Apabetalone Lowers Serum Alkaline Phosphatase in CVD Patients With and Without CKD and Improves Cardiovascular Risk

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Background

Patients with cardiovascular disease (CVD) with or without chronic kidney disease (CKD) have considerable residual risk despite optimal standard of care. Alkaline phosphatase (ALP) has been suggested as a modifiable CVD risk factor. Apabetalone, a bromodomain and extraterminal (BET) inhibitor selective for bromodomain 2 (BD2) lowers ALP in a dose-response fashion. In phase 2 studies apabetalone treatment was associate with a significant 44% reduction in CVD events. We sought to determine whether this CVD risk reduction by apabetalone is associated with the concomitant lowering of serum ALP.

Methods

In a pooled phase 2 post-hoc analysis of 795 CVD patients on standard of care treatment including statins, of which 11.8% had CKD as defined by eGFR <60 m/min/1.73m^2 (n=94; 71=apabetalone; 23=placebo) we assessed the effect of apabetalone vs. placebo treatment for up to 24 weeks on the incidence of CVD events and serum ALP.

Results

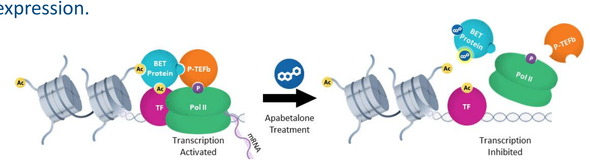
Apabetalone treatment decreased serum ALP in CKD and non-CKD CVD patients by 12.5% and 8.6%, respectively (12 weeks), and 19.9% and 6.5%, respectively (24 weeks) (all p<0.01). Further analysis on the whole population showed that baseline ALP (median 72 U/L) predicted MACE (death, non-fatal myocardial infarction, coronary revascularization, or hospitalization for cardiovascular causes), independent of high sensitivity C-reactive protein (hsCRP), sex, age, study, established CVD risk factors, CKD, and treatment allocation (hazard ratio [HR] per standard deviation [SD] 1.6, 95% CI 1.2-2.1, p<0.001). In the apabetalone group, a 1 SD reduction in ALP was associated with a HR for MACE of 0.58 (95% CI 0.43-0.78, p<0.001).

Summary

Serum ALP predicts strongly the residual cardiovascular risk, independent of hsCRP, established cardiovascular risk factors and CKD, in patients with cardiovascular disease on statin treatment. Apabetalone lowers serum ALP and may prevent the incidence of new cardiovascular events. The phase 3 BETonMACE CVD outcomes study reporting H2 2019, will provide further insights about apabetalone's ALP reduction and potential causality for CVD events.

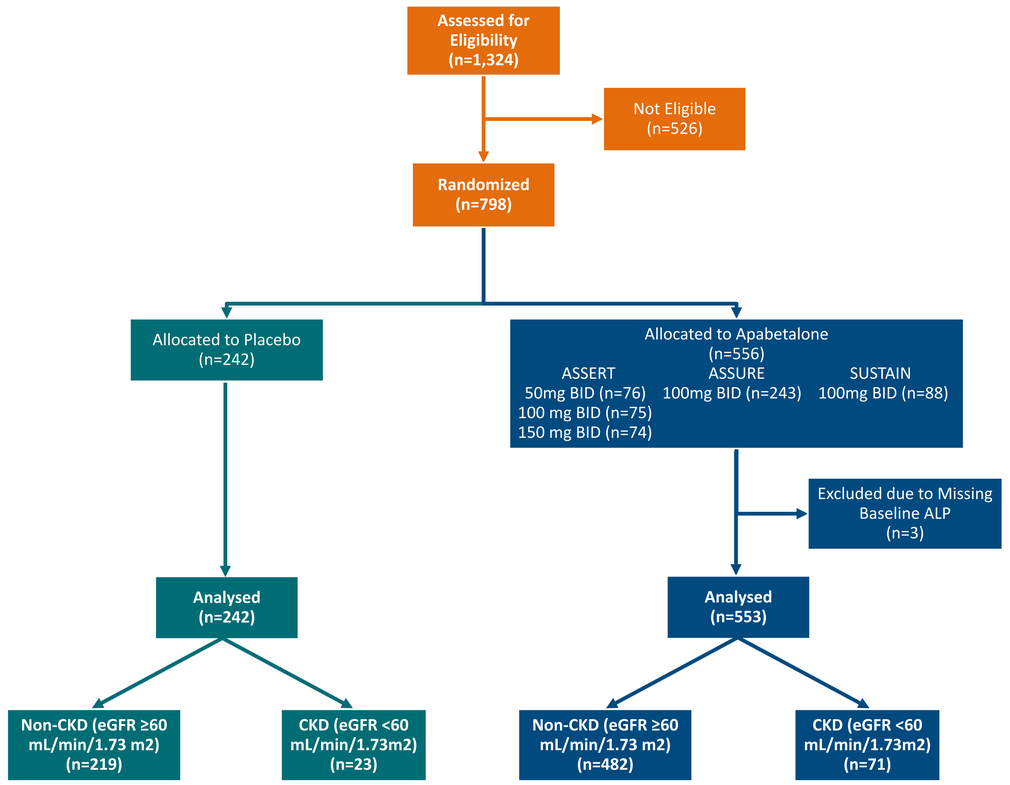
Apabetalone Mechanism of Action

BET proteins control gene transcription through interactions with transcription factors and recruitment of RNA polymerase II. Apabetalone binds to bromodomains in BET proteins, causing their release from chromatin and downregulation of BET sensitive gene expression.

