Flecainide for atrial fibrillation in the Emergency Department: time for a rethink?

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Introduction

Atrial fibrillation (AF) is incredibly common with a worldwide prevalence of approximately 1% in the general population¹ and accounting for up to 3% of all National Health Service (NHS) expenditure as a conservative estimate. AF and atrial flutter probably account for around 10% of all emergency admissions in the United Kingdom (UK)², a figure that continues to increase. Indeed, data worldwide shows that patients with atrial fibrillation are more likely to require longer hospital stays with higher rates of cardiovascular and non-cardiovascular complications³.

NHS England defines atrial fibrillation as an "ambulatory care sensitive condition", that is, a condition where community management can potentially abrogate the need for hospital admission². Although for the majority of patients appropriate rate control^{4,5} and consideration of anticoagulant therapy^{6,7} remain the mainstay of treatment, in selected patients acute cardioversion in the Emergency Department (ED) may be appropriate: facilitating a rapid return to a controlled ventricular rate, an improvement in symptoms and potentially allowing early discharge from the Emergency Department with any necessary follow-up.

Cardioversion - safe when done safely

Cardioversion can be carried out with very low complication rates if performed by an experienced operator and with necessary precautions taken. Potential adverse events can be stratified into acute versus late complications. Proarrhythmia includes generation of malignant ventricular tachyarrhythmia or post-cardioversion bradycardia. Medium- to long-term complications revolve around the thrombo-embolic risk of cardioversion, which has been shown to be low when appropriate pre- and post-procedural anticoagulation is utilised (or deemed unnecessary in low-risk patients)⁸. In the ED setting, there is a suggestion that electrical cardioversion is probably slightly safer⁹ and more effective¹⁰ than chemical cardioversion for recent onset AF, although both options overall provide safe options to facilitate discharge¹¹. Indeed, there is evidence to show that up to 70% of patients presenting with new-onset AF will spontaneously cardiovert within 24 hours if the episodes are of <48 hours duration^{12–14}, with longer episodes still demonstrating modest rates of self-termination¹⁵. An ongoing randomised controlled trial aims to compare acute cardioversion versus a "wait and see" approach in the ED¹⁶. Patients demonstrating haemodynamic instability should be electrically cardioverted on an emergent basis¹⁷.

ED cardioversion – an admission avoided

In the ED, staffing and workload pressures may pose a challenge when considering the availability of procedural sedation. Coupled with cost-effectiveness issues, chemical cardioversion may be seen as the preferred pragmatic approach. Indeed in the United States, cardioversions represent the biggest reason for admission of AF patients¹⁸, with a significant cost burden. If this can be undertaken in the ED to facilitate discharge then this represents an additional benefit. In the United Kingdom, the mainstay of chemical cardioversion therapy remains amiodarone and flecainide. Amiodarone demonstrates variable efficacy in acute AF cardioversion with limited success in the short term or at modest doses^{19–23}.

Flecainide – a potent antiarrhythmic with important considerations

Flecainide was first made commercially available within Europe in 1982, marketed under the trade name 'Tambocor'. It is a Vaughn-Williams Class 1C anti-arrhythmic drug which acts on sodium channels, prolonging their diastolic recovery time and decreasing the maximum upstroke velocity of the fast inward sodium current. It reduces the amplitude of cardiac potentials within the atrial, ventricular and His-Purkinje tissues, slowing conduction and prolonging the action potential duration in atrial and ventricular muscle but shortening it in the latter. At high heart rates, due to its affinity to open-state sodium channels and shortened diastolic time, its anti-arrhythmic effects are enhanced. Its oral bioavailability is ~90% with rapid onset of peak levels within 2-3 hours²⁴. The British National Formulary lists the following indications for Flecainide: "AV-nodal reciprocating tachycardia, arrhythmias associated with accessory pathways, disabling symptoms of paroxysmal atrial fibrillation in patients without left ventricular dysfunction" as well as ventricular tachycardia or disabling premature ventricular contractions²⁵.

Indeed, following the increased incidence of premature death seen in use with patients with impaired left ventricular function in the Cardiac Arrhythmia Suppression Trial (CAST²⁶), ischaemic or structural heart disease have remained contra-indications. A further relative contra-indication pertains to the risk of 1:1 AV conduction in potential atrial flutter²⁷, especially in young patients using a "pill in the pocket" approach. Therefore a beta-blocker or calcium channel blocker is usually co-prescribed to suppress conduction across the AV node. Finally, Flecainide can cause fatal ventricular arrhythmias in patients with Brugada syndrome and can even unmask a previously unknown diagnosis of the disease²⁸.

Flecainide in the ED – an appropriate environment?

