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Prospective randomized double-blind study of efficacy and safety of 1c class antiarrhythmic agent (propafenone) for supraventricular arrhythmias in septic shock compared to amiodarone

Acronym: PRASE – Propafenone versus amiodarone in septic shock

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Abstract

Introduction: Supraventricular arrhythmias contribute to a haemodynamic compromise in septic shock. A retrospective study generated the hypothesis that propafenone could be more effective than amiodarone in achieving and maintaining sinus rhythm. The success of cardioversion might be predicted by certain echocardiographic parameters, which can guide the decision whether to aim for rhythm or rate control.

Methods and Analysis: The trial includes septic shock patients with new-onset arrhythmia, but without severe impairment of the left ventricular ejection fraction. After baseline echocardiography, the patient is randomised to receive a bolus and maintenance dose of either amiodarone or propafenone. The primary outcome is the proportion of patients that have achieved rhythm control at 24 hours after the start of the infusion. The secondary outcomes are the percentages of patients that needed rescue treatments (DC cardioversion or unblinding and cross over of the antiarrhythmics), recurrence of arrhythmias, ICU mortality, 28-day and 1-year mortality. In the post-hoc analysis we separately assess subgroups of patients with pulmonary hypertension and right ventricular dysfunction. In the exploratory part of the study we assess whether the presence of a transmitral diastolic A wave and its higher velocity-time integral is predictive for the sustainability of mechanical sinus rhythm and whether the indexed left atrial endsystolic volume is predictive of recurrent arrhythmia. Considering that the restoration of sinus rhythm within 24h occurred in 74% of the amiodarone-treated patients and in 89% of patients treated with propafenone, we plan to include 200 patients to have an 80% chance to demonstrate the superiority of propafenone at p=0.05.

Ethics and Dissemination: The trial is recruiting patients according to its 2nd protocol version approved by the University Hospital Ethical Board on the 6th October 2017. The results will be disseminated through peer reviewed publications and conference presentations.

Trial registration: ClinicalTrials.gov Identifier: NCT03029169, registered on 24.1.2017

Key words: supraventricular arrhythmia, septic shock, propafenone, amiodarone, intensive care

Article Summary: Strengths and limitations of this study

- Randomized controlled trial comparing propafenone versus amiodarone in septic shock patients with normal to moderately reduced EF_LV should prove the superior efficacy of propafenone.
- The trial should prove the safety of the 1C class agent propafenone given within the summary of product characteristics – in contrast to the older trials on non-ICU patients.
- Actively pursuing sinus rhythm may contribute to the therapy of diastolic dysfunction with a positive impact on the outcome.
- A complex echocardiography assessment may contribute to the decision whether to aim for rhythm or for rate control therapy. The application of simple echo parameters may be suggested as part of the focused critical care echocardiography performed by an intensivist on a patient with arrhythmia of unknown duration.
- Due to scarcity of data in current literature the hypotheses are based on a single large retrospective study on septic shock patients with SV arrhythmias.

Introduction

The incidence of supraventricular (SV) arrhythmias varies between 8-25% in the critically ill depending on the illness severity [1-5]. The new onset SV arrhythmias are contributor to the diastolic and systolic heart failure [6]. The loss of the atrial systole associates with two to five times increased mortality among critically ill patients [1-3] which is in contrast to a lacking evidence that reverting back to sinus rhythm (SR) improves outcome [7 8]. The uncertainty whether to aim for rate control rather than for rhythm control therapy originates also from the observed recurrence of arrhythmias and the side effects of the antiarrhythmics. Moreover, a recent study on perioperative atrial fibrillation (AF) included the same antiarrhythmic agents and showed similar rates of electric cardioversion in 25% of the patients recruited either to a rhythm control or a rate control arm demonstrating the significant overlap between both approaches [9].

Besides improving oxygenation, preload and electrolyte corrections, electric cardioversion is indicated in unstable patients with no contraindications and is more feasible in combination with an antiarrhythmic agent due to high rates of an early relapse of atrial fibrillation [10].

The data on various antiarrhythmic medications in current literature shows some important limitations, particularly the absence of an echocardiographic protocol before deciding on treatment [6]. Some of the available studies lack an attempt to avoid potentially unfeasible medication in an unstable, critically ill patient. For example, a large pool (36%) of patients in sepsis was medicated with calcium channel blockers which can help with rate control at the cost of reducing ventricular contractility and promotion of vasodilatation. These side effects may critically impact upon haemodynamic stability in a patient with left ventricular

compromise and/or septic vasoplegia [11]. In the studies suggesting beneficial effects of betablockers [12-15] the haemodynamic monitoring did not include echocardiography and the comparisons to control patients were fraught with high mortality of the control group [13].

Several limitations have to be considered prior to beta-blocker administration in septic shock patients. These are especially exclusion of the severe LV systolic dysfunction, valve and conduction disorders [14 16].

The mainstay of antiarrhythmic therapy[6] is represented by amiodarone which is preferred for its lower cardiodepressant side effect compared to other agents and electric cardioversion [17-20]. The adverse effects of amiodarone involve thyroid function [21 22], corneal microdeposits, hepatic dysfunction [23 24], interstitial pneumonia and pulmonary fibrosis [25 26], skin discoloration and neuropathies [27 28]. Hypotension may occur due to amiodarone's vasodilatatory effects and QTc prolongation associates with the occurence of torsades-des-pointes type of ventricular tachycardia. Extensive use of amiodarone contrasts with its multiorgan side effects and its application even in cardiology patients with normal LV systolic function [29 30] demonstrates poor compliance with current guidelines [31].

The use of 1C class antiarrhythmic drugs in the treatment of SV arrhythmias in the critically ill has not been properly evaluated. There are only a few case reports available describing serious adverse effects apparently related to their dose related cardiotoxicity [32-34]. The use of 1C agents has been discouraged by reports describing poor outcome during long term administration in the cardiology population [32]. Consequently, 1C class agents like propafenone and flecainide [35], are scarcely used in the critically ill. In contrast to flecainide and encainide, propafenone is derived from propandiolamine, which is a chemical compound of betablockers and acts on the rapid depolarizing phase (phase 0) and also, to a minimal extent, on beta-adrenergic receptors [36-38]. Compared to flecainide, propafenone also lacks any evidence of its relationship to mortality [39].

Our retrospective study [4 5] suggests that propafenone might be feasible to restore SR without an adverse effect on haemodynamics and with a possible benefit on the outcome of the septic shock patients (Fig.1) [4 5]. A chance to cardiovert seemed to be significantly higher under propafenone than in amiodarone and was close to the cardioversion rates of the betablocker metoprolol. No secondary arrhythmias or conduction disorders requiring treatment other than adjustment of the rate of infusion were observed [4 5]. A typical patient benefiting from propafenone has has normal to moderately reduced left ventricular systolic function. Another recent retrospective study found faster and more succesful cardioversion with propafenone as compared to amiodarone for new onset atrial fibrillation in an emergency department. The safety profiles of the two agents were not different [40].

The current trial is intended to prospectively verify the efficacy and safety of propafenone administered under echocardiography control in the critically ill with septic shock. The trial also challenges the concept of amiodarone applied as a relatively toxic universal antiarrhythmic agent with a similar short-term safety profile as propafenone, whilst being slower and less efficient in cardioverting a supraventricular arrhythmia in a septic shock patient.

The authors also hypothesize that actively pursuing sinus rhythm and cardioverting patients may contribute to the therapy of diastolic dysfunction with a positive impact on mortality [7]. An echocardiography driven prediction of cardioversion in the critically ill patients has not been explored in the available literature. It seems that the degree of dependence of the left ventricular filling on atrial systole would be an important entity when deciding between rhythm and rate control in SV arrhythmia in septic critically ill patients. The rate control modality should be reserved for a chronic persistant AF and in situations when sinus rhythm is difficult to maintain due to high dosage of vasoactive agents.

Methods/Design

We designed a prospective double blinded randomized trial comparing propafenone to amiodarone administered for a SV arrhythmia in critically ill patients with septic shock.

