Introduction

Stroke is the leading cause of death and the biggest culprit for adult disability. The 2005 statistics estimated that ≈5.8 million deaths worldwide were caused by stroke. In Korea, stroke was responsible for 59.6 deaths per 100,000 in 2007, being the second leading cause of death after cancer and the most fatal single organ disease, according to Statistics Korea. The rate is considerably high even among the OECD member countries. At the current speed of population aging in Korea, the incidence of stroke is expected to triple by 2030, calling for urgent corrective actions. Once developing, stroke might lead to severe disability and death. Primary prevention should be stressed more than with any other disease. Timely and proper treatment is also crucial to minimize post-stroke disability. A number of studies so far have suggested reliable, evidence-based methods for stroke prevention and treatment. Their proper implementation in the clinical practice is the best way to prevent stroke and minimize post-stroke disability.

The Clinical Practice Guidelines (CPGs) for Stroke, a systemic review of the vast scientific evidence available, is aimed at helping physicians determine the best possible treatment at the point of care. Many countries have successfully developed and implemented their own guidelines on stroke. Precedents are found not only in the United States and Europe but in neighboring Japan and even some South East Asian countries. Physicians here have mainly relied on the US and European guidelines. Uniform application of foreign guidelines, however, is potentially risky since the healthcare systems vary from country to country. Given the anticipated rise in stroke as a result of the fast population aging at home, it is of crucial importance to develop, distribute, and implement our own stroke guidelines tailored to the local needs.

A guideline, by definition, is aimed at improving decision making by doctors and patients by suggesting the evidence-based medical practices for general medical situations. The ultimate discretion is always with the
physician in charge who has a broad perspective of various factors in play in each patient. The present Guidelines, therefore, is not to limit practice of medicine by any healthcare professional, nor to provide reference for the insurance claim evaluation. Furthermore, it should never serve as a basis for legal judgment of a medical care provided under a specific clinical situation. With the sponsorship of Ministry of Health and Welfare ‘National Clinical Research Coordination Center Support Program’, the Guidelines have been put together by analyzing relevant data of foreign origin and modifying them to the local healthcare environment. While the local data does not account for a vast part of the Guidelines, we expect to see more of them included in the future revisions, as the ongoing studies come up with tangible results. Being the first of its kind in Korea, the Guidelines might not be as complete as they should be. That having been said, we hope that it could become a practical help for clinical physicians to ensure better care of stroke.

1. Epidemiology

The traditional definition of stroke by the World Health Organization (WHO) is a sudden focal - or at times global - neurological impairment of a cerebrovascular origin (blockage; cerebral ischemia or infarction, rupture; cerebral hemorrhage) that persists beyond 24 hours or is interrupted by death within 24 hours. The neurological deficit is called transient ischemic attack (TIA) if resolved completely within 24 hours.

Being one of the most fatal diseases, stroke accounted for 5.8 million deaths worldwide in 2005, according the WHO. In Korea, it was responsible for 59.6 deaths per 100,000 in 2007, being the second leading cause of death after cancer and the most fatal single organ disease [source: the Statistics Korea]. In the 2005, Korea National Health and Nutrition Examination Survey, the lifetime prevalence of diagnosed stroke in adults aged ≥19 was 15.9 per 1,000 (16.44 in men and 15.37 in women). By age, the prevalence was 6.53 in 40s, 24.26 in 50s, 57.96 in 60s, and 67.45 in 70s, showing a dramatic increase
after the age of 50s.
For stroke incidence, no local cohort data is available. According to the insurance claim records and death rates in 2004, there were a total of 104,937 acute stroke cases in Korea, 164 cases per 100,000 (95% CI: 149 - 178). Of them, new onsets were 75.61%. By type, ischemic stroke accounted for 61.6%, hemorrhagic stroke 26.9%, and the unclassified 11.5%. The overall stroke incidence was higher in women, which was structural with a bigger elderly population in women than in men. Men had higher per-100,000 rates in all age groups.

2. Guideline coverage

The CPGs for Stroke covers primary prevention of stroke in adults, acute treatment and rehabilitation, and secondary prevention. Pediatric stroke and meticulous surgery techniques are not included. By type, ischemic stroke is primarily focused, with brief mentioning of intracerebral hemorrhage. Subarachnoid hemorrhage is excluded.

3. Objectives

The CPGs for Stroke is aimed at improving decision making by physicians who provide acute and chronic stroke care, such as neurologists, neurosurgeons, rehabilitation specialists, internal medicine specialists, family doctors, and vascular interventionalists, by suggesting the evidence-based standard medical practices for general stroke situations. The ultimate discretion is always with the physician in charge who has a broad perspective of various factors in play in each patient. The present CPGs, therefore, is not to limit practice of medicine by any healthcare professional, nor to provide reference for the insurance claim evaluation. Furthermore, it should never serve as a basis for legal judgment of a medical care provided under a specific clinical situation.
4. Developmental process

1) Content determination
The CPGs for Stroke has three main subjects; primary prevention of stroke and risk management, acute stroke management, and secondary prevention of stroke. The items under each subject were selected by the Guidelines Development Task Force Team (TFT), a group of 5 created in May 2006. They then went through approval by the Supervising Committee and review, modification and supplementation by the Writing Committee. The Writing Committee, with 3 subgroups for each main subject, reviewed the TFT-selected items and determined the final items to be included.

2) Descriptive method determination
The TFT devised the CPGs development manual after 7 meetings. First, the team members went over all available relevant foreign guidelines and selected the 4 most reliable ones from the American Stroke Association (ASA), the European Union Stroke Initiative (EUSI), the Scottish Intercollegiate Guidelines Network (SIGN), and the Royal College of Physician (RCP). The developmental framework was created by analysis and summarization of the evidences and recommendations from those guidelines. References were separately searched and analyzed. Facing the variability in defining the recommendations / evidences from guideline to guideline, the authors adopted suggestions from the US Agency for Health Care Policy and Research. The subgroups in the Writing Committee searched for additional literature published later than the reference search period of the latest guideline in their field in order to reflect the most up-to-date evidence. References published by June 30 2007 were included.

3) Writing Committee formation
The Supervising Committee designated one Principal Writer for each main subject. The Principal Writers then recommended candidate members based on regional difference and specialties. With approval from the Supervising Committee, the candidates became members of the Writing Committee.
4) Writing process
Under the leadership of each Principal Writer, the subgroups of the Writing Committee completed wordings under their respective subject. Disagreement was resolved through discussion and by the majority decision. After primary review by the Principal Writers and internal correction, a preliminary CPGs was created and sent to the Supervising Committee.

5) Review by the Supervising Committee
Members of the Supervising Committee reviewed and discussed the preliminary version. After needed correction, a revised version was created.

6) Review by independent experts
The revised version was sent for review by independent professionals from relevant academic societies. Their inputs were discussed internally, and after needed modification, the final version became available.

7) Future revisions
The CPGs for Stroke will be revisited every 2 to 3 years in accordance with the TFT-devised revision protocol. When an important issue arises or a revision request is made before the Supervising Committee, the members will determine legitimacy issue by issue. For any non-scheduled revision, the details such as background and procedures will be published in the form of academic paper along with the revised recommendation.
5. **Level of evidence / Grade of recommendation**

In general, development of the clinical practice guidelines involves a comprehensive review of the relevant literature, evidence analysis, and determination of levels of evidence (LOE) / grades of recommendation (GOR) by experts. LOE refers to how strong evidence a specific medical practice is supported with, while GOR implies how strongly the medical practice is recommended. The present CPGs for Stroke used the method suggested by the US Agency for Health Care Policy and Research to define LOE and GOR;

<table>
<thead>
<tr>
<th>Level</th>
<th>Type of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>Evidence obtained from meta-analysis of randomized controlled trials.</td>
</tr>
<tr>
<td>Ib</td>
<td>Evidence obtained from at least one randomized controlled trial.</td>
</tr>
<tr>
<td>IIa</td>
<td>Evidence obtained from at least one well-designed controlled study without randomization.</td>
</tr>
<tr>
<td>III</td>
<td>Evidence obtained from at least one other type of well-designed quasi-experimental study.</td>
</tr>
<tr>
<td>IV</td>
<td>Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.</td>
</tr>
<tr>
<td>V</td>
<td>Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities.</td>
</tr>
<tr>
<td>Grade</td>
<td>Recommendation</td>
</tr>
<tr>
<td>---------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>A (evidence Levels Ia, Ib)</td>
<td>Required - at least one randomized controlled trial as part of the body of literature of overall good quality and consistency addressing specific recommendation.</td>
</tr>
<tr>
<td>B (evidence Levels IIa, IIb, III)</td>
<td>Required - availability of well conducted clinical studies but no randomized clinical trials on the topic of recommendation.</td>
</tr>
<tr>
<td>C (evidence level IV)</td>
<td>Required - evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates absence of directly applicable studies of good quality.</td>
</tr>
<tr>
<td>GPP (Good practice points)</td>
<td>Recommended best practice based on the clinical experience of the guideline development group.</td>
</tr>
</tbody>
</table>

6. Sponsorship

The CPGs for Stroke was developed under the sponsorship of the Health & Medical Technology R&D Program (A060171). Run by Ministry of Health & Welfare of Korea, the Program is part of the bigger Clinical Research Center Project aimed at boosting the national clinical research activities in major disease areas.

The Clinical Research Center for Stroke, headed by Professor Byung-Woo Yoon at Seoul National University Hospital, was launched in May 2006 with 6 subtasks to be undertaken over 9 years. The ultimate research goal at the Center is to prepare, distribute, and help implement the Korean Clinical Practice Guidelines for Stroke. The present CPGs is the first tangible outcome of the research work.

Participating researchers including members of supervising committees, advisory board, task force team for CPGs development protocol and writing committee did not receive any financial support in cash or in kind other than sponsored by the above-mentioned Program, and thus are free from influences from government institutions, pharmaceutical companies, medical institutions, or any other interest group.

October 2010

Clinical Research Center for Stroke (CRCS)
Addendum
The Clinical Practice Guidelines for Stroke was officially published in Korean in October 2009. In recognition of the need to enhance global awareness and international exchange of the Guidelines, the CRCS Operating Committee decided to publish the Guidelines in English. Translation began in February 2010, and the final English version became available in May 2010. While the Korean version of the Guidelines includes broad contents under each chapter, the English version serves as a condensed summary of each chapter.

※ The CPGs has been accredited by the following academic societies
   (as of July 10 2010)
   - The Korean Stroke Society
   - The Korean Neurological Association
   - The Korean Society of Geriatric Neurology
   - The Korean Society of Cerebrovascular Surgeons
   - The Korean Society of Interventional Neuroradiology
   - The Korean Society of Intravascular Neurosurgery

※ The CPGs is accessible online (http://www.stroke-crc.or.kr).
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Primary prevention of stroke
1.1 Non-modifiable risk factors

1.1.1 Age

Introduction
The risk of stroke rises with increasing age because of the progression of risk factors for stroke and aging of cerebrocardiovascular systems. The stroke risk doubles every 10 years beyond the age of 55.\(^1,2\)

Korean recommendations
None

1.1.2 Gender

Introduction
The incidence of stroke is higher in men than in women, which is attributable not only to biological factors but to difference in lifestyles related to stroke risk factors.

Korean recommendations
None

1.1.3 Low birth weight

Introduction
In a prior study, low birth weight was associated with an increased risk of stroke incidence and mortality.\(^1\) It has been suggested that maternal nutrition during pregnancy might affect off-springs’ stroke risk and stroke mortality in their adulthood. It might partly explain a regional disparity in stroke incidence and mortality within a country.

Korean recommendations
None

1.1.4 Genetic factors

Introduction
Genetic factors play a role in development of stroke risk factors such as hypertension and diabetes, and also influence on the susceptibility to the effect of stroke risk factors. Several rare genetic disorders vulnerable to stroke have been identified. At present, genetic factors are considered non-modifiable. However, research is under way to treat malfunctioning genes or directly correct deficiencies due to gene abnormalities.

Korean recommendations
1. Evidence is insufficient to recommend a genetic screening for primary stroke prevention [GOR: GPP].
1.2. Well-documented and modifiable risk factors

1.2.1 Hypertension

Introduction
Hypertension is the most prevalent modifiable and the highest population-attributable risk factor for stroke. Hypertension is more strongly associated with stroke than with coronary arterial disease (CAD). Compelling evidences have shown that blood pressure (BP) control reduces the stroke risk.

