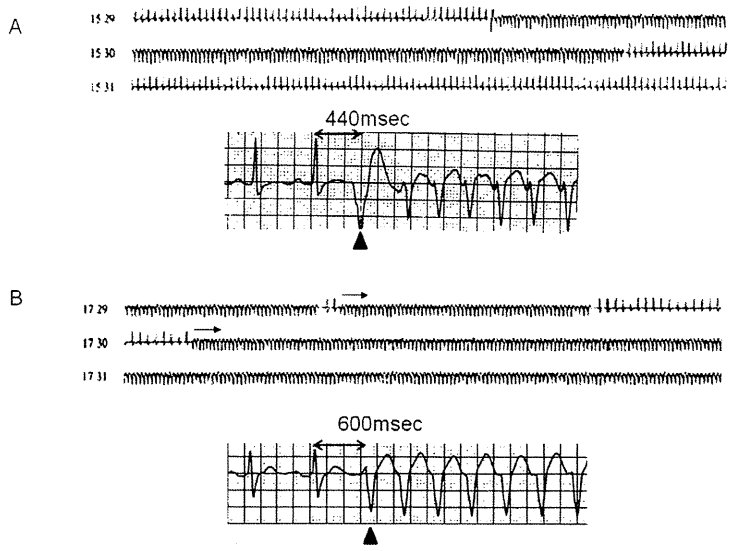

Figure 2. Recurrent ventricular tachycardia (VT) observed on the monitoring electrocardiogram (ECG) before and after amiodarone. Recurrent VT was suddenly observed on her monitoring ECG (A). After intravenous amiodarone, VT became more incessant and the duration of VT prolonged still more (B). Before amiodarone administration, relatively short coupled premature ventricular complex (PVC) (the coupling interval was 440 ms), of which morphology was different from that of VT, induced recurrent VT (A). After amiodarone, VT was reproducibly triggered by PVC of which morphology was same as that of VT and the coupling interval of initiating PVC was relatively longer (600 ms) (B).

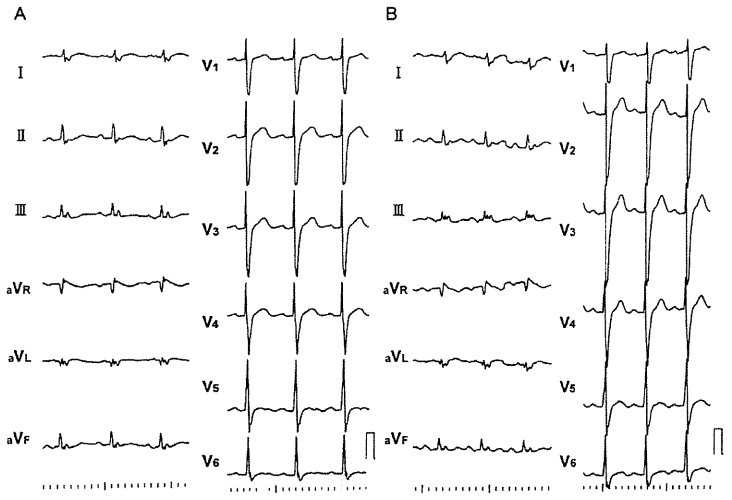

Figure 3. Twelve-lead electrocardiograms (ECGs) during sinus rhythm before and after amiodarone. Before amiodarone, QRS duration was 130 msec and QTc interval was 370 msec on the ECG (A). After amiodarone, QRS duration and QTc interval were prolonged to 160 msec and 400 msec (B).

nism of this VT.

Intravenous amiodarone inhibits sodium channels, inward L-type calcium channels, and has noncompetitive β-blockade effect, but the potassium channel blockade effect became more apparent after long-term therapy. It was possible that blockade of L-type calcium channels and β-blockade could suppress automaticity and triggered activity. However, in this case, the mechanism of VT was thought to be likely due to re-entry, these effects can just slow the VT rate. The slight prolongation of QT interval can be explained by potassium channel blockade effect of intravenous amiodarone. The prolongation of QRS duration, the decline of VT rate, and the change of QRS morphology of the initiating PVC after intravenous amiodarone suggested that the acute effect of amiodarone infusion mainly developed sodium channel blockade. The coupling interval between the

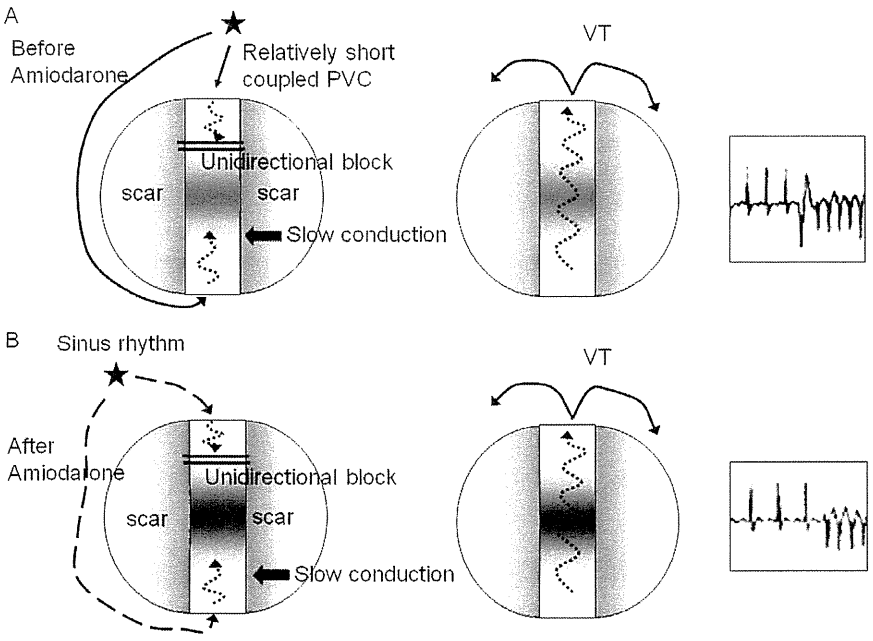

Figure 4. Illustration of postulated mechanism of ventricular tachycardia (VT) before and after amiodarone. Before amiodarone administration, relatively short coupled premature ventricular complex caused unidirectional block in critical slow pathway zone, and retrograde conduction formed the reentrant circuit resulting in recurrent VT (A). After amiodarone administration, its blocking effect of sodium channel could create the unidirectional block in the critical slow conduction zone even during sinus rhythm and induced the incessant monomorphic VT (B).

initiating PVC and the next beat of VT was nearly identical to VT cycle length.

We depicted the postulated mechanism of VT in this case as shown in Fig. 4. Sodium channel blockade of amiodarone was thought to create the unidirectional block in the critical slow conduction zone even during sinus rhythm and induced the incessant monomorphic VT as a proarrhythmia. At the time of admission, the morphology of occasional PVC was similar to that of documented incessant VT, and QRS duration was 150 ms, this was relatively longer than the QRS duration before amiodarone. These findings suggested that a similar proarrhythmic situation had occurred in this patient at that time for some reasons but the difference between the coupling intervals of PVCs at the time of admission and after amiodarone determined whether the arrhythmias were sustained or not. Subsequent intravenous nifekalant, which promptly inhibits IKr channels and prolongs effective refractory period of ventricular myocardium in the critical slow pathway, could make VT disappeared completely. This successful suppression of VT could result from combination effects of amiodarone and nifekalant.

It was possible that amiodarone suppressed the original initiating PVC and accordingly the initiating PVC was changed. The effects of amiodarone other than sodium channel blockade could affect initiating PVC. But, nifekalant, IKr inhibitor, which has little effect on sodium and calcium channels, swept the initiating PVC away. This indicated that the initiating PVC was due to re-entrant mechanism rather than abnormal automaticity and triggered activity which depended on mainly intracellular sodium and calcium ion concentrations. In addition, (i) amiodarone usually suppressed the abnormal automaticity and triggered activity, (ii) a similar QRS prolongation was observed at the time of hospitalization and after amiodarone when similar PVC were found and VT worsened, (iii) the coupling interval between the initiating PVC and the preceding QRS was nearly constant, (iv) sustained VT was suppressed concomitant with the complete suppression of the PVCs after nifekalant administration. These also support our re-entrant hypothesis that sodium channel blockade affected on this patient. Furthermore, Duff et al demonstrated experimentally that sodium channel blocker precipitated monomorphic VT and its inducibility was suppressed by potassium channel blocker (11). Their experiment also supports our hypothesis. However, we could not completely exclude the possibility of initiating PVC from the exit-site of critical slow conduction after amiodarone. Initiating PVC from the exit-site could be analogous to the QRS morphology of VT and the coupling interval between the 1st and 2nd beat of VT could be similar to VT cycle length.

We encountered incessant monomorphic VT induced after injection of intravenous amiodarone. It is important to be aware of the proarrhythmic effect of amiodarone which may lead to an electrical storm of monomorphic VT.

The authors state that they have no Conflict of Interest (COI).

References

1. Vassallo P, Trohman RG. Prescribing amiodarone. JAMA **298**: 1312-1322, 2007.
2. Singh BN. Amiodarone: historical development and pharmacologic profile. Am Heart J **106**: 788-797, 1983.
3. Hohnloser SH, Klingenheben T, Singh BN. Amiodarone-associated proarrhythmic effects. A review with special reference to torsade de pointes tachycardia. Ann Intern Med **121**: 529-535, 1994.
4. Brown MA, Smith WM, Lubbe WF, Norris RM. Amiodarone-induced torsades de pointes. Eur Heart J **7**: 234-239, 1986.
5. Goldschlager N, Epstein AE, Naccarelli GV, et al; Practice Guidelines Sub-committee, North American Society of Pacing and Electrophysiology (HRS). A practical guide for clinicians who treat patients with amiodarone: 2007. Heart Rhythm **4**: 1250-1259, 2007.
6. Kusano KF, Hata Y, Yumoto A, Emori T, Sato T, Ohe T. Torsade de pointes with a normal QT interval associated with hypokalemia: a case report. Jpn Circ J **65**: 757-760, 2001.
7. Geng DF, Jin DM, Wang JF, Luo YJ, Wu W. Clinical study of amiodarone-associated torsade de pointes in Chinese people. Pacing Clin Electrophysiol **29**: 712-718, 2006.
8. Tomlinson DR, Cherian P, Betts TR, Bashir Y. Intravenous amiodarone for the pharmacological termination of haemodynamically-tolerated sustained ventricular tachycardia: is bolus dose amiodarone an appropriate first-line treatment? Emerg Med J **25**: 15-18, 2008.
9. Marill KA, deSouza IS, Nishijima DK, Stair TO, Setnik GS, Ruskin JN. Amiodarone is poorly effective for the acute termination of ventricular tachycardia. Ann Emerg Med **47**: 217-224, 2006.
10. Marill KA, deSouza IS, Nishijima DK, et al. Amiodarone or procainamide for the termination of sustained stable ventricular tachycardia: an historical multicenter comparison. Acad Emerg Med **17**: 297-306, 2010.
11. Duff HJ, Stemler M, Thannhauser T, Laganiere S, Rude E, Lester W. Proarrhythmia of a class Ic drug: suppression by combination with a drug prolonging repolarization in the dog late after infarction. J Pharmacol Exp Ther **274**: 508-515, 1995.

