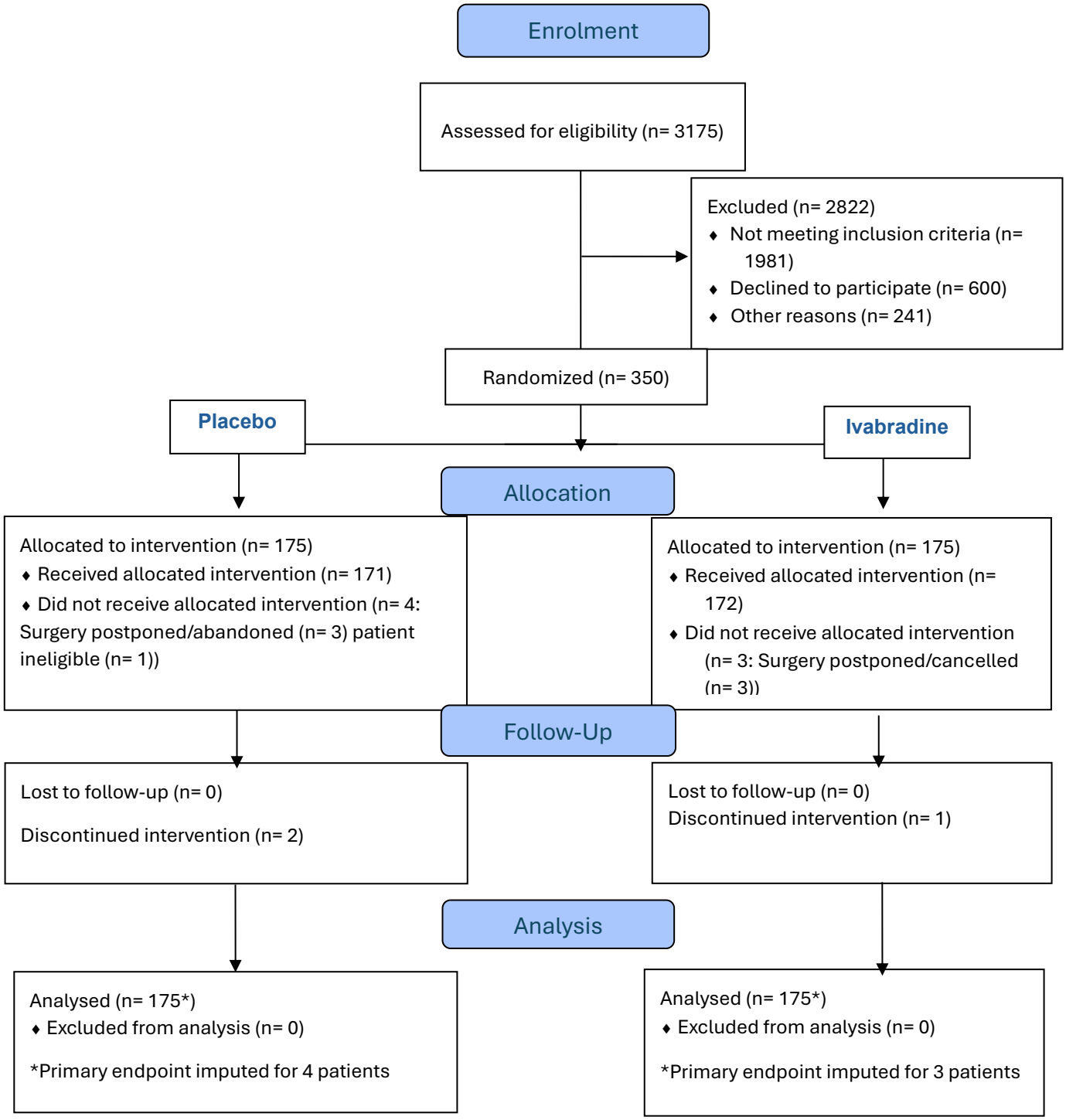
FUNNY Trial Basic Results

Participant Flow



Baseline Characteristics

Baseline Characteristics	Number of patients with available data - no. (%)		Summary measure	
	Placebo (n=175)	**Ivabradine** (n=175)	**Placebo**	**Ivabradine**
Sex - (n, %)	175 (100%)	175 (100%)		
Male			98 (56.0%)	92 (52.6%)
Female			77 (44.0%)	83 (47.4%)
Age (years)	175 (100%)	175 (100%)		
Mean (SD)			69.3 (8.2)	69.4 (7.7)
Median (IQR)			69 (63-75)	70 (63-76)
Ethnicity - (n, %)	175 (100%)	175 (100%)		
White			117 (66.9%)	121(69.1%)
Mixed or Multiple ethnic groups			5 (2.9%)	5 (2.9%)
Black, African, Caribbean or Black British			23 (13.1%)	24 (13.7%)
Asian or Asian British			16 (9.1%)	11 (6.3%)
Other			14 (8.0%)	14 (8.0%)
Height (cm)	175 (100%)	175 (100%)	166.5 (10.0) 167 (159-173)	166.2 (10.5) 165 (158-175)
Weight (kg)	175 (100%)	175 (100%)	85.3 (18.3) 83 [71-98]	85.7 (18.3) 83 (73-97)
Body mass index ($kg.m^2$)	175 (100%)	175 (100%)	30.9 (6.5) 29.4 (26.1-35.5)	31.0 (5.9) 30.4 (26.9-35.0)
Current smoker (within last 14 days) (n, %)	175 (100%)	175 (100%)	21 (12.0%)	26 (14.9%)
Chronic comorbid disease - (n, %)				
Chronic Obstructive Pulmonary Disease	175 (100%)	175 (100%)	15 (8.6%)	25 (14.3%)

Asthma	175 (100%)	175 (100%)	21 (12.0%)	20 (11.4%)
Interstitial lung disease or pulmonary fibrosis	175 (100%)	175 (100%)	3 (1.7%)	3 (1.7%)
Ischaemic heart disease	175 (100%)	175 (100%)	31 (17.7%)	27 (15.4%)
Congestive heart failure	175 (100%)	175 (100%)	6 (3.4%)	6 (3.4%)
Diabetes mellitus (type I or II)	175 (100%)	175 (100%)	82 (46.9%)	73 (41.7%)
Liver cirrhosis	175 (100%)	175 (100%)	5 (2.9%)	4 (2.3%)
Active cancer	175 (100%)	175 (100%)	63 (36.0%)	76 (43.4%)
Stroke or transient ischaemic attack	175 (100%)	175 (100%)	14 (8.0%)	24 (13.7%)
Peripheral vascular disease	175 (100%)	175 (100%)	14 (8.0%)	14 (8.0%)
Hypertension	175 (100%)	175 (100%)	158 (90.3%)	161 (92.0%)
