estudos de Insuficiência Cardíaca da Sociedade Portuguesa de Cardiologia.

Introduction

Sacubitril/valsartan modulates the neurohormonal axis by inhibiting both angiotensin receptors and neprilysin, and improves neurohormonal balance more than blocking the renin-angiotensin-aldosterone system (RAAS) alone.[1] The Prospective comparison of ARNi with ACEi to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial validated this new treatment option for patients with heart failure (HF) with reduced ejection fraction (HFrEF).[2]

In the PARADIGM-HF trial, patients receiving sacubitril/valsartan had a 20% lower risk of cardiovascular death and lived up to two years longer than those receiving enalapril.[3,4] This impact on cardiovascular death was driven by a similar decrease in the risk of sudden death and death due to worsening HF, unlike what was observed with angiotensin-converting enzyme inhibitors (ACEIs), which showed no impact on sudden death.[5] Sacubitril/valsartan was also more effective than enalapril in slowing disease progression, by decreasing the risk of worsening HF requiring hospitalization or emergency admission and the need for intensification of therapy, HF devices or cardiac transplantation. Overall, the results indicate that sacubitril/valsartan should be started in the earliest symptomatic stages of the disease.[3,6]

As PARADIGM-HF has excellent robustness for a cardiovascular trial, sacubitril/valsartan has been included as a new treatment option with a strong level of recommendation (class I, level of evidence B) in the main international guidelines.[7–9] The Web Addenda of the 2016 European Society of Cardiology (ESC) guidelines provide practical guidance on the use of certain HF drugs, but not on sacubitril/valsartan. The authors propose to provide similar guidance for sacubitril/valsartan in the current document.

Guidance

Sacubitril/valsartan, an angiotensin receptor-neprilysin inhibitor (ARNI), is indicated in adult patients for the treatment of symptomatic chronic HFrEF to further reduce the risk of HF hospitalization and cardiovascular death.[10] When initiating sacubitril/valsartan, ACEIs, angiotensin receptor blockers (ARBs), and direct renin inhibitors (if prescribed) must be discontinued. Moreover, any patient pretreated with an ACEI should undergo a 36-hour washout period prior to initiating sacubitril/valsartan, in order to avoid increased risk of angioedema. This is not necessary when switching from an ARB to an ARNI.[11,12]

When initiating sacubitril/valsartan, it is important to ensure that blood pressure (BP) is adequate (systolic BP >100 mmHg) and potassium level is <5.5 mmol/l. Estimated glomerular filtration rate should be $\geq$30 ml/min/1.73 m^2; below this value, sacubitril/valsartan must be used with caution, and is not recommended in end-stage renal disease and in patients undergoing hemodialysis. Sacubitril/valsartan should not be used in the presence of primary or severe hepatic impairment (Child-Pugh class C); primary hepatic impairment should be suspected in the absence of other signs of congestion. However, if hepatic enzymes are elevated due to hepatic congestion, this should not be considered a contraindication for sacubitril/valsartan.

Most of the clinical evidence of benefit comes from patients in New York Heart Association (NYHA) functional class II/III (70% of patients included in PARADIGM-HF were

Table 1 Practical guidance on the use of sacubitril/valsartan in patients with heart failure with reduced ejection fraction.

