

## Bleeding Risk With Ischemic Stroke Therapy

**To the Editor:** Within a period of only 2 months, 3 articles<sup>1-3</sup> have been published on bleeding risk among patients with stroke who were treated with warfarin and intravenous thrombolysis, highlighting the scientific controversies and clinical uncertainties related to this issue. A heightened risk of symptomatic intracerebral hemorrhage (sICH) was demonstrated in a single-center patient series with high-quality ascertainment of warfarin intake<sup>1</sup> and in 2 meta-analyses,<sup>1,2</sup> whereas Dr Xian and colleagues<sup>3</sup> reported a null association. The latter evaluation<sup>3</sup> represents the largest experience on the safety of thrombolysis in patients with acute stroke treated with warfarin, but difference in sample size is unlikely to fully explain the discrepancy among the studies. Differences in methods and patient enrollment deserve consideration.

First, in the American Heart Association Get With The Guidelines—Stroke (GWTG-Stroke) Registry, only about half of the patients who were treated with warfarin, who had an international normalized ratio (INR) of 1.7 or less, and who were eligible for intravenous thrombolysis in the United States actually received intravenous tissue plasminogen activator (tPA).<sup>3</sup> Treatment selection may have occurred on a patient or physician level and potentially caused an underestimation of the actual bleeding risk.<sup>3</sup> The treated patients may have been more likely to have a lower assumed bleeding risk, and the physicians may have been more experienced. Treatment selection could be addressed by an additional analysis confined to centers where patients with stroke who were treated with warfarin (INR  $\leq$  1.7) also were treated with tPA as a standard procedure (eg, treatment rates >90%) rather than on an individual basis.

Second, warfarin treatment was coded as present in the GWTG-Stroke Registry when the patient was taking warfarin within 7 days of the index stroke admission. Accordingly, this group subsumes patients taking warfarin up to the day of stroke as well as patients stopping warfarin for reasons like surgical procedures and subsequently having an ischemic stroke.<sup>4</sup> In the latter group, coagulation may already have normalized or some patients may even have become hypercoagulable, which has been proposed to occur after warfarin withdrawal as a rebound phenomenon (ie, rebound thrombin generation),<sup>5</sup> and could account for the paradoxical reduction in sICH rates among patients with low INR (range: 0.8-0.9).<sup>3</sup> It would be of interest to see data on bleeding risk according to the time between the last dose of warfarin and stroke manifestation, and also data from an analysis confined to patients who were taking warfarin up to the day of or to the day before the stroke, which is the

most challenging group of patients for physicians in the setting of stroke.

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**Conflict of Interest Disclosures:** The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

1. Ruecker M, Matosevic B, Willeit P, et al. Subtherapeutic warfarin therapy entails an increased bleeding risk after stroke thrombolysis. *Neurology*. 2012; 79(1):31-38.
2. Miedema I, Luijckx GJ, De Keyser J, Koch M, Uyttenboogaart M. Thrombolytic therapy for ischaemic stroke in patients using warfarin: a systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry*. 2012;83(5):537-540.
3. Xian Y, Liang L, Smith EE, et al. Risks of intracranial hemorrhage among patients with acute ischemic stroke receiving warfarin and treated with intravenous tissue plasminogen activator. *JAMA*. 2012;307(24):2600-2608.
4. Broderick JP, Bonomo JB, Kissela BM, et al. Withdrawal of antithrombotic agents and its impact on ischemic stroke occurrence. *Stroke*. 2011;42(9):2509-2514.
5. Palareti G, Legnani C. Warfarin withdrawal: pharmacokinetic-pharmacodynamic considerations. *Clin Pharmacokinet*. 1996;30(4):300-313.

**To the Editor:** Dr Xian and coauthors<sup>1</sup> reported no increased risk of sICH among patients with acute ischemic stroke treated with tPA and warfarin before treatment with thrombolysis. This finding is in contrast with the results from 2 meta-analyses on this subject, which both found a more than 2-fold increased risk for developing sICH in patients with warfarin pretreatment.<sup>2,3</sup> The difference in results could be caused by several factors.

First, the authors mentioned possible selection bias, with almost 50% of patients with warfarin use who were eligible for tPA treatment not receiving it, probably because of physicians' concerns about expected adverse events. They found similar demographic, medical history, and clinical characteristics among both groups. Variables such as early ischemic changes on computed tomography or leukoariosis were not reported and could have influenced a physician's decision to start or withhold tPA.

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Second, the median INR in the warfarin treatment group was 1.2 compared with 1.0 in the control group, and only 15% of patients presented with INR levels between 1.5 and 1.7. This small difference in INR levels between the 2 groups may reflect selection bias and could have influenced the sICH rates.

Third, the authors do not report serial measurements of INR after tPA. Ruecker et al<sup>3</sup> showed an increase in INR levels in patients with warfarin pretreatment and sICH in the first 6 hours after tPA. It would be interesting to assess whether the occurrence of sICH was related to an increase in INR after tPA.

