筑　波　大　学

博 士 （医 学） 学 位 論 文

Optimal interruption time of dabigatran oral administration to ablation (O-A time) in patients with atrial fibrillation: Integrated analysis of 2 randomized controlled clinical trials

（心房細動アブレーション周術期におけるダビガトラン内服からアブレーション開始迄の至適時間の検討：2つの無作為化試験に対する統合解析）

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論　文　概　要 (Thesis Abstract)

○ 論文題目

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【目的】

心房細動に対するカテーテルアブレーション周術期において、脳梗塞などの塞栓性合併症のリスクを軽減するため抗凝固療法を行うことが必須であることが示されている。一方で手技に伴う出血性合併症にも注意が必要であり、ジレンマが生じている。近年では抗凝固薬として従来のワルファリンに代わり、より半減期の短い直接経口抗凝固薬を使用することが一般的となっている。半減期が短いことから侵襲的治療の前の中断期間が最小限に抑えられることが大きなメリットとなっているが、カテーテルアブレーション周術期に最小限の中断をすべきかについてははっきりしていない。最近の臨床研究では、直接経口抗凝固薬のひとつであるダビガトランを周術期に継続して治療を行う方法、または最低限の中断で治療を行う方法ともに有用であることが示されている。そのことから、本邦のガイドラインではダビガトランを中断せずに治療を行うことがクラス 1 で、出血性合併症を軽減するために、治療直前の 1 回あるいは 2 回の直接経口抗凝固薬の中断することがクラス 2a で推奨されている。そのため、周術期における抗凝固療薬の内服法は各施設によって違いがみられるのが現状である。そこで本研究は、心房細動アブレーション周術期における、ダビガトランの至適中断時間について明らかにすることを目的とし、ガイドラインの元データとなった先行 2 論文の統合解析を行った。

【対象と方法】

この 2 つの論文は、現時点で参照可能なアブレーション周術期におけるワルファリンとダビガトランの効果・安全性を直接比較した、ただ 2 つの前向き無作為化試験であり、同試験を対象とした。

① Uninterrupted Dabigatran versus Warfarin for Ablation in Atrial Fibrillation (RE-CIRCUIT ClinicalTrials.gov number, NCT02348723)

② Safety and efficacy of minimally interrupted dabigatran vs uninterrupted warfarin therapy in adults undergoing atrial fibrillation catheter ablation: A randomized clinical trial (ABRIDGE-J umin.ac.jp Identifier: UMIN000013129)

両試験のダビガトラン群の 535 名を抽出し、患者個人データよりダビガトラン最終内服からアブレーション施行までの時間（Time of dabigatran oral administration to ablation: O-A time）を算出した。O-A time が 8 時間未満、8 以上 24 時間未満、24 時間以上の 3 群に分類し、両試験の安全性評価基準である大出血イベントの発生率をエンドポイントとして解析を行った。
大出血の定義は両試験ともに International Society of Thrombosis and Hemostasis の基準を用いており、本研究でも採用した。

【結果】

大出血イベントは O-A time が 8 時間未満群で 1.9%、8 時間以上 24 時間未満群で 0%、24 時間以上群では 3.5% であり、3 群間に有意差が認められた。2 群間の検証では、8 時間以上 24 時間未満群は 24 時間以上群と比較して優位に大出血イベントが少なかった（リスク差 3.5%、95%信頼区間 0.5%-10%）。一方で、8 時間以上 24 時間未満群と 8 時間未満群では、8 時間以上 24 時間未満群でイベントは少ない傾向にあるものの、有意差は認められなかった（リスク差 1.9%、95%信頼区間 -0.2%-4.5%）。また術中の静注による抗凝固薬（ヘパリン）の使用量は、O-A time の増加とともに有意に増加した。

【考察】

本研究の結果からは、以下のような O-A time が望ましいと考えた。
・ダビガトランの O-A time は 24 間以内にすべき。
・8－24 時間が望ましい可能性がある。
この理由として、術中に使用したヘパリンの投与量、およびダビガトランの薬物動態、薬理作用を元に考察した。
過去の報告では、侵襲的手術やアブレーション周術期においてヘパリンブリッジを行うと、出血性合併症が増加することが報告されており、24 時間以上群でヘパリン投与量が多いことが、出血が増えた原因として考えられた。一方で、ダビガトランの血中濃度は内服後 2 時間でピークとなり、4－6 時間で 70%程度が代謝される。ダビガトランはワルファリンに比べて、血管損傷時に正常な止血反応が保たれているという報告があり、ワルファリンに比較して出血性合併症が少ないとされている。ダビガトランの血中濃度のピーク時に手技を行うことは、出血を増やす可能性があるが、ピークを避けつつもある程度の効果を残すことで、ヘパリンの投与量を抑制することができ、できるだけ止血作用を阻害しないことが、出血リスク低減に寄与するのではないかと考えた。
一方で本研究には、2 つの研究の患者背景が異なるという大きなリミテーションがある。主に海外で行われた試験と本邦で行われた試験であるという違いがあるため、人種差やダビガトランの用量の違いが挙げられる。本研究の結果を一般化するためにはさらなる研究が必要と考えられる。

