Systematic study of cilostazol on secondary stroke prevention: a meta-analysis

Yining Qian and Qi Bi

Abstract

Background: To study the efficacy and safety of cilostazol on ischemic stroke prevention and treatment, systematic reviews of related clinical randomized controlled trials were analyzed.

Methods: We searched the main databases for eligible trials including literature from January 1966 to November 2012 in MEDLINE, reports from 1980 to November 2012 in EMBASE, and all the studies published in EBSCO, Springer, Ovid, and Cochrane library citations. We also searched for keywords, including cilostazol and aspirin. RevMan 5.0 software was used to conduct the meta-analysis.

Results: Our search yielded five eligible trials. The effects of cilostazol and aspirin on ischemic stroke prevention and treatment were almost equal (combined odds ratio (OR) 0.78, 95% confidence interval (CI) (0.59, 1.04)). Additionally, both magnetic resonance angiography (MRA) and transcranial Doppler (TCD) examination showed that cilostazol could significantly decrease the incidence of intracranial artery stenosis exacerbation (MRA: combined OR 0.22, 95% CI (0.07, 0.68); TCD: combined OR 0.17, 95% CI (0.05, 0.51)). In terms of adverse reactions, there were slightly fewer incidences of major bleeding with cilostazol than with aspirin (combined OR 0.38, 95% CI (0.24, 0.60)), and there was no difference in the number of heart palpitations between cilostazol and aspirin. However, the incidence of gastrointestinal disorders, dizziness, and headaches caused by cilostazol was greater.

Conclusions: Cilostazol might be a more effective and safer alternative to aspirin for patients with ischemic stroke. Further studies are required to confirm whether cilostazol is a suitable therapeutic option for secondary stroke prevention in larger cohorts of patients with ischemic stroke.

Keywords: Cilostazol, Ischemic stroke, Systematic reviews

Background

Ischemic stroke, which indicated that ischemia is caused by blockage, is a major cause of death and disability worldwide, and contributes significant financial burdens [1]. Owing to this severe cost of ischemic stroke, secondary prevention, namely preclinical prevention, plays an important role in reducing mortality and morbidity [2]. Antiplatelet treatment is a mainstay in acute and long-term secondary stroke prevention [3]. The most widely used antiplatelet drug for stroke prevention is aspirin, which significantly reduces the recurrence rate of ischemic stroke [4]. However, the clinical application of aspirin is limited due to major hemorrhagic adverse effects. Although several studies concluded that the advantages of aspirin are enough to outweigh the risk of hemorrhagic infarctions in most populations [5], the potential of adverse effects for the application of aspirin still cannot be ignored, particularly for individuals in Asia [6]. Moreover, many studies also found that despite regular antiplatelet treatment, some patients experienced thromboembolic events [7-9]. Those patients are clinically designated as aspirin resistant or non-responders. The incidence of low response or non-response to aspirin ranges between 5% and 60% [9]. Therefore, searching for antiplatelet agents with minimum complications and drug resistant is important.

Cilostazol has been shown to be an alternative to aspirin for secondary prevention in patients with non-cardioembolic ischemic stroke [10]. Cilostazol is a selective phosphodiesterase 3 (PDE3) inhibitor, possessing a potentially powerful means to produce various pleiotropic effects.
Currently, promoting evidence shows that cilostazol can serve as an antiplatelet agent. The effects of cilostazol on stroke prevention are caused by its protective effect against secondary cerebral infarctions [11]. Although cilostazol is widely used for the treatment of intermittent claudication with peripheral artery occlusion and for the prevention of ischemic stroke [12], reported clinical outcomes on its efficacy and side effects are conflicting, and systemic reviews are needed. In our paper, we assess the safety and efficacy of cilostazol versus aspirin for secondary stroke prevention in current clinical randomized controlled trials, aiming to provide guidance for their clinical application.

Methods

Search strategies

We fully researched MEDLINE, EMBASE, EBSCO, Springer, Ovid, and Cochrane library citations.

1) MEDLINE: January 1966 to November 2012, including established searches using a Cochrane Randomized Controlled Trials filter to identify randomized controlled trials combined with terms that will include cilostazol and aspirin.

2) EMBASE: 1980 to November 2012.

3) The Cochrane Central Register of Controlled Trials.

4) All reference lists of identified studies in EBSCO, Springer, Ovid, and Cochrane library citations.

