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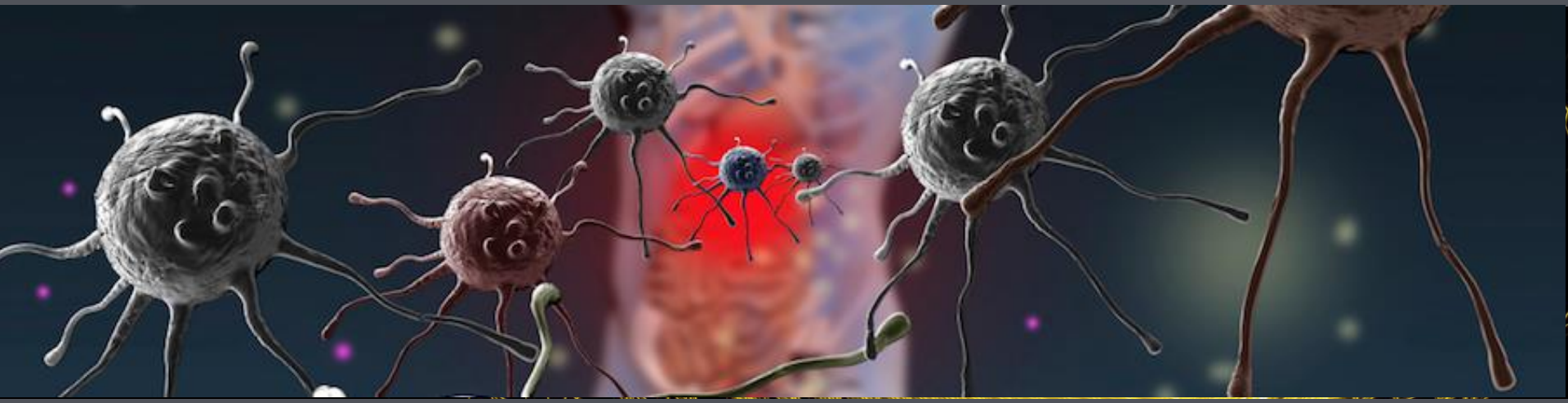
DIET & INFLAMMATION-RELATED FACTORS IN CVD



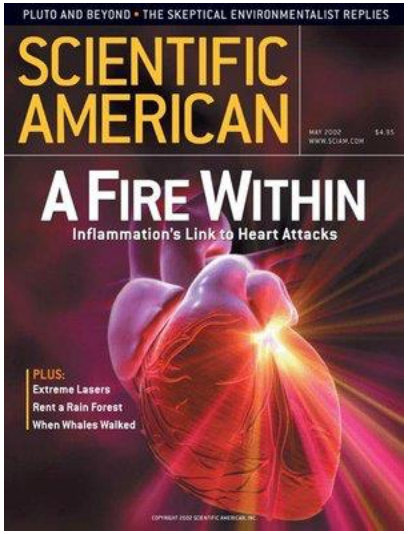
Parveen Yaqoob

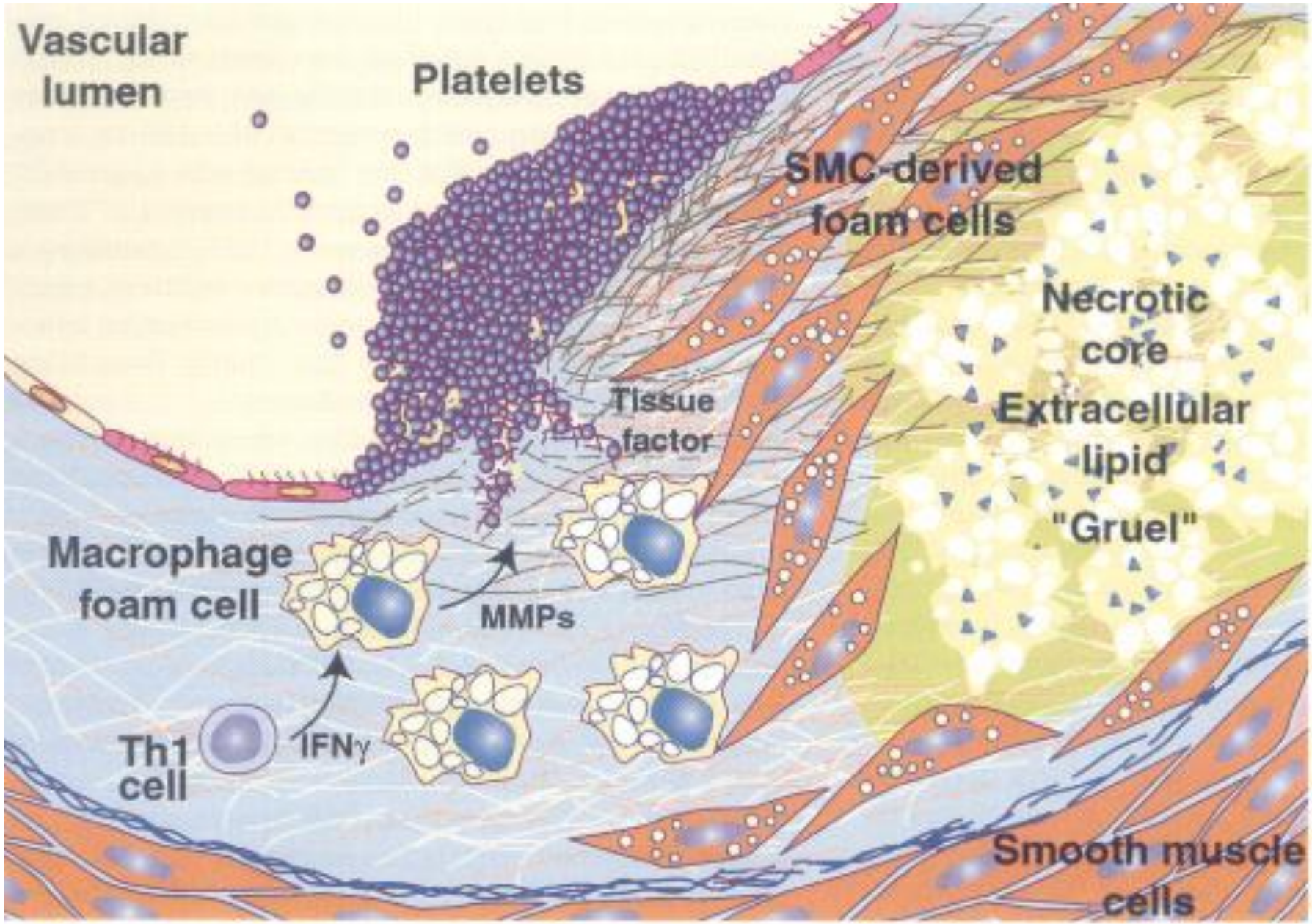
Professor of Nutritional Physiology

Pro-Vice Chancellor Research & Innovation

SCOPE OF LECTURE

- Role of inflammation in CVD
- Criteria for evaluation of novel inflammatory risk markers
- C-reactive protein; strengths and weaknesses of evidence of association with CVD
- Dietary strategies to reduce low-grade inflammation




Vascular lumen
Platelets
SMC-derived foam cells
Necrotic core
Extracellular lipid
"Gruel"
Tissue factor
Macrophage foam cell
MMPs
Th1 cell
IFNγ
Smooth muscle cells

EVALUATION OF NOVEL RISK MARKERS

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1. **Proof of concept:** Do levels of the novel marker differ between subjects with and without the disease?
2. **Prospective validation:** Does the novel marker predict development of disease in a prospective cohort?
3. **Incremental value:** Does the novel marker add predictive information to established, standard risk markers?
4. **Clinical utility:** Does the novel risk marker change predicted risk sufficiently to change recommended therapy?
5. **Clinical outcomes:** Does use of the novel risk marker improve clinical outcomes?
6. **Cost-effectiveness:** Does use of the marker improve clinical outcomes sufficiently to justify additional costs of testing and treatment?

