Rationale and design of ApoA-I Event Reducing in Ischemic Syndromes II (AEGIS-II): A phase 3, multicenter, double-blind, randomized, placebo-controlled, parallel-group study to investigate the efficacy and safety of CSL112 in subjects after acute myocardial infarction

C. Michael Gibson, MS, MD,[a] John J. P. Kastelein, MD,[b] Adam T. Phillips, MD,[a] Philip E. Aylward, MD,[c] Megan K. Yee, MPH,[a] Michal Tendera, MD,[d] Stephen J. Nicholls, MD, PhD,[e] Stuart Pocock, PhD,[f] Shaun G. Goodman, MD, MSc,[g] John H. Alexander, MD, MHS,[h] A. Michael Lincoff, MD,[i] Christoph Bode, MD,[j] Danielle Duffy, MD,[k] Mark Heise, PhD,[k] Gail Berman, MD,[l] Sojaita Jenny Mears, MS,[k] Pierluigi Tricoci, MD, PhD, MHS,[h,k,1] Lawrence I. Deckelbaum, MD,[k] P. Gabriel Steg, MD,[m] Paul Ridker, MD,[n] and Roxana Mehran, MD[o] ***Boston, MA; Amsterdam, the Netherlands; Adelaide, Melbourne, Australia; Katowice, Poland; London, United Kingdom; Ontario, Canada; Durham, NC; Cleveland, OH; Freiburg, Germany; King of Prussia, PA; Paris, France; and New York, NY***

Acute myocardial infarction (MI) patients remain at high risk for recurrent events. Cholesterol efflux, mediated by apolipoprotein A-I, removes excess cholesterol from atherosclerotic plaque and transports it to the liver for excretion. Impaired cholesterol efflux is associated with higher cardiovascular (CV) event rates among both patients with stable coronary artery disease and recent MI. CSL112, a novel intravenous formulation of apolipoprotein A-I (human) derived from human plasma, increases cholesterol efflux capacity.

AEGIS-II is a phase 3, multicenter, double-blind, randomized, placebo-controlled, parallel-group trial investigating the efficacy and safety of CSL112 compared to placebo among high-risk acute MI participants. Eligibility criteria include age ≥ 18 years with type 1 (spontaneous) MI, evidence of multivessel stable coronary artery disease, and presence of diabetes requiring pharmacotherapy, or ≥2 of the following: age ≥ 65 years, prior MI, or peripheral artery disease. A target sample of 17,400 participants will be randomized 1:1 to receive 4 weekly infusions of CSL112 6 g or placebo, initiated prior to or on the day of discharge and within 5 days of first medical contact. The primary outcome is the time to first occurrence of the composite of CV death, MI, or stroke through 90 days. Key secondary outcomes include the total number of hospitalizations for coronary, cerebral, or peripheral ischemia through 90 days and time to first occurrence of the composite primary outcome through 180 and 365 days.

AEGIS-II will be the first trial to formally test whether enhancing cholesterol efflux can reduce the rate of recurrent major adverse CV events. (Am Heart J 2021;231:121-7.)

From the [a]From PERFUSE Study Group, Cardiovascular Division, Departments of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, [b]Department of Vascular Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands, [c]South Australian Health and Medical Research Institute, Flinders University and Medical Centre, Adelaide, Australia, [d]Department of Cardiology and Structural Heart Disease, Medical University of Silesia, Katowice, Poland, [e]Monash Cardiovascular Research Centre, Monash University, Melbourne, Australia, [f]Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, United Kingdom, [g]Canadian VIGOUR Centre, University of Alberta, Edmonton, Alberta, and St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada, Duke Clinical Research Institute, Cardiovascular Division, Department of Medicine, Duke University Health, Durham, NC, [i]Department of Cardiovascular Medicine, Cleveland Clinic Foundation, Cleveland, OH, [j]Heart Center, Faculty of Medicine, University of Freiburg, Freiburg, Germany, [k]CSL Behring, LLC, King of Prussia, PA, [l]Paratek Pharmaceuticals, King of Prussia, PA, [m]Assistance Publique–Hopitaux de Paris, and Université de Paris, Paris, France, [n]Center for Cardiovascular Disease Prevention, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, and [o]Cardiovascular Institute, Mount Sinai, New York, NY.

