Supplemental Material
Supplemental Methods:

Study samples

All the study protocols for each of the studies was approved by the local institutional review boards or equivalent committees. Informed consent forms were voluntary signed by all the participants. The clinical trials at each of the institutions included in this meta-analysis were conducted in accordance with regulations set forth by the Declaration of Helsinki and local regulatory agencies.

PEAR (Pharmacogenomic Evaluation of Antihypertensive Responses)

The details of the PEAR study have been described previously\(^1\). PEAR was a prospective randomized, crossover clinical trial, which included hypertensive patients with mild to moderate uncomplicated hypertension. In brief, patients of both genders and of any race and ethnicity between ages of 17-65 years were included in the study. Secondary HTN, known history of cardiovascular disease (CVD) or diabetes were exclusions from PEAR. Before the initiation of HTN treatment, patients went on a washout for at least three-four weeks to revert to their hypertensive BP state. Patients were then randomized to an eight-week, monotherapy treatment with either atenolol (ATN) 50mg daily or hydrochlorothiazide (HCTZ) 12.5mg daily, followed by the addition of the other drug (i.e. ATN added to HCTZ, and HCTZ added to ATN). For BP phenotype, a composite BP response of home, office and ambulatory BP measurement was used. For the analysis included herein, only participants with European American ancestry (EA) who were treated with β-blocker monotherapy and had available genome-
wide genotype data were included. Genotyping was performed using Illumina Human Omni1M Quad Beadchip. (Illumina, San Diego, CA, USA)

PEAR-2

The details of PEAR-2 study have been published previously\(^2\) \(^3\). PEAR-2 was a prospective, randomized trial that assessed the genetic factors contributing to variable BP response following sequential monotherapy with metoprolol (β-blocker) and chlorthalidone (thiazide-like diuretic). Like PEAR, adult participants between 18 and 65 years of age, from both sex, and of any race/ethnicity who had mild to moderate, uncomplicated, HTN, were recruited into the study and underwent an anti-hypertensive treatment washout period for three-four weeks. Exclusion criteria was like that of PEAR. Upon confirmation of HTN criteria and BP readings, participants were started on metoprolol tartrate (50mg twice daily), and treatment was up titrated to a maximum dose of 100mg twice daily, followed by a second hypertensive washout, and treatment with chlorthalidone. While office and home BP readings were collected in PEAR-2, the average home BP measurements were used to create the BP response phenotype to metoprolol monotherapy. For this analysis, participants with EA ancestry who were treated with metoprolol monotherapy and had available genome-wide data were included. Genome-wide data were generated using Illumina Human Omni2.5S Beadchip (Illumina, San Diego, CA).
LIFE-Fin (Finnish Arm of the Losartan Intervention For Endpoint Reduction in Hypertension Study)

LIFE was a prospective, randomized, multicenter (Scandinavia, UK, USA), double-blind, double-dummy, active-controlled study that aimed at evaluating the long-term treatment effects of losartan compared with atenolol among 9193 hypertensive patients with signs of left ventricle hypertrophy (LVH) indicated by their ECG. The details of the study have been published elsewhere⁴. Adult patients with 55-80 years of age, who had office systolic BP (SBP) of 160-200 mmHg or diastolic BP (DBP) of 95–115 mmHg, were included in the study. They underwent a two-week antihypertensive treatment-washout period during which placebo treatment was used. The baseline BP was derived from BP at the end of the washout period. Patients were then randomized to either losartan or atenolol, with a subsequent addition of HCTZ, to achieve a target BP of <140/90mmHg. Patients were followed at two, four and six months intervals after starting the medication, then every six-months for a total follow-up period of 4.8 years. Office BP readings were recorded at each visit and used to create BP response phenotype.

For the current study, DNA samples from Finnish participants of the LIFE pharmacogenetic sample were available. Herein, we selected 202 participants on monotherapy treatment with atenolol 50 mg daily at two months of the study and used office BP data at 2 months after start of the treatment to calculate the BP responses. The DNA samples were genotyped using Illumina Human OmniExpress-12 BreadChip (Illumina, Inc., San Diego, CA, USA).
GENRES (Genetics of Drug Responsiveness in Essential Hypertension)

