**Angiotensinogen Gene Polymorphism, Plasma Angiotensinogen, and Risk of Hypertension and Ischemic Heart Disease**

**A Meta-Analysis**

Amar Akhtar Sethi, Børge Grønne Nordestgaard, Anne Tybjærg-Hansen

**Objective**—The aim of this study was to investigate whether the M235T polymorphism in the angiotensinogen gene was associated with angiotensinogen levels, systolic and diastolic blood pressure, hypertension, and risk of ischemic cardiovascular disease in different ethnic populations.

**Methods and Results**—One hundred twenty-seven studies published between January 1992 and March 2002 examining the association of angiotensinogen gene polymorphisms with the above-mentioned end points were selected. Pooled effect sizes and Mantel-Haenszel odds ratios were calculated using Review Manager. In white subjects, genotype was associated with a stepwise increase in plasma angiotensinogen levels of 5% (95% CI, 2% to 8%; $P=0.0004$) in MT heterozygotes and 11% (7% to 15%; $P<0.00001$) in TT homozygotes compared with MM individuals. Correspondingly, genotype was associated with a stepwise increase in aggregated odds ratio for hypertension of 1.08 (95% CI, 1.01 to 1.15) in MT individuals and 1.19 (1.10 to 1.30) in TT individuals in white subjects and of 1.29 (95% CI, 0.96 to 1.74) and 1.60 (1.19 to 2.15) in Asian subjects. M235T genotype did not predict systolic or diastolic blood pressure or risk of ischemic heart disease or myocardial infarction in either ethnic group.

**Conclusions**—Angiotensinogen M235T genotype was associated with a stepwise increase in angiotensinogen levels in white subjects and a corresponding increase in risk of hypertension in both white and Asian subjects. *(Arterioscler Thromb Vasc Biol. 2003;23:1269-1275.)*

**Key Words:** meta-analysis ■ blood pressure ■ genetics ■ hypertension ■ cardiovascular disease

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Hypertension is a multifactorial disorder because of the interaction of many risk genes and environmental factors such as obesity, dietary salt intake, alcohol consumption, and stress. Approximately 20% to 60% of the population variability in blood pressure is genetically determined. In the first report linking a gene to hypertension, Jeunemaitre et al suggested that the M235T polymorphism in the angiotensinogen gene in the homozygous TT state was associated with an approximate 20% increase in plasma angiotensinogen and an odds ratio for hypertension of 1.95 compared with the MM wild type. The mechanistic explanation behind this was that a higher throughput in the renin-angiotensin system might increase blood pressure by the actions of angiotensin II on sodium reabsorption in the kidneys and by vessel constriction. Apart from hypertension, which is a well-established risk factor for ischemic cardiovascular disease, many researchers were also prompted to investigate whether polymorphisms in the angiotensinogen gene were independent risk factors for ischemic cardiovascular disease.

In the last decade, hundreds of studies either supporting or rejecting the findings of the initial study have been published. In the late 1990s, 3 independent meta-analyses suggested a 22% to 32% increase in risk of hypertension in Japanese and white individuals carrying the TT genotype. The largest of these meta-analyses included 20,397 individuals. With the publication of several more recent studies, including our own studies based on the Copenhagen City Heart Study, the present meta-analysis now includes 45,267 individuals and investigates the association of M235T with plasma angiotensinogen levels and systolic and diastolic blood pressure with the risk of hypertension, ischemic heart disease, and myocardial infarction in 3 different ethnic groups stratified by sex.

**Methods**

**Data Sources**

A computerized literature search on PubMed from January 1992 until March 2002 was performed using the following index terms:
angiotensinogen gene, mutations, polymorphisms, systolic blood pressure, diastolic blood pressure, pulse pressure, angiotensinogen concentration, angiotensinogen levels, plasma angiotensinogen, hypertension, essential hypertension, elevated blood pressure, ischemic heart disease, coronary artery disease, myocardial infarction, ischemic cerebrovascular disease, and stroke. The following constraints were applied to the search: (1) only articles in English were used; (2) studies were only on human subjects; and (3) at least one of the polymorphisms was examined in the angiotensinogen gene: M235T, T174M, G(-6)A, or A(-20)C. Furthermore, reference lists of published studies were assessed and reviews scrutinized for missing studies. This search identified 471 articles.

Study Selection
Only studies examining the association of angiotensinogen gene polymorphisms with either plasma angiotensinogen levels, systolic or diastolic blood pressure, risk of hypertension, or risk of ischemic heart or ischemic cerebrovascular disease were selected. This selection left 127 studies that were scrutinized in detail, but because there were very few studies (between 1 and 4 studies) of each the A(-20)C, G(-6)A, and T174M polymorphisms, the present meta-analyses were restricted to M235T. Because only 2 studies examined M235T and risk of ischemic cerebrovascular disease, this end point was excluded.

The exclusion criteria (see http://atvb.ahajournals.org) restricted the number of studies to 9 on plasma angiotensinogen levels (Table I, available online at http://atvb.ahajournals.org), 11 on systolic and diastolic blood pressure (Table II, available online), 41 on hypertension (Table III, available online), and 21 on ischemic heart disease and myocardial infarction (Table IV, available online). In total, these meta-analyses included 63 studies with 45,267 participants; 36 studies were excluded (table available from authors).

