

ANMCO POSITION PAPER: Use of sacubitril/valsartan in hospitalized patients with acute heart failure

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KEYWORDS

Acute heart failure;
Sacubitril/valsartan

Sacubitril/valsartan (S/V) has been shown to reduce the risk of cardiovascular death or heart failure hospitalization and improve symptoms in chronic heart failure with reduced ejection fraction compared with enalapril. After 7 years since the publication of the results of PARADIGM-HF, further insight has been gained with potential new indications. Two prospective randomized multicentre studies (PIONEER-HF and TRANSITION) in patients hospitalized for acute heart failure (AHF) have shown an improved clinical outcome and biomarker profile as compared with enalapril, and good tolerability, safety, and feasibility of initiating in-hospital administration of S/V. Furthermore, some studies have highlighted the favourable effects of S/V in attenuating adverse myocardial remodelling, supporting an early benefit after treatment. Observational data from non-randomized studies in AHF report that in-hospital and pre-discharge prescription of evidence-based drugs associated with better survival still remain suboptimal. Additionally, the COVID-19 pandemic has also negatively impacted on outpatient activities. Therefore, hospitalization, a real crossroad in the history of heart failure, must become a management and therapeutic opportunity

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for our patients. The objective of this ANMCO position paper is to encourage and facilitate early S/V administration in stabilized patients during hospitalization after an AHF episode, with the aim of improving care efficiency and clinical outcome.

Introduction

Nearly 7 years ago a new drug combination (ARNI, composed of a well-known antagonist of angiotensin II, valsartan, and an original antagonist molecule of neprilysin, sacubitril) breaks into the static scenario of the pharmacological therapy for chronic heart failure (HF) with reduced systolic function. The PARADIGM-HF¹ Study, published in September 2014, showed that in about 4100 patients, predominantly in NYHA class II (72%), sacubitril/valsartan (S/V), compared with enalapril, was much more effective, prompting therefore, a revision of the therapeutic ‘paradigm’ recommended so far. In fact, the study showed that the new therapy reduced cardiovascular mortality or hospitalizations for HF (primary endpoint, –20%), all-cause mortality (–16%), hospitalizations for HF (–21%), cardiovascular mortality (–20%), and the risk of sudden death (–20%).

Patients treated with S/V showed a progressive reduction, from the first 4 weeks of therapy, of the levels of the N-terminal fragment of the type B natriuretic propeptide (NT-proBNP), a strong and direct surrogate of the observed benefits with the new therapy. The benefits were evident in all age groups (although it was proportionally less in patients ≥ 75 years), in all left ventricle ejection fraction (EF) strata (from $\leq 35\%$), in all NYHA classes (but proportionally less evident in NYHA class IV), in all strata of NT-proBNP ($>400/600$ pg/mL), regardless of other cardiovascular therapies [beta-blocker, angiotensin-converting enzyme inhibitor (ACE inhibitor), digital, implantable defibrillator/cardiac resynchronization therapy].

These evidences, associated with a high tolerability, has led the International Scientific Societies to include the drug in the guidelines with a similar class I recommendation, level of evidence B for the European ones² and B-R for the American ones.³ The 2021 European guideline anticipations, presented during the Heart Failure Congress (29 June to 1 July), suggest to consider its use also in patients not previously treated with ACE inhibitor/angiotensin receptor antagonist (ARB) (class IIb, level B), as already proposed by the American guidelines.³

In March 2017, S/V was included in the refund scheme of the National Health System, with a prescription limited by a therapeutic plan circumscribed to ‘PARADIGM-HF-like’ patients only, regardless of the evolutionary changes of the clinical scenarios, which have occurred since the publication of the results of the study to date, suggesting the necessity of an extensive updating.

Due to the results of some controlled studies and registries from the real world, the potential and therapeutic capacity of this new drug class have progressively expanded. In fact, these have confirmed the beneficial effects of the drug class on other categories of patients, besides the one

initially considered. However, in addition to the scientific evidence, which still represents the therapeutic guide that must lead the clinician to the choice of therapy, the recent management and health upheavals related to the COVID-19 pandemic have also contributed to changing the clinical scenarios.

The hospital role, in relation to the management programmes for HF treatment, appears even more crucial, pending the interrelations with the territory, already notoriously heterogeneous and only partially structured effectively at national level and which hopefully in the near future will be re-designed and adapted to the new social-healthcare context, through organizational changes, which at the moment, are only perceivable.

