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Emerging trends in sacubitril/valsartan research
A bibliometric analysis of the years 1995–2021

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Abstract

Background: Sacubitril/valsartan has been approved for the treatment of heart failure (HF) patients with reduced ejection fraction; since then, it gradually became a new star drug in the therapy of HF. Nevertheless, the effectiveness of sacubitril/valsartan remains under investigation. Thus far, only a few bibliometric studies have systematically analyzed the application of sacubitril/valsartan.

Methods: Publications on sacubitril/valsartan were retrieved from the Web of Science Core Collection on April 29, 2021. Data were analyzed using Microsoft Excel 2019 (Redmond, WA), VOS viewer (Redmond, WA), and Cite Space V (Drexel University, Philadelphia, PA).

Results: A total of 1309 publications on sacubitril/valsartan published from 1995 to 2021 were retrieved. The number of publications regarding sacubitril/valsartan increased sharply in the last 6 years (2015–2021), and American scholars authored >40% of those publications. Most were published in the *European Journal of Heart Failure*, the United States was the bellwether with a solid academic reputation in this area. Solomon published the highest number of related articles and was the most frequently cited author. "Heart failure" was the leading research hotspot. The keywords, "inflammation," "fibrosis," and "oxidative stress" appeared most recently as research fronts.

Conclusions: Research attention should be focused on clinical trial outcomes. Considering its effectiveness in HF, the mechanisms and further applications of sacubitril/valsartan may become research hotspots in the future and should be closely examined.

Abbreviations: AT1 = angiotensin II receptor type 1, HF = heart failure, HFpEF = HF with preserved ejection fraction, HFrEF = HF with reduced ejection fraction, IF = impact factor, WoSCC = Web of Science Core Collection.

Keywords: bibliometric analysis, CiteSpace, publication trend, Sacubitril/valsartan, VOS viewer, WoSCC

1. Introduction

Sacubitril/valsartan, also known by its brand name Entresto, is an established agent among drugs used for the treatment of heart failure (HF). It is a fixed-dose combination medication consisting of the neprilysin inhibitor sacubitril and the angiotensin receptor blocker valsartan.[1,2] Furthermore, it has been recommended that sacubitril/valsartan replaces treatment with an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker in HF with reduced ejection fraction (HFrEF) patients.[1,3] This combination has also been described as an "angiotensin receptor-neprilysin inhibitor."[4,5] In 2015, this drug was approved for clinical application in the United States and European Union.[1]

Sacubitril is a precursor of sacubitrilat and can be converted into sacubitrilat by esterase.[6] Sacubitrilat inhibits the activity of enzyme neprilysin, which is a neutral endopeptidase that degrades vasoactive peptides (e.g., natriuretic peptides, bradykinin, and adrenomedullin).[7] Furthermore, it causes blood vessel dilation and reduction of extracellular fluid volume via sodium excretion.[5]

PL, J-HX, M-JX contributed equally to this study.

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The datasets generated during and/or analyzed during the current study are publicly available.

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Valsartan blocks the angiotensin II receptor type 1 (AT1),[8] which is found on both vascular smooth muscle cells and the zona glomerulosa cells of the adrenal gland.[9] Angiotensin causes vasoconstriction and adrenal aldosterone secretion without AT1 blockade. Secretion of aldosterone acts on the distal tubular cells of the kidney. It enhances sodium reabsorption, which induces an expansion of the extracellular fluid volume, and blockade of AT1 leads to blood vessel dilation and reduction of extracellular fluid volume.[10]

Monotherapy with neprilysin inhibitors has exhibited limited efficacy in treating hypertension and HF.[11] A decrease in neprilysin activity contributes to a reduction in the enzymatic breakdown of angiotensin II, which increases the systemic angiotensin II levels and negates the positive effects of this drug family in the treatment of cardiovascular disease.[12] The combination of a neprilysin inhibitor and an angiotensin-converting enzyme inhibitor effectively reduces angiotensin II levels and demonstrates superior effectiveness in lowering blood pressure than ACE inhibition alone.[13] Although the combination of a neprilysin inhibitor with an angiotensin receptor blocker instead of and ACE inhibitor is associated with a relative risk of angioedema, it has also demonstrated superior efficacy in treating moderate-severe HF versus treatment with an ACE inhibitor.[3,14] Neprilysin also plays a role in clearing the protein amyloid beta from the cerebrospinal fluid. Amyloid beta contributes to the development of Alzheimer disease; hence, there is concern that treatment with sacubitril/valsartan may promote the development of Alzheimer disease.[15,16]

Bibliometric analysis plays a vital role in organizing the currently available knowledge and exploring research trends in numerous fields through quantitative analysis of the scientific literature. It provides new insight into the range of research topics and predicts future directions for researchers in relevant fields.[17–19]

2. Methods

2.1. Search strategies

The Science Citation Index Expanded database of the Web of Science Core Collection (WoSCC) was used to download all data on April 29, 2021. The following search terms were used: ("sacubitril *" OR "sacubitril/valsartan *" OR "sacubitril/valsartan tablet*" OR "Entresto*" or "angiotensin receptor-neprilysin inhibitor*" or "neprilysin inhibitor*"). All articles (except meeting abstracts, corrections, book chapters, retractions, and reprints) published between 1945 and 2021 were included.

2.2. Data collection and analysis

Data regarding the year of publication; outputs of countries/regions, institutions, journals, and authors; the number of citations; and the Hirsch index (H-index) were collected from all records downloaded from the WoSCC by 2 independent authors (PL, J-HX). The H-index refers to an academic journal, or scholar/country/region which published H articles, each cited at least H times. A reliable indicator was used to evaluate the scientific impact of an author or a country. The impact factor (IF) of a journal was obtained from Journal Citation Reports 2019. Any disagreements regarding data analysis were resolved by discussion with a third investigator (YLL). Subsequently, the data were input into the VOS viewer (Leiden University, Leiden, the Netherlands), Cite Space V (Drexel University, Philadelphia, PA), and Microsoft Excel 2019 (Redmond, WA) software for analysis of fundamental metrics. Ethics committee or institutional is not applicable in this study.

