Study design of Dal-GenE, a pharmacogenetic trial targeting reduction of cardiovascular events with dalcetrapib

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The objectives of precision medicine are to better match patient characteristics with the therapeutic intervention to optimize the chances of beneficial actions while reducing the exposure to unneeded adverse drug experiences. In a retrospective genome-wide association study of the overall neutral placebo-controlled dal-Outcomes trial, the effect of the cholesteryl ester transfer protein (CETP) modulator dalcetrapib on the composite of cardiovascular death, myocardial infarction or stroke was found to be influenced by a polymorphism in the adenylate cyclase type 9 (*ADCY9*) gene. Whereas patients with the AA genotype at position rs1967309 experienced fewer cardiovascular events with dalcetrapib, those with the GG genotype had an increased rate and the heterozygous AG genotype exhibited no difference from placebo. Measurements of cholesterol efflux and C-reactive protein (CRP) offered directionally supportive genotype-specific findings. In a separate, smaller, placebo-controlled trial, regression of ultrasonography-determined carotid intimal-medial thickness was only observed in dalcetrapib-treated patients with the AA genotype. Collectively, these observations led to the hypothesis that the cardiovascular effects of dalcetrapib may be pharmacogenetically determined, with a favorable benefit-risk ratio only for patients with this specific genotype. We describe below the design of dal-GenE, a precision medicine, placebo-controlled clinical outcome trial of dalcetrapib in patients with a recent acute myocardial infarction with the unique feature of selecting only those with the AA genotype at rs1967309 in the ADCY9 gene. (Am Heart J 2020;222:157-165.)

Cardiovascular (CV) diseases remain the leading cause of mortality in the world despite the current standard of care.[1] Proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors can produce very low levels of low-density lipoprotein (LDL) cholesterol and have resulted in a reduction of 15% in composite primary cardiovascular event rates.[2-4] This creates the opportunity for further improvement of clinical outcomes with non-LDL-based approaches such as those that target high-density lipoproteins (HDL) and vascular inflammation.[5]

In addition to their effect on reverse cholesterol transport, HDL particles have anti-inflammatory, anti-oxidative and anti-thrombotic effects.[6] Whether these HDL functions are altered in patients with established cardiovascular disease or after an acute coronary syndrome is not certain. However, despite raising HDL-cholesterol, the cholesteryl ester transfer protein (CETP) modulator dalcetrapib had a neutral overall effect on cardiovascular events in the dal-Outcomes study.[7] Dalcetrapib treatment also increased high-sensitivity C-reactive protein by 18%, a seemingly paradoxical effect in light of the anticipated action of HDL on inflammation. This discrepancy between the potential cardio-protective effects of HDL particles and the neutral dal-Outcomes results as well as the unexpected pro-inflammatory effect of dalcetrapib led us to hypothesize that sub-groups of patients may respond differently to this medication.[8]

The pharmacogenomic analysis of dal-Outcomes showed that the single nucleotide polymorphism

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rs1967309 in the adenylate cyclase type 9 (*ADCY9*) gene influenced the effects of dalcetrapib on CV outcomes.[9] Patients with the AA genotype benefited from a 39% reduction in the primary composite cardiovascular endpoint when treated with dalcetrapib compared to placebo, AG heterozygotes had a neutral result, while those with the GG genotype suffered a 25% increase in risk.[9] This pharmacogenomic analysis used a different primary outcome measure than the parent clinical trial. The pre-specified primary endpoint of the pharmacogenomic analysis included coronary revascularization, while the parent trial did not, in order to increase the total number of events considered. Supporting ultrasonography data from the dal-Plaque-2 study showed regression, stability and progression, respectively, of carotid atherosclerosis for each of the three genotypes (AA, AG and GG) in the dalcetrapib group.[9] Concordant findings were also obtained for the changes over time in cholesterol efflux and systemic inflammation (as evaluated by high-sensitivity C-reactive protein).[10] Indeed, the significant increase in this inflammatory biomarker with dalcetrapib occurred only in patients with the GG and AG genotypes.

