ADCY9 Genetic Variants and Cardiovascular Outcome with Evacetrapib

A Nested Case-Control Study

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Disclosure

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Background

- Four CETP Inhibitors have been studied in CV outcome trials without showing compelling benefits, including dalcetrapib, with a reported HR of 1.04 in the DalOutcomes trial (n=15,871).
- A post hoc 5,749 patient pharmacogenetic substudy reported that dalcetrapib-treated patients with the AA genotype for an *ADCY9* SNP (rs1967309) had a 39% reduction in MACE.
- An unusual finding was a 27% increase in MACE in patients with the alternate GG genotype.
- Subsequently, a new clinical outcome trial was initiated to study only patients with the AA genotype reported to show benefit for dalcetrapib (NCT02525939).

Objectives

We sought to replicate the observations reported for this SNP using a nested case-control design for a different CETP inhibitor, evacetrapib, studied in the ACCELERATE outcome trial.

Methods

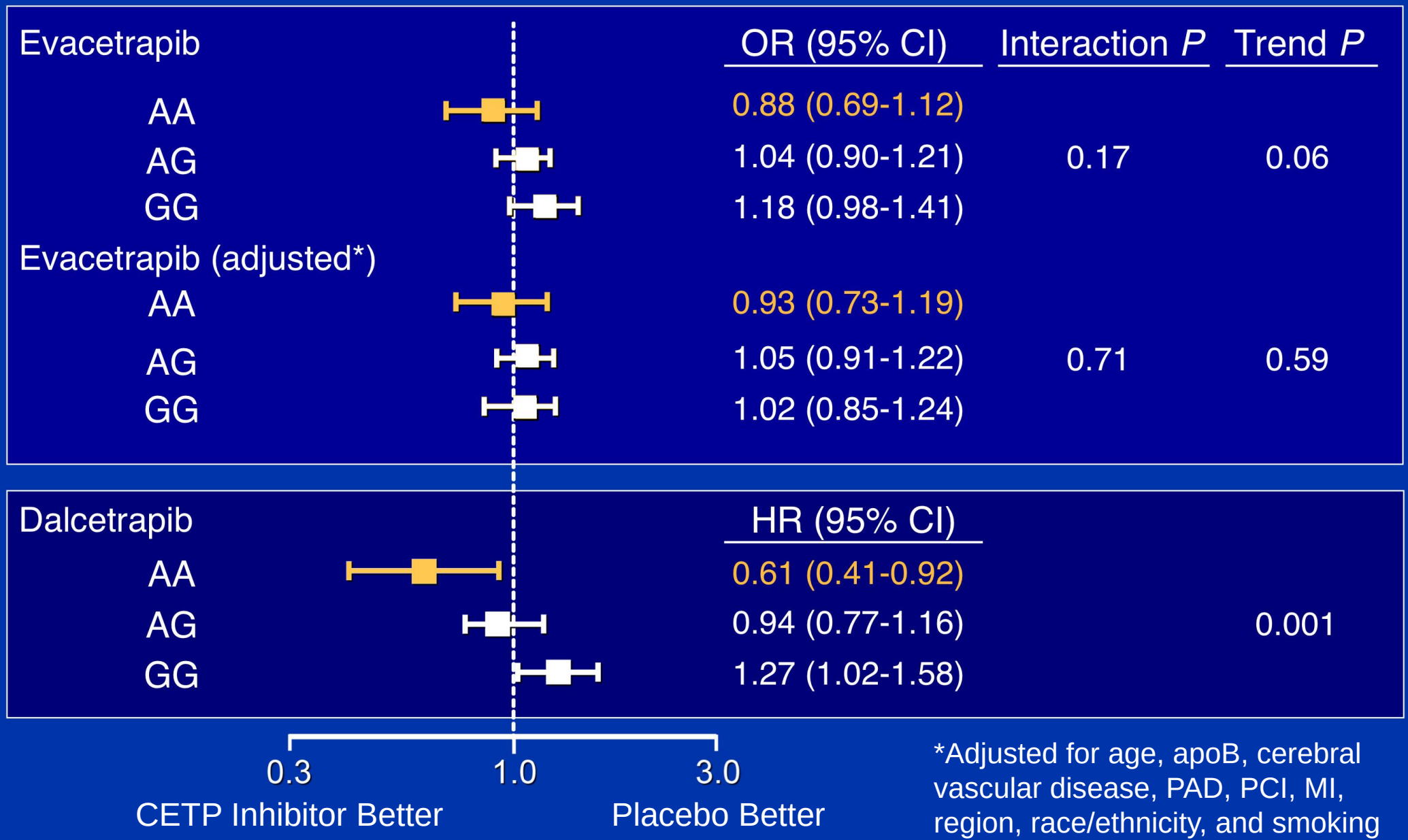
- The ACCELERATE Trial randomized 12,092 patients to evacetrapib or placebo, stopping for futility with a final HR of 1.01 (95% CI, 0.91-1.11)
- Genotyping was performed using the Axiom Biobank™ array in 1427 patients with events and 1532 matched controls.
- The primary endpoint was the OR for 5 component MACE* comparing evacetrapib and placebo-treated patients using conditional logistic regression analysis.
- Additional analyses compared the OR for the effect per minor allele and the relationship between genotype and biomarkers.

