

Anti-Inflammatory Treatment With Colchicine in Acute Myocardial Infarction A Pilot Study

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Background—Inflammatory processes have been identified as key mediators of the deleterious effects of ischemia/reperfusion in ST-segment-elevation myocardial infarction. Colchicine is a substance with potent anti-inflammatory properties, suitable for safe use in patients with cardiovascular disease. The purpose of this study was to test the hypothesis that a short course of colchicine treatment could lead to reduced infarct size.

Methods and Results—Patients presenting with ST-segment-elevation myocardial infarction ≤ 12 hours from pain onset (treated with primary percutaneous coronary intervention) were randomly assigned to colchicine or placebo for 5 days. The primary outcome parameter was the area under the curve of creatine kinase-myocardial brain fraction concentration. A subset of patients underwent cardiac MRI with late gadolinium enhancement 6 to 9 days after the index ST-segment-elevation myocardial infarction. One hundred fifty-one patients were included (60 in the MRI substudy). The area under the creatine kinase-myocardial brain fraction curve was 3144 (interquartile range [IQR], 1754–6940) $\text{ng}\cdot\text{h}^{-1}\cdot\text{mL}^{-1}$ in the colchicine group in comparison with 6184 (IQR, 4456–6980) $\text{ng}\cdot\text{h}^{-1}\cdot\text{mL}^{-1}$ in controls ($P<0.001$). Indexed MRI-late gadolinium enhancement–defined infarct size was 18.3 (IQR, 7.6–29.9) $\text{mL}/1.73\text{ m}^2$ in the colchicine group versus 23.2 (18.5–33.4) $\text{mL}/1.73\text{ m}^2$ in controls ($P=0.019$). The relative infarct size (as a proportion to left ventricular myocardial volume) was 13.0 (IQR, 8.0–25.3) % and 19.8 (IQR, 13.7–29.8) %, respectively ($P=0.034$).

Conclusions—These results suggest a potential benefit of colchicine in ST-segment-elevation myocardial infarction, but further clinical trials are necessary to draw secure conclusions, especially considering the fact that the present study was not powered to assess clinical end points.

Clinical Trial Registration—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT01936285.

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Key Words: area under curve ■ creatine kinase, MB form ■ gadolinium
■ magnetic resonance imaging ■ neutrophil ■ troponin T

Over the past years, a substantial volume of evidence has accumulated identifying inflammatory processes as key mediators of the deleterious effects of ischemia/reperfusion-related phenomena in patients presenting with ST-segment-elevation myocardial infarction (STEMI).^{1–4} Nevertheless, equally impressive is the lack of clinically applicable therapeutic strategies that could mitigate these processes, thus providing significant cardioprotection.

Clinical Perspective on p 1403

Despite the well-known fact that inflammation plays an important role in coronary artery disease development and progression,^{5,6} there have been few attempts to systematically examine the potential role of anti-inflammatory treatment in this setting, possibly because of a lack in anti-inflammatory agents without the adverse cardiovascular safety profile of corticosteroids and nonsteroidal anti-inflammatory drugs.^{7–9}

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Colchicine is a substance with potent anti-inflammatory properties, having a unique mechanism of action, which allows for safe use in patients with cardiovascular disease.¹⁰

The purpose of the present clinical study was to test the hypothesis that a short course of treatment with colchicine could lead to reduced infarct size in patients presenting with STEMI and treated with primary percutaneous coronary intervention.

Methods

This was a prospective, double-blinded, placebo-controlled study, performed in 2 primary percutaneous coronary intervention referral hospitals in the greater Athens area, whereas MRI studies were all performed in a third (separate) center. Patients presenting with STEMI, ≤ 12 hours from the onset of chest pain, from July 2013 until March 2015, were included. Main exclusion criteria were: age ≤ 18 or ≥ 80 years, active inflammatory or infectious disease or known malignancy, current treatment with corticosteroids or other anti-inflammatory agents, known hypersensitivity to colchicine or current chronic treatment with colchicine, severe renal failure (estimated glomerular filtration rate $<30 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$), hepatic failure (Child-Pugh class B or C), cardiac arrest, ventricular fibrillation or cardiogenic shock as presenting symptom, stent thrombosis, angina within 48 hours before infarction, previous myocardial infarction, occlusion of the left main or left circumflex coronary artery or with evidence of coronary collaterals to the region at risk on initial coronary angiography, presence of metallic implants (ferromagnetic material), and inability or unwillingness to provide informed consent. The protocol was approved by the institutional review boards and was implemented in accordance with the provisions of the Declaration of Helsinki. All patients provided informed consent.

After completion of the diagnostic coronary angiography, patients were randomly assigned (using a 1:1 allocation scheme based on a computer-generated randomization algorithm – an R language script was used for this purpose) to receive colchicine, starting with a loading dose of 2 mg (1.5 mg initially followed by 0.5 mg 1 hour later) and continuing with 0.5 mg twice daily, or placebo, for 5 days (Figure 1). Patients with $<60 \text{ kg}$ body weight received 0.5 mg once daily. Monitoring of adverse events focused on gastrointestinal manifestations, hepatotoxicity, myelotoxicity, and myotoxicity. Operators and personnel involved in patient follow-up and management were blinded as to patient allocation (patient treatment was identified by a serial number; assignment records were kept in a digital file that was unlocked after conclusion of the last patient follow-up procedures and database locking).

All patients received standard-of-care treatment for STEMI. During primary percutaneous coronary intervention, bivalirudin, heparin, and glycoprotein IIb/IIIa inhibitors were used at the discretion of the treating interventionalist. Standard medical therapy was administered, including β -blockers, statins, acetyl-salicylic acid, and ticagrelor or prasugrel at recommended daily dosages.

The primary outcome parameter was the area under the curve of creatine kinase-myocardial brain fraction (CK-MB) concentration over 72 hours after admission (calculated using the Simpson summing rule¹¹). CK-MB was measured on admission and every 4 hours thereafter. Maximal high-sensitivity troponin T was a secondary outcome measure during the same time period. A subset of patients from the total cohort underwent cardiac MRI with late gadolinium enhancement (LGE) 6 to 9 days after the index STEMI (MRI subgroup). In this subgroup, absolute myocardial infarct volume, determined by LGE, was the primary outcome measure. Myocardial infarct volume indexed to body surface area and relative infarct size (proportion of absolute infarct volume to left ventricular myocardial volume) were secondary outcome measures.