Results
Tables I through IV (available online) show the characteristics of studies included in this meta-analysis of associations of M235T in the angiotensinogen gene with plasma angiotensinogen levels, systolic and diastolic blood pressure, risk of hypertension, and risk of ischemic heart disease and myocardial infarction, respectively. Average allele frequencies of 235T were 0.43 in white subjects, 0.76 in Asian subjects (versus white subjects, P<0.0001), and 0.83 in black subjects (versus white subjects, P<0.0001; versus Asian subjects, P<0.0001). The exclusion criteria (see http://atvb.ahajournals.org) restricted the number of studies to 9 on plasma angiotensinogen levels (Table I, available online at http://atvb.ahajournals.org), 11 on systolic and diastolic blood pressure (Table II, available online), 41 on hypertension (Table III, available online), and 21 on ischemic heart disease and myocardial infarction (Table IV, available online). In total, these meta-analyses included 63 studies with 45,267 participants; 36 studies were excluded (table available from authors).

Association of M235T Genotype With Plasma Angiotensinogen Levels
Plasma angiotensinogen level was significantly increased in white MT heterozygotes by 5% (95% CI, 2 to 8; P<0.0004) and in TT homozygotes by 11% (7% to 15%; P<0.0001) compared with MM homozygotes (Figure 1). When stratified by sex or hypertension, the increase in plasma angiotensinogen levels when comparing MT or TT individuals versus MM were (1) 4% (2% to 10%; P<0.02) and 13% (7% to 19%; P<0.0004), respectively, in women; (2) 6% (1% to 11%; P<0.02) and 11% (5% to 17%; P=0.0006), respectively, in men; (3) 4% (1% to 7%; P=0.01) and 10% (6% to 14%; P<0.0001), respectively, in normotensive subjects, and (4) 7% (2% to 12%; P=0.01) and 12% (4% to 20%; P=0.002), respectively, in hypertensive subjects. Test of heterogeneity was significant (P=0.004) for studies on white hypertensive subjects (TT versus MM), reducing the effect size from 12% to 8% (17% to 33%; P=0.5) when applying the random effects model.

Increases in plasma angiotensinogen levels in Asian and black subjects were nonsignificant for all comparisons with the MM genotype, which in these populations accounts for only approximately 4% of individuals as opposed to 25% to 35% in white subjects. The number of studies in each of these ethnic groups was limited to 1 or 2 (Figure 1).
isons in both white subjects (total and stratified by sex) and Asian subjects (Figure 2; data not shown for diastolic blood pressure). Associations were also nonsignificant when the random effects model was applied. One Asian study suggested an association between 235T and decreased systolic blood pressure, resulting in significant tests of heterogeneity for both comparisons (MT versus MM, \(P = 0.0002\); TT versus MM, \(P = 0.0003\)). Exclusion of this particular study removed the heterogeneity, and the associations of genotype with increased systolic blood pressure became significant for both comparisons (MT versus MM, \(2.9 \text{ mm Hg} [0.02 \text{ to } 5.7] ; P = 0.05\); TT versus MM, \(3.2 \text{ mm Hg} [0.4 \text{ to } 5.9] ; P = 0.02\)). Heterogeneity was also found in analyses of diastolic blood pressure, but associations remained nonsignificant when the study by Suwazono et al was removed.

Association of M235T Genotype With Blood Pressure As a Dichotomous Variable

White MT and TT individuals had a pooled odds ratio for hypertension of 1.08 (95% CI, 1.01 to 1.15) and 1.19 (1.10 to 1.30), respectively, compared with the MM genotype (Figure 3). Test for heterogeneity was significant for the comparison of TT versus MM (\(P = 0.0006\)), and the odds ratio increased to 1.29 (1.10 to 1.50) when applying the random effects model. M235T genotype was associated with similar trends when data were stratified by sex.

Asian MT and TT individuals had a pooled odds ratio for hypertension of 1.08 (95% CI, 1.01 to 1.15) and 1.19 (1.10 to 1.30), respectively, compared with MM homozygotes (Figure 3). Furthermore, a test for linear trend was significant (OR, 1.23 [1.11 to 1.37]; \(P = 0.0001\)). Genotype was associated with similar trends when data were stratified by sex.

In black subjects, M235T genotype did not predict risk of hypertension (Figure 3), and in addition, test for linear trend was not significant (OR, 1.15 [0.90 to 1.45]; \(P = 0.26\)).

Association of M235T Genotype With Risk of Ischemic Heart Disease and Myocardial Infarction

No significant change in the risk of ischemic heart disease or myocardial infarction was found for MT or TT individuals compared with MM homozygotes (Figure 4); this was true for both white and Asian subjects and for both pooled data and data stratified by sex. No significant trend test was found for Asian subjects (OR, 1.13 [1.00 to 1.29]; \(P = 0.06\)). Seven of 18 analyses were tested significant for heterogeneity, but odds ratios remained insignificant when random effects models were applied.

