TO001 - Free Communication

Session S 38 Cardiovascular and renal protection - effects of SGLT2 inhibitors and GLP-1 receptor agonists in people with CKD and type 2 diabetes

EFFECTS OF THE BET-INHIBITOR APABETALONE ON CARDIOVASCULAR EVENTS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS AND ACUTE CORONARY SYNDROME, ACCORDING TO PRESENCE OR ABSENCE OF CHRONIC KIDNEY DISEASE. A BET ON MACE TRIAL REPORT.

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Presented by

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ERA-EDTA
June 9, 2020

BETonMACE Committees

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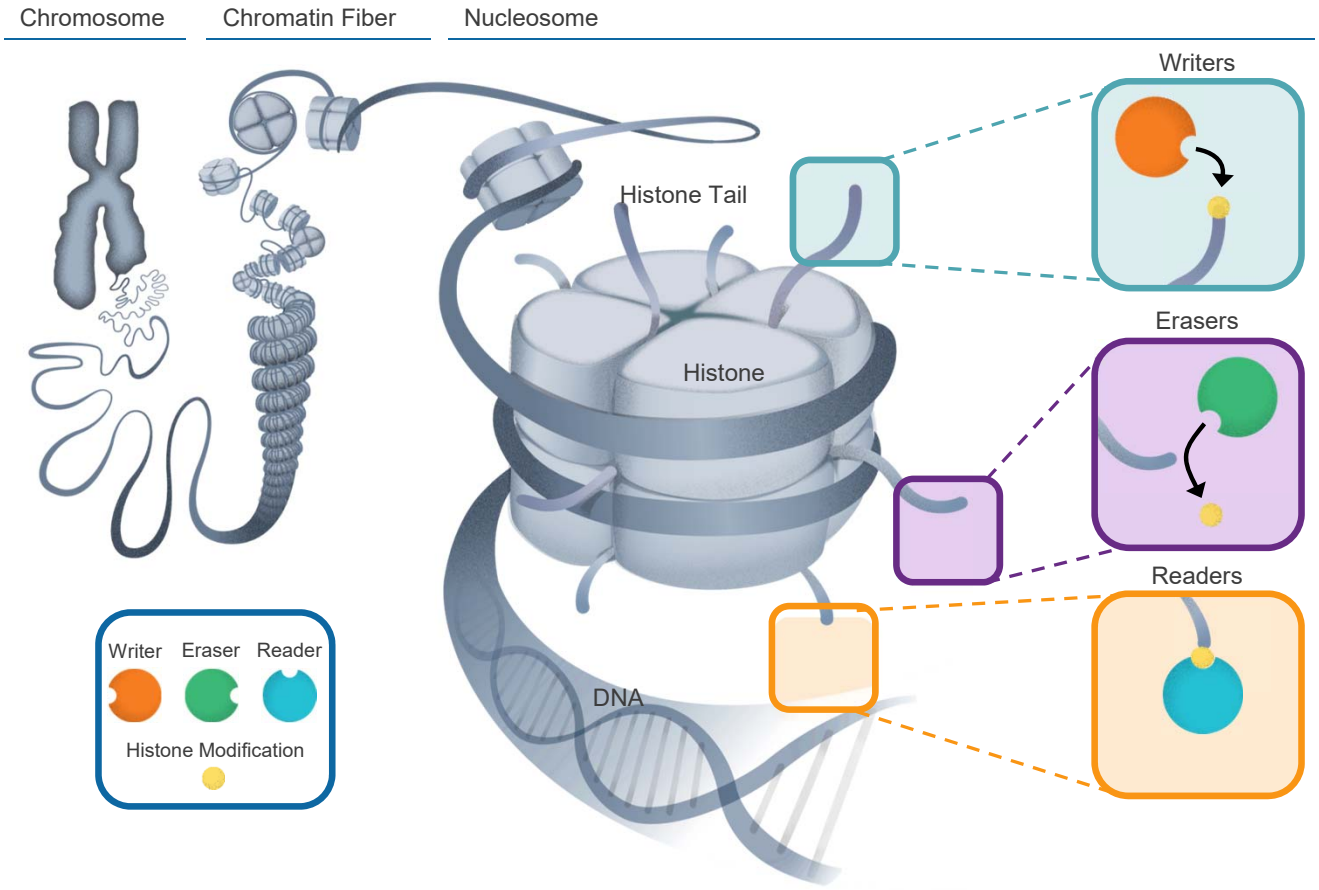
Slovakia	D. Pella
Taiwan	C. E. Chiang

