

SUPPLEMENTAL MATERIAL

SUPPLEMENTAL METHODS

Pharmacy Claims and Estimation of Beta Blocker Exposure

To examine medication exposure of the BB class equivalent doses across agents were established. This was based on what proportion of a target dose for each specific agent was used, taken as the target dose for systolic HF used in clinical trials, or the maximum daily dose for BB agents that are not approved for use in treating systolic HF (e.g., atenolol). Specifically, these target/maximal daily doses were 50mg for carvedilol, 200mg for metoprolol (for both long-acting and short-acting formulations), 10mg for bisoprolol, 100mg for atenolol, and 600 mg for labetalol. For example, 25 mg of carvedilol per day (i.e. 12.5 mg twice daily) was considered a 0.5 BB dose equivalent.

Chronic exposure to BB was then calculated as the drug-equivalent strength (described above) multiplied by the quantity of medication dispensed in a 6-month time block, divided by the total number of days in the 6-month time block. A specific BB exposure estimate was calculated for each patient for each day of follow up. Individual exposure measures reflected average exposure over the previous 6 months and could vary daily and could include periods of no exposure.

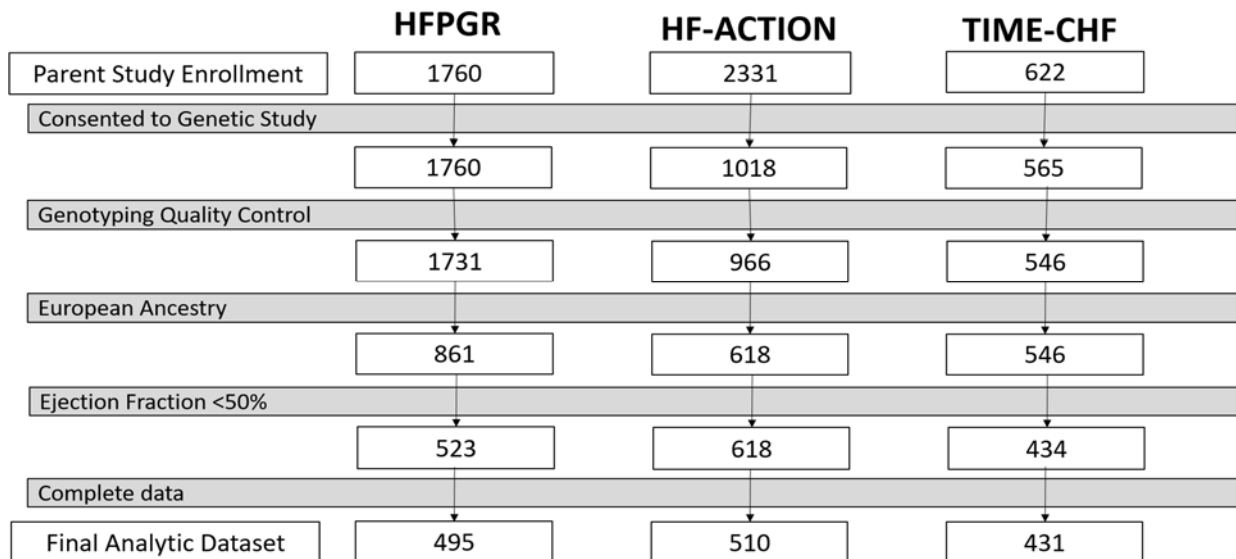
SUPPLEMENTAL FIGURE LEGENDS

Supplemental Figure 1. HFPGR = Henry Ford Pharmacogenomic Registry³⁵; TIME-CHF = the Trial of Intensified vs Standard Medical Therapy in Elderly Patients With Congestive Heart Failure³⁶; HF-ACTION = the Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training³⁷;

Supplemental Figure 2. Q-Q plot of the GWAS (Derivation cohort)

