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Effect of selective BET protein inhibitor apabetalone on cardiovascular outcomes in patients with acute coronary syndrome and diabetes: Rationale, design, and baseline characteristics of the BETonMACE trial

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Background After an acute coronary syndrome (ACS), patients with diabetes remain at high risk for additional cardiovascular events despite use of current therapies. Bromodomain and extra-terminal (BET) proteins are epigenetic modulators of inflammation, thrombogenesis, and lipoprotein metabolism implicated in atherothrombosis. The BETonMACE trial tests the hypothesis that treatment with apabetalone, a selective BET protein inhibitor, will improve cardiovascular outcomes in patients with diabetes after an ACS.

Design Patients (n = 2425) with ACS in the preceding 7 to 90 days, with type 2 diabetes and low HDL cholesterol (≤40 mg/dl for men, ≤45 mg/dl for women), receiving intensive or maximum-tolerated therapy with atorvastatin or rosuvastatin, were assigned in double-blind fashion to receive apabetalone 100 mg orally twice daily or matching placebo. Baseline characteristics include female sex (25%), myocardial infarction as index ACS event (74%), coronary revascularization for index ACS (80%), treatment with dual anti-platelet therapy (87%) and renin-angiotensin system inhibitors (91%), median LDL cholesterol 65 mg per deciliter, and median HbA1c 7.3%. The primary efficacy measure is time to first occurrence of cardiovascular death, non-fatal myocardial infarction, or stroke. Assumptions include a primary event rate of 7% per annum in the placebo group and median follow-up of 1.5 years. Patients will be followed until at least 250 primary endpoint events have occurred, providing 80% power to detect a 30% reduction in the primary endpoint with apabetalone.

Summary BETonMACE will determine whether the addition of the selective BET protein inhibitor apabetalone to contemporary standard of care for ACS reduces cardiovascular morbidity and mortality in patients with type 2 diabetes. Results are expected in 2019. (Am Heart J 2019;217:72-83.)

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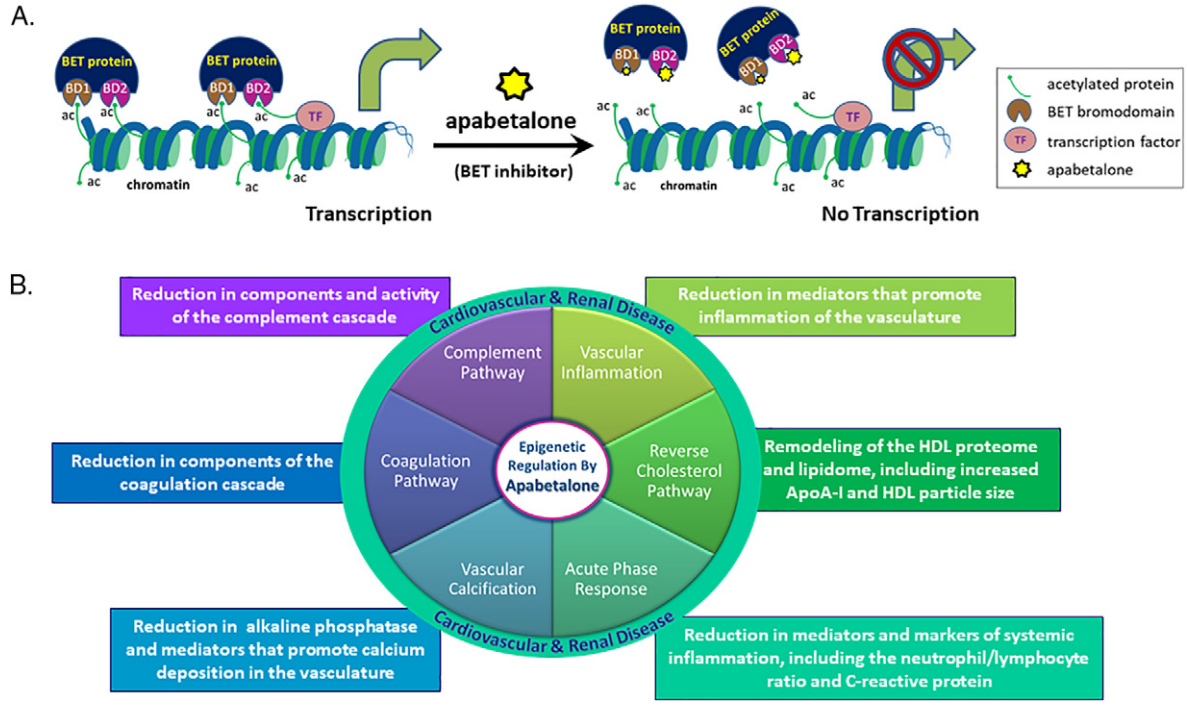
Figure 1



Schematic representation of apabetalone's mechanism of action at an epigenetic level and resultant effects on proteins and pathways relevant to atherosclerosis, renal disease and vascular dementia.A, BET proteins bind acetylated lysine (ac) on histones or transcription factors (TF) via bromodomains (BD), and recruit transcriptional machinery to drive expression of BET sensitive genes. Gene transcription is represented by the large green arrow. Apabetalone targets bromodomains in BET proteins, causing release from chromatin and downregulation of BET-sensitive gene transcription. Yellow star size indicates selectivity of apabetalone for bromodomain 2 (BD2).B, Inhibition of transcription by a BET inhibitor may affect multiple pathways and mediators underlying cardiovascular, renal disease, and cognition, including reductions in components and activity of the complement and coagulation cascades, attenuation of systemic and vascular inflammation and vascular calcification, and beneficial effects on reverse cholesterol transport via the HDL proteome and lipidome.

