

REVIEW ARTICLE

Cardioversion in Non-Valvular Atrial Fibrillation

Hermann H. Klein, Hans-Joachim Trappe

SUMMARY

Background: Atrial fibrillation is the most common type of cardiac arrhythmia and is associated with elevated rates of stroke, heart failure, hospital admission, and death. Its prevalence in the overall population is 1.5% to 2%. To convert atrial fibrillation to sinus rhythm, cardioversion is needed.

Methods: This review is based on pertinent articles published from 2004 to December 2014 that were retrieved by a selective PubMed search employing the terms “atrial fibrillation” and “cardioversion.”

Results: In electrical cardioversion, a defibrillator is used to pass a pulse of current between two electrodes. In pharmacological cardioversion, antiarrhythmic drugs are given intravenously or orally. Electrical cardioversion results in sinus rhythm in more than 85% of patients; pharmacological cardioversion results in sinus rhythm in about 70% of patients with recent-onset atrial fibrillation. As a rule, cardioversion should be carried out only under effective therapeutic anticoagulation with heparin, a vitamin K antagonist, or a new oral anticoagulant drug. If atrial fibrillation has been present for more than 48 hours, cardioversion must be preceded by transesophageal echocardiography to rule out blood clot in the left atrium, or else the patient is pretreated with an anticoagulant drug for at least 3 weeks. As cardioversion can transiently impair left atrial pumping function, anticoagulation is usually maintained for 4 weeks after the procedure. The decision whether to continue anticoagulation beyond this point is based on the risk of stroke, as assessed with the CHA₂DS₂-VASC score.

Conclusion: The main risks of cardioversion—thromboembolism and clinically significant hemorrhage—occur in 1% of cases or less (in the first 30 days after treatment) if the procedure is carried out as recommended in therapeutic guidelines. Serious complications still occur, but they are rare.

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Atrial fibrillation is the most common of the serious cardiac rhythm disturbances in the adult population. Typically, atrial fibrillation is diagnosed by means of an electrocardiogram (ECG). The prevalence of atrial fibrillation is 1.5 to 2% in the general population. At age 80 years, approximately 10% of the population have atrial fibrillation (1, 2).

About 40% of patients with atrial fibrillation also have valvular heart disease (e1). Most of the large studies on atrial fibrillation focused on non-valvular atrial fibrillation where no serious valvular heart disease is present. Atrial fibrillation is associated with a marked increase in mortality (1.7-fold, [e2]), stroke (4-fold, [e3]) and heart failure (6-fold, [e2]).

The signs and symptoms of atrial fibrillation can vary widely. Common complaints include:

- Dyspnea (49%)
- Fatigue (49%)
- Palpitations (43%)
- Dizziness (37%)
- Angina pectoris (20%)

However, these complaints may also be caused by other concomitant diseases (3).

Atrial fibrillation is classified into five types (4):

- First detected atrial fibrillation
- Paroxysmal atrial fibrillation (maximum duration 1 week)
- Persistent atrial fibrillation (duration 1 week to 1 year)
- Long-standing persistent atrial fibrillation (duration more than 1 year)
- Permanent atrial fibrillation where the constant presence of the arrhythmia is accepted and no further attempt to control the rhythm is made.

To assess the risk for embolism and stroke in patients with atrial fibrillation, the CHA₂DS₂-VASC score was introduced.

Where:

C = congestive heart failure

H = arterial hypertension

A = age

D = diabetes mellitus

S = status post stroke or transient ischemic attack

VA = vascular disease, such as status post myocardial infarction, and

Sc = female sex.

One point is scored for each of the following: C, H, age 65–74 years, D, VA, and Sc.

Helios Klinikum Warburg, Idar-Oberstein, Germany: Prof. Dr. med. Klein, Prof. Dr. med Trappe

Two points are scored for each of the following: age >74 years and status post stroke (S₂).

