Metabolic Syndrome Clusters and the Risk of Incident Stroke
The Atherosclerosis Risk in Communities (ARIC) Study

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Background and Purpose—Little is known about the metabolic syndrome (MetS) and the risk of incident stroke. This study is designed to identify particular clusters of MetS components that carry the highest risk of incident stroke.

Methods—We analyzed the public use data from the population-based Atherosclerosis Risk in Communities study. At baseline, 14,993 stroke-free middle-aged individuals were followed-up over 9 years for incident stroke. MetS components were defined according to the National Heart, Lung, and Blood Institute/American Heart Association criteria. Incident stroke was identified using a standardized incident events identification and classification protocol. Proportional hazard models were used to assess the RRs and 95% CIs of ischemic stroke associated with MetS and its different clusters.

Results—At baseline, the prevalence of MetS was 39%. The mean age was 54, with 26% blacks and 55% females. The hazard ratio of incident ischemic stroke associated with MetS among women (hazard ratio, 2.41; 95% CI, 1.69 to 3.49) and men (hazard ratio, 2.11; 95% CI, 1.56–2.85) was similar. There was a dose–response relationship between the numbers of MetS components and the risk of incidence stroke. Persons with either elevated blood pressure or elevated fasting glucose in the clusters to form a MetS had the highest risk for incident stroke (hazard ratio, 2.74–4.16 comparing to the reference group) than MetS without these 2 components (hazard ratio, ≤2.00 comparing to the reference group).

Conclusions—The data support the need to target MetS, especially MetS, with these 2 highest risk components (elevated blood pressure or elevated fasting glucose) in the clusters. (Stroke. 2009;40:200-205.)

Key Words: atherosclerosis ■ cohort study ■ metabolic syndrome ■ stroke risk factors

The metabolic syndrome (MetS) is a clustering of several interrelated metabolic risk factors of atherosclerotic arterial disease. Insulin resistance is the major underlying cause of MetS. MetS is highly prevalent (25%) in the United States population. Approximately 47 million adults in the United States and one-quarter of the world’s adults have MetS. It is likely to continue increasing because of increase in obesity and lack of physical activity. Currently, there is a disagreement on how to define MetS. Several organizations, including the US Adult Treatment Panel III of the National Cholesterol Education Program, the National Heart, Lung, and Blood Institute/American Heart Association, the American Association of Clinical Endocrinology, the European Group for the Study of Insulin Resistance, the World Health Organization, and the International Diabetes Federation, have proposed unique definitions for the diagnosis of metabolic syndrome. In 2006, the AHA and the American Stroke Association identified MetS as the less well-documented and potentially modifiable risk factor for ischemic stroke.

Stroke is the leading cause of disability and the third leading cause of death in the US, with >700 000 incidents of stroke and >160 000 stroke-related deaths reported annually. However, little is known about the particular MetS clusters and the risk differences in the development of ischemic stroke. Therefore, we performed this study to investigate: (1) whether MetS is associated with the risk of incident ischemic stroke; (2) whether there is a dose–response relationship between the number of MetS components and the incident of stroke; and (3) whether any combinations or clusters of the MetS components carry greater risk of incident ischemic stroke.

Subjects and Methods

Study Population
We used the public-use data from the Atherosclerosis Risk in Communities (ARIC) Study. ARIC, sponsored by National Heart, Lung, and Blood Institute, is a population-based cohort study of atherosclerotic cardiovascular disease. This cohort consists of 15,792 middle-aged biracial individuals randomly selected from 4 US communities (Suburban Minneapolis, Minn; Washington County, Md; Forsyth County, NC; and Jackson, Miss). Baseline examination was conducted during 1987 to 1989. The cohort members were contacted yearly by telephone and followed-up by a...
trial annual clinical reexamination. The identification of a stroke event was supported by an annual telephone follow-up and a community surveillance system in place to identify potential cardiovascular-related hospitalizations in the study area hospitals. Medical record from all potential cardiovascular disease events related hospitalizations and all death certificates were obtained and abstracted. The involved health care providers and next of kin were interviewed to obtain symptoms, time of symptoms, and any other finding relevant to stroke that were not included in the hospital records. The relevant data for the classification of a stroke event included the type and duration of patients’ initial neurological symptoms, their medical history, results of medical procedures, medications, reports from imaging (CT or MRI), autopsy findings, and other supportive clinical evidence. Final diagnosis of the cardiovascular events was made by a panel of physicians, subject to final adjudication by a cardiovascular specialist.18–20 The ARIC study follow-up data to the end of 1998, over 9 years, were used for our study sample of 14,993 subjects, after excluding baseline stroke history and individuals without data in the classification of MetS. Among them, 210 participants had stroke develop, and 188 were ischemic strokes.