Ray KK et al. BETonMACE Randomized Clinical Trial. ***JAMA. 2020.***

BETonMACE Background & Rationale

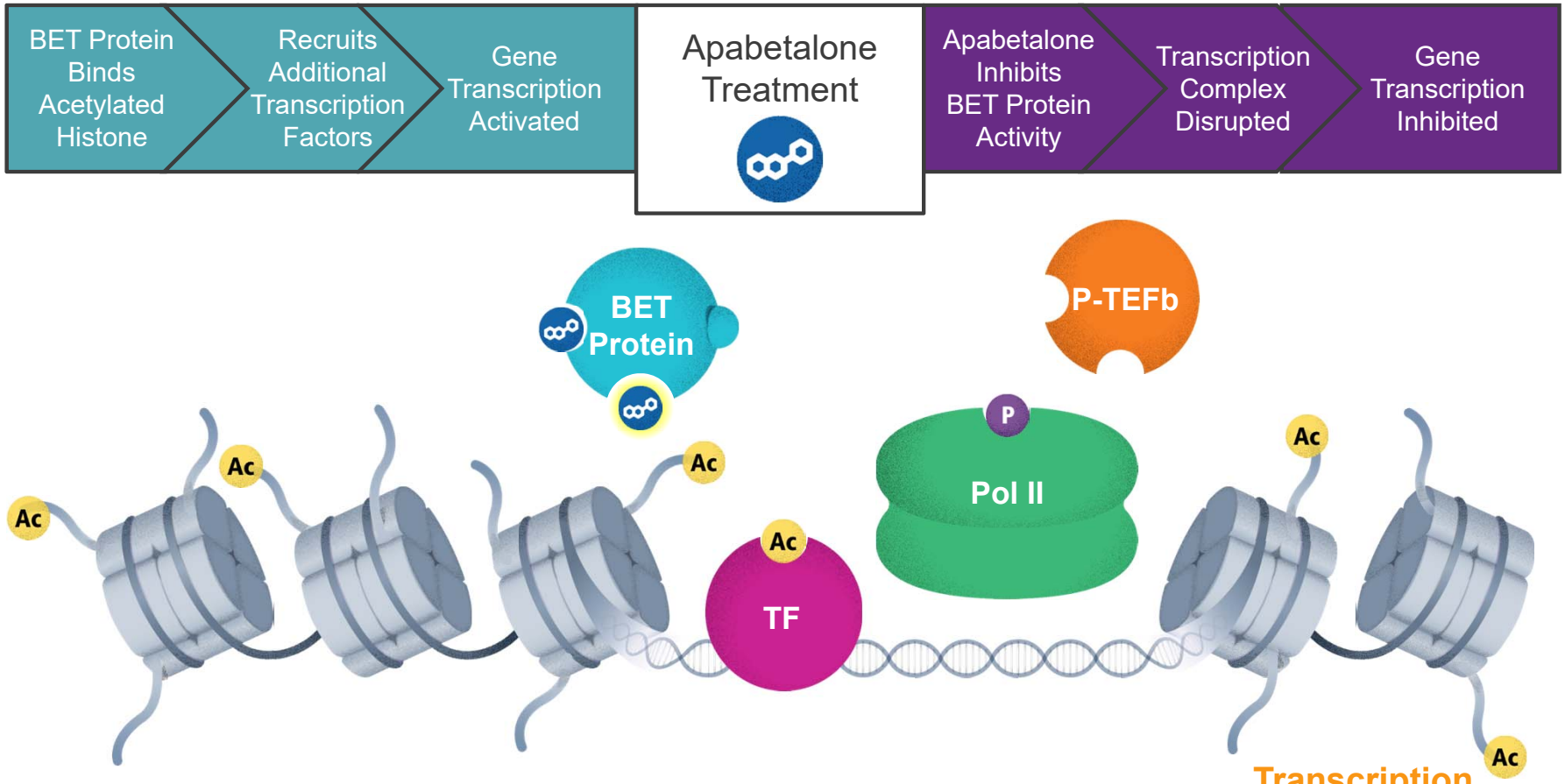
- Bromodomain and extraterminal proteins are epigenetic regulators of gene transcription.



- Epigenetics refers to **modifications** to chromatin that regulate its activity
- Transcription is regulated by **addition, removal, or recognition** of these modifications.
- **Acetylation** is associated with **active transcription** regions of chromatin
- **Bromodomain and Extraterminal Domain (BET)** proteins bind to acetylated histones and recruit additional transcription factors to drive gene expression

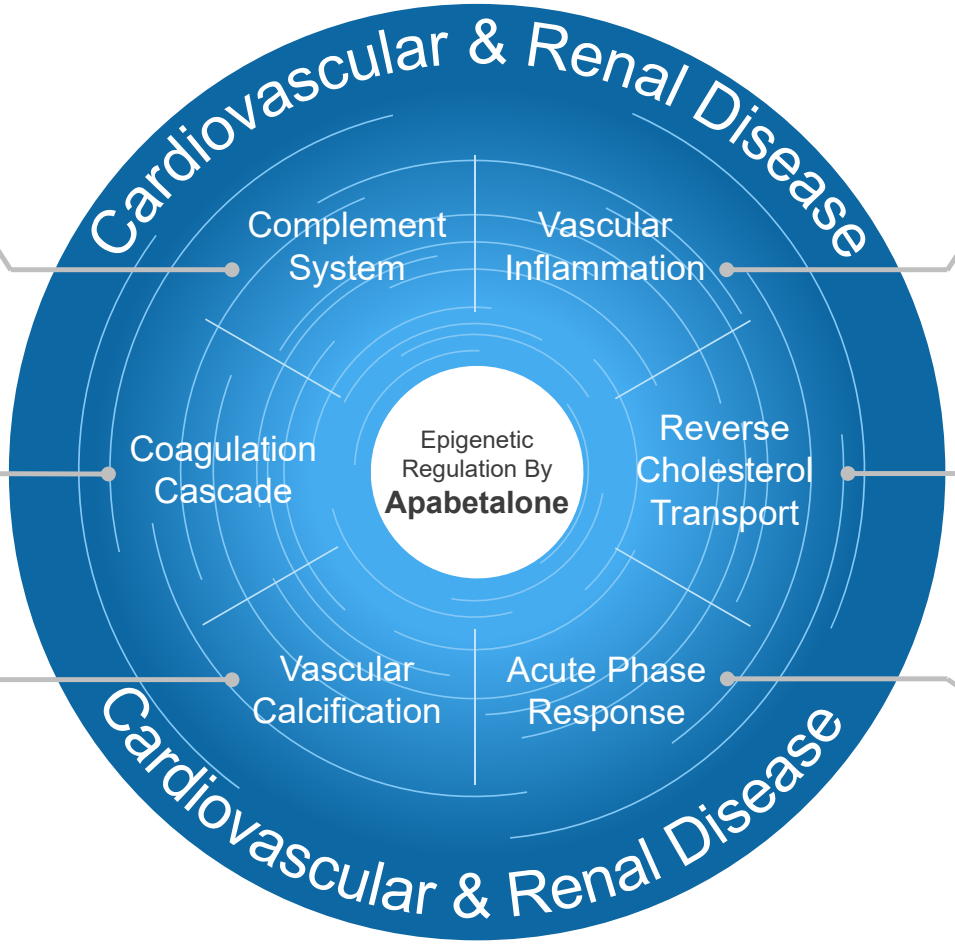
Haarhaus M, Gilham D, Kulikowski E, Magnusson P and Kalantar-Zadeh K. Pharmacologic epigenetic modulators of alkaline phosphatase in chronic kidney disease. *Curr Opin Nephrol Hypertens. 2020;29(1):4-15.*

BET Inhibition by Apabetalone



Apabetalone is a selective bromodomain and extra-terminal (BET) protein inhibitor targeting bromodomain 2 and is hypothesized to have potentially favorable effects on pathways related to atherothrombosis.