Korean recommendations
1. Regular BP monitoring is recommended in adults, particularly in the elderly or those with other cerebrocardiovascular risk factors (GOR: GPP).
2. Lifestyle modification is recommended for prevention and treatment of hypertension (weight loss if overweight, low-fat/low-salt diet, exercise, moderate drinking, and no smoking). If necessary, drug therapy should be initiated to lower BP (LOE: Ia, GOR: A).
3. The target BP is <140/90 mmHg for primary prevention of stroke (LOE: Ia, GOR: A).
4. In patients with diabetes and/or renal disease, the target BP is <130/80 mmHg (LOE: Ia, GOR: A).
5. Systolic hypertension in the elderly should be treated with the same principles and methods as other hypertension (LOE: Ia, GOR: A).
6. For primary stroke prevention, an adequate BP control is the most important rather than choosing a specific class of antihypertensive agent. However, given no compelling indications, calcium channel blockers or renin-angiotension system inhibitors are recommended over beta-blockers, (LOE: Ia, GOR: A).

1.2.2 Smoking

Introduction
The epidemiologic studies have indicated that smoking is a potent risk factor for stroke. Smoking exerts both acute effect o thrombogenesis and chronic effect of accelerating atherosclerosis.

Korean recommendations
1. Smoking should be ceased, and smokers should be strongly advised to quit (LOE: III, GOR: B).
2. Secondary smoking should be avoided (LOE: III, GOR B).
3. Counseling, nicotine replacement therapy, and oral smoking cessation aids should be considered in smokers (LOE: Ia, GOR: A).
1.2.3 Diabetes

Introduction
Diabetes is one of the modifiable risk factors for stroke. Large-scale, case-control studies have demonstrated that diabetes is an independent risk factor for ischemic stroke. While strict blood pressure control and lipid lowering with a statin reduce the stroke risk, the evidence that a tight blood glucose control could reduce stroke risk is lacking. However, as it is widely recognized that blood glucose control prevents microvascular complications, a strict blood glucose control is recommended. If patients with diabetes have hypertension or hyperlipidemia, more rigorous control of BP or blood lipid is required.

Korean recommendations
1. In diabetes patients, comprehensive and aggressive evaluations and treatments are needed to manage not only blood glucose but other risk factors such as hypertension, hyperlipidemia, and smoking together (LOE: Ib, GOR: A).
2. In diabetes patients, a more aggressive and rigorous blood glucose control is recommended for prevention of cerebrocardiovascular events (LOE: Ia, GOR: A). The recommended target BP and LDL cholesterol level are <130/80mmHg (LOE: Ib, GOR: A) and <100mg/dL (LOE: Ia, GOR: A), respectively. For type 2 diabetes patients who have additional risk factors, aggressive lipid lowering with a statin is recommended for primary prevention of stroke (LOE: Ib, GOR: A).

1.2.4 Atrial fibrillation

Introduction
Atrial fibrillation (AF) is a major risk factor of stroke, and its prevalence increases with age. Cardioembolic stroke attributed to AF is more severe than other types of ischemic stroke, usually resulting in a severe disability. Anticoagulation or antiplatelet therapy can significantly reduce the cardioembolic stroke in patients with AF.

Korean recommendations
1. In AF patients with valvular heart disease (particularly those with mechanical valves), anticoagulation is recommended (LOE: Ia, GOR: A).
2. In non-valvular AF, antithrombotic treatment (warfarin or aspirin) is recommended for primary stroke prevention. Selection of treatment (warfarin or aspirin) should be individualized based on thromboembolic risk, bleeding risk, patient’s preference, and feasibility of anticoagulation monitoring (LOE: Ia, GOR: A).
3. For high-risk patients (annual stroke risk ≥4%) without contraindications to anticoagulation, warfarin (INR 2.0-3.0) is recommended (LOE: Ia, GOR: A).
4. Warfarin (INR 2.0-3.0) is also recommended for primary prevention of stroke in elderly AF patients aged 75 and over (LOE: Ib, GOR: A).
1.2.5 Other cardiac conditions

Introduction

Other cardiac conditions that increase the risk of cardioembolic stroke include dilated cardiomyopathy, valvular heart disease (mitral valve prolapse, endocarditis, and prosthetic valves), and congenital heart disease (patent foramen ovale, atrial septal defect, and atrial septal aneurysm). Acute myocardial infarction (MI) increases the risk of cardioembolic stroke by formation of ventricular wall thrombi or developing AF.

Open heart surgery has a higher risk of stroke than other types of surgery.

Korean recommendations

1. For patients with ST-elevated MI who have a cardiac condition of increased cardioembolic risk (AF, mural thrombus, akinetic regions, for example), combination therapy with antiplatelet (aspirin etc.) and anticoagulant is reasonable. Duration of the anticoagulant therapy should be determined based on the cardiac conditions: long-term anticoagulation for those with persistent AF, and at least 3 months anticoagulation for those with mural thrombi or akinetic left ventricular segments (LOE: Ib, GOR: A).

2. Warfarin may be considered in severe left ventricular dysfunction, whether or not heart failure is present (LOE: IV, GOR: C).

3. Treatment of cardiac conditions associated with an elevated risk of stroke, such as valvular heart disease, angina pectoris, and acute MI, should follow the general practice guidelines for heart disease (GOR: GPP).

4. For patients undergoing coronary bypass surgery who have a high risk (advanced age [≥65], left main coronary artery stenosis, peripheral vascular disease, history of TIA or stroke, or carotid bruits upon auscultation), evaluating stroke risk such as carotid stenosis should be considered (GOR: GPP).

Table. The CHADS2 risk stratification and treatment recommendations in non-valvular AF

<table>
<thead>
<tr>
<th>CHADS2 Score</th>
<th>Risk level</th>
<th>Rate of stroke</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Low</td>
<td>1.0%/year</td>
<td>Aspirin (75-325 mg daily)</td>
</tr>
<tr>
<td>1</td>
<td>Low to Medium</td>
<td>1.5%/year</td>
<td>Warfarin INR 2-3 or aspirin (75-325 mg daily) †</td>
</tr>
<tr>
<td>2*</td>
<td>Medium</td>
<td>2.5%/year</td>
<td>Warfarin INR 2-3 †</td>
</tr>
<tr>
<td>3</td>
<td>high</td>
<td>5.0%/year</td>
<td>Warfarin INR 2-3</td>
</tr>
<tr>
<td>≥4</td>
<td>Very high</td>
<td>&gt;7%/year</td>
<td>Warfarin INR 2-3</td>
</tr>
</tbody>
</table>

Congestive heart failure, hypertension, advanced age [≥75], or diabetes scores 1, while stroke or TIA scores 2.

* CHADS2 evaluation is for primary prevention only. All non-valvular AF patients with history of stroke or TIA are considered at high risk even at Score 2 and need the anticoagulation treatment as such.

† Variables include patient preference, the risk of bleeding, and feasibility of the periodic INR tests. At the CHADS2 score of 1, prevention of 1 stroke per year requires warfarin treatment of 100 patients (number needed to treat = 100). Precise warfarin dosing is thus critical to get the desired treatment effect.
1.2.6 Dyslipidemia

**Introduction**

Inconsistent findings for the association between cholesterol level and stroke observed in earlier epidemiological studies were likely attributable to indiscriminating hemorrhagic and ischemic stroke. Recent studies showed that increased total cholesterol and/or LDL cholesterol is associated with an increased ischemic stroke risk in both men and women. Lower level of HDL-cholesterol is associated with ischemic stroke only in men. Clinical trials and meta-analyses during the last decade demonstrated that lowering cholesterol with statins is effective in primary and secondary prevention of cerebrocardiovascular diseases. For ischemic stroke, statins were also effective in primary and secondary prevention.

**Korean recommendations**

1. Determination of the target LDL cholesterol follows the general guidelines;
   1) For patients with coronary artery disease or equivalent risk (such as carotid artery disease, peripheral vascular disease, abdominal aneurysm, and diabetes), <100 mg/dL.
   2) For patients with 2 or more risk factors, <130 mg/dL.
   3) For patients with 1 or fewer risk factors, <160 mg/dL.

   (Risk factors: smoking, hypertension, HDL cholesterol <40 mg/dL, history of coronary artery disease in the first degree family members [male aged <55 and female <65], and age [men ≥45 and women 55 ≥1] [LOE: Ia, GOR: A].

2. For hypertensive patients with or at high risk of CAD, statin treatment along with lifestyle modification is recommended even at a normal LDL cholesterol level [LOE: Ia, GOR: A].

3. In diabetic adults, the target LDL cholesterol of <100 mg/dL is recommended [LOE: Ia, GOR: A].

4. For type 2 diabetes patients who also have other risk factors, lipid-lowering with statins is recommended for primary prevention of stroke [LOE: Ib, GOR: A].

5. For patients with CAD and a low HDL cholesterol level, niacin or gemfibrozil may be recommended along with weight loss, physical activity, and smoking cessation [LOE: Ib, GOR: A].

1.2.7 Asymptomatic carotid stenosis

**Introduction**

15–20% of ischemic stroke is caused by extracranial carotid stenosis. Asymptomatic carotid stenosis is increasingly detected with advances in diagnostic technologies. According to western studies, asymptomatic carotid stenosis of ≥50% affects 5-10% of the elderly population aged 65 and over, while stenosis of ≥80% is found in about 1%. The annual stroke rate in patients with asymptomatic carotid stenosis of 50-99% is about 1-3.4%. Prophylactic carotid endarterectomy (CEA) or angioplasty and stenting may be considered in patients with severe carotid stenosis.
Korean recommendations
1. In patients with asymptomatic carotid stenosis, other treatable stroke risk factors should be evaluated and rigorously treated (GPP).
2. In patients with asymptomatic carotid stenosis ≥50%, antiplatelet treatment is recommended unless contraindicated (LOE: IIa, GOR: B). For patients with stenosis <50%, decision of antiplatelet treatment should be individualized (GPP).
3. In asymptomatic carotid stenosis (60-99%), prophylactic CEA is recommended if the surgery-related morbidity and mortality is less than 3%. Selection of subjects requires careful review of comorbidities, expected years of life, patient preferences, and other patient factors (LOE: Ia, GOR: A).
4. In patients with asymptomatic carotid stenosis who have comorbidities increasing operative risk, carotid angioplasty and stenting may be a reasonable alternative to CEA (LOE: IIa, GOR: B).

1.2.8 Postmenopausal hormone therapy

Introduction
In women, stroke risk dramatically increases after menopause. Experimental or observational studies suggested that postmenopausal hormone therapy might prevent cerebrocardiovascular events and decrease the stroke severity. However, on the contrary, clinical trials have demonstrated that the postmenopausal hormonal therapy increases stroke risk.

Korean recommendations
1. Postmenopausal hormone therapy is not recommended for primary prevention of stroke (LOE: Ia, GOR: A).
2. If postmenopausal hormone therapy is needed for other indications, adequate explanation and counseling about the elevated cerebrocardiovascular risk should be provided (GOR: GPP).

1.2.9 Diet and nutrition

Introduction
Adequate intake of fruits and vegetables helps to prevent stroke. Restricting sodium intake and taking potassium-enriched diet also have an effect of stroke prevention which seems to be exerted via BP reduction.

Korean recommendations
1. A low-sodium / high-potassium diet is recommended for BP reduction and stroke prevention (LOE: Ia, GOR: A). The recommended daily intake is ≤2.3g (100mmol) for sodium or ≤6g for salt and ≥4.7g (120 mmol) for potassium.
2. It is recommended to increase dietary intake of fruits, vegetables, and low-fat dairy products (low-fat milk, cheese, yogurt, etc.) and to decrease saturated and total fat intake (LOE: Ib, GOR: A).
3. A diet rich in fruits and vegetables (at least 5 servings daily) is recommended (LOE: III, GOR: B).
4. A weight loss diet is recommended for those with a high body mass index (BMI) (LOE: Ib, GOR: A).

1.2.10 Physical activity

Introduction
Regular physical activity reduces premature death and cerebrocardiovascular mortality and morbidity. Physical activity also helps to prevent stroke. The effects seem to be attributable to blood pressure reduction, glucose control, and weight loss.

Korean recommendations
1. Increasing physical activity is recommended for primary prevention of stroke (LOE: III, GOR: B).
2. Regular daily exercise of moderate intensity for 30 minutes or longer is recommended to prevent stroke (LOE: III, GOR: B).

