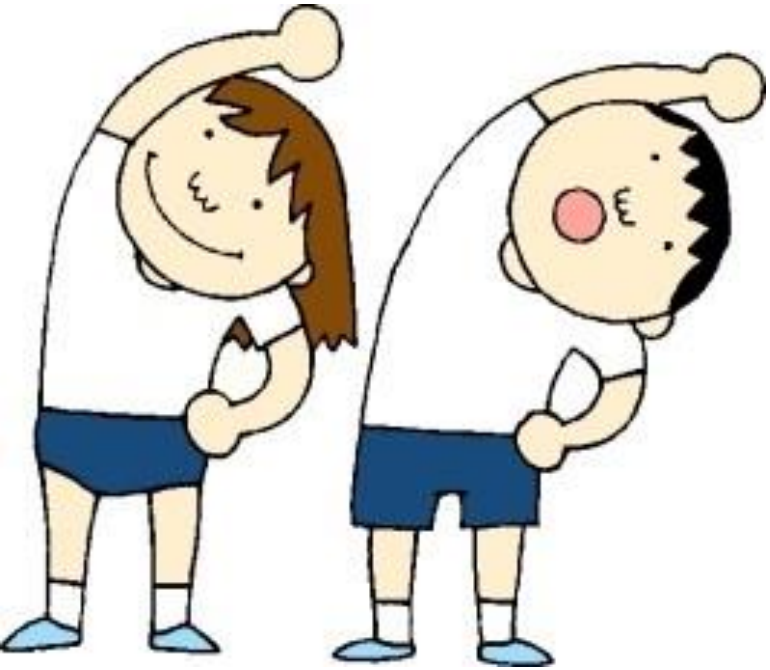
Session: Current advances of management in vascular disease



Anti-inflammatory Strategies for Preventing CV Events

고대 구로병원 심혈관센터 김응주

Anti-inflammatory Strategies for Preventing CV Events

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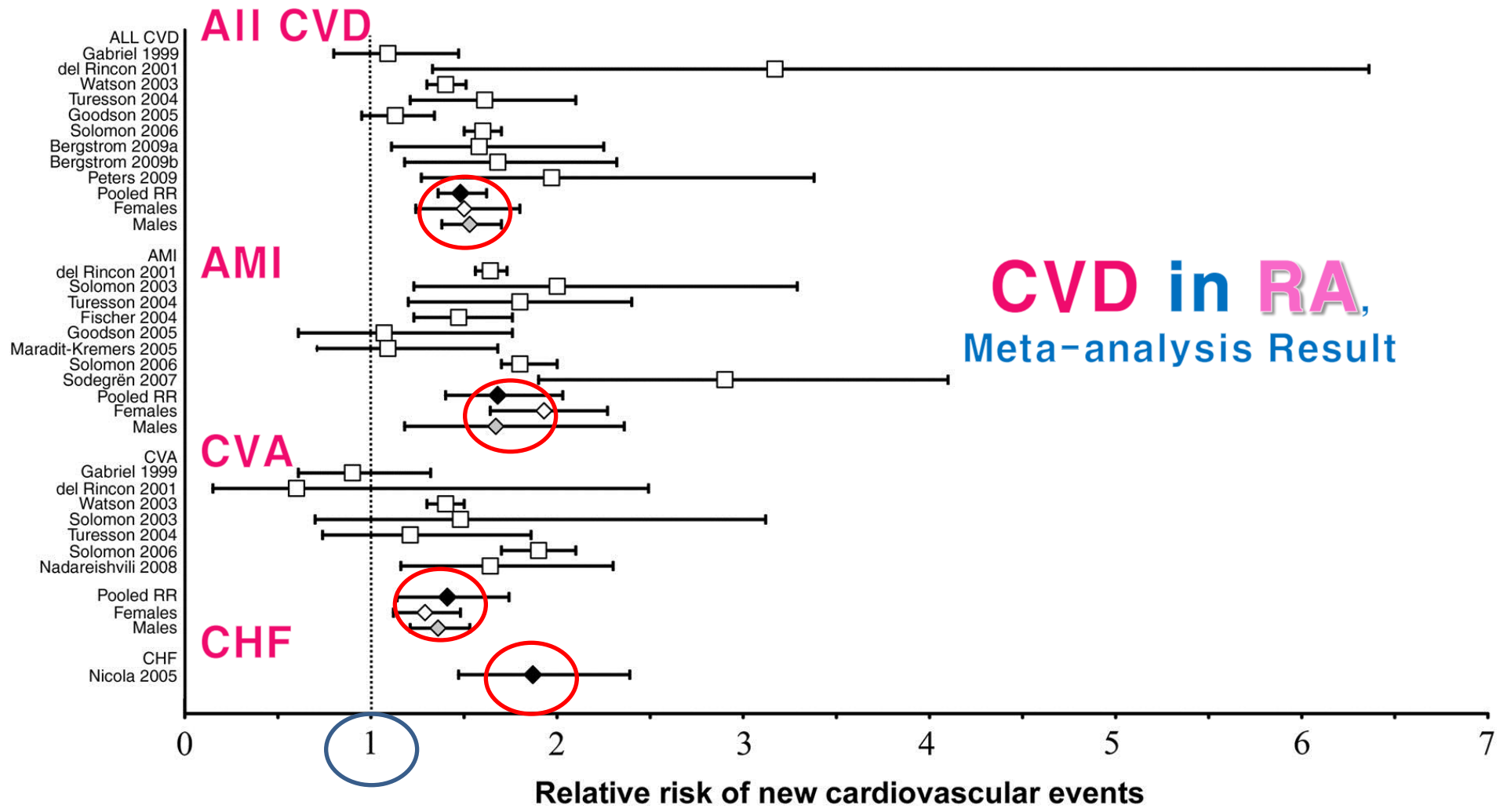
Inflammation & CVD

Anti-inflammatory Interventions

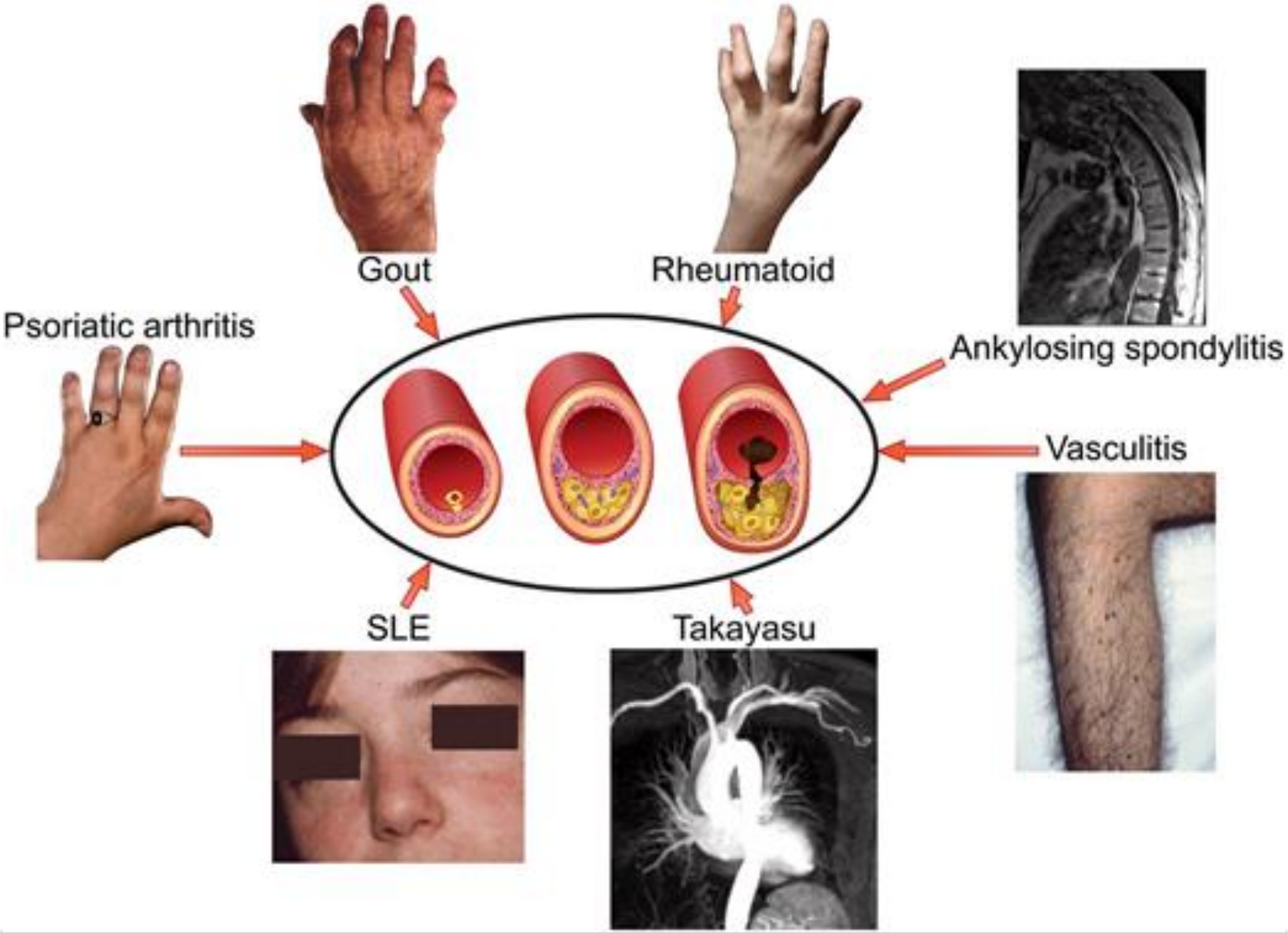
NSAIDs & CV Risk

Inflammation & CVD



Ann Rheum Dis 2012;71:1524-9

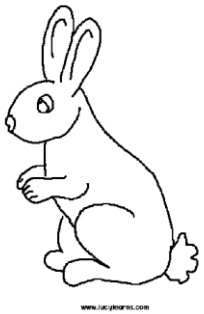
Inflammation & CVD



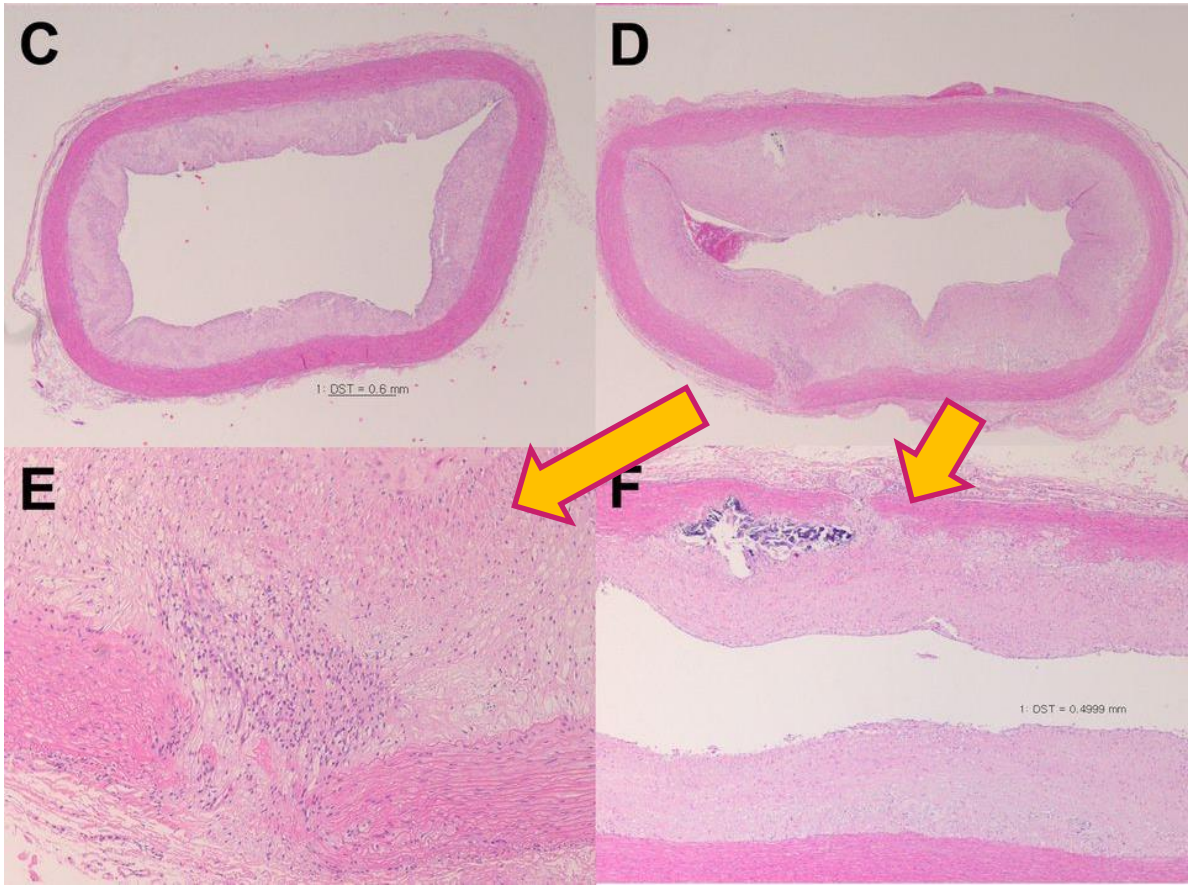
European Heart Journal (2015) 36, 482–489

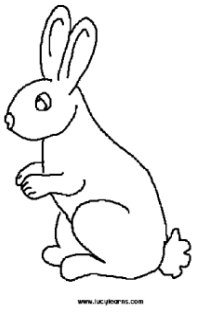
Inflammation & CVD

Twenty male New Zealand white rabbits
(12 weeks old at the beginning of the experiment)



1% Chol. diet
N=5





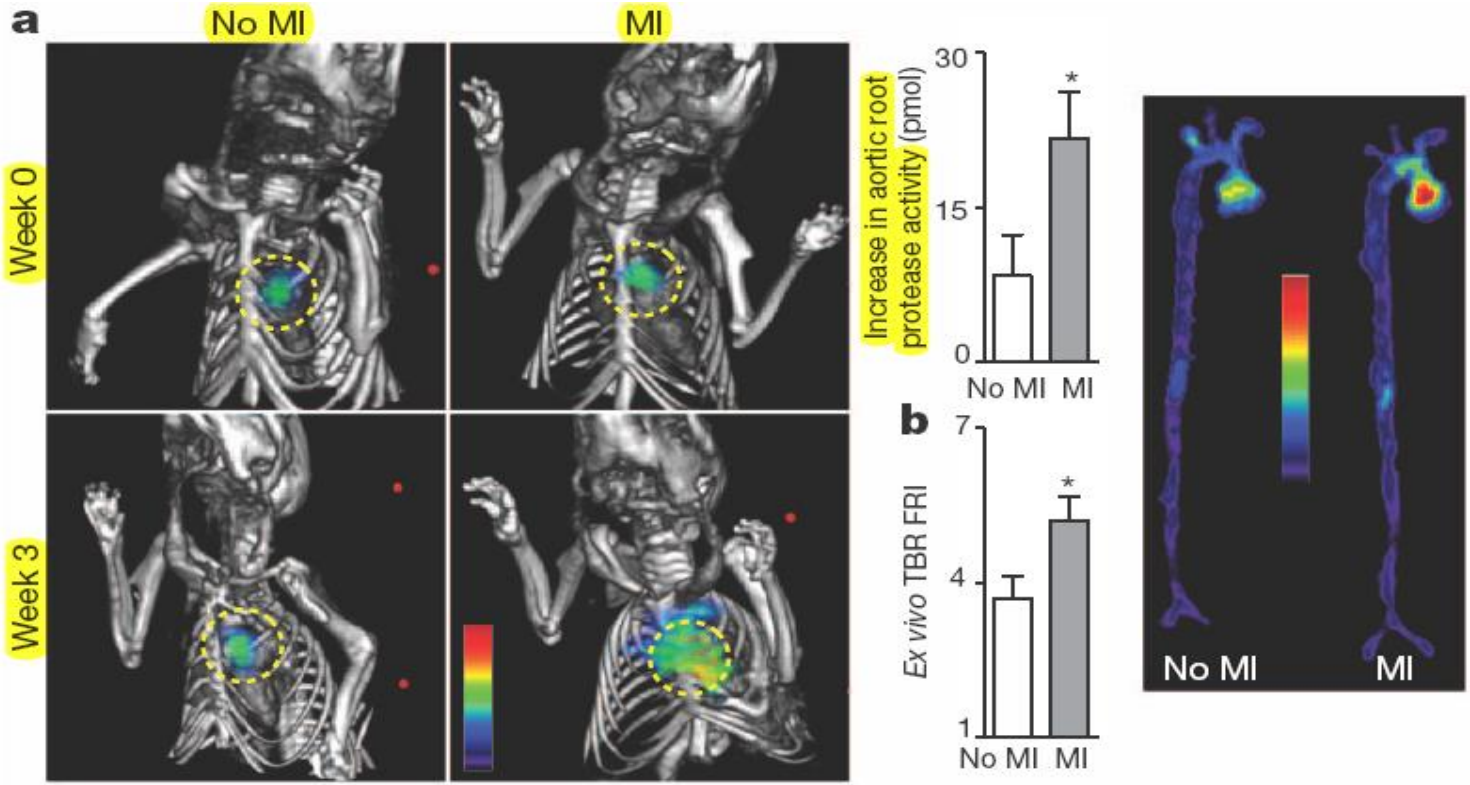
1% chol. diet +
1%CGN/SC q 3wk
For 3 mo
N=5