[1]P. T. was affiliated with Duke Clinical Research Institute prior to employment at CSL Behring.

All authors have received research grant support from the sponsor of the study. D. Duffy, M. Heise, G. Berman, S. J. Mears, P. Tricoci, and L. I. Deckelbaum are employees of CSL Behring. The authors are solely responsibly for the design and conduct of this study, all study analyses, the drafting and editing of the paper, and its final contents. All authors have materially participated in the manuscript preparation, provided critical contributions to the manuscript, and approved the final submitted version.

Submitted November 21, 2019; accepted October 6, 2020.

Reprint requests: C. Michael Gibson, MS, MD, Beth Israel Deaconess Medical Center, Cardiovascular Division, 930 Commonwealth Ave, Boston, MA 02215.

E-mail: mgibson@bidmc.harvard.edu

[1] P. T. was affiliated with Duke Clinical Research Institute prior to employment at CSL Behring.

0002-8703

https://doi.org/10.1016/j.ahj.2020.10.052

Despite advances in therapeutic strategies, acute myocardial infarction (AMI) patients remain at high risk for recurrent ischemic events. Approximately 60% of recurrent cardiovascular (CV) events (CV death, MI, or stroke) from the first year occur within the first 90 days following the index event.[1] The overwhelming body of data with current low-density lipoprotein–directed therapies consistently demonstrates a reduction in recurrent CV events in the chronic phase, although risk remains high despite intensive statin therapy in the very early period following an AMI.[2-6] Morbidity and mortality associated with both the index coronary event and recurrent CV events are as high as 20% per year.[7,8] Therefore, there remains a critical unmet need for effective and safe therapies that target the high-risk period that immediately follows AMI.

Reverse cholesterol transport removes excess cholesterol from arteries containing atherosclerotic plaque and transports it to the liver for excretion.[9,10] The first step in this process is known as *cholesterol efflux* and is mediated in part by apolipoprotein A-I (apoA-I), the chief protein component of high-density lipoprotein (HDL).[11] Cholesterol efflux is associated with CV events independent of other traditional risk factors.[12-15] Additionally, cholesterol efflux has demonstrated an inverse correlation with all-cause mortality among ST-elevation myocardial infarction (STEMI) patients.[16] Subsequent to an acute coronary syndrome (ACS) event, cholesterol efflux is reduced, with lowest levels around 2 to 5 days before returning to baseline approximately 30 days after an event.[17-19] During the acute phase response following an ACS event, the protein cargo of native HDL particles may be altered or lipids may be oxidized, rendering HDL efflux capacity less efficient. A novel infusible human plasma-derived apoA-I that robustly elevates cholesterol efflux with relatively modest increases in apoA-I may be less susceptible to such acute phase modification and might retain functionality during this time period. Therefore, it has been suggested that pharmacotherapies which increase apoA-I and elevate cholesterol efflux capacity may be beneficial among post-AMI patients.[20]

Promotion of cholesterol efflux has been observed with infusions of previous formulations of apoA-I.[21] MDCO-216, a recombinant dimeric ApoA-I Milano, a mutant form of apoA-I, demonstrated an 80% increase in ATP-binding cassette A1 (ABCA1)–dependent cholesterol efflux compared to placebo.[22] CER-001, a bioengineered recombinant of wild-type apoA-I, demonstrated a 6% increase in ABCA1-dependent cholesterol efflux.[23] However, in randomized placebo-controlled coronary imaging studies, both formulations failed to demonstrate short-term plaque reduction compared to placebo.[22,24] In contrast, CSL112, a novel intravenous formulation of native apoA-I purified from human plasma developed for use in patients with ACS to reduce the risk of CV death, MI, and stroke, demonstrated more favorable pharmacodynamic (PD) properties compared to MDCO-216 and CER-001, with an increase in ABCA1-dependent cholesterol efflux by approximately 330%.[21,25] It should be noted that although the methods used to measure cholesterol efflux were similar, there are no direct head-to-head comparisons of these agents.