【結論】

ダビガトラン内服中の患者において、心房細動に対するカテーテルアブレーションを行う場合、アブレーション施行前のダビガトランの中断時間は 8 時間以上 24 時間未満が適切である可能性がある。

Abstract

Background: RE-CIRCUIT (NCT02348723) and ABRIDGE-J (UMIN000013129) are recently published randomized clinical trials showing that anticoagulation therapy with dabigatran during the periprocedural period of catheter ablation (CA) for atrial fibrillation (AF) was associated with fewer complications. However, the dabigatran administration protocols were different (uninterrupted in RE-CIRCUIT and minimally interrupted in ABRIDGE-J). The aim of this present study was to clarify the optimal interruption time of dabigatran Oral administration to Ablation (O-A time).

Methods: We conducted an integrated analysis of the 2 prospective trials. The endpoint of the study was the incidence of major bleeding events during and up to 8 weeks after CA across participants with different O-A times.

Results: The 535 patients in the dabigatran groups of the 2 trials were divided into 3 groups based on their O-A times (<8 hours, n = 258; 8-24 hours, n = 191; >24 hours, n = 86). Major bleeding events occurred in 5 patients (1.9 %) in the <8 hours group, and 3 (3.5 %) in the >24 hours group; however, no major bleeding events occurred in the 8-24 hours group (3 group-comparison; p = 0.026). No thromboembolic complication was observed in any of the 3 O-A time groups.

Conclusion: In patients undergoing CA for AF using dabigatran as a periprocedural anticoagulant, an O-A time of 8 to 24 hours was associated with no bleeding complications. These data suggest that an O-A time of 8 to 24 hours may be a very appropriate option, especially in a low thromboembolic-risk patient.

Introduction

Catheter ablation (CA) for atrial fibrillation (AF) is a well-established treatment.[1] One of the most important complications associated with CA are thromboembolic events. Systemic anticoagulation during periprocedural period is essential for the reduction of these risks. On the other hand, bleeding complications associated with CA is also important, which poses a dilemma.[1-4] With the advent of direct oral anticoagulants (DOACs) with a shorter half-life, an increasing number of patients with AF undergo CA with DOAC therapy, instead of the conventional warfarin therapy. The short half-life has the great benefit of minimizing the discontinuation prior to invasive treatment including CA. In fact, recent randomized clinical trials (RCTs)[5-9], cohort studies,[10-12] and meta-analyses[13-14] have showed that uninterrupted or minimally interrupted DOACs are associated with lower or non-inferior risk of bleeding and thromboembolic events compared with uninterrupted warfarin. The 2017 consensus statement on AF ablation[1] recommends performing CA without anticoagulant interruption with warfarin or dabigatran (class I); however, it also stated that holding 1 to 2 doses of DOAC prior to CA is reasonable (class IIa).

Dabigatran etexilate (a DOAC) is an oral prodrug that is rapidly converted by a serum esterase to dabigatran, a potent, direct, competitive inhibitor of thrombin. Its serum half-life is 12 to 17 hours[15]. Although dabigatran is used during the periprocedural period of CA in many institutions, its administration protocols in AF patients undergoing CA are diverse. RE-CIRCUIT (NCT02348723)[5] and ABRIDGE-J (UMIN000013129)[6] are recently published RCTs showing that dabigatran therapy was

associated with fewer bleeding complications compared with warfarin therapy; however, the dabigatran administration protocols immediately prior to CA were different between the 2 trials. In RE-CIRCUIT, CA was performed with uninterrupted dabigatran use. In ABRIDGE-J, 1 or 2 doses of dabigatran were put on hold prior to CA. The 2 prospective trials have showed that the incidence of bleeding events slightly differs across participants with different interruption time of dabigatran prior to CA. However, due to the low number of major bleeding events in both trials, the interruption time of dabigatran was not identified as a predictor of bleeding risk. The aim of this present study was to provide further information concerning the optimal interruption time of dabigatran Oral administration to Ablation (O-A time) using an integrated analysis of these 2 prospective trials.

