Role of sacubitril/valsartan in glycemic control of cardiac patients with diabetes: a systematic review

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ABSTRACT

Due to vasculopathy occurring as a diabetic complication, patients with diabetes usually have cardiac comorbidities. One of these comorbidities is heart failure, where sacubitril/valsartan has become a cornerstone in the recent guidelines. However, some glycemic control benefits have been proposed for this medication in recent years. This study aims to explore the literature to evaluate the glycemic control that could be achieved through sacubitril/valsartan in patients with heart failure and diabetes. A literature search was carried out using the PubMed database for the duration between 2010 and 2020. Search terms included a combination of “heart failure”, “diabetes”, “glycemic control”, and “sacubitril/valsartan”. The results were then filtered to comprise original research articles investigating how sacubitril/valsartan controls the glycemic levels in diabetic patients with heart failure. Selected trials mentioned the type of diabetes under investigation. A total of 264 articles were retrieved. Following the exclusion of articles on animals and including trials only on humans, 24 articles appeared. Seven articles were considered eligible, which were published between 2010 and 2020, covering a total of 4017 patients with heart failure and diabetes. Besides the anti-remodeling benefit of sacubitril/valsartan for heart failure patients, it was also found to help in glycemic control when diabetes is present as a comorbidity.

Keywords: Heart failure, diabetes, glycemic control, sacubitril/valsartan, systematic review.

Introduction

The epidemiology of chronic heart failure is explained by the over-activation of both water-retaining and sodium neurohormones [1]. This over-activation can have a deleterious effect, which can lead to cardiac fibrosis [2]. Accordingly, the vast majority of heart failure medications in the recent guidelines’ targets decrease the impact of neurohormones on the cardiac muscle to reduce both morbidity and mortality [3]. The novel pharmacological agents that target neuropeptides are the neprilysin inhibitors, primarily sacubitril combined with valsartan [4]. Compared to the angiotensin-converting enzyme inhibitor (ACEI), the new agent, sacubitril/valsartan (Entresto®), is a combined angiotensin receptor combined with the prototype of the neprilysin inhibitor (ARNI) [5]. This combination showed significantly improved morbidity and mortality in patients with heart failure who have had an elevated juxtaglomerular fraction in one of the most extensive studies in heart failure - the PARADIGM-HF trial. This benefit was reported after a long-term follow-up for more than 2 years [6,7]. Nevertheless, the measured outcomes of sacubitril/valsartan were unable to demonstrate a reduction in the prevalence of new-onset diabetes compared to ACEIs. However, only a few patients had new-onset diabetes within the study’s duration, which was regarded as non-significant [8,9]. Furthermore, previous investigations have evaluated the impact of neprilysin inhibitors on insulin sensitivity [10,11]. It has been shown that sacubitril/valsartan has improved insulin sensitivity in patients with both obesity and hypertension [12,13]. However, the data available on the novel sacubitril/valsartan combination regarding its control of diabetic patients’ glycemic levels are still unclear, and further investigations are still needed [14,15]. Therefore, this systematic review aims to...
explore the benefit that could be achieved for diabetic patients with heart failure who are on sacubitril/valsartan as part of their anti-failure measure.

**Literature Search**

This systematic review of the literature was carried out on the PubMed database in the duration between 2010 and 2020 to evaluate the ability of the sacubitril/valsartan combination to control blood glucose levels in patients having diabetes and heart failure. Search terms included were a combination of “heart failure”, “diabetes”, “glycemic control” and “sacubitril/valsartan”. All titles, as well as abstracts that resulted from this search, were examined extensively. The results were then selected to include original research articles investigating glycemic control with sacubitril/valsartan. Additionally, the selected trials mentioned the type of diabetes under investigation. Only articles published in the English language were categorized as relevant articles, which were further examined in the second stage. The following stage was deciding the inclusion criteria to choose the studies eligible for this systematic review. Abstracts were then examined manually to select the appropriate abstracts to be included. The inclusion criteria were the presence of sufficient details on the type of diabetes. Moreover, trials recruiting only patients with both heart failure and diabetes were included. Furthermore, references of selected trials were reviewed to identify any related studies. Finally, the essential data sets were obtained from the final record of eligible articles and summarized. Data were statistically estimated in the form of frequencies (number of cases) and valid percentages for categorical variables. Mean and standard deviations (minimum and maximum) were used to describe a numerical variable. All statistical calculations were carried out through the computer program IBM Statistical Package for the Social Science (IBM Corp, Armonk, NY, release 26) for Microsoft Windows. Before conducting any study-related procedures, institutional approval was obtained. There was no need to get a consent form, as the study did not involve any interventions on patients.