Primary aims

The trial should prove that propafenone is more efficient than amiodarone in cardioverting a SV arrhythmia in patients with normal to moderately reduced EF_LV at 24h from the onset. The rationale stems from the retrospective data set where the primary cardioversion rate of SV arrhythmia under propafenone was 88.9% versus 73.5% under amiodarone [4 5]. The authors also expect faster cardioversion under propafenone and lower rates of arrhythmia recurrence in the propafenone group. Despite prejudices arising particularly from the CAST trial and case reports on dose dependent toxicity, research should prove the safety of the 1C class agent propafenone given within the summary of product characteristics [33 35]. The retrospective study [4 5] has shown that the ICU and 28-day mortalities of patients treated with propafenone were better than the parameters of the amiodarone patients. In other words, the propafenone administration did not increase mortality as suggested by the older trials on non-ICU patients [32-34]. Moreover, patients with a supraventricular arrhythmia treated with propafenone had significantly better adjusted 12-month survival than the critically ill treated with amiodarone (Fig.1). If proven, the physicians could avoid a widespread use of amiodarone in the critically ill.

The cardioverted patients (rhythm control) may showcase better outcome parameters (ICU mortality, 28-day mortality, 1-year mortality) than those remaining in an acute onset arrhythmia (rate control). A rationale beyond this hypothesis is in the pilot study [4 5] which also included patients with severe LV dysfunction and associated higher rates of recurrent SV arrhythmias. Focusing on only normal to moderate LV systolic dysfunction may minimize bias associated with arrhythmia treatment of patients with severe LV systolic dysfunction. Likewise, those patients were included in the published trials dealing with either 1C class antiarrhythmics (e.g. CAST trial,[32]) or in the trials studying rhythm vs rate control (e.g. AFFIRM, RACE or AF-CHF Trial,[9 41-43]). Due to high success of rhythm control therapy (74.4% and 87% excluding chronic AF) in the retrospective study on 234 patients [4 5], the group with

persisting acute onset SV arrhythmia was significantly smaller in number causing an asymmetry in statistic evaluation. This may also account for not signicantly better outcome of the cardioverted versus those remaining in the SV arrhythmias (Fig.2).

Secondary aims

The presence of a transmitral diastolic A wave and its higher velocity-time integral (VTI) at 4h post cardioversion would indicate a presence of mechanical sinus rhythm. A small or negligible A wave may represent only the electric sinus in the absence of its mechanical correlate. This finding could be related to the increased indexed left atrial end-systolic volume (LAVi) and to a recurrence of a SV arrhythmia[44 45]. The LAVi in all patients and altered filling pressures estimated by echocardiography could be predictive of the arrhythmia recurrence [46 47].

Propafenone would be more efficient than amiodarone in patients with pulmonary hypertension and RV dysfunction without left ventricular systolic dysfunction.

A left ventricular relaxation disorder and a pseudonormal LV filling are more dependent on atrial kick compared to the restrictive LV filling which is often accompanied by a dilated poorly contracting left atrium. The classic stratification of diastolic dysfunction relates to patient´s prognosis in septic shock [48]. Hence, a complex echo assessment may contribute to the decision whether to aim for rhythm or for rate control only. The evaluation of the doppler parameters will depend on rhythm, heart rate, regularity of arrhythmia and peripheral pulse deficit [44 46].

Flow chart (Fig.3, Fig.4) and study setting

Patients are randomized by the unblinded team lead by a research nurse. The planned number of included patients is 100 in each arm of the study with a total of 220 randomized patients. A dropout of 10% is anticipated. The estimated duration of the study is 4 years including follow up. The patients have been recruited since November 2017 in three university hospital ICUs. The department of Anaesthesia and Intensive Care of the General University Hospital has been performing for years as a teaching centre for critical care echocardiography and ultrasound. Together with the Coronary Care Unit of the General University Hospital both departments are integrated as a Complex Cardiovascular Centre. The department of Anaesthesia and Intensive Care of the University Hospital Vinohrady is a mainstay of the Complex Prague Traumacentre.

Inclusion Criteria

The study targets patients in septic shock with a new onset SV arrhythmia or known paroxysmal SV arrhythmia who show normal or mildly to moderately reduced LV systolic function according to the echocardiography examination (i.e. EF_LV >/=35%). A diagnosis of

septic shock is made according to the 2016 definition[49] as sepsis with a vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg or greater. The arterial lactate level should be greater than 2 mmol/L in the absence of hypovolemia or low cardiac output. The highest arterial lactate level is recorded, i.e. lactate <2.0 mmol/l at the time of randomization does not exclude a patient from the study. This might also be justified by the reported incidence of the sepsis related cardiac dysfunction which is highest 72-96h after an onset of septic shock [50]. The presence of a suspected infection is for the purpose of this study defined as a positivity of at least one inflammatory marker of the monitored CRP and PCT and a clinical decision to administer antibiotic treatment for a specified infection source.

Exclusion Criteria

The study respects all exclusion criteria for a blinded administration of propafenone or amiodarone. These are severe LV systolic dysfunction (i.e. EF<35%), a history indicating more than 1st degree AV block and a high dose vasopressor therapy represented by continuous noradrenaline administration of more than 1.0 ug/kg.min. Contraindications to randomisation are known intolerance to amiodarone or propafenone, iodine allergy and an active thyroid disease other than chronic hormone substitution for benign goiter. Chronic persistant AF represents an exclusion while known chronic paroxysmal AF is not an exclusion criterion. Patients dependent on a pacemaker or after a Maze procedure are also excluded.

Interventions and research protocol

Patients will have a haemodynamic examination provided according to the study protocol. With the onset of arrhythmia, the usual treatment is expected including preload correction, reduction of unnecessary vasopressors, ion supplementation (aiming particularly for K^+ >4.0 mM and Mg^{2+} > 1.0 mM) and maintenance of tissue oxygen delivery. Echocardiography should also guide optimization of preload.

The complex protocol is formatted in an electronic case report form (CRF). After checking up the inclusion and exclusion criteria the CRF allocates the patients randomly using built in software (www.randomization.com) into the propafenone or amiodarone arm.

The patient´s characteristics include the illness severity scores, source of septic shock, data on mechanical ventilation and homeostasis, baseline haemodynamic data, baseline laboratory data, patient´s medications, haemodynamic data at proposed steps plus follow up data including outcome.

Haemodynamic evaluation includes ICU standard plus echocardiography. The study team involves 8 intensivists with an European Accreditation in Echocardiography (either ESC or EACTA backed) and three qualified cardiologists-intensivists.

By no means is an antiarrhythmic given out of the summary of product characteristics. Both arms will have standard treatment, there are no limits to electric cardioversion as part of

treatment which is indicated anytime in haemodynamic compromise and in signs of low cardiac output or not sufficient perfusion pressures due to arrhythmia.
The propafenone arm constitutes administering a bolus of 35-70 mg of intravenous propafenone followed by a continuous infusion of 400-840 mg/24h in a black syringe. The amiodarone arm constitutes administering a bolus of 150-300 mg of intravenous amiodarone followed by a continuous infusion of 600-1800 mg/24h in a black syringe.
A 12-lead ECG is taken every 12h whilst the antiarrhythmic infusion. Besides echocardiography pre-randomization the control echocardiography is performed 1h post cardioversionand 4h post cardioversion. Echocardiography is performed also every day until cardioversion, it is also mandatory in any kind of haemodynamic instability. All the Doppler measurements are recorded at end-expiration and 3 cardiac cycles, when sinus rhythm, and 5-10, during arrhythmia, are analysed and averaged. All recordings should be acquired with an ECG (lead II), and ideally, at the speed of 100 mm/s.
If electrically cardioverted in addition to administered pharmacotherapy, then echocardiography is performed 1h post cardioversion and 4h post cardioversion.
If cardioverted later than until 24h then echocardiographies are performed at 1h and 4h after cardioversion, the times of cardioversion and arrhythmia relapses are always recorded.

Primary outcome measures

1. The efficacy in restoration of sinus rhythm assessed as the proportion of patients who are in sinus rhythm 24 hours after the beginning of the infusion of the study drug and remain in sinus rhythm until discharge from ICU. Primary outcome will be assessed in all randomised patients (i.e. intention to treat analysis).
2. A-priori defined subgroup analysis: Primary outcome will be analysed in the following subgroups of patients:

a) with and without indexed left atrial endsystolic volume (LAVi) higher than >40 ml/m^2.
b) with and without pulmonary hypertension (defined as PAPs >40 mmHg) associated with moderate to severe RV dysfunction (dilated RV with TAPSE <15 mm)

Secondary outcome measures

1. The cumulative proportion of patients receiving rescue treatment for arrhythmia defined as direct current cardioversion or an alternative antiarrhythmic drug during the first 24 hours (cross-over from one arm to the other resulting in unblinding of the study, e.g. from amiodarone to propafenone due to a persisting arrhythmia or from propafenone to amiodarone due to a decrease in LV systolic function).