Interestingly, inactivation of *Adcy9* in genetically-modified mice protects from atherosclerosis and vascular inflammation and improves endothelial function, but only in the absence of CETP.[11] The multiple observed interactions between ADCY9 and CETP both in mice and patients suggest that they represent a real biological phenomenon and not a spurious statistical association. Accordingly, we have designed and are conducting the dal-GenE study to test prospectively the hypothesis that dalcetrapib will have cardiovascular benefits when administered to patients with the favorable genotype. The study design and protocol are similar to those of dal-Outcomes, except for the genetic inclusion criterion. We describe and discuss the design of this study, as well as the statistical and logistical considerations underpinning this first large-scale cardiovascular precision medicine trial targeting atherosclerotic disease.

Methods

Study objectives

The primary study objective of dal-GenE is to prospectively test the pharmacogenetic hypothesis that dalcetrapib reduces CV morbidity and mortality (the composite of CV death, resuscitated cardiac arrest, non-fatal myocardial infarction (MI) and non-fatal stroke) in participants with a documented recent acute coronary syndrome (ACS) and the AA genotype at variant rs1967309 in the *ADCY9* gene. The secondary objective is to assess the potential of dalcetrapib to reduce other clinically important events, such as hospitalization for ACS, unanticipated coronary revascularization and worsening heart failure, in combination with the primary endpoint. Additional objectives include the confirmation of long-term safety, as well as effects on lipids, diabetes and high sensitivity C-reactive protein.

Study design

dal-GenE is a double-blind, parallel group, placebo-controlled randomized trial in patients recently hospitalized for ACS and confirmed to have the AA genotype at variant rs1967309 in the ADCY9 gene. Participants are enrolled across 819 investigational sites located in North America, South America, Europe, Middle East, Africa, Australia and New Zealand. All screened patients provide written informed consent, duly reviewed and approved by governing regulatory and ethics authorities before any study-specific procedures are performed. Screening procedures, comprised of ACDY9 genotyping conducted at one of three regionally distributed laboratory testing sites and the collection of demographic information, are performed at the time of the index ACS event or anytime thereafter, with the condition that randomization occurs within the mandated window of 1-3 months after the index event.

The investigational Cobas® ADCY9 Genotype CTA system (Roche Molecular Systems Inc.) used for centralized and controlled genetic testing has been validated for accuracy through comparisons with Sanger sequencing. This is a real-time PCR test for the qualitative detection and identification of the rs1967309 genotype in the ADCY9 gene in DNA derived from whole blood. Genetic testing results are available to the clinical research site within 4 days of the blood draw.

Those subjects meeting the genetic testing criterion, all other inclusion criteria and no exclusion criteria were eligible for randomization. Eligible subjects were stabilized on contemporary evidence-based medical care for status post-ACS as individually prescribed by the treating physician and completed all planned revascularization procedures prior to randomization. A total of 6149 eligible patients have been randomized to 600 mg of dalcetrapib or placebo daily in a 1:1 ratio. Patients continue in the trial until the time at which approximately 582 primary events will have occurred and have been positively adjudicated by an independent Clinical Endpoint Committee (CEC). Subjects visit the clinic 1 and 6 months after randomization, and visits thereafter take place every 6 months for efficacy and safety assessments until completion of the trial.

Study population

A total of 44,990 patients with recent ACS have been screened for this study in order to identify 6149 participants meeting the single genetic criterion and other inclusion/no exclusion criteria required for randomization, particularly given the overall prevalence of AA genotype at rs1967309 in the ADCY9 gene of approximately 20% in the general population.

Table I. Inclusion criteria

1. Both male and female subjects age 45 years and over at screening visit
2. Signed informed consent (approved by Institutional review Board (IRB)/Independent Ethics Committee (IEC)) obtained prior to any study specific screening procedures
3. AA genotype at variant rs1967309 in the ADCY9 gene as determined by Cobas ADCY9 Genotype CTA testing, conducted at a designated investigational testing site (ITS)
4. Clinically stable, i.e. free of ischemic symptoms at rest or with minimal exertion for at least 1 week prior to randomization
5. Prior to randomization, subject must have evidence of guidelines-based management of LDL-C, at a minimum to include medical and dietary treatment to a target level of LDL-C <100 mg/dl (<2.6 mmol/L). Subjects with an LDL-C level ≥100 mg/dl (≥2.6 mmol/L) may be randomized if they cannot reach the target goal of less than 100 mg/dl despite lipid-lowering regimen, or are unable to tolerate lipid-lowering regimen
6. Recently hospitalized for an acute coronary syndrome (between 1 and 3 months following the index event), defined as the occurrence of at least one of the following events:

6.1 Myocardial infarction

6.1.1 Spontaneous myocardial infarction

A diagnosis of a qualifying MI event is defined by a rise and/or fall of cardiac biomarkers (preferably cardiac troponin) with at least one determination greater than the 99th percentile upper reference limit (URL) plus at least one of the following described below:

6.1.1.1 Symptoms of myocardial ischemia, or
6.1.1.2 New or presumed new significant ST-segment-T wave (ST-T) changes or new left bundle branch block, or
6.1.1.3 Development of pathological Q waves in the ECG, or
6. 1.1.4 Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality, or
6.1.1.5 Identification of an intracoronary thrombus by angiography

6.1.2 Procedure-Related Myocardial Infarction after Percutaneous Coronary Intervention (PCI)

A procedure-related MI after PCI is defined as an increase of cardiac troponin values with at least one determination greater than 5 times the 99th percentile URL in patients with normal baseline values (less than or equal to 99th percentile URL) or a rise of cardiac troponin values >20% if the baseline values are elevated and are stable or falling; plus at least one of the following described below:

- Symptoms suggestive of myocardial ischemia
- New ischemic ECG changes
- Imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality
- Angiographic findings consistent with a procedural complication

6.2 Hospitalization for ACS (ECG Abnormalities without Biomarkers):

A diagnosis of a qualifying ACS event without increases in cardiac biomarkers will require admission to hospital or emergency room (exceeding 23 h) with symptoms presumed to be caused by myocardial ischemia with an accelerating tempo in the prior 48 hours and/or prolonged (at least 20 minutes) rest chest discomfort and new ECG findings (or presumed new if no prior ECG available) as described below and at least one of the following:

- at least 50% stenosis of an epicardial coronary artery
- positive exercise or pharmacologic stress indicating reversible ischemia
- presence of pathologic Q-waves on ECG

Examples of new ECG findings include:

- New or presumed new ST depression of at least 0.5 mm in at least 2 contriguous leads or T wave inversion of at least 1 mm in leads with predominant R wave or R/S >1 in at least 2 contriguous leads
- New or presumed new ST elevation at the J point in at least 2 contiguous leads with the following cut-off points: ≥0.2 mV in men and ≥0.15 mV in women in leads V2-V3 and/or ≥0.1 mV in other leads or new or presumed new left bundle branch block (LBBB)
- New tall R wave of at least 40 ms in V1 and R/S ≥1 in V1 and/or V2 with concordant positive T wave in the absence of a conduction defect
- New Q waves ≥30 ms wide and at least 1 mm deep in any 2 leads of a contriguous lead grouping or Q wave >20 ms or QS complex in leads V2 and V3 (these criteria also apply to silent MI detected during a routine follow-up visit)

Participants are randomly assigned to treatment groups in a 1:1 ratio, stratified by region and the type of ACS index event, to ensure equal numbers receive active treatment and placebo in these strata.

All enrolled participants have presented with an ACS event within the previous 1 to 3 months (Table I). In addition, all patients (male and female) included in the study are at least 45 years old, clinically stable, and have evidence of guidelines-based management of LDL-C, at a minimum including medical and dietary treatment to a target level of LDL-C <100 mg/dL (<2.6 mmol/L). Patients are excluded from participation in the trial for reasons of safety and inability to successfully and compliantly complete the trial as described in Table II. All participants included in the study receive instructions on a heart healthy diet, are counseled on appropriate life style modifications such as weight control, physical activity, and smoking cessation and receive contemporary evidence-based medical care for status post-ACS as individually prescribed by the treating physician. (See Fig. 1.)