Methods

Study overview

An integrated summary of effectiveness using the integrated analysis of these 2 prospective trials (RE-CIRCUIT and ABRIDGE-J) was performed (summaries of both trials are shown in **Table 1**). RE-CIRCUIT was a prospective RCT in patients undergoing CA for AF. The complete study design, methodology, and primary results were published previously.[5] In brief, eligible patients were randomly assigned to anticoagulation with dabigatran 150 mg twice daily (bid) or international normalized ratio (INR)-adjusted warfarin. CA was performed with uninterrupted anticoagulation (**Figure 1A**). ABRIDGE-J[6] was also a prospective RCT that enrolled patients undergoing CA of AF in Japan. Eligible patients were randomly assigned to anticoagulation with dabigatran (150 or 110 mg bid; the 110 mg bid dose was administered to patients with moderate renal disorders [creatinine clearance 30 to 50 mL/min], those concomitantly receiving p-glycoprotein antagonists, or those with a high risk of bleeding) or INR-adjusted warfarin. CA was performed with minimally interrupted dabigatran (1-2 doses were put on hold before ablation) or uninterrupted warfarin. Heparin bridging based on the Japanese recommendations and guidelines[16] was recommended if dabigatran therapy was discontinued at least 24 hours prior to CA. After the CA procedure, dabigatran therapy was resumed (**Figure 1B**). In both trials, an activated clotting time (ACT) of more than 300 seconds was achieved and maintained during CA by administration of unfractionated heparin. The 2 trials were performed in accordance with the provisions of the Declaration of Helsinki and the International Conference on Harmonization Good

Clinical Practice Guidelines. All patients provided written informed consent before entering the 2 trials. The protocol of this integrated analysis was approved by the institutional review board (IRB) of the University of Tsukuba (R01-093). It was also confirmed that re-acquisition of written informed consent for the secondary use of data was not required by the IRB.

Patient population

Patients with documented paroxysmal or persistent non-valvular AF that were scheduled to undergo CA were eligible for treatment with dabigatran. Full details of the RE-CIRCUIT and ABRIDGE-J inclusion/exclusion criteria have been published previously.[5-6]

Endpoints

The endpoint of this study was the incidence of adjudicated major bleeding events, as defined by the International Society on Thrombosis and Hemostasis (ISTH),[17] during and up to 8 weeks after the CA. The definition was the same for the 2 trials. Considering the original 2 trials and daily practice, O-A times were classified into less than 8 hours (<8 hours group; uninterrupted with shorter intervals), 8 to 24 hours (8-24 hours group; uninterrupted but with a longer interval or hold 1 dose), and more than 24 hours (>24 hours group; hold 2 doses).

Statistical analysis

The analyzed population in this study was based on the definitions of RE-CIRCUIT and ABRIDGE-J, and thus included all randomly assigned patients who had taken at least one study drug and had undergone the CA procedure. In comparisons of the baseline clinical characteristics, continuous variables were presented as medians and interquartile ranges. The Kruskal-Wallis test was used to compare between the 3 O-A time groups. Categorical variables were reported as absolute values and percentages and were compared using Fisher's exact test. In the primary analysis, the difference in incidence of adjudicated major bleeding events between the O-A time groups was evaluated using Fisher's exact test. In pair-wise comparisons between the 8-24 hours group and other groups, the difference in the incidence and its 95% exact confidence interval (CI) were estimated and assessed using Fisher's exact test. In all analyses, P-values of <0.05 were considered to indicate significance. All statistical analyses were performed by a biostatistician (Gosho and Ohigashi) with the use of SAS version 9.4 (SAS Institute Inc., Cary, NC).

Results

Patient characteristics

In RE-CIRCUIT, 635 patients underwent CA (dabigatran, n = 317; warfarin, n = 318), while in ABRIDGE-J, 442 underwent CA (dabigatran, n = 220; warfarin, n = 222). Regarding the evaluation of O-A time, 2 patients in the RE-CIRCUIT trial had missing CA times. The remaining 535 patients in the dabigatran groups in both trials were divided into 3 groups based on their O-A time (<8 hours, n = 258; 8-24 hours, n = 191; >24 hours, n = 86) (**Figure 2**). The baseline characteristics are shown in **Table 2, 3**. Due to differences in the participants of the 2 trials, there were significant differences in several baseline characteristics (e.g., age, body-mass index [BMI], ethnicity, and non-steroidal anti-inflammatory drugs [NSAIDs] use). The dabigatran dose was 150 mg and 110 mg bid in 255 patients (99%) and 3 patients (1%) in the <8 hours group, 111 patients (58 %) and 80 patients (42%) in the 8-24 hours group, and 46 patients (53%) and 40 patients (47%) in the >24 hours group, respectively (p <0.001).

Endpoint

Overall, 8 patients developed major bleeding events (**Table 4**). In the <8 hours group, pericardial tamponade/effusion occurred in 2 patients and vascular access bleeding in 2 patients. These 4 events occurred on the day of CA. Gastrointestinal bleeding occurred in 1 patient 36 days after CA. In the >24 hours group, pericardial effusion, intraperitoneal bleeding, and vascular access bleeding occurred in 1

patient each. All 3 patients had 2 doses of their dabigatran treatment interrupted without heparin bridging before CA and had suffered the major bleeding events on the day of or one day after the procedure. However, no major bleeding events occurred in the 8-24 hours group (3 group-comparison; p = 0.026, **Figure 3**). Furthermore, the incidence of major bleeding events was significantly higher in the >24 hours group than in the 8-24 hours group (risk difference [RD], 3.5%; 95% CI, 0.5% to 10%; p = 0.029). The incidence in the <8 hours group was higher than that in the 8-24 hours group, but there was no statistical difference between the 2 groups (RD, 1.9%; 95% CI, -0.2% to 4.5%; p = 0.075). No thromboembolic complication was observed in any of the 3 O-A time groups.

