

LODOCO – Colchocine Research

Mark Nidorf

Chairs: Craig Cheetham, Paul Camp

Colchicine for 2^o Prevention of Cardiovascular Disease

LoDoCo2 - An Australian-Dutch Collaboration

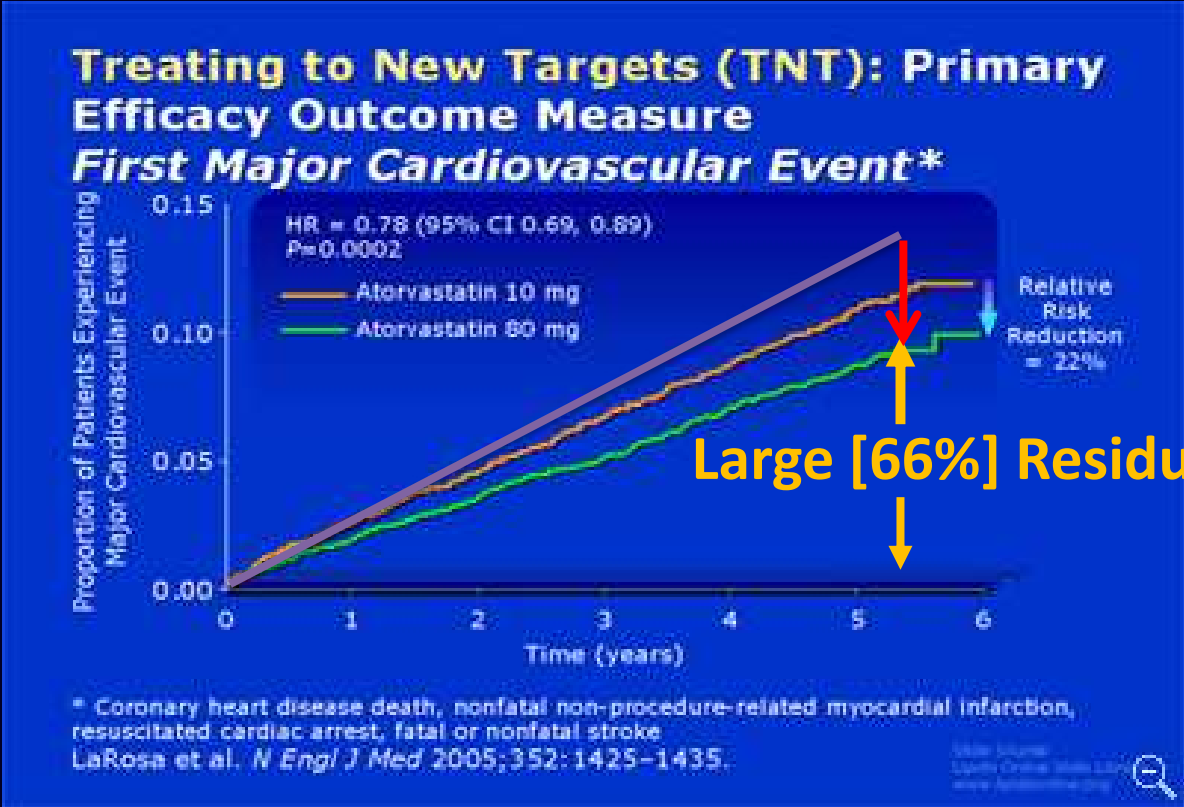


Atherosclerosis is the Major Cause of Heart-Attack Stroke and Sudden Death in the Western World

Bypass & PTCA may improve short term symptoms in some patients
Neither of these interventions halt the progression of the disease
Both create new problems in of themselves

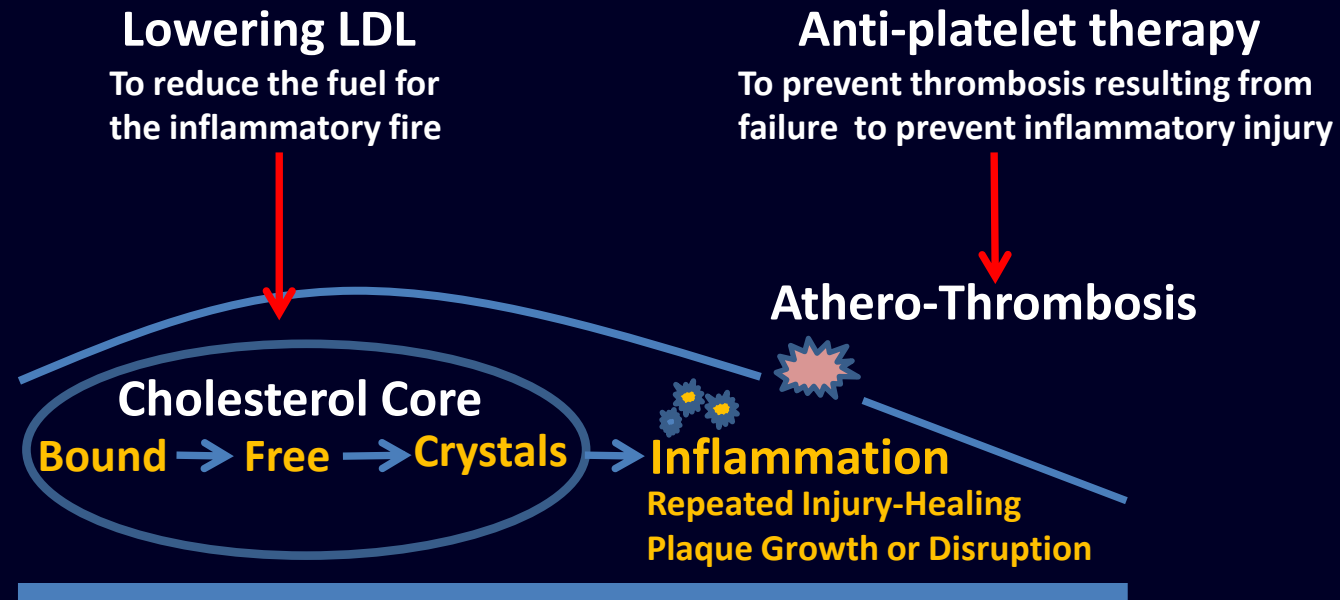
The only way to improve the long-term outcome of patients with atherosclerosis is to alter the underlying processes that drive the disease

