Current antithrombotic treatment in East Asia: Some perspectives on anticoagulation and antiplatelet therapy

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Arterial thromboembolism has become more prevalent in East Asia as the population has aged and social and economic environments have changed drastically. However, clinical data from Asia are limited. The prevalence and incidence of thrombotic diseases may differ from those of European and American countries (1). Moreover, the most effective doses of antithrombotic agents in Asian regions may differ from those in Western countries (2). In this brief review, we inspected the latest progression in antithrombotic treatment among Asian populations.

Atrial fibrillation-related thromboembolism and antithrombotic therapy in East Asia

The age-adjusted prevalence of atrial fibrillation (AF) may be lower among Asians compared with that among Caucasians (3). Epidemiological studies conducted in communities in China, Japan, Korea, and Singapore revealed that the prevalence of AF ranged from 0.56% to 1.6% (4–8). However, Asian patients have a five- to six-fold higher stroke risk (Table 1) (8–13).

Although the efficacy of anticoagulants for the prevention of AF-related thromboembolism in patients with non-valvular AF (NVAF) is well established in Western populations, anticoagulation therapy is not commonly given to Asian patients with NVAF, probably because of the risk of critical bleeding during treatment, which may be especially higher among Asian patients. Warfarin-related intracranial haemorrhage in Asian patients was reported to be 1.75 per 100 patient-years, which is significantly higher than that in Caucasians (0.34 per 100 patient-years) (14). Whether aspirin can replace warfarin as an antithromboembolism agent or whether a lower intensity of anticoagulation is as effective but much safer in Asian patients with NVAF has been debated (Table 2) (15–18). In terms of bleeding risk assessment, the consensus document from the European Heart Rhythm Association (EHRA) may be a good reference for Asian patients with AF (19).

It is of no surprise that aspirin is less effective in prevention of stroke in patients with NVAF. A prospective, randomised, multicentre trial from Japan recruited 871 patients with NVAF and randomised them to aspirin therapy (150–200 mg/day) or no treatment. The trial was stopped early because of the low possibility of superiority of aspirin compared with no treatment. The primary endpoints, which included cardiovascular death, symptomatic brain infarction, and transient ischaemic attack, were...

Table 1: Atrial fibrillation and stroke risk.

<table>
<thead>
<tr>
<th>Study</th>
<th>Mean age, years</th>
<th>Stroke (% per year) AF</th>
<th>Relative risk AF No AF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ma, China (10)</td>
<td>71</td>
<td>5.3</td>
<td>—</td>
</tr>
<tr>
<td>Shibata, Japan (11)</td>
<td>65</td>
<td>5.0</td>
<td>0.90</td>
</tr>
<tr>
<td>Lee, Taiwan (8)</td>
<td>70</td>
<td>4.9</td>
<td>0.45</td>
</tr>
<tr>
<td>Framingham, USA (12)</td>
<td>70</td>
<td>4.1</td>
<td>0.74</td>
</tr>
<tr>
<td>Whitehall, UK (13)</td>
<td>60</td>
<td>1.8</td>
<td>0.26</td>
</tr>
</tbody>
</table>

Table 2: Studies on stroke prevention for patients with atrial fibrillation in Asia.

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Country</th>
<th>Patients</th>
<th>Antithrombotic strategy</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sato/2006 (15)</td>
<td>Japan NVAF n=871</td>
<td>Aspirin 150 to 200 mg/d vs. placebo</td>
<td>A low dosage of aspirin was neither effective nor safe</td>
<td></td>
</tr>
<tr>
<td>Hu/2006 (16)</td>
<td>China NVAF n=828</td>
<td>Adjusted-dose warfarin (INR 2–3) vs. aspirin (150 to 160 mg/d)</td>
<td>Adjusted-dose warfarin was superior to aspirin</td>
<td></td>
</tr>
<tr>
<td>Yamaguchi/2000 (17)</td>
<td>Japan NVAF n=115</td>
<td>Low-intensity warfarin (INR 1.5 to 2.1) vs. conventional-intensity (INR 2.2 to 3.5)</td>
<td>Annual rate of ischaemic stroke did not differ significantly, but low-intensity warfarin was safer</td>
<td></td>
</tr>
<tr>
<td>Suzuki/2007 (18)</td>
<td>Japan NVAF n=667</td>
<td>Target INR value was set at 1.6–2.6</td>
<td>Incidence of major bleeding was 2.38%, which is higher than in Western patients INR ≥2.27 was an independent risk factor for major bleeding</td>
<td></td>
</tr>
</tbody>
</table>

NVAF, non-valvular atrial fibrillation; INR, international normalised ratio; d, days.
similar in the two groups [3.1% (2.1%–4.6%) per year in the aspirin group vs. 2.4% (1.5%–3.5%) per year in the control group], while aspirin showed a trend of increased risk of major bleeding (1.6% vs. 0.4%) (15). A multicentre randomised trial compared the efficacy of aspirin at 150 to 160 mg once daily with adjusted-dose warfarin (international normalised ratio [INR], 2.0–3.0) in Chinese patients. After a mean follow-up period of 19 months, the primary end point of death or ischaemic stroke in the aspirin group was significantly higher than that in the warfarin group [6.0% vs. 2.7%; odds ratio [OR], 0.44 (0.198–0.960)] (16).

