DHZ

Deutsches Herzkompetenz Zentrum
Innovativ. Menschlich. Nah.

EBERHARD KARLS
UNIVERSITÄT
TÜBINGEN

Neue Konzepte in der Sekundärprophylaxe von kardiovaskulären Risikopatienten - was sagen uns COMPASS und CANTOS?

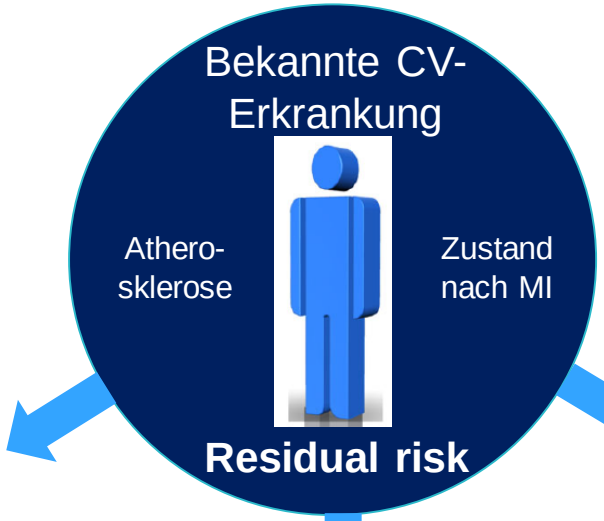
Professor Dr. Tobias Geisler

Medizinische Klinik III, Abteilung für Kardiologie und Kreislauferkrankungen,
Universitätsklinikum der Eberhard-Karls-Universität Tübingen, Germany

Interessenskonflikte

Company Name	*Relationship*
Eli Lilly / Daiichi Sankyo	*Research / educational grants, honoraria, consultant*
Astra Zeneca	*Honoraria, consultant*
MSD	*Honoraria*
The Medicines Company	*Research grants, honoraria*
Bristol Myers Squibb	*Research / educational grants, honoraria, consultant*
Bayer HealthCare	*Research / educational grants, honoraria, consultant*
Boehringer Ingelheim	*Consultant, Honoraria*

Sekundärprävention bei kardiovaskulären Risikopatienten



Residual cholesterol risk

→zusätzliche LDL-Senkung
Ezetimibe/PCSK9-Hemmer

Residual thrombotic risk

→Langfristig gesteigerte antithrombotische Therapie
COMPASS, PEGASUS

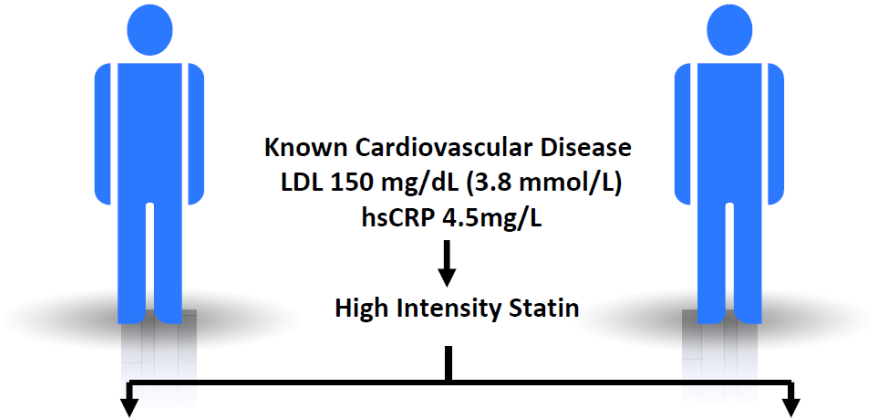
Residual inflammatory risk

→Interleukin 1-β Antikörper
CANTOS
Patientenselektion: hsCRP ↓

Modifiziert nach Ridker, European Heart Journal (2016) 37, 1720–1722

Residual Inflammatory Risk:
Addressing the Obverse Side of the Atherosclerosis Prevention Coin

Ridker PM. Eur Heart J 2016;37:1720-22



"Residual Cholesterol Risk"

LDL 110 mg/dL (2.8 mmol/L)
hsCRP 1.8 mg/L

Additional
LDL Reduction

IMPROVE-IT : Ezetimibe 6% RRR
FOURIER/SPIRE: PCSK9 Inhibition q2 weeks 15% RRR

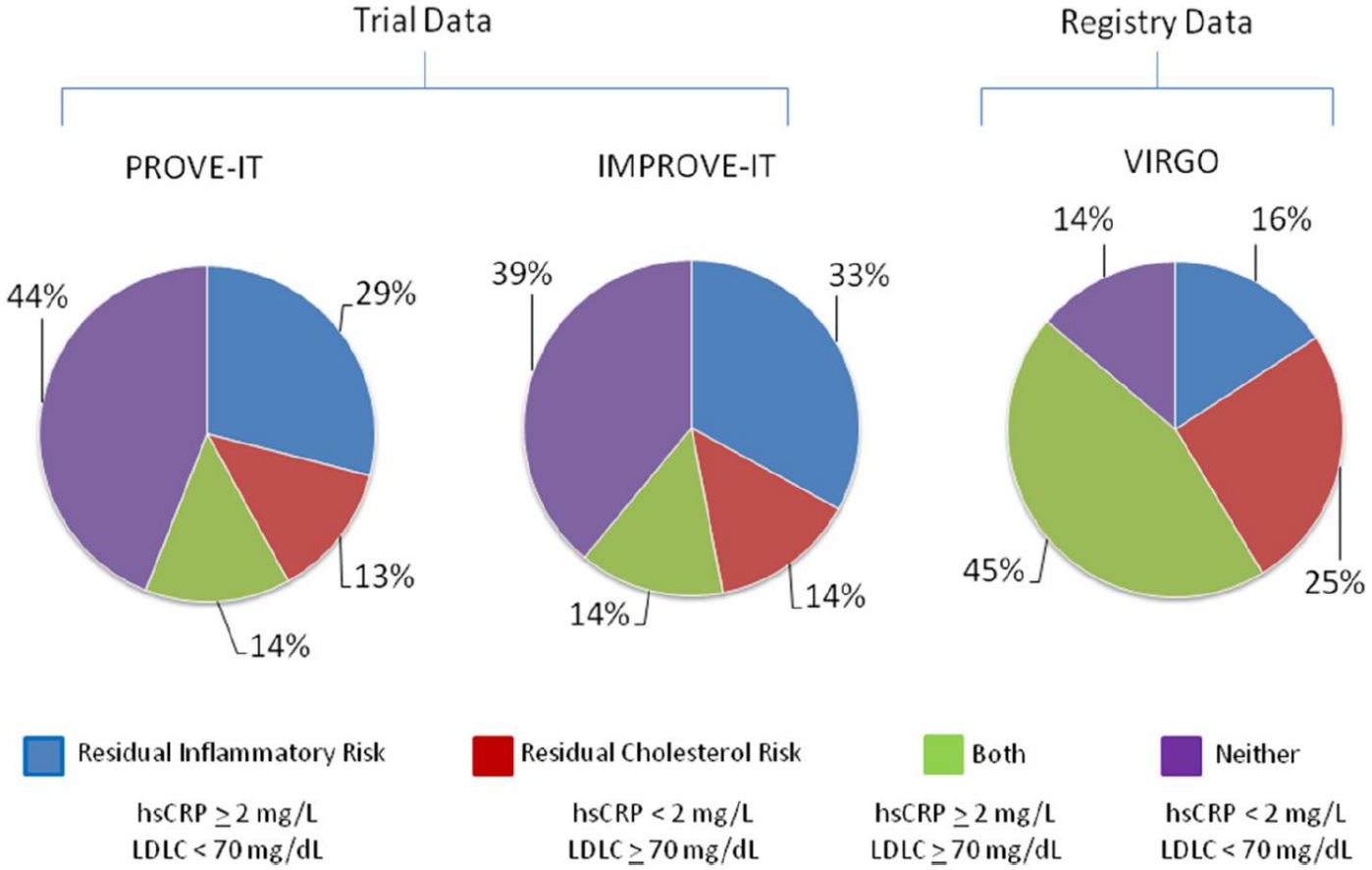
"Residual Inflammatory Risk"

LDL 70 mg/dL (1.8 mmol/L)
hsCRP 3.8 mg/L

Additional
Inflammation Reduction

No Prior Proof of Concept

Residual cholesterol and inflammatory risk



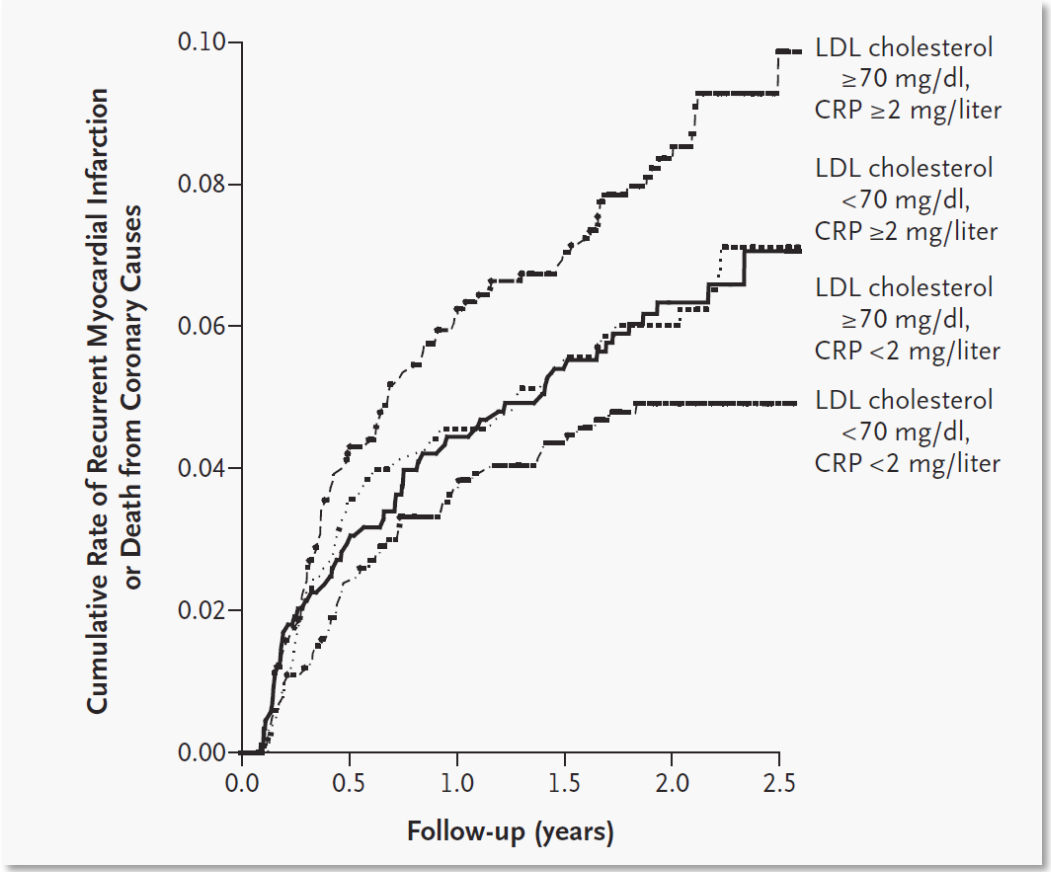
***Ridker Circ Res*. 2017;120:617-619**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

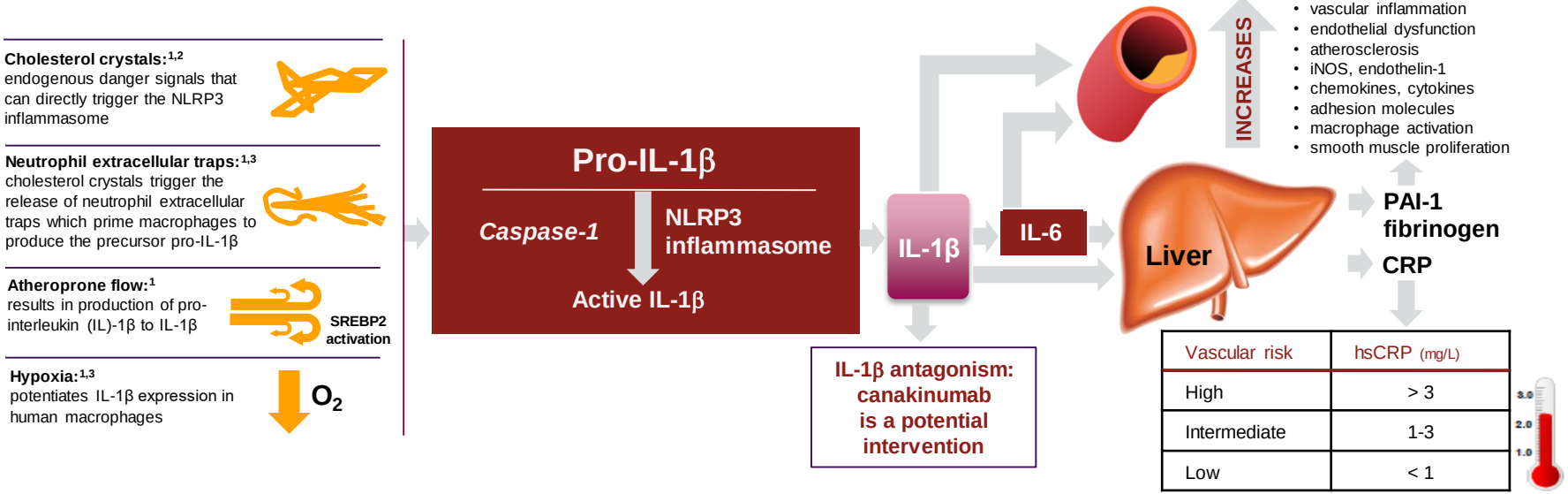
C-Reactive Protein Levels and Outcomes after Statin Therapy

Paul M Ridker, M.D., Christopher P. Cannon, M.D., David Morrow, M.D., Nader Rifai, Ph.D., Lynda M. Rose, M.S., Carolyn H. McCabe, B.S., Marc A. Pfeffer, M.D., Ph.D., and Eugene Braunwald, M.D., for the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI 22) Investigators



IL-1β is an important player in vascular inflammation

Multiple factors known to associate with atherosclerosis have recently been found to activate the crucial IL-1β–producing NLRP3 inflammasome[1]



CRP, C-reactive protein; hsCRP, high sensitivity C-reactive protein; IL, interleukin; NLRP3, nucleotide-binding oligomerization domain-like receptor protein 3 pyrin domain containing 3; iNOS, inducible nitric oxide synthase; PAI-1, plasminogen activator inhibitor-1; SREBP2, sterol regulatory element-binding protein; 1. Ridker P. M. et al. 2016.Circ. Res;118;145-156. 2. Abela G.S. et al. 2016 Jul 1;37(25):1959-67;3. Folco E. J. et al. 2014.Circ Res; 2;115(10):875-83

How does canakinumab work?