Fourth, in contrast to the previous systematic reviews, Xian et al<sup>1</sup> do not report data on functional outcomes, which is important after tPA treatment. If a slight increase in sICH does not lead to an overall worse functional outcome, then tPA treatment may be justified in this subgroup of patients.

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**Conflict of Interest Disclosures:** The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

1. Xian Y, Liang L, Smith EE, et al. Risks of intracranial hemorrhage among patients with acute ischemic stroke receiving warfarin and treated with intravenous tissue plasminogen activator. *JAMA*. 2012;307(24):2600-2608.
2. Miedema I, Luijckx GJ, De Keyser J, Koch M, Uyttenboogaart M. Thrombolytic therapy for ischaemic stroke in patients using warfarin: a systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry*. 2012;83(5):537-540.
3. Ruecker M, Matosevic B, Willeit P, et al. Subtherapeutic warfarin therapy entails an increased bleeding risk after stroke thrombolysis. *Neurology*. 2012;79(1):31-38.

**In Reply:** Dr Kiechl and colleagues raise concerns that patients treated with warfarin in our study may have had lower bleeding risk (ie, a favorable treatment selection bias). Our data, however, do not support this assumption. Among all patients with stroke treated with warfarin prior to hospitalization, those treated with tPA actually had more severe strokes (median National Institutes of Health stroke scale scores: 14 vs 9) and higher predicted risk of sICH (median predicted sICH rate: 5.0% vs 3.1%) (both  $P < .001$ ). This may explain why our results differed from prior smaller studies if those studies did not fully account for this adverse treatment selection. While we could not assess individual physicians' experience with the data, our model accounted for hospital-level clustering. Furthermore, the overall sICH rate in patients treated with warfarin (5.7%) is comparable with rates reported in nonselective patient populations outside of randomized controlled trials (5.2%).<sup>1</sup> Thus, it is unlikely that patient or hospital-level treatment selection biased the results.

Kiechl et al also inquire about a rebound phenomenon when anticoagulation levels dip after discontinuing warfarin. In our study, less than 6% (107/1802) of patients treated with warfarin had an INR of less than 1.0. Even if

these patients were excluded, the association of warfarin use with sICH rate in patients treated with tPA remained nonsignificant. While our data do not contain the exact time between the last warfarin dose and occurrence of stroke, the fact that many patients taking warfarin in our study had subtherapeutic INRs reflects real-world findings of lower adherence to warfarin in which patients often are not in their target INR range.<sup>2</sup> Rather than suggesting a binary decision to not give tPA to any stroke patient who is taking warfarin (or to not treat those who had taken warfarin within 7 days), our data support current practice guidelines recommending consideration of tPA for all eligible patients treated with warfarin if they had an admission INR of 1.7 or lower.<sup>3</sup>

Dr Miedema and colleagues note certain unmeasured clinical factors (including early ischemic changes on computed tomography or leukoaraiosis) could still confound our results. While these radiological findings are predictors of sICH risk,<sup>4,5</sup> when present they would likely lower a physician's decision to use tPA in both patients treated with warfarin and in patients not treated with warfarin, and thus would not have had a major effect on our comparative safety findings.

Second, we agree that the majority of patients treated with warfarin in our study had low INRs and further data are needed on the safety of tPA treatment in those with higher INRs. Third, while the association between serial INR measurements after tPA treatment and sICH risk is of interest, the decision to treat must be made after the first INR measurement.

Third, we agree that longitudinal, functional, and neurological outcomes data would be helpful to confirm benefits of tPA in patients treated with warfarin. Because the benefit of tPA increases with increasing stroke severity,<sup>6</sup> we suspect that patients treated with warfarin, who had generally more severe strokes, would likely benefit as much or more from treatment as patients not treated.

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1. Graham GD. Tissue plasminogen activator for acute ischemic stroke in clinical practice: a meta-analysis of safety data. *Stroke*. 2003;34(12):2847-2850.
2. Gladstone DJ, Bui E, Fang J, et al. Potentially preventable strokes in high-risk patients with atrial fibrillation who are not adequately anticoagulated. *Stroke*. 2009;40(1):235-240.
3. Adams HP Jr, del Zoppo G, Alberts MJ, et al; American Heart Association; American Stroke Association Stroke Council; Clinical Cardiology Council; Cardiovascular Radiology and Intervention Council; Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Out-

comes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. *Stroke*. 2007;38(5):1655-1711.

4. Derex L, Hermier M, Adeleine P, et al. Clinical and imaging predictors of intracerebral haemorrhage in stroke patients treated with intravenous tissue plasminogen activator. *J Neurol Neurosurg Psychiatry*. 2005;76(1):70-75.

5. Neumann-Haefelin T, Hoelig S, Berkefeld J, et al; MR Stroke Group. Leukoaraiosis is a risk factor for symptomatic intracerebral hemorrhage after thrombolysis for acute stroke. *Stroke*. 2006;37(10):2463-2466.

