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Knowledge domain and emerging trends in sacubitril/valsartan study from 2008 to 2023 – a visualized conclusive analysis based on novel scientometric tools

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Abstract. – OBJECTIVE: This study aimed to determine the evolution of sacubitril-valsartan research and analyze the publications quantitatively and qualitatively.

MATERIALS AND METHODS: We used the bibliometric method and a combination of CiteSpace_6.1.6 and VOSviewer_1.6.18 to identify top authors, countries, institutions, co-cited articles, co-cited journals, keywords, and trends. This study prioritized key aspects in the existing global research on Entresto (Sacubitril/Valsartan) to assess our depth of knowledge in this field and identify potential insights. The objective was to generate a reference for the utilization of the "angiotensin receptor-neprilysin inhibitor" (ARNI).

RESULTS: From 2008 to 2022, citations of sacubitril-valsartan showed an upward trend. VOSviewer keyword analysis of 3,408 publications identified 624 keywords and divided them into seven different clusters. The clustered network was constructed based on 1,191 references cited by 3,408 publications that met the terms, where the clustered network of sacubitril-valsartan was presented. These publications can be regarded as fundamental to Entresto's research. Analysis of co-cited reference clusters showed that other than Entresto's novel application in other diseases, the new combination with other medication or mechanical assistance therapies against heart failure was Entresto's latest focus. Analysis of citation bursts showed that the rank of the top 25 keywords, according to the chronological sequence, marked Entresto's research entering a new era of exploring the extended application in other diseases and novel combinations with other diverse therapies.

CONCLUSIONS: We found that emerging new mechanisms in sacubitril-valsartan therapy intended for more targets in the pathogenesis of specific diseases will be the focus of further studies.

Key Words:
Sacubitril/Valsartan, Entresto, Heart failure, Myocardial infarction, Hypertension, Kidney protection.

Introduction

Sacubitril-Valsartan (LCZ696), also named "Entresto" (brand), is a fixed-dose medication mainly used for chronic heart failure with reduced ejection fraction (HFrEF), sometimes acute heart failure and myocardial infarction (MI), along with other standard medicine therapies [e.g.beta-blockers, mineralocorticoid receptor antagonist (MRA), Sodium-glucose cotransporter 2 (SGLT2)][1,2]. Instead of being separated, this new medicine combines sacubitril (neprilysin inhibitor) with valsartan (angiotensin receptor blocker), which is recommended as a replacement for the single use of an angiotensin receptor blocker (ARB) or an ACE inhibitor (ACEI) in patients with the HFrEF[2]. This combination is currently described as an "angiotensin receptor-neprilysin inhibitor" (ARNI), which is increasingly important in HF therapies[3].

Materials and Methods

Data Source and Search Strategy

In this study, literature was searched using the Web of Science™ Core Collection (WoSCC). The searched topics include: Entresto, sacubitril-valsartan, sacubitril/valsartan, LCZ696 (the structural formula of sacubitril-valsartan), ARNI or neprilysin inhibitor; document type: not limited; time span: 2008-2023 (retrieved date: 31st, August 2023). The language was restricted to English only. "Full records and top cited references" were retrieved, and raw data were converted into DOC and XLS formats, which enabled further analysis of the bibliometric tools we used.

Statistical Analysis

In this study, CiteSpace and VOSviewer were applied for comprehensive science mapping analysis of extensive bibliographic metadata.

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CiteSpace v6.1.6 was employed to analyze the time trends of keywords, capture keywords with strong citation bursts (CBs), develop visualization maps, and recognize co-cited authors/references. In addition, VOSviewer v1.6.17 was applied to recognize associations between journals and construct a collaboration network, which included the term clustering, authors/institutions/countries, and journals/authors citation systems.

In total, 3,408 publications on "Sacubitril-Valsartan" were obtained. CiteSpace defines links and nodes in the visualization knowledge maps. Different nodes in the maps indicate authors or countries, while the link among nodes represents each association between collaboration or co-citation. Scientific articles were analyzed to establish the clusters, time zone or timeline view, dual-map overlays, and co-citation networks. The process of "clustering" in CiteSpace was conducted to determine various subtopics among these publications. VOSviewer was used to perform the keyword co-occurrence density analysis.

Results

Distribution of Articles by Year of Publication

WoSCC is commonly employed to extract scientific data. Based on WoSCC, 3,408 manuscripts have been published. The first literature on sacubitril-valsartan that met the search criteria was published in 2008; therefore, we selected articles from 2008 to 2023 because of the limited number of articles published before 2008. After 2014, the articles published on sacubitril-valsartan reached approximately a double-digit number each year. The number of published articles was an ever-increasing output per year before 2020. During the period of 2008-2022, citations of sacubitril-valsartan showed an upward trend (Figure 1). In the preliminary analysis, these papers were cited 58,759 times during this period, and every article was cited 17.24 times on average.

Keyword Co-Occurrence Cluster and Article Co-Citation Cluster Analyses of Research Hotspots

VOSviewer keyword analysis of 3,408 publications identified 624 keywords and divided them into seven different clusters (Figure 2) with different colors, which are linked with all other keywords. CiteSpace article analysis divided all co-cited articles into seven clusters (0# Alzheimer's disease, 1# heart failure, 2# hypertension, 3# beta blockers, 4# oxidative stress, 5# exercise capacity, 6# type 2 diabetes), of which main sub-networks were shown in Figure 3. Their landmark articles were also labeled.

