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Review

Periprocedural Anticoagulation for Cardioversion of Acute Onset Atrial Fibrillation and Flutter: Evidence Base for Current Guidelines

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See article by Stiell et al., pages 1296–1300 of this issue.

ABSTRACT

The practice of electrical or pharmacological cardioversion (CV) to restore sinus rhythm in patents with symptomatic atrial fibrillation (AF) or atrial flutter has been a part of clinical practice for more than 100 years. For almost as long as CV has been performed, it has been recognized that the act of restoring sinus rhythm is associated with an increased risk of stroke and systemic embolism, and that oral anticoagulant (OAC) therapy can be used to prevent peri-CV thromboembolism. Although it has been widely accepted that OAC therapy is necessary to prevent thromboembolism in patients with chronic AF/atrial flutter who undergo CV, previous clinical practice recommendations have suggested that OAC therapy may be omitted in patients at low risk of stroke. However, in recent years, evidence has emerged

RÉSUMÉ

Le recours à la cardioversion électrique ou pharmacologique pour rétablir le rythme sinusal chez les patients présentant une fibrillation auriculaire ou un flutter auriculaire (FA) symptomatique fait partie de la pratique clinique depuis plus de 100 ans. Depuis presque aussi longtemps, on reconnaît que cette intervention visant à rétablir le rythme sinusal est associée à un risque accru d'accident vasculaire cérébral (AVC) et d'embolie systémique, et qu'une anticoagulothérapie par voie orale peut être utilisée dans la prévention de la thromboembolie en contexte de cardioversion. Bien que la nécessité de l'anticoagulothérapie par voie orale soit largement reconnue pour prévenir la thromboembolie chez les patients qui présentent une FA ou un flutter auriculaire chronique et qui subissent une cardioversion, les

For the patient who experiences uncomfortable palpitation, the quieting of the heart is a welcome relief from chaotic thumping.

—Bernard Lown, 1967

Electrical or pharmacological cardioversion (CV) to restore sinus rhythm in patents with symptomatic atrial fibrillation (AF) or atrial flutter (AFL) has been a part of clinical practice for more than 100 years.[1] Within a few years after the introduction of quinidine for the CV of AF/AFL, reports of thromboembolic events temporally related to the re-establishment of sinus rhythm began to appear.[2,3] This association was also noted in early publications of case series of patients treated with direct current CV.[4] In aggregate, early observational studies from the 1960s reported a 1.76% rate of thromboembolism after the CV of chronic AF in patients not receiving oral anticoagulant (OAC) drugs.[2-5] In contrast, the rate of thromboembolism was much lower in patients who received OACs before CV, with only a 0.45% rate of thromboembolism within 30 days of CV (Fig. 1).[5] Although none of these studies were randomized, the results were compelling, especially because patients who received OACs were objectively at higher risk of thromboembolism owing to a high prevalence of rheumatic mitral stenosis (valvular AF/AFL) or a history of a previous thromboembolic event.

These observational results led to early recommendations regarding OAC use surrounding the CV of AF/AFL. Initially, the Lown group recommended initiation of OACs 3 weeks before the planned CV, with OAC continuation for 1 week after CV.[4] In 1980, the same group expanded on their previous recommendations by stating "anticoagulation prior to CV is unnecessary in the patient with the acute onset of AF or if its duration has been less than a week. However, many patients who are aware that they have experienced a change in rhythm, underestimate the time onset of the fibrillation. Thus, in view of the potential for embolic events within this group of patients, we routinely anticoagulate patients for a period of three weeks prior to CV. Following CV, anticoagulation is maintained for one month."[6] No other rationale was provided for the change in treatment duration, nor for the recommendations themselves.

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from several sources challenging these historical conventions. In 2018 the Canadian Cardiovascular Society AF guidelines updated the previous recommendations regarding CV of acute onset AF, and the use of peri-CV anticoagulation. In this article we present an extensive review of the evidence informing the previous recommendations, as well as the novel evidence that informed the change in recommendations. In addition, the current Canadian Cardiovascular Society AF guideline recommendations are examined within the context of contemporary international major society guidelines.

recommandations antérieures en pratique clinique laissaient entendre que l'anticoagulothérapie par voie orale n'était pas obligatoire chez les patients exposés à un risque moindre d'AVC. Toutefois, au cours des dernières années, des données probantes provenant de diverses sources remettent en question ces conventions du passé. En 2018, la Société canadienne de cardiologie a mis à jour les recommandations relatives à la cardioversion en cas de FA d'apparition soudaine et l'usage de l'anticoagulation en contexte de cardioversion. Dans cet article, nous présentons un examen approfondi des données probantes associées aux recommandations antérieures et des nouvelles données ayant suscité la mise à jour des recommandations. De plus, les recommandations actuelles des lignes directrices de la Société canadienne de cardiologie sur la prise en charge de la fibrillation auriculaire sont évaluées dans le contexte des lignes directrices contemporaines des principales sociétés à l'échelle mondiale.

In the mid-1990s Laupacis et al. reaffirmed the same 3-week pre-/4 weeks post-CV OAC recommendation for chronic AF; however, they shortened the duration of "acute onset AF" from < 7 days to < 48 hours.[7] The rationale given for this 48-hour window was on the basis of the "implicit assumption that there has been insufficient time for thrombus formation to have occurred in the atria," however, the authors note that "there are, unfortunately, no reliable data to support this assumption."[7] Subsequently, the 48-hour definition of acute AF/AFL became enshrined in clinical practice.

