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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

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5	2	antiarrhythmic agent (propafenone) for supraventricular arrhythmias in septic
6 7	3	shock compared to amiodarone
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9	5	Acronym: PRASE – <u>Pr</u> opafenone versus <u>a</u> miodarone in <u>se</u> ptic shock
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2	1	Abstract
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5 6	-	Introduction: Supraventricular arrhythmias contribute to a haemodynamic compromise in
7	4	septic shock. A retrospective study generated the hypothesis that propatenone could be
8 9	5	more effective than amiodarone in achieving and maintaining sinus rhythm. The success of
10	6	cardioversion might be predicted by certain echocardiographic parameters, which can guide
11 12	7	the decision whether to aim for rhythm or rate control.
13	8	Methods and Analysis: The trial includes septic shock patients with new-onset arrhythmia.
14 15	9	but without severe impairment of the left ventricular ejection fraction. After baseline
15 16	10	echocardiography, the patient is randomised to receive a bolus and maintenance dose of
17	11	either amiodarone or propafenone. The primary outcome is the proportion of patients that
18 19	12	have achieved rhythm control at 24 hours after the start of the infusion. The secondary
20	13	outcomes are the percentages of patients that needed rescue treatments (DC cardioversion
21 22	14	or unblinding and cross over of the antiarrhythmics), recurrence of arrhythmias, ICU
22	15	mortality, 28-day and 1-year mortality. In the post-hoc analysis we separately assess
24	16	subgroups of patients with pulmonary hypertension and right ventricular dysfunction. In the
25 26	17	exploratory part of the study we assess whether the presence of a transmitral diastolic A
27	18	wave and its higher velocity-time integral is predictive for the sustainability of mechanical
28 29	19	sinus rhythm and whether the indexed left atrial endsystolic volume is predictive of
30	20	recurrent arrhythmia. Considering that the restoration of sinus rhythm within 24h occurred
31 22	21	in 74% of the amiodarone-treated patients and in 89% of patients treated with propafenone,
32 33	22	we plan to include 200 patients to have an 80% chance to demonstrate the superiority of
34	23	propafenone at p=0.05.
35 36	24	Ethics and Dissemination: The trial is recruiting patients according to its 2 nd protocol version
37	25	approved by the University Hospital Ethical Board on the 6 th October 2017. The results will be
38 39	26	disseminated through peer reviewed publications and conference presentations.
40	27	Trial registration: ClinicalTrials.gov Identifier: NCT03029169, registered on 24.1.2017
41 42	28	
42 43	29	
44	30	Key words: supraventricular arrhythmia, septic shock, propafenone, amiodarone, intensive
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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.

18 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 patients¹⁻³ which is in contrast to a lacking evidence that reverting back to sinus rhythm (SR) improves outcome 78. 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 60

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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 therapy⁶ 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}, intersticial 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 ⁴⁵ 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)⁴⁵. 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 ⁴⁵. 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

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1 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

4 been explored in the available literature. It seems that the degree of dependence of the left

- 5 ventricular filling on atrial systole would be an important entity when deciding between
- 6 rhythm and rate control in SV arrhythmia in septic critically ill patients. The rate control
- 7 modality should be reserved for a chronic persistant AF and in situations when sinus rhythm
- 8 is difficult to maintain due to high dosage of vasoactive agents.

10 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.

15 Primary aims

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The trial should prove that propafenone is more efficient than amiodarone in cardioverting a 16 SV arrhythmia in patients with normal to moderately reduced EF LV at 24h from the onset. 17 The rationale stems from the retrospective data set where the primary cardioversion rate of 18 SV arrhythmia under propafenone was 88.9% versus 73.5% under amiodarone ⁴⁵. The 19 20 authors also expect faster cardioversion under propafenone and lower rates of arrhythmia 21 recurrence in the propafenone group. Despite prejudices arising particularly from the CAST 22 trial and case reports on dose dependent toxicity, research should prove the safety of the 1C 23 class agent propafenone given within the summary of product characteristics ^{33 35}. The 24 retrospective study ⁴⁵ has shown that the ICU and 28-day mortalities of patients treated 25 with propafenone were better than the parameters of the amiodarone patients. In other 26 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 27 28 treated with propafenone had significantly better adjusted 12-month survival than the 29 critically ill treated with amiodarone (Fig.1). If proven, the physicians could avoid a 30 widespread use of amiodarone in the critically ill. 31 The cardioverted patients (rhythm control) may showcase better outcome parameters (ICU 32 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 ⁴⁵ which 33 34 also included patients with severe LV dysfunction and associated higher rates of recurrent SV 35 arrhythmias. Focusing on only normal to moderate LV systolic dysfunction may minimize bias 53 54 36 associated with arrhythmia treatment of patients with severe LV systolic dysfunction. 55 37 Likewise, those patients were included in the published trials dealing with either 1C class 56 antiarrhythmics (e.g. CAST trial,³²) or in the trials studying rhythm vs rate control (e.g. 57 38 58 AFFIRM, RACE or AF-CHF Trial,^{9 41-43}). Due to high success of rhythm control therapy (74.4%) 39 59 and 87% excluding chronic AF) in the retrospective study on 234 patients ⁴⁵, the group with 40 60

