REVIEW ARTICLE

Leveraging Mendelian Randomization and Genome-wide Association Data for Drug Repurposing in Heart Failure

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Abstract

Heart failure (HF) is a major global health challenge. It causes high morbidity, mortality, and economic burden. Despite therapeutic advances, long-term outcomes remain poor, and benefits have stagnated. This drives the search for novel, cost-effective treatments, including drug repurposing (DR). This review highlights Mendelian randomization (MR) and genome-wide association study (GWAS) data as key tools for DR and target identification in HF. GWAS, MR analyses, and integrative genomics datasets were used to investigate the genetics of HF and drug targets. This GWAS-MR-based review presents evidence for repurposing GWAS-MR tools, such as Proprotein convertase subtilisin kexin9 inhibitors, urate-lowering drugs, and lipid-modifying drugs, for HF treatment. It also discusses how to prioritize HF drug targets and reduce confounding and reverse causality. GWAS and MR together provide a genetically informed approach for HF therapy and target discovery. These methods can speed up target selection and optimize precision HF treatment using suitable datasets. The author anticipates that future advances in GWAS and MR data will further their use for DR in HF.

Key words: Drug repurposing, genome-wide association study, heart failure, Mendelian randomization, precision medicine

INTRODUCTION

Heart failure (HF) is a major contributor to global illness and death (morbidity and mortality). It is a leading cause of hospital admission due to heart and blood vessel (cardiovascular) problems worldwide.[1] HF is highly complex and varied (heterogeneous), with several disease processes (pathophysiological pathways) causing worsening HF and reducing the heart's ability to pump blood around the body.[2-4] Despite advances with drugs such as angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, and sodium-glucose cotransporter 2 inhibitors, progress in HF therapy has slowed. Outcomes have stagnated, putting patients at higher risk and leading to increased deaths and hospitalizations. This also leads to a poor quality of life and worsens it, along with increased treatment costs due to longer hospital stays.[5,6] These patterns highlight the urgency of identifying disease causes and developing cost-effective, practical strategies, including genetic research methods, such as Mendelian randomization (MR) and genome-wide association studies (GWAS).[7]

MR is a genetic instrumental variable-based method. It enhances causal estimation of modifiable risk factors using observational data. MR controls for confounding (when other variables affect both cause and effect) and reverse causation (when it is unclear whether the outcome influences the exposure). It is a cost-effective, scalable system for ranking risk factors and substantiating drug targets. MR is especially useful when randomized controlled trials (RCTs) – studies that randomly assign participants to different interventions – are infeasible. It exploits the random assignment of genetic variants at conception.[8] GWAS are extensive, hypothesis-free studies. They identify statistical relationships between common genetic variants (frequent differences in DNA) and complex phenotypes (observable traits or diseases). By discovering novel loci (genetic locations) and clarifying

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Received: 22-02-2026
Revised: 24-03-2026
Accepted: 31-03-2026

biological pathways, GWAS aid understanding of polygenic disease (conditions influenced by many genes) and risk prediction. GWAS contribute to medicine and agriculture.[9] Drug repurposing (DR) is a process of identifying and applying approved pharmaceuticals or those in development for new purposes. This approach could reduce the time to develop new medicines, lower costs, and lower clinical risk. It can broaden therapeutic opportunities in cancer, rare disorders, infections, and cardiovascular diseases.[10]

In this review, the author reports on the critical roles of MR and GWAS in advancing DR in HF, including their mechanisms of action, drug targets, and the repurposing of existing drugs. A literature search was conducted in PubMed, Scopus, and Web of Science for studies published between 2010 and 2025 using the keywords "Mendelian randomization," "GWAS," "heart failure," and "drug repurposing." Studies were screened based on relevance to genetic causal inference in HF, and duplicate or non-human studies were excluded.

