HYPERTENSION AND STROKE SUBTYPES: A CAUSATIVE ROLE OR SIMPLE ASSOCIATION?

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INTRODUCTION
Stroke is the second leading cause of death worldwide following CV disease, associ-ated with poor prognosis, a high rate of recurrence, increased mortality and rising co-sts to the health care system. The complex and multifactorial pathogenesis of stroke determines a broad range of clinical and outcomes. Among the traditional factors, hypertension is a critical determinant of the increased risk for developing ischemic stroke (IS) and haemorrhagic stroke (HS). More than 12 million strokes are attributable to elevated blood pressure (BP) with an increased risk of acute stroke in prehypertension and younger population. [1] The differences in the incidence of stroke depend on race, ethnicity, gender, age, socioeconomic status. African Americans have a higher increased risk for stroke compared to non-blacks stroke when compared to non-blacks stroke. More recently, genetic components, gene mutations associated with fa-lite metabolism, chronic stress, short-term use of nonsteroidal anti-inflammatory drugs in hypertensives, job strain and long working hours have been demonstrated to substantially increase the risk of stroke. Women have a higher incidence of primary or recurrent strokes and associated death with the underlying mechanisms not entirely understood. The gender specific stroke-related risk factors including pregnancy, pre-eclampsia, gestational hypertension, normotensive preeclampsia, menopause, hormone replacement therapy, metabolic syndrome, obesity, atrial fibrillation (AF), migraine with aura and smoking may play critical role in this scenario. [2]

Over the past 2 years we have seen an increase in identified risk factors (HR) of recurrent stroke and nearly two-thirds of them have a clear evidence that they correlate with the risk of recurrent stroke. [3] Despite concern raised over cerebral perfusion, blood flow and BP levels after stroke, ample evidence demonstrates that a reduction in BP is the most important interven-tion for primary and secondary stroke prevention with the gradual reduction in stroke mortality largely attributable to improved hypertension control. [4,5]

ISCHEMIC STROKE
IS accounts for 87% of all strokes with the remaining 13% attributable to haemor-rhagic stroke (HS). More than 150 known causes of stroke have been identified to date with numerous classification systems (e.g. ISchemic Stroke Registry, Oxford Community Stroke Project, TOAST, SSTOAST, ASCD classification) defining the subtypes of acute IS. While there are some strengths and limitations regarding the various classification systems, the narrow time window for therapeutic action in acute IS critically requires the appropriate identification of stroke subtype and underlying cause. Clinical outcomes after stroke, stroke recurrence rates and approaches for sec-ondary prevention are strongly dependent on stroke subtype. Recent advances in brain imaging have contributed to the precise identification of stroke subtype likely resulting in improved clinical outcomes. This indicates that consistent categorization of patients according to stroke type and associated mechanisms is crucial in clinical trials in acute IS. Likewise, the use of detailed stroke subtyping system consistently applied among clinicians and researchers is relevant in meta-analysis and clinical trials assessing the effectiveness of therapies and clinical trials looking into the treatment of underlying diseases.