BET Protein Inhibition with Apabetalone Favorably Impacts Pathways Implicated in Cardiovascular and Kidney Disease



Apabetalone reduces the expression of multiple components of the complement cascade

Wasiak et al. 2017

Apabetalone reduces the expression of several factors within the coagulation system

Wasiak et al. 2017

Levels of alkaline phosphatase and other drivers of vascular calcification are lowered by apabetalone

Gilham et al. 2019

Treatment with apabetalone reduces mediators that drive endothelial activation, monocyte recruitment and plaque destabilization

Tsujikawa et al. 2019

Apabetalone contributes to remodeling of the HDL proteome and lipidome, including increased ApoA-1 and HDL particle size

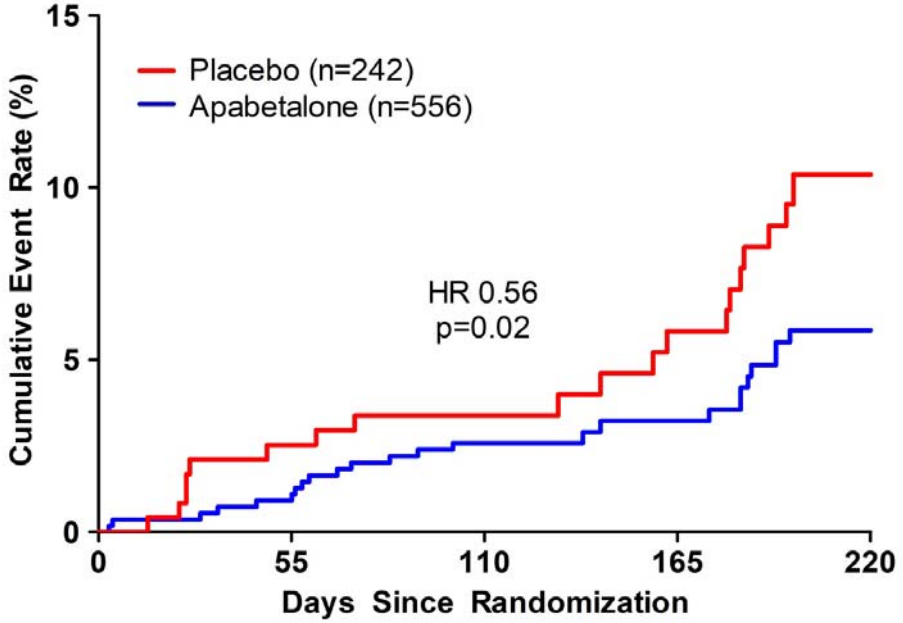
Jahagirdar et al. 2014

Apabetalone reduces markers of systemic inflammation including acute phase reactants

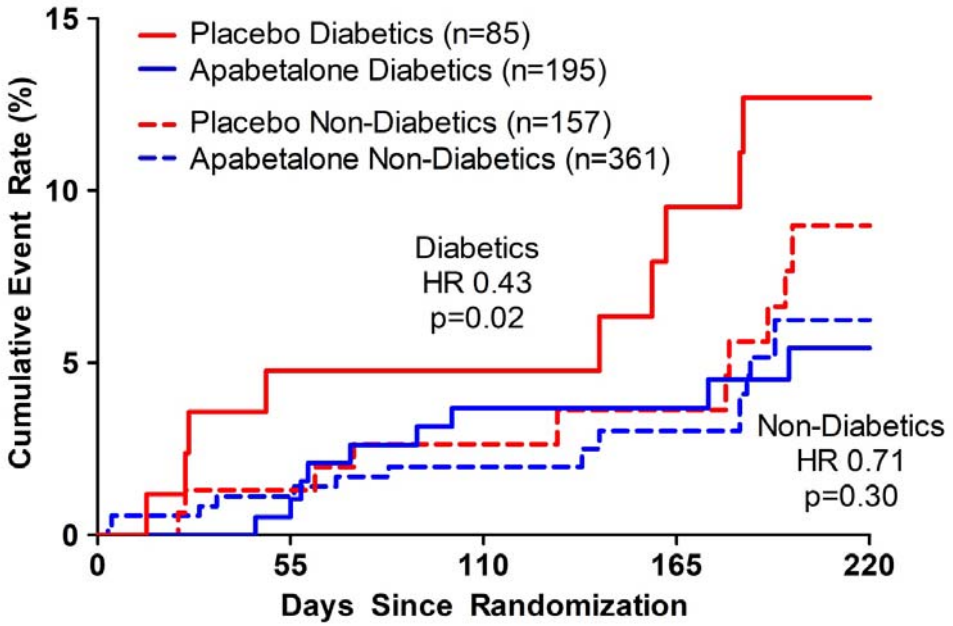
Wasiak et al. 2019

Phase 2 Trials Suggest Potential CV Benefit with Apabetalone

MACE Incidence in Total Patient Group



MACE Incidence by Presence of Diabetes



- 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 and 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

Ray KK, Nicholls SJ, Buhr KA, Ginsberg HN, Johansson JO, Kalantar-Zadeh K, Kulikowski E, Toth PP, Wong N, Sweeney M, Schwartz GG, Investigators BE and Committees. Effect of Apabetalone Added to Standard Therapy on Major Adverse Cardiovascular Events in Patients With Recent Acute Coronary Syndrome and Type 2 Diabetes:. ***JAMA. 2020.***

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*

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Statistical Assumptions

- A sample size of 2,400 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)

