Polygenic Score for Beta-Blocker Survival Benefit in European Ancestry Patients with Reduced Ejection Fraction Heart Failure

David E Lanfear, Jasmine A Luzum, Ruicong She, Hongsheng Gui, Mark P Donahue, Christopher M O'Connor, Kirkwood F Adams, Sandra Sanders-van Wijk, Nicole Zeld, Micha T. Maeder, Hani N Sabbah, William E Kraus, Hans-Peter Brunner-La Rocca, Jia Li & L Keoki Williams

Beta-blockers (BB) are mainstay therapy for heart failure with reduced ejection fraction (HFrEF). However, individual patient responses to BB vary, which may be partially due to genetic variation. The goal of this study was to derive and validate the first polygenic response predictor (PRP) for BB survival benefit in HFrEF patients. Derivation and validation analyses were performed in n=1,436 total HF patients of European descent and with EF <50%. The PRP was derived in a random subset of the Henry Ford Pharmacogenomic Registry (HFPGR; n=248), and then validated in a meta-analysis of the remaining patients from HFPGR (n=247), the TIME-CHF (n=431), and HF-ACTION trial (n=510). The PRP was constructed from a genome-wide analysis of BB* genotype interaction predicting time to all-cause mortality, adjusted for MAGGIC score, genotype, level of BB exposure, and BB propensity score. Five-fold cross-validation summaries out to 1000 SNPs identified optimal prediction with a 44 SNP score and cutoff at the 30th percentile. In validation testing (n=1188) greater BB exposure was associated with reduced all-cause mortality in patients with low-PRP score (n=251; HR=0.19 [95% CI=0.04-0.51], =0.0075), but not high-PRP score (n=937; HR=0.84 [95% CI=0.53-1.3], =0.448), a difference that was statistically significant (interaction =0.0235). Results were consistent regardless of atrial fibrillation, EF (≤40% vs. 41-50%), or when examining cardiovascular death. Among patients of European ancestry with HFrEF, a PRP distinguished patients who derived substantial survival benefit from BB exposure from a larger group that did not. Additional work is needed prospectively test clinical utility and to develop PRPs for other population groups and other medications.