Low-Dose Tissue Plasminogen Activator and Standard-Dose Tissue Plasminogen Activator in Acute Ischemic Stroke in Asian Populations: A Review

Siva Seeta Ramaiah^a Bernard Yan^{a, b}

^aMelbourne Brain Centre, Royal Melbourne Hospital, Melbourne, Vic., and ^bNeurointervention Service, Department of Radiology, Royal Melbourne Hospital (RMH), Parkville, Vic., Australia

Key Words

Low-dose tissue plasminogen activator · Standard-dose tissue plasminogen activator · Thrombolysis · Acute ischemic stroke · Asian population

Abstract

Background: The burden of stroke is becoming an important issue in Asian countries, where half of the world's population lives. In Western populations, standard-dose intravenous tissue plasminogen activator (tPA) at a dose of 0.9 mg/kg administered up to 4.5 h following acute ischaemic stroke has been shown to improve clinical outcomes. However, the dosage of tPA in Asian populations varies, partly influenced by treatment costs in developing countries and the perceived racial differences in treatment response. Furthermore, no randomized controlled trial of intravenous tPA thrombolysis has been carried out in Asia with the exceptions of observational and multicentre registries in Japan. **Summary of the Review:** This review aims to examine the current use of low-dose tPA in Asian populations with particular emphasis on its clinical benefits. Historically, the findings of 2-chain tPA (alteplase) trials in the early 1990s were the basis of low-dose tPA in Japan, and standard-dose tPA was chosen taking into account a pilot dose escalation study.

Most of the trials incorporating low-dose tPA suggested that low-dose tPA has clinical efficacy comparable with the standard dose and that it is associated with a lower incidence of symptomatic haemorrhage. It follows that consensus regarding the dosage of tPA is wanting. **Conclusions:** Standard-dose tPA would be a reasonable choice in Asian populations until the results are available from randomized controlled studies comparing low-dose with standard-dose tPA.

© 2013 S. Karger AG, Basel

Introduction

Stroke is one of the leading causes of disability and death in developed and developing countries [1, 2]. Intravenous tissue plasminogen activator (tPA; 0.9 mg/kg) remains the only proven effective drug treatment for acute ischaemic stroke (AIS) since its approval by the US FDA in 1996 [3]. Although 1 in 17 patients in the National Institute of Neurological Disorders and Stroke trial (NINDS) tPA cohort had haemorrhagic transformation, the trial showed that patients treated with tPA were at least 30% more likely to have an excellent outcome at 3 months [3, 4]. The more recent European Cooperative Acute Stroke Study III (ECASS III) trial provided addi-

tional evidence that a treatment benefit of intravenous tPA still exists up to 4.5 h following the onset of stroke [5].

In Asia, thrombolytic treatment has not been widely applied despite the 3 million deaths annually secondary to AIS occurring in relatively younger age groups (35–64 years old) compared to Western populations [6, 7]. One of the reasons of the lower rates of tPA utilization is tPA-related intracerebral haemorrhage which is due to racial differences in blood coagulation and fibrinolysis [8].

Although the recommended dose of intravenous tPA according to the NINDS [3], the Alteplase Thrombolysis for Acute Non-Interventional Therapy in Ischemic Stroke (ATLANTIS) [9], and the ECASS III trials [5] is 0.9 mg/kg body weight (maximum 90 mg), 0.6 mg/kg is the only approved dosage in Japan since 2005 for the treatment of patients within 3 h of onset based on the results of the Japan Alteplase Clinical Trial (J-ACT), which suggested clinical benefits [10]. Subsequent studies, J-ACT2 and Japan post-Marketing Alteplase Registration Study (J-MARS), also demonstrated a favourable outcome in both efficacy and safety with a lower dose of alteplase (0.6 mg/kg) in the Japanese population [11, 12]. In the absence of randomized evidence and given the uncertainty regarding the dosages and safety of thrombolysis in Asia (outside the Japanese population), we conducted a review comparing low-dose and standard-dose tPA.

