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Research article

Benefits of sacubitril/valsartan administration and physical training in cardiac rehabilitation: current trends and bibliometric analysis of the years 2015-2024

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Abstract: Introduction. Heart failure, with its economic and social burden and increasing incidence in the general population, is a global problem. Since 2015, a new class of drugs with angiotensin and neprilysin re-ceptor inhibitory action, namely the combination of sacubitril and valsartan (S/V), has been introduced in the treatment of HF. The study aimed to perform a bibliometric analysis of the available knowledge and assess research trends through quantitative analysis of the literature related to the use of S/V and physical training in HF. Methods. In the study, we used the Web of Science database, period 2015-January 2024. The data obtained was processed with Vos viewer and Microsoft Excel. The results obtained and their interpretation provided an overview of the most relevant and prolific journals, countries, authors, and organizations. Conclusion. After marketing approval, the publication trend was upward until 2023, when the number of publica-tions decreased significantly. Our study shows that although the number of publications de-creased, updates of treatment guidelines were published, and a significant number of articles supporting the benefits of S/V treatment in chronic HF (with reduced or preserved ejection frac-tion) but also in acute forms were published. Although the number of articles on cardiac rehabilitation is low, this is highlighted in treatment guidelines and studies have emerged assessing the reasons why patients do not follow a cardiac rehabilitation programme. Cardiac rehabilitation is important for its physiological benefits: improving VO2max, myocardial blood flow and endothelial function. Health policies should be put in place to raise awareness of the importance of cardiac rehabilitation, including distances to a rehabilitation centre.

Keywords: sacubitril/valsartan; heart failure; cardiac rehabilitation; bibliometric analysis

1. Introduction

A comprehensive definition of heart failure has yet to be found, as this condition is one of the clinical syndromes that are easier to recognize than to define. The term heart failure, introduced by H. Vaquez in 1913, defines the inability of the heart to function normally [1]. Heart failure (HF), with its economic and social burden and increasing incidence in the general population (over the next decade), is a global problem [2]. The risk factors identified in the development of HF are hypertension, metabolic syndrome, sedentary lifestyle, dyslipidemia and smoking. Associated factors identified in HF are type 2 diabetes mellitus (T2DM), chronic kidney disease, and overweight [3].

The effectiveness of the currently administered medication is assessed by morbidity and mortality. The Food and Drug Administration (FDA) has approved a few drugs to reduce symptoms in chronic or decompensated HF and no drugs for treating HF with preserved ejection fraction (HFpEF). There are drugs recommended in HF to alleviate the characteristic symptoms of this pathology [2]. The results obtained by medication administration are modest. For this reason, ongoing research is being done to understand the pathophysiological mechanisms and to act therapeutically at the molecular level [4-6]. In the 1980s*, diuretics, digoxin and inotropic vasodilators were used; in the 1990s, milrinone and flosequinan were used in incipient forms with good results. This was followed by a series of studies evaluating mortality and morbidity, beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor antagonists (ARBs), mineralocorticoid receptor antagonists (MRAs) and isosorbide/hydralazine (Figure 1) [2].

The neurohormonal mechanism (sympathetic nervous system and renin-angiotensin-aldosterone pathway) is increasingly important. It has been shown that the introduction of drugs acting at this level reduces mortality and increases the quality of life of HF patients. The renin-angiotensin-aldosterone system regulates vascular tone (vasoconstriction) and blood pressure (renal sodium and water retention). Impaired cardiac function stimulates the renin-angiotensin-aldosterone system and sympathetic vegetative nervous system (VNS). Prolongation of this activation leads to cardiac edema (via water and Na retention), myocardial hypertrophy, fibrosis and apoptosis [7].

Figure 1. Medication administered in heart failure.

Progression of HF is characterized by damage to the structure and number of myocytes and, therefore, to the geometry of the left ventricle. Of course, drugs that will reverse this mechanism will be able to increase left ventricle function [8]. In the treatment of HF, the treatment aims to restore neurohormonal balance; despite treatment, the disease progresses.

Since 2015, a new class of drugs with angiotensin and neprilysin receptor inhibitory action (ARNI), namely the combination of sacubitril and valsartan (Entresto), also known as LCZ696, has been introduced in the treatment of HF [9]. The molecular formula is C96H120N12Na6O21 (PubChem, 23.12.2023). It has been clinically proven that international guidelines recommend combining two or more active substances in a single tablet [10].

1.1. The mechanism of action of sacubitril/valsartan (S/V)

1.1.1. Neprilysin activity

The natriuretic peptide has vasodilatory, diuretic, and neurohormonal effects; at the cardiac level, the effect stimulates myocardial relaxation and is anti-fibrotic. The enzyme that promotes natriuretic peptide degradation is neprilysin [11].

Neprilysin, a zinc-dependent metalloprotease, causes the degradation of vasoactive peptides (figure 2), resulting in vasodilatation that will decrease cardiac output. In addition to these vasoactive peptides, angiotensin (and its precursors) is also degraded.

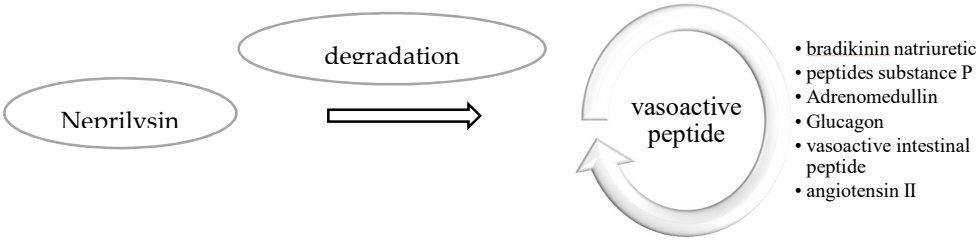


Figure 2. Vasoactive peptides influenced by neprilysin.

1.1.2. The mechanism of action of sacubitril

Sacubitril inhibits neprilysin (an endopeptidase distributed throughout the body, in the kidneys, central nervous system, lungs, intestines, neutrophils, fibroblasts and endothelial cells) and causes blood pressure reduction. It is a precursor of sacubitrilat (figure 3), which acts on neprilysin (with a role in degrading vasoactive peptides) [12]. The inhibitory effects of neprilysin (natriuretic, vasodilator and antiproliferative) are limited in the treatment of hypertension and HF. The combination with valsartan confers a pluripotent action, and its efficacy in resistant hypertension has been proven [13].

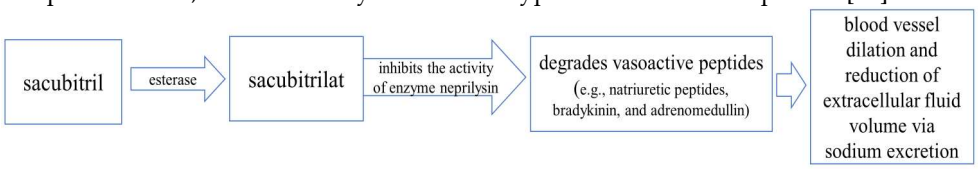


Figure 3. Mechanism of action of sacubitril.

