Rationale and design of the EXenatide Study of Cardiovascular Event Lowering (EXSCEL) trial

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Exenatide once-weekly is an extended release formulation of exenatide, a glucagon-like peptide–1 receptor agonist, which can improve glycemic control, body weight, blood pressure, and lipid levels in patients with type 2 diabetes mellitus (T2DM). The EXenatide Study of Cardiovascular Event Lowering (EXSCEL) will compare the impact of adding exenatide once-weekly to usual care with usual care alone on major cardiovascular outcomes.

EXSCEL is an academically led, phase III/IV, double-blind, pragmatic placebo-controlled, global trial conducted in 35 countries aiming to enrol 14,000 patients with T2DM and a broad range of cardiovascular risk over approximately 5 years. Participants will be randomized (1:1) to receive exenatide once-weekly 2 mg or matching placebo by subcutaneous injections. The trial will continue until 1,360 confirmed *primary composite cardiovascular end points*, defined as cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke, have occurred.

The primary efficacy hypothesis is that exenatide once-weekly is superior to usual care with respect to the primary composite cardiovascular end point. EXSCEL is powered to detect a 15% relative risk reduction in the exenatide once-weekly group, with 85% power and a 2-sided 5% alpha. The primary safety hypothesis is that exenatide once-weekly is noninferior to usual care with respect to the primary cardiovascular composite end point. Noninferiority will be concluded if the upper limit of the CI is <1.30.

EXSCEL will assess whether exenatide once-weekly can reduce cardiovascular events in patients with T2DM with a broad range of cardiovascular risk. It will also provide long-term safety information on exenatide once-weekly in people with T2DM. ClinicalTrials.gov Identifier: NCT01144338 (Am Heart J 2016;174:103-10.)

Background

Type 2 diabetes mellitus (T2DM) is a growing global epidemic affecting approximately 350 million people,[1] the majority of whom will die from cardiovascular disease.[2,3] Epidemiological analyses of United Kingdom Prospective Diabetes Study data from newly diagnosed T2DM identified higher low-density lipoprotein cholesterol, lower high-density lipoprotein cholesterol, hyperglycemia, hypertension, and smoking as potentially modifiable cardiovascular risk factors.[4] However, even after adjustment for these factors, people with T2DM remain at double the cardiovascular risk as those without T2DM.[5] Although the prevalence of cardiovascular disease has declined progressively in the general population, the higher relative risk for cardiovascular disease in people with T2DM has not changed over the last 50 years.[6] It would therefore be advantageous if new glucose-lowering medications could reduce cardiovascular risk, in addition to improving glycemic control.

Exenatide (Byetta, AstraZeneca, Wilmington, DE) is the first in class glucagon-like peptide (GLP)–1 receptor agonist. It reduces glucose levels in people with T2DM by a number of mechanisms, including enhancing insulin secretion in a glucose-dependent manner, thus

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minimizing the risk of hypoglycemia in the absence of an insulin secretagogue or exogenous insulin. Exenatide has also been shown to have beneficial effects on blood pressure and blood lipids and to facilitate weight loss.[7-11] Mechanistic data suggest that exenatide can improve cardiac function in patients with chronic heart failure,[12] improve endothelial dysfunction,[13] and reduce infarct size after ST-segment elevation myocardial infarction.[12,14] A patient-level integrated meta-analysis showed no evidence for increased cardiovascular disease risk with use of exenatide in subjects with T2DM,[15] whereas a retrospective analysis of a medical and pharmaceutical insurance claims database found a lower relative cardiovascular disease risk associated with exenatide treatment than with other glucose-lowering drugs.[16] A small increase in heart rate has been observed with GLP-1 receptor agonists, which appears to be a class effect.[17]

The EXenatide Study of Cardiovascular Event Lowering (EXSCEL) will evaluate the effect of a once-weekly formulation of exenatide (Bydureon)[18] on major cardiovascular events when given in addition to usual care.

Study design

Overview

EXSCEL is a multinational, placebo-controlled, double-blind, parallel-group pragmatic trial randomizing patients with T2DM to receive once-weekly exenatide or matching placebo (unloaded microspheres), in addition to their usual care (Figure). It will assess the impact of once-weekly exenatide therapy in approximately 14,000 patients, with or without known cardiovascular disease, from heterogeneous practice environments in 35 countries from North and South America, Europe, Africa, Asia, and Australasia. EXSCEL is planned to continue until 1,360 patients with a confirmed *primary composite cardiovascular end point* (defined as cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) have been accrued or until the independent Data Safety Monitoring Board (DSMB) recommends otherwise. All patients who prematurely discontinue study treatment should continue subsequent study visits and posttreatment follow-up evaluations.