Kim & Seo et al PLoS One. 2014 ;9:e97841

Inflammation & CVD

- **MI accelerates atherosclerosis** (ApoE KO mice)

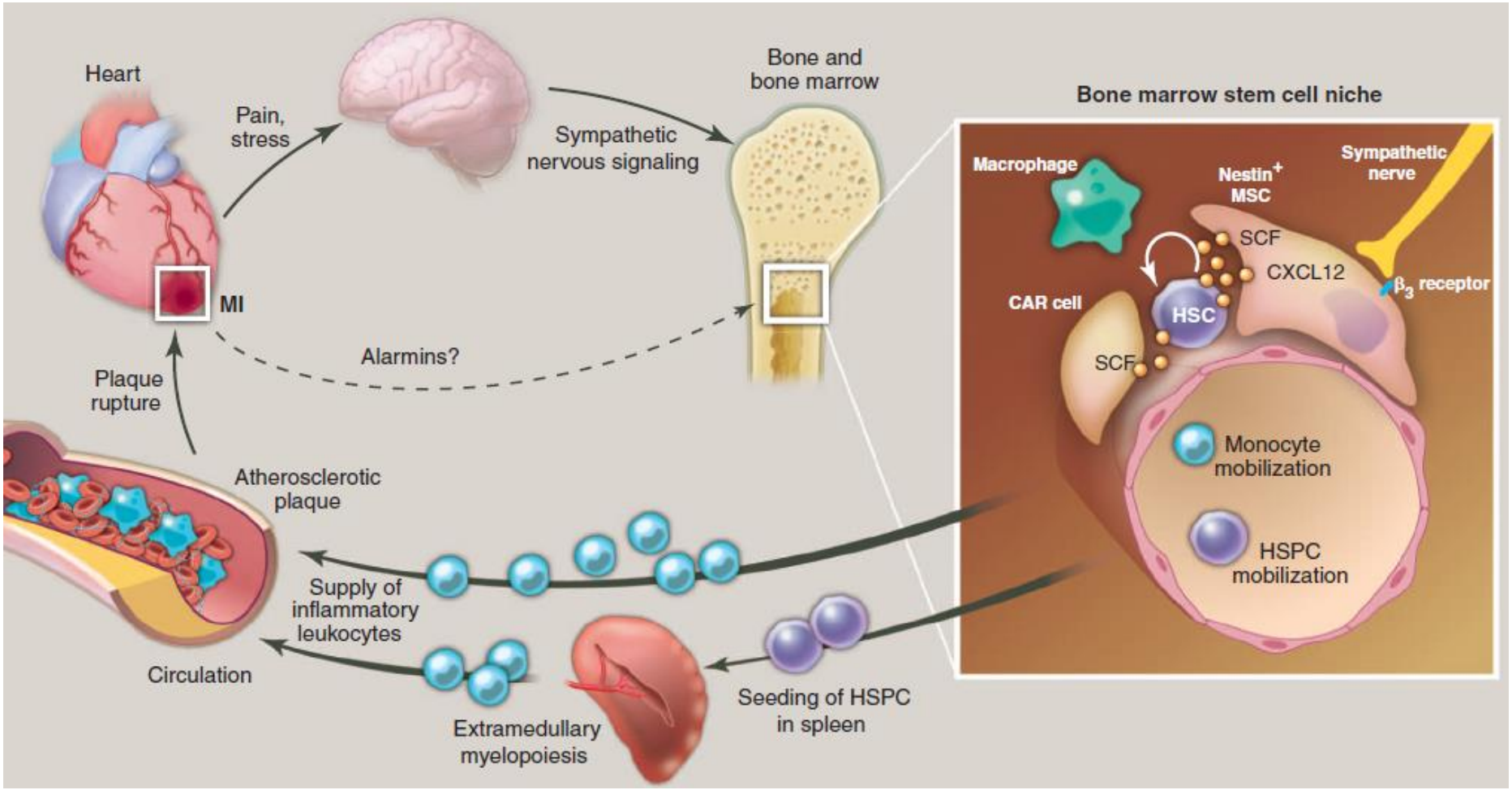
- The inflammatory linkage between the BM, spleen and blood following an AMI **may intensify the chronic inflammatory process involved in atherosclerosis**, independently from the primary myocardial wound site.



Nature. 2012;487:325-9

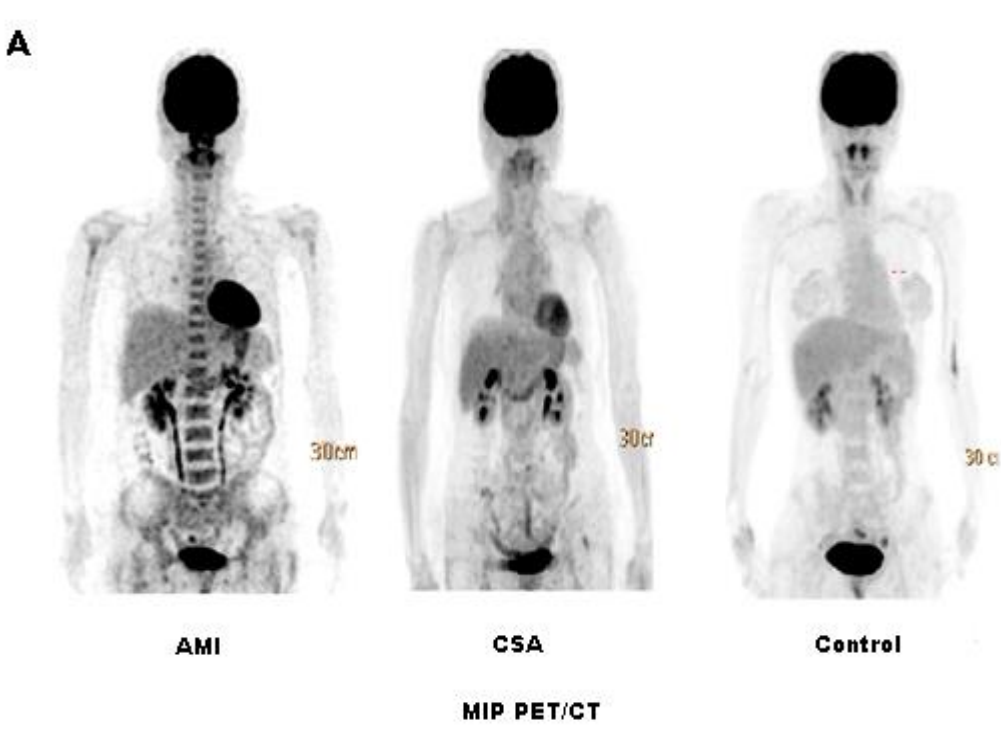
Inflammation & CVD

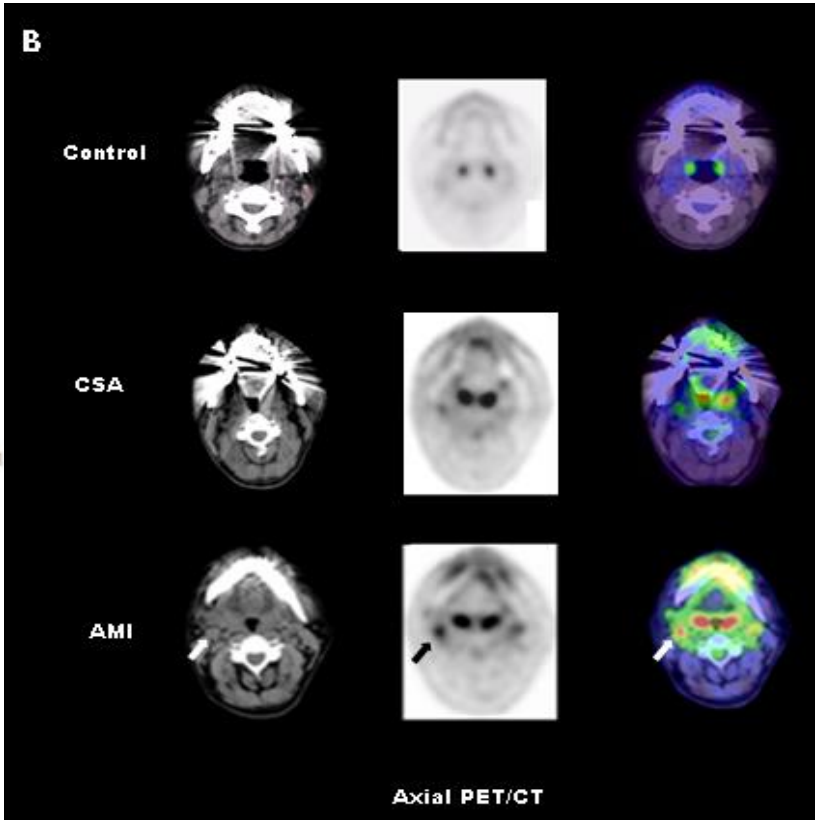
- Organ networks that lead to acceleration of atherosclerotic disease after MI



Science. 2013;339:161-66.

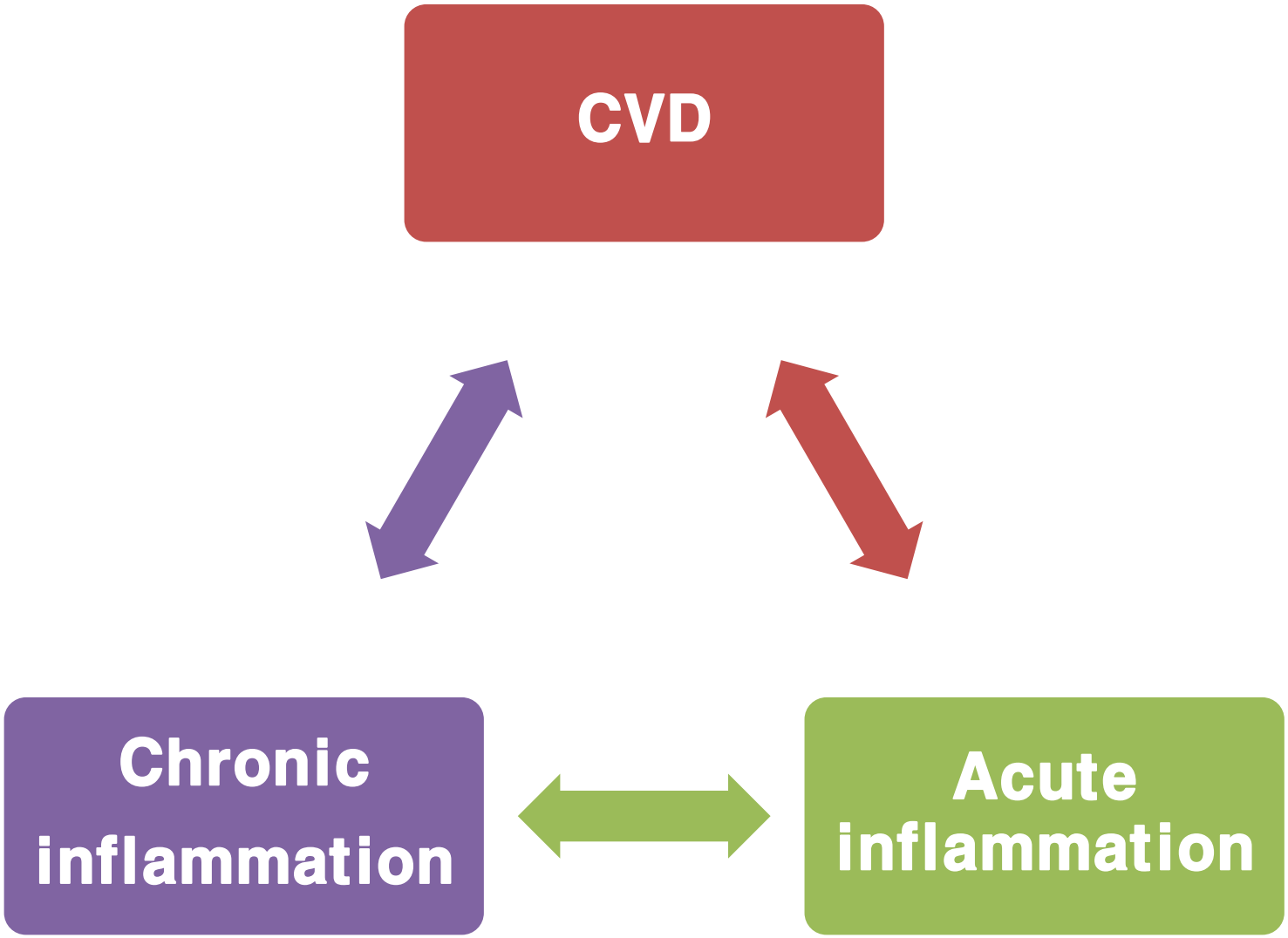
Inflammation & CVD





Kim & Seo et al. Circulation CV Imaging. 2014;7:454-60.

〈Inflammation & CVD〉



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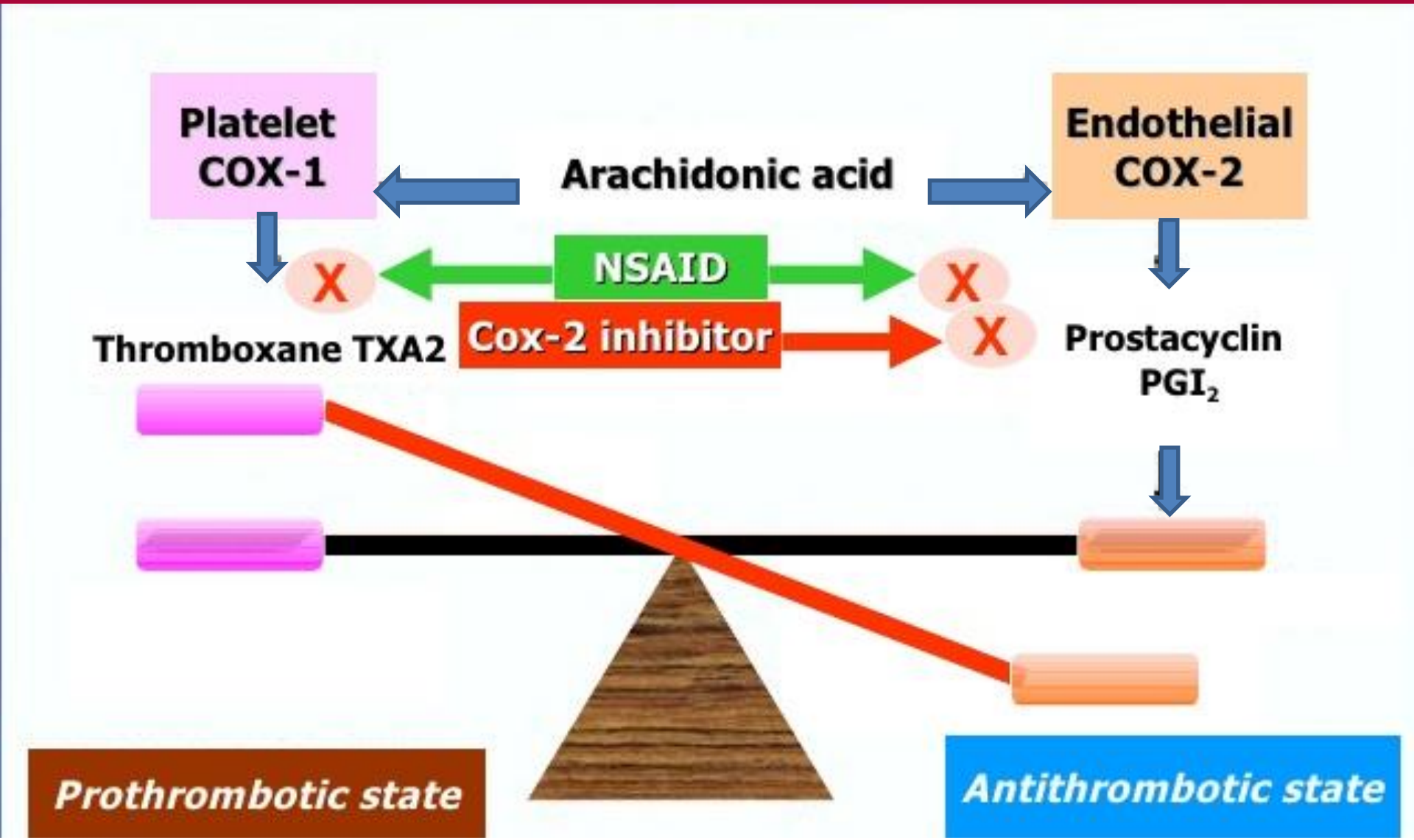
NSAIDs & CV Risk, mechanism



N Eng J Med. 2004;351:1709-11, N Eng J Med. 2001;345:433-42
Clin Exp Rheumatol. 2001;19:S41-4

Non-steroidal Anti-inflammatory Drugs and Thrombotic Cardiovascular Events

Findings from Epidemiological Studies

Joint Meeting of the Arthritis Advisory Committee and Drug Safety and Risk Management Advisory Committee
February 10-11, 2014

Andrew D. Mosholder, MD, MPH
Medical Officer
FDA Center for Drug Evaluation and Research
Office of Pharmacovigilance and Epidemiology
Division of Epidemiology II

NSAIDs & Thrombotic CV Event Risk

Questions

1. Does thrombotic CV risk vary by compound?
2. Is risk present from the start of NSAID Tx?
3. Are there patient subgroups who are more vulnerable to risk?
4. Do higher dosages convey more risk?