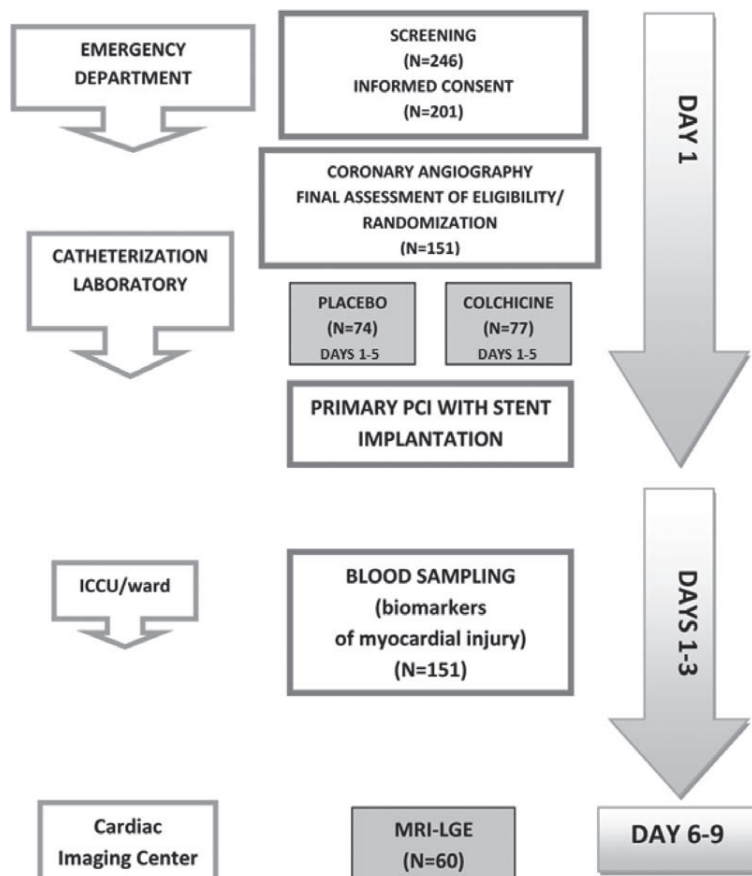


Figure 1. Study flow chart. All patients were screened at the emergency department and consent was sought. Final eligibility was determined in the catheterization department, as per protocol requirements. All exclusions at this stage were the result of protocol provisions. ICCU indicates intensive coronary care unit; LGE, late gadolinium enhancement; and PCI, percutaneous coronary intervention.

Blood samples for high-sensitivity troponin T (Elecsys Troponin T hs assay, Roche Diagnostics; lower detection limit 5 pg/mL) and CK-MB (Elecsys CK-MB assay, Roche Diagnostics; lower detection limit <0.1 ng/mL) measurement, and other analyses (complete blood count, biochemistries, including high-sensitivity C-reactive protein, etc), as well, were obtained at baseline (on admission), every 4 hours for the first 72 hours postpresentation, and every 12 hours thereafter. All patients had a standard transthoracic echocardiographic study performed before discharge, whereupon left ventricular ejection fraction was calculated with the modified Simpson rule.

Cardiac MRI

The cardiac MRI protocol was performed on a 1.5T Siemens Symphony system (Erlangen, Germany). Approximately 8 to 9 minutes after administration of 0.015 to 0.02 mmol/kg of gadobutrol (Gadovist, Bayer Hellas AG), a multiphase inversion-recovery steady-state free precession scan ("TI-scout") was acquired in the mid short-axis plane to determine the optimal inversion time (TI) to null normal myocardium for delayed enhancement imaging. The time that corresponded to the image with sufficiently nulled myocardium was input as the TI into the subsequent inversion recovery segmented turbo flash sequence used for delayed enhancement imaging. Typically, the TI spanned 230 to 330 ms over the course of the study. Other imaging parameters were: repetition time/echo time/flip = 700 ms/4.18 ms/25 deg, 8 mm thickness, field of view = 255×340 mm, 192×256, and 25 segments. Acquisition was performed in the short axis, covering the left ventricle from base to apex. In addition, single slices were acquired in the long axis, 4-chamber and 3-chamber views. The TI was increased as needed as time passed (10–20 minutes after gadobutrol administration). To quantify the myocardial scar, short-axis delayed enhancement images were analyzed by using the freely available for research purposes software Segment, version 1.9 R2354 (<http://segment.heiberg.se>; Figure 2).

Sample Size Estimation and Statistical Analysis

Preliminary measurements in patients presenting with STEMI at our institution had an area under the CK-MB concentration curve in the first 72 hours of ≈6000 U [(ng/mL)×h] with a standard deviation of ≈3000 U. It was calculated that, to detect a 25% reduction in the primary outcome measure with 85% probability (type II error probability 0.15), at an α -level (type I error probability) of 0.05, 150 subjects would have to be included. Analysis was performed on an

intention-to-treat basis (all randomly assigned patients). Continuous variables were expressed as median (25th–75th percentile). Comparisons of central tendencies and correlations were tested using nonparametric tests (Mann-Whitney *U* and Spearman, respectively). Categorical variables were expressed as counts and percentages and compared by using the χ^2 test (or Fisher exact test, if the generated 2×2 contingency tables contained cells with expected counts ≤5). SPSS 17 software package (SPSS Inc, Chicago, IL) and R language were used for all analyses. *P* values <0.05 (2-sided) were considered as indicative of statistical significance.

Results

One hundred fifty-one patients (104 male) were included in the final analysis (77 in the colchicine group and 74 controls). Sixty (41 male) of these patients were included in the MRI substudy. The epidemiological and clinical characteristics of the 2 cohorts (as a whole and divided in the 2 treatment arms) are summarized in the Table. The 2 treatment arms were similar in respect to important baseline parameters, both in the whole cohort (the only notable trend was a nonsignificantly higher thrombus burden in the colchicine arm) and the MRI subgroup. The MRI subgroup characteristics did not differ in any significant way from those of the total cohort.

Total Cohort

The median number of CK-MB measurements per patient was 16 (15–16; without any significant difference between treatment groups; *P*=0.226). The area under the curve of CK-MB concentration was 3144 (1754–6940) ng·h·mL⁻¹ in the colchicine group in comparison with 6184 (4456–6980) ng·h·mL⁻¹ in patients who took placebo (*P*<0.001; Figure 3). A similar difference was observed in maximum troponin values: median maximum high-sensitivity troponin T was 19 763 (6692–51 922) pg/mL and 45 550 (19 706–75 556) pg/mL in the colchicine and control arms, respectively (*P*=0.001), although one cannot fail to note the marked dispersion of values in the colchicine group, also obvious in the area-under-the-CK-MB-curve boxplot graph (Figure 3). The predischarge