GENRES is a randomized, placebo-controlled, double-blind, cross-over, single-center study that investigated the molecular genetics of drug response in essential HTN. The details of the study have been described previously\(^5\), \(^6\). Moderately hypertensive Finnish men with 35–60 years of age who had repeated measurements of DBP $\geq$95mmHg or used antihypertensive medication(s) were included in the study. Exclusion criteria included the use of three or more antihypertensive drugs, secondary hypertension or significant additional co-morbidity. Patients' antihypertensive treatment was stopped for at least 4 weeks prior to starting the study drugs. The study included a four-week, run-in placebo period, followed by four-week drug monotherapy periods that were separated by four-week placebo treatment periods. During the drug periods, the patients received (in a randomized order, in a rotational fashion) losartan 50mg, bisoprolol 5mg, HCTZ 25mg, or amlodipine 5mg daily. Office BP measurements after a 30-minute rest in the sitting position were recorded at the end of each treatment or placebo period. For the present study, we selected 216 participants with office BP response data to bisoprolol treatment available. Means of all (up to four) placebo treatment periods were used as the baseline levels for the calculation of BP responses. These patients had genome-wide genotype data on Illumina Human OmniExpress-12 BreadChip (Illumina, Inc., San Diego, CA, USA).

Pharmacogenomics of beta blocker Sardinian Study (BBSS)

PHSS was a Pharmacogenomic study conducted at Hypertension and Related Disease Centre of the AOU-University of Sassari, Italy. The aim of the study was to find genetic markers of response to the antihypertensive drug atenolol in Essential Hypertension
Four hundred and three never treated Caucasian essential hypertensive patients, whose blood pressure was found SBP ≥ 140 or DBP ≥ 90 mmHg at the first visit (week-8), were screened. Only patients with asymptomatic, mild-to-moderate essential hypertension were screened. A complete absence of major systemic disease and of any kind of treatment was also required. The absence of whatever kind of concurrent disease was a prerequisite for patients’ eligibility to the study.

After a run-in period of 8 weeks under controlled dietary conditions (sodium 100-140 mEq/day and potassium 50-70 mEq/day), during which a complete diagnostic workout was performed to define the presence of high BP and to exclude secondary forms of hypertension (week 0), all the patients started Atenolol 50 mg b.i.d for 4 weeks. To avoid the interference of the effect of previous treatments which may last up to six months after drug withdrawal, only never treated EH were enrolled in the study. The run-in period to confirm the presence of BP≥140/90 was decided according to International Guidelines on High Blood Pressure and to the Ethics Committee of the University of Sassari.

During this period, BP and side effects were monitored every 2 weeks. BP was measured by automated electronic devices (OMRON 7051 IT) between 8:00 and 10:00 AM, in the sitting position, on the dominant arm: three readings were obtained in each occasion by the same nurse in a quiet room and in the absence of the physician: the average of the three readings was used as reference value. Genomic DNA, collected at week 0 from the peripheral blood, was extracted with Macherey-Nagel kit: NucleoSpin Blood XL, Düren, Germany. All samples were genotyped at “Genomic and Bioinformatics laboratory” of University of Milan, using the Illumina Human1M-Duo array
within the HYPERGENES project and the Illumina HumanOmniExpress array (Illumina Inc, San Diego, CA, USA), within the InterOmix project (http://www.interomics.eu/).

**INVEST (INternational VErapamil SR-Trandolapril)**

INVEST was an international, prospective, multicenter, randomized trial. The details of the study including the inclusion/exclusion criteria have been published elsewhere. Patients older than 50 years of age, with essential hypertension and documented coronary artery disease (CAD) were randomized to receive either verapamil SR (calcium antagonist strategy; CAS) or atenolol (β-B strategy). Trandolapril or HCTZ were added respectively, to the treatment arms if target BP control was not achieved (<140/90 mm Hg or <130/85 mm Hg if patients were diabetic or have renal impairment). Patients were initially followed up every six weeks for the first six months, then every 6 months thereafter for recording of BP, assessing of patients’ overall well-being, adverse events, and drug compliance, for an average follow-up period of 2.7 years. INVEST-GENES is the genetic sub-study of INVEST which included 5979 INVEST participants with DNA samples of whom, 1529 had genome-wide data generated on Illumina OmniExpress Exome chip. Herein, a total of 74 participants with EA ancestry who had BP response data to atenolol monotherapy treatment were analyzed.

**ASCOT UK/ASCOT SC**

ASCOT study is an investigator-led, multi-center trial, which included over 19,000 hypertensive patients, aged 40-79 years at baseline, with an average SBP of 140/90 mmHg on-treatment and 160/100 mmHg off-treatment. The details of this study have
been published previously\textsuperscript{10}. Patients with no history of coronary heart disease who had at least three risk factors for CVD such as LVH, type II diabetes mellitus, peripheral artery disease, previous stroke/TIA, smoking, and male sex older than 55 years. The study investigated the outcome of amlodipine, a CAS compared with atenolol (βB-based strategy) among hypertensive patients at a moderate risk for CVD. BP was measured at randomization clinic visit and subsequently, at follow-up visits scheduled initially at six weeks, three months, six months, and every six months interval thereafter. BP measurement post-atenolol monotherapy treatment taken at each person’s first follow-up visit was used to define BP response phenotype. 745 Europeans from UK and Ireland were genotyped using Illumina HumanCNV 370 chip and 773 Europeans from Scandinavia were genotyped using the Illumina Human Omni Exome Express v8.1 and comprised the ASCOT UK and ASCOT-Sc cohorts, respectively.
Table S1. Clinical Characteristics of African American participants from PEAR and PEAR-2.