Classification of MetS Status
Baseline MetS was defined by using the National Heart, Lung, and Blood Institute/American Heart Association criteria as the presence of ≥3 of the following components: (1) high waist circumference, >102 cm for men and >89 cm for women; (2) high blood pressure (BP), systolic blood pressure ≥130 mm Hg, diastolic blood pressure ≥85 mm Hg, or receiving pharmacological therapy for hypertension; (3) low high-density lipoprotein cholesterol, <40 mg/dL for men and <50 mg/dL for women; (4) elevated blood triglyceride, ≥150 mg/dL; and (5) elevated plasma glucose (HG), fasting glucose ≥100 mg/dL or receiving pharmacological treatment for diabetes.3

Data were collected using the following methods: blood pressure level was measured as the average of the second and the third measures of sitting blood pressure. After fasting for 8 hours, evaluation of elevated glucose was performed. Waist circumference, triglycerides, and high-density lipoprotein cholesterol were gauged using protocols mentioned on previous studies.21–26 Consistent protocols were used to assess handlings, blood draws, and blood assays.27

Ascertainment of Incident Ischemic Stroke
Potential cardiovascular and cerebral vascular events were identified by community surveillance, annual telephone contact, and triannual clinical re-examination. Information on hospitalization and visit to physicians were ascertained by interview with participants, the next of kin, and health care providers. Hospital charts were abstracted, and death certificates were obtained for all potential cardiovascular and cerebral vascular events. The information on potential cases was reviewed by a panel of physicians to ascertain and classify the cardiovascular and cerebral vascular events. Adjudication by a neurologist or cardiologist was required if the expert panel could not reach a consensus on the diagnosis. The ARIC Study case identification procedures have been previously reported.17

Covariates
At baseline, risk factor for ischemic stroke and demographics variables were collected from participants conforming with standardized protocols.28 The following covariates were included in this analysis: age, race, education level, cigarette smoking, body mass index, calculated percent of total energy intake that was generated from saturated fatty acid, and low-density lipoprotein cholesterol level. At baseline, history of stroke was identified by a home interview and clinical examination.17

Statistical Methods
Summary statistics (means, SDs, and proportions) were used to characterize the study population. Poisson regression model was used to estimate the adjusted incidence density of incident stroke. Multivariable proportional hazard regression model was performed to assess the relative risk (RR) of ischemic stroke associated with MetS and its different clusters. All data analyses were conducted with SAS 9.1 software.

Results
Baseline Characteristics From Individuals Free of Stroke
From the ARIC baseline cohort, we excluded individuals with a history of stroke, retaining 14,993 individuals to form the study population of this analysis. The characteristics of the entire study population, stratified by gender and MetS status, are shown in Table 1. There were 5844 individuals with MetS at baseline. The mean age of the entire cohort was 54 years. There were more black females (37%) than black American males (16%) with MetS. As expected, individuals with MetS were more likely to have hypertension and diabetes, regardless of gender. This is because these 2 conditions were part of the definition of MetS.

