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CLINICAL PERSPECTIVE

Idiopathic ventricular fibrillation associated with early repolarization is a new arrhythmia syndrome entity, although early repolarization has been considered benign for decades. Early repolarization is a heritable electrocardiographic phenotype and there is a positive family history in 10 to 20% of patients with idiopathic ventricular fibrillation associated with early repolarization. Recent studies have identified the causative genes of the arrhythmia, all of which are associated also with Brugada syndrome. In this study, SCN5A, which encodes the predominant cardiac sodium channel α subunit and is critical for cardiac conduction, was screened in patients with idiopathic ventricular fibrillation associated with early repolarization. The screening identified 3 patients carrying an SCN5A mutation, and His-ventricular interval was prolonged in all patients. All of the mutations are predicted to substitute amino acids highly conserved across species and failed to produce any detectable sodium current. To identify electrophysiological characteristics in idiopathic ventricular fibrillation associated with early repolarization, we compared electrocardiograms between patients with the arrhythmia and healthy controls. We found that patients with the arrhythmia exhibited slower heart rate and slower cardiac conduction properties than controls. Our findings suggest that there are underlying electrophysiological abnormalities resulting in slow heart rate, slow cardiac conduction, early repolarization, and ventricular fibrillation, partially explained by sodium channel dysfunction. Idiopathic ventricular fibrillation associated with early repolarization and Brugada syndrome share genetic, clinical, and pharmacological characteristics, but other factors that modify the clinical phenotypes are unknown. Further studies to identify the modifiers are warranted.

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Cardiac resynchronization therapy to prevent life-threatening arrhythmias in patients with congestive heart failure

Takashi Kurita, MD, PhD,[a,*] Takashi Noda, MD, PhD,[b] Takeshi Aiba, MD, PhD,[b] Ikutaro Nakajima, MD,[b] Wataru Shimizu, MD, PhD,[b] Koichiro Motoki, MD, PhD,[a] Ryobun Yasuoka, MD, PhD,[a] Shunichi Miyazaki, MD, PhD,[a] Shiro Kamakura, MD, PhD[b]

[a]*Department of Medicine, Division of Cardiology, Faculty of Medicine, Kinki University, Osaka, Japan*
[b]*Division of Cardiology, National Cerebral and Cardiovascular Center, Osaka, Japan*

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Abstract Various clinical data demonstrate that cardiac resynchronization therapy (CRT) provides a favorable structural as well as electrical remodeling. The CArdiac Resynchronization–Heart Failure study, which tested the pure effect of CRT (using CRT devices without the capability of defibrillation) clearly showed a significant reduction in the total mortality by partly preventing sudden cardiac death. The antiarrhythmic effects of CRT are explained, at least in part, by ionic and genetic modulation of ventricular myocytes. It has been revealed in animal experiments to mimic disorganized ventricular contraction that CRT reverses down-regulation of certain K^+ channels and abnormal Ca^{2+} homeostasis in the failing heart. However, CRT can be proarrhythmic in some particular cases especially in the early phase of this therapy. According to our study, proarrhythmic effects after CRT can be observed in approximately 10% of patients. The relatively high incidence of the proarrhythmic effects of CRT may promote a trend toward selecting CRT-D rather than CRT-P.

Keywords: Cardiac resynchronization therapy; Ventricular tachyarrhythmia; Heart failure; Proarrhythmic effect; Antiarrhythmic effect

Introduction

Various clinical data demonstrate that cardiac resynchronization therapy (CRT) provides a favorable structural as well as electrical remodeling.[1-5] The CArdiac Resynchronization–Heart Failure (CARE-HF) study, which tested the pure effect of CRT (using CRT devices without the capability of defibrillation) clearly showed a significant reduction in the total mortality by partly preventing sudden cardiac death (SCD).[5,6] The antiarrhythmic effects of CRT are attributable to reversal of structural and electrical remodeling of the left ventricle (LV) in association of heart failure toward the creation of substrates for reentry of excitation.

However, epicardial LV pacing can also be proarrhythmic through an induction of heterogeneous ventricular depolarization and repolarization resulting from nonphysiological propagation of excitation.[7-9] In the present article, we discuss such a dual potential of CRT toward prevention and promotion of arrhythmias.

Proarrhythmic effects of CRT

Fig. 1 shows a representative case in whom the proarrhytmic effects of CRT were highly suspected. This patient had a long history (>20 years) of heart failure and complete left bundle branch block (CLBBB) without any significant ventricular arrhythmias. The first VF episode developed only 6 days after implantation of CRT-P, giving us a warning against a proarrhythmic risk of CRT even in patients without history of serious ventricular arrhythmias.

Our study

We investigated "early development of lethal arrhythmic events after CRT."[10] The condition of patients enrolled was defined as follows: (1) no previous episodes of sustained VT/VF or syncope before the CRT implantation, (2) new development of sustained VT/VF, SCD, or appropriate shocks delivered by a CRT-D within 6 months after implantation of CRT. Fifty-one consecutive patients

* Corresponding author. Department of Medicine, Division of Cardiology, Faculty of Medicine, Kinki University, 377-2 Ohono-Higashi, Osaka-Sayama, Osaka 589-8511, Japan.
E-mail address: kuritat@med.kindai.ac.jp

