Point-of-Care International Normalized Ratio Testing Accelerates Thrombolysis in Patients With Acute Ischemic Stroke Using Oral Anticoagulants

Timolaos Rizos, Christian Herweh, Ekkehart Jenetzky, Christoph Lichy, Peter Arthur Ringleb, Werner Hacke and Roland Veltkamp

Stroke. 2009;40:3547-3551; originally published online August 20, 2009;
doi: 10.1161/STROKEAHA.109.562769
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628

Point-of-Care International Normalized Ratio Testing Accelerates Thrombolysis in Patients With Acute Ischemic Stroke Using Oral Anticoagulants

Timolaos Rizos, MD; Christian Herweh, MD; Ekkehart Jenetzky, MD; Christoph Lichy, MD, MSc; Peter Arthur Ringleb, MD; Werner Hacke, MD, PhD; Roland Veltkamp, MD

Background and Purpose—Thrombolysis in patients using oral anticoagulants (OAC) and in patients for whom information on OAC status is not available is frequently delayed because the standard coagulation analysis procedure in central laboratories (CL) is time-consuming. By using point-of-care (POC) coagumeters, international normalized ratio (INR) values can be measured immediately at the bedside. The accuracy and effectiveness of POC devices for emergency management in acute ischemic stroke has not been tested.

Methods—In phase 1, the reliability of emergency INR POC measurements in comparison to CL was determined. In phase 2, patients with ischemic stroke admitted within the time frame for systemic thrombolysis and who were either using OAC or for whom information on OAC status was not available were enrolled. Patients received thrombolysis if POC INR was ≤1.5. Precision and time gain was recorded for INR as measured by POC vs CL.

Results—In phase 1 (n=113), Bland-Altman analysis showed close agreement between POC and CL, and Pearson correlation was highly significant (r=0.98; P<0.01). In phase 2, 48 patients were included, of whom 70.8% were using OAC; 23 patients received thrombolysis. After subtracting the time needed for the diagnostic work-up, the net time gain was 28±12 minutes (mean±SD).

Conclusions—Measuring INR by POC in an emergency setting is sufficiently precise in OAC acute stroke patients and substantially reduces the time interval until INR values are available and therefore may hasten the initiation of thrombolysis. **(*Stroke*. 2009;40:3547-3551.)**

Key Words: acute ischemic stroke ■ emergency room ■ INR ■ oral anticoagulants ■ point of care ■ thrombolysis

Intravenous thrombolysis with recombinant tissue plasminogen activator is currently the only effective medical therapy for acute ischemic stroke.[1–3] As recently demonstrated, recombinant tissue plasminogen activator is effective within a time frame of 4.5 hours,[1] but its effectiveness strongly depends on the time interval between symptom onset and start of treatment.[4] Consequently, any delay in initiating thrombolytic treatment should be avoided.

Atrial fibrillation is already a leading cause of ischemic stroke worldwide, but its contribution to the burden of stroke will increase considerably as the prevalence of atrial fibrillation is increasing in aging populations.[5,6] Because oral anticoagulation with vitamin K antagonists (OAC) with a target international normalized ratio (INR) of 2 to 3 is by far the most effective therapy for preventing stroke in atrial fibrillation[7] the number of stroke-prone patients using OAC will also increase considerably, resulting in more patients using OAC who present with an acute stroke at emergency departments. Patients taking OAC pose a particular challenge for the emergency management of stroke. Although elevated INR values are generally considered to contraindicate systemic thrombolysis, many patients using OAC present with subtherapeutic INR levels and thus still qualify for thrombolytic therapy.[8–10] In contrast to acute stroke patients not using OAC, in whom thrombolytic therapy is initiated at many centers without waiting for the time-consuming central laboratory (CL) analysis of plasmatic coagulation tests, it is mandatory to determine INR values in stroke patients using OAC or when information regarding the OAC status (eg, aphasic patients) is not available. Prospective data regarding the delay in initiating thrombolytic treatment caused by CL INR measurements in the emergency setting of acute stroke are lacking.

Originally designed for self-measurement of INR in OAC outpatients, several studies have shown that point-of-care (POC) devices for INR measurements are reliable and safe for

Received July 13, 2009; accepted July 27, 2009.

From Department of Neurology (T.R., C.L., P.A.R., W.H., R.V.), University of Heidelberg, Germany; Department of Neuroradiology (C.H.), University of Heidelberg, Germany; and Department of Clinical Epidemiology and Aging Research (E.J.), German Cancer Research Center (DKFZ), Heidelberg, Germany.