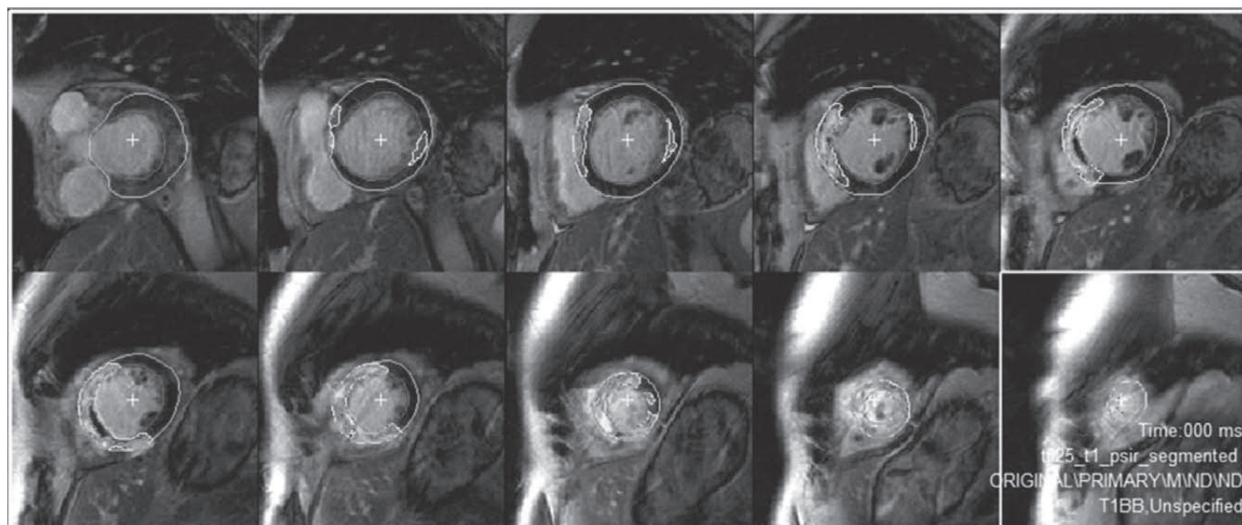


Figure 2. MRI-LGE images. Example of scar delineation using the Segment software with the weighted area method (infarcted pixels are weighted with their signal intensity). The yellow line denotes the complete affected area (scar), and the pink line is a graphical representation of the corresponding weighted area. Microvascular obstruction is indicated in red. For further information, read Heiberg et al.¹² LGE indicates late gadolinium enhancement.

Table. Demographic, Clinical, and Procedural Patient Characteristics per Randomization Group

Variable	Total (N=151)			MRI Subset (n=60)		
	Control	Colchicine	P Value	Control	Colchicine	P Value
	(n=74)	(n=77)		(n=29)	(n=31)	
Age, y	58 (51–68)	58 (52–64)	0.800	57 (50–66)	59 (54–66)	0.277
Male sex	52 (70)	52 (68)	0.716	20 (69)	21 (68)	0.919
Body mass index, kg/m ²	27.1 (24.6–30.8)	27.1 (25.3–30.7)	0.611	27.4 (24.4–30.5)	28.1 (26–31.4)	0.420
Body surface area, m ²	1.89 (1.79–1.98)	1.90 (1.79–1.98)	0.855	1.92 (1.78–1.99)	1.91 (1.79–2.02)	0.865
eGFR, mL·min ⁻¹ ·1.73 m ⁻²	84 (56–99)	75 (55–100)	0.836	86 (57–100)	81 (60–101)	0.982
Smoking	36 (49)	43 (56)	0.376	15 (52)	15 (48)	0.796
Diabetes mellitus	19 (26)	13 (17)	0.186	8 (28)	6 (19)	0.451
Dyslipidemia	35 (47)	44 (57)	0.226	13 (45)	16 (52)	0.599
Hypertension	29 (39)	31 (40)	0.893	7 (24)	12 (39)	0.225
Ischemia time, min	180 (146–237)	173 (141–223)	0.609	183 (148–231)	172 (146–227)	0.673
Baseline hs-TnT, pg/mL	34 (8–304)	37 (9–361)	0.786	22 (7–462)	35 (8–403)	0.982
Baseline CK-MB, ng/mL	44 (35–71)	59 (33–74)	0.984	44 (37–76)	43 (34–73)	0.923
Baseline neutrophil count, /μL	7131 (5913–7950)	6947 (5929–8935)	0.587	6800 (5761–7997)	6643 (5577–9230)	0.559
Baseline CRP, mg/L	2.46 (1.02–5.22)	2.39 (1.18–4.60)	0.553	2.81 (1.11–4.97)	2.31 (1.16–3.58)	0.847
Culprit vessel						
LAD	40 (54)	44 (57)	0.703	17 (59)	16 (52)	0.586
RCA	34 (46)	33 (43)		12 (41)	15 (48)	
TIMI thrombus burden	4 (3–5)	5 (4–5)	0.068	4 (3–5)	5 (3–5)	0.241
TIMI flow 3 post-PCI	57 (77)	53 (69)	0.258	24 (83)	21 (68)	0.179

Continuous variables are summarized as median (interquartile range). Categorical variables are presented as count (percentage). CRP indicates C-reactive protein; eGFR, estimated glomerular filtration rate (Cockcroft-Gault); hs-TnT, high-sensitivity troponin T; LAD, left anterior descending; PCI, primary percutaneous coronary intervention; RCA, right coronary artery; and TIMI, thrombolysis in myocardial infarction.

echocardiographic left ventricular ejection fraction was 53 (44–59) % in the colchicine group versus 46 (38–51) % in controls ($P=0.003$).

MRI Subgroup

MRI-LGE–defined infarct size, both in terms of absolute infarct volume and relative infarct size (proportion of infarct to left ventricular myocardial volume) was smaller in colchicine-treated individuals (Figure 4). Absolute infarct volume was 25.1 (20.0–35.9) mL in controls as opposed to 18.8 (8.1–28.5) mL in the colchicine group ($P=0.019$). After normalization for body surface area, the corresponding indexed infarct sizes were 23.2 (18.5–33.4) mL/1.73 m² versus 18.3 (7.6–29.9) mL/1.73 m² ($P=0.019$). The relative infarct size was 19.8 (13.7–29.8) % and 13.0 (8.0–25.3) %, respectively (Figure 4). Biomarker-defined infarct size was also lower in colchicine-treated patients of the MRI subset, similarly to the total cohort (Figure 4). As expected, there was a significant correlation between MRI- and biomarker-defined infarct size, which suggests good internal consistency of the data (Figure 5A).

Study Treatment Discontinuation and Adverse Effects

Overall, 23 of 151 patients discontinued treatment before taking all study drug doses. The discontinuation rate was 26% in the colchicine group (20 of 77 patients), as opposed to 4% in the control group (3 of 74 patients; $P<0.001$). The reason

for discontinuing the study drug was reported as diarrhea in 16 of 23 cases (15 belonged to the colchicine group and 1 to the control group) and nausea/vomiting in 3 cases (all in the colchicine group). In 1 case, marked elevation in serum alanine aminotransferase was reported as the reason for study drug discontinuation (up to ≈ 5 times the upper reference limit, without any sequelae). No cases of myelotoxicity were reported. In-hospital death occurred in 1 patient of the colchicine group and 1 of the control group (on days 4 and 5 of hospitalization, respectively).

The area under the curve of CK-MB concentration was 2312 (1201–5743) ng·h·mL⁻¹ in patients of the colchicine group who completed treatment ($n=57$) versus 5920 (2998–8858) ng·h·mL⁻¹ in those who stopped treatment ($n=20$; $P=0.003$). The corresponding values for absolute infarct size in the MRI subgroup were 12.4 (6.8–25.9) mL in patients who completed colchicine treatment ($n=24$) versus 29.1 (26.1–36.6) mL in those who discontinued ($n=7$; $P=0.008$).

Inflammatory Markers

Maximal neutrophil count (the highest neutrophil count measured during hospitalization) was 7543 (6549–10 118) /μL in the colchicine group in comparison with 8922 (7880–10 307)/μL in controls ($P=0.008$). It was significantly associated with relative and absolute MRI-LGE infarct size (Figure 5B), and with the area under the CK-MB curve (Spearman ρ 0.79; $P<0.001$). These correlations were significant independently of study treatment (colchicine or placebo).

