Individualized Medical Decision Making

Necessary, Achievable, but Not Yet Attainable

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The need is urgent to provide older persons with individualized information about the benefits and harms of different diagnostic and treatment strategies. This need results from the growing recognition of the heterogeneity in outcomes in older persons with differing comorbidity profiles. The heterogeneity of benefits and harms resulting from treatment is not yet as well appreciated. Warfarin vs aspirin therapy for the reduction of stroke risk in nonvalvular atrial fibrillation provides an example of a treatment for which the benefit-to-harm ratio may actually reverse according to an older person’s comorbidities, thus highlighting the importance of basing this treatment decision on individualized outcome data. Despite the wealth of studies in nonvalvular atrial fibrillation, many assumptions are necessary to calculate patient-specific outcomes, and these assumptions may lead to substantial overestimation or underestimation of benefits and harms. Improving care for patients with comorbidities will require substantive increases in the efforts and resources allocated to the collection and dissemination of outcome data for patients with varying comorbidities.

Evidence is growing for the need to use patient-specific data regarding the expected benefits and harms of different diagnostic and treatment strategies to inform medical decision making. It is well recognized that the average benefits and risks as measured in randomized controlled trials (RCTs) may not apply to the individual patient. This is particularly true for older patients, in whom comorbid conditions and functional disability can diminish the benefits of standard diagnostic and therapeutic strategies. For example, an 81-year-old woman with no comorbidities has a life expectancy of 13.8 years after a diagnosis of stage 1 colon cancer, whereas an 81-year-old woman with 3 or more comorbidities has a life expectancy of only 4.9 years.

COMORBIDITIES AND THE NEED FOR INDIVIDUALIZED MEDICAL DECISION MAKING

Treatment decisions in older adults with varying comorbidities are frequently even more complex than are those involving testing because they require an individualized assessment of outcomes associated with multiple options. To illustrate the importance of basing treatment decisions on individualized patient data in clinical practice, we present the example of anticoagulation in nonvalvular atrial fibrillation (NVAF). This is a clinical scenario in which benefits (ie, stroke risk reduction) and harms (ie, increased bleeding risk) of treatment vary considerably such that the benefit-to-harm ratio can reverse according to the patient’s specific comorbid conditions. Significant advances have been made to improve decision making at the individual patient level, including the use of prediction rules, risk calculators, and

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decision aids. However, despite these advances, the ability to provide individualized outcome assessments based on available data remains limited. Because gaps in knowledge regarding outcomes can result in underestimates and overestimates of benefits and harms, it is expected that treatment decisions would differ if based on more accurate outcome data.

VARIABILITY IN EXPECTED OUTCOMES

The decision regarding therapy for reducing stroke risk in NVAF involves trade-offs among bleeding, stroke, and inconveniences associated with 3 options: warfarin therapy, aspirin therapy, and no therapy. A recent meta-analysis of 29 RCTs (mean patient age, 71 years; 35% women) found a greater absolute reduction in stroke risk and a small incremental risk of major hemorrhage associated with warfarin therapy compared with aspirin therapy. As a result, guidelines recommend the use of warfarin for patients at moderate or high risk for stroke who do not have an absolute contraindication to warfarin. In contrast, several observational studies have demonstrated that the risk of bleeding associated with warfarin therapy is not small. In a population-based study using Medicare data, the rate of bleeding resulting in hospitalization ranged from 1.9 to 12.3 per 100 patient-years.

Several observational studies have demonstrated that the risk of stroke and the risk of bleeding vary according to patient comorbidities. Because of this variability in risk, there is a large range in the incremental risks and benefits associated with warfarin therapy, aspirin therapy, and no therapy. The Table provides examples of the 5-year risks of stroke and bleeding, converted from annualized outcome rates, associated with each treatment option for two 70-year-old men with different comorbidities. Baseline stroke and bleeding risks with warfarin therapy were based on validated risk calculators derived from observational, population-based data. The risks of stroke with warfarin and aspirin use were derived by applying the 67% and 21%, respectively, reduction in stroke risk associated with these 2 therapies published in a meta-analysis of RCT data. Risk calculators are unavailable for risk of bleeding with no therapy and with aspirin therapy; therefore, these risks were taken from a systematic review.