More recently, evidence has emerged from several sources challenging these conventions and warranting their re-evaluation. First, several studies have shown that left atrial thrombus can be documented in a significant proportion of patients who present within 48 hours of AF onset (4%-43% of patients), suggesting that thrombus formation does occur more rapidly than had been previous assumed.[8-10] Second, several studies that examined the mechanism of *de novo* thrombus formation after CV have shown that the mechanical and prothrombotic abnormalities induced by AF persist beyond the acute episode. Although left atrial contractile function is impaired during active fibrillation, sinus rhythm restoration paradoxically results in further impairment in left atrial emptying. This impairment is greatest immediately after CV, with recovery only occurring after 2-3 weeks of sustained sinus rhythm (Fig. 2).[11-13] Likewise, acute episodes of AF result in platelet activation, thrombin generation, and endothelial dysfunction, a constellation of abnormalities that can persist for up to 7 days after CV.[14-16] These observations suggest that CV within 48 hours of AF onset should not necessarily be considered to be without risk, and use of OACs in this setting might be justified.

Clinical Evidence Regarding Stroke Prevention in the Peri-CV Period

Observational studies of patients with nonacute AF/AFL (AF episode durations > 48 hours) have reported a risk of a thromboembolism in the 30 days after CV of 1.76%-2.39% in those who received no or inadequate OAC therapy and 0.20%-0.45% in those who received adequate OAC therapy (defined as therapeutic OACs for at least 3 weeks before the CV; Fig. 1).[4,5,17-28] Accordingly, despite the lack of randomized data, there is widespread agreement with respect to the need for oral anticoagulation pre- and post-CV in the patients who present with AF/AFL of > 48 hours' duration.

Conversely, patients who present with symptomatic AF/AFL of < 48 hours' duration have long been considered, on a theoretical basis, to have a low risk of thromboembolism after CV. This practice has been supported by several observational reports of short-term outcomes after CV in patients with acute AF, in which only 12 patients experienced thromboembolism in the 30 days after CV (0.27% monthly risk; 4836 CVs; 4380 patients).[8,26,27,29-40] Although this risk is comparable with that of elective CV in chronic AF/AFL patients who receive OACs, the observed 30-day rate of thromboembolism far exceeds the expert consensus-based Canadian Cardiovascular Society (CCS) AF guideline threshold for recommending OACs (1.5% per year, or 0.12% per 30 days).[41-43] Moreover, it is important to recognize that these reports are limited by selection bias, largely describing low risk patients (69% of these patients had a **C**ongestive Heart Failure, **H**ypertension, **A**ge, **D**iabetes, **S**troke/Transient Ischemic Attack ($CHADS_2$) score of 0-1) who presented in a stable state early in the 48-hour window of their acute AF/AFL episode (mean duration of symptomatic AF/AFL was 6.0 hours), some of which were receiving OAC drugs on an ongoing basis at the time of CV (28% of patients).

Several recent data sets with a focus on patients with AF/AFL who underwent CV in the absence of OAC therapy provide a more disquieting viewpoint. Most notable are the Cleveland Clinic Study[44] and the **Fin**nish **C**ardio**V**ersion (FinCV) study[45-50]; however, analyses from the ANTI-Kogulation registry,[8] the Danish National Patient Registry,[51] and from the Swedish National Patient Registry,[52] also provide insight (Fig. 1).

The report from the Cleveland Clinic[44] retrospectively determined outcomes from a prospectively-collected database of consecutive, unselected patients who underwent CV of acute onset AF (< 48 hours' duration) in the Electrophysiology Laboratory of the Cleveland Clinic between 1996 and 2012. Patients were classified in 3 groups: (1) patients with adequate oral anticoagulation (international normalized ratio [INR] ≥ 2.0; 898 CVs in 709 patients with a mean