Correspondence to Roland Veltkamp, MD, Department of Neurology, University Heidelberg, INF 400, 69120 Heidelberg. Germany. E-mail Roland.Veltkamp@med.uni-heidelberg.de

Stroke **is available at http://stroke.ahajournals.org** **DOI: 10.1161/STROKEAHA.109.562769**

self-monitoring purposes.[11–14] The precision of POC measurements in the emergency setting of acute stroke, however, is largely unknown. Importantly, the time gain for stroke patients who are candidates for thrombolysis by using POC has not been investigated to date.

The main purpose of our study, therefore, was to assess the usefulness of a POC coagumeter for the emergency management of acute ischemic stroke. In the first phase of the study, we evaluated whether INR measurements by POC are sufficiently precise in the setting of a neurological emergency department. Thereafter, we measured the potential time gain for initiating thrombolysis provided by POC use as compared to CL INR measurements.

Materials and Methods

A 2-phase, prospective, observational monocenter study was conducted between November 2007 and March 2009 at the neurological emergency department of the University of Heidelberg. All study procedures were approved by the institutional ethics committee. All patients or their representatives gave informed consent.

Phase 1 of the study was performed to ascertain that INR measurement using a POC coagumeter device in an emergency setting was sufficiently precise. In a nonconsecutive manner, patients admitted to our emergency department who were known to be using or suspected of using OAC were enrolled in the study. Blood samples were drawn simultaneously in our emergency department to determine INR values using the bedside POC and by routine analytic technique in our CL. The time to obtaining INR results from POC and CL was noted. To test agreement between the POC and CL measurements, a Bland-Altman analysis was performed,[15] for which the paired differences were plotted against the mean of the 2 data values. The limits of agreement represent the 95% reference range of comparable measurements and are defined as ± 1.96 SD.[15,16] Additionally, Pearson correlation coefficients between POC and CL were calculated.

The second phase of the study was primarily performed to assess the gain in time until INR values were available when measuring INR by using POC as compared to CL, which would then allow thrombolysis to be initiated earlier in OAC stroke patients. In a nonconsecutive manner, patients with acute ischemic stroke presenting in time for systemic thrombolytic therapy who were either currently using OAC or for whom the OAC status was not available (eg, severe aphasia, no documentation) were enrolled in the study. In all patients treated with recombinant tissue plasminogen activator initially and at discharge, National Institute of Health Stroke Scale Scores (NIHSSS)[17] and time window to treatment since onset of symptoms were documented. The ultimate decision regarding thrombolysis was based on the INR and on common clinical and neuroradiological inclusion/exclusion criteria.[3] Patients with a POC INR >1.5 were excluded from intravenous thrombolysis unless CL revealed an INR ≤ 1.5. Blood samples for POC and CL INR measurements were drawn simultaneously, promptly after admission, and the time of POC determination was recorded. The CL technician was alerted via telephone about the emergency status and asked to report to the responsible emergency care physician immediately when the CL INR values were available. As in phase 1, the concordance of INR values as measured by POC and CL was tested by using the Bland-Altman technique and Pearson correlation. The time interval until CL INR values were available and the time needed to perform the head CT was recorded. The effective net time gain for initiating thrombolysis resulting from the use of POC compared to CL was calculated after subtracting the time for performance and interpretation of the CT. Throughout the whole study, a single POC device was used (Coaguchek XS; Roche). Times for blood sampling, sample delivery, and communication procedures between the emergency department and the CL remained unchanged throughout the study.

After 24 hours all patients receiving recombinant tissue plasminogen activator underwent routine follow-up CT. Post hoc, CT images were rated by a neuroradiologist who was blinded to whether patients were using OAC before treatment for the presence of intracerebral hemorrhage or hemorrhagic transformation according to SITS-MOST criteria.[18] To evaluate correlations between the presence of intracerebral hemorrhage or hemorrhagic transformation and initial INR level, a Mann-Whitney U test was conducted. Level of significance was set at $P<0.05$. Data were analyzed using the Statistical Package for the Social Sciences (SPSS, Version 16; SPSS Corporation).

