Dabigatran Versus Warfarin in Patients With Atrial Fibrillation
An Analysis of Patients Undergoing Cardioversion

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Background—The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial compared dabigatran 110 mg BID (D110) and 150 mg BID (D150) with warfarin for stroke prevention in 18 113 patients with nonvalvular atrial fibrillation. Methods and Results—Cardioversion on randomized treatment was permitted. Pre-cardioversion transeosophageal echocardiography was encouraged, particularly in dabigatran-assigned patients. Data from before, during, and 30 days after cardioversion were analyzed. A total of 1983 cardioversions were performed in 1270 patients: 647, 672, and 664 in the D110, D150, and warfarin groups, respectively. For D110, D150, and warfarin, transeosophageal echocardiography was performed before 25.5%, 24.1%, and 13.3% of cardioversions, of which 1.8%, 1.2%, and 1.1% were positive for left atrial thrombi. Continuous treatment with study drug for ≥3 weeks before cardioversion was lower in D110 (76.4%) and D150 (79.2%) compared with warfarin (85.5%; P<0.01 for both). Stroke and systemic embolism rates at 30 days were 0.8%, 0.3%, and 0.6% (D110 versus warfarin, P=0.71; D150 versus warfarin, P=0.40) and similar in patients with and without transeosophageal echocardiography. Major bleeding rates were 1.7%, 0.6%, and 0.6% (D110 versus warfarin, P=0.06; D150 versus warfarin, P=0.99). Conclusions—This study is the largest cardioversion experience to date and the first to evaluate a novel anticoagulant in this setting. The frequencies of stroke and major bleeding within 30 days of cardioversion on the 2 doses of dabigatran were low and comparable to those on warfarin with or without transeosophageal echocardiography guidance. Dabigatran is a reasonable alternative to warfarin in patients requiring cardioversion. Clinical Trial Registration—URL: http://www.ClinicalTrials.gov. Unique identifier: NCT00262600. (Circulation. 2011;123:131-136.)

Key Words: anticoagulants ■ arrhythmia ■ atrial fibrillation ■ cardioversion ■ stroke prevention

Cardioversion (both electric and pharmacological) in patients with atrial fibrillation is associated with an increased risk of thromboembolic events.1-3 Risk is higher (5% to 7%) if anticoagulation is inadequate.4,5 With adequate anticoagulation, the risk of thromboembolic events is much lower (0.7% to 0.8%).6 For patients with atrial fibrillation of ≥48 hours duration, the current recommendation is therapeutic anticoagulation for at least 3 weeks before and 4 weeks after cardioversion.7,8

Clinical Perspective on p 136

Warfarin is currently the only US Food and Drug Administration–approved oral anticoagulant for the treatment of atrial fibrillation. Dabigatran is a novel oral anticoagulant that is a potent, competitive, and reversible direct thrombin inhibitor. It has a rapid onset of action, with peak plasma concentration occurring 0.5 to 2 hours after administration, and a half-life of 12 to 17 hours.9,10 The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial was a multicenter, prospective, randomized, noninferiority trial that compared dabigatran 110 mg BID (D110) and 150 mg BID (D150) administered in a blinded manner with open-label warfarin for stroke prevention in 18 113 patients with nonvalvular atrial fibrillation.11,12 D110 was similar to and D150 was superior to warfarin for the prevention of
thromboembolism and stroke, but the efficacy and safety of dabigatran in the setting of cardioversion are uncertain. This report is a posthoc analysis of patients who underwent cardioversion in RE-LY and is the first report describing the experience of a novel, orally active anticoagulant in the setting of cardioversion.

Methods

All patients who underwent cardioversion during their participation in the RE-LY trial were included in this analysis. The study protocol recommended maintenance of the assigned study drug during cardioversion. As a safety measure, transesophageal echocardiography (TEE) was encouraged if cardioversion was planned for within the first 60 days after randomization. The protocol also recommended maintenance of the assigned study drug during cardioversion; time in hours since the last dose of dabigatran was recorded, as was whether it was TEE guided and, if so, whether any spontaneous echo contrast or left atrial thrombi were identified. The method of cardioversion (electric or pharmacological) was recorded, as was whether it was TEE guided and, if so, whether any spontaneous echo contrast or left atrial thrombi were identified. Stroke and systemic embolism and major bleeding episodes within 30 days of the cardioversion were the major outcome measures.