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3	1	persisting acute onset SV arrhythmia was significantly smaller in number causing an
4 5	2	asymmetry in statistic evaluation. This may also account for not signicantly better outcome
6	3	of the cardioverted versus those remaining in the SV arrhythmias (Fig.2).
7	4	
8 9	5	Secondary aims
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11 12	6	The presence of a transmitral diastolic A wave and its higher velocity-time integral (VTI) at 4h
13	7	post cardioversion would indicate a presence of mechanical sinus rhythm. A small or
14	8	negligible A wave may represent only the electric sinus in the absence of its mechanical
15 16	9	correlate. This finding could be related to the increased indexed left atrial end-systolic
17	10	volume (LAVi) and to a recurrence of a SV arrhythmia ^{44 45} . The LAVi in all patients and altered
18	11	filling pressures estimated by echocardiography could be predictive of the arrhythmia
19 20	12	recurrence ^{46 47} .
20	13	Propafenone would be more efficient than amiodarone in patients with pulmonary
22	14	hypertension and RV dysfunction without left ventricular systolic dysfunction.
23 24	15	A left ventricular relaxation disorder and a pseudonormal LV filling are more dependent on
25	16	atrial kick compared to the restrictive LV filling which is often accompanied by a dilated
26	17	poorly contracting left atrium. The classic stratification of diastolic dysfunction relates to
27 28	18	patient's prognosis in septic shock ⁴⁸ . Hence, a complex echo assessment may contribute to
29	19	the decision whether to aim for rhythm or for rate control only. The evaluation of the
30 21	20	doppler parameters will depend on rhythm, heart rate, regularity of arrhythmia and
32	 21	peripheral pulse deficit ^{44 46}
33	22	
34 35	22	Flow chart (Fig 3 Fig 4) and study setting
36	20	
37	24	Patients are randomized by the unblinded team lead by a research purse. The planned
38 39	25	number of included nations is 100 in each arm of the study with a total of 220 randomized
40	20	nations A dropout of 10% is anticipated. The estimated duration of the study is 4 years
41 42	22	including follow up. The patients have been recruited since November 2017 in three
43	20	university hospital ICUs. The department of Anaesthesia and Intensive Care of the General
44	20	University Hospital loss been performing for years as a teaching centre for critical care
45 46	21	echocardiography and ultrasound. Together with the Coronary Care Unit of the General
47	27	University Hespital both departments are integrated as a Compley Cardiovascular Control
48 40	52 22	The department of Apposthesia and Intensive Care of the University Hespital Vinebrady is a
49 50	33	me department of Anaestnesia and intensive care of the Oniversity Hospital Vinoniady is a
51	34	mainstay of the complex Prague Traumacentre.
52 53	35	
55	36	Inclusion Criteria
55	37	
56 57	38	The study targets patients in septic shock with a new onset SV arrhythmia or known
58	39	paroxysmal SV arrhythmia who show normal or mildly to moderately reduced LV systolic
59	40	function according to the echocardiography examination (i.e. EF_LV >/=35%). A diagnosis of
60		