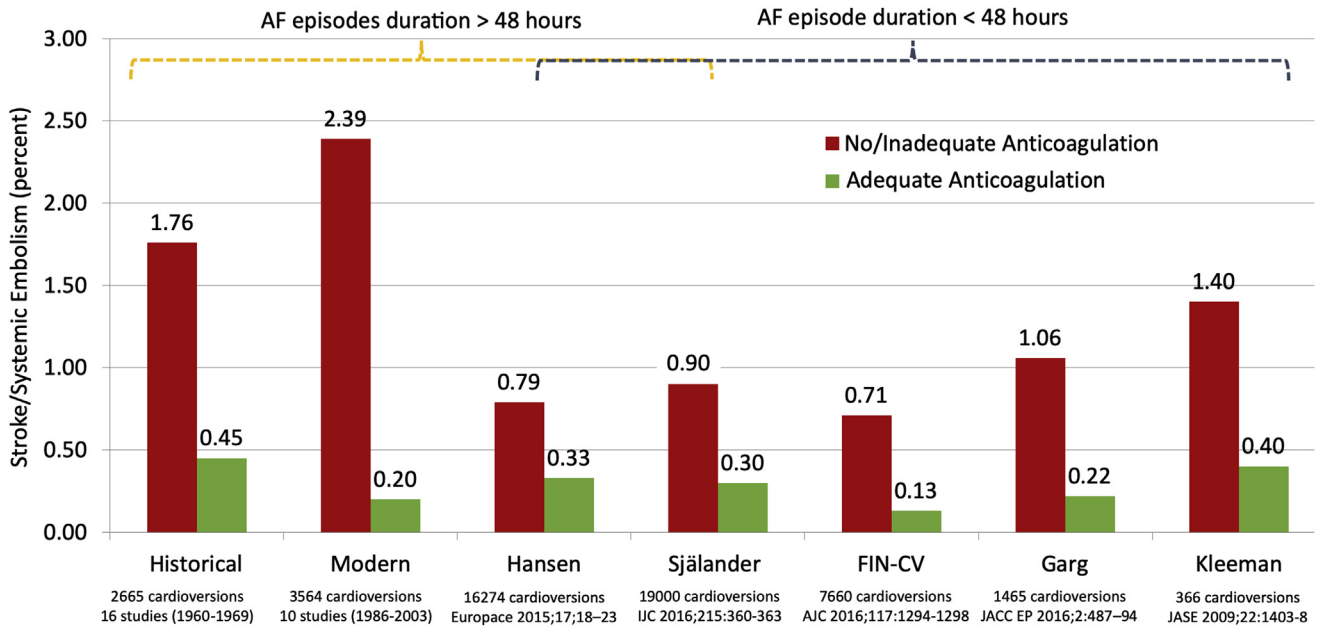

Figure 1. Thirty-day incidence of thromboembolic events after cardioversion (CV) of atrial fibrillation (AF)/atrial flutter (AFL) according to peri-CV anticoagulation status. **Red bars** show the incidence with no or inadequate anticoagulation; **green bars** show the incidence with adequate anticoagulation. For data points derived from more than 1 study, the data of the studies were combined by determining sample size-weighted means (pooling). The left pair of bars is derived from an analysis of 16 historical observational studies of long-lasting AF/AFL from the 1960s ("Historical"). The second pair of bars is derived from an analysis of 10 recent observational trials of long-lasting AF/AFL from 1986-2003 ("Modern"). The remaining pairs of bars reflect contemporary studies. The studies by Hansen and Sjalander represent overlap populations in which the **red bars** show the incidence with no or inadequate anticoagulation (by inference, those with acute AF/AFL); **green bars** show the incidence with adequate anticoagulation (by inference, those with long-lasting AF/AF). The 3 rightmost pairs of bars exclusively include patients who presented with AF/AFL of < 48 hours' duration. Although the risk of a post-CV thromboembolic event is lower in patients with AF/AFL of < 48 hours' duration, the risk is still substantial and significantly higher than the 0.12% monthly risk threshold for recommending oral anticoagulation therapy in the Canadian Cardiovascular Society AF guidelines. FinCV, **Fin**nish **C**ardio**V**ersion.

Congestive Heart Failure, **H**ypertension, **A**ge (≥75 years), **D**iabetes, **S**troke/Transient Ischemic Attack, **V**ascular Disease, **A**ge (65-74 years), **S**ex (Female) (CHA_2DS_2-VASc) score of 2.62 ± 1.7); (2) patients with subtherapeutic oral anticoagulation (INR, 1.5-2.0; 116 CVs in 106 patients with a mean CHA_2DS_2-VASc score of 2.10 ± 1.6); and (3) patients with no oral anticoagulation (INR ≤ 1.5; 567 CVs in 7484 patients with a mean CHA_2DS_2-VASc score of 2.34 ± 1.7). The 30-day post-CV rate of a thromboembolism was substantially higher in patients with no oral anticoagulation or subtherapeutic oral anticoagulation (0.88%; 6 events after 683 CVs) compared with those with therapeutic oral anticoagulation (0.22%; 2 events after 898 CVs; odds ratio [OR], 4.8; $P = 0.03$).

The FinCV studies were retrospective, observational studies that determined outcomes in catchment-area patients who underwent CV in 2 central hospitals, 3 university hospitals, and 3 regional hospitals in Finland between 2003 and 2016. The programs enrolled consecutive patients in whom electrical or pharmacological CV was attempted for acute AF < 48 hours' duration (FinCV; 3143 patients, 7660 CVs), consecutive patients in whom elective electrical CV was attempted for persistent AF > 48 hours' duration (FinCV2; 1271 patients, 1894 CVs), and patients with AF using non-vitamin K OACs (NOACs) in whom electrical or pharmacological CV was attempted (FinCV3; 1028 patients, 1298 CVs). The program, in aggregate, reported the short-term outcomes after 10,852 pharmacologic or electrical CVs in 5441 patients. The published analyses of this multicentre cohort included: (1) the risk factors for thromboembolism after 5116 successful CVs performed in 2481 patients with acute AF that were performed without pre- or post-CV OACs[45]; (2) the relationship between the duration of AF before CV and thromboembolism within 30 days after 5116 successful CVs in 2481 patients with acute AF that were performed without pre-CV or post-CV OAC drugs[46]; (3) the incidence and risk factors for mortality, 30-day post-CV thromboembolism, and acute complications after 4356 CVs performed in 2530 patients with acute AF who received OAC drugs[49]; (4) the relationships between baseline stroke risk (measured according to the CHA_2DS_2-VASc score), OAC use, and the 30-day post-CV incidence of thromboembolism in 3143 patients who underwent 7660 attempted CVs[47]; (5) the interactions among the most significant predictors of 30-day risk of thromboembolism (age, sex, and time to CV) in patients with acute AF who underwent electrical CVs in the absence of periprocedural OAC drug use (4715 CVs)[48]; and (6) the relationship between OAC intensity (pre-CV and post-CV) and 30-day post-CV thromboembolism in 1021 patients who underwent 1424 electrical CVs in whom complete INR monitoring was available.[50]

Together these 6 reports showed the following key findings: (1) in the absence of OAC use, time to CV is a very strong predictor of 30-day risk of thromboembolism

