v. 2, n. 37, 2022

International Journal of Health Science

COLCHICINE IN ATHEROSCLEROTIC CORONARY ARTERY DISEASE: NEW CHALLENGES FOR AN OLD DRUG

José Marcos Girardi
Professor of the Post graduate program of Sabin Teaching and Research.
University Hospital – Federal University of Juiz de Fora – MG
Sabincor
http://lattes.cnpq.br/2263234698325942

Antônio Alves do Couto
Professor of Cardiology , Fluminense Federal University.
Niterói – Rio de Janeiro
http://lattes.cnpq.br/3405057415489038

Abstract: The aim of this review was to summarize current data that support the efficacy and safety of colchicine therapy in atherosclerotic cardiovascular disease. Vascular inflammation plays a central role in coronary atherosclerosis, and the anti-inflammatory action of colchicine in low doses (0.5 mg per day) has a recognized effect on reducing ischemic events. We conducted a bibliographic review that included free access publications from the PubMed platform, using the descriptors "colchicine" and "coronary disease". There were included meta-analysis studies, randomized controlled trials, reviews and systematic reviews between 2018 and 2022. Colchicine has important actions in the interruption of cellular inflammatory activities, as it binds to free tubulin dimers, preventing elongation of the microtubule, and interferes with intracellular protein trafficking, secretion, and ionic organization of homeostasis. It also impairs neutrophils recruitment, inhibits nuclear factor-kappa B (NF- κ B) signaling and affects inflammatory receptor protein 3 (NLPR3) activation, leading to the suppression of interleukins 1 β , 18 and 6 release. Gastrointestinal intolerance limits its use in 10% of patients approximately. Attention is needed for drug interactions with CYP3A4 and p-glycoprotein inhibitors/competitors. Its use in acute and chronic coronary syndromes and in coronary angioplasty procedures have been studied in several trials, showing promising results. However, an increase in cases of non-cardiovascular death in patients treated with colchicine was observed in a meta-analysis study, in comparison with placebo or standard therapy. Thus, it is imperative to identify those who will adapt or be harmed by colchicine treatment. In conclusion, coronary arteriopathy is the leading cause of mortality in the world, it justifies the research of low-cost agents that can minimize the impact of this pathology.

Keywords: Colchicine, coronary disease, review.

INTRODUCTION

Colchicine is an alkaloid derived from *Colchicum autumnale* , one of the oldest drugs in the world and has been used to treat joint pain for over 3500 years (EVANS, 2009). It was first mentioned in the medical literature on *EbersPapyrus* around 1500 BC. Its use continued for centuries and was prescribed by Avicenna . It was reported in the London *Pharmacopoeia* in 1618, its active ingredient was discovered in 1800 and in 1884 Alfred Houdé refined the purification process to obtain a pure crystallized component (KARAMANOU et al., 2018). The name ' colchicine ' is derived from the legendary kingdom of Colchis from where Jason retrieved the Golden Fleece (NERLEKAR; BEALE; HARPER, 2014). It is currently used to treat gout, familial Mediterranean fever, and pericardial diseases. In addition to the classic indications, it has been investigated for the treatment of Coronavirus 2019 infection with initially promising results and prevention and treatment of atherosclerotic cardiovascular disease (BANACH; PENSON, 2021), by inhibiting multiple cellular pro-inflammatory pathways (D'AMARIO et al. ., 2021).

There is a strong association between inflammation and the development of atherosclerosis (HANSSON, 2005). In addition to lipid-lowering treatments, investigating the potential effects of anti-inflammatory drugs on atherosclerosis and cardiovascular disease has become an important field of research. Several biological processes contribute to the pathophysiology of atherosclerosis. Endothelial dysfunction, inflammation and oxidative stress are important in the genesis and progression of the disease (HANSSON, 2005; TUVALI et al., 2022), accelerated by risk factors.

Thus, the increasing interest of researchers in the new applications of this old drug is a strong demand for a comprehensive understanding of its efficacy and safety in coronary atherosclerotic disease, object of this review.

METHODOLOGY

The study was developed through the methodology of literature review, search for articles through the PubMed platform , using descriptors for indexing scientific articles - Descriptors in Health Sciences (DeCS): "*colchicine*" *and* "*coronary disease* ".

The following types of articles were included: meta-analysis, randomized controlled trials, review and systematic review, all dealing with studies in humans and in the English language. The scope selected for the research was between 2018 and 2022, and the search was carried out in May 2022, identifying available and open access articles.

RESULTS

In a first survey, 23 articles were selected. Initially, titles and abstracts covering the specific theme were analyzed. Articles that dealt with topics such as Covid-19 (2), lupus (1) and gout (1) were excluded, totaling 19 articles that support this bibliographic analysis. From this selection, other sources cited by them were incorporated, according to the focus of this review.