Historical Reasons for Standard-Dose tPA

Two pilot dose escalation studies by Brott et al. [13] and Haley et al. [14] were the basis for standard-dose tPA. In the first pilot study, the investigators tested doses of 0.35 ($n = 6$), 0.60 ($n = 12$), 0.85 ($n = 30$), 0.95 ($n = 25$) and 1.08 ($n = 1$) mg/kg within 90 min of symptom onset on patients aged 18–80 years with acute cerebral ischaemia leading to a serious measurable deficit [13]. The study demonstrated a higher proportion of major neurological improvement at 24 h in the 0.85 mg/kg tier (55%) compared with the 0.6 mg/kg tier (33%), with no symptomatic intracranial haemorrhage (SICH) when a dose of ≤ 0.85 mg/kg was used [13]. In the second study, Haley et al. [14] tested three doses of tPA in patients presenting within 90–180 min after symptom onset [0.6 ($n = 8$), 0.85 ($n = 6$) and 0.95 ($n = 6$) mg/kg] and observed SICH in the two higher doses with a risk of SICH approximating 17% in doses of ≥ 0.85 mg/kg. Different efficacy at lower doses of tPA in these pilot trials was never tested and a proposed trial to compare 0.6 with 0.9 mg/kg of tPA in the mid-1990s was not approved for funding by the NINDS [15].

Historical Reasons for Low-Dose tPA

In Japan, three randomized double-blind trials of alteplase were conducted 20 years ago in embolic stroke patients treated within 6 h of onset [16–18]. Alteplase is a 2-chain form of tPA glycoprotein of 527 amino acids produced by gene recombinant technology from a culture of Chinese hamster ovary cells with very similar properties (biologically and pharmacologically) to alteplase [16]. Based on the angiographic recanalization rate, 20 million international units (MIU) of alteplase proved to be superior to placebo [17]. Twenty MIU (equal to 0.33 MIU/kg or 0.6 mg/kg of tPA) were comparable to 30 MIU regarding both angiographic recanalization and clinical improvement in this dose comparison study [18]. However, SICH occurred in 13.8% of patients who had received 30 MIU [18]. From the financial standpoint, low-dose tPA (i.e. which generally requires the use of a single 50-mg vial of Actilyse[®], Boehringer Ingelheim) is the preferred option for patients in China and Taiwan who cannot afford the full dose (i.e. 2 vials).

Arguments for Low-Dose tPA

Based on the three randomized trials on alteplase, the J-ACT [10] was undertaken with an alteplase dose of 0.6 mg/kg, which is equivalent to 20 MIU per person or 0.33 MIU/kg at a mean body weight of 60 kg [10]. The J-ACT is a prospective cohort study (table 1) that evaluated 103 patients within 3 h of AIS and showed equivalent clinical outcomes but a reduced risk of SICH compared to expected rates from the standard 0.9 mg/kg dose [10]. 37% of patients in the J-ACT had a modified Rankin Scale (mRS) score of 0–1 at 3 months and a 5.8% rate of SICH [10].

Mori et al. [11], in a magnetic resonance angiography (MRA)-based prospective cohort study (J-ACT2), enrolled 58 ischaemic stroke patients within 3 h of onset who had MRA-documented middle cerebral artery occlusion [11]. The dose of alteplase was similar to the J-ACT study (0.6 mg/kg) and the vascular outcome was evaluated by MRA at 6 and 24 h after symptom onset based on the modified Mori scale. Recanalization was noted on MRA in 51.7% of patients at 6 h and in 69.0% of patients at 24 h after symptom onset. A favourable clinical outcome (mRS score of 0–1 at 3 months after onset) was achieved in 46.6% of patients with none having SICH [11]. The J-MARS [12] was conducted for 2 years enrolling 7,492 patients in 942 centres to investigate whether thrombolysis with 0.6 mg/kg intravenous alteplase could

