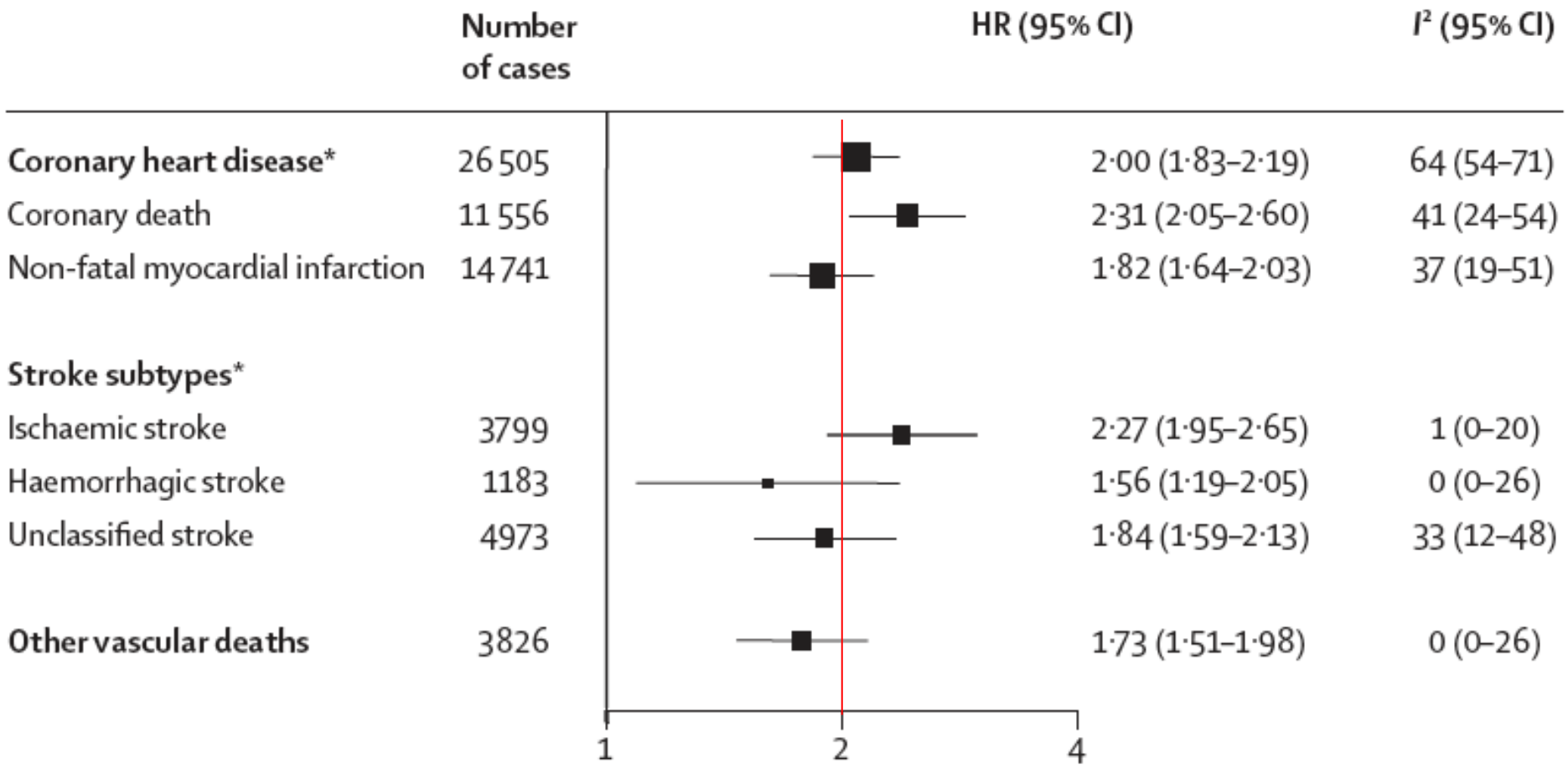
Cardiology Update® 2013

Update on Cardiovascular Outcome Trials in Diabetes

Rury R. Holman, FMedSci
NIHR Senior Investigator
11th February 2013

Radcliffe Department of Medicine
UNIVERSITY OF OXFORD
DIABETES TRIALS UNIT
The Oxford Centre for Diabetes, Endocrinology and Metabolism
NHS
National Institute for Health Research

Residual Vascular Risk in People with Diabetes

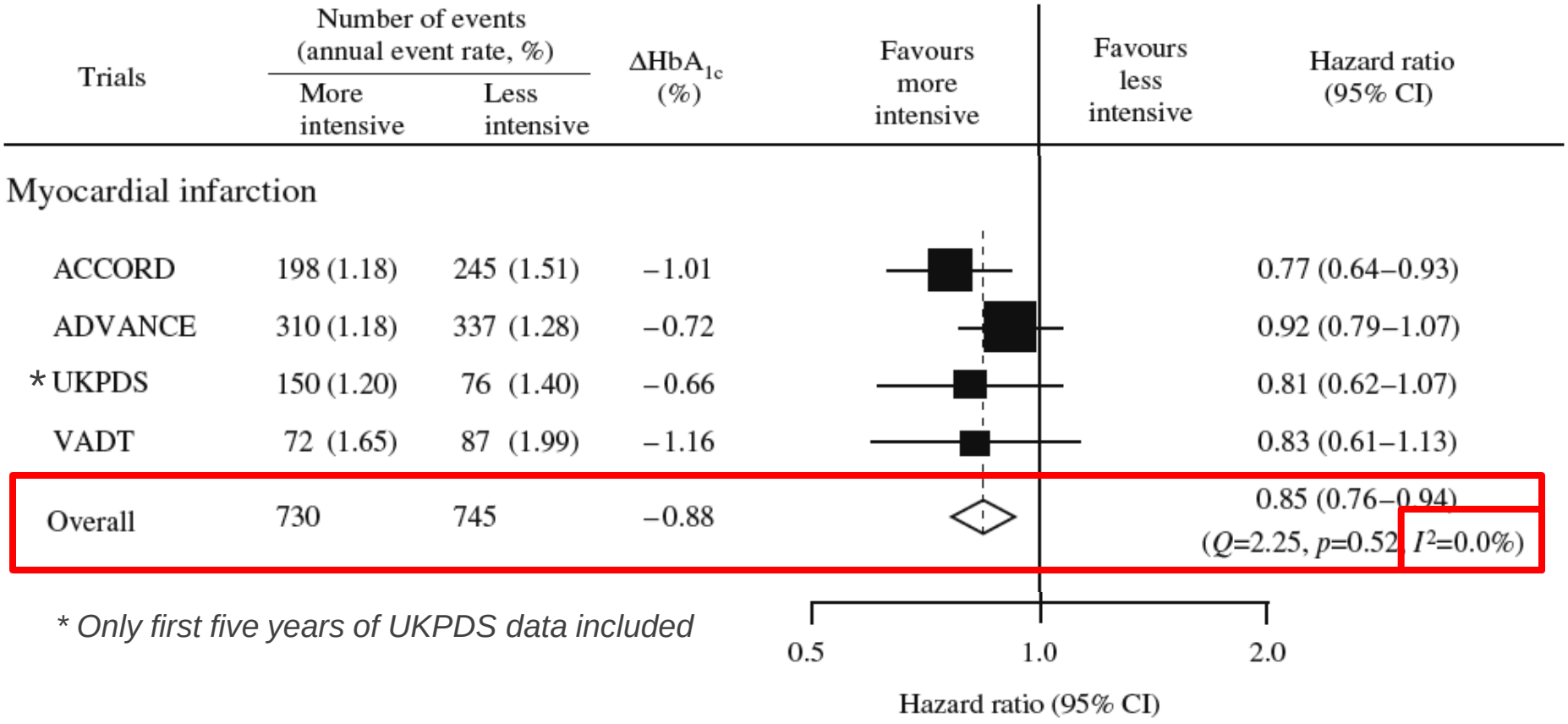


Analyses based on 530,083 participants from 102 prospective studies.
HRs adjusted for age, smoking status, body-mass index and systolic blood pressure, and, where appropriate, stratified by sex and trial arm.

Emerging Risk Factors Collaboration. Lancet 2010;375:2215–22

Impact of Glycaemic Lowering

ACCORD, ADVANCE, UKPDS & VADT meta-analysis of fatal and non-fatal myocardial infarction



** Only first five years of UKPDS data included*

CONTROL Group. Diabetologia 2009;52:2288-2298

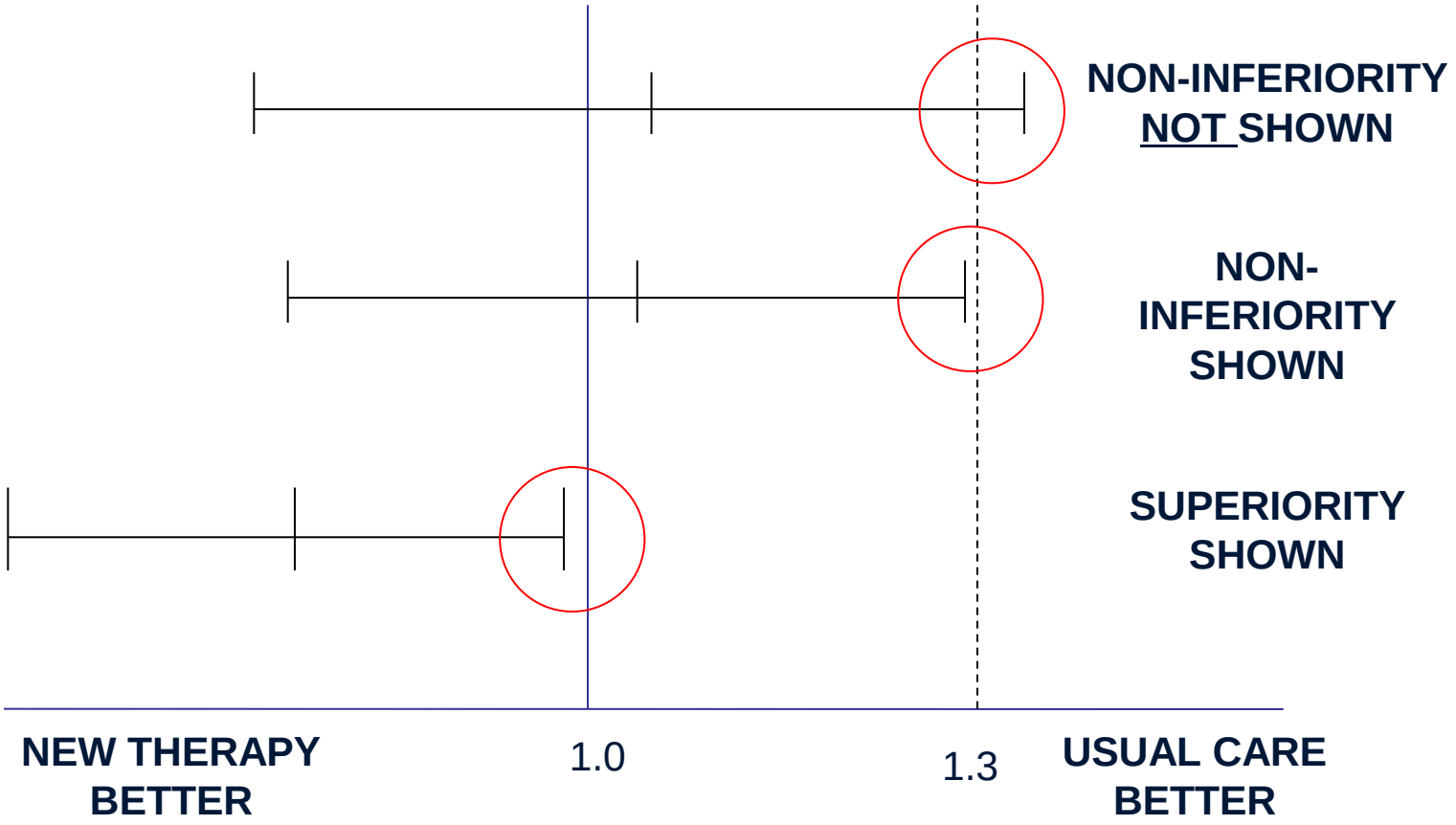
T2DM Therapy Safety Issues

TRIAL		DRUG	ISSUE	
UGDP	1969	Tolbutamide	MI	<0.05
UGDP	1971	Phenformin	MI	<0.05
Lilly	1988	Proinsulin	MI	n.s.
VA Study	1994	Intensive insulin	MI	n.s.
DPP	2000	Troglitazone	Liver	n.s.
Meta analysis	2005	Muriglitazar†	CVD	<0.03
ADOPT	2006	Rosiglitazone	Fractures	<0.01
Meta analysis	2007	Rosiglitazone*	CVD	<0.043
ACCORD	2008	Intensive glucose control	Death	<0.04

† *Nissen & Wolski, JAMA 2005;294:2581–6*
* *Nissen & Wolski, NEJM 2007;356:2457-7*

FDA Guidance for Industry Dec 2008

Before approval, a randomized cardiovascular event driven trial is required to rule out an unacceptable harm



Major CV Outcome Trials in T2DM

Pre 2000 (5)

- DCCT
- Kumamoto
- UGDP
- UKPDS

2000-2008 (8)

- ACCORD
- Advance
- Bari 2D
- Heart 2D
- NAVIGATOR
- ProACTIVE
- RECORD
- VADT

2009 to date (15)

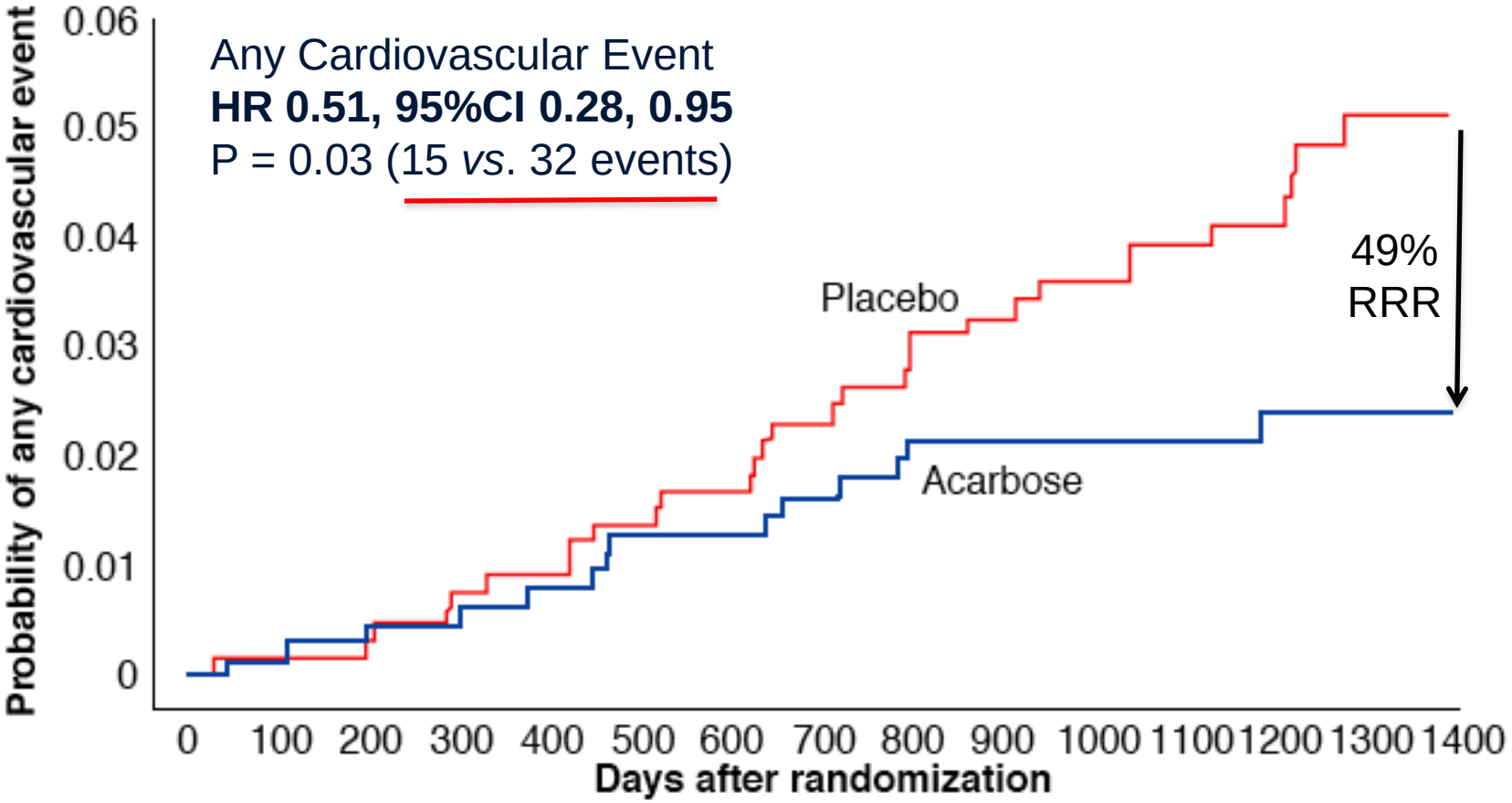
- ORIGIN
- ACE
- ALECARDIO
- CANVAS
- CAROLINA
- ELIXA
- EXAMINE
- EXSCEL
- GLINT
- LEADER
- LOOK AHEAD
- REWIND
- SAVOR-TIMI53
- TECOS
- TIDE

CV Outcome Trials in T2DM
Alphaglucosidase Inhibitors

- Accumulating evidence suggests there is a close association between “prediabetes” and cardiovascular disease
- Post prandial hyperglycaemia may explain the excess risk seen in diabetes and “prediabetes”
- Alphaglucosidase inhibitors delay breakdown of polysaccharides to monosaccharides, delaying their absorption to lower in the bowel and enhancing GLP-1 secretion

STOP-NIDDM – 2˚ CV Outcome

Acarbose 100 mg TID

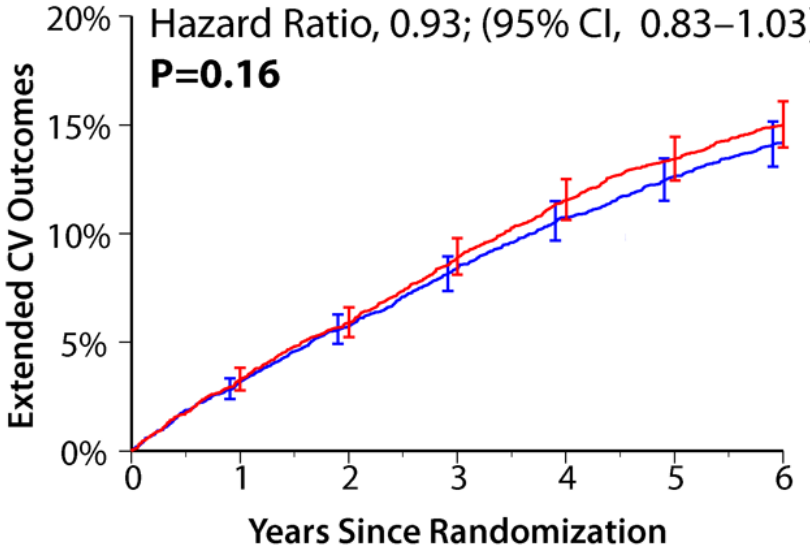


No. at risk

Placebo	686	675	667	658	643	638	633	627	615	611	604	519	424	332	232
Acarbose	682	659	635	622	608	601	596	590	577	567	558	473	376	286	203

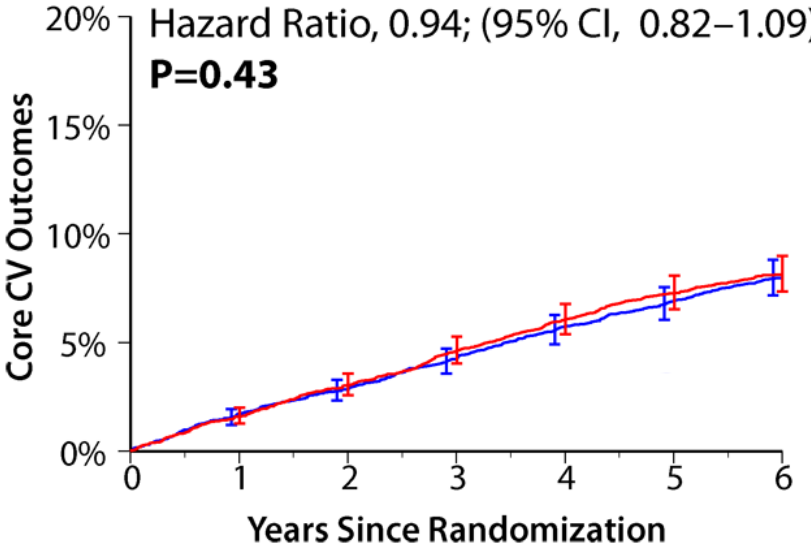
Chiasson et al. JAMA 2003;290:486-94.

NAVIGATOR Cardiovascular Outcomes



Placebo 707 events (15.2%)
Nateglinide 658 events (14.2%)
7% RRR

Nateglinide 60 mg TID



Placebo 387 events (8.3%)
Nateglinide 365 events (7.9%)
6% RRR

Holman RR et al, N Engl J Med, 2010

Ace

Acarbose Cardiovascular Evaluation

- Secondary CVD prevention trial in 7,500 patients with CVD & IGT
- 150 hospitals in PRC and HK
- ISRCTN number: 91899513
- www.ace-study.org

Chair: Rury Holman, University of Oxford, UK

Co-Chairs: Hu Dayi, University of Peking People's Hospital, Beijing, China

Pan Changyu, Chinese PLA General Hospital, Beijing, China

Sponsor: University of Oxford

Funding: Bayer HealthCare

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...in an academic collaboration with

Bayer HealthCare
Bayer Schering Pharma

ACE Trial Design

- Secondary prevention trial in 7,500 Chinese patients with cardiovascular disease and impaired glucose tolerance
- Conducted in 150 Hospitals in the People's Republic of China and Hong Kong
- Evaluating the double-blind **addition** of acarbose (50 mg) or matching placebo three times a day to fully optimised usual cardiovascular disease care
- Primary endpoint is the time to the first occurrence of:
  - Cardiovascular death
  - Non-fatal myocardial infarction
  - Non-fatal stroke
- Academically led, analysed and reported with an independent Data Safety Monitoring Board
- Results expected 2018

Holman RR et al. Diabetes & Vascular Disease Research 2007;4:Suppl 1:S40

CV Outcome Trials in T2DM
DPP-4 Inhibitors

- Improve glycaemic control by inhibiting the metabolism and inactivation of the incretin hormones GLP-1 and GIP

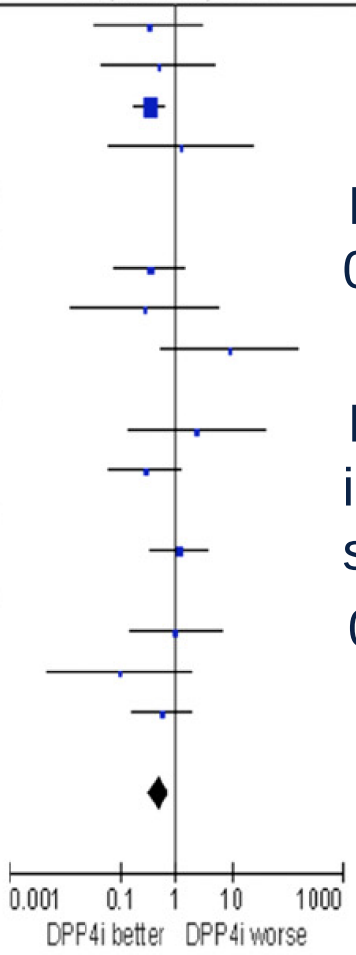
DPP-4 inhibitors – A CVD Meta-analysis

18RCTs. 4,998 randomized to DPP-4 inhibitors and 3,546 to a comparator. Median duration of therapy 46.4 weeks

First Author	DPP4i Events	DPP4i Total	Comparator Events	Comparator Total	Weight	Risk Ratio M-H, Random, 95% CI
Aschner	1	528	3	522	3.7%	0.33 [0.03, 3.16]
Bosi E	1	300	2	294	3.3%	0.49 [0.04, 5.37]
Chan	10	65	12	26	37.7%	0.33 [0.16, 0.67]
Defronzo	2	264	0	64	2.1%	1.23 [0.06, 25.24]
Foley	0	546	0	546		Not estimable
Foley Je	0	29	0	30		Not estimable
NCT00316082	4	291	3	74	8.6%	0.34 [0.08, 1.48]
NCT00374907	0	20	1	16	1.9%	0.27 [0.01, 6.21]
NCT00698932	4	284	0	284	2.2%	9.00 [0.49, 166.39]
NCT00918879	0	107	0	106		Not estimable
NCT01263496	5	391	0	83	2.3%	2.36 [0.13, 42.22]
Pfutzner	2	335	7	328	7.7%	0.28 [0.06, 1.34]
Pi-Sunyer	0	262	0	92		Not estimable
Rosenstock	11	306	3	95	11.9%	1.14 [0.32, 4.00]
Rosenstock J	0	396	0	202		Not estimable
Schweizer	2	169	2	166	4.9%	0.98 [0.14, 6.89]
Schweizer A	0	526	2	254	2.0%	0.10 [0.00, 2.01]
Williams-Herman	3	179	11	364	11.7%	0.55 [0.16, 1.96]
Total (95% CI)		**4998**		**3546**	**100.0%**	**0.48 [0.31, 0.75]**
Total events	45		46			

Heterogeneity: Tau² = 0.00; Chi² = 11.22, df = 12 (P = 0.51); I² = 0%

Test for overall effect: Z = 3.28 (P = 0.001)



RR of any CV event
0.48 (0.31 to 0.75, p=0.001)

RR for nonfatal myocardial infarction or acute coronary syndrome
0.40 (0.18 to 0.88, p=0.02)

Am J Cardiol 2012;110:826 – 833

CV Outcome Trials in T2DM
DPP-4 Inhibitors

Trial	Treatment	Inclusion criteria	Primary endpoint	Number of patients
EXAMINE	Placebo Alogliptin	T2DM HbA1c 6.5 – 11.0% ≥ 18 years ACS	CV death, MI, stroke	5400
TECOS	Placebo Sitagliptin	T2DM HbA1c 6.5 – 8.0% ≥ 50 years CVD	CV death, MI, stroke or UA	14500
SAVOR (TIMI-53)	Placebo Saxagliptin	T2DM HbA1c ≥ 6.5% ≥ 40 years CVD/CV risk factors	CV death, MI, stroke	16500
CAROLINA	Glimepiride Linagliptin	T2DM HbA1c 6.5-8.5% 40-85 years CVD/CV risk factors/ diabetes end organ damage	CV death, MI, stroke or UA	6000

TRIAL EVALUATING **CARDIOVASCULAR**

TECOS

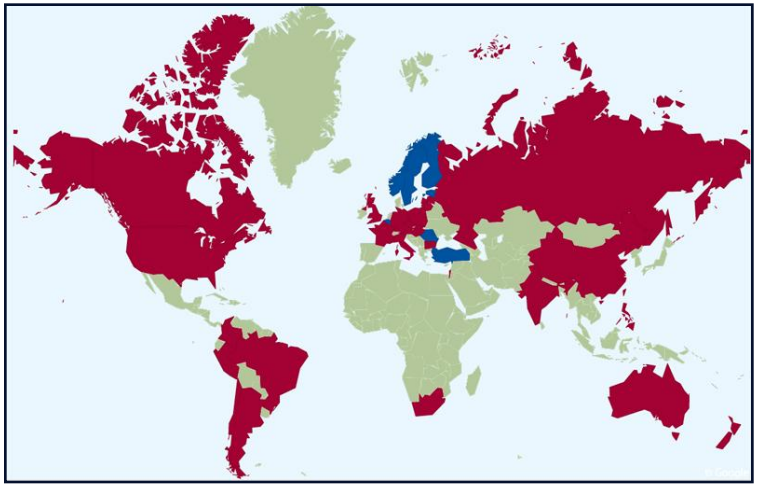
OUTCOMES WITH **SITAGLIPTIN**

- CVD outcome trial in 14,500 patients with CVD and T2DM
- >600 sites in 40 countries
- ClinTrials.gov: NCT00790205
- www.tecos-study.org

Joint-Chairs: Rury Holman, University of Oxford, UK
Rob Califf, Duke Clinical Research Institute, North Carolina, US

Sponsor: Merck

Funding: Merck



Duke Clinical Research Institute
DUKE UNIVERSITY MEDICAL CENTER

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The Oxford Centre for Diabetes, Endocrinology and Metabolism

…in an academic collaboration with

MERCK

TECOS Trial

- Multinational, randomised, placebo-controlled, double-blind, pragmatic, secondary cardiovascular prevention trial in patients with pre-existing cardiovascular disease and type 2 diabetes under conditions of **glycaemic equipoise**
- Sitagliptin (100 mg) or matching placebo once daily, given in **addition to usual care**
- Academic led, analysed and reported
- Event driven (1300 adjudicated primary events)
- Primary Endpoint is the time to the first occurrence of:
  - Cardiovascular death
  - Nonfatal myocardial infarction or nonfatal stroke
  - Hospitalization for unstable angina
- Results expected 2015

Diabetes 2009;59:Suppl 1:A555

TECOS
TRIAL EVALUATING CARDIOVASCULAR OUTCOMES WITH SITAGLIPTIN

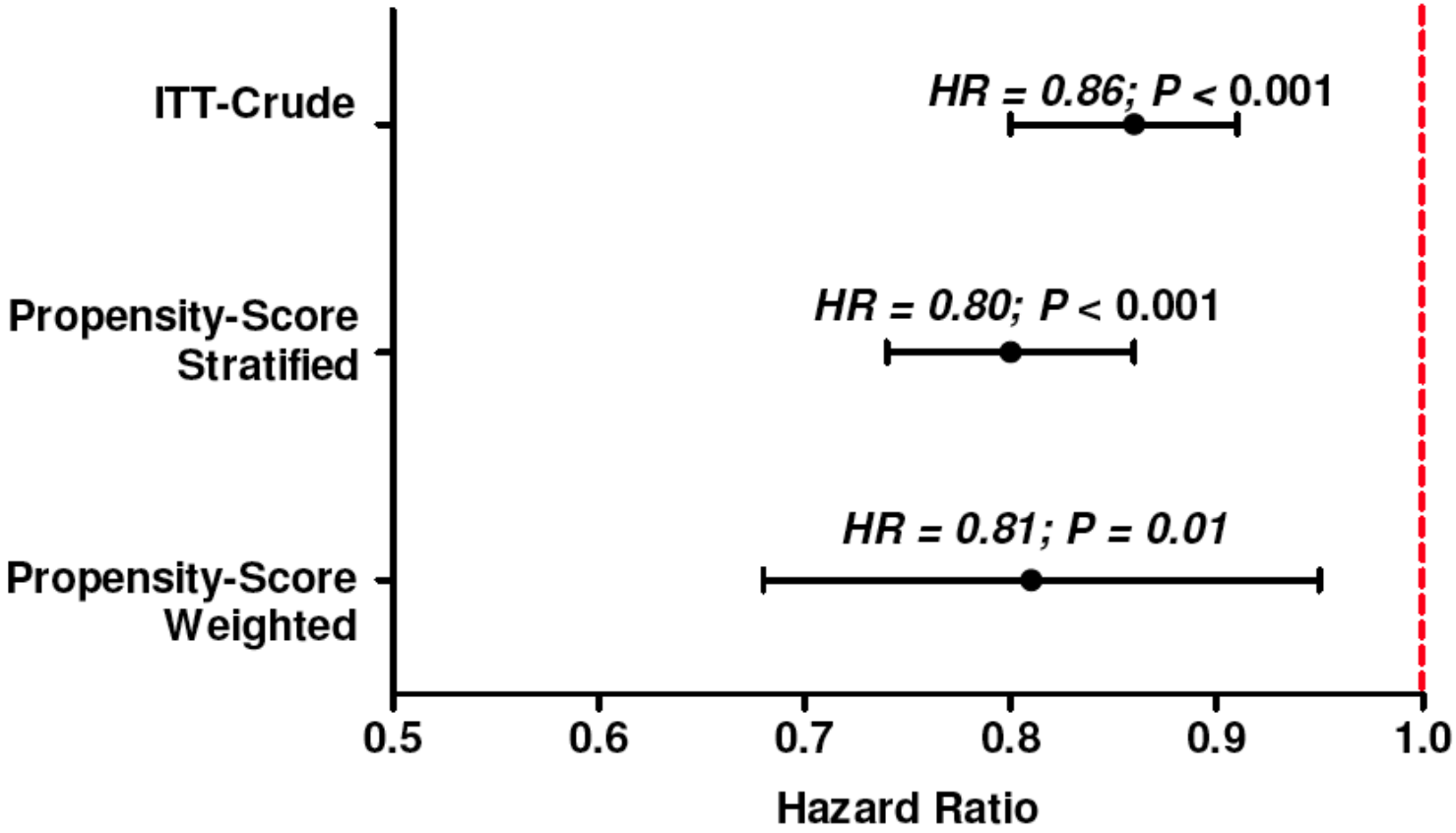
CV Outcome Trials in T2DM
GLP-1 Receptor Agonists

Shown in randomized clinical trials to:

- Augment endogenous insulin secretion and reduce glucagon secretion in a glucose dependent manner
- Slow gastric emptying
- Improve glycaemic control
- Reduce blood pressure
- Promote weight loss

Exenatide CVD Meta-analysis

39,275 T2DM patients treated with exenatide twice daily versus 381,218 patients were treated with other glucose-lowering therapies.



Error bars represent 95% CIs. Propensity Score-Stratified = propensity score, stratified by decile

Best JH et al. Diabetes Care January 2011 34:90-95

CV Outcome Trials in T2DM
GLP-1 Receptor Agonists

Trial	Treatment	Inclusion criteria	Primary endpoint	Number of patients
ELIXA	Placebo Lixisenatide	T2DM HbA1c 6.0% - 10.0% ACS	CV death, MI, stroke or UA	6000
EXSCEL	Placebo Exenatide	T2DM HbA1c 7.0% - 10.0% CVD in 60%	CV death, MI or stroke	9500
LEADER	Placebo Liraglutide	T2DM HbA1c ≥ 7.0% ≥50 years + CVD ≥60 years + CV risk factors	CV death, MI or stroke	8754
REWIND	Placebo Dulaglutide	T2DM, HbA1c < 9.5% ≥50 yrs + CVD ≥55 yrs + subclinical CV ≥60 yrs + ≥2 CV risk factors	CV death, MI or stroke	9600

EXSCEL

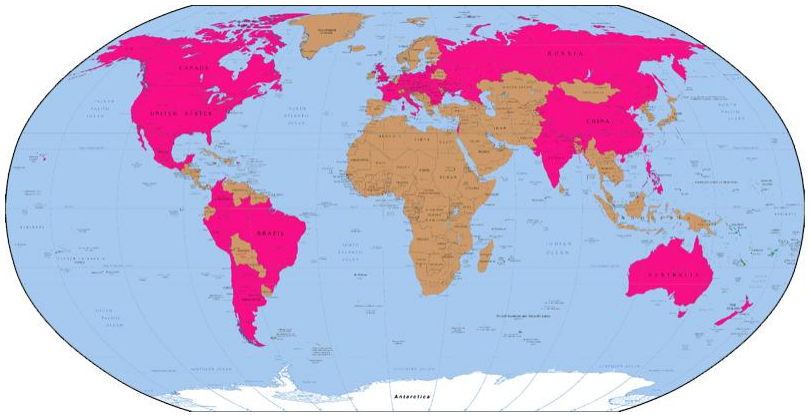
Exenatide Study of Cardiovascular Event Lowering

- CVD outcome trial in 9,500 pts with/without CVD and T2DM
- >500 sites in 36 countries
- ClinTrials.gov: NCT01144338
- www.exscel-study.org

Joint-Chairs: Rury Holman, University of Oxford, UK
Rob Califf, Duke Clinical Research Institute, North Carolina, US

Sponsor: Amylin

Funding: Amylin



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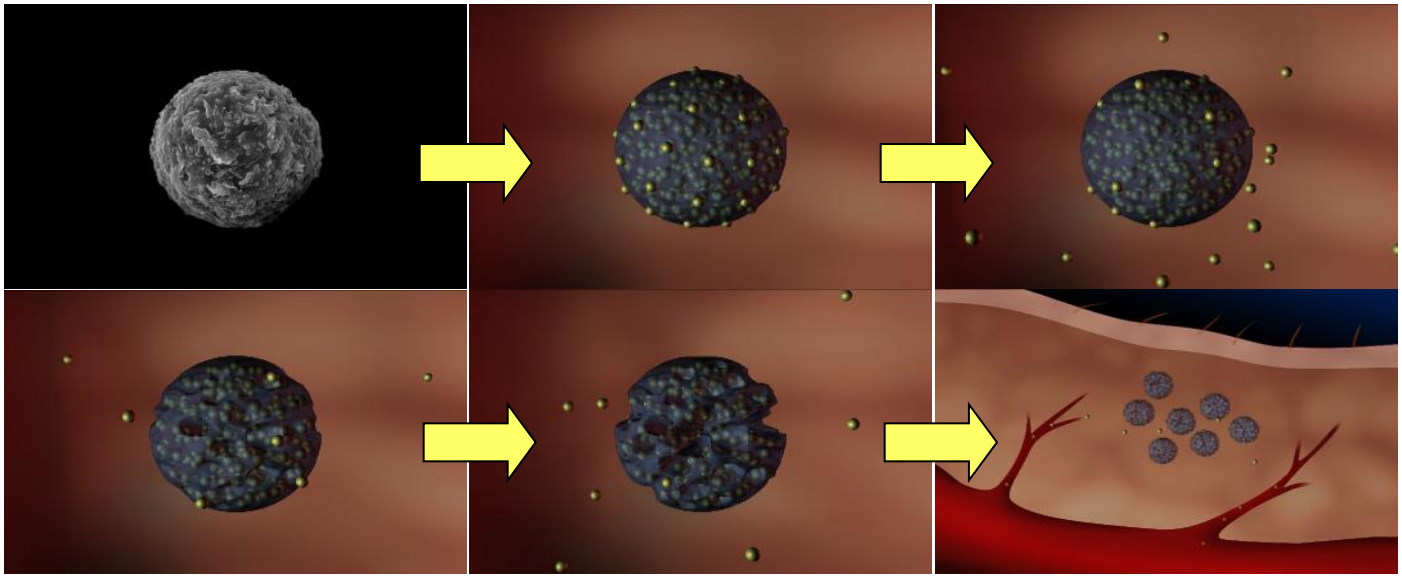
AMYLIN

Exenatide Once Weekly (Bydureon)

Biodegradable polymeric microspheres for extended release



Exenatide once weekly received EMA and FDA approval in June 2011 and January 2012, respectively

EXSCEL
Exenatide Study of Cardiovascular Event Lowering

EXSCEL Trial

- Exenatide QW (2 mg) or matching placebo once weekly, given **in addition to usual care**
- Primary Endpoint
  - time to the first occurrence of:
    - Cardiovascular death
    - Nonfatal myocardial infarction
    - Nonfatal stroke
- Event driven
  - requires 1591 confirmed primary endpoint events
  - 90% power to detect a 15% relative risk decrease
- Results expected 2018

EXSCEL
Exenatide Study of Cardiovascular Event Lowering

CV Outcome Trials in T2DM
SGLT2 Inhibitors

Trial	Treatment	Inclusion criteria	Primary endpoint	Number of patients
CANVAS	**Placebo Canagliflozin**	**T2DM, HbA_{1c} 7.0-10.0% High CV risk, ≥30 years**	**CV death, MI or stroke**	**6-7000**

CV Outcome Trials in T2DM
Dual PPAR Agonists

Trial	Treatment	Inclusion criteria	Primary endpoint	Number of patients
ALECARDIO	**Placebo Aleglitazar**	**T2DM and hospitalization for acute coronary syndrome within the previous 2–6 weeks**	**CV death, MI or stroke**	**6-7000**

Look AHEAD: Study Design

Action for HEAlth in Diabetes

- Investigation of long-term health effects of intentional weight loss with lifestyle modification
- > 5000 overweight or obese adults with type 2 diabetes; up to 11.5 years of followup
- Standard medical care vs standard medical care with intensive lifestyle intervention for 4 years
  - Goal of lifestyle intervention
    - Weight reduction of ≥7% in the first year
    - Maintain ≥175 minutes per week of moderate intensity physical activity at the end of 6 months
- Outcome measures: time to first occurrence of
  - Primary – CV death, nonfatal myocardial infarction, or nonfatal stroke
  - Secondary – all-cause mortality, coronary artery bypass grafting and/or percutaneous coronary angioplasty, hospitalization for CHF, carotid endarterectomy, or peripheral vascular procedures

Look AHEAD Research Group. *Control Clin Trials*. 2003;24:610-28.

Look AHEAD Stopped for Futility

U.S. Department of Health and Human Services
NIH News
National Institutes of Health

National Institute of Diabetes and Digestive and Kidney Diseases

www.niddk.nih.gov

For Immediate Release
Friday, Oct. 19, 2012

CONTACT:
Amy Reiter
301-496-3583

Weight loss does not lower heart disease risk from type 2 diabetes

Intervention stopped early in NIH-funded study of weight loss in overweight and obese adults with type 2 diabetes after finding no harm, but no cardiovascular benefits

CV Outcome Trials in T2DM
Metformin

Shown in UKPDS to:

- Reduce risk of MI by 39%, p=0.010
- Reduce risk of death by 36%, p=0.011

With a legacy effect 10 years later of:

- Reduced risk of MI by 33%, p=0.005
- Reduced risk of death by 27%, p=0.002

GLINT
Glucose Lowering In Non-diabetic hyperglycaemia Trial

- Primary CVD prevention
- 11,834 patients with non-diabetic hyperglycaemia & without CVD
- UK Multicentre Trial

Rury Holman (Joint-Chair)
Nick Wareham (Joint-Chair)

Angie Bethel (Joint Clinical Lead)
Simon Griffin (Joint Clinical Lead)

Sponsor: University of Cambridge
Funding: NIHR Health Technology Assessment Programme

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UNIVERSITY OF CAMBRIDGE
MRC Epidemiology Unit

GLINT Trial

- Men and women aged ≥40 years with a 10-year CVD risk ≥20%, with an HbA1c ≥5.5% and <6.5%, and no prior history of diabetes / CVD in general practices in England
- Metformin SR (500 mg) or matching placebo TID
- Primary Endpoint
  - Cardiovascular death
  - Nonfatal myocardial infarction
  - Nonfatal stroke
- Secondary endpoints include cancer
- Pilot phase 2013-2015
- Main trial 2015-17 with follow-up to 2022
- Results expected 2023

GLINT

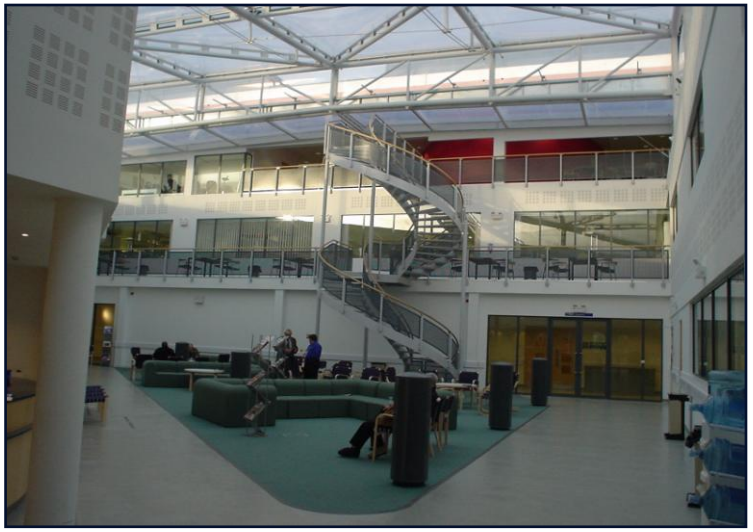
But we need ‘Smart’ Trials

- Trials are moving into a new era
- We should be testing multiple interventions in factorial or head to head designs to be more efficient and more informative
- When testing drugs within the same class, data from similar trials should be utilised to inform design and sample size requirements
- Trials will likely still be powered on the time to the first primary endpoint but subsequent events also need to be evaluated to capture the full impact of treatments, for both benefits and risks

Radcliffe Department of Medicine

Thank you

NHS National Institute for Health Research



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Established in 1985

www.dtu.ox.ac.uk