Session Title: Hypertension and Vascular Disease: From the Lab to Trials [OR1401]

Effect of Apabetalone on Major Adverse Cardiovascular Events in Patients with Chronic Kidney Disease, Diabetes, and Recent Acute Coronary Syndrome: Results from the BETonMACE Trial

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Presented by

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ASN Kidney Week

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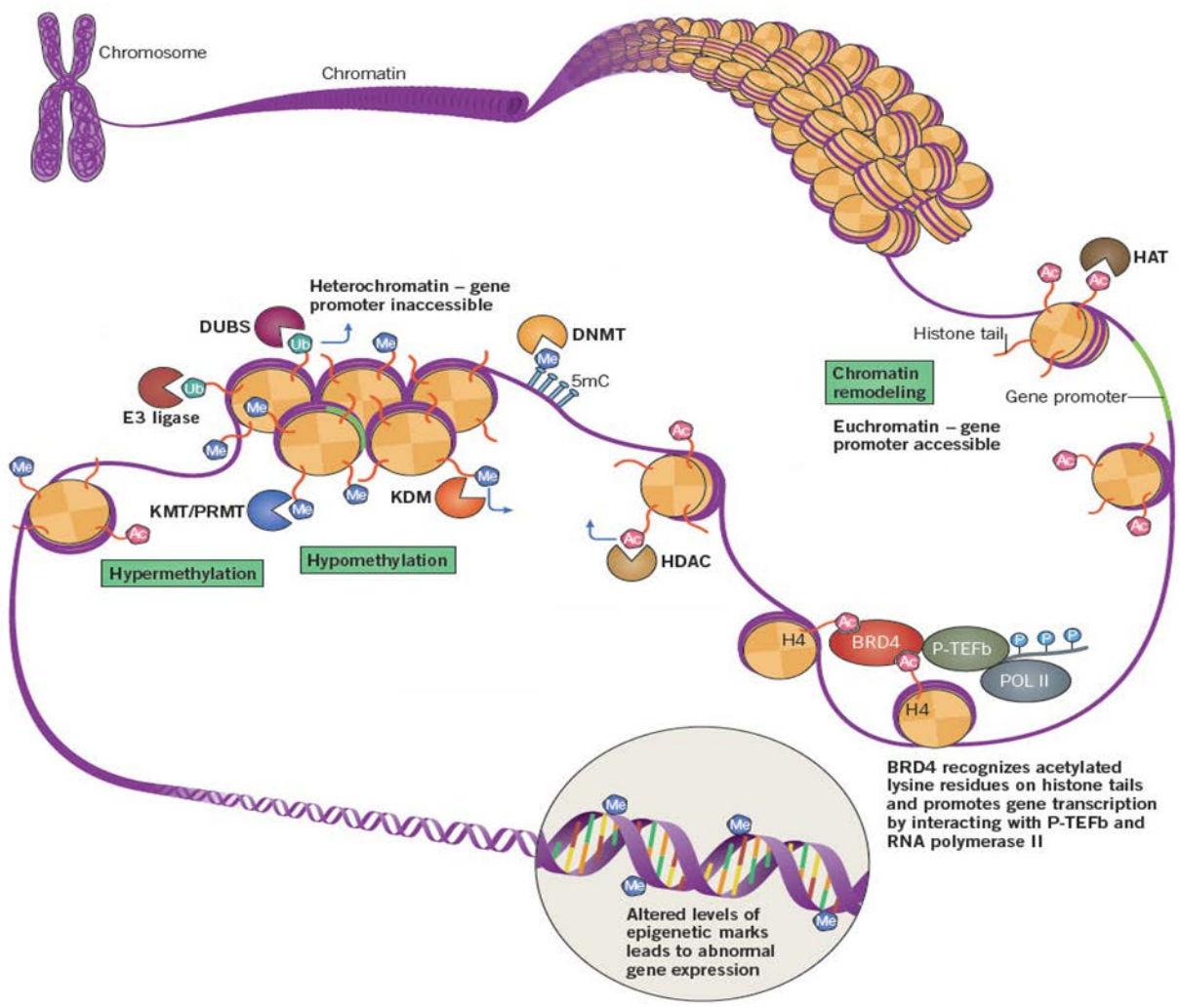
Apabetalone Background & Rationale