1	septic shock is made according to the 2016 definition ⁴⁹ as sepsis with a vasopressor
2	requirement to maintain a mean arterial pressure of 65 mm Hg or greater. The arterial
3	lactate level should be greater than 2 mmol/L in the absence of hypovolemia or low cardiac
4	output. The highest arterial lactate level is recorded, i.e. lactate <2.0 mmol/l at the time of
5	randomization does not exclude a patient from the study. This might also be justified by the
6	reported incidence of the sensis related cardiac dysfunction which is highest 72-96h after an
7	onset of sentic shock ⁵⁰ The presence of a suspected infection is for the purpose of this
, Q	study defined as a positivity of at least one inflammatory marker of the monitored CRP and
0	PCT and a clinical decision to administer antibiotic treatment for a specified infection source
10	
10	Exclusion Critoria
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13	The study respects all exclusion criteria for a blinded administration of propafenone or
14	amiodarone. These are severe LV systolic dysfunction (i.e. EF<35%), a history indicating more
15	than 1 st degree AV block and a high dose vasopressor therapy represented by continuous
16	noradrenaline administration of more than 1.0 ug/kg.min. Contraindications to
17	randomisation are known intolerance to amiodarone or propafenone, iodine allergy and an
18	active thyroid disease other than chronic hormone substitution for benign goiter. Chronic
19	persistant AF represents an exclusion while known chronic paroxysmal AF is not an exclusion
20	criterion. Patients dependent on a pacemaker or after a Maze procedure are also excluded.
21	
22	Interventions and research protocol
23	
24	Patients will have a haemodynamic examination provided according to the study protocol.
25	With the onset of arrhythmia, the usual treatment is expected including preload correction.
26	reduction of unnecessary vasopressors, ion supplementation (aiming particularly for K ⁺ >4.0
27	mM and $Mg^{2+} > 1.0$ mM) and maintenance of tissue oxygen delivery. Echocardiography
28	should also guide optimization of preload.
29	The complex protocol is formatted in an electronic case report form (CRE). After checking up
30	the inclusion and exclusion criteria the CRF allocates the patients randomly using built in
31	software (www.randomization.com) into the propafenone or amiodarone arm.
32	The patient's characteristics include the illness severity scores, source of septic shock, data
33	on mechanical ventilation and homeostasis, baseline haemodynamic data, baseline
34	laboratory data, patient's medications, haemodynamic data at proposed steps plus follow up
35	data including outcome.
36	Haemodynamic evaluation includes ICU standard plus echocardiography. The study team
37	involves 8 intensivists with an European Accreditation in Echocardiography (either ESC or
38	EACTA backed) and three qualified cardiologists-intensivists.
39	By no means is an antiarrhythmic given out of the summary of product characteristics. Both
40	arms will have standard treatment, there are no limits to electric cardioversion as part of
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1 2		
2 3	1	treatment which is indicated anytime in haemodynamic compromise and in signs of low
4	2	cardiac output or not sufficient perfusion pressures due to arrhythmia
5 6	2	The propatence arm constitutes administering a bolus of 35-70 mg of intravenous
7	1	proparenone followed by a continuous infusion of $400-840$ mg/24h in a black syringe. The
8	5	amiodarone arm constitutes administering a bolus of 150-300 mg of intravenous
9 10	5	amiodarone followed by a continuous infusion of 600-1800 mg/24h in a black syringe
11	7	A 12-lead ECG is taken every 12b whilst the antiarrhythmic infusion. Besides
12 13	, Q	a 12-lead LCG is taken every 121 whilst the antiannything indusion. Desides
14	0	cardioversion and the post cardioversion. Echocardiography is performed also every day until
15 16	10	cardioversion and 4n post cardioversion. Echocardiography is performed also every day until
10	10	manufactory in any kind of nachodynamic instability. An the Doppler
18	11	F 10, during arrhythmia, are analysed and averaged. All recordings should be acquired with
19 20	12	an ECC (load II) and ideally at the speed of 100 mm/s
21	14	If electrically cardioverted in addition to administered pharmacethorapy, then
22	14	achecardiography is performed 1h post cardioversion and 4h post cardioversion
23 24	15	If cardioversion later than until 24b then echocardiographics are performed at 1b and 4b
25	10	after cardioverted later than until 2411 then echocardiographies are performed at 11 and 411
26 27	10	after cardioversion, the times of cardioversion and armythma relapses are always recorded.
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29	19	
30 31	20	Primary outcome measures
32	21	1 The office put in restauction of since whether account of the properties of restignts
33 34	22	1. The efficacy in restoration of sinus mythin assessed as the proportion of patients
35	23	who are in sinus mythin 24 hours after the beginning of the infusion of the study drug and
36	24	remain in sinus mythim until discharge from ICO. Primary outcome will be assessed in all
37 38	25	randomised patients (i.e. Intention to treat analysis).
39	26	2. A-priori defined subgroup analysis: Primary outcome will be analysed in the following
40 41	27	subgroups of patients:
42	28	a) with and without indexed left atrial endsystolic volume (LAVI) higher than >40 mi/m ² .
43	29	b) with and without pulmonary hypertension (defined as PAPs >40 mmHg) associated with
44 45	30	moderate to severe RV dysfunction (dilated RV with TAPSE <15 mm)
46	31	
47 49	32	
40 49	33	Secondary outcome measures
50	34	
51 52	35	1. The cumulative proportion of patients receiving rescue treatment for arrhythmia
53	36	defined as direct current cardioversion or an alternative antiarrhythmic drug during the first
54	37	24 nours (cross-over from one arm to the other resulting in unblinding of the study, e.g.
55 56	38	trom amiodarone to propatenone due to a persisting arrhythmia or from propatenone to
57	39	amiodarone due to a decrease in LV systolic function).
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3	1	2. The cumulative proportion of patients receiving rescue treatment for arrhythmia
4 5	2	defined as direct current cardioversion, cross-over to the alternative study drug or other
6	3	antiarrhythmic drug during ICU stay.
7	4	3. Mortality at discharge from ICU, at 28 days and at 1 year.
8 9	5	4. Vasopressor-free days at day 28.
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11 12	7	
13	8	Safety issues and patient's monitoring
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15 16	10	Besides cardioversion monitoring the TTE is also acquired in any kind of haemodynamic
17	11	instability (i.e. change in vasopressor support). This is important to avoid administering a
18 10	12	potentialy cardiodepressant propafenone in a patient developing septic cardiomyopathy. 12
20	13	hourly 12-lead ECG for monitoring of conduction times (PQ, QRS, QTc) is performed while
21	14	the patient is on the antiarrhythmic infusion. In case of an AV block of the first degree or
22	15	extension of the conduction times (ORS or OTc) the slowing or temporary ceasing of the
24	16	medication in relation to heart rate is mandatory. Adjustment of the infusion rate or
25 26	17	eventual termination of an antiarrhythmic medication does not exclude the patient from the
20 27	18	study. Ceasing of medication after reaching sinus rhythm does not exclude the patient too. If
28	-0 19	an infusion is interrupted and restarted then the number of infusion hours are counted up as
29 30	20	a sum of infusion hours.
31	21	In case of a progression of septic cardiomyopathy and a decrease of contractility (decrease
32	22	of FELV to $<35\%$) or a progression of mitral regurgitation with a risk of low cardiac output the
33 34	23	study drug is unblinded and propatenone discontinued. Further treatment is decided by the
35	24	clinician. If the study is unblinded due to haemodynamic instability, the second drug after
36 37	25	study arm cross-over is administered without an initial bolus.
38	26	Anytime the patient becomes baemodynamically unstable or has another reason (as per
39 40	27	discretion of the treating clinician) to benefit from electric cardioversion (DCC), then DCC is
40 41	28	delivered without delay.
42	29	Should there be a concern at any point in time about the safety of the drug, the treating
43 44	30	clinicians are encouraged to unblind the treatment drug without delay, and alter the
45	31	treatment accordingly. The course of the trial is regularly reported to the hospital Ethical
46 47	32	Board which acts as the research supervising body. The minimum frequency of the report is
47	33	once per vear throughout the duration of the trial which is proposed from 2018 till 2021
49	34	
50 51	35	Statistics and nower analysis
52	36	
53	37	The logistic regression and time-to-event (Cox) regression with and without adjustment for
54 55	20	haseline nations' characteristics will be applied in the statistic analysis. The multivariate
56	30	analysis will include the nationts' haseline narameters which would be correlated with an
57 58	۸U	analysis with include the patients' baseline parameters which would be correlated with all
59 60	40	analysed outcome parameter and will be innomogenously distributed within the study