Discussion

In the present meta-analysis of 45,267 subjects, the M235T mutation in the angiotensinogen gene was associated with a 5% increase in levels of plasma angiotensinogen in white MT heterozygotes, which increased to 11% in white TT homozygotes compared with MM homozygotes. In agreement with this, white MT heterozygotes and TT homozygotes had a significant 8% and 19% increase in risk of hypertension, respectively, compared with MM homozygotes. A similar trend was observed in Asian individuals, where TT homozygotes had a 60% increased risk of hypertension compared with MM homozygotes whereas MT heterozygotes had an intermediate though borderline increase in risk. Finally, these trends were similar in both sexes in both ethnic groups.

The present meta-analyses adds an important new insight, because previous meta-analyses were smaller and only examined Japanese subjects, only examined white subjects, or included some highly selective patients and even used some individuals twice.

Plasma Angiotensinogen Levels

The present results correspond well with those of a previous meta-analysis, although for the subgroup analysis of women we found effect sizes less than half of those previously reported. This discrepancy could be attributable to ethnic heterogeneity in the former meta-analysis or that the number of women investigated was only half that of the present study.

The increase in plasma angiotensinogen levels in white subjects was similar for the various subgroup analyses. We cannot confirm nor reject an association between M235T and angiotensinogen levels in Asian subjects, because there was only 1 study included in this analysis. The results can only be used to compare plasma angiotensinogen levels between ethnic groups and do not exclude an association between M235T and plasma angiotensinogen levels in Asian subjects. Because M235T is associated with a stepwise increase in risk...
of hypertension as a function of genotype, it seems reasonable that genotype would predict increased levels of angiotensinogen if investigated in a larger sample. In addition to the smaller number of participants, high allele frequencies of 235T (0.80 to 0.95) in both Asian and black compared with white subjects (0.40 to 0.50) could explain the lack of positive findings in these ethnic groups, because a very large number of individuals would be required to detect even a moderate association with genotype.

Blood Pressure As a Continuous Variable

Systolic and diastolic blood pressure did not change as a function of M235T genotype in 10,315 healthy white and Asian subjects. However, when excluding the study by Suwazono et al from the analyses in Asian subjects, effects sizes became just significant for systolic blood pressure in both comparisons. The results of Suwazono et al may at least in part be explained by the fact that they selected their population by hypertension (68 subjects with blood pressure 140/90 mm Hg and 128 with blood pressure <140/90 mm Hg). If the T-allele is associated with hypertension as suggested in the present meta-analysis, this allele would be underrepresented in the study of Suwazono et al, and this could influence their findings. Even though a mild increase in systolic blood pressure is observed, it must be interpreted with caution, and more studies would be needed to rule out chance findings.

In contrast to our findings, a previous meta-analysis found systolic and diastolic blood pressure slightly elevated (2.15 mm Hg, \( P = 0.02 \) and 1.48 mm Hg, \( P = 0.04 \), respectively) when TT homozygotes were compared with MM individuals in 5,289 subjects of mixed ethnic origin. However, this meta-analysis included (1) studies not only of healthy individuals but also of patients with diabetic nephropathy and ischemic cerebrovascular disease; (2) intervention studies; and (3) population studies of mixed ethnic origin. The above-mentioned patient categories are normally characterized by high blood pressure values because of their primary disease. If 235T is associated with hypertension, positive findings might be more likely in these groups. Likewise, lack of association of genotype with variation in blood pressure in our study might be attributable to the association being too mild to be detected in a healthy population or to misclassification of some individuals, which is more likely, because blood pressure in many studies relied on a single measurement.

Blood Pressure As a Dichotomous Variable

We found a modest but significant increase of 8% and 19% in white MT and TT individuals. Asian TT homozygotes had a 60% increased risk of hypertension compared with MM.
homozygotes as well as a significant test for linear trend (OR, 1.23; \(P\) < 0.0001). Our findings correspond well with earlier meta-analyses and do not suggest that the relations between this polymorphism and hypertension are different in Asian compared with white individuals, as has been reported previously. However, the latter study had less than half the number of subjects of the present meta-analysis (\(n = 1995\) versus 5181) and only found a significant association for heterozygous individuals, suggesting perhaps that this was a chance finding.

Neither previous meta-analyses nor the present meta-analysis found an association between M235T and hypertension in black subjects. A possible explanation could be the very high-allele frequency of 235T in black individuals, making it very difficult to detect mild associations unless examining a very large population sample.

### Risk of Ischemic Heart Disease

Lack of an association in the present meta-analysis between M235T and risk of ischemic heart disease or myocardial infarction is in agreement with a previous report on white and Asian subjects. However, the excess risk of 11% in TT versus MM homozygotes observed in white subjects as well as the test for trend in Asian subjects were both borderline significant (\(P = 0.07\) and \(P = 0.06\), respectively).

