Intracranial hemorrhage and platelet transfusion after administration of anti-platelets agents: Fukushima Prefecture

Fukushima J. Med. Sci.,
Vol. 62, No. 1, 2016

[Original Article]

Intracranial hemorrhage and platelet transfusion after administration of anti-platelets agents : Fukushima Prefecture

Yuhko Suzuki[1)], Taku Sato[2)], Jun Sakuma[2)], Masahiro Ichikawa[2)], Yugo Kishida[2)], Keiko Oda[2)], Yoichi Watanabe[3)], Takeshi Goto[4)], Masahiro Sato[5)], Kenneth E. Nollet[1)], Kiyoshi Saito[2)] and Hitoshi Ohto[1)]

[1)]Department of Blood Transfusion and Transplantation Immunology, Fukushima Medical University, Fukushima, Japan, [2)]Department of Neurosurgery, Fukushima Medical University, Fukushima, Japan, [3)]Department of Neurosurgery, Fukushima Red Cross Hospital, Fukushima, Japan, [4)]Department of Neurosurgery, Hoshi General Hospital, Koriyama, Japan, [5)]Department of Neurosurgery, Fujita General Hospital, Kunimi, Japan

(Received December 22, 2015, accepted March 24, 2016)

Abstract

We conducted a case series study to assess intracerebral hemorrhage (ICH) in the context of anti-platelets agents (APAs) and platelet (PLT) transfusion in Fukushima Prefecture.

This study included patients who were newly diagnosed with ICH between January 2008 and June 2014 in the neurosurgical hospitals of Fukushima Prefecture. Four of ten neurosurgical hospitals responded to our questionnaire. Of 287 ICH patients, 51 (20.6%) were on APA therapy, of whom PLT transfusion was given to only one persistently bleeding patient who was on dual anti-platelet therapy. In a follow-up survey, 30 out of 51 ICH patients on APA therapy, average age 75 years, were analyzed, of whom 21 (70%) were male. The predominant underlying disease was diabetes mellitus. It is interesting to note that peripheral artery disease and aortic aneurysm were among the indications for APAs. ICH was mainly observed supratentorially. Hematoma enlargement was observed in 13 (44.8%) cases. By day 7, 3 patients (10%) had died from complications of ICH. In this study, we show that ICH during APA therapy matched what was observed in Kanagawa Prefecture. Whether or not a national survey differs, we anticipate greater statistical validity and an opportunity to improve patient outcomes in Japan and around the world.

Key words : Anti-platelet agents, Intracranial hemorrhage, Platelet transfusion

Introduction

Japan's aging society and growing Westernization of lifestyle, including high calorie and animal fat intake, have contributed to the number of people suffering from arteriosclerotic disease[1,2)].

Among the anti-platelet agents (APAs) widely used around the world, acetylsalicylic acid (aspirin) predominates. The US FDA approved aspirin for secondary prevention of acute coronary syndrome (ACS) in 1985. Japan followed in 2,000, adding aspirin for prevention of arteriosclerotic disease.

Many guidelines for coronary heart disease (CHD), cerebral infarction (CI), peripheral artery disease (PAD), diabetes mellitus (DM) and several kinds of arrhythmia recommend ongoing APA therapy for primary and secondary prevention[3-9)], including dual APA therapy (DAPT) in some guidelines[10,11)]. Along with the advantages of APA therapy, potentially fatal hemorrhagic complications are also recognized[12-14)]. APAs are double-edged swords, especially hazardous in the absence of standardized, reliable protocols to reverse platelet dysfunction.

ICH continues to be a predominant cause of

Corresponding author : Yuhko Suzuki, M.D., Ph.D. E-mail : ysuzuki-hki@umin.ac.jp
https://www.jstage.jst.go.jp/browse/fms http://www.fmu.ac.jp/home/lib/F-igaku/

death in Japan[15,16], and worldwide[17,18]. Focal symptoms depend on the site(s) affected. The usually acute onset means there is no time to stop APAs before ICH. To treat bleeding into the central nervous system, Japanese guidelines recommend higher platelet counts. Many reports and systemic reviews show inferior survival of ICH patients on APA therapy[19]. Even with many APAs currently in use and no standard reversal protocols, we showed platelet transfusion (PLT) was useful in a single institution's practice[20]. Through ongoing dialog with neurosurgeons and emergency physicians, we have recognized various practice patterns and biases in regard to the use of PLT transfusion for ICH patients.

