The Metabolic Syndrome, Independent Of Its Components, Is A Risk Factor For Stroke And Death, But, Not For Coronary Heart Disease Among Hypertensive Patients In The ASCOT-BPLA

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Short title: Metabolic syndrome and cardiovascular disease risk

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Submitted 2 December 2009 and accepted 27 March 2010.

Additional information for this article can be found in an online appendix at http://care.diabetesjournals.org

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**Objective:** To evaluate whether in hypertensive patients, the risk of cardiovascular disease is greater in association with the metabolic syndrome (MetS) or the sum of its individual components.

**Methods:** Cox models were developed to assess the influence of age, sex, ethnicity, and the individual components of MetS on risk associated with the MetS (using several definitions) of coronary outcomes, stroke and all-cause mortality.

**Results:** MetS was significantly associated with coronary outcomes, stroke and all-cause mortality after adjusting for age, sex and ethnicity. However, when the model was further adjusted for the individual components, the MetS was associated with significantly increased risk of stroke (hazard ratio [95%CI]: 1.34[1.07-1.68]) and all-cause mortality (1.35[1.16-1.58]) but not coronary outcomes (fatal-coronary heart disease plus non-fatal myocardial infarction: 1.16 [0.95-1.43] and total-coronary events: 1.06 [0.91-1.24]).

**Conclusions:** MetS, independent of its individual components, is associated with increased risk of stroke and all-cause mortality but not coronary outcomes.
Studies in the recent past evaluating the usefulness of the metabolic syndrome (MetS) have provided equivocal results\textsuperscript{1-4}. The database from the blood pressure-lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT-BPLA)\textsuperscript{5} provides an excellent opportunity to evaluate whether in hypertensive patients the risk of cardiovascular (CV) disease and death is greater in association with the MetS or the sum of its individual components.

**RESEARCH DESIGN AND METHODS**

Details of the study design and methods of the ASCOT-BPLA-trial have been described previously\textsuperscript{5}.

Definitions: Body mass index (BMI) $>30$ Kg/m$^2$ was used instead of waist circumference in defining MetS as waist circumference was not measured in ASCOT-BPLA. The original NCEP-ATPIII definition\textsuperscript{6} of MetS [ATP 6.1] was considered as the primary definition in these analyses. In addition the updated NCEP-ATPIII\textsuperscript{7} [ATP 5.6], International Diabetes Federation\textsuperscript{8} [IDF] and two other definitions (ASCOT 6.1 and ASCOT 5.6: modifications of ATP 6.1 and ATP 5.6 by excluding ‘or presence of diabetes’ component from the fifth criterion, respectively) were also considered. The latter two were included to reduce some of the increased CV risk conferred by the presence of diabetes at baseline.

**Outcomes**: Fatal-coronary heart disease (CHD) plus non-fatal myocardial infarction (MI), total coronary events, stroke and all-cause mortality were pre-specified outcomes.

**Statistical analyses.** Three separate Cox models were developed for each of the pre-specified outcome using the ATP 6.1 definition of MetS. Model-1: unadjusted MetS; Model-2: adjusted for age, sex & ethnicity; Model-3: included model-2 plus all the individual components (used as continuous variables where linear) of the MetS. Risk (hazard ratios ) associated with all five definitions of the MetS for each of the four pre-specified outcomes was compared. Sensitivity assessment by excluding all subjects with the presence of diabetes (or missing values) at baseline were done in Cox models using the ATP 6.1 definition.

**RESULTS**

Of 19257 hypertensive patients randomised in ASCOT-BPLA, 8434 (43.8\%) had the MetS based on the ATP 6.1 definition.

**MetS and rates of coronary and stroke events and death using ATP 6.1 definition.** In model-1, MetS was associated with a significantly increased risk of coronary events (fatal CHD plus non-fatal MI: hazard ratio 1.24 [95\%confidence interval: 1.09-1.41] and total coronary events: 1.25[1.14-1.35]), but not for total stroke (1.07 [0.93-1.24]), nor for all-cause mortality (1.07 [0.97-1.19]). In model-2, the relationship of the MetS with coronary outcomes became more significant and stronger, and it significantly predicted total stroke (1.18[1.02-1.36]) and all-cause mortality (1.23[1.11-1.35]). However, when model-2 was further adjusted for the individual components of the MetS (Model-3), the association between MetS and total stroke (1.34 [1.07-1.68]), and all-cause mortality (1.35 [1.16-1.58]) became stronger and remained significant, while the association with coronary outcomes attenuated and became insignificant (fatal-CHD plus non-fatal MI: 1.16 [0.95-1.43] and total coronary events: 1.06 [0.91-1.24]) (see the online appendix available at http://care.diabetesjournals.org). These relationships remained unchanged on sensitivity analyses after excluding patients with diabetes at baseline.

**Different definitions of MetS and coronary and stroke events, and death.** The results, for each of the definitions used, showed a
consistent trend of the MetS significantly predicting the fatal-CHD and non-fatal MI, and total coronary events in model 1 and 2, but not in model-3 (Figure 1a and 1b) By contrast, the association between the MetS regardless of the definition used with stroke and all-cause mortality was not apparent in model 1 but became increasingly apparent in models two and three such that in model three the results consistently showed the MetS to be an independent predictor of total stroke and all-cause mortality after adjusting for its individual components (Figure 1c and 1d).

