Intracranial Atherosclerotic Stroke: Specific Focus on the Metabolic Syndrome and Inflammation

Oh Young Bang, MD, PhD

Corresponding author
Oh Young Bang, MD, PhD
Department of Neurology, Stroke and Cerebrovascular Center, Samsung Medical Center, Sungkyunkwan University School of Medicine, 50 Irwon-dong, Gangnam-gu, Seoul 135-710, South Korea.
E-mail: nmboy@unitel.co.kr

Current Atherosclerosis Reports 2006, **8:**330–336
Current Science Inc. ISSN 1523-3804
Copyright © 2006 by Current Science Inc.

Stroke is the second leading cause of mortality worldwide and is well suited for prevention because it has a high prevalence, high burden of economic cost, well-defined modifiable risk factors, and effective prevention measures. Atherosclerosis is one of the major mechanisms of ischemic stroke, but the apparent differences in risk factors for intra- and extracranial atherosclerosis are unclear and the mechanisms that underlie strokes in patients with intracranial atherosclerosis are not well known. Consequently, patients with intracranial stenosis receive the same treatment as those with carotid atherosclerosis. Several novel substances have emerged recently as risk factors for atherosclerosis. Specifically, it has recently been suggested that both the metabolic syndrome, which refers to a constellation of metabolic risk factors that are linked to insulin resistance, and vascular inflammation are associated with increased risk of coronary heart disease and stroke. The results of the studies reviewed here suggest that these factors play a differential role in the development of atherosclerotic stroke between the intra- and extracranial arterial systems.

Introduction

Despite the fact that most cardiovascular events are explained by conventional risk factors such as hypertension, diabetes mellitus, smoking, and dyslipidemia, many cardiovascular events occur in patients without such modifiable risk factors. Therefore, many risk factor candidates for atherosclerosis have been proposed.

Over the past two decades, a striking increase in the number of people with the metabolic syndrome has taken place. This increase is associated with the global epidemic of obesity and diabetes [1]. Recently, the Adult Treatment Panel III (ATP III) identified the components of the metabolic syndrome and defined this syndrome as the presence of three or more of the following risk factors: 1) abdominal obesity; 2) elevated triglyceride levels (≥ 150 mg/dL); 3) low high-density lipoprotein cholesterol levels (< 40 mg/dL for men, < 50 mg/dL for women); 4) hypertension (systolic blood pressure ≥ 130 mm Hg or diastolic blood pressure ≥ 85 mm Hg); and 5) impaired fasting glucose levels (≥ 110 mg/dL) [2].

Of the other potential novel risk factors currently being investigated, C-reactive protein (CRP) is among the most promising. It is generally accepted that inflammation is involved in plaque rupture, and there is an association between elevated CRP concentrations and increased risk of ischemic events or high-risk unstable plaque morphology.

This review highlights these two important emerging risk factors, the metabolic syndrome and inflammatory markers, in the development of intracranial atherosclerotic stroke.

Intracranial and Extracranial Atherosclerosis

Intracranial atherosclerotic stenosis is responsible for ischemic stroke in 5% to 10% of white patients and is the cause of stroke in up to 33% of Hispanic, black, and Asian stroke patients [3–5]. Therefore, intracranial stenosis is probably just as important as carotid bifurcation stenosis.

In addition to evidence based on anatomic studies of the morphology of arterial beds [6,7], several clinical studies have suggested that the mechanism of stroke may be different between patients with intracranial atherosclerosis and those with extracranial atherosclerosis. There are three lines of evidence to support this.

First, atherosclerosis is frequently localized to either the intra- or extracranial arterial system rather than occurring in both systems [8••]. The simultaneous development of intra- and extracranial arterial lesions within the same patient is infrequent [8••], and it was reported that patients without carotid bifurcation disease were more likely to progress to intracranial atherosclerosis than those

Table 1. Association of the metabolic syndrome with intracranial atherosclerosis: multiple regression analysis results

	Intracranial atherosclerosis*		Extracranial atherosclerosis*	
Variable	**Odds ratio (95% CI)**	***P* value**	**Odds ratio (95% CI)**	***P* value**
Age, per 1-year increase	–	0.705	1.03 (1.01–1.06)	0.009
Male sex	–	0.991	0.53 (0.29–0.98)	0.044
Hypertension	–	0.229	–	0.886
Diabetes	–	0.521	–	0.971
Smoking	–	0.88	–	0.413
Low-density lipoprotein	–	0.15	–	0.15
Previous stroke history	–	0.177	2.35 (1.10–3.73)	0.024
History of coronary heart disease	–	0.974	2.35 (0.88–6.22)	0.087
C-reactive protein, per 1-mg/dL increase	–	0.306	1.18 (0.98–1.42)	0.08
Metabolic syndrome		0.004		0.283
1 component	2.39 (0.83–6.90)†	0.108	–	0.081
2 components	3.70 (1.32–10.38)†	0.013	–	0.89
3 components	4.49 (1.61–12.54)†	0.004	–	0.619
4 components	6.58 (2.31–18.76)†	<0.001	–	0.541
5 components	5.92 (1.59–22.11)†	0.008	–	0.349

