


openheart Type 2 myocardial infarction and myocardial injury: eligibility for novel medical therapy to derisk clinical trials

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ABSTRACT

Background Patients with type 2 myocardial infarction (T2MI) and other mechanisms of nonthrombotic myocardial injury have an unmet therapeutic need. Eligibility for novel medical therapy is generally uncertain. **Methods** We predefined colchicine, eplerenone and ticagrelor as candidates for repurposing towards novel therapy for T2MI or myocardial injury. Considering eligibility for randomisation in a clinical trial, each drug was classified according to indications and contraindications for therapy and survival for at least 24 hours following admission. Eligibility criteria for prescription were evaluated against the Summary of Medical Product Characteristics. Consecutive hospital admissions were screened to identify patients with ≥ 1 high-sensitivity troponin-I value > 99 th percentile. Endotypes of myocardial injury were adjudicated according to the Fourth Universal Definition of MI. Patients' characteristics and medication were prospectively evaluated.

Results During 1 March to 15 April 2020, 390 patients had a troponin I $>$ URL. Reasons for exclusion: type 1 MI $n=115$, indeterminate diagnosis $n=42$, lack of capacity $n=14$, death < 24 hours $n=7$, duplicates $n=2$. Therefore, 210 patients with T2MI/myocardial injury and 174 (82.8%) who survived to discharge were adjudicated for treatment eligibility. Patients who fulfilled eligibility criteria initially on admission and then at discharge were colchicine 25/210 (11.9%) and 23/174 (13.2%); eplerenone 57/210 (27.1%) and 45/174 (25.9%); ticagrelor 122/210 (58.1%) and 98/174 (56.3%). Forty-six (21.9%) and 38 (21.8%) patients were potentially eligible for all three drugs on admission and discharge, respectively.

Conclusion A reasonably high proportion of patients may be considered eligible for repurposing novel medical therapy in secondary prevention trials of type 2 MI/myocardial injury.

BACKGROUND

Type 2 myocardial infarction (MI) and nonischaemic myocardial injury confer a worse prognosis than type 1 MI,¹ yet there are no evidence-based medical therapies. High-sensitivity troponin assays are recommended in practice guidelines for use in routine clinical practice, leading to more patients with

Key questions

What is already known about this subject?

- Clinical trials in patients with type 2 myocardial infarction or myocardial injury are limited by the level of heterogeneity and comorbidities within the target population.
- As a result, little evidence is available to provide evidence-based management to these patients, with current treatment strategies focused on empirical secondary prevention.

What does this study add?

- This hypothetical study provides a pragmatic and contemporary insight into the proportion of consecutively screened patients who would be eligible for treatment with three repurposed agents—colchicine, eplerenone and ticagrelor—chosen for their application in other cardiovascular disorders and varied index of contraindications to therapy.

How might this impact on clinical practice?

- Despite a comorbid and elderly patient population, 21.8% of patients would be eligible for all three potential agents in a secondary prevention or 21.9% in an acute intervention trial when restricting eligibility to include no absolute or relative contraindication.
- This potential population can be increased substantially by allowing patients with relative contraindications, that is, age greater than 65 years; to be considered eligible.

nonischaemic myocardial injury or type 2 MI being diagnosed.² Despite their high mortality, no secondary prevention trials have been undertaken in type 2 MI and prior post-MI trials have focused on type 1 MI.

Pharmacotherapeutic strategies for type 2 MI or myocardial injury could involve one of three approaches (1) repurposing, (2) re-evaluation of current guideline-recommended therapies which have mainly been derived from trials involving patients with type 1 MI and (3) novel therapy. The success or failure of delivering a clinical trial is determined by several factors, notably enrolment rates and the safety of the participants. The proportion

of patients possessing eligibility criteria in the target population is a key uncertainty for the design and implementation of a clinical trial, that is inevitably associated with some level of uncertainty.

