HOSPITAL CHRONICLES 2011, 6(3): 104–109

EDITORIAL

New Oral Anticoagulants Poised to Usurp the Throne of Vitamin K Antagonists After Over Half a Century

Antonis S. Manolis, MD,[1] Theodora A. Manolis, MS[2]

[1]First Department of Cardiology, Evagelismos General Hospital, Athens, Greece; [2]Patras University School of Medicine, Patras, Greece

ABSTRACT

Only after the elapse of over half-a-century of warfarin's reign are we witnessing significant progress in anticoagulation therapy with the advent of new anticoagulants with predictable pharmacologic profile obviating the need for the routine and burdening coagulation monitoring unlike therapy with vitamin K antagonists. Furthermore, these novel agents are devoid of any food interactions and have limited drug-drug interactions since they are minimally metabolized via the cytochrome P450. These unique pharmacokinetic properties have ushered in a new era in anticoagulation therapy with the continuing development of specific direct factor IIa (thrombin) and factor Xa inhibitors. An overview of these novel anticoagulant agents is herein attempted.

KEY WORDS: *vitamin K antagonists; anticoagulation therapy; warfarin; acenocoumarol; direct thrombin inhibitors; factor Xa inhibitors; dabigatran; rivaroxaban; apixaban*

ABBREVIATIONS
ACS = acute coronary syndrome(s)
AF = atrial fibrillation
EMA = European Medicines Agency
FDA = Federal Drug Administration (USA)
INR = international normalized ratio
p-GP = p-glycoprotein
VKA – vitamin K antagonist
VTE = venous thromboembolism

Correspondence to:
Antonis S. Manolis, MD, First Department of Cardiology, Evagelismos Hospital, Athens, Greece; e-mail: asm@otenet.gr

Manuscript received June 20, 2011; Accepted after revision June 30, 2011

Conflict of Interest: None declared

Vitamin K antagonists (VKAs) (coumarins), warfarin being the most commonly used agent, and acenocoumarol or phenindione available in Greece and other countries, despite numerous disadvantages, have essentially been the gold standard and the sole form or option of oral anticoagulants available for over half a century, shown to effectively treat thromboembolism.[1,2] Vitamin K antagonists act indirectly to antagonize the effect of vitamin K required for the synthesis of active clotting factors II, VII, IX, X and anticoagulant proteins C, S and Z, thus reduce the amount of these clotting factors, thereby producing anticoagulation. Specifically, carboxylation of these coagulation factors does not take place because vitamin K is required in this reaction and VKAs inhibit regeneration of vitamin K by interfering with vitamin K epoxide reductase. However, the use of VKAs has had serious and severe inherent limitations of safety and efficacy, significant inter- and intra-patient variability in dose-response, with dose titration requiring cumbersome monitoring via laboratory testing of the international normalized ratio (INR). These agents have a narrow therapeutic window, a plethora of drug and food interactions and unpredictable and variable response also dependent on age and/or genetic status and underlying medical conditions.[2] These drawbacks have compromised patient compliance and have led to under-treatment and difficult anticoagulation control, which remains a medical challenge. Several reasons may emerge for not taking a VKA, such as patient refusal, patient's decision to discontinue the drug for inconvenience or difficulty in maintaining the INR in the therapeutic range, physician's judgment regarding the inappropriateness of prescribing the drug, or the

inability to monitor the INR due to lack of or difficulty in accessing a laboratory or lack of family support or assistance with this inconvenient process. Until now, patients who are not able or willing to take a VKA have had no alternative. Only recently, have market competitors begun to emerge with the development of new oral anticoagulants, which are direct thrombin or active factor Xa inhibitors.[3-6]

The disadvantages of conventional anticoagulant therapy have led investigators to search for the development of new alternative agents promising to overcome these drawbacks while matching or surpassing the efficacy of VKAs.[3-6] Thus, a new approach has been investigated of directly targeting a single factor to inhibit in the clotting pathway, which is quite different from the mechanism of action for VKAs, whereby the hepatic synthesis of multiple clotting factors is antagonized. Several more specific oral compounds have been developed and tested, which achieve their anticoagulant effect by stoichiometrically inhibiting a single activated clotting factor, either thrombin (factor IIa) or factor Xa (Fig. 1). Reversible inhibition is considered important for lowering the bleeding risk. These novel agents confer a more predictable and stable anticoagulant response, not interfering with diet, and having fewer interactions with other drugs. They also provide the convenience of oral fixed-dose regimens not requiring the tedious monitoring with laboratory testing. All these positive attributes may have a favorable impact on patient compliance.