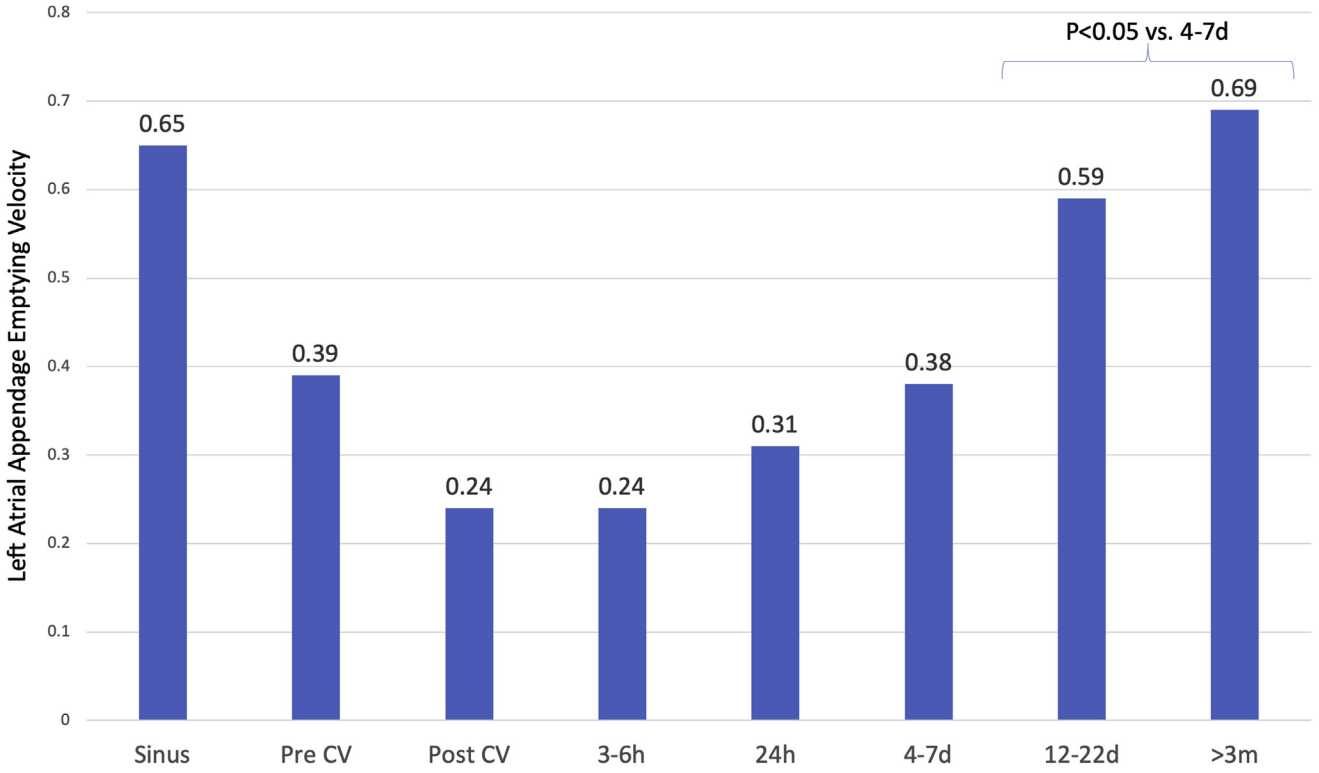

Figure 2. Time course of left atrial mechanical dysfunction associated with atrial fibrillation and sinus rhythm restoration. CV, cardioversion. Data from Goldman et al.,[13] Manning et al.,[12] and Grimm et al.[11]

(Fig. 3)[46]; (2) in those who do not receive OACs before or after CV the incidence of thromboembolism is significantly higher in patients with AF episode durations of 12-48 hours than in patients with CV < 12 hours after AF onset (1.1% [30 of 2767 patients] vs 0.33% [8 of 2440 patients], respectively)[46]; (3) for those who receive OACs, AF episode duration was not associated with the incidence of thromboembolism (0.1% for < 24 hours, 0% for 24-48 hours, 0% for 48 hours-30 days, and 0.2% for > 30 days)[49]; (4) in the absence of OAC use before or after CV, the 4 independent predictors of the risk of thromboembolism 30 days post-CV were older age (OR, 1.05; 95% confidence interval [CI], 1.02-1.08 per year; $P < 0.001$), female sex (OR, 2.1; 95% CI, 1.1-4.0; $P = 0.03$), heart failure (OR, 2.9; 95% CI, 1.1-7.2; $P = 0.03$), and diabetes mellitus (OR, 2.3; 95% CI, 1.1-4.9; $P = 0.03$)[45,47]; and (5) therapeutic oral anticoagulation

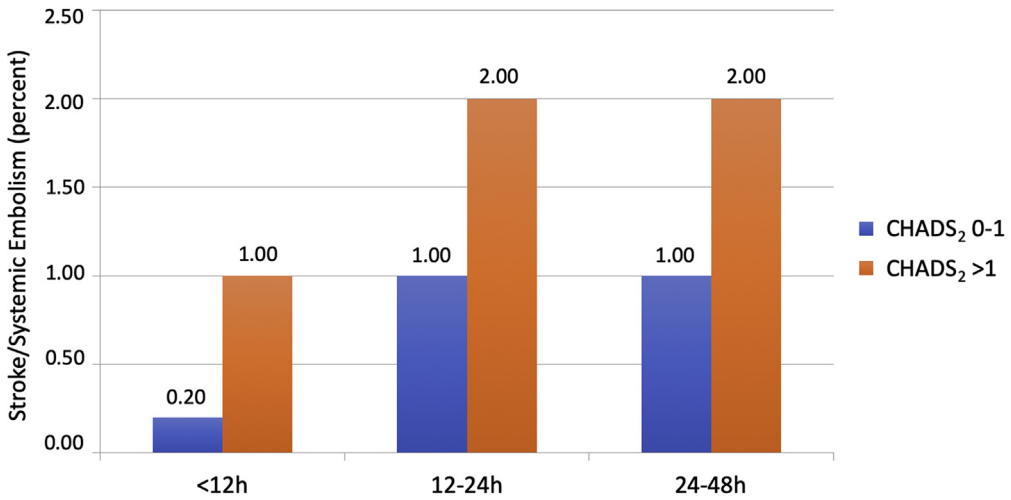

Figure 3. Thirty-day incidence of thromboembolic events after cardioversion of atrial fibrillation/atrial flutter according to atrial fibrillation episode duration and baseline risk of stroke/systemic embolism, estimated according to **C**ongestive Heart Failure, **H**ypertension, **A**ge, **D**iabetes, **S**troke/Transient Ischemic Attack ($CHADS_2$) score. Data from Nuotio et al.[46]