1.1.2. The mechanism of action of valsartan

Valsartan was approved in 2002 for the treatment of HF; it has a role in reducing mortality through its angiotensin I receptor-blocking effect [14, 15]. Therefore, Entresto is a fixed-dose combination of sacubitril and valsartan, approved for the treatment of heart failure because of neprilysin inhibitor (sacubitril) and angiotensin I receptor blocker (valsartan). Yancy CW et al. (2016) support the recommendation that S/V replace HF treatment with reduced ejection fraction [16-18].

1.2. Effects of S/V and physical exercise on cardiac rehabilitation

The pathophysiological mechanisms of S and V, through inhibition of ventricular remodeling, antifibrobic effect [19, 20]], improvement of serological indicators underlie the increase in physical performance. Improvement of cardiac function, in patients with chronic S/V treatment, supporting the importance of S/V in cardiac rehabilitation [21].

It was long considered that recovery had no benefit in HF patients, moreover, it was even banned especially with congestive forms. Rest is recommended for certain periods. Physical exertion remains to be recommended correlated with the functional status of the myocardium. Exercise is a diagnostic and prognostic tool in addition to its therapeutic role. Physical training has a role in primary prevention but also in secondary prevention. A number of studies support the correlation between cardiorespiratory fitness and risk of cardiovascular disease and mortality [22].

Functional, structural, cellular and molecular adaptations of the heart have been shown to occur following the adoption of a specific physical training program [23]. Lower physical activity (assessed with valid questionnaires) is associated with higher incidence of HF [24].

Cardiorespiratory fitness has been shown to have an inverse relationship with HF risk. Increasing exercise capacity by one MET (study of 20,642 participants, mean age 49 years) reduces the risk of hospitalization by 20% [25]. Published work on large cohorts has

demonstrated associations between higher fitness levels and favourable left ventricular structure and function.

According to the Heart Failure Association Guidelines moderate exercise is recommended in HF. Aerobic training can be continuous, moderate intensity or interval training. Physical training stimulates the peripheral mechanisms of adaptation to exercise so that cardiac function will not be impaired. A symptom-limited exercise test is recommended before starting training.

Heart rate (HR), dependent on the degree of myocardial damage, is correlated with sympathetic tone. The effect of exercise training on sympathetic hyperactivity is less and therefore on HR. The increase in exercise capacity is achieved without alteration in EF of SV and without increase in pulmonary capillary pressure; therefore, cardiac output does not increase, SV performance is not influenced. Physical training stimulates the release of a relaxing factor in the vascular endothelium, with reduced sympathetic vasoconstrictor effect. The role of physical training in HF patients is to prevent deconditioning. In this respect, it is recommended to implement a concrete training programme. Thus it is recommended: daily training at home and 3-4 times a week in a rehabilitation centre. Recommended exercise intensity is low, up to 70-85% of maximal HR obtained on exercise test, but not exceeding 135-140 beats/minute. On the Borg scale it is recommended not to exceed 12-14 effort intensity level.

Supervised aerobic exercise is recommended with a warm-up period at the beginning of the exercise and a cool-down period at the end. Training duration is between 20-60 minutes 3-5 days a week at 50-80% of maximum exercise capacity [26]. There are studies that have proven the superior effectiveness of high intensity interval training [27].

1.3. Bibliometric analysis

Bibliometrics is a science that deals with „the organization, ranking and evaluation" of scientific publications at different levels (institutions, country, World) [28]. Through quantitative evaluation of publications, bibliometric analysis provides information on research and publication trends in various fields. The choice of database and search algorithm is essential to obtain the analysis, so the Web of Science (W.o.S) database was chosen as it comprises most of the relevant papers and has also citation indexing capability [29].

The study aimed to perform a bibliometric analysis of the available knowledge and assess research trends through quantitative analysis of the literature related to the use of S/V and exercise in cardiac rehabilitation of HF patients. The results obtained and their interpretation will provide an overview of the most relevant and prolific journals, countries, authors, and organizations.

2. Results

2.1. Publication output and temporal trend

Articles published between 1975-2024 (24.01.2024) were selected for bibliometric analysis and mapping. A total of 6064 publications were identified; after eliminating corrections, book chapters, reprints, and reissues, 5271 articles (3070 articles, 835 review articles, the rest meeting abstracts) belonging to 138 categories were identified; an article can be classified into several categories.

In the following, we refer to the period 2015 (the year of approval of the therapeutic combination S/V) – 2024 (24.01.2024). We identified 3046 publications (2301 articles and 745 reviews) belonging to 118 categories. The following categories had the highest number of allocated manuscripts: Cardiac Cardiovascular Systems 1357 (44.55 %), Pharmacology Pharmacy 484 (15.89 %), Medicine General Internal 273 (8.96 %), Biochemistry Molecular Biology 177 (5.811 %), Neurosciences 167 (5.48 %). Figure 4 represents, in a format of Treemap, the top ten W.o.S. categories.

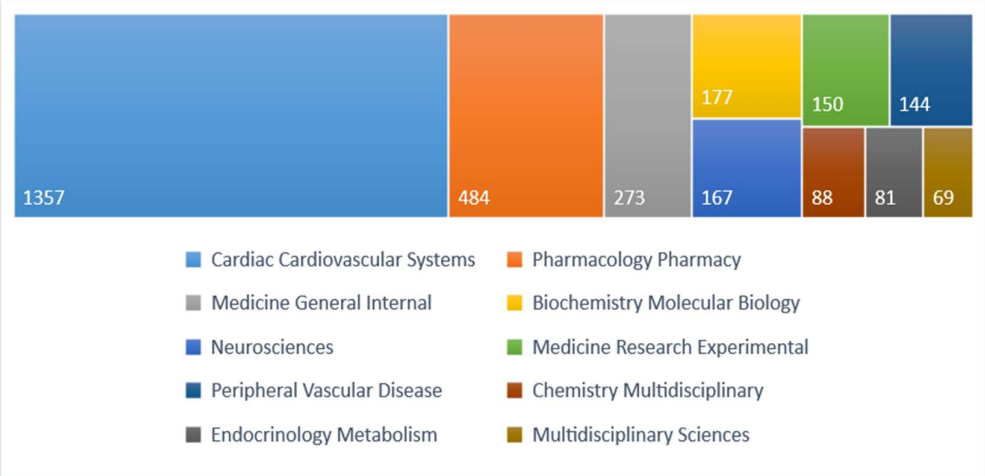


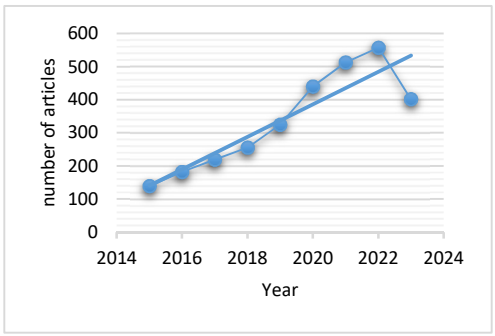
Figure 4. Treemap visualization of Categories by W.o.S.

