Supplement

Type 2 Myocardial Infarction and Myocardial Injury: Eligibility for Novel Medical Therapy to De-risk Clinical Trials

Table 1 – Patient characteristics at initial screening (n = 346)

	All endotypes	Type 1 MI	Type 2 MI	Myocardial injury - Cardiac	Myocardial injury - non-cardiac	P Value
	n = 346	n = 115	n = 79	n = 69	n = 83	
Male, n (%)	183 (52.9%)	69 (37.7%)	37 (20.2%)	39 (21.3%)	38 (20.8%)	0.1
Age (IQR), years	70.0 (20.0)	68.0 (20.0)	74.0 (19.0)	72.0 (25.0)	72.0 (21.0)	0.150*
Caucasian ethnicity, n (%)[1]	330 (95.4%)	107 (93.0%)	76 (96.2%)	66 (95.7%)	79 (95.2%)	0.51
Duration of admission, days (IQR)	5.0 (12.0)	3.0 (5.0)	7.0 (15.0)	6.0 (16.0)	9.0 (10.0)	**<0.001***
Initial troponin, ng/L (IQR)	82.5 (301)	306 (2843)	66 (258)	58 (139)	52 (70)	**<0.001***
Peak troponin, ng/L (IQR)	148 (349)	912 (7921)	112 (505)	79 (223)	70 (105)	**0.012***
History of smoking, n (%)	200 (57.8%)	74 (64.3%)	41 (51.9%)	35 (50.7%)	50 (60.2%)	0.19
Obesity, n (%)	67 (19.4%)	22 (19.1%)	17 (21.5%)	9 (13.0%)	19 (22.9%)	0.446
Diabetes Mellitus, n (%)	93 (26.9%)	36 (31.3%)	20 (25.3%)	12 (17.4%)	25 (30.1%)	0.183

Chronic Pulmonary Disease (not asthma) , n (%)	76 (22.0%)	22 (19.1%)	19 (24.1%)	12 (17.4%)	23 (27.7%)	0.365
Asthma, n (%)	35 (10.1%)	6 (5.2%)	10 (12.7%)	9 (13.0%)	10 (12.0%)	0.205
Liver Disease, n (%)	5 (1.4%)	1 (0.9%)	3 (3.8%)	0 (0.0%)	1 (1.2%)	0.223
Chronic Neurological Disorder, n (%)	15 (4.3%)	4 (3.5%)	1 (1.3%)	3 (4.3%)	7 (8.4%)	0.147
Malignant Neoplasm, n (%)	37 (10.7%)	7 (6.1%)	12 (15.2%)	8 (11.6%)	10 (12.0%)	0.217
Chronic haematological disease, n (%)	24 (7.0%)	4 (3.5%)	4 (5.1%)	8 (11.6%)	8 (9.6%)	0.125
Connective tissue disorder, n (%)	20 (5.8%)	7 (6.1%)	4 (5.1%)	1 (1.4%)	8 (9.6%)	0.192
Dementia, n (%)	19 (5.5%)	5 (4.3%)	4 (5.1%)	3 (4.3%)	7 (8.4%)	0.599
Peripheral vascular disease, n (%)	2 (0.6%	0 (0.0%)	0 (0.0%)	1 (1.4%)	1 (1.2%)	0.456
Infection, n (%)	86 (24.9%)	8 (7.0%)	26 (32.9%)	14 (20.3%)	36 (43.4%)	**<0.0005**
COVID-19, n (%)	36 (10.4%)	0 (0.0%)	14 (17.7%)	4 (5.8%)	18 (21.7%)	**<0.0005**
Renal impairment, n (%)	108 (31.2%)	29 (25.2%)	23 (29.1%)	22 (31.9%)	33 (39.8%)	0.261
Anaemia, n (%)	69 (19.9%)	11 (9.6%)	11 (13.9%)	18 (26.1%)	29 (34.9%)	**<0.0005**
Heart failure, n (%)	155 (44.8%)	54 (47.0%)	31 (39.2%)	39 (56.5%)	31 (37.3%)	0.14
Structural heart disease, n (%)	22 (6.4%	7 (6.1%)	4 (5.1%)	11 (15.9%)	0 (0.0%)	**<0.001**

