CSL 112 (Apolipoprotein A-I) Infusions and Cardiovascular Outcomes in Patients With Acute Myocardial Infarction (ApoA-I Event Reducin G in Ischemic S yndromes II (AEGIS-II) Trial)

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On Behalf of the AEGIS-II Committees and Investigators

Disclosures

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Baim Institute

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Equity :

nference, Inc.

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Consultant

Angel/Avertix Medical
AstraZeneca
Bayer
Beren Therapeutics
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Boston Clinical Research Institute
Bristol-Myers Squibb
Cardiovascular Research Foundation
CeleCor Therapeutics
Esperion
EXCITE International ($0 Received)
Fortress Biotech
Janssen/ J&J
MashUp MD
MD Magazine
Microport
Novartis
NovoNordisk
Pfizer
PLxPharma
Smart Medics
Solstic Health/New Amsterdam Pharma
Somahlution/Marizyme
Vectura
WedMD
Woman As One

Spouse: Employee of Boston Clinical Research Institute, has equity

Angel/Avertix Medical
AstraZeneca
Bayer/Janssen/ J&J
Beren Therapeutics
Bioclinica
Boehringer Ingelheim
Boston Clinical Research Institute
Boston Scientific
Bristol-Myers Squibb
Cardiovascular Research Foundation
CeleCor Therapeutics
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PhaseBio
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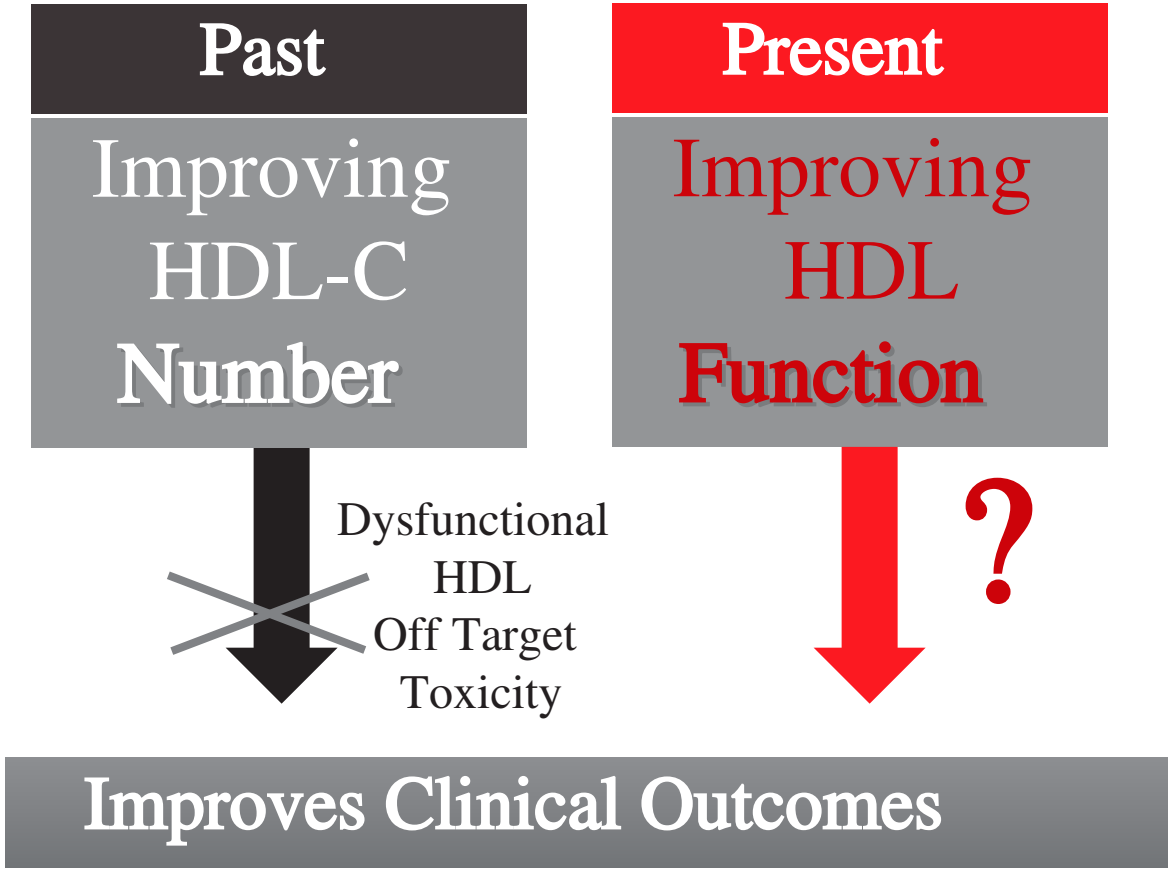
PLxPharma
Revance Therapeutics
Samsung
SFJ
SCAI
Solstic Health/New Amsterdam Pharma
Somahlution/Marizyme
Vectura
Woman As One

Evolution in the "HDL Hypothesis"

- The main role of HDL-C is to carry cholesterol from cells to the liver, where hepatocytes degrade cholesterol for excretion via bile
- Higher HDL-C associated with lower events , but therapies that **raise HDL-C numbers** **have not reduced events**
- We hypothesized **that improving HDL function by infusing human ApoA-1** , the primary functional component of HDL, would **improve outcomes**



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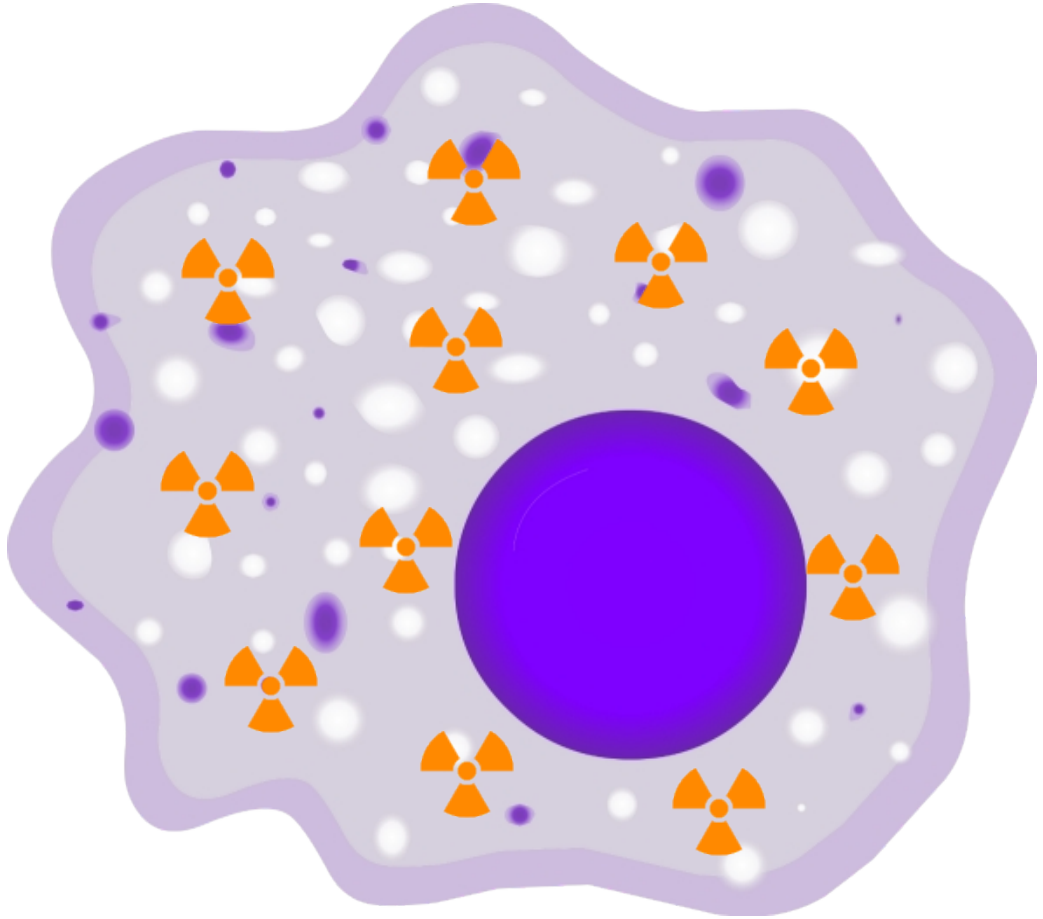
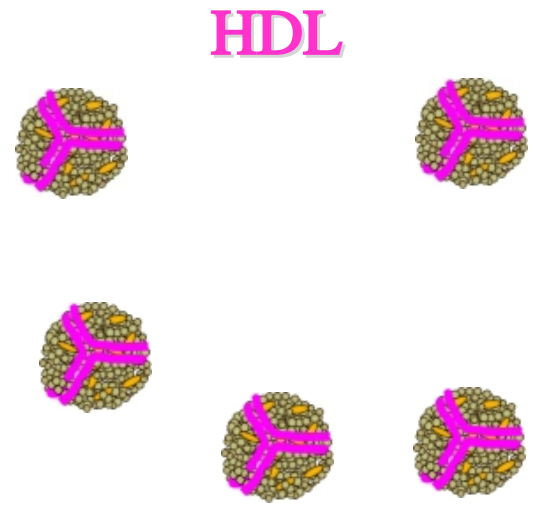
HDL, high-density lipoprotein