Hlatky et al (2009) Scientific Statement from the AHA, Criteria for evaluation of novel markers of cardiovascular risk. Circulation, 119, 2408-2416

INFLAMMATORY RISK MARKERS

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Inflammatory marker	Extent of evidence	Limitations
CRP	Large prospective studies & a number of meta-analyses. Highly sensitive assays & international standards	Levels raised in other conditions and causality not established.
Fibrinogen	Large prospective studies & some meta-analyses	Levels closely correlated with CRP-limited additional value?
SAA	Small prospective cohort studies	Not clear whether association is independent of confounders
Albumin	Some large prospective cohort studies & at least 1 meta-analysis	Non-specific; large number of conditions associated with low levels
Leukocyte count	Several prospective studies & systematic reviews	Inconsistent adjustment for well-established risk factors
ESR	Small prospective cohort studies	Primarily reflects fibrinogen levels; non-specific?
Immune complexes	Small prospective cohort studies	Complex, time-consuming; exact role unclear
Cytokines/growth factors	Small prospective cohort studies, especially for IL-6	Strongly associated with CRP; non-specific?
Soluble adhesion molecules	Prospective cohort studies (inconsistent)	Meta-analysis shows no predictive power over lipids
Heat shock proteins	Case-control studies only	Clinical relevance debated

C-REACTIVE PROTEIN

Quintile	Range (mg/L)	Risk estimate
1	0.1-0.7	Low
2	0.7-0.1	Mild
3	1.2-1.9	Moderate
4	2.0-3.8	High
5	>3.8	Highest

RELATIVE RISK OF FUTURE CVD ACCORDING TO BASELINE CRP

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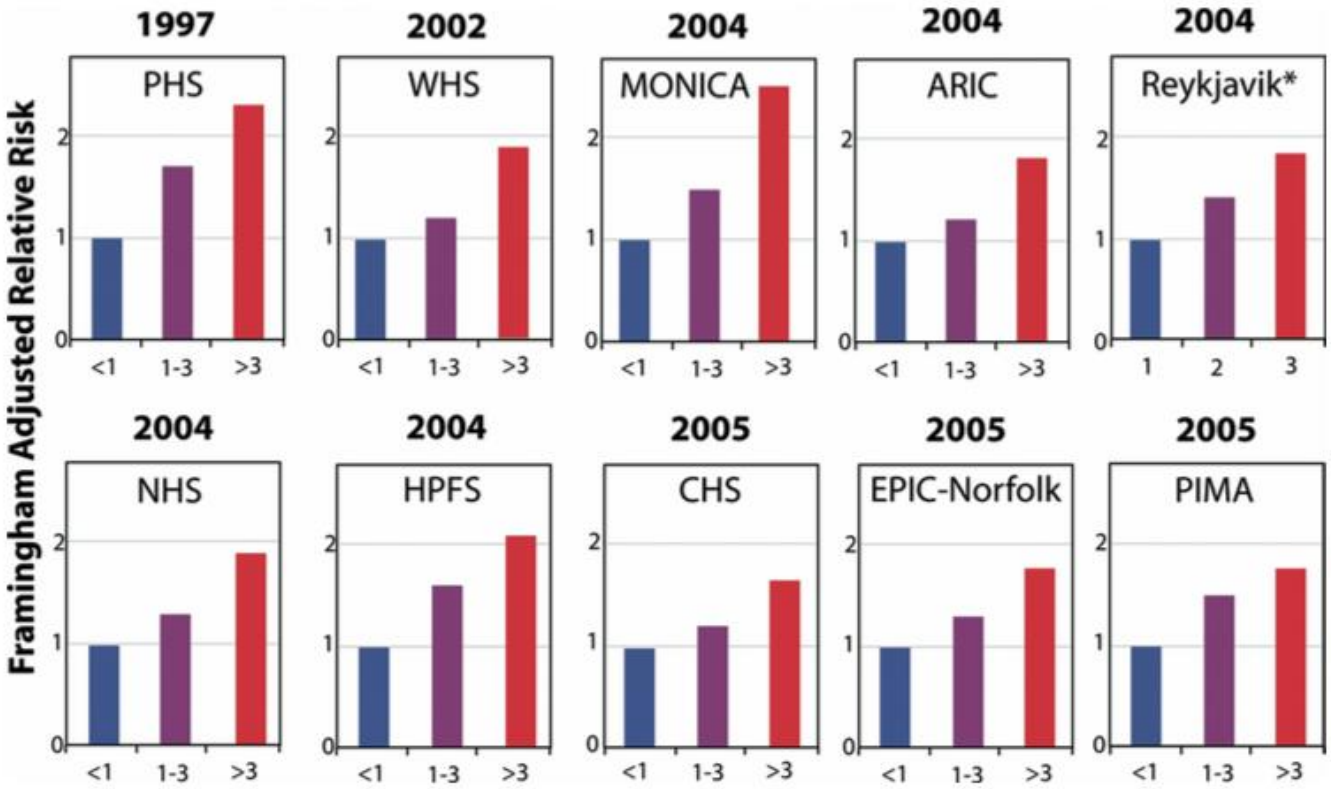

Libby & Ridker (2006) JACC 48, A33-46

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EMERGING RISK FACTOR COLLABORATION:
ASSOCIATIONS BETWEEN HS-CRP AND CV OUTCOMES

	RR	95% CI
Unadjusted		
CHD	1.68	1.59, 1.78
Ischaemic stroke	1.46	1.32, 1.61
Vascular mortality	1.82	1.66, 2.00
Adjusted for conventional risk factors & fibrinogen		
CHD	1.23	1.07, 1.42
Ischaemic stroke	1.32	1.18, 1.49
Vascular mortality	1.34	1.18, 1.52

