STUDY PROTOCOL

Ivabradine in the Acute Management of Cardiogenic Shock - IVASHOCK - A Double-Blind Randomized Controlled Trial

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NICVD
NATIONAL INSTITUTE OF CARDIOVASCULAR DISEASES

Ivabradine in the Acute Management of Cardiogenic Shock - IVASHOCK-a double-blind randomized controlled trial

Background

Cardiogenic shock (CS) is a low cardiac output state that leads to hypoperfusion and Multi organ failure [1]. Acute myocardial infarction (AMI) is leading cause of CS and accounts for 30 % of cases [2]. CS is accompanied by compensatory tachycardia that helps to increase cardiac output (CO) in failing heart. However there is an inverted U-shape relationship between cardiac output and heart rate (HR), where CO increases to maximum with increasing HR and further increase in HR is associated with decline in CO. Moreover, there is an abnormal Bowditch-Treppe effect in left ventricular (LV) systolic dysfunction, where the force-frequency relationship is either absent or inverse. This results in the heart's inability to increase the force of contraction in response to an increased pacing rate. [3] Inappropriate increase in HR reduces the diastolic period and systolic volume and is an independent mortality risk factor [4]. Furthermore, In CS, inotropes and vasopressors are essential for augmenting CO and improving organ perfusion; however, their use often leads to a further increase in heart rate [5]. Beta blockers (BB), though effective in AMI, have limited role in acute decompensation and are contraindicated in CS [6]. In this situation, an agent that selectively inhibits HR may be beneficial. Ivabradine, a selective HR lowering agent that primarily inhibits If – channel in sinus node without affecting myocardial contractility [7]. Its use has been approved in chronic heart failure in combination with BB and has been effective in reducing composite rate of CV death and heart failure hospitalization [8]. However Ivabradine use in STEMI-CS is debatable where traditional HR limiting agents cannot be used. A Few case series have shown beneficial effect of ivabradine in patients presented with acute decompensated heart failure and receiving inotropic support [9-12].

There has been one small randomized clinical trial, 58 STEMI-CS patients were divided in two groups. Primary endpoints included halving NT-proBNP levels, while secondary endpoints were cardiovascular death, hospital readmission, and clinical improvement. Ivabradine significantly reduced heart rate and improved left ventricular diastolic function. NT-proBNP levels decreased significantly in the ivabradine group, and in-hospital mortality was lower, though not statistically significant due to its small sample size (14.3% in the control group and 6.7% in the ivabradine) . No adverse events were reported in the ivabradine group. However this trial has limitations including small sample size and NT-proBNP level as primary end point. [13]

In a case series, ivabradine was used in patients with cardiogenic shock, and invasive hemodynamic measurements were taken during initiation and titration at defined intervals within 48 hours. Ivabradine was well tolerated, with a significant reduction in pulmonary artery wedge pressure (30.4 ± 4.8 vs. 24 ± 5.1 mmHg, $P = 0.04$) and right atrial pressure (16.8 ± 6.2 vs. 9 ± 4.3 mmHg, $P = 0.0002$). Additionally, mixed venous oxygen saturation (51 ± 8.8 vs. 64.8 ± 5.3%, $P < 0.04$), stroke volume (37.2 ± 7.6 vs. 49.2 ± 12.9 mL, $P < 0.04$) and right and left ventricular stroke

work index improved. The limitations of this study were its observational nature and very small sample size [14].

NICVD is the world's largest primary PCI center, where 6-8% of STEMI patients present with cardiogenic shock. Mortality still remain in the range of 60-70% range despite timely revascularization. This highlights an opportunity to study the effect of Ivabradine in this patient population.

Hypothesis

In STEMI patients with cardiogenic shock, the addition of Ivabradine to standard care will improve the SCAI shock category by at least one class and lead to overall clinical improvement compared to placebo.

