Colchicine (LODOCO™)
National Drug Monograph
October 2023

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description/Mechanism of Action[1]

- Although the mechanism for reducing cardiovascular events is unknown, colchicine inhibits tubulin polymerization, microtubule generation and consequently prevents the activation, degranulation, and migration of neutrophils. Colchicine may also interfere with activation of interleukin-1β through intracellular interference of inflammasome complex assembly in neutrophils and monocytes. These anti-inflammatory effects are consistent with clinical evidence demonstrating that colchicine reduces high-sensitivity C-reactive protein (hs-CRP).

Indication(s) Under Review in This Document[1]

- To reduce the risk of myocardial infarction (MI), stroke, coronary revascularization, and cardiovascular death in adult patients with established atherosclerotic disease (ASCVD) or with multiple risk factors for cardiovascular disease.

Dosage Form(s) Under Review

- 0.5 mg tablet, taken once daily

Clinical Evidence Summary

Efficacy Considerations

- There have been two clinical trials[2-3] comparing colchicine to placebo (or control-no colchicine in the LoDoCo trial) in patients with stable cardiovascular disease (CVD) and two placebo-controlled trials of colchicine in patients randomized within 30 days of myocardial infarction (MI)[4] or initiated during the index hospitalization in patients with acute coronary syndrome (ACS) with coronary artery disease on coronary angiography, managed with percutaneous coronary intervention (PCI) or medical therapy[5]. There is also a 2-year follow-up of patients' s/p ACS[5-6] and a study of a single dose of colchicine vs. placebo given prior to PCI.[7] The primary outcome measure in all of the trials consisted of a composite of various CVD events with a median follow-up ranging from 12-36 months. Guideline directed medical therapies were maximized in the trials of stable patients and in those presenting with MI or ACS including statins, aspirin and other antiplatelet agents.
- Efficacy data are summarized in Table 1

Table 1: Efficacy results from clinical trials

Study	Design	Results	Adverse Events/Comments
LoDoCo 2013[2] **Nidorf, et al.** **Stable CVD**	PROBE design (N=532) Patients with stable CVD were randomized to Col 0.5 mg/d* vs. no Col in addition to taking secondary CV therapies (e.g., high dose statins, ASA <u>Primary outcome:</u> Composite of ACS, OOH cardiac arrest and non-cardioembolic stroke Components of ACS: Stent related or non-stent related. Median follow-up 36 months	Col N=282 No Col N=250 <u>Primary Outcome</u>: Col N=15 (5.3%) No Col N=40 (16%) HR 0.33, 0.18-0.59, P<0.001 ARR 10.7%, NNT 9-11[a] <u>Individual Endpoints:</u> ACS: Col N=13 (4.6%) No Col N=34 (13.6%) HR 0.33, 0.18-0.63, P<0.001 No difference in stent-related events. Non-stent-related AMI and UA both statistically less events in Col vs. Pla No differences in OOH cardiac arrest or non-cardioembolic stroke. <u>Deaths:</u> No Col: N=10 5 of presumed cardiac arrest, 2 OOH cardiac arrest, 2 cardiogenic shock after AMI and 1 after bypass surgery. Col: N=4 All non-CV causes	Early W/D N=32 (11%)-within 30 days Late W/D N=30 (11%)-after 30 days *If patients W/D from Col due to GI intolerance or nonadherence within the first month (run-in period), another patient was placed on Col to ensure adequate numbers on Col. Patients who withdrew were continued in the study and included in the intent to treat analysis (n=39) More patients on CCB in Col group and more on BB in control group (No Col). A sensitivity analysis with adjustments showed no difference from the primary analysis.
LoDoCo2 2020[3] **Nidorf, et al.** **Stable CVD**	R, DB, PC MC (N=5522) After 4-week run-in to determine tolerance to Col, eligible patients were R to Col 0.5 mg or Pla once daily in addition to taking secondary prevention therapies (e.g., statins, antiplatelet agents, etc.) <u>Primary Outcome</u>: Composite of CV death, MI, ischemic stroke or ischemia driven coronary revasc. Median follow-up of 28.6 months	Col N=2762 Pla N=2760 <u>Primary Outcome:</u> Col N=187 (6.8%) Pla N=264 (9.6%), HR 0.69, 0.57-0.83, P<0.001 ARR 2.8%, NNT 36 <u>Other Endpoints:</u> According to the hierarchical testing plan, several other secondary composite endpoints, ischemia driven coronary	6528 patients began run-in, 1006 (15.4%) were not R, primarily due to GI ADEs 10.5% of R patients discontinued in each group. Gout occurred less commonly in Col vs. Pla (1.4% vs. 3.4%, respectively, 95% CI 0.28-0.58) <u>Myalgia</u>: Col N=384 (21.2%)