*Patients of nonatherosclerotic subtypes were used as the reference group.
†Compared with patients with no components of the metabolic syndrome.

with extracranial disease [9]. In addition, there is higher prevalence of a previous history of coronary heart disease (CHD) in patients with extracranial carotid atherosclerosis than in patients with middle cerebral artery (MCA) atherosclerosis [8••]. The prevalence of carotid stenosis in patients with CHD was reported to be unexpectedly high in a sample of the Japanese population [10].

Second, the pattern of stroke recurrence may differ between the two subtypes of atherosclerotic stroke. Unlike in patients with intracranial large artery atherosclerosis, recurrent strokes in patients with extracranial atherosclerosis are often unpredictable with respect to the site of recurrence and degree of pre-existing stenosis [11]. No patients with extracranial atherosclerosis had recurrences that were caused by intracranial large-artery atherosclerosis and vice versa.

Finally, the infarct patterns may differ between the two subtypes of atherosclerotic strokes. The infarct pattern in patients with MCA atherosclerosis often includes deep perforating and internal border-zone infarcts, whereas territorial infarcts and superficial perforator infarcts (which are suggestive of fatal and minor ruptures of plaques, respectively) are associated with extracranial carotid atherosclerosis [12]. This indicates that a different pathogenesis may underlie extracranial versus intracranial atherosclerosis. All such findings are in line with a previous report based on autopsy data showing that, in contrast to extracranial arterial stenosis, intracranial plaques are usually stable and fibrous and do not represent embolic foci [13,14].

The Metabolic Syndrome and Inflammation As Novel Risk Factors for Ischemic Strokes

The risk factors for intra- and extracranial atherosclerotic stroke have been compared in numerous studies [3,15–18], but it remains unclear whether there are differences between the risk factors associated with these two subtypes of ischemic stroke. After reporting that there were no significant differences in conventional risk factors between intra- and extracranial atherosclerotic stroke [8••], novel risk factors for these two types of atherosclerosis were investigated recently [19••]. The concentrations of inflammatory markers such as CRP and fibrinogen were higher in patients with extracranial atherosclerosis than in patients with intracranial atherosclerosis, which suggested that plaques associated with the latter stroke subtype may be more stable than those associated with the former subtype [8••]. In contrast, metabolic syndrome was observed more frequently in patients with intracranial atherosclerosis than in patients with extracranial atherosclerosis or other stroke subtypes [19••]. Patients with more severe metabolic abnormalities were more likely to have intracranial atherosclerosis after adjustment for other risk factors (Table 1). By contrast, such association was

