REVIEW

Pharmacological Treatment of Tachyarrhythmias in Acute Myocardial Infarction - a Review

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ABSTRACT

Acute myocardial infarction (AMI) causes severe metabolic and electrophysiological changes that induce silent or symptomatic life-threatening arrhythmias. Ventricular arrhythmias and atrial fibrillation are common during the early phase of AMI and are also important prognostic factors. Rapid identification and treatment of these arrhythmias can be life-saving, since in-hospital mortality rises dramatically in patients who develop arrhythmias with a fast ventricular rate following an AMI. Along with myocardial revascularization, adequate pharmacological therapy of hemodynamically relevant arrhythmias is generally useful. Since there are no controlled randomized trials comparing different antiarrhythmic drugs (AADs) in AMI, optimal decision making is based on medical societies guidelines recommendations and clinical judgement.

Keywords: atrial fibrillation, acute myocardial infarction, ventricular arrhythmias, antiarrhythmic drugs.

REZUMAT

Infarctul miocardic acut (IMA) cauzează modificări metabolice și electrofiziologice care pot induce aritmii clinic silențioase sau amenințătoare de viață. Aritmiile ventriculare și fibrilația atrială sunt frecvente în timpul fazei acute a IMA și reprezintă factori importanți de prognostic. Identificarea rapidă și tratamentul prompt al acestor aritmii poate fi salvator de viață. Mortalitatea intraspitalicească crește dramatic la pacienții care dezvoltă aritmii cu frecvență ventriculară înaltă după IMA. Împreună cu revascularizarea miocardică, tratamentul farmacologic adecvat al aritmiilor cu impact hemodinamic este în general util. Deoarece nu există trialuri randomizate care să compare diverse medicamente antiaritmice în IMA, decizia terapeutică optimă se bazează pe recomandările ghidurilor societăților de cardiologie și pe judecata clinică.

Cuvinte cheie: fibrilație atrială, infarct miocardic acut, aritmii ventriculare, medicamente antiaritmice.

INTRODUCTION

Both atrial and ventricular arrhythmias may occur in the setting of acute myocardial infarction (AMI). Therapy for AMI and arrhythmia management are now based increasingly on invasive approaches, with early reperfusion therapy as paramount action. In addition to myocardial revascularization, a 'wait and see' strategy for arrhythmias with no or moderate haemodynamic relevance seems reasonable[1]. However, when arrhythmias result in hemodynamic instability, careful use of antiarrhythmic drugs is generally recommended and alternative treatment options such as electrical cardioversion or catheter ablation should be considered. Frequently, sustained ventricular tachyarrhythmias (VAs) may lead to hemodynamic collapse and warrant immediate treatment[2]. While the urgent treatment for VAs with haemodynamic instability remains direct current cardioversion (DCC), recurrent sustained VAs requires drug therapy. Atrial fibrillation (AF) may also require urgent treatment when it presents with a fast ventricular rate which results in hemodynamic deterioration[2].The management of other arrhythmias is also based mainly on symptoms and their hemodynamic impact.

SUPRAVENTRICULAR ARRHYTHMIAS

AF is the most frequent supraventricular arrhythmia occurring in up to 21% of the patients presenting with

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ST elevation acute myocardial infarction (STEMI)[1,3]. AF occurring in STEMI patients is associated with a worse short- and long-term prognosis[1]. Significant multivariable predictors of AF include three-vessel coronary artery disease and initial thrombolysis, advanced age, higher peak creatine kinase levels, worse Killip class and increased heart rate[4]. Lower socioeconomic status seems to predict prevalence of AF in some populations in a similar fashion to other cardiovascular diseases[5,6].

In the acute setting, AF results in reduced cardiovascular performance through a variety of mechanisms. These include loss of atrioventricular synchrony and atrial systole, reduced ejection time due to high ventricular rates, and rhythm irregularity[7,8]. Patients with AMI and AF have a more adverse clinical course of their disease due to older age, increased number of comorbidities, worse Killip class, severe LV dysfunction, more extensive coronary artery disease and poorer perfusion after thrombolysis or primary PCI9. Moreover, the presence of AF adds a burden on the therapeutical decisions considering the need for anticoagulation.