Substantial differences exist between the 3 apoA-I formulations. Mutant ApoA-I Milano in MDCO-216 was shown to promote catabolism of endogenous apoA-I,[22] which has not been observed with other formulations. All 3 formulations differ in type and amount of phospholipids used, which are important because different lipid combinations affect the ability of HDL to promote cholesterol efflux.[26] Additionally, CSL112 elevates lecithin cholesterol acyltransferase activity, which is responsible for the esterification of cholesterol, an important step in reverse cholesterol transport because it allows for a greater load to cholesterol to be transported.[27] Esterification of cholesterol is inhibited with MDCO-216, and the phospholipid component of CER-001 may lead to impaired cholesterol esterification.[28,29]

A total of 1060 participants have received at least 1 infusion of CSL112 in 7 completed studies. A phase 2b study in AMI participants demonstrated an immediate and dose-dependent 2.06-fold rise in apoA-I plasma concentrations after the initial 6-g CSL112 infusion followed by a gradual return to baseline over approximately 5-7 days.[25] Additionally, a rapid increase in HDL-C and significant dose-dependent elevations in pre-β HDL and global cholesterol efflux were noted with CSL112.[30,31] A third phase 1 study was conducted in adults with normal renal function and moderate renal impairment (chronic kidney disease stage 3), which confirmed that a dose adjustment was not needed for impaired renal function.[30,32] A phase 2a clinical trial in participants with stable atherosclerotic disease demonstrated that a single CSL112 infusion was well tolerated and caused an immediate increase in cholesterol efflux capacity and apoA-I levels.[33] The phase 2b study in AMI participants with normal or mildly impaired renal function at high risk of subsequent CV events demonstrated that administration of 4 weekly infusions of CSL112 was well tolerated with no significant change in liver or kidney function. Acute enhancement of cholesterol efflux and apoA-I was also observed.[25] Results were similar in a subsequent third phase 2 study among participants with AMI and moderate renal impairment.[34]

This manuscript describes the AEGIS-II trial (ClinicalTrials.gov NCT03473223), a phase 3, multicenter, double-blind, randomized, placebo-controlled, parallel-group trial designed to investigate whether CSL112 can safely reduce the risk of major adverse CV events (MACE) through 90 days, a period of unmet clinical need. High-risk post-AMI participants with multivessel coronary artery disease are being enrolled.

Study design

Study operations

This trial, funded by CSL Behring, was collaboratively designed by members of the executive committee and the sponsor. Executive and steering committees, chaired by Dr C. Michael Gibson, are responsible for trial conduct and oversight. The executive committee is comprised of principal investigators and other recognized leaders in the field of ACS, lipidology, and biostatistics, and a representative of the sponsor.

An unblinded Independent Data and Monitoring Committee (IDMC), consisting of qualified scientists not affiliated with investigators or the sponsor, was selected by the executive committee. The IDMC is responsible for the following: review of safety data at planned intervals and identifying any safety concerns that arise during the course of the study, review of efficacy and safety data during prespecified interim analyses for futility and efficacy, requesting an interim safety review if needed, monitoring any potential risk of an immune response to CSL112 and apoA-I and recommending the number of samples to be assayed, and providing recommendations regarding study conduct including study progression and termination. Additionally, the IDMC will monitor unblinded suspected MACE and other safety data.

An independent Clinical Events Committee (CEC) will review and adjudicate all suspected MACE outcomes while blinded to treatment assignment. The occurrence of potential hepatic injury based on laboratory tests (alanine aminotransferase and total bilirubin), clinical assessments, and new or worsening heart failure events will also be reviewed and adjudicated in a blinded fashion.

Study objectives

The primary objective of the study is to evaluate the efficacy of 4 weekly infusions of CSL112 on reducing MACE compared with placebo in participants with AMI.

Study population and patient selection

Patients eligible for enrollment include adults at least 18 years of age with type 1 (spontaneous) MI defined by the Third Universal Definition of MI,[35-37] with multivessel coronary artery disease defined as ≥50% stenosis on 2 or more epicardial artery territories or the left main artery during a prior cardiac catheterization or cardiac catheterization during the index ACS event, or prior percutaneous coronary intervention (PCI) and ≥50% stenosis of at least 1 epicardial artery territory different from the prior revascularized artery, or prior multivessel coronary bypass grafting. Additionally, participants must have the presence of established CV risk factor(s), defined as pharmacologic treatment for diabetes mellitus, or at least 2 of the following: age ≥ 65 years, prior history of MI, or peripheral arterial disease (PAD).