CHEMICAL STRUCTURE

Colchicine has the formula C22H25NO6 with the chemical name: N -[(7S)-5,6,7,9-tetrahydro-1,2,3,10-tetramethoxy-9-oxobenzo (a)heptalen-7-yl) acetamide] (Figure 1). It contains three rings highly involved in tubulin binding , acting to modify this binding: the A ring prevents the formation of a complex, the C ring produces inactive compounds with no affinity for tubulin , and the B ring does not prevent colchicine from binding to tubulin. to tubulin , but affects their interaction, modulating the activation energy of the reaction (KOFLER et al., 2021).

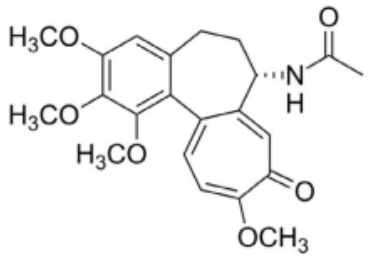

Figure 1- Chemical structure of colchicine (KOFLER et al., 2021).

MECHANISMS OF ACTION

The mechanisms through which colchicine exerts anti-inflammatory properties are multiple and complex (BANACH; PENSON, 2021**).** Perhaps the most outstanding is the ability to bind free tubulin dimers which, when incorporated, block subsequent microtubule polymerization (ANDREU; TIMASHEFF, 1982; SLOBODNIK et al., 2018; JIA et al., 2020).

By binding to soluble tubulins, it can prevent microtubule elongation or, at higher doses, induce microtubule depolymerization (AKODAD et al., 2020). Colchicine destabilizes the cytoskeleton of cellular processes that require dynamic polymerization of tubulin (TERKELTAUB , 2009), including cell division, cell migration and shape, intracellular protein trafficking, secretion, ionic homeostasis and organelle organization (AKODAD et al., 2020).

As colchicine / tubulin complexes form and become embedded in elongated microtubule structures , these limit microtubular extension, at nanomolar concentration contributing to their therapeutic effects (ROBINSON et al., 2022).

The mechanism is dose-dependent and appears to be directly responsible, at least *in vitro* , for the effects on cell migration, cytokine

release and intracellular trafficking, with an important role in the interruption of cellular inflammatory activities (SLOBODNIK et al., 2018).

Colchicine inhibits neutrophil adhesion and recruitment, suppressing the release of the chemotactic agent leukotriene B4 , altering L- selectin expression (CRONSTEIN et al., 1995), and neutrophil deformity (PASCHKE et al., 2013; SLOBODNIK et al., 2013; SLOBODNIK et al., 1995). al., 2018). Interacts with neutrophil function, inhibition of inflammasome receptor protein 3 (NLPR3), with suppression of Interleukin (IL)-1β, IL-18 and IL-6 release (OPSTAL et al., 2020; SLOBODNIK et al., 2018; GROSLAMBER; PY, 2018; ANDREIS; IMAZIO; DE FERRARI, 2021 ; TUCKER et al., 2021).

Nuclear Factor kappa Beta (NF - kB) is essential in cell signaling of pathophysiological processes. Its activation favors the production of IL-6, IL-8 and Tumor Necrosis Factor-Alpha (TNF-α), activating endothelial cells, neutrophils, monocytes, causing endothelial dysfunction. Inhibition of this pathway is also an important mechanism of action of colchicine (ZHANG et al., 2022).

When used in low doses, other actions have been described, such as increased activity of cyclic adenosine monophosphate (cAMP), one of the most important secondary messengers, involved as a modulator of physiological processes; modulation of the expression of adhesion proteins (E- selectin , L- selectin); suppression of endothelial rolling and adhesion (CRONSTEIN et al., 1995), IL-8 and on the prostanoid systems , contributing to anti-inflammatory actions (ROBINSON et al., 2022).

METABOLISM AND ADVERSE EFFECTS

Colchicine is rapidly absorbed after oral administration, peak plasma concentrations occur within 1-2 h and its bioavailability ranges from 24 to 88% (MARTINON et al., 2006). It accumulates in inflammatory cells, with an intraleukocyte concentration higher than in plasma. Although it can cross the placenta and distribute into breast milk, no clinical impact on the fetus has been observed (D' AMARIO et al., 2021).