3. Results

3.1. Publication output and temporal trend

A total of 1309 publications, including 1013 original articles and 296 reviews, met the inclusion criteria. The annual publication output before 2015 was minimal. However, there was a >4-fold increase in the annual publication output from 2015 (73 publications) to 2020 (339 publications); the overall trends of cumulative citations and the publication output were similar (Fig. 1A). In the first 4 months of 2021, a total of 81 articles had been published. According to the development tendency, the predicted number of studies on sacubitril/valsartan currently in progress is approximately 250. Nevertheless, the noted decrease in the number of publications does not indicate a decreasing interest in research on sacubitril/valsartan because clinical research requires considerable amounts of follow-up time.

3.2. Distribution by country/region and institution

All articles were published by 34 countries/regions and 1707 institutions. The top 10 countries/regions in terms of the number of publications were the United States (549, 41.94%), followed by Italy (177, 13.52%), Germany (116, 8.86%), Scotland (114, 8.71%), England (108, 8.25%), Canada (101,7.72%), China (99, 7.56%), Switzerland (81, 6.18%), Spain (85,6.49%), and Sweden (73, 5.58%; Fig. 1B).

In terms of total citations, the United States ranked first (14,870) among all included countries/regions, followed by Scotland (7806), Canada (6882), and England (6269; the top 10 countries are shown in Fig. 1C). However, with regarding to the citation/article ratio, Sweden (77.6) ranked first and was followed by Scotland (68.47), Canada (68.14), and England (58.05; Fig. 1C).

For a comprehensive investigation of international collaborations, we used the VOS viewer to construct a network visualization map of publications on sacubitril/valsartan among all countries/regions (Fig. 2A). Different colors were used to identify countries/regions with cooperative relationships, and color similarity indicates a closer cooperative relationship. As shown in Figure 2, countries/regions with higher degrees of co-operation are shown with the same color, and the width of the lines represents the magnitude of the collaborations. Countries with a higher total link strength have a larger dot. As shown in Figure 2A, the United States had the highest total link strength (1,006,824). This result indicates that the United States participated in most collaborations with other countries worldwide. Italy, Germany, and France were the countries that collaborated the most with the United States. The cluster indicated with green color was led by the People's Republic of China, collaborating with India, Japan, Switzerland, and South Korea.

The top 10 productive institutions (in terms of the number of articles) conducting relevant research are shown in Table 1. The leading institutions were Novartis Pharmaceuticals (116, 8.86%), Brigham Women's Hospital (107, 8.17%), University Glasgow (104, 7.94%), Baylor University (70, 5.34%), and Harvard Medical School (64, 4.89%). Next, we used the VOS viewer to conduct a co-authorship analysis to reveal potential collaborations among institutions (Fig. 2B).

3.3. Distribution by journal

The 1309 publications related to research on sacubitril/valsartan were published in 410 academic journals. The top 10 productive and co-cited journals (≥10 citations) are listed in Table 2. The *European Journal of Heart Failure* (IF of 11.627 in 2019) published the highest number of research studies in this field (65, 4.966%), followed by *ESC Heart Failure* (60, 4.583%), *JACC: Heart Failure* (46, 3.514%), *Journal of The American College Of Cardiology* (39, 2.9796%), *International*

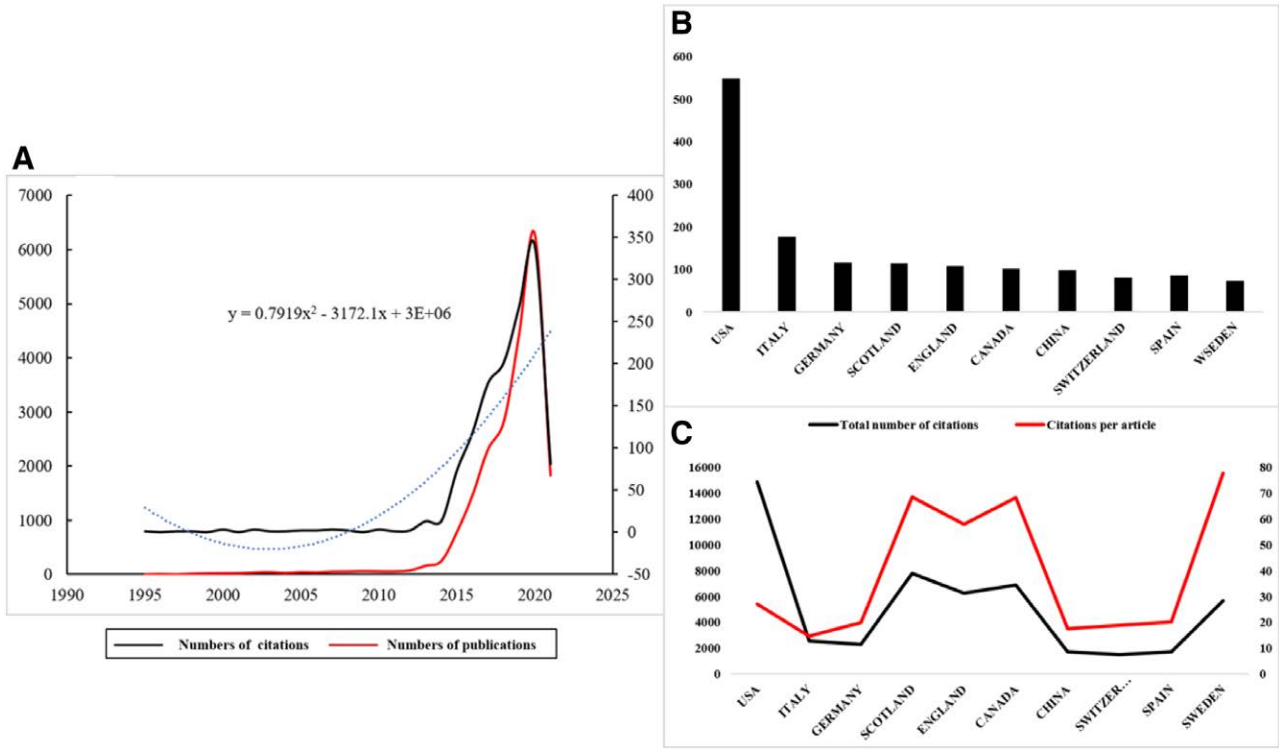

Figure 1. Trends in the number of relevant publications and analysis of countries/regions conducting research on sacubitril/valsartan. (A) Annual worldwide publication output and number of citations. (B) Publication output of the top 10 countries. (C) Citations per article, and total number of citations for the top 10 countries/regions.

