How to get the most from “liquid gold” samples

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Biomarkers

- A major area of confluence between
  - Basic
  - Clinical, and
  - Population health
  - Research and Strategies

Enormous and often asynchronous growth in knowledge in these different domains

Why Determine a Biomarker(s)

- Can biomarker be measured : accurately and reproducibly, with assay that is accessible, and allows high throughput at reasonable cost?
- Does biomarker add new information : strong and consistent association with outcome(s), adding to usual methods of assessment
- Can aid clinical management : superior performance to existing diagnostic tests, associated risk is modifiable with specific therapy, or biomarker-guided therapy or monitoring enhances care
- It may enable identification of a new therapeutic target, eg from genetic epidemiology

LIPID Biomarker Analyses

Samples taken at			Used in
Baseline			b. Definitive Studies
Year	1	Plasma	Definitive Studies
	2		
	4		a. Pilot Studies
	5		Pilot Studies
	6		Pilot Studies
Close-out		Plasma, whole blood	a. Definitive Studies & REST STORED

EVALUATION OF INCREMENTAL GAIN
(and the EVOLUTION of METHODOLOGY)

- Establish association: Hazard ratio
- Improve discrimination: Sensitivity, specificity, C-statistic (ability to distinguish between two individuals who will and who will not develop an event)
- Improve calibration: Goodness of fit. Compare deciles of observed and predicted risk
- Improve risk classification of low/intermediate/high risk groups: Net reclassification index (% moved to different group). Limitations now recognised.
- Mediation analyses

With aim of improved management decisions and outcomes

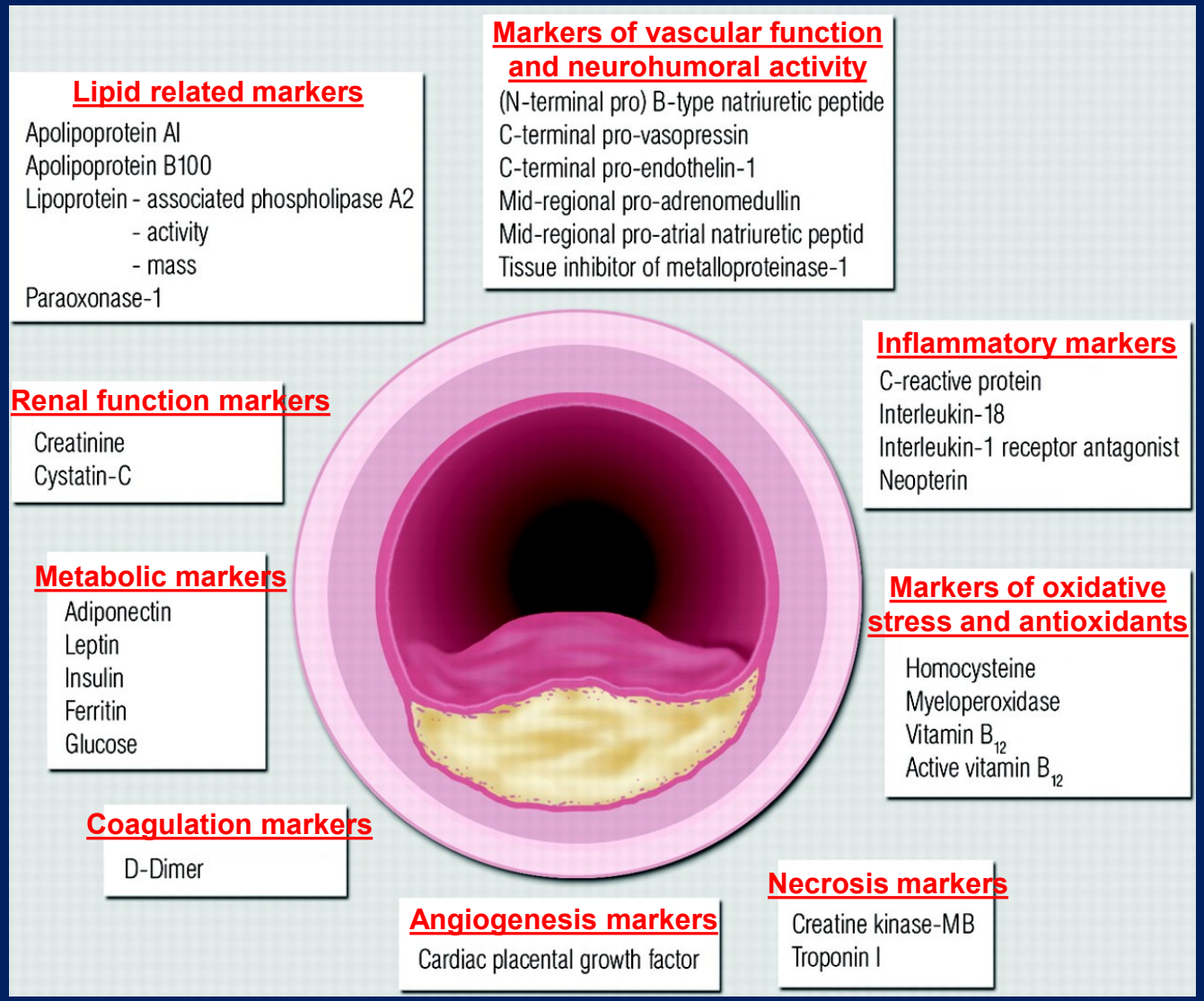
Proportion of Treatment Effect Explained by On-Study Lipid Levels