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2 3	1	groups regardless of the randomisation. The required number of natients is based on the
4	2	nower analysis and data from the nilot retrospective study ⁴⁵
5 6	2	The entry parameters for the sample size analysis were estimated by the probabilities of
7	2	cardioversion of 75% for the amiodarone group and 00% for the propationer group within
8	4	Cardioversion of 75% for the annouarone group and 90% for the propatenone group within
9 10	5	24h from the onset of arrhythmia, randomisation ratio 1:1, $p=0.05$ and power 0.8. To
11	6	achieve a statistically significant difference under these conditions 100 patients need to be
12	7	included into each group, altogether 200 patients into the trial. Assuming 10% drop out the
13 14	8	authors plan to randomize 220 patients.
14	9	
16	10	Ethics approval and dissemination:
17	11	
10	12	The local ethical approvals have been received from the Ethics Committee of the 1 st Medical
20	13	Faculty and General University Hospital (No. 1691/16 S-IV) and from the Ethics Committee of
21	14	the 3 rd Medical Faculty and University Hospital Kralovske Vinohrady. The written informed
22	15	consent is sought from the patient's next of kin. The results will be disseminated through
24	16	peer reviewed publications and conference presentations. The study repository will be
25 26	17	created with the dataset available after study completion. The recruitment has begun
20	18	through the electronic case report form on the 23^{rd} October 2017 and is expected to be
28	19	completed in December 2021
29	20	
31	20	Limitations and conclusions
32	21	
33 34	22	The available literature on SV arrhythmias in centre shock shows critically ill patients with a
35	23	high mandiable interactive UDDV rate of 000% and high maters of CDDT (27, 210%) 45. Up to normally
36	24	high predicted mortality, IPPV rate of 99% and high rates of CRRT (27-31%) ¹⁹ . Op to now an
37 38	25	the authors adhered to the septic shock criteria based on volume non-responsive SIRS with a
39	26	need for a vasopressor and antibiotic therapy administered for an infectious source ⁵¹ .
40	27	Applying the novel septic shock criteria of 2016 ⁴⁹ may increase specificity at the cost of
41 42	28	lacking sensitivity to include even those who could potentially benefit from septic shock
43	29	therapy 52 . If applying the results of the current trial to less severe patients, e.g. those
44	30	classified according to the older criteria, the SOFA score and a median arterial lactate level
45 46	31	may serve as controls adjusting studied population in context of the novel septic shock
47	32	criteria published in 2016 ⁴⁹ .
48	33	The hypothesis that propafenone might be superior to amiodarone in cardioverting newly
49 50	34	appearing SV arrhythmia with an impact on the long term outcome may not be proved due
51	35	to the confounding factors of the retrospective study ⁴⁵ . Albeit being statistically
52	36	insignificant, the LV systolic function was mildly higher in propafenone and betablocker
53 54	37	patients compared to those on amiodarone. The severe LV systolic dysfunctions were
55	38	medicated with amiodarone as well as patients on a higher dosage of noradrenaline
56	39	compared to the patients with moderate to mild LV systolic dysfunction and the lower
57 58	40	dosage of noradrenaline in the propafenone and betablocker groups ⁴⁵
59	40	assabe of nordarename in the proparenone and betablocker groups .
60		

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 45. 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 ⁴⁵. 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.

38
 37
 39 Funding

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10	5	This sponsor did not have any role in study design, collection, analysis and interpretation of
11 12	6	the data, in the writing of the paper and in the decision to submit the article for publication.
12	7	
14 15	8	Competing interests: None
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o 9	4	
10	5	Fig 1 . Univariate analysis showing long term survival of the propagenon patients similar to
11 12	5	the metaprolol group and higher than in the amindarone medicated patients in sentic shock
12	7	(IIII) $7c(1,06,2,2)$ n=0.024). Conside from the author's nilet retrasportive study ⁴
14	/	(HR1.76(1.06; 2.3),p=0.024). Copied from the author's phot retrospective study
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16	9	Fig.2: Multivariate analysis showing insignificant 12-month benefit in cardioverting septic
18	10	shock patients to sinus rhythm (HR0.67.p=0.113). Copied from the author's pilot
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23	13	Fig.3: Flowchart of the study
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27 28	15	Fig.4: SPIRIT table for the schedule of enrolment, interventions, and assessments
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Adjusted MsQrvival estimates Page 20 of 26



Page 21 of 26 Flowchart of prospective randomized double blinded study of efficacy and safety of 1c class antiarrhythmic agent (propafenone) in septic shock



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3 3 3 3 4 4 4 4 4 4 4 4 4 5 5 5 5	5678901234567890123
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			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	Х							
Informed consent	х							
Allocation		Х						
12-lead ECG	х		х	Х	Х			
Transthoracic echocardiography (TTE)	х	QR	х	х	х			
Hemodynamic assessment	х	9	х	х	Х	X***	X***	X***
Laboratory data	х							
Concomitant medications	Х		C					
INTERVENTIONS:				N				
Propafenone bolus		х		2				
Propafenone cont. infusion			Х	х	Х			
Amiodarone bolus		х						
Amiodarone cont. infusion			Х	Х	х	1		

