Findings from large clinical trials of anti-inflammatory drugs and vitamins to prevent heart attack and stroke

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Disclosures

FINANCIAL DISCLOSURE: No Conflicts to Disclose.

UNLABELED/UNAPPROVED USES DISCLOSURE:
No Unlabeled or Unapproved Agents to Disclose.

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Educational Need/Practice Gap

Agents which reduce inflammation have lead to a decrease in the incidence of heart attack and stroke and improved outcomes in those who develop the disease. We will systematically review high-quality studies which demonstrate this assertion.

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Objective

1. Appreciate that heart attack and stroke are inflammatory disorders.

2. Understand that targeting the underlying cause (inflammation) with diet, lifestyle changes, and drugs can avert thrombotic disorders.

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Lecture Content

1. Anti-inflammatory agents and cardiovascular disease (CVD):
   i. Published Data
   ii. Ongoing Studies
2. Vitamins and CVD
   i. Published Data
   ii. Ongoing Studies
3. Conclusions
   Take-home points

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CVD is an Inflammatory Disorder

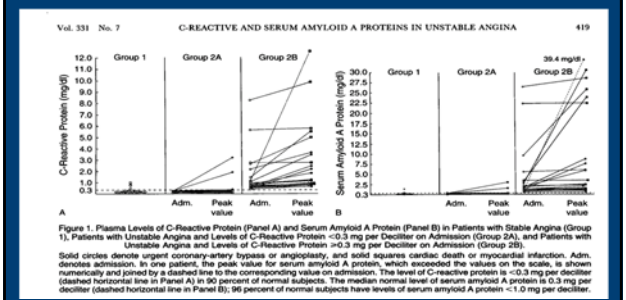

Figure 1. Plasma Levels of C-Reactive Protein (Panel A) and Serum Amyloid A Protein (Panel B) in Patients with Stable Angina (Group 1), Patients with Unstable Angina and Levels of C-Reactive Protein <0.3 mg per Deciliter on Admission (Group 2A), and Patients with Unstable Angina and Levels of C-Reactive Protein ≥0.3 mg per Deciliter on Admission (Group 2B).

Solid circles denote urgent coronary-artery bypass or angioplasty, and solid squares cardiac death or myocardial infarction. Adm. denotes admission. In one patient, the peak value for serum amyloid A protein, which exceeded the values on the scale, is shown numerically and joined by a dashed line to the corresponding value on admission. The level of C-reactive protein is <0.3 mg per deciliter (dashed horizontal line in Panel A) in 90 percent of normal subjects. The median normal level of serum amyloid A protein is 0.3 mg per deciliter (dashed horizontal line in Panel B); 95 percent of normal subjects have levels of serum amyloid A protein <1.0 mg per deciliter.

- Proposed that CAD involves "possible inflammation" in the coronary arteries
- Ascertained that inflammatory markers predict adverse events in UA.

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Liuzzo et al. N Engl J Med. 1994 Aug 18;331(7):417-24

The use of Aspirin in CAD

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Discovery of Platelets

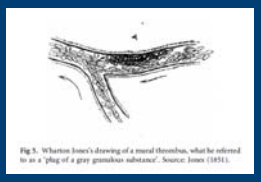
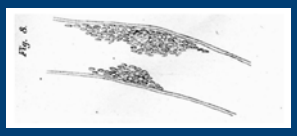


Fig 5. Wharton Jones's drawing of a mural thrombus, what he referred to as a 'plug of a gray granulous substance'. Source: Jones (1851).

'Whereas under normal conditions they (the platelets, D.B.B) float isolated in the plasma, when subject to an influence that leads to thrombosis, they adhere to one another to form an accumulation. The blood platelets, free in the blood stream and being hurried along are held up by other platelets that they come into contact with as they become stickier than they are under normal conditions.'

In further experiments he beat fresh blood with a little bundle of threads for varying periods of time and examined the threads microscopically. He found that after 60 s of beating the threads were covered only with platelets (Fig 8), but after 90 s what he called 'fibrous material' was deposited on top of the layer of platelets.



