EXECUTIVE COMMITTEE

PRESIDENT
Dr Lam Tat Chung, Paul
林達聰醫生

VICE PRESIDENT
Dr Tsang Wah Tak, Kenneth
曾華德醫生

HON. SECRETARY
Dr Chan Tak Hin
陳德輝醫生

HON. TREASURER
Dr Wong Chun Yu, Benjamin
王錦宇醫生

COMMITTEE MEMBER
Dr Kung Wai Chee, Annie
關慧慈醫生

EDITORS
Dr Au Wing Yan
區永仁醫生

Dr Chan Hin Lee, Henry
陳衍恩醫生

Dr Chan Tak Hin
陳德輝醫生

Dr Chen Yi Tin
陳以天醫生

Dr Kung Wai Chee, Annie
關慧慈醫生

Dr Lam Tat Chung, Paul
林達聰醫生

Dr Lam Cheung Cheung, Barbara
梁常晴醫生

Professor Leung Wai Keung
梁偉恒教授

Dr Ng Fook Hong
吳福鴻醫生

Professor Brian Tomlinson
湯林森教授

Dr Tsang Wah Tak, Kenneth
曾華德醫生

Professor Tse Hung Fat
謝鴻發教授

Dr Wong Chun Yu, Benjamin
王錦宇醫生

Dr Young Chi Keung
楊志強醫生

CONTENTS

61 Editorial
Dr Lam Tat Chung, Paul (林達聰醫生)
Professor Tse Hung Fat (謝鴻發教授)

Pictorial Medical History (10)
Dr Lam Tat Chung, Paul (林達聰醫生)

62 An Update on Transcatheter Aortic Valve Implantation
Professor Tse Hung Fat (謝鴻發教授)
Dr Chan Pak Hei, Michael (陳柏羲醫生)

66 Updates on Male and Female Pattern Hair Loss
Dr Hau Kwun Cheung (侯韜翔醫生)

70 Tiotropium: Friend or Foe?
Dr Wong Wai Leung (王偉樑醫生)
Date: 26 October 2014 (Sunday)
Time: 11:00am to 4:00pm*
Venue: Ballroom One-Three, 18/F, The Mira Hotel Hong Kong, 118 Nathan Road, Tsimshatsui, Kowloon, Hong Kong

--- Renowned speakers include ---

**Up to date Review of Clinical Management Of Alcoholic Liver Disease (ALD) and Non-Alcoholic Fatty Liver Disease (NAFLD)**

Objective: To provide the most recent recommendations & guidance for the treatment of ALD and NAFLD.

Speaker: **Professor Mark Thursz**  
*Professor of Hepatology, Imperial College London, UK. Past Secretary General EASL*

**Liver Injury: Diagnosis and Treatment Options in the Light of Guidelines**

Objective: To give an overview of the pharmacological basis & potential role of SAMe in ALD/NAFLD.

Speaker: **Professor José M Mato**  
*CIC bioGUNE, Basque, Spain*

**Prediction of fibrosis progression in viral hepatitis**

Objective: To provide an understanding of liver fibrosis progression in the management of chronic viral hepatitis, and its future risk of cirrhosis and various complication including hepatocellular carcinoma.

Speaker: **Associate Professor Grace LH Wong**  
*Gastroenterology and Hepatology, Faculty of Medicine, The Chinese University of Hong Kong*

**The recommendations and advancement of viral hepatitis related liver protection**

Objective: To provide the most recent recommendations for the viral hepatitis related liver-protect treatment.
To provide the role of SAMe in viral hepatitis.