Because there is some concern that Asians might experience a substantially higher risk for warfarin-related intracranial haemorrhage than Western individuals (14), the rationale of using lower-intensity anticoagulation in Asian patients has been studied. A multicentre, prospective, randomised trial conducted in Japan aimed to determine the optimal intensity of warfarin therapy for secondary prevention of stroke in patients with NVAF. The study found that low-intensity warfarin (INR 1.5–2.1) seems safer than conventional-intensity (INR 2.2–3.5) treatment without impairment of the antithrombosis effects (17). Although this point has been argued about among Asian specialists, the target INR was always set at 1.6 to 2.6 in clinical practice (18). Although one small-scale randomised trial suggests that under optimal monitoring, usual anticoagulant intensity (INR 2.0–3.0) is effective and safe for moderate-to-high-risk Chinese patients with AF (16), more robust data are required to address this important clinical problem.

Although warfarin is recommended as antithrombotic therapy in Asian AF guidelines (20, 21), there is a large variation in the prescription rate. A small-registry study (22) reported that 36% of Japanese patients with AF aged >85 years and 61% of those aged 75 to 84 years were on anticoagulation therapy. However, warfarin is extremely underused in Chinese patients with AF. An epidemiological survey conducted in 2004 in China showed that only 2.7% of patients were on oral anticoagulation therapy (4). Even today, the use of warfarin does not exceed 10% in patients with AF and anticoagulation indications. Closure of the gap in practice is of critical value and is currently underway in China. Of the many patients on aspirin in the Japanese J-TRACE Study, 31% of patients with AF were treated with aspirin despite the fact that it was not demonstrated to be safe or effective (23). This is in line with an international prospective registry in which a high proportion of patients with AF at high risk of atherothrombosis were treated with antiplatelet therapy (24). There are few data on optimal antithrombotic treatment for patients who have had a coronary stent in Asia; the consensus document from North America may provide some useful perspectives (25).

New oral anticoagulants may change the pattern of antithrombotic therapy worldwide (26). The RE-LY (27), ROCKET-AF (28), and ARISTOTLE (29) studies proved the new agents dabigatran, rivaroxaban, and apixaban superior or not inferior to warfarin for stroke prevention in patients with AF (Table 3); the rate of either stroke or systemic embolism and the bleeding risk associated with new agents in Asian patients were consistent with the global results of these trials. However, there are still insufficient data on these new drugs in Asian patients, especially warfarin-naive patients (30). Moreover, their high price will be an important barrier for their widespread use in many resource-limited Eastern countries.

### Table 3: Stroke or systemic embolism and major bleeding in patients with atrial fibrillation in Asia in RELY, ROCKET-AF, and ARISTOTLE trials.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Region</th>
<th>No. (%)</th>
<th>Follow-up</th>
<th>Stroke or systemic embolism</th>
<th>Major bleeding (including non-major bleeding in ROCKET AF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RELY (27)</td>
<td>East Asia</td>
<td>1648 (9.1)</td>
<td>2 years</td>
<td>Dabigatran 110 mg: 1.87 %/year (global: 1.53 %/year)</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dabigatran 150 mg: 1.77 %/year (global: 1.11 %/year)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Warfarin: 2.28 %/year (global: 1.69 %/year)</td>
<td></td>
</tr>
<tr>
<td>ROCKET AF (28)</td>
<td>Asian Pacific</td>
<td>1055 (7.4)</td>
<td>707 days</td>
<td>Rivaroxaban 20 mg: 4.27% (global: 3.8%)</td>
<td>Rivaroxaban 20 mg: 26.43% (global: 20.75%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Warfarin: 5.12% (global: 4.32%)</td>
<td>Warfarin: 25.67% (global: 20.34%)</td>
</tr>
<tr>
<td>ARISTOTLE (29)</td>
<td>Asian Pacific</td>
<td>2916 (16.02)</td>
<td>1.8 years</td>
<td>Apixaban 10 mg: 2.0 %/year (global: 1.27 %/year)</td>
<td>Apixaban 10 mg: 2.1 %/year (global: 2.13 %/year)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Warfarin: 3.1 %/year (global: 1.60 %/year)</td>
<td>Warfarin: 4.1 %/year (global: 3.09 %/year)</td>
</tr>
</tbody>
</table>

**Antiplatelet therapy for coronary atherosclerotic disease in East Asia**

Besides arterial embolism, arterial thrombosis is another concern attracting much attention in East Asia. Antiplatelet therapy has long been considered the cornerstone for prevention of arterial thrombosis. However, a few contentious issues remain, such as optimal use of antiplatelet therapy for primary and secondary prevention and prevention of stent thrombosis after implantation of drug-eluting stents (DES). Studies in Asia have addressed some important issues related to antiplatelet therapy.