Comparison of heparin dosing between the 3 groups

The total dose of heparin administered to maintain an ACT >300 seconds during CA was compared between the 3 groups (**Figure 4**). A higher dose was needed in patients with a longer OA time (3 group-comparison; p <0.001).

Discussion

Main findings

To the best of our knowledge, RE-CIRCUIT and ABRIDGE-J are the only 2 RCTs to report that dabigatran is associated with a significantly lower rate of major bleeding events than INR-adjusted warfarin. No thromboembolic complication occurred in the dabigatran groups of either trial. Integrated analysis of the 2 trials demonstrated that patients in the 8-24 hours group did not develop any major bleeding complications. In fact, patients in the >24 hours group had a significantly higher incidence rate of major bleeding. Our findings support the notion that periprocedural use of dabigatran is safe, especially with <24 hours of interruption prior to CA. While our analysis suggests that the lowest bleeding risk is seen with 8-24 hours of interruption, pair-wise comparison of <8 and 8-24 hour groups showed no difference.

Anticoagulation implications of a short period of interruption of dabigatran

Regarding the pharmacokinetics of dabigatran, the peak plasma concentrations occur within 2 hours of administration. After the peak is reached, levels fall in a biphasic manner consistent with a rapid distribution phase and resulting in a more than 70% decrease within 4 to 6 hours of administration.[18] In this study, a lower dose of heparin was needed to maintain an ACT >300 seconds in patients with a shorter O-A time. Since dabigatran can prolong ACT in a dose-dependent manner[19], the shorter O-A time suggested that the anticoagulant effect of dabigatran was sustained. In addition, the ABRIDGE-J trial[6] showed that activated partial thromboplastin time (APTT) at baseline (41.2 seconds) was longer

than that after holding 1 and 2 doses (36.7 seconds and 32.2 seconds, respectively). Since dabigatran can also prolong APTT in a dose-dependent manner[19], the anticoagulant effect of dabigatran persisted up to the time of vascular puncture in the <8 hours group, which might have led to the increased incident of major bleeding events. In fact, a recent report showed that the effect of the suture technique at vascular access sites on hemostasis after AF ablation with uninterrupted DOAC was small.[20]

In contrast, we must balance the bleeding risk with thromboembolic risk. A shorter period of interruption may be associated with a slightly higher bleeding risk, but it also results in more effective anticoagulation. While no thromboembolic complication occurred in our study, our study included patients with low thromboembolic risk (most patients had a CHADS2 score of 2 or less) and the sample size was too small to draw any conclusions about thromboembolic risk. Additionally, asymptomatic thromboembolic events have been reported to increase after cryoballoon AF ablation with interrupted dabigatran therapy.[21] For a patient presenting AF for ablation with a high thromboembolic risk profile, continuous anticoagulation with <8 hours of interruption may be of benefit in reducing the thromboembolic risk.

Considerations for intermediate interval prior to CA

A recent report has showed that the levels of prothrombin fragments 1+2 (F1+2, a marker of thrombin generation) increase after a vascular puncture during DOAC (dabigatran, rivaroxaban, and apixaban) therapy.[22] Since this thrombin generation-preserving effect has been confirmed after holding 1 dose of

DOAC prior to puncture, it might have suppressed the major bleeding events in the 8-24 hours group. Furthermore, the same report mentioned that this effect was more pronounced with dabigatran than with rivaroxaban and apixaban. In fact, uninterrupted rivaroxaban and apixaban have only demonstrated non-inferiority to warfarin for major bleeding events[7-8], while dabigatran is the only DOAC that has shown superiority to warfarin. Additionally, no thromboembolic complication was observed in our study. The ABRIDGE-J trial[7] showed that APTT in patients holding 1 dose of dabigatran (36.7 seconds) was longer than in those holding 2 doses (32.2 seconds), indicating the moderate sustainability of the anticoagulant at the start of CA in the 8-24 hours group. Recent RCTs[23-24] also revealed that both uninterrupted and minimally interrupted DOACs were associated with a very low rate of thromboembolic complication for low-risk patients too. Dabigatran with 8 to 24 hours of interruption might be a well-balanced protocol with anticoagulant and preservation of thrombin generation properties that can help prevent both hemorrhagic and thromboembolic complications at least for low thromboembolic-risk patients.

Disadvantages of a long interval prior to CA

In this study, all 3 major bleeding events in the >24 hours group occurred during or immediately after CA. Since dabigatran preserves thrombin generation, the effect of dabigatran and heparin is not entirely additive. A previous RCT[25] and meta-analysis[26] showed that heparin bridging due to warfarin interruption increases not only thromboembolic but also bleeding events during CA for AF. Similarly, increasing heparin dosing due to long interruption of dabigatran might have increased major bleeding

events, especially intraprocedural bleeding. Instability of the anticoagulant effect due to interruption or change of drug might increase the risk of complications.