Inclusion criteria

The published studies should be randomized controlled trials (RCTs), in which the patients were randomly grouped and accepted different interventions for comparison. All patients in the studies should have a medical history of ischemic stroke or transient ischemic attack and meet WHO criteria [13]. Patients should be older than 18 years. Therapeutic effects studied should include the incidence of ischemic stroke, the state of exacerbation of intracranial artery stenosis, and changes to the intima-media thickness. The following side effects should be noted: major bleeding, including intracranial hemorrhage and massive hemorrhage needing hospital blood transfusion, palpitation, gastrointestinal disorders (diarrhea, constipation, and so on), headaches, and dizziness.

Exclusion criteria are non-RCTs, patients with a history of gastrointestinal bleeding, bloody urine, conjunctival hemorrhage or patients with serious diseases, such as malignant neoplasm, heart failure, or renal failure.

Quality assessment and data extraction

Quality assessment included the adequacy of the random allocation method, the hidden nature of the random allocation method, the adoption of blinding methods, and evaluation of withdrawals.

Extracted data included: (1) general information: such as the topic of research, authors, the sources of

Figure 1 Forest plots of comparison of the incidence of ischemic stroke between cilostazol and aspirin groups in prevention and cure of ischemic stroke.

Heterogeneity test, chi-square statistic with degrees of freedom and \( P \) value; inconsistency among results, \( I^2 \) test for overall effect; \( Z \) statistic with \( P \) confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel method.

Figure 2 Forest plots of comparison of the progression of intracranial artery stenosis (by magnetic resonance angiography) between cilostazol and aspirin groups in prevention and cure of ischemic stroke.

Heterogeneity test, chi-square statistic with degrees of freedom and \( P \) value; inconsistency among results, \( I^2 \) test for overall effect; \( Z \) statistic with \( P \) value. CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel method.
literatures and so on; (2) research characteristics: design scheme, research strategies, implementation methods, measures to prevent bias, main test results and so on; (3) outcome measures: such as follow-up time, treatment of data from patients lost to follow-up or withdrawing from the study, curative effects and side effects, collection of headcounts of each group and the number of various events.

Statistical analysis
Meta-analysis was carried out by RevMan 5.0 provided by the Cochrane Collaboration. Odds ratios (OR) were used to determine effect size, along with 95% confidence interval (CI). Heterogeneity in results across studies was examined using the chi-square or tau- square test. When heterogeneity was not observed ($P > 0.01, I^2 \leq 56\%$), the effect size was calculated based on a fixed-effects model; otherwise a random-effects model was used. The overall effect estimate was analyzed by Mantel-Haenszel method. All efficacy index analysis followed the principle of intentional analysis.

Results
Eligible trials
Using this retrieval method, five eligible trials published between 2005 and 2011 were found [14-18], containing 4,052 cases of patients from different countries including Japan, Korea, and China. Among the five eligible trials, four compared the efficacy of cilostazol and aspirin [14-17], and one compared cilostazol and a placebo based on aspirin usage [18]. With respect to main curative effects, four analyzed the incidence of ischemic stroke [14-17], and two analyzed exacerbation of intracranial artery stenosis [16,18], but no RCTs referred to intima-media thickness in carotid arteries of stroke patients. Regarding side effects, four analyzed major bleeding, dizziness and headaches [14-17], three analyzed palpitation [14,15,17], and three analyzed gastrointestinal disorders [14-16]. All five trials applied a random and double-blind method, but only one used allocation concealment [15].

Efficacy analysis
Incidence of ischemic stroke
Four trials [14-17] compared the incidence of ischemic stroke in cilostazol groups and aspirin groups. A fixed-effects model was chosen, because of the poor heterogeneity ($P = 0.77, I^2 = 0\%$). The combined OR was 0.78 and 95% CI (0.59, 1.04), with no statistical significance ($Z = 1.68, P = 0.09$). Therefore, no difference was observed between cilostazol and aspirin groups in prevention and cure of ischemic stroke (see Figure 1).

Progression of intracranial artery stenosis
Two studies [16,18] focused on the progression of intracranial artery stenosis, with placebo and aspirin as the control, respectively. Magnetic resonance angiography (MRA) and transcranial Doppler (TCD) were applied in both studies to examine arteriostenosis. There was no heterogeneity in the results of MRA examination among studies ($P = 0.25, I^2 = 23\%$), and a fixed-effects model was adopted. The
combined OR was 0.22 with 95% CI (0.07, 0.68), with statistical significance ($Z = 2.63$, $P = 0.009$). Therefore, according to MRA examination, cilostazol was more effective than aspirin in preventing intracranial artery stenosis progression (see Figure 2).