Up to 20% of the drug is excreted in the urine, while most undergoes enterohepatic recirculation , excreted via bile and feces with a half-life of 20 hours (NIDORF et al., 2013; D'AMARIO et al., 2021). Colchicine is a substrate for transport via cytochrome P3A4 (CYP3A4) and P-glycoprotein - transmembrane drug carrier protein - responsible for its metabolism and elimination. Interactions have been reported in association with P-glycoprotein inhibitors or CYP3A4 inhibitors, resulting in impaired colchicine metabolism and toxicity (D' AMARIO et al., 2021). Fibrates and statins show interactions with colchicine (mostly simvastatin, atorvastatin, but not ezetimibe and niacin), as well as carvedilol, non-dihydropyridine calcium channel blockers, amiodarone, digoxin, and quinidine (SLOBODNICK et al., 2018; AKODAD et al., 2020; ŞEN et al., 2021; IMAZIO; NIDORF, 2021; ANDREIS et al., 2021; D'AMARIO et al., 2021). It is important to pay attention to clinical guidelines and their use should be monitored (Chart 1).

Strong inhibitors of CYP 3A4	Moderate CYP3A4 inhibitors	P-glycoprotein inhibitors
clarithromycin	cimetidine	amiodarone
diltiazem	ciprofloxacin	carvedilol
Itraconazole	cyclosporine	clarithromycin
ketoconazole	Erythromycin	Itraconazole
ritonavir	fluconazole	quinidine
	verapamil	ranolazine
	statins	ritonavir

	fibrotes	verapamil
	fluoxetine	digoxin
		simvastatin
		cyclosporine

Table 1: Pharmacological interactions between colchicine and cardiovascular drugs (SLOBODNICK et al., 2018; AKODAD et al., 2020; ŞEN et al., 2021; IMAZIO; NIDORF, 2021; ANDREIS et al., 2021; D' AMARIO et al. ., 2021).

When administering colchicine with a statin, it may be desirable to choose one that is not metabolized by the CYP3A4 enzyme, such as pravastatin , rosuvastatin (SLOBODNICK et al., 2018) or pitavastatin (ŞEN et al., 2021). Dose adjustment is recommended in the elderly population and those with renal or hepatic impairment (SLOBODNICK et al., 2018; ŞEN et al., 2021).

Gastrointestinal symptoms such as colic, diarrhea, and abdominal pain are common, however, the rate of gastrointestinal events was not significant in a meta-analysis (ŞEN et al., 2021). They are more evident at high doses and of less clinical importance at low doses (0.5 mg/day). Less common side effects include myalgia, rash, alopecia, hepatotoxicity, with pre-existing liver disease or renal dysfunction increasing this likelihood (SYKES et al., 2021).

Another meta-analysis (ANDREIS et al., 2021) evaluated 14,983 patients and demonstrated that colchicine use was associated with gastrointestinal phenomena, mainly diarrhea, also observed with drug discontinuation, compared to placebo. At a dose of 0.5 mg daily and in patients who received colchicine for periods longer than 6 months, the risk was similar to placebo. Gastrointestinal intolerance to colchicine is transient and this could explain why the risk of discontinuation decreases with longer periods of treatment, it is useful, if necessary, to temporarily divide the daily dose, reduce dairy intake and add spasmolytics and antidiarrheals to the dose treatment.

Prophylactic dosing to prevent cardiovascular disease is unclear. Most clinical trials recommend 0.5-1.0 mg/day for the treatment of gout and pericarditis (ANDREIS et al., 2021). Overdosage (6.0-8.0 mg) can have fatal consequences, due to the interaction with tubulin of myocardial cells, leading to cardiac arrhythmias, hemodynamic instability (ANDREIS et al., 2021), multiple organ failure and death. when the dose exceeds 0.8 mg/kg (ZHANG et al., 2022). There is no specific antidote for overdose, and conservative treatment, with gastric lavage, measures to prevent shock and symptoms, are usually sufficient (ZHANG et al., 2022).

COLCHICINE IN THE VASCULAR INFLAMMATORY PROCESS

Since the mid-twentieth century, substantial progress has been made in the prevention of cardiovascular diseases through the identification and control of risk factors, such as the relationship between the increase in low-density lipoprotein (LDL-Cholesterol), its accumulation in the subendothelial layer and genesis of atheromatosis. Initially, dietary approaches were made to reduce LDL-Cholesterol, with restriction of saturated fat and, later, the development of drugs such as statins (BANACH; PENSON, 2021). These drugs reduce the rate of atherosclerotic cardiovascular events by approximately 25% for each mmol /L (approximately 18 mg/ dL) reduction in LDL cholesterol for each year of therapy (COLLINS et al., 2016). Likewise, *proprotein convertase subtilisin/kecxin typ 9* (PCSK9), which act on hepatic receptors, reduce LDL-C more incisively, with additional reductions in the risk of events (BANACH; PENSON, 2021).

However, the residual risk of atherosclerotic disease remains high even

among patients who are optimally treated, evidencing the role of vascular inflammation (JIA et al., 2020).