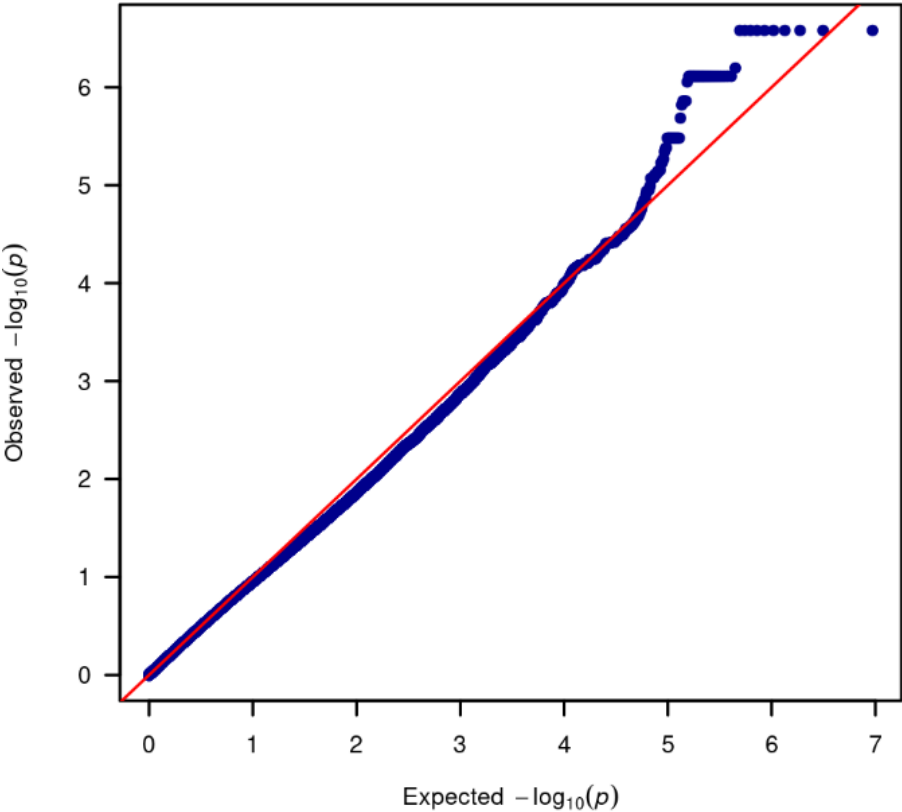
SUPPLEMENTAL FIGURES

Supplemental Figure 1.



Supplemental Figure 2.

Q-Q plot of genomic controlled p-values



SUPPLEMENTAL TABLES

Supplemental Table 1. Propensity Score Balance Check: Weighted Standardized Differences for each Cohort.

Variable	HFPGR-Derivation	HFPGR-Test	HF-ACTION	TIME-CHF
Age	0.026	0.011	0.317	0.06
Sex	0.051	0.03	0.112	0.03
COPD	0.058	0.152	0.085	0.019
Atrial Fibrillation	0.04	0.109	0.067	0.008
Ischemic Etiology	0.008	0.087	0.217	0.13
Stroke	0.212	0.131	0.202	0.047
Diabetes	0.191	0.059	0.09	0.033
Vascular Disease	0.004	0.165	0.164	0.037
Creatinine	0.004	0.057	0.112	0.01
Hypertension	0.025	0.012	NA	0.185

Supplemental Table 2. List of 44 SNPs included in the BB polygenic response predictor (PRP) .