2. The cumulative proportion of patients receiving rescue treatment for arrhythmia defined as direct current cardioversion, cross-over to the alternative study drug or other antiarrhythmic drug during ICU stay.
3. Mortality at discharge from ICU, at 28 days and at 1 year.
4. Vasopressor-free days at day 28.

Safety issues and patient´s monitoring

Besides cardioversion monitoring the TTE is also acquired in any kind of haemodynamic instability (i.e. change in vasopressor support). This is important to avoid administering a potentialy cardiodepressant propafenone in a patient developing septic cardiomyopathy. 12 hourly 12-lead ECG for monitoring of conduction times (PQ, QRS, QTc) is performed while the patient is on the antiarrhythmic infusion. In case of an AV block of the first degree or extension of the conduction times (QRS or QTc) the slowing or temporary ceasing of the medication in relation to heart rate is mandatory. Adjustment of the infusion rate or eventual termination of an antiarrhythmic medication does not exclude the patient from the study. Ceasing of medication after reaching sinus rhythm does not exclude the patient too. If an infusion is interrupted and restarted then the number of infusion hours are counted up as a sum of infusion hours.

In case of a progression of septic cardiomyopathy and a decrease of contractility (decrease of EFLV to <35%) or a progression of mitral regurgitation with a risk of low cardiac output the study drug is unblinded and propafenone discontinued. Further treatment is decided by the clinician. If the study is unblinded due to haemodynamic instability, the second drug after study arm cross-over is administered without an initial bolus.

Anytime the patient becomes haemodynamically unstable or has another reason (as per discretion of the treating clinician) to benefit from electric cardioversion (DCC), then DCC is delivered without delay.

Should there be a concern at any point in time about the safety of the drug, the treating clinicians are encouraged to unblind the treatment drug without delay, and alter the treatment accordingly. The course of the trial is regularly reported to the hospital Ethical Board which acts as the research supervising body. The minimum frequency of the report is once per year throughout the duration of the trial which is proposed from 2018 till 2021.

Statistics and power analysis

The logistic regression and time-to-event (Cox) regression with and without adjustment for baseline patients´ characteristics will be applied in the statistic analysis. The multivariate analysis will include the patients´ baseline parameters which would be correlated with an analysed outcome parameter and will be inhomogenously distributed within the study

groups regardless of the randomisation. The required number of patients is based on the power analysis and data from the pilot retrospective study [4 5].
The entry parameters for the sample size analysis were estimated by the probabilities of cardioversion of 75% for the amiodarone group and 90% for the propafenone group within 24h from the onset of arrhythmia, randomisation ratio 1:1, p=0.05 and power 0.8. To achieve a statistically significant difference under these conditions 100 patients need to be included into each group, altogether 200 patients into the trial. Assuming 10% drop out the authors plan to randomize 220 patients.

Ethics approval and dissemination:

The local ethical approvals have been received from the Ethics Committee of the 1st Medical Faculty and General University Hospital (No. 1691/16 S-IV) and from the Ethics Committee of the 3rd Medical Faculty and University Hospital Kralovske Vinohrady. The written informed consent is sought from the patient´s next of kin. The results will be disseminated through peer reviewed publications and conference presentations. The study repository will be created with the dataset available after study completion. The recruitment has begun through the electronic case report form on the 23rd October 2017 and is expected to be completed in December 2021.

Limitations and conclusions

The available literature on SV arrhythmias in septic shock shows critically ill patients with a high predicted mortality, IPPV rate of 99% and high rates of CRRT (27-31%) [4 5]. Up to now all the authors adhered to the septic shock criteria based on volume non-responsive SIRS with a need for a vasopressor and antibiotic therapy administered for an infectious source [51].
Applying the novel septic shock criteria of 2016 [49] may increase specificity at the cost of lacking sensitivity to include even those who could potentially benefit from septic shock therapy [52]. If applying the results of the current trial to less severe patients, e.g. those classified according to the older criteria, the SOFA score and a median arterial lactate level may serve as controls adjusting studied population in context of the novel septic shock criteria published in 2016 [49].
The hypothesis that propafenone might be superior to amiodarone in cardioverting newly appearing SV arrhythmia with an impact on the long term outcome may not be proved due to the confounding factors of the retrospective study [4 5]. Albeit being statistically insignificant, the LV systolic function was mildly higher in propafenone and betablocker patients compared to those on amiodarone. The severe LV systolic dysfunctions were medicated with amiodarone as well as patients on a higher dosage of noradrenaline compared to the patients with moderate to mild LV systolic dysfunction and the lower dosage of noradrenaline in the propafenone and betablocker groups [4 5].

The retrospective study included also patients with a cross-over from a not successful antiarrhythmic therapy to another group during 24 hours as part of the rhythm control strategy. This increased the pool of the propafenone patients after administering the agent in patients who were not able to cardiovert and maintain sinus rhythm on amiodarone [4 5]. This might represent a so far not reported synergistic effect of the two antiarrhythmic agents on achieving a high cardioversion rate, yet with a very acceptable safety profile [4 5]. The current prospective trial allows a cross-over between the arms however, only in a haemodynamic instability and with immediate unblinding.

The observed median age in an adult ICU varies around 55-65 years. The age related prevalence of hypertension and ischaemic heart disease suggests a large proportion of patients with a benefit of atrial systole and thus an indication for the rhythm control approach [7]. The prevalence of newly occuring SV arrhythmias and the broad spectrum of potentially reversible triggers in the critically ill offer an opportunity for cardioversion in closely monitored patients rather than in ambulatory patients in cardiology. Moreover, septic shock is often fraught with diastolic dysfunction and to restore sinus rhythm might be of paramout importance for the therapy of diastolic heart failure.

List of abbreviations: AF atrial fibrillation, APACHE II acute physiologic and chronic health evaluation, AV atrio-ventricular, CRRT continuous renal replacement therapy, CRP C reactive protein, DCC direct current cardioversion, DO2/VO2 oxygen delivery/oxygen consumption, EF ejection fraction, EF_LV ejection fraction of left ventricle, ICU intensive care unit, K+ plasmatic potassium, LA left atrium, LAVi indexed end-systolic left atrial volume, LV left ventricle/ left ventricular, LVOT left ventricular outflow tract, Mg2+ plasmatic magnesium, PAPs pulmonary artery systolic pressure, PCT procalcitonin, PRCT prospective controlled randomized trial, RV right ventricle, SIRS systemic inflammatory response syndrome, SOFA sequential organ function assessment, SR sinus rhythm, SV supraventricular, TAPSE tricuspid annular plane excursion, TTE transthoracic echocardiography, VTI velocity-time integral

Author Contributions

MB – study coordinator, concept and design, drafting, revisions and approval of articles, provision of funding. PW, FD – concept and design, electronic case report form, statistics, article revisions, data collection. MP, JR, MO, VM, MM, TB, RS, JP, PB, ES, MF, ZS, MS – data collection, article revisions. OS – article revisions, data collection, unblinded team coordination.