No heterogeneity was observed in results of TCD examination among studies ($P = 0.16$, $I^2 = 50\%$), and a fixed-effects model was applied. The combined OR was 0.17 with 95% CI (0.05, 0.51), with statistical significance ($Z = 3.12$, $P = 0.002$). Therefore, according to TCD examination, cilostazol was superior to the control in prevention and treatment of intracranial artery stenosis progression (see Figure 3).

**Adverse effects analysis**

**Major bleeding**

Four eligible studies [14–17] compared the incidence of major bleeding in cilostazol and aspirin groups. Since no heterogeneity was observed ($P = 0.93$, $I^2 = 0\%$), a fixed-effects model was chosen. The combined OR was 0.38 and 95% CI (0.24, 0.60), with statistical significance ($Z = 4.15$, $P < 0.0001$). Thus, the incidence of major bleeding was slightly reduced with cilostazol, compared with aspirin (see Figure 4).

**Palpitation**

Three trials [14,15,17] compared the incidence of palpitation in cilostazol and aspirin groups. A random-effects model was used for the heterogeneity ($P < 0.01$, $I^2 = 94\%$). The combined OR was 0.96 with 95% CI (0.15, 6.21), with no statistical significance ($Z = 0.04$, $P = 0.97$). So there was no difference in the side effect of heart palpitations between cilostazol and aspirin (see Figure 5).

**Gastrointestinal disorders**

Three trials [14–16] compared the incidence of gastrointestinal disorders in cilostazol and aspirin groups. A fixed-effects model was used for the poor heterogeneity ($P = 0.61$, $I^2 = 0\%$). The combined OR was 1.23 with 95% CI (1.04, 1.46), with statistical significance ($Z = 2.40$, $P = 0.02$) (see Figure 6). Thus, the incidence of gastrointestinal disorders caused by cilostazol was higher than the incidence of gastrointestinal disorders caused by aspirin.

**Dizziness**

Four studies [14–17] compared the incidence of dizziness in cilostazol and aspirin groups. Fixed-effects model was used for the poor heterogeneity ($P = 0.58$, $I^2 = 0\%$). The combined OR was 1.44 with 95% CI (1.15, 1.80), with statistical significance ($Z = 3.18$, $P = 0.001$). Therefore, there was more dizziness associated with cilostazol than with aspirin (see Figure 7).

**Headache**

Four studies [14–17] compared the incidence of headache in cilostazol and aspirin groups. A fixed-effects model was used for the poor heterogeneity ($P = 0.09$, $I^2 = 55\%$). The combined OR was 1.78 with 95% CI (1.52, 2.10), with
statistical significance ($Z = 6.97, P < 0.00001$). Therefore, the prevalence of headaches with cilostazol was higher than that with aspirin (see Figure 8).

**Discussion**

Several antiplatelet agents, as suitable options for the secondary prevention drugs of ischemic stroke, are currently recommended by the American Heart Association and the American Stroke Association [19], such as aspirin, cilostazol, and clopidogrel [20,21].

Among these antiplatelet agents, aspirin is often prescribed as a mainstay agent for secondary stroke prevention because therapeutic monitoring is not required, it achieves a significant reduction in the absolute risk of acute ischemic and it is significantly lower in cost than all other antiplatelet agents [22]. Although aspirin has these advantages for secondary stroke prevention, in pooled analyses, it is reported [23] that its use is also associated with dosage-related gastrointestinal and intracranial hemorrhages. A significantly increase in the absolute risk of hemorrhagic stroke (+12 per 10,000 persons) has been reported, which translated to a relative risk increase of 84% with aspirin therapy [5]).

Recent clinical trial evidence suggests that cilostazol, a selective PDE3 inhibitor, may be a safer and more effective alternative than aspirin for secondary stroke prevention in Asian patients. Cilostazol's utility is approved as a medication for ischemic stroke prevention by the Food and Drug Administration because it exerts antiplatelet and antithrombotic effects [24]. Studies reported that cilostazol reversibly inhibits the activation of PDE-3A, which is mainly distributed in platelets, heart muscle, and vascular smooth muscle. Cilostazol blocks platelet adenosine uptake and adenosine-induced platelet activation, to prevent platelet aggregation [25]. *In vitro* and *in vivo* data further demonstrate that cilostazol induces the expression of prostacyclin, which is the endothelium-derived antiplatelet compound, while aspirin allows for platelet aggregation through inhibition of COX and prostacyclin formation [26,27].