Speaker: **謝青 教授**  
*上海交通大学医学院附属瑞金医院, 感染科科主任, 傳染病與流行病學教研室主任, 博士生導師, 主任醫師*

---

*Lunch and refreshments will be provided. Pre-registration is required.*

For more details on registration, please see [www.SOPHYSICIANSHK.org](http://www.SOPHYSICIANSHK.org) or contact your Abbott representative or **Michelle Lee @ Tel: 2806 4252**

Free for Members, Associate Members and Invited Guests of the Society of Physicians. Other doctors: Please pay $100 on admission (do not mail your cheque).
In this issue, we feature an article on Transcatheter Aortic Valve Implantation. This procedure was pioneered about ten years ago, and has become increasingly more popular in the last few years. It is still under refinement and further investigation, but represents great potential for patients requiring aortic valve replacements who cannot undergo open heart surgery. Both cardiologists and non-cardiologists should be aware of its indications and complications, and the case selection criteria for patients suitable for TAVI.

The article on Male and Female Pattern Hair Loss helps us to understand common myths about hair loss, and brings us the latest regarding hair physiology, appropriate hygiene and management. Although not a life threatening condition, hair loss certainly plays an important part in one’s self esteem and psychological well being.

The last article on Tiotropium reviews several key articles in the use of anticholinergic agents in the management of COPD and asthma. It is most useful for General Physicians and Family Doctors who deal with such patients on a daily basis. This review will save you a lot of time having to look up the papers yourself.

I hope you will all benefit from reading this issue of the Journal.

CULT (FOLLOWERS) OF ASCLEPIUS

Over time, the Temples of Asclepius increased in sophistication and glamour. At the height of their glory, there were over 200 such temples around the then-known civilized world, including one situated on the Tiber Island in Rome.
Introduction

Degenerative aortic stenosis (AS) is a common condition in the elderly and its prevalence is increasing with the ageing population. Conventionally, symptomatic severe AS is treated with surgical aortic valve replacement (sAVR), particularly in the younger population and those with acceptable surgical risk. For unsuitable or very high-risk surgical candidates transcatheter aortic valve implantation (TAVI) is a feasible alternative to sAVR.1,2 Its use has grown exponentially in the past decade since its introduction in 2002 by Alain Cribier.3 It is estimated that over 100,000 implants have been performed worldwide since its introduction, with the most commonly implanted bioprostheses being the balloon-expandable Edward SAPIEN valve (Edwards Lifesciences, Irvine, CA, USA) and the self-expanding Medtronic CoreValve (Medtronic, Inc., Minneapolis, MN, USA). Despite the growing use of this technology, there are still several clinical challenges to be addressed in TAVI.

Patient selection

TAVI is currently indicated for “inoperable” or high-risk surgical candidates. Ideally, proper patient selection should allow us to identify patients with comorbidities that prohibit sAVR or deem the patient too high risk, warranting the alternative treatment of TAVI. As this decision may potentially affect the patient’s life expectancy and quality of life, a multidisciplinary “Heart Team” involving cardiologists, cardiothoracic surgeons, cardiac-imaging radiologists, geriatricians, nurses, physiotherapists and occupational therapists should be responsible for offering the most appropriate treatment, taking into account both clinical and psychosocial aspects.

Pre-procedural imaging

Multi-detector computed tomography

Precise aortic annulus sizing is key to accurately selecting prosthesis size. Multi-detector computed tomography (MDCT) is the most widely used imaging modality for annulus sizing,7 with three-dimensional trans-esophageal echocardiography (3D-TEE) and magnetic resonance imaging (MRI) being feasible alternatives. Due to the elliptical geometry of the annulus, use of annulus perimeter and area in guiding prosthesis size selection is advocated to avoid over- and under-sizing of TAVI bioprostheses.9 In addition, MDCT can provide information on vascular access including vessel size and presence of atherosclerotic disease (Figure 1), angulation of ascending aorta, aortic valve calcification and its relationship to coronary ostia, which can have an impact on the chance of coronary obstruction. Occasionally, incidental findings such as malignancy may affect the decision-making process of the Heart Team.