Key exclusion criteria include (1) ongoing *hemodynamic instability* defined as New York Heart Association Class III or IV heart failure within the last year, Killip Class III or IV, sustained or symptomatic hypotension (systolic blood pressure <90 mm Hg), or left ventricular ejection fraction <30%; (2) evidence of *hepatobiliary disease* defined as active hepatic dysfunction or active biliary obstruction, chronic cirrhosis or infectious or inflammatory hepatitis, or alanine aminotransferase >3× the upper limit of normal or total bilirubin >2× the upper limit of normal; (3) evidence of *severe chronic kidney disease* defined as estimated glomerular filtration rate <30 mL/min/1.73 m^2 calculated with the Chronic Kidney Disease Epidemiology Collaboration equation; (4) scheduled coronary bypass graft surgery after randomization; and (5) body weight <50 kg.

All participants undergoing angiography, and thereby exposed to intravenous contrast, must demonstrate *stable renal function* at least 12 hours after contrast exposure, defined as an increase in serum creatinine of <0.3 mg/dL from the precontrast serum creatinine value. A full detailed list of the inclusion and exclusion criteria can be found in Supplemental Table I.

Randomization and study drug protocol

Enrolled participants will be stratified by index MI type (STEMI vs non–STEMI), management of index MI (PCI vs medical management), and region (North America, Latin America, Western Europe, Central and Eastern Europe, Asia Pacific) and then randomized using Interactive Response Technology in a 1:1 ratio to receive either 6 g CSL112 or placebo. The placebo being used in the trial is a diluted form of albumin (25% albumin diluted to 4.4%) that is similar in color and foaming properties to CSL112 and will be given in the same volume as the active treatment to maintain the blinding principles of the study. The 6-g dose of CSL112 was chosen based on the renal and hepatic safety profile in the AEGIS-I and CSL112_2001 trials, as well as pharmacokinetic (PK)-PD models demonstrating the relationship between 6 g CSL112 and apoA-I exposure and cholesterol efflux capacity, derived from AEGIS-I data.[25,34,38] Published animal and human studies have demonstrated that elevation of plasma apoA-I can produce strong reduction of plaque cholesterol in an interval as short as 1 week.[39,40] All participants will receive 4 consecutive weekly intravenous infusions of study drug, with infusions occurring approximately 5 to 8 days apart during the active treatment period. First infusion will be given on or before the day of hospital discharge and within 5 days of presentation to the hospital for evaluation and treatment of the index MI. All 4 infusions will be administered within 30 days of the first infusion, during this period of high risk for a recurrent cardiovascular event. A detailed overview of the design and timeline of the study is presented in Figure 1.

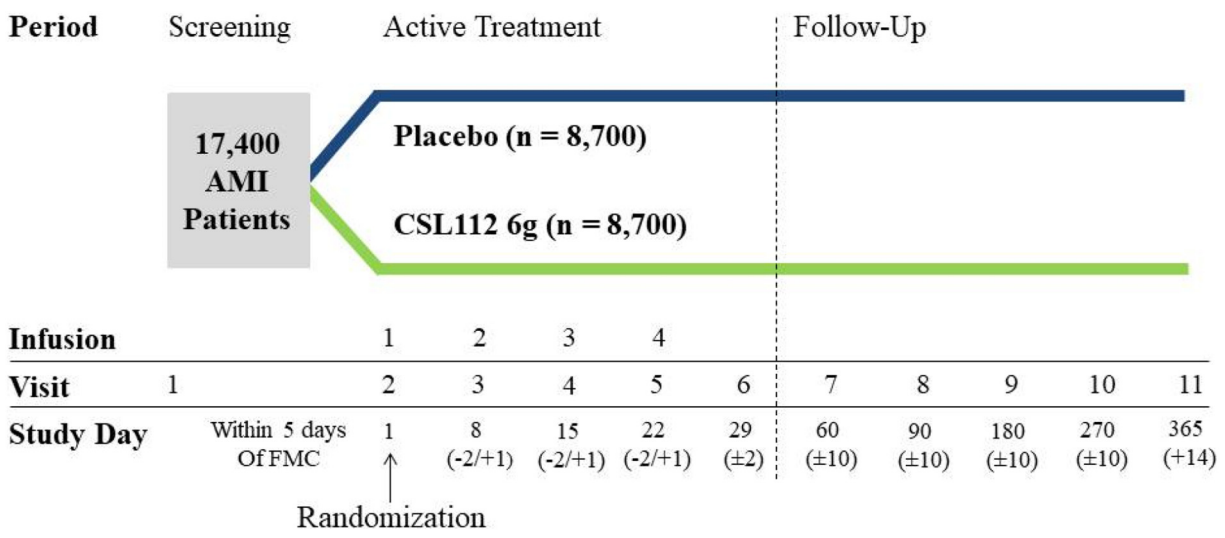

Figure 1

Study design and timeline.*FMC*, first medical contact.

