Prognostic Factors and Pattern of Long-Term Recovery with MLC601 (NeuroAiD™) in the Chinese Medicine NeuroAiD Efficacy on Stroke Recovery – Extension Study

Narayanaswamy Venketasubramanian^a Chun Fan Lee^a Sherry H. Young^b
San San Tay^b Thirugnanam Umapathi^c Annabelle Y. Lao^g
Herminigildo H. Gan^h Alejandro C. Baroque IIⁱ Jose C. Navarroⁱ
Hui Meng Chang^d Joel M. Advincula^k Sombat Muengtawepong^o
Bernard P.L. Chan^e Carlos L. Chua^j Nirmala Wijekoon^s H. Asita de Silva^s
John Harold B. Hiyadan^l Nijasri C. Suwanwela^m K.S. Lawrence Wong^r
Nippon Pongvarinⁿ Gaik Bee Eow^p Christopher L.H. Chen^f for the CHIMES-E
Study Investigators

^aRaffles Neuroscience Centre, ^bChangi General Hospital, ^cNational Neuroscience Institute – Tan Tock Seng Campus, ^dNational Neuroscience Institute – Singapore General Hospital Campus, ^eNational University Hospital, National University Health System, and ^fNational University of Singapore, Clinical Research Centre, Singapore, Singapore; ^gDavao Medical School Foundation Hospital, San Pedro Hospital, Davao, ^hJose Reyes Memorial Medical Center, San Lazaro Compound, ⁱUniversity of Santo Tomas Hospital, and ^jPhilippine General Hospital, University of the Philippines Manila, Manila, ^kWest Visayas State University Medical Center, Lapaz, Iloilo City, and ^lBaguio General Hospital and Medical Center, Baguio, Philippines; ^mChulalongkorn University, and ⁿSiriraj Hospital, Bangkok, and ^oThammasat University, Pathum Thani, Thailand; ^pPenang Hospital, Penang, Malaysia; ^qSchool of Public Health, The University of Hong Kong, Hong Kong, and ^rChinese University of Hong Kong, Prince of Wales Hospital, Shatin, China; ^sUniversity of Kelaniya, Ragama, Sri Lanka

Key Words

Acute stroke · Stroke recovery · MLC601 · NeuroAiD ·
Prognosis · Clinical trial · Long-term outcome

Abstract

Background: The Chinese Medicine NeuroAiD Efficacy on Stroke recovery – Extension (CHIMES-E) study is among the few acute stroke trials with long-term outcome data. We aimed to evaluate the recovery pattern and the influence of

prognostic factors on treatment effect of MLC601 over 2 years. **Methods:** The CHIMES-E study evaluated the 2 years outcome of subjects aged ≥ 18 years with acute ischemic stroke, National Institutes of Health Stroke Scale (NIHSS) score 6–14, pre-stroke modified Rankin Scale (mRS) score ≤ 1 included in a multicenter, randomized, double-blind, placebo-controlled trial of MLC601 for 3 months. Standard stroke care and rehabilitation were allowed during follow-up with mRS score being assessed in-person at month (M) 3 and by telephone at M1, M6, M12, M18 and M24. **Results:** Data from

880 subjects were analyzed. There was no difference in baseline characteristics between treatment groups. The proportion of subjects with mRS score 0–1 increased over time in favor of MLC601 most notably from M3 to M6, thereafter remaining stable up to M24, while the proportion deteriorating to mRS score ≥ 2 remained low at all time points. Older age ($p < 0.01$), female sex ($p = 0.06$), higher baseline NIHSS score ($p < 0.01$) and longer onset to treatment time (OTT; $p < 0.01$) were found to be predictors of poorer outcome at M3. Greater treatment effect, with more subjects improving on MLC601 than placebo, was seen among subjects with 2 or more prognostic factors (OR 1.65 at M3, 1.78 at M6, 1.90 at M12, 1.65 at M18, 1.39 at M24), especially in subjects with more severe stroke or longer OTT. **Conclusions:** The sustained benefits of MLC601 over 2 years were due to more subjects improving to functional independence at M6 and beyond compared to placebo. Selection of subjects with poorer prognosis, particularly those with more severe NIHSS score and longer OTT delay, as well as a long follow-up period, may improve the power of future trials investigating the treatment effect of neuroprotective or neurorestorative therapies.