Trans-esophageal echocardiography

Intra-operative TEE can provide a real-
time biplane and 3D assessment of aortic valve and annulus prior to, and during, valve deployment, which greatly impacts precise valve positioning. TEE is also the current gold standard for determining the aetiology and severity of paravalvular aortic regurgitation (AR) after prosthesis deployment. Unfortunately, the use of TEE during TAVI usually requires general anaesthesia and endotracheal intubation. Now, with TAVI procedures being performed under local anaesthesia, the mandatory use of TEE becomes controversial. The motivation to eliminate the need for general anaesthesia has increased the interest in using intracardiac echocardiography (ICE) to guide TAVI procedures. However, single-plane ICE cannot provide accurate annulus sizing nor reliably assess paravalvular AR, thus limiting its use in TAVI.10

Assessing the severity of aortic stenosis
Severe AS is defined as an aortic valve area (AVA) <1 cm², a mean transvalvular gradient >40 mmHg and maximum jet velocity >4 m/s.11,12 Occasionally, discordant findings may be encountered with a proportion of patients having low-flow, low-gradient AS in the presence of low left ventricular ejection fraction (LVEF). In these cases, low-dose dobutamine stress echocardiography may help to distinguish true-severe AS from pseudo-severe AS – when the valve area increases together with the stroke volume and transvalvular gradient. In true-severe AS, the AVA remains unchanged despite low-dose dobutamine. However, when low-flow, low-gradient AS occurs in the setting of normal LVEF, potential errors in measuring the transvalvular gradient should be excluded and the confounding effect of body size can be eliminated by calculating the indexed AVA, which, if less than 0.6 cm²/m², indicates severe AS.

Procedural considerations
Choosing the most suitable access route for the patient is important for a successful TAVI procedure. Potential vascular access sites commonly used for TAVI include: transfemoral (TF), transapical (TA), transsubclavian and transaortic (Figure 2A–D). According to a large registry, 75% of TAVI procedures are performed using TF approach13 which is considered the least invasive approach. With the currently available delivery sheaths of 16–20 F, minimal femoral and iliac arterial diameters should be 6–6.5 mm without undue tortuosity or heavy calcification to allow a TF-TAVI. In the PARTNER II trial, lower profile SAPIEN XT system allows major vascular complication rate to be reduced from 15.5% to 9.6% (p=0.04).14

Although the TA approach avoids peripheral access issues, potential limitations include longer length of stay compared with TF-TAVI and increased risk of 30-day and 1-year all
cause mortalities; however, this may be influenced by the difference in patient co-morbidities between the two approaches. Other adverse outcomes associated with TA-TAVI include higher bleeding rate and greater patient discomfort due to the requirement of antero-lateral thoracotomy. In summary, the choice of a suitable access site is determined by clinical factors, anatomical considerations and the experience of the Heart Team.

Procedural complications

Stroke

Major strokes post-TAVI remain one of the most devastating complications, they can negate the clinical benefit of TAVI and have a negative impact on a patient’s quality of life. MRI studies have demonstrated that silent embolism occurs in up to 80% of TAVI procedures. With smaller delivery catheters, reduced or no pre-dilatation and employment of cerebral protection devices, the TAVI-related stroke rate is expected to decrease. A recent meta-analysis showed an improved peri-procedural stroke rate of 1.5% and a 30-day stroke rate of 3.3%.

Paravalvular aortic regurgitation

Moderate to severe paravalvular AR occurs in 11.7% of TAVI as shown by a recent meta-analysis and was associated with increased all-cause mortality. Accurate sizing of aortic annulus and choosing appropriate prosthesis are crucial in avoiding paravalvular AR. The depth of implanted bioprostheses and malapposition due to bulky calcification are other common associated risk factors and further post-dilatation or consideration of valve-in-valve or vascular plug implantation are possible bail-out strategies. Newer TAVI devices, such as Edwards SAPIEN 3, Medtronic Evolut R and Boston Scientific Lotus (Figure 3A–C), have been developed with the aim of reducing this devastating complication by improving sub-valvular fixation or allowing retrieval and repositioning of bioprosthesis. Additional advantages of some of these devices include lower profile of delivery system and wider range of choices for access route.