The sponsor of the trial, AstraZeneca, participated in the design of the trial and protocol in collaboration with the academic members of the executive committee. The sponsor was responsible for submission of the protocol for approval by national regulatory authorities. The sponsor had no role in data collection, in data analysis, or in the decision to submit the manuscript for publication. The authors are solely responsible for the drafting and editing of the article and its final contents.

Trial population

Adults with T2DM, with or without additional cardiovascular risk factors or prior cardiovascular events, are eligible if their usual care hemoglobin A1c (HbA1c) is 48 mmol/mol to 86 mmol/mol (6.5% to 10.0%) inclusive. Study participants can be treated with up to 3 oral glucose-lowering drugs of any type or insulin (alone or in combination with up to 2 oral glucose-lowering drugs). Detailed inclusion and exclusion criteria and the rationale for their selection are outlined in Supplementary Appendix A. During the trial, patients will still be managed by their usual care provider and treated according to local standards of care for diabetes and cardiovascular risk factor management. They will attend study clinics only for provision of study medication and follow-up. In some cases, the site investigator may also be the usual care provider.

Study drug

Patients will be allocated centrally at random in a 1:1 ratio to receive once-weekly subcutaneous injections of exenatide (Bydureon) 2 mg or matching placebo stratified by whether or not they have a history of cardiovascular disease. Once-weekly exenatide was approved for the treatment of patients with T2DM by the European Medicines Agency in 2011 and the United States Food and Drug Administration (FDA) in 2012. It acts by augmenting insulin secretion and reducing glucagon secretion in a glucose-dependent manner.[19] Once-weekly exenatide was developed by encapsulating exenatide in microspheres of a biodegradable polymer, resulting in sustained drug delivery over a period of weeks after subcutaneous injection.[18]

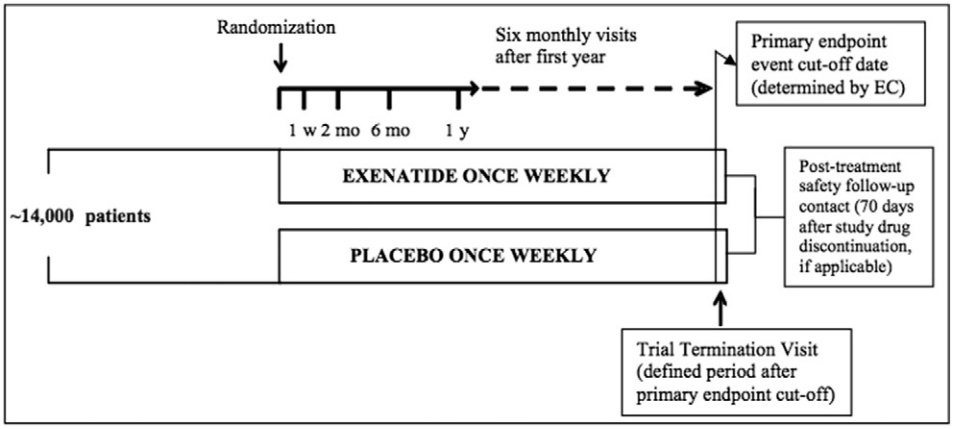
Concurrent glycemic therapy

It is expected that patients will see their usual care provider at least twice per year for routine care. Although there is no requirement to achieve glycemic equipoise between the 2 randomized groups, it is anticipated that there will be little or no between-group difference in achieved glucose levels during the double-blind treatment period, as diabetes therapy will be adjusted by the usual care providers according to local guidelines. This can involve the addition or substitution of any glucose-lowering therapies, including insulin, but excluding GLP-1 receptor agonists. Concomitant medication changes are permitted at any time, but unless there are safety concerns, usual care providers will be asked to avoid them immediately after randomization while HbA1c levels are reflecting the initial effect of study medication.

Treatment protocol and follow-up

EXSCEL is a pragmatic trial[20] designed to investigate the effectiveness of once-weekly exenatide with a view to providing generalizable results. The entry criteria are consistent with the range of patients who might receive once-weekly exenatide in routine clinical practice, including those at high and moderate cardiovascular risk.

