PREVALENCE OF DRUG-GENE INTERACTIONS FOLLOWING ACUTE MYOCARDIAL INFARCTION: AN OBSERVATIONAL STUDY USING DATA FROM THE UK BIOBANK

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Summary

+ Actionable drug-gene interactions (DGIs) are common among patients following acute myocardial infarction (AMI), affecting about 1 in 8 individuals (12.9%) in the two years after their event.
+ Substantial DGIs, defined as those with high predicted clinical impact due to specific genetic variants, were identified in 4.1% of patients. The most frequent involved clopidogrel with CYP2C19 and statins with SLCO1B1.
+ Combining genetic and prescribing data into clinical care may help close an important medicines optimisation gap in this high-risk group.

Background

- Common genetic variants can alter the function of enzymes responsible for drug metabolism, potentially leading to reduced efficacy or increased risk of adverse drug reactions[1].
- Several international groups, including the Clinical Pharmacogenetics Implementation Consortium (CPIC)[2] and the Dutch Pharmacogenetics Working Group (DPWG)[3], have developed therapeutic recommendations based on these drug-gene interactions (DGIs).
- These recommendations support dose adjustments or alternative therapies when DGIs are identified; these are known as actionable DGIs.
- Despite the availability of these guidelines and the burden of coronary heart disease[4], there is limited evidence on the prevalence of actionable DGIs in patients following cardiovascular events, such as acute myocardial infarction (AMI).
- Understanding the burden of DGIs in this high-risk population may reveal opportunities to use pharmacogenomic data to optimise prescribing and improve patient outcomes.

Objectives

To estimate the prevalence of actionable DGIs in patients following incident AMI and assess the commonality drug-gene combinations in the identified DGIs for this cohort.

Methods

Study design and population

- This was a retrospective cohort study using data from the UK Biobank – a cohort of 500,000 individuals living in the UK and aged 40-69 years at the time of recruitment[5].
- We included participants who experienced their first AMI after their baseline visit to a UK Biobank assessment centre and before 31 December 2017. Individuals with missing genotype information or primary care prescription data were excluded from the analysis.

Identification of drug-gene interactions

- Actionable DGIs were identified based on recommendations from the CPIC and the DPWG. Medication data were extracted from linked primary care records for the 2 years following each individual's incident AMI.
- Metaboliser phenotypes were determined using activity scores or CPIC standard diplotype-to-phenotype tables.
- Genetic variants in the following genes were included in the analysis to identify DGIs.

Table 1. Genetic variants assessed to identify actionable drug-gene interactions. SNP: Single Nucleotide Polymorphism.

Gene	Variants assessed	SNP IDs
CYP2C9	*2, *3	rs1799853, rs1057910
CYP2C19	*2, *17	rs4244285, rs12248560
CYP3A5	*3	rs776746
CYP2D6	*3, *4, *9, *10, *41	rs35742686, rs3892097, rs5030656, rs1065852, rs28371725
SLCO1B1	*5/*15	rs4149056
TPMT	*3A, *3B, *3C	rs1800460, rs1800460, rs1142345

Statistical analysis

For each individual, we recorded the number of actionable DGIs during the 2-year follow-up. Substantial DGIs were defined as those involving homozygous or compound heterozygous genotypes, expected to have a significant impact on drug metabolism or response.

Results

- We identified 6,820 individuals from the UK Biobank who experienced an incident AMI during the study period. The mean age was 60 years (SD=7), and 72.2% were male.
- In the 2 years following AMI, 883 individuals (12.9%) had at least one actionable DGI, and 227 individuals (3.3%) had multiple DGIs.

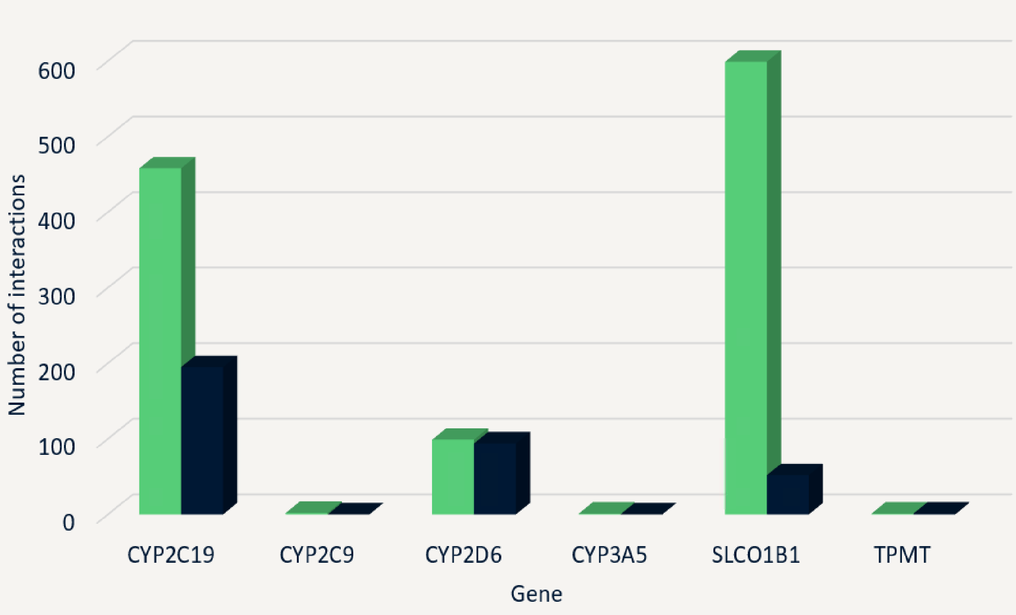

Figure 1. Number drug-gene interactions per gene following acute myocardial infarction.

Total: Number of DGIs across all individuals; Substantial: defined as those involving homozygous or compound heterozygous genotypes , expected to have a significant impact on drug metabolism or response

- A total of 1,160 actionable and 342 substantial DGIs were identified among individuals during the study period. Substantial DGIs were found in 4.1% of patients.
- 26 distinct drug-gene pairs were studied, with 18 pairs identified with at least one individual with an DGI across the dataset. The most common DGIs in this cohort were atorvastin-*SLCO1B1* (n=442), clopidogrel-*CYP2C19* (n=324), and simvastatin-*SLCO1B1* (n=157).
- The most common substantial DGIs were clopidogrel-*CYP2C19* (n=103) and amitriptyline-*CYP2D6* (n=63).

Conclusions

- DGIs are common after AMI, with nearly 13 percent of patients exposed to at least one actionable interaction.
- A significant proportion of patients (over 4 percent) had substantial DGIs likely to affect drug response or safety.
- There is a clear opportunity for medicines optimisation in post-AMI care through the use of pharmacogenomic information. This is especially salient given the increasing rates of multimorbidity and polypharmacy resulting in exposure to more mediations.
- Integrating genetic data with prescribing systems could improve treatment effectiveness and reduce adverse drug reactions in this high-risk population.

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