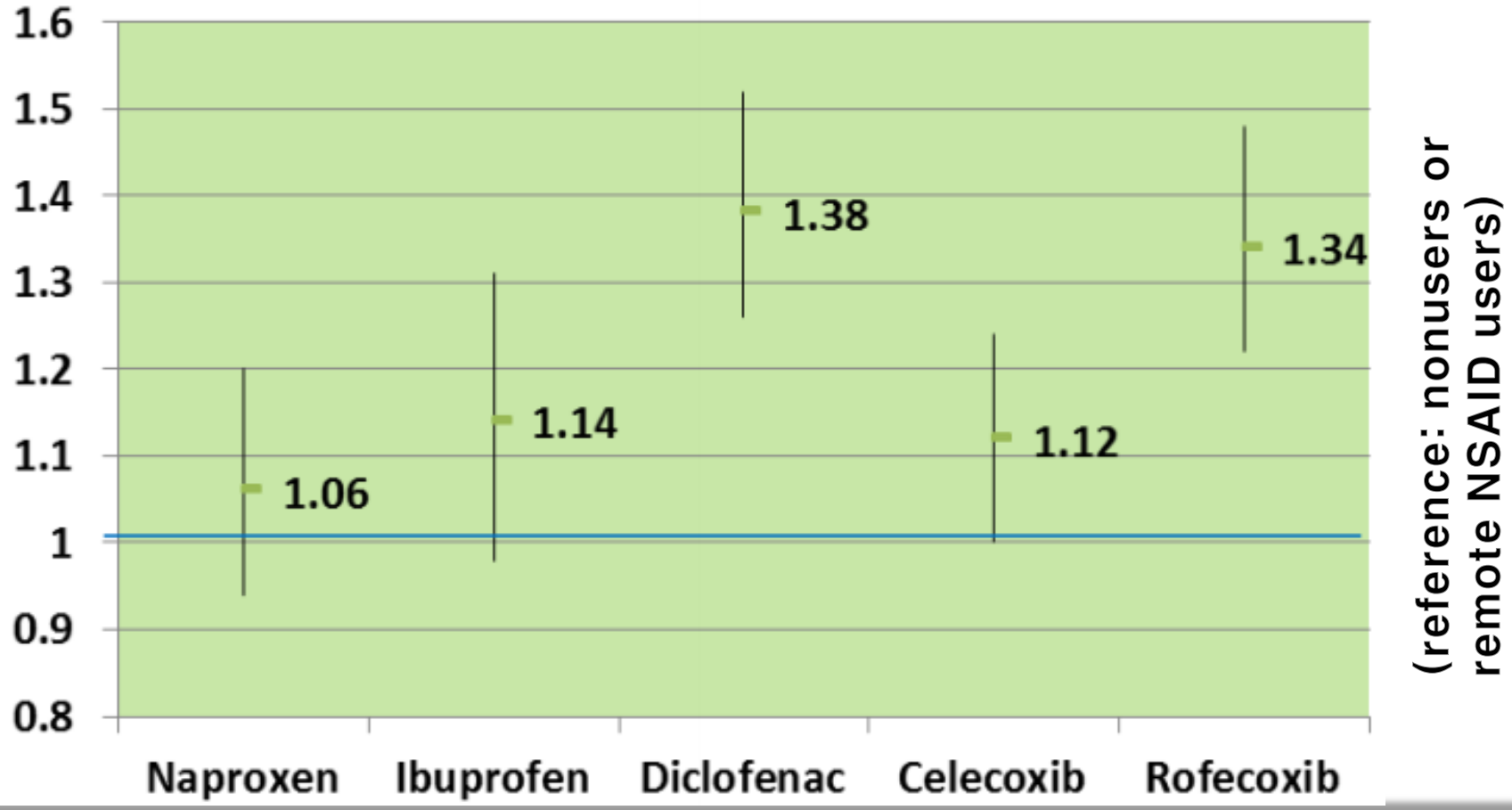
NSAIDs & Thrombotic CV Event Risk

1. Does thrombotic CV risk vary by compound?

- Findings from epidemiology studies vary
- More data are available on frequently used NSAIDs
- In general, some frequent patterns across studies:
  - Lower thrombotic CV risk estimates: **naproxen**
  - Higher thrombotic CV risk estimates: **diclofenac, rofecoxib**
- Risk estimates reflect not only the **compound** but the **doses** at which it was used in the study
- Differences in CV risk estimates by compound could reflect use by **different types of patients**

CV risk vary by compound?

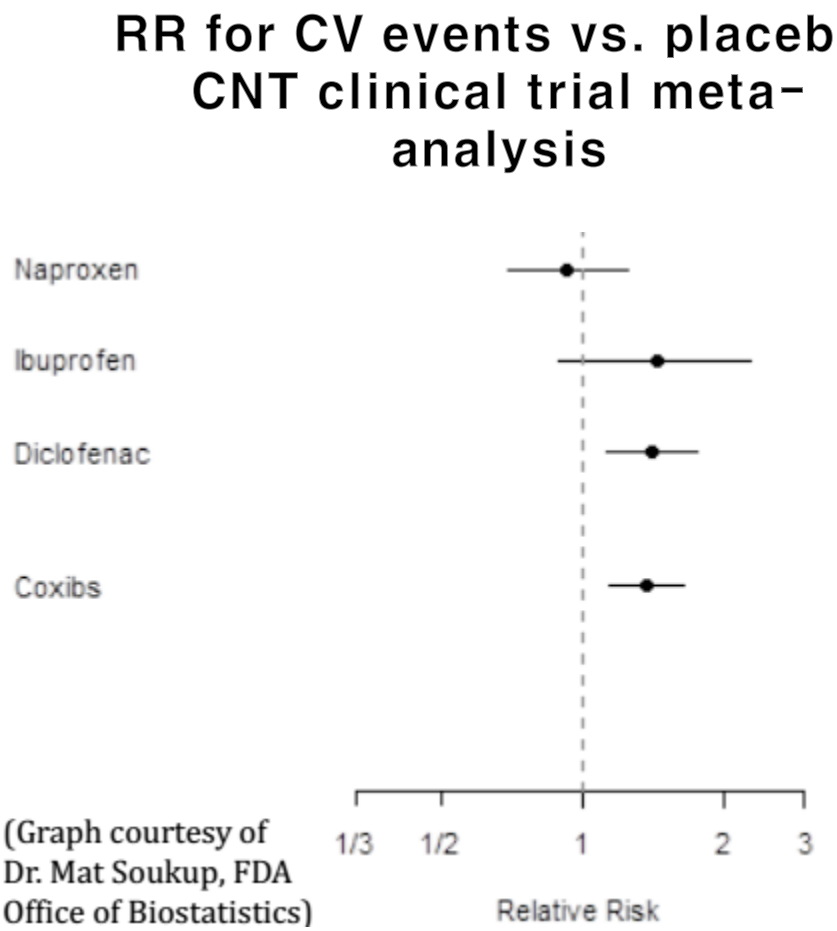
RR Estimates For MI: SOS Meta-analysis of 25 Observational Studies of NSAIDs



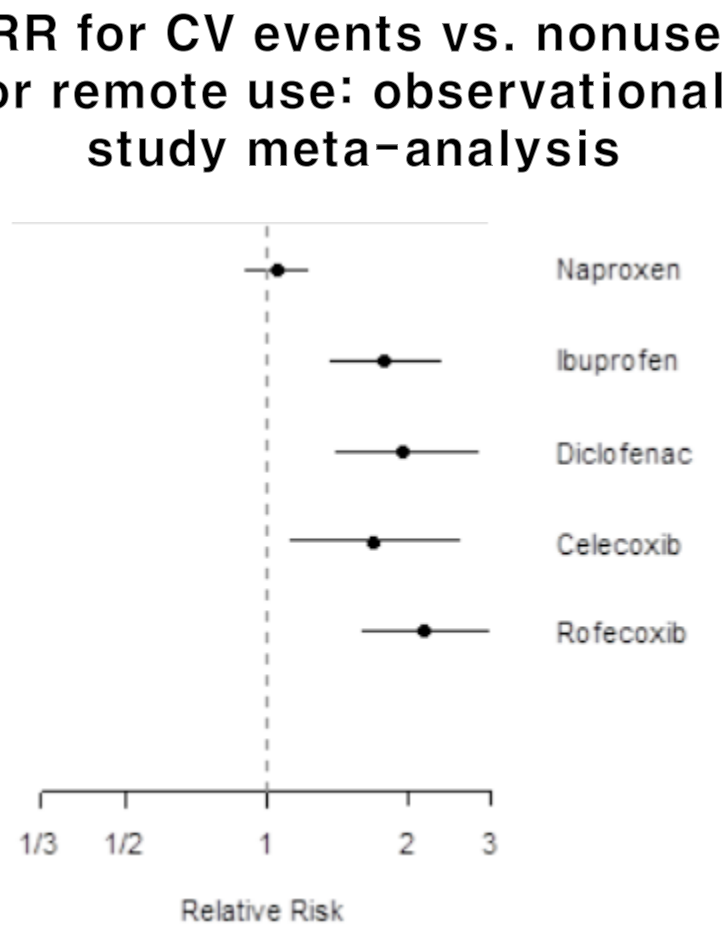
Varas-Lorenzo et al. Pharmacoepidemiol. Drug Saf. 2013

CV risk vary by compound?

Risk Estimates by Compound for Higher Dose Levels



(Graph courtesy of Dr. Mat Soukup, FDA Office of Biostatistics)



CNT Collaboration, Lancet 2013 ; PLoS Med. 2011

1. Does thrombotic CV risk vary by compound?

- Evaluation is confounded by dose, however:
- Lesser risks generally seen with naproxen

NSAIDs & Thrombotic CV Event Risk

2. Is risk present from the start of NSAID Tx?

- Various time courses for CV risk reported
- Different mechanisms may operate at different times
  - Plt aggregation, reduced vasodilation → immediate risk
  - Atherogenesis, vascular remodeling → long term risk
- In systematic review of NSAID observational studies, 9/12 studies → new users showed elevated CV risk in 1st mo
- 2 clinical trials of coxibs given for 10-14 days after CABG found an increased risk of MI and stroke

Grosser et al. 2006
PLoS Med 2011

From the start of NSAID Tx?

Observational Studies of NSAIDs Finding No Latency of Thrombotic CV Risk

Initial time period associated with CV risk	Population	Outcome Risk estimate (CI)	NSAIDs showing increased CV risk	Reference
5.8 days (first quartile for duration of use)	Quebec residents ≥66 y.o., no past MI	Hospitalized MI RR=1.70 (1.26-2.31)	Rofecoxib	Levesque et al. 2006
1 week	Danish, Post MI	Death or re-MI HR=1.45 (1.29-1.62)	Multiple	Schjerning Olsen et al. 2011
1-2 weeks	Finnish adults	First MI OR=1.39 (1.23-1.58)	Not separated	Helin-Salmivaara et al. 2006
1 month	Australian veterans	Hospitalized MI IRR=1.31 (1.12-1.53)	Not separated	Pratt et al. 2010

RR rate ratio, HR hazard ratio, OR odds ratio, IRR incidence rate ratio

From the start of NSAID Tx?

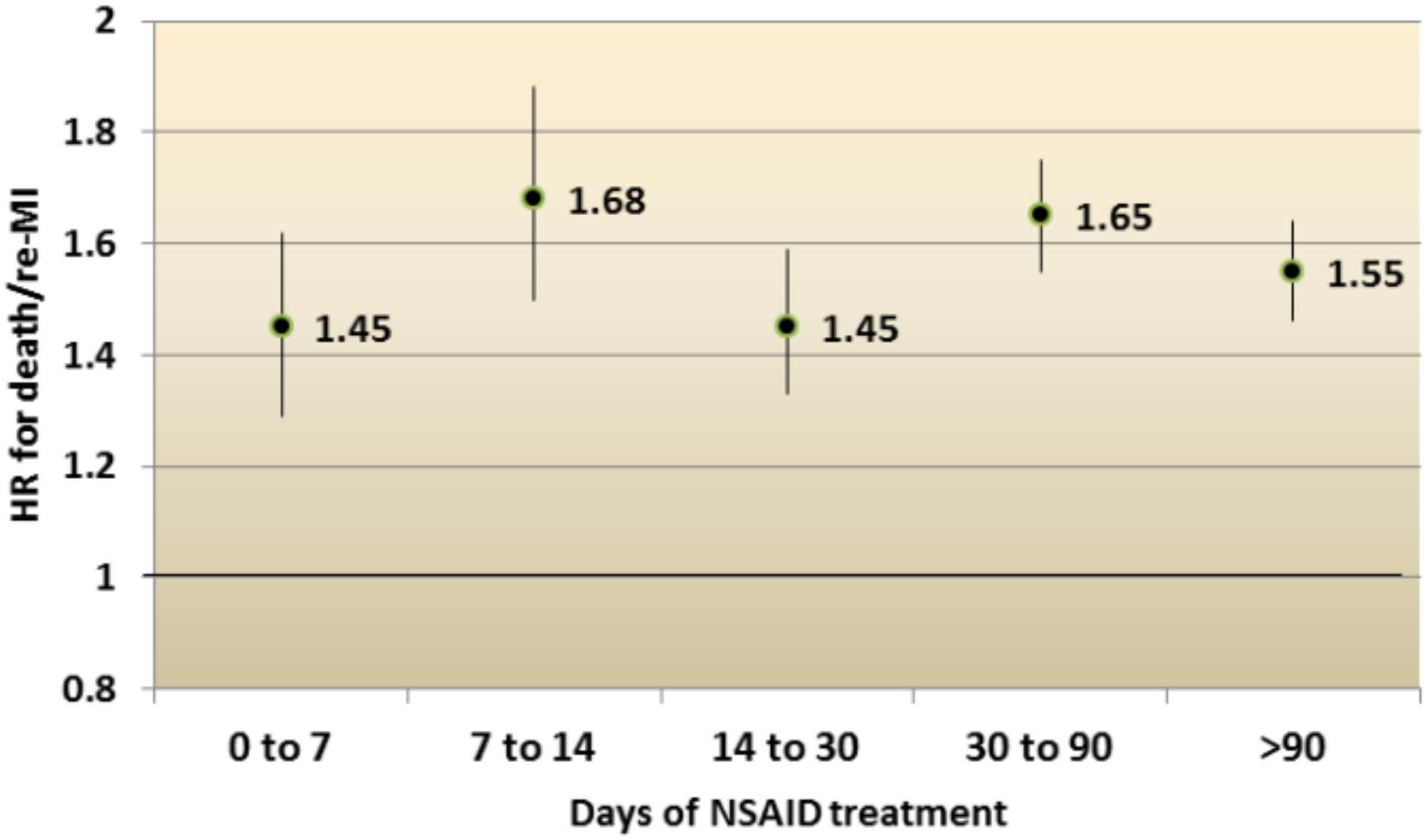
Observational Studies of NSAIDs Finding No Latency of Thrombotic CV Risk

Initial time period associated with CV risk	Population	Outcome Risk estimate (CI)	NSAIDs showing increased CV risk	Reference
1 month	Canadians without CV disease	MI or coronary death OR nap=2.84 (1.43–5.63) OR ibu=2.49 (1.12–5.53)	Naproxen & ibuprofen	Varas-Lorenzo et al. 2009
1 month	40-84 y.o. with no CV disease, UK	MI HR=3.43 (1.66--7.07)	Coxibs	Hammad et al. 2008
60 days	Penna. Medicare	Hospitalized MI or ischemic stroke RR=1.14 (1.01–1.29)	Rofecoxib	Solomon et al. 2006
1st prescription	40+ y.o., UK	MI RR=1.23 (1.15–1.31)	Traditional NSAIDs	van Staa et al. 2008

RR rate ratio/relative rate, HR hazard ratio, OR odds ratio

From the start of NSAID Tx?

