GenHAT

# Scientific Evaluation of the Impact of Interventions Associated with Genetic Risk Factor Information

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# Algorithm for Treatment of Hypertension


**Lifestyle Modifications**

**Not at Goal Blood Pressure (<140/90 mmHg)**
**(<130/80 mmHg for those with diabetes or chronic kidney disease)**

**Initial Drug Choices**

**Without Compelling Indications**

**Stage 1 Hypertension**
(SBP 140–159 or DBP 90–99 mmHg)
Thiazide-type diuretics for most.
May consider ACEI, ARB, BB, CCB, or combination.

**Stage 2 Hypertension**
(SBP ≥160 or DBP ≥100 mmHg)
2-drug combination for most (usually thiazide-type diuretic and ACEI, or ARB, or BB, or CCB)

**With Compelling Indications**

**Drug(s) for the compelling indications**
Other antihypertensive drugs (diuretics, ACEI, ARB, BB, CCB) as needed.

**Not at Goal Blood Pressure**

Optimize dosages or add additional drugs until goal blood pressure is achieved.
Consider consultation with hypertension specialist.

# Compelling Indications for Individual Drug Classes

| Compelling Indication | Initial Therapy Option |
|---|---|
| Heart failure | THIAZ, BB, ACEI, ARB, ALDO ANT |
| Post myocardial infarction | BB, ACEI, ALDO ANT |
| High CAD Risk | THIAZ, BB, ACEI, CCB |
| Diabetes | THIAZ, BB, ACEI, ARB, CCB |
| Chronic kidney disease | ACEI, ARB |
| Recurrent stroke prevention | THIAZ, ACEI |

# Pharmacogenetics
## Can we use genetics to guide antihypertensive therapy?

The Pharmacogenomics Journal (2002) 2, 309–317

www.nature.com/tpj

ORIGINAL ARTICLE

# Pharmacogenetic approaches to hypertension therapy: design and rationale for the Genetics of Hypertension Associated Treatment (GenHAT) study

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**ABSTRACT**
The Genetics of Hypertension Associated Treatment (GenHAT) study will determine whether variants in hypertension susceptibility genes interact with antihypertensive medication to modify coronary heart disease (CHD) risk in hypertensives. GenHAT is an ancillary study of the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial, ALLHAT, a double-blind, randomized trial of 42 418 hypertensives, 55 years of age or older, with systolic or diastolic hypertension and one or more risk factors for

# Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)

ALLHAT

**Eligible for BP trial:**

- Hypertension
- >55 years
- At least 1 other CVD risk factor →
  - H/O MI or Stroke
  - Revascularization procedure
  - Major ST depression/T wave inversion
  - ASCVD
  - Type II Diabetes Mellitus
  - HDL < 35 mg/dl X2
  - LVH
  - Current smoker

**42,418 Eligable Participants Enrolled & Randomized to 5 years of Double-Blind Treatment**

- Chlorthalidone
- Amlodipine
- Lisinopril
- Doxazosin → Discontinued due to higher relative risk of CVD events in doxazosin compared to chlorthalidone group