Measuring HDL Function Instead of HDL-C Number: Measuring Cholesterol Efflux Capacity From Macrophages

Macrophages with radioactive cholesterol are added to the patient's blood and the amount of radioactive cholesterol taken up by the HDL is measured

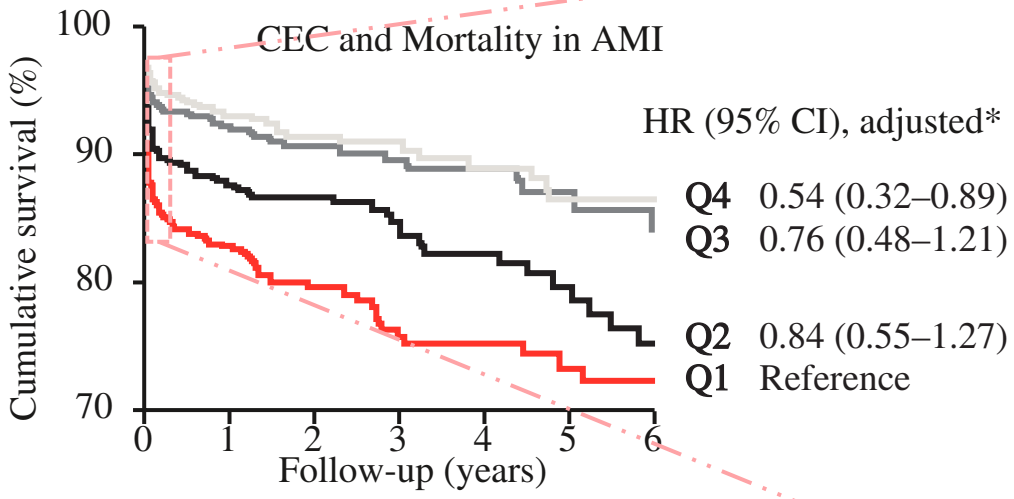


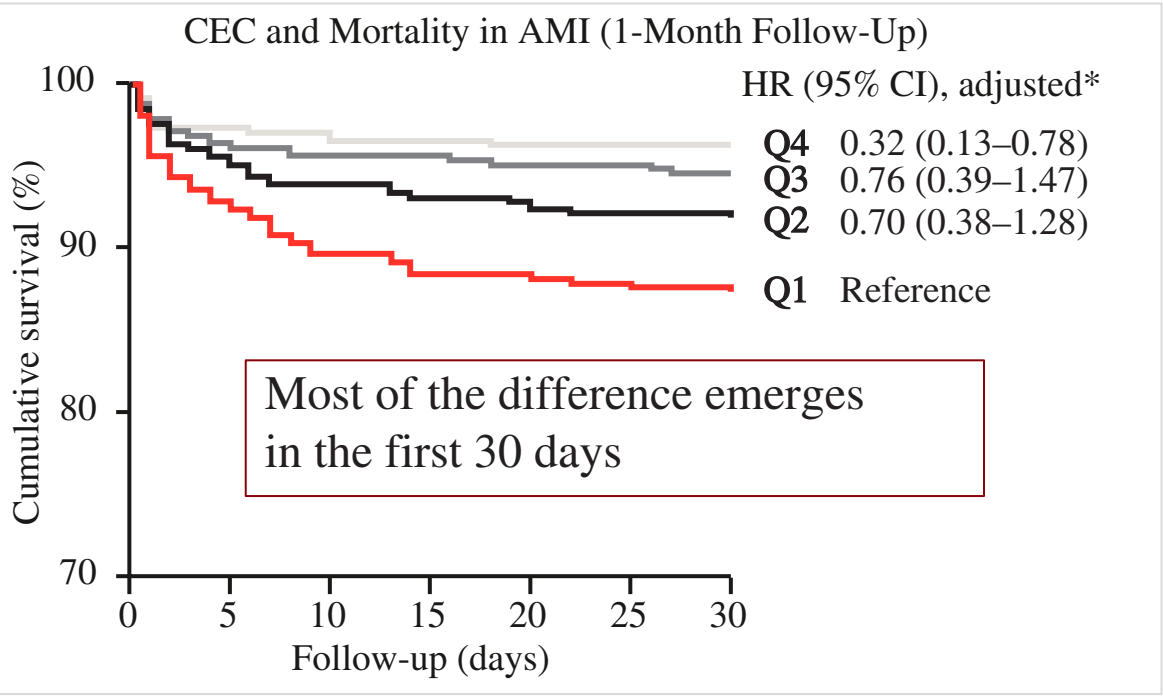
Macrophage With Radioactive Cholesterol



HDL From Patients Blood

Improved Cholesterol Efflux Capacity (CEC) Is Associated With Improved 6 Year Survival Following MI





Q1, Q2, Q3 and Q4 relate to the quartiles of CEC measured, in both figures.

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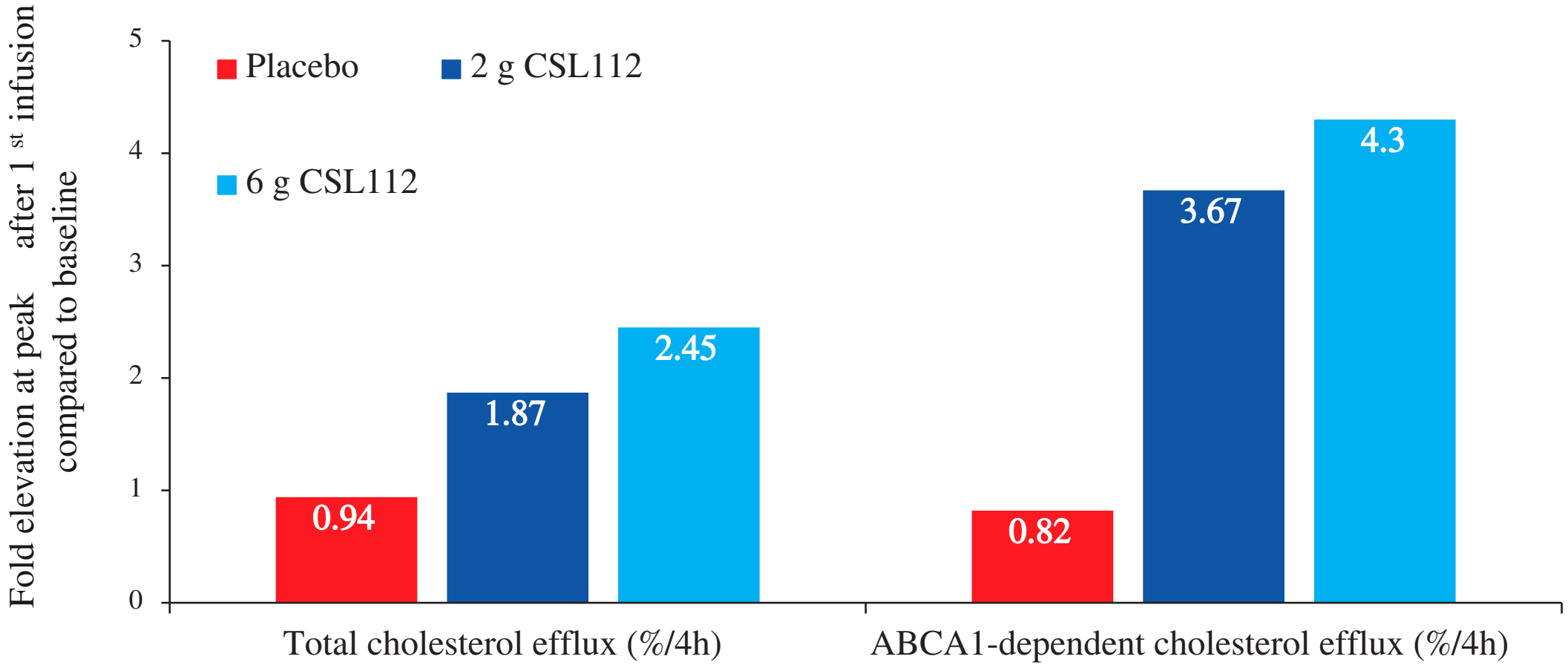
Age and sex, CV risk factors and prognostic factors of MI. AMI, acute myocardial infarction; CEC, cholesterol efflux capacity; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction; Q, quartile