Conduction abnormalities

The occurrence of conduction disturbances and subsequent need for permanent pacemaker implantation (PPM) remains a major concern after TAVI procedures. A meta-analysis revealed a significant difference in requirement for PPM post-TAVI between the two commonly implanted TAVI devices, 6.5% with SAPIEN vs 25.8% with CoreValve (p<0.001). This maybe attributable to valve design and the potential for deeper implantation into the left ventricular outflow tract, causing injury to the atrioventricular (AV) node and left bundle branches. A recent study has also demonstrated that male sex, intraprocedural AV block and baseline conduction abnormalities (first-degree AV block, left anterior hemiblock and right bundle branch block) were also predictors of PPM implantation after TAVI.

Future direction and challenges

With the exponential growth in the use of TAVI procedures worldwide and a trend towards lower procedural complications, there may be value in treating lower-risk surgical patients with TAVI. Ongoing trials such as SURTAVI (CoreValve) and PARTNER II (SAPIEN XT valve) are examining the feasibility and outcomes of TAVI for intermediate-risk AS patients (STS score 4–8%). Some studies have also examined the efficacy of TAVI in patients with pure AR and patients with failing bioprostheses or homografts. However, further robust evidence is needed before the indications for TAVI can be extended further to these subsets of patients.

Conclusion

TAVI provides a worthwhile option for high-risk or unsuitable surgical candidates with symptomatic severe AS. Despite the impressive growth in its use in the past decade, attention should now be focused on improving patient risk stratification, device and access route selection, and reducing procedural complications before its clinical indication can be expanded further.

References


A complete list of references can be downloaded from www.SOPHYSICIANSHK.org
First-line treatment for chronic hepatitis B (CHB) in adults\textsuperscript{1,3} Maximizing outcomes in CHB out to 7 years

One liver. One life. One VIREAD.

- Potent and sustained viral suppression\textsuperscript{4}
- 0\% resistance detected through 7 years\textsuperscript{2,4}
- Regression of fibrosis or cirrhosis\textsuperscript{5}

Abbreviated Prescribing Information

**Presentation:** Film-coated tablet containing 300 mg of tenofovir disoproxil fumarate (TDF).

**Indications:** 1. Treatment of chronic hepatitis B (CHB) in adults. 2. In combination with other antiretroviral medicinal products for treatment of HIV-1 infected adults and pediatric patients 12 years of age and older.

**Dosage:** Adults: One tablet once daily taken orally, without regard to food. Pediatric patients: CHB: Not recommended; HIV-1: One tablet once daily taken orally, without regard to food for patients ≥12 years of age and ≥35 kg.

**Elderly:** Insufficient data to make dose recommendations for patients >65 years. The dosing interval of VIREAD should be adjusted in patients with baseline creatinine clearance <50 ml/min.

**Contraindications:** None.

**Warnings and Precautions:** Lactic acidosis/severe hepatomegaly with steatosis; severe exacerbation of hepatitis after discontinuation of anti-HBV treatment; new onset or worsening renal impairment; coadministration with products containing TDF or adefovir disoproxil; patients coinfected with HIV-1 and HBV; decreases in bone mineral density; fat redistribution; immune reconstitution syndrome; early virologic failure. Interactions & Side effects: refer to Package Insert.

Before prescribing, please consult full prescribing information which is available upon request.

Viread is a registered trademark.


Gilead Sciences Hong Kong Limited
Room 2603, 26th Floor, Hysan Place, 100 Hennessy Road, Causeway Bay, Hong Kong
Tel: (852) 3129 2037 Fax: (852) 2856 2611
Hair structure and growth

Hair is largely made up of dead cells and keratin which form the cuticle, cortex and medulla. There are three kinds of hair:

- Lanugo hair is found on newborns and is usually not pigmented and shed shortly after birth
- Vellus hair is short and thin, like those hairs found on babies
- Terminal hair is thick and long and found after puberty

Hair grows from hair follicles and each follicle can have 1–4 hairs. All the hair follicles we have are already present at birth and no new hair follicles will be formed afterwards. There are approximately 5 million hair follicles covering our body, except our palms and soles, of which only 2% is on our scalp. There, the density of hair follicles is about 39.6 (standard deviation [SD] ±10.8)/4 mm², corresponding to around 100,000 hair follicles.¹

This 2% of hair can greatly affect our appearance and the perception of youth and age. Loss of hair, or alopecia, can be of great psychosocial stress, especially when the hair loss is premature.