Objective

To study the impact of early initiation of Ivabradine on the progression of cardiogenic shock severity in STEMI patients, as defined by the Society for Cardiovascular Angiography and Interventions (SCAI) shock classification

Definitions

STEMI:

- New ST Elevation at the J point in V2-3 of at least two contiguous leads
  - ≥2mm in men
  - ≥1.5mm in women
- New ST Elevation in the J point of at least 1mm in two contiguous leads (except for V2-3)

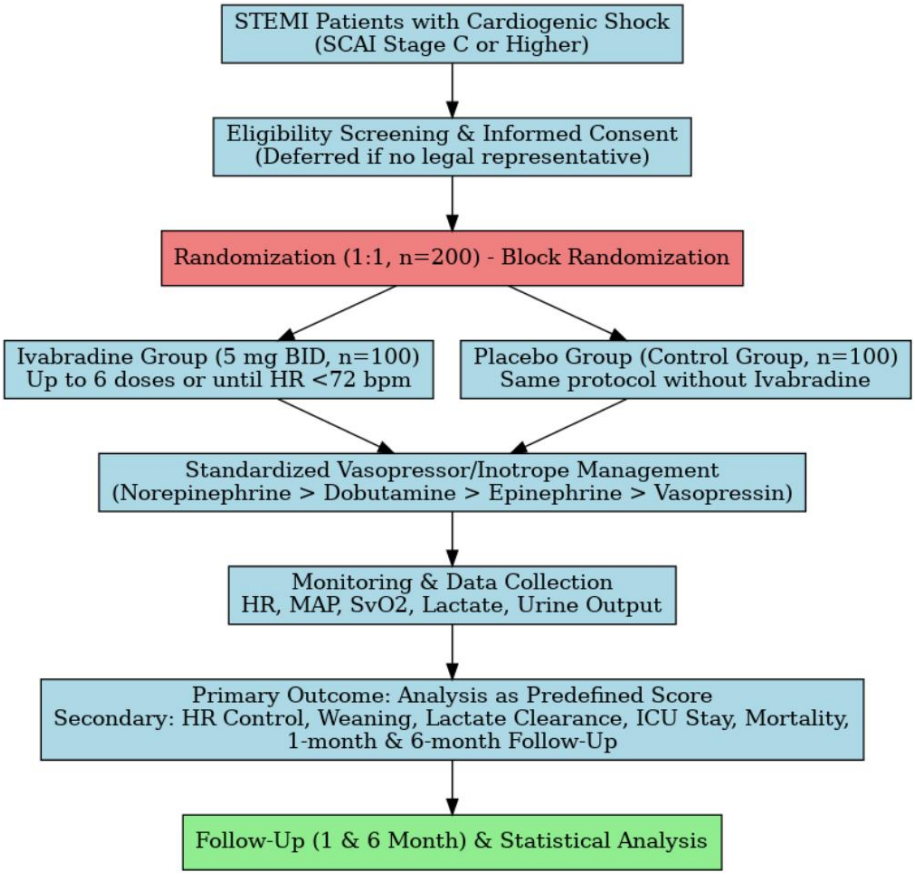
Cardiogenic Shock:

- SBP <90 mm Hg for >30 min or vasopressor support to maintain SBP >90 mm Hg
- Evidence of end-organ damage (UO <30 mL/h or cool extremities)
- Hemodynamic criteria: CI <2.2 and PCWP >15 mm Hg

SCAI Cardiogenic Shock Classification:

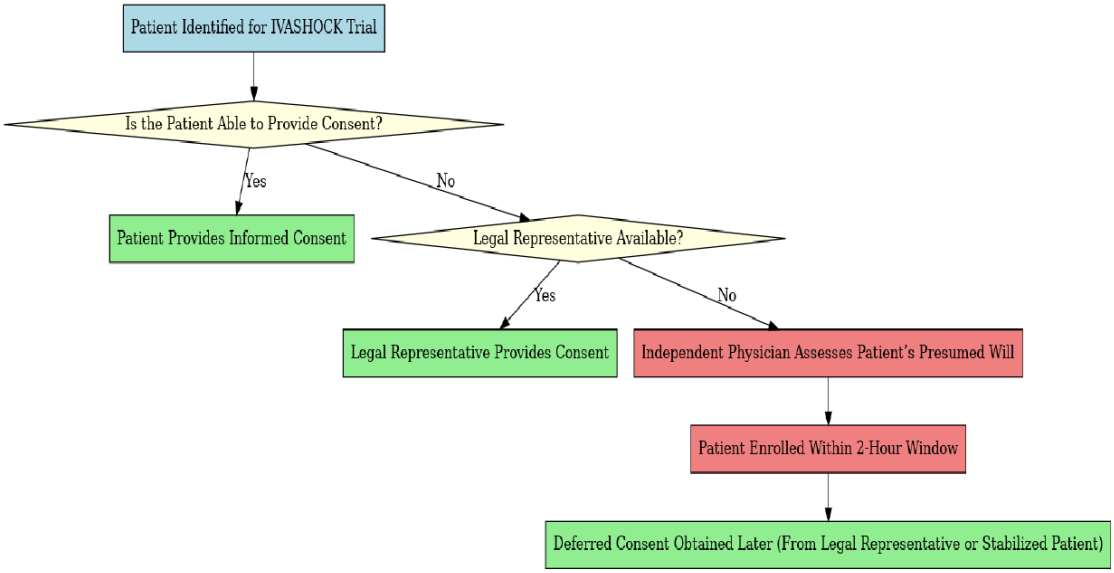
- Stage A: At risk for CS, with an unremarkable physical exam and normal mentation
- Stage B: Beginning CS, with clinical evidence of hemodynamic instability, such as hypotension or tachycardia
- Stage C: Classic CS, with hypoperfusion that requires intervention (inotrope, pressor or mechanical support, including ECMO) beyond volume resuscitation to restore perfusion. These patients typically present with relative hypotension
- Stage D: Deteriorating CS, with failure to stabilize despite initial interventions
- Stage E: Extremis CS, with cardiovascular collapse and respiratory failure

- **Material and Methods:**



IVASHOCK trial design & randomization

- **Study design:** This is a randomized double-blinded, placebo-controlled trial aimed at evaluating the effect of ivabradine in patients with STEMI complicated by cardiogenic shock (CS).
- **Setting:** NICVD Karachi
- **Duration of study**: 9 months
- **Study population:** Patients with STEMI with CS (SCAI Class ≥ C)
- **Consent:** Since patients with cardiogenic shock (CS) are often unable to provide informed consent due to cerebral hypoperfusion or mechanical ventilation, consent will be obtained from their legal representatives whenever possible. Given the critical 2-hour enrollment window, if no legal representative is available at the time of inclusion, an independent physician will assess the situation and act in accordance with the patient's presumed will. In such cases, written consent will be obtained later, either from the legal representative or from the patient once stabilized. This approach has been adopted in multiple cardiogenic shock trials [15-18]



- **Treatment Protocol:** Consecutive patients fulfilling the inclusion/exclusion criteria will be randomly assigned to intervention or control group **within 2 hours of CCU admission**. Patients will be randomized in 1:1 ratio using the block randomization method.
    - **Placebo Group (Standard Care + Placebo):** Patients will receive the standard treatment protocol for STEMI with CS, including guideline-directed medical therapy, inotropic/vasoactive agents as needed, and mechanical circulatory support when indicated plus **Placebo** at a starting dose of 5 mg twice daily and will be given 6 fixed doses. **Placebo** administration will continue until initiation of beta blocker or heart rate remains less than 72 bpm.
    - **Treatment Group (Standard Care + Ivabradine)**: Patients will receive standard treatment for STEMI, including guideline-directed medical therapy (GDMT) and revascularization. Standardized vasopressor and inotropic support, as described in the protocol, will be administered following randomization. In the treatment arm, patients will receive ivabradine at a dose of 5 mg twice daily, continued for six doses or until heart rate (HR) < 72 bpm, as a safety marker.
- **Hemodynamic Support and Vasopressor Management:**

  The management of cardiogenic shock in this trial follows an institutional standard approach to vasopressor and inotropic therapy.