Prevalence of MetS and Individuals MetS Components
In the late 1980s during the ARIC Study baseline examination, 39% of this population-based sample had MetS (≥3 components), as shown in Table 2. Prevalence of MetS for black men, black women, white men, and white women were 34%, 50%, 40%, and 34%, respectively. Prevalence among

Table 1. Baseline Characteristics, Mean (SD) or Proportions, of Study Population Stratified by Sex and MetS Status

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Entire Cohort, N=14,993</th>
<th>MetS, N=3,224</th>
<th>No MetS, N=11,065</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>54.0 (5.7)</td>
<td>55.0 (5.6)</td>
<td>53.0 (5.6)</td>
</tr>
<tr>
<td>Race, % black</td>
<td>26</td>
<td>37</td>
<td>23</td>
</tr>
<tr>
<td>Cigarette smoking, %</td>
<td>26</td>
<td>24.8</td>
<td>24.8</td>
</tr>
<tr>
<td>Less than high school, %</td>
<td>23</td>
<td>33</td>
<td>17</td>
</tr>
<tr>
<td>Saturated fatty acid, %</td>
<td>12.0 (3.0)</td>
<td>11.7 (3.0)</td>
<td>12.0 (3.0)</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>214.8 (42.0)</td>
<td>227.0 (46.5)</td>
<td>212.0 (40.3)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.7 (5.3)</td>
<td>31.6 (6.0)</td>
<td>25.6 (5.1)</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>137.5 (39.3)</td>
<td>147.4 (47.7)</td>
<td>129.4 (39.5)</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>34</td>
<td>62</td>
<td>17</td>
</tr>
<tr>
<td>Type 2 diabetes, %</td>
<td>11</td>
<td>25</td>
<td>2.4</td>
</tr>
</tbody>
</table>

Women, N=8,261

Men, N=6,732
the 5e MetS was the highest for elevated waist circumference (53%), followed by HG (49%), HBP (43%), low high-density lipoprotein cholesterol (39%), and elevated triglycerides (28%). After stratifying by gender, women had higher prevalence of elevated waist circumference than men (66% in women in contrast to 38% in men). However, men had higher prevalence of low high-density lipoprotein cholesterol, elevated triglycerides, and HG than women (43%, 33%, and 56% in men, in contrast to 36%, 24%, and 43% in women, respectively). There were no differences among genders for HBP (42% and 44% in women and men, respectively).

**Prospective Relationship of MetS With Incident Stroke**

In 9 years of follow-up, there were 210 cases of incident stroke, and 188 of them were classified as incident ischemic stroke among baseline stroke-free individuals. As Table 3 shows, the incidence density (95% CI) of stroke on the entire cohort was 26.5 (22.2–31.8) among individuals with MetS, in contrast to 8.18 (5.0–13.4) per 10 000 person-year among those without MetS. In terms of RR, individuals with MetS had a significantly increased risk of stroke than those without MetS (RR, 2.24; 95% CI, 1.8–2.8). The multivariable-adjusted RR (95% CI) for incident stroke associated with MetS among women (RR, 2.41; 95% CI, 1.69–3.49) and men (RR, 2.11; 95% CI, 1.56–2.85) was similar. The interaction between gender and MetS in relationship to stroke was not statistically significant (P > 0.05).

Figure illustrates the dose–response relationship between the numbers of MetS components and RR (95% CI) incident stroke after 9 years of follow-up. The numbers of events of incident stroke for those individuals with 1 to 5 MetS component were 43, 61, 80, 70, and 38, respectively. For this analysis we compared individuals without any component of MetS (reference group) with those with 1 to 5 MetS components. The multivariable-adjusted hazard ratio (HR) for incident stroke was 1.36 (95% CI, 0.768–2.42), 1.72 (95% CI, 0.989–3.00), 2.48 (95% CI, 1.44–4.23), 3.59 (95% CI, 2.08–6.21), and 4.82 (95% CI, 2.68–8.68), respectively. P < 0.01 for linear trends in HRs for incident stroke.