*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

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

Section/item	ltem No	Description	Addressed on page number
Administrative inf	ormatior		
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	5a	Names, affiliations, and roles of protocol contributors	1, 11
responsibilities	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
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1	Introduction			
3 4 5	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
6 7		6b	Explanation for choice of comparators	3,4,5
8 9	Objectives	7	Specific objectives or hypotheses	5, 6
10 11 12 13	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
14 15	Methods: Participa	nts, inte	erventions, and outcomes	
16 17 18	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
19 20 21	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
22 23 24	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7, 8 , 9
23 26 27 28		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
29 30 31		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7, 8, 9
32 33		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7, 8, 9
34 35 36 37 38	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
40 41 42	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
43 44 45			For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

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1 2	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
3 4 5	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	5,6,7,8
6 7	Methods: Assignm	ent of i	nterventions (for controlled trials)	
8 9	Allocation:			
10 11 12 13 14	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
16 17 18 19	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
20 21 22	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to	7, 8, 9
23 24 25 26	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
26 27 28 29		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's	7, 8, 9
30 31	Methods: Data coll	ection,	management, and analysis	
32 33 34 35 36 37 38 39 40 41	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
42 43 44 45 46			For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	3

1 2 3 4	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_
5 6 7	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
8 9		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	5, 6, 7, 8, 9, _
10 11 12 13		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
14 15	Methods: Monitorir	ng		
16 17 18 19 20	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
21 22 23 24		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
25 26 27	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
28 29 30	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
31 32	Ethics and dissemi	ination		
33 34 35 36	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	10
37 38 39 40 41	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
42 43 44 45			For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	4

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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	i.
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 recomm Amendments to the p "Attribution-NonComr	nended protocol mercial-	that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarifica should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Cc -NoDerivs 3.0 Unported" license.	ation on the items. ommons	
		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml		5

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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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Manuscript ID	bmjopen-2019-031678.R1
Article Type:	Protocol
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Secondary Subject Heading: C	ardiovascular medicine, Anaesthesia, Infectious diseases
Keywords: A	dult intensive & critical care < ANAESTHETICS, Echocardiography ARDIOLOGY, Pacing & electrophysiology < CARDIOLOGY
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	Manuscripts

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3 4	1	Efficacy and safety of 1c class antiarrhythmic agent (propafenone) for
5	2	supraventricular arrhythmias in septic shock compared to amiodarone:
6 7	3	protocol of a prospective randomized double-blind study
/ 8	4	
9	5	Acronym: PRASE – <u>Pr</u> opafenone versus <u>a</u> miodarone in <u>se</u> ptic shock
10	6	
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36	~ .	
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39	25	Abstract: 297 words
40	25	
41	26	Body of the text: 3979 words
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43	27	ClinicalTrials.gov Identifier: NCT03029169
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1 ว		
2	1	Abstract
4 5	2	
5 6	- 3	Introduction: Supraventricular arrhythmias contribute to baemodynamic compromise in
7	<u>л</u>	sentic shock A retrospective study generated the hypothesis that propatenone could be
8 9	5	more effective than amiodarone in achieving and maintaining sinus rhythm. Certain
10	6	echocardiographic parameters may predict a successful cardioversion and help in the
11	7	decision on rhythm or rate control strategy
12	, 8	Methods and Analysis: The trial includes sentic shock nations with new-onset arrhythmia
14	q	but without severe impairment of the left ventricular ejection fraction. After baseline
15 16	10	echocardiography, the patient is randomized to receive a holus and maintenance dose of
17	11	either amindarone or propatenone. The primary outcome is the proportion of patients that
18 10	12	have achieved rhythm control at 24 hours after the start of the infusion. The secondary
20	12	outcomes are the percentages of patients that peeded rescue treatments (DC cardioversion
21	1/	or unblinding and cross over of the antiarrhythmics) the recurrence of arrhythmias ICU
22 23	14	mortality 28-day and 1-year mortality. In the nost-hoc analysis we senarately assess
24	16	subgroups of patients with pulmonary hypertension and right ventricular dysfunction. In the
25 26	10	exploratory part of the study we assess whether the presence of a transmitral diastolic A
20 27	18	wave and its higher velocity-time integral is predictive for the sustainability of mechanical
28	10	sinus rhythm and whether the indexed left atrial endsystolic volume is predictive of
29 30	20	recurrent arrhythmia. Considering that the restoration of sinus rhythm within 24h occurred
31	20	in 74% of the amiodarone-treated natients and in 89% of the natients treated with
32 33	21	propatenone, we plan to include 200 patients to have an 80% chance to demonstrate the
33 34	22	superiority of propatenone at $n=0.05$
35	23	Ethics and Dissemination: The trial is recruiting nations according to its 2 nd protocol version
36 37	24	approved by the University Hospital Ethical Board on the 6 th October 2017 (No 1691/16S-IV)
38	25	The results will be disseminated through peer reviewed publications and conference
39 40	20	nresentations
41	28	Trial registration: Clinical Trials gov Identifier: NCT03029169 registered on 24.1.2017
42	20	
43 44	30	
45	31	Key words: supraventricular arrhythmia, septic shock, propafenone, amiodarone, intensive
46 47	32	care
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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 ⁷⁸. 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.