Kaptoge et al (2010) Lancet 375, 132-140

EMERGING RISK FACTOR COLLABORATION

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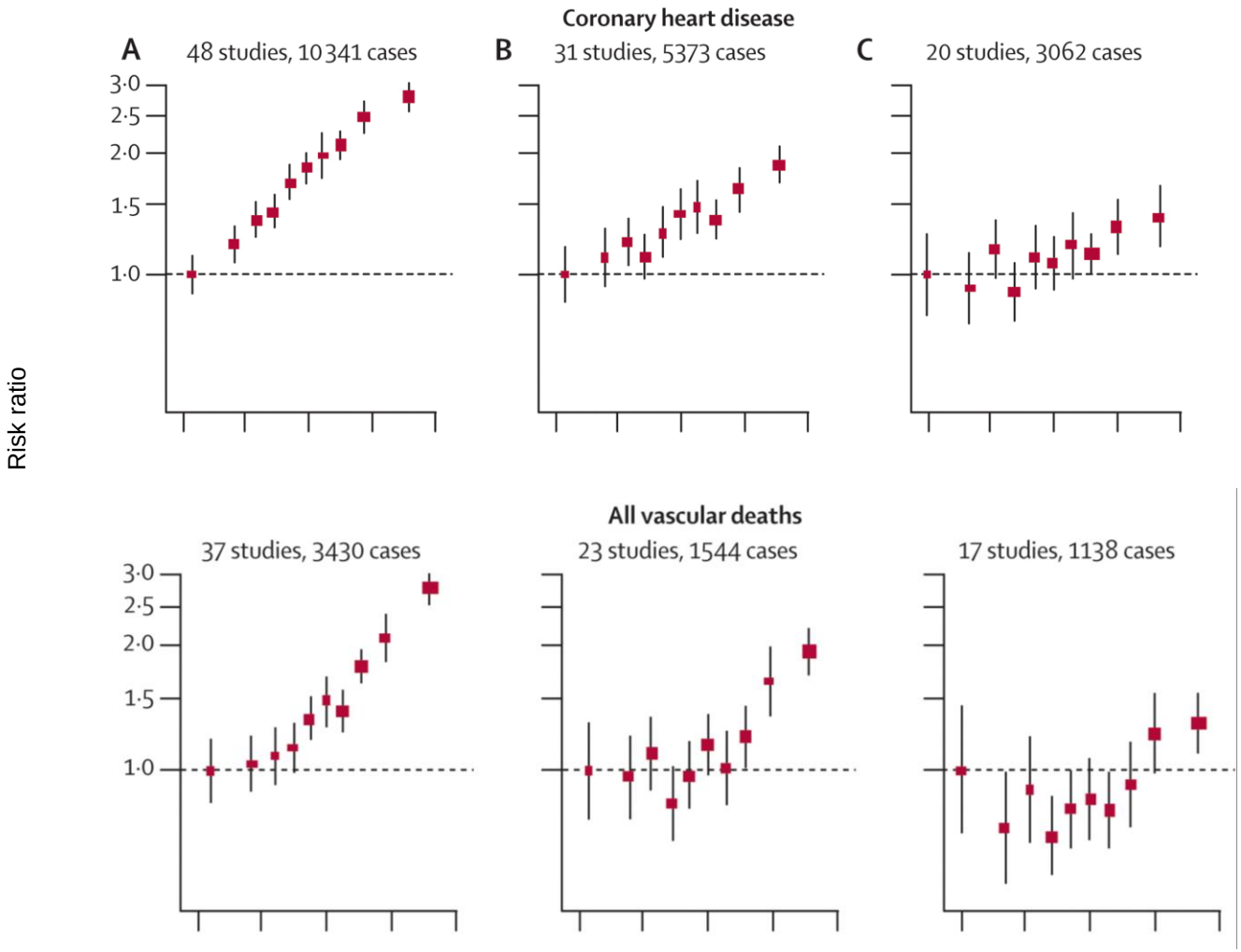
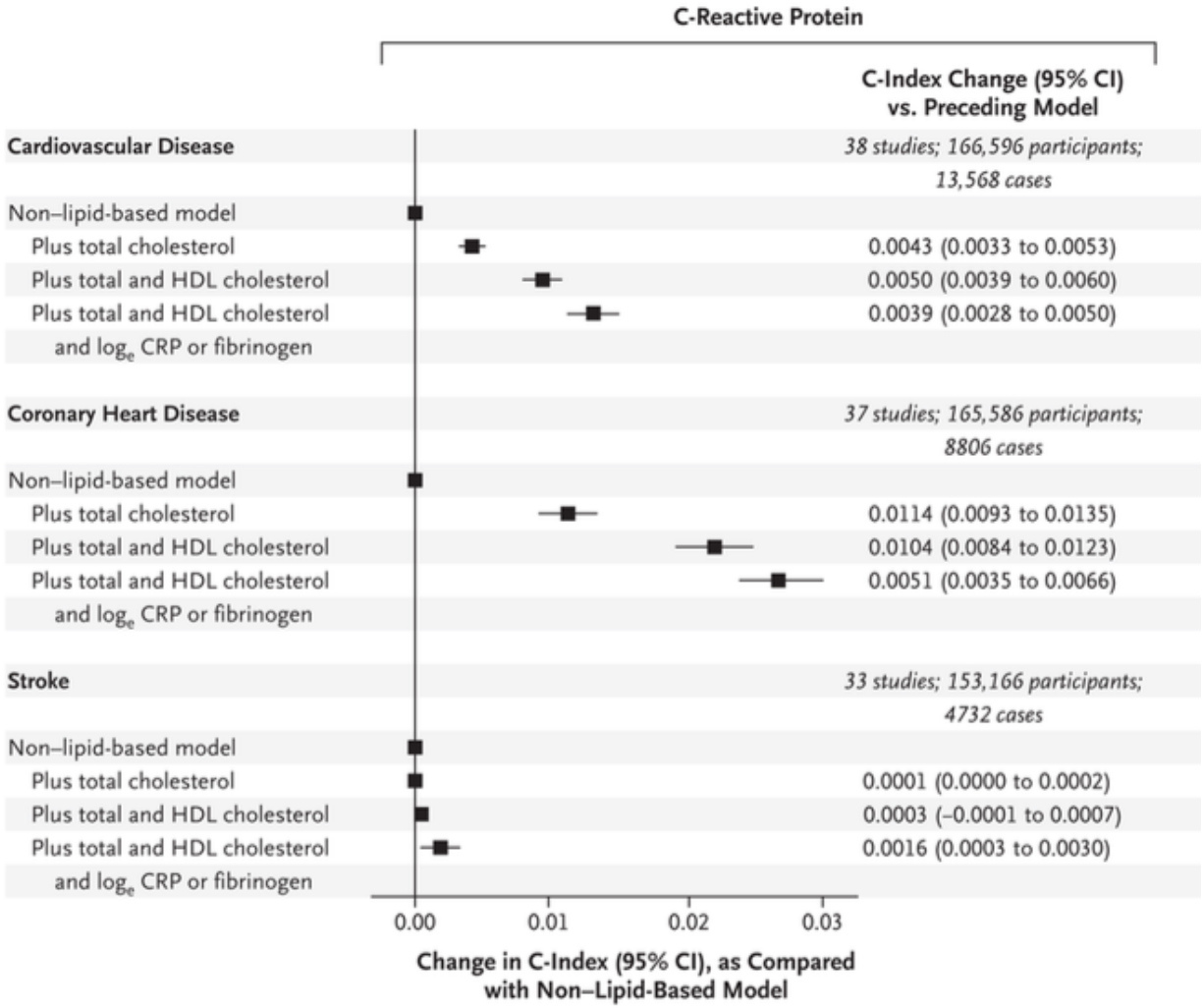


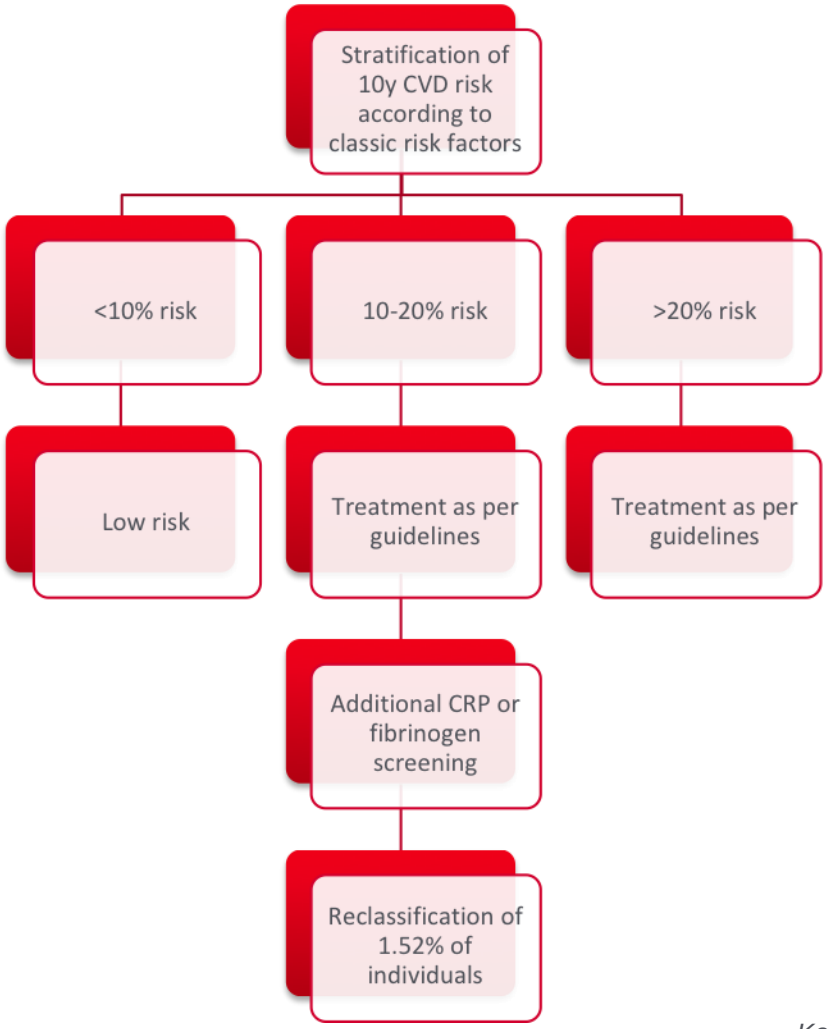
Kaptoge et al (2010) Lancet 375, 132-140

IMPROVEMENT IN PREDICTIVE ABILITY?



