PERSONALIZED BENEFIT-HARM INFORMATION INFLUENCES PATIENT DECISIONS REGARDING WARFARIN

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ABSTRACT

Background
Providing information tailored to an individual patient's potential for benefit and harm, sufficient to allow for informed decision-making, is both time consuming and complicated.

Objective
We sought to determine whether presentation of different levels of personalization of chances of benefit and harm would influence patient decisions regarding warfarin treatment for atrial fibrillation (AF).

Methods
Randomized sequence study recruited participants 55 years or older who were at risk for atrial fibrillation but not currently taking warfarin. Using a standardized decision aid, patients considered 5 scenarios involving 3 levels of personalization (average, individualized, and individualized combined). The primary outcome was the simulated decision whether or not to take warfarin. Secondary outcomes included decisional conflict, factors influencing the decision and preferences for decision-making involvement.

Results
71 of 75 patients randomized (mean age 69.8 yr, 50.7% female) completed the study. Compared with the presentation of average risks of benefit and harm, the tailored information by clinical prediction rule or by combined benefit-harm scenarios caused a significant change in the decision to take warfarin ($p<0.0001$). Presentation of the competing risk of death with and without treatment also had a significant effect on treatment choice ($p<0.0001$). At most, 46 (64.8%) reported being willing to take warfarin. Mean decisional conflict between presentation types did not differ, but patients rated the combined benefit-harm presentation as the most helpful ($p = 0.04$).

Conclusion
Information tailored towards individual chances of benefit and harm, although more complex, is preferred by patients and can change treatment decisions.

Key Words: *Warfarin, benefit-harm relationships, decisional conflict, patient decision aids, atrial fibrillation*

Warfarin is the most commonly prescribed anticoagulant in North America, and is amongst the top 20 most prescribed drugs in both Canada and United States, with approximately 38 million prescriptions annually.[1,2] The drug is used for several indications including atrial fibrillation

(AF) where it reduces the risk of stroke by approximately 64% but increases the risk for major bleeding,[3] including intracranial bleeding. At a population level, although the stroke benefits are undisputed, warfarin is also amongst the main drug-related causes of hospitalizations of seniors, primarily because of bleeding.[4]

Past literature has addressed patient perceptions of health outcomes associated with warfarin use, showing that some patients rate a major stroke to be as devastating as death and are more willing to incur a bleed if it means preventing a stroke[5,6] A smaller number of patients fear bleeding the most and are reluctant to take warfarin.[7] Both types of patients seem to be helped by decision aids that outline the chances and consequences of stroke and bleeds with and without warfarin. Knowledge improves as does confidence in making a decision.[7,8] Current tools for decision-making for warfarin in AF generally present information based on overall mean rates of outcomes from randomized trials;[9] although, newer versions using clinical prediction rules (CPRs) are being evaluated.[10] However, many patients have risk factor profiles that significantly alter their chances of benefit and harm with warfarin therapy compared to the average results from trials, and this difference in benefit-harm profiles may have a significant effect on their decision to take warfarin. For example, presentation of personalized risk of stroke has been shown to influence patients' decision to begin warfarin treatment, potentially resulting in treatment rates significantly lower than recommended.[11]

The most commonly used CPR for stroke risk in unanticoagulated patients with AF, suggests that risk varies from approximately 2% to 18% yearly, depending on the presence of comorbidity.[12] Similarly, a validated CPR for major bleeding while on warfarin therapy, shows that these rates vary from approximately 1% to 12% per patient-year.[13] While the CPR approach is a useful step towards tailoring therapy, it is limited by several factors. First, each CPR is derived from a different group of patients. Second, individual patients wish to know their own unique benefit (stroke prevention) *and* harm (bleeding) profile, specifically their chance of benefit without harm versus harm without benefit versus both benefit and harm versus neither. Third, competing risks are very relevant for AF patients, who tend to be elderly with considerable co-morbidity and an increased mortality rate.[14,15] A retrospective cohort study measured the 3-year mortality for AF patients (mean age 73 yr) in a Kaiser-Permanente HMO who were not treated with warfarin, at approximately 36%.[16] This was reduced by 33.8% for those taking warfarin. Our clinical experience suggests that patients are rarely made aware of their individual (as opposed to average) chances of benefit and harm with warfarin therapy, if they are offered numerical probabilities at all. Poor patient understanding of the benefit and harm associated with warfarin therapy in previous studies suggests that presentation of treatment information may not have occurred or the decision regarding warfarin was made by the clinician alone.[17,18]

Our objective in this study was to determine whether older individuals at risk for AF would make different decisions about warfarin therapy when information on the main outcomes (stroke and bleeding) was based on data tailored to specific risk profiles versus outcomes based on population average risks.

