THROMBOSIS

COMPASS Topline Results

A Randomized Controlled Trial of Rivaroxaban for the Prevention of Major Cardiovascular Events in Patients With Coronary or Peripheral Artery Disease

(Cardiovascular OutcoMes for People Using Anticoagulation StrategieS)

Study number 15786

www.clinicaltrials.gov/show/NCT01776424

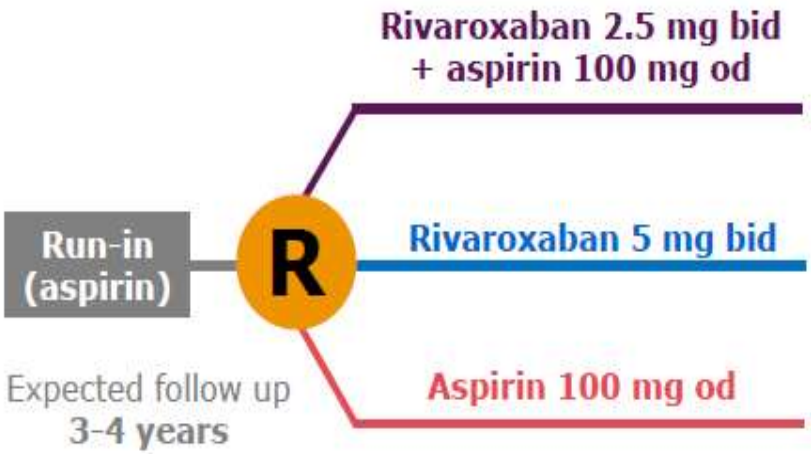
Co-PIs: John Eikelboom & Stuart Connolly
SC Chair: Salim Yusuf
SC Co-Chair: Keith Fox

COMPASS DESIGN

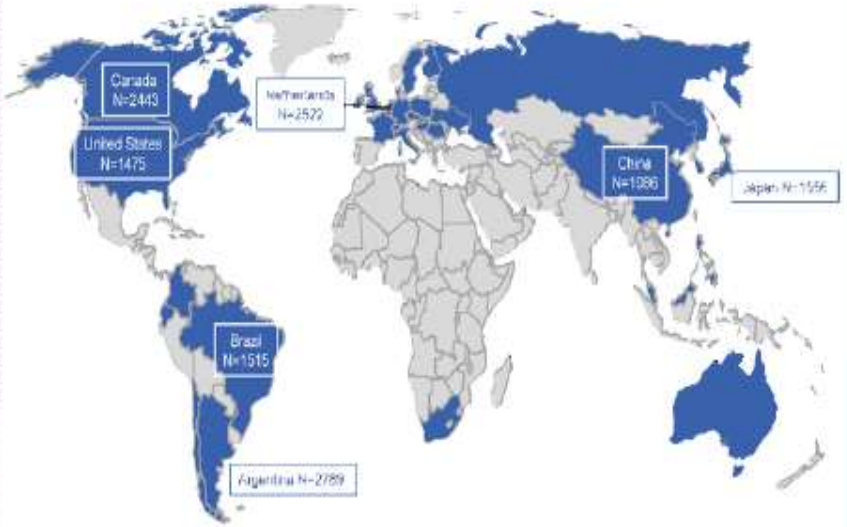
COMPASS

Stable CAD or PAD

2,200 with a primary outcome event

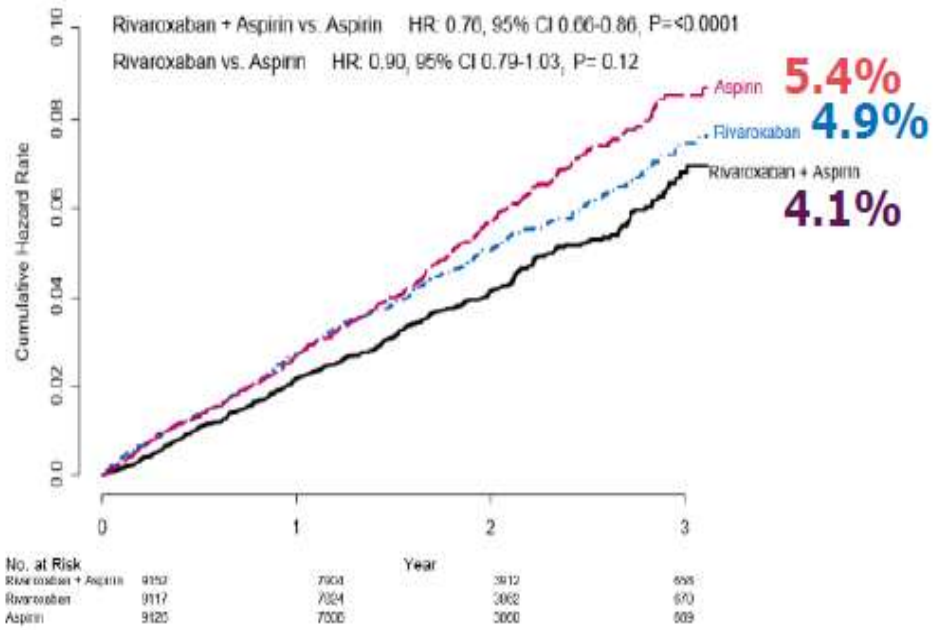


602 sites, 33 countries



S. Anand (Hamilton, CA) 1157

PRIMARY OUTCOME: CV DEATH, STROKE, MI



Primary components

Outcome	R + A N=9,152	A N=9,126	Rivaroxaban + Aspirin vs. Aspirin	
			HR (95% CI)	p
CV death	1.7%	2.2%	0.78 (0.64-0.96)	0.02
Stroke	0.9%	1.6%	0.58 (0.44-0.76)	<0.0001
MI	178 1.9%	2.2%	0.86 (0.70-1.05)	0.14

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MAJOR BLEEDING

Outcome	R + A N=9,152	R N=9,117	A N=9,126	Rivaroxaban + Aspirin vs. Aspirin		Rivaroxaban vs. Aspirin	
	N (%)	N (%)	N (%)	HR (95% CI)	P	HR (95% CI)	P
Major bleeding	(3.1%)	(2.8%)	(1.9%)	1.70 (1.40-2.05)	<0.0001	1.51 (1.25-1.84)	<0.0001
Fatal	(0.2%)	(0.2%)	(0.1%)	1.49 (0.67-3.33)	0.32	1.40 (0.62-3.15)	0.41
Non fatal ICH*	(0.2%)	(0.4%)	(0.2%)	1.10 (0.59-2.04)	0.77	1.69 (0.96-2.98)	0.07
Non-fatal other critical organ*	(0.5%)	(0.5%)	(0.3%)	1.43 (0.89-2.29)	0.14	1.57 (0.98-2.50)	0.06

* symptomatic

NET CLINICAL BENEFIT

Rivaroxaban 2.5 mg bid plus aspirin 100 mg od:

- **Reduces CV death, stroke, MI**
- **Increases major bleeding without a significant increase in fatal, intracranial or critical organ bleeding**
- **Provides a net clinical benefit**

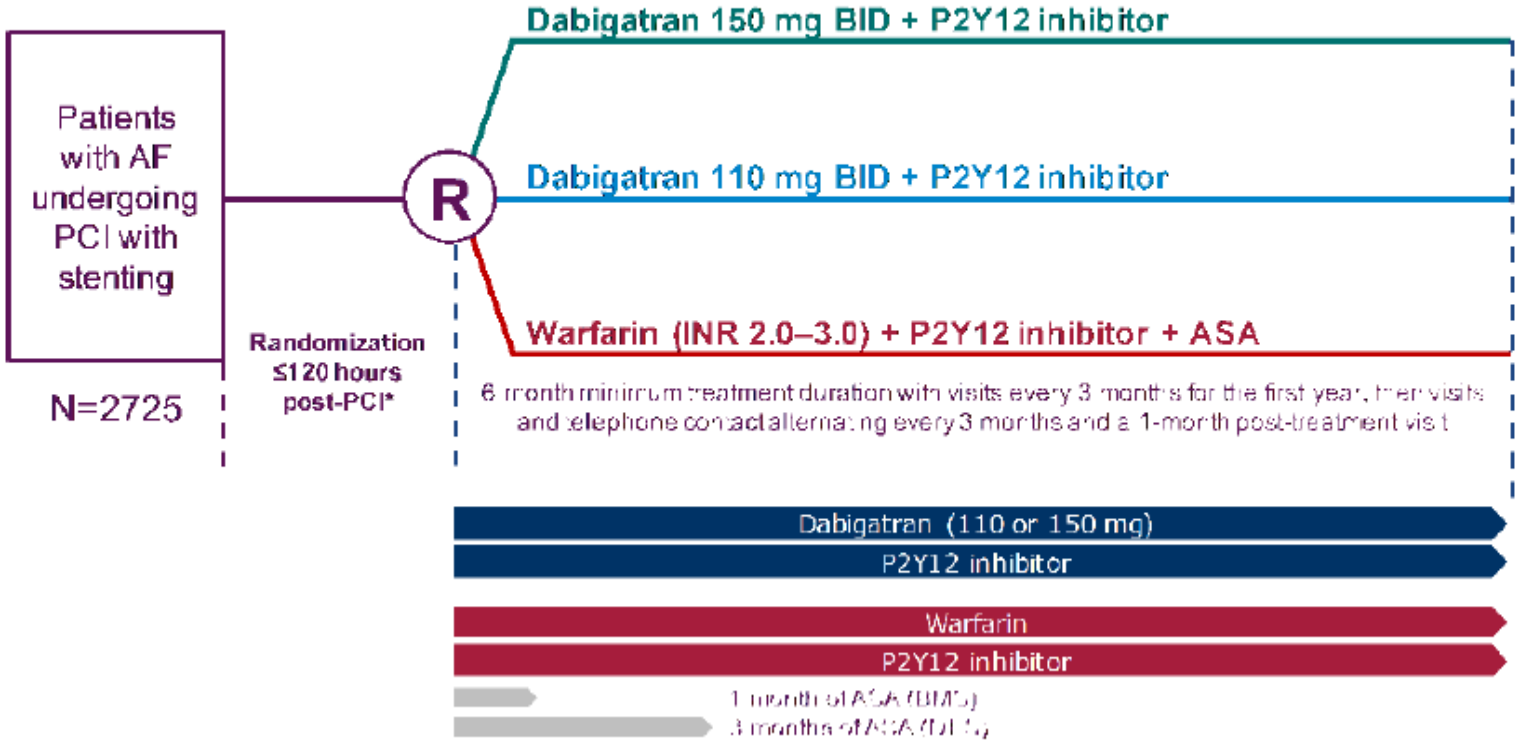
Outcome	R + A N=9,152	A N=9,126	Rivaroxaban + Aspirin vs. Aspirin	
	N (%)	N (%)	HR (95% CI)	P
Net clinical benefit (Primary + Severe bleeding events)	431 (4.7%)	534 (5.9%)	0.80 (0.70-0.91)	0.0005

No significant benefit of rivaroxaban alone

S. Anand (Hamilton, CA) 1157

RE-DUAL PCI TRIAL

Multicenter, randomized, open-label trial following a PROBE design



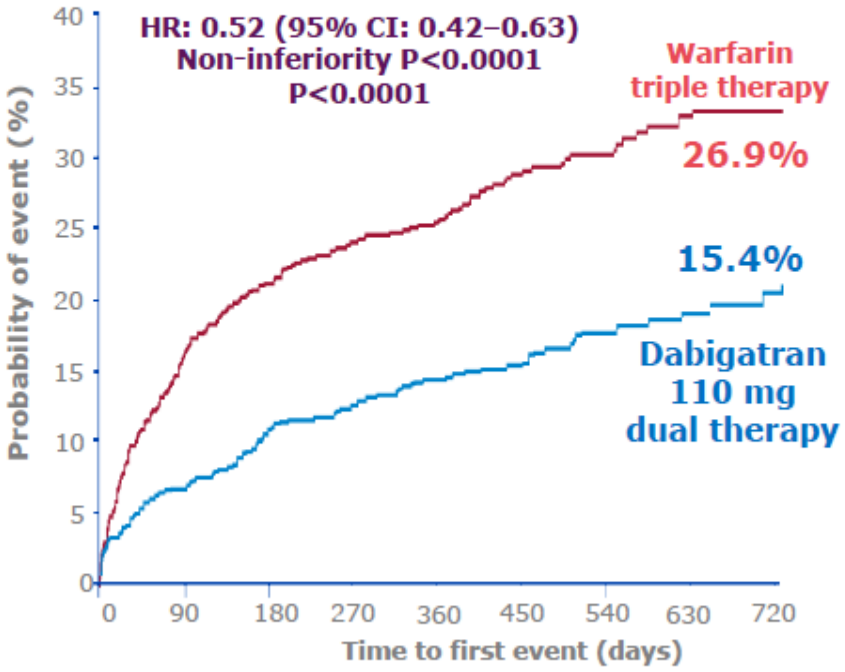
RE-DUAL PCI:

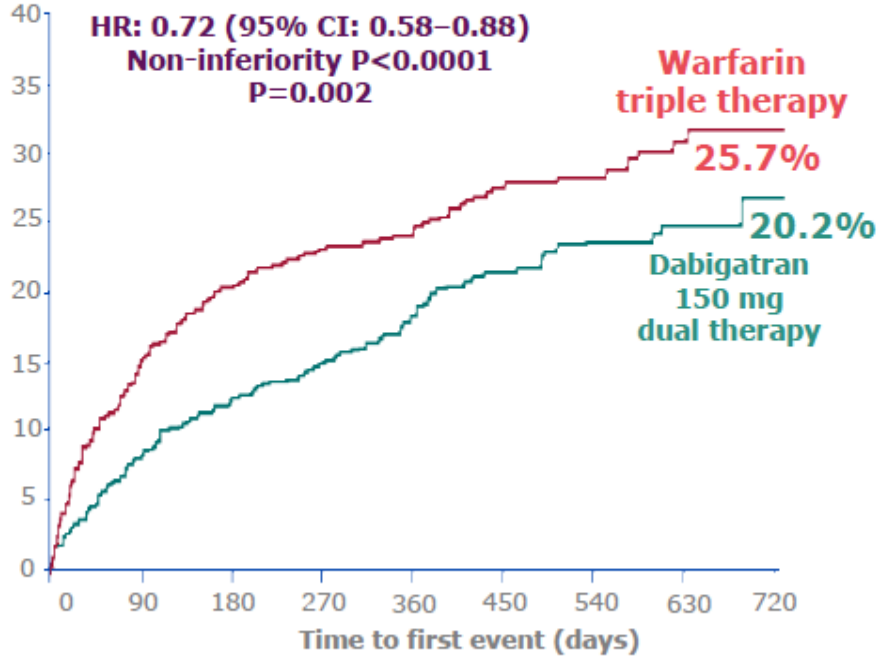
Mean duration of follow-up: ~14 months

C.P. Cannon (Boston, US) 1920

RE-DUAL PCI TRIAL – PRIMARY ENDPOINT

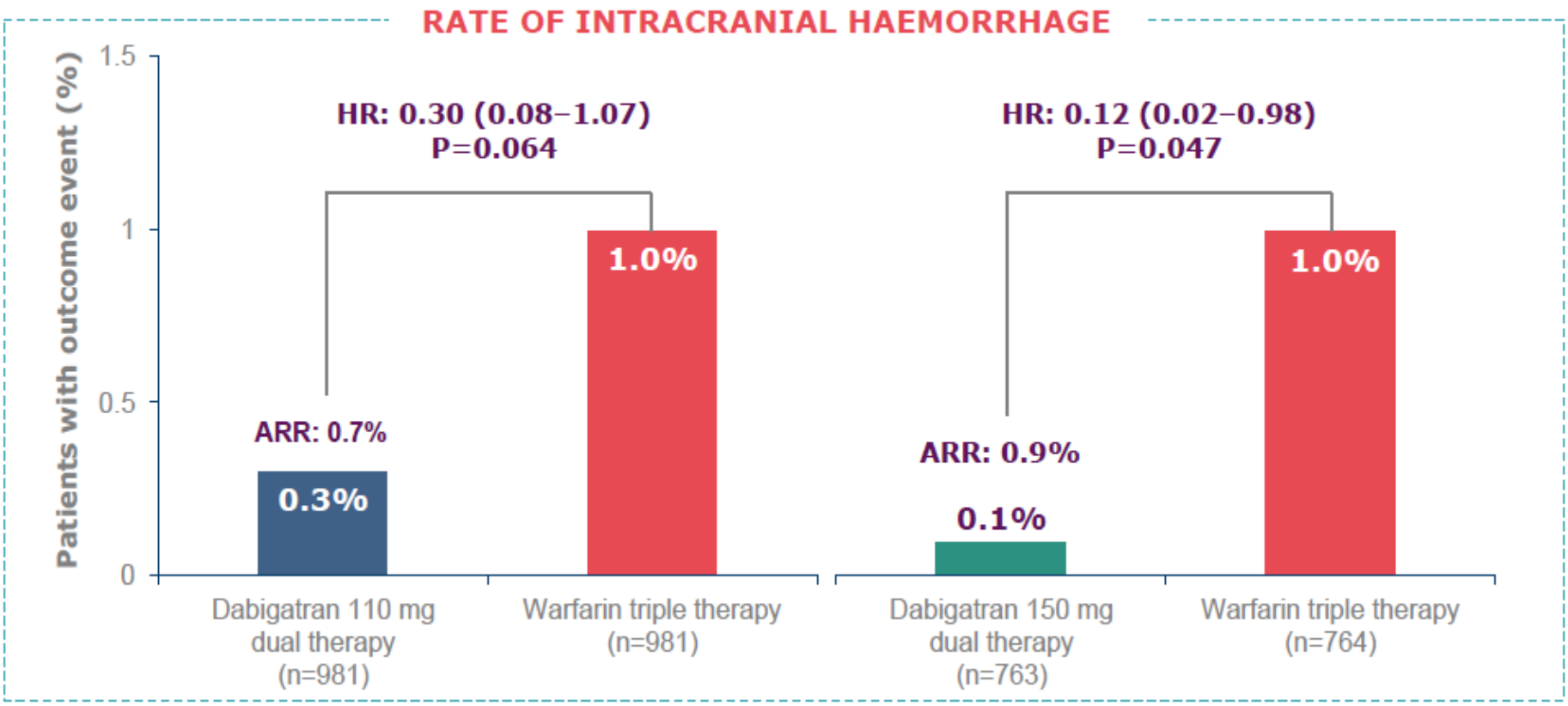
Time to first major bleeding event or clinically relevant non-major bleeding event





C.P. Cannon (Boston, US) 1920

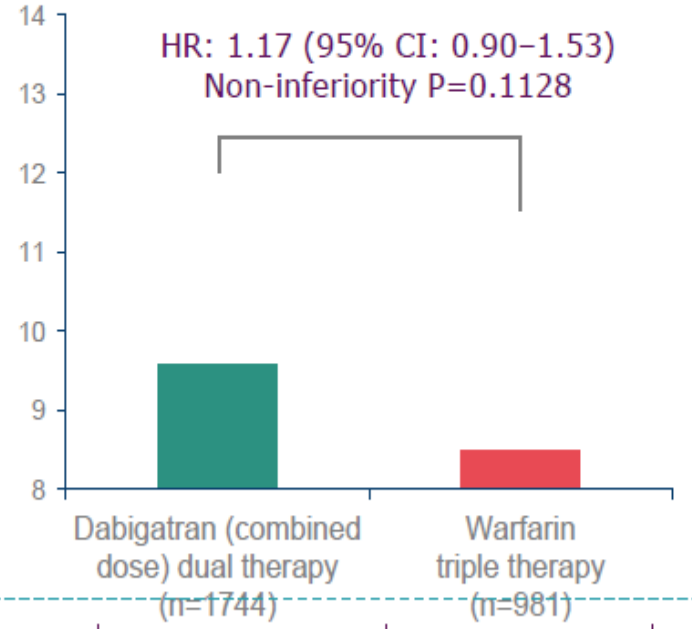
RE-DUAL PCI TRIAL - IMPORTANT BLEEDS



C.P. Cannon (Boston, US) 1920

RE-DUAL PCI TRIAL - ISCHEMIC EVENTS

All-cause death, MI, stroke or systemic embolism



Stent thrombosis	1.5%	0.8%	HR 1.86 (0.79–4.40)

- **In patients with atrial fibrillation and stenting,**

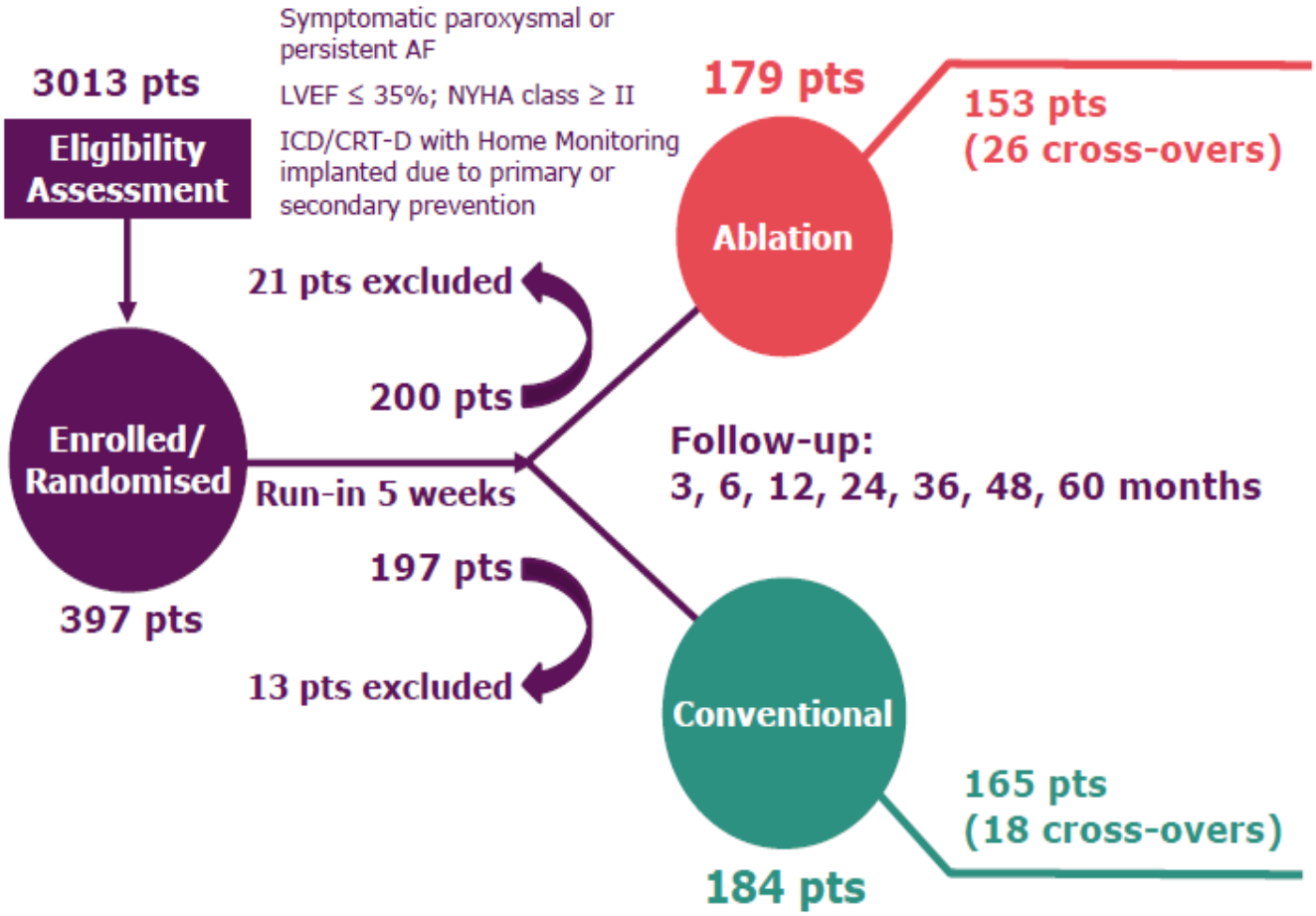
  dual therapy (dabigatran and a P2Y12 inhibitor) is superior regarding the bleeding risk reduction and noninferior regarding thromboembolic events

  compared to triple therapy (warfarin, P2Y12 inhibitor, ASS)

C.P. Cannon (Boston, US) 1920

ARRHYTHMIAS

CASTLE-AF

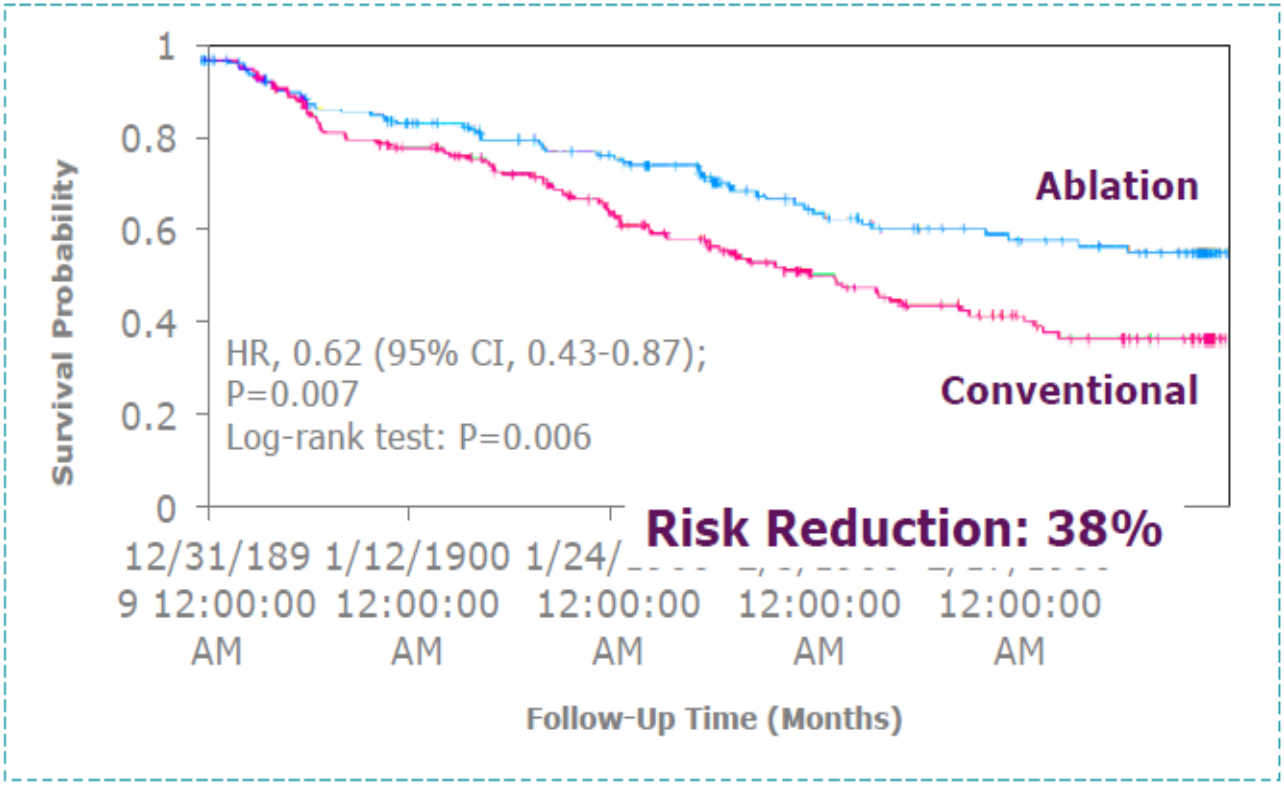


Primary Endpoint

All-cause mortality + Worsening heart failure admissions

N. Marrouche (Salt Lake City, USA) 1148

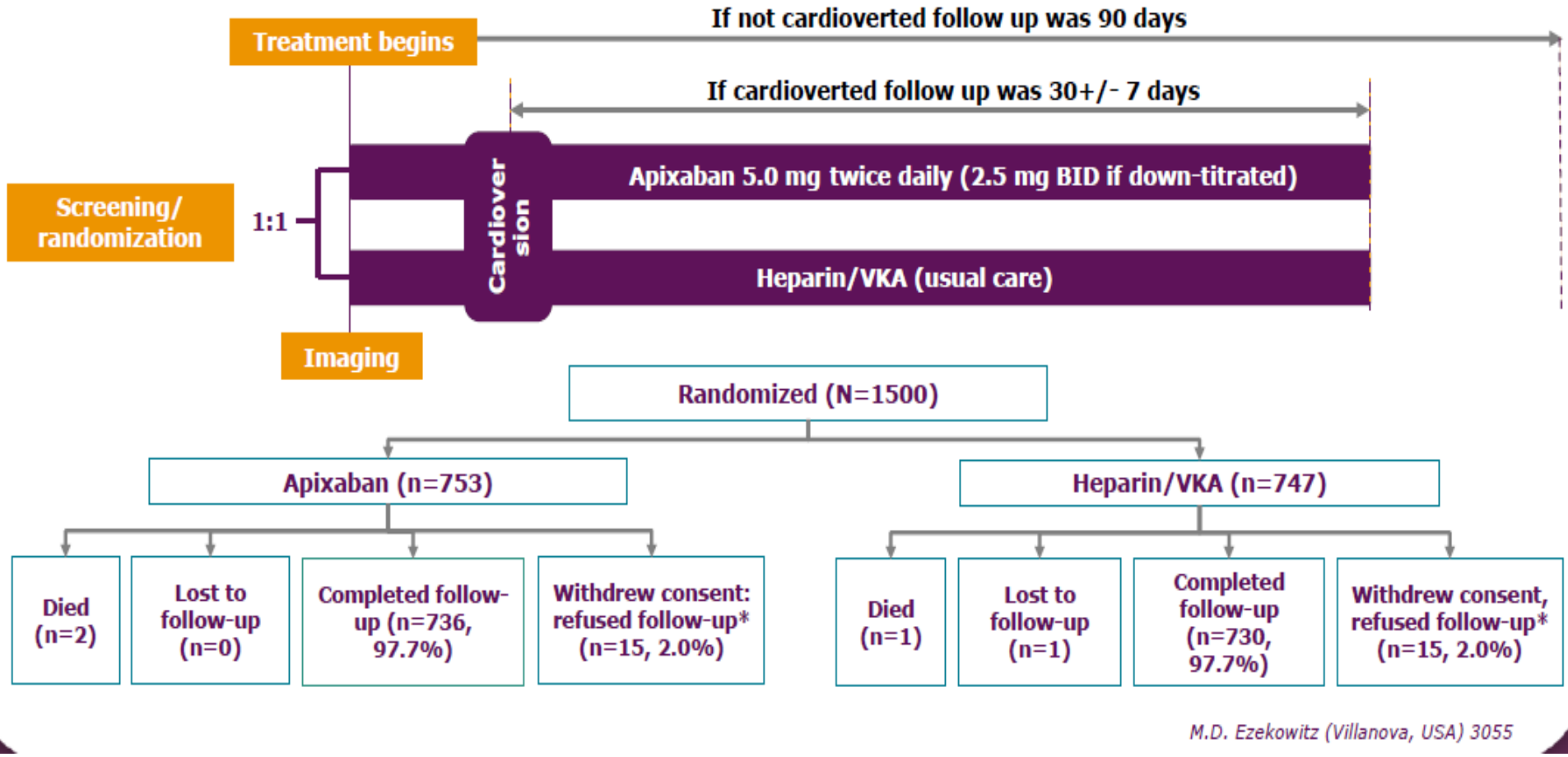
RESULTS-CASTLE AF: 1° COMPOSITE ENDPOINT



All cause mortality: HR: 0.53 (95% CI, 0.32-0.86); P=0.011 Log-rank test: P=0.009

N. Marrouche (Salt Lake City, USA) 1148

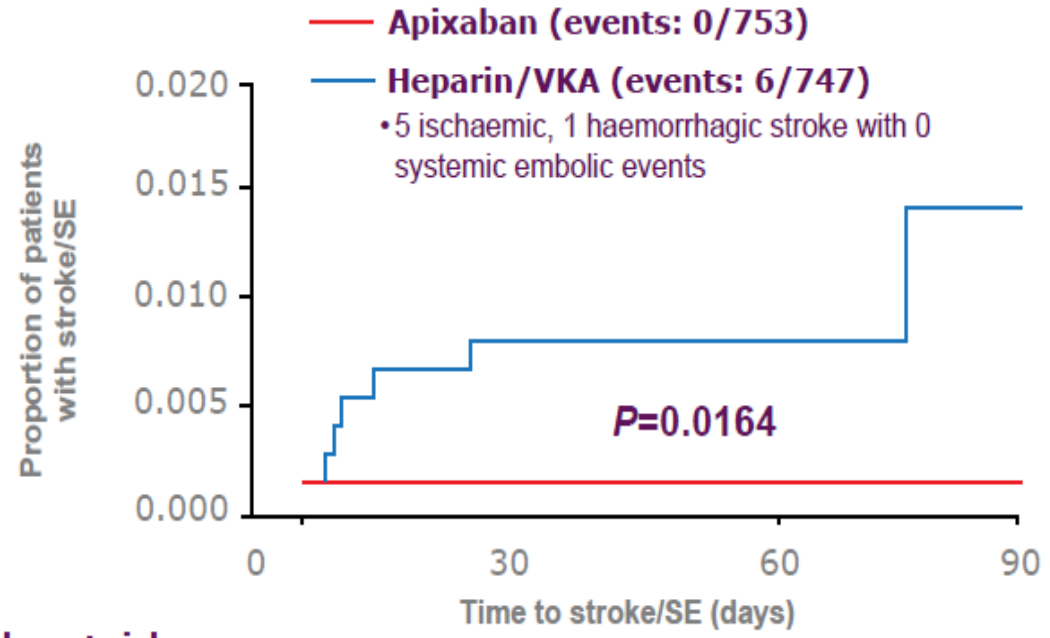
EMANATE: APIXABAN VERSUS VKA PLUS HEPARIN FOR CARDIOVERSION OF AF



M.D. Ezekowitz (Villanova, USA) 3055

EMANATE: OUTCOME EVENTS

Stroke/SE



Number at risk

Apixaban	752	614	199	55
Heparin/VKA	747	565	231	88

Safety outcomes N = 1456

	Apixaban Total (n=735)	Apixaban Loading Dose Subset (n=342)	Heparin/ VKA Total (n=721)
Major bleeds	3	(1)	6
Clinically relevant non -major bleeds	11	(4)	13

*Randomised and received ≥ 1 dose of study medication (by treatment received)

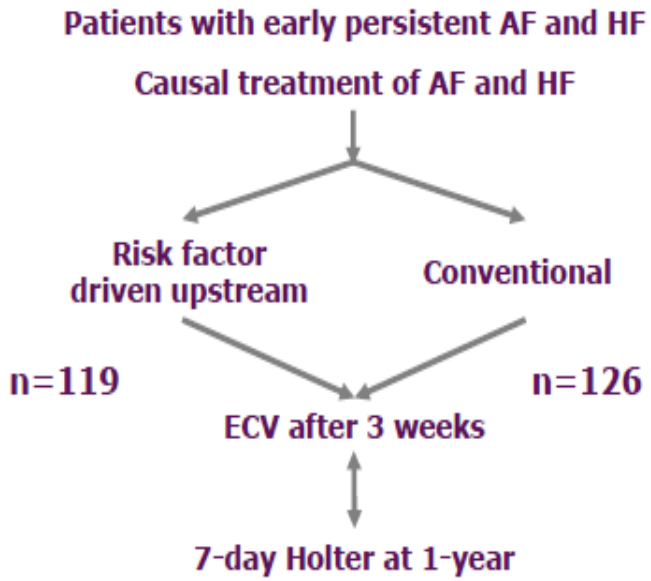
Loading dose for Apixaban: 10 mg
Imaging guided cardioversion

One patient's adjudicated stroke date was one day prior to randomisation; thus at Day 0, only 1499 were at risk for stroke.
No patients had SE. ITT population. SE = systemic embolism

RACE 3: THE ROUTINE VERSUS AGGRESSIVE UPSTREAM RHYTHM CONTROL FOR PREVENTION OF EARLY PERSISTENT ATRIAL FIBRILLATION IN HEART FAILURE STUDY

Design

Early symptomatic persistent AF:
Total persistent AF duration >7 days and <6 months, a history of ≤1 ECV



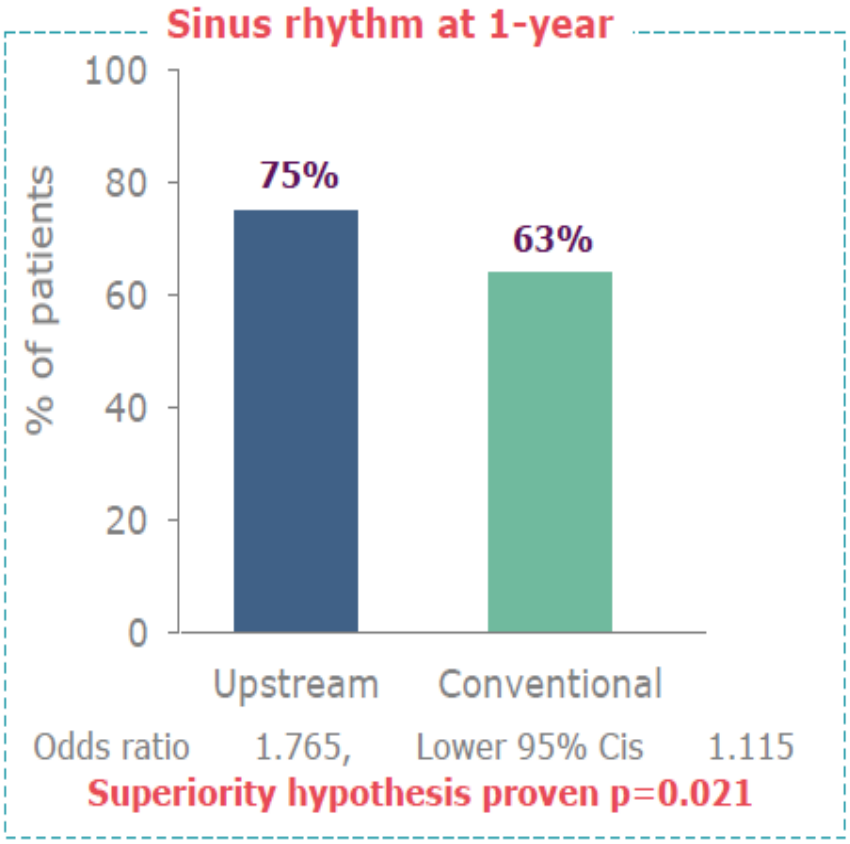
On top of that in the upstream group:

1. Mineralocorticoid receptor antagonists
2. Statins
3. ACE-inhibitors and/or angiotensin-receptor blockers
4. Cardiac rehabilitation:
   - physical activity
   - dietary restrictions
   - counselling

In both groups rhythm control and HF therapy according to guidelines

RACE-3

Primary endpoint:
Presence of sinus rhythm, defined as sinus rhythm during the 7-day Holter at 1-year



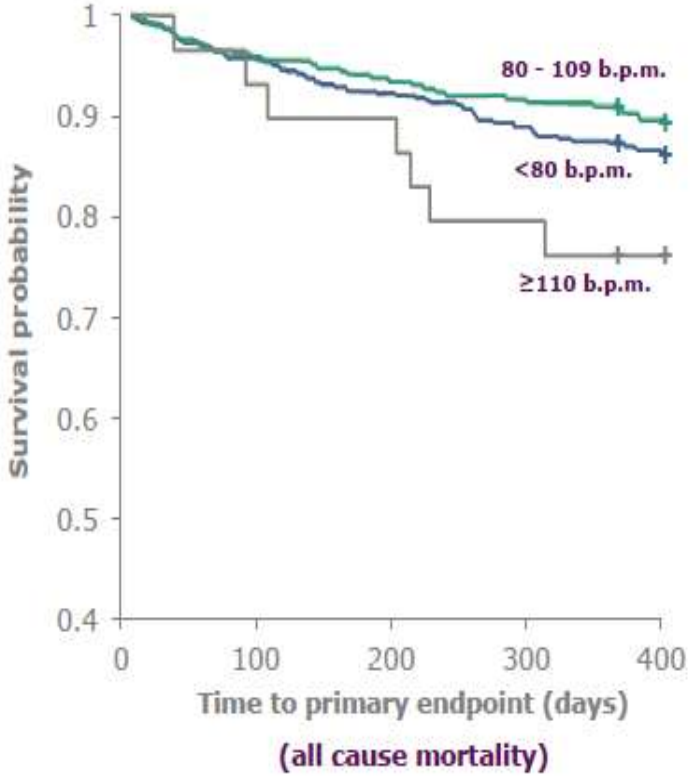
The RACE 3 study demonstrates that risk factor driven upstream therapy, including treatment of risk factors and change of lifestyle, is effective and feasible.

I.C. Van Gelder (Groningen, NL) 1145

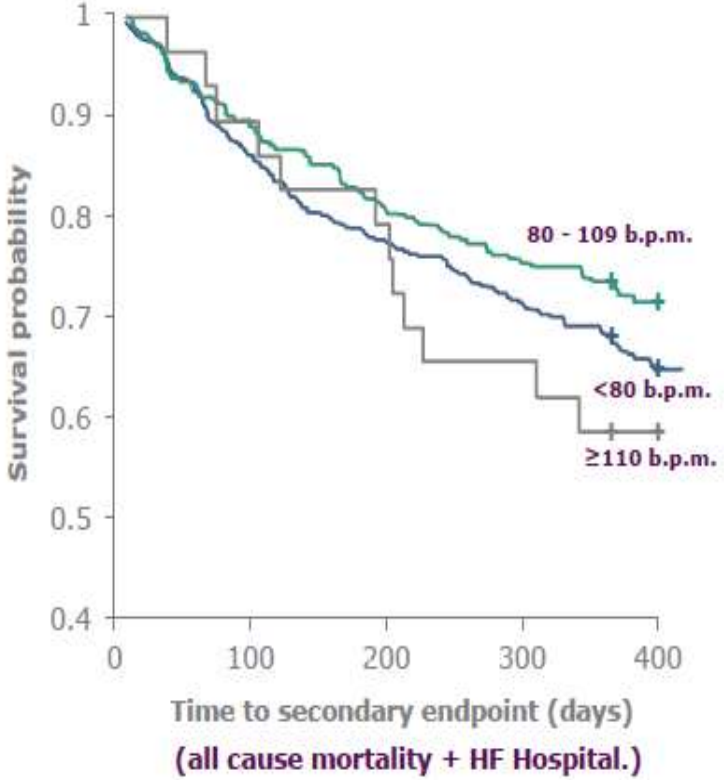
HEART FAILURE

DO BETA-BLOCKERS IMPROVE ONE-YEAR SURVIVAL IN HEART FAILURE PATIENTS WITH ATRIAL FIBRILLATION? – RESULTS FROM THE ESC-HF REGISTRY

1st CHAIR AND DEPARTMENT of CARDIOLOGY
MEDICAL UNIVERSITY of WARSAW



(all cause mortality)

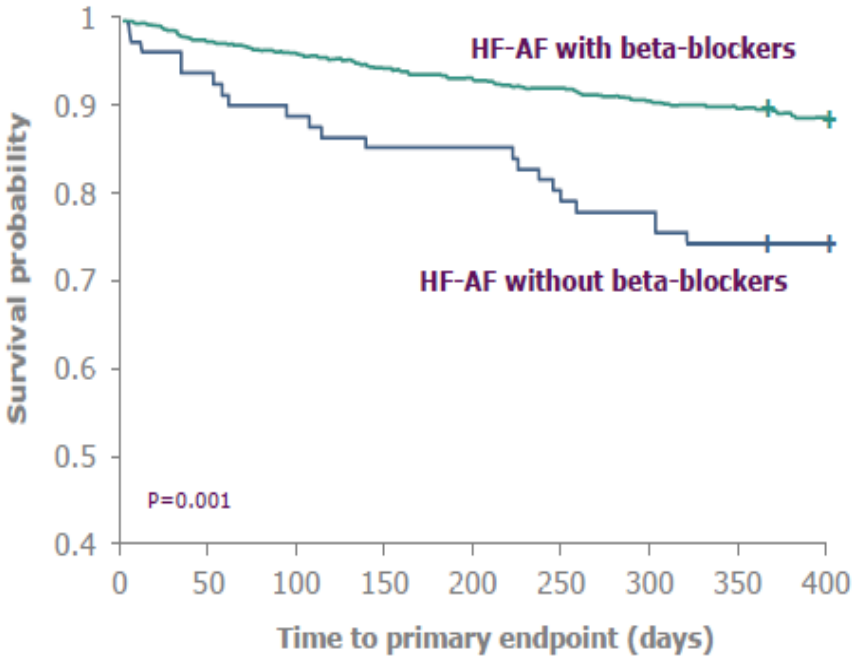


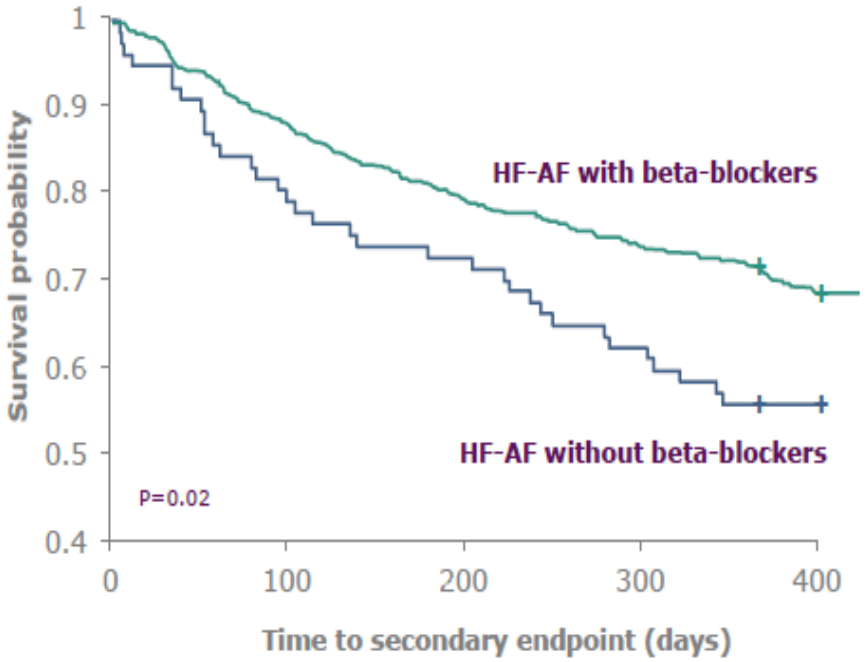
(all cause mortality + HF Hospital.)

b.p.m. – beats per minute

K. Ozieranski (Warsaw, PL) 4899

DO BETA-BLOCKERS IMPROVE ONE-YEAR SURVIVAL IN HEART FAILURE PATIENTS WITH ATRIAL FIBRILLATION? – RESULTS FROM THE ESC-HF REGISTRY





Beta-blockers	0.52 (0.31-0.89)	0.02	0.74 (0.49-1.11)	0.14

AF – atrial fibrillation, HF – heart failure

K. Ozieranski (Warsaw, PL) 4899

ADHERENCE TO BETA-BLOCKERS AND LONG-TERM RISK OF HEART FAILURE AND MORTALITY AFTER A MYOCARDIAL INFARCTION: A STUDY OF 40,697 PATIENTS IN THE SWEDEHEART REGISTRY

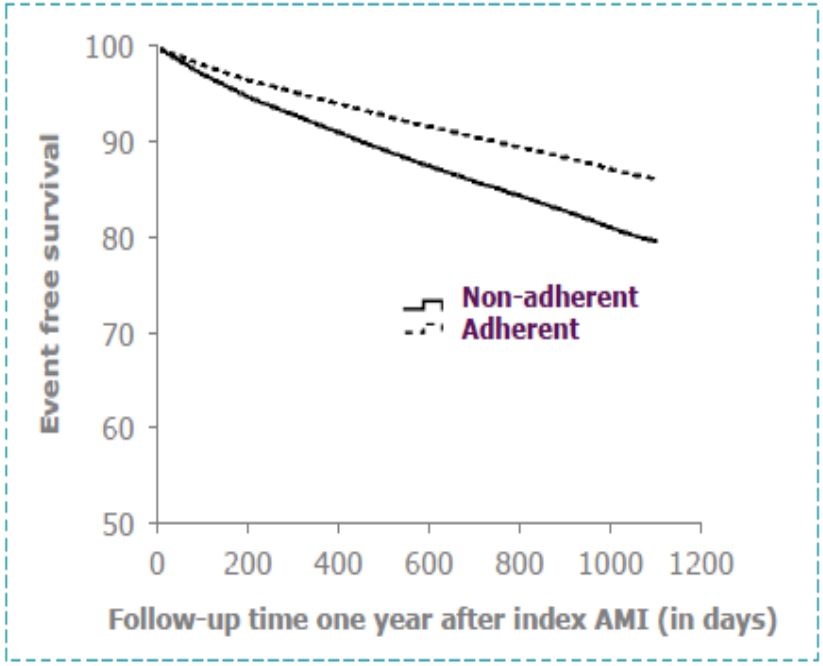
Results:

- At discharge 90.7% (n=36,869) of all patients were prescribed a beta-blocker.
- Among 1-year survivor AMI patients, 31.1% (n=12,003) were non-adherent to beta-blockers one year after the index AMI.

AIMS: To investigate the association between adherence to beta-blocker treatment after a first AMI and long-term risk of heart failure (HF) or death.

Adjusted

ALL: 0.79 (0.73-0.85)
NEF: 0.84 (0.75-0.95)
REF: 0.70 (0.61-0.80)
HFNEF: 0.90 (0.74-1.10)
HFREF: 0.73 (0.63-0.85)



L.A. Desta (Stockholm, SE) 5134

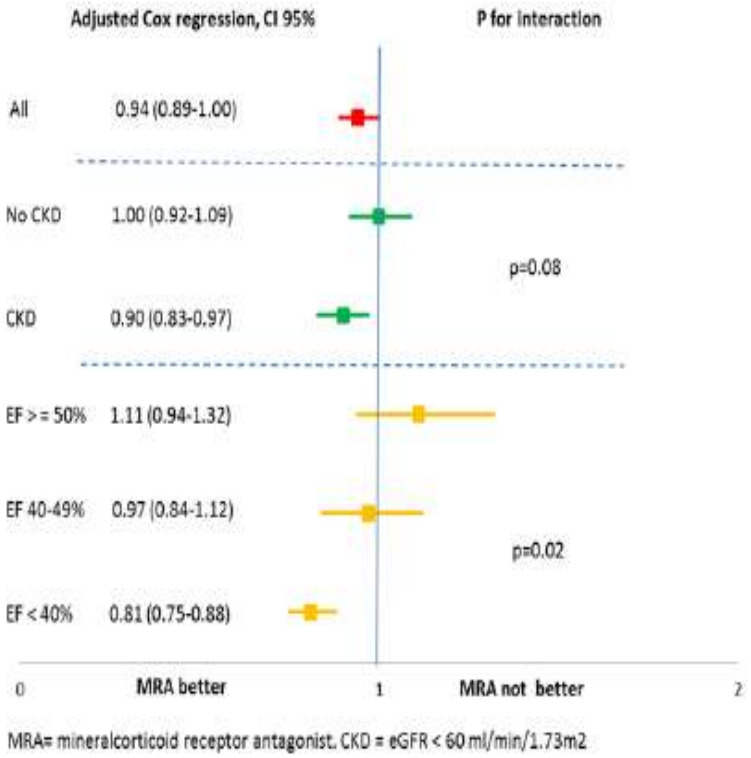
LONG-TERM OUTCOME IN MYOCARDIAL INFARCTION PATIENTS WITH HEART FAILURE TREATED WITH MINERALOCORTICOID RECEPTOR ANTAGONISTS IN RELATION TO EJECTION FRACTION AND KIDNEY FUNCTION

SWEDEHEART

Karolinska Institutet

n= 70.508

Kaplan Meier: 3 year mortality in patients without and with MRA



MRA= mineralcorticoid receptor antagonist. CKD = eGFR < 60 ml/min/1.73m2

Conclusion:

7.4 % had MRA at discharge and MRA was more common in patients with EF < 40% and equally common in patients with and without CKD

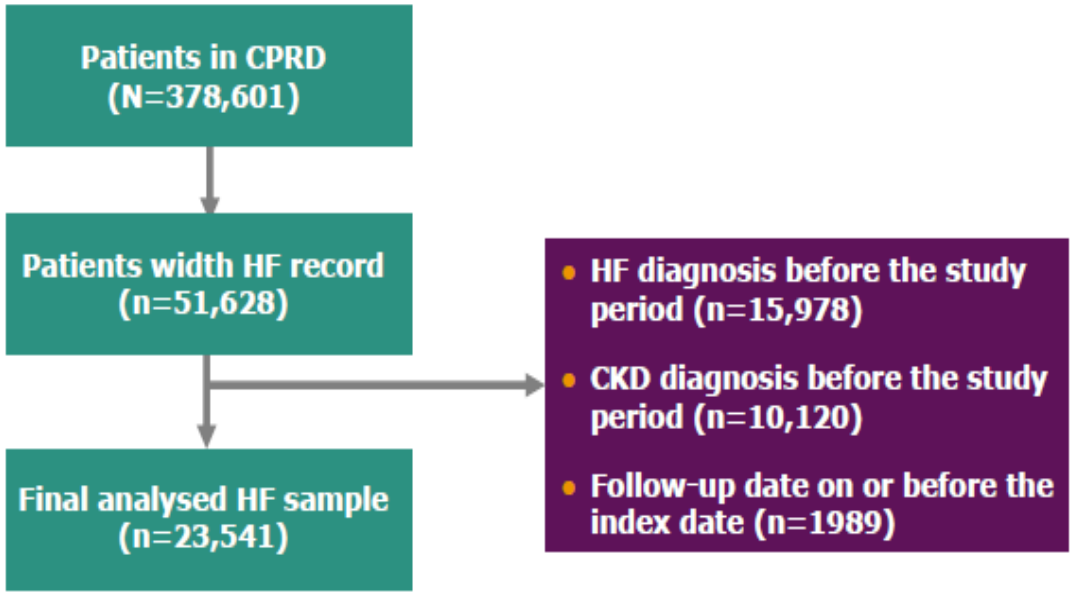
After adjustment, MRA was associated with lower 3 year mortality in EF < 40%, but not in EF 40-49% and EF > 50%

The association between MRA and 3 year mortality was not significantly different in patients with and without CKD

I. Lofman (Stockholm, SE) 249

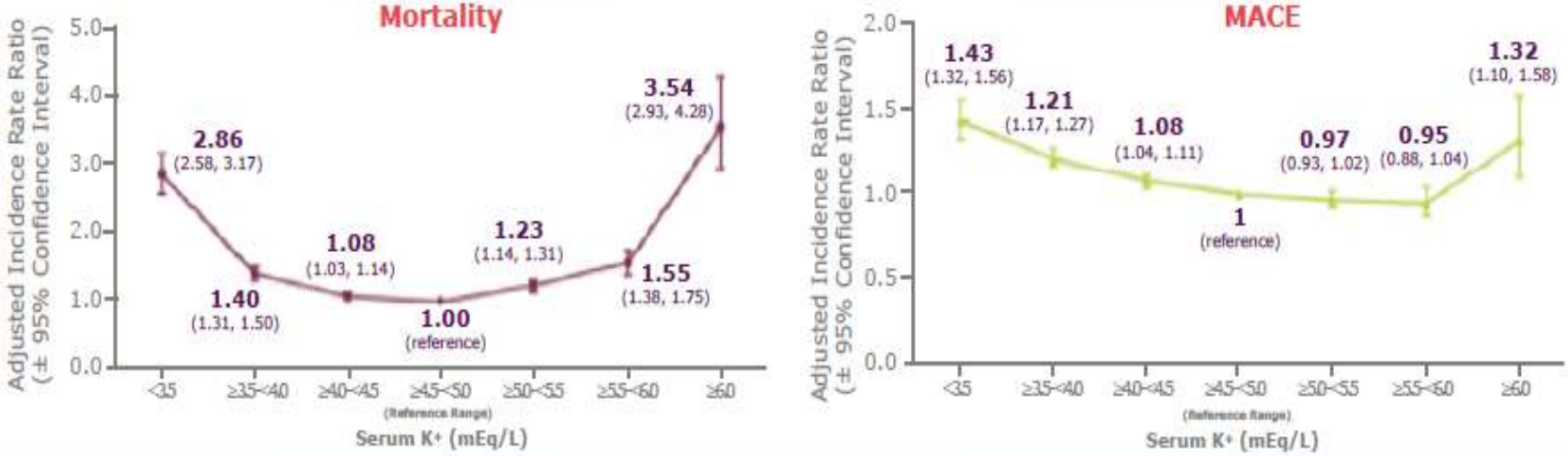
ASSOCIATION BETWEEN SERUM POTASSIUM AND CLINICAL OUTCOMES IN UK PATIENTS WITH HEART FAILURE

- **Primary care data for 2006-2015 extracted from the Clinical Practice Research Datalink (CPRD)**
  - Electronic database of anonymous longitudinal records for >11m patients from 674 primary care practices across UK



ASSOCIATION BETWEEN SERUM POTASSIUM AND CLINICAL OUTCOMES IN UK PATIENTS WITH HEART FAILURE

- **This real-world analysis indicates U-shaped patterns of association between K+ and incidence of mortality and MACE**
  - K+ levels outside the normal range were associated with greater risks of mortality and MACE
  - Results support the need for close monitoring of K+ and prompt treatment of hypo- and hyperkalaemia in patients with HF



Risk of mortality is 3.5 times greater for patients with K+ ≥6 mEq/L compared to those with normokalaemia

L. Qin (Gaithersburg, US) 4901

ELEVATED POTASSIUM LEVELS IN PATIENTS WITH CONGESTIVE HEART FAILURE: INCIDENCE AND CLINICAL OUTCOMES – A DANISH POPULATION BASED COHORT STUDY

Matched cohort analysis in patients with HK versus matched comparisons[1] without HK

Outcome event	6-mo. Hazard ratio (95% CI) before HK event	6-mo. Hazard ratio (95% CI) after HK event	Prior-event-rate-ratio adjusted hazard ratio
Any hospital outpatient contact	1.19 (1.16-1.23)	1.68 (1.63-1.74)	1.41
Any acute hospitalization	1.16 (1.12-1.20)	2.57 (2.48-2.66)	2.22
Hospitalization with any cardiac diagnosis	1.09 (1.04-1.13)	2.33 (2.24-2.41)	2.14
Hospitalization with ventricular arrhythmia	0.99 (0.84-1.17)	2.10 (1.80-2.45)	2.12
Hospitalization with cardiac arrest	0.67 (0.37-1.20)	4.73 (3.32-6.74)	7.08
Hospitalization with ICU admission	1.01 (0.88-1.16)	4.92 (4.44-5.45)	4.85
Death	NA	3.16 (2.99-3.35)	--

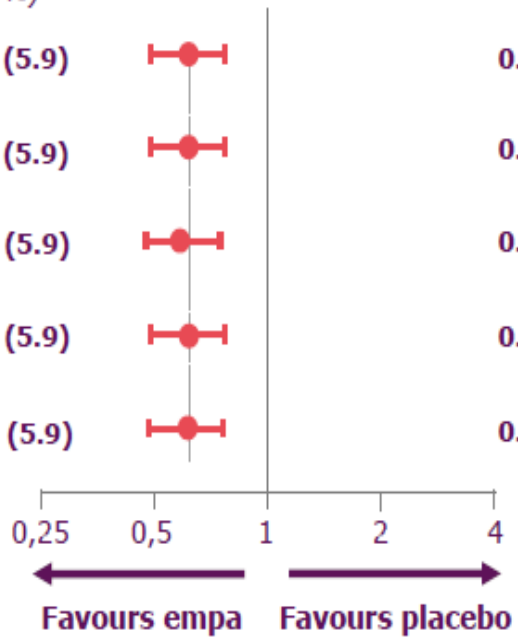
1 HF comparisons without HK individually matched to heart failure patients with HK on gender, age, time since heart failure diagnosis, heart failure treatment, Charlson Comorbidity index (CCI) score category, presence of HK-associated conditions (diabetes, CKD, or hypertension), and presence or absence of HK-associated drug use (ACEis, ARBs, potassiumsparing diuretics, or potassium supplements), see text.

R.W. Thomsen (Aarhus, DK) 5827

EMPAGLIFLOZIN REDUCES MORTALITY IN ANALYSES ADJUSTED FOR CONTROL OF BLOOD PRESSURE, LOW DENSITY LIPOPROTEIN CHOLESTEROL AND HbA1c OVER TIME

CV death

	Empagliflozin	Placebo	HR (95% CI)	HR (95% CI)
	N with event / N analysed (%)			
Main analysis	172/4687 (3.7)	137/2333 (5.9)		0.62 (0.49, 0.77)
Adjusted for control of blood pressure	172/4687 (3.7)	137/2333 (5.9)		0.61 (0.49, 0.76)
Adjusted for control of LDL-cholesterol	167/4615 (3.6)	136/2308 (5.9)		0.59 (0.47, 0.75)
Adjusted for control of HbA1c	172/4685 (3.7)	137/2333 (5.9)		0.62 (0.49, 0.78)
Adjusted for control of blood pressure, LDL-cholesterol and HbA1c	167/4614 (3.6)	136/2308 (5.9)		0.61 (0.48, 0.76)

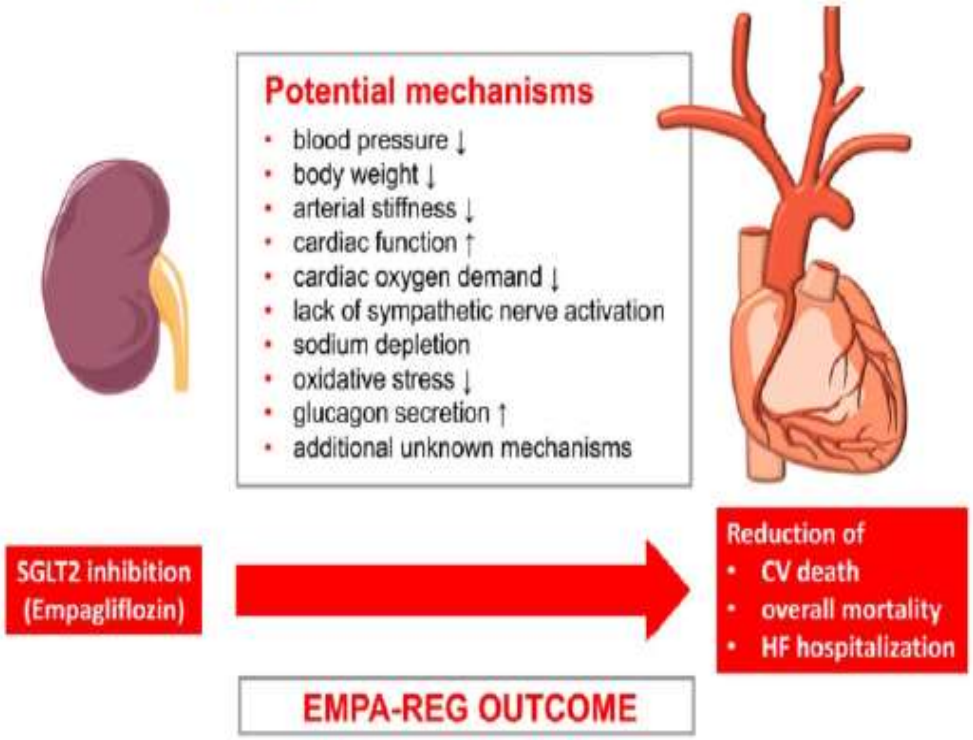


Cox regression analysis in patients treated width ≥1 dose of study drug

D. Fitchett (Toronto, CA) 4903

EMPAGLIFLOZIN REDUCES THE DOXORUBICINE-INDUCED MYOCARDIAL DYSFUNCTION

Objective: Empagliflozin and EMPA-REG Outcome



J. Butler (Atlanta, US) 2960

Marx et al, European Heart Journal 2016

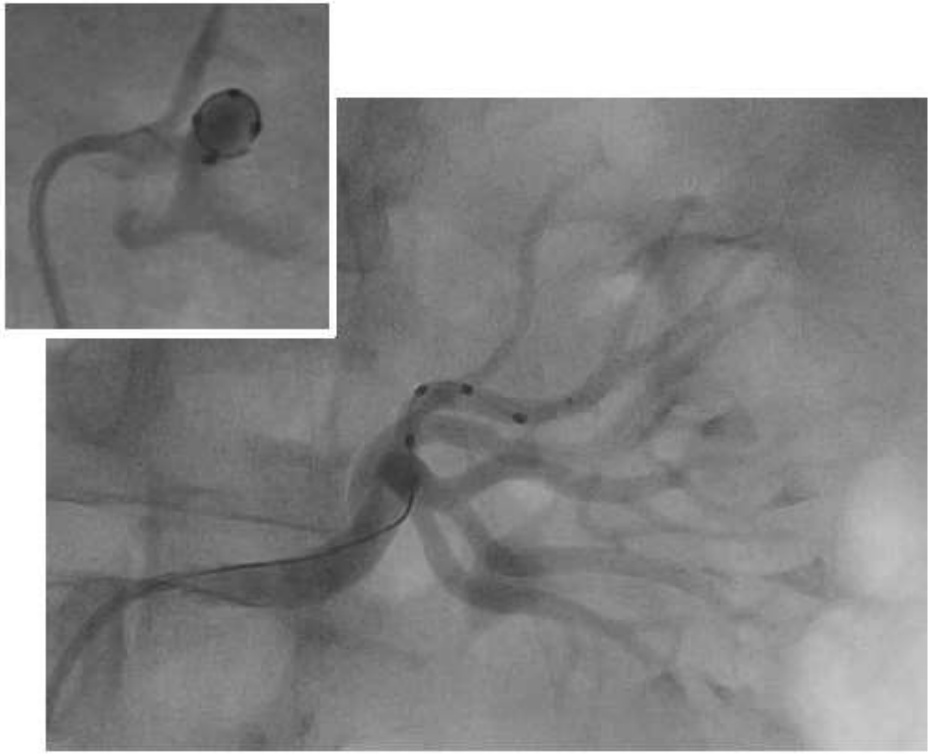
HYPERTENSION

Investigation of catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications: Three-month results from the randomized, sham-controlled, proof of concept SPYRAL HTN-OFF MED Trial

SPYRAL HTN Clinical Program

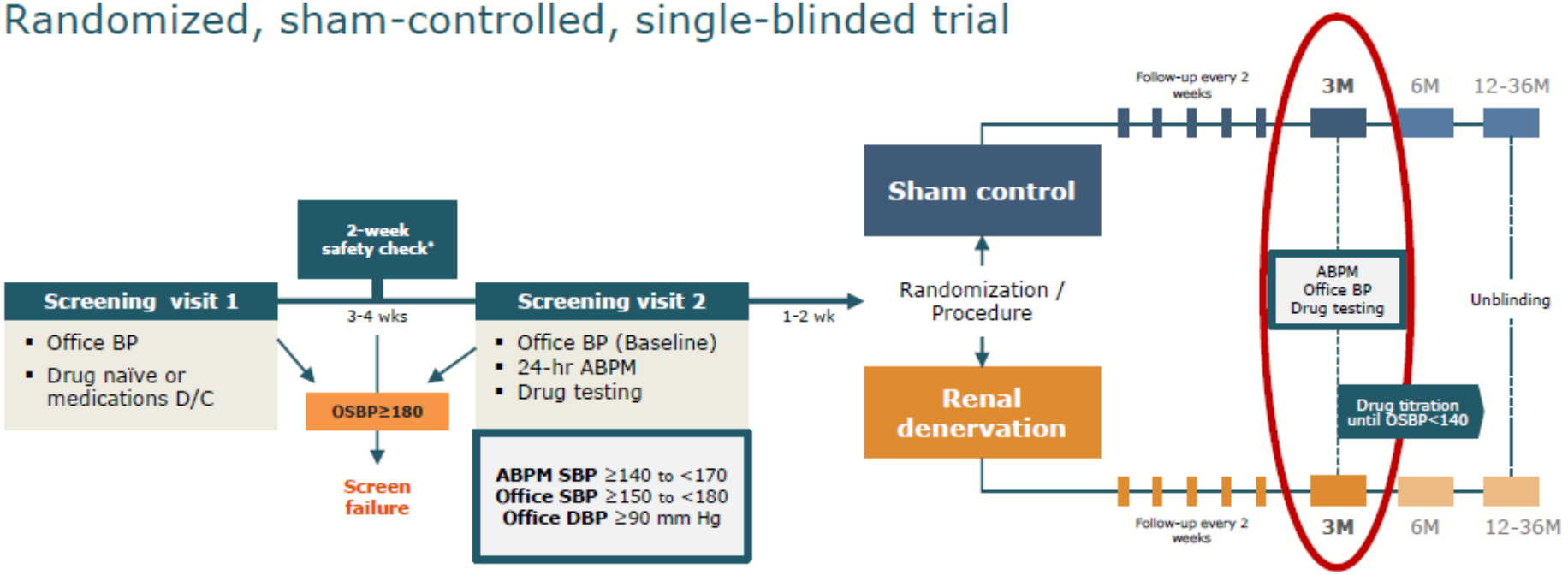
Study Device: Symplicity Spyral™ Catheter

- Multi-electrode catheter with quadrantic vessel contact for simultaneous ablation in up to 4 electrodes
- 60-second simultaneous energy delivery
- Vessel diameter range: 3 – 8 mm
- Flexible catheter allows branch treatment
- 6F guiding catheter compatible



SPYRAL HTN – OFF MED
Study Design

Randomized, sham-controlled, single-blinded trial

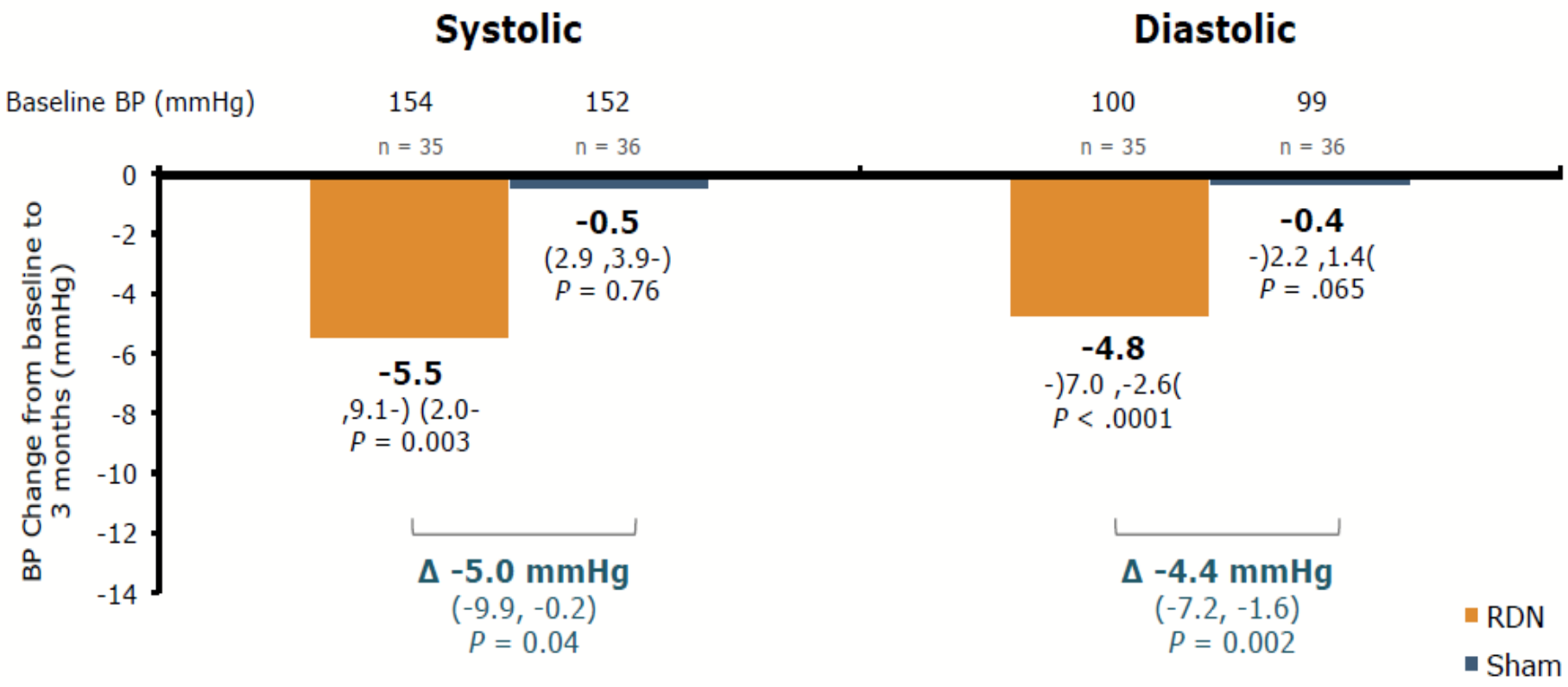


*Only for patients discontinuing anti-hypertensive medications

Kandzari D, et al. *Am Heart J.* 2016;171:82-91.

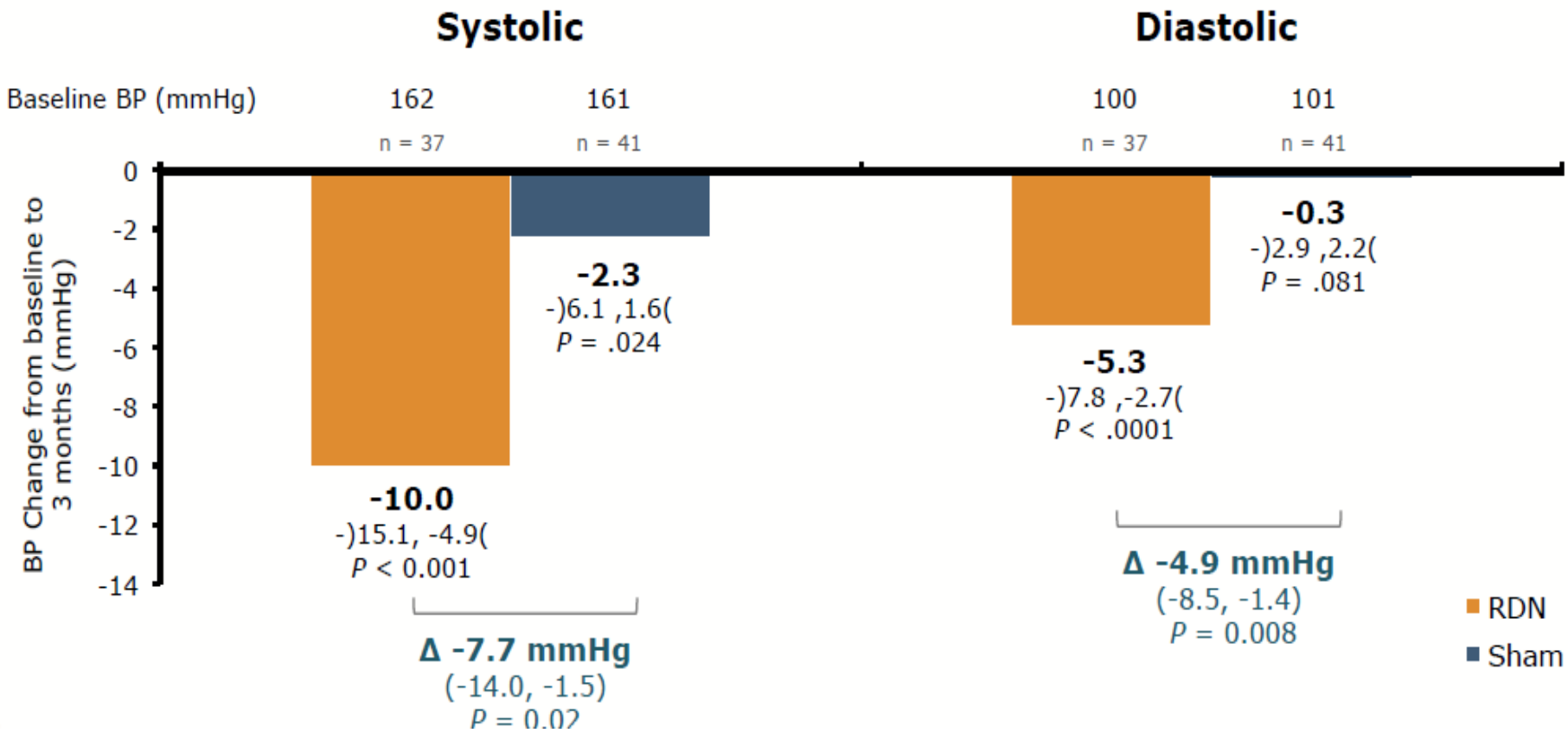
SPYRAL HTN – OFF MED

Blood Pressure Change from Baseline to 3 Months: 24-Hr ABPM



SPYRAL HTN – OFF MED

Blood Pressure Change from Baseline to 3 Months: Office BP



SPYRAL HTN Clinical Program

Advances of SPYRAL HTN Compared to SYMPLICITY HTN-3

	Medications	Patients	Procedure
SYMPLICITY HTN -3	▪ 5.1 prescribed anti-HTN drugs at randomization ▪ No drug adherence testing	▪ Resistant hypertension patients (OSBP 180 ± 16) ▪ No diastolic cutoff	▪ Mono-electrode, sequential ablation system ▪ Mostly inexperienced operators without proctoring ▪ Main artery RDN only ▪ Ablations per pt: 11.2 ± 2.8
SPYRAL HTN OFF MED	▪ No anti-HTN drugs at time of randomization ▪ Drug adherence testing by serum and urine	▪ Moderate hypertension patients (OSBP 162 ± 7) ▪ Excluding ISH patients (ODBP 101 ± 7)	▪ Four-electrode, simultaneous ablation system ▪ Highly experienced operators with proctoring ▪ Main + branches RDN ▪ Ablations/pt: 43.8 ± 13.1

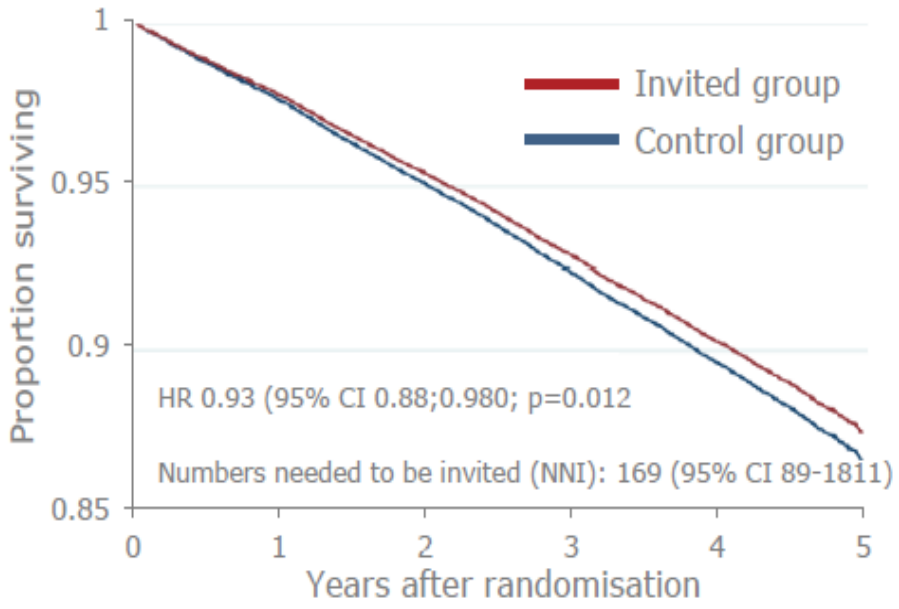
SPYRAL HTN – OFF MED
Conclusions

- **Biologic proof of principle** for the efficacy of renal denervation
- **Clinically meaningful blood pressure reductions** at 3 months
  - In mild to moderate hypertensive patients treated with RDN
  - In the absence of anti-hypertensive medications compared to sham control
- **No major safety events**
  - Despite a more complete denervation procedure that extended into renal artery branch vessels
- **The results of this feasibility study will inform the design of a larger pivotal trial**

PREVENTIVE CARDIOLOGY

SCREENING FOR CVD – TRIPLE VASCULAR SCREENING

The Viborg Vascular (VIVA) randomised screening trial



7% reduction in all-cause mortality

- **Screening for CVD risk not convincing although AAA screening reduces AAA mortality (but not overall mortality)**
- **Does triple vascular screening for AAA, PAD and hypertension reduce overall mortality in 65-74 year old men?**

→ **50,168 randomised**

→ **Attendance 75%**

→ **3.3% AAA**

→ **11% PAD**

→ **10% hypertension**

J. Lindholt (Odense, DK) 3061

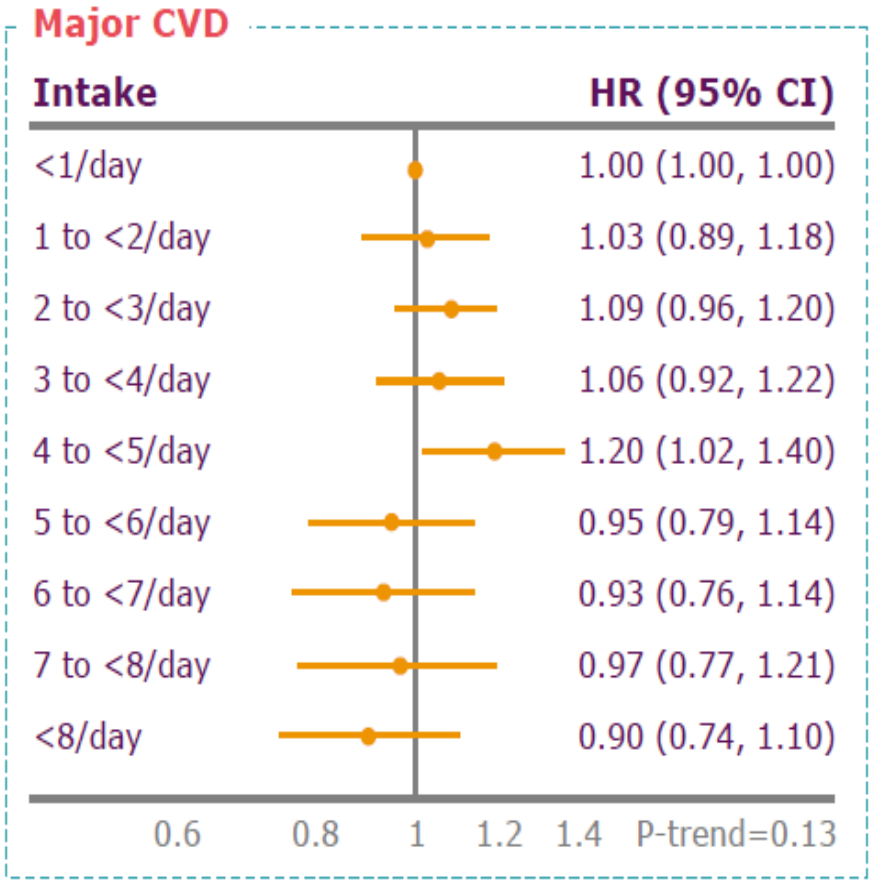
CHALLENGING GUIDELINES – THE PURE STUDY

PURE

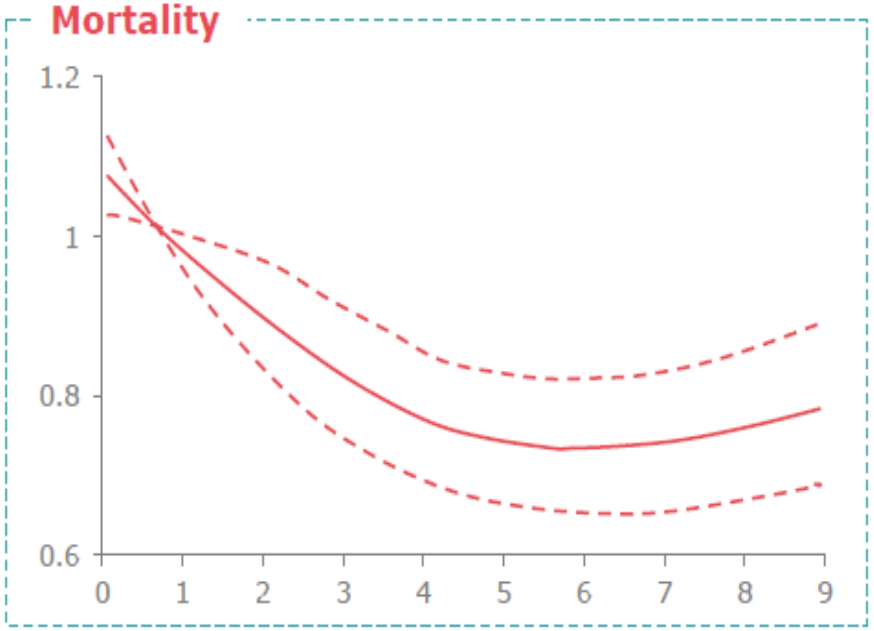
- Prospective cohort study
- General population samples from 667 urban/rural communities in 18 countries
- N=135,335
- Food Frequency questionnaire
- Outcome: major CVD and mortality

A. Mente (Hamilton, CA) 4966
M. Dehghan (Hamilton, CA) 4967

PURE – FRUIT, VEGETABLES AND LEGUMES



- Moderately lower risk of mortality but not CVD
- Maximum benefit at 3-4 servings



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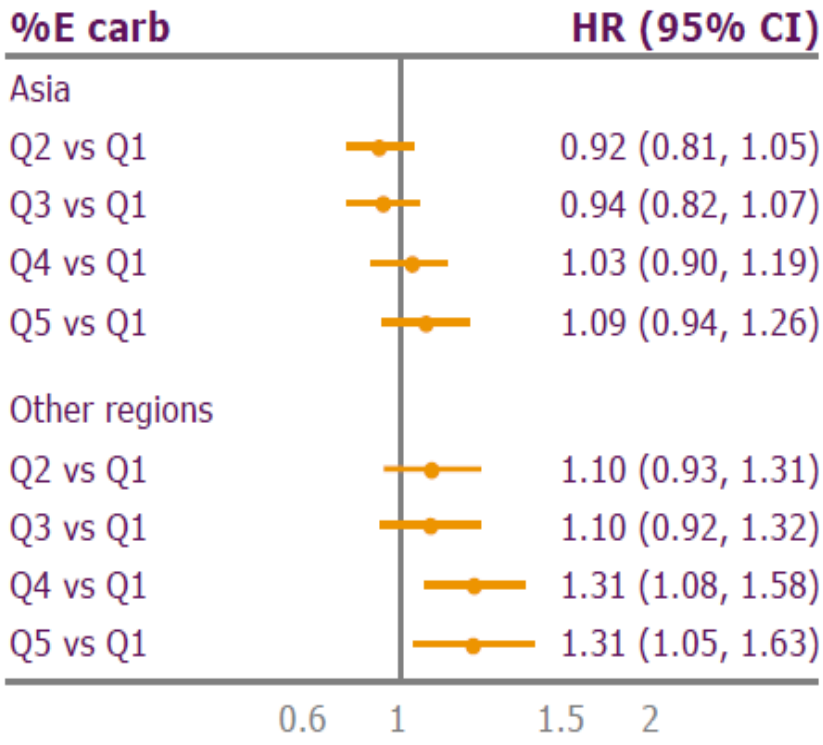
PURE – DIETARY FAT AND CARBOHYDRATES

Dietary fats are protective but carbohydrates are harmful

Mortality



- Decreasing overall mortality with increasing consumption of saturated fat (SFA) but no effect on CVD mortality.
- Increasing mortality with increasing consumption of carbohydrates.
- Authors conclude: current guidelines recommending <10% saturated fat not supported by data.
- Results challenge current guideline recommendations on intake of saturated fat and carbohydrates.

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

Marc S. Sabatine, M.D., M.P.H., Robert P. Giugliano, M.D., Anthony C. Keech, M.D., Narimon Honarpour, M.D., Ph.D., Stephen D. Wiviott, M.D., Sabina A. Murphy, M.P.H., Julia F. Kuder, M.A., Huei Wang, Ph.D., Thomas Liu, Ph.D., Scott M. Wasserman, M.D., Peter S. Sever, Ph.D., F.R.C.P., and Terje R. Pedersen, M.D., for the FOURIER Steering Committee and Investigators*

Sabatine MS, et al. N Engl J Med. 2017 Mar 17. [Epub ahead of print]

Background

- Proprotein convertase subtilisin/kexin type 9 (PCSK9)

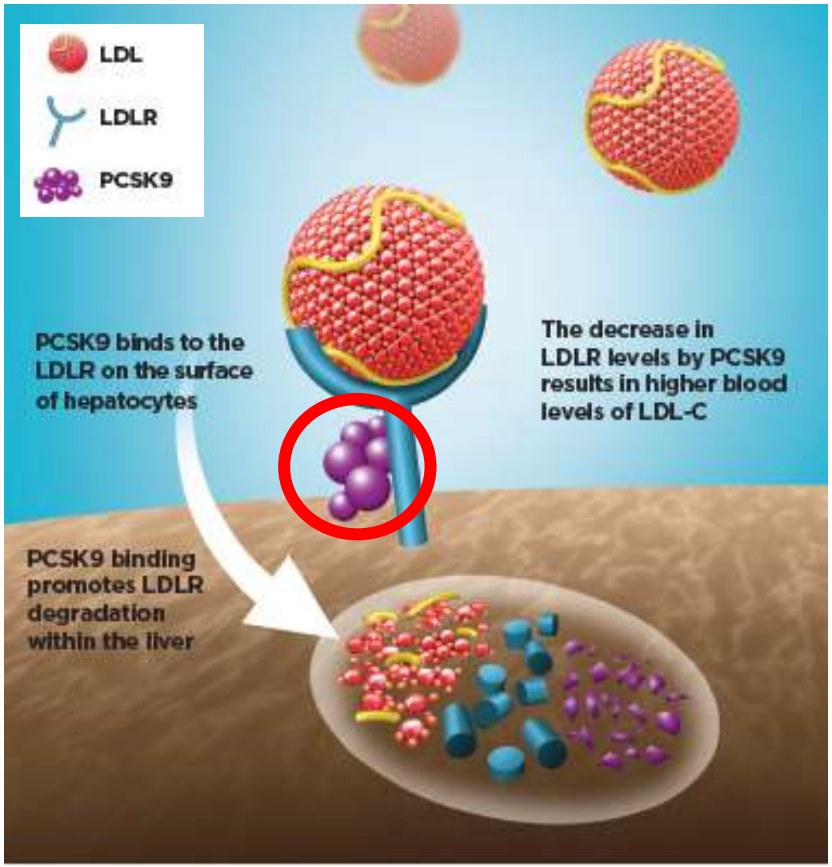


Image available from: https://www.repathahcp.com/

Evolocumab Mechanism of Action

- Fully humanized monoclonal antibody

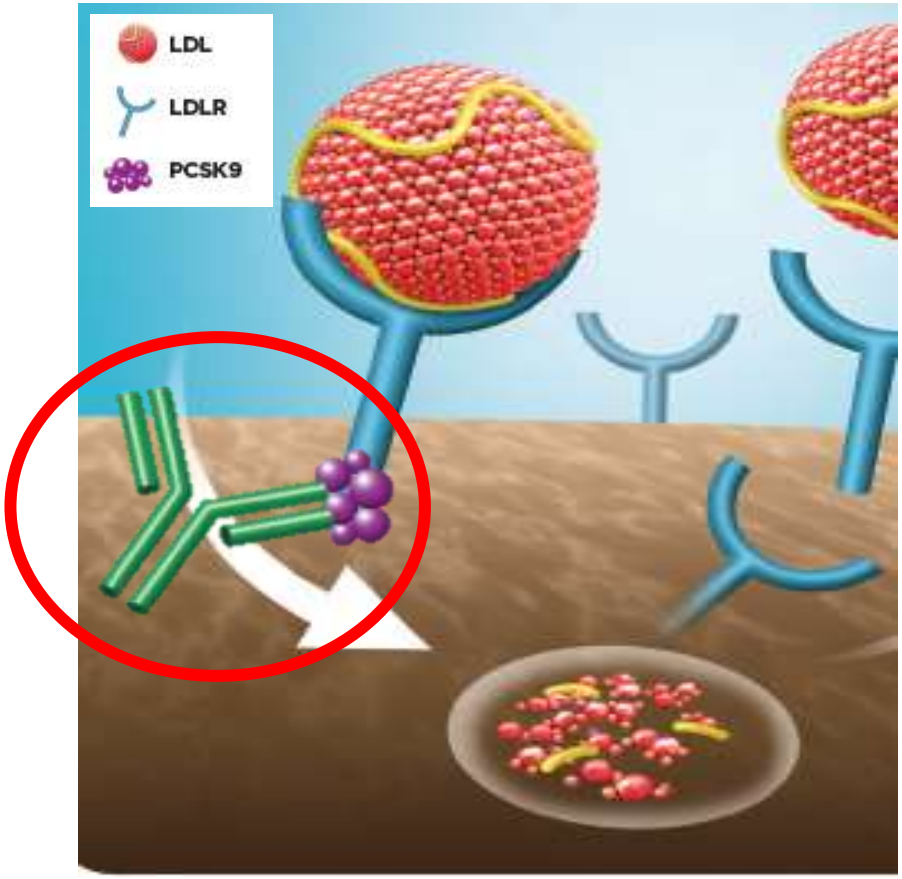
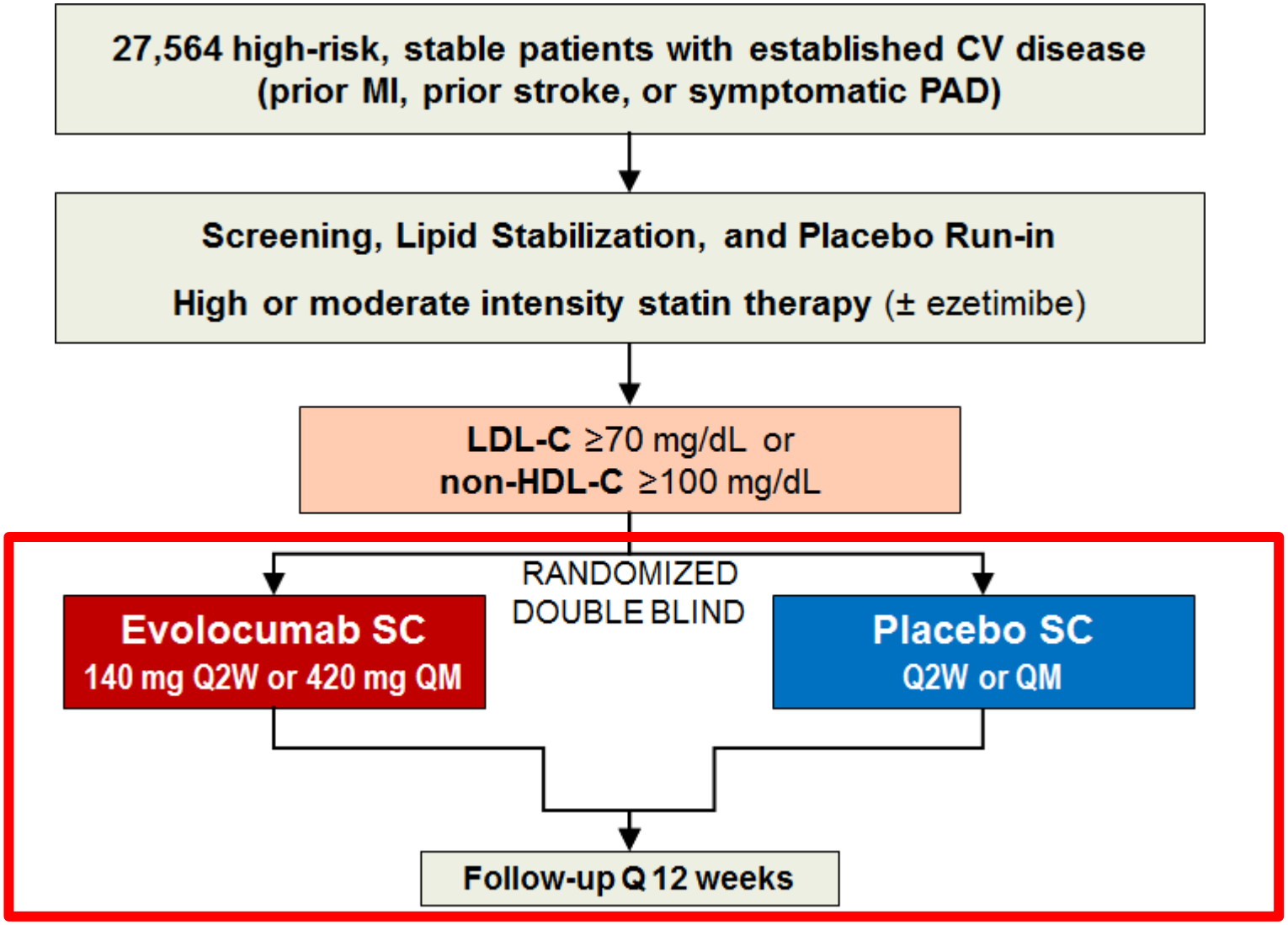


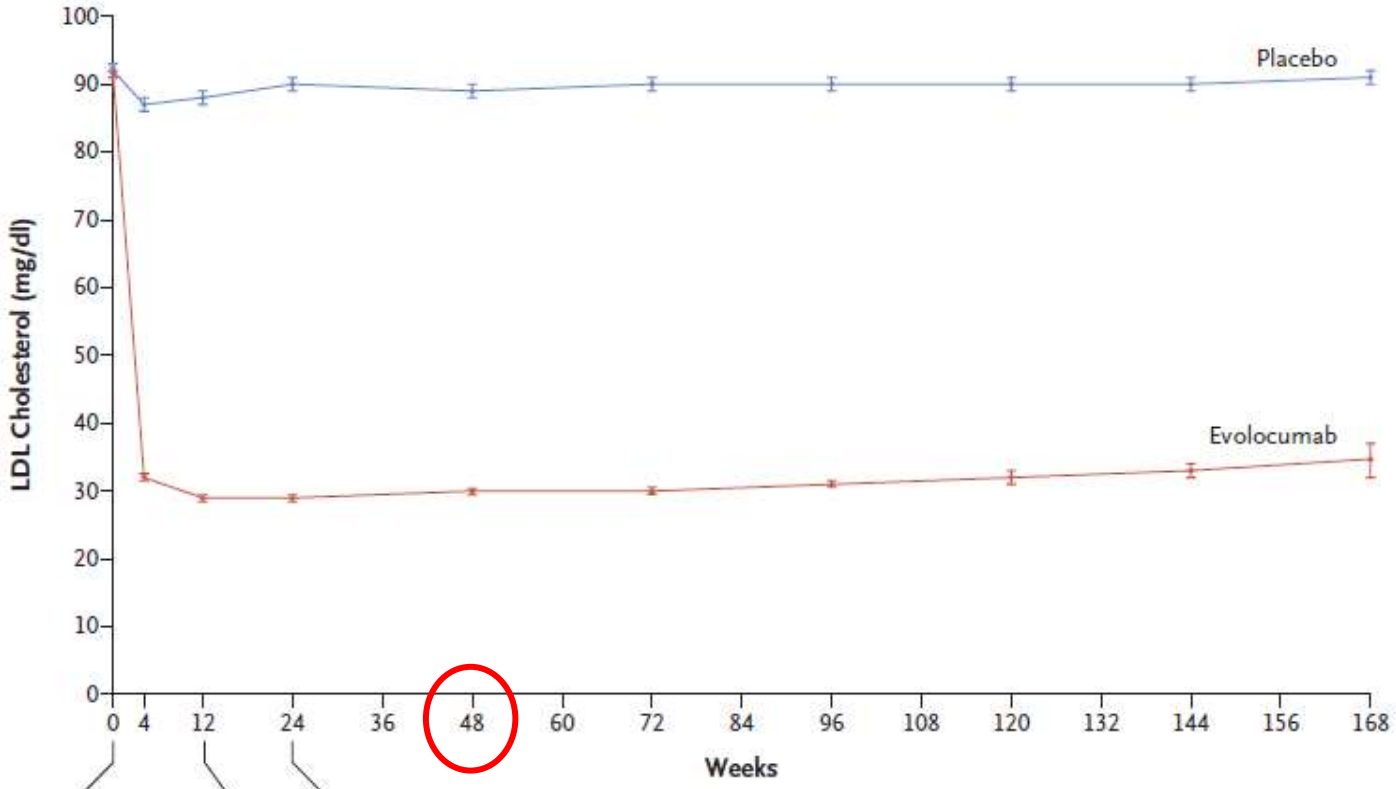
Image available from: https://www.repathahcp.com/

Study Design



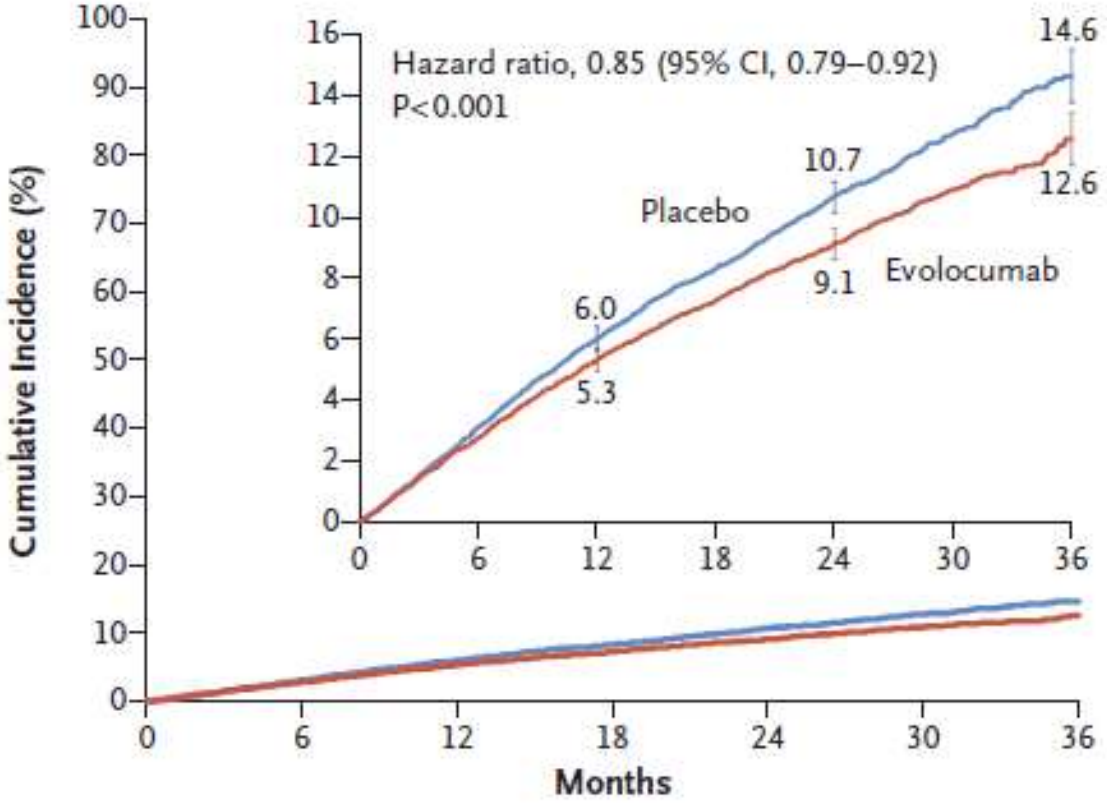
LDL-C l

LDL Cholesterol	Evolocumab	Placebo
≤ 70 mg/dL	87%	18%
≤ 40 mg/dL	67%	0.5%
≤ 25 mg/dL	42%	< 0.1%



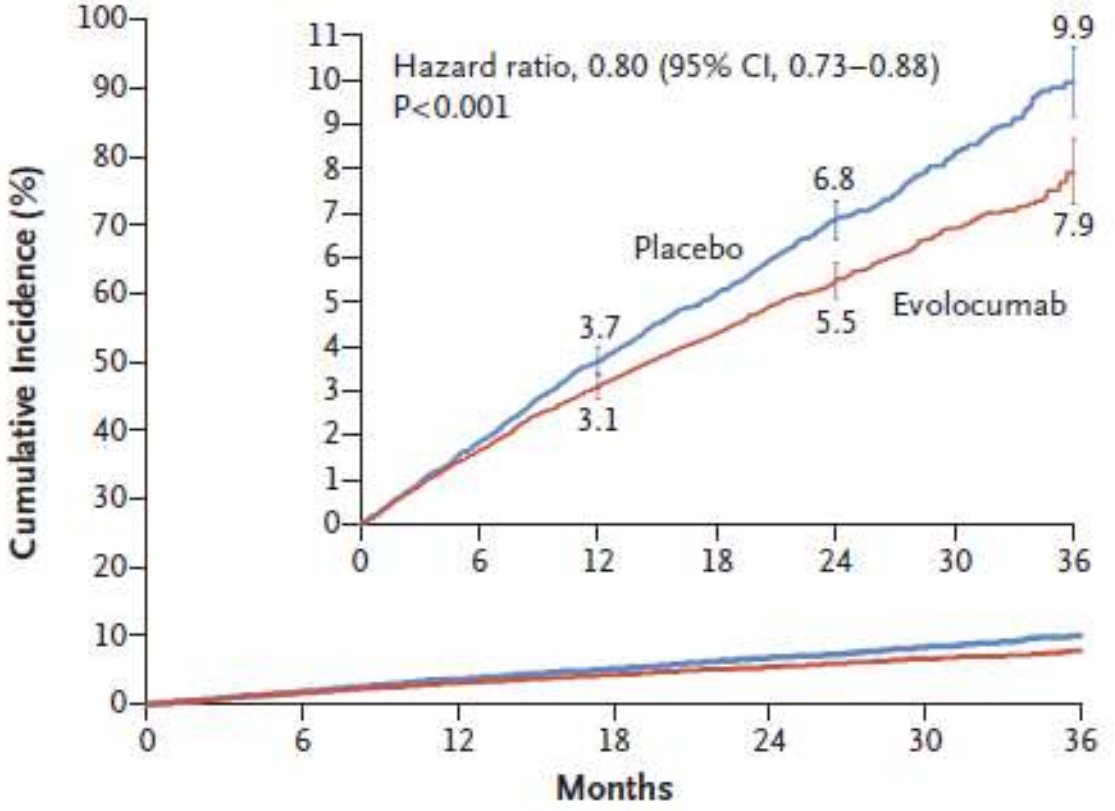
No. at Risk										
Placebo	13,779	13,251	13,151	12,954	12,596	12,311	10,812	6926	3352	790
Evolocumab	13,784	13,288	13,144	12,964	12,645	12,359	10,902	6958	3323	768
Absolute difference (mg/dl)		54	58	57	56	55	54	52	53	50
Percentage difference		57	61	61	59	58	57	55	56	54
P value		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Primary Endpoint



No. at Risk							
Placebo	13,780	13,278	12,825	11,871	7610	3690	686
Evolocumab	13,784	13,351	12,939	12,070	7771	3746	689

Key Secondary Efficacy Endpoint



No. at Risk							
Placebo	13,780	13,449	13,142	12,288	7944	3893	731
Evolocumab	13,784	13,501	13,241	12,456	8094	3935	724

Study Conclusions

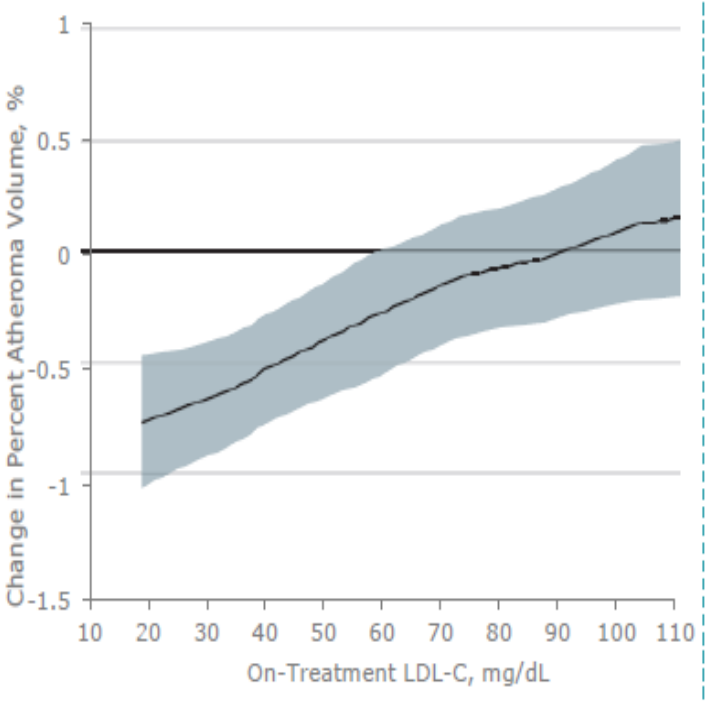
- When added to statin therapy, evolocumab lowered LDL cholesterol levels by 59% from baseline compared to placebo, from a median of 92 mg/dL to 30 mg/dL
- ↓ risk of the primary composite endpoint by 15% and ↓ risk of the key secondary endpoint by 20%
- Magnitude of risk reduction shown to increase over time
- No effect of additional LDL-C lowering on cardiovascular death or all-cause mortality
- Injection-site reactions were significantly higher in the evolocumab group compared to the placebo group

LDL REDUCTION – PCSK9 INHIBITION

GLAGOV Trial

Evolucumab reduces LDL-C and percent atheroma volume

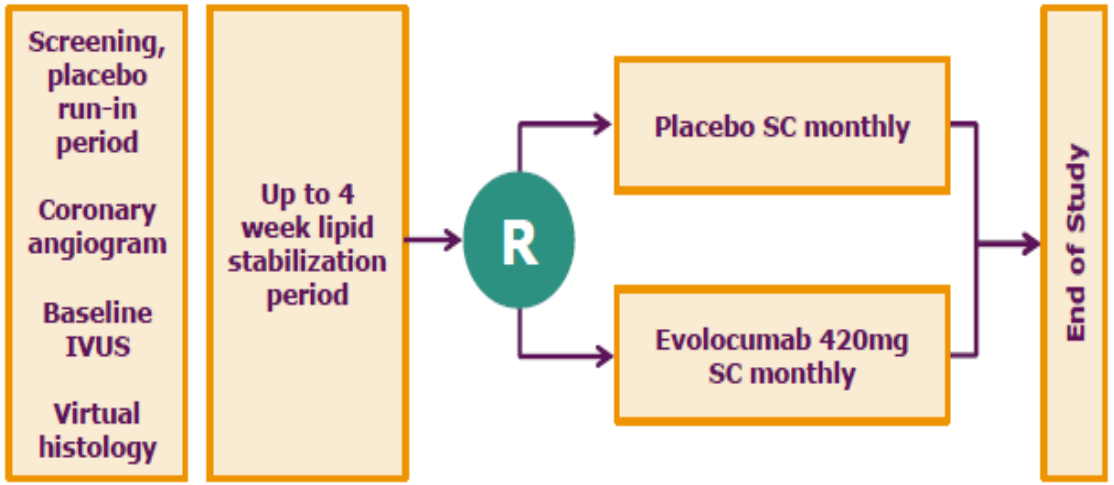
Post Hoc



JAMA 2017

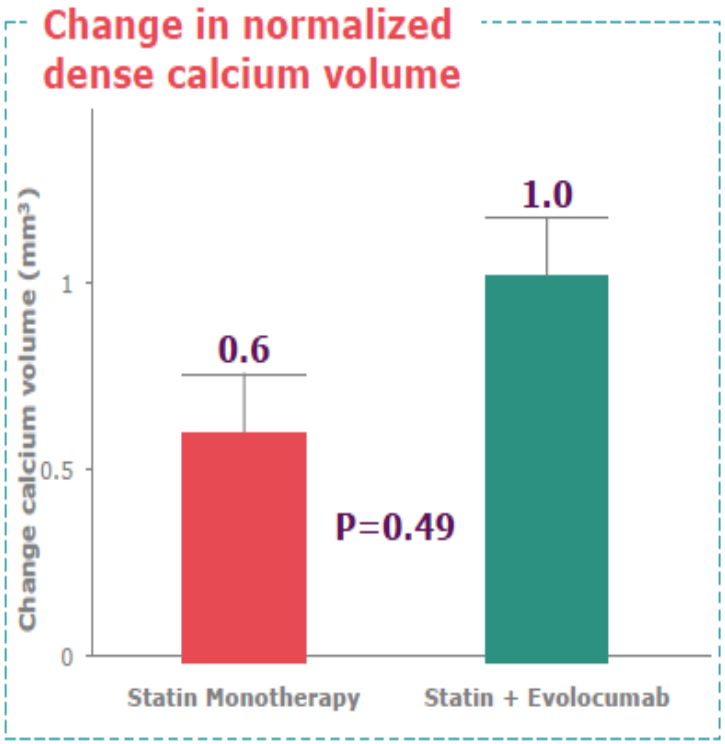
GLAGOV Trial Schematic

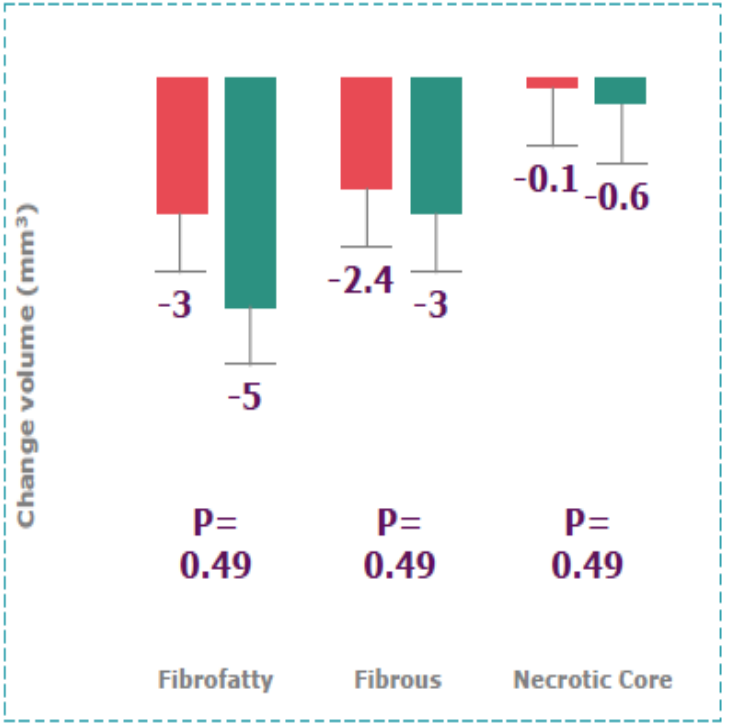
968 pattients with angiographic CAD, stable statin dose and LDL-C ≥80 mg/dL OR 60-80 mg/dL and 1 major or 3 minor risk factors



LDL REDUCTION – PCSK9 INHIBITION

GLAGOV Trial

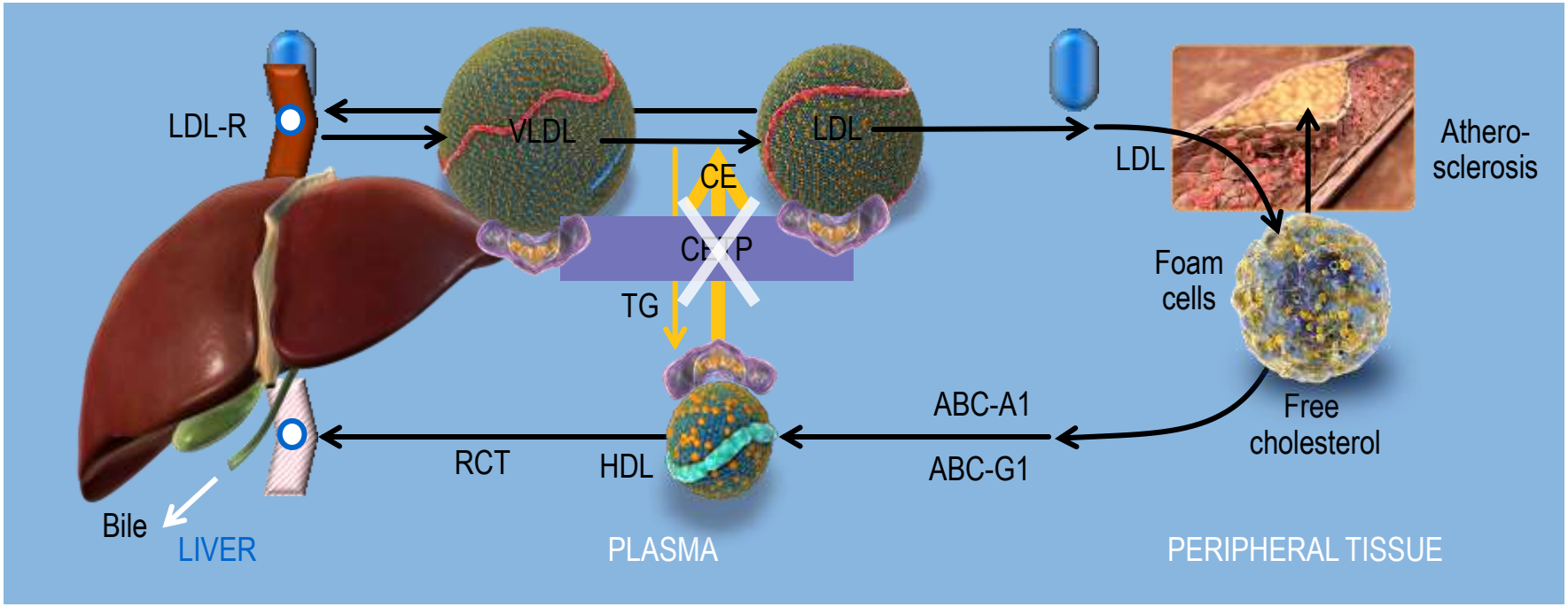




Evolocumab added to statin induces plaque regression but does not change plaque composition

S.J. Nicholls (Adelaide, AU) 5896

Role of CETP in Atherosclerosis



- Human CETP deficiency
  - ↑ in HDL-C (codominant)
  - ↓CVD
- Reducing CETP activity →↓atherosclerosis in animal models

LDL REDUCTION – CETP INHIBITION

REVEAL

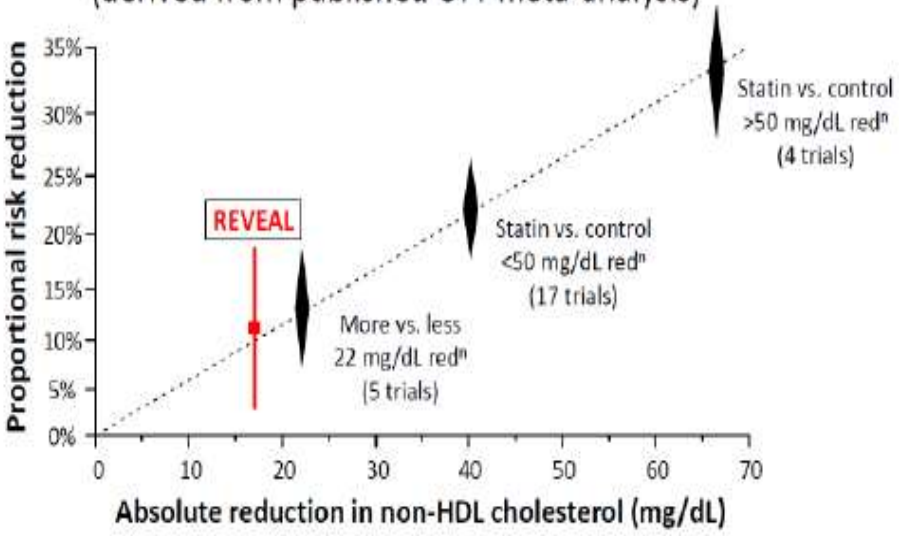
REVEAL: Randomized placebo-controlled trial of anacetrapib added to statin in 30,449 patients with atherosclerotic vascular disease

Effects of anacetrapib on lipids at trial midpoint

Measurement	Absolute difference		Proportional difference
	mg/dL	SI units	
HDL cholesterol	+43	+1.1 mmol/L	104%
Apolipoprotein AI	+42	+0.4 g/L	36%
LDL cholesterol			
- Direct (Genzyme)	-26	-0.7 mmol/L	-41%
- Beta-quantification*	-11	-0.3 mmol/L	-17%
Apolipoprotein B	-12	-0.1 g/L	-18%

Proportional reduction in Coronary death or MI vs. absolute reduction in non-HDL cholesterol

(derived from published CTT meta-analysis)



No excess of mortality, cancer or other serious adverse events
Small increase in blood pressure and small reduction in kidney function

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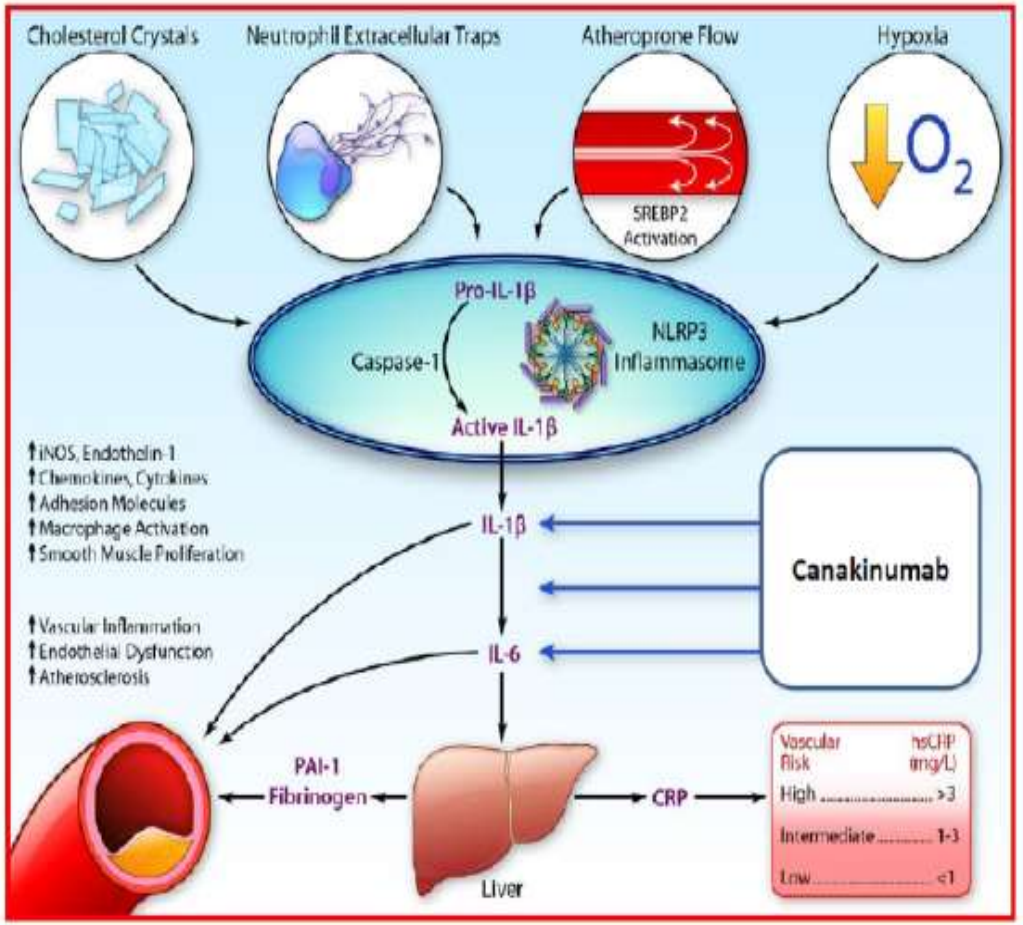
INFLAMMATION

CANTOS
Canakinumab Anti-Inflammatory Thrombosis Outcomes Study

Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS)



P. Ridker (Boston, US) 1151

INFLAMMATION

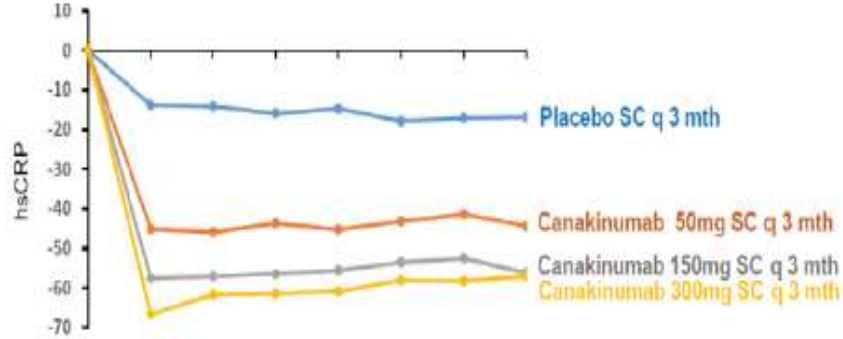
CANTOS
Canakinumab Anti-Inflammatory Thrombosis Outcomes Study

Stable CAD (post MI)
On Statin, ACE/ARB, BB, ASA
Persistent Elevation
of hsCRP (≥2mg/L)

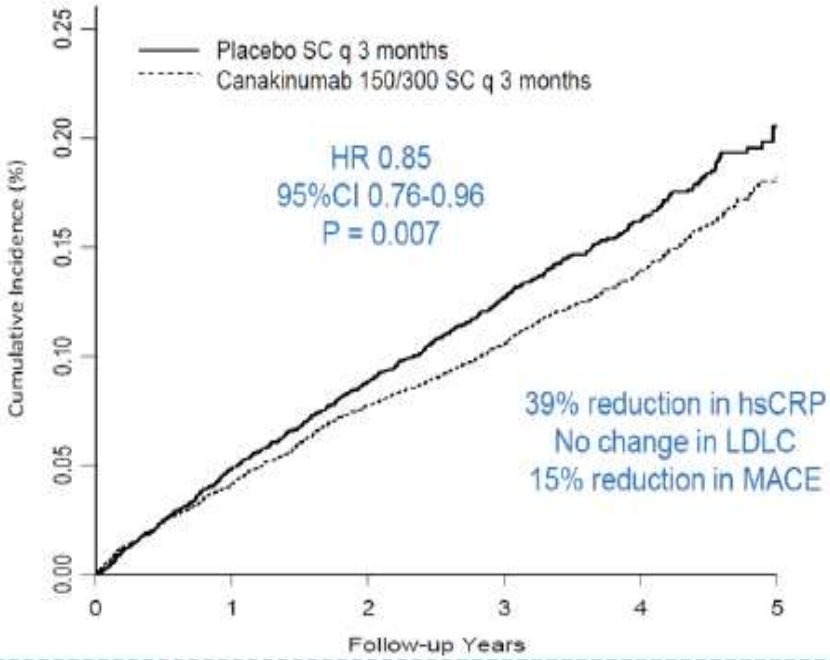
R

- Randomised Canakinumab 50 mg SC q 3 months
- Randomised Canakinumab 150 mg SC q 3 months
- Randomised Canakinumab 300 mg SC q 3 months
- Randomised Placebo SC q 3 months

N=10,061
39 countries
April 2011 – June 2017
1490 Primary Events



CANTOS: Primary Cardiovascular Endpoint (MACE)



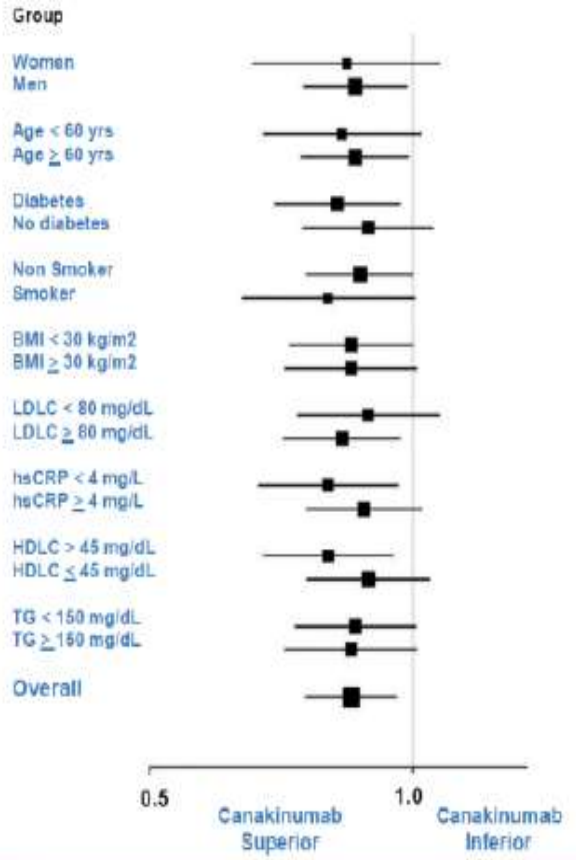
No effect on CVD or all-cause mortality (HR 0.94)

P. Ridker (Boston, US) 1151

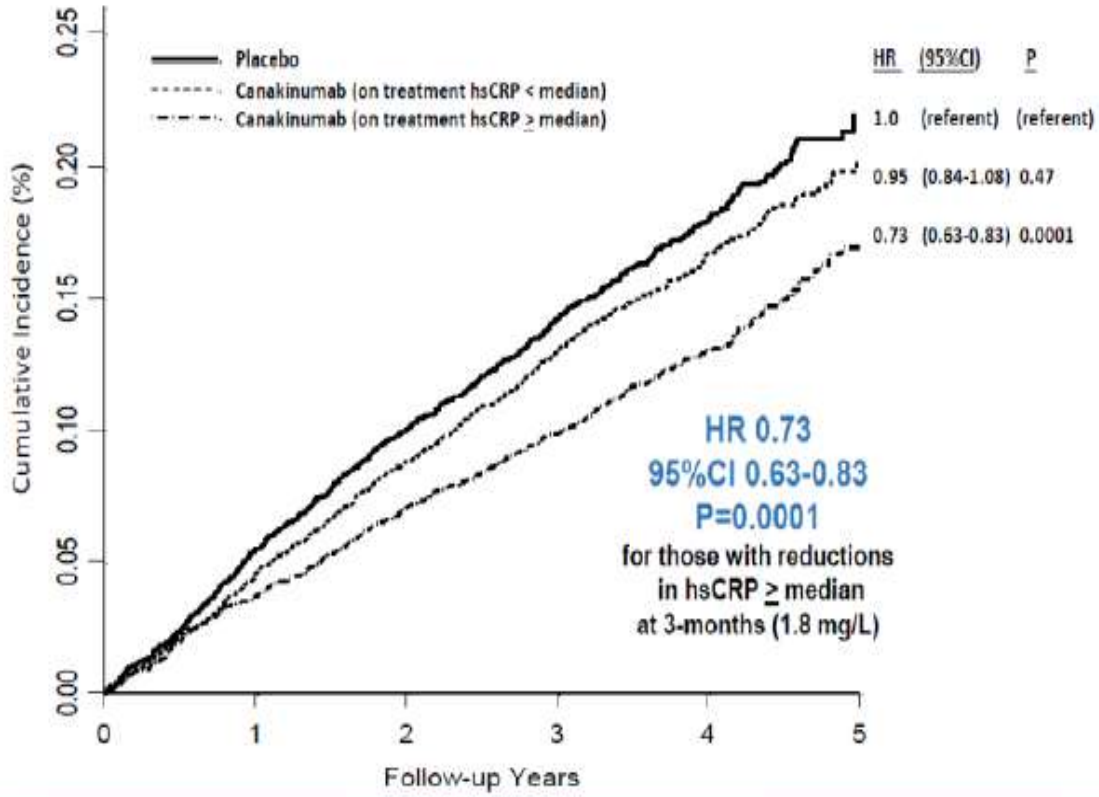
INFLAMMATION

CANTOS
Canakinumab Anti-Inflammatory Thrombosis Outcomes Study

MACE



CANTOS: Greater Risk Reduction Among Those With Greater hsCRP Reduction (MACE+)



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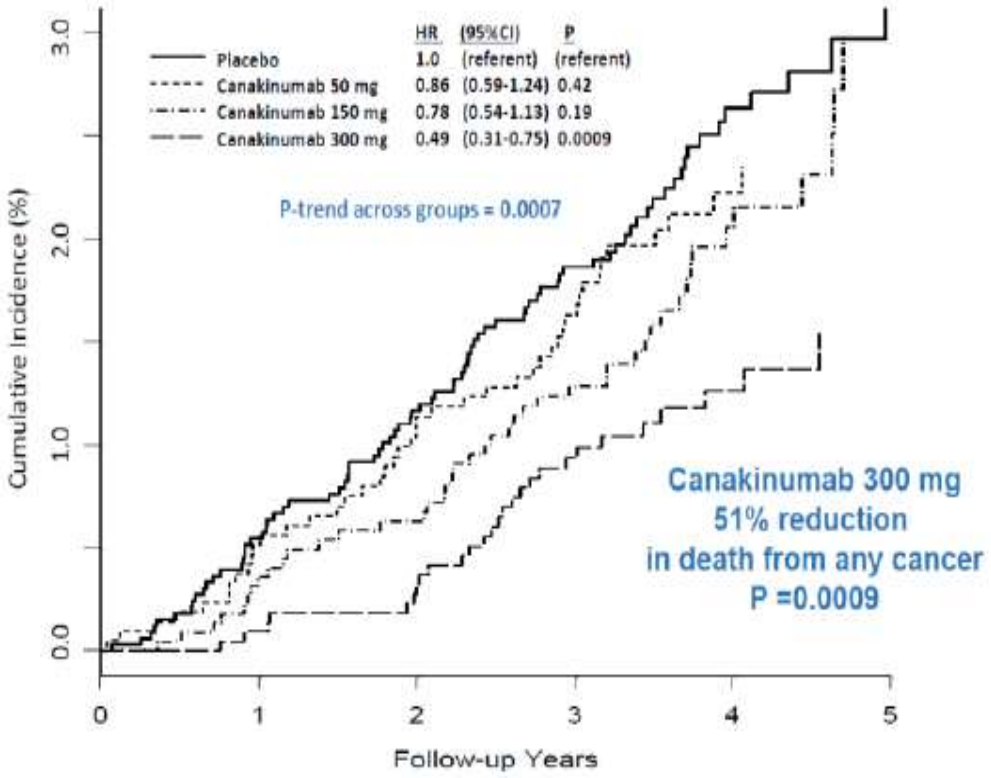
INFLAMMATION

CANTOS
Canakinumab Anti-Inflammatory Thrombosis Outcomes Study

CANTOS: Additional Non-Cardiovascular Clinical Benefits

Cancer Mortality



- Proof of concept that targeting inflammation (IL-1b) targets the atherosclerotic process
- Price currently prohibitive (approx 14000 Euro/150 mg per dose)
- Await further trials targeting inflammation & follow-up on safety, including infection

P. Ridker (Boston, US) 1151

R

- Reduce inflammation
- Reduce BP with renal denervation
- Reduce events with Rivaroxaban
- Respect HDL (negative study for anacetrapib)