The Process of Atherosclerosis Can Be Modified by Lowering LDL in a Dose Dependent Manner



The PCSK9 Trials will determine if there is a limit to the benefits of lowering LDL

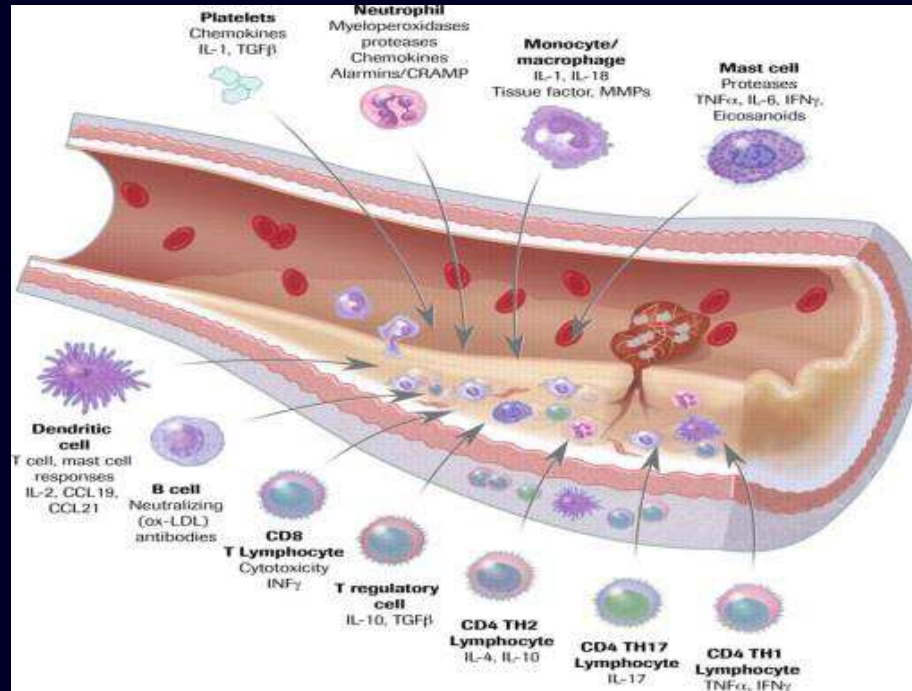
The Current Paradigm for 2° Prevention of Atherosclerosis Does Not Directly Target the Disease Process



To Modify the Natural History of Atherosclerosis we Need to Modify all of the Processes that Drive it