Figures adapted from Guerin, M. et al. J Am Coll Cardiol. 2018;72:3259–69

CSL112 Is *Human* ApoA-1 Purified From Human Plasma, Reconstituted With Phosphatidylcholine, Stabilized With Sucrose; Suitable For IV Infusion & Produces a Significant, Dose-Dependent Improvement in Cholesterol Efflux in Post-MI Patients



In Phase II trials, CSL112 produced a dramatic, dose-dependent increase in apoA-I levels and cholesterol efflux

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Gibson CM, et al. Circulation 2016;134:1918–30.

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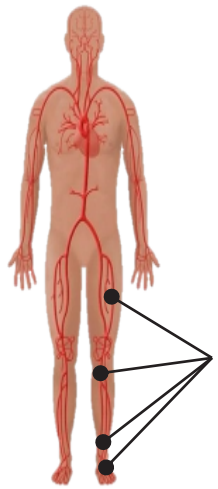
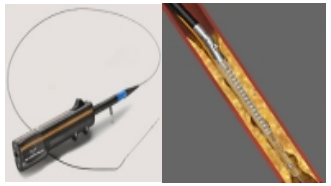
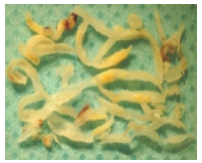
Histology Data from Human Femoral Arteries:

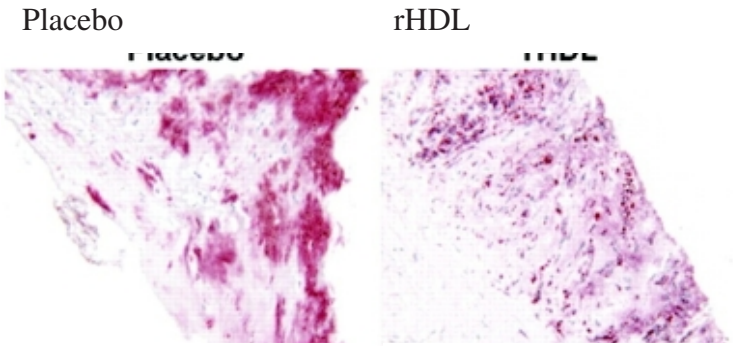
ApoA-I Infusion Reduces Macrophage & Fat Content in Plaque

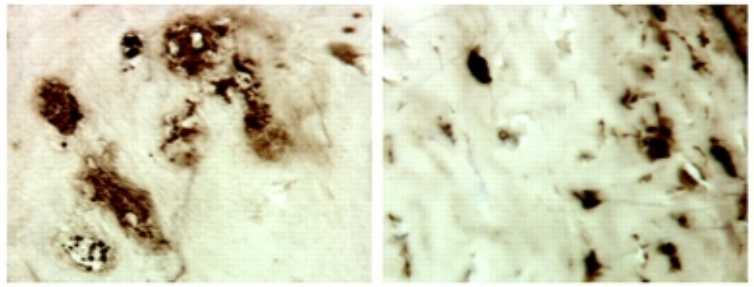
A s ingle infusion of ApoA-I (CSL111) reduced femoral plaque by >50% in 5–7 days [1]

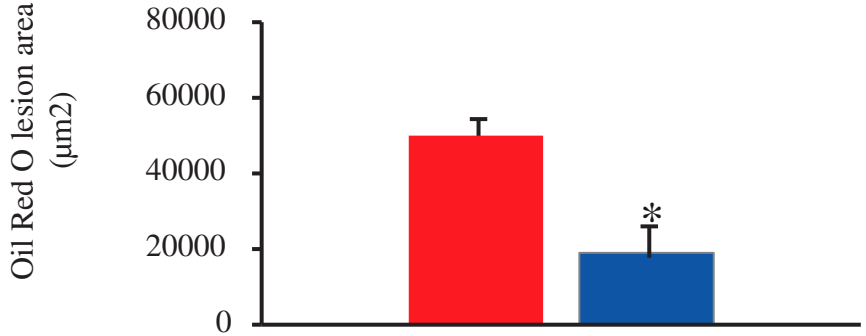


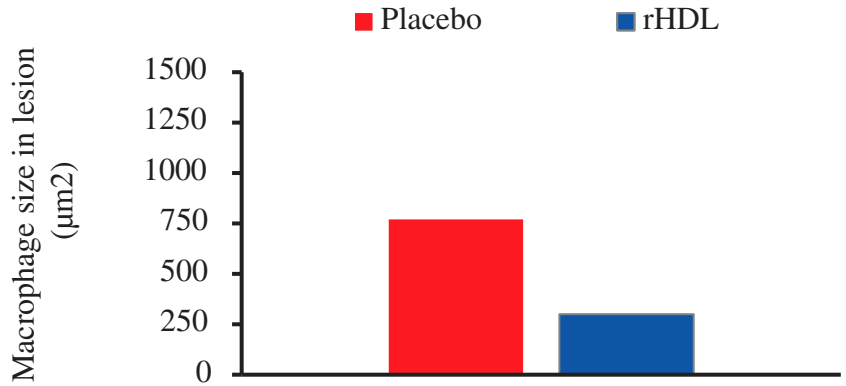












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Shaw et al. Circ Res. 2008;103:1084-91

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Hypothesis of the AEGIS 2 Trial

Prior Observations:

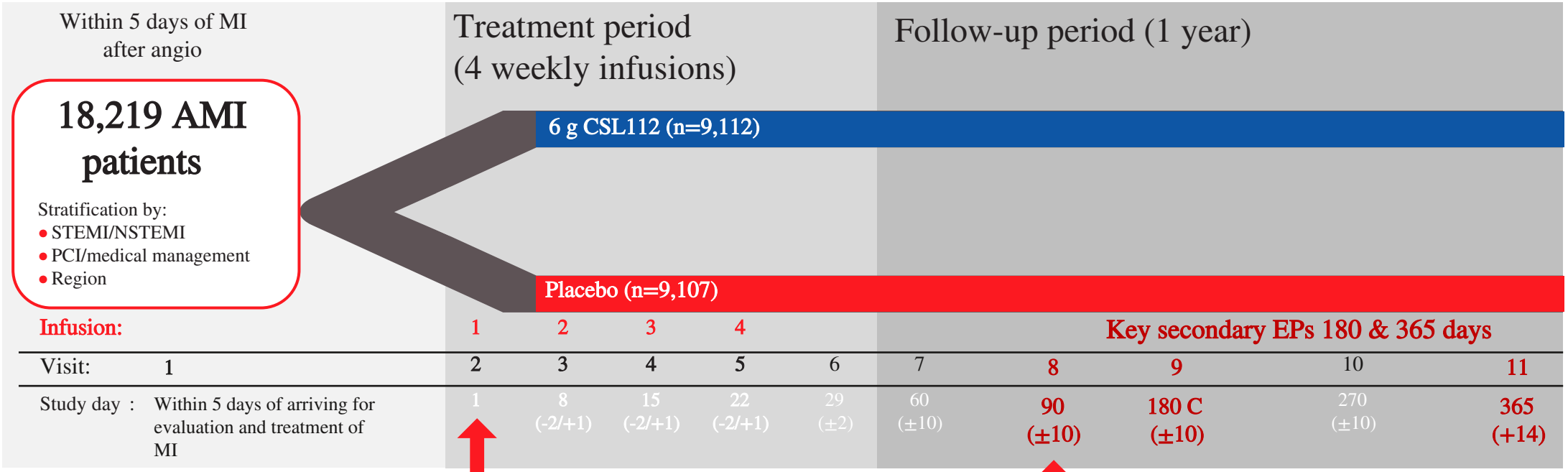
- CSL 112 ApoA-1 infusions improved cholesterol efflux in the setting of MI and reduced fat and macrophage content in atherosclerotic plaque
- Improved cholesterol efflux is associated with improved CV outcomes in the setting of MI

