Examining the safety of recently approved drugs for cardiovascular disease using a large database

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INTRODUCTION

- Cardiovascular disease (CVD) remains the leading cause of death in the US. for decades. Drug therapies play an important role in the effective management of CVDs.
- Between 2014 and 2021, the US Food and Drug Administration (FDA) approved a total of 17 new drug therapies for a CVD indication. After these drugs were approved, the FDA continues its vigilance through active post-marketing surveillance programs to ensure their safety.
- To aid in post-marketing surveillance, the FDA's Center for Drug Evaluation and Research (CDER) relies on the FDA Adverse Event Reporting System (FAERS).
- The objective of this study was to evaluate post-marketing safety profile of CVD drugs approved between 2014 and 2021, utilizing the FAERS database.

METHODS

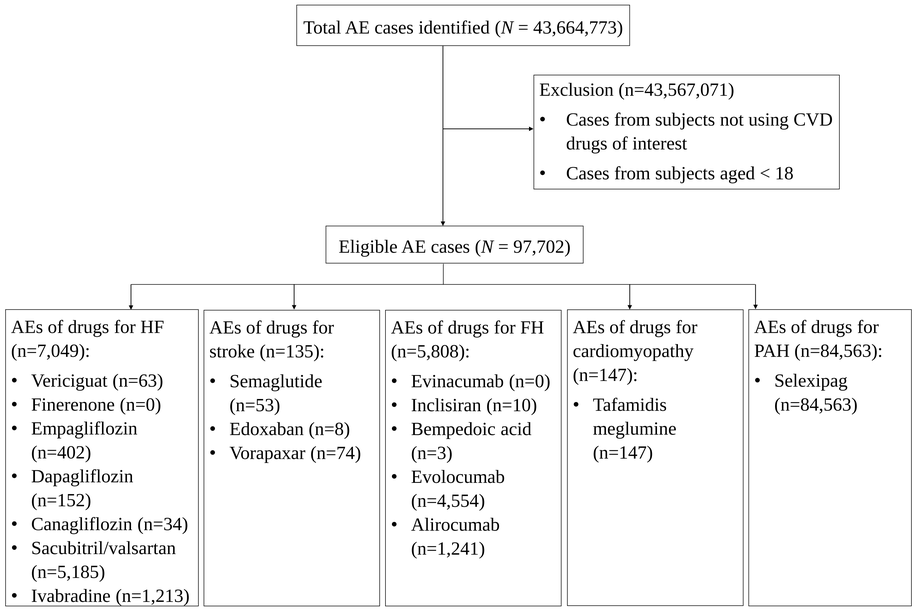
- Our analysis focused on adverse events (AEs) within the FAERS database that specifically attributed AEs to the approved CVD drugs.
- We accessed AE reports spanning from first quarter (Q1) 2014 through Q1 2023 in the FAERS data files. This extended timeframe to 2023 was chosen to provide a buffer of two years for the accumulation of AE reports following drug approval.
- A list of CVD drugs approved by the FDA was identified from the FDA website. These drugs were subsequently classified into five distinct categories: heart failure (HF), stroke, familiar hypercholesterolemia (FH), cardiomyopathy, and pulmonary arterial hypertension (PAH) (Figure 1).
- We conducted a disproportionality analysis for drugs with 500 or more AE reports. The results from our disproportionality analysis were presented with the reported odds ratio (ROR) along with its 95% confidence interval (CI).

RESULTS

- Figure 1 shows the process of identifying relevant AEs associated with the CVD drugs. A total of 43,664,773 AEs were identified in FAERS databases. Of these cases, 43,567,071 AEs were excluded, leaving eligible 97,702 cases.