Colchicine inhibits neutrophil microtubule formation with anti-inflammatory effects. Recent trials in coronary heart disease have confirmed that colchicine has antiatherosclerotic effects that reduce the risk of cardiovascular events. These trials mainly included patient with type 1 MI leaving an evidence gap for patients with type 2 MI or myocardial injury.^{3–7} Eplerenone is a selective mineralocorticoid receptor antagonist (MRA). MRAs reduce adverse ventricular remodelling relevant to type 2 MI or myocardial injury and improve prognosis overall in patients with left ventricular dysfunction following acute MI.^{8,9} One of the few clinical trials to describe patients with type 2 MI was PEGASUS-TIMI-54.¹⁰ In this trial, 21 162 patients with recent MI (including 13% with type-2 MI) were randomised to receive ticagrelor (60 mg or 90 mg two times per day) or placebo. Ticagrelor reduced the risk of combined cardiovascular mortality, MI or stroke at 3 years (both doses) compared with placebo.¹⁰

We, therefore, predefined colchicine, eplerenone and ticagrelor as candidate medicines for evaluation in secondary prevention clinical trials in patients with type 2 MI or myocardial injury. The potential eligibility of affected patients for these medicines is unknown. We studied the characteristics of patients hospitalised with type 2 MI and nonischaemic myocardial injury in order to determine the potential eligibility for one or more of these medicines in the theoretical context of enrolment into a randomised, controlled trial of each medication.

METHODS

Design and setting

A longitudinal cohort study was undertaken in a large urban academic medical centre (Queen Elizabeth University Hospital, Glasgow, United Kingdom: catchment population n=6 50 000) between 1 March and 15 April 2020. The study protocol and proforma were predefined and Caldicott guardian approval for the use of patient-identifiable data was obtained before starting the project. Routinely collected (usual care) data were gathered by clinicians who were members of the usual care medical team, and ethics approval or explicit patient consent was not required.

Screening strategy to identify the target population

The study had three sequential stages. The screening and adjudications were led by a team of acute medical physicians (MB, TK, OP and RS) supervised by two experienced cardiologists (KM and CB). The first step was to identify hospitalised patients with a troponin I >URL based on a screen in real-time of laboratory records. The second stage was to assess the available clinical information for the episode of care in order to determine the endpoint according to the fourth Universal Definition of MI (UDMI). The third step focused on the

subgroup with a diagnosis of type 2 MI or nonischaemic myocardial injury.

Patients with an elevated troponin-I concentration (Abbott Architect TnI assay) based on a clinically indicated test were identified from laboratory-sourced records of ≥ 1 hs-TnI result >99th percentile sex-specific upper reference limit (sex-specific URL; 99th centile: men:>34 ng/L; women:>16 ng/L). The acute medical physicians adjudicated individual patient records and assigned endotypes of myocardial injury according to the fourth UDMI in real-time. The adjudications were supported by the cardiologists (KM and CB). In cases of diagnostic ambiguity, endotypes were determined by consensus agreement. Only patients with type 2 MI or nonischaemic myocardial injury, subclassified by inciting aetiology (cardiovascular, noncardiovascular), were included in the assessment for drug eligibility.

Electronic patient records (NHS Greater Glasgow and Clyde Health Board: Clinical Portal, Trakcare) were reviewed and details on demographics and medical history were recorded. In-hospital outcomes including mortality and duration of stay were also obtained.

Determining the study population (type 2 MI or myocardial injury)

Inclusion: (1) index admission with ≥ 1 hs-TnI value >99th sex-specific URL, (2) ≥ 18 years or older. Exclusion: (1) indeterminate diagnosis due to incomplete (or inaccessible) electronic patient records. Additional exclusion criteria were assessed prospectively using information that became available during the in-patient stay, (2) deaths <24 hours following admission and (3) lack of capacity (dementia/cognitive impairment).

Endotypes of nonthrombotic myocardial injury (type 2 MI, cardiac nonischaemic myocardial injury, noncardiac nonischaemic myocardial injury) were included in the screening criteria. Those with type 1 MI and other phenotypes of myocardial injury according to the Fourth UDMI were omitted.

Assessment of potential eligibility for novel medical therapy

We assessed the Electronic Medicines Compendium for the Summary of Medical Product Characteristics (SmPC) for colchicine, eplerenone and ticagrelor.^{11–13} Drug-specific prescribing information were also checked using reference prescribing guidelines^{4,14} and information from a recent clinical trial of colchicine.¹⁵

The clinical team assessed each patient according to predefined eligibility criteria for prescription of each drug in the theoretical context of a clinical trial. Eligibility included the absence of (1) a clinical indication for therapy, (2) an absolute contraindication and (3) a relative contraindication (caution). In addition, we took advantage of our recent experience in the COLCOT trial, which randomised patients within 30 days of type 1 MI to colchicine 0.5 mg daily or placebo. In addition to applying the SmPC criteria for colchicine, we also included the criteria for the COLCOT trial as a framework to inform the eligibility criteria and inclusion in

a type 2 MI or myocardial injury trial.¹⁵ The flow diagram for our study is shown in figure 1.