The data analysis shows that the publication trend has increased since 2015 (over 100 articles, review/year, N=139). The increasing trend is maintained until 2022 (N=557), followed by a decrease in 2023 (N=402) (Figure 5a). figure 5b), and the remaining 2.24% were published in other languages (Russian, Spanish, Italian, French, etc.).

2.2. Assessment of the Most Prolific Nations

During the period under review, the total number of nations contributing to scientific output was 106. The United States remains the most significant contributor of published papers (1011, 33.19%) (Figure 5d). The average citation/paper published by the United States is 33.22, indicating that these papers significantly impacted the field. China ranks second in terms of the number of articles that have been published (481, 15.79%) and has an average citation/article of 16.23. In third place is Italy, with 374 articles (12.28 % of articles published) and an average citation/article of 24.13, ranking it higher. Regarding citations, the top places are Scotland, with an average of 60.79 citations/article (169 articles) and Canada, with an average of 53.70/article (196 articles). The top 10 contributing nations (number of articles and total number of citations) are shown in figure 5c.

The top 10 institutions researching S/V are included in Figure 5d (number of articles/citations). The three most productive institutions are Harvard Medical School/Harvard University (United States), Novartis Pharmaceuticals (Switzerland), and Brigham Women's Hospital (United States).



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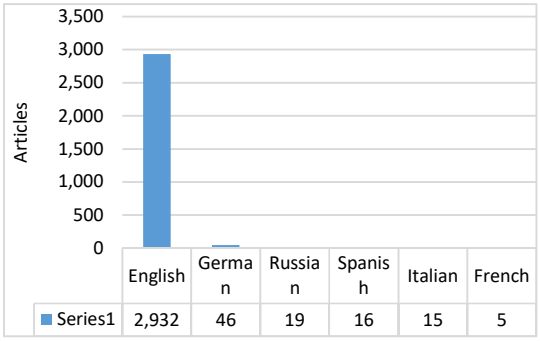

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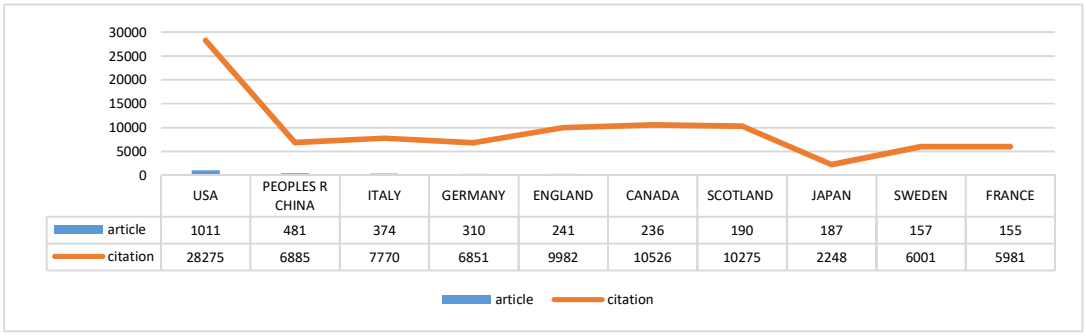

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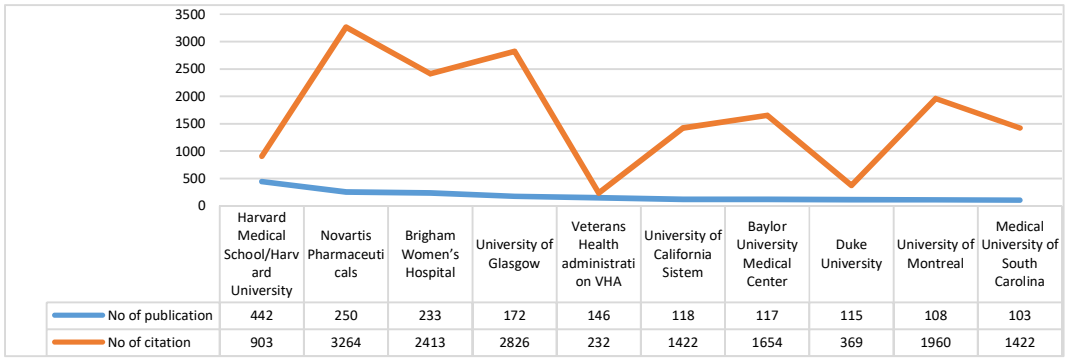


d.

Figure 5. a. No. articles/year; b. distribution according to language; c. the number of citations/articles/countries; d. top 10 productive institutions conducting research on S/V.

2.3. Distribution by journal

The 3046 publications were published in 199 journals. The most significant publications that published articles containing the keywords mentioned are listed in Table 1. ESC HEART FAILURE published the most articles containing the selected keywords, representing 3.54%. In second place is the EUROPEAN JOURNAL OF HEART FAILURE with 101 articles, and in third place is JACC HEART FAILURE with 66 articles. In terms of average citations/article, CIRCULATION (n=178.76) ranks first, followed by JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY with 102.51 citations/article, but the number of articles published in CIRCULATION is 25. The most cited journal is the NEW ENGLAND JOURNAL OF MEDICINE (8798 citations), with an impact factor of 158.5 (2022). It is followed by CIRCULATION (7436 citations) with IF 37.8, JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY (6144 citations). Table 1 lists in descending order the top 10 journals and the number of co-cited and Figure 6, obtained with VoS viewer, shows the collaborations between the journals.

Table 1. Top 10 productive journals and co-cited journals publishing research on S/V.

Journals	No. of Papers	No. of Citations	Average No. of Citations/ Article	Publishing Entity	Source	Co-citation	TLS
ESC HEART FAILURE	108	1121	10.38	WILEY PERIODICALS, INC	NEW ENGLAND JOURNAL OF MEDICINE	8798	790984
EUROPEAN JOURNAL OF HEART FAILURE	101	3702	36.65	WILEY, HOBOKEN, NJ	CIRCULATION	7436	844540
JACC HEART FAILURE	66	2396	36.30	ELSEVIER KIDLINGTON, OXON, ENGLAND	JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY	6144	78558
FRONTIERS IN CARDIOVASCULAR MEDICINE	55	196	3.56	FRONTIERS MEDIA SA, LAUSANNE, SWITZERLAND	EUROPEAN JOURNAL OF HEART FAILURE	6056	510538
INTERNATIONAL JOURNAL OF MOLECULAR SCIENCES	45	323	7.17	MDPI, BASEL, SWITZERLAND	EUR HEART J	4513	417348
JOURNAL OF CLINICAL MEDICINE	45	302	6.71	MDPI, BASEL, SWITZERLAND	LANCET	3576	356082
CIRCULATION HEART FAILURE	44	1836	41.72	LIPPINCOTT WILLIAMS & WILKINS PHILADELPHIA, PA	JACC HEART FAILURE	2331	274535
JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY	43	4408	102.51	ELSEVIER SCIENCE INC.	CIRCULATION HEART FAILURE	2293	288201
INTERNATIONAL JOURNAL OF CARDIOLOGY	41	409	9.98	ELSEVIER IRELAND LTD, IRELAND	HYPERTENSION	1865	165958
SCIENTIFIC REPORTS	39	255	6.53	NATURE PORTFOLIO, BERLIN, GERMANY	JAMA-J AM MED ASSOC	1860	249782

TLS - Total link strength.