METHODS

Ethics

Approval was granted by St. Joseph's Healthcare Hamilton Research Ethics Board (REB) #07-2944, Hamilton, Ontario and the McMaster University/Hamilton Health Sciences Research Ethics Board, (REB) #08-430, Hamilton, Ontario.

Design

This was a randomized sequence study with blocked design and block size of 6.

Participants

Participants were recruited from outpatient clinics and from internal medicine wards in Hamilton, Ontario. Inclusion criteria were age at least 55 years; ability to read and understand English; and cognitively intact (error score of < 6 of 28 on the Orientation Memory Concentration Test (OMCT).[19] Exclusion criteria included a diagnosis

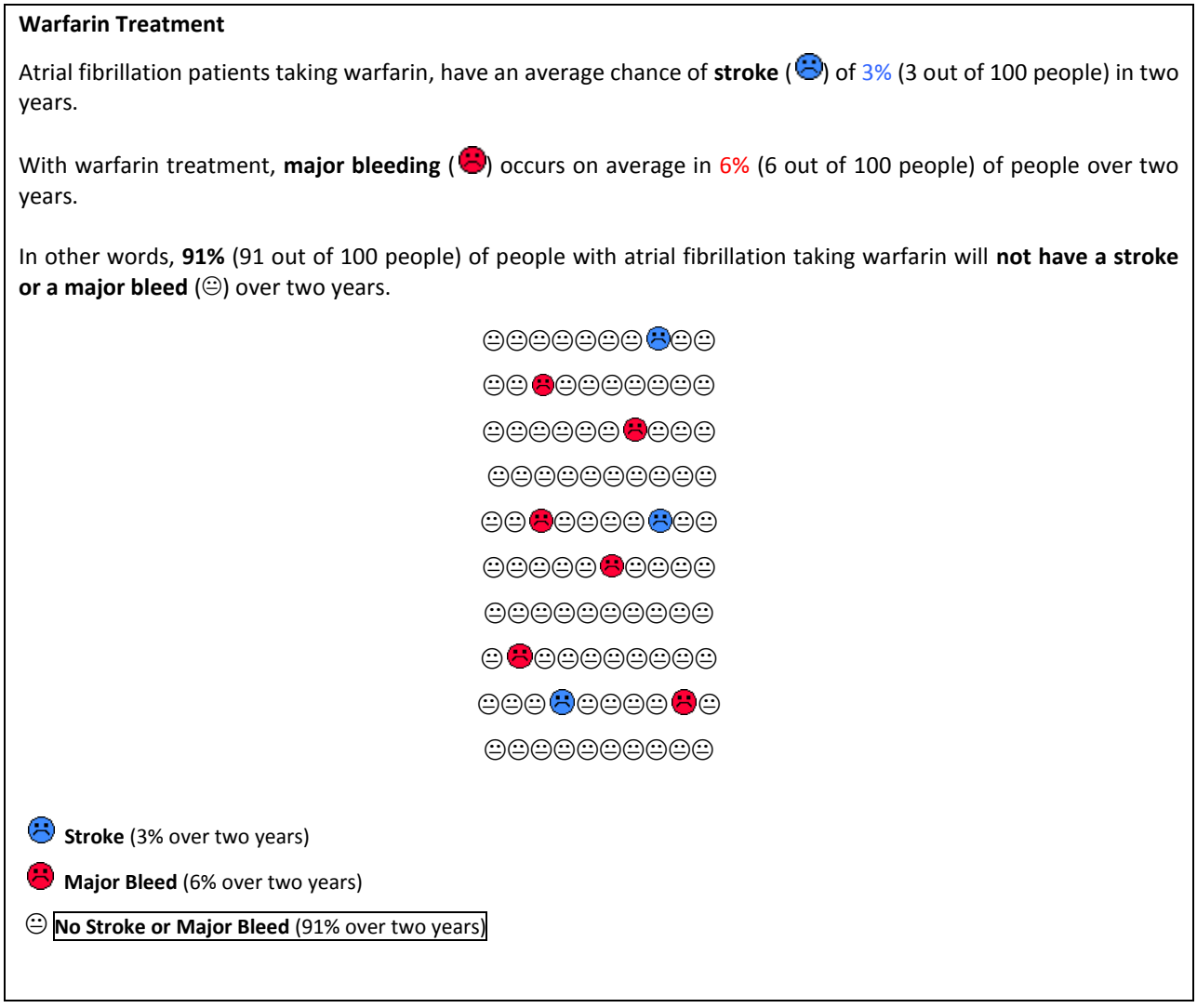
of AF or current or recent (within the previous 5 years), or active prescription for anticoagulants.