Analysis of Top Co-Cited Articles

The clustered network was constructed based on 1,191 references cited by 3,408 publications that met the terms, where the clustered network

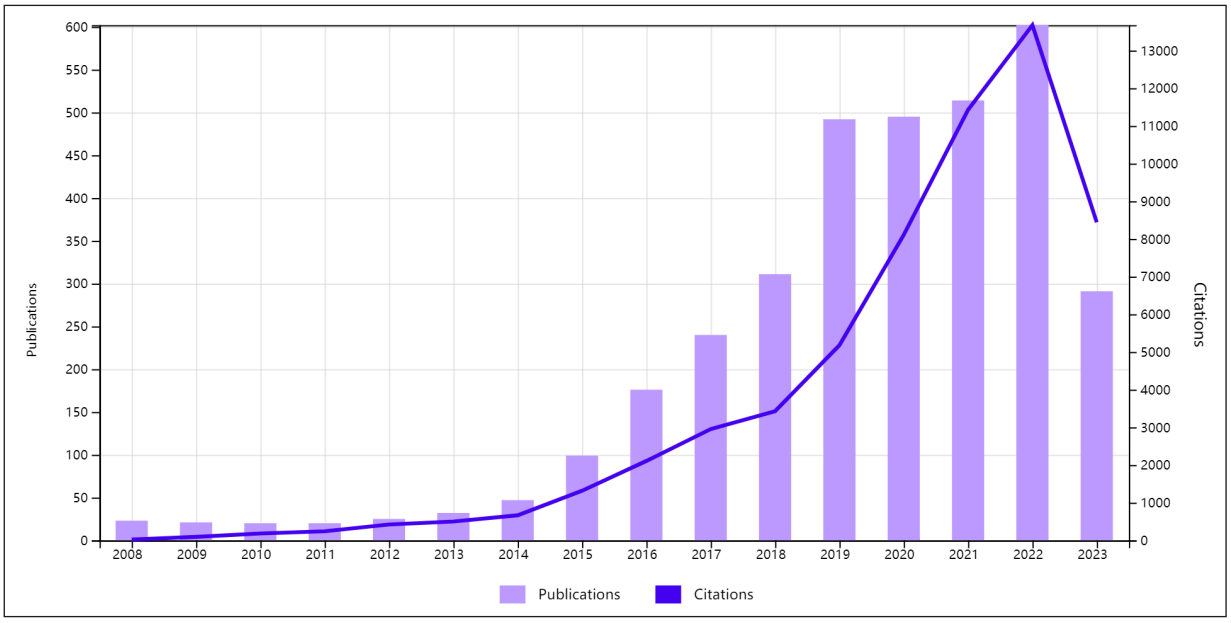

Figure 1. Trends in the number of scientific articles on sacubitril-valsartan research between 2008 and 2023.

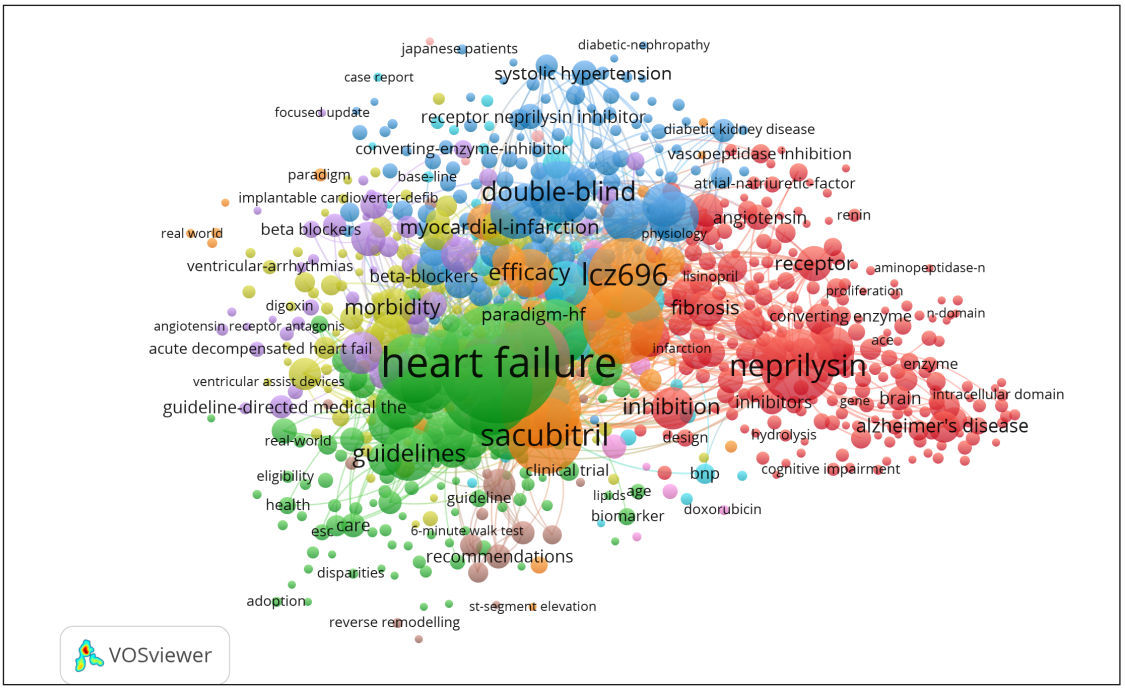

Figure 2. The clustering map of keywords shows 624 keywords with at least one occurrence divided into 7 clusters.

of sacubitril-valsartan was presented. The knowledge maps contained references with high citation count and centrality. The top 10 co-cited articles, their cited frequency, titles, and main ideas are shown in Table I. These publications can be regarded as fundamental to Entresto's research.