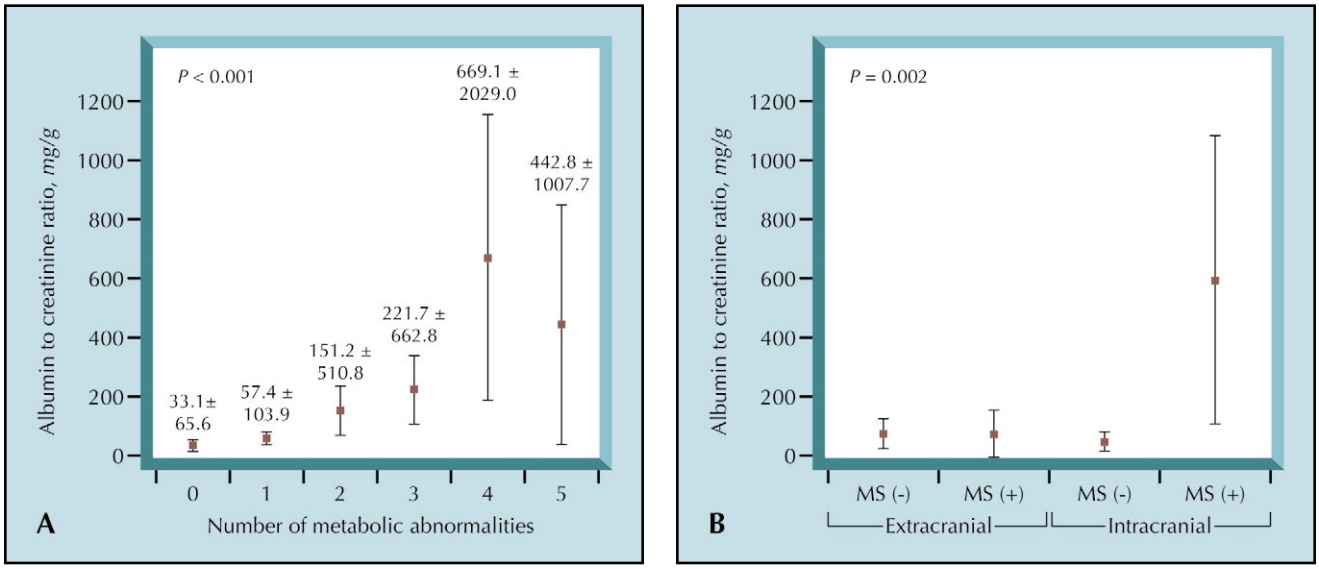

Figure 1. Association between urine microalbumin concentration, metabolic syndrome (MS), and stroke. **A,** Association between urine microalbumin concentration and metabolic abnormalities. The urine microalbumin concentration was higher in patients with four to five metabolic abnormalities than in patients with zero to three metabolic abnormalities ($P < 0.001$). **B,** Urine microalbumin concentration in patients with intracranial atherosclerotic stroke versus in patients with extracranial atherosclerotic stroke. (*Data from* Bang et al. [19••.)

not observed in patients with extracranial atherosclerosis. Urine microalbumin concentration, an important criterion in the World Health Organization definition of atherosclerosis [20], was reported to be associated with metabolic syndrome [21]. The concentration of urine microalbumin was related closely to the degree of metabolic abnormality, and a high concentration of urine microalbumin was associated with intracranial but not extracranial atherosclerotic stroke (Fig. 1) (Bang, Unpublished data).

Numerous studies have addressed the independent association between the metabolic syndrome and CHD-related mortality; the relative hazard ratio for these factors has been reported to range from 1.5 to 5.0 [22••]. CRP was an independent predictor of cardiovascular disease in middle-aged and older men and women [23–25]. However, there have been relatively few studies of these factors in patients with ischemic stroke, and the available data are variable [26–31]. Compared with CHD, stroke is a heterogeneous condition, and different risk factor profiles are associated with different subtypes of stroke, reflecting the particular etiopathology that underlies each subtype. Therefore, the impact of metabolic syndrome and inflammation may depend on the stroke subtype (eg, atherosclerotic, cardioembolic, lacunar) [19••,29] as well as the site of atherosclerosis [8••,19••]. In fact, when a cohort is divided into four groups based on CRP concentrations and the presence or absence of metabolic syndrome, intracranial atherosclerosis was most prevalent in patients with metabolic syndrome and low concentrations of CRP (Fig. 2).

In previous studies of the cardiovascular risks for inflammation and metabolic syndrome in healthy subjects, it was suggested that inflammation within

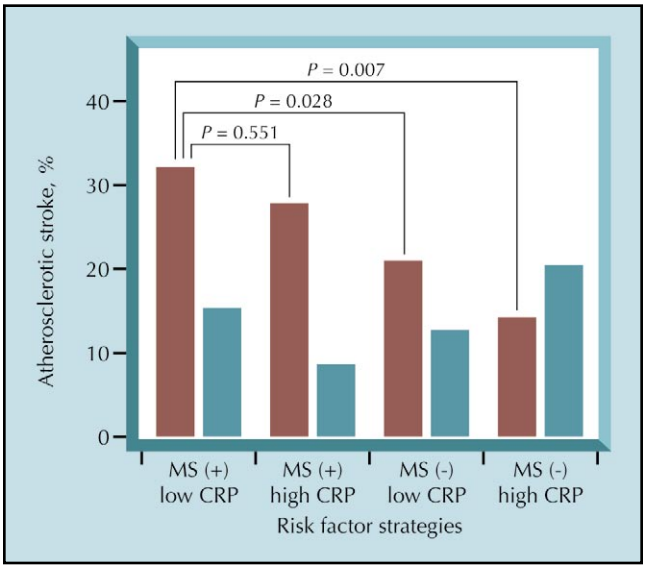

Figure 2. The impact of the metabolic syndrome (MS) and C-reactive protein (CRP) concentration on atherosclerotic stroke. *Black bars* and *gray bars* correspond to patients with intra- and extracranial atherosclerosis, respectively. *Low* and *high* refer to CRP concentrations of 0.3 mg/dL or less and greater than 0.3 mg/dL, respectively.

the vasculature might be an important pathogenic link between cardiovascular diseases and metabolic syndrome [32•]. Elevated CRP concentrations in patients with metabolic syndrome [33,34] were reported to have prognostic value concerning cardiovascular risk [32•,35]. However, our study of stroke patients revealed a weak correlation between the degree of inflammation and the degree of metabolic abnormality (Bang, Unpublished data). This does not preclude an association between metabolic abnormalities and inflammation, but it does differentiate