Study follow-up and outcomes

Study assessments will occur at screening, before and after each infusion visit, and at the end of the active treatment period. Follow-up study assessments will occur at day 60 and day 90 and then every 90 days until day 365. Study conclusion will occur at least 365 days after the last subject is randomized (Figure 1).

The primary efficacy outcome is the time to first occurrence of the MACE composite of CV death, MI, or stroke from the time of randomization through 90 days. All MI types are included in the primary end point.

Key secondary outcomes, which further explore the efficacy of CSL112, include the total number of hospitalizations for coronary, cerebral, or peripheral ischemia from the time of randomization through 90 days, and time to first occurrence of the composite of CV death, MI, or stroke from the time of randomization through 180 days and through 365 days.

Other secondary outcomes include time to first occurrence of each component of the primary efficacy composite separately (CV death, MI, and stroke) from time of randomization through 90 days; time to first occurrence of CV death, type 1 MI, or stroke from the time of randomization through 90, 180, and 365 days; as well as time to occurrence of all-cause death from time of randomization through 365 days. Secondary outcomes assessing safety include the number of participants with adverse events through 90 days, treatment-related adverse events through the end of study, and serious adverse events through the end of study. Additionally, changes in clinical laboratory assessments from baseline will be described. A full list of study outcomes, including exploratory outcomes, which assess the efficacy of CSL112 throughout various time periods and on the total burden of disease, examine medical resource utilization, and characterize the PK profile of CSL112, can be found in Supplemental Table II.

Analysis populations

Efficacy analyses will be completed in the intent-to-treat population which includes all participants randomized to receive either CSL112 or placebo, and analyses will be conducted according to the randomized treatment group, regardless of the treatment actually received. All safety analyses will be completed in the safety population which contains all randomized participants who received at least a partial dose of study drug, and analyses will be based on the treatment the subject actually receives.

Statistical considerations

Final sample size will be based on CEC-adjudicated MACE rates, which will be monitored throughout the enrollment phase. Sample size was calculated assuming CSL112 will have a 20% relative risk reduction (hazard ratio = 0.80) compared to placebo in the primary outcome through 90 days of follow-up after randomization. Assuming a 1-sided α of .025, 1,004 confirmed MACE events will provide at least 90% power. It is estimated that approximately 17,400 participants will be enrolled, assuming no dropouts and a 90-day placebo event rate of 6.4%. Sample size calculation takes into account 3 planned interim analyses performed at 30%, 50%, and 70% of the target number of CEC-adjudicated

events (approximately 301, 502, and 703 events, respectively).

Sample size adjustment will be based on blinded event rates pooled across both randomized groups. Permissible sample sizes range from a minimum of 15,000 to a maximum of 20,600 participants.

The first and second interim analyses will assess futility, and the third interim analysis will assess efficacy. The futility boundary is based on 2-sided 95% CI and specifies that no underlying treatment difference exists if the lower boundary of the confidence interval excludes a hazard ratio of 0.80. The efficacy stopping boundary is set at a hazard ratio < 0.753 (1-sided .000083 α level) using an α spending function from the P family with a parameter value of 16. If the primary null hypothesis is not rejected at the interim efficacy analysis, a 1-sided α level of .024999 at the final analysis will be used. Actual significance level will be recomputed using an α spending function at the time of analysis if the observed numbers of events are different from those expected.

Cumulative event rates using the Kaplan-Meier method will be calculated for the primary efficacy outcome according to the randomized treatment group. A covariate adjusted Cox regression model including fixed effects for treatment, region, index MI type, index MI management, age, diabetes, PAD, prior MI, and an interaction term for index MI type and index MI management will be fitted to estimate the hazard ratio and 2-sided 95% CI, as well as a 1-sided Wald *P* value ($P < .025$ for significance).