- Very Early work on the Platelet – 1851 (Discovery)

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Brewer, D. British J. Haematology 133 (2006)

Platelet Purine Release and Thrombosis

THE AGGREGATION OF BLOOD PLATELETS

By G. V. R. Born and M. J. Cross

From the Department of Pharmacology, Royal College of Surgeons of England, Lincoln's Inn Fields, London, W.C. 2

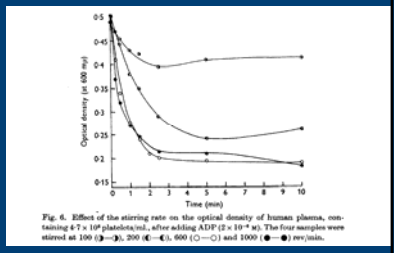

Fig. 6. Effect of the stirring rate on the optical density of human plasma, containing 4·7 × 10⁸ platelets/ml., after adding ADP (2×10^{-6} M). The four samples were stirred at 100 (▶—▶), 200 (◀—◀), 600 (○—○) and 1000 (●—●) rev./min.

Early work on the Platelet - 1963 (Purines are Important)

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Born and Cross J. Physiology 168 (1963)

First Anti-Platelet Agent

The Effect of Salicylates on the Hemostatic Properties of Platelets in Man

Harvey J. Weiss, Louis M. Aledort, and Shaul. Kochwa

From the Department of Medicine (Hematology), The Mount Sinai Hospital and School of Medicine of the City University of New York, New York 10029 and The City Hospital at Elmhurst, New York 11373

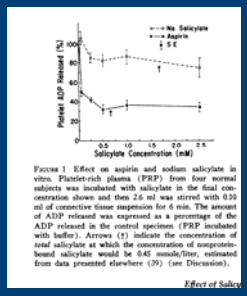

Figure 1 Effect on aspirin and sodium salicylate in vitro. Platelet-rich plasma (PRP) from four normal subjects was incubated with salicylate in the final concentration shown and then 2.6 ml was stirred with 0.10 ml of connective tissue suspension for 6 min. The amount of ADP released was expressed as a percentage of the ADP released in the control specimen (PRP incubated with buffer). Arrows (↑) indicate the concentration of *total* salicylate at which the concentration of nonprotein-bound salicylate would be 0.45 mmole/liter, estimated from data presented elsewhere (39) (see Discussion).

Effect of Salicy

- Early work on the Platelet (First Anti-platelet agent).
- Aspirin has anti-thrombotic, anti-neoplastic, and anti-inflammatory properties.

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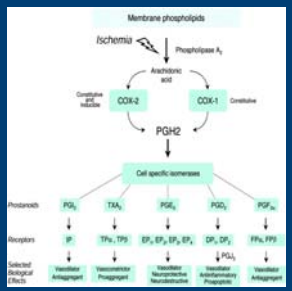
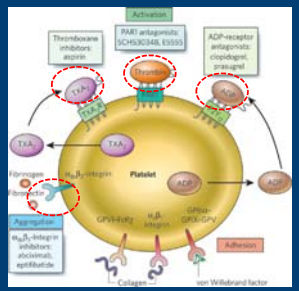
Weiss et al. J Clin Invest. 47 (1968)

Platelet Receptor Antagonists are the Standard of Care for Secondary Prevention of MI



Iadecola and Gorelick Stroke ; 36: 182-18 (2005)



Mackman *et al.* Nature 451, 914-918 (2008)

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Aspirin and Primary Prevention

Effect of Aspirin on Vascular and Nonvascular Outcomes

Meta-analysis of Randomized Controlled Trials

Sreenivasa Rao Kondapally Seshasai, MD, MPhil; Shanelle Wijesuriya, MA, MBBChir; Rupa Sivakumaran, MA, MBBChir; Sarah Nethercott, MA, MBBChir; Sebhat Erqou, MD, PhD; Naveed Sattar, MD, PhD; Kausik K. Ray, MD

- Purpose: Net benefit of low dose ASA use in primary prevention still not settled.
- Aim: Select the highest quality RCTs which show outcome data over a number of years to ascertain the use of ASA in primary prevention.
- Design: Meta-analysis of 9 high quality trials (~1000 patients) over a mean observational period of 6 years.