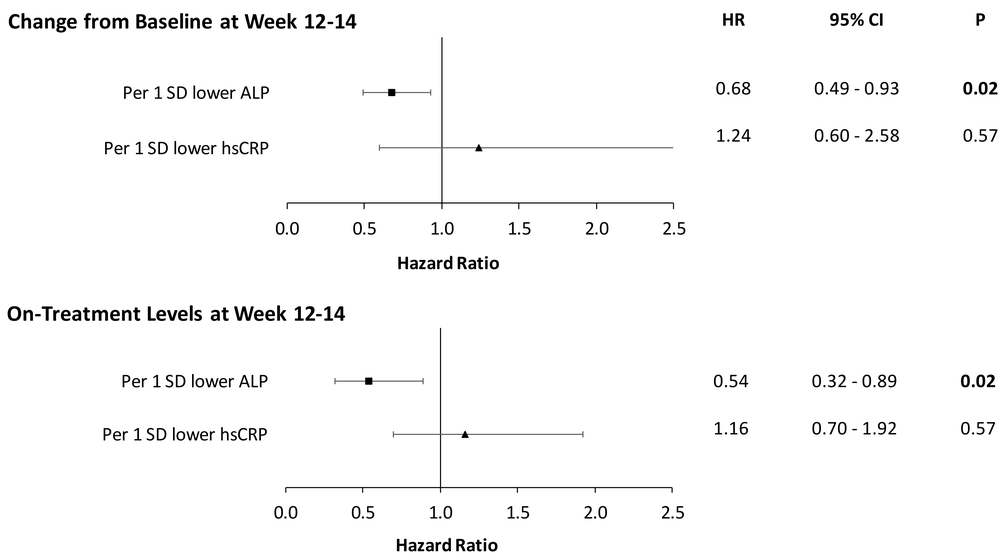


BET: bromodomain and extraterminal proteins
ac: acetylated lysine residue on DNA associated proteins
BD: bromodomain
TF: transcription factor

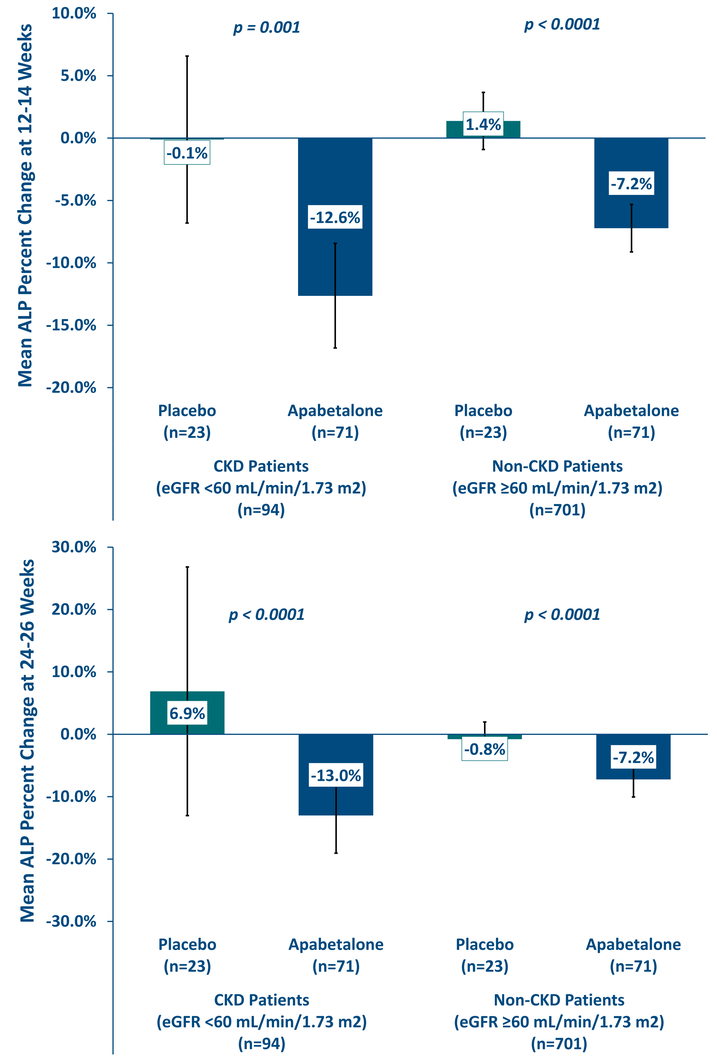
Pooled Phase 2 Trials: Patient Disposition



Apabetalone Lowers Risk of MACE in CVD Patients with High Serum ALP



Apabetalone Lowers Serum ALP



Error bars represent 95% CI
P-values calculated using Mann-Whitney U Test

Summary and Conclusions

- Serum ALP predicts residual CV risk.
  - This is independent of hsCRP, established CV risk factors, and CKD.
- Apabetalone lowers serum ALP.
  - This reduction is more pronounced in CKD patients (eGFR <60 mL/min/1.73 m^2) vs. those without CKD (eGFR ≥60 mL/min/1.73 m^2).
  - Apabetalone may prevent the incidence of new CV events.
    - A one SD reduction in ALP in the apabetalone treated group was associated with a MACE hazard ratio of 0.58.
- Apabetalone is being evaluated for its effects on CV events and reduction in serum ALP in the Phase 3 BETonMACE trial (reporting H2 2019).