**Clusters of MetS**

Identification of any particular cluster of MetS with the greatest risk of incident stroke was performed by combing the 16 possible MetS clusters according to clinical importance of MetS components and the total number of MetS components an individual had. These recombinations of MetS clusters yield the following 7 mutually exclusive subgroups: group 1 is the reference group, including individuals without any of the MetS components. Group 2 to 4, includes individuals with 3 components, who were grouped into 3 subgroups:-- persons with both high blood pressure and high glucose in the cluster (group 2), persons with either high blood pressure or high fasting glucose (group 3), and persons with neither high blood pressure nor high fasting glucose in the cluster (group 4). Group 5 and 6, includes individuals with 4 components who were grouped into 2 subgroups: persons with both high blood pressure and high glucose in the cluster (group 5), and persons with either high blood pressure or high fasting glucose (group 6). Group 7 includes all individuals who had all 5 MetS components at baseline examination. Multivariable proportional hazard model was used to compare these subgroups with the same reference group (group 1), and the RR associated with being in any of these subgroups are shown in Table 4. For individuals with 3 MetS components, persons who had HBP and HG (group 2) and persons who had either HBP or HG (group 3) had the greater risk of an incident ischemic stroke (HR, 2.82; 95% CI, 1.57–5.07; and HR, 2.74; 95% CI, 1.51–4.98, respectively) than those with neither of these 2 components (group 4) (HR, 1.34; 95% CI, 0.38–4.59). For individuals with 4 MetS components, persons with HBP and HG (group 5) had greater risk of an incident ischemic stroke (HR, 4.16; 95% CI, 2.35–7.38) than those with either HBP or HG (group 6) (HR, 3.25; 95% CI, 1.69–6.23). As expected, individuals with all 5 components of MetS (group 7) had the highest risk of incident stroke (HR, 4.92; 95% CI, 2.73–8.87).

**Discussion**

In this population baxed, middle-aged, biracial cohort, we found that persons with MetS have a significantly higher risk of incident ischemic stroke than those without MetS. Furthermore, persons with MetS that had either elevated blood pressure or elevated fasting glucose in the cluster have the highest risk of incident stroke. The pattern of these associa-

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**Table 3. Multivariable Adjusted* Incident Density (10 000 Person-Years) and RR (95% CI) of Incident Stroke Associated With MetS**

<table>
<thead>
<tr>
<th>MetS Components</th>
<th>Entire Cohort, N = 14 993</th>
<th>Women, N = 8261</th>
<th>Men, N = 6732</th>
</tr>
</thead>
<tbody>
<tr>
<td>MetS status at baseline, %</td>
<td>39.0 39.0 38.9</td>
<td>48.8 42.9 56.2</td>
<td>52.8 65.5 37.3</td>
</tr>
<tr>
<td>Elevated waist circumference, %</td>
<td>27.7 38.9 23.7</td>
<td>48.8 38.9 23.7</td>
<td>52.8 65.5 37.3</td>
</tr>
<tr>
<td>Elevated blood pressure, %</td>
<td>27.7 38.9 23.7</td>
<td>48.8 38.9 23.7</td>
<td>52.8 65.5 37.3</td>
</tr>
<tr>
<td>Low HDL cholesterol, %</td>
<td>38.9 27.7 38.9</td>
<td>48.8 27.7 38.9</td>
<td>38.9 65.5 37.3</td>
</tr>
<tr>
<td>Elevated triglyceride, %</td>
<td>38.9 27.7 38.9</td>
<td>48.8 27.7 38.9</td>
<td>38.9 65.5 37.3</td>
</tr>
<tr>
<td>Elevated fasting glucose, %</td>
<td>38.9 27.7 38.9</td>
<td>48.8 27.7 38.9</td>
<td>38.9 65.5 37.3</td>
</tr>
<tr>
<td>MetS status at baseline, %</td>
<td>39.0 39.0 38.9</td>
<td>48.8 42.9 56.2</td>
<td>39.0 39.0 38.9</td>
</tr>
</tbody>
</table>

*Adjusted for age, race, education level, and cigarette smoking.
tions remained after adjusting for various confounding factors. These findings are very valuable because currently MetS is a modifiable risk factor for ischemic stroke, but the relationship between MetS and stroke has not been well-documented in population-based studies.16

Out of all the different proposed criteria for the definition of MetS, we decided to use the National Heart, Lung, and Blood Institute/American Heart Association definition. The main differences of the National Heart, Lung, and Blood Institute/American Heart Association criterion to the ATP-III are: (1) it was developed more recently, in 2005; and (2) the definition for elevated fasting glucose was reduced from ≥110 mg/dL to ≥100 mg/dL.3 Therefore, lowering the glucose threshold could help the classification of MetS toward stroke risk.29 Published studies performed by our group have looked at the association of MetS with the risk of incident coronary heart diseases and all-cause mortality in the ARIC population.30 For the purpose of this particular study, we used similar approaches like those shown by Hong et al30 to look at MetS and the risk of incident stroke in the ARIC cohort.