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REVIEW

Antithrombotic Therapy in Atrial Fibrillation

– Evaluation and Positioning of New Oral Anticoagulant Agents –

Satoshi Ogawa, MD, PhD; Yukihiro Koretsune, MD, PhD; Masahiro Yasaka, MD, PhD; Yoshifusa Aizawa, MD, PhD; Hirotsugu Atarashi, MD, PhD; Hiroshi Inoue, MD, PhD; Shiro Kamakura, MD, PhD; Koichiro Kumagai, MD, PhD; Hideo Mitamura, MD, PhD; Ken Okumura, MD, PhD; Kaoru Sugi, MD, PhD; Takeshi Yamashita, MD, PhD

Atrial fibrillation (AF) is the most common cardiac rhythm disorder and a major risk factor for stroke. For more than 60 years, warfarin has been the only approved anticoagulant for prevention of stroke in patients with AF. Although highly effective, it has many limitations that make its use difficult. Therefore, several novel anticoagulants are under development to overcome the limitations of warfarin, and some of these have entered phase III clinical trials. Dabigatran is an oral, reversible direct thrombin inhibitor approved in Europe and in several other countries for the prevention of venous thromboembolism after elective knee and hip replacement surgery. It has also been approved in the United States and Japan for the prevention of stroke and systemic embolism in patients with non-valvular AF. In this review, the mechanism of action and pharmacological properties of new anticoagulants are described in detail, and the correct use of dabigatran in clinical practice is discussed. (*Circ J* 2011; **75:** 1539–1547)

Key Words: Anticoagulation; Atrial fibrillation; Dabigatran; Stroke; Warfarin

Atrial fibrillation (AF), the most common cardiac rhythm disorder and a major risk factor for stroke, exacts a high toll in morbidity and mortality and imposes an enormous economic burden.[1] In the United States, AF is responsible for at least 15–20% of all strokes[2] and AF independently increases the risk of ischemic stroke by 4- to 5-fold.[2] In 2010, the estimated direct and indirect costs of stroke were US$73.7 billion.[2] The prevalence of AF increases significantly in the elderly, affecting an estimated 9–14% of the general population >80 years of age in North America and Western Europe.[3,4] In Japan, the increase in the prevalence of AF in people aged over 70 years has been slower than in Western countries, with AF affecting only around 3% of the general population >80 years of age.[4–6] Based on the medium variant estimates of the Population Projection for Japan, the absolute number of AF patients is estimated to be >1 million in the year 2030.[6]

It is also important to consider that coagulation activity is increased in the left atrium of patients with paroxysmal AF during the non-paroxysmal period (ie, during sinus rhythm),[7] something that was not previously recognized.[7] Accordingly, these patients are at high risk of developing cerebral thromboembolism, even during sinus rhythm, and anticoagulation therapy may be more beneficial than antiplatelet therapy.

Vitamin K antagonists (VKA) were first introduced more than 60 years ago and until recently, they were the only orally active anticoagulants available for clinical use.[8] Warfarin is the most widely used oral VKA for the long-term prophylaxis of thrombosis. Moreover, its use has increased as new clinical conditions capable of leading to thrombosis have been identified.

Warfarin reduces the risk of stroke in patients with non-valvular AF by 68%.[9] Although highly effective, it has several limitations, including a narrow therapeutic window,[9]

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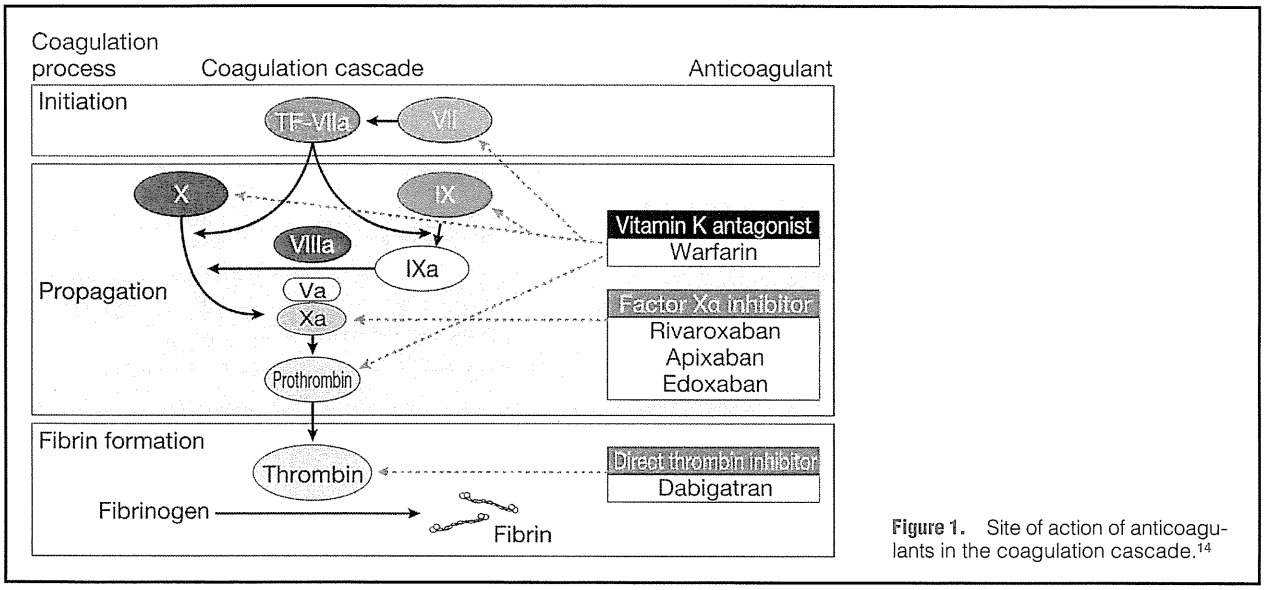


Figure 1. Site of action of anticoagulants in the coagulation cascade.[14]

increased risk of hemorrhage compared with control therapy,[10] multiple food and drug interactions, and the need for frequent laboratory monitoring.[11,12] As a result, the therapeutic range is achieved in less than two-thirds of patients in clinical practice,[13] and only half of elderly patients with appropriate indications for VKAs are actually prescribed oral anticoagulants.[14] Surprisingly, an analysis of the J-TRACE study revealed that, among patients with a $CHADS_2$ score of 6, the use of warfarin was actually lower in women than in men.[15] Strategies to enhance the anticoagulant effect of warfarin have been evaluated but are limited for various reasons. For example, triple therapy comprising warfarin, aspirin and clopidogrel reduced the rate of major adverse cardiac and cerebral events compared with dual therapy comprising aspirin plus clopidogrel in patients with AF undergoing drug-eluting stent implantation.[16] However, triple therapy was associated with an increased risk of overall bleeding. In another study, warfarin was administered with bucolome, a nonsteroidal antiinflammatory drug, which reduced the dose of warfarin required to maintain the international normalized ratio (INR) within an acceptable range.[17] However, this approach did not affect the frequency of stroke or major bleeding.

These limitations have fueled efforts to develop new oral anticoagulants that are effective, safe, and convenient to use. A small number of novel anticoagulant agents (eg, oral direct thrombin inhibitors (DTIs) and factor Xa inhibitors) have reached phase III clinical trials for prevention of stroke and systemic embolism in patients with nonvalvular AF (NVAF).[1,18] Dabigatran, a reversible DTI, has been approved in Europe and in several other countries for the prevention of venous thromboembolism after elective hip and knee replacement, and is in advanced clinical development for other thromboembolic diseases.[19] In 2011 it was approved in Japan for the prevention of stroke and systemic embolism in patients with NVAF. This review will assess new oral anticoagulant agents for the prevention of stroke and systemic embolism in patients with NVAF, compare their stages of development, and address the properties, mechanisms of action, and proper clinical use of dabigatran specifically.

Characteristics of New Anticoagulant Agents

All anticoagulant agents inhibit thrombin activity by interrupting factors in the coagulation cascade, including a series of reactions that include amplification, fibrin formation, and the change from fibrinogen to fibrin (Figure 1).[14] Both the intrinsic coagulation pathway (involving factors XII, XI, IX and VIII) and the extrinsic pathway (involving factor VII) end in the same common pathway, activation of factor X to factor Xa.[1]

Together with factor Va, factor Xa forms the prothrombinase complex that activates prothrombin (factor II) to thrombin (factor IIa).[1] Unlike indirect anticoagulants, such as heparins, which require antithrombin III to inhibit factor Xa or factor IIa, the novel orally available anticoagulants directly inhibit factor Xa or factor IIa. Thrombin not only activates fibrinogen into fibrin (factor 1a), but also activates factors V, VII, VIII, IX and XIII. Thus, blocking thrombin efficiently inhibits coagulation.[1]

The new oral anticoagulants have a rapid onset of action and can be given at fixed doses without routine coagulation monitoring; thus, they may simplify treatment paradigms and improve clinical outcomes.[8] Factor Xa is a particularly attractive target for effective anticoagulation because it is positioned at the convergence point of the intrinsic and extrinsic coagulation pathways. Factor Xa catalyzes the conversion of prothrombin to thrombin–1 molecule of Factor Xa leads to the generation of >1,000 thrombin molecules.[20]

Direct factor Xa inhibitors block factor Xa and thus, indirectly, the generation of thrombin. Because direct inhibition of factor Xa does not affect the activity of existing thrombin, it may preserve hemostasis. In clinical terms, this might translate into efficacy with low bleeding risk.[18] This conclusion requires further results of several ongoing clinical trials.

The other attractive target is direct inhibition of thrombin, the final mediator in the coagulation cascade that leads to the production of fibrin.[20] Thrombin is a potent activator of platelets.[8] In addition to inactivating free thrombin, DTIs are also able to inactivate fibrin-bound thrombin–an important trigger of thrombus expansion.[21,22] Synthetic, small-molecule DTIs represent a new therapeutic class of antithrombotic

Table 1. Characteristics of Oral Anticoagulants Under Development in Japan[8,31]

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target factor	Thrombin	Xa	Xa	Xa
$t_{1/2}$ (h)	12–14	9–13	8–15	6–11[31]
t_{max} (h)	0.5–2	2–4	1–4	1–1.5[31]
Bioavailability	6.5% (humans)	67–86% (animals)	49% (humans)	60% (animals)
Protein binding	35%	92–95%	87%	40–59%
Metabolism	Glucuronidation	CYP3A4/2J2[8]	CYP3A4[8]	CYP3A
Renal excretion	80%	33%	25%	35–39%
Prodrug	Yes	No	No	No
Company	Boehringer Ingelheim	Bayer/ Johnson & Johnson	Bristol-Myers Squibb/ Pfizer	Daiichi Sankyo

Table 2. Large-Scale Clinical Studies of Oral Anticoagulants Developed in Japan in Patients With Nonvalvular Atrial Fibrillation

Target	Drug	Clinical trial	No. of patients/treatments	$CHADS_2$ score	Study status
Thrombin inhibitors	Dabigatran	RE-LY	n=18,113/Dabigatran (110 or 150 mg b.i.d.), Warfarin	≥1	Published[11,12]
Factor Xa inhibitors	Rivaroxaban	ROCKET-AF	n=14,264/Rivaroxaban (20 mg q.d.), Warfarin	≥2	Completed[35]
		J-ROCKET-AF	n=1,200/Rivaroxaban (15 mg q.d.), Warfarin	≥2	Completed
	Apixaban	ARISTOTLE	n=18,206/Apixaban (5 mg b.i.d.), Warfarin	≥1	Ongoing[36]
		AVERROES	n=5,599/Apixaban (5 mg b.i.d.), Aspirin	≥1	Published[37]
	Edoxaban	ENGAGE-AF	n=20,500/Edoxaban (30 or 60 mg q.d.), Warfarin	≥2	Ongoing

agents that may overcome the limitations of VKAs.[23]

Ximelagatran, a prodrug of the active metabolite melagatran, was the first oral agent in the new class of reversible DTIs.[23,24] In an extensive phase III clinical program, it was evaluated for several indications,[25,26] including the prevention and treatment of venous thromboembolism[26–28] and the prevention of stroke in patients with AF.[29,30] It was also approved in Europe for the prevention of venous thromboembolism after total hip or total knee replacement surgery, and has demonstrated potential for preventing thromboembolic events in patients with AF. However, it was subsequently withdrawn from the market because of hepatotoxicity.[23] Nonetheless, the ximelagatran studies provided evidence that effective anticoagulation could be achieved with fixed-dose oral agents, without the need for frequent patient coagulation monitoring.

In addition to dabigatran, other new agents in the most advanced stages of clinical development for stroke prevention and AF include the direct factor Xa inhibitors rivaroxaban, apixaban and edoxaban.[8] The characteristics of these drugs and the status of phase III trials are shown in Tables 1 and 2, respectively. Although rivaroxaban, apixaban and edoxaban all target factor Xa, their pharmacological characteristics differ widely.[8,31] In terms of metabolism, all 3 drugs are metabolized by members of the cytochrome P450 family, suggesting that these drugs may be susceptible to drug or food interactions, although the clinical implications of this need to be formally evaluated.