		revasc and MI favored Col vs. Pla, no differences were observed for ischemic stroke, death from any cause or CV death. **<u>Death any cause:</u>** **Col N=73 (2.6%)** **Pla N=60 (2.2%), HR 1.21, 0.86-1.71** <u>CV Death:</u> Col N=20 (0.7%) Pla N=25 (0.9%), HR 0.8, 0.44-1.44	Pla N=334 (18.5%), 95% CI 1.01-1.31. All-cause death was numerically higher in Col vs. Pla (See results column)
COLCOT 2019[4] Tardif, et al. **Within 30 days of MI**	R, DB, PC, MC (N=4745) Eligible patients included adults within 30 days of a MI, completed planned percutaneous revasc. procedures and treated with guideline directed therapies including high dose statins who were R to Col 0.5 mg or Pla daily. <u>Primary Outcome:</u> Composite of CV death, resuscitated cardiac arrest, MI, stroke or urgent hospitalization for angina requiring coronary revasc. in a time-to-event analysis. Median follow-up of 22.6 months	Col N=2366 Pla N=2379 Mean time after MI to enrollment was 13.5 days <u>Primary Outcome:</u> Col N=131 (5.5%) Pla N=170 (7.1%), HR 0.77, 0.61-0.96, p=0.02 ARR 1.6%, NNT 62.5 Analysis of individual components of the primary endpoint showed differences were due to a reduction in stroke and urgent hospitalization for angina requiring coronary revasc. No other differences noted. >95% of patients were receiving aspirin, another antiplatelet agent and statins.	ADEs related to Col or Pla were similar (16% vs. 15.8%, respectively). Overall, serious ADEs did not differ (16.4% Col vs. 17.2% Pla). GI ADEs were reported once in 17.5% Col vs. 17.6% Pla. Diarrhea was reported in 9.7% Col vs. 8.9% Pla Nausea was more common with Col vs. Pla (1.8% vs. 1%, respectively, p=0.02) Pneumonia was reported as a serious ADE more often with Col 0.9% vs. Pla 0.4%, p=0.03.
Australian COPS[5] Tong, et al. **ACS-R during index hospitalization**	R, DB, PC, MC-single country (Australia) (N=795) Eligible patients included adults presenting with ACS and evidence of CAD on coronary angiography and managed with either PCI or medical therapy were R to Col 0.5 mg or Pla twice daily for 1 month and then 0.5 mg or Pla once daily for the remaining 11 months. All patients were started on guideline directed	Col N=396 Pla=399 <u>Primary Outcome:</u> Col 6.1% (N=24) Pla 9.5% (N=38), p=0.09 No differences noted in secondary or sensitivity analyses except for urgent revasc. which favored Col vs. Pla (p=0.037)	Study D/C occurred in 61 (15%) Col vs. 33 (8%) Pla, p=0.88. Most common reason for D/C was GI intolerance (9% vs. 4%, respectively) or personal choice (4% vs. 2%, respectively) Higher incidence of death in Col vs. Pla, specifically non-CV death (see results column).