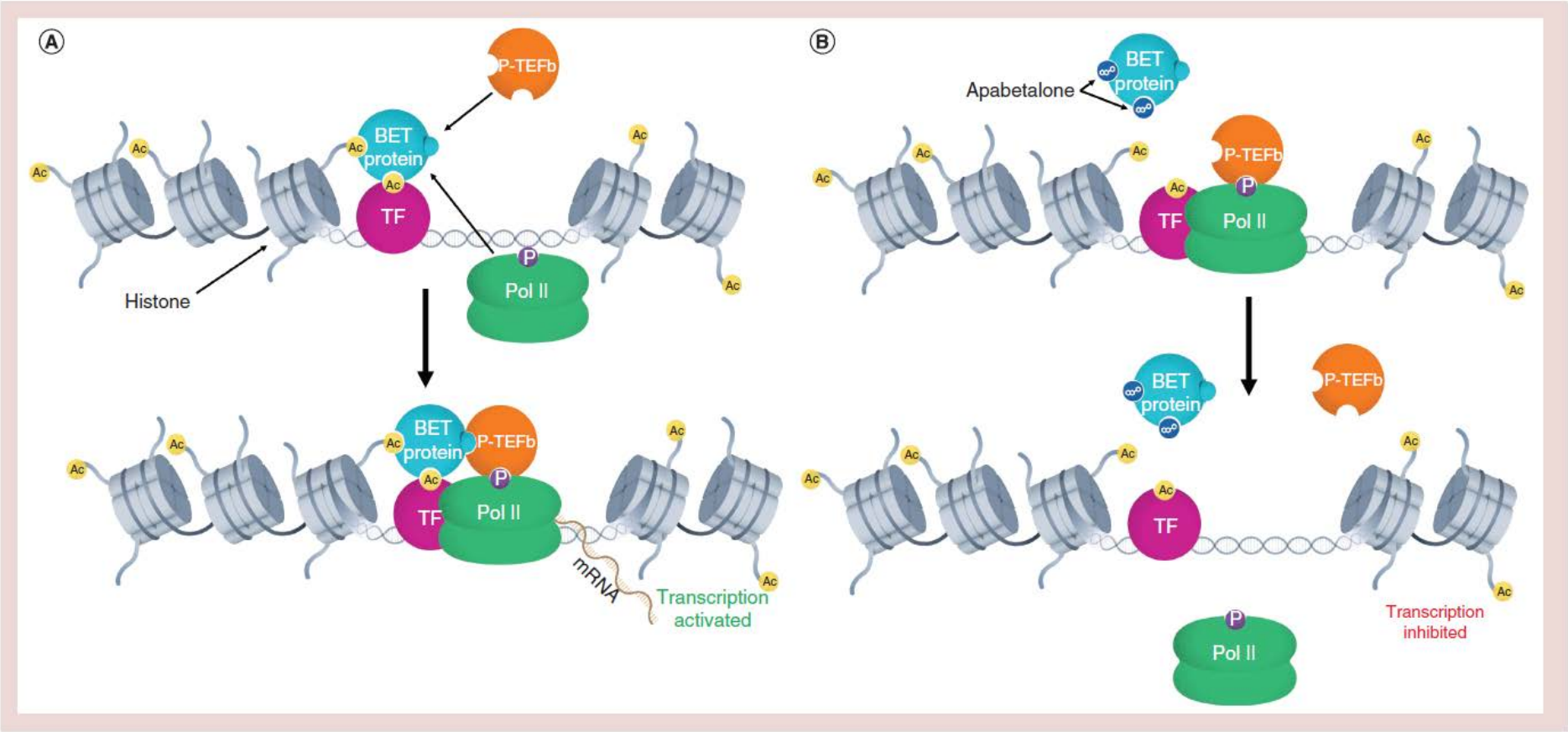
- Bromodomain and extraterminal proteins are epigenetic regulators of gene transcription.