Key secondary outcomes will be tested using a 1-sided .025 significance level, adjusted for multiplicity. Time to first occurrence of CV death, MI, or stroke through 180 and 365 days will be compared by treatment using the same methods as the primary efficacy outcome analysis. Mean rate of hospitalization for coronary, cerebral, or peripheral ischemia per 90 days will be reported by planned treatment group. Groups will be compared using a negative binomial regression model with fixed effects for treatment, region, index MI type, index MI management, age, diabetes, PAD, prior MI, and an interaction term for index MI type and index MI management, as well as the log-transformed duration of follow-up within 90 days. The log link function will be used, and a 1-sided *P* value as well as the rate ratio (CSL112:placebo) and its 2-sided 95% CI will be reported.

Multiplicity is adjusted for in 2 ways. Inflation of type I error due to the interim efficacy analysis will be controlled using an α spending function from the P family as described. Multiplicity concerns from testing the primary and key secondary end points will be addressed using a serial gatekeeping procedure[41] for 3 defined families of null hypotheses to control the overall error rate at a 1-sided .025 level. If the primary null hypothesis (first family of hypothesis) is rejected, hypotheses associated with the second family will be tested using the Hochberg procedure at a 1-sided .025 type 1 error level. If both family 2 null hypotheses are rejected, testing will proceed to the family 3 at a 1-sided .025 level. If significance is not achieved at any step of the procedure, the formal testing process stops and any remaining secondary outcomes will be considered exploratory. A table of the 3 defined families of the null hypotheses for the serial gatekeeping procedure can be found in Supplemental Table III.

Protocol amendment

During the course of the study, it was noted that the blinded aggregate primary end point event rates were lower than anticipated. Therefore, 2 major changes were implemented that did not fundamentally alter the study purpose or patient population. The first was to enhance the risk profile of the study population to require patients to have either pharmacologically treated diabetes mellitus or any 2 or more of the other established risk factors (age $\geq$ 65 years, prior MI, or peripheral arterial disease) versus the original requirement that subjects have only 1 of these risk factors. The second modification was to expand the definition of MI within the composite primary end point to include all MIs and not just type 1 MIs as originally designed. In recognition of the limitations in the classification of MI in subtypes, which is largely based on subjective assessment, especially when distinguishing between type 1 and type 2, the aim was to reduce a potentially negative impact on sensitivity and misclassification in accounting for MI in the primary end point.[42]

Conclusions

The AEGIS-II trial is phase 3, multicenter, double-blind, randomized, placebo-controlled, parallel-group study designed to investigate the efficacy and safety of 4 weekly CSL112 infusions on short-term rates of recurrent CV events among post-AMI participants. Higher cholesterol efflux capacity is associated with a lower risk of cardiovascular events, and CSL112 improves cholesterol efflux. This phase 3 trial will test in turn whether CSL112 therefore improves the time to first occurrence of the composite of CV death, MI, or stroke through 90 days. Key secondary outcomes include the total number of hospitalizations for coronary, cerebral, or peripheral ischemia through 90 days, as well as time to first occurrence of the primary efficacy composite through 180 and 365 days. Additional information on CSL112's safety and PK/PD profile, including cholesterol efflux measurements, will also be collected. Participant enrollment began in March 2018.

Author statement

All authors have received research grant support from the sponsor of the study. D. Duffy, M. Heise, G. Berman, S. J. Mears, P. Tricoci, and L. I. Deckelbaum are

employees of CSL Behring. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper, and its final contents. All authors have materially participated in the manuscript preparation, provided critical contributions to the manuscript, and approved the final submitted version.

Acknowledgements

This study is funded by CSL Behring.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2020.10.052.