Hair growth cycle

Hair grows from the hair bulb where it receives nutrients and melanin for its colour. It can grow for 2–6 years, this is the anagen phase and about 90% of hair is in this phase. About 1% is in the catagen phase, a transitional phase in which hair detaches from blood supply, stops growing and the hair follicle starts to shrink. This takes about 3 weeks. The telogen phase, the resting phase, is where hair shedding occurs, this involves around 10% of hair. Finally, a new hair bulb grows and the cycle restarts.

Pattern hair loss

Androgenetic alopecia (AGA) is commonly used to describe male pattern baldness but can also be used to describe pattern hair loss in women. In terms of reflecting the underlying aetiology, the term AGA is now considered to be over-simplified. Hair shedding occurs every day, with around 50–100 scalp hairs shed each day, a consistent loss of >100 hairs per day is considered significant hair loss. There are different causes of hair loss; however, 95% of hair loss is genetic. Both male and female pattern hair loss (MPHL and FPHL) represent the respective patterns of hair loss that occur in each sex unrelated to other causes of diffuse hair loss. Both are often familial and have a polygenetic inheritance. Follicular size can change under systemic and local influences, thus affecting the hair density and quality. In men, androgens are one of the most important regulators of hair regrowth.

Male pattern hair loss

Pattern hair loss is the commonest cause of hair loss in men; it typically occurs between puberty and age 30 but can occur any time between the late teenage and 40–50 years of age. An estimated 40% of men suffer from this pattern hair loss and most men have a 50% chance of experiencing it by 50 years of age. Among different androgens, dihydrotestosterone (DHT) was established as the key androgen in shortening of the anagen growth phase and progressive follicular miniaturization that accompanies each hair growth, loss, and regrowth. The pattern of hair loss is often predictable and consistent among different ethnic populations. These features are considered as hallmarks of the disease.

Female pattern hair loss

FPHL is thought to start between puberty and 20s, with a second peak in the early 40s and is also likely to begin in women aged over 50 years. An estimated 25% of women suffer from FPHL; however, accurate identification of the factors that produce FPHL has remained elusive. The following conditions, or an interplay of one another, may cause the manifestations of FPHL:¹²³

- Hormone changes
- Genetic polymorphisms of sex hormone receptors
- Cell programmed death
- Individual follicle cycle pattern
- Molecular ecology of hair growth
The pattern is not likely to be obviously recognizable but involves a diffuse thinning or frontal accentuation that is mostly in the frontoparietal and temporal region of the scalp. Hairs are miniaturized without hair breakage, patchy loss or scalp scarring. It may not have any obvious hereditary association on history taking or family history recall. Hence, before making the diagnosis of AGA in women, medical causes must be ruled out, for example, thyroid disease, medications or inadequate dietary protein and iron.

**Microscopic assessment of hair loss**

Microscopic scalp hair assessment and trichoscopy can provide early signs of hair loss. This includes the density of hair follicles or hair, the hair growth per follicle and the hair thickness. There are around 110 follicles and 250 pieces of hair per 1 cm² scalp for Asians. The smaller the number of follicles (with hair) in an assessed area, the higher the risk of atrophied hair follicles. For Asians, there are generally around 2–3 hairs per follicle and if the majority of hair follicles grow only a single hair, this implies the potential risk of atrophied hair follicles and sign of scalp aging. Thinning of hair is also another sign...
of scalp aging due to atrophied hair follicles.

Common myths
There are numerous myths pertaining to hair loss: The prevalence of the condition, the psychological and social embarrassment, the limited treatment options, the slow response to treatment of hair regrowth and the long-term commitment required for successful treatment. These are also some of the limiting factors in current alopecia management.

