

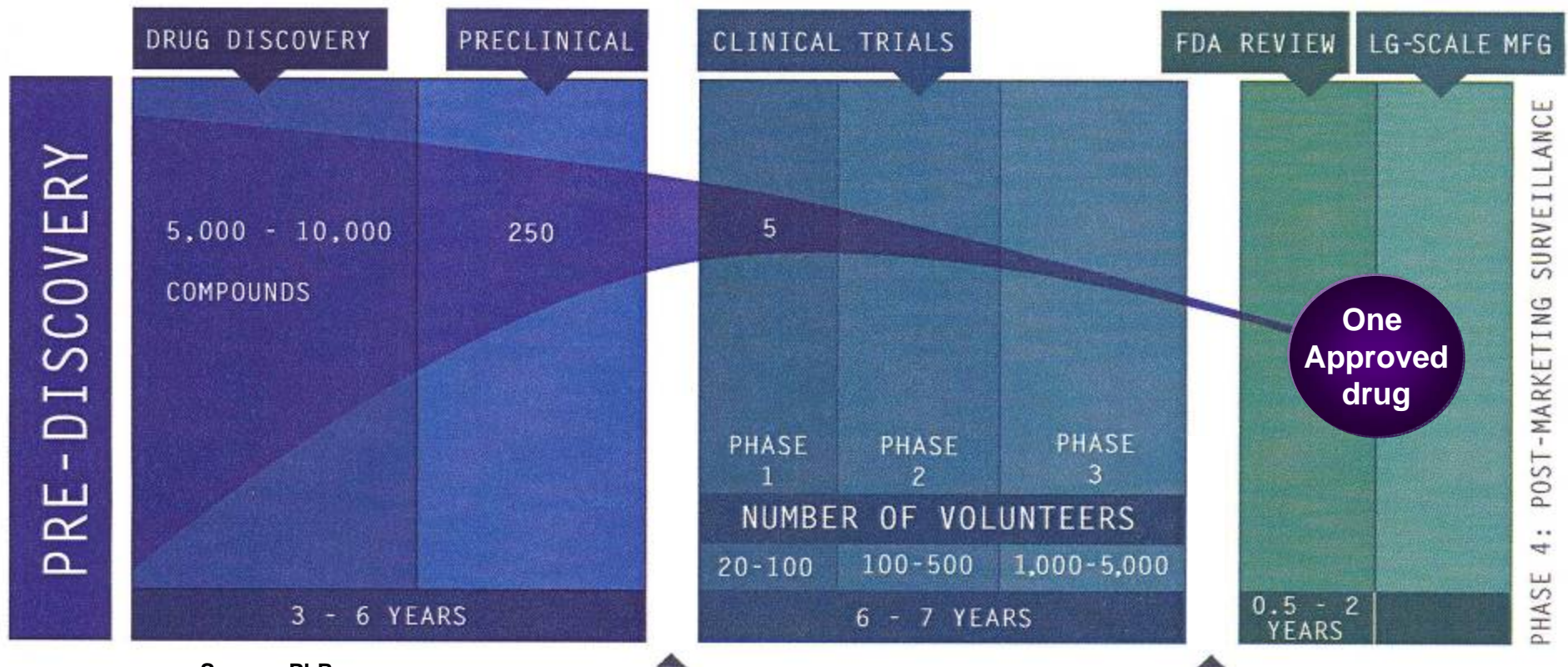


Working Together for the Future: Industry Perspective

**Catriona McMahon, MD
Vice-President, Medical Affairs
AstraZeneca Canada Inc.**

R&D Challenges: Time and Cost

- It takes 10 -15 years and costs an estimated \$500 million - 2 billion \$ (US) from the time a drug is discovered to when it is available for patients
- For every 5,000-10,000 compounds that enter the R&D pipeline, ultimately only one receives approval



Source: PhRma

Need to Accelerate Discovery and Development

Health Canada

Drug Development

Value to Public Health

Academia

Industry



Morbidity & Mortality Trials: “Gold Standard”