Only recently have these observations been explored to reduce cardiovascular risk. This gap can be explained by the lack of prior knowledge of the mechanisms involved in atherosclerosis, lack of selective inhibitors and skepticism of this approach due to poor outcomes when non-specific anti-inflammatory agents such as corticosteroids have been used in the setting of acute myocardial infarction (AMI). (GIULIANO et al., 2003) in addition to the increased incidence of cardiovascular events in individuals treated with anti-inflammatory cyclooxygenase 2 (Cox-2) inhibitors (PATRONO, 2016; RIDKER, 2019; ŞEN et al., 2021).

Thus, vascular inflammation is considered to have a central role in the pathophysiology of atherosclerosis and colchicine , due to its anti-inflammatory properties, has been shown to be beneficial in secondary prevention (AKODAD et al., 2020; KEARNEY et al., 2021).

Among patients undergoing cardiac surgery, the perioperative use of colchicine compared with placebo reduced the incidence of post- pericardiotomy syndrome. In patients with AMI or chronic coronary syndrome (CCS), colchicine reduced the need for revascularization (SYKES et al., 2021).

A recent retrospective study of patients with gout identified that colchicine was associated with a 49% relative risk reduction in the primary composite endpoint of AMI, stroke, and transient ischemic attack compared with patients not using colchicine , as well as a relative reduction in 73% risk of all-cause mortality (SLOBODNICK et al., 2018).

The inflammatory risk in patients undergoing coronary angioplasty procedure is clinically relevant. A retrospective study that evaluated 7,026 individuals after the intervention proposed that high levels of C-Reactive Protein (CRP) were correlated with all-cause mortality and the risk of AMI. A pioneering study demonstrated that colchicine can prevent elevation of biomarkers in an acute coronary event, as it suppressed the increase in IL-6 and CRP concentrations after coronary angioplasty (SHA et al., 2020; KAO; HUANG, 2022).

The effects of eight anti-inflammatory drugs (pexelizumab, anakinra, colchicine, darapladib, varespladib, canakinumab, inclacumab and losmapimod) were studied for outcomes in patients with coronary artery disease . The drugs demonstrated a modest reduction in events when compared with placebo. Colchicine demonstrated a beneficial effect in reducing the risk of revascularization after AMI and significantly reducing the incidence of stroke, compared to placebo and lower chances of cardiovascular events compared to other agents (WUDEXI et al., 2021). Thus, based on the findings of several studies, we found that colchicine may play a relevant role in atherosclerosis.

COLCHICINE IN ACUTE AND CHRONIC CORONARY SYNDROMES

Update and review article highlights the effects of colchicine in the setting of atherosclerotic cardiovascular disease. Its action in increasing survival, reducing left ventricular remodeling by inhibiting the accumulation of granulocytes in affected cells, highlighting the potential to reduce the extent and propagation of the inflammatory process observed during AMI (SLOBODNICK et al., 2018). Pleiotropic effects of colchicine demonstrate cardioprotective properties and these data provided the basis for subsequent clinical trials (TUVALI et al., 2022).

Colchicine treatment has been linked

to inhibition of myocardial cell apoptosis, ventricular hypertrophy, anti-fibrotic effects and anti-arrhythmic effects in an animal model of heart failure (AKODAD et al., 2020). Several studies have advocated the use of colchicine at low doses (0.5 to 1.0 mg/day) in various scenarios with ACS. Most of these have been short-lived and concentrated in relatively small populations (BANACH; PENSON, 2021).

Meta-analysis provided evidence that colchicine administration early or at the time of coronary angioplasty reduces major cardiovascular events (27%). This risk reduction for primary outcome was primarily driven by lower rates of revascularization, cerebral ischemia, and stent thrombosis, the latter considered the greatest benefit (AW et al., 2022).

The early administration of colchicine in acute coronary syndrome (ACS) seems to reduce the damage caused by ischemia, while its administration in patients with CCS promotes plaque stabilization and healing. (D'AMARIO et al., 2021). Deftereos et al. (2015) examined 151 patients with AMI and ST-segment elevation. Colchicine was administered after angioplasty and continued for 5 days. Although cardiac enzyme levels and infarct size by cardiac magnetic resonance imaging were significantly reduced (p=0.019), there was no reduction in adverse events. These results suggest a potential benefit of colchicine in AMI with ST -segment elevation (SLOBODNICK et al., 2018; TUCKER et al., 2021; KAO; HUANG, 2022).

An observational study with 80 patients (VAIDYA et al., 2018), evaluated the use of low-dose colchicine in ACS as part of the optimized medical treatment with atheroma plaque imaging as the final outcome. After 12.6 months, the therapy significantly decreased plaque volume and CRP levels. Despite study limitations, such as the small number of participants, the results provide a rationale for future research (TUVALI et al., 2022).