MR AND GWAS STUDIES

DR studies with binary (yes/no) and continuous (range of values) traits aim to determine whether a medicine's main effect is effective and whether it can be used in the same way as a new medicine. These studies also seek to encourage new interactions between genes and drugs, and to share new knowledge, meanings, and uses for existing drugs.[11] GWAS data are commonly used to examine the effects of different genetic variants on a trait.[12] GWAS loci are specific regions of the genome that are likely to harbor genetic variants associated with certain traits. Several bioinformatics databases provide tools for linking genetic variants to known traits or to publicly available GWAS summary statistics.[13] This enables researchers to explore genetic data and better understand the genetic basis of traits.[14] For example, HaploReg and RegulomeDB use dbSNP, a database of genetic variants, to retrieve gene details for specific variants found in GWAS summary statistics.[15,16] In addition to these databases, the recall-by-genotype model offers a fast, accurate way to share data across different genetic variants from various GWAS.[17]

As described earlier, MR utilizes genetic variants as instrumental variables to infer potential causal relationships between exposures and disease outcomes. The principles of MR are based on Mendel's laws of inheritance and instrumental variable estimation methods, which enable the inference of causal effects in the presence of unobserved confounding.[18] MR can provide genetically informed evidence suggesting potential causal relationships between exposures and disease outcomes. Before the development of MR, clinical experimental studies were used to establish causality, if randomization of subjects in clinical studies – the gold standard of obtaining unbiased post-causal in many cases – can be applied.[19] The key problem with clinical experiment studies is ethical, human, financial, and practical constraints, which mean that only small studies can be designed to investigate a limited number of exposures and the survey's relevance to application populations.[20,21]

Causal inference would therefore be enhanced if causal relationships could not only be tested using a method that circumvents the problems of unmeasured confounding and avoidance, but also provide knowledge at the population level. Significant progress has been made to expand the analysis of non-linear treatments in an applied MR setting.[22] These include assessing the direction of causal effects, which are null due to a violation of the exclusion restriction criterion from reverse causality, and using combinations of genetic variants in an MR approach.[23] This was conducted, for example, to estimate the causal relationship between high-density lipoprotein cholesterol and type 2 diabetes.[24] While several MR studies have identified lipid-related targets, such as proprotein convertase subtilisin kexin9 (PCSK9) and 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), as potential therapeutic candidates, differences in GWAS sample sizes, instrument selection, and methods for correcting for pleiotropy lead to variability in effect estimates across studies.

APPLICATIONS OF GWAS DATA IN DR

Despite inherent limitations, MR analysis has been considered a powerful method to infer causality between drug targets and drug indications.[25] The final assessment of discovered DR must go through clinical trials and the practice of drug repositioning, all of which involve systematically assessing the safety and efficacy of a repurposed drug in the context of the drug-disease association.[26] Most importantly, GWAS data can provide clues to potential side effects and relationships of drugs.[27] Furthermore, GWAS summary data could be utilized as an essential part of MR analysis for DR.[28] GWAS summary statistics are increasing exponentially due to the rapid development of DNA chip-based genotyping technology, and international, multi-consortia studies are aggregating GWAS meta-analysis data across various phenotypes.[29] Because large-effect-size loci are key in identifying drug targets, mounting GWAS loci does not directly increase the rate of drug development, but there are interesting benefits.[30] First, GWAS loci target the root causes of diseases, not the symptoms.[31] Therefore, evaluating suggested drug targets is recognized as an essential process in drug development. Second, molecular traits strongly associated with GWAS loci can provide not only genomic-based validation of drug targets but also clues for predicting which existing drugs might have beneficial effects on a given disease or be liable to new on- or off-target effects.[32]

MECHANISMS OF DR IN HF TREATMENT

HF is a complex and multifaceted clinical syndrome. It is the endpoint of many cardiovascular diseases.[33] Among

patients with coexisting multimorbidities, such as diabetes and hypertension, HF affects about 50% of individuals.[34] The heterogeneity in HF etiology complicates the selection of appropriate therapeutic strategies. This makes it harder to reduce the economic burden and improve patient care.[35] MR and GWAS data provide strong statistical support for novel drug treatments in individuals with diverse comorbidities, including those associated with HF. This support holds potential to guide multi-target DR for HF treatment.[36]