Analysis of Co-Cited Reference Clusters

To determine co-cited reference clusters, the 1,191 top co-cited papers in 3,408 original publications were mapped in a hierarchical order using the clustered network (Figure 4a-b and Figure 5) applied two different algorithms to present the

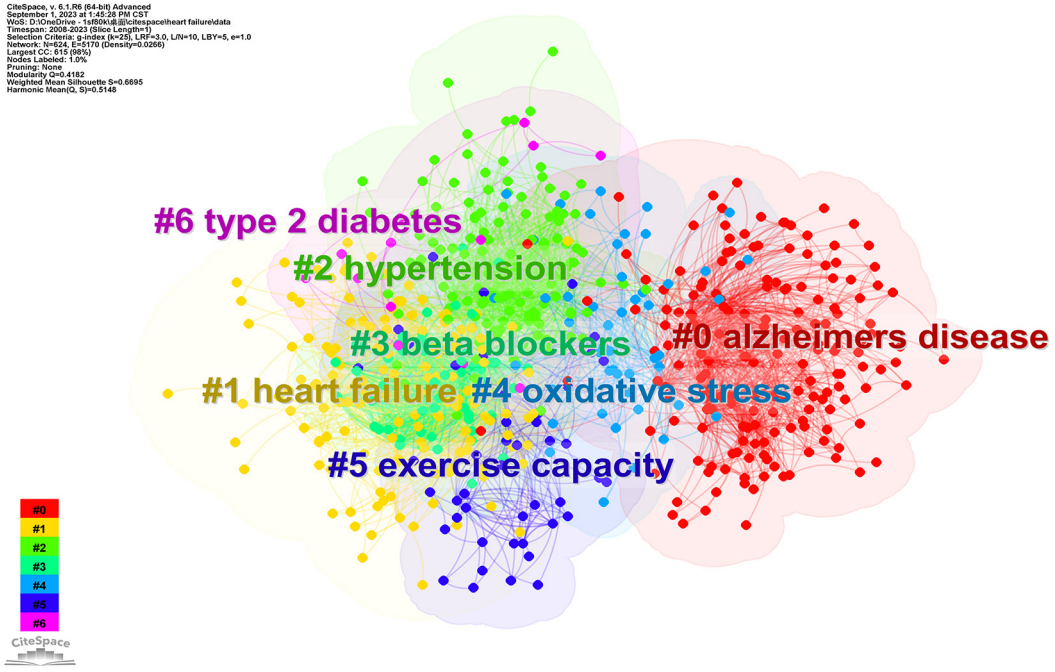

Figure 3. Co-citation and cluster analysis on sacubitril-valsartan and the corresponding sub-networks.

Table I. The top 10 co-cited articles with their authors, journals, titles and core ideas.

Authors	Cited Frequency	Journal	Title	Year	Core ideas	Type
McMurray et al[9]	600	NEW ENGL J MED	Angiotensin-neprilysin inhibition versus Enalapril in heart failure	2014	LCZ696 was more effective than enalapril in decreasing the rates of hospitalization and mortality for HF[3].	Double-blind Trial
Ponikowski et al[4]	413	EUR HEART J	2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure	2016	Sacubitril-Valsartan can replace ACE-I to further decrease the rates of hospitalization and mortality in HF patients with HFrEF who remain symptomatic despite optimal treatment with MRA, beta-blocker or ACE-I[4].	Guideline
Velazquez et al[6]	330	NEW ENGL J MED	Angiotensin–Neprilysin Inhibition in Acute Decompensated Heart Failure	2019	The initiation of sacubitril-valsartan reduced NT-proBNP concentrations than enalapril in patients with HF with PEF who were hospitalized for acute decompensated HF (ADHF). The rates of angioedema, symptomatic hypotension, hyperkalemia and worsening renal function were not obviously different between the two groups[6].	Randomized trial
Solomon et al[7]	306	NEW ENGL J MED	Angiotensin–Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction	2019	Sacubitril-Valsartan did not reduce the rates of hospitalization and cardiovascular mortality in HF patients, with a preserved ejection fraction of 45% or greater compared with valsartan[8].	Clinical Trial
McMurray et al[3]	260	NEW ENGL J MED	Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction	2019	Patients with heart failure and a reduced ejection fraction who received dapagliflozin had a lower risk of worsening heart failure or death from cardiovascular causes than those who received a placebo, regardless of the presence or absence of diabetes[9].	Clinical Trial
Packer et al[11]	208	CIRCU-LATION	Angiotensin receptor neprilysin inhibition compared with Enalapril on the risk of clinical progression in surviving patients with heart failure	2015	Angiotensin/neprilysin inhibitor was more superior to angiotensin-converting enzyme inhibitor (ACEI) for preventing clinical progression in surviving HF patients[5].	Double-blind Trial
Yancy et al[12]	198	CIRCU-LATION	2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure	2017	The combined treatment of ACE inhibitors (Level-of-Evidence: A), OR ARNI (Level-of-Evidence: B-R), OR ARBs (Level-of-Evidence: A), together with aldosterone antagonists and blockers is recommended for reducing morbidity and mortality in chronic HFrEF patients (COR I). In patients with symptomatic chronic HFrEF NYHA class II/III who tolerate ARB or ACE inhibitor, replacement with ARNI is recommended to further decrease mortality and morbidity (COR I; Level-of-Evidence: B-R)[12].	Guideline
Januzzi et al[10]	195	JAMA	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	2019	In this exploratory study of patients with HFrEF treated with sacubitril-valsartan, a reduction in NT-proBNP concentration was marginally significant with improvements in cardiac volume and function markers at 12 months. The observed reversal of cardiac remodeling may provide a mechanistic explanation for the effects of sacubitril-valsartan in HFrEF patients[10].	Clinical Trial
Packer et al[5]	185	NEW ENGL J MED	Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure	2020	Regardless of the presence or absence of diabetes, among patients receiving recommended therapy for heart failure, those in the empagliflozin group had a lower incidence of cardiovascular death or hospitalization for heart failure than those in the placebo group[11].	Randomized controlled trial
Solomon et al[8]	148	LANCET	The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomized controlled trial	2012	LCZ696 markedly decreased NT-proBNP level compared with valsartan in HF patients with preserved ejection fraction at 12 weeks, with no significant side effects. However, these effects need to be tested prospectively[7]. trial	Randomized, parallel-group, double-blind multicenter