Hypothesis:

- CSL 112 infusion will improve CV outcomes in the setting of MI

ApoA-1 Event Reducin G in Ischemic Syndromes II

A phase 3, multicenter, double-blind, randomized, placebo-controlled, event-driven, parallel-group study



Multivessel Disease
AND
either Drug Treated Diabetes
OR
2 of the following:
≥65 years
Prior MI
PAD

ITT analysis. Two-sided **type I error of 0.05** with **90% power** on an assumed **hazard ratio of 0.80** for the primary endpoint with an observed **event rate of 5%** at 75% of the way through the trial led to a required **sample size of 18,200** , targeting **905 primary events**

Cumulative event rates using the Kaplan-Meier method were calculated for the primary efficacy endpoint and other time to event endpoints. A covariate-adjusted Cox regression model including fixed effects for treatment, region, index MI type, index MI management, age, diabetes, peripheral arterial disease, prior MI, and an interaction term for index MI type and index MI management was fitted to estimate the hazard ratio and two-sided 95% confidence interval

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AMI, acute myocardial infarction; MI, myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction. Gibson CM, et al. Am Heart J. 2021;231:121–7.

Trial Leadership

Executive Committee:

C. Michael Gibson, MS, MD (Chairman); Robert A. Harrington, MD, (Co-Chairman)

John Alexander, MD, MHS; Philip A. Aylward, BM, BCh, PhD; Deepak Bhatt, MD, MPH; Christoph Bode, MD; Shaun Goodman, MD, MS c; John Kastelein, MD, PhD; Kenneth Mahaffey, MD; A. Michael Lincoff, MD; Roxana Mehran, MD; Stephen J. Nicholls, MBBS, PhD;

National Lead Investigators

18,226 participants at **886 sites in 49 countries** were randomized between March 2018 and November 2022

(Argentina) Cecilia Bahit, MD;
(Australia) Gemma Figtree, MB BS, DPHIL (OXON), FRACP, FCSANZ, FAHA;
(Austria) Kurt Huber, MD, FESC, FACC, FAHA;
(Belgium) Pascal Vranckx, MD;
(Brazil) Renato Lopes, MD, MHS, PhD; (Brazil) Jose Carlos Nicolau, MD, PhD;
(Bulgaria) Nina Gotcheva, MD, PhD;
(Canada) Kevin Bainey, MD, MSc;
(Chile) Juan Carlos Prieto, MD;
(Colombia) Miguel Urina Triana, MD, MSc, PhD, FACC;
(Czech Republic) Miroslav Solar, MD;
(Denmark) Svend Eggert Jensen, MD, PhD, FESC; (Denmark) Morten Bøttcher, MD PhD;
(Estonia) Margus Viigimaa, MD, PhD, FESC;
(Finland) Mika Laine, MD;
(France) Gilles Montalescot, MD, PhD;
(Georgia) Tamaz Shaburishvili;
(Germany) Daniel Duerschmied, MD;
(Greece) Dimistris Tousoulis, MD;
(Hong Kong) Michael Lee, MD;
(Hungary) Bela Merkely, MD, PhD;
(Israel) Basil Lewis, MD;
(Italy) Giuseppe Ambrosio, MD, PhD;
(Japan) Satoshi Yasuda, MD;
(Latvia) Andrejs Erglis, MD;
(Lithuania) Rimvydas Slapikas, MD, PhD;
(Malaysia) Alan Fong, MD;
(Mexico) Jose Luis Leiva Pons, MD;
(Netherlands) Jan H. Cornel, MD;
(New Zealand) Harvey White, MD;
(Norway) Vibeke Juliebø, MD;
(Peru) Manuel Horna, MD, FACC, FASE, FESC;
(Poland) Jaroslaw Trebacz, MD;
(Portugal) João Morais, MD;
(Romania) Dragos Vinereanu, MD;
(Russia) Sergey Zenin, MD;
(Serbia) Nebojsa Tasic, MD;
(Singapore) Jack Tan, MD;
(Slovakia) Jan Murin, MD, PhD;
(South Africa) Lesley Burgess, MD;
(South Korea) Hyun Jae Kang, MD;
(Spain) Angel Cequier Fillat, MD;
(Sweden) Emil Hagström, MD;
(Switzerland) Stephan Windecker, MD;
(Taiwan) Jiunn-Lee Lin, MD;
(Thailand) Piyamitr Sritara, MD, PhD;
(Turkey) Umit Guray, MD;
(United Kingdom) Vijay Kunadian, MD;
(Ukraine) Alexandr Parkhomenko, MD;
(United States) Marc Bonaca, MD, MPH, Thomas Povsic, MD.

We would like to thank **Dr. Anthony Gershlick,** the country leader of the United Kingdom, and **Dr. Amadeu Betriu** , the country leader of Spain for their enormous contribution to the study prior to their untimely deaths. We miss them as friends and colleagues.

Baseline Characteristics

Type of index MI - no. (%)	CSL 112	Placebo
STEMI	**4606 (50.5)**	**4600 (50.5)**
NSTEMI	4506 (49.5)	4507 (49.5)
PCI performed for index MI – no. (%)	**8037 (88.2)**	**7997 (87.8)**
Medications at time of Randomization – no. (%)		
Aspirin	8489 (93.2)	8473 (93.0)
P2Y12 inhibitor or other anti-platelet agent	8508 (93.4)	8490 (93.2)
HMG CoA reductase inhibitor (statin)	**8429 (92.5)**	**8424 (92.5)**
High intensity statin therapy^^	6871 (75.4)	6890 (75.7)
Median lipid level (IQR) – mg/dL**		
Total Cholesterol	160 (133-192)	159 (133-190)
LDL Cholesterol	**84 (61-112)**	**84 (62-111)**
HDL Cholesterol	**39 (33-46)**	**39 (33-47)**
Triglycerides	156 (117-212)	153 (117-208)