Tachyarrhythmia, n (%)	49 (14.2%)	7 (6.1%)	18 (22.8%)	21 (30.4%)	3 (3.6%)	**<0.0005**
Non-plaque rupture coronary event[2]	4 (1.2%)	2 (1.7%)	0 (0.0%)	2 (2.9%)	0 (0.0%)	0.254
Charlson comorbidity index, mean (IQR)	4.0 (12.0)	3.5 (4.0)	5.0 (4.0)	4.0 (3.0)	5.0 (4.0)	**0.015***
Charlson 10-year life expectancy index, mean (IQR)	53.0% (75.0%)	65.0% (88.0%)	21.0% (77.0%)	53.0% (75.0%)	21.0% (77.0%)	**0.027***
In-hospital mortality, n (%)	55 (15.9%)	9 (7.8%)	18 (22.8%)	8 (11.6%)	20 (24.1%)	**0.004**
Revascularisation, n (%)	53 (15.3%)	52 (45.2%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	**<0.0005**
Coronary angiography, n (%)	70 (20.2%)	64 (55.7%)	1 (1.3%)	4 (5.8%)	1 (1.2%)	**<0.0005**
Coronary artery bypass grafting, n (%)	4 (1.2%)	4 (3.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.085
Survivors with unplanned readmission~ (n = 293)	63 (18.2%)	20 (17.4%)	13 (16.5%)	14 (20.3%)	16 (19.3%)	0.924
Days until unplanned readmission (n = 63) (IQR)	19.0 (25.0)	23.0 (23.0)	16.0 (24.0)	18.0 (21.0)	24.0 (30.0)	0.949*

P values provided for comparison between endotypes. Significance set at <0.05 for 95% Confidence. Chi-square for nominal categorical variables; *Kruskal-Wallis one-way ANOVA for continuous numerical variables. [1]Ethnicity includes 3 Arab patients, 3 South Asian patients and 12 West Asian patients with no statistically significant difference across all groups (p = 0.51). [2]Non-plaque rupture coronary event: coronary embolus, coronary dissection, coronary spasm

Table 2 – Pre-admission and discharge prescribed medications regardless of eligibility for trial

	Pre-admission therapy n = 231		**Therapy on discharge** n = 185		**P Value***
Beta-blocker	**69**	**29.9%**	**77**	**41.6%**	**0.002**
Anti-platelet[1]	**67**	**29.0%**	**70**	**37.8%**	**0.003**
Statin	97	42.0%	85	45.9%	0.075
Colchicine	0	0.0%	4	2.2%	0.083
MRA[2]	12	5.2%	22	11.9%	0.114
ACE-I[3]/ARB[4]	71	30.7%	64	34.6%	0.789

*Fisher's Exact Test with two-tailed, 95% significance. [1]Aspirin, Ticagrelor, Clopidogrel. [2]Mineralocorticoid receptor antagonist. [3]Angiotensin-converting enzyme inhibitor. [4]Angiotensin II receptor antagonist.

Table 3 – Eligibility for treatment with colchicine

Eligibility for inclusion		Initial cohort n = 210		Discharge cohort n = 174	
1	Males & Females aged greater than 18 years able to consent	193	91.9%	157	90.2%
2	A diagnosis of type 2 MI or acute myocardial injury presenting within the last 30 days	210	100.0 %	174	100.0 %
3	If patient is female, patient is either not of childbearing potential, defined as postmenopausal for at least 1 year or surgically sterile, or is of childbearing potential and practicing at least one method of contraception and preferably two complementary forms of contraception including a barrier method (e.g. male or female condoms, spermicides, sponges, foams, jellies, diaphragm, intrauterine device (IUD)) throughout the study and for 30 days after study completion;	192	91.4%	158	90.8%