The aim of this paper is to present the current state of knowledge on cardioversion in non-valvular atrial fibrillation. Using the key words “atrial fibrillation“ and “cardioversion,“ a literature search was conducted in the PubMed database, covering the last 10 years up to December 2014.

Indications for the restoration of sinus rhythm in atrial fibrillation

None of the large studies on cardioversion in atrial fibrillation conducted so far was able to demonstrate improvements in prognosis for the hard endpoints “death“ and “stroke rate“ (5–9). However, these studies included only very few patients younger than 60 years of age. Cardioversion is thus primarily aimed at improving existing symptoms. The *Box* shows the indications for cardioversion as recommended in the guidelines (4). In a 2012 survey of 57 electrophysiological centers in Europe, 75% of hospitals reported to perform more than 100 cardioversion procedures annually (10). According to data from a prospective European registry, treatment for maintaining sinus rhythm is provided for approx. 60% of patients with atrial fibrillation (between 48.7% in Italy and 72% in France), with 18.1% of patients receiving electrical cardioversion and 19.5% pharmacological cardioversion (11).

Anticoagulation and/or transesophageal echocardiography before cardioversion

Before cardioversion, anticoagulation therapy for 3–4 weeks or transesophageal echocardiography are recommended to ensure the absence of left atrial thrombi (4, 12). In patients with recent onset of atrial fibrillation, a thrombus is detected in approx. 10 and 0.6% of cases in the left and right atrial appendage, respectively (13). In these patients, cardioversion should only be performed after dissolution of intracardiac thrombi by means of effective anticoagulation.

Anticoagulation in cardioversion of atrial fibrillation

When Lown (14) introduced the method of electrical cardioversion to treat atrial fibrillation, the risk of thromboembolism during the period immediately after the intervention was already known. In 1992, a retrospective analysis of 454 electrical cardioversions of atrial fibrillation found an incidence of embolic events of 1.32%; no patient with thromboembolism was on anticoagulation therapy (15). The timing of thromboembolic events after electrical cardioversion of atrial fibrillation was described based on data from 32 studies conducted between 1966 and 1997 (16). Among a total of 4621 electrical cardioversions, 92 thromboembolic events were identified; almost all these events (except for four cases) occurred within the first seven days after cardioversion. A recently published retrospective analysis of 16 274 first-time electrical cardioversions performed in Denmark between 2000 and 2008 found a

BOX

Indications for the restoration of sinus rhythm in atrial fibrillation*

- Recent-onset atrial fibrillation
- Sinus-rhythm maintaining therapy as the long-term treatment goal
- Marked symptoms due to atrial fibrillation
- High heart rate or hemodynamic instability due to pre-excitation
- High heart rate plus myocardial ischemia or hypotension or heart failure if the heart rate cannot be rapidly reduced with pharmacotherapy

*modified according to (4)

more than twofold increase in the risk of thromboembolic events during the first 30 days after the intervention among patients receiving no anticoagulation therapy during and after cardioversion (17). The thromboembolic incidence rate was 4 and 10.33 per 100 patient-years for the group with and without prior oral anticoagulant therapy, respectively. The risk of thromboembolism then fell within 360 days to 1.84 and 3.18 per 100 patient-years with and without anticoagulation, respectively.

The CHA₂DS₂-VASc score had no impact on the occurrence of thromboembolic events with and without anticoagulation within 30 days after cardioversion. For a CHA₂DS₂-VASc score of 0 and 1, the risk of thromboembolism after cardioversion without anticoagulation versus with anticoagulation was 2.21-fold increased, while a 2.4-fold increase was noted for CHA₂DS₂-VASc scores above 2. Aspirin did not significantly reduce the risk of cardioversion-related thromboembolism. The retrospective analysis of this study does not allow to draw conclusions as to why the anticoagulant therapy received by the patients was so variable. The risk of cardioversion-related thromboembolic events is lower in patients with atrial fibrillation of <48 h duration without risk factors; therefore, only heparin anticoagulation at the time of cardioversion is recommended and no subsequent anticoagulant therapy (4). In patients with risk factors for thromboembolism, oral anticoagulant therapy is required over a period of at least four weeks after cardioversion. This recommendation is backed by a recent retrospective Finnish study evaluating the incidence of thromboembolic events after 5116 cardioversions (88% electrical) within 30 days in 2481 patients with atrial fibrillation <48 h duration without anticoagulation (18). Altogether 38 thromboembolic events were noted (0.7% of the cardioversions). In 10 of these cases, the CHA₂DS₂-VASc