Study endpoints

The primary endpoint of this study is the time from randomization to first occurrence of any component of the composite endpoint, which includes CV death, resuscitated cardiac arrest, non-fatal MI, and non-fatal stroke, as positively adjudicated by the clinical endpoint committee. Each component of the primary composite endpoint will also be reported. The secondary endpoints are the times from randomization to a) the composite of the primary endpoint plus hospitalization for ACS (with ECG abnormalities) or unanticipated coronary

Table II. Exclusion criteria

1. Females who are pregnant or breast-feeding
2. Women of childbearing potential (women who are not surgically sterile or postmenopausal defined as amenorrhea for >12 months) who are not using at least one method of contraception
3. New York Heart Association (NYHA) Class III or IV heart failure
4. Last known hemoglobin <10 g/dL
5. Index ACS event presumed due to uncontrolled hypertension
6. Systolic blood pressure (BP) >180 mmHg and/or diastolic blood pressure >110 mmHg by the time of randomization despite anti-hypertensive therapy
7. Last known serum triglyceride level >500 mg/dL (>5.65 mmol/L) as assessed within 6 months prior to randomization
8. Last known hemoglobin A1c (HbA1c) >10% as assessed within 6 months prior to randomization
9. Subjects with clinically apparent liver disease, e.g., jaundice, cholestasis, hepatic synthetic impairment, or active hepatitis
10. Last known ALT or AST level >3 times the upper limit of normal (ULN) or last known alkaline phosphatase level >2 times the ULN as assessed within 6 months prior to randomization (excluding index event)
11. History of persistent and unexplained creatine phosphokinase (CPK) levels >3 times the ULN as assessed within 6 months prior to randomization (excluding index event)
12. Last known serum creatinine >2.2 mg/dL (195 μmol/L) as assessed within 6 months prior to randomization
13. Previous exposure to anacetrapib or evacetrapib, or documented allergic reaction to any CETP inhibitor
14. History of malignancy (except for curatively treated basal cell or squamous cell carcinoma of the skin) during the 1 year prior to the screening
15. Any clinically significant medical condition that according to the investigator could interfere with the conduct of the study
16. Subjects whose life expectancy is shorter than 3 years
17. Presence of any last known laboratory value as evaluated prior to randomization that is considered by the investigator to potentially limit the patient's successful participation in the study
18. Current alcohol or drug abuse or history thereof within 2 years prior to screening that would likely interfere with compliance, based on investigator assessment
19. Subjects who have received any investigational drug within 1 month of randomization, or who expect to participate in any other investigational drug or device study during the conduct of this trial
20. Subjects unable or unwilling to comply with protocol requirements, or deemed by the investigator to be unfit for the study
21. Subjects who have undergone coronary artery bypass graft (CABG) between the index event and randomization

revascularization; and b) the composite of the primary endpoint plus hospitalization for new or worsening heart failure (Table III). Exploratory endpoints include changes from baseline to 6 months in blood levels of lipid subfractions and high-sensitivity C-reactive protein. Treatment safety, including effects on diabetes, is evaluated through the assessment of adverse events and laboratory measurements.

Sample size calculation

The target sample size of 6000 randomized participants was calculated assuming an expected relative risk reduction of 22% and a statistical significance defined as a two-sided alpha of 0.05. The trial will have 85% power when 582 patients have experienced a positively adjudicated primary event in the combined treatment groups assuming a 2.8-year recruitment period, a 1% yearly lost to follow-up rate, and a 7% event rate at 2 years following randomization to the placebo group. In this event-driven trial, the minimum detectable effect of dalcetrapib compared to placebo at study end will be 15%.

Statistical analyses

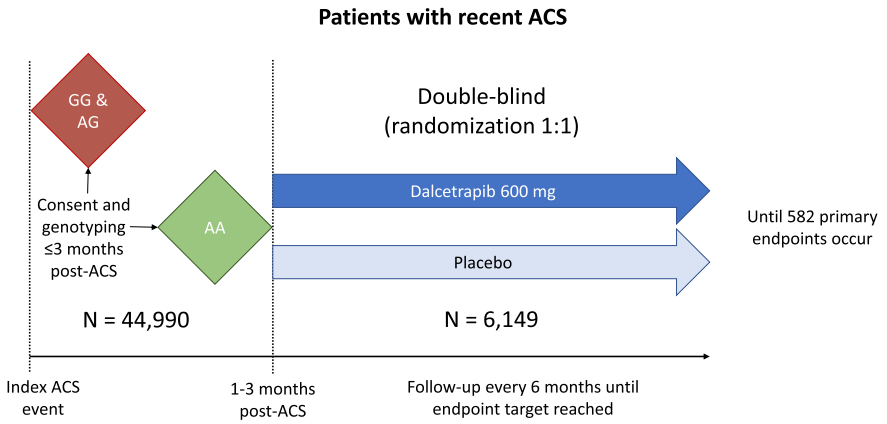
The analyses will be performed on the intention-to-treat population, which includes all randomized patients. A stratified Cox proportional hazards model will be used to analyze the primary endpoint. Time to event will start at randomization and subjects who are lost to follow-up (while event-free) will be censored at the time that they are last known to be event-free. The null (H_0) and alternative (H_A) hypotheses to be tested with the above Cox model are H_0: $\lambda = 1$ versus H_A: $\lambda \neq 1$ where λ is the assumed constant hazard ratio for the time to occurrence of the composite events of the primary endpoint for the dalcetrapib and placebo groups. The hazard ratio, within strata, will be assumed to depend on treatment alone. The analyses will be conducted at the 0.05 significance level.