Results

Phase 1

In phase 1, 113 patients were enrolled (62 male). Mean age of this group was 76 (range, 28–95; SD, 11). Bland-Altman analysis revealed a mean deviation of paired differences of 0.02 (SD, 0.27), resulting in limits of agreement of -0.52 to $+0.56$ (Figure 1A). Precision of INR values depended on INR intervals. Absolute deviations and limits of agreement improved for INR values ≤ 2 (mean, 0.12; SD, 0.09; limits of agreement, -0.08 to $+0.32$), indicating an increasing agreement between POC and standard CL measurements in INR values ≤ 2. Pearson correlation showed a highly significant correlation between POC and CL INR values ($r=0.98$; $P<0.01$; Figure 1B).

Phase 2

In the second phase, 48 patients with ischemic stroke presenting within the time frame for systemic thrombolysis in our emergency department were included (male, 22). Mean age was 78 years (range, 34–96; SD, 10). At the time of presentation, 34 patients were using OAC, and 23 of the 48 patients received intravenous thrombolytic treatment.

Similar to phase 1, the precision of INR measurements according to POC as compared to CL was evaluated in these 48 patients (Figure 2). Bland-Altman analysis revealed a mean deviation of paired differences of 0.09 (SD, 0.17), resulting in limits of agreement of -0.23 to $+0.41$. In addition, Pearson correlation showed a highly significant correlation between POC and laboratory INR values ($r=0.97$; $P<0.01$).

Mean time until availability of CL INR in all phase 2 patients was 47 minutes (range, 31–95; SD, 14). After accounting for clinical and neuroradiological evaluation, the mean effective time gain when using POC compared to CL INR measurements was 28 minutes (range, 11–64; SD, 12). The time gain until possible start of thrombolysis when using POC in contrast to CL is presented in Figure 3, using intervals of 15 minutes.

Except for 3 patients, treatment was administered according to POC INR levels (in 2 patients POC revealed INR levels of 1.6 and in 1 POC revealed INR levels of 1.8, whereas CL results in these 3 patients showed INR levels ≤ 1.5). Analysis of the follow-up head CT performed 24 hours after stroke according to SITS-MOST criteria in patients who received thrombolysis (n=23) demonstrated small petechiae along the margins of the infarct (HI 1) in 3 patients and more confluent petechiae within the infarct area but without a space-occupying effect in 2 patients (HI 2). None of the patients