The Arterial Wall is Aflame With Activity

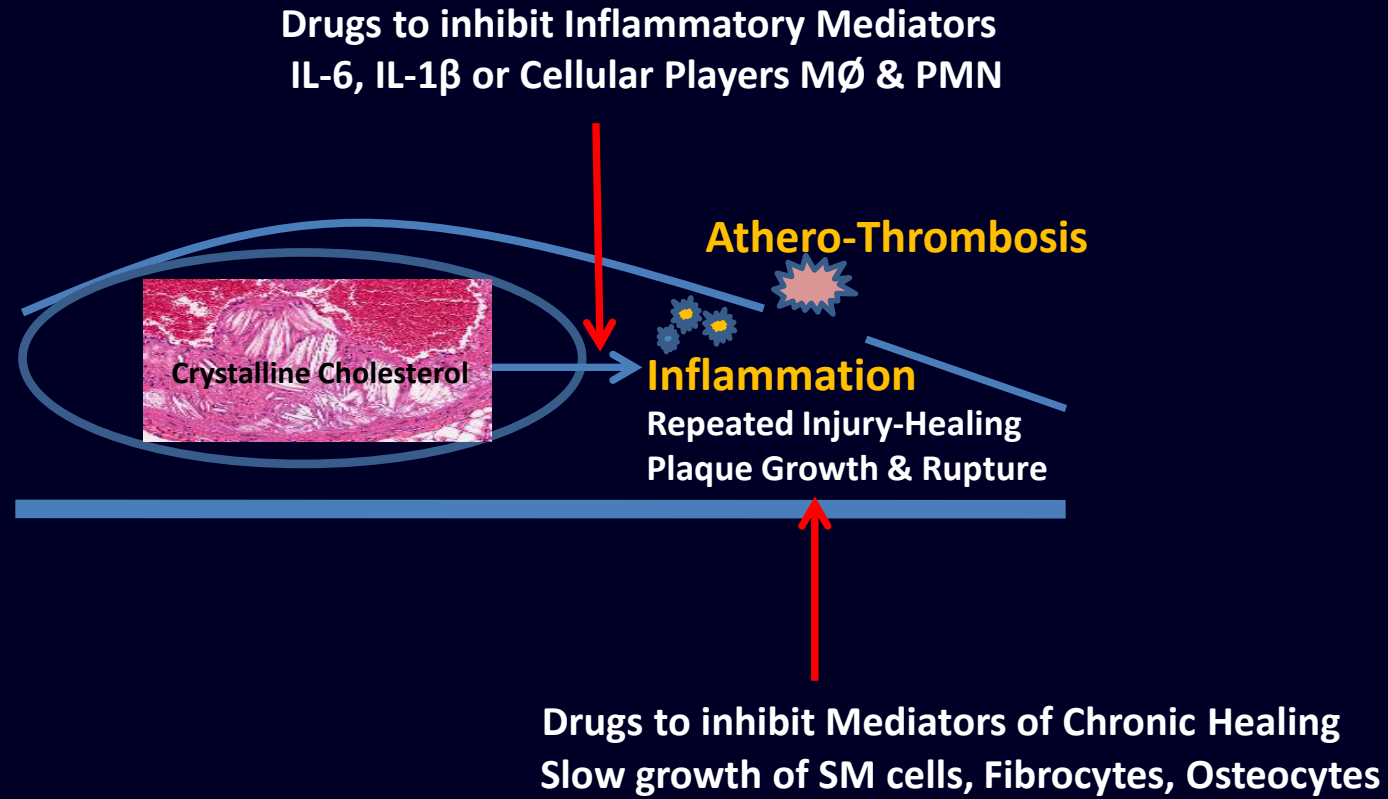
Inflammatory
Injury



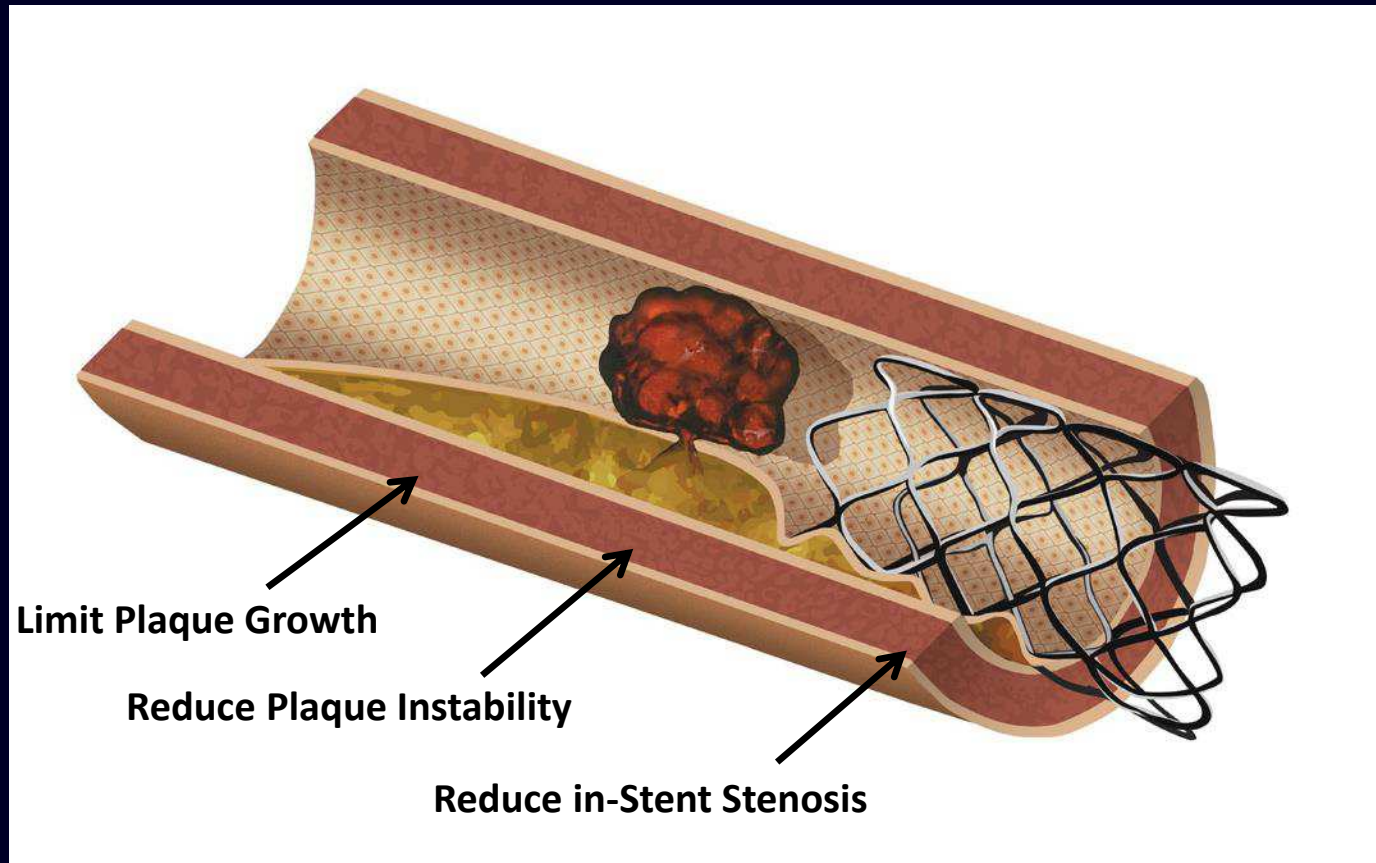
Chronic
Healing

The Next Frontier in the Treatment of Atherosclerosis

The promise that targeting the underlying inflammatory & healing processes in atherosclerotic plaque will improve clinical outcomes



Therapies Must Target a Number of Processes



Well tolerated, safe over decades, affordable & readily available

The Journey into the Use of Colchicine for 2° Prevention of Cardiovascular Disease





Colchicine

Uses

Therapeutic use of >2000 years

Recognized as an effective treatment for acute pericarditis

Long-term use is highly effective for 2^o prevention of gout & FMF

Actions

Taken up rapidly & avidly by Macrophages & Neutrophils

Prevents & Dampens IL-1 β release & Dampens Neutrophil function

Promotes favourable healing by reducing the growth of vascular smooth muscle cells, fibrocytes & osteophytes