Secondary endpoints are expressed as time to event and analyses similar to that for the primary endpoint will be conducted. The changes from baseline in lipid subfractions and high-sensitivity C-reactive protein levels will be compared between treatment groups using an analysis of covariance adjusting for baseline value and for the two stratification factors, ACS index event type and region. Estimates of treatment effect will be presented with 95% confidence intervals and *P*-values.

In order to control the type I error that results from the multiplicity of endpoints, the secondary endpoints will be formally tested using the Hochberg's step-up procedure only if the primary analysis results in significant treatment effect at $P < .05$. Otherwise, statistical tests for the secondary endpoints will be presented solely for illustrative purposes.

The primary and secondary efficacy endpoints will also be evaluated within subgroups of subjects using Cox proportional hazards models, adding to the models a term for the factor defining the subgroup and a term for the interaction between the factor and the treatment group. This interaction term will be tested at the 0.1 significance level and will determine whether the treatment effect is affected by the presence of the factor. In addition, under

Figure 1



Design of the dal-GenE trial.

Table III. Primary and secondary efficacy endpoints

Primary endpoint:
- Time from randomization to the first occurrence of any component of the composite endpoint which includes CV death, resuscitated cardiac arrest, non-fatal MI and non-fatal stroke, as positively adjudicated by the clinical endpoint committee
- Each component of the primary composite endpoint will also be reported

Secondary endpoints:
- Time from randomization to the first occurrence of CV death, resuscitated cardiac arrest, non-fatal MI, non-fatal stroke, or hospitalization for ACS (with ECG abnormalities) or unanticipated coronary revascularization
- Time from randomization to the first occurrence of CV death, resuscitated cardiac arrest, non-fatal MI, non-fatal stroke, or hospitalization for new or worsening heart failure

the proposed models, the treatment effect will be estimated and presented with 95% confidence intervals within subgroups.

A futility analysis will be conducted by the independent Data Safety Monitoring Board (DSMB), which will determine if there is sufficient evidence of efficacy to justify continuation of the trial to its completion. This futility assessment, performed when approximately 70% of the target number of patients with a first positively adjudicated primary endpoint is reached (which corresponds to 407 patients), will be based on the conditional power of the trial derived under various relative risk reduction assumptions.

In order to characterize further the potential treatment effect, an analysis of the primary endpoint will be conducted with the hazard ratio assumed to depend on, in addition to study treatment, the potentially prognostic factor of baseline HDL-C. The latter will be included in the stratified Cox proportional hazards model used for the primary analysis to provide an estimate of treatment effect that adjusts for HDL-C at baseline. Treatments will also be examined with respect to the incidence of adverse events, serious adverse events and adverse events leading to premature study withdrawal or dose modifications. Adverse events will be grouped and summarized by body system as defined by the latest version of the Medical Dictionary for Regulatory Activities (MedDRA), following classification of investigator assessments into MedDRA preferred terms.

The dal-GenE study is funded by DalCor Pharmaceuticals. The authors are solely responsible for the design of the study, all study analyses, the drafting and editing of the paper and its final contents.