Lipid Parameters	Risk Reduction,† % (95% CI)	*P*	PTE, % (95% CI)
CHD death and nonfatal MI (n=8202)*			
None	25 (14–34)	<0.001	NA
Total cholesterol	14 (−1–26)	0.069	48 (9–88)
LDL cholesterol	13 (−2–26)	0.094	52 (10–94)
HDL cholesterol	22 (12–32)	<0.001	11 (2–20)
Triglycerides	23 (12–32)	<0.001	9 (1–17)
Apolipoprotein A1	22 (12–32)	<0.001	11 (3–19)
Apolipoprotein B	9 (−6–22)	0.233	67 (24–110)
Total cholesterol, HDL	9 (−7–22)	0.267	67 (27–106)

Simes et al for LIPID Investigators. Circulation. 2002;105:1162-1169.

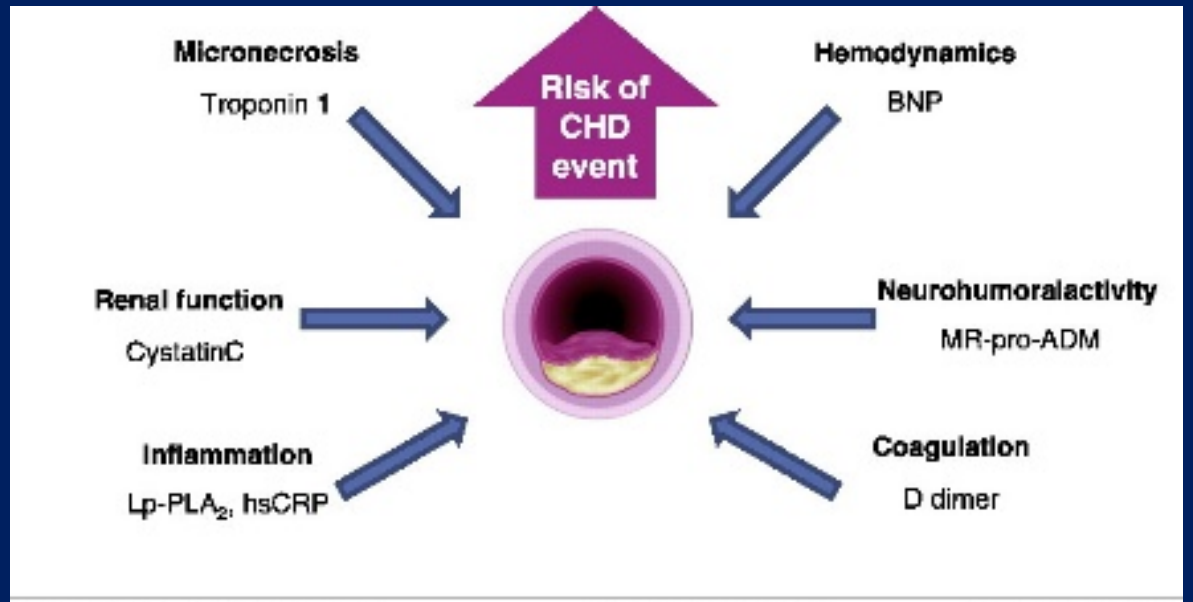
LIPID Biomarker Analyses: Important Collaborations

Biomarkers in the MORGAM Cohorts



Blankenberg S et al. Circulation 2010; 121: 2388-2397

LIPID Biomarker Analyses : Summary Graphic



Pathophysiological pathway	Biomarker	Baseline prognostic			Change to 1 year prognostic
		Individual (Figure 1)	NRI* (Table 3)	Multivariable (Figure 2)	Multivariable (Figure 4)
Micronecrosis	Sensitive TN1	Yes	5.5%	Yes	Yes
Hemodynamics	BNP	Yes	4.3%	Yes	Yes
Renal function	Cystatin C	Yes	2.5%	Yes	
Coagulation	D-dimer	Yes	0.6%	Yes	
Neurohumoral	MR-pro-ADM	Yes	1.5%	No	
Inflammation	hsCRP	Yes	0.3%	No	
Inflammation	Lp-PLA$_2$ activity	No	–	No	Yes