References

1. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361(11):1045-57.
2. Schwartz GG, Olsson AG, Ezekowitz MD, et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. JAMA 2001;285(13):1711-8.
3. Berwanger O, Santucci EV, de Barros ESPGM, et al. Effect of loading dose of atorvastatin prior to planned percutaneous coronary intervention on major adverse cardiovascular events in acute coronary syndrome: the SECURE-PCI randomized clinical trial. JAMA 2018;319(13):1331-40.
4. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med 2015;372(25):2387-97.
5. Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. N Engl J Med 2018;379(22):2097-107.
6. Ray KK, Cannon CP, McCabe CH, et al. Early and late benefits of high-dose atorvastatin in patients with acute coronary syndromes. J Am Coll Cardiol 2005;46(8):1405-10.
7. Goldberg RJ, Currie K, White K, et al. Six-month outcomes in a multinational registry of patients hospitalized with an acute coronary syndrome (the Global Registry of Acute Coronary Events [GRACE]). Am J Cardiol 2004;93(3):288-93.
8. Morrow DA. Cardiovascular risk prediction in patients with stable and unstable coronary heart disease. Circulation 2010;121(24):2681-91.
9. Remaley AT, Amar M, Sviridov D. HDL-replacement therapy: mechanism of action, types of agents and potential clinical indications. Expert Rev Cardiovasc Ther 2008;6(9):1203-15.
10. Tardif JC, Heinonen T, Noble S. High-density lipoprotein/apolipoprotein A-I infusion therapy. Curr Atheroscler Rep 2009;11(1):58-63.
11. Tall AR. An overview of reverse cholesterol transport. Eur Heart J 1998;19(Suppl A):A31. 35.
12. Khera AV, Cuchel M, de la Llera-Moya M, et al. Cholesterol efflux capacity, high-density lipoprotein function, and atherosclerosis. N Engl J Med 2011;364(2):127-35.
13. Rohatgi A, Khera A, Berry JD, et al. HDL cholesterol efflux capacity and incident cardiovascular events. N Engl J Med 2014;371(25):2383-93.
14. Zhang J, Xu J, Wang J, et al. Prognostic usefulness of serum cholesterol efflux capacity in patients with coronary artery disease. Am J Cardiol 2016;117(4):508-14.
15. Liu C, Zhang Y, Ding D, et al. Cholesterol efflux capacity is an independent predictor of all-cause and cardiovascular mortality in patients with coronary artery disease: a prospective cohort study. Atherosclerosis 2016;249:116-24.
16. Guerin M, Silvain J, Gall J, et al. Association of serum cholesterol efflux capacity with mortality in patients with ST-segment elevation myocardial infarction. J Am Coll Cardiol 2018;72(25):3259-69.
17. Soares AAS, Tavoni TM, de Faria EC, et al. HDL acceptor capacities for cholesterol efflux from macrophages and lipid transfer are both acutely reduced after myocardial infarction. Clin Chim Acta 2018;478:51-6.
18. Gille A, Wright SD, Tortorici M, et al. CSL112 restores cholesterol efflux in patients immediately after acute myocardial infarction. Circulation 2018;136(A16500).
19. Ray KK, Ditmarsch M, Kallend D, et al. The effect of cholesteryl ester transfer protein inhibition on lipids, lipoproteins, and markers of HDL function after an acute coronary syndrome: the dal-ACUTE randomized trial. Eur Heart J 2014;35(27):1792-800.
20. Siddiqi HK, Kiss D, Rader D. HDL-cholesterol and cardiovascular disease: rethinking our approach. Curr Opin Cardiol 2015;30(5):536-42.
21. Rader DJ. Apolipoprotein A-I infusion therapies for coronary disease: two outs in the ninth inning and swinging for the fences. JAMA Cardiol 2018;3(9):799-801.
22. Nicholls SJ, Puri R, Ballantyne CM, et al. Effect of infusion of high-density lipoprotein mimetic containing recombinant apolipoprotein A-I Milano on coronary disease in patients with an acute coronary syndrome in the MILANO-PILOT Trial: a randomized clinical trial. JAMA Cardiol 2018;3(9):806-14.
23. Zheng KH, van der Valk FM, Smits LP, et al. HDL mimetic CER-001 targets atherosclerotic plaques in patients. Atherosclerosis 2016;251:381-8.
24. Nicholls SJ, Andrews J, Kastelein JJP, et al. Effect of serial infusions of CER-001, a pre-beta high-density lipoprotein mimetic, on coronary atherosclerosis in patients following acute coronary syndromes in the CER-001 Atherosclerosis Regression Acute Coronary Syndrome Trial: a randomized clinical trial. JAMA Cardiol 2018;3(9):815-22.
25. Michael Gibson C, Korjian S, Tricoci P, et al. Safety and tolerability of CSL112, a reconstituted, infusible, plasma-derived apolipoprotein A-I, after acute myocardial infarction: the AEGIS-I trial (ApoA-I Event Reducing in Ischemic Syndromes I). Circulation 2016;134(24):1918-30.
26. Fournier N, Paul JL, Atger V, et al. HDL phospholipid content and composition as a major factor determining cholesterol efflux capacity from Fu5AH cells to human serum. Arterioscler Thromb Vasc Biol 1997;17(11):2685-91.
27. Diditchenko S, Gille A, Pragst I, et al. Novel formulation of a reconstituted high-density lipoprotein (CSL112) dramatically enhances ABCA1-dependent cholesterol efflux. Arterioscler Thromb Vasc Biol 2013;33(9):2202-11.
28. Kempen HJ, Gomaraschi M, Simonelli S, et al. Persistent changes in lipoprotein lipids after a single infusion of ascending doses of MDCO-216 (apoA-IMilano/POPC) in healthy volunteers and stable coronary artery disease patients. Atherosclerosis [Internet] 2016;255:17-24.Available from. https://doi.org/10.1016/j.atherosclerosis.2016.10.042.