Location (GRCh37)	rsID	Imp. r ²	Coef f.	MA F	p-value	Ref	Alt	Gene (SNP type)	Functional annotation in HaploReg [#] and GWAS catalog associations
12:10538664 5	rs4331189	0.95	4.36	0.14	2.63E-07	T	C	C12orf45	eQTL for C12orf45, SLC41A2, and MGC40397
12:10535324 4	rs4075503	0.90	4.33	0.14	8.83E-07	G	T	none	eQTL for SLC41A2 and C12orf45; possible reg. role to promoter histone mark, enhancer histone mark, DNase, Proteins bound & Motifs changed.
5:2655779	rs16870234	0.91	4.58	0.25	1.38E-06	A	G	none	Possible regulatory role to enhancer histone marks and motifs changed
5:102978477	rs75087282	0.86	4.71	0.12	1.52E-06	A	G	none	possible regulatory role to 4 altered motifs
12:10804807 2	rs28548659	0.98	4.72	0.10	3.30E-06	T	C	BTBD11 (intronic)	Possible regulatory role to 11 altered motifs
4:11263913	rs782760	0.88	3.60	0.28	4.14E-06	C	A	none	Possible regulatory role to enhancer histone marks (ESDR and ESC) and motifs changed (FAC1, RREB-1, Zfp105)
3:32526153	rs367841	0.86	3.97	0.32	5.39E-06	T	C	CMTM6 (intronic)	eQTL for CMTM6 and CMTM7; possible regulatory role to promoter histone marks (BLD), enhancer histone marks (ESDR, BLD), DNase, Proteins bound and Motifs changed.
20:50686015	rs6013374	0.88	4.02	0.16	5.49E-06	C	T	none	Possible regulatory role to Motifs changed (Evi-1)
19:57887748	rs189508091	0.84	4.00	0.19	5.91E-06	C	A	ZNF547 (intronic)	eQTL for ZNF304, CTC-444N24.13, ZNF749; possible regulatory role to DNase (SKIN).
12:29688202	rs299453	0.67	3.87	0.35	7.16E-06	T	C	TMTC1 (intronic)	Possible reg. role to enhancer histone marks (LNG, FAT, BLD), DNase (ESDR, MUS), proteins bound (CEBPB) and motifs changed (TATA, TBX5)
12:29683110	rs299445	0.66	3.86	0.35	7.65E-06	C	T	TMTC1 (intronic)	Possible regulatory to enhancer histone mark (BLD) and motifs changed.
12:10520008 8	rs9737956	0.70	4.35	0.12	8.34E-06	T	C	SLC41A2 (intronic)	Possible regulatory role to motifs changed (Irx)
3:175421845	rs6773175	0.85	4.07	0.16	8.50E-06	A	G	NAALADL2 (intronic)	Possible reg role to enhancer histone marks (GI) & motifs changed (Nrf-2)
3:10455742	rs34912	0.87	3.39	0.32	1.01E-05	T	A	ATP2B2 (intronic)	eQTL for GHRLOS; possible regulatory role to motifs changed (EBF, NF-KappaB, SZF1-1)
18:68373609	rs2457492	0.84	3.15	0.25	1.12E-05	G	A	none	Possible regulatory role to enhancer histone mark (BLD)
13:82134871	rs2225686	0.97	3.22	0.47	1.14E-05	T	G	none	Possible regulatory role to motifs changed (Myc, NF-kappaB, ZBTB33)
12:29701516	rs299468	0.71	3.80	0.35	1.14E-05	C	T	TMTC1 (intronic)	Possible regulatory role to enhancer histone mark (MUS) & DNase (BLD).
17:48724199	rs34221557	0.90	3.22	0.47	1.40E-05	A	C	ABCC3 (intronic)	Possible regulatory role to enhancer histone marks and motifs changed.
5:102981016	rs60529740	0.83	5.12	0.12	1.57E-05	T	G	none	Possible regulatory role to enhancer histone marks and motifs changed.
9:14782367	rs10810237	0.87	3.72	0.17	1.59E-05	C	T	FREM1 (intronic)	Possible regulatory role to Motifs changed (HNF1, Ncx).
9:14790092	rs10756612	0.89	3.71	0.17	1.77E-05	A	C	FREM1 (intronic)	Possible regulatory role to DNase and motifs changed
19:14839160	rs4808387	0.86	3.99	0.28	1.88E-05	C	T	ZNF333 (intronic)	eQTL for ZNF333, EMR2, DNAJB1 and ADGRE2; possible regulatory role to motifs changed (Irf).
8:26380683	rs56098448	0.86	4.13	0.29	2.00E-05	A	T	DPYSL2 (intronic)	Possible regulatory role to motifs changed.
19:57688175	rs34335569	0.88	3.82	0.19	2.11E-05	A	G	none	eQTL for DUXA; possible regulatory role to motifs changed.
2:172525144	rs1399958*	NA	4.14	0.12	2.12E-05	T	C	none	eQTL for CYBRD1, HAT1, and AC068039.4; possible regulatory role to enhancer histone marks and motifs changed.
8:133095617	rs62521322	0.83	3.71	0.42	2.51E-05	G	T	HHLA1 (intronic)	none
10:22101608	rs2666763	0.57	3.49	0.34	2.55E-05	G	A	DNAJC1 (intronic)	possible regulatory role to motifs changed (E2F, TBX5, Zfx)
3:148661164	rs4681163	0.81	3.31	0.23	2.68E-05	G	A	none	eQTL for CPA3; possible regulatory role to enhancer histone marks and