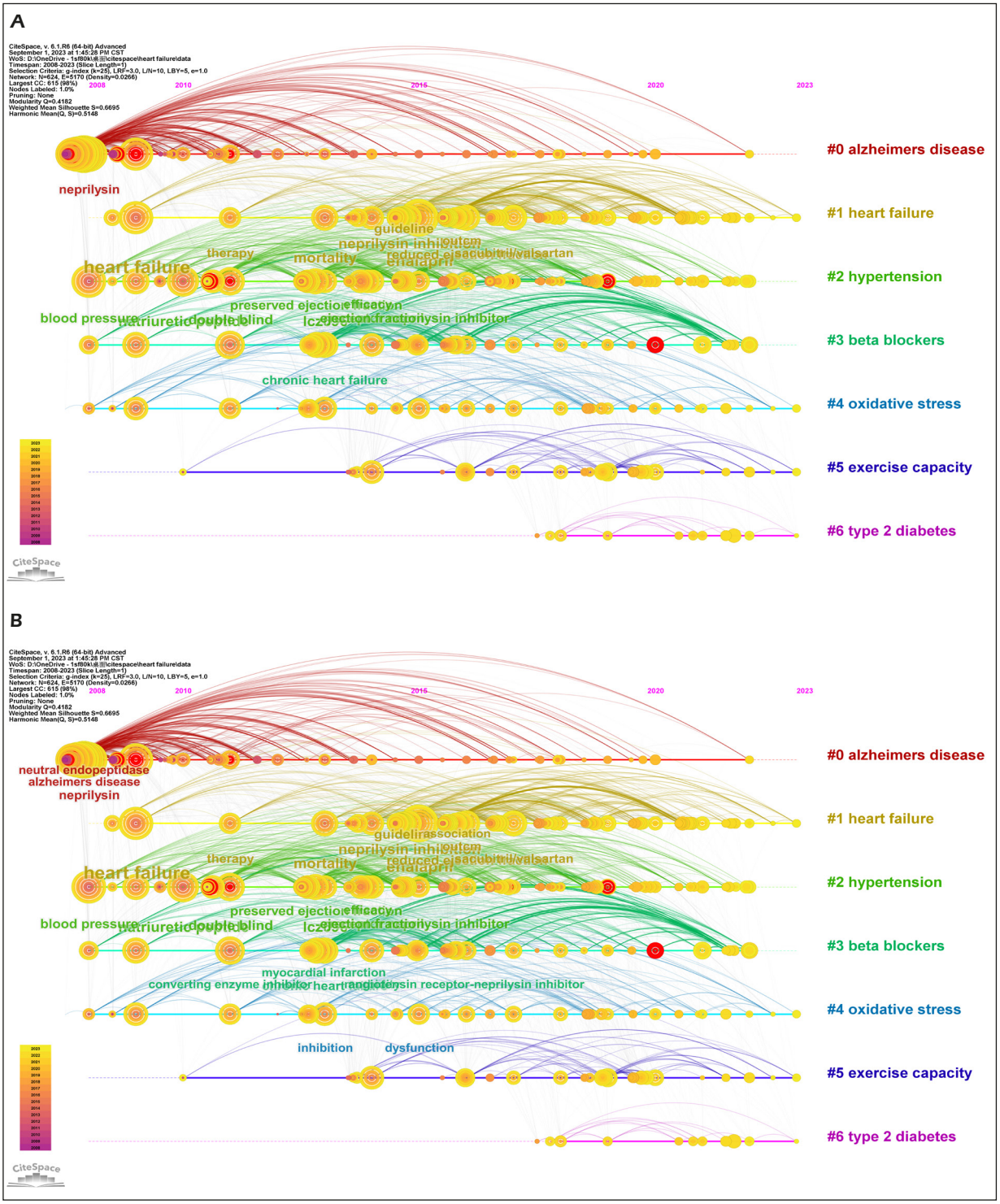

Figure 4. Analysis of co-cited reference clusters that 1,191 top co-cited papers in 3,408 original publications were mapped in hierarchical order using the clustered network. **A**, The timeline1 of co-citation clusters. Top seven clusters are labeled on the right and landmark articles are labeled. **B**, The timeline2 of co-citation clusters.