significantly decreases the risk of a post-CV thromboembolism.[45-48,50,53] Relative to the last observation, for patients with acute AF of < 48 hours' duration the incidence of thromboembolism in those who do not receive OACs at the time of CV was significantly higher than in patients who were receiving OACs (0.71% [38 events in 5362 encounters] vs 0.13% [3 events in 2298 encounters]; $P = 0.001$).[47] When parsed according to CHA_2DS_2-VASc score, OAC use significantly reduced the rate of definite thromboembolism in those with CHA_2DS_2-VASc score of ≥ 2 (0.2% [3 of 1708] vs 1.1% [28 of 2590]; $P = 0.001$), but the benefit of OACs was not statistically significant in patients with a CHA_2DS_2-VASc score of 0-1 (0.0% [0 of 590] vs 0.40% [10 of 2772]; $P = 0.23$). Of note, 10 of the 38 (26%) definite thromboembolic events that occurred in the 30 days after successful CV in patients who received no pre- or post-CV oral anticoagulation, occurred in patients with a CHA_2DS_2-VASc score of 0-1.

The ANTIKogulation Registry was a prospective, single-centre, observational study designed on an intention to cardiovert basis.[8] The registry included 366 patients with acute AF of < 48 hours' duration who underwent CV with or without pre-existing oral anticoagulation. Those without pre-existing oral anticoagulation received heparin before CV. Oral anticoagulation was continued for ≥ 4 weeks after CV in all patients regardless of $CHADS_2$ score. Of the 152 patients who were not receiving pre-CV OACs, 75 patients (49%) had a pre-CV transesophageal echocardiogram (TEE) that revealed a left atrial thrombus in 3 patients (4%). Of the 214 patients who did receive pre-CV OACs, 130 patients (61%) had a pre-CV TEE that revealed a left atrial thrombus in 0 patients (0%). This difference was statistically significant ($P = 0.02$). A stroke or transient ischemic attack (TIA) occurred within 30 days in 3 of the 358 patients who spontaneously converted (25 patients) or in whom CV was attempted (333 patients). The rates of stroke or TIA were 0.4% (1/214 patients) in those who received pre-CV OACs, and 1.4% in those without pre-CV OACs (2/144 patients). This difference did not meet statistical significance. Of note, each of the 3 patients with a stroke or TIA had a $CHADS_2$ score of 0.

Two other recent reports have indirectly assessed the thromboembolic risk associated with CV of acute AF/AFL in the absence of oral anticoagulation—a report from the Danish National Patient Registry[51] and a report from the Swedish National Patient Registry.[52] Each of these reports used administrative databases to evaluate the 30-day rate of thromboembolism after CV of AF/AFL as a function of the presence or absence of pre-CV OAC use. Although these databases did not include information related to the duration of AF/AFL, the authors proposed that it would be reasonable to assume that CV would have been performed in patients without previous OAC use if the AF/AFL episode was acute (eg, < 48 hours' duration), whereas CV would have been performed in patients with previous OAC use if the AF/AFL was chronic or sustained (eg, > 48 hours duration). In the Danish analysis,[51] the 30-day incidence of thromboembolic after direct current CV was 1.06% (54 events in 5084 patients) in those who did not receive pre-CV OACs and 0.29% (32 events in 11,190 patients) in those who received pre-CV OACs. Although the rate was not explicitly reported, thromboembolism did occur in patients with $CHADS_2$ or CHA_2DS_2-VASc scores of 0 or 1. In the Swedish analysis,[52] the crude 30-day incidence of thromboembolism in patients who did not receive pre-CV OACs at 0.86% (104 of 12,152 patients) was statistically significantly higher than that in patients who received pre-CV OAC therapy at 0.33% (35 of 10,722 patients). After adjustment for the unequal distributions of the CHA_2DS_2-VASc factors, the OR for thromboembolism in the 30 days after CV was 2.54 (95% CI, 1.70-3.79; $P < 0.001$) in a comparison of patients who did not receive pre-CV OACs with patients who received pre-CV OACs. This database was also subjected to an analysis in which 9500 patients who did not receive periprocedural OACs were matched with 9500 patients who received periprocedural OACs on the basis of their propensity to have received oral anticoagulation as indexed by the components of the CHA_2DS_2-VASc score and of the **H**ypertension, **A**bnormal Renal/Liver Function, **S**troke, **B**leeding History or Predisposition, **L**abile INR, **E**lderly (> 65 Years), **D**rugs/Alcohol Concomitantly (HAS-BLED) score.[52] Patients who did not receive peri-CV OACs were more likely to have thromboembolism (OR, 2.51; 95% CI, 1.69-3.75; $P < 0.001$), with similar rates of major bleeding when compared to those receiving OAC (OR, 1.00; 95% CI, 0.48-2.10). With their assumption that CV would not be performed in the absence of OACs if the AF duration was > 48 hours, the authors conclude that performing a CV for patients with AF < 48 hours' duration without OACs is associated with a greater risk of thromboembolism than performing a CV for patients with AF > 48 hours' duration who received OACs.

CV of Acute AF/AFL in Patients at Low Thromboembolism Risk

The risk of thromboembolism after CV in patients with acute symptomatic AF/AFL of < 48 hours' duration with a CHA_2DS_2-VASc score of 0-1 remains controversial. Although the reports from the Cleveland Clinic and the Swedish registry observed no thromboembolism in such patients, the rate of thromboembolism in patients with a CHA_2DS_2-VASc score of 0-1 who were not receiving OACs was 0.4% in the FinCV study.[44,46,52] Even in patients with time to CV of < 12 hours the risk of thromboembolism with CHA_2DS_2-VASc scores of 0-1 remained significant at 0.2%,[46] an event rate that exceeds the CCS AF guideline 30-day risk threshold for recommending OACs of 0.12%. Likewise, as previously mentioned, all strokes in the ANTIKogulation Registry occurred in patients with a $CHADS_2$ score of 0 (overall event rate 1.3% in the 30 days after CV). Although the authors of the Danish cohort did not report the incidence of post-CV thromboembolic complications in patients with low CHA_2DS_2-VASc scores, the authors did report similar hazard ratios (HRs) for stroke/systemic embolism for patients with CHA_2DS_2-VASc scores of 0-1 as well as for those with scores ≥ 2 (HR, 2.21 [95% CI, 0.79-6.77] and HR, 2.40 [95% CI 1.46-3.95], respectively). Last, the FibStroke study[53] identified 78 ischemic strokes and 22 definite TIAs in 99 patients that occurred within 30 days of direct current CV of AF/AFL. Of these 100 thromboembolic complications, 77% were after CV of acute AF/AFL and 63% occurred in patients who did not receive OACs. Of the patients who developed a stroke/TIA after CV of AF/AFL, 21% had a low risk of a thromboembolic complication (eg, CHA_2DS_2-VASc score of 0-1).