Here we report prefecture-wide practice and outcome data pertaining to : 1) ICH during APA therapy, and 2) PLT transfusion practices in ICH.

Patients and Methods

Ethics : This study (2014, #2062) was approved by the Ethics Committee of Fukushima Medical University, which is guided by local policy, national law, and the World Medical Association Declaration of Helsinki. As this was a retrospective study, informed consent was deemed to be unnecessary, on the condition that patient information was anonymized prior to analysis.

Patients : This study included patients who were newly diagnosed with ICH between January 2008 and June 2014 in the neurosurgical hospitals of Fukushima, a Japanese prefecture of approximately 2 million residents.

Male and female patients at least 20 years old, with recent ICH diagnosed by computed tomography (CT) and no evidence of traumatic cerebral hemorrhage, were eligible for inclusion. Exclusion criteria included intracranial ruptured aneurysm, bleeding arteriovenous malformation, tumor, and if the ICH occurred during pregnancy or just after delivery.

A dedicated multidisciplinary team attended to all surgical and medical issues.

Agents : Aspirin, clopidogrel, and ticlopidine were the predominant APAs in our analyses, as in our previous study[20].

Methods : This is a case series study. Initially, we sent a questionnaire to the 10 neurosurgical hospitals in Fukushima prefecture. This questionnaire was to establish how many ICH patients were on APA therapy and whether PLT transfusion was used for any ICH patients with or without APA. As follow-up, we collected detailed data of ICH patients on APA therapy. The following admission data were collected, reviewed and analyzed as in our previous study[20] : age ; sex ; Glasgow Coma Scale (GCS, 3-15 ; 3 being the worst, and 15 the best) ; clinical background ; complications before onset of ICH ; elapsed time, defined as the duration between estimated onset and arrival at our hospital ; administration of anti-thrombotic agents (ATAs) including APAs and anticoagulants ; and laboratory data on arrival, including prothrombin time (PT), activated partial thromboplastin time (aPTT), platelet count, and fibrinogen. Outcomes on day 7 and day 90 were recorded. Observation time was defined as the duration from the date of onset of ICH to the date of death or to the end of the follow-up, as previously studied.

Results

Four of ten (40%) neurosurgical hospitals responded to our questionnaire. Fifty-one (20.6%) out of 287 ICH patients were on APA therapy, among whom PLT transfusion was given to just one patient on dual anti-platelet therapy.

As follow-up, 30 out of 51 ICH patients taking APAs were further analyzed (Table 1 and 2). Their

Table 1. Characteristics of ICH patients with APAs. (N=30)

Factors	Unit	Data
Male		21 (70)
age	y.o	75 (67.5, 79.3)
Observation time	day	62 (22, 381.3)
Underlying Disease		
Chronic renal failure		9 (30)
Diabetes Mellitus		14 (46.7)
Coronary heart disease		9 (30)
Cerebral Infarction, TIA		11 (36.7)
Atrial fibrillation		4 (13.3)
Valvular disease of the heart		4 (13.3)
Hypertension		23 (76.7)
Peripheral artery disease		1 (3.3)
Aortic aneurysm		5 (16.7)
Coronary risk factors		
0		5 (16.7)
1		11 (36.7)
2		10 (33.3)
3		4 (13.3)

ICH : intracranial hemorrhage. APA : anti-platelets agents. Numerical variable : N (%). Continuous variable : median (25^{th}, 75^{th})

Table 2. Characteristics of ICH patients with APAs.

Factors	Total number	Unit	Results
Glasgow coma scale	30	(3-15)	14 (7.8, 15)
ICH	30		
subcortical			12 (40)
supratentorial			15 (50)
infratentorial			3 (10)
Volume of hematoma	30	cm^3	26 (4, 84)
Enlargement	30		13 (44.8)
Laboratory data			
platelet	29	$10^3/\mu L$	190 (133, 224)
prothrombin time	29	%	93.2 (46.05, 102.8)
aPTT	29	sec	27.6 (24.85, 32.2)
fibrinogen	19	mg/dL	278 (223, 318)
Outcome 7^{th} day	30		
dead			3 (10)
alive			27 (90)

ICH : intracranial hemorrhage. APA : anti-platelets agents. aPTT : activated partial thromboplastin time. Numerical variable : *N* (%). Continuous variable : median (25^{th}, 75^{th})

median age was 75 years, of whom 21 (70%) were male and 23 (76.7%) had hypertension. The predominant underlying disease was diabetes mellitus. It is interesting to note that peripheral artery disease and aortic aneurysm were reported in the context of APA therapy. ICH was mainly reported as supratentorial. Hematoma enlargement was observed in 13 (44.8%) cases. By day 7, 3 patients (10%) had died from complications of ICH.