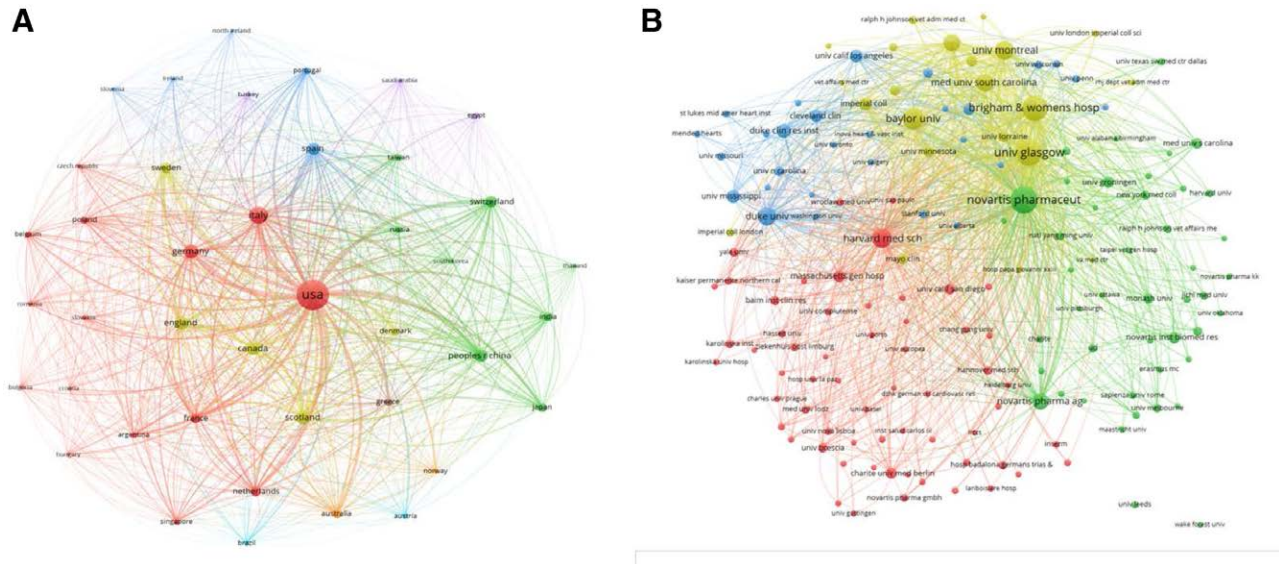

Figure 2. Network visualization map of countries/regions and institutions conducting research on sacubitril/valsartan constructed using the VOS viewer. (A) Collaboration analysis of countries/regions. (B) Collaboration analysis of institutions.

Journal of Cardiology (30, 2.291%), *Circulation: Heart Failure* (23, 1.757%), *Cardiology* (22, 1.681%), *JAMA Cardiology* (22, 1.681%), *European Heart Journal* (20, 1.527%), and *Circulation* (19, 1.451%). Despite the low number of publications, *Circulation* had the highest IF in 2019 (23.603) among the 10 most productive journals. In addition, *Circulation* had the highest H-index (570) among all journals. Four of the 10 most productive journals had a high IF (>10). The most frequently co-cited journal was the *New England Journal of Medicine* (4551 citations), with the highest IF in 2019 (74.699) and H-index (352). The following most frequently co-cited journals were *Circulation* (3761 citations), *Journal of the American College of Cardiology* (3715 citations), *European Journal of Heart Failure* (3195 citations), *European Heart Journal* (2496 citations), *Lancet* (2077 citations), *Circulation: Heart Failure* (1276 citations), *Hypertension* (1128 citations), *JACC: Heart Failure* (950 citations), and the *Journal of The American Medical Association* (910). Furthermore, we used the VOS viewer to reveal potential collaborations among journals (Fig. 3).

Table 1

Top 10 productive institutions conducting research on sacubitril/valsartan.

Institutes	Numbers of publications	Numbers of citation	Average numbers of citation	H-index	Location
Novartis Pharmaceuticals	116	9947	49.24	48	Switzerland
Brigham Women's Hospital	107	8560	80	43	United States
University of Glasgow	104	7680	73.85	42	Scotland
Baylor University	70	2486	35.51	30	United States
Harvard Medical School	64	1599	24.98	20	United States
University of Montreal	59	6168	104.54	33	Canada
Duke University	52	1013	19.48	15	Canada
Medical University of South Carolina	50	1985	39.7	25	United States
University of Gothenburg	44	4807	109.25	29	Sweden
Duke Clinical Research Institute	39	718	18.41	14	Canada

Table 2

Top 10 productive journals and co-cited journals publishing research on of sacubitril/valsartan.

Journal	Count	Number of citations	Number of citations per article	H-index	Latest impact factor	Co-cited journal	Citations	Total link strength
European Journal of Heart Failure	65	1566	24.09	119	15.53	*Circulation*	3761	250,807
ESC Heart Failure	60	223	3.72	13	4.41	*New England Journal of Medicine*	4551	232,537
JACC Heart Failure	46	1231	26.76	46	12.04	*Journal of The American College of Cardiology*	3175	204,934
Journal of the American College of Cardiology	39	2261	57.97	419	24.09	*European Journal of Heart Failure*	3195	179,228
International Journal of Cardiology	30	264	8.8	108	4.16	*European Journal of Heart Failure*	2496	146,664
Circulation: Heart Failure	23	298	13.55	88	8.79	*Lancet*	2077	129,269
Cardiology	22	83	3.77	29	1.67	*Circulation: Heart Failure*	1,87	83,167
JAMA Cardiology	22	298	13.55	30	14.68	*Hypertension*	1128	70,749
European Heart Journal	20	910	45.5	286	29.98	*Journal of The American Medical Association*	910	60,750
Circulation	19	1106	58.21	570	29.69	*JACC: Heart Failure*	950	53,157