- Canakinumab is a selective, high-affinity, fully human antibody that binds to IL-1ß, and prevents it from activating the IL-1 receptor and initiating an inflammatory cascade[1-3]
- Inhibition of IL-1ß is expected to:
  - Slow atheroma formation and progression
  - Improve plaque stability
  - Decrease CV risk associated with inflammation and atherosclerosis progression
  - Reduce subsequent CV events, as shown in CANTOS[4]

CANTOS, canakinumab anti-inflammatory thrombosis outcomes study; CV, cardiovascular; IL-1ß, interleukin-1 beta. NLRP3, nucleotide-binding oligomerization domain-like receptor **protein** 3 pyrin domain containing 3; 1. Ridker PM, et al. Eur Heart J. 2014;35(27):1782-1791; 2. Ridker PM. Circ Res. 2016;118(1):145-156; 3. Ridker PM, et al. Am Heart J. 2011;162(4):597-605; 4. Ridker PM, et al. N Engl J Med 2017;377(12):1119-31

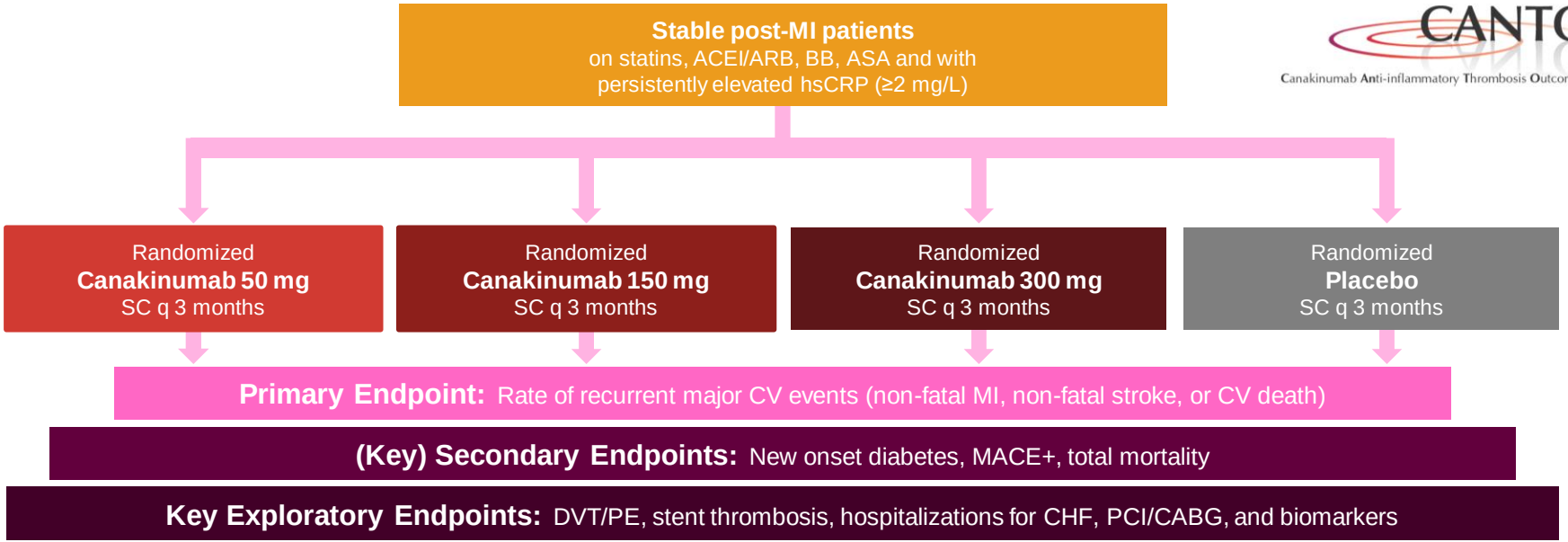
Bisherige Indikationen für Canakinumab

- Canakinumab was approved for the treatment of cryopyrin-associated periodic syndromes (CAPS) by the U.S. Food and Drug Administration (FDA) in June 2009 and by the European Medicines Agency in October 2009

- CAPS is a spectrum of autoinflammatory syndromes including familial cold autoinflammatory syndrome, Muckle–Wells syndrome, and neonatal-onset multisystem inflammatory disease.

- In September 2016, FDA approved the use of canakinumab on 3 additional rare and serious auto-inflammatory diseases: Tumor necrosis factor receptor associated periodic syndrome (TRAPS), Hyperimmunoglobulin D syndrome (HIDS)/Mevalonate kinase deficiency (MKD) and Familial Mediterranean fever (FMF).

CANTOS: Study design



Planned: 1,400 Primary endpoints (1,490 confirmed MACE)

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ASA, acetylsalicylic acid; BB, beta blockers; CABG, coronary artery bypass grafting; CHF, congestive heart failure; CV, cardiovascular; DVT, deep vein thrombosis; hsCRP, high-sensitivity C-reactive protein; MACE, major adverse cardiovascular events; MACE+, major adverse cardiovascular events + hospitalization for unstable angina pectoris requiring revascularization; MI, myocardial infarction; PCI, percutaneous coronary intervention; PE, pulmonary embolism; RRR, relative risk reduction; SC, subcutaneous; q 3 months, every 3 months. 1. Ridker PM, et al. Am Heart J. 2011;162:597-605; 2. Ridker PM, et al. N Engl J Med 2017;377(12):1119-31

CANTOS Inclusion criteria

- Men and women of non-child-bearing potential
- Aged ≥18 years
- Documented spontaneous MI ≥30 days before randomization
- hsCRP ≥2 mg/L
  - Collected <60 days prior to visit 2
  - ≥28 days after qualifying MI or after any PCI performed separately
  - On stable long-term (≥4 weeks) CV medications

CANTOS Exclusion criteria

- Pregnant or nursing women
- Any of the following conditions or diseases:
  - Planned coronary revascularization or any major non-cardiac surgical or endoscopic procedure within the past 6 months
  - Multi-vessel CABG surgery within the past 3 years
  - Symptomatic patients with NYHA class IV HF
  - Uncontrolled hypertension (SBP >160 mmHg or DBP >100 mmHg) or uncontrolled diabetes
  - History of ongoing, chronic or recurrent infectious disease including tuberculosis (active or latent) infection or risk factors for TB
  - Prior malignancy (other than basal cell skin carcinoma)
  - Nephrotic syndrome or eGFR <30 mL/min/1.73 m^2 per MDRD formula or kidney transplant
  - Known active or recurrent hepatic disorder [including cirrhosis, hepatitis B and hepatitis C], or ALT/AST levels > 3 times ULN or total bilirubin > 2 times ULN
  - Suspected or proven immunocompromised state, including HIV infection
  - Biologic drugs targeting the immune system

ALT, alanine transaminase; AST, aspartate transaminase; CANTOS, canakinumab anti-inflammatory thrombosis outcomes study; CABG, coronary artery bypass graft; CV, cardiovascular; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HF, heart failure; HIV, human immunucleotide-binding oligomerization domaineficiency virus, hsCRP, high-sensitivity C-reactive protein; MDRD, modification of diet in renal disease; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; TB, tuberculosis; ULN, upper limit of the normal range. 1. Ridker PM, et al. Am Heart J. 2011;162:597-605; 2. Ridker PM, et al. N Engl J Med 2017;377(12):1119-31

CANTOS: Baseline characteristics (1/2)

	Placebo	Canakinumab			
	(n=3,344)	50 mg (n=2,170)	150 mg (n=2,284)	300 mg (n=2,263)	All doses (n=6,717)
Age (years), mean (SD)	61.1 (10.0)	61.1 (10.1)	61.2 (10.0)	61.1 (10.1)	61.1 (10.1)
Female, n (%)	865 (25.9)	541 (24.9)	575 (25.2)	606 (26.8)	1,722 (25.6)
Race, n (%)					
Caucasian	2,652 (79.3)	1,772 (81.7)	1,808 (79.2)	1,804 (79.7)	5,384 (80.2)
Black	106 (3.2)	61 (2.8)	67 (2.9)	84 (3.7)	212 (3.2)
Asian	388 (11.6)	232 (10.7)	278 (12.2)	265 (11.7)	775 (11.5)
Other	198 (5.9)	105 (4.8)	131 (5.7)	110 (4.9)	346 (5.2)
Diabetes, n (%)	1333 (39.9)	854 (39.4)	954 (41.8)	888 (39.2)	2696 (40.1)
History of CHF‡, n (%)	721 (21.6)	451 (20.8)	478 (20.9)	523 (23.1)	1452 (21.6)
History of Hypertension, n (%)	2644 (79.1)	1751 (80.7)	1814 (79.4)	1799 (79.5)	5364 (79.9)
History of Dyslipidemia, n (%)	3251 (97.2)	2128 (98.1)	2206 (96.6)	2201 (97.3)	6535 (97.3)
Lipid lowering therapy, n (%)	3132 (93.7)	2038 (94.0)	2114 (92.7)	2113 (93.5)	6265 (93.4)
Statin, n (%)	3045 (91.1)	1990 (91.7)	2065 (90.6)	2057 (91.1)	6112 (91.1)

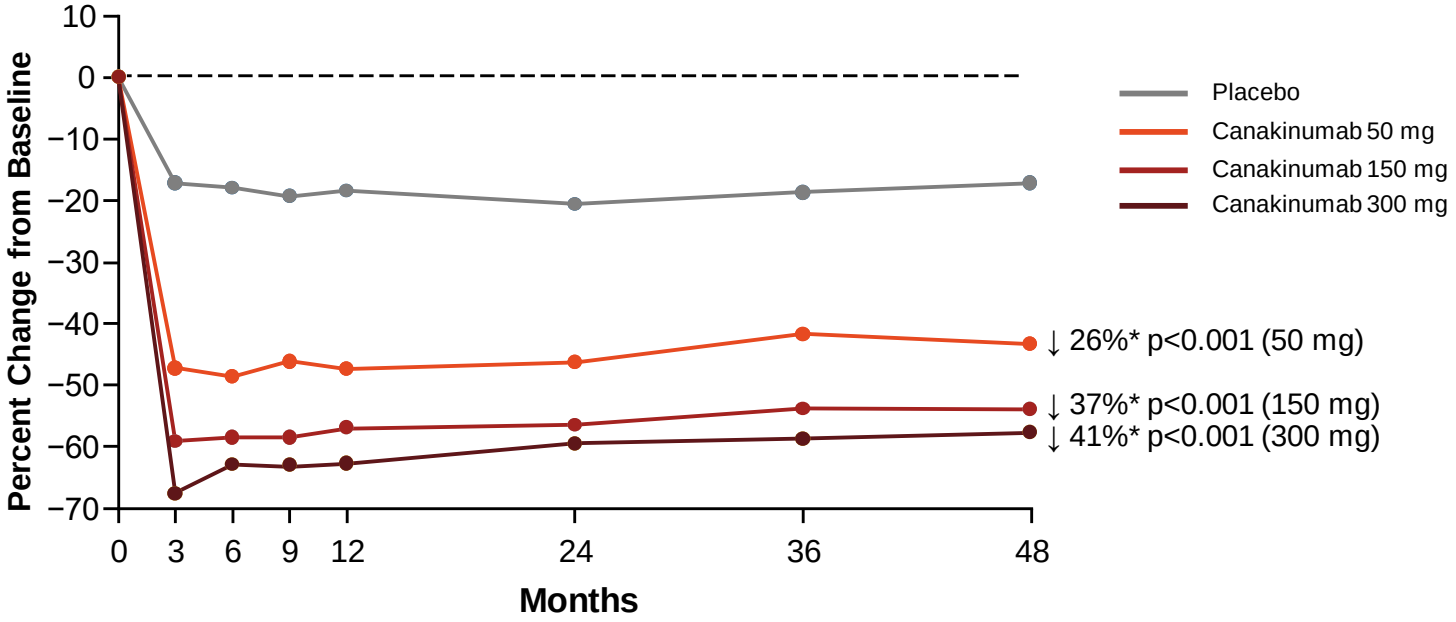
CANTOS, canakinumab anti-inflammatory thrombosis outcomes study; SD, standard deviation; CHF, chronic heart failure 1. Ridker PM, et al. N Engl J Med 2017;377(12):1119-31; 2. Novartis data on file.

CANTOS: Baseline characteristic (2/2)

	Placebo	Canakinumab			
	(n=3344)	50 mg (n=2170)	150 mg (n=2284)	300 mg (n=2263)	All doses (n=6717)
Smoking Status, n (%)					
Current Smoker	765 (22.9)	531 (24.5)	534 (23.4)	536 (23.7)	1601 (23.8)
Former Smoker	1619 (48.4)	1033 (47.6)	1061 (46.5)	1040 (46.0)	3134 (46.7)
BMI, median, kg/m^2 (IQR)	29.7 (26.6, 33.8)	29.9 (26.6, 33.9)	29.8 (26.5, 33.7)	29.8 (26.5, 33.8)	29.9 (26.6, 33.8)
hsCRP, median, mg/L (IQR)	4.1 (2.75, 6.85)	4.25 (2.80, 7.15)	4.25 (2.85, 7.05)	4.15 (2.85, 7.15)	4.2 (2.80, 7.10)
IL-6, median, ng/L (IQR)	2.61 (1.80, 4.06)	2.53 (1.80, 4.17)	2.56 (1.74, 4.11)	2.59 (1.79, 4.08)	2.56 (1.77, 4.13)
eGFR, mL/min/1.73m^2 (IQR)	79.0 (65.0, 93.0)	79.0 (64.0, 92.0)	79.0 (64.5, 93.0)	78.0 (64.0, 93.0)	78.5 (64.0, 93.0)
Total cholesterol, mg/dL (IQR) *(mmol/L)*	161 (137, 190) *(4.2)*	159 (136, 189) *(4.1)*	159 (136, 188) *(4.1)*	161 (137, 189) *(4.2)*	160 (136, 189) *(4.1)*
HDL-cholesterol, mg/dL (IQR) *(mmol/L)*	44.5 (37.1, 52.6) *(1.2)*	43.7 (37.0, 52.2) *(1.1)*	43.7 (36.3, 52.0)* *(1.1)*	44.0 (36.7, 53.0) *(1.1)*	43.7 (36.7, 52.2)* *(1.1)*
LDL-cholesterol Median, mg/dL *(mmol/L)*	82.8 (64.2, 107.5) *(2.1)*	81.2 (62.3, 106.0) *(2.1)*	82.4 (63.4, 106.0) *(2.1)*	83.5 (64.0, 108.0) *(2.2)*	82.0 (63.0, 106.7) *(2.1)*
Triglycerides, mg/dL (IQR) *(mmol/L)*	139 (100, 194) *(1.6)*	140 (102, 198) *(1.6)*	139 (101, 196) *(1.6)*	138 (103, 194) *(1.6)*	139 (102, 196) *(1.6)*

p-value <0.05 in comparison to placebo; BMI, body mass index; CANTOS, canakinumab anti-inflammatory thrombosis outcomes study; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; IQR, interquartile range; LDL, low-density lipoprotein; 1. Ridker PM, et al. N Engl J Med 2017;377(12):1119-31; 2. Novartis data on file.