- **Sample size:** This randomized controlled trial (RCT) will enroll a total of 200 participants, with 100 patients assigned to each arm. Participants will be randomized in a 1:1 ratio to receive either treatment or placebo.
- **Block randomization:** Blocked randomization list was created with the help of Sealed Envelope Ltd.

  Total sample size: 200, Block Size=4, number of blocks =50
- **Concealment:** Allocation schema will remain accessible to the randomization and allocation team and will be communicated to the screening and recruitment team on a block-on-block basis.

- **Interim analysis:** After enrollment of 100 (50%) randomized patients, the primary endpoint will be assessed. If it differs considerably from the estimated success rate, an adaptation of the sample size will be performed in consultation with the steering committee, considering the feasibility of continuing recruitment and the necessity to maintain at least 70% of the power of the trial.

Sample selection:

Sampling Technique: Non-probability consecutive sampling

Inclusion Criteria

1. Patients aged 18–75 years diagnosed with STEMI complicated by cardiogenic shock (CS) as defined by SCAI shock classification C:
   - Signs of Hypoperfusion include:
     a. SBP <90 OR MAP <60 OR >30 mmHg drops from baseline AND drugs/device used to maintain BP above these targets
     b. Cold, clammy extremities
     c. Urine output <30 mL/h
     d. Pulmonary congestion (either crackles, congestion in chest X-ray or B-lines in lung US)
     e. Mixed venous oxygen saturation ≤ 65%
2. Severe Left ventricular (LV) dysfunction or right ventricular (RV) infarction
3. Heart rate (HR) ≥ 100 bpm (Sinus Rhythm) in whom beta-blocker therapy cannot be initiated, including:
   - On inotropic or vasopressor support
   - Requiring an intra-aortic balloon pump (IABP)
   - With Killip class III or IV
   - Requiring BiPAP or mechanical ventilation

Exclusion Criteria

1. Age ≥ 75 years
2. CPR > 12 mints
3. Atrial fibrillation
4. Complete Heart Block
5. Heart rate of < 100 bpm
6. End stage renal disease
7. Extensive comorbidities
   1. Prior CVA
   2. Malignancy
8. Pregnancy
9. Ongoing Participation in Other Trials

Outcomes

Primary endpoint

Efficacy: At least one level improvement in SCAI shock classification after **randomization (compared to baseline SCAI shock classification)**, assessing the progression or improvement in cardiogenic shock severity.

- Weaning from inotropes or vasopressors or normalization of BP
- HR <100 bpm
- Pulmonary Congestion Improvement
- Initiation of GDMT (Beta Blocker and ACEi or ARBs)
- Urine output ≥ 1 liter/day or ≥30ml/hour
- SpO2 improving to ≥ 95%
- Serum lactate <2mmol/L
- Mixed venous oxygen saturation (SvO2) ≥ 65%

Change in SCAI shock classification will be based on a score system, where scoring will be incorporating four important parameters: Mean arterial pressure (MAP), mixed venous oxygen saturation (SvO2), urine output and arterial lactate level. Each parameter will be assigned a score from 0 to 3 based on predefined cutoffs. MAP scoring will be based on vasopressor requirements, with a score of 0 for MAP <65 mmHg with two agents, 2 for MAP >65 mmHg with one agents, and 3 for MAP >65 mmHg without support. SvO_2 scoring will range from 0 for SvO_2 <60%, 1 for 60–70%, 2 for 70–80%, and 3 for >80%. Urinary output scoring will be 0 for <10 mL/hr, 1 for 10–20 mL/hr, 2 for 20–30 mL/hr, and 3 for >30 mL/hr. Lactate clearance scoring will be 0 for lactate >8 mmol/L, 1 for 4–8 mmol/L, 2 for 2–4 mmol/L, and 3 for <2 mmol/L.