By inhibiting factor Xa, rivaroxaban attenuates generation of thrombin from prothrombin and also inhibits factor-induced thrombin generation.[32] As a consequence, prothrombin time increases with factor Xa inhibition in a dose-dependent manner.[1] The half life of rivaroxaban is 7–11 h. Rivaroxaban is largely excreted by the renal system; two-thirds of it is metabolized in the liver and one-third undergoes unchanged renal excretion.[33]

The ROCKET-AF (Randomized, Double-Blind Study Comparing Once Daily Rivaroxaban With Adjusted-Dose Oral Warfarin for the Prevention of Stroke in Subjects With Non-Valvular Atrial Fibrillation) study is the first phase III study comparing rivaroxaban with warfarin for prevention of stroke in patients with NVAF.[34] Rivaroxaban showed noninferiority to warfarin but not superiority in high-risk patients (mean $CHADS_2$ score: 3.5). Rates of bleeding on rivaroxaban were similar to those on warfarin.[35]

Apixaban is excreted via non-renal routes. The half-life of apixaban is 8–15 h and it has 49% bioavailability. A large phase III trial in patients with AF, the ARISTOTLE (Apixaban for the Prevention of Stroke in Subjects with Atrial Fibrillation trial) comparing the oral direct factor Xa drug to warfarin, is currently being conducted. Enrollment of 18,206 patients has been completed, and study results are expected in September 2011.[36] The AVERROES trial (A Phase III Study of Apixaban in Patients with Atrial Fibrillation) compared apixaban with aspirin.[37] The endpoint was a composite of stroke or systemic embolism in patients with AF unsuitable for VKAs. The study was halted prematurely because of superior efficacy of the study drug in reducing thromboembolic events. A total of 2,808 patients treated with apixaban showed a 55% reduction in stroke or systemic embolism without excessive risk of increased bleeding compared with aspirin.[37]

One of the newest oral direct factor Xa inhibitors, edoxaban, has a shorter half-life than the other drugs, but may also reach its maximal effect (ie, t_{max}) more quickly, possibly

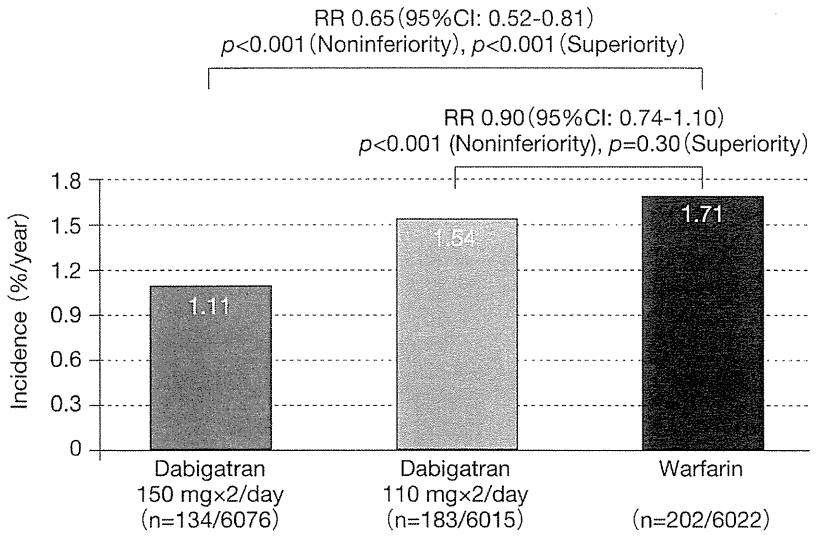


Figure 2. Primary endpoint of the RE-LY study (incidence of stroke or systemic embolism).[11,12] RR, relative risk. CI, confidence interval.

due to its lower protein binding. Like apixaban, it is excreted via non-renal routes. So far, one phase I trial has been published.[31] A phase III study comparing its effects with those of warfarin in patients with AF is currently being performed (ENGAGE-AF-TIMI 48 trial [Global Study to Assess the Safety and Effectiveness of DU-176b vs. Standard Practice of Dosing With Warfarin in Patients With Atrial Fibrillation]: NCT00781391).

A recent trial of the DTI dabigatran has shown that the drug significantly reduces stroke risk in patients with AF compared with warfarin, with a better safety profile than warfarin.[11,12] At the time of writing, dabigatran was the only novel anticoagulant to be approved in Japan.[1] As summarized in Table 2, several large-scale studies have recently been completed or are ongoing for rivaroxaban, apixaban and edoxaban. In the absence of results from these studies and because these drugs have not yet received approval in Japan, we have focused this review on the data available for dabigatran. Our objective is to help inform physicians in Japan on the best use of this drug.

Characteristics and Clinical Results of a New Anticoagulant Drug: Dabigatran

Characteristics of Dabigatran

Dabigatran etexilate is the prodrug of dabigatran, a non-peptide direct thrombin (factor IIa) inhibitor[9,23] (Figure 1). Following oral administration, dabigatran etexilate is rapidly hydrolyzed in vivo by serum esterase to its active form, dabigatran.[38] It is absorbed through the gastrointestinal tract, reaching a peak plasma concentration 0.5–2 h after administration.[9] It has a bi-exponential distribution phase,[9] with a terminal half-life that ranges from 12 to 17 h.[39] Approximately 80% of the drug is excreted unchanged by the kidneys, with the remainder eliminated in bile.[23,38]

The absolute bioavailability of dabigatran is 6.5%.[9,39] Because cytochrome P450 is not involved in the metabolism of the drug, and there is no induction or inhibition of cytochrome P450 enzyme activity, it has few drug interactions.[1,38] Furthermore, limiting the intake of foods containing vitamin K is not required.[39] The stable pharmacokinetics and pharmacodynamics of dabigatran allow fixed-dose administration without coagulation monitoring.

Mechanisms of Action of Dabigatran

Thrombin, a plasma serine protease, plays a central role in coagulation and hemostasis. Produced by the proteolytic cleavage of prothrombin, it catalyzes the conversion of fibrinogen to fibrin, leading to thrombus formation.[23] By directly and specifically interacting with the active site of thrombin, univalent DTIs such as dabigatran inactivate fibrin-bound thrombin.[40]

Thrombin is also the most potent physiological agonist of platelet activation and aggregation.[23] Dabigatran competitively inhibits human thrombin in a concentration-dependent manner,[41] displaying highly selective and rapid but reversible binding to thrombin. Reversible binding may contribute to safer and more predictable anticoagulant treatment than has been observed with drugs that bind noncovalently and irreversibly.[23]

Clinical Results of Dabigatran

The efficacy and safety of dabigatran for preventing stroke or systemic embolism in patients with NVAF was evaluated in an international collaborative phase III clinical study (Randomized Evaluation of Long Term Anticoagulant Therapy: RE-LY) in which the drug was compared with dose-adjusted warfarin (INR: 2.0–3.0).[9] The study has recently been completed.[11,12] In this non-inferiority trial, 18,113 patients (including 326 Japanese patients) with AF and at least one risk factor for stroke were randomized to receive fixed doses of dabigatran [110 mg (n=6,015) or 150 mg b.i.d. (n=6,076)] or dose-adjusted warfarin (n=6,022). The yearly rates of stroke or systemic embolism were 1.71% with warfarin, 1.54% with 110 mg dabigatran b.i.d. (P<0.001 for non-inferiority) and 1.11% with 150 mg dabigatran b.i.d. (P<0.001 for non-inferiority; P<0.001 for superiority); thus, 150 mg dabigatran b.i.d. showed a significantly greater reduction in risk than warfarin (ie, superiority) (Figure 2). The rates of major bleeding, a primary safety outcome, were 3.57% per year with warfarin vs. 2.78% per year with 110 mg dabigatran b.i.d. (P=0.003) and 3.32% per year with 150 mg dabigatran b.i.d. (P=0.32)

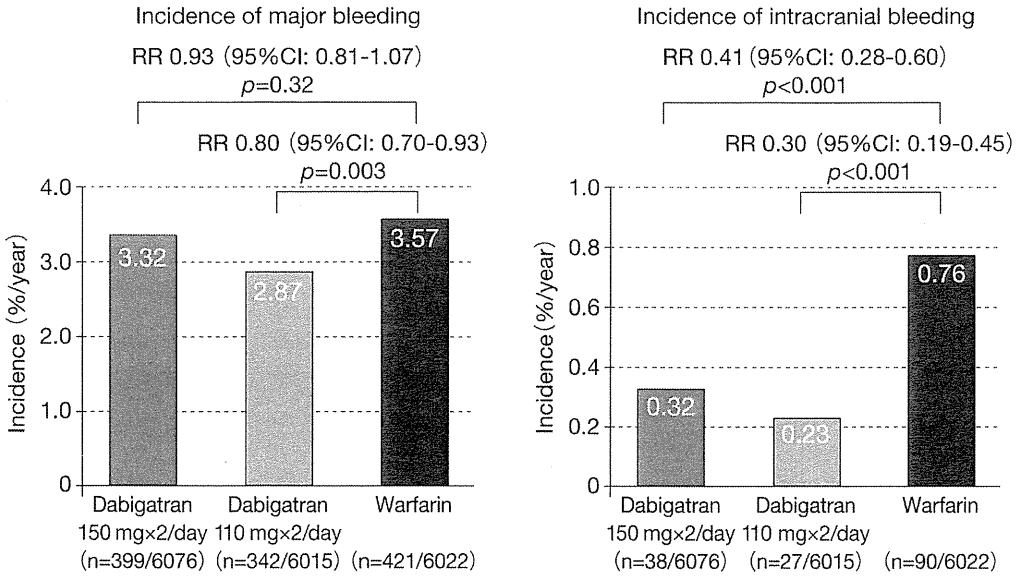
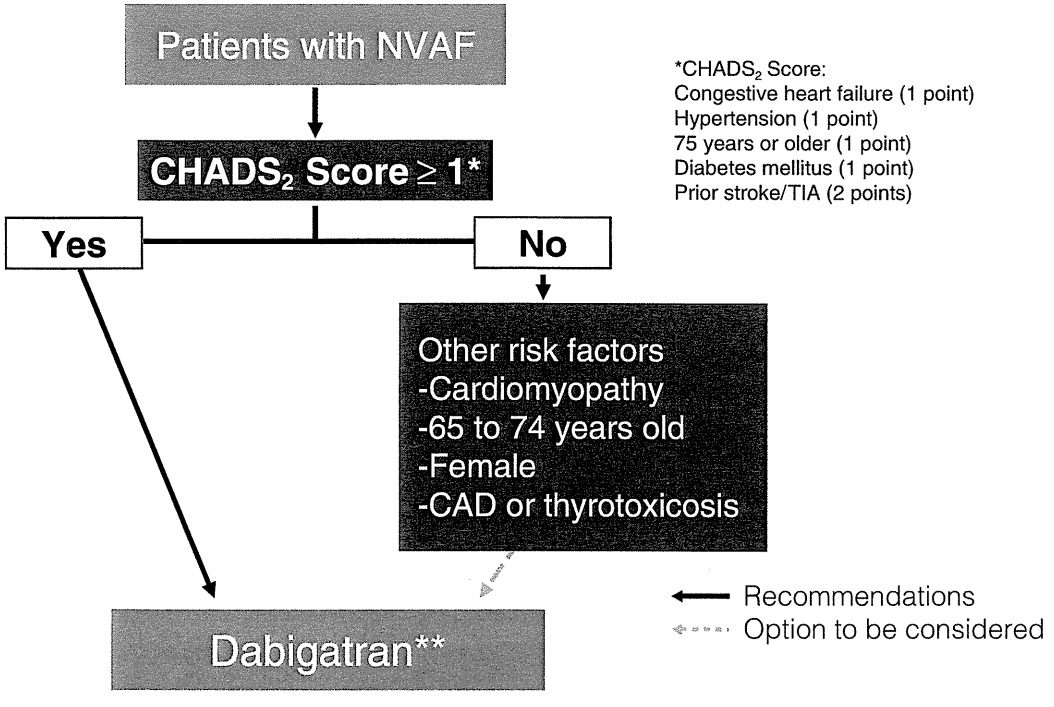


Figure 3. Incidence of major bleeding in the RE-LY study.[11,12] RR, relative risk. CI, confidence interval.



**The recommended dose of dabigatran etexilate for adults is 150 mg twice daily taken orally.
The dose can be reduced to 110 mg twice daily as needed.
For the following patients, a dose of 110 mg twice daily can be considered
-moderate renal impairment (30–50 mL/min CrCL)
-concomitant use of P-glycoprotein inhibitor (oral)
-70 years or older
-history of gastrointestinal bleeding

Figure 4. Antithrombotic therapy for atrial fibrillation with dabigatran.