1.2.11 Obesity

Introduction
For Korean, obesity is defined as a BMI (Body Mass Index; body weight [kg] / height [meter]^2) ≥ 25. Abdominal obesity is defined as a waist circumference ≥ 90 cm (men) or ≥ 85 cm (women). In the 2005 Korean National Health and Nutrition Examination Survey, the prevalence of obesity in adults 20 and older was 31.7% (35.1% in men and 28.0% in women), a significant increase from the 26.3% (25.0% in men and 27.0% in women) in the 1998 survey. The risk of stroke is known to increase in proportion to the severity of obesity.

Korean recommendations
1. Weight reduction lowers BP (LOE: Ia, GOR: A), which leads to reducing stroke risk (LOE: III, GOR: B).
1.3 Less well-documented or potentially modifiable risk factors

1.3.1 Metabolic syndrome

Introduction
Metabolic syndrome refers to a constellation of multiple conditions comprising abdominal obesity, dyslipidemia, impaired glucose tolerance, and hypertension along with insulin resistance. With the recent surge in its prevalence, metabolic syndrome is associated with an increased risk of not only diabetes but cerebrocardiovascular diseases such as stroke. Among diverse diagnostic criteria for metabolic syndrome, the one for Asians devised by the International Diabetes Federation is widely employed (Table in below). ¹

Korean recommendations
1. Metabolic syndrome is a risk factor for stroke. Lifestyle modification and drug therapy are recommended for each of its components (LOE: III, GOR: B).

Table. Metabolic syndrome as defined by the International Diabetes Federation ¹

<table>
<thead>
<tr>
<th>Abdominal obesity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist circumference*: Men ≥ 90cm, Women ≥ 80cm (in Asians)</td>
</tr>
<tr>
<td>Abdominal obesity plus at least 2 of the following conditions</td>
</tr>
<tr>
<td>Serum triglyceride: &gt; 150mg/dL [1.7mmol/L] or drug-controlled</td>
</tr>
<tr>
<td>HDL cholesterol: Men &lt; 40mg/dL [1.03mmol/L], Women &lt; 50mg/dL [1.29mmol/L], or drug-controlled</td>
</tr>
<tr>
<td>Blood pressure: SBP &gt; 130mmHg or DBP &gt; 80mmHg or drug-controlled</td>
</tr>
<tr>
<td>Fasting blood glucose: ≥ 100mg/dL [5.6mmol/L] or diagnosis with type 2 diabetes (For ≥ 100mg/dL, an additional oral glucose tolerance test is not needed for the diagnosis purpose, but is recommended for the treatment purpose.)</td>
</tr>
</tbody>
</table>

¹ A BMI ≥ 30kg/m² is regarded abdominal obesity, irrespective of the waist circumference.

1.3.2 Alcohol

Introduction
A number of retrospective cohort studies have reported that mild or moderate drinking, particularly of grape wine, may reduce stroke risk. Heavy drinking, however, is known to increase stroke risk.
Korean recommendations
1. Heavy drinking should be avoided for various health purposes. With regard to stroke prevention, no more than 2 drinks per day for men or 1 drink per day for non-pregnant women may be protective against stroke (LOE: III, GOR: B).

1.3.3. Drug abuse

Introduction
Drug abuse is a chronic disease with a high recurrence rate. In addition to causing numerous health problems, it has a serious social implication. Use of cocaine, amphetamine, or heroin is associated with stroke.¹

Korean recommendations
1. Sympathomimetics such as cocaine, amphetamine, or heroin increase risk of stroke and should not be used (LOE: III, GOR: B).
2. Medical counseling to drug abusers can be useful (LOE: IV, GOR: C).

1.3.4. Oral contraceptives

Introduction
The evidence that oral contraceptives might be associated with ischemic stroke came from earlier studies investigating the 1st generation agents containing high doses of estrogen. Newer formulations with lower estrogen content appear safe in terms of the risk of stroke.

Korean recommendations
1. In women with no risk factor for stroke, low estrogen containing oral contraceptives are less likely to increase the risk of stroke (LOE: III, GOR: B).
2. In women with risk factors for stroke such as smoking and thromboembolism, avoiding oral contraceptives is reasonable (LOE: III, GOR: B).
3. If use of oral contraceptives is needed despite presence of stroke risk factors, a rigorous treatment of the risk factors would be helpful (LOE: IV, GOR: C).

1.3.5. Sleep disordered breathing

Introduction
Sleep disordered breathing (SDB) is closely associated with major risk factors for stroke such as hypertension and abdominal obesity. Some investigators have insisted that SDB is an independent risk factor for stroke.¹ SDB is a main cause of refractory hypertension hardly controlled with drug therapy, and successful treatment of SDB led to a significant BP reduction.¹ The complicated interaction between SDB and stroke risk factors, however, makes it difficult to determine whether SDB is a direct cause of stroke or an instigator of other risk factors. Data on whether treating SDB reduces stroke is lacking.
Korean recommendations
1. In patients with a history of cerebrocardiovascular diseases or with stroke risk factors such as obesity and hypertension, the screening for SDB symptoms including habitual snoring and daytime sleepiness is reasonable. For patients with refractory hypertension in particular, referral to sleep specialists may be considered for a proper assessment (LOE: III, GOR: B).
2. Evidence is insufficient to recommend a routine SDB screening and treatment for primary prevention of stroke (LOE: III, GOR: B).

1.3.6 Migraine

Introduction
Migraine begins mostly before age of 40 and persists through the remaining lifetime. The prevalence of migraine is about 12%, and it is three times higher in women than in men.\(^1\) The association of migraine with stroke has been reported in young women.

Korean recommendations
1. There are insufficient data to recommend a migraine prophylaxis for primary prevention of stroke in migraine women (including the ones with aura) [LOE: IV, GOR: C].

1.3.7 Hyperhomocysteinemia

Introduction
Homocysteine is an amino acid produced in the methionine metabolism. Its blood level was shown to be positively correlated with the risk of cerebrocardiovascular diseases such as coronary artery disease and stroke in numerous prospective observational studies, case-control studies, and meta-analyses. Some vitamins such as folic acid, cobalamin [vitamin B12], and pyridoxine [vitamin B6] can effectively reduce blood homocysteine levels. Nonetheless, the causal relationship between an elevated blood homocysteine level and cerebrocardiovascular events including stroke remains obscure.

Korean recommendations
1. For population with inadequate dietary folic acid intake, folic acid supplementation aimed at reduction in the blood homocysteine level may be considered for primary prevention of stroke [GPP].
2. For patients with a high risk for cerebrocardiovascular events (diabetes or coronary artery disease, for example), use of vitamin B6 aimed at reduction in the blood homocysteine level might increase the risk of ischemic heart disease and thus requires a caution [LOE: IIa, GOR: B].

1.3.8 Hypercoagulability

Introduction
Hypercoagulability can be suspected if stroke occurs in young patients without risk factors. Antiphospholipid antibodies are found frequently in young female patients with cerebral
infarction. However, while acquired or hereditary hypercoagulability is associated with venous thrombosis, its association with ischemic stroke has not been demonstrated. In patients with patent foramen ovale (PFO), whether the hypercoagulability contributes to developing ischemic stroke needs further research.

**Korean recommendations**
1. There are insufficient data to provide a specific recommendation for primary prevention of stroke in patients with inherited or acquired hypercoagulability (LOE: III, GOR: B).
2. Hypercoagulability might be present in patients with antiphospholipid antibody syndrome or cancer. However, evidence is lacking with regard to the use of antiplatelets or anticoagulants for primary prevention of stroke in these patients (LOE: III, GOR: B).

### 1.3.9 Inflammation

**Introduction**
Risk factors or medical conditions that lead to damage and inflammation in cerebrovascular endothelial cells increase the risk of intravascular thrombosis and stroke. Atherosclerosis, a major cause of stroke, is a chronic inflammatory disease following vascular endothelial damages. However, inflammatory surrogate markers for stroke have not been well-defined.

**Korean recommendations**
1. Evidence is insufficient to recommend a routine hs-CRP screening for the evaluation of cerebrocardiovascular risk (LOE: IV, GOR: C).
2. In patients with a high risk for stroke, an aggressive control of the risk factors is recommended, regardless of hs-CRP level (LOE: Ia, GOR: A).
3. In patients with a moderate risk for stroke, hs-CRP level may be considered to determine the intensity of risk factor control (LOE: III, GOR: B).

### 1.3.10 Infection

**Introduction**
Recent infection within 1 week might promote a thrombosis that could potentially lead to stroke. Microorganisms such as Chlamydia pneumoniae, Cytomegalovirus, Helicobacter pylori, and gram-negative germs responsible for periodontal disease have been reported to be associated with atherosclerosis. Various pathogens encountered through lifetime might be involved in diverse stages of stroke development.

**Korean recommendations**
1. Even with seropositivity for pathogens potentially associated with stroke, evidence is insufficient to recommend antibiotics aimed at these pathogens for primary prevention of stroke (LOE: IV, GOR: C).
1.3.11 Asymptomatic lacunes and white matter change

Introduction
Brain MRI of healthy people commonly reveals asymptomatic lacunes or white matter changes. Asymptomatic lacunes are observed in about 20% of elderly population aged 60 to 90. Asymptomatic lesions are 5 times higher in number than symptomatic lesions. Asymptomatic and symptomatic lacunes share the same risk factors. White matter change is common in the elderly, with almost 100% prevalence in those aged 85. On the T2-weighted MRI or proton density weighted image, the change is detected by the high intensity signal seemingly produced by a focal increase in the water content following white matter loss. The risk factors for white matter change include hypertension, atherosclerosis, and history of smoking.

Korean recommendations
1. If asymptomatic lacunes or white matter changes are detected on brain MRI in the absence of stroke history, the treatment strategy for primary prevention of stroke should be made by taking concomitant risk factors into account (LOE: IV, GOR: C).
1.4 Aspirin for primary prevention of stroke

Introduction
Aspirin is a prototype antiplatelet of which effects in secondary prevention of cerebrocardiovascular events have been proven by numerous clinical trials. However, a meta-analysis of 5 primary prevention trials which mostly enrolled men failed to demonstrate the benefit of aspirin for reducing stroke although aspirin did reduce the overall cerebrocardiovascular disease. In a recent study exclusively enrolling women, however, aspirin was effective in primary prevention of stroke, particularly for high risk women.

Korean recommendations
1. For both men and women with one or more cerebrocardiovascular risk factors in their mid ages or older, low-dose aspirin (75-325mg, once daily) can be recommended for primary prevention of overall cerebrocardiovascular events (LOE: Ia, GOR: A).
2. In men, aspirin is not recommended for primary prevention of ischemic stroke, but can be recommended for primary prevention of ischemic heart disease (LOE: Ia, GOR: A).
3. In women, aspirin can be recommended for primary prevention of ischemic stroke, but is not recommended for primary prevention of ischemic heart disease (LOE: Ia, GOR: A). The effect of aspirin to prevent ischemic stroke is particularly evident in women aged 65 and over who have 1 or more risk factors among hypertension, dyslipidemia, and diabetes.
4. A long-term, regular use of aspirin significantly increases the risk of bleeding such as cerebral hemorrhage. A thorough individualized evaluation of benefit [preventive effects] and risk [bleeding] profile is reasonable (LOE: Ia, GOR: A). Also notable is the unique epidemiological characteristics in Korea as compared to Western countries where, the incidence of cerebral hemorrhage is relatively high, while the coronary heart disease incidence is relatively low (GPP).
2.1 Stroke care system

2.1.1 Prehospital management and field treatment: EMS/119

**Introduction**
Stroke is a medical - or sometimes surgical- emergency. In a number of studies, use of the national emergency medical service (EMS/119) as an initial response to stroke was associated with a shorter time to hospital and a higher thrombolysis treatment rate compared with other responses. Training of the emergency medical service professionals and systemic patient management are critical to successful stroke care.

**Korean recommendations**
1. Use of the EMS/119 is recommended for transfer of a stroke patient to hospital (LOE: III, GOR: B).
2. The EMS team takes a stroke patient in the shortest time possible to a hospital that provides proper stroke care (GOR: GPP).

2.1.2 Stroke units and stroke centers

**Introduction**
A stroke unit or center is an independent treatment unit made up of multidisciplinary teams, facilities, and guidelines exclusively dedicated to stroke care. They have become increasingly significant for successful stroke care.