Differences in background of bleeding risk between the 2 trials

Some background characteristics were considerably different between the 3 groups due to differences in the participants of the 2 trials. Particularaly, prior gastrointestinal bleeding and NSAID use were the most frequent in the <8 hours group. These might have affected the incidence rate of major bleeding events, especially in the <8 hours group. Additionally, the characteristic factors should be statistically adjusted using multivariate analysis when comparing the incidence of major bleeding in different O-A time groups. However, multivariate analysis was difficult to perform since the incidence rate was too low, with no events in the 8-24 hours group. On the other hand, there was no apparent difference in background factors other than NSAIDs use between patients with and without major bleeding **(Table 5**).

Limitations

This study has several limitations other than the background differences mentioned above. First, there were several differences in the intervention protocols between the 2 trials. Particularly, ABRIDGE-J permitted 2 different doses of dabigatran (150 mg or 110 mg bid) and heparin bridging. These might

have affected the incidence rate of major bleeding events. Second, some consistent parameters related to bleeding in the 2 trials were not available (e.g., actual ACT values during CA or HAS-BLED score). Third, the exclusion criteria of the trials were slightly different (e.g., RE-CIRCUIT excluded patients with permanent AF and left atrial size ≥60 mm). Detailed differences are described in Supplemental Table 1. Fourth, although the definition of major (satisfying the ISTH criteria) and minor (clinical bleeding events that did not satisfy the ISTH criteria for major bleeding events) bleeding was the same in the 2 trials, the incidence rate of minor bleeding events was significantly different (19% in the warfarin group of RE-CIRCUIT and 2% in the warfarin group of ABRIDGE-J, $p < 0.001$). While the cause of this discrepancy is uncertain, it may be related to the vague definition of minor bleeding. Thus, we considered that it was difficult to quantitatively assess the incidence rate of minor bleeding events. On the other hand, the incidence rate of major bleeding events in the warfarin groups of both trials was similar (7% in RE-CIRCUIT and 5% in ABRIDGE-J, $p = 0.35$), and the definition of major bleeding was clear and valid. Thus, only the incidence rate of major bleeding events was evaluated as an endpoint. Fifth, complication rate including major bleeding events depends on the operator's skill. Since the 2 original RCTs were conducted in relatively high-volume centers in the respective country, our results may not be widely generalizable. Sixth, our analysis was not designed to detect the differences in thromboembolic risk. Not only was the population of enrolled patients a low thromboembolic-risk population, but the number of subjects was too small to detect differences in thromboembolic risk.

Although these limitations cannot be overlooked, the results of our integrated analysis suggest that the

dabigatran administration protocol is related to the risk of major breeding. Future studies are required to establish the optimal administration protocol for not only dabigatran but also other DOACs.

Conclusion

In patients undergoing CA for AF using dabigatran as a periprocedural anticoagulant, an O-A time of > 24 hours was associated with the highest bleeding risk. An O-A time of 8 to 24 hours was associated with no bleeding complications. These data suggest that an O-A time of 8 to 24 hours is optimal when considering the perspective of bleeding risk at the time of AF ablation. However, from a thromboembolic prevention perspective, the optimal interruption period remains poorly defined but is likely to be <8 hours. From a clinical perspective, we suggest that the interruption period be <24 hours. In high thromboembolic-risk patients, no interruption may be optimal. However, in a low thromboembolic-risk patient, minimal interruption may be a very appropriate option.

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Source

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Tables

Table 1. Summary of the 2 included trials

	RE-CIRCUIT	ABRIDGE-J
Publication year	2017	2019
Study design	Randomized clinical trial	Randomized clinical trial
Sample size	635 dabigatran, 317 warfarin, 318 from 104 sites in 11 countries	442 dabigatran, 220 warfarin, 222 from 28 sites in Japan
Dabigatran administration protocol	Uninterrupted	Minimally interrupted (1-2 doses were put on hold before ablation)
Key inclusion criteria	Patients with NVAF ● planned ablation of AF ● 18 years of age or older ● eligible for dabigatran	Patients with NVAF ● planned ablation of AF ● 20 to 85 years ● eligible for dabigatran
Key exclusion criteria	● Permanent AF ● AF secondary to an obvious reversible cause ● Valvular AF ● Left atrial size ≥60 mm	● Valvular AF ● Hemodynamically significant mitral valve stenosis ● Rheumatic heart disease
Follow-up period	8 weeks	3 months
Primary outcomes	Incidence of **major bleeding events as defined by ISTH**	Incidence of embolism
Secondary outcomes	Incidence of the following events ● Composite of stroke, systemic embolism, or TIA ● Minor bleeding events ● Composite of major bleeding events and thromboembolic events	Incidence of the following events ● **Major bleeding events as defined by ISTH** ● All-cause death ● Composite incidence of all bleeding events, thromboembolic events, and all-cause death
Public trial registry	ClinicalTrials.gov Number: NCT02348723	umin.ac.jp Identifier: UMIN000013129