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2 3	1	Particularly the severe LV systolic dysfunction and conduction disorders should be excluded
4	2	prior to beta-blocker administration in the sentic shock patients ^{13 15} .
5 6	3	The mainstay of antiarrhythmic therapy ⁶ is represented by amiodarone which is preferred
7	4	for its lower cardiodepressant side effect compared to other agents and electric
8 9	5	cardioversion ¹⁶⁻¹⁹ . Extensive use of amiodarone contrasts with its multiorgan side effects
10	6	and its application even in patients with normal LV systolic function ^{20 21} demonstrates poor
11 12	7	compliance with current guidelines 22 . Hypotension may occur due to amiodarone's
12	8	vasodilatatory effects and OTc prolongation associates with the occurrence of torsades-des-
14	9	pointes type of ventricular tachycardia. In the long term administration the adverse effects
15 16	10	involve particularly thyroid function 23 , hepatic dysfunction 24 , interstitial pneumonia and
17	11	pulmonary fibrosis ²⁵⁻²⁷ .
18 10	12	The use of 1C agents has been discouraged by studies describing poor outcome during long
20	13	term administration in the cardiology population ²⁸ . Few available case reports demonstrate
21	14	serious adverse effects apparently related to the dose related cardiotoxicity ²⁸⁻³⁰ .
22	15	Consequently, 1C class agents like propafenone and flecainide ³¹ , are scarcely used in the
24	16	critically ill. In contrast to flecainide and encainide, propafenone is derived from
25 26	17	propandiolamine, which is a chemical compound of betablockers and acts on the rapid
27	18	depolarizing phase (phase 0) and also, to a minimal extent, on beta-adrenergic receptors ³²⁻
28 20	19	³⁴ . Compared to flecainide, propafenone also lacks any evidence of its relationship to
30	20	mortality ³⁵ .
31 22	21	Our retrospective study ⁴⁵ suggests that propafenone might be feasible to restore SR
32 33	22	without an adverse effect on haemodynamics and with a possible benefit on the outcome of
34	•	the septic shock patients (Fig.1) ⁴⁵ . A chance to cardiovert seemed to be significantly higher
25	23	
35 36	23 24	under propafenone than in amiodarone and was close to the cardioversion rates of the
35 36 37	23 24 25	under propafenone than in amiodarone and was close to the cardioversion rates of the betablocker metoprolol. No secondary arrhythmias or conduction disorders requiring
35 36 37 38 39	23 24 25 26	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 ⁴⁵ . Another recent
35 36 37 38 39 40	23 24 25 26 27	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 ⁴⁵ . Another recent retrospective study found faster and more succesful cardioversion with propafenone as
35 36 37 38 39 40 41	23 24 25 26 27 28	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 ⁴⁵ . 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
35 36 37 38 39 40 41 42 43	23 24 25 26 27 28 29	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 ⁴⁵ . 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 .
35 36 37 38 39 40 41 42 43 44	23 24 25 26 27 28 29 30	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 ⁴⁵ . 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
35 36 37 38 39 40 41 42 43 44 45 46	23 24 25 26 27 28 29 30 31	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 ⁴⁵ . 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
35 36 37 38 39 40 41 42 43 44 45 46 47	23 24 25 26 27 28 29 30 31 32	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 ⁴⁵ . 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
35 36 37 38 39 40 41 42 43 44 45 46 47 48 49	23 24 25 26 27 28 29 30 31 32 33	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
35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50	23 24 25 26 27 28 29 30 31 32 33 34	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
35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51	23 24 25 26 27 28 29 30 31 32 33 34 35	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 ⁴⁵ . 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
35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53	23 24 25 26 27 28 29 30 31 32 33 34 35 36	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 ⁴⁵ . 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
 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 	23 24 25 26 27 28 29 30 31 32 33 34 35 36 37	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 .
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1 We designed a prospective double blinded randomized trial comparing propafenone to

2 amiodarone administered for a SV arrhythmia in critically ill patients with septic shock.

4 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 ⁴⁵. 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 ⁴⁵ 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 ⁴⁵ 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 ⁴⁵, 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).

52 35 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 arrhythmia⁴¹⁴². The LAVi in all patients and altered

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1 2		
3	1	filling pressures estimated by echocardiography could be predictive of arrhythmia
4 5	2	recurrence ^{43 44} .
6	3	Propafenone could be more efficient than amiodarone in patients with pulmonary
7	4	hypertension and RV dysfunction without left ventricular systolic dysfunction.
8 9	5	A left ventricular relaxation disorder and a pseudonormal LV filling are more dependent on
10	6	the atrial kick compared to the restrictive LV filling which is often accompanied by a dilated
11 12	7	poorly contracting left atrium. The classic stratification of diastolic dysfunction relates to the
13	8	patient's prognosis in septic shock ⁴⁵ . Hence, a complex echo assessment may contribute to
14 15	9	the decision whether to aim for rhythm or for rate control only. Evaluation of the doppler
16	10	parameters will depend on rhythm, heart rate, regularity of arrhythmia and peripheral pulse
17 19	11	deficit ^{41 43} .
19	12	
20	13	Flow chart and study setting
21 22	14	
23	15	Patients are randomized by the unblinded team lead by a research nurse. The planned
24 25	16	number of included patients is 100 in each arm of the study with a total of 220 randomized
26	17	patients. A dropout of 10% is anticipated. The estimated duration of the study is 4 years
27	18	including follow up. The patients have been recruited since November 2017 in three
28 29	19	university hospital ICUs. The department of Anaesthesia and Intensive Care of the General
30	20	University Hospital has been performing for years as a teaching centre for critical care
31 32	21	echocardiography and ultrasound. Together with the Coronary Care Unit of the General
33	22	University Hospital both departments are integrated as a Complex Cardiovascular Centre.
34 25	23	The department of Anaesthesia and Intensive Care of the University Hospital Vinohrady is a
35 36	24	mainstay of the Complex Prague Traumacentre.
37	25	
38 39	26	Inclusion Criteria
40	27	
41 42	28	The study targets adult patients (16-85 years) in septic shock with a new onset SV
43	29	arrhythmia or known paroxysmal SV arrhythmia who show normal or mildly to moderately
44 45	30	reduced LV systolic function according to the echocardiography examination (i.e. EF_LV
45 46	31	>/=35%)(Fig.3). A diagnosis of septic shock is made according to the 2016 definition ⁴⁶ as
47	32	sepsis with a vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg or
48 49	33	greater. The arterial lactate level should be greater than 2 mmol/L in the absence of
50	34	hypovolemia or low cardiac output. The highest arterial lactate level is recorded, i.e. lactate
51 52	35	<2.0 mmol/l at the time of randomization does not exclude a patient from the study. This
53	36	might also be justified by the reported incidence of sepsis related cardiac dysfunction which
54	37	is highest 72-96h after the onset of septic shock ⁴⁷ . The presence of a suspected infection is
55 56	38	for the purpose of this study defined as a positivity of at least one inflammatory marker of
57	39	the monitored CRP and PCT and a clinical decision to administer antibiotic treatment for a
58 50	40	specified infection source.
60	41	