TABLE 1

Antiarrhythmic agents for pharmacological cardioversion*

| Agent | Primary dose regimen | Subsequent dose regimen | Notes |
|-------------|--|-------------------------|---|
| Amiodarone | 5 mg/kg BW IV over 1 h | approx. 50 mg/h | Potential acute adverse events: phlebitis, hypotension |
| Flecainide | 2mg/kg BW IV over 10 min or 200–300 mg orally | | Not in patients with marked structural heart disease, risk of QRS interval widening, QT prolongation, and atrial flutter with fast conduction |
| Propafenone | 2 mg/kg BW IV over 10 min or 450–600 mg orally | | Not in patients with marked structural heart disease, risk of QRS interval widening and atrial flutter with fast conduction |
| Vernakalant | 3 mg/kg BW IV over 10 min | | Limited approval |

* modified according to (4)

score was 0–1. The thromboembolic events occurred between day 1 and day 27 (median: day 2). The highest risk for thromboembolism was observed in patients with heart failure, diabetes mellitus and age >60 years. The lowest risk of thromboembolism was found in non-heart-failure patients <60 years (0.2%).

Etiology of thromboembolism after cardioversion

Atrial stunning is considered to be the primary cause of thromboembolism after cardioversion (19). While in the presence of atrial fibrillation no atrial contractions occur, there is still some degree of movement of blood in the left atrium and atrial appendage. Restoration of sinus rhythm by means of cardioversion can initially cause a deterioration of blood flow in the left atrium and the left atrial appendage (19), promoting local blood clot formation. Atrial stunning has been observed after transthoracic electrical, internal electrical, pharmacological, and spontaneous cardioversion (19). The longer the period of atrial fibrillation before cardioversion, the longer atrial stunning may persist (20). Typically, left atrial function returns to normal within one week after cardioversion; however, in patients with long-standing atrial fibrillation the process of normalization may take a month (20).

Anticoagulants in cardioversion

Heparins, vitamin K antagonists or novel oral anticoagulants can be used to ensure effective anticoagulation at the time of cardioversion, while aspirin does not offer adequate protection. With unfractionated heparin, an initial intravenous bolus of 60–80 units/kg body weight (BW) is followed by intravenous therapy aimed at extending the activated partial thromboplastin time to about 50–70 seconds (21). Adequate anticoagulation for cardioversion can also be achieved with enoxaparin at a dose of 1 mg/kg BW subcutaneously twice daily (22). Certoparin is another low

molecular weight heparin which has been used (23). Effective anticoagulation using a vitamin K antagonist (e.g. warfarin, phenprocoumon) is thought to be achieved at international normalized ratio (INR) values in the range of 2 to 3 (21). With cardioversion, an INR >2.5 appears to better prevent thromboembolic events (24). Rivaroxaban is the first novel oral anticoagulant to be compared with vitamin K antagonists in a prospective study on cardioversion (mostly electrical). About 1000 patients received rivaroxaban in a dose of 20 mg/d (creatinine clearance >50 mL/min) or 15 mg/d (creatinine clearance 30–49 mL/min) in two strategies (long or short pre-treatment) or a vitamin K antagonist (25). Rivaroxaban was administered orally between three weeks and, at the latest, four hours before cardioversion. Two strokes (0.2%) and one fatal hemorrhage were observed. No significant differences between rivaroxaban and vitamin K antagonists were found for the endpoints of this study. Post-hoc subgroup analyses of the large pivotal studies on novel oral anticoagulants indicate that dabigatran (26) and apixaban (27) may also be effective anticoagulants in a cardioversion setting. As yet, no prospective data on these agents are available.

