UNIVERSITY OF CAMBRIDGE

Cardiovascular Experimental Medicine

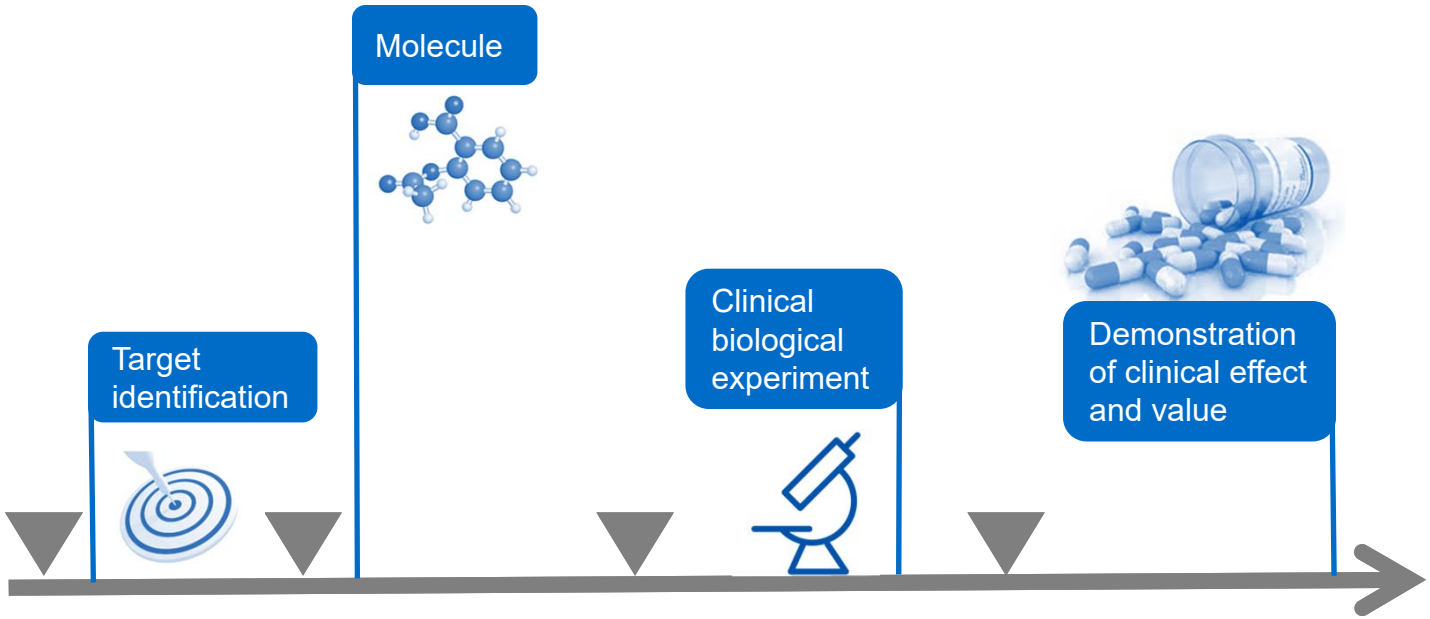
accelerating proof-of-mechanism and concept

Ian Wilkinson

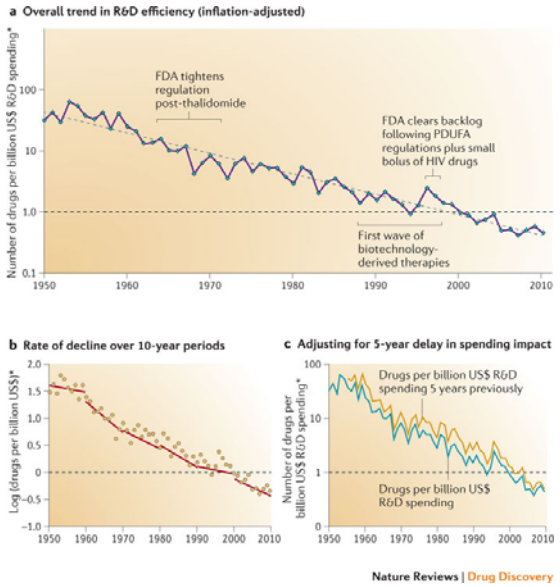
Experimental Medicine and Immunotherapeutics

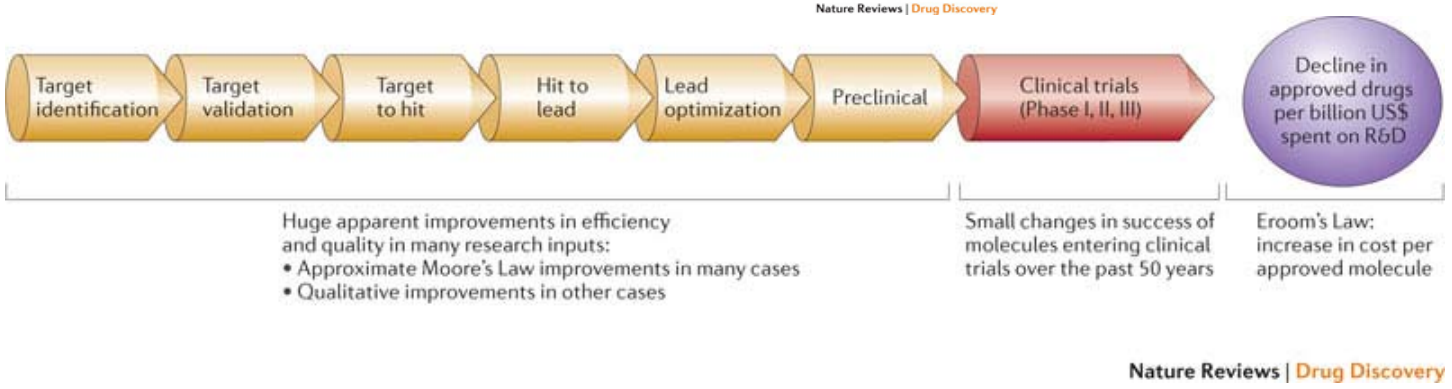
Major Decision in R&D

Steps in discovering and developing medicines



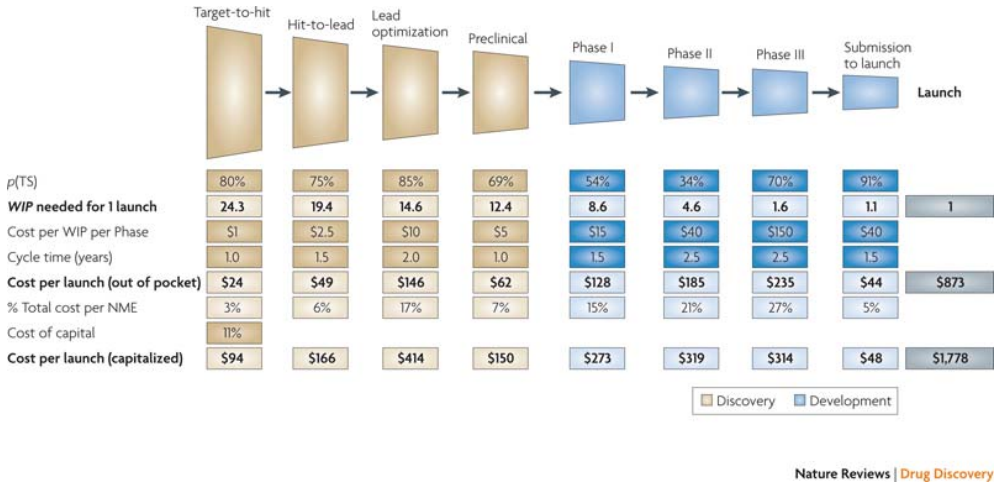
The classical Drug Development Pipeline is in Trouble

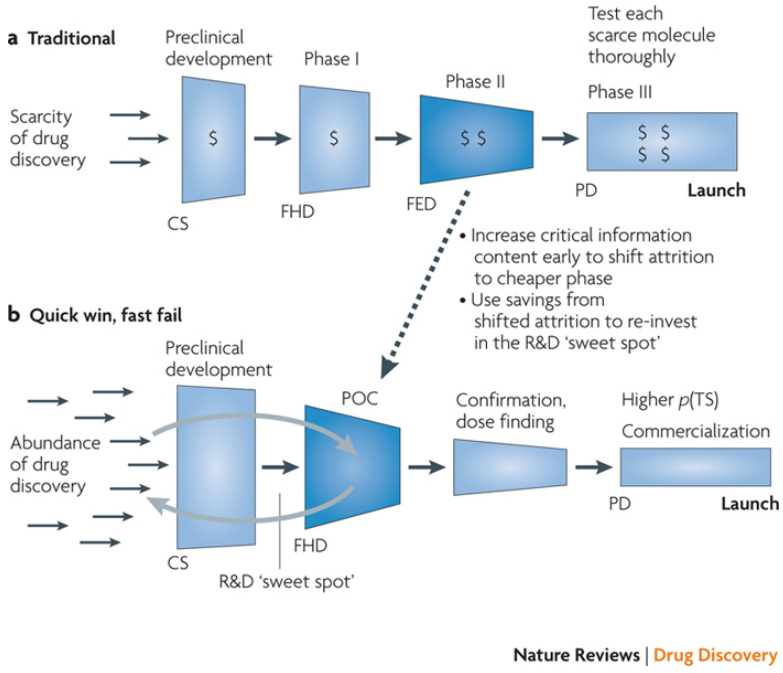




Nature Reviews Drug Discovery 2012; 11:191

Improving the Process





Proof-of-Mechanism

- Demonstrate key aspects of the anticipated pharmacological profile
  - ‘Drug-target engagement’ – the first step of translation
  - Explore PK/PD relationships – assist with dose selection
  - Often employs biomarkers
  - Often ignored in phase I or IIa – ‘*a missed opportunity*’

Biomarkers

- FDA definition

  "A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention"

- Uses

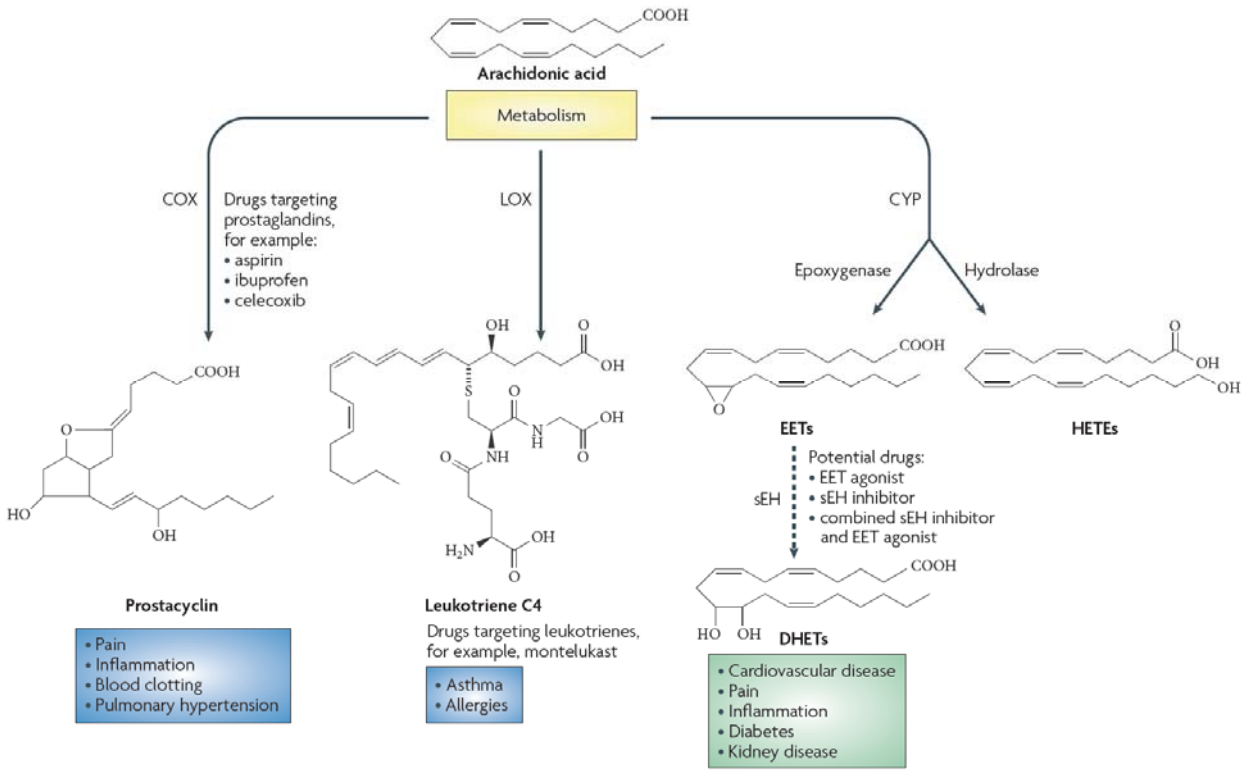
  Faster proof of concept and better stop/go decisions at early stage of clinical development

- Examples

  oCT
  oFDG-PET
  oMRI/MRS
  oBlood pressure
  oArterial stiffness
  oForearm blood flow
  oCRP
  oHeat shock protein

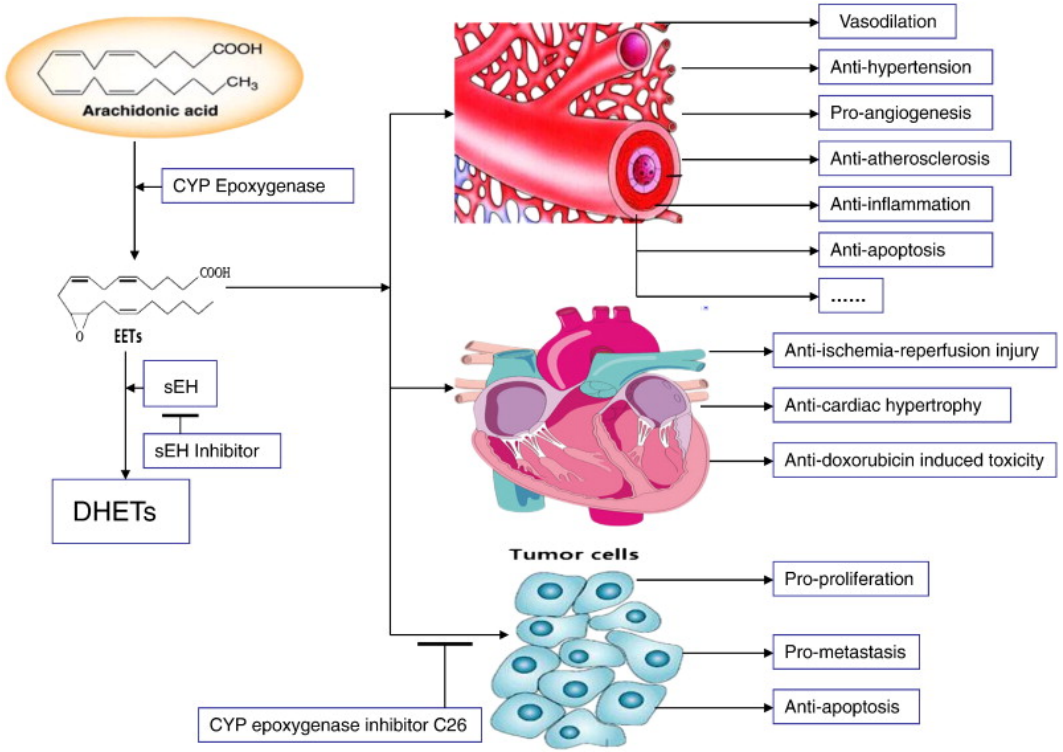
Epoxyeicosatrienoic Acids (EETS):

Arachadonic acid metabolites

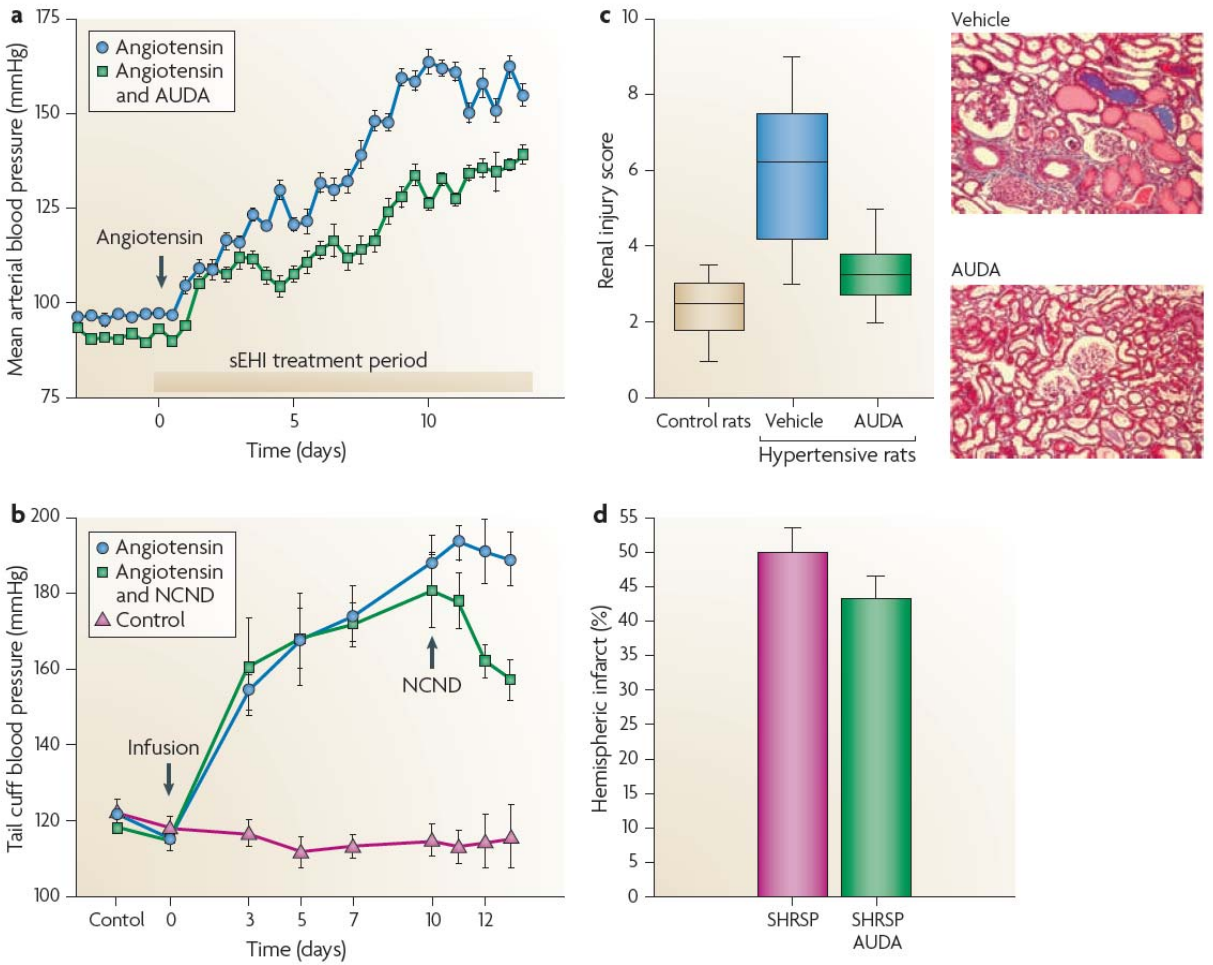


Nature Reviews Drug Discovery 2008; 8: 794

EET: Effects and a Plausible Target

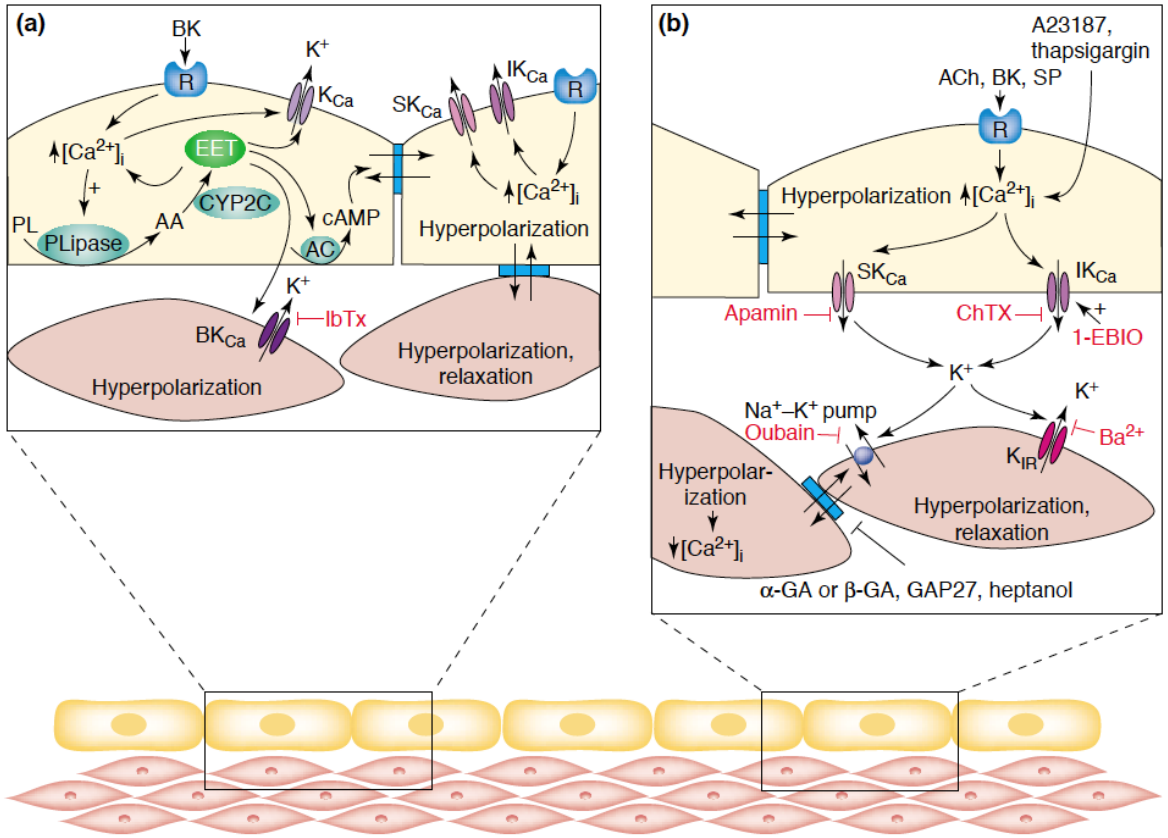


Effects of SEH inhibitors in a Rat Hypertension Model



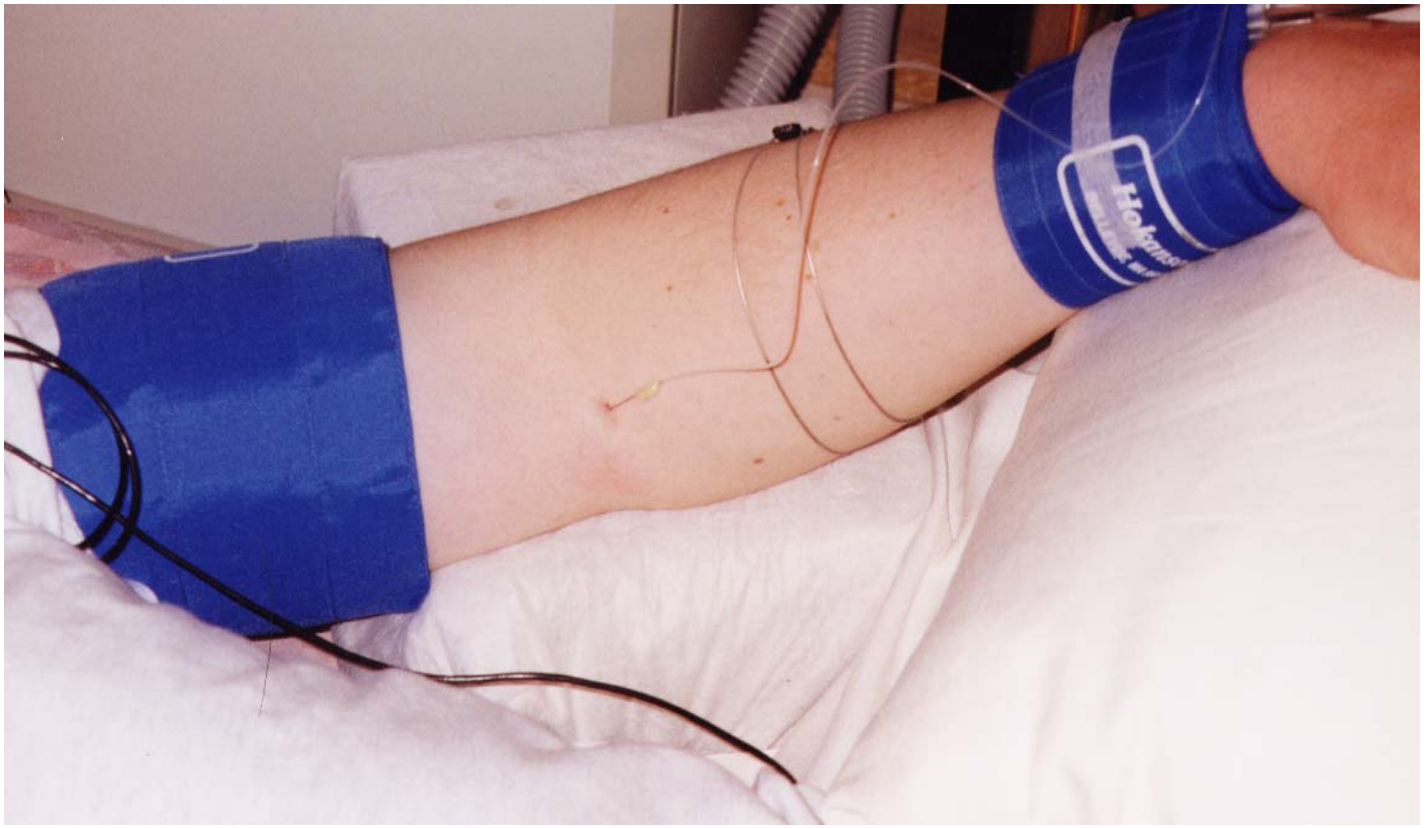
Clin. Sci. 2009;116: 61

EDHF and Epoxyeicosatrienoic Acids (EETs)

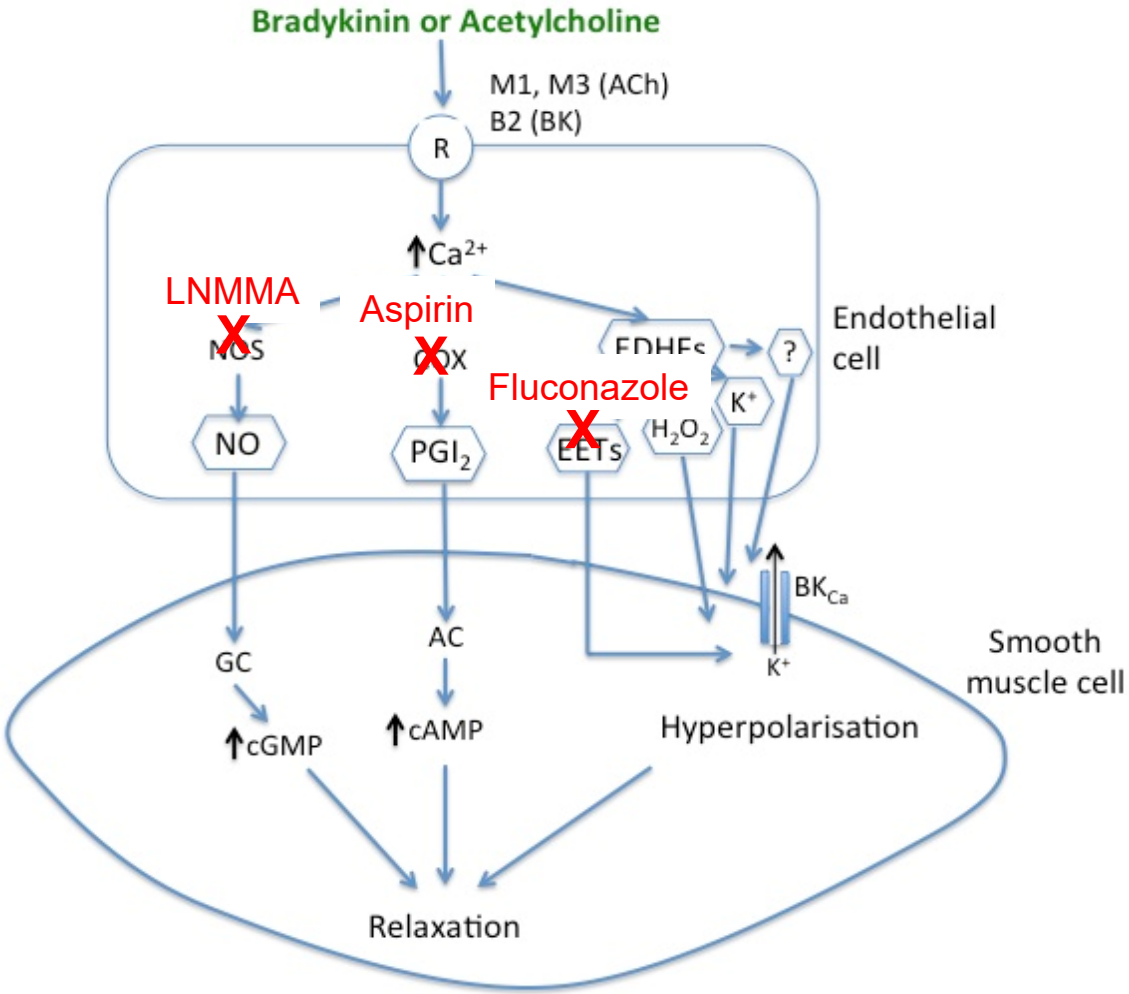


Trends in Pharmacological Sciences 2002;8:374

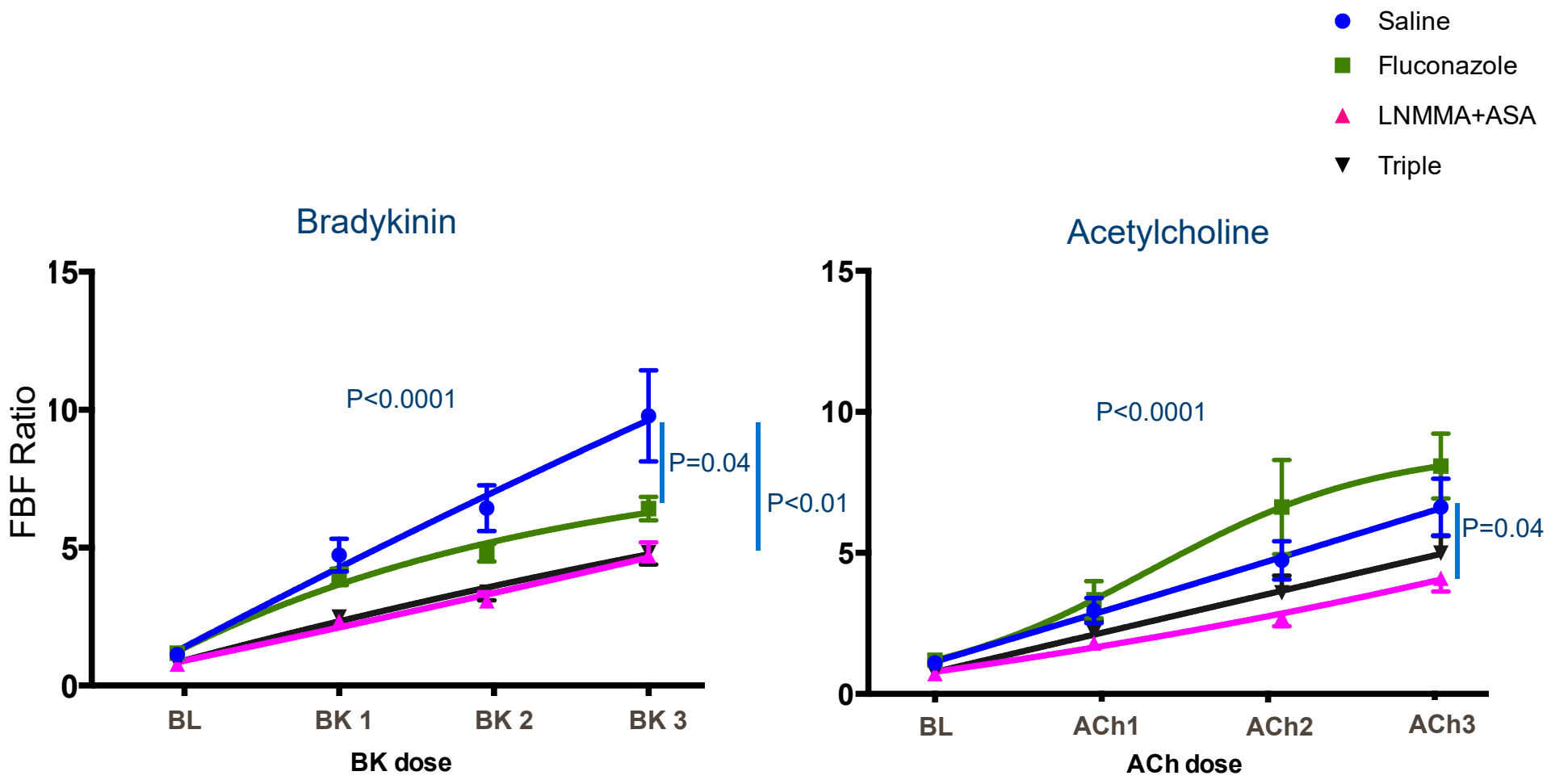
Forearm Plethysmography and ia Drug Infusion



Agonists and inhibitors

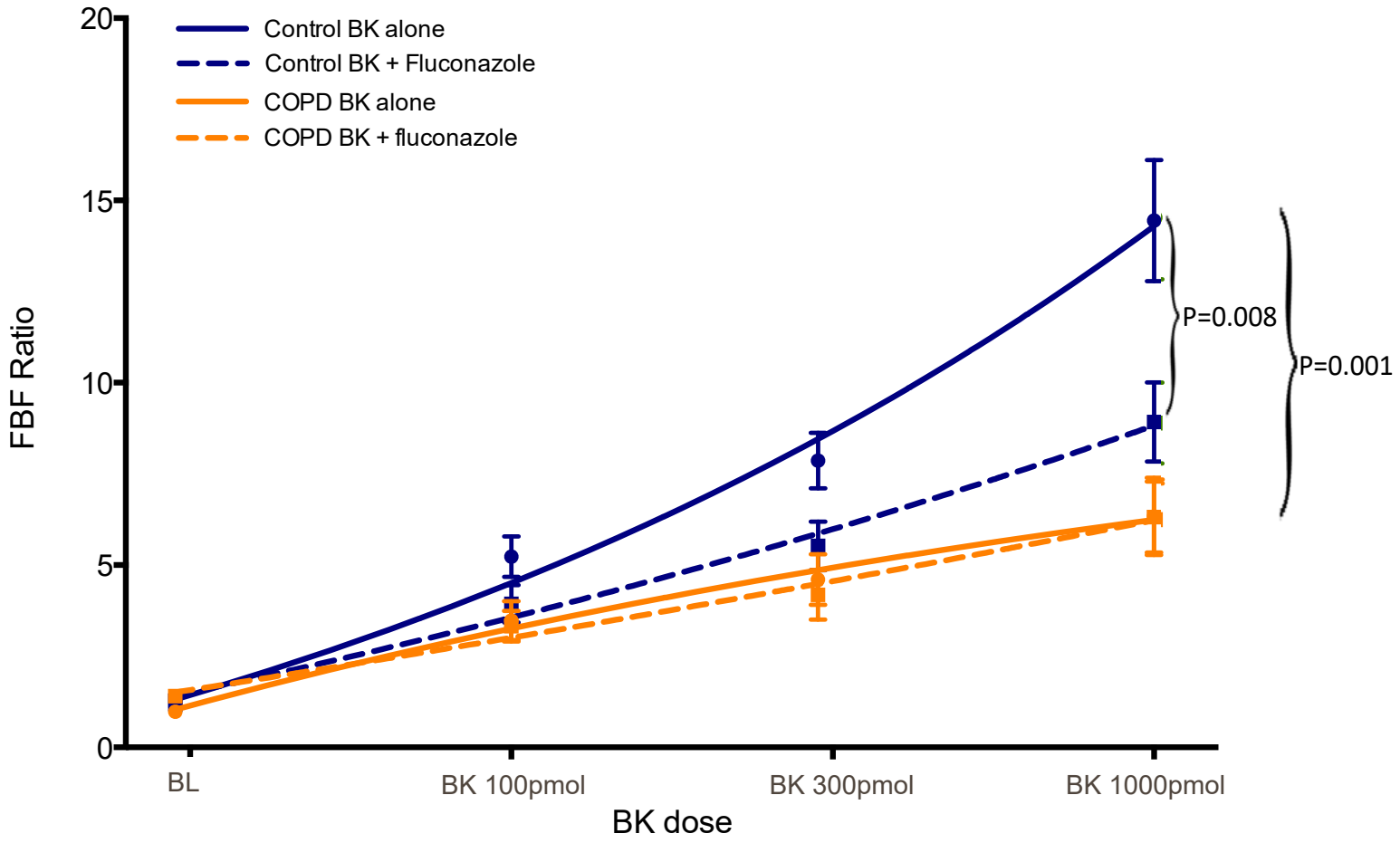


EETs: Agonist responses



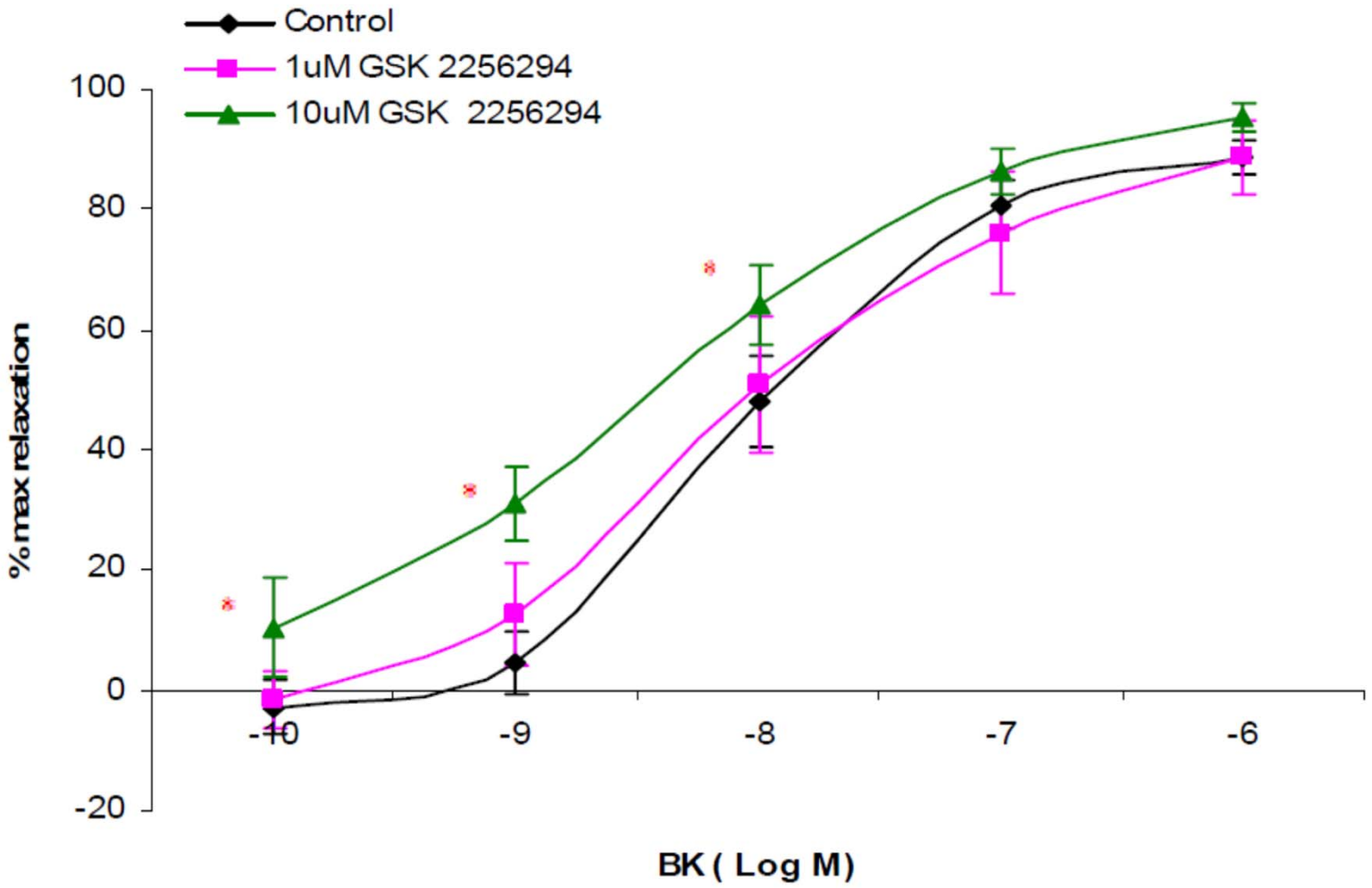
Yang unpublished data

Vascular EETs Generation in COPD



Yang et al. *Chest* 2016; in press

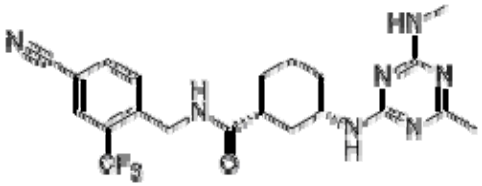
SHE Inhibition in Human Vessels *ex vivo*

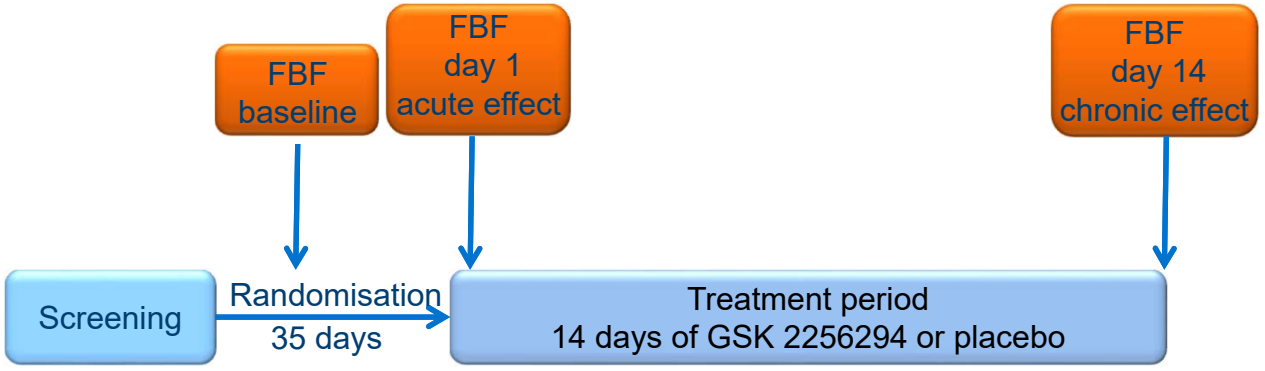


Yang et al. *Chest* 2016; in press

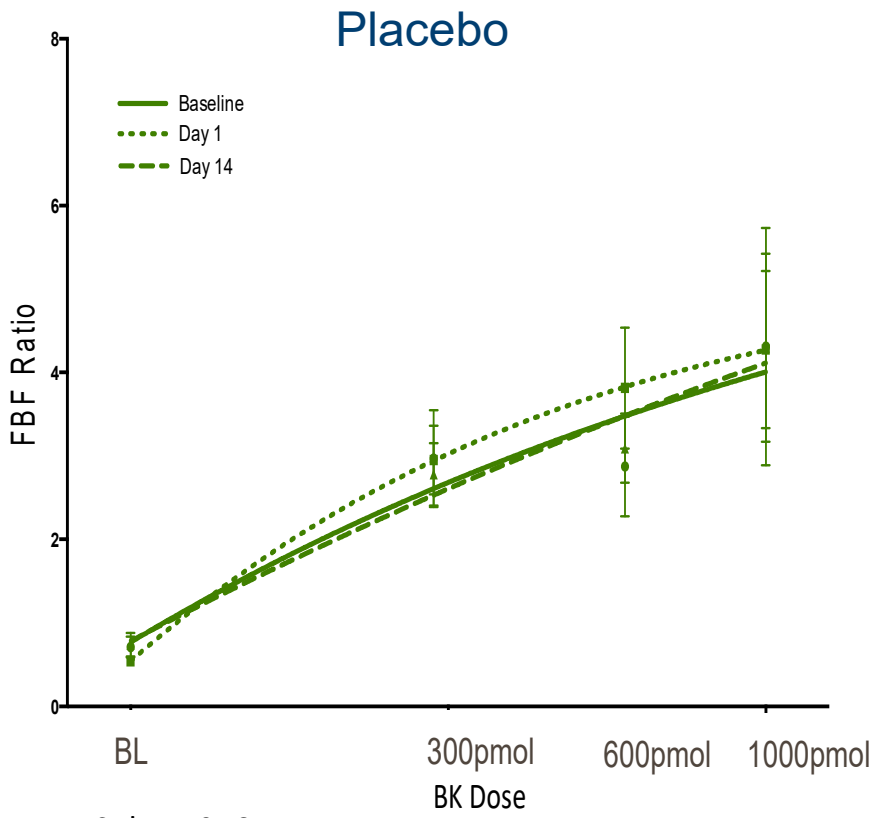
SEH inhibition

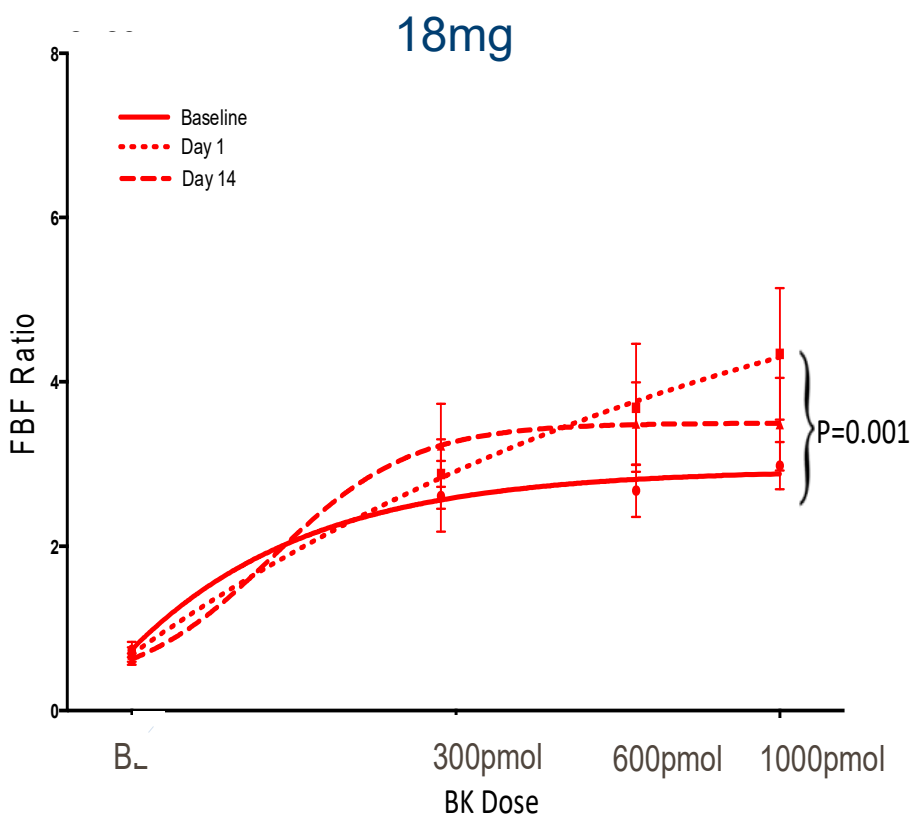
- First time in human clinical trial to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of single and repeat doses of an SEH inhibitor (GSK 2256294) in obese smokers.





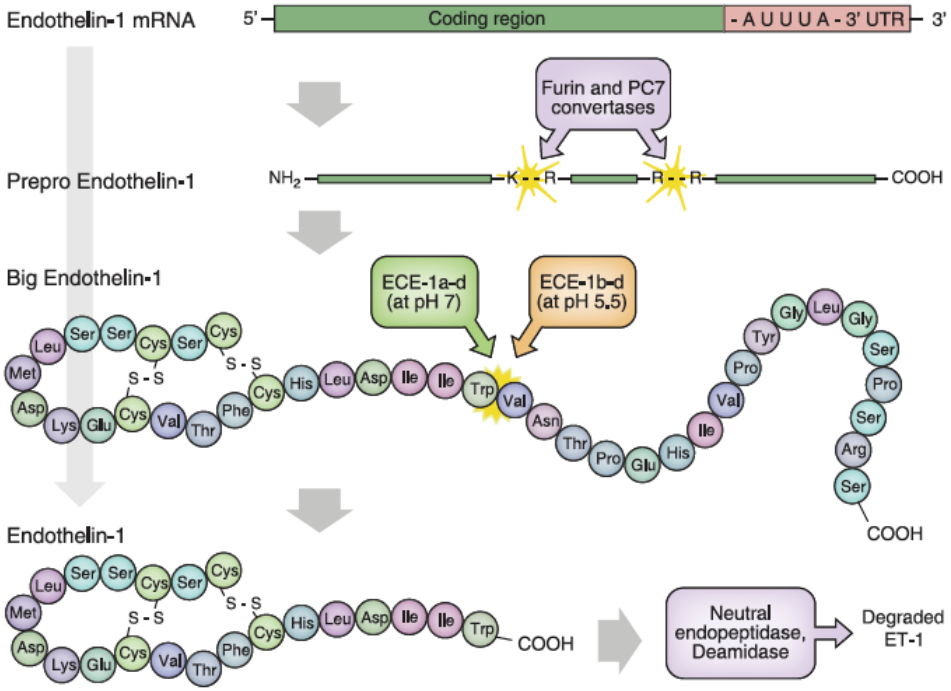
Response: 18mg

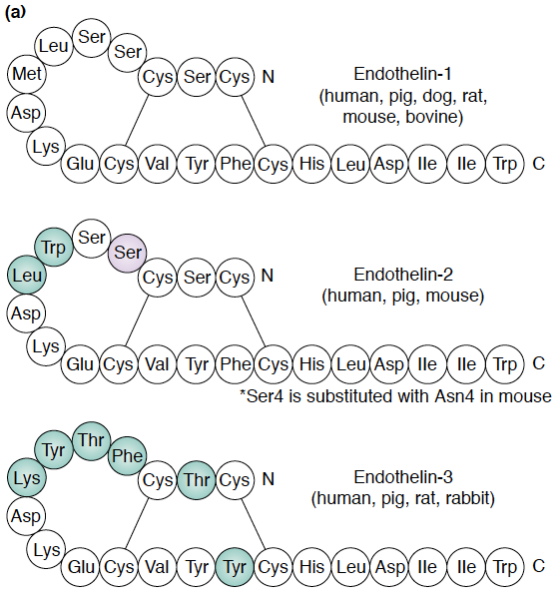




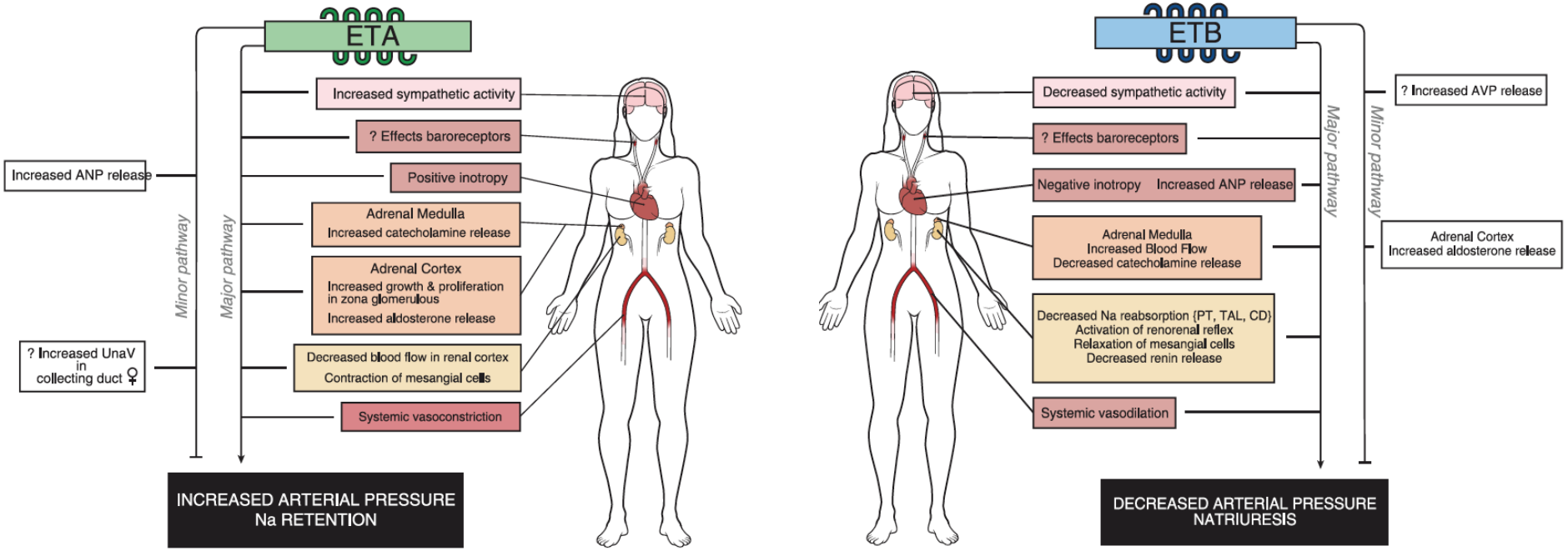
Yang et al. *Chest* 2016; in press

Human Endothelins



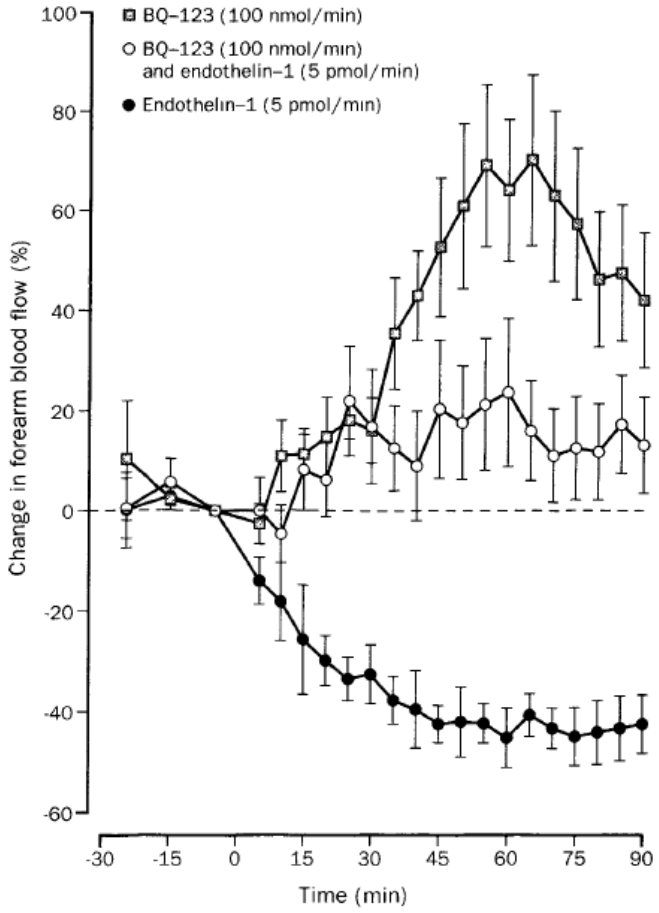


Endothelins: Integrated physiological effects



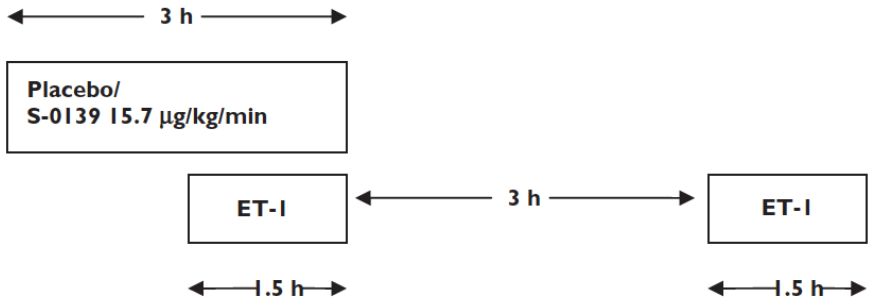
Physiol Rev2011; 91: 1–77

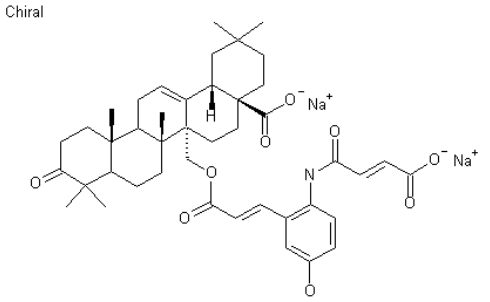
Endothelin-1 is a Vasoconstrictor and Regulates Basal Tone in Man

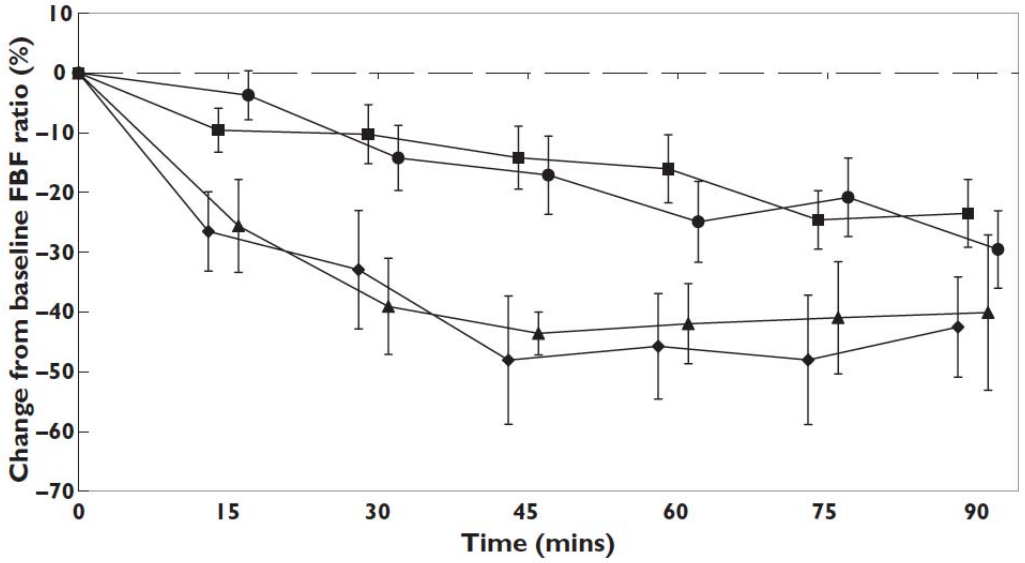


Haynes Lancet 1994;344:852

Endothelin Antagonists: prolonged effects







Lunnon et al. *BJCP* 2010; 69:252

Proof-of-Concept

- Demonstrate efficacy in modifying the disease process
  - ‘Does what it says on the box’ – Phase IIa
  - Usually rely on surrogate markers or biomarkers
  - Statistical approach – ‘mini phase 3’

Surrogate Markers

- FDA definition

  "a biomarker that is intended to substitute for a clinical endpoint. A surrogate endpoint is expected to predict clinical benefit or harm (or lack of benefit or harm) based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence"

  •Uses

  o Proof of concept

  o Registration

- Examples

  oDiastolic blood pressure

  oLDL cholesterol

  o6 minute walk test

  o(HDL cholesterol)

  o(HbA1c)

Potentially Useful Cardiovascular Surrogates

- Blood pressure
- Endothelial function
- Vascular inflammation
- Aortic stiffness

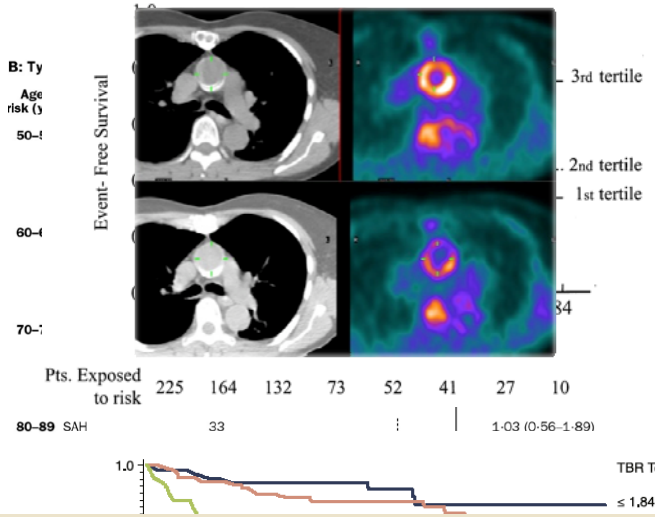
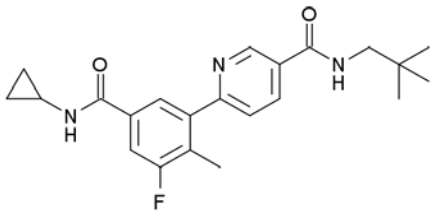


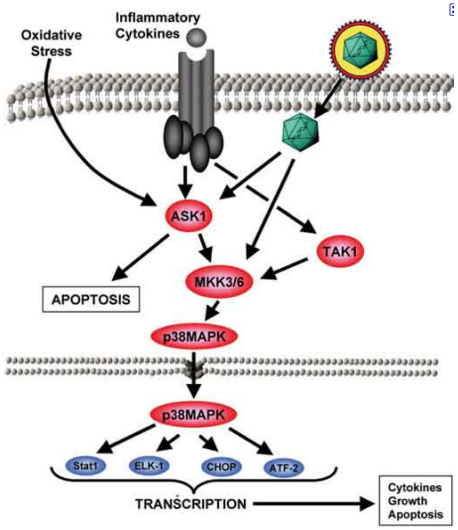
Table 1 Pooled Adjusted Hazard Ratios (95% CIs) of a 1-SD Increase in Log_e-Transformed aPWV for All-Cause Mortality, CVD Mortality, CHD Events, Stroke Events, and CVD Events

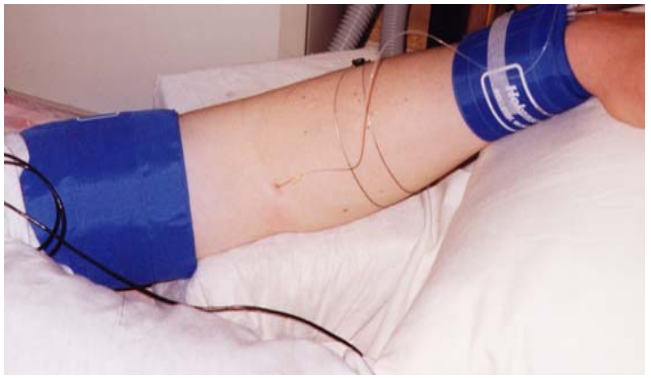
	Model 1*	Model 2*	Model 3*
CHD events (n = 1,195)	1.35 (1.22–1.50)	1.32 (1.18–1.48)	1.23 (1.11–1.35)
CVD events (n = 1,785)	1.45 (1.30–1.61)	1.37 (1.23–1.52)	1.30 (1.18–1.43)
Stroke events (n = 641)	1.54 (1.34–1.78)	1.37 (1.21–1.54)	1.28 (1.16–1.42)
CVD mortality (n = 395)	1.41 (1.27–1.56)	1.35 (1.20–1.53)	1.28 (1.15–1.43)
All-cause mortality (n = 2,041)	1.22 (1.16–1.27)	1.20 (1.15–1.26)	1.17 (1.11–1.22)

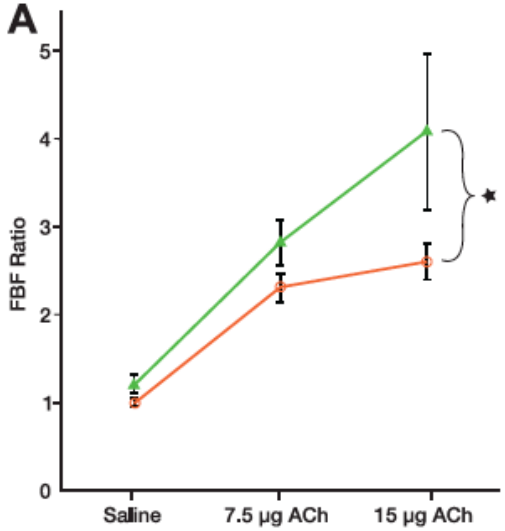
Proof-of-concept in Hypercholesterolaemics

Losmapimod a p38 MAPKinase Inhibitor





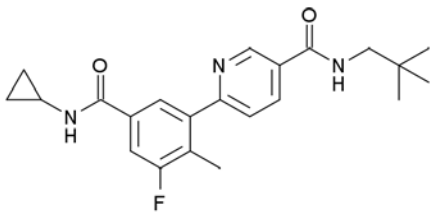


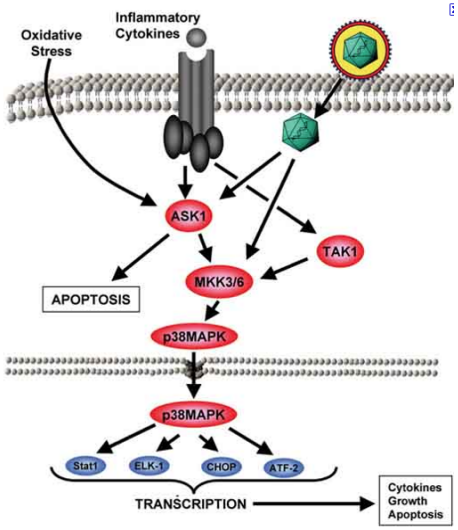


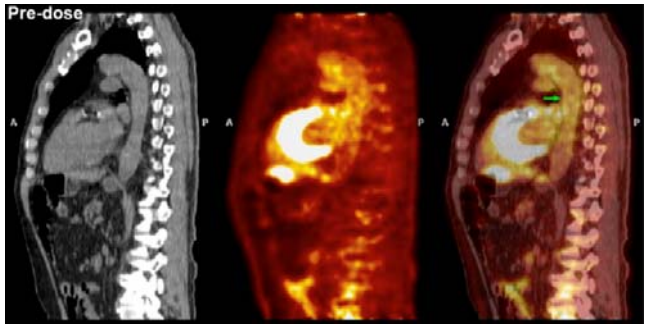
Cheriyan *Circulation*. 2011;123:515-523

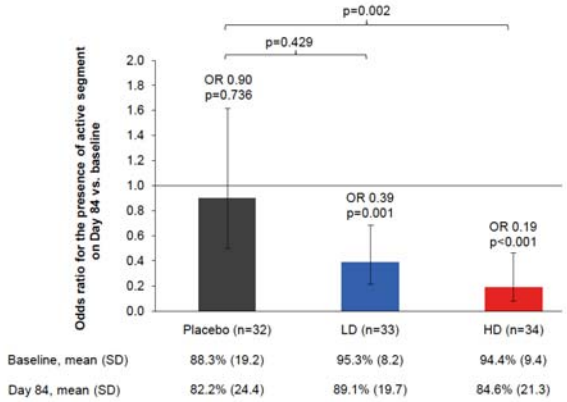
Proof-of-concept in Stable CVD

Losmapimod a p38 MAPKinase Inhibitor





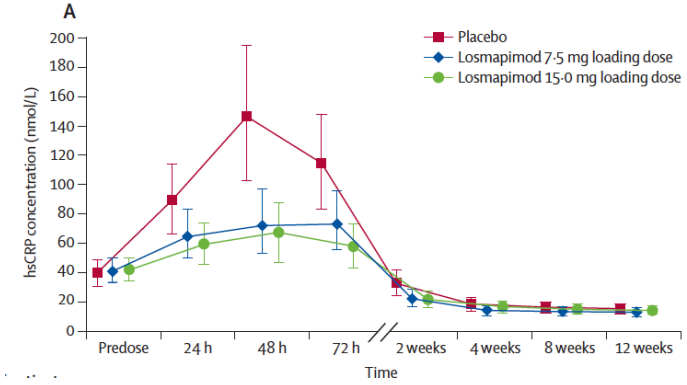




Elkhawad *JACC Imaging* 2012;5:911

Proof-of-concept in NSTEMI

Losmapimod a p38 MAPKinase Inhibitor



	Day 3–5		Week 12	
	Adjusted mean*	Difference between groups (95% CI)	Adjusted mean*	Difference between groups (95% CI)
Infarct size (% of left ventricle)				
All losmapimod	5·93	−2·38 (−5·44 to 0·69), difference −29% (p=0·13)	4·13	−2·19 (−4·78 to 0·40), difference −35% (p=0·10)
Placebo	8·31		6·32	
LVEF (%)				
All losmapimod	56·86	4·72 (−0·06 to 9·51), difference 9% (p=0·05)	60·28	5·14 (0·28 to 10·00), difference 9% (p=0·0387)
Placebo	52·13		55·14	
LVEDV (mL)				
All losmapimod	127·18	−19·89 (−38·74 to −1·03), difference −14% (p=0·0390)	127·74	−20·09 (−37·01 to −3·18), difference −14% (p=0·0207)
Placebo	147·06		147·83	
LVESV (mL)				
All losmapimod	56·13	−15·51 (−28·84 to −2·19), difference −22% (p=0·0231)	51·47	−16·52 (−28·91 to −4·13), difference −24% (p=0·0098)
Placebo	71·65		67·99	

LVEF=left ventricular ejection fraction. LVEDV=left ventricular end-diastolic volume. LVESV=left ventricular end-systolic volume. *Adjusted for baseline troponin I concentration and time from chest-pain onset to treatment.

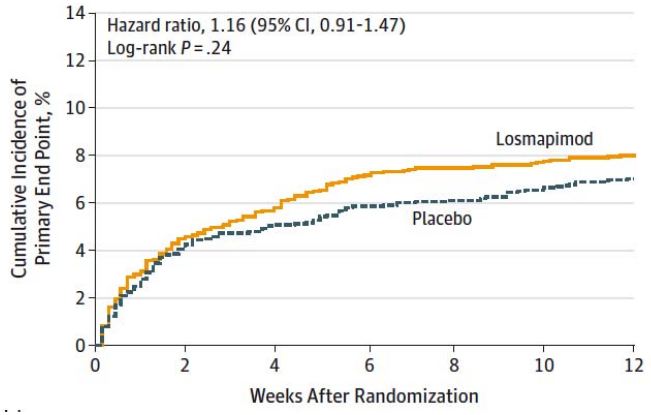
Newby *Lancet* 2012;384:1187

Phase 3
Acute MI

Original Investigation

Effect of Losmapimod on Cardiovascular Outcomes in Patients Hospitalized With Acute Myocardial Infarction
A Randomized Clinical Trial

Michelle L. O'Donoghue, MD, MPH; Ruchira Glaser, MD, MSCE; Matthew A. Cavender, MD; Philip E. Aylward, BM, BCh, PhD; Marc P. Bonaca, MD, MPH; Andrzej Budaj, MD, PhD; Richard Y. Davies, MS; Mikael Dellborg, MD; Keith A. A. Fox, MBChB; Jorge Antonio T. Gutierrez, MD; Christian Hamm, MD; Robert G. Kiss, MD, PhD; František Kovar, MD, PhD; Julia F. Kuder, MA; Kyung Ah Im, PhD; John J. Lepore, MD; Jose L. Lopez-Sendon, MD; Ton Oude Ophuis, MD, PhD; Alexandr Parkhomenko, MD; Jennifer B. Shannon, MS; Jindrich Spinar, MD; Jean-Francois Tanguay, MD; Mikhail Ruda, MD, PhD; P. Gabriel Steg, MD; Pierre Theroux, MD; Stephen D. Wiviott, MD; Ian Laws, PhD; Marc S. Sabatine, MD, MPH; David A. Morrow, MD, MPH; for the LATITUDE-TIMI 60 Investigators



Newby *JAMA* 2016;315:1591

COPD – an Inflammatory Condition?

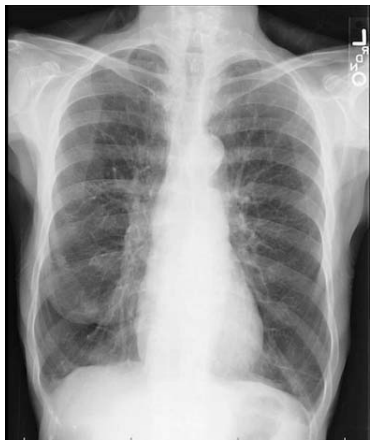
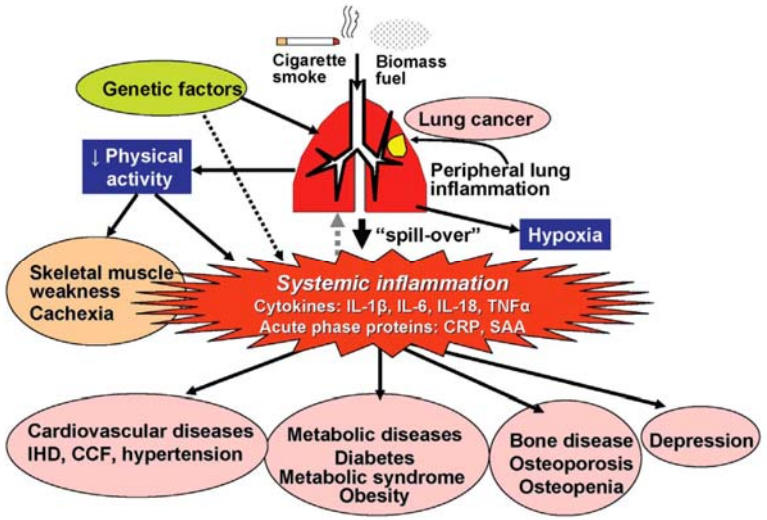


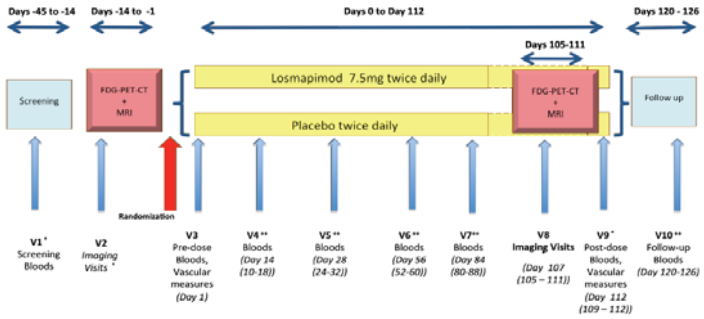
TABLE 1 Ranking of causes of death after 25 yrs of follow-up of males and females aged 45–64 in the Renfrew and Paisley (MIDSPAN) Study

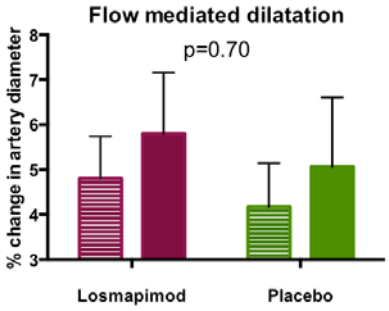
Ranking	Cause of death %	
	Males	Females
1	Coronary heart disease 36	Cancer 30
2	Cancer 30	Coronary heart disease 28
3	Stroke 10	Stroke 15
4	Respiratory 9	Respiratory 8
5	Other 7	Other 9
6	Other cardiovascular disease 6	Other cardiovascular disease 7
7	Digestive 2	Digestive 3

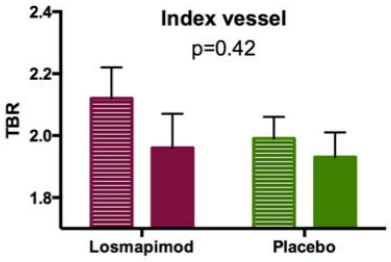


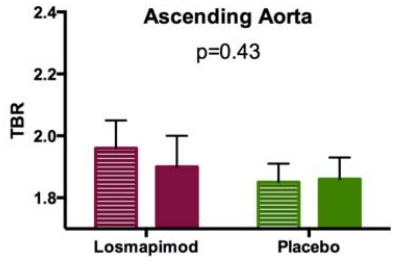
Eur Respir J 2006; 27: 627 & PLoS Med 2010; 7(3): e1000220

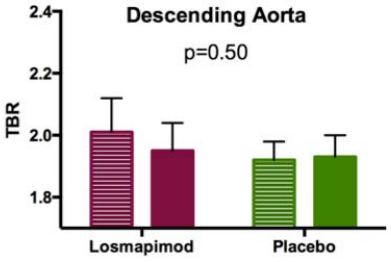
Lospamimod in COPD: Endothelial Function and Vascular Inflammation

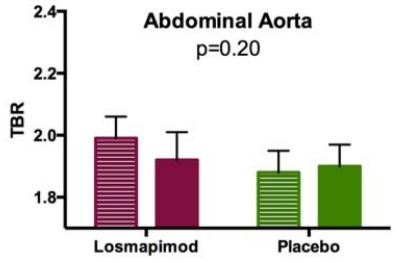


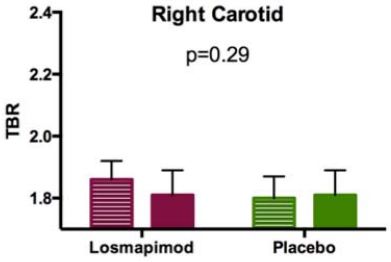


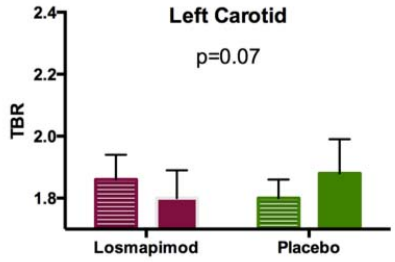






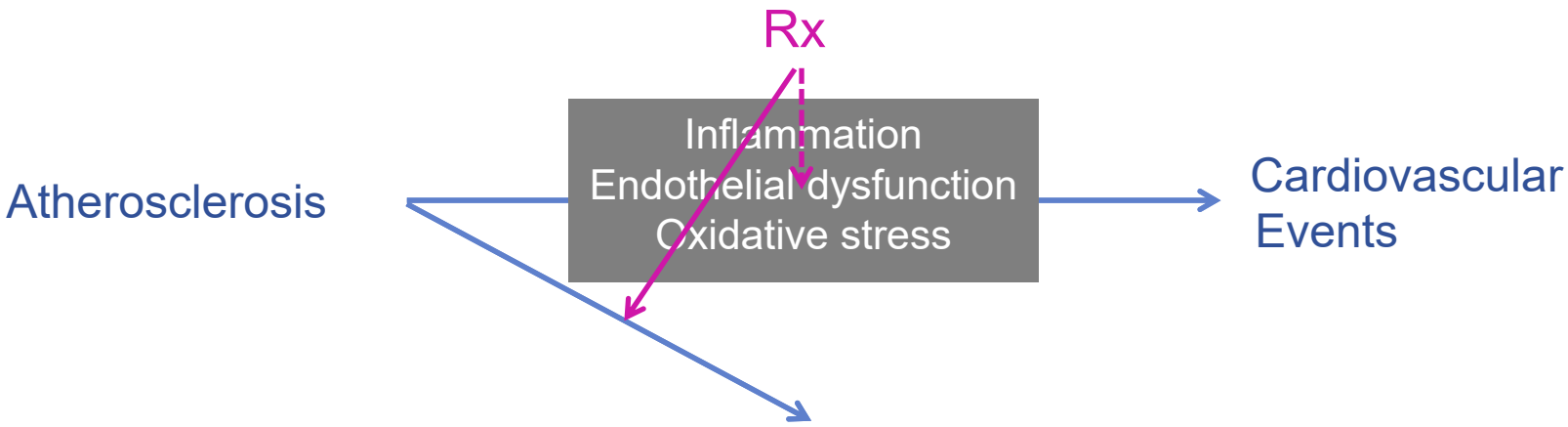






Proof-of-Concept: Lessons

- Biomarker and surrogate validity
  - Accuracy, repeatability, stability
  - Predictive value
  - Predicts effect of Rx



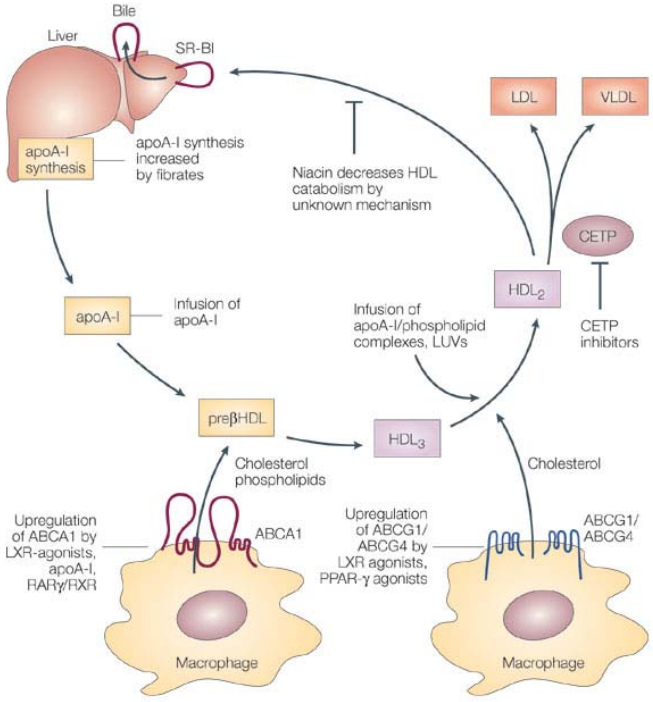
Proof-of-Concept: Lessons

- Correct paradigm and disease
  - Anti-inflammatory effect is relatively weak (failed in RhA)
    - ✓ Chronic low level inflammation – stable CAD, hypercholesterolaemia
    - ✘ Acute severe inflammation – MI or COPD
  - Anti-inflammatory effect is relatively short-lived
    - ✓ Acute MI
    - ✘ Stable CAD, hypercholesterolaemia

Back Translation

- Understanding why things haven't worked out
  - Disprove surrogates or paradigms
  - Invalidate targets
  - Better understand disease processes or mechanisms

HDL

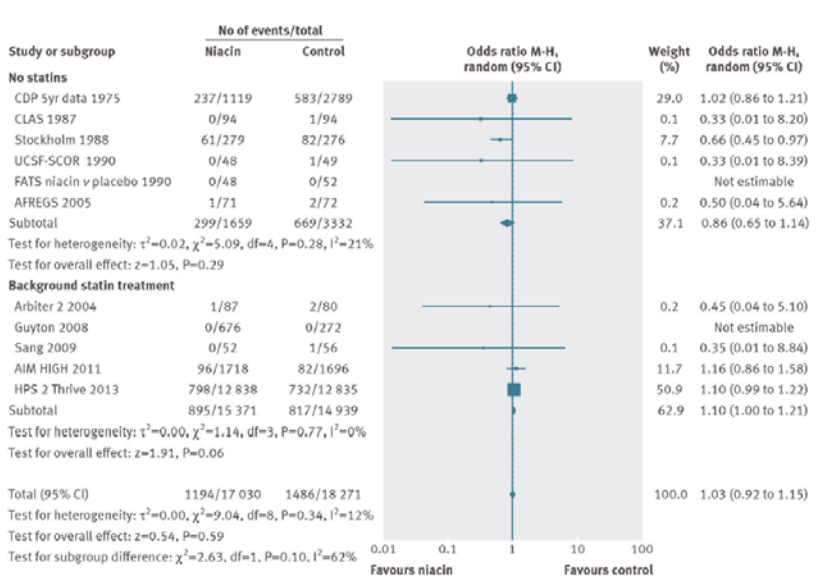


Nature Reviews | Drug Discovery

	Mean (SD) or No. (No. of CVD Cases)	Hazard Ratio[a] (95% CI)
Conventional risk factors		
Age at survey, y	56.42 (8.41)	1.87 (1.73-2.02)
Sex		
Men	68 520 (7734)	NA[b]
Women	71 061 (4500)	NA[b]
Current smoking		
No	102 261 (7137)	1.0 [Reference]
Yes	37 320 (5097)	1.79 (1.66-1.94)
History of diabetes		
No	131 610 (10 722)	1.0 [Reference]
Yes	7971 (1512)	2.04 (1.76-2.35)
Systolic blood pressure, mm Hg	135.19 (18.38)	1.31 (1.26-1.37)
Traditional lipids, mg/dL		
Total cholesterol	226 (42.5)	1.22 (1.17-1.27)
HDL-C	51.4 (14.7)	0.83 (0.78-0.87)
Triglyceride[c]	115 (80-168)[d]	1.19 (1.15-1.23)

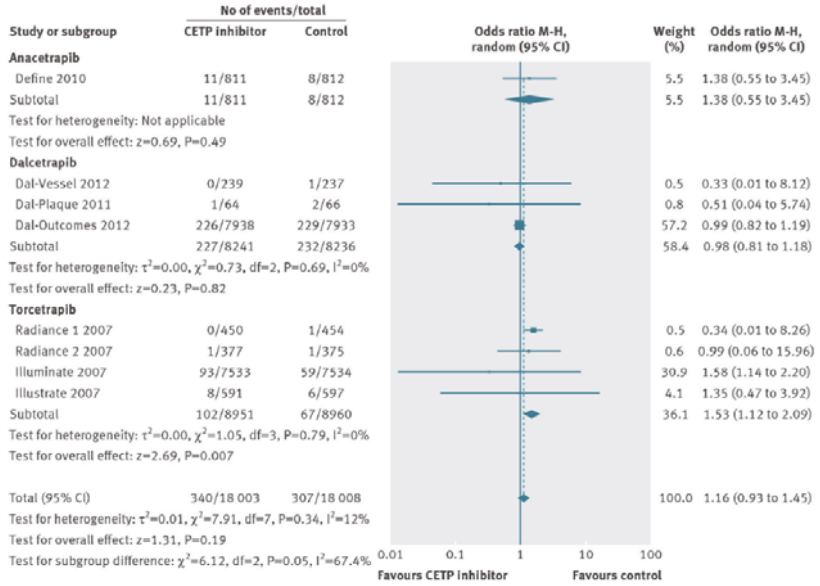
Emerging Risk Factors Collaboration JAMA. 2012;307:2499

Effect of HLD Raising Drugs



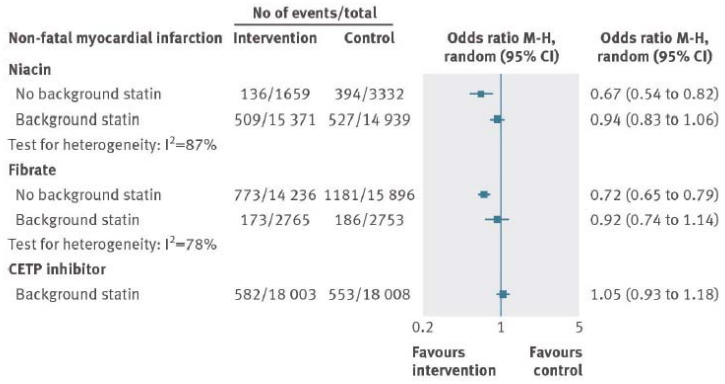
Study or subgroup	No of events/total: Niacin	Control	Odds ratio M-H, random (95% CI)	Weight (%)	Odds ratio M-H, random (95% CI)
No statins					
CDP 5yr data 1975	237/1119	583/2789		29.0	1.02 (0.86 to 1.21)
CLAS 1987	0/94	1/94		0.1	0.33 (0.01 to 8.20)
Stockholm 1988	61/279	82/276		7.7	0.66 (0.45 to 0.97)
UCSF-SCOR 1990	0/48	1/49		0.1	0.33 (0.01 to 8.39)
FATS niacin *v* placebo 1990	0/48	0/52			Not estimable
AFREGS 2005	1/71	2/72		0.2	0.50 (0.04 to 5.64)
Subtotal	299/1659	669/3332		37.1	0.86 (0.65 to 1.14)
Test for heterogeneity: τ^2=0.02, χ^2=5.09, df=4, P=0.28, I^2=21%					
Test for overall effect: z=1.05, P=0.29					
Background statin treatment					
Arbiter 2 2004	1/87	2/80		0.2	0.45 (0.04 to 5.10)
Guyton 2008	0/676	0/272			Not estimable
Sang 2009	0/52	1/56		0.1	0.35 (0.01 to 8.84)
AIM HIGH 2011	96/1718	82/1696		11.7	1.16 (0.86 to 1.58)
HPS 2 Thrive 2013	798/12 838	732/12 835		50.9	1.10 (0.99 to 1.22)
Subtotal	895/15 371	817/14 939		62.9	1.10 (1.00 to 1.21)
Test for heterogeneity: τ^2=0.00, χ^2=1.14, df=3, P=0.77, I^2=0%					
Test for overall effect: z=1.91, P=0.06					
Total (95% CI)	1194/17 030	1486/18 271		100.0	1.03 (0.92 to 1.15)
Test for heterogeneity: τ^2=0.00, χ^2=9.04, df=8, P=0.34, I^2=12%					
Test for overall effect: z=0.54, P=0.59					
Test for subgroup difference: χ^2=2.63, df=1, P=0.10, I^2=62%					

0.01 0.1 1 10 100
Favours niacin Favours control



Study or subgroup	No of events/total: CETP inhibitor	Control	Odds ratio M-H, random (95% CI)	Weight (%)	Odds ratio M-H, random (95% CI)
Anacetrapib					
Define 2010	11/811	8/812		5.5	1.38 (0.55 to 3.45)
Subtotal	11/811	8/812		5.5	1.38 (0.55 to 3.45)
Test for heterogeneity: Not applicable					
Test for overall effect: z=0.69, P=0.49					
Dalcetrapib					
Dal-Vessel 2012	0/239	1/237		0.5	0.33 (0.01 to 8.12)
Dal-Plaque 2011	1/64	2/66		0.8	0.51 (0.04 to 5.74)
Dal-Outcomes 2012	226/7938	229/7933		57.2	0.99 (0.82 to 1.19)
Subtotal	227/8241	232/8236		58.4	0.98 (0.81 to 1.18)
Test for heterogeneity: τ^2=0.00, χ^2=0.73, df=2, P=0.69, I^2=0%					
Test for overall effect: z=0.23, P=0.82					
Torcetrapib					
Radiance 1 2007	0/450	1/454		0.5	0.34 (0.01 to 8.26)
Radiance 2 2007	1/377	1/375		0.6	0.99 (0.06 to 15.96)
Illuminate 2007	93/7533	59/7534		30.9	1.58 (1.14 to 2.20)
Illustrate 2007	8/591	6/597		4.1	1.35 (0.47 to 3.92)
Subtotal	102/8951	67/8960		36.1	1.53 (1.12 to 2.09)
Test for heterogeneity: τ^2=0.00, χ^2=1.05, df=3, P=0.79, I^2=0%					
Test for overall effect: z=2.69, P=0.007					
Total (95% CI)	340/18 003	307/18 008		100.0	1.16 (0.93 to 1.45)
Test for heterogeneity: τ^2=0.01, χ^2=7.91, df=7, P=0.34, I^2=12%					
Test for overall effect: z=1.31, P=0.19					
Test for subgroup difference: χ^2=6.12, df=2, P=0.05, I^2=67.4%					

0.01 0.1 1 10 100
Favours CETP inhibitor Favours control

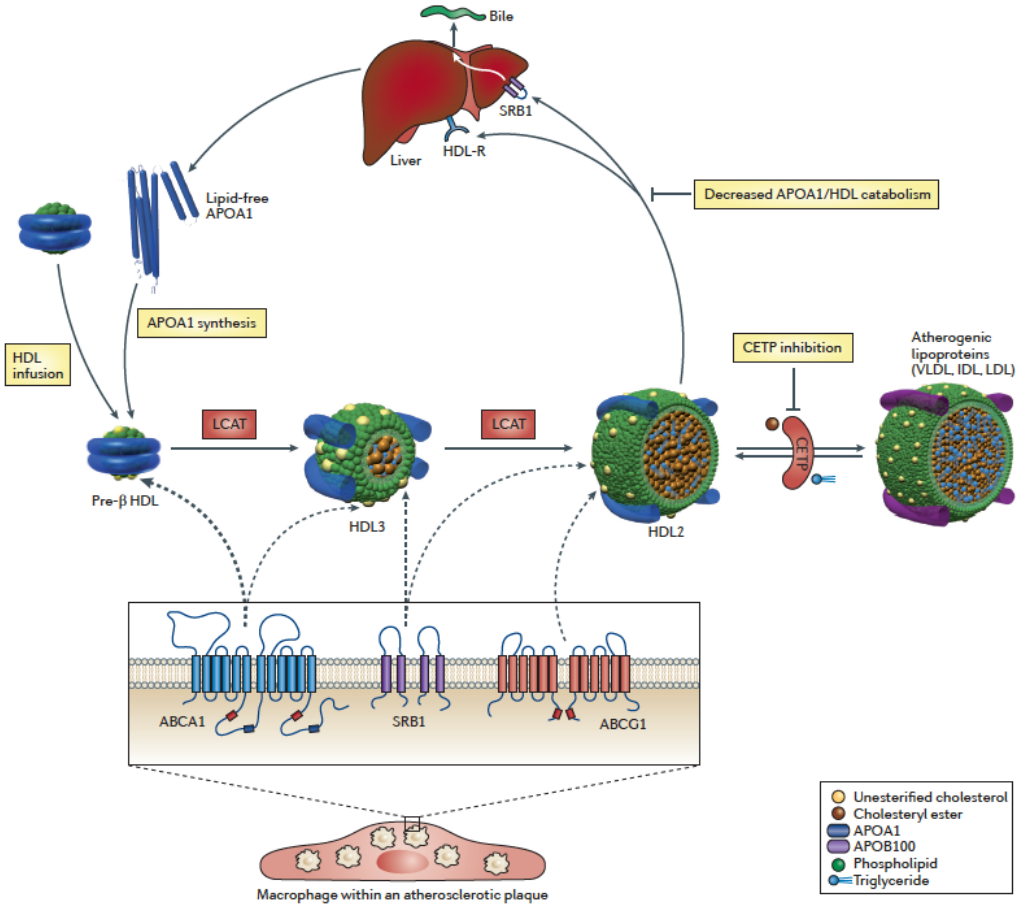


Non-fatal myocardial infarction	No of events/total: Intervention	Control	Odds ratio M-H, random (95% CI)	Odds ratio M-H, random (95% CI)
Niacin				
No background statin	136/1659	394/3332		0.67 (0.54 to 0.82)
Background statin	509/15 371	527/14 939		0.94 (0.83 to 1.06)
Test for heterogeneity: I^2=87%				
Fibrate				
No background statin	773/14 236	1181/15 896		0.72 (0.65 to 0.79)
Background statin	173/2765	186/2753		0.92 (0.74 to 1.14)
Test for heterogeneity: I^2=78%				
CETP inhibitor				
Background statin	582/18 003	553/18 008		1.05 (0.93 to 1.18)

0.2 1 5
Favours intervention Favours control

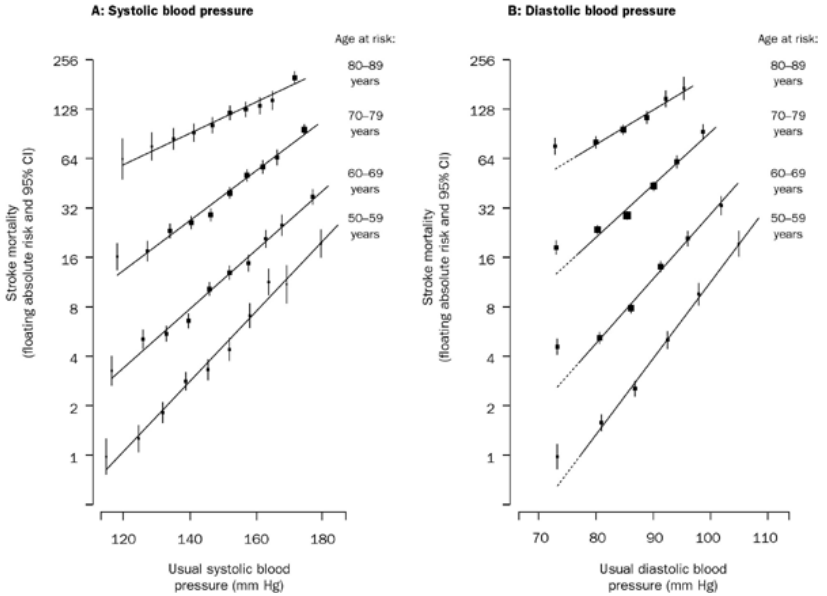
Keene et al *BMJ* 2014;349:g4379

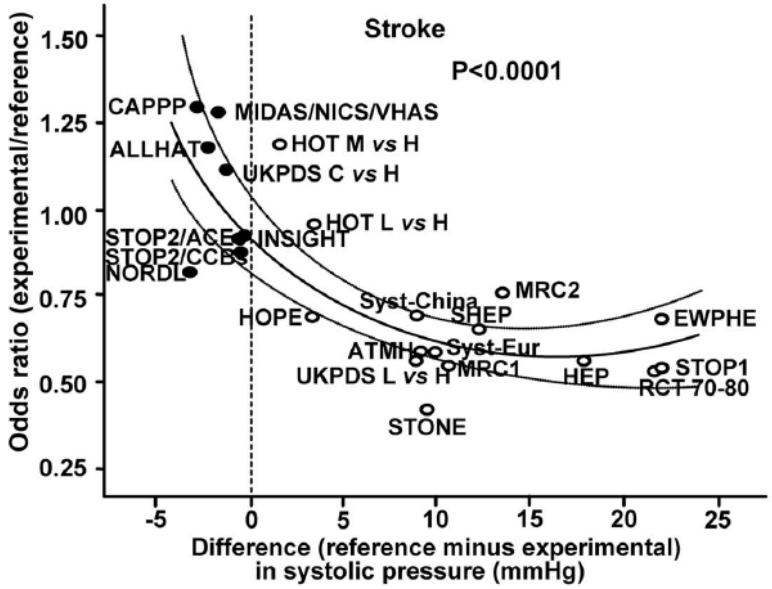
Complexity of HDL



Nature Reviews Drug Discovery 2014; 13:445

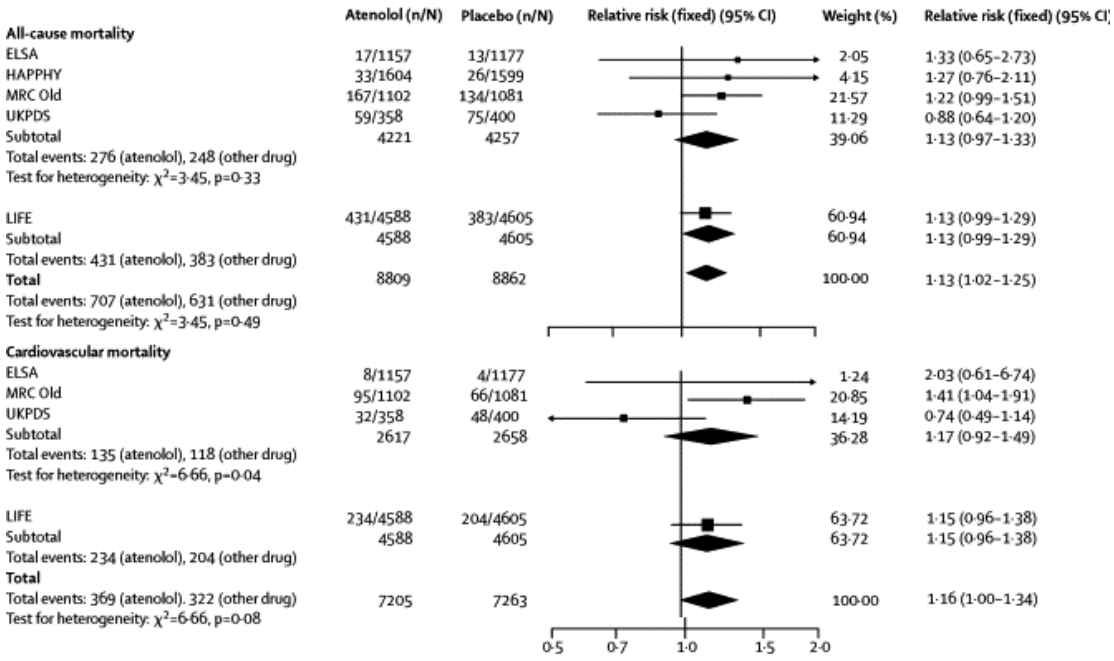
Blood Pressure and CVD





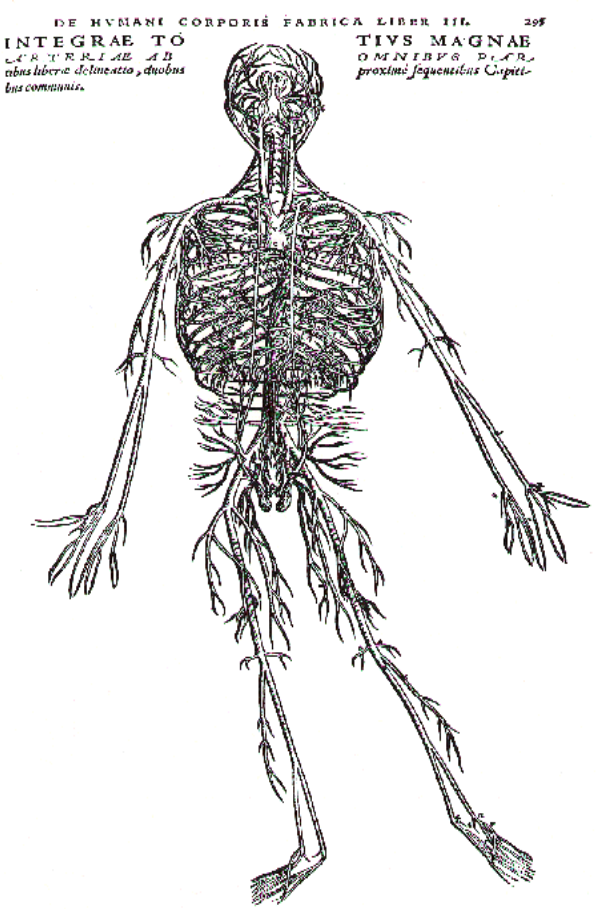
Lancet 2002; **360:** 1903-13 and *Hypertension* 2007; 50:154

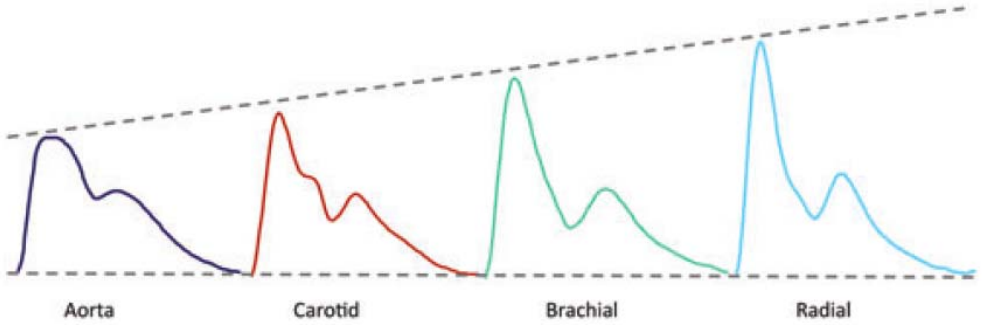
Meta-analysis of Comparative Studies With Atenolol in Hypertension

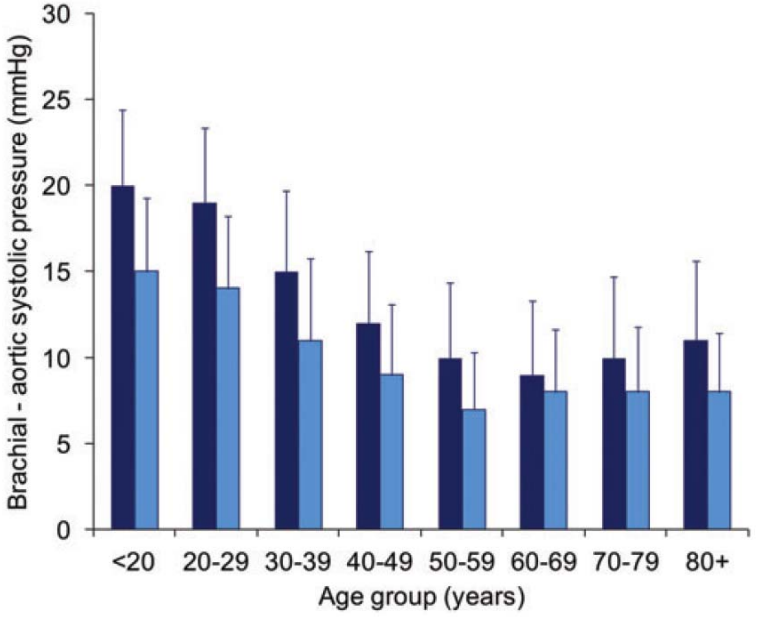


Carlberg et al. Lancet 2005;**364**:1684

Pressure Amplification





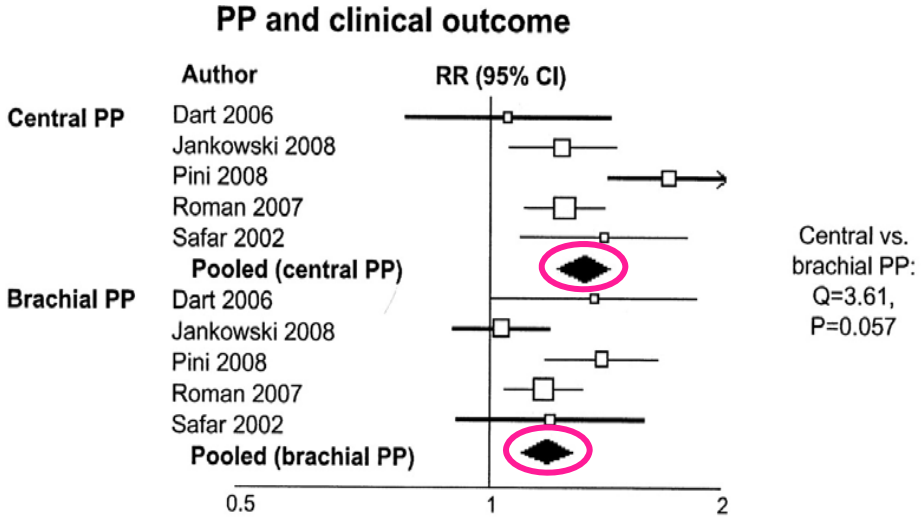


McEniery et al. Eur Heart J 2014

Central versus Brachial Pressure and Cardiovascular Risk

Source	Year, Country	Population	Design	Parameter	End Point
Saba et al[16]*†	1993, United States	Normotensives	Cross-sectional	Carotid AIx	LVMI, carotid thickness
Boutouyrie et al[17]*†	1999, France	Hypertensives	Cross-sectional	Carotid PP	Carotid thickness
Boutouyrie et al[18]*†	2000, France	Hypertensives	Longitudinal (9-month FU)	Carotid PP	Carotid IMT reduction with treatment
Roman et al[19]	2000, United States	Normotensives, Hypertensives	Cross-sectional	Carotid systolic BP	Relative LV wall thickness
Waddell et al[20]*†	2001, Australia	CAD	Cross-sectional	Carotid BP	Extent of CAD
Nishijima et al[21]*	2001, Japan	Suspected CAD	Cross-sectional	Aortic fractional PP	Incident CAD
Nurnberger et al[22]	2002, Germany	Healthy+CVD	Cross-sectional	Carotid AIx	CV risk scores
Philippe et al[23]*	2002, France	CAD	Cross-sectional	Aortic PP	Extent of CAD
Hayashi et al[24]*	2002, Japan	Suspected CAD	Cross-sectional	Aortic AIx	Incident CAD
De Luca et al[25]†	2004, REASON Study	Hypertensives	Longitudinal (1-year FU)	Carotid PP	LVMI reduction
Weber et al[26]	2004, Austria	Suspected CAD	Cross-sectional	Aortic AP, AIx	Incident CAD
Jankowski et al[27]*	2004, Poland	CAD	Cross-sectional	Aortic BP	Extent of CAD
Danchin et al[28]*	2004, France	Suspected CAD	Cross-sectional	Aortic PP	Incidence and extent of CAD
Booth et al[29]	2004, United Kingdom	Systemic vasculitis	Cross-sectional	Aortic AIx	Disease activity
Roman et al[30]	2007, United States	High-risk	Cross-sectional	Aortic PP	Carotid IMT and mass
Hashimoto et al[31]†	2007, Japan	Hypertensives	Longitudinal (1-year FU)	Aortic AIx	LVMI reduction with treatment

AIx indicates augmentation index; CAD, coronary artery disease; CV, cardiovascular; FU, follow-up; IMT, intima–media thickness; LV, left ventricular; LVMI, left ventricular mass index.
*Central pressure measured directly.
†These studies have shown incremental value of central indices over peripheral BP.



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Hypertension 2007;50:154. & *Eur Heart J* 2010;31:1865.

Comparative Effects of Antihypertensive Drugs Classes on Aortic Pressure ISH

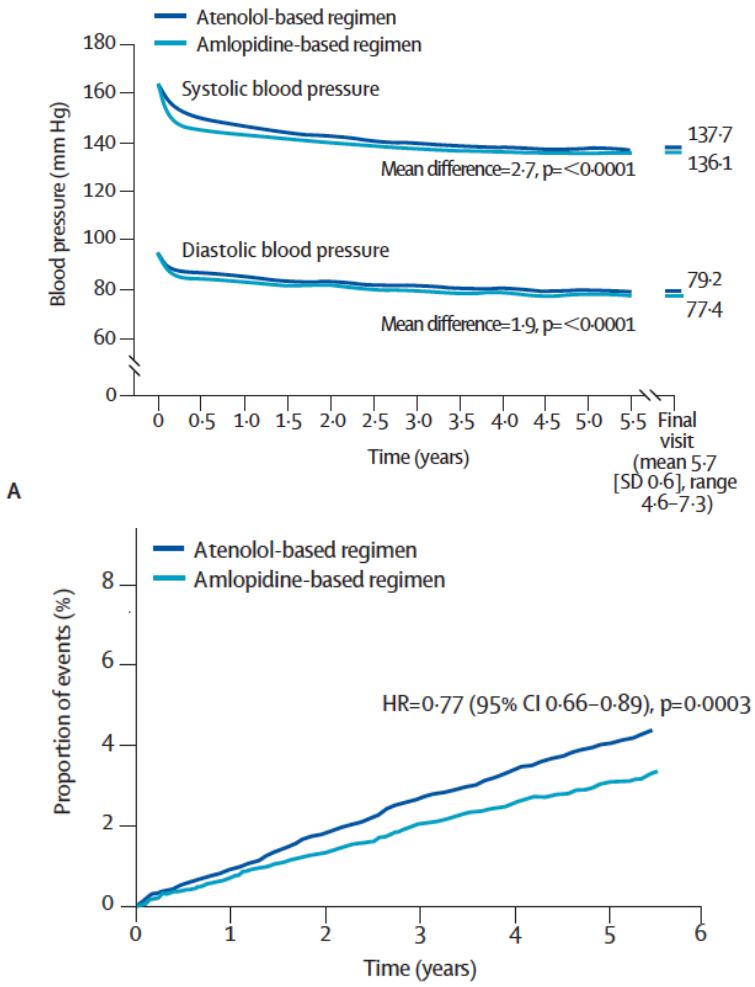
Table 2. Hemodynamic Indices Before and After the 10-Week Active Therapy Period

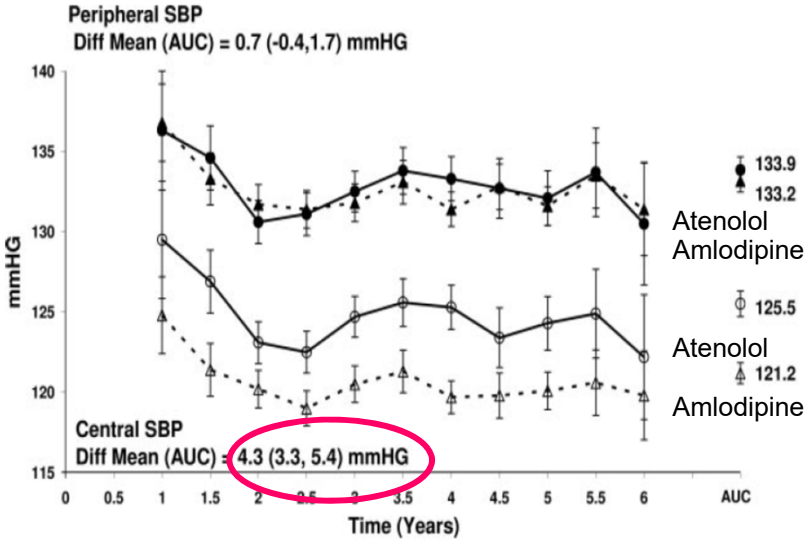
	Perindopril		Atenolol		Lercanidipine		Bendrofluazide		2-Way ANOVA, Time, Drug
Parameter	Placebo	10 wk	Placebo	10 wk	Placebo	10 wk	Placebo	10 wk	
Peripheral SBP, mm Hg	153±3	136±4*	156±2	138±4*	146±2	133±3*	154±3	140±3*	<0.001, 0.1
Peripheral DBP, mm Hg	80±2	75±2*	84±2	76±3*	80±2	79±3	85±2	82±3	<0.001, 0.3
Peripheral PP, mm Hg	72±4	61±4*	72±3	62±3*	66±3	54±4*	69±4	58±4*	<0.001, 0.3
Central SBP, mm Hg	140±4	123±4*	144±3	130±4*	132±2	118±3*	139±2	126±2*	<0.001, 0.02‡
Central PP, mm Hg	58±4	46±3*	59±2	53±3	51±3	38±4*	53±4	42±3*	<0.001, 0.02‡§
P1 height, mm Hg	42±3	36±3*	42±2	35±2*	37±2	30±2*	39±2	32±2*	<0.001, 0.1
PP amplification	1.33±0.08	1.35±0.06	1.24±0.03	1.17±0.02*	1.31±0.04	1.42±0.06	1.33±0.04	1.38±0.04	0.2, 0.03‡
MAP, mm Hg	104±2	96±2*	108±2	97±3*	102±2	97±2	109±2	102±2*	<0.001, 0.1
HR, bpm	71±3	73±3	67±2	57±3*	73±2	75±3	75±3	77±3	0.4, 0.001†‡§
AP, mm Hg	15±2	10±2*	17±2	19±2	14±2	8±2*	13±2	11±2	0.002, 0.02‡
AIx, %	25±3	20±4	29±2	34±2*	26±2	19±3*	25±3	24±3	0.2, 0.03†‡§
Aortic PWV, m/s	9.01±0.59	9.34±0.47	9.64±0.50	8.82±0.46	9.54±0.60	9.79±0.89	10.25±0.28	10.55±0.57	0.9, 0.4

McKenzie et al *Hypertension* 2009;54:409

ASCOT Study

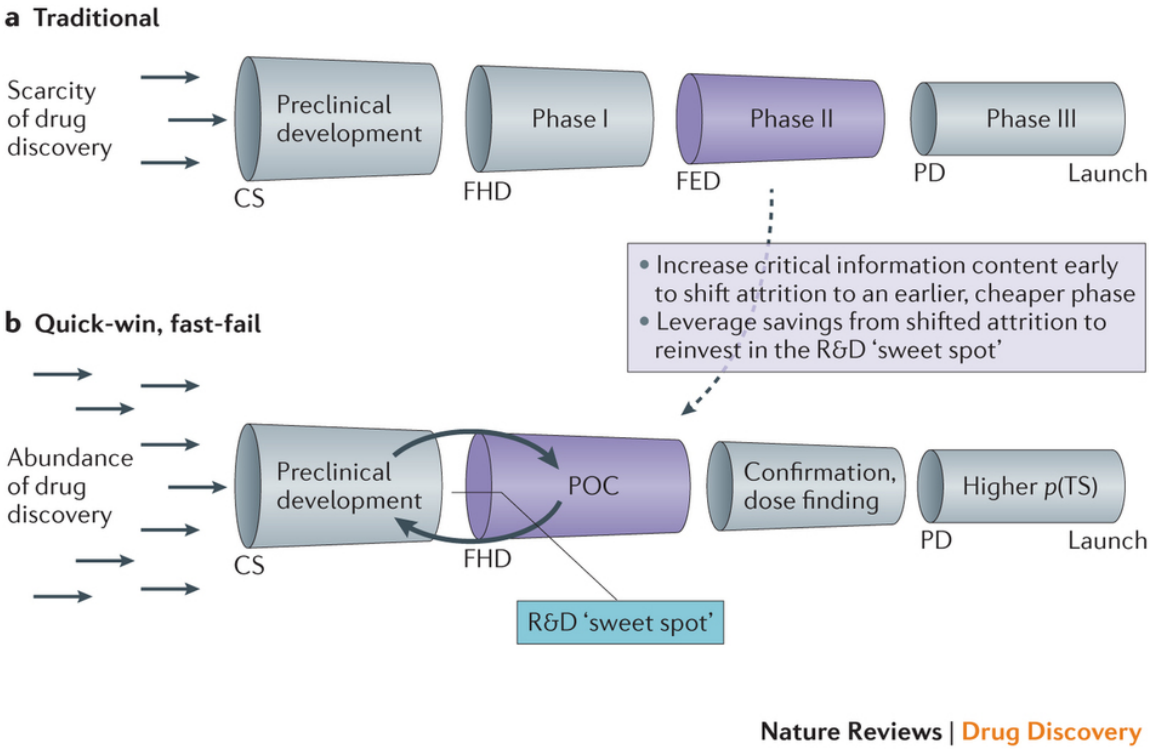
n=19,257, mean age 63





B Dahlof Lancet 2005;366:895 & CAFÉ. *Circulation* 2006; **113**:

Improving the Process



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