Figure



Design of the EXSCEL trial: It is planned to continue until 1,360 patients with a confirmed primary composite cardiovascular end point have been accrued.

To minimize interference with usual care, the number of monitoring visits will be limited. Patients will be trained at randomization to self-administer once-weekly exenatide and seen at 1 week to have their self-injection observed. Subsequently, patients will be seen at 2 months, 6 months, and every 6 months thereafter until study close out (Figure).

At all visits postrandomization, there will be an assessment of clinical events and serious adverse events, as well as a review of concomitant medication and adherence to study medication. At annual visits, additional procedures will include ascertainment of blood pressure, body weight, and heart rate; and the most recent HbA1c, lipid profile, and serum creatinine data will be ascertained opportunistically from local laboratory usual care records. Patients will also be asked to complete a standardized self-reported health status questionnaire (European Quality of Life-5 Dimensions).[21] The first patient was randomized on 18 June 2010, and follow-up will continue until a total of 1,360 patients with an adjudicated and confirmed primary composite cardiovascular outcome have been accrued.

Primary outcomes

The EXSCEL primary efficacy hypothesis is that once-weekly exenatide is superior to usual care with respect to the adjudicated primary composite cardiovascular end point. The primary safety hypothesis is that once-weekly exenatide is noninferior to usual care with respect to the adjudicated primary cardiovascular composite end point.

Secondary outcomes

Adjudicated secondary end points are all-cause mortality, the individual components of the primary composite cardiovascular outcome (cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke), hospitalization for acute coronary syndrome, and hospitalization for heart failure (Supplementary Appendix B lists all secondary and exploratory efficacy end points).

Participant safety

Adverse events will be monitored over the course of the trial, starting from the time of randomization and through the duration of the patient's participation, including the 70-day posttrial medication follow-up period. In this pragmatic trial, only adverse events that are serious or lead to discontinuation of study medication will be recorded. EXSCEL will use both patient- and investigator-directed education to minimize the risk of hypoglycemia. Symptoms and appropriate management of hypoglycemia will be reviewed at all study visits. Usual care providers will be responsible for the adjustment of concomitant therapy. Two or more severe episodes (hypoglycemia requiring assistance) between visits, despite appropriate titration of glucose-lowering therapies, will trigger permanent discontinuation of study medication.

Patients with an estimated glomerular filtration rate (eGFR) <30 mL/(min 1.73 m^2) (calculated using Modification of Diet in Renal Disease–4)[22] will be excluded because exenatide is renally excreted.[23] During the trial, patients with 2 successive values less than this eGFR threshold will be discontinued from study medication. If a usual care annual creatinine value is not available, it will be measured by the site to support patient safety.

In view of concerns raised in animal studies about a possible increase in thyroid C-cell adenomas and carcinomas,[24,25] the FDA has requested that calcitonin be assayed by a central laboratory at screening and annually thereafter. These will be scrutinized centrally. If the screening value is >40 ng/L or a subsequent annual value

is ≥50 ng/L, study medication will be permanently discontinued and the patient referred for clinical evaluation.

Statistical considerations

Sample size and power calculations

The sample size was estimated initially to be 9,600, assuming an annual 3.8% primary composite cardiovascular end point event rate, 1% annual lost to follow-up rate, 5% annual study drug discontinuation rate, and with a 60:40 ratio of those with or without a history of cardiovascular disease. Given that the observed (blinded) overall primary end point event rate to date was lower than expected, the sample size was increased to 14,000 in 2013, and the proportion of patients with history of cardiovascular disease at entry increased to approximately 70%. The power to assess the primary safety objective of noninferiority of once-weekly exenatide compared with placebo will be >90%.

Analysis plan

Kaplan-Meier curves for time to the first occurrence of a primary composite end point event will be used to depict the accumulation of events over time for the once-weekly exenatide and placebo treatment groups. The hazard ratio comparing the time to first occurrence of the primary composite end point event for the once-weekly exenatide-treated group with that of the placebo-treated group and its 95% CI will be estimated using a Cox proportional hazards model stratified by baseline and cardiovascular risk group (prior cardiovascular event or no prior cardiovascular event) and using treatment group as a covariate. Proportionality of the hazards over time by randomized treatment group will be tested.