Practice of electrical cardioversion for atrial fibrillation

Electrical cardioversion is typically performed under continuous ECG monitoring and intravenous procedural anesthesia (10); given the risk of ventricular fibrillation and asystole, provisions for resuscitation measures should be made. The electrodes of the defibrillator/cardioverter can be placed in the anterior–left lateral (apical) or anterior–posterior position so that the heart is located between the two electrodes. The most effective way to position the electrodes with older monophasic defibrillators was the anterior–posterior arrangement (28). Using biphasic defibrillators, higher cardioversion rates are achieved today at lower

TABLE 2

Descriptive presentation of adverse events related to electrical or pharmacological cardioversion of atrial fibrillation from studies with more than 1000 patients

| Study Study type Reference | Thromboembolism (TE) within 30 days after cardioversion | Major bleeding | Other complications |
|---|---|---|--|
| X-VerT; open, randomized comparison of rivaroxaban and vitamin K antagonists (VKA) in non-valvular atrial fibrillation >48 h duration, n = 978 rivaroxaban, n = 492 VKA (2014 [25]). | Based on patients – Rivaroxaban: 2 strokes (0.2%) – VKA: 2 strokes (0.41%) | Based on patients – Rivaroxaban 0.61%, one fatal bleeding – VKA (0.8%), two fatal bleedings | Not reported |
| Post-hoc subgroup analysis from the open, randomized controlled comparative study dabigatran 110 mg BID (D110, n = 647), dabigatran 150 mg BID (D150, n = 672), warfarin (W, n = 664) (2011 [26]) | Based on cardioversions – D110 5 (0.77%) – D150 2 (0.30%) – W 4 (0.60%) | Based on cardioversions – D110 11(1.7%) – D150 4 (0.6%) – W 4 (0.6%) | Not reported |
| FinCV study, 5116 cardioversions in 2481 patients with atrial fibrillation <48 h duration without anticoagulation, 88% electrical, retrospective cohort analysis (2013 [18]) | Based on cardioversions – TE: 38 (0.7%) – 3 fatal strokes (0.06%) | No major bleeding | Not reported |
| FinCV study on cardiac rhythm complications after 6906 electrical cardioversions (ECV) in 2868 patients with atrial fibrillation <48 h, retrospective cohort analysis (2013 [e5]) | N/A | N/A | – Asystole >5 seconds 51 (0.7%) – in 7 ECV short successful resuscitation, 2 patients required external pacemaker stimulation, no occurrence of ventricular tachycardia or ventricular fibrillation |
| Warfarin to prevent embolism at the time of cardioversion for atrial fibrillation, 1609 cardioversions in 1438 anticoagulated patients, retrospective cohort analysis (2002 [24]) | – 6 TE (0.37% of cardioversions), – 1 fatal stroke – With INR >2.5 no TE | 2 major bleedings | Not reported |
| Risk of thromboembolism in first electrical cardioversion (ECV) with (WA) and without (WOA) anticoagulation, retrospective cohort analysis (2015 [17]) | – TE based on 100 patient-years – Within 30 days after ECV: WA: 4.0; WOA: 10.3 – Within 360 days after ECV: WA: 1.84; WOA: 3.18 | Not reported | Not reported |
| Euro Heart Survey, prospective registry study, ECV n = 712, PCV n = 1989 (2012, [34]) | – Transient ischemic attack ECV 2 (0.3%), PCV 12 (1.3%) | ECV 9 (1.3%), PCV 10 (1.0%) | – Ventricular tachycardia ECV: 7 (0.9%), PCV: 5 (0,5%) – Ventricular fibrillation ECV: 3 (0.4%), PCV: 0 – Asystole ECV: 2 (0.3%), PCV: 7 (0.7%) – Heart failure ECV: 7 (1.1%), PCV: 9 (1,0 %) |