Table 1. Trials incorporating low-dose tPA

Publication	Patients, n	tPA dose, mg/kg	Favourable clinical outcomes at 3 months ^a			SICH ^b			Death within 3 months, n
			n	%	95% CI	n	%	95% CI	
Yamaguchi et al. [10], 2006 (J-ACT)	103	0.6	38/103	36.9	28.0–46.5	6/103	5.8	2.4–11.7	10/103 (9.7)
Yoneda et al. [33], 2007	20	0.6	5/20	25	9.8–47	1/20	5	0.2–22.2	3/20 (15)
Toyoda et al. [34], 2009 (SAMURAI register)	600	0.6	199/600	33.2	29.5–37.0	23/600	3.8	2.6–5.7	43/600 (7.2)
Sharma et al. [25], 2010	48/130	0.6	17/48	35.4	22.9–49.6	7/48	14.5	6.6–26.7	5/48 (10)
Chao et al. [20], 2010 (TTT-AIS)	116/241	0.72±0.07	48/116	41.4	32.7–50.5	3/116	2.6	0.7–6.9	8/116 (6.9)
Mori et al. [11], 2010 (J-ACT II)	58	0.6	27/58	46.6	34.0–59.4	0/58	0	0–5.0	1/58 (1.7)
Nakagawara et al. [12], 2010 (J-MARS)	7,492	0.6	1,631/4,944	33.1	31.8–34.4	259/7,492	3.5	2.5–6.2	985/7,492 (13.1)
Nguyen et al. [21], 2010	48/121	0.62 (0.6–0.86)	27/48	56.3	42.1–69.7	1/48	2.1	0.1–9.8	1/48 (2.1)
Zhou et al. [23], 2010	54/105	0.6–0.8	20/54	37	25.0–50.4	2/54	3.9	0.6–11.7	9/54 (17)
Chen et al. [22], 2012	105	0.7 (0.66–0.74)	39/95	41.1 ^c	NA	5/105	4.8	NA	8/105 (7.6)
Pan et al. [26], 2013	31 vs. 33	<0.75 vs. 0.75–0.90	16/31 vs. 20/33	51.5 vs. 61.2	NA	3/31 vs. 5/33	9.1 vs. 16.1	NA	1/31 (3.2) vs. 1/33 (3)

Figures in parentheses are ranges or percentages. NA = Not available.

^a Defined by an mRS score of 0–1 unless otherwise specified. ^b Defined as intracranial haemorrhage within 36 h resulting in neurological deterioration (increase in NIHSS score by ≥4 points) unless otherwise specified. ^c Favourable clinical outcome assessed in patients with a prestroke mRS score of ≤1.

be safe and effective in routine clinical practice for Japanese patients [12]. The study demonstrated 33% favourable outcome in the efficacy analysis of 4,944 patients. In the safety analysis of 7,492 patients, the incidence of SICH was 3.5% within 36 h and the overall mortality rate was 13.1% [12]. The results of the J-MARS were comparable with a similar post-marketing study in the European Union, the Safe Implementation of Thrombolysis in Stroke Monitoring Study (SITS-MOST), which used an alteplase dose of 0.9 mg/kg [19].

Studies outside Japan also demonstrated a favourable outcome in both efficacy and safety analyses with a lower

dose of alteplase [20–22]. In the Vietnamese population, Nguyen et al. [21] conducted a prospective study in 48 patients choosing a similar treatment protocol to that of the NINDS trial but with a lower dose of tPA (range, 0.6–0.86 mg/kg). Compared with the standard dose, patients treated with low-dose intravenous tPA were more likely to achieve functional independence at 3 months (34.2% with standard-dose vs. 56.3% with low-dose tPA; $p = 0.01$) with only 1 patient having SICH in the low-dose group compared to 4 patients in the standard-dose alteplase group [21]. In the Chinese population, Chao et al. [20] demonstrated in the Taiwan Thrombolytic Therapy

for Acute Ischemic Stroke (TTT-AIS) study that the standard dose of 0.9 mg/kg alteplase might not be optimal for treating aged Chinese patients. In their study, the authors recruited 241 patients with tPA indication and exclusion criteria similar to the SITS-MOST study [23], of whom 116 and 125 received a low dose (0.72 ± 0.07) and a standard dose (0.9 mg/kg), respectively. The lower-dose group demonstrated a higher percentage of functional independence (mRS score 0–1) of 41.4% in all age groups, and in those aged ≥ 70 years, the rate in the low-dose group was 53.6 versus 32.6% in the standard-dose group [20]. The investigators found that patients who were given the standard dose had twice the risk of having SICH (8.0 vs. 2.6%, respectively) and of dying within 3 months (12.8 vs. 6.9%) compared with those on the lower dose [20]. In another Taiwan-based study, Chen et al. [22] recruited 261 patients in a retrospective, two-centre study, of whom 105 and 156 received a low dose (0.7 mg/kg) and a standard dose (0.9 mg/kg), respectively. The study demonstrated no difference between the standard-dose and the low-dose groups regarding a favourable outcome in patients with an mRS score of ≤ 1 at 3 months (38.4 and 41.1%, respectively; $p = 0.676$), and the occurrence of SICH was non-significantly lower in the standard-dose group than in the low-dose group (2.6 vs. 4.8%, respectively; $p = 0.34$) [22].

To sum up, the studies in this section included prospective cohort studies and post-marketing observational studies. There were no randomized controlled studies to investigate the safety profile of low-dose tPA. However, there was a suggestion that low-dose tPA was associated with a lower incidence of SICH.