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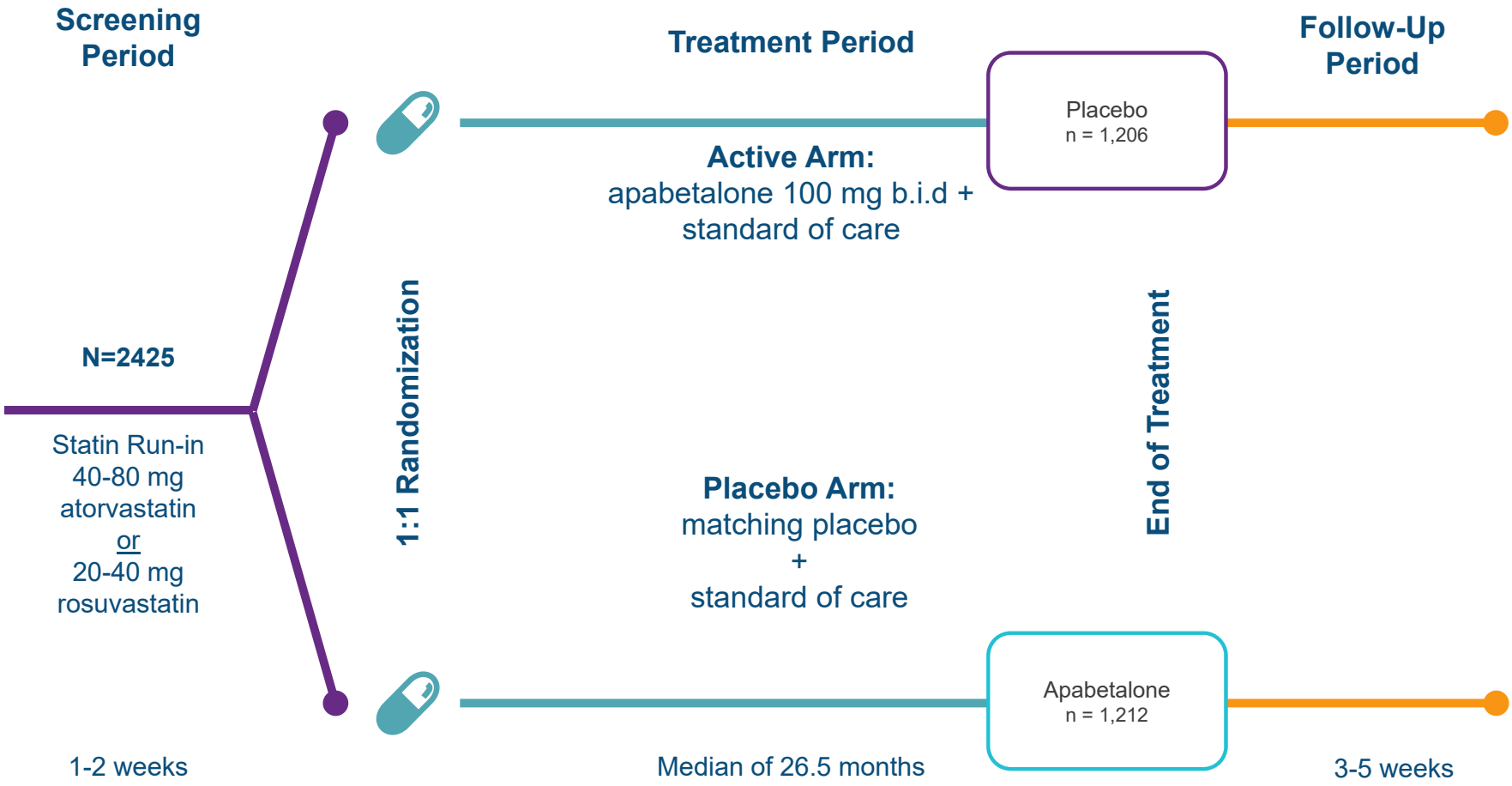
BETonMACE Study Design



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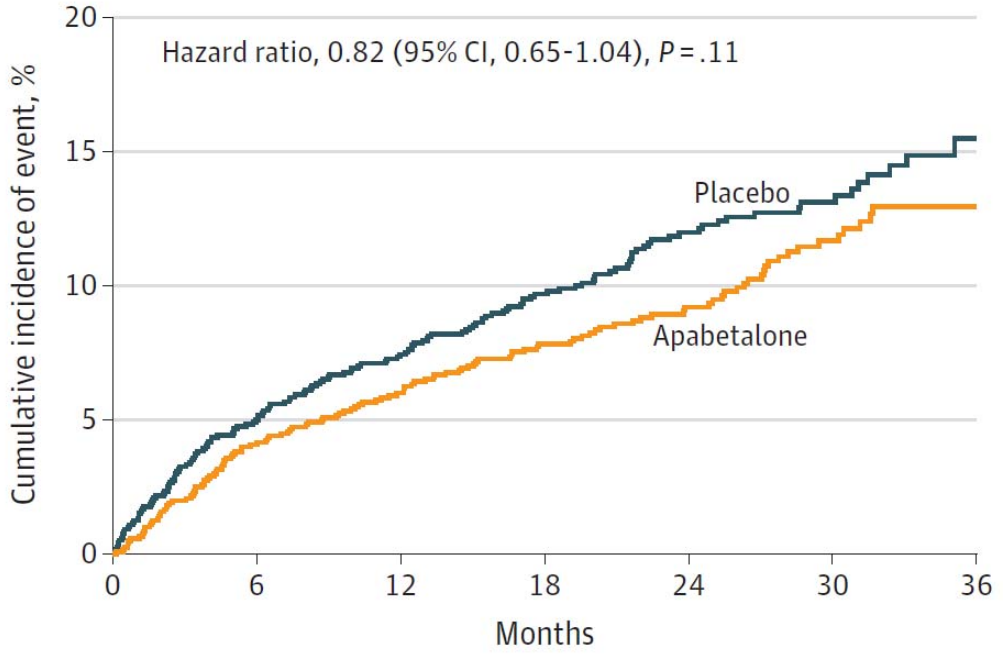
BETonMACE Baseline Characteristics