**Korean recommendations**
1. It is recommended that stroke patients be treated at a stroke unit or a stroke center (primary or comprehensive) (LOE: Ia, GOR: A).
2.2 Acute evaluation

2.2.1 History taking, physical / neurological exams, and lab tests

Introduction
Acute ischemic stroke is treatable only within a short period of time after onset. A prompt diagnosis and evaluation of the ischemic infarction is critical. Systemic protocols and teams dedicated for stroke care enable a fast decision making along the course of clinical diagnosis, diagnostic tests, and early treatment determination. History taking, physical examinations, and neurological examination represent core evaluations needed for clinical diagnosis. They are ultimately aimed at providing definite diagnosis and checking the patient against indications / contraindications of acute treatments such as recombinant tissue plasminogen activator (rt-PA). Since time is a critical variable in the emergency care, it is recommended that the number of tests for the diagnostic purpose should be limited.

Korean recommendations
1. Hospitals providing stroke care prepare the clinical guidelines for a prompt diagnosis and evaluation of stroke [LOE: IV, GOR: C].
2. The early tests for acute stroke include respiratory rate, pulse, blood pressure, and body temperature as well as neurological examinations [LOE: IV, GOR: C].
3. Use of NIHSS (the NIH Stroke Scale) is recommended for early evaluation of the stroke severity [LOE: III, GOR: B].
4. The basic diagnostic tests for stroke include complete blood counts, blood glucose, electrolytes, renal function, PT-INR, and aPTT [LOE: IV, GOR: C].
5. Clinical heart examinations and 12-lead ECG are performed in all stroke patients [LOE: III, GOR: B].
6. Simple chest X-ray may be selectively used in patients with acute ischemic stroke [LOE: IV, GOR: C].
7. The cerebrospinal fluid (CSF) test may be performed in patients suspected of having subarachnoid hemorrhage that is not detected on CT or MRI [LOE: IV, GOR: C].
8. Electroencephalography (EEG) is recommended in patients having symptoms suggestive of seizures as an early sign or a complication of stroke [LOE: III, GOR: B].
2.2.2 Emergency neuroimaging

Introduction
The brain imaging tests have become increasingly significant with the advance in acute stroke treatment. Findings on the size/location of the lesion, vessel status, and presence of hemorrhage influence the decision of short-term and long-term treatment strategy. They help to assess the salvageable area of ischemic brain tissue, vessels, and cerebral hemodynamics, and determine the target patients for reperfusion by enabling the risk evaluation for hemorrhage or by viewing of the vascular occlusion. CT and MRI may be selected as an early imaging tool.

Korean recommendations
1. A prompt brain imaging test should be performed in patients suspected of having acute stroke (GOR: GPP).
2. In most cases, non-enhanced CT provides critical information for treatment decision in the ER (GOR: GPP).
3. Use of the multi-modality CT or MRI is recommended since they help improve the diagnosis and treatment of acute ischemic cerebral infarction (LOE: Ib, GOR: A).
4. For the intra-arterial drug administration or intervention, the vascular imaging tests (CT angiography, MRA, conventional angiography, and vascular ultrasound) that provide cranio-cervical vascular information are needed (LOE: IIb, GOR: B).
2.3 Acute treatment

2.3.1 General supportive care

2.3.1.1. Airway, ventilator, and oxygen supply

Introduction
Adequate oxygen supply and respiration may be important to maintain the metabolic function of the ischemic penumbra. Infarctions involving large area of brain or brainstem might present with respiratory dysfunction, which could further lead to aspiration pneumonia, heart failure, pulmonary embolism, or aggravation of chronic lung disease. Early intubation for artificial ventilation may be needed in patients with severe respiratory distress, severe hypoxemia / hypercapnea, or impaired consciousness. The evidence is insufficient, however, to recommend a uniform oxygen supply in all patients with cerebral infarction.

Korean recommendations
1. Intubation or, if necessary, mechanical ventilation is recommended in patients with decreased consciousness and/or impaired respiration. Intubation may also be helpful in patients at risk of respiratory failure from bulbar palsy [LOE: IV, GOR: C].
2. A supplemental oxygen supply is not recommended in cerebral infarction without hypoxia [LOE: III, GOR: B].

2.3.1.2. Fever

Introduction
An elevated body temperature increases the metabolic rates, further aggravating the brain tissue damage in acute cerebral infarction. If fever arises in those patients, a thorough test for infection is essential. Adequate use of antibiotics and antipyretics is needed.

Korean recommendations
1. The body temperature of a patient with acute cerebral infarction should be maintained normal as far as possible [LOE: II, GOR: B].
2. If fever exists, the infection site and causative pathogens should be investigated to ensure a proper antibiotic treatment [LOE: IV, GOR: C].
3. If fever exists, reducing body temperature may be helpful [LOE: IV, GOR: C], and antipyretics may be used [LOE: IIa, GOR: B].

2.3.1.3. Cardiac rhythm

Introduction
Cardiac rhythm abnormality is found in up to 15 to 30% of the post-cerebral infarction patients. In most cases, however, it has been there as a risk factor, and the detection is
rather coincidental with the diagnosis of the infarction. There are reports, however, that if a certain area of brain is affected, a secondary cardiac abnormality such as arrhythmia follows. Heart failure, acute MI, and sudden death may be included in the clinical course of cerebral infarction. Maintaining a proper cardiac output, heart rate, and normal blood pressure is essential in the management of stroke.

Korean recommendations
1. Cardiac rhythm monitoring is considered during the acute phase of cerebral infarction [LOE: IV, GOR: C].

2.3.1.4. Blood pressure

Introduction
BP elevation is commonly observed during the acute phase of ischemic cerebral infarction. Proper BP monitoring and control is important. In the ischemic lesions, the autoregulation of cerebral blood flow is disturbed, letting the mean arterial pressure (MAP) have a direct impact on the cerebral blood flow. An abrupt reduction in BP should be avoided, therefore, to ensure an adequate cerebral perfusion. An excessive drop in BP during the acute phase of stroke, though rare, may be treated with fluid supply or inotropic agents.

Korean recommendations
1. For SBP ≤220 mmHg or DBP ≤120 mmHg in acute ischemic stroke, a deferral of aggressive BP lowering is recommended [LOE: IV, GOR: C].
2. If the thrombolytic therapy is under way, BP lowering agents can be used to lower SBP < 185 mmHg and DBP <110 mmHg [LOE: IV, GOR: C].
3. Though a uniform BP lowering is not recommended in acute ischemic stroke, an adequate BP reduction is needed in the following conditions that increase the risk for hypertensive complications: hypertensive encephalopathy, aortic aneurysm with renal artery invasion [LOE: Ia, GOR: A], heart dysfunction, aortic dissection, acute MI, acute renal failure, and intravenous heparin use [LOE: IV, GOR: C].
4. For hypotension occurring in acute stroke patients, the causal analysis is recommended. Hypovolemia, if present, may be corrected with saline supplementation. Correction is also recommended for arrhythmia that reduces cardiac output [LOE: IV, GOR: C].

2.3.1.5. Blood glucose

Introduction
In acute stroke patients, hyperglycemia may be induced by stress or acute illness even without history of diabetes. It might also represent new diagnosis of diabetes or aggravation of existing diabetes by acute illness. Hyperglycemia adversely affects the prognosis of cerebral infarction, whether the patient is diabetic or not, and might require a temporary insulin treatment. Hypoglycemia, on the other hand, might present symptoms similar to cerebral infarction. The differential diagnosis and treatment is needed.
2.3.1.6. Volume expansion, hemorheologic therapy

Introduction
Maintaining cerebral infusion is important to prevent a further infarction progression and to minimize damage to the ischemic penumbra. Some argue that hemodilution may reduce the infarction size by improving cerebral flow to the damaged brain tissue.

Korean recommendations
1. Evidence is insufficient for a uniform recommendation of hemodilution and volume expansion in all acute cerebral infarction patients to improve symptoms or prognosis. Their use may be considered in certain patients, however [LOE: IV, GOR: C].

2.3.2 Prevention and management of medical complications

2.3.2.1. Prophylaxis of deep vein thrombosis

Introduction
While the risk of deep vein thrombosis (DVT) increases with neurological impairment, its clinical expression (as pulmonary embolism, for example) is only in about 1%. Prevention is important since DVT represents an obstacle to recovery from stroke and rehabilitation, and might lead to severe respiratory symptoms.

Korean recommendations
1. Early rehabilitation may be useful for DVT prevention in acute stroke [LOE: III, GOR C].
2. In the high risk groups for DVT, subcutaneous heparin injection may be used, but the increased risk of bleeding should be considered [LOE: Ia, GOR: A]. Low molecular weight heparin (LMWH) may be used in place of heparin [LOE: Ib, GOR: A].
3. Antiplatelets are also moderately effective in prevention of DVT, and they should be used in patients with acute cerebral infarction [LOE: Ia, GOR: A].
4. Though the effects of monotherapy with compressive stockings or pneumatic compression machines on DVT prevention are not clear, their use may be considered as an adjunctive to other treatments if hypercoagulability is suspected or in upper/lower limb paralysis [LOE: IIb, GOR: B].

2.3.2.2. Nutrition

Introduction
In many acute stroke patients, an adequate nutrition intake is hard to achieve because of dysphagia. Dietary nutrition is further limited in unconscious patients due to the risk of aspiration pneumonia. The resulting nutrition imbalance or malnutrition adversely affects the recovery of stroke patients.

Korean recommendations
1. In acute stroke patients, the screening for dysphagia and nutritional status should be performed as early as possible after admission [LOE: IIb, GOR: B].
2. For patients with an inadequate oral nutrition intake, a nasogastric tube should be used for supply of nutrients and medications. While treating dysphagia, periodic reevaluations is required to review the necessity for maintaining the tube (LOE: IIb, GOR: B).
3. Though efforts should be made to restore the nutritional balance in patients with malnutrition, a uniform use of dietary supplements in all stroke patients is not necessary (LOE: Ib, GOR: A).
4. Percutaneous endoscopic gastrostomy may be considered if the nasogastric tube is required for a long time or its maintenance is difficult for other reasons (LOE: IV, GOR: C).

2.3.2.3. Pressure sore

Introduction
Pressure sore is a complication of long-term hospitalization. Once developed, it is hard to treat and likely to prolong the hospitalization. Prevention is very important.

Korean recommendations
1. Frequent examinations for pressure sore are recommended in stroke patients (GOR: GPP).
2. Early mobilization may be helpful in prevention of pressure sore (GOR: C, LOE: IV).
3. If early mobilization is not possible, frequent position changes in bed or use of an air mattress may be considered (GOR: B, LOE: IIb).

2.3.2.4. Aspiration pneumonia

Introduction
Dysphagia in acute stroke often leads to aspiration pneumonia, which is a significant cause of death during the acute phase of stroke.

Korean recommendations
1. If fever arises in stroke patients, the evaluation for aspiration pneumonia is needed before treatment determination (GOR: GPP).
2. Before starting oral feeding, proper screenings (for dysphagia, for example) are needed to identify those at high risk of aspiration pneumonia (GOR: B, LOE: III).
3. If the risk is determined high, the nasogastric tube is recommended over oral feeding (GOR: C, LOE: IV).

2.3.2.5. Urinary tract infection

Introduction
Urinary tract infection or UTI is an important complication of acute stroke, which might adversely affect the neurological prognosis unless detected and treated early.

Korean recommendations
1. If UTI is confirmed, a proper antibiotic treatment is needed (GOR: GPP).
2. Prophylactic use of antibiotics for prevention of UTI is not recommended (GOR: GPP).
3. Bladder catheterization is recommended only if necessary for the shortest possible time (GOR: C, LOE: IV).
2.3.3 Thrombolysis

2.3.3.1. Intravenous thrombolysis

Introduction
Vascular occlusion by thrombus and/or embolus in acute stroke (ischemic infarction) typically presents the ischemic core at the center of the lesion and surrounding ischemic penumbra. The goal of the acute treatment is to salvage the penumbral tissue by restoring blood flow over the occluded blood vessels. Thrombolysis is an aggressive therapy to help revascularization, but also innate with the risk of serious cerebral hemorrhage. Screening of potential beneficiaries is important in this regard. Treatment with recombinant tissue plasminogen activator (rt-PA) was approved by the US FDA in 1995 with the NINDS rt-PA study.

Korean recommendations
1. In the ischemic stroke patients who arrive at the hospital within 3 hours from onset, use of rt-PA should be considered (LOE: Ia, GOR: A).
2. For the use, hemorrhage should be excluded by the imaging tests. Treatment with rt-PA should be based on the Indications below.