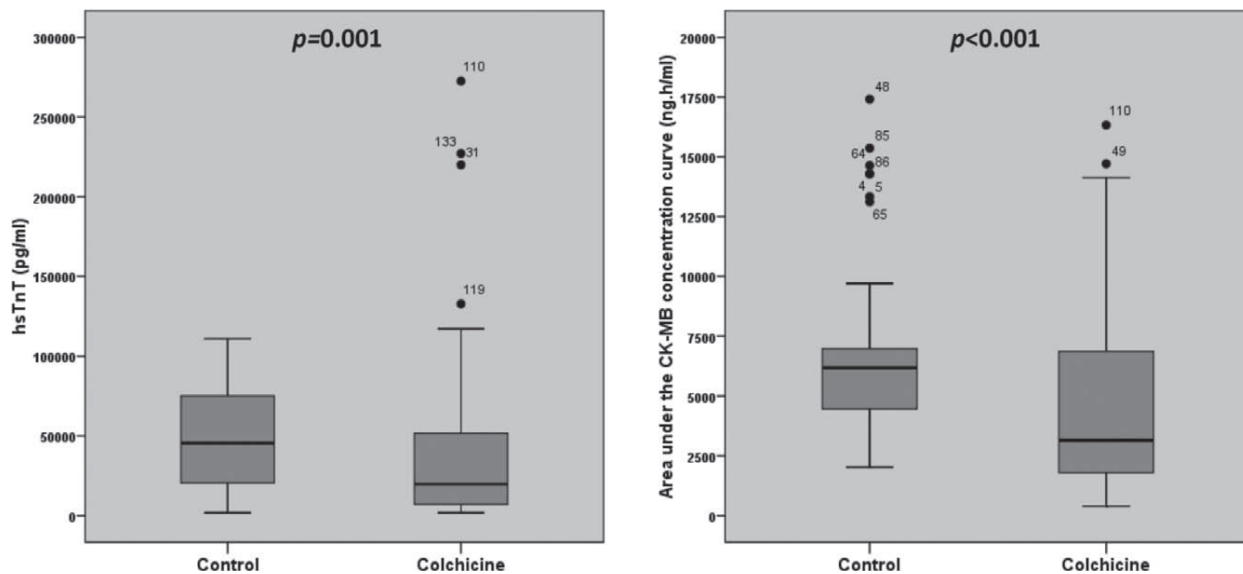


Figure 3. Myocardial injury biomarkers in the total cohort. Boxplot graphs illustrating the distribution of highest post-MI hs-TnT (**left**) and area under the curve of CK-MB concentration (**right**) in the total of 151 patients (the thick horizontal black line corresponds to the median, the box to the interquartile range, and the whiskers to the range bar extreme values, which are represented by dots and are defined as data points found outside 1.5 times the interquartile range, below or above the 25th and 75th percentiles, respectively). CK-MB indicates creatine kinase-myocardial brain fraction; hs-TnT, high-sensitivity troponin T; and MI, myocardial infarction.

Maximal C-reactive protein levels were also higher in the control group than in the colchicine-treated patients (63.8 [34.7–103.4] mg/L versus 42.9 [16.3–71.4] mg/L; $P=0.019$). Maximal C-reactive protein was correlated (although less strongly than neutrophil count) with relative MRI-LGE infarct size (Spearman ρ 0.42; $P=0.001$), indexed absolute infarct size (Spearman ρ 0.43; $P=0.001$), and the area under the CK-MB curve (Spearman ρ 0.38; $P<0.001$).

Discussion

The results of this prospective randomized study indicate that treatment with colchicine in patients with STEMI undergoing primary percutaneous coronary intervention is associated with smaller infarct size, as defined by both biomarker release and MRI-LGE. This effect was accompanied by a substantial treatment-related difference in markers of post-myocardial infarction inflammatory response, namely neutrophil count and C-reactive protein. These latter parameters were quite strongly associated with infarct size.

Inflammation has been shown to be implicated in several processes involved in the sequence of events that follow the obstruction of an epicardial coronary artery in the context of STEMI, including thrombus composition,¹³ endothelial function,^{14,15} postinfarction myocardial function,^{16,17} clinical events,^{18–22} and, even, peri-infarct kidney injury.²³ There is also evidence that timelier reperfusion leads to a blunted inflammatory response,²⁴ whereas C-reactive protein levels following STEMI are predictive of left ventricular remodeling,²⁵ and inflammatory mediators are correlated with biomarkers of cardiac dysfunction.²⁶ Most importantly, specific components of the cellular inflammatory response have been shown to be strongly correlated with STEMI-related myocardial damage: monocyte response has been associated with severe myocardial injury and poor functional outcome after STEMI,²⁷ and

neutrophil peaks have been found to predict MRI-defined infarct size.²⁸ In view of this evidence, the significant inverse correlation of colchicine treatment with post-STEMI neutrophil rise, which was observed in the present study, suggests a potential mechanism of the observed beneficial effect of colchicine (along with the observed association of neutrophil count with infarct size, which was strong for all patients independently of treatment allocation).

Colchicine is a drug with well-known anti-inflammatory properties, shown to be safe in various settings of cardiovascular disease.^{29–31} Its unique effects stem from its ability to interfere with microtubule polymerization. At a structural level, each hollow microtubule is assembled from 13 parallel protofilaments, which in turn comprise alternating, very tightly linked, α - and β -tubulin subunit pairs organized along a longitudinal axis.³² Colchicine binds to the intradimeric α - β interface, in the center of the tubulin heterodimer.^{33–35} By interfering with microtubule polymerization, colchicine affects virtually every process that requires cytoskeletal changes, including cell mitosis, exocytosis, and motility, and, mainly owing to its pharmacokinetics, these effects are particularly potent on inflammatory cells.³⁶ Inhibition of interleukin-1 production by activated neutrophils, downregulation of tumor necrosis factor- α receptors in macrophages and endothelial cells, and impairment of the adhesion of neutrophils to the vascular endothelium, probably through modulation of endothelial E-selectin and neutrophil L-selectin surface expression, are some of the ways colchicine affects inflammatory responses.^{36,37}

Experimental or clinical data regarding the role of colchicine in STEMI are sparse. In 1 study, in an open-chest canine model of reperfusion injury, the number of circulating neutrophils, neutrophil cytotoxicity, and neutrophil myocardial accumulation after 6 hours of reperfusion were reduced in