In contrast with aspirin for stroke prevention, which mainly has an antiplatelet effect, cilostazol also exerts vasodilatory effect and increases human carotid, cerebral, coronary, and dermal blood flow [27,28]. Emerging evidence suggests that cilostazol inhibits the PDE-3 enzyme in human smooth muscle cells, leading to effects on vasculature. These effects include inhibition of human smooth muscle proliferation by growth factors, reversal of intracranial atherosclerotic lesions, and improvements in cerebral blood flow [18,29]. Additionally, cilostazol increases levels of vascular endothelial growth factor, which serves to repair damaged vascular epithelium [27]. In our analysis, we collectively found a trend for the improvement of the efficacy of cilostazol over aspirin. Moreover, the combined properties of antiplatelet, antithrombotic, and effects on vasculature...
favorably contribute to the utility of cilostazol for stroke prevention [30].

Intracranial arterial stenosis is one of the most common causes of stroke worldwide and is associated with a high risk of recurrent stroke. Therefore, its prevention can reduce the risk of ischemic stroke. A randomized study of 135 patients with symptomatic intracranial arterial stenosis showed that treatment with cilostazol significantly reduced progression of the stenosis [31]. Moreover, cilostazol also significantly prevented progression of carotid artery intima-media thickness [32], which is an indicator of atherosclerosis and an established risk factor for stroke [33,34]. In our study, we found that cilostazol can significantly prevent progression of intracranial artery stenosis aggravation, as determined using MRA and TCD (MRA: combined OR 0.22, 95% CI (0.07, 0.68); TCD: combined OR 0.17, 95% CI (0.05, 0.51)).

It is well known that major bleeding is a main side effect of antiplatelet drugs, including aspirin. Some reported papers hint that there is evidence of fewer incidences of bleeding with cilostazol than with clopidogrel or aspirin [35], and our study confirmed those results (combined OR 0.38, 95% CI (0.24,0.60)). With respect to palpitation, the effect with cilostazol is almost as the same as that with aspirin, but cilostazol is associated with more minor adverse effects, such as gastrointestinal disorders (combined OR 1.23, 95% CI (1.04, 1.46)), dizziness (combined OR 1.44, 95% CI (1.15, 1.80)) and headaches (combined OR 1.78, 95% CI (1.52, 2.10)).

Conclusion
Our meta-analysis of five RCTs investigated the safety and efficacy outcomes in ischemic stroke patients treated with cilostazol. The results showed that cilostazol might be a more effective and safer alternative to aspirin for patients with ischemic stroke. However, the number of surveys in the literature was limited and there might be a publication bias on application and interpretation. Additionally, recruited papers introduced little on allocation concealment, which is an important measure to ensure the quality of RCTs. Besides, there are few RCT studies focused on the effect of cilostazol on intracranial arterial stenosis and increased intima-media thickness in patients with ischemic stroke. Further trials should examine the safety and efficacy of cilostazol in larger cohorts of patients and in comparison with other drugs currently used in secondary stroke prevention.

Abbreviations
CI: Confidence interval; df: Degrees of freedom; MRA: Magnetic resonance angiography; OR: Odds ratio; PDE3: Phosphodiesterase 3; RCT: Randomized controlled trial; TCD: Transcranial Doppler.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
YNQ and QB conceived of the study, participated in its design and coordination, draft the manuscript participated in performed the statistical analysis. Both authors read and approved the final manuscript.

Received: 25 September 2013 Accepted: 12 November 2013
Published: 6 December 2013

