• Biomarkers in the Diagnosis of Dementia
   Dr Tsang Kin Lun (曾建倫醫生)

• Recent Advances in Therapeutics in Osteoporosis
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• Treatment of Left Main Disease in 2011
   Dr Ho Hung Kwong, Duncan (何鴻光醫生)

• Update on ADHD in Children and Adults
   Dr Lam Tat Chung, Paul (林達聰醫生)
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Editorial

We are very glad to see that the Journal has entered its third year of production. Last year, eight issues were published and we intend to do the same this year. The work had been basically smooth, and we had excellent feedback from the doctors and support from the advertisers. We are very grateful to our editors, contributors and all those who had put in their time and hard work.

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Contribution of Articles

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Overcoming everyday challenges in Alzheimer’s

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Biomarkers in the Diagnosis of Dementia

Key words: Dementia (失智症), biomarkers (生物標記), cerebrospinal fluid (腦脊液)

Dementia as a major and growing disease burden needs no emphasis. A local study conducted 20 years ago showed a prevalence of 6% in subjects older than 70 years. Two years ago, another study revealed a prevalence of very mild dementia and mild dementia of 8% and 9%, respectively, in the elderly aged 70 years.1 Two years ago, another study revealed a prevalence of very mild dementia.

There is still a lack of standardization of neuropsychometric screening tools due to the diversity of culture, language and level of literacy. The Mini Mental State Examination (MMSE) has its limitation as an initial screening tool because it lacks comprehensiveness in assessing different aspects of cognition.4 The complex neuropsychometric testing is lengthy and not easily performed in usual clinical settings.

Dementia is preceded by a long prodrome of mild cognitive impairment (MCI), and the conversion rate of MCI to dementia is roughly 10% to 15% per year.5 It is critical to have a prognostic marker to predict clinical outcome.6 In an analogy to the diagnosis of diabetes mellitus or some other endocrinological disorders, a numerical value of biomarker is most welcomed to aid the diagnosis of dementia.

From Laboratory to Bedside

Alzheimer’s disease (AD) is the commonest cause of dementia, followed by vascular dementia. Pathological hallmarks of AD are brain amyloid plaques (extracellular deposits composed largely of the amyloid-β [Aβ] peptide) and intraneuronal neurofibrillary tangles (NFTs, composed of hyperphosphorylated forms of the microtubule-associated protein, tau).7 These pathological features predate clinical symptoms by as long as 10 to 20 years. They are commonly seen in MCI patients, and are present in 50% of individuals over 75 years of age.8 The onset of very mild dementia is best correlated, not with plaque or NFT burden, but with significant synaptic and neuronal loss. Even in specialized dementia centres, it is very difficult to diagnose AD at its earliest clinical stages.

Plasma Biomarkers

A biomarker derived from peripheral blood is most welcomed, but this is still largely in the discovery phase in the context of dementia. In the pathogenesis of AD, Aβ peptides are formed after sequential cleavage of the amyloid precursor protein (APP), a transmembrane glycoprotein of undetermined function. When APP is cleaved, a number of isoforms of 36 to 43 amino acid residues in length are formed. The most common isoforms are Aβ40 and Aβ42; the shorter form is typically produced by cleavage that occurs in the endoplasmic reticulum, while the longer form is produced by cleavage in the trans-Golgi network. The Aβ40 form is the more common of the two, but Aβ42 is more fibrillogenic and is thus associated with disease states.9 Theoretically, plasma Aβ42 is elevated in AD patients. This was proven in some studies, but there was considerable overlap with controls or patients with other forms of dementia.10 The trend of decline over time of these plasma markers may predict the speed of decline of cognition.

Another way of using plasma markers is the scoring system approach. A risk score can be derived using various markers including C-Reactive protein and interleukin-10, which have been associated with inflammation, plus the individuals’ demographics such as age, education and genetic information; the test’s accuracy can be more than 90%.9 However, the calculation is complex, and statistical validation is awaited. Clinical application of plasma dementia biomarkers is not yet recommended at this stage.
Positron Emission Tomography

Imaging compounds, notably Pittsburgh compound-B (PiB), can selectively bind to amyloid-β in vitro and in vivo. This technique, combined with positron emission tomography (PET), has been used to image areas of plaque deposits in AD patients. The 11C-PiB ligand is distributed rapidly to all grey-matter regions in the brain, and is selectively retained in regions where it binds. Typically, data from cerebral regions are normalized to 11C-PiB retention in the cerebellum. The ligand binds to amyloid deposits not only in the parenchyma, but also in cerebral blood vessels that apparently can be the major source of signal. The sensitivity of 11C-PiB-PET against a standard of expert clinical diagnosis of AD is high (around 90%), but autopsy investigations will be needed to assess this finding further. The specificity of the 11C-PiB-PET signal for AD and congophilic amyloid angiopathy (vs other changes) is currently under investigation. PiB does not seem to bind to cortical Lewy bodies. PiB-PET scan is available locally and costs HK$10,000 to HK$15,000.