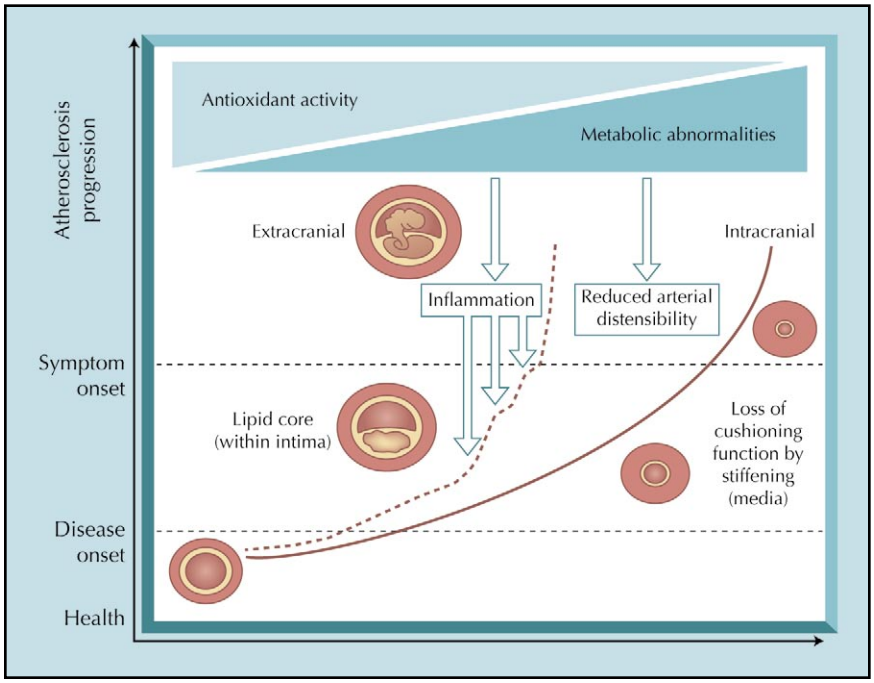

Figure 3. Mechanisms related to the metabolic syndrome and inflammation that are proposed to underlie the development of atherosclerotic stroke in various sites.

the pathogenic mechanisms that underlie intracranial and extracranial atherosclerotic stroke. Moreover, factor analysis has indicated that inflammation may represent a pathophysiologic pathway that is distinct and independent from metabolic syndrome [36]. This suggests that inflammation may contribute to the risk of cardiovascular disease independent of the insulin-resistance syndrome via a separate underlying process [36].

Interaction Between the Metabolic Syndrome and Intracranial Atherosclerotic Stroke

There are three possible explanations for the high frequency of the metabolic syndrome in patients with intracranial atherosclerosis. The first, oxidative stress, which is associated with the metabolic syndrome, has been suggested to play a role in endothelial dysfunction and subsequent atherosclerosis [36–38]. It was reported that adults with the metabolic syndrome have suboptimal concentrations of several antioxidants [39]. An autopsy study revealed that intracranial arteries responded with accelerated atherogenesis when the antioxidant protection of these arteries was decreased to a relatively greater extent than in extracranial arteries [40]. The authors of the aforementioned study suggested that the progression of atherosclerosis within intracranial arteries might be partly attributable to reduced intracellular defenses against oxygen free radical–mediated processes. Therefore, it is conceivable that intracranial arteries become susceptible to oxidative stress, resulting in atherosclerotic stroke, particularly under conditions of increased oxidative stress, such as those in patients with the metabolic syndrome.

Second, although the metabolic syndrome may play an important role in the early course (presymptomatic) of atherosclerosis in the extracranial system as shown in ultrasound-based studies of intimal medial thickness (IMT) [41–44], thrombotic arterial occlusion usually follows rupture of an unstable atherosclerotic plaque [45], and inflammation may be necessary for the development of symptomatic plaque rupture, either minor or fatal [46,47]. Recently, Iglseder et al. [48] reported an independent negative association of adiponectin (an adipose-derived factor) concentrations with early atherosclerosis (carotid IMT), whereas there was no relationship with atheromatous stroke (atherosclerotic plaques). Although the metabolic syndrome is associated with atherosclerosis, the association between the metabolic syndrome and atherosclerotic progression is less clear [49,50]. In contrast, although there is only a modest association between CRP concentration and imaging-based measures of subclinical atherosclerosis, there is a strong relationship between serum CRP concentrations and the coronary plaque burden and acute rupture defined at autopsy [51]. Therefore, it is conceivable that intracranial atherosclerotic stroke may be predominant in patients with metabolic syndrome in the absence of a profound inflammatory reaction within the extracranial arterial system (Fig. 3). Intracranial atherosclerosis may represent either arteriosclerosis (loss of cushioning function due to stiffening) [52] or the stable subtype of atherosclerosis [53] in which silent plaque ruptures and healing result in the progression of stenosis. Recently, it was reported that metabolic abnormalities (in the absence of inflammation) [54•] and insulin resistance [55,56] may cause a loss of the cushioning function by affecting arterial distensibility. This concurs with a previous transcranial Doppler-based study of the association between diabetes and increased intracranial arterial resistance [57]. Additional studies in patients with metabolic syndrome using transcranial Doppler may help document such changes in intracranial arterial systems.