- 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

https://www.tocris.com/research-area/epigenetics-in-cancer

BET Inhibition by Apabetalone

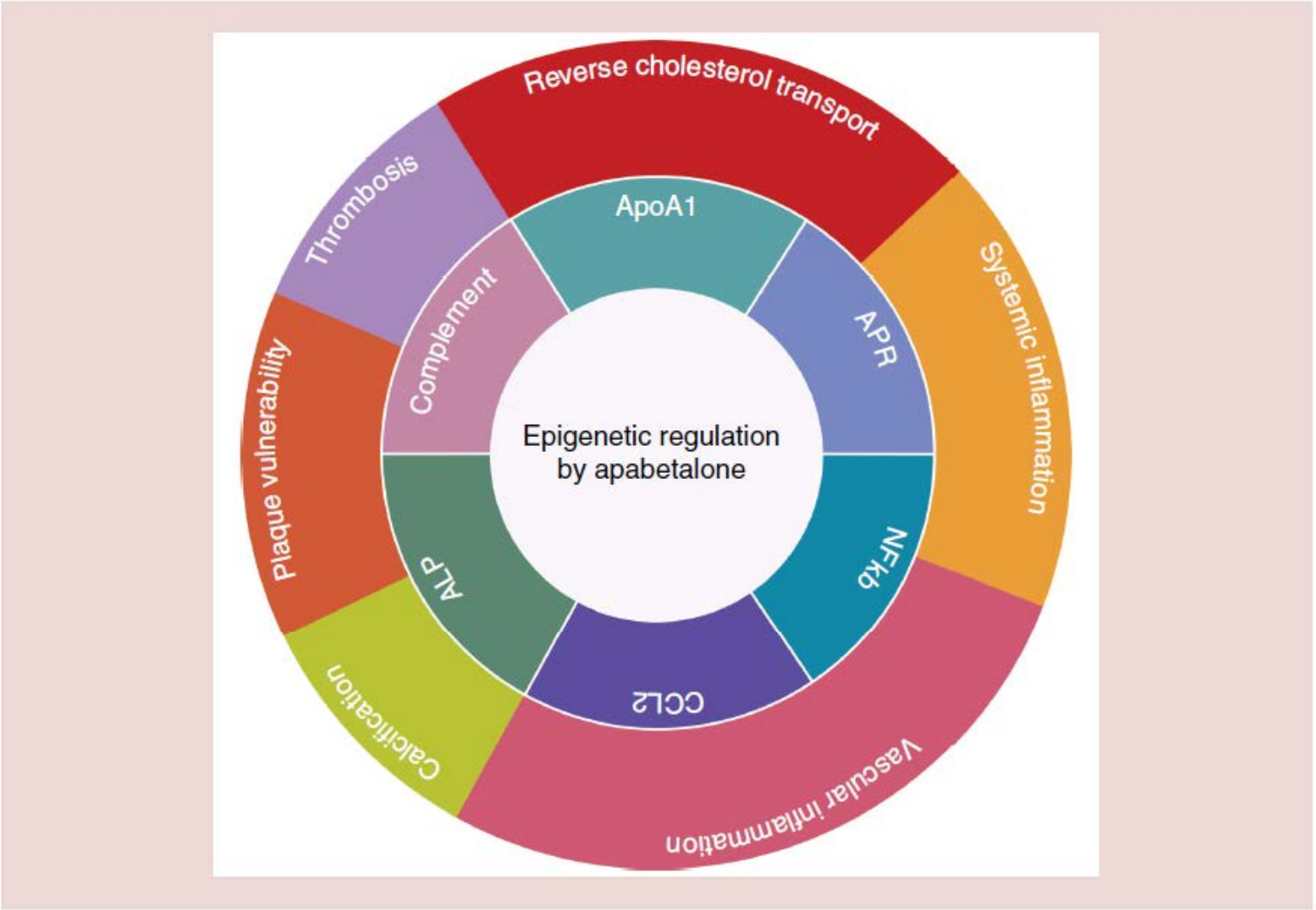


(A) The complex of BET protein and histone initiates binding of additional transcription promoting enzymes like P-TEFb and Pol II. This initiates the transcription process. (B) The function of apabetalone: apabetalone competitively binds to the acetyl-binding sites of BET proteins. This leads to dissociation of the BET protein from the histone and TF resulting in disintegration of the entire complex and inhibition of transcription.

Pol II: RNA polymerase II; TF: Transcription factor.

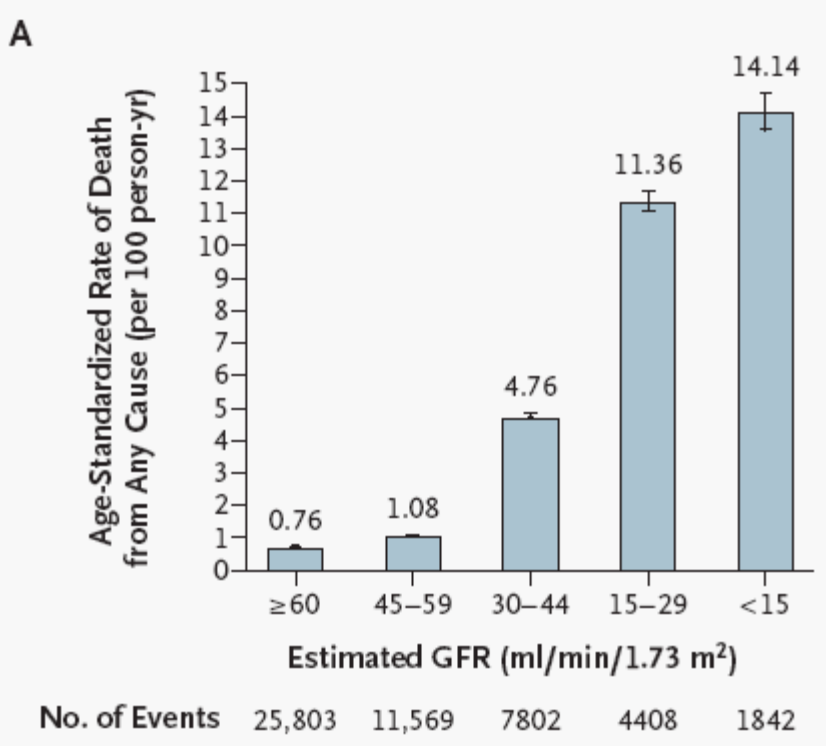
Brandts, J and Ray, KK. Apabetalone – BET protein inhibition in cardiovascular disease and Type 2 diabetes. ***Future Cardiology. 2020.***