* CV death, stroke, MI, coronary revascularization, or hospitalization fro unstable angina

Selected Baseline Clinical Characteristics

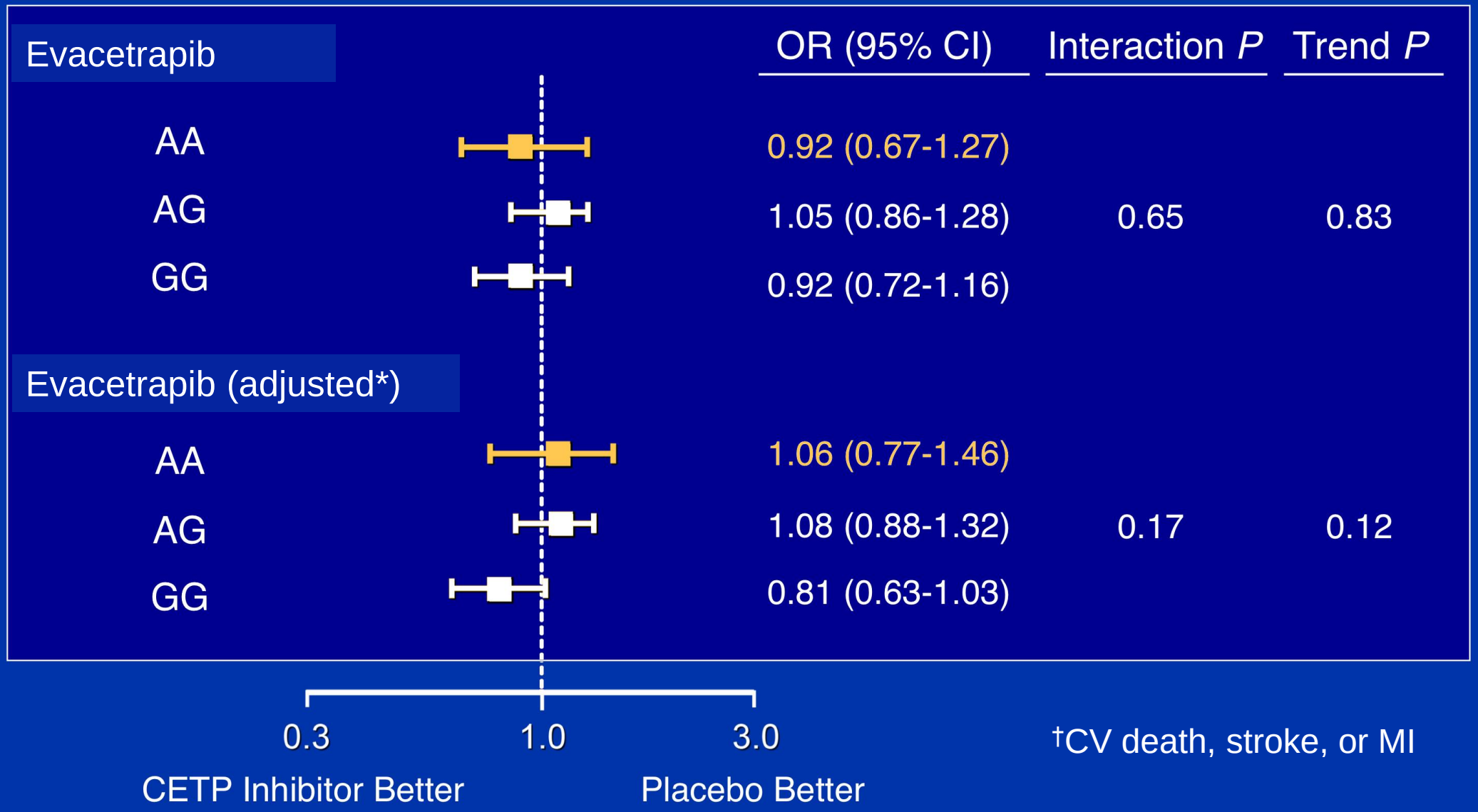
Parameter	Patients with events (n=1427)		Patients without events (n=1532)	
Characteristics	Evacetrapib (n=719)	Placebo (n=708)	Evacetrapib (n=763)	Placebo (n=769)
Age (years)	65.6	65.7	65.3	66.0
Female	22.0%	24.7%	21.8%	23.7%
Caucasian	85.1%	88.7%	85.2%	87.8%
BMI (kg/m2)	30.9	31.1	32	31.5
Hypertension	93.6%	93.1%	91.3%	93.1%
Diabetes	72.7%	76.8%	76.4%	75.8%
Smoking	17.5%	15.1%	13.6%	13.0%
Prior MI	65.4%	62.1%	55.0%	55.4%
LDL-C (mg/dL)	84.3	83.7	80.0	80.8

