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Viewpoint

Safe Cardioversion for Patients With Acute-Onset Atrial Fibrillation and Flutter: Practical Concerns and Considerations

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See article by Andrade and Mitchell, pages 1301–1310 of this issue.

ABSTRACT

In this Viewpoint concerns raised by Canadian emergency physicians regarding recommendations 2 and 6 from the recent Canadian Cardiovascular Society 2018 update for atrial fibrillation are discussed. These recommendations narrow the window for safe cardioversion and suggest 4 weeks of anticoagulation for all patients who undergo urgent cardioversion regardless of their CHADS-65 status. We discuss the implications of Grading of Recommendations, Assessment, Development, and Evaluation weak recommendations on the basis of low-quality evidence.

RÉSUMÉ

Il est question dans ce point de vue des préoccupations soulevées par des urgentologues canadiens concernant les recommandations 2 et 6 provenant de la récente mise à jour 2018 des lignes directrices de la Société canadienne de cardiologie en matière de fibrillation auriculaire. Ces recommandations réduisent la fenêtre pendant laquelle il est sûr d'effectuer une cardioversion et suggèrent l'administration d'un anticoaguant pendant 4 semaines à tous les patients qui subissent une cardioversion d'urgence, sans égard au score CHADS-65. Nous traitons de l'incidence qu'a la méthodologie GRADE (*Grading of Recommendations Assessment, Development and Evaluation*) à l'endroit des recommandations faibles reposant sur des données probantes de faible qualité.

The Canadian Cardiovascular Society (CCS) recently published the 2018 focused update of guidelines for the management of atrial fibrillation (AF) and atrial flutter (AFL).[1] For physicians who frequently care for patients with acute-onset AF or AFL, the 2018 update suggested 2 significant changes in practice compared with previous versions of the guidelines, with the objective of reducing the risk of thromboembolic complications in patients who undergo cardioversion (CV) for acute AF or AFL. The first change redefines which patients can safely undergo CV. The second change recommends at minimum 4 weeks of anticoagulation for all patients who undergo CV for acute AF or AFL. Both suggestions were given "weak recommendation" status on the basis of "low-quality evidence" according to the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) standards.[2] The goal of this Viewpoint is to review the new guidelines and their supporting evidence, the implications of GRADE weak recommendations, and suggest a practical way

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Table 1. Recommendations 2 and 6 in the 2018 CCS update

Recommendation number	Recommendation
2	We suggest that pharmacological or electrical cardioversion of symptomatic AF or AFL without at least 3 weeks of previous therapeutic anticoagulation be reserved for patients with the following characteristics (Weak Recommendation, Low-Quality Evidence): i. 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); ii. Patients with NVAF and a $CHADS_2$ score < 2 who present after 12 hours but within 48 hours of AF onset.
6	We suggest that, in the absence of a strong contraindication, 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). Thereafter, we recommend that the need for ongoing antithrombotic therapy should be on the basis of the risk of stroke as determined by the CCS Algorithm ("CHADS-65"; Strong Recommendation, Moderate-Quality Evidence). Values and preferences for recommendation 6. This approach places relatively greater emphasis on the benefits of stroke prevention compared with the risks of bleeding with a short course of anticoagulation therapy. Although it might be possible to parse these risks either on the basis of patient characteristics or the duration of acute AF/AFL, the CCS AF Guidelines Committee at this point has chosen to simplify by recommending anticoagulation for 1 month after cardioversion for all such patients in the absence of a strong contraindication.

AF, atrial fibrillation; AFL, atrial flutter; CCS, Canadian Cardiovascular Society; $CHADS_2$, **C**ongestive Heart Failure, **H**ypertension, **A**ge, **D**iabetes, **S**troke/Transient Ischemic Attack; NOAC, novel oral anticoagulant; NVAF, nonvalvular atrial fibrillation.

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forward for clinicians. This article represents the opinions of the authors and is not an official CCS guideline document.