### Limitations

Results from the present as well as other meta-analyses should be interpreted with caution, because the quality and reliability of the results depend on the quality of the studies included. Ideally, cases should be matched with controls or at least controls selected from the same background population to take confounding into account. However, studies included in the present meta-analysis were not homogeneous with respect to selection, definition, or characterization of cases and controls. Analyses of hypertension, for example, included 15 studies of cases sampled from the general population, primary care centers, or self-referral centers, whereas 8 studies had cases sampled from special hypertension clinics; controls were selected from various places, such as primary care clinics, the general population, blood donors, previous studies, healthy family registers, spouses, or self-referrals. In addition, 6 of 22 studies recruited subjects for reasons other than investigating hypertension. Very few studies were based on a homogeneous population providing full phenotypic characteristics or detailed selection criteria for cases and controls. The application of standardized rules requiring uniform predefined selection criteria for all participants in any case-control study before publication and entering into meta-analyses has been suggested earlier.

Although meta-analysis of randomized clinical trials is a straightforward methodology, applying it to nonrandomized studies such as an association study becomes critical because of the great potential of bias within each of the pooled studies. The meta-analysis by itself cannot make these biases disappear.

### Figure 4

Risk of ischemic heart disease in white and Asian subjects as a function of M235T genotype. Odds ratio (95% CI) for MT (left) and TT (right) versus MM. Separate analysis for myocardial infarction as well as sex-stratified results are shown. *Significant heterogeneity test.
most important risk factors, eg, age and smoking, resulting in the confounding of phenotype in cases and controls.\textsuperscript{16} Although publication bias cannot be excluded, we believe it to be a minor problem in the present meta-analysis, because each funnel plot was independently scrutinized by 2 authors and no evidence of publication bias was found. Finally, a limitation of this study is that our results were extracted directly from published articles and not from original data provided by the authors.

Conclusions

In the present meta-analysis of 45 267 subjects, M235T genotype was associated with a stepwise increase in angiotensinogen levels in white subjects and a significant but moderate increase in risk of hypertension in both white and Asian subjects. Genotype did not predict (1) plasma angiotensinogen levels in Asian and black subjects, (2) hypertension in black subjects, or (3) systolic or diastolic blood pressure or risk of ischemic heart disease or myocardial infarction in either ethnic group.

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References


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Methods

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Studies were excluded if: (1) the number of individuals in each genotype group was not listed, (2) only combinations of mutations were investigated, (3) the number of individuals in case- and control-groups was not listed, (4) the same participants were used in a previous study, (5) SD or
SEM values were not reported, (6) it was an intervention study, (7) a study based upon a mixed ethnical population, (8) plasma angiotensinogen levels or blood pressure values were not reported for each genotype separately, (9) blood pressure was not measured in healthy control subjects, (10) plasma angiotensinogen levels were measured in patients with ischemic heart disease, and (11) analysis on hypertension was performed exclusively in patients with familial hypercholesterolemia, diabetes mellitus or cerebrovascular disease. These exclusion criteria restricted the number of studies to 9 on plasma angiotensinogen levels (Table I), 11 on systolic- and diastolic blood pressure (Table II), 41 on hypertension (Table III), and 21 on ischemic heart disease and myocardial infarction (Table IV). In total, these meta-analyses included 63 studies with 45,267 participants; 36 studies were excluded (table available from authors).

**Data extraction**

Data were collected as it appeared in the original studies; however, in some studies the mean age, standard deviations of systolic blood pressure, diastolic blood pressure, or plasma angiotensinogen levels were calculated\(^3-18\). In studies only quoting allele frequencies, the Hardy-Weinberg equilibrium, \(p^2 + q^2 + 2pq = 1\), was used to calculate the number of individuals in each genotype group. Data were extracted separately for subjects of different ethnic origin, and women and men where possible.

To overcome problems due to the use of different methods and different units of measurement for the analysis of plasma angiotensinogen between studies, we calculated the percent change in MT and TT subjects relative to MM subjects. In the majority of studies, blood pressure was measured with subjects at rest in the supine or sitting position. In 33 of the 41 studies included, hypertension was defined as ongoing treatment with antihypertensive drugs and/or by the following cut-off values for systolic- and diastolic blood pressure: (1) =140/90 mmHg, (2) =160/90 mmHg,
(3) =160/95 mmHg. Depending on the study, the number of blood pressure measurements varied from one to five, with three being the most frequent.

Ischemic heart disease patients were individuals who fulfilled one or more of the following criteria: (1) diagnoses of myocardial infarction or angina pectoris, (2) stenosis (>25% to >75% or more) on coronary angiography, (3) myocardial ischemia on an exercise test, and (4) percutaneous transluminal coronary angioplasty or coronary artery bypass graft surgery.

Myocardial infarction was defined as the presence of at least two of the following: (1) characteristic chest pain, (2) elevation of cardiac enzymes, and (3) electrocardiographic results consistent with a myocardial infarction.

**Statistical analyses**

All statistical analyses were performed by Review Manager 4.1.1 (The Cochrane Collaboration). Depending on whether the data was continuous or categorical, a pooled-effect size or a Mantel-Haenszel odds ratio was calculated; a P-value <0.05 on a z test was considered significant. For all meta-analyses: (1) studies were ordered by statistical weight, (2) a random-effects model was applied as well as a fixed-effects model, since the choice of model is debatable\textsuperscript{19}, (3) in case of heterogeneity between studies (P-value below 0.05 on a $\chi^2$ test) results using the random effects model were stated in the text as well, and (4) publication bias was examined visually as funnel plot asymmetry: no asymmetry was observed for any end-points examined for the comparisons of MT and TT versus MM for Whites (Figure I), Asians, and Blacks (data not shown).