OACs After CV

The time period immediately after CV is a high-risk period for thromboembolism. Although some of the emboli might originate from thrombi formed before CV, a significant proportion originate from thrombi formed after sinus rhythm is established.[8-16] The importance of effective post-CV oral anticoagulation was addressed indirectly within the FinCV2 study, and more directly within the Danish cohort and ANTIKogulation study.[8,50,51,53] The FinCV2 study showed a subtherapeutic oral anticoagulation (INR < 2.0) within 21 days after CV of nonacute AF (AF episode duration > 48 hours) in 22.8% of patients with therapeutic oral anticoagulation at the time of CV. Those in whom the oral anticoagulation was subtherapeutic after CV had an increased incidence of thromboembolism (1.7% vs 0.3%; $P = 0.03$).[50] The Danish cohort examined the utility of OAC initiation after CV in previously OAC-naive patients. Compared with the reference of patients with previous and with subsequent oral anticoagulation, the risk of a post-CV thromboembolism was evident only in patients with no previous and no subsequent oral anticoagulation (HR, 2.47; 95% CI, 1.49-4.27).[51] Those in whom oral anticoagulation was initiated only after CV had a similar risk of thromboembolism compared with those with previous and with subsequent oral anticoagulation (HR, 0.97; 95% CI, 0.33-2.8). This was similarly observed in the ANTIKogulation study, in which the rates of stroke or TIA were similar between those who received OACs only after CV, and those who received OACs before and after CV.[8]

The 2018 CCS Guidelines

The data presented herein provided the impetus for the CCS AF guidelines committee to re-evaluate the practice of oral anticoagulation surrounding CV. Although the most recommendations regarding oral anticoagulation are unchanged compared with the previous CCS AF guidelines, significant changes occurred in 2 domains: thromboembolic risk stratification before CV and recommendations for oral anticoagulation after CV (Fig. 4).

With respect to the former, the observational evidence suggests that the common practice of performing CV in the absence of previous oral anticoagulation for patients with nonvalvular AF/AFL who present within 48 hours of AF/AFL onset might not be as safe as was previously assumed. Nevertheless, the CCS AF Guideline Committee recognized the advantages of prompt restoration of sinus rhythm in