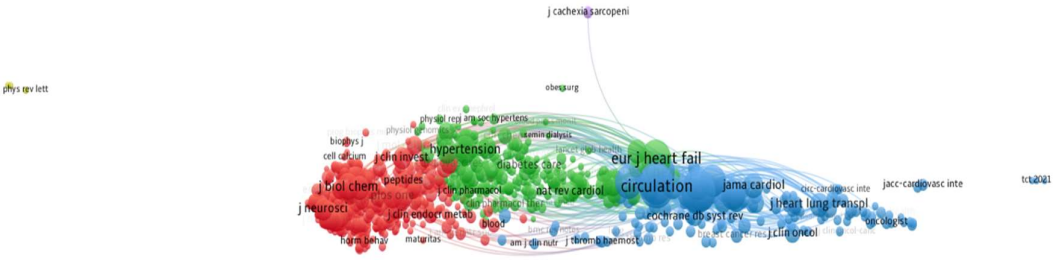


Figure 6. Collaboration analysis of journals (TLS).

2.4. Distribution by author

The 3046 publications were published in 199 journals. A total of 200 authors have published 3046 articles and reviews. The most productive authors are Solomon SD, with a total of 155 articles, with an average of 46.99 citations/article, followed by Packer M., with 107 articles, with an average of citations of 64.45. McMurray JJV comes third with 92 articles, and the average citation/article is 63.23 (Table 2). Regarding citations, Zile MR

leads with an average of 69.50/article. Figure 7 shows co-citations between authors (VoS viewer).

Table 2. Top 10 most productive authors and most cited authors.

Author	Count	First author's affiliation	No. of citations	Average no. of citations	H-index	Co-cited author	No. of citations	TLS
Solomon SD	155	Harvard Medical School	7284	46.99	132	McMurray, John J. V.	2608	75174
Packer M.	107	Baylor University Medical Center	6896	64.45	82	Packer M	1558	75297
McMurray J.J.V.	92	University of Glasgow Medical	5818	63.23	184	Solomon SD	1291	49773
Zile M.R.	81	University of South Carolina	5630	69.50	78	Yancy CW	861	32581
Desai A.S.	74	Harvard Medical School	3928	53.08	73	Ponikowski P	859	28793
Butler J.	68	University of Mississippi	3377	49.66	101	Pitt B	696	34155
Swelberg K.	64	University of Gothenburg	4352	68.00	95	Desai AS	518	20315
Rouleau J.	61	University of Montreal's Faculty of Medicine	4007	65.68	69	Yusuf S	492	25372
Vaduganathan M.	60	Harvard Medical School	2167	36.12	65	Swedberg K	454	21959
Jhund P.S.	56	University of Glasgow	2858	51.03	66	Velazquez EJ	433	18164

TLS - Total link strength.

2.5. Analysis of co-cited references

The most cited articles, published between 2015 and 2024 (January) are listed in Table 3. At the ranking top is ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the exceptional contribution of the Heart Failure Association (HFA) of the ESC, from 2016, author P Ponikowski et al. (N=602 citations). It is followed by the article published by EJ Velazquez et al. (2019), entitled "Angiotensin-Neprilysin Inhibition in Acute Decompensated Heart Failure", with several 354 citations.

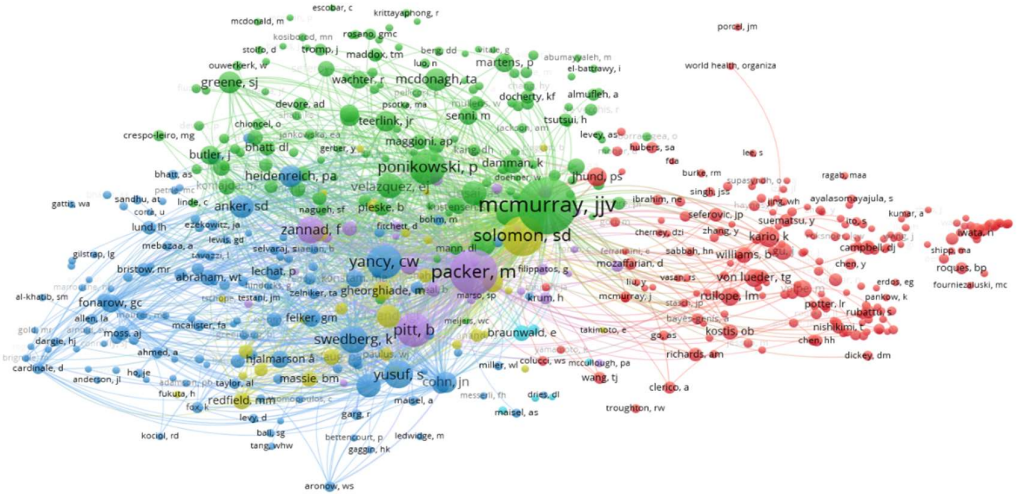


Figure 7. Map with the most important co-citations between authors who published articles with S/V.

The third place is occupied by the article "Angiotensin-Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction" published by SD Solomon et al. Table 3 shows that 4 of the top 10 most cited articles are published in the NEW ENGLAND JOURNAL OF MEDICINE. The most cited article in the period evaluated is published in the EUROPEAN JOURNAL OF HEART FAILURE.

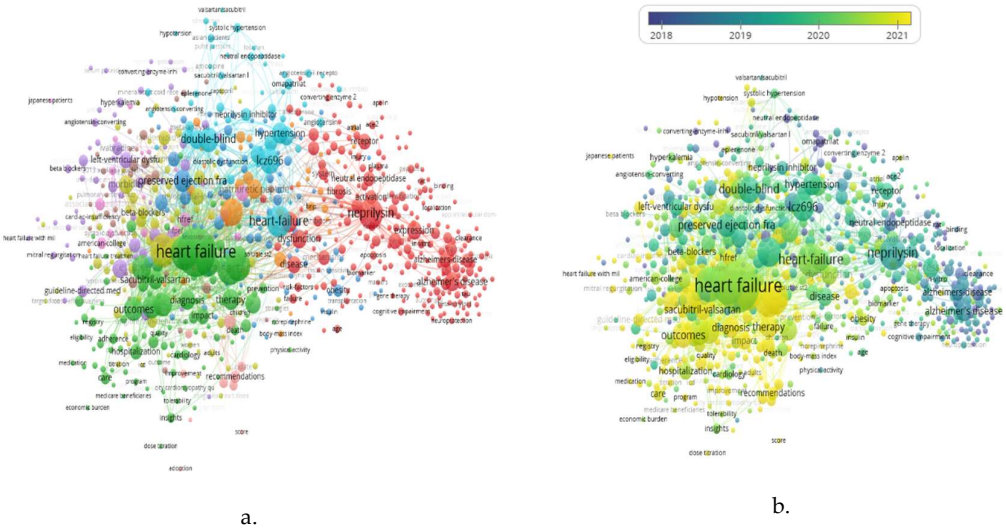
Table 3. Top 10 co-cited references in the field of S/V research.