Pathophysiology

The most common etiology of AF in the setting of AMI appears to be atrial stretching due to heart failure with elevation in left atrial pressures[10]. In patients with AMI complicated with severely depressed left ventricle systolic function, AF is precipitated or exacerbated by on-going atrial ischemia or infarction, abnormalities of autonomic regulation, increased sympathetic tone[11], pericardial inflammation and by iatrogenic factors such as positive inotropic agents. One must also consider the reverse relationship between AF and AMI: AF with rapid ventricular response could also lead to a Type II MI. In this case, invasive therapy may not be warranted[12].

Acute pharmacological management of AF

Typically, recent onset AF is well-tolerated and no specific treatment is required, except anticoagulation. Episodes are often repetitive and may last from minutes to hours[2]. However, when it leads to hemodynamic instability, urgent treatment is needed to ensure rate control or return to sinus rhythm[1]. When the fast ventricular rate results in haemodynamic collapse, direct current cardioversion is generally required.

Parenteral anticoagulation

Parenteral anticoagulation is recommended in addition to antiplatelet therapy in all AMI patients undergoing PCI[1]. AF may be only a transient arrhythmia accompanying an acute MI, in an anticoagulant-naive patient. Consequently, in the periprocedural setting, parenteral anticoagulation is indicated. Routine of unfractionated heparin (UFH)is recommended[1]. As an alternative to UFH, routine use of enoxaparin i.v. should be considered[1].

Amiodarone

If an acute rhythm control strategy is pursued, amiodarone is the only pharmacological option[1]. Intravenous amiodarone could facilitate electrical cardioversion and/or decrease the risk for early recurrence of AF after electrical cardioversion[1]. Amiodarone may also be considered for rate control, if this strategy is chosen[1,11], with an initial dose of 5 mg/kg in 1 h followed by 50 mg/h[12].

Beta-blockers

Intravenous beta-blockers, including esmolol, propranolol and metoprolol are indicated for rate control and to reduce myocardial oxygen demands, if no clinical signs of acute heart failure (AHF) or hypotension are present[13,14]. In these cases, the negative inotropic effect of β-blockers may result in further compromise of pump function. In the setting of AMI without AHF, short-acting beta blockers are preferred to allow rapid adjustment of the dose, based on the patient's blood pressure and heart rate response. Close to the time of discharge, longer-acting beta blockers may be preferred.

Digoxin

In selected patients, intravenous digitalis should be considered for rate control when concomitant AHF and hypotension are present[15]. Usual dosage is 0.25 mg each 2 h up to 1.5 mg[12]. Digoxin is ineffective in converting recent onset AF to sinus rhythm16. However, data from the ARISTOTLE AF trial showed that digoxin was independently associated with higher mortality rate in patients with AF regardless of HF[17]. In these patients, the risk of death increased with higher serum digoxin concentrations[17]. Among patients whose digoxin levels were greater than 1.2 ng/ml, the death rate increased by 56%[17].

Nondihydropyridine calcium antagonists

Administration of nondihydropyridine calcium antagonists might be considered to slow a rapid ventricular response in patients with AMI and AF only in the absence of significant HF or hemodynamic instability[11].

Vernakalant, flecainide and propafenone should not be used for rhythm control in patients with AMI[11].