As can be seen in the Table, expected outcomes calculated using the best-available data vary markedly according to the individual’s comorbidities. Moreover, specific comorbidities differentially affect the risk of stroke and bleeding. For example, in the case of a 70-year-old man with well-controlled hypertension, heart failure, diabetes mellitus, and non-ulcer-related abdominal pain, the first 3 comorbid conditions increase his baseline risk of stroke but not bleeding, and the last comorbid condition modestly increases his risk of bleeding with aspirin therapy but not with warfarin therapy. In contrast, for a 70-year-old man with poorly controlled hypertension, renal disease, and a history of a fall, only the first comorbid condition increases his baseline stroke risk, whereas all the comorbidities increase his bleeding risk.

Despite the availability of numerous studies and formal meta-analyses, the best-available calculations of individualized benefit and harm in NVAF still depend on a variety of assumptions because of the absence of data needed to provide individualized estimates. Herein we outline how the absence of these data affects decision making at the individual patient level.

GAPS IN AVAILABLE DATA

Duration of Follow-up

The decision of whether to initiate aspirin or warfarin therapy is based on the trade-off between the expected reduction in stroke risk and the increase in bleeding risk in the long-term, yet RCTs have an average follow-up of less than 1.5 years per patient. The absolute number of outcomes in this short time frame is small and does not reflect the larger absolute difference in outcomes associated with therapy in the long-term that may be more meaningful to patients. To generate long-term outcome data, outcome rates must be extrapolated from person-year rates. This conversion assumes that rates remain constant across time. This assumption, although widely applied, may not be accurate. On the one hand, the risks of bleeding with warfarin therapy have been shown to be highest in the months after initiation of therapy and to subsequently decrease with time. Therefore, long-term bleeding rates calculated from short-term studies may overestimate the risk of bleeding. On the other hand, a patient in whom comorbid conditions accumulate across time might be expected to be at even higher risk for bleeding.

Baseline Risk of Adverse Events

Recognition of the need to quantify the risk of adverse events resulting from treatment has generally not

### Table. Five-Year Risk of Stroke and Bleeding Associated With No Treatment, Aspirin Therapy, and Warfarin Therapy in the Treatment of NVAF According to Comorbid Conditions

<table>
<thead>
<tr>
<th>Comorbid Condition</th>
<th>No Medication</th>
<th>Aspirin Therapy</th>
<th>Warfarin Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>26</td>
<td>21</td>
<td>9</td>
</tr>
<tr>
<td>Bleeding</td>
<td>4</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Stroke</td>
<td>13</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Bleeding</td>
<td>2</td>
<td>4</td>
<td>34</td>
</tr>
</tbody>
</table>

Abbreviation: NVAF, nonvalvular atrial fibrillation.
been accompanied by recognition of the need to quantify these same outcomes without treatment. The lack of data regarding baseline risks of adverse events supports the assumption that these rates are negligible, as evidenced, for example, by the presentation of bleeding risk as zero in an NVAF decision aid. Failure to present baseline rates of adverse outcomes, however, leads to overestimates of the harm associated with therapy. For example, if baseline bleeding risks were not included in the Table, the incremental risks associated with aspirin and warfarin therapy would seem larger. Data available for calculating baseline bleeding risk are limited to a study that adjusted for only the most basic risk factors using relative risks pooled from heterogeneous studies.

Choice of Outcomes

Risks and harms of different treatment options are generally presented in terms of disease-specific outcomes. Yet, several studies have demonstrated that the outcomes of greatest importance to individuals are the sequelae of these diseases. In NVAF, what may matter most to patients is not the risk of stroke or bleeding but rather the risks of functional and cognitive disability. Functional outcomes of stroke can be extrapolated from other stroke cohorts, but no studies, to our knowledge, examine these outcomes in patients with NVAF, and data are limited describing what happens to patients who survive a major bleed. One study demonstrated a 30-day mortality risk after major hemorrhage that exceeded the rate of intracranial bleeding, suggesting that a proportion of extracranial bleeds were fatal, but no population-based study, to our knowledge, has examined survival and functional outcomes associated with different subtypes of bleeding.