Timing of the eligibility assessment in relation to the clinical care pathway

Clinical status may evolve during an episode of care, and this influences the status of drug prescription. Accordingly, we predefined a sequential approach to determining eligibility for the study medicines. The clinical criteria for each medicine were sequentially assessed at two study time points: (1) following admission (≤ 24 hours) and (2) at discharge. The rationale for this approach has recently been supported by evidence that the benefit of colchicine in patients with recent MI may be greatest when initiated < 3 days of the index MI.¹⁵

COVID-19

This study was undertaken during the SARS-CoV2 (COVID-19) pandemic. COVID-19-positive patients were coded based on either laboratory evidence of SARS-CoV-2 infection by real-time PCR (Roche Cobas 6800 or Seegene Allplex

2019-nCoV) assay and/or positive radiological diagnosis (chest CT, chest radiograph) but negative biospecimen. The pandemic may have enriched the study population with patients diagnosed with type 2 MI or myocardial injury.

Statistics

The statistical analyses were performed using IBM Statistics SPSS (V. 24.0). χ^2 (or Fisher's exact test) are calculated for categorical characteristic variables. Kruskal-Wallis one-way analysis of variance tests were performed for multiple independent numerical continuous variables.

RESULTS

Three hundred and ninety patients were acutely hospitalised and had an elevated hs-TnI between 1 March and 15 April 2020. Of these, 42 had an indeterminate diagnosis due to inaccessible electronic records and two records were excluded due to duplication. A further 115 patients with type 1 MI were then excluded from the drug eligibility assessment.