Genotype and CV Outcome: 5 Component MACE



*Adjusted for age, apoB, cerebral vascular disease, PAD, PCI, MI, region, race/ethnicity, and smoking

Genotype and CV Outcome: 3 Component MACE†



†CV death, stroke, or MI

*Adjusted for age, apoB, cerebral vascular disease, PAD, PCI, MI, region, race/ethnicity, and smoking

Effect of Each Minor (A) Allele: 5 Component MACE

Treatment	Genotype	Patients with events	Patients without events	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Evacetrapib	AA	125	130	0.99 (0.89-1.10)	1.02 (0.91-1.14)
	AG	349	379		
	GG	245	254		
Placebo	AA	143	129	1.15 (1.03-1.27)	1.06 (0.95-1.19)
	AG	353	378		
	GG	212	262		

Effect of Each Minor (A) Allele: 3 Component MACE

Treatment	Genotype	Patients with events	Patients without events	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Evacetrapib	AA	74	181	1.03 (0.90-1.20)	1.02 (0.88-1.18)
	AG	191	537		
	GG	131	368		
Placebo	AA	81	191	1.01 (0.88-1.17)	0.87 (0.75-1.00)
	AG	191	540		
	GG	143	331		

Effect of the rs1967309 *ADCY9* SNP on Biomarkers

Changes in Biomarkers	Treatment	AA genotype	AG genotype	GG Genotype	P value
LDL-C (mg/dL)	Evacetrapib	-26.4	-25.4	-25.2	0.81
	Placebo	5.2	3.1	4.1	0.40
HDL-C (%)	evacetrapib	123	126	123	0.50
	Placebo	0.4	0.2	0.01	0.97
hsCRP (%)	Evacetrapib	16	14	10	0.74
	Placebo	6	8	6	0.95
Systolic BP (mmHg)	Evacetrapib	0.8	2.0	1.5	0.48
	Placebo	-1.8	-0.3	-0.4	0.28

Comparing the Studies: Statistical Considerations

AA Genotype Patients	Dalcetrapib	Evacetrapib
CETP inhibitor-treated patients with events	38	125
Placebo-treated patients with events	59	143
Total AA genotype patients with events	97	268
Hazard Ratio or Odds Ratio	0.61 (0.41-0.92)	0.88 (0.69-1.12)

- A hazard ratio calculated based on 38 events may represent a statistically unstable estimate.
- To achieve 38 events, the dalcetrapib study used a different broader end point rather than the primary DalOutcomes end point.
- Although genome-wide significance was observed for the SNP in the dalcetrapib arm, the genotype-by-treatment interaction was only nominally significant.

Limitations

- Although dalcetrapib and evacetrapib are both CETP inhibitors, they may have different on-target or off-target effects.
- The studied patient populations were different, consisting of ACS patients in DalOutcomes and high risk vascular disease patients in ACCELERATE.
- The confidence intervals for both studies are relatively wide, which makes precise estimates of the relationship between SNPs and CV outcomes challenging.

Conclusions

- A evacetrapib nested case-control study did not confirm the association between the rs1967309 SNP and CV outcome previously reported for dalcetrapib.
- The unadjusted odds ratios were 0.88 for 5 component MACE and 0.93 when adjusted for CV risk factors, in both cases with confidence intervals crossing unity.
- 5-component MACE showed a non-significant trend across genotypes directionally similar to dalcetrapib, not evident when adjusted for CV risk factors or for 3-component MACE.
- Genetic effects of each minor (A) allele and the association with CV biomarkers showed no significant relationship.

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ADCY9 Genetic Variants and Cardiovascular Outcomes With Evacetrapib in Patients With High-Risk Vascular Disease

A Nested Case-Control Study

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IMPORTANCE A pharmacogenetic analysis of dalcetrapib, a cholesteryl ester transfer protein inhibitor, reported an association between a single-nucleotide polymorphism (SNP) in the *ADCY9* gene (rs1967309) and reduction in major adverse cardiovascular events despite a neutral result for the overall trial.

OBJECTIVE To determine whether the association between the SNP in the *ADCY9* gene and a reduction in major adverse cardiovascular events could be replicated for another cholesteryl ester transfer protein inhibitor, evacetrapib, in patients with high-risk vascular disease.

Editor's Note

Supplemental content

Final Thoughts

GWAS studies are now commonly performed for large outcome trials. The large number of evaluated SNPs creates the potential for therapeutic insights, but also raises the risks of false discovery. Replication of results is a key component required to confirm preliminary findings. Whether the pharmacogenetic relationships reported for dalcetrapib represents a paradigm-shifting discovery or a false signal awaits the results of the current outcome trial in patients with the AA genotype.