Main Author (Year)	Title of the Paper	Scientific Periodical	Citations	TSL
P Ponikowski et al. (2016)	2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC	EUROPEAN JOURNAL OF HEART FAILURE	602	8914
EJ Velazquez et al. (2019)	Angiotensin-Neprilysin Inhibition in Acute Decompensated Heart Failure	NEW ENGLAND JOURNAL OF MEDICINE	354	6566
SD Solomon et al. (2019)	Angiotensin-Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction	NEW ENGLAND JOURNAL OF MEDICINE	328	6034
M Packer et al. (2015)	Angiotensin receptor neprilysin inhibition compared with enalapril on the risk of clinical progression in surviving patients with heart failure	CIRCULATION	307	5433
JV McMurray et al. (2019)	Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction	NEW ENGLAND JOURNAL OF MEDICINE	304	5956
CW Yancy et al. (2017)	ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America	CIRCULATION	242	3989
JV Januzzi Jr. et al. (2019)	Association of Change in N-Terminal Pro-B-Type Natriuretic Peptide Following Initiation of Sacubitril-Valsartan Treatment with Cardiac Structure and Function in Patients with Heart Failure with Reduced Ejection Fraction	JAMA	221	4125
M Packer et al. (2020)	Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure	NEW ENGLAND JOURNAL OF MEDICINE	214	4457
AS Desai et al. (2015)	Effect of the angiotensin-receptor-neprilysin inhibitor LCZ696 compared with enalapril on mode of death in heart failure patients	EUROPEAN HEART J	155	3370
AS Desai (2019)	Effect of Sacubitril-Valsartan vs Enalapril on Aortic Stiffness in Patients with Heart Failure and Reduced Ejection Fraction: A Randomized Clinical Trial	JAMA	147	3018

2.6. Keyword analysis

For analyzing the authors keywords, we used VOS viewer. The number of keywords in all considered articles was 4014. Keywords that appeared at least five times were

considered. The number of selected keywords was 309. The analysis results in 14 clusters; keywords are distributed according to the type of studies: clinical, paraclinical, cost-effectiveness, guidelines, pharmacovigilance, mechanisms of action, clinical and paraclinical manifestations, and therapeutic responses of other organs. The most common were heart failure (n=962), sacubitril (n=405), S/V, neprilysin, heart failure with reduced ejection fraction, LCZ696, ARNI, Alzheimer's disease". The map of keyword co-occurrence is shown in figure 8a. The size of the bubbles is proportional to the frequency of occurrence of the keywords. In figure 8b., blue to yellow colors show the years of the appearance of the articles, and light colors indicate more recent articles.



a. b.

Figure 8. a. Analysis of the keywords used in the articles analysed with VOS viewer. b. The map with the time overlaps of the keywords.

2.7. Cardiac rehabilitation

The role of S/V in cardiac rehabilitation together with exercise is supported by 9 articles and a review, period 2020-2023. Rehabilitation of HF patients is an important aspect of therapy, especially those with HFrEF. Therapeutic guidelines emphasize the support of drug treatment with specific physical training performed in cardiac rehabilitation wards. In the most cited article (3366) from 2022, AHA/ACC/HFSA Guideline for the Man-agement of Heart Failure: Executive Summary: A Report of the American College of Cardi-ology/American Heart Association Joint Committee on Clinical Practice Guidelines published by PA Heidenreich et al. [30], cardiac rehabilitation and the level of activity the HF patient should follow are supported, along with instructions on medication, diet and weight monitoring. The importance of physical training in reducing mortality and hospitalisations is supported. Initiation of physical training is recommended under medical supervision, after an assessment of exercise capacity. Strength, balance, mobility and endurance exercises are recommended. Meta-analyses show that cardiac rehabilitation leads to an increase in the duration of training gradually in a HF patient and thus to an increase in quality of life.

3. Discussion

This study, containing a bibliometric analysis, follows research trends on S/V treatment, the first approved combination for treating HF with reduced ejection fraction. In 2017, following the American College of Cardiology/American Heart Association/Heart Failure Society of America (ACC/AHA/HFSA) guideline update, the combination was introduced into HF management. Studies have been published evaluating clinical outcomes, mechanisms of action, safety and efficacy of administration of the preparation, and adverse reactions (hypotension, angioedema, oliguria, progressive azotemia,

diarrhea, acute tubular necrosis and renal failure) [31] that occurred following the treatment with S/V. Studies support the efficacy of S/V through its unique mechanism of action by combining the effects of the two components. Anti-remodeling and cardioprotective effects have been reported [32]. Another aspect evaluated was the mortality rate and readmission rate [33].

Superior results have been demonstrated in terms of improvement of HF symptoms, death rate, and readmission rate in HFrEF patients on S/V compared to enalapril (standard of care) [34], results also supported in the PARADIGM-HF study [32].

The number of publications on S/V has increased considerably if we refer to the bibliometric analysis published in 2021 (Lai P et al.). A total of 1309 publications were reported from 1995 to 2021. In contrast, after the approval of the marketing of the combination for symptom control in HF, from 2015 to 2024, 3046 publications were identified (articles and reviews). However, in 2023, the trend decreased in publications (328 articles and 100 reviews). The explanation is not, the lack of interest in S/V research; clinical trials require considerable follow-up time.

We still followed the research directions in 2023. Studies have been focused on the pathophysiological mechanisms and mode of action of sacubitril combined with valsartan [35], long-term treatment efficacy, incidence of adverse reactions, and development or updating of treatment guidelines.

3.1. Guidelines published in 2023

Lisi Dm published significant changes to the HF treatment guidelines. It places the S/V combination as the first recommendation without initial dose titration [36]. Also, in 2023, the ESC Scientific Document Group published updates to the treatment of HF, *2023 Focused Update of the 2021 ESC, Guidelines for the diagnosis and treatment of acute and chronic heart failure* [37]. Kaplon-Cieslicka, A et al. published a practical guideline for treating HF, in which increased emphasis is placed on individualizing treatment according to cardiac and extracardiac comorbidities [38].