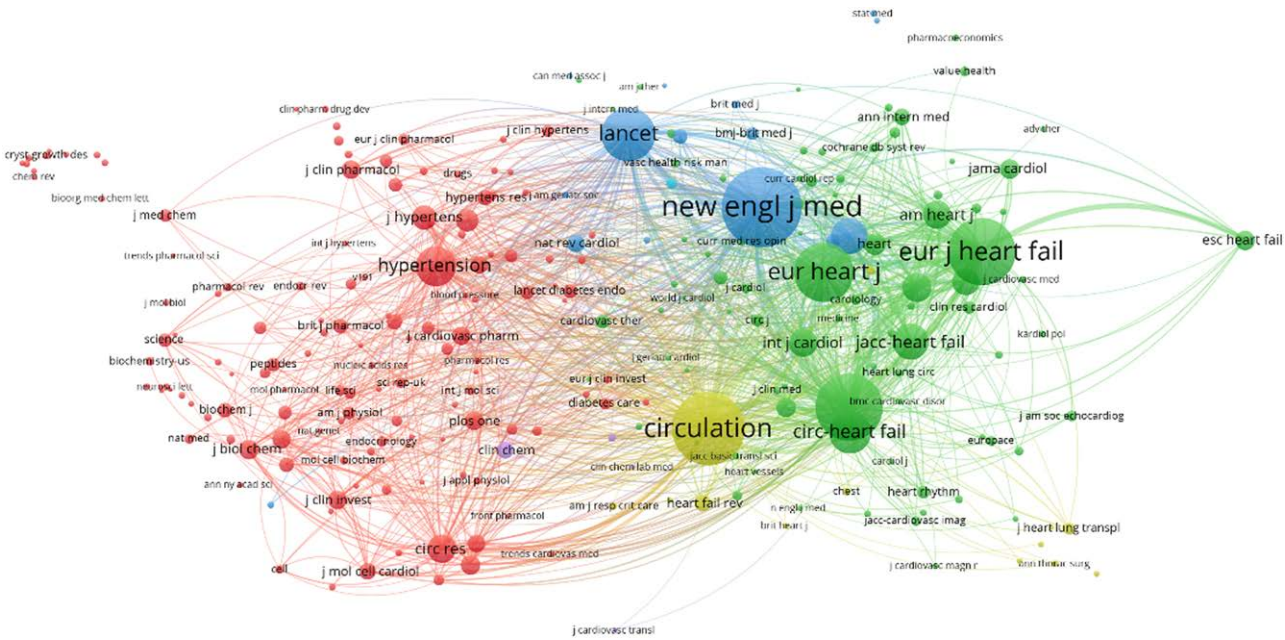

Figure 3. Collaboration analysis of journals.

3.4. Distribution by author

A total of 5903 authors contributed to all output analyzed in this study. The top 10 productive authors are shown in Table 3. Solomon ranked first in terms of the number of publications (95), followed by McMurray (93), Packer (82), Zile (56), Swedberg (44), and Desai (43). The network visualization map of the co-cited authors is shown in Figure 4. The size of the nodes was associated with the frequency of author co-citation; the ranking included Solomon (6306 citations), Packer (6120 citations), McMurray (6090 citations), Zile (5050 citations), and Swedberg (4853 citations; Table 3). Eight of the 10 most productive authors (i.e., Solomon, McMurray, Packer, Zile, Swedberg, Desai, Rouleau, and Jhund) were also among the most frequently co-cited authors.

3.5. Analysis of co-cited references

The top 10 co-cited references are shown in Table 4. A network map of co-cited references, consisting of the 20 most frequently cited articles among 214 references, was constructed (Fig. 5A). Interestingly, we found that 6 of the top 10 co-cited references were published by the *New England Journal of Medicine* (IF: 74.699 and H-index: 933) and Lancet (IF: 60.392 and H-index: 747). Moreover, the top 2 articles authored by McMurray et al and Solomon et al were also published by those 2 journals, respectively. For a better understanding of the co-cited references, we also constructed a network map to visualize the key clusters of co-cited references (Fig. 5B). The high modularity Q score of the clustering map (0.662) and the mean silhouette value of 0.736 indicated the stable network structure of the map, while the values of the clusters were sufficiently high. Cluster #0, labeling the "first-in-class angiotensin receptor neprilysin inhibitor," was the largest cluster consisting of 60 references, followed by "patient with HF" (cluster #1), "controlled trial" (cluster #2), and "ejection fraction" (cluster #3; Table 5). We also performed a temporal co-citation analysis to determine changes in co-cited references over time (Fig. 6). Consistent with the results shown in Figure 1A, >95% of articles were published after 2014, and the number of publications sharply increased in 2015. First-in-class angiotensin receptor neprilysin inhibitor (cluster #0) was a relatively early research hotspot. However, cluster #1 (patient with HF) and cluster #2 (controlled trial) had the largest nodes and warmest colors, and contained most publications. These observations indicate that this clustering reflects the current primary hotspot and future direction of research on sacubitril/valsartan.

3.6. Analysis of keyword co-occurrence clusters and burst keywords

We used the VOS viewer to create a knowledge map of the co-occurrence of all keywords or author keywords including 395 terms (defined as those that occurred more than 5 times; Fig. 7A). The size of the circles represents the frequency of keyword occurrence; larger circles denote more frequent keyword occurrence. An overlay visualization of the keywords over time is shown in Figure 7B. The different colors (from purple, blue, green, to yellow) utilized on the time course correspond to the appearance of keywords over the average time (i.e., from early to recent years). During the early stage of research, "atrial-natriuretic-peptide," "neutral endopeptidase," and even "Alzheimer's disease" were the major topics in this field. However, more recently, "fibrosis," "arrhythmias," "management," "oxidative stress," and "inflammation" became hot topics in this field of research.

We detected burst keywords with the strongest citation bursts related to this field using Cite Space V to further determine the hotspots and research fronts over time. We particularly focused our attention on keywords that started to burst in the past 5 years (Fig. 8). The top 3 strongest strengths included "randomized trial" (burst strength: 8.4326), "ivabradine" (burst strength: 6.6064), and "left ventricular dysfunction" and "neprilysin inhibitor ICZ696" (burst strength: 6.3934 for both).

4. Discussion

4.1. General information

In 2014, the US Food and Drug Administration approved the use of sacubitril/valsartan for the treatment of HFrEF. Notably, 52 relevant articles were published between 1995 and 2014. This reflects the long research process for any drug prior to its application in clinical practice. The annual publication output rapidly increased since 2014 and is currently stable. Of note, a double-blind clinical trial involving 8442 HF patients with an ejection fraction ≤40% was published in 2014; this publication has the highest frequency of citations.[3] This trial firmly laid the foundation for the efficacy of sacubitril/valsartan in the therapy of HFrEF and significantly advanced this research field. Standardized and personal treatment are becoming increasingly popular. Guidelines are the essential basis for treating a disease; as expected, the latest guideline for the management of HF (authored by Yancy et al[20]) demonstrated the second-highest frequency of citation.