Drug development is a long, costly, and often failing process. Due to high drug failure rates, DR is an attractive alternative for drug development.[37] Traditional DR methods rely on pre-clinical or clinical experiments. Both approaches are time-consuming and expensive. With new genetic and genomic methods, it is now feasible to evaluate if drugs have intended on-target or unintended off-target effects with high confidence.

Pharmacogenomics research can use genetic data to support DR in several scenarios.[38] First, genetic markers can be identified and used to categorize patients by potential drug response.[39] In this way, existing drugs whose efficacy is tied to off-target side effects might be repurposed as indication-specific prescriptions.[40] Second, genetic variation can guide the development of new treatment strategies. This may improve the clinical use of medications, address underutilization of clinical effectiveness, reduce clinical cardiotoxicity, or increase patient adherence.[41] Using genetics and genomics in pharmacogenomics research and clinical practice is thus a crucial challenge for effective DR for HF.

MR can also be used to identify a target more likely to have a therapeutic effect and less likely to cause side effects.[42] GWASs have been carried out a lot when hundreds of thousands of samples are available; these summary statistics can be used to determine whether a potential target has a beneficial or harmful effect (e.g., the impact of cholesterol, diastolic blood pressure, type 2 diabetes on HF, and the effect of warfarin, metoprolol, digoxin, and atorvastatin on HF were tested). A recent study showed that an integrated platform (heterogeneity in dependent instruments) is available to test for pleiotropy and identify potential drug targets.[43] Notably, some of these single-nucleotide polymorphisms targeting genes identified from GWAS were located in non-coding regions [Figure 1].[44]

CASE STUDIES OF SUCCESSFUL DR IN HF

MR can selectively block genes, making it superior to drug connectivity [Table 1]. Characterized drug targets in the therapeutic drug target database were relevant to MR results.[45] Clinical trial remnants linked drugs to known therapeutic effects, and treatment outcomes correlated

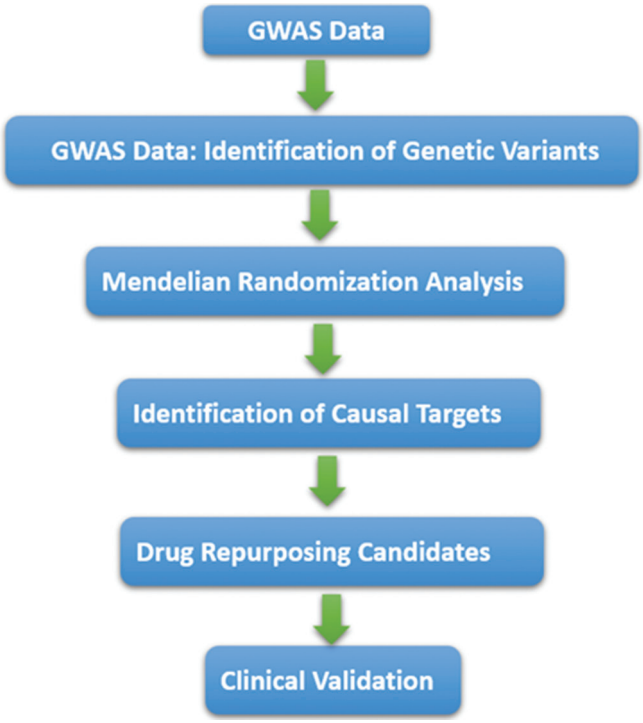

Figure 1: Mendelian randomization-based drug repurposing workflow

Table 1: Potential drug targets identified through MR and GWAS for heart failure

Gene	Biological pathway	Drug	Clinical status
PCSK9	Lipid metabolism	PCSK9 inhibitors	Approved
HMGCR	Cholesterol synthesis	Statins	Approved
IL6R	Inflammatory signaling	Tocilizumab	Investigational
NPC1L1	Cholesterol absorption	Ezetimibe	Approved

