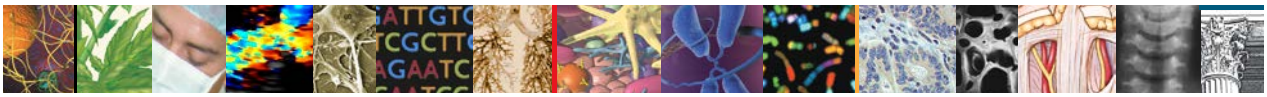

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

DECEMBER 12, 2013

Pharmacogenetics and Coumarin Dosing — Recalibrating Expectations

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Coumarin anticoagulants, though effective, are notoriously difficult to dose. Several factors make these drugs ideally suited for genetically tailored therapy: they have narrow therapeutic indexes; interpatient variability in dose requirements is high (e.g., warfarin is available in at least nine dose strengths with an order-of-magnitude difference between the lowest and highest); and among the known determinants of dose requirements, genetic variation explains the largest proportion of variability.

Anticoagulant-associated morbidity and mortality remain unacceptably high, and consideration of patient-specific factors in the initiation and maintenance of therapy with coumarin anticoagulants is critical. To that end, the Food and Drug Administration (FDA) recognized the importance of considering genetic variations in conjunction with clinical variables by updating the warfarin label in 2007. At that time, precise warfarin-dose needs in patients with various *CYP2C9* and *VKORC1* genotypes were not well established; therefore, the label simply raised awareness of genetic variation as important for consideration. A second label revision in 2010 reflected more detailed pharmacogenetic dosing that was based on emerging data.[1] This label did not recommend that dosing be predicated on genetic test results, but rather noted that genotype, if known, should be considered in dose selection and follow-up.

Coumarin pharmacogenetic testing is not routinely performed despite extensive scientific evidence establishing *CYP2C9* and *VKORC1* variations as important to coumarin-dose requirements. The biomedical research and clinical communities are largely undecided as to the usefulness of incorporating pharmacogenetic information into coumarin prescribing decisions. An often-cited reason is the paucity of randomized, controlled trials showing the superiority of genotype-informed dosing strategies over routine care. As reported in this issue of the *Journal*, three randomized, controlled trials tested related hypotheses yet arrived at different results. Careful assessment of these trials is necessary in order to reframe the dialogue regarding evidentiary assessment of coumarin pharmacogenetics.

In the Clarification of Optimal Anticoagulation through Genetics (COAG) trial, patients in whom warfarin therapy was being initiated were randomly assigned to dose determination

by either a clinical algorithm that mathematically accounts for known nongenetic determinants of warfarin-dose requirements or a pharmacogenetic algorithm that also includes *CYP2C9* and *VKORC1* genotype (see article by Kimmel et al., pages 2283–2293). Over the course of 4 weeks, the mean percentage of time in the therapeutic range did not differ significantly between groups (approximately 45% in both groups), nor did the time to achievement of the first therapeutic international normalized ratio (INR), the time to a stable warfarin dose, or a composite safety end point of over- and undercoagulation (time to any INR of ≥4, major bleeding episode, or thromboembolism). The pharmacogenetic algorithm was associated with a lower percentage of time in the therapeutic range through 4 weeks among black patients. Maintenance doses predicted by the pharmacogenetic algorithm were slightly better correlated with actual observed maintenance doses than were doses predicted by the clinical algorithm; many patients in both groups (about one third) required significantly higher or lower maintenance doses than the routinely prescribed 5 mg.

Verhoef et al. (pages 2304–2312) and Pirmohamed et al. (pages 2294–2303) report the results of two randomized, controlled trials from the European Pharmacogenetics of Anticoagulant Therapy (EU-PACT) Group. Verhoef et al. used a strategy that was similar to that used in the COAG trial (a genotype-based algorithm vs. a clinical-based algorithm), but in contrast with the COAG trial, the EU-PACT trials assessed the primary end point at 12 weeks, and the dose adjustments were managed according to local clinical practices after the initial dosing phase (whereas the COAG trial used standardized dose-adjustment techniques). Verhoef et al. found no significant difference between algorithmic strategies in the primary end point of percentage of time in the therapeutic range over 12 weeks; the pharmacogenetic algorithm, however, performed better than the clinical-only algorithm on this measure over the first 4 weeks (the time point for primary end-point assessment in the COAG trial).

A question of public health interest is whether pharmacogenetic-informed algorithms are superior to local standards of care. That was the question tested by Pirmohamed et al., who compared a genotype-based algorithm to a 3-day loading-dose regimen (nonalgorithmic) followed by usual care, also examined over a 12-week period. This trial showed that pharmacogenetic-guided initiation of warfarin therapy resulted in a greater percentage of time in the therapeutic range, fewer excessive INRs, a shorter median time to therapeutic INR, and fewer dose adjustments. Also impressive was that the curves for the percentage of time in the therapeutic range separated quite early between the genotype-guided and control groups (in the first 5 to 10 days) and did not converge over the course of 12 weeks — results suggesting a sustained benefit of early intervention.