Finally, atherogenesis, including the effects of plasma lipids [58], within the intracranial vascular bed might be different from atherogenesis that occurs in coronary or extracranial carotid arteries. Hemodynamic conditions affect atherogenesis and might also modify the effects of circulating agents in different vascular beds.

Perspectives: Definition of the Metabolic Syndrome and Treatment of These Risk Factors

Clinical criteria for the diagnosis of the metabolic syndrome have been recommended by at least four organizations [2,20,59–61]. The various definitions of metabolic syndrome differ not only in the criteria used to define each component (such as abdominal obesity or hyperglycemia) but also in the basic factors required for diagnosis. For example, the World Health Organization's definition requires insulin resistance; the definition proposed by the International Diabetes Federation requires abdominal obesity; and no single factor is required in the definition put forward by the ATP III. The differences among the definitions of metabolic syndrome result mainly from clinical simplification and ethnic differences.

The most remarkable differences among the definitions and those with potential clinical implications are whether the definition allows for the diagnosis of the metabolic syndrome in the presence of type 2 diabetes and ongoing treatment for dyslipidemia or hypertension [61]. Because of the high prevalence of hypertension and diabetes in patients with stroke or CHD, most previous studies of the prevalence of metabolic syndrome in such patients often used the ATP III criteria with some modifications to diagnose metabolic syndrome (eg, participants who reported current use of antihypertensive or antidiabetic medication were designated as having high blood pressure or diabetes, respectively). The International Diabetes Federation's definition explicitly allows for the treatment of hypertriglyceridemia (a low concentration of high-density lipoprotein cholesterol, hypertension, and diabetes) to be counted [61]. Further comparative studies are needed to elucidate the associations between the different definitions of the metabolic syndrome and major vascular events, especially intracranial atherosclerotic stroke.

The primary goal of management in an individual with the metabolic syndrome is to reduce risk for clinical atherosclerotic disease. The ATP III recommended increased emphasis on the management of the metabolic syndrome through lifestyle changes (weight control and increased regular physical activity) [2]. Many stroke patients with the metabolic syndrome may also benefit from aggressive management of metabolic risk factors (such as hypertension and atherogenic dyslipidemia), given the clinical trials that have documented the efficacy of lipid and blood pressure treatment to reduce CHD [2,62]. It is not known the extent to which stroke events would be reduced from optimal control of these risk factors in patients with the metabolic syndrome; however, in patients with CHD, optimal control of blood pressure and lipids resulted in preventing about 80% of CHD events [62]. In addition, there is growing evidence that several drugs (eg, fibrates, thiazolidinediones, and angiotensin-converting enzyme inhibitors) used to treat metabolic risk factors have been reported to act as insulin sensitizers and reduce CRP. Antiplatelet agents are generally not indicated in nondiabetic individuals for primary prevention. However, the use of antiplatelet agents may be considered for primary prevention of vascular disease in patients with the metabolic syndrome because of the substantially increased risk of acute vascular events in this group [63,64].

Statins, inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase, are well known plaque stabilizers. The use of a statin after ischemic stroke is associated with a reduction in CRP levels and an improved prognosis that is independent of lowering lipid levels; the greatest reduction of risk is observed in patients with relatively high CRP levels [65]. For this reason, the National Cholesterol Education Program recently extended the indication of statin use to those with carotid occlusive disease, even in those with normocholesterolemia [2]. Patients with intracranial atherosclerosis had stable plaques with lower levels of CRP and a higher frequency of hemodynamic strokes than patients with extracranial atherosclerosis [8••,12–14]. Further studies are required to elucidate the effects of plaque stabilizers, such as a statin, in patients with intracranial atherosclerosis.

Conclusions

The pathogenesis of intracranial atherosclerosis may differ from that of extracranial atherosclerosis, particularly with regard to metabolic abnormalities and inflammation. Further studies in different populations, such as different ethnic groups, and larger cohorts are warranted. Prospective studies are also needed to assess the impact of treating metabolic abnormalities and vascular inflammation as a strategy for preventing intracranial atherosclerosis.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Zimmet P: **Global and social implications of the diabetes epidemic.** *Nature* 2001, **414:**782–787.
2. **Third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). Final report.** *Circulation* 2002, **106:**3143–3421.