Nevertheless, stress, diet, smoking, obesity and vigorous weight loss contribute to hair loss. Different kinds of hair styling and treatment like teasing, hair dyeing, perming, chemical hair spray or frequent and inappropriate hair washing and blow drying will increase hair loss through hair shaft breakage or scalp injury as well as hair root damage.

Unfortunately, the condition is often not regarded as a disease. The treatment options available in the market and the hair products that claim to have therapeutic effects are poorly regulated. Current medical science has enabled us to understand the pathogenesis as well as provide evidence-based treatment for the disease. Our clinical advice and management should be to deliver the best quality and up-to-date professional treatment.

Management and treatment
Patients presenting with hair thinning or loss should first be informed that this may be pathological or hereditary hair loss. An empathetic approach should be used and a detailed history and examination undertaken. Microscopic assessments like trichoscopy are often useful and can facilitate a thorough evaluation of the hair shaft, density and scalp condition. A thorough differential diagnosis list is vital, bearing in mind that this may be the only time the patient receives medical attention to their hair loss. The selection of treatment depends on the hair loss pattern, severity, gender and cost. Early initiation of treatment is key to prevent more hair loss and reduce psychological consequences. Additionally, patient education and counseling is important to ensure the patient has reasonable expectations of treatment outcomes and adheres to treatment.

There are numerous publications related to the understanding and treatment of hair loss. In one S3 guideline, the researchers identified 43 studies supporting topical minoxidil, 18 studies supporting the use of finasteride, 2 studies supporting the use of dutasteride, 9 studies supporting the use of oral and topical hormones and 14 studies supporting the use of miscellaneous oral and topical agents. However, not all of these reach a high level for recommendation. Therefore, we need to adhere to the latest guidelines and consensus for management of pattern hair loss.

Currently approved pharmacological treatments include topical minoxidil and oral finasteride tablets. Non-pharmacological treatments like hair transplantation, hairpieces, prostheses or laser treatments are also helpful.

Minoxidil is an antihypertensive medication with peripheral vasodilator properties which, when taken systemically, causes hypertrichosis. Once topically applied, minoxidil is converted to minoxidil sulfate, a potassium channel opener which relaxes vascular smooth muscle and increases blood flow. However, this may not be the reason for hair growth and the exact mechanism of action is still unknown, but it is postulated to be a non-specific biological response modulator.

Minoxidil can promote hair growth by prolonging the anagen phase of the hair cycle, enlarging miniaturized follicles and reversing the miniaturization process by increasing follicular size and hair shaft diameter. It also shortens the telogen phase, keeping more follicles in the growth phase at the same time, making it possible to see improved coverage of the scalp.

Topical minoxidil is available as a 2% and 5% preparation, both have proven clinical efficacy with a good safety profile. They stabilize hair loss in >80% of patients and stimulate hair growth in about 60% of patients. The most common side effect is irritation to scalp (dermatologic adverse events) and minoxidil has no effect on hormones, unlike oral finasteride. The 5% preparation has shown greater efficacy on stimulation of hair growth than the 2% preparation when used in men, but there may not be enough data to recommend the 5% preparation instead of the 2% preparation in women. In order to achieve the best result compliance must be emphasized to the patient. The preparation should be applied directly to the scalp twice-daily, especially in the early stages of treatment. It should be explained that it could take up to 16 weeks of consecutive use for a more visible result, even though a temporary increase in telogen hair loss is possible during the first month before the anagen phase is induced. Treatment needs to be continued to maintain efficacy.

