Effect of BET Protein Inhibition With Apabetalone on Cardiovascular Outcomes in Patients With Acute Coronary Syndrome and Diabetes

Results of the BETonMACE Trial

American Heart Association Presentation

November 16, 2019

BETonMACE: Committees

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BETonMACE: Acknowledgements

Contributions from 13 countries at 195 sites:

Country	National Lead Investigator(s)
Argentina	A. Lroenzatti, M. Vico
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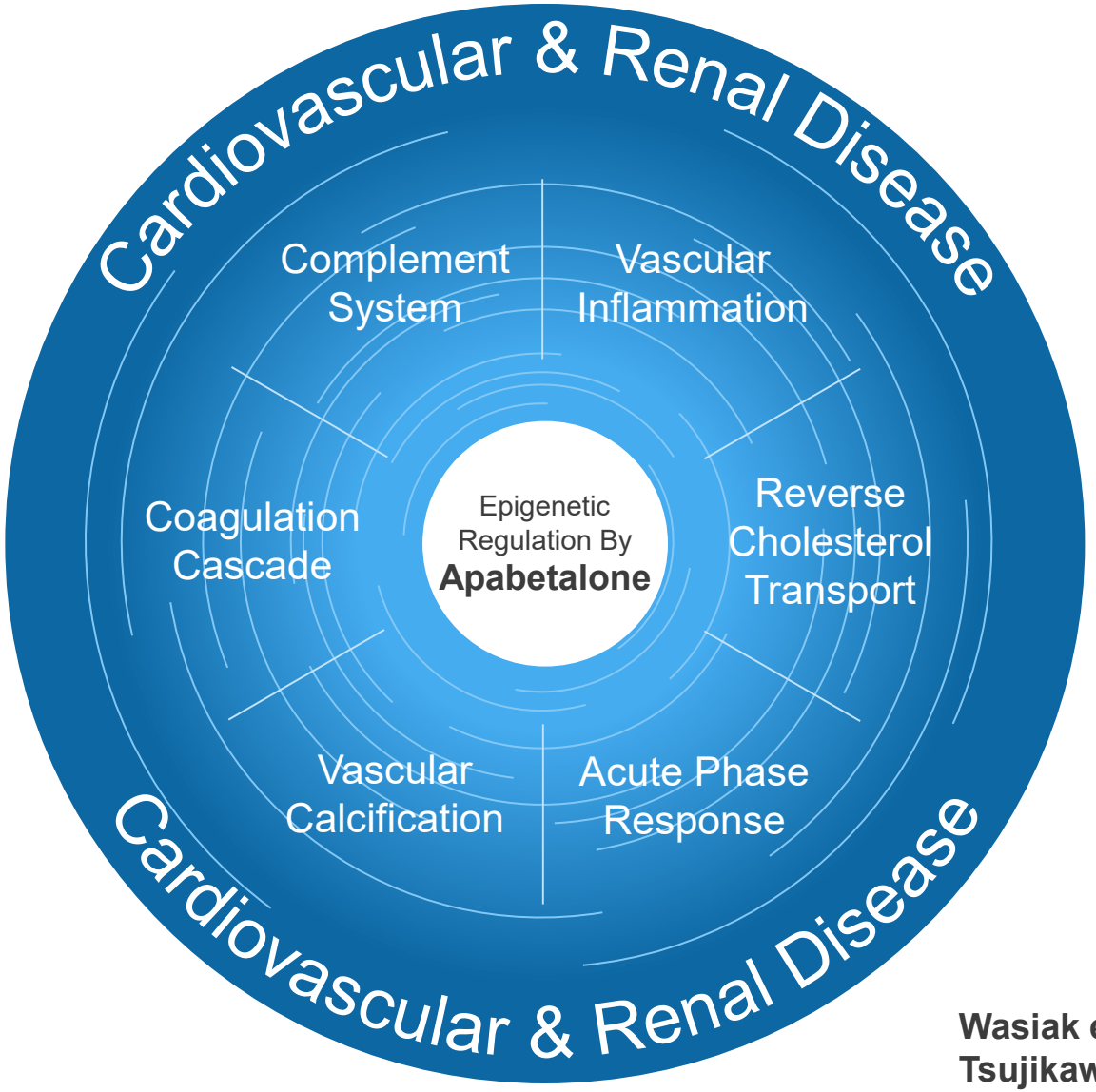
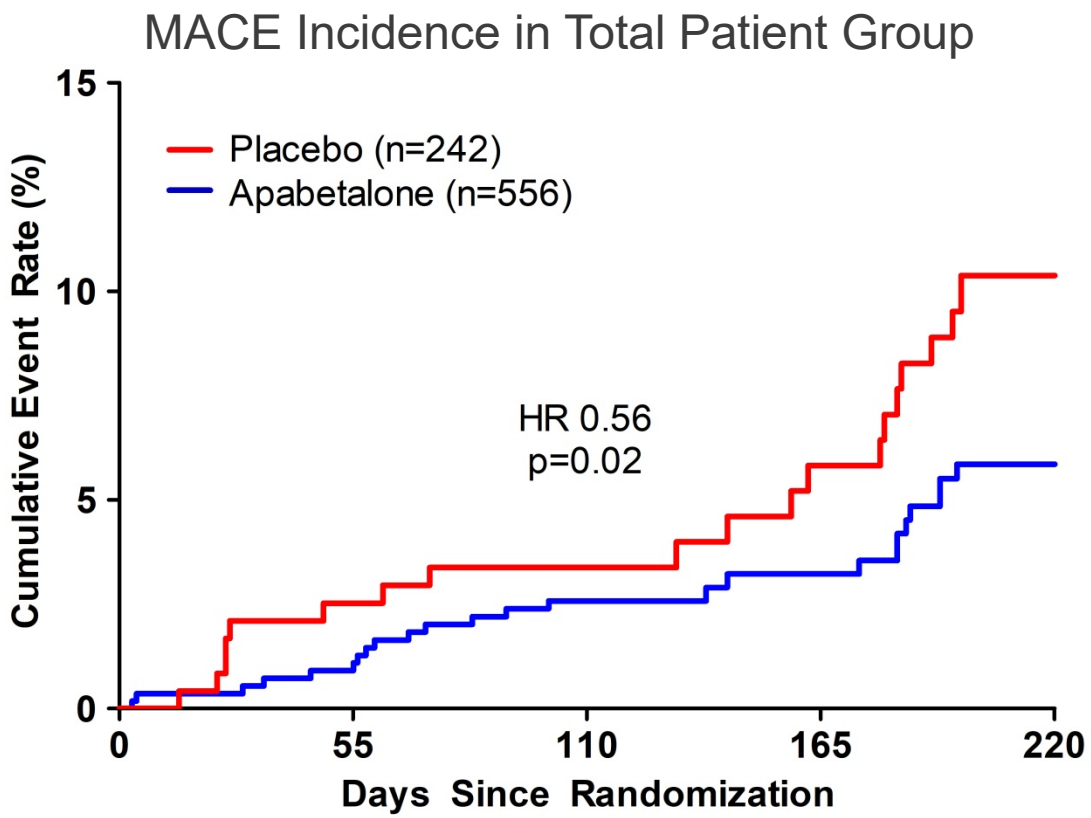
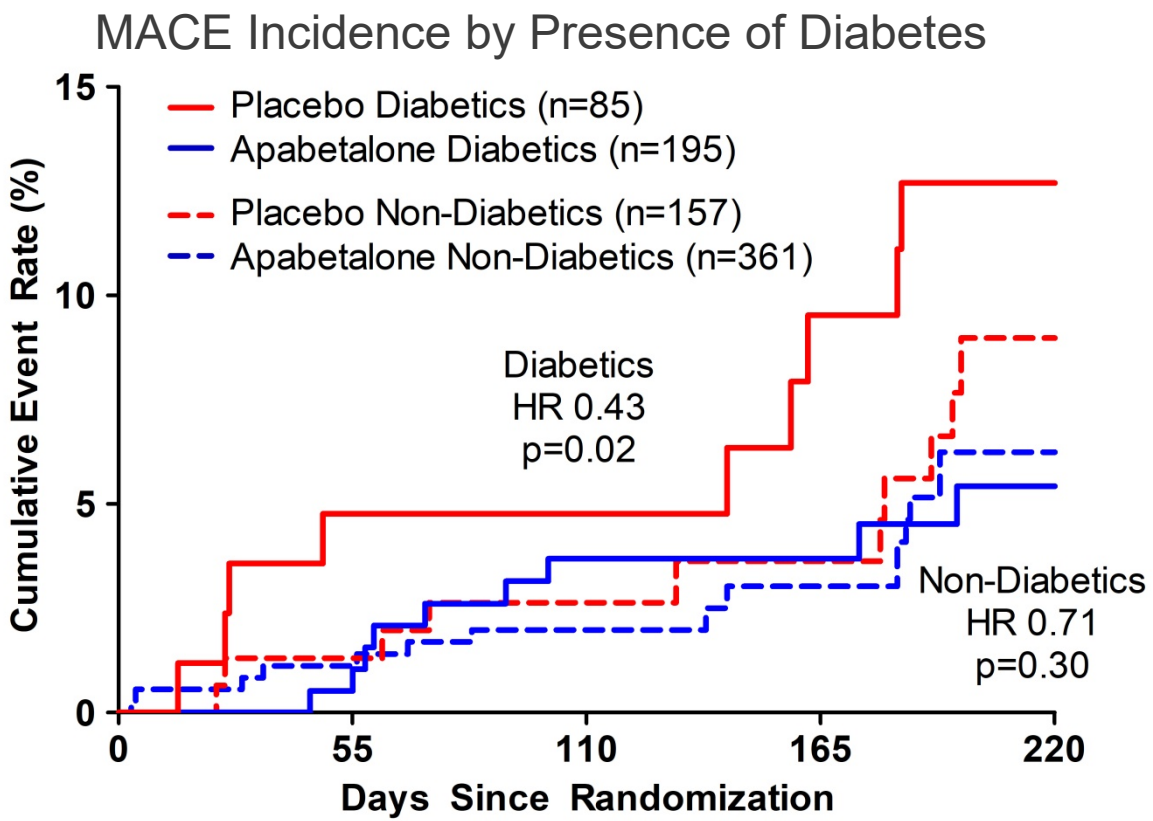
BET Protein Inhibition with Apabetalone Favorably Impacts Pathways Implicated in Cardiovascular and Kidney Disease



Wasiak et al. 2017; Gilham et al. 2019; Tsujikawa et al. 2019; Jahagirdar et al. 2014

Phase 2 Trials Suggest Potential CV Benefit with Apabetalone





- MACE (major adverse cardiovascular events) including death, myocardial infarction, coronary revascularization, and hospitalization for cardiovascular causes.
- Other characteristics associated with greater effect of apabetalone in pooled Phase 2 were low HDL-C and high hsCRP
- **Data shown are aggregate from the following trials: ASSERT;ASSURE;SUSTAIN. *Nicholls Am J Cardiovasc Drugs 2018***

BETonMACE: Inclusion/ Exclusion Criteria

Key Inclusion Criteria

- **Type 2 Diabetes Mellitus**
  - HbA1c >6.5% or history of diabetes medication use
- **Acute coronary syndrome 7-90 days prior to the screening visit**
  - Unstable angina (limited to 25% of participants) or acute myocardial infarction
- **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

Key Exclusion Criteria

- **Planned further coronary revascularization** at time of screening visit
- **Previous or current diagnosis of severe heart failure** (New York Heart Association Class IV)
- **Coronary artery bypass grafting** within 90 days prior to Visit 1.
- **Severe renal impairment** as determined by any one of the following:
  - eGFR <30 mL/min/1.7m^2 at screening visit
  - need for dialysis
- **Evidence of cirrhosis** from liver imaging or biopsy, or **liver transaminases (ALT or AST) >1.5x the upper limit of normal** range at screening visit

BETonMACE: Study Endpoints

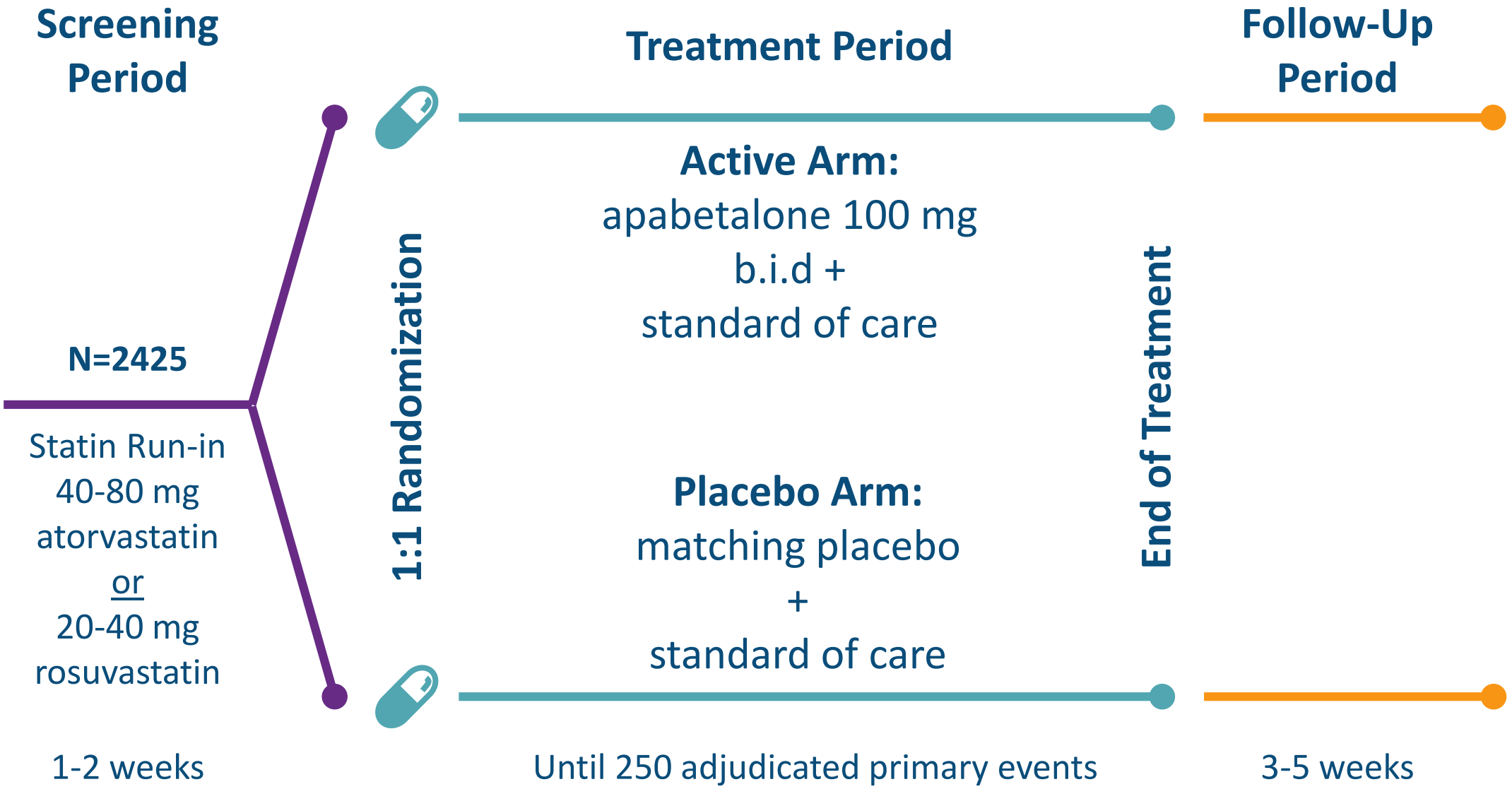
- **Primary Endpoint**
  - Time to first occurrence of CV death or non-fatal MI or stroke
    - Pre-specified sensitivity analysis excluding deaths of undetermined cause from endpoint
- **Key Secondary Endpoints**
  - Time to first 4-part MACE: primary endpoint + hospitalization for CV events*
  - Total (first and recurrent) non-fatal MI or stroke, and CV death
  - Time to first CV Death or Non-fatal MI
  - Time to first coronary heart disease death or non-fatal MI
  - Individual components of primary endpoint
  - All-cause death
  - Hospitalization for congestive heart failure (CHF)

*Unstable angina or urgent or emergency coronary revascularization at least 30 days after the index ACS

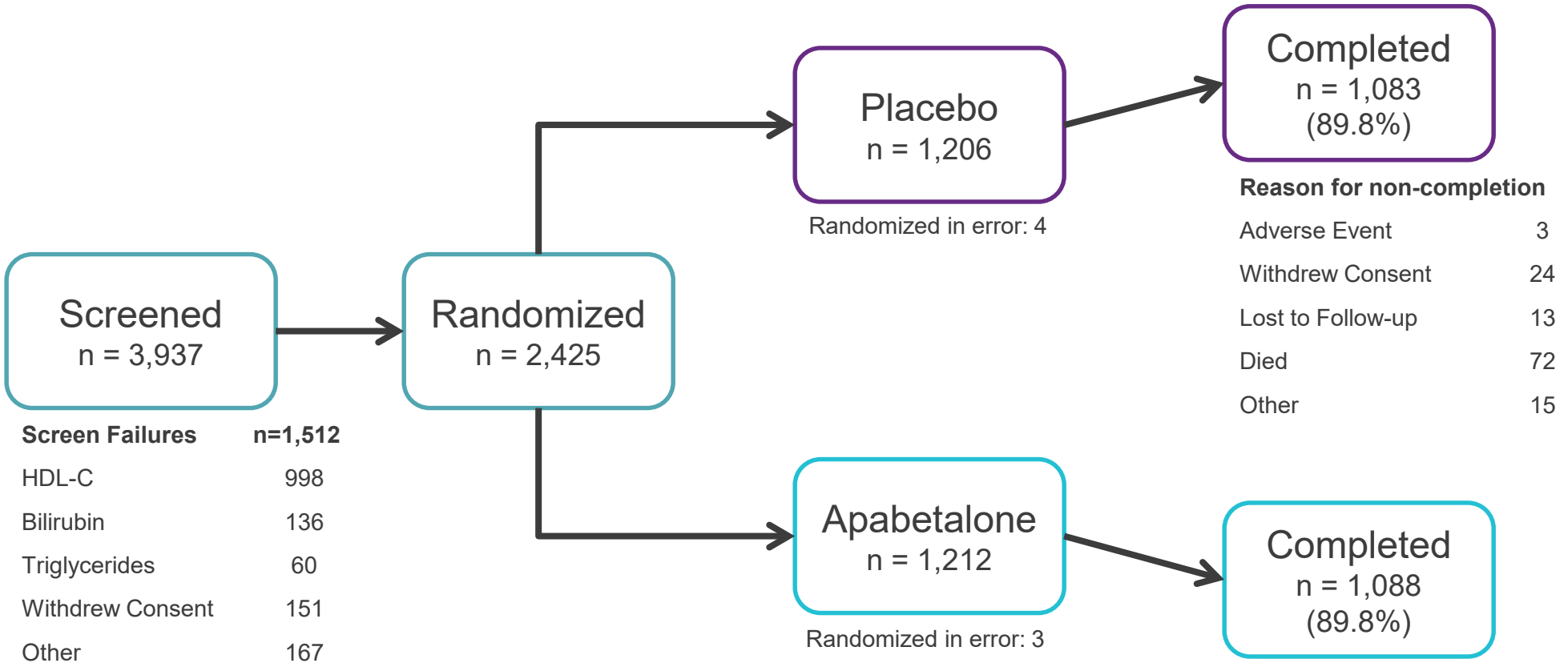
Statistical assumptions

- A sample size of 2400 randomized subjects was predicted to yield 80% power for the primary analysis under the following assumptions:
  - Total number of events: 250
  - 2-sided type 1 error rate: α=5%
  - 10.5% event rate in the placebo arm at 18 months
  - 30% relative risk reduction (7.47% event rate at 18 months in the apabetalone arm)

BETonMACE: Study Design



BETonMACE: Patient Disposition



Screen Failures	n=1,512
HDL-C	998
Bilirubin	136
Triglycerides	60
Withdrew Consent	151
Other	167

Reason for non-completion	
Adverse Event	3
Withdrew Consent	24
Lost to Follow-up	13
Died	72
Other	15

Reason for non-completion	
Adverse Event	2
Withdrew Consent	31
Lost to Follow-up	7
Died	61
Other	26

95.7% of randomized patients had full ascertainment of the primary outcome through the planned observation period or else were known to be deceased
Vital status known for 99.2% of randomized patients

Baseline Characteristics, Prior Medical and Index ACS History

	Apabetalone (n=1212)	Placebo (n=1206)
Median age, yrs	62.0	62.0
Male sex- %	74.8	74.0
Body mass index, kg/m^2	30.2	30.3
Hypertension - %	89.4	87.8
eGFR Mean ± SD, mL/min/1.73m^2	104.9	101.7
Duration of diabetes – yrs	8.4	8.7
Index acute coronary syndrome – %		
Myocardial infarction	73.0	74.0
STEMI	38.4	38.6
NSTEMI	34.1	35.1
Unstable angina	26.7	25.0
PCI for index acute coronary syndrome	79.8	79.2
Time from index ACS to randomization – days	38	38

Baseline Characteristics: Cardiovascular and Diabetes Medications

Cardiovascular and Diabetes Medications (%)	Apabetalone (N=1212)	Placebo (N=1206)
Atorvastatin	51.2	51.4
Rosuvastatin	48.8	48.6
High intensity statin	89.9	90.5
ACE inhibitors/ angiotensin II blockers	92.3	92.0
Beta blockers	91.0	90.2
Antiplatelet agents	98.7	99.1
Dual antiplatelet agents	87.2	88.3
Metformin	83.3	82.0
Insulin	36.7	38.5
Sulfonylureas	30.0	28.5
DPP4 inhibitors	14.9	14.8
SGLT2 inhibitors	12.4	12.3
GLP1 receptor agonists	3.4	3.7

BETonMACE: Baseline Laboratory Parameters

Baseline Laboratory Parameters	Apabetalone (n=1212)	Placebo (n=1206)
HbA1c, %	7.4 (6.8-8.7)	7.3 (6.4-8.6)
eGFR, ml/min/1.73m^2 †	104.9 ± 39.3	101.7 ± 38.6
Total cholesterol, mg/dL	134.8 ± 35.3	136.8 ± 38.2
LDL cholesterol, mg/dL	69.7 ± 29.8	70.9 ± 32.4
HDL cholesterol, mg/dL	33.3 ± 5.1	33.3 ± 5.1
Triglycerides, mg/dl	144.4 (110.7-194.9)	149.7 (116.0-201.9)
Alkaline phosphatase, U/L	83.3 ± 38.2	81.9 ± 34.8
Alanine aminotransferase, units/L	25.3 ± 14.3	25.4 ± 14.7
Total bilirubin, µmol/L	9.8 ± 4.2	9.9 ± 4.2
High sensitivity C-reactive protein §	2.9 (1.3-5.9)	2.7 (1.1-6.1)

† Estimated glomerular filtration rate (eGFR) was calculated using the Cockcroft Gault method, based on age and weight at baseline.
§ High-sensitivity C-Reactive Protein was assessed in only a subset of patients. Triglycerides expressed as median and IQR

BETonMACE: Efficacy Results

Change in Biochemical Parameters (from baseline at 100 weeks)

Biochemical parameters	Apabetalone (n=1212)	Placebo (n=1206)	P value Change from baseline
HDL cholesterol, mg/dL	+16.2%	+10.4%	0.001
LDL cholesterol, mg/dL	+11.5%	+14.9%	0.35
eGFR, ml/min/1.73m^2	-0.4	+2.1	0.03
Hemoglobin A1c, %	+0.05	+0.15	0.32
Serum glucose, mg/dL	+4.4%	+7.8%	0.74
Alkaline phosphatase, U/L	-4.8	+2.2	0.003
hCRP §	-17.1%	-16.7%	0.72

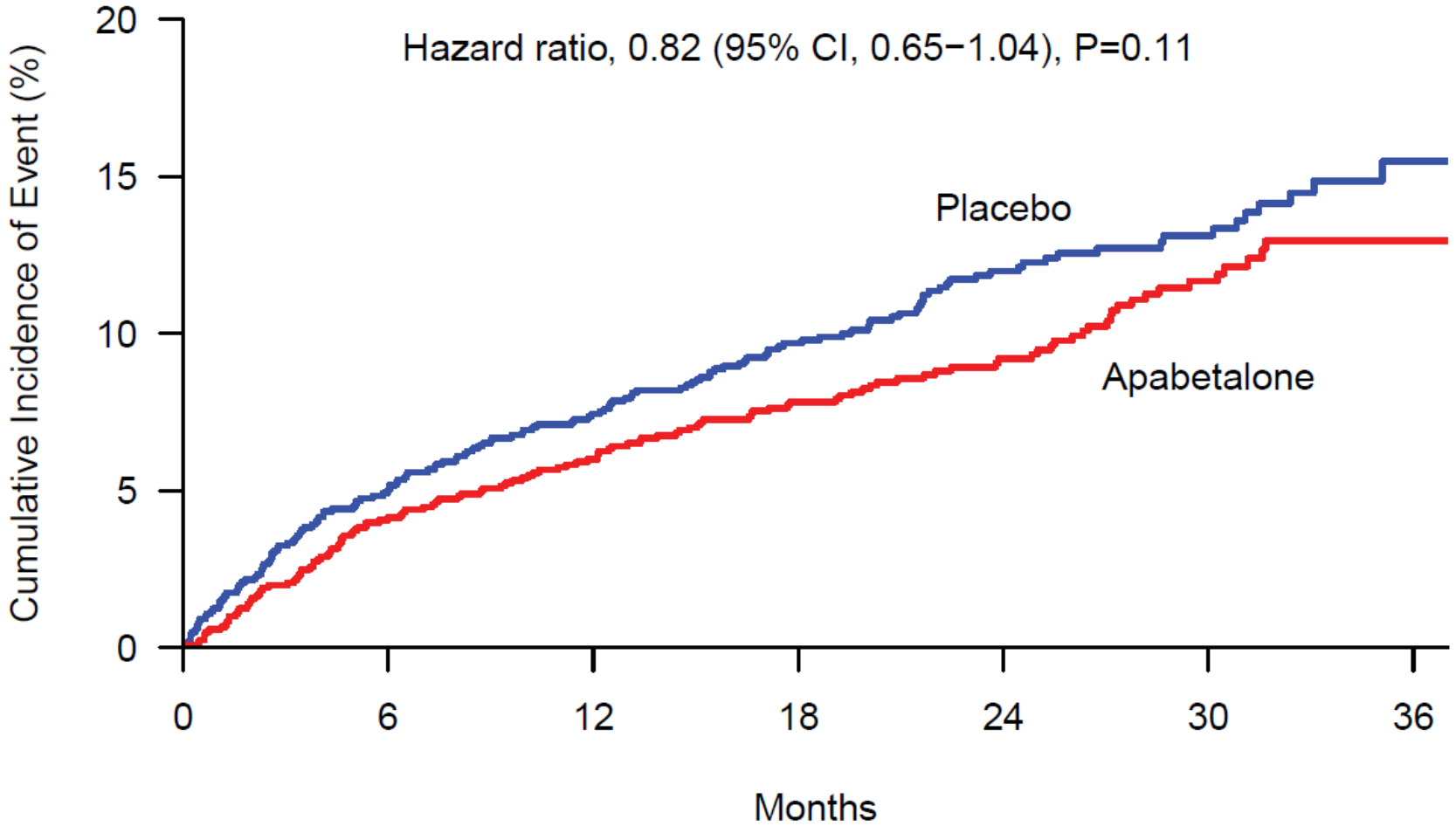
Changes are % changes where indicated (%) otherwise absolute changes if not specified

§-at 52 weeks, only at centers in Hungary and Argentina

Primary Efficacy End Point: CV Death, Non-Fatal MI and Stroke (N=274)

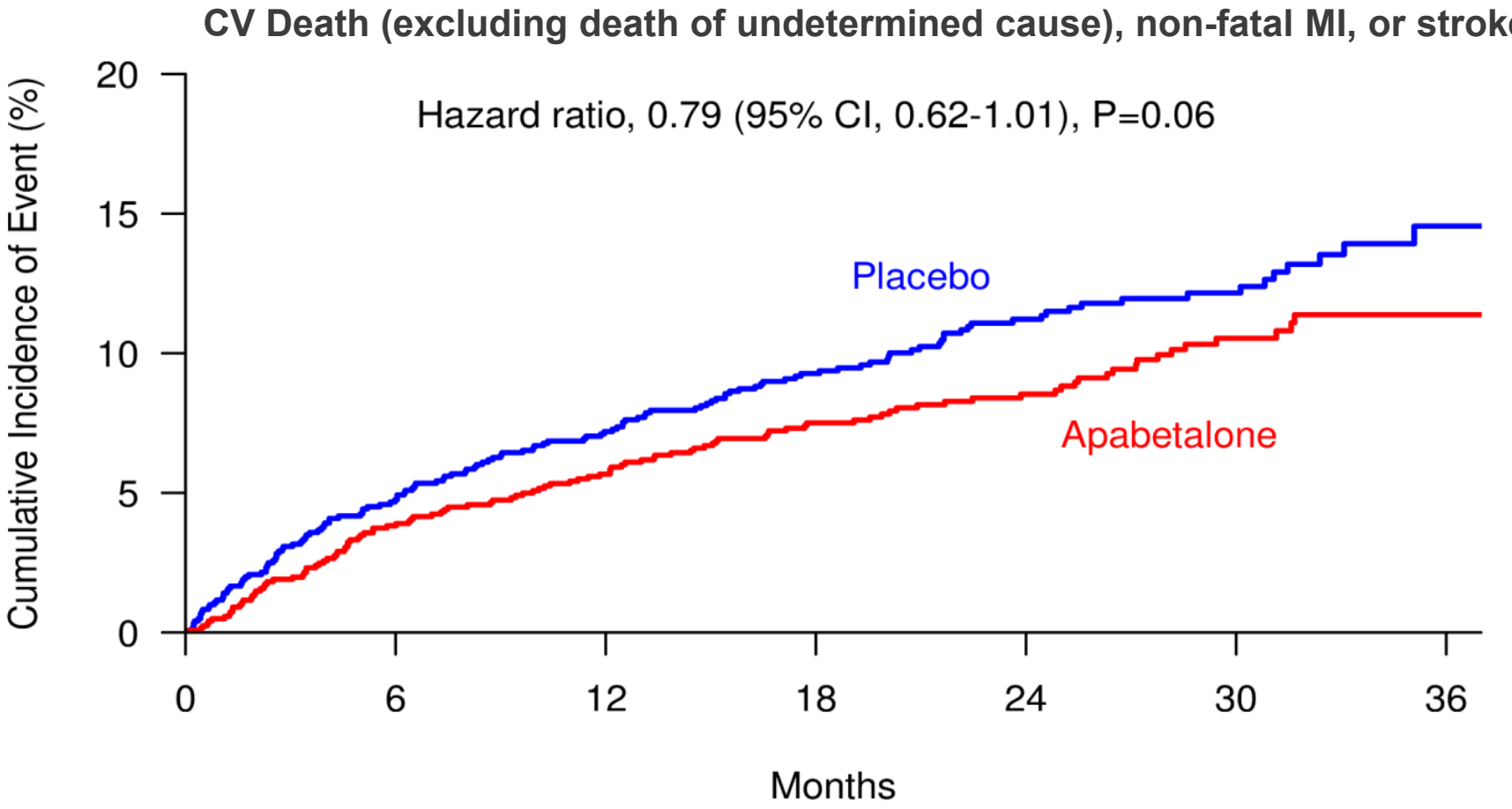
Median follow-up
26 months

Primary Endpoint:
Placebo 12.4%
Apabetalone 10.3%



No. at Risk							
Placebo	1206	1135	1102	937	641	383	108
Apabetalone	1212	1151	1114	950	672	397	107

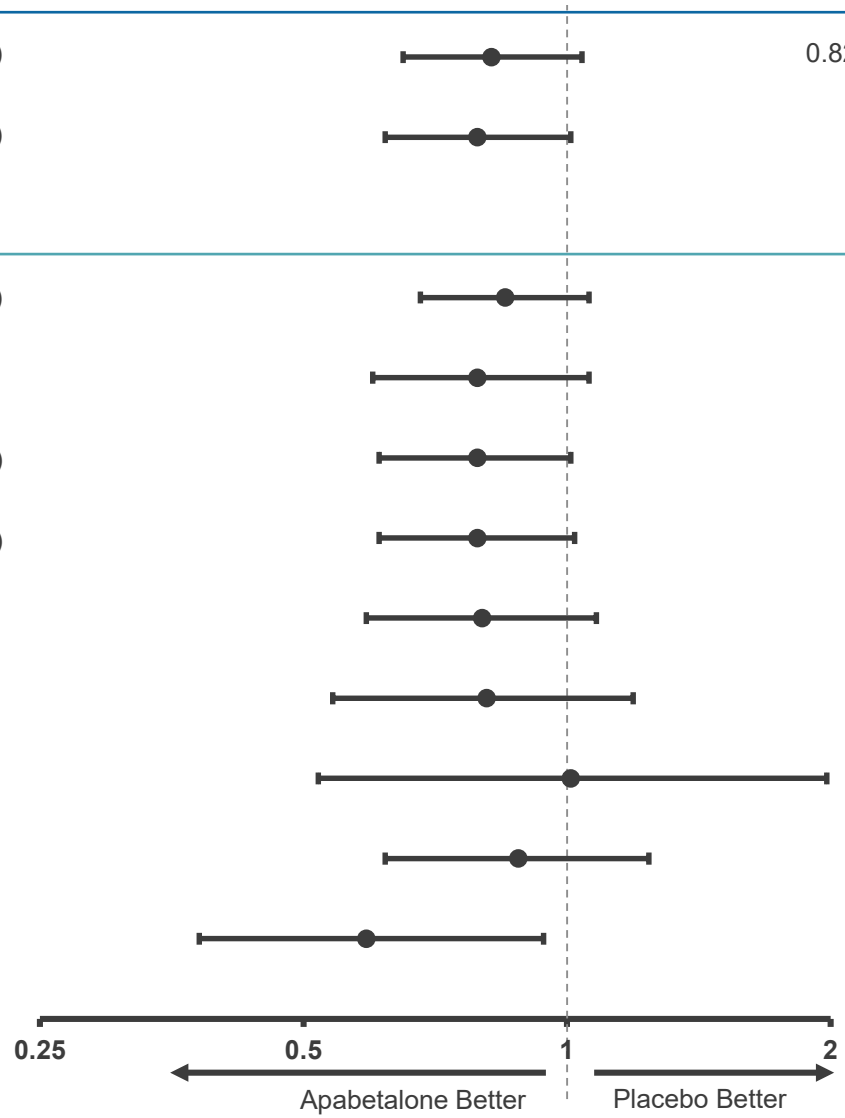
Prespecified Primary End Point Sensitivity Analysis: Excluding Deaths of Undetermined Cause



No. at Risk							
Placebo	1206	1135	1101	937	641	383	108
Apabetalone	1212	1150	1113	949	671	396	107

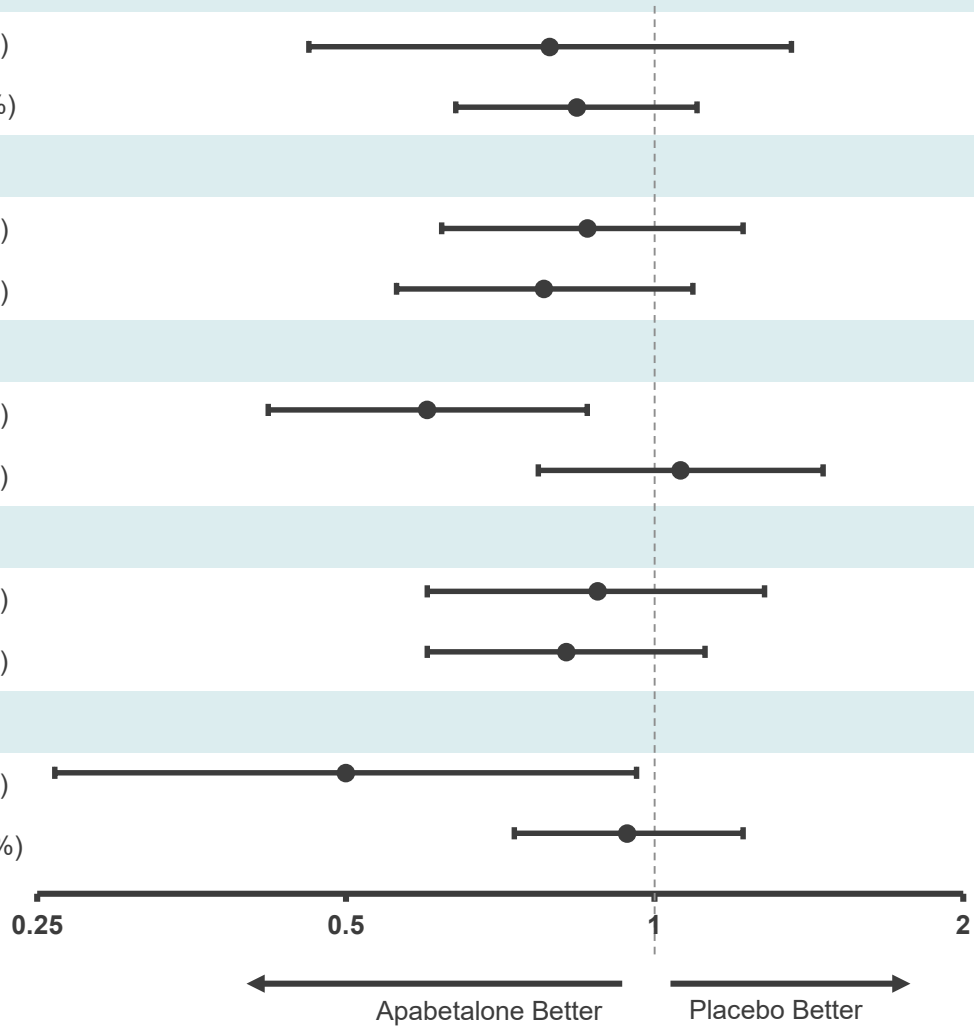
End Points

Primary End Point	Apabetalone	Placebo	Hazard Ratio (95% CI)
	no. of events (%)		
First occurrence of primary end point	125 (10.3%)	149 (12.4%)	0.82 [0.65, 1.04] p=0.11
First occurrence of primary end point, excluding undetermined death	113 (9.3%)	140 (11.6%)	0.79 [0.62, 1.01]
Key Secondary End Points			
First occurrence of primary end point or hospitalization for unstable angina or urgent or emergency revascularization procedure	144 (11.9%)	166 (13.8%)	0.85 [0.68, 1.06]
First and recurrent primary end point events	171	203	0.79 [0.60, 1.06]
Cardiovascular death or non-fatal myocardial infarction	112 (9.2%)	139 (11.5%)	0.79 [0.61, 1.01]
Coronary heart disease death or non-fatal myocardial infarction	110 (9.1%)	136 (11.3%)	0.79 [0.61, 1.02]
Non-fatal myocardial infarction	77 (6.4%)	94 (7.8%)	0.80 [0.59, 1.08]
Cardiovascular death	45 (3.7%)	55 (4.6%)	0.81 [0.54, 1.19]
Stroke	17 (1.4%)	17 (1.4%)	1.01 [0.52, 1.98]
All cause mortality	61 (5.0%)	69 (5.7%)	0.88 [0.62, 1.24]
First hospitalization for congestive heart failure	29 (2.4%)	48 (4.0%)	0.59 [0.38, 0.94]



Primary End Point in Pre-specified Subgroups

Subgroup	Apabetalone	Placebo	Hazard Ratio (95% CI)	P Value
	no. of events/patients (%)			
Sex				
Female	23/305 (7.5%)	32/313 (10.2%)	0.79 [0.46, 1.36]	0.70
Male	102/907 (11.2%)	117/893 (13.1%)	0.84 [0.64, 1.10]	
Statin				
Rosuvastatin	62/591 (10.5%)	71/586 (12.1%)	0.86 [0.62, 1.22]	0.67
Atorvastatin	63/621 (10.1%)	78/620 (12.6%)	0.78 [0.56, 1.09]	
LDL cholesterol				
< Median	48/595 (8.1%)	78/597 (13.1%)	0.60 [0.42, 0.86]	0.024
≥ Median	77/618 (12.5%)	71/606 (11.7%)	1.06 [0.77, 1.46]	
Hemoglobin A1c				
< Median	51/563 (9.1%)	60/595 (10.1%)	0.88 [0.60, 1.28]	0.79
≥ Median	73/639 (11.4%)	85/599 (14.2%)	0.82 [0.60, 1.12]	
Estimated glomerular filtration rate				
< 60	13/124 (10.4%)	35/164 (21.3%)	0.50 [0.26,0.96]	0.032
≥ 60	112/1084 (10.3%)	114/1041 (11.0%)	0.94 [0.73, 1.22]	



Safety Overview

Variable	Apabetalone (n=1212)	Placebo (n=1207)
Adverse events - n (%)		
Patients with at least one adverse event	830 (68.5)	820 (67.9)
Adverse event leading to discontinuation	114 (9.4)	69 (5.7)
Serious adverse events – n (%)		
Patients with at least one SAE	354 (29.2)	339 (28.1)
Death	61 (5.0)	72 (6.0)
Cardiovascular deaths	34 (2.8)	42 (3.5)
Liver Function		
ALT >3x ULN	78 (6.4)	18 (1.5)
ALT >5x ULN	40 (3.3)	9 (0.7)
Bilirubin >2x ULN	7 (0.6)	9 (0.7)
Hy's law	0	0
Discontinuation due to LFT elevation – n (%)	35 (2.9)	11 (0.9)

BETonMACE Summary

- Apabetalone did not have a significant effect on incidence of the primary endpoint (CV death, non-fatal MI or stroke)
  - Observed event rate in placebo group (9.7%) was somewhat lower than anticipated (10.5%) at 18 months
  - Study was powered on a 30% reduction in risk of primary endpoint, and was underpowered to detect a smaller difference in events
- Apabetalone was generally well tolerated with an overall incidence of adverse events similar to that in the placebo group. However, discontinuation of treatment due to elevated liver function tests was more frequent with apabetalone.

BETonMACE Conclusions

- First cardiovascular outcomes trial assessing the potential of epigenetic modification with BET protein inhibition shows promise
- Favorable trends were observed for the primary endpoint and key components except stroke with a nominal difference in heart failure hospitalization
- Further studies of this approach are warranted