	therapies including ASA, other antiplatelet drug, statins, etc. Primary Outcome: Composite of death, ACS, ischemia-driven urgent revasc. and non-cardioembolic stroke. Minimum follow-up of 12 months	There were differences in death (Col 8 vs. Pla 1, p=0.047), non-CV death (Col 5 vs. Pla 0, p=0.023) >95% of patients were receiving aspirin, another antiplatelet agent, and statins.	Study underpowered (power calculations estimated based upon several assumptions indicated that 1009 patients were needed for 80% power and 5% significance to detect differences) N=795 Baseline factor of family history of IHD was statistically higher in the Col vs. Pla group Phone follow-up may be susceptible to reporting biases and potentially omitting reporting of events.
Australian COPS[6] Tong, et al. **2-year follow-up**	Complete follow-up data were available for 765 (96%) study patients. Colchicine was stopped after 12 months, follow-up reported 12 months after treatment stopped.	Primary Outcome (24 months): Col 8.1% (N=32) Pla 13.5% (N=54), p=0.02 Deaths: Col 9 vs. Pla 4, HR 2.28, 0.7-7.4, p=0.17 Non-CV Deaths: Col 5 vs. Pla 2, HR 2.54, 0.49-13, p=0.27 Individual components of the primary outcome did not differ statistically except urgent revasc.	Authors suggest a legacy effect of 12 months of colchicine, increased deaths require additional studies to address concerns over safety and appropriate candidates for Col therapy.
Colchicine PCI[7] Shah, et al. **Colchicine prior to PCI**	R, DB, PC, single-site study Patients having PCI were R to pre-procedural Col 1.8 mg or Pla Primary Outcome: Composite of death, non-fatal MI and target vessel revasc. at 30 days and PCI-related MI/injury	Col=206 Pla=194 Primary Outcome: *Composite:* Col 11.7% vs. Pla 12.9%, p=0.82 *PCI-related MI:* Col 2.9% vs. 4.7%, p=0.49 *PCI-related myocardial injury* Col 57.3% Pla 64.2%, p=0.19	Sub-study measuring interleukin-6 and hs-CRP levels after PCI showed lesser increase in these inflammatory markers with Col vs. Pla 24 hours after PCI. Clinical significance, unclear.

ACS=acute coronary syndrome, ADEs=adverse drug events, AMI=acute myocardial infarction, ASA=acetylsalicylic acid-aspirin, BB=beta-blocker, CAD=coronary artery disease, CCB=calcium channel blocker, Col=colchicine, CVD=cardiovascular

disease, DB=double-blind, GI=gastrointestinal MC=multicenter, hs-CRP=high-sensitivity C-Reactive Protein, MI=myocardial infarction, OOH=out of hospital, PC=placebo-controlled, PCI=percutaneous coronary intervention, Pla=placebo, PROBE=prospective, randomized, observer blind endpoint, R=randomized, UA=unstable angina. W/D=withdrawal

