MedStar Heart & Vascular Institute | Cleveland Clinic Heart and Vascular Institute

Knowledge and Compassion **Focused on You**

How Important Is Inflammation As Determined By C-Reactive Protein (CRP) Levels In Predicting Adverse Cardiac Events: What Drugs Can Lower This Risk

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VEITH SYMPOSIUM® Connecting The Vascular Community

Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship	Company
• Grant/Research Support	• Philips • Medtronic • Amgen • Boston Scientific • Biotronik • PI CARDIA • Cordis/MedAlliance
• Consulting Fees/Honoraria	

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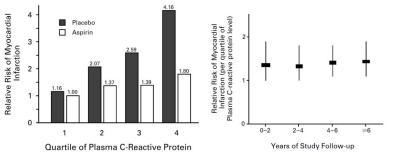
Knowledge and Compassion **Focused on You**

Low Grade Systemic Inflammation *Precedes* By Many Years the Onset of Vascular Events

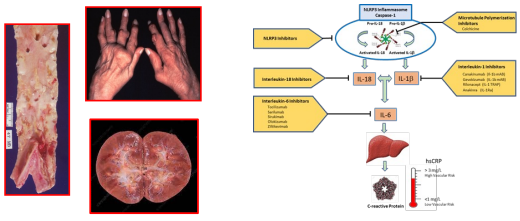

The New England Journal of Medicine

INFLAMMATION, ASPIRIN, AND THE RISK OF CARDIOVASCULAR DISEASE IN APPARENTLY HEALTHY MEN



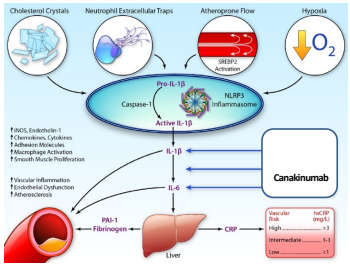
Ridker ESC 2017

Can Targeted Inflammation Inhibition Reduce Cardiovascular Event Rates and Improve Renal Function?



Ridker PM. Circulation 2020;141:787-789

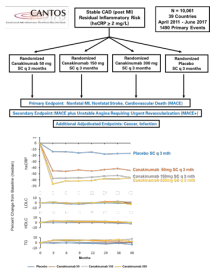
From CRP to IL-6 to IL-1: Moving Upstream to Identify Novel Targets for Atheroprotection

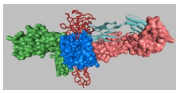


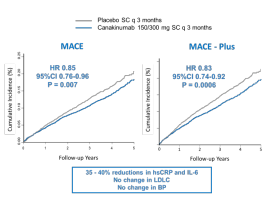
Ridker ESC 2017

Ridker PM. Circ Res 2016;118:145-156.

Canakinumab, a Human Monoclonal Antibody Neutralizing IL-1β

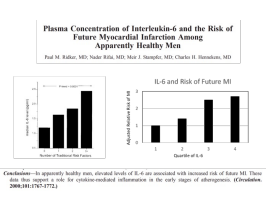


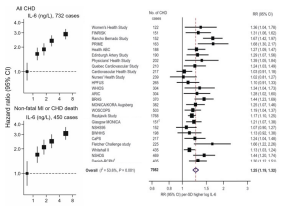




Ridker et al, N Engl J Med. 2017;377:1119-31

IL-6 Levels Are a Powerful Predictor of Future Cardiovascular Events





Ridker et al Circulation 2000;101:1767-1772

Kaptoge et al, Eur Heart J 2014;35:578-589

ZEUS: Study design

A randomised, parallel-group, double-blind, placebo-controlled trial (recruiting)

Ziltivekimab, a narrow spectrum fully human monoclonal antibody targeting the IL-6 ligand that is being developed specifically for atherosclerosis.