Arguments for Standard-Dose tPA in Asian Patients

A meta-analysis of about 3,700 patients included in many large randomized trials in North America and Europe examining intravenous tPA administered to AIS patients up to 4.5 h after symptom onset provides very strong evidence of the overall net benefit of the standard-dose regimen (0.9 mg/kg) [24]. Although there has never been any randomized clinical trial testing the efficacy of standard-dose tPA therapy in Asian AIS patients, a few retrospective studies have shown its feasibility and safety [25–27]. In a study conducted in Singapore, Sharma et al. [25] reported their experience with AIS patients given low-dose intravenous tPA (maximum 50 mg) from 2000 to 2006 and later switched to standard-dose intravenous tPA (maximum 90 mg) in a retrospective cohort design

involving 48 and 82 patients, respectively. 59% of the patients achieved functional independence (mRS score 0–1) at 3 months with standard-dose tPA, compared with 35% in the low-dose group ($p = 0.011$) and SICH occurred more frequently with the low dose (14.5%) than with the standard dose (1.2%; $p = 0.004$) [25]. In a Thai population study, Suwanwela et al. [27] prospectively recruited 34 patients following the inclusion and exclusion criteria of the NINDS tPA trial, who were subjected to standard-dose intravenous tPA (0.9 mg/kg). 47% of the patients achieved a favourable clinical outcome (mRS score 0–1) with a 5.9% rate of SICH [27]. In a Han Chinese population retrospective study, Zhou et al. [23] recruited 105 patients of all AIS patients treated with tPA within 4.5 h of onset of whom 51 patients received a standard dose of intravenous tPA (0.9 mg/kg) and the remaining 23 and 31 patients received 0.6–0.7 and 0.8 mg/kg, respectively [23]. 51.1% achieved a favourable clinical outcome (mRS score 0–1) at 3 months in the standard group, compared with 38.7% patients in the 0.8 mg/kg group and 34.8% patients in the 0.6–0.7 mg/kg group with a similar rate of SICH (3.9% according to ECASS III criteria) in both groups [23].

To sum up, the studies in this section included several case series in Asian populations, but the number of patients remained small. There was a trend towards less favourable clinical recovery in patients who received low-dose tPA.

Why the Difference between Asians and Caucasians?

Iso et al. [35] demonstrated a higher amount of measured antigens of tPA and plasminogen activator inhibitor 1 in Caucasian than in Japanese populations. Other major differences between both populations were the absence of factor V Leiden and prothrombin mutations in the Japanese population, and the rarity of polymorphism of a platelet integrin, the glycoprotein IIIa 33Leu/Pro [28]. Apart from potential differences in the haemostatic profile of Japanese patients, there are well-documented differences in the genetic polymorphism pattern in Caucasians. Recently, in a genome-wide association study of four population-based cohorts, 19,602 white persons were recruited by the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium which reported two single nucleotide polymorphisms, rs11833579 and rs12425791, to be significantly associated with the incidence of ischaemic stroke [29]. However, another study in the Japanese population by

Matsushita et al. [30] identified rs12425791 to be significantly associated with the incidence of atherothrombotic stroke whereas rs11833579 was not. The authors postulated that the failure of replication of an association between ischaemic stroke and rs11833579 was due to the weak linkage disequilibrium between a true causative variant in the Japanese population and that particular single nucleotide polymorphism [30]. Furthermore, it is well described that Asian patients are at a higher risk of intracranial atherosclerosis with reported rates of 33–50% in China, 47% in Thailand, 56.3% in Korea and 47.9% in Singapore [31]. This has also led to the speculation that there may be differing dosing requirements in Asia.

Future Studies

A large-scale randomized clinical trial is needed, though challenging, to show the real difference in the effects of the two doses of tPA in AIS patients. A realistic solution would be a non-inferiority study to determine the optimum dose of tPA. Perhaps the recently launched trial Enhanced Control of Hypertension and Thrombolysis in Stroke Disease (ENCHANTED) would settle the controversy of tPA dose in AIS. ENCHANTED being

a quasi-factorial randomized controlled study was designed to address 4 key questions in which 2 pertinent issues are whether low-dose tPA (0.6 mg/kg) is truly equivalent in efficacy, or even safer (low risk of SICH), to the standard dose (0.9 mg/kg), not just in Asians with AIS but also in other population groups around the world. Two other objectives of ENCHANTED are the effect of intensive blood pressure lowering on outcomes and the risk of SICH.