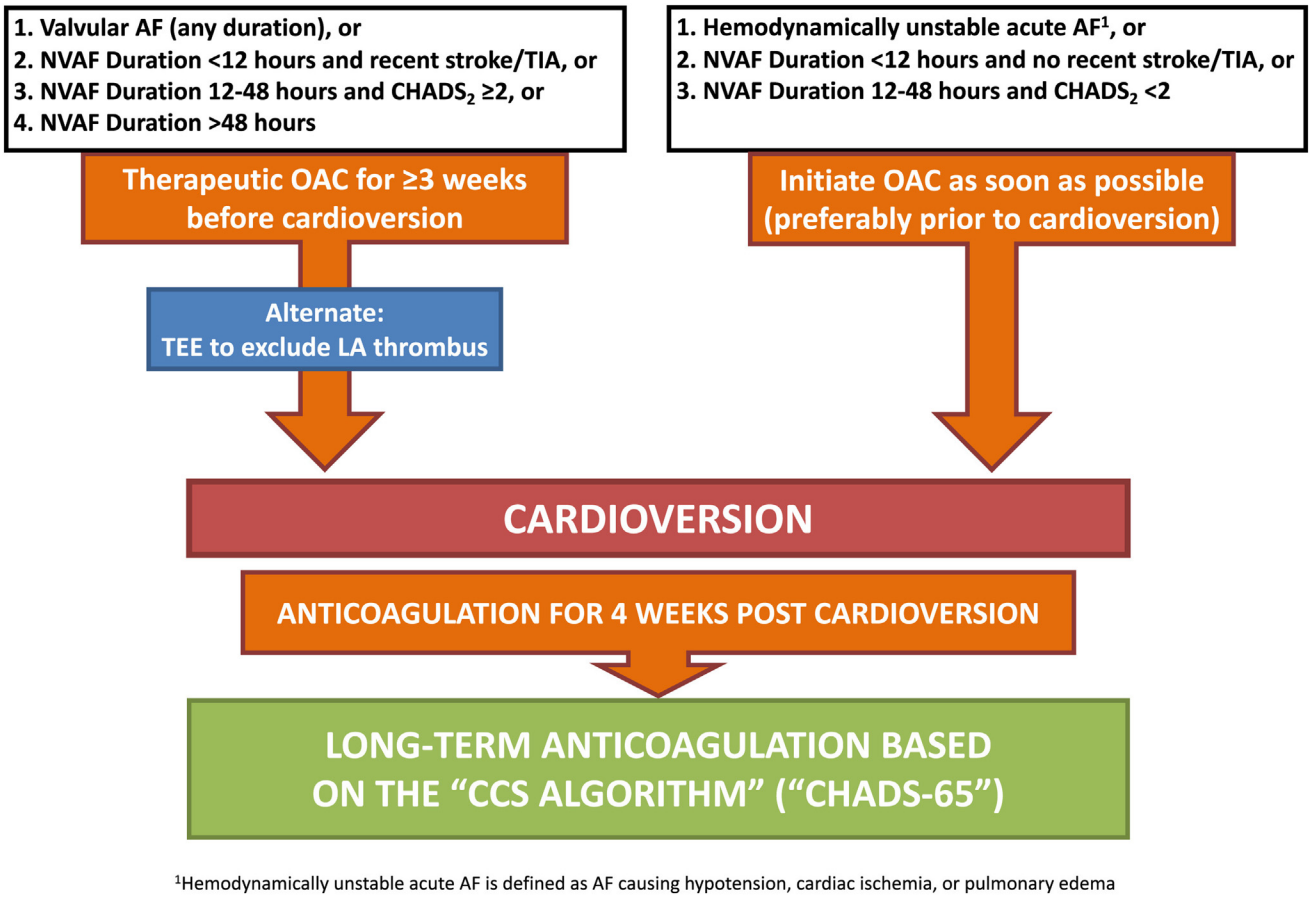

Figure 4. The 2018 Canadian Cardiovascular Society (CCS) atrial fibrillation (AF) guideline recommendations for oral anticoagulation in the context of cardioversion for patients with symptomatic atrial fibrillation or flutter. $CHADS_2$, **C**ongestive Heart Failure, **H**ypertension, **A**ge, **D**iabetes, **S**troke/Transient Ischemic Attack; LA, left atrial; NVAF, nonvalvular atrial fibrillation (defined as atrial fibrillation in the absence of mechanical heart valves, rheumatic mitral stenosis, or moderate to severe nonrheumatic mitral stenosis); OAC, oral anticoagulant; TEE, transesophageal echocardiogram; TIA, transient ischemic attack. Reproduced from Andrade et al.[41] with permission from Elsevier.

Table 1. Contemporary major society guidelines regarding early cardioversion of acute onset NVAF/AFL

Source	Guideline	Comment
Canadian Cardiovascular Society[41]	Cardioversion of symptomatic AF or AFL without at least 3 weeks of previous therapeutic anticoagulation (or use of the TEE approach) reserved for patients with NVAF who present with a clear AF onset within 12 hours in the absence of recent stroke or transient ischemic attack (within 6 months) or in patients with a $CHADS_2$ score < 2 who present after 12 hours but within 48 hours of AF onset	Weak recommendation, low-quality evidence
American Heart Association/American College of Cardiology/Heart Rhythm Society[54]	For patients with AF or AFL of 48 hours' duration or longer, or when the duration of AF is unknown, anticoagulation with warfarin (INR 2.0-3.0), a factor Xa inhibitor, or direct thrombin inhibitor is recommended for at least 3 weeks before and at least 4 weeks after cardioversion, regardless of the CHA_2DS_2-VASc score or the method (electrical or pharmacological) used to restore sinus rhythm	By exclusion, this indirectly permits the immediate cardioversion of patients with AF/AFL of $<$ 48 hours' duration
National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand[56]	Anticoagulation for 3 weeks or a transesophageal echocardiogram (to document absence of LA thrombus) is recommended before cardioversion in patients with $>$ 48 hours or an uncertain duration of AF	By excluding them, this permits the immediate cardioversion of patients with AF/AFL of $<$ 48 hours' duration
European Society of Cardiology[55]	Early cardioversion can be performed without TEE in patients with a definite duration of AF $<$ 48 hours	Class of recommendation IIa (conflicting evidence but weighted toward recommendation)
Taiwan Heart Rhythm Society[57]	In OAC-naive patients who have an AF duration of $<$ 48 hours, there are insufficient data on safe substitution of LMWH/UFH with NOACs. Therefore, LMWH/UFH should be given and followed by TEE to exclude atrial thrombus	Recommends TEE-guided approach to immediate cardioversion of acute AF/AFL
American College of Chest Physicians[58]	For patients with AF of documented duration of $\leq$ 48 hours undergoing elective cardioversion (electrical or pharmacologic), we suggest starting anticoagulation at presentation (LMWH or UFH at full venous thromboembolism treatment doses) and proceeding to cardioversion rather than delaying cardioversion for 3 weeks of therapeutic anticoagulation or a TEE-guided approach	Weak recommendation, low-quality evidence

AF, atrial fibrillation; AFL, atrial flutter; $CHADS_2$, **C**ongestive Heart Failure, **H**ypertension, **A**ge, **D**iabetes, **S**troke/Transient Ischemic Attack; CHA_2DS_2-VASc, **C**ongestive Heart Failure, **H**ypertension, **A**ge ($\geq$75 years), **D**iabetes, **S**troke/Transient Ischemic Attack, **V**ascular Disease, **A**ge (65-74 years), **S**ex (Female); INR, international normalized ratio; LA, left atrial; LMWH, low molecular-weight heparin; NOAC, non-vitamin K oral anticoagulant; NVAF, nonvalvular atrial fibrillation; OAC, oral anticoagulant; TEE, transesophageal echocardiography; UFH, unfractionated heparin.

patients with acute AF/AFL. Accordingly, the CCS AF Guideline Committee revised their previous recommendation to suggest that pharmacological or electrical CV of symptomatic AF/AFL without at least 3 weeks of previous oral anticoagulation be reserved for nonvalvular AF/AFL patients at the lowest risk of thromboembolism. On the basis of the available evidence this population would include nonvalvular AF/AFL patients without recent stroke or TIA (within 6 months) who present with a clear AF/AFL onset within 12 hours, and patients with a $CHADS_2$ score < 2 who present after 12 hours but within 48 hours of AF/AFL onset. Considering the lack of randomized data the strength of the recommendation was graded as weak, on the basis of low-quality evidence.[41] Other patients with acute AF/AFL would require TEE assessment or 3 weeks of oral anticoagulation before nonemergent CV.