1. Ischemic stroke with definite neurological deficit.
2. Neurological deficit with no spontaneous improvement.
3. Neurological deficit that is not too mild.
5. Treatment is best started within 3 hours from the onset.
6. No head trauma or stroke within the past 3 months.
7. No myocardial infarction within the past 3 months.
8. No gastrointestinal or urinary tract bleeding within the past 3 weeks.
9. No major surgery within the past 2 weeks.
10. No arterial puncture at a noncompressible site within the past 7 days.
11. No history of intracranial hemorrhage.
12. Blood pressure controlled at SBP ≤ 185mmHg and DBP ≤ 110mmHg.
13. No signs of bleeding or trauma (including fractures) on physical examination.
14. Oral anticoagulants not in use or INR ≤ 1.7 if in use.
15. aPTT maintained normal in case of heparin use within the past 48 hours.
16. Platelet counts ≥ 100,000mm3.
17. Blood glucose levels ≥ 50mg/dL (2.7mmol/L).
18. No post-seizure status with neurological deficit.
19. No multilobar infarction with the low attenuation lesion on CT taking up more than 1/3 of the hemisphere.
20. Patients and caregivers should be aware of the benefits and risks associated with the treatment.
3. The rt-PA Treatment is associated with a significant increase in cerebral hemorrhage over non-treatment. The risk should be fully understood (LOE: Ia, GOR: A).
4. Intravenous streptokinase significantly increase the risk of hemorrhage and should be avoided (LOE: Ia, GOR: A).
5. Other than rt-PA, the effects of intravenous thrombolitics (urokinase, tenecteplase, and desmoteplase) have not been proven (LOE: IV, GOR: C).
6. The intravenous rt-PA treatment should start as early as possible following the evaluation of indications and contraindications (LOE: Ia, GOR: A).

2.3.3.2. Intra-arterial thrombolysis

Introduction
Compared with the intravenous route, the intra-arterial thrombolysis (IAT) is associated with a higher revascularization rate. Its efficacy was demonstrated in the PROACT II study using pro-urokinase. The prospective, randomized, phase III clinical trial, however, failed to obtain the FDA approval. Other large-scale controlled clinical trials on IAT are scarce in number. Nonetheless, the procedure is of a wide clinical use for stroke care in many countries.

Korean recommendations
1. IAT may be considered in patients with middle cerebral arterial or internal carotid arterial occlusion within the past 6 hours who are not eligible for (GOR: A, LOE: Ib) or contraindicated to (GOR: B, LOE: III) the intravenous thrombolysis (IVT) for reasons such as major surgery.
2. The IAT-performing institutions should have the cerebral angiography devices ready for immediate mobilization and well-trained vascular interventionalists. They are advised to prepare specific guidelines to improve decision making by the IAT specialists (GOR: B, LOE: III).
3. IAT may be used in patients with posterior circulation stroke such as basilar artery occlusion, according to the internal standards of each institution (GOR: C, LOE: IV).

2.3.4 Antiplatelet agents

Introduction
Ischemic stroke is mostly due to cerebral vascular occlusion by thrombus or embolus. Use of aspirin during the acute phase is expected to decrease death, disability, recurrence, and other cardiovascular events associated with ischemic stroke.

Korean recommendations
1. In the hemorrhage-excluded, acute ischemic stroke patients, the oral administration of aspirin should start within 24 to 48 hours of onset [the loading dose 160-300mg] (LOE: Ia, GOR: A).
2. Aspirin can not replace acute interventions including IVT (LOE: Ia, GOR: A).
3. Aspirin should not be taken within 24 hours of thrombolysis (LOE: Ia, GOR: A).
4. Intravenous injection of the glycoprotein IIb/IIIa receptor antagonists, including abciximab, is not recommended in patients with acute ischemic stroke (LOE: Ib, GOR: A).
2.3.5 Anticoagulants

Introduction
Though anticoagulants are widely used for the prophylactic treatment of ischemic stroke, their usefulness in acute patients is still controversial. No consensus has been made on what to choose, when and how to administer, how much to give, or how long. Evidence from the large-scale, controlled studies so far has been insufficient to support use of anticoagulants as a treatment of acute ischemic stroke.

Korean recommendations
1. There is no scientific evidence on the usefulness of heparin used within 48 hours of ischemic cerebral infarction. It might increase the risk of bleeding, compared with aspirin (LOE: Ia, GOR: A).
2. LMWH or heparinoids is not recommended as an early treatment of cerebral infarction (LOE: Ia, GOR: A).
3. Use of anticoagulants within 24 hours of rt-PA administration is not recommended (LOE: IIa, GOR: B).

2.3.6 Neuroprotectants

Introduction
A number of different neuroprotectants whose effects were shown in animal experiments have failed to demonstrate efficacy in clinical trials. The large-scale randomized controlled trials (RTCs) of NMDA receptor antagonists, calcium channel blockers, magnesium, free radical scavengers, cell membrane stabilizers, and therapeutic hypothermia all have failed to prove efficacy. While the causal analysis is needed, clinical trials are under way to investigate the possibility of a shortened treatment duration or improved efficacy of combinations.

Korean recommendations
1. Treatment with neuroprotectants during the acute phase of ischemic cerebral infarction is not recommended in general (LOE: Ia, GOR: A).

2.3.7 Treatment of neurologic complications

2.3.7.1. ICP elevation, brain edema and hemorrhagic transformation

Introduction
Brain edema is usually seen within 24 to 48 hours of cerebral infarction. Edema in a gross infarction invading the cerebral hemisphere or cerebellum causes ICP elevation and herniation, leading to loss of consciousness and even death in severe cases.

Korean recommendations
1. A gross cerebral infarction invading the cerebral hemisphere or cerebellum is highly likely
to cause brain edema and ICP elevation. A close, intensive monitoring is reasonable to reduce the edema and prevent a neurological aggravation (LOE: III, GOR: B).

2. If hydrocephalus is caused by the cerebellar infarction or for other reasons, the extraventricular drainage is needed to reduce ICP (LOE: III, GOR: B).

3. Surgical decompression is needed if the signs of brainstem compression arise in a large cerebellar infarction (LOE: III, GOR: B).

4. Different medical decompressions, including osmotherapy, may be used to treat the malignant edema following cerebral infarction. The effects of hyperventilation are short-lasting, and the prognosis is unclear. Medical decompressions may delay the need for surgery (LOE: III, GOR: B).

5. Surgical decompression for malignant edema caused by the hemispheric infarction might save lives as well as achieving neurological improvement. Determinants of the surgery include age and location of the lesion (the non-dominant or dominant hemisphere). Surgery may be recommended in severe patients, but a thorough discussion with the patient is needed about the risk of unfavorable outcomes such as lifetime disability (LOE: IIa, GOR: B).

6. No particular treatment exists for asymptomatic hemorrhagic transformation following cerebral infarction. Symptomatic hemorrhagic transformation is treated according to the treatment guidelines for cerebral hemorrhage. BP control may be considered to reduce the risk of hemorrhagic transformation following thrombolysis or carotid stent placement (LOE: IV, GOR: C).

7. Use of the routine-dose or high-dose corticosteroids aimed at ICP reduction is not recommended in cerebral infarction because of uncertain effects and the increased risk of infection (LOE: Ib, GOR: A).

2.3.7.2. Seizures

Introduction
Seizures in acute stroke are mostly focal and develop within 24 hours of the onset. Secondary generalized seizures are not unusual. While intermittent seizures are believed unassociated with the stroke prognosis, status epilepticus, though rare, might threaten lives.

Korean recommendations
1. A uniform anticonvulsant prophylaxis is not considered in patients with no post-stroke seizures (LOE: IV, GOR: C).
2. Early seizures in acute stroke may be treated in the same way as the seizures occurring in the acute phase of other neurological disorders (LOE: IV, GOR: C).
3. The anticonvulsant treatment may be considered if early seizures are likely to worsen the stroke or progress into status epilepticus (LOE: IV, GOR: C).
4. For a lobar hemorrhage, a prophylactic use of anticonvulsants for about 1 month and a gradual discontinuation thereafter may be considered if no seizure is observed (LOE: IV, GOR: C).
2.4 Treatment of intracerebral hemorrhage

2.4.1 Medical treatment of intracerebral hemorrhage

2.4.1.1. ICP control

Introduction
According to the Western reports, cerebral hemorrhage accounts for 10-15% of total stroke, with 30-day mortality of 35-52% and half the deaths occurring within the first 2 days. ICP elevation and brain edema following cerebral hemorrhage are associated with high mortality. The brain tissue damage and shifts following hemorrhage induces ICP elevation. Further clinical aggravation is caused by hemorrhage expansion, edema or ischemia in the surroundings, hydrocephalus, or secondary intracranial hemorrhage. In some patients with an elevated ICP and decreased consciousness, close ICP monitoring is needed. Medical decompression needs to take precedence over surgery.

Korean recommendations
1. Treatment and monitoring at the intensive care unit (ICU) is recommended in acute hemorrhage patients because of the need for ICP elevation monitoring, BP control, intubation, and mechanical ventilation (LOE: III, GOR: B).
2. For control of an elevated ICP, a gradual treatment is considered. The patient head should be elevated by about 30° for a start. Limited use of analgesics and/or sedatives may be considered in patients with pain and/or unstable conditions (LOE: IV, GOR: C).
3. A more aggressive ICP control includes use of mannitol and hypertonic saline solution, CSF drainage via the ventricular catheter, neuromuscular blockade, and hyperventilation. In general, maintaining CPP at ≥ 70 mmHg is recommended along with a close monitoring of ICP and blood pressure (LOE: IV, GOR: C).

2.4.1.2. Medical treatment of the anticoagulant-associated intracerebral hemorrhage

Introduction
If intracerebral hemorrhage occurs in patients on anticoagulants such as warfarin or heparin, the increase in PT-INR (prothrombin time-international normalized ratio) or aPTT (activated partial thromboplastin time) is correlated with the hematoma enlargement and prognosis. A prompt correction is imperative.

Korean recommendations
1. In the heparin-induced intracerebral hemorrhage, heparin should be discontinued immediately. Protamine sulfate may be considered to reverse the effects of heparin (LOE: IV, GOR: C).
2. In the warfarin-induced intracerebral hemorrhage, warfarin should be discontinued immediately. Intravenous vitamin K may be considered to reverse the effects of warfarin,
together with the coagulation factor replacement (LOE: IV, GOR: C).
3. Prothrombin complex concentrates, factor IX complex concentrates, and recombinant factor VIIa normalize the INR more rapidly with a smaller volume, compared with fresh frozen plasma. They may be used to correct the clotting abnormalities in intracerebral hemorrhage, but also present the risk of thromboembolism. Fresh frozen plasma may be recommended as an alternative, but it requires a slow, large-volume infusion (LOE: IV, GOR: C).

2.4.1.3. Blood pressure management after intracerebral hemorrhage

Introduction
BP control in acute cerebral hemorrhage should be individualized to presence / absence of chronic hypertension, ICP elevation, age, cause of hemorrhage, and the time of onset in each patient. Despite some disagreement, treating hypertension is generally recommended in acute cerebral hemorrhage in order to prevent re-bleeding from the ruptured small arteries.

Korean recommendations
1. The following guidelines are recommended for BP control in acute intracerebral hemorrhage (LOE: III, GOR: B).

Table 1. Treatment guidelines for hypertension in spontaneous intracerebral hemorrhage

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Bolus dose</th>
<th>Infusion rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labetalol</td>
<td>5-20mg, every 15 minutes</td>
<td>2mg/min (up to 300mg/day)</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>No indication</td>
<td>5-15mg/hour</td>
</tr>
<tr>
<td>Esmolol</td>
<td>250μg/Kg, loading dose</td>
<td>25 - 300μg/Kg per minute</td>
</tr>
<tr>
<td>Enalapril</td>
<td>1.25 - 5 mg, every 6 hours</td>
<td>No indication</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>5 - 20mg, every 30 minutes</td>
<td>1.5 - 5μg/Kg per minute</td>
</tr>
<tr>
<td>Nipride</td>
<td>No indication</td>
<td>0.1 - 10μg/Kg per minute</td>
</tr>
<tr>
<td>Nitroglycerine</td>
<td>No indication</td>
<td>20 - 400μg/min</td>
</tr>
</tbody>
</table>

For enalapril, the first test dose of 0.625mg is recommended to avoid excessive drop in BP.
2.4.2 Surgical treatment of intracerebral hemorrhage

Introduction
The ideal surgical treatment of intracerebral hemorrhage involves minimization of the brain damage associated with the surgery itself and a fast removal of the largest hematoma possible. Many different surgery methods, either tried or being developed, are available. In some cases, conservative treatment might have priority over surgery, depending on the location and size of the hemorrhage. Clear guidelines are needed in this regard. Though guidelines are also needed on an intracerebral hemorrhage secondary to cerebral aneurysm or cerebral arteriovenous malformation that requires surgical removal too, only primary intracerebral hemorrhage is focused in the present CPG.