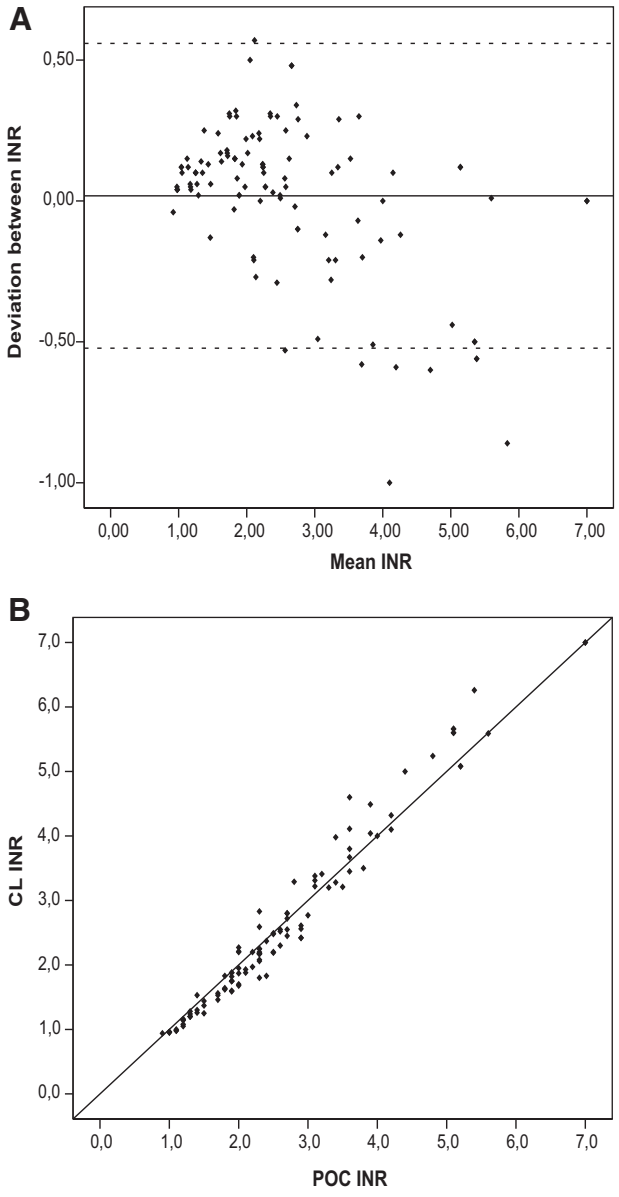

Figure 1. A, Bland-Altman bias plot for POC in comparison to CL results for patients in study phase 1 (n=113). Analysis revealed a mean deviation of paired differences of 0.02 (continuous line) with SD of 0.27, yielding limits of agreement of −0.52 to +0.56 (broken lines). Absolute deviations and limits of agreement improved for INR values ≤2, indicating an increasing precision of the POC device for INR values ≤2. B, Scatterplot of bivariate INR POC and CL data of phase 1 patients, indicating high agreement between POC and CL results.

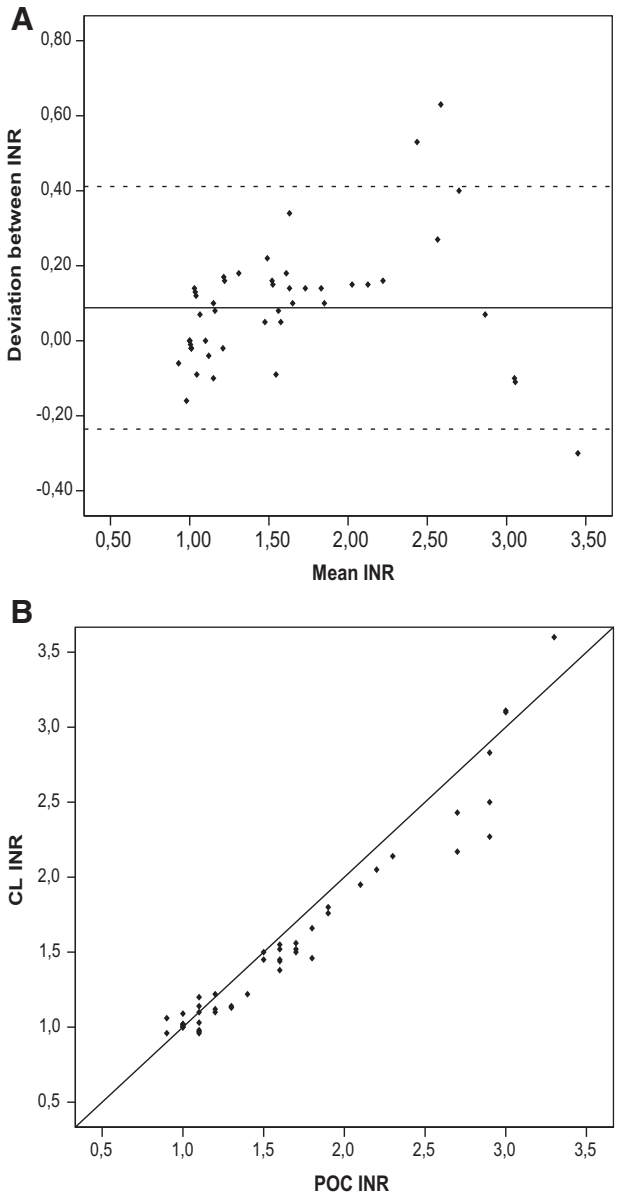

Figure 2. A, Bland-Altman bias plot for POC in comparison to CL results for patients with ischemic stroke admitted within the timeframe for systemic thrombolysis who were either using OAC or for whom information about OAC status was not available (n=48). Analysis revealed a mean deviation of paired differences of 0.17 (continuous line) with SD of 0.09, resulting in limits of agreement of −0.23 to +0.41 (broken lines). POC tended to slightly overestimate the INR in comparison to CL values. B, Scatterplot for phase 2 patients, indicating again close agreement between POC and CL results.

experienced a parenchymatous hemorrhage after thrombolysis. There was no significant correlation between INR level and development of petechiae (U=79.0; P=0.35).

Discussion

The effectiveness of thrombolysis in acute stroke depends strongly on the interval between symptom onset and administration of the thrombolytic drug.[4] Therefore, every effort should be taken to accelerate acute stroke management ("time is brain").[19] Initiation of thrombolysis is delayed in stroke patients using OAC because INR measurements in CL using standard analytic techniques are time-consuming. The major new findings of the present study are: (1) POC measurements of the INR are sufficiently precise for emergency management of thrombolysis in acute stroke; and (2) the use of a POC substantially reduces the time interval until INR values are available and therefore may hasten initiation of thrombolysis.

