Background

- Genetic risk scores (GRS) comprised of single nucleotide polymorphisms (SNPs) associated with CAD have been shown to predict CV risk in 1° and 2° prevention populations.
- We tested whether a new, expanded CAD-GRS predicted risk of recurrent coronary events in patients presenting with acute coronary syndromes ACS.

Methods

- IMPROVE-IT (IMPROved Efficacy International Trial) demonstrated a significant benefit of adding ezetimibe to simvastatin in lowering LDL-C levels and reducing CV events

Genotyping and QC

- 7,971 subjects in the genetics substudy were genotyped by the Merck custom Axiom chip and passed the vendor’s QC.
- Genotypes were imputed using the 1000 Genomes European reference panel.
- 6,402 subjects of European descent who passed the standard genetic QC criteria were included in the analysis.

Results

- Patients with higher CAD-GRS tended to be younger, non-smokers, had prior CAGB and were previously treated with lipid lowering therapy [Table].

CAD-GRS

- Started with 2,213 SNPs that were significantly associated with coronary heart disease (CHD) at a genome-wide level in previous analyses (Nickpay M, et al. Nat Genet 2015).
- Linkage disequilibrium pruning at r2<0.2 resulted in 73 uncorrelated genome-wide significant SNPs.
- A CAD-GRS for each subject was calculated by summing the number of risk alleles for each SNP weighted by the log of the odds ratio (OR) for CHD reported in the literature.

Outcomes

- Cox proportional hazard models were used to assess the risk of the prespecified 2° CHD outcome of CHD death, MI or urgent coronary revascularization for each quintile (Q) of genetic risk. Subjects were divided in low (Q1), intermediate (Q2-4) and high (Q5) genetic risk.
- Models were adjusted for the clinical factors included in the TIMI Risk Score for Secondary Prevention.

Conclusions

- An expanded GRS comprised of 73 CAD-associated SNPs identifies patients presenting with ACS who are at significantly increased risk of recurrent coronary events independent of clinical risk factors.
- Patients with the highest burden of genetic risk tended to derive the largest relative and absolute clinical benefit from ezetimibe therapy.