ECV, electrical cardioversion; INR, international normalized ratio of prothrombin time; WA, with anticoagulation; WOA, without anticoagulation; PCV, pharmacological cardioversion; TE, thromboembolism; VKA, vitamin K antagonists; W, warfarin

energy levels (29). With this technology, electrode positioning and the geometry of energy transfer are of minor importance (30). In patients with implanted pacemakers or defibrillators, the electrodes should ideally be placed at a distance >8 cm from the unit in an anterior–posterior arrangement (31). The electrical discharge of the defibrillator is synchronized with the R wave in the electrocardiogram (14, 32). Using a biphasic defibrillator, it is advisable to start with a shock energy of 100 J in patients with atrial fibrillation of less than 48-hour duration and 150 J in

patients with longer-standing atrial fibrillation (33). According to a large prospective registry study, sinus rhythm is initially restored by electrical cardioversion in approximately 88% of cases (34). Predictors of successful cardioversion include the absence of chronic obstructive pulmonary disease, paroxysmal atrial fibrillation, and a short history of atrial fibrillation. If sinus rhythm cannot be achieved even with the use of maximum energy, a new attempt can be made about 3 minutes after the last shock application as body resistance is lower at that time (32). Another

way to improve the chance of successful electrical cardioversion is the oral administration of amiodarone (35) or propafenone (36) before the procedure. In individual difficult cases (e.g. patients with significant obesity), internal cardioversion may be considered (32). In patients with atrial fibrillation and implantable cardioverter-defibrillator (ICD), the ICD can be used for internal cardioversion. However, with approximately 30% the success rate is lower than with external cardioversion (37).

Pharmacological cardioversion

In clinical practice, it is easier to attempt pharmacological cardioversion as it does not require anesthesia. The European guidelines for the management of atrial fibrillation (4) list as drugs recommended for pharmacological cardioversion amiodarone, flecainide, ibutilide, propafenone, and vernakalant; however, ibutilide is not available in Germany and vernakalant was granted limited marketing authorization (*Table 1*).

Besides intravenous administration, amiodarone can also be given orally in high doses (30 mg/kg) for cardioversion in recent-onset atrial fibrillation (38). With the “pill in the pocket” approach, oral propafenone or flecainide is used for cardioversion in patients with atrial fibrillation <48 h duration without or with only minor structural heart disease under ECG monitoring. Patients who underwent the supervised treatment without problems can repeat it independently outside the hospital, should arterial fibrillation recur.

Success rates of electrical and pharmacological cardioversion

Two large prospective registry studies provide a very good overview on cardioversion in Europe (34, 39). According to these studies, pharmacological cardioversion is typically performed in patients with new-onset or paroxysmal atrial fibrillation (median duration of present atrial fibrillation episode: 0.5–2 days [34]) and electrical cardioversion in patients with persistent atrial fibrillation (median duration of present atrial fibrillation episode: 30 days [34]). Electrical cardioversion was successfully performed in 88% of 712 patients (34) and 90% of 1946 patients (39), respectively. Sinus rhythm was pharmacologically restored in 71% of 1089 patients (34) and 69% of 1026 patients (39). After one year, in 70% of patients with successful cardioversion sinus rhythm was observed in the electrocardiogram (34). No randomized study comparing the success rates achieved with electrical versus pharmacological cardioversion was found in the literature.

Complications after cardioversion of atrial fibrillation

In *Table 2*, the main complications of cardioversion reported in studies with more than 1000 patients are listed, primarily related to thromboembolic events, bleeding and arrhythmia. Complication rates are typically <1% of patients treated; however, individual patients may experience serious adverse events.

Open questions

What thromboembolic risk is associated with cardioversion despite anticoagulation?