MAJOR Limitations

- Large number of trial volunteers: clinical endpoint trials in CVD may require 10,000 – 15,000 volunteers.
 - JUPITER: N=17,802
 - ONTARGET: N=25,620
- Long follow-up: a 4-5 years of follow-up mean 7-8 years for from start to finish.
- Direct Cost: dampen enthusiasm to develop new therapies

Clinical Realities

- Atherosclerosis is clinically asymptomatic during its early stages of disease:
 - Incomplete identification and treatment of risk factors
 - Adherence to therapies: challenging
- Studies on the incidence of vascular disease require lengthy follow-up and large patient numbers
- **Epidemiological, intervention-based studies and meta-analyses have all confirmed that atherosclerosis imaging (QCA, IVUS and B-mode ultrasound) is a useful surrogate marker of future cardiovascular disease**

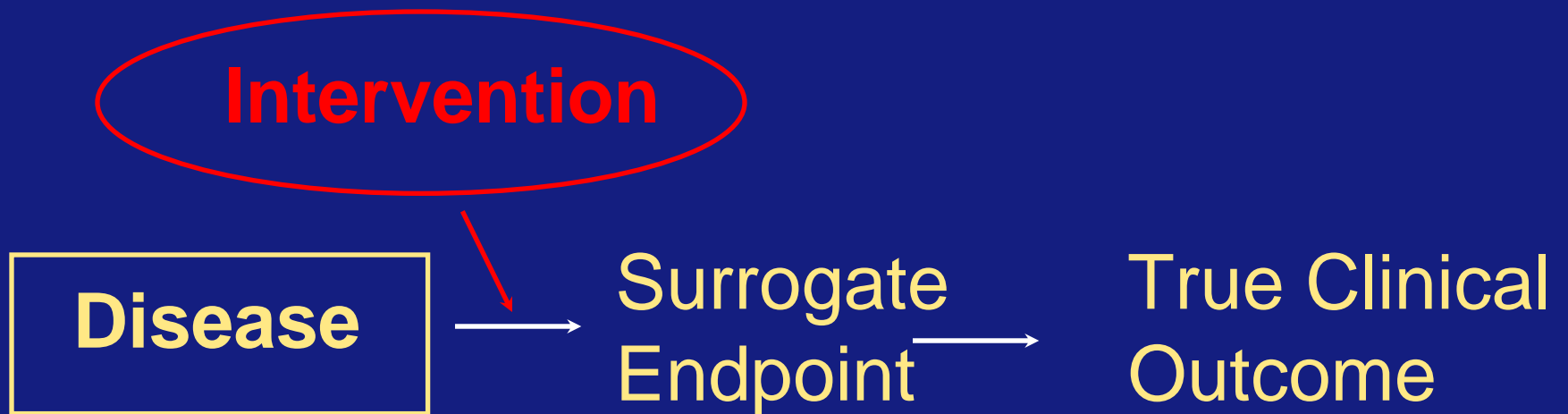
Moving Forward

1. Validated surrogate markers: NOT a replacement for well-conducted clinical outcome trials.
2. Need to facilitate both discovery and clinical development without sacrificing basic regulatory standards of safety and efficacy.
3. Share and recognize the need for the application of new tools (eg. Atherosclerosis imaging surrogate endpoints) in drug development and new indication licensing to address the epidemic of cardiovascular diseases.

Thank you!

Catriona.McMahon1@astrazeneca.com

Model for an Ideal Surrogate Endpoint



- All mechanisms of action of the intervention on the true endpoint are mediated through the surrogate.