Factor Xa has a strategic role in the coagulation cascade (Fig. 1), acting proximal to thrombin at the crossroad of the contact activation (intrinsic) and the tissue factor (extrinsic) coagulation pathways, which activate the final common pathway and lead to the formation of fibrin. Active factor Xa hydrolyzes and activates prothrombin to thrombin. *Thrombin*, being the most important part of the coagulation cascade, has a broad array of functions, with a primary role in the conversion of fibrinogen to fibrin, the scaffolding of a hemostatic plug and in thrombin-mediated feedback activation of coagulation factors V and VIII.

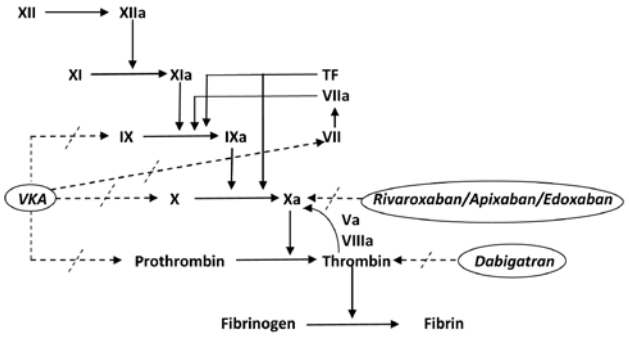

FIGURE 1. Mechanism of action of oral anticoagulants in the coagulation cascade. TF = tissue factor; VKA = vitamin K antagonists.

NOVEL ORAL ANTICOAGULANTS

Novel oral agents like the thrombin inhibitor dabigatran etexilate and the factor Xa inhibitors rivaroxaban and apixaban, have already become available for prevention of deep venous thromboembolism after orthopedic procedures, such as elective hip and knee arthroplasty, while other factor Xa inhibitors (edoxaban, betrixaban, darexaban) are being evaluated in phase II and III clinical trials.[3-20] The initial results of the studies employing these new compounds are promising and provide evidence of improvement in treatment of venous thromboembolism (VTE) and in the prevention of stroke in patients with non-valvular atrial fibrillation (AF). In general there two separate groups of new oral anticoagulant agents: the direct thrombin inhibitors (gatrans) and the direct factor Xa inhibitors (xabans).

DABIGATRAN

Dabigatran etexilate (Pradaxa®, Boehringer Ingelheim)[3-10] is the prodrug of dabigatran, a non-peptide, reversible oral direct thrombin (factor IIa) inhibitor, with a half-life of 12-17 hours (h). It reaches peak plasma concentration within 0.5-2 h. About 80% of the drug is excreted unchanged by the kidneys, while the remainder is eliminated via the bile. Cytochrome P450 is not involved in the metabolism of the drug and thus this new agent has few drug-drug interactions. However, the drug is a substrate for the p-glycoprotein (p-GP) system and has therefore interactions with amiodarone, clarithromycin and verapamil and thus the dose should be decreased in these situations. Dabigatran should actually not be co-administered with quinidine, a potent p-GP inhibitor. Inducers of p-GP, like rifampin, may decrease dabigatran's availability. Absorption of dabigatran is not affected by antacids or histamine 2 blockers. Proton pump inhibitors may reduce drug concentration slightly but do not produce clinically relevant problems. Food containing vitamin K has no effect on the drug action. Galenic formulation of the drug with tartaric acid to optimize its absorption in an acidic milieu accounts for its gastrointestinal side effects, mainly dyspepsia. Its stable pharmacokinetics and pharmacodynamics allow for a fixed dose administration without monitoring of coagulation. Patients with a creatinine clearance of 30 - 50 mL/min should receive a lower dose; the drug should be avoided in patients with a creatinine clearance of <30 mL/min. There is apparently no need to monitor drug therapy with use of any laboratory test; however, the drug has an inconsistent and dose-dependent effect on ecarin clotting time (ECT), thrombin time (TT), INR, and activated partial thromboplastin time (aPTT). Todate, there is no known antidote for dabigatran.