Why?			Ref.
To improve the natural course of the disease by further reducing the risk of HF hospitalization and mortality			8
In whom and when?			
Indications 1. Adult patients with heart failure and reduced ejection fraction (LVEF <40%) 2. Replacement of ACEI/ARB in patients who remain in NYHA class II-IV despite treatment with an ACEI/ARB, a beta-blocker and a MRA 3. Patients should have SBP ≥100 mmHg and serum potassium level <5.5 mmol/l			8,12,15
Contraindications 1. Concomitant use with ACEI or ARB[a] 2. Concomitant use with aliskiren-containing medicines in patients with diabetes or with renal impairment (eGFR <60 ml/min/1.73 m^2)[a] 3. Previous history of angioedema 4. Severe hepatic impairment, biliary cirrhosis or cholestasis (Child-Pugh class C)[b]			
Cautions during treatment and reasons to seek specialist advice 1. Symptomatic hypotension 2. Impaired/worsening renal function[c] 3. Hyperkalemia (serum potassium ≥5.5 mmol/l)			10
What dose?			
Population	Initial dose	Titration	
Patients on moderate or high-dose ACEI Equivalent of enalapril ≥10 mg twice daily Patients on moderate or high-dose ARB Equivalent of valsartan ≥80 mg twice daily	49/51 mg twice Daily (if previous ACEI, ensure 36h washout period[d])	Double the dose at 2-4 weeks	10,12
Patients on low-dose ACEI Equivalent of <10 mg of enalapril twice daily Patients on low-dose ARB Equivalent of valsartan ≤80 mg twice daily ACEI/ARB-naïve patients Patients with severe renal impairment (eGFR <30 ml/min/1.73 m^2) Patients with moderate hepatic impairment (Child-Pugh class B) Elderly patients (age ≥75 years)	24/26 mg twice daily (if previous ACEI, ensure 36-hour washout period[d])	Double the dose every 3-4 weeks	
How to use?			
If natriuretic peptides are assessed for monitoring HF decompensation, NT-proBNP should be used, not BNP Monitor blood pressure regularly Check renal function Monitor serum potassium levels			8,10

Table 1 (*Continued*)

Trouble-shooting	
Hypotension *If symptomatic hypotension occurs, consider*[e]: 1. adjustment of doses of concomitant medication 2. temporary down-titration of sacubitril/valsartan 3. discontinuation of sacubitril/valsartan	8,10
Worsening renal function If clinically significant deterioration of renal function occurs, down-titration should be considered	
Hyperkalemia *If hyperkalemia occurs, consider*[e]: 1. adjustment of concomitant potassium-sparing drugs 2. temporary down-titration of sacubitril/valsartan 3. discontinuation of sacubitril/valsartan *If serum potassium level is ≥5.5 mmol/l discontinuation is recommended*	
Angioedema If angioedema occurs, sacubitril/valsartan should be immediately discontinued and must not be reintroduced.	
What to discuss with the patient	
Involve patients in the decision-making process *Ensure patients understand the beneficial impact of the drug on prognosis to improve long-term adherence to therapy* *Inform patients about potential side effects:* dizziness and hypotension angioedema, itching and rash	

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor-neprilysin inhibitor; eGFR: estimated glomerular filtration rate; AST/ALT: aspartate transaminase/alanine transaminase ratio; LVEF: left ventricular ejection fraction; NT-proBNP: N-type pro-B-type natriuretic peptide; NYHA: New York Heart Association; RAAS: renin-angiotensin-aldosterone system; SBP: systolic blood pressure; SmPC: Summary of Product Characteristics.

[a] Dual RAAS inhibition is not recommended.

[b] Limited clinical experience with Child-Pugh class C patients or AST/ALT levels two times normal

[c] Decline in renal function is defined as 0.3 mg/dl increase in serum creatinine. However, if the patient is clinically stable, consider maintaining the dose of sacubitril/valsartan and assess renal function after 2 weeks.

[d] Same period should be considered if patients switch from ARNI to ACEI.

[e] See SmPC for detailed information.

in NYHA class II). Therefore, sacubitril/valsartan should be initiated in the early stages of the disease.

The optimal timing for switching from ACEIs/ARBs to sacubitril/valsartan has continued to evolve in the light of new clinical evidence and experience. The 2016 ESC guidelines on HF recommend switching in symptomatic patients after titration of an ACEI/ARB, a beta-blocker and a mineralocorticoid receptor antagonist (MRA) to maximally tolerated evidence-based doses.[8] The most recent American College of Cardiology/American Heart Association (ACC/AHA) expert consensus document[9] suggests that switching can be performed earlier, regardless of maximum tolerated doses of ACEIs/ARBs and/or introduction of an MRA. Use of an MRA, although also recommended to improve outcomes, is not considered mandatory prior to changing a patient to an ARNI.[9,13]

Sacubitril/valsartan should be initiated according to the patient's profile and the background RAAS inhibition therapy. If tolerated, the target dose is 97/103 mg twice daily.