Table 2. Clinical characteristics

O-A time		<8 hours	8-24 hours	>24 hours	p value
	N	258	191	86	
Age	year	60.0 (53.0-67.0)	63.0 (56.0-70.0)	64.0 (55.0-70.0)	0.001
Male gender	N (%)	187 (72)	150 (79)	63 (73)	0.32
BMI	kg/m2	27.2 (23.9-30.7)	25.2 (22.5-28.1)	24.5 (22.1-26.3)	<0.001
CHADS2 score	N (%)				0.19
0		104 (40)	66 (35)	34 (40)	
1		93 (36)	82 (43)	26 (30)	
2		50 (19)	29 (15)	18 (21)	
≥3		11 (4)	14 (7)	8 (9)	
Ejection fraction	%	60.0 (55.0-65.0)	65.0 (60.0-70.0)	65.9 (60.0-71.0))	<0.001
Atrial fibrillation	N (%)				0.46
Paroxysmal		171 (66)	123 (64)	55 (64)	
Persistent		70 (27)	47 (25)	21 (24)	
Longstanding persistent		17 (7)	21 (11)	10 (12)	
Ethnicity	N (%)				<0.001
White		184 (72)	43 (24)	3 (3)	
Black/African American		3 (1)	1 (1)	0 (0)	
Asia		68 (27)	134 (75)	83 (97)	
Hawaiian/Pacific Islander		1 (0)	0 (0)	0 (0)	
(Missing)		2	13	0	

Table 3. Medical history

O-A time		<8 hours	8-24 hours	>24 hours	p value
	N	258	191	86	
Medical history	N (%)				
Congestive heart failure		28 (11)	8 (4)	3 (3)	0.009
Previous stroke		9 (3)	11 (6)	5 (6)	0.46
Previous coronary artery disease		27 (10)	10 (5)	2 (2)	0.017
Previous gastrointestinal bleeding		21 (8)	2 (1)	1 (1)	<0.001
Renal dysfunction		8 (3)	10 (5)	4 (5)	0.51
Diabetes mellitus		25 (10)	25 (13)	16 (19)	0.086
Hypertension		134 (52)	111 (58)	44 (51)	0.36
Medication use	N (%)				
Antiplatelet drugs		0 (0)	11 (6)	6 (7)	<0.001
Proton-pump inhibitors		54 (21)	41 (21)	12 (14)	0.31
H2 blockers		14 (5)	5 (3)	1 (1)	0.12
NSAIDs		46 (18)	9 (5)	1 (1)	<0.001
Dose of dabigatran during perioperative period	N (%)				<0.001
150 mg bid		255 (99)	111 (58)	46 (53)	
110 mg bid		3 (1)	80 (42)	40 (47)	

Table 4. Details of major bleeding events

*1 = day of CA, † Dose of dabigatran (mg bid)

Table 5. Clinical characteristics of patients with and without major bleeding events

		Major bleeding	No major bleeding	p value
	N	8	529	
Age	year	65.0(60.5-74.5)	62.0(54.0-68.0)	0.14
Male gender	N(%)	4(50)	397(75)	0.12
BMI	kg/m^2	27.6(23.8-31.8)	25.9(23.2-29.2)	0.50
CHADS2 score	N(%)			0.050
0		0(0)	205(39)	
1		5(63)	197(37)	
2		3(38)	94(18)	
≥3		0(0)	33(6)	
Ejection fraction	%	70.0(65.0-75.0)	62.0(58.0-67.0)	0.15
Atrial fibrillation	N(%)			0.52
Paroxysmal		6(75)	345(65)	
Persistent		1(13)	137(26)	
Longstanding persistent		1(13)	47(9)	
Medical history	N(%)			
Congestive heart failure		0(0)	39(7)	1.00
Previous stroke		1(13)	24(5)	0.32
Previous coronary artery disease		1(13)	38(7)	0.46
Previous gastrointestinal bleeding		1(13)	23(4)	0.31
Renal dysfunction		1(13)	21(4)	0.29
Diabetes mellitus		0(0)	66(12)	0.60
Hypertension		7(88)	282(53)	0.075
Medication use	N(%)			
Antiplatelet drugs		0(0)	17(3)	1.00
Proton-pump inhibitors		4(50)	103(19)	0.054
H2 blockers		0(0)	20(4)	1.00
NSAIDs		3(38)	54(10)	0.043
Dose of dabigatran during perioperative period				0.69
150 mg twice daily		7(88)	407(77)	
110 mg twice daily		1(13)	122(23)	
Race	N(%)			1.00
White		4(50)	228(44)	
Black/African Amer.		0(0)	4(1)	
Asia		4(50)	281(55)	
Hawaiian/Pacif. Isle		0(0)	1(0)	
(Missing)		0	15	

No significant differences were found in baseline characteristics, such as BMI, CHADS2 score, past medical history and race, between patients with and without major bleeding events in the dabigatran group. Regarding the medication, there were no significant differences in antiplatelet drug use and dose of dabigatran. However only in NSAIDs use, more patients with major bleeding events had taken NSAIDs.