Risk of Death/Re-MI Associated with NSAID Tx
Population: Danish Post-MI Patients



Schjerning Olsen et al. Circulation 2011

From the start of NSAID Tx?

Case-control Study of MI in Finland

Table 4 Risk of first time MI among current users of NSAIDs stratified by the duration of continuous therapy (days) in categories

	Cases	Controls	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[a]
Non-users	20 645	92 524	1.00 (Reference)	1.00 (Reference)
Any NSAIDs				
1–14	542	1 509	1.55 (1.39–1.73)	1.39 (1.23–1.58)
15–30	436	1 344	1.37 (1.22–1.54)	1.22 (1.06–1.40)
31–90	670	1 807	1.43 (1.29–1.58)	1.25 (1.11–1.41)
91–180	631	1 551	1.74 (1.57–1.93)	1.54 (1.36–1.74)

Helin-Samivaara et al. Eur Heart J 2006

2. Is risk present from the start of NSAID treatment?

- Risk is observable from start of NSAID treatment

NSAIDs & Thrombotic CV Event Risk

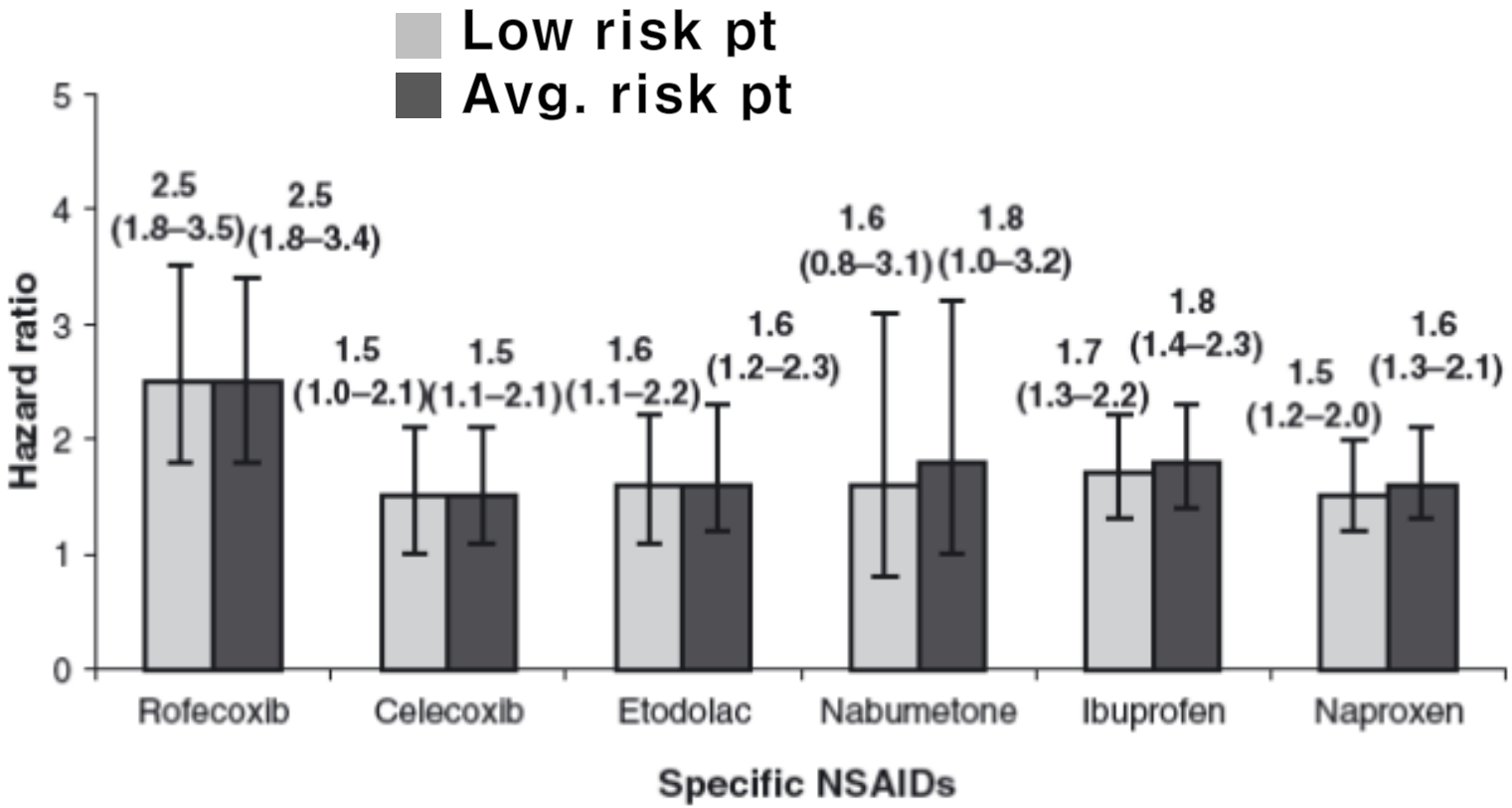
3. Are there patient subgroups who are more vulnerable to risk?

- Post MI
- Heart Failure
- Hypertension
- Other CV risk factors

  - Clinically relevant increases in CV events with NSAIDs observable both in vulnerable populations and apparently healthy populations
  - Absolute risks substantially higher for vulnerable patients
  - Relative risks appear similar for high CV risk vs. healthy patients

Who are more vulnerable to risk?

Similar RR in Different CV risk groups



Outcome=MI, Ref= periods of no NSAID use

VA & Medicare Claims Analysis, Abraham et al., Aliment.Pharmacol.Ther. 2007

Who are more vulnerable to risk?

Estimated Person-years of NSAID use associated with 1 excess death (any cause), by Compound & Patient characteristics (unadjusted)

Compound	Post-MI patients	Heart failure patients	Healthy individuals
Rofecoxib	13	9	24
Celecoxib	14	14	24
Diclofenac	24	11	104
Ibuprofen	45	53	446
Naproxen	n.a.	51	1329

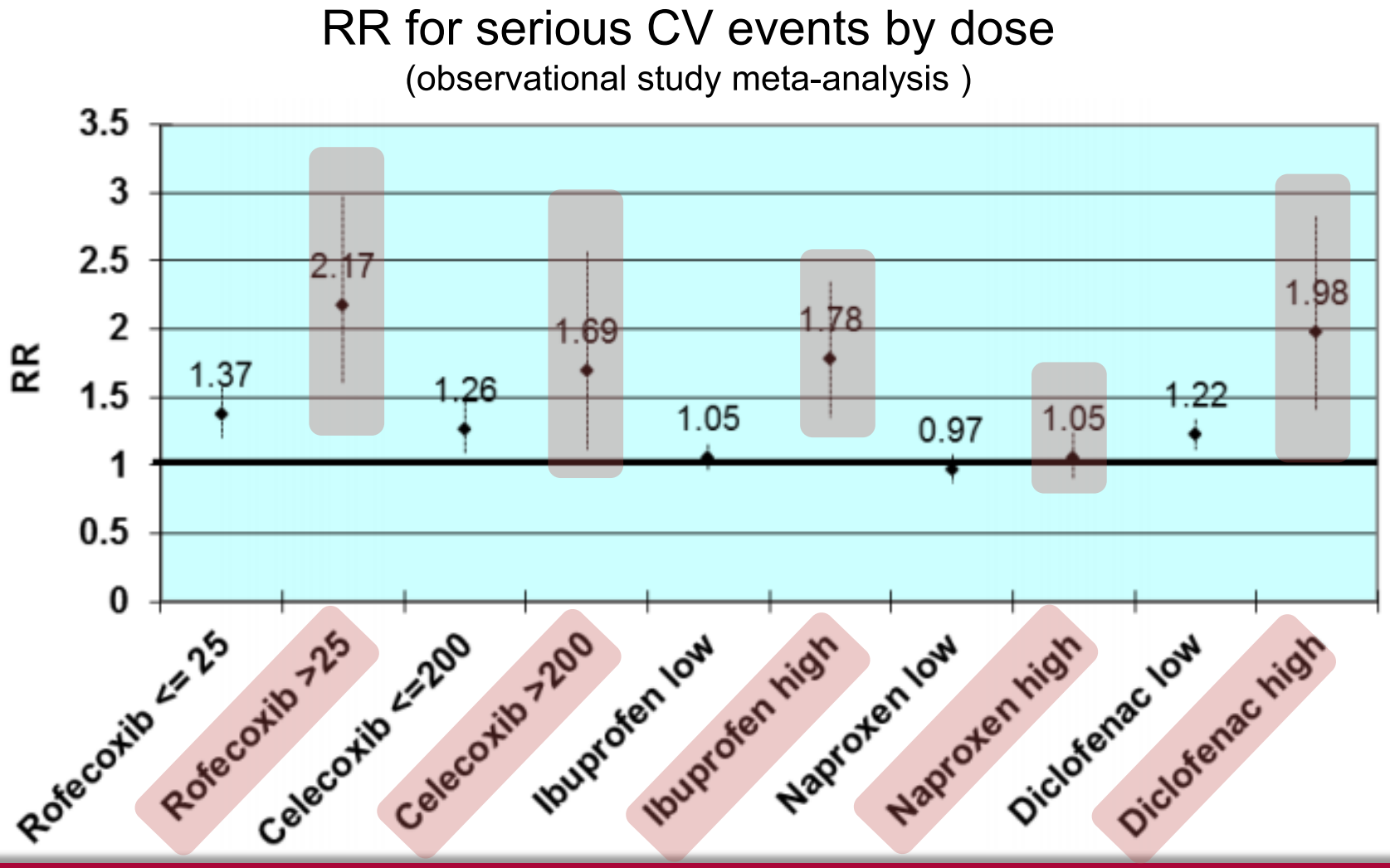
Danish National Healthcare Data, Gislason et al., Circulation 2006; Gislason et al. Arch Intern Med 2009; Fosbøl et al. CPT 2009

3. Are there patient subgroups who are more vulnerable to risk?

- Vulnerable patients experience more CV events, but CV events are also increased in healthy individuals

NSAIDs & Thrombotic CV Event Risk

4. Do higher dosages convey more risk?



McGettigan & Henry, PLoS Medicine 2011

Higher dosage, More risk ?

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 29, 2016 VOL. 375 NO. 26

Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen r Arthritis

Steven E. Nissen, M.D., Neville D. Y s, M.D., Daniel H. S on, M.P.H., Thomas F üscher, M.D., Peter Libby, M.D., M. Elaine Hus D., David Y. Graham, M Jeffrey S. Borer, M.D., Lisa M. sniewski, R.N. Katherine E. Wolsk H., Qiuqing Wang, M.S. u Menon, M.D., Frank Ruschitzk M.D., Michael Gaffn D., Bruce Beckerman, M.D nuela F. Berger, M.D., Weihang B Ph.D., A. Michael Lincoff, M.D., fo PRECISION Trial Investigators*

200 (~400)mg/d
Dose increase is permitted only for RA pt

700~1000 mg/d

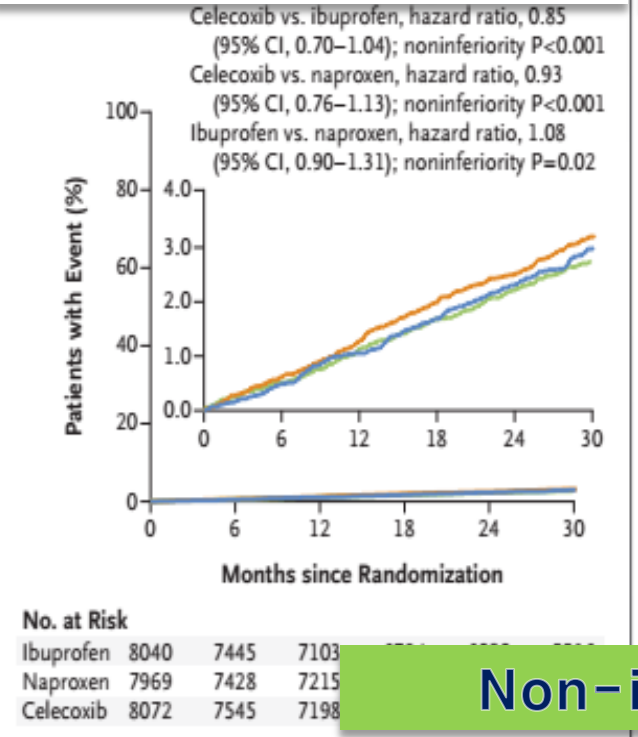
1800~2400 mg/d

N Eng J Med 2016;375:2519-29

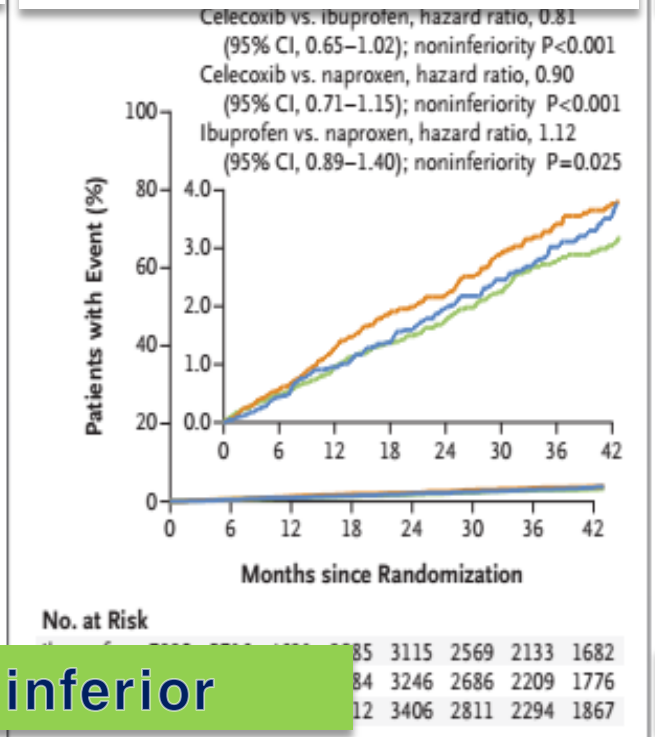
Higher dosage, More risk ?