Therefore, the hospitalization phase represents, in times of organizational fluidity, a steady point, even if prognostically critical, in the clinical journey of the HF patient, which involves a very large portion of the population, if we consider that about 1 million people in the USA alone, are annually hospitalized for acute HF.⁴

It therefore becomes imperative, once the clinical framework has been determined, to maximize the opportunity during hospitalization, and to immediately implement the drug therapies that have proved effective in reducing future adverse events, especially if started straight away and without delegating or postponing the therapeutic optimization to the post-discharge outpatient phase.

The purpose of this ANMCO position paper is to provide the clinical cardiologist with a series of useful elements in order to optimize the drug therapy before discharge in patients hospitalized for acute, *de novo*, or worsened HF.^{3,5}

Scientific evidence

Studies in patients hospitalized for acute heart failure

In 2019, two studies were published, which focused on the use of S/V in acute HF patients, the PIONEER-HF⁶ and TRANSITION.⁷ The two studies had the peculiarity of having enrolled, compared with PARADIGM-HF Study, a significant number of ‘naïve’ patients, i.e. without history of HF (34.6% in PIONEER-HF and 28.8% in TRANSITION) nor previously treated with renin-angiotensin-aldosterone system inhibitors (54.1% in PIONEER-HF and 24.3% in TRANSITION).

The TRANSITION⁷ is basically a safety and ‘strategic approach’ study: it compared, in 1002 patients, two different randomization methods of initiating S/V after HF hospitalization, before and after discharge, demonstrating an excellent tolerability of the drug in both contexts. The two groups of patients did not show any significant difference in the percentage of patients that reached and maintained

at 10 weeks, for at least 2 weeks, the dosage of 49/51 or 97/103 mg bid [62.1% vs. 68.5%; relative risk (RR) 0.91, 95% confidence interval (CI) 0.83-0.99] or any dosage (86.0% vs. 89.6%; RR 0.96, 95% CI 0.92-1.01). In the two groups, the largest number of enrolments occurred in the 3 days before and after discharge, with the higher percentage of enrolments in the 2 days before and after discharge. No significant difference has been observed for the incidence of adverse events and for discontinuation of the drug due to adverse effects (7.3% vs. 4.9%; RR 1.49, 95% CI 0.90-2.46).

The final message is that starting S/V in a stabilized patient within the last 5 days of hospitalization or in the first days of discharge, does not make any difference, although introducing the therapy during hospitalization, could limit, for various reasons, the therapeutic inertia, which could influence the subsequent implementation in the outpatient phase.

Instead, the PIONEER-HF⁶ was specifically designed to compare S/V to enalapril started during hospitalization for acute HF and provides a series of useful messages for intra-hospital drug management. The main endpoint was the reduction of NT-proBNP compared with baseline, assessed at 8 weeks from randomization. The safety endpoints—incidence of worsening renal function, hyperkalaemia, symptomatic hypotension, and angioedema—were also evaluated. Randomization could occur after at least 24 h to 10 days from hospital admission and after haemodynamic stabilization (defined as the maintenance of systolic blood pressure ≥ 100 mmHg in the previous 6 h without increasing the dosage of i.v. diuretics, or the use of i.v. vasodilators in the previous 6 h and i.v. inotropes in the previous 24 h). The choice of the initial dosage was based on blood pressure values according to a pre-specified algorithm. The reduction of NT-proBNP in the S/V group was greater than in the enalapril group (−46.7% vs. −25.3%; $P < 0.001$), which was already significant at 1 week. In a subsequent ‘open label’ phase of the study (8-12 weeks), the transition from the enalapril group to the S/V group showed a further reduction in NT-proBNP (−37.4%).⁸

No significant differences were observed in the incidence of worsening of renal function, hyperkalaemia, symptomatic hypotension, or angioedema between the groups treated with S/V or enalapril. However, about a fifth of the patients suspended S/V treatment at 8 weeks, although, after the same time, 55.2% of patients in the S/V group and 60.8% of patients in the enalapril group were able to tolerate the maximal dosage of the drug.