So far, POC for INR measurements have been investigated primarily in outpatient self-management trials of patients administered long-term OAC.[12,13] In these studies, the quality

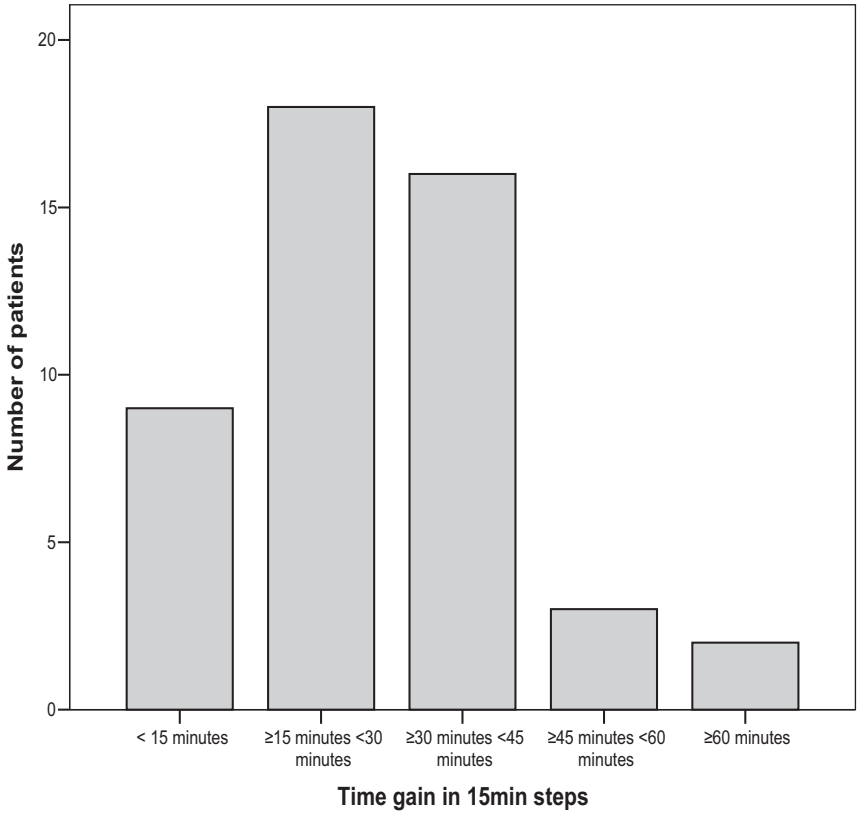

Figure 3. Time gain until possible start of treatment in phase 2 patients (n=48) presented in 15-minute steps.

of INR control did not differ between POC and standard monitoring methods.[12,14] Hence, POC devices are considered to be a reliable and effective alternative for outpatient monitoring of long-term anticoagulation.[11,13,20] In contrast, data regarding the use of INR POC devices in emergency departments are very limited. Green et al[20] reported on INR measurements using a POC that provided reliable and rapid INR results in 150 patients, including 49 patients with acute ischemic stroke, but the stroke population was not precisely described in that study. The results from phases 1 and 2 of our study underscore the fact that the POC device used in our study is sufficiently precise for managing acute ischemic stroke. No patient was treated because of falsely low POC INR values in our study. However, the precision of POC INR devices may differ. The device that was used in the present study had already shown a strong correlation to standard laboratory methods in INR ranges, especially up to 2.0, in other studies.[11,22,23] In addition, the mean differences in the cluster of results for INR up to 2.0 on the Bland-Altman plot for the device were much smaller than those of other analyzers tested in previous studies.[22,23] Nevertheless, the reliability of each POC device should be evaluated locally before using it in emergency settings, including ischemic stroke. Although INR values measured by POC were generally highly consistent with CL results in the present study, our device measured INR values just above the locally set limit for excluding thrombolysis (>1.5) in 3 patients, whereas CL INR was ≤1.5. These 3 patients received thrombolytic treatment only after the CL INR values were obtained, whereas all others were treated based on POC results. Therefore, thrombolysis should not be excluded based on borderline POC INR measurements alone but should be reconsidered when the CL "gold standard" INR values are available.