Furthermore, the clinical benefits of sacubitril/valsartan in HF with preserved ejection fraction (HFpEF) patients were first observed in the PARAMOUNT trial.[21] The investigators concluded that sacubitril/valsartan significantly reduced the levels of *N*-terminal pro-B-type natriuretic peptide versus valsartan alone at 12 weeks and was well tolerated. These findings supported the use of sacubitril/valsartan in HFpEF patients. Nevertheless, additional studies are warranted to clarify whether this treatment improved patient outcome. It is expected that the publication output in this field of research will increase in the following years.

Table 3

Top 10 productive authors and co-cited authors involved in research on sacubitril/valsartan.

Author	Count	Number of citations	Average number of citations	H-index	Co-cited author	Count	Number of citations	Total link strength
Solomon	95	7379	77.67	40	Solomon	85	6306	711
McMurray	93	7363	79.17	40	Packer	75	6120	557
Packer	82	7076	86.29	37	McMurray	67	6090	499
Zile	56	5616	100.29	33	Zile	51	5050	475
Swedberg	44	5370	122.05	31	Swedberg	41	4853	399
Desai	43	5165	120.12	24	Desai	39	4404	364
Rouleau	39	5137	131.72	27	Rouleau	34	4310	345
Jhund	36	1566	43.5	18	Lefkowitz	30	3920	316
Butler	35	1853	52.94	15	Shi	25	3893	278
Fonarow	35	1879	53.69	16	Jhund	31	1102	271

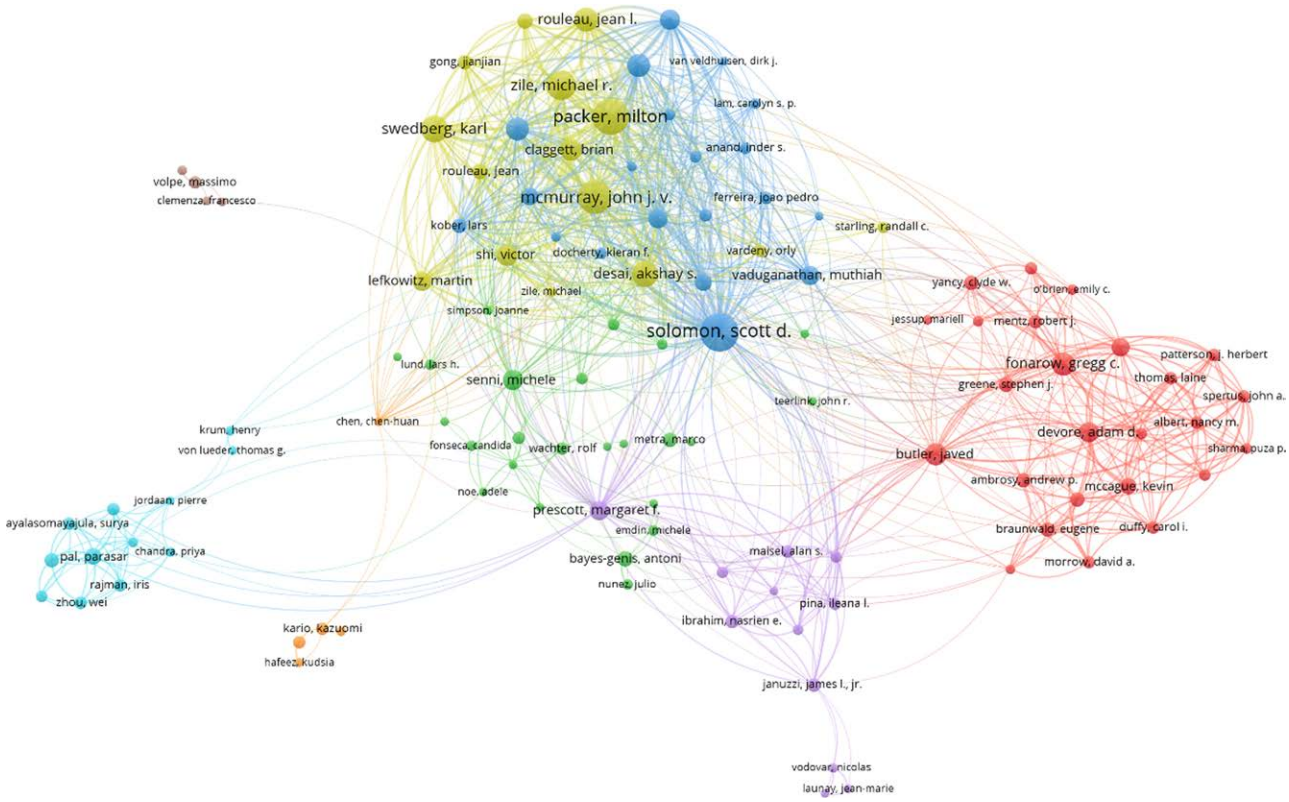

Figure 4. Network visualization map of co-cited authors of articles related to research on sacubitril/valsartan constructed using the VOS viewer.

Table 4

Top 10 co-cited references in the field of sacubitril/valsartan research.