The combination of death from any cause, HF re-hospitalization, implantation of a left ventricular mechanical assistance device or list placement for cardiac transplant as an explorative endpoint and cardiovascular death or re-hospitalization for HF as a secondary composite endpoint, were also evaluated. Patients treated with S/V, compared with patients randomized to enalapril, had a significantly lower risk of death from any cause, HF re-hospitalization, implantation of a left ventricular mechanical assistance device or list inclusion for heart transplantation [hazard ratio (HR) 0.58, 95% CI 0.40-0.85; $P = 0.005$] with an even lower risk (9.2% vs. 15.2%; HR 0.58, 95% CI 0.39-0.87; $P = 0.007$) of cardiovascular death or re-hospitalization for HF.

The analysis of the only HF re-hospitalizations showed a significant reduction both in the time to the first event and in the total number of re-hospitalizations (41 vs. 64 events; HR 0.64, 95% CI 0.42-0.97; $P = 0.037$). These results confirm the PARADIGM-HF sub-analysis that demonstrated both the ability of S/V to reduce HF hospitalizations at 30 days after randomization compared with enalapril and the ability to reduce the risk of re-hospitalization for each cause at 30 days.⁹

More specific, subsequent analyses have shown that the effects of S/V on the course of biomarkers other than NT-proBNP [significant increase in urinary cGMP and reduction of the ‘soluble suppression of tumorigenicity-2’ (sST2)], were already evident after 1 week, and became relevant at 4 weeks, likewise for troponin.¹⁰ At 30 days from the start of therapy, these effects result in an early separation of the curve of clinically relevant events, with a consistent effect up to 8 weeks.¹¹ This supports the message that an early start of the drug, without waiting for the so-called transition phase from hospital to home, guarantees a significant protection against death/re-hospitalization events, which influence the high risk of this delicate phase.

The results of the analysis performed in both studies with respect to patients with ‘de novo’ HF or not currently in treatment with ACE inhibitors/ARBs deserve to be mentioned. In the PIONEER-HF, no interaction was noted between a history of HF ($P < 0.35$) or previous treatment with ACE inhibitors/ARBs ($P < 0.88$) and the effects of S/V compared with enalapril on cardiovascular mortality or HF re-hospitalization.¹² In the TRANSITION sub-analysis that compared patients with *de novo* HF to those with an HF history,¹³ the first reached the target dose at the 10th week with a significantly higher percentage (56% vs. 45%; RR 1.30, 95% CI 1.12-1.52; $P < 0.001$). Fewer serious adverse events and permanent discontinuation of therapy were also observed. Moreover, the introduction of S/V did not prevent the concomitant initiation and titration of the recommended therapies. Finally, ‘de novo’ patients showed a faster and higher reduction of NT-proBNP and high-sensitivity troponin T values, and lower rates of re-hospitalization for HF and for all causes. The message is that the ‘de novo’ subgroup represents patients in an early stage of the disease, deserving of a rapid optimization of the drug therapy, in particular of S/V.

Recently, the results of two new trials have been published adding further elements for the usage of S/V and that currently tend to limit its use to unselected populations. In the PARADISE-MI study,¹⁴ which involved stabilized patients affected by myocardial infarction within 1 week of randomization, with an EF $\leq 40\%$ and/or signs of HF, S/V shown to be only partially advantageous compared with ramipril, and equivalent in safety and tolerability. The entity of the reduction of the composite primary endpoint of cardiovascular death, hospitalizations for HF or subsequent HF development, was 10% in patients treated with S/V compared with those treated with ramipril. The reduction, however, did not reach the significant pre-specified threshold reduction of 15%. The percentage of adverse events was equivalent, as well as the incidence of angioedema, hyperkalaemia or worsening of renal and hepatic function; episodes of hypotension were observed mostly in patients

treated with S/V, while cough was more frequent in those treated with ramipril.