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Competing interests: None

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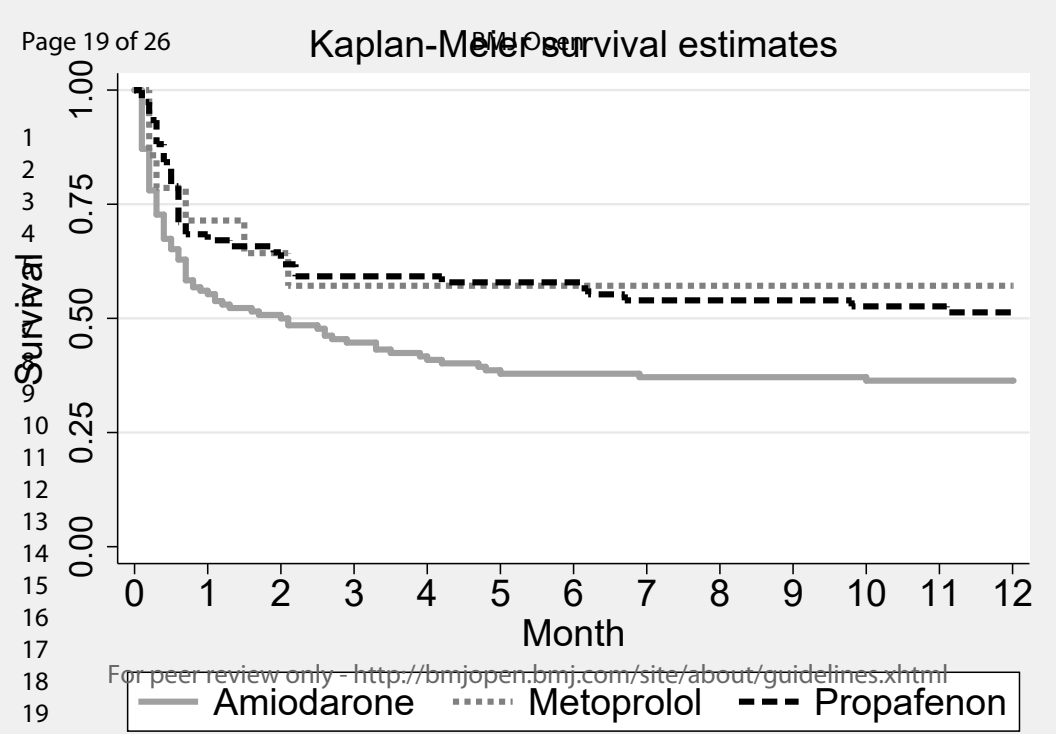
Legends to figures

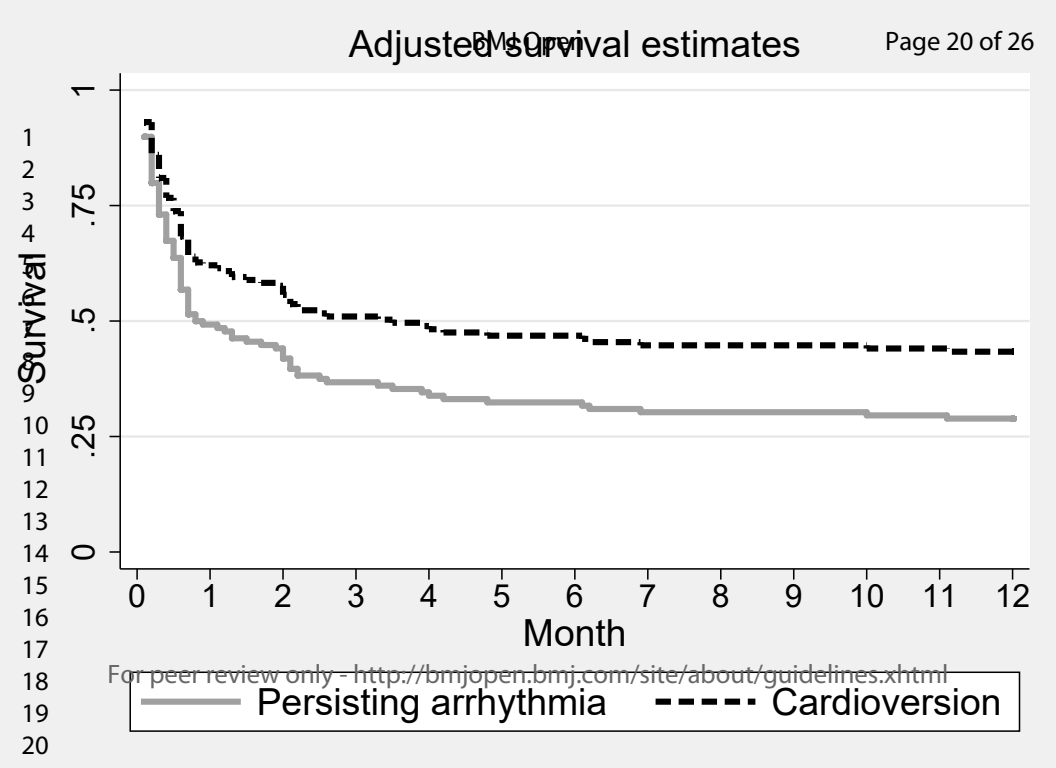
Fig.1: Univariate analysis showing long term survival of the propafenon patients similar to the metoprolol group and higher than in the amiodarone medicated patients in septic shock (HR1.76(1.06; 2.3),p=0.024). Copied from the author´s pilot retrospective study [4]

Fig.2: Multivariate analysis showing insignificant 12-month benefit in cardioverting septic shock patients to sinus rhythm (HR0.67,p=0.113). Copied from the author´s pilot retrospective study [4]

Fig.3: Flowchart of the study

Fig.4: SPIRIT table for the schedule of enrolment, interventions, and assessments





Flowchart of prospective randomized double blinded study of efficacy and safety of 1c class antiarrhythmic agent (propafenone) in septic shock

Acronym: PRASE – Propafenone versus amiodarone in septic shock

SV arythmia: AF, flutter, SVT…

1.) Sepsis and administration of noradrenaline due to hypotension non-responsive to correction of preload
2.) Elevation of arterial lactate >2.0 mmol/l during the course of disease, i.e. may be present before or during arrhythmia
3.) Positivity of at least one of the CRP or PCT
4.) Administration of antibiotics for an infectious source

Echocardiography: LV systolic function must be normal or mildly to moderately reduced

Exclusion Criteria:

- Severe LV systolic dysfunction
- More than 1st degree AV block
- High dose vasopressor therapy with continuous noradrenaline > 1.0 ug/kg.min
- Known intolerance to amiodarone or propafenone (incl. active thyroid disease other than chronic hormone substitution)
- Absence of septic shock
- Chronic AF - known chronic paroxysmal AF is not an exclusion criterion.
- Dependence on pacemaker
- Status after MAZE procedure
- Iodine allergy

Randomisation

Propafenone arm

Amiodarone arm

			STUDY PERIOD					
	Screening	Randomisation through electronic CRF	Visits			ICU outcome	28-days outcome	12m-outcome
TIMEPOINT	$-T_1$	0	T_{+1h}*	T_{+4h}*	T_x**			
Septic shock criteria JAMA 3/2016	X							
Informed consent	X							
Allocation		X						
12-lead ECG	X		X	X	X			
Transthoracic echocardiography (TTE)	X		X	X	X			
Hemodynamic assessment	X		X	X	X	X***	X***	X***
Laboratory data	X							
Concomitant medications	X							
INTERVENTIONS:								
Propafenone bolus		X						
Propafenone cont. infusion			X	X	X			
Amiodarone bolus		X						
Amiodarone cont. infusion			X	X	X			

*Visits: 12-lead ECG every 12h on infusion, TTE per 24h of arrhythmia and +1h after cardioversion, +4h after cardioversion, TTE in any instability

***Tx* – day on antiarrhythmic infusion

***Alive/dead, sinus/persistent arrhythmia

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	1, 2, 10
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	11,12
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 11
	5b	Name and contact information for the trial sponsor	12
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	12
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	2,10

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	____3,4,5_____
	6b	Explanation for choice of comparators	____3,4,5_____
Objectives	7	Specific objectives or hypotheses	____5, 6_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	____5, 6_____
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	____6_____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	____6, 7_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	____7, 8 , 9__
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	____7, 8, 9___
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	____7, 8, 9___
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	____7, 8, 9___
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	____8, 9_____
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	____7, 8, Fig.3, Fig.4

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	____2, 9, 10_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	____5,6,7,8____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	____7, 8, 9____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	____7, 8, 9____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	____7, 8, 9____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	____7, 8, 9____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	____7, 8, 9____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	____8, 9, 12___
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	____8, 9_____

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	____7,8,9,10_
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	____9,10_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	____5, 6, 7, 8, 9, _
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	____9,10_____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	____9, 10____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	____9, 10_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	____9, 10_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	____9, 10_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____10_____
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	_____2, 10 ___

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	11,12
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	2, 10
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	2,12
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	available upon request in Czech
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Efficacy and safety of 1c class antiarrhythmic agent (propafenone) for supraventricular arrhythmias in septic shock compared to amiodarone: protocol of a prospective randomized double-blind study

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Primary Subject Heading:	Intensive care

Secondary Subject Heading:	Cardiovascular medicine, Anaesthesia, Infectious diseases
Keywords:	Adult intensive & critical care < ANAESTHETICS, Echocardiography < CARDIOLOGY, Pacing & electrophysiology < CARDIOLOGY

Efficacy and safety of 1c class antiarrhythmic agent (propafenone) for supraventricular arrhythmias in septic shock compared to amiodarone: protocol of a prospective randomized double-blind study

Acronym: PRASE – Propafenone versus amiodarone in septic shock

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Abstract

Introduction: Supraventricular arrhythmias contribute to haemodynamic compromise in septic shock. A retrospective study generated the hypothesis that propafenone could be more effective than amiodarone in achieving and maintaining sinus rhythm. Certain echocardiographic parameters may predict a successful cardioversion and help in the decision on rhythm or rate control strategy.