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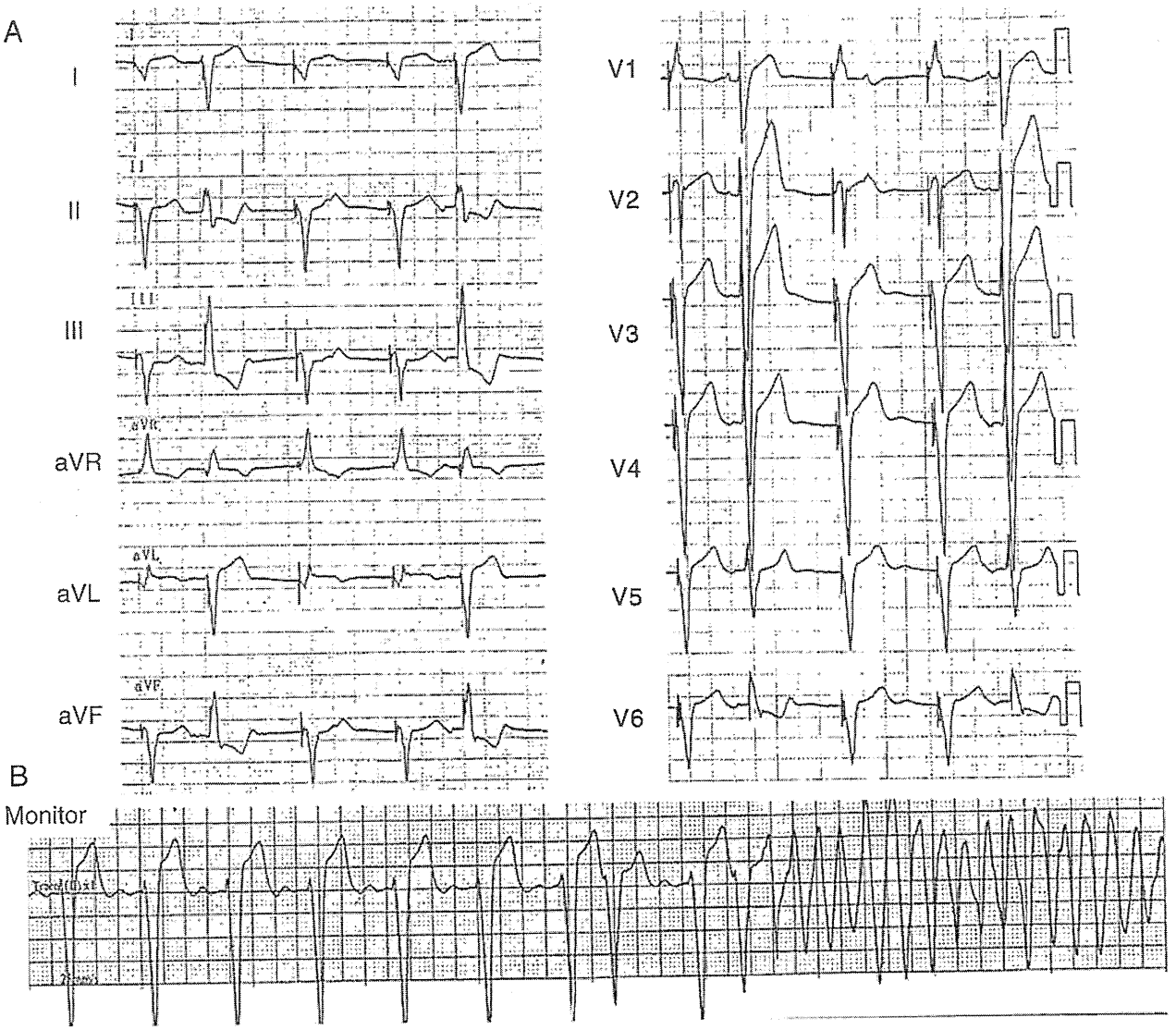

Fig. 1. A case with newly development of VF 6 days after implantation of CRT pacemaker (CRT-P). A, CRT-P was implanted in heart failure patient with CLBBB and permanent AF. Because of AF, occasional conducted QRS complexes with CLBBB configuration are seen. B, This patient had a long history (>20 years) of heart failure and CLBBB without any significant ventricular arrhythmias. The patient showed the first VF episode only 6 days after implantation of CRT-P, giving us a warning against a proarrhythmic risk of CRT.

who underwent CRT were included in this study. We excluded the patients who had a worse New York Heart Association (NYHA) functional class after the CRT and who had VT episodes that were terminated only by antitachycardia pacing. The early development of lethal arrhythmic events after the CRT was observed in 6 (11.7%) of 51 patients. They were divided into 2 groups according to the presence of early phase events: a group with events (group E, n = 6) and a group without events (group non-E, n = 45), and we compared several clinical parameters such as the baseline NYHA functional class, response to CRT (responder or nonresponder), underlying heart disease, antiarrhythmic drug usage, and preexisting arrhythmias (atrial fibrillation [AF] and nonsustained VT [NSVT]) between the 2 groups. There was no significant difference between the 2 groups for all the parameters except for preexisting arrhythmias. Preexisting AF and NSVT of 5 bursts or more were observed more frequently in group E than group non-E (6/6 vs 20/45, $P < .01$ and 6/6 vs 17/45, $P < .01$, respectively, Fig. 2). These observations suggest that preexisting AF and NSVT may be important predictors for the proarrhythmic risk of CRT implantation regardless of the hemodynamic response of the subjects.

Mechanism of the proarrhythmic effects of CRT

The transvenous insertion of an LV lead into a cardiac vein on the epicardial surface of the heart is an essential technique to obtain safe and stable long-term LV pacing.[11] This technique produces nonphysiological propagation of the excitation from the epicardium to endocardium and may lead to an increase in the dispersion of the repolarization because the epicardial ventricular muscle having shorter action potential duration (APD) is excited earlier than the endocardial ventricular muscle having longer APD. This

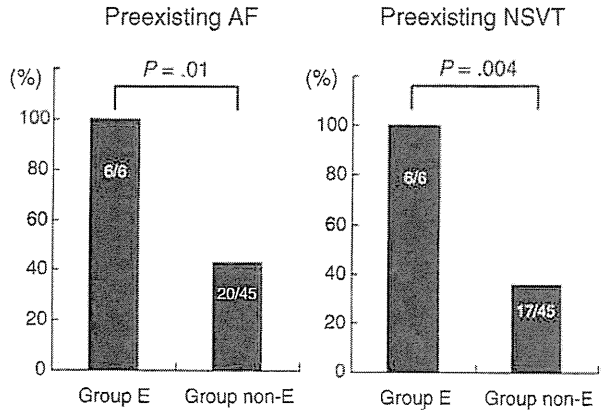

Fig. 2. Preexisting arrhythmias in the patients with (group E) and those without (group non-E) early development of lethal arrhythmic events after CRT. Preexisting AF and NSVT were observed more frequently in group E than group non-E (6/6 vs 19/45, $P < .01$, and 6/6 vs 17/45, $P < .01$, respectively).