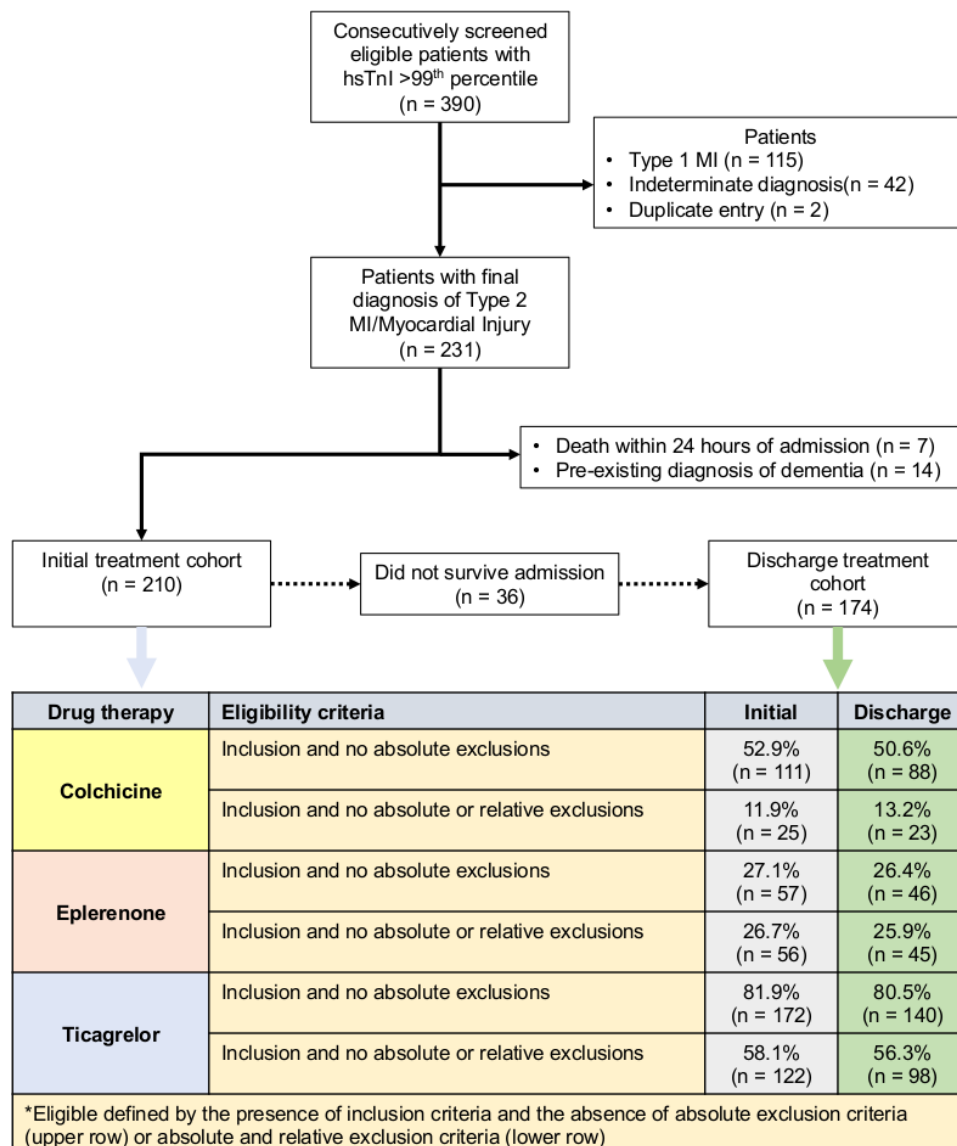


Figure 1 Flow diagram and summary of patient eligibility. MI, myocardial infarction.

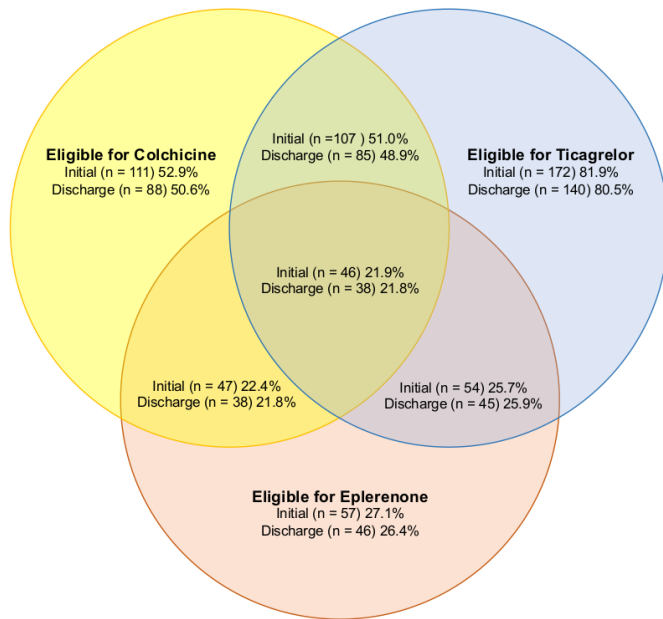


Figure 2 Flow diagram and summary of eligibility for novel medical therapy with no absolute contraindication for therapy.

Of the remaining 231 patients eligible for drug eligibility assessment, an index diagnosis of type 2 MI occurred in 79 patients and a diagnosis of nonischaemic myocardial injury occurred in 152 patients (cardiac n=69; noncardiac n=83).

Eligibility analysis

Figures 1 and 2 illustrate patient flow from screening laboratory troponin results, endotype evaluation and adjudication of drug-specific eligibilities. Of 231 patients with type 2 MI or nonischaemic myocardial injury who might be considered as potential candidates for participation in a clinical trial, 210 patients (49.0% women) were considered for inclusion following an initial assessment and 21 were excluded (death within 24 hours of admission: n=7 (3.0%); lack of capacity to consent (dementia/cognitive impairment): n=14 (6.1%)). Of these, at the point of discharge, 174 patients (51.7% women) were eligible, with exclusion of 57/231 (in-hospital death: n=43 (18.6%); lack of capacity to consent (dementia/cognitive impairment): n=14 (6.1%)).

Patient characteristics across groups

Online supplemental table 1 summarises the participants' characteristics. Age, sex and ethnicity were not different between the endotype groups. Compared with the excluded type 1 MI group, patients with type 2 MI or nonischaemic myocardial injury had higher 10-year predicted mortality, but quantitatively smaller initial and peak hsTnI values. Hospital readmission rate was comparable between all endotypes with one in five patients readmitted (median, 19.0 days (IQR, 25.0)). Invasive coronary angiography was infrequently performed in patients with type 2 MI (1.3%, n=1), noncardiac myocardial injury (1.2%, n=1) and cardiac myocardial injury (5.8%, n=4). Percutaneous coronary intervention was undertaken

in one patient with cardiac myocardial injury and no patients in any of these groups underwent surgical revascularisation.