Trial Compliance and Follow Up

90% of subjects completed all 4 infusions

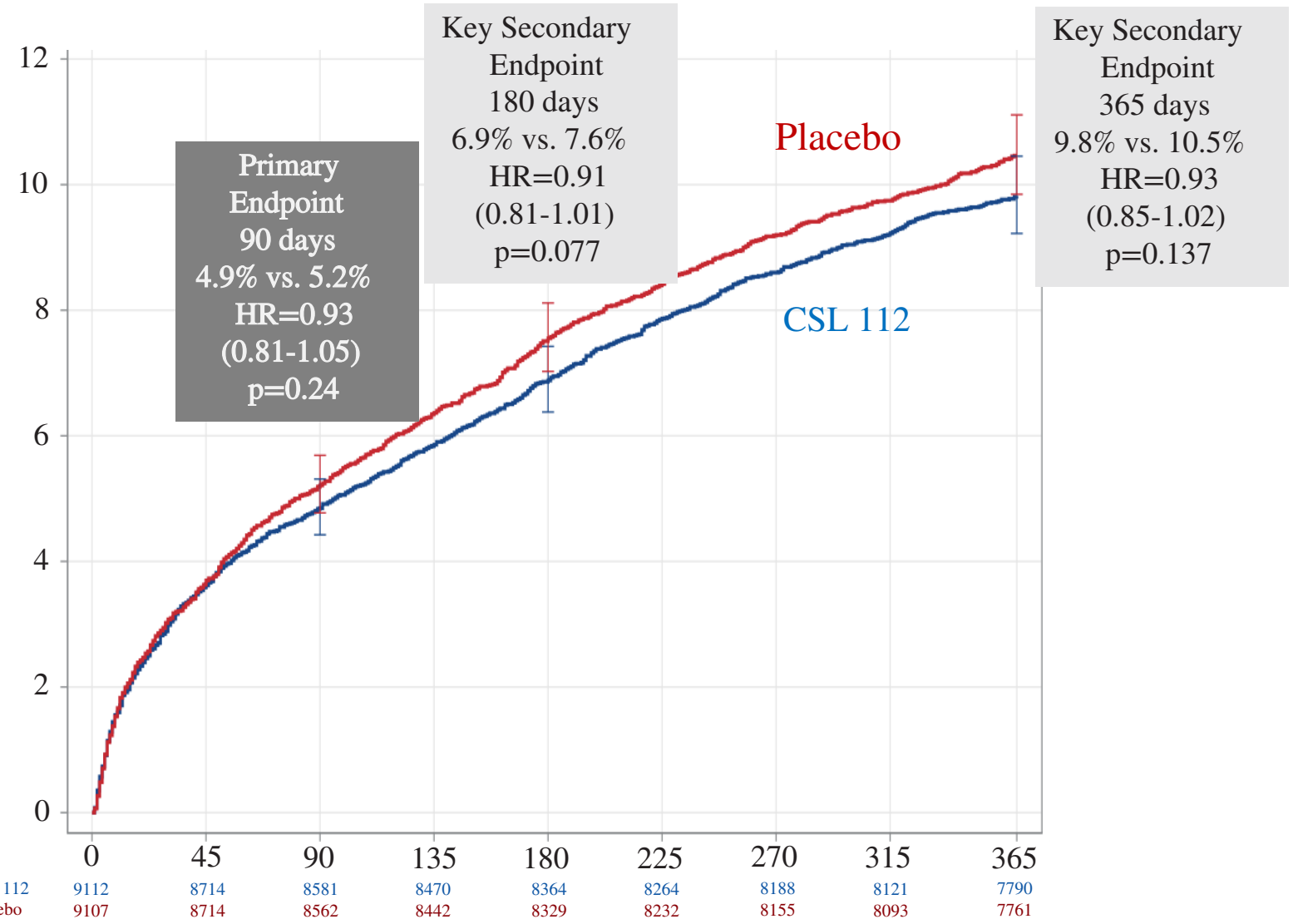
99.5% of subjects completed 90 days of follow-up

99% completed 365 days of follow-up

1 patient lost to follow up in each group

Primary Endpoint

Time to First Occurrence of CV Death, MI or Stroke



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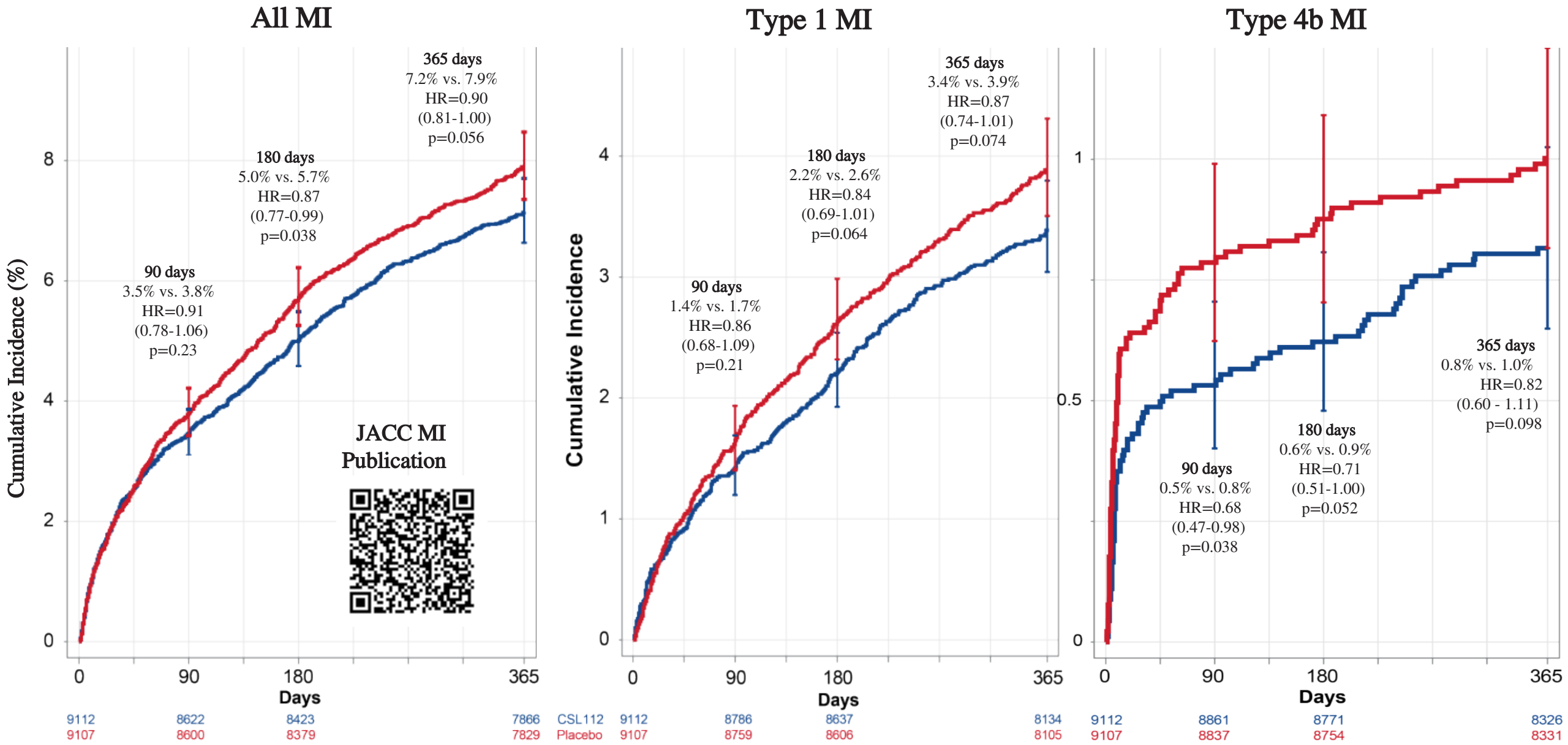
Other Key Pre-Specified Secondary Endpoints

End Point	CSL112 (N = 9112)	Placebo (N = 9107)	Hazard Ratio or Rate Ratio (95% CI)
Key Secondary Efficacy Endpoints			
Hospitalizations for coronary, cerebral, or peripheral ischemia per 90 days of follow-up – no. hospitalizations, mean rate*	433 (0.045)	442 (0.047)	0.97 (0.84–1.12)
Other Secondary Efficacy End Points and Components of the Composite Endpoint			
All-cause death at 365 days — no. (%)	341 (3.8)	345 (3.8)	0.98 (0.84–1.14)
CV death through 180 days — no. (%)	150 (1.7)	169 (1.9)	0.88 (0.71–1.10)
CV death through 365 days — no. (%)	230 (2.6)	242 (2.7)	0.94 (0.79–1.13)
MI through 180 days — no. (%)	**450 (5.0)**	**513 (5.7)**	***0.87 (0.77–0.99)***
MI through 365 days— no. (%)	**638 (7.2)**	**705 (7.9)**	**0.90 (0.81–1.00)**
Stroke through 180 days — no. (%)	81 (0.9)	71 (0.8)	1.13 (0.82–1.56)
Stroke through 365 days — no. (%)	115 (1.3)	109 (1.2)	1.05 (0.89–1.36)