may set a sage for reentry of excitation causing VT/VF. Spatially heterogenous prolongation of APD in the ventricle of failing hearts may further facilitate the initiation and perpetuation of reentrant arrhythmias.[12,13]

Right ventricular (RV) pacing induces a significant LBBB pattern and sometimes leads to the deterioration in the LV function. Upgrading from a traditional RV pacemaker to a biventricular (Bi-V) pacemaker is highly recommended for patients with a reduced cardiac function and atrioventricular (AV) block (block).[14]

Recently, an intriguing case of idiopathic dilated cardiomyopathy with heart failure and complete AV block was reported by Ikutomi et al,[15] where upgrading from the preexisting VDD pacemaker to CRT-D resulted in a significant proarrhythmia. Upgrading from the preexisting VDD pacemaker to CRT-D was performed aiming to improve the heart failure. A marked QT prolongation and torsade de pointes (TdP) occurred immediately after switching from RV pacing to LV or Bi-V pacing. Several weeks later, however, Bi-V pacing caused only moderate QT prolongation without TdP induction. The Bi-V pacing was able to be continued thereafter, and QT interval shortened gradually in association with improvement of heart failure. It is suggested from this report that proarrhythmic risk of Bi-V pacing is most remarkable in the early phase of CRT, and it may decrease in the remote phase probably through a reversal of (or adaptation to) the electrical remodeling of the heart.

Another mechanism of proarrhythmia with CRT is relevant to preexisting anatomical structure in favor of reentry. We experienced a case of nonischemic dilated cardiomyopathy (65 year old man) with heart failure, complete AV block and permanent AF. ICD had been implanted for the treatment of monomorphic sustained VT. During a 3-year follow-up period, the patient experienced sporadic electrical therapies, but his heart failure condition deteriorated gradually to NYHA III/IV. We, therefore, decided to upgrade from ICD to CRT-D. A CRT-D was implanted through thoracotomy. He responded well to CRT-D, giving rise to an improvement of NYHA class from III/IV to II. One month later, however, he was admitted in the emergency department of our hospital because of frequent episodes of sustained monomorphic VT (an electrical storm). The VT was terminated repeatedly by antitachycardia pacing (Fig. 3A). There were no other factors of proarrhythmia (such as worsening of heart failure or electrolyte imbalance) than Bi-V pacing. After switching from Bi-V to RV pacing, the electrical storm terminated immediately (Fig. 3B). When the pacing turned back to Bi-V pacing, the electrical storm reappeared right away (Fig. 3B). The proarrhythmia of Bi-V pacing in this patient could be explained by an entrance of wave front from LV pacing site into preexisting reentry circuits. Anisotropic fiber orientation in the LV myocardium or summation of depolarizing waves is considered to be involved in such events favoring the electrical storm.[16,17]

Future device

Advanced technology using transseptal (transmitral) lead approach will provide safe and stable endocardia LV pacing in near future.[18] This technique will resolve proarrhythmic issues of epicardial approach by producing more physiological propagation of depolarization through LV, and it will also allow us to implant the LV lead regardless of cardiac vein anatomy.

Antiarrhythmic effects of CRT

CRT is expected to prevent life-threatening ventricular arrhythmias in the failing heart because the procedure would cause a reversal of structural and electrical remodeling, favoring reentry of excitation.[1-7] Tanabe et al[19] reported the apparent antiarrhythmic effect of CRT in a patient with idiopathic dilated cardiomyopathy who experienced an electrical storm (frequent monomorphic sustained VT) after implantation of ICD. They performed an acute study with Bi-V pacing before the CRT-D implantation and confirmed an immediate improvement in the systemic hypotension and degree of mitral regurgitation during the Bi-V pacing. Application of CRT to this patient resulted in an immediate hemodynamic improvement in association with complete elimination of the electrical storm, which had been resistant to pharmacological therapies.

An analysis of the combined InSync-ICD and Contact-CD patients demonstrated that CRT was associated with no significant change in the incidence of polymorphic VT or monomorphic VT.[20] However, other reports showed data revealing that the incidence of malignant VT was reduced following CRT.[19,21-23] Based on these results, CRT has favorable or at least no harmful effects on substrates for VT/VF in heart failure patients.

As previously mentioned, the CARE-HF study demonstrated a significant improvement in the SCD rate.[6] However, in that trial, the survival curves showing the freedom from all causes of death in the control and CRT group began to separate approximately 200 days after the randomization. On the other hand, the survival curves of SCD started to separate after approximately 700 days. The