Because the studies included in the meta-analyses measured plasma angiotensinogen levels using different methods and different units of measurement, data were compared as the percentage change in MT and TT genotypes relative to the MM genotype set as 100%. However, since this comparison assumes a normal distribution of the data, plasma angiotensinogen levels
(mean and standard deviation) were logarithmically transformed to approximately fit a normal
distribution. Data on plasma angiotensinogen are shown as percentage change in MT and TT
compared to MM genotype on untransformed data, but all statistics were performed on the
transformed data. The approximated mean plasma angiotensinogen levels (=X) and the equivalent
variances were transformed logarithmically using the following equation:

$$
\mu \approx \ln(X) - \frac{1}{2} \ln\left(\frac{SD^2}{X^2} + 1\right) \quad \text{and} \quad \sigma \approx \ln\left(\frac{SD^2}{X^2} + 1\right)^{1/2},
$$

respectively, before they were entered into the meta-analyses.

All figures are shown with pooled effect sizes and odds ratios calculated by a fixed-effects model.

Since low frequency of the MM genotype in Asians and Blacks may restrict the
usefulness of the comparisons made, a nonparametric test for linear trend across the three genotype
groups was performed for the analyses of hypertension and ischemic heart disease in these ethnic
groups. Each study was weighted according to its study size, and MM genotype was the reference
genotype.

References


Figure legends

Figure I.
Funnel plots for the comparisons of MT (left panels) and TT (right panels) versus MM for plasma angiotensinogen levels (panel a and b), systolic blood pressure (panel c and d), hypertension (panel e and f), and ischemic heart disease (panel g and h) for Whites. The graph shows a plot of standard error (SE) as a function of effect size (panel a-d) or odds ratio (panel e-h) for all outcomes. Each circle represents a study. The vertical line indicates the pooled effect size/odds ratio for the outcome. The broken lines indicate the 95% confidence interval of the pooled effect size/odds ratio.
Table 1. Characteristics of studies included in the meta-analysis of the association of M235T in the angiotensinogen gene with plasma angiotensinogen levels.

<table>
<thead>
<tr>
<th>Author and year of publication</th>
<th>Study design</th>
<th>Population</th>
<th>n</th>
<th>Mean age ± SD (years)</th>
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<th>Allele frequency 235T</th>
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*Gender stratified data available. †No SD available. ‡Includes normotensive individuals as well. NR= not reported
Table 2. Characteristics of studies included in the meta-analysis of the association of M235T in the angiotensinogen gene with systolic- and diastolic blood pressure.

<table>
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<th>Population</th>
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<td>Twin study</td>
<td>General</td>
<td>69</td>
<td>33±14</td>
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<td>Fardella CE et al, 1998&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Cross-sectional</td>
<td>Normotensive</td>
<td>62</td>
<td>43±14</td>
<td>♀+♂</td>
<td>0.52</td>
<td>Chile</td>
</tr>
<tr>
<td>Kiema T-R et al, 1996&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Cross-sectional</td>
<td>General</td>
<td>466</td>
<td>51±6</td>
<td>♀+♂</td>
<td>0.47</td>
<td>Finland</td>
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<td>Bigda J et al, 1997&lt;sup&gt;25&lt;/sup&gt;</td>
<td>Cross-sectional</td>
<td>Normotensive</td>
<td>145</td>
<td>23±2</td>
<td>♂</td>
<td>0.60</td>
<td>Poland</td>
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<td>Bennett CL et al, 1993&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Cross-sectional</td>
<td>Normotensive</td>
<td>94</td>
<td>46±10</td>
<td>♀+♂</td>
<td>0.39</td>
<td>UK</td>
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<tr>
<td>Hingorani AD et al, 1996&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Cross-sectional</td>
<td>Normotensive</td>
<td>187</td>
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<td>Tiret L et al, 1995&lt;sup&gt;8&lt;/sup&gt;</td>
<td>Cross-sectional</td>
<td>General</td>
<td>625</td>
<td>53±8</td>
<td>♂</td>
<td>0.47</td>
<td>France and Northern Ireland</td>
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<tr>
<td>Sethi AA et al, 2001&lt;sup&gt;122&lt;/sup&gt;</td>
<td>Cross-sectional</td>
<td>General</td>
<td>7126</td>
<td>55±18</td>
<td>♀+♂</td>
<td>0.40</td>
<td>Denmark</td>
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<td><strong>Asian</strong></td>
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<td>Iwai N et al, 1995&lt;sup&gt;27&lt;/sup&gt;</td>
<td>Cross-sectional</td>
<td>Referrals</td>
<td>347</td>
<td>55±11</td>
<td>♀+♂</td>
<td>0.80</td>
<td>Japan</td>
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<tr>
<td>Suwazono Y et al, 1999&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Cross-sectional</td>
<td>Company workers</td>
<td>194</td>
<td>41±11</td>
<td>♂</td>
<td>0.82</td>
<td>Japan</td>
</tr>
<tr>
<td>Kishimoto T et al, 2001&lt;sup&gt;29&lt;/sup&gt;</td>
<td>Cohort</td>
<td>Factory workers</td>
<td>1000</td>
<td>37±10</td>
<td>♀+♂</td>
<td>0.80</td>
<td>Japan</td>
</tr>
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</table>

<sup>1</sup>Only gender stratified data available. <sup>2</sup>Gender stratified data available.
Table 3. Characteristics of studies included in the meta-analysis of the association of M235T in the angiotensinogen gene and risk of hypertension.