Table 3. Timing of Discontinuation of Dabigatran Before Surgery for Each Level of Renal Function[19]

Renal function (Ccr, ml/min)	Half-life (h)*	Timing of discontinuation after last dose of dabigatran before surgery	
		Standard risk of bleeding	High risk of bleeding**
>80	13 (11–22)	24 h	2–4 days
>50 to ≤80	15 (12–34)	24 h	2–4 days
>30 to ≤50	18 (13–23)	≥48 h	4 days
≤30†	27 (22–35)	2–5 days	>5 days

*Data from renal impairment study in healthy volunteers, geometric mean (range).
**Types of surgery associated with a high risk of bleeding (or major surgery where complete hemostasis may be required) include but are not limited to cardiac surgery, neurosurgery, abdominal surgery or surgeries involving a major organ. Other procedures such as spinal anesthesia may also require complete hemostatic function. Other important determinants of bleeding risk include advancing age, comorbidities (eg, major cardiac, respiratory or liver disease) and concomitant use of antiplatelet therapy.
†Dabigatran is contraindicated for use in these patients.
Ccr, creatinine clearance rate.

(Figure 3). The rates of intracranial bleeding were 0.76% per year with warfarin, 0.23% per year with 110 mg dabigatran b.i.d. (P<0.001) and 0.32% per year with 150 mg dabigatran b.i.d. (P<0.001) (Figure 3).[11,12]

Based on these results, 110 mg dabigatran b.i.d. was associated with similar rates of stroke and systemic embolism and lower rates of major bleeding, and 150 mg dabigatran b.i.d. was associated with lower rates of stroke and systemic embolism but similar rates of major bleeding, compared with warfarin. Furthermore, both doses of dabigatran were associated with significantly lower rates of intracranial bleeding.[42] Overall, the RE-LY trial showed that dabigatran etexilate is a valid alternative to warfarin for oral anticoagulation in patients with AF and at risk of stroke.[11,12]

Patients in the RE-LY study had NVAF and at least one risk factor for stroke (previous stroke, transient ischemic attack or systemic embolism, left ventricular dysfunction, age ≥75 years, or ≥65 years with hypertension, coronary artery disease, or type 2 diabetes). Thus, the RE-LY findings in this population represent a significant breakthrough in anticoagulation management.[43]

Correct Clinical Use of Dabigatran

Dabigatran is a viable alternative to warfarin, offering greater efficacy, safety and convenience for many patients.[43] The effective use of the drug requires that the risk of bleeding be reduced and prevention of stroke be maximized. Based on the results of the RE-LY study and on subanalyses from that study,[11,12] appropriate therapeutic methods were evaluated for the use of the drug as anticoagulant therapy for AF patients. The RE-LY study included 5,775 patients (31.9%) with a $CHADS_2$ score of 0–1,[11] and consistent efficacy and safety profiles were observed in subgroups of patients with $CHADS_2$ scores of 0–1, 2 and 3–6.[44]

Evidence-based data suggest that dabigatran is recommended for patients with NVAF and a $CHADS_2$ score ≥1 (Figure 4) (Class I, Evidence level B).[11,12,44] The optimal dosage and frequency of administration in adults seems to be 150 mg (2×75-mg capsules) b.i.d., which can be reduced to 110 mg (1×110-mg capsule) b.i.d. as needed. In patients with moderate renal dysfunction (creatinine clearance of 30–50 ml/min), with concomitant use of P-glycoprotein inhibitors, aged ≥70 years, and with history of gastrointestinal bleeding, 110 mg dabigatran b.i.d. can be considered. For patients with a $CHADS_2$ score <1 and other risk factors, including cardiomyopathy, age 65–74 years, female, coronary artery disease, or thyrointoxication, dabigatran is an option to be considered.[11,12,44]

Administration of Dabigatran During Cardioversion In the RE-LY study, dabigatran and warfarin were administered continuously during cardioversion. Data collected before, during and 30 days after cardioversion were analyzed. A total of 1,983 cardioversions were performed in 1,270 patients during the RE-LY study. Most cardioversions were electric, being performed in 85.6%, 81.9% and 83.3% of patients in the 110 mg and 150 mg dabigatran groups, and the warfarin group, respectively.[45] The incidence of stroke or generalized embolism within 30 days of cardioversion was 0.77%, 0.30% and 0.60%, respectively. Major bleeding was infrequent in all groups. The RE-LY trial showed that dabigatran and warfarin offer similar efficacy in patients undergoing cardioversion.[45]

The Japanese guidelines for AF recommend that warfarin should be administered for 3 weeks before and 4 weeks after cardioversion in patients with AF lasting ≥48 h (or of unknown duration) to achieve an INR of 2.0–3.0 in patients <70 years old, or an INR of 1.6–2.6 in patients ≥70 years old.[4] A subgroup analysis of the RE-LY study revealed that the administration of dabigatran offers a safe alternative to warfarin for the prevention of stroke in AF patients undergoing cardioversion.[45] Thus, although warfarin is recommended in the current guidelines,[4] dabigatran could be used instead, but with better safety (Class I, Evidence level B).

Tooth Extraction or Surgery Treatment with antithrombotic drugs should be continued during tooth extraction.[4] Randomized controlled trials and observational studies have reported that tooth extraction can be safely performed in patients receiving antithrombotic drugs.[46–49] It is generally considered that the same recommendation applies to dabigatran, although there is currently no evidence from patients undergoing tooth extraction.

Patients with therapeutic levels of dabigatran undergoing elective surgery or invasive procedures are at increased risk of bleeding; therefore, surgical interventions may require temporary discontinuation of dabigatran therapy.[19] Depending on the degree of renal impairment and risk of bleeding, dabigatran should be stopped at least 24 h before elective surgery.[19]

In patients at higher risk of bleeding or in major surgery where complete hemostasis may be required, dabigatran should be stopped 2–4 days before surgery (Table 3)[19] and an alternative therapy, such as heparin, should be considered. The same criteria for discontinuing anticoagulant therapy before surgery were used in the RE-LY study.

Once postoperative hemostasis is confirmed, the administration of dabigatran should be restarted as soon as clinically indicated.[19] Because of its rapid onset, bridging to heparin at restart is generally unnecessary, unless oral administration is not feasible, in which case parenteral heparinization should be considered.[19]

Treatment of Bleeding Bleeding is the major adverse reaction of anticoagulant drugs and is associated with significant morbidity and long-term adverse outcomes, including increased rates of mortality.[50–52] In the event of bleeding complications in patients receiving dabigatran, general emergency treatment should be conducted.

Dabigatran should be discontinued temporarily or permanently depending on the severity of hemorrhagic complications. The cause of bleeding should be confirmed and surgical hemostasis performed. Because dabigatran predominantly undergoes renal excretion, adequate diuresis should be maintained. Other supportive strategies to control severe bleeding include mechanical compression and transfusion of blood products (packed red cells or fresh frozen plasma, depending on associated anemia or coagulopathy), hemodialysis[19,53] and high-volume hemofiltration.[54] Within 2 h of oral administration, gastric lavage and adsorption to activated charcoal can be considered.

Recombinant activated factor VII (rFVIIa; NovoSeven®, Novo Nordisk, Bagsvaerd, Denmark)[55] and prothrombin complex concentrates[56] can also be useful to rapidly reverse coagulopathy. However, there are no published clinical data on the use of these agents in patients receiving dabigatran and information is limited for the other new oral anticoagulants.[57] Therefore, their use in treating anticoagulant-associated bleeding is based on a combination of preclinical data, anecdotal case reports, and the absence of alternative therapies that might be effective.[58]

Methods of Switching Between Anticoagulant Drugs

Dabigatran is a viable alternative to warfarin, improving efficacy and safety in many respects for many patients.[43] To switch from warfarin to dabigatran, the administration of warfarin should be discontinued until the INR is <2.0.[9] To switch from dabigatran to other injectable anticoagulant drugs, the change should be made 12 h after the administration of dabigatran. To transfer patients from other injectable anticoagulant drugs to dabigatran, dabigatran should be administered 2 h before the next dose or at the time of discontinuation in the case of continuous intravenous injection.

Future Scenarios for Antithrombotic Therapy for AF

Anticoagulation remains the cornerstone for the prevention and treatment of thromboembolic disorders, which are among the major causes of morbidity and mortality.[8] Well-established agents, although effective, have significant limitations.[8] Warfarin reduces the risk of stroke in patients with AF, but increases the risk of hemorrhage and is difficult to use.[11,12]

The new oral anticoagulants may provide better alternatives to warfarin for stroke prevention in patients with AF because they do not require routine coagulation monitoring or dose adjustment. They are administered orally at fixed doses, have a rapid onset of action, predictable pharmacokinetics and pharmacodynamics, and minimal food–drug or drug–drug interactions.[8] Adopting the novel oral agents will considerably simplify the therapeutic strategy. In the acute treatment phase, an oral regimen will be sufficient for the whole treatment duration, without the need for bridging therapy from a parenteral anticoagulant.[8] A single-drug therapy would provide convenience both within and outside the hospital setting. Indeed, the introduction of new oral anticoagulants may reduce the length of hospital stay, facilitating discharge, particularly in patients who cannot or are unwilling to carry out subcutaneous injection themselves.

Clinical studies have established the non-inferiority, or even superiority, of several regimens of the new oral agents compared with conventional therapy.[8] In the RE-LY trial, for example, the rate of intracranial bleeding among patients treated with dabigatran was less than one-third of that among patients treated with warfarin, without a reduction in the efficacy against stroke. The benefit of dabigatran may be explained in part by the twice-daily dosing regimen. Because dabigatran has a half-life of 12–17 h, twice-daily dosing reduces the variability in the anticoagulation effect, especially compared with that of warfarin, which is difficult to control. Warfarin inhibits several components of the coagulation pathway, including factors II, VII, IX and X, and proteins C and S. In contrast, dabigatran selectively inhibits thrombin, and may have antithrombotic efficacy while preserving some of the other hemostatic mechanisms in the coagulation system. In this way, it might mitigate the risk of bleeding such as intracranial hemorrhage.[11]

Many physicians have concerns about administering warfarin, because it has a narrow therapeutic window and requires routine coagulation monitoring and dose adjustment.[8] A meta-analysis showed that in community-based practice in the United States, patients with AF who received warfarin spent only 51% of their time within the therapeutic INR of 2.0–3.0,[59] leaving them at risk of either thromboembolism or bleeding complications.

Dabigatran (a DTI) could replace warfarin in this indication, especially because of its superior efficacy and better safety profile.[8] The RE-LY trial confirmed that the former is a valid alternative to conventional therapy in patients with NVAF at risk of stroke.[43] After a decade of failures, these findings signify a breakthrough in anticoagulation management.[43]

However, novel anticoagulant agents have potential limitations. Of particular concern is that there are no antidotes to any of the novel oral agents with anticoagulant activity. Accordingly, clinicians must be aware of the risk of potentially severe hemorrhage, particularly in patients undergoing surgery. However, the lack of specific antidotes (in case immediate reversal is needed) is a theoretical rather than a practical liability for the newer agents because their half-lives are relatively short compared with that of warfarin, meaning the risk of severe hemorrhage is much reduced.[8]

Dabigatran has been approved in the United States and in Japan for the prevention of stroke and systemic embolism in patients with NVAF. Studies on the use of dabigatran in tooth extraction have yet to be conducted. Meanwhile, phase III clinical trials for the factor Xa inhibitors have only recently been or are yet to be completed or published. Despite their known benefits, physicians in general practice are often unwilling to adopt new therapies, and it may take many years for findings from such studies as RE-LY to filter down to routine clinical care. For this reason, it is important for specialists to promote knowledge about dabigatran and advocate its widespread use. To ensure patient safety, however, it is equally vital to educate physicians about guidelines on its appropriate administration. In these ways, we can make it easier for physicians to prescribe effective levels of anticoagulation and easier for patients to comply with treatment plans.