**Eligible for Lipid Trial:**
Fasting LDL-C 120-189 mg/dl
or 100-129 if history of CHD

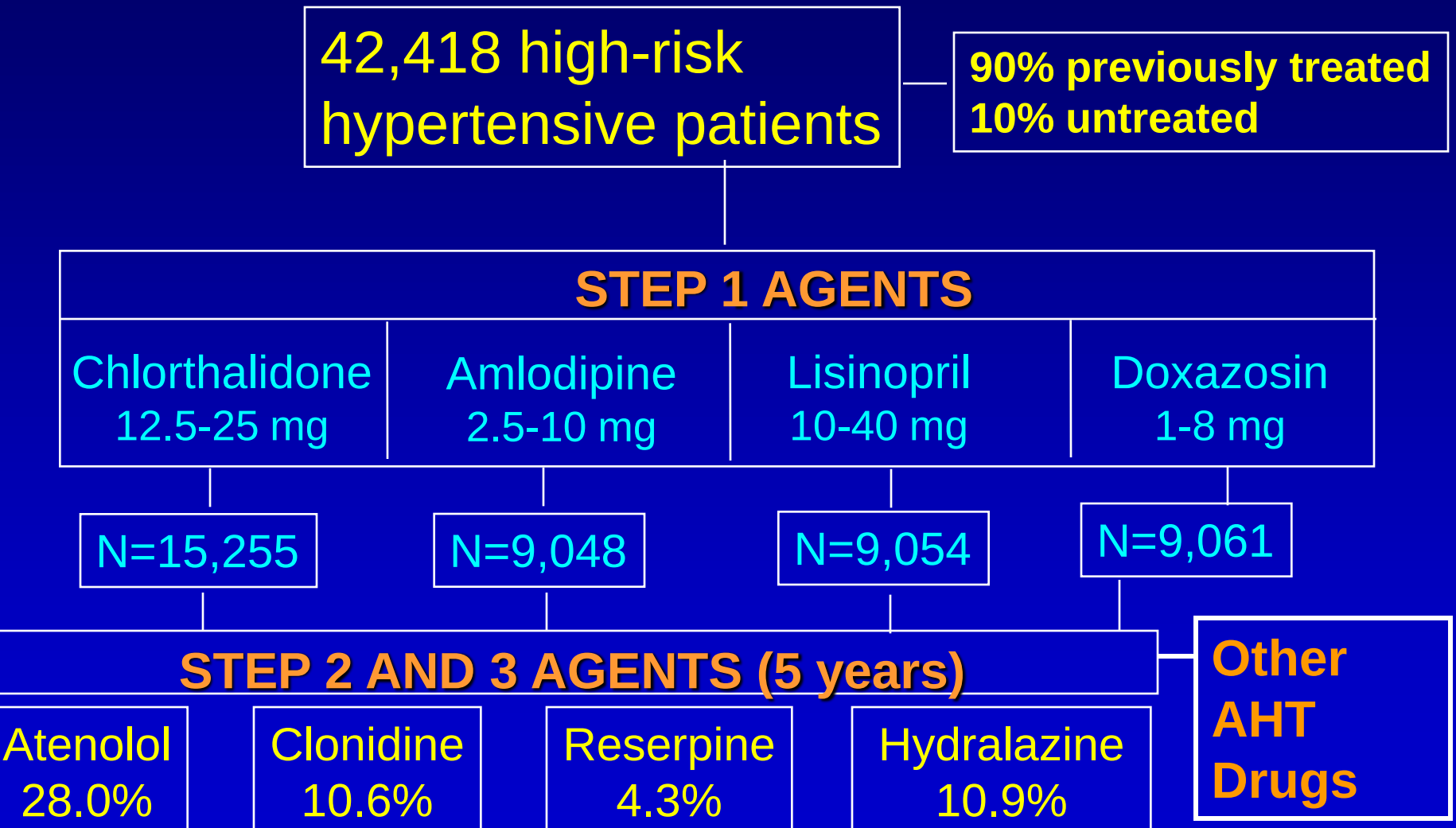
- Pravastatin
- Usual Care

**Predefined Subgroups**
-Age (<65 y; 65+y)
-Gender
-Race (Black; Non-Black)
-Diabetes (Diabetic; Non-Diabetic)

**BP Trial Primary End Points:**
-Fatal CHD & Non-Fatal MI

**BP Trial Secondary End Points:**
-All-cause mortality
-Stroke
-Combined CHD –Fatal CHD, non-fatal MI, coronary revascularization, hospitalized angina
-Combined CVD – combined CHD, stroke, lower extremity revascularization, treated angina, fatal / hospitalized / treated heart failure (HF), hospitalized or outpatient peripheral arterial disease (PAD)
-Other – renal (reciprocal serum creatinine, ESRD, estimated GFR) and cancer

