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Pharmacogenetic Risk Scores for Perindopril Clinical and Cost Effectiveness in Stable Coronary Artery Disease: When Are We Ready to Implement?

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Pharmacogenetic Risk Scores for Perindopril Clinical and Cost Effectiveness in Stable Coronary Artery Disease: When Are We Ready to Implement?

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In this issue of the *Journal of the American Heart Association*, Oemrawsingh et al present a very interesting and well-executed analysis of clinical and pharmacogenetic risk scores for perindopril effectiveness in 8726 patients with stable coronary artery disease.[1] Their results demonstrate that the clinical risk score can predict patient risk but not the relative risk reduction of the therapy, which was homogeneous across clinical risk groups. In contrast, the pharmacogenetic risk scores could differentiate patients in terms of the effectiveness of therapy; in the 26.5% of patients with a risk score >2, perindopril was *not* associated with clinical benefit (primary end point: cardiovascular mortality, nonfatal myocardial infarction, or resuscitated cardiac arrest), while an enhanced benefit was seen in the remaining 73.5%. The authors then added to this by quantifying the clinical and cost implications of various clinical and pharmacogenetic risk score strategies. Genetically testing all patients and only treating those with a pharmacogenetic risk score ≤2 was equally clinically effective and more cost-effective compared to standard care (ie, no genetic testing, all patients are treated with perindopril).

By combining the pharmacogenetic risk score with a published clinical risk score[2] and analyzing the cost-effectiveness of the combination, this study by Oemrawsingh et al is an important extension of their initial publication of the pharmacogenetic risk score in 2010.[3] The current study

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has several strengths: large sample size, randomized controlled data, assessment of pharmacogenetic risk factors in the context of clinical risk strata, inclusion of a cost-effectiveness analysis, and the relative simplicity of the pharmacogenetic score. However, like many excellent publications, this one prompts as many questions as it answers. Are we ready to accept the likelihood that 1 in 4 stable coronary artery disease patients are treated ineffectively (or perhaps even harmfully?) with perindopril, wasting precious resources and effort? Should we implement pharmacogenetic tailored therapy now, and if not, when will we have sufficiently convincing data to do so? While the United States Food and Drug Administration (FDA) has incorporated genetics into the prescribing information for >130 drugs[4] (Table), and the Clinical Pharmacogenetics Implementation Consortium has published 33 guidelines on pharmacogenetic information (Table),[5] pharmacogenetics has not achieved significant use in cardiology. There are several important barriers including logistical and educational concerns,[6] but equally important and relevant to the work by Oemrawsingh et al are the cost implications and unclear standards for levels of evidence required to justify pharmacogenetic testing.

Regarding costs, the current work is very helpful. Oemrawsingh et al estimated the cost to genotype all 3 variants used in their pharmacogenetic risk score to be only €15 euros (approximately $17 USD), and currently, 2.5 million genetic variants in an individual patient can be simultaneously tested in a single sample for around $300 USD. For comparison, a single comprehensive metabolic panel, which is often repeated annually, costs around $600. Unlike many other types of laboratory tests, the patient's DNA is static, and thus genetic testing only needs to be performed once to provide lifetime results. Despite the declining costs of genetic testing and examples of cost-effectiveness as reported by Oemrawsingh et al, the barrier that patients and providers most often face is lack of reimbursement for pharmacogenetic testing (not only in the United States but in Europe as well).[7,8] Pharmacogenetic tests for most cardiovascular drugs are not reimbursed, except for clopidogrel and warfarin. For example, 7 different third-party payers, including Medicare, have

Table. Cardiovascular Drugs With Pharmacogenetic Information Included in the US FDA Prescribing Information and CPIC guidelines.

