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Evidence for Clinical Implementation of Pharmacogenomics in Cardiac Drugs

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Abstract

Objective: To comprehensively assess the pharmacogenomic evidence of routinely used drugs for clinical utility.

Methods: Between January 2, 2011, and May 31, 2013, we assessed 71 drugs by identifying all drug/genetic variant combinations with published clinical pharmacogenomic evidence. Literature supporting each drug/variant pair was assessed for study design and methods, outcomes, statistical significance, and clinical relevance. Proposed clinical summaries were formally scored using a modified AGREE (Appraisal of Guidelines for Research and Evaluation) II instrument, including recommendation for or against guideline implementation.

Results: Positive pharmacogenomic findings were identified for 51 of 71 cardiovascular drugs (71.8%), representing 884 unique drug/variant pairs from 597 publications. After analysis for quality and clinical relevance, 92 drug/variant pairs were proposed for translation into clinical summaries, encompassing 23 drugs (32.4% of drugs reviewed). All were recommended for clinical implementation using AGREE II, with mean ± SD overall quality scores of 5.18±0.91 (of 7.0; range, 3.67-7.0). Drug guidelines had highest mean ± SD scores in AGREE II domain 1 (Scope) (91.9±6.1 of 100) and moderate but still robust mean ± SD scores in domain 3 (Rigor) (73.1±11.1), domain 4 (Clarity) (67.8±12.5), and domain 5 (Applicability) (65.8±10.0). Clopidogrel (*CYP2C19*), metoprolol (*CYP2D6*), simvastatin (rs4149056), dabigatran (rs2244613), hydralazine (rs1799983, rs1799998), and warfarin (*CYP2C9/VKORC1*) were distinguished by the highest scores. Seven of the 9 most commonly prescribed drugs warranted translation guidelines summarizing clinical pharmacogenomic information.

Conclusion: Considerable clinically actionable pharmacogenomic information for cardiovascular drugs exists, supporting the idea that consideration of such information when prescribing is warranted.

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Each year, more than 2 million patients experience adverse drug reactions (ADRs), the fifth leading cause of death in the United States.[1] In particular, cardiovascular drugs are a common cause of ADRs.[2,3] It is estimated that 53,457 individuals of all ages are treated annually in emergency departments for ADRs to cardiovascular agents.[2] In adults older than 65 years, cardiovascular drugs are implicated in a sizable fraction of hospitalizations for ADRs, most notably warfarin (33.3%) and antiplatelet agents (13.3%), among others.[3]

In addition to the harm caused by drug-related toxicities, the health care system wastes resources when medications are ineffective. Intolerance and suboptimal response rates to cardiovascular drugs have been widely reported.[4-7] For example, the response rate to any given hypertension medication is approximately 50%, regardless of the class of medication.[4,8] In general, drugs are developed based on their effectiveness in large, carefully selected populations; a drug's performance in that setting is less informative when treating individual patients.[5,9] Thus, there is a need to better identify therapies that are more likely to be beneficial and less likely to cause harm to individual patients, who show remarkable variability in their response to medications.[10,11]

Pharmacogenomics, the study of genetic variation in drug response, has enabled the identification of genetic variants that impact response or toxicity to several prominent cardiovascular drugs.[5,9,12-16] Although the effective

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clinical translation of this information has the potential to guide the selection and dosing of medications,[4,17] few cardiovascular drug pharmacogenomic findings have been translated into clinical practice.[18,19] This gap in translation exists for numerous reasons, including lack of knowledge and cost-effectiveness concerns.[19] Foremost among these, however, is the need to establish clinical utility.[16,20] Yet, as exemplified by the cases of clopidogrel and warfarin, even when a Food and Drug Administration (FDA) label is changed in recognition of the potential clinical impact of pharmacogenomic evidence, controversy concerning the implementation of this information persists.[16,18,21-29] In light of these challenges, there is considerable disagreement concerning the overall strength of pharmacogenomic evidence, with some researchers[30,31] arguing that the evidence is considerable and others[32,33] refuting its overall usefulness.

Because cardiovascular drugs are widely prescribed,[34] this study aimed to rigorously assess the state of potential clinical utility for the pharmacogenomic evidence surrounding cardiovascular drugs, a necessary foundation for clinical implementation. We systematically assessed the quality and quantity of pharmacogenomic data to permit and inform clinical implementation projects that will ultimately determine utility on clinical outcomes. We sought to critically appraise the pharmacogenomic literature and propose translation-enabling clinical summaries on a drug-by-drug basis. We hypothesized that the composite amount of clinically relevant pharmacogenomic information for cardiovascular drugs would provide considerable evidence for a major contribution to drug-prescribing decisions.

METHODS

Data Collection

From publicly available sources, including all FDA-approved drugs and the Pharmacogenomics Knowledge Database (PharmGKB),[35] a list of commonly prescribed cardiovascular drugs was selected (Supplemental Appendix A, available online at http://www.mayoclinicproceedings.org). For each drug, a manual literature search of PubMed was performed. The formal search began in January 2011, but inclusion of papers was not restricted by this date; rather, any publication from any month and year until May 2013 that met the search criteria was included for subsequent review. The search criterion used was *[drug name] polymorphism*. Only articles that assessed a link between a germline genetic variant and a pharmacologic or clinical outcome were included. Non—English-language articles, articles concerning in vitro studies, pediatric studies, manuscripts simply describing literature searches, and reviews were excluded. All articles meeting these inclusion and exclusion criteria were then formally reviewed using the process described herein. The complete date range of the study was January 2, 2011, to May 31, 2013.

Data Assessment

The unit of study, the drug/variant pair, refers to a specific drug and genetic variant (eg, hydrochlorothiazide and rs1799752). The drug/variant pairs reported in each article were cataloged with supporting PubMed identifiers in a database built to support a larger clinical pharmacogenomics implementation project, the 1200 Patients Project.[36] This database catalogs a list of pharmacogenomic publications and reported drug/variant pairs for more than 650 drugs.[36] The publication concerning each pair in the database is classified as positive pharmacogenomic information if the authors reported a positive genotype-phenotype association or as negative pharmacogenomic information if the association was not reported as significant; these designations were verified during the literature review and were corrected if necessary after reviewing the paper. Drug/variant pairs were then first stratified regarding their supporting evidence using 4 criteria: (1) a drug/variant pair with 3 or more positive supporting publications in the 1200 Patients Project database ("3+ studies"); (2) a drug/variant pair independently clinically annotated (publicly available pharmacogenomic "clinical annotation" on the PharmGKB webpage[35]) by PharmGKB ("PharmGKB"); (3) both (1) and (2) ("3+ studies and PharmGKB"); and (4) none of the above ("other"). The PharmGKB data used for these analyses were captured between January 1, 2012, and May 31, 2013.

Each positive publication supporting a cardiovascular drug/variant pair was then comprehensively assessed. Pharmacogenomic associations were assessed for study cohort