The most relevant finding of our study is that the use of an INR POC drastically shortens the interval until INR values are available. Despite all efforts to accelerate availability of these values from the CL, including instantly informing the CL technician, CL INR measurements in patients with ischemic stroke presenting within the time frame for systemic thrombolysis were only available after a mean time of 47 minutes. Latency of CL INR availability in phase 1, in which the technician was not informed, and phase 2 did not differ significantly (data not shown), suggesting that the delay in receiving the CL results was mainly caused by the time needed to conduct the analysis and to transport the blood. To some extent, however, the time gain will vary among institutions, depending on local conditions. To our knowledge, the delay caused by awaiting CL INR values in emergency situations such as hyperacute ischemic stroke has barely been studied to date. In our investigation the use of POC decreased the time required to obtain an INR value; therefore, thrombolytic therapy could be started earlier. Even when taking the time needed to perform the CT into account, the mean time gain was ≈30 minutes, and in individual cases >1 hour. These findings are in accordance with results reported by Green et al,[21] who found an even larger delay caused by CL INR measurements compared to POC. Besides rapidly identifying stroke patients who could receive thrombolysis despite the fact that they are currently using OAC as based on an INR ≤1.5, instant POC measurements of INR levels that prohibit systemic thrombolysis can help to guide the diagnostic

work-up and subsequent therapeutic procedures at an early stage. For example, in patients with severe strokes and INR >1.5, rapid vascular imaging and interventional therapeutic measures can be considered.

Beyond examining the usefulness of POC in the management of acute ischemic stroke, our study revealed some relevant aspects regarding OAC patients with acute ischemic stroke. First, 59% of acute stroke patients that were currently using OAC and presenting in time for thrombolysis had subtherapeutic INR levels (<2.0). This is in accordance with other studies that reported inadequate INR levels in 41% to 74.2% of acute stroke patients.[10,24,25] Second, in terms of hemorrhagic complications of thrombolysis in OAC acute stroke patients, our follow-up imaging data suggest that intravenous thrombolysis is safe in these patients when INR is ≤1.5.

Although our study has limitations, including a small sample size, nonconsecutive patient enrollment, and having been performed at only 1 center, our findings are of intuitive clinical relevance for the growing number of patients that are either using OAC or for whom information on OAC use is unavailable. In these patients, INR measurements with a POC device are sufficiently precise and can substantially shorten the interval until INR values are available as compared to CL analysis and consequently hasten the initiation of thrombolysis.

Acknowledgments

The authors thank the nursing staff of the neurological emergency room for their help with the POC measurements.

Sources of Funding

Department of Neurology, University of Heidelberg.

Disclosure

R.V. is supported by an Else-Kröner Memorial Scholarship.