Stoke was defined as the sudden onset of a focal neurological deficit in a location consistent with the territory of a major cerebral artery and categorized as ischemic, hemorrhagic, or unspecified. Hemorrhagic transformation of ischemic stroke was not considered hemorrhagic stroke. Intracranial hemorrhage consisted of hemorrhagic stroke and subdural or subarachnoid hemorrhage. Systemic embolism was defined as an acute vascular occlusion of an extremity or organ documented by means of imaging, surgery, or autopsy. Major bleeding was defined as a reduction in the hemoglobin level of at least 20 g/L, transfusion of at least 2 U blood, or symptomatic bleeding in a critical area or organ. Separate intention-to-treat analyses were performed for all cardioversions and for first cardioversions only.

The RE-LY trial was funded by Boehringer Ingelheim and was coordinated by the Population Health Research Institute (Hamilton, ON, Canada), where the data were analyzed. An Operations Committee made up of the 2 coprincipal investigators (Michael D. Ezekowitz, MBChB, DPhil, FRCP, Stuart J. Connolly, MD), 2 cochairs (Lars Wallentin, MD, PhD, Salim Yusuf, FRCP, DPhil), and 2 sponsor representatives (Paul A. Reilly, PhD, Manfred Haehl, MD), with assistance from an international steering committee, was responsible for the design, conduct, data analysis, and reporting of the study. The study was approved by all appropriate national regulatory authorities and ethics committees. All patients provided written informed consent.

All authors of this posthoc analysis vouch for the accuracy and completeness of the data and the analysis. All end points and major bleeding events were adjudicated by an end-point committee blinded to treatment assignment.

Results

A total of 1983 cardioversions were performed in 1270 patients during the course of the RE-LY trial: 647, 672, and 664 in the D110, D150, and warfarin groups, respectively (Table 1). Most cardioversions were performed on protocol-assigned study drug taken for at least 3 weeks before cardioversion (76.4%, 79.2%, and 85.5% in D110, D150, and warfarin; D110 versus warfarin, P=0.0001; D150 versus warfarin, P<0.0001; Table 2). Patients were switched to a nonstudy oral anticoagulant for a minority of cardioversions (9.7%, 8.6%, and 5.4% in D110, D150, and warfarin; D110 versus warfarin, P=0.003; D150 versus warfarin, P=0.02). Patients were rarely switched to aspirin alone, aspirin plus clopidogrel, intravenous heparin, low-molecular-weight heparin, or any other antithrombotic, and very few patients were not on any antithrombotic therapy at the time of cardioversion. The majority of patients continued on RE-LY protocol-assigned study drug after cardioversion (85.8%, 88.7%, and 94.3% in D110, D150, and warfarin; D110 versus warfarin, P<0.0001; D150 versus warfarin, P=0.0003).
TEE was performed before cardioversion more often in patients assigned to dabigatran than in those receiving study warfarin (25.5%, 24.1%, and 13.3% for D110, D150, and warfarin, respectively; D110 versus warfarin, \(P < 0.0001\); D150 versus warfarin, \(P < 0.0001\); Table 1). There was no difference in the incidence of left atrial spontaneous echo contrast (21.2%, 27.2%, and 31.8% of TEEs in the D110, D150, and warfarin groups, respectively) or left atrial appendage thrombus (1.8%, 1.2%, and 1.1%, respectively).

The majority of cardioversions were electric: 85.6%, 81.9%, and 83.3% in D110, D150, and warfarin, respectively (Table 1). The remainder were pharmacological except for 2 cardioversions in the D110 group that were reported as "spontaneous." Normal sinus rhythm was achieved at discharge in 87.5%, 88.7%, and 89.6% of cardioversions in D110, D150, and warfarin, respectively.