References
1. Henon H, Godefroy O, Leys D, Mounier-Vehier F, Lucas C, Rondepeire P, Duhamel JJ, Pruvo J. Early predictors of death and disability after acute cerebral ischemic event. Stroke. 1995, 25:392–398.
2. Hamms H, Prass K, Meisel C, Kehrmert J, Rogge W, Drenckhahn C, Göbler J, Bereswill S, Göbel U, Wernecke KD. Preventive antibacterial therapy in acute ischemic stroke: a randomized controlled trial. PLoS One 2008, 3(2):e158.
3. Antipatelet Trials’ Collaboration. Collateral overview of randomised trials of antplatelet therapy: I. prevention of death, myocardial infarction, and stroke by prolonged antplatelet therapy in various categories of patients. BMJ 1994, 308:110–116.
4. Rother J, Alberts MJ, Touze E, Mas JL, Hill MD, Michel P, Bhatt DL, Aichner FT, Goto S, Matsumoto M, Ohman EM, Okada Y, Uchijima S, D’Agostino R, Hirsch AT, Wilson PW, Stieg PG. Risk factor profile and management of cerebrovascular patients in the REACH Registry. Cerebrovasc Dis 2008, 25:366–374.
5. He J, Whelton PK, VU B, Klag MJ. Aspirin and risk of hemorrhagic stroke: a meta-analysis of randomized controlled trials. JAMA 1998, 280:1930–1935.
6. Kubo M, Kiyohara Y, Kato I, Tanizaki Y, Arima H, Nagai K, Nakamura H, Okubo K, Iida M. Trends in the incidence, mortality, and survival rate of cardiovascular disease in a Japanese community: the Hisayama study. Stroke 2003, 34:2349–2354.
7. Levine S, Brey R, Joseph C, Hlavat M. Risk of recurrent thromboembolic events in patients with focal cerebral ischemia and antiphospholipid antibodies. The antiphospholipid antibodies in stroke study group. Stroke 1992, 23:129.
8. Bath PM, Iddenden R, Bath FJ. Low-molecular-weight heparins and heparinoids in acute ischemic stroke a meta-analysis of randomized controlled trials. Stroke 2000, 31:1770–1778.
9. Mijailjov MD, Shugaa G, Bloch S, Covicovic-Sternic N, Alekic V, Borstein NM. Clinical consequences of aspirin and clopidogrel resistance: an overview. Acta Neurologica Scandinavica 2013, 128:213–219.
10. Kazal AK, Naqvi I, Husain MR, Kehalani BA. Cilostazol versus aspirin for secondary prevention of vascular events after stroke of arterial origin. Cochrane Database Syst Rev 2011, 1(T0008076).
11. Gotto F, Tohghi H, Hiri S, Tarsahi A, Fukusuchi Y, Otomo E, Shinozaya Y, Itoh E, Matsuda T, Sawada T. Cilostazol stroke prevention study: a placebo-controlled double-blind trial for secondary prevention of cerebral infarction. J Stroke Cerebrovasc Dis 2000, 9:147–157.
12. Patel DS, Anand IS, Bhatt PA. Evaluation of antidepressant and anxiolytic activity of phosphodiesterase 3 inhibitor - cilostazol. Indian J Psychol Med 2012, 34:124–128.
13. Hataano S. Experience from a multicentre stroke register: a preliminary report. Bull World Health Organ 1976, 54:541–553.
14. Lee YS, Bae HJ, Kang DW, Lee SH, Yu K, Park JM, Cho YI, Hong KS, Kim DE, Kwon SU, Lee KB, Rha JH, Koo J, Han MG, Lee SJ, Lee JH, Jung SW, Lee BC, Kim JS. Cilostazol in acute ischemic stroke treatment (CAIST trial): a randomized double-blind non-inferiority trial. Cerebrovasc Dis 2011, 32:65–71.
15. Shinozaya Y, Katayama Y, Uchijima S, Yamaguchi T, Handa S, Matsuo K, Ohashi Y, Tanahashi N, Yamamoto H, Genka C, Kitagawa Y, Kusuda H, Nishimura K, Tsutsumia M, Koresutara Y, Sawada T, Harnada C. Cilostazol for prevention of secondary stroke (CSSP 2): an aspirin-controlled, double-blind, randomised non-inferiority trial. Lancet Neurol 2010, 9:595–608.
16. Guo JJ, Xu E, Lin Q, Zeng J, Xie HF. Effect of cilostazol on cerebral arteries in secondary prevention of ischemic stroke. Neurosci Bull 2009, 25:383–390.
17. Huang Y, Cheng Y, Wu J, Li Y, Xu E, Hong Z, Lu Z, Zhang W, Ding M, Gao X, Fan D, Zeng J, Wong K, Lu C, Xiao J, Yao C. Cilostazol as an alternative to aspirin after ischaemic stroke: a randomised, double-blind, pilot study. Lancet Neurol 2008, 7:494–499.
18. Kwon SJ, Cho YJ, Koo JS, Bae HJ, Lee YS, Hong KS, Lee JH, Kim JS: Cilostazol prevents the progression of the symptomatic intracranial arterial stenosis: the multicenter double-blind placebo-controlled trial of cilostazol in symptomatic intracranial arterial stenosis. *Stroke* 2005, 36:782–786.