2:20669737	rs12988451	0.96	3.58	0.44	2.70E-05	A	G	none	motifs changed.
4:166456085	rs6828706	0.92	3.06	0.29	2.72E-05	T	C	none	eQTL for AC023137.2; possible regulatory role to enhancer histone marks, protein bounded (FOXA1), and motifs changed.
18:3056415	rs60971978	0.78	3.79	0.30	2.98E-05	T	G	none	possible regulatory role to motifs changed (LUN-1).
17:10829256	rs4527059	0.96	3.89	0.21	3.19E-05	A	G	none	Imporant regulatory role to enhancer histone marks and motifs changed.
7:101285877	rs2527834	0.99	3.60	0.44	3.32E-05	T	C	none	Imporant regulatory role to DNase and motifs changed.
6:109554233	rs12528081	0.93	4.14	0.36	3.41E-05	T	C	none	possible regulatory role to motifs changed.
1:54772851	rs4413992	0.74	3.26	0.40	3.48E-05	A	G	SSBP3 (intronic)	eQTL for CD164, RP11-425D10.10 and CCDC162P; possible regulatory role to motifs changed (Smad).
11:12921701	rs4514425	0.91	3.43	0.30	3.59E-05	T	C	none	Possible reg. role to enhancer histone marks & motifs changed (HEN1).
2									Possible regulatory role to DNase and motifs changed.
10:34802967	rs4934638*	NA	3.32	0.23	3.61E-05	T	C	PARD3 (intronic)	Possible regulatory role to enhancer histone marks and motifs changed.
19:2058694	rs10416900	0.61	3.75	0.16	3.65E-05	T	C	none	Possible regulatory role to DNase and motifs changed.
1:116067883	rs61797384	0.86	5.15	0.13	3.90E-05	C	T	none	eQTL for VANGL1; possible regulatory role to enhancer histone marks, DNase, and motifs changed.
3:44350264	rs2171574	0.85	3.19	0.16	3.92E-05	A	G	TOPAZ1 (intronic)	eQTL for ZNF660, TCAIM, LINC00694, and RP11-424N24.2
3:10474448	rs34854	0.79	3.27	0.22	3.97E-05	T	C	ATP2B2 (intronic)	eQTL for GHRLOS and ATP2B2; possible regulatory role to enhancer histone marks, DNase, proteins bound and motifs changed.
17:77090828	rs60764725	0.89	3.72	0.23	4.04E-05	C	T	RBFOX3 (intronic)	eQTL for ENGASE; possible regulatory role to enhancer histone marks, DNase and motifs changed.
4:120522172	rs10518335	0.97	3.20	0.22	4.15E-05	T	C	PDE5A (intronic)	eQTL for USP53, RP11-33B1.1, RP11-33B1.4, and PDE5A; possible reg. role to motifs changed. GWAS association with acute myeloid leukemia
10:21889138	rs6577189	0.86	3.25	0.35	4.29E-05	A	G	MLLT10 (intronic)	eQTL for MLLT10; possible regulatory role to enhancer histone marks & motifs changed. GWAS association to urinary albumin to creatinine ratio.

* SNP genotyped on array (all others were imputed). P values shown are for the SNP*BB interaction term in the derivation

cohort (HFPGR-derivation) with genomic control. Imp.= Imputation