References

1. Hacke W, Kaste M, Bluhmki E, Brozman M, Davalos A, Guidetti D, Larrue V, Lees KR, Medeghri Z, Machnig T, Schneider D, von Kummer R, Wahlgren N, Toni D. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med*. 2008;359:1317–1329.
2. Adams HP, Adams RJ, Brott T, del Zoppo GJ, Furlan A, Goldstein LB, Grubb RL, Higashida R, Kidwell C, Kwiatkowski TG, Marler JR, Hademenos GJ. Guidelines for the early management of patients with ischemic stroke: A scientific statement from the Stroke Council of the Am Stroke Association. *Stroke*. 2003;34:1056–1083.
3. European Stroke Organisation (ESO) Executive Committee; Collective Name: ESO Writing Committee. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. Cerebrovasc Dis. 2008;25:457–507.
4. Hacke W, Donnan G, Fieschi C, Kaste M, von Kummer R, Broderick JP, Brott T, Frankel M, Grotta JC, Haley EC, Kwiatkowski T, Levine SR, Lewandowski C, Lu M, Lyden P, Marler JR, Patel S, Tilley BC, Albers G, Bluhmki E, Wilhelm M, Hamilton S. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, *ECASS, and NINDS rt-PA stroke trials Lancet*. 2004;363:768–774.
5. Lakshminarayan K, Solid CA, Collins AJ, Anderson DC, Herzog CA. Atrial fibrillation and stroke in the general medicare population: a 10-year perspective (1992 to 2002). *Stroke*. 2006;37:1969–1974.
6. Furberg CD, Psaty BM, Manolio TA, Gardin JM, Smith VE, Rautaharju PM. Prevalence of atrial fibrillation in elderly subjects (the Cardiovascular Health Study). *Am J Cardiol*. 1994;74:236–241.
7. Aguilar MI, Hart R. Oral anticoagulants for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic attacks. *Cochrane Database Syst Rev*. 2005; CD001927.
8. Indredavik B, Rohweder G, Lydersen S. Frequency and effect of optimal anticoagulation before onset of ischaemic stroke in patients with known atrial fibrillation. *J Intern Med*. 2005;258:133–144.
9. Ay H, Arsava EM, Gungor L, Greer D, Singhal AB, Furie KL, Koroshetz WJ, Sorensen AG. Admission international normalized ratio and acute infarct volume in ischemic stroke. *Ann Neurol*. 2008;64:499–506.
10. Newman DH, Zhitomirsky I. The prevalence of nontherapeutic and dangerous international normalized ratios among patients receiving warfarin in the emergency department. *Ann Emerg Med*. 2006;48:182–189.
11. Ryan F, Shea SO, Byrne S. The reliability of point-of-care prothrombin time testing. A comparison of CoaguChek S and XS INR measurements with hospital laboratory monitoring. *Int J Lab Hematol*. 2008; (epub ahead of print).
12. Cromheecke ME, Levi M, Colly LP, de Mol BJ, Prins MH, Hutten BA, Mak R, Keyzers KC, Büller HR. Oral anticoagulation self-management and management by a specialist anticoagulation clinic: a randomised cross-over comparison. *Lancet*. 2000;356:97–102.
13. Ansell J, Jacobson A, Levy J, Völler H, Hasenkam JM. International Self-Monitoring Association for Oral Anticoagulation. Guidelines for implementation of patient self-testing and patient self-management of oral anticoagulation. International consensus guidelines prepared by International Self-Monitoring Association for Oral Anticoagulation. *Int J Cardiol*. 2005;99:37–45.
14. Cosmi B, Palareti G, Moia M, Carpenedo M, Pengo V, Biasiolo A, Rampazzo P, Morstabilini G, Testa S. Accuracy of a portable prothrombin time monitor (Coagucheck) in patients on chronic oral anticoagulant therapy: a prospective multicenter study. *Thromb Res*. 2000;100: 279–286.
15. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet*. 1986;1:307–310.
16. Bland JM, Altman DG. Applying the right statistics: analyses of measurement studies. *Ultrasound Obstet Gynecol*. 2003;22:85–93.
17. Brott T, Adams HP Jr, Olinger CP, Marler JR, Barsan WG, Biller J, Spilker J, Holleran R, Eberle R, Hertzberg V. Measurements of acute cerebral infarction: a clinical examination scale. *Stroke*. 1989;20: 864–870.
18. Anonymous. SITS-MOST (EMEA) study protocol. http://www.acutestroke.org/index.php?module=ContentExpress&func=display&ceid=29&meid=6. Accessed July 13, 2009.
19. Saver JL. Time is brain—quantified. *Stroke*. 2006;37:263–266.
20. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. Am College of Chest Physicians. Pharmacology and management of the vitamin K antagonists: Am College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*. 2008;133:160S–198S.
21. Green TL, Mansoor A, Newcommon N, Stephenson C, Stewart E, Hill MD. Reliability of point-of-care testing of INR in acute stroke. *Can J Neurol Sci*. 2008;35:348–351.
22. Moore GW, Henley A, Cotton SS, Tugnait S, Rangarajan S. Clinically significant differences between point-of-care analysers and a standard analyser for monitoring the International Normalized Ratio in oral anticoagulant therapy: a multi-instrument evaluation in a hospital outpatient setting. *Blood Coagul Fibrinolysis*. 2007;18:287–292.
23. Hentrich DP, Fritschi J, Müller PR, Wuillemin WA. INR comparison between the CoaguChek S and a standard laboratory method among patients with self-management of oral anticoagulation. *Thromb Res*. 2007;119:489–495.
24. Petursson P, Sveinbjornsdottir S, Einarsson G, Thornorgeirsson G, Oenundarson PT, Arnar DO. Prevalence of atrial fibrillation and use of warfarin among patients with ischemic stroke. *Laeknabladid*. 2004;90: 561–565.
25. Gladstone DJ, Bui E, Fang J, Laupacis A, Lindsay MP, Tu JV, Silver FL, Kapral MK. Potentially preventable strokes in high-risk patients with atrial fibrillation who are not adequately anticoagulated. *Stroke*. 2009;40: 235–240.