Discussion

The consistent *ADCY9* genotype-dependent effects of the CETP inhibitor dalcetrapib on CV clinical outcomes, carotid atherosclerosis, cholesterol efflux and high-sensitivity C-reactive protein formed the basis for the launch of the dal-GenE randomized controlled trial.[8-10] Further evidence of an interplay between these two gene products was obtained from genetically-modified mice, with ADCY9 inactivation clearly protecting from atherosclerosis and vascular inflammation and improving endothelial function in the absence of CETP.[11]

A genotype-dependent result was also reported with the CETP inhibitor evacetrapib, albeit with a smaller

effect size and despite the methodological issues associated with that case-control analysis.[12] Indeed, one of the concerns was that the secondary analysis did not involve random selection of control subjects.[13] Nevertheless, a meta-analysis of the dalcetrapib and evacetrapib data yielded a relative risk reduction of 20% in CV event rates when patients with the AA genotype at rs1967309 received the CETP inhibitor compared to placebo.[14] In contrast, the effects of anacetrapib were not affected by *ADCY9* genotype in REVEAL.[15, 16] The differences in chemical structures, binding sites and functional effects of dalcetrapib and anacetrapib may at least in part explain the different pharmacogenomic results.[17] The strong CETP inhibition caused by anacetrapib reduces the fractional clearance rate of HDL's ApoA-I[18] and physiologically resembles complete CETP deficiency with its very large HDL particles.[19] In contrast, dalcetrapib causes partial CETP modulation of heterotypic transfer of cholesteryl esters between HDL and Apo-B containing lipoproteins, without affecting homotypic transfers between HDL particles.[20]

The different populations treated with dalcetrapib in dal-Outcomes[7] and anacetrapib in REVEAL (15) – 100% and 0% of patients with recent ACS respectively – might also have affected the results.

While anacetrapib induced a significant 10% relative risk reduction in the overall REVEAL study, its accumulation in fat for more than 5 years led the manufacturer to discontinue its clinical development.[16] In contrast, the safety and tolerability profile of dalcetrapib has been demonstrated with the dosage (600 mg daily) beyond which no additional pharmacodynamic benefit is obtained.[21] Accordingly, the same dosage of dalcetrapib is used in dal-GenE.

Although the analysis of patient subgroups in clinical trials is notoriously fraught with hazard, the specific group of responsive patients identified in previous dalcetrapib studies is defined by genotype and not based on a reversible, less definitive, phenotype. Nevertheless, these hypothesis-generating results require confirmation in a large study. The sample size of 6149 patients in the CV event-driven dal-genE study will allow the detection of a 15% relative risk reduction with statistical significance. This assumes a primary endpoint rate of 7% at 2 years in the placebo group based in part on dal-Outcomes, but the incidence of the myocardial infarction component could likely be higher in dal-GenE compared to the previous dal-Outcomes study because of current widespread use of the high-sensitivity troponin assay in clinical practice. The effect size of dalcetrapib in patients with the AA genotype deserves discussion. Although a relative risk reduction of 39% was observed with dalcetrapib in the dal-Outcomes discovery cohort,[9] this result may have been inflated by the so-called winner's curse, or overestimation of effect size, in initial genetic studies. As previously mentioned, a meta-analysis of pharmacogenomic results of dalcetrapib and evacetrapib yielded a 20% improvement of CV outcomes with CETP inhibition.[14] In light of the recently observed relative risk reduction of 15% in the composite primary endpoint of large-scale trials with injectable PCSK9 inhibitors,[2-4] we believe that a similar benefit obtained with oral dalcetrapib treatment on a background of standard-of-care therapies would be clinically relevant.

The dal-GenE study also represents the first combined clinical development of a new anti-atherosclerosis therapy and its companion diagnostic test. This diagnostic has been carefully tested prior to utilization in the clinical trial and is robust, and the evaluation was submitted to the authorities as part of the investigational device exemption. The risk of an incorrect result of this genetic test is less than 1 in 70,000, and this will further decrease with additional assessments over time. This is particularly important because of the increased risk associated with treating patients with the GG genotype. Genetic testing was performed at three central laboratories (including the University of Montreal Beaulieu-Saucier Pharmacogenomics Center), and results were provided within 4 days of blood draw for the approximately 44,990 patients screened in 31 countries. The execution of the dal-GenE study attests to the feasibility of performing large international pharmacogenetics-guided CV clinical trials. The importance of this demonstration lies in the emergence of precision medicine to optimize efficacy by tailoring treatment strategies to personal patient characteristics, and the necessary randomized controlled trials to prove the value of such approaches. The widespread adoption of genotyping by local research teams and participants was better than anticipated, which supports the fact that the cardiovascular field is ready for pharmacogenetic strategies.