RESULTS (cont'd)

Figure 1. Flowchart for identifying adverse events of CVD drugs approved between 2014 and 2021



- Among the recently approved CVD drugs, five (sacubitril/valsartan, ivabradine, evolocumab, alirocumab, and selexipag) had more than 500 AE reports. Of these, three drugs (evolocumab, alirocumabl, and selexipag) have been already investigated in previous studies for their AEs using the FAERS data source and the same analytical method (disproportionality). Therefore, we opted to exclude these three drugs from our disproportionality analysis to prevent redundancy. Consequently, we focused on two drugs (sacubitril/valsartan and ivabradine) for our disproportionality analysis.
- Figure 2 demonstrates the results from our disproportionality analyses focusing on sacubitril/valsartan. Compared to other CVD drugs, sacubitril/valsartan was associated with significant disproportionality in several AEs such as hypotension (ROR: 3.98, 95% CI: 3.44–4.61), cardiac failure (ROR: 4.80, 95% CI: 3.82–6.05), dizziness (ROR: 1.43, 95% CI: 1.15–1.77), cough (ROR: 2.19, 95% CI: 1.70–2.82), asthenia (ROR: 1.67, 95% CI: 1.28–2.17), acute kidney injury (ROR: 8.24, 95% CI: 6.05–11.22), and wight loss (ROR: 1.83, 95% CI: 1.38–2.42). Dyspnea was less frequently reported among sacubitril/valsartan users (ROR: 0.76, 95% CI: 0.63–0.93).
- Figure 3 shows the results from disproportionality analyses with ivabradine. Ivabradine, compared to other CVD drugs, exhibited a disproportionately higher ROR for tachycardia (ROR: 11.94, 95% CI: 8.35–17.08), dizziness (ROR: 2.56, 95% CI: 1.68–3.90), fatigue (ROR: 1.74, 95% CI: 1.09–2.79), and abnormal feeling (ROR: 4.40, 95% CI: 2.70–7.18).

RESULTS (cont'd)

Figure 2. Reporting odds ratio for adverse events of sacubitril/valsartan

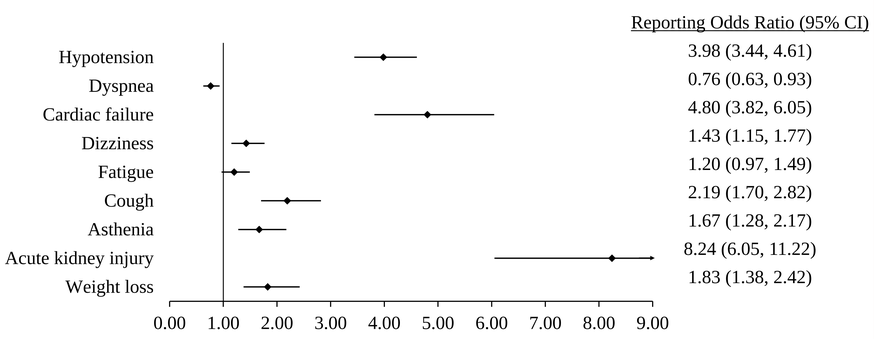
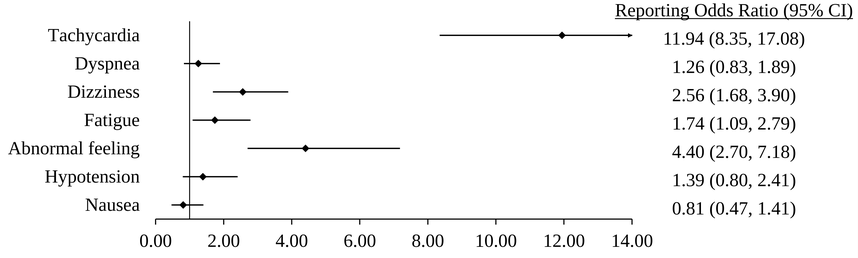


Figure 3. Reporting odds ratio for adverse events of ivabradine



DISCUSSION

- The results from our disproportionality assessment revealed significant disproportionality in several AEs among users of sacubitril/valsartan. For example, we found the AEs such as hypotension and acute kidney injury could be potentially associated with sacubitril/valsartan, which aligns with previous warnings issued by the FDA. Our disproportionality analysis also showed other AEs such as cardiac failure, dizziness, cough, asthenia, and weight loss. Thus, sacubitril/valsartan users should remain vigilant for these AEs and closely monitor for their occurrence during the course of treatment.
- Our analysis also revealed that ivabradine had a higher reporting of tachycardia, dizziness, fatigue, and abnormal feeling. This finding complements the information provided in the FDA-approved label of ivabradine. Therefore, our study results, coupled with the FDA warning, emphasize the importance of vigilant monitoring for these events among ivabradine users.