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Acute rate control in atrial fibrillation: an urgent need for the clinician

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Rate and rhythm control are still considered equivalent strategies for symptom control using the Atrial Fibrillation Better Care algorithm recommended by the recent atrial fibrillation guideline. In acute situations or critically ill patients, a personalized approach should be used for rapid rhythm or rate control. Even though electrical cardioversion is generally indicated in haemodynamically unstable patients or for rapid effective rhythm control in critically ill patients, this is not always possible due to the high percentage of failure or relapses in such patients. Rate control remains the background therapy for all these patients, and often rapid rate control is mandatory. Short and rapid-onset-acting beta-blockers are the most suitable drugs for acute rate control. Esmolol was the classical example; however, landiolol a newer very selective beta-blocker, recently included in the European atrial fibrillation guideline, has a more favourable pharmacokinetic and pharmacodynamic profile with less haemodynamic interference and is better appropriate for critically ill patients.

Rate and rhythm strategy in acute situations

Atrial fibrillation (AF) represents the common electrical phenotype for complex and heterogenous clinical situations and risk factors. The complexity of the clinical manifestation, background pathology and management in AF patients resulted recently in the proposal of a holistic and integrated however simplified approach—the 'Atrial Fibrillation Better Care' (ABC) algorithm.[1] The ABC pathway proved to streamline the personalized management in AF and is associated with a lower risk of major outcomes and health-related costs in real-world observational studies.[2–5] The three pillars of the ABC pathway represent anticoagulation and avoiding stroke (A), better symptom management (B) and cardiovascular risk factors and comorbidities optimization (C), respectively. For better symptom management, the rhythm and rate strategy are considered equivalent, and they point exclusively to the quality of life and the autonomy of AF patients and not to increased life expectancy. However, recent studies[6,7] emphasized the beneficial role of early rhythm control on cardiovascular outcomes including stroke and heart failure. The magnitude of this effect and the impact on healthcare resources and hospitalizations were not yet established with clarity.[8,9] Whilst the ABC pathway represents the practical axis for chronic management of AF, the acute cases with AF impose a different and sometimes difficult approach. These cases include patients with haemodynamic instability due to arrhythmia but also acute care patients (such as patients in intensive care units (ICUs), severely ill patients or in the postoperative period) with incidental AF.

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Strengths and weaknesses of electrical cardioversion

There is a consensus in recommending emergent electrical cardioversion in patients with haemodynamic instability due to or aggravated by AF. Electrical cardioversion (ECV) is more efficient and safer compared with any protocol of pharmacologic cardioversion. The traditional use of amiodarone for cardioversion in unstable patients is not supported by the low conversion rate, delayed conversion, extracardiac effects, multiple drug-to-drug interactions and lower efficacy in hyperadrenergic critical patients.[10,11] Vernakalant is more efficient compared with amiodarone even in patients with mild heart failure; however, it is not recommended in haemodynamically unstable patients.[1] Electric cardioversion terminates AF in over 90% of cases, whilst pharmacological cardioversion has a success rate of 50-70% in new-onset or paroxysmal AF.[12]

Elective ECV implies sedation with midazolam and/or propofol as well as blood pressure and oximetry monitoring.[13] Although this is a safe procedure, atropine/isoproterenol or temporary transcutaneous pacing should be available in case of complications such as bradycardia or asystole. Some evidence supports the superiority of anteroposterior electrode positioning,[14,15] whilst others do not find the positioning of electrical pads of major importance for the success of cardioversion.[16] Several protocols using escalating energy or fixed high energy for conversion were proposed.[17,18] ECV is also safer than pharmacological cardioversion in pre-excited AF. In this case, atrioventricular node-modulating drugs and class Ia and Ic antiarrhythmic drug therapies (AADs) should be avoided. Amiodarone may also be unsafe in this scenario.[19-21] Nevertheless, in the absence of a specific reason for choosing one of the two methods of cardioversion (electric vs. pharmacological), the choice between the two should be shared between the physician and the patient's preferences.