Korean recommendations
1. If cerebral herniation is suspected or if loss of consciousness is rapid, early craniotomy may be considered [LOE: IV, GOR: C].
2. Craniotomy is considered for a lobar hemorrhage located within 1 cm from the surface with the consciousness level of GCS 9-12 [LOE: IIb, GOR: B].
3. Craniotomy is recommended for a cerebellar hemorrhage of ≥ 3 cm in diameter or for symptoms suggestive of the brainstem compression or hydrocephalus [LOE: IIb, GOR: B].
4. For hemorrhages located deep inside the brain, a non-craniotomy surgery may be considered [LOE: IV, GOR: C].
5. For intraventricular hemorrhages, thrombolysis via the ventricular puncture may be considered [LOE: IV, GOR: C].

2.4.1.4. Seizure prevention and treatment

Introduction
In general, the rate of epilepsy is higher following intracerebral hemorrhage than ischemic stroke. Epilepsy requires a proper treatment since it might worsen the neurological conditions or increase the midline shifting.

Korean recommendations
1. Post-cerebral hemorrhage seizures should warrant use of proper anticonvulsants [LOE: Ib, GOR: A].
2. A short-term use of anticonvulsants immediately following a lobar hemorrhage may decrease the risk of early seizures and is recommended [LOE: IIa, GOR: B].
3. Anticonvulsants used in cerebral hemorrhage should be gradually discontinued if no recurrence is observed. In case of recurrence, a chronic therapy may be considered [LOE: IV, GOR: C].
2.5 Rehabilitation in acute stroke

2.5.1 Timing of rehabilitation

Introduction
Early rehabilitation in stroke is known to prevent complications such as DVT, joint contracture, and pressure sores. It also improves functional recovery in the transfer activity or activity of daily living. Rehabilitation should begin, therefore, once the patients regain medical and neurological stabilization. The exact timing might be influenced by the severity of stroke and neurological status in each patient. Therapy intensity should be individualized, too.

Korean recommendations
1. Rehabilitation therapy in an acute stroke patient should begin as early as possible once the patient is medically stabilized [LOE: Ia, GOR: A].

2.5.2 Intensity of rehabilitation

Introduction
Intensity of the post-stroke rehabilitation might be affected by variables such as patient compliance, degree of the brain damage, medical stabilization, and cognitive/motor impairment. While determining the intensity is important, it is difficult to standardize the intensity or to quantify different components of the rehabilitation therapy.

Korean recommendations
1. In stroke patients, an adequate rehabilitation therapy within the patient adaptability is recommended for functional recovery [LOE: Ia, GOR: A].
2. A continuous and repetitive use of the skills learned from rehabilitation is recommended [LOE: Ia, GOR: A].

2.5.3 Underlying approach to rehabilitation

Introduction
Many different rehabilitation techniques have been tried to reduce the impairment with and improve the functions for daily activities. They can be classified by the type of stimulations, specificity of trainings, or difference in the learning principles applied. It is very significant that all members of the rehabilitation team recognize the importance of a consistent approach to rehabilitation and to provide it in a way to maximize the functional recovery. Motor re-learning and many other techniques are currently available, but comparative analysis is difficult due to the wide variability in the makeup or outcomes of different rehabilitation techniques.
Korean recommendations
1. An individualized combination and application of the rehabilitation techniques including motor re-learning, neurophysiological approach, and biomechanics is recommended for motor function improvement [LOE: Ia, GOR: A].
2. Involvement of patients and caregivers in the rehabilitation goal setting is recommended [LOE: IIb, GOR: B].
3. Rehabilitation goals should be set both in the short and long terms. Achievement evaluation and goal resetting are considered [LOE: IV, GOR: C].

2.5.4 Prevention of complications

Introduction
Common post-stroke complications include pressure sore, aspiration pneumonia, joint contracture, falls and fractures, and pain. Once developing, they undermine rehabilitation, adversely affecting the prognosis. An effective prevention of potential complications will contribute to a great degree to improving the outcomes of rehabilitation.

Korean recommendations
1. The post-stroke pressure sore compromises functional recovery. Preventive measures are reasonable [LOE: III, GOR: B].
2. Periodic skin evaluations, right postures, and frequent position changes are considered for prevention of pressure sore [LOE: IV, GOR: C].
3. Maintaining the right postures is recommended for prevention of the post-stroke joint contracture [LOE: Ia, GOR: A].
4. Early mobilization is recommended for prevention of the post-stroke complications including joint contracture, aspiration pneumonia, central pain, and DVT [LOE: III, GOR: B].
5. Risk evaluation for falls and fractures is recommended in stroke patients [GOR: GPP].
6. Evaluation of the pain arising in stroke patients is needed [GOR: GPP].
Secondary prevention of stroke
3.1. Risk factor management

3.1.1 Hypertension

Introduction
Primary prevention of stroke by hypertension treatment was shown to be 30 to 40% risk reduction of stroke in randomized controlled trials (RCTs). Nonetheless, evidence is relatively insufficient for hypertension treatment aimed at secondary prevention of stroke. A large-scale meta-analysis of the RCTs showed that hypertension treatment in stroke patients significantly lowered the mortality and recurrence of stroke and other cardiovascular events.

Korean recommendations
1. In patients with stroke or TIA, antihypertensive treatment beyond the hyperacute phase reduces recurrent stroke and other cardiovascular events (LOE: Ia, GOR: A). The benefit of antihypertensive treatment is independent of prior history of hypertension. Adequate BP control is therefore recommended in all patients with stroke (LOE: Ib, GOR: A).
2. Determination of the antihypertensives and target BP should be individualized after taking into account of characteristics of patient such as steno-occlusion in intra- and extracranial vessels, diabetes, and renal disease (LOE: IV, GOR: C).
3. Although selection of the antihypertensives after stroke or TIA is still controversial because of insufficient evidence, combination therapy of ACE inhibitors with diuretics may be considered (LOE: Ib, GOR: A).
4. For an adequate BP control, drug therapy should be accompanied by lifestyle modifications (LOE: IV, GOR: C).

3.1.2 Diabetes

Introduction
The prevalence of diabetes is 15 to 33% of patients with ischemic stroke. Diabetes is an important predictor of stroke recurrence and is also known to be highly associated with the multiple lacunar infarction. Several clinical trials have shown that blood glucose control reduced the risk of microvascular complications. Accordingly, most of practice guidelines for secondary prevention of stroke and cardiovascular events are recommending blood glucose control. Evidence is limited, however, on the effect of blood glucose control on macrovascular complications.

Korean recommendations
1. For prevention of microvascular (LOE: Ia, GOR: A) and macrovascular (LOE: Ila, GOR: B) complications in stroke patients with diabetes, rigorous glucose control to near normal level is recommended.
2. A target HbA1c level of 7% or less would be reasonable (LOE: IIb, GOR: B).
3.1.3 Hyperlipidemia

**Introduction**

Hyperlipidemia is an important risk factor of coronary arterial disease (CAD), but its association with stroke has not been clear. The diverse stroke mechanisms in addition to the similar one to CAD mechanism might attribute to this unclear association. For hemorrhagic stroke, a number of cohort studies have suggested that low cholesterol levels were associated with an increased incidence and mortality of hemorrhagic stroke. The suggestion is particularly notable for Korea that has more hemorrhagic stroke patients compared with western countries. On the other hand, hyperlipidemia is considered an important risk factor of ischemic stroke, particularly for atherosclerotic stroke, as demonstrated by many statin clinical trials. In addition to reducing cholesterol levels, statins might have pleiotropic effects.

**Korean recommendations**

1. Hyperlipidemia in patients with TIA or ischemic stroke should be treated. For patients with atherosclerotic ischemic stroke or in ischemic stroke with CAD co-morbidity, treatment should follow the NCEP-ATP III guidelines. Lifestyle modification, diet control, and drug therapy should be combined. For drug therapy, use of statins is recommended (LOE: Ia, GOR: A).
2. In symptomatic atherosclerotic ischemic stroke or ischemic stroke coexisting with CAD, the target LDL cholesterol is < 100mg/dL (LOE: Ia, GOR: A).
3. For high risk patients with multiple risk factors, a more aggressive treatment might be considered (LOE: Ia, GOR: A).

3.1.4 Smoking

**Introduction**

Smoking is a major independent risk factor for ischemic stroke in all ages, genders, and races. Compared with non-smokers, the risk of stroke almost doubles in smokers. The mechanism for the increased risk of stroke includes hemodynamic changes and atherosclerotic vascular stenosis.

**Korean recommendations**

1. Smoking cessation should be strongly recommended in stroke patients who smoke (LOE: IV, GOR: C).
2. Avoidance of secondary smoking should also be recommended in stroke patients (LOE: IIb, GOR: B).

3.1.5 Alcohol

**Introduction**

Alcohol drinking is one of the independent risk factors for stroke. Hypertension, hypercoagulability, drop in cerebral blood flow, and atrial fibrillation might be related to the increased risk.

**Korean recommendations**

1. Stroke patients with heavy alcohol consumption should be recommended to stop or to reduce their drinking to less than 1 (for non-pregnant women) or 2 (for men) drinks per day (LOE: IV, GOR: C).
### 3.1.6 Obesity

**Introduction**

Obesity and overweight are considered to be associated with stroke. The increase of stroke risk is proportional to the increase of obesity.

**Korean recommendations**

1. Weight gain is associated with the increased risk of stroke in a dose-response relationship. An aggressive weight reduction is recommended in the overweight or obese patients (LOE: IV, GOR: C).

### 3.1.7 Physical activity and exercise

**Introduction**

Studies have suggested that physical activity might be inversely related to the risk of stroke, but data from well-designed controlled trials are lacking. Physical activity and exercise are known to curb the risk of stroke by reducing the risk factors.

**Korean recommendations**

1. Physical activity and exercise might reduce the risk of stroke through blood pressure reduction, weight loss, and changes in blood cholesterol levels. Therefore, regular exercise is recommended (LOE: IV, GOR: C).

### 3.1.8 Diet

**Introduction**

Numerous studies have shown that dietary habits are associated with the risk of stroke. A sufficient intake of fruits and vegetables is known to reduce the risk of stroke. Minerals intake such as high sodium and low potassium intake are also associated with the increased stroke risk.

**Korean recommendations**

1. Reducing daily sodium intake and increasing potassium intake is recommended for stroke prevention (GOR: GPP).
2. A sufficient intake of fruits and vegetables may be beneficial for stroke prevention (GOR: GPP).

### 3.1.9 Hyperhomocysteinemia

**Introduction**

Hyperhomocysteinemia might contribute to the development of atherosclerosis that leads to stroke and CAD. It is not clear, however, whether vitamins such as folic acid that reduce blood homocysteine levels decrease the risk of stroke.

**Korean recommendations**

1. For ischemic stroke or TIA patients with hyperhomocysteinemia, homocysteine-lowering vitamins might be considered, given their low cost and treatment-associated risk as compared to those of other risk factors control (LOE: IV, GOR: C).

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**Secondary prevention of stroke**
3.2. Antithrombotic therapy for
noncardioembolic stroke or TIA

3.2.1 Antiplatelet therapy

3.2.1.1. Aspirin

Introduction
Use of the low-dose aspirin is known effective in prevention of the thrombotic and embolic cerebral infarction. The acetyl group of aspirin binds to platelet membranes, irreversibly inhibiting cyclooxygenase and thromboxane A2 synthesis. Aspirin exerts effects, via these mechanisms, to prevent the recurrence of occlusive arterial diseases such as MI, cerebral infarction, and peripheral vascular disease.

Korean recommendations
1. Aspirin (50-300mg daily) can be recommended for prevention of recurrent ischemic symptoms in patients with noncardioembolic ischemic stroke and TIA (LOE: Ia, GOR: A).