Drug	Source	Summary of Pharmacogenetic Information
Carvedilol	US FDA	"Retrospective analysis of side effects in clinical trials showed that poor 2D6 metabolizers had a higher rate of dizziness during up-titration"
Clopidogrel	US FDA	"Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers." (Black Box Warning)
Clopidogrel	CPIC	"The CPIC Dosing Guideline for clopidogrel recommends an alternative antiplatelet therapy (eg, prasugrel, ticagrelor) for CYP2C19 poor or intermediate metabolizers if there is no contraindication."
Isosorbide and hydralazine	US FDA	"Hydralazine is metabolized by acetylation . . . About 50% of patients are fast acetylators and have lower exposure" "In patients with heart failure, mean absolute bioavailability of a single oral dose of hydralazine 75 mg varies from 10% to 26%, with the higher percentages in slow acetylators."
Metoprolol	US FDA	"Metoprolol is metabolized predominantly by CYP2D6, an enzyme that is absent in about 8% of Caucasians (poor metabolizers) and about 2% of most other populations." "Poor metabolizers and extensive metabolizers who concomitantly use CYP2D6 inhibiting drugs will have increased (several-fold) metoprolol blood levels, decreasing metoprolol's cardioselectivity."
Prasugrel	US FDA	"There is no relevant effect of genetic variation in CYP2B6, CYP2C9, CYP2C19, or CYP3A5 on the pharmacokinetics of prasugrel's active metabolite or its inhibition of platelet aggregation."
Propafenone	US FDA	"Simultaneous use with both a CYP3A4 and CYP2D6 inhibitor (or in patients with CYP2D6 deficiency) should be avoided."
Propranolol	US FDA	"In healthy subjects, no difference was observed between CYP2D6 extensive metabolizers (EMs) and poor metabolizers (PMs) with respect to oral clearance or elimination half-life."
Quinidine	US FDA	"Quinidine is not metabolized by cytochrome P450IID6, but therapeutic serum levels of quinidine inhibit the action of cytochrome P450IID6, effectively converting extensive metabolizers into poor metabolizers. Caution must be exercised whenever quinidine is prescribed together with drugs metabolized by cytochrome P450IID6."
Ticagrelor	US FDA	"In a genetic substudy cohort of PLATO, the rate of thrombotic CV events in the BRILINTA arm did not depend on CYP2C19 loss of function status."
Simvastatin	CPIC	"The FDA recommends against 80 mg daily simvastatin dosage. In patients with the C allele at SLCO1B1 rs4149056, there are modest increases in myopathy risk even at lower simvastatin doses (40 mg daily); if optimal efficacy is not achieved with a lower dose, alternate agents should be considered."
Warfarin	US FDA	"CYP2C9 and VKORC1 genotype information, when available, can assist in selection of the initial dose of warfarin." (A table of expected warfarin maintenance doses based on CYP2C9 and VKORC1 genotypes is provided.)
Warfarin	CPIC	"The best way to estimate the anticipated stable dose of warfarin is to use the algorithms available on http://www.warfarindosing.org." (This recommendation is from 2011. CPIC guideline authors are aware of more recently published warfarin pharmacogenetic studies and will incorporate them into an updated guideline.)

Data from http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics and with guidelines published by CPIC (www.PharmGKB.org). 2D6 indicates cytochrome P450 family 2 subfamily D member 6; CPIC, Clinical Pharmacogenetics Implementation Consortium of the U.S. National Institutes of Health's Pharmacogenomics Research Network; CYP2B6, cytochrome P450 family 2 subfamily B member 6; CYP2C9, cytochrome P450 family 2 subfamily C member 9; CYP2C19, cytochrome P450 family 2 subfamily C member 19; CYP2D6, cytochrome P450 family 2 subfamily D member 6; CYP3A4, cytochrome P450 family 3 subfamily A member 4; CYP3A5, cytochrome P450 family 3 subfamily A member 5; P450IID6, cytochrome P450 family 2 subfamily D member 6; PLATO, trial of ticagrelor vs clopidogrel in patients with acute coronary syndromes; SLCO1B1, solute carrier organic anion transporter family member 1B1; US FDA, United States Food and Drug Administration; VKORC1, vitamin K epoxide reductase complex subunit 1.