<table>
<thead>
<tr>
<th>Author and year of publication</th>
<th>Study design</th>
<th>Cases/Controls</th>
<th>Mean age ± SD (years)</th>
<th>Sex</th>
<th>Definition of Hypertension</th>
<th>Allele frequency 235T</th>
<th>Country</th>
</tr>
</thead>
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<tr>
<td><strong>White</strong></td>
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<td>Case-control</td>
<td>64/62</td>
<td>52±13 49±14</td>
<td>♀♂</td>
<td>BP &gt;140/90 mmHg</td>
<td>0.52</td>
<td>Chile</td>
</tr>
<tr>
<td>Caulfield M et al, 1994</td>
<td>Case-control</td>
<td>63/64</td>
<td>61↑ NR 49±14</td>
<td>♀♂</td>
<td>DBP &gt;95 mmHg or drugs</td>
<td>0.49</td>
<td>UK</td>
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<td>Barley, J et al, 1994</td>
<td>Case-control</td>
<td>64/74</td>
<td>NR NR 61±13</td>
<td>♀♂</td>
<td>BP &gt;140/90 mmHg</td>
<td>0.40</td>
<td>UK</td>
</tr>
<tr>
<td>Fernandez-Llama, P et al, 1998</td>
<td>Case-control</td>
<td>75/75</td>
<td>55±9 40±9</td>
<td>♀♂</td>
<td>BP &gt; 160/100 mmHg</td>
<td>0.50</td>
<td>Spain</td>
</tr>
<tr>
<td>Borecki, IB et al, 1997</td>
<td>Case-control</td>
<td>32/32</td>
<td>61±6 61±6</td>
<td>♀♂</td>
<td>Drug treatment</td>
<td>0.38</td>
<td>USA</td>
</tr>
<tr>
<td>Jeunemaitre X et al, 1993</td>
<td>Case-control</td>
<td>132/132</td>
<td>47±9 44±9</td>
<td>♀♂</td>
<td>Drug treatment</td>
<td>0.38</td>
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<tr>
<td>Monzor UF et al, 1994</td>
<td>Case-control</td>
<td>112/124</td>
<td>46±11 47±14</td>
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<td>Schmidt S et al, 1995</td>
<td>Case-control</td>
<td>219/219</td>
<td>51±13 46±12</td>
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<td>BP ≥140/90 mmHg and/or drugs or BP ≥145/95 mmHg</td>
<td>0.41</td>
<td>Germany</td>
</tr>
<tr>
<td>Rodriguez-Perez JC et al, 2001</td>
<td>Cross-sectional</td>
<td>106/209</td>
<td>54±10</td>
<td>♀♂</td>
<td>BP &gt;140/90 mmHg and drugs</td>
<td>0.43</td>
<td>Spain</td>
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<tr>
<td>Wang WYS et al, 1999</td>
<td>Case-control</td>
<td>111/190</td>
<td>53±12 48±10</td>
<td>♀♂</td>
<td>Drug treatment</td>
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<td>Australia</td>
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<tr>
<td>Fornage M et al, 1998</td>
<td>Case-control</td>
<td>104/195</td>
<td>62±10 62±9</td>
<td>♀♂</td>
<td>BP &gt;140/90 mmHg and drugs</td>
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<td>USA</td>
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<td>Rodriguez-Perez JC et al, 2000</td>
<td>Case-control</td>
<td>237/241</td>
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<td>BP &gt;140/90 mmHg and drugs</td>
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<td>Spain</td>
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<tr>
<td>Vasku A et al, 1998</td>
<td>Case-control</td>
<td>163/202</td>
<td>50±9 46±3</td>
<td>♀♂</td>
<td>Drug treatment</td>
<td>0.40</td>
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<td>Jeunemaitre X et al, 1992</td>
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<td>Drug treatment</td>
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<td>USA and France</td>
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<td>Jeunemaitre X et al, 1997</td>
<td>Case-control</td>
<td>477/364</td>
<td>49±8 46±8</td>
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<td>BP ≥95 mmHg and/or drugs</td>
<td>0.38</td>
<td>France</td>
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<tr>
<td>Johnson AG et al, 1999</td>
<td>Cohort</td>
<td>389/366</td>
<td>69±7 69±7</td>
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<td>BP ≥160/90 mmHg</td>
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<td>Kiema T-R et al, 1996</td>
<td>Case-control</td>
<td>508/523</td>
<td>51±6 51±6</td>
<td>♀♂</td>
<td>Drug treatment</td>
<td>0.47</td>
<td>Finland</td>
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<tr>
<td>Tiert L et al, 1998</td>
<td>Case-control</td>
<td>779/532</td>
<td>44±10 49±9</td>
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<td>DBP ≥100 mmHg and/or drugs</td>
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<tr>
<td>Sethi AA et al, 2001</td>
<td>Case-control</td>
<td>4773/4038</td>
<td>63±12 51±15</td>
<td>♀♂</td>
<td>BP ≥140/90 mmHg and drugs</td>
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<td>Denmark</td>
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### Asian