19. Fuster V, Kasper SE, Adams R, Albers GW, Bush RL, Fagán SC, Halperin JL, Johnston SC, Katzan I, Kernan WN, Mitchell PH, Oskiage B, Paisley YY, Sacco RL, Schwamm LH, Wasterhill-Smoller S, Turan TN, Wentworth D: Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2011, 42:227–276.

20. Urbano LA, Bogousslavsky J: Antiplatelet drugs in ischemic stroke: from monotherapy to combined treatment. *Cerebrovasc Dis* 2004, 17(Suppl 1):74–80.

21. Symeonidis A, Kourakis-Symeonidis A, Seimeni U, Galani A, Giannakoulas N, Fragapanagou E, Titiskou M, Matsouka P, Zoumbos N: Ticlopidine-induced aplastic anemia: two new case reports, review, and meta-analysis of 35 additional cases. *Am J Hematol* 2002, 71:24–32.

22. Gent M, Blakely JA, Easton JD, Ellis DJ, Hachinski VC, Harbison JW, Panak E, Roberts RS, Sicurella J, Turpie AG: The Canadian American Ticlopidine Study (CATS) in thromboembolic stroke. Design, organization, and baseline results. *Stroke* 1988, 19:1203–1210.

23. Serebruany VL, Steinhubl SR, Berger PB, Malinin AI, Baggish JS, Bhatt DL, Topol EJ: Analysis of risk of bleeding complications after different doses of aspirin in 192,036 patients enrolled in 31 randomized controlled trials. *Am J Cardiol* 2005, 95:1218–1222.

24. Ansara AJ, Shiltz DL, Slavens JB: Use of cilostazol for secondary stroke prevention: an old dog with new tricks? *Ann Pharmacother* 2012, 46:394–402.

25. Ikeda Y: Antiplatelet therapy using cilostazol, a specific PDE3 inhibitor. *Thromb Haemost* 1999, 82:435–438.

26. Goto S: Cilostazol: potential mechanism of action for antithrombotic effects accompanied by a low rate of bleeding. *Atherosclerosis Suppl* 2005, 6:3–11.

27. Liu Y, Shakur Y, Yoshitake M, Kambayashi Ji J: Cilostazol (pletal): a dual inhibitor of cyclic nucleotide phosphodiesterase type 3 and adenosine uptake. *Cardiovasc Drug Rev* 2001, 19:369–386.

28. Kambayashi J, Liu Y, Sun B, Shakur Y, Yoshitake M, Czerwiec F: Cilostazol as a unique antithrombotic agent. *Curr Pharm Des* 2003, 9:2289–2302.

29. Kai Y, Watanabe M, Morioka M, Hirano T, Yano S, Ohmori Y, Kawano T, Hamada J, Kunatsu J: Cilostazol improves symptomatic intracranial artery stenosis - evaluation of cerebral blood flow with single photon emission computed tomography. *Surg Neurol International* 2011, 2:9.

30. Lugnier C: Cyclic nucleotide phosphodiesterase (PDE) superfamily: a new target for the development of specific therapeutic agents. *Pharmacol Ther* 2006, 109:366–398.

31. Sallustio F, Rotondo F, Di Legge S, Starzone P: Cilostazol in the management of atherosclerosis. *Curr Vasc Pharmacol* 2010, 8:363–372.

32. Shinoda-Tagawa T, Yamasaki Y, Yoshida S, Kajimoto Y, Tsujino T, Hakui N, Matsumoto M, Hori M: A phosphodiesterase inhibitor, cilostazol, prevents the onset of silent brain infarction in Japanese subjects with Type II diabetes. *Diabetologia* 2002, 45:188–194.

33. Touboul PJ, Elbaz A, Koller C, Lucas C, Adrai V, Chechu F, Amarenco P: Common carotid artery intima-media thickness and brain infarction: the Étude du Profil Génétique de l’Infarctus Cérébral (GENIC) case–control study. *The GENIC Investigators. Circulation* 2000, 102:313–318.

34. Holland P, Zeki S, Koudstaal PJ, Bots ML, Grobbbee DE, Hofman A, Witterman JC, Breeteler MM: Comparison between measures of atherosclerosis and risk of stroke: the Rotterdam study. *Stroke* 2003, 34:2367–2372.

35. Wilhite DB, Comerota AJ, Schmieder FA, Throm RC, Gaughan JP, Rao AK: Managing PAD with multiple platelet inhibitors: the effect of combination therapy on bleeding time. *J Vasc Surg* 2003, 38:710–713.