With respect to the latter point, the available data suggest that omitting OACs after the CV of acute nonvalvular AF/AFL might not be as safe as was previously thought. Specifically, the available data suggest that the risk of thromboembolism after CV of acute onset AF/AFL in the absence of oral anticoagulation is greater than that observed in patients who undergo CV from chronic AF/AFL who are receiving OACs. Moreover, OAC initiation at the time of CV appears to offer the same beneficial reduction in the incidence of post-CV thromboembolism as it does in patients receiving chronic OACs for stroke prevention,[51] without substantially increasing the risk of major bleeding (30-day rate of major bleeding of 0.1% in the 1859 patients in whom oral anticoagulation was initiated only after CV, compared with 0.2% in the 10,293 patients without pre- and post-CV oral anticoagulation; personal email communication May 29, 2019).[52] Because of these observations the CCS AF Guideline Committee revised their previous recommendation to suggest that, in the absence of a strong contraindication, all patients receive a minimum of 4 weeks of oral anticoagulation after electrical or pharmacologic CV of AF/AFL (adjusted-dose warfarin or a NOAC). Because of the lack of randomized data the strength of the recommendation was graded as weak, on the basis of low-quality evidence.[41] Thereafter, the CCS AF guidelines recommend that the need for ongoing oral anticoagulation should be on the basis of the risk of thromboembolism as determined by the CCS Algorithm ("CHADS-65"; strong recommendation, moderate-quality evidence).[41] Because previous guidelines recommended immediate anticoagulation after CV in patients with nonvalvular AF/AFL with a CHADS-65 score of $\geq$ 1, the revised recommendation is new only for patients younger than the age of 65 years with a $CHADS_2$ score of 0 (CHADS-65 score of 0).

Comparison With Other Contemporary AF Guidelines

Because of the relative limitations associated with the data surrounding CV of acute onset AF/AFL it is anticipated that practice recommendations might vary between jurisdictions.

Table 2. Contemporary major society guidelines regarding anticoagulation after cardioversion of low-risk acute nonvalvular AF/AFL

Source	Guideline	Comment
Canadian Cardiovascular Society[41]	All patients who undergo cardioversion of AF/AFL receive at least 4 weeks of therapeutic anticoagulation (adjusted-dose warfarin or a NOAC) after cardioversion	Weak recommendation, low-quality evidence
American Heart Association/ American College of Cardiology/Heart Rhythm Society[54]	For patients with AF or AFL of < 48 hours' duration with a CHA_2DS_2-VASc score of 0 in men or 1 in women, administration of heparin, a factor Xa inhibitor, or a direct thrombin inhibitor, vs no anticoagulant therapy, may be considered before cardioversion, without the need for postcardioversion oral anticoagulation	Class of recommendation IIb (weak recommendation), quality of evidence B-NR
National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand[56]	Anticoagulation is recommended at the time of electrical or pharmacological cardioversion, and for at least 4 weeks postprocedurally	In the text, "it is reasonable for patients with lone AF (without thromboembolic risk factors) and a known arrhythmia onset time within 48 hours prior, to undergo cardioversion without administering one month of periprocedural anticoagulation"
European Society of Cardiology[55]	In patients without stroke risk factors, anticoagulation is recommended for 4 weeks after cardioversion	Class of recommendation Ib (but coupled with recommendation for long-term anticoagulation in higher-risk patients)
Taiwan Heart Rhythm Society[57]	After cardioversion, continuous NOAC treatment is mandatory for at least another 4 weeks, irrespective of CHA_2DS_2-VASc score. Long-term use of NOACs depends on the CHA_2DS_2-VASc score	Strength of recommendations not provided in these guidelines
American College of Chest Physicians[58]	After successful cardioversion to sinus rhythm, we recommend therapeutic anticoagulation (with VKA or full adherence to NOAC therapy) for at least 4 weeks rather than no anticoagulation, regardless of baseline stroke risk	Weak recommendation, low-quality evidence

AF, atrial fibrillation; AFL, atrial flutter; B-NR, moderate-quality nonrandomized data; CHA_2DS_2-VASc, **C**ongestive Heart Failure, **H**ypertension, **A**ge (≥75 years), **D**iabetes, **S**troke/Transient Ischemic Attack, **V**ascular Disease, **A**ge (65-74 years), **S**ex (Female); NOAC, non-vitamin K oral anticoagulant; VKA, vitamin K antagonist.

With respect to the timing of CV for acute onset AF the CCS AF guidelines are the only ones to substratify the candidacy for CV on the basis of the risk of thromboembolism (eg, $CHADS_2 < 2$ vs ≥ 2) and duration of the AF episode (episode onset < 12 hours vs ≥ 12-48 hours). Other societies, with the exception of Taiwan, permit the immediate CV of patients with AF/AFL of < 48 hours' duration in the absence of oral anticoagulation and/or TEE (Table 1).[54-58] The Taiwan Heart Rhythm Society recommends a TEE before CV of for all unanticoagulated patients who present with acute AF/AFL.[57]

After CV of acute nonvalvular AF/AFL the consensus is slightly more clear, with the CCS,[41] American College of Chest Physicians,[36] Taiwan Heart Rhythm Society,[57] National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand,[56] and the European Society of Cardiology[55] all recommending anticoagulation for at least 4 weeks after CV (Table 2). Only the American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines suggest that no oral anticoagulation is required after CV of acute onset AF/AFL.[54] Despite the relative consensus, these major society guidelines individually recognize that the quality of evidence surrounding post-CV anticoagulation is low, thus the strength of recommendation is predominantly weak (with the exception of the European Society of Cardiology. which provided a stronger class Ib recommendation).

Conclusions

The contemporary management of OAC before and after CV of AF and AFL will continue to evolve as the evidence base matures and new trials are published. Until then, review of the available data suggest that a strategy of routine post-CV anticoagulation might be associated with optimal patient outcomes.

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