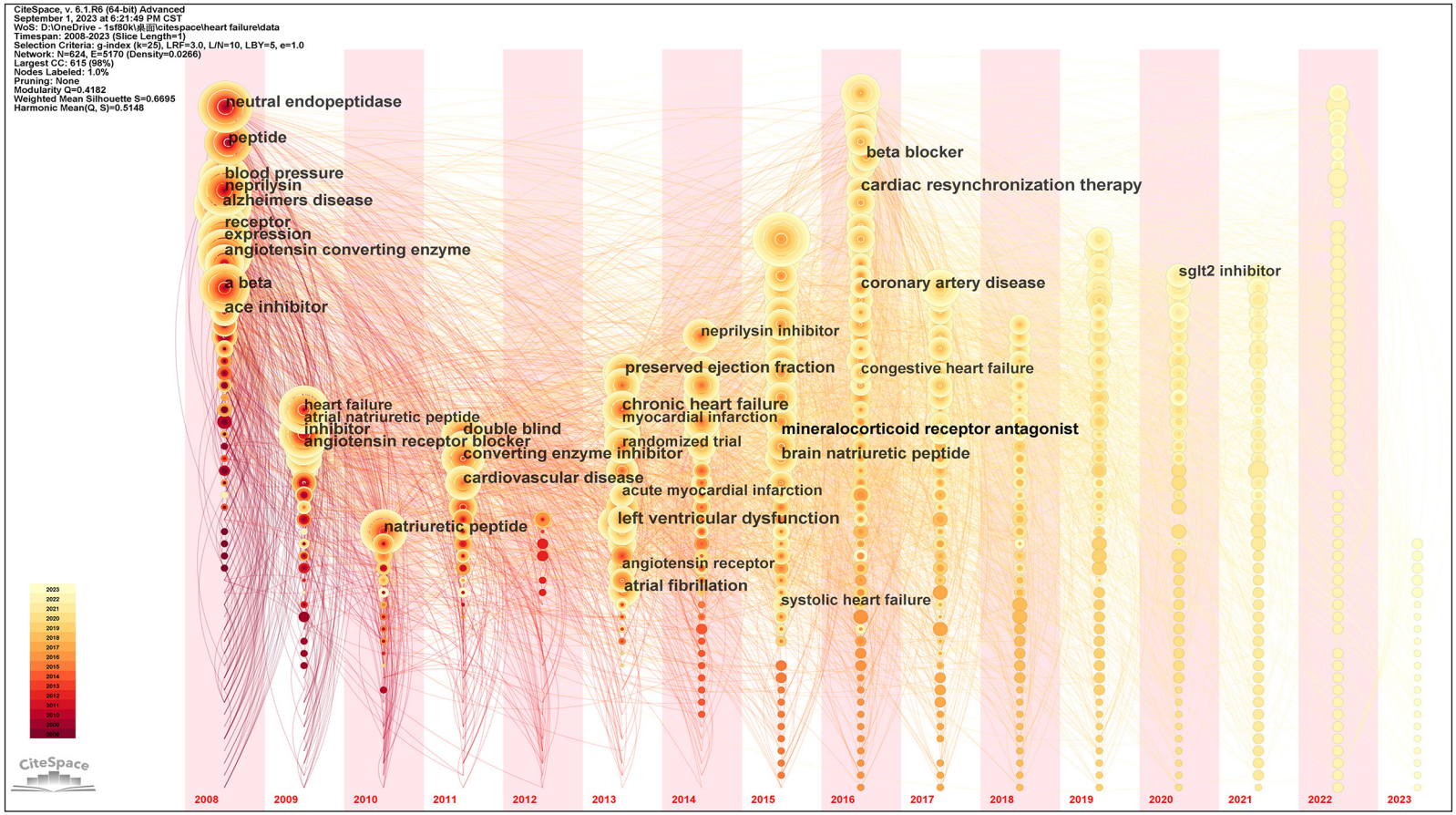

Figure 5. The timeline of co-citation clusters within each year between 2008 and 2023.

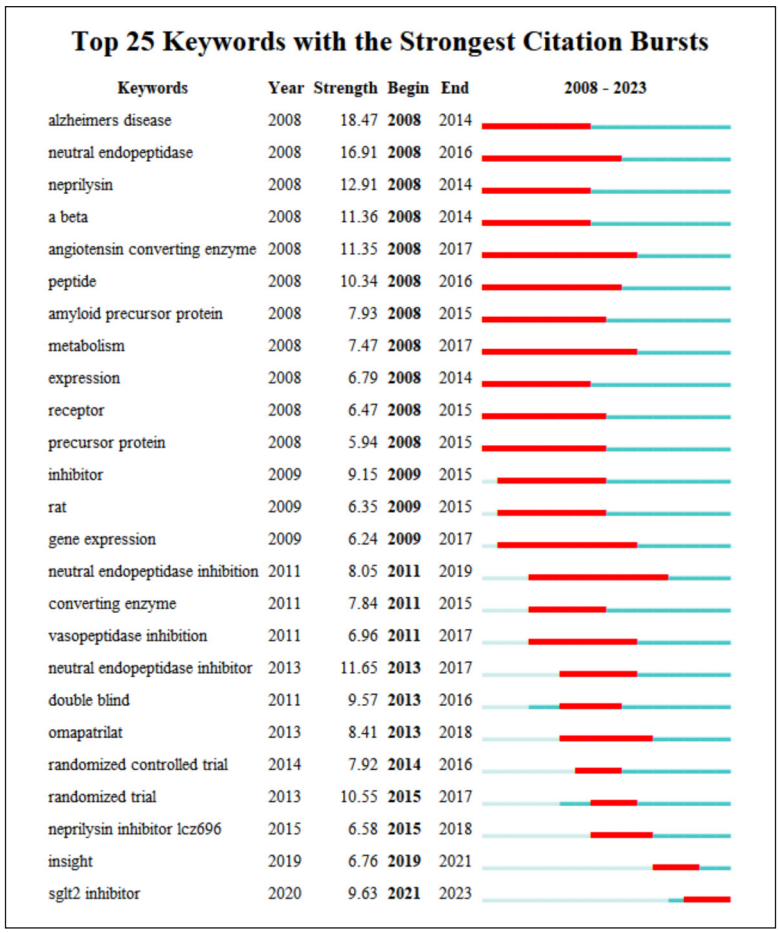

Figure 6. Top 25 Keywords with the strongest CBs in articles on sacubitril-valsartan published during 2008-2023.

citation bursts (CBs) of cited references. Each node represents a cited reference, and each cluster represents a thematic concentration or a distinct specialty. The references with high citation count and centrality can be found in the citation reference knowledge map. The total co-citation number of the associated references is proportional to the area of each node. In Figure 4a/b, the co-cited references are clearly clustered into seven major sub-clusters, as mentioned above, from which we can see the emerging trends of Entresto's novel application in other diseases, including endocrinology and neurology etc. In Figure 5, the co-cited references were arranged based on the timeline within each year from 2008 to 2023, from which we could discover that other than Entresto's novel application in other diseases, the new combination with other medication or mechanical assistance therapies against the heart failure was the latest focus of Entresto.