Cerebrospinal Fluid Biomarkers

Up till now, cerebrospinal fluid (CSF) biomarkers have been shown most promising in diagnosing and predicting AD. The leading biomarkers are, understandably, Aβ, tau and phosphorylated forms of tau. Unlike Aβ, which is a secreted peptide, tau is a microtubule-associated protein found within the cytosol of neurons. In AD, tau becomes hyperphosphorylated (p-tau) and twists to form paired helical filament, which are constituents of NFTs. Elevated CSF p-tau has been shown to correlate with NFT load, but is also seen in cell deaths associated with head trauma and acute stroke. There are many studies assessing the accuracy of combining CSF p-tau with other markers such as Aβ42 and Aβ40 in the prediction of cognitive decline. The most valuable is the CSF Aβ42/p-tau ratio. Model building and validation have relied on data from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) database (www.loni.ucla.edu/ADNI). The CSF “AD signature” is low Aβ42 and high p-tau. The sensitivity of the test was 90% in those with AD, 72% in those with MCI, and 36% in controls. The specificity was only 62%. If the CSF AD signature is identified in MCI subjects, the chance of progression to AD in 5 years approaches 100%. This high predictive value has been widely publicized, but we should bear in mind the overall small number of subjects (n=57) that was studied. In Europe, lumbar puncture is a standard practice in many memory clinics where tests of CSF biomarkers are considered a diagnostic procedure, even in nonresearch hospitals.

Biomarkers in Other Types of Dementia

Next prevalent to AD is vascular dementia. Additional biomarkers studied in this entity are those of atherosclerosis, such as highly-sensitive C-reactive protein, fibrinogen and interleukin-6. However, development is less mature than in AD, and candidates ready for standardization and widespread application have not been identified as yet. Biomarker studies on Levy body disease and frontotemporal dementia are even rarer.

Future Perspective

Since no single biomarker exclusive to any type of dementia has been identified, a panel of biomarkers may offer appropriate sensitivity, specificity, and positive and negative predictive values. Large longitudinal studies on these are underway across the continents.

To date, there is no reliable blood test. PET scan is useful in differentiating the types of dementia. Lumbar puncture offers great promise. CSF biomarkers may not provide higher sensitivity in diagnosing AD, but may allow more accurate and earlier diagnosis. They can be used to design and evaluate preventive trials by allowing one to enroll individuals who are in the preclinical stages of the disease. By combining with sensitive cognitive outcome measures, CSF biomarkers could also be used to monitor response to therapy.

Ethical issues are an important concern as there is currently no cure for dementia. Once people become demented, they can no longer plan for their financial future or dictate their end-of-life care. An early diagnosis of AD, rather than late, permits a person more autonomy in directing his or her future. However, an early diagnosis of AD may have negative psychological consequences in an otherwise well-functioning person who must now consider an inexcusable decline towards a state of personal oblivion. Consequently, the pros and cons of early diagnosis must be carefully weighed in each individual prior to any confirmatory test. Neurologists may need to sharpen their lumbar puncture needles at this stage, though not necessarily stocking them up.

References:

**Introduction**

Osteoporosis is a silent epidemic and a major public health problem in adults over 55 years of age, with a lifetime risk of osteoporotic fracture of 50% in women and 25% in men. Osteoporotic fractures, particularly those of the hip, are associated with a significant economic impact; the direct costs of managing osteoporotic fractures in the USA were estimated to be $19 billion in 2005.1

Several effective treatments are available for osteoporosis. While existing treatments have reduced the incidence of osteoporotic fractures, research is ongoing to identify new and more potent therapies.

**Bone Remodelling Cycle**

The bone remodelling cycle includes a well orchestrated sequence of events in the following four stages:

1. Activation of osteoclast precursors that mature into multinuclear osteoclasts under the direction of cytokines and hormones;
2. Resorption of bone by osteoclasts, resulting in a resorption cavity – a process that lasts for about 3 weeks;
3. Reversal of the resorption signal; and
4. Formation of new bone that fills up the resorption cavity – a process that lasts for several months. (Figure 1)

Osteoclast precursors and mature osteoclasts are derived from the monocyte/macrophage lineage of haematopoietic stem cells in the bone marrow. These cells need activation by two essential cytokines, M-CSF (macrophage colony stimulating factor) and RANKL (receptor activator of NF kappa B ligand) that are produced by marrow stromal cells and osteoblasts. M-CSF is responsible for proliferation, survival and differentiation of osteoclast precursors, and RANKL is the most important cytokine that primes the precursor cells for osteoclast differentiation. It binds to the receptor RANK on the surface of osteoclast precursors and osteoclasts, and is the key activator of osteoclast formation and action. This regulation of osteoclast formation and action is antagonized by a local inhibitor called osteoprotegerin (OPG) that is secreted by local mesenchymal cells and osteoblasts and binds to the RANKL.