3.2.1.2. Thienopyridines

Introduction
Ticlopidine and clopidogrel are thienopyridine antiplatelets used for secondary prevention of stroke in patients with non-cardioembolic ischemic stroke. They can be used as an initial therapy for secondary prevention along with aspirin monotherapy. Since ticlopidine is potentially associated with serious complication of neutropenia, clopidogrel has a better safety profile.

Korean recommendations
1. Clopidogrel monotherapy may be an initial therapy in noncardioembolic ischemic stroke, along with aspirin monotherapy and the aspirin plus extended-release dipyridamole combination (LOE: Ib, GOR: A).
2. Clopidogrel and other alternatives are recommended in patients with aspirin hypersensitivity (LOE: Ib, GOR: A).
3. Although ticlopidine might be superior to aspirin for secondary stroke prevention (LOE: 1b, GOR: A), caution is required, however, for the risks of neutropenia (LOE: Ib, GOR: A).

3.2.1.3. Other antiplatelet agents: triflusal, dipyridamole, and cilostazol

Introduction
Antiplatelets are used for secondary prevention of noncardioembolic ischemic stroke. In addition to aspirin and clopidogrel, other agents such as triflusal and cilostazol have been approved and widely used for secondary stroke prevention in Korea. Both of the agents have different mechanisms or sites of action from those of aspirin and clopidogrel, and have been reported to have a lower risk of bleeding. The combination of extended-release dipyridamole and aspirin was superior to aspirin in secondary prevention of stroke, it is not available in Korea.
Korean recommendations
1. The combination of low-dose aspirin and extended-release dipyridamole can be an initial therapy for secondary prevention of stroke (LOE: Ib, GOR: A).
2. Triflusal and cilostazol may be considered for secondary stroke prevention if aspirin or clopidogrel is difficult to use (LOE: II, GOR: B).
3. Triflusal may be recommended for secondary prevention of stroke in patients who are at risk of serious bleedings such as cerebral hemorrhage, but require antiplatelet therapy (LOE: Ib, GOR: A).

3.2.2 Anticoagulation

Introduction
Previous studies have investigated whether anticoagulants have an equal or greater efficacy in preventing secondary stroke when compared to antiplatelets in patients with noncardioembolic ischemic stroke or TIA. However, so far, clinical trials of oral anticoagulants have failed to demonstrate a superior efficacy to the antiplatelets in secondary stroke prevention while showing higher rates of serious bleeding complications.

Korean recommendations
1. For prevention of the recurrent noncardioembolic ischemic stroke or TIA, anticoagulants are recommended over oral anticoagulants (LOE: Ia, GOR: A).

3.2.3 Use of antiplatelets in specific conditions

3.2.3.1. Recurrent ischemic stroke during antiplatelets use

Korean recommendations
1. The combination of low-dose aspirin and extended-release dipyridamole can be an initial therapy for secondary prevention of stroke (LOE: Ib, GOR: A).
2. Triflusal and cilostazol may be considered for secondary stroke prevention if aspirin or clopidogrel is difficult to use (LOE: II, GOR: B).
3. Triflusal may be recommended for secondary prevention of stroke in patients who are at risk of serious bleedings such as cerebral hemorrhage, but require antiplatelet therapy (LOE: Ib, GOR: A).

3.2.1.4. Antiplatelet combination therapy

Introduction
Antiplatelets with different mechanisms of action have been combined to prevent more effectively the recurrence of noncardioembolic ischemic stroke or TIA. While the aspirin plus dipyridamole combination significantly decreased the recurrence of ischemic stroke and TIA, the clopidogrel plus aspirin combination has shown rather disappointing results of increased bleeding complications except for in patients who have both ischemic stroke and ischemic heart disease. Research is still ongoing to identify a better antiplatelet combination that could provide a more effective prevention of the recurrence and that can be used for patients who had stroke during antiplatelet monotherapy.

Korean recommendations
1. Compared with the aspirin monotherapy, the aspirin plus extended release dipyridamole combination may be more effective in preventing the recurrence of noncardioembolic ischemic stroke or TIA (LOE: Ia, GOR: A).
2. The clopidogrel + aspirin combination may be effective in secondary prevention of stroke in some stroke patients with CAD (unstable angina or non Q-wave MI). The risk of intracranial hemorrhage should be considered, however (LOE: Ia, GOR: A).
3. Cilostazol may be considered in patients with symptomatic intracranial arterial stenosis (LOE: III, GOR: B).
Introduction
If ischemic stroke recurs in patients already taking antiplatelets, the acceptable treatment options include a switch to other antiplatelets with different modes of action or add-on of a new antiplatelet. The decision requires a comprehensive review of data of efficacy and side effects which were reported by recent clinical trials of combination antiplatelet therapies. Selection of antiplatelets should be individualized based on risk factors, clinical characteristics, and drug tolerability of each patient.

Korean recommendations
1. Evidence is lacking for increasing aspirin dose in patients with recurrent ischemic stroke who have been already taking aspirin. Also, data are lacking for switching to another antiplatelet or combination therapy in these patients. Therefore, selection of antiplatelet(s) should be individualized based on patients’ clinical characteristics and drug-specific risks (LOE: IV, GOR: C).

2. Based on physician’s discretion and individual patients’ profiles, the fixed-dose combination of aspirin and extended release dipyridamole may be used following stroke recurrence in patients with non-cardioembolic stroke who are already taking aspirin for secondary prevention. If the extended release dipyridamole cannot be used, clopidogrel monotherapy may be used as an alternative. Data for use of other antiplatelets in this clinical setting are insufficient (LOE: IV, GOR: C).

3. For patients with non-cardioembolic ischemic stroke who have been already taking non-aspirin antiplatelets, data from clinical trials are lacking to recommend a specific antiplatelet therapy for secondary stroke prevention (LOE: IV, GOR: C).

3.2.3.2. Ischemic stroke with cerebral hemorrhage

Introduction
There is no clear evidence on the efficacy and safety of the antithrombotics in patients with ischemic stroke coexisting with hemorrhage. Cerebral infarction can develop in patients with a previous cerebral hemorrhage, and the post-thrombolysis cerebral hemorrhage may develop in relation to the previous hemorrhage. The uncertainty of clinical evidence spells the need for further clinical studies. In patients with AF coexisting with a lobar hemorrhage or a deep hemorrhage, use of anticoagulants should weigh between the recurrence of hemorrhage and the risk of ischemia, with the greatest concern given to the patient quality of life. Use of antiplatelets following cerebral hemorrhage should be considered only in those at low risk of re-bleeding. With the advance in the brain imaging technology, cerebral microbleeds are increasingly detected by the low signal intensity lesions on the gradient-echo MRI. In most cases, they are suggestive of clinically asymptomatic microvascular bleedings. The association of the antithrombotic treatment with cerebral microbleeds is still controversial, and further prospective research is needed.

Korean recommendations
1. Determining whether to resume the antithrombotic treatment or not following cerebral hemorrhage should be based on the risk of thrombosis, re-current hemorrhage, and the overall risk profile in each patient (LOE: IV, GOR: C).

2. In patients with the anticoagulation-associated cerebral hemorrhage, the anticoagulants might be switched into antiplatelets in patients with low risk of recurrent thromboembolism or high risk of bleeding tendency. The anticoagulation therapy should resume, however, if the risk of cerebral emolism is clearly high. Timing of the re-administration may be 7 to 10 days later from the cerebral hemorrhage (LOE: III, GOR: B).

3. Reliable studies about the relation between microbleeds and antithrombotics have not been reported. Therefore, the restrictions for using antithrombotics in patients with microbleeds on MR imaging should not be necessary (LOE: IV, GOR: C).
3.3. Antithrombotic therapy for cardioembolic stroke or TIA

3.3.1 Anticoagulants

Introduction
While cardioembolic stroke is shown to represent about 20% of ischemic stroke in western countries, the prevalence of cardioembolic stroke from hospital-based stroke registry in Korea is reportedly lower. Though the exact pathologic mechanism in each patient is hard to identify, cardioembolic stroke is generally suspected in ischemic stroke patients with a heart abnormality associated with a high risk of embolism. A list of such conditions is provided in the Table below. The patients with these cardiac conditions have been predicted to show the annual rate of ischemic stroke \( \geq 2\% \).

Table. Cardiac conditions to increase the risk of ischemic stroke

- Left atrial thrombus
- Left ventricular thrombus
- Atrial fibrillation
- Paroxysmal atrial fibrillation
- Sick sinus syndrome
- Sustained atrial flutter
- Recent myocardial infarction, within 1 month
- Rheumatoid mitral or aortic valve disease
- Bioprosthetic and mechanical heart valves
- Chronic myocardial infarction with a low ejection fraction of less than 28%
- Symptomatic congestive heart failure with an ejection fraction of less than 30%
- Dilated cardiomyopathy
- Nonbacterial thrombotic endocarditis

Korean recommendations
1. Because patients with stroke or TIA coexists with potential sources of cardioembolism might have higher possibility of recurrent cardioembolic stroke or TIA, unless contraindicated, warfarin treatment (INR 2.0-3.0) should be recommended (LOE: III, GOR: C, GPP).

3.3.2 Antiplatelet therapy or combination therapy

Introduction
Warfarin is known as the first-line preventive treatment for cardioembolic stroke, especially in patients with AF. If the patients are contraindicated to anticoagulation or if ischemic stroke recurs despite an adequate anticoagulation therapy, the following options may be considered; increasing the anticoagulation strength, switching to antiplatelets, or combining with antiplatelets.
Korean recommendations
1. In patients with cardioembolic ischemic stroke or TIA in whom the anticoagulation therapy cannot be used, aspirin can be considered for secondary prevention (GOR: GPP).

3.3.3 Treatments for stroke patients with other specific conditions

3.3.3.1. Atrial fibrillation

Introduction
About 16% (11% to 29%) of cerebral infarction is reported attributable to nonvalvular AF in western countries.\(^1\)\(^-\)\(^4\) The prevalence rate is relatively low in Korea at 8.4%, according to the hospital-based epidemiological data published in 1993 in Korea.\(^5\) Nonetheless, stroke occurrence in AF patients is reported at an annual rate of \(\approx 4.5\%\),\(^6\) and the rate of recurrence is particularly high at 12% in those with previous stroke due to AF. Risk factors such as advanced age, congestive heart failure, hypertension, diabetes, and previous thromboembolism further increases the risk. AF now has a greater implication than ever before in rapidly aging society including Korea since its prevalence markedly increases with age.\(^8\)

Korean recommendations
1. Warfarin treatment (INR 2.0 - 3.0) is recommended, unless contraindicated, in patients with ischemic stroke or TIA coexisting with sustained or paroxysmal AF (LOE: Ia, GOR: A).
2. If anticoagulants cannot be used, aspirin can be used instead (LOE: Ia, GOR: A). A recommended daily dose of aspirin is 325mg. In Korea, a prescribable dose of 300mg may be considered (LOE: IV, GOR: GPP).
3. For the recurrence of ischemic stroke or TIA in the AF patients already receiving adequate anticoagulation therapy, increasing the therapeutic target to INR 2.5-3.5 or initiating a combination with antiplatelets may be considered (LOE: IV, GOR: C).

3.3.3.2. Congestive heart failure

Introduction
Cardiomyopathy with a low left ventricular ejection fraction (LVEF) is known as a cause for cardiogenic ischemic stroke. Cardiomyopathy is classified into ischemic cardiomyopathy resulting from CAD and non-ischemic dilated cardiomyopathy. The lower the LVEF, the higher the risk of stroke. Therefore, aggressive secondary prevention of stroke is required in congestive heart failure with a low LVEF.

Korean recommendations
1. Warfarin or antiplatelets may be considered for secondary prevention of stroke in cardiomyopathy with a low LVEF (GOR: GPP).
3.3.3.3. Acute myocardial infarction

Introduction
Acute myocardial infarction (MI) with the left ventricular thrombus is one of the major risk factors of cardioembolic ischemic stroke. Ischemic stroke is more frequently developed during the acute phase of anterior wall MI.

Korean recommendations
1. In patients with ischemic stroke or TIA following acute MI with left ventricular thrombus, warfarin treatment (INR 2.0 - 3.0) of 3 to 12 months is reasonable, unless contraindicated (LOE: IIa, GOR: B).
2. Aspirin should continue throughout anticoagulation treatment (LOE: Ia, GOR: A).