Methods and Analysis: The trial includes septic shock patients with new-onset arrhythmia, but without severe impairment of the left ventricular ejection fraction. After baseline echocardiography, the patient is randomized to receive a bolus and maintenance dose of either amiodarone or propafenone. The primary outcome is the proportion of patients that have achieved rhythm control at 24 hours after the start of the infusion. The secondary outcomes are the percentages of patients that needed rescue treatments (DC cardioversion or unblinding and cross over of the antiarrhythmics), the recurrence of arrhythmias, ICU mortality, 28-day and 1-year mortality. In the post-hoc analysis we separately assess subgroups of patients with pulmonary hypertension and right ventricular dysfunction. In the exploratory part of the study we assess whether the presence of a transmitral diastolic A wave and its higher velocity-time integral is predictive for the sustainability of mechanical sinus rhythm and whether the indexed left atrial endsystolic volume is predictive of recurrent arrhythmia. Considering that the restoration of sinus rhythm within 24h occurred in 74% of the amiodarone-treated patients and in 89% of the patients treated with propafenone, we plan to include 200 patients to have an 80% chance to demonstrate the superiority of propafenone at p=0.05.

Ethics and Dissemination: The trial is recruiting patients according to its 2nd protocol version approved by the University Hospital Ethical Board on the 6th October 2017 (No.1691/16S-IV). The results will be disseminated through peer reviewed publications and conference presentations.

Trial registration: ClinicalTrials.gov Identifier: NCT03029169, registered on 24.1.2017

Key words: supraventricular arrhythmia, septic shock, propafenone, amiodarone, intensive care

Article Summary: Strengths and limitations of this study

- Randomized controlled trial comparing propafenone versus amiodarone in septic shock patients with normal to moderately reduced EF_LV should eliminate the bias of previous trials where patients with all levels of LV systolic function and various illness severities were compared.
- The trial should answer the issue of safety of the 1C class agent propafenone given within the summary of product characteristics in the critically ill – in contrast to the older trials on less severely ill patients.
- The outcomes of cardioverted patients with improved diastolic function will be compared to matched patients who remain in persisting arrhythmias.
- The analysis of applied complex echocardiography protocol may propose simple echo parameters which may help in the decision on rhythm versus rate control approach.
- Due to the scarcity of data in the current literature the hypotheses are based on a single large retrospective study on septic shock patients with SV arrhythmias.

Introduction

The incidence of supraventricular (SV) arrhythmias varies between 8-25% in the critically ill depending on the illness severity [1-5]. New onset SV arrhythmias are a contributor to diastolic and systolic heart failure [6]. Loss of atrial systole associates with two to five times increased mortality among critically ill patients [1-3] which is in contrast to lacking evidence that reverting back to sinus rhythm (SR) improves outcome [7 8]. The uncertainty whether to aim for rate control rather than for rhythm control therapy also originates from the observed recurrence of arrhythmias and the side effects of the antiarrhythmics.

Besides improving oxygenation, preload and electrolyte corrections, the electric cardioversion is indicated in unstable patients with no contraindications and is more feasible in combination with an antiarrhythmic agent due to high rates of an early relapse of atrial fibrillation [9].

The data on various antiarrhythmic medications in the current literature shows some important limitations, particularly the absence of an echocardiographic protocol before deciding on treatment [6]. Some of the available studies lack an attempt to avoid potentially unfeasible medication in an unstable, critically ill patient. For example, a large pool (36%) of patients in sepsis was medicated with calcium channel blockers which can help with rate control at the cost of reducing ventricular contractility and promotion of vasodilatation. These side effects may impact upon haemodynamic stability in a patient with left ventricular compromise and/or septic vasoplegia [10]. In the studies suggesting beneficial effects of betablockers [11-14] haemodynamic monitoring did not include echocardiography and the comparisons to control patients were fraught with high mortality of the control group [12].

Particularly the severe LV systolic dysfunctionand conduction disorders should be excluded prior to beta-blocker administration in the septic shock patients [13 15].

The mainstay of antiarrhythmic therapy[6] is represented by amiodarone which is preferred for its lower cardiodepressant side effect compared to other agents and electric cardioversion [16-19]. Extensive use of amiodarone contrasts with its multiorgan side effects and its application even in patients with normal LV systolic function [20 21] demonstrates poor compliance with current guidelines [22]. Hypotension may occur due to amiodarone's vasodilatatory effects and QTc prolongation associates with the occurence of torsades-des-pointes type of ventricular tachycardia. In the long term administration the adverse effects involve particularly thyroid function [23], hepatic dysfunction[24], interstitial pneumonia and pulmonary fibrosis[25-27].

The use of 1C agents has been discouraged by studies describing poor outcome during long term administration in the cardiology population [28]. Few available case reports demonstrate serious adverse effects apparently related to the dose related cardiotoxicity [28-30]. Consequently, 1C class agents like propafenone and flecainide [31], are scarcely used in the critically ill. In contrast to flecainide and encainide, propafenone is derived from propandiolamine, which is a chemical compound of betablockers and acts on the rapid depolarizing phase (phase 0) and also, to a minimal extent, on beta-adrenergic receptors [32-34]. Compared to flecainide, propafenone also lacks any evidence of its relationship to mortality [35].

Our retrospective study [4 5] suggests that propafenone might be feasible to restore SR without an adverse effect on haemodynamics and with a possible benefit on the outcome of the septic shock patients (Fig.1) [4 5]. A chance to cardiovert seemed to be significantly higher under propafenone than in amiodarone and was close to the cardioversion rates of the betablocker metoprolol. No secondary arrhythmias or conduction disorders requiring treatment other than adjustment of the rate of infusion were observed [4 5]. Another recent retrospective study found faster and more succesful cardioversion with propafenone as compared to amiodarone for new onset atrial fibrillation in an emergency department. The safety profiles of the two agents were not different [36].

The current trial is intended to prospectively verify the efficacy and safety of propafenone administered under echocardiography control in the critically ill with septic shock. The trial also challenges the concept of amiodarone applied as a relatively toxic universal antiarrhythmic agent with a similar short-term safety profile as propafenone, whilst being slower and less efficient in cardioverting a supraventricular arrhythmia in a septic shock patient. The authors also hypothesize that actively pursuing sinus rhythm and cardioverting patients may contribute to the therapy of diastolic dysfunction with a positive impact on mortality [7].

Methods/Design

We designed a prospective double blinded randomized trial comparing propafenone to amiodarone administered for a SV arrhythmia in critically ill patients with septic shock.

Primary aims

The trial should prove that propafenone is more efficient than amiodarone in cardioverting a SV arrhythmia in patients with normal to moderately reduced EF_LV at 24h from the onset. The rationale stems from the retrospective data set where the primary cardioversion rate of SV arrhythmia under propafenone was 88.9% versus 73.5% under amiodarone [4 5]. The authors also expect faster cardioversion under propafenone and lower rates of arrhythmia recurrence in the propafenone group. Despite prejudices arising particularly from the CAST trial and case reports on dose dependent toxicity, research should prove the safety of the 1C class agent propafenone given within the summary of product characteristics [29 31]. The retrospective study [4 5] has shown that the ICU and 28-day mortalities of patients treated with propafenone were better than the parameters of the amiodarone patients. In other words, propafenone administration did not increase mortality as suggested by the older trials on non-ICU patients [28-30]. Moreover, patients with a supraventricular arrhythmia treated with propafenone had a significantly better adjusted 12-month survival than the critically ill treated with amiodarone (Fig.1). If proven, physicians could avoid a widespread use of amiodarone in the critically ill.