**Optimal use of antiplatelet agents after implantation of DES**

Early discontinuation of clopidogrel plus aspirin (dual antiplatelet therapy [DAT]) has been identified as a risk factor for late
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Stent thrombosis in patients with implanted DES (31, 32). Current guidelines recommend that DAT should be given for at least 12 months after DES in patients at low bleeding risk (33). However, the optimal duration of DAT and the risk–benefit ratio for long-term DAT remain uncertain.

A valuable Korean trial included 2,701 patients who had undergone DES implantation and were free of major adverse cardiac or cerebrovascular events and major bleeding for a period of at least 12 months. These patients were randomised to receive standard DAT or aspirin alone (34). The cumulative risk of the composite rate of myocardial infarction (MI) or cardiac death at two years was 1.8% with DAT, compared with 1.2% with aspirin monotherapy [hazard ratio, 1.65 (0.80–3.36)]. Moreover, the individual risks of MI, stroke, stent thrombosis, repeat revascularisation, major bleeding, and death were not significantly different between the two groups. Therefore, a prolonged period of DAT for more than 12 months in patients after DES implantation was no more effective than aspirin monotherapy.

Another concern about antiplatelet therapy is aspirin or clopidogrel resistance. However, the data on Asian patients were limited. A registry study in Hong Kong, China used the VerifyNow Aspirin Assay to determine aspirin responsiveness of 468 stable patients with coronary artery disease and noted that the prevalence of aspirin resistance was 27.4% (35). Another study showed that the prevalence of aspirin resistance was slightly lower (19.2%); in this study, aspirin responsiveness was determined by the Ultegra Rapid Platelet Function Assay-ASA (36). Several small studies have demonstrated that the prevalence of clopidogrel resistance in East Asian patients ranges from 14% to 22.28% (37–39). According to the established evidence, the data on clopidogrel or aspirin resistance between East Asian and European patients are similar.

Clopidogrel, a selective phosphodiesterase-3 inhibitor, has long been considered to be an antiplatelet agent in some East Asian countries. It has been shown to prevent recurrent thrombotic events of ischaemic stroke in Northeast Asia (40, 41). Established evidence demonstrated that adjunctive cilostazol in addition to standard DAT (triple antiplatelet therapy [TAT]) intensifies platelet inhibition in patients with no or a low response to standard DAT (42, 43). Several studies have shown that TAT decreases the risks of stent thrombosis, MI, and cardiac death after stenting compared with DAT (44–48) (Table 4). However, the influence of Cilostazol-based triple antiplatelet therapy on ischaemic complication after drug-eluting stent implantation (CILON-T) (47), a recently published multicentre randomised trial, demonstrated that there was no difference in the composite rate of cardiac death, non-fatal MI, ischaemic stroke, or target lesion revascularisation between patients on TAT and those on DAT (8.5% vs. 9.2%; P = 0.74) at the six-month follow-up.

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Liver dysfunction associated with thienopyridine therapy is a rather specific concern in Japan. In a randomised study of ticlopidine (200 mg/day) versus clopidogrel (75 mg/day), the incidence of hepatic dysfunction was 12% in the ticlopidine group and 4% in the clopidogrel group at 52 weeks (49). Furthermore, a meta-analysis of two Japanese studies also confirmed that 34 patients taking thienopyridines developed hepatic dysfunction (50). Although the mechanism of hepatic dysfunction in Japanese patients taking thienopyridines is yet to be elucidated, case-control studies have suggested the potential contribution of the specific haplotype HLA-A*3303 in Japanese patients with hepatic dysfunction (51). Further studies are expected to investigate the safety concerns surrounding clopidogrel among Asian patients.