The ideal of rapid conversion to sinus rhythm (SR) in acute situations and critically ill patients has several limitations. First, the success rate of ECV in acute non-critically or critically patients hospitalized in ICU is lower than presumed,[22,23] often below 30%. There are few adverse reactions linked to ECV however, renal dysfunction complicating ECV was communicated in up to 17% of patients and this could have a negative outcome impact in severely ill patients.[24,25] Second, despite the immediate success, there is a high rate of immediate relapse AF (IRAF). Not only the IRAF rate is high but also maintaining SR in such patients is problematic because of safety and efficacy concerns linked to the AAD. Despite clear guideline indications for periprocedural anticoagulation in patients suffering ECV, it is not always easy to apply it to the acute care of ICU patients. Moreover, the incidence of thromboembolism is higher in critically ill patients and patients with advanced heart disease. AF is very prevalent in cancer surgical or non-surgical patients; it ranges from up to one-third of lung cancers and 4.4% of colorectal cancers to 9.2% of oesophageal cancers and 10.3% of thyroid cancers undergoing surgery.[26] Cancer interferes with AF substrate in many ways including direct tumoural effect, the implication of cancer therapy, paraneoplastic effects, inflammation, autonomic nervous system imbalance, cancer-related comorbidities or surgery. The incidence of uncontrolled AF in cancer patients is accompanied by increased mortality, hospital admissions and length of stay. The perioperative period of cardiac or non-cardiac surgical patients is characterized by increasing AF risk, especially in patients with cardiac substrate modification, however under the threshold for AF before surgery. Surgery may cause electrical (decrease in conduction time, a decrease of action potential duration and induction of triggered activity through calcium handling alterations) or substrate remodeling (connexin alterations, fibrosis).[27] Some transient factors increase the AF susceptibility only in the immediate postoperative period. Not only the ECV has a lower success rate in acutely ill patients but a spontaneous restoration of SR is achieved in 78–83% of recent onset AF[10,28] during 48 h. In many acutely ill patients (sepsis, trauma, surgery…), the arrhythmia resolve in a short time spontaneously or after the underlying cause is properly treated. Therefore, a 'wait and see' attitude is considered non-inferior compared with early ECV. Irrespective of the decision for rhythm strategy or the possibility to convert to and maintain SR, the rate-control strategy should be generally applied to all patients.

Acute heart rate control

A high rate is an independent strong predictor for mortality[29] adding to the deleterious effects determined by the irregular rhythm and loss of atrial contribution to the cardiac output in patients with AF. Moreover, the negative effect of high heart rate (HR) is amplified in acutely ill patients with blunted adaptation and flattened Bowditch effect. In such patients, HR strategy is the first recommended[11] and often the only possible. Several classes of drugs are effective in decreasing HR: beta-blockers, non-dihydropyridine calcium blockers, amiodarone or digoxin.

Strengths and weaknesses of different drugs for acute heart rate control

Digoxin has the important limits of being ineffective when the sympathetic tone is increased (as in acute illness) and of increased mortality, especially in patients with severe cardiac substrate.[30,31] Amiodarone is too much used as a rate controller in acutely ill patients and ICU settings despite important extracardiac adverse effects (especially thyroid and hepatic interferences), many drug-to-drug interactions, delayed effect and the risk of hypotension during intravenous administration. The recent European AF guideline recommends beta-blockers, verapamil and diltiazem for rate control in patients with the left ventricular ejection fraction (EF) above 40%, beta-blockers and digoxin when EF is below 40% and amiodarone for patients with severely depressed EF.[1] However, it should be emphasized that diltiazem is safe and effective in patients with moderate