In summary, the RANKL/OPG is a common central pathway regulating differentiation and activation of osteoclasts by osteoblasts.2 4 (Figure 2)

Once the multinucleated osteoclasts have matured, they attach to bone surface and seal off a resorption zone. Osteoclasts secrete various enzymes and acid into this zone, causing bone resorption. Cathepsin K is a protease that degrades bone matrix and other factors such as acid, causing dissolution of bone mineral.

In the reversal phase, mononuclear cells line the resorptive cavity and form a cement line (glycoprotein) that helps in attaching osteoblasts. Osteoblast precursors are derived from the stromal mesenchymal cells and converted into mature osteoblasts under the influence of many growth factors, hormones and cytokines. Osteoblasts synthesize collagenous bone matrix and then complete its mineralization, leading to the formation of new bone. (Figure 1)
formation of bone matrix proteins such as collagen type 1, osteopontin, osteocalcin, bone-specific alkaline phosphatase and bone sialoprotein.

Recent research has shown that several proteins are essential for osteoblast proliferation, differentiation and survival. Of particular importance is the Wingless type and integrase 1 (Wnt/β-Catenin pathway). Mutations in the low-density lipoprotein receptor-related protein 5 (LRP5) gene can lead to either osteoporosis or high bone mass. The various factors in this pathway regulate the formation of osteoblasts, inhibit apoptosis of osteoblasts and increase their lifespan.

As bone formation continues, osteoblasts are embedded deeper in bone and become osteocytes that are interconnected through dendritic processes within the canaliculi of bone. Osteocytes comprise about 95% of bone cells, and are sensitive to mechanical strain. Osteocytes can resorb adjacent bone, promote mineralization and inhibit bone formation by secreting sclerostin that acts on the Wnt signalling pathway in osteoblasts.

In a state of normal bone remodelling, bone formation closely matches bone resorption. In other words, each packet of bone that is removed is replaced by the same amount of bone. The greatest change in bone remodelling occurs at menopause, when there is an increase in the number of resorption cavities but bone formation does not increase proportionately, and resorption cavities are not completely filled with new bone. This results in a permanent loss of bone mass.

Treatment and Prevention of Osteoporosis: Established Therapies

Antiresorptive Agents

Most of the antiresorptive agents available today also inhibit bone formation after several months, and this limits the effect on increasing bone mass. Drugs that uncouple bone resorption from bone formation potentially have a greater effect in terms of increasing bone mass.

Bisphosphonates are currently the drug of choice for prevention and treatment of primary osteoporosis. They reduce fractures in the spine and nonvertebral sites by 50% to 60%. Bisphosphonates attach to the hydroxyapatite in bone. As bone is resorbed, the drug is taken up by the osteoclasts. Bisphosphonates without a nitrogen atom in the molecule (eg, etidronate, clodronate, tiludronate) are incorporated by adenine triphosphate and cause apoptosis of osteoclasts, whereas bisphosphonates with a nitrogen atom in the molecule (eg, pamidronate, alendronate, ibandronate, risedronate, zolendronate) alter the cytoskeleton of osteoclasts and decrease osteoclast activity and function by inhibiting an enzyme in the mevalonate pathway.

Selective oestrogen receptor modulators (SERMs) (eg, raloxifene, bazedoxifene, lasofoxifene) probably exert their effect on bone in a similar way as oestrogen. These compounds reduce the incidence of spine fractures but not nonvertebral fractures, whereas oestrogen reduces both types of fractures, suggesting that the efficacy of SERMs is similar to that of low-dose oestrogen.

Calcitonin directly suppresses osteoclast function by binding to a calcitonin receptor on osteoclasts. In a large study of 1,255 postmenopausal women with established osteoporosis, calcitonin nasal spray significantly reduced the risk of new vertebral fractures by 33%. The effect on nonvertebral fractures was nonsignificant. Due to its relatively low potency, calcitonin is generally reserved only for the treatment of osteoporosis in women who are >5 years since menopause and are unable to take other medications, or in men with mild bone loss.

Anabolic Agents

Parathyroid Hormone

An important differential effect of parathyroid hormone (PTH) on bone was noted many years ago when chronically elevated levels of PTH were shown to cause bone resorption. This is due to binding of PTH to the PTH receptor on osteoblasts and increasing production of RANKL, which activates bone resorption. (Figure 2) However, when small intermittent pulses of PTH are given, there is an anabolic action despite increasing bone resorption.