Conclusions

There are wide variations in the dosing of intravenous tPA for AIS with the tendency to use lower dosages in Asian populations. The low-dose intravenous tPA is an attractive option due to reduced costs and is proposed as a solution to overcome the underutilization of thrombolysis in developing countries [32]. However, given that lack of level 1 evidence for low-dose tPA, we would recommend the application of standard-dose tPA in Asian populations until the results are available from randomized controlled studies comparing low-dose with standard-dose tPA.

References

- Donnan G, Fisher M, Macleod M, Davis S: Stroke. *Lancet* 2008;371:1612–1623.
- Murray CJ, Lopez AD: Mortality by cause for eight regions of the world: global burden of disease study. *Lancet* 1997;349:1269–1276.
- The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 1995;333:1581–1587.
- Saver JL: Number needed to treat estimates incorporating effects over the entire range of clinical outcomes: novel derivation method and application to thrombolytic therapy for acute stroke. *Arch Neurol* 2004;61:1066–1070.
- Hacke W, Kaste M, Bluhmki E, et al: Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med* 2008;359:1317–1329.
- Poungvarin N: Stroke in the developing world. *Lancet* 1998;352(suppl III):19–22.
- Feigin VL: Stroke epidemiology in the developing world. *Lancet* 2005;365:2160–2161.
- Ueshima S, Matsuo O: The differences in thrombolytic effects of administered rt-PA between Japanese and Caucasians. *Thromb Haemost* 2002;87:544–546.
- Clark WM, Wissman S, Albers GW, et al: Recombinant tissue-type plasminogen activator (alteplase) for ischemic stroke 3 to 5 hours after symptom onset. The ATLANTIS study: a randomized controlled trial. Alteplase thrombolysis for acute noninterventional therapy in ischemic stroke. *JAMA* 1999;282:2019–2026.
- Yamaguchi T, et al: Alteplase at 0.6 mg/kg for acute ischemic stroke within 3 hours of onset: Japan Alteplase Clinical Trial (J-ACT). *Stroke* 2006;37:1810–1815.
- Mori E, Minematsu K, Nakagawara J, Yamaguchi T, Sasaki M, Hirano T, et al: Effects of 0.6 mg/kg intravenous alteplase on vascular and clinical outcomes in middle cerebral artery occlusion. Japan Alteplase Clinical Trial II (J-ACT II). *Stroke* 2010;41:461–465.
- Nakagawara J, Minematsu K, Okada Y, Tanahashi N, Nagahiro S, Mori E, et al: Thrombolysis with 0.6 mg/kg intravenous alteplase for acute ischemic stroke in routine clinical practice. The Japan post-Marketing Alteplase Registration Study (J-MARS). *Stroke* 2010;41:1984–1989.
- Brott TG, Haley EC Jr, Levy DE, Barsan W, Broderick J, Sheppard GL, Spilker J, Kongable GL, Massey S, Reed R, Marler JR: Urgent therapy for stroke. 1. Pilot study of tissue plasminogen activator administered within 90 minutes. *Stroke* 1992;23:632–640.
- Haley EC Jr, Levy DE, Brott TG, Sheppard GL, Wong MC, Kongable GL, Torner JC, Marler JR: Urgent therapy for stroke. Part II. Pilot study of tissue plasminogen activator administered 91–180 minutes from onset. *Stroke* 1992;23:641–645.
- Khatrri P, Broderick JP, Pancioli AM: Risk of thrombolysis-associated intracerebral hemorrhage: the need to compare apples with apples. *Stroke* 2005;36:1109–1110.
- Mori E, Yoneda Y, Tabuchi M, Yoshida T, Ohkawa S, Ohsumi Y, Kitano K, Tsutsumi A, Yamadori A: Intravenous recombinant tissue plasminogen activator in acute carotid artery territory stroke. *Neurology* 1992;42:976–976.
- Yamaguchi T, Hayakawa T, Kiuchi H: Intravenous tissue plasminogen activator ameliorates the outcome of hyperacute embolic stroke. *Cerebrovasc Dis* 1993;3:269–272.
- Yamaguchi T, Hayakawa T, Kiuchi H: Clinical efficacy and safety of intravenous tissue plasminogen activator in acute embolic stroke: a randomized, double-blind, dose comparison study of alteplase; in Yamaguchi T, et al (eds): *Thrombolytic Therapy in Acute Ischemic Stroke III*. Tokyo, Springer, 1995, pp 223–229.