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 parenchyma²⁷ 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 $K^+ > 4.0 \text{ mM}$ and $Mg^{2+} > 1.0 \text{ mM}$) 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.

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2		
3	1	A 12-lead ECG is taken every 12h whilst on the antiarrhythmic infusion. Besides
4 5	2	echocardiography pre-randomization the control echocardiography is performed 1h post
6	3	cardioversion and 4h post cardioversion. Echocardiography is also performed every day until
7	4	cardioversion, it is also mandatory in any kind of haemodynamic instability. All the Doppler
o 9	5	measurements are recorded at end-expiration and 3 cardiac cycles when in sinus rhythm and
10	6	5-10 during arrhythmia are analysed and averaged. All recordings should be acquired with an
11 12	7	ECG (lead II), and ideally, at the speed of 100 mm/s.
13	8	If electrically cardioverted in addition to administered pharmacotherapy, then
14	9	echocardiography is performed 1h post cardioversion and 4h post cardioversion.
15 16	10	If cardioverted later than within 24h after randomization then echocardiography is
17	11	performed at 1h and 4h after cardioversion. The times of cardioversion and arrhythmia
18 10	12	relapses are always recorded.
20	13	If a patient spontaneously cardioverts before the drug is administered, i.e. between
21	14	randomization and drip initiation, the patient is monitored accordingly and included in the
22 23	15	intention-to-treat analysis
24	16	
25	17	
26 27	18	Primary outcome measures
28	10	
29 30	20	1 The efficacy in restoration of sinus roythm assessed as the proportion of nationts
31	20	who are in sinus rhythm 24 hours after the beginning of the infusion of the study drug and
32	21	remain in sinus rhythm until discharge from ICU. The primary outcome will be assessed in all
33 34	22	randomised nations (i.e. intention-to-treat analysis)
35	23	A priori defined subgroup analysis: Primany outcome will be analysed in the following
36 27	24	2. A-phon defined subgroup analysis. Frinary outcome will be analysed in the following subgroups of patients:
37 38	25	subgroups of patients. a) with and without indexed left atrial and vetalic volume (IAVi) higher than >40 ml/m ²
39	20	a) with and without nulmonany hyportension (defined as PAPs >40 mmHg) associated with
40 41	27	b) with and without pullionary hypertension (defined as PAPS 240 mining) associated with moderate to covere BV dycfunction (dilated BV with TABSE <15 mm)
42	28	moderate to severe RV dystunction (dilated RV with TAPSE <15 mm)
43	29	
44 45	30	
46	31	Secondary outcome measures
47 49	32	
40 49	33	1. The cumulative proportion of patients receiving rescue treatment for arrhythmia
50	34	defined as direct current cardioversion or administration of an alternative antiarrhythmic
51 52	35	drug during the first 24 hours (cross-over from one arm to the other resulting in unblinding
53	36	of the study, e.g. from amiodarone to propatenone due to a persisting arrhythmia or from
54	37	propatenone to amiodarone due to a decrease in LV systolic function).
55 56	38	2. The cumulative proportion of patients receiving rescue treatment for arrhythmia
57	39	defined as direct current cardioversion, cross-over to the alternative study drug or another
58 59	40	antiarrhythmic drug during ICU stay.
60	41	3. Mortality at discharge from ICU, at 28 days and at 1 year.

4. 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.

Vasopressor-free days at day 28.