Several phase 3 clinical trials have showed comparable efficacy of dabigatran with that of enoxaparin in the setting of VTE prevention after hip or knee surgery (RE-NOVATE,

RE-MODEL, RE-MOBILIZE) or with warfarin for secondary VTE prevention (RE-COVER, RE-SONATE, RE-MEDY) and with warfarin for stroke prevention in patients with atrial fibrillation (RE-LY) (Table 1).[6-10,16-19] The RE-LY trial has recently demonstrated that dabigatran is an effective alternative for oral anticoagulation with VKAs for stroke prevention in >18000 patients with atrial fibrillation.[6-10] After initial failures with similar medications (e.g. ximelagatran, charged with liver dysfunction), these results constitute a breakthrough in anticoagulation therapy. In the RE-LY trial,[7] in patients with atrial fibrillation and at least one additional risk factor for stroke, after a median follow-up of two years, dabigatran 150 mg bid reduced both stroke and intracranial and life-threatening hemorrhage more effectively without any

TABLE 1. Novel Oral Anticoagulant Agents

Agent	Brand Name	Manufacturer(s)	Mechanism of Action	Dose (Disease)	Trials (Disease)
Dabigatran etexilate*	Pradaxa®	Boehringer Ingelheim	Direct thrombin inhibitor	220 mg qd (VTE) 110 mg bid (AF) 150 mg bid (AF)	RE-NOVATE (VTE), RE-MODEL (VTE), RE-MOBILIZE (VTE), RE-COVER (VTE), RE-MEDY (VTE), RE-SONATE (VTE), RE-DEEM (ACS), RE-LY (AF)
Rivaroxaban**	Xarelto®	Bayer / Johnson & Johnson	Direct factor Xa inhibitor	10 mg qd (VTE) 20 mg qd (AF)	RECORD 1-4 (VTE), MAGELLAN (VTE), EINSTEIN (VTE), ATLAS TIMI 46 & 51 (ACS), ROCKET-AF (AF)
Apixaban***	Eliquis®	Bristol-Myers Squibb/Pfizer	Direct factor Xa inhibitor	2.5 mg bid (VTE) 5 mg bid (AF)	APROPOS (VTE), ADVANCE 1-3 (VTE), ADOPT (VTE), AMPLIFY (VTE), APPRAISE (ACS), AVERROES (AF)†, ARISTOTLE (AF) ‡
Edoxaban	Lixiana®	Daiichi Sankyo	Direct factor Xa inhibitor	30 or 60 mg qd	STARS E-3 (VTE), HOKUSAI (VTE), ENGAGE AF TIMI-48 (AF)
Betrixaban		Portola/Merck	Direct factor Xa inhibitor	15-40 bid or 40-80 mg qd	EXPERT (VTE), EXPLORE Xa (AF)
Darexaban (YM-150)		Astellas	Direct factor Xa inhibitor	30 or 60 mg qd/bid	ONYX-2/-3 (VTE), PEARL (VTE), RUBY-1 (ACS), OPAL-2 (AF)
Letaxaban (TAK-442)		Takeda	Direct factor Xa inhibitor	40-80 mg bid	Phase II trial (VTE)
Eribaxaban (PD0348292)		Pfizer	Direct factor Xa inhibitor	0.1-2.5 mg qd	Phase II trial (VTE)
LY517717		Eli Lilly	Direct factor Xa inhibitor	25-150 mg qd	Phase II trial (VTE)
AZD0837		Astra Zeneca	Direct thrombin inhibitor	300 mg qd	Phase II trial (VTE)
Sofigatran (MCC 977)		Mitsubishi Pharma	Direct thrombin inhibitor	?	Phase II trial (VTE)
Tecarfarin (ATI-5923)		ARYx Therapeutics	VKA	6-29 mg qd	EmbraceAC (AF/VTE, etc)

ACS=acute coronary syndrome; AF=atrial fibrillation; VTE=venous thromboembolism

*Approved in Canada and by the European Medicines Agency (EMA) for VTE prevention after orthopedic surgery. Also approved in the USA (by the FDA on 19/10/2010), in Canada and 12 other countries (EMA approval pending) for stroke prevention for patients with non-valvular atrial fibrillation.

**Approved in >110 countries, including the EU and Canada, and most recently (1/7/2011) by the FDA (USA) for VTE prevention after orthopedic surgery

***Approved by the European Medicines Agency (EMA) for VTE prevention after orthopedic surgery

†apixaban vs aspirin, ‡apixaban vs coumadin

significant increase in overall major hemorrhages compared with warfarin, whereas the lower dose of dabigatran (110 mg bid) while non-inferior at reducing risk of stroke, it reduced intracranial, life-threatening, and major bleeding. Dyspepsia was a more frequent side-effect of dabigatran (11-12%) compared with warfarin (~6%). Importantly, dabigatran did not cause hepatotoxicity. However, a word of caution relates to the occurrence of bleeding while receiving dabigatran (there was a higher rate of gastrointestinal bleeding with dabigatran at the 150-mg dose than with warfarin), as there is no specific antidote for this drug, which has a half-life of 12-17 hours. Supportive therapy for severe bleeding may include transfusions of fresh-frozen plasma, packed red blood cells, or exploratory surgery if indicated.