The cardioverted patients (rhythm control) may showcase better outcome parameters (ICU mortality, 28-day mortality, 1-year mortality) than those remaining in an acute onset arrhythmia (rate control). A rationale beyond this hypothesis is in the pilot study [4 5] which also included patients with severe LV dysfunction and associated higher rates of recurrent SV arrhythmias. Focusing on only normal to moderate LV systolic dysfunction may minimize bias associated with arrhythmia treatment of patients with severe LV systolic dysfunction. Likewise, patients with severe LV dysfunction were also included in the published trials dealing with either 1C class antiarrhythmics (e.g. CAST trial,[28]) or in the trials studying rhythm vs rate control (e.g. AFFIRM, RACE or AF-CHF Trial,[37-40]). Due to high success of rhythm control therapy (74.4% and 87% excluding chronic AF) in the retrospective study on 234 patients [4 5], the group with persisting acute onset SV arrhythmia was significantly smaller in number causing an asymmetry in statistic evaluation. This may also account for not signicantly better outcome of the cardioverted versus those remaining in the SV arrhythmias (Fig.2).

Secondary aims

The presence of a transmitral diastolic A wave and its higher velocity-time integral (VTI) at 4h post cardioversion would indicate a presence of mechanical sinus rhythm. A small or negligible A wave may represent only the electric sinus in the absence of its mechanical correlate. This finding could be related to the increased indexed left atrial end-systolic volume (LAVi) and to a recurrence of a SV arrhythmia[41 42]. The LAVi in all patients and altered

filling pressures estimated by echocardiography could be predictive of arrhythmia recurrence [43 44].

Propafenone could be more efficient than amiodarone in patients with pulmonary hypertension and RV dysfunction without left ventricular systolic dysfunction.

A left ventricular relaxation disorder and a pseudonormal LV filling are more dependent on the atrial kick compared to the restrictive LV filling which is often accompanied by a dilated poorly contracting left atrium. The classic stratification of diastolic dysfunction relates to the patient´s prognosis in septic shock [45]. Hence, a complex echo assessment may contribute to the decision whether to aim for rhythm or for rate control only. Evaluation of the doppler parameters will depend on rhythm, heart rate, regularity of arrhythmia and peripheral pulse deficit [41 43].

Flow chart and study setting

Patients are randomized by the unblinded team lead by a research nurse. The planned number of included patients is 100 in each arm of the study with a total of 220 randomized patients. A dropout of 10% is anticipated. The estimated duration of the study is 4 years including follow up. The patients have been recruited since November 2017 in three university hospital ICUs. The department of Anaesthesia and Intensive Care of the General University Hospital has been performing for years as a teaching centre for critical care echocardiography and ultrasound. Together with the Coronary Care Unit of the General University Hospital both departments are integrated as a Complex Cardiovascular Centre. The department of Anaesthesia and Intensive Care of the University Hospital Vinohrady is a mainstay of the Complex Prague Traumacentre.

Inclusion Criteria

The study targets adult patients (16-85 years) in septic shock with a new onset SV arrhythmia or known paroxysmal SV arrhythmia who show normal or mildly to moderately reduced LV systolic function according to the echocardiography examination (i.e. EF_LV >/=35%)(Fig.3). A diagnosis of septic shock is made according to the 2016 definition[46] as sepsis with a vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg or greater. The arterial lactate level should be greater than 2 mmol/L in the absence of hypovolemia or low cardiac output. The highest arterial lactate level is recorded, i.e. lactate <2.0 mmol/l at the time of randomization does not exclude a patient from the study. This might also be justified by the reported incidence of sepsis related cardiac dysfunction which is highest 72-96h after the onset of septic shock [47]. The presence of a suspected infection is for the purpose of this study defined as a positivity of at least one inflammatory marker of the monitored CRP and PCT and a clinical decision to administer antibiotic treatment for a specified infection source.

Exclusion Criteria

The study respects all exclusion criteria for a blinded administration of propafenone or amiodarone. These are severe LV systolic dysfunction (i.e. EF<35%), a history indicating more than the 1st degree AV block and high dose vasopressor therapy represented by continuous noradrenaline administration of more than 1.0 ug/kg.min. Contraindications to randomisation are known intolerance to amiodarone or propafenone, iodine allergy and an active thyroid disease other than chronic hormone substitution for benign goiter. An interstitial pneumonia is not considered a contraindication to randomization with regards to delayed effects of amiodarone upon the lung parenchyma [27] and expected short period of its administration. Similarly, liver dysfunction is not a contraindication for amiodarone assuming a titrated short duration of the medication. Chronic persistant AF represents an exclusion while known chronic paroxysmal AF is not an exclusion criterion. Patients dependent on a pacemaker or after a Maze procedure are also excluded.

Interventions and research protocol

Screened patients will have a haemodynamic examination provided according to the study protocol. With the onset of arrhythmia, the usual treatment is expected including preload correction, reduction of unnecessary vasopressors, ion supplementation (aiming particularly for K^+ >4.0 mM and Mg^{2+} > 1.0 mM) and maintenance of tissue oxygen delivery. Echocardiography should also guide optimization of preload.

The complex protocol is formatted in an electronic case report form (CRF). After checking up the inclusion and exclusion criteria the CRF allocates the patients randomly using built in software (www.randomization.com) into the propafenone or amiodarone arm (Fig.3).

The patient´s characteristics include the illness severity scores, source of septic shock, data on mechanical ventilation and homeostasis, baseline haemodynamic data, baseline laboratory data, patient´s medications, haemodynamic data at proposed steps plus follow up data including outcome (Fig.4).

Haemodynamic evaluation includes ICU standard plus echocardiography (Fig.4). The study team involves 8 intensivists with a European Accreditation in Echocardiography (either ESC or EACTA backed) and three qualified cardiologists-intensivists.

By no means is an antiarrhythmic given out of the summary of product characteristics. Both arms will have standard treatment, there are no limits to electric cardioversion as part of the treatment which is indicated at anytime in haemodynamic compromise and in signs of low cardiac output or insufficient perfusion pressures due to arrhythmia.

The propafenone arm constitutes administering a bolus of 35-70 mg of intravenous propafenone followed by a continuous infusion of 400-840 mg/24h in a black syringe. The amiodarone arm constitutes administering a bolus of 150-300 mg of intravenous amiodarone followed by a continuous infusion of 600-1800 mg/24h in a black syringe.

A 12-lead ECG is taken every 12h whilst on the antiarrhythmic infusion. Besides echocardiography pre-randomization the control echocardiography is performed 1h post cardioversion and 4h post cardioversion. Echocardiography is also performed every day until cardioversion, it is also mandatory in any kind of haemodynamic instability. All the Doppler measurements are recorded at end-expiration and 3 cardiac cycles when in sinus rhythm and 5-10 during arrhythmia are analysed and averaged. All recordings should be acquired with an ECG (lead II), and ideally, at the speed of 100 mm/s.

If electrically cardioverted in addition to administered pharmacotherapy, then echocardiography is performed 1h post cardioversion and 4h post cardioversion.

If cardioverted later than within 24h after randomization then echocardiography is performed at 1h and 4h after cardioversion. The times of cardioversion and arrhythmia relapses are always recorded.

If a patient spontaneously cardioverts before the drug is administered, i.e. between randomization and drip initiation, the patient is monitored accordingly and included in the intention-to-treat analysis.

Primary outcome measures

1. The efficacy in restoration of sinus rhythm assessed as the proportion of patients who are in sinus rhythm 24 hours after the beginning of the infusion of the study drug and remain in sinus rhythm until discharge from ICU. The primary outcome will be assessed in all randomised patients (i.e. intention-to-treat analysis).
2. A-priori defined subgroup analysis: Primary outcome will be analysed in the following subgroups of patients:

a) with and without indexed left atrial endsystolic volume (LAVi) higher than >40 ml/m^2.
b) with and without pulmonary hypertension (defined as PAPs >40 mmHg) associated with moderate to severe RV dysfunction (dilated RV with TAPSE <15 mm)

Secondary outcome measures

1. The cumulative proportion of patients receiving rescue treatment for arrhythmia defined as direct current cardioversion or administration of an alternative antiarrhythmic drug during the first 24 hours (cross-over from one arm to the other resulting in unblinding of the study, e.g. from amiodarone to propafenone due to a persisting arrhythmia or from propafenone to amiodarone due to a decrease in LV systolic function).
2. The cumulative proportion of patients receiving rescue treatment for arrhythmia defined as direct current cardioversion, cross-over to the alternative study drug or another antiarrhythmic drug during ICU stay.
3. Mortality at discharge from ICU, at 28 days and at 1 year.