In a trial of PTH1-34 treatment involving >1,600 osteoporotic women, the incidence of vertebral fractures was reduced by 65% and nonvertebral fractures by 35% with a 20 μg dose. PTH-related peptide (PTHrP) appears to have the same action and may well be developed as an osteoporosis drug in coming years. Research is continuing to develop more potent PTH analogues that can permit optimization of signalling duration, thus reducing the potential for resorptive actions of PTH on bone. Transdermal PTH is completing clinical trials and may soon become another treatment option for osteoporosis.
**Sorption in both diseases.** is the main cause of increased bone resorption in rheumatoid arthritis and cancer, as RANKL inhibitors osteoclast action through an effect on the calcium sensing receptor, causing apoptosis. In two pivotal clinical trials involving 1,649 and 5,092 postmenopausal women with osteoporosis, strontium ranelate 2 g/day reduced the risk of new vertebral fractures by about 50% and 39%, respectively. 13,14

**Denosumab**
Denosumab is a human monoclonal antibody to RANKL that blocks the activation of osteoclasts, thereby decreasing bone resorption. (Figures 1 and 2) It is a powerful inhibitor of bone resorption. In a recently conducted study involving 7,688 osteoporotic women, denosumab 60 mg given subcutaneously every 6 months reduced the risk of new radiographic vertebral fractures by 68%, hip fractures by 40%, and nonvertebral fractures by 20%. 15 There were no significant differences in the incidence of serious adverse events compared with placebo, except for a small increase in skin infections including cellulitis. Denosumab can also be used to decrease bone resorption in patients with rheumatoid arthritis and cancer, as RANKL is the main cause of increased bone resorption in both diseases.

**New Antiresorptive Therapies for Osteoporosis**

**Cathepsin K Inhibitors**
Cathepsin K is a cysteine protease that is selectively expressed in osteoclasts and causes degradation of bone matrix proteins. (Figure 2) In a trial evaluating odanacatib, a selective cathepsin K inhibitor, given as a weekly oral dose for 2 years to >400 postmenopausal women with osteopenia or osteoporosis, there was a dose-dependent increase in spine (5.5%) and hip bone mineral density (3.2%) and decrease in bone resorption markers. 16

**Osteoporogenin**
Osteoporogenin (OPG) binds to RANKL, hence preventing its binding to RANK and the activation of osteoclasts. (Figure 2) It can be considered as a natural antibody to RANKL. In a phase I clinical trial involving 52 healthy postmenopausal women (age 40–70 years), OPG decreased the resorption marker urinary N-telopeptide (NTx) by 80% by day 4 after a single dose, and the effect gradually decreased to 17% after 6 weeks of follow-up. However, antibodies to OPG appeared after several months, and this has therefore limited its future use as a treatment for osteoporosis.

**New Anabolic Therapies for Osteoporosis**

**Sclerostin-neutralizing Antibodies**
Sclerostin is a protein secreted by osteocytes after primary mineralization to limit further bone formation by osteoclasts. Normally, sclerostin acts on osteoblasts via LRP6 and LRP6 receptors to inhibit the Wnt pathway. In rat and monkey models of osteoporosis, treatment with a monoclonal antibody to sclerostin (Scl-Abill) markedly increased bone formation on trabecular, periostial, endocortical and intracortical surfaces after 5 weeks of treatment. 16 Clinical trials on the use of sclerostin antibodies in treatment of osteoporosis may soon start.

**Bone Morphogenetic Proteins**
Bone morphogenetic proteins (BMPs) are growth factors belonging to the transforming growth factor beta (TGF-β) superfamily. They are potent bone inducers and are being used in clinical studies on local fracture healing. For example, activin acts through soluble activin receptor type IIA (ActRIIA) to stimulate osteoclasts and inhibit osteoblasts. ACE-011 (ActRIIA-IgG1) is a human glycosylated dimeric fusion protein consisting of ActRIIA linked to the Fc domain of human immunoglobulin G1. By binding to activin, ACE-011 prevents activin from binding to endogenous receptors, and thus acts as a decoy. In a phase I clinical trial involving 48 healthy postmenopausal women, a single dose of ACE-011 resulted in a rapid and sustained dose-dependent increase in serum levels of bone-specific alkaline phosphatase. 19

**Summary**
Advances in therapy for low bone mass may be on the horizon as a result of increased understanding of the mechanisms underlying osteoblast, osteoclast and osteocyte biology. New anabolic agents acting on the calcium-sensing receptor and Wnt signalling pathway, and new antiresorptive agents that might have less effect on bone formation than currently available therapies offer promise for the treatment of low bone mass. Additional therapies, especially those for patients with established fractures, are needed to reduce the burden of this disease.

**References:**
18. Li X, Ominsky MS, Warmington KS, et al. Sclerostin antibody treatment for patients with established fractures, a single dose of ACE-011 resulted in a rapid and sustained dose-dependent increase in serum levels of bone-specific alkaline phosphatase. 19
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Significant left main (LM) stenosis is found in approximately 4% of patients undergoing diagnostic coronary angiography, and has been shown to portend high mortality. Trials comparing coronary artery bypass grafting (CABG) with medical therapy have shown a mortality reduction in patients who are suitable for surgery. Since these original trials were published, percutaneous coronary intervention (PCI) has emerged as an alternative to CABG for the treatment of coronary artery disease (CAD). Still, PCI is designated a Class III indication in patients who are CABG candidates, and is a Class IIa indication in unsuitable candidates for CABG.2