Tonkin et al. Int J Cardiol 2015

Some Important Considerations

Biological plausibility in itself is not enough

Carefully distinguish a risk factor and risk marker

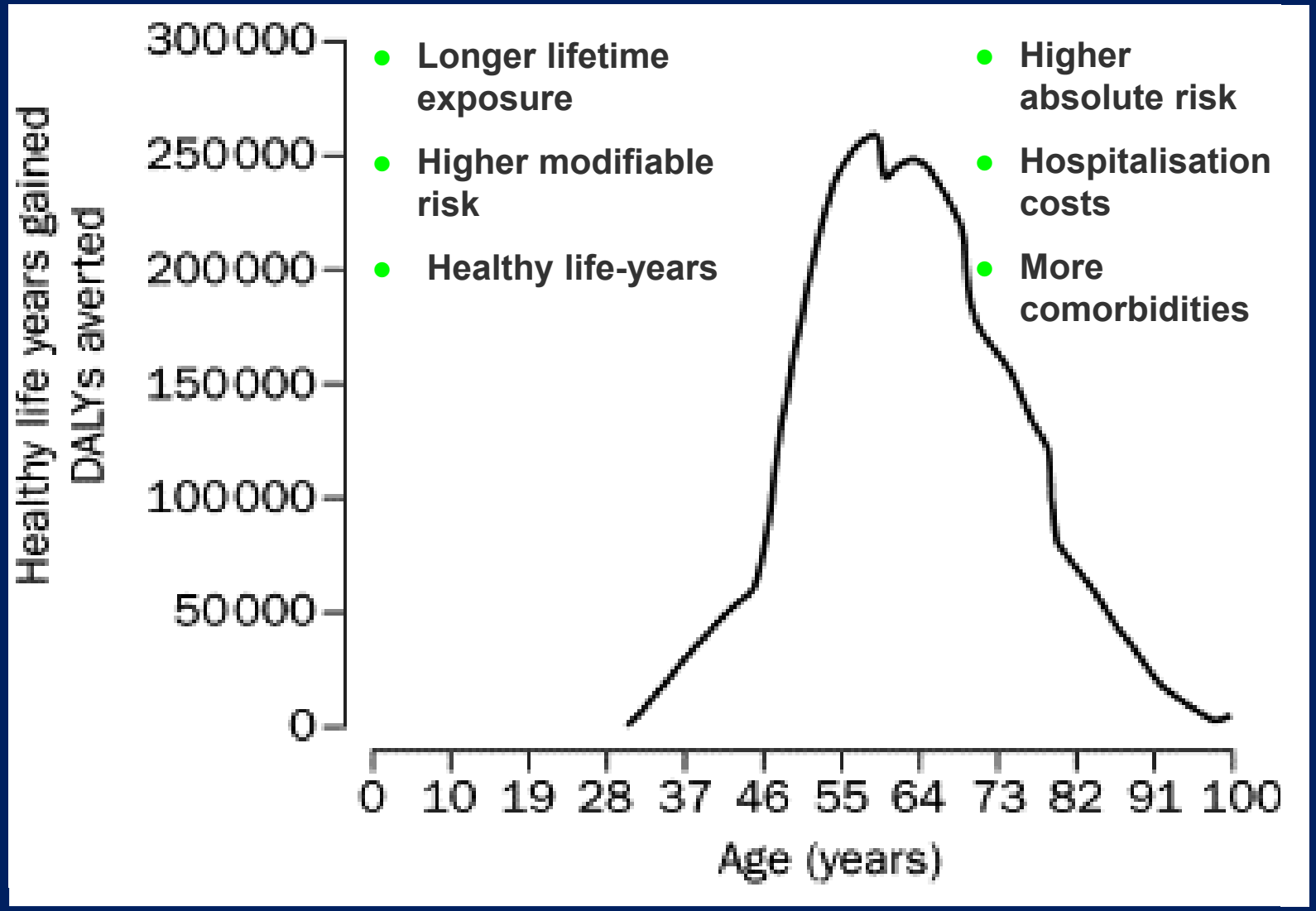
Frequent correlations between markers

The need to consider and account for what are often many comparisons

Document analysis and statistical plan before embarking on analyses

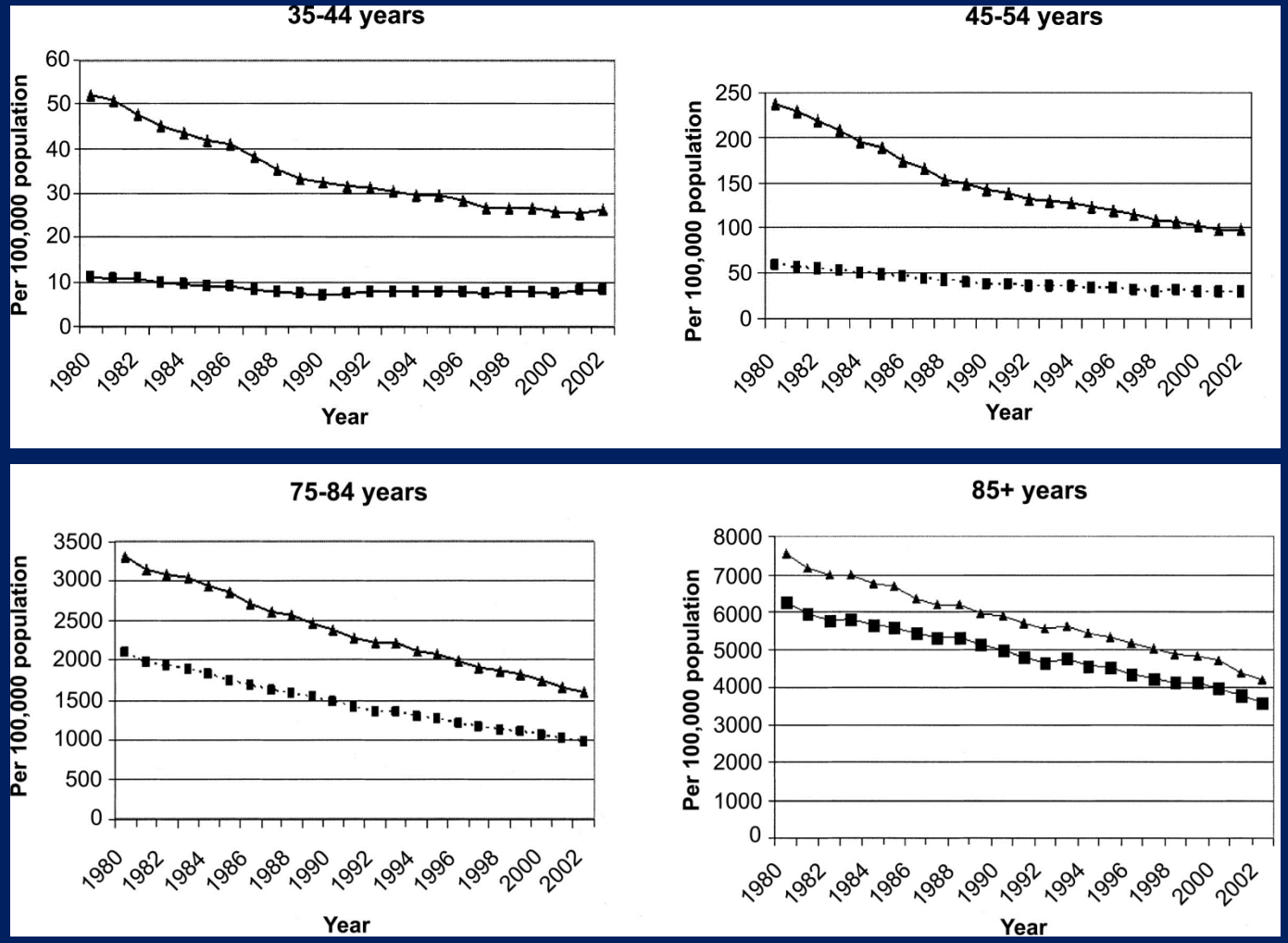
Any ethical implications ?