6. Sandercock P, Wardlaw JM, Lindley RI, et al; IST-3 collaborative group. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial. *Lancet*. 2012;379(9834):2352-2363.

## Computed Tomographic Screening for Lung Cancer

**To the Editor:** In the systematic review by Dr Bach and colleagues,<sup>1</sup> the American Cancer Society, the American College of Chest Physicians, the American Society of Clinical Oncology, and the National Comprehensive Cancer Network recommended that computed tomography (CT) for lung cancer screening be offered to those meeting National Lung Screening Trial (NLST) criteria. While evidence-based, these criteria limit screening to current or former smokers aged 55 to 74 years with a 30 pack-year or longer history. However, age and pack-years alone are not the best predictors of lung cancer risk.<sup>2-4</sup> Patient selection for CT screening using these 2 criteria results in only a 1% annual detection rate for lung cancer,<sup>1</sup> and less than 50% of all those who will develop lung cancer would be eligible for screening.<sup>3</sup>

One solution to the low overall sensitivity is to optimize the group screened. Multivariate risk models for lung cancer, which include other risk factors in addition to age and pack-years (eg, chronic obstructive pulmonary disease, family history, body mass index, and genetic markers), have shown superior risk prediction to those using age and smoking exposure alone.<sup>2</sup> When chronic obstructive pulmonary disease is included with age and pack-year criteria, for example, the detection rate for lung cancer increases approximately 2- to 5-fold or 4% to 6% annually,<sup>3</sup> equivalent to 1 lung cancer case detected per 17 to 25 individuals screened rather than 1 in 100 individuals screened. Incorporating a multivariate approach would allow the inclusion of individuals at equivalent or higher risk for lung cancer than those meeting the currently recommended criteria.<sup>4</sup>

We agree with Bach et al<sup>1</sup> that a lack of cost-effectiveness information and a self-pay approach remain important obstacles to the adoption of CT screening. Lung cancer screening based on CT has been estimated to be 3- to 5-fold more costly than currently accepted screening programs,<sup>5</sup> although we await the cost-effectiveness analysis from the NLST. If an annual lung cancer detection rate of 1% is found to be cost-effective, then we propose a multivariate approach be used to include more individuals at equivalent or higher risk for lung cancer than those identified by the NLST criteria. Alternatively, if a 1% annual detection rate is too low to be cost-effective, a multivariate approach

would allow identification of individuals at much higher risk,<sup>2</sup> and the subsequent increase in detection rate would make CT screening more acceptable.<sup>1,5</sup> We recommend that analyses of existing CT screening trials be done to test these hypotheses further.

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1. Bach PB, Mirkin JN, Oliver TK, et al. Benefits and harms of CT screening for lung cancer: a systematic review. *JAMA*. 2012;307(22):2418-2429.

2. Tammemagi CM, Pinsky PF, Caporaso NE, et al. Lung cancer risk prediction: Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial models and validation. *J Natl Cancer Inst*. 2011;103(13):1058-1068.

3. El-Zein RA, Young RP, Hopkins RJ, Etzel CJ. Genetic predisposition to chronic obstructive pulmonary disease and/or lung cancer: important considerations when evaluating risk. *Cancer Prev Res (Phila)*. 2012;5(4):522-527.

4. National Comprehensive Cancer Network. Guidelines on lung cancer screening. [http://www.nccn.org/professionals/physician\\_gls/f\\_guidelines.asp](http://www.nccn.org/professionals/physician_gls/f_guidelines.asp). Accessed August 15, 2012.

5. McMahon PM, Kong CY, Bouzan C, et al. Cost-effectiveness of computed tomography screening for lung cancer in the United States. *J Thorac Oncol*. 2011;6(11):1841-1848.

**In Reply:** My colleagues and I believe that it is crucial to focus guidelines on what is known from the evidence. The review noted the characteristics of individuals for whom low-dose CT screening has been shown to reduce mortality. Dr Young and colleagues propose using a risk prediction model to select individuals for screening instead of using the characteristics of the individuals who have been studied.

While risk prediction is an intriguing area of research, Young and colleagues' approach may overlook important factors in the risk-benefit calculus.<sup>1</sup> For instance, while identifying patients at increased risk of cancer is important (ie, these are the individuals who may benefit from screening), there are factors other than risk to consider when determining the magnitude of the expected benefits and risks.

Some major risk factors for lung cancer, including elevated age, heavy smoking, and underlying lung disease, are also associated with reduced life expectancy. Therefore, higher risk of lung cancer may be inversely proportional to potential gains in quality-adjusted life-years for each death from lung cancer prevented. Low-dose CT screening itself may be less effective in certain high-risk individuals. It can be harder to detect cancer in the presence of extensive scarring related to several lung diseases that elevate risk.

These conditions are frequently associated with more benign nodules and an increased risk of complications from invasive procedures. The underlying assumption of Young and colleagues' argument that the efficacy of low-dose CT