The primary efficacy hypothesis of superiority will be assessed by a superiority analysis in the intent-to-treat (ITT) population. Superiority will be concluded if the upper limit of the 95% CI is <1.00. Appropriate alpha adjustment will be made for the 2 formal interim efficacy analyses that will be performed by the independent DSMB statistician. These are planned to occur after approximately one-third and two-thirds of the 1,360 primary composite cardiovascular events required have been adjudicated.

The primary safety hypothesis will be assessed by a noninferiority analysis in the ITT population. Noninferiority will be concluded if the upper limit of the 95% CI is <1.30, as per the 2008 FDA Guidance.[26] Secondary and exploratory efficacy end points (Supplementary Appendix B) will be analyzed individually in the ITT population. Prespecified subgroup analyses for the primary composite cardiovascular outcome are listed in Supplementary Appendix C.

Biomarker and genetic assessments

Two optional substudies are included in EXSCEL for the first 9,600 patients to be recruited. A genetic substudy aims to collect whole blood samples at baseline for future genetic research, and a biomarker substudy will collect urine and blood samples before study drug exposure and annually thereafter for proteomic and metabolomic research. Separate consent will be obtained for each of these substudies.

Health economic analysis

EXSCEL will collect physician-reported data on resource use and patient-reported quality of life to undertake cost-effectiveness analyses relevant to the countries taking part in the study. Resource use data on hospitalizations, visits, and medications will be combined with appropriate national unit costs to calculate a cost per patient per year. Quality of life data will be combined with survival data to calculate quality-adjusted time in the trial per patient.

Study organization

EXSCEL is run jointly by 2 academic research organizations, the Duke Clinical Research Institute (Durham, NC) and the University of Oxford Diabetes Trials Unit (Oxford, UK), in an academic collaboration with pharmaceutical companies. Amylin Pharmaceuticals Inc (San Diego, CA) was the original sponsor, later joined in an alliance with Eli Lilly and Company (Indianapolis, IN). Subsequently, sponsorship transitioned to Bristol-Myers Squibb (Princeton, NJ) and AstraZeneca (Gaithersburg, MD) with the acquisition of Amylin by Bristol-Myers Squibb and has now transitioned to AstraZeneca alone, with Amylin being a wholly owned subsidiary of AstraZeneca.

Overall responsibility for the oversight and management of the trial lies with the EXSCEL Executive Committee, which is composed of 11 individuals, comprising 9 senior independent academic representatives who are experts in their field and 2 sponsor representatives. A clinical events committee (CEC), blinded to treatment allocation and consisting of physicians including endocrinologists, cardiologists, and oncologists, will adjudicate all components of the primary composite cardiovascular outcome, secondary end points, and all cases of neoplasm and pancreatitis. The EXSCEL DSMB, comprising independent statisticians and specialists in diabetology, cardiovascular medicine, gastroenterology, and endocrine neoplasia, is responsible for active surveillance of safety data including all cases of neoplasm and pancreatitis. Members of the executive committee, CEC, and DSMB are listed in Supplementary Appendix D.

Ethical considerations

The EXSCEL trial complies with the Declaration of Helsinki, its subsequent revisions, and Good Clinical Practice Guidelines. Institutional review board approval has been obtained for all sites, and subjects sign informed consent before any study procedures commence. EXSCEL is registered on www.clinicaltrials.gov (NCT01144338).

Discussion

The EXSCEL trial will determine whether once-weekly exenatide, on top of usual diabetes care, reduces cardiovascular events in patients with T2DM compared with usual diabetes care without a GLP-1 receptor agonist.

EXSCEL is the largest GLP-1 receptor agonist cardiovascular outcome trial to date, recruiting 14,000 participants, and differs from other ongoing studies in a number of respects. Designed from the outset to test for superiority for the primary composite cardiovascular outcome, it will follow participants for up to 7 years with an expected median >3 years. EXSCEL will have around 30% of patients with no history of prior cardiovascular disease to permit evaluation of possible primary, as well as secondary, cardiovascular risk reduction. By contrast, the ELIXA trial using lixisenatide (NCT01147250) involves only patients with a recent history of acute coronary syndrome, whereas the REWIND trial using dulaglutide (NCT01394952) requires prior cardiovascular disease or the presence of at least 2 cardiovascular risk factors. Similarly, the SUSTAIN trial using semaglutide (NCT01720446) requires the presence of subclinical or overt cardiovascular disease. The LEADER trial using liraglutide (NCT01179048) uses a standardized recommendation for the treatment of risk factors.