Guideline Changes and Rationale

Although the 2018 update makes 18 recommendations in total, this article has a focus on recommendations 2 and 6 (Table 1, Fig. 1). Recommendation 2 now restricts safe CV to patients with nonvalvular AF who present within 12 hours of onset if no recent stroke or transient ischemic attack, or who present within 12-48 hours if their **C**ongestive Heart Failure, **H**ypertension, **A**ge, **D**iabetes, **S**troke/Transient Ischemic Attack ($CHADS_2$) score is < 2. This updates the previous "48-hour rule" that has been recommended by the CCS since 1996 by restricting safe CV to patients who present very early or who are at low risk of stroke. This change was primarily informed by several European studies, described herein, but was rated according to the GRADE system as a weak recommendation on the basis of low-quality evidence.[3,4] GRADE is described in more detail in the section, *GRADE and Implications of a Weak Recommendation*.

Recommendation 6 suggests that, in the absence of a strong contraindication, all patients who undergo CV of AF/AFL receive at least 4 weeks of therapeutic anticoagulation. Previous CCS guidelines recommended lifelong anticoagulation for patients at higher risk of stroke but did not suggest anticoagulation for those at low risk. The CCS panelists decided to place relatively "greater emphasis on the benefits of stroke prevention compared with the risks of bleeding." Although the panel acknowledged that "it might be possible to parse these risks either on the basis patient characteristics or the duration of acute AF/AFL" the panel chose to simplify the recommendation by suggesting anticoagulation for 1 month after CV for all patients.

Challenges to Emergency Medicine

Acute-onset AF or AFL is a common Emergency Department (ED) presentation in Canada with an estimated 50,000 visits per year.[5] Canadian ED physicians have gradually changed their practice in recent years to aggressive rhythm control in the ED with relatively little involvement of cardiologists. Increasingly, these physicians are using chemical or electrical CV followed by early discharge home.[6,7] In 2018, with funding from the Cardiac Arrhythmia Network, the Canadian Association of Emergency Physicians (CAEP) formally adapted the previous CCS AF guidelines for ED use.[8] The panelists included 3 cardiologists including 1 author of this article (A.S.) but CAEP sought widespread input from the cardiology and emergency medicine communities. The CAEP guidelines encourage CV using drug or shock, early ED discharge with appropriate follow-up, and prescription of oral anticoagulants (OACs) for all patients who are **C**ongestive Heart Failure, **H**ypertension, **A**ge, **D**iabetes, **S**troke (CHADS-65)-positive.

CAEP members have expressed concern about recommendations 2 and 6 and report that they are being informed by their cardiology colleagues that these are now "standard of care" despite the weak recommendation designation. Emergency physicians find recommendation 2 to be challenging in its reliance on $CHADS_2$ to guide decision-making on the timing of CV, which is at odds with recent encouragement to use the CHADS-65 algorithm.[8,9] We note that recommendation 3 further offers the option of transesophageal echocardiography to assure safety of urgent CV. Unfortunately, this procedure is rarely available on a same-day basis in Canadian hospitals. Recommendation 2, however, is otherwise largely similar to the CAEP best practice statement, which considered the recent evidence that associates duration of symptoms with thromboembolic risk. CAEP issued a similar recommendation that only patients currently receiving OACs or at low risk of stroke be offered CV for AF/AFL of > 24 hours' duration. Therefore, recommendation 2 is unlikely to represent a substantial practice change for Canadian emergency physicians.

Recommendation 6, however, represents a substantial practice change for Canadian emergency physicians when caring for patients with AF/AFL and who are CHADS-65-negative. Because of the paucity of evidence that OACs reduce the risk of stroke for these low-risk patients, Canadian emergency physicians are concerned at the prospect of broadly prescribing OACs to young patients. Such patients might participate in activities that might lead to head injuries (eg, contact sports, cycling) and might be at higher risk of