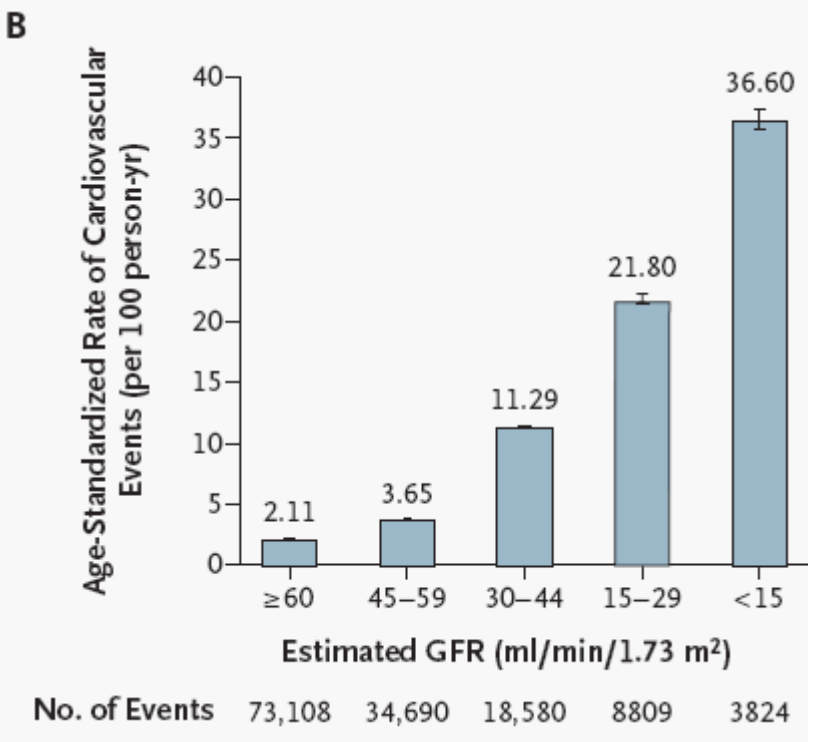
BET Protein Inhibition with Apabetalone Favorably Impacts Pathways Implicated in Cardiovascular and Kidney Disease



Brandts, J and Ray, KK. Apabetalone – BET protein inhibition in cardiovascular disease and Type 2 diabetes. ***Future Cardiology. 2020.***

Unmet Need in CKD





- **In this large, 3-year follow-up study, cardiovascular death rates increased from**
  - **2 per 100 patient-years** in those with **eGFR>60** ml/min/1.73 m^2 to **3.65 per 100 patient-years** in those with **eGFR 45-59** ml/min/1.73 m^2 and;
  - **11 per 100 patient-years** in those with **eGFR 30-44** ml/min/1.73 m^2
- **These findings highlight the clinical and public health importance of chronic renal insufficiency in regard to cardiovascular risk**

Go, A.S. et al. Chronic Kidney Disease and the Risks of Death, Cardiovascular Events, and Hospitalization. ***NEJM. 2004.***