In this population of individuals free of stroke at baseline, 39% had MetS. There were 14% individuals with 0 MetS components. The proportions of having 1, 2, 3, 4, and 5 components of MetS were 24%, 23%, 20%, 13%, and 6%, respectively. There was no difference in the prevalence of MetS between females (39%) and males (38.9%). These results were similar to those using the Third National Health and Nutrition Examination Survey, in which they also found little difference among men (24.0%) and women (23.4%) in the prevalence of MetS.31 The black population has a higher prevalence of MetS than whites (44% for blacks and 37% for whites). This result differs from published studies in which they found similar prevalences of MetS between blacks and whites.31,32 However, we found that black women have a higher prevalence of MetS than black men and whites. This is comparable to a previous study that reported similar findings.33 The high prevalence of MetS in black women is largely attributable to higher frequency of increased waist circumference, higher prevalence of HBP, and higher prevalence of diabetes among black women.

In terms of absolute risk, the risk of incidence stroke per 10 000 person-year was higher among males than females (34 vs 22 per 10 000 person-year among persons with MetS, and 16.5 vs 10.3 per 10 000 person-year among persons without MetS) after adjusting for age, race, education level, and cigarette smoking. In terms of RR attributable to MetS, it was

### Table 4. Identification of the MetS Clusters With Greatest Risk for Incident Stroke

<table>
<thead>
<tr>
<th>No MetS Components</th>
<th>N of Participants</th>
<th>N of Events</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBP + HG + TG, HBP + HG + HDL, HBP + HG + WC</td>
<td>2121</td>
<td>16</td>
<td>1.00</td>
</tr>
<tr>
<td>HBP + TG + HDL, HBP + TG + WC, HBP + HDL + WC, HG + TG + HDL, HG + TG + WC, HG + HDL + WC</td>
<td>1316</td>
<td>43</td>
<td>2.82 (1.57, 5.07)</td>
</tr>
<tr>
<td>TG + HDL + WC</td>
<td>1420</td>
<td>34</td>
<td>2.74 (1.51, 4.98)</td>
</tr>
<tr>
<td>HBP + HG + TG + HDL, HBP + HG + TG + WC, HBP + HG + HDL + WC</td>
<td>326</td>
<td>3</td>
<td>1.34 (0.388, 4.59)</td>
</tr>
<tr>
<td>HBP + TG + HDL + WC, HG + TG + HDL + WC</td>
<td>1113</td>
<td>44</td>
<td>4.16 (2.35, 7.38)</td>
</tr>
<tr>
<td>HBP + HG + TG + HDL + WC</td>
<td>817</td>
<td>21</td>
<td>3.25 (1.69, 6.23)</td>
</tr>
<tr>
<td>HBP + HG + TG + HDL + WC</td>
<td>852</td>
<td>38</td>
<td>4.92 (2.73, 8.87)</td>
</tr>
</tbody>
</table>

Adjusted for age, sex, and race.

Each MetS cluster was compared to individuals without any MetS components (reference group).

HDL indicates low high-density lipoprotein cholesterol; TG, elevated blood triglycerides; WC, elevated waist circumference.

Figure. Dose–response relationship between number of MetS components and the RR of incident ischemic stroke. RR and 95% CI. From proportional hazard model adjusted for age, sex, race, education level, current cigarette smoking, and percent of saturated fatty acid. Reference group includes individuals without any MetS components.
similar for men and women (RR, 2.11 for men and RR, 2.41 for women). This lack of difference in RR between men and women differs from effect modification by gender on the relationship between MetS and coronary arterial disease in the same population. The gender modification of the MetS and stroke association has been inconsistent. For example, the Northern Manhattan Study (NMS) demonstrated that the effect of MetS on stroke risk was slightly higher among women (HR, 2.0; 95% CI, 1.3–3.1) than among men (HR, 1.1; 95% CI, 0.6–1.9). However, the Cardiovascular Health Study showed that age- and race-adjusted HRs for stroke were greater among men (HR, 1.51; 95% CI, 1.08–2.12) than women (HR, 0.94; 95% CI, 0.73–1.21). These differences demonstrate the need of further studies in assessing the effects of gender on the association between MetS and stroke.