These eligibility criteria were chosen to select a cohort for which a decision regarding warfarin therapy could be a near-future reality but did not necessitate a change in their current therapeutic management.

Instrument Development

An updated AF information audiotape and booklet previously developed and used by our group was used to provide participants with information on clinical consequences and treatment options of AF.[7] Outcome descriptions for stroke and major bleeding were expressed in terms of both severity and impact on patient lifestyle. Major strokes were defined as those which left patients functionally dependent on others or which were fatal, with warfarin decreasing the severity of ischemic strokes.[3,20,21] Major bleeds were defined as those leading to hospitalization, requiring a blood transfusion, or leading to death, and were sub-typed as gastrointestinal (GI) bleeding and intracranial hemorrhage (ICH).[22] A sample page of the decision aid is illustrated in Figure 1.

FIG. 1 Sample Page from Decision Aid



We developed three types of presentations, discussing a total of 5 benefit-harm profile scenarios (one 'average' profile, three tailored clinical prediction rule profiles illustrating benefit versus harm trade-offs distinctly different than average, and one combined benefit-harm profile). The differences in risks of benefit and harm presented in each scenario are illustrated in Table 1.

Rates of stroke and major bleeds for the 'average' scenario were based on best available current evidence.[3,23,24] The three tailored CPR scenarios were developed to test participants' understanding of the materials and concepts, and their adherence to 'logic' in treatment choices. The first and second scenarios presented outcomes as a low benefit-high harm profile (4% risk of stroke without anticoagulation and 17% risk of bleeding on warfarin) and high benefit-low harm profile (8% risk of stroke without anticoagulation and 4% risk of bleeding on warfarin), respectively, with obvious treatment choices (warfarin in the first case, no treatment in the second scenario). The third scenario was high benefit-high harm (17% risk of stroke with no treatment and 17% risk of bleed on warfarin), aimed at determining how patients weigh similarly high risks of stroke and major bleeding. The combined benefit-harm profile was based on our prior work using polytomous logistic regression to populate the four outcome categories[16] using both meta-analyses of randomized trials and an observational cohort.[25] Too few patients had both a stroke and a major bleed, leaving three individualized combined benefit-harm outcome states (stroke and no bleed, bleed and no stroke, no stroke and no bleed).

Each profile scenario portrayed two- year rates of stroke and major bleeding, using text percentages (e.g. 1%), natural frequencies (e.g. 1 out of 100), and pictograms. Each pictogram visually represented an AF population with 100 faces, with expected outcomes (stroke and major bleeding) designated by sad blue and red faces respectively, scattered throughout in proportion to expected rates.

All materials were aimed at a Grade 8 reading level. All descriptions were recorded onto an audio device, to provide patients with self-selected speed of verbal narration as they proceeded through the booklet. Study instruments were pre-tested using a convenience sample of 10 adults whose feedback on clarity, usability, design and face validity of the instruments and outcome tools, was incorporated.