However, in patients with advanced HF and reduced EF (<25%), the results of the LIFE¹⁵ study did not confirm the expectations, as S/V did not result superior to valsartan in reducing the NT-proBNP values at 24 weeks, which was the primary endpoint, nor in improving clinical outcomes. The trial was suspended ahead of time in March 2020 because of the high-risk events in vulnerable patients caused by the COVID-19 pandemic. The protocol and the pre-specified statistical design established to analyse 400 patients, but in the end, in order to avoid any risk of infection, only 335 were taken into consideration. The nominal statistical power for the primary endpoint was reduced from 88% to 79% (area under the curve for percentage variations of NT-proBNP from baseline to 24 weeks). The enrolled patients were more compromised than those enrolled in other studies: EF \leq 20%, mean systolic blood pressure of \sim 113 mmHg, higher incidence of atrial fibrillation, mean glomerular filtration rate of 64.3 mL/min/1.73 m², higher baseline NT-proBNP values (1875 pg/mL), mean age 60 years, and about a third were women. Neither treatment reduced the median of NT-proBNP values below the baseline and no difference was observed between S/V and valsartan in relation to the secondary endpoints of days alive outside the hospital and HF events (103.2 vs. 111.2; $P=0.45$). Neither were any differences observed for tertiary endpoints, cardiovascular mortality or hospitalizations for HF (HR 1.32; $P=0.20$), hospitalizations for HF (HR 1.24; $P=0.33$) and cardiovascular death or for all causes. In terms of tolerability, the mean S/V dose was 195.3 mg vs. 154.4 mg of valsartan (in both, 48% of the patients reached the target dose). Hypotension was observed in 17% of the S/V group and in 12% of the valsartan group ($P=0.16$), hyperkalaemia in 17% and 9% ($P=0.035$), respectively, and a similar worsening of renal function was observed in 4%.

Pending subsequent analysis, these apparently reductive results in relation to S/V treatment confirm that not all acute HF patients are to be considered in the same manner nor is it possible to hypothesize the same response to treatment. In particular, the population of patients with advanced HF is very different compared with the less compromised one (see the results in 'naïve' patients), due to the major coexistent organ impairment, both cardiac and renal, which undoubtedly limits the extent of the drug therapy response compared with those cases with less severe forms of HF. On the other hand, as indirectly reported in PIONEER-HF, the introduction of any neurohormonal therapy (i.e. ACE inhibitor, angiotensin receptor blockers, beta-blocker, or S/V) in severely unstable and compromised patients should be managed with extreme caution and clinical attention.¹⁶ In addition, it was considered, based on the results of the LIFE¹⁷ Study that a chronic hyperactivity of the renin-angiotensin-aldosterone system could lessen or cancel the effect of natriuretic peptides on the heart and on the cardiovascular and renal system.

However, in the real world—of which the registries, differently to the trials, represent a more reliable source of information—a recent analysis from the extensive database of patients discharged after an acute HF episode, part of the Get With The Guidelines-HF¹⁸ Registry, underlines how

the characteristics and outcomes of patients potentially eligible for PIONEER-HF differ only slightly compared with those encountered in clinical practice, thus indicating that the results of the trial can be widely generalized, involving up to 70% of hospitalized patients, considering only the presence of a glomerular filtrate rate \geq 30 mL/min/1.73 m², a systolic blood pressure \geq 100 mmHg and no need of ventricular assistance or inotropes for prolonged periods. The patients with explicit contraindications to S/V therapy were only 7%. The most frequent cause of exclusion from the active treatment cohort was a glomerular filtrate rate $<$ 30 mL/min/1.73 m² or persistent hypotension.

Effects on reverse remodelling

Although S/V improves clinical outcomes in different clinical contexts, the explanation of its benefits still remained elusive, although a reduction in the NT-proBNP values in all models of HF was associated with an improvement in systolic function. A link between the drug action and a reduction of the pro-fibrotic signal suggested that a reverse remodelling could be a plausible mechanism.¹⁹ However, besides some limited monocentric observations of a benefit on left ventricular function, only recently, after the results of three targeted studies, it has strengthened the evidence that patients treated with S/V are placed, compared with those treated with traditional therapy, on a reverse remodelling trajectory that is a significant predictor of clinical events and of lower risk at follow-up.

The prospective, multicentre, open and single-arm PROVE-HF Study²⁰ evaluated the correlation between changes in NT-proBNP concentration and changes in cardiac volume and function values in 794 patients with HF and reduced EF after 12 months of S/V therapy, compared with baseline. Significant correlations were observed from baseline to 12 months between the variation of NT-proBNP (with a reduction of 32% compared with baseline) and significant changes in all echocardiographic parameters [EF, indexed left atrial volume (LAVi), telediastolic volume (LVEDVi), indexed left ventricular telesystolic (LVESVi), and the E/e' ratio] at 6 months, becoming more evident at 1 year. The EF increased from a median of 28.2% to 37.8% (difference 9.4%, $P<0.001$), while the LVEDVi decreased from a median of 86.93 to 74.15 mL/m² (difference -12.25 , $P<0.001$) and LVESVi went from a median of 61.68 to 45.46 mL/m² (difference -15.29 , $P<0.001$). The LAVi and the E/e' ratio also decreased significantly.