Akrami et al (2021) demonstrated that the addition of low-dose colchicine to clinical treatment in patients with ACS could be effective in reducing major cardiac events. However, Kofler et al. (2021) observed in a meta -analysis of randomized trials an increase in non-cardiovascular death in patients treated with colchicine compared to placebo or standard therapy. Regardless of dose or duration of therapy, colchicine treatment did not show any significant association with all-cause cardiovascular mortality. The analysis revealed that patients with atherosclerotic coronary artery disease treated with colchicine appear to have lower rates of MI and stroke/transient ischemic attack compared to placebo or standard therapy (KOFLER et al., 2021).

The COLCOT trial (Colchicine Cardiovascular Outcomes Trial) demonstrated clinical effects of colchicine on ACS (TARDIF et al., 2019). This study was carried out in 167 centers (12 countries), 4,745 patients with a mean age of 61 years and a recent diagnosis of AMI (up to 30 days). They were randomized to receive colchicine 0.5 mg daily or placebo for an average of 4 years, 13.5 days after AMI. The primary composite endpoint compared the rate of cardiovascular death, resuscitated cardiac arrest, AMI, cerebral ischemia, or urgent hospitalization for angina leading to coronary revascularizations (D'AMARIO et al., 2021). Cardiovascular event rates were 5.5% in the colchicine group and 7.1% in the placebo group (p = 0.02). (JIA et al., 2020; TUCKER et al., 2021; KAO; HUANG, 2022).

Finally, the potential benefit of post-procedural treatment with colchicine was highlighted in a secondary analysis of COLCOT (BOUABDALIAOUI, et al., 2020). This study recruited 4661 participants with recent AMI, of which 93% underwent

coronary angioplasty, randomized to colchicine 0.5 mg daily or placebo up to 30 days after the event (TARDIF et al., 2019; TUCKER et al., 2021) . In this secondary analysis, starting colchicine up to 3 days after the event was associated with a greater reduction in the final outcome when compared to starting after 3 days; above this period there was no significant difference in the final outcome between colchicine and placebo, indicating that the benefit in the secondary prevention of AMI is achieved by reducing inflammation in the post-acute procedure setting (TUCKER et al., 2021).

The trial LoDoCo (Low Dose Colchicine trial) was an open-label study of 531 participants that showed reduced risk for acute events in subjects with CCS treated with colchicine ($p < 0.001$) (NIDORF et al., 2013; JIA et al., 2020).

The LoDoCo2 trial (Low -Dose Colchicine 2 trial) enrolled 5522 patients (mean age 66 years) with SCC and no acute cardiovascular events in the 6 months prior to randomization (NIDORF et al, 2020). It was based on the results of the LoDoCo and COLCOT studies to analyze colchicine (n=2762) versus placebo (n=2760) in cardiovascular events. Patients were excluded if they had severe valvular heart disease, severe heart failure, moderate to severe renal impairment, or side effects.

Coronary artery disease was documented by invasive coronary angiography, coronary CT angiography , or calcium score above 400 Agatston units. Patients underwent an initial 1-month run where they received 0.5 mg colchicine daily and randomized 1:1 to receive 0.5 mg colchicine daily or placebo. The final outcome was a composite of cardiovascular death, spontaneous AMI, ischemic stroke, or ischemic coronary revascularization. At an average of 29 months, there were 451 events, 6.8% in the colchicine group and 9.6% in the placebo group. The absolute event rates per 100 person-years were 2.5 and 3.6, respectively ($p < 0.001$). There were similar rates of cancer diagnosis, hospitalization for infection, pneumonia, and gastrointestinal reason in both groups. Gout was significantly less prevalent in those treated with colchicine (JIA et al., 2020).

The study was limited by the absence of data on CRP, few females (15%) and recruitment from a high cardiovascular risk group. As expected, colchicine was associated with a high incidence of gastrointestinal intolerance. However, the trial suggests that for patients with CCS, colchicine may be useful as an additional therapy in secondary prevention. Future studies may assist in the analysis of subgroups that will benefit the most (KEARNEY et al., 2020; TUVALI et al., 2022).

In the LoDoCo2 study, a pre -randomization period was used, in which potential participants who experienced adverse effects left the trial prior to allocation. Thus, adverse effects reported in the randomized portion of the trial likely underestimate the expected prevalence in the clinic. Diarrhea was reported in 9.7% in the treatment group, compared to 8.9% in the placebo. Studies with statins indicate that the drucebo effect (whereby a patient experiences adverse drug reactions as a result of the expectation of such effects) explains a substantial proportion of muscle soreness reported in patients receiving statins for hypercholesterolemia . This can limit adherence to life-saving preventive drugs (BANACH; PENSON, 2021).