Kaptoge et al (2012) NEJM 367, 1310-1320

IMPROVEMENT IN PREDICTIVE ABILITY?



Kaptoge et al (2012) NEJM 367, 1310-1320

THE JUPITER TRIAL

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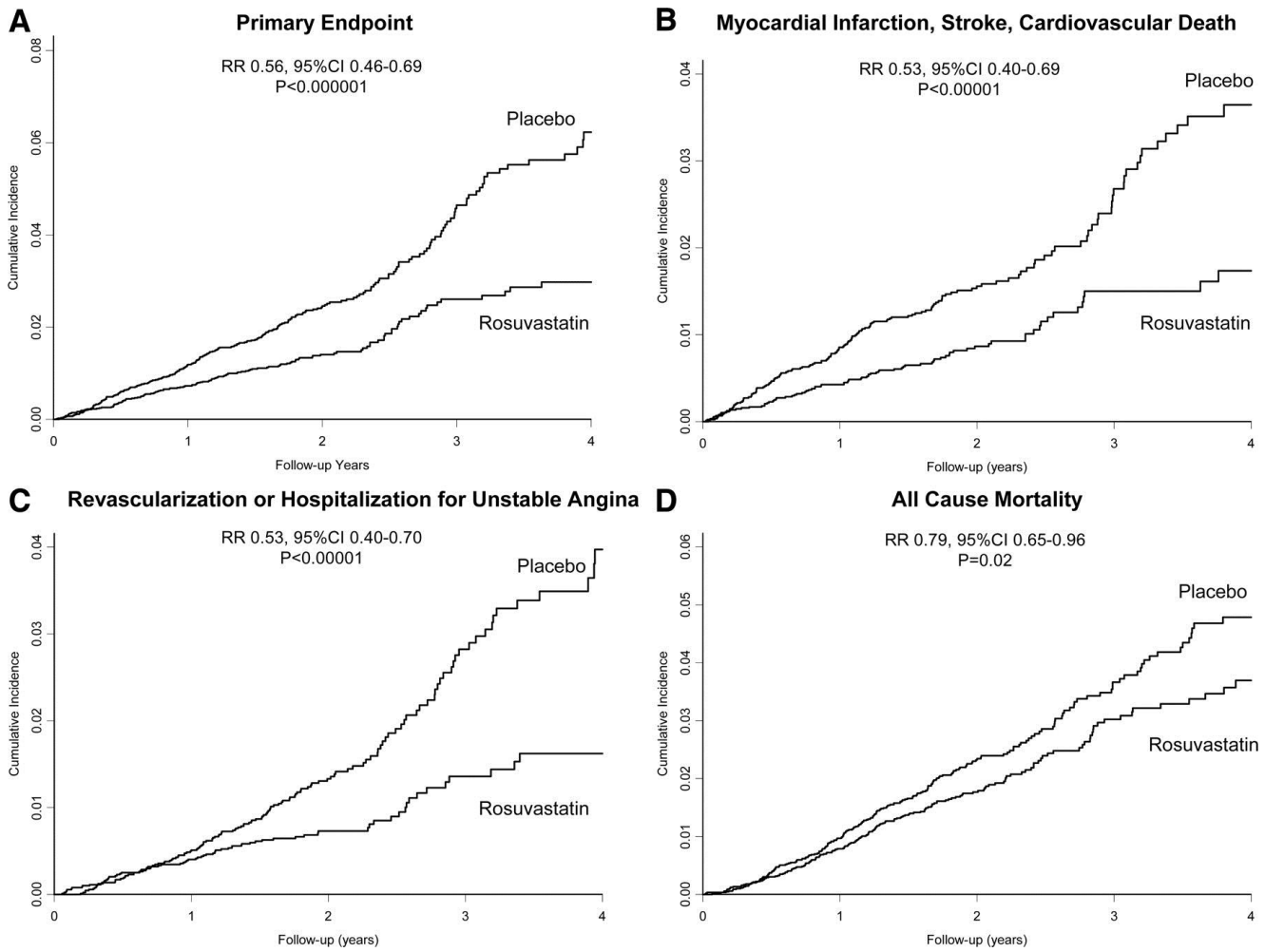
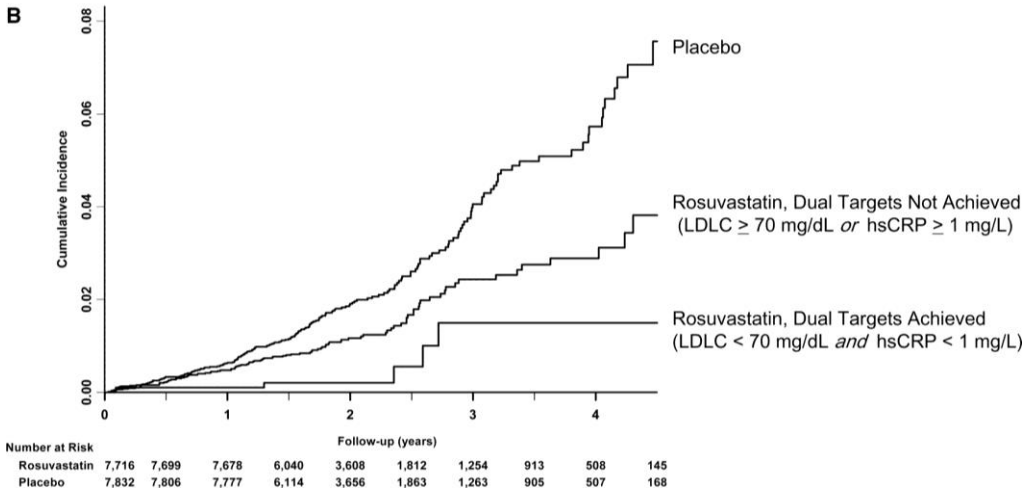


17,802 intermediate risk subjects
LDL-C <3.4 mM
hs-CRP >2 mg/L

50% reduction LDL-C
37% reduction hs-CRP

Ridker et al (2008) NEJM 359, 2195-2207

THE JUPITER TRIAL



17,802 intermediate risk subjects
LDL-C <3.4 mM
hs-CRP >2 mg/L

50% reduction LDL-C
37% reduction hs-CRP

Limitations

- Post-hoc analysis suggested that elevated hs-CRP did not independently predict a preferential benefit of statin therapy
- Trial did not include a group with low LDL-C AND low hs-CRP

Ridker et al (2008) NEJM 359, 2195-2207

GUIDELINES ON USE OF SERUM HS-CRP IN MANAGEMENT OF PRIMARY PREVENTION OF CVD

- Agency for Healthcare Research & Quality: ‘insufficient evidence’.
- American College of Cardiology & AHA: Class IIb for asymptomatic intermediate risk individuals (usefulness less well established by evidence, but may be considered) and Class III (not recommended) for asymptomatic high risk or young low risk individuals.
- Canadian Cardiovascular Society: Class IIa ‘should be considered’.
- European Association for Cardiovascular Prevention & Rehabilitation (EACPR): Class IIb for patients with unusual or moderate CVD risk profile and Class III for asymptomatic low risk and high risk individuals.