reimbursed for a clopidogrel pharmacogenetic test, with an 85% reimbursement rate.[9] Although Oemrawsingh et al demonstrated cost-effectiveness for their perindopril pharmacogenetic strategy, cost-effectiveness is often not enough to gain reimbursement. According to case studies published in 2010, the strongest predictor of pharmacogenetic test reimbursement is the strength of available evidence.[7]

In terms of level of evidence, the PERGENE study and idea of pharmacogenetic-guided treatment for angiotensin-converting enzyme (ACE) inhibitors in stable coronary artery disease still needs some additional steps. We feel most observers would agree that the pharmacogenetic risk score presented by Oemrawsingh et al must be, at a minimum,

replicated in an independent data set before it can be taken forward. However, this should be quite achievable, and should be a high-priority research topic. We also do not know that the same pharmacogenetic effect is at play for other ACE inhibitors, though a class effect seems likely. Ideally a validating study could answer both of these questions (ie, testing a distinct patient cohort and a different ACE inhibitor). Another issue is that the mechanisms of the genetic variants used in the pharmacogenetic risk score are unknown (Figure); the authors selected genetic variants based on linkage disequilibrium.[3] Moreover, linkage disequilibrium differs depending on ancestry, and thus this pharmacogenetic risk score may not be applicable to patients who are not of
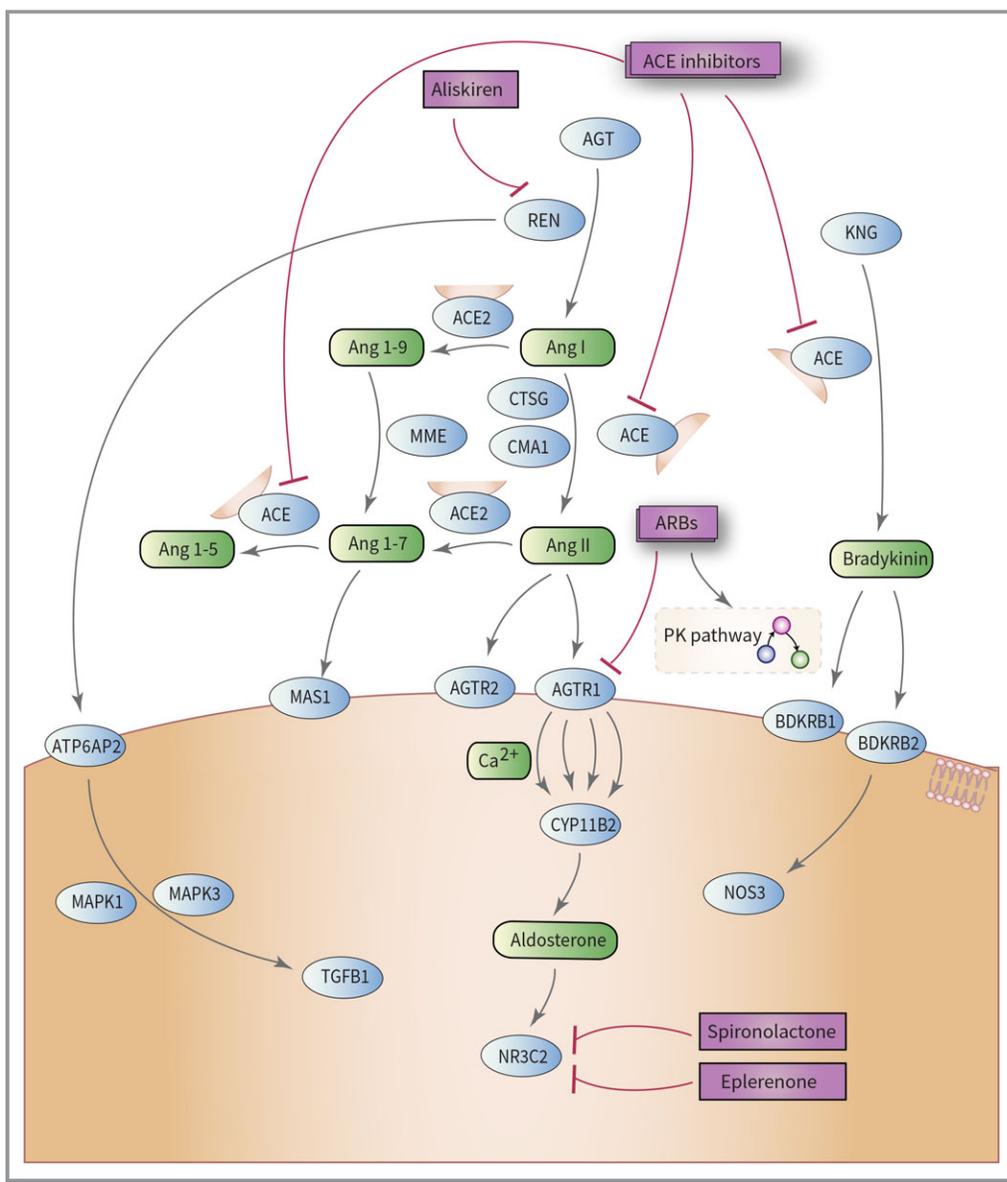
Figure. Agents acting on the renin–angiotensin system pathway ©PharmGKB. Reproduced with permission from the Pharmacogenomics Knowledge Base (PharmGKB) and Stanford University (https://www.pharmgkb.org/pathway/PA165110622#PGG).[5] ACE indicates angiotensin-converting enzyme; AGT, angiotensinogen; AGTR1, angiotensin II receptor type 1; AGTR2, angiotensin II receptor type 2; Ang, angiotensin; ARB, angiotensin receptor blocker; ATP6AP2, ATPase H+ transporting accessory protein 2; BDKRB1, bradykinin receptor B1; BDKRB2, bradykinin receptor B2; CMA1, chymase 1; CTSG, cathepsin G; CYP11B2, cytochrome P450 family 11 subfamily B member 2; KNG, kininogen; MAPK1, mitogen-activated protein kinase 1; MAPK3, mitogen-activated protein kinase 3; MAS1, MAS1 proto-oncogene; MME, membrane metallo-endopeptidase; NOS3, nitric oxide synthase 3; NR3C2, nuclear receptor subfamily 3 group C member 2; PK, pharmacokinetic; REN, renin; TGFB1, transforming growth factor β1.