In this study, drug interactions between colchicine and the most commonly prescribed cardiovascular drugs were evaluated to provide clinicians with guidance, warnings, and precautions. In some patients, the concomitant drug may be discontinued and/ or replaced with an alternative treatment,

such as carvedilol by another beta-blocker or non - dihydropyridines by other drugs, or colchicine may be discontinued if concomitant treatment is used short-term. These patients should be closely monitored with clinical and laboratory assessments (ŞEN et al., 2020).

Two other studies investigated the effect of colchicine on chronic inflammation after coronary angioplasty. in the trial LoDoCo -MI (Low-Dose Colchicine after myocardial Infarction), administration of colchicine 0.5 mg daily for 30 days post-procedure was shown to be safe and with adequate tolerance, successfully reducing the rate of re-hospitalization in 237 patients with AMI (HENNESSY et al., 2019; KAO ; HUANG, 2022; TUCKER et al., 2021), with a modest, statistically non-significant, reduction in CRP in this period.

In another study, 44 participants with AMI and ST -segment elevation underwent primary angioplasty (AKODAD et al., 2017). 1 mg of colchicine per day was administered immediately after the procedure and this did not change the peak of CRP on admission. Possibly the dose and time of administration may have been insufficient to promote a robust anti-inflammatory effect (TUCKER et al., 2021). Unlike LoDoCo2, colchicine was associated with a small but higher incidence of hospitalization for nonfatal pneumonia (0.9% *versus* 0.4%, p=0.03).

New studies with colchicine in ACS were recently published (2020). The COLCHICINE-PCI trial and the COPS trial. The COLCHICINE-PCI trial (SHA et al., 2020) investigated the effects of colchicine in 400 patients at a dose of 1.8 mg on myocardial ischemia related to coronary angioplasty. The administration of colchicine pre-procedure attenuated the elevation of IL-6 and CRP when compared to placebo. In the COPS trial 795 patients were randomized to receive colchicine 0.5 mg twice daily for the first month and then 0.5 mg daily for 11 months or placebo and optimized medical treatment (TONG et al., 2020). The primary outcome was a composite of all-cause death, urgent revascularization, and non-cardioembolic ischemic stroke. There were 24 events in the colchicine group and 38 in the placebo group (p=0.09). Unlike trials LoDoCo and COLCOT tended to have a higher all-cause mortality rate. Like the COLCOT the incidence of other adverse effects including gastrointestinal did not differ between groups (colchicine 23% versus placebo 24.3%) (IMAZIO; NIDORF, 2021). In the COPS study, the colchicine dosage was higher than in COLCOT and initiated during the hospitalization of the event (as opposed to the mean of 13.5 after randomization in COLCOT) and may have contributed to the different results (TUVALI et al., 2022).

The CLEAR-SYNERGY study is an ongoing multicenter study. Evaluates colchicine versus placebo and spironolactoneversus placebo in AMI patients undergoing primary percutaneous coronary intervention in relation to major primary outcomes after 12 months. It will evaluate the potential impact of colchicine in the clinical scenario where the plaques have a higher inflammatory composition (TUVALI et al., 2022).

CONCLUSIONS

The prescription of low-dose colchicine in atherosclerotic coronary artery disease may reduce cardiac events, as a result of myocardial protection and plaque stabilization, requiring evaluation in different types of stents and alternative dosage regimens. Current data do not yet point to routine use in patients with coronary atherosclerosis. It is important to emphasize that, as coronary artery disease is the leading cause of mortality in the world, we need low-cost agents that can mitigate this impact. Colchicine has the potential to

reduce the inflammatory process and further studies are imperative to better understand this strategy.

Patients who use colchicine should be carefully monitored to avoid complications from drug interactions, especially with statins, as it is common for patients with coronary artery disease to use these drugs for secondary prevention. It seems that with the use of colchicine in low doses, advocating statins that do not have significant metabolism through the CYP3A4 (P450) system and continuous monitoring, we can reduce the risk. It remains to be seen in which scenarios these adverse effects would be more evident, if in fact they limit use.

Although it is not possible to reach a definitive conclusion about the higher incidence of non-cardiovascular death in patients using colchicine , this fact observed in some studies cannot be ignored, and it is necessary to identify patients who will adapt or be harmed by colchicine treatment.

REFERENCES

AKODAD, M. et al. COLIN trial: Value of colchicine in the treatment of patients with acute myocardial infarction and inflammatory response. **Archives of Cardiovascular Diseases**, v. 110, n. 6–7, p. 395–402, 1 jun. 2017.

AKODAD, M. et al. Colchicine and myocardial infarction: A review. **Archives of Cardiovascular Diseases**, v. 113, n. 10, p. 652–659, 1 out. 2020.