	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

Ray KK, Nicholls SJ, Buhr KA, Ginsberg HN, Johansson JO, Kalantar-Zadeh K, Kulikowski E, Toth PP, Wong N, Sweeney M, Schwartz GG, Investigators BE and Committees. Effect of Apabetalone Added to Standard Therapy on Major Adverse Cardiovascular Events in Patients With Recent Acute Coronary Syndrome and Type 2 Diabetes:. ***JAMA. 2020.***

BETonMACE Primary Efficacy Endpoint

- CV Death, Non-Fatal MI and Stroke (Total number of events = 274)



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

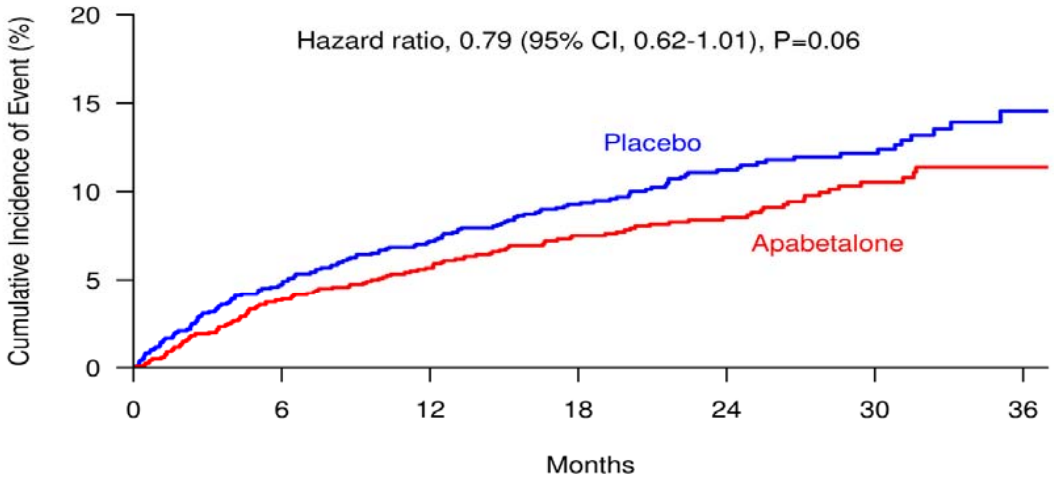
Median follow-up of 26.5 months

Primary Endpoint:
Placebo = **12.4%**
Apabetalone = **10.3%**

Ray KK, Nicholls SJ, Buhr KA, Ginsberg HN, Johansson JO, Kalantar-Zadeh K, Kulikowski E, Toth PP, Wong N, Sweeney M, Schwartz GG, Investigators BE and Committees. Effect of Apabetalone Added to Standard Therapy on Major Adverse Cardiovascular Events in Patients With Recent Acute Coronary Syndrome and Type 2 Diabetes:. ***JAMA. 2020.***

Prespecified Primary End Point Sensitivity Analysis Excluding Deaths of Undetermined Cause

CV Death (excluding death of undetermined cause), non-fatal MI, or stroke

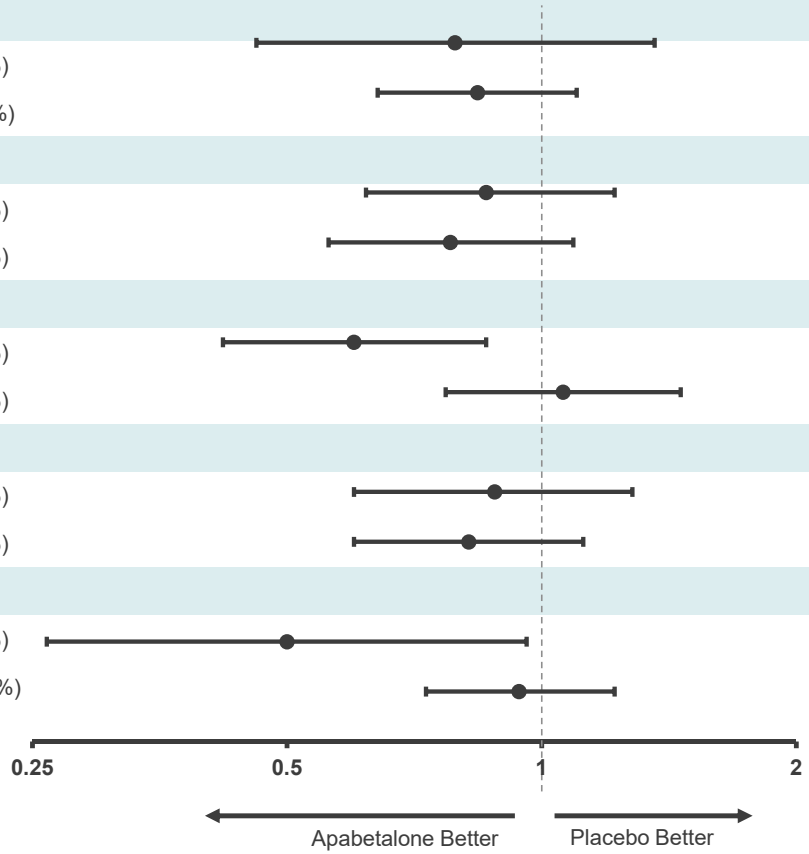


No. at Risk							
Placebo	1206	1135	1101	937	641	383	108
Apabetalone	1212	1150	1113	949	671	396	107

Ray KK, Nicholls SJ, Buhr KA, Ginsberg HN, Johansson JO, Kalantar-Zadeh K, Kulikowski E, Toth PP, Wong N, Sweeney M, Schwartz GG, Investigators BE and Committees. Effect of Apabetalone Added to Standard Therapy on Major Adverse Cardiovascular Events in Patients With Recent Acute Coronary Syndrome and Type 2 Diabetes:. ***JAMA. 2020.***

Primary Endpoint in Prespecified 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]	



BETonMACE Summary

- Apabetalone did not have a significant effect on incidence of the primary endpoint (CV death, non-fatal MI or stroke)
  - Lower than anticipated event rate in placebo group (9.7% observed, 10.5% predicted at 18 months)
  - Study was powered on a 30% reduction in risk of primary endpoint, and was underpowered to detect a smaller event reduction
- 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.