TABLE 1: Chance of Benefit or Harm Quoted for Each Profile Scenario Presentation Type[1]

Outcome	Average	Low benefit-high harm	High benefit-low harm	High benefit-high harm	Combined benefit-harm
Stroke on No Rx*	9%	4%	8%	17%	N/A
Stroke on Warfarin	3%	N/A	N/A	N/A	N/A
Major Bleed on No Rx*	2%	N/A	N/A	N/A	N/A
Major Bleed on Warfarin	6%	17%	4%	17%	N/A
Stroke & Major Bleed on No Rx*	N/A	N/A	N/A	N/A	NR
Stroke & Major Bleed on Warfarin	N/A	N/A	N/A	N/A	NR
No Stroke & No Major Bleed on No Rx*	89%	N/A	N/A	N/A	94%
No Stroke & No Major Bleed on Warfarin	91%	N/A	N/A	N/A	92%
Stroke & No Major Bleed on No Rx*	N/A	N/A	N/A	N/A	3%
Stroke & No Major Bleed on Warfarin	N/A	N/A	N/A	N/A	2%
Major Bleed & No Stroke on No Rx*	N/A	N/A	N/A	N/A	3%
Major Bleed & No Stroke on Warfarin	N/A	N/A	N/A	N/A	6%

[1]Numbers are estimated 2-year risks; * No Rx = no treatment; N/A = not applicable to this scenario; NR = not reported as numbers too small to be considered reliable.

Intervention

The intervention consisted of a single visit, including assessment of eligibility, written informed consent, and completion of the study. Patients successfully passing a cognition screen[26] were randomized to one of three sequences in which the benefit-harm scenarios were presented. A research assistant was with participants at all times to assist with technical questions.

Outcomes

The primary outcome was the patient's simulated decision whether to start warfarin therapy, evaluated immediately after presentation of each of the 5 scenarios.

Secondary outcomes included comprehension of the material using the Atrial Fibrillation Information Questionnaire (AFIQ)[7]; decisional conflict; preferences for presentation type and delivery; involvement in decision-making; and external influences on decisions. The AFIQ was 10 true-false questions that a reasonably informed patient should be able to answer, such as whether warfarin reduces the risk of stroke, requires regular blood monitoring, etc. Decisional Conflict, which measures uncertainty regarding treatment choices, the reasons for it, and satisfaction with decisions, was assessed using a 13-question version of the Decisional Conflict Scale (DCS).[27] Scores were normalized to a percentage between 0 and 100%, with low scores (less decisional conflict) associated with implementation of treatment decisions.[27]

Analysis

The primary outcome compared within-patient treatment decisions between average, high benefit-high harm, and the combined benefit-harm presentation scenarios using Cochran's Q test for binary outcomes. Friedman's test was used to analyze the decisional conflict and presentation helpfulness comparisons. Preferences for including competing risk of death were analyzed using McNemar's test. All statistical analyses were conducted using SPSS version 16.0.

RESULTS

Seventy-one of the 75 randomized (94.7%) patients were able to complete the study. Their mean age was 69.8 years (SD = 9.3) and 50.7% were female (Table 2). A small minority of patients (5, 7.0%) were remote former users of warfarin or had a history of stroke or major bleed**.** Fifty-seven (80.3%) participants had at least one vascular risk factor or previous event, confirming that this group was representative of patients who would be asked to consider taking warfarin should they develop AF. The mean time to complete the entire decision-making exercise, including the evaluations, was 73.0 minutes (SD 12.6). Many patients needed some clarification assistance from the RA. After reviewing the decision aid, comprehension test scores were high with 63 (88.8%) having one or fewer incorrect answers, suggesting that the material on atrial fibrillation and anticoagulation was understood. Analysis of the primary outcome showed that the presentation type had a significant impact on treatment choice, even with the two 'obvious choice' scenarios removed ($p<0.0001$) (Table 3). The highest proportion of patients (46, 64.8%) chose warfarin after considering the average benefit-harm scenario where 2-year risk of stroke was 9% without warfarin and risk of major bleed was 6% on warfarin. The individualized CPR scenarios showed the expected shift away from warfarin when the scenario changed from high benefit-low harm to high harm-low benefit. For the high benefit-high harm profile, 29 (40.8%) of the study participants chose warfarin while 42 (59.2%) chose no treatment. After considering the individualized combined scenario, 19 (26.8%) of patients chose warfarin suggesting that explicit presentation of the chance of not having stroke or bleeding led many patients to not choose warfarin. The addition of information on the risk of death (2-year risk of death, 32% for no treatment versus 25% for warfarin) also had a significant influence on treatment choice in that the switch from no treatment to warfarin (17, 23.9%) was significantly more common than switching from warfarin to no treatment (2, 2.8%) ($p<0.0001$). Fifteen (21.1%) patients chose no treatment while 10 (14.1%) chose warfarin regardless of scenario, despite the wide ranging chances of benefit and harm