# Randomized Design of ALLHAT Hypertension Trial



GenHAT

# Genetics of Hypertension Associated Treatment

- GenHAT is ancillary pharmacogenetics study
- ALLHAT, randomized double- blind active-controlled, clinical outcome trial conducted between 2/94 – 3/02
- 42,418 hypertensive patients (47% female, 36% Black), 55+ years old with 1+ CHD risk factors.
- Mean follow-up of 4.9 years
- DNA isolated from stored blood clots
- 39, 144 available for genetic analysis

GenHAT

# METHODS

- Isolate DNA
- Punch 1.5 mm disk, purify
- Amplify DNA
  - Negative control (water)
- Anonymize samples
- Genotype testing
  - includes known control samples
  - “no template” reaction (monitor contamination)
  - blind duplicates

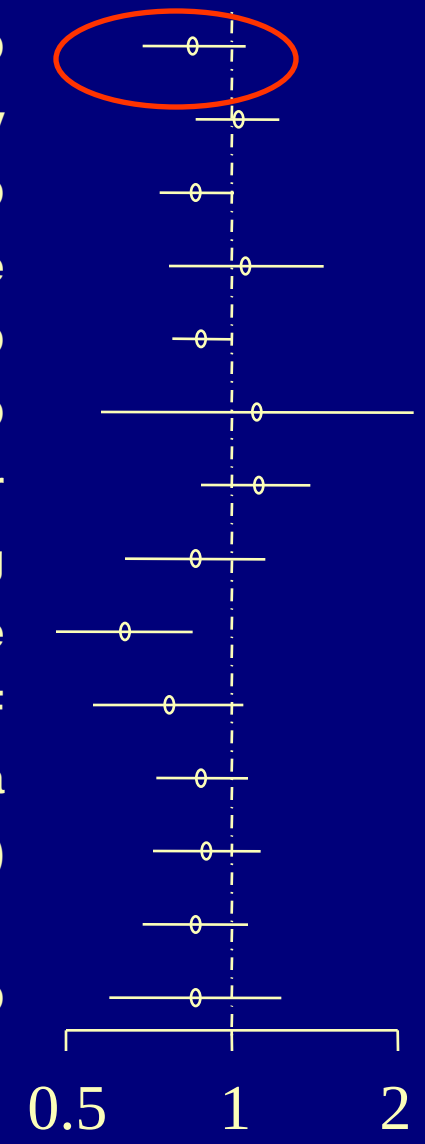
GenHAT

# α-adducin gene

- A genetic variant in α–adducin has been associated with renal sodium reabsorption and salt-sensitive hypertension
- Whether this genetic variant modifies the effect of diuretic therapy on the incidence of myocardial infarction (MI) and stroke is unknown.

Davis BR, Arnett DK, Boerwinkle E et al.
*The Pharmacogenomics Journal 2007; 7:112-122*