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<tr>
<th>Study</th>
<th>Design</th>
<th>Cases/Controls</th>
<th>BP Threshold</th>
<th>p-value</th>
<th>Location</th>
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<tr>
<td>Cheung BMY et al, 1998</td>
<td>Case-control</td>
<td>101/103</td>
<td>53±15, 41±13 ♂+♀</td>
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<td>China</td>
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<tr>
<td>Chiang FT et al, 1997</td>
<td>Case-control</td>
<td>102/49</td>
<td>64±10, 55±14 ♂+♀</td>
<td>0.84</td>
<td>China</td>
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<tr>
<td>Hata A et al, 1994</td>
<td>Case-control</td>
<td>105/81</td>
<td>61±3, 34±3 NR</td>
<td>0.76</td>
<td>Japan</td>
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<tr>
<td>Morise T et al, 1995</td>
<td>Case-control</td>
<td>80/100</td>
<td>52±8, 49±6 ♂+♀</td>
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<td>Nishiuma S et al, 1995</td>
<td>Cohort</td>
<td>64/149</td>
<td>NR</td>
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<td>Cohort</td>
<td>143/858</td>
<td>37±10, NR</td>
<td>0.80</td>
<td>Japan</td>
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<td>Thomas GN et al, 2000</td>
<td>Case-control</td>
<td>232/178</td>
<td>48±10, 41±10 ♂+♀</td>
<td>0.83</td>
<td>China</td>
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<td>Kario K et al, 1999</td>
<td>Case-control</td>
<td>235/103</td>
<td>70±9, ♂+♀</td>
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<tr>
<td>Sato N et al, 2000</td>
<td>Case-control</td>
<td>180/195</td>
<td>59±10, 59±13 ♂+♀</td>
<td>0.79</td>
<td>Japan</td>
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<tr>
<td>Iso H et al, 2000</td>
<td>Case-control</td>
<td>229/229</td>
<td>65±9, 65±9 ♂+♀</td>
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<td>Japan</td>
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<tr>
<td>Frossard PM et al, 1998</td>
<td>Case-control</td>
<td>135/61</td>
<td>53±12, 53±14 ♂+♀</td>
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<td>Kato N et al, 2000</td>
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<td>66±11, 59±13 ♂+♀</td>
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### Black

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<tr>
<th>Study</th>
<th>Design</th>
<th>Cases/Controls</th>
<th>BP Threshold</th>
<th>p-value</th>
<th>Location</th>
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<tbody>
<tr>
<td>Rotimi C et al, 1997</td>
<td>Case-control</td>
<td>116/138</td>
<td>54±12, 54±14 ♂+♀</td>
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<td>Barley J et al, 1994</td>
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<td>NR</td>
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<tr>
<td>Rotimi C et al, 1994</td>
<td>Case-control</td>
<td>57/130</td>
<td>43±9, 51±13 ♂+♀</td>
<td>0.83</td>
<td>USA</td>
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<tr>
<td>Caulfield M et al, 1995</td>
<td>Case-control</td>
<td>213/93</td>
<td>NR</td>
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<tr>
<td>Borecki IB et al, 1997</td>
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<td>37/160</td>
<td>60±6, 59±6 ♂+♀</td>
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<td>Forrester T et al, 1996</td>
<td>Cross-sectional</td>
<td>93/74</td>
<td>NR</td>
<td>0.80</td>
<td>Jamaica</td>
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</table>

*Median. †Gender stratified data available. ‡Cases and controls combined. §No SD available. BP= blood pressure. SBP= systolic blood pressure. DBP= diastolic blood pressure. NR= not reported.
Table 4. Characteristics of studies included in the meta-analysis of the association of M235T in the angiotensinogen gene with risk of ischemic heart disease and myocardial infarction.