Myocardial Infarction Event Rates by MI Type

Secondary Endpoint; All Patients Included



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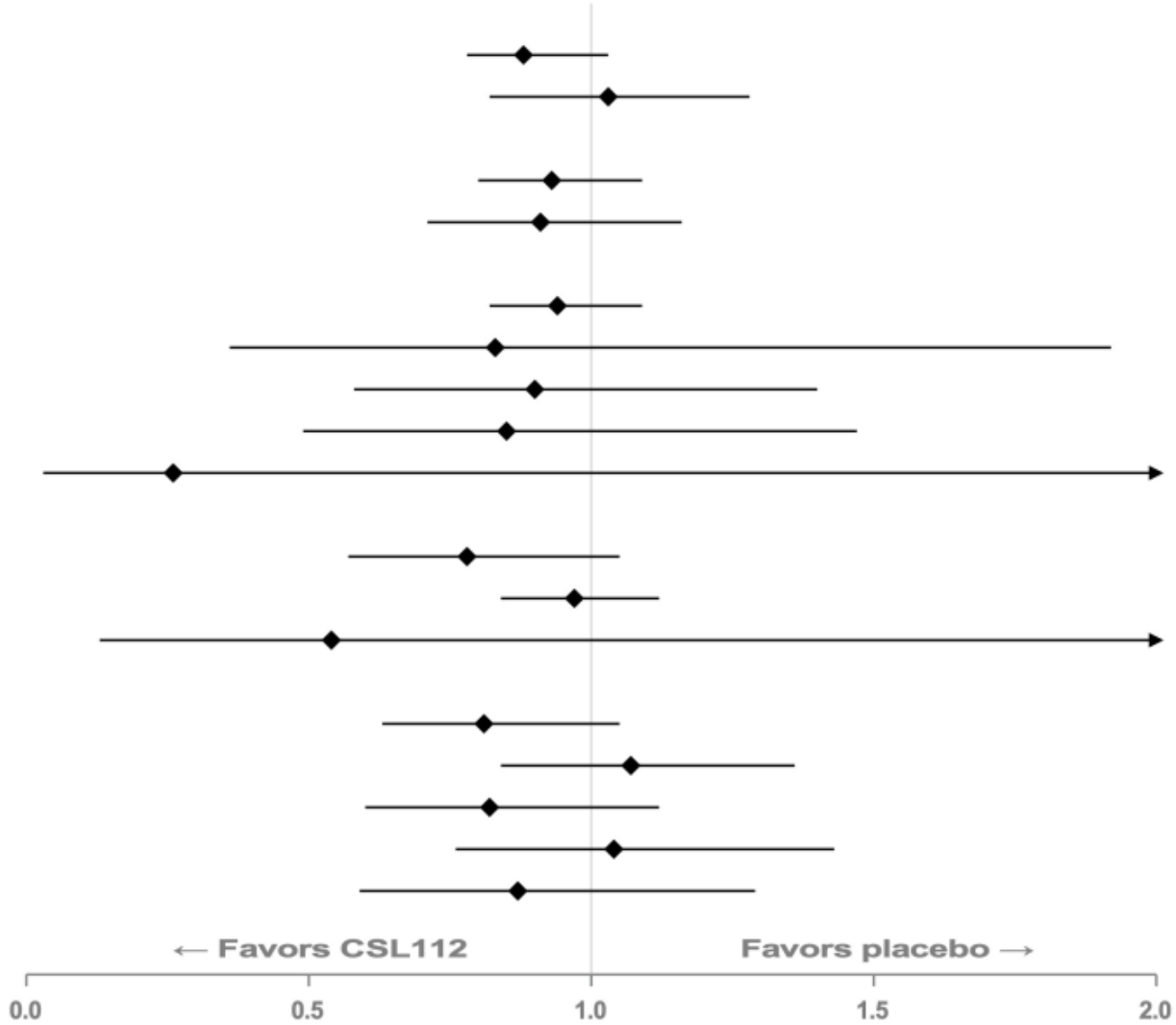
Safety Findings

- Overall, there were similar rates of adverse events with CSL112 compared to placebo.
- There were no imbalances in all hypersensitivity events (serious and non-serious). The number of immune system disorder events (e.g. hypersensitivity or anaphylactoid reactions) leading to discontinuation from investigational product were low but were higher in the CSL112 group compared with the placebo group **(14 vs 4 events, p=0.02).**
- There were **less acute kidney injury events in the CSL112 arm** (defined by changes in creatinine through the active treatment period): **570 (6.3%) vs 650 (7.2%)(p=0.02).**
- There were no **significant** imbalances in potential hepatic injury events (defined as ALT >3x ULN with Tbili >2x ULN or ALT >5x ULN), or new or worsening heart failure events (based on adjudication)

Primary Endpoint Subgroups

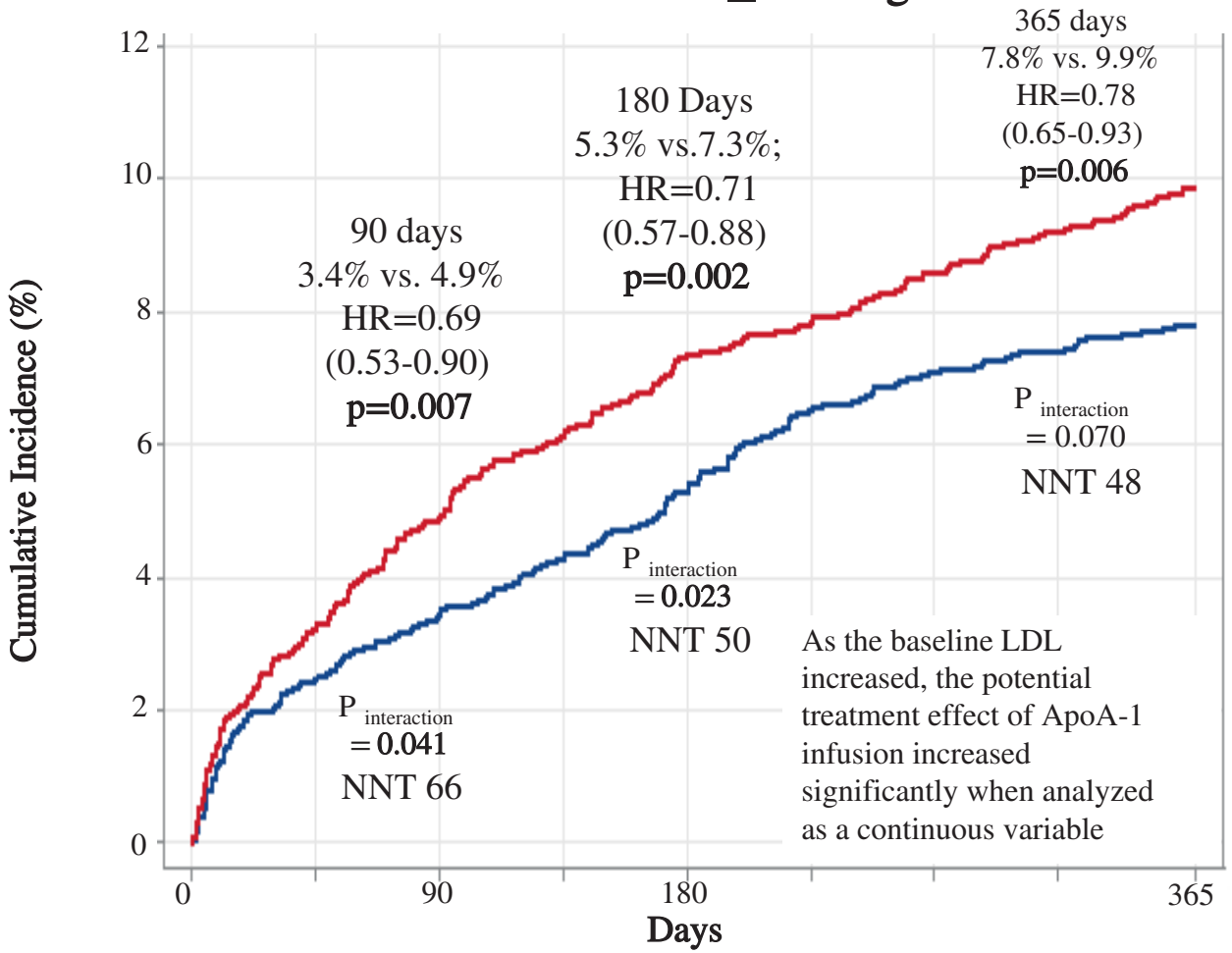
Subgroup	CSL112	Placebo	HR (95% CI)
Age			
>=65 years old	284/5418 (5.2%)	318/5341 (6.0%)	0.88 (0.78-1.03)
<65 years old	155/3694 (4.2%)	154/3766 (4.1%)	1.03 (0.82-1.28)
Sex			
Male	314/6786 (4.6%)	333/6721 (5.0%)	0.93 (0.80-1.09)
Female	125/2326 (5.4%)	139/2386 (5.8%)	0.91 (0.71-1.16)
Race			
White	368/7769 (4.7%)	385/7698 (5.0%)	0.94 (0.82-1.09)
Black/African-American	10/181 (5.5%)	12/181 (6.6%)	0.83 (0.36-1.92)
Asian	37/743 (5.0%)	42/781 (5.4%)	0.90 (0.58-1.40)
Other	23/373 (6.2%)	29/402 (7.2%)	0.85 (0.49-1.47)
Not reported	1/46 (2.2%)	4/45 (8.9%)	0.26 (0.03-2.33)
Ethnicity			
Hispanic	75/1566 (4.8%)	97/1596 (6.1%)	0.78 (0.57-1.05)
Non-Hispanic	360/7410 (4.9%)	370/7383 (5.0%)	0.97 (0.84-1.12)
Not reported	3/132 (2.3%)	5/123 (4.1%)	0.54 (0.13-2.24)
Region [1]			
Central and Eastern Europe	107/3134 (3.4%)	130/3136 (4.1%)	0.81 (0.63-1.05)
Western Europe	135/2459 (5.5%)	128/2455 (5.2%)	1.07 (0.84-1.36)
Latin America	73/1456 (5.0%)	88/1453 (6.1%)	0.82 (0.60-1.12)
North America	77/1178 (6.5%)	73/1175 (6.2%)	1.04 (0.76-1.43)
Asia Pacific	47/885 (5.3%)	53/888 (6.0%)	0.87 (0.59-1.29)