References

1. Schirmer SH, Baumhäkel M, Neuberger HR, Hohnloser SH, van Gelder IC, Lip GY, et al. Novel anticoagulants for stroke prevention in atrial fibrillation: Current clinical evidence and future developments. *J Am Coll Cardiol* 2010; **56:** 2067–2076.
2. Writing Group Members, Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, et al. Heart disease and stroke statistics–2010 update: A report from the American Heart Association. *Circulation* 2010; **121:** e46–e215.
3. Feinberg WM, Blackshear JL, Laupacis A, Kronmal R, Hart RG. Prevalence, age distribution, and gender of patients with atrial fibrillation: Analysis and implications. *Arch Intern Med* 1995; **155:** 469–473.
4. JCS Joint Working Group. Guidelines for pharmacotherapy of atrial fibrillation (JCS 2008): Digest version. *Circ J* 2010; **74:** 2479–2500.
5. Ohsawa M, Okayama A, Sakata K, Kato K, Itai K, Onoda T, et al. Rapid increase in estimated number of persons with atrial fibrillation in Japan: An analysis from national surveys on cardiovascular diseases in 1980, 1990 and 2000. *J Epidemiol* 2005; **15:** 194–196.
6. Inoue H, Fujiki A, Origasa H, Ogawa S, Okumura K, Kubota I, et al. Prevalence of atrial fibrillation in the general population of Japan: An analysis based on periodic health examination. *Int J Cardiol* 2009; **137:** 102–107.
7. Koretsune Y. The incidence of ischemic stroke: Paroxysmal AF vs persistent/permanent AF. *Circ J* 2009; **73:** 1393–1394.
8. Mavrakanas T, Bounameaux H. The potential role of new oral anticoagulants in the prevention and treatment of thromboembolism. *Pharmacol Ther* 2011; **130:** 46–58.
9. Ezekowitz MD, Connolly S, Parekh A, Reilly PA, Varrone J, Wang S, et al. Rationale and design of RE-LY: Randomized evaluation of long-term anticoagulant therapy, warfarin, compared with dabigatran. *Am Heart J* 2009; **157:** 805–810, 810.e801–e802.
10. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: Antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007; **146:** 857–867.
11. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009; **361:** 1139–1151.
12. Connolly SJ, Ezekowitz MD, Yusuf S, Reilly PA, Wallentin L; Randomized Evaluation of Long-Term Anticoagulation Therapy Investigators. Newly identified events in the RE-LY trial. *N Engl J Med* 2010; **363:** 1875–1876.
13. Matchar DB, Samsa GP, Cohen SJ, Oddone EZ, Jurgelski AE. Improving the quality of anticoagulation of patients with atrial fibrillation in managed care organizations: Results of the managing anticoagulation services trial. *Am J Med* 2002; **113:** 42–51.
14. Umer Usman MH, Raza S, Raza S, Ezekowitz M. Advancement in antithrombotics for stroke prevention in atrial fibrillation. *J Interv Card Electrophysiol* 2008; **22:** 129–137.
15. Inoue H, Nozawa T, Hirai T, Goto S, Origasa H, Shimada K, et al. Sex-related differences in the risk factor profile and medications of patients with atrial fibrillation recruited in J-TRACE. *Circ J* 2010; **74:** 650–654.
16. Gao F, Zhou YJ, Wang ZJ, Shen H, Liu XL, Nie B, et al. Comparison of different antithrombotic regimens for patients with atrial fibrillation undergoing drug-eluting stent implantation. *Circ J* 2010; **74:** 701–708.
17. Obata H, Watanabe H, Ito M, Hirono S, Hanawa H, Kodama M, et al. Effects of combination therapy with warfarin and bucolome for anticoagulation in patients with atrial fibrillation. *Circ J* 2010; **75:** 201–203.
18. Kubitza D, Haas S. Novel factor Xa inhibitors for prevention and treatment of thromboembolic diseases. *Expert Opin Invest Drugs* 2006; **15:** 843–855.
19. van Ryn J, Stangier J, Haertter S, Liesenfeld KH, Wienen W, Feuring M, et al. Dabigatran etexilate--a novel, reversible, oral direct thrombin inhibitor: Interpretation of coagulation assays and reversal of anticoagulant activity. *Thromb Haemost* 2010; **103:** 1116–1127.
20. Mann KG. The biochemistry of coagulation. *Clin Lab Med* 1984; **4:** 207–220.
21. Kumar R, Béguin S, Hemker HC. The effect of fibrin clots and clot-bound thrombin on the development of platelet procoagulant activity. *Thromb Haemost* 1995; **74:** 962–968.
22. Weitz JI. New oral anticoagulants in development. *Thromb Haemost* 2010; **103:** 62–70.
23. Stangier J. Clinical pharmacokinetics and pharmacodynamics of the oral direct thrombin inhibitor dabigatran etexilate. *Clin Pharmacokinet* 2008; **47:** 285–295.
24. Weitz JI, Bates SM. New anticoagulants. *J Thromb Haemost* 2005; **3:** 1843–1853.
25. Testa L, Andreotti F, Biondi Zoccai GG, Burzotta F, Bellocci F, Crea F. Ximelagatran/melagatran against conventional anticoagulation: A meta-analysis based on 22,639 patients. *Int J Cardiol* 2007; **122:** 117–124.
26. Francis CW, Berkowitz SD, Comp PC, Lieberman JR, Ginsberg JS, Paiement G, et al. Comparison of ximelagatran with warfarin for the prevention of venous thromboembolism after total knee replacement. *N Engl J Med* 2003; **349:** 1703–1712.
27. Schulman S, Wåhlander K, Lundström T, Clason SB, Eriksson H, THRIVE III Investigators. Secondary prevention of venous thromboembolism with the oral direct thrombin inhibitor ximelagatran. *N Engl J Med* 2003; **349:** 1713–1721.
28. Fiessinger JN, Huisman MV, Davidson BL, Bounameaux H, Francis CW, Eriksson H, et al. Ximelagatran vs low-molecular-weight heparin and warfarin for the treatment of deep vein thrombosis: A randomized trial. *JAMA* 2005; **293:** 681–689.
29. Olsson SB, Executive Steering Committee of the SPORTIF III Investigators. Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin in patients with non-valvular atrial fibrillation (SPORTIF III): Randomised controlled trial. *Lancet* 2003; **362:** 1691–1698.
30. Albers GW, Diener HC, Frison L, Grind M, Nevinson M, Partridge S, et al. Ximelagatran vs warfarin for stroke prevention in patients with nonvalvular atrial fibrillation: A randomized trial. *JAMA* 2005; **293:** 690–698.
31. Ogata K, Mendell-Harary J, Tachibana M, Masumoto H, Oguma T, Kojima M, et al. Clinical safety, tolerability, pharmacokinetics, and pharmacodynamics of the novel factor Xa inhibitor edoxaban in healthy volunteers. *J Clin Pharmacol* 2010; **50:** 743–753.
32. Gerotziafas GT, Elalamy I, Depasse F, Perzborn E, Samama MM. In vitro inhibition of thrombin generation, after tissue factor pathway activation, by the oral, direct factor Xa inhibitor rivaroxaban. *J Thromb Haemost* 2007; **5:** 886–888.
33. Kubitza D, Becka M, Mueck W, Zuehlsdorf M. Safety, tolerability, pharmacodynamics, and pharmacokinetics of rivaroxaban [an oral, direct factor Xa inhibitor] are not affected by aspirin. *J Clin Pharmacol* 2006; **46:** 981–990.
34. ROCKET AF Study Investigators. Rivaroxaban-once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation: Rationale and design of the ROCKET AF study. *Am Heart J* 2010; **159:** 340–347, e341.
35. Patel MR, ROCKET AF Executive Steering Committee. Stroke prevention using the oral direct factor Xa inhibitor rivaroxaban compared with warfarin in patients with nonvalvular atrial fibrillation (ROCKET AF). *Circulation* 2010; **122:** 2215–2226 (abstract 21839).
36. Lopes RD, Alexander JH, Al-Khatib SM, Ansell J, Diaz R, Easton JD, et al. Apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation (ARISTOTLE) trial: Design and rationale. *Am Heart J* 2010; **159:** 331–339.
37. Connolly SJ, Eikelboom J, Joyner C, Diener HC, Hart R, Golitsyn S, et al. Apixaban in patients with atrial fibrillation. *N Engl J Med* 2011; **364:** 806–817.
38. Blech S, Ebner T, Ludwig-Schwellinger E, Stangier J, Roth W. The metabolism and disposition of the oral direct thrombin inhibitor, dabigatran, in humans. *Drug Metab Dispos* 2008; **36:** 386–399.
39. Stangier J, Rathgen K, Stähle H, Gansser D, Roth W. The pharmacokinetics, pharmacodynamics and tolerability of dabigatran etexilate, a new oral direct thrombin inhibitor, in healthy male subjects. *Br J Clin Pharmacol* 2007; **64:** 292–303.
40. Hauptmann J, Stürzebecher J. Synthetic inhibitors of thrombin and factor Xa: From bench to bedside. *Thromb Res* 1999; **93:** 203–241.
41. Wienen W, Stassen JM, Priepke H, Ries UJ, Hauel N. In-vitro profile and ex-vivo anticoagulant activity of the direct thrombin inhibitor dabigatran and its orally active prodrug, dabigatran etexilate. *Thromb Haemost* 2007; **98:** 155–162.
42. Gage BF. Can we rely on RE-LY? *N Engl J Med* 2009; **361:** 1200–1202.
43. Heidbuchel H, Verhamme P. Dabigatran for stroke prevention in atrial fibrillation: From RE-LY to daily clinical practice. *Acta Cardiol* 2010; **65:** 491–497.
44. Oldgren J, Alings M, Darius H, Eikelboom J, Ezekowitz M, Parekh A, et al, editors. Dabigatran versus warfarin in atrial fibrillation patients with low, moderate, and high CHADS2 Score: A RE-LY subgroup analysis. *In*: Proceedings of ACC10, March 14–16, 2010. Atlanta: American College of Cardiology.

45. Nagarakanti R, Ezekowitz MD, Oldgren J, Yang S, Chernick M, Aikens TH, et al. Dabigatran versus warfarin in patients with atrial fibrillation: An analysis of patients undergoing cardioversion. *Circulation* 2011; **123:** 131–136.
46. Evans IL, Sayers MS, Gibbons AJ, Price G, Snooks H, Sugar AW. Can warfarin be continued during dental extraction? Results of a randomized controlled trial. *Br J Oral Maxillofac Surg* 2002; **40:** 248–252.
47. Ardekian L, Gaspar R, Peled M, Brener B, Laufer D. Does low-dose aspirin therapy complicate oral surgical procedures? *J Am Dent Assoc* 2000; **13:** 331–335.
48. Morimoto Y, Niwa H, Yoneda T, Kimura K, Yasaka M, Minematsu K. Hemostatic management of tooth extraction in patients undergoing antithrombotic therapy. *J Jpn Stomatol Soc* 2004; **53:** 74–80 (in Japanese).
49. Makiura N, Yasaka M, Minematsu K. Management of hemorrhagic complications at dental extraction in patients treated with warfarin. *Jpn J Stroke* 2005; **27:** 424–427 (in Japanese).
50. Rao SV, O'Grady K, Pieper KS, Granger CB, Newby LK, Van de Werf F, et al. Impact of bleeding severity on clinical outcomes among patients with acute coronary syndromes. *Am J Cardiol* 2005; **96:** 1200–1206.
51. Eikelboom JW, Mehta SR, Anand SS, Xie C, Fox KA, Yusuf S. Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. *Circulation* 2006; **114:** 774–782.
52. Manoukian SV, Feit F, Mehran R, Voeltz MD, Ebrahimi R, Hamon M, et al. Impact of major bleeding on 30-day mortality and clinical outcomes in patients with acute coronary syndromes: An analysis from the ACUITY Trial. *J Am Coll Cardiol* 2007; **49:** 1362–1368.
53. Stangier J, Rathgen K, Stähle H, Mazur D. Influence of renal impairment on the pharmacokinetics and pharmacodynamics of oral dabigatran etexilate: An open-label, parallel-group, single-centre study. *Clin Pharmacokinet* 2010; **49:** 259–268.
54. Benz K, Nauck MA, Böhler J, Fischer KG. Hemofiltration of recombinant hirudin by different hemodialyzer membranes: Implications for clinical use. *Clin J Am Soc Nephrol* 2007; **2:** 470–476.
55. Sartori MT, Imbergamo S, Zanon E, Bonaccorso G, Pittoni G, Feltracco P, et al. Effect of recombinant activated factor VII in critical bleeding: Clinical experience of a single center. *Clin Appl Thromb Hemost* 2009; **15:** 628–635.
56. Leissinger CA, Blatt PM, Hoots WK, Ewenstein B. Role of prothrombin complex concentrates in reversing warfarin anticoagulation: A review of the literature. *Am J Hematol* 2008; **83:** 137–143.
57. Fernlöf G, Sjöström BM, Lindell KM, Wall UE. Management of major bleedings during anticoagulant treatment with the oral direct thrombin inhibitor ximelagatran or warfarin. *Blood Coagul Fibrinolysis* 2009; **20:** 667–674.
58. Crowther MA, Warkentin TE. Managing bleeding in anticoagulated patients with a focus on novel therapeutic agents. *J Thromb Haemost* 2009; **7**(Suppl 1)**:** 107–110.
59. Baker WL, Cios DA, Sander SD, Coleman CI. Meta-analysis to assess the quality of warfarin control in atrial fibrillation patients in the United States. *J Manag Care Pharm* 2009; **15:** 244–252.