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**Table 4: Cilostazol in addition to standard dual antiplatelet treatment after implantation of drug-eluting stents.**

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Study type</th>
<th>Patients</th>
<th>Follow-up</th>
<th>Main outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee SW (44)</td>
<td>Korea</td>
<td>Registry</td>
<td>3,012</td>
<td>30 days</td>
<td>Stent thrombosis was significantly lower in TAT than DAT (0.1% vs. 0.5%; P = 0.024).</td>
</tr>
<tr>
<td>DECREASE (45)</td>
<td>Korea</td>
<td>Registry</td>
<td>3,099</td>
<td>12 months</td>
<td>MI (HR 0.233, 95% CI 0.08 to 0.70, P = 0.0097) and stent thrombosis (HR 0.136, 95% CI 0.04 to 0.52, P = 0.0036) were significantly lower in TAT.</td>
</tr>
<tr>
<td>KAMIR (46)</td>
<td>Korea</td>
<td>Registry</td>
<td>4,203</td>
<td>8 months</td>
<td>TAT reduced risk of cardiac death (OR, 0.52; 95% CI, 0.32 to 0.84; P = 0.007), and MACE (OR, 0.74; 95% CI, 0.58 to 0.95; P = 0.019) than DAT.</td>
</tr>
<tr>
<td>CILON-T (47)</td>
<td>Korea</td>
<td>Multi-centre Randomised</td>
<td>960</td>
<td>6 months</td>
<td>The composite of cardiac death, MI, ischaemic stroke, or TLR between TAT and DAT was comparable (8.5% vs. 9.2%, P = 0.74).</td>
</tr>
<tr>
<td>Han YL (48)</td>
<td>China</td>
<td>Single-centre Randomised</td>
<td>1,212</td>
<td>12 months</td>
<td>TAT reduced risk of the composite of cardiac death, MI, stroke, or TVR (10.3% vs. 15.1%; P = .011).</td>
</tr>
</tbody>
</table>

DAT, dual antiplatelet therapy; TAT, triple antiplatelet therapy; OR, odds ratio; HR, hazard ratio; CI, confidence interval; MI, myocardial infarction; TVR, target vessel revascularisation; MACE, major adverse cardiac events.
Lower use of antiplatelet agents for prevention of cardiovascular disease

Lower use of evidence-proven agents in prevention of cardiovascular disease is a common issue worldwide, especially among Asian patients. The Reduction of Atherothrombosis for Continued Health (REACH) registry revealed that aspirin for patients with atherosclerotic disease in Japan was much less commonly used (54.5%) than the global REACH average (67.3%) (52, 53). The Chinese Registry of Acute Coronary Events (CRACE) reported that only 34% of male patients and 39% of female patients with acute coronary syndrome used aspirin at enrollment (54).

Lower use of aspirin may be mainly because of overestimation of bleeding risk in East Asian countries. There are no direct safety comparisons of aspirin between Western and Asian cohorts. However, there is evidence that the risk for gastrointestinal (GI) ulceration is quite different between these two populations. Compared with European and American individuals, Helicobacter pylori infection is much more common among Asians (55). As a result, Asian patients may be more susceptible to GI ulceration, and lower doses of aspirin with or without concomitant gastroprotective agents may be a reasonable option. Genetic differences related to cytochrome P-450 polymorphisms may also influence GI bleeding risk.

Risk of GI bleeding can be minimised with a low-dose strategy. Aspirin at 75 mg daily is estimated to reduce the risk of GI bleeding by 40% compared with 300 mg daily and by 30% compared with 150 mg daily (56). Asian physicians tended to prescribe a wider range of aspirin dosages (57, 58), and recent published data also showed that lower doses of aspirin were prescribed to patients in Asia (excluding Japan) and Japan than in non-Asian regions (108.0 ± 56.7 mg/day vs. 99.2 ± 22.7 mg/day vs. 148.7 ± 109.4 mg/day, respectively; p < 0.0001) (1). However, optimal dosing of aspirin for Asian patients awaits further study in future comparative trials.

Cilostazol may be effective in preventing cardiovascular events in patients with type 2 diabetes mellitus. The Diabetic Athero-sclerosis Prevention by Cilostazol (DAPC) study evaluated the efficacy of cilostazol in preventing the progression of atherosclerosis in patients with type 2 diabetes mellitus and mild atherosclerosis in four Asian countries and demonstrated that treatment with cilostazol had a significant effect on regression of intima-media thickness in the common carotid artery during a two-year aspirin treatment period (59).

Several ongoing studies in Asian countries may draw international attention in the coming years. The Japanese Primary Prevention Project (JPPP) carries the highest expectations. Because the effects of aspirin on primary prevention of cardiovascular events are still controversial, this study aims to evaluate the risk-to-benefit ratio of low-dose aspirin in Japanese individuals aged 60 to 85 years with hypertension, dyslipidaemia, or diabetes mellitus (60). The study cohort will be followed for a mean of four years; patient recruitment was completed in June 2007. A total of 14,466 patients were randomised to receive either aspirin at 100 mg/day or no aspirin. A composite of non-fatal MI, stroke, and cardiac death will be evaluated. Other studies may also be interesting because they may address some clinically important issues, including efficacy of aspirin and statins in special populations such as patients with systemic lupus erythematosus.

Conflicts of interest
None declared.

References