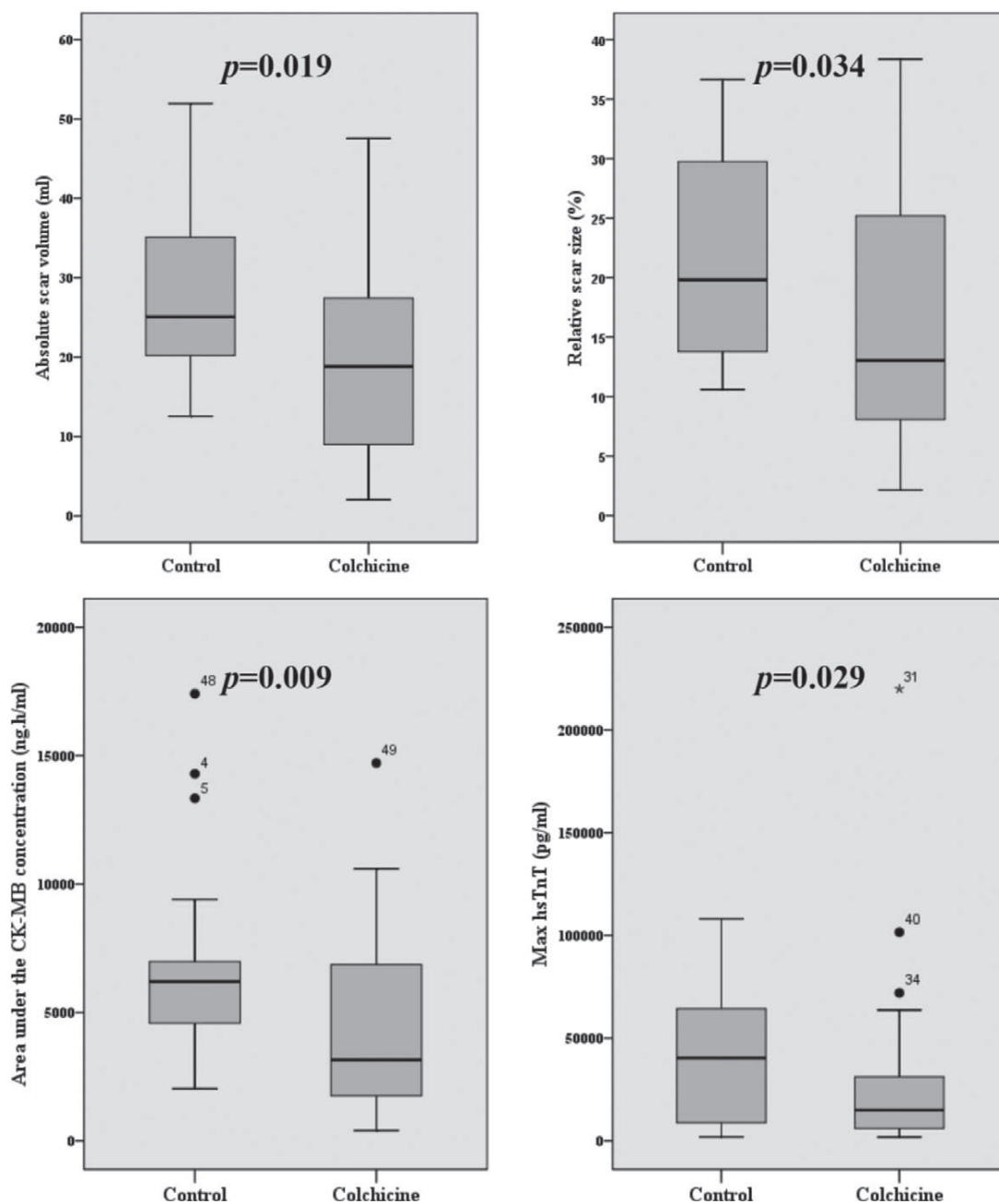


Figure 4. MRI- and biomarker-defined infarct size in the MRI subgroup. Boxplot graphs illustrating the distribution of infarct size descriptors in the 2 treatment arms in patients who underwent cardiac MRI (see Figure 3 for explanation of boxplot elements). CK-MB indicates creatine kinase-myocardial brain fraction; and hs-TnT, high-sensitivity troponin T.

colchicine-treated dogs, although there was no difference in infarct size.³⁸ To our knowledge, no study has assessed the effect of colchicine on infarct size in humans. Raju et al³⁹ studied a mixed population of 80 patients with STEMI, non-ST-segment-elevation acute coronary syndrome, and ischemic stroke and found no difference in C-reactive protein between patients on colchicine and controls 30 days after the index event (a time point at which one would expect acute inflammatory processes to have subsided even in patients not taking any anti-inflammatory treatment, which renders this finding difficult to interpret in a clinically meaningful way). On the

other hand, colchicine has already been shown to be associated with reduced myocardial damage in another setting of ischemia/reperfusion myocardial insult, namely that of cardiac surgery.⁴⁰

Studies of other agents with anti-inflammatory action have given varying results in improving outcomes following STEMI. In 2 small studies, an interleukin-1 inhibitor was associated with a lower incidence of heart failure after the index myocardial infarction.^{41,42} However, in another study in patients with non-ST-segment-elevation acute coronary syndrome, the same agent, despite a significant reduction

