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ORIGINAL ARTICLE

Is the PARADIGM-HF cohort representative of the real-world heart failure patient population?

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KEYWORDS
Heart failure;
Sacubitril/valsartan;
Reduced ejection fraction;
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Abstract
Introduction: A new drug with prognostic impact on heart failure, sacubitril/valsartan, has been introduced in current guidelines. However, randomized trial results can be compromised by lack of representativeness. We aimed to assess the representativeness of the PARADIGM-HF trial in a real-world population of patients with heart failure.
Methods: We reviewed the records of 196 outpatients followed in a heart failure clinic between January 2013 and December 2014. After exclusion of 44 patients with preserved ejection fraction, the inclusion and exclusion criteria of the trial were applied.
Results: Of the 152 patients with systolic heart failure, 106 lacked one or more inclusion criteria and 45 had at least one exclusion criterion. Considering only patients with ejection fraction $\leq$35% (HFrEF) (n=88), 43 patients lacked at least one inclusion criterion and 25 patients had at least one exclusion criterion. Combining the inclusion and exclusion criteria, 24.3% of patients with systolic HF (ejection fraction $\leq$50%) and 42% of patients with HFrEF would be eligible for the PARADIGM-HF trial.
Conclusion: One in four patients with systolic HF followed in a heart failure outpatient clinic would fulfill the reference study criteria for treatment with the new drug, sacubitril/valsartan.
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PALAVRAS-CHAVE
Insuficiência cardíaca;
Sacubitril-valsartan;
Fração de ejeção reduzida;
Terapêutica médica

Será a coorte do PARADIGM-HF representativa da população do mundo real de doentes com insuficiência cardíaca?

Resumo
Introdução: Um novo medicamento com impacto prognóstico em doentes com insuficiência cardíaca foi introduzido nas *guidelines* mais recentes. Contudo, os resultados de estudos aleatorizados podem ser prejudicados pela falta de representatividade. Os autores ambicionam avaliar a representatividade do estudo PARADIGM-HF numa população do mundo real de doentes com insuficiência cardíaca.
Métodos: Foram revistos os registos de 196 pacientes seguidos em consulta dedicada a insuficiência cardíaca de um hospital terciário entre janeiro de 2016 e dezembro de 2014. Após exclusão de 44 doentes com fração de ejeção preservada, os critérios de inclusão e exclusão foram aplicados.
Resultados: Dos 152 doentes com insuficiência cardíaca com disfunção sistólica, 106 não preenchiam um ou mais critérios de inclusão e tinham pelo menos um critério de exclusão. Considerando apenas os doentes com fração de ejeção $\leq$ 35% (N = 88), 43 doentes não preenchiam pelo menos um critério de inclusão e 25 tinham pelo menos um critério de exclusão. Combinando os critérios de inclusão e exclusão, 24,3% dos doentes com fração de ejeção < 50% e 42% dos doentes com fração de ejeção ventricular esquerda reduzida seriam elegíveis para o estudo PARADIGM-HF.
Conclusão: Um em cada quatro doentes com insuficiência cardíaca sistólica, seguidos em ambulatório na consulta de insuficiência cardíaca, cumpririam os critérios do estudo de referência que levou à aprovação do novo fármaco inibidor dos recetores de angiotensina e da neprilisina.
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Introduction

The mainstay of the management of chronic systolic heart failure (HF) is neurohormonal blockade specifically targeting the sympathetic nervous system and the renin-angiotensin-aldosterone system.[1–3] Yet, despite the use of beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), and aldosterone receptor antagonists in optimized doses, mortality and morbidity remain high in these patients.[1]

Several randomized controlled trials over a period of more than a decade exploring other potential therapeutic targets, such as endothelin, vasopressin and tumor necrosis factor alpha, failed to demonstrate further reductions in mortality.[4–7] This period of consecutive negative study outcomes ended in 2014, when the PARADIGM-HF trial results were reported. In PARADIGM-HF the combination of a neprilysin inhibitor (sacubitril) and an ARB (valsartan) was superior to enalapril in reducing the risk of death from cardiovascular causes and hospitalization for heart failure in patients with chronic systolic HF on optimized medical therapy.[8]

After its efficacy is proven, a new drug has to show effectiveness under real-life conditions.[9,10] In a real-world setting, the representativeness of randomized clinical trials findings may be limited, since these studies are conducted under idealized and rigorously controlled conditions that may compromise their external validity. Ineligibility rates in cardiology trials show that as many as 25-67% of the general disease population are excluded from these trials.[11,12] Therefore, we aimed to assess the representativeness of PARADIGM-HF in a real-world population of patients with systolic HF.

Methods

Population and design

The records of all outpatients (n=196) followed in the heart failure clinic of a tertiary university-affiliated hospital between January 2013 and December 2014 were reviewed. Standard of care includes a regular clinical assessment every 3-6 months, drug titration, follow-up inquiry and serial N-terminal pro-brain natriuretic peptide (NT-proBNP) measurement. All data are included in a prospective registry. Patients with preserved left ventricular ejection fraction (LVEF), defined as LVEF $\geq$50%, were excluded (n=44). The inclusion and exclusion criteria of the PARADIGM-HF trial were subsequently applied to the remaining population.

Patients were considered eligible for treatment with sacubitril/valsartan if they fulfilled all of the following criteria: New York Heart Association (NYHA) functional class II-IV; LVEF $\leq$35%; NT-proBNP $\geq$600 pg/ml. Furthermore, eligible patients had to be taking enalapril 10 mg twice daily (used as an entry criterion in PARADIGM-HF) or equivalent (defined by target dosage in the current guidelines) as part of their optimal medical therapy.[1] All LVEF measurements were obtained by two-dimensional transthoracic echocardiography. Patients were considered ineligible for treatment

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