GBD Group: Benefits of CVD Intervention by Age



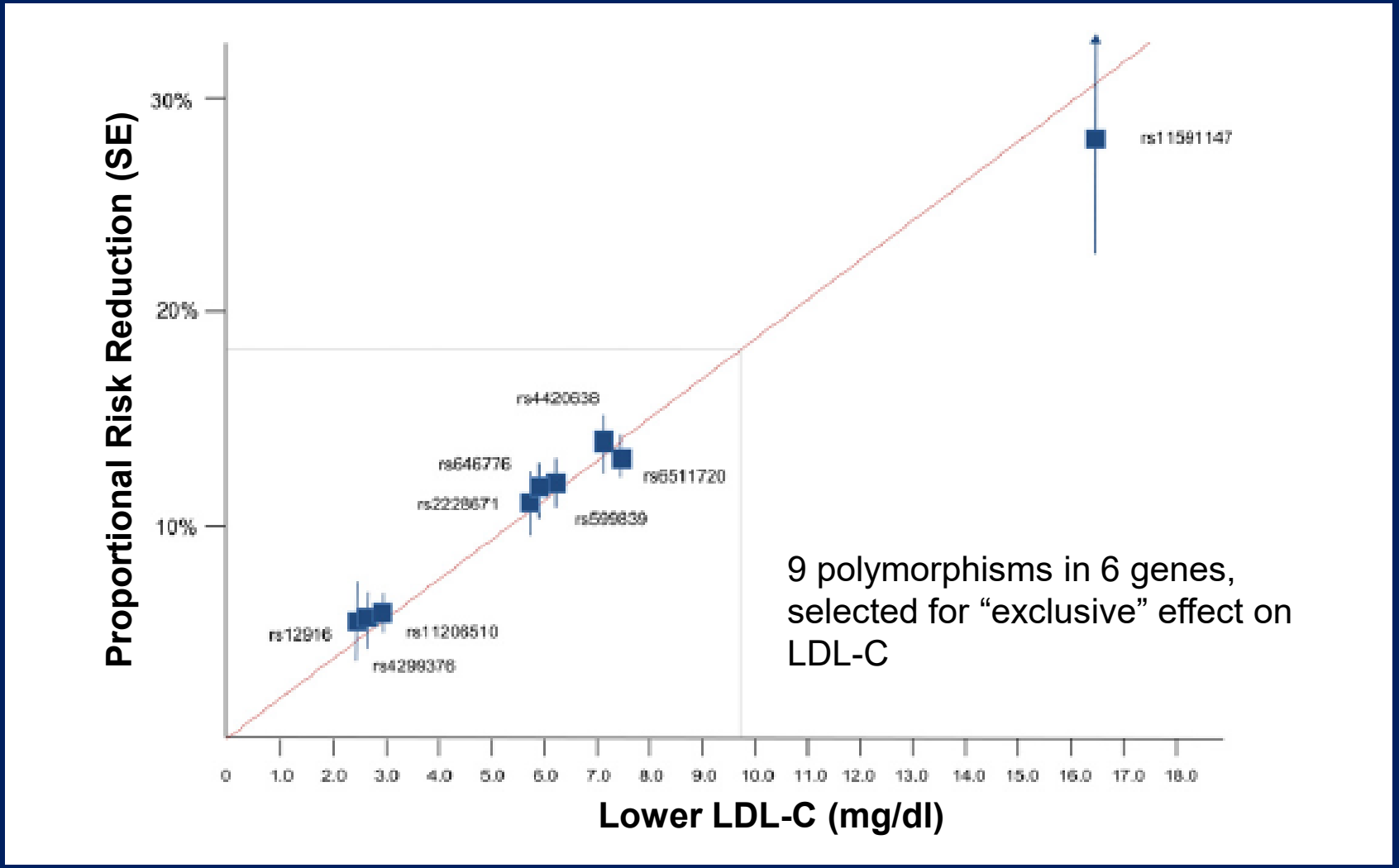
CJL Murray et al, Lancet 2003;361:717-725

Trends in Age-Specific CHD Mortality Rates: USA