3.2. Evaluation of cardiovascular risk factors associated with HF

The prevalence of hypertension is high (about 47% in the U.S.), and several classes of drugs are used to treat it. However, many treatment-resistant cases have been recorded [39].

According to the review published by Krishnarao, K and Krim, SR, resistant hypertension occurring in patients with post-ventricular assist device (LVAD) implants may benefit from treatment with ARNI, especially for patients with CF-LVAD [40]. The S/V treatment applied to patients with HF after AMI (acute myocardial infarction) proved to be more efficient than ACEi/ARB [41]. Meta-analysis performed in 2023 (N=17,541 patients) assessed whether there were significant differences in the association of HF risk factors with ARNI versus ACEI/ARB treatment; results did not demonstrate improvement in cardiovascular events in HF patients associated with ARNI treatment [42]. The antihypertensive effects of S/V are superior to olmesartan in controlling hypertension, as supported by the meta-analysis of Almarjan, AI et al. [43].

3.3. Pathophysiological mechanisms in HF and mechanisms of action

Several studies evaluate the pathophysiological mechanisms in HF and the mechanisms of action of S/V [8, 11, 44-52]. The 36-patient study published by Karaayvaz, EB and Güz, G, supports the alteration of dynamic coronary flow characteristics in patients with HFrEF [53]. S/V effects on inhibition of ventricular remodeling in patients with AMI after percutaneous coronary intervention are beneficial in preventing HF occurrence [19]. Some studies also assess inhibition of ventricular remodeling by S/V administration [35, 54-56]. Lee, VV et al. evaluate the antifibrotic potential of S/V in hypertensive heart disease [20]. The prospective study (N=11 patients) published by Nakamura, A et al. followed the effects on plasma natriuretic peptide levels and myocardial remodeling after switching S/V treatment with angiotensin receptor blocker (ARB). The results showed that changing therapy favored worsening HF and return of

myocardial remodeling [57]. In patients with HFrEF (An Analysis of the PARADIGM-HF Trial), a higher cGMP (Cyclic Guanosine Monophosphate)/BNP (B-Type Natriuretic Peptide) ratio was associated with better outcomes [58].
Another aspect followed by published studies has been the pathophysiological mechanisms and effects of ARNI on pulmonary hypertension in HF [59-61].

Neprilysin is known to interfere with lipid metabolism. Engeli S et al. published the results of a multicentre study in which they followed the effect of S/V on lipolysis and adipose tissue during rest and exercise for 8 weeks. This study does not support the hypothesis that the cardiovascular effects of S/V are associated with changes in lipid metabolism during exercise [62].

3.4. Effects on mortality and the number of admissions

Based on the PARADIGM-HF study which demonstrated decreased mortality and readmissions in HFrEF patients treated with S/V, the REAL.IT study was conducted (study period 2016-2019). The number of patients included in the study was 924. The study showed increased ejection fraction and decreased NYHA class (III to II in 37% of patients evaluated). Hospitalizations for HF were 19.6% and the death rate (during the follow-up of patients) was 3.8%, but only 1.3% from vascular causes [63]. The financial-economic impact of S/V treatment in patients with HFrEF versus those treated with enalapril was also analyzed. Although initial costs are high, costs decrease by reducing readmissions [64]. Argentina's cost per life-year (relative to quality) favored S/V over enalapril [65].

3.5. Therapeutic efficiency of S/V in HF and titration of S/V doses

Many articles and systematic reviews have aimed to evaluate the therapeutic efficacy and safety of administering S/V at different doses [44, 66]. The study by Dattilo G et al. on 70 HFrEF patients treated with S/V, monitored for 60 months, demonstrated reduced NT-pro-BNP values and improved sonographic parameters; the 6MWT and Kansas City Cardiomyopathy Questionnaire gait test were statistically significantly increased. All evaluated clinical and paraclinical parameters improved continuously over the five years without reaching the plateau phase [67].

Butt JH, along with Scott Solomon, John J.V. McMurray, Zile MR, and Milton Packer (first authors ranked in the top 10 most productive authors), examined the relationship between red cell distribution width (considered a prognostic marker in patients with HF) and the results of S/V administration compared with valsartan. S/V resulted in a slight reduction in red cell distribution width [68].

The randomized, double-blind trial (PARACYS-RV) published by Chaix, MA et al. studied the efficacy of S/V in HF patients with systolic dysfunction of a morphologic right ventricle in the systemic position [69]. The incidence of mortality in HF patients treated with S/V was lower than in those treated with enalapril, and hemoglobin levels decreased less in S/V patients [70]. The study published by Zhao D highlights the effects of S/V on the improvement of the NYHA class.

3.6. *Safety of administration in HF associated pathologies*

The safety and efficacy of ARNI administration in association with reduced renal function in patients with HFrEF has been debated in several articles and reviews [71-80]. The study published by Liu et al. (2023), including 65 patients, supports decreased readmissions in patients with HF associated with end-stage renal disease (dialysis patients) [78, 81]. The increased incidence of diabetes mellitus leads a considerable number of articles to refer to the association of diabetes with HF [82, 83].

Another article published by Hu WS et al. estimated the incidence rate of dementia in patients treated with ARNI (reported per 1000 person-years). A lower risk of developing dementia in these patients is claimed [84]. However, studies in rats (N=72) show an increased risk of Alzheimer's disease and worsening of tested parameters [85].

Khan MS et al., in their published review, present current challenges and attempt to define future directions for optimizing HF management in patients with diabetes and chronic kidney disease [86, 87].

Improved nutritional status has been shown in elderly patients with HF (N=55) who underwent treatment with ARNI, with dose adjustment according to the patient's blood pressure [88]. Pulmonary hypertension (pre- and postcapillary) may benefit from treatment with ARNI [89].

Clinical trials have examined the association of ARNI treatment with improvement in cardiovascular events due to atherosclerosis without any results being shown (meta-analysis by Ravani, LV [90]. Cardio ankle vascular index improves with increasing dose of ARNI [91]. A study of 409 patients with HFrEF and irreversible myocardial injury treated with ARNI from 2017-2020 shows treatment efficacy, regardless of HF etiology [92].

A retrospective study included 204 patients with HFpEF, LVEF (left ventricular ejection fraction) ≥40%, treated with S/V from October 2020 to March 2022, followed by up-titration (dose increase above 24/26 mg BID) over 12 weeks. The study shows that approximately half of patients included in treatment did not undergo up-titration; less than 10% of patients included in treatment discontinued S/V treatment [93]. The prospective, single-center study (N=250), conducted between 2015 and 2021, evaluated the effect of the S/V versus V combination on atrial volume index (by MRI measurement) in patients with pre-HFpEF. The results are superior when administering the S/V combination [94].

3.7. *Association with SLGLT2 inhibitors*

A meta-analysis published by Huang Y et al. evaluates the efficacy concerning several hospitalizations, death rates, and renal function outcomes in the context of a combination of ARNIs with SLGLT2 inhibitors in HFrEF patients, reporting superior results compared to monotherapy with ARNIs or SLGLT2 inhibitors [95, 96].