4	History of cardiovascular disease (NB A history of cardiovascular disease includes hypertension, ischaemic heart disease or cerebrovascular disease.	134	63.8%	114	65.5%
5	Patient must be treated according to national guidelines (including anti-platelet therapy, statin, renin-angiotensin-aldosterone system (RAAS) inhibitor (preferably angiotensin converting-enzyme (ACE) inhibitor) and beta-blocker, as clinically appropriate;	71	33.8%	63	36.2%
6	Patient must be able and willing to comply with the requirements of this study protocol.	145	69.0%	141	81.0%
Colchicine trial exclusion factors (SMPC*)		Initial cohort n = 210		Discharge cohort n = 174	
Absolute contraindication					
1	Cancer or lymphoproliferative disease within the last 3 years, other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix;	22	10.5%	19	10.9%
2	Gastrointestinal disease - Inflammatory bowel disease (Crohn's disease or ulcerative colitis) or patient with chronic diarrhoea;	2	1.0%	1	0.6%

3	Blood disorders - Significantly abnormal blood results determined to be non-transient through repeat testing during the past 30 days: - haemoglobin < 115g/L, - white blood cell count < 3.0 X 109/L, - platelet count <110 X 109/L, - ALT > 3 times the upper limit of normal (ULN), - total bilirubin > 2 times ULN (unless due to Gilbert syndrome, which is allowed) - Creatinine > 2 times ULN;	50	23.8%	40	23.0%
4	Cirrhosis, chronic active hepatitis or severe hepatic disease;	3	1.4%	2	1.1%
5	Female patient who is pregnant, or breast-feeding or is considering becoming pregnant during the study or for 6 months after the last dose of study medication	0	0.0%	0	0.0%
6	Currently taking colchicine for other indications (mainly chronic indications represented by Familial Mediterranean Fever or gout).	0	0.0%	0	0.0%
7	Allergic reaction or significant sensitivity to colchicine;	1	0.5%	1	0.6%
8	eGFR less than 10 mL/ minute/1.73 m2 (BNF caution)	19	9.0%	18	10.3%
Relative contraindication/caution					
9	New York Heart Association Class III-IV heart failure	15	7.1%	14	8.0%
10	Left ventricular ejection fraction of less than 35%,	21	10.0%	20	11.5%
11	Recent stroke (within the past 3 months),	5	2.4%	3	1.7%

12	Pneumonia	41	19.5%	20	11.5%
13	Poorly controlled medical condition	6	2.9%	5	2.9%
14	Cardiogenic shock or with hemodynamic instability	5	2.4%	3	1.7%
15	Pre-existent progressive neuromuscular disease or patient with CPK level > 3 times the upper limit of normal (unless due to MI, which is allowed) as measured within the past 30 days and determined to be non-transient through repeat testing;	1	0.5%	0	0.0%
16	Currently using or intended chronic systemic steroid therapy (oral or intravenous)	13	6.2%	11	6.3%
17	Elderly (65 years or older) (BNF caution)	134	63.8%	113	64.9%
Study reason**					
18	Clinically significant drug or alcohol abuse in the last year	7	3.3%	7	4.0%
19	Research study medication <30 days or 5 half-lives prior to the Screening visit (whichever is longer);	2	1.0%	1	0.6%
20	Patient is considered by the investigator, for any reason, to be an unsuitable candidate for the study.	58	27.6%	29	16.7%

*Summary of Medicinal Product Characteristics https://www.medicines.org.uk/emc/product/6415/smpc

** Study reason – colchicine has a narrow therapeutic index. Recent clinical trials [14] have included additional exclusion criteria to reduce the possibility of toxicity arising from treatment with colchicine. Accordingly, these criteria were also evaluated in this study.