WEAKNESSES IN USING HS-CRP IDENTIFIED BY EACPR

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- Multiplicity of confounders and dependence on classical risk factors
- Lack of diagnostic precision for risk of CVD
- Lack of specificity- similar risk for non-CVD causes of morbidity & mortality (eg other low-grade inflammatory disease)
- Lack of evidence for causal relationship
- Lack of specific therapeutic strategies or agents targeting circulating CRP and showing reduction in CVD incidence
- Cost effectiveness of extra test not established.

THE CANTOS TRIAL

CANAKINUMAB ANTI-INFLAMMATORY THROMBOSIS OUTCOMES STUDY

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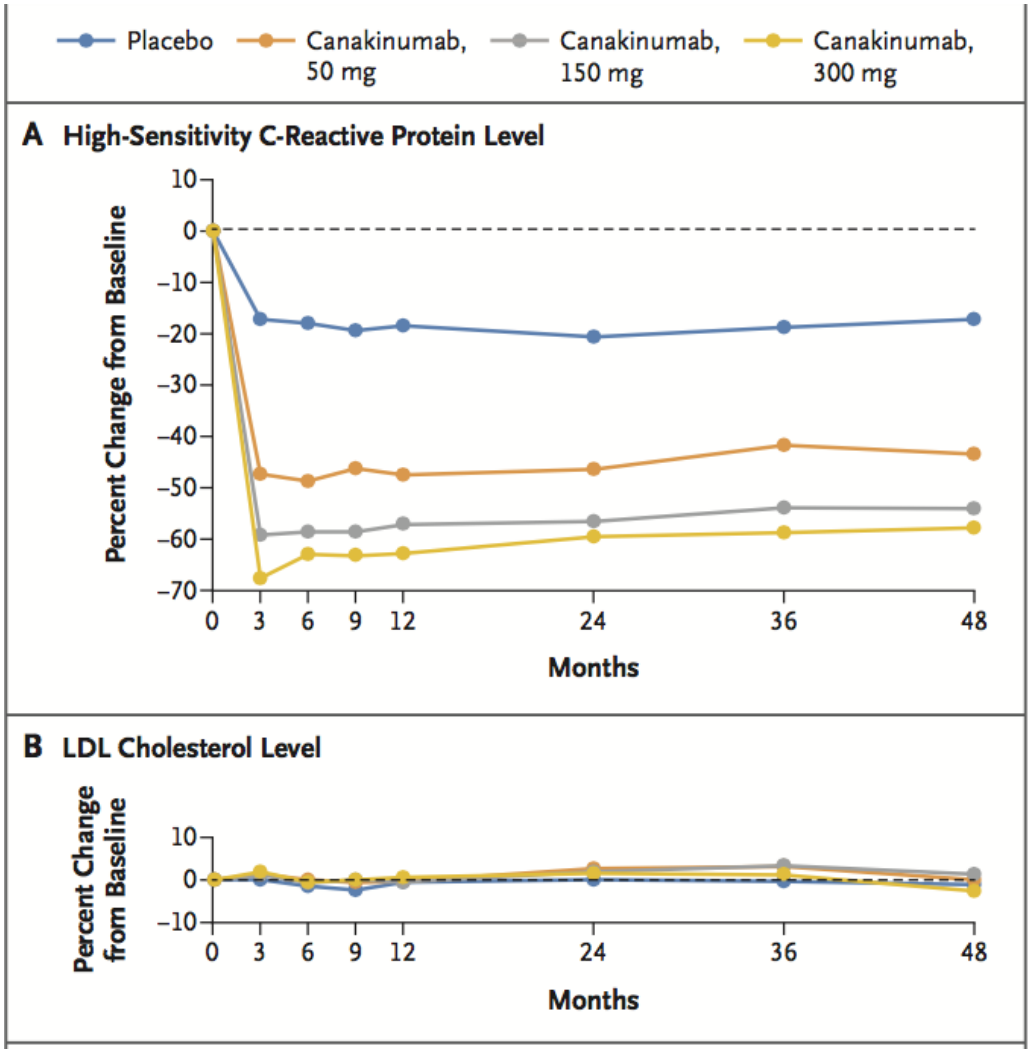
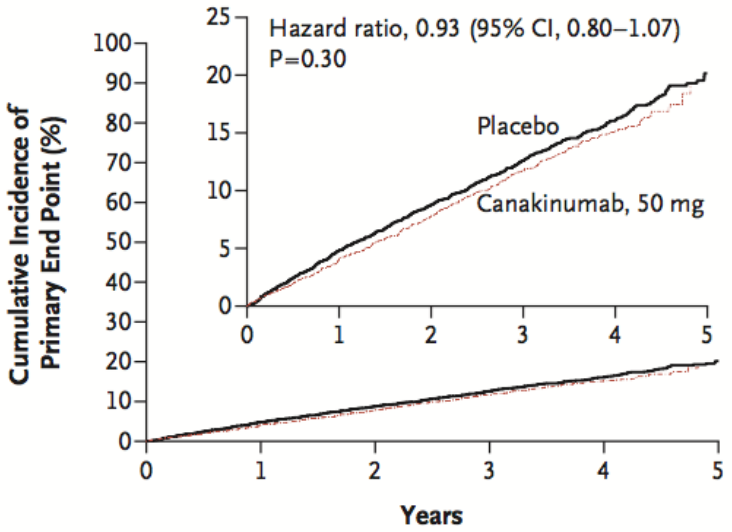


- 10,061 patients with previous MI
- Hs-CRP >2 mg/L
- mAb to Il-1β at 3 doses, subcutaneously every 3 months
- Primary endpoint nonfatal MI, nonfatal stroke, CVD death

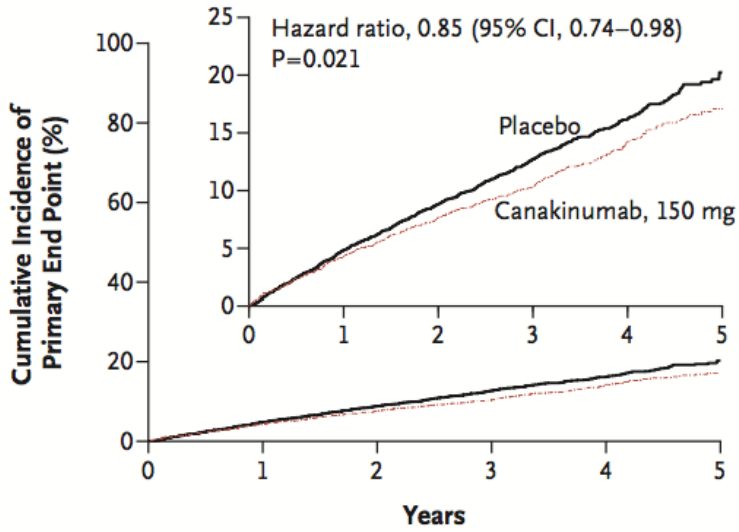
Ridker et al (2017) NEJM 377, 1119-1131

A **Primary End Point with Canakinumab, 50 mg, vs. Placebo**



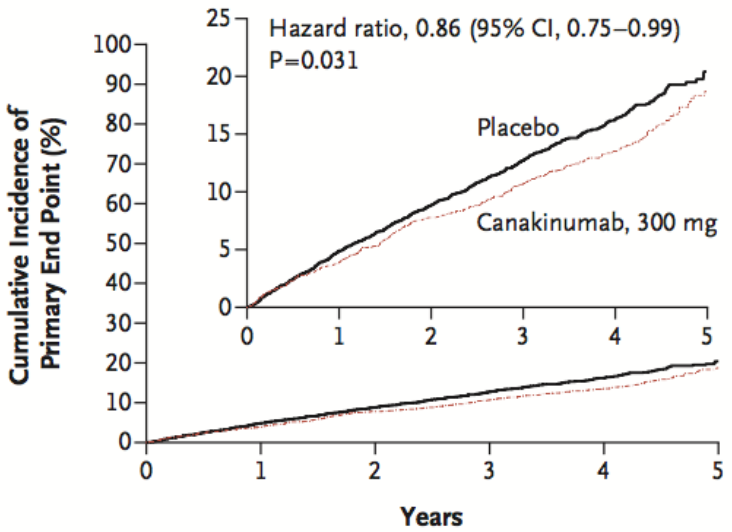
No. at Risk						
Placebo	3344	3141	2973	2632	1266	210
Canakinumab	2170	2057	1950	1713	762	47