The score will be calculated at the time of enrollment and reassessed daily to evaluate changes in SCAI classification over time.

Parameter	Score 0	Score 1	Score 2	Score 3
Mean Arterial Pressure (MAP)	< 65 mmHg despite ≥ 2 agents	< 65 mmHg with 1 agent or ≥65 with ≥ 2 agents	> 65 mmHg with 1 agent	> 65 without support
Mixed Venous Oxygen Saturation (SvO_2)	< 50%	50–59%	60–69%	> 70%
Urine Output (mL/hr)	< 10 mL/hr	10–19 mL/hr	20–30 mL/hr	> 30 mL/hr
Arterial Lactate Level (mmol/L)	> 8 mmol/L	4–8 mmol/L	2–3 mmol/L	< 2 mmol/L

SvO_2, MAP, urine output, and lactate will be measured every 6 hours on Day 1 and every 8 hours on Days 2 and 3. Scoring based on these parameters will be performed daily. Routine laboratory tests, ECG, and creatinine clearance will be assessed daily as part of standard clinical practice, as outlined in Figure below (diagram for data acquisition).

	Arrival in CCU	At time of randomization (2 Hours)	Day 1				Day 2			Day 3		
			6 H	12 H	18H	24H	8H	16H	24H	8H	16H	24H
In and Exclusion criteria		✓										
Consent		✓										
ECG	✓						✓			✓		
ECHO			✓									
Routine labortory	✓			✓			✓			✓		
Creatinine clearance	✓			✓			✓			✓		
Vital Status	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Mean Arterial Pressure (MAP)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Arterial Lactate level		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Mixed venous oxygen saturation (SvO2)		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Urine Output	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Heart Rate	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Score		✓	✓				✓			✓		

Diagram of data acquisition

Safety: Safety parameters will be included.

- Sinus Node Dysfunction/ symptomatic bradycardia
- New Atrial fibrillation/ flutter
- High grade AV block
- Hypotension temporally related to study drug
- Ventricular Arrythmia
- Bleeding event

- Ischemic stroke/TIA
- Acute kidney injury

Secondary endpoints

- Change in Heart rate and mean arterial pressure
- ECG ST segment resolution
- In-hospital Mortality
- Length of ICU stay (hours)
- Mixed venous oxygen saturation and lactate level
- One- and six-month outcome

A clinical events committee whose members are unaware of study-group assignments will independently adjudicate all potential endpoints.

Data protection and confidentiality: Patients will be identified by the patient ID, random number, and date of birth. The patient's name will not be noted on the study documents to maintain patient's confidentiality.

Steering committee: The steering committee will be responsible for overseeing the good execution and administrative progress of the protocol; will meet regularly to monitor patient accrual, non-compliance with the protocol at individual centers, to act upon the recommendations of DSMB, and to determine policy regarding individual publications arising from data generated from the performance of the study.

Data and safety monitoring board: The clinical data and safety monitoring board (DSMB) will be a group of individuals with pertinent expertise that reviews on a regular basis accumulating data from the ongoing clinical trial. The DSMB advises regarding the continuing safety of trial subjects and those yet to be recruited, as well as the continuing validity and scientific merit of the trial. The DSMB may suggest early trial termination. However, since both study drugs have been tested in large clinical trials, are approved for the indications used in practice guidelines, no formal interim analysis is planned.

Event Adjudication Committee: The primary and secondary endpoints will be assessed by an event adjudication committee (EAC). The members will review endpoints reported by trial investigators to determine whether the endpoints meet the protocol-specified criteria. The adjudicator will be masked to the assigned treatment group to maintain unbiased evaluation.

Amendments: Any amendments to the protocol, as well as associated informed consent form changes, will be submitted to the ERC/IRB and competent authorities. Written approval must be obtained prior to implementation.