Ford E & Capewell S. JACC 2007; 50: 2128-32

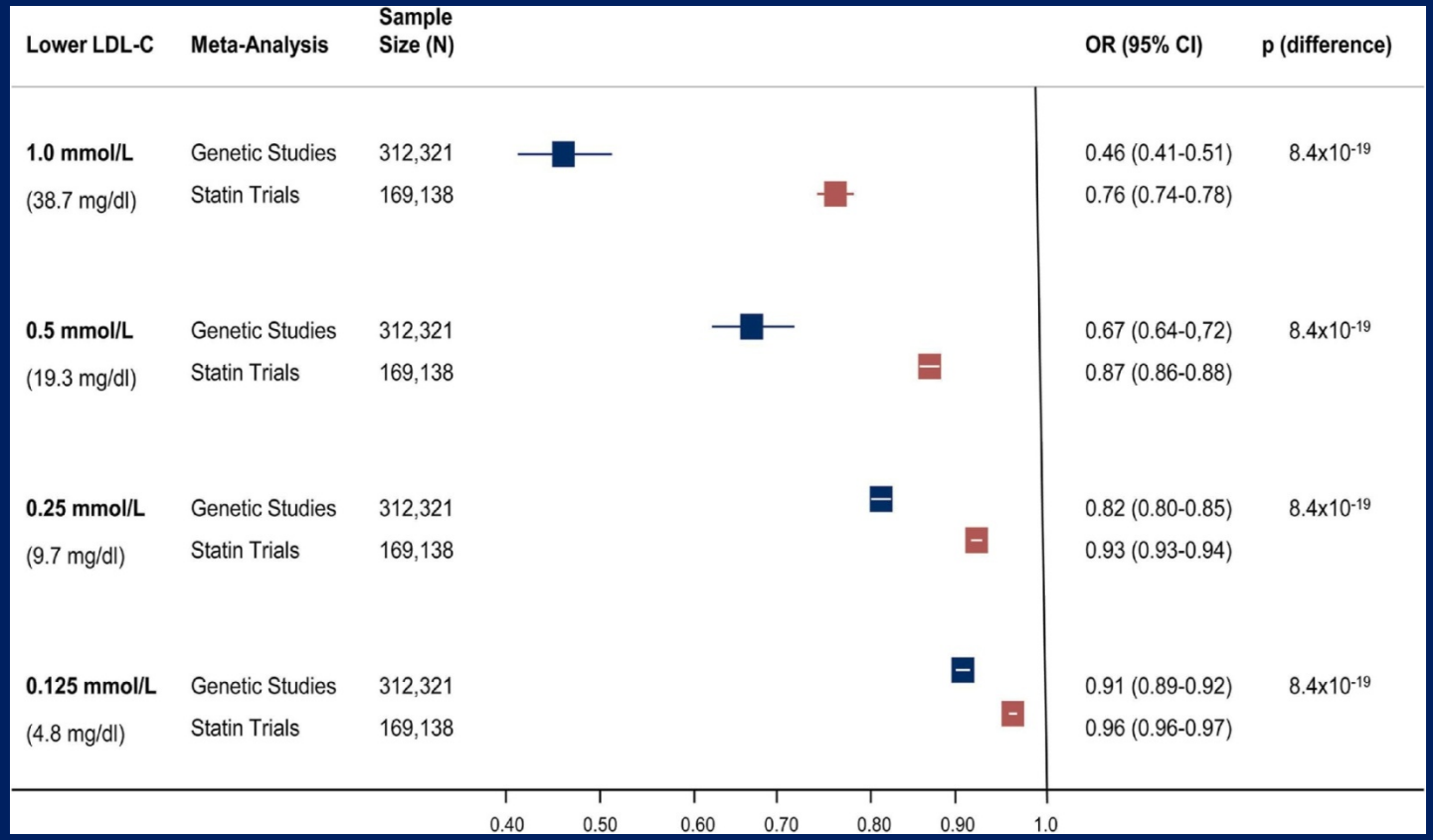
Genetic Epidemiology : Meta-analysis of log-linear effect of each unit long-term exposure to lower LDL-C on CHD risk