[a]Authors report NNT 11, calculated ARR 10.7%=9.3

- **Summary of Efficacy-Clinical Trials**
  - Clinical Trials in Patients with Stable Coronary Artery Disease (CAD)
    - The benefit of colchicine vs. placebo in reducing CV events was observed in two randomized controlled trials in patients with stable coronary disease (CAD) including the LoDoCo[2] and LoDoCo2[3] trials. LoDoCo was an observer blinded trial that randomized 532 patients with stable CVD to colchicine 0.5 mg vs. placebo daily and followed for median of 36 months. A primary outcome occurred in 5.3% of patients receiving colchicine vs. 16% of patients receiving placebo (HR 0.33, 0.18-0.59, p<0.001, ARR 10.7%, NNT 9.3).
    - To confirm the findings of the smaller, unblinded LoDoCo trial, LoDoCo2 was conducted and included 5522 patients with stable CAD followed for a median of 28.6 months. A primary outcome occurred in 6.8% of colchicine vs. 9.6% of placebo recipients (HR 0.69, 0.57-0.83, p=0.001, ARR 2.8%, NNT 35). The difference in events between colchicine and placebo in LoDoCo2 were driven primary by a reduced risk for MI and ischemia driven coronary revascularization. *Adverse events are reported in the Safety Considerations section.*
    - Limitations of LoDoCo included observer-blinded only, small sample size, ability to add patients to the colchicine arm when a prior subject withdrew due to gastrointestinal (GI) intolerance or adherence problems within the first month and baseline characteristics were not equal between groups (users of beta-blockers or calcium channel blockers).
  - Clinical Trials of Acute Coronary Syndrome/Myocardial Infarction (MI)
    - The benefit of colchicine in reducing CV events was observed in the COLCOT[4] trial which randomized patients hospitalized with MI to either colchicine 0.5 mg or placebo daily within 30 days of their MI. A primary outcome occurred in 5.5% of colchicine and 7.1% of placebo recipients (HR 0.77, 0.61-0.96, p=0.02, ARR 1.6%, NNT 62.5). Reduction in stroke and urgent hospitalization for angina leading to coronary revascularization were predominantly responsible for differences between groups.
    - A separate published analysis (post-hoc) of the data demonstrated that the benefit of colchicine appeared to be greatest if initiated within < 3 days of the MI (<3 days: HR 0.52, 0.32-0.84 vs. 4-7 days: HR 0.96, 0.53-1.75 and > 8 days: HR 0.82, 0.61-1.11).[8]
    - The Australian COPS study randomized 795 patients presenting with ACS and having evidence of CAD on coronary angiography to colchicine 0.5 mg or placebo during the index hospitalization; patients were followed for a minimum of 12 months. A primary outcome occurred in 6% (24 events) in the colchicine vs. 9.5% (38 events) placebo group (p=0.09).[5] The investigators planned for 1009 patients to be randomized but only 795 participated. Limitations include short term follow-up (minimum 12 months) and study underpowered based upon power calculations.
    - A 2-year follow-up to the Australian COPS study was published reporting a primary event occurred in 8.1% colchicine vs. 13.5% placebo recipients (p=0.02). The authors

comment that 12 months after stopping colchicine and showing a CV benefit may support a legacy effect of colchicine.[6]

- Clinical Trial of Colchicine Prior to Percutaneous Coronary Intervention (PCI)
    - A single site study examined the effect of administering colchicine vs. placebo prior to PCI on PCI-related myocardial injury and composite outcome of death, nonfatal MI and target vessel revascularization at 30 days and PCI-related MI. A single dose of colchicine vs. placebo prior to PCI did not result in differences in outcome measures between groups.[7]

Safety Considerations

Safety Results from Clinical Trials:

- Overall, gastrointestinal complaints were the most common adverse event reported with colchicine, including nausea and diarrhea. In the first month of the two trials involving patients with stable CVD, 11-15% withdrew consent early due primarily to GI-related adverse events. Myalgia was reported statistically more often with colchicine vs. placebo in the LoDoCo2 study.[3]
- Non-CV death was numerically increased in LoDoCo2[3] and statistically higher after 12 months of colchicine in the Australian COPS[5] trial. The Australian COPS study is limited by short-term minimum follow-up of 12 months and being underpowered based upon power calculations.
- Incidence of pneumonia was statistically higher in patients on colchicine vs. placebo in the COLCOT trial[4] involving patients hospitalized with MI.

Table 2: Safety results from clinical trials

Study	Results	Comments
LoDoCo 2013[2] **Nidorf, et al.** **Stable CVD**	Early W/D N=32 (11%)-within 30 days Late W/D N=30 (11%)-after 30 days	Authors comment that side effects (GI) may be a factor limiting widespread use of Col.
LoDoCo2 2020[3] **Nidorf, et al.** **Stable CVD**	6528 patients began run-in, 1006 (15.4%) were not R, primarily due to GI ADEs 10.5% of patients discontinued in each group. Myalgia: Col N=384 (21.2%) Pla N=334 (18.5%), 95%CI 1.01-1.31. **All-Cause Death:** **Col N=73 (2.6%)** **Pla N=60 (2.2%), HR 1.21, 0.86-1.71** CV Death: Col N=20 (0.7%)	Gout occurred less commonly in Col vs. Pla (1.4% vs. 3.4%, respectively, 95% CI 0.28-0.58) Trend of all-cause death was higher in Col vs. Pla (See results column) Myalgia was statistically higher in Col vs. Pla (See results column)

