Supplementary Appendix

Effect of apabetalone added to standard therapy on major adverse cardiovascular events in patients with recent acute coronary syndrome and type 2 diabetes: a randomized clinical trial

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On behalf of the BETonMACE Investigators and Committees**

*KKR and GGS contributed equally to the manuscript

**Listed in Section 1 of this Appendix

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2. Trial Registration

Registration for study RVX222-CS-015 was submitted to ClinicalTrials.gov on 10/25/2015.

- The first patient was screened on 11/04/2015 and was randomized on 11/11/2015.

3. Laboratory analytical methods

Clinical laboratory samples were collected and analyzed for calculated LDL cholesterol (LDL-C), Triglycerides (TG), Total Cholesterol (TC), HDL cholesterol (HDL-C), high-sensitivity C-reactive protein (hsCRP), alkaline phosphatase (ALP), alanine transaminase (ALT), bilirubin, gamma-glutamyl transferase (GGT), creatinine and estimated glomerular filtration rate (eGFR) at clinic visits as per the study protocol. All analyses were performed at a central laboratory (ICON).

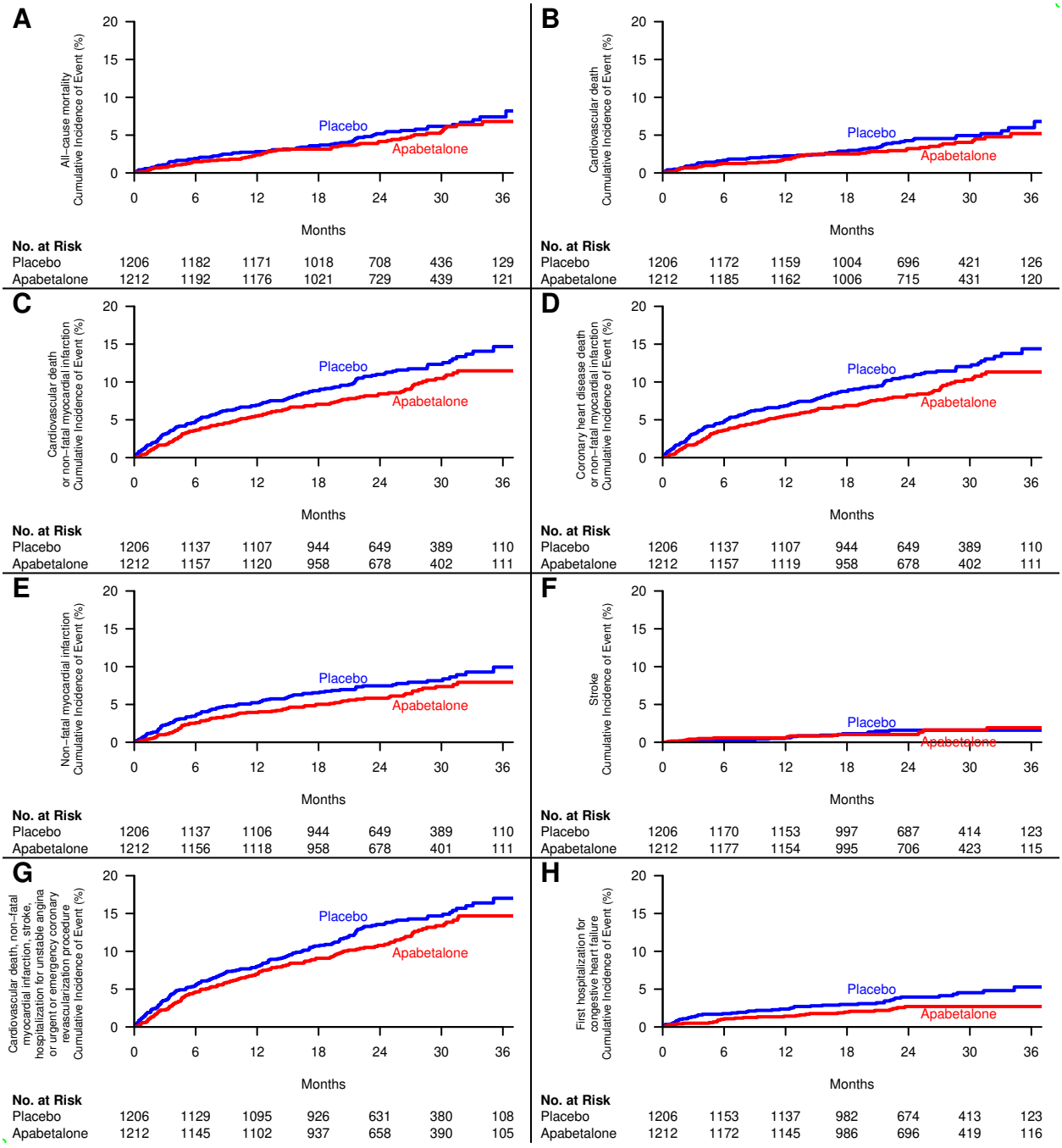
- **LDL-C** was calculated using the Friedewald equation: LDL-C in mg/dl = total cholesterol – (HDL-C + TGs/5).
    - **If TGs** exceeded 400 mg/dl, direct measurement of LDL-C was performed using the MULTIGENT Direct LDL assay on the Abbott ARCHITECT analyzer.
- **Total cholesterol and TGs** were quantified using enzymatic methods and the Abbott ARCHITECT System instrumentation.
- **HDL-C was** quantified using the Ultra HDL assay run on the Abbott ARCHITECT analyzer.
- **hsCRP** was measured using the MULTIGENT CRP Vario immunoassay run on the Abbott ARCHITECT analyzer.
- **ALP:** Alkaline phosphatase catalyzes the hydrolysis of colorless p-nitrophenyl phosphate (p-NPP) to give p-nitrophenol and inorganic phosphate. At the pH of the assay (alkaline), the p-nitrophenol is in the yellow phenoxide form. The rate of absorbance increase at 404 nm is directly proportional to the alkaline phosphatase activity in the sample. Analyzed on the Abbott ARCHITECT system.
- **ALT:** ALT present in the sample catalyzes the transfer of the amino group from L-Alanine to 2-Oxoglutarate, in the presence of Pyridoxal-5'-Phosphate, forming Pyruvate and L-Glutamate. Pyruvate in the presence of NADH and Lactate Dehydrogenase (LD) is reduced to L-Lactate. In this reaction NADH is oxidized to NAD. The reaction is monitored by measuring the rate of decrease in absorbance at 340 nm due to the oxidation of NADH to NAD. Analyzed on the Abbott ARCHITECT system.
- **Bilirubin:** bilirubin assay is based on the reaction of bilirubin with a diazo reagent to form the colored compound azobilirubin. The increase in absorbance at 548 nm due to azobilirubin is directly proportional to the total bilirubin concentration. Analyzed on the Abbott ARCHITECT system.
- **GGT:** GGT catalyzes the transfer of the gamma-glutamyl group from the donor substrate (L-gamma-glutamyl-3-carboxy-4-nitroanilide) to the glycylglycine acceptor to yield 3-carboxy-4-nitroaniline. The rate of the absorbance increase at 412 nm is directly proportional to the GGT in the sample. Analyzed on the Abbott ARCHITECT system.
- **Creatinine**: At an alkaline pH, creatinine in the sample reacts with picrate to form a creatinine-picrate complex. The rate of increase in absorbance at 500 nm due to the formation of this complex is directly proportional to the concentration of creatinine in the sample. Analyzed on the Abbott ARCHITECT system.
- **eGFR** was calculated using the Cockford-Gault formula:

eGFR in mL/min/1.73m^2 = (140 – Age) ×Weight in kg × [1.23 for men or 1.04 for women] / serum creatinine in umol/L
eGFR was calculated from available serum creatinine data and age and weight at baseline.

4. Supplementary eFigures

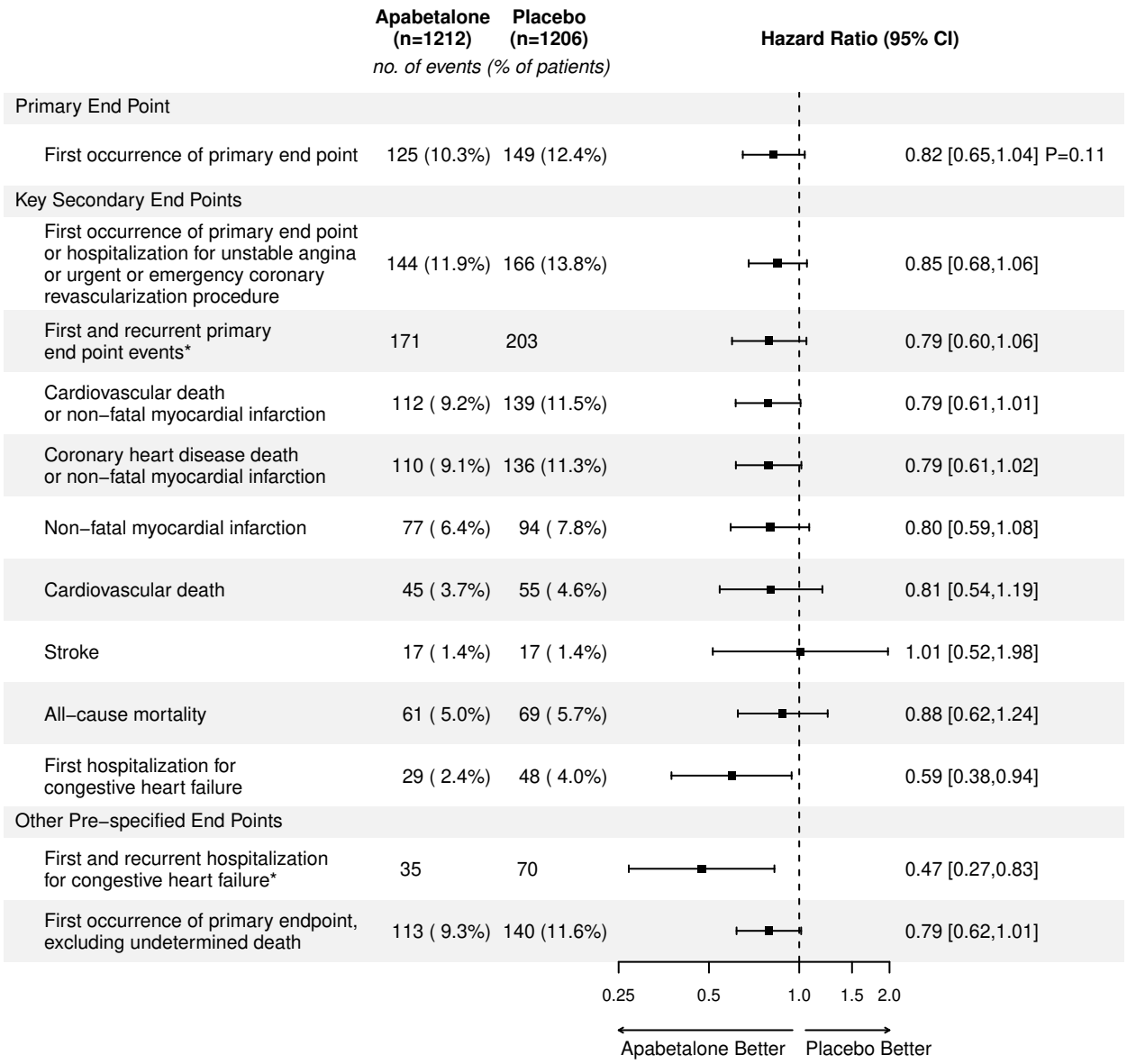
eFigure 1. Kaplan-Meier estimates of pre-specified secondary endpoints.

Panel A, shows all-cause mortality; Panel B, shows cardiovascular death; Panel C, shows cardiovascular death or non-fatal myocardial infarction; Panel D, shows coronary heart disease death or non-fatal myocardial infarction; Panel E, shows non-fatal myocardial infarction; Panel F, shows stroke; Panel G, shows cardiovascular death, non-fatal myocardial infarction, stroke, hospitalization for unstable angina or urgent or emergency coronary revascularization procedures; Panel H, shows first hospitalization for congestive heart failure



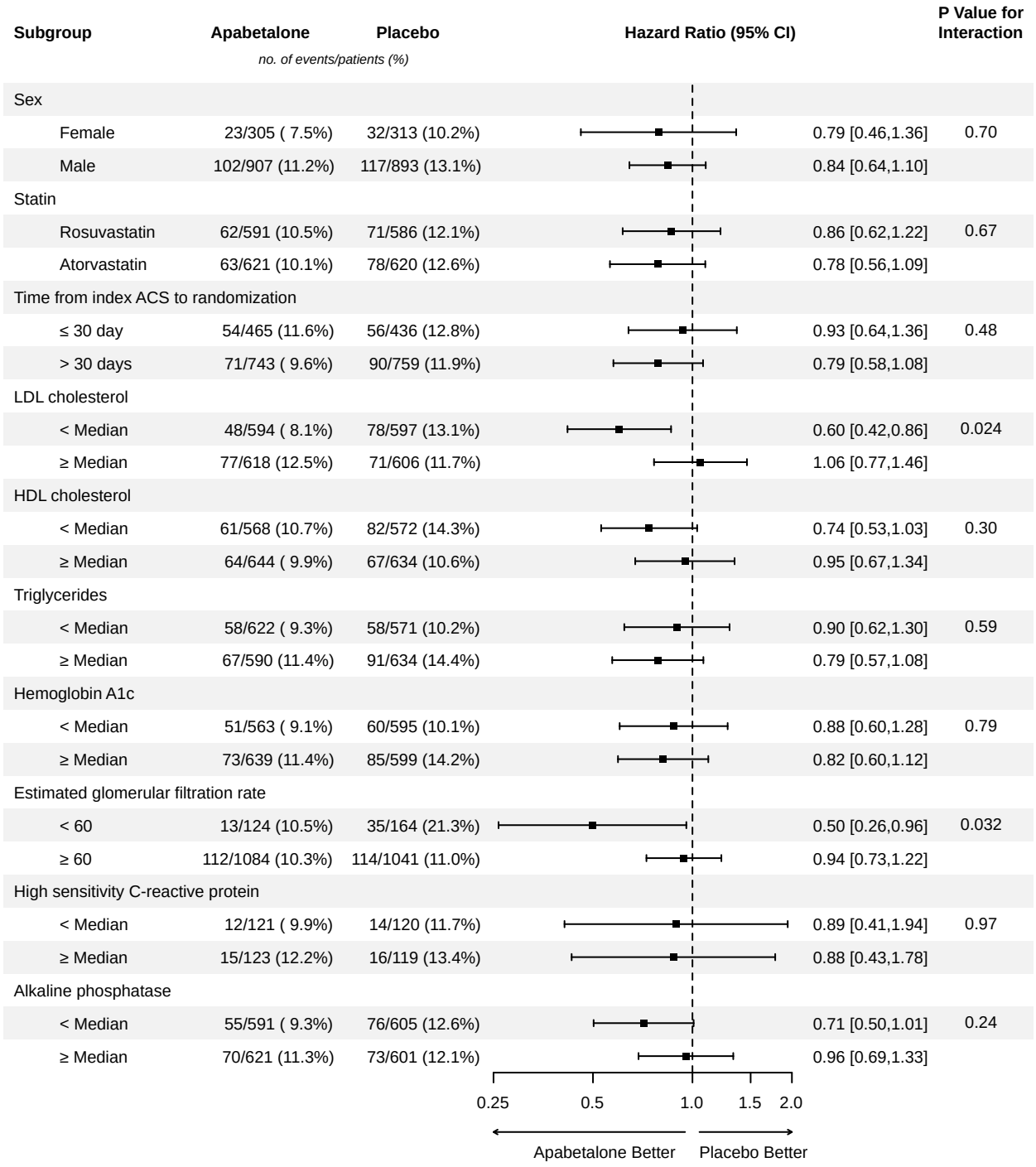
eFigure 2. Hazard ratios for primary and secondary end point events.

The primary end point comprised cardiovascular death, non-fatal myocardial infarction or stroke. The primary endpoint was not significantly modified by assigned treatment; therefore, the pre-specified hierarchical hypothesis testing statistical plan states that no statistical inference of significance (or lack) should be drawn from secondary endpoints. Hazard ratios and confidence intervals for secondary endpoints are provided for descriptive purposes only. Numbers of events (% of patients) in each treatment group are shown, as are hazard ratios and 95% confidence intervals. *First and recurrent event endpoints include multiple events per patient. Total number of events experienced by treatment group are given.



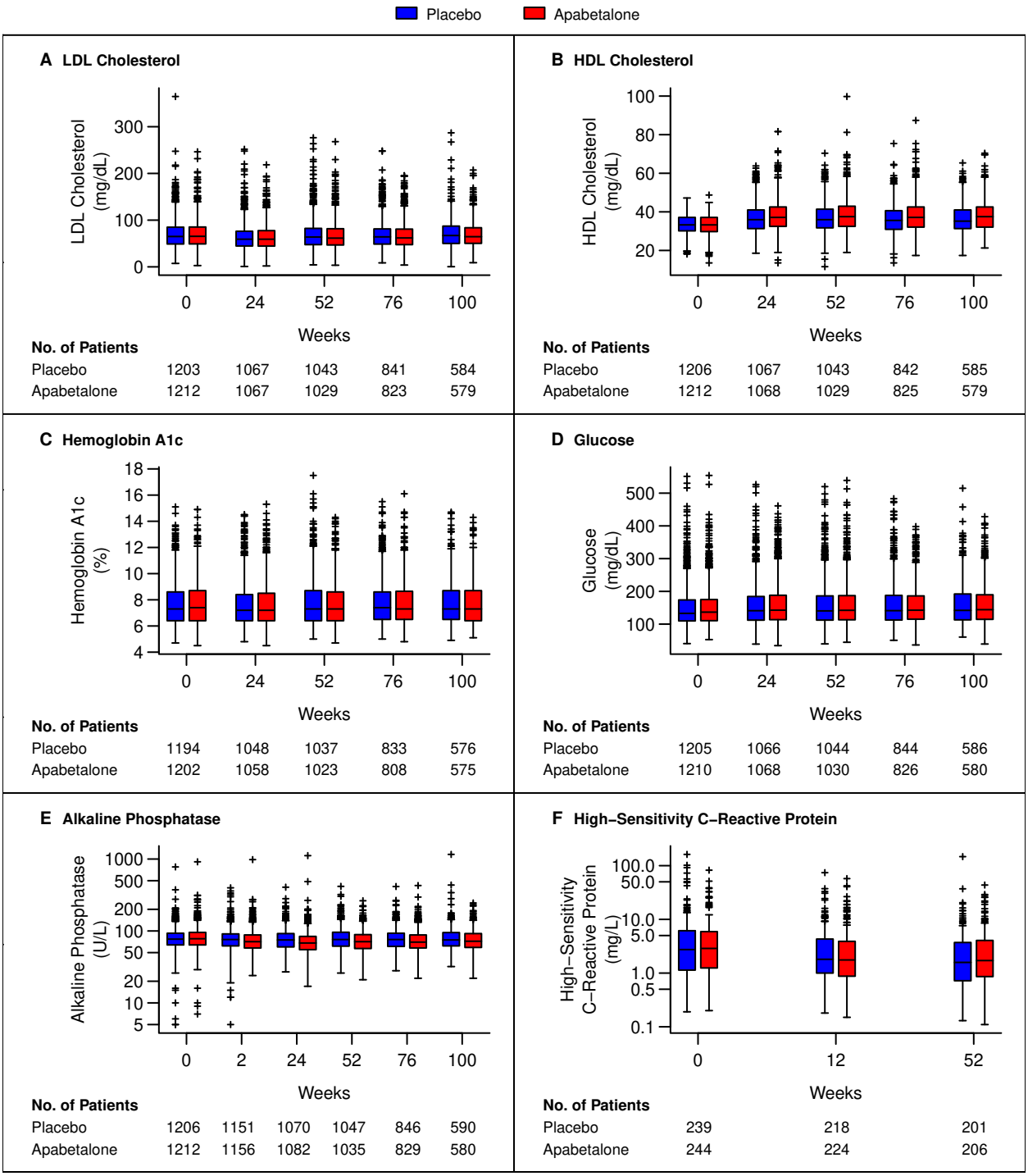
eFigure 3. Effect of apabetalone on the primary efficacy end point by pre-specified subgroup

Values shown represent hazard ratios (HR) and 95% confidence intervals (CI) for the primary endpoint (first occurrence of cardiovascular death, non-fatal myocardial infarction, or stroke) for pre-specified baseline subgroups. Also shown are number of first events, numbers of patients, and percentage of patients with an event. P-values for treatment/subgroup interaction are based on a Cox proportional hazards model stratified by statin and region (or, for the statin subgroups, region only). No adjustment was made for multiple comparisons.



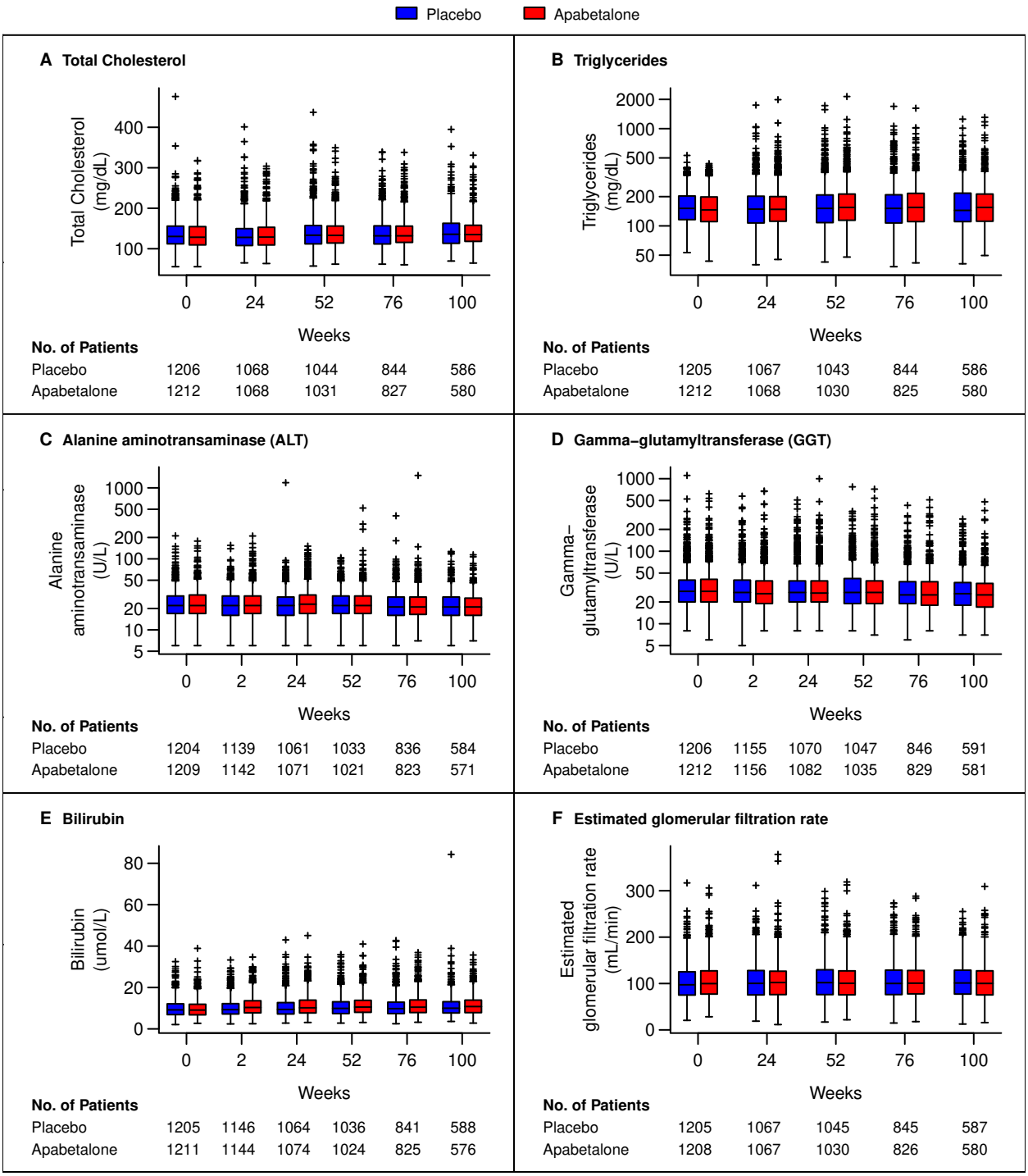
eFigure 4. Effect of apabetalone versus placebo on biomarkers over time

The effect of apabetalone versus placebo on levels of (A) LDL cholesterol (B) HDL cholesterol (C) hemoglobin A1c (D) glucose (E) alkaline phosphatase (F) high sensitivity C-reactive protein (hs-CRP) over time are shown as box and whisker plots. Apabetalone increased HDL cholesterol and reduced alkaline phosphatase by 24 weeks (P <0.001 for both). To convert LDL and HDL cholesterol to millimoles per liter multiply by 0.02586 and to convert glucose to millimoles per liter multiply by 0.05556.



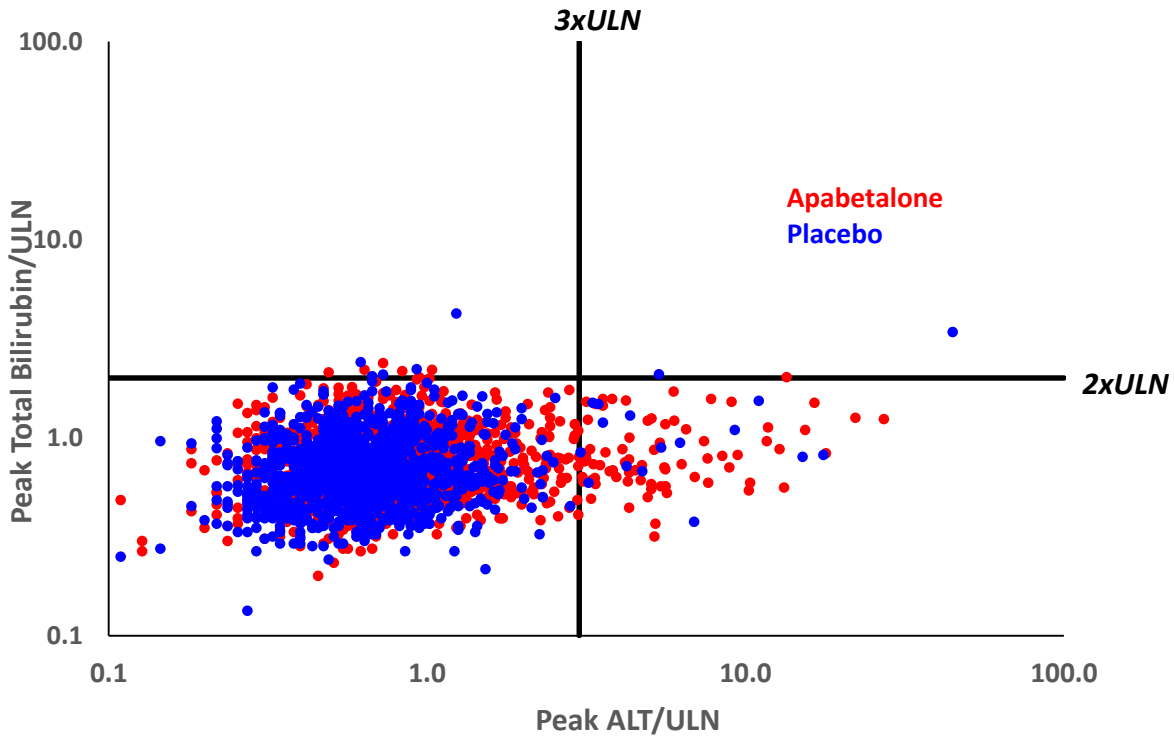
eFigure 5. Effect of apabetalone versus placebo on additional selected biochemical measures over time

The effect of apabetalone versus placebo on levels of (A) total cholesterol (B) triglycerides (C) alanine aminotransaminase (D) gamma-glutamyl transferase (E) bilirubin (F) estimated glomerular filtration rate are shown as box and whisker plots. To convert total cholesterol to millimoles per liter multiply by 0.02586 and to convert triglycerides to millimoles per liter, multiply by 0.01129.



eFigure 6. eDISH plot assessing liver adverse events

The standard assessment method using an evaluation of drug-induced serious hepatotoxicity (eDISH) plot of alanine transaminase (ALT) concentration versus bilirubin concentration as measured relative to upper limit of normal range (ULN) showed that events were confined to Temple's Corollary segment of the plot with no Hy's Law events [ALT>3xULN and total bilirubin >2xULN] in the quadrant known to be associated with drug-induced hepatotoxicity. The single data point on the borderline of this quadrant with active therapy was a 72-year old male in Israel who took a single dose of study medication following randomization then discontinued study medication due to headache but remained in the study for follow-up. Ten months following discontinuation of study drug, laboratory tests showed simultaneous elevation of ALT (peak 13.5X ULN) and bilirubin (peak 2X ULN) coupled with serious adverse events of cholelithiasis and choledocholithiasis. This case was considered to reflect cholelithiasis/choledocholithiasis and to be unrelated to study medication.



5. eTable. System organ class treatment-emergent adverse events with at least 2% incidence in either group

System organ class adverse event	Apabetalone (N=1212)	Placebo (N= 1207)	RR (95% CI)
Infections and Infestations	291 (24.0)	296 (24.5)	0.98 (0.85-1.13)
Nasopharyngitis	46 (3.8)	56 (4.6)	0.82 (0.56-1.20)
Urinary tract infection	58 (4.8)	40 (3.3)	1.44 (0.97-2.14)
Influenza	43 (3.5)	47 (3.9)	0.91 (0.61-1.37)
Bronchitis	25 (2.1)	32 (2.7)	0.78 (0.46-1.30)
Pneumonia	27 (2.2)	26 (2.2)	1.03 (0.61-1.76)
Upper respiratory tract infection	29 (2.4)	24 (2.0)	1.20 (0.70-2.05)
Cardiac Disorders	260 (21.5)	278 (23.0)	0.93 (0.80-1.08)
Angina	74 (6.1)	76 (6.3)	0.97 (0.71-1.32)
Angina unstable	58 (4.8)	41 (3.4)	1.41 (0.95-2.08)
Acute myocardial infarction	42 (3.5)	50 (4.1)	0.84 (0.56-1.25)
Cardiac failure	22 (1.8)	38 (3.1)	0.58 (0.34-0.97)
Gastrointestinal Disorders	186 (15.3)	170 (14.1)	1.09 (0.90-1.32)
Diarrhea	43 (3.5)	44 (3.6)	0.97 (0.64-1.47)
Abdominal pain	12 (1.0)	24 (2.0)	0.50 (0.25-0.99)
Nausea	26 (2.1)	7 (0.6)	3.70 (1.61-8.49)
Musculoskeletal	143 (11.8)	183 (15.2)	0.78 (0.63-0.95)
Myalgia	37 (3.1)	33 (2.7)	1.12 (0.70-1.77)
Back pain	17 (1.4)	28 (2.3)	0.60 (0.33-1.10)
Pain in extremity	15 (1.2)	26 (2.2)	0.57 (0.31-1.08)
Arthralgia	11 (0.9)	24 (2.0)	0.46 (0.22-0.93)
Metabolism and nutrition disorders	148 (12.2)	170 (14.1)	0.87 (0.71-1.06)
Worsening diabetes mellitus	93 (7.7)	93 (7.7)	1.00 (0.76-1.31)
Vascular Disorders	135 (11.1)	142 (11.8)	0.95 (0.76-1.18)
Hypertension	72 (5.9)	72 (6.0)	1.00 (0.73-1.37)
Investigations	160 (13.2)	86 (7.1)	1.85 (1.44-2.38)
ALT increase	64 (5.3)	18 (1.5)	3.54 (2.11-5.94)
General Disorders	111 (9.2)	109 (9.0)	1.01 (0.79-1.30)
Non-cardiac chest pain	33 (2.7)	39 (3.2)	0.84 (0.53-1.33)
Blood and Lymphatic System Disorders	52 (4.3)	52 (4.3)	1.00 (0.68-1.45)
Anemia	36 (3.0)	40 (3.3)	0.90 (0.58-1.40)

6. Narratives of two cases of elevated alanine aminotransferase and bilirubin

There were two cases with simultaneous elevation of alanine aminotransferase (ALT) $\geq$ 3X ULN and bilirubin $\geq$ 2X ULN.

The first patient was a 39-year old male in Taiwan randomized to placebo. At enrollment, he had normal liver function tests but was seropositive for hepatitis B surface antigen (HBsAg) and e antigen (HBeAg), seronegative for hepatitis B e-antibody, and to have hepatitis B viral load of 1.1 million IU/mL. He was not receiving antiviral therapy for hepatitis B at randomization. Five months after randomization he reported fatigue and jaundice was noted. ALT peaked at 43X ULN and bilirubin at 3.4X ULN. Study medication was discontinued. HBsAg and HBeAg remained positive throughout. Hepatitis B viral load reached 1.6 million IU/ml at 4 months post randomization, then decreased to 16,534 IU/mL three months later. Anti-HBe antibody titer became positive six months following randomization. This case was considered to be spontaneous hepatitis B flare reflecting immune clearance of hepatitis B virus with possible HBeAg to anti-HBe seroconversion.

The second patient was a 72-year old male in Israel randomized to apabetalone. The patient took a single dose of study medication following randomization then discontinued study medication due to headache but remained in the study for follow-up. Ten months following discontinuation of study medication laboratory tests showed simultaneous elevation of ALT (peak 13.5X ULN) and bilirubin (peak 2X ULN) coupled with serious adverse events of cholelithiasis and choledocholithiasis. This case was considered to reflect cholelithiasis/choledocholithiasis to be unrelated to study medication.