Ference BA et al. JACC 2012; http://dx.doi.org/10.1016/j.jacc.2012.09.017

Comparative CHD Risk Reduction of Life-long* and Later LDL-C Lowering: Mendelian Randomisation and CTTC (RCT) Analyses

*CHD = CVD death, nfMI, cor. revasc. (where possible)



*** 3-fold greater reduction in CHD risk/unit lower LDL-C**

Ference BA et al. JACC 2012; http://dx.doi.org/10.1016/j.jacc.2012.09.017

The “….omics” Revolution

The Pragmatic Approach

"Kill them. For the Lord knows who are His."

(When asked by a crusader how to distinguish the Cathars from the Catholics in Catalonia)

Arnaud Almaric, Abbott of Citeaux, ca 1209

Biomarker Application: Number Needed to Screen

NNS = (1/ [Risk* x Rel. Risk for Marker x RRR Treatment] /P**

where

*Risk predicted by base model

**P = Proportion of people at risk level (R) who have the marker

CM Rembold BMJ 1998; 317: 307-12

Number Needed to Screen : Modelled for JUPITER

- NNS = (1/ [0.10[1] x 1.5[2] x 0.44[1]]) /0.14[3]

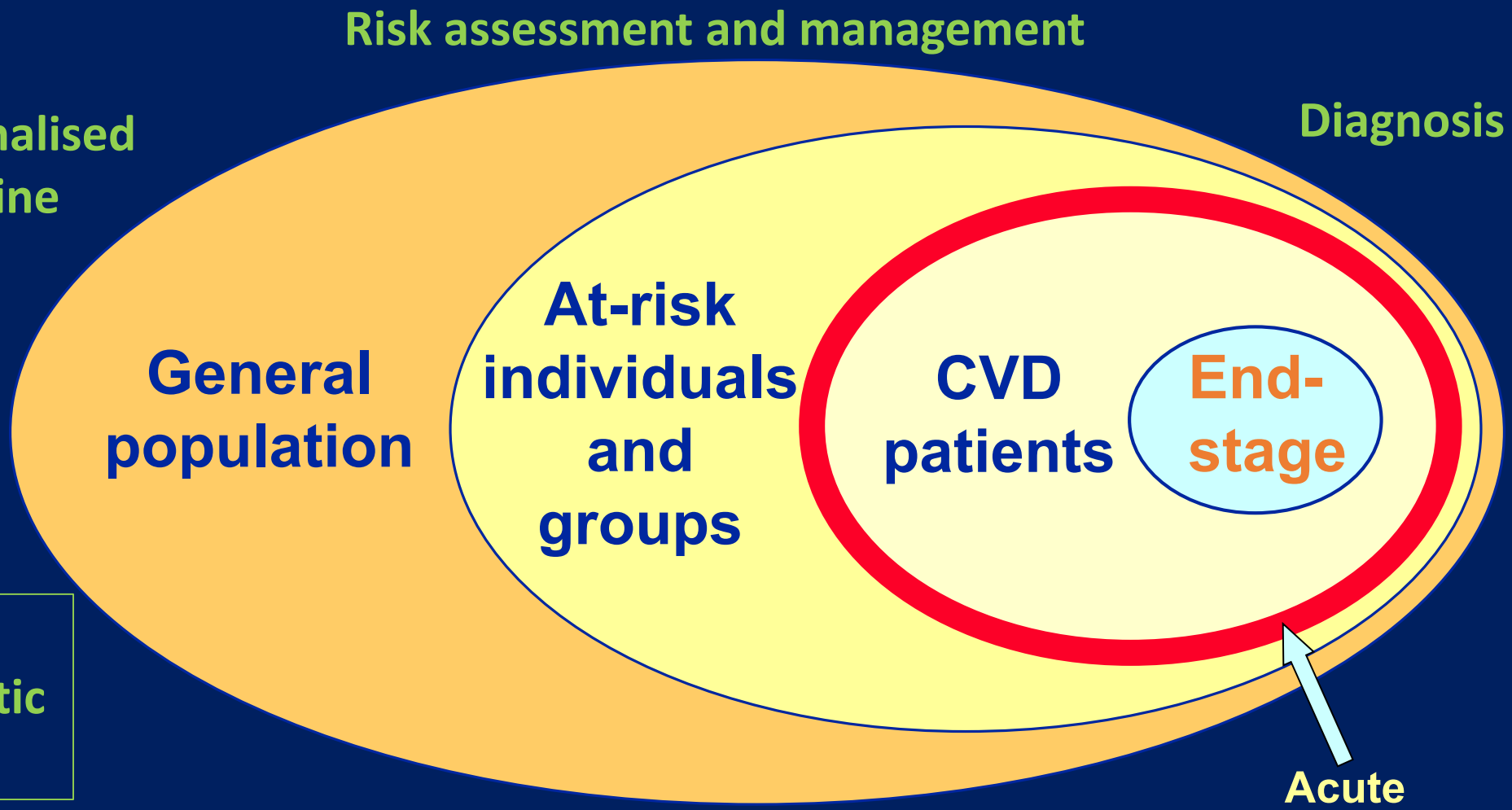
  = Approximately 90 subjects screened to prevent one major JUPITER CVD event over 10 years