Stroke and systemic embolic event rates within 30 days of cardioversion were low (0.77%, 0.30%, and 0.60% in D110, D150, and warfarin, respectively; D110 versus warfarin, \(P = 0.71\); D150 versus warfarin, \(P = 0.45\); Table 1). Stroke and systemic embolism rates were similar in patients with TEE before cardioversion (0.61%, 0.00%, and 1.14% for D110, D150, and warfarin, respectively; D110 versus warfarin, \(P = 0.65\); D150 versus warfarin, \(P = 0.17\) and without TEE (0.83%, 0.39%, and 0.52% for D110, D150, and warfarin, respectively; D110 versus warfarin, \(P = 0.54\); D150 versus warfarin, \(P = 0.75\)). For the primary end point, the Kaplan-Meier curves and hazard rates were plotted for D110 and D150 versus warfarin (the Figure). Hazard rates were low. The \(P\) values for the log-rank tests were 0.71 and 0.40, respectively, leading to 30-day survival probability estimates of 0.994 and 0.997. The first 3 events in the D110 and warfarin groups occurred within the first 5 days after cardioversion, whereas the first event for the D150 group occurred on day 13.

Major bleeding was infrequent in all groups (1.7%, 0.6%, and 0.6% in D110, D150, and warfarin, respectively). Table 2 presents the antithrombotic therapy before and during cardioversion.
3 shows the characteristics of patients who had outcome events. We performed a separate analysis for first cardioversions of each patient. The results were consistent with those from all cardioversions. There were 1270 first-time cardioversions, with 413, 421, and 436 in the D110, D150, and warfarin groups, respectively. The stroke and systemic embolic event rates were low (0.48%, 0.48%, and 0.46% in D110, D150, and warfarin; D110 versus warfarin, \( P = 0.96 \); D150 versus warfarin, \( P = 0.97 \)). Major bleeding rates were low (2.66%, 0.48%, and 0.46% in D110, D150, and warfarin; D110 versus warfarin, \( P = 0.009 \); D150 versus warfarin, \( P = 0.97 \)).

Eight patients were not followed up for the full 30 days after cardioversion. Seven of them died and 1 withdrew consent and refused follow-up. Among the deaths, 6 were characterized as vascular and 1 as respiratory failure. For 3 of these patients, cardioversion occurred in the setting of an acute hospitalization.

Table 3. Outcome Events and Antithrombotic Therapy of Patients Who Had Events Within 30 Days After Cardioversion

<table>
<thead>
<tr>
<th>Event</th>
<th>Stroke or Systemic Embolism Events, ( n (% ) )</th>
<th>Major Bleeding Events, ( n (% ) )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>D110</td>
<td>D150</td>
</tr>
<tr>
<td>Total (&lt;30 d after cardioversion)</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>TEE before cardioversion</td>
<td>1 (20)</td>
<td>1 (25)</td>
</tr>
<tr>
<td>Left atrial spontaneous echo contrast</td>
<td>1 (25)</td>
<td>1 (25)</td>
</tr>
<tr>
<td>Left atrial appendage thrombus</td>
<td>1 (25)</td>
<td>1 (25)</td>
</tr>
<tr>
<td>Antithrombotic therapy before and during cardioversion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomized treatment for ( \geq 3 ) wk before cardioversion</td>
<td>3 (60)</td>
<td>1 (50)</td>
</tr>
<tr>
<td>Randomized treatment for &lt;3 wk before cardioversion</td>
<td>1 (9 )</td>
<td>1 (25)</td>
</tr>
<tr>
<td>Aspirin with clopidogrel</td>
<td>1 (20)</td>
<td></td>
</tr>
<tr>
<td>Aspirin without clopidogrel</td>
<td></td>
<td>1 (25)</td>
</tr>
<tr>
<td>Nonstudy oral anticoagulant</td>
<td>1 (20)</td>
<td>1 (25)</td>
</tr>
<tr>
<td>Intravenous heparin</td>
<td>1 (20)</td>
<td>1 (25)</td>
</tr>
<tr>
<td>Low–molecular-weight heparin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td></td>
<td>1 (9 )</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>1 (50)</td>
</tr>
<tr>
<td>Antithrombotic therapy within 30 d after cardioversion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomized treatment</td>
<td>3 (60)</td>
<td>2 (100)</td>
</tr>
<tr>
<td>Aspirin with clopidogrel</td>
<td>3 (60)</td>
<td></td>
</tr>
<tr>
<td>Aspirin without clopidogrel</td>
<td>1 (50)</td>
<td>1 (9 )</td>
</tr>
<tr>
<td>Nonstudy oral anticoagulant</td>
<td>2 (40)</td>
<td>1 (50)</td>
</tr>
<tr>
<td>Parenteral anticoagulant</td>
<td>1 (50)</td>
<td>1 (25)</td>
</tr>
</tbody>
</table>

Patients could be on more than one of the above therapies concurrently.