BMI, body-mass index; NSAIDs, non-steroidal anti-inflammatory drugs.

Figure

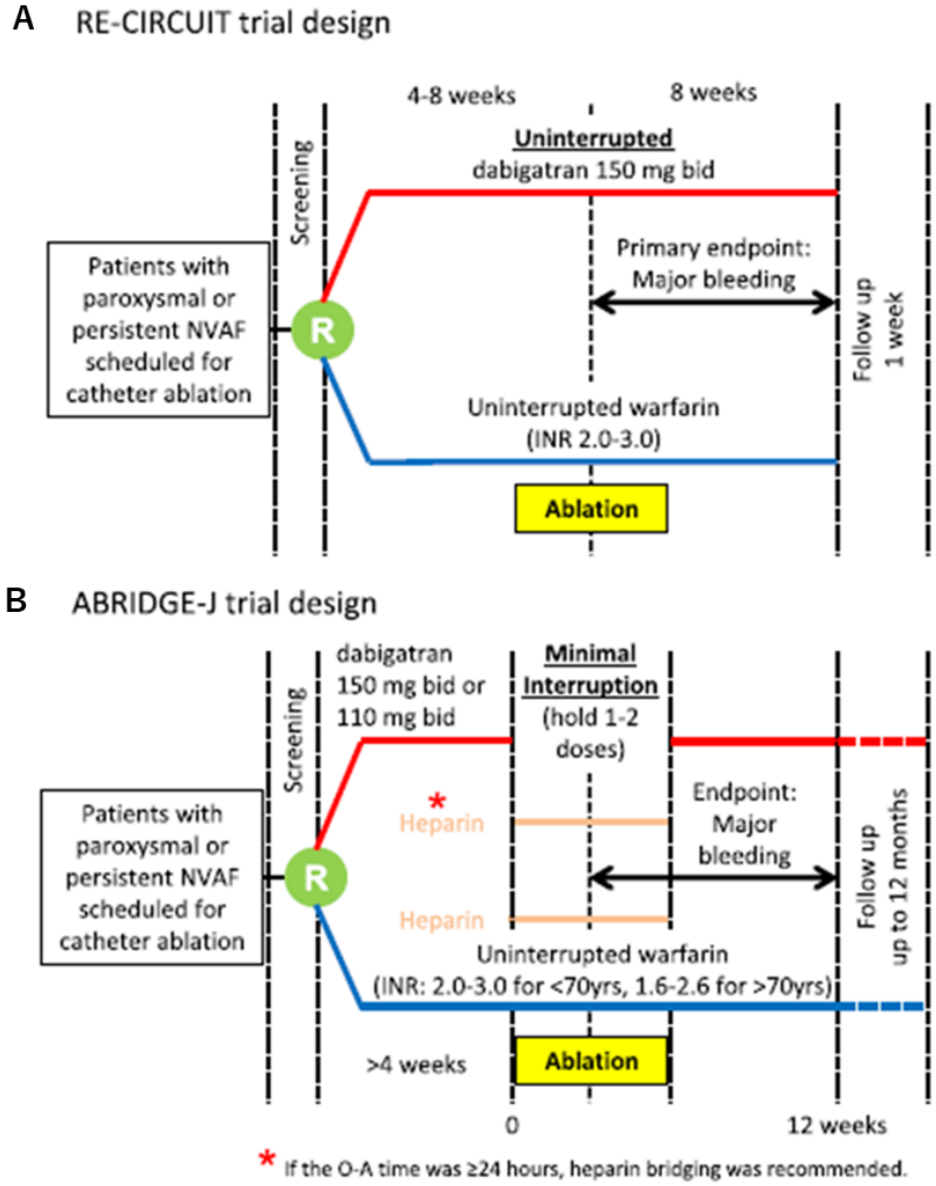


Figure 1

NVAF, non-valvular atrial fibrillation; R, randomization; bid, twice daily; INR, international normalized ratio