Large artery atherosclerotic disease subtype
Large artery atherosclerosis (LAA) appears to be an important target for primary prevention of stroke. Intracranial atherosclerosis underlying stroke development is highly prevalent in China and Thailand with similar findings in Japan, Singapore and Korea. [6] More recently, the Rotterdam study has assessed the Caucasian popula-tion-attributable risk (PAR) for having a stroke secondary to calcification in each of the four vessel beds (intracranial carotid artery, extracranial carotid artery, internal carotid, coronary arteries). [7] Using the formula which provides a measure between 0% and 100% based on the relative risk and the presence of calcification, intracranial carotid artery atherosclerosis accounted for 75% of all strokes, calcification of aortic arch contributed to 45% of strokes and extracranial carotid artery calcification accounted for 25% of acute cerebrovascular events [8] indicating that intracranial LAA is the most common vascular lesion and major risk factor for stroke. Given that the sum of PARs exceeds 100%, a possible interaction between risk factors cannot be ruled out. Hemodynamically significant stenosis or occlusion of a major brain artery or branch penitential arteries correlated with diabetes or arteriopathy is important in the inductive stroke, in IS. [9] Strokes with hypertension, diabetes, metabolic syndrome, dyslipidemia and aortic or coronary plaque are at high risk of developing LAA stroke with a strong likelihood of atherosclerotic vascular disease in other peripheral arteries accompanying concomitant intracranial atherosclerosis. [10] Intracranial large artery disease (ICLAD) plays a leading causative role in IS and is particularly prevalent among Asians [11] with hypertension being a strong independent risk factor for ICLAD but not extracranial carotid disease. However, traditional risk factors such as age, hyperlipidemia, diabetes and ischemic heart disease are associated with both atherosclerotic sites, intracranial and extracranial. [12] Cardio-aortic embolism subtype
Available data indicate that cardioembolic stroke (CES) comprises 14-30% of all strokes and 20-29% of all cerebral infarctions in North American and Eu-ropean populations. [13] Numerous cardio-atrial sources have been shown as critical contributors to high primary risk of cerebral embolism with the most clinically rele vant including AF, recent percutaneous arterial mechanical interventions, dilated cardiomyopathy, atrial septal defect and atrial myxoma. This last entity is not part of the general population though their direct relation to the CES mechanisms have been less appa rent. [14] The presence for example of large atheromas in the ascending aorta and the aortic arch has been linked to an increased risk of CES in patients over the age of 60 and in patients after cardiopulmonary bypass or cardiac catheterization. However, it remains unclear whether atheroma thickness is a direct mechanism underlying stroke or a marker for other conditions (i.e., general atherosclerosis or intracranial athero-scrosis). This causality partly explains the findings of the Rotterdam study in which intracranial atherosclerosis was a major risk factor for stroke. Moreover, the presen-ce of calcification within the atheroma has been found to decrease the risk of stroke as compared to non-calcified lesions (ulcerations or mobile components in the atheroma). Several clinical characteristics are indicative of CES including sudden onset of neurological deficit, raised level of consciousness, spectular shrinking deficit syndrome (sudden onset of a major hemispheric stroke syndrome followed by abrupt recovery associated with migration of an embolus), Wernicke’s aphasia or glo- bal aphasia in the absence of hemiparesis. [15] The short and long-term prognosis of patients with CES differs from other stroke subtypes with the high rate of recurrent stroke and in-patient mortality at one month. [16] Patients with IS and AF commonly have worsened neurological recovery, clinical prognosis and high risk for recurrent stroke when compared to patients with non-ischemic stroke. [17] Several recent studies have focused on ex-isting alcohol intake, hypertension, valvular heart disease, neurosurgery and trauma. [18] Strokes have been observed with ex-istence of alcohol intake, hypertension, valvular heart disease, neurosurgery and trauma. [19] Strokes have been observed with ex-istence of alcohol intake, hypertension, valvular heart disease, neurosurgery and trauma. [20] Strokes have been observed with existing alcohol intake, hypertension, valvular heart disease, neurosurgery and trauma. [21] Many patients with CES and AF may have been underrepresented in previous studies.

Small artery occlusion (Cerebral small vessel disease, CSD) subtype
Cerebral SVD (CSVD) accounts for 25-40% of all ischemic strokes. The presence of clini-cal features and radiological signs of typical small infarcts confirm small artery occlusion stroke type. Patients with LS or branch stroke lesions with a diameter ranging from 0.2 to 15-20 mm fall into this category. [22] Several studies have recognized two types of US with possibly different vascular pathology, lipothalmo-sis and microatheroma. [23] Patients with LS may present with a single lacune which is likely to have atherosclerotic risk factors or multiple lacunes with strong link to hypertension. [24] The strong association between lipohyalinosis and hypertension has been documented in several studies. [25] Neurological outcome, recurrent stroke and increased mortality risk in patients with lacunar stroke and at least one asympto-matic lacunar lesion have been shown to be worse when compared to LS lacking these lesions. [26] The contribution of hypertension and diabetes as independent determinants of multiple LS is well recognized. [27] Resonance imaging studies have found that reduced estimated glomerular filtration rate (eGFR) has been linked to CSD (i.e., reduced white matter volume, increased white matter lesions, small brain volume) independently of CV risk factors. [28] Patients with lower eGFR appear to have more LS. [29] The close association between lipohyalinosis and CSVD that causes white matter lesions and lacunes have been observed in hypertensive and normotensive. [30] However, not all patients with LS have presented with a history of elevated BP or glucose levels indicating that pathophysiology of CSVD is more complex than anticipated. Atherosclerotic carotid plaque or cardiac embolic source has been shown to be contributing mechanisms underlying LS with or without presence of hypertension and diabetes. There is evidence linking genetic predisposition, parental history of stroke, gene poly-morphism and inflammatory markers to small vascular inflammatory. [31] The term ‘hypertensive cerebral small vessel stroke’ is broad and includes LS and hypertensive primary (non-traumatic) deep intracerebral haemorrhage (ICH). Similar to LS, hypertension is not an underlying cause of primary ICH. Other contributors such as high monocyte count beyond traditional risk factors (i.e. cur-rent smoking status and hyperlipidemia) has been related to the development of deep LS in patients with hypertensive small vessel disease stroke but not deep ICH. [32] The presence of LS and white matter lesions on MRI substantially in-creased the risk of vascular and nonvascular death, and future IS in patients with symmetric atherosclerotic disease. [33] Whether silent clinically asymptomatic
infants have prognostic significance merits further research.

Other determined causes
This category includes the conditions that bore close temporal and spatial association with acute cerebral infarction including nonatherosclerotic vasculopathies (e.g. fibromuscular dysplasia, large vessel disease, intracranial aneurysms, stroke), and concomitant nonvascular etiologies (e.g. multiple system atrophy, carcinomatous meningitis, infectious arteriitis, Castleman’s disease, etc.).

Undetermined causes
The proportion of substantial patients suffered an ICH has a defined background.