European ancestry. Given this, and the well-recognized racial variation in effectiveness of many cardiovascular medications, additional validation studies of this pharmacogenetic test in patients of non-European ancestry are necessary and would be required prior to contemplating using it for clinical purposes in other racial groups.

Assuming that the Oemrawsingh et al findings can be replicated, should this strategy then be clinically implemented? First consider the myriad of nongenetic patient factors that we constantly use to guide cardiovascular drug therapy without prospective trial data. For example, co-treatment of omeprazole with clopidogrel is often avoided due

to a drug–drug interaction *without prospective trial data*. However, the pharmacogenetic effects on clopidogrel are just as strong as the drug–drug interaction with omeprazole.[10] Warfarin dose is empirically decreased in patients starting amiodarone due to a drug–drug interaction *without prospective trial data*.[11] However, the pharmacogenetic effects on warfarin dose are stronger than the drug–drug interaction with amiodarone.[12] Patients are advised to avoid grapefruit juice while taking simvastatin due to a drug–food interaction *without prospective trial data*.[13] However, the pharmacogenetic effects on simvastatin blood concentrations are just as large as the effects of the drug–food interaction with grapefruit juice.[14] Similar to nongenetic factors used to guide drug therapy, the decision to use pharmacogenetic testing should consider the total risks and benefits, including, for example, the severity of potential side effects averted, or the difference in efficacy, and even the cost/potential savings.