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ORIGINAL ARTICLE
Heart Failure

Significant Increase in the Incidence of Ventricular Arrhythmic Events After an Intrathoracic Impedance Change Measured With a Cardiac Resynchronization Therapy Defibrillator

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Background: Cardiac resynchronization therapy defibrillator (CRT-D) devices are now capable of monitoring changes in intrathoracic impedance. Intrathoracic impedance monitoring resulting in a fluid index threshold crossing has been proven to predict heart failure (HF) exacerbations. We retrospectively investigated the relationship between changes in intrathoracic impedance and the occurrence of arrhythmic events.

Methods and Results: From 282 patients with New York Heart Association class III or IV HF who were implanted with a CRT-D device with a fluid index feature based on intrathoracic impedance monitoring capabilities, arrhythmic events were retrospectively analyzed in terms of the threshold crossings. The patients were divided into 2 groups: those with fluid index threshold crossings and those without threshold crossings. A total of 4,725 tachyarrhythmic events were reported in 129 patients (46%), and there were 221 fluid index crossing events in 145 patients (51%) during 10.0±3.2 months. Tachyarrhythmic events were more frequently recorded in patients with threshold crossing events than in those who did not experience a threshold crossing (3,241 vs. 1,484 events, P<0.0001). Ventricular tachyarrhythmic events mainly occurred within the first 30 days after the threshold crossing event; however, a similar trend was not observed for the atrial tachyarrhythmic events.

Conclusions: Intrathoracic impedance monitoring may predict arrhythmic events, especially ventricular arrhythmias, in patients with HF and provides an additional management tool. (*Circ J* 2011; **75:** 2614–2620)

Key Words: Arrhythmia; Heart failure; Implantable cardioverter-defibrillator; Intrathoracic impedance

Several studies have suggested that intrathoracic impedance monitoring may be useful for the early detection of cardiac decompensation in patients with heart failure (HF).[1–9] Yu et al reported that the intrathoracic impedance correlated inversely with pulmonary capillary wedge pressure and net fluid loss in HF patients hospitalized for fluid overload.[1] Cardiac resynchronization therapy defibrillator (CRT-D) devices are now capable of monitoring intrathoracic impedance using a fluid index algorithm that can automatically alert the clinician or patient if the intrathoracic impedance decreases significantly. A decrease in intrathoracic impedance may primarily indicate pulmonary fluid accumulation because of cardiac decompensation. Furthermore, Catanzariti et al showed that a device-based algorithm facilitated the detection of HF deterioration and reduced the number of HF hospitalizations.[7]

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Although intrathoracic impedance monitoring was developed to detect clinical deterioration of HF, its application for predicting the occurrence of arrhythmias has not been fully explored. The aim of this analysis was to evaluate the relationship between changes in intrathoracic impedance and the subsequent occurrence of cardiac arrhythmias.

Methods

Study Design

The study patient cohort was determined retrospectively from the Concerto-AT study,[10] an international, multicenter, pro-

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Table 1. RR Analysis of Arrhythmic Episodes

Parameter	All arrhythmias		Atrial arrhythmias		Ventricular arrhythmias	
	RR (95%CI)	P value	RR (95%CI)	P value	RR (95%CI)	P value
TC	1.87 (1.75–1.99)	<0.0001	2.01 (1.86–2.16)	<0.0001	1.55 (1.37–1.74)	<0.0001
Baseline NYHA	3.01 (2.78–3.26)	<0.0001	2.31 (2.09–2.55)	<0.0001	5.48 (4.79–6.28)	<0.0001
Sex	1.28 (1.20–1.36)	<0.0001	1.07 (0.99–1.15)	0.072	2.08 (1.86–2.34)	<0.0001
Age	1.00 (1.00–1.00)	<0.0001	1.01 (1.00–1.01)	0.002	1.00 (1.00–1.01)	0.142

RR, relative risk; CI, confidence interval; TC, threshold crossing; NYHA, New York Heart Association.

spective, non-randomized clinical trial evaluating the efficacy of atrial cardioversion in patients with chronic HF. A total of 282 patients from 41 institutions in the United States, Europe, and Japan who were successfully implanted with a CRT-D device (Concerto, Medtronic, Minneapolis, MN, USA) between January 27, 2006 and May 22, 2007 were included in this analysis. The detailed patient selection criteria have been previously described.[10] Briefly, patients were eligible if they had a standard indication for a CRT-D device, QRS duration ≥120 ms, New York Heart Association (NYHA) functional class III or IV HF, and left ventricular ejection fraction (LVEF) ≤35%, despite optimal medical therapy. Patients with permanent atrial fibrillation (AF) were excluded. All patients were required to meet all enrollment inclusion criteria, have no exclusion criteria, and provide written informed consent.

Intrathoracic Impedance Monitoring Algorithm

The CRT-D device used in the study had several additional diagnostic capabilities for HF management, including intrathoracic impedance monitoring. The details of the intrathoracic impedance monitoring and derived OptiVol fluid index algorithm used in the study device have been described in detail previously.[1,4,6] In brief, intrathoracic impedance was calculated once daily as an average of 64 impedance measurements between the right ventricular defibrillation lead coil and the CRT-D device can, which was measured every 20 min from 12 PM to 5 PM, the best time of day to observe a fluid overload condition, in order to minimize the effects of respiration and posture on impedance. The daily impedance was compared with a reference, which tracked the trends in the preceding daily impedance values. The cumulative difference between the daily and reference impedances was used to calculate the OptiVol fluid index. The device was programmed to store the data if the fluid index increased above a programmed threshold, nominally set at 60 ohm-days, which came from the results of a previous study.[1] The fluid index was inactive for the first 34 days after device implantation to allow for 30 days of post-implant pocket healing and 4 days to draw the reference impedance.

Device Programming and Definitions

Baseline device programming including arrhythmic event detection and treatment was at the discretion of the implanting physician. A full interrogation of the CRT-D device was performed at each visit. Arrhythmic events implied there were either atrial or ventricular tachyarrhythmias. Atrial tachyarrhythmias included atrial tachycardia (AT), atrial flutter (AFL), and AF. Sustained ventricular tachycardia (VT) or fibrillation (VF) was considered a ventricular tachyarrhythmic event. Non-sustained or self-terminating VT was excluded from the analysis. Arrhythmic events that occurred within the first 34 days after the implant procedure were excluded from the analysis because the thoracic impedance fluid index had not been established. The study patients were classified into 2 groups: with and without OptiVol fluid index threshold crossings. Patient follow-up occurred at 1, 3, 6, and 12 months post-device implantation.

Statistical Analysis

Baseline characteristics were compared between the patients with and without a fluid index crossing. Exploratory analyses, including a contingency table analysis and univariate regression, were conducted to evaluate the association between fluid index crossings and patients' baseline characteristics such as age, sex, and cardiac disease history. The Poisson regression method was then applied to investigate whether a fluid index threshold crossing was a predictor of arrhythmic events after adjustment for the patient's baseline characteristics.[11]

Results

Study Patients

The baseline characteristics of all the study patients were described in detail previously.[10] In brief, 71% were male, 93% had NYHA class III HF, 56% had ischemic cardiomyopathy, and the median age was 68.3 years. The mean QRS duration was 157.0±23.4 ms, and the mean LVEF was 23.3±6.8%. Baseline medications included angiotensin-converting inhibitors or angiotensin receptor blockers (87%), β-blockers (88%), and diuretics (85%). In terms of a history of arrhythmias, 112 patients (40%) had atrial arrhythmias, including AT, AFL, and AF, and 129 (46%) had ventricular arrhythmias, including sustained VT (18%) and VF (10%), at baseline. The mean follow-up duration was 10.0±3.2 months.

Arrhythmic Events

A total of 4,725 arrhythmic events occurred at least 34 days post-device implantation in 129 (46%) study patients, including 3,521 atrial events in 90 patients and 1,204 ventricular events in 70 patients. Ventricular arrhythmic events were successfully treated with antitachycardia pacing in 897 (74.5%) and direct current shock deliveries in 107 (8.9%) episodes; 200 (16.6%) ventricular events were not treated because the cycle lengths of most of those events were detected as only being in the MONITOR zone, which was programmed by each of the investigators.

In the regression analysis, the exploratory variables considered for the analysis were threshold crossing events, patient sex, age at device implantation, baseline NYHA functional class, LVEF, QRS duration, and ischemic vs. non-ischemic HF. As a result, the arrhythmic events were significantly associated with the occurrence of a fluid index threshold crossing, higher NYHA class at baseline, female sex, and age (Table 1). In particular, the occurrence of a fluid index threshold crossing and higher NYHA class at baseline were strongly associated with arrhythmic events during the follow-up period (relative

Table 2. Characteristics of TC (+) and TC (–) Groups at Enrolment

	TC (+) group* (n=145)	TC (–) group† (n=137)	P value
Male, n (%)	102 (70)	99 (72)	0.13
Age, years	68±12	66±11	0.23
NYHA functional class, n (%)			0.08
III	138 (95)	123 (90)	
IV	7 (5)	14 (10)	
QRS duration, ms	154.5±21.8	159.7±24.8	0.07
LVEF, %	22.8±6.8	23.7±6.8	0.30
Cause of heart failure, n (%)			0.18
Ischemic	88 (61)	70 (51)	
Non-ischemic	55 (38)	61 (45)	
Medications, n (%)			
ACE inhibitors or ARBs	123 (85)	121 (88)	0.39
Antiarrhythmic class I	9 (6)	4 (3)	0.26
Antiarrhythmic class III	35 (24)	32 (23)	0.88
β-blockers	127 (88)	121 (88)	0.85
Digitalis	50 (34)	58 (42)	0.18
Diuretics	119 (82)	122 (89)	0.10
Complete AV block, n (%)	9 (6)	12 (9)	0.41
Atrial tachyarrhythmias, n (%)	60 (41)	52 (38)	0.34
Ventricular tachyarrhythmias, n (%)	68 (47)	61 (45)	0.34

*Patients with TCs of the fluid index; †Patients with no TCs of the fluid index.
LVEF, left ventricular ejection fraction; ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; AV, atrioventricular. Other abbreviations see in Table 1.

Table 3. Relationship Between TC Episodes and Arrhythmic Events

	TC (+) group (n=145)*		TC (–) group (n=137)†		P value‡
	Episode	Patient	Episode	Patient	
VT/VF	753	36	451	34	0.002
AT/AF	2,488	52	1,033	38	<0.0001
Total	3,241	70	1,484	59	<0.0001

*Patients who had TCs of the fluid index; †patients who had no TCs of the fluid index; ‡P values were compared between the 2 groups using the number of episodes.
VT, ventricular tachycardia; VF, ventricular fibrillation; AT, atrial tachycardia; AF, atrial fibrillation. Other abbreviation see in Table 1.

risk (RR) 1.87, 95% confidence interval (CI) 1.75–1.99, P< 0.0001; and RR 3.01, 95%CI 2.78–3.26, P<0.0001, respectively). A fluid index threshold crossing and higher NYHA class at baseline were also strongly associated with atrial arrhythmic events (RR 2.01, 95%CI 1.86–2.16, P<0.0001; and RR 2.31, 95%CI 2.09–2.55, P<0.0001, respectively). The multiple regression analysis also suggested that a higher NYHA class at baseline was a risk factor for ventricular arrhythmias (RR 5.48, 95%CI 4.79–6.28, P<0.0001). Patients with fluid index threshold crossing events were 1.55-fold as likely to have ventricular events (RR 1.55, 95%CI 1.37–1.74, P<0.0001) as those without crossing events.