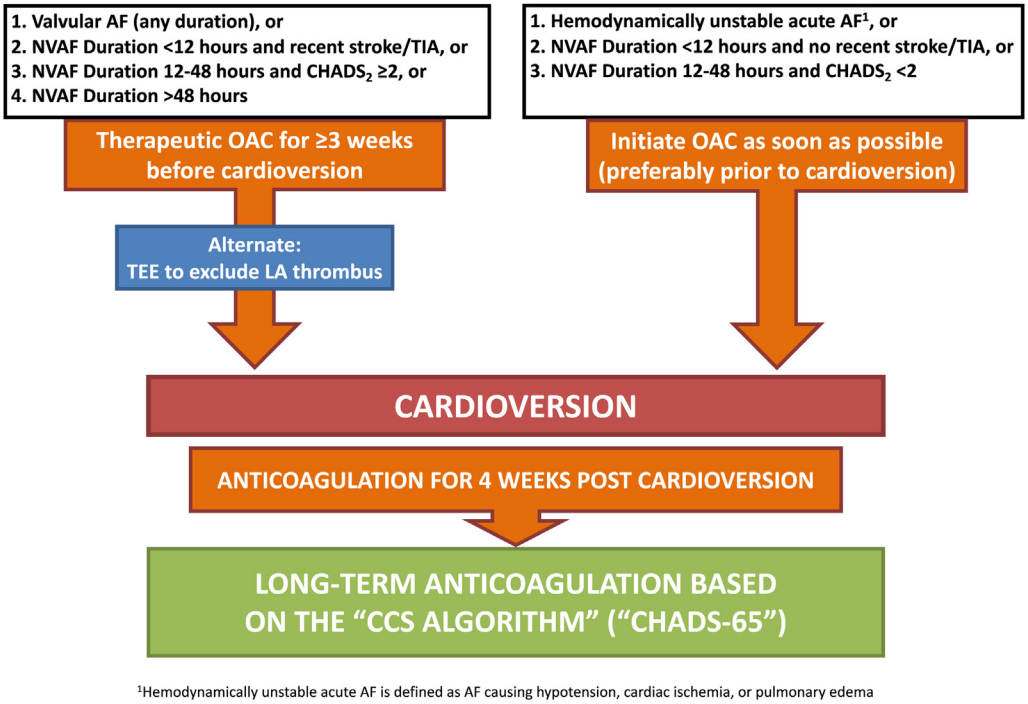

Figure 1. Oral anticoagulation pathway in the context of cardioversion for atrial fibrillation or flutter. AF, atrial fibrillation; CCS, Canadian Cardiovascular Society; CH ADS_2, **C**ongestive Heart Failure, **H**ypertension, **A**ge, **D**iabetes, **S**troke/Transient Ischemic Attack; LA, left atrial; NVAF, nonvalvular atrial fibrillation; OAC, oral anticoagulant; TEE, transesophageal echocardiogram. Reproduced from Andrade et al.[1] with permission from Elsevier.

bleeding than they are of thromboembolic complications. In addition to the bleeding risk in the absence of clear evidence of benefit, prescription of OACs to CHADS-65-negative patients poses other patient-important challenges. Warfarin in naive patients might take considerable time to initiate and stabilize, missing the period of highest risk. Access to novel OACs is not equal across jurisdictions. In some provinces, there are considerable challenges unless costs are borne by the patient, particularly for those younger than age 65 years. Previous studies have shown that it is challenging to initiate OACs in the ED setting, even for patients with an elevated $CHADS_2$ score, who should receive lifelong anticoagulation.[10] Furthermore, it is unclear whether primary care physicians will be comfortable managing these patients appropriately in follow-up. Although described as a weak recommendation, the suggestion to prescribe a minimum of 4 weeks of OAC treatment carries substantial weight and risks an unwarranted change in practice across the board rather than, as the GRADE system encourages, prompting physicians to apply evidence on a patient-specific basis at the bedside.

Summary of Studies That Informed the Changes (See Related Article by Andrade and Mitchell[11])

The historical 48-hour safety threshold for CV, although empirically developed (see review by Andrade and Mitchell[11] in this issue of the *Canadian Journal of Cardiology*), has been adopted widely into clinical practice.[9] Seven observational cohort studies and 3 recent randomized trials (from 2019) that were specifically limited to the patients in question (AF duration $\leq$ 48 hours) conducted in $>$ 4200 patients documented that thromboembolic events are rare (7 of 4200 patients; 0.17%) after CV for acute AF/AFL.[6,12-18] Although the CCS AF Guideline Panel previously closely examined this topic,[9,19] several large retrospective analyses have called the 48-hour safety threshold into question. A series of retrospective analyses of 10,852 CVs in 5441 patients from Finland suggested that CV in patients with 12-48 hours of symptoms was associated with a higher thromboembolic risk (30 of 2777 patients; 1.1%) compared with CV in patients with $<$ 12 hours of symptoms (8 of 2440 patients; 0.33%).[4] There was no such time-dependent effect for patients who were receiving OACs.[20]

Observational studies also suggest that OACs offer an important reduction in stroke risk for patients who undergo CV for acute AF/AFL. A single-centre, retrospective analysis of CV for AF/AFL of $<$ 48 hours' duration, in patients with, without, or with inadequate anticoagulation, showed higher 30-day thromboembolic events in among patients with no or inadequate OAC treatment (6 events after 683 direct current CVs; 0.88%) compared with patients with adequate OAC treatment (2 events after 898 direct current CVs, 0.22%; odds ratio, 4.8; $P = 0.03$), although the number of events is quite small.[21] In addition to a time-dependent effect, the Finnish registry analyses suggested that the benefit of OACs was greatest in patients with a **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) (CHA_2DS_2-VASc) $\geq$ 2, but not statistically demonstrable in those with CHA_2DS_2-VASc 0 or 1.

Retrospective analyses from 2 large registries composed of > 15,000 and 22,000 patients who underwent CV, each showed higher rates of 30-day thromboembolic events without OAC use, even after propensity-matching.[22,23] Event rates with (32 of 11,190 [0.3%] and 35 of 10,722 [0.3%], respectively) and without (52 of 5084 [1.0%] and 104 of 12,152 [0.9%], respectively) OACs were remarkably consistent across all 3 large retrospective analyses. Importantly, in the larger study, there were no events among 4941 patients in the lowest risk subgroup (CHA_2DS_2-VASc 0 or 1) and who were not receiving OACs, a detail not clarified in the other study. Unfortunately, whether time of onset was more or less than 48 hours was not known in these studies.

The most contemporary prospective data on the effect of CV in 6 Canadian EDs documented a single stroke among 1091 patients who underwent CV at < 48 hours without OACs.[6] The mean time to CV was short (7.7 ± 9.6 hours), but more than half had a $CHADS_2$ score ≥ 1, and only 32.1% were taking OACs at the time of CV. Only 3 patients underwent transesophageal echocardiography in the ED and few (4.8%) were prescribed OACs at discharge. By 30 days, only 49.3% of eligible patients were taking OACs. A recent randomized controlled trial, published after the guidelines, compared rhythm outcomes among 437 patients who underwent early or delayed CV. OAC use was not prescribed and only 2 strokes were recorded at 30 days, 1 in each arm.[18] Two other randomized trials, not yet published, followed 480 patients treated in the ED with CV for 30 days and showed no strokes.[24,25] Prospective studies, even when taken together, have insufficient events to determine the effect of OACs on CV, although the rate of stroke in contemporary practice appears to be remarkably low.

The challenge is not unlike others in the study of rare outcomes, except that the clinical effect of stroke is large, making the low event rate clinically relevant. Only retrospective studies, with their concomitant limitations (eg, not specifically limited to patients with AF < 48 hours' duration and started OACs at ED discharge as per guideline recommendations), are sufficiently large to assess the effect of OAC on stroke rates in the ED. Further, a 30-day stroke rate of 1% noted in retrospective data without OACs, if true, is clinically unacceptably high. No prospective comparative study is sufficiently powered or likely to be sufficiently large to measure a 0.7% difference in stroke rate with OACs, as suggested by retrospective data. Nor are there clear data to guide therapeutic decisions for patients at low risk of stroke, for whom there is no apparent benefit of short-term OACs in the previously-mentioned observational studies.

Until these prospectively collected data are available, decision-makers and guideline writers face a dilemma; to make a recommendation on the basis of low-quality retrospective data, as limited as it is, or overlook a signal of potential clinically important harm, reassured by a very small number of prospective events.

GRADE and Implications of a Weak Recommendation

The GRADE system is a formal approach for developing clinical practice guidelines that involves a rigourous approach for grading evidence and a structured approach for translating summarized evidence into recommendations.[2] A strength of this system is that there is separation between the classification of the quality of evidence and the strength of the recommendations that emerge. In GRADE, the quality of evidence can be ranked as high, moderate, low, or very low, depending on study limitations, inconsistency of results, indirectness of evidence, imprecision, or reporting bias. Similarly, GRADE offers 2 levels for the strength of a recommendation—strong and weak. The quality of evidence clearly influences the given strength of a recommendation, and the practical test is whether further research is very unlikely to change confidence in estimates of treatment effect. However, several other factors can influence whether a recommendation should be strong or weak, including equipoise about relative merit of treatment effects vs negative side effects, incorporation of patient values and preferences, and uncertainty about cost-effectiveness. Some guideline panels have used the words, "conditional" or "discretionary" in lieu of "weak" to make more explicit that other factors beyond the strength of evidence should be incorporated into clinical decisions.

To optimally implement weak recommendations into clinical practice, the clinician must balance an imperfect set of supporting evidence—with concomitant uncertainty in treatment effects and treatment hazards for a specific patient—as well as incorporate that patient's individual values and preferences.[26] When done well, this approach is a form of shared decision-making.[27] It is important to recognize that clinical practice guidelines are not a substitute for patient-focused clinical judgement at the bedside, and that it is expected that evidence-based practice will not result in uniformity of practice because uncertainty about risks and benefits or values and preferences are incorporated into individual clinical decisions.[28]

How Should Clinicians Proceed?

Clinical practice guidelines provide us the bridge between best practice, policy, local contexts, and patient choice. The GRADE system has been used in the previous and current AF guidelines because it balances all of these to provide values and preferences, weight of evidence, and practical tips as it pertains to the recommendations. Evaluation of evidence can be challenging but as clinicians, we must weigh the quality of evidence to guide therapeutic decision-making for our acute AF/AFL patients.

From the previous paragraphs, it is clear as to how to proceed with a patient who is positive using the CHADS-65 algorithm: they should all receive oral anticoagulation after CV indefinitely, unless there is an absolute contraindication. Again, it is important to note that among the many observational studies on the topic of CV of acute AF, very few assess outcomes in these particular patients (ie, most study patients did not receive OACs according to their stroke risk on ED discharge). For patients who do not require OACs on the basis of the CHADS-65 algorithm, a weak recommendation means that anticoagulation for 4 weeks ought not be considered either mandatory or the standard of care, but rather an opportunity to apply patient-focused clinical judgement. Consideration of duration of AF, female sex, presence of vascular disease and other comorbidities, as well as patient preference, might push the decision toward oral

anticoagulation for 4 weeks after CV, whereas in the absence of those it might be reasonable to forego OACs. The risk in wide application of oral anticoagulation post CV is bleeding, especially for those engaged in activities prone to head injury. This must be weighed against the risk of a thromboembolic event post CV. Current evidence does not provide clear guidance; hence, it is left to the clinician to exercise best judgement. Fortunately, the risk of thromboembolism after CV and the risk of bleeding associated with a simple 4-week course of OACs are low in a patient who is CHADS-65-negative. These data should inform a patient-specific decision on the relative merits of short-term OAC use for patients with a CHADS-65 score of 0. In the absence of high-quality evidence, the previous discussion provides context to the CCS weak recommendation for the use of OACs for 4 weeks post CV.

Disclosures

The authors have no conflicts of interest to disclose.

References

1. Andrade JG, Verma A, Mitchell LB, et al. 2018 Focused update of the Canadian Cardiovascular Society guidelines for the management of atrial fibrillation. Can J Cardiol 2018;34:1371-92.
2. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924-6.
3. Airaksinen KE, Gronberg T, Nuotio I, et al. Thromboembolic complications after cardioversion of acute atrial fibrillation: the FinCV (Finnish CardioVersion) study. J Am Coll Cardiol 2013;62:1187-92.
4. Nuotio I, Hartikainen JE, Gronberg T, et al. Time to cardioversion for acute atrial fibrillation and thromboembolic complications. JAMA 2014;312:647-9.
5. O'Reilly DJ, Hopkins RB, Healey JS, et al. The burden of atrial fibrillation on the hospital sector in Canada. Can J Cardiol 2013;29:229-35.
6. Stiell IG, Clement CM, Rowe BH, et al. Outcomes for ED patients with recent-onset atrial fibrillation and flutter (RAFF) treated in Canadian hospitals. Ann Emerg Med 2017;69:562-71.
7. Scheuermeyer FX. New frontiers in Canadian atrial fibrillation management. CJEM 2018;20:323-4.
8. Stiell IG, Scheuermeyer FX, Vadeboncoeur A, et al. CAEP acute atrial fibrillation/flutter best practices checklist. Can J Emerg Med 2018;20:334-42.
9. Verma A, Cairns JA, Mitchell LB, et al. 2014 Focused update of the Canadian Cardiovascular Society guidelines for the management of atrial fibrillation. Can J Cardiol 2014;30:1114-30.
10. Scheuermeyer FX, Innes G, Pourvali R, et al. Missed opportunities for appropriate anticoagulation among emergency department patients with uncomplicated atrial fibrillation or flutter. Ann Emerg Med 2013;62:557-65.
11. Andrade JG, Mitchell LB. Periprocedural anticoagulation for cardioversion of acute onset atrial fibrillation and flutter: evidence base for current guidelines. Can J Cardiol 2019;35:1301-10.
12. Weigner MJ, Caulfield TA, Danias PG, et al. Risk for clinical thromboembolism associated with conversion to sinus rhythm in patients with atrial fibrillation lasting less than 48 hours. Ann Intern Med 1997;126:615-20.
13. Michael JA, Stiell IG, Agarwal S, et al. Cardioversion of paroxysmal atrial fibrillation in the emergency department. Ann Emerg Med 1999;33:379-87.
14. Gallagher MM, Hennessy BJ, Edvardsson N, et al. Embolic complications of direct current cardioversion of atrial arrhythmias: association with low intensity of anticoagulation at the time of cardioversion. J Am Coll Cardiol 2002;40:926-33.
15. Burton JH, Vinson DR, Drummond K, et al. Electrical cardioversion of emergency department patients with atrial fibrillation. Ann Emerg Med 2004;44:20-30.
16. Stiell IG, Clement CM, Perry JJ, et al. An aggressive protocol for rapid management and discharge of emergency department patients with recent-onset episodes of atrial fibrillation and flutter. Can J Emerg Med 2010;12:181-91.
17. Scheuermeyer FX, Grafstein E, Stenstrom R, et al. Thirty-day outcomes of emergency department patients undergoing electrical cardioversion for atrial fibrillation or flutter. Acad Emerg Med 2010;17:408-15.
18. Pluymaekers NAHA, Dudink EAMP, Luermans JGLM, et al. Early or delayed cardioversion in recent-onset atrial fibrillation. N Engl J Med 2019;380:1499-508.
19. Stiell IG, Macle L. Canadian Cardiovascular Society atrial fibrillation guidelines 2010: management of recent-onset atrial fibrillation and flutter in the emergency department. Can J Cardiol 2011;27:38-46.
20. Hellman T, Kiviniemi T, Nuotio I, et al. Optimal timing for cardioversion in patients with atrial fibrillation. Clin Cardiol 2018;41:966-71.
21. Garg A, Khunger M, Seicean S, et al. Incidence of thromboembolic complications within 30 days of electrical cardioversion performed within 48 hours of atrial fibrillation onset. JACC Clin Electrophysiol 2016;2:487-94.
22. Hansen ML, Jepsen RM, Olesen JB, et al. Thromboembolic risk in 16 274 atrial fibrillation patients undergoing direct current cardioversion with and without oral anticoagulant therapy. Europace 2015;17:18-23.
23. Sjalander S, Svensson PJ, Friberg L. Atrial fibrillation patients with CHA2DS2-VASc >1 benefit from oral anticoagulation prior to cardioversion. Int J Cardiol 2016;215:360-3.
24. Scheuermeyer FX, Andolfatto G, Christenson J, et al. Electrical vs chemical cardioversion in patients with acute atrial fibrillation: a multicenter parallel group randomized controlled clinical trial. Acad Emerg Med, in press.
25. Stiell IG, Perry JJ, Birnie D, et al. A randomized controlled trial of drug vs electrical cardioversion for recent-onset atrial fibrillation (abstract). Acad Emerg Med 2019;26(suppl 1):S22.
26. Neumann I, Santesso N, Akl EA, et al. A guide for health professionals to interpret and use recommendations in guidelines developed with the GRADE approach. J Clin Epidemiol 2016;72:45-55.
27. Stiggelbout AM, Van der Weijden T, De Wit MP, et al. Shared decision making: really putting patients at the centre of healthcare. BMJ 2012;344:e256.
28. Djulbegovic B, Guyatt GH. Evidence-based practice is not synonymous with delivery of uniform health care. JAMA 2014;312:1293-4.