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

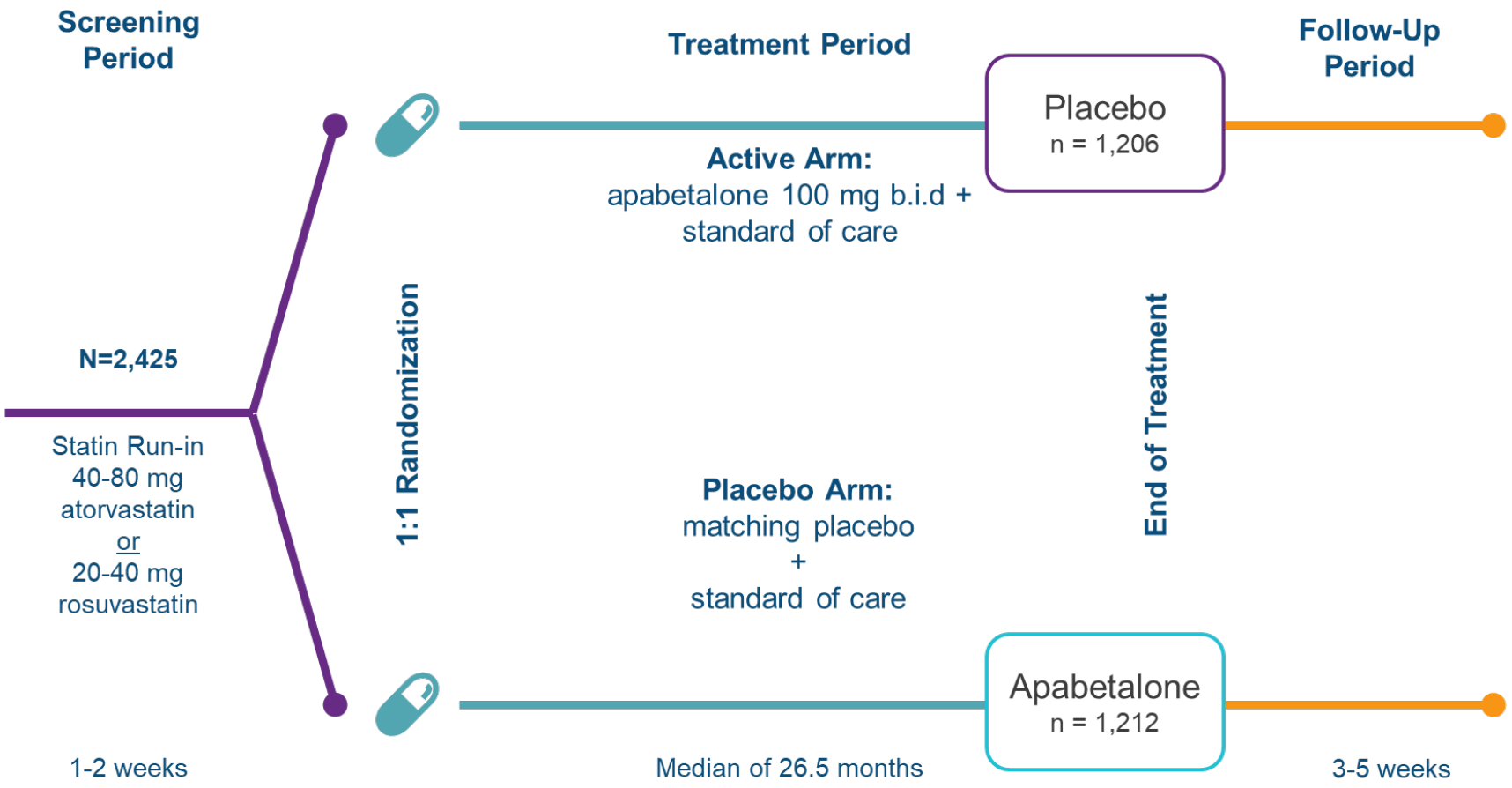
Ray KK, Nicholls SJ, Buhr KA, Ginsberg HN, Johansson JO, Kalantar-Zadeh K, Kulikowski E, Toth PP, Wong N, Sweeney M, Schwartz GG, Investigators BE and Committees. Effect of Apabetalone Added to Standard Therapy on Major Adverse Cardiovascular Events in Patients With Recent Acute Coronary Syndrome and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

BETonMACE Study Endpoints and Subgroup

- **Primary Endpoint**
  - Time to first occurrence of CV death or non-fatal MI or stroke
- **Key Secondary Endpoints Included**
  - Hospitalization for congestive heart failure (CHF)
- **Pre-specified Subgroup**
  - Patients with eGFR<60 at baseline (defined as CKD stage 3)
- **Post-hoc Analysis**
  - Time to first occurrence of CV death, non-fatal MI, stroke or hospitalization for CHF

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 Design and Primary Outcome



- The primary outcome occurred in 274 patients: 125 (10.3%) in apabetalone-treated patients and 149 (12.4%) in placebo-treated patients (hazard ratio, 0.82 [95%CI, 0.65-1.04]

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%
Blood Pressure (mmHg)	Systolic: 129.2 (15.0) Diastolic: 76.5 (8.9)	Systolic: 129.4 (15.3) Diastolic: 74.9 (9.4)	0.89 0.01	Systolic: 128.2 (16.0) Diastolic: 74.7 (10.0)	Systolic: 131.0 (14.4) Diastolic: 75.3 (8.6)
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).