Discussion
The major finding of this study was that stroke and systemic embolism and major bleeding rates after cardioversion were low in both the dabigatran- and warfarin-assigned groups. Cardioversion was first conceived and used in patients with atrial fibrillation in the late 1950s and early 1960s. The risk of thromboembolism is highest during the first week after cardioversion (5.6%) in the absence of adequate anticoagulation. In a nonrandomized, prospective cohort study of 437 patients, Bjerkelund and Orning were the first to demonstrate the role of precardioversion anticoagulation therapy in reducing the risk of stroke after cardioversion. The use of anticoagulation in the setting of cardioversion has undergone limited evaluation in randomized prospective trials, and the current recommendation of therapeutic anticoagulation with warfarin for at least 3 weeks before and 4 weeks after cardioversion is based on small, nonrandomized observational and retrospective studies.

TEE is a moderately invasive, well-tolerated diagnostic imaging technique that allows excellent visualization of the left atrium and left atrial appendage. TEE has excellent sensitivity and specificity for the identification of left atrial thrombi. The Assessment of Cardioversion Using Transesophageal Echocardiography (ACUTE) trial including 1222 patients demonstrated comparable risk of thromboembolic events with both the conventional strategy of 3 weeks of warfarin before cardioversion and the TEE-guided strategy of short-term anticoagulation with intravenous unfractionated heparin or warfarin and immediate cardioversion (0.5% and 0.8%, respectively; \( P = 0.50 \)). These event rates are similar to those found in RE-LY. The TEE-guided group in the ACUTE study had a significantly lower risk of bleeding in the pericardioversion period compared with the conventional group (2.9% versus 5.5%; \( P = 0.031 \)), which was probably related to the longer total duration of anticoagulation in the
conventional group. The absence of left atrial thrombus on TEE does not preclude the need for intracardioversion and postcardioversion anticoagulation.\textsuperscript{23} In the present analysis, the use of TEE was higher in patients assigned to dabigatran compared with those assigned to warfarin. This difference might be attributable to study guidance or investigator preference for cardioverting with prior TEE on an experimental therapy, in this case, dabigatran.

The Anticoagulation in Cardioversion using Enoxaparin (ACE) trial, which included 496 patients, showed noninferiority of enoxaparin to unfractionated heparin plus a vitamin K antagonist in reducing the risk of stroke and embolic complications.\textsuperscript{24} Newer anticoagulants have been evaluated in the setting of atrial fibrillation but not during cardioversion. The Stroke Prevention Using an Oral Thrombin Inhibitor in Atrial Fibrillation (SPORTIF) III and V trials, which tested ximelagatran in patients with atrial fibrillation, excluded patients who had planned cardioversion.\textsuperscript{25,26} For unplanned cardioversion, patients were allowed to discontinue study medication for 60 days and were switched to nonstudy anticoagulation.\textsuperscript{27} Similarly, in the Prevention of Embolic and Thrombotic Events in Patients With Persistent Atrial Fibrillation (PETRO) study, a 12-week phase 2 trial comparing the efficacy and safety of dabigatran with warfarin, patients with planned cardioversion were excluded. For cardioversion during the trial, patients were switched to heparin and/or warfarin.\textsuperscript{28}

A major drawback of warfarin in the setting of cardioversion is its delayed onset of action and the need for heparin infusion or low-molecular-weight heparin as bridging therapy if the patient’s international normalized ratio is not in the therapeutic range or the patient is new to vitamin K antagonists. Because dabigatran achieves therapeutic blood levels within 2 hours and steady-state concentration in 2 to 3 days after twice-daily administration,\textsuperscript{29} it has the advantage of being more suitable for outpatient management, and its use may prove economical by avoiding hospitalization.