A significant positive dose–response relationship was found between the numbers of MetS components and the risk incident stroke after adjusting for age, sex, race, education level, cigarette smoking, and calculated percent of total energy intake generated from saturated fatty acid. In other words, the more MetS components an individual has (up to 5 components), the higher the risk of an incident stroke. A study using the Cardiovascular Disease Risk Factors Two-Township Study found similar results. They also showed a dose–response effect of MetS components and risk of ischemic stroke.

Our study identified that persons with either elevated blood pressure or elevated glucose components in the formation of a diagnosis of MetS had the greatest risk for incident ischemic stroke, which, to our knowledge, is the first population-based study to examine this issue. When we compared different combinations of MetS components to persons without any MetS component (reference group), individuals with all 5 MetS components have ~5-fold greater risk of incident stroke. Among individuals with 4 MetS components, persons having elevated blood pressure and elevated glucose to form MetS had 4-times higher risk of incident ischemic stroke than the reference group, and persons with either elevated blood pressure or elevated glucose to form MetS had 3-times higher the risk. Among individuals with 3 MetS components, persons having either elevated blood pressure or elevated glucose (including persons having both components) to form MetS had almost 3-fold greater risk of incident stroke than the reference group, as compared to RR of 1.34 for persons without these 2 components to form MetS (persons with higher waist circumference, elevated triglycerides, and low high-density lipoprotein cholesterol). We consider this one of the most important findings from this study because it indicates that greater efforts/resources should be targeted on these 2 components to reduce the burden of MetS-related stroke in the general population. Previous studies, 1 of them using the same population and another using a type 2 diabetes population, have examined MetS clusters and risk of incident atherosclerotic coronary arterial disease and the prevalence of atherosclerotic vascular disorders. Both reported similar findings on the importance of blood pressure and glucose components in relationship to their outcomes.

A few limitations of this study should be recognized. First, the use of middle-aged (45–64 years) individuals limited the number of incident ischemic stroke cases, because the risk of stroke doubles for each decade after age 60. The resulting small number of incident stroke events greatly limited our ability to perform analysis comparing the entire 16 possible clusters of MetS components. In several strata, there were no incident stroke cases. We overcame this limitation by combining smaller strata based on our previous experience with the incident coronary heart disease and the clinical importance of the MetS components. Second, the ARIC cohort was selected from 4 geographically diverse US communities. Therefore, these results may not be representative of other communities in the US. However, there are several strengths demonstrated by this study that should also be acknowledged. First, to our knowledge, this is the first study evaluating different clusters of MetS in the development of stroke in middle-age biracial Americans. Second, the ARIC study included a large number of blacks and is currently one of the longest prospective cohort studies with a large number of risk factor variables available to assess many health problems that are affecting our society, including MetS and stroke. Third, the ARIC study has used standardized protocols and procedures for data collection, incident event classification, and well-established quality control procedures to monitor and assure data quality. Therefore, the information bias is minimized from using the ARIC study data. This advantage also makes the study results more relevant clinically and more applicable in public health interventions to target or prevent MetS, reducing the public health burden of stroke.

In conclusion, ~40% of middle-aged Americans had MetS in the late 1980s. Persons with MetS have a significantly higher risk of incident ischemic stroke than those without MetS. Moreover, there is a dose–response relationship between the number of MetS components and the risk of incident ischemic stroke. Most importantly, persons with MetS that have either elevated blood pressure or elevated fasting glucose in the cluster have the greatest risk for ischemic stroke. These data support the need to target MetS, especially MetS with these 2 highest risk components in the clusters, to reduce the burden of ischemic stroke.

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Disclosures
Dr Jingping Mo is currently an employee of Pfizer, Inc. All other authors have no disclosures to report. This article does not necessarily express the opinions of the ARIC study, National Heart, Lung, and Blood Institute, or Pfizer, Inc.

References


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