	Pla N=25 (0.9%), HR 0.8, 0.44-1.44	
COLCOT 2019[4] Tardif, et al. **R-within 30 days of MI**	ADEs related to Col or Pla were similar (16% vs. 15.8%, respectively). Overall, serious ADEs did not differ (16.4% Col vs. 17.2% Pla). GI ADEs were reported once in 17.5% Col vs. 17.6% Pla. Diarrhea was reported in 9.7% Col vs. 8.9% Pla Nausea was more common with Col vs. Pla (1.8% vs. 1%, respectively, p=0.02) Pneumonia was reported as a serious ADE more often with Col 0.9% vs. Pla 0.4%, p=0.03.	Deaths were not different between groups.
Australian COPS[5] Tong, et al. **ACS-R during index hospitalization**	<u>Deaths</u> Col 8 vs. Pla 1, p=0.047 <u>Non-CV death:</u> Col 5 vs. Pla 0, p=0.023 Study D/C occurred in 61 (15%) Col vs. 33 (8%) Pla, p=0.88. Most common reason for D/C was GI intolerance (9% vs. 4%, respectively) or personal choice (4% vs. 2%, respectively)	Higher incidence of death in Col vs. Pla, specifically non-CV death (see results column). 5/8 patients were still taking Col at the time of their death Study underpowered.
Australian COPS[6] Tong, et al. **2-year follow-up**	<u>Deaths:</u> Col 9 vs. Pla 4, HR 2.28, 0.7-7.4, p=0.17 <u>Non-CV Deaths:</u> Col 5 vs. Pla 2, HR 2.54, 0.49-13, p=0.27	None
Colchicine PCI[7] Shah, et al. **Colchicine prior to PCI**	Chest pain and GI symptoms were most common ADEs reported. Chest pain did not differ but GI symptoms were more common in the Col vs. Pla groups (9.3 vs. 3.2%, respectively)	None

ACS=acute coronary syndrome, ADE(s)=adverse drug events, CAD=coronary artery disease, Col=colchicine, CVD=cardiovascular disease, D/C=discontinued, GI=gastrointestinal, MI=myocardial infarction, OOH=out of hospital, PC=placebo-controlled, PCI=percutaneous coronary intervention, Pla=placebo, R=randomized, W/D=withdrawal

- **Boxed warnings: None**

- **Contraindications:**
    - Avoid concurrent use of strong CYP3A4 inhibitors or P-glycoprotein (P-gp) inhibitors with colchicine. Life-threatening and fatal colchicine toxicity have been reported in patients taking colchicine with these agents.
    - Avoid use in patients with renal failure (CrCl <15 mL/min) and severe hepatic impairment.
    - Avoid use in patients with pre-existing blood dyscrasias and in patients who are hypersensitive to colchicine or to any of it ingredients.
- **Other warnings / precautions**:
    - **Blood dyscrasia**: colchicine can cause myelosuppression, leukopenia, granulocytopenia, thrombocytopenia and aplastic anemia. These events can be life-threatening or fatal. Gastrointestinal symptoms may be the initial sign of colchicine toxicity and therefore, patients reporting these symptoms should be evaluated for toxicity. Combined use of drugs that inhibit or decrease the metabolism of colchicine or the presence of hepatic or renal impairment can increase the risk for these blood disorders.
    - **Neuromuscular toxicity**: colchicine can cause neuromuscular toxicity and rhabdomyolysis. Concomitant use of colchicine with drugs known to reduce metabolism of colchicine or use in patients with hepatic or renal impairment increases the risk of developing neuromuscular toxicity. Gastrointestinal symptoms are generally the first sign and should prompt evaluation for toxicity.
        - Concurrent use of colchicine with statins, gemfibrozil, fenofibrate or fenofibric acid may increase the risk for myopathy.
    - **Concurrent use of colchicine and moderate inhibitors of CYP3A4**: concomitant use of moderate inhibitors of CYP 3A4 should be avoided in patients with risk factors that increase systemic exposure of colchicine (e.g., presence of hepatic or renal impairment).
    - **Use in patients with hepatic or renal impairment**: although use of colchicine in patients with severe hepatic or renal impairment or renal failure is contraindicated, patients with any degree of hepatic or renal impairment should be monitored closely for adverse events that may lead to colchicine toxicity.
- **Adverse reactions**
    - **Common**-gastrointestinal adverse events (e.g., diarrhea, nausea, vomiting, abdominal cramping) and myalgia
    - **Serious Adverse events / Deaths / Discontinuation:**
        - In two trials, incidence of myalgia (LoDoCo2)[3] and pneumonia (COLCOT)[4] were statistically higher with colchicine vs. placebo.
        - Non-CV deaths: In two trials (LoDoCo2 and Australian COPS), numerical or statistical higher number of deaths in the colchicine group vs. placebo.
        - After first month of colchicine or during initial run-in phase (LoDoCo and LoDoCo2, respectively), differences in study withdrawal did not differ between colchicine and placebo.