In this intention-to-treat analysis, thromboembolic event rates were low for all assigned treatment groups with no significant differences, both for all cardioversions and when limited to first cardioversions. Stroke and systemic embolism rates were similar for both conventional and TEE-guided cardioversions, suggesting that cardioversion could be performed on patients on dabigatran regardless of the use of TEE. Major bleeding was infrequent in all groups, with a slightly higher rate in the D110 arm compared with warfarin. However, the use of nonstudy anticoagulant and antiplatelet therapies before cardioversion was higher in both the D110 and D150 arms compared with warfarin, and the use of these therapies after cardioversion was greater only in the D110 arm (Table 2). These rates suggest that investigators were not as comfortable using dabigatran alone as warfarin alone in the pericardioversion period. The rate of major bleeding in the overall RE-LY results was lowest in the D110 arm.

The RE-LY trial was not powered to show a difference in stroke and systemic embolism among its 3 arms in the setting of cardioversion. The low event rates precluded a rigorous statistical analysis between groups. A definitive superiority study is unlikely to be feasible. We estimate that the sample size required for 80% power at a 1-sided significance level of 0.05 would range from 14 666 to 38 400 cardioversions, assuming a stroke and systemic embolism rate of 0.6% in the warfarin arm and between 0.3% and 0.4% in the D150 arm. This is a retrospective analysis of patients undergoing cardioversion. Case report forms used in the study were not prospectively designed to collect complete echocardiogram details. Therefore, measurements such as left atrial size, presence and severity of mitral regurgitation, and thrombus size and mobility were not collected. The data from this posthoc analysis of cardioversion in the RE-LY trial, which is the largest experience of cardioversion to date, are an important guide for future physician practice relative to the use of dabigatran in the setting of cardioversion.

The RE-LY trial confirmed the efficacy and safety of warfarin in cardioversion in a large cohort of warfarin-treated patients. It also allowed comparison with the new oral anticoagulant dabigatran. The results show that the 2 drugs are comparable in this setting.

Acknowledgments
We gratefully acknowledge the 18 113 patients who participated in the trial, the Steering Committee of the trial,\textsuperscript{12} and the staff at each site.

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Drs Ezekowitz, Oldgren, Yusuf, and Connolly received research grants, consulting fees, and lecture fees from Boehringer Ingelheim Pharmaceuticals, Inc. Dr Flaker received research grants and consulting fees from Boehringer Ingelheim. Drs Bragada and Kamenský received lecture fees from Boehringer Ingelheim. Dr Reilly is an employee of Boehringer Ingelheim. Dr Parekh received grant support from Boehringer Ingelheim. Dr Yusuf receives support from an endowed chair of the Heart and Stroke Foundation of Ontario. The other authors report no disclosures.

References
Cardioversion in atrial fibrillation is associated with an increased thromboembolic risk. The current recommendation is therapeutic anticoagulation with warfarin for at least 3 weeks before and 4 weeks after cardioversion; this recommendation is based on small nonrandomized observational and retrospective studies. Dabigatran is a novel oral direct thrombin inhibitor with rapid onset of action (peak levels in 2 hours) and a half-life of 12 to 17 hours. It was recently approved for stroke prevention in patients with nonvalvular atrial fibrillation. The RE-LY (randomised evaluation of long-term anticoagulant therapy) study was designed to compare the efficacy and safety of dabigatran with warfarin in a large cohort of patients with nonvalvular atrial fibrillation. The study enrolled 18,133 patients with nonvalvular atrial fibrillation who were randomized to receive dabigatran 110 mg, dabigatran 150 mg, or warfarin. The primary endpoints of the study were stroke and major bleeding within 30 days of cardioversion. The 2 doses of dabigatran were low and comparable to those on warfarin, with or without transesophageal echocardiography guidance. This posthoc analysis is the largest cardioversion experience to date and was performed during the RE-LY study.
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Dabigatran, 동물동전환을 시행하는 심방세동 환자에서도 warfarin을 대신할 수 있다.

최 가 준 교수 서울대병원 심장내과

Summary

배경
RE-LY 연구에서는 비판막성 심방세동 18,113명의 환자에서 뇌경색 예방을 위해 dabigatran 110mg bid(D110), 150mg bid(D150) 용법을 기존의 warfarin 치료와 비교하였다.