AKRAMI, M. et al. Effects of colchicine on major adverse cardiac events in next 6-month period after acute coronary syndrome occurrence; a randomized placebo-control trial. **BMC Cardiovascular Disorders**, v. 21, n. 1, 1 dez. 2021.

ANDREIS, A. et al. Colchicine efficacy and safety for the treatment of cardiovascular diseases. **Internal and Emergency Medicine**, v. 16, n. 6, p. 1691–1700, 1 set. 2021.

ANDREIS, A.; IMAZIO, M.; DE FERRARI, G. M. Colchicine for the treatment of cardiovascular diseases: old drug, new targets. **Journal of cardiovascular medicine (Hagerstown, Md.)**, v. 22, n. 1, p. 1–8, 1 jan. 2021.

ANDREU, J. M.; TIMASHEFF, S. N. Tubulin bound to colchicine forms polymers different from microtubules. **Proceedings of the National Academy of Sciences of the United States of America**, v. 79, n. 22, p. 6753–6756, 1982.

AW, K. L. et al. Colchicine for symptomatic coronary artery disease after percutaneous coronary intervention. **Open Heart**, v. 9, n. 1, 6 jan. 2022.

BANACH, M.; PENSON, P. E. Colchicine and Cardiovascular Outcomes: a Critical Appraisal of Recent Studies. **Current Atherosclerosis Reports**, v. 23, n. 7, 1 jul. 2021.

BOUABDALLAOUI, N. et al. Time-to-treatment initiation of colchicine and cardiovascular outcomes after myocardial infarction in the Colchicine Cardiovascular Outcomes Trial (COLCOT). **European Heart Journal**, v. 41, n. 42, p. 4092–4099, 7 nov. 2020.

COLLINS, R. et al. Interpretation of the evidence for the efficacy and safety of statin therapy. **The Lancet**, v. 388, n. 10059, p. 2532–2561, 19 nov. 2016.

CRONSTEIN, B. N. et al. Colchicine alters the quantitative and qualitative display of selectins on endothelial cells and neutrophils. **The Journal of clinical investigation**, v. 96, n. 2, p. 994–1002, 1995.

D'AMARIO, D. et al. Colchicine in ischemic heart disease: the good, the bad and the ugly. **Clinical Research in Cardiology**, v. 110, n. 10, p. 1531–1542, 1 out. 2021.

DEFTEREOS, S. et al. Anti-Inflammatory Treatment With Colchicine in Acute Myocardial Infarction: A Pilot Study. **Circulation**, v. 132, n. 15, p. 1395–1403, 13 out. 2015.

EVANS, W. C. Pharmacological activities of natural products. In: SAUNDERS (Ed.). **Trease and Evans Pharmacognosy**. 16. ed. [s.l: s.n.]. p. 45–52.

GIUGLIANO, G. R. et al. Meta-analysis of corticosteroid treatment in acute myocardial infarction. **The American journal of cardiology**, v. 91, n. 9, p. 1055–1059, 1 maio 2003.

GROSLAMBERT, M.; PY, B. F. Spotlight on the NLRP3 inflammasome pathway. **Journal of inflammation research**, v. 11, p. 359–374, 2018.

HANSSON, G. K. Inflammation, atherosclerosis, and coronary artery disease. **The New England journal of medicine**, v. 352, n. 16, p. 1685–1695, 21 abr. 2005.

HENNESSY, T. et al. The Low Dose Colchicine after Myocardial Infarction (LoDoCo-MI) study: A pilot randomized placebo controlled trial of colchicine following acute myocardial infarction. **American heart journal**, v. 215, p. 62–69, 1 set. 2019.

IMAZIO, M.; NIDORF, M. Colchicine and the heart. **European Heart Journal**, v. 42, n. 28, p. 2745–2760, 21 jul. 2021.

JIA, X. et al. Highlights from Studies in Cardiovascular Disease Prevention Presented at the Digital 2020 European Society of Cardiology Congress: Prevention Is Alive and Well. **Current Atherosclerosis Reports**, v. 22, n. 12, 1 dez. 2020.

KAO, T. W.; HUANG, C. C. Inflammatory Burden and Immunomodulative Therapeutics of Cardiovascular Diseases. **International Journal of Molecular Sciences**, v. 23, n. 2, 1 jan. 2022.

KARAMANOU, M. et al. Isolating Colchicine in 19th Century: An Old Drug Revisited. **Current pharmaceutical design**, v. 24, n. 6, p. 654–658, 16 jan. 2018.

KEARNEY, A. et al. Advances in Clinical Cardiology 2020: A Summary of Key Clinical Trials. **Advances in Therapy**, v. 38, n. 5, p. 2170–2200, 1 maio 2021.