Analysis of Citation Bursts

CB analysis identifies articles that attract the attention of research scholars. We detected CBs between 2008 through 2023 according to an analysis of 3,408 publications. The blue line depicts the timeline and a red segment on the blue timeline denotes the time interval for CBs, revealing the starting time, ending time, and duration of CBs. Among the top 25 keywords with the highest CB strength, those with research importance showing the evolutionary trend of sacubitril-valsartan were of particular interest (Figure 6). The rank of the top 25 keywords according to the chronological sequence marked Entresto's research entering a new era of exploring the extended application

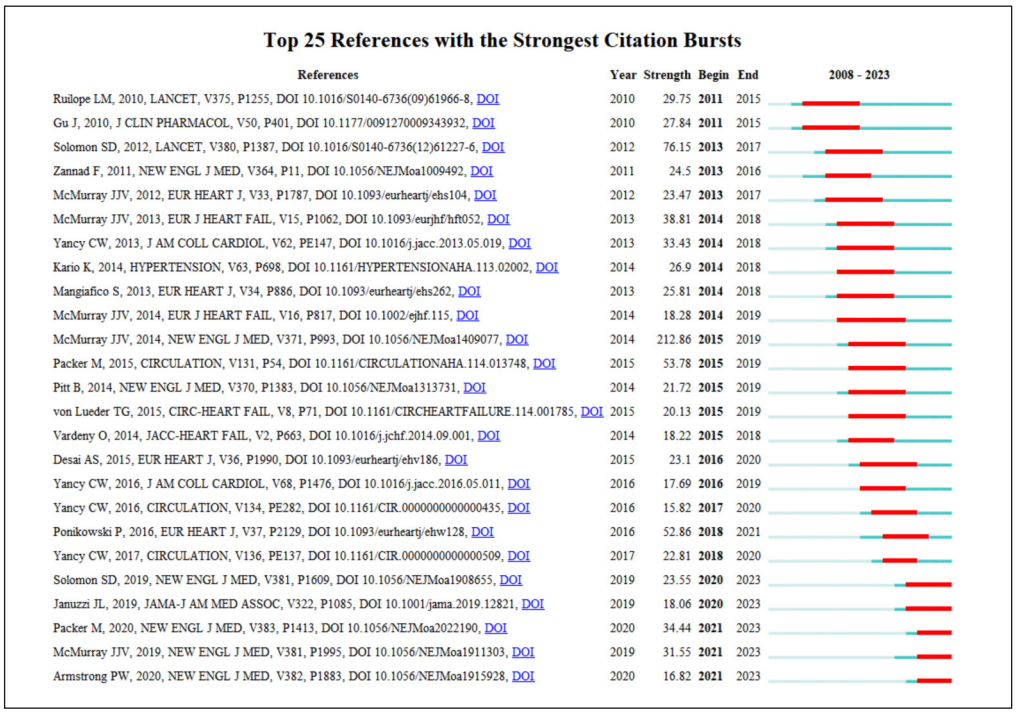

Figure 7. Top 25 references with the strongest CBs quoted in 3,408 articles.

in other diseases and novel combinations with other diverse therapies.

Discussion

In this research, information visualization was used to analyze the publications on sacubitril-valsartan from 2008 to 2023. According to the knowledge domain and emerging trends, an increasing number of scientific articles was identified over the past fifteen years, which indicates that sacubitril-valsartan has become an increasingly important area of study and a subject of growing interest. The burst of research activity after the year 2016 may be attributed to the fact that some scientific articles related to Entresto have had a significant impact on understanding the function and the mechanism of sacubitril-valsartan, which aroused the attention of many researchers in this field, thus increasing the number of critical publications.

Among the top 10 co-cited articles, Solomon et al[4] first illustrated that LCZ696 markedly decreased the NT-proBNP level compared with valsartan in HF patients with preserved ejection fraction (PEF) at 12 weeks, with no significant side effects. However, they added that these effects need to be tested prospectively. However, later, Solomon et al[5] reported that sacubitril-valsartan did not reduce the rates of hospitalization and cardiovascular mortality in HF patients, with a PEF of 45% or greater compared with valsartan, which posed a challenge for subsequent researchers. McMurray et al[6] elucidated that LCZ696 was more beneficial than enalapril in treating patients with systolic HF, and PARADIGM-HF may change our approach to neurohormonal modulation in HF. McMurray et al[2] suggested that LCZ696 was more effective than enalapril in decreasing the rates of hospitalization and mortality for HF, which was still within the range of an ejection fraction of less than 40% (HFrEF). In recent years, these authors put forward that patients with heart failure and a reduced ejection fraction who received dapagliflozin had a lower risk of worsening heart failure or death from cardiovascular causes than those who received a placebo, regardless of the presence or absence of diabetes[6]. Within the same year, Januzzi et al[7] raised that in the exploratory study of patients with HFrEF treated with sacubitril-valsartan, a reduction in NT-proBNP concentration was marginally significant with improvements in cardiac volume and function markers at 12 months. The observed reversal of cardiac remodeling may provide a mechanistic explanation for the effects of sacu-

