Editorial

Colchicine in Cardiovascular Disease: Repurposing an Ancient Gout Drug

The use of colchicine in gout dates back 2 millennia, with Alexander of Tralles clearly describing its use in gout in his work *Therapeutica* (circa 550 AD),[1] as recounted in the historical review by Hartung.[2] It was used in the Middle Ages, but its propensity to cause gastrointestinal adverse effects and potential toxicity at high doses rendered its use intermittent. According to Hartung, its first appearance in a pharmacopeia for use in gout was in *The London Pharmacopoeia* of 1618. Its modern use was recognized by 1819[3] and carefully detailed by Garrod in 1859.[4] The rapid and effective action of colchicine in gout was clearly described by the famous wit ("I never read a book before reviewing it: it prejudices a man so"), the Reverend Sydney Smith in 1838: "On Sunday I was on crutches utterly unable to put foot on the ground, on Tuesday I walked 4 miles such is the power of Colchicium".[5] Colchicine is now recognized as a potent anti-inflammatory drug for acute gout flares, and it is in widespread continuous low-dose use in the Eastern Mediterranean for familial Mediterranean fever.

Scattered references to a potential role of colchicine in cardiovascular medicine appeared in the writings of Arab physicians of the 11th century,[6] its role in dropsy and pleural effusions appeared in the writings of Baron Anton Stoerk in the 18th xentury,[7] and a synergistic effect between digitalis and colchicine was referred to in the 19th century.[8]

In the current era, the use of colchicine for cardiovascular disease has until recently been limited to a relatively niche role in the treatment of pericarditis. During the 1980s, use of colchicine for pericarditis was widespread but inconsistent, and it was put on an evidence-based footing with the first report of a randomized trial in 1990.[9] The potential for repurposing colchicine for cardiovascular disease was recognized in the accompanying editorial.[10] Subsequent explorations of its role in atherosclerosis, pericarditis, and atrial fibrillation reflect a rapidly increasing evidence base on the importance of inflammation in a variety of cardiovascular diseases[11] and the challenges in targeting it to improve cardiovascular outcomes.[12]

This special section of the journal features 5 excellent reviews of the current place of colchicine in cardiovascular medicine, each authored by international leaders in their respective areas of research. The first 3 articles outline the potential role of colchicine in atherosclerotic vascular disease, and the 2 subsequent articles explore its role in pericarditis and atrial fibrillation.

The first article, by Nidorf and Thompson,[13] outlines the rationale for evaluating colchicine in atherosclerosis. The authors briefly review the progress in tackling the inflammatory component of atherosclerosis since it was highlighted by Russell Ross in his seminal paper of 1999. [11] Since then, there have been a series of disappointments and false starts, most recently with methotrexate,[14] but the potential to tackle atherosclerotic inflammation has finally been realized with the recent completion of the Canakinumab Antiinflammatory Thrombosis Outcome Study (CANTOS) trial, which found that inhibiting the interleukin 1β pathway with canakinumab could improve outcomes.[15] The emphasis in the Nidorf and Thompson article is in presenting evidence that the challenges of limiting atherosclerotic inflammation are more complicated than inhibiting a single pathway. They review recent research that highlights the role of cholesterol crystals in activating the NLRP3 inflammasome and the involvement of neutrophil leukocytes in promoting inflammation and instability in the atherosclerotic plaque, drawing parallels between the crystallopathy of gout and instability in the atherosclerotic plaque. In brief, colchicine can inhibit inflammation at multiple sites.

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The article by Fiolet and colleagues[16] reviews the background of several large trials of colchicine in stable coronary heart disease and especially the ongoing 5500-patient Low Dose Colchicine 2 (LoDoCo2) trial,[17] which builds on the finding that colchicine is capable of rapidly restoring an elevated high-sensitivity C-reactive protein level[18] and the highly encouraging results from 2013 of the 500-patient LoDoCo trial[19] in patients with stable coronary heart disease.

The article by Vaidya et al.[20] focuses on the potential for colchicine to limit the inflammatory processes that occur during an acute coronary syndrome. Because the pathophysiologic mechanisms of acute coronary syndrome are likely to differ from stable coronary heart disease, they review the inflammatory processes of plaque instability in detail and provide a summary of their own pioneering work on a plaque-stabilizing effect of colchicine on coronary computed tomographic imaging.[21] They provide a summary of the key large trials under way in this clinical setting, primarily the 5500-patient Colchicine Cardiovascular Outcomes Trial (COLCOT).[22]

In a future issue of the Journal, Dr. Massimo Imazio will summarize the series of well-conducted trials led by his research group in Turin, which found that colchicine now has a clear evidence-based role in treatment of acute and recurrent pericarditis but less so in constrictive pericarditis. Colchicine is already recommended in guidelines for the treatment of acute and recurrent pericarditis.[23]

The final article in the series is by Deftereos and colleagues from Athens[24] and explores the use of colchicine to target inflammation in preventing recurrences of atrial fibrillation. Atrial fibrillation in the postoperative period after coronary artery bypass surgery and after catheter ablation for pulmonary vein isolation is associated with increased cardiovascular morbidity. Trials investigating the role of colchicine in these clinical settings have been encouraging, but meta-analyses of these studies have been contradictory because of issues with patient selection. The authors provide a well-informed analysis of these trials, concluding that there is strong evidence for the use of colchicine in atrial fibrillation after coronary artery bypass surgery less so for after pulmonary vein isolation, but this is still being explored.