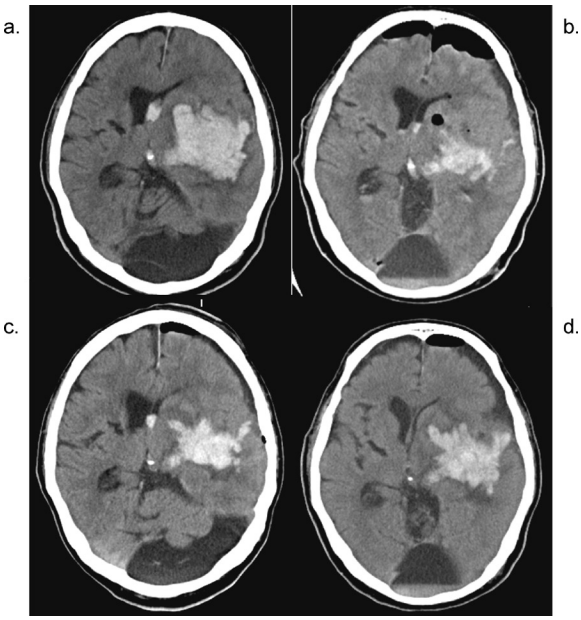
Aspirin was the predominant APA (Table 3). Dual APA therapy was done for 4 (13.3%) patients. Another 8 took warfarin and 1 took rivaroxaban along with their APAs. Other agents with anti-platelets effects, prostaglandin I_2 and EPA, were also prescribed for non-arteriosclerotic underlying diseases such as lumbar canal stenosis and hyperlipidemia.

One patient with ICH was given PLTs. Six months prior, he received surgical catheterization and coil embolization for a right intracavernous internal carotid artery aneurysm. Thereafter, he was prescribed aspirin and clopidogrel. He was transferred to our hospital by air ambulance. On arrival, three hours after symptom onset, his CT scan revealed an ICH of 100 cm^3 in the left putamen (Figure a). His Glasgow coma score was 7, and his laboratory coagulation profile and other test results were within reference limits. His hematoma rapidly expanded, and his coma progressed. After evacuating the hematoma (Figure b), 10 PLT units were given for oozing (a "unit" is based on what can be derived

Table 3. Details of APAs

Agents	Number
ASA	22 (73.3)
ASA + Ticlopidine	2 (6.7)
ASA + Clopidogrel	2 (6.7)
Ticlopidine	2 (6.7)
Clopidogrel	2 (6.7)

APAs : anti-platelets agents.
ASA : acetylsalicylic acid (Aspirin)
Numerical variables are given N (%).



Figure

from 200 mL whole blood, but in practice PLTs are collected by apheresis). Even then the hematoma expanded (Figure c), but eventually stabilized and regressed (Figure d). No adverse events attributable to PLT transfusion were observed. Thirty days later, he was alive with aphasia and hemiplegia.

Discussion

In this survey of practice and outcomes in Fukushima Prefecture, we found that 20.6% of ICH patients (51 of 287) were on APA therapy before onset, of whom PLTs were transfused to only one patient on DAPT with rapid hematoma expansion after ICH diagnosis. In this cohort, various anti-coagulants were co-administered with APAs before onset. Underlying diseases for which APAs were prescribed were more various than those we reported from Kanagawa Prefecture[20].