Ray KK, Nicholls SJ, Buhr KA, Ginsberg HN, Johansson JO, Kalantar-Zadeh K, Kulikowski E, Toth PP, Wong N, Sweeney M, Schwartz GG, Investigators BE and Committees. Effect of Apabetalone Added to Standard Therapy on Major Adverse Cardiovascular Events in Patients With Recent Acute Coronary Syndrome and Type 2 Diabetes:. ***JAMA. 2020.***

Baseline Demographic Data of the CKD Subgroup

	eGFR ≥ 60	eGFR < 60 (CKD Stage 3-4)	P-value	Placebo (eGFR <60)	Apabetalone (eGFR <60)
N	N=2,125	N=288		N=164	N=124
Age (yr)	61 (54-67)	**71 (65-76)**	<0.001	**70.6 (7.9)**	**69.8 (7.9)**
Sex					
Male	1,628 (76.6)	**168 (58.3)**	<0.001	**91 (56%)**	**76 (63%)**
Race					
White	1,879 (88.4)	**235 (81.6)**	<0.001	**136 (83%)**	**95 (79%)**
Asian	28 (1.3)	**11 (3.8)**		**5 (3.1%)**	**6 (5.0%)**
Other	218 (10.3)	**42 (14.6)**		**13 (8.0%)**	**14 (11.6%)**
BMI	30.6 (4.9)	**27.4 (3.9)**	<0.001	**27.6 (4.1)**	**27.3 (3.6)**
Hypertension	1,876 (88%)	**263 (91)**	0.15	**91%**	**91%**
Duration of diabetes (yr)	8.2 (7.3)	**11.3 (9.1)**	<0.001	**11.9 (9.1)**	**10.5 (9.2)**
eGFR, mL/min/1.73 m^2	110.8 (35.4)	**48.6 (8.8)**	<0.001	**median eGFR 49 (41 – 56)**	**median eGFR 51 (41 – 56)**

Note: 186 patients with CKD Stage 3 and 102 patients with CKD Stage 4 in the CKD subgroup

BETonMACE CKD Group - Results

- CKD vs. non-CKD patients were older (71 vs. 61 years, P<0.001) with more females (42% vs. 23%, P<0.001) and self-identified non-white patients (18% vs. 12%, P<0.001).

- CKD patients had a longer mean duration of diabetes (11.3 vs. 8.2 years, P<0.001) and were less likely to be treated with metformin (69% vs. 84%, P<0.001) and SGLT2 inhibitors (6% vs. 13%, P=0.001).

- CKD patients had **higher serum alkaline phosphatase** (91 vs. 81 U/L, P=0.02) and lower alanine aminotransferase (23 vs. 26 U/L, P=0.01).

Hazard Ratios (HR) for Composite and Component Events by CKD Group

	eGFR < 60			eGFR ≥ 60		
	Placebo Evt/n (%)	Apabetalone Evt/n (%)	HR (95% CI)	Placebo Evt/n (%)	Apabetalone Evt/n (%)	HR (95% CI)
MACE	35/164 (**21.3**)	13/124 (**10.5**)	**0.50** [0.26,0.96]	114/1041 (11.0)	112/1084 (10.3)	**0.94** [0.73,1.22]
MACE + HCHF	41/164 (**25.0**)	16/124 (**12.9**)	**0.48** [0.26,0.89]	132/1041 (12.7)	123/1084 (11.3)	**0.89** [0.70,1.14]
Components						
CV death	17/164 (10.4)	6/124 (4.8)	**0.47** [0.18,1.21]	38/1041 (3.7)	39/1084 (3.6)	0.98 [0.63,1.54]
Non-fatal MI	20/164 (12.2)	9/124 (7.3)	**0.60** [0.27,1.34]	74/1041 (7.1)	68/1084 (6.3)	0.88 [0.63,1.22]
Non-fatal Stroke	6/164 (3.7)	2/124 (1.6)	**0.55** [0.11,2.79]	11/1041 (1.1)	15/1084 (1.4)	1.35 [0.62,2.94]
HCHF	14/164 (8.5)	3/124 (2.4)	**0.26** [0.07,0.94]	34/1041 (3.3)	26/1084 (2.4)	0.74 [0.45,1.24]