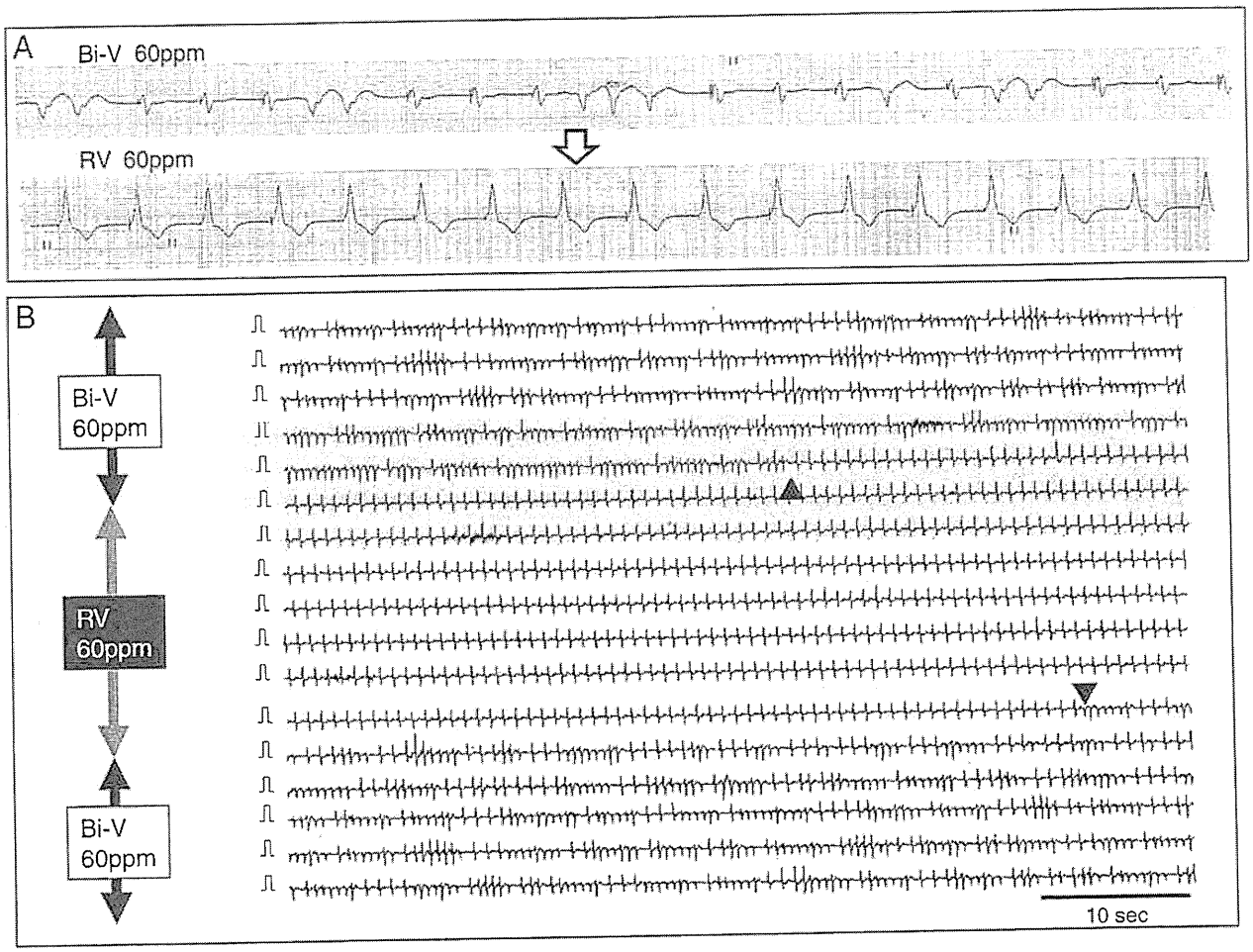

Fig. 3. Proarrhythmic effects of CRT in a patient of dilated cardiomyopathy (65-year-old man) with heart failure, complete AV block, and permanent AF. ICD had been implanted for the treatment of monomorphic sustained VT. Because of deterioration of heart failure, we upgraded from ICD to CRT-D. He responded well to CRT, giving rise to improvement of NYHA classes. One month later, however, he was experienced frequent episodes of sustained monomorphic VT, which were terminated repeated by antitachycardia pacing (A). After switching from Bi-V to RV pacing, the electrical storm terminated immediately (B, upward arrowhead). When the pacing turned back to Bi-V, the electrical storm reappeared right away (B, downward arrowhead). ppm indicates pacing per minute, RV, right ventricular pacing.

antiarrhythmic effect of CRT to prevent SCD might require sufficient time for reversal of structural and electrical remodeling of the heart, although this interpretation remains to be substantiated.

Effects on AF

The incidence of AF increases with an advancing NHYA cardiac functional class.[24,25] The contribution of the atrial contraction to the cardiac performance in a normal heart is considered to be small. However, the development of AF in a failing heart significantly affects the cardiac dysfunction by diminishing the atrial kick (AV synchrony). Inappropriate rapid ventricular rate with irregular R-R intervals may also contribute the cardiac dysfunction.[26-28]

Optimization of the left AV conduction delay and a simultaneous contraction of the entire LV reduces the LV end-diastolic pressure, leading to a reduction of wall stress in the LV and LA in favor or termination and prevention of AF. We experienced 2 cases in whom long-lasting AF was terminated and sinus rhythm has been maintained thereafter. Because we did not expect the termination of the AF after the CRT, we did not implant an atrial lead. In cases with unexpected restoration of sinus rhythm as in this patient, Bi-V pacing with the VVI mode may provoke pacemaker syndrome. We need to lean certain parameters predicting conversion from AF to sinus rhythm after CRT implantation.

Delnoy et al[29] reported their experience in 96 CRT patients with permanent or persistent AF. They implanted atrial leads in patients with AF lasting less than 2 years and followed them up for 2 years. Antiarrhythmic drug therapy (mainly amiodarone) was used after CRT implantation to resume or to preserve sinus rhythm. In that study, 25% of 96 AF patients were in sinus rhythm after 1 year. Eight patients received cardioversion at the time of the implant, whereas 16 patients reverted to sinus rhythm spontaneously. At 2 years, 21% of the AF group was in sinus rhythm. This study suggests that amiodarone treatment after cardioversion is promising in CRT patients with AF for resumption and preservation of sinus rhythm. They recommended that the implantation of an atrial lead may have merit in CRT patients with AF lasting less than 2 years. AV synchrony obtained by an atrial lead may dramatically improve the

heart failure, but in the case of those without a lead, reversion to sinus rhythm may provoke pacemaker syndrome and an insufficient improvement.

Genetic aspects of reverse electrical remodeling

The electrophysiologic hallmark of cells and tissue isolated from failing hearts is the prolongation of the APD and a conduction delay.[30,31] In human studies and a number of animal models of heart failure, functional down-regulation of K^+ currents and alterations in depolarizing Na^+ and Ca^{2+} currents and transporters are demonstrated. In experiments on dog of heart failure induced by dyssynchronous LV contraction (DHF), Aiba et al[12] and Aiba and Tomaselli[13] have shown that CRT partially restores DHF-induced ion channel remodeling and abnormal Ca^{2+} homoeostasis and attenuates the regional heterogeneity of APD. CRT was also shown to improve β-adrenergic responsiveness of Ca^{2+} handling in the DHF model. Such electrophysiological changes induced by CRT may suppress ventricular arrhythmias favoring a better survival.[32]

Conclusions

CRT can be proarrhythmic in some particular cases especially in the early phase of this therapy until electrical reverse remodeling has become established. According to our study, proarrhythmic effects after CRT can be observed in approximately 10% of patients. The relatively high incidence of the proarrhythmic effects of CRT may promote a trend toward selecting CRT-D rather than CRT-P.