Despite application of contemporary evidence-based therapies including prompt coronary revascularization, dual anti-platelet therapy, and intensive lipid lowering, major adverse cardiovascular events (MACE) recur with high frequency after an acute coronary syndrome (ACS). This risk is particularly high among patients with type 2 diabetes (T2DM), who comprise approximately one third of ACS cases.[1-3] Although patients with ACS and T2DM derive substantial absolute benefit from intensive lipid lowering,[4,5] their residual risk remains higher than for patients with ACS without T2DM. Although recent placebo-controlled trials have demonstrated cardiovascular efficacy of glucagon-like peptide-1 receptor agonists or sodium-glucose cotransporter-2 (SGLT2) inhibitors in patients with T2DM and established cardiovascular disease,[6] no diabetes medication has been shown to reduce MACE in patients with recent ACS. Trials that evaluated the GLP1 receptor agonist lixasenatide,[7] the dipeptidyl peptidase 4 inhibitor alogliptin,[8] or the peroxisome proliferator-activated receptor alpha and gamma agonist aleglitazar[9] showed neutral cardiovascular outcomes compared with placebo in patients with T2DM and ACS, and no trial has evaluated an SGLT2 inhibitor after ACS. Thus, there remains an unmet need for new therapies to mitigate cardiovascular risk in this population.

Heightened inflammation and a pro-oxidative and thrombogenic milieu are contributory factors in the pathogenesis of atherosclerosis and ACS and are increased among those with T2DM.[10] Bromodomain and extraterminal (BET) proteins are a family of four epigenetic readers (BRD2, BRD3, BRD4 and BRDT) that regulate gene transcription. BET proteins have two bromodomains (BD1 and 2) that bind acetylated lysines on transcription factors and chromatin with high affinity[11] and are recruited through these interactions to the promoters and enhancers of genes that control cell identity, differentiation, and proliferation.[12] On the promoters and enhancers, the BET proteins act as a scaffold, binding positive transcription elongation factor

b to stimulate RNA polymerase II dependent transcription of the proximal genes.[13,14] Many diseases, however, alter acetylation markers, directing BET proteins to inappropriate genes. BRD4, the most characterized BET protein family member, is known to redistribute to the enhancers and promoters of genes that drive pathologic processes including cancer, fibrosis, autoimmunity, inflammation, and thrombogenesis.[12,15-19] Notably, inflammation is increasingly recognized as a driver of atherosclerosis through BRD4-dependent epigenetic dysregulation.[16,20] Epigenetic modulation of inflammation and thrombosis may be particularly important in the pathogenesis of cardiovascular events in type 2 diabetes.[21]

BET inhibitors are small molecule epigenetic modifiers with therapeutic potential in several disease states including atherosclerosis. BET inhibitors bind to BET bromodomains, preventing their interaction with acetylated lysines.[11,14,22] Apabetalone is a BET inhibitor that selectively targets the BD2 bromodomain with 20 to 30-fold selectivity over BD1[23,24] (Figure 1A). BD2 selective binding results in differential effects on transcription when compared to the pan BET inhibitor, JQ1, which targets both bromodomains with equal affinity.[23-25] Apabetalone was originally developed as a lipid modifying agent, based on preclinical observations that it induced hepatic synthesis of apolipoprotein (apo) A-I and enhanced cholesterol efflux capacity of high-density lipoprotein (HDL) particles.[26] Subsequently, it was shown that apabetalone has the potential to modulate a variety of pathways and processes involved in atherothrombosis (Figure 1B), including the repression of immune, inflammatory and pro-atherosclerotic genes in ex vivo treated human whole blood cells and reduction in the severity of atherosclerosis in hyperlipidemic ApoE deficient mice.[27-29] Prophylactic and therapeutic treatment with apabetalone significantly reduced aortic lesion formation and lowered levels of circulating adhesion molecules and cytokines in hyperlipidemic apoE−/− mice. Apabetalone also impacts gene transcription within the acute phase response,[27,30] complement and coagulation[29] pathways in primary human hepatocytes, and vascular calcification in vascular smooth muscle cells.[31]

Three placebo-controlled Phase 2 trials comprising a total of 798 patients evaluated the effects of 3 to 6 months of treatment with apabetalone (50-150 mg orally twice daily) on lipid parameters, coronary atherosclerosis, and safety.[32-34] A pooled analysis of these trials showed that apabetalone increased apolipoprotein A-I and high-density lipoprotein cholesterol (HDL-C) up to approximately 6% and large HDL particles up to 23% (all $P < .001$) and decreased in high sensitivity C-reactive protein by −21.1% ($P = .04$). In 323 patients with angiographic coronary artery disease randomized 3:1 to apabetalone 100 mg twice daily or placebo and followed for 26 weeks, there was no difference between groups in percent atheroma volume assessed by serial intravascular ultrasound. However, in pooled analysis of the Phase 2 trials, the incidence of death, myocardial infarction, coronary revascularization, or hospitalization for cardiovascular causes was reduced with apabetalone compared with placebo (5.9% vs 10.4%, $P = .02$). Event reduction with apabetalone compared with placebo appeared to be more prominent in patients with conditions associated with BET system activation such as T2DM (5.4% vs 12.7%, P = .02), elevated high sensitivity C-reactive protein levels (5.4 vs 14.2%; $P = .02$), and low baseline HDL cholesterol (HDL-C) <39 mg/dL (5.5% vs 12.8%, $P = .01$).[34] These findings suggest that although apabetalone did not modify plaque volume over a period of 6 months, there may have been a favorable effect on plaque stability.

Among 556 patients randomized to apabetalone, alanine aminotransferase (ALT) elevation to more than 3 times upper limit of normal was observed in approximately 8%, compared with none of the 242 patients receiving placebo. ALT elevation usually occurred between 4 and 12 weeks of exposure to apabetalone, with rapid normalization to baseline levels either with ongoing treatment (when maximum transaminase elevation was <5 times upper limit of normal) or upon cessation of treatment (when maximum ALT level was >8 times upper limit of normal), as specified in the study protocols.

A post hoc analysis of the two longer duration phase 2 trials demonstrated that apabetalone increased the estimated glomerular filtration rate in participants with chronic kidney disease (CKD) and lowered alkaline phosphatase in a dose-dependent manner over 24 to 26 weeks, compared with placebo.[35] The former finding led to the hypothesis that epigenetic modulation by BET inhibition may potentially offer a novel therapeutic strategy to treat both cardiovascular disease and progressive kidney function loss in patients with CKD. In CKD patients, a single dose of apabetalone reduced circulating cytokines and acute phase response proteins within 12 hours of treatment.[36] Alkaline phosphatase is an inflammatory biomarker that is associated with vascular calcification,[37] incident coronary heart disease,[38] small vessel cerebrovascular disease,[39] and stroke,[40] and predicts death in patients with cardiovascular disease.[41] Its levels are elevated in both brain and plasma in Alzheimer's disease[42] and may promote the neurotoxicity of tau protein.[43]

This might have particular importance in patients with cardiovascular disease and T2DM, among whom vascular cognitive dementia is prevalent.

Based on the preclinical data described above and the pooled results of Phase 2 clinical trials with apabetalone, the BETonMACE trial was designed to test the hypothesis that apabetalone, compared with placebo, reduces cardiovascular mortality and morbidity with acceptable safety in patients with recent ACS, T2DM, and low HDL-C

Table I. Inclusion and principal exclusion criteria

Inclusion criteria:
- Age ≥18 years
- Acute coronary syndrome (unstable angina or acute myocardial infarction) 7-90 days prior to the screening visit. The number of subjects qualifying based on unstable angina is limited to 25% of the total number of subjects.
  - Qualifying unstable angina requires all of the following to be satisfied:
    - Ischemic pain or discomfort in chest or associated referral areas at rest or with minimal exertion
    - ECG changes with new or presumed new ST elevation, ST depression, or T-wave inversion
    - Objective evidence of obstructive coronary artery disease based upon new or presumed new evidence of myocardial ischemia or infarction by perfusion imaging, regional wall motion abnormality, epicardial coronary artery stenosis ≥70% by coronary angiography, need for coronary revascularization for the index ACS event.
  - Qualifying acute myocardial infarction requires two of the following three criteria to be satisfied:
    - Characteristic ischemic chest pain or pain in associated referral areas
    - Elevation of troponin T, troponin I, or creatine kinase MB isoform above the upper limit of normal for the laboratory
    - Development of new Q-waves in at least two adjacent ECG leads, or development of a new dominant R wave in V1
- Type 2 diabetes, requiring at least one of the following criteria to be met:
  - Documented history of type 2 diabetes
  - History of taking diabetes medication
  - Hemoglobin A1c ≥6.5% at the screening visit
- Low HDL cholesterol [<40 mg/dL (1.04 mmol/L) for males; <45 mg/dL (1.17 mmol/L) for females at the screening visit.
- Ability to initiate or continue high intensity atorvastatin or rosuvastatin therapy.
- For women of childbearing potential, negative urine pregnancy test and willingness to maintain medically reliable non-hormonal contraceptive therapy or abstinence during the study.
- Have given signed informed consent to participate in the study.

Principal exclusion criteria:
- Related to likelihood of non-modifiable events
  - Coronary artery bypass grafting within 90 days prior to the screening visit or planned coronary revascularization or cardiac surgery within 90 days after the screening visit.
  - Uncontrolled hypertension (2 consecutive measurements of sitting systolic blood pressure> 180 mm Hg or diastolic blood pressure> 100 mm Hg at the screening visit).
  - Previous or current diagnosis of severe heart failure (New York Heart Association Class IV) or a documented left ventricular ejection fraction (LVEF) of <25%.
  - Uncontrolled ventricular or supraventricular arrhythmia within 4 weeks prior to the screening visit.
- Related to safety, tolerability, or use of specific medications
  - Estimated glomerular filtration rate less than 30 mL/min/1.7m^2 at the screening visit, or current need for dialysis.
  - Liver disease or dysfunction based upon evidence of cirrhosis from liver imaging or gastric varices, active hepatitis, prior portacaval shunt procedure, or Child-Pugh score ≥5 points; ALT or AST >1.5 times upper limit of normal or total bilirubin above upper limit of normal at the screening visit.
  - Treatment with immunosuppressant medication within 1 year of the screening visit, treatment with fibrates at any dose or niacin/nicotinic acid at 250 mg or more daily within 30 days of the screening visit, or concurrent use of cyclosporine, clavulanic acid, diclofenac, acetaminophen (>1 g daily).
  - History of intolerance to atorvastatin or rosuvastatin.
  - Triglycerides >400 mg/dL (4.52 mmol/L) at the screening visit.
  - Female subjects who are pregnant.
- Related to absorption or metabolism of study medication
  - Conditions which might affect absorption or metabolism of the study medication, including untreated or incompletely treated thyroid dysfunction, cholecystitis, inflammatory bowel disease, or prior gastric bypass.
- Related to prognosis, reliability, ethics, or data validity
  - Any malignancy within the past 2 years, except for localized basal cell carcinoma of the skin.
  - Drug or alcohol abuse within 12 months of the screening visit.

levels. Exploratory outcomes include effects of apabetalone on renal function in patients with baseline CKD and on cognitive function in elderly patients.