Infections (COVID-19 and non-COVID-19) were more frequent in patients with type 2 MI or nonischaemic myocardial injury in addition to anaemia, structural heart disease and tachyarrhythmia.

Prescribed medications during standard clinical care

The prescriptions of cardiovascular medicines at the point of hospitalisation and at the point-of-discharge are summarised in online supplemental table 2. There were no differences in cardiovascular drug prescriptions by endotype. Four patients were prescribed colchicine therapy in-hospital/at discharge.

Initial treatment eligibility group

Relative and absolute contraindications were evaluated. Overall, 179 (85.2%) of the 210 potentially eligible patients met the essential defined criteria for colchicine. One hundred and eleven (52.9% of initial cohort) met essential inclusion criteria and had no absolute contraindication to therapy (online supplemental table 3). Fewer patients (40.0%; n=84) were eligible once study exclusions (in-hospital death within 24 hours, ineligible by incapacity) were applied; fewer still (11.9%; n=25) were eligible after considering all of the relative, absolute and study-defined exclusions. Therefore, 25/210 (11.9%) of the initial cohort were eligible for inclusion in a clinical trial of colchicine, if informed consent was given.

Eplerenone could be initiated during admission in 57/210 (27.1%) and 56 (26.7%) patients without absolute or combined absolute/cautionary contraindications, respectively (see online supplemental table 4). A complete breakdown of the criteria and grading are provided in online supplemental tables 3 to 5.

Finally, ticagrelor could potentially be initiated as an acute intervention in 172 (81.9%) of 210 patients who fulfilled the inclusion criteria and lacked an absolute contraindication. When both absolute and relative (cautionary) contraindications were applied, 122 (58.1%) remained theoretically eligible for treatment with ticagrelor (see online supplemental table 5).

Discharge treatment eligibility group

Thirty-six (17.1%) of 210 patients died during the index admission; including 22 who died from COVID-19. One hundred and seventy-four (82.9%) of 210 patients were included in the subgroup for whom data were available at discharge. Of these, 145 (83.3%) patients met the essential criteria for inclusion.

Following adjustment for contraindications, cautioned use or patient ineligibility for study reasons, 23 of 174 patients were theoretically eligible for treatment with colchicine at discharge. The percentage of patients potentially eligible for colchicine at the point of discharge increased to 44.8% if stringency was to be relaxed and cautions for prescribing (relative contraindications) were discounted: elderly age

(n=113), concomitant systemic steroids (n=11), active or recent pneumonia (n=20) or left ventricular ejection fraction (LVEF) less than 35% (n=20).

Eplerenone could potentially be commenced in 45 out of 174 (25.9%) patients eligible for trial inclusion at discharge.

Five patients had an absolute contraindication to ticagrelor with 140 of 174 (80.5%) remaining eligible for treatment at discharge. With additional consideration for cautionary factors applied, then the proportion of patients potentially eligible for receiving ticagrelor reduced to 98/145 (56.3%) (online supplemental table 5).

Eligibility for all three medications

Considering eligibility for all three medicines, 46 (21.9%) and 38 (21.8%) patients were eligible for all three medications on admission and at discharge, respectively (figure 2).

DISCUSSION

We have prospectively documented the potential eligibility of patients with type 2 MI or nonischaemic myocardial injury for repurposing three candidate medicines in the theoretical context of a randomised, controlled trial. The data are contemporary, prospectively evaluated and relatively unselected. Our results should help to derisk the design and implementation of a future clinical trial in type 2 MI or nonischaemic myocardial injury involving one of these medicines.

We considered the potential eligibility of the patients for these candidate therapies in relation to the acute care pathway, first following hospital admission and second at discharge. We found that 111 (52.9%) patients admitted with type 2 MI or nonischaemic myocardial injury might be eligible without absolute contraindications for a trial of early (in-hospital) initiation of colchicine, 57 (27.1%) would be eligible for secondary prevention trials with eplerenone and 172 (81.9%) with ticagrelor. Considering patients surviving through to discharge, 88 (50.6%), 140 (80.5%) and 46 (26.4%) were eligible for colchicine, eplerenone and ticagrelor therapy, respectively. Age >65 years was a relative caution for the prescription of colchicine and eplerenone.