방법 및 결과
본 연구에서는 무작위배정 후, 동품동전환이 허용되었 다. 동품동전환 전 경식도 심초음파 시험을 독려하였고, 특히 dabigatran군에서는 전담시험이었다. 동품동전환 전, 전환 기간 중, 전환 후 30일 동안의 자료를 분석하였 다. 연구에서는 1,270명의 환자에서 총 1,983번의 동품 동전환이 시행되었고, D110, D150, warfarin군에서 각각 647, 672, 664번의 동품동전환이 시행되었다. 경식도 심초음파 검사는 각각 25.5%, 24.1%, 13.3%의 환자에서 동품동전환 전에 시행되었고, 검사 결과 1.8%, 1.2%, 1.1%의 환자에서 정상 범위이 발견되었다. 동품동전환 전 연구약물의 3주 이상 지속적으로 사용한 환자의 비율은 D110군(76.4%)과 D150군(79.2%)에서 warfarin군(85.5%, P<0.01) 양군 모두에 비하여 낮았다. 30일 동안의 뇌경색이나 전신 색전증의 발생률은 각각의 군에 서 0.8%, 0.3%, 0.6%였고(D110군 warfarin군, P=0.71; D150군 warfarin군, P=0.40), 경식도 심초음파를 시행한 군과 시행하지 않은 군에서의 발생률은 비슷하였다. 두 요 출혈의 비도는 각각 1.7%, 0.6%, 0.6%이었다(D110군 warfarin군, P=0.06; D150군 warfarin군, P=0.99).

결론
본 연구는 지금까지의 연구 중 동품동전환을 대상으 로 한 가장 규모가 큰 연구이고, 동품동전환 시 새로운 항응고제의 효과를 평가한 최초의 연구이다. 동품 동전환 후 30일 동안의 뇌경색과 주요 출혈의 비도는 Dabigatran 두 용량군 모두에서 낮았으며, warfarin군과 비슷하였다. 이러한 결과는 경식도 심초음파의 시행 여부에 무관하였다. Dabigatran은 동품동전환을 요하는 환자에서 warfarin을 대체할 수 있는 적절한 약제이다.
심방세동 환자에서 전기적 혹은 약물 이용을 이용한 동물적 전환은 혈전색전증의 완료한 위험을 가지고 있다. 특히, 시술 전후 동정을 항응고치료가 충분하지 않으면 그 위험도는 5-7%로 적지 않다. 하지만 혈전색전증의 위험도가 약 0.7-0.8%로 많이 감소한다고 한다. 현재의 기본적인 치료지침은 48시간 이상 지속된 심방세동의 경우 동정을 항응고치료를 시행하는 것이고, 현재까지 warfarin만이 FDA로부터 심방세동의 항응고치료로 허가된 유일한 약제였다. 그러나 최근 RE-LY 연구 결과를 토대로 dabigatran이 심방세동 환자의 뇌경색 예방목적으로 FDA 승인을 받았다. Dabigatran이 새로운 항응고제는 thrombin의 강력한 경정역제이며, 적혈구 간섭 억제제(direct inhibitor), 작용 시작이 빨라서 최고 혈장농도가 복용 후 0.5-2시간에 생성되며 반감기는 12-17시간이다.

RE-LY 연구는 단기, 상방적, 무작위배정, 비별등 (noninferiority) 연구로, 비판적 사법적 심방세동 환자에서 뇌경색의 예방을 위하여 dabigatran 110mg bid 유효과 150mg bid 유효을 명백 방법으로 open-label warfarin과 비교하였다. 연구 결과, 혈전색전증과 뇌경색의 예방 효과 측면에서 D110은 warfarin과 유사하였고 오히려 D150은 우세하였다. 그러나 동물정환 치료 시 새로운 항응고제의 효과와 안전성은 연구를 바탕으로 본 연구에서 RE-LY 환자군 중 동물정환을 시행하였던 군을 대조적으로 posthoc 연구를 시행하였다. 연구 결과, 동물정환 치료 후 30일까지의 뇌경색, 전신 혈전색전증, 주요 죽음의 발생률은 dabigatran과 warfarin 양군 모두에서 높지 않았고, dabigatran의 warfarin과 대조한 결과를 보여주었다.

본 연구는 동물정환 시, 새로운 경계용 항응고제의 효과를 평가한 최초의 연구로, 세계의 의학의 역사가 있다. 이제까지 동물정환 치료 시, enoxaparin 약제를 이용하여 기존 항응고치료와 대동한 결과를 보여준 연구는 없으나, 심방세동 환자군에서 ximelagatran과 같은 새로운