Celecoxib Ibuprofen Naproxen

1’ outcome (ITT)

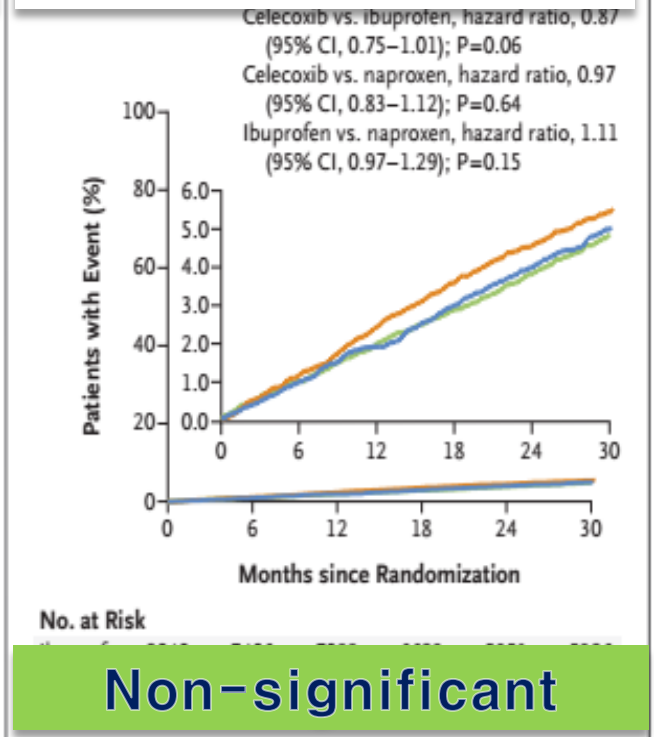


1’ outcome (on-Tx)



Non-inferior

MACE



Non-significant

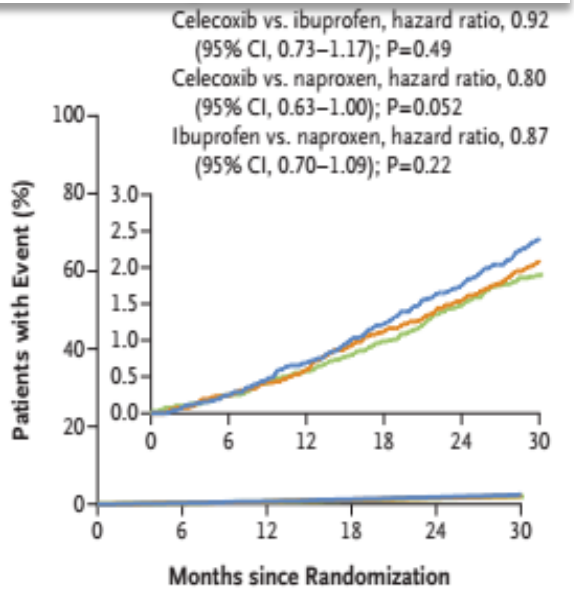
* 1’outcome = death from CV causes, including hemorrhagic death; nonfatal MI; or nonfatal stroke

N Eng J Med 2016;375:2519-29

Higher dosage, More risk ?

Celecoxib Ibuprofen Naproxen

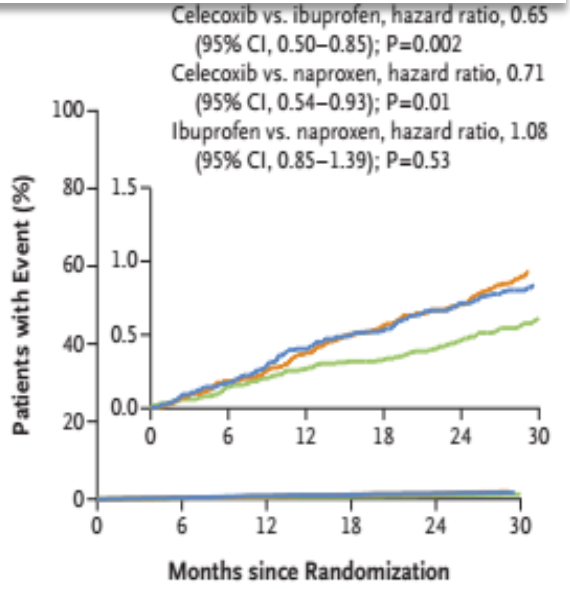
Any Death



No. at Risk

Non-significant

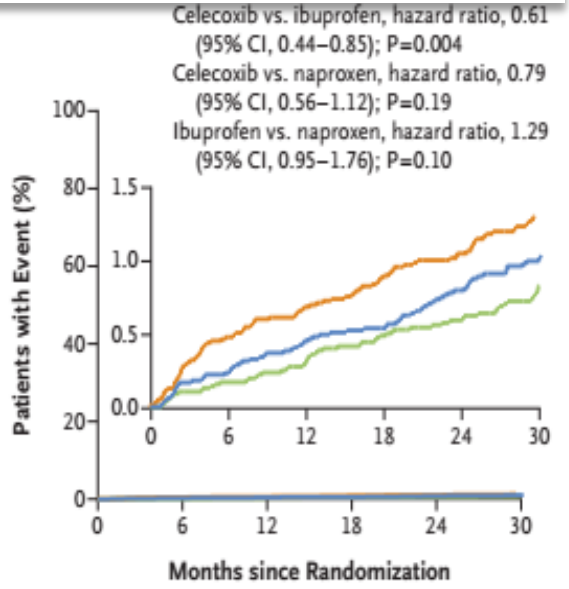
Serious GE events



No. at Risk

Ibuprofen	8040	7449	7109	6794	6079	5505
Naproxen	7969	7427	7113	6814	6099	5507
Celecoxib	8072	7549	7216	6896	6233	5674

Renal events



No. at Risk

Ibuprofen	8040	7440	7116	6820	6113	5552
Naproxen	7969	7433	7141	6852	6147	5556
Celecoxib	8072	7556	7234	6907	6256	5701

N Eng J Med 2016;375:2519-29

4. Do higher dosages convey more risk?

- Higher dosages are observed to convey greater risk

Prescription NSAID Labels includes the following Information:

- The risk of heart attack or stroke can occur as early as the first weeks of using an NSAID. The risk may increase with longer use of the NSAID.
- The risk appears greater at higher doses.
- Newer information makes it less clear that the risk for heart attack or stroke is similar for all NSAIDs; however, this newer information is not sufficient for us to determine that the risk of any particular NSAID is definitely higher or lower than that of any other particular NSAID.
- NSAIDs can increase the risk of heart attack or stroke in patients with or without heart disease or risk factors for heart disease.

FDA Drug Safety Communication
https://www.fda.gov/Drugs/DrugSafety/ucm451800.htm

Prescription NSAID Labels includes the following Information:

- In general, patients with heart disease or risk factors for it have a greater likelihood of heart attack or stroke following NSAID use than patients without these risk factors because they have a higher risk at baseline.
- Patients treated with NSAIDs following a first heart attack were more likely to die in the first year after the heart attack compared to patients who were not treated with NSAIDs after their first heart attack.
- There is an increased risk of heart failure with NSAID use.

FDA Drug Safety Communication
https://www.fda.gov/Drugs/DrugSafety/ucm451800.htm

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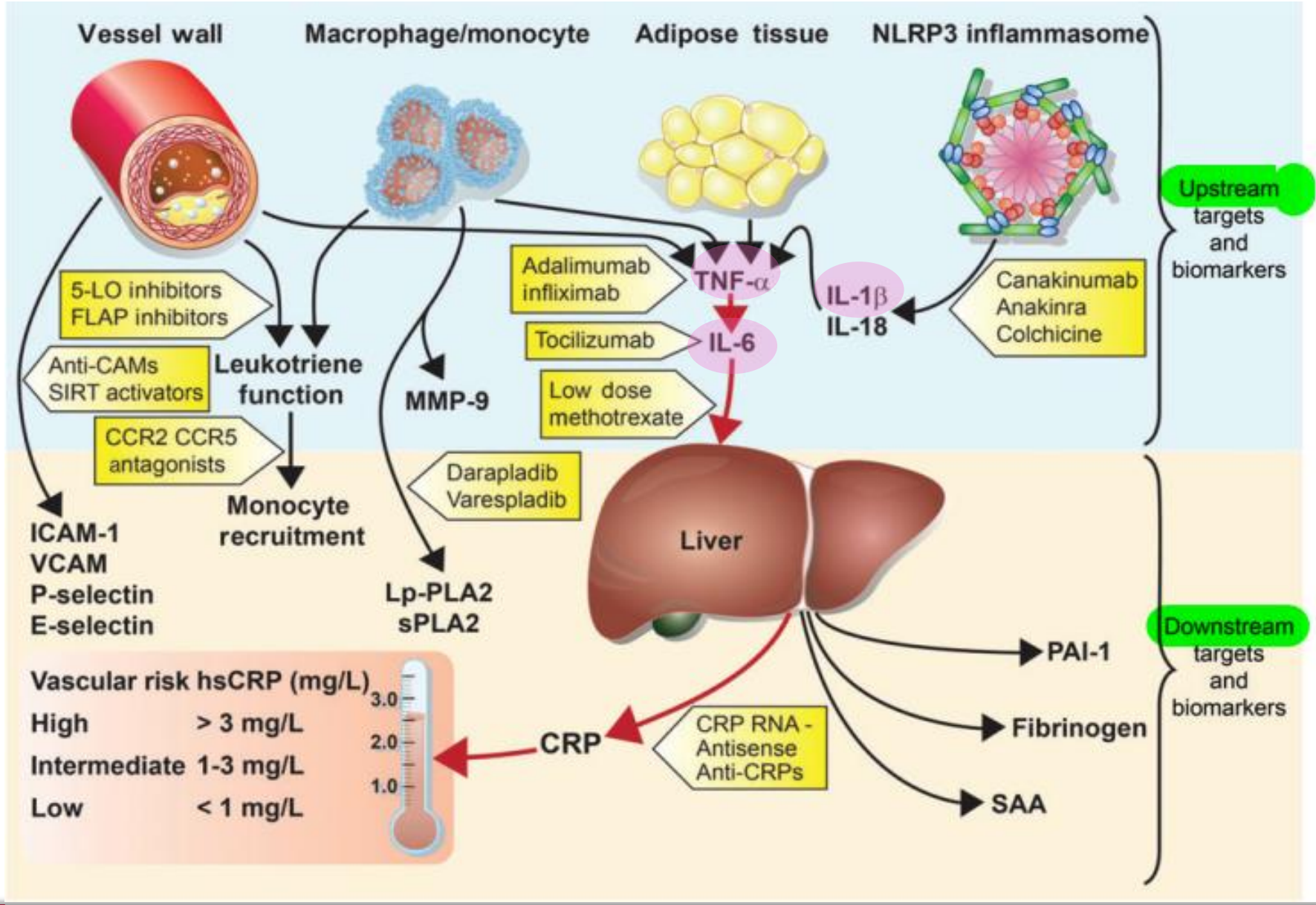
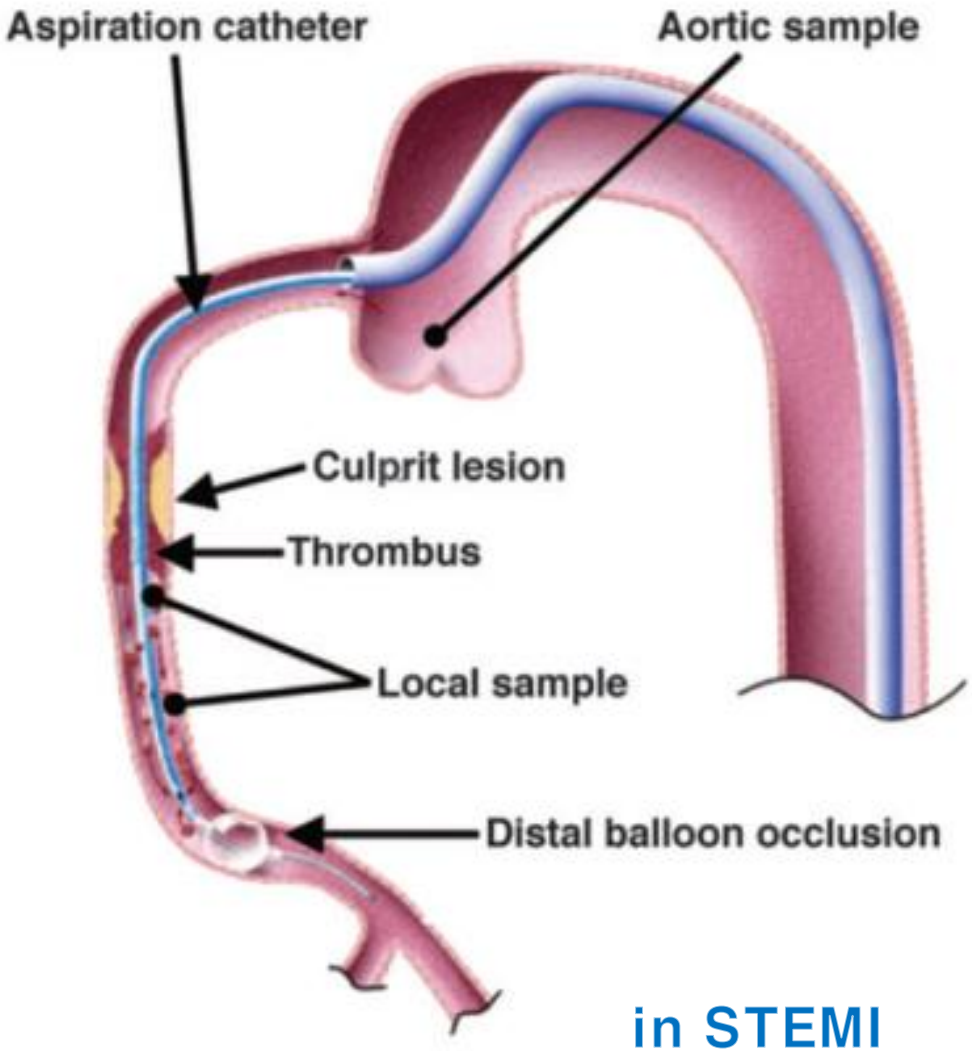
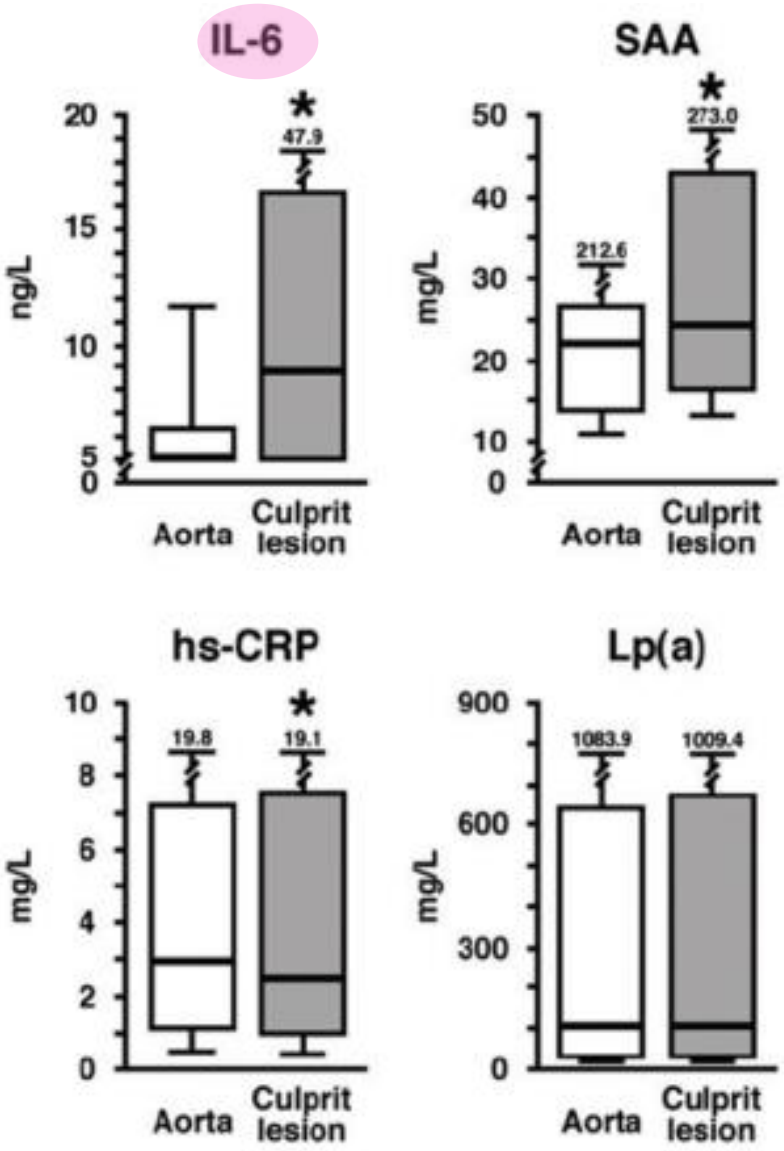