Other Considerations

- **Drug-Drug interactions:**
  - **Strong CYP3A4 inhibitors-Avoid concomitant use with colchicine.** Examples include atazanavir, clarithromycin, darunavir/ritonavir, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, tipranavir/ritonavir.
  - **Moderate CYP3A4 inhibitors-**Significant increase in systemic exposure to colchicine anticipated. Monitor patients for signs of colchicine toxicity. **Avoid concomitant use in patients with existing hepatic or renal impairment.** Examples include amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir (prodrug of amprenavir) and verapamil.
  - **Grapefruit or Grapefruit Juice-Avoid grapefruit or grapefruit juice in patients taking colchicine.** Anticipate increased systemic exposure of colchicine.
  - **P-Glycoprotein (P-gp)-Avoid concomitant use with colchicine.** Significant increase in systemic exposure to colchicine anticipated. Examples include cyclosporine and ranolazine.
  - **Statins or Fibrates-**Monitor patients on statins and/or fibrates closely since addition of colchicine to stable lipid-lowering regimens may result in an increased risk for myopathy or rhabdomyolysis.
  - **Others include digoxin and oral contraceptives.** Close monitoring is recommended since digoxin is substrate for P-pg and since colchicine may interact with hormonal contraceptives and lead to increased GI adverse events.
- **Special Populations:**
  - **Pregnancy-**Animal data suggest colchicine causes embryofetal toxicity and altered postnatal development at exposures within or above therapeutic range. Observational studies, case series and case reports do not suggest an increased risk for birth defects or miscarriage in pregnant women with rheumatic disease (e.g., rheumatoid arthritis, Behcet's disease or Familial Mediterranean Fever (FMF) treated with colchicine during pregnancy.
  - **Lactation-**developmental health benefits of breastfeeding should be weighed along with the mother's clinical need for colchicine and the potential for adverse events on the infant or from the mother's underlying condition.
  - **Renal impairment-**Avoid use in patients with renal failure/severe renal impairment (CrCl <15 mL/min) and use with caution in patients with any degree of renal impairment. Avoid use in patients with any degree of renal impairment and receiving moderate CYP3A4 inhibitors.
  - **Hepatic impairment-**Avoid use in patients with severe hepatic impairment and use with caution in patients with any degree of hepatic impairment. Avoid use in patients with any degree of hepatic impairment and receiving moderate CYP3A4 inhibitors.

Other Therapeutic Options

Alternative Colchicine products/doses are listed in table 3 below

Table 3 Treatment Alternatives

Drug	Formulary status	Clinical Guidance	Other Considerations
Colchicine (LODOCO) 0.5 mg tab	TBD	Reduce CV risk in patients with ASCVD or without ASCVD but with multiple risk factors	Dose is 0.10 mg lower than contacted colchicine product (0.6 mg tablet), release characteristics do not differ. *This product is not a sustained-release tablet.*
Colchicine (CHOLCRYS) 0.6 mg tab	F	Treatment of gout flares and Familial Mediterranean Fever (FMF)	N/A
Colchicine (MITIGARE) 0.6 mg cap	F	Prophylaxis of gout flares	N/A
Colchicine (GLOPERBA) liquid	NF	Prophylaxis of gout flares	N/A
Colchicine Generics-0.6 mg tab *Contract*	F	Used in all settings, no label available for generics	N/A