Planned Surgical Procedure (n, %)	175 (100%)	175 (100%)		
Surgery involving the gut			25 (14.3%)	24 (13.7%)
All other surgery			150 (85.7%)	151 (86.3%)
Participating Site (n, %)	175 (100%)	175 (100%)		
Barts Health NHS Trust (Royal London Hospital), England			127 (72.6%)	126 (72.0%)
Hôpitaux Universitaires de Genève, Geneva, Switzerland			38 (21.7%)	38 (21.7%)
NHS Golden Jubilee Hospital, Glasgow, Scotland			10 (5.7%)	11 (6.3%)
Surgical procedure performed (n, %)	171[a] (97.7%)	172[b] (98.3%)		
Surgery involving the gut			22 (12.9%)	26 (15.1%)
All other surgery			149 (87.1%)	146 (84.9%)
Pre-operative blood test results				

Haemoglobin ($g.l^{-1}$)	172 (98.3%)	171 (97.7%)		
Mean (SD)			133.2 (18.3)	135.2 (18.5)
Median (IQR)			134 (121.5-144.5)	137 (125-147)
Creatinine ($\mu mol\ l^{-1}$)	170 (97.1%)	170 (97.1%)		
Mean (SD)			92.0 (42.3)	88.0 (32.5)
Median (IQR)			82 (68-104)	83 (69-97)
Estimated GFR ($ml.min.1.73m^2$)*	170 (97.1%)	170 (97.1%)	75.6 (22.1) 80.2 (60.8-93.6)	75.9 (19.7) 78.3 (61.9-91.6)
Neutrophil count ($n.10^9\ l^{-1}$)	142 (81.1%)	147 (84.0%)	4.95 (2.67) 4.5 [3.5-6]	4.89 (2.29) 4.7 [3.5-5.7]
Lymphocyte count ($n.\ 10^9\ l^{-1}$)	142 (81.1%)	149 (85.1%)	1.97 (1.01) 1.7 (1.4-2.3)	2.22 (2.23) 1.81 (1.4-2.5)
Neutrophil/lymphocyte ratio	141 (80.6%)	147 (84.0%)	3.35 (3.72) 2.53 (1.65-3.71)	2.83 (2.04) 2.35 (1.75-3.64)
Albumin ($g.l^{-1}$)	135 (77.1%)	129 (73.7%)	43.3 (3.8) 44 (41-46)	43.7 (3.8) 44 (42-46)
NT-proBNP ($pg.ml^{-1}$)	172 (98.3%)	173 (98.9%)	196.5 (333.9) 81 (42.5-173.5)	179.5 (320.1) 83 (36-199)
>100$pg.ml^{-1}$ (n; %)	172 (98.3%)	173 (98.9%)	71 (41.3%)	77 (44.5%)
Cardiometabolic medications (n, %)				
ACE-I	175 (100%)	175 (100%)	61 (34.9%)	56 (32.0%)
ARB	175 (100%)	175 (100%)	53 (30.3%)	42 (24.0%)
Beta blocker	175 (100%)	175 (100%)	40 (22.9%)	45 (25.7%)
Calcium channel antagonist (for blood pressure)	175 (100%)	175 (100%)	78 (44.6%)	84 (48.0%)