Ref: Fleming, DeMets. Ann Intern Med. 1996

Clinicians use surrogates in daily practice

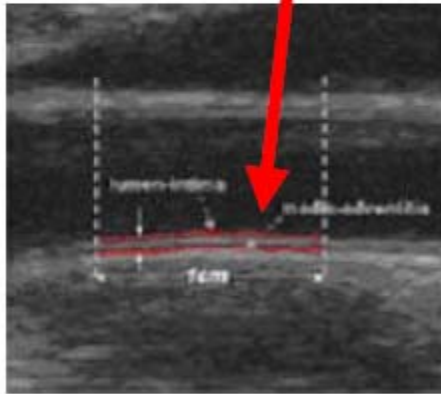
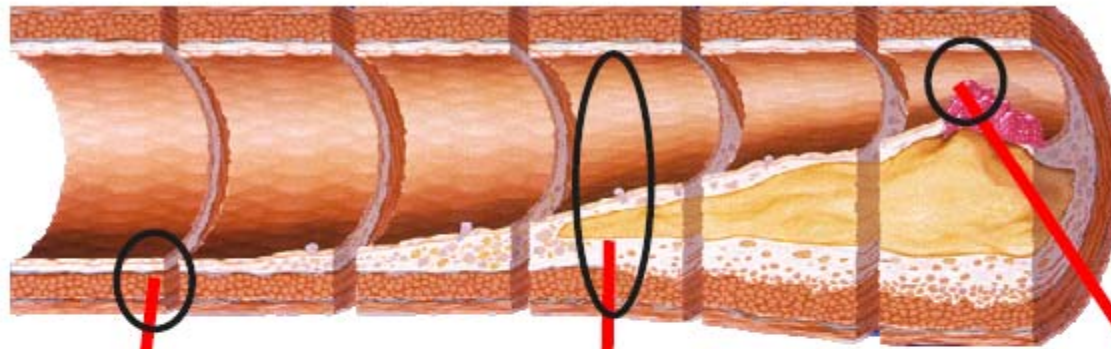
- **To select patients:**
 - Global risk scores algorithms
- **To guide and guide therapeutic treatments:**
 - LDL-C, Blood Pressure, Glucose, etc..



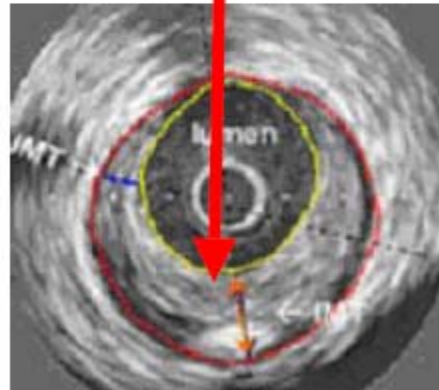
Atherosclerosis — a surrogate of clinical efficacy?

- There is a growing body of evidence linking positive effects on atherosclerosis with clinical outcomes
- Imaging techniques are widely used in clinical trials to examine atherosclerosis progression:
 - Can provide useful intermediate endpoints
 - Can be more useful than biomarker studies.¹
- Imaging trials of lipid lowering therapies have shown benefits with regards to disease progression that are consistent with benefits in myocardial infarction, stroke and death as reported in larger, lengthier cardiovascular outcomes trials.²

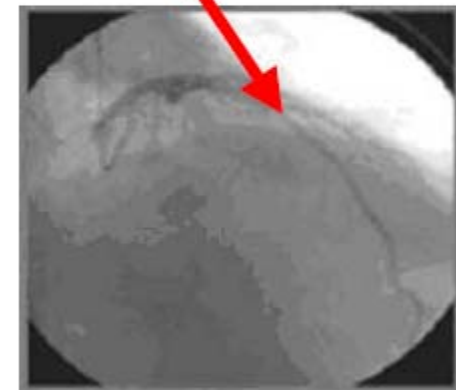
Imaging Technologies in Atherosclerosis: Surrogate of Disease