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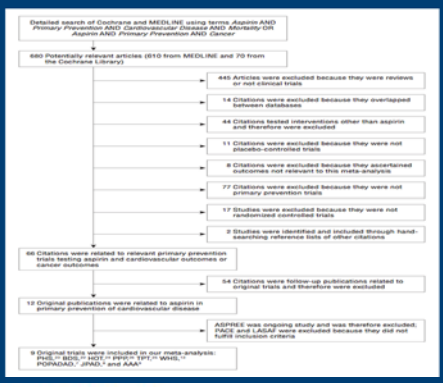
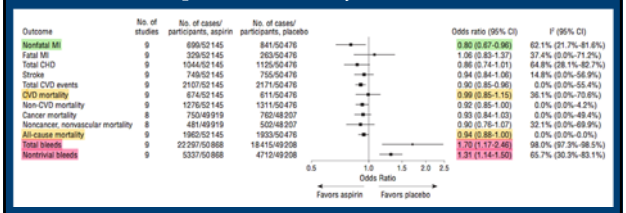
Seshasai et al Arch Intern Med. 2012 Feb 13;172(3):209-16

Aspirin and Primary Prevention



Seshasai et al Arch Intern Med. 2012 Feb 13;172(3):209-16

Aspirin and Primary Prevention



Conclusions:

- Once daily ASA did does not appear to have a protective effect for the purposes of primary prevention.
- ASA does appear to slightly decrease the risk of M.I. (OR [0.08-0.96]) which is driven by non-fatal M.I.s
- NNT for non-fatal M.I. was 162 with NNH 73 for non-trivial bleeding issues.

Seshasai et al Arch Intern Med. 2012 Feb 13;172(3):209-16

Aspirin and Primary Prevention

Original Investigation

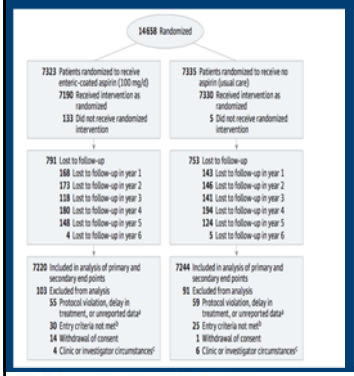
Low-Dose Aspirin for Primary Prevention of Cardiovascular Events in Japanese Patients 60 Years or Older With Atherosclerotic Risk Factors
A Randomized Clinical Trial

Yasuo Ikeda, MD; Kazuyuki Shimada, MD; Tamio Teramoto, MD; Shinichiro Uchiyama, MD; Tsutomu Yamazaki, MD; Shinichi Oikawa, MD; Masahiro Sugawara, MD; Katsuyuki Ando, MD; Mitsuru Murata, MD; Kenji Yokoyama, MD; Naoki Ishizuka, PhD

- Purpose: Prior studies have shown low-dose ASA to decrease adverse vascular events in patients with various cardiovascular co-morbidities. ASA use in Japan for the purposes of primary prevention is not wide-spread.
- Aim: To assess the effect of 100 mg ASA on Japanese patients 60+ years with multiple risk factors for CAD over a six year observational period.

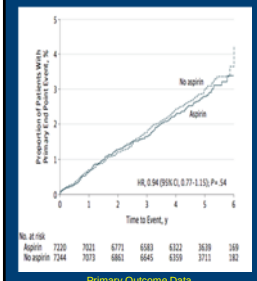
Ikeda *et al.* JAMA. 2014 Dec 17;312(23):2510-20.

Aspirin and Primary Prevention

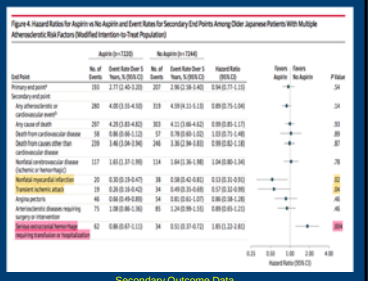


Ikeda *et al.* JAMA. 2014 Dec 17;312(23):2510-20.

Aspirin and Primary Prevention



Primary Outcome Data



Secondary Outcome Data

Conclusions:

- Once daily ASA did not decrease composite endpoint of death, non-fatal stroke and non-fatal M.I. in an elderly Japanese population.
- Study was terminated early on the grounds of futility.

Ikeda *et al.* JAMA. 2014 Dec 17;312(23):2510-20.

Aspirin and Primary Prevention - Summary

- FDA issued a statement in 2014: ASA use for primary prevention is considered reasonable in some patients, though discussion with primary physician and the patient is very important.
- Aspirin clearly has mortality benefit and decreases adverse vascular events in patients with a prior M.I. or stroke.
- Concomitant NSAID use with ASA (especially ibuprofen) compete with ASA for cyclo-oxygenase inhibition, and therefore can precipitate adverse vascular events in patients at risk.