In conclusion, the dal-GenE study is the first pharmacogenetic randomized trial targeting the reduction of cardiovascular events in patients with a recent acute myocardial infarction and a specific genotype. It is fully recruited and the results are expected by early 2021.

Disclosures

Dr Tardif has received research grant and honoraria from Amarin; research grant from Astra-Zeneca; research grant, honoraria and minor equity interest from DalCor; research grant from Esperion; research grant from Ionis; research grant and honoraria from Sanofi; research grant and honoraria from Servier; a patent on pharmacogenomics-guided CETP inhibition was obtained and Drs. Tardif and Dubé are mentioned as authors.

Dr Dubé has a minor equity interest in DalCor and has received honoraria from DalCor.

Dr Pfeffer receives research support from Novartis; he serves as a consultant for AstraZeneca, Corvidia, DalCor, GlaxoSmithKline, Jazz, MyoKardia, Novartis, Novo

Nordisk, Roche, Sanofi, Servier and Takeda; and has equity in DalCor.

Dr Waters has received remuneration for participation in clinical trial committees from CSL Ltd, Daiichi Sankyo, DalCor, the Medicines Company, Novo Nordisk, Regeneron, Resverlogix, and Sanofi, and honoraria for lectures from DalCor and Pfizer.

Dr Koenig reports personal fees (consulting) from DalCor and consulting fees from AstraZeneca, Novartis, Pfizer, The Medicines Company, Kowa, and Amgen; personal fees (honorarium for lectures) from AstraZeneca, Sanofi and Berlin-Chemie; grants and non-financial support (provision of reagents for biomarker measurements free of charge) from Roche Diagnostics, Beckmann, Singulex, and Abbott, outside the submitted work.

Dr Maggioni has received personal fees for participation in study committee from DalCor, and personal fees for participation in study committees from Bayer, Novartis and Fresenius.

Dr McMurray reports grants paid to his institution and fees as steering committee member from DalCor Pharma UK for the Dal-GenE study, during the conduct of the study; grants paid to his institution and fees as steering committee member from Oxford University and Bayer; grants paid to his institution from Theracos; grants paid to his institution and fees as steering committee from Abbvie; grants paid to his institution from Pfizer, Merck AstraZeneca, GlaxoSmithKline and Novartis.

Dr White reports grants paid to his institution and fees as steering committee member from DalCor Pharma UK for the Dal-GenE study, during the conduct of the study; grants paid to his institution and fees as steering committee member from Eli Lilly, from National Institutes of Health (USA), Omthera Pharmaceuticals, Eisai, CSL Behring, American Regent, Sanofi-Aventis Australia, and Esperion; and personal fees for interview from AstraZeneca outside the submitted work.

Drs Heinonen and Black are employed by and have equity interest in DalCor.

Other authors report no conflicts.

Appendix A. Committees

Executive Committee: Jean-Claude Tardif (Chair), Marie-Pierre Dubé, Wolfgang Koenig, Aldo P. Maggioni, John J.V. McMurray, Vincent Mooser, David Waters.

National Leaders Committee: Juhani Airaksinen, Arif Al-Nooryani, Philippe Aylward, Colin Berry, Vera Bittner, Lesley Burgess, Rafael Diaz, Ronen Durst, Emil Hagstrom, J.. Wouter Jukema, Lars Kober, Wolfgang Koenig, Bartek Krakowiak, Simon Kouz, Philippe L. L'Allier, Eran Leitersdorf, Jose Lopez-Sendon, Aldo P. Maggioni, Vyacheslav Mareev, Gerald Maurer, Béla Merkely, Michael Miller, Jan Murin, José Carlos Nicolau, Stephane Noble, Fausto J. Pinto, Francois Roubille, Philippe Gabriel Steg, Mariya Tokmakova, Dragos Vinereanu, David D. Waters, Harvey D. White, Mehmet Birhan Yilmaz

Clinical Events Committee: Peter Finn, Akshay Desai, Eldrin F. Lewis

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Appendix B. dal-GenE Investigators

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