**Results**

A total of 264 articles were retrieved by searching the PubMed database. Following the exclusion of articles on animals and including trials only on humans, 24 articles appeared. After searching the abstracts and checking for the eligibility criteria in identified potential abstracts, a total of seven articles [16-22] were considered as eligible to be included in our systematic review, which were published between 2010 and 2020, covering a total of 4017 patients with heart failure and diabetes. Out of the included seven studies, six studies had a prospective design [16-19,21,22], while only one study was a case report [20]. Furthermore, all the included studies recruited patients with heart failure with reduced ejection fraction and diabetes. Simultaneously, the concomitant anti-diabetic medications varied between oral and injectable anti-diabetic agents, where oral anti-diabetics were included in five studies [16-20], while insulin was included in only two studies [21,22]. A list of studies included in the review along with their a summary of their results is provided in Table 1.

**Discussion**

Cardiovascular diseases represent both micro and macrovascular complications for diabetes; accordingly, many patients are on anti-diabetic and cardiac medications concomitantly [18]. To reduce the incidence of diabetes complications, blood glucose levels should be controlled [12]. Hence, the use of medicines essential for cardiac disease and which could help in glycemic control would be beneficial in this patient population [20]. The present review examined the medical literature to explore glycemic control in patients with heart failure with reduced ejection fraction and diabetes on sacubitril/valsartan combination. The study revealed that sacubitril/valsartan showed promising results in the control of blood glucose level at acceptable HbA1c values in patients with type 2 diabetes, who are on either oral anti-diabetic agents or insulin. The benefit of sacubitril/valsartan on glycemic control has been confirmed through the included studies. Anderson et al. [16], in a recent randomized cross-over study, demonstrated that sacubitril/valsartan combination could significantly increase the levels of gastrin and cholecystokinin, which in turn can control postprandial glycemic levels. Similarly, Wewer et al. [19] revealed that sacubitril/valsartan combination could increase glucagon-like peptide-1 (GLP-1) levels significantly higher than that produced by sitagliptin therapy ($p = 0.0023$). Accordingly, the variety of sitagliptin with sacubitril/valsartan could positively affect patients with concomitant heart failure, yet hypoglycemia should be monitored cautiously [19].

Despite the postprandial control benefit, sacubitril/valsartan showed to achieve long-term control of blood glucose levels by monitoring HbA1c levels in Mazza et al.’s [17] investigation. The prospective case-control study on 108 type 2 diabetes patients showed significantly lower levels of HbA1c in the sacubitril/valsartan group than the oral sacubitril/valsartan anti-diabetic group, with acceptable side effects and adherence profile [17]. These findings were also confirmed by Stassinios et al. [18], which showed a consistent reduction in HbA1c levels over 3 and 6 months compared to oral anti-diabetic agents. Also, Gamarra et al. [20] had similar observations in a case report, which showed a significant and progressive reduction in the level of HbA1c over 4 months of follow-up. Not only oral hypoglycemics have been evaluated, but also insulin therapy has been examined. A post-hoc analysis of Seferovic et al. [21] demonstrated that sacubitril/valsartan combination group showed a significantly lower incidence of oral anti-diabetic with insulin than the enalapril group, due to significantly better glycemic control with sacubitril/valsartan [21]. Furthermore, Jordan et al. [22] also carried out a case-control study on 50 patients with type 2 diabetes on insulin therapy. After 2 months of follow-up, Jordan et al. [22] illustrated that the insulin sensitivity
Table 1. List of studies.