Multiple studies have established the safety of Flecainide in the treatment of AF in the acute as well as outpatient setting^{29–34}. However, these study settings all stringently excluded patients with appropriate contra-indications at enrolment as well as during monitoring. With all the conflicting pressures on time and staffing levels in the ED, as well as varying levels of confidence and competence in managing cardiovascular emergencies, is it safe for Emergency Department clinicians to initiate Flecainide therapy for acute AF management? With difficulties in some NHS Trusts with accessing old

medical notes and/or imaging, it may be difficult to ascertain whether there is pre-existing cardiac disease as a contra-indication. Access to urgent cardiological advice or echocardiography, especially out-of-hours, may be limited. There may be diagnostic uncertainty or concerns regarding ECG interpretation in the patient with narrow complex tachycardia. Finally, in a young patient presenting with new-onset atrial fibrillation, there may be an underlying structural cause such as an undiagnosed cardiomyopathy or arrhythmic disorder. Indeed, a recent audit of ED AF management in a local hospital showed a guarter of patients were not appropriately assessed for anticoagulation at time of cardioversion. Given the variability of ED basic management, perhaps we should focus on simplicity to ensure a high quality of the basic care of AF patients in the ED; appropriate anticoagulation, rate control and if necessary, safe electrical cardioversion and appropriate specialist referral and/or follow up. Interestingly, analyses support simple rate control measures as highly cost-effective^{35,36}. With a greater emphasis on rate control and anticoagulation in recent guidelines¹⁷, perhaps these should receive greater consideration within acute or emergency settings.

Conclusion

We live in the era of specialised medicine, where the field of cardiac rhythm management is complex and constantly evolving. It may be that our stretched and pressurised ED and acute medical colleagues would benefit from a focus on simplicity on acute AF management at the front door. Where feasible, early specialist involvement may be most appropriate for more complex rhythm control strategies and discussions regarding ongoing medical or invasive approaches. This may obviate the need for admission and prevent inappropriate or ineffective therapy. Ambulatory clinics with specialist arrhythmia input may be one way forward in coping with rising demand in today's health climate.

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References

- 1. Go AS, Hylek EM, Phillips K a., et al. Prevalence of Diagnosed Atrial Fibrillation in Adults. Jama 2001;285(18):2370.
- 2. Emergency admissions for Ambulatory Care Sensitive Conditions characteristics and trends at national level. 2014;
- 3. Christiansen CB, Olesen JB, Gislason G, Lock-Hansen M, Torp-Pedersen C. Cardiovascular and non-cardiovascular hospital admissions associated with atrial fibrillation: a Danish nationwide, retrospective cohort study. BMJ Open 2013;3(1):e001800.
- 4. Olshansky B, Rosenfeld LE, Warner AL, et al. The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study: approaches to control rate in atrial fibrillation. J Am Coll Cardiol 2004;43(7):1201–8.
- 5. Van Gelder IC, Groenveld HF, Crijns HJGM, et al. Lenient versus Strict Rate Control in Patients with Atrial Fibrillation. N Engl J Med 2010;362(15):1363–73.
- 6. Lip GYH, Lim HS. Atrial fibrillation and stroke prevention. Lancet Neurol 2007;6(11):981–93.
- 7. Freedman B, Potpara TS, Lip GYH. Stroke prevention in atrial fibrillation. Lancet 2016;388(10046):806–17.