Continuous Use of Low Dose Colchicine is Safe

Long-term daily doses of up to 2mg/d is FDA approved [FMF]

5-10% experience mild early GI effects - dose related*

Myo-, BM toxicity & Death limited to cases of intentional over-dose

It has no detrimental effects on renal or hepatic function**

Serious drug interactions are limited - Clarithromycin***

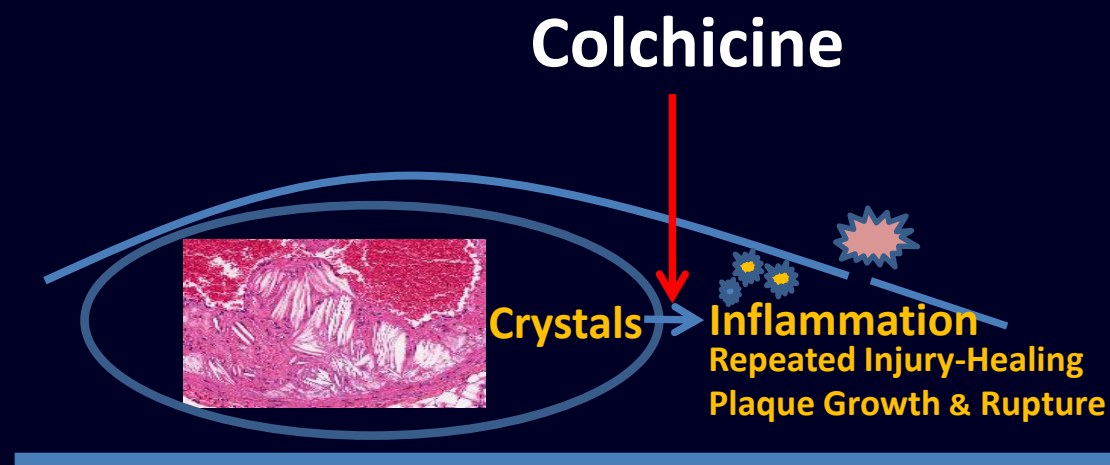
* 98% tolerate 0.25mg/day

** Used in advanced renal failure and cirrhosis

*** Nexium 7



Given its Relevant Biologic Effects & Proven Safety Long-Term Colchicine May Improve the Clinical Outcome of Patients with Stable Coronary Artery Disease





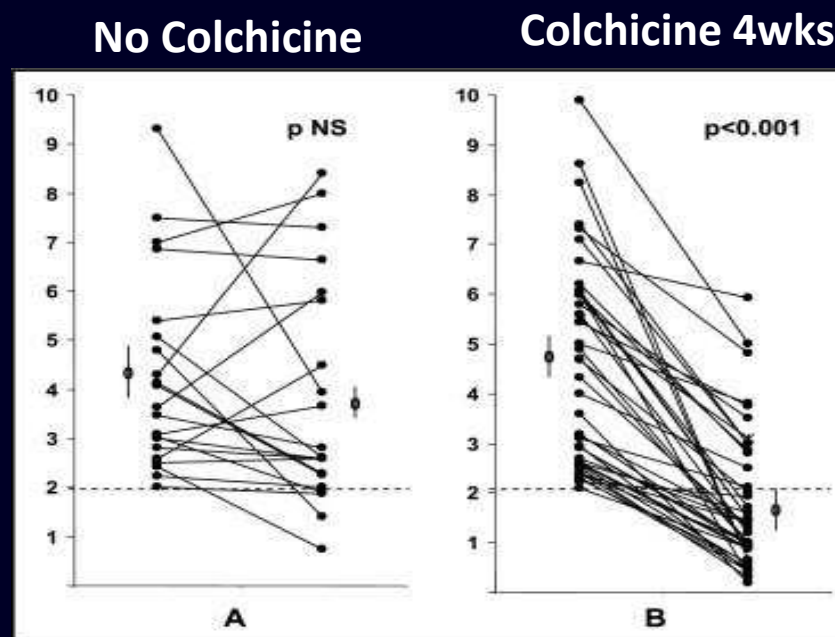
When Clinicians take their Ideas from Bench to Bedside it Requires a Leap of Faith

**... they need to go forward aware of uncertainties but
'in the confident hope of a miracle'***

* Admiral Martin de Bertendona,
Commander of the [Spanish Armada] Levant squadron
Expressing doubts about the chances of success of the invasion of England



Colchicine Can Rapidly Reduce Inflammation [hs-CRP] in Pts with Stable Coronary Disease over Aspirin & Statins



Nidorf SM et al. 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;99:805-7

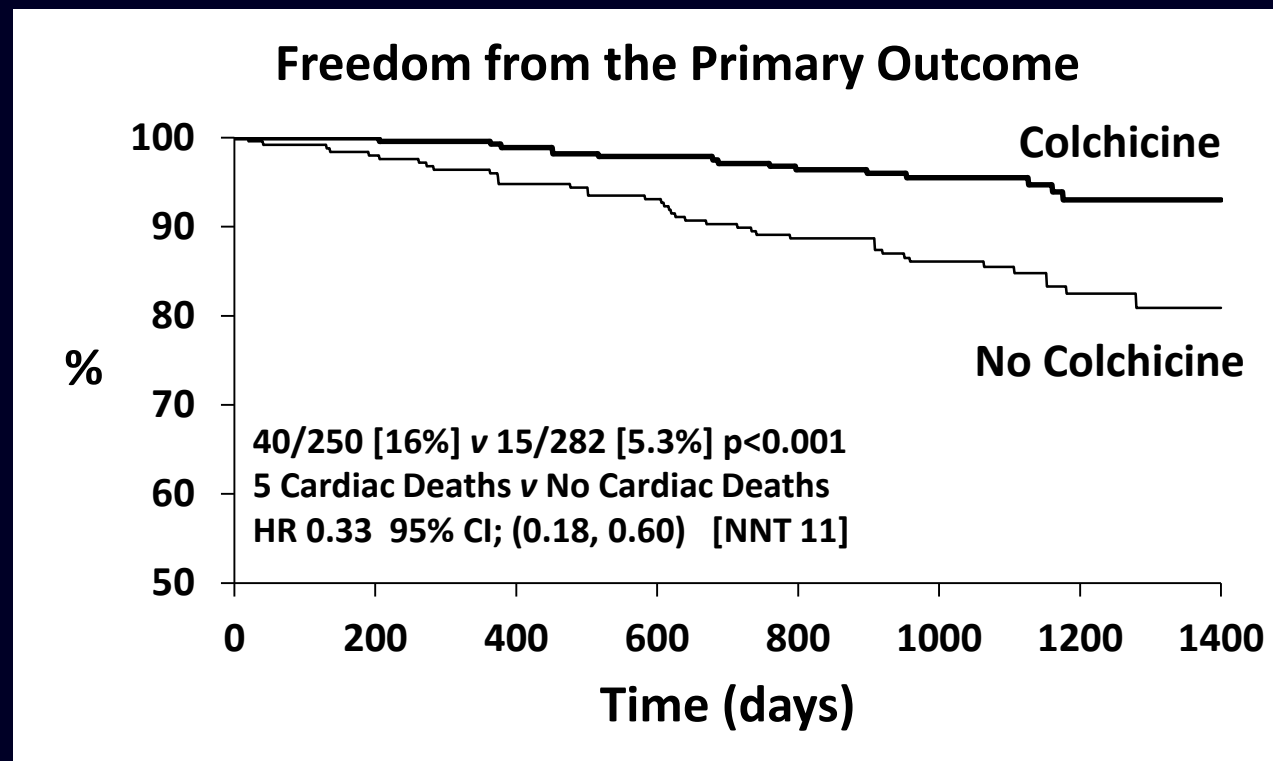
If Colchicine can reduce hs-CRP can it improve clinical outcome?



LoDoCo Trial

The Effect of Colchicine for 2° Prevention of CVD

1st trial to support the potential of anti-inflammatory in IHD



Nidorf SM et al. Low-dose colchicine for secondary prevention of cardiovascular disease JACC 61;2013: 404 - 406



Low Dose Colchicine has been demonstrated to:

- Limit plaque growth & stent re-stenosis in animal studies**
- Reduce hs-CRP, IL-6, IL-1 β in pts with stable & unstable CAD**
- Reduce the extent of in-stent stenosis in diabetics with bare stents**
- Reduce myocardial reperfusion injury post AMI & CABG**

Added support for its potential for 2^o prevention in CAD

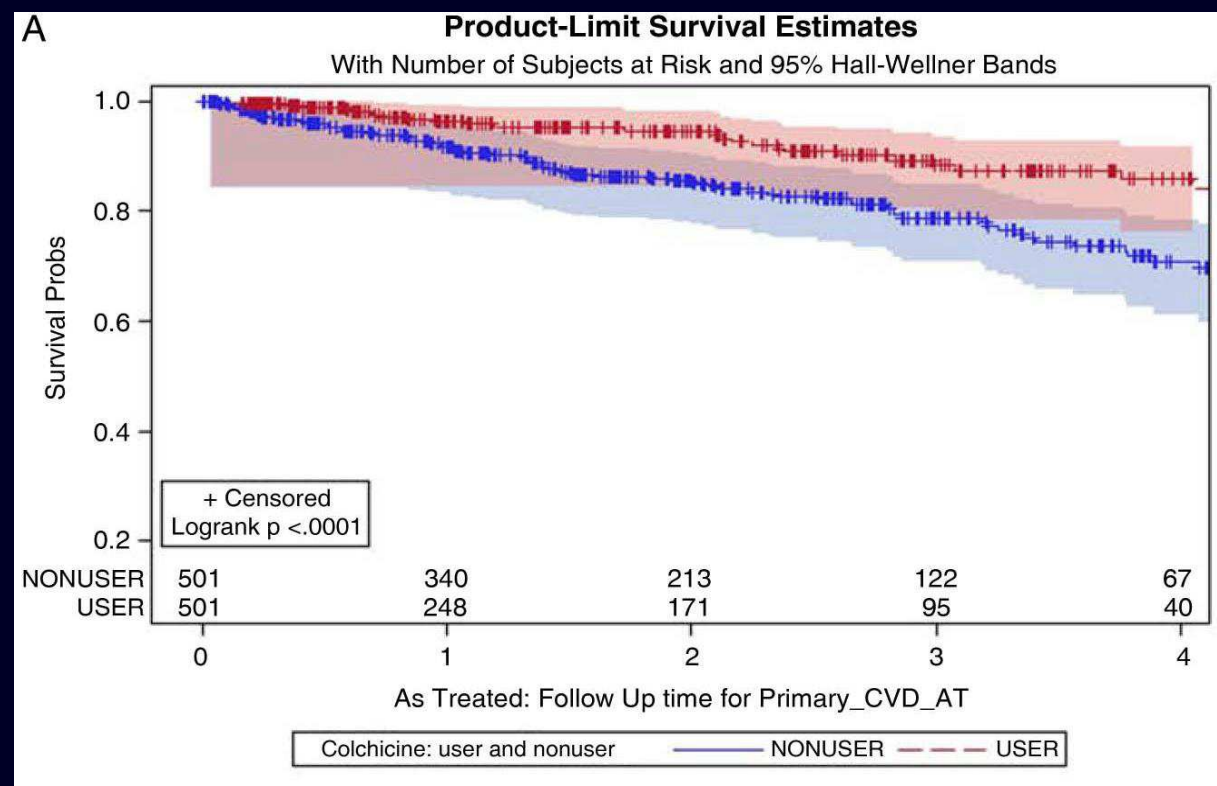
- 2 Meta-analyses Colchicine in pts \pm CV Disease
reduced risk of AMI & CV Death**
- 2 Retrospective cohort studies in patients with gout**

Colchicine for prevention of cardiovascular events. Cochrane Database. 2016 Jan

Verma S, Eikelboom JW, Nidorf SM, Al-Omran M, Gupta N, Teoh H, et al. Colchicine in cardiac disease: a systematic review and meta-analysis of randomized controlled trials. BMC cardiovascular disorders. 2015;15(1):1



Patients With Gout who Receive Colchicine are Less Likely to Suffer a CV Event

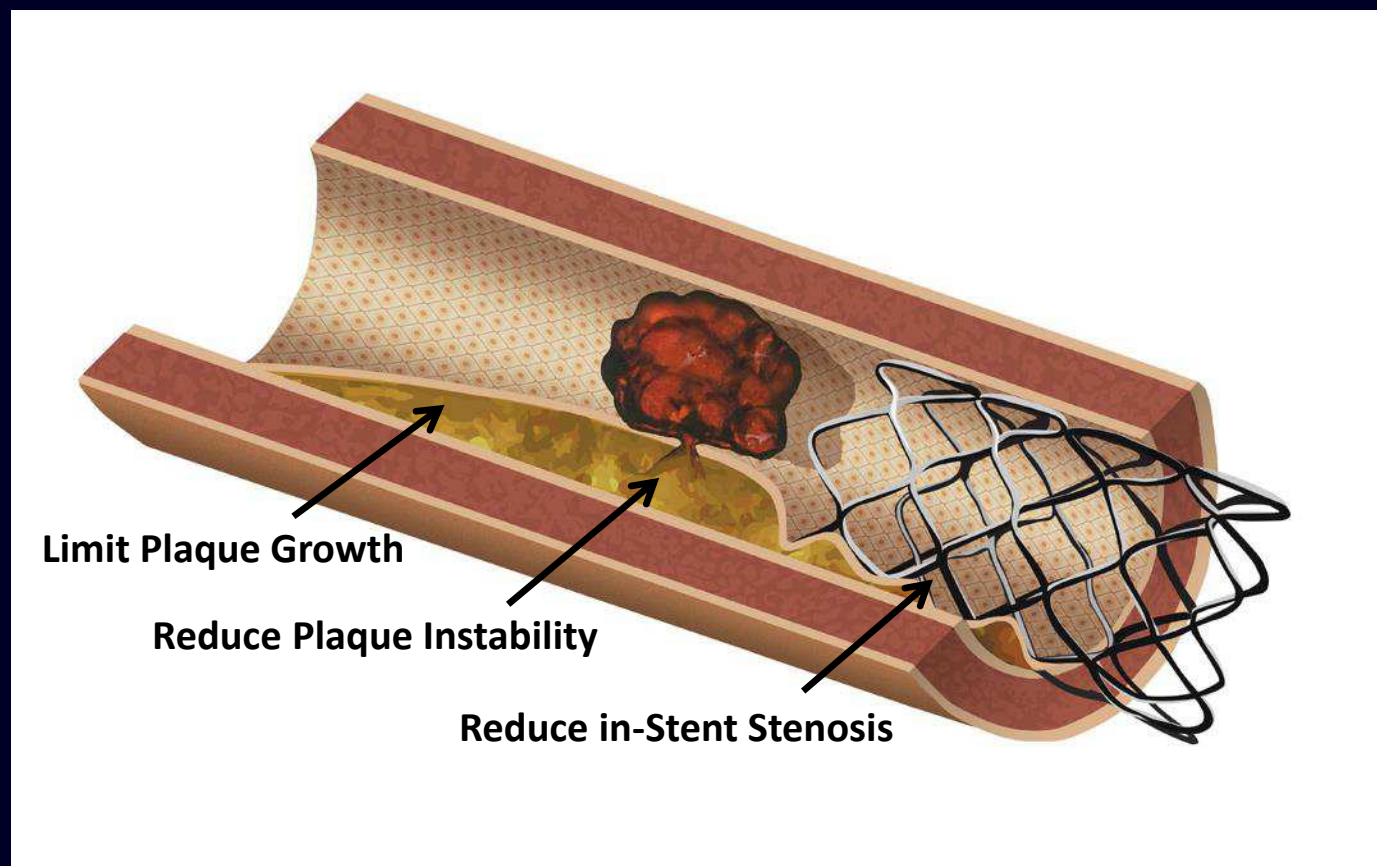


Effects of colchicine on risk of cardiovascular events and mortality among patients with gout: a cohort study using electronic medical records linked with Medicare claims Daniel H Solomon, *annrheumdis-2015*

Colchicine use is associated with decreased prevalence of myocardial infarction in patients with gout. Crittenden DB *The Journal of rheumatology* 2012;39:1458-64.



Colchicine May Fulfil Many of the Requisites for 2° Prevention of Atherosclerosis



Well tolerated, safe over decades, affordable & readily available



Whilst LoDoCo1 'put Colchicine on the Map'
LoDoCo2 will Confirm its Place in the World




Ongoing Trials of Low Dose Colchicine in CV Disease

CLINICAL TRIAL

**IF YOU HAVE
CORONARY
DISEASE**

you may be eligible to take part
in our innovative clinical research



The LoDoCo2 Trial
Initiated by the Cardiologists in this Practice
in association with The Heart Research Institute of WA,
Ethics approval from Sir Charles Gairdner Hospital and
with generous support from GenesisCare.

The LoDoCo2 Trial

~4,000 Pts with Stable CAD

WA & Netherlands

Began August 2014 - WA >85% recruited

COLCOT

Colchicine Cardiovascular Outcome Trial

~3,000 Pts Post ACS

Montreal Heart Canada

Began Dec 2015

~ 7,000 people with coronary disease will be
recruited to a LoDoCo type trial



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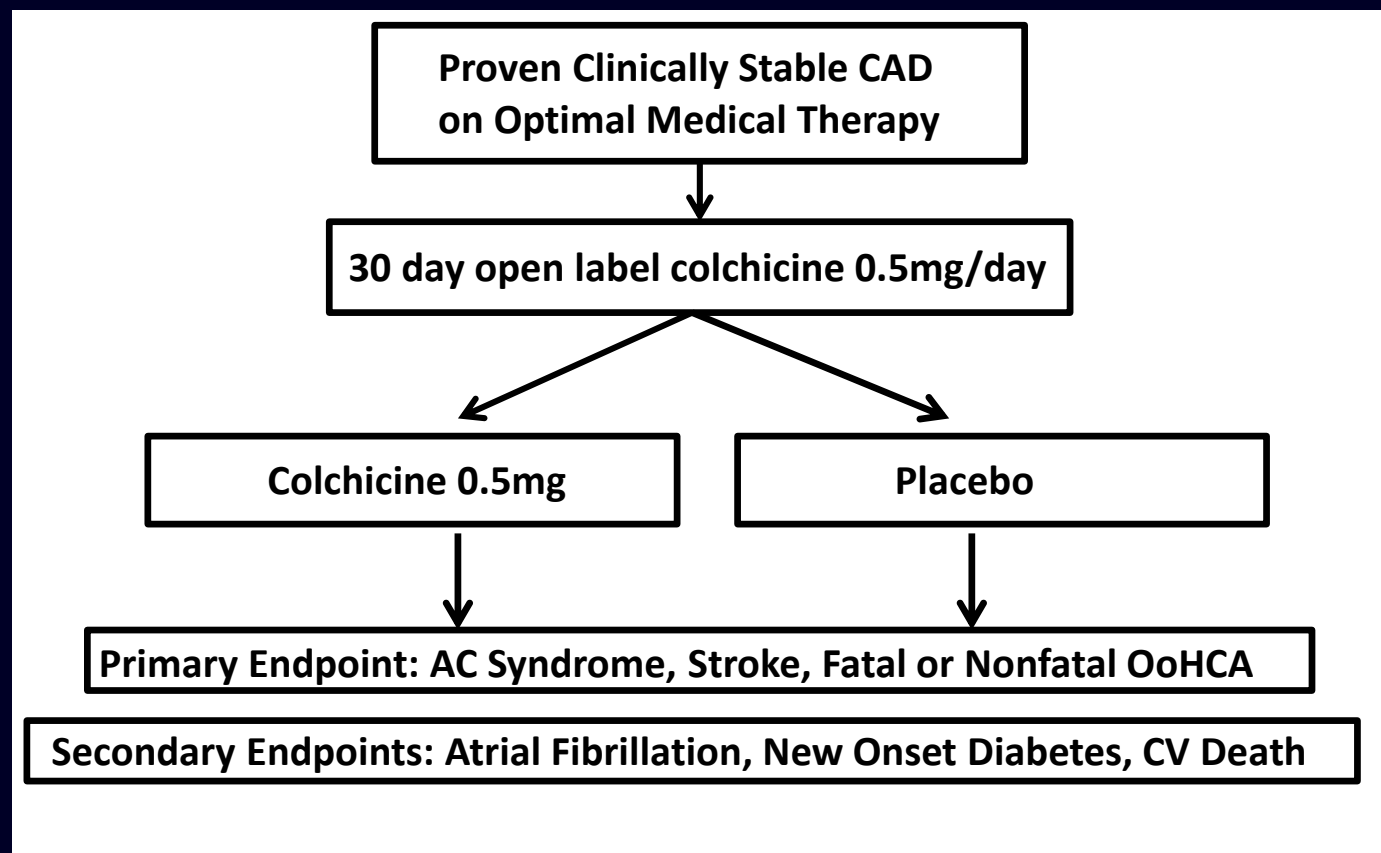
The LoDoCo2 Trial

- Prospectively Randomized Double Blinded Placebo Controlled Trial of 0.5mg/d Colchicine in people with stable coronary disease
- Event driven outcome – Mean follow up 3 years
- To confirm efficacy and safety of LD colchicine for 2^o Prevention
- **Initiative from the Cardiologists within HCWA - No conflicts of interest**
- Aspen Pharma have supplied active & placebo at no cost
- HRI supported application for Ethics & Governance via QEII
- Recruitment began in August 2014
- NHMRC Funding Approved November 2014
- **Now to be strongly supported with a bolus recruitment effort by WCN**

[ACTRN12614000093684 –ANZCTR]



The Low Dose Colchicine Trial (LoDoCo2)





DO YOU HAVE CORONARY DISEASE?

Ask your Cardiologist if you are eligible to take part in the next phase of our innovative clinical research into the possible prevention of Heart Attacks and Strokes



Autumn Crocus - the source of Colchicine

The LoDoCo2 Trial

Initiated by the Cardiologists in this Practice in association with The Heart Research Institute of WA, Ethics approval from Sir Charles Gairdner Hospital and with generous support from Genesis Care.