Author	Title	Journal	DOI	Citations	Year	Total link strength
McMurray et al	Angiotensin-neprilysin inhibition versus enalapril in heart failure	*New England Journal of Medicine*	10.1056/nejmoa1409077	929	2014	8879
Solomon et al	The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomized controlled trial	*Lancet*	10.1016/s0140-6736(12)61227-6	280	2012	4382
Ponikowski et al	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 Heart Journal*	10.1093/eurheartj/ehw128	376	2016	4139
Packer et al	Angiotensin receptor neprilysin inhibition compared with enalapril on the risk of clinical progression in surviving patients with heart failure	*Circulation*	10.1161/circulationaha.114.013748	238	2015	3425
Yusuf et al	Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure	*New England Journal of Medicine*	10.1056/nejm199108013250501	185	1991	3349
Packer et al	Comparison of omapatrilat and enalapril in patients with chronic heart failure: the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE)	*Circulation*	10.1161/01.cir.0000029801.86489.50	166	2002	3088
Gu et al	Pharmacokinetics and pharmacodynamics of LCZ696, a novel dual-acting angiotensin receptor neprilysin inhibitor (ARNi)	*The Journal of Clinical Pharmacology*	10.1177/0091270009343932	208	2010	3043
Pitt	The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators	*The New England Journal of Medicine*	10.1056/nejm199909023411001	156	1999	2822
Ruilope et al	Blood pressure reduction with LCZ696, a novel dual-acting inhibitor of the angiotensin II receptor and neprilysin: a randomized, double-blind, placebo-controlled, active comparator study	*Lancet*	10.1016/s0140-6736(09)61966-8	181	2010	2771
Kostis et al	Omapatrilat and enalapril in patients with hypertension: the Omapatrilat Cardiovascular Treatment vs Enalapril (OCTAVE) trial	*Lancet*	10.1016/j.amjhyper.2003.09.014	147	2004	2732

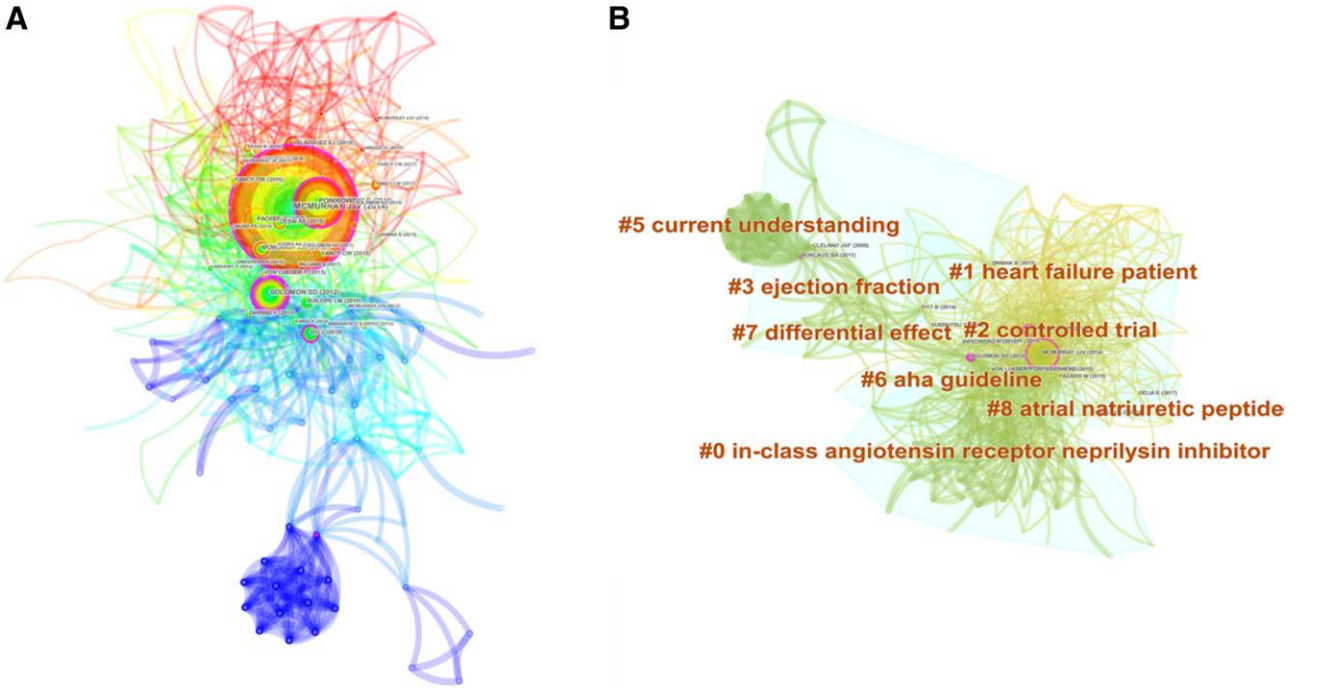

Figure 5. Analysis of references to sacubitril/valsartan. (A) Network map of co-cited references. (B) Network map of co-cited clusters.

Table 5

Clusters of co-cited references in the field of sacubitril/valsartan research.

Cluster ID	Size	Silhouette	Year	Main terms
#0	60	0.669	2012	Heart failure; therapy; novel perspectives; system; natriuretic peptide degradation
#1	52	0.420	2018	Heart failure; patients; Delphi consensus panel; readmission; care bundle
#2	40	0.605	2016	Heart failure; physicians; regadenoson; adverse events; frequency
#3	26	0.730	2012	Heart failure; ejection fraction; treatment; pathophysiology; advances
#5	14	0.974	2011	Heart failure; ejection fraction; emerging drug strategies; emerging concepts; current understanding
#6	12	0.824	2012	Heart failure; valsartan; latest evidence; place; therapy
#7	8	0.888	2017	Valsartan; heart failure; implantable cardioverter-defibrillator use; sudden cardiac death; paradigm-hf analysis
#8	6	0.919	2017	Heart failure; valsartan; atrial natriuretic peptide; treatment; reduced election fraction