An argument often used against comparing genetic to nongenetic factors to guide drug therapy is that nongenetic factors are usually readily available, but genetic test results are not. However, keep in mind that we also delay drug therapy based on nongenetic factors. For example, the initiation of ACE inhibitor therapy is delayed until the return of laboratory results ruling out renal insufficiency. Moreover, the lack of readily available genetic test results may no longer be an issue since many institutions and laboratories (http://www.ncbi.nlm.nih.gov/gtr/) now offer pharmacogenetic testing. More importantly, with the continually decreasing cost and increasing scale of genetic testing, it is anticipated that genetics will ultimately become a routine part of the electronic medical record for all patients. Thus, there are many current situations where genetic information could impact clinical decisions in terms of "best available evidence," even if it does not meet the commonly held evidence–based medicine standards of having multiple clinical trials on a single intervention.

A second consideration is whether we are holding pharmacogenetics to an unequal standard. In a 2015 Scientific Statement by the American Heart Association,[15] the authors recommended against pharmacogenetic testing for clopidogrel because "... no clinical trials assessing the utility of a CYP2C19 genotype test to guide and tailor therapy in a way that leads to improved patient outcomes have been published ..." However, in the same 2015 Scientific Statement, the authors endorse genetic testing for long QT syndrome, stating it "can potentially help guide patient management," and they provide recommendations for potential interventions *without prospective trial data*. Moreover, in cancer treatment guidelines, pharmacogenetic recommendations for thiopurine drugs are widely accepted but not informed by a randomized controlled trial.[16,17]

The standard of evidence required for the clinical implementation of pharmacogenetic testing is widely debated.[18] The "gold standard" of evidence for pharmacogenetic appli-

cations, as stated in a 2012 Special Report on Cardiovascular Pharmacogenomics in the *Journal of the American Heart Association* is "a prospective trial with treatment determined by genotype and with a clinical end point as the primary outcome ..."[19] The study by Oemrawsingh et al falls short of this because it is a retrospective analysis of a prospective clinical trial. However, the authors of the 2012 Special Report do state "... it also recognized that it would be very difficult to sustain and fund a large number of such trials." This is an understatement; it would be nearly impossible to perform a genetically guided randomized trial for every possible drug and indication, particularly drugs that are already FDA approved. Indeed, a single prospective trial takes several years to complete and costs tens of millions of dollars (or more). The authors of the 2012 Special Report go on to say "... in some cases the weight of evidence from observational studies may be so compelling as to render prospective trials unnecessary."[19] We agree with this assertion and posit that what is needed is more clarity regarding what this level of evidence should look like so that widely acceptable and achievable standards can exist. We would propose that retrospective analyses of multiple prospective clinical trials validating a specified pharmacogenetic approach should be adequate evidence. As a further step, if there is evidence from 1 clinical trial (as in the case of the current study), validation in an independent, adequately sized, and well–phenotyped observational cohort (or vice versa) is likely enough to justify clinical pharmacogenetic implementation. This is of course a debatable point, but with a strong preponderance of evidence, and the best interest of all patients in mind, we feel it may be most satisfactory. The alternative of ignoring congruent data from multiple large studies and simply continuing a standard of care that is wasteful (and even potentially harmful) in an easily identifiable subgroup of patients seems unappealing.

In conclusion, the study by Oemrawsingh et al is an important contribution despite the fact that the pharmacogenetic association is not new. It spotlights a practical path forward to precision medicine for ACE inhibitors in stable coronary artery disease, and it quantifies the motivation for doing so in terms of clinical and cost-effectiveness. The major limitation of the study is the lack of a sufficient replication data set. If validation testing can be achieved, then clinical care can be fundamentally altered. While there are other scientific questions remaining regarding the mechanisms of the genetic variants, the alternative therapy in patients with a pharmacogenetic risk score >2, and application in non-European ancestry patients, these can be addressed in additional future studies. More important is to hear this as a wake-up call so that the clinical and scientific communities can reach a better consensus regarding when and how to put findings like these into action clinically. Improved care for our patients is waiting.

Disclosures

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