Safety issues and patient's monitoring

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1		
2 3	1	The primary outcome (properties of patients that have achieved shuther control at 24 hours
4	1 2	after the start of the infusion) will be analyzed using logistic regression and time to event
5	2	ander the start of the infusion) will be analysed using logistic regression and time to event
7	3	analysis (Cox regression). The secondary outcomes (proportion of patients that needed
8	4	rescue treatments), recurrence of arrhythmias, ICO mortality, 28-day and 1-year mortality
9 10	5	will be analysed using logistic regression. If significant differences in baseline characteristics
10	6	are found between analysed groups then multivariate regression for adjustments to these
12	7	variables will be performed.
13 14	8	The required number of patients is based on the power analysis and data from the pilot
15	9	retrospective study ⁴⁵ . The entry parameters for sample size analysis were estimated by the
16	10	probabilities of cardioversion of 75% for the amiodarone group and 90% for the
17 18	11	propafenone group within 24h from the onset of arrhythmia, randomisation ratio 1:1,
19	12	p=0.05 and power 0.8. To achieve a statistically significant difference under these conditions
20	13	100 patients need to be included into each group, altogether 200 patients into the trial.
21 22	14	Assuming 10% drop out the authors plan to randomize 220 patients.
23	15	
24	16	Ethics approval and dissemination:
25 26	17	
27	18	The local ethical approvals have been received from the Ethics Committee of the 1 st Medical
28	19	Faculty and General University Hospital (No. 1691/16 S-IV) and from the Ethics Committee of
29 30	20	the 3 rd Medical Faculty and University Hospital Kralovske Vinohrady. The written informed
31	21	consent is sought from the patient's next of kin. The results will be disseminated through
32 33	22	peer reviewed publications and conference presentations. The study repository will be
34	23	created with the dataset available after study completion. The recruitment has begun
35	24	through the electronic case report form on the 23 rd October 2017 and is expected to be
36 37	25	completed in December 2021.
38	26	
39	20	Patient and Public Involvement
40 41	27	
42	20	Patients and public are not involved in the design and conduct of the study. The results of
43	29	the trial will be discominated to the involved nationts and their payt of kin upon their
44 45	30	the trial will be disseminated to the involved patients and their next of kin upon their
46	31	requests, which is offered during collection of the informed consents.
47	32	
40 49	33	Limitations and conclusions
50	34	
51 52	35	The available literature on SV arrhythmias in septic shock shows critically ill patients with a
52 53	36	high predicted mortality, IPPV rate of 99% and high rates of CRRT (27-31%) ⁴⁵ . Up to now all
54	37	the authors adhered to the septic shock criteria based on volume non-responsive SIRS with a
55 56	38	need for a vasopressor and antibiotic therapy administered for an infectious source ⁴⁸ .
57	39	Applying the novel septic shock criteria of 2016 ⁴⁶ may increase specificity at the cost of
58	40	lacking sensitivity to include even those who could potentially benefit from septic shock
59 60	41	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 2016⁴⁶. 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 ⁴⁵. 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 ⁴⁵. 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 ⁴⁵. 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 ⁴⁵. 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

1		
2 3	1	Author Contributions
4	T	
5	2	MB – study coordinator, concept and design, drafting, revisions and approval of articles,
7	3	provision of funding. PW, FD – concept and design, electronic case report form, statistics,
8	4	article revisions, data collection. MP,JR,MO,VM,MM,TB,RS,JP,PB,ES,MF,ZS,MS – data
9 10	5	collection, article revisions, OS – article revisions, data collection, unblinded team
10	6	coordination
12	7	
13	,	
14	0	Funding
16	9	Funding
17	10	
18 19	11	The protocol has received a four year (2018-2022) grant support from the Czech Health
20	12	Research Council, AZV No.NV18-06-00417, commencing on the 1 st of May 2018.
21	10	
22 23	13	
24	14	Competing interests: None
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7 8	3	Legends to figures
9	4	
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11 12	6	the metoprolol group and higher than in the amiodarone medicated patients in sentic shock
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17	9	Fig.2: Multivariate analysis showing insignificant 12-month benefit in cardioverting septic
18	10	shock patients to sinus rhythm (HR0.67,p=0.113). Copied from the author's pilot
19 20	11	retrospective study 4
21	12	
22	12	Fig 2: Elowchart of the study
23 24	15	rig.3. Howenalt of the study
25	14	
26 27	15	Fig.4: SPIRIT table for the schedule of enrolment, interventions, and assessments
28	16	
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Adjusted MsQrvival estimates Page 20 of 26



Page 21 of 26 Flowchart of prospective randomized double blinded study of efficacy and safety of 1c class antiarrhythmic agent (propafenone) in septic shock



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			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	Х							
Informed consent	х							
Allocation		х						
12-lead ECG	х		х	Х	Х			
Transthoracic echocardiography (TTE)	х	Q	х	х	х			
Hemodynamic assessment	х	9	х	х	Х	X***	X***	X***
Laboratory data	х							
Concomitant medications	Х		C					
INTERVENTIONS:				N				
Propafenone bolus		х		2				
Propafenone cont. infusion			Х	х	x			
Amiodarone bolus		Х						
Amiodarone cont. infusion			х	Х	х	1		

*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

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

Section/item	ltem No	Description	Addressed on page number
Administrative inf	ormatior		
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	5a	Names, affiliations, and roles of protocol contributors	1, 11
responsibilities	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
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1	Introduction			
3 4 5	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
6 7		6b	Explanation for choice of comparators	3,4,5
8 9	Objectives	7	Specific objectives or hypotheses	5, 6
10 11 12 13	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
14 15	Methods: Participa	nts, inte	erventions, and outcomes	
16 17 18	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
19 20 21	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
22 23 24	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7, 8 , 9
23 26 27 28		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
29 30 31		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7, 8, 9
32 33		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7, 8, 9
34 35 36 37 38	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
40 41 42	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
43 44 45			For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

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1 2	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
3 4 5	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	5,6,7,8
6 7	Methods: Assignm	ent of i	nterventions (for controlled trials)	
8 9	Allocation:			
10 11 12 13 14 15	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
16 17 18 19	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
20 21 22	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7, 8, 9
23 24 25 26 27 28 29	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
30 31	Methods: Data coll	ection,	management, and analysis	
32 33 34 35 36 37 38 39 40 41 42 43 44 45 46	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
			For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	3

1 2 3 4	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_
5 6 7	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
8 9		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	5, 6, 7, 8, 9, _
10 11 12 13		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
14 15	Methods: Monitorir	ng		
16 17 18 19 20	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
21 22 23 24		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
25 26 27	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
28 29 30	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
31 32	Ethics and dissemi	ination		
33 34 35 36	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	10
37 38 39 40 41	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
42 43 44 45			For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	4

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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	i.
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 recomm Amendments to the p "Attribution-NonComr	nended protocol mercial-	that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarifica should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Cc -NoDerivs 3.0 Unported" license.	ation on the items. ommons	
		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml		5