TABLE 2 Participant Demographics

Demographic Variable	# Participants (%) (n=71)
Gender (female)	36 (50.7)
Age, mean (SD; range) years	69.8 (9.3; 55 to 90)
Education Level	
Elementary only	19 (26.8)
Secondary school only	25 (35.2)
College or university	22 (31.0)
Post-graduate school	5 (7.0)
Cognition Error Score (OCMT)*	
0	36 (50.7)
2	24 (33.8)
4	9 (12.7)
6	2 (2.8)
Warfarin Use	
Current	0 (0.0)
Previous (> 5 years ago)	5 (7.0)
Never	66 (93.0)
Anti-platelet Agent Use	
Current	32 (45.1)
Previous	39 (54.9)
At least 1 Vascular Condition**	57(80.3)
Past history of Stroke	
Yes	5 (7.0)
No	63 (88.7)
Don't know	3 (4.2)
Past history of Major Bleed	
Yes	7 (9.9)
No	63 (88.7)
Don't know	1 (1.4)

* OCMT scored out of 28. ** included congestive heart failure, TIA, valvular heart disease, hypertension, diabetes, hyperlipidemia

TABLE 3 Treatment Choices and Ratings of Presentation Type

Presentation Method	Chose Warfarin N (%)	DCS Score mean (SD)[§]	Presentation Type Helpful* Mean (SD)	Presentation Type Confusing** Mean (SD)
Average Profile	46 (64.8)	21.11 (11.1)	1.97 (0.74)	3.86 (0.85)
Tailored 1 (Low benefit - high harm)	16 (22.5)	21.45 (10.3)		
Tailored 2 (High benefit - low harm)	44 (62.0)	22.91 (13.7)	1.97 (0.81)	3.72 (0.93)
Tailored 3 (High benefit- high harm)	29 (40.8)	24.89 (12.7)		
Combined benefit/harm Profile	19 (26.8)	21.51 (11.6)	1.79 (0.65)	3.92 (0.79)
p-value	<.001[a]	0.097[b]	0.035[b]	0.13[b]

[*] 1 (strongly agree) to 5 (strongly disagree) -lower score is better; [**] 1 (strongly agree) to 5 (strongly disagree) -higher score is better; [§] DCS = Decisional Conflict Scale; [a] Cochran's Q; [b] Friedman test

TABLE 4 Factors Influencing Treatment Decisions

Factor	N (%)
I am afraid of having/know someone who has had, a stroke	62 (87.3)
I am afraid of having/know someone who has had, a serious bleeding complication	35 (49.3)
I don't like the idea of having to take another pill	20 (28.1)
I don't like the effect the medication will have on my lifestyle	15 (21.1)[a]
I know someone with atrial fibrillation	12 (16.9)
I don't want to have regular blood tests	10 (14.1)

* participants could select more than 1 factor; [a] significant impact on treatment choice ($p<0.01$)

The more complex combined benefit-harm presentation type was preferred over the other two types (45, 63.4%), with higher scores for helpfulness in making decisions (mean Likert score 1.79 vs. 1.97 for the other types), p = 0.035, and similar scores for confusing (p = 0.13), (Table 3). Mean decisional conflict scores were not significantly different for the different presentation types (p=0.097).

Only the potential impact of warfarin on lifestyle had a significant influence on treatment choice, (p=0.007) although stroke and bleeding were mentioned more commonly (Table 4). Sixty-one (85.9%) of patients selected their physician (versus 11.3% for pharmacist and 2.8% for nurse) as the preferred source for information on benefits and harms of medication, with 25 (35.2%) preferring an in-person verbal discussion instead of audio booklet (20, 28.2%), pamphlet (18, 25.4%), or electronic source (8, 11.3%). On 'who should decide whether you should take warfarin', 68 (95.8%) of patients chose a shared decision-making model with 3 (4.2%) preferring that their physician alone make the decision.