The American Food & Drug Administration (FDA) approved dabigatran on October 19, 2010 for anticoagulant use in patients with nonvalvular AF.[20] However, only the higher dose (150 mg bid) was approved for patients with a creatinine clearance >30 mL/min. In patients with severe renal insufficiency (creatinine clearance 15 to 30 mL/min) half the dose (75 mg bid) was recommended, which however was not evaluated in the RE-LY trial. For the same indication, dabigatran has also been approved in Canada and at least 12 other countries and awaits approval by the European Medicines Agency (EMA). Dabigatran is the first new oral anticoagulant to become available for clinical use in over half a century. Dabigatran has also been approved in Canada and by the EMA for VTE prevention after orthopedic surgery.

Other novel oral anticoagulant agents which have received or are next in line to receive approval for marketing for venous thromboembolism and stroke prevention in patients with VTE or AF include the factor Xa inhibitors, rivaroxaban, apixaban, edoxaban, betrixaban and darexaban (Table 1).[11-20]

RIVAROXABAN

Rivaroxaban (Xarelto®, Bayer/Johnson & Johnson),[17-20] an oral direct factor Xa inhibitor, is an oxazolidinone derivative, has a half-life of up to 12 h in the elderly, and up to 9 h at steady state in healthy young subjects. It reaches peak plasma concentration within 2-4 h. Two thirds of the drug are metabolized; two thirds are eliminated renally. Rivaroxaban is metabolized in the liver involving cytochrome P450 (CYP3A4, CYP2J2). It affects prothrombin time more than aPTT and it can be monitored by anti-factor-Xa assays if desired.

Rivaroxaban has been approved in Canada and by the EMA and most recently by the FDA for VTE prevention after orthopedic surgery. In the RECORD trials, the drug prevented venous thromboembolism in the orthopedic surgical setting significantly better than enoxaparin, with no increased bleeding risk. The EINSTEIN trial[11] included 3449 patients with acute deep vein thrombosis; 1731 were given rivaroxaban (15 mg bid for 3 weeks, followed by 20 mg qd) and 1718 were given enoxaparin plus a VKA. The primary efficacy outcome was recurrent venous thromboembolism. Rivaroxaban had non-inferior efficacy with respect to the primary outcome (36 events [2.1%], vs 51 events with enoxaparin–vitamin K antagonist [3.0%]; hazard ratio, 0.68; P<0.001). The principal safety outcome (bleeding) occurred in 8.1% of the patients in each group. In the continued-treatment study (EINSTEIN-Extension), which included 602 patients in the rivaroxaban group and 594 in the placebo group, rivaroxaban had superior efficacy (8 events [1.3%], vs 42 with placebo [7.1%]; hazard ratio, 0.18; P<0.001). Four patients in the rivaroxaban group had nonfatal major bleeding (0.7%), versus none in the placebo group (P = 0.11).

Rivaroxaban was also assessed in the ROCKET-AF trial in 14264 patients with AF and found to be non-inferior to warfarin.[13] Rivaroxaban was given at a dose of 20 mg qd (or 15 mg qd in patients with renal impairment). The primary end point was a composite of stroke and non-cerebral embolism; rivaroxaban was found to be superior to warfarin by 21% with regards to the primary endpoint in patients who remained on treatment over the course of the 40-month trial; it was not superior to warfarin in the stricter intention-to-treat analysis. In terms of bleeding, the rates of the composite major and non-major clinically relevant bleeding were comparable in the rivaroxaban- and warfarin-treatment arms, with less fatal bleeding and intracranial hemorrhage observed among those treated with the new drug. Major bleeding occurred in 395 patients, at a rate of 3.60 per 100 patient-years, in the warfarin-treated patients, and in 386 patients, or at a rate of 3.45 per 100 patient-years, in the rivaroxaban-treated patients (p=0.576).