Projected Place in Therapy

- Based upon data from NHANES 2017-March 2020, the prevalence of cardiovascular disease (including coronary heart disease, heart failure, stroke and hypertension) in U.S. adults aged ≥ 20 years was approximately 48.6% and increases with age, regardless of gender.[9] Death from heart disease and stroke exceed that of cancer and chronic lower respiratory disease combined.
- Veterans were found to be at a higher risk for new onset heart disease vs. non-Veterans (RR 1.483, 95% CI 1.176-1.871, adjusted for covariates) based upon data from a 20-year cohort of the Health and Retirement Study.[10]
- The potential for anti-inflammatory drugs to reduce residual cardiovascular risk in high-risk patients with stable cardiovascular disease or after acute coronary syndrome/MI is supported by findings from clinical trials involving colchicine demonstrating a reduction in relative risk for adverse cardiovascular events of approximately 30% in patients with stable disease[3] and 23% in patients after a MI[4] despite receiving guideline directed medical therapies (e.g., >95% receiving high dose statins, aspirin and other anti-platelet agents). Additionally, a collaborative analysis of three trials in patients with or at high-risk for atherosclerotic cardiovascular disease (ASCVD) receiving statin therapy (N=31,245) reported that residual inflammatory risk was associated with an increased risk for major adverse cardiovascular events (MACE) (adjusted HR 1.31, 1.2-1.43, p<0.0001), cardiovascular mortality (HR 2.68, 2.22-3.23, p<0.0001) and all-cause mortality (HR 2.42, 2.12-2.77, p<0.0001) when comparing the quartile with the highest high-sensitivity C-Reactive Protein (hs-CRP) level quartile to the lowest hs-CRP level quartile.[11] In the clinical trials of colchicine, hs-CRP was not collected for all patients, only subgroups of patients. Therefore, it is unclear if appropriate patient selection must include hs-CRP levels ≥ 2 mg/dL. However, some authors are recommending including hs-CRP level as part of the decision to treat, based upon findings from the collaborative meta-analysis.[11-12]
- In the LoDoCo2 study, in patients with chronic coronary disease, non-CV death was numerically higher in the colchicine group vs. placebo. In the Australian COPS study, in patients randomized to colchicine 0.5 mg twice daily for one month then 0.5 mg daily, there was a statistically significant increase in non-CV deaths in the colchicine group. However, the Australian COPS study is limited by small population size, short follow-up duration (minimum of 12 months) and being underpowered.
- Guidance published in 2023 for the management of patients with chronic coronary disease (CCD) recommends addition of colchicine for secondary prevention in patients with CCD to reduce recurrent ASCVD events.[13]
    - The guidance further notes that because of colchicine's narrow therapeutic index, potential for drug-drug interactions and risk for toxicity at therapeutic doses, there is a need for a highly individualized approach to patient selection, limiting colchicine to patients who remain at very high risk despite maximally tolerated guideline directed medical therapies until further data are available.
    - Because patients with creatinine clearance <50mL/min were excluded from trials, use should be avoided in patients with eGFR <30 mL/min/m^2.
    - The authors also note that despite the positive results of LoDoCo2, non-CV death was numerically higher in the colchicine vs. placebo group.