4. Vasopressor-free days at day 28.

Safety issues and patient´s monitoring

Besides cardioversion monitoring, TTE is also acquired in any kind of haemodynamic instability (i.e. change in vasopressor support). This is important to avoid administering a potentialy cardiodepressant propafenone in a patient developing septic cardiomyopathy. 12 hourly 12-lead ECG for the monitoring of conduction times (PQ, QRS, QTc) is performed while the patient is on the antiarrhythmic infusion. In case of an AV block of the first degree or extension of the conduction times (QRS or QTc) the slowing or temporary ceasing of the medication in relation to heart rate is mandatory. Adjustment of the infusion rate or eventual termination of an antiarrhythmic medication does not exclude the patient from the study. Cessation of medication after reaching sinus rhythm equally does not exclude the patient. If an infusion is interrupted and re-started then the number of infusion hours are counted up as a sum of infusion hours.

In case of progression of septic cardiomyopathy and a decrease of contractility (decrease of EFLV to <35%) or a progression of mitral regurgitation with a risk of low cardiac output the study drug is unblinded and propafenone discontinued. Further treatment is decided by the clinician. If the study is unblinded due to haemodynamic instability, the second drug after study arm cross-over is administered without an initial bolus.

Anytime the patient becomes haemodynamically unstable or has another reason (as per discretion of the treating clinician) to benefit from electric cardioversion (DCC), then DCC is delivered without delay.

Should there be a concern at any point in time about the safety of the drug, the treating clinicians are encouraged to unblind the treatment drug without delay and alter the treatment accordingly. The course of the trial is regularly reported to the hospital Ethical Board which acts as the research supervising body. The minimum frequency of the report is once per year throughout the duration of the trial which is proposed from 2018 till 2021.

Statistics and power analysis

All analysis will be conducted in R Core Team (2019) and will be available together with the raw data. Exploratory data analysis will be performed for both baseline and outcome parameters. Continuous parameters will be described as means and standard deviations and as medians and the interquartile ranges if not normally distributed. Log-normally distributed parameters will be logarithmically transformed if needed. Binary data will be described as counts and frequencies. Statistical significances of differences between groups will be described as odds ratio, hazard ratio or mean difference according to the type of analysis with 95% confidence interval. Both intention-to-treat and per protocol analysis will be performed.

The primary outcome (proportion of patients that have achieved rhythm control at 24 hours after the start of the infusion) will be analysed using logistic regression and time to event analysis (Cox regression).The secondary outcomes (proportion of patients that needed rescue treatments), recurrence of arrhythmias, ICU mortality, 28-day and 1-year mortality will be analysed using logistic regression. If significant differences in baseline characteristics are found between analysed groups then multivariate regression for adjustments to these variables will be performed.

The required number of patients is based on the power analysis and data from the pilot retrospective study [4 5]. The entry parameters for sample size analysis were estimated by the probabilities of cardioversion of 75% for the amiodarone group and 90% for the propafenone group within 24h from the onset of arrhythmia, randomisation ratio 1:1, p=0.05 and power 0.8. To achieve a statistically significant difference under these conditions 100 patients need to be included into each group, altogether 200 patients into the trial. Assuming 10% drop out the authors plan to randomize 220 patients.

Ethics approval and dissemination:

The local ethical approvals have been received from the Ethics Committee of the 1st Medical Faculty and General University Hospital (No. 1691/16 S-IV) and from the Ethics Committee of the 3rd Medical Faculty and University Hospital Kralovske Vinohrady. The written informed consent is sought from the patient´s next of kin. The results will be disseminated through peer reviewed publications and conference presentations. The study repository will be created with the dataset available after study completion. The recruitment has begun through the electronic case report form on the 23rd October 2017 and is expected to be completed in December 2021.

Patient and Public Involvement

Patients and public are not involved in the design and conduct of the study. The results of the trial will be disseminated to the involved patients and their next of kin upon their requests, which is offered during collection of the informed consents.

Limitations and conclusions

The available literature on SV arrhythmias in septic shock shows critically ill patients with a high predicted mortality, IPPV rate of 99% and high rates of CRRT (27-31%) [4 5]. Up to now all the authors adhered to the septic shock criteria based on volume non-responsive SIRS with a need for a vasopressor and antibiotic therapy administered for an infectious source [48]. Applying the novel septic shock criteria of 2016 [46] may increase specificity at the cost of lacking sensitivity to include even those who could potentially benefit from septic shock therapy [49]. If applying the results of the current trial to less severe patients, e.g. those

classified according to the older criteria, the SOFA score and a median arterial lactate level may serve as controls adjusting the studied population in context of the novel septic shock criteria published in 2016 [46].

The hypothesis that propafenone might be superior to amiodarone in cardioverting newly appearing SV arrhythmia with an impact on the long term outcome may not be proved due to the confounding factors of the retrospective study [4 5]. Albeit being statistically insignificant, LV systolic function was mildly higher in the propafenone and betablocker patients compared to those on amiodarone. The severe LV systolic dysfunctions were medicated with amiodarone, the same being applied to patients on a higher dosage of noradrenaline compared to the patients with moderate to mild LV systolic dysfunction and those with a lower dosage of noradrenaline in the propafenone and betablocker groups [4 5]. The retrospective study also included patients with a cross-over from an unsuccessful antiarrhythmic therapy to another group during 24 hours as part of the rhythm control strategy. This increased the pool of the propafenone patients after administering the agent in patients who were not able to cardiovert and maintain sinus rhythm on amiodarone [4 5]. This, so far, might represent an unreported synergistic effect of the two antiarrhythmic agents on achieving a high cardioversion rate, yet with a very acceptable safety profile [4 5]. The current prospective trial allows a cross-over between the arms however, only in a haemodynamic instability and with immediate unblinding.

The observed median age in an adult ICU varies around 55-65 years. The age related prevalence of hypertension and ischaemic heart disease suggests a large proportion of patients with a benefit of atrial systole and thus an indication for the rhythm control approach [7]. The prevalence of newly occuring SV arrhythmias and the broad spectrum of potentially reversible triggers in the critically ill offer an opportunity for cardioversion in closely monitored patients rather than in ambulatory patients in cardiology. Moreover, septic shock is often fraught with diastolic dysfunction and to restore sinus rhythm might be of paramout importance for the therapy of diastolic heart failure.

List of abbreviations: AF atrial fibrillation, APACHE II acute physiologic and chronic health evaluation, AV atrio-ventricular, CRRT continuous renal replacement therapy, CRP C reactive protein, DCC direct current cardioversion, DO2/VO2 oxygen delivery/oxygen consumption, EF ejection fraction, EF_LV ejection fraction of left ventricle, ICU intensive care unit, K+ plasmatic potassium, LA left atrium, LAVi indexed end-systolic left atrial volume, LV left ventricle/ left ventricular, LVOT left ventricular outflow tract, Mg2+ plasmatic magnesium, PAPs pulmonary artery systolic pressure, PCT procalcitonin, PRCT prospective controlled randomized trial, RV right ventricle, SIRS systemic inflammatory response syndrome, SOFA sequential organ function assessment, SR sinus rhythm, SV supraventricular, TAPSE tricuspid annular plane excursion, TTE transthoracic echocardiography, VTI velocity-time integral

Author Contributions

MB – study coordinator, concept and design, drafting, revisions and approval of articles, provision of funding. PW, FD – concept and design, electronic case report form, statistics, article revisions, data collection. MP,JR,MO,VM,MM,TB,RS,JP,PB,ES,MF,ZS,MS – data collection, article revisions. OS – article revisions, data collection, unblinded team coordination.