Advances in PCI technology and technique have led some interventionists to operate outside these guidelines. With the introduction of drug-eluting stents (DES) and other adjunctive PCI devices, the respective values of CABG and PCI were reassessed based on contemporary clinical trials. The SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) randomized trial is one of the landmark trials to provide an evidence base to determine the most appropriate treatment option for patients in a ‘real-world’ population seen by the surgeons and the interventional cardiologists in their daily practice.3 After fierce argument, the American College of Cardiology/American Heart Association PCI Guidelines were updated in 2009, with LM stenting being raised from a Class III indication to a Class Iib (level B) indication.4 In 2010, the European Society of Cardiology guidelines were revised, and LM (isolated or in conjunction with single-vessel disease) stenting was upgraded from Class IIb (level C) to IIa (level B).5

SYNTAX Trial Results

The need for repeat revascularization, and the occurrence of in-stent restenosis and thrombosis remain the Achilles heel of PCI. SYNTAX is a randomized, controlled clinical trial comparing PCI using the Taxus Express2 paclitaxel-eluting coronary stent system (Boston Scientific Corporation, Natick, MA, USA) with contemporary CABG surgery in 1,800 patients with the most complex CAD, specifically LM and three-vessel disease.3

The SYNTAX investigators reported that most of the preoperative characteristics were similar in the two groups.3 The rate of major adverse cardiac or cerebrovascular events (MACCE) at 12 months was significantly higher in the PCI group compared with CABG (17.8% vs 12.4%; p=0.002), which was driven by an increased rate of repeat revascularization (13.5% vs 5.9%; p<0.001). As a result, the primary combined MACCE endpoint for noninferiority was not met. At 12 months, the rates of death and myocardial infarction (MI) were similar between the two groups; stroke was significantly more likely to occur with CABG than with PCI (2.2% vs 0.6%; p=0.003). The investigators concluded that CABG remains the standard of care for most patients with three-vessel or left main coronary artery (LMCA) disease, because the use of CABG, as compared with PCI, resulted in lower rates of the combined MACCE (all-cause death, stroke, MI, and repeat revascularization) endpoint at 1 year.

Nevertheless, in the LM subset of patients, overall MACCE in the PCI group was comparable with CABG (22.3% with CABG vs 26.8% with PCI) at 3 years.6 The overall safety outcomes (death/cerebrovascular accident [CVA]/MI) with CABG and PCI were also similar (14.3% with CABG vs 13.0% with PCI). There was a higher rate of revascularization in the PCI group (20% vs 11.7% with CABG), and a higher rate of CVA in the CABG group (4% vs 1.2% with PCI). PCI outcomes were excellent relative to CABG in isolated LM and LM plus single-vessel disease. Thus, the investigators concluded that revascularization with PCI provides comparable safety and efficacy outcomes to CABG for patients with LM disease.

The SYNTAX Score

The SYNTAX score has been developed as a tool to characterize the coronary vasculature prospectively with respect to the number of lesions and their func-
It is applied to predict cardiac mortality and major adverse cardiovascular events (MACE), and therefore helps in the selection of different treatment modalities for different patients. In particular, when the SYNTAX score is low (<22) or intermediate (23–32), PCI may be a more favourable treatment approach. It thus echoed with the ULTIMA registry of 279 patients treated with PCI for LM disease. This registry helped determine which patients did best with nonsurgical treatment. The overall 12-month mortality was 9%, but when patients were divided according to risk (low risk: <75 years of age, ejection fraction >40%, large vessels >3 mm; high risk: older, surgical rejects, cardiogenic shock, LM bifurcation disease, high EuroSCORE [European System for Cardiac Operative Risk Evaluation]), the outcomes were considerably different, with 1-year mortality of 3.4% for the low-risk group and 28% for the high-risk group. The spectrum of patients treated with PCI, including the inclusion of surgical rejects, has led to variance in mortality (3.1% to 20.2%) after follow-up of 6 to 31 months. Thus, contemporary PCI for LM disease in low-risk patients appears to show low mortality and low incidence of need for repeat procedure.

### Left Main Stenting Techniques

Although the left main stem is only 1 to 2 cm long, it is divided into 3 portions: the aorto-ostium, the mid-body and the distal bifurcation (into the left anterior descending and the left circumflex arteries). Park et al reported a lower restenosis rate after LMCA nonbifurcation intervention compared with bifurcation intervention (1.7% vs 10.9%). Similarly, the risk of target vessel revascularization (TVR) was significantly lower in nonbifurcation vs bifurcation intervention (3% vs 13%). Currently available evidence suggests that results are less favourable when distal LM lesions are treated by a two-stent approach compared with a single-stent approach. The target lesion revascularization (TLR) rate is relatively low (<5%) with the single-stent approach, even for distal LM lesions, and is nearly equivalent to results obtained with DES for ostial or mid-LM lesions. However, patients with distal LM lesions treated with two-stent techniques showed a TLR rate of as high as 25%, with restenosis confined mainly to the left circumflex ostium.