bitril-valsartan in HFrEF patients. Subsequently, Packer et al[8] also pointed out in the next year that regardless of the presence or absence of diabetes, among patients receiving recommended therapy for heart failure, those in the empagliflozin group had a lower incidence of cardiovascular death or hospitalization for heart failure than those in the placebo group. Besides, they[9] demonstrated that angiotensin/neprilysin inhibitor was superior to angiotensin-converting enzyme inhibitor (ACEI) for preventing clinical progression in surviving HF patients. Senni et al[10] reported that the process of starting or increasing the dosage of sacubitril-valsartan from 50 to 200 mg twice daily over a period of 3 or 6 weeks showed a tolerability profile similar to that of other therapies for heart failure. More gradual uptitration can increase the chance of attaining the target dose of sacubitril/valsartan in patients transitioning from lower doses of ACEI/ARBs. Ponikowski et al[11] ulteriorly proved that sacubitril-valsartan could replace ACE-I to further decrease the rates of hospitalization and mortality in HF patients with HFrEF who remain symptomatic despite optimal treatment with MRA, beta-blocker, or ACE-I. Next, in a new guideline in 2017, Yancy et al[12] updated the consensus that the combined treatment of ACE inhibitors (Level-of-Evidence: A), OR ARNI (Level-of-Evidence: B-R), OR ARBs (Level-of-Evidence: A), together with aldosterone antagonists and blockers is recommended for reducing morbidity and mortality in chronic HFrEF patients (COR I). In patients with symptomatic chronic HFrEF NYHA class II/III who tolerate ARB or ACE inhibitor, replacement with ARNI is recommended to further decrease mortality and morbidity (COR I; Level-of-Evidence: B-R). Velazquez et al[13] further proposed that the initiation of sacubitril-valsartan reduced NT-proBNP concentrations more than enalapril in patients with HF with PEF who were hospitalized for acute decompensated HF (ADHF). The rates of angioedema, symptomatic hypotension, hyperkalemia, and worsening renal function were not obviously different between the two groups, which paved the way for the application of sacubitril-valsartan in ADHF patients.

By integrating the most influential twenty-five references together with the most significant citation bursts (Figure 7) and other relevant publications associated with crucial research on Entresto, we primarily deduce the progress of sacubitril-valsartan during the previous fifteen years as outlined below.

We discovered that earlier in 2010, it has already been preliminarily proven[14,15] that compared with valsartan, a novel, orally bioavailable, dual-acting LCZ696 is effective against high blood pressure, suggesting that the drug can be used to treat hypertension and cardiovascular diseases, especially heart failure. This opened the era of new medical therapy for these two types of diseases with a large group of patients on this planet. In 2012, a breakthrough in the comparison between ARNI and ACE was made, which further demonstrated the positive function of sacubitril-valsartan in HF patients with PEF4. In 2013, a branch trial[16] in PARADIGM-HF research demonstrated the superiority of sacubitril-valsartan over ACEI in systolic HF. Within the same year, a review about the effects of neprilysin inhibitor (NEPinh) and/or other therapeutic agents brought us to a new age of neurohormonal modulation in HF and hypertension, which also showed fewer side effects like angioedema from ARNI than VPIs (Human vasoactive peptidase inhibitor) such as omapatrilat, etc. In 2014, the results from sacubitril-valsartan research began to increase significantly. The priority of sacubitril-valsartan over ACEI and ARB in HFrEF has been further suggested[17]. In addition, one study[18] showed that LCZ696 is effective against hypertension in Asian populations and is well-tolerated and safe. In 2015, LCZ696 was found[19] to be able to attenuate cardiac dysfunction and remodeling after MI, especially the effective inhibition of cardiac hypertrophy/fibrosis, compared to angiotensin receptor blockers or neprilysin inhibitors in all age groups.

In 2016, relevant achievements made explosive progress. Two authoritative guidelines[11,20] were published that year. One from the ESC11 affirmed that sacubitril-valsartan could be an alternative option to ACE-I for reducing the rates of hospitalization and mortality in patients with HFrEF who remain symptomatic despite optimal treatment with MRA, beta-blocker, or ACE-I. Another guideline[20] from ACC/AHA/HFSA also supported this point, so did another two branches of research in PARADIGM-HF[21,22], from which it was discovered that PARADIGM-HF was an essential study to push sacubitril-valsartan research. Besides, fundamental research[23] on the pharmacokinetic and pharmacodynamic profiles of LCZ696, which reviewed the pivotal phase III study of this medicine, showed that LCZ696 treatment was well tolerated and inhibited neprilysin/renin-angiotensin-aldosterone system (RAAS) in HFrEF patients, as indicated by the changes in plasma biomarkers. Beyond that, within the same year, there was an interesting ARNI study[24] that summarized the reasons for the non-implementation of heart failure.

In 2017, Entresto formally entered the global market, bringing more important research into this medicine. The representative ones were mainly from 2017 to 2020. Two studies[25,26] confirmed the atherothrombotic and electrophysiological benefits of sacubitril-valsartan, respectively. A branch study[27] in PARADIGM-HF supported full-dose Entresto therapy for systolic hypertension. Notably, in 2017, a review[28] opened the age of better defining the mechanisms that are intrinsic to the cardiac muscle at the levels of myocytes, interstitium, capillaries mitochondria, etc. The review also unveiled neurohormonal pathways associated with vasoconstriction and vasodilation in peripheral circulation. This discovery prompted a commitment to extended patient follow-ups after ARNI treatment to enhance our understanding of its expected "real-world" safety and efficacy[29]. Nevertheless, the evidence grade of the clinical application for Entresto in the new 2017 ESC guideline[12] still did not change compared to the previous guideline (Class I; Level B-R).

In 2018, more studies[30] of Entresto in chronic kidney disease (CKD) were reported as sacubitril-valsartan was found to be more beneficial to CKD-related cardiovascular abnormality (mainly including cardiac hypertrophy/fibrosis, oxidative stress, inflammation, and mitochondrial dysfunction/depletion) than valsatan. The benefits of Entresto on these cellular mechanisms were also mentioned and proven in MI research, from which it was discovered that the mechanisms in heart and kidney protection share a common way in some aspects. This encourages further investigation into the collaborative research of sacubitril-valsartan within the realm of the intersection between chronic heart disease (CHD) and chronic kidney disease (CKD). Compared to enalapril, sacubitril-valsartan gradually reduced the rate of epidermal growth factor receptor (eGFR) and enhanced cardiovascular outcomes in CKD patients, although leading to a modest increase in urinary albumin-to-creatinine ratio (UACR)[31]. In an observational study[32] with a 1-year follow-up, sacubitril-valsartan exhibited beneficial effects on albuminuria and kidney function similar to irbesartan and additional effects of regulating cardiac biomarkers and blood pressure in CKD patients. In more perspectives, another ARB, instead of valsartan, provided more convincing evidence. In addition, sacubitril-valsartan can reverse the ventricular remodeling of both cardiac diastolic and systolic functions[33].