- 19 Wahlgren N, Ahmed N, Dávalos A, Ford GA, Grond M, Hacke W, Hennerici MG, et al: Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. *Lancet* 2007;369:275–282.
- 20 Chao AC, Hsu HY, Chung CP, Liu CH, Chen CH, Teng MM, et al: Outcomes of thrombolytic therapy for acute ischemic stroke in Chinese patients: the Taiwan Thrombolytic Therapy for Acute Ischemic Stroke (TTT-AIS) study. *Stroke* 2010;41:885–890.
- 21 Nguyen TH, Truong ATL, Ngo MB, et al: Patients with thrombolysed stroke in Vietnam have an excellent outcome: results from the Vietnam Thrombolysis Registry. *Eur J Neurol* 2010;17:1188–1192.
- 22 Chen C-H, Hsieh C-Y, Lai T-B, Chuang M-T, Chen W-L, Sun M-C: Optimal dose for stroke thrombolysis in Asians: low dose may have similar safety and efficacy as standard dose. *J Thromb Haemost* 2012;10:1270–1275.
- 23 Zhou XY, Wanga SS, Collins ML, Davis SM, Yan B: Efficacy and safety of different doses of intravenous tissue plasminogen activator in Chinese patients with ischemic stroke. *J Clin Neurosci* 2010;17:988–992.
- 24 Lees KR, Bluhmki E, von Kummer R, Brott TG, Toni D, Grotta JC, Albers GW, Kaste M, Marler JR, Hamilton SA, Tilley BC, Davis SM, Donnan GA, Hacke W, ECASS, ATLANTIS, NINDS and EPITHET rt-PA Study Group, Allen K, Mau J, Meier D, del Zoppo G, De Silva DA, et al: Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. *Lancet* 2010;375:1695–1703.
- 25 Sharma VK, Tsivgoulis G, Tan JH, Ong BKC, Chan BPL, Teoh HL: Feasibility and safety of intravenous thrombolysis in multiethnic Asian stroke patients in Singapore. *J Stroke Cerebrovasc Dis* 2010;19:424–430.
- 26 Pan S-M, Liu J-F, Liu M, Shen S, Li H-J, Dai L-H, Chen X-J: Efficacy and safety of a modified intravenous recombinant tissue plasminogen activator regimen in Chinese patients with acute ischemic stroke. *J Stroke Cerebrovasc Dis* 2013;22:690–693.
- 27 Suwanwela NC, Phanthumchinda K, Likitjaroen Y: Thrombolytic therapy in acute ischemic stroke in Asia: the first prospective evaluation. *Clin Neurol Neurosurg* 2006;108:549–552.
- 28 Murata M: Genetic polymorphisms associated with thrombotic disorders in the Japanese population. *Fibrinol Proteol* 2000;14:155–164.
- 29 Ikram MA, Seshadri S, Bis JC, Fornage M, DeStefano AL, Aulchenko YS, et al: Genome-wide association studies of stroke. *N Engl J Med* 2009;360:1718–1728.
- 30 Matsushita T, Umeno J, Hirakawa Y, Yonemoto K, Ashikawa K, Amitani H, Ninomiya T, et al: Association study of the polymorphisms on chromosome 12p13 with atherothrombotic stroke in the Japanese population. *J Hum Genet* 2010;55:473–476.
- 31 Wong LKS: Global burden of intracranial atherosclerosis. *Int J Stroke* 2006;1:158–159.
- 32 Durai Pandian J, Padma V, Vijaya P, Sylaja PN, Jagaralpudi MKM: Stroke and thrombolysis in developing countries. *Int J Stroke* 2007;2:17–26.
- 33 Yoneda Y, Yamamoto S, Hara Y, Ohta K, Matsushita M, Yamamoto D, et al: Post-licensed 1-year experience of systemic thrombolysis with tissue plasminogen activator for ischemic stroke in a Japanese neuro-unit. *Clin Neurol Neurosurg* 2007;109:567–570.
- 34 Toyoda K, Koga M, Naganuma M, et al: Routine use of intravenous low dose recombinant tissue plasminogen activator in Japanese patients: general outcomes and prognostic factors from the SAMURAI Register. *Stroke* 2009;40:3591–3595.
- 35 Iso H, Folsom AR, Koike KA, Sato S, Wu KK, Shimamoto T, Iida M, Komachi Y: Antigens of tissue plasminogen activator and plasminogen activator inhibitor 1: correlates in non-smoking Japanese and Caucasian men and women. *Thromb Haemost* 1993;70:475.