Changes in Key Cardiovascular Variables in CKD Group

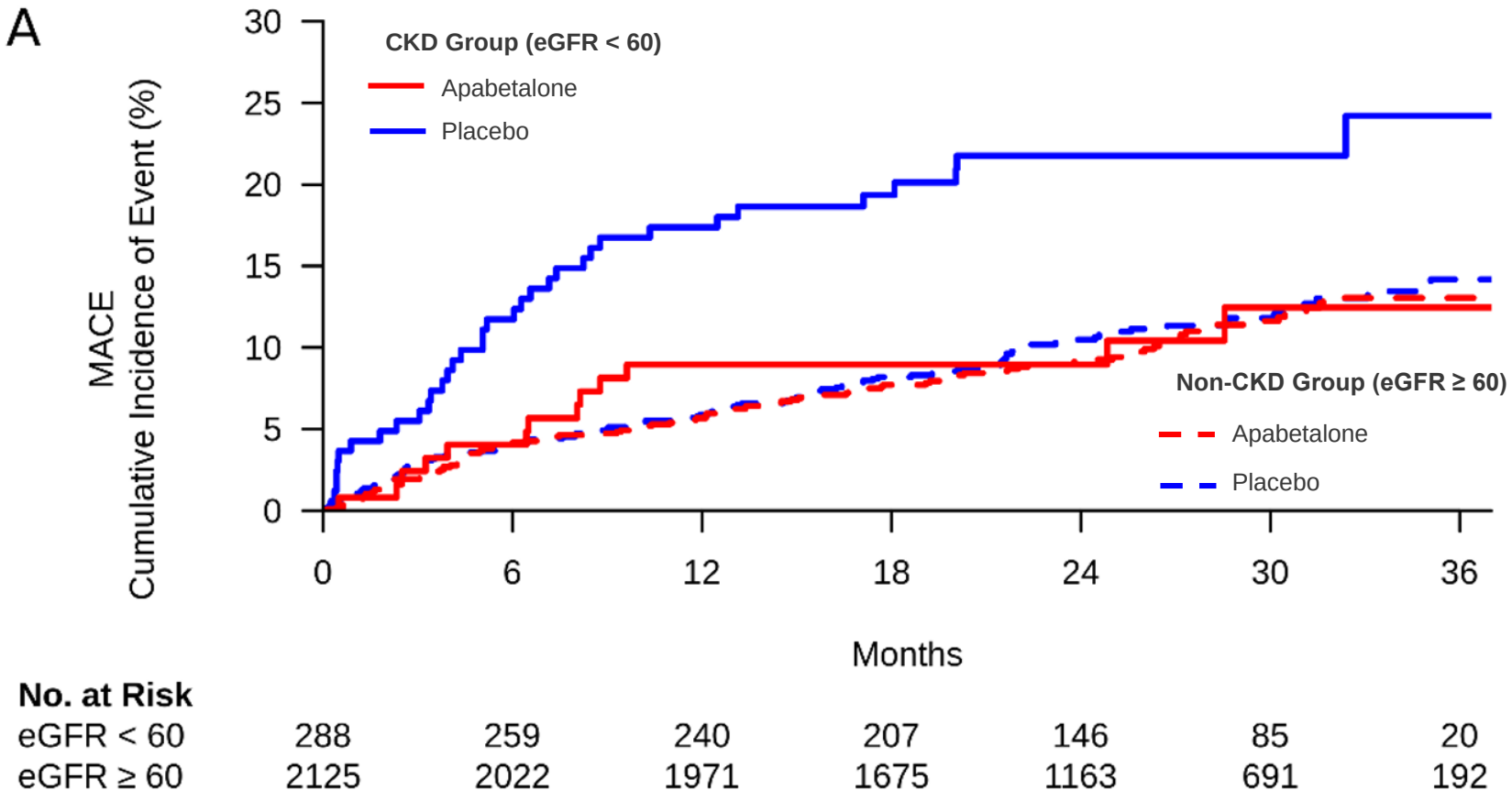
	eGFR < 60		
	Placebo mean (SD)	**Apabetalone mean (SD)**	**Adjusted Diff. [95% CI]**
LDL-C	-0.4 (70.0)	2.6 (70.1)	2.3 [-3.4,8.1]
HDL-C	10.4 (20.3)	15.1 (23.6)	**4.7 [2.8,6.6]**
Cholesterol	0.7 (24.9)	3.9 (27.7)	**2.7 [0.6,4.8]**
Triglycerides	11.8 (64.4)	15.3 (58.5)	2.9 [-2.3,8.1]
HbA1c*	0.00 [-0.60,0.60]	0.00 [-0.80,0.50]	-0.10 [-0.20,0.00]
Serum Glucose	7.4 (67.9)	9.3 (66.4)	2.9 [-2.4,8.3]
hsCRP*	-15.0 [-54.6,26.3]	-25.9 [-61.5,24.5]	-7.8 [-19.6,4.1]
ALP	-1.2 (20.8)	-9.3 (22.0)	**-7.8 [-9.9,-5.7]**
Blood Pressure	Diastolic: -1.5 (10.2) Systolic: -0.4 (17.8)	Diastolic: 0.4 (10.1) Systolic: 1.4 (16.1)	Diastolic: **2.1 [0.1,4.5]** Systolic: 1.7 [-0.5,7.1]

Note: bold indicates statistical significance between treatment groups
(12 weeks interval for CRP, otherwise 24 weeks for all other laboratory values)

**data shown as median [IQR]*

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

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



CKD Group (eGFR<60)

Placebo Events - 35/164 (21.3%)

