Role of the target-specific oral anticoagulants

A comparison with warfarin in patients with atrial fibrillation undergoing cardioversion

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Abstract

Introduction: Atrial fibrillation (AF) is a common cardiac arrhythmia with a prevalence of 2.9%. Direct-current cardioversion (DCCV) is a safe and effective way of restoring sinus rhythm. However there is a risk of stroke and thromboembolism associated with cardioversion. To minimize this risk it is recommended that the patient takes anticoagulants for at least three weeks prior to the procedure and at least four weeks after. Warfarin has been used for this purpose for several decades; however there are some downsides with warfarin. Recent trials have shown that the newer target-specific oral anticoagulants (TSOAC), formerly called NOACs, are just as effective and safe as warfarin and may overcome some of the obstacles with warfarin treatment.

Objective: The objective of this work was to compare the TSOACs with warfarin in patients undergoing DCCV to treat AF by answering the following questions: What is the efficacy of TSOACs compared to warfarin in reducing the risk of stroke and systemic embolism associated with DCCV? What is the safety of TSOACs with regard to major bleeding risk compared to warfarin? Can an increased use of a TSOAC in conjunction with DCCV reduce delays and procedure cancellations?

Method: This is a literature study and the articles were found through searches on PubMed and Web of Science. Searches were made from Apr 6 2015 to May 4 2015. Examples of search terms used are cardioversion, dabigatran, rivaroxaban and novel oral anticoagulants. Only articles comparing any of the three TSOACs approved in Sweden with warfarin in the setting of DCCV in AF were included.

Results: This study is based on eight original articles. The studies showed that dabigatran, rivaroxaban and apixaban are as efficient as warfarin when it comes to reduce the risk of stroke or systemic embolism (SE) associated with electric cardioversion. The results also show that the risk of a major bleed is similarly low between warfarin and TSOACs. It is also suggested that the use of a TSOAC instead of warfarin can reduce delays and cancellations of cardioversion.

Discussion: Even though event rates were similar in the different treatment groups the low absolute number of events and cardioversions performed limits the statistical power of the studies. There are however obvious advantages with the TSOACs compared to warfarin, such as fewer interactions with other drugs and no dietary concern, standard doses and no need of coagulation monitoring in the normal case. Another advantage is the rapid on-set action of the TSOACs and adequate anticoagulation is achieved faster than with warfarin. This can shorten the time to reach therapeutic range and the pre-treatment time before DCCV.

Conclusion: Our conclusion is that the TSOACs are at least as effective and safe as warfarin in the setting of DCCV and the advantage of fast on-set action can be used to minimize delays and cancellations of DCCV.

Keywords: Atrial fibrillation, Cardioversion, Target-specific oral anticoagulants, warfarin
List of abbreviations

AF: Atrial fibrillation
ARISTOTLE: Apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation
CHADS$_2$: Congestive heart failure, hypertension, age $\geq$ 75 years, diabetes mellitus, prior stroke or TIA or thromboembolism [doubled]
CHA$_2$DS$_2$VASc: Congestive heart failure, hypertension, age $\geq$75 years [doubled], diabetes mellitus, prior stroke or TIA or thromboembolism [doubled], vascular disease, age 64-74 years, sex category
CI: Confidence interval
CVA: Cerebrovascular accident
DCCV: Direct current cardioversion
ECG: Electrocardiogram
EHRA: European heart rhythm association
HRQoL: Health-related quality of life
INR: International normalized ratio
ISTH: International society of thrombosis and haemostasis
LA: Left atrial
MI: Myocardial infarction
NOAC: Novel oral anticoagulants
PAE: Peripheral arterial embolism
QALY: Quality adjusted life years
RELY: The randomized evaluation of long-term anticoagulation therapy
ROCKET AF: Efficacy and safety study of rivaroxaban with warfarin for the prevention of stroke and non-central nervous system systemic embolism in patients with non-valvular atrial fibrillation
RR: Relative risk
R-R: R-wave-to-R-wave
SE: Systemic embolism
TF: Tissue factor
TIA: Transient ischemic attack
TSOAC: Target-specific oral anticoagulants
TTE: Transesophageal echocardiogram
TTR: Time in therapeutic range
X-VeRT: Explore the efficacy and safety of once-daily oral rivaroxaban for the prevention of cardiovascular events in patients with non-valvular atrial fibrillation scheduled for cardioversion
Atrial fibrillation (AF) is a very common sustained cardiac arrhythmia with a prevalence of 2.9% in the Swedish population. The prevalence of AF increases with age up to 85 years of age and the prevalence increases rapidly after 65 years [1].

AF means irregular and very rapid atrial rate, 350-600 impulses per minute. There are often so called ectopic focuses adjacent to the orifice of the pulmonary veins in the left atrium. These focuses compete with the sinus node causing the high frequency. The impulses are passed over irregularly to the ventricles due to blockage of the rapid impulse frequency by the AV-node and the His bundle [2].

AF has three classifications according to duration of the episodes. Paroxysmal AF is self-terminated within seven days. Persistent AF lasts more than a week and requires conversion back to sinus rhythm. And finally permanent AF where the arrhythmia is accepted as chronic and no attempts to restore sinus rhythm are being made [3].

Symptoms of AF vary between patients [4]. The symptoms can be measured on a scale of one through four; the EHRA-score (European Heart Rhythm Association) as illustrated in the table below [3].

<table>
<thead>
<tr>
<th>EHRA I</th>
<th>No symptoms.</th>
</tr>
</thead>
<tbody>
<tr>
<td>EHRA II</td>
<td>Mild symptoms. Trouble during heavy exertion.</td>
</tr>
<tr>
<td>EHRA III</td>
<td>Moderate symptoms. Trouble at low exertion.</td>
</tr>
<tr>
<td>EHRA IV</td>
<td>Pronounced symptoms. Trouble at rest.</td>
</tr>
</tbody>
</table>

**EHRA:** European Heart Rhythm Association

While some people with AF do not have clinical signs at all others may have a variety of symptoms. Common symptoms are fatigue, palpitations, dyspnea and even syncope though fatigue is the most common. Diagnosis can be made using an electrocardiogram (ECG). Characteristics on an ECG with AF are irregular R-R (R-wave-to-R-wave) intervals, absence of P-waves and irregular atrial activity [4].

![AF ECG](http://commons.wikimedia.org/wiki/Category:ECG_graphs_of_atrial_fibrillation#/media/File:Af
tib_ecg.jpg)

The biggest risk for developing AF is high age but there are other risk factors as well. Cardiovascular diseases such as hypertension, ischemic heart disease, heart failure, cardio myopathy and valvular heart disease can all lead to AF. Other risk factors include overconsumption of alcohol, hyperthyroidism, lung disease, overweight and
sleep apnea. AF can also have genetic causes or be triggered by serious infections or surgery. AF may even occur without cardiovascular disease or any other risk factor [3].

AF is associated with a certain risk of deterioration of other heart disease or even developing heart disease, such as heart failure [4]. It also increases the risk of stroke and/or thromboembolism up to five times if left untreated [4, 5]. This is due to the formation of atrial thrombi, often in the left atrial appendage [4].

How great the risk of stroke or thromboembolism is also depends on other factors and can be estimated using a point scoring system. Two scoring systems are CHADS$_2$ (table 2) and the newer CHA$_2$DS$_2$-VASc (table 3). The risk of stroke and/or thromboembolism can be reduced with the use of anticoagulant drugs (dabigatran, rivaroxaban, apixaban (in this work referred to as target-specific oral anticoagulants, TSOAC) or warfarin). However these anticoagulant agents run a certain risk of bleeding which may be fatal. When choosing a treatment it is important to balance benefits with risk [4].

### Table 2: Thromboembolic risks with AF according to CHADS$_2$

<table>
<thead>
<tr>
<th>Letter</th>
<th>Risk factor</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>Congestive heart failure</td>
<td>1</td>
</tr>
<tr>
<td>H</td>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>A</td>
<td>Age ≥75 years</td>
<td>1</td>
</tr>
<tr>
<td>D</td>
<td>Diabetes Mellitus</td>
<td>1</td>
</tr>
<tr>
<td>S</td>
<td>Prior stroke/TIA/thromboembolism</td>
<td>2</td>
</tr>
</tbody>
</table>

### Table 3: Thromboembolic risks with AF according to CHA$_2$DS$_2$-VASc

<table>
<thead>
<tr>
<th>Letter</th>
<th>Risk factor</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>Congestive heart failure</td>
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<td>Diabetes Mellitus</td>
<td>1</td>
</tr>
<tr>
<td>S</td>
<td>Prior stroke/TIA/thromboembolism</td>
<td>2</td>
</tr>
<tr>
<td>V</td>
<td>Vascular disease</td>
<td>1</td>
</tr>
<tr>
<td>Sc</td>
<td>Sex category (female)</td>
<td>1</td>
</tr>
</tbody>
</table>

### Direct-current (DC) cardioversion

There are different ways of trying to restore normal sinus rhythm in patients with AF. These methods include antiarrhythmic drugs, a procedure called catheter ablation and synchronized DC cardioversion. However rhythm control is not appropriate for all patients and these strategies of rhythm control may not work in all cases.

DC cardioversion means trying to restore sinus rhythm using an electrical current to the heart. The electric shock is synchronized with the QRS-complex in order to avoid inducing ventricular fibrillation. Ventricular fibrillation can occur when a shock is delivered during ventricular repolarization on the T-wave. If the cardioversion is unsuccessful it is possible to repeat the procedure several times [4].
DCCV is per se associated with a certain risk of stroke. This is due to left atrial stunning that can lead to increased risk of thrombus formation in the left atrium. To minimize the risk, adjuvant anticoagulant therapy in conjunction with cardioversion is recommended [6]. A thrombotic event is very rare more than one week after cardioversion. The highest risk of suffering from stroke or SE is within the first few days after the procedure. In a study by Berger and Schweitzer [7] 96% of thrombotic events occurred within the first three days.

DCCV can be either acute or scheduled. Acute cardioversion can be performed if AF has lasted for less than 48 hours. In this case there is often no need for anticoagulation therapy prior to the cardioversion. Depending on other risk factors anticoagulants may be indicated even after cardioversion, and in some cases, when CHA2DS2-VASc-score is ≥ 2, there may be need of anticoagulation during the time before cardioversion [3, 4]. In the case of cardioversion in patients who are taking warfarin, cardioversion can be carried out if INR is within therapeutic range. If the patient is taking any of the TSOACs (rivaroxaban, dabigatran or apixaban) cardioversion can proceed when compliance is established. If uncertain, a transesophageal echocardiogram (TEE) can be made to rule out cardiac thrombus [3]. If the patient is not currently taking any anticoagulants and AF has lasted for more than 48 hours cardioversion should not be performed acutely. Anticoagulant therapy with either TSOACs or warfarin should be commenced for at least three weeks before cardioversion and continued for at least four weeks after DCCV [3, 4].

**The coagulation cascade**

In order to understand the anticoagulant effect of warfarin and the TSOACs we need to have an overview of the coagulation cascade. As illustrated in figure 3, there are two pathways leading to coagulation: the intrinsic/contact activation pathway and the extrinsic/tissue factor pathway. These two pathways meet and form the common pathway. This activates factor X to factor Xa. Coagulation is initiated in the extrinsic pathway, when tissue factor (TF) interacts with plasma factor VIIa, this in turn activates IX and X which result in the formation of thrombin. This primes the intrinsic pathway and more thrombin is formed which then acts on fibrinogen to form a fibrin clot. The two pathways are thus not separate ways of activation, but occur simultaneously and “cross-talk” [8].

![Figure 2: This is a typical set-up of an elective cardioversion. A shows the cardiac rhythm before the procedure and B shows the rhythm after the cardioversion. The patient is prepared with cardioversion pads attached to the chest. [http://commons.wikimedia.org/wiki/File:Cardioversion.jpg?uselang=sv ]](http://commons.wikimedia.org/wiki/File:Cardioversion.jpg)
**Warfarin and the TSOACs**

Warfarin is an oral anticoagulant drug that has been used since the 1950s for preventing stroke in patients with AF [4]. Warfarin is a vitamin K antagonist (VKA) and its anticoagulant effect comes from competitively blocking the reduction of Vitamin K to Vitamin KH$_2$. Vitamin KH$_2$ is necessary in activating coagulation proteins prothrombin factor VII, IX and X. Sensitivity for warfarin varies between different individuals. High age for example makes the body more sensitive to warfarin. Other factors that affect the sensitivity are absorption, metabolic clearance, genetic factors, congestive heart failure, hepatic impairment or concomitant use of other drugs. This means that the same dosage may have very different effect on different people. Some people may only need an extremely low dose, while others seem more or less resistant to the drug. The sensitivity can also vary in the same person. It is therefore necessary to regularly measure the levels of prothrombin complex in the blood. This value is expressed in International normalized ratio (INR) and the normal value is 1. When treating AF a desirable INR lies between 2.0 and 3.0. The first week of warfarin therapy requires an INR check almost every day and then once or twice a week until maintenance dose. From here the INR is measured every four to six weeks [9]. There is strong evidence for the efficacy of warfarin but there are also several downsides with it. The increased risk of bleeding in the brain and in general is one. Also warfarin has a very narrow therapeutic window and interacts with a lot of common drugs. It also interacts with food containing vitamin K [4], it is therefore important not to make any vast alterations in the diet [9]. The close monitoring of the INR can also be quite inconvenient for the patient [4].

The target-specific anticoagulants, dabigatran, rivaroxaban and apixaban, have been the alternative to warfarin in reducing the risk of stroke for some time now. Dabigatran was the first TSOAC to be approved in the USA for the purpose to reduce the risk of stroke in patients with AF [4]. Dabigatran etexilate is a small pro-drug molecule that converts to dabigatran by hydrolysis in plasma and liver [10]. Dabigatran is a direct thrombin inhibitor [4, 10] and therefore inhibits the formation of thrombi [10].
The second TSOAC to be approved is rivaroxaban [4]. Rivaroxaban is an extremely selective and direct factor Xa inhibitor. The inhibition of this factor cancels both pathways of the coagulation cascade preventing the formation of thrombin and thrombi [11].

The third TSOAC to be approved is apixaban [4]. Apixaban is as rivaroxaban a selective and direct factor Xa inhibitor. Nor apixaban or rivaroxaban has any effect on the platelet aggregation but inhibits it indirectly by preventing the formation of thrombin [12].

There are several advantages with the TSOACs compared with warfarin. There is no need for INR-testing, which is required regularly with warfarin. The TSOACs do not have as many drug-drug interactions and there is no need for dietary concerns. Their pharmacological profiles are more predictable and they have a faster onset and offset of action. It is therefore not necessary with bridging parenteral anticoagulant therapy during initiation. Bridging therapy may not be needed in patients on chronic therapy undergoing invasive surgery and therefore needs a brief interruption in anticoagulant therapy. However the fast onset and offset action requires a high level of compliance that is not as crucial with warfarin. Even one missed dose of a TSOAC can increase the risk of stroke and additional anticoagulant therapy can be needed. Another downside with the TSOACs is the lack of an antidote. However, the short half-lives of these agents lessen the need for an antidote [4].

Three major trials have led to the approval of the TSOACs to reduce the risk of stroke in patients with AF. The RE-LY- trial compared warfarin to dabigatran, the ROCKET AF-trial compared rivaroxaban to warfarin and in the ARISTOTLE- trial warfarin was compared to apixaban. All trials showed that the TSOACs were as effective as warfarin in reducing the risk for stroke and thromboembolism. The trials also showed a similar or better safety regarding major bleeding. Since then, several trials have been made that compares warfarin with the TSOACs. A handful of studies, including post-hoc analysis of these three major trials, have compared the TSOACs with warfarin in the setting of electrical cardioversion. Even though warfarin has been proved to reduce the risk of stroke associated with cardioversion significantly it may not be suitable for all patients [4]. There is a need for an alternative to warfarin and the aim of this work is to examine whether the TSOACs are in fact a good alternative.

**Objective**

The objective of this work was to compare the target-specific oral anticoagulants with warfarin in patients undergoing direct-current cardioversion to treat atrial fibrillation by answering the following questions:

- What is the efficacy of the target-specific oral anticoagulants compared to warfarin in reducing the risk of stroke and systemic embolism associated with direct-current cardioversion?
- What is the safety of the target-specific oral anticoagulants with regard to major bleeding risk compared to warfarin?
- Can an increased use of a target-specific oral anticoagulants in conjunction with direct-current cardioversion reduce delays and procedure cancellations?
Method

This is a literature study. The articles were found through searches on PubMed and Web of Science between April 6 2015 and May 4 2015. Search terms include “cardioversion” and “dabigatran” as well as the MeSH terms “rivaroxaban” and “apixaban”. The articles on Web of Science were found through free text searches. Table 4 shows the date of searches, search terms, limitations, number of hits and selected references on PubMed and table 5 shows dates, search terms, number of hits and selected references on Web of science.

<table>
<thead>
<tr>
<th>Date</th>
<th>Search terms</th>
<th>Limitations</th>
<th>Number of hits</th>
<th>Selected references (in reference list)</th>
</tr>
</thead>
<tbody>
<tr>
<td>150406</td>
<td>Cardioversion AND dabigatran</td>
<td>Humans</td>
<td>41</td>
<td>13,15,18</td>
</tr>
<tr>
<td>150406</td>
<td>Cardioversion AND rivaroxaban (MeSH)</td>
<td>Humans</td>
<td>20</td>
<td>17</td>
</tr>
<tr>
<td>150406</td>
<td>Cardioversion AND apixaban (MeSH)</td>
<td>Humans</td>
<td>14</td>
<td>-</td>
</tr>
<tr>
<td>150406</td>
<td>Novel oral anticoagulants AND cardioversion</td>
<td>Humans</td>
<td>21</td>
<td>14</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Date</th>
<th>Search terms</th>
<th>Search within results of</th>
<th>Number of hits</th>
<th>Selected references (in reference list)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015-04-10</td>
<td>Cardioversion</td>
<td>Dabigatran</td>
<td>54</td>
<td>-</td>
</tr>
<tr>
<td>2015-04-10</td>
<td>Cardioversion</td>
<td>Rivaroxaban</td>
<td>25</td>
<td>16</td>
</tr>
<tr>
<td>2015-04-10</td>
<td>Cardioversion</td>
<td>Apixaban</td>
<td>16</td>
<td>-</td>
</tr>
<tr>
<td>2015-05-04</td>
<td>Elective cardioversion</td>
<td>Waiting time</td>
<td>5</td>
<td>19</td>
</tr>
<tr>
<td>2015-05-04</td>
<td>Elective cardioversion</td>
<td>Cancellation</td>
<td>5</td>
<td>20</td>
</tr>
</tbody>
</table>

Articles were selected after reading the abstracts. Articles that did not compare TSOACs with warfarin were excluded so were articles that did not treat the matter of DCCV. Systemic reviews and meta-analysis were not included.
Results

This literature review is based on eight different articles. Six articles investigated efficacy and safety (table 6) and three articles the subject of cancelled and delayed cardioversions. Four studies were multi-national [13, 16-18], two studies were conducted in Canada [15, 20], one in USA [14] and one in Ireland [19].

Efficacy

A comprehensive overview over the conclusions on efficacy and safety data with regard to the aims of the study is given out in table 7.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Days of follow-up</th>
<th>Number of DCCV on TSOAC*/VKA**</th>
<th>Groups</th>
<th>End-point efficacy</th>
<th>End-point safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nagarakanti et al. 2011</td>
<td>Post-hoc of prospective, randomized, open label study</td>
<td>30</td>
<td>1319/664</td>
<td>Dabigatran 150 mg</td>
<td>Stroke, systemic embolism</td>
<td>Major bleeding</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dabigatran 110 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Warfarin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coleman et al. 2015</td>
<td>Retrospective cohort study</td>
<td>56</td>
<td>926/372</td>
<td>Dabigatran</td>
<td>Cerebro-vascular accident, TIA, peripheral arterial embolism</td>
<td>Important bleeding</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rivaroxaban</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Apixaban</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Warfarin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kochhäuser et al. 2014</td>
<td>Retrospective cohort study</td>
<td>30</td>
<td>429/900</td>
<td>Dabigatran</td>
<td>Stroke, TIA</td>
<td>Clinically important bleeding</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rivaroxaban</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Warfarin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cappato et al. 2014</td>
<td>Prospective, randomized, open label study</td>
<td>30</td>
<td>1002/502</td>
<td>Rivaroxaban</td>
<td>Stroke, TIA, peripheral embolism, myocardial infarction, cardio-vascular death</td>
<td>Major bleeding</td>
</tr>
<tr>
<td>Piccini et al. 2013</td>
<td>Post-hoc of prospective, randomized, double blind study</td>
<td>60</td>
<td>160/160</td>
<td>Rivaroxaban Warfarin</td>
<td>Stroke, systemic embolism</td>
<td>Major or non-major clinically relevant bleeding</td>
</tr>
<tr>
<td>---------------------</td>
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<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Flaker et al. 2014</td>
<td>Post-hoc analysis of prospective, randomized, double blind study</td>
<td>30</td>
<td>331/412</td>
<td>Apixaban Warfarin</td>
<td>Stroke, systemic embolism</td>
<td>Major bleeding</td>
</tr>
</tbody>
</table>

**TSOAC** target specific oral anticoagulants; **VKA** Vitamin K antagonists

(Nagarakanti et al.:) Dabigatran vs warfarin in patients with atrial fibrillation: An analysis of patients undergoing cardioversion (2011 #13)

In the post-hoc analysis of the RE-LY (The randomized evaluation of long-term anticoagulation therapy) - trial by Nagarakanti et al. [13] warfarin was compared with dabigatran 110 mg/d (D110) and 150 mg/d (D150) in patients undergoing cardioversion and patients were followed up for 30 days after cardioversion. The major outcome measures regarding efficacy were stroke and systemic embolism. Inclusion criteria in the RE-LY-trial were age ≥75 years, documented AF and prior stroke or TIA. Exclusion criteria were valvular or liver disease, resent stroke and an increased risk of hemorrhage. The specific data studied in connection with cardioversion were: antithrombotic therapy prior to cardioversion (more or less than three weeks), during and after the cardioversion, time since the last dose of dabigatran prior to cardioversion, the use of any other oral or systemic anticoagulant and aspirin with or without clopidogrel and whether a TEE had been made and if so findings of TEE. The type of cardioversion was also recorded. Out of a total of 1983 cardioversions in 1270 patients in the RE-LY study, 1657 were DCCVs. Out of these 1983, 647 cardioversions were assigned to the D110 group, 672 to D150 and 664 to the warfarin group. The majority of cardioversions were performed according to protocol assigned drug taken at least three weeks prior to cardioversion, 85.5% in the warfarin group and 76.4% and 79.2% in the D110 and D150-groups respectively. In 7.9% of the cases patients were switched to a non-study oral anticoagulant, 12% switched to another oral anticoagulant (aspirin with or without clopidogrel, intravenous heparin or low-molecular-weight-heparin) and 1.8% were not on any antithrombotic therapy at the time for cardioversion. A majority (90%) continued on protocol assigned study-drug after the cardioversion (85.8% for warfarin, 88.7% for D110 and 94.3% for D150). A TEE was performed before cardioversion in 21% of the patients, 25% within the dabigatran groups and 16% within the warfarin group.

Stroke or systemic embolism event rates were 0.77 % (5 patients) in the D110 group, 0.30% (2 patients) for D150 and 0.60% (4 patients) for warfarin (D110 versus warfarin, p=0.71; D150 versus warfarin, p=0.45). In conclusion, there were no significant
differences regarding stroke and SE between warfarin and the two dabigatran groups [13].

(Coleman et al.:) Novel oral anticoagulants for DC cardioversion procedures: Utilization and clinical outcomes compared with warfarin (2015 #14)

A comparison of warfarin with the three TSOACs regarding efficacy was performed by Coleman et al. [14] at Cleveland Clinic in patients undergoing electrical cardioversion. The primary measures regarding efficacy was cerebrovascular accident (CVA), transient ischemic attack (TIA) and peripheral arterial embolism (PAE). The incidence rate was achieved from the electronic medical record of each patient. Those included in the study were patients who had undergone direct-current cardioversion sometime between January 1 2009 and December 2013. Other inclusion criteria were treatment with an oral anticoagulant for at least three weeks before the cardioversion alternatively had undergone a TEE showing no left atrial thrombus and had continued treatment with an anticoagulant drug for four weeks or longer after the cardioversion. This information was collected from electronic medical records and the follow-up period was eight weeks. A total of 5320 DC-cardioversions were performed. Out of these 4647 ended up in the final analysis. 647 were not included due to insufficient follow-up. Warfarin was used as anticoagulant therapy in the majority of the patients, 80.1% (3721 pcs.). Dabigatran was used in 15.5% (719), rivaroxaban in 3.4 % (159) and apixaban in 1.0% (48).

Out of the 3721 patients taking warfarin 36 (0.97%) suffered from CVA or TIA. CVA or TIA occurred in 15 (1.62%) patients taking any of the TSOACs, whereof 12 (1.67%) were taking dabigatran, three (1.89%) were taking rivaroxaban and no one among those taking apixaban. Even though the rates of CVA/TIA were higher with TSOACs the difference was not significant (warfarin versus TSOACs, p=0.110) [14].

(Kochhäuser et al.:) Comparison of outcomes after cardioversion or atrial fibrillation ablation in patients with differing periprocedural anticoagulation regimens (2014 #15)

This retrospective study by Kochhäuser et al. [15] compares dabigatran and rivaroxaban with warfarin. The study was performed in Southlake regional health center in Ontario, Canada. Patients included (n=900) had undergone electrical cardioversion or catheter ablation somewhere between October 2010 and October 2013 and were retrospectively analyzed. The patients were divided into three separate groups: Warfarin, dabigatran or rivaroxaban depending on which anticoagulant they used. For the patients undergoing electrical cardioversion it was recommended with anticoagulation therapy at least three weeks before and four weeks after the procedure. Anticoagulation therapy prior to cardioversion was confirmed according to weekly INR between 2.0 and 3.0. Compliance to TSOAC was based on self-reports from the patients. Anticoagulation therapy continued without interruptions for at least four weeks and longer if the CHADS2-score indicated risk for thromboembolism. For patients with less than three weeks of anticoagulant therapy a TEE was performed to rule out left atrial (LA) thrombus. Primary outcomes were stroke and TIA. The patients were routinely followed-up at the center. The median follow-up time was six months, ranging from four to eight months. There were a total of 900 patients undergoing cardioversion during this period that matched the inclusion criteria. Out of these 900, 471 took warfarin, 288 took dabigatran and 141 took rivaroxaban. The Baseline characteristics were similar between the three groups regarding: age, gender, CHADS2-score and CHA2DS2-VASc-score.
There were no events of stroke in any of the three treatment arms (p=0.99). There was one event of TIA in the dabigatran group. However this was not significant (p=0.70) [15].

**(Cappato et al.): Rivaroxaban vs vitamin K antagonist for cardioversion in atrial fibrillation (2014 #16)**

The X-VerT (explore the efficacy and safety of once daily rivaroxaban for the prevention of cardiovascular events in patients with non-valvular atrial fibrillation scheduled for cardioversion)-trial, by Cappato et al. [16], was a multinational, randomized, open-label, parallel group study and was designed to examine efficacy and safety of rivaroxaban compared to VKA in patients with AF undergoing cardioversion. The study took place in 141 centers in 16 different countries and went on from October 3 2012 until September 25 2013. Patients ≥18 years scheduled for cardioversion were eligible for the trial. Out of 1584 screened patients 1504 were randomized to either rivaroxaban 20 mg daily (15 mg daily if creatinine clearance was between 30 and 49 mL/min) or dose adjusted VKA. 1002 patients were randomized to rivaroxaban and 502 patients to VKA. The cardioversion performed could either be early with one to five days of rivaroxaban or VKA prior to cardioversion, or delayed with three to eight weeks of antiocoagulation therapy before the procedure. This decision of early or delayed cardioversion was made by the local investigator. The majority of cardioversions were DCCVs. The patients could be naïve to oral anticoagulation therapy or experienced. Exclusion criteria were haemodynamically significant mitral valve stenosis, prosthetic heart valves, known left atrial (LA) thrombi, severe disabling stroke within the previous three months and any stroke or TIA up to two weeks or three days respectively before randomization. Primary efficacy outcomes were defined as stroke or TIA, peripheral embolism, myocardial infarction (MI) and cardiovascular death. An independent, blinded committee determined the number and type of events. 1167 patients underwent cardioversion within the time range of 1-5 days or 21-25 days after randomization.

There were two events of stroke in each treatment group (rivaroxaban: 0.20%; 95% Confidence interval (CI) 0.04-0.71%; VKA: 0.41% 95% CI 0.07-1.41%). There was one event of SE in the VKA treatment group and no events of SE in the rivaroxaban group. The relative risk (RR) was 0.50; 95% CI 0.15-1.73. In conclusion there was no significant difference regarding stroke or SE between the two groups [16].

**(Piccini et al.:) Outcomes after cardioversion and atrial fibrillation ablation in patients treated with rivaroxaban and warfarin in the ROCKET AF trial (2013 #17)**

This is a post-hoc analysis of the ROCKET AF-trial by Piccini et al. [17] and the aim was to compare warfarin with rivaroxaban in patients undergoing cardioversion or catheter ablation to treat AF regarding efficacy and safety. Inclusion criteria were: Age ≥18 years, documented AF and CAHDS₂-score ≥2. The primary end points for efficacy were stroke and systemic embolism (SE). A total of 14264 patients were randomized in the ROCKET AF-trial. The median age at randomization was 73 years, the median CHADS₂-score was 3.0, 81% had persistent AF and 52% had a history of stroke or TIA. The median follow-up was 2.1 years. All together 321 patients underwent either cardioversion or catheter ablation. The warfarin group contained 161 patients and the rivaroxaban group 160 patients. 143 patients underwent a total of 181 cardioversions.

The rate of stroke and SE within the first 60 days was similar between the two treatment arms. Three events in the warfarin group (1.86%) and three events in the rivaroxaban group (1.88%). RR was 1.38; 95% CI 0.61-3.11. In conclusion there was no significant difference between the treatment groups [17].
(Flaker et al.) Efficacy and safety of apixaban in patients after cardioversion for atrial fibrillation (2014 #18)

This is a post-hoc analysis of the ARISTOTLE trial by Flaker et al. [18] and it compares warfarin with apixaban in patients with AF undergoing DCCV. The patients would have to have AF and at least one of the following risk factors: Older than 75 years, previous stroke, TIA or SE, symptomatic heart failure or left ventricular ejection fraction and pharmacologically treated diabetes or hypertension. Exclusion criteria were AF due to a reversible cause, mitral stenosis, requirement of anticoagulants for other reasons than AF, stroke within the previous seven days, a need for aspirin with or without clopidogrel and renal insufficiency. Patients were randomized to either dose adjusted warfarin or apixaban 5 mg daily. The apixaban dose was adjusted to 2.5 mg twice daily in patients who had at least two of the following criteria: Older than 80 years, a body weight of less than 60 kg and a serum creatinine level of more than 1.5 mg/dl. Primary efficacy outcomes include stroke and SE. The clinical events were reported as the number of first unique events within 30 days after cardioversion. A total of 540 patients underwent 743 cardioversions and 75% of these cardioversions were performed within the first year of follow-up. 412 cardioversions were assigned to the warfarin group and 331 to the apixaban group. Minimum duration of warfarin therapy prior to cardioversion was four days, and one day for apixaban. Baseline demographics such as gender, age, cardiac risk factors, type of AF and CHADS2-score were similar in the warfarin and apixaban groups.

There were no events of stroke or SE in any of the treatment groups (Apixaban: 95% CI 0-1.0%; warfarin: 95% CI 0-1.2%) [18].

Safety

The six studies comparing TSOAC with warfarin regarding efficacy also treated the matter of safety (table 6). The study design of these articles has already been described in the efficacy part.

(Nagarakanti et al.) Dabigatran vs warfarin in patients with atrial fibrillation: An analysis of patients undergoing cardioversion (2012 #13)

This post-hoc analysis by Nagarakanti et al. [13] compared dose-adjusted warfarin with dabigatran (150 mg and 110 mg daily) regarding safety. The primary end point was major bleeding. Major bleeding is in this study was defined as a reduction of 20g/L or more in the hemoglobin level, transfusion of at least two positive test for blood in urine, or a symptomatic bleeding in a vital organ or critical area.

Major bleeding events occurred 11 times in the dabigatran 110 mg- group (1.7%), and four times each in the dabigatran 150 mg and the warfarin- group (0.6% and 0.6% respectively). The rate of major bleed was slightly higher in the D110 group compared to warfarin, however this was not a significant difference (D110 1.7% versus warfarin 0.6%: p=0.06; D150 0.6% versus warfarin 0.6%: p=0.99) [13].

(Coleman et al.) Novel oral anticoagulants for DC cardioversion procedures: Utilization and clinical outcomes compared with warfarin (2015 #14)
Coleman et al. [14] defined safety as bleeding that would require a blood transfusion, death due to bleeding or any apparent bleeding that require medical treatment.

There were 38 events of bleeding in the warfarin group and five events total in the three TSOAC groups (warfarin 1.02% versus TSOAC 0.5%; p=0.247). The five events in the TSOAC groups all occurred in the dabigatran group (warfarin 1.02% versus dabigatran 0.7% p=0.534. Thus there were no events of major bleed in the rivaroxaban or apixaban groups (warfarin 1.02% versus rivaroxaban 0.00% p=0.405; warfarin 1.02% versus apixaban 0.00% p=0.613. In conclusion there were no significant difference in major bleeding between warfarin and any of the TSOACs [14].

(Kochhäuser et al.:) Comparison of outcomes after cardioversion or atrial fibrillation ablation in patients with differing periprocedural anticoagulation regimens (2014 #15)

In the study by Kochhäuser et al. [15] clinically important bleeding was compared between the warfarin, dabigatran and rivaroxaban groups. Bleedings that required transfusion, hospitalization or cessation of anticoagulant treatment for more than seven days were considered clinically important.

There were no clinically important bleeding in any of the three treatment groups (p=0.99) [15].

(Cappato et al.:) Rivaroxaban vs vitamin K antagonist for cardioversion in atrial fibrillation (2014 #16)

This analysis by Cappato et al. [16] compares the incidence rates of major bleeding between patients taking warfarin and patients taking rivaroxaban. Major bleeding was defined according to the International Society of Thrombosis and Haemostasis (ISTH) criteria.

Major bleed occurred six times in the rivaroxaban group (0.61%; 95% CI 0.26-1.27%) and four times in the warfarin group (0.80%; 95% CI 0.27-2.00%). The RR was 0.76; 95% CI 0.21-2.67. In conclusion there was no significant difference regarding major bleeding between warfarin and rivaroxaban [16].

(Piccini et al.:) Outcomes after cardioversion and atrial fibrillation ablation in patients treated with rivaroxaban and warfarin in the ROCKET AF trial (2013 #17)

In this study [17] the safety end point was both major and non-major clinically relevant bleeding.

Among the patients assigned to rivaroxaban bleeding (both major and non-major) occurred 30 times (18.75%), and in the warfarin group bleeding occurred 21 times (13.04%). Only six events of bleeding occurred within the first 30 days. [17].

(Flaker et al.:) Efficacy and safety of apixaban in patients after cardioversion for atrial fibrillation (2014 #18)

In this analysis by Flaker et al. [17] safety was major bleeding and was compared between warfarin and apixaban. Major bleeding is defined according to ISTH- criteria.
Major bleeding was similarly low in both groups and occurred once in each treatment arm (apixaban: 0.3%; warfarin 0.2%). [18].

Table 7: Summary of outcomes regarding efficacy and safety

<table>
<thead>
<tr>
<th>Study</th>
<th>Efficacy outcome rates TSOAC</th>
<th>Efficacy outcome rates warfarin</th>
<th>p-value/RR** (95% CI**)</th>
<th>Safety outcome rates TSOAC</th>
<th>Safety outcome rates warfarin</th>
<th>p-value/RR** (95% CI**)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nagarakanti et al. [13]</td>
<td>D110: 0.77% (n=647) D150: 0.30% (n=672)</td>
<td>0.60% (n=664)</td>
<td>p=0.71</td>
<td>D110: 1.70% D150: 0.60%</td>
<td>0.60%</td>
<td>p=0.06</td>
</tr>
<tr>
<td>Coleman et al. [14] (n=4647)</td>
<td>Dabigatran: 1.67% (n=719) Rivaroxaban: 1.89% (n=159) Apixaban: 0.00% (n=48)</td>
<td>0.97% (n=3721)</td>
<td>p=0.112</td>
<td>Dabigatran: 0.70% Rivaroxaban: 0.00% Apixaban: 0.00%</td>
<td>1.02%</td>
<td>p=0.534</td>
</tr>
<tr>
<td>Kochhäuser et al. [15] (n=900)</td>
<td>Dabigatran: 0.00% (n=288) Rivaroxaban: 0.00% (n=141)</td>
<td>0.00% (n=471)</td>
<td>p=0.99</td>
<td>0.00%</td>
<td>0.00%</td>
<td>p=0.99</td>
</tr>
<tr>
<td>Cappato et al. [16] (n=1504)</td>
<td>Rivaroxaban: 0.20% (n=1002)</td>
<td>0.61% (n=502)</td>
<td>RR=0.50; 0.15-1.73</td>
<td>0.61%</td>
<td>0.80%</td>
<td>RR=0.76; 0.21-2.67</td>
</tr>
<tr>
<td>Piccini et al. [17] (n=321)</td>
<td>Rivaroxaban: 1.88% (n=160)</td>
<td>1.86% (n=161)</td>
<td>RR=1.38; 0.61-3.11</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Flaker et al. [18] (n=743)</td>
<td>Apixaban: 0.00% (n=331)</td>
<td>0.00% (n=412)</td>
<td>-</td>
<td>0.3%</td>
<td>0.2%</td>
<td>-</td>
</tr>
</tbody>
</table>

*TSOAC target-specific oral anticoagulants **RR relative risk ***CI confidence interval

Efficacy defined as stroke or SE. Safety defined as major bleed. Efficacy outcomes in the Coleman et al. study also include TIA. Outcomes within 30 days after cardioversion except for Piccini et al with 60 days and Coleman et al. with eight weeks. The study by Piccini et al. includes patients who underwent catheter ablation.

Three of the studies included here were post-hoc analyses of randomized trials [13,17,18], two studies were retrospective [14,15] and one study was a prospective randomized open label trial [16]. Four of the studies were multinational [13,16-18] and two were single-center studies [14,15]. The primary end-points were quite similar in all studies, however the safety end-point in the study by Piccini et al. [17] included non-major bleeding. In the post-hoc analyses [13,17,18], the included patients were required to have at least one risk factor. This was not a requirement in the other three studies. Most of the studies included patients undergoing pharmacological cardioversions as
well as DCCV [13,15-18] and one study even included catheter ablation [17]. The population size differed some between the groups, from 321 procedures [17] to 4647 [14]. The follow-up period was 30 days in all studies but two. In the study by Piccini et al. [17], the follow-up period was 60 days and in the study by Coleman et al. [14], the follow-up period was eight weeks. The result was however similar in all six studies: the risk of suffering from stroke or major bleeding was very low and there was no significant difference between the TSOACs and warfarin regarding efficacy or safety.

**Cardioversion delays**

Three studies included in the present work treated the matter of delays and cancellations (Table 8).

**(Cappato et al.): Rivaroxaban vs vitamin K antagonist for cardioversion in atrial fibrillation (2014 #16)**

In the study by Cappato et al. [16] 77.6% of the patients underwent cardioversion within the time range (early: 1-5 days, or delayed: 25-25 days). In the rivaroxaban group 417 patients were scheduled to undergo delayed cardioversion and 321 (77.0%) underwent cardioversion within the time range. In the warfarin group 215 patients were scheduled for delayed cardioversion and 78 patients (36.3%) had their cardioversion as planned (p=0.001). In conclusion, there was a significantly higher part of patients taking warfarin that could not undergo DCCV as planned compared to those taking dabigatran. The difference was mainly due to difficulties in achieving adequate anticoagulation [16].

**(Collison et al.:) Use of novel oral anticoagulants results in shorter waiting times for elective DC cardioversion (2014 #19)**

In a retrospective review by Collison et al. [19] the aim was to see if an increased use of TSOAC could reduce delays for elective DCCV. They used an electronic database of elective direct-current cardioversion admissions to the coronary care unit in the university hospital in Galway, Ireland. The recorded data contained information in gender, age, date of booking the procedure and the day it was performed, anticoagulant described and if the cardioversion was successful or not. From January 5 2010 to February 25 2014 there were 533 admissions. In 438 admissions warfarin was the drug prescribed and in 95 admissions any of the TSOACs were used. The mean waiting time for admissions on warfarin was 60 days, and 40 days on a TSOAC (p=0.001). In conclusion, there was a significant difference in mean days waiting between warfarin and the TSOACs. [19].

**(Halperin et al.:) Dabigatran use improves efficiency of care by reducing cancellations and delays in patients undergoing elective cardioversion for atrial fibrillation (2012 #20)**

In a study by Halperin et al. [20] from 2012 the aim was to see if dabigatran could reduce procedural delays and cancellations compared to warfarin in patients scheduled to undergo DCCV. The study period was three months and patients who were eligible and not taking any anticoagulant were recommended to use dabigatran.

There was a significant difference in number of cancellation between dabigatran and warfarin. Cancellations occurred in 4.8% of the patients taking dabigatran. Among the patients taking warfarin, cancellations occurred in 30% of the procedures (p<0.01).
This resulted in an increase in mean days waiting from 16.1 +/- 9 for patients taking dabigatran to 28.1 +/- 27 for patients taking warfarin (p<0.01) [20].

Table 8: Summary of results regarding cardioversion delays and cancellations

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Number of cardioversions scheduled</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cappato et al. 2014</td>
<td>Prospective, randomized, open label</td>
<td>1504 (Warfarin: 502 Rivaroxaban: 1002)</td>
<td>Significantly more patients taking warfarin could not undergo cardioversion as planned</td>
</tr>
<tr>
<td>Collison et al. 2014</td>
<td>Retrospective cohort study</td>
<td>533 (Warfarin: 438 TSOAC: 95)</td>
<td>The mean waiting time was significantly shorter for patients taking TSOAC compared to warfarin</td>
</tr>
<tr>
<td>Halperon et al. 2012</td>
<td>Prospective cohort study</td>
<td>Dabigatran - Warfarin -</td>
<td>A significant difference in cardioversion cancellations in favor of TSOAC</td>
</tr>
</tbody>
</table>

TSOAC: Target-specific oral anticoagulants

The three studies treating the matter of delayed and cancelled DCCVs differ in study design. One study was a prospective randomized trial [16], one study was a retrospective cohort study [19] and one was a prospective cohort study [20]. Two of the studies were performed in one single center and one study was multinational. Two of the studies investigated the difference in days waiting between patients taking a TSOAC and warfarin [19,20]. Both studies showed a significant difference between the two groups in favor of the TSOACs. One study also compared the rate of cancelled procedures [19] and found that significantly more patients taking warfarin had to cancel their DCCVs. In the study by Cappato et al. [16], the number of patients that could not undergo DCCV as planned was significantly higher among patients taking warfarin than rivaroxaban. All three studies showed significant advantages with the TSOACs compared to warfarin regarding delayed and/or cancelled DCCV- procedures.

**Discussion**

This was a literature study based on eight different articles. The strength with a literature study is the easy access to material. With studies from several different countries, the result may be applicable to a wide population. This review is solely based on original articles, which is a strength. However the review was based on a relatively low number of articles.

**Efficacy and safety**

The purpose of this work was to compare TSOAC with warfarin regarding efficacy and safety in patients with AF undergoing DCCV. Several studies have shown that the
TSOACs are at least as effective and safe as warfarin in reducing the risk of stroke in patients with AF. There are however only a limited number of studies investigating efficacy and safety in patients with AF undergoing DCCV.

The risk of suffering from stroke or SE in conjunction with DCCV is estimated to be between 5% and 7% without adequate anticoagulant therapy. The use of warfarin reduces that risk to somewhere between 0.5% and 1.6% [21].

All studies included in the present work included only a small number of events both with warfarin and with any of the TSOACs, consistent with the notion of a residual risk between 0.5% and 1.6% despite anticoagulation. However, the relatively small number of events makes it difficult to decide whether the observed differences between the treatment regimens were significant or not. The lack of significant difference between warfarin and the TSOACs in any of the studies included is possibly due to the low number of events. Another interpretation is that the risks of chance findings are high.

The fact that some of the studies included here had relatively small populations undermines their statistical power even further and the risk of confounding factors is palpable. In some of the included studies, there were no events of stroke or major bleeding in some of the treatment groups. However, due to the low number of patients in these groups we can’t really make any conclusions based on these results. It has been calculated that it would require at least 30 000 patients to prove that the TSOAC are similar to warfarin, and 38 000 patients to show that the TSOAC are superior to warfarin [21]. The small number of events in the TSOAC groups is however somewhat reassuring regarding their safety and efficacy, and the conclusion of several systematic reviews and meta-analysis on the subject is that the TSOACs are at least equally safe and effective as warfarin [21-23].

Three of the studies included here were post-hoc analyses. Post-hoc analyses are not designed to answer the question of interest and therefore require careful interpretation. The grade of evidence is normally lower for the results from a post-hoc analysis and they are more useful for generating hypotheses. Two of the studies were performed in only one center. This makes the result from these studies less applicable.

In the study by Coleman et al. [14] there were no embolic events among those patients who had undergone a TEE prior to DCCV. This could suggest that an early cardioversion strategy with a TSOAC and a TEE are safe for the patients [14]. This conclusion is consistent with the findings in the study by Cappato et al. [16]. However, in the study by Nagarakanti et al. [13] the rate of stroke or SE was similar among patients who had undergone a TEE prior to DCCV and patients without a TEE. This could indicate that a TEE may not be necessary prior to DCCV when using dabigatran.

The analysis by Nagarakanti et al. [13] compares warfarin to dabigatran in two different doses, 110 mg daily and 150 mg daily. Events were rare in all groups, but major bleeding occurred illogically slightly more often in the D110 group. This could be due to the fact that a non-study anticoagulant or antiplatelet therapy was used more frequently before cardioversion in the dabigatran groups. After cardioversion the use of non-study therapy was highest in the D110 group. However in the overall RELY-trial major bleeding rates were lowest in the D110 group. Two other studies compares warfarin to more than one TSOAC [14,15]. Though the TSOACs are not compared with each other, a small retrospective cohort study by Yadlapati et al. concludes no significant differences between dabigatran and rivaroxaban [24].

It is suggested in Nagarakantis [13] analysis that investigators were more reluctant to use dabigatran alone than to use warfarin alone prior to the cardioversion. However the RELY-trial was the first large-scale trial to compare dabigatran to warfarin and
dabigatran had not been used much when this trial started. Perhaps today in the light of the results from other studies and more clinical experience, physicians may feel more comfortable with using dabigatran alone as an anticoagulant [13].

In the studies by Coleman et al. [13] and Piccini et al. [17] event rates were slightly higher than in the other studies included. The follow-up periods were longer in these two studies, eight weeks and 60 days, respectively, compared to 30 days in the other studies. This could explain the somewhat higher event rates in these two studies. The biggest risk of suffering from stroke due to DCCV occurs within the first week after the procedure [26]. Most of the included studies have a short follow-up period of only 30 days. Recommendations are that anticoagulant treatment should go on for at least 28 days after cardioversion [3]. After 30 days it is probably more likely that an event is due to AF rather than the cardioversion. In the study by Coleman et al. [14] it is not specified in this study when the events occurred and it is likely that some of the events were not associated with the cardioversion. The high event rates in the study by Piccini et al. is also probably due to the fact that only patients with moderate to high risk of stroke were included in the study. Also, as much as 81% of the patients had persistent AF. Coleman et al.:s study confirms the theory that complications are associated with high CHADS2 and CHA2DS2VASc-scores [14].

Unfortunately, the included studies did not fit the aim of the present study perfectly. In the study by Piccini et al. [17] the main purpose was not to compare warfarin with the TSOACs. Two of the studies [15,17] were not exclusively dealing with DCCV, but rather with catheter ablation. Patients undergoing pharmacological cardioversion were unfortunately also included in several of the included studies. The efficacy end-points were quite similar in all studies, however the study by Coleman et al. [14] included TIA in their results, which could make that result more difficult to compare to the other studies. In the study by Piccini et al. [17], safety end-point was defined as both major and non-major bleeding. This explains the high rates of bleeding in this study. This result is however not relevant from our perspective.

Several reviews, systematic reviews and meta-analysis [21-23, 25] compare the TSOACs with warfarin in patients undergoing DCCV. These reviews include the post-hoc analysis of the RELY-trial [13], the ROCKET AF-trial [17] and the ARISTOTLE-trial [17] as well as the X-Vert-trial [16]. This literature study also includes the retrospective studies by Coleman et al. [14] and Kochhäuser et al. [15]. All studies indicate that the TSOACs are an effective and safe alternative to warfarin regarding DCCV. However, the studies included here have limitations and the study design differ between the studies. Also the end-points are somewhat different between the studies and several of these studies also include pharmacological cardioversion and catheter ablation. These limitations could make it more difficult to draw any certain conclusions.

As mentioned earlier, the majority of studies in this work are based on post-hoc analyses. Two studies were retrospective and observational in nature and finally one study had an open-label randomization. There is obviously need for more studies in larger populations that are designed for and solely focus on the use of TSOACs in the setting of DCCV. This study treats the TSOACs as a group and it would be interesting with more studies comparing the different TSOACs with each other.

**Cardioversion delays**

There are several obvious advantages with the TSOACs compared to warfarin. Warfarin interacts with many commonly used drugs as well as some foods. To reach a stable INR within therapeutic range in warfarin treatment may take weeks or even months [18], on
average it takes 12 weeks from therapy start to procedure [26]. The fast onset action of the TSOACs is likely to reduce the delays due to a shorter time of pre-treatment.

In the studies by Collison et al. [19] and Halperin et al. [20] it is suggested that the use of a TSOAC instead of warfarin in the setting of cardioversion could reduce delays and cancellations. However these articles contained only a limited amount of information regarding methods and the authors did not include the possibility of bias. Also there was no information regarding population size in the study by Halperin [20]. For these reasons it is hard to decide how reliable these studies actually are.

The current recommendation by the social board in Sweden is that adequate anticoagulation therapy shall commence at least three weeks prior to DCCV [26]. Even though the studies by Coleman et al. [14] and Cappato et al. [16] suggest that a short pre-treatment time with a TSOAC in conjunction with a TEE would be as safe as a long term treatment, we do not have enough data to establish the safest time interval of pre-treatment anticoagulation therapy.

The result from the study by Cappato et al. [16] strengthens the notion that a TSOAC instead of warfarin could overcome DCCV delays and cancellations. Cardioversions could be delayed and cancelled due to inability to reach adequate anticoagulation therapy. For the patients this means prolonged warfarin therapy and risk of bleeding events associated with warfarin therapy. The duration of arrhythmia would also be longer for the patient. These risks may be overcome with a TSOAC instead of warfarin as prophylactic therapy. Based on this aspect, a TSOAC may be safer for some patients than warfarin.

The need for regular INR-monitoring in patients taking warfarin is quite inconvenient for the patient. In a study by Alegret et al. [27] health-related quality of life (HRQoL) is compared between patients undergoing DCCV taking either warfarin or a TSOAC. Not unexpectedly, the study shows that patients taking a TSOAC experienced a better HRQoL compared to patients taking warfarin. However this difference disappeared after six months of treatment [27]. This could be due to the less frequent INR-testing once the individual maintenance dose has been found.

The problem with the TSOACs is the requirement of compliance. The majority of patients undergoing cardioversion are older and treatment adherence may be difficult to achieve.

If the patient is warfarin naïve or the INR is not within therapeutic range, heparin infusion or low-molecular-weight-heparin as bridging therapy could be needed until optimum INR is established. Since the TSOACs reach therapeutic blood levels and steady state within a few days it would be more suitable for outpatient management, and it may be more economical by avoiding hospitalization [13].

In an analysis of the RELY-trial by Wallentin et al. [28] the relationship between INR-control and events regarding safety and efficacy was studied. INR-control can be measured in TTR (time in therapeutic range). It was suggested in this study that a high TTR causes fewer events [28]. In a cost-effectiveness study by Davidson et al. [29] it is suggested that a low TTR could lead to increased costs. This is because inadequate anticoagulation therapy could lead to more events of stroke. A good TTR is also suggested to increase life expectancy and increase QALYs (quality-adjusted life years) [29]. In the study by Coleman et al. [14] a significant relationship between INR and the time of bleeding events was demonstrated [14]. This aspect was not dealt with in the other studies included in the present review, however that would have been of interest.
It seems that TSOACs could reduce delays and cancellations of cardioversions. However more and sufficiently powered studies primarily designed to answer this question are required to determine the safety of a shorter pre-treatment time with TSOACs.

Warfarin therapy is a cheap, proven and efficient way of reducing the risk of stroke associated with DCCV. However, the TSOACs seem to be a satisfactory alternative to warfarin and with more studies comparing warfarin with the TSOACs in the setting of DCCV we are likely to see an increased use of the TSOACs in the future. Further studies on pre-treatment times are necessary so that we can determine the safest and most efficient anticoagulation therapy in the setting of DCCV.

**Conclusion**

The target-specific oral anticoagulants seem to be at least as effective and safe as warfarin in the setting of direct-current cardioversion and the advantage of fast on-set action can be used to minimize delays and cancellations of direct-current cardioversion.

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References