Carotid Ultrasound-IMT

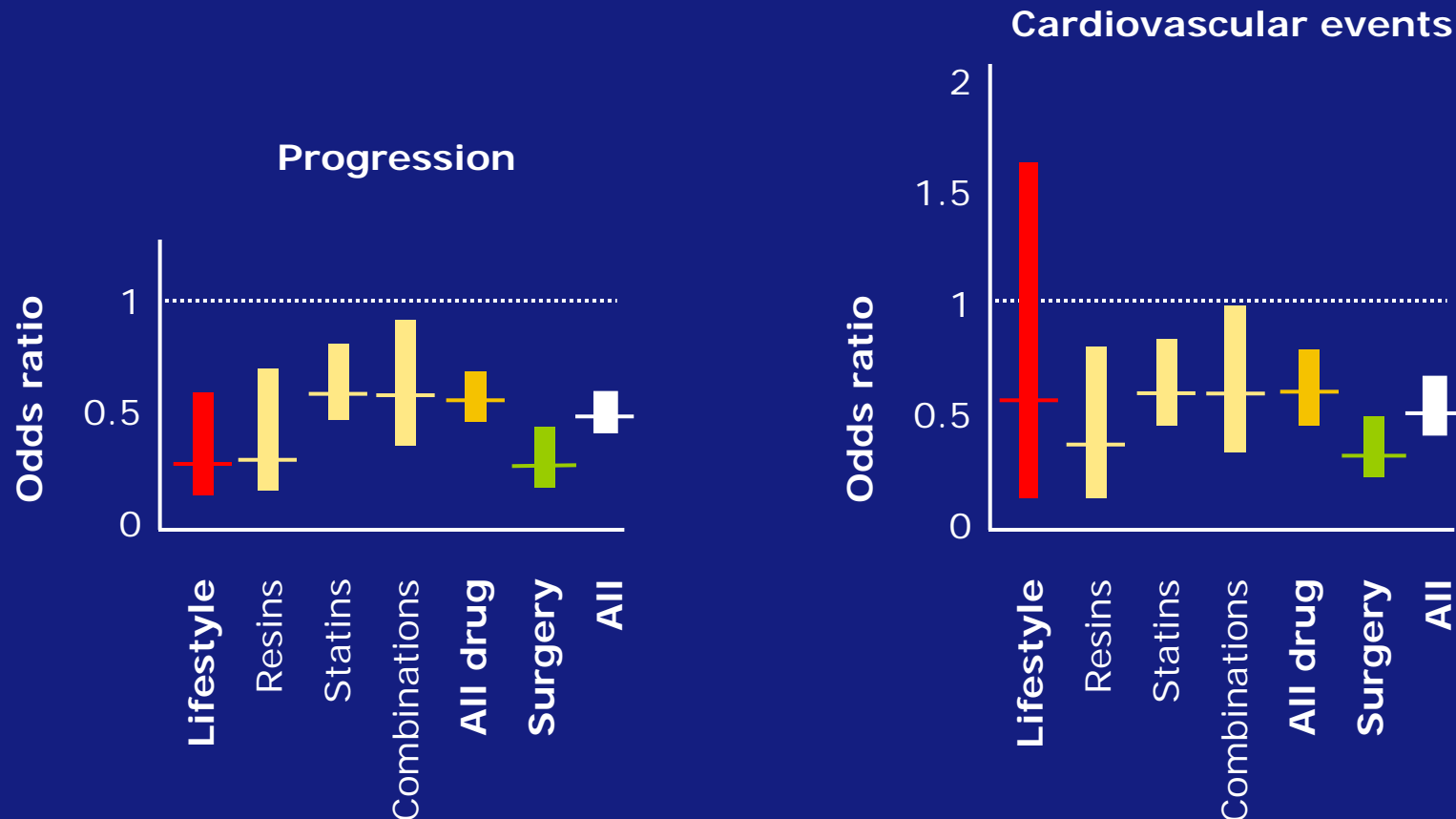


IVUS-PAV



QCA-% stenosis

Intervention has favourable effects on angiographic and clinical outcomes

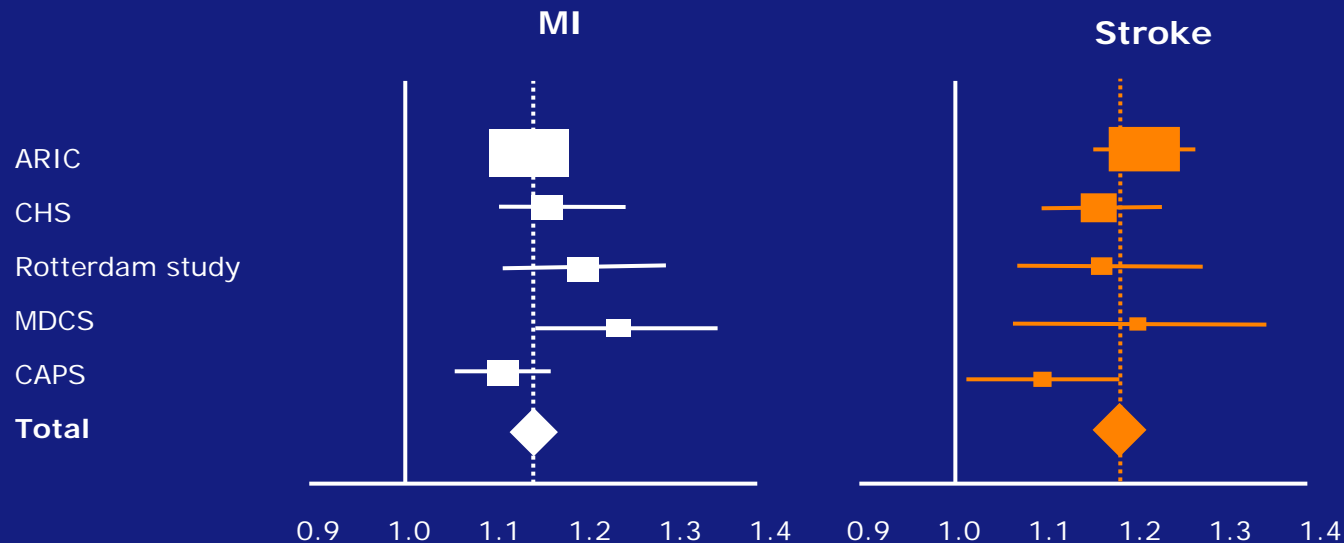


Odds ratios for angiographically determined disease progression and cardiovascular events by type of intervention and for all trials. Horizontal bars represent the 95% confidence intervals. If the 95% confidence interval crosses unity, the result is not statistically significant.

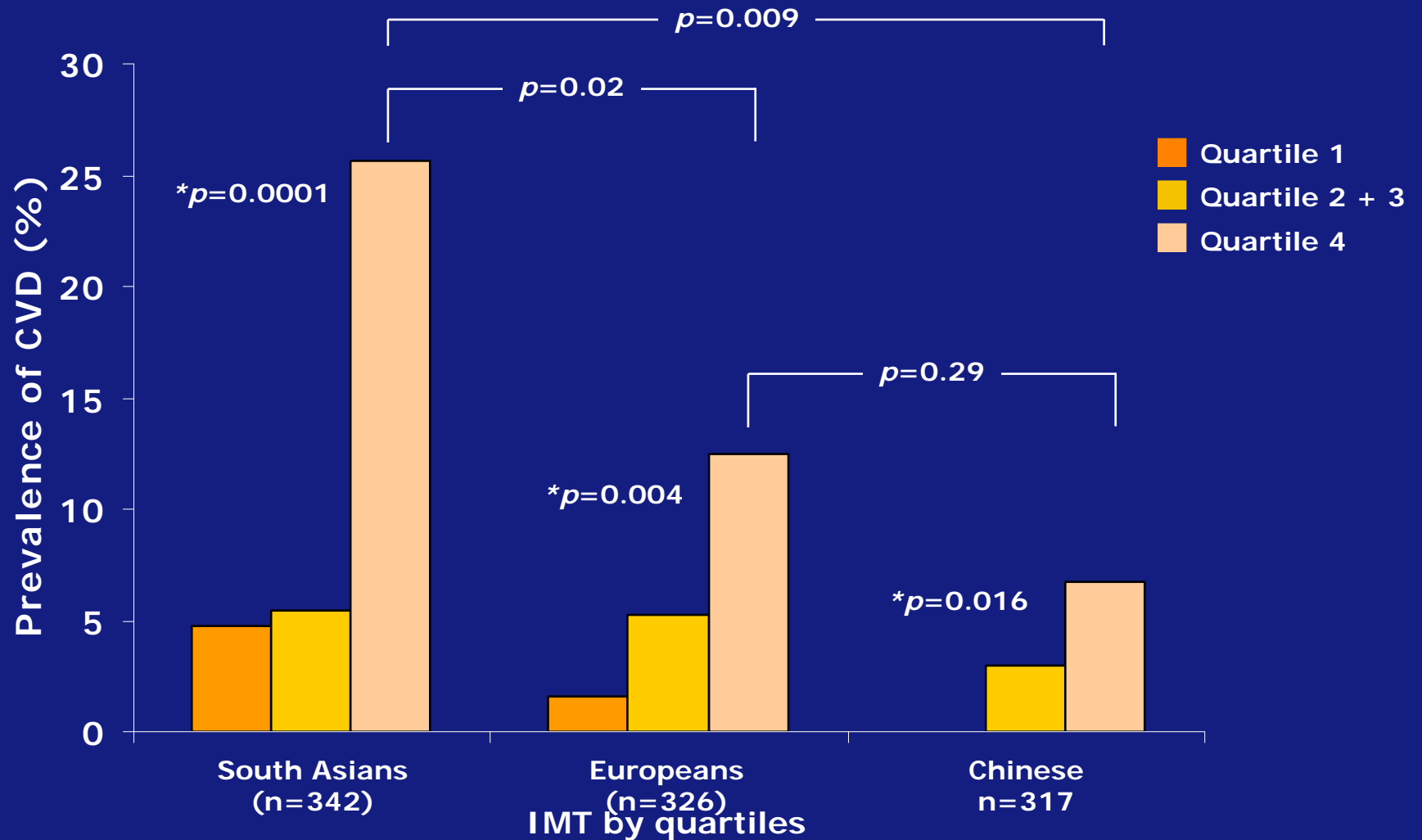
A meta-analysis of 8 IMT studies suggests that carotid IMT is a strong predictor of future vascular events

HR for MI and stroke per 0.1 mm difference in CCA IMT, adjusted for age and sex

	Myocardial infarction			Stroke		
	HR	[95% CI]	n	HR	[95% CI]	n
ARIC	1.13	[1.10–1.17]	13,204	1.21	[1.17–1.25]	14,165
CHS	1.15	[1.10–1.22]	4476	1.17	[1.12–1.23]	4476
Rotterdam study	1.19	[1.12–1.26]	2267	1.17	[1.09–1.26]	5479
MDCS	1.23	[1.14–1.33]	5163	1.20	[1.06–1.33]	5163
CAPS	1.11	[1.05–1.17]	5052	1.10	[1.02–1.19]	5052
Total	1.15	[1.12–1.17]	30,162	1.18	[1.12–1.17]	30,162



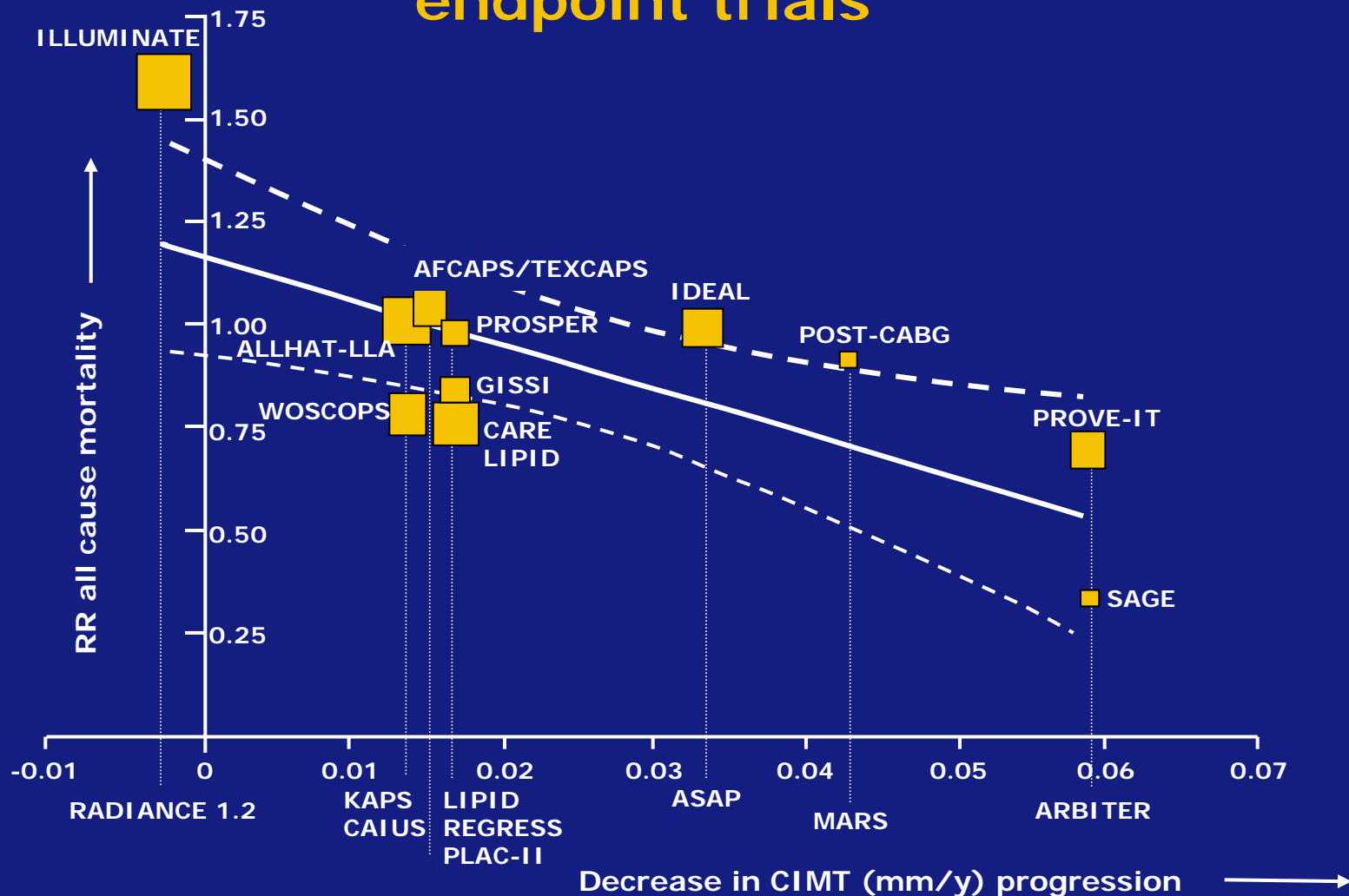
Increased IMT correlates with cardiovascular disease in three different ethnic groups living in Canada: SHARE



*p-value for trend across the quartiles of each ethnic group

Adapted from Anand S, et al. *Lancet* 2000; **356**:279–84.

Comparison of imaging trials and clinical endpoint trials



B-mode CIMT trials that assessed lipid-lowering drug efficacy are shown on the x-axis and are set out against relative risk (RR) of all-cause mortality from endpoint trials that have assessed similar lipid-lowering drugs (y-axis). The decrease in CIMT progression on the x-axis expresses the annualised difference between the active treatment group and the control group. The slope of the linear regression curve is $r = -0.70$ ($p = 0.01$).

Adapted from Duivenvoorden R, *et al.* *Curr Opin Lipidol* 2007; **18**:613–21. Reproduced with permission from Lippincott Williams & Wilkins.

Atherosclerosis Imaging

Regulatory filings for supplemental indications of slowing the progression of atherosclerosis using QCA or carotid ultrasound

Compound	Imaging Type: Endpoints	Supporting Studies	Imaging Indication
Lovastatin (Mevacor, 1995)	QCA: MLD, percentage of stenosis; cIMT, mean change in maximum IMT	QCA: CCAIT, MARS, FATS; cIMT, ACAPS	Slow progression of CAD
Pravastatin (Pravachol, 1996)	QCA: MLD; cIMT, mean change in maximum IMT, change in mean IMT	QCA: PLAC I, REGRESS; cIMT, PLAC II, REGRESS, KAPS	Slow progression of CAD
Simvastatin (Zocor, 1996)	QCA: MLD	QCA: MAAS	Slow progression of coronary atherosclerosis; reduce new lesion and total occlusions (Canada)
Fluvastatin (Lescol, 1997)	QCA: MLD	QCA: LCAS	Slow progression of CAD
Niacin (Niaspan, 1997) + resin	QCA: global change score, percentage of stenosis	QCA: CLAS, FATS	Slow progression or promote regression of CAD