3.3.3.4. Valvular heart disease

Introduction
Embolism recurs in 30-65% of the patients with rheumatic mitral valve disease with previous embolism. Mitral valve repair alone has known not to be reduced the risk of systemic embolism. Aggressive antithrombotic therapy should be considered for the prevention of embolism.
As for prosthetic valves, the risk of embolism varies depending on the site and type of the valve, presence/absence of anticoagulant or antiplatelet treatment and its intensity, and history of embolism. For example, mitral valve replacement with “St. Jude Medical bileaflet valves” is known to be associated with an annual thromboembolism rate of 22% without medical therapy, therefore adequate anti-thrombotic therapy should be considered.

Korean recommendations
1. Warfarin treatment (INR 2.0-3.0) is recommended, unless contraindicated, in ischemic stroke or TIA coexisting with rheumatic mitral valve disease, regardless of the presence of AF (LOE: III, GOR: B).
2. Patients with recurrent embolism despite of anticoagulants in ischemic stroke or TIA coexisting with rheumatic mitral valve disease, a combination of warfarin with the low-dose aspirin (100mg daily) can be considered (LOE: IV, GOR: C).
3. Warfarin treatment (INR 2.5-3.5) is recommended, unless contraindicated, in ischemic stroke or TIA that occurs after mechanical heart valve replacement (LOE: IIb, GOR: B).
4. Patients with recurrent embolism following mechanical heart valve replacement despite of anticoagulants, a combination of warfarin with the low-dose aspirin (100mg daily) is recommended (LOE: IIa, GOR: B).
5. Warfarin treatment (INR 2.0-3.0) may be considered in ischemic stroke or TIA that onsets after bioprosthetic valve replacement without other cause for the thromboembolism (LOE: IV, GOR: C).
3.4. Surgical or interventional treatment of large artery steno-occlusive disease

3.4.1 Extracranial carotid artery stenosis

3.4.1.1. Carotid endarterectomy

Introduction
Cerebral infarction associated with carotid stenosis has been on the increasing in Korea. The mechanism for the ischemic stroke in patients with carotid stenosis is embolism or direct compromised perfusion. A number of studies have demonstrated that carotid endarterectomy (CEA) could significantly reduce ischemic stroke secondary to carotid stenosis.

Korean recommendations
1. CEA is recommended in patients with severe carotid stenosis (70-99%) who have had TIA or cerebral infarction within the last 6 months. CEA performed by experienced surgeons with a low periprocedural morbidity and mortality is recommended (LOE: Ib, GOR: A).
2. In patients with moderate carotid stenosis (50-69%) who have recently had TIA or ischemic stroke, CEA should be determined based on patient age, gender, comorbidity, and severity of the first symptoms (LOE: Ib, GOR: A).
3. Medical management is recommended over surgery in patients with mild carotid stenosis (< 50%) (LOE: Ib, GOR: A).
4. In patients aged 40 to 75 with asymptomatic moderate carotid stenosis (60-99%), considering CEA is reasonable if the life expectancy is over 5 years (LOE: Ib, GOR: A). CEA performed by experienced surgeons with a low periprocedural morbidity and mortality is recommended.
5. CEA performed within 2 weeks of the ischemic symptoms may be expected Improved prognosis (LOE: Ib, GOR: A).

3.4.1.2. Carotid artery angioplasty and stenting

Introduction
While CEA is the primary modality used to treat symptomatic severe carotid stenosis, carotid angioplasty and stenting (CAS) may be considered in patients with surgically inaccessible lesion, high-risk for surgery candidate, re-stenosis followed by CEA, or non-atherosclerotic carotid stenosis. However, there are no established guidelines, however, regarding the indications or efficacy of CAS.

Korean recommendations
1. Carotid stent placement may be recommended if CEA is difficult to perform for medical reasons (LOE: IIb, GOR: B).
2. Stent placement is considered reasonable when performed by highly skilled interventionists with a low per-procedural morbidity and mortality (LOE: IIb, GOR: B).
3. Stent placement may be considered in symptomatic (≥ 70%) or asymptomatic (≥ 80%) carotid stenosis (LOE: IV, GOR: C).
4. The clopidogrel plus aspirin combination therapy may be initiated shortly before stenting procedure and maintain throughout and at least 1 month after the procedure (LOE: IV, GOR: C).

3.4.2 Vertebralbasilar artery stenosis

Introduction
Studies on the treatment of occlusive vertebrobasilar artery disease are mostly case series, with very few large-scale RCTs. Atherosclerotic stenosis is common at the origin of the vertebral artery and over the intracranial part of it. The areas are also prone to arterial dissection. To determine which treatment is superior, medical or surgical, more randomized trials are needed.

Korean recommendations
1. For repetitive ischemic symptoms in patients with vertebrobasilar artery stenosis despite an adequate medical treatments, stent placement may be considered for intravascular intervention (LOE: IV, GOR: C).

4. The clopidogrel plus aspirin combination therapy may be initiated shortly before stenting procedure and maintain throughout and at least 1 month after the procedure (LOE: IV, GOR: C).

3.4.3 Intracranial artery stenosis

Introduction
Atherosclerotic stenosis of intracranial arteries is one of the most significant causes of ischemic stroke. Though the risk of stroke recurrence is relatively high despite drug therapy, no effective prevention - including surgery - has been known yet. With the recent development in the interventional devices and techniques, angioplasty has gained a new significance as a method for stroke prevention. Angioplasty can improve blood flow by dilating the narrowed vessels, but its use for stroke prevention has only been introductory. The safety and usefulness should be determined in more reliable studies.

Korean recommendations
1. If drug therapy fails in atherosclerotic stenosis of intracranial arteries (50% and greater), angioplasty or self-expandable stent placement may be considered for stroke prevention (LOE: IV, GOR: C).
2. There is insufficient evidence that stenting is superior to angioplasty as a prevention of atherosclerotic stenosis of intracranial arteries (LOE: IV, GOR: C).

3.4.4 Extracranial-intracranial artery bypass surgery

Introduction
If cerebrovascular blockage occurs, collateral circulation restores blood flow to the affected part of the brain. Disturbance in the compensation leads to TIA or cerebral infarction. The extracranial-intracranial (EC/IC) bypass surgery may be considered in the events to improve blood flow and prevent the recurrence of cerebral infarction. There is no clear conclusion, however, that the EC/IC bypass surgery is superior to drug therapy.

Korean recommendations
1. The EC/IC bypass surgery is not routinely recommended in symptomatic carotid occlusion (LOE: I b, GOR: A)
2. The EC/IC bypass surgery may be performed in some carotid occlusion patients who have recently had cerebral infarction or TIA, if a treatment effect is expected after the cerebral blood flow evaluation (LOE: IV, GOR: C).
3. The EC/IC bypass surgery is not recommended during the acute phase (LOE: III, GOR: B).
3.5. Management of other specific conditions

3.5.1 Secondary prevention of intracerebral hemorrhage

Introduction
To identify and manage the risk factors for cerebral hemorrhage presents high morbidity and mortality is important in preventing its recurrence. Hypertension is considered as one of the most critical risk factor, and adequate blood pressure control could reduce the risk of hemorrhage recurrence in half. This is equally important for those without history of hypertension.

Korean recommendations
1. A thorough hypertension treatment is needed for prevention of recurrent cerebral hemorrhage [LOE: Ia, GOR: A].
2. Avoiding smoking or heavy drinking is reasonable for secondary prevention of cerebral hemorrhage [LOE: III, GOR: B].

3.5.2 Secondary prevention of ischemic stroke mixed with cerebral hemorrhage

Introduction
There is no clear consensus on the safety and efficacy of the antithrombotic treatment in ischemic stroke coexisting with cerebral hemorrhage. Cerebral infarction might develop in patients with a previous hemorrhage, and on the contrary, cerebral hemorrhage might not be unusual in the post-thrombolytic stage. In patients with AF coexisting with a lobar hemorrhage or a deep hemorrhage, use of anticoagulants should weigh between the recurrence of hemorrhage and the risk of ischemia, with the greatest concern given to the patient quality of life. Use of antiplatelets following cerebral hemorrhage should be considered only in those at low risk of re-bleeding.

Korean recommendations
1. Determining whether to resume the antithrombotic treatment or not following cerebral hemorrhage should be based on the risk of thrombosis, recurrent hemorrhage, and the overall risk profile in each patient [LOE: IV, GOR: C].
2. In patients with the anticoagulation-associated cerebral hemorrhage, the anticoagulants might be switched into antiplatelets in patients with low risk of recurrent thromboembolism or high risk of bleeding tendency. The anticoagulation therapy should resume, however, if the risk of cerebral embolism is clearly high. Timing of re-administration may be 7 to 10 days later from the cerebral hemorrhage [LOE: III, GOR: B].

3.5.3 Arterial dissection

Introduction
Extracranial carotid or vertebral artery dissection is a main cause of stroke in young adults. It may lead to ischemic stroke by causing arterial embolism or steno-occlusion of the proximal
arteries. And also, thrombosis occurs following formation of pseudo-aneurysm. Extensive dissection involving the intracranial vertebrobasilar artery may cause subarachnoid hemorrhage due to the arterial rupture. Management of ischemic stroke with arterial dissection is aimed for prevention of stroke recurrence and healing of the dissected vessels. Management should include anticoagulants (intravenous heparin or oral anticoagulants), antiplatelets, stent placement for endovascular treatment, and surgery.

Korean recommendations
1. Use of anticoagulants or antiplatelets for 3–6 months is recommended in ischemic stroke or TIA with extracranial artery dissection [LOE: IIa, GOR: B]. Long-term antiplatelet therapy may be considered beyond 3–6 months [LOE: IV, GOR: C].
2. Stenting is recommended if ischemic events recur despite of best medical management [LOE: III, GOR: B]. Surgery could be considered in patients who are not candidates for stenting [LOE: IV, GOR: C].

3.5.4 Patent foramen ovale and atrial septal aneurysm

Introduction
Patent foramen ovale (PFO) is a relatively common congenital heart disease. It is a major underlying cause in cryptogenic ischemic stroke or TIA in the young. The risk of stroke is known to rise particularly high if atrial septal aneurysm (ASA) coexists.

Korean recommendations
1. The screening for PFO or ASA is reasonable in young patients with cryptogenic ischemic stroke [LOE: III, GOR: B].
2. Use of antiplatelets is reasonable in patients with cryptogenic ischemic stroke with PFO [LOE: IIb, GOR: B].
3. Warfarin treatment may be considered in patients with cryptogenic ischemic stroke with PFO and other conditions, such as hypercoagulable disease or deep vein thrombosis [LOE: IV, GOR: C].
4. There is insufficient evidence regarding the usefulness of PFO closure in patients with first-ever ischemic stroke with PFO. However, it may be considered in cryptogenic ischemic stroke recurs despite of adequate medical therapy [LOE: III, GOR: B].

3.5.5 Antiphospholipid antibody syndrome

Introduction
Antiphospholipid antibodies are found in about 1–6.5% of the general population, with higher rates in the elderly or in the lupus patients. Of stroke patients, they are observed in 8.2–9.7%, and the association with stroke is particularly high in younger stroke patients aged 50 and below. Antiphospholipid antibody syndrome (APS) is a rare clinical condition that may cause venous and arterial occlusion of multiple organs, miscarriage, and/or livedo reticularis. The widely varying clinical presentations and the difficulty in diagnosis act as barriers to the well-designed clinical trials on APS treatment. Currently available practice guidelines for APS provide only limited information.
Korean recommendations
1. antiplatelets should be recommended in patients with cryptogenic ischemic stroke or TIA and positive antiphospholipid antibodies [LOE: III, GOR: B].
2. In patients with ischemic stroke or TIA who fulfill the diagnostic criteria of APS, including venous and arterial thrombosis of multiple organs, miscarriage, and livedo reticularis, use of oral anticoagulants (INR 2-3) should be recommended [LOE: III, GOR: B].

3.5.6 Venous Infarction

Introduction
Venous infarction presents widely varying symptoms including headache, focal neurological deficit, seizures, impaired consciousness, and papilledema. Diagnosis is elusive with only minute changes detected on CT and MRI. Though invasive angiography was used for definite diagnosis in the past, the MR venogram is of the widest use now. Venous infarction in many cases coexists with hemorrhage and vasogenic edema. Unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) have been in use for medical therapy, despite lack of evidence from the large-scale RCTs.

Korean recommendations
1. UFH or LMWH may be used in venous infarction even in cerebral hemorrhage coexist [LOE: IIa, GOR: B].
2. Use of oral anticoagulants is reasonable for the first 3-6 months followed by antiplatelet therapy in patients with venous infarction [LOE: IV, GOR: C].