A patient-level integrated meta-analysis has showed no evidence for an increased cardiovascular disease risk associated with the use of exenatide twice-daily in subjects with T2DM,[15] whereas a retrospective analysis of a medical and pharmaceutical insurance claims database found a lower relative cardiovascular disease risk associated with exenatide twice-daily treatment than with other glucose-lowering drugs.[16] However, these database studies have several limitations including their retrospective nature, short duration, low baseline cardiovascular risk in the populations observed, and low cardiovascular disease event rates. These prior studies, while promising, are insufficient in establishing the cardiovascular safety and efficacy of exenatide once-weekly in a population at increased risk of cardiovascular disease. Since EXSCEL was designed, 2 cardiovascular safety studies of dipeptidyl peptidase–4 (DPP-4) inhibitors saxagliptin[27] and alogliptin[28] have reported noninferiority to placebo with respect to their primary cardiovascular safety outcomes.

There are several mechanisms whereby once-weekly exenatide could potentially have a beneficial effect on cardiovascular outcomes. It improves hyperglycemia and other cardiovascular risk factors such as blood pressure, lipids, and body weight without increasing the risk of hypoglycemia.[7-11] In addition, further pleiotropic effects on the cardiovascular system, through both GLP-1 receptor–mediated and other mechanisms, have been suggested.[29] Studies in animal models suggest beneficial effects of GLP-1 on atherogenesis by inhibiting the inflammatory response in macrophages and endothelial adhesion[30] and modulating endothelial function.[31,32] Further cardioprotective effects, by means of increased coronary flow,[29] reduced myocardial infarct size,[33] and improved left ventricular function, have also been suggested by animal data.[30,34] Human mechanistic studies are consistent with these findings demonstrating an improvement in flow-mediated vasodilation in the postprandial state,[13] reduced infarct size in patients with ST-segment elevation myocardial infarction,[12,14] and an improvement in left ventricular ejection fraction in patients with heart failure.[35] These data together justify the conduct of a large-scale, adequately powered outcome trial testing for the superiority of a diabetes treatment regimen containing once-weekly exenatide on cardiovascular outcomes.

Safety considerations

Studies with supratherapeutic GLP-1 receptor agonist doses in rodents have shown an increase in thyroid C-cell adenomas and carcinomas.[24,33] In contrast to rodents, GLP-1 receptor expression on primate thyroid C-cells is very low, and no changes have been observed with in vitro stimulation of human C-cells by GLP-1 receptor agonists.[10,24] Patients with a personal or family history of medullary thyroid cancer or multiple endocrine neoplasia type 2 will be excluded from ESXCEL. Patients randomized into EXSCEL will have their study medication discontinued if their screening calcitonin value is >40 ng/L or subsequent annual values are ≥50 ng/L.

Concerns have been raised about the potential association of incretin-based therapies with pancreatitis and pancreatic cancer.[36,37] Any putative cases of pancreatitis or neoplasm of any type reported in EXSCEL participants will be captured as clinical events of interest and adjudicated. These data, along with observations from other long-term studies, will contribute to clarifying the risk-benefit analysis of these therapies.

As once-weekly exenatide is cleared by renal filtration and subsequent tubule degradation,[23] patients with an eGFR <30 mL/(min 1.73 m^2) will be excluded, and study medication will be discontinued in those whose eGFR falls below this value on 2 successive measurements.

The recently reported results of the SAVOR TIMI 53 trial showed an unexpected but statistically significant

27% increased relative risk for hospitalization for congestive heart failure with saxagliptin, a DPP-4 inhibitor.[26] Although the mechanism of action of DPP-4 inhibitors differs from that of GLP-1 receptor agonists, hospitalization for congestive heart failure is a prespecified EXCSEL secondary outcome, with all putative events adjudicated by the CEC and reviewed regularly in an unblinded manner by the DSMB.

Challenges

More than a dozen concurrent cardiovascular outcome trials are currently ongoing, aiming to collectively enroll in excess of 100,000 patients with T2DM,[38] creating a competitive environment for recruitment. In addition, the increasing availability of open-label once-weekly exenatide and other GLP-1 receptor agonists further constrains the number of eligible participants.

Retaining participants in EXSCEL and achieving high concordance with an injectable therapy create a challenge, especially as 50% of participants will receive placebo injections for a number of years. However, all patients who prematurely discontinue study treatment will be encouraged to continue subsequent study visits and posttreatment follow-up evaluations.