Indeed, CRT can be antiarryhthmic. Even in the early phase after beginning CRT, it immediately improves the hemodynamic situation. A decrease of the LV endodiastolic pressure would ameliorate the stretch-induced arrhythmogenic alterations of ionic currents. In patients who ideally respond to CRT, it creates structural reverse remodeling accompanied by electrical reverse remodeling in the remote phase. Once such a striking reverse remodeling has been established, CRT acts as a potent antiarrhythmic treatment thereafter.

The antiarrhtymic effects of CRT have come to be explained by the viewpoint of the ionic and genetic regulation of the myocytes.

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INTERNAL MEDICINE

□ CASE REPORT □

Incessant Monomorphic Ventricular Tachycardia Induced by the Proarrhythmic Effect of Amiodarone

Hisaki Makimoto, Takashi Noda, Takashi Kurita, Ikutaro Nakajima, Teruki Yokoyama, Atsushi Doi, Yuko Yamada, Hideo Okamura, Kazuhiro Satomi, Takeshi Aiba, Wataru Shimizu, Kazuhiro Suyama, Naohiko Aihara and Shiro Kamakura

Abstract

This case report describes incessant monomorphic ventricular tachycardia (VT), not Torsade de Pointes, induced by intravenous amiodarone in a 48-year-old woman with dilated cardiomyopathy. VT was reproducibly triggered by short coupled premature ventricular complex (PVC) with different morphology from VT. After amiodarone infusion, the coupling interval of initiating PVC was prolonged, and moreover, the morphology of initiating PVC became the same as that of VT. Though amiodarone has become the first line drug to treat ventricular tachyarrhythmias in patients with cardiac dysfunction, it is important to be aware of its proarrhythmic effect, which may lead to an electrical storm of monomorphic VT.

Key words: monomorphic ventricular tachycardia, amiodarone, proarrhythmia, Torsade de Pointes, class III antiarrhythmic

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Introduction

Ventricular tachycardia/fibrillation (VT/VF) is one of the major causes of death in patients with structural heart disease. Amiodarone, which is classified as a class-III antiarrhythmic agent, is considered as the most efficacious agent even for patients with severe cardiac dysfunction (1). Amiodarone has been broadly used in the emergency department of outpatient clinics, and it is also well known that the electrophysiological effect of amiodarone is different when it is administered orally or intravenously (2). Although proarrhythmic effects of amiodarone are rare, some patients occasionally develop polymorphic VT of Torsade de Pointes (TdP) (3, 4). We present an unusual case with incessant monomorphic VT, not TdP, induced after amiodarone infusion.

Case Report

A 48-year-old woman was admitted to our hospital due to sudden palpitation, and dyspnea. She had been diagnosed as idiopathic dilated cardiomyopathy when she was 24 years old and treated with carvedilol, digoxin, and enalapril. Her family history included dilated cardiomyopathy in her brother, sister, and son. She had been seemingly healthy until the morning of the day of admission. She suddenly recognized palpitation, dyspnea, and cold sweat when she was riding her bicycle. Though those symptoms were relieved with 15 minutes' rest, she felt disturbed pulse. She presented to our emergency department immediately.

She felt no symptom on admission. Chest radiogram showed cardiomegaly. Her electrocardiogram (ECG) showed sinus rhythm of 84 beats/min with occasional premature ventricular complexes (PVCs) (Fig. 1A). After admission, we evaluated her clinical picture. Her echocardiogram showed a markedly dilated left ventricle (Dd/Ds 77/63 mm) with the left ventricular ejection fraction of 17%. Blood tests revealed no significant abnormalities including electrolyte disturbance. Suddenly, recurrent ventricular tachycardia (VT) was observed on her monitoring ECG during the hospitalization (Fig. 1B). There were no significant triggers of

Division of Arrhythmia and Electrophysiology, Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, Japan
Received for publication April 1, 2011; Accepted for publication July 22, 2011
Correspondence to Dr. Takashi Noda, tnoda@hsp.ncvc.go.jp

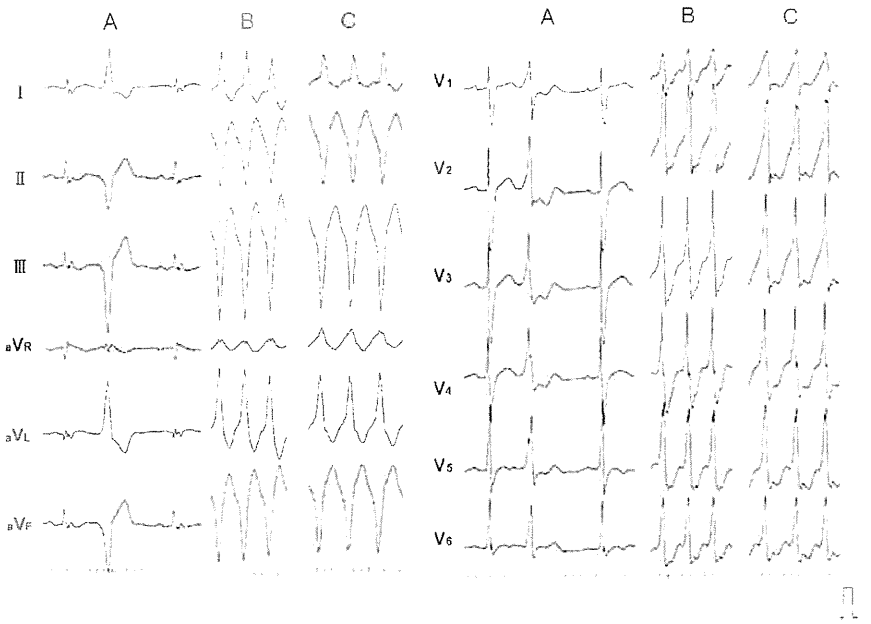

Figure 1. Twelve-lead electrocardiograms (ECGs) on admission and during ventricular tachycardia (VT) before and after amiodarone. The ECG showed sinus rhythm of 84 beats per minute with first degree atrio-ventricular block, and occasional premature ventricular complexes (PVC) (A). Before amiodarone administration, the QRS morphology of incessant VT was right bundle branch block morphology with superior axis (B). After amiodarone administration, the QRS morphology of VT was also similar to that of VT before amiodarone, but VT rate decreased to 150 beats per minute (C).