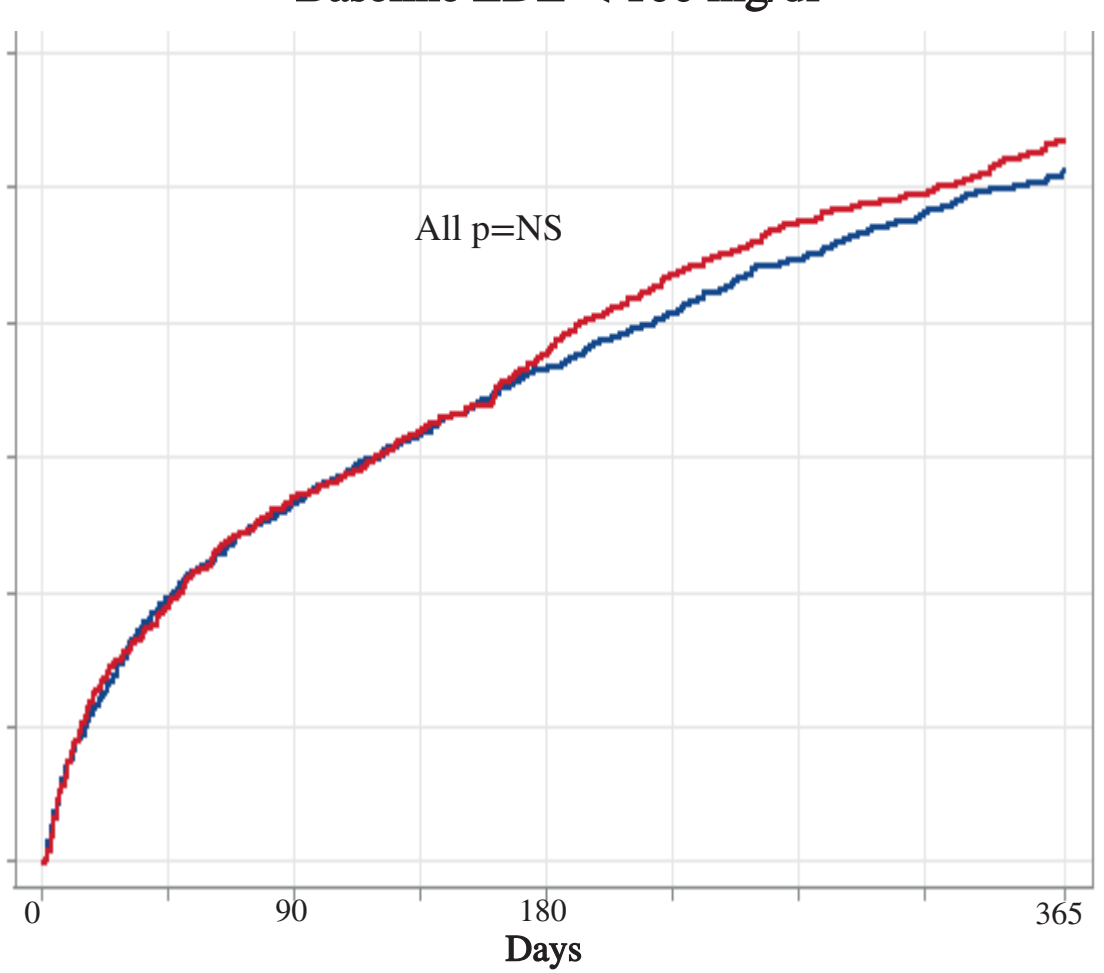
Secondary and Exploratory Hypothesis Generating Analyses

Primary MACE Endpoint Lower In Patients With Baseline Hyperlipidemia (LDL-C ≥ 100, All On Statins)

Baseline LDL ≥ 100 mg/dl



Baseline LDL < 100 mg/dl



CSL 112	2655	2551	2496	2348	5198	4882	4759	4412
Placebo	2649	2514	2444	2285	5229	4910	4784	4440

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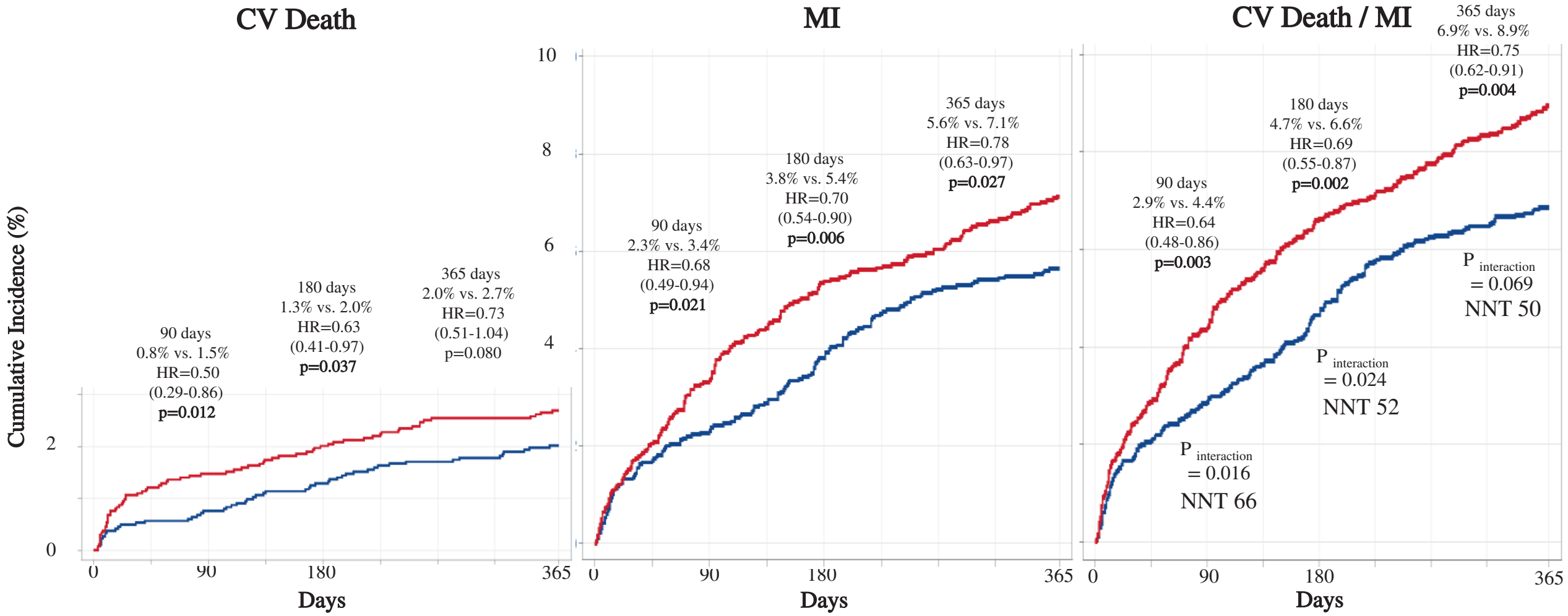
Patients with Baseline Hyperlipidemia (LDL-C ≥ 100, All on Statins)