# Gene-Treatment Interactions in Men



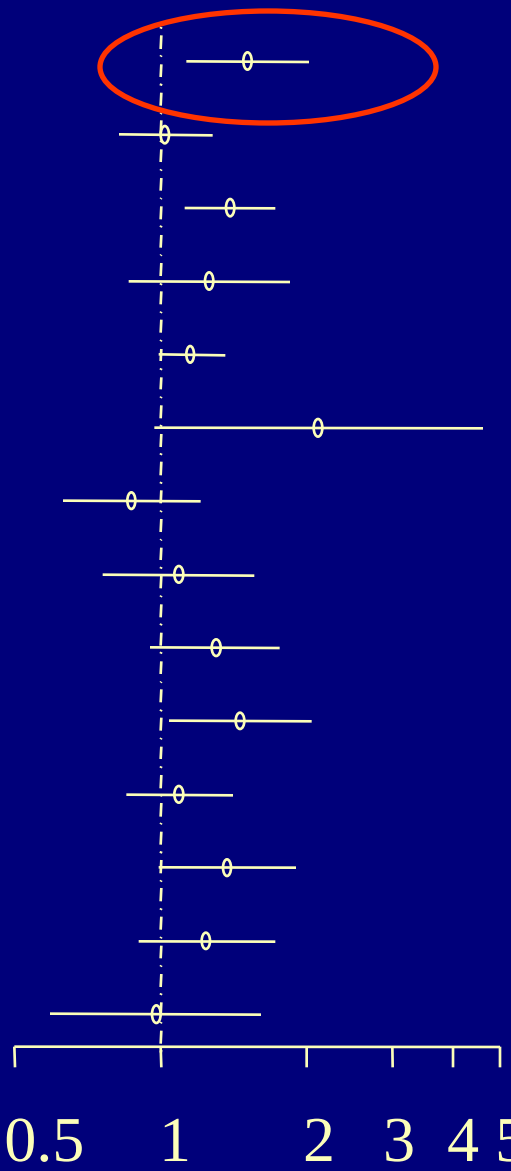

| | | P-Value* |
|---|---|---|
| CHD | 0.85 (0.69 - 1.06) | 0.002 |
| All-Cause Mortality | 1.03 (0.86 - 1.22) | 0.994 |
| Combined CHD | 0.86 (0.74 - 1.01) | 0.000 |
| Stroke | 1.06 (0.77 - 1.47) | 0.494 |
| Combined CVD | 0.88 (0.78 - 1.00) | 0.009 |
| ESRD | 1.11 (0.58 - 2.14) | 0.218 |
| Cancer | 1.12 (0.88 - 1.39) | 0.231 |
| GI Bleeding | 0.86 (0.64 - 1.15) | 0.305 |
| Heart Failure | 0.64 (0.48 - 0.85) | 0.001 |
| Hospitalized/Fatal HF | 0.77 (0.56 - 1.05) | 0.006 |
| Angina | 0.88 (0.73 - 1.07) | 0.194 |
| Angina (Hospitalized) | 0.90 (0.72 - 1.13) | 0.040 |
| Coronary Revascularizations | 0.86 (0.69 - 1.07) | 0.066 |
| PAD | 0.86 (0.60 - 1.23) | 0.685 |

* For gender-gene-treatment interaction

Lower C/(A+L) HR for persons with GT/TT genotype

Higher C/(A+L) HR for persons with GT/TT genotype

# Gene-Treatment Interactions in Women



| | | P-Value* |
|---|---|---|
| CHD | 1.51 (1.13 - 2.02) | 0.002 |
| All-Cause Mortality | 1.02 (0.82 - 1.28) | 0.994 |
| Combined CHD | 1.39 (1.12 - 1.72) | 0.000 |
| Stroke | 1.26 (0.86 - 1.85) | 0.494 |
| Combined CVD | 1.15 (0.99 - 1.36) | 0.009 |
| ESRD | 2.11 (0.97 - 4.62) | 0.218 |
| Cancer | 0.87 (0.63 - 1.21) | 0.231 |
| GI Bleeding | 1.09 (0.76 - 1.56) | 0.305 |
| Heart Failure | 1.30 (0.95 - 1.76) | 0.001 |
| Hospitalized/Fatal HF | 1.46 (1.04 - 2.05) | 0.006 |
| Angina | 1.09 (0.85 - 1.41) | 0.194 |
| Angina (Hospitalized) | 1.37 (0.99 - 1.90) | 0.040 |
| Coronary Revascularizations | 1.24 (0.90 - 1.72) | 0.066 |
| PAD | 0.98 (0.59 - 1.61) | 0.685 |

0.5 1 2 3 4 5

* For gender-gene-treatment interaction

Lower C/(A+L) HR for persons with GT/TT genotype

Higher C/(A+L) HR for persons with GT/TT genotype

GenHAT

# Conclusions

- The α-adducin Gly460Trp polymorphism is not an important modifier of antihypertensive treatment on CV risk.

- Results suggest women Trp460 carriers may have increased CDH risk if treated with C vs. A+L.

-This finding needs to be confirmed in other studies to have implications for hypertension treatment.