The rate of ICH with APAs was 20.6% in this survey, versus 15.27% in our previous study[20] and 17.9% in the BAT study[21]. Actually, there is no statistical significance between our two areas ; both show around 20% of new ICH patients taking APAs before onset. Among those affected, PLT transfusion and other interventions may be necessary. Among the agents used to reverse APA effects, PLTs act directly to reverse functional interference by APAs. There are opinions in favor of PLTs[20,22] and opposed[23,24]. If effectiveness of PLT transfusion is to be proved, appropriate timing and volume to achieve hemostasis must be addressed. Actually, our patient who received PLT transfusion oozed and his hematoma expanded. He may have needed a larger dose of PLTs, and perhaps subsequent PLT transfusion(s). This patient evoked other questions such as adequate monitoring to confirm the function of platelets, frequency of PLT transfusion, and so on.

The most common barrier to urgent PLT transfusion is availability. Japan's ageing society reduces the supply of blood donors while increasing the demand for transfusion. Moreover PLT shelf life is only 4 days. In this situation, unassigned PLTs are held at Japanese Red Cross centers. "Just-in-time delivery" is a hallmark of Japanese inventory logistics, but our typical 30-40 minute delay between a clinician's request and a product's arrival is unduly long when there is critical bleeding or hemorrhagic stroke risk. The prospect of PLTs derived from induced Pluripotent Stem (iPS) cells is much anticipated[25]. As for other agents to reverse effects of APAs, recombinant activated factor VII (rVIIa) and DDAVP have been recommended in European and other guidelines[26-28], but with little supporting evidence. Moreover, rVIIa is very expensive.

Our survey identified several types of anticoagulants given in conjunction with APA therapy, of which warfarin was the most predominant, with a long history of use and reliable ways to reverse its effects (e.g., vitamin K, fresh frozen plasma) if hemorrhagic complications arise. More recently, several kinds of non-vitamin K antagonist oral anticoagulants (NOACs) have become available, which are more convenient for having fewer hemorrhagic complications[29,30], fewer fatal hemorrhagic complications[31], and no need for patients to restrict their intake of specific foods such as green vegetables. However, hemorrhagic complication induced by NOACs warrant special concerns different from warfarin, such as giving prothrombin complex concentrate (PCC)[32], rVIIa[33,34] or specific neutralizing antibodies[35].

Finally, underlying diseases in which APAs are given were more various than in our previous study[20]. Patients with peripheral artery disease (PAD) or aortic aneurysm were observed in this survey. Recently, patients with PAD are increasing in Japan and worldwide, and the use of APAs to reduce mortality following vascular surgery is supported by ACC/AHA guidelines since 2011[36]. So the use of APAs will likely increase.

Now a nationwide survey is underway, assessing management strategies for ICH with APAs, especially, to clarify the advantage of PLT transfusion for ICH with APAs and to optimize the timing and dosing of PLTs. In this pilot study from Fukushima prefecture study, we found the occurrence of ICH with APA therapy was the same as in Kanagawa Prefecture. Whether or not a national survey differs, we anticipate greater statistical validity and an opportunity to improve patient outcomes in Japan and around the world.

Acknowledgements

We thank to cardiologists Prof. Takeishi and Dr. Suzuki for their advice of cardiac guidelines associated with APAs, Mr. Kashimura at the Fukushima Red Cross Blood Center for his up-to-date knowledge of blood supply and demand. Among other colleagues to whom we are grateful, Dr. Aya Goto in FMU's Department of Public Health and Dr. Yoshiko TAMAI in Hirosaki University Hospital's department of Transfusion gave excellent advice about our research design.