In 2019, some findings[34] from PARADIGM-HF indicated that sacubitril-valsartan might notably decrease several biomarkers associated with profibrotic signaling in HFrEF, reiterating the significance of the "fibrosis" aspect. Except for this point, sacubitril-valsartan did not show increased risks of symptomatic hypotension, hyperkalemia, and worsening renal function than ACEI[13]. Although one study[35] showed the effectiveness of sacubitril-valsartan in HFrEF patients with renal failure in real-world practice, which has further expanded its use in HFrEF, the clinical application of Entresto in HF patients with a PEF of 45% or greater is still not idea[15].

In 2020, the PIONEER-HF research further indicated the function of sacubitril-valsartan in acute decompensated HF[36,37]. PARAGON-HF trial[32] brought positive proof of sacubitril-valsartan use in heart failure with preserved ejection fraction (HFpEF). Biomarkers reflecting extracellular matrix homeostasis show an elevation in heart failure with preserved ejection fraction (HFpEF), potentially altered by Entresto, thereby contributing valuable prognostic information[38]. This research, as part of the PARADIGM-HF study, completed the application of sacubitril-valsartan in HFpEF patients to some extent. The absolute and relative benefits of sacubitril-valsartan compared to valsartan in HFpEF may be amplified when initiated in the high-risk window after hospitalization, although further confirmation is necessary[39]. The baseline and mean achieved systolic blood pressure (SBP) of 120-129 mmHg indicated the lowest-risk HFpEF patients. Baseline SBP did not affect the therapeutic effect of sacubitril-valsartan, and the blood pressure-lowering effect of sacubitril-valsartan might not account for its effects on outcomes, regardless of gender[40]. In patients with HFpEF, sacubitril-valsartan decreased the risk for renal events, and gradually declined the rate of eGFR, compared with valsartan alone[41]. Another study[42] clarified that after acute decompensated heart failure (ADHF), the first-line therapy with sacubitril-valsartan in newly diagnosed HFrEF, together with the initiation of other guideline-directed therapies, exhibits a better risk-benefit profile than in patients with prior HFrEF. Therefore, early treatment with sacubitril-valsartan can delay disease progression in newly diagnosed HFrEF. Additionally, it has been reported[43] that sacubitril-valsartan reduces the risk of sudden cardiac death (SCD), showing efficacy irrespective of the presence of an implantable cardioverter defibrillator (ICD) or just the eligibility to implant an ICD, particularly among both ICD

users and those with non-ischemic cardiomyopathy. Significantly, in both 2019 and 2020, there was a growing emphasis on the utilization of SGLT2 inhibitors, whether in the context of heart failure with reduced EF or preserved EF.

From 2021 to 2023, the PROVE-HF study continued to provide evidence for sacubitril-valsartan, which is related to NT-proBNP[44]. On the other hand, in patients with HF, sacubitril-valsartan decreased the risk of severe adverse renal outcomes and gradually declined the rate of eGFR, compared with enalapril or valsartan, regardless of baseline renal functions[45]. However, some studies have questioned these positive outcomes. For example, the status of sacubitril-valsartan therapy among patients with acute myocardial infarction was challenged by a study[46] with a large number of patients published at the end of the year 2022, in which better clinical benefits of ramipril were unveiled. Beyond that, especially in the recent two years (2022-2023), as mentioned above, the relevant studies seemed to pay more attention to the fresh application intended for other diseases and the innovative combination with other various therapies.

Compared with conventional reviews, CiteSpace- and VOSviewer-based analyses provide better insights into the research trends, but there are some limitations. It is required to merge similar words during the analyses; otherwise, many repetitive consequences will be covered. Although only original articles were included in most of the analyses, all article types were included during the co-cited reference analysis. At times, the rank of the top co-cited articles is, to some extent, dependent on the published years. In addition, these references can only represent the most prevailing ones with the highest bursts, which implies some breakthrough accomplishments; they cannot represent all the mainstream ideas and achievements. In this article, we have cited quite a few other tightly related articles in discussion with significant results in the past decade to further support and explain the top 25 references above (Figure 7), including the latest breakthroughs in 2023. However, they were ranked and highly selected based on the number of citations. Thus, we still need more citations to comprehensively clarify the Entresto in a systematic review.

Conclusions

Our understanding of Entresto has advanced remarkably over the past 15 years due to bursts of high-quality research. Through information visualization, we identified research trends and current status in the field and offered the collected information for future research directions. It is believed that Entresto is related to the pathogenesis of more diseases than presently known. Comparing Entresto with other medicines, we believe that more comprehensive mechanisms of Entresto in more disorders can be the foci of future associated studies.

Conflict of Interest

The authors have no relevant financial or non-financial interests to disclose.

Authors' Contributions

All the authors were involved in the conception and design of the study. Material preparation, data collection, and analysis were conducted by Jia-Cheng Rong, Xue-Chen Zhao, Bo-Han Lu, and Lei Huang. The first draft of this final manuscript was prepared by Xue-Chen Zhao and revised by other authors, especially Jia-Cheng Rong (Corresponding Author). All authors have read and approved the final manuscript.

Data Availability

All datasets were generated from the sincere analysis created by CiteSpace and VOSviewer, which were completely based on references obtained from the Web of Science Core Collection. These datasets supporting the reported results can be found in this article and are available in the supplementary materials.

Ethics Approval

Not applicable.

Informed Consent

Not applicable.

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