Statistical analysis

Primary analysis will be done on the intention-to-treat principle.

Definition of analysis population: Analysis of the primary endpoint will be performed according to the intention to treat (ITT) principle, i.e., in all patients that have been randomized, irrespective of their protocol adherence or continued participation in the study.

The safety endpoint of bradycardic complications will be analyzed in a modified intention to treat (mITT) population, i.e., all randomized patients that received at least one dose of the study medication.

Statistical Analysis Plan: For primary endpoints Win ratio analysis 1. improvement in total shock sore from baseline to 72 hours patients with greater increase wins 2. Lower vasoactive inotropic support at 72 hours patients with fewer support wins. if same number, patient with lower total dose wins 3. lactate recovery Lactate <2 at 72 hours wins. 4. mixed venous oxygen recovery mixed venous oxygen recovery ≥65% wins. 5. urine output recovery urine output ≥30ml/hr wins. 6. Heart rate control HR < 100 wins only if no bradycardia or block or new AF/flutter. Categorical variables such as demographics and medical history data will be summarized using frequencies and proportions and will be compared using the chi-square test or Fisher's exact test, as appropriate. Continuous data will be summarized using mean ± standard deviation or median [25th, 75th percentiles] and will be compared using Student t test or nonparametric Wilcoxon rank-sum test depending on the type of distribution of the analyzed variable. Univariable and multivariable binary logistic regression models will be used to estimate the treatment effect and to identify possible interactions in the treatment effect between pre-specified subgroups. All analyses will be performed in a blind manner regarding the randomly assigned treatment. Statistical tests will be two-sided, with a significance level of 0.05.

Pre-specified subgroup analysis: Analysis of the primary endpoint will be performed in pre-specified subgroups according to age (dichotomized at the age of ≥ 55 years), sex, smoking status, weight (dichotomized at a weight of < 60 kg), presence of diabetes mellitus, and renal function.

Quality Control and Quality Assurance

Ethics: Consent will be taken as described in method section.

Data gathering and monitoring: The trial will be reviewed by the IRB of the NICVD, Karachi, Pakistan. It will be registered on clinical trials.gov. Data will be recorded and stored in the clinical trials unit of NICVD.

Data capturing: The printed form of the REDCap version of CRF will be used for data collection.

Data Handling and Record Keeping:

- **Source data:** Research coordinators will perform primary data collection based on documented hospital chart reviews. The required data for this study will be documented on paper-based CRFs. Appendix provides a complete case report form containing the requested data. Collected data will be entered into RedCap, anonymized, and used for analysis.
- **Data Management and Integrity:** The integrity of the database forms the cornerstone of the final statistical analysis. Trained and specialized data management personnel will meticulously enter the data from transmitted Case Report Forms (CRFs) into an electronic database. To mitigate the risk of errors stemming from human entry, a comprehensive set

of detailed plans and monitoring systems will be implemented to ensure strict adherence to the study protocol, fostering uniformity in data collection.

- **Data Storage:** All relevant clinical trial documents including case report forms will be stored for at least 10 years after the end of the clinical trial by GCP standards.

Funding: Funding will be provided by Atco Pharmaceutical Company LTD .The sponsor will have no role in the design, execution, analysis, or results of the clinical trial.

Amendments: Any amendments to the protocol, as well as associated informed consent form changes, will be submitted to the ERC/IRB and competent authorities. Written approval must be obtained prior to implementation.

Quality Control Audit: The trial sponsor will perform an audit to ensure the correct assignment of the drug.

Data gathering and monitoring: The trial will be reviewed by the IRB of the NICVD, Karachi, Pakistan. It will be registered on clinicaltrials.gov. Data will be recorded and stored in the clinical trials unit of NICVD.

Data protection and confidentiality: Patients will be identified by the patient ID, random number and date of birth. The patient's name will not be noted on the study documents to maintain patient's confidentiality.

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