B **Primary End Point with Canakinumab, 150 mg, vs. Placebo**



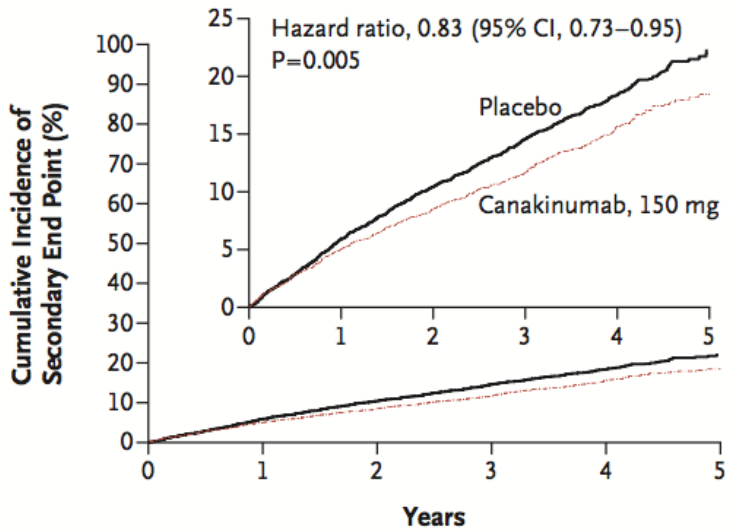
No. at Risk						
Placebo	3344	3141	2973	2632	1266	210
Canakinumab	2284	2151	2057	1849	907	207

C **Primary End Point with Canakinumab, 300 mg, vs. Placebo**



No. at Risk						
Placebo	3344	3141	2973	2632	1266	210
Canakinumab	2263	2149	2038	1819	938	199

D **Key Secondary End Point with Canakinumab, 150 mg, vs. Placebo**



No. at Risk						
Placebo	3344	3107	2921	2578	1238	206
Canakinumab	2284	2135	2039	1824	892	201

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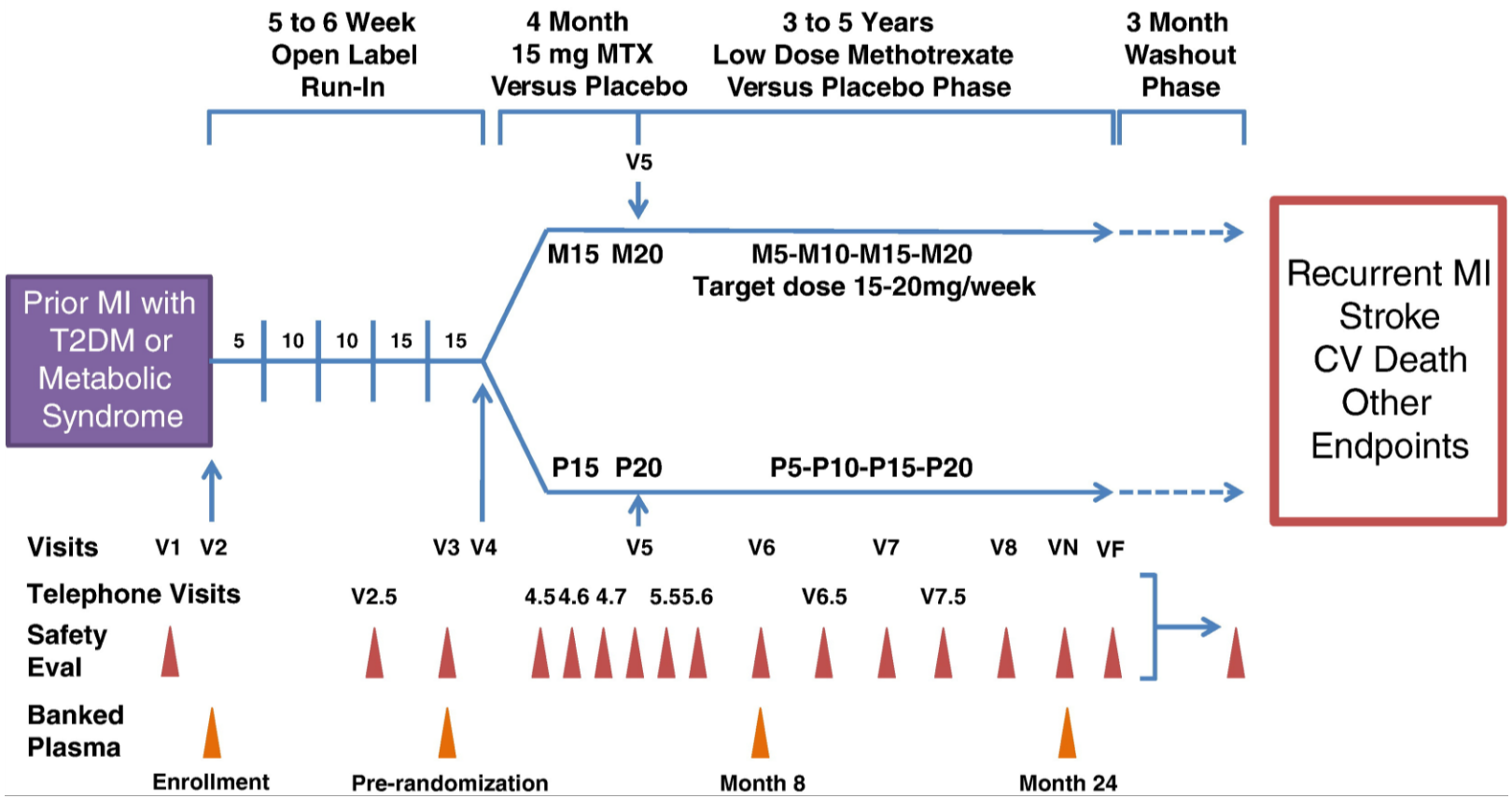
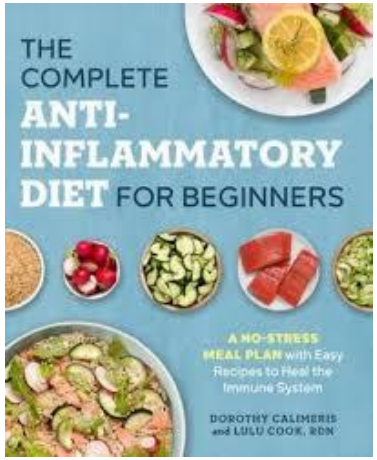
CARDIOVASCULAR INFLAMMATION REDUCTION TRIAL (CIRT)



Everett et al (2013) Am Heart J 199-207, e15

STRATEGIES TO REDUCE LOW-GRADE INFLAMMATION

- Reduce overweight and obesity
- Healthy eating patterns, eg Mediterranean Diet
- Dietary fat patterns
- N-3 PUFA
- Antioxidants, vitamin E, plant bioactives