Association Between Intrathoracic Impedance and Arrhythmias

All 282 eligible study participants were grouped into 2 analysis cohorts: patients with at least 1 fluid index threshold crossing (TC (+) group, n=145) and those without a fluid index threshold crossing (TC (–) group, n=137). There were no significant differences between the 2 groups in the baseline characteristics (Table 2). Arrhythmic events in the TC (+) group occurred significantly more frequently than that in the TC (–) group (P<0.0001) (Table 3). Moreover, a statistically significant association was observed between fluid index threshold crossings and both atrial and ventricular arrhythmic events.

Time Course of Arrhythmic Events

In order to determine if intrathoracic impedance monitoring could be used as an indicator of the occurrence of arrhythmic events, the temporal relationship between the fluid index threshold crossings and subsequent arrhythmic events was investigated. Of the TC (+) group patients, 70 (48%) had at least 1 arrhythmic event during the follow-up period. Moreover, 45 of the TC (+) patients experienced arrhythmic events after a threshold crossing. Ventricular arrhythmic events occurred after a threshold crossing in 23 patients (16%) in the TC (+) group (Figure 1). An analysis of the time course of those ventricular arrhythmic events showed that a significantly greater proportion of ventricular arrhythmic events occurred within 1 month of a fluid index threshold crossing than occurred at least 1 month after a fluid index threshold crossing (55.8% vs. 44.2%, P=0.0359) (Figure 2). In contrast, the proportion of atrial arrhythmic events occurring at least 1 month following a threshold crossing was significantly higher than that occurring within 1 month of a fluid index threshold crossing (54.9% vs. 45.1%, P=0.0004) (Figure 3). In summary, ven-

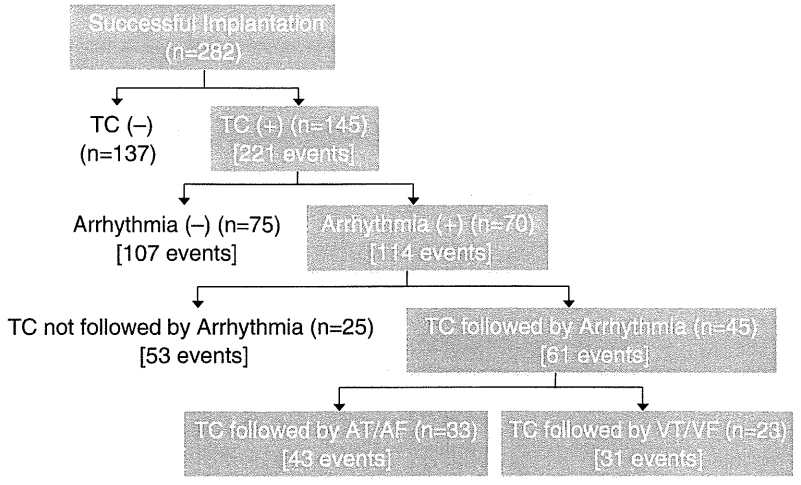

Figure 1. Event time assessment. Of 282 patients 145 (51%) had threshold crossing (TC) events. Atrial and ventricular arrhythmic events occurred after TCs in 33 and 23 TC(+) patients, respectively; 11 TC(+) patients experienced both atrial and ventricular arrhythmic events after TCs. AT, atrial tachycardia; AF, atrial fibrillation; VT, ventricular tachycardia; VF, ventricular fibrillation.

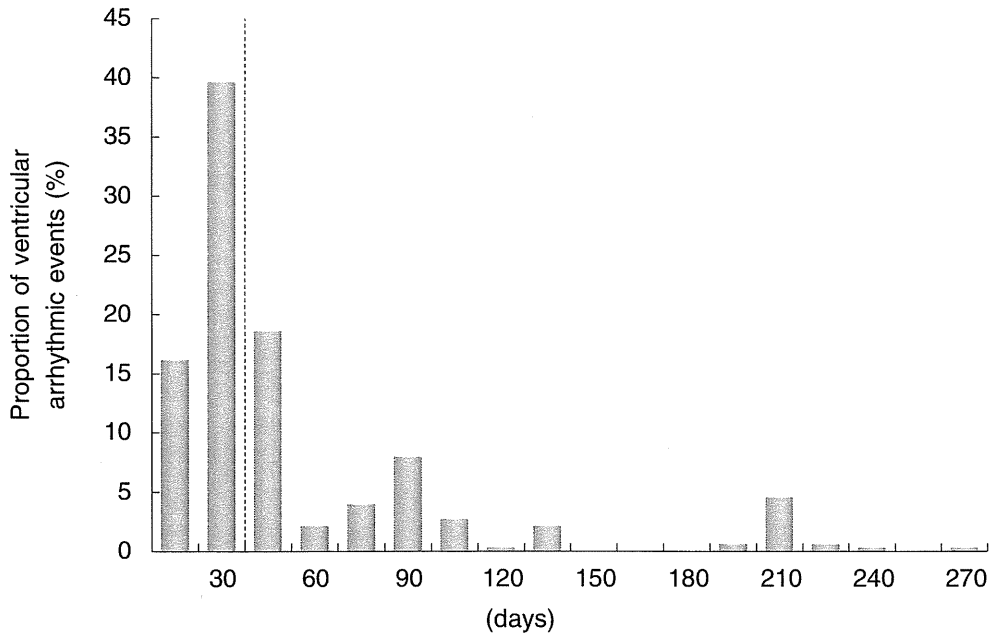

Figure 2. Relationship between the proportion of ventricular arrhythmic events after a fluid index threshold crossing (TC) and the period of time from the occurrence of the TC. The proportion of ventricular arrhythmic events within 1 month of a fluid index TC was significantly higher than that after 1 month (55.8% vs. 44.2%, P=0.0359).

tricular arrhythmic events were more likely to occur within 1 month after a threshold crossing. However, no such trend was observed for the atrial arrhythmic events.

Discussion

Sudden cardiac death is often associated with severe HF, presumably because of ventricular tachyarrhythmias.[12–14] The occurrence of ventricular arrhythmias may increase because of the existence of myocardial mechanoelectrical feedback[15,16] or the hemodynamic consequences of sympathoadrenergic hyperactivity,[17] concomitant with deteriorating HF. Similarly, the prevalence of atrial tachyarrhythmias, including AF, increases with the severity of HF.[18–22] HF results in changes to the atrium that predispose it to the development and maintenance of atrial arrhythmias.[23] Decreased atrial refractory periods, slowed atrial conduction, or increased heterogeneity during atrial repolarization can promote the development and maintenance of atrial arrhythmias.[24] Prior studies have focused their attention on intrathoracic impedance as an indicator of HF decompensation. However, consideration has also been given to additional applications of intrathoracic impedance monitoring in the man-

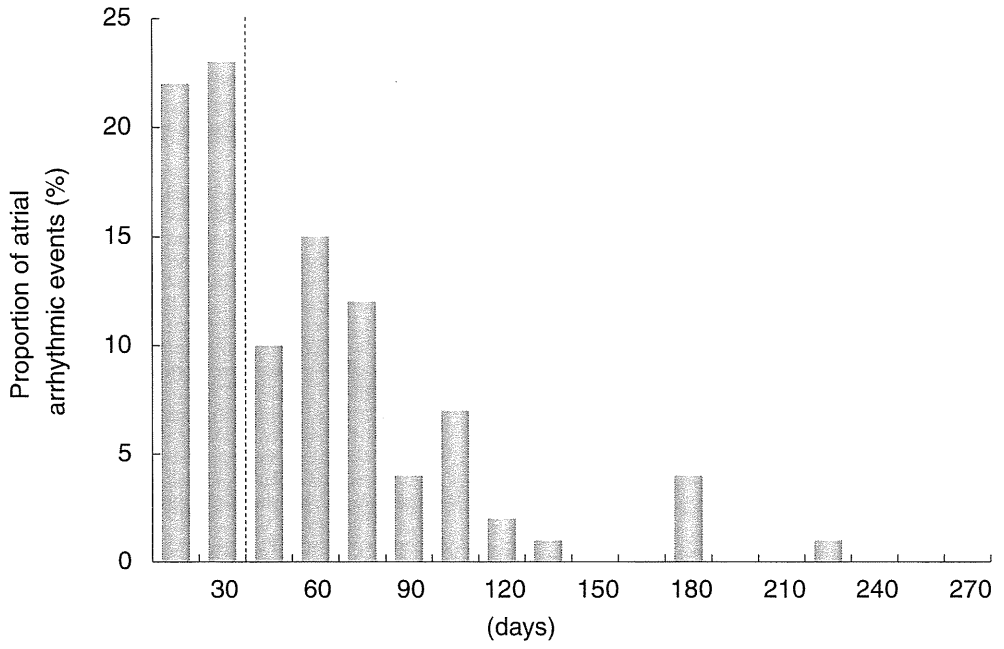

Figure 3. Relationship between the proportion of atrial arrhythmic events after a fluid index threshold crossing (TC) and the period of time from the occurrence of the TC. The proportion of atrial arrhythmic events after 1 month of the TC was significantly higher than that within 1 month (54.9% vs. 45.1%, P=0.0004).

agement of HF. Andriulli et al reported a case of repeated VT episodes preceded by an acutely lowered thoracic impedance recorded with a CRT-D device.[25] Moore et al reported that ventricular arrhythmic episodes were preceded by cumulative differences between the averaged daily and reference impedance on the dates leading up to the ventricular arrhythmic events, which was used as a diagnostic indicator rather than the OptiVol fluid index.[26] As for atrial arrhythmic events, Jhanjee et al reported that worsening pulmonary congestion evidenced by fluid index threshold crossings was associated with an increase in the frequency of atrial arrhythmias, and that those arrhythmias may be responsible for triggering episodic pulmonary congestion more often than previously suspected.[27]

Our retrospective observational study both confirmed and extended these findings by demonstrating a relationship between changes in intrathoracic impedance and the occurrence of cardiac arrhythmias within a large patient cohort. We investigated the temporal relationship between ventricular and atrial arrhythmic events and changes in intrathoracic impedance using the OptiVol fluid index. A multiple regression analysis revealed that both the occurrence of a fluid index threshold crossing and a higher NYHA class at baseline were independent predictors of atrial arrhythmic events, ventricular events, and the total number of arrhythmic events. Additionally, the patients with fluid index threshold crossings had significantly more atrial and ventricular arrhythmic events than those without threshold crossings during the follow-up period. These data suggest that cardiac arrhythmias are closely related to the fluid index threshold crossings, which in turn correlates with an increasing severity of HF. We, therefore, propose that changes in intrathoracic impedance can be regarded as a warning for cardiac arrhythmias, which tend to progress in parallel with exacerbation of HF.

Benefits of Early Warning of Cardiac Arrhythmias

Ventricular arrhythmic events sometimes result in the delivery of ICD shocks, which can be painful and increase the patient's anxiety. Additionally, Poole et al reported that the patients who received ICD shocks for arrhythmias had a substantially higher risk of death than similar patients who did not receive such shocks.[28] If changes in intrathoracic impedance can predict the occurrence of ventricular arrhythmias, effective early medical management may prevent the delivery of ICD shocks, resulting in a significant benefit to the patient.

Additional Considerations

The report by Moore et al[26] and our analysis suggest that the application of intrathoracic impedance monitoring as an indicator of the occurrence of ventricular arrhythmic events may lack specificity. Vollmann et al reported that the fluid index threshold crossing alert detected clinical HF deterioration with a 60% sensitivity (95%CI 46–73) and positive predictive value of 60% (95%CI 46–73) at the nominal threshold setting of 60 ohm-days.[5] Predicting the occurrence of an arrhythmia based on a cardiac overload that may result in HF cannot exceed the accuracy of predicting clinical HF deterioration using the intrathoracic impedance system. Furthermore, arrhythmias do not always appear at the time of HF deterioration. There also might be some prolonged cycle length ventricular events that are undetectable by the device programming, which induce cardiac deterioration and lead to a change in intrathoracic impedance. Thus, the observation that ventricular arrhythmias occurred after the threshold crossing in 16% of the TC(+) group patients in this study was reasonable and potentially clinically meaningful.