APIXABAN

Apixaban (Eliquis®, Pfizer/Bristol-Myers Squibb),[17-20] a direct Xa inhibitor, has a half-life of 8-15 h and reaches peak plasma concentration within 1-4 h. It was evaluated in the AVERROES trial[12] against aspirin in 5599 patients with AF for whom VKA therapy was unsuitable and found to be superior to aspirin with fewer cases of stroke or systemic embolism (1.6% per year vs 3.7% per year; hazard ratio 0.45; p<0.001) without significantly increasing the risk of major bleeding or intracranial hemorrhage.[12] The incidence of major bleeding was 1.4% per year in the apixaban group and 1.2% in the aspirin group (p=0.57). The full results of the ARISTOTLE trial comparing apixaban (5 mg bid) with warfarin in over 18000 patients with atrial fibrillation are still pending;[15] a preliminary press release indicates that apixaban was non-inferior to warfarin, and that apixaban "also met the key secondary end-points of superiority on efficacy and on major bleeding compared with warfarin."[15] Apixaban just recently received approval for use in the 27 countries of the European Union for the prevention of venous thromboembolic (VTE) events in patients who have undergone elective hip- or knee-replacement surgery.

OTHER NOVEL AGENTS[17-22]

Edoxaban (Lixiana®, Daiichi Sankyo) has a short half-life of 8–10 hours, and is mainly eliminated via the kidneys. The ENGAGE AF TIMI-48 trial compares two doses of edoxaban (30 and 60 mg once daily) with INR-adjusted warfarin for stroke prevention in patients with AF. Enrolment has been completed with 21 107 patients, and trial completion is scheduled for mid-2012. **Betrixaban** (Portola/Merck) has a bioavailability of 47%, a half-life of 19 h and is excreted almost unchanged in bile. A completed phase II, randomized, open-label VTE prevention trial (EXPERT) in patients undergoing total knee replacement provided evidence for the efficacy and safety of betrixaban (15 or 40 mg bid) compared with enoxaparin (30 mg bid) in 215 patients. **Darexaban** (YM-150, Astellas) is another direct factor Xa inhibitor, being evaluated in VTE, acute coronary syndromes (ACS) and AF patients in phase II and III trials. Preliminary results report a favorable efficacy and safety profile of the drug in comparison with enoxaparin in patients with VTE, and a promising safety profile in comparison with warfarin in patients with AF. Important potential advantages over other similar drugs are claimed regarding its lack of cytochrome P3A4 inhibition and hence drug-drug interactions and its better gastrointestinal tolerability.

AZD-0837 (AstraZeneca) is a prodrug and another reversible direct thrombin inhibitor. This agent is similar to ximelagatran apparently without the associated liver toxicity. Its half-life is 9 hours. It is metabolized by cytochrome 2C9, 2C19, and 3A4. AZD-0837 is eliminated by both renal and hepatic pathways. Preliminary data from 2 studies in 955 and 250 patients respectively with AF indicated a similar or lower incidence of bleeding than warfarin, however the drug produced a higher incidence of dyspepsia compared with warfarin leading to more frequent discontinuation of treatment. Although not powered to detect any significant differences, the studies indicated a low incidence of stroke or VTE among all groups.[20]

Sofigatran (MCC 977, Mitsubishi Pharma) is also a direct thrombin inhibitor which is in phase II clinical trials for treatment of deep vein thrombosis. **TTP889** (Transtech Pharma) is a novel anticoagulant agent, a factor IXa (reversible) inhibitor, first used in a phase II clinical trial for VTE, but in the dose employed the drug was ineffective. Finally, **Tecarfarin** (ATI-5923, ARYx Therapeutics)[23] is a new oral VKA, which, unlike warfarin, is not metabolized via the cytochrome P450 (designed to be metabolized through the esterase pathway), thus avoiding several potential drug-drug interactions. The agent is compared with warfarin in phase II/III trials in patients with AF and other groups requiring anticoagulation.[23]

LIMITATIONS

The shorter half-life of these new agents will probably improve their safety profile and obviate the need for pre-operative anticoagulation "bridging", but, on the other hand, it will also pose a risk of inferior protection if doses are missed. Some of these new drugs are substrates for P-glycoprotein and they are metabolized by cytochrome P-450 3A4.[19] Hence, caution is advised to avoid the concomitant use of drugs that inhibit these pathways, such as azole antifungal agents or protease inhibitors. Other limitations of these new drugs may relate to gastrointestinal side effects, mode of metabolism and route of elimination. Also specific antidotes are not available for any of them, albeit their short half-life may prove advantageous in this regard. Finally, the cost issue is very important, as the cost of these new agents will be much higher than that of VKAs, and needs to be factored into the decision-making process with any of the new anticoagulants.