GWAS: Genome-wide association study, MR: Mendelian randomization, PCSK9: Proprotein convertase subtilisin/kexin type 9, HMGCR: 3-hydroxy-3-methylglutaryl-coenzyme A reductase, IL6R: Interleukin, NPC1L1: Niemann-pick C1-like 1

positively with MR.[46] Thus, in clinical development, DNA testing was included in research assessing the risk of acute cardiovascular diseases, drug metabolic effects, and treatments, such as stroke, due to possible market risks.[47] In DR, the risk of gout – a common comorbidity with HF – increases with uric acid levels. Allopurinol, which lowers uric acid,[48] was associated with lower HF risk in genetically defined uric acid studies, suggesting it may be beneficial.[49]

MR studies can help reposition drugs. The *HMGCR* gene encodes a key enzyme in cholesterol biosynthesis and is the target of statins. Studies using HMGCR genetic variants show that genetically proxied inhibition of HMGCR lowers LDL cholesterol and reduces cardiovascular risk.[50] About

117 million people have sequences predicting decreased HMGCR function. This suggests some patients may benefit intentionally or off-target from this drug.[51]

CHALLENGES AND LIMITATIONS IN DR FOR HF

HF is a complex clinical disorder that is the endpoint of many cardiovascular diseases, such as coronary heart disease, hypertension, and valve dysfunction, as identified by the standard clinical definition of HF (ejection fraction of <0.40) accepted by the American College of Cardiology and the European Society of Cardiology guidelines.[52] The main limitation of traditional HF treatment is that it focuses on improving circulation and water excretion through diuretics, digitalis, vasodilators, ACE inhibitors, and β-blockers, but does not address the HF condition. In cases of HF with a low EF (i.e., with 0.37 ± 0.05), one-third of it is due to systolic HF, in which the heart's pumping function is impaired, and two-thirds is due to diastolic HF, in which the filling function of the heart is affected.[53] The availability of outcome data after cardiac medication prescription is valuable but is often not prospectively collected in accordance with present HF care recommendations.[54] This is a process that may form part of a real-world evidence piece when predicting what may be associated with a particular drug treatment.[55] The use of the UK Biobank in MR studies has limitations, as it is often based on people of European descent, and inferences in other ethnic groups are less reliable due to over- or under-representation based on calculated *P*-values.[56] However, the large population intentionally collected, with deep phenotypic and genetic data, is advantageous, particularly for examining the genomic basis of rare diseases or investigating unexplained lived experiences.[57]

One of the critical aspects in DR is the availability of high-quality data sources.[58] In addition to being of high quality, the data from these sources should be interpretable for the disease of interest and the drug.[59] For phenome-wide MR studies, the use of the UK Biobank is particularly advantageous, especially where HF is the disease of interest, with over 200,000 individuals meeting the outcome criteria, and studies of more than 500,000 persons can provide data for the exposure of interest.[60] The use of Hospital Episode Statistics data, combined with primary care data, also includes information on people with HF managed in the community who require no hospital care, which is particularly important given the high rate of hospital readmissions after acute decompensation with HF.[61] This system provides a rich database comprising validated primary and secondary care data linked to critical endpoints, such as the hospital record, the death register, and potentially the cancer register.[62]

To ensure fair representation, effective use of trial knowledge requires early and thorough application of social and ethical principles in drug development.[63] The same approach should be incorporated into the planning of trials that use matched medications for similar conditions.[64] Prospective testing and comparison of endpoints between treatment groups can then reveal differences in ICD risks that may support differences in inadequate treatment effects.[65]

