Synopsis

Title of the study	Remote Ischaemic Preconditioning for Heart Surgery
Short Titel	RIPHeart - Study
Indication	Patients undergoing isolated on-pump coronary-artery bypass graft (CABG) surgery
Study design	The study is a prospective, multicentre, randomised, controlled clinical study.
Primary endpoints	The primary endpoint is defined as a composite of • all-cause mortality • non-fatal myocardial infarction • any new stroke and/or • acute renal failure until hospital discharge (with a maximum of 14 days after surgery)
Secondary endpoints	1. The occurrence of any individual component of the composite endpoint at 30 days and 3 and 12 months after surgery (phone interview) 2. The cumulative duration of invasive ventilator support (up to d30 post operation) 3. The cumulative duration of non-invasive ventilation (up to d 30 post operation) 4. Length of stay on the intensive care (ICU) 5. Need of catecholamines 6. Total hospital stay 7. Troponin T (preoperative, 6, 12, 24, and 48 h after surgery) 8. Troponin I (preoperative, 6,12, 24, and 48 h after surgery) 9. Renal function 10. Vasopressor and inotropic support (yes/ no) 11. New onset of atrial fibrillation 12. Incidence of postoperative delirium within 4 days after surgery (yes/no) 13. Use of any delirium medication within 4 days after surgery (yes/no) 14. Use of any cardiac assist devices intraoperative and postoperative within 30 days (yes/no)
Sample size	N= 2070 patients, N=1035 per group
Study population	Key inclusion criteria: ▪ patients ≥ 18 years ▪ on-pump isolated coronary-artery bypass graft (CABG) surgery ▪ Informed consent Key exclusion criteria: ▪ Off-pump precedure ▪ concomitant diagnosis (e.g., ejection fraction <30%, diabetes mellitus, Instable angina pectoris, increased baseline troponin concentration; dialysis) ▪ nicorandil and/or sulfonylurea and/or $P2Y_{12}$ platelet receptor inhibitors ▪ pregnancy
Interventions	Experimental intervention: RIPC will be induced prior to skin incision by 4 cycles of upper limb ischaemia (5 min blood pressure cuff inflations to a pressure of at least 220 mmHg and 5 min cuff deflations).

	Control interventions: Sham-RIPC will be induced by 4 cycles of 'pseudo'-ischaemia (5 min blood-pressure cuff inflations to a pressure of at least 220 mmHg and 5 min cuff deflations) using a dummy arm, under Sevoflurane based anaesthesia Duration of intervention per patient: 40 minutes Follow-up per patient: Discharge, 30 days, month 3, 6 and 12 after surgery
Statistical Analysis	Efficacy: The primary endpoints AUC of cTnT and AKI will be compared in the following way: Firstly, the experimental arm (RIPC group) will be compared with the Sham-RIPC arm. Secondly, if results are significant for at least one of the two co-primary endpoints, the experimental arm will be compared with the RIPC/Propofol arm for the two primary endpoints. Group comparisons will be tested using appropriate 2 sample tests (t-test in case of normal distribution or Wilcoxon-Mann-Whitney test otherwise for AUC of cTnT) and the χ^2-test for AKI. Description of the primary efficacy analysis and population: Tests will be two-sided using Bonferroni-corrected significance levels of alpha = 2.5 % to account for the two primary endpoints. Power estimation bases on a power of 95 % for the comparisons of RIPC vs. Sham-RIP. All patients with available co-primary endpoints will be included in the analysis population. Safety: Safety data on RIPC will be evaluated descriptively and summarised by treatment arm, including all recruited study patients (safety population). Secondary endpoints will be compared between the treatment arms with t-tests, Wilcoxon-Mann-Whitney tests, χ^2-tests and log-rank test. Furthermore, appropriate regression models will be used for adjusted analysis.