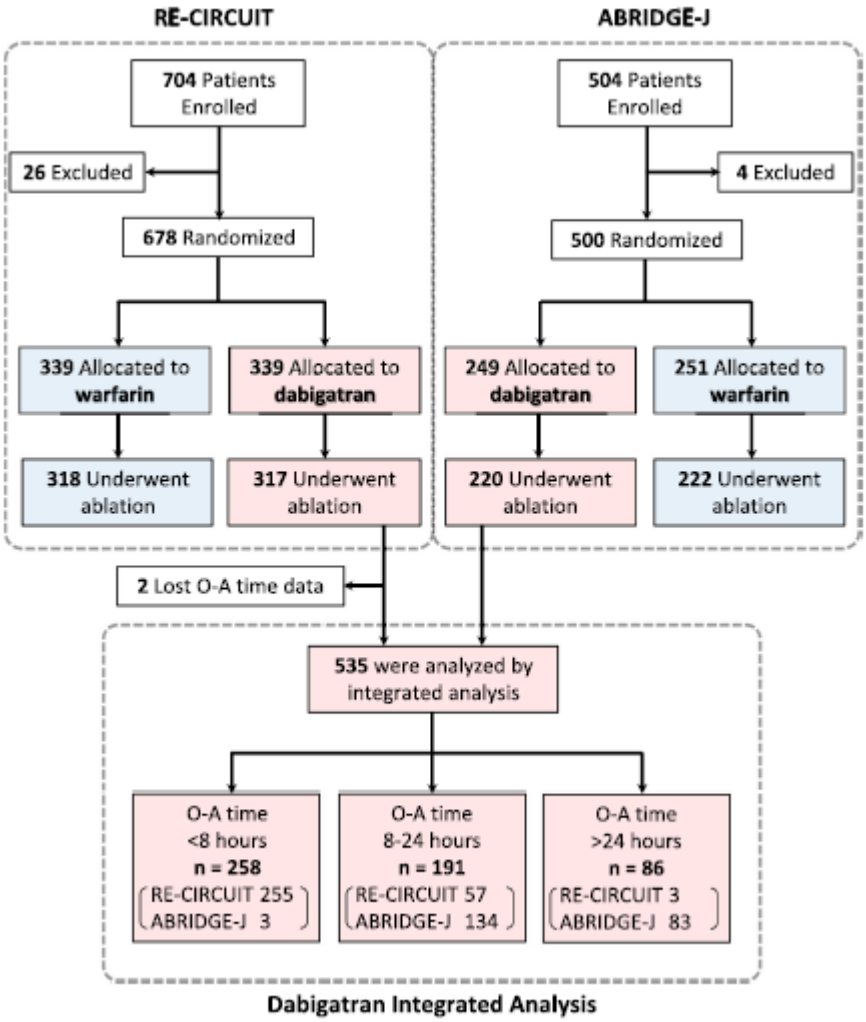
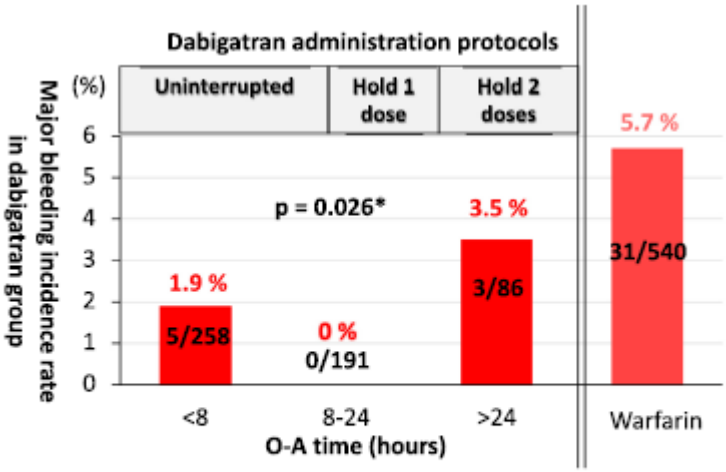


Figure 2

O-A time, interruption time of dabigatran oral administration to ablation



comparison between each 2 groups

O-A time	p-value	RD	95% CI
0-8 vs 8-24	0.075	1.9%	-0.2% - 4.5%
24- vs 8-24	0.029	3.5%	0.5% - 10%

Figure 3

*p-value of 3 group-comparison

O-A time, interruption time of dabigatran oral administration to ablation; RD, risk difference; CI, confidence interval

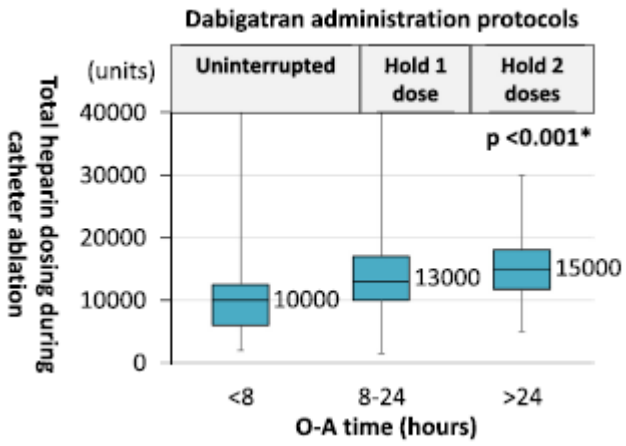


Figure 4

*p-value of 3 group-comparison

O-A time, interruption time of dabigatran oral administration to ablation