3. Sacco RL, Kargman DE, Gu Q, Zamanillo MC: **Race-ethnicity and determinants of intracranial atherosclerotic cerebral infarction. The Northern Manhattan Stroke Study.** *Stroke* 1995, **26:**14–20.
4. Wityk RJ, Lehman D, Klag M, et al.: **Race and sex differences in the distribution of cerebral atherosclerosis.** *Stroke* 1996, **27:**1974–1980.
5. Wong KS, Huang YN, Gao S, et al.: **Intracranial stenosis in Chinese patients with acute stroke.** *Neurology* 1998, **50:**812–813.
6. Moossy J: **Morphology, sites and epidemiology of cerebral atherosclerosis.** *Res Publ Assoc Res Nerv Ment Dis* 1966, **41:**1–22.
7. Mitchell JR, Schwartz CJ: **Relationship between arterial disease in different sites. A study of the aorta and coronary, carotid, and iliac arteries.** *BMJ* 1962, **5288:**1293–1301.
8.•• Bang OY, Lee PH, Yoon SR, et al.: **Inflammatory markers, rather than conventional risk factors, are different between carotid and MCA atherosclerosis.** *J Neurol Neurosurg Psychiatry* 2005, **76:**1128–1134.

These data demonstrate that inflammatory markers, rather than conventional risk factors, reveal clinical and radiologic differences between patients with extracranial and intracranial atherosclerosis.

9. Akins PT, Pilgram TK, Cross DT 3rd, Moran CJ: **Natural history of stenosis from intracranial atherosclerosis by serial angiography.** *Stroke* 1998, **29:**433–438.
10. Tanimoto S, Ikari Y, Tanabe K, et al.: **Prevalence of carotid artery stenosis in patients with coronary artery disease in Japanese population.** *Stroke* 2005, **36:**2094–2098.
11. Shin DH, Lee PH, Bang OY: **Mechanisms of recurrence in subtypes of ischemic stroke: a hospital-based follow-up study.** *Arch Neurol* 2005, **62:**1232–1237.
12. Lee PH, Oh SH, Bang OY, et al.: **Infarct patterns in atherosclerotic middle cerebral artery versus internal carotid artery disease.** *Neurology* 2004, **62:**1291–1296.
13. Lammie GA, Sandercock PA, Dennis MS: **Recently occluded intracranial and extracranial carotid arteries. Relevance of the unstable atherosclerotic plaque.** *Stroke* 1999, **30:**1319–1325.
14. Schumacher HC, Tanji K, Mangla S, et al.: **Histopathological evaluation of middle cerebral artery after percutaneous intracranial transluminal angioplasty.** *Stroke* 2003, **34:**e170–173
15. Gorelick PB, Caplan LR, Hier DB, et al.: **Racial differences in the distribution of anterior circulation occlusive disease.** *Neurology* 1984, **34:**54–59.
16. Caplan LR, Gorelick PB, Hier DB: **Race, sex and occlusive cerebrovascular disease: a review.** *Stroke* 1986, **17:**648–655.
17. Yasaka M, Yamaguchi T, Shichiri M: **Distribution of atherosclerosis and risk factors in atherothrombotic occlusion.** *Stroke* 1993, **24:**206–211.
18. White H, Boden-Albala B, Wang C, et al.: **Ischemic stroke subtype incidence among whites, blacks, and Hispanics: the Northern Manhattan Study.** *Circulation* 2005, **111:**1327–1331.
19.•• Bang OY, Kim JW, Lee JH, et al.: **Association of the metabolic syndrome with intracranial atherosclerotic stroke.** *Neurology* 2005, **65:**296–298.

This article demonstrates for the first time the role of the metabolic syndrome in the development of intracranial atherosclerosis.

20. Alberti KG, Zimmet PZ: **Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus: provisional report of a WHO consultation.** *Diabetes Med* 1998, **15:**539–553.
21. Rowley K, O'Dea K, Best JD: **Association of albuminuria and the metabolic syndrome.** *Curr Diab Rep* 2003, **3:**80–86.
22.•• Eckel RH, Grundy SM, Zimmet PZ: **The metabolic syndrome.** *Lancet* 2005, **365:**1415–1428.

This is an overview of the pathophysiology and management of the metabolic syndrome, and it shows the association between further cardiovascular events and this syndrome.