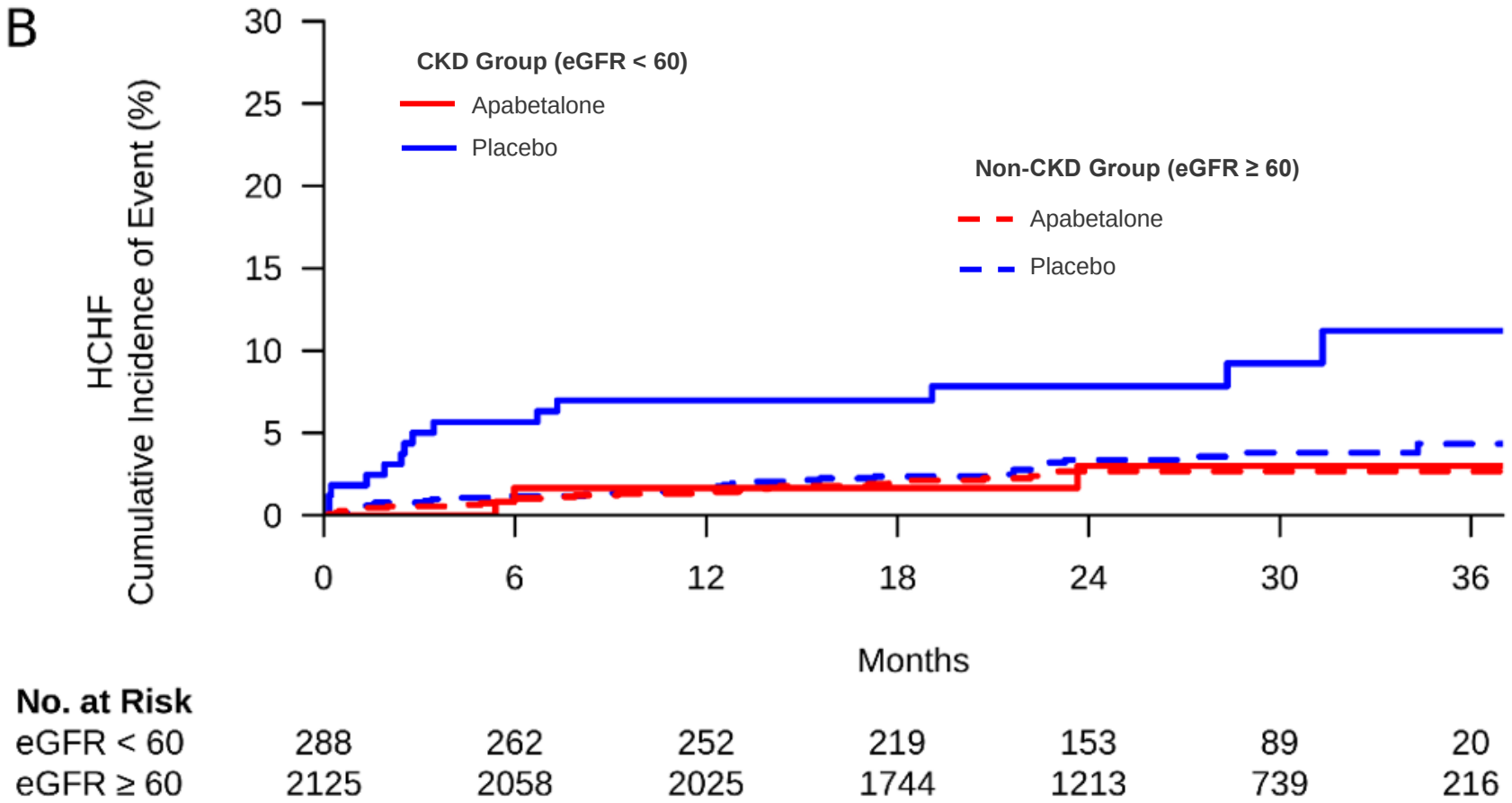
Apabetalone Events - 13/124 (10.5%)

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

Note: HR calculated using Cox proportional hazard model with stratification by statin and country

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%)