Optimizing the result depends on how good the operators are at dealing with bifurcation disease with different techniques. Many original techniques involved the use of two stents, with various methods utilized (crush, culotte) to cover the origin of both vessels. Increasingly, single so-called provisional (simplified) stenting has become a standard method of dealing with bifurcation disease. Such considerations are important since the mean incidence of bifurcation disease in all LM series is 53%, with ostial or body disease making up the rest. Intravascular ultrasound (IVUS) is essential in LM stenting. IVUS evaluation before the stenting procedure not only measures the degree of stenosis, plaque involvement and anatomic configuration, but also helps select the stent of the most appropriate length and diameter, and the best stenting strategy. Postprocedural IVUS interrogation is very helpful in the detection of stent underexpansion, incomplete lesion coverage and suboptimal stent wall apposition. The impact was well illustrated by the difference in all-cause mortality at 3 years after LM DES implantation with or without IVUS guidance (4.8% vs 14.4%).

### Conclusion

In conclusion, treatment of LM disease by PCI is no longer a Class III indication. With contemporary PCI technology and careful patient selection, catheter-based treatment may be comparable to CABG in long-term safety and efficacy.

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**Case Study**

A 51-year-old gentleman with history of inferior MI 10 years ago presented with unstable angina. Angiogram showed triple-vessel disease with LM bifurcation involvement. Successful PCI to distal LM and right coronary artery (RCA) was performed.
Update on ADHD in Children and Adults

Attention deficit hyperactivity disorder (ADHD) is a common condition affecting 8% of children, 6% of adolescents and 4% of adults. Whilst the condition has long been recognized in children, its prevalence in adults and the disruption it can cause to professional, family and personal lives have come to wide attention only more recently.

Clinically, three subtypes of ADHD can be distinguished. (Table 1) Boys tend to suffer from the hyperactive/impulsive type. They are the ones who tend to be disruptive in classrooms, noisy and naughty, and are often picked up by the teacher or parent for assessment. Girls tend to suffer from the inattentive type. Hence, they are often not identified. In a clinical sample, boys typically outnumber girls by 10 to one, but in a population survey, boys only outnumber girls by two to one. Hence, of every girl diagnosed, three to four are missed. Functional impairments that can occur with ADHD include psychiatric comorbidity, school failure, poor peer relationships, legal difficulties, smoking and substance abuse, accidents and injuries, family conflict, and parental stress. Aetiological factors associated with the disorder are listed in Table 2.

Table 1. ADHD subtypes and estimated prevalence

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<th>Estimated prevalence by age</th>
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<tr>
<td>Children: 8%</td>
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<td>Adolescents: 6%</td>
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<td>Adults: 4%</td>
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<tr>
<th>DSM-IV Text Revision ADHD Types</th>
<th>Estimated prevalence</th>
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<tbody>
<tr>
<td>Combined</td>
<td>60%</td>
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<tr>
<td>Predominantly inattentive</td>
<td>30%</td>
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<tr>
<td>Predominantly hyperactive/impulsive</td>
<td>10%</td>
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<th>Gender distribution</th>
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<tr>
<td>Clinical sample: Boys : girls</td>
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<td>Population survey: Boys : girls</td>
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</tbody>
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DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th edition

Key words:
Attention deficit hyperactivity disorder (ADHD) (注意力不足過動症), adults (成人), neurobiology (神經生物學), treatment (治療)

Symptoms and Diagnosis

Table 2. Aetiological factors associated with ADHD

<table>
<thead>
<tr>
<th>1. Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Developmental factors</td>
</tr>
<tr>
<td>Maternal use of alcohol/nicotine</td>
</tr>
<tr>
<td>Low birth weight</td>
</tr>
<tr>
<td>3. Central nervous system insults</td>
</tr>
<tr>
<td>Head injury</td>
</tr>
<tr>
<td>Viral infection</td>
</tr>
<tr>
<td>Birth injury, foetal distress</td>
</tr>
<tr>
<td>4. Psychosocial</td>
</tr>
<tr>
<td>Poverty</td>
</tr>
<tr>
<td>Single parent</td>
</tr>
<tr>
<td>Psychiatric illness in parents</td>
</tr>
</tbody>
</table>

Figure. Natural course of ADHD symptom regression
Symptoms in Children vs Adults

The symptoms of ADHD tend to wane as the child grows into adulthood. Each group of symptoms regresses at different stages of life, with hyperactivity declining first, followed by impulsivity and lastly by inattention. (Figure) Therefore, clinical features in adults are different from those in children. (Table 3) Clues that alert doctors to consider the diagnosis in adults include a history of childhood ADHD, frequent change of jobs or marriages, driving accidents, and poor performance at work. Some patients present with anxiety or depressive symptoms resulting from poor adaptation in interpersonal relationship or work environment.