References

1. Kitamura A, Sato S, Kiyama M, Imano H, Iso H, Okada T, *et al*. Trends in the incidence of coronary heart disease and stroke and their risk factors in japan, 1964 to 2003 : The akita-osaka study. J Am Coll Cardiol, **52** : 71-79, 2008.
2. Rumana N, Kita Y, Turin TC, Murakami Y, Sugihara H, Morita Y, *et al*. Trend of increase in the incidence of acute myocardial infarction in a japanese population : Takashima ami registry, 1990-2001. Am J Epidemiol, **167** : 1358-1364, 2008.
3. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (caprie). Caprie steering committee. Lancet, **348** : 1329-1339, 1996.
4. Harker LA, Boissel JP, Pilgrim AJ, Gent M. Comparative safety and tolerability of clopidogrel and aspirin : Results from caprie. Caprie steering committee and investigators. Clopidogrel versus aspirin in patients at risk of ischaemic events. Drug Saf, **21** : 325-335, 1999.
5. Bhatt DL, Hirsch AT, Ringleb PA, Hacke W, Topol EJ. Reduction in the need for hospitalization for recurrent ischemic events and bleeding with clopidogrel instead of aspirin. Caprie investigators. Am Heart J, **140** : 67-73, 2000.
6. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without st-segment elevation. N Engl J Med, **345** : 494-502, 2001.
7. Steinhubl SR, Berger PB, Mann JT, 3rd, Fry ET, DeLago A, Wilmer C, *et al*. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention : A randomized controlled trial. JAMA, **288** : 2411-2420, 2002.
8. Sabatine MS, Cannon CP, Gibson CM, Lopez-Sendon JL, Montalescot G, Theroux P, *et al*. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with st-segment elevation. N Engl J Med, **352** : 1179-1189, 2005.
9. Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE, *et al*. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. N Engl J Med, **354** : 1706-1717, 2006.
10. Bhatt DL, Flather MD, Hacke W, Berger PB, Black HR, Boden WE, *et al*. Patients with prior myocardial infarction, stroke, or symptomatic peripheral arterial disease in the charisma trial. J Am Coll Cardiol, **49** : 1982-1988, 2007.
11. Palacio S, Hart RG, Pearce LA, Benavente OR. Effect of addition of clopidogrel to aspirin on mortality : Systematic review of randomized trials. Stroke, **43** : 2157-2162, 2012.
12. Toyoda K, Yasaka M, Iwade K, Nagata K, Koretsune Y, Sakamoto T, *et al*. Dual antithrombotic therapy increases severe bleeding events in patients with stroke and cardiovascular disease : A prospective, multicenter, observational study. Stroke, **39** : 1740-1745, 2008.
13. Berger PB, Bhatt DL, Fuster V, Steg PG, Fox KA, Shao M, *et al*. Bleeding complications with dual antiplatelet therapy among patients with stable vascular disease or risk factors for vascular disease : Results from the clopidogrel for high atherothrombotic risk and ischemic stabilization, management, and avoidance (charisma) trial. Circulation, **121** : 2575-2583, 2010.
14. Hamon M, Lemesle G, Tricot O, Meurice T, Deneve M, Dujardin X, *et al*. Incidence, source, determinants, and prognostic impact of major bleeding in outpatients with stable coronary artery disease. J Am Coll Cardiol, **64** : 1430-1436, 2014.
15. Tanaka H, Ueda Y, Date C, Baba T, Yamashita H, Hayashi M, *et al*. Incidence of stroke in shibata, japan : 1976-1978. Stroke, **12** : 460-466, 1981.
16. Kiyohara Y, Kubo M, Kato I, Tanizaki Y, Tanaka K, Okubo K, *et al*. Ten-year prognosis of stroke and risk factors for death in a japanese community : The hisayama study. Stroke, **34** : 2343-2347, 2003.
17. Sacco S, Marini C, Toni D, Olivieri L, Carolei A. Incidence and 10-year survival of intracerebral hemorrhage in a population-based registry. Stroke, **40** : 394-399, 2009.
18. Rincon F, Mayer SA. The epidemiology of intracerebral hemorrhage in the united states from 1979 to 2008. Neurocrit Care, **19** : 95-102, 2013.
19. Thompson BB, Bejot Y, Caso V, Castillo J, Christensen H, Flaherty ML, *et al*. Prior antiplatelet therapy and outcome following intracerebral hemorrhage : A systematic review. Neurology, **75** : 1333-1342, 2010.
20. Suzuki Y, Kitahara T, Soma K, Konno S, Sato K, Suzuki S, *et al*. Impact of platelet transfusion on survival of patients with intracerebral hemorrhage after administration of anti-platelet agents at a tertiary emergency center. PLoS One, **9** : e97328, 2014.
21. Toyoda K, Yasaka M, Nagata K, Nagao T, Gotoh J, Sakamoto T, *et al*. Antithrombotic therapy influences location, enlargement, and mortality from intracerebral hemorrhage. The bleeding with antithrombotic therapy (bat) retrospective study. Cerebrovasc Dis, **27** : 151-159, 2009.
22. Naidech AM, Liebling SM, Rosenberg NF, Lindholm PF, Bernstein RA, Batjer HH, *et al*. Early platelet transfusion improves platelet activity and may improve outcomes after intracerebral hemorrhage. Neurocrit Care, **16** : 82-87, 2012.
23. Creutzfeldt CJ, Weinstein JR, Longstreth WT, Jr.,