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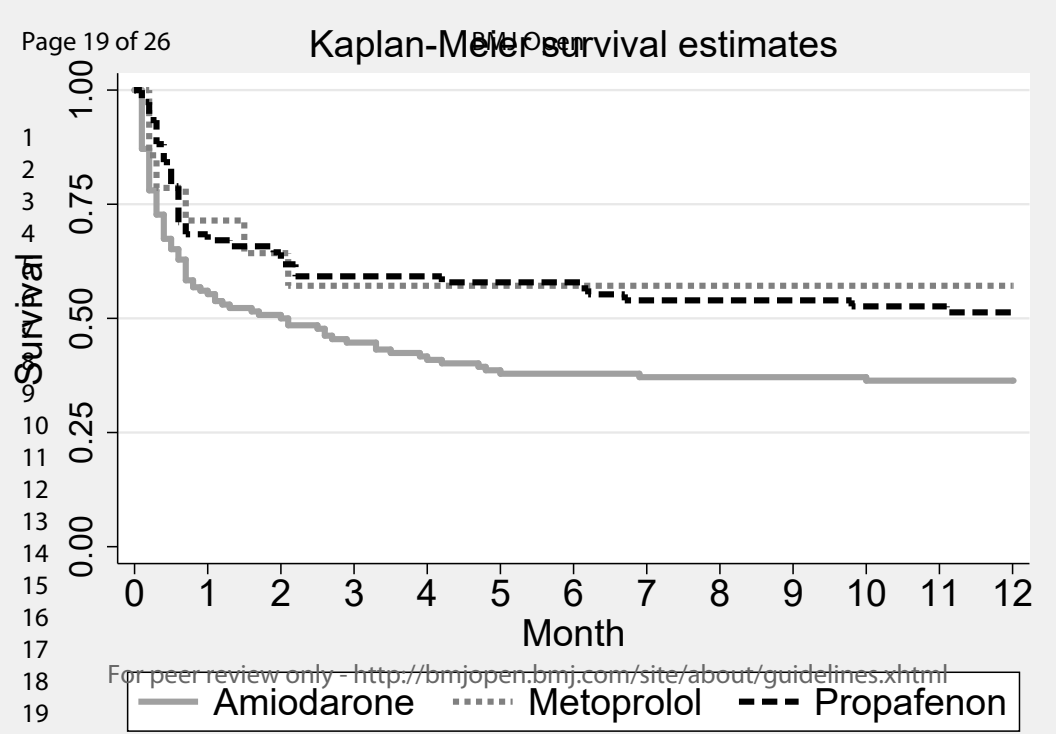
Legends to figures

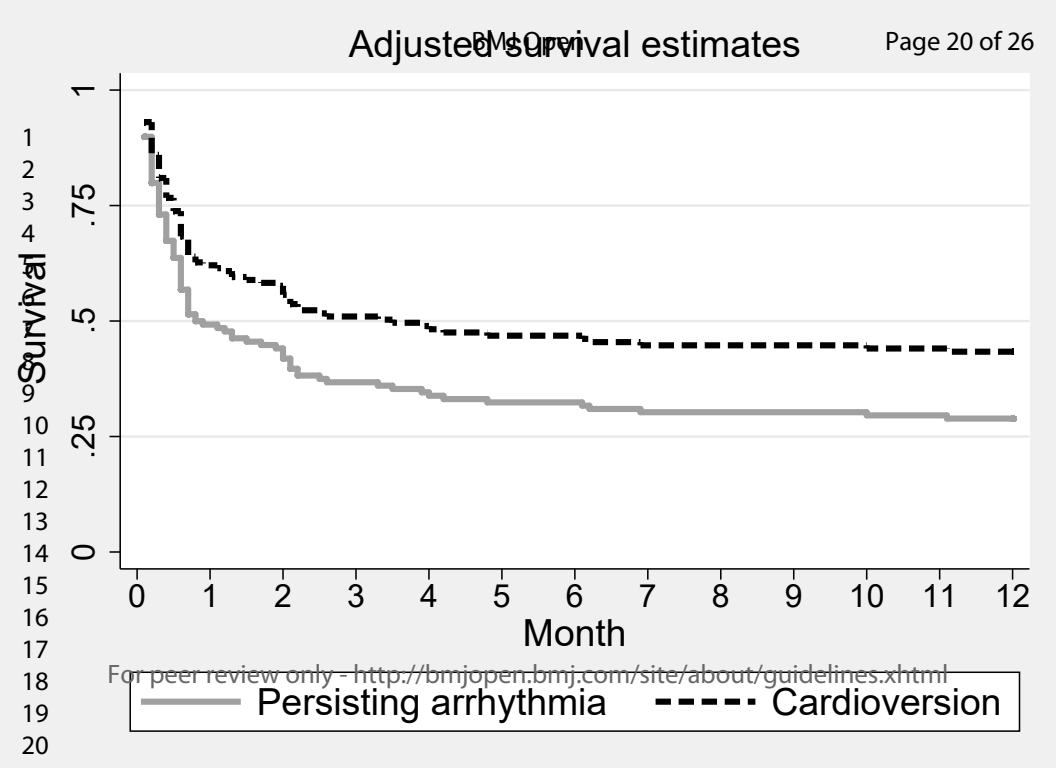
Fig.1: Univariate analysis showing long term survival of the propafenon patients similar to the metoprolol group and higher than in the amiodarone medicated patients in septic shock (HR1.76(1.06; 2.3),p=0.024). Copied from the author´s pilot retrospective study [4]

Fig.2: Multivariate analysis showing insignificant 12-month benefit in cardioverting septic shock patients to sinus rhythm (HR0.67,p=0.113). Copied from the author´s pilot retrospective study [4]

Fig.3: Flowchart of the study

Fig.4: SPIRIT table for the schedule of enrolment, interventions, and assessments





Flowchart of prospective randomized double blinded study of efficacy and safety of 1c class antiarrhythmic agent (propafenone) in septic shock

Acronym: PRASE – Propafenone versus amiodarone in septic shock

SV arythmia: AF, flutter, SVT…

1.) Sepsis and administration of noradrenaline due to hypotension non-responsive to correction of preload
2.) Elevation of arterial lactate >2.0 mmol/l during the course of disease, i.e. may be present before or during arrhythmia
3.) Positivity of at least one of the CRP or PCT
4.) Administration of antibiotics for an infectious source

Echocardiography: LV systolic function must be normal or mildly to moderately reduced

Exclusion Criteria:

- Severe LV systolic dysfunction
- More than 1st degree AV block
- High dose vasopressor therapy with continuous noradrenaline > 1.0 ug/kg.min
- Known intolerance to amiodarone or propafenone (incl. active thyroid disease other than chronic hormone substitution)
- Absence of septic shock
- Chronic AF - known chronic paroxysmal AF is not an exclusion criterion.
- Dependence on pacemaker
- Status after MAZE procedure
- Iodine allergy

Randomisation

Propafenone arm

Amiodarone arm

			STUDY PERIOD					
	Screening	Randomisation through electronic CRF	Visits			ICU outcome	28-days outcome	12m-outcome
TIMEPOINT	$-T_1$	0	T_{+1h}*	T_{+4h}*	T_x**			
Septic shock criteria JAMA 3/2016	X							
Informed consent	X							
Allocation		X						
12-lead ECG	X		X	X	X			
Transthoracic echocardiography (TTE)	X		X	X	X			
Hemodynamic assessment	X		X	X	X	X***	X***	X***
Laboratory data	X							
Concomitant medications	X							
INTERVENTIONS:								
Propafenone bolus		X						
Propafenone cont. infusion			X	X	X			
Amiodarone bolus		X						
Amiodarone cont. infusion			X	X	X			

*Visits: 12-lead ECG every 12h on infusion, TTE per 24h of arrhythmia and +1h after cardioversion, +4h after cardioversion, TTE in any instability

***Tx* – day on antiarrhythmic infusion

***Alive/dead, sinus/persistent arrhythmia

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	1, 2, 10
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	11,12
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 11
	5b	Name and contact information for the trial sponsor	12
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	12
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	2,10

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	____3,4,5_____
	6b	Explanation for choice of comparators	____3,4,5_____
Objectives	7	Specific objectives or hypotheses	____5, 6_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	____5, 6_____
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	____6_____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	____6, 7_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	____7, 8 , 9__
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	____7, 8, 9___
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	____7, 8, 9___
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	____7, 8, 9___
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	____8, 9_____
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	____7, 8, Fig.3, Fig.4

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	____2, 9, 10_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	____5,6,7,8____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	____7, 8, 9____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	____7, 8, 9____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	____7, 8, 9____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	____7, 8, 9____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	____7, 8, 9____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	____8, 9, 12___
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	____8, 9_____

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	____7,8,9,10_
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	____9,10_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	____5, 6, 7, 8, 9, _
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	____9,10_____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	____9, 10____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	____9, 10_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	____9, 10_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	____9, 10_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____10_____
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	_____2, 10 ___

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	11,12
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	2, 10
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	2,12
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	available upon request in Czech
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.