Repurposing an established therapy is, theoretically, an attractive proposition since the safety of the medicine is generally well understood, derisking the trial. Considering efficacy, supporting information on the efficacy of repurposing candidates may already exist in a related disease area. Patients with type 2 MI or nonischaemic myocardial injury have distinct characteristics, including older age and prevalent comorbidity. Furthermore, enrolling patients into a drug trial during acute care raises particular challenges to trial recruitment, including the feasibility of obtaining written informed consent, meeting enrolment milestones and, of course, the type of clinical endpoints to assess the safety and efficacy of the repurposed medicine. A White Paper review of type 2 MI by DeFilippis *et al*¹⁶ identifies a paucity of clinical evidence

from randomised, controlled, secondary prevention. In our study, we attempted to enhance the relevance of the results for colchicine by drawing on relevant criteria from the COLCOT trial, which reflects contemporary prescribing, although in patients with type 1 MI.

Colchicine

Colchicine is an anti-inflammatory drug extracted from *Colchicum autumnale* (autumn crocus). Colchicine is guideline indicated in the management of myopericarditis and, recently, has been shown to be an effective treatment in reducing composite cardiovascular end points including stroke and readmission with angina in patients' postacute MI and in stable coronary artery disease.^{3-5,17} Colchicine is a tricyclic, lipid-soluble alkaloid reaching peak plasma volume 60 min after oral administration with long half-life duration. Increased concentrations within neutrophils are in keeping with its potent anti-inflammatory properties.¹⁸ While colchicine has been used therapeutically for thousands of years, it was not approved by the FDA until 2009. Colchicine is now indicated therapy for pericarditis and gout, and it may lower the incidence of post-operative or post-ablation atrial fibrillation.^{6,7,19,20} In patients with either acute MI or stable coronary disease colchicine reduces the need for repeat revascularisation, which may be explained by its antiatherosclerotic effects.^{4,5,21-23} Colchicine has been investigated in large randomised controlled trials in patients with COVID-19. Preprint data from the COLCORONA trial described a reduction in the composite of hospitalisation and mortality among nonhospitalised patients with COVID-19 when treated with colchicine versus placebo (4.6% vs 6.0%; OR, 0.75; 95% CI 0.57 to 0.99; p=0.04).²⁴ In hospitalised patients with COVID-19, the RECOVERY investigators found no effect of colchicine on 28-day mortality (20% colchicine vs 19% usual care alone; risk ratio 1.02 (95% CI 0.94-1.11); p=0.63).²⁵ However, it is unclear whether colchicine might be beneficial in patients with myocardial injury or type 2 MI and COVID-19 disease as data in this subgroup are lacking.

The most common side effect of oral colchicine administration is gastrointestinal upset, occurring in up to 20% of patients and 20% of reasons for discontinuation. Less common (combined <5%) potential side effects include myalgia, rash, alopecia or hepatotoxicity. Pre-existing liver disease or poor creatinine clearance increase the likelihood of side effects. In the Australian COPS Trial and LoDoCo2 Trials, colchicine was associated with an increase in noncardiovascular deaths.^{5,17} Colchicine has immunosuppressive effects and in the COLCOT trial, pneumonia was more common in colchicine-treated patients (p=0.03).^{4,26} A systematic review and meta-analysis of 35 randomised control trials have not borne out an increased risk of infection with colchicine.²⁷

Eplerenone

Aldosterone plays an important role in the pathophysiological mechanisms of heart failure and mediates the

deleterious downstream effects of renin-angiotensin-aldosterone system activation, including endothelial dysfunction, cardiovascular inflammation, myocardial fibrosis, ventricular remodelling and increased arrhythmogenicity. Plasma concentrations early post-MI are independently associated with increased all-cause mortality.²⁸