Conclusion

In summary, EXSCEL is an ongoing multinational, double-blind, placebo-controlled, randomized trial of once-weekly exenatide that will provide important data on its long-term cardiovascular safety and potential cardiovascular benefit. Given its pragmatic design, inclusion of patients with a broad range of cardiovascular risk, and no restrictions on concomitant glucose-lowering therapies (other than GLP-1 receptor agonists), the trial is expected to provide results that are generalizable and directly transferable to daily patient care.

Conflicts of interest

R.R.H. has received research support from Bayer, BMS, and Merck; attended advisory boards with Amgen, Bayer, Elcelyx, Merck, Novartis, and Novo Nordisk; and given lectures supported by Bayer.

M.A.B. has received research funding from Novartis and Bayer.

J.G. has received consulting fees, speaker fees, travel expenses, and/or research support from Amylin, AstraZeneca, Boeringher Ingelhiem, Bristol-Myers Squibb, Lilly, Merck Sharp & Dohme, Novo Nordisk, Sanofi, and Takeda.

A.F.H. has received research grants from AstraZeneca, Bristol-Myers Squibb, Janssen, and Novartis and honoraria from Bristol-Myers Squibb and Janssen.

H.S. (none).

Z.D. (none).

J.K. (none).

N.S.K. is an employee and stockholder of AstraZeneca.

R.J.M. received research support from AstraZeneca, Bristol-Myers Squibb, and Novartis.

A.O. (none).

J.B.B. is an investigator and/or consultant without any direct financial benefit under contracts between his employer and the following companies: Amylin Pharmaceuticals, Inc, Andromeda, Astellas, Astra Zeneca, Bayhill Therapeutics, Inc, Boehringer Ingelheim GmbH & Co KG, Bristol-Myers Squibb Company, Catabasis, Cebix, Inc, CureDM, Diartis Pharmaceuticals, Elcelyx Therapeutics, Inc, Eli Lilly and Company, Exsulin, Genentech, GI Dynamics, GlaxoSmithKline, Halozyme Therapeutics, F. Hoffmann-La Roche, Ltd, Intarcia Therapeutics, Johnson & Johnson, Lexicon, LipoScience, Macrogenics, Medtronic, Merck, Metabolic Solutions Development Co, Metabolon, Inc, Metavention, Novan, Novo Nordisk A/S, Orexigen Therapeutics, Inc, Osiris Therapeutics, Inc, Pfizer, Inc, Quest Diagnostics, Rhythm Pharmaceuticals, Sanofi, Spherix, Inc, Takeda, ToleRx, Transpharma Medical Ltd, TransTech Pharma, Veritas, and Verva. He is a paid consultant to PhaseBio Pharmaceuticals Inc and has received stock options for that effort.

J.C.C. received research grant and/or honoraria for consultancy and/or giving lectures from AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Merck Sharp & Dohme, Novo Nordisk, Pfizer, and/or Sanofi. All proceeds have been donated to the Chinese University of Hong Kong to support research and education. The Chinese University of Hong Kong has received research grants and sponsorships from these companies.

N.I. is an employee and stockholder of Bristol-Myers Squibb.

S.K. is an employee and stockholder of Bristol-Myers Squibb.

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S.P.M. reports grants from The Medicines Company, Novo Nordisk, Abbott Vascular, Amylin Pharmaceuticals, Boston Scientific, Volcano Corporation, and Terumo Medical. He has received consulting fees from Novo Nordisk and St. Jude Medical.

P.Ö. is an employee and stockholder of AstraZeneca.

M.J.P. reports institutional research grants from AstraZeneca and Merck and consulting/honoraria from Theracos (DSMB member).

N.P. has received research grants from Servier and speaking honoraria from Servier, Novo Nordisk, and Amgen.

L.E.P. was an employee and stockholder of Amylin Pharmaceuticals at the time of trial initiation.

A.R. received remuneration for Advisory board meetings from Merck, Sharp & Dohme, and AstraZeneca; honoraria for lectures from Bayer, Novo Nordisk, Eli Lilly, Merck, Sharp & Dohme, and Novartis; and research grant from Merck, Sharp & Dohme.

B.Z. reports grants support from Merck, Boehringer Ingelheim, and Novartis. He serves on medical advisory boards for Eli Lilly, Merck, Novo Nordisk, Janssen, Takeda, and Astra Zeneca.

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Appendix. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ahj.2015.12.009.

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