Table 4 – Eligibility for treatment with eplerenone

Eligibility for inclusion		**Initial cohort** n = 210		**Discharge cohort** n = 174	
1	Males & Females aged greater than 18 years able to consent	193	91.9%	157	90.2%
2	A diagnosis of Type 2 MI or acute myocardial injury presenting within the last 30 days	210	100.0 %	174	100.0 %
3	If patient is female, patient is either not of childbearing potential, defined as postmenopausal for at least 1 year or surgically sterile, or is of childbearing potential and practicing at least one method of contraception and preferably two complementary forms of contraception including a barrier method (e.g. male or female condoms, spermicides, sponges, foams, jellies, diaphragm, intrauterine device (IUD)) throughout the study and for 30 days after study completion;	192	91.4%	158	90.8%

4	History of cardiovascular disease (NB A history of cardiovascular disease includes hypertension, ischaemic heart disease or cerebrovascular disease.	134	63.8%	114	65.5%
5	Patient must be treated according to national guidelines (including anti-platelet therapy, statin, renin-angiotensin-aldosterone system (RAAS) inhibitor (preferably angiotensin converting-enzyme (ACE) inhibitor) and beta-blocker, as clinically appropriate;	71	33.8%	63	36.2%
6	Patient must be able and willing to comply with the requirements of this study protocol.	145	69.0%	141	81.0%
Eplerenone exclusion or caution criteria (SMPC* CI/Caution)		**Initial cohort** n = 210		**Discharge cohort** n = 174	
Absolute contraindication					
1	Hyperkalaemia	16	6.9%	12	6.9%
2	eGFR less than 30ml/min/1.73 m2	45	19.5%	33	19.0%
3	Severe hepatic impairment	1	0.4%	1	0.6%
Relative contraindication/caution					

4	Elderly	128	55.4%	109	62.6%

*Summary of Medicinal Product Characteristics https://www.medicines.org.uk/emc/product/1981/smpc

Table 5 – Eligibility for treatment with Ticagrelor

Eligibility for inclusion		**Initial cohort** n = 210		**Discharge cohort** n = 174	
1	Males & Females aged greater than 18 years able to consent	193	91.9%	157	90.2%
2	A diagnosis of Type 2 MI or acute myocardial injury presenting within the last 30 days	210	100.0 %	174	100.0 %
3	If patient is female, patient is either not of childbearing potential, defined as postmenopausal for at least 1 year or surgically sterile, or is of childbearing potential and practicing at least one method of contraception and preferably two complementary forms of contraception including a barrier method (e.g. male or female condoms, spermicides, sponges, foams, jellies, diaphragm, intrauterine device (IUD)) throughout the study and for 30 days after study completion;	192	91.4%	158	90.8%

4	History of cardiovascular disease (NB A history of cardiovascular disease includes hypertension, ischaemic heart disease or cerebrovascular disease.	134	63.8%	114	65.5%
5	Patient must be treated according to national guidelines (including anti-platelet therapy, statin, renin-angiotensin-aldosterone system (RAAS) inhibitor (preferably angiotensin converting-enzyme (ACE) inhibitor) and beta-blocker, as clinically appropriate;	71	33.8%	63	36.2%
6	Patient must be able and willing to comply with the requirements of this study protocol.	145	69.0%	141	81.0%
Ticagrelor exclusion or caution criteria (SMPC* CI/Caution)		**Initial cohort** n = 210		**Discharge cohort** n = 174	
Absolute contraindication					
1	Active bleeding	7	3.0%	5	2.9%
2	History of intracranial haemorrhage	5	2.2%	2	1.1%
3	Hepatic impairment (severe)	1	0.4%	1	0.6%
4	Pregnancy or breast feeding	0	0.0%	0	0.0%

Relative contraindication / caution					
5	Asthma	19	8.2%	14	8.0%
6	Bradycardia (without pacemaker)	3	1.3%	3	1.7%
7	COPD	29	12.6%	24	13.8%
8	Hyperuricaemia	10	4.3%	8	4.6%
9	Increased risk of bleeding	16	6.9%	15	8.6%
10	Second- or third-degree AV block (without pacemaker)	3	1.3%	3	1.7%
11	Sick sinus syndrome (without pacemaker)	0	0.0%	0	0.0%
12	Hepatic impairment (moderate)	0	0.0%	0	0.0%

*Summary of Medicinal Product Characteristics https://www.medicines.org.uk/emc/product/5767/smpc