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Year</th>
<th>Study design</th>
<th>Sample size</th>
<th>Type of diabetes</th>
<th>Type of anti-diabetic</th>
<th>Objective</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andersen et al.</td>
<td>2020</td>
<td>Open-labeled, randomized cross-over</td>
<td>9</td>
<td>Type 2</td>
<td>Oral</td>
<td>To examine sacubitril's effect on meal-induced actions on gastrin and cholecystokinin concentrations</td>
<td>Sacubitril/valsartan elevated the post-prandial plasma levels for both gastrin and cholecystokinin by 80% ((p = 0.004)) and 60% ((p = 0.003)), respectively. Sacubitril/valsartan elevates the postprandial plasma concentrations of gastrin and cholecystokinin in type 2 diabetes. Thus, the results suggest that the neprilysin-mediated degradation of gastrin and cholecystokinin is physiologically related and could play a role in heart failure and diabetic patients treated with sacubitril/valsartan.</td>
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<tr>
<td>Mazza et al.</td>
<td>2020</td>
<td>Prospective case-control</td>
<td>108</td>
<td>Type 2</td>
<td>Oral</td>
<td>To examine the influence of sacubitril/valsartan on blood glucose level</td>
<td>Blood glucose and HbA1c values were reduced in both treatment groups, but they were lower in the ARNI group ((p &lt; 0.05)). No patient rejected to continue the study, and no side effects to the ARNI treatment were observed.</td>
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<tr>
<td>Stassinos et al.</td>
<td>2019</td>
<td>Prospective cohort</td>
<td>52</td>
<td>Type 2</td>
<td>Oral</td>
<td>To investigate reductions in HbA1c in patients receiving the novel therapy.</td>
<td>38.5% had diabetes mellitus. HbA1c decreased to 5.6 and 5.7 (interquartile range 0.83) ((p = 0.012)) at 3 and 6 months of treatment, respectively, compared to baseline values. Diabetic patients showed a more significant relative reduction in HbA1c ((8%) ((p = 0.013)). There was a significant association between changes in HbA1c levels from initiation to 3 months of therapy.</td>
</tr>
<tr>
<td>Wewer et al.</td>
<td>2019</td>
<td>Open-labeled cross-over</td>
<td>19</td>
<td>Type 2</td>
<td>Oral</td>
<td>To investigate the effects of neprilysin inhibition by sacubitril/valsartan alone or combined with a sitagliptin on plasma level of GLP-1 in men.</td>
<td>Sacubitril/valsartan increased the postprandial plasma level of GLP-1 by 67%, ((p = 0.0023)). Furthermore, an increased level of intact GLP-1 more than sitagliptin alone ((p &lt; 0.01)) was noted. Sacubitril/valsartan, combined with sitagliptin, achieved a higher level of GLP-1 than sitagliptin alone.</td>
</tr>
<tr>
<td>Gamarra et al.</td>
<td>2018</td>
<td>Case report</td>
<td>1</td>
<td>Type 2</td>
<td>Oral</td>
<td>To evaluate insulin requirement after sacubitril/valsartan in a patient with diabetes and on insulin infusion</td>
<td>At follow-up, we observed a progressive reduction ((-22%)) of daily insulin requirement (mainly for boluses) due to the frequent occurring of postprandial hypoglycemic events, confirmed by the worsening of low blood glucose. After 4 months, sacubitril/valsartan therapy showed more significant time in range 70-180 mg/dl, lower high blood glucose, and a reduction in mean glycemia, resulting in a lower HbA1c value.</td>
</tr>
<tr>
<td>Seferovic et al.</td>
<td>2017</td>
<td>Post-hoc analysis of the PARADIGM-HF</td>
<td>3778</td>
<td>Type 2</td>
<td>Insulin</td>
<td>To evaluate the influence of sacubitril/valsartan versus enalapril on HbA1c.</td>
<td>HbA1c concentrations decreased by 16% in the enalapril group and 26% in the sacubitril/valsartan group ((p = 0.002)). HbA1c levels were persistently lower in the sacubitril/valsartan group than in the enalapril group over the 3-year follow-up. The new use of insulin was 29% lower with sacubitril/valsartan ((p = 0.052)). Fewer patients required oral anti-hyperglycemic therapy ((p = 0.073)) in the sacubitril/valsartan group.</td>
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<tr>
<td>Jordan et al.</td>
<td>2017</td>
<td>Case-control</td>
<td>50</td>
<td>Type 2</td>
<td>Insulin</td>
<td>To evaluate insulin sensitivity with sacubitril/valsartan</td>
<td>Sacubitril/valsartan was correlated to a significant increase in the insulin sensitivity index ((SI)). At week 8, the SI trended to be higher after treatment with sacubitril/valsartan.</td>
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</table>
index had significantly improved after the administration of sacubitril/valsartan with insulin. However, the present review has some limitations that should be considered in any future studies. All the studies included patients with type 2 diabetes, while no studies evaluated the benefit of sacubitril/valsartan in patients with type 1 diabetes. Additionally, novel injectable anti-diabetic agents were not assessed in combination with sacubitril/valsartan. Finally, this is considered to be the first systematic review to give an updated insight from the literature during the last 10 years on a description of glycemic control in diabetic patients with heart failure with reduced ejection fraction on anti-diabetic agents.

**Conclusion**

From this review, it is concluded that sacubitril/valsartan is a promising combination therapy for patients having heart failure with reduced ejection fraction and diabetes, particularly type 2 diabetes, when administered in combination with anti-diabetic agents, either oral hypoglycemic or insulin. Further studies are required to show if patients with type 1 diabetes and those on new injectable anti-diabetic agents (i.e., exenatide) might benefit from sacubitril/valsartan similar to patients with type 2 diabetes on insulin or oral hypoglycemics.

**Conflict of interest**

The authors declare that there is no conflict of interest regarding the publication of this article.

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**Consent for publication**

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**Ethical approval**

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