Eur Heart J 2014;35:1782–91

Anti-inflammatory Interventions



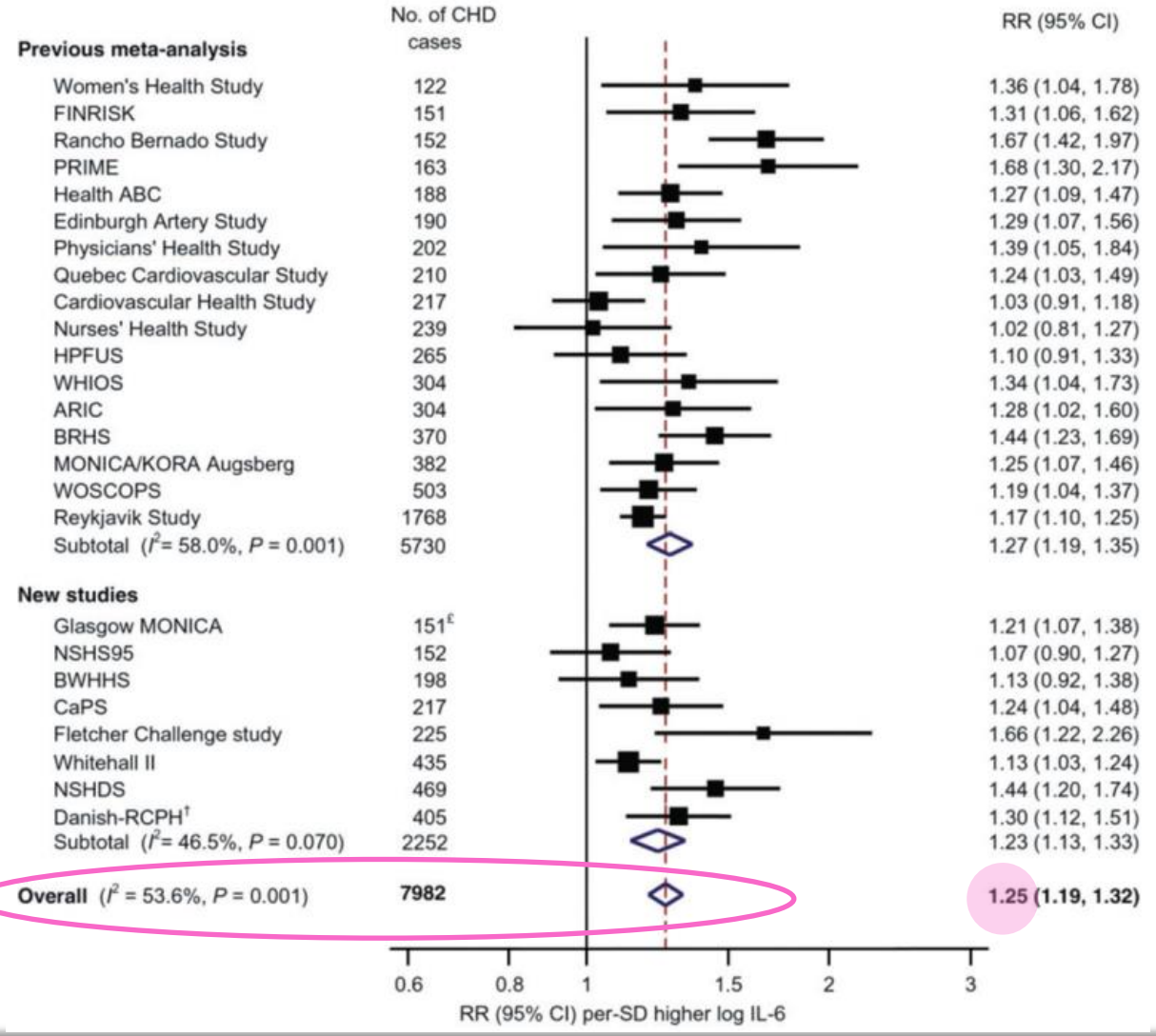
in STEMI



Circulation 2005;111:1355–1361

Anti-inflammatory Interventions

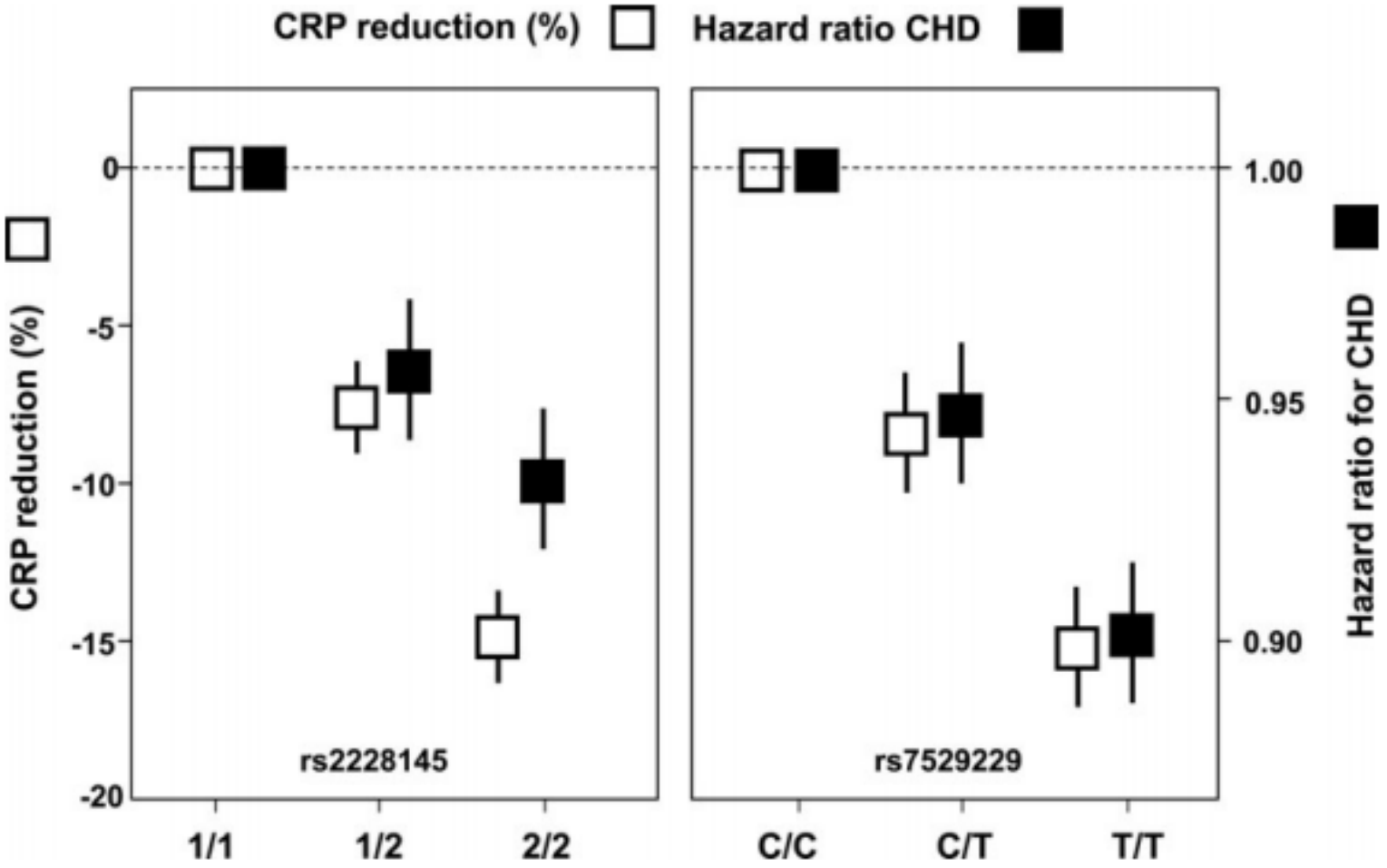
IL-6 & future vascular events



Eur Heart J 2014;35:578–89

Anti-inflammatory Interventions

Genetic polymorphism in IL-6 regulatory pathway associate with lower CRP & with future lower vascular events



Lancet 2012;379:1205-13, 1214–24

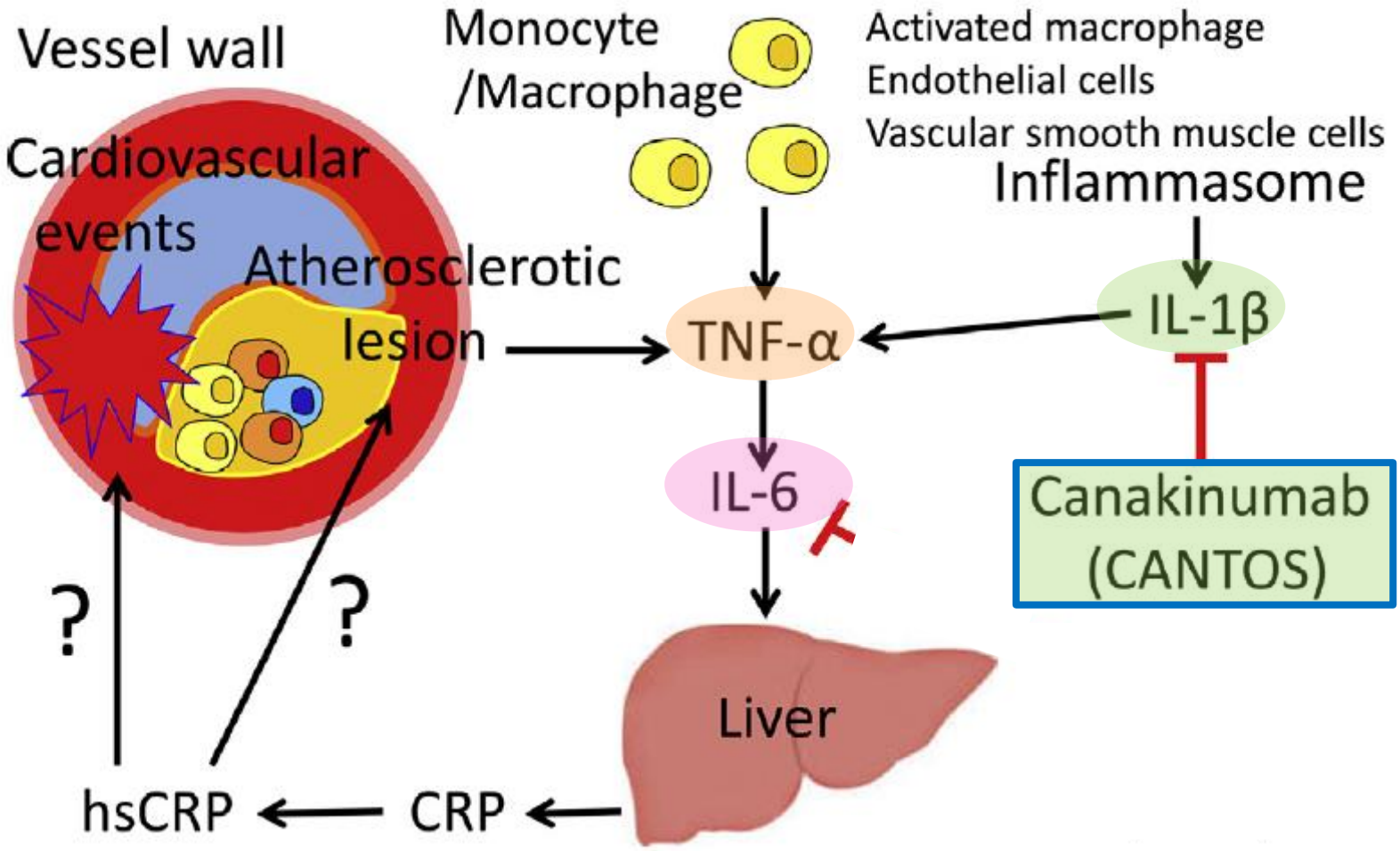
Anti-inflammatory Interventions

Clinical trials of anti-inflammatory therapy in CVD

Drug	Target	Trial	Size	Sponsor	Status
A. Agents impacting on the IL-6 signalling pathway					
Canakinumab	IL-1β	CANTOS	10 000	Novartis	Enrolling
Methotrexate	IL-6,TNF	CIRT	7 000	NHLBI	Enrolling
Anakinra	IL-1Ra	IL-HEART	190	UK-MRC	Completed
Colchicine	multiple	LoDoCo	532	HRS, Aus	Positive
Tocilizumab	IL-6	Entracte	3 000	Hoffmann	Enrolling
Etanercept	TNF	Entracte	3 000	Hoffmann	Enrolling
B. Agents impacting on alternative inflammatory pathways					
Succinobucol	Ox-LDL	ARISE	6 144	AtheroGenics	Negative
Varespladib	$sPLA_2$	VISTA-16	5 000	Anthera	Negative
Darapladib	Lp-PLA_2	STABILITY	15 000	GSK	Enrolled
Darapladib	Lp-PLA_2	SOLID-TIMI-52	13 000	GSK	Enrolled
Inclacumab	P-Selectin	SELECT-ACS	544	Roche	Completed
Inclacumab	P-Selectin	SELECT-CABG	380	Roche	Enrolled