23. Kuller LH, Tracy RP, Shaten J, Meilahn EN: **Relation of C-reactive protein and coronary heart disease in the MRFIT nested case-control study. Multiple Risk Factor Intervention Trial.** *Am J Epidemiol* 1996, **144:**537–547.
24. Tracy RP, Lemaitre RN, Psaty BM, et al.: **Relationship of C-reactive protein to risk of cardiovascular disease in the elderly. Results from the Cardiovascular Health Study and the Rural Health Promotion Project.** *Arterioscler Thromb Vasc Biol* 1997, **17:**1121–1127.
25. Ridker PM, Rifai N, Rose L, et al.: **Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events.** *N Engl J Med* 2002, **347:**1557–1565.
26. Isomaa B, Almgren P, Tuomi T, et al.: **Cardiovascular morbidity and mortality associated with the metabolic syndrome.** *Diabetes Care* 2001, **24:**683–689.
27. Lakka HM, Laaksonen DE, Lakka TA, et al.: **The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men.** *JAMA* 2002, **288:**2709–2716.
28. Pyorala M, Miettinen H, Halonen P, et al.: **Insulin resistance syndrome predicts the risk of coronary heart disease and stroke in healthy middle-aged men: the 22-year follow-up results of the Helsinki Policemen Study.** *Arterioscler Thromb Vasc Biol* 2000, **20:**538–544.
29. Kawamoto R, Tomita H, Oka Y, Kodama A: **Metabolic syndrome as a predictor of ischemic stroke in elderly persons.** *Intern Med* 2005, **44:**922–927.
30. Milionis HJ, Rizos E, Goudevenos J, et al.: **Components of the metabolic syndrome and risk for first-ever acute ischemic nonembolic stroke in elderly subjects.** *Stroke* 2005, **36:**1372–1376.
31. Rost NS, Wolf PA, Kase CS, et al.: **Plasma concentration of C-reactive protein and risk of ischemic stroke and transient ischemic attack: the Framingham study.** *Stroke* 2001, **32:**2575–2579.
32.• Ridker PM, Buring JE, Cook NR, Rifai N: **C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14 719 initially healthy American women.** *Circulation* 2003, **107:**391–397.

This article describes the role of high-sensitivity CRP in the metabolic syndrome and describes for the first time how high-sensitivity CRP can improve risk detection in this setting.

33. Vikram NK, Misra A, Dwivedi M, et al.: **Correlations of C-reactive protein levels with anthropometric profile, percentage of body fat and lipids in healthy adolescents and young adults in urban North India.** *Atherosclerosis* 2003, **168:**305–313.
34. Rutter MK, Meigs JB, Sullivan LM, et al.: **C-reactive protein, the metabolic syndrome, and prediction of cardiovascular events in the Framingham Offspring Study.** *Circulation* 2004, **110:**380–385.
35. Sattar N, Gaw A, Scherbakova O, et al.: **Metabolic syndrome with and without C-reactive protein as a predictor of coronary heart disease and diabetes in the West of Scotland Coronary Prevention Study.** *Circulation* 2003, **108:**414–419.
36. Sakkinen PA, Wahl P, Cushman M, et al.: **Clustering of procoagulation, inflammation, and fibrinolysis variables with metabolic factors in insulin resistance syndrome.** *Am J Epidemiol* 2000, **152:**897–907.
37. Cai H, Harrison DG: **Endothelial dysfunction in cardiovascular diseases: the role of oxidant stress.** *Circ Res* 2000, **87:**840–844.
38. Lee KU: **Oxidative stress markers in Korean subjects with insulin resistance syndrome.** *Diabetes Res Clin Pract* 2001, **54(Suppl 2):**S29–S33.
39. Ford ES, Mokdad AH, Giles WH, Brown DW: **The metabolic syndrome and antioxidant concentrations: findings from the Third National Health and Nutrition Examination Survey.** *Diabetes* 2003, **52:**2346–2352.