BET on MACE CKD group - Results

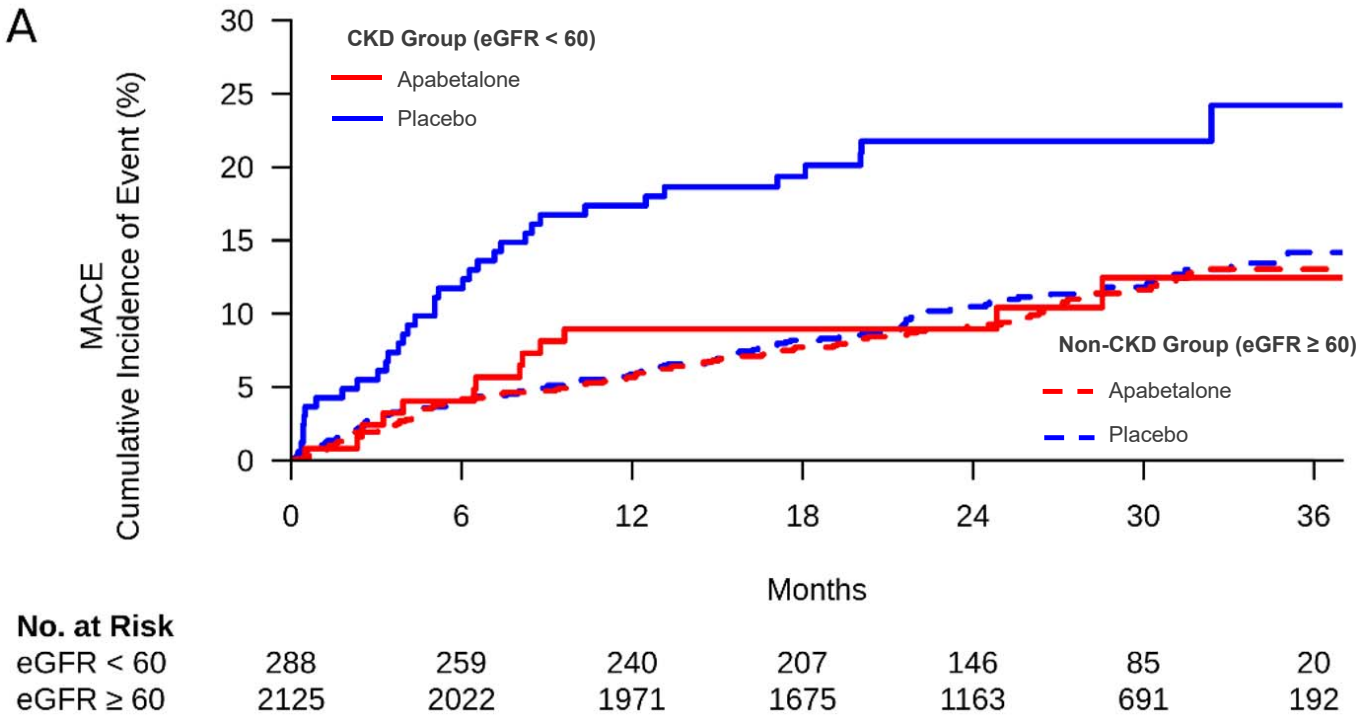
- Under placebo, CKD patients exhibited higher CVD prevalence, i.e.
  - 35/164 (21.3%) vs.114/1041 (11.0%) (HR=**2.40**, 95% CI [1.67, 3.44]) for ischemic CVD/MACE
  - 14/164 (8.5%) vs. 34/1041 (3.3%) (HR=**3.19**, 95% CI [1.66,6.12], P<0.001) for HCHF.

- Under apabetalone, CKD group showed dramatic event reductions compared to placebo:
  - HR=0.50 (95% CI [0.26, 0.96], P=0.034) for MACE
  - HR=0.26 (95% CI [0.07,0.94], P=0.028) for HCHF

- The Kaplan-Maier curves show the much more pronounced CVD risk reduction in the CKD vs. non-CKD group with early and widening curve-separation over the 36 months treatment period.

Kaplan-Meier Estimates by CKD/Non-CKD for MACE Apabetalone Compared to Placebo

MACE: Composite of CV death, non-fatal MI and stroke



No. at Risk							
eGFR < 60	288	259	240	207	146	85	20
eGFR ≥ 60	2125	2022	1971	1675	1163	691	192

CKD Group (eGFR<60)

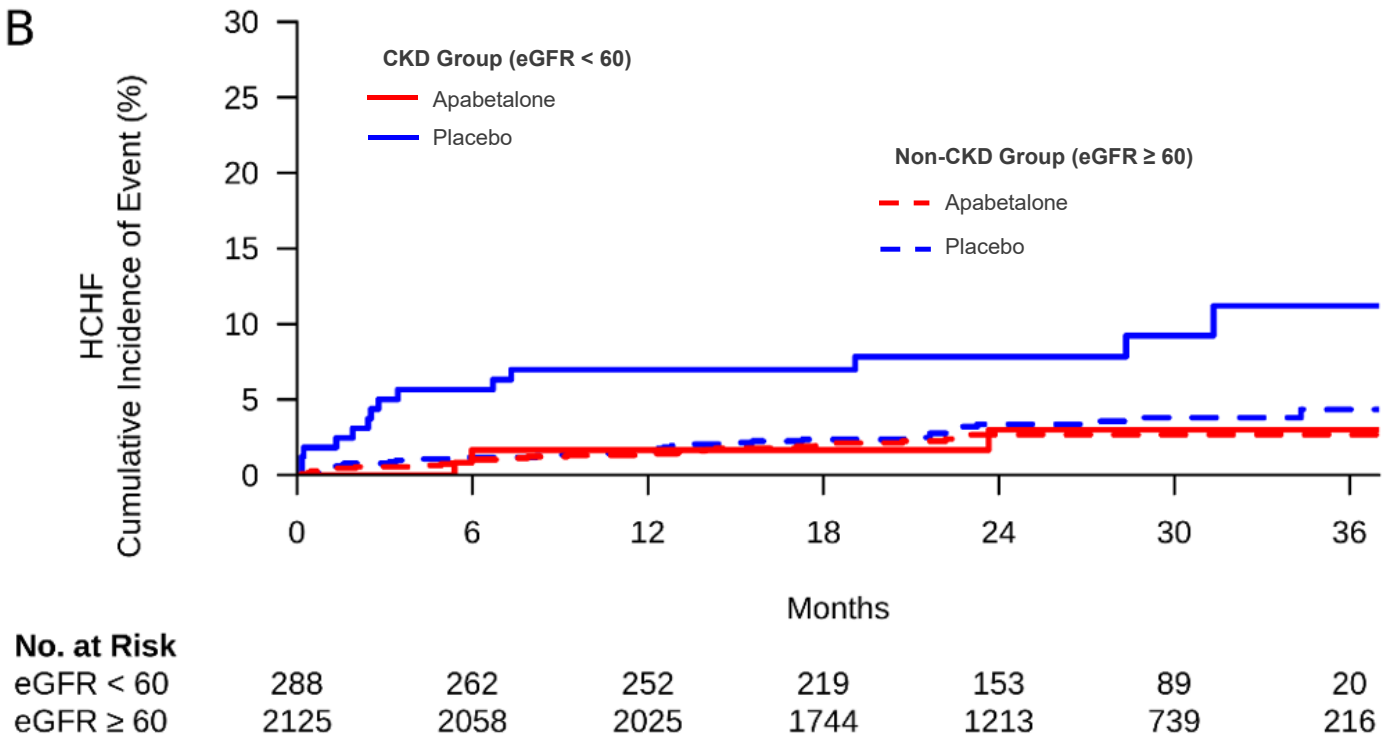
Placebo Events - 35/164 (21.3%)