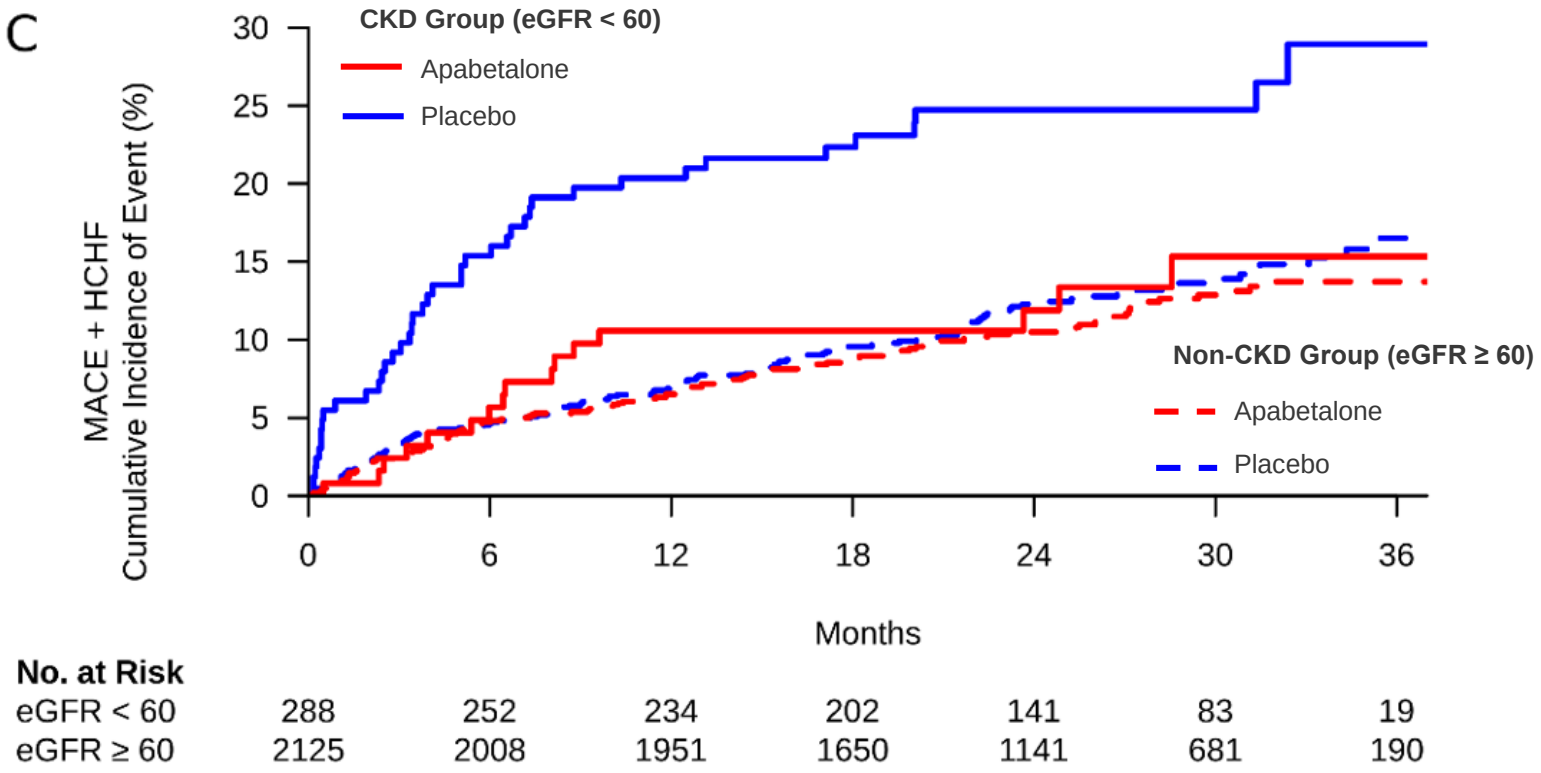
Apabetalone Events - 3/124 (2.4%)

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

Note: HR calculated using Cox proportional hazard model with stratification by statin and country

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)



CKD Group (eGFR<60)

Placebo Events - 41/164 (25.0%)

Apabetalone Events - 16/124 (12.9%)

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

Note: HR calculated using Cox proportional hazard model with stratification by statin and country

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

	eGFR < 60			
	Placebo Event/n (%)	**Apabetalone Event/n (%)**	**Unadjusted HR (95% CI)**	**Adjusted HR (95% CI)**
MACE	35/164 (**21.3**)	13/124 (**10.5**)	**0.46** [0.24,0.86]	**0.50 [0.26,0.96]**
MACE + HCHF	41/164 (**25.0**)	16/124 (**12.9**)	**0.47** [0.27,0.84]	**0.48** [0.26,0.88]
Components				
CV death	17/164 (10.4)	6/124 (4.8)	**0.44** [0.18,1.13]	**0.47** [0.18,1.24]
Non-fatal MI	20/164 (12.2)	9/124 (7.3)	**0.56** [0.25,1.22]	**0.59** [0.26,1.33]
Non-fatal Stroke	6/164 (3.7)	2/124 (1.6)	**0.41** [0.08,2.04]	**0.57** [0.11,2.97]
HCHF	14/164 (8.5)	3/124 (2.4)	**0.27** [0.08,0.94]	**0.25** [0.07,0.92]

Note: (i) Unadjusted HR calculated using Cox Proportional Hazard Model
(ii) Adjusted HR calculated using Cox Proportional Hazard Model stratified for country and baselines statin and adjusted for sex and age

BETonMACE CKD Group - Results

- Under apabetalone, CKD group showed significant event reductions compared to placebo
- Apabetalone treatment demonstrated a statistically significant reduction in ALP compared to placebo
- 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.

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

- There remains a large unmet need for CVD events in high-risk CKD patients.
- In this Phase III RCT, diabetic CKD patients with a recent acute coronary syndrome (ACS) exhibited a high prevalence of CVD events (2.4 times for MACE and 3.2 for HCHF compared to non-CKD patients).
- Apabetalone reduced this cardiovascular risk by 50% in diabetic CKD patients with prior ACS.
- Apabetalone significantly reduced ALP compared to placebo in CKD patients.
- Apabetalone may offer 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.