The randomized, multicentre, double-blind EVALUATE-HF²¹ Study, which compared the effect of S/V vs. enalapril on aortic stiffness and cardiac remodelling in 464 patients with HF and an EF \leq 40%, showed that S/V significantly improved the LAVi, LVEDVi, LVESVi, and the mitral E/e' ratio when compared with enalapril.

Finally, in the PRIME²² study, S/V vs. valsartan provoked an evident decrease of the functional mitral insufficiency, with a reduction of the effective regurgitating area, of the LVEDVi and LAVi, and of the E/E' ratio. In support of these studies, a meta-analysis of seven clinical studies showed an improvement of the volumes and a reduction of the left ventricle hypertrophy compared with ACE inhibitors/ARBs, even after a short follow-up, already evident at 3 months.²³

Italian monocentric data reported an early and progressive benefit on left ventricular remodelling, identified through strain search but not through standard echocardiography, which instead identified benefits at 6 months.²⁴

On the basis of the considerations expressed so far, further and concrete evidence emerges towards the early use of S/V, offering the possibility of predicting, already at 3 months, not only a prognostic improvement but also a rise of the systolic function, through an early optimized therapy since hospitalization. This represents, in our opinion, a further useful element for the management of patients, for example defibrillator candidates in primary prevention, minimizing the arrhythmic risk related to the time needed for therapy optimization, while waiting for its positive effects on reverse remodelling and improvement of the EF.²⁵

The organizational background and the near future

Despite the guidelines have highlighted, and several Consensus documents even vigorously reiterated, that hospitalization for acute HF represents an important opportunity for clinical and therapeutic reevaluation and that the hospital is the ideal place to begin or uptitrate recommended drug, the usage of these treatments at discharge, although increased compared with hospital admission, is still unsatisfactory,²⁶⁻²⁸ despite the described long-term prognostic benefits.

This happens despite we learnt from the first registries on beta-blockers that if a patient did not start or was not discharged on a beta-blocker, he/she only had a 20% chance of continuing to take it during the outpatient phase.^{29,30} This situation represents an important 'gap' that needs to be overcome to ensure an effective and optimized treatment to the patient before discharge,³¹ thus limiting the risk of a lack of implementation of the recommended drugs, also subsequent to possible inter-current haemodynamic or renal instability.

The experience in Italy looks better, at least from a cardiological management perspective. According to the data collected in the BLITZ-HF³² study, hospitalized patients are discharged with a high percentage of recommended therapies (anti-aldosterone 76%, beta-blockers 87.7%, ACE inhibitors/ARB 75.1%), with a still low percentage for ARNI (4.6%), probably not very realistic in times when the evidence of hospitals implementation was not yet available, and the factual limitations of the therapeutic plan influenced their use. What, however, seems noteworthy is the low percentage of outpatient visits scheduled at discharge, about 44.6%, despite what is suggested by the literature^{2,3,33} and in the ANMCO^{34,35} Position Papers. Above all, it is important to note that these data were obtained from Cardiology Centers with a structured outpatient management of post-hospitalized patients. Furthermore, if we consider that hospitalization for HF is not prevalently managed by Cardiology Units but mostly by Internal Medicine Departments, these data appear even more critical and worthy of an organizational reflection.

The recent COVID-19 pandemic has also revealed a patchy adequacy of the territory management, confirming

the presence of area for organizational improvement necessary for an appropriate management of HF.^{34,35} The hospitals remain, at least for now while waiting for the remodulation of the post-COVID-19 outpatient system, a steady point for the patient hospitalized for HF, for his/her diagnostic and assessment potential as well as for therapeutic optimization.

In addition, in our opinion, a cardiological direction cabin is deemed fundamental for all patients hospitalized for HF, with the further need for an increasingly closer interaction between cardiologist and other professional figures, extending the recommended therapeutic implementation to the internal medicine units, as soon as possible.

Recommendations and proposals

All patients hospitalized for acute HF and an EF <40% should be considered potential candidates for S/V treatment, with the exception of patients with evident contraindications or history of angioedema.^{36,37} The clinical criteria and parameters to facilitate their identification are indicated in *Table 1*.