- Consistent with the recommendations from the AHA/ACC Joint Committee Guidelines for the management of patients with chronic coronary artery disease, colchicine can be considered in carefully selected high-risk patients with established ASCVD receiving maximally tolerated guideline directed therapies (e.g., statins, ezetimibe, etc.) to prevent recurrent ASCVD events. The decision to use hs-CRP $\geq$ 2 mg/dL as a deciding factor is recommended by some authors but is not based upon direct evidence from the trials reviewed.
    - Since colchicine has a narrow therapeutic index, hepatic and renal function should be determined and an assessment of all medications for potential drug-drug interactions with colchicine must be done prior to initiating colchicine in appropriately selected patients.
    - Colchicine should be avoided in patients receiving strong inhibitors of CYP3A4 or inhibitors of P-glycoprotein and in patients with severe hepatic or renal impairment, including patients with eGFR <30 mL/min/m^2, consistent with recommendations from the ACC/AHA Joint Committee Guidelines.
    - Colchicine should also be avoided in patients receiving moderate inhibitors of CYP3A4 inhibitors and with any degree of hepatic or renal impairment.
    - Gastrointestinal symptoms are the most common adverse events reported with colchicine and initial symptoms of colchicine toxicity. Patients reporting these symptoms should be closely monitored and evaluated for toxicity. Refer to monograph sections for other potential drug-drug interactions (e.g., statins, fibrates, etc.).
- Although the clinical trials used colchicine 0.5 mg in the trials, the 0.6 mg dose has been used in the US for managing gout, Familial Mediterranean Fever (FMF), pericarditis, etc. for years and is available as a generic drug. As such, preference is given to the 0.6 mg dose. If the patient develops intolerable GI symptoms, a trial of the 0.5 mg dose may be considered. However, there is a lack of evidence to support that the 0.5 mg tablet will be better tolerated than the 0.6 mg. In clinical trials, the 0.5 mg dose GI intolerance primarily led to early discontinuation or patients not being randomized in 11% and 15% of patients, respectively. Currently, there is a lack of a clear and compelling reason to select the 0.5 mg tablet over the 0.6 mg national contracted tablet.

References

1. Colchicine (LODOCO) Prescribing Information. Distributed by: AGEPHA Pharma USA, LLC 181 New Road, Suite 304 Parsippany, NJ 07054 https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/215727s000lbl.pdf (Accessed 10-10-23)
2. 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.
3. Nidorf SM, Fiolet ATL, Mosterd A, et al. Colchicine in Patients with Chronic Coronary Disease. N Engl J Med 2020;383:1838-1847.
4. Tardif, JC, Kouz S, Waters DD, et al. Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction. N Engl J Med 2019;381:2497-2505.
5. Tong DC, Layland J. Colchicine in Patients with Acute Coronary Syndrome. The Australian COPS Randomized Clinical Trial. Circulation 2020;142:1890-1900.
6. Tong DC, Bloom JE, Quinn S, et al. Colchicine in Patients with Acute Coronary Syndrome. Two-Year Follow-Up of the Australian COPS Randomized Clinical Trial. Circulation 2021;144:1584-1586. (Research Letter)
7. Shah B, Pillinger M, Zhong J, et al. Effects of Acute Colchicine Administration Prior to Percutaneous Coronary Intervention: The COLCHICINE-PCI Randomized Trial. Circ Cardiovasc Interv 2020; Apr;13(4):e008717. PMID: 32295417
8. Bouabdallaoiu N, Tardif JC, Waters DD, et al. Time-to-Treatment Initiation of Colchicine and Cardiovascular Outcomes in the Colchicine Cardiovascular Outcomes Trial (COLCOT). European Heart Journal 2020;41:4092-4099.
9. Tsao, CW, Aday AW, Almarzooq ZI, et al. Heart Disease and Stroke Statistics-2023 Update: A Report from the American Heart Association. Circulation 2023;147:e93-621.
10. Assari S. Veterans and Risk of Heart Disease in the United States. A Cohort with 20 Years of Follow Up. Int J Prev Med 2014;5:703-709.
11. Ridker PM, Bhatt DL, Pradhan AD, et al. Inflammation and Cholesterol as Predictors of Cardiovascular Events Among Patients Receiving Statin Therapy: A Collaborative Analysis of Three Randomized Trials. Lancet 2023;401:1293-1301.
12. Nelson K, Fuster V, Ridker PM. Low-Dose Colchicine for Secondary Prevention of Coronary Artery Disease. JACC Review Topic of the Week. J Am Coll Cardiol 2023;82:648-660.
13. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients with Chronic Coronary Artery Disease: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. Virani SS, Newby LK, Arnold SV, et al. Circulation 2023;148:e9-e119.

Prepared October 2023. Contact person: Catherine Kelley, PharmD, National PBM Clinical Pharmacy Program Manager, Formulary management, VA Pharmacy Benefits Management Services (12PBM)