The benefits of combining the two types of inhibitors are supported by some other articles [97-105]. Combination therapy is not effective in reducing mortality in patients with non-ischemic dilated cardiomyopathy (NIDCM) with implantable cardioverter defibrillators [106]. The Empire HF trial (Larsen, JH et al.) followed the effect of ARNI on the outcome of empagliflozin administration on cardiac structure and function [107].

3.8. *Safety and tolerability*

Mark C. Petrie, along with prolific authors Scott D. Solomon and John J.V. McMurray, published the PARADISE-MI Trial, comparing the effects of S/V with ramipril in patients with AMI (N=5661 patients with AMI and EF≤40%)[108]. Alkhuraisi F et al. published a study on physician adherence and patient dose tolerance (N=450 patients), highlighting the importance of standardized protocols [109]. The applicability of ARNI treatment in HFrEF, HF with preserved ejection fraction (HFpEF), and improved ejection fraction (HFimpEF) from the perspective of Indian cardiologists is studied [110].

A systematic review published by Jain, A et al. supports decreased hospitalization rates, improved Kansas Quality of Life scores, and decreased side effects after S/V versus enalapril [111]. An 18-month retrospective study of 122 patients with acute decompensated HF supports the safety and efficacy of S/V treatment in these patients [112]. Post hoc analysis (N=104 patients) of the TRANSITION Study, comparing initiation of S/V before and after discharge of patients, supports a low treatment discontinuation rate [113]. A retrospective study supports a 5-year mortality rate reduced by 17.3%, improvement in long-term FEVS and NT-proBNP levels and good nutritional status [114]. The multicenter PANORAMA-HF study (phase II/III) followed the efficacy of administration in children with HF. Children were divided into three groups according to age (6-18 years, 2-6 years, <2 years) [115]. Also, older adults with HFrEF may benefit from S/V treatment, according to the published narrative review by van der Linden, L et al [116]. The systematic review by Haddad CN et al. shows promising effects in improving cardiac function in patients with Duchenne muscular dystrophy cardiomyopathy [117]. Evidence has also been obtained regarding improving biventricular systolic function and neurohormonal activation by administration of ARNI in congenital heart disease patients

(N=35 patients) [118]. Based on the stroke risk patient model, I-Preserve and PARAGON-HF study, (N=8924) identified a subset of patients at increased risk of stroke; for this reason, prophylactic anticoagulation is justified [119]. Arriola-Montenegro J et al. studied the safety of S/V administration in patients with non-alcoholic fatty liver disease associated with HFrEF [120].

3.9. Anti-arrhythmic effect of S/V

Treatment with ARNI has been associated with a reduction in ventricular arrhythmias after switching to ACEi/ARB, result supported by the systematic review published by Pozzi, A. et al. [121] but does not reduce the risk of atrial fibrillation [122]. Another retrospective study (2017-2022, N=170) followed the progression of atrial fibrillation in patients treated with ARNI. The study's results support the superiority of ARNI versus ARB in decreasing the risk of progression from paroxysmal to persistent form [123]. The study published by Zhu MX et al. does not support the superiority of S/V versus V treatment on nonvalvular atrial fibrillation in patients without HF. S/V is not superior to valsartan for short-term treatment of AF patients without HF in terms of improvement of NT-proBNP levels and cardiac function [124].

3.10. Adverse reactions

An adverse reaction that requires careful monitoring as BP is arterial hypotension; its prevalence is 16% [114]. Neprilysin inhibitors interfere with bradykinin catabolism, which plays a role in triggering drug-induced angioedema [125]. Reported adverse effects on renal function are infrequent, but they should be monitored during S/V administration [126]. A case of alopecia has been reported as an adverse reaction [127].

3.11. Phenomapping

Phenomapping published by Sung, KT et al. gathers information on cardiac characteristics of HF patients on S/V treatment [128].

3.12. Cardiac rehabilitation

The role of S/V in cardiac rehabilitation is supported by 9 articles and a review, period 2020-2023. Rehabilitation of HF patients is an important aspect of therapy, especially those with HFrEF. There are a small number of studies (RCTs) evaluating the quality of life of HFrEF patients. Meta-analysis (458 studies) published in 2023 by Bhattacharjee P and Khan Z, followed exercise tolerance and quality of life of HFrEF patients. The results support the improvement in quality of life of HFrEF patients compared to the control group [129].

Therapeutic guidelines emphasize the support of drug treatment with specific physical training in cardiac rehabilitation wards. However, cardiac rehabilitation is insufficiently recommended. The study published by Alexandre A et al (2022) followed the barriers to enrolling patients in a cardiac rehabilitation programme [130]. The Cardiac Rehabilitation Barriers Scale was used for 214 patients with HFrEF. Only 35% of the patients interviewed followed cardiac rehabilitation treatment (34% of these patients were following S/V treatment). The reasons (highlighted by patients) for not following rehabilitation treatment were lack of medical indication (31%), presence of associated pulmonary disease, patient refusal (11%) and distance to a rehabilitation centre (9%).

A multicenter study (2023) of 234 patients with HFrEF (67% S/V-treated patients), followed up for 3-6 months, shows that only 20.6% of patients included in the study were recommended to continue treatment in rehabilitation wards with the main indication HF [131]. For the assessment of exercise capacity in HF patients, most studies use the 6-minute walk test (6MWT). A result below 350 m indicates an increased risk of mortality and an increase in walking distance by 50 m is considered relevant. Sgorbini L et co (2017) published a study supporting an increase in walking distance of 436 m in patients included in the study after one month of S/V at the maximum dose [132].

Study of 81 patients with acute myocardial infarction and left HF after percutaneous coronary intervention (PCI), published by Chen C et al in 2021, demonstrates increased walking distance (6-minute walk test) in patients with S/V-associated treatment compared to the control group. Also, heart rate was lower during the test and no significant differences were reported in relation to O2 saturation. This performance is explained by the improvement of serological indicators and cardiac function, underlining the importance of S/V in cardiac rehabilitation [21].

The 12-month study (N=134 HFrEF patients) published by Giallauria, F et al (2020) highlights the favorable effects of S/V therapy on autonomic function, functional capacity and ventilation [133].

The study of 98 patients, published by Wang, YY (2021), highlights the significant improvement in scores of the Minnesota living with heart failure ques-tionnaire, the self-assessed anxiety scale (SAS) and the self-assessed depression scale (SDS) in patients who underwent a physical training program. Cardiopulmonary function was significantly improved by increased exercise capacity. Echocardiographic and serological parameters (NT-proBNP and hscTnT levels) also improved [134].

The OUTSTEP-HF prospective, randomised, double-blind study, published in 2020 by Massimo F. Piepoli, Edelmann, F et co., compared the effects of S/V treatment and physical training versus enalapril and physical training. They evaluated 621 HFrEF patients randomized 1:1 for 12 weeks. Over the course of the study, the 6MWT showed an increase in walking distance of more than 30 m in 51% of patients in the S/V group. At the end of treatment the results showed no statistically significant differences in the 6MWT, non-sedentary physical activity and HF signs [135, 136].