Heart rate limiting calcium channel antagonist (verapamil/diltiazem)	175 (100%)	175 (100%)	2 (1.1%)	3 (1.7%)
Doxazosin	175 (100%)	175 (100%)	10 (5.7%)	9 (5.1%)
Diuretic	175 (100%)	175 (100%)	43 (24.6%)	37 (21.1%)
Statin	175 (100%)	175 (100%)	115 (65.7%)	112 (64.0%)
Nitrate	175 (100%)	175 (100%)	9 (5.1%)	8 (4.6%)
Anti-platelet agents	175 (100%)	175 (100%)	65 (37.1%)	58 (33.1%)
Warfarin	175 (100%)	175 (100%)	0 (0%)	2 (1.1%)
DOACs (e.g. dabigatran, apixaban)	175 (100%)	175 (100%)	7 (4.0%)	8 (4.6%)
Any other anticoagulation established pre-operatively (e.g. LMWH)	175 (100%)	175 (100%)	4 (2.3%)	4 (2.3%)
Metformin	175 (100%)	175 (100%)	50 (28.6%)	54 (30.9%)
Insulin	175 (100%)	175 (100%)	25 (14.3%)	16 (9.1%)
Any other diabetic medication	175 (100%)	175 (100%)	48 (27.4%)	39 (22.3%)

**Estimated GFR calculated by CKD-EPI calculation (2021).*

[a]3 patients did not have planned surgery and 1 patient withdrawn as ineligible in study group 0.

[b]3 patients did not have planned surgery in study group 1.

Outcome Measures

Table 1: Primary and secondary outcomes

1. Troponin-T ≥15 ng/L on days 1, 2 or 3 after surgery with a pre-operative value <15 ng/L *OR* Troponin-T increase ≥5 ng/L on day 1, 2 or 3 after surgery with a pre-operative value ≥15ng/L; 2. defined by Post Operative Morbidity Survey; 3. Clavien Dindo defined complications up to 30 days after surgery.

Outcomes	**Number of patients with available data - no. (%)**		**Summary measure**		**Treatment effect** **Odds ratio (95% CI)** **Ivabradine: Placebo**	**P-value**
	Placebo (n = 171/175)	**Ivabradine (n = 172/175)**	**Placebo**	**Ivabradine**		
Primary outcome						
Myocardial injury associated with morbidity within 7 days of surgery (n; %)	171/175	172/175	55 (32.2%)	59 (34.3%)	1.22 (0.74-2.00)[a]	0.44
Secondary outcomes						
					Treatment effect **Mean difference (95% CI)**	
Peak level Troponin-T ($ng.ml^{-1}$)	172/175	172/175	18.9 (22.0)	18.2 (19.1)	1.27 (-1.35 – 3.89)[b]	P=0.34
					Treatment effect **Odds ratio (95% CI)**	
Troponin increase meeting MINS criteria (n; %)[1]	172/175	172/175	66 (38.4%)	70 (40.7%)	1.16 (0.71- 1.91) [a]	0.55
Morbidity within 7 days after surgery (n; %)[2]	172/175	172/175	128 (74.4%)	128 (74.4%)	0.96 (0.55-1.68) [a]	0.90
Clavien Dindo defined complications *grade ≥ II* (n; %)[3]	172/175	172/175	74 (43.0%)	83 (48.3%)	1.33 (0.84-2.12) [a]	0.23
Mortality at 180 days (n; %)	172/175	173/175	4 (2.3%)	3 (1.7%)	0.74 (0.16-3.36)[c]	0.70

[a]adjusted for age, gender, surgical procedure, duration of surgery, pre-operative heart rate, IHD, diabetes, congestive heart failure, CVA, eGFR(<59ml/min/1.73m2), PVD and hypertension as fixed effects and centre as a random effect.