An immediate transition to valsartan³⁶ should be considered from the first day, in patients already in treatment with ACE-inhibitors, in order to avoid the 36 h break in the subsequent switch to S/V. The same attention and monitoring applied to the use of any drug with neurohormonal activity should be reserved to the implementation of S/V in patients with acute HF.^{37,38} The greater risk of hypotension requires particular attention, also in relation to the presence of concomitant hypovolaemia (often subclinical, aggressive diuretic therapy): in this case, our advice is, besides correcting the hypovolaemia, to review the diuretic dose in view of initiating S/V, and possibly a 12 h diuretic washout. However, we must consider that using S/V may potentiate diuresis and that the diuretic dose should be reduced or even suspended, before considering the patient intolerant to S/V.³⁹

The S/V dose titration is a prerogative of the drug and this partly affects the clinical long-term benefits. In hospitalized patients, however, our recommendation is to initiate with a low dosage (24/26 mg bid) and if possible increase it slowly.^{8,36,38} The message from the international literature is 'Go Slow',^{36,40} considering that the benefits demonstrated in the Pioneer-HF study in terms of efficacy and safety of S/V compared with enalapril are valid in all various dosages, even in patients that did not tolerate an initial titration towards the target dose.⁴¹

It is never pleonastic to emphasize that all discharged patients after acute HF should be included in a specific personalized follow-up programme. In this context, patients who have initiated S/V need an early reassessment for dose modulation,³⁷ and so do those patients who have not yet started S/V, but who can still benefit from an early post-discharge start, as evidenced by TRANSITION.⁷

Summary

Sacubitril/valsartan has shown to be effective in reducing clinical outcome in outpatients with chronic HF. Seven

Table 1 Clinical criteria and parameters for selecting patients hospitalized for acute heart failure for sacubitril/valsartan therapy

- Ejection fraction <40%
- *De novo* (consider it elective) or recurrent HF
- HF of any aetiology (carefully evaluation in case of early post-infarctual aetiology)
- Treated or not with ACE-inhibitor/ARBs
- eGFR >30 mL/min/1.73 m²
- K < 5.2 mEq/L
- No hepatic impairment (bilirubin >3 mg/dL) or prevailing fragility
- Stable patient
 - SBP ≥110 mmHg in the previous 24 h; (>6 h: SBP ≥100 mmHg, asymptomatic, no signs of peripheral hypoperfusion);
 - No diuretic dose increase in the previous 6-24 h;
 - No treatment with inotropes or vasodilators drugs in the previous 24 h
- If already on treatment, discontinue ACE-inhibitor 36 h before initiating S/V

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor antagonists; eGFR, glomerular filtration rate; HF, heart failure; SBP, systolic blood pressure; S/V, sacubitril/valsartan.

years after the publication of the PARADIGM-HF study, the potential and therapeutic spaces of this new pharmacological class have progressively expanded, supported by the results of several controlled studies and registries from the real world, confirming the benefit to other categories of patients. In particular, the evidence that the drug improves the systolic function through an early ventricular remodeling, and that it is widely tolerated and more effective than enalapril even in patients hospitalized for acute HF, as we can see from the randomized PIONEER-HF and TRANSITION trials, has extended the possibility of its use also to hospitalized acute HF patients. Although hospitalization is a prognostically negative event in the history of HF, it must become a management and therapeutic opportunity to be exploited, especially in times after the COVID-19 pandemic in which the outpatient and territorial organizational activities have been strongly challenged. The purpose of this ANMCO position paper is to provide the clinical cardiologist with a series of useful elements to encourage this line of behaviour in order to optimize the drug therapy before discharge in patients hospitalized for acute, *de novo*, or worsened HF and which has already been recommended and covered by the guidelines.

Data availability

The data that support the findings of this study are available from the corresponding author, GDT, upon reasonable request.

Conflict of interest: The Authors declare that there is no conflict of interest.

Disclaimers

This Position Paper was originally published in the Italian language in 'Position paper ANMCO: Utilizzo di sacubitril/

valsartan nel paziente ricoverato con scompenso cardiaco acuto', official journal of Italian Federation of Cardiology (IFC), published by Il Pensiero Scientifico Editore. Translated by a representative of the Italian Association of Hospital Cardiologists (ANMCO) and reprinted by permission of IFC and Il Pensiero Scientifico Editore.

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