Effects of Treatment of Comorbid Conditions

Coronary artery disease is a prevalent comorbid condition in patients with NVAF. Aspirin and warfarin are frequently recommended as treatment for patients with these 2 conditions. This combination does not improve stroke prevention and may not provide added protection against myocardial infarction. Combination therapy, however, increases overall bleeding risk. In addition, despite the lack of data delineating the incremental benefits or risks of triple therapy, there is a rising use of prolonged dual antiplatelet therapy plus warfarin in patients with NVAF and coronary artery disease who undergo percutaneous coronary interventions. Even fewer data are available regarding the incremental harms and benefits for this treatment regimen.

Categorization of Risk

Even when data are available to calculate individualized outcomes, risk categories (eg, low vs high stroke risk), rather than absolute risks, are frequently used to simplify calculation and presentation of the outcomes. These categories are, however, defined by arbitrary cutoff points. For example, one set of guidelines recommends warfarin therapy for any patient with a single stroke risk factor included in the CHADS2 (congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, and previous stroke or transient ischemic attack) risk index and aspirin therapy for patients without these factors. A patient with any 1 of these factors has a risk of 2.8 per 100 patient-years of having a stroke. A patient without any of these factors has a risk of stroke of 1.9 per 100 patient-years. The absolute difference between these rates is not large. Because patients vary in the amount of risk they are willing to accept to prevent a stroke, relying on the same “cut-off” point for all patients does not respect individual patient values. Moreover, several studies have shown that patients’ values often differ from those of physicians, and it is probable that many patients would disagree with the population-based cut-off points chosen by investigators.

ADDRESSING THE GAPS IN AVAILABLE DATA

The illustration of treatment decision making in NVAF demonstrates that despite a wealth of clinical trials and epidemiological studies of AF, substantial gaps remain in the ability to determine patient-specific outcomes. These gaps are not specific to NVAF but rather are indicative of limitations in current approaches to the collection of outcome data. It has previously been argued that obtaining individualized assessments of the risks and benefits related to available options requires that RCT data be supplemented by comprehensive observational data. This effort, however, needs to go beyond the call for the use of observational data to identify adverse events. Observational data are also required to generate expected rates of adverse outcomes without treatment and estimates of treatment-related outcomes for patients with varying comorbidities across meaningful time frames. Databases should include a catalog of a broad set of health outcomes, including sequelae of disease-specific physical, cognitive, and psychosocial outcomes in representative patient populations possessing a wide range of comorbid conditions.

Obtaining these data will require considerable expansion of current cohort studies. Comprehensive systematic assessments across large and diverse patient populations are now possible given the use of unified electronic medical record systems. The Veterans Aging Cohort Study demonstrates the feasibility of combining clinical, laboratory, and pharmacy data to facilitate the development of computerized individualized decision support systems. The single study of NVAF examining the functional sequelae of bleeding was conducted in a cohort of persons receiving their care from Kaiser Permanente of Northern California. Quality measures, such as mandating the use of functional assessment questionnaires, are an example of the potential means by which functional status and mental health can be tracked across time.

Informed decision making depends on the electronic medical record not only for its inputs but also for its outputs. The electronic medical record allows for the possibility of capturing patients’ relevant risk factors and calculating updated individualized outcome estimates, which (1) eliminates the presenta-
tion of categorical rather than continuous risk estimates, (2) allows for reexamination of outcomes as the patient’s risk profile changes, and (3) allows relevant patient information to be available in clinical offices in real time so that it can be more fully used in decision making.

In conclusion, different comorbidity profiles can have clinically significant effects on the expected harms and benefits related to available treatment options. This variability in outcomes highlights the potentially harmful consequences of using average data to inform medical decisions and provide a strong argument that decision making must be based on the expected risks and benefits for each individual patient. However, enabling physicians to make medical decisions based on individualized expected outcomes will require substantive increases in the efforts and resources allocated to the collection and dissemination of data for patients with varying comorbidities.

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