[1] P. Ridker et al. NEJM 2008; 359: 2195-207

[2] J. Danesh et al. NEJM 2004; 350: 1387-97

[3] E.Spatz et al. Circulation Cardiovasc. Qual. Outcomes 2009; 2: 41-48

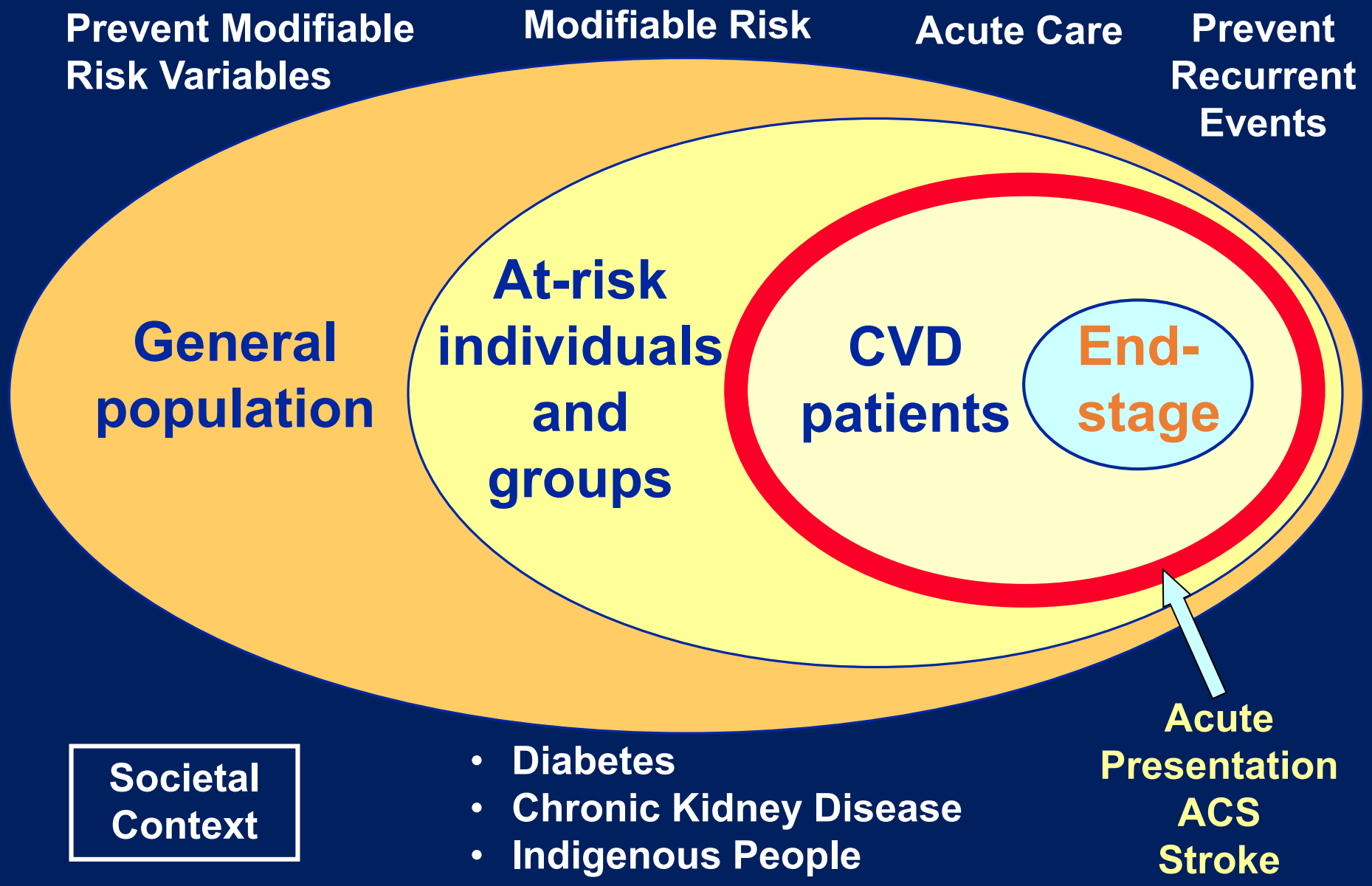
A CONCEPTUAL FRAMEWORK



Modified from A Tonkin, Atherosclerosis and Heart Disease, 2003