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THE CRESSIDA STUDY

	Baseline		Follow-up		Main comparison between groups[2]	*P* value[3]
	DG (n = 82)	Control (n = 83)	DG (n = 80)	Control (n = 82)		
Vascular function						
FMD,[4] %	5.61 ± 3.00[5]	5.33 ± 3.24	4.94 ± 2.54	5.44 ± 3.30	−0.62 (−1.48, 0.24)	0.16
GTN,[6] %	11.27 ± 4.83	10.63 ± 4.94	11.78 ± 5.63	10.98 ± 4.24	0.17 (−1.20, 1.53)	0.80
Supine central SBP, mm Hg	109.1 ± 13.8	109.9 ± 12.4	105.0 ± 11.6	109.4 ± 12.4	−3.5 (−5.4, −1.6)	<0.001
Supine central DBP, mm Hg	75.1 ± 8.1	75.7 ± 8.5	72.2 ± 7.6	75.5 ± 8.8	−2.4 (−3.8, −1.1)	0.001
Supine heart rate, beats/min	57.5 ± 7.4	57.1 ± 8.3	55.2 ± 7.7	57.8 ± 9.2	−1.8 (−3.3, −0.3)	0.022
$PWV_{c\text{-}f}$, m/s	7.65 ± 1.31	7.39 ± 1.09	7.43 ± 1.22	7.61 ± 1.14	−0.29 (−0.52, −0.07)	0.011
hsCRP,[7] mg/dL	0.7 (0.3, 1.9)	1.0 (0.3, 2.1)	0.5 (0.2, 1.7)	1.3 (0.6, 2.4)	−36% (−48, −7)	0.017

Redilinger et al (2015) AJCN 101, 922-930

ATTICA STUDY- INFLAMMATORY MARKERS BY TERTILE OF MEDITERRANEAN DIET SCORE

	Tertile of Diet Score			
	1st (0–20)	2nd (21–35)	3rd (36–55)	p Value*
White blood cell (×1,000 counts)	7.4 ± 1.3	6.9 ± 2.7	6.2 ± 1.4	0.001
C-reactive protein (mg/l)	2.0 ± 1.8	1.8 ± 2.1	1.6 ± 1.5	0.01
Fibrinogen (mg/dl)	319 ± 79	309 ± 76	302 ± 74	0.02
Interleukin-6 (pg/ml)	2.1 ± 0.9	1.84 ± 1.1	1.45 ± 0.99	0.02
Homocysteine (μmol/l)	12.4 ± 5.8	11.7 ± 6.4	10.5 ± 6.0	0.03
Tumor necrosis factor-alpha (pg/ml)	5.8 ± 1.3	5.5 ± 1.4	5.1 ± 2.1	0.07
Amyloid A (mg/l)	5.2 ± 6.2	4.4 ± 4.6	3.6 ± 5.4	0.19

*Unadjusted p values by analysis of variance. Data are presented as the mean value ± SD.

- 1500 men + 1500 women from Attica area of Greece
- Aged 18-89y
- Greater adherence to MD score associated with reduced inflammatory markers

Chrysohoou et al., (2004) J Am Coll Cardiol 44, 152-8

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MEDITERRANEAN DIET PATTERN & INFLAMMATION META-ANALYSIS

Table 2 Pooled estimates of effect size (95% confidence intervals) expressed as weighted mean difference for the effects of MD vs. control intervention diets on outcomes of inflammation and endothelial function.

Outcomes	No. of studies	Sample size	MD	95% CI	*p*-values	Inconsistency I^2	Egger test Begg's test
CRP (mg/l)	14	1942	−0.98	[−1.48, −0.49]	<0.0001	91%	0.945 0.547
IL-6 (pg/ml)	6	1077	−0.42	[−0.73, −0.11]	0.008	81%	0.480 0.851
AD (μg/ml)	2	286	1.69	[0.27, 3.11]	0.02	78%	/
FMD (%)	2	210	1.86	[0.23, 3.48]	0.02	43%	/
ICAM-1 (ng/ml)	2	586	−23.73	[−41.24, −6.22]	0.008	34%	/
E-Selectin (ng/ml)	2	161	−0.67	[−6.51, 5.16]	0.82	20%	/

Abbreviations: AD, adiponectin; CRP, high sensitive C-reactive protein; FMD, flow mediated dilatation; ICAM-1, Intercellular Adhesion Molecule 1; IL-6, Interleukin 6; VCAM-1, Vascular Adhesion Molecule 1.

Schwingshackl & Hoggman (2014) Nutr Metab Cardiovasc Dis 24, 929-939

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Effect of whole grains on markers of subclinical inflammation

Michael Lefevre and Satya Jonnalagadda

- Epidemiological studies: each serving of wholegrain reduces CRP by 7%
- Intervention studies do not demonstrate a clear effect on inflammatory markers

Nutr Rev (2012) 70, 387-396

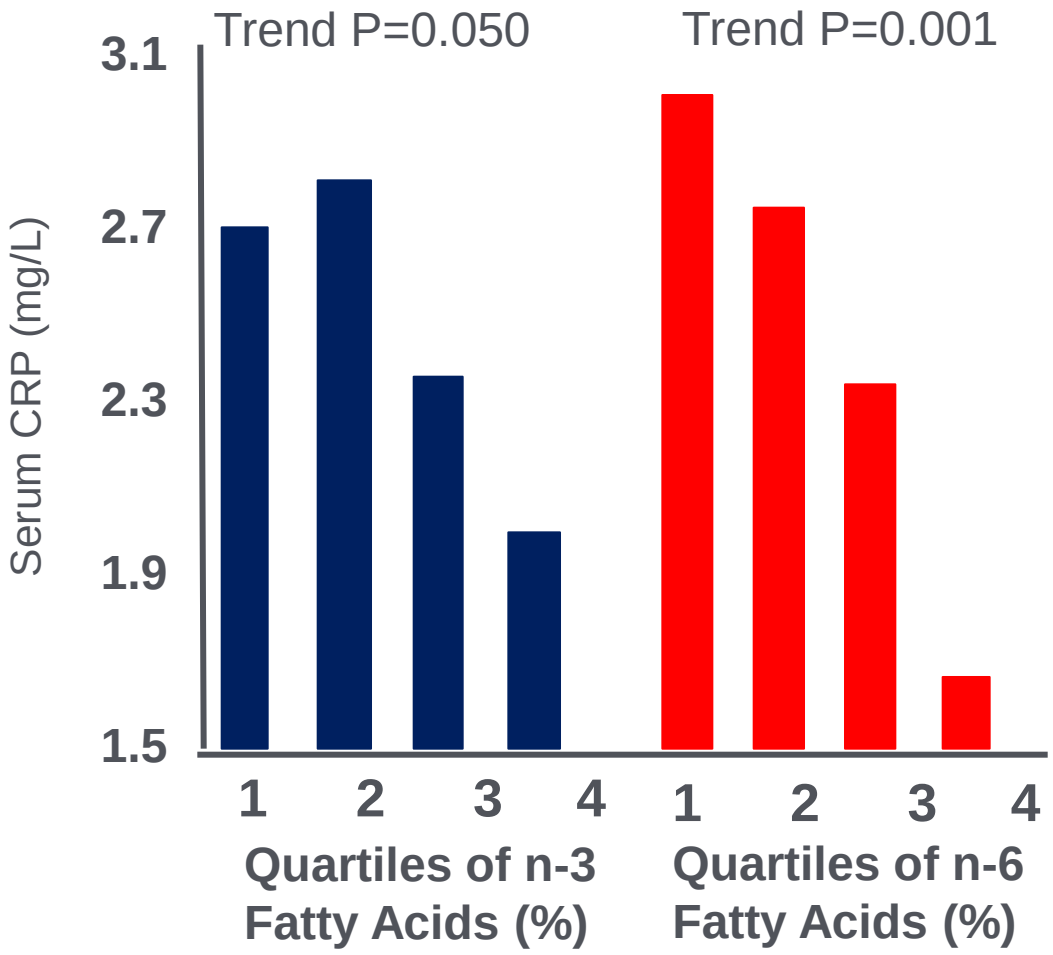
Oats and CVD risk markers: a systematic literature review