CSL 112	2655	2619	2599	2490	2655	2566	2513	2372	2655	2566	2513	2372
Placebo	2649	2599	2576	2455	2649	2526	2461	2306	2649	2526	2461	2306

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Conclusions

- Among AMI patients with multivessel disease and additional cardiovascular risk factors on guideline directed background therapies, 4 weekly infusions of CSL112 compared with placebo did not significantly reduce the primary endpoint of CV death, MI or stroke through 90 days.
- There was consistency in the primary endpoint in pre-specified subgroups.
- The drug was well tolerated.

Conclusions: Secondary & Exploratory Hypothesis Generating Endpoints

- As the baseline LDL-C increased, the potential treatment effect of ApoA-1 infusion increased significantly when analyzed as a continuous variable
- There was a positive interaction term such that the treatment effect in those patients with an LDL-C $\geq$ 100 mg / dl was statistically significant while it was not in those with an LDL < 100 mg/dl
- The benefit on ApoA-1 infusions in hyperlipidemic patients is biologically plausible, but the observation is hypothesis generating and requires prospective validation.
- The trends seen for the individual components of CV death and MI are consistent with the a priori proposed biologic effect of plaque stabilization.

Back Up Slides

Differentiating CSL112 from other ApoA-I Infusion Therapies

CSL112 results in much larger increases in ApoA-I, cholesterol efflux and ABCA1-dependent cholesterol efflux than other ApoA-I therapies and activates LCAT

	CSL112 (6 g)	CER-001 (3 mg/kg)	MDCO-216 (20 mg/kg)
ApoA-I levels	Increase *[1] ↑106%	Increase †[2] ↑6%	Hypercatabolism ‡[3] ⇩
Total Cholesterol efflux	Increase *[1] ↑145%	Increase †[2] ↑6%	Not available ‖[3]
ABCA1-dependent cholesterol efflux	Increase *[1] ↑330%	No change †[2]	Not available ‖[3,4]
LCAT	Activated [5]	Inhibited [6-8]	Inhibited [9,10]

Data not from head-to-head studies

ABCA1, ATP-binding cassette transporter A1; apoA-I, apolipoprotein A-I; LCAT, lecithin-cholesterol acyltransferase; RCT, reverse cholesterol transport

*Measured before and immediately after 2-hour infusion; †Measured before and 1 hour after infusion; ‡Timing of measurement not reported; ‖Data not available for MILANO-PILOT; however, limited data at the 20 mg/kg dose from Phase 1 suggests an increase in ABCA1-dependent efflux.

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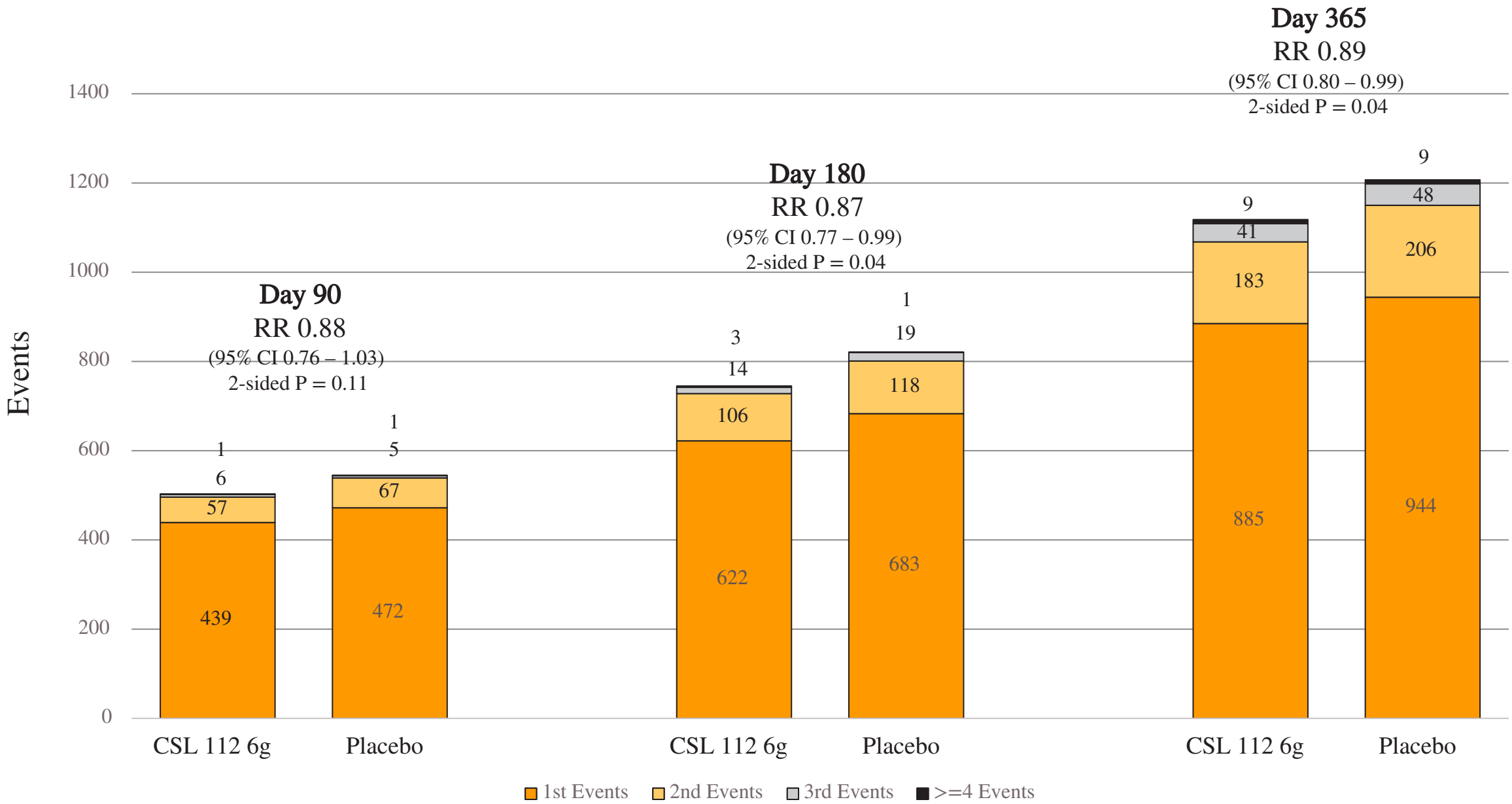
Multiple Event Analysis: CV Death, MI and Stroke



Slide by C. Michael Gibson, M.S., M.D.

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