The diagnosis of ADHD in adults requires the onset of some symptoms before the age of 7. This has caused difficulties as recall of the patient is often inaccurate or impossible. Some patients with classical adult symptoms do present after the age of 7. In view of recent research findings, it is likely that in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V), the Committee on ADHD will raise the age limit to onset at 12 years.¹ Some authors have proposed that onset before adulthood may be a more appropriate criterion.²,³

Assessment and Rating

Various scales have been used for assessment and rating of ADHD. Among them, the Adult ADHD Self-Report Scale (ASRS-v 1.1) symptom checklist has been widely utilized.⁴ Part A of the scale consists of six questions. If the patient scores 4 or more answers in the shaded boxes, he/she is very likely to suffer from ADHD. The sensitivity is 68.7% and the specificity 99.5%. The other 12 questions in part B provide further information on other symptoms of the patient.

ADHD is associated with a very high rate of comorbidities. (Table 4) Thus, when treating other psychiatric illnesses, it is reasonable for doctors to always be vigilant of comorbid ADHD in the patient. Conversely, patients with ADHD should be screened for mood or anxiety disorders. Certain screening questions are useful. (Table 5)

Neurobiology and Heritability

Recent studies have shed light on the neurobiology of ADHD. Castellanos et al performed magnetic resonance imaging (MRI) scans on 152 cases and 139 controls, and found that patients had smaller brain volume in all regions, with a 3.2% reduction in cerebral volume and 3.5% reduction in cerebellar volume.⁵ There was no gender difference. The reduction in brain volume correlated with the severity of ADHD and persisted with age. Medication was found to improve brain volume.

The areas of the brain which are important for attention include the dorsolateral prefrontal cortex, which is important for executive function, the right frontal area, which is important for alertness, and the dorsolateral prefrontal cortex, which is important for selective attention. In adults with ADHD, brain volumes in these areas are decreased as seen on MRI.⁶ Functional MRI also shows failure of cognitive activation of the anterior cingulate.⁷

---

Table 3. Clinical features of ADHD in children vs adults

<table>
<thead>
<tr>
<th>Children</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has difficulty sustaining attention</td>
<td>Has difficulty sustaining attention to reading or paperwork</td>
</tr>
<tr>
<td>Does not follow through</td>
<td>Has poor concentration</td>
</tr>
<tr>
<td>Cannot organize</td>
<td>Manages time poorly</td>
</tr>
<tr>
<td>Loses things</td>
<td>Misplaces things</td>
</tr>
<tr>
<td>Does not listen</td>
<td>Has difficulty finishing tasks</td>
</tr>
<tr>
<td>Squirms and fidgets</td>
<td>Shows inner restlessness</td>
</tr>
<tr>
<td>Runs or climbs excessively</td>
<td>Fidgets when seated</td>
</tr>
<tr>
<td>Cannot play or work quietly</td>
<td>Selects active jobs by himself/herself</td>
</tr>
<tr>
<td>Seems “on the go”, “driven by a motor”</td>
<td>Feels overwhelmed</td>
</tr>
<tr>
<td>Blurs out answers</td>
<td>Drives too fast, has traffic accidents</td>
</tr>
<tr>
<td>Cannot wait for his or her turn</td>
<td>Impulsively changes jobs</td>
</tr>
<tr>
<td>Intrudes on or interrupts others</td>
<td>Is irritable or quick to get angry</td>
</tr>
</tbody>
</table>

Table 4. Comorbidities associated with ADHD

<table>
<thead>
<tr>
<th>Children</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oppositional defiant disorder</td>
<td>Alcohol and drug abuse</td>
</tr>
<tr>
<td>Conduct disorder</td>
<td>Mood disorder</td>
</tr>
<tr>
<td>Mood/anxiety disorder</td>
<td>Anxiety disorder</td>
</tr>
<tr>
<td>Learning disability</td>
<td></td>
</tr>
<tr>
<td>Language impairment</td>
<td></td>
</tr>
<tr>
<td>Mental retardiation</td>
<td></td>
</tr>
<tr>
<td>Tic/Tourette</td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td></td>
</tr>
<tr>
<td>Alcohol and drug abuse</td>
<td>50%</td>
</tr>
<tr>
<td>Mood disorder</td>
<td>38%</td>
</tr>
<tr>
<td>Anxiety disorder</td>
<td>47%</td>
</tr>
</tbody>
</table>

¹The neurochemical defects of ADHD point to hypofunctioning of the dopaminergic and noradrenergic systems”

The neurochemical defects of ADHD point to hypofunctioning of the dopaminergic and noradrenergic systems, and medical treatment is aimed at augmentation of these systems. ADHD is a highly inheritable condition, as shown by twin studies, family...
and heritability studies. The concordance rate for monozygotic twins is 50%, and that for dizygotic twins is 30%. First-degree relatives have a five-fold increased risk of inheriting the disorder. It has a heritability coefficient of nearly 0.8, making it one of the most inheritable of all medical and psychiatric conditions.