GenHAT

# ACE Insertion-Deletion (ID) Gene

**Common variation in the gene that encodes the angiotensin converting enzyme is defined by the insertion(I) or deletion(D) of 287 bp of nonsense DNA in intron 16 resulting in 3 genotypes (DD, ID, II). The ACE I/D polymorphism can result in different levels of ACE activity.**

Arnett DK, Davis BR, Boerwinkle E, et al.
*Circulation 2005;* 111:3374-3383.

# Gene-Treatment Interactions for Clinical Outcomes (Interaction Hazard Ratios)

| | L vs. C+A | L vs. C | L vs. A | L vs. D |
|---|---|---|---|---|
| CHD | 1.04 | 1.06 | 1.00 | 0.84 |
| Total mortality | 0.99 | 0.99 | 0.98 | 0.89 |
| Combined CHD | 1.00 | 0.99 | 1.02 | 0.90 |
| Stroke | 0.93 | 0.96 | 0.87 | 1.02 |
| Combined CVD | 0.99 | 0.99 | 1.00 | 1.03 |
| ESRD | 1.08 | 1.16 | 0.97 | 0.90 |
| Heart failure | 0.91 | 0.89 | 0.94 | 0.94 |

There were no significant gene-treatment interactions for any of the clinical outcomes.

# GenHAT Conclusions

- The association between type of antihypertensive medication and CHD or other major ALLHAT secondary outcomes (total mortality, combined CVD, HF, etc.) in high-risk hypertensives does not differ across genotypes of the ACE I/D polymorphism

# *NPPA T2238C* Gene

- The *NPPA* gene encodes the precursor from which atrial natriuretic polypeptide (ANP) is derived.
- ANP acts as a diuretic in that it controls extracellular fluid volume and electrolyte homeostasis.
- Given the diuretic action of ANP, it is possible that individuals with a "high risk" phenotype (minor C allele of *NPPA* T2238C → impaired production of ANP) might have more favorable outcomes with a diuretic than other antihypertensive drug classes.

Lynch AI, Davis BR, Boerwinkle E, et al.
*JAMA 2008;* 299: 296-307

# Genotype (NPPA T2238C) x Treatment Interaction Results – CHL vs AML HRs by Genotype for Clinical Outcomes

| | CHD | Stroke | All-Cause Mortality |
|---|---|---|---|
| TT | 1.09 | 1.26 | 1.12 |
| TC | 0.90 | 0.82 | 0.98 |
| CC | 0.86 | 1.18 | 0.87 |
| P value for interaction | .03 | 0.01 | 0.05 |

# Conclusions

- The NPPA T2238C variant was associated with modification of antihypertensive medication effects on cardiovascular disease and BP.
- Minor C allele carriers experienced more favorable outcomes (CHD, stroke, mortality) on a diuretic (vs. calcium channel blocker), whereas TT allele carriers had more favorable outcomes on a calcium channel blocker (vs. diuretic).

# Genetic Variants Included in Gene Panel Predicting CHD Risk Score in GenHAT

| Chlorthalidone | Amlodipine | Lisinopril |
|---|---|---|
| NOS3 *-690* | MMP1 *-1607* | PAI1 *-675* |
| AGT *-6* | F5 *arg506gln* | AGT *-6* |
| ICAM1 *gly214agr* | NPPA *T2238C* | PON1 *-108* |
| SELE *ser128agr* | PDE4D *SNP3* | MMP12 N122S |
| | PON1 *-108* | |
| | MMP9 R668Q | |

GenHAT

# Conclusions

- The pharmacogenetic study of complex disease phenotypes such as hypertension and its sequelae is illustrated by GenHAT
- There are logistical demands
  - tens of thousands of participants
  - long-term follow-up
  - multiple outcome phenotypes
  - subgroup analysis
- But there is the potential of identifying clinically useful genetic markers

# Conclusions

- May not have immediate clinical implications
- It moves us along the path toward individualized treatment guided by genetics
- Given the leap from pharmacogenetic knowledge to clinical practice, it is essential that
  - findings such as those in GenHAT be replicated
  - gene x gene and gene x environment interactions be thoroughly explored
  - cost-benefit analyses be conducted