Becker KJ, McPharlin TO, Tirschwell DL. Prior antiplatelet therapy, platelet infusion therapy, and outcome after intracerebral hemorrhage. J Stroke Cerebrovasc Dis, **18** : 221–228, 2009.
24. Ducruet AF, Hickman ZL, Zacharia BE, Grobelny BT, DeRosa PA, Landes E, *et al*. Impact of platelet transfusion on hematoma expansion in patients receiving antiplatelet agents before intracerebral hemorrhage. Neurol Res, **32** : 706–710, 2010.
25. Nakamura S, Takayama N, Hirata S, Seo H, Endo H, Ochi K, *et al*. Expandable megakaryocyte cell lines enable clinically applicable generation of platelets from human induced pluripotent stem cells. Cell Stem Cell, **14** : 535–548, 2014.
26. McMillian WD, Rogers FB. Management of prehospital antiplatelet and anticoagulant therapy in traumatic head injury : A review. J Trauma, **66** : 942–950, 2009.
27. Beshay JE, Morgan H, Madden C, Yu W, Sarode R. Emergency reversal of anticoagulation and antiplatelet therapies in neurosurgical patients. J Neurosurg, **112** : 307–318, 2010.
28. Spahn DR, Bouillon B, Cerny V, Coats TJ, Duranteau J, Fernandez-Mondejar E, *et al*. Management of bleeding and coagulopathy following major trauma : An updated european guideline. Crit Care, **17** : R76, 2013.
29. Hori M, Matsumoto M, Tanahashi N, Momomura S, Uchiyama S, Goto S, *et al*. Safety and efficacy of adjusted dose of rivaroxaban in japanese patients with non-valvular atrial fibrillation : Subanalysis of j-rocket af for patients with moderate renal impairment. Circ J, **77** : 632–638, 2013.
30. Hylek EM, Held C, Alexander JH, Lopes RD, De Caterina R, Wojdyla DM, *et al*. Major bleeding in patients with atrial fibrillation receiving apixaban or warfarin : The aristotle trial (apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation) : Predictors, characteristics, and clinical outcomes. J Am Coll Cardiol, **63** : 2141–2147, 2014.
31. Mega JL, Braunwald E, Murphy SA, Plotnikov AN, Burton P, Kiss RG, *et al*. Rivaroxaban in patients stabilized after a st-segment elevation myocardial infarction : Results from the atlas acs-2-timi-51 trial (anti-xa therapy to lower cardiovascular events in addition to standard therapy in subjects with acute coronary syndrome-thrombolysis in myocardial infarction-51). J Am Coll Cardiol, **61** : 1853–1859, 2013.
32. Honickel M, Treutler S, van Ryn J, Tillmann S, Rossaint R, Grottke O. Reversal of dabigatran anticoagulation ex vivo : Porcine study comparing prothrombin complex concentrates and idarucizumab. Thromb Haemost, **113** : 728–740, 2015.
33. Perzborn E, Heitmeier S, Laux V, Buchmuller A. Reversal of rivaroxaban-induced anticoagulation with prothrombin complex concentrate, activated prothrombin complex concentrate and recombinant activated factor vii in vitro. Thromb Res, **133** : 671–681, 2014.
34. Franchini M, Crestani S, Frattini F, Sissa C, Bonfanti C. Hemostatic agents for bleeding : Recombinant-activated factor vii and beyond. Semin Thromb Hemost, **41** : 342–347, 2015.
35. Glund S, Moschetti V, Norris S, Stangier J, Schmohl M, van Ryn J, *et al*. A randomised study in healthy volunteers to investigate the safety, tolerability and pharmacokinetics of idarucizumab, a specific antidote to dabigatran. Thromb Haemost, **113** : 2015.
36. Rooke TW, Hirsch AT, Misra S, Sidawy AN, Beckman JA, Findeiss LK, *et al*. 2011 accf/aha focused update of the guideline for the management of patients with peripheral artery disease (updating the 2005 guideline) : A report of the american college of cardiology foundation/american heart association task force on practice guidelines. J Am Coll Cardiol, **58** : 2020–2045, 2011.