depressed EF.[32] Moreover, a recent systematic review and meta-analysis in patients with paroxysmal AF[33] comparing diltiazem with metoprolol for rate control has shown a superior efficacy of the first one at 5, 10 and 15 min. Metoprolol remains a good therapeutic alternative, especially in a situation with an increased sympathetic tone; however, the efficacy is limited to critically ill patients by the relatively long time to the maximum of action (20 min), weak β1 selectivity (β1/β2:2.3), dose adjustment requirements in renal failure, limited use in patients with respiratory pathology and a long elimination half-time (3–4 h), making difficult the reversal of an excessive bradycardic effect. What is needed often in critically ill patients with incidental high rate AF is a potent, rapid and short-acting agent with minimal negative haemodynamic impact. Traditionally, esmolol was considered the prototype because of the good selectivity (β1/β2:33), short half-time (9 min) and convenient duration of action (10–20 min). However, esmolol has important negative inotropic actions, because it is racemic of R- and S-enantiomers; the R-enantiomer is responsible for the negative inotropic effect and lowering of the blood pressure, whilst S-enantiomer is a pure rate lowering.[34] Esmolol efficacy is also blunted by tolerance and rebound phenomenon because of the up-regulation of the blocked receptor (chaperoning effect).[35] Landiolol is a relatively new rapid-acting beta-blocker surpassing some of the limitations of esmolol. It is a very selective beta-blocker (β1/β2:255) with a limited negative effect on inotropy or blood pressure being a pure S – enantiomer.[36] Because of the high β1 selectivity, the metabolization to non-pharmacologic active metabolites and inactivation in circulation by plasma esterases, the drug seems very adapted for critically ill patients with comorbidities. Landiolol has a very short plasma half-time (4 min) and a small volume of distribution[37] which implies a small quantity to achieve the desired plasma concentration and weak tissue distribution with less potential toxicity. Landiolol has a very rapid onset of action (up to 1 min) and reaches the steady state in 15 minutes when administered in continuous intravenous (iv) infusion and less than 5 min when a loading bolus is administred.[37] The short duration of action (below 15 min) increases the safety and manageability of this drug. It proved to be preferable to amiodarone in patients with postoperative paroxysmal AF.[38] Because of the pharmacokinetic properties (noticed previously), landiolol is more effective in decreasing HR as compared with esmolol at low dosages.[35,39] Different from esmolol, landiolol has minimal dose-dependent electrophysiologic actions on sodium and calcium currents and action potential duration[40] which confers a favourable inotropic profile. Indeed, a recent prospective observational study emphasized the low rate of adverse effects in patients with heart failure and AF or flutter.[41] Lower dosages infusions (starting with 1 μg/kg/min to 10 μg/kg/min) are well tolerated in New York Heart Association (NYHA) III–IV heart failure patients with EF below 40%. Different from esmolol, tolerance or rebound phenomenon is not expected with landiolol because the last is lacking of the receptor up-regulation effect (chaperoning activity).[42] There are few and predictable drug–drug interactions for landiolol in acute or peri-operative settings: dihydropyridine calcium channel blockers (CCBs), inhalation anaesthetics or barbiturates increase the risk of hypotension and non-dihydropyridine CCB or antiarrhythmics may worsen cardiac conduction abnormalities. Suxamethonium increases the landiolol bradycardia, and landiolol prolongs suxamethonium-induced neuromuscular blockade.[43]

Clinical scenarios

Prevention and treatment of POAF after cardiovascular and non-cardiac surgery

Prophylaxis

Postoperative atrial fibrillation (POAF) is a frequent complication of cardiac surgery, with an incidence as high as 30–50%.[44–47] This is of particular interest, as patients who develop POAF have a higher risk of complications, higher costs for hospitalization and increased risk of mortality.[48]

The issue of landiolol for the prevention and treatment of POAF after cardiac surgery has been disputed in observational studies[49–52] as well as randomized controlled trials (RCTs).[53–56]

Landiolol's effect on POAF prevention has been addressed in several meta-analyses[57–60] comprising the aforementioned studies. Results are consistent, proving that landiolol reduces the incidence of POAF without increasing the risk of major complications.

For off-pump coronary artery bypass graf (CABG) surgery, landiolol significantly reduced the incidence of POAF.[61,62] The prophylactic effect applies also in the context of CABG with cardiopulmonary bypass,[55] even in patients with left ventricular (LV) dysfunction.[63]

Despite the beneficial effect of POAF prophylaxis after cardiac surgery, complication rate and mortality appear not to be influenced by landiolol.[60]

Of note, intraoperative infusion of landiolol appears not to be enough for the prevention of POAF. The optimal strategy seems to include oral β-blockers preoperatively and landiolol initiated intraoperatively or immediately after surgery.[64,65]

What is more, the bioavailability of oral beta-blockers appears to be decreased following cardiac surgery,[66] and so intravenous administration of landiolol seems to add value to its properties.

The contribution of landiolol in decreasing the incidence of POAF is probably a sum of the adrenergic inhibition and regulation of the inflammatory response.

Management of POAF

Besides prophylaxis, landiolol is also useful for the treatment of POAF after cardiac surgery.[54]

Comparative data from RCTs are only available regarding diltiazem.[54] Landiolol has a higher response for HR control and faster return to SR than diltiazem, but the conversion rate was not improved.