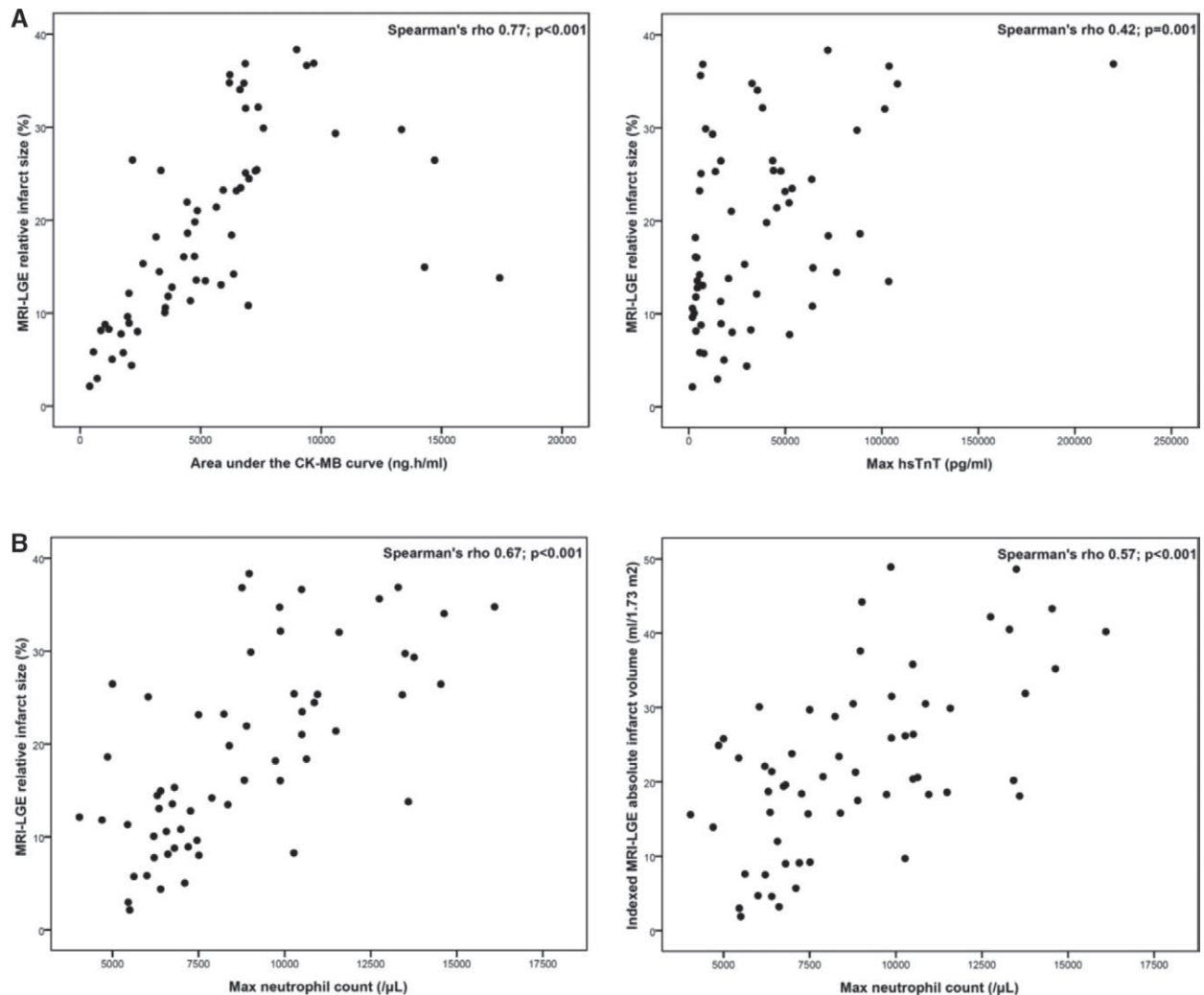


Figure 5. **A**, Correlations between biomarkers and MRI-defined infarct size. Scatterplots of biochemical vs imaging descriptors of infarct size illustrating an expected relationship between these 2 measures of infarct size. **B**, Correlations between neutrophil count and MRI-defined infarct size. Scatterplots of maximal postinfarction neutrophil absolute count vs relative (as a proportion of the left ventricular mass) and body surface area-indexed absolute infarct size. CK-MB indicates creatine kinase-myocardial brain fraction; hs-TnT, high-sensitivity troponin T; and LGE, late gadolinium enhancement.

in biomarkers of inflammation, was associated with more recurrent events at 1 year (although it should be noted that this study was not designed to evaluate clinical end points and, in any case, non-ST-segment-elevation acute coronary syndrome pathophysiology differs substantially from that of STEMI).⁴³ Of note, the immunosuppressive agent cyclosporine has been shown to have a beneficial effect on infarct size in STEMI⁴⁴; although the authors suggest that cyclosporine had a cardioprotective effect as a result of inhibition of the opening of mitochondrial permeability-transition pores, the possibility that its immunosuppressive action may also have played a role in the observed effect cannot be discounted. In any case, interest in this area of research remains unabated, with large clinical trials of novel anti-inflammatory agents underway.⁴⁵

In this context, the findings of the present study are quite remarkable, given that a favorable effect of treatment was found in all studied parameters (biomarkers and cardiac

MRI). It is possible that the broadness of colchicine effects (affecting various pathways of the inflammatory processes) is an advantage in the complex pathophysiological interplay between inflammation, ischemia, and reperfusion in reperfused STEMI. However, one should probably go beyond statistical significance and note, by observing the distribution of evaluated infarct sizes in colchicine-treated patients (eg, in Figure 3), that there was a marked dispersion of values, possibly indicating considerable heterogeneity in the drug effect (or, even more probably, a result of the considerable proportion of premature discontinuation of the study drug). This observation, along with the fact that the study was not powered to demonstrate differences in hard clinical end points, must define the boundaries in generalizing these results: they are certainly compelling, pointing toward potential usefulness of colchicine in this setting, but further studies are definitely necessary to draw secure clinical conclusions.

Study Limitations

The studied measures of infarct size (CK-MB output and MRI-LGE infarct size) are well validated in this setting, with good correlation with prognosis^{46,47} – although limitations can arise both in the case of CK-MB (eg, when different sampling intervals are used in the concentration versus time plot and when comparing patients with altered enzyme kinetics) and in the case of MRI (probably the most important factor is the timing of the measurement relative to the index event). These potential sources of error were carefully kept to a minimum in the present study.

Sources of Funding

This was an investigator-initiated and -funded study.

Disclosures

None.