[b]adjusted for pre-operative troponin, age, gender, surgical procedure, duration of surgery, pre-operative heart rate, IHD, diabetes, congestive heart failure, CVA, eGFR(<59ml/min/1.73m2), PVD and hypertension as fixed effects and centre as a random effect.

[c] model unadjusted due to small number of outcomes

Table 2. Post Operative Morbidity

	Day 3 after surgery		**Day 7 after surgery**	
	Placebo (n = 149[a] /175)	**Ivabradine** (n =147[b] /175)	**Placebo** (n = 74/175)	**Ivabradine** (n = 81/175)
Pulmonary (n; %)	22 (14.8%)	28 (19.1%)	6 (8.1%)	7 (8.6%)
Infectious (n; %)	41 (27.5%)	46 (31.3%)	26 (35.1%)	26 (32.1%)
Renal (n; %)	36 (24.2%)	36 (24.5%)	14 (18.9%)	16 (19.8%)
Gastrointestinal (n; %)	33 (22.2%)	25 (17.0%)	8 (10.8%)	6 (7.4%)
Cardiovascular (n; %)	10 (6.7%)	5 (3.4%)	3 (4.1%)	3 (4.1%)
Neurological (n; %)	12 (8.1%)	8 (5.4%)	3 (4.1%)	5 (6.2%)
Wound (n; %)	0 (0%)	1 (0.7%)	1 (1.4%)	0 (0%)
Haematological (n; %)	5 (3.4%)	6 (4.1%)	3 (4.1%)	2 (2.5%)
Pain (n; %)	22 (14.8%)	22 (15.0%)	6 (8.1%)	7 (8.6%)
Mobility (n; %)	86 (57.7%)	78 (53.1%)	40 (54.1%)	45 (55.6%)

[a]22 patients discharged before day 3, 3 patients did not have surgery, and 1 patient was withdrawn in study group 0.

[b]25 patients discharged before day3 and 3 did not have surgery in study group 1

Adverse Events

Table 3: Adverse events

Adverse Events - no. (%)	Summary measure	
	Placebo (n = 175/175)	**Ivabradine** (n = 175/175)
Patients with ≥ 1 adverse event	47 (26.9%)	56 (32.0%)
Total number of adverse events	60	65
Number of adverse events per patient		
0	128 (73.1%)	119 (68.0%)
1	37 (21.1%)	48 (27.4%)
2	8 (4.6%)	7 (4.0%)
3+	2 (1.2%)	1 (0.6%)
Type of adverse event (n, %) *		
Bradycardia requiring rescue therapy/pacing.[1]	8 (4.6%)	10 (5.7%)
Atrial fibrillation.[2]	3 (1.7%)	2 (1.1%)
Tachycardia requiring treatment.[3]	9 (5.1%)	5 (2.9%)
Hypotension requiring pressor infusion.[4]	26 (14.9%)	30 (17.1%)
Phosphenes	0 (0%)	0 (0%)
Other	11 (6.3%)	15 (8.6%)

1. <45bpm, detected as part of routine clinical care within the first 6 postoperative days.

2. detected as part of routine clinical care within the first 6 postoperative days.

3. >100bpm sinus rhythm, detected as part of routine clinical care within the first 6 postoperative days.

4. Hypotension defined as MAP<60mmHg, detected as part of routine clinical care within the first 6 postoperative days.

**Results are given as number of patients (%) with each type of event. One patient in placebo group had 2 tachycardia events. Two patients in each group had two other events and one patient in the ivabradine group had 3 other events.*

Table 4: Serious adverse events

Serious adverse events - no. (%)	**Summary measure**	
	Placebo (n = 175/175)	**Ivabradine** (n = 175/175)
Patients with ≥1 Serious adverse events	5 (2.9%)	6 (3.4%)
Total number of SAEs	5	6
Type of SAEs		
Death	1 (0.6%)	2 (1.1%)
Life-threatening complication	2 (1.1%)	1 (0.6%)
Prolonged existing hospital stay or required re-admission	2 (1.1%)	3 (1.7%)
Significant disability or incapacity	0 (0%)	0 (0%)
Other important medical event	0 (0%)	0 (0%)