²⁹ MRA (nonselective: spironolactone; selective: eplerenone) reduce both the risk of death and hospitalisation in selected patients following acute MI with LVEF \leq 40% and clinically evident heart failure.^{9 29 30} REMINDER was a randomised, placebo-controlled, double-blind trial of eplerenone in patients presenting with acute MI without heart failure.³¹ After 10.5 months, the primary endpoint occurred in 92 (18.2%) and 149 patients (29.4%) in the eplerenone and placebo groups, respectively (HR 0.58; 95% CI 0.45 to 0.76; $p < 0.01$). This result was driven by a treatment-related reduction in NTproBNP. In the HOMAGE trial, patients with risk factors for heart failure (mean age 73 years, 26% women, 71% prior MI), including an increased NT-proBNP and no prior history of heart failure, were randomised to receive spironolactone or standard care.³² In addition to a treatment-related reduction in NT-proBNP (mean difference -57 ; 95% CI -81 to -33 ng/L; $p < 0.0001$) spironolactone also reduced type 1 collagen degradation reflected by a reduction in carboxy terminal propeptide of type 1 procollagen (mean difference -8.1 ; 95% CI -11.9 to -4.3 μ g/L; $p < 0.0001$) (primary endpoint). Considering mechanisms, this anti-fibrotic effect may reduce left ventricular stiffness, which would lead to a favourable reduction in NT-proBNP. Potentially, MRA therapy may be beneficial to which would lead to a favourable reduction in NT-proBNP. Potentially, MRA therapy may be beneficial to patients with type 2 MI and this possibility merits prospective evaluation.

Spironolactone has antiandrogenic side effects such as gynecomastia or impotence. The development of selective nonsteroidal MRAs such as eplerenone, and MR modulators such as finerenone, which reduce the likelihood of hyperkalaemia, have a more favourable side effect profile.³⁰

Ticagrelor

A reversible cyclopentyl triazolopyrimidine, orally active, selective adenosine diphosphate (P2Y₁₂) receptor antagonist—ticagrelor is indicated for patients with acute coronary syndromes.³³ The platelet inhibition and patient outcome trial found that ticagrelor reduced composite MI, stroke or death compared with clopidogrel in patients who were both medically managed or who underwent revascularisation.³⁴ However, ticagrelor increased major bleeding compared with placebo and aspirin.³⁵ Patients with type 2 MI or myocardial injury may have an increased risk of 30-day major adverse cardiovascular events compared with type 1 MI (20% vs 9%), highlighting competing risks and benefits.

Additional therapies

We have selected novel therapies based on their established efficacy and safety in other forms of cardiovascular

disease. There are limited data available on other candidate therapies in type 2 MI, including beta blockers, statins and angiotensin-converting enzyme receptor inhibitors/angiotensin receptor blockers and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors.^{36 37} Favourable effects of alirocumab, when added to intensive statin therapy, were reported in a prespecified analysis from the ODYSSEY OUTCOMES trial (effects of alirocumab on types of MI).³⁸ The novel findings were a reduction in the incidence of recurrent MI, either type 1 or type 2, in patients with elevated low-density lipoprotein cholesterol after an index acute coronary syndrome. Alirocumab was well tolerated with a favourable side-effect profile. The findings in prior studies, and our own, support the rationale for randomised, controlled, clinical trials.

Limitations

While patients have been designated as potentially eligible within the index admission, the diagnosis of type 2 MI or myocardial injury may not be suspected or confirmed based on the initial troponin I measurement. In our population, 20.5% had changes in diagnosis arising between the initial aetiology of hsTnI elevation and the final diagnosis of type 2 MI, including 32 (15.2%) initially coded as type 1 MI. The relatively small number of patients with type 2 MI or myocardial injury identified within the study period is a limitation.

COVID-19 was a primary or secondary diagnosis in 35 (16.7%) of the initially eligible patients and a significant primary cause of in-hospital mortality for 22 patients (10.4%). COVID-19 and its sequelae are likely to be a relevant public health problem for the foreseeable future.³⁹ COVID-19 is associated with myocardial injury and type 2 MI in unscheduled care.⁴⁰

CONCLUSIONS

Patients with type 2 MI or myocardial injury are commonly multimorbid. Despite this, a reasonably high proportion of these patients may be considered eligible for repurposing novel medical therapy in secondary prevention trials.

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Competing interests Professor Colin Berry is employed by the University of Glasgow which holds consultancy and research agreements for his work with companies that have commercial interests in the diagnosis and treatment of angina. The companies include Abbott Vascular, Astra Zeneca, Boehringer Ingelheim, GSK, HeartFlow, Menarini, Novartis, and Siemens Healthcare. The other authors do not have any potential conflicts of interest.

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Data availability statement The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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