- 8. Airaksinen KEJ, Grönberg T, Nuotio I, et al. Thromboembolic Complications After Cardioversion of Acute Atrial Fibrillation: The FinCV (Finnish CardioVersion) Study. J Am Coll Cardiol 2013;62(13):1187–92.
- de Paola AA V, Figueiredo E, Sesso R, Veloso HH, Nascimento LOT, SOCES Investigators. Effectiveness and costs of chemical versus electrical cardioversion of atrial fibrillation. Int J Cardiol 2003;88(2–3):157–66.
- 10. Michael JA, Stiell IG, Agarwal S, Mandavia DP. Cardioversion of paroxysmal atrial fibrillation in the emergency department. Ann Emerg Med 1999;33(4):379–87.
- 11. Stiell IG, Clement CM, Perry JJ, et al. Association of the Ottawa Aggressive Protocol with rapid discharge of emergency department patients with recent-onset atrial fibrillation or flutter. CJEM 2010;12(3):181–91.
- 12. Dell'Orfano JT, Patel H, Wolbrette DL, Luck JC, Naccarelli G V. Acute treatment of atrial fibrillation: spontaneous conversion rates and cost of care. Am J Cardiol 1999;83(5):788–90, A10.
- 13. Doyle B, Reeves M. "Wait and see" approach to the emergency department cardioversion of acute atrial fibrillation. Emerg Med Int 2011;2011:545023.
- 14. Geleris P, Stavrati A, Afthonidis D, Kirpizidis H, Boudoulas H. Spontaneous conversion to sinus rhythm of recent (within 24 hours) atrial fibrillation. J Cardiol 2001;37(2):103–7.
- 15. Tejan-Sie SA, Murray RD, Black IW, et al. Spontaneous conversion of patients with atrial fibrillation scheduled for electrical cardioversion. J Am Coll Cardiol 2003;42(9):1638–43.
- 16. Dudink E, Essers B, Holvoet W, et al. Acute cardioversion vs a wait-and-see approach for recent-onset symptomatic atrial fibrillation in the emergency department: Rationale and design of the randomized ACWAS trial. Am Heart J 2017;183:49–53.
- 17. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Europace 2016;18(11).
- 18. Le Heuzey J-Y, Paziaud O, Piot O, et al. Cost of care distribution in atrial fibrillation patients: the COCAF study. Am Heart J 2004;147(1):121–6.
- 19. Khan IA, Mehta NJ, Gowda RM. Amiodarone for pharmacological cardioversion of recent-onset atrial fibrillation. Int J Cardiol 2003;89(2):239–48.
- 20. Letelier LM, Udol K, Ena J, et al. Effectiveness of Amiodarone for Conversion of Atrial Fibrillation to Sinus Rhythm. Arch Intern Med 2003;163(7):777.
- 21. Nadarasa K, Williams MJA. Single High Oral Dose Amiodarone for Cardioversion of Recent Onset Atrial Fibrillation. Hear Lung Circ 2012;21(8):444–8.
- 22. Balla I, Petrela E, Kondili A. Pharmacological conversion of recent atrial fibrillation: a randomized, placebo-controlled study of three antiarrhythmic drugs. Anadolu Kardiyol Dergisi/The Anatol J Cardiol 2011;
- 23. Chevalier P, Durand-Dubief A, Burri H, Cucherat M, Kirkorian G, Touboul P. Amiodarone versus placebo and class ic drugs for cardioversion of recent-onset atrial fibrillation: a meta-analysis. J Am Coll Cardiol 2003;41(2):255–62.
- 24. Tamargo J, Capucci A, Mabo P. Safety of Flecainide. Drug Saf 2012;35(4):273-89.
- 25. FLECAINIDE ACETATE : British National Formulary [Internet]. [cited 2017 Jan 24];Available from: https://www.evidence.nhs.uk/formulary/bnf/current/2-cardiovascular-system/23-anti-arrhythmic-drugs/232-drugs-for-arrhythmias/supraventricular-and-ventricular-arrhythmias/flecainide-acetate
- Echt DS, Liebson PR, Mitchell LB, et al. Mortality and Morbidity in Patients Receiving Encainide, Flecainide, or Placebo. N Engl J Med 1991;324(12):781–8.
- 27. Boriani G, Diemberger I, Biffi M, Martignani C, Branzi A. Pharmacological Cardioversion of Atrial Fibrillation. Drugs 2004;64(24):2741–62.
- 28. Gasparini M, Priori SG, Mantica M, et al. Flecainide test in Brugada syndrome: a reproducible but risky tool. Pacing Clin Electrophysiol 2003;26(1 Pt 2):338–41.
- 29. Cosio FG, Aliot E, Botto GL, et al. Delayed rhythm control of atrial fibrillation may be a cause of failure to prevent recurrences: reasons for change to active antiarrhythmic treatment at the time of the first detected episode. Europace 2008;10(1):21–7.
- 30. Wehling M. Meta-analysis of Flecainide Safety in Patients with Supraventricular Arrhythmias. Arzneimittelforschung 2011;52(7):507–14.
- 31. Aliot E, Capucci A, Crijns HJ, Goette A, Tamargo J. Twenty-five years in the making: flecainide is safe and effective for the management of atrial fibrillation. Europace 2011;13(2):161–73.

- Alboni P, Botto GL, Baldi N, et al. Outpatient Treatment of Recent-Onset Atrial Fibrillation with the "Pill-in-the-Pocket" Approach. N Engl J Med 2004;351(23):2384– 91.
- 33. Khan IA. Oral loading single dose flecainide for pharmacological cardioversion of recent-onset atrial fibrillation. Int J Cardiol 2003;87(2–3):121–8.
- 34. McNamara RL, Tamariz LJ, Segal JB, Bass EB. Management of atrial fibrillation: review of the evidence for the role of pharmacologic therapy, electrical cardioversion, and echocardiography. Ann Intern Med 2003;139(12):1018–33.
- 35. HAGENS V, VERMEULEN K, TENVERGERT E, et al. Rate control is more costeffective than rhythm control for patients with persistent atrial fibrillation ? results from the RAte Control versus Electrical cardioversion (RACE) study. Eur Heart J 2004;25(17):1542–9.
- 36. Marshall DA, Levy AR, Vidaillet H, et al. Cost-effectiveness of rhythm versus rate control in atrial fibrillation. Ann Intern Med 2004;141(9):653–61.