References

- Braunwald E, Kloner RA. Myocardial reperfusion: a double-edged sword? *J Clin Invest*. 1985;76:1713–1719. doi: 10.1172/JCI112160.
- Entman ML, Michael L, Rossen RD, Dreyer WJ, Anderson DC, Taylor AA, Smith CW. Inflammation in the course of early myocardial ischemia. *FASEB J*. 1991;5:2529–2537.
- Turer AT, Hill JA. Pathogenesis of myocardial ischemia-reperfusion injury and rationale for therapy. *Am J Cardiol*. 2010;106:360–368. doi: 10.1016/j.amjcard.2010.03.032.
- Christia P, Frangogiannis NG. Targeting inflammatory pathways in myocardial infarction. *Eur J Clin Invest*. 2013;43:986–995. doi: 10.1111/eci.12118.
- Ross R. Atherosclerosis is an inflammatory disease. *Am Heart J*. 1999;138(5 pt 2):S419–S420.
- Klingenberg R, Luscher TF. Inflammation in coronary artery disease and acute myocardial infarction - is the stage set for novel therapies? *Curr Pharm Des*. 2012;18:4358–4369.
- Fitzgerald GA. Coxibs and cardiovascular disease. *N Engl J Med*. 2004;351:1709–1711. doi: 10.1056/NEJMp048288.
- Nussinovitch U, de Carvalho JF, Pereira RM, Shoenfeld Y. Glucocorticoids and the cardiovascular system: state of the art. *Curr Pharm Des*. 2010;16:3574–3585.
- Olsen AM, Fosbøl EL, Lindhardtsen J, Andersson C, Folke F, Nielsen MB, Køber L, Hansen PR, Torp-Pedersen C, Gislason GH. Cause-specific cardiovascular risk associated with nonsteroidal anti-inflammatory drugs among myocardial infarction patients—a nationwide study. *PLoS One*. 2013;8:e54309. doi: 10.1371/journal.pone.0054309.
- Deftereos S, Giannopoulos G, Papoutsidakis N, Panagopoulou V, Kossyvakis C, Raisakis K, Cleman MW, Stefanadis C. Colchicine and the heart: pushing the envelope. *J Am Coll Cardiol*. 2013;62:1817–1825. doi: 10.1016/j.jacc.2013.08.726.
- Jeffreys H, Jeffreys BS. *Methods of Mathematical Physics*. 3rd ed. Cambridge, England: Cambridge University Press; 1988:286–288.
- Heiberg E, Ugander M, Engblom H, Götzberg M, Olivecrona GK, Erlinge D, Arheden H. Automated quantification of myocardial infarction from MR images by accounting for partial volume effects: animal, phantom, and human study. *Radiology*. 2008;246:581–588. doi: 10.1148/radiol.2461062164.
- Sadowski M, Zabczyk M, Undas A. Coronary thrombus composition: links with inflammation, platelet and endothelial markers. *Atherosclerosis*. 2014;237:555–561. doi: 10.1016/j.atherosclerosis.2014.10.020.
- Adlbrecht C, Wurm R, Humenberger M, Andreas M, Redwan B, Distelmaier K, Klappacher G, Lang IM. Peri-interventional endothelin-A receptor blockade improves long-term outcome in patients with ST-elevation acute myocardial infarction. *Thromb Haemost*. 2014;112:176–182. doi: 10.1160/TH13-10-0832.
- Gomaraschi M, Ossoli A, Favari E, Adorni MP, Sinagra G, Cattin L, Veglia F, Bernini F, Franceschini G, Calabresi L. Inflammation impairs eNOS activation by HDL in patients with acute coronary syndrome. *Cardiovasc Res*. 2013;100:36–43. doi: 10.1093/cvr/cvt169.
- Mayyas FA, Al-Jarrah MI, Ibrahim KS, Alzoubi KH. Level and significance of plasma myeloperoxidase and the neutrophil to lymphocyte ratio in patients with coronary artery disease. *Exp Ther Med*. 2014;8:1951–1957. doi: 10.3892/etm.2014.2034.
- Lipkova J, Parenica J, Duris K, Helanova K, Tomandl J, Kubkova L, Vasku A, Goldbergova Pavkova M. Association of circulating levels of RANTES and -403G/A promoter polymorphism to acute heart failure after STEMI and to cardiogenic shock. *Clin Exp Med*. 2015;15:405–414. doi: 10.1007/s10238-014-0294-5.
- He J, Li J, Wang Y, Hao P, Hua Q. Neutrophil-to-lymphocyte ratio (NLR) predicts mortality and adverse-outcomes after ST-segment elevation myocardial infarction in Chinese people. *Int J Clin Exp Pathol*. 2014;7:4045–4056.
- Sawant AC, Adhikari P, Narra SR, Srivatsa SS, Mills PK, Srivatsa SS. Neutrophil to lymphocyte ratio predicts short- and long-term mortality following revascularization therapy for ST elevation myocardial infarction. *Cardiol J*. 2014;21:500–508. doi: 10.5603/CJ.a2013.0148.
- van Diepen S, Newby LK, Lopes RD, Stebbins A, Hasselblad V, James S, Roe MT, Ezekowitz JA, Moliterno DJ, Neumann FJ, Reist C, Mahaffey KW, Hochman JS, Hamm CW, Armstrong PW, Granger CB, Theroux P, APEX AMI Investigators. Prognostic relevance of baseline pro- and anti-inflammatory markers in STEMI: an APEX AMI substudy. *Int J Cardiol*. 2013;168:2127–2133. doi: 10.1016/j.ijcard.2013.01.004.
- Lindberg S, Pedersen SH, Mogelvang R, Galatius S, Flyvbjerg A, Jensen JS, Bjerre M. Soluble form of membrane attack complex independently predicts mortality and cardiovascular events in patients with ST-elevation myocardial infarction treated with primary percutaneous coronary intervention. *Am Heart J*. 2012;164:786–792. doi: 10.1016/j.ahj.2012.08.018.
- Theroux P, Armstrong PW, Mahaffey KW, Hochman JS, Malloy KJ, Rollins S, Nicolau JC, Lavoie J, Luong TM, Burchenal J, Granger CB. Prognostic significance of blood markers of inflammation in patients with ST-segment elevation myocardial infarction undergoing primary angioplasty and effects of pexelizumab, a C5 inhibitor: a substudy of the COMMA trial. *Eur Heart J*. 2005;26:1964–1970. doi: 10.1093/eurheartj/ehi292.
- Guerchicoff A, Stone GW, Mehran R, Xu K, Nichols D, Claessen BE, Guagliumi G, Witzentichler B, Henriques JP, Dangas GD. Analysis of biomarkers for risk of acute kidney injury after primary angioplasty for acute ST-segment elevation myocardial infarction: results of the HORIZONS-AMI trial. *Catheter Cardiovasc Interv*. 2015;85:335–342. doi: 10.1002/ccd.25620.
- Brunetti ND, Correale M, De Gennaro L, Cuculo A, Pellegrino PL, Di Biase M. Blunted inflammatory response in STEMI patients timely reperused. *J Cardiovasc Med (Hagerstown)*. 2014;15:48–52. doi: 10.2459/JCM.0b013e328365c13a.
- Urbano-Moral JA, Lopez-Haldon JE, Fernandez M, Mancha F, Sanchez A, Rodriguez-Puras MJ, Villa M, Lopez-Pardo F, Diaz de la Llera L, Valle JJ, Martinez A. Prognostic value of different serum biomarkers for left ventricular remodelling after ST-elevation myocardial infarction treated with primary percutaneous coronary intervention. *Heart*. 2012;98:1153–1159. doi: 10.1136/heartjnl-2012-301636.
- van Diepen S, Roe MT, Lopes RD, Stebbins A, James S, Newby LK, Moliterno DJ, Neumann FJ, Ezekowitz JA, Mahaffey KW, Hochman JS, Hamm CW, Armstrong PW, Theroux P, Granger CB. Baseline NT-proBNP and biomarkers of inflammation and necrosis in patients with ST-segment elevation myocardial infarction: insights from the APEX-AMI trial. *J Thromb Thrombolysis*. 2012;34:106–113. doi: 10.1007/s11239-012-0691-0.
- van der Laan AM, Hirsch A, Robbers LF, Nijveldt R, Lommerse I, Delewi R, van der Vleuten PA, Biemond BJ, Zwaginga JJ, van der Giessen WJ, Zijlstra F, van Rossum AC, Voermans C, van der Schoot CE, Piek JJ. A proinflammatory monocyte response is associated with myocardial injury and impaired functional outcome in patients with ST-segment elevation myocardial infarction: monocytes and myocardial infarction. *Am Heart J*. 2012;163:57–65.e2. doi: 10.1016/j.ahj.2011.09.002.
- Husser O, Bodi V, Sanchis J, Nunez J, Mainar L, Chorro FJ, Lopez-Lereu MP, Monmeneu JV, Chaustre F, Forteza MJ, Trapero I, Dasi F, Benet I, Riegger GA, Llacer A. White blood cell subtypes after STEMI: temporal evolution, association with cardiovascular magnetic resonance-derived infarct size and impact on outcome. *Inflammation*. 2011;34:73–84. doi: 10.1007/s10753-010-9209-0.
- Nidorf SM, Eikelboom JW, Budgeon CA, Thompson PL. Low-dose colchicine for secondary prevention of cardiovascular disease. *J Am Coll Cardiol*. 2013;61:404–410. doi: 10.1016/j.jacc.2012.10.027.