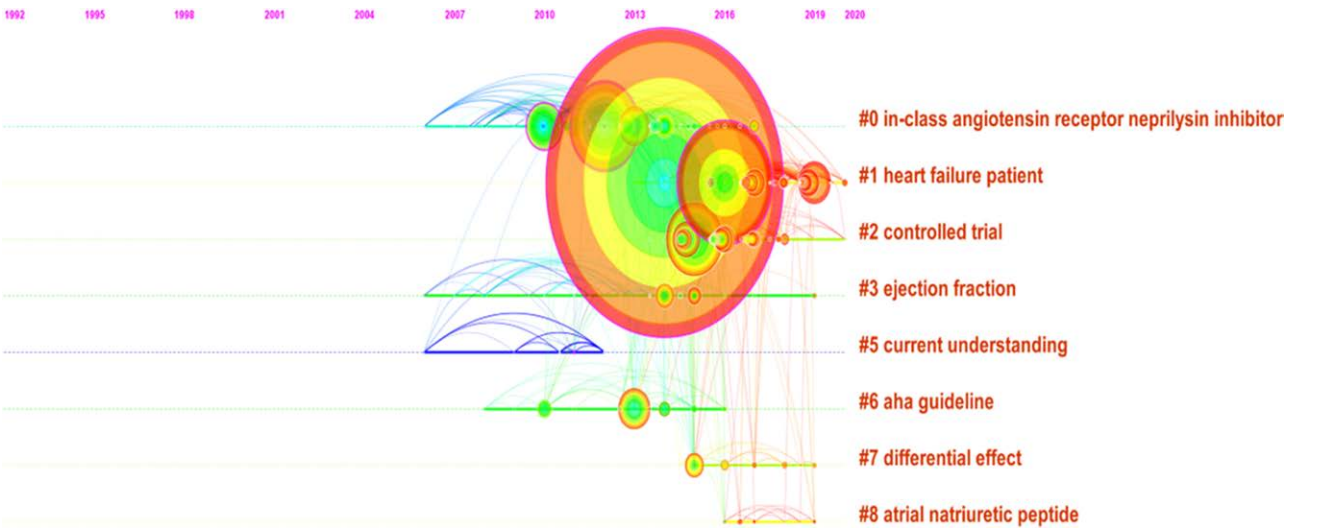

Figure 6. Timeline view of co-cited references related to research on sacubitril/valsartan.

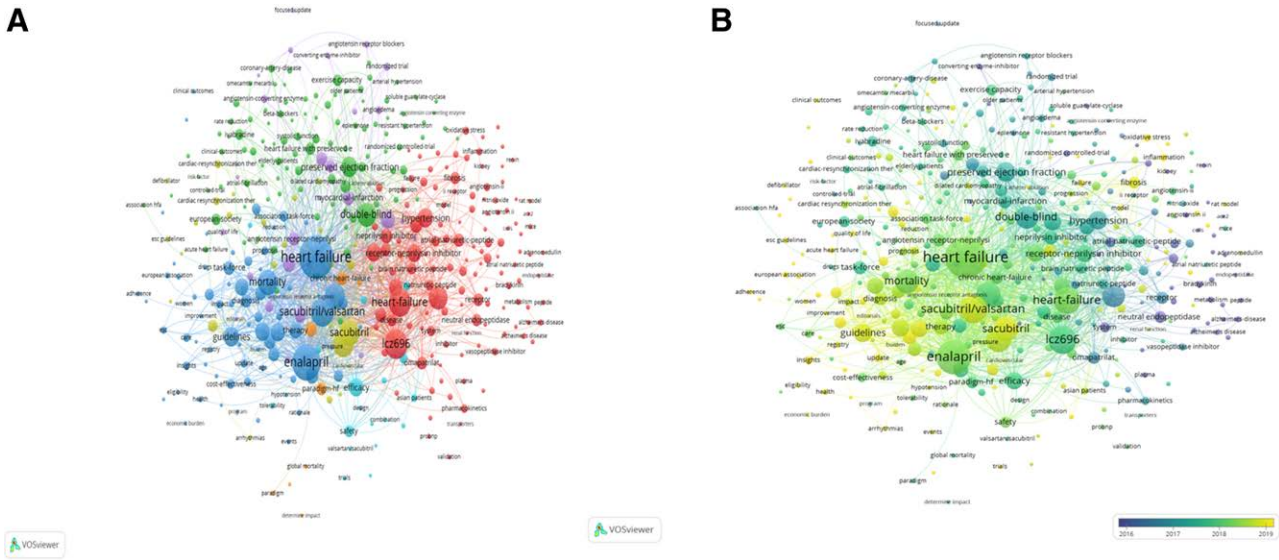

Figure 7. Analysis of author keywords in publications related to research on sacubitril/valsartan. (A) Network visualization map of co-occurring author keywords constructed using the VOS viewer. (B) Overlay visualization of co-occurring author keywords over time using the VOS viewer.

Keywords	Year	Strength	Begin	End	2016 - 2021
randomized trial	2016	8.4326	**2016**	2017	
ivabradine	2016	6.6064	**2016**	2017	
left ventricular dysfunction	2016	6.3934	**2016**	2017	
neprilysin inhibitor lcz696	2016	6.3934	**2016**	2017	
clinical trial	2016	4.078	**2016**	2018	
european society	2016	6.2363	**2017**	2018	
beta blocker	2016	5.8882	**2017**	2018	
paradigm hf	2016	5.1925	**2017**	2018	
cost effectiveness	2016	4.845	**2017**	2018	
systolic hypertension	2016	3.6771	**2017**	2019	
neutral endopeptidase	2016	5.5152	**2018**	2019	
biomarker	2016	4.7283	**2018**	2019	
association	2016	3.4768	**2018**	2019	
2013 accf/aha guideline	2016	5.1701	**2019**	2021	
angiotensin neprilysin inhibition	2016	4.2442	**2019**	2021	
echocardiography	2016	3.8476	**2019**	2021	

Figure 8. Keywords with periods of burst from 2016 onward in articles related to research on sacubitril/valsartan.

The earliest research on sacubitril/valsartan was conducted by scholars in the United Kingdom.[18,22] However, the United States was the main driving force and developed a high academic reputation in sacubitril/valsartan research based on its highest number of publications, highest total number of citations, and high average number of citations. Notably, Scotland, England, Canada, and Sweden had relatively low total research output. However, their high total number of citations and high average number of citations indicate that the research conducted in these countries was of high quality and exerted a potentially significant influence on future developments in this field. Furthermore, Novartis Pharmaceuticals (Basel, Switzerland) was the most productive institution worldwide and collaborated closely with numerous other agencies. In addition, institutions in the United States and Canada were active in research concerning sacubitril/valsartan; 4 and 3 institutions, respectively, ranked among the top 10

productive institutions in this field of research. Three of the 10 most active journals had IFs >20, namely *Circulation* (23.603), *Journal of the American College of Cardiology* (20.589), and *European Heart Journal* (22.673). These 3 journals were also among the leading co-cited journals (ranking first, third, and fourth, respectively), reflecting that they have been vital information resources. Notably, the *New England Journal of Medicine* ranked second among the co-cited journals with the highest IF (74.699) and H-index (352). This journal has an established position related to the contributions of landmark clinical trials; thus, it is recognized as an important resource of basic research and played an essential role in this research field.[3]