Methods

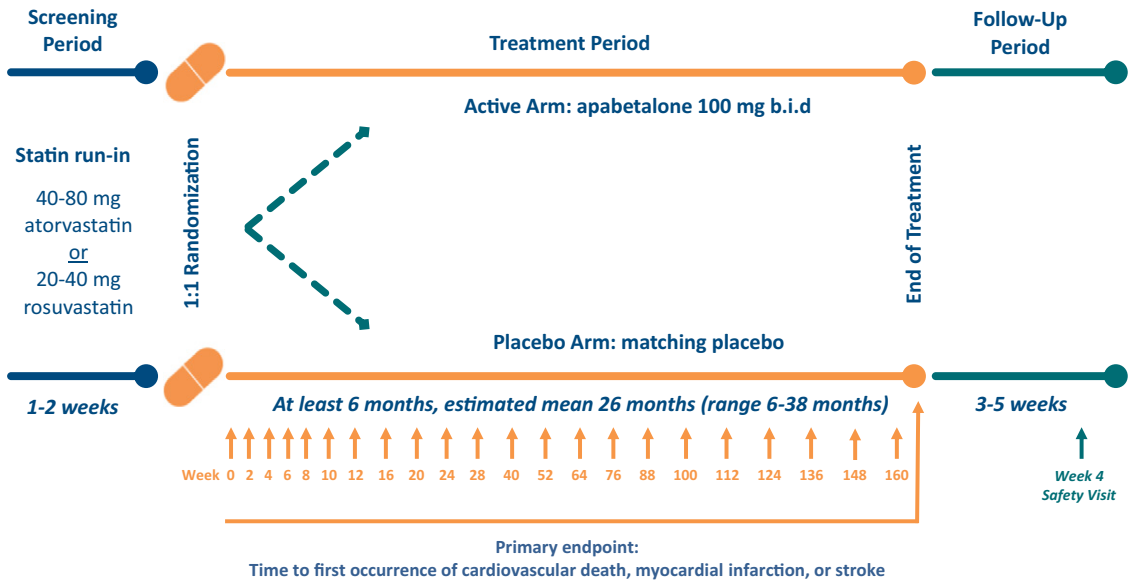
Study objective

BETonMACE (www.clinicaltrials.gov NCT02586155) is an international, multicenter, randomized, double-blind, placebo-controlled study in 2425 patients with recent ACS, T2DM, and low HDL-C conducted at 195 sites in 13 countries. The protocol was developed by an independent academic Executive Committee (Appendix A) in conjunction with the sponsors. The study is approved in each participating center by the responsible Institutional Review Board or Ethics Committee. The primary objective is to evaluate whether apabetalone (100 mg orally twice daily), initiated 7 to 90 days after an index ACS event, reduces the time to the composite outcome of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke.

Study population

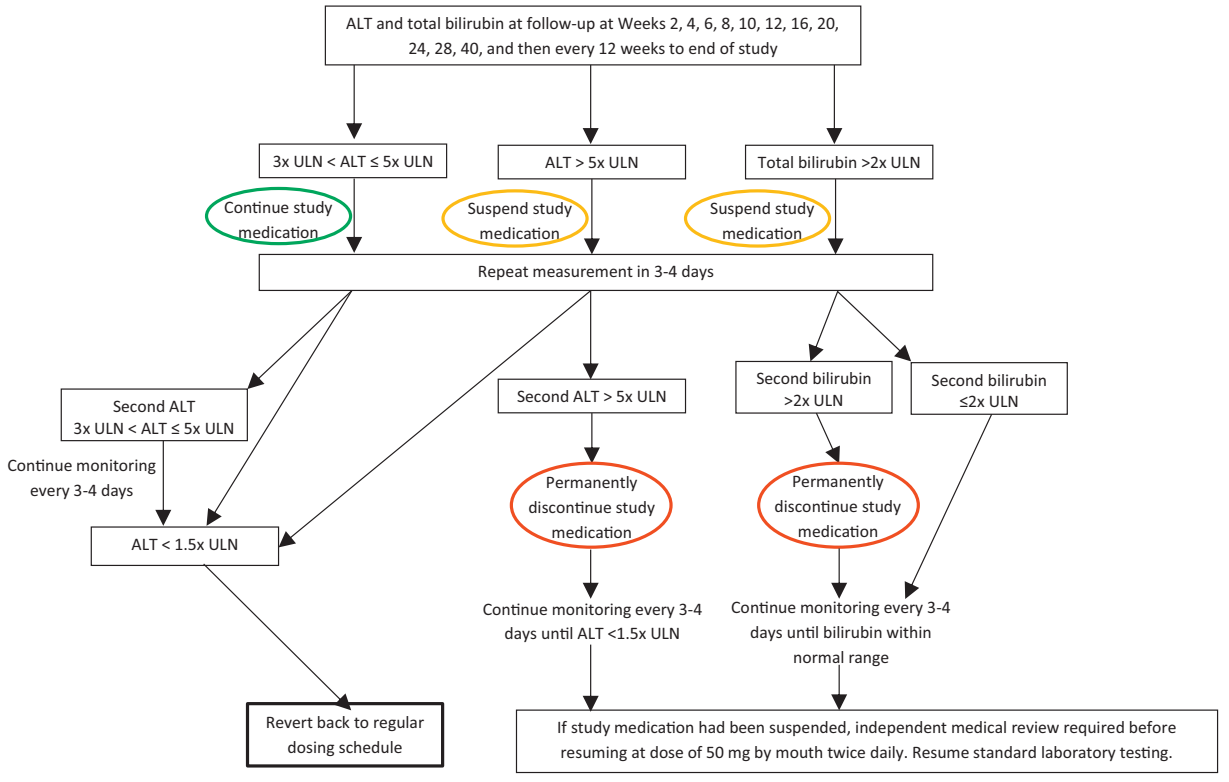
Principal inclusion and exclusion criteria are shown in Table I. The trial enrolled male and female patients at least 18 years of age who were hospitalized for ACS (acute myocardial infarction or unstable angina) and had T2DM and low HDL-C levels. Qualifying acute myocardial

Figure 2



Schematic representation of study design, procedures, and outcomes. Vertical arrows indicate times of study visits.

Figure 3



Algorithms for assessment and management of liver safety.

Table II. Definitions of efficacy measures[51]

Cardiovascular death:

Any death with a clear relationship to underlying cardiovascular disease, including death due to acute myocardial infarction or stroke, heart failure, complication of a cardiac or vascular procedure where the cause of death is clearly related to the procedure, ruptured aneurysm, pulmonary embolism, sudden death, unobserved and unexpected death, and other death that cannot be attributed to a nonvascular cause.

Acute non-fatal myocardial infarction:

- Defined and sub-classified in accordance with ACC/AHA/ESC Universal Definition of Myocardial Infarction
- Silent myocardial infarction is not considered part of the primary end point

Stroke

An acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction, embolism, or hemorrhage, defined by at least one of the following:

- Pathological, imaging, or other objective evidence of acute, focal cerebral, spinal, or retinal ischemic injury or hemorrhage in a defined vascular distribution
- Symptoms of acute cerebral, spinal, or retinal ischemic injury persisting ≥24 hours or until death, with other etiologies excluded

Hospitalization for unstable angina:

Admission to hospital or emergency department with symptoms of myocardial ischemia occurring at rest or with minimal exertion, requiring in addition both of the following:

- *New or presumed new ischemic ECG changes*, defined by ST depression ≥0.05 mV in two contiguous leads; ST elevation ≥0.1 mV at the J point in two contiguous leads other than V2-V3, or ST elevation in leads V2-V3 ≥ 0.2 mV in men ≥40 years old, ≥0.25 mV in men <40 years old, or ≥ 0.15 mV in women; T inversion ≥0.3 mV in two contiguous leads with prominent R wave or R/S ratio> 1; or LBBB.
- *Definite contemporary evidence of coronary obstruction* by need for coronary revascularization procedure or at least one epicardial stenosis ≥70%. Procedures or stenoses due only to restenosis at prior percutaneous intervention site are excluded.

Non-elective coronary revascularization procedure:

The procedure is considered urgent, emergency, or salvage according to the following definitions:

- *Urgent:* The procedure should be performed on an inpatient basis and prior to discharge because of significant concerns about the risk of myocardial ischemia, myocardial infarction, and/or death. Patients who are outpatients or in the emergency department at the time that the cardiac catheterization is requested would warrant hospital admission based on their clinical presentation.
- *Emergency:* The procedure should be performed as soon as possible because of substantial concerns that ongoing myocardial ischemia and/or MI could lead to death. "As soon as possible" refers to a patient who is of sufficient acuity that one would cancel a scheduled case to perform this procedure immediately in the next available room during business hours, or one would activate the on-call team were this to occur during off-hours.
- *Salvage:* The procedure is a last resort. The patient is in cardiogenic shock when the procedure begins or within the last ten minutes prior to the start o

f the case; or during the diagnostic portion of the case, the patient received chest compressions or was on unanticipated circulatory support.

Heart failure requiring hospitalization:

An event that meets all of criteria 1-4:

1 Admission to hospital with a primary diagnosis of heart failure (in the opinion of the Clinical Events Committee) for a duration of at least 24 hours (or a change in calendar date if the hospital admission and discharge times are unavailable)

2 New or worsening symptoms due to heart failure on presentation, including at least one of the following:

- Dyspnea (dyspnea with exertion, dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea)
- Decreased exercise tolerance
- Fatigue
- Symptoms of worsened end-organ perfusion (e.g. abdominal fullness or discomfort)
- Other symptoms of volume overload (e.g. swelling of lower extremities, increase in abdominal girth, increase in body weight)

3. *Objective evidence of new or worsening heart failure*, consisting of at least two physical examination findings OR one physical examination finding and at least one laboratory, imaging, or hemodynamic criterion from among the following:

- Physical examination findings considered to be due to heart failure, including new or worsened:
  - Peripheral edema
  - Increasing abdominal distention or ascites (in the absence of primary hepatic disease)
  - Pulmonary rales/crackles/crepitations
  - Increased jugular venous pressure and/or hepatojugular reflux
  - S3 gallop
  - Clinically significant or rapid weight gain thought to be related to fluid retention (usually >3-4 pounds in 3-4 days).
- Laboratory, imaging, or hemodynamic evidence of new or worsening heart failure, if obtained within 24 hours of presentation, including new or worsening:
  - Increased B-type natriuretic peptide (BNP)/ N-terminal pro-BNP (NTproBNP) concentrations consistent with decompensation of heart failure (such as BNP> 500 pg/mL or NT-proBNP >2000 pg/mL). In patients with chronically elevated natriuretic peptides, a significant increase should be noted above baseline.
  - Radiographic evidence of pulmonary congestion
  - Non-invasive (e.g., echocardiographic) evidence of clinically significant elevated left- or right-sided ventricular filling pressure or low cardiac output.
  - Invasive diagnostic evidence of elevated ventricular filling pressure(s) with right heart catheterization showing a pulmonary capillary wedge pressure (pulmonary artery occlusion pressure) ≥ 18 mmHg, central venous pressure ≥ 12 mmHg, or a cardiac index <2.2 L/min/m^2

4. *Initiation or intensification of treatment for heart failure*, including at least one of the following:

- Augmentation of oral diuretic therapy
- Intravenous diuretic, inotrope, vasopressor or vasodilator therapy
- Mechanical or surgical intervention, including:
- Mechanical circulatory support (e.g., intra-aortic balloon pump, ventricular assist device, extracorporeal membrane oxygenation, total artificial heart

Table III. Efficacy and safety measures

Primary Endpoint

Time from randomization to the first occurrence of adjudication-confirmed cardiovascular death, non-fatal myocardial infarction, or stroke.

Key Secondary Endpoints

1. Time from randomization to the first occurrence of adjudication-confirmed major adverse cardiovascular event defined as any of the following:
   - Cardiovascular death
   - Non-fatal myocardial infarction
   - Stroke
   - Hospitalization for cardiovascular events which include:
     - Unstable angina requiring evidence of new or presumed new progressive obstructive coronary disease, OR
     - Emergency revascularization procedures at any time and urgent revascularization procedures ≥30 days after the index events prior to randomization
2. Total incidence of cardiovascular death, non-fatal myocardial infarction, or stroke
3. Time from randomization to cardiovascular death or non-fatal MI
4. Time from randomization to coronary heart disease death or non-fatal myocardial infarction
5. Time from randomization to non-fatal myocardial infarction
6. Time from randomization to cardiovascular death
7. Time from randomization to stroke
8. All-cause death
9. Incidence of hospitalization for congestive heart failure

Other Secondary Endpoints

- The percent change in apolipoprotein A1, apolipoprotein B, LDL-C, HDL-C, and triglycerides over time within and between treatment groups
- The change from baseline in hemoglobin A1c, fasting glucose, and fasting insulin within and between treatment groups
- Changes in alkaline phosphatase within and between treatment groups for all subjects and according to quartiles of baseline alkaline phosphatase concentration
- Changes from baseline in kidney function in subgroup population with estimated glomerular filtration rate< 60 mL/min/1.7m^2 within and between treatment groups
- Change in Montreal Cognitive Assessment (MoCA) score in all patients at least 70 years of age, and in those at least 70 years of age with baseline MoCA <26 within and between treatment groups

Exploratory Endpoints

- The percent change in hsCRP, fibrinogen, and inflammatory cytokines within and between treatment groups
- Transcription/mRNA change in whole blood from baseline to 6 weeks treatment within and between treatment groups
- Change in health-related quality of life as measured using the EQ-5D-5 L

Safety Endpoints

Incidence of any adverse event, serious adverse events, vital sign measurements, clinical laboratory evaluations, and physical examination findings

infarction required at least two of the following: symptoms of myocardial ischemia at rest or with minimal exertion, elevated cardiac biomarkers, or new or presumed new Q waves on electrocardiography. Qualifying unstable angina required symptoms of myocardial ischemia at rest or with minimal exertion, electrocardiographic changes consistent with acute myocardial ischemia, and evidence of obstructive coronary disease from imaging studies or performance of a coronary revascularization procedure for the index event. The presence of T2DM was based upon a medical history of that condition or use of diabetes medication, or baseline hemoglobin A1c ≥6.5%. HDL-C c was required to be <40 mg/dl in men or <45 mg/dl in women.

Key exclusion criteria included planned further coronary revascularization or cardiac surgery within 90 days of the screening visit; severe heart failure (New York Heart Association Class IV) or left ventricular ejection fraction <25%; estimated glomerular filtration rate <30 ml/min/1.7m^2; fasting triglycerides >400 mg/dl; evidence of cirrhosis or active hepatitis, liver transaminases >1.5 times upper limit or normal, or total bilirubin above the upper limit of normal; uncontrolled hypertension; recent or ongoing use of HDL increasing fibrates and niacin (>250 mg daily), as well as ALT inducing therapies including cyclosporine, clavulanic acid, diclofenac, acetaminophen (>1 g daily); and a history of intolerance to atorvastatin or rosuvastatin. The overall screen failure rate was 38% and 5% of screened subjects failed due to abnormal liver enzymes or bilirubin.

Study procedures

Figure 2 illustrates the key phases of the trial. Patients providing informed consent entered a screening period of 1 to 2 weeks to determine laboratory criteria for eligibility and to continue or begin therapy with atorvastatin (40-80 mg daily) or rosuvastatin (20-40 mg daily). Atorvastatin 20 mg or rosuvastatin 10 mg were allowed for recognized factors limiting the dose (eg, advanced age, low body mass, or drug interactions).

Table IV. Baseline characteristics of all patient and subset with chronic kidney disease

	All Patients		CKD (eGFR <60 mL) sub-group		Non-CKD (eGFR ≥60 mL) sub-population		CKD subgroup vs non-CKD sub-population
Characteristic	N	Value	N	Value	N	Value	*P*
Demographics							
Age (y)	2425	62 (55 – 68)	262	71 (66 – 77)	2163	61 (54 – 67)	*P* < .0001 ‡
≥70	485	20%	151	58%	334	15%	*p* < .0001
Male	1806	74%	152	58%	1654	76%	*P* < .0001
Race, white	2115	87%	213	81%	1902	88%	0.002
Index ACS Event:							
Myocardial infarction**	1787	74%	197	75%	1590	74%	0.56
Unstable angina	625	26%	63	24%	562	26%	0.50
PCI management of index ACS event	1930	80%	191	73%	1739	80%	0.004
Medical History							
Hypertension	2144	88%	240	92%	1904	88%	0.09
Statin treatment at time of screening	2151	98%	2372	97%	1922	98%	0.13
Smokers	313	13%	17	6.5%	296	14%	0.001
Prior stroke	184	7.6%	26	9.9%	158	7.3%	0.13
Lipid-Lowering Medications:							
Atorvastatin	1245	51%	141	54%	1104	51%	0.40
20 mg	127	5.2%	24	9.2%	103	4.8%	0.003
40 mg	716	30%	85	32%	631	29%	0.27
80 mg	402	17%	32	12%	370	17%	0.04
Rosuvastatin	1180	49%	122	46%	1058	49%	0.40
10 mg	82	3.4%	10	3.8%	72	3.3%	0.68
20 mg	736	30%	80	31%	656	30%	0.94
40 mg	362	15%	32	12%	330	15%	0.19
Ezetimibe	43	1.8%	8	3.1%	35	1.6%	0.10
Diabetes medications							
Insulin	769	32%	90	34%	679	31%	0.33
Metformin	1866	77%	169	65%	1697	78%	*P* < .0001
Sulfonylureas	608	25%	73	28%	535	25%	0.27
DPP4 inhibitors	157	6.5%	30	11%	127	5.9%	0.001
SGLT2 inhibitors	122	5.0%	7	2.7%	115	5.3%	0.06
GLP1 receptor agonists	51	2.1%	2	0.8%	49	2.3%	0.11
Cardiovascular medications							
ACE inhibitors / ARBs	2174	90%	233	89%	1941	90%	0.69
Beta blockers	2146	88%	232	89%	1914	88%	0.98
Antiplatelet agents	2392	99%	261	100%	2131	99%	0.15
Dual antiplatelet agents	2086	86%	226	86%	1860	86%	0.91
Laboratory values							
eGFR (mL/min/1.73 m^2)	2413	99 (76-127)	262	49 (41-55)	2151	104 (84-131)	*p* < .0001 ‡
LDL-C (mg/dL)	2395	65 (49-85)	262	66 (48-91)	2133	65 (49-85)	0.62 ‡
HDL-C (mg/dL)	2413	33 (30-37)	262	34 (30-37)	2151	33 (30-37)	0.29 ‡
HbA1c (%)	2369	7.30 (6.40-8.70)	257	7.20 (6.40-8.50)	2112	7.30 (6.40-8.70)	0.27 ‡
Alkaline phosphatase† (U/L)	2424	78 (64-94)	262	80 (64-97)	2162	77 (64-94)	0.07 ‡
ApoA-1† (mg/dL)	483*	118 (109-129)	50*	119 (108-133)	433*	118 (109-129)	0.95 ‡
hsCRP† (mg/L)	493*	2.81 (1.20-6.15)	53*	3.45 (1.12-8.43)	440*	2.74 (1.12-5.93)	0.23 ‡
Fibrinogen† (mg/L)	471*	385 (318-454)	51*	396 (332-452)	420*	384 (316-454)	0.32 ‡
Platelets (10^9/L)	2295	249 (207-301)	251	241 (197-307)	2044	250 (208-300)	0.34 ‡
Neutrophil/lymphocyte ratio	2313	2.57 (1.99-3.36)	251	2.87 (2.20-3.90)	2062	2.54 (1.95-3.31)	*p* < .0001 ‡

Results for continuous variables are presented as median values (interquartile range); results for categorical values are percentages.
ACE, Angiotensin converting enzyme; *ACS*, acute coronary syndrome; *ARB*, angiotensin receptor blocker; *CABG*, coronary artery bypass grafting; *DPP4*, dipeptidyl peptidase-4; *eGFR*, estimated glomerular filtration rate; *GLP1*, glucagon-like peptide 1; *hsCRP*, high-sensitivity C-reactive protein; *PCI*, percutaneous coronary intervention; *SGLT2*, sodium glucose loop transporter 2.
† Results from randomization visit, whereas all other values are from screening visit.
* Conducted on a subset only in Hungary and Argentina.
** NSTEMI 841 or 47%; STEMI in 937 or 53% of the total MIs.
‡ Mann-Whitney *U* test; all other *P* values by χ^2 test.

Other background therapies were determined by the investigator to be consistent with standards of care for management of patients following ACS.

Patients meeting all inclusion criteria and who did not fulfill any of the exclusion criteria were randomized in a 1:1 ratio to receive apabetalone 100 mg orally twice daily or matching placebo. The time window for randomization 7 to 90 days after the index ACS was chosen to allow clinical stabilization and complete planned coronary revascularization, while remaining within the period of accentuated cardiovascular risk following ACS. Follow-up visits occur every 2 weeks until Week 12, then every 4 weeks until week 28, then every 12 weeks until the common study end date. Four weeks after last visit on treatment, a final follow-up visit is conducted. At randomization and at multiple time points after randomization patients are assessed for study end points and adverse events, and blood and urine samples are collected for measurements of hematology and chemistry studies including muscle and kidney function tests; hemoglobin A1c; and inflammatory markers including high sensitivity C-reactive protein. Optionally, samples are collected for DNA analysis at baseline and mRNA analysis at baseline and 6 weeks after randomization. The Montreal Cognitive Assessment (MoCA) test[44] is performed in participants at least 70 years old at randomization, and again at 52 weeks, 100 weeks, and end of study. To assess quality of life, the EQ-5D-5 L survey instrument[45] is administered at baseline, Weeks 24, 52, 76, 100 and end of study.

Because of the increased incidence of transaminase elevations with apabetalone in Phase 2 studies, frequent monitoring of liver safety was specified in the BETonMACE protocol. Liver function testing was performed at each follow-up visit, with the safety algorithm shown in Figure 3. If any measurement of ALT was elevated to more than 3 times the upper limit of normal (ULN) or total bilirubin was elevated to more than 2 times ULN, repeat testing was performed every 3 to 4 days until ALT was less than 1.5 times ULN or bilirubin was within normal limits, respectively. During repeat testing, study medication was continued if ALT was elevated to levels up to 5 times ULN, with suspension for any measurement of ALT more than 5 times ULN or total bilirubin more than 2 times ULN. If a second measurement of ALT was greater than 5 times ULN or a second measurement of bilirubin was greater than 2 times ULN, study medication was permanently discontinued. If study medication had been suspended due to ALT elevation that has a likely cause other than study medication, it could be resumed at 50 mg twice daily once ALT had returned to less than 1.5 times ULN and resumption had been approved by the medical monitors and sponsor. After resumption, additional liver function testing was performed according to the original study schedule. Suspension or continuation of statin therapy following ALT elevation was at the investigator's discretion according to normal clinical practice.

Study outcomes

Criteria and definitions for each type of ischemic event are provided in Table II. Primary and secondary efficacy measures are shown in Table III. The primary efficacy measure is time to first occurrence of cardiovascular death, non-fatal myocardial infarction or stroke. Key secondary end points, evaluated in hierarchical sequence, include time to first occurrence of the composite of the primary endpoint plus hospitalization for unstable angina or a non-elective coronary revascularization procedure, cardiovascular death or non-fatal myocardial infarction, the individual components of the primary endpoint, all-cause death, and incidence of hospitalization for congestive heart failure. Other secondary endpoints include changes within and between treatment groups over time in lipids and apolipoproteins A1 and B, fasting plasma glucose, hemoglobin A1c, alkaline phosphatase, and estimated glomerular filtration rate (eGFR) among the subset with baseline eGFR less than 60 ml/min/1.73 m^2. Exploratory endpoints include changes within and between groups in plasma high sensitivity C-reactive protein and inflammatory cytokines, RNA profile in leukocytes, health-related quality of life assessed with the EQ-5D-5 L and cognitive function assessed with the MoCA. An independent Data Safety Monitoring Board consisting of experts in cardiology, diabetes, and nephrology and a statistician monitors safety data on a quarterly basis during the study. Safety assessments include incidence of adverse events, vital sign measurements, clinical laboratory evaluations, and physical examination findings.

Statistical considerations

The apabetalone and placebo groups will be compared using a two-sided stratified log-rank test. With the assumption of 250 primary endpoint events, a 2-sided type 1 error rate of 5%, and cumulative incidence of the primary endpoint of 10.5% in the placebo arm at 18 months,[4,5,7-9] a sample size of 2400 patients followed for a median of 18 months provides 80% power to detect a 30% relative risk reduction with apabetalone (7.47% incidence of the primary endpoint at 18 months). The protocol allowed for a possible interim analysis for futility at 75% information (188 adjudicated primary endpoints), but none was performed due to temporal proximity of this condition to the projected study end date. If superiority of apabetalone is established for the primary endpoint, a sequential gate-keeping approach will be used to control the overall Type I error rate in testing the key secondary endpoints.

Study organization

The BETonMACE trial was conceived by the independent academic Executive Steering Committee in conjunction with the sponsor. The Executive Committee, composed of three academic cardiologists, a nephrologist, a lipidologist,

an endocrinologist, and non-voting sponsor representatives, is responsible for oversight and guidance of the study. An independent academic statistician will perform or confirm all statistical analyses of the final data. Academic national leaders oversee protocol implementation and site performance in each participating country. Site and data management and analysis are coordinated by PPD Ltd.

Baseline characteristics of the patients

Baseline characteristics of the patients. Enrollment began in November 2015 and ended in July 2018 with 2425 participants randomized. Key baseline characteristics are shown in Table IV and include median age 62 years, 25% female sex, white race 87%, high intensity atorvastatin or rosuvastatin treatment at time of screening 98%, unstable angina as the index ACS event 26%, coronary revascularization prior to randomization for management of the index ACS 80%; and median HbA1c 7.3%, LDL-C 65 mg/dl (1.68 mmol/L), and HDL-C 33 mg/dl (0.85 mmol/L).

The CKD population (n = 262, 10.8%) with baseline eGFR <60 ml/min/1.73 m^2, compared to the total population, was older, more likely female and comprised fewer current smokers (Table IV).

MoCA was performed in the 70 and older population (n = 469, 19%). The median (IQR) MoCA score was 25.0 (22.0-27.0) and more than half of this population (n = 246, 52%) had a baseline score of ≤25 suggesting some form of cognitive impairment.

Discussion

Despite contemporary evidence-based treatments, patients with ACS and T2DM remain at high risk for recurrent ischemic cardiovascular events.[4,5,7-9]

BET proteins, acting as epigenetic modulators of gene transcription, may promote conditions that lead to recurrent ischemic events after ACS by increasing expression of proinflammatory and prothrombotic mediators.[10,16,21] Conversely, selective BET protein inhibition by apabetalone, by attenuating expression of those mediators and increasing expression of apolipoprotein A1,[23,26,29,46-48] has the potential to offer beneficial vascular effects after ACS, as schematized in Figure 1. Notably, studies to date suggest that BET protein inhibition with apabetalone shifts a perturbed proinflammatory, prothrombotic milieu towards a resting, less atherogenic state. This is particularly relevant given that inflammation and thrombosis are important mechanisms for host defense and healing but tend to be maladaptive in patients with coronary disease. Chronic suppression of inflammation could theoretically increase the risk of infections[49] and anti-thrombotic effects could possibly adversely affect bleeding risk as observed with novel anticoagulants.[50] Although such adverse effects were not observed in Phase 2 studies, the longer-term safety of BET inhibition is an important consideration in BETonMACE.

Post hoc analyses of phase 2 studies with apabetalone suggest favorable cardiovascular effects in patients with stable coronary heart disease, particularly those with diabetes, low HDL-C, or elevated hsCRP.[34] Hence the pivotal proof of concept BETonMACE trial was designed to recruit specifically those patients with a high medical need most likely to benefit from this approach, rather than a broad cardiovascular disease cohort. As the first Phase 3 cardiovascular outcomes trial to evaluate a BET protein inhibitor, BETonMACE will test the hypothesis that treatment with apabetalone, compared with placebo, reduces ischemic cardiovascular events in patients with recent ACS, diabetes, and low HDL-C. In addition, BETonMACE will provide the largest and longest evaluation to date of the safety of BET protein inhibition with apabetalone. Lastly, exploratory assessments of apabetalone's effects on kidney function and cognition are pre-specified endpoints.

Appendix A. Committees

Executive Steering Committee: Kausik K. Ray, MD MPhil, Chair; Henry Ginsberg, MD, Kamyar Kalantar-Zadeh, MD PhD, Stephen J. Nicholls, MD PhD, Gregory G. Schwartz, MD PhD, Peter P. Toth, MD PhD. Sponsor representatives: Michael Sweeney, MD, Jan O. Johansson, MD PhD, Ewelina Kulikowski PhD, Norman Wong, MD.

National Leaders: Argentina, Marisa Vico, MD and Alberto Lorenzatti, MD; Mexico, Edmundo Bayram Llamas, MD; Bulgaria, Maria Milanova, MD; Croatia, Zeljko Popovic, MD; Germany, Henning Ebelt, MD; Hungary, Róbert Kiss, MD PhD; Israel, Basil Lewis, MD; Poland, Maciej Banach, MD PhD; Serbia, Milan Pavlovic, MD; Slovak Republic, Daniel Pella, MD PhD; Taiwan, Chern-En Chiang, MD PhD.

Data Safety Monitoring Board: Eva Lonn, MD, (Chair); Lawrence Alan Leiter, MD.

David Waters, MD, Michael Szarek, PhD, Paul Watkins, MD, Judith Currier, MD.

Clinical Events Committee: John J.V. McMurray, MD (Chair), Mark Petrie, MD, Eugene Conolly, MD, Pradeep Jhund, MD, Ninian, Lang, MD, Matthew Walters, MD.

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