29. Rye KA, Hime NJ, Barter PJ. The influence of sphingomyelin on the structure and function of reconstituted high density lipoproteines. J Biol Chem 1996;271(8):4243-50.
30. Easton R, Gille A, D'Andrea D, et al. A multiple ascending dose study of CSL112, an infused formulation of ApoA-I. J Clin Pharmacol 2014;54(3):301-10.
31. Gille A, Easton R, D'Andrea D, et al. CSL112 enhances biomarkers of reverse cholesterol transport after single and multiple infusions in healthy subjects. Arterioscler Thromb Vasc Biol 2014;34(9):2106-14.
32. Tortorici MA, Duffy D, Evans R, et al. Pharmacokinetics and safety of CSL112 (apolipoprotein A-I [human]) in adults with moderate renal impairment and normal renal function. Clin Pharmacol Drug Dev 2018;8(5):628-36.
33. Tricoci P, D'Andrea DM, Gurbel PA, et al. Infusion of reconstituted high-density lipoprotein, CSL112, in patients with atherosclerosis: safety and pharmacokinetic results from a phase 2a randomized clinical trial. J Am Heart Assoc 2015;4(8), e002171.
34. Gibson CM, Kerneis M, Yee MK, et al. The CSL112-2001 trial: safety and tolerability of multiple doses of CSL112 (apolipoprotein A-I [human]), an intravenous formulation of plasma-derived apolipoprotein A-I, among subjects with moderate renal impairment after acute myocardial infarction. Am Heart J 2018;208:81-90.
35. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. Eur Heart J 2012;33(20):2551-67.
36. Leonardi S, Lopes RD, Steg PG, et al. Implications of different criteria for percutaneous coronary intervention-related myocardial infarction on study results of three large phase III clinical trials: the CHAMPION experience. Eur Heart J Acute Cardiovasc Care 2018;7(2):158-65.
37. Leonardi S, Truffa AA, Neely ML, et al. A novel approach to systematically implement the universal definition of myocardial infarction: insights from the CHAMPION PLATFORM trial. Heart 2013;99(17):1282-7.
38. Tortorici MA, Gille A, Liss C, et al. Direct augmentation of cholesterol efflux capacity in AMI patients: a PKPD substudy of AEGIS-I. Eur Heart J 2017;38(suppl_1). August 2017, ehx502.P1106.
39. Shaw JA, Bobik A, Murphy A, et al. Infusion of reconstituted high-density lipoprotein leads to acute changes in human atherosclerotic plaque. Circ Res 2008;103(10):1084-91.
40. Murphy AJ, Funt S, Gorman D, et al. Pegylation of high-density lipoprotein decreases plasma clearance and enhances antiatherogenic activity. Circ Res 2013;113:e1-9.
41. Dmitrienko A, D'Agostino Sr RB, Huque MF. Key multiplicity issues in clinical drug development. Stat Med 2013;32(7):1079-111.
42. Gard A, Lindahl B, Batra G, et al. Interphysician agreement on subclassification of myocardial infarction. Heart 2018;104:1284-91.