When monitoring a patient newly treated with sacubitril/valsartan, it is important to measure BP regularly and to reassess the indication for all concomitant medications that could reduce BP, such as diuretics or antihypertensive drugs that do not have disease-modifying properties.

Renal function and serum potassium should be monitored on starting sacubitril/valsartan. In the PARADIGM-HF trial, patients receiving sacubitril/valsartan were less likely to experience renal impairment and hyperkalemia requiring discontinuation of the study medication than those on enalapril.[3] If a patient experiences clinically significant hyperkalemia, the concomitant medications should be adjusted. If serum potassium remains ≥5.5 mmol/l, discontinuation of sacubitril/valsartan should be considered. PARADIGM-HF demonstrated that, compared with enalapril, sacubitril/valsartan enhanced the possibility of using MRAs safely, due to a lower incidence of hyperkalemia.[14] Monitoring of renal function and serum potassium is recommended between two and four weeks after starting the therapy and at each dose titration (until maximum tolerated dose), at three months, and every six months thereafter.

Patients on sacubitril/valsartan should be monitored for N-terminal pro-B-type natriuretic peptide (NT-proBNP) instead of B-type natriuretic peptide (BNP) levels. BNP is a substrate for neprilysin, the enzyme that is inhibited by sacubitril. Therefore, an increase in BNP levels cannot be interpreted as a biomarker of HF decompensation or used for risk stratification.[3]

When sacubitril/valsartan is being considered, patients should be involved and should play a central role in the decision-making process. They should understand the drug's indications and dosing, recognize the common side effects, and know when to inform a healthcare professional. Furthermore, patients should be aware of the benefit of taking the drug as prescribed and its impact on disease progression, in order to improve long-term adherence to therapy (Table 1).[8]

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Conflicts of interest

Cândida Fonseca has received fees from Novartis, Servier, Orion, Roche, Bayer and Vifor (companies that develop and market tests and/or treatments in the area of HF) for HF consulting, sitting on clinical study steering committees and giving lectures at congresses and other scientific sessions. Dulce Brito has received fees from Novartis, Orion, Roche, Servier, St. Jude and Vifor (companies that develop and market tests and/or treatments in the area of HF) for HF consulting, and has given talks at congresses and other scientific sessions. She also reports consultancy and research fellowships from Genzyme-Sanofi and consultancy and lecture fees from Pfizer, and has attended meetings sponsored by Shire Human Genetic Therapies (companies that develop and market treatments in the area of cardiomyopathies). Jorge Ferreira has received consulting and speaker fees from Amgen, AstraZeneca, Boehringer-Ingelheim, Merck-Sharp & Dohme, Novartis, and Orion. Fátima Franco has received consulting and speaker fees from Novartis. João Morais received honoraria within the last two years from pharmaceutical companies for consulting activities (Bayer Healthcare, Astra Zeneca, Merck Sharp & Dhome, Novartis) and fees for lectures (Boehringer Ingelheim, Bial, Servier, Daiichi Sankyo, Boston Scientific). He is also National Coordinator for the PARADISE-MI trial on sacubitril/valsartan in patients with myocardial infarction. José Silva Cardoso was national coordinator of the PARADIGM-HF study and was a consultant for Novartis, AstraZeneca Pharmaceuticals, Orion, Pfizer, Servier and Vifor (companies that develop and market treatments for HF). He has sat on steering committees for clinical studies sponsored by Novartis, Orion and Pfizer and has received honoraria as a speaker in sessions on HF and research fellowships from Novartis, Abbott, AstraZeneca Pharmaceuticals, Bial, Boehringer Ingelheim, Menarini, Merck Serono, Merck Sharp & Dohme, Orion, Pfizer, Sanofi, Servier and Vifor.

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