The propensity for bias of observational studies means that reduced reliance on RCTs is now unlikely.[66] Moreover, MR is not without its drawbacks.[67] From an ethical point of view, limiting the analysis only to studies in which genetic information was already collected for other medical purposes can lead to the deployment of the "as available" principle.[68] This principle enables the study to be conducted on the extant substrate rather than with an ethical duty to perform further tests.[69] Although the focus is on genetic predisposition, the information typically comes from HWE studies that do not require consistent evaluation of minority frequencies to detect gene-disease associations.[70] Future MR studies should prioritize multi-ancestry GWAS datasets to ensure that genetically inferred drug targets are applicable to diverse global populations.

FUTURE DIRECTIONS AND OPPORTUNITIES

We propose that MR for HF can be systematically and broadly applied to the development of diagnostic biomarkers. This can be done using large-scale-omic datasets, including transcriptomic, proteomic, and metabolomic datasets.[60] Given the many treatment options under consideration and in clinical trials for HF, dose-response data on relevant agents are urgently needed. These data, based on the above findings, will support efficient treatment design and target validation.[71]

Overall, MR analysis and previous analyses of HF GWAS data have shown that HF susceptibility loci have significant downstream effects on HF development and progression.[72] Using data from both animal models and human databases, such as DrugBank and DGI, we found that some drugs used to treat HF were previously shown to reduce the risk of developing HF in studies of other diseases. Notably, this was observed in prior studies on cancer.[73] These findings suggest that accumulated genetic data on human diseases may inspire new treatments for diverse diseases.[74]

The MR approach has been chosen to assess the causal relationship between PCSK9 inhibitors and HF. Specifically, this is a genetic linkage experiment of the type done in animal models of HF.[75] The congenic region carrying the human PCSK9 signal was derived from an outbred genetic background (coronary atherosclerosis-susceptible). It was bred onto the human inbred genetic background to produce six separate congenic strains. These then underwent left anterior descending coronary artery ligation to mimic a heart attack. This condition can be experimentally treated with a PCSK9 inhibitor (alirocumab), which improves survival, reduces morbidity, and improves ventricular performance.[76] Among

the six congenic and the parental lines, four congenic lines showed significantly improved survival and less morbidity than the parental line in the days after myocardial infarction. This included three long-term survivors up to 50 days with complete anatomical remodeling. Two more lines, although ultimately moribund, showed temporary improvement in HF phenotype.[77] This study, which combines GWAS, known drug actions, and animal validation, provides evidence that PCSK9 inhibitors could be used as a potential HF drug.[78]

The increasingly large datasets from GWAS, combined with powerful statistical and computational genetics tools, offer new opportunities. They allow for the development and evaluation of repurposed uses for drugs that are observed to associate with genetic risk factors.[65] For example, genetic findings have established new drug targets. This led to the development of PCSK9 inhibitors, a new class of cholesterol-lowering drugs. HF biomarker data show that those with genetically reduced PCSK9 levels have a reduced risk of HF.[79] Thus, human genetic data established the concept of using these drugs to prevent HF before any human clinical trial data were available.[80] A similar approach can be considered for a candidate drug targeting the NPC1 gene. This drug likely binds the angiotensin receptor two and has shown a strong association with HF in a trans-ethnic GWAS meta-analysis.[65]

CONCLUSION

HF is a complex and multifactorial syndrome that is recognized as a significant public health epidemic. Despite the availability of treatments, the management of HF remains a challenging quest. Drug development is inherently risky and expensive. DR is the repackaging of established drugs for new uses, thus reducing costs and saving time. Our review illustrates how data science and computational approaches can accelerate drug development, reduce resource waste, and improve quality of life for the HF patient population.

ACKNOWLEDGMENT

The author extends his appreciation to the Northern Border University, Arar, knowledge, skills and abilities, for providing the necessary facilities and support for this work.

ETHICAL DISCLOSURE

None required.

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Source of Support: Nil. **Conflicts of Interest:** None declared.