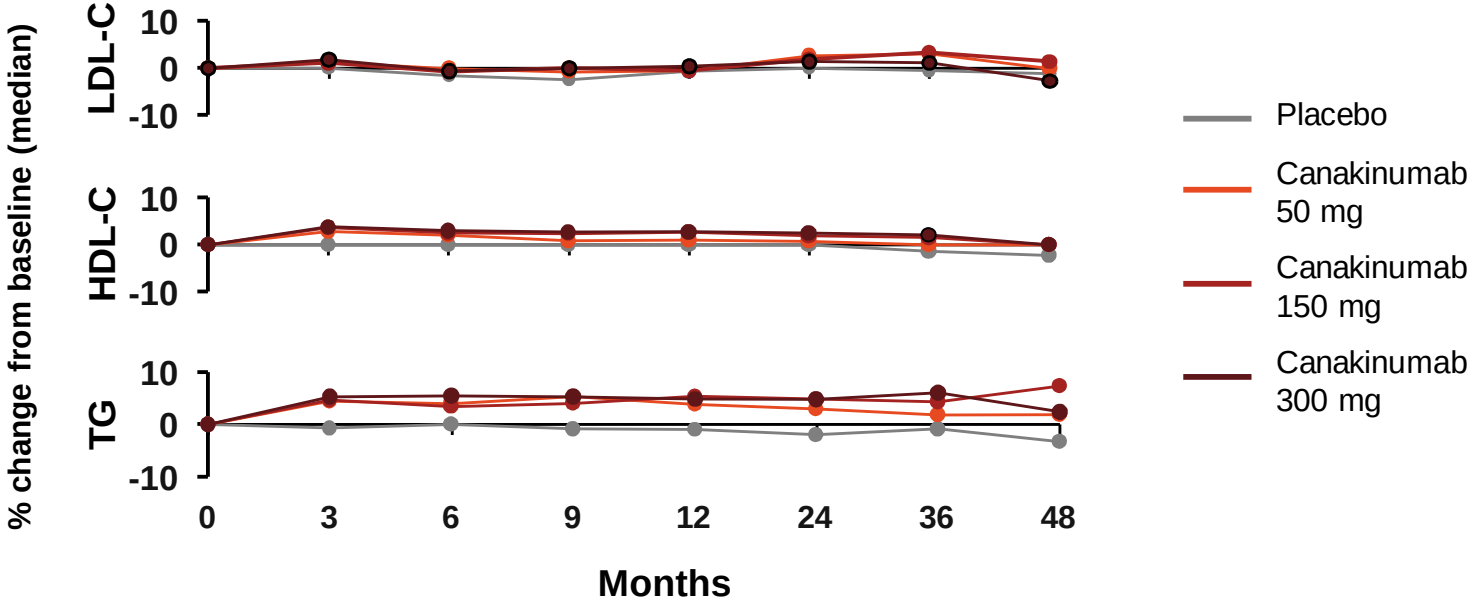
Canakinumab reduced hsCRP at all 3 doses over 48 months relative to placebo (n=10,061)



*% greater reduction than in the placebo group. hsCRP, high-sensitivity C-reactive protein. 1. Ridker PM, et al. N Engl J Med 2017;377(12):1119-31

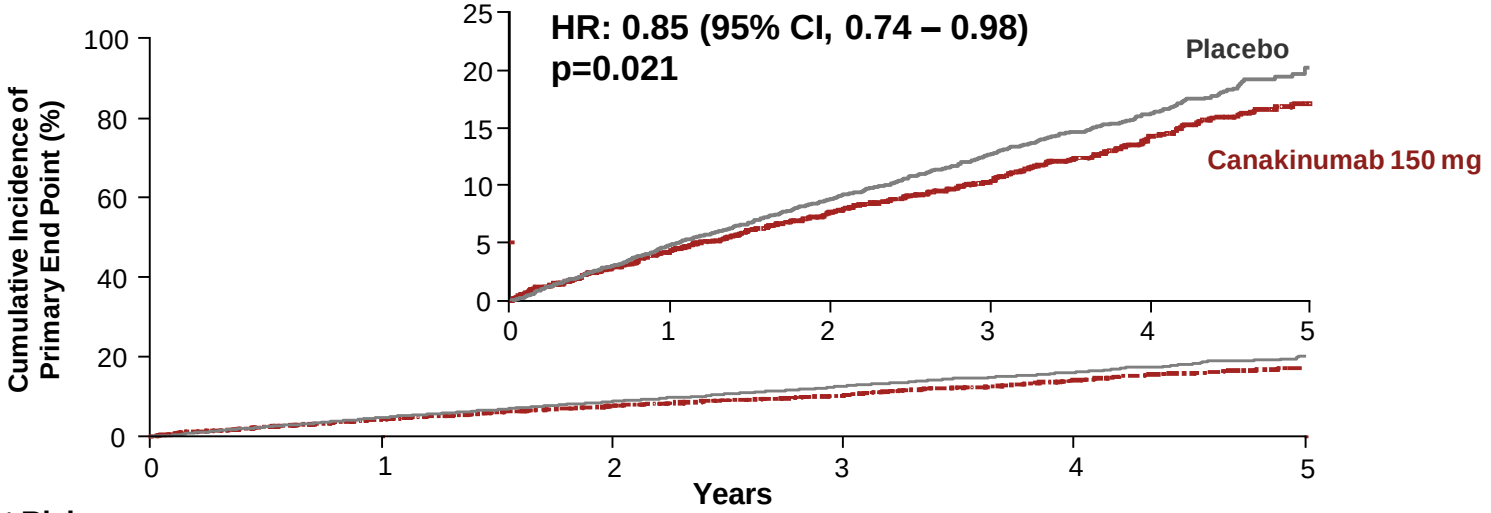
Effect of canakinumab on lipids

- Canakinumab use resulted in no reduction in LDL-C or HDL-C vs placebo arm over 48 months and a 4–5% median increase in TG



HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides. 1. Ridker PM, et al. N Engl J Med 2017;377(12):1119-31

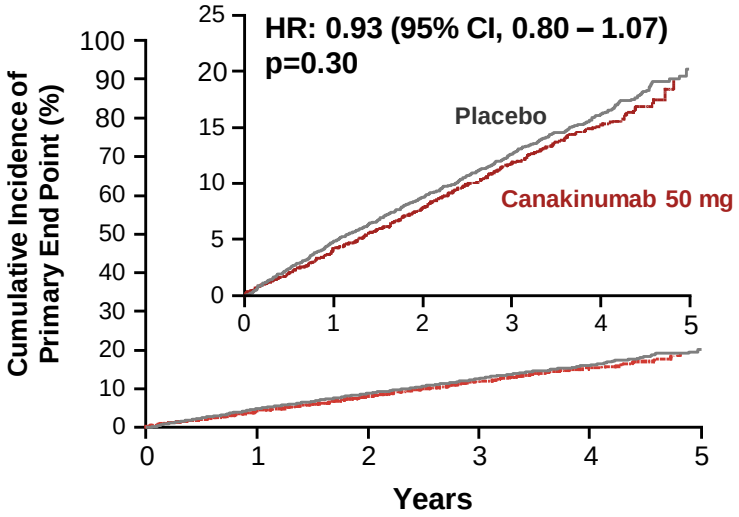
Primary endpoint: 15% reduction in risk of MACE observed for 150 mg canakinumab dose



No. at Risk						
Placebo	3344	3141	2973	2632	1266	210
Canakinumab	2284	2151	2057	1849	907	207

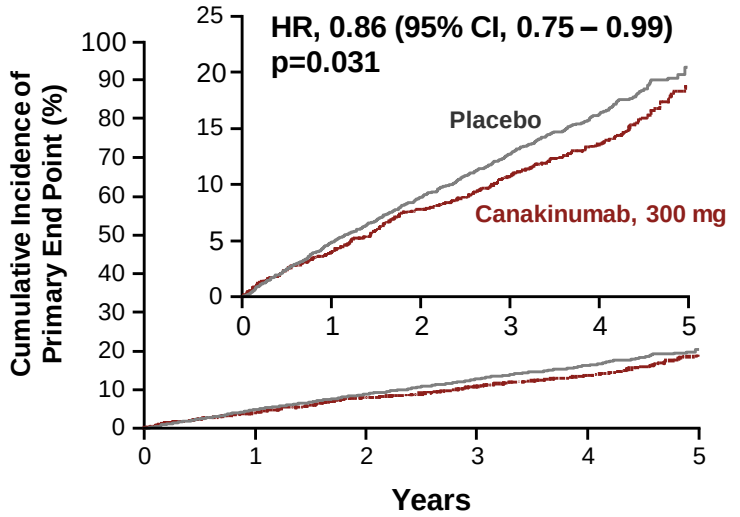
P-value statistically significant compared to placebo, adjusted for multiplicity and accounting for two efficacy interim analyses, in accordance with the pre-specified closed-testing procedure (threshold p=0.02115); CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular event. 1. Ridker PM, et al. N Engl J Med 2017;377(12):1119-31; 2. Novartis data on file.

Primary endpoint: 50 mg / 300 mg canakinumab doses



No. at Risk

Placebo	3344	3141	2973	2632	1266	210
Canakinumab	2170	2057	1950	1713	762	47

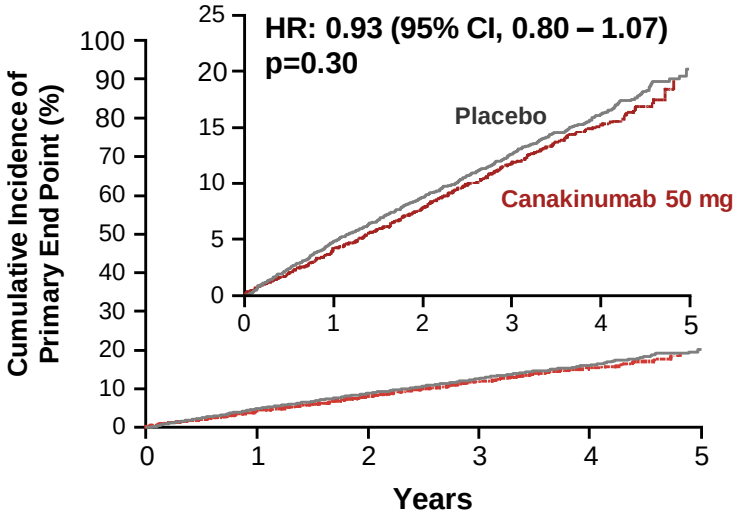


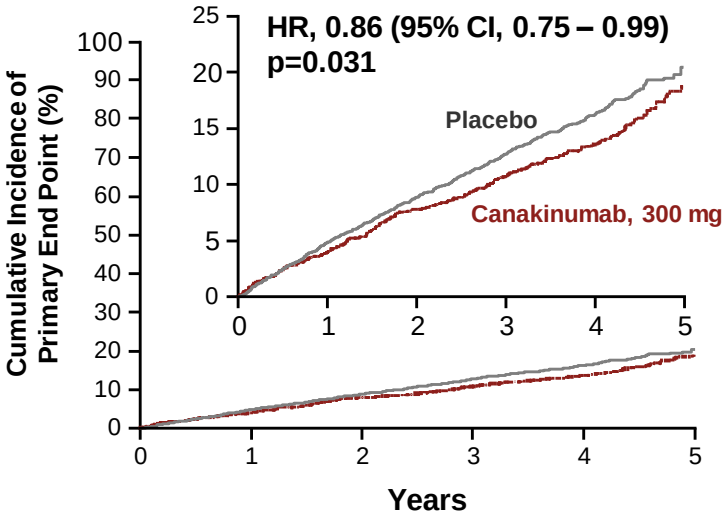
No. at Risk

Placebo	3344	3141	2973	2632	1266	210
Canakinumab	2263	2149	2038	1819	938	199

P-values not statistically significant compared to placebo based on the prespecified closed-testing procedure (threshold p=0.02115 for 50 mg dose, threshold p=0.01058 300 mg dose). CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular event . 1. Ridker PM, et al. N Engl J Med 2017;377(12):1119-31;

Primary endpoint: 50 mg / 300 mg canakinumab doses





No. at Risk

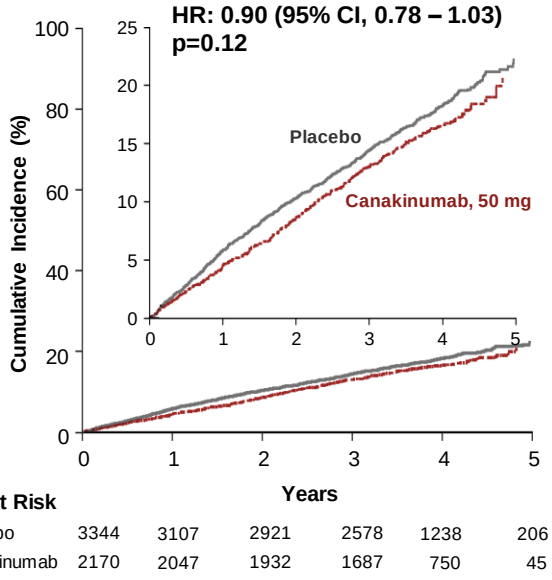
Placebo	3344	3141	2973	2632	1266	210
Canakinumab	2170	2057	1950	1713	762	47

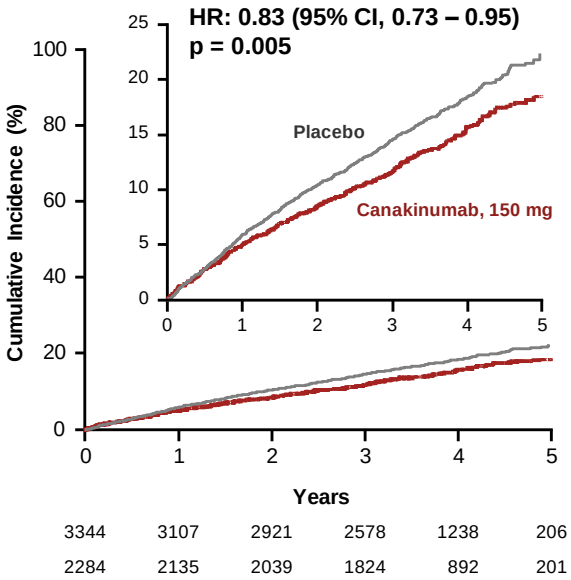
No. at Risk

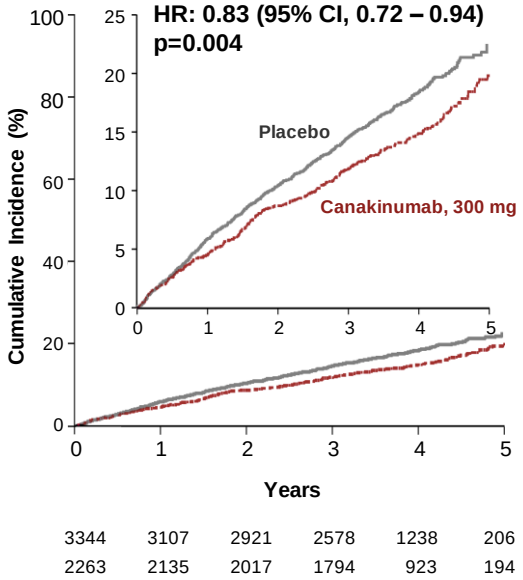
Placebo	3344	3141	2973	2632	1266	210
Canakinumab	2263	2149	2038	1819	938	199

P-values not statistically significant compared to placebo based on the prespecified closed-testing procedure (threshold p=0.02115 for 50 mg dose, threshold p=0.01058 300 mg dose). CI, confidence interval; HR, hazard ratio; 1. Ridker PM, et al. N Engl J Med 2017;377(12):1119-31;

Key secondary endpoint: MACE + hospitalization for unstable angina requiring revascularization







No. at Risk						
Placebo	3344	3107	2921	2578	1238	206
Canakinumab	2170	2047	1932	1687	750	45
	3344	3107	2921	2578	1238	206
	2284	2135	2039	1824	892	201
	3344	3107	2921	2578	1238	206
	2263	2135	2017	1794	923	194

P-value statistically significant compared to placebo, adjusted for multiplicity and accounting for two efficacy interim analyses, in accordance with the pre-specified closed-testing procedure (threshold p=0.00529). CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular event . 1. Ridker PM, et al. N Engl J Med 2017;377(12):1119-31

Adverse event and tolerability profile

	Placebo	Canakinumab		
	Placebo N=3348 n (%)	50 mg N=2170 n (%)	150 mg N=2285 n (%)	300 mg N=2263 n (%)
Subjects with at least one AE	2914 (87.0)	1872 (86.3)	1970 (86.2)	1987 (87.8)
AEs suspected to be related to study drug	474 (14.2)	267 (12.3)	350 (15.3)	355 (15.7)
Subjects who permanently discontinued study drug due to AEs	244 (7.3)	142 (6.5)	164 (7.2)	175 (7.7)
AEs leading to study treatment interruption	399 (11.9)	228 (10.5)	270 (11.8)	268 (11.8)

Infections

	Placebo	Canakinumab				p-value	
Adverse event	Placebo N=3348 n/100 py (n)	50 mg N=2170 n/100 py (n)	150 mg N=2285 n/100 py (n)	300 mg N=2263 n/100 py (n)	All doses N=6717 n/100 py (n)	p-value for trend across doses	p-value for combined dose groups
Subjects with at least one SAE	11.96 (1202)	11.41 (741)	11.71 (812)	12.33 (836)	11.82 (2389)	0.43	0.79
Any SAE infection	2.86 (342)	3.03 (230)	3.13 (258)	3.25 (265)	3.14 (753)	0.12	0.14
Fatal infection/sepsis	0.18 (23)	0.31 (25)	0.28 (24)	0.34 (29)	0.31 (78)	0.09	0.02

AE, adverse event; Py, person years; SAE, serious adverse event. 1. Novartis data on file.

Adverse events: Hepatic and other safety topics of interest

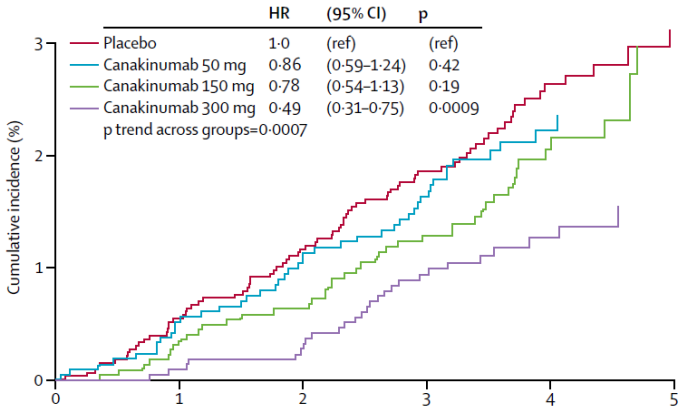
Adverse event/laboratory parameter	Placebo	Canakinumab				p-value	
	Placebo N=3348 n/100 py (n)	50 mg N=2170 n/100 py (n)	150 mg N=2285 n/100 py (n)	300 mg N=2263 n/100 py (n)	All doses N=6717 n/100 py (n)	p-value for trend across doses	p-value for combined dose groups
Any malignancy‡	1.88 (231)	1.85 (144)	1.69 (143)	1.72 (144)	1.75 (431)	0.31	0.38
Fatal malignancy‡	**0.64 (81)**	**0.55 (44)**	**0.50 (44)**	**0.31 (27)**	**0.45 (115)**	**0.0007**	**0.016**
Injection site reaction*	0.23 (29)	0.27 (21)	0.28 (24)	0.30 (26)	0.28 (71)	0.49	0.36
Leukopenia	**0.24 (30)**	**0.30 (24)**	**0.37 (32)**	**0.52 (44)**	**0.40 (100)**	**0.002**	**0.013**
Neutropenia	0.06 (7)	0.05 (4)	0.07 (6)	0.18 (15)	0.10 (25)	0.014	0.17
Any Hemorrhage	4.01 (462)	3.33 (249)	4.15 (327)	3.82 (301)	3.78 (877)	0.94	0.31
Thrombocytopenia	**0.43 (53)**	**0.56 (44)**	**0.54 (46)**	**0.71 (60)**	**0.60 (150)**	**0.022**	**0.031**
Drug-induced liver injury (SAE)*	0.18 (23)	0.15 (12)	0.13 (11)	0.05 (4)	0.11 (27)	0.0039	0.0541

All adverse event categories are based on standardized MedDRA queries or classification levels, except those otherwise indicated; *Sponsor categorization of adverse events of special interest ‡Including malignancies adjudicated by the Cancer Endpoint Adjudication Committee.
Py, person years; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event

1. Ridker PM, et al. N Engl J Med 2017;377(12):1119-31

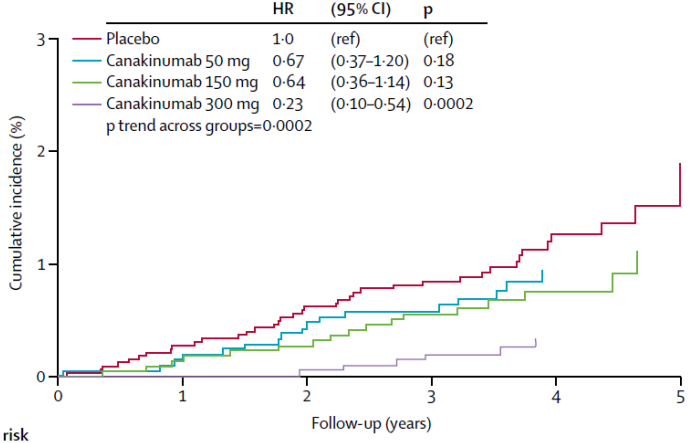
Decreased cumulative incidence of fatal malignancies

All fatal cancer



Number at risk						
Placebo	3344	3255	3162	2868	1423	257
Canakinumab 50 mg	2170	2117	2054	1845	838	57
Canakinumab 150 mg	2284	2221	2163	1972	998	243
Canakinumab 300 mg	2263	2204	2139	1949	1013	227

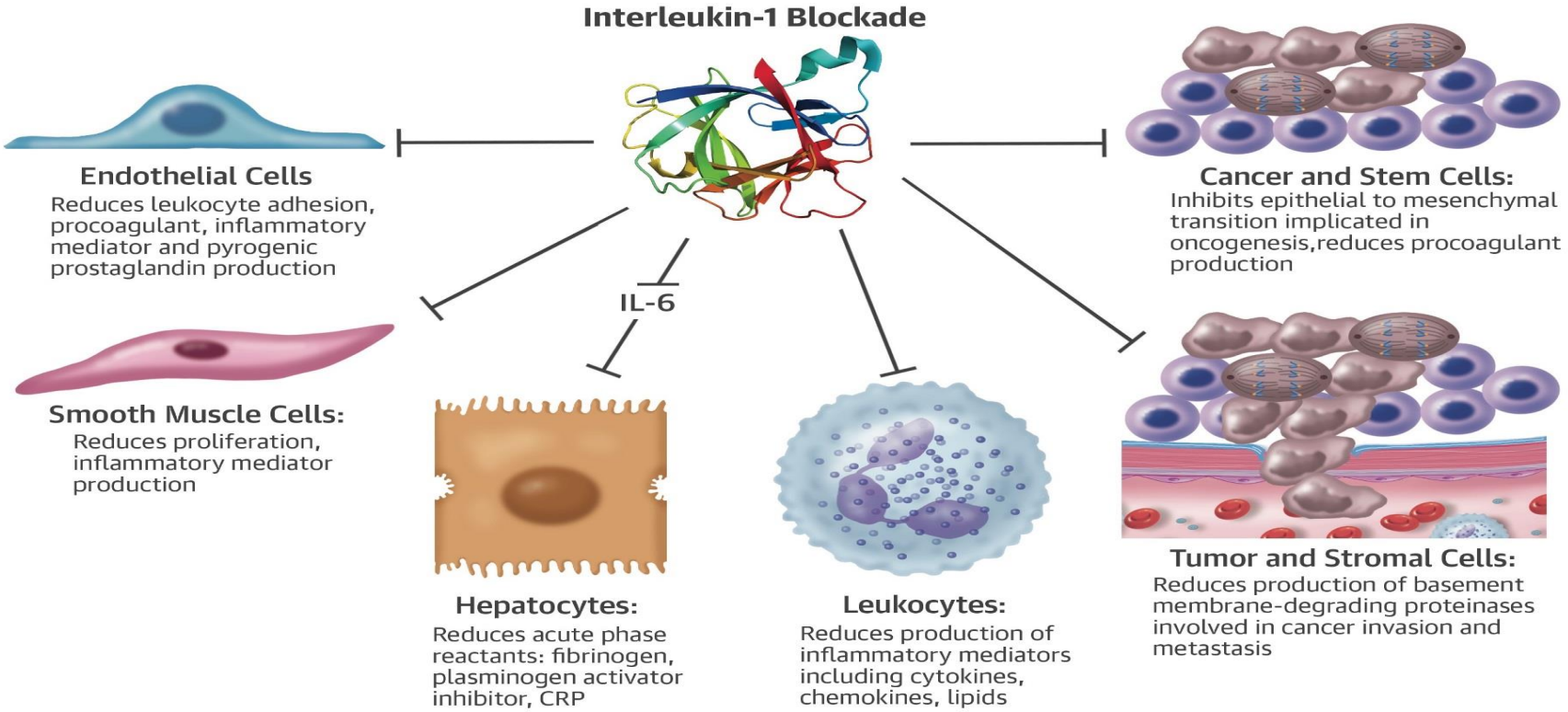
Fatal lung cancer



Number at risk						
Placebo	3344	3255	3162	2868	1423	257
Canakinumab 50 mg	2170	2117	2054	1845	838	57
Canakinumab 150 mg	2284	2221	2163	1972	998	243
Canakinumab 300 mg	2263	2204	2139	1949	1013	227

CI, confidence interval; HR, hazard ratio 1. Ridker PM et al, Lancet. 2017 Aug 25. pii: S0140-6736(17)32247-X. doi: 10.1016/S0140-6736(17)32247-X. [Epub ahead of print]

Ridker et al, Lancet. 2017;390(10105):1833-1842.



Libby P. Interleukin-1 Beta as a Target for Atherosclerosis: Biologic Basis for CANTOS and Beyond. JACC 2017 (October 31, 2017)

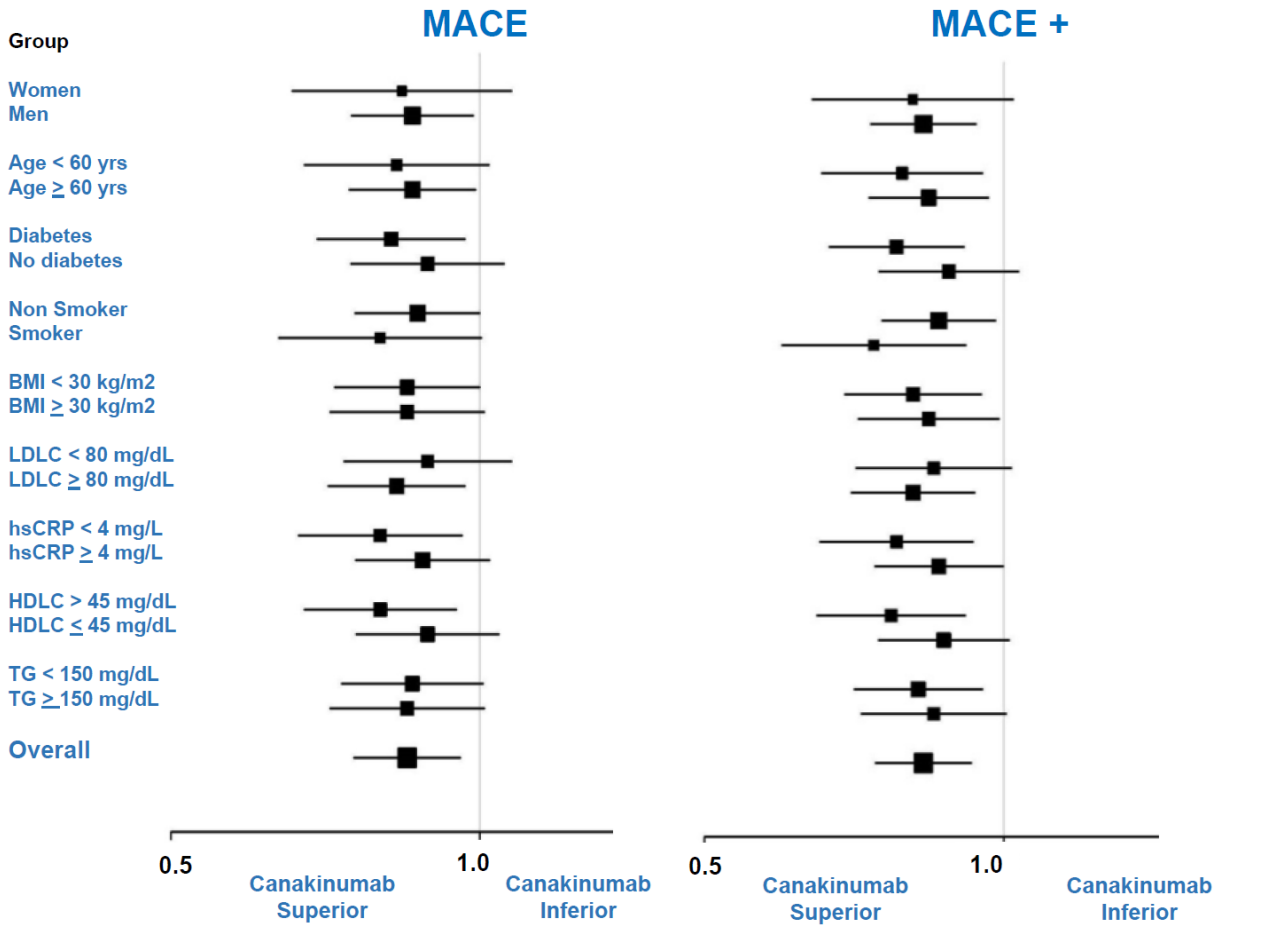
Summary of CANTOS results

CANTOS

Cardiology Trials Assessing DMARD/Biologic Effects on CV Outcomes			
Study	**CIRT**	**CANTOS**	**OXI**
Title	CV Inflammation Reduction Trial	Canakinumab Anti-inflammatory Thrombosis Outcomes Study	Hydroxychloroquine for the Prevention of CV Events in Myocardial Infarction
DMARD, Interventions	**Methotrextate** (15-20/wk), PBO	**Canakinumab** (50,150,300mg), PBO	**Hydroxychloroquine** (400mg) or PBO
Pts (N)	CAD, MI, DM, MS (7000)	Post MI, CAD w/ hsCRP > 2.0mg/dl (17200)	Post-MI patients (2500)
Endpoint	Major CVE, Mortality	Time to major CVE (MI, CVA, CVD death)	360 events - Death, MI, hospitalization for unstable angina, urgent PTCA, CABG
Start date	April 2013	April 2011	February 2016
Completion	December 2018	February 2017	June 2018
ClinicalTrials.gov	NCT01594333	NCT01900600	NCT02648464

Welche Patienten profitieren?

CANTOS: Consistency of Effect Across All Patient Groups



Ridker ESC 2017

CANTOS Sensitivity Analysis V: Multivariable Adjusted Hazard Ratios for Additional Pre-Specified Cardiovascular Outcomes According to On-treatment hsCRP Levels Above or Below 2 mg/L After Drug Initiation

Clinical Outcome		Placebo (N = 3182)	Canakinumab On-treatment hsCRP ≥ 2mg/L (N = 2868)	Canakinumab On-treatment hsCRP < 2 mg/L (N = 3484)
MACE	HR (adjusted) 95% CI P	1.0 Referent Referent	0.90 0.79-1.02 0.11	0.75 0.66-0.85 <0.0001
MACE - Plus	HR (adjusted) 95% CI P	1.0 Referent Referent	0.91 0.81-1.03 0.14	0.74 0.66-0.83 <0.0001
CV Death	HR (adjusted) 95% CI P	1.0 Referent Referent	0.99 0.82-1.21 0.95	0.69 0.56-0.85 0.0004
All-Cause Mortality	HR (adjusted) 95% CI P	1.0 Referent Referent	1.05 0.90-1.22 0.56	0.69 0.58-0.81 <0.0001

HRs adjusted for age, gender, smoking, HTN, diabetes, BMI, baseline hsCRP, Baseline LDLC

Ridker, presented at AHA 2017

CANTOS Sensitivity Analysis VI: Consistent Effects at All Doses of Canakinumab (MACE)

Canakinumab Dose		Placebo	Canakinumab On-treatment hsCRP ≥ 2mg/L	Canakinumab On-treatment hsCRP < 2 mg/L
50 mg SC q 3 months	HR (adjusted) 95% CI P	1.0 Referent Referent	0.96 0.80-1.14 0.63	0.78 0.63-0.96 0.02
150 mg SC q 3 months	HR (adjusted) 95% CI P	1.0 Referent Referent	0.86 0.71-1.04 0.11	0.75 0.62-0.91 0.003
300 mg SC q 3 months	HR (adjusted) 95% CI P	1.0 Referent Referent	0.87 0.71-1.07 0.18	0.74 0.62-0.88 0.0009

HRs adjusted for age, gender, smoking, HTN, diabetes, BMI, baseline hsCRP, Baseline LDLC

The proportions of those treated who achieved hsCRP levels < 2 mg/L were 44%, 55%, and 65% in the 50mg, 150mg, and 300mg canakinumab groups, respectively.

Sekundärprävention bei kardiovaskulären Risikopatienten

Residual cholesterol risk

→zusätzliche LDL-Senkung
Ezetimibe/PCSK9-Hemmer

Residual thrombotic risk

→Langfristig gesteigerte antithrombotische Therapie
COMPASS, PEGASUS

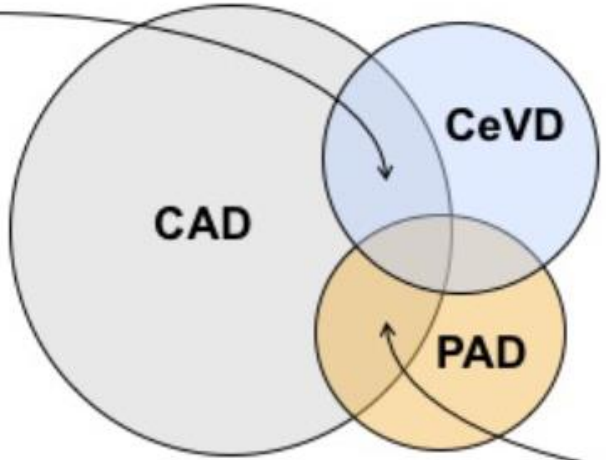
Residual inflammatory risk

→Interleukin 1-β Antikörper
CANTOS
Patientenselektion: hsCRP ↓

Modifiziert nach Ridker, European Heart Journal (2016) 37, 1720–1722

REACH Register: Substantielle Überlappung zwischen KHK und cAVK/pAVK

24.7% of patients with CAD had concomitant disease in other vascular beds

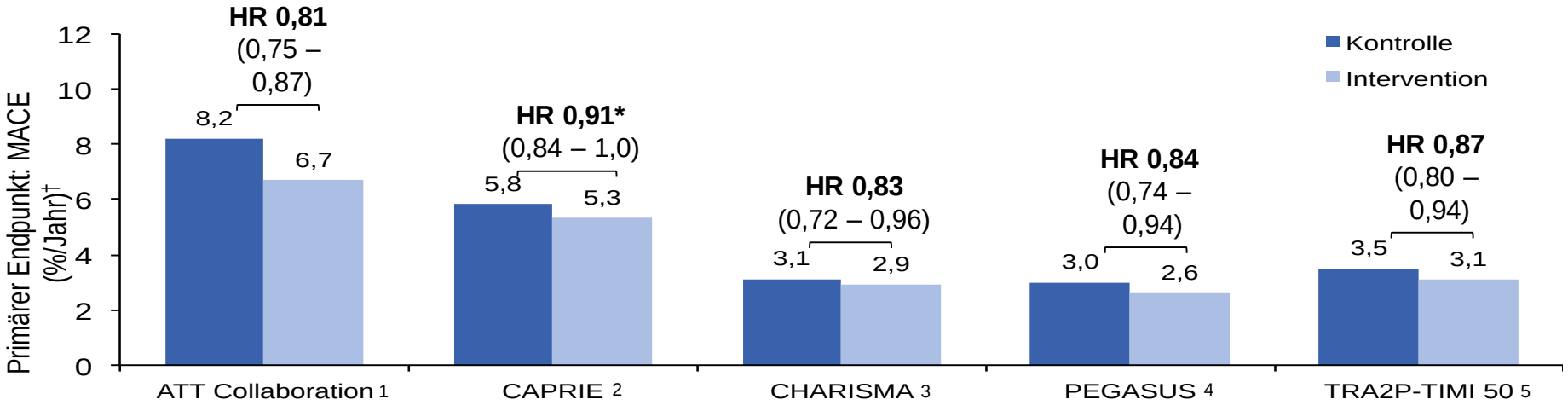


N=40,258

61.5% of patients with PAD had concomitant disease in other vascular beds

Bhatt DL, et al. JAMA 2006;295:180-189

Chronische KHK oder pAVK
Risiko für vaskuläre Ereignisse trotz optimaler Therapie



% Einsatz der Standardtherapien	Kontrolle ASS	ASS, Clopidogrel	Placebo + ASS / Clopidogrel + ASS	Placebo + ASS / Ticagrelor + ASS	Vorapaxar, Placebo + ASS ± Thienopyridin
ACE-Hemmer/ARB	Metaanalyse aus 16 Studien	n.a.	bis zu 85,3	80,4	73,5
Statin/ lipidsenkend		n.a.	77,1 - 89,3	92,4	91,0

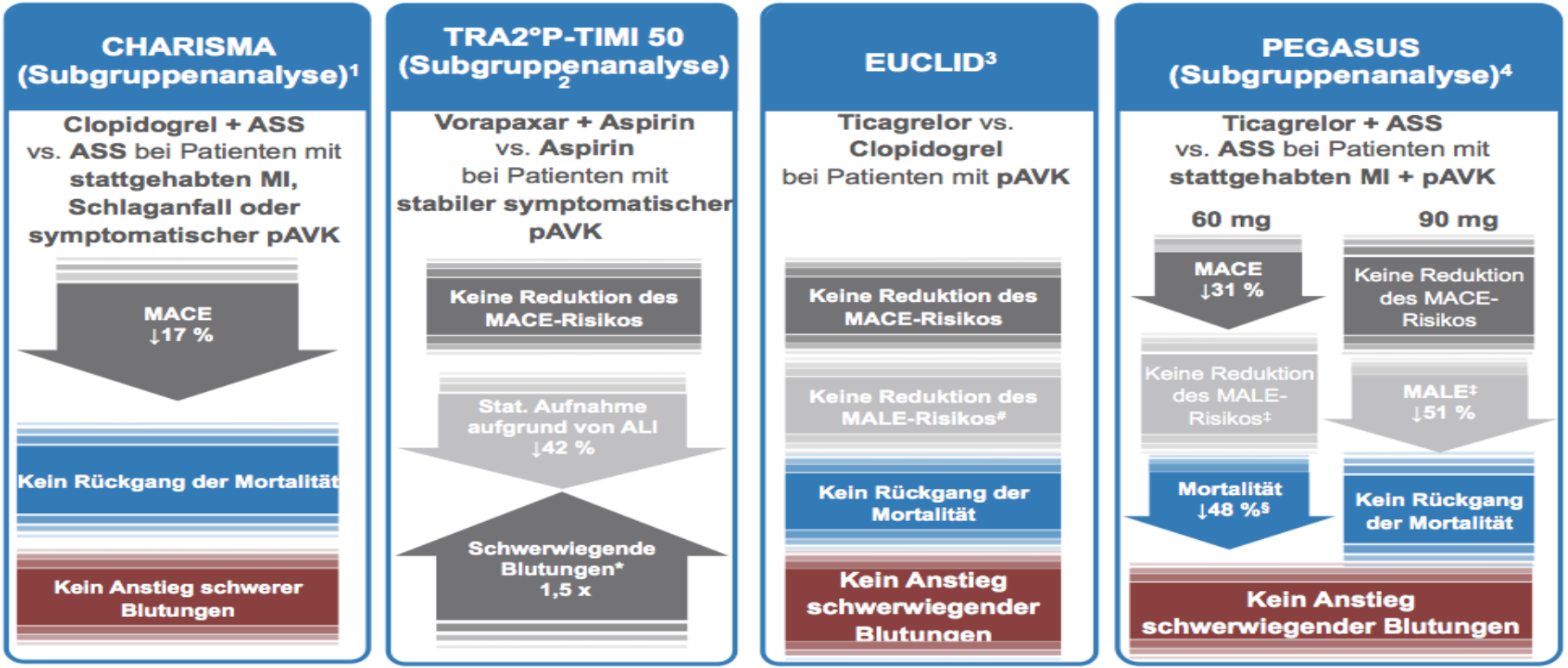
*Schätzung basierend auf nachgewiesener RRR

†Schätzung basierend auf nachgewiesenem prozentualen Gesamtanteil der medianen Nachverfolgung innerhalb von 28 Monaten (CHARISMA-Studie) und nachgewiesenen dreijährigen Kaplan-Meier-Raten (PEGASUS und TRA2P-TIMI50)

ACE: Angiotensin konvertierendes Enzym, ARB: Angiotensin-Rezeptorblocker, ASS: Acetylsalicylsäure, n.a.: nicht verfügbar

1. ATT Collaboration. *Lancet* 2009;373:1849–1860; 2. CAPRIE Steering Committee. *Lancet* 1996;348:1329–1339; 3. Bhatt DL *et al*. *J Am Coll Cardiol* 2007;49:1982–1988; 4. Bonaca MP *et al. N Engl J Med* 2015;372:1791–1800; 5. Morrow DA *et al. N Engl J Med* 2012;366:1404–1413

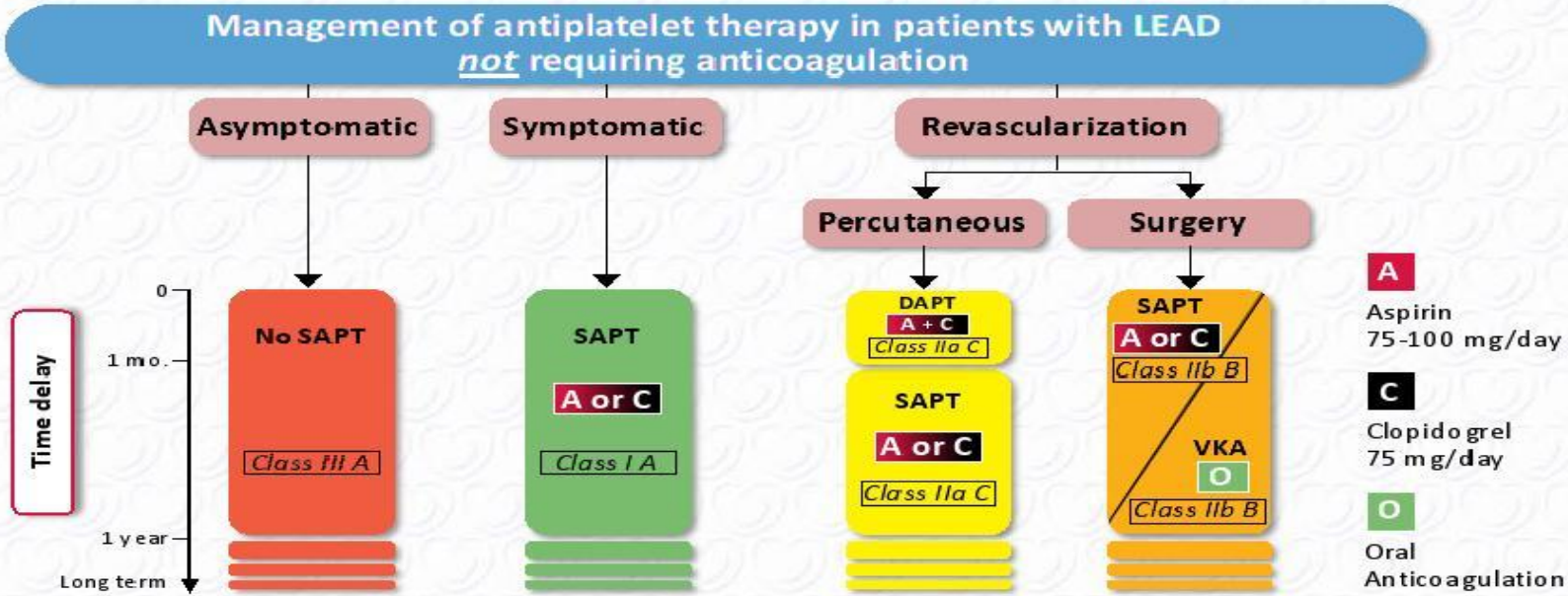
Eine intensivierte Thrombozytenaggregationshemmung bei Patienten mit pAVK führte zu unterschiedlichen Ergebnisse.



*Periphere Bypassoperation oder Beinamputation aufgrund von CLI oder einer sonstigen Intervention aufgrund der pAVK (individuelle Endpunkte); #Stat. Aufnahme aufgrund von ALI oder Revaskularisation der unteren Extremitäten (individuelle Endpunkte); ‡Kombination von ALI oder peripherer Revaskularisation; §Keine Reduktion der Mortalität in der Gesamt-Studienpopulation[5] 1. Bhatt DL *et al*, *J Am Coll Cardiol* 2007;49:1982–1988 ; 2. Bonaca MP *et al*, *Circulation* 2013;127:1522–1529; 3. Hiatt WR *et al*, *N Engl J Med* 2017;376:32–40; 4. Bonaca MP *et al*, *J Am Coll Cardiol* 2016;67:2719–2728; Bonaca MP *et al, N Engl J Med* 2015;372:1791–1800

Antiplatelet therapy in patients with lower extremity artery disease

ESC European Society of Cardiology



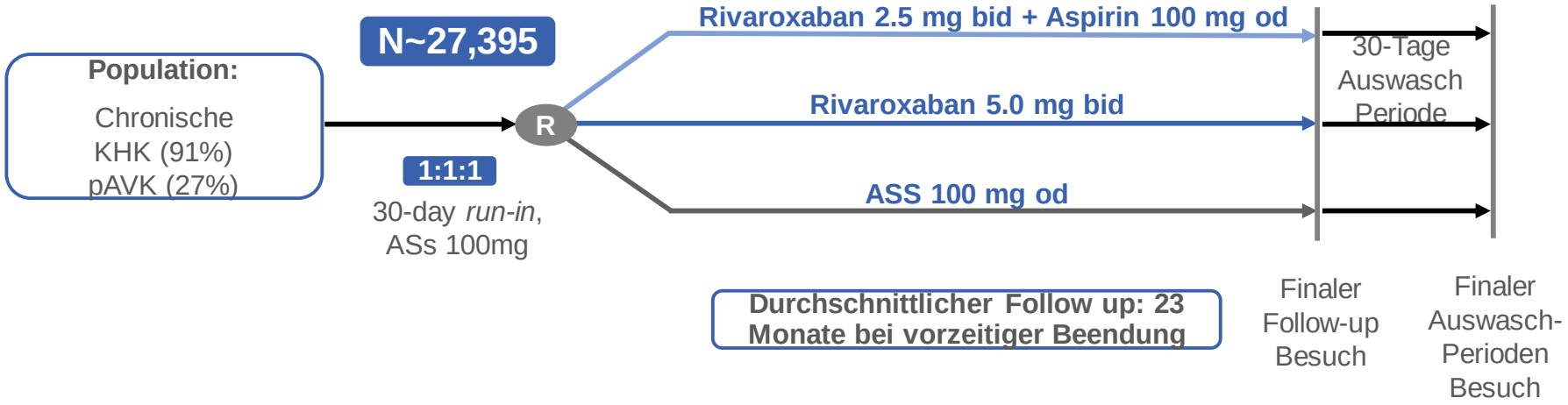
2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with ESVS (European Heart Journal 2017; doi:10.1093/eurheartj/ehx095)

COMPASS

Studiendesign

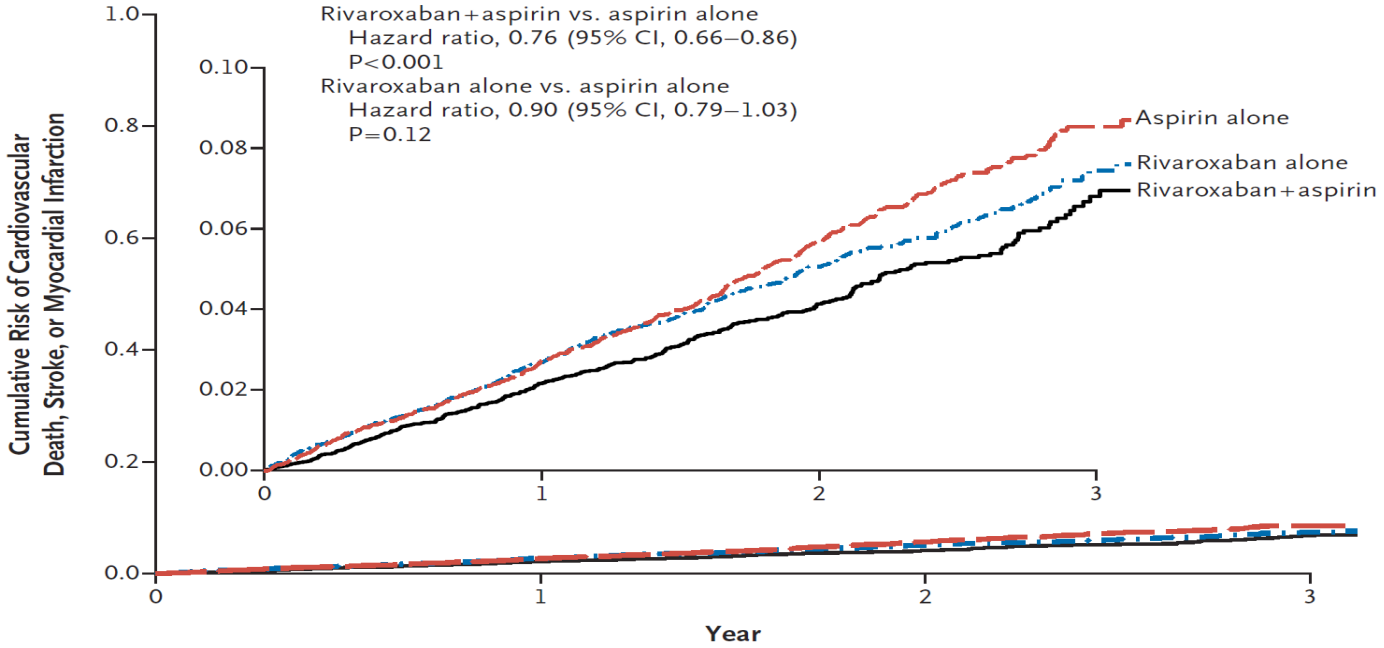
Studienziel

- Untersuchung der Wirksamkeit und Sicherheit von Rivaroxaban, Rivaroxaban plus ASS oder ASS alleine zur Reduktion von Herzinfarkt, Schlaganfall und kardiovaskulärem Tod bei Patienten mit KHK oder pAVK



KHK: koronare Herzerkrankung, pAVK: periphere arterielle Verschlusskrankheit,; ASS: Acetylsalicylsäure, MI: Myokardinfarkt, CV: kardiovaskulär

Antithrombotische Therapie in der stabilen Phase der KHK/pAVK – COMPASS primärer Wirksamkeitsendpunkt



No. at Risk				
Aspirin alone	9126	7808	3860	669
Rivaroxaban alone	9117	7824	3862	670
Rivaroxaban+aspirin	9152	7904	3912	658

Eikelboom et al, NEJM 2017

COMPASS: Primary Components

Outcome	R + A N=9,152	A N=9,126	Rivaroxaban + Aspirin vs. Aspirin	
	N (%)	N (%)	HR (95% CI)	p
CV death	160 (1.7%)	203 (2.2%)	0.78 (0.64-0.96)	0.02
Stroke	83 (0.9%)	142 (1.6%)	0.58 (0.44-0.76)	<0.0001
MI	178 (1.9%)	205 (2.2%)	0.86 (0.70-1.05)	0.14

Eikelboom et al. for the COMPASS investigators, NEJM 2017

Primärer Sicherheitsendpunkt
Modifizierte ISTH-Definition

ISTH-Definition für schwere Blutungen[1]	Modifizierte ISTH-Definition für schwere Blutungen (COMPASS)
• Tödliche Blutungen und/oder • symptomatische Blutungen in einem kritischen Bereich oder Organ (z. B. intrakranial) und/oder • **Blutungen, die zu einem Abfall der Hämoglobin-Konzentration auf ≥ 20 g/l führten oder ≥ 2 Einheiten Vollblut- oder Erythrozytentransfusionen erforderlich machten**	• Tödliche Blutungen und/oder • symptomatische Blutungen in einem kritischen Bereich oder Organ (z. B. intrakranial) oder • **Einblutungen in einen Operationsbereich mit erforderlicher erneuter Operation und/oder** • **Blutungen, die zur stationären Aufnahme führten**

Anders als die Standard ISTH Kriterien wurden alle Blutungen, die zu einer Vorstellung in der Notaufnahme oder einer stationären Aufnahme führten, als schwer angesehen.

COMPASS

1. Schulman S *et al*, *J Thromb Haemost* 2005;3:692–694

Major Bleeding

Outcome	R + A	R	A	Rivaroxaban 2.5 BID + Aspirin vs. Aspirin		Rivaroxaban 5 BID vs. Aspirin	
	N (%)	N (%)	N (%)	HR (95% CI)	P	HR (95% CI)	P
Major bleeding	288 (3.1%)	255 (2.8%)	170 (1.9%)	**1.70 (1.40-2.05)**	<0.0001	**1.51 (1.25-1.84)**	<0.0001
Fatal	15 (0.2%)	14 (0.2%)	10 (0.1%)	**1.49 (0.67-3.33)**	0.32	**1.40 (0.62-3.15)**	0.41
Non fatal ICH*	21 (0.2%)	32 (0.4%)	19 (0.2%)	**1.10 (0.59-2.04)**	0.77	**1.69 (0.96-2.98)**	0.07
Non-fatal other critical organ*	42 (0.5%)	45 (0.5%)	29 (0.3%)	**1.43 (0.89-2.29)**	0.14	**1.57 (0.98-2.50)**	0.06

** symptomatic*

COMPASS: Secondary Outcomes

Outcome	R + A N=9,152	A N=9,126	Rivaroxaban + Aspirin vs. Aspirin	
	N (%)	N (%)	HR (95% CI)	P*
CHD death, IS, MI, ALI	329 (3.6%)	450 (4.9%)	0.72 (0.63-0.83)	<0.0001
CV death, IS, MI, ALI	389 (4.3%)	516 (5.7%)	0.74 (0.65-0.85)	<0.0001
Mortality	313 (3.4%)	378 (4.1%)	0.82 (0.71-0.96)	0.01

* pre-specified threshold P=0.0025

- **Definition:** Kombination aus KV-bedingtem Tod, Schlaganfall, MI, tödliche Blutung oder symptomatische Einblutung in ein kritisches Organ
  - **Der klinische Nettonutzen beinhaltet die Kombination aus tödlichen Ereignissen und nicht tödlichen Ereignissen mit irreversiblen Schädigungen**

Endpunkt	Rivaroxaban 2,5 mg 2 x tgl. + ASS 100 mg N = 9152	ASS 100 mg N = 9126	Rivaroxaban 2,5 mg 2 x tgl. + ASS 100 mg vs ASS 100 mg	
			HR (95 % KI)	*p*-Wert
Klinischer Nettonutzen	431 (4,7 %)	534 (5,9 %)	0,80 (0,70 – 0,91)	< 0,001

Eikelboom JW *et al. N Engl J Med* 2017; DOI: 10.1056/NEJMoa1709118

COMPASS

Rivaroxaban with or without aspirin in patients with stable coronary artery disease: an international, randomised, double-blind, placebo-controlled trial

*Stuart J Connolly, John W Eikelboom, Jackie Bosch, Gilles Dagenais, Leanne Dyal, Fernando Lanas, Kaj Metsarinne, Martin O'Donnell, Anthony L Dans, Jong-Won Ha, Alexandr N Parkhomenko, Alvaro A Avezum, Eva Lonn, Liu Lisheng, Christian Torp-Pedersen, Petr Widimsky, Aldo P Maggioni, Camilo Felix, Katalin Keltai, Masatsugu Hori, Khalid Yusoff, Tomasz J Guzik, Deepak L Bhatt, Kelley R H Branch, Nancy Cook Bruns, Scott D Berkowitz, Sonia S Anand, John D Varigos, Keith A A Fox, Salim Yusuf, on behalf of the COMPASS investigators**

Summary

Background Coronary artery disease is a major cause of morbidity and mortality worldwide, and is a consequence of acute thrombotic events involving activation of platelets and coagulation proteins. Factor Xa inhibitors and aspirin each reduce thrombotic events but have not yet been tested in combination or against each other in patients with stable coronary artery disease.

Methods In this multicentre, double-blind, randomised, placebo-controlled, outpatient trial, patients with stable coronary artery disease or peripheral artery disease were recruited at 602 hospitals, clinics, or community centres in 33 countries. This paper reports on patients with coronary artery disease. Eligible patients with coronary artery disease had to have had a myocardial infarction in the past 20 years, multi-vessel coronary artery disease, history of stable or unstable angina, previous multi-vessel percutaneous coronary intervention, or previous multi-vessel coronary artery bypass graft surgery. After a 30-day run in period, patients were randomly assigned (1:1:1) to receive rivaroxaban (2·5 mg orally twice a day) plus aspirin (100 mg once a day), rivaroxaban alone (5 mg orally twice a day), or aspirin alone (100 mg orally once a day). Randomisation was computer generated. Each treatment group was double dummy, and the patients, investigators, and central study staff were masked to treatment allocation. The primary outcome of the COMPASS trial was the occurrence of myocardial infarction, stroke, or cardiovascular death. This trial is registered with ClinicalTrials.gov, number NCT01776424, and is closed to new participants.

Findings Between March 12, 2013, and May 10, 2016, 27 395 patients were enrolled to the COMPASS trial, of whom 24 824 patients had stable coronary artery disease from 558 centres. The combination of rivaroxaban plus aspirin reduced the primary outcome more than aspirin alone (347 [4%] of 8313 *vs* 460 [6%] of 8261; hazard ratio [HR] 0·74, 95% CI 0·65–0·86, p<0·0001). By comparison, treatment with rivaroxaban alone did not significantly improve the primary outcome when compared with treatment with aspirin alone (411 [5%] of 8250 *vs* 460 [6%] of 8261; HR 0·89, 95% CI 0·78–1·02, p=0·094). Combined rivaroxaban plus aspirin treatment resulted in more major bleeds than treatment with aspirin alone (263 [3%] of 8313 *vs* 158 [2%] of 8261; HR 1·66, 95% CI 1·37–2·03, p<0·0001), and similarly, more bleeds were seen in the rivaroxaban alone group than in the aspirin alone group (236 [3%] of 8250 *vs* 158 [2%] of 8261; HR 1·51, 95% CI 1·23–1·84, p<0·0001). The most common site of major bleeding was gastrointestinal, occurring in 130 (2%) patients who received combined rivaroxaban plus aspirin, in 84 (1%) patients who received rivaroxaban alone, and in 61 (1%) patients who received aspirin alone. Rivaroxaban plus aspirin reduced mortality when compared with aspirin alone (262 [3%] of 8313 *vs* 339 [4%] of 8261; HR 0·77, 95% CI 0·65–0·90, p=0·0012).

Interpretation In patients with stable coronary artery disease, addition of rivaroxaban to aspirin lowered major vascular events, but increased major bleeding. There was no significant increase in intracranial bleeding or other critical organ bleeding. There was also a significant net benefit in favour of rivaroxaban plus aspirin and deaths were reduced by 23%. Thus, addition of rivaroxaban to aspirin has the potential to substantially reduce morbidity and mortality from coronary artery disease worldwide.

Funding Bayer AG.

Introduction

Coronary artery disease is a global medical problem and a leading cause of morbidity and mortality.[1] Patients with coronary artery disease are at risk for myocardial infarction, ischaemic stroke, and cardiovascular death. The underlying pathophysiology of these events in patients with atherosclerosis is rupture or erosion of an atherosclerotic plaque which exposes the sub-endothelial matrix to circulating blood.[2] This activates both platelet aggregation and the coagulation cascade, which leads to

Published Online November 10, 2017 http://dx.doi.org/10.1016/S0140-6736(17)32458-3

See Online/Comment http://dx.doi.org/10.1016/S0140-6736(17)32816-7

*Members listed in the appendix

Population Health Research Institute, McMaster University and Hamilton Health Sciences, Hamilton, ON, Canada (Prof S J Connolly MD, Prof J W Eikelboom MBBS, L Dyal MSc, E Lonn MD, S S Anand MD, Prof S Yusuf MBBS); **School of Rehabilitation Science, McMaster University, Hamilton, ON, Canada** (J Bosch PhD); **Institut Universitaire de Cardiologie et Pneumologie de Québec, Québec, QC, Canada** (Prof G Dagenais MD); **Universidad de la Frontera, Temuco, Chile** (Prof F Lanas PhD); **Department of Medicine, Turku University Central Hospital and Turku University, Turku, Finland** (K Metsarinne MD); **Department of Medicine, National University of Ireland, Galway, Ireland** (M O'Donnell MB); **Department of Medicine, University of Philippines, Manila, Philippines** (Prof A L Dans MD); **Yonsei University College of Medicine, Seoul, Korea** (Prof J-W Ha MD); **Institute of Cardiology, Kiev, Ukraine** (Prof A N Parkhomenko MD); **Instituto Dante Pazzanese de Cardiologia & University Santo Amaro, Sao Paulo, Brazil** (Prof A A Avezum MD); **FuWai Hospital, CAMS, Beijing, China** (Prof L Lisheng MD); **University of Aalborg, Aalborg, Denmark** (Prof C Torp-Pedersen MD); **Charles University, Prague, Czech Republic** (Prof P Widimsky MD); **ANMCO**

Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial

*Sonia S Anand, Jackie Bosch, John W Eikelboom, Stuart J Connolly, Rafael Diaz, Peter Widimsky, Victor Aboyans, Marco Alings, Ajay K Kakkar, Katalin Keltai, Aldo P Maggioni, Basil S Lewis, Stefan Störk, Jun Zhu, Patricio Lopez-Jaramillo, Martin O'Donnell, Patrick J Commerford, Dragos Vinereanu, Nana Pogosova, Lars Ryden, Keith A A Fox, Deepak L Bhatt, Frank Misselwitz, John D Varigos, Thomas Vanassche, Alvaro A Avezum, Edmond Chen, Kelley Branch, Darryl P Leong, Shrikant I Bangdiwala, Robert G Hart, Salim Yusuf; on behalf of the COMPASS Investigators**

Summary

Background Patients with peripheral artery disease have an increased risk of cardiovascular morbidity and mortality. Antiplatelet agents are widely used to reduce these complications.

Methods This was a multicentre, double-blind, randomised placebo-controlled trial for which patients were recruited at 602 hospitals, clinics, or community practices from 33 countries across six continents. Eligible patients had a history of peripheral artery disease of the lower extremities (previous peripheral bypass surgery or angioplasty, limb or foot amputation, intermittent claudication with objective evidence of peripheral artery disease), of the carotid arteries (previous carotid artery revascularisation or asymptomatic carotid artery stenosis of at least 50%), or coronary artery disease with an ankle–brachial index of less than 0·90. After a 30-day run-in period, patients were randomly assigned (1:1:1) to receive oral rivaroxaban (2·5 mg twice a day) plus aspirin (100 mg once a day), rivaroxaban twice a day (5 mg with aspirin placebo once a day), or to aspirin once a day (100 mg and rivaroxaban placebo twice a day). Randomisation was computer generated. Each treatment group was double dummy, and the patient, investigators, and central study staff were masked to treatment allocation. The primary outcome was cardiovascular death, myocardial infarction or stroke; the primary peripheral artery disease outcome was major adverse limb events including major amputation. This trial is registered with ClinicalTrials.gov, number NCT01776424, and is closed to new participants.

Findings Between March 12, 2013, and May 10, 2016, we enrolled 7470 patients with peripheral artery disease from 558 centres. The combination of rivaroxaban plus aspirin compared with aspirin alone reduced the composite endpoint of cardiovascular death, myocardial infarction, or stroke (126 [5%] of 2492 *vs* 174 [7%] of 2504; hazard ratio [HR] 0·72, 95% CI 0·57–0·90, p=0·0047), and major adverse limb events including major amputation (32 [1%] *vs* 60 [2%]; HR 0·54 95% CI 0·35–0·82, p=0·0037). Rivaroxaban 5 mg twice a day compared with aspirin alone did not significantly reduce the composite endpoint (149 [6%] of 2474 *vs* 174 [7%] of 2504; HR 0·86, 95% CI 0·69–1·08, p=0·19), but reduced major adverse limb events including major amputation (40 [2%] *vs* 60 [2%]; HR 0·67, 95% CI 0·45–1·00, p=0·05). The median duration of treatment was 21 months. The use of the rivaroxaban plus aspirin combination increased major bleeding compared with the aspirin alone group (77 [3%] of 2492 *vs* 48 [2%] of 2504; HR 1·61, 95% CI 1·12–2·31, p=0·0089), which was mainly gastrointestinal. Similarly, major bleeding occurred in 79 (3%) of 2474 patients with rivaroxaban 5 mg, and in 48 (2%) of 2504 in the aspirin alone group (HR 1·68, 95% CI 1·17–2·40; p=0·0043).

Interpretation Low-dose rivaroxaban taken twice a day plus aspirin once a day reduced major adverse cardiovascular and limb events when compared with aspirin alone. Although major bleeding was increased, fatal or critical organ bleeding was not. This combination therapy represents an important advance in the management of patients with peripheral artery disease. Rivaroxaban alone did not significantly reduce major adverse cardiovascular events compared with asprin alone, but reduced major adverse limb events and increased major bleeding.

Funding Bayer AG.

Introduction

Patients with carotid artery disease or with peripheral artery disease of the lower extremities are at high risk for major adverse cardiovascular events,[1–3] and patients with peripheral artery disease of the lower extremities are also at high risk for major adverse limb events such as severe limb ischaemia and amputation.[4] In addition to smoking cessation and exercise, statins, angiotensin converting enzyme (ACE) inhibitors, and antiplatelet agents (aspirin or a P2Y12 inhibitor) are used to reduce vascular complications.[4–6] Anticoagulant therapies have not been shown to be superior to antiplatelet therapy in peripheral artery disease and have unacceptably high rates of major bleeding.[7] Specifically, high intensity (international

Published Online November 10, 2017 http://dx.doi.org/10.1016/S0140-6736(17)32409-1

See Online/Comment http://dx.doi.org/10.1016/S0140-6736(17)32847-7

*Members listed in the appendix

Population Health Research Institute, McMaster University and Hamilton Health Sciences, Hamilton, ON, Canada (Prof S S Anand MD, J Bosch PhD, J W Eikelboom MBBS, Prof S J Connolly MD, D P Leong MBBS, Prof S I Bangdiwala PhD, Prof R G Hart MD, Prof S Yusuf MBBS); **Department of Medicine** (Prof S S Anand, J W Eikelboom, Prof S J Connolly, D P Leong, Prof R G Hart, Prof S Yusuf); **and School of Rehabilitation Sciences** (J Bosch), **McMaster University, Hamilton, ON, Canada; Estudios Clínicos Latino America and Instituto Cardiovascular de Rosario, Rosario, Argentina** (R Diaz MD); **Cardiocenter, University Hospital Kralovske Vinohrady and Third Faculty of Medicine, Charles University Prague, Prague, Czech Republic** (Prof P Widimsky MD); **Dupuytren University Hospital, Limoges, France** (Prof V Aboyans MD); **Amphia Ziekenhuis and Werkgroep Cardiologische centra Nederland, Utrecht, Netherlands** (M Alings MD); **Thrombosis Research Institute and University College London, London, UK** (Prof A K Kakkar MBBS); **2nd Department of Internal Medicine, Semmelweis University, Budapest, Hungary** (K Keltai MD); **ANMCO Research Center, Florence, Italy** (Prof A P Maggioni MD); **Lady Davis Carmel Medical Centre**

Primärer Wirksamkeitsendpunkt: MACE (I)

Dualer Wirkansatz mit vaskulärer Dosis Rivaroxaban, 2,5 mg 2x tägl. + ASS führte zu Reduktion von MACE um 26 %

Primärer Wirksamkeits-endpunkt	Rivaroxaban 2,5 mg 2 x tägl. + ASS n = 8.313	ASS n = 8.261	Rivaroxaban 2,5 mg 2 x tägl. + ASS vs ASS	
	n (%)	n (%)	HR (95% KI)	*p-Wert*
MACE	**347 (4)**	**460 (6)**	**0,74 (0,65–0,86)**	**<0,0001**
KV-bedingter Tod	139 (2)	184 (2)	0,75 (0,60–0,93)	0,010
Schlaganfall	74 (1)	130 (2)	0,56 (0,42–0,75)	<0,0001
Ischämisch/ unspezifisch	60 (1)	120 (2)	0,50 (0,36–0,67)	<0,0001
Hämorrhagisch	14 (<1)	10 (<1)	1,39 (0,62–3,32)	0,43
MI	169 (2)	195 (2)	0,86 (0,71–1,05)	0,15

ASS: Acetylsalicylsäure, MACE: major adverse cardiovascular events, HR: hazard ratio, KI: Konfidenzintervall, KV: kardiovaskulär, MI: Myokardinfarkt

Connolly SJ *et al*. *Lancet* 2017; doi:10.1016/S0140-6736(17)32816-7.

Primärer Sicherheitsendpunkt

Primärer Sicherheits-endpunkt	Rivaroxaban 2,5 mg 2 x tägl. + ASS n = 8.313	ASS n = 8.261	Rivaroxaban 2,5 mg 2 x tägl. + ASS vs ASS	
	(%)	n (%)	HR (95% KI)	*p*-Wert
Schwere Blutungen	**263 (3)**	**158 (2)**	**1,66 (1,37–2,03)**	**<0,0001**
tödlich	14 (<1)	9 (<1)	1,55 (0,67–3,58)	0,30
ICB	19 (<1)	19 (<1)	0,99 (0,52–1,87)	0,98
Kritische Organe	36 (<1)	25 (<1)	1,42 (0,85–2,36)	0,18
andere	194 (2)	105 (1)	1,85 (1,46–2,34)	<0,0001

ASS: Acetylsalicylsäure, HR: hazard ratio, KI: Konfidenzintervall, ICB: intrakranielle Blutung

Connolly SJ *et al*. *Lancet* 2017; doi:10.1016/S0140-6736(17)32816-7.

Subgruppenanalysen (I)

=155.8 mg/dl

Subgruppe	Rivaroxaban 2.5 mg 2 x tägl. + ASS	ASS als Monotherapie	HR (95% KI)	HR (95% KI)	p-Wert
Baseline total cholesterol					0·89
<4 mmol/L	138/4045	177/3988		0·76 (0·60–0·94)	
≥4 mmol/L	209/4244	283/4262		0·74 (0·62–0·89)	
Peripheral artery disease					0·37
Yes	94/1656	138/1641		0·67 (0·52–0·87)	
No	253/6657	322/6620		0·77 (0·66–0·91)	
Non-smokers receiving lipid-lowering drugs, β blockers, and either an ACE inhibitor or angiotension receptor blocker					0·89
Yes	150/3431	194/3406		0·75 (0·61–0·93)	
No	197/4882	266/4855		0·74 (0·61–0·89)	
TIMI risk score†					0·92
0–1	57/2611	77/2582		0·73 (0·52–1·03)	
2	88/2399	108/2316		0·79 (0·59–1·04)	
3–8	202/3303	275/3363		0·74 (0·61–0·88)	
Overall	**347/8313**	**460/8261**		**0·74 (0·65–0·86)**	

0·5 1·0 2·0 4·0

Favours low-dose rivaroxaban + aspirin

Favours aspirin alone

0,1 1 10

Rivaroxaban 2,5 mg 2x tägl. + ASS besser

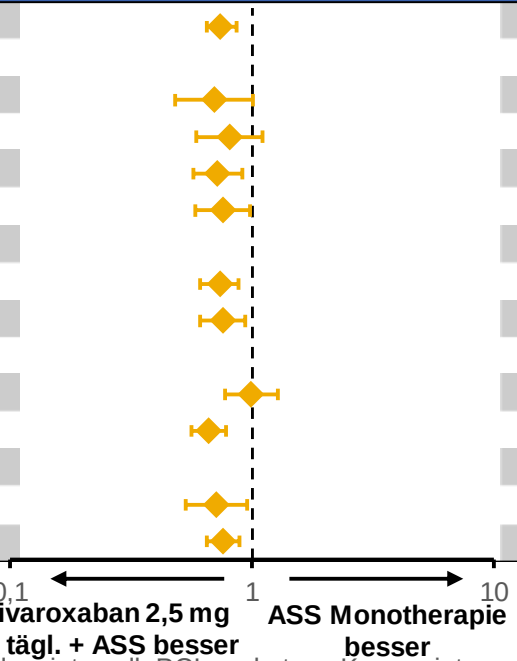
ASS Monotherapie besser

; #Nichtraucher, Lipidsenkende Therapie, β-Blocker und ein ACEI / ARB
ASS: Acetylsalicylsäure, HR: hazard ratio, KI: Konfidenzintervall,, TIMI: Thrombolysis in Myocardial Infarction,,

Connolly SJ *et al*. *Lancet* 2017; doi:10.1016/S0140-6736(17)32816-7.

Subgruppenanalysen (II)

Subgruppe	Rivaroxaban 2.5 mg 2 x tägl. + ASS n/N (%)		ASS Monotherapie n/N (%)		HR (95% KI)	*p*-Wert
Alle Patienten	347/8.313	(4)	460/8.261	(6)	0,74 (0,65–0,86)	
MI in Anamnese						0,93
vor < 2 Jahren	49/1.218	(4)	67/1.205	(6)	0,70 (0,48–1,01)	
vor 2–5 Jahren	71/1.612	(4)	91/1.665	(5)	0,81 (0,59–1,10)	
vor ≥5 Jahren	127/2.824	(4)	174/2.849	(6)	0,72 (0,57–0,91)	
Kein MI	100/2.661	(3.8)	128/2.540	(5)	0,76 (0,58–0,98)	
PCI/PTCA in Anamnese						0,85
Ja	201/4.971	(4)	270/4.905	(6)	0,74 (0,61–0,88)	
Nein	146/3.342	(4)	190/3.356	(6)	0,76 (0,61–0,94)	
ACVB in Anamnese						0,01
Ja	121/2.232	(5)	117/2.143	(5)	0,99 (0,77–1,28)	
Nein	226/6.081	(4)	343/6.119	(6)	0,66 (0,56–0,78)	
MI oder PCI oder ACVB vor >2 Jahren						0,71
Ja	78/2.269	(3)	102/2.141	(5)	0,71 (0,53–0,95)	
Nein	269/6.044	(4)	358/6.120	(6)	0,76 (0,65–0,89)	

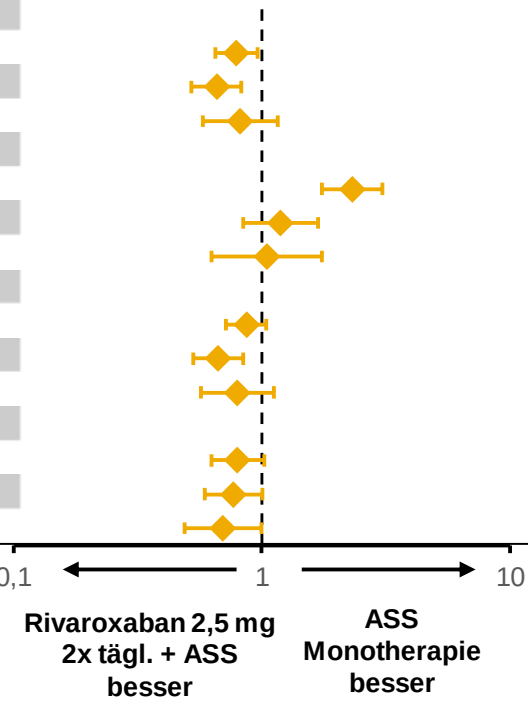


MI: Myokardinfarkt, ASS: Acetylsalicylsäure, HR: hazard ratio, KI: Konfidenzintervall, PCI: perkutane Koronarintervention, PTCA: perkutane Koronarangiographie , ACVB: Aortokoronare Venenbypass-Operation,

Connolly SJ *et al*. *Lancet* 2017; doi:10.1016/S0140-6736(17)32816-7.

Wirksamkeits- und Sicherheitsergebnisse nach Behandlungdauer

	Rivaroxaban 2.5 mg 2 x tägl. + ASS n/N (%)		ASS Monotherapie n/N (%)		HR (95% KI)	HR (95% KI)
MACE						
<1 Jahr	176/8.313	(2)	221/8.261	(3)		0,79 (0,65–0,96)
1–<2 Jahre	113/7.228	(2)	169/7.125	(2)		0,66 (0,52–0,83)
>2 Jahre	58/3.655	(2)	70/3.621	(2)		0,82 (0,58–1,16)
Schwere Blutung						
<1 Jahr	163/8.313	(2)	70/8.261	(1)		2,32 (1,75–3,07)
1–<2 Jahre	70/7.189	(1)	59/7.183	(1)		1,19 (0,84–1,68)
>2 Jahre	30/3.626	(1)	30/3.628	(1)		1,05 (0,63–1,75)
Klinischer Nettonutzen						
<1 Jahr	207/8.313	(2)	237/8.261	(3)		0,87 (0,72–1,04)
1–<2 Jahre	124/7.201	(2)	182/7.112	(3)		0,67 (0,53–0,84)
>2 Jahre	61/3.637	(2)	75/3.604	(2)		0,80 (0,57–1,12)
Gesamtmortalität						
<1 Jahr	117/8.313	(1)	145/8.261	(2)		0,80 (0,63–1,02)
1–<2 Jahre	93/7.323	(1)	120/7.242	(2)		0,77 (0,59–1,01)
>2 Jahre	52/3.743	(1)	74/3.762	(2)		0,70 (0,49–1,00)



MACE: major adverse cardivascular events, ASS: Acetylsalicylsäure, HR: hazard ratio, KI: Konfidenzintervall,

Connolly SJ *et al*. *Lancet* 2017; doi:10.1016/S0140-6736(17)32816-7.

CAD and PAD
Subgroups for Primary Outcome

Outcome	R + A N=9,152	A N=9,126	Rivaroxaban + Aspirin vs. Aspirin
	N (%)	N (%)	HR (95% CI)
CAD	347 (4.2%)	460 (5.6%)	0.74 (0.65-0.86)
PAD	126 (5.1%)	174 (6.9%)	0.72 (0.57-0.90)

Den Primären Endpunkten der COMPASS-Studie wurden pAVK-spezifische Endpunkte hinzugefügt

- Der primäre kardiovaskuläre Endpunkt war MACE, definiert als:
  - Kombination von KV-bedingtem Tod, Schlaganfall oder MI

- Der primäre Extremitäten-Endpunkt waren schwerwiegende unerwünschte Ereignisse der Extremitäten (MALE), definiert als:
  - schwere Extremitätenischämie, die zu einer Intervention führte (Angioplastie, Bypass-Operation, Amputation, Thrombolyse)
  - Majoramputation aufgrund vaskulärer Insuffizienz oberhalb des Vorfußes

Anand SS *et al, Lancet* 2017;doi:10.1016/S0140-6736(17)32757-5

COMPASS

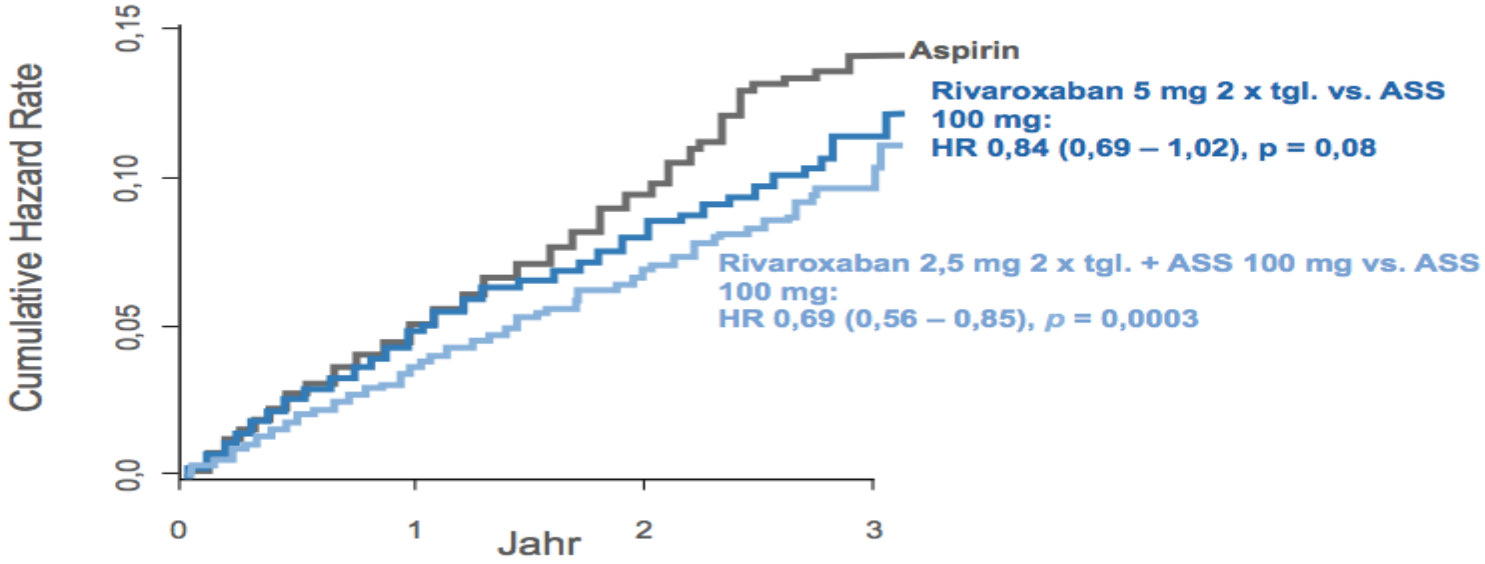
PAD Patients in COMPASS

PAD Groups	Number of patients
All Patients	7,470
Symptomatic PAD Limbs	4,129
Carotid Disease	1,919
CAD + Low ABI (<0.90) only	1,422

Mean Follow-up: 21 months

Anand et al, *Lancet* (in press)

RRR von 31% bei MACE oder MALE einschließlich Majoramputationen mit Rivaroxaban 2,5 mg 2 x tägl. + ASS versus ASS Monotherapie bei Patienten mit pAVK



Number at risk				
Rivaroxaban + ASS	2492	2069	893	124
Rivaroxaban	2474	2023	864	147
ASS	2504	2034	911	113

Anand SS *et al, Lancet* 2017;doi:10.1016/S0140-6736(17)32757-5

COMPASS

pAVK spezifische Wirksamkeitsendpunkte

Rivaroxaban 2,5 mg 2 x tägl. + ASS führte im Vergleich zur ASS Monotherapie zu einer signifikanten Reduktion von MALE (RRR 46%) einschließlich der Majoramputationen (RRR 70 %).

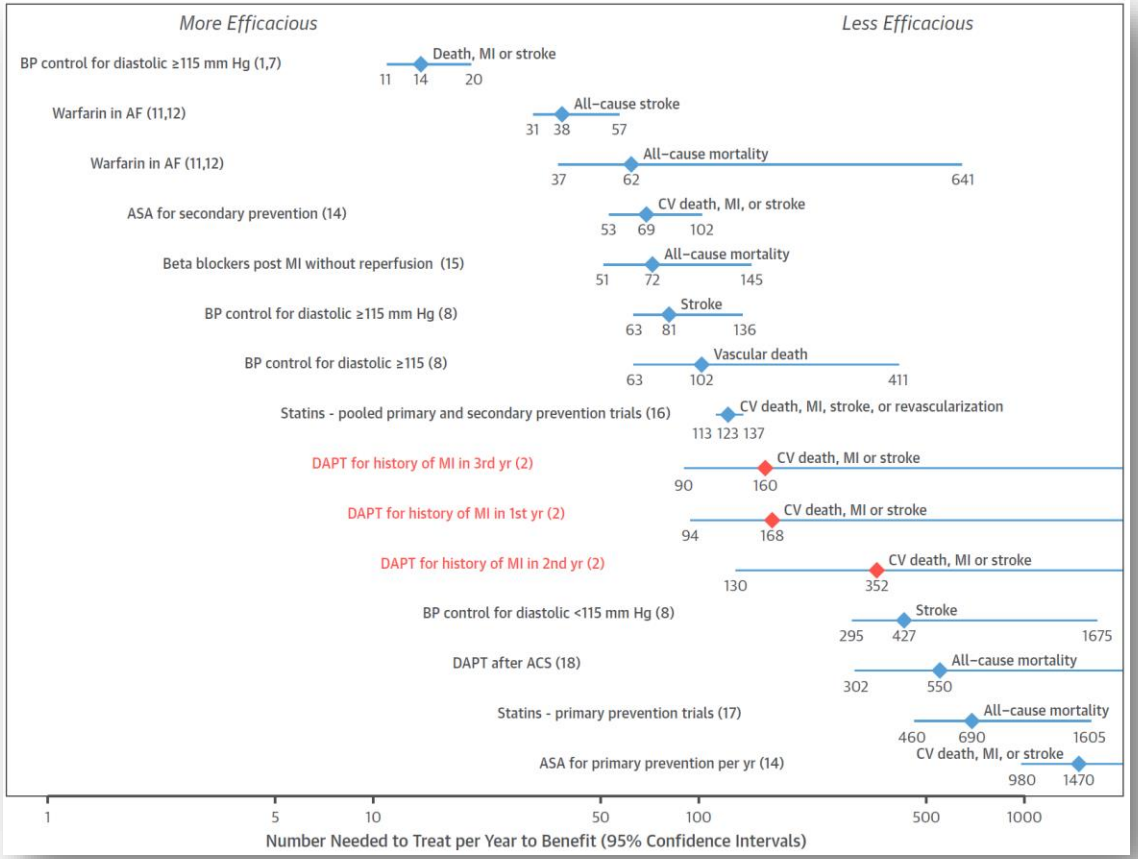
Endpunkt	Rivaroxaban 2,5 mg 2 x tägl. + ASS n = 2492 n (%)	ASS n = 2504 n (%)	Rivaroxaban 2,5 mg 2 x tägl. + ASS vs. ASS HR (95% KI)	*p*-Wert
MALE*	30 (1,2)	56 (2,2)	0,54 (0,35 – 0,84)	0,005
Majoram-putation	5 (0,2)	17 (0,7)	0,30 (0,11 – 0,80)	0,01

* MALE einschließlich Majoramputationen

Anand SS *et al, Lancet* 2017;doi:10.1016/S0140-6736(17)32757-5

COMPASS

Risk reduction in the context of other concepts of secondary prevention – number needed to treat



Bittl JA, Maron DJ. J Am Coll Cardiol. 2017 Sep 12;70(11):1376-1378.

Therapy	Indication / enrichment	NNT	Absolute risk reduction
Canakinumab 150mg all- **CANTOS** all patients	Post MI	**78** (2 years)	0.64%
Canakinumab 150mg („responders“)	Post MI	**50** (2 years) **30** (3.7 years) **16** (5 years)	1.8%
Ticagrelor 60mg bid – **PEGASUS** all patients	Post MI	**79** (3 years)	
	Post MI, Label population (MI ≤2years, termination of DAPT≤1year)	**58.8** (3 years)	1.7%
	Post MI, PAD	**20** (3 years)	4.1%
Rivaroxaban 2x2.5mg - **COMPASS** all patients	CAD/PAD	**76** (~2 years)	1.3%
	PAD	**50** (~2 years)	2%
	CAD+PAD	**33** (~2 years)	3%
PCSK9 Inhibition (Evolucumab) - **FOURIER** all patients	Atherosclerotic disease	**74** (~2years)	1.5%
	PAD	**29** (2.5 years)	3.5%
	Prior MI <2 years	**35**	2.9%
	Multivessel disease	**29**	3.4%

Ridker, NEJM 2017, Ridker Lancet 2017, Bonaca NEJM 2015, Bonaca JACC 2016, Eikelboom NEJM 2017, Conolly Lancet 2017, Anand Lancet 2017, Sabatine NEJM 2017, Bonaca, Circulation 2018

Previous Stroke Status and Outcomes

Outcome	Rivaroxaban plus Aspirin (N=9152)		Aspirin (N=9126)		Rivaroxaban plus Aspirin vs. Aspirin		
	N Pts	%/yr	N Pts	%/yr	HR (95% CI)	P	P inter
Stroke							0.40
No Previous Stroke	8801	0.4	8791	0.7	0.60 (0.45-0.80)	0.0006	
Previous Stroke	351	0.7	335	3.4	0.42 (0.19-0.92)	0.03	
Ischemic or uncertain stroke							0.28
No Previous Stroke	8801	0.4	8791	0.7	0.54 (0.40-0.74)	0.0001	
Previous Stroke	351	1.1	335	3.4	0.33 (0.14-0.77)	0.01	

Previous stroke ARR = 2.7%

NNT = 37

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE
www.phri.ca

Mike Sharma on behalf of the COMPASS Investigators presented at the ISC 2018

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

Subgroup: CAD and PAD

Mean cost per participant (R+A vs. A)	N	Events (R+A vs. A)	Procedures (R+A vs. A)	Total Difference (R+A vs. A) $USD
CAD only	13277	-382	22	-360
PAD only	1699	-205	-1065	-1270
CAD + PAD	3297	-922	-741	-1663
2 or more vascular beds	4158	-1069	-615	-1684

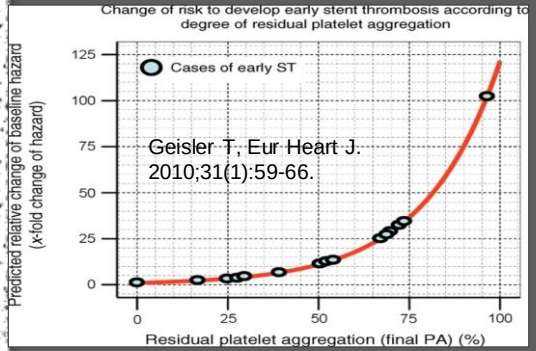
Andre Lamy on behalf of the COMPASS Investigators presented at the AHA 2017

Different focus on platelet targeted strategies according to time

Index event / PCI

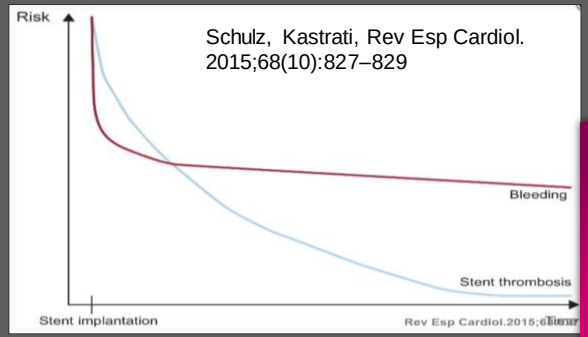
Acute Phase

effective inhibition of platelet aggregation



Stable Phase- Minimum Duration of DAPT, stent associated risk

1 month BMS/DCS
6 months DES
12 months ACS
? months BVS



Longterm Phase, stent independent risk

Balancing ischaemic versus bleeding risk:

Vessel Disease in multiple locations, CAD+PAD, heart failure

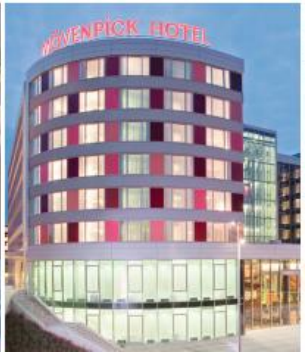
Clinical / Genetic Risk Factors (Scores)

? ? ? ? ?

Patient selection (enrichment of risk factors to reduce NNT, economic reasons), identification of most suitable concept (antiplatelet, -coagulation, -inflammatory, -lipid)

Time

THROMBOSE FORUM2018



Vielen Dank für die Aufmerksamkeit