30. Deftereos S, Giannopoulos G, Panagopoulou V, Bouras G, Raisakis K, Kossyvakis C, Karageorgiou S, Papadimitriou C, Vastaki M, Kaoukis A, Angelidis C, Pagoni S, Pyrgakis V, Alexopoulos D, Manolis AS, Stefanadis C, Cleman MW. Anti-inflammatory treatment with colchicine in stable chronic heart failure: a prospective, randomized study. *JACC Heart Fail*. 2014;2:131–137. doi: 10.1016/j.jchf.2013.11.006.
31. Deftereos S, Giannopoulos G, Efremidis M, Kossyvakis C, Katsivas A, Panagopoulou V, Papadimitriou C, Karageorgiou S, Doudoumis K, Raisakis K, Kaoukis A, Alexopoulos D, Manolis AS, Stefanadis C, Cleman MW. Colchicine for prevention of atrial fibrillation recurrence after pulmonary vein isolation: mid-term efficacy and effect on quality of life. *Heart Rhythm*. 2014;11:620–628. doi: 10.1016/j.hrthm.2014.02.002.
32. Nogales E, Whittaker M, Milligan RA, Downing KH. High-resolution model of the microtubule. *Cell*. 1999;96:79–88.
33. Downing KH. Structural basis for the interaction of tubulin with proteins and drugs that affect microtubule dynamics. *Annu Rev Cell Dev Biol*. 2000;16:89–111. doi: 10.1146/annurev.cellbio.16.1.89.
34. Ravelli RB, Gigant B, Curmi PA, Jourdain I, Lachkar S, Sobel A, Knossow M. Insight into tubulin regulation from a complex with colchicine and a stathmin-like domain. *Nature*. 2004;428:198–202. doi: 10.1038/nature02393.
35. Bhattacharyya B, Panda D, Gupta S, Banerjee M. Anti-mitotic activity of colchicine and the structural basis for its interaction with tubulin. *Med Res Rev*. 2008;28:155–183. doi: 10.1002/med.20097.
36. Terkeltaub RA. Colchicine update: 2008. *Semin Arthritis Rheum*. 2009;38:411–419. doi: 10.1016/j.semarthrit.2008.08.006.
37. Cronstein BN, Molad Y, Reibman J, Balakhane E, Levin RI, Weissmann G. Colchicine alters the quantitative and qualitative display of selectins on endothelial cells and neutrophils. *J Clin Invest*. 1995;96:994–1002. doi: 10.1172/JCI118147.
38. Forrat R, Sebbag L, Ferrera R, Hadour G, Canet E, Tabib A, de Lorgieril M. Effect of colchicine on circulating and myocardial neutrophils and on infarct size in a canine model of ischemia and reperfusion. *J Cardiovasc Pharmacol*. 1996;27:876–883.
39. Raju NC, Yi Q, Nidorf M, Fagel ND, Hiralal R, Eikelboom JW. Effect of colchicine compared with placebo on high sensitivity C-reactive protein in patients with acute coronary syndrome or acute stroke: a pilot randomized controlled trial. *J Thromb Thrombolysis*. 2012;33:88–94. doi: 10.1007/s11239-011-0637-y.
40. Giannopoulos G, Angelidis C, Kouritis VK, Dedeilias P, Filippatos G, Cleman MW, Panagopoulou V, Siasos G, Tousoulis D, Lekakis J, Deftereos S. Usefulness of colchicine to reduce perioperative myocardial damage in patients who underwent on-pump coronary artery bypass grafting. *Am J Cardiol*. 2015;115:1376–1381. doi: 10.1016/j.amjcard.2015.02.036.
41. Abbate A, Kontos MC, Grizzard JD, Biondi-Zoccai GG, Van Tassell BW, Robati R, Roach LM, Arena RA, Roberts CS, Varma A, Gelwix CC, Salloom FN, Hastillo A, Dinarello CA, Vetrovec GW; VCU-ART Investigators. Interleukin-1 blockade with anakinra to prevent adverse cardiac remodeling after acute myocardial infarction (Virginia Commonwealth University Anakinra Remodeling Trial [VCU-ART] Pilot study). *Am J Cardiol*. 2010;105:1371–1377.e1. doi: 10.1016/j.amjcard.2009.12.059.
42. Abbate A, Van Tassell BW, Biondi-Zoccai G, Kontos MC, Grizzard JD, Spillman DW, Oddi C, Roberts CS, Melchior RD, Mueller GH, Abouzaki NA, Rengel LR, Varma A, Gambill ML, Falcao RA, Voelkel NF, Dinarello CA, Vetrovec GW. Effects of interleukin-1 blockade with anakinra on adverse cardiac remodeling and heart failure after acute myocardial infarction [from the Virginia Commonwealth University-Anakinra Remodeling Trial (2) (VCU-ART2) pilot study]. *Am J Cardiol*. 2013;111:1394–1400. doi: 10.1016/j.amjcard.2013.01.287.
43. Morton AC, Rothman AM, Greenwood JP, Gunn J, Chase A, Clarke B, Hall AS, Fox K, Foley C, Banya W, Wang D, Flather MD, Crossman DC. The effect of interleukin-1 receptor antagonist therapy on markers of inflammation in non-ST elevation acute coronary syndromes: the MRC-ILA Heart Study. *Eur Heart J*. 2015;36:377–384. doi: 10.1093/eurheartj/ehu272.
44. Piot C, Croisille P, Staat P, Thibault H, Rioufol G, Mewton N, Elbelghiti R, Cung TT, Bonnefoy E, Angoulvant D, Macia C, Raczka F, Sportouch C, Gahide G, Finet G, André-Fouët X, Revel D, Kirkorian G, Monassier JP, Derumeaux G, Ovize M. Effect of cyclosporine on reperfusion injury in acute myocardial infarction. *N Engl J Med*. 2008;359:473–481. doi: 10.1056/NEJMoa071142.
45. O'Donoghue ML, Glaser R, Aylward PE, Cavender MA, Crisp A, Fox KA, Laws I, Lopez-Sendon JL, Steg PG, Theroux P, Sabatine MS, Morrow DA. Rationale and design of the Losmapimod To Inhibit p38 MAP kinase as a Therapeutic target and modify outcomes after an acute coronary syndrome trial. *Am Heart J*. 2015;169:622–630.e6. doi: 10.1016/j.ahj.2015.02.012.
46. Bagai A, Schulte PJ, Granger CB, Mahaffey KW, Christenson RH, Bell G, Lopes RD, Green CL, Lincoff AM, Armstrong PW, Roe MT. Prognostic implications of creatine kinase-MB measurements in ST-segment elevation myocardial infarction patients treated with primary percutaneous coronary intervention. *Am Heart J*. 2014;168:503–511.e2. doi: 10.1016/j.ahj.2014.06.008.
47. Kim HW, Farzaneh-Far A, Kim RJ. Cardiovascular magnetic resonance in patients with myocardial infarction: current and emerging applications. *J Am Coll Cardiol*. 2009;55:1–16. doi: 10.1016/j.jacc.2009.06.059.

CLINICAL PERSPECTIVE

In this study, a short course of colchicine treatment or placebo was administered to 151 patients with ST-segment-elevation acute myocardial infarction treated with primary percutaneous coronary intervention. Colchicine was started in the catheterization laboratory and was continued for 5 days. The primary end point was the area under the creatine kinase-myocardial brain fraction curve over the first 72 hours of hospitalization and, in a subset of 60 patients, infarct size was also assessed with cardiac MRI with late gadolinium enhancement 6 to 9 days after the index myocardial infarction. Both biomarker- and MRI-late gadolinium enhancement-defined infarct size was smaller in patients of the active treatment group. Infarct size was positively associated with markers of inflammation (neutrophil count and C-reactive protein), and colchicine treatment was correlated with lower levels of these markers. The findings suggest a role for anti-inflammatory treatment in the peri-infarct period. Although the study was not powered to assess clinical outcomes, the surrogate outcome measures that were used are well-established correlates of prognosis and clinical events. Still, for any firm recommendations for colchicine treatment in patients with acute myocardial infarction to be made, a larger study with clinical end points would be needed.