Although intrathoracic impedance measurements as currently implemented in implantable devices may not perform ideally

as an indicator of arrhythmic events, tailored use in combination with consideration of the patient's history and the impedance trend at the time of the event may be useful. However, the hypothesis that changes in intrathoracic impedance predict the occurrence of arrhythmias requires prospective validation.

Study Limitations

This retrospective study is subject to the limitations of all such studies. First, no randomization or blinding was applied. Second, all arrhythmic events used for the analysis were based on the device diagnosis and the programmed settings determined only by the physician's discretion. The atrial arrhythmia detection criteria of the device requires an atrioventricular conduction of 2:1 or greater for a minimum of 32 ventricular cycles. Atrial arrhythmic events are detected when the median atrial cycle length is less than a minimum value programmed by the physician. Helmut et al reported that the positive predictive values of atrial arrhythmic episodes were 95.3% and 95.7% for previous devices.[29] The ventricular arrhythmia detection algorithm operates to discriminate between supraventricular and ventricular tachyarrhythmias based on atrial and ventricular depolarization timing, ventricular cycle length regularity, AF criteria and far-field criteria.[30,31] Stadler et al demonstrated a positive predictive accuracy of 91.5% for the detection of ventricular arrhythmia episodes.[30] Third, the data for antitachycardia pacing episodes or direct current shock deliveries were not available for analysis in relation to the fluid index threshold crossings in this study. Finally, in regard to the fluid index setting, the nominal detection threshold value of 60 ohm-days used in this study demonstrated a 76.9% sensitivity in the large-scale observational study by Vollman et al.[5] However, some studies have reported that the positive predictive value of this proposed threshold for the OptiVol index related HF is relatively low.[1,4,32] Our data also showed that the fluid index threshold was crossed before atrial and ventricular arrhythmic events with a positive predictive value of 19% and 14%, respectively. The OptiVol index was developed to predict HF deterioration and may be affected by other events (eg, pneumonia, pleural effusion, pocket infection, drinking, etc). Ypenburg et al suggested that the nominal programmed fluid index threshold was not specific for the assessment of HF, and proposed that a threshold value of 120 ohm-days would provide a reasonable balance between sensitivity and specificity.[32] Further prospective studies in larger populations are needed to assess this hypothesis.

Conclusions

In this retrospective study of patients with NYHA class III and IV HF and who were implanted with CRT-D devices, arrhythmic events were associated with a dramatic change in the intrathoracic impedance-derived fluid index. Further prospective clinical trials are required to confirm the relationship between arrhythmic events and intrathoracic impedance monitoring, and to determine whether device-based fluid index monitoring can facilitate preemptive therapy to reduce the occurrence of arrhythmic events in patients with HF.

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References

1. Yu CM, Wang L, Chau E, Chan RHW, Kong SL, Tang MO, et al. Intrathoracic impedance monitoring in patients with heart failure: Correlation with fluid status and feasibility of early warning preceding hospitalization. *Circulation* 2005; **112:** 841–848.
2. Kee K, Naughton MT. Heart failure and the lung. *Circ J* 2010; **74:** 2507–2516.
3. Soga Y, Ando K, Arita T, Hyodo M, Goya M, Iwabuchi M, et al. Efficacy of fluid assessment based on intrathoracic impedance monitoring in patients with systolic heart failure. *Circ J* 2011; **75:** 129–134.
4. Wang L. Fundamentals of intrathoracic impedance monitoring in heart failure. *Am J Cardiol* 2007; **99**(Suppl)**:** 3G–10G.
5. Vollmann D, Nägele H, Schauerte P, Wiegand U, Butter C, Zanotto G, et al; for the European Insync Sentry Observational Study Investigators. Clinical utility of intrathoracic impedance monitoring to alert patients with an implanted device of deteriorating chronic heart failure. *Eur Heart J* 2007; **28:** 1835–1840.
6. Lüthje L, Drescher T, Zenker D, Vollmann D. Detection of heart failure decompensation using intrathoracic impedance monitoring by a triple-chamber implantable defibrillator. *Heart Rhythm* 2005; **2:** 997–999.
7. Catanzariti D, Lunati M, Landolina M, Zanotto G, Lonardi G, Iacopino S, et al. Monitoring intrathoracic impedance with an implantable defibrillator reduces hospitalizations in patients with heart failure. *Pacing Clin Electrophysiol* 2009; **32:** 363–370.
8. Knackstedt C, Mischke K, Schimpf T, Waringer J, Fache K, Frechen D, et al. Integration of automatic intrathoracic fluid content measurement into clinical decision making in patients with congestive heart failure. *Pacing Clin Electrophysiol* 2008; **31:** 961–967.
9. Wang L, Lahtinen S, Lentz L, Rakow N, Kaszas C, Ruetz L, et al. Feasibility of using an implantable system to measure thoracic congestion in an ambulatory chronic heart failure canine model. *Pacing Clin Electrophysiol* 2005; **28:** 404–411.
10. Crossley GH, Aonuma K, Haffajee C, Shoda M, Meijer A, Bauer A, et al; for the Concerto-AT Study Investigators. Atrial fibrillation therapy in patients with a CRT defibrillator with wireless telemetry. *Pacing Clin Electrophysiol* 2009; **32:** 13–23.
11. Stokes M, Davis C, Koch G. Categorical data analysis using the SAS system. 2nd edn. Cary, NC: SAS Institute Inc, 2000; 347–361.
12. Doval HC, Nul DR, Grancelli HO, Perrone SV, Bortman GR, Curiel R. for grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina (GESICA). Randomised trial of low-dose amiodarone in severe congestive heart failure. *Lancet* 1994; **344:** 493–498.
13. MERIT-HF Study Group. Effect of metprolol CR/XL in chronic heart failure: Metoprolol CR/XL randomized intervention trial in congestive heart failure (MERIT-HF). *Lancet* 1999; **353:** 2001–2007.
14. Takigawa M, Noda T, Kurita T, Aihara N, Yamada Y, Okamura H, et al. Predictors of electrical storm in patients with idiopathic dilated cardiomyopathy: How to stratify the risk of electrical storm. *Circ J* 2010; **74:** 1822–1829.
15. Franz MR, Cima R, Wang D, Profitt D, Kurz R. Electrophysiological effects of myocardial stretch and mechanical determinants of stretch-activated arrhythmias. *Circulation* 1992; **86:** 968–978.
16. Hansen DE, Craig CS, Hondeghem LM. Stretch-induced arrhythmias in the isolated canine ventricle: Evidence for the importance of mechanoelectrical feedback. *Circulation* 1990; **81:** 1094–1105.
17. Sabbah HN, Goldberg AD, Schoels W, Kono T, Webb C, Brachmann J, et al. Spontaneous and inducible ventricular arrhythmias in a canine model of chronic heart failure: Relation to hemodynamics and sympathoadrenergic activation. *Eur Heart J* 1992; **13:** 1562–1572.
18. Dries DL, Exner DV, Gersh BJ, Domanski MJ, Waclawiw MA, Stevenson LW. Atrial fibrillation is associated with an increased risk for mortality and heart failure progression in patients with asymptomatic and symptomatic left ventricular systolic dysfunction: A retrospective analysis of the SOLVD trials. *J Am Coll Cardiol* 1998; **32:** 695–703.
19. SOLVD investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med* 1992; **327:** 685–691.
20. Carson PE, Johnson GR, Dunkman WB, Fletcher RD, Farrell L, Cohn JN. for the V-HeFT VA Cooperative Studies Group. The influence of atrial fibrillation on prognosis in mild to moderate heart failure. *Circulation* 1993; **87**(Suppl VI)**:** VI-102–VI-110.
21. Torp-Pedersen C, MollerM, Bloch-Thomsen PE, Kober L, Sandoe E, Egstrup K, et al; for the Danish Investigations of Arrhythmia and Mortality on Dofetilide Study Group. Dofetilide in patients with congestive heart failure and left ventricular dysfunction. *N Engl J Med* 1999; **341:** 857–865.
22. CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med* 1987; **316:** 1429–1435.

23. Maisel WH, Stevenson LW. Atrial fibrillation in heart failure: Epidemiology, pathophysiology, and rationale for therapy. *Am J Cardiol* 2003; **91**(Suppl): 2D–8D.
24. Wijffels MCEF, Kirchof CJHJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation: A study in awake chronically instrumented goats. *Circulation* 1995; **92:** 1954–1968.
25. Andriulli J, Coles J, Hettrick DA. Association between decreased intrathoracic impedance and ventricular tachyarrhythmias. *Int J Cardiol* 2008; **123:** 333–334.
26. Moore HJ, Peters MN, Franz MR, Karasik PE, Singh SN, Fletcher RD. Intrathoracic impedance preceding ventricular tachyarrhythmia episodes. *Pacing Clin Electrophysiol* 2010; **33:** 960–966.
27. Jhanjee R, Templeton GA, Sattiraju S, Nguyen J, Sakaguchi S, Lu F, et al. Relationship of paroxysmal atrial tachyarrhythmias to volume overload: Assessment by implanted transpulmonary impedance monitoring. *Circ Arrhythmia Electrophysiol* 2009; **2:** 488–494.
28. Poole JE, Johnson GW, Hellkamp AS, Anderson J, Callans DJ, Raitt MH, et al. Prognostic importance of defibrillator shocks in patients with heart failure. *N Engl J Med* 2008; **359:** 1009–1017.
29. Helmut P, Anne MG, Reece H, Douglas AH. Accuracy of atrial tachyarrhythmia detection in implantable devices with arrhythmia therapies. *Pacing Clin Electrophysiol* 2004; **27:** 983–992.
30. Stadler RW, Gunderson BD, Gillberg JM. An adaptive interval-based algorithm for withholding ICD therapy during sinus tachycardia. *Pacing Clin Electrophysiol* 2003; **26:** 1189–1201.
31. Wilkoff BL, Kuhlkamp V, Volosin K, Ellenbogen K, Waldecker B, Kacet S, et al. Critical analysis of dual-chamber implantable cardioverter-defibrillator arrhythmia detection: Results and technical considerations. *Circulation* 2001; **103:** 381–386.
32. Ypenburg C, Bax JJ, van der Wall EE, Schalij MJ, van Erven L. Intrathoracic impedance monitoring to predict decompensated heart failure. *Am J Cardiol* 2007; **99:** 554–557.

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Randomized trial of angiotensin II-receptor blocker vs. dihydropiridine calcium channel blocker in the treatment of paroxysmal atrial fibrillation with hypertension (J-RHYTHM II Study)

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Aims Atrial fibrillation (AF) is a common arrhythmia frequently associated with hypertension. This study was designed to test the hypothesis that lowering blood pressure by angiotensin II-receptor blockers (ARB) has more beneficial effects than by conventional calcium channel blockers (CCB) on the frequency of paroxysmal AF with hypertension.

Methods and results The Japanese Rhythm Management Trial II for Atrial Fibrillation (J-RHYTHM II study) is an open-label randomized comparison between an ARB (candesartan) and a CCB (amlodipine) in the treatment of paroxysmal AF associated with hypertension. Using daily transtelephonic monitoring, we examined asymptomatic and symptomatic paroxysmal AF episodes during a maximum 1 year treatment. The primary endpoint was the difference in AF frequency between the pre-treatment period and the final month of the follow-up. The secondary endpoints included cardiovascular events, development of persistent AF, left atrial dimension, and quality-of-life (QOL). The study enrolled 318 patients (66 years, male/female 219/99, 158 in the ARB group and 160 in the CCB group) treated at 48 sites throughout Japan. At baseline, the frequency of AF episodes (days/month) was 3.8 ± 5.0 in the ARB group vs. 4.8 ± 6.3 in the CCB group (not significant). During the follow-up, blood pressure was significantly lower in the CCB group than in the ARB group ($P < 0.001$). The AF frequency decreased similarly in both groups, and there was no significant difference in the primary endpoint between the two groups. There were no significant differences between the two groups in the development of persistent AF, changes in left atrial dimension, occurrence of cardiovascular events, or changes in QOL.

Conclusions In patients with paroxysmal AF and hypertension, treatment of hypertension by candesartan did not have an advantage over amlodipine in the reduction in the frequency of paroxysmal AF (umin CTR C000000427).

Keywords Atrial fibrillation • Hypertension • Renin–angiotensin system • Candesartan • Amlodipine • Secondary prevention • Upstream therapy

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