Apabetalone Events - 13/124 (10.5%)

Hazard Ratio = 0.50 [95%CIs: 0.26,0.96]

Kaplan-Meier Estimates by CKD/Non-CKD for MACE Apabetalone Compared to Placebo

Hospitalizations for Congestive Heart Failure (HCHF)



CKD Group (eGFR<60)

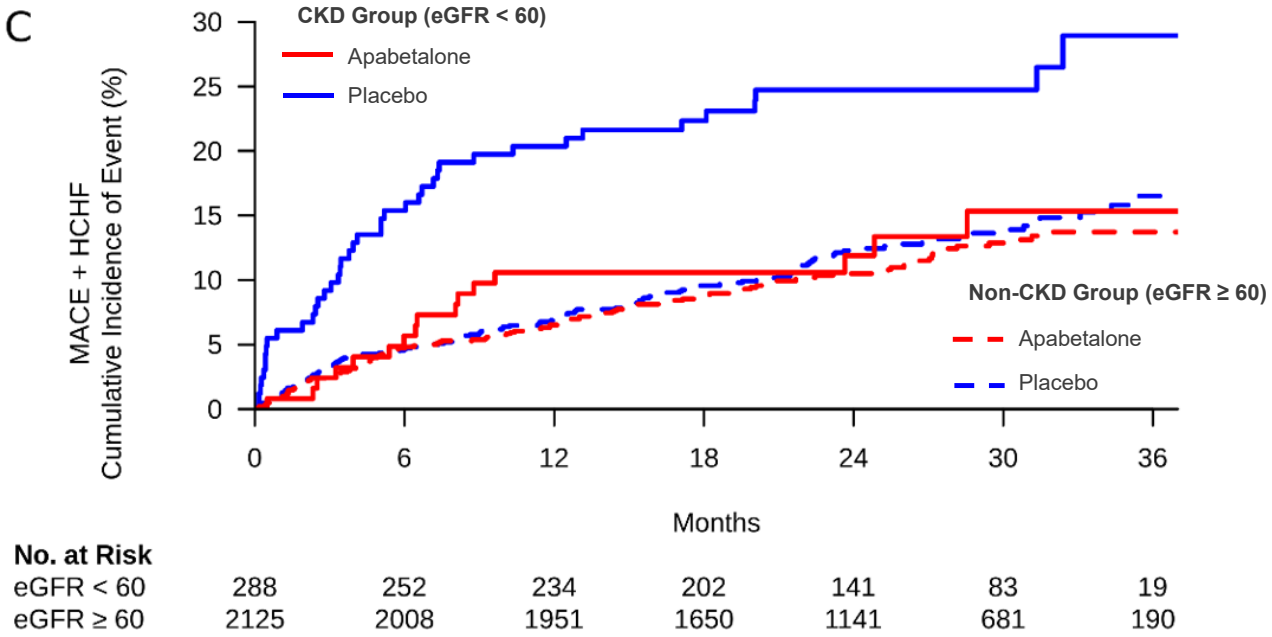
Placebo Events - 14/164 (8.5%)

Apabetalone Events - 3/124 (2.4%)

Hazard Ratio = 0.26 [95%CIs: 0.07,0.94]

Kaplan-Meier Estimates by CKD/Non-CKD for MACE Apabetalone Compared to Placebo

Composite of CV death, non-fatal MI, stroke and hospitalizations for Congestive Heart Failure (HCHF)



No. at Risk

eGFR < 60	288	252	234	202	141	83	19
eGFR ≥ 60	2125	2008	1951	1650	1141	681	190

CKD Group (eGFR<60)

Placebo Events - 41/164 (25.0%)

Apabetalone Events - 3/124 (12.9%)

Hazard Ratio = 0.48 [95%CIs: 0.26,0.89]

Safety of Apabetalone in CKD Patients

- Apabetalone was well tolerated with similar number a subjects in both groups experiencing AE's [119 (72.6%) and 88 (71.0%) in the placebo and apabetalone groups, respectively].
- A significantly lower number of subjects in the apabetalone group had serious adverse events (29% vs 43% p=0.02).
- The majority of this difference was in cardiovascular SAE's (12% vs 25%) reflecting the efficacy results of the apabetalone.
- Only two subjects in each group had hepatic transaminases greater than 5X ULN on close laboratory monitoring requiring discontinuation of study therapy.

Limitations of the CKD Study

- Relatively small portion of the parent trial: 288 CKD patients out of 2,425
- Less balanced randomization among 288 CKD patients
- Limited to CKD Stages 3a and 3b (given exclusion criteria of eGFR<30 ml/min/1.73)
- Lack of urine data: No albuminuria data were collected
- eGFR changes over time were not different
- Non-diabetic CKD patients were not studied

Conclusions

- This is the first cardiovascular outcomes trial assessing the potential of epigenetic modification with BET protein inhibition “apabetalone” and shows promise
- In this Phase III RCT, diabetic CKD patients with a recent acute coronary syndrome (ACS) exhibited a high prevalence of CVD (2.4 times for MACE and 3.2 for HCHF).
- Apabetalone reduced this enormous cardiovascular risk by 50% in diabetic CKD patients with prior ACS.
- Apabetalone offers a safe and effective oral pharmacotherapy for reducing cardiovascular risk in form of major cardiac events in patients with diabetes, CKD Stage 3, and prior ACS.
- Additional studies using apabetalone in CKD patients are warranted.