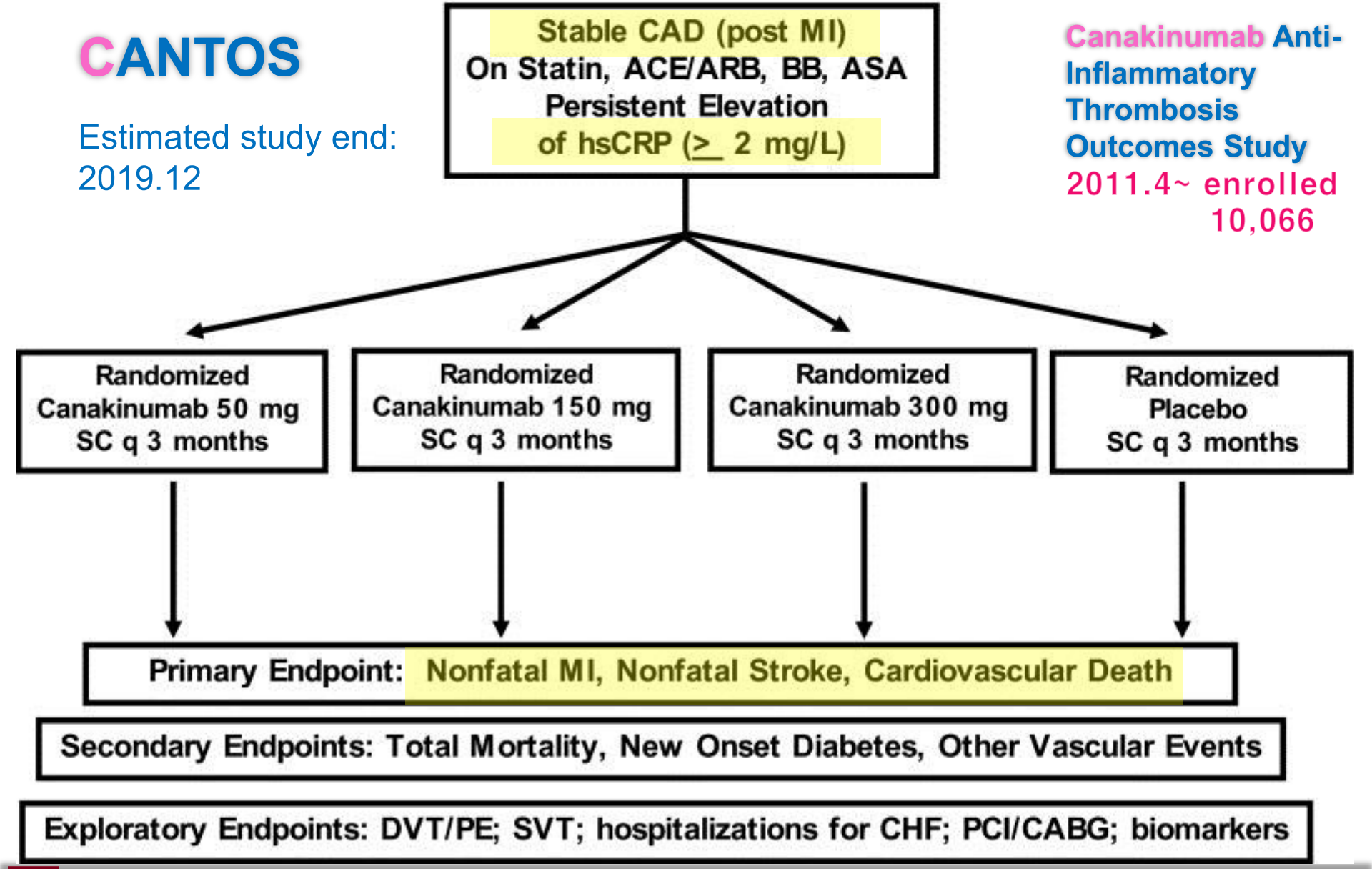
Eur Heart J 2014;35:1782–91

Anti-inflammatory Interventions



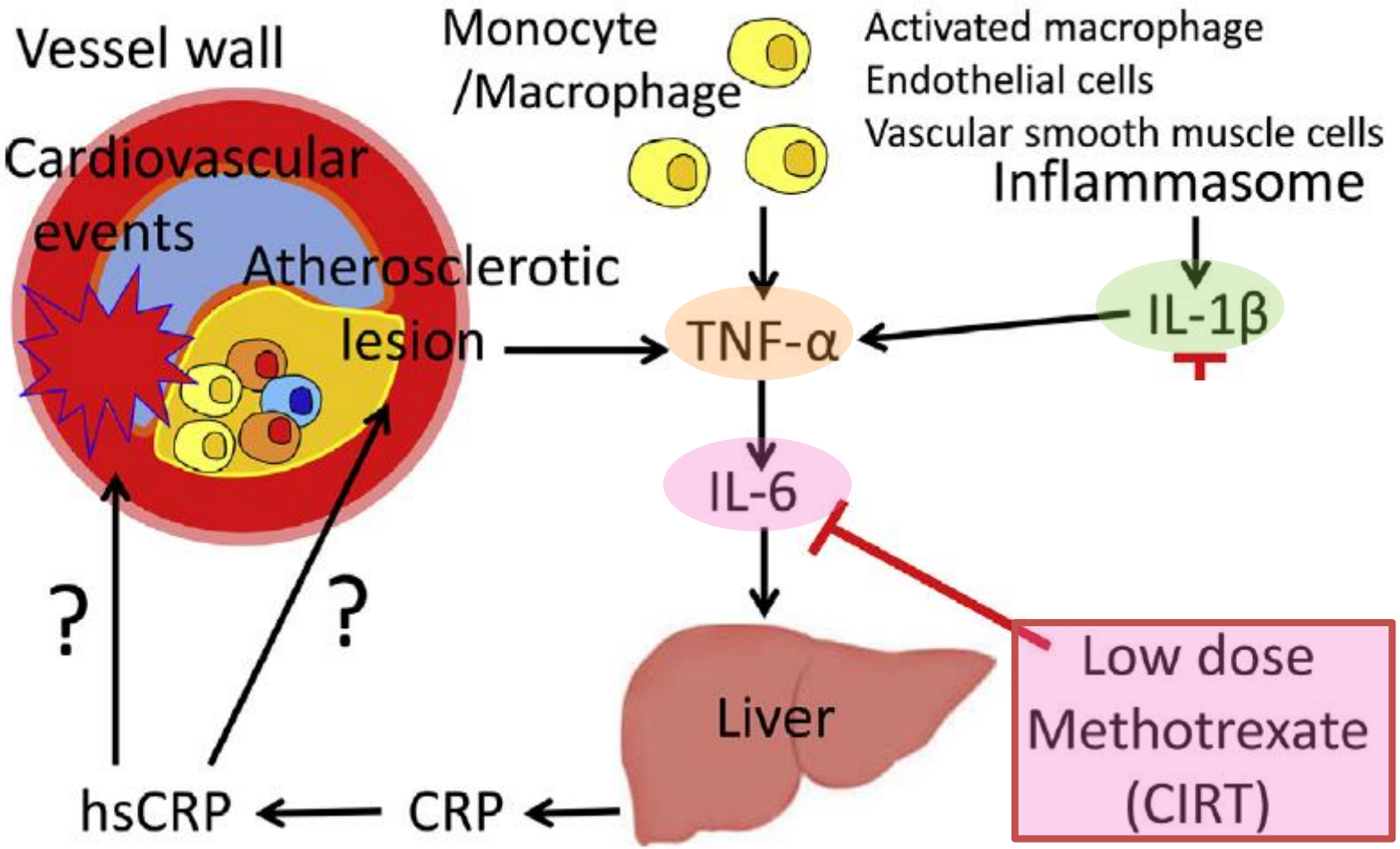
Journal of Cardiology 2015;66:1–8

Anti-inflammatory Interventions



Trans Am Clin Climatol Assoc. 2013;124:174–90.

Anti-inflammatory Interventions

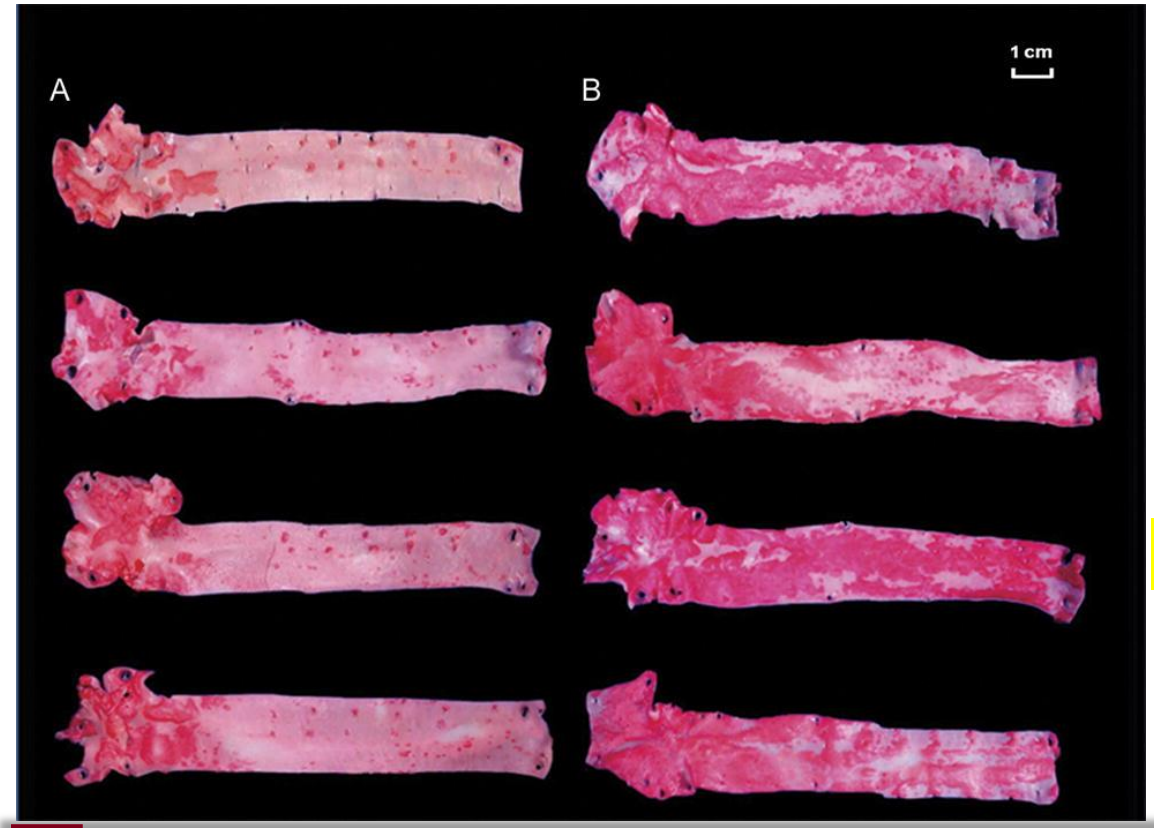


Journal of Cardiology 2015;66:1–8

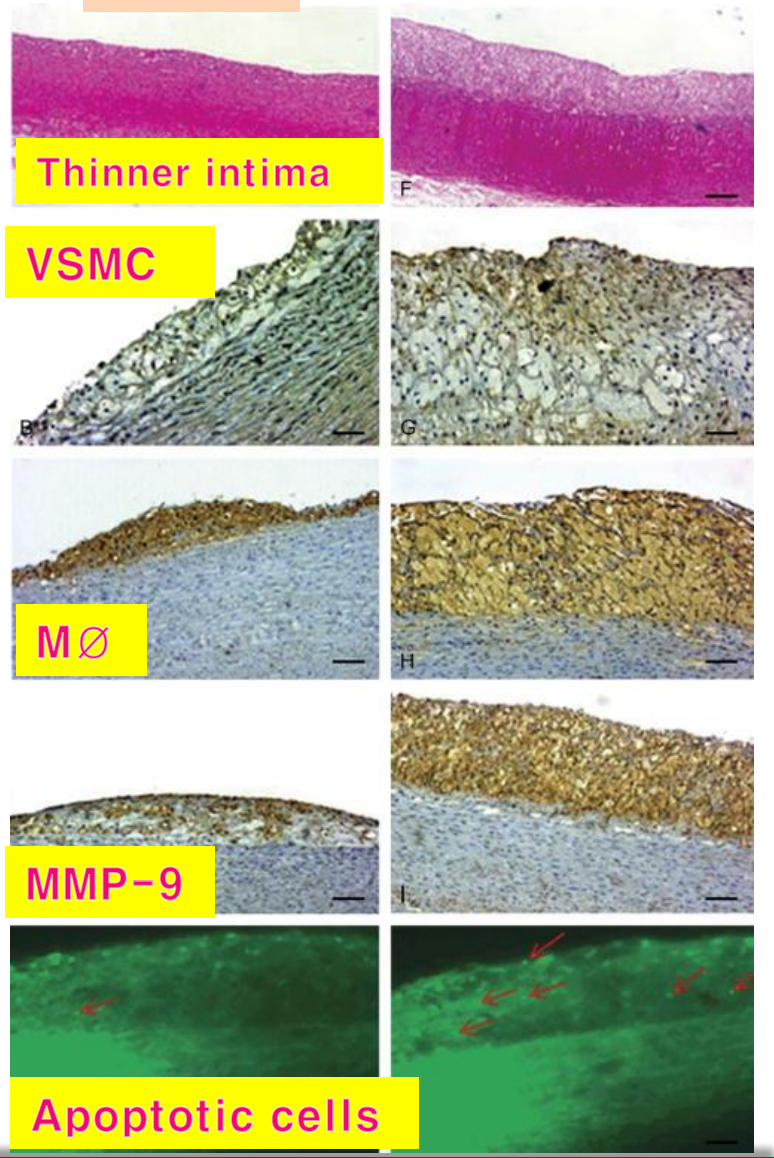
Anti-inflammatory Interventions

Tx with LDM inhibits Atherogenesis in cholesterol-fed Rabbits

LDM



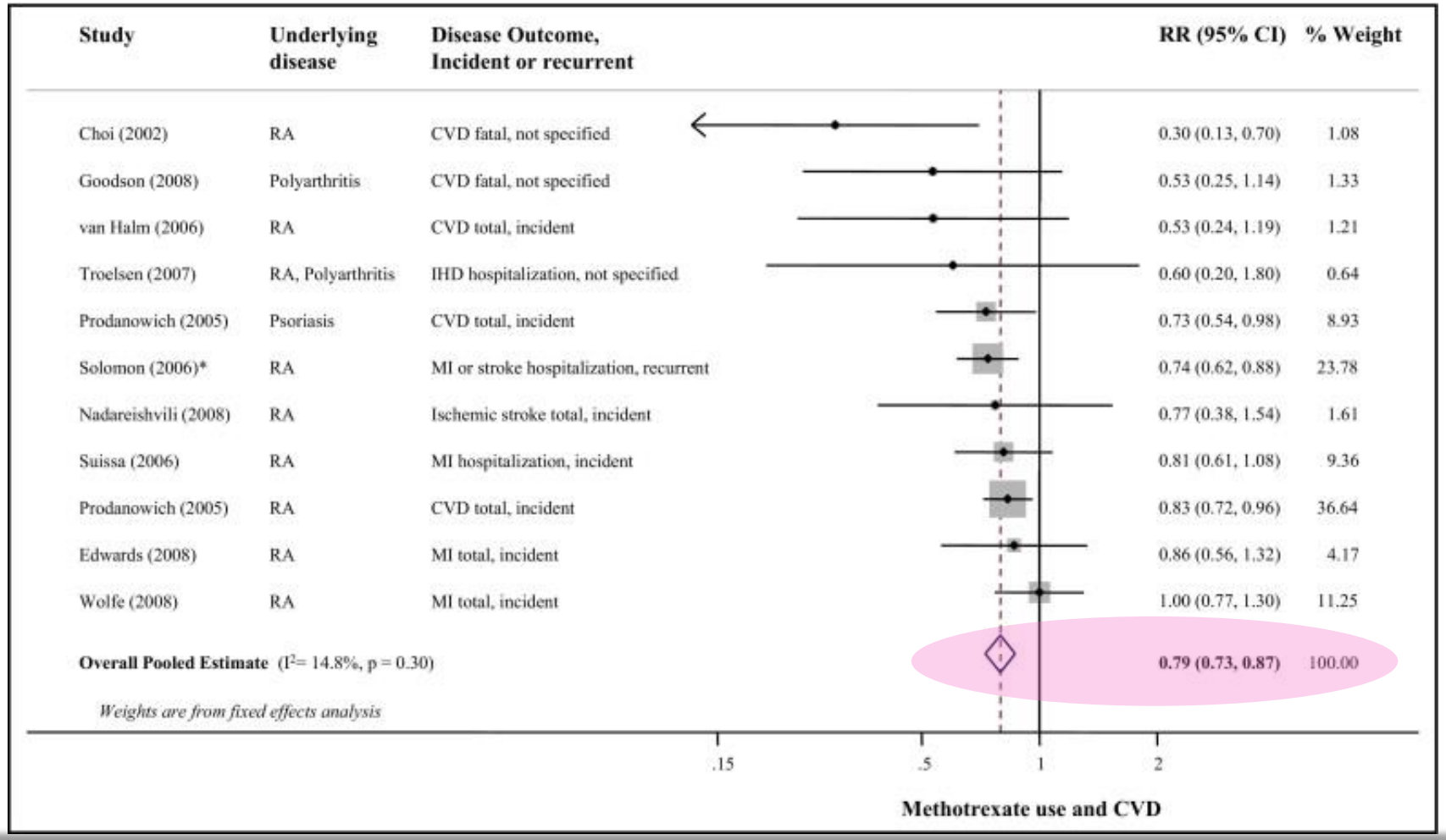
LDM



J Cardiovasc Pharmacol 2012;59:308–314

Anti-inflammatory Interventions

- A meta-analysis for the patients with RA or PsA (psoriatic arthritis) taking LDM: RRR 21% for CVD

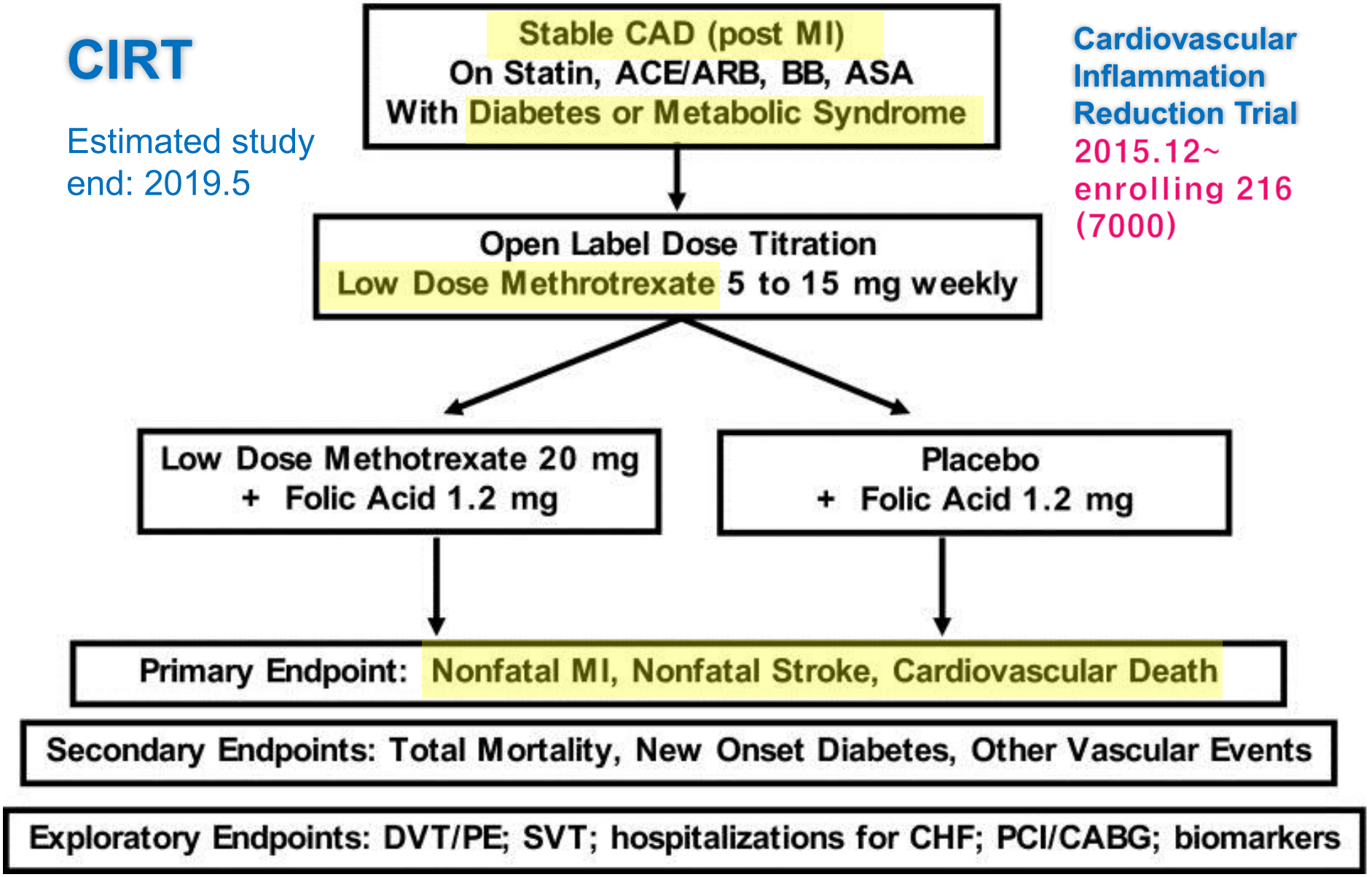


Am J Cardiol 2011;108:1362–1370

Anti-inflammatory Interventions

CIRT

Estimated study end: 2019.5



Cardiovascular Inflammation Reduction Trial
2015.12~
enrolling 216 (7000)

Trans Am Clin Climatol Assoc. 2013; 124: 174–190.