4.2. Author and cited reference analysis

Seven of the prominent investigators of the double-blind trial group published in the *New England Journal of Medicine* were among the 10 most productive authors in terms of the number of articles: Solomon (95), McMurray (93), Packer (82), Zile (56), Swedberg (44), Desai (43), and Rouleau (39). They contributed 34.53% of the total number of publications in this field. Moreover, 8 of these prolific authors (i.e., Solomon, McMurray, Packer, Zile, Swedberg, Desai, Rouleau, and Jhund) were among the top 10 co-cited authors, suggesting the high quality of their articles. Among the top 10 co-cited references, 8 were randomized controlled trials, 1 was a guideline, and 1 was a pharmacodynamics study of sacubitril/valsartan. In addition, these studies have been regarded as reliable reference resources for subsequent research. Notably, the double-blind trial led by McMurray in 2014 was the most influential article, indicating that sacubitril/valsartan was superior to enalapril in reducing the risks of death and hospitalization due to HF. This trial laid a research foundation for the further application of sacubitril/valsartan and is recognized as a critical milestone. Solomon et al[21] found that sacubitril/valsartan significantly reduced the levels of *N*-terminal pro-B-type natriuretic peptide versus valsartan at 12 weeks and was well tolerated in patients with preserved ejection fraction. Notably, this was the first extensive clinical trial in patients with preserved ejection fraction.[21] In addition, research on other applications of sacubitril/valsartan has been conducted. The double trial conducted by Ruilope et al[23] in 2017 showed that dual-acting LCZ696 provided complementary and fully additive reduction of blood pressure compared with valsartan, suggesting that this drug holds promise for the therapy of hypertension and other cardiovascular diseases. In 2002, Packer et al[24] found that omapatrilat reduced the risk of death and hospitalization in patients with chronic HF; however, it was not significantly effective versus ACE inhibition alone in reducing the risk of a primary clinical event. Kostis et al[13] found that omapatrilat provided broadly superior antihypertensive efficacy to that of enalapril when used in a setting resembling clinical practice. Although the development of angioedema was more common with omapatrilat than enalapril, the occurrence of life-threatening angioedema was rare.[13]

As shown in the timeline view of co-cited references, most studies were published after 2013 and the number of publications increased sharply in 2015; this is consistent with the data shown in Figure 1A. Cluster #1 (patient with HF) had the warmest color and largest nodes scattered on the timeline. Cluster #2 (controlled trial) contained numerous hotspot nodes with red rings. These results indicate that these were the most recently formed clusters and the most popular research hotspots and directions. Therefore, more clinical trials were conducted, and more clinical applications would be verified. In addition, more high-quality basic research to clarify the mechanism of sacubitril/valsartan has also been performed.

4.3. Keyword analysis

We used the VOS viewer to analyze author keywords and visualize 2 clusters, which included terms related to mechanisms and clinical trials. We combined the findings with the results of the overlay visualization of co-occurring author keywords and the burst keywords. We found that the new directions for research on sacubitril/valsartan included inflammation, oxidative stress, fibrosis, and arrhythmia (e.g., defibrillator and cardiac resynchronization therapy). HFpEF recently became a hot spot, and its detailed mechanism remains unclear. An increasing number of studies have demonstrated that inflammation, oxidative stress, and fibrosis play a crucial role in the development of HFpEF.[25,26] Sacubitril/valsartan has shown effectiveness in HFpEF, although the full clinical benefits should be tested prospectively.[21] Based on the ongoing research conducted in this field, it is reasonable to think that researchers will recommend the application of sacubitril/valsartan to the treatment of HFpEF in the near future.

Clinical trials of sacubitril/valsartan have also been performed. Relevant research hotspots have focused on adverse cardiovascular outcomes (e.g., the risk of hypotension, hospitalization due to HF and cardiovascular death, and renal impairment), consistent with the top 10 co-cited references. Sacubitril/valsartan has been associated with a risk of hypotension, but not severe hypotension. Moreover, studies confirmed the effectiveness of sacubitril/valsartan on HFrEF patients in real-world practice, including those with advanced renal impairment.[27] The PARADIGM-HF trial found that the occurrence of hypotension was more common with sacubitril/valsartan than enalapril, but did not significantly affect the rate of permanent discontinuations of treatment. Patients with hypotension during the run-in period and those who did not develop hypotension derived similar benefits from sacubitril/valsartan compared with enalapril.[28] In the TITRATION study involving 458 patients, it was suggested that low systolic blood pressure should not prevent clinicians from considering the initiation of treatment with sacubitril/valsartan. This is because, among patients in whom the treatment was gradually titrated, those with a systolic blood pressure ≥100 mm Hg achieved and maintained the target dose of sacubitril/valsartan.[29] Since the first evidence of the superiority of sacubitril/valsartan to enalapril in reducing the risks of death and hospitalization due to HF,[3] increasing clinical evidence provides an essential basis for the addition of sacubitril/valsartan to the guideline-recommended therapies for HF.

5. Limitations

Several limitations of this study must be acknowledged. First, only a single database was used to collect the data. This database is a reliable resource for publications and citations, despite the lower number of documents and journals contained compared with other databases (e.g., Google Scholar, PubMed, or Scopus). Second, numerous factors could influence the citation rates, including both journal and author self-citations; our analysis only assessed the information regarding citations, but did not consider other factors. Third, the value of contributions to the field cannot be quantified solely based on the number of citations. Fourth, studies on sacubitril/valsartan published in Chinese and other languages may not be included in the WoSCC. Hence, this analysis may not be an accurate representation of the complete literature available on this topic. Finally, we selectively analyzed the characteristics of the information; thus, some other crucial points and details may have been overlooked.

6. Conclusion

As showed in this study, lot of studies have been conducted to confirm the medical value of Sacubitril/valsartan since 2015. The United States has made the largest contribution to this field. The most productive institution was Novartis Pharmaceuticals. The most popular journal in this field was *European Journal of Heart*

Failure, and Solomon was the most productive author. The *New England Journal of Medicine* was the most co-cited journal. Research attention should be focused on clinical trial outcomes, such as cardiovascular death and HF hospitalization. Considering its effectiveness in HF, the mechanisms and further applications of sacubitril/valsartan may become research hotspots in the future and should be closely examined.

Author contributions

PL, YLL, and YMZ designed the study. PL and JHX collected the data. PL, MJX, JHY, JHX, KJT, JYL, WTZ, and DC analyzed the data and drafted the manuscript. YLL revised and approved the final version of the manuscript.

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