<table>
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<th>Author and year of publication</th>
<th>Study design</th>
<th>Cases/Controls</th>
<th>Mean age ± SD (years)</th>
<th>Sex</th>
<th>End point</th>
<th>Allele frequency 235T</th>
<th>Country</th>
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<tr>
<td>Ludwig EH et al, 1997&lt;sup&gt;53&lt;/sup&gt;</td>
<td>Case-control</td>
<td>58/55</td>
<td>NR</td>
<td>NR</td>
<td>♀+♂</td>
<td>IHD</td>
<td>0.43</td>
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<tr>
<td>Wenzel K et al, 1997&lt;sup&gt;54&lt;/sup&gt;</td>
<td>Case-control</td>
<td>111/102</td>
<td>42&lt;sup&gt;3&lt;/sup&gt;</td>
<td>38&lt;sup&gt;8&lt;/sup&gt;</td>
<td>♀+♂</td>
<td>IHD</td>
<td>0.39</td>
</tr>
<tr>
<td>Winkelmann BR et al, 1999&lt;sup&gt;55&lt;/sup&gt;</td>
<td>Case-control</td>
<td>329/92</td>
<td>56±10&lt;sup&gt;4&lt;/sup&gt;</td>
<td>♀</td>
<td>IHD, MI</td>
<td>0.41</td>
<td>Germany</td>
</tr>
<tr>
<td>Fatini J et al, 2000&lt;sup&gt;56&lt;/sup&gt;</td>
<td>Case-control</td>
<td>205/209</td>
<td>60±5</td>
<td>51±6</td>
<td>♀+♂</td>
<td>IHD</td>
<td>0.39</td>
</tr>
<tr>
<td>Fernández-Arcás N et al, 1999&lt;sup&gt;16&lt;/sup&gt;</td>
<td>Case-control</td>
<td>167/150</td>
<td>67±7</td>
<td>69±10</td>
<td>♀+♂</td>
<td>MI</td>
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<tr>
<td>Fomicheva EV et al, 2000&lt;sup&gt;57&lt;/sup&gt;</td>
<td>Case-control</td>
<td>798/152</td>
<td>67&lt;sup&gt;3&lt;/sup&gt;</td>
<td>11&lt;sup&gt;1&lt;/sup&gt;</td>
<td>♂</td>
<td>MI</td>
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<tr>
<td>Reinhardt D et al, 2000&lt;sup&gt;58&lt;/sup&gt;</td>
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<td>184/155</td>
<td>57±11</td>
<td>56±14</td>
<td>♀+♂</td>
<td>IHD</td>
<td>0.46</td>
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<tr>
<td>Rodríguez-Pérez JC et al, 2001&lt;sup&gt;37&lt;/sup&gt;</td>
<td>Case-control</td>
<td>299/315</td>
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<td>54±10</td>
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<td>Ludwig EH et al, 1997&lt;sup&gt;53&lt;/sup&gt;</td>
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<td>255/245</td>
<td>NR</td>
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<td>Olivieri O et al, 2001&lt;sup&gt;59&lt;/sup&gt;</td>
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<td>♀+♂</td>
<td>IHD, MI</td>
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<td>Katsuya T et al, 1995&lt;sup&gt;60&lt;/sup&gt;</td>
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<td>422/406</td>
<td>62±7&lt;sup&gt;4&lt;/sup&gt;</td>
<td>♀+♂</td>
<td>IHD</td>
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<td>♂</td>
<td>IHD, MI</td>
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<td>Tiret L et al, 1995&lt;sup&gt;8&lt;/sup&gt;</td>
<td>Case-control</td>
<td>630/741</td>
<td>54±8</td>
<td>53±8</td>
<td>♂</td>
<td>MI</td>
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<td>Sethi AA et al, 2001&lt;sup&gt;61&lt;/sup&gt;</td>
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<td>943/7975</td>
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<td>56±15</td>
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<td>IHD, MI</td>
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<tr>
<td>Cong ND et al, 1998&lt;sup&gt;61&lt;/sup&gt;</td>
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<td>104/170</td>
<td>65±9</td>
<td>NR</td>
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<td>Kamitani A et al, 1995&lt;sup&gt;62&lt;/sup&gt;</td>
<td>Case-control</td>
<td>103/103</td>
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<td>54±10</td>
<td>♂</td>
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<tr>
<td>Ishigami T et al, 1995&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Case-control</td>
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<td>Ko Y-L et al, 1997&lt;sup&gt;15&lt;/sup&gt;</td>
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<td>267/337</td>
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<td>IHD, MI</td>
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<tr>
<td>Ichihara S et al, 1997&lt;sup&gt;63&lt;/sup&gt;</td>
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<td>327/352</td>
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<td>Yamakawa-Kobayashi K et al, 1995&lt;sup&gt;64&lt;/sup&gt;</td>
<td>Case-control</td>
<td>315/380</td>
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<td>51±8</td>
<td>♀+♂</td>
<td>IHD</td>
<td>0.80</td>
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</tbody>
</table>

<sup>*</sup>Gender stratified data available. <sup>†</sup>SD not reported. <sup>‡</sup>For cases and controls combined. <sup>§</sup>Median age. IHD= ischemic heart disease. MI= myocardial infarction.
FIGURE LEGENDS

Figure I

Funnel plots for the comparisons of MT (left panels) and TT (right panels) versus MM for plasma angiotensinogen levels (panel a and b), systolic blood pressure (panel c and d), hypertension (panel e and f), and ischemic heart disease (panel g and h) for Whites. The graph shows a plot of standard error (SE) as a function of effect size (panel a-d) or odds ratio (panel e-h) for all outcomes. Each circle represents a study. The vertical line indicates the pooled effect size/odds ratio for the outcome. The broken lines indicate the 95% confidence interval of the pooled effect size/odds ratio.