KOFLER, T. et al. Colchicine in patients with coronary artery disease: A systematic review and meta-analysis of randomized trials. **Journal of the American Heart Association**, v. 10, n. 16, 17 ago. 2021.

MARTINON, F. et al. Gout-associated uric acid crystals activate the NALP3 inflammasome. **Nature**, v. 440, n. 7081, p. 237–241, 9 mar. 2006.

NERLEKAR, N.; BEALE, A.; HARPER, R. W. Colchicine — a short history of an ancient drug. **Medical Journal of Australia**, v. 201, n. 11, p. 687–688, 1 dez. 2014.

NIDORF, S. M. et al. Low-dose colchicine for secondary prevention of cardiovascular disease. **Journal of the American College of Cardiology**, v. 61, n. 4, p. 404–410, 29 jan. 2013.

NIDORF, S. M. et al. Colchicine in Patients with Chronic Coronary Disease. **New England Journal of Medicine**, v. 383, n. 19, p. 1838–1847, 5 nov. 2020.

OPSTAL, T. S. J. et al. Colchicine Attenuates Inflammation Beyond the Inflammasome in Chronic Coronary Artery Disease: A LoDoCo2 Proteomic Substudy. **Circulation**, v. 142, n. 20, p. 1996–1998, 17 nov. 2020.

PASCHKE, S. et al. Technical Advance: Inhibition of neutrophil chemotaxis by colchicine is modulated through viscoelastic properties of subcellular compartments. **Journal of Leukocyte Biology**, v. 94, n. 5, p. 1091–1096, 1 nov. 2013.

PATRONO, C. Cardiovascular effects of cyclooxygenase-2 inhibitors: a mechanistic and clinical perspective. **British journal of clinical pharmacology**, v. 82, n. 4, p. 957–964, 2016.

RIDKER, P. M. et al. Low-Dose Methotrexate for the Prevention of Atherosclerotic Events. **New England Journal of Medicine**, v. 380, n. 8, p. 752–762, 21 fev. 2019.

ROBINSON, P. C. et al. Consensus Statement Regarding the Efficacy and Safety of Long-Term Low-Dose Colchicine in Gout and Cardiovascular Disease. **American Journal of Medicine**, v. 135, n. 1, p. 32–38, 2022.

ŞEN, S. et al. Colchicine for cardiovascular therapy: A drug interaction perspective and a safety meta-analysis. **Anatolian Journal of Cardiology**, v. 25, n. 11, p. 753–761, 1 nov. 2021.

SHAH, B. et al. Effects of Acute Colchicine Administration Prior to Percutaneous Coronary Intervention: COLCHICINE-PCI Randomized Trial. **Circulation: Cardiovascular Interventions**, 2020.

SLOBODNICK, A. et al. Update on colchicine, 2017. **Rheumatology (Oxford, England)**, v. 57, n. 1, p. i4–i11, 1 jan. 2018.

SYKES, R. et al. Type 2 myocardial infarction and myocardial injury: Eligibility for novel medical therapy to derisk clinical trials. **Open Heart**, v. 8, n. 1, 2 jun. 2021.

TARDIF, J.-C. et al. Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction. **The New England journal of medicine**, v. 381, n. 26, p. 2497–2505, 26 dez. 2019.

TERKELTAUB, R. A. Colchicine Update: 2008. **Seminars in Arthritis and Rheumatism**, v. 38, n. 6, p. 411–419, jun. 2009.

TONG, D. C. et al. Colchicine in Patients With Acute Coronary Syndrome: The Australian COPS Randomized Clinical Trial. **Circulation**, v. 142, n. 20, p. 1890–1900, 17 nov. 2020.

TUCKER, B. et al. Inflammation during percutaneous coronary intervention— prognostic value, mechanisms and therapeutic targets. **Cells**, v. 10, n. 6, 1 jun. 2021.

TUVALI, O. et al. Colchicine in Atherosclerotic Vascular Disease:The Good, the Bad, and the Ugly. **The Israel Medical Association Journal**, v. 24, p. 191–197, 2022.

VAIDYA, K. et al. Colchicine Therapy and Plaque Stabilization in Patients With Acute Coronary Syndrome: A CT Coronary Angiography Study. **JACC. Cardiovascular imaging**, v. 11, n. 2 Pt 2, p. 305–316, 1 fev. 2018.

WUDEXI, I. et al. Comparative Effectiveness of Anti-Inflammatory Drug Treatments in Coronary Heart Disease Patients: A Systematic Review and Network Meta-Analysis. **Mediators of Inflammation**, v. 2021, 2021.

ZHANG, F. SHUN et al. Therapeutic potential of colchicine in cardiovascular medicine: a pharmacological review. **Acta Pharmacologica Sinica 2021**, p. 1–18, 19 jan. 2022.