Anti-inflammatory Interventions

Clinical trials of anti-inflammatory therapy in CVD

Drug	Target	Trial	Size	Sponsor	Status
A. Agents impacting on the IL-6 signalling pathway					
Canakinumab	IL-1β	CANTOS	10 000	Novartis	Enrolling
Methotrexate	IL-6,TNF	CIRT	7 000	NHLBI	Enrolling
Anakinra	IL-1Ra	IL-HEART	190	UK-MRC	Completed
Colchicine	multiple	LoDoCo	532	HRS, Aus	Positive
Tocilizumab	IL-6	Entracte	3 000	Hoffmann	Enrolling
Etanercept	TNF	Entracte	3 000	Hoffmann	Enrolling
B. Agents impacting on alternative inflammatory pathways					
Succinobucol	Ox-LDL	ARISE	6 144	AtheroGenics	Negative
Varespladib	$sPLA_2$	VISTA-16	5 000	Anthera	Negative
Darapladib	Lp-PLA_2	STABILITY	15 000	GSK	Enrolled
Darapladib	Lp-PLA_2	SOLID-TIMI-52	13 000	GSK	Enrolled
Inclacumab	P-Selectin	SELECT-ACS	544	Roche	Completed
Inclacumab	P-Selectin	SELECT-CABG	380	Roche	Enrolled

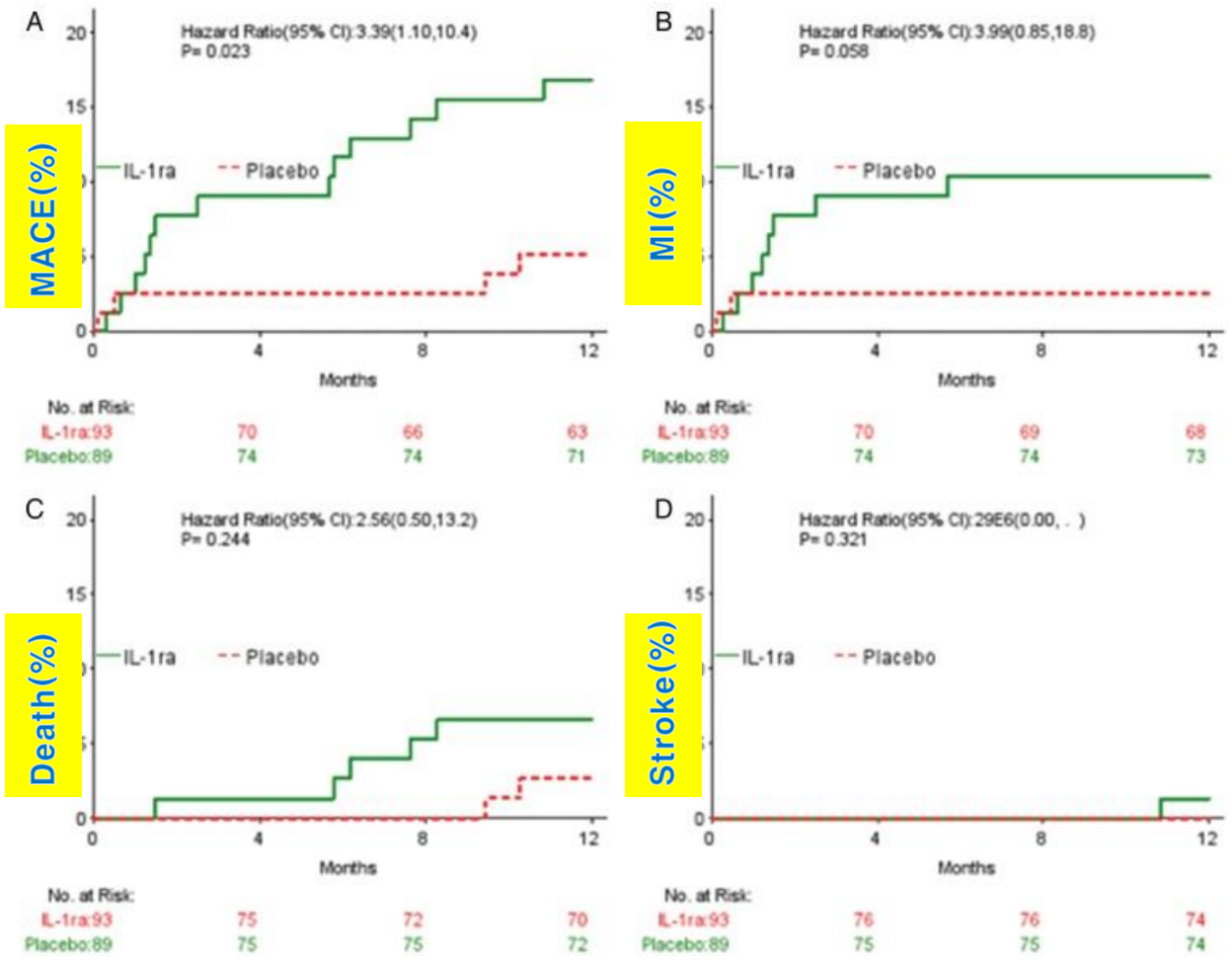
Eur Heart J 2014;35:1782–91

Anti-inflammatory Interventions

The effect of interleukin-1 receptor antagonist therapy on markers of inflammation in non-ST elevation acute coronary syndromes: the MRC-ILA Heart Study

A phase II, double-blinded, RCT recruited 182 NSTE-ACS patients

: negative



Eur Heart J 2015;36:377-84

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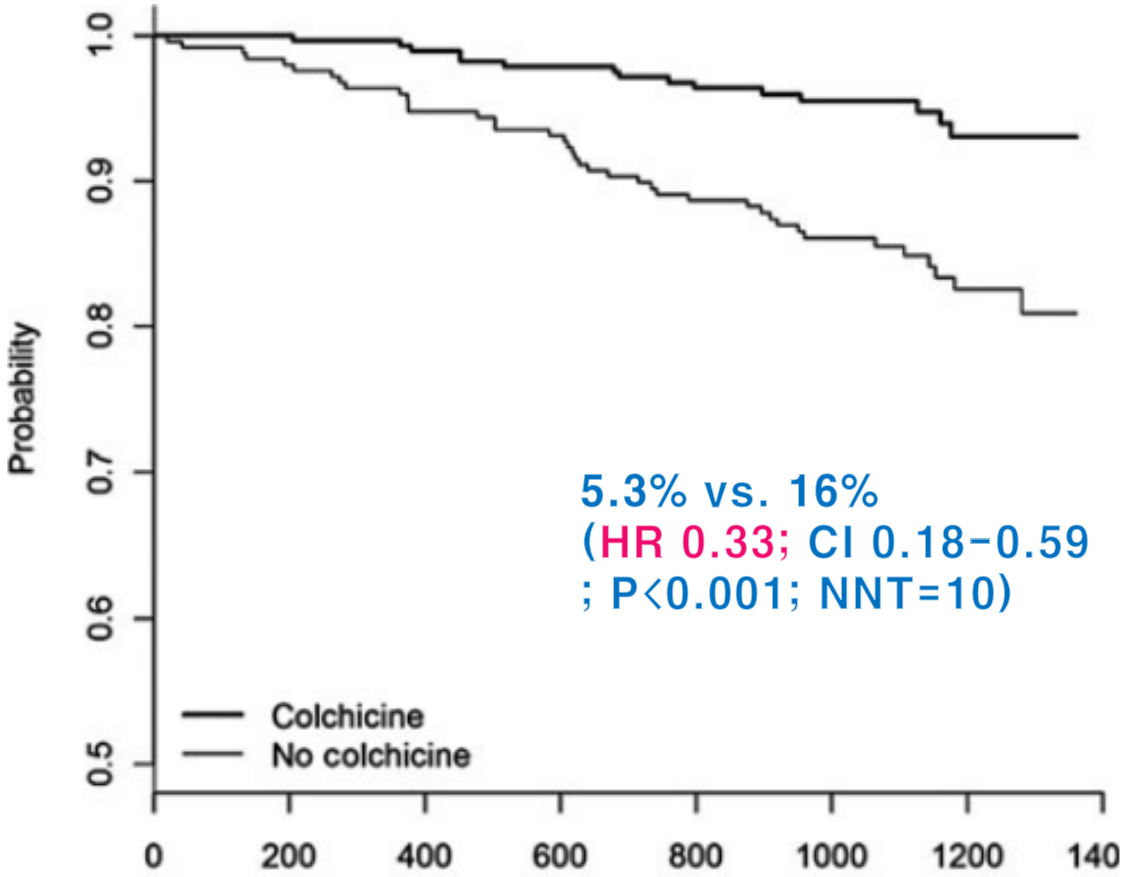
Colchicine	multiple	LoDoCo	532	HRS, Aus	Positive

- **Colchine** has several anti-inflammatory properties
  - Anti-tubulin effects inhibiting neutrophil function
  - Modest effect on NLRP3 inflammasome → ↓ CRP

Eur Heart J 2014;35:1782–91

Anti-inflammatory Interventions

- **LoDoCo trial**
  - 532 pts with stable CAD, PROBE open-label study
  - 1' EP=recurrent ACS, cardiac arrest, non-embolic stroke



- > 20% were intolerant & stopped Tx due to adverse GI effects
- **Large-scale, fully blinded trials of colchicine in secondary prevention are warranted**

Am J Cardiol 2011;108:1362–1370

Anti-inflammatory Interventions

Clinical trials of anti-inflammatory therapy in CVD

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- Moderate-severe RA pt (>=50 yr) with Hx of CAD or multiple CV risk factors
- IL-6 (tocilizumab) vs. TNF (etanercept) target, No placebo
- Whether results can generalize is uncertain

Eur Heart J 2014;35:1782–91

Anti-inflammatory Interventions

Clinical trials of anti-inflammatory therapy in CVD

- ARISE (Pt with recent ischemia, phase III, RCT, n=6144) 1'EP=MACE
  - Either **succinobucol (anti-oxidant)** or placebo
  - **No benefit** for 1'EP
  - Increased AE: hemorrhage, lipid, HTN, AF

- VISTA-16 (ACS pt, double-blind RCT, n=5145) 1'EP=MACE
  - Either **varespladib (sPLA2 inhibitor)** or placebo
  - Stopped early due to **no benefit**

B. Agents impacting on alternative inflammatory pathways

Succinobucol	Ox-LDL	ARISE	6 144	AtheroGenics	Negative
Varespladib	$sPLA_2$	VISTA-16	5 000	Anthera	Negative
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Lancet 2008;371:1761-8
JAMA 2014;311:252-60

Anti-inflammatory Interventions

Clinical trials of anti-inflammatory therapy in CVD

- STABILITY & SOLID-TIMI 52 (phase III, RCTs)
  - Efficacy and safety of the **darapladib (Lp-PLA2 inhibitor)**, in patients with stable CHD and ACS, respectively
  - In both studies, darapladib **failed** to reduce the risk of major coronary events as compared to placebo.
  - Significantly higher rates of drug discontinuation, and adverse side effects such as diahrrea and malodorous feces, urine, and skin, as compared to placebo
  - Suggest that **Lp-PLA2** may be a **biomarker** of vascular inflammation **rather than a causal** pathway of cardiovascular (CV) diseases.

B. Agents impacting on alternative inflammatory pathways

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Glob Cardiol Sci Pract.2015;2015:6

Anti-inflammatory Interventions

Clinical trials of anti-inflammatory therapy in CVD

- SELECT-ACS (Phase II, NSTEMI, n=544)
  - **Inclacumab (P-selectin antibody) or placebo**
  - 5 mg/kg-no effect ; 20 mg/kg- ↓Troponin, CK-MB
- SELECT-CABG (Phase II, scheduled CABG, n=384)
  - 1'efficacy= % of SVG stenosis >50% @1yr
  - **Inclacumab (P-selectin antibody,** 20 mg/kg**) or placebo**
  - **No benefit** for 1'Efficacy (placebo 26.4% vs. test 22.4%), MACE

Etanercept	TNF	Entracte	3000	Hoffmann	Enrolling
B. Agents impacting on alternative inflammatory pathways					
Succinobucol	Ox-LDL	ARISE	6144	AtheroGenics	Negative
Varespladib	$sPLA_2$	VISTA-16	5000	Anthera	Negative
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J Am Coll Cardiol 2013;61:2048–55
J Am Coll Cardiol 2016;67:344-6

Anti-inflammatory Interventions

Immunization for Atherosclerosis

Kuang-Yuh Chyu, MD, PhD,

Model	Immune component	Effect on atherosclerosis
ApoE/RAG-1	T and B cell deficiency	Decrease; no effect if mice on high-fat diet
ApoE/RAG-2	T and B cell deficiency	No effect
LDLR/RAG-1	T and B cell deficiency	Delayed
ApoE/SCID	T and B cell deficiency	Decrease
ApoE/CD1d	Natural killer T cell deficiency	Decrease
ApoE/CD1d	Natural killer T cell deficiency	Decrease
LDLR/complement 3	Defect in classical and alternative pathways	Increase
ApoE/complement 5	Defect in terminal complement complex	No effect
ApoE/Myd-88 or ApoE/TLR4	Defect in innate immunity	Decrease
ApoE/Myd-88	Defect in innate immunity	Decrease
Splenectomy in ApoE-/- mice	Defect in adaptive immunity	Increase
B cell deficiency in LDLR-/- mice	Defect in adaptive immunity	Increase

Curr Atheroscler Rep. 2007;9:104-9

Anti-inflammatory Interventions

Immunization for Atherosclerosis

Kuang-Yuh Chyu, MD, PhD,
Jan Nilsson, MD, PhD, and Prediman K. Shah, MD

List of immunogens that have been used in immunization studies

Heat shock protein 65 [60–62]

β2-glycoprotein I [63]

Atheroprotection via active immunization

Native low-density lipoprotein [31,64]

Malondialdehyde–low-density lipoprotein [65,66]

Apolipoprotein B-100 peptides [36,37]

Phosphorylcholine head group on oxidized phospholipid [11]

Cholesteryl ester transfer protein [49,67]

Curr Atheroscler Rep. 2007;9:104-9

<Anti-inflammatory Interventions> _1

- The inflammatory system is simultaneously redundant, compensatory, and crucial for survival
- Evaluation of risks as well as benefits must drive the development of anti-inflammatory therapies in this class (eg. COX-2 inhibitor)
- However, as proven among these with RA and inflammatory bowel disease, long-term treatment with systemic anti-inflammatory agents can be accomplished safely

- In addition to the therapies described here, multiple alternative approaches to inflammation inhibition are being developed
  - targeted steroid delivery systems such as Nanocort
  - infusion of reconstituted HDL-c
  - imaging-based approaches to inflammation detection and targeted intervention
  - Gene-based therapy

<Anti-inflammatory Interventions>_2

- The near future will see publication of several massive trials directly testing the inflammatory hypothesis of atherosclerosis

- The core results of these trials—including those that do and do not inhibit the central IL-1, TNF-a, and IL-6 pathway—will tell us a great deal about whether anti-inflammatory therapies will eventually become a cornerstone of vascular risk reduction

- If successful, these trials will usher in a new era in which the treatment of chronic vascular disease moves beyond the reduction of LDL-cholesterol alone.

감사합니다.

GURO HOSPITAL