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Individualized Medical Decision Making: Necessary, Achievable, but Not Yet Attainable

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Abstract

There is an urgent need to provide older persons with individualized information regarding the benefits and harms of different diagnostic and treatment strategies. This need results from the growing recognition of the heterogeneity in outcomes among older persons with differing comorbidity profiles. The importance of heterogeneity in outcomes has been most thoroughly described in cancer screening. The heterogeneity of benefits and harms resulting from treatment is not yet as well appreciated. Warfarin versus aspirin for the reduction of stroke risk in nonvalvular atrial fibrillation (NVAF) 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 NVAF, many assumptions are necessary to calculate patient-specific outcomes, and these assumptions may lead to substantial over- or under-estimation of benefits and harms. Improving care for patients with co-morbidities will require substantive increases in the efforts and resources allocated towards the collection and dissemination of outcome data for patients with varying comorbidities.

Keywords

Comorbidity; outcomes; decision making

Comorbidities and the need for individualized medical decision-making

Evidence is growing for the need to utilize 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.[1, 2] This is particularly true for older patients, in whom comorbid conditions and functional disability can diminish the benefits of standard diagnostic and therapeutic strategies.[3, 4] For example, an 81 year old woman with no comorbidities has a life expectancy of 13.8 years following a diagnosis of stage 1 colon cancer, whereas an 81 year old woman with three or more comorbidities has a life expectancy of only 4.9 years.[5]

Treatment decisions in older adults with varying comorbidities are frequently even more complex than 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

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anticoagulation in nonvalvular atrial fibrillation (NVAF). This is a clinical scenario in which benefits (i.e. stroke risk reduction) and harms (i.e. increased bleeding risk) of treatment vary considerably, such that the benefit to harm ratio can reverse according to the patients' 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 decision aids.[6] However, despite these advances, our ability to provide individualized outcome assessments based on currently available data remains limited. Because the gaps in knowledge regarding outcomes can result in under- and over-estimates of both 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 three options: warfarin, aspirin and no therapy. A recent meta-analysis of 29 RCTs (mean age of 71 years, 35% women) found a greater absolute reduction in stroke risk and a small incremental risk of major hemorrhage associated with warfarin compared to aspirin.[7] 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.[8] In contrast, a number of observational studies have demonstrated that the risk of bleeding associated with warfarin is not small.[9–12] In a population-based study utilizing Medicare data, the rate of bleeding resulting in hospitalization ranged from 1.9 to 12.3 per 100 patient-years.[9]

Several observational studies have demonstrated that both the risk of stroke and the risk of bleeding vary according to patients' comorbidities.[9–11, 13] Because of this variability in risk, there is a large range in the incremental risks and benefits associated with warfarin, aspirin and, no treatment. The table provides examples of the 5-year risks of stroke and bleed, converted from annualized outcome rates,[14] associated with each option for two 70-year old men with different comorbidities. The baseline stroke risk and risk of bleeding with warfarin were based on validated risk calculators derived from observational, population-based data.[9, 15] The risks of stroke with warfarin and aspirin were derived by applying the 67% and 21% reduction in stroke risk associated with these two therapies published in meta-analysis of RCT data.[7] Risk calculators are not available for risk of bleeding with no treatment and with aspirin; therefore, these risks were taken from a systematic review.[16]

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 bleed. 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 three comorbid conditions increase his baseline risk of stroke but not bleeding, and the last comorbid condition modestly increases his risk of bleeding with aspirin but not warfarin. 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 while all the comorbidities increase his bleeding risk.

Despite the availability of a large number of studies and formal meta-analyses, the best available calculations of individualized benefit and harm in NVAF still depend upon a number of assumptions because of the absence of data needed to provide individualized estimates. The following paragraphs outline how the absence of these data affects decision making at the individual patient level.

Gaps in currently available data

Duration of follow-up

The decision on whether to initiate aspirin or coumadin is based on the trade-off between the expected reduction in stroke risk and increase in bleeding risk over the long term, yet RCTs have an average follow-up of less than 1.5 years per patient.[7] The absolute number of outcomes over this short time frame is small and fails to reflect the larger absolute difference in outcomes associated with therapy over the long term that may be more meaningful to patients. In order to generate long-term outcome data, outcome rates must be extrapolated from person-year rates. This conversion assumes that rates remain constant over time. This assumption, while widely applied, may not be accurate. On one hand, the risks of bleeding with coumadin have been shown to be highest in the months following initiation of therapy and to subsequently decrease over time.[17] Therefore, long-term bleeding rates calculated from short-term studies may overestimate risk of bleeding. On the other hand, a patient in whom comorbid conditions accumulate over time might be expected to be at even higher risk of bleed.