The series of articles place the role of colchicine cardiovascular disease in clear perspective. There is exciting potential and strong rationale for colchicine to reduce the residual risk of atherosclerotic vascular disease beyond what has already been achieved with statins and antiplatelet therapy. More than 10,000 patients are involved in ongoing randomized controlled trials in atherosclerotic vascular disease. Further exploration in ongoing clinical trials will possibly extend colchicine's role in pericarditis and clearly define its place in postoperative and post-ablation atrial fibrillation.

The results of the current round of clinical trials and the directions for future research summarized in this Specialty Update will determine whether this ancient gout drug can be successfully repurposed as a widely available, inexpensive, and relatively tolerable therapy for widespread use in cardiovascular disease.

CONFLICTS OF INTEREST

No relevant conflicts of interest.

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REFERENCES

1. Puschmann T, ed. *Alexander of Tralles (6th cent. A.D.)*. 1879. Therapeutica.

2. Hartung EF. History of the use of colchicium and related medicaments in gout with suggestions for further research. *Ann Rheum Dis*. 1954;13:190–200.
3. Scudamore C. *A Treatise on the Nature and Cure of Gout and Rheumatism*. 3rd ed. Philadelphia: Earle; 1819.
4. Garrod AB. *The Nature and Treatment of Gout and Rheumatic Gout*. London: Watson and Maberly; 1859.
5. Wallace S. *A Wit and his Gout: The Reverend Sydney Smith Arthritis and Rheumatism*. vol. 6. 1962:610–615. https://onlinelibrary.wiley.com/doi/pdf/10.1002/art.1780050609. Accessed November 20, 2018.
6. Ruegg K. *Beitraege zur Geschichte de offizinellen Drogen Crocus Acorus Calamus and Colchicum" (Diss. Phil. Basel). Schahl, Stetten/Basel*. 1936.
7. Stoerck A. *An Essay on the Use and Effects of the Root of the Colchicum Autumnale, or Meadow-Saffron*. 1764. trans. from Latin. Becket and De Hondt, London.
8. Hammond WA. *Med Month NY Rev*. 1861;15:81.
9. Guindo J, Rodriguez de la Serna A, Ramió J, de Miguel Diaz MA, Subirana MT, Perez Ayuso MJ, et al. Recurrent pericarditis. Relief with colchicine. *Circulation*. 1990;82:1117–1120.
10. Adolph RJ. Old drugs with new uses. Colchicine for treatment of recurrent pericarditis. *Circulation*. 1990;82:1505–1506.
11. Ross R. Atherosclerosis — an inflammatory disease. *N Engl J Med*. 1999;340:115–126.
12. Maffia P, Cirino G. Targeting inflammation to reduce cardiovascular disease risk. *Br J Pharmacol*. 2017;174:3895–3897.
13. Nidorf SM, Thompson PL. Why colchicine should be considered for secondary prevention of atherosclerosis: an overview. *Clin Ther*. 2019;41:41–48.
14. Ridker PM, Everett BM, Pradhan A, MacFadyen JG, Solomon DH, Zaharris E, et al. CIRT Investigators. Low-dose methotrexate for the prevention of atherosclerotic events. *N Engl J Med*. 2018 Nov 10. https://doi.org/10.1056/NEJMoa1809798 [Epub ahead of print].
15. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C. CANTOS Trial Group. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med*. 2017;377:1119–1131.
16. Fiolet ATL, Nidorf SM, Mosterd A, Cornel JH. Colchicine in stable coronary artery disease. *Clin Ther*. 2019;41:30–40.
17. The LoDoCo2 Trial: a randomised controlled trial on the effect of low dose Colchicine for secondary prevention of cardiovascular disease in patients with established, stable coronary artery disease The Australian and New Zealand Clinical Trial Registry. http://www.anzctr.org.au/TrialSearch.aspx?searchTxt=LoDoCo2&isBasic=True Accessed 2 Jan 2018.
18. Nidorf M, Thompson PL. Effect of colchicine (0.5 mg twice daily) on high-sensitivity C-reactive protein independent of aspirin and atorvastatin in patients with stable coronary artery disease. *Am J Cardiol*. 2007;99:805–807.
19. 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.
20. Vaidya K, Martínez G, Patel S. The role of colchicine in acute coronary syndromes. *Clin Ther*. 2019;41:11–20.
21. Vaidya K, Arnott C, Martínez GJ, Ng B, McCormack S, Sullivan DR, et al. Colchicine therapy and plaque stabilization in patients With acute coronary syndrome: a CT coronary angiography study. *JACC Cardiovasc Imaging*. 2018;11(2 Pt 2):305–316.
22. Colchicine Cardiovascular Outcomes Trial (COLCOT) https://clinicaltrials.gov/ct2/show/NCT02551094. Accessed 2 Jan 2018.
23. Adler Y, Charron P, Imazio M, Badano L, Barón-Esquivias G, Bogaert J, et al. ESC Scientific Document Group. 2015 ESC Guidelines for the diagnosis and management of pericardial diseases: The Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC)Endorsed by: The European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2015;36(42):2921–2964.
24. Deftereos SG, Vrachatis DA, Angelidis C, Vrettou AR, Sarri EK, Giotaki SG, et al. The role of colchicine in treating postoperative and post-catheter ablation atrial fibrillation. *Clin Ther*. 2018 Sep 11:S0149–S2918. https://doi.org/10.1016/j.clinthera.2018.08.008. pii: S0149-2918(18)30371-0. [Epub ahead of print].

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