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Effect of Apabetalone on Cardiovascular Events in Diabetes, CKD, and Recent Acute Coronary Syndrome

Results from the BETonMACE Randomized Controlled Trial

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Abstract

Background and objectives CKD and type 2 diabetes mellitus interact to increase the risk of major adverse cardiovascular events (*i.e.*, cardiovascular death, nonfatal myocardial infarction, or stroke) and congestive heart failure. A maladaptive epigenetic response may be a cardiovascular risk driver and amenable to modification with apabetalone, a selective modulator of the bromodomain and extraterminal domain transcription system. We examined this question in a prespecified analysis of BETonMACE, a phase 3 trial.

Design, setting, participants, & measurements BETonMACE was an event-driven, randomized, double-blind, placebo-controlled trial comparing effects of apabetalone versus placebo on major adverse cardiovascular events and heart failure hospitalizations in 2425 participants with type 2 diabetes and a recent acute coronary syndrome, including 288 participants with CKD with eGFR <60 ml/min per 1.73 m^2 at baseline. The primary end point in BETonMACE was the time to the first major adverse cardiovascular event, with a secondary end point of time to hospitalization for heart failure.

Results Median follow-up was 27 months (interquartile range, 20–32 months). In participants with CKD, apabetalone compared with placebo was associated with fewer major adverse cardiovascular events (13 events in 124 patients [11%] versus 35 events in 164 patients [21%]; hazard ratio, 0.50; 95% confidence interval, 0.26 to 0.96) and fewer heart failure–related hospitalizations (three hospitalizations in 124 patients [3%] versus 14 hospitalizations in 164 patients [9%]; hazard ratio, 0.48; 95% confidence interval, 0.26 to 0.86). In the non-CKD group, the corresponding hazard ratio values were 0.96 (95% confidence interval, 0.74 to 1.24) for major adverse cardiovascular events, and 0.76 (95% confidence interval, 0.46 to 1.27) for heart failure–related hospitalization. Interaction of CKD on treatment effect was $P=0.03$ for major adverse cardiovascular events, and $P=0.12$ for heart failure–related hospitalization. Participants with CKD showed similar numbers of adverse events, regardless of randomization to apabetalone or placebo (119 [73%] versus 88 [71%] patients), and there were fewer serious adverse events (29% versus 43%; $P=0.02$) in the apabetalone group.

Conclusions Apabetalone may reduce the incidence of major adverse cardiovascular events in patients with CKD and type 2 diabetes who have a high burden of cardiovascular disease.

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Introduction

CKD is found in at least 10% of the general adult population and is associated with a high burden of cardiovascular disease and poor clinical outcomes. A leading cause of CKD is type 2 diabetes mellitus, which in some regions is found in half of all patients with CKD (1). Both diabetes and CKD are strongly associated with higher risk of coronary and cerebrovascular disease, congestive heart failure, and death. The potentiation of cardiovascular risk by CKD, with or without diabetes as its etiology, is associated with abnormal inflammation, dysregulation of the renin-angiotensin system, dyslipidemia, platelet hyperreactivity, endothelial dysfunction, vascular calcification, and a prothrombotic milieu (2). In addition, alkaline phosphatase is typically elevated in patients with CKD, which may contribute to risk of cardiovascular disease (3). Whereas cholesterol lowering with statins (4) and treatment with some other agents, including sodium-glucose transport protein 2 (SGLT2) inhibitors (5) or glucagon-like peptide-1 agonists (6,7), have reduced cardiovascular risk in patients with moderate CKD, residual risk remains substantial. Thus, there is a major unmet need to lower the residual risk of cardiovascular morbidity and death in patients with CKD.

Epigenetic modulators are novel pharmacologic agents that modify gene transcription. Bromodomain

and extraterminal (BET) domain proteins function as epigenetic readers and interact with active chromatin to open regions of DNA containing genes accessible for transcription (8–11). BET proteins bind acetylated lysine residues on histones, transcription factors, and histone remodelers, forming molecular scaffolds between chromatin and transcriptional machinery to facilitate transcription and mRNA production (8–11), and, by doing so, they contribute to maladaptive gene expression in various models of cardiovascular disease (12,13). Hence, BET protein inhibition may alter disease-driven cellular responses in persons with high risk of cardiovascular disease, including those with CKD (12–18). Apabetalone is an oral BET inhibitor with selectivity for binding bromodomain 2 with anti-inflammatory and alkaline phosphatase–lowering properties (14–18). The phase 3 BETonMACE (Effect of RVX000222 on Time to Major Adverse Cardiovascular Events in High-Risk T2DM Subjects With CAD) trial compared treatment with apabetalone versus placebo in patients with type 2 diabetes, low HDL cholesterol, and recent acute coronary syndrome. Apabetalone treatment resulted in fewer major adverse cardiovascular events (MACE), but the effect did not reach statistical significance (17,18). In this prespecified analysis, we examined the effects of apabetalone or placebo according to the presence of moderate CKD.

Materials and Methods

The design (17) and main results (18) of the phase 3 BETonMACE trial have been reported. Following the Declaration of Helsinki guidelines, the trial was overseen by a blinded, independent, academic steering committee, and safety was continuously assessed by an independent data safety and monitoring committee. BETonMACE was an event-driven, randomized, double-blind, placebo-controlled, multicenter trial performed at 190 sites in 13 countries from November 11, 2015 through July 3, 2019. It included 2425 participants, aged ≥18 years, with type 2 diabetes, low HDL cholesterol levels (<40 mg/dl in men or <45 mg/dl in women), and recent acute coronary syndrome (acute myocardial infarction or unstable angina 7–90 days before randomization) (18). Exclusion criteria included an eGFR <30 ml/min per 1.73 m^2, liver transaminase levels >1.5 times the upper limit of normal, and total bilirubin level greater than the upper limit of normal. Participants were classified as having CKD at baseline if their eGFR was <60 ml/min per 1.73 m^2 body surface area, calculated with the Cockcroft–Gault equation. Eligible participants were randomized 1:1 to receive 100 mg apabetalone orally twice daily (n=1215) or matching placebo (1210), in addition to intensive statin treatment and other standard care. Treatment allocation was stratified by country and background statin type, using block randomization with a block size of four, and assignment was done using an interactive internet-response system from a computer-generated randomization list (18). The sponsor, academic steering committee, and principal investigators were blinded to treatment allocation, whereas the data-safety monitoring board was unblinded to treatment allocation for safety data only. The primary outcome was time to the first occurrence of cardiovascular death, nonfatal myocardial infarction, or stroke, together referred to as MACE. Hospitalization for heart failure was a secondary outcome. Outcomes were adjudicated by an events committee composed of cardiologists and neurologists who were blinded to treatment assignment. Analyses of the effects of assigned treatment on MACE and on hospitalization for heart failure according to the presence or absence of CKD were prespecified in the supplemental statistical analysis plan (see Supplemental Appendix 1) that was developed and accepted before unblinding the study results. The analysis of effects of treatment on the composite of MACE or hospitalization for heart failure according to CKD status was *post hoc* and exploratory. Due to the nature of this clinical research, participants of the BETonMACE study were not asked for their data to be shared publicly.

Statistical Analyses

Statistical analyses were conducted in accordance with the prespecified statistical analysis plan (see supplement 1 in Ray *et al.* [18]) using the full analysis set, *i.e.*, all randomized subjects who received any amount of study therapy and had at least one measurement of the assessment of interest. The CKD and non-CKD subgroups were prespecified subgroups. Baseline characteristics were summarized for CKD and non-CKD subgroups, and by treatment arm for the CKD subgroup, as mean (SD) or median (interquartile range [IQR]) for continuous variables, and counts and percentages for categoric variables. Changes in clinical chemistry variables were analyzed using analysis of covariance models with baseline biomarker value, statin, and country as covariates; the primary coefficient of interest was the between-treatment group difference in change from baseline, referred to herein as the adjusted difference. Adjusted differences were calculated for the CKD and non-CKD groups, and interaction P values were calculated from the analysis of covariance model to assess differences in treatment effect between CKD and non-CKD groups. Time-to-event (MACE or heart failure hospitalization) analyses were conducted using a log-rank test to calculate P values, and a Cox proportional-hazards model to estimate the hazard ratio (HR) with 95% confidence interval (95% CI), with stratification by statin and country and with adjustment for sex and age; event counts and percentages were also summarized. Such analyses were conducted within the placebo group to compare rates between CKD and non-CKD groups, and within the CKD and non-CKD groups, respectively, to assess treatment effects. A Cox model was also used to calculate interaction P values for treatment and CKD/non-CKD group status. Kaplan–Meier analyses assessing time to events by treatment and CKD group were also conducted.

Results

Of a total 2425 participants in the BETonMACE trial, 1215 were assigned to apabetalone and 1210 to placebo (18). A total of 288 participants (12%) had CKD upon study entry, defined as an eGFR of 30–59 ml/min per 1.73 m^2. Of these, 124 patients were assigned to apabetalone and 164 to placebo. The aggregate CKD subgroup included 186 participants (65%) with CKD stage 3a (eGFR 45 to

<60 ml/min per 1.73 m^2) and 102 participants (35%) with CKD stage 3b (eGFR <45 ml/min per 1.73 m^2). Mean (SD) eGFR among those with CKD and without CKD was 49 (9) and 111 (35) ml/min per 1.73 m^2, respectively.

Figure 1 shows patient flow chart in the CKD subgroup of the BETonMACE trial. Table 1 shows the baseline demographic and clinical characteristics of the trial participants according to CKD category. In the full trial cohort and the CKD and no-CKD subgroups, baseline characteristics were generally well balanced between treatment groups (18). Participants with CKD were, on average, 10 years older than those without CKD, were more likely to be female, less likely to be of White race or a current smoker, and had a longer duration of type 2 diabetes. There was no significant difference in proportion of the type of qualifying recent acute coronary syndrome (*i.e.*, acute myocardial infarction versus unstable angina by CKD category), but, among those with myocardial infarction, the proportion without ST elevation was greater in those with CKD.

As shown in Table 1, irrespective of CKD or non-CKD, >90% of participants received inhibitors of the renin-angiotensin pathway, β-blockers, and antiplatelet agents. Fewer participants with CKD than those with non-CKD were treated with metformin (69% versus 84%) or SGLT2 inhibitors (6% versus 13%), while those in the CKD group had a longer mean duration of diabetes (11.3 versus 8.2 years). Among laboratory markers, cholesterol (total, LDL, HDL), triglyceride, and high-sensitivity C-reactive protein levels were similar between the CKD and no-CKD categories; however, mean alkaline phosphatase was 10 U/L higher and mean alanine aminotransferase was 3 U/L lower among those with CKD. Participants with CKD had lower diastolic BP (74.9 [SD, 9.4] versus 76.5 [SD, 8.9] mm Hg) and higher neutrophil/lymphocyte ratio (2.9 [IQR, 2.2–3.9] versus 2.5 IQR, 1.9–3.3]), a marker of inflammation.

The changes in clinical chemistry over the course of the study from baseline to week 24 (week 12 for high-sensitivity C-reactive protein) across CKD status and treatment groups are shown in Table 2. Apabetalone decreased serum alkaline phosphatase compared with placebo, with a greater decrease among participants with CKD (mean, 7.8 U/L) compared with participants without CKD (mean, 1.4 IU/L; interaction $P=0.004$). Apabetalone produced a modest increase in HDL cholesterol concentration that was of a similar magnitude in CKD and no-CKD groups. No other laboratory parameter showed significant treatment by CKD-category interaction.

Upon study completion at a median follow-up period of 27 months (IQR, 20–32 months), participants in the placebo group with CKD experienced a higher incidence of MACE than those without CKD (35 events in 164 patients [21%] versus 114 events in 1041 patients [11%]; HR, 2.40; 95% CI, 1.67 to 3.44; $P<0.001$). Similarly, participants in the placebo group with CKD were more likely to be hospitalized for heart failure (14 hospitalizations in 164 patients [9%] versus 34 hospitalizations in 1041 patients [3%]; HR, 3.19; 95% CI, 1.66 to 6.12; $P<0.001$).

Overall, in the trial, a total of 274 participants experienced a primary MACE end point, including 125 patients

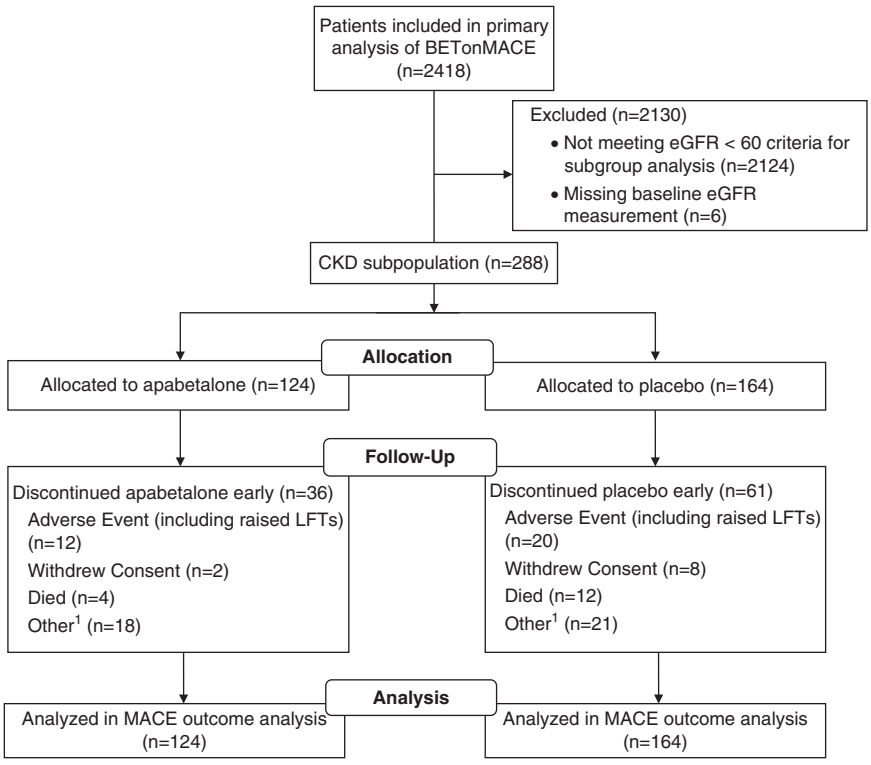

Figure 1. | Patient flow in the CKD subgroup of the BETonMACE trial of apabetalone for reduction of adverse cardiovascular events in patients with acute coronary syndrome and type 2 diabetes. [1]Discontinuation due to patient preference. LFTs, liver function tests; MACE, major adverse cardiovascular events.

Table 1. Demographic, clinical, pharmacologic, and laboratory characteristics of the BETonMACE trial participants at baseline according to CKD status and assigned treatment group

Characteristics	Full Study Cohort according to CKD Status[a]		Patients with CKD by Assigned Treatment Group[b]	
	eGFR ≥60 ml/min per 1.73 m^2 (no-CKD)	eGFR <60 ml/min per 1.73 m^2 (CKD)	Placebo (eGFR <60 ml/min per 1.73 m^2)	Apabetalone (eGFR <60 ml/min per 1.73 m^2)
No. of participants	2125	288	164	124
Age, yr	61 (54–67)	71 (65–76)	71 (66–77)	70 (65–75)
Female, *n* (%)	497 (23)	120 (42)	72 (44)	48 (39)
White race, *n* (%)	1879 (88)	235 (82)	137 (84)	98 (79)
Asian race, *n* (%)	28 (1)	11 (4)	5 (3)	6 (5)
Body mass index, kg/m^2	30.6 (4.9)	27.4 (3.9)	27.5 (4.1)	27.2 (3.6)
Hypertension history, *n* (%)	1876 (88)	263 (91)	148 (90)	115 (93)
Smoking status, *n* (%)	253 (12)	19 (7)	11 (7)	8 (6)
Diabetes duration, yr	8.2 (7.3)	11.3 (9.1)	11.9 (9.1)	10.5 (9.1)
Prior myocardial infarction, *n* (%)	300 (14)	49 (17)	27 (16)	22 (18)
Prior revascularization, *n* (%)	442 (21)	71 (25)	37 (23)	34 (27)
Index acute coronary syndrome[c]				
Myocardial infarction, *n* (%)	1560 (74)	215 (75)	126 (78)	89 (72)
NSTEMI, n (%)	718 (46)	116 (55)	68 (55)	48 (54)
STEMI, n (%)	835 (54)	96 (45)	56 (45)	40 (45)
Unstable angina, *n* (%)	553 (26)	70 (25)	36 (22)	34 (28)
Time from index ACS, d	38 (25–63)	35 (23–57)	36 (23–58)	33 (23–54)
Cardiovascular medications, *n* (%)				
Atorvastatin	1084 (51)	153 (53)	91 (55)	62 (50)
Rosuvastatin	1041 (49)	135 (47)	73 (45)	62 (50)
Intensive statin therapy	1929 (91)	247 (86)	139 (85)	108 (87)
Ezetimibe	50 (2)	17 (6)	13 (8)	4 (3)
ACE inhibitors or ARB	1957 (92)	268 (93)	154 (94)	114 (92)
β-Blockers	1925 (91)	262 (91)	150 (91)	112 (90)
Antiplatelet agents	2099 (99)	287 (99)	164 (100)	123 (99)
Diabetes medications, *n* (%)				
Metformin	1794 (84)	200 (69)	104 (63)	96 (77)
Insulin	787 (37)	121 (42)	74 (45)	47 (38)
Sulfonylureas	619 (29)	88 (31)	46 (28)	42 (34)
DPP4 inhibitors	307 (14)	51 (18)	28 (17)	23 (19)
SGLT2 inhibitors	279 (13)	18 (6)	9 (5)	9 (7)
GLP1 receptor agonists	81 (4)	5 (2)	4 (2)	1 (0.8)
Other[d]	90 (4)	17 (6)	10 (6)	7 (6)
Biochemical parameters				
Serum creatinine, mg/dl	0.90 (0.21)	1.4 (0.5)	1.4 (0.5)	1.4 (0.4)
eGFR, ml/min per 1.73 m^2	111 (35)	49 (9)	48 (9)	49 (9)
eGFR 45 to <60 ml/min per 1.73 m^2	N/A	186 (65)	104 (63)	82 (66)
eGFR <45 ml/min per 1.73 m^2	N/A	102 (35)	57 (35)	41 (33)
HbA1c, %	7.3 (6.4–8.7)	7.2 (6.4–8.5)	7.1 (6.4–8.4)	7.3 (6.5–8.6)
Serum glucose, mg/dl	152 (61)	149 (66)	147 (65)	151 (68)
Total cholesterol, mg/dl	135 (35)	140 (46)	145 (49)	134 (41)
LDL cholesterol, mg/dl	70 (30)	73 (39)	77 (42)	69 (35)
HDL cholesterol, mg/dl	33 (5)	33 (6)	34 (6)	33 (5)
Triglycerides, mg/dl	147 (113–200)	157 (117–202)	163 (130–205)	145 (107–190)

Table 1. (Continued)

Characteristics	Full Study Cohort according to CKD Status[a]		Patients with CKD by Assigned Treatment Group[b]	
	eGFR ≥60 ml/min per 1.73 m^2 (no-CKD)	eGFR <60 ml/min per 1.73 m^2 (CKD)	Placebo (eGFR <60 ml/min per 1.73 m^2)	Apabetalone (eGFR <60 ml/min per 1.73 m^2)
Alkaline phosphatase, U/L	81 (29)	91 (71)	90 (61)	93 (83)
Alanine aminotransferase, U/L	26 (14)	23 (18)	24 (22)	21 (10)
Systolic BP (mm Hg)	129 (15)	129 (15)	128 (16)	131 (14)
Diastolic BP (mm Hg)	77 (9)	75 (9)	75 (10)	75 (9)
Total bilirubin, umol/L	0.6 (0.2)	0.6 (0.3)	0.6 (0.3)	0.6 (0.3)
hsCRP, mg/L	2.7 (1.2–5.9)	3.2 (1.1–7.6)	3.9 (1.1–10.1)	3.0 (1.3–5.7)
NLR	2.5 (1.9–3.3)	2.9 (2.2–3.9)	2.9 (2.2–4.0)	2.8 (2.1–3.7)

Continuous variables are presented as mean (SD) or median (interquartile range). Categoric variables are presented as *n* (%). NSTEMI, non–ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; ACS, acute coronary syndrome; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; DPP4, dipeptidyl peptidase-4; SGLT2, sodium-glucose cotransporter 2; GLP1, glucagon-like peptide 1; N/A, not applicable; HbA1c, hemoglobin A_{1C}; hsCRP, high-sensitivity C-reactive protein; NLR, neutrophil/lymphocyte ratio.

[a]Data for the full study cohort according to baseline CKD status.

[b]Data for the CKD subgroup according to assigned treatment group.

[c]There was no significant difference in proportion of myocardial infarction versus unstable angina as an index event (P=0.61); but, among those with myocardial infarction as the index event, there were significant differences in proportion of STEMI versus non-STEMI (P=0.03).

[d]Other diabetes medications include acarbose, pioglitazone, and repaglinide.

(10%) in the apabetalone group and 149 patients (12%) in the placebo group (HR, 0.82; 95% CI, 0.65 to 1.04; P=0.11) (18). Table 3 shows the case mix–adjusted effect of assigned treatment on cardiovascular outcomes according to CKD category. In the CKD subgroup, apabetalone was associated with a reduced hazard for MACE (HR, 0.50; 95% CI, 0.26 to 0.96) and heart failure hospitalization (HR, 0.25; 95% CI, 0.07 to 0.92; P=0.04). In contrast, in the subgroup without CKD, apabetalone's effect on MACE (HR, 0.96; 95% CI, 0.74 to 1.24) and heart failure hospitalization (HR, 0.76; 95%, CI 0.46 to 1.27) was nonsignificant. The interaction of treatment and CKD category on MACE and MACE plus hospitalization for heart failure was 0.032 and 0.033, respectively. Supplemental Table 1 shows minimally adjusted HRs, *i.e.*, stratified for statin and country, in accordance with the primary analyses of the BETonMACE study (18), suggesting that inclusion or exclusion of multivariable adjustment had little effect on the summary estimates.

For the composite of time to first event of hospitalization for MACE or heart failure, the observed HR was 0.48 (95% CI, 0.26 to 0.88), whereas the observed HR was 0.91 (95% CI, 0.71 to 1.17) in the participants without CKD. Treatment HRs were also numerically lower in the CKD subgroup compared with the non-CKD subgroup for cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke.

Kaplan–Meier survival plots for MACE, heart failure hospitalization, and their composite are shown in Figure 2 according to CKD subgroup. By log-rank analysis, apabetalone was associated with fewer MACE, hospitalizations for heart failure, and their combination in the CKD subgroup, whereas the apabetalone effects were nonsignificant in the non-CKD subgroup. In participants with CKD, there was early, continued, and sustained curve separation, whereas the curve separation was less pronounced in the participants without CKD.

Overall in BETonMACE, more participants allocated to apabetalone than placebo discontinued the study drug (114 [9%] versus 69 [6%] participants) for reasons including liver-enzyme elevations (35 [3%] versus 11 [0.9%] patients), as described elsewhere (18). In the CKD population, more participants allocated to placebo than apabetalone discontinued the study drug (20 [12%] versus 12 [10%] patients). Table 4 shows that, among participants with CKD, similar numbers of participants in the apabetalone and placebo groups experienced adverse events (119 [72%] versus 88 [71%] patients), and fewer participants in the apabetalone group had serious adverse events (29% versus 43%; P=0.02). Only two subjects in each group had a hepatic transaminase level that was greater than the five-fold upper limit of normal on close laboratory monitoring, which required discontinuation of the study therapy in line with the study protocol.

Discussion

In the BETonMACE trial, assignment to apabetalone or placebo did not significantly affect the primary MACE outcome in 2425 participants with type 2 diabetes, low HDL cholesterol, and recent acute coronary syndrome. However, in a proof-of-concept trial with a novel chemical entity agent, it is important to explore effects in key

Table 2. Change in clinical chemistry variables by CKD subgroup

Parameter	eGFR <60 ml/min per 1.73 m^2			eGFR ≥60 ml/min per 1.73 m^2			Interaction *P* Value[b]
	Placebo	Apabetalone	Adjusted Difference (95% CI)[a]	Placebo	Apabetalone	Adjusted Difference (95% CI)[a]	
LDL cholesterol, mg/dl	−0.4 (70.0)	2.6 (70.1)	2.3 (−3.4 to 8.1)	−2.2 (42.4)	−1.1 (47.1)	−3.4 (−19.5 to 12.7)	0.51
HDL cholesterol, mg/dl	10.4 (20.3)	15.1 (23.6)	4.7 (2.8 to 6.6)	14.0 (25.8)	17.8 (23.8)	3.9 (−1.5 to 9.3)	0.79
HbA1c, %[c]	0.00 (−0.60–0.60)	0.00 (−0.80–0.50)	−0.10 (−0.20 to 0.00)	0.00 (−0.62–0.40)	−0.10 (−0.80–0.50)	−0.00 (−0.30 to 0.20)	0.35
Serum glucose, mg/dl	7.4 (67.9)	9.3 (66.4)	2.9 (−2.4 to 8.3)	−0.1 (73.1)	1.1 (82.3)	2.0 (−13.1 to 17.0)	0.90
Alkaline phosphatase, U/L	−1.2 (20.8)	−9.3 (22.0)	−7.8 (−9.9 to −5.7)	−6.9 (51.7)	−6.6 (32.5)	1.4 (−4.5 to 7.3)	0.004
hsCRP, mg/L[c,d]	−15.0 (−54.6–26.3)	−25.9 (−61.5–24.5)	−7.8 (−19.6 to 4.1)	−18.8 (−49.0–23.2)	−36.1 (−69.4–15.3)	−11.7 (−48.4 to 25.6)	0.74
Cholesterol, mg/dl	0.7 (24.9)	3.9 (27.7)	2.7 (0.6 to 4.8)	−1.4 (24.0)	0.9 (23.3)	−0.7 (−6.5 to 5.2)	0.29
Triglycerides, mg/dl	11.8 (64.4)	15.3 (58.5)	2.9 (−2.3 to 8.1)	−4.7 (31.1)	2.8 (35.1)	4.2 (−10.5 to 18.8)	0.87
Alanine aminotransferase, U/L	7.0 (117.0)	16.1 (73.7)	8.6 (0.2 to 17.0)	−3.2 (53.2)	31.5 (84.8)	27.3 (3.5 to 51.1)	0.15
Systolic BP, mm Hg	−0.4 (17.8)	1.4 (16.1)	1.7 (−0.5 to 7.1)	0.15 (15.0)	−0.18 (15.1)	1.3 (−0.38 to 1.9)	0.02
Diastolic BP, mm Hg	−1.5 (10.2)	0.4 (10.1)	2.1 (0.1 to 4.5)	0.15 (9.3)	−0.18 (9.7)	0.88 (−0.40 to 1.1)	0.03
γ-Glutamyl transferase, U/L	7.4 (59.2)	5.9 (55.8)	−1.6 (−7.4 to 4.1)	2.3 (52.4)	16.9 (145.7)	14.0 (−2.3 to 30.2)	0.08
Total bilirubin, mg/dl	8.6 (35.1)	27.1 (47.4)	16.7 (6.3 to 27.0)	11.1 (42.4)	22.1 (44.9)	10.4 (6.7 to 14.1)	0.26
eGFR, ml/min per 1.73 m^2	1.7 (16.8)	−0.8 (18.5)	−2.5 (−4.0 to −0.9)	5.3 (16.6)	3.8 (13.6)	−1.8 (−6.1 to 2.6)	0.77

Percentage or absolute changes from baseline to 24 wk, except for hsCRP, for which the change is from baseline to 12 wk. Changes are shown as mean (SD) or median (interquartile range). 95% CI, 95% confidence interval; HbA1c, hemoglobin A_{1C}; hsCRP, high-sensitivity C-reactive protein.

[a]Adjusted differences are shown as either mean or Hodges pseudo-median with 95% CI.

[b]Interaction P values indicate whether the observed treatment difference varies with baseline CKD subgroup.

[c]Changes are shown as median (interquartile range).

[d]For hsCRP, 12-wk interval; otherwise 24 wk for all other laboratory values.

Table 3. Effects of apabetalone versus placebo on primary and secondary outcomes across CKD

Variable	eGFR <60 ml/min per 1.73 m^2			eGFR ≥60 ml/min per 1.73 m^2			Interaction *P* Value[a]
	Placebo Event/ *n* (%)	Apabetalone Event/ *n* (%)	Adjusted HR (95% CI)	Placebo Event/ *n* (%)	Apabetalone Event/ *n* (%)	Adjusted HR (95% CI)	
Primary outcome							
MACE	35/164 (21)	13/124 (11)	0.50 (0.26 to 0.96)	114/1041 (11)	112/1084 (10)	0.96 (0.74 to 1.24)	0.03
Composite events							
MACE and CHF	41/164 (25)	16/124 (13)	0.48 (0.26 to 0.88)	132/1041 (13)	123/1084 (11)	0.91 (0.71 to 1.17)	0.03
Components							
CV death	17/164 (10)	6/124 (5)	0.47 (0.18 to 1.24)	38/1041 (4)	39/1084 (4)	1.02 (0.98 to 1.60)	0.12
Nonfatal MI	20/164 (12)	9/124 (7)	0.59 (0.26 to 1.33)	74/1041 (7)	68/1084 (6)	0.89 (0.64 to 1.24)	0.26
Nonfatal stroke	6/164 (4)	2/124 (2)	0.57 (0.11 to 2.97)	11/1041 (1)	15/1084 (1)	1.36 (0.62 to 2.96)	0.20
CHF hospitalization	14/164 (9)	3/124 (2)	0.25 (0.07 to 0.92)	34/1041 (3)	26/1084 (2)	0.76 (0.46 to 1.27)	0.12

Shown are events and total subjects counts, percentage rates, HRs, and 95% CIs for indicated composite and component end points. All analyses are stratified for statin and country and adjusted for age and sex. See also Supplemental Table 1 for minimally adjusted HRs. HR, hazard ratio; 95% CI, 95% confidence interval; MACE, major adverse cardiovascular events; CHF, congestive heart failure; CV, cardiovascular; MI, myocardial infarction.

[a]Interaction *P* values indicate differences by CKD status in the effect of apabetalone on event rates.

subgroups that may point to populations most likely to achieve treatment benefit. The observed HR of 0.50 for MACE, 0.25 for heart failure hospitalization, and 0.48 for MACE plus heart failure hospitalization in the participants with CKD is on top of standard of care, including high-intensity statin treatment and other evidence-based procedures and treatments for acute coronary syndrome. The interaction *P* value tests for difference by CKD status in the effect of apabetalone on event rates were significant for MACE.

Both type 2 diabetes and CKD are independently associated with high risk of cardiovascular disease (19). In addition, patients with coronary disease and either diabetes or CKD have a much higher risk of additional MACE than patients without either of these concomitant conditions (20). The excess risk of cardiovascular disease among patients with CKD may be related to factors beyond hyperlipidemia and hypertension (21). Although statins (4) and glucagon-like peptide-1 receptor agonists reduce MACE, and SGLT2 inhibitors (5) reduce heart failure in patients with type 2 diabetes and CKD, there is a high residual risk of these events. It has been hypothesized that nontraditional factors, including inflammation, endothelial dysfunction, and vascular calcification, may contribute to the residual risk (22) and may be driven, in turn, by a maladaptive epigenetic response (23). It is important to note that the reduction in risk of MACE and heart failure hospitalization with apabetalone occurred without an effect of treatment on kidney function as measured by eGFR, in contrast to SGLT2 inhibitors and some other agents, in which composite end points could be affected by CKD protection or reducing proteinuria (5). Therefore, other mechanisms of potential benefit of apabetalone, which are unique to CKD, may play a role in our findings, as recently described by Wasiak *et al.* (14), who showed a pronounced correction of the highly perturbed plasma proteome in patients with CKD stages 4–5. Although transcriptional regulation by selective BET inhibition has the trait of multiple small corrections of plasma markers toward normal levels, a noteworthy finding in our analysis pertains to serum alkaline phosphatase, an emerging cardiovascular risk factor in CKD and non-CKD populations (24). Both the expression and circulating level of alkaline phosphatase are elevated in CKD (3). In phase 2 studies, the reduction in serum alkaline phosphatase by apabetalone treatment was consistent (25) and predicted cardiovascular event reduction (16). In the BETonMACE trial, baseline serum alkaline phosphatase was 10 U/L higher in participants with versus without CKD (Table 1). In the CKD subgroup, apabetalone treatment resulted in a more pronounced enzyme reduction than in the non-CKD subgroup. This suggests that alkaline phosphatase may be a biomarker for apabetalone's effects, potentially through the hypothesized role of alkaline phosphatase in promoting endothelial dysfunction (26) and vascular calcification (15).

Our study is subject to several limitations, including the aforementioned small sample size of the CKD subgroup, comprising 12% of the entire trial population, which led to a suboptimal balance of treatment assignment. Participants with severe CKD (eGFR <30 ml/min per 1.73 m^2) were excluded; however, among adults with an eGFR of <60 ml/min per 1.73 m^2, >90% of participants were in

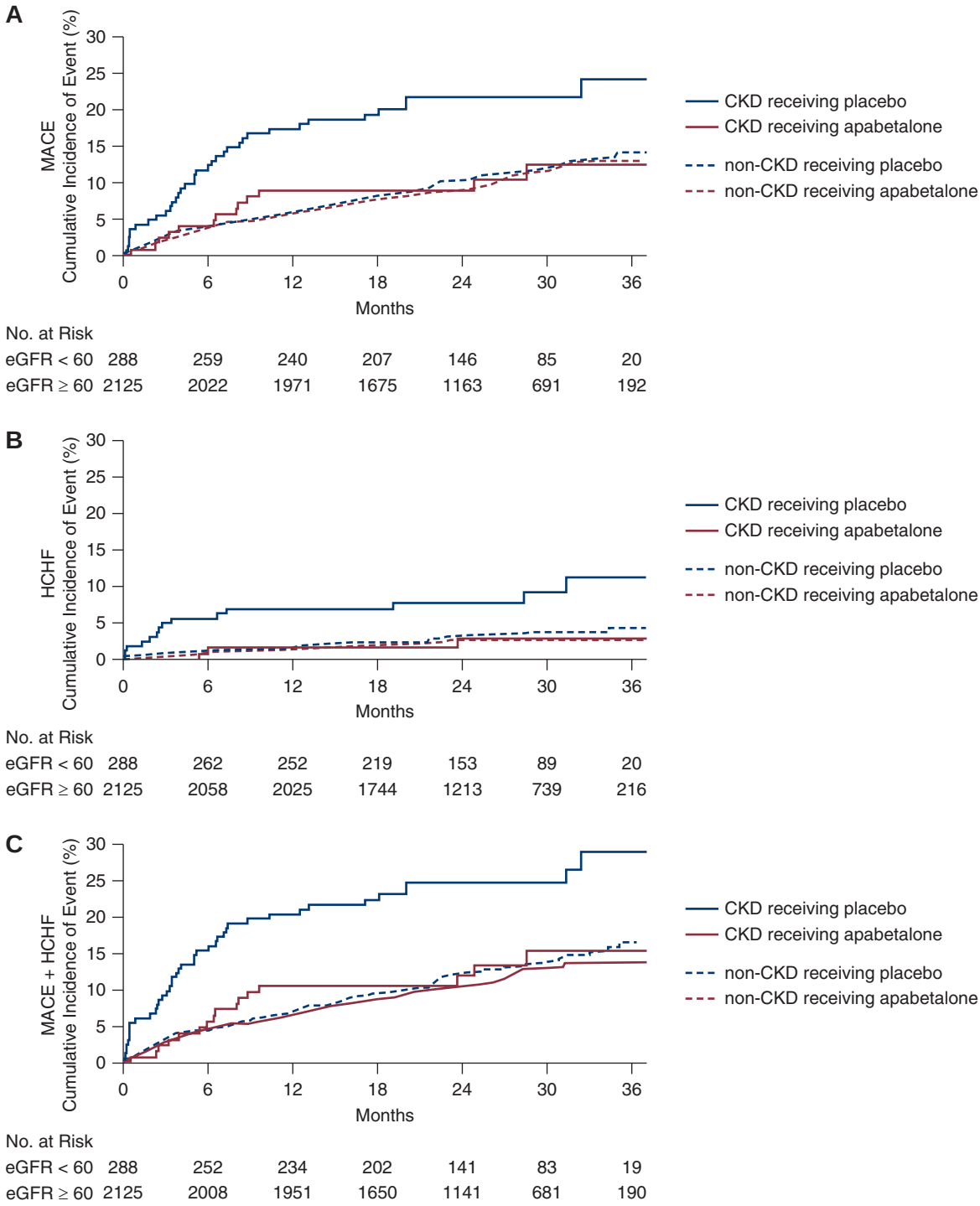

Figure 2. | **Kaplan–Meier estimates by treatment and CKD/non-CKD group for (A) MACE, (B) HCHF, and (C) the composite MACE plus HCHF.** In each panel, four curves are shown: CKD subjects receiving placebo (solid blue) and apabetalone (solid red), and non-CKD subjects receiving placebo (dashed blue) and apabetalone (dashed red). Number of subjects at risk is shown for CKD and non-CKD groups, aggregated over treatment. HCHF, hospitalization for congestive heart failure.

the 30–60 ml/min per 1.73 m^2 range (1). The trial was restricted to patients with type 2 diabetes, so we cannot assess the potential effect of apabetalone in patients with nondiabetic CKD. However, type 2 diabetes is the leading cause of CKD, and evidence is consistent that an association of cardiovascular risk with CKD exists irrespective of the presence or absence of diabetes (27). In BETonMACE, urine samples were not collected, so presence or absence of albuminuria and its modification by apabetalone remains unknown. In BETonMACE, markers of mineral metabolism, including parathyroid hormone, were not collected, so modification of bone turnover in patients with CKD by

Table 4. Adverse events in apabetalone versus placebo across CKD status[a]

Variable	Patients without CKD by Assigned Treatment Group		Patients with CKD by Assigned Treatment Group	
	Placebo (eGFR ≥60 ml/min per 1.73 m^2) (n=1041)	Apabetalone (eGFR ≥60 ml/min per 1.73 m^2) (n=1084)	Placebo (eGFR <60 ml/min per 1.73 m^2) (n=164)	Apabetalone (eGFR <60 ml/min per 1.73 m^2) (n=124)
Patients with at least one adverse event (%)[a]	699 (67)	739 (68)	119 (73)	88 (71)
Frequent adverse events[b,c]				
Acute myocardial infarction	38 (4)	38 (4)	12 (7)	4 (3)
Alanine aminotransferase increased	12 (1)	60 (6)	6 (4)	4 (3)
Angina	65 (6)	65 (6)	11 (7)	9 (7)
Anemia	30 (3)	32 (3)	10 (6)	4 (3)
Cardiac failure	24 (2)	19 (2)	14 (9)	3 (2)
Diarrhea	33 (3)	36 (3)	11 (7)	7 (6)
Hypertension	65 (6)	61 (6)	7 (4)	9 (7)
Nasopharyngitis	47 (5)	41 (4)	9 (5)	5 (4)
Pneumonia	16 (2)	23 (2)	10 (6)	4 (3)
Urinary tract infection	29 (3)	49 (5)	11 (7)	9 (7)
Unstable angina	36 (3)	56 (5)	5 (3)	2 (2)
Worsening diabetes mellitus	55 (5)	69 (6)	7 (4)	7 (6)

[a]Adverse events were assessed in the safety population, which includes all patients who received at least one dose of study drug medication.
[b]Includes treatment-emergent adverse events only, defined as those occurring after the first dose and within 14 d of the last dose of the study drug.
[c]Defined as occurring with a frequency of ≥5% in any of the CKD or treatment groups.

apabetalone remains unknown. During the BETonMACE trial, no significant change in eGFR in any group or subgroup was detected, which could be related to a mix of participants with likely evolving glomerular hyperfiltration, which often precedes diabetic nephropathy.

In conclusion, in this phase 3, randomized, controlled post–acute coronary syndrome trial in patients with type 2 diabetes, the participants with CKD were highly responsive to apabetalone treatment, with a 50% nominal reduction of MACE over 27 months. BETonMACE is the first cardiovascular outcome trial assessing the effect of epigenetic modification with BET protein inhibition. This prespecified, CKD subgroup analysis of BETonMACE suggests that apabetalone may offer a safe and effective oral pharmacotherapy for reducing cardiovascular risk in participants with CKD, diabetes, and recent acute coronary syndrome. A confirmatory apabetalone trial in patients with CKD and cardiovascular disease is warranted to corroborate the findings in BETonMACE.

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All members of the academic steering committee contributed to the interpretation of the data, including the sponsor coauthors.

Supplemental Material

This article contains the following supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.16751020/-/DCSupplemental.

Supplemental Summary 1. Collaborator information.

Supplemental Appendix 1. Statistical analysis plan.

Supplemental Table 1. Minimally adjusted hazard ratios (HR) for composite and component events in apabetalone versus placebo across CKD status for major adverse cardiovascular events (MACE).

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*The list of nonauthor contributors is extensive and has been provided in the Supplemental Summary 1.

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Supplemental Material

Appendix A: Statistical Analysis Plan

Table A: Minimally adjusted hazard ratios (HR) for composite and component events in apabetalone vs placebo across CKD status for major adverse cardiovascular events (MACE).

Appendix A: Statistical Analysis Plan

A Phase III multi-center, double-blind, randomized, parallel group, placebo-controlled clinical trial in high-risk type 2 diabetes mellitus (T2DM) subjects with coronary artery disease (CAD) to determine whether bromodomain extraterminal domain (BET) inhibition treatment with RVX000222 increases the time to major adverse cardiovascular events (MACE)

Final

Supplemental Statistical Analysis

Plan: Renal Version 14
Date: September 12, 2019

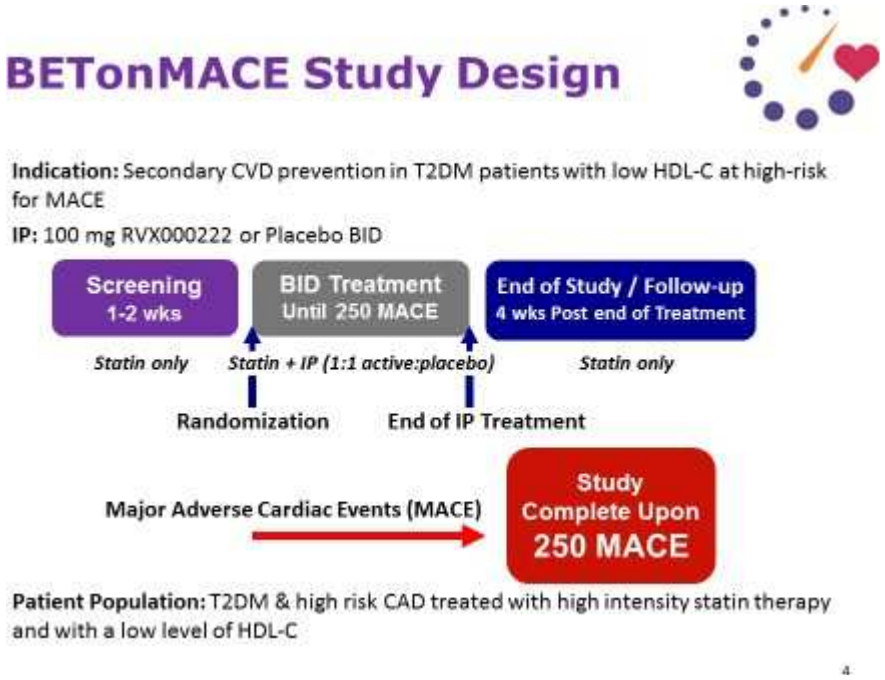
Prepared by:

Kam Kalantar-Zadeh, U of Irvine, CA, and Jan Johansson, Resverlogix

on behalf of BETonMACE Clinical Steering Committee.

Background: BETonMACE is a pivotal phase 3 trial in 2425 post-ACS patients with diabetes and low HDL-C levels. Its primary objective is to evaluate whether treatment with apabetalone 100 mg bid vs. placebo (standard of care treatment with randomization 1:1) increases time to first occurrence of the composite endpoint of 3-point major adverse cardiovascular events (3P-MACE) defined as occurrence of any of cardiovascular (CV) death, non-fatal myocardial infarction (MI), or stroke. It is powered to detect a hazard ratio (HR) for 3P-MACE of 0.7 with a target number of 250 primary events (first occurrence of 3P- MACE). A key secondary endpoint is "broadly defined MACE", defined as the composite of 3P-MACE (CV death, non-fatal MI and stroke) and hospitalization for CVD events (defined as either (i) unstable angina with evidence of new or presumed new progressive obstructive coronary disease; or (ii) emergence revascularization procedures at any time or urgent revascularization procedures at least 30 days after the pre-randomization index event). Additional secondary and exploratory endpoints are also defined.
The overall design is shown in Figure 1 below; for a more detailed discussion of the design and a summary of baseline results, see the American Heart Journal manuscript (accepted July 2019).

Figure 1. BETonMACE principle study design



In BETonMACE approximately 11% (n=250) of the patients have compromised renal function at randomization/baseline as defined by eGFR (estimated glomerular filtration rate) of 30 - <60 mL/min/1.73² , i.e., Chronic Kidney Disease (CKD) stage 3A (eGFR 45 - <60), and stage 3B (eGFR 30 - <45 mL/min/1.73²). Additionally, a number of patients will develop de novo CKD during the trial, i.e. having

eGFR ≥60 at randomization and declining to <60 mL/min/1.73² during the course of the study. Estimated mean treatment duration at termination of patients in BETonMACE is 26 months (range 8-44 months).

The BETonMACE formal *Statistical Analysis Plan* (hereafter, "main SAP") was initially submitted to FDA on Sept 1, 2018 with clarifying amendment submitted June 2019. The current version is *Final Version 3.0, dated 10 June 2019.* It includes as a secondary endpoint the apabetalone vs. placebo effects on renal function, i.e., eGFR change within and between treatment arms over time, in the patients with a baseline eGFR <60 mL/min/1.73² at randomization.

The purpose of this BETonMACE supplemental/"academic" renal SAP is to pre-specify more detailed analyses of the effect of randomization to apabetalone vs. placebo on renal function. The analysis objectives are to evaluate the hypotheses that:

a) Apabetalone delays or reverses progression of CKD (renal tissue effects)
b) Apabetalone lowers a composite of renal and CVD events
c) The effect of apabetalone on CVD events varies by baseline CKD status

The analyses proposed in this renal SAP will be fully pre-specified and finalized prior to unblinding of the trial data. Except where otherwise indicated, analyses conducted under this SAP will use the same general analysis conventions (e.g., statistical approaches, analysis sets, time point definitions, etc.) as documented in the main SAP.

<u>Analysis Objective 1 –Evaluate the hypothesis that apabetalone delays or reverses progression of CKD (renal tissue effects)</u>

For the analyses below, we will define the following seven "baseline renal subgroups" of BETonMACE patients:

- All patients (the full analysis set [FAS], as defined in the main SAP)
- CKD subpopulation (subset of FAS with baseline eGFR <60 mL/min/1.73²)
    - CKD stage 3A subpopulation (subset with eGFR 45 - <60 mL/min/1.73²)
    - CKD stage 3B subpopulation (subset with eGFR 30 - <45 mL/min/1.73²)
- Non-CKD subpopulation (subset with baseline eGFR ≥60 mL/min/1.73²)
- CKD subpopulation (subset of FAS with baseline eGFR <90 mL/min/1.73²)
- Non-CKD subpopulation (subset with baseline eGFR ≥90 mL/min/1.73²)

Baseline Characteristics

To characterize the baseline renal subgroups, we will produce subgroup summaries (see example Table 1 below) of baseline characteristics to include demographics, relevant concomitant medications at baseline, ACS category (MI, UA +/- PTCA), statin (rosuvastatin vs. atorvastatin), etc. overall and by randomized treatment group. We will produce similar subgroup summaries of baseline clinical chemistry (see example Table 2 below).

CKD Prevention Paradigm

To assess the effect of apabetalone on the prevention of *de novo* CKD (prevention paradigm assessment), we will evaluate **in the non-CKD baseline renal subgroup(s):**

a) Descriptives statistics (means, SDs, quantiles) for measured values, and absolute and percent change from baseline by treatment at all time points of eGFR, serum creatinine, serum albumin, serum ALP, and hsCRP.
b) Linear mixed effects models of these analytes by time to estimate change/year.
c) Counts and percentages (see example Table 3 below) by treatment of number of patients reaching different CKD stages based on eGFR <60, <45, <30 <15 and dialysis during study, within the first year, and within the second year.
d) Counts and percentages by treatment of number of patients with:
    i. eGFR decrease by 25%, 33.3 %, and 50% from baseline, respectively
    ii. Serum-creatinine increase by 33.3%, 50% and 100% from baseline, respectively

The above analyses will be conducted overall and by statin subgroup (atorvastatin vs. rosuvastatin).

CKD Treatment Paradigm

To assess the effect of apabetalone on the prevention or slowing of progression of CKD (treatment paradigm assessment), we will evaluate **in the CKD baseline renal subgroup,** the same set of analyses described in the "CKD Prevention Paradigm" section above.

a) Figures Absolute and % Change in eGFR, serum-creatinine, serum albumin over time, serum ALP, hsCRP calculate changes over time, e.g. per year for the variables for each group Table 3 (example below) number of patients from the 6 groups reaching CKD stage with eGFR <60, <45, <30, and <15 mL/min/1.73² and number of patient starting dialysis (during study and estimated per year for all variables).
b) number of patients in the 6 groups, who during the course of the study:
    i. have eGFR decrease 25%, 33.3 %*, and 50%, respectively
    ii. have an increase of serum-creatinine of 33.3%, 50%* and 100%, respectively
    iii. require dialysis

Analysis Objective 2 – Evaluate the hypothesis that apabetalone lowers a composite of renal and CVD events

We will define and analyze a composite of renal and CVD events in accordance with the approach taken in the Credence study (Perkovic et al. NEJM June 13, 2019). Since the post-ACS BETonMACE population at baseline has higher CVD risk and less severe degree of renal disease than in the Credence study, we adopt a composite event definition with a renal component that is slightly relaxed to allow for more renal events. The "renal/CV composite" is defined as the first of either broadly defined MACE (as defined above) or a "renal event" defined by a ≥50% serum creatinine increase from baseline or a ≥33.3% eGFR decrease from baseline.

We will conduct analyses of time to first renal/CV composite event consisting of:

(a) Kaplan-Meier analysis by treatment
(b) Estimation of the hazard ratio (HR) with 95% confidence interval using a Cox proportional hazard model with stratification by country and statin. A log-rank statistic will be used.
(c) Additional subgroup analyses as described in the main SAP (including the rosuvastatin and atorvastatin subgroups), if warranted by the overall results.

We will also conduct analyses of total (first and recurrent) renal/CV composite events consisting of:

(a) Estimation of the mean cumulative incidence functions by treatment
(b) Estimation of the hazard ratio with 95% confidence intervals based on the Andersen-Gill generalization of the Cox model using a random frailty effect (per subject with gamma distribution). A Wald test will be used for testing the significance of the treatment effect. As in the main SAP, an analysis stratified by country and statin will be used.
(c) Additional subgroup analyses as described in the main SAP (including the rosuvastatin and atorvastatin subgroups, as well as age, sex, baseline LDL, HDL, hsCRP, etc.), if warranted by the overall results.

Similar analysis will also be conducted on the renal component (>50% serum creatinine increase from baseline or a ≥33.3% eGFR decrease from baseline) alone.

Analysis Objective 3 – Evaluate the hypothesis that the effect of apabetalone on CVD events varies by baseline CKD status

The main SAP includes analyses of CVD events by subgroup for the CKD (eGFR <60) and Non-CKD (eGFR
≥60) baseline renal subgroups. We will also conduct CVD event analyses for the additional baseline renal subgroups defined above (CKD stage 3A and CKD stage 3B). These analyses will include analyses of total (first and recurrent) broadly defined MACE, time to first 3P-MACE, CV mortality, and all-cause mortality. Given the high prevalence of congestive heart failure in the CKD population we will also calculate CV-death, CHF hospitalizations (first, and total) alone and together (ref. DAPA-HF, McMurray et al. ESC 2020).

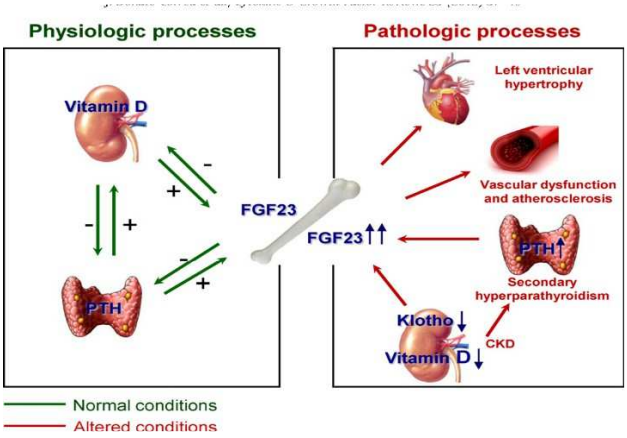
Similar apabetalone vs. placebo analysis for effects on events will also be performed for eGFR <90 vs. eGFR =>90.

*Contingency analyses based on archive sample biomarker analysis.

Following a statistically significant favorable effect on eGFR by apabetalone vs. placebo, additional analysis may be performed and assessed for baseline and change characteristics, including:

- Cystatin C (as creatinine independent GFR assessment),
- Parathyroid Hormone (PTH),
- Vitamin D, Vitamin B6/pyridoxal-5'-phosphate ((PLP),
- Pyrophosphate (PPi), Osteoprotegerin, and,
- Klotho and FGF23 (established risk factor for osteoporosis and CHF).

For general rationale, see Figure below and Lu and Hu 2017 (Lu X, Hu MC. Klotho/FGF23 Axis in Chronic Kidney Disease and Cardiovascular Disease. Kidney Dis (Basel). 2017 Jul;3(1):15-23).



In addition, following significant effects on eGFR, indicating renal function preservation, a non-biased proteomics assessment will be considered. The objective is to better understand the detailed MoA of apabetalone on renal tissue preservation.

Urine analysis for protein/creatinine-ratio is performed in Russia at baseline, 6 months and yearly. We only expect about 4 patients to have CKD and two patients with CKD to be treated with apabetalone out of the 35 Russian participants. As anecdotal cases we will follow over-time-change in urine protein-to-creatinine-ratio and change in serum eGFR, creatinine, albumin, hsCRP and ALP.

Missing values: For addressing missing values Mixed-Effect Model Repeated Measure (MMRM) model will be applied as a rule, and when not appropriate last-value-carried-forward model. Reference: Siddiqui O[1], Hung HM, O'Neill R. J Biopharm Stat. 2009;19(2):227-46. MMRM vs. LOCF: a comprehensive comparison based on simulation study and 25 NDA datasets.

Table 1. Baseline demographics, all patients, non-CKD, CKD, CKD stage 3a, CKD stage 3B (5 groups)

Parameter	All patients (n=)	non-CKD (n=)	CKD eGFR 30-59	CKD Stage 3A (n=)	CKD Stage 3B
Age (years)					
Male (%)					
Cucasian (%)					
Randomizatiion inclusion criteria;					
Acute coronary syndrome/myocardial infarction					
Unstable angina					
PTCA/stenting					
Diabetes History (medium years)					
History of taking diabetes medication Yes%					
History of taking diabetes medication No%					
HbA1c ≥6.5% at Visit 1					
BMI (kg/m2)					
Hypertension (%)					
ACS history (%)					
Smoker (%)					
Standard of care medication;					
Insulin (%)					
Oral DM medication (%)					
Metformine					
Sulfonylureas					
glyburide/glibenclamide(DiaBeta, Glynase, or Micronase)					
glimepiridine(Amaryl)					
chlorpropamide(Diabinase)					
glipizide (Glucotrol)					
tolazamide) (Tolinaze)					
Tolbutamide					
GLP-1 agonist (%)					
exenatide (Byetta/Bydureon)					
liraglutide (Victoza, Saxenda)					
lixisenatide (Lyxumia)					
albiglutide (Tanzeum)					
dulaglutide (Trulicity)					
semaglutide (Ozempic)					
SGLT2 inhibitor (%)					
canagliflozin (Invokana) dapagliflozin (Farxiga) empagliflozin (Jardiance) empagliflozin/linagliptin (Glyxambi) empagliflozin/metformin (Synjardy) dapagliflozin/metformin (Xigduo XR)					
Atorvastatin (%)					
Rosuvastatin (%)					
ACE-inhib.					
lisinopril (Zestril), benazepril (Lotensin) and enalapril (Vasotec)					
ARBs					
losartan(Cozaar), valsartan (Diovan) and irbesartan (Avapro)					
B-blockers (%)					
Antiplatelet agents (%)					
Double antiplatelets agents (%)					
*Mann-Whitney U-test, Groups 1-2, 1-3, 2-3, 4-5					

Table 2. Baseline serum chemistry CKD populations

Parameter	All patients (n=)	non-CKD (n=)	CKD/eGFR 30-59	CKD Stage 3A (n=)	CKD Stage 3B
Alkaline Phosphatase†, U/L (n=)					
eGFR, mL/min/1.73 m2 (n=)					
Albumin, g/dL					
LDL-C, mg/dL					
(n=) HDL-C,					
mg/dL (n=)					
Apolipoprotein A-I†, mg/dL (n=)					
hsCRP†, mg/L (n=)					
Fibrinogen‡, mg/L (n=)					
HbA1c, % (n=)					
Platelets, 10^9/ L (n=)					
NLR, ratio (n=)					
LD					
Bilirubin					
GGT					
other values are from visit 1/screening					
Statistical analysis groups 1-2, 1-3,2-3, 4-5					

Table 3. Apabetalone all, apabetalone + Rosuva, apabetalone +Atorva vs. placebo all, placebo +Rosuva, placebo + Atorva (total 6 groups) effects in preventing non-CKD patients (eGFR ≥60 mL/min/ 1.73²) deteriorate to CKD stages

Non-CKD population reaching	ABL All	ABL Rosuva	ABL Atorva	Placebo All	PL Rosuva	PL Atorva
During study eGFR;	All					
<60						
<45						
<30						
<15						
starting dialysis						
First year;						
<60						
<45						
<30						
<15						
starting dialysis						

<u>Supplemental Table A</u>: Minimally adjusted hazard ratios (HR) for composite and component events in apabetalone vs placebo across CKD status for major adverse cardiovascular events (MACE).

		eGFR < 60 ml/min/1.73 m^2	eGFR ≥ 60 ml/min/1.73 m^2	
		HR (95% CI)	**HR (95% CI)**	**Int. P-Value**
Primary Outcome				
	MACE	**0.50** [0.26,0.96]	0.94 [0.73,1.22]	0.032
Composite Events				
	MACE + CHF	**0.48** [0.26,0.89]	0.89 [0.70,1.14]	0.033
Components				
	CV death	0.47 [0.18,1.21]	0.98 [0.63,1.54]	0.12
	Non-fatal MI	0.60 [0.27,1.34]	0.88 [0.63,1.22]	0.26
	Non-fatal stroke	0.55 [0.11,2.79]	1.35 [0.62,2.94]	0.20
	CHF hospitalization	**0.26** [0.07,0.94]	0.74 [0.45,1.24]	0.12

Abbreviations: eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; MACE, major adverse cardiovascular events; HCHF, hospitalization for congestive heart failure; CHF, congestive heart failure

Shown are HRs and 95% CIs for indicated composite and component endpoints. All analyses are stratified for statin and country, in accordance with the primary analyses.[18] Interaction P-value tests for difference by CKD status in the effect of apabetalone on event rates.

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Petersburg City Outpatient Clinic #109, St. Petersburg); Elena Kulibaba (State Budgetary Healthcare Institution of Vladimir Region City Hospital No. 4, Vladimir); Olga Smolenskaya (Ural State Medical University, Yekaterinburg); Nikolay Tarasov (Federal Budget Healthcare Institution Medici - sanitary unit of Ministry of internal affairs of Russ, Kemerovo); Zaur Shogenov (Moscow City State Budgetary Healthcare Institution City Clinical Hospital named after V.V. Veresayev, Moscow); Leonid Strongin (City Hospital 13, Nizhniy Novgorod); Anatoly Kuzin (City Clinical Hospital #6, Chelyabinsk); Valeriy Makukhin (Krasnodar Regional Clinical Hospital #2, Krasnodar); Konstantin Nikolaev (State Budgetary Healthcare Institution of Novosibirsk Region City Clinical Hospital No. 19, Novosibirsk); Sergey Tereschenko (Russian Cardiology Research and Production Center, Moscow); Natalya Vezikova (Republican Hospital n.a. V.A. Baranov, Petrozavodsk).

Serbia (462 patients enrolled): Vladimir Miloradovic (Clinical Center Kragujevac, Kragujevac); Milan Pavlovic (Clinical Center Nis, Nis); Marina Deljanin Ilic (Institute Niska Banja, Niska Banja); Dragan Simic (Clinical Center of Serbia, Belgrade); Georgina Pudar-Brankovic (Euromedik, Belgrade); Tanja Jozic (Clinical Center of Serbia, Belgrade); Slobodan Dodic (Institute of Cardiovascular Diseases of Vojvodina, Sremska Kamenica); Arsen Ristic (Clinical Center of Serbia, Belgrade); Sasa Hinic (Clinical Hospital Center Bezanijska Kosa, Belgrade); Vladimir Mitov (Health Center Zajecar, Zajecar); Natasa Stokuca-Korac (Institute of Cardiovascular Diseases Dedinje, Belgrade); Edita Stokic (Clinical Centre of Vojvodina, Novi Sad); Vera Celic (KBC Dr Dragisa Misovic Dedinje, Belgrade); Nebojsa Despotovic (Clinical Hospital Centar Zvezdara, Belgrade); Dragan Dincic (Military Medical Academy, Belgrade); Biljana Putnikovic Tosic (Clinical Hospital Centre Zemun, Belgrade); Aleksandar Selakovic (General Hospital Uzice, Uzice).

Slovakia (169 patients enrolled): Daniel Pella (CARDIO D&R, s.r.o. Kosice, Kosice); Milan Banik (MEDI M&M s.r.o., Moldava nad Bodvou); Jan Fedacko (CARDIO D&R, s.r.o. Kosice, Kosice); Karol Micko (KARDIOMED s.r.o., Lucenec); Tibor Duris (Cardioinvest s. r. o., Nove Zamky); Martin Kokles (Univerzitna nemocnica Bratislava, Bratislava); Beata Lachova (DIAB s.r.o., Roznava); Andrej Dzupina (ALIAN, s.r.o, Bardejov); Juraj Mazur (Kardio-Onkologia, s.r.o., Dolny Kubin); Ingrid Buganova (MEDIVASA, s.r.o., Zilina); Milan Behuncik (Nemocnica Zeleznicne zdravotnictvo Kosice – ZVET ZDRAVIA - PPDS, Kosice); Silvia Vadinova (Nemocnica s poliklinikou Nove Mesto nad Vahom n.o., Nove Mesto nad Vahom). Taiwan (38 patients enrolled): Hung-I Yeh (Mackay Memorial Hospital-Taipei branch, Taipei); Chern-En Chiang (Taipei Veterans General Hospital, Taipei); Cheng-Hen Lee (National Cheng Kung University Hospital, Tainan); I-Chang Hsieh (Chang Gung Medical Foundation Linkou Branch, Taoyuan); Lin Jiunn-Lee (National Taiwan University Hospital, Taipei); We-Hsiang Lin (Tri-Service General Hospital, Taipei); Yen-Wen Wu (Far Eastern Memorial Hospital, New Taipei); Chien Hsun Hsia (Changhua Christian Hospital, Changhua); Ping Han Lo (China Medical University Hospital, Taichung).