The SILICOFCM study (Tafelmeier M et co., 2020) followed the effect of S/V and lifestyle on cardiac functional capacity [137]. The PARALLAX study (Sanjiv J Shah et co, 2021), the largest study providing in-formation on associations between quality of life and exercise capacity in patients with HF and preserved ejection fraction treated with S/V [138].

Regarding the contribution of publications by country, the USA remains in first place; China follows it, ranked seventh in the 2021 bibliometric analysis [16]. The number of publications on S/V has increased considerably if we refer to the year 2021 (Lai et al.). A total of 1,309 publications were reported from 1995 to 2021, whereas after the approval of the marketing of the combination for symptom control in HFrEF from 2015 to 2024, 3,046 publications were identified (articles and reviews).

Regarding the contribution of publications by country, the USA remains in first place (1011 articles), followed by China (481 articles). Italy, previously in second place with 177 articles [16], moves to third place with 374. In the top of most cited articles, Scotland leads (60.79 citations/article), followed by Canada with an average of 53.70 citations /article. Sweden was first in the previously published analysis, with Scotland in second.

ESC HEART FAILURE, EUROPEAN JOURNAL OF HEART FAILURE, and JACC HEART FAILURE remain the most productive journals.

The most productive authors are Solomon SD, with a total of 155 articles, with an average of 46.99 citations/article, followed by Packer M., with 107 articles, with average citations of 64.45. McMurray JJV takes third place with 92 articles, and the average citation/article is 63.23. In the 2021 analysis, Solomon SD also occupies first place; McMurray JJV, originally in second place, moves up to third place, and Packer M., from third place, moves up to second. In terms of citations, Zile MR leads with an average of 69.50. The author's co-cited analysis shows that the top three places are occupied by McMurray, John J. V., Packer M, and Solomon SD; thus, Solomon SD moves from first to third place.

The three most cited articles from 2015 to 2024 are "ESC Guidelines for the diagnosis and treatment of acute and Chronic Heart Failure: The Task Force for the diagnosis and treatment of acute and Chronic Heart Failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC" (2016), "Angiotensin-Neprilysin Inhibition in Acute Decompensated Heart Failure" (2019), "Angiotensin-Neprilysin Inhibition in Heart Failure with Preserved Ejection

Fraction" (2019). The article published by P Ponikowski (2016), "ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure", moves from third place (376 citations) to first place (602 citations) in our analysis.

Strengths and Limitations

The strengths are primarily represented by the period evaluated after the approval of the marketing of the combination, when the number of published studies increased significantly. These bibliometric analyses show the publication trend on the analyzed subject and research directions.

The limitation of a single database, comprising a smaller number of journals, is the first limitation of this study. Another limitation of the study is the possibility that some articles need to be indexed in WoS.

4. Materials and Methods

4.1. Search strategies

The search algorithm used consisted of the keywords ALL = (sacubitril *" OR "sacubitril/valsartan *" OR " angiotensin receptor neprilysin inhibitor *" OR "Entresto*" OR " angiotensin receptor-neprilysin inhibitor *" OR " LCZ696*" OR "ARNI*" OR " Entresto R*" OR " neprilysin inhibitor *" AND "physical exercise". All articles (except meeting abstracts, corrections, book chapters, retractions, and reprints) published between 1975 and 2024 (24.01.2024) were considered. The database used was the Web of Science (W.o.S). We used this database because it contains high-quality publications and a significant number of citations, although the value of an article depends on several factors, not being based only on the number of citations.

4.2. Data collection and analysis

Data collected refer to the year of publication, authors, organizations in the field, number of citations, Hirsch index, impact factor of a journal (obtained from Journal Citation Reports 2019), and number of journals published by rate. Two independent persons performed data collection. The data obtained were processed with VoSviewer version 1.6.20 (Leiden University, The Netherlands) and the built-in analysis tools available within W.o.S. In addition, the required information was extracted from W.o.S. as tab-delimited files containing the entire record and references of the cited papers using the export function.

Microsoft Excel 2019 (Redmond, WA) was used to analyze fundamental computer programs. Charts generated by VOSviewer represent collaborative relationships between countries. Individual bubble size is correlated with the number of published articles. Collaboration between countries is characterized by a curve whose thickness correlates with the level of collaboration. The color of the bubble differs according to the cluster to which the country belongs; the cluster consists of the countries that publish together. The journals' median publication year and citation mapping were generated with the same program. The color of the bubble shows the color of the publication year, and the size is related to the number of papers published in the respective journal. The color palette, between dark blue and yellow, expresses the year of publication. Darker blue suggests early publication, while lighter colors, including yellow, indicate later publication. Thus, the resulting map, by color palette, shows the distribution of articles on the map over time.

Keyword co-occurrence network and keyword bubble maps were also generated for each period. Darker colors suggest fewer citations, and lighter colors and yellow show more citations. The intensity of the color correlates with the average number of citations of the article (containing the keyword). The bubble size indicates the number of occurrences; the color indicates the number of hits, the width of the bands linking the keywords shows the number of co-occurrences.

The ethics or institutional committee does not apply in this study.

5. Conclusions

With all the promising results on improving cardiac function obtained by administering known classes of drugs in HF, research continues in the direction of discovering new molecules. The effects of the guanylate cyclase stimulator (vericiguat), selective cardiac myosin activator (omecamtiv, mecarbil) and cardiac myosin inhibitors (aficamten, mavacamten) are being studied [139]]. Therapeutic strategies and new treatment directions in HF cardiac fibrosis (exosomes, nanoparticles) are contained in the publication by Bertaud, A. et al. [140]].

Evidence accumulates on the benefits of polypill strategies (combinations of active substances) in preventing cardiovascular disease.

Through this analysis, we obtained an update on the publication trend on the therapeutic progress achieved in the treatment of HF and on the risk factors for HF using a S/V combination. After marketing approval, the publication trend was upward until 2023, when the number of publications decreased significantly. Our study shows that although the number of publications decreased, updates of treatment guidelines were published, and a significant number of articles supporting the benefits of S/V treatment in chronic HF (with reduced or preserved ejection fraction) but also in acute forms were published. Research results, which took years and included many patients, have also been published on the pathophysiological mechanisms of HF and the mechanisms of action of S/V, adverse reactions, drug combinations, etc.

Although the number of articles on cardiac rehabilitation is low, this is highlighted in treatment guidelines and studies have emerged assessing the reasons why patients do not follow a cardiac rehabilitation programme.

Cardiac rehabilitation is important for its physiological benefits: improving VO2max, myocardial blood flow and endothelial function.

Health policies should be put in place to raise awareness of the importance of cardiac rehabilitation, including distances to a rehabilitation centre.

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