Prevention of POAF after non-cardiac surgery

POAF is also common after non-cardiac surgery, with an incidence ranging from 10% to 20% or even higher.[67] It can complicate a patient's clinical course, prolong hospitalization and increase mortality.[68,69]

RCTs for preventing POAF with landiolol after non-cardiac surgery are available. Some of these RCTs demonstrate a reduction in the incidence of POAF, but one study showed non-superiority to standard care.[70-73] One RCT showed an additional benefit of landiolol in lowering the rate of non-haemodynamic complication.[70]

Acute heart failure and left ventricular dysfunction

The prevalence of concomitant AF in HF patients is high and implies worse prognosis.[74]

β-blockers are to be used cautiously in the presence of LV dysfunction because of their negative inotropic effect that may trigger HF decompensation. For this reason, alternative medication is sought, often with different, but not necessarily less important side effects (e.g. amiodarone, digoxin).

Several studies have shown a beneficial effect of using landiolol in the setting of acute HF or LV dysfunction. It lowers HR with good tolerability and without determining an important BP decrease.[75-78] Compared to digoxin, patients with AF/AFL and low EF treated with landiolol had a better rate of achieving target HR and a neutral safety profile.[78] However, there are no RCTs comparing landiolol with amiodarone for HR control in the presence of cardiac dysfunction.

In decompensated HF patients with low EF, landiolol safely and effectively aids control of rapid AF, avoiding short-term major adverse events.[79]

Case reports show a safe profile for landiolol in AF and decompensated HF in the setting of severe thyroid dysfunction, with feasible and effective switching to bisoprolol.[80]

In tachycardic HF patients in the absence of AF/AFL, when an increased sympathetic drive is the trigger for increased HR, landiolol is still beneficial for optimal

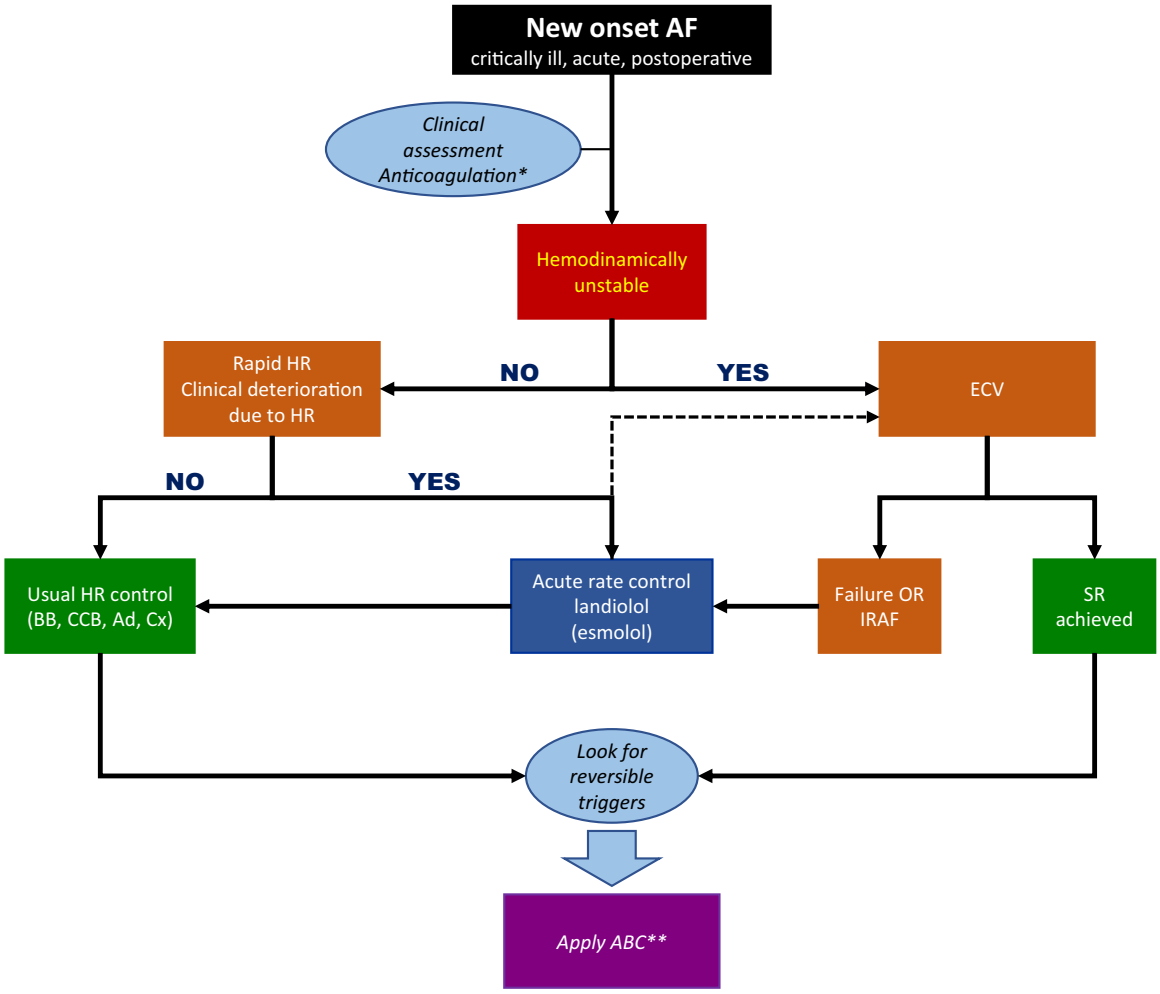

Figure 1 Proposed algorithm for rate and rhythm control in acute, critically ill, or postoperative patients. If acute rate control is inefficient, electrical cardioversion should be attempted (dotted line). Ad: amiodarone; BB: beta-blockers; Dx: Digoxin/Digitoxin. *Anticoagulation following guideline recommendation. **ABC: Atrial Fibrillation Better Care algorithm (see text).

control, without dangerously decreasing blood pressure.[75] What is more, rehospitalization for HF was also lower.

These results highlight the potential benefit of landiolol as first-line therapy in HF patients who need HR control, with emphasis on close monitoring of the haemodynamic status. Landiolol could also be used as a bridge to the reintroduction of oral β-blocker after haemodynamic stabilization of hospitalized HF patients.

Intensive care unit

Needless to say that AF is common in ICU patients. Management includes correction of hypovolemia and electrolyte imbalances, followed by judicious medical treatment.

Catecholamine therapy-induced AF is also common, and its management is controversial and unclear. However, efforts should be made to escape the vicious circle of inotropes. This could potentially be accomplished using landiolol, which optimizes HR without decreasing the favourable haemodynamic effects of inotropes.

In patients who require catecholamine support following cardiovascular surgery, with consequent tachycardia, low-dose landiolol therapy may safely decrease HR and improve haemodynamic parameters, as suggested by a small retrospective study.[81] The same study determined that landiolol could also improve stroke volume index (through improved ventricular-arterial coupling). This is true even for patients who require high doses of catecholamines when the negative chronotropic action of landiolol did not diminish with co-administration of dobutamine.[81]

In tachycardic patients with acute decompensated HF not receiving inotropes, low-dose landiolol (1.5 μg/kg/min) associated with milrinone therapy increased haemodynamic parameters (pulmonary capillary wedge pressure (PCWP), stroke volume index (SVI)), the effect that disappeared at higher doses of landiolol ($\geq$3 μg/kg/min).[82] Landiolol added to milrinone was superior to milrinone monotherapy for improvement of cardiac function in refractory rapid AF and decompensated HF.

Case reports also suggest a potential benefit from associating landiolol with levosimendan in patients with decompensated HF, tachycardia and impaired cardiac output.[83]

As so, landiolol may be considered an adjunct therapy in an emergency setting when milrinone, levosimendan or even standard inotropes seem not to provide the desired effect.

Landiolol is also useful to stabilize patients as the bridge to cardiac resynchronization therapy (CRT), catheter ablation, cardiac surgery or implantation of LV assist device.[84,85]

Sepsis-induced arrhythmias

Septic patients who develop AF have a particular benefit from HR lowering therapies. Some studies support landiolol as superior to standard rate-controlling therapy (calcium blockers, amiodarone, disopyramide), with no significant complication related to hypotension or bradycardia.[86,87]

There are several case reports of successful management of high rate AF in septic patients, using landiolol[86,88] and an ongoing RCT on this subject.[89] The potential use of landiolol in this scenario is of particular interest, as mortality and complication rate in sepsis are still high.

In *Figure 1* is shown a proposed algorithm for rate and rhythm control in acute, critically ill or postoperative patients developing a new episode of AF.

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Data availability

Not applicable.

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