Oral finasteride is the first and only FDA-approved once-a-day pill for treating AGA, except in the case of bitemporal receding hairlines. It is only indicated for use in men because of the potential for male foetus abnormalities. Thus, women of childbearing potential should not handle crushed or broken tablets. It also has the potential for sexual side effects discouraging some consumers from use, 3.8% of 945 men reported one or more of the following: Decreased libido, erectile dysfunction, ejaculation disorder (decreased volume of ejaculate) and discontinuation due to drug-related sexual adverse experiences as compared with 20 of 934 men (2.1%) treated with placebo (p=0.04). Resolution occurred in men who discontinued therapy with finasteride due to these side effects and in most of those who continued therapy. The incidence of sexual

September 2014
adverse experiences decreased to ≤0.3% by year 5 of treatment with finasteride. The relationship between long-term use of finasteride and male breast neoplasia is currently unknown. Although finasteride-treated men must avoid donating blood, transfer of the drug in sexual intercourse is considered minimal and use of a condom is not necessary for this reason. It is known that finasteride reduces the Prostate Specific Antigen (PSA) level, therefore, if treatment is started after the age of 45 years, monitoring of PSA level should be considered. PSA levels should be doubled to compensate for the reduction due to finasteride, resulting in an interpretation of the test remaining accurate. Finasteride treatment has to be continuous to maintain its therapeutic effect.

Other oral options include dutasteride, oral hormones and anti-androgen medications. However, there is little evidence to support the use of oral or topical hormonal treatment in men and women with AGA and limited evidence that oral cyproterone acetate may be helpful in women with AGA and hyperandrogenism.

Hair transplantation can be considered to improve male pattern hair loss in suitable patients with sufficient donor hair supply and medically controlled or spontaneously stabilized AGA, especially for the frontoparietal area. It can also be considered in female patients with sufficient donor hair.

References
COPD is ranked the 4th leading cause of death worldwide, with an estimated 3.02 million deaths in 2004. Long-acting anticholinergic is widely known to be an important pharmacological therapy in the management of COPD. Use of tiotropium in COPD has been incorporated into the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline.

A foe?

In 2004, tiotropium was approved by the Food Drug Administration (FDA) in the USA as the first long-acting anticholinergic bronchodilator for treatment of COPD. A randomized, double-blind trial comparing 4 years of therapy with either tiotropium or placebo (patients were allowed to use all respiratory medications except inhaled anticholinergic) for patients with COPD showed that tiotropium treatment was associated with improvements in lung function, quality of life (St George’s Respiratory Questionnaire score), lower risk of exacerbation-related hospitalizations and respiratory failure (UPLIFT trial).

However, a meta-analysis by Singh et al published in September 2008 suggested that inhaled anticholinergics (ipratropium and tiotropium) were associated with an increased risk of cardiovascular (CV) death, myocardial infarction or stroke among patients with COPD (relative risk, 1.58; 95% confidence interval [CI] 1.2–2.06; p<0.001).

In a further meta-analysis published in 2011, both 10 µg and 5 µg doses of tiotropium Respimat were found to be associated with an increased risk of mortality (relative risk 1.52; 95% CI, 1.06–2.16; p=0.02). This finding contradicted the safety analysis from pooled data of tiotropium trials and UPLIFT.

Table 1. Safety data from pooled analysis of tiotropium trials and UPLIFT

<table>
<thead>
<tr>
<th>Attribute</th>
<th>29 Pooled trials (N=13,544)</th>
<th>UPLIFT (N=5,992)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study duration (months)</td>
<td>1–12</td>
<td>48</td>
</tr>
<tr>
<td>Patient-years (placebo group)</td>
<td>3,065</td>
<td>8,499</td>
</tr>
<tr>
<td>Patient-years (tiotropium group)</td>
<td>4,571</td>
<td>9,222</td>
</tr>
<tr>
<td>Relative risk (95% CI)</td>
<td>1.37 (0.73–15.6)</td>
<td>0.95 (0.70–1.29)</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.71 (0.51–0.99)</td>
<td>0.73 (0.56–0.95)</td>
</tr>
<tr>
<td>Death from cardiovascular cause</td>
<td>0.97 (0.54–1.75)</td>
<td>0.85 (0.74–0.98)</td>
</tr>
</tbody>
</table>