arrhythmia such as a change in drug dosage, electrolyte disturbance, infection, or exercise. VT rate was 170 beats/min and she complained of palpitation.

After 125 mg of amiodarone was administered intravenously over 10 minutes, continuous intravenous administration (40 mg per hour) was given. An hour after starting amiodarone, the VT rate decreased to 150 beats/min but the duration of VT was still prolonged (Fig. 1C). Moreover, the morphology of the initiating PVC was changed. Before amiodarone, VT was triggered by PVC of which the morphology differed from that of VT (Fig. 2A). After one hour of intravenous amiodarone, the culprit PVC in the baseline was completely eliminated, and then sustained VT was triggered by the PVC, whose morphology was virtually identical to the sustained VT (Fig. 2B).

During sinus rhythm, QRS duration was prolonged from 130 ms to 160 ms, and the corrected QT interval was also prolonged from 370 ms to 400 ms (Fig. 3). VT of more than 3 beats was found three times and they lasted in total for 4 minutes and 10 seconds in the 15-minute period before amiodarone. Before discontinuation of amiodarone, VT was found to occur 5 times and lasted for 9 minutes and 40 seconds in the 15-minute period.

We discontinued amiodarone, and administered 12 mg of nifekalant, pure IKr blocker, over 5 minutes intravenously followed by a continuous dose of 9 mg per hour. About 7 minutes after starting nifekalant, VT disappeared completely. QRS duration was not changed (160 ms), but the corrected QT interval was markedly prolonged to 520 ms.

Administration of sotalol (80 mg per day) made it possible to withdraw nifekalant. Because her heart rate tended to be low, and an increase in β-blocker dosage was considered necessary, CRT-D implantation was conducted. After the increase of carvedilol to 10 mg per day, she was discharged from our hospital.

Discussion

Several studies have demonstrated the usefulness of intravenous amiodarone and it is now recommended as a first-line drug for treatment of VT (5). While intravenous amiodarone is generally regarded as a safe treatment, there are several reports on proarrhythmia inducing TdP under certain conditions including electrolyte imbalance (3, 4, 6, 7). In the present case, incessant monomorphic VT, not TdP, was induced after injection of intravenous amiodarone. As far as we know, this is the first report on monomorphic VT induced after amiodarone infusion. Moreover, the amiodarone efficacy in the treatment of stable VT has not been fully elucidated (8-10).

The incessant VT in this patient, who had structural heart disease, maintained regular beats and was reproducibly induced by relatively short coupled PVC. VT always terminated and reappeared spontaneously and the VT cycle length was gradually prolonged (about 10%) before spontaneous termination. These findings supported the reentrant mecha-

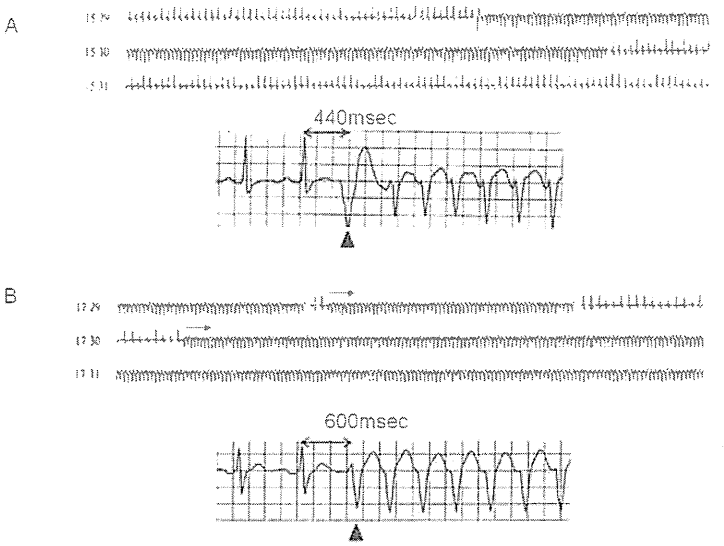

Figure 2. Recurrent ventricular tachycardia (VT) observed on the monitoring electrocardiogram (ECG) before and after amiodarone. Recurrent VT was suddenly observed on her monitoring ECG (A). After intravenous amiodarone, VT became more incessant and the duration of VT prolonged still more (B). Before 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).

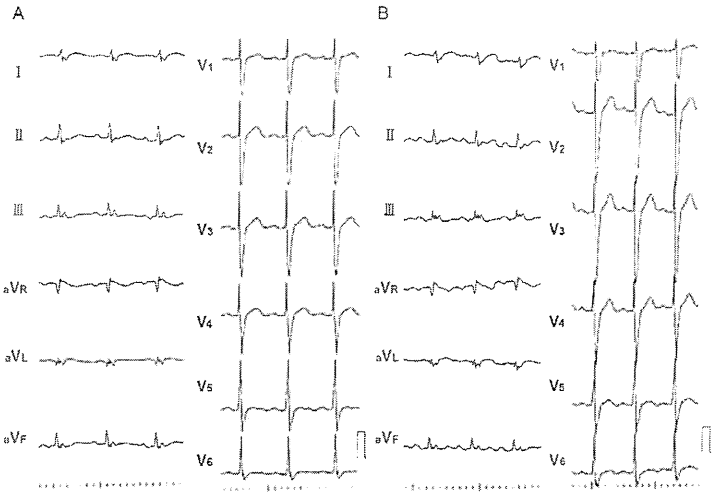

Figure 3. Twelve-lead electrocardiograms (ECGs) during sinus rhythm before and after amiodarone. Before amiodarone, QRS duration was 130 msec and QTc interval was 370 msec on the ECG (A). After amiodarone, QRS duration and QTc interval were prolonged to 160 msec and 400 msec (B).