Frank Thies[1]*, Lindsey F. Masson[2,3], Paolo Boffetta[4,5] and Penny Kris-Etherton[6]

No effects of oats on inflammatory markers (69 studies)

BJN (2014) 112, S19-S30

PLASMA FATTY ACID COMPOSITION AND CRP

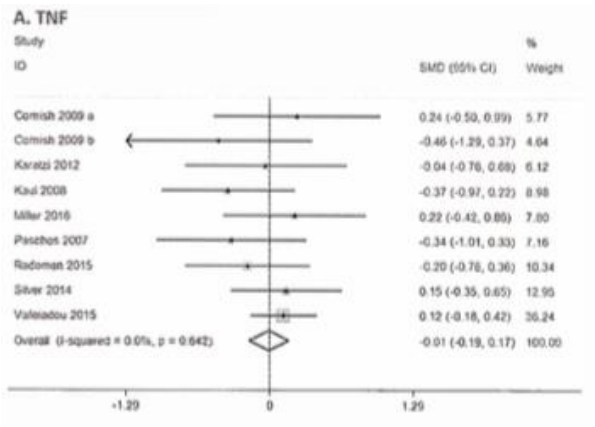


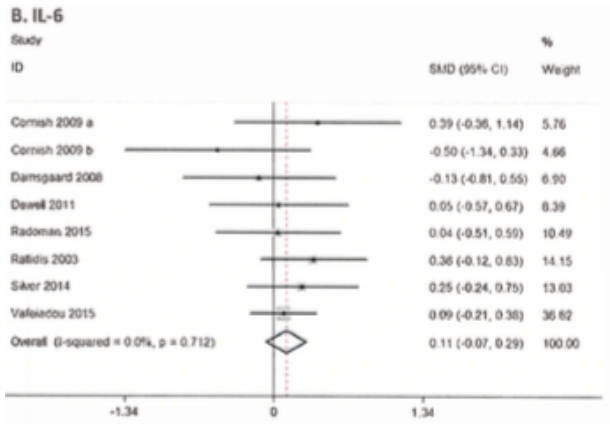
- 1123 subjects
- Aged 20-98y

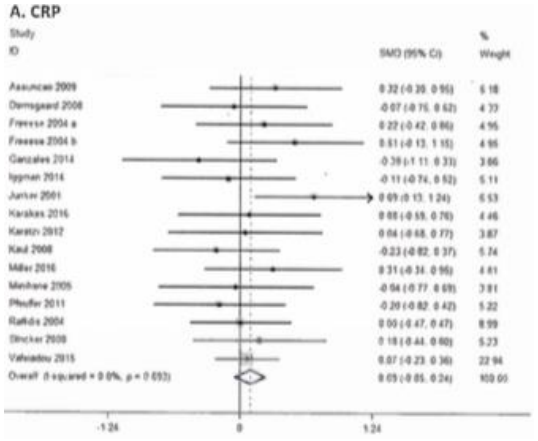
Ferucci et al., (2006)
J Clin Endocrinol Metab 91, 439-446

SYSTEMATIC REVIEW OF DIETARY LA AND INFLAMMATORY MARKERS

- 30 RCTs involving 1377 subjects
- No relationship between LA intake & inflammatory markers







Su et al., (2017) Food & Function 8, 3091

DIETARY FISH INTAKE, N-3 PUFA AND INFLAMMATORY MARKERS

Marker	EPA + DHA		Nonfried Fish†		Fried Fish	
	Age Adjusted	Multivariate Adjusted	Age Adjusted	Multivariate Adjusted	Age Adjusted	Multivariate Adjusted
Log CD40L (ng/ml)‡	−0.23 (0.54)	0.42 (0.27)	−0.08 (0.57)	0.17 (0.24)	−0.49 (0.04)	−0.11 (0.68)
Log hs-CRP (mg/L)§	−1.24 (<0.01)	−0.24 (0.31)	−0.38 (<0.01)	−0.17 (0.03)	0.74 (<0.01)	0.16 (0.35)
Log IL-6 (pg/ml)‖	−0.88 (<0.01)	−0.37 (<0.01)	−0.28 (<0.01)	−0.16 (<0.01)	0.29 (<0.01)	−0.07 (0.46)
Log E-selectin (ng/ml)‡	−0.31 (0.24)	0.07 (0.79)	−0.13 (0.19)	0.01 (0.88)	0.16 (0.36)	0.08 (0.66)
Log fibrinogen (mg/dl)¶	−0.09 (0.03)	−0.05 (0.24)	−0.04 (<0.01)	−0.03 (0.84)	0.06 (0.06)	−0.01 (0.80)
Log sTNF-R1 (pg/ml)‡	−0.53 (<0.01)	−0.26 (0.06)	−0.09 (0.07)	−0.05 (0.31)	−0.11 (0.22)	−0.09 (0.35)
Log sICAM-1 (ng/ml)#	−0.55 (<0.01)	−0.16 (0.06)	−0.08 (<0.01)	0.01 (0.96)	−0.24 (<0.01)	−0.17 (0.01)
Log MMP-3 (ng/ml)‡	−0.79 (0.02)	−0.69 (0.03)	−0.14 (0.25)	−0.18 (0.12)	0.02 (0.92)	−0.05 (0.81)
Log MMP-9 (ng/ml)‡	−0.31 (0.29)	0.50 (0.11)	0.09 (0.41)	0.16 (0.14)	−0.23 (0.22)	−0.07 (0.74)

- 5677 men from different ethnic backgrounds
- Aged 45-84y

MESA study: He et .al, (2009) Am J Cardiol 103, 1238-1243

Review

Nutrition and Inflammation in Older Individuals: Focus on Vitamin D, *n*-3 Polyunsaturated Fatty Acids and Whey Proteins

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Andrea Ticinesi [1,2], Tiziana Meschi [1,2], Fulvio Lauretani [1], Giovanna Felis [3], Fabrizio Franchi [4], Carlo Pedrolli [5], Michela Barichella [6], Giuseppe Benati [7], Sergio Di Nuzzo [2], Gian Paolo Ceda [2,8] and Marcello Maggio [2,8,*]

2016

"After the analysis, we conclude that there is sufficient evidence for an anti-inflammatory effects in aging only for n-3 PUFA intake, while the few existing intervention studies do not support a similar activity for vitamin D and whey supplements"

Lipids (2013) 48:319–332
DOI 10.1007/s11745-013-3774-6

REVIEW

N-3 Polyunsaturated Fatty Acids: Relationship to Inflammation in Healthy Adults and Adults Exhibiting Features of Metabolic Syndrome

Lindsay E. Robinson · Vera C. Mazurak

Overall, existing data support the consumption of n-3 PUFA-rich fish on a regular basis for many positive health outcomes, one of which is likely to be a role in reducing inflammation, especially in MetS.

SUMMARY

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- Chronic, low-grade inflammation underlies CVD, but not clear whether it plays a causal role.
- CRP has emerged as the strongest inflammatory marker for CVD; other surrogate markers remain inferior in terms of discriminatory power.
- Controversy regarding inclusion of hs-CRP in guidelines for primary prevention of CVD.
- Anti-inflammatory drugs being trialled for treatment of CVD; further research required.
- Growing body of data describing effects of dietary patterns on inflammatory markers.
- Mediterranean diet consistently associated with reduction in levels of inflammatory markers, but evidence for other prudent dietary patterns not so consistent and may be simply associated with weight loss.
- Some evidence for effects of dietary fatty acids on inflammatory markers, but further research required.