Genes found to be involved include the HTR1B (serotonin receptor 1B), SLC6A4 (serotonin transporter gene), SNAP 25 (controlling the presynaptic engulfment of dopamine), DPH (dopamine beta hydroxylase gene), DR 4 (dopamine receptor 4) and DR 5 (dopamine receptor 5) genes.8

### Table 5. Screening questions for comorbid conditions

<table>
<thead>
<tr>
<th>Anxiety: Suspect if answer is yes to any of these questions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have you had a spell or attack when all of a sudden you felt frightened, anxious, or uneasy? (Panic disorder)</td>
</tr>
<tr>
<td>Have you been bothered by nerves, or feeling anxious or on edge for 6 months? (Generalized anxiety disorder)</td>
</tr>
<tr>
<td>Have you had a problem being anxious or uncomfortable around people? (Social anxiety disorder)</td>
</tr>
<tr>
<td>Have you had recurrent dreams or nightmares of trauma or avoidance of trauma reminders? (Post-traumatic stress disorder)</td>
</tr>
</tbody>
</table>

**Depression: Suspect if answer is yes to either question**

- During the past 2 weeks, have you felt down, depressed, or hopeless?
- During the past 2 weeks, have you felt little interest or pleasure in doing things?

**Bipolar disorder: Suspect if answer is yes to either question**

- Are you a person who has frequently experienced ups and downs in mood during your life?
- Do these mood swings occur without cause?

### Table 6. Medications for ADHD

<table>
<thead>
<tr>
<th>Medications currently available in Hong Kong</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Methylphenidate (Ritalin):</td>
</tr>
<tr>
<td>• A short-acting stimulant with properties similar to amphetamine.</td>
</tr>
<tr>
<td>• Starting dose for children &gt;6 years of age is 5 mg once or twice daily (breakfast and lunch). Dose increase may be made weekly.</td>
</tr>
<tr>
<td>• Common side effects include nervousness, insomnia and decreased appetite. Growth retardation and psychosis are more serious complications.</td>
</tr>
<tr>
<td>• The long-acting formulation of methylphenidate is taken once daily.</td>
</tr>
<tr>
<td>2. Methylphenidate extended release (Concerta):</td>
</tr>
<tr>
<td>• A longer duration of action than the long-acting formulation of methylphenidate.</td>
</tr>
<tr>
<td>3. Atomoxetine (Strattera):</td>
</tr>
<tr>
<td>• A long-acting noradrenergic reuptake inhibitor and nonstimulant.</td>
</tr>
<tr>
<td>• Common side effects include loss of appetite, nausea and vomiting.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medications approved overseas</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Dexmethylphenidate (Focalin and Focalin XR):</td>
</tr>
<tr>
<td>• A purified active isomer of methylphenidate.</td>
</tr>
<tr>
<td>• Available in regular and extended-release formulations.</td>
</tr>
<tr>
<td>2. Mixed amphetamines salts (Adderal) and mixed amphetamin salts, extended release (Adderal XR)</td>
</tr>
<tr>
<td>3. Dextroamphetamine (Dexedrine) and dextroamphetamine, long acting (Dexedrine Spansule)</td>
</tr>
<tr>
<td>4. Lisdexamfetamine (FDA Feb 2007, for adults):</td>
</tr>
<tr>
<td>• A prodrug of amphetamine, converted in the body to amphetamine.</td>
</tr>
<tr>
<td>• Low abuse potential as not effective when smoked, inhaled or injected.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other medications in the pipeline</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Super long-acting mixed amphetamines salts (SPD465):</td>
</tr>
<tr>
<td>• Duration of action up to 16 hours (current formulations on the market have duration of up to 12 hours).</td>
</tr>
<tr>
<td>2. Guanfacine extended release (GXR):</td>
</tr>
<tr>
<td>• Guanfacine is a noradrenergic receptor agonist formerly used to treat hypertension.</td>
</tr>
<tr>
<td>• The extended-release formulation shows promise as a drug for treatment of ADHD.</td>
</tr>
<tr>
<td>3. Methylphenidate transdermal system (MTS)</td>
</tr>
<tr>
<td>4. Partial agonists of nicotinic acetylcholine receptors (ABT 089)</td>
</tr>
</tbody>
</table>

### Treatment

ADHD is underdetected and undertreated, both in children and adults. Only about half of the diagnosed children are taking medication. In the National Comorbidity Survey Replication study, only 10.9% of adults between the ages of 18–44 years who met the criteria for treatment had been treated in the prior year.9 Medication is the mainstay of treatment for ADHD. (Table 6) In general, long-acting preparations are preferred. Stimulants generally have a higher efficacy than nonstimulants. When using stimulants in adults, particular attention has to be exercised in patients with cardiac risk, such as patients with a family history of sudden cardiac death, syncope, arrhythmia, hypertension or ischaemic heart disease.

### References:

“每月一粒，全面護骨！”

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小龍女

全新上市

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標語

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網址：www.sanofi-aventis.hk

參考資料：

* 喜愛正常飲食的病人和患者可同時於維生素D和鈣

注意事項：
1. 服用前請詳閱說明書
2. 請遵守醫生指示
3. 如有任何不適，請立即停用並諮詢醫生

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Dr Ho Hung Kwong, Duncan (何鴻光醫生)
MBBS (HK), MRCP (UK), FRCP (Edin),
FHKAM (Med)
Specialist in Cardiology

References: