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Paris, France, August 28, 2011*



Vascular Effects and Safety of Dalcetrapiib in Patients
with or at Risk of Coronary Heart Disease –
the dal-VESSEL Randomised Clinical Trial

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investigators

Disclosures

- The presenting author has received:
 - Research grants from Pfizer, Eli Lilly and Merck
 - Consultancy or lecture fees from CSL, Merck, Pfizer and F. Hoffmann-La Roche Ltd
- The dal-VESSEL study was sponsored by F. Hoffmann-La Roche Ltd, Basel, Switzerland

dal-Vessel - Background

- Lowering of low-density lipoprotein cholesterol (LDL-C) through statin use is a highly effective method of improving cardiovascular outcome in a broad range of patients¹⁻³
- However, despite optimal statin use, significant risk remains⁴
- Agents that act on cholesteryl ester transfer protein (CETP) activity to raise high-density lipoprotein cholesterol (HDL-C) levels are currently being investigated as a new therapeutic option

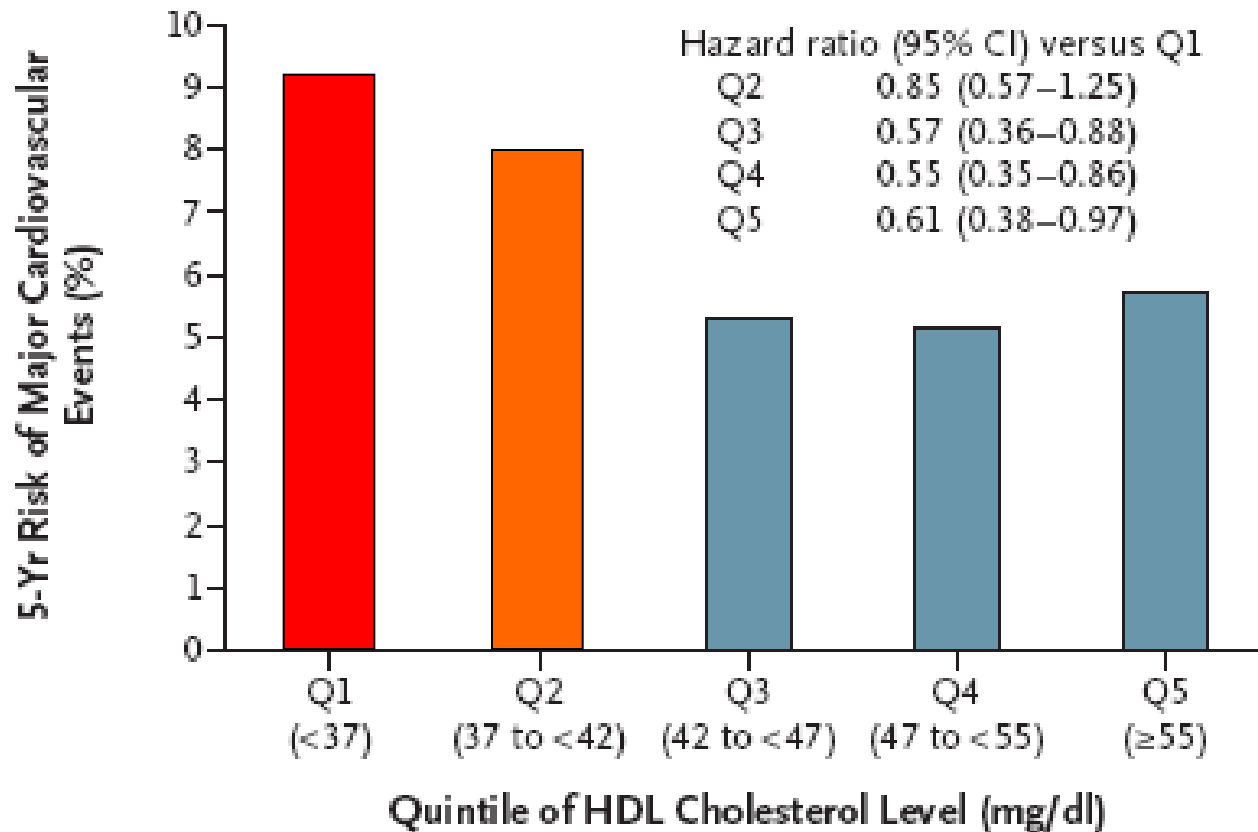
1. Sharrett AR et al. Circulation. 2001;104:1108-1113

2. Law MR et al. BMJ. 2003;326:1423

3. Baigent C et al. Lancet. 2005;366:1267-1278

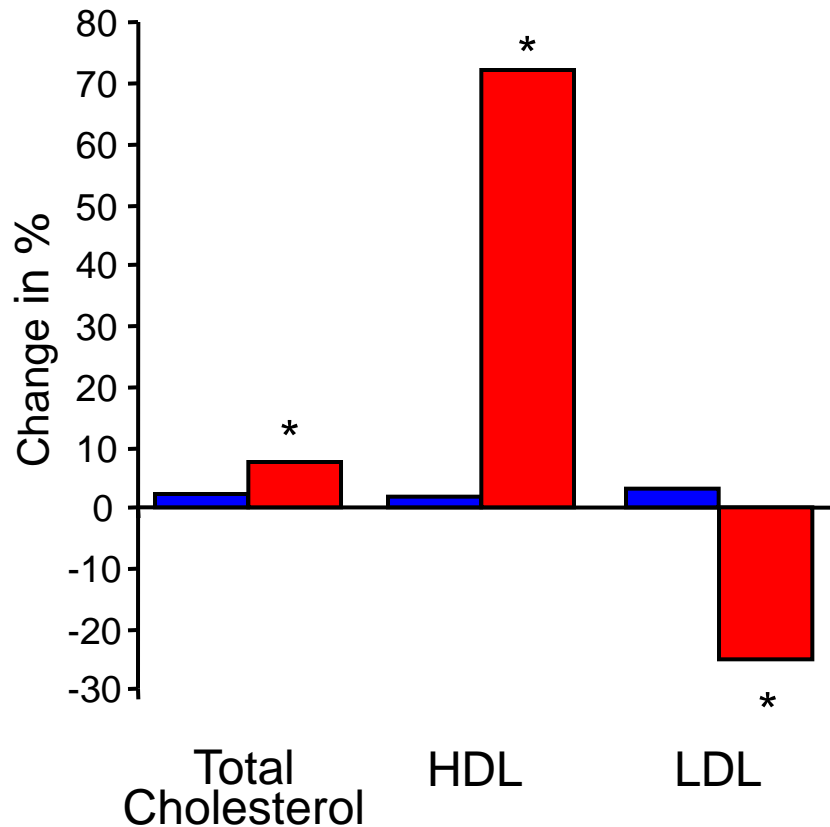
4. Barter P et al. N Engl J Med. 2007;357:1301-1310

Reduced HDL Cholesterol is associated with increased cardiovascular risk – *despite intense statin therapy*

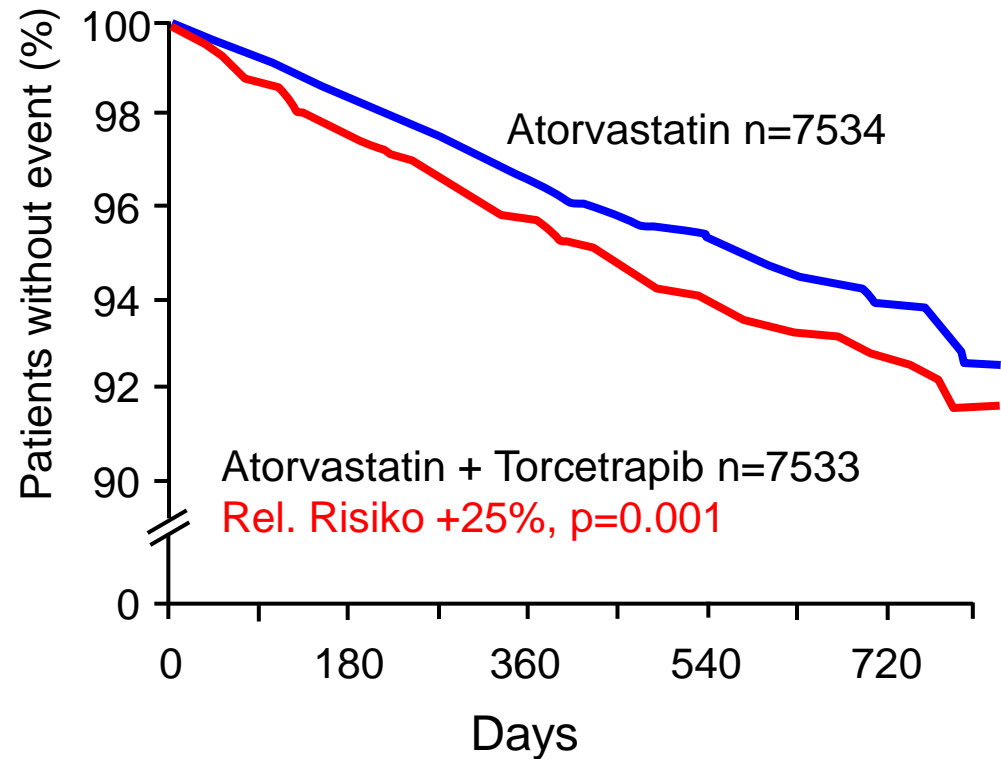


Torcetrapib in Highrisk Patients - ILLUMINATE

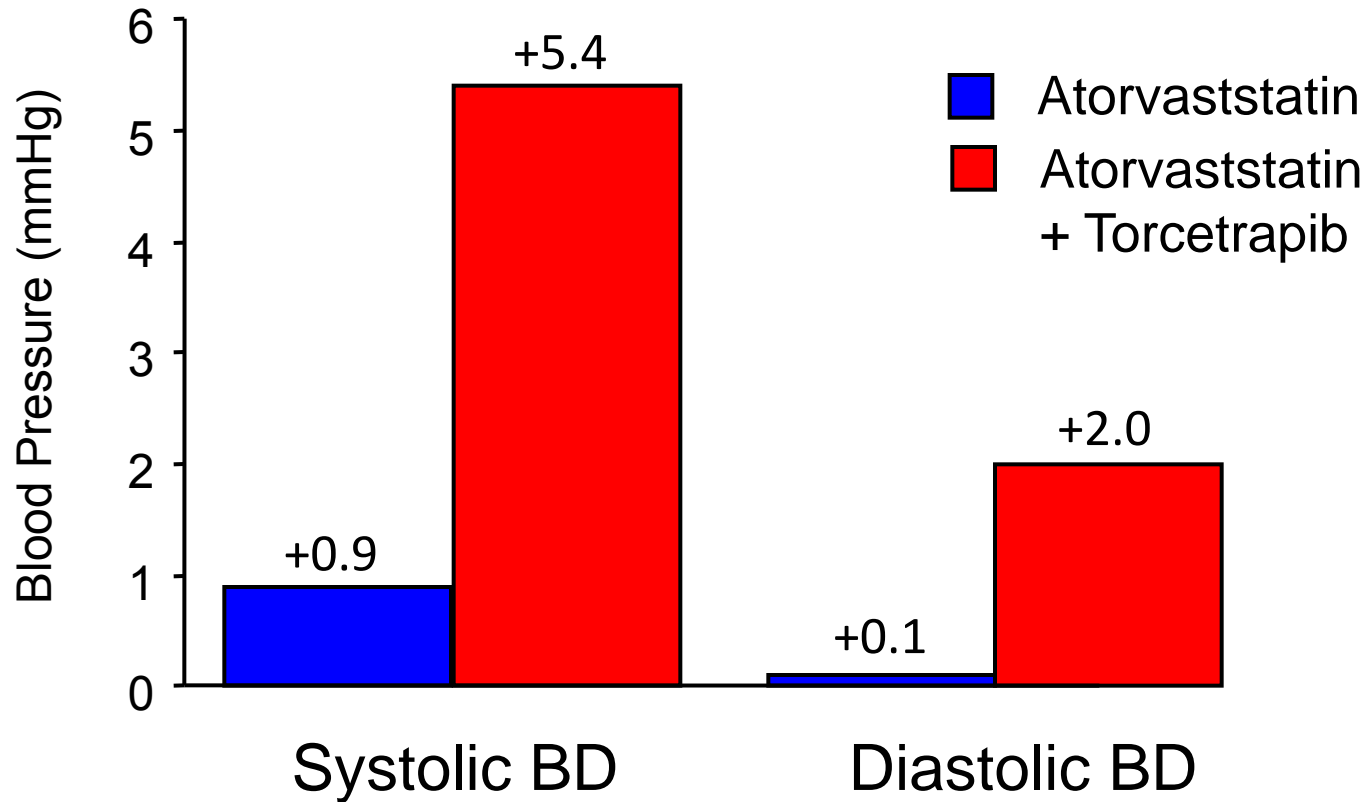
Change in Lipid Levels



Cardiovascular Events



Torcetrapib and Blood Pressure - ILLUMINATE

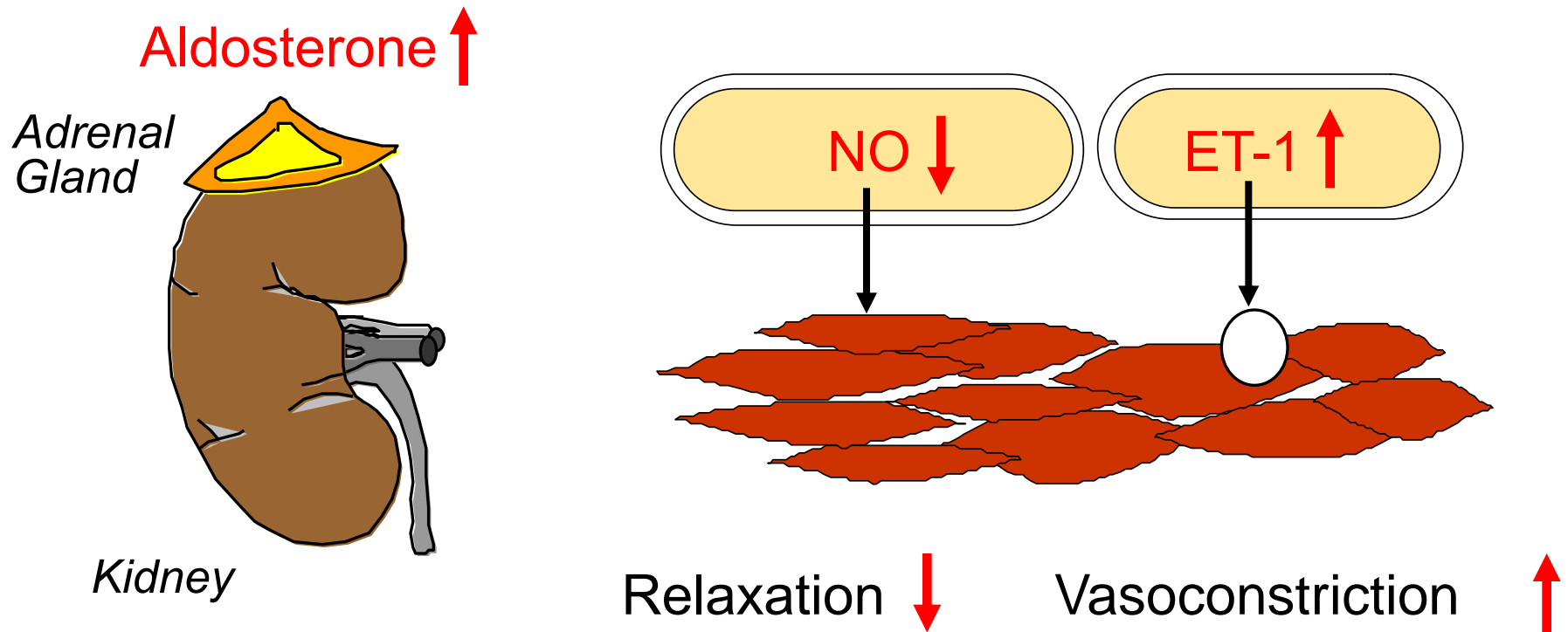


Baseline (mmHg)

123.0

73.8

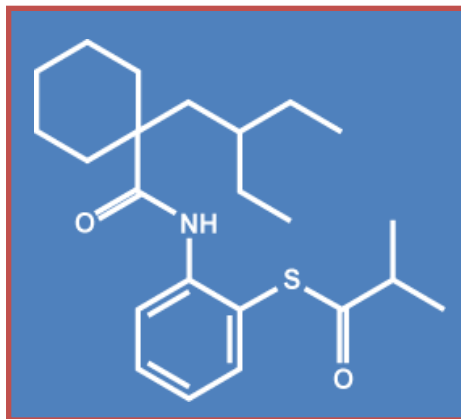
Mechanisms of Endothelial Dysfunction and Hypertension with Torcetrapib



dal-Vessel - Dalcetrapib

- Dalcetrapib acts on CETP activity, decreasing CETP activity and increasing HDL-C by up to 36%^{1,2}
- To date, dalcetrapib has not exhibited any of the off-target effects associated with the CETP inhibitor torcetrapib²⁻⁴

*dalcetrapib*⁵
Molecular weight: 389.60
Lipophilicity: cLogP ~7



1. Niesor EJ et al. *J Lipid Res* 2010;51:3443-3454
2. Stein EA et al. *Am J Cardiol* 2009;104:82-91
3. Stroes ESG et al. *Br J Pharmacol* 2009;158:1763-1770
4. Stein EA et al. *Eur Heart J*. 2010;31:480-48
5. <http://www.ama-assn.org/ama1/pub/upload/mm/365/dalcetrapib.doc>

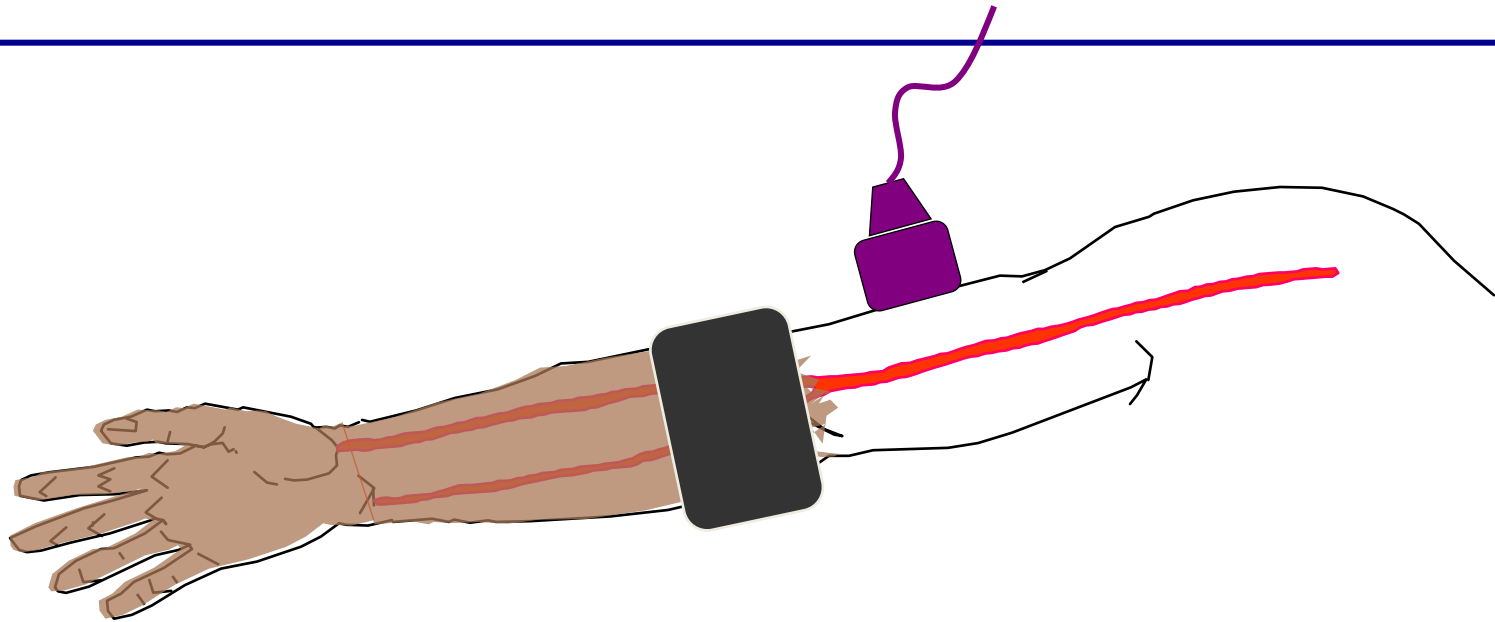
dal-VESSEL – Concept of the trial

- The current study, *dal-VESSEL*, was designed to further investigate the safety of dalcetrapib and aimed to rule out any adverse effects of dalcetrapib on endothelial function and blood pressure^{1,2}
- To facilitate this, flow mediated dilatation (FMD) was to be used to provide an assessment of endothelial function
- Blood pressure was to be assessed by ambulatory blood pressure monitoring (ABPM)

1. <http://clinicaltrials.gov/ct2/show/NCT00655538>. Accessed August 2011

2. Kastelein JJ et al. *Curr Med Res Opin.* 2011;27:141-150

Pal-Vessel – Flow-mediated Dilation (FMD)



1 min

5 min

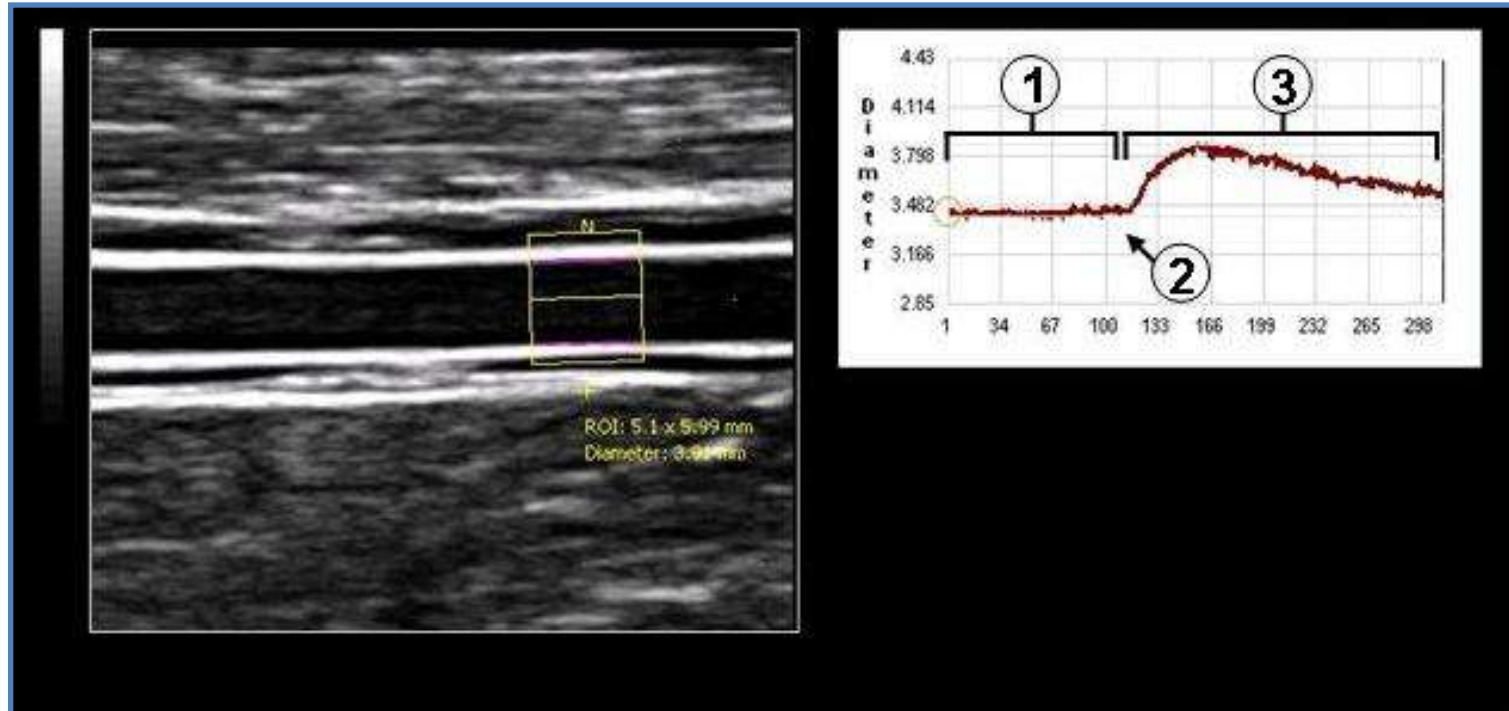
3 min

Baseline

Cuff inflated

Post hyperaemia

B-mode Ultrasound of Brachial Artery FMD



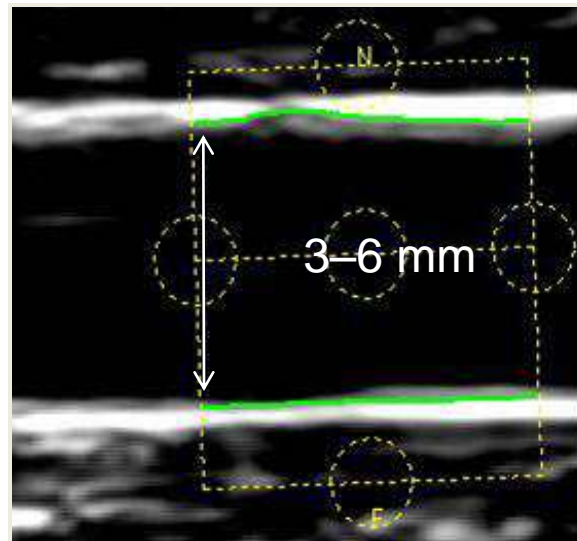
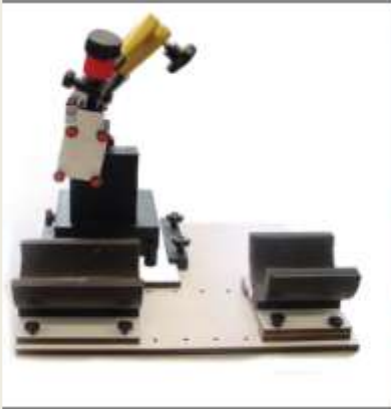
From Kastelein JJ et al. *Curr Med Res Opin.* 2011;27:141-50.

1. Baseline diameter period
2. Cuff release
3. Post-ischaemia period

Recruiting Centers dal-VESSEL



Standardization of Flow-mediated Dilation



1. 1 US Device
2. Armrest
3. Core Lab

Standardization of Flow-mediated Dilation

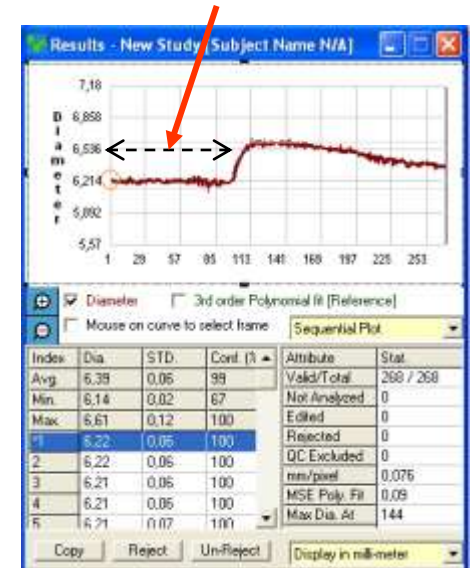
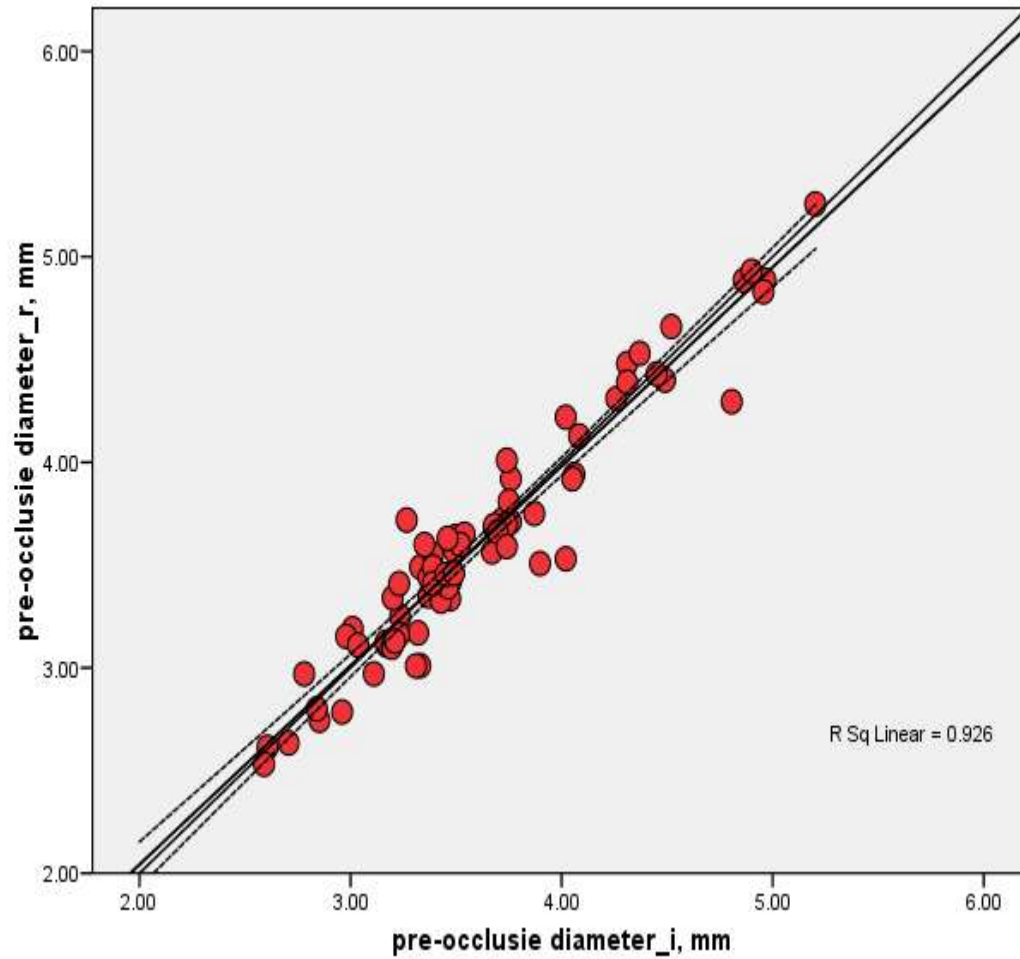
Lectures

Practical Courses

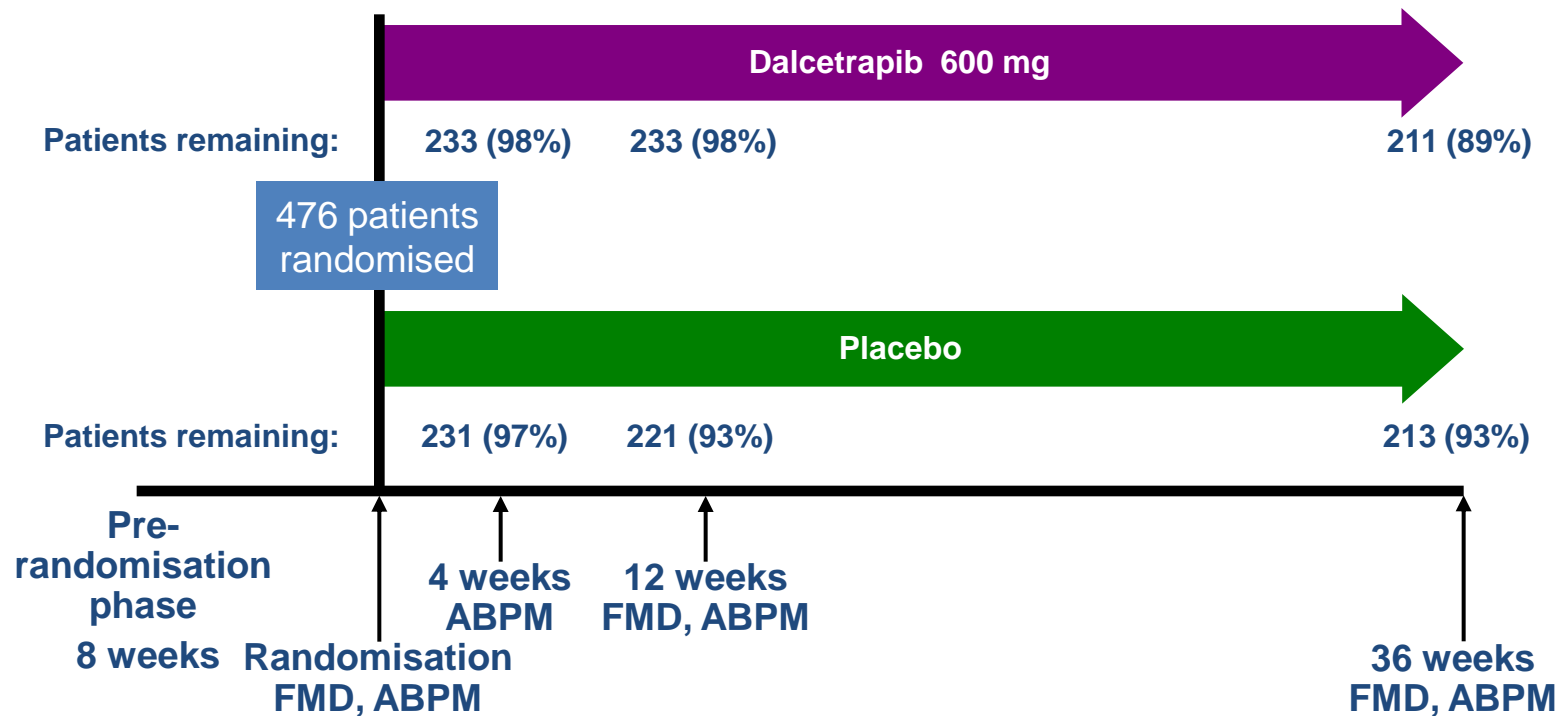


1. Central Training Courses for Sonographers
2. Certification Process
3. Blinded Analysis in Core Lab by expert Readers

dal-Vessel – Reproducibility of FMD



dal-Vessel - Study design



- Double-blind randomised, placebo-controlled, parallel-group multicentre FMD/ABPM study in patients with CHD or CHD-risk equivalent¹

Patients with CHD or CHD-risk equivalent and HDL-C <50 mg/dL (<1.29 mmol/L), with background therapy to manage CV risk factors. Follow-up at 4, 12 and 36 weeks.

Primary endpoints: FMD at 12 weeks; ABPM at 4 weeks

Additional assessments: FMD at 36 weeks; ABPM at 12 and 36 weeks

¹Kastelein JJ et al. Curr Med Res Opin 2011; 27:141-150

dal-Vessel - Endpoints

- Primary endpoints:
 - Change from baseline of FMD of the right brachial artery after 5 min of cuff occlusion at 12 weeks
 - 24-hour ABPM at week 4
- Secondary endpoints:
 - Change from baseline of FMD after 36 weeks
 - Change in ABPM after 12 and 36 weeks
 - Changes in lipids
 - Standard safety parameters

dal-VESSEL – Patient Flow

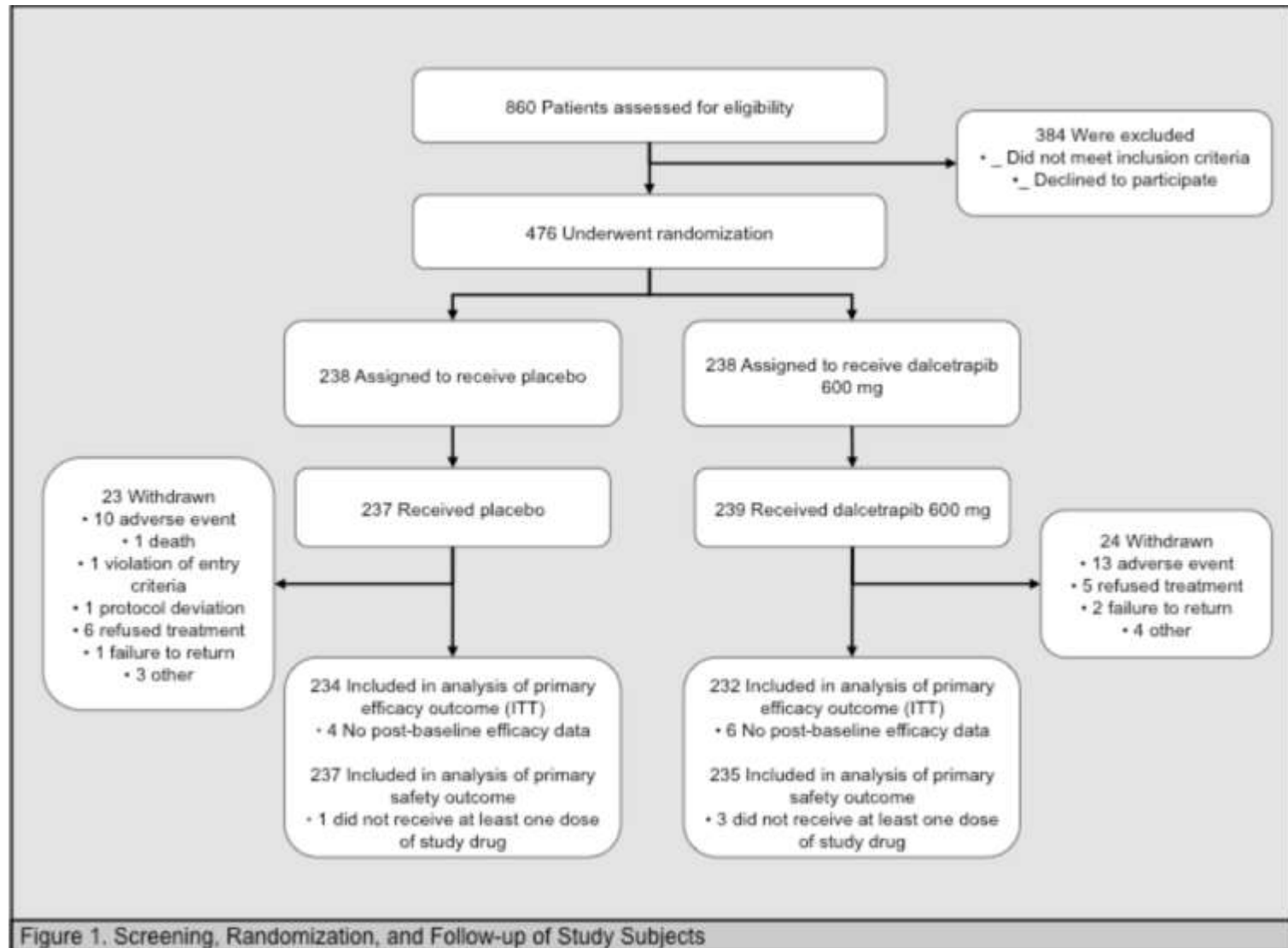


Figure 1. Screening, Randomization, and Follow-up of Study Subjects

dal-Vessel – Baseline characteristics

Characteristic*	Placebo (n=234)	Dalcetrapib (n=232)
Age, years	61.9 ± 7.92	62.3 ± 7.05
Male sex, n (%)	211 (90)	211 (91)
Body-mass index	28.7 ± 4.4	29.6 ± 4.8
Medical history of, n. (%)		
Coronary heart disease	155 (66)	147 (63)
Symptomatic carotid artery disease	18 (8)	16 (7)
Peripheral arterial disease	16 (7)	24 (10)
Abdominal aortic aneurysm	5 (2)	6 (3)
Type II diabetes	102 (44)	108 (47)
Hypertension	175 (75)	171 (74)
Smoker, n (%)		
Ever	191 (82)	181 (78)
Current	57 (24)	65 (28)
Statin use [†] , n (%)	228 (97)	223 (94)

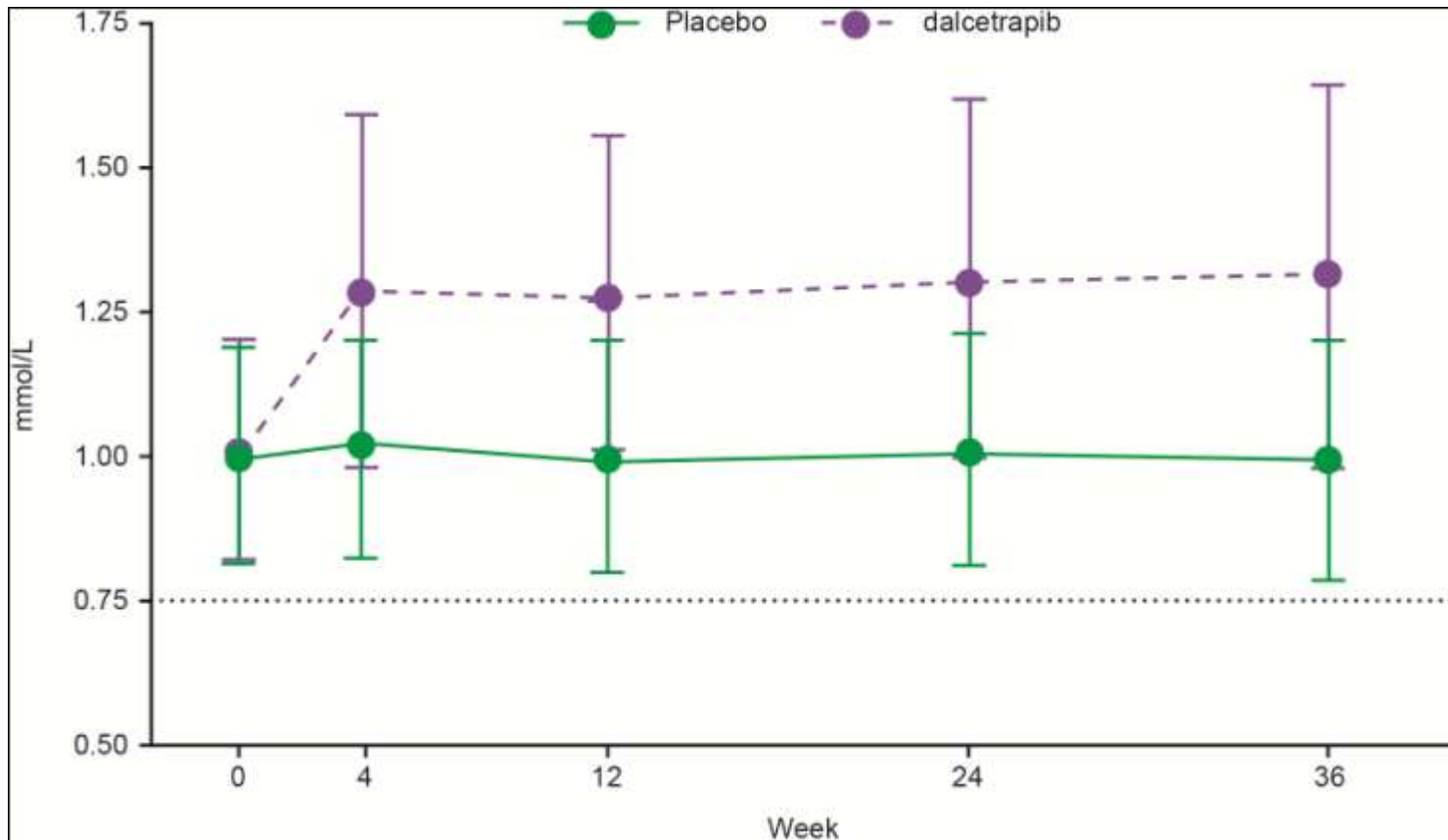
*All data reported as mean (SD); [†]patients with at least one treatment, multiple occurrences of the same treatment in one individual counted only once

dal-Vessel – Baseline lipids

Characteristic*	Placebo (n=234)	Dalcetrapib (n=232)
Total cholesterol, mmol/L [†]	3.802 ± 0.563	3.945 ± 0.665
HDL-C, mmol/L [†]	0.995 ± 0.185	1.013 ± 0.190
LDL-C, mmol/L [†]	2.051 ± 0.457	2.108 ± 0.553
Triglycerides, mmol/L [‡]	1.654 ± 0.733	1.819 ± 0.916
apoA-I mmol/L	1.333 ± 0.189	1.347 ± 0.178
apoB mmol/L	0.874 ± 0.170	0.895 ± 0.185

*All data reported as mean (SD); [†]to convert to mg/dL, multiply by 38.6; [‡]to convert to mg/dL, multiply by 88.5

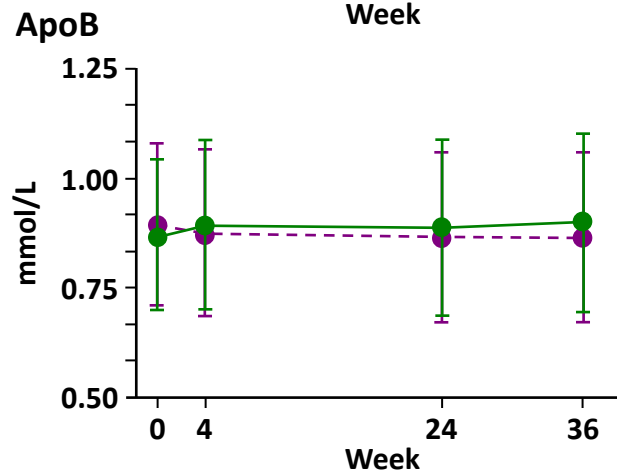
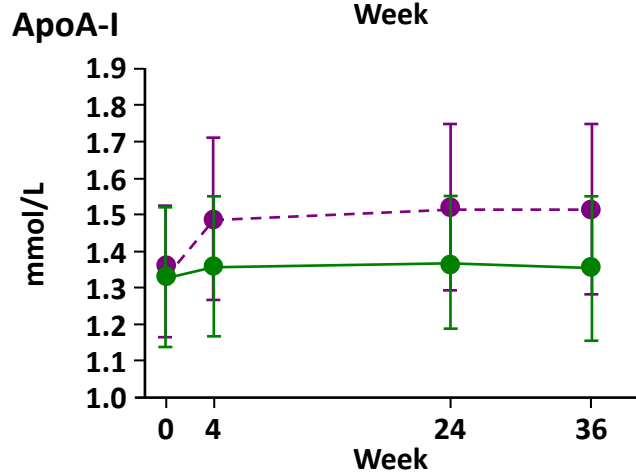
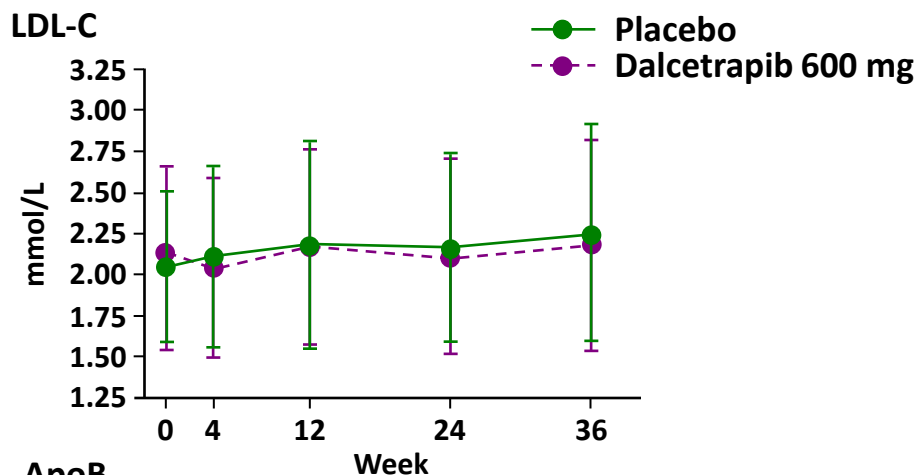
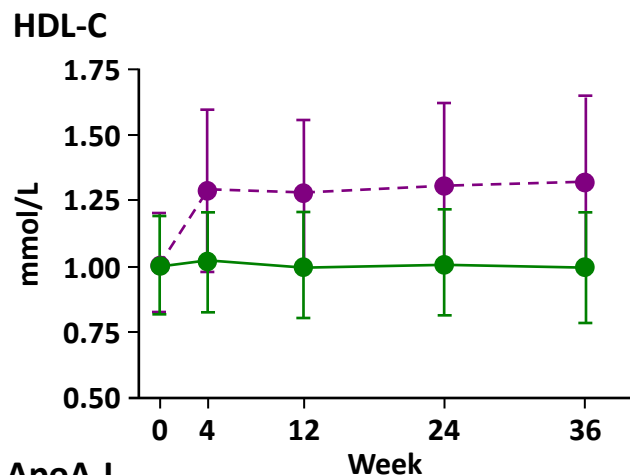
dal-Vessel – HDL-C levels increased with dalcetrapib over 36 weeks



HDL-C % change from baseline:

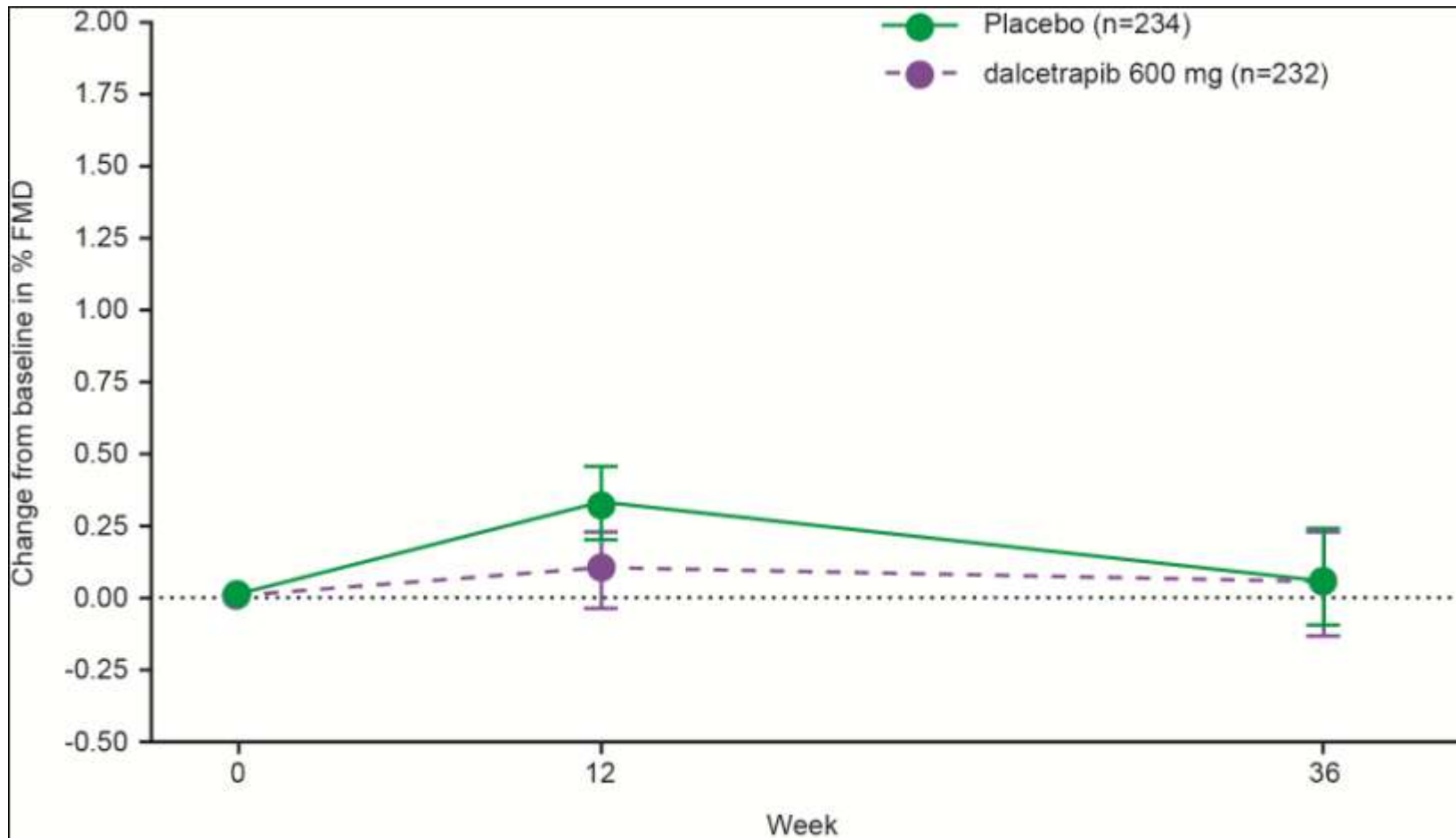
- wk4 placebo 2.73 ± 1.27 , dalcetrapib 27.50 ± 1.28 $p < 0.0001$
- wk36 placebo -0.14 ± 1.42 , dalcetrapib 30.70 ± 1.45 , $p < 0.0001$

dal-Vessel – Lipids over 36 weeks



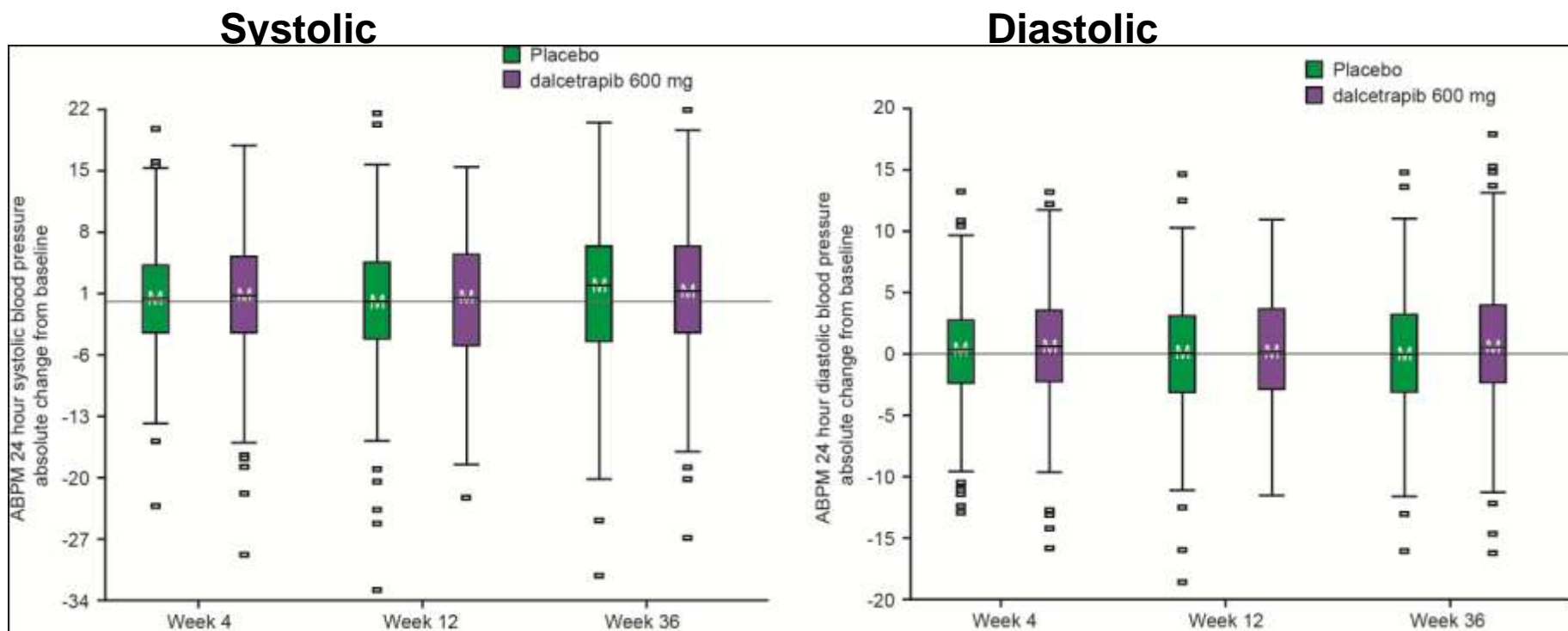
Data presented as absolute values at each timepoint, mean \pm SD; placebo n=211 and dalcetrapib n=207 for HDL-C and LDL-C; placebo n=209 and dalcetrapib n=206 for ApoA-I and ApoB

Baseline FMD exhibited no significant change with dalcetrapib over 36 weeks



Data reported as least squares mean (SE) absolute change from baseline in %FMD at weeks 12 and 36

dal-Vessel - ABPM was unchanged with dalcetrapib over 36 weeks



Data are box-whisker plots ± 1.5 *interquartile range

dal-Vessel – Change in biomarkers

Biomarker	Placebo (LSM [SE] % change)	Dalcetrapib (LSM [SE] % change)	Placebo-corrected change (LSM [95% CI])
hs-CRP	171.2 (90.2)	49.0 (91.7)	-122.2 (-358, 114), p=0.31
IL6	67.8 (15.8)	41.8 (16.1)	-26.0 (-67.3, 15.3), p=0.22
sP-selectin	0.2 (1.5)	-1.8 (1.6)	-2.1 (-6.1, 2.0), p=0.32
sE-selectin	6.1 (1.9)	6.0 (2.0)	-0.1 (-5.1, 4.9), p=0.98
Soluble intracellular adhesion molecule	2.0 (0.9)	1.1 (1.0)	-0.96 (-3.4, 1.5), p=0.44
Soluble vascular adhesion molecule	1.9 (0.8)	3.6 (0.8)	1.7 (-0.3, 3.8), p=0.09
Lipoprotein-associated phospholipasesA2s*	5.8 (3.3)	23.2 (3.3)	17.4 (8.8, 26.1), p<0.0001
Matrix-metallproteinase-3	3.4 (2.1)	3.5 (2.1)	0.0 (-5.4, 5.5); p=0.99
Matrix-metallproteinase-9	20.4 (10.8)	28.1 (11.0)	7.8 (-20.4, 35.9), p=0.59
Myeloperoxidase	36.4 (18.1)	13.2 (18.4)	-23.1 (-70.2, 23.9), p=0.33
Tissue plasminogen activator	15.9 (5.5)	8.9 (5.6)	-7.0 (-21.3, 7.3), p=0.34
Plasminogen activator inhibitor 1-activity	14.7 (3.5)	16.9 (3.6)	2.2 (-7.1, 11.4), p=0.64
Plasminogen activator activity 1-antigen	42.5 (7.6)	38.8 (7.7)	-3.7 (-23.5, 16.0), p=0.71

*Lp-LPA2 includes mass for both LDL and HDL

dal-Vessel – Safety parameters

Adverse Events (AEs)	Placebo (n=236)	Dalcetrapib (n=236)
Patients with at least one AE, n (%)	160 (68)	170 (72)
Total number of AEs, n	483	437
Patients with at least one:		
Clinical adverse AE leading to discontinuation, n (%)	9 (4)	11 (5)
Serious AE, n (%)	14 (6)	12 (5)
Drug-related serious AE, n (%)	2 (1)	1 (<1)
AE leading to death, n (%)	0 (0)	0 (0)
Most common AEs, n (%)		
Nasopharyngitis	42 (18)	38 (16)
Influenza	15 (6)	9 (4)
Diarrhoea	26 (11)	27 (11)
Back pain	16 (7)	8 (3)
Headache	13 (6)	10 (4)

dal-Vessel – Adjudicated CV events*

Adjudicated Cardiovascular Events, n	Placebo	Dalcetrapib
Major CV event†		
Death from coronary heart disease	1	0
Non-fatal myocardial infarction	3	2
Hospitalisation for acute coronary syndrome	1	0
Resuscitated cardiac arrest	0	0
Stroke	0	0
Subtotal	5	2
Other adjudicated events		
Revascularisation	7	9

*Adjudicated by an independent Clinical Endpoint Committee; a patient can have more than one event

†As defined by dal-OUTCOMES study protocol

Results from dal-PLAQUE

- The results from dal-PLAQUE also provide reassurance regarding the safety of dalcetrapib
- dal-PLAQUE was a multicentre study using non-invasive simultaneous multimodality imaging (MRI and PET/CT) to assess structural and inflammatory indices of atherosclerosis
- MRI results: significant reduction in total vessel area with dalcetrapib versus placebo after 24 months; the wall area was numerically reduced versus placebo
- PET/CT results: no evidence of a pro-inflammatory effect of dalcetrapib
- **Sunday, August 28, 2–6 pm; Poster Zone C**
Author (Zahi A. Fayad) present 3.30–4.30 pm

dal-Vessel – Conclusions

- Dalcetrapib reduced CETP activity, increased Apo A1 and elevated HDL-C levels by 31% without affecting LDL or ApoB100.
- Dalcetrapib did not cause endothelial dysfunction, but also did not improve it.
- In contrast to torcetrapib, dalcetrapib did not have an effect on ABPM, providing further reassurance regarding the safety of the compound.
- This trial also demonstrates the feasibility of using FMD to test the influence of novel cardiovascular compounds on the biology of the vessel wall and endothelial function in particular.

Acknowledgments: Participating Centres

- Switzerland: Univerisity Hospital Zürich, George Noll; CardioCentro Ticino, Lugano, Tiziano Mocetti
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- Germany: Klinikum der Johann Wolfgang Goethe-Univeristät , Frankfurt am Main, Stephan Fichtlscherer; Klinikum der Johannes Gutenberg-Universität Mainz, Mainz, Thomas Münzel
- Austria: Universitäres Lehrkrankenhaus Feldkirch, Feldkirch, Heinz Drexel
- France: Hôpital Européen Georges Pompidou, Paris, Alain Simon
- Netherlands: Academic Medical Center, Amsterdam, Mieke D. Trip; Westfries Gasthuis Hoorn, Hoorn, Dick C.G.Basart; UMC Utrecht, Utrecht, Frank L.J. Visseren; Osterscheide Ziekenhuis, Goes, A.H Liem; Andromed b.v. Rotterdam, Rotterdam, Wouter van Kempen; Andromed Breda BV, Jan Jonker, Vicdan Kose; Andromed Eindhoven Bianca Lokhorst ; Andromed Leiden Irma Agous; Andromed Oost Velp, Jacqueline Hoogendijk; Andromed Noord Groningen, Jeroen Tiebesl; Andromed Oost Velp, Jacqueline Hoogendijk and Andromed Zoetermeer, Lenie de Schipper