| Ethnic Validation Cohorts | PEAR | PEAR-2 |
|---------------------------|------|--------|
| N                         | 150  | 168    |
| Age, years                | 47.2 ± 8.5 | 50.0 ± 9.2 |
| Female, N (%)             | 107 (71.3%) | 89 (53.0%) |
| Body Mass Index, kg/m²    | 31.6 ± 6.3 | 30.8 ± 5.2 |
| Baseline SBP (mm/Hg)      | 151.3 ± 12.1 | 147.5 ± 10.6 |
| Baseline DBP(mm/Hg)       | 99.0 ± 5.7  | 95.6 ± 6.1 |
| Post treatment SBP (mm/Hg)| 137.3±12.8 | 142.7±13.1 |
| Post treatment DBP (mm/Hg)| 84.9±7.4   | 89.8±7.9 |
| Delta SBP (∆SBP) (mm/Hg) | -5.1±9.2   | -4.7±10.5 |
| Delta DBP (∆SBP) (mm/Hg) | -5.1±5.9   | -5.7±6.7 |

Values are presented as mean ± standard deviation unless otherwise noted. SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure
Table S2. *In silico* analysis of the SNPs in LD with the replicated SNP rs28404156 using regulome DB and Haploreg v4.1.

| SNP        | BP       | LD with the index SNP (rs28404156) | R-squared | D’ | Score | Potential Regulatory Function | Correlated gene | Tissue                  |
|------------|----------|------------------------------------|-----------|----|-------|--------------------------------|----------------|-------------------------|
| rs28404156 | 15737732 | 1                                  | 1         | 1  | No data | -                              | FAM200B        |                         |
| rs4301112  | 15717226 | 0.82                               | 0.96      |    | No data | -                              | CD38           | Heart_Atrial_Appendage |
| rs28532698 | 15721619 | 0.82                               | 0.96      | 6  | other  | eQTL + TF binding / DNase peak | CD38           | Heart_Atrial_Appendage |
| rs10001565 | 15722573 | 0.82                               | 0.96      | 1f | eQTL + TF binding / DNase peak | CD38 BST1 FBXL5 | Heart_Atrial_Appendage | Whole Blood Whole Blood |
| rs12643475 | 15723514 | 0.86                               | 0.97      | 5  | TF binding or DNase peak       | BST1 FBXL5     | Heart_Atrial_Appendage | Whole Blood             |
| rs9942212  | 15724150 | 0.88                               | 0.98      | No data | -                      | -                | -                       |
| rs7667512  | 15731560 | 0.93                               | 0.97      | 3a | TF binding + any motif + DNase peak | BST1 FBXL5     | Whole Blood              | Whole Blood Whole Blood |
| rs7672311  | 15731690 | 0.95                               | 0.98      | 1f | eQTL + TF binding / DNase peak | BST1 FBXL5     | Whole Blood Whole Blood |
| rs12649015 | 15733020 | 0.95                               | 0.98      | No data | -                      | -                | -                       |
| rs33936701 | 15737559 | 0.97                               | 0.98      | 6  | other  | FAM200B                      | Arterial_Tibial |                         |
| rs28641514 | 15737722 | 0.98                               | 1         | 6  | other  | FAM200B                      | Arterial_Tibial |                         |
| rs12646913 | 15739276 | 0.91                               | 0.96      | 5  | TF binding or DNase peak       | BST1 FBXL5     | Whole Blood | Whole Blood |

The SNPs that have evidence of potential regulatory function from both the databases are in bold.
Figure S1. Change in systolic blood pressure post β₁-blocker treatment by rs28404156 genotype.

Systolic Blood Pressure change post to β₁-blocker treatment among PEAR, PEAR-2, GENRES, LIFE-Fin and BB-SS by BST1 rs28404156 genotype. Systolic blood pressure change for all studies is adjusted for pretreatment systolic blood pressure levels, age, sex, and principal components. P values are for contrast of least square adjusted means between genotype groups. PEAR: Pharmacogenomic Evaluation of Antihypertensive Response, GENRES: Genetics of Drug Responsiveness in Essential Hypertension, LIFE-Fin: Finnish Arm of the Losartan Intervention For Endpoint Reduction in Hypertension Study and BB-SS: Pharmacogenomics of beta blocker Sardinian Study.
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