6,200 participants

Serum hsCRP ≥2 mg/L

Evidence of ASCVD

CKD defined by:

UACR>= 200 mg/g and eGFR ≥ 60 mL/min/1.73 m²

or

eGFR ≥15 and <60 mL/min/1.73 m²

Objective	Primary endpoint	Secondary confirmatory endpoints
To demonstrate the superiority of ziltivekimab 15 mg s.c. once-monthly in reducing the risk of MACE compared to placebo	Time to first occurrence of 3-point MACE: • CV death • non-fatal MI • non-fatal stroke	• Time to first occurrence of expanded MACE † • Number of hospitalisations for HF or urgent HF visit • Time to occurrence of all-cause mortality • Time to first occurrence of a composite CKD endpoint*

† CV death, non-fatal MI, non-fatal stroke or hospitalisation for unstable angina pectoris requiring urgent coronary revascularisation, *sustained reduction in eGFR, death from kidney failure, onset of persistent eGFR <15 mL/min/1.73 m² or initiation of chronic kidney replacement therapy

ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; CVOT, cardiovascular outcome trial; eGFR, estimated glomerular filtration rate; HF, heart failure; hsCRP, high-sensitivity C-reactive protein; MACE, major adverse cardiovascular event; MI, myocardial infarction; UACR, urine albumin-to-creatinine ratio

ClinicalTrials.gov. Trial ID NCT05021835. Available from https://clinicaltrials.gov/ct2/show/NCT05021835 [accessed 23 Feb 2022]

ARTEMIS: ziltivekimab in AMI

Trial design features
- Double blinded
- 18 months recruitment
- 2 years total duration
- Hazard ratio 0.80
- Power 90%, alpha 5%
- Placebo event rate:
  - 9.0% year 1
  - 3.5% year 2
- Loss rate 3.5%/year

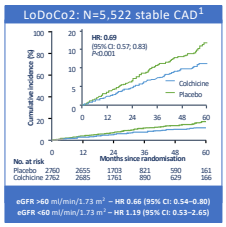
Trial objective

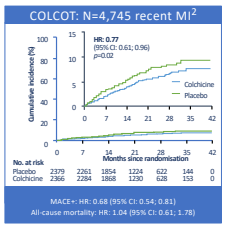
To demonstrate the superiority of ziltivekimab 15 mg s.c. once-monthly versus placebo, both added to standard of care, in reducing the risk of MACE in patients with AMI

Primary endpoint:
- Time to the first occurrence of 3-point MACE: cardiovascular death, non-fatal MI and non-fatal stroke

Confirmatory secondary endpoints (hierarchy):
- Time to the first occurrence of expanded MACE; cardiovascular death, non-fatal MI, non-fatal stroke, urgent revascularisation, hospitalisation for HF, urgent HF visit
- HF-composite endpoint: hospitalisation for HF, urgent HF visit, outpatient diagnosis of HF*
- Time to CV death
- Time to all cause death

Colchicine Reduces Cardiovascular Risk
Now FDA approved for high-risk patients





CAD, coronary artery disease; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MACE, major adverse cardiovascular event; MACE+, MACE plus heart failure and thromboembolic events; MI, myocardial infarction

1. Nidorf SM et al. N Engl J Med 2020;383:1838–1847; 2. Tardif JC et al. N Engl J Med 2019;381:2497–2505; 3. Samuel M et al. Can J Cardiol 2021;37:776–785; 4. Ridker PM and Rane M. Circulation Research 2021;128:1728–1746

FDA Approval of low dose colchicine 0.5 mg po - June 20, 2023

FDA approves colchicine, the first anti-inflammatory drug for treating cardiovascular disease

Dave Fornell | June 20, 2023 | Pharmaceutics

----------**INDICATIONS AND USAGE**----------

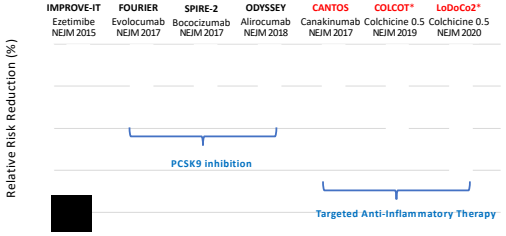
LODOCO is an alkaloid indicated:

- to reduce the risk of myocardial infarction (MI), stroke, coronary revascularization, and cardiovascular death in adult patients with established atherosclerotic disease or with multiple risk factors for cardiovascular disease (1).

----------**DOSAGE AND ADMINISTRATION**----------

The recommended dosage is 0.5 mg orally once daily. (2.1).

Anticipated Benefits of Ezetimibe, PCSK9 inhibition, and Colchicine 0.5 mg Following Aggressive Use of Statin Therapy



Circulation 2023;148:1071-1073

CLEAR OASIS 9 Trial

Population Health Research Institute

7000 patients diagnosed with Acute Myocardial Infarction (MI) referred for PCI

SYNERGY stent recommended for use when available*

Randomized within 72 hours of PCI 2x2 Factorial

Colchicine | Placebo

Randomized

Spironolactone | Placebo | Spironolactone | Placebo

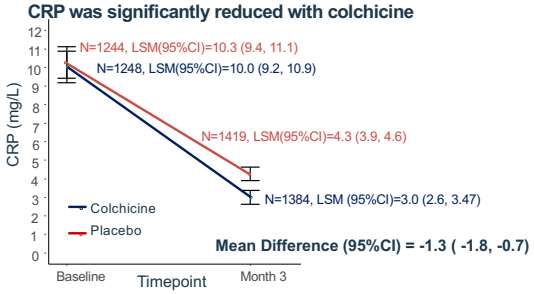
Primary Outcome

Colchicine vs. placebo: Composite of CV death, MI, stroke or ischemia driven revascularization over duration of follow-up

Hamilton Health Sciences | McMaster University

CRP was significantly reduced with colchicine

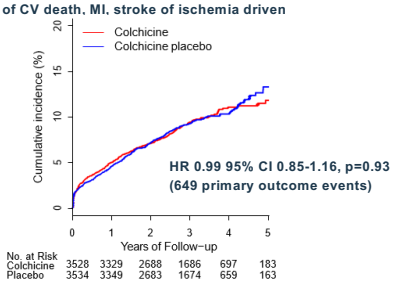
Population Health Research Institute



Hamilton Health Sciences | McMaster University

Primary outcome of CV death, MI, stroke of ischemia driven revascularization

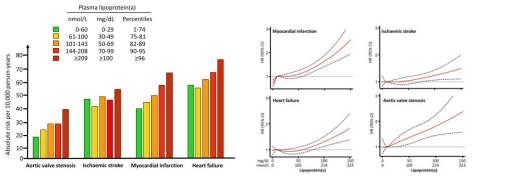
Population Health Research Institute



Hamilton Health Sciences | McMaster University

Lp(a) Induces a Pro-Inflammatory and Pro-Migratory Profile that is Attenuated with Potent Lp(a) Lowering

Lp(a) Concentrations and Risk of Clinical Outcomes



Absolute and relative risks of aortic valve stenosis, ischaemic stroke, myocardial infarction and heart failure as a function of increasing plasma Lp(a) concentration in the general population. Top panel shows the absolute risk per 10000 person-years, and the lower panel shows hazard ratios as solid red line with 95% confidence intervals as dotted black lines; when the lower 95% confidence interval no longer overlap the hazard ratios reference value of 1.0 for the median Lp(a) concentration, risk is significantly elevated. Based on data from 70 286 White individuals in the Copenhagen General Population Study with a median 7.4 years of follow-up. Data provided by Prof. Børge G. Nordestgaard and Dr. Anne Langsted.

Kronenberg F et al. Eur Heart J. 2022; 43: 3925–3946.

Targeting Inflammation: Implications for practice

- Following statin therapy, clinicians consider using an anti-inflammatory agent?
  - *Consideration of **colchicine 0.5 mg po qd** for those with stable atherosclerosis and normal eGFR and high CRP. For Primary and Secondary prevention*
  - *Consideration of **bempedoic acid** which, like statin therapy, reduces both LDL-C and hsCRP*
  - *Consideration of **GLP1r agonists** and **SGLT2 inhibitors**, all of which have concomitant anti-inflammatory effects.*

Thank you for your attention