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

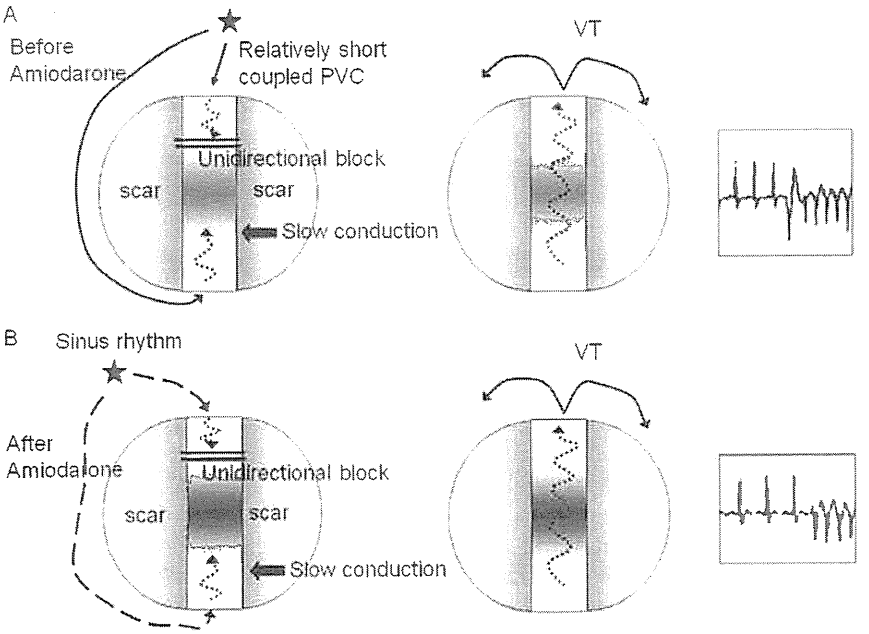

Figure 4. Illustration of postulated mechanism of ventricular tachycardia (VT) before and after amiodarone. Before amiodarone administration, relatively short coupled premature ventricular complex caused unidirectional block in critical slow pathway zone, and retrograde conduction formed the reentrant 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).

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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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Mita Hospital, International University of Health and Welfare, Tokyo (S.O.); Institute for Clinical Research, Osaka National Hospital, Osaka (Y.K.); Department of Cerebrovascular Medicine, National Hospital Organization, Kyushu Medical Center, Fukuoka (M.Y.); Niigata University Graduate School of Medical and Dental Science Cardiology, Niigata (Y.A.); Department of Internal Medicine and Cardiology, Nippon Medical School, Tama-Nagayama Hospital, Tokyo (H.A.); The Second Department of Internal Medicine, University of Toyama, Graduate School of Medicine, Toyama (H.I.); Division of Arrhythmia and Electrophysiology, Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, Osaka (S.K.); Heart Rhythm Center, Fukuoka Sanno Hospital, Fukuoka (K.K.); Cardiovascular Department, Saiseikai Central Hospital, Tokyo (H.M.); Cardiology, Respiratory Medicine and Nephrology, Hirosaki University Graduate School of Medicine, Aomori (K.O.); Division of Cardiovascular Medicine, Toho University, Ohashi Hospital, Tokyo (K.S.); and The Cardiovascular Institute, Tokyo (T.Y.), Japan

Writing Group Members: S.O., Y.K., M.Y.

Writing Committee Members: Y.A., H.A., H.I., S.K., K.K., H.M., K.O., K.S., T.Y.

Mailing address: Satoshi Ogawa, MD, PhD, Mita Hospital, International University of Health and Welfare, 1-4-3 Mita, Minato-ku, Tokyo 108-8329, Japan. E-mail: sogawa@iuhw.ac.jp

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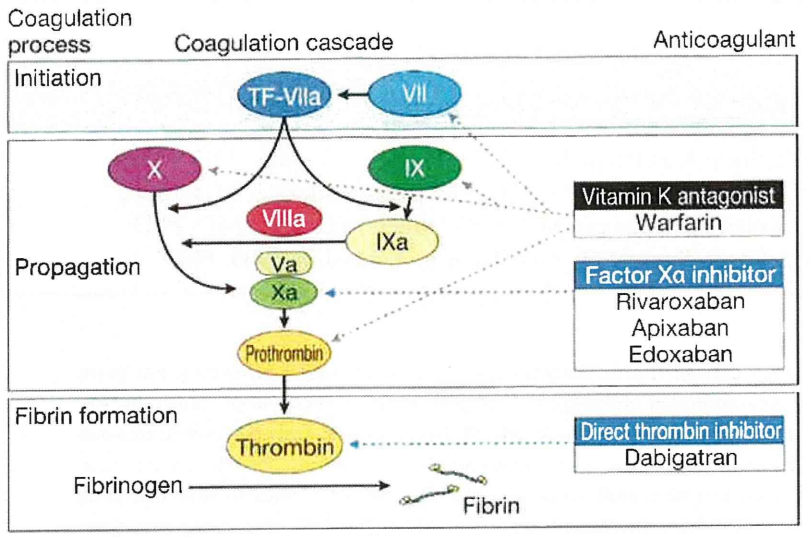


Figure 1. Site of action of anticoagulants in the coagulation cascade.[14]

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 Ia), 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 non-inferiority 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