DISCUSSION

Although there is an extensive literature on decision aids to support patients in shared decision making for a number of conditions, there is a paucity of literature on the influence of personalizing the content on patient's decisions about treatment.[28] This study's primary results suggest that patients would make different decisions regarding warfarin treatment when presented with personalized outcome information, as compared with average population outcome information. This result is not surprising, yet for most therapies there are no validated tools to help providers or patients adequately quantify each patient's individual chances of risk and benefit with and without therapy. Furthermore, as outlined above, the current clinical prediction rule (CPR) approach to tailoring benefit and harm estimates to individual patients is flawed. Our results suggest that not only is the tailored, combined benefit-harm approach to information preferred by patients, but information on important competing risks such as death, also has a significant effect on patient choice. The wide variability in affinity towards warfarin across patients may be unsettling for many evidence-based providers and policy makers but is consistent with previous studies.[6,7,29,30] In this study, approximately 1 in 5 patients would not choose warfarin even in face of very high stroke risk and low bleeding risk. This is an important issue given the common use of rates of warfarin prescribing for atrial fibrillation as a quality of care benchmark. At the other end of the spectrum, approximately 14% of patients said they would always choose warfarin regardless of the risks, even with much higher risk of bleeding than stroke (17% versus 4%). This wide range of acceptability of warfarin treatment is presumably rooted in the varying utilities or values assigned to strokes, bleeds, taking medicines and following through with laboratory monitoring.

The strong preference to receive benefit-harm information from physicians rather than other healthcare professionals and the desire for a shared decision-making model illustrates one of the current major conundrums in healthcare. How to most efficiently use physician time yet ensure that patients are fully informed of their own personal risks and allow sufficient time for discussion and decision? Feasibility is indeed a significant barrier to informed shared decision-making at present. Although the average completion time of 73 minutes included questionnaires that would not be used in regular clinical practice, we estimate that the decision-making process with generation of the patient's own chance of benefit and harm estimates, would take at least 30 minutes. A compromise may be required, where patients review a decision aid tailored to their individual risk profile and make an initial decision choice on their own, leaving adequate time for a very focused discussion with their physician. The potential for decision aids to create significant patient-provider disagreement on the 'right' course of action also needs further consideration.

There are several limitations in this study beyond the small sample size. However, even with the small sample, we were able to show striking, statistically significant differences in treatment choices. We were not able to recruit the most relevant patient population, those who must decide on warfarin therapy. These patients are currently not centrally identified anywhere, would be very difficult to recruit in large numbers in a timely manner and the seamless integration of a decision-making

exercise into care, where the prescriber feels that anticoagulation should be started semi-urgently, would be a problem. Second, without an additional qualitative component to the study, it is difficult to know whether choices of therapies were based on a full understanding of the content or whether they might be negotiable with further discussion with an expert healthcare provider. Third, the decision aid itself could be improved. For example, the timeline perspective of 2 years during which most patients have no events may need to be lengthened to avoid portraying a false sense of security. In addition, comparing the severity and frequency of the outcomes avoided to other common activities (seatbelts, equipment safety guards, etc), and allowance for the patient's own physician to further discuss the implications of the patient's decision-making, might be helpful.

There is a clear need for future research in this area, especially on strategies that preserve patient autonomy while supporting the use of evidence-based therapies which can effectively prevent disease and disability. Misaligned treatment goals between clinicians, patients and drug policy makers, likely leads to dissatisfaction with care at best, non-compliance and adverse health outcomes at worst. While recent access to new oral anticoagulants for AF may suggest less demand for detailed benefit and harm discussions, their similarity to warfarin in benefit and harm, the lack of an antidote for bleeding and problems in patients with renal impairment, mean that patient values will still be an important part of the decision-making with these drugs as well.

CONCLUSION

Our study suggests that patients prefer more detailed, complete and tailored information on benefits and harms of therapy before making a treatment decision and that such information can change treatment decisions. In the absence of well-developed decision support tools that can calculate a patient's own risk of stroke without bleed, bleed without stroke, neither bleed or stroke, or death, we suggest that clinicians do the best tailoring they can for patients using current clinical prediction rules.

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