CONCLUSIONS
These analyses of 19257 hypertensive patients suggest that the MetS, independently of its components, is associated with increased risk of stroke and death but, not of coronary outcomes.
The lack of any synergy among the individual components of the MetS on the risk of coronary outcomes seen in our analyses is in keeping with findings of some\textsuperscript{3, 4} but not all the previous reports.\textsuperscript{1, 2} To compare our findings with the studies which adjusted for classical confounders, we further adjusted our model-3 for confounders such as smoking, alcohol intake, number of CV risk factors, and randomised antihypertensive regimen, but this did not change the association of the MetS with either fatal-CHD plus non-fatal MI (1.10 [0.90-1.35]) or total coronary events (1.01 [0.96-1.17]).
The finding of an increased risk of incident stroke associated with the MetS, independent of its constituent components and regardless of the definition used, extends the findings of previous reports.\textsuperscript{9, 10} Given the potential implications of these findings, we further adjusted model-3 with inclusion of confounders such as previous history of stroke/TIA, number of CV risk factors, alcohol intake, smoking, history of previous antihypertensive therapy, randomised-treatment allocation, and found no change in association of the MetS and incident stroke (1.31[1.04-1.64]).

None of the previous studies\textsuperscript{11, 12} have reported on the risk of death associated with the MetS adjusted for all its constituent components. Since in our analyses, the MetS independently of its components was not associated with a significantly increased risk of CV mortality (1.19 [0.93-1.53]), this suggests that if the increased risk of all-cause mortality associated with the MetS is true, the increase must be due to non-CV causes. Two thirds of the 953 non-CV deaths in the ASCOT-population were due to cancer which has previously been found to be associated with the MetS in observational studies\textsuperscript{13}.
The use of BMI instead of waist circumference in our definition of the MetS is a possible limitation of this study. However, BMI has been used as part of the MetS in previous widely accepted studies,\textsuperscript{11, 14} and has been shown to have a comparable predictive capability.\textsuperscript{15} The major strength of this study is its power to examine several CV outcomes and all-cause mortality while using various definitions of the MetS in the same population.
In summary, our findings suggest that, after adjusting for its individual components, the MetS is associated with increased risk of strokes and all-cause mortality but not coronary outcomes in hypertensive population.

Author contributions
AKG researched and analysed data, and wrote manuscript. NP contributed to discussion and reviewed/ edited on the manuscript. PSS and BD reviewed/edited the manuscript.

ACKNOWLEDGEMENTS
We are thankful to all the ASCOT executives and investigators for granting permission to use the ASCOT-BPLA database for this analysis.
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Funding: NP and PSS have received funding support from NIHR Biomedical Research Centre funding scheme. The ASCOT Study was an investigator-led study supported mainly by Pfizer Inc, New York with funding also provided by the Servier Research Group, Paris, France. Disclosures: AKG, BD, PS, and NP do not have any conflicts of interests related to this publication.

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**Figure legends:**

**Figure 1:** Different definitions of the metabolic syndrome and risk of coronary, stroke and death outcomes.

*Figure 1a:* Risk of fatal CHD* and non-fatal MI associated with metabolic syndrome

*Figure 1b:* Risk of total coronary events † associated with metabolic syndrome

*Figure 1c:* Risk of stroke associated with metabolic syndrome

*Figure 1d:* Risk of all-cause mortality associated with metabolic syndrome

Model 1 = Univariate MS ; Model 2 = Model 1 plus age, sex & ethnicity ; Model 3 = Model 2 plus Fasting plasma glucose, triglyceride, HDLc, SBP & BMI .

NF= Non-fatal ; F= Fatal ; CHD= Coronary heart disease

* Fatal CHD includes death from MI, acute coronary syndrome or sudden death attributable to ischaemic heart disease

† Total coronary events includes fatal and non-fatal CHD, unstable angina, fatal and non-fatal heart failure
Fig 1a

Metabolic Syndrome definitions

| Definition | Hazard Ratio | Model 1 | Model 2 | Model 3 |
|------------|--------------|---------|---------|---------|
| IDF        | 0.9 1 1.1 1.2 1.3 1.4 |         |         |         |
| ASCOT5.6   | 0.9 1 1.1 1.2 1.3 1.4 |         |         |         |
| ASCOT6.1   | 0.9 1 1.1 1.2 1.3 1.4 |         |         |         |
| ATP5.6     | 0.9 1 1.1 1.2 1.3 1.4 |         |         |         |
| ATP6.1     | 0.9 1 1.1 1.2 1.3 1.4 |         |         |         |

Fig 1b

Metabolic Syndrome definitions

| Definition | Hazard Ratio | Model 1 | Model 2 | Model 3 |
|------------|--------------|---------|---------|---------|
| IDF        | 0.9 1 1.1 1.2 1.3 1.4 |         |         |         |
| ASCOT5.6   | 0.9 1 1.1 1.2 1.3 1.4 |         |         |         |
| ASCOT6.1   | 0.9 1 1.1 1.2 1.3 1.4 |         |         |         |
| ATP5.6     | 0.9 1 1.1 1.2 1.3 1.4 |         |         |         |
| ATP6.1     | 0.9 1 1.1 1.2 1.3 1.4 |         |         |         |
Fig 1c

Fig 1d