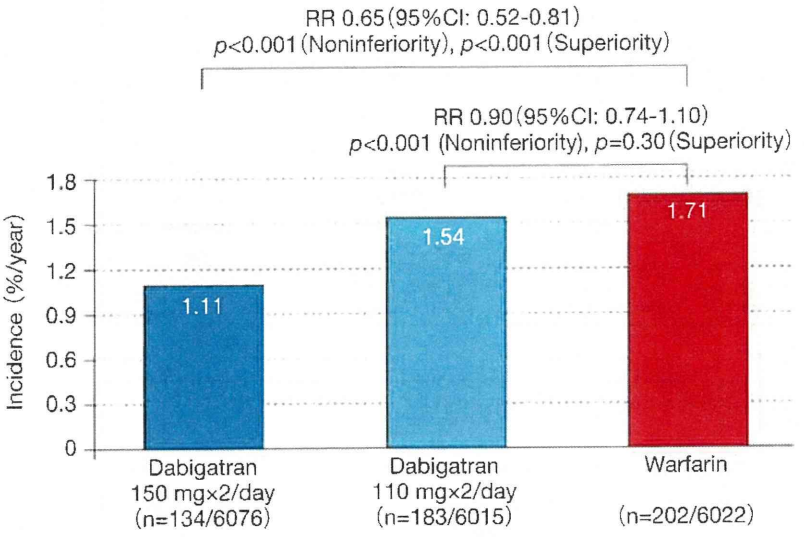


Figure 2. Primary endpoint of the RE-LY study (incidence of stroke or systemic embolism).[11,12] RR, relative risk. CI, confidence interval.

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)

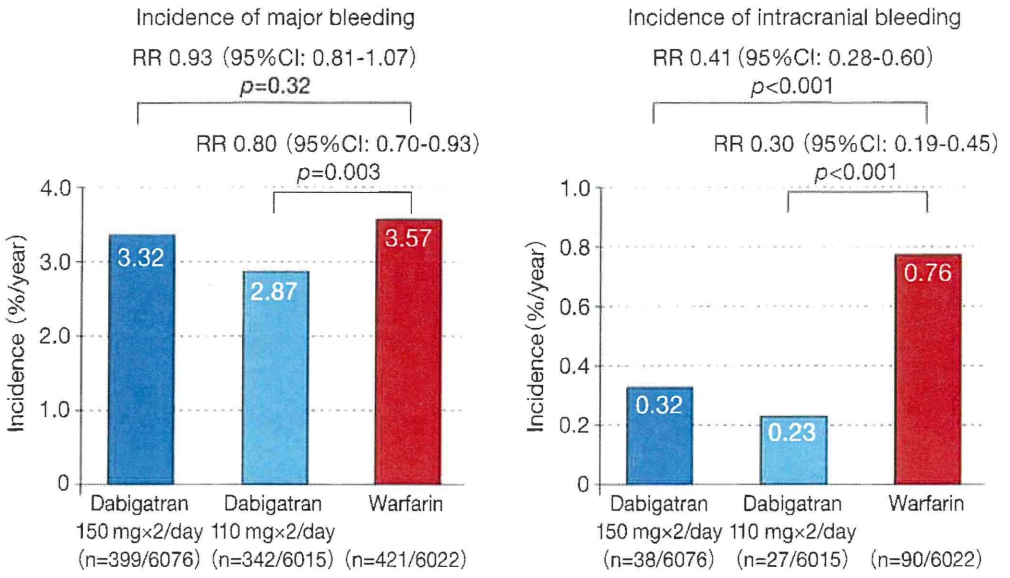
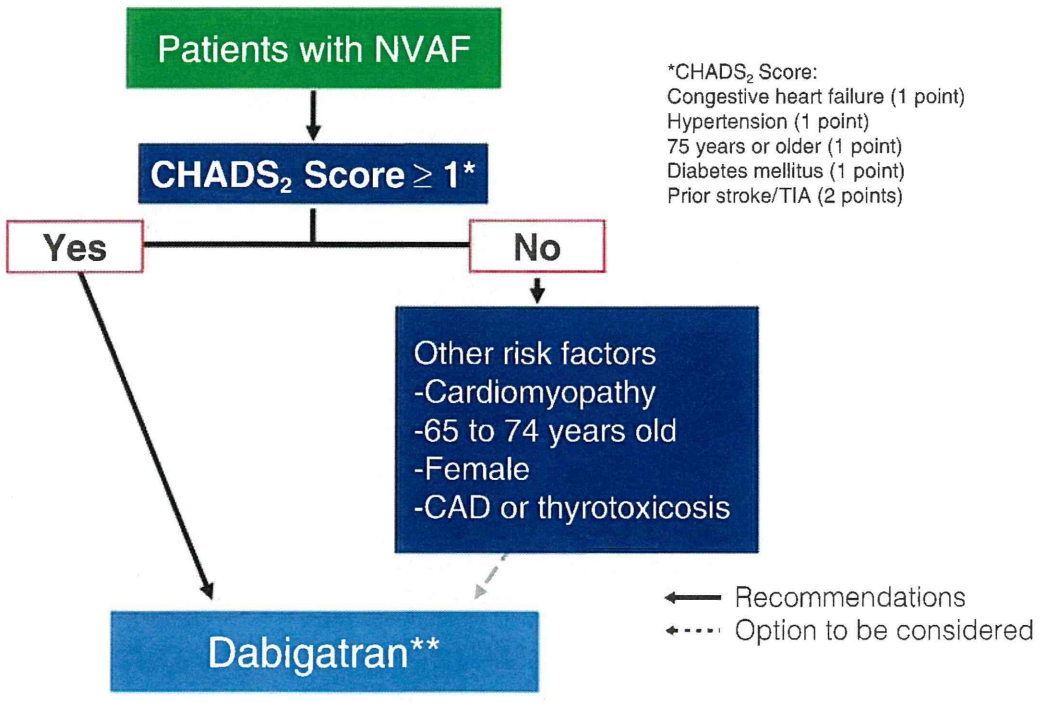


Figure 3. Incidence of major bleeding in the RE-LY study.[11,12] RR, relative risk. CI, confidence interval.



**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.[49] 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.[39]

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[39,53] 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.[14]

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.