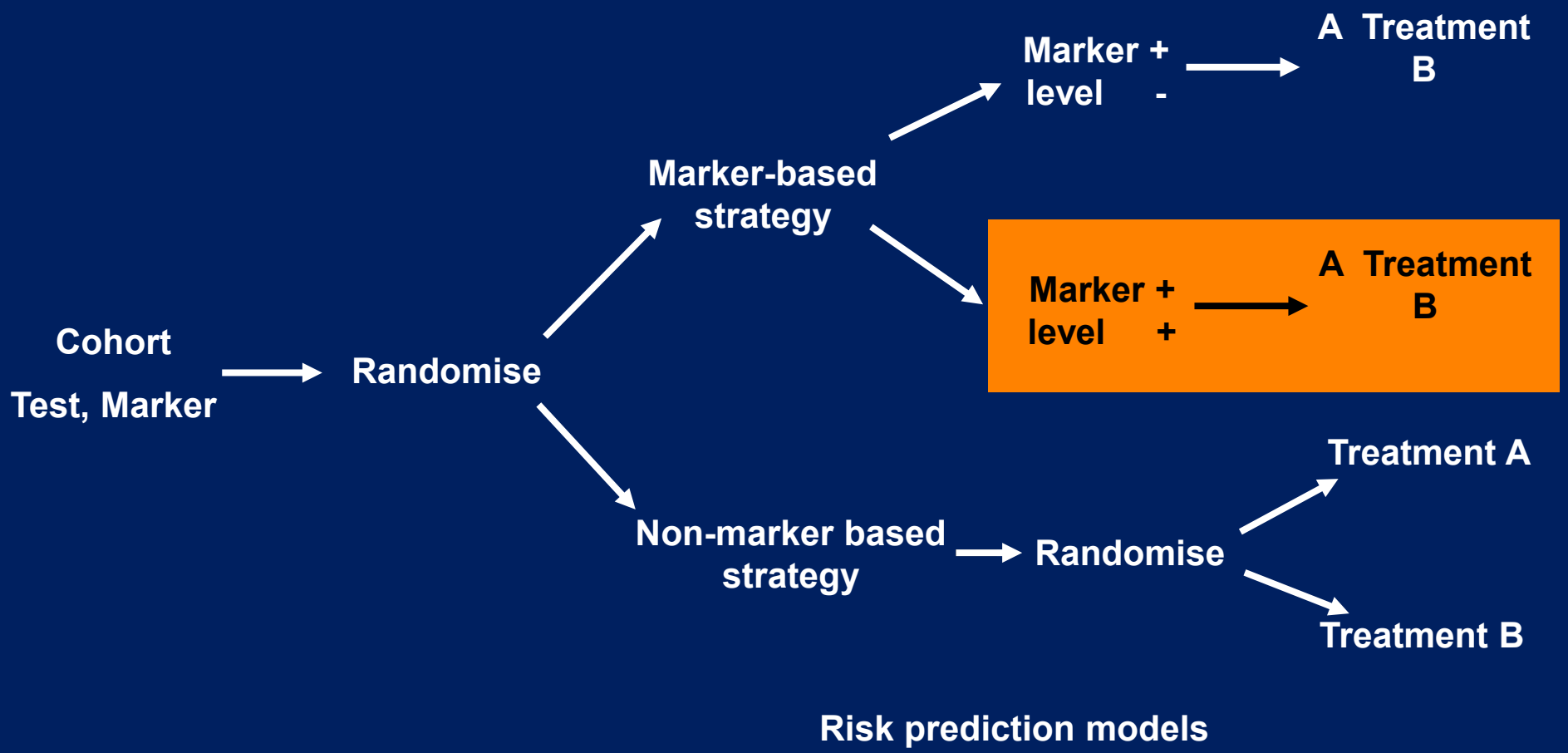
ACKNOWLEDGEMENT: LIPID Study Group

A FRAMEWORK FOR STRATEGIES



Modified from A Tonkin, Atherosclerosis and Heart Disease, 2003

TESTING IMPACT ON OUTCOMES



After Sargent et al. JCO 2005; 1387-97