Vitamins in CVD

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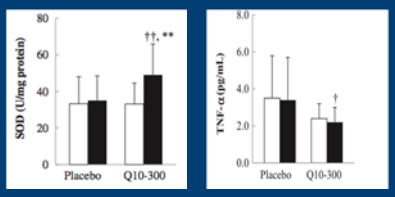
Vitamins and Coronary Artery Disease (CAD)



- Co-Q10 is an antioxidant which can be lowered by Statin medications.
- All patients with CAD defined by coronary angiography randomly assigned to placebo or Co-Q10 at 300 mg/day for 2 months.
- Inflammatory markers and anti-oxidant activity assessed in plasma.
- Summary: small study, no clinical outcome data, though antioxidant activity and inflammatory marker concentration is less after Co-Q10 supplementation.

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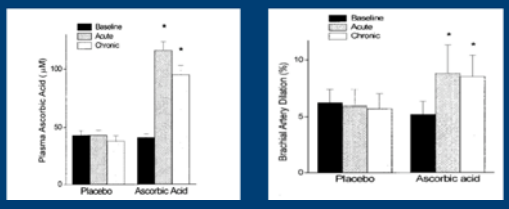
Lee et al. Nutr J. 2013 Nov 6;12(1):142

Vitamins and CAD



- All patients had CAD (at least 1 vessel > 50% by coronary angiography).
- Vitamin C (acute dose 2 g) or chronic dose (500 mg/day x 30 d) administered in a randomized manner and each subject had forearm blood flow (FBF) assessed before and after the study.
- Summary: No clinical outcome data, though Vitamin C appears to enhance the protective reactive hyperemic response after both acute and chronic dosing.

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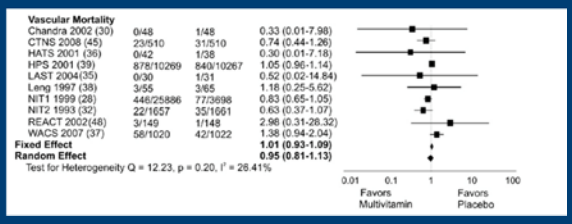
Gokce et al. Circulation. 1999 Jun 29;99(25):3234-40

Vitamins and CAD



- Meta-analysis of randomized controlled trials which looked for mortality benefit from vitamin supplementation.
- 91074 patient with 8994 deaths.
- Average supplementation of vitamins was for 43 months.
- Summary: no net effect of supplements on vascular causes of death [RR 1.01 (0.93-1.09)]

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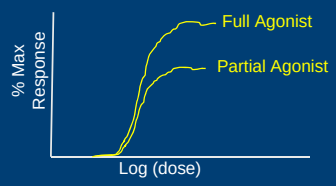
Macpherson et al. Am J Clin Nutr. 2013 Feb;97(2):437-44

A lessen from pharmacology



- A lack of efficacy or partial efficacy may be the result of dose.
- Pharmacologic dose-response profiles are meaningful.
- Many clinical investigations using vitamins were conducted using non-pharmacologic doses, or multi-vitamin formulations.

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Newer and Interesting Studies

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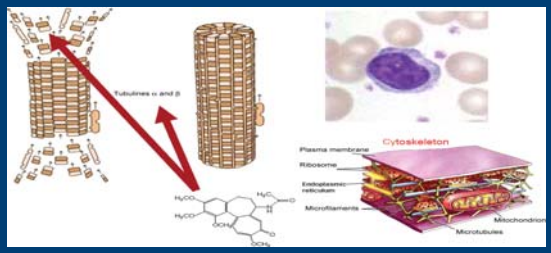
Colchicine



- Interferes with microtubule polymerization – the "track" upon which inflammatory white blood cells are delivered.
- Colchicine has been uses for many inflammatory disorders including gout, refractory pericarditis, relapsing polychondritis, and familial Mediterranean fever.

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Imazio et al. Eur Heart J. Volume 30, Issue 5, 2009

Colchicine

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

- Purpose: If colchicine is an anti-inflammatory agent, perhaps it may be useful in averting some of the pathophysiological aberrancies in CAD?
- Aim: Provide low-dose, daily colchicine to patients with stable CAD and assess outcome.