The Australian NEWS 3
Friday, November 8, 2013

Gout medication reduces risk of heart attack

A West Australian-led study has found a patient's risk of heart attack could be dramatically reduced by taking a common medication to treat gout.

More than 500 people participated in the Heart Research Institute study at Perth's Sir Charles Gairdner Hospital. Some were given the drug colchicine.

Lead researcher Peter Thompson says the results are very exciting.

"When we gave the drug to the patients compared with those who did not receive the drug, the risk of heart attack was reduced by half and the side effects were minimal," he said.

"Larger and more detailed studies are yet required to check that there are no unusual or unexpected side effects, but at this stage, it's looking highly promising."

Professor Thompson says the results could change the way heart disease is treated around the world.

"This is a drug which is relatively inexpensive and widely available and has quite dramatic effects and other drugs are being trialled and developed but they are quite expensive and relatively inaccessible," he said.

Low-dose colchicine for secondary prevention of cardiovascular disease. Nidorf SM, Eikelboom JW, Budgen CA, Thompson PL. Journal of the American College of Cardiology 61:2013:404-406, February 2014.

Success relates to

The ability to rapidly recruit a large number of pts*

The ability to embed complex trial logistics into the everyday routines in the Practice

Driven and Engaged Doctor Group

Dedicated Staff

* If WCN can effect a rapid bolus recruitment LoDoCo2 could be fully recruited in 6m



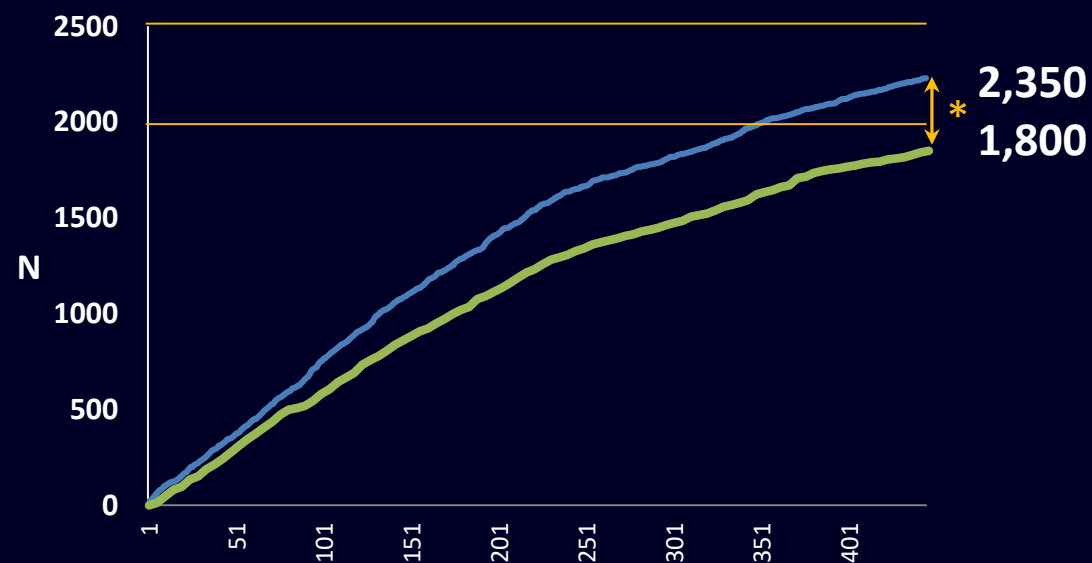
Integration the LoDoCo2 Trial into the Practice

- 1] All clinics are **pre-screened** a week in advance
- 2] Suitable **patients are identified** by colour code on the day list
This allows patients to be identified as they come into the Practice
Reception staff hand over reading material before they are seen
- 3] **Cardiologist** talk to the trial and prepare for **consent** [note in record]
- 4] Signed consent forms taken by **secretaries who provide open label TM**
This process is logged to ensure all TM stock is accounted for
Patients given written instructions about dosing



Recruitment & Randomization into LoDoCo2

1 Practice - 10 Recruiting Cardiologists



* **20% drop out before randomization**

10% Unwilling some because they were keen not to be denied colchicine

10% Early Intolerance – 95% GI - bloating, reflux, diarrhoea, constipation, 5% other

>85% of these pts (98% of all pts) tolerate 0.25mg, and some go on to tolerate 0.5mg



Is LoDoCo2 going to be Relevant in the New World of PCSK9 Inhibitors & Canakinumab

ESC CONGRESS ROME 2016 13:05 | Berlin

CLINICAL RESEARCH Clinical Trial

Low-Dose Colchicine for Secondary Prevention of Cardiovascular Disease

Stefan M. Nidorf, MD, MBBS,* John W. Eikelboom, MBBS,† Charley A. Budgeon, BSc (Hons),‡ Peter L. Thompson, MD§
Perth, Australia, and Hamilton, Ontario, Canada

HR 0.33
95% CI (0.18, 0.59)
p<0.001

Nidorf, SM, et al; JACC 2013; 61:404-10.

Paul M RIDKER (Boston - US)



Absolutely YES

Lowering LDL Will Never Completely Dampen the Inflammatory Flame

CANTOS is +ve So There Will Be Intense Interest in Colchicine

Because it implies that the IL-1 β pathway is important but leaves open the question as to how best to block it

Colchicine Like Canakinumab targets the IL-1 β pathway

Colchicine Unlike Canakinumab;

Also targets the chronic healing responses to inflammatory injury

Is inexpensive and widely available

Is well tolerate - 90% tolerate 0.5mg/d & 98% tolerate 0.25mg/d

Has proven long-term safety over decades even at higher dose