Table 1				
Dabigatran	CrCl>30mL/min-150mg b.d	CrCl=30-49mL/min-110mg b.d	CrCl=15-30mL/min-75 mg b.d	CrCl<15mL/min-Avoid
Apixaban	CrCl>15mL/min-5mg b.d	Any 2 (>80yrs, <60kg, SCr>1,5mg/dl)-2,5mg b.d		CrCl<15mL/min-Avoid
Rivaroxaban	CrCl>50mL/min-20mg o.d	CrCl=15-50mL/min-15mg o.dzx		CrCl<15mL/min-Avoid
Edoxaban	CrCl>50mL/min- 60mg o.d	CrCl=30-49mL/min-30mg o.d	CrCl=15-30mL/min 30mg o.d	CrCl<15mL/min-Avoid

Note: CrCl = creatinine clearance as calculated by Cockcroft-Gault formula, AF = atrial fibrillation, BD = twice daily regimen, NOAC = non-vitamin K antagonist oral anticoagulant, OD = once daily regimen, VTE = venous thrombembolism
Adapted from Paul David Morris, Karan Saraf, Pankaj Garg, Paul Sheridan, Robert Storey - Non-Vitamin K antagonist oral anticoagulants (NOACs): Clinical Evidence and therapeutic considerations[19]

Post-procedural management of AF

Patients with AF and moderate-to-severe thromboembolic risk (CHA_2DS_2-VASc score ≥2) should be adequately treated with oral anticoagulants (either vitamin K antagonists or novel oral anticoagulants) to reduce the risk of stroke or systemic embolism[2]. Consequently, patients with AMI and AF require combined antithrombotic therapy which results in a significant bleeding risk. Concomitant risks of cerebro-vascular and coronary ischemic events and bleeding need to be balanced when deciding the duration and the type of antithrombotic therapy[11]. Generally, dual antithrombotic therapy with a novel oral anticoagulant (NOAC) and a P2Y12 inhibitor (preferably clopidogrel) is recommended for the first 12 months after percutaneous coronary intervention (PCI) for an acute coronary syndrome (ACS), since it results in less major bleeding than triple therapy18. NOACs and the recommended doses are show in Table 1.

However, in AF patients with AMI, at least a short course of triple therapy (e.g. ≤1 week) is desirable[11] and should be continued up to one month when the bleeding risks are low and ischemic concerns prevail[1]. These recommendations are based on the results of four RCTs which compared dual therapy with a P2Y12 inhibitor (mostly clopidogrel) plus a NOAC—dabigatran 110 mg or 150 mg b.i.d. (REDUALPCI)[20], rivaroxaban 15 mg o.d. (PIONEER AF-PCI)[21], apixaban5 mg b.i.d. (AUGUSTUS)[22] or edoxaban 60 mg o.d.(ENTRUST-AF PCI)[23]—vs. triple therapy with a VKA in AF patients with a recent ACS or undergoing PCI. All trials have shown a significant reduction of major or clinically significant bleeding, comparable rates of ischemic stroke, AMI and stent thrombosis with dual (NOAC + P2Y12) vs. triple (VKA + P2Y12 + aspirin) therapy. Since patients with AMI who develop AF are usually frail, with severe cardiovascular diseases and multiple comorbidities, they frequently have a high risk for both thrombotic and bleeding events. Consequently, the duration of the triple antithrombotic therapy should always take into consideration the balance between these risks. Assessment of ischemic and bleeding risks should be done using validated risk predictors (e.g. CHA_2DS_2-VASc, ABC, and HAS-BLED) with a focus on modifiable risk factors[24].

For paroxysmal AF, long-term antiarrhythmic therapy is not indicated when moderate to severe left ventricular systolic dysfunction or HF are absent[25] associated with increased in-hospital and long-term mortality rates. This notion is based on data collected before thrombolysis and additional modem methods of treatment became widely available, and no information is available on the significance of PAF in the general population with AMI in the thrombolytic era. The aim of the present study was to define the incidence, associated clinical parameters, and short- and long-term prognostic significance of PAF in patients with AMI in the thrombolytic era. Methods and Results - A prospective, nationwide survey was conducted of 2866 consecutive patients admitted with AMI in all[25] coronary care units in Israel during January/February 1992, 1994, and 1996 (thrombolytic era [TE].

In patients with AMI complicated with LV dysfunction, angiotensin-converting enzyme inhibitors appears to reduce the incidence of AF[26,13].