© 2016 The Author(s)
Published by S. Karger AG, Basel

Introduction

There are very few proven therapies in acute ischemic stroke that reduce disability and/or death apart from revascularization strategies such as intravenous and endovascular thrombolysis or thrombectomy, decompression surgery for ‘malignant’ cerebral infarction and organized in-patient stroke care [1, 2]. Neuroprotection, aimed at restricting injury to the brain following an ischemic insult by preventing neuronal cell death in the salvageable penumbra during the first hours of acute phase, has shown promising results in experimental studies [3], but have failed in many clinical trials due to a variety of factors including patient selection and length of follow-up.

More recently, therapeutic modalities to enhance the self-reparative processes in the brain after injury have emerged. MLC601 has shown neurorestorative and neuroprotective properties in cellular and animal models [4, 5]. As neurorestorative processes require time, it is expected that clinical benefits would gradually accrue and appear only after a longer period of observation following treatment initiation. This hypothesis has recently been confirmed in the Chinese Medicine NeuroAiD Efficacy on Stroke recovery – Extension (CHIMES-E) study which showed that a 3-month treatment course of MLC601 after

an acute ischemic stroke increased the odds of achieving functional independence at 6 months and beyond [6]. Recovery from stroke, however, is dynamic and deterioration may occur even after initial improvement [7]. It is thus important to understand the pattern of long-term recovery of subjects with stroke in a neurorestorative trial. In addition, we recently showed in the CHIMES study how predictors of functional outcome, such as age, sex, baseline National Institutes of Health Stroke Scale (NIHSS) score, and treatment delay, affect the ability of demonstrating treatment effect of a therapy for stroke recovery at 3 months [8, 9].

We hypothesized that the long-term benefit of MLC601 was (1) due to improvement in functional outcomes persisting over time among patients who received MLC601, and (2) greater in patients with poorer prognosis for recovery who have the potential to respond to treatment. Therefore, in this study, we aimed to evaluate the pattern of recovery and the influence of prognostic factors on treatment effect of MLC601 over 2 years in the CHIMES-E study.

Methods

Analyses were performed using data from the CHIMES and CHIMES-E studies. The CHIMES study is a randomized double-blind placebo-controlled trial of subjects with ischemic stroke of intermediate severity allocated to either MLC601 or placebo for 3 months as add-on treatment to standard therapies [10]. Briefly, patients were included if they were 18 years or older, had an ischemic stroke in the preceding 72 h with NIHSS score of 6–14, brain imaging findings compatible with cerebral infarction and a pre-stroke Modified Rankin Scale (mRS) score of ≤ 1 . Subjects were randomized to receive either MLC601 or matching placebo at a dose of 4 capsules 3 times daily for 3 months. Each 400 mg MLC601 capsule contained extracts from 9 herbal components (Radix astragali, Radix salviae mitorrhizae, Radix paeoniae rubra, Rhizoma chuanxiong, Radix angelicae sinensis, Carthamus tinctorius, Prunus persica, Radix polygalae and Rhizoma acori tatarinowii) and 5 non-herbal components (Hirudo, Eupolyphaga seu steleophaga, Calculus bovis artifactus, Buthus martensii and Cornu saigae tataricae).

CHIMES-E is a planned extension study to evaluate the long-term outcome of subjects included in CHIMES up to 2 years from stroke [6]. Treatment allocation blinding was maintained throughout the CHIMES-E study and all subjects received standard stroke care and appropriate rehabilitation as prescribed by the treating physician.

Subjects were included in this analysis if they had the primary outcome, that is the mRS score, which was assessed in-person at month (M) 3 and by telephone at M1, M6, M12, M18 and M24. Logistic regression analyses were performed to identify the predictors of mRS score ≥ 2 and to assess the association between number of predictors and mRS. ORs and the corresponding 95% CIs ad-

Fig. 1. Comparison of ORs of achieving mRS score ≤ 1 at different time points in the overall CHIMES-E cohort (**a**) and in subjects with at least 2 prognostic factors for poorer outcome, that is, older age, female sex, baseline NIHSS score ≥ 10 and time to first dose ≥ 48 h (**b**).

justed for age, sex, NIHSS score, pre-stroke mRS score and stroke onset to initiation of study treatment time (OTT) were used to estimate treatment effects overall and according to presence of predictors for poorer outcome. Percentages of subjects who improved to mRS score ≤ 1 or worsened to ≥ 2 at each time point were plotted. The numbers needed to treat (NNT) were calculated using the inverse of absolute differences (ADs) to estimate the clinical benefit of MLC601.

Results

CHIMES-E included 880 subjects (MLC601, $n = 446$; placebo, $n = 434$) with mean age 61.8 ± 11.3 years, 36% women having mean baseline NIHSS score of 8.6 ± 2.5 . Baseline characteristics of subjects were similar between the treatment groups as previously described [6].

Overall, the odds of functional independence, defined as achieving mRS score ≤ 1 , increased over time in favor of MLC601 reaching statistical significance at M6, M12 and M18 (fig. 1a). The proportion of subjects improving to mRS score 0–1 increased most at M3 and M6 and remained stable over the next 18 months (fig. 2a). Overall, 26% on MLC601 and 28% on placebo achieved mRS score ≤ 1 at M1. This difference increased over subsequent months in favor of MLC601: 49 vs. 45% at M3, 55 vs. 46% at M6, 56 vs. 48% at M12, 56 vs. 48% at M18 and 56 vs.

50% at M24 for MLC601 and placebo, respectively. On the other hand, the proportion of subjects deteriorating to mRS score ≥ 2 remained low in both groups at all time points. At M24, 14 subjects on MLC601 and 19 subjects on placebo worsened to mRS score ≥ 2 . Both groups similarly showed 1 recurrent stroke and 3 deaths, but no cognitive decline.

The predictive variables for mRS score ≥ 2 at M3 were age > 60 years ($p < 0.01$), baseline NIHSS score 10–14 ($p < 0.01$), OTT > 48 h ($p < 0.01$) and female sex ($p = 0.06$). Increasing number of predictors was associated with worse mRS scores at M3 (cumulative OR 0.49, 95% CI 0.44–0.55), M6 (cumulative OR 0.51, 95% CI 0.45–0.57), M12 (cumulative OR 0.51, 95% CI 0.45–0.57), M18 (cumulative OR 0.52, 95% CI 0.46–0.58) and M24 (cumulative OR 0.52, 95% CI 0.46–0.58). Greater treatment effects were seen among subjects with at least 2 prognostic factors for poorer outcome for all time points showing ORs of 1.65 (95% CI 1.12–2.42) at M3, 1.78 (95% CI 1.19–2.66) at M6, 1.90 (95% CI 1.27–2.85) at M12, 1.65 (95% CI 1.11–2.46) at M18 and 1.39 (95% CI 0.94–2.07) at M24 (fig. 1b). As expected, fewer subjects achieved mRS 0–1 at M1, but the relative proportion of subjects with better mRS scores over time was more evident in those treated with MLC601 than those treated with placebo (fig. 2b).

Fig. 2. Proportions of subjects improving to mRS 0–1 or deteriorating to mRS score >2 over time in the overall CHIMES-E cohort (a) and among subjects with at least 2 prognostic factors for poor outcome, that is, older age, female sex, baseline NIHSS score ≥10 and time to first dose ≥48 h (b). NA = MLC601; P = placebo.

Table 1. Comparison of numbers needed to treat to gain an additional patient achieving mRS score ≤1 in overall study population and subgroups according to stroke severity and treatment delay

	Overall				NIHSS ≥10				OTT ≥48 h			
	n	AD, %	OR (95% CI)	NNT	n	AD, %	OR (95% CI)	NNT	n	AD, %	OR (95% CI)	NNT
Month 3	982	3.8	1.28 (0.96–1.69)	27	325	9.5	1.63 (0.94–2.81)	11	482	9.3	1.57 (1.06–2.34)	11
Month 6	872	8.0	1.50 (1.11–2.02)	13	288	12.6	1.75 (1.00–3.07)	8	427	12.1	1.72 (1.13–2.62)	9
Month 12	871	7.1	1.42 (1.05–1.91)	14	288	16.7	2.15 (1.22–3.78)	6	427	11.6	1.67 (1.10–2.55)	9
Month 18	864	6.4	1.36 (1.01–1.84)	16	286	15.7	1.99 (1.15–3.46)	7	422	10.5	1.57 (1.03–2.40)	10
Month 24	856	5.3	1.31 (0.97–1.77)	19	280	13.4	1.76 (1.00–3.09)	8	415	8.9	1.48 (0.97–2.26)	12

Treatment effects among older subjects were 1.33 (95% CI 0.89–1.97) at M3, 1.69 (95% CI 1.12–2.55) at M6, 1.60 (95% CI 1.06–2.41) at M12, 1.40 (95% CI 0.89–2.20) at M18, and 1.35 (95% CI 0.86–2.12) at M24. ORs for female subgroup were 1.84 (95% CI 1.15–2.94) at M3, 1.83 (95% CI 1.12–2.99) at M6, 1.75 (95% CI 1.07–2.85) at M12, 1.57 (95% CI 0.96–2.56) at M18 and 1.35 (95% CI 0.83–2.20) at M24. However, more severe NIHSS score and longer OTT as individual variables increased treatment effect size and reduced NNT for all time points to

almost the same magnitude as subjects with combinations of any 2 or more prognostic factors for poor outcome (table 1).

Discussion

Our analyses of long-term data from the CHIMES-E study provide important insights into the recovery patterns of post-stroke subjects and the influence of prognostic

sis on treatment effect in a stroke recovery trial. We have previously reported the overall benefit of MLC601 on functional independence at 6 months and beyond [6]. In this study, we demonstrate that the benefit was due to a larger proportion of subjects on MLC601 attaining functional independence by 6 months, thereafter maintaining their functional independence for up to 2 years, with fewer subjects deteriorating over time. In addition, we showed that subjects who have relatively poorer prognosis for recovery after a stroke are likely to obtain more benefit from treatment with MLC601.

Acute stroke trials often follow subjects only for the first 3 months. This short period of observation may be insufficient to provide stroke patients with ample time to recover as brain reorganization and repair are complex continuing processes that may take many months and even years [11]. Furthermore, it has been shown that transition from functional independence to dependency from 3 month to 1 year after a stroke is significant [7]. At 5 years, deterioration in functional and motor outcome may be observed with a return to the level measured at 2 months after a stroke, particularly among subjects who are older and have suffered from a more severe stroke [12]. These observations challenge the 3-month follow-up often used as end point for evaluating stroke outcome [13].

Our study included subjects with stroke of mild to moderate severity with a median baseline NIHSS score of 8 (interquartile scores of 7 and 10) [6]. As can be seen in the placebo group, more than a quarter of the subjects recovered to an independent functional state at 1 month and more than 45% were independent at 3 months after a stroke. As previously described, post-stroke patients recover best during the first 3 months after a stroke [14]. Patients with mild stroke recover fully by the third month. On the other hand, while steep recovery was seen among patients with moderate to severe strokes during the first 3 months as well, this was not complete and the rate of recovery plateaus thereafter. Therefore, it is expected that treatment effects can be best demonstrated at 6 months and beyond in subjects who still have room to improve.

Identification of such subjects for inclusion in a stroke recovery clinical trial is vital as such subjects will have the potential to benefit from investigational therapies. We have identified several factors that predict poorer outcomes at 3 months, namely older age, female sex, worse baseline stroke severity and longer delay between stroke onset and initiation of treatment [6, 8–10, 15]. The same factors were reported in many in other previous studies [16–22] and were also found to predict dete-

rioration at 1 and 5 years after a stroke [7, 12, 22–24]. Many of our subjects did not experience deterioration at 2 years; it was most likely due to exclusion of severe strokes in the trial. Nevertheless, we did see lower proportions of subjects with poorer prognosis achieving functional independence (i.e., mRS score ≤ 1) at all the time points and a trend for more long-term deterioration. Indeed, this led to the detection of larger treatment effects with relatively more subjects with poorer prognosis on MLC601 improving over time with less deterioration in the long run compared to placebo. This can represent as much as 138 additional patients achieving functional independence at 12 months for every 1,000 patients treated.

Among the prognostic factors we studied, we considered stroke severity (measured by NIHSS) and treatment window (indicated by OTT) as more important factors because they represent inherent disease- and treatment-related variables to consider in designing clinical studies or in clinical practice with a strong influence on outcome after stroke. We recently showed that subjects with moderately severe stroke and/or longer stroke OTT improve the power of detecting differences in recovery between treatment groups at 3 months [9]. In this present analysis, NIHSS score and OTT individually improve the power even more after longer observations of up to 18 months, and NNT is low and stable over time, especially in subjects with more severe strokes. The gradual decline in AD at 24 months is again seen and suggests that treatment longer than the 3-month regimen given in the study may be needed to maximize the brain repair processes in more subjects.

There are some limitations in this study. As mentioned, our trial included only subjects with stroke of mild to moderate severity within 72 h. Whether the same findings can be seen in very severe cases or in longer time windows is unclear. The analyses were performed post-hoc. On the other hand, the strength of our study is that our trial is one of the few stroke trials providing long-term data collected with full blinding maintained throughout.

In conclusion, the sustained benefits seen with MLC601 were due to more post-stroke subjects improving to functional independence at 6 months and beyond with very few subjects deteriorating over time compared to placebo. Prognostic factors for poorer outcome, particularly baseline stroke severity and treatment delay, improve the power of demonstrating the treatment effect of MLC601. Furthermore, our results indicate that longer observations and treatment duration can maximize the recovery potential of subjects included in post-acute stroke trials.

Future stroke trials should consider long-term follow-up of selected subjects who have relatively poorer prognosis and have the potential for recovery.

CHIMES-E Study Investigators

Singapore – Narayanaswamy Venketasubramanian, Chistopher L.H. Chen, Sherry H. Young, Marlie Jane Mamaug, San San Tay, Shrikant Pande, Umapathi Thirugnanam, Rajinder Singh, Hui Meng Chang, Deidre Anne De Silva, Bernard P.L. Chan, Vijay Sharma, Teoh Hock Luen. Philippines – Jose C Navarro, Herminigildo H. Gan, Annabelle Lao, Alejandro Baroque II, Johnny Lokin, John Harold B. Hiyadan, Ma. Socorro Sarfati, Randolph John Fangonillo, Neil Ambasing, Carlos Chua, Ma. Cristina San Jose, Joel Advincula, Eli John Berame. Thailand – Niphon Pongvarin, Sombat Muengtaweepongsa, Songkram Chotickanuchit, Nijasri Suwanwela. Sri Lanka – H. Asita de Silva, Udaya Ranawake, Nirmala Wijekoon. Hong Kong – K.S. Lawrence Wong. Malaysia – Gaik Bee Eow.

Sources of Funding

The CHIMES-E study was supported by the CHIMES Society, a non-profit organization, and grants were received by CLHC from the National Medical Research Council of Singapore (NMRC/1288/2011 and NMRC/1096/2006).

Disclosure Statement

The authors received funding for the trial and accommodation and transportation support for meetings from the CHIMES Society. Moleac (Singapore) provided grants to the CHIMES Society of which the society had sole discretion on use. J.C.N. has minor shares in E*Chimes, the Philippine distributor of NeuroAiD™. Other than CHIMES funding for the trial, the other authors and investigators do not have any conflict of interest to declare.

References

- 1 Jauch EC, Saver JL, Adams HP Jr, Bruno A, Connors JJ, Demerschalk BM, et al; American Heart Association Stroke Council; Council on Cardiovascular Nursing; Council on Peripheral Vascular Disease; Council on Clinical Cardiology: Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2013;44: 870–947.
- 2 Powers WJ, Derdeyn CP, Biller J, Coffey CS, Hoh BL, Jauch EC, et al; American Heart Association Stroke Council: 2015 American heart association/American stroke association focused update of the 2013 guidelines for the early management of patients with acute ischemic stroke regarding endovascular treatment: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2015;46: 3020–3035.
- 3 Sutherland BA, Minnerup J, Balami JS, Arba F, Buchan AM, Kleinschnitz C: Neuroprotection for ischaemic stroke: translation from the bench to the bedside. *Int J Stroke* 2012;7:407–418.
- 4 Heurteaux C, Widmann C, Moha ou Maati H, Quintard H, Gandin C, Borsotto M, Veyssiere J, Onteniente B, Lazdunski M: NeuroAiD: properties for neuroprotection and neurorepair. *Cerebrovasc Dis* 2013;35(suppl 1):1–7.
- 5 Quintard H, Borsotto M, Veyssiere J, Gandin C, Labbal F, Widmann C, Lazdunski M, Heurteaux C: MLC901, a traditional Chinese medicine protects the brain against global ischemia. *Neuropharmacology* 2011;61:622–631.
- 6 Venketasubramanian N, Young SH, Tay SS, Umapathi T, Lao AY, Gan HH, Baroque AC 2nd, Navarro JC, Chang HM, Advincula JM, Muengtaweepongsa S, Chan BP, Chua CL, Wijekoon N, de Silva HA, Hiyadan JH, Suwanwela NC, Wong KS, Pongvarin N, Eow GB, Lee CF, Chen CL: Chinese medicine NeuroAiD efficacy on stroke recovery – extension study (CHIMES-E): a multicenter study of long-term efficacy. *Cerebrovasc Dis* 2015;39:309–318.
- 7 Ullberg T, Zia E, Petersson J, Norrving B: Changes in functional outcome over the first year after stroke: an observational study from the Swedish stroke register. *Stroke* 2015;46: 389–394.
- 8 Chankrachang S, Navarro JC, De Silva DA, Towanabut S, Chua CL, Lee CF, Venketasubramanian N, Wong KS, Bousser MG, Chen CL; CHIMES Study Investigators: Prognostic factors and treatment effect in the CHIMES study. *J Stroke Cerebrovasc Dis* 2015;24:823–827.
- 9 Venketasubramanian N, Lee CF, Wong KS, Chen CL: The value of patient selection in demonstrating treatment effect in stroke recovery trials: lessons from the CHIMES study of MLC601 (NeuroAiD). *J Evid Based Med* 2015;8:149–153.
- 10 Chen CL, Young SH, Gan HH, Singh R, Lao AY, Baroque AC 2nd, Chang HM, Hiyadan JH, Chua CL, Advincula JM, Muengtaweepongsa S, Chan BP, de Silva HA, Towanabut S, Suwanwela NC, Pongvarin N, Chankrachang S, Wong KS, Eow GB, Navarro JC, Venketasubramanian N, Lee CF, Bousser MG; CHIMES Study Investigators: Chinese medicine neuroaid efficacy on stroke recovery: a double-blind, placebo-controlled, randomized study. *Stroke* 2013;44:2093–2100.
- 11 Carmichael ST: Emergent properties of neural repair: elemental biology to therapeutic concepts. *Ann Neurol* 2016;79:895–906.
- 12 Meyer S, Verheyden G, Brinkmann N, Dejaeger E, De Weerd W, Feys H, Gantenbein AR, Jenni W, Laenen A, Lincoln N, Putman K, Schuback B, Schupp W, Thijs V, De Wit L: Functional and motor outcome 5 years after stroke is equivalent to outcome at 2 months: follow-up of the collaborative evaluation of rehabilitation in stroke across Europe. *Stroke* 2015;46:1613–1619.
- 13 Lees KR, Selim MH, Molina CA, Broderick JP: Early versus late assessment of stroke outcome. *Stroke* 2016;47:1416–1419.
- 14 Duncan PW, Goldstein LB, Matchar D, Divine GW, Feussner J: Measurement of motor recovery after stroke. Outcome assessment and sample size requirements. *Stroke* 1992; 23:1084–1089.
- 15 Fabiaña NL, Lee CF, Gan R, Venketasubramanian N, Wong KS, Bousser MG, Chen CP, De Silva DA; CHIMES Study Investigators: Using the full span of the SPAN-100 index to predict functional outcome in the CHIMES study. *Int J Stroke* 2015; 10:E21.
- 16 Rabinstein A, Rundek T: Prediction of outcome after ischemic stroke: the value of clinical scores. *Neurology* 2013;80:15–16.
- 17 König IR, Ziegler A, Bluhmki E, Hacke W, Bath PM, Sacco RL, Diener HC, Weimar C; Virtual International Stroke Trials Archive (VISTA) Investigators: Predicting long-term outcome after acute ischemic stroke: a simple index works in patients from controlled clinical trials. *Stroke* 2008;39:1821–1826.
- 18 Gorelick PB: How baseline severity affects efficacy and safety outcomes in acute ischemic stroke intervention trials. *Ann N Y Acad Sci* 2012;1268:85–94.

- 19 Knoflach M, Matosevic B, Rücker M, Furtner M, Mair A, Wille G, Zangerle A, Werner P, Ferrari J, Schmidauer C, Seyfang L, Kiechl S, Willeit J; Austrian Stroke Unit Registry Collaborators: Functional recovery after ischemic stroke – a matter of age: data from the Austrian Stroke Unit Registry. *Neurology* 2012;78:279–285.
- 20 Weimar C, König IR, Kraywinkel K, Ziegler A, Diener HC; German Stroke Study Collaboration: Age and National Institutes of Health Stroke Scale Score within 6 hours after onset are accurate predictors of outcome after cerebral ischemia: development and external validation of prognostic models. *Stroke* 2004;35: 158–162.
- 21 Frankel MR, Morgenstern LB, Kwiatkowski T, Lu M, Tilley BC, Broderick JP, Libman R, Levine SR, Brott T: Predicting prognosis after stroke: a placebo group analysis from the National Institute of Neurological Disorders and Stroke rt-PA Stroke Trial. *Neurology* 2000;55: 952–959.
- 22 Andersen KK, Andersen ZJ, Olsen TS: Predictors of early and late case-fatality in a nationwide Danish study of 26,818 patients with first-ever ischemic stroke. *Stroke* 2011;42: 2806–2812.
- 23 Feigin VL, Barker-Collo S, Parag V, Senior H, Lawes CM, Ratnasabapathy Y, Glen E; AS-TRO study group: Auckland stroke outcomes study. Part 1: gender, stroke types, ethnicity, and functional outcomes 5 years poststroke. *Neurology* 2010;75:1597–1607.
- 24 Kammersgaard LP, Jørgensen HS, Reith J, Nakayama H, Pedersen PM, Olsen TS; Copenhagen Stroke Study: Short- and long-term prognosis for very old stroke patients. *The Copenhagen Stroke Study. Age Ageing* 2004;33:149–154.