Table 2. Risk of death of using tiotropium Respimat vs tiotropium Handihaler

<table>
<thead>
<tr>
<th>Variable</th>
<th>Tiotropium Respimat 2.5 µg (N=5,730)</th>
<th>Tiotropium Respimat 5 µg (N=5,711)</th>
<th>Tiotropium Handihaler 18 µg (N=5,694)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death in follow-up analysis</td>
<td>440 (7.7)</td>
<td>423 (7.4)</td>
<td>439 (7.7)</td>
<td>1.00 (0.87–1.14)</td>
</tr>
<tr>
<td>Death in as-treated analysis</td>
<td>359 (6.3)</td>
<td>326 (5.7)</td>
<td>357 (6.3)</td>
<td>1.00 (0.86–1.16)</td>
</tr>
<tr>
<td>Adjudicated primary cause of death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular cause</td>
<td>119 (2.1)</td>
<td>113 (2.0)</td>
<td>101 (1.8)</td>
<td>1.17 (0.90–1.53)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>10 (0.2)</td>
<td>11 (0.2)</td>
<td>3 (0.1)</td>
<td></td>
</tr>
<tr>
<td>Sudden death</td>
<td>82 (1.4)</td>
<td>67 (1.2)</td>
<td>68 (1.2)</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>10 (0.2)</td>
<td>14 (0.2)</td>
<td>11 (0.2)</td>
<td></td>
</tr>
<tr>
<td>Other cardiovascular cause</td>
<td>17 (0.3)</td>
<td>21 (0.4)</td>
<td>19 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Respiratory cause</td>
<td>143 (2.5)</td>
<td>148 (2.6)</td>
<td>155 (2.7)</td>
<td></td>
</tr>
<tr>
<td>Neoplasm</td>
<td>110 (1.9)</td>
<td>100 (1.8)</td>
<td>95 (1.7)</td>
<td></td>
</tr>
<tr>
<td>Undetermined or unknown cause</td>
<td>35 (0.6)</td>
<td>27 (0.5)</td>
<td>37 (0.6)</td>
<td></td>
</tr>
<tr>
<td>Other cause</td>
<td>33 (0.6)</td>
<td>35 (0.6)</td>
<td>51 (0.9)</td>
<td></td>
</tr>
<tr>
<td>Death of patients with previous cardiac arrhythmia, according to vital status at follow-up</td>
<td>79 (13.1)</td>
<td>65 (10.6)</td>
<td>78 (12.9)</td>
<td>1.02 (0.74–1.39)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.81 (0.58–1.12)</td>
</tr>
</tbody>
</table>
of UPLIFT trial which showed relative risk of stroke, myocardial infarction and death from CV causes in the tiotropium group to be 0.95, 0.71 and 0.73, respectively.3

These two meta-analyses triggered substantial concern as CV morbidity and mortality rates are already higher for patients with COPD than for the general population. In an epidemiological cohort published in 2005, CV morbidity and mortality rates were higher in the COPD cohort than in the general population (standardized rate ratios of 1.9 and 2.0, respectively).6

In view of these conflicting data and rising public health concern, the FDA convened a meeting in November 2009 to review the data on CV morbidity and mortality risk of this long-acting anticholinergic. They came to the conclusion that the data provided by the UPLIFT trial3 had adequately addressed the issues of CV and stroke risk raised by the Singh et al meta-analysis. In view of the large sample size, lengthy follow-up period, pre-specified safety endpoints and adequate safety profile data provided by UPLIFT3 and the potential methodological limitations of the Singh et al meta-analysis, the FDA concluded that use of tiotropium was not associated with increased risk of stroke, CV disease or death (Table 1).7

A large randomized trial was designed to address the potential risk of tiotropium Respimat. TIOtropium Safety and Performance In Respimat (TIOSPIR) trial, published in August 2013, was a randomized, double-blind, parallel-group trial involving 17,135 patients with COPD.8 This trial evaluated the safety and efficacy of tiotropium Respimat at a once-daily dose of 2.5 µg or 