Colchicine in Patients with Chronic Coronary Disease
Reviewer: Jayme Holland

Background:

- Chronic coronary disease has been well recognized as a progressive inflammatory process.
- Patients with chronic coronary disease remain at high risk for acute cardiovascular events despite current available treatment.
- Colchicine is an anti-inflammatory medication with broad cellular inhibition effects that showed promising results in previous trials for patients with cardiovascular events.
- The 2013 Low-Dose Colchicine Trial (LoDoCo) enrolled patients with stable chronic coronary disease to colchicine or usual care. It showed decreased risk of acute cardiovascular events: ACS, non-cardioembolic stroke or out of hospital cardiac arrest. However, there was lack of placebo-control and blinding, and there were only 532 patients enrolled.
- The 2019 Colchicine Cardiovascular Outcomes Trial (COLCOT) involved patients with a myocardial infarction within 30 days. 4745 patients were enrolled in either the colchicine or placebo group. There was a decreased composite endpoint of cardiovascular events – driven by decreased angina and stroke.
- The Low-Dose Colchicine 2 (LoDoCo 2) Trial was conducted to expand on the results found in the original LoDoCo trial. They sought to determine whether colchicine compared to placebo prevents cardiovascular events in patients with chronic coronary disease.

What They Did:

- This was a randomized, controlled, double-blind, event-driven trial comparing 0.5mg of colchicine once daily to placebo in patients with chronic coronary disease.
- Recruitment started on August 4, 2014 at 13 centers in Western Australia. On October 27, 2016, recruitment was expanded to include 30 centers in the Netherlands. Enrollment was completed December 3, 2018.
- A 1 month open-label run-in phase occurred in which patients received 0.5 mg of colchicine daily
    - Patients who were in stable condition and had no unacceptable side effects, had adhered to open-label colchicine regimen and remained willing to participate were randomized
- Patients were randomized in 1:1 ratio in a double-blind manner to receive 0.5mg of colchicine once daily or matching placebo through the use of a computerized algorithm, with stratification according to country

Outcomes:

- Primary endpoint:
    - Composite of cardiovascular death, spontaneous (nonprocedural) myocardial infarction, ischemic stroke, or ischemia-driven coronary revascularization
- Secondary endpoints – tested in a hierarchical fashion:

    - Composite of cardiovascular death, spontaneous myocardial infarction or ischemic stroke
    - Composite of spontaneous myocardial infarction or ischemia driven coronary revascularization
    - Composite of cardiovascular death or spontaneous myocardial infarction
    - Ischemia-driven coronary revascularization
    - Spontaneous myocardial infarction
    - Ischemic stroke
    - Death from any cause
    - Cardiovascular death

Inclusion:

- Patients 35 to 82 years old were eligible if they had any evidence of coronary disease on:
    - Invasive coronary angiography OR
    - Computed tomography angiography OR
    - Coronary-artery calcium score of at least 400 Agatston units on coronary-artery calcium scan
- Clinically stable condition for at least 6 months

Exclusion:

- Moderate-to-severe renal impairment
- Severe heart failure
- Severe valvular heart disease
- Known side effects from colchicine

Results:

- 5522 patients underwent randomization
    - 2762 in colchicine group
    - 2760 in placebo group
- Primary Endpoint:
    - Composite of cardiovascular death, spontaneous (nonprocedural) myocardial infarction, ischemic stroke, or ischemia driven coronary revascularization (CI 0.57-0.83 p< 0.001)
- Secondary endpoint(s): (hierarchical fashion)
    - Composite of cardiovascular death, spontaneous myocardial infarction or ischemic stroke (CI 0.57-0.92 p = 0.007)
    - Composite of spontaneous myocardial infarction or ischemia driven coronary revascularization (CI 0.55-0.83 p < 0.001)
    - Composite of cardiovascular death or spontaneous myocardial infarction (CI 0.55-0.92 p = 0.01)
    - Ischemia-driven coronary revascularization (CI 0.6-0.94 p = 0.01)
    - Spontaneous myocardial infarction (CI 0.53-0.93 p = 0.01)
    - Ischemic stroke

    - Death from any cause
    - Cardiovascular death
- Additional end points
    - Any myocardial infarctions (CI 0.54-0.95)
        - Spontaneous or procedural
- Adverse Outcomes:
    - Non-cardiovascular outcomes occurred more frequently in colchicine group (not statically significant)
    - Gout occurred in 38 patients (1.4%) in colchicine group compared to 95 patients (3.4%) in placebo (CI 0.28-0.58)
    - Myalgia (CI 1.01-1.31) – only in Netherlands cohort

Strengths:

- There was a large sample size used with statistical power being achieved.
- This study used a large number of centers in 2 different countries.
- Blinding, randomization, and placebo control was performed.

Limitations:

- Study not performed in the United States.
- Statistics used did not provide straight forward endpoints.
- This study used multiple composite endpoints that muddied data.
- The patient population is not generalizable to those typically seen in the United States. There were low rates of females, hypertension, diabetes, and poor renal function seen in this study population.
- Baseline characteristics did not include ethnicities of patients.
- There were no vital signs reported and thus no ability to determine if patients' medications were providing the best benefit prior to initiating this additional therapy.
- The use of a run-in period could have provided a more ideal patient population than typically seen in clinical practice.
- 0.5 mg of colchicine was used in this trial; only 0.6 mg is available in the United States.

Discussion:

- These results provide some support for the potential benefits of anti-inflammatory therapy in patients with coronary disease. Colchicine may provide some advantage; however, it is not a benign drug and has many prominent side effects that could be harmful to patients. The patient population seen in this study cannot be extrapolated to match the typical patients seen in Arkansas. The use of a run-in period provided an even more ideal population that was adherent to the medications and did not experience any side effects. Although not statistically significant, there was actually higher non-cardiovascular mortality seen in patients in the colchicine group. More studies are needed displaying the use of colchicine in patients with chronic coronary disease prior to this medication becoming a standard of practice.

Author's conclusion:

- "Among patients with chronic coronary disease, most of whom were already receiving proven secondary prevention therapies, 0.5 mg of colchicine once daily resulted in a 31% lower relative risk of cardiovascular death, spontaneous myocardial infarction, ischemic stroke, or ischemia-driven coronary revascularization (the primary endpoint)."

Clinical Take Home Point:

- This trial provided some favorable data for the use of colchicine in patients with chronic coronary disease. The statistical analysis used in this trial was changed to include hierarchical testing in January 2020. The adjustment to data analysis and use of multiple composite endpoints muddied the results of this trial. More studies should be performed before initiating colchicine as standard of treatment in practice.

References:

Nidorf SM, et al. Colchicine in Patients with Chronic Coronary Disease. N Engl J Med. 2020 Nov 5;383(19):1838-1847. doi: 10.1056/NEJMoa2021372. Epub 2020 Aug 31. PMID: 32865380.