Several points may help place these results into practical context. The reported trials (and other similarly designed studies) included frequent INR measurement irrespective of the participant's assigned intervention group. This strategy allows for dense sampling for construction of primary and other efficacy end points but makes it difficult to get a true estimate of the intervention's effectiveness. Specifically, many coumarin-treated patients are not cared for in anticoagulation clinics or other settings where frequent monitoring is the rule; in addition, many patients are unable or unwilling to report for frequent blood draws. Any differential effect between one intervention and another may be obscured, since either strategy, when combined with frequent adjustments based on INR, is likely to be superior to what is currently practiced in the community. Furthermore, the COAG trialists and Verhoef et al. assessed whether dosing algorithms that consider genetics in addition to clinical variables perform better than clinical algorithms alone. It is not surprising that these trials failed to meet their primary end points, because it is unlikely that the addition of one or two explanatory covariates, affecting a relatively small proportion of the overall trial population, would substantially affect the performance of a multivariable model, especially in settings in which frequent INR monitoring is conducted.

Minimizing bleeding and thromboembolic risks is the goal of optimized coumarin dosing: the percentage of time in the therapeutic range is intended to be a surrogate for prevention of such events. Use of the pharmacogenetic algorithm in the COAG trial was associated with a trend toward fewer major bleeding events (1% vs. 4%) and fewer clinically relevant nonmajor bleeding events over the entire follow-up period, especially in black patients (6% vs. 13%). Verhoef et al. report no major bleeding events in the pharmacogenetic-algorithm group and one in the clinical-algorithm group. Pirmohamed et al. report no clinically significant bleeds re-

quiring hospitalization in the pharmacogenetic group, whereas three such events occurred in the control group. These trends, which are consistent across studies, suggest that uncommon but clinically meaningful outcomes should be considered in addition to intermediate end points (e.g., percentage of time in the therapeutic range) in a totality-of-evidence approach to assessing the usefulness of pharmacogenetic approaches.

The public's expectations for pharmacogenetics may arguably be declining. Logistic and evidentiary challenges have converged to create disillusionment regarding the relevance of pharmacogenetics. Many observers have called for randomized, controlled trials to address the translation lag. Methodologic rigor is critical in evidence assessment, and it is equally important to design experiments to definitively clarify issues of public health relevance. Randomization, in and of itself, does not accomplish this end. Rather, the choice of control, the treatment setting, characteristics of the population tested, the analytic approach, and end-point definition are likely to be the key considerations that determine the public health relevance of pharmacogenetic trials in the future. Future trials should use various methods to assess the clinical usefulness of pharmacogenetic interventions; these may include designs focused on assessing efficacy (emphasis on internal validity), effectiveness (emphasis on generalizability), and implementation effectiveness (emphasis on adoption and uptake).[2] These approaches are not mutually exclusive and, if combined, may expedite assessment of the effects of pharmacogenetic interventions on patients, providers, and health systems.[3,4]

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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DOI: 10.1056/NEJMp1314529

New Insights into the Dementia Epidemic

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Described in the early 1980s as "The Silent Epidemic," dementia in the elderly will soon become a clarion call for public health experts worldwide. The epidemic is largely explained by the prevalence of dementia in persons 80 years of age or older. In most countries around the world, especially wealthy ones, this "old old" population will continue to grow, and since it accounts for the largest proportion of dementia cases, the dementia epidemic will grow worldwide. The combined effects of longer lives and the dramatic bulge of baby boomers reaching old age will magnify the epidemic in future decades.

Although demographics will drive an increase in the number of dementia cases, recent reports — generally based on population-based community studies or survey data — point to declining age-specific prevalence or incidence rates among people born later in the first half of the 20th century (see table). We believe these reports are intriguing and inform our understanding of potentially modifiable factors that contribute to the epidemic of this common and often tragic condition. Knowing about contributing factors is especially important for the study and development of prevention strategies, and prevention is often the key to better control of epidemics, including epidemics of chronic diseases.

In 2005, Manton and colleagues published an intriguing article entitled "Declining Prevalence of Dementia in the U.S. Elderly Population."[1] On the basis of their analysis of 17 years of national long-term care surveys, conducted from 1982 through 1999, they reported a decrease in dementia prevalence from 5.7% to 2.9% during that period. They pointed to higher levels of education, a reduction in stroke rates, and other factors as possible contributors to the decrease.

This report was followed by an analysis of the U.S. Health and Retirement Study, an ongoing population-based, longitudinal survey of a nationally representative sample of adults 51 years of age or older.[2] In 1993, 12.2% of surveyed adults 70 years of age or older had cognitive impairment,