Baseline risk of adverse events

The recognition of the need to quantify the risk of adverse events resulting from treatment[18] has generally not 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 atrial fibrillation decision aid.[19] 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 would appear larger. Unfortunately, the data available for calculating baseline bleeding risk are limited to a paper which adjusted for only the most basic risk factors,[16] using relative risks pooled from heterogeneous studies.[20]

Choice of outcomes

Risks and harms of different treatment options are generally presented in terms of disease-specific outcomes. Yet, a number of 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 bleed, but rather the risks of functional and cognitive disability.[21–23] Functional outcomes for stroke can be extrapolated from other stroke cohorts, but there are no studies examining these outcomes among patients with NVAF, and there are very limited data available describing what happens to patients surviving a major bleed.[17] One study demonstrated a 30-day mortality rate after major hemorrhage that exceeded the rate of intracranial bleeding[10] suggesting that a proportion of extracranial bleeds were fatal, but no population-based study 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. Both aspirin and coumadin are frequently recommended for patients with these two conditions.[8] This combination does not improve stroke prevention[24] and may not provide added protection against myocardial infarction.[24] Combination therapy, does however, increase overall bleeding risk.[24] In addition, despite the lack of data delineating the incremental benefit or risks of triple therapy, there is a rising use of prolonged dual antiplatelet therapy plus coumadin among patients with NVAF and coronary artery disease who undergo percutaneous coronary interventions.[25] Even fewer data are available regarding the incremental harms and benefits for this treatment regimen.[26]

Categorization of risk

Even when data are available to calculate individualized outcomes, risk categories (e.g. low versus high stroke risk),[19] rather than absolute risks, are frequently used to simplify the calculation and presentation of the outcomes. These categories are, however, defined by arbitrary cut-off points. For example, one set of guidelines recommends coumadin for any patient with a single stroke risk factor included in the CHADS2 risk index and aspirin for patients without these factors. A patient *with* any one 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" for all patients does not respect individual patient values. Moreover, several studies have shown that patients' values often differ from those of physicians,[27–30] and it is probable that many patients would disagree with the population-based cut-offs chosen by investigators.

Addressing the gaps in currently available data

The illustration of treatment decision making in NVAF demonstrates that, despite a wealth of clinical trials and epidemiologic studies of atrial fibrillation, substantial gaps remain in our 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.[18] This effort, however, needs to go beyond the call for the use of observational data to identify adverse events.[18] 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 over meaningful time periods. Databases should include a catalogue of a broad set of health outcomes, including sequelae of disease-specific physical, cognitive, and psychosocial outcomes among 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 (EMR) systems.[31] 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.[32] The single study in NVAF examining the functional sequelae of bleeds was conducted within a cohort of persons receiving their care within Kaiser Permanente of Northern California.[17] Quality measures, mandating the use of functional assessment questionnaires, are an example of the potential means by which functional status and mental health can be tracked over time.[33]

Informed decision making depends upon the EMR not only for its "inputs," but also for its "outputs." The EMR allows for the possibility of capturing patients' relevant risk factors and calculating updated individualized outcome estimates which 1) eliminates the presentation of categorical, rather than continuous, risk estimates, 2) allows for a re-examination of outcomes as the patients' 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 utilized in decision making.

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 utilizing 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 clinicians to make medical decisions based on individualized expected outcomes will require substantive increases in the efforts and resources allocated towards the collection and dissemination of data for patients with varying comorbidities.

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Table

Five-year risk of stroke and bleeding associated with no treatment, aspirin, or warfarin in the treatment of NVAF according to comorbid conditions:

70 year old man with well-controlled hypertension, heart failure, diabetes mellitus, and non- ulcer-related abdominal pain:			
	No medication	**Aspirin**	**Warfarin**
Stroke	26%	21%	9%
Bleed	4%	7%	9%
70 year old man with poorly controlled hypertension, renal disease, and history of a fall:			
	No medication	Aspirin	Warfarin
Stroke	13%	10%	5%
Bleed	2%	4%	34%