REFERENCES

1. Ansell J, Hirsh J, Hylek E, et al. American College of Chest Physicians. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; 133(Suppl 6):160S-198S.
2. Holbrook AM, Pereira JA, Labiris R, et al. Systematic overview of warfarin and its drug and food interactions. *Arch Intern Med* 2005;106:1095-1106.
3. Garcia D, Libby E, Crowther MA. The new oral anticoagulants. *Blood* 2010; 115;15-20.
4. Steffel J, Braunwald E. Novel oral anticoagulants: focus on stroke prevention and treatment of venous thrombo-embolism. *Eur Heart J* 2011 Mar 18. doi:10.1093/eurheartj/ehr052 [Epub ahead of print]
5. Schirmer SH, Baumhδkel M, Neuberger HR, et al. Novel anticoagulants for stroke prevention in atrial fibrillation: current clinical evidence and future developments. *J Am Coll Cardiol* 2010;56:2067-2076.
6. Wallentin L, Yusuf S, Ezekowitz MD, et al. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. *Lancet* 2010;376(9745):975-983.
7. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009; 361:1139–1151.
8. Wann LS, Curtis AB, Ellenbogen KA, et al. 2011 ACCF/AHA/HRS Focused update on the management of patients with atrial fibrillation (update on dabigatran): A report of the American College of Cardiology Foundation/American Heart Asso-

ciation Task Force on Practice Guidelines. *J Am Coll Cardiol* 2011;57:1330-1337. *Circulation* 2011;123:1144-1150.
9. Hankey GJ, Eikelboom JW. Dabigatran etexilate: a new oral thrombin inhibitor. *Circulation* 2011;123:1436-1450.
10. Manolis AS. Dabigatran: An alternative to warfarin after over half a century. *Rhythmos* 2011;6:1-2.
11. The EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med* 2010;363:2499-2510.
12. Connolly SJ, Eikelboom J, Joyner C, et al for the AVERROES Steering Committee and Investigators. Apixaban in patients with atrial fibrillation. *N Engl J Med* 2011; 364:806-817.
13. Mahaffey KW, Fox KAA. Rivaroxaban Once-daily oral direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF). (http://sciencenews.myamericanheart.org/pdfs/ROCKET_AF_pslides.pdf).
14. Hylek EM. Therapeutic potential of oral factor Xa inhibitors. *N Engl J Med* 2010; 363: 2559-2561.
15. Bristol-Myers Squibb. Eliquis (apixaban) meets primary and key secondary endpoints in phase 3 ARISTOTLE study [press release]. June 22, 2011. Available at: http://www.bms.com/news/press_releases/pages/default.aspx?RSSLink=http://www.businesswire.com/news/bms/20110622006923/en&t=634444126192849398
16. Ogawa S, Koretsune Y, Yasaka M, et al. Antithrombotic therapy in atrial fibrillation – evaluation and positioning of new oral anticoagulant agents. *Circ J* 2011; 75:1539–1547.
17. Perzborn E. Factor Xa inhibitors: new anticoagulants for secondary haemostasis. *Hamostaseologie* 2009; 29:260–267.
18. Harbrecht U. Old and new anticoagulants. *Hamostaseologie* 2011; 31:21–27.
19. Ahrens I, Lip GYH, Peter K. New oral anticoagulant drugs in cardiovascular disease. *Thromb Haemost* 2010; 104:49–60.
20. Clayville LR, Anderson KV, Miller SA, St Onge EL. New options in anticoagulation for the prevention of venous thromboembolism and stroke. *P T* 2011;36:86-99.
21. Astellas R&D meeting(25/5/2011): http://www.net-ir.ne.jp/e-pre/4503r1105e/parts/material0.pdf
22. Eriksson BI, Turpie AG, Lassen MR, et al; ONYX-2 STUDY GROUP. Prevention of venous thromboembolism with an oral factor Xa inhibitor, YM150, after total hip arthroplasty. A dose finding study (ONYX-2). *J Thromb Haemost* 2010;8:714-721.
23. Ellis DJ, Usman MH, Milner PG, Canafax DM, Ezekowitz MD. The first evaluation of a novel vitamin K antagonist, tecarfarin (ATI-5923), in patients with atrial fibrillation. *Circulation* 2009;120:1029-1035.