Thromboembolic complications occur within 30 days after cardioversion despite adequate anticoagulation with a probability between 0% (27) and 1.6% (22). The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) compared the novel oral anticoagulant dabigatran in doses of 150 mg (D150) twice daily and 110 mg (D110) twice daily with the oral vitamin K antagonist warfarin (W) in 18 113 patients with atrial fibrillation (40). The annual rate of stroke or systemic embolism was 1.53% (D110), 1.11% (D150) and 1.69% (W), respectively. In this prospective study, 1270 patients underwent 1983 cardioversions, analyzed post-hoc as a subgroup (26). Stroke and systemic embolism occurred within 30 days after cardioversion in 0.77% (D110: 5 of 647), 0.3% (D150: 2 of 672) and 0.6% (W: 4 of 664) of cardioversions. By calculating the annual thromboembolism rates in the three treatment groups of the total study based on a period of 30 days and then comparing them with the thromboembolism rates within 30 days after cardioversion, it is revealed that thromboembolic events occurred 3-times (D150), 4-times (W) and 6-times (D110), respectively, more frequently in the month after cardioversion compared with the remaining months of the study. If the thromboembolism rates after cardioversion were based on patients rather than cardioversions performed, the calculated risk of thromboembolic events associated with cardioversion would even be greater. This is supported by the very large retrospective study on cardioversion from Denmark (17) which found that even with anticoagulation the risk of thromboembolism within the first 30 days after cardioversion was more than twice as high compared with the remaining follow-up period. As these are very large, trustworthy studies, it is reasonable to assume that cardioversion increases the overall small risk of systemic embolism, including stroke, despite anticoagulation. The current guidelines recommend that a patient with a CHA₂DS₂-VASc score of 0 should receive effective anticoagulation for medically performed cardioversion, while this is not required for a patient with atrial fibrillation or spontaneous cardioversions (4). Based on the information available after the publication of the large retrospective 2015 cardioversion study from Denmark, it is clear that even patients with a CHA₂DS₂-VASc score of 0 undergoing medically performed cardioversion should receive effective anticoagulation which is in line with the guideline recommendations (4) that were not previously supported by evidence from studies.

Should patients with interventional or surgical closure of the left atrial appendage receive anticoagulation for cardioversion?

With no pertinent studies available, this question cannot be answered. In case no anticoagulation therapy is initiated, it should at least be ensured that the left atrial appendage is completely closed (e4) and no thrombi are present in the left atrium.

KEY MESSAGES

- The indication for electrical or pharmacological cardioversion is based on the signs and symptoms of the patient. So far, no convincing evidence is available to support a positive impact of the restoration of sinus rhythm on prognosis.
- Conversion to sinus rhythm is to be expected in 90% of electrical cardioversions with biphasic defibrillators and in 70% of pharmacological cardioversions of recent-onset atrial fibrillation.
- Effective anticoagulation is required for each cardioversion procedure, regardless of the CHA₂DS₂-VASc score. Only patients with atrial fibrillation <48h duration and a CHA₂DS₂-VASc score of 0 do not require therapeutic anticoagulation for four weeks after cardioversion. Subsequent further anticoagulation therapy is based on the CHA₂DS₂-VASc score.
- Complications after cardioversion, especially thromboembolic events (stroke) and major bleeding, are not common (approx. 0.5% to 1.0% in each case).
- Cardioversion should be indicated with caution as the comparatively rare complications can be devastating for individual patients.

Conflict of interest statement

The authors declare that no conflict of interest exists.

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Corresponding author

Prof. Dr. med. Hermann H. Klein
 Medizinische Klinik II, Helios Klinikum Warburg
 Langwiesen Straße 13, 55743 Idar-Oberstein, Germany
 hermann@klein-devries.de

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Supplementary material to:

Cardioversion in Non-Valvular Atrial Fibrillation

by Hermann H. Klein and Hans-Joachim Trappe

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