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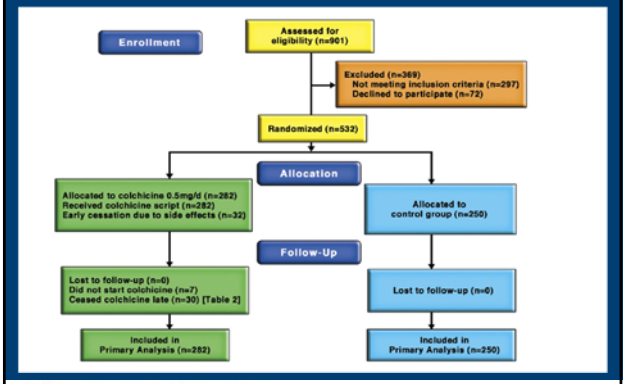
Nidorf J Am Coll Cardiol. 2013 Jan 29;61(4):404-10

Colchicine



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Nidorf J Am Coll Cardiol. 2013 Jan 29;61(4):404-10

Colchicine

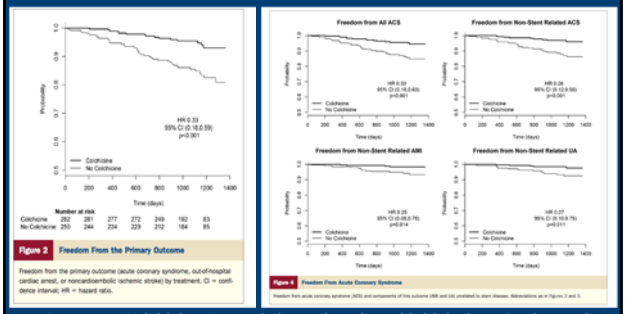

Figure 2 Freedom From the Primary Outcome

Freedom from the primary outcome (acute coronary syndrome, out-of-hospital cardiac arrest, or noncardioembolic ischemic stroke) by treatment. CI = confidence interval; HR = hazard ratio.

- Outcome: Colchicine 0.5 mg/g in conjunction with high dose Statins and standard anti-platelet therapy decreased atheroembolic events in patients with stable CAD.

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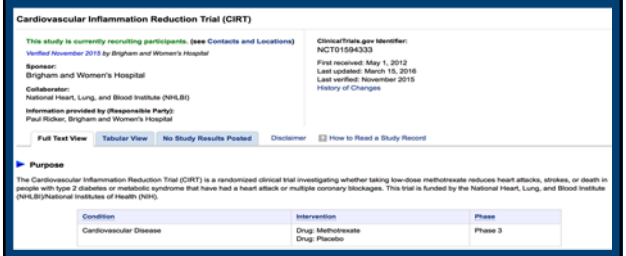
Nidorf J Am Coll Cardiol. 2013 Jan 29;61(4):404-10

Methotrexate



Cardiovascular Inflammation Reduction Trial (CIRT)

This study is currently recruiting participants. (see Contacts and Locations)
Verified November 2015 by Brigham and Women's Hospital

Sponsor:
Brigham and Women's Hospital

Collaborator:
National Heart, Lung, and Blood Institute (NHLBI)

Information provided by (Responsible Party):
Paul Ridker, Brigham and Women's Hospital

ClinicalTrials.gov Identifier:
NCT01594333

First received: May 1, 2012
Last updated: March 15, 2016
Last verified: November 2015
History of Changes

Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a Study Record

Purpose

The Cardiovascular Inflammation Reduction Trial (CIRT) is a randomized clinical trial investigating whether taking low-dose methotrexate reduces heart attacks, strokes, or death in people with type 2 diabetes or metabolic syndrome that have had a heart attack or multiple coronary blockages. This trial is funded by the National Heart, Lung, and Blood Institute (NHLBI)/National Institutes of Health (NIH).

Condition	Intervention	Phase
Cardiovascular Disease	Drug: Methotrexate Drug: Placebo	Phase 3

Ongoing Clinical Study:

- A well-known propensity for MI and CVA exists in patients with inflammatory disorders, including rheumatoid arthritis.
- Data exists to show patients with RA treated with MTX have lower adverse vascular events.
- RCT to show if low-dose MTX prevents adverse vascular events in patients at risk.

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Conclusions

- Aspirin reduces some CVD events by its antiplatelet effects but in primary prevention bleeding risk needs to strongly considered. Keep in mind that aspirin dose matters.
- Multivitamin ingestion has not been shown to reduce CVD events.
- Colchicine appears to have CVD event protective effects.
- Stay tuned for results of methotrexate effects on CVD in those with CAD, diabetes or metabolic syndrome.

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