40. D'Armiento FP, Bianchi A, de Nigris F, et al.: **Age-related effects on atherogenesis and scavenger enzymes of intracranial and extracranial arteries in men without classic risk factors for atherosclerosis.** *Stroke* 2001, **32:**2472–2480.
41. Hulthe J, Bokemark L, Wikstrand J, Fagerberg B: **The metabolic syndrome, LDL particle size, and atherosclerosis: the atherosclerosis and insulin resistance (AIR) study.** *Arterioscler Thromb Vasc Biol* 2000, **20:**2140–2147.
42. Davis PH, Dawson JD, Riley WA, Lauer RM: **Carotid intimal-medial thickness is related to cardiovascular risk factors measured from childhood through middle age: the Muscatine Study.** *Circulation* 2001, **104:**2815–2819.
43. Urbina EM, Srinivasan SR, Tang R, et al.: **Impact of multiple coronary risk factors on the intima-media thickness of different segments of carotid artery in healthy young adults (The Bogalusa Heart Study).** *Am J Cardiol* 2002, **90:**953–958.
44. Raitakari OT, Juonala M, Kahonen M, et al.: **Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study.** *JAMA* 2003, **290:**2277–2283.
45. Davies MJ, Richardson PD, Woolf N, et al.: **Risk of thrombosis in human atherosclerotic plaques: role of extracellular lipid, macrophage and smooth muscle content.** *Br Heart J* 1993, **69:**377–381.
46. Liuzzo G, Biasucci LM, Gallimore JR, et al.: **The prognostic value of C-reactive protein and serum amyloid A protein in severe unstable angina.** *N Engl J Med* 1994, **331:**417–424.
47. Danesh J, Whincup P, Walker M, et al.: **Low grade inflammation and coronary heart disease: prospective study and updated meta-analyses.** *BMJ* 2000, **321:**199–204.
48. Iglseder B, Mackevics V, Stadlmayer A, et al.: **Plasma adiponectin levels and sonographic phenotypes of subclinical carotid artery atherosclerosis: data from the SAPHIR Study.** *Stroke* 2005, **36:**2577–2582.
49. Hsia J, Bittner V, Tripputi M, Howard BV: **Metabolic syndrome and coronary angiographic disease progression: the Women's Angiographic Vitamin & Estrogen Trial.** *Am Heart J* 2003, **146:**439–445.
50. Mellen PB, Cefalu WT, Herrington DM: **Diabetes, the metabolic syndrome, and angiographic progression of coronary arterial disease in postmenopausal women.** *Arterioscler Thromb Vasc Biol* 2006, **26:**189–193.
51. Burke AP, Tracy RP, Kolodgie F, et al.: **Elevated C-reactive protein values and atherosclerosis in sudden coronary death: association with different pathologies.** *Circulation* 2002, **105:**2019–2023.
52. O'Rourke M: **Mechanical principles in arterial disease.** *Hypertension* 1995, **26:**2–9.
53. Burke AP, Kolodgie FD, Farb A, et al.: **Healed plaque ruptures and sudden coronary death: evidence that subclinical rupture has a role in plaque progression.** *Circulation* 2001, **103:**934–940.
54.• Whincup PH, Gilg JA, Donald AE, et al.: **Arterial distensibility in adolescents: the influence of adiposity, the metabolic syndrome, and classic risk factors.** *Circulation* 2005, **112:**1789–1797.
This article demonstrates that adiposity and its metabolic consequences are associated with adverse effects in the function and structure of the arterial wall by showing diminished arterial distensibility.
55. Salomaa V, Riley W, Kark JD, et al.: **Non–insulin-dependent diabetes mellitus and fasting glucose and insulin concentrations are associated with arterial stiffness indexes: the ARIC Study: Atherosclerosis Risk in Communities Study.** *Circulation* 1995, **91:**1432–1443.
56. Giltay EJ, Lambert J, Elbers JM, et al.: **Arterial compliance and distensibility are modulated by body composition in both men and women but by insulin sensitivity only in women.** *Diabetologia* 1999, **42:**214–221.
57. Tkac I, Troscak M, Javorsky M, et al.: **Increased intracranial arterial resistance in patients with type 2 diabetes mellitus.** *Wien Klin Wochenschr* 2001, **113:**870–873.
58. Shahar E, Chambless LE, Rosamond WD, et al.: **Atherosclerosis Risk in Communities Study. Plasma lipid profile and incident ischemic stroke: the Atherosclerosis Risk in Communities (ARIC) study.** *Stroke* 2003, **34:**623–631.
59. Balkau B, Charles MA: **Comment on the provisional report from the WHO consultation. European Group for the Study of Insulin Resistance (EGIR).** *Diabet Med* 1999, **16:**442–443.
60. Einhorn D, Reaven GM, Cobin RH, et al.: **American College of Endocrinology position statement on the insulin resistance syndrome.** *Endocr Pract* 2003, **9:**237–252.
61. Ford ES: **Prevalence of the metabolic syndrome defined by the International Diabetes Federation among adults in the U.S.** *Diabetes Care* 2005, **28:**2745–2749.
62. Wong ND, Pio JR, Franklin SS, et al.: **Preventing coronary events by optimal control of blood pressure and lipids in patients with the metabolic syndrome.** *Am J Cardiol* 2003, **91:**1421–1426.
63. Pearson TA, Blair SN, Daniels SR, et al.: **AHA Guidelines for Primary Prevention of Cardiovascular Disease and Stroke: 2002 Update: Consensus Panel Guide to Comprehensive Risk Reduction for Adult Patients Without Coronary or Other Atherosclerotic Vascular Diseases. American Heart Association Science Advisory and Coordinating Committee.** *Circulation* 2002, **106:**388–391.
64. Rothwell PM: **Prevention of stroke in patients with diabetes mellitus and the metabolic syndrome.** *Cerebrovasc Dis* 2005, **20(Suppl 1):**24–34.
65. Di Napoli M, Papa F: **Inflammation, statins, and outcome after ischemic stroke.** *Stroke* 2001, **32:**2446–2447.