Statin therapy, possibly owing to an antiinflammatory effect, has been associated with a reduction in paroxysmal AF in patients with ischemic heart disease. In a retrospective study of over 3300 patients presenting with AMI and in sinus rhythm, early statin therapy (prescription within 48 hours of hospitalization) was associated with a reduced risk of AF[27].

In patients at risk of gastrointestinal bleeding, concomitant use of proton-pump inhibitors is reasonable[28].

VENTRICULAR ARRHYTHMIAS

Ventricular tachyarrhythmias (VAs) commonly appear early in ischemia and markedly increase the risk of mortality in patients with an AMI[29]. The incidence of VAs has declined with the use of reperfusion strategies but they still occur in 6-8% of the AMI patients[30].

Pathophysiology

The mechanisms of arrhythmogenesis depend on the stage of evolution of an AMI. Acute ischemia results in harmful consequences on the myocardial metabolism causing anaerobic glycolysis leading to acidosis and accelerated potassium efflux from the myocytes[31]. This generates electrolyte imbalance and electrical instability, which facilitate VAs development in the early phase of AMI[31]. Myocardial reperfusion may also result in abrupt changes in ionic and electrical balance promoting life-threatening Vas[32,12]. Acute phase arrhythmias arise in the first 30 to 60 minutes and are attributed to reentry and abnormal automaticity[33]. Chronic phase VAs appear after more than 48 hours following an AMI and are usually re-entrant and scar mediated, owing to a large MI resulting in a severely depressed LV function and LV remodeling. Monomorphic ventricular tachycardia (VT) is generally scar-related and is the typical presentation in patients with older fibrotic infarct areas in the myocardium[12].

General management

Management of VAs is dependent on whether the arrhythmia is sustained or non-sustained, and if it results in hemodynamic compromise or occurs in an otherwise stable patient. The timing of the VA relative to the AMI plays another important role in the therapeutical decision. AMI related VAs can occur in multiple instances: pre-reperfusion VAs, reperfusion-induced VAs, early post-reperfusion VAs (within 48 h), late post-reperfusion VAs (>48 h after reperfusion), post-discharge arrhythmias[12]. Ventricular fibrillation (VF) is the most frequent mechanism of prehospital sudden cardiac death (SCD)[12] and warrants immediate DCC. The development of VF in patients with an AMI, if occurring within the first 48 h, is associated with an increase in early mortality, but little or no increase in long term mortality after hospital discharge[34,12]. Recurrent VF and/or polymorphic VT may be an indicator of incomplete reperfusion or recurrence of acute ischemia (e.g. acute stent thrombosis)[35]. Urgent coronary angiography should consequently be considered[36].

Generally, sustained VAs (monomorphic or polymorphic) which result in hemodynamic instability call for rapid treatment by DCC. Non-sustained, recurrent or well-tolerated VAs require correction of the underlying ischemic substrate, possible added triggers and should not be treated with anti-arrhythmic drugs before reperfusion.

If ongoing myocardial ischemia is suspected to be responsible for the VA, coronary angiography and prompt and complete revascularization is the mainstay of treatment[37,1]. Correction of electrolyte imbalances (especially hypokalemia and hypomagnesemia) is recommended in patients with VT and/or VF1. Hypokalemia during an AMI is a risk factor for VF. In the GISSI-2 trial, the probability of VF among patients with a serum potassium <3.6 mEq/L was almost twice as high as among patients with a higher serum potassium[38]. Statin therapy has been showed to lower the incidence of premature ventricular complexes (PVCs) and non-sustained VT in patients with ACS[39]. Drugs that inhibit the renin-angiotensin-aldosterone system, namely angiotensin converting enzyme (ACE) inhibitors also reduce the incidence of VAs in AMI[40]. For the temporary management of malignant VT/VF refractory to usual treatment, deep sedation (preferably with benzodiazepines) is a viable therapeutic option which provides a reduction of the sympathetic drive associated with post-MI Vas[41,42]. For patients with AMI without VAs, prophylactic antiarrhythmic drug treatment, with the exception of beta-blockers is not indicated and may be harmful[2].

Antiarrhythmic drugs

The use of antiarrhythmic drugs (AAD) for VAs in AMI has been questioned and is largely based on observational data. Controlled randomized trials on the use of AAD for VAs in AMI are lacking[2]. Prophylactic treatment with AADs is not indicated (with the possible exception of beta-blockers[43]) and may be harmful1. Useful antiarrhythmics, their classification, mechanisms of action, indications, dosing and possible side-effects are shown in Table 2.

Beta-blockers

Beta-blockers are first-line therapy in the management of VA in patients with AMI[36]. Intravenous beta-blocker treatment is indicated for patients with VAs, in the absence of contraindications[1]. VAs in the early or acute stages of an MI are in part related to enhanced automaticity, resulting from elevated catecholamines and beta receptor stimulation. At cellular level, the favorable electrophysiological effects of beta-blockers include decreased automaticity, which reduces the predisposition for triggered VA, and reduced conduction velocity, which impacts on the stability of re-entrant circuits[29]. Beta-blocker use in the first 24 hours after AMI was associated with reduced in-hospital mortality in patients with sustained VT/VF[44]. In the CAPRICORN trial, Carvedilol was shown to have significant anti-arrhythmic effects after AMI, suppressing both atrial and ventricular arrhythmias in these patients[45].

Table 2

Class	Mechanism	Drug name	Indications	Adult Dose	Side Effects & Warnings
Ib	Net effect: Depress conduction with NO change in or shortened APD (repolarization) MOA: Weakly blocks fast Na+ channels: ↓ membrane responsiveness; may shorten APD & end resting membrane potential (ERP) by ↑ K+ conductance	Lidocaine	Approved: VF, VT	1-1.5 mg/kg IV/IO x1; 0.5-0.75 mg/kg IV repeat in 3-5 min (max 3 mg/kg) Maintenance: 30-50 ug/kg/min	SE: Hypotension; neuro (↓ CNS, dizziness, drowsiness and seizures at high levels). Warnings: prophylactic use in AMI; (Warning: reduce maintenance dose if liver disease or left ventricular dysfunction); Adam-Stokes Syndrome. Pregnancy Risk: B
II	Net effect: ↓ chronotropy & inotropy by inhibition of β	Esmolol & other β-blockers	Approved: VT, AFib, AFlutter, Intraoperative HTN	Doses vary based on indication. Please see prescribing recommendations.	SE: Bradycaerdia, hypotension, exacerbation of heart failure, bronchospasm Warning: Asthma (especially moderate to severe), decompensated HF Pregnancy Risk: C
III	Net effect: Prolong repolarization (recovery) by effective refractory period and APD. MOA: inhibition of K+ conductance	Amiodarone	Approved: VT, VF Other Uses: AFib, AFlutter, PSVT	Inj: Pulseless VT/VF: 300 mg IV/IO push in 20 cc ; Other VT/VF: 150 mg IV x 10 min, then 360 mg IV x 6h, then 540 mg x 18h	Note: Can be used in patients with impaired left ventricular dysfunction and WPW. SE: Hypo & hyperthyroidism (inj&tab contain 37% iodine), pulmonary fibrosis, liver toxicity, blue discoloration of skin, optic neuropathy/neuritis, QT prolongation. Warning: heart block; Pregnancy Risk: D
	Net effect: ↓ chronotropy & inotropy; MOA: ↓ SA & AV nodal conduction of Ca+ through a blockade of voltage gated Ca+ channels	Diltiazem	Approved: AFib, AFlutter	15-20 mg IV x 2 min; Repeat in 15 min at 20-25 mg	SE: Bradycardia, HB, worsening of HF, ↓ BP Warnings: WPW, sick sinus syndrome, HB Pregnancy Risk: C
		Verapamil	Approved: Angina, AFib, AFlutter	2.5-5 mg IV over 2 min; then 5-10 mg (if needed) q15-30min (max dose 20mg).	
Other	Net effect: ↓ chronotropy & ↓ inotropy; MOA: PNS; ↑ gK & ↑ gCa	Digoxin	Approved: AFib, Aflutter HF	0.4-0.6 mg IV over ≥5 min; may repeat 0.1-0.3 mg IV over ≥5 min	SE: Arrhythmias, N/V Warnings: Bradycardia, HB, renal failure, hypokalemia. Pregnancy Risk: C

Note: Doses provided are general recommendations for acute care situations and should be verified for the indication being treated. Use of this chart does not replace clinical judgement. AFib = atrial fibrillation, AFlutter = Atrial Flutter, APD = action potential duration, Caps = capsule, CrCl = creatinine clearance, HB = heart block, HTN = hypertension, Inj = Injection, IR = immediate release, IV = intravenous, MOA= mode of action, NS = normal saline, Pgp = P-glycoprotein, MDR3 = multidrug resistant protein 3, PAF = paroxysmal atrial fibrillation, PNS = parasympathetic nervous system, PO = by mouth, PSVT: paroxysmal supraventricular tachycardia, SR = sustained release, Tabs = tablets, VT = ventricular tachycardia, VF = ventricular fibrillation, WPW = Wolf-Parkinson-White.
Adapted from a chart created & reviewed by: Anthony Busti, MD, PharmD, FNLA, FAHA; Krystal Haase, PharmD, BCPS, FCCP; Sarah Dehoney, PharmD, BCPS.

Furthermore, in patients with severe recurrent VAs such as VT/VF storm, an intravenous beta-blocker can be useful[46]. The mortality reduction observed with beta-blockade in the first 24 hours after AMI suggested that patients with sustained VAs benefited from acute beta-blockade without an increase in worsening heart failure[44].

Amiodarone

Intravenous amiodarone is recommended for treatment of recurrent polymorphic VT[1]. Amiodarone has a wide spectrum of action that includes blockade of depolarizing sodium currents and potassium channels that generate repolarizing currents. This results in prolongation of the refractoriness of the His-Purkinje system and ventricular contractile fibers thus preventing micro reentry[47]. Consequently, amiodarone may inhibit or terminate VAs by decreasing automaticity and re-entry[36]. Amiodarone (150–300 mg i.v. bolus) should be considered to acutely suppress recurrent VT or VF[36]. However, over the long term, amiodaro-

ne treatment may result in increased mortality at 6 months[30]. This outcome is most likely explained by confounding factors (e.g. patients with worse prognosis received amiodarone)[30]. It may also occur due to residual adverse effects from amiodarone, possibly by further reducing myocardial contractility in already severely depressed left ventricles[47,48]. Intravenous amiodarone may cause phlebitis (it is advisable to use a large peripheral vein, avoid administration >24 h and use preferably volumetric pump) and arterial hypotension[12].

Lidocaine

Lidocaine may be used to treat recurrent VT with haemodynamic deterioration despite repetitive electrical cardioversion, if beta-blockers, amiodarone and overdrive stimulation are not effective or applicable[1,2]. An observational study by Piccini et al suggested that lidocaine might be preferred over amiodarone for the treatment of sustained VT/VF complicating acute MI[30]. In the first hours after VAs complicating acute MI, both amiodarone and lidocaine are associated with better survival[30]. On longer term, amiodarone use was associated with a higher risk of death at 30 days and 6 months, while lidocaine use did not result in benefit or harm[30].

CONCLUSION

Both supraventricular and ventricular arrythmias which occur in the setting of an AMI are associated with a worse short- and long-term prognosis, increasing the risk of mortality in these patients. Adequate use of antiarrhythmic drugs in the management of hemodynamically relevant arrhythmias is generally useful. At the same time, it is also challenging since, with the exception of beta-blockers, data derived from randomized clinical trials on antiarrhythmic drugs in the management of patients with AMI and life-threatening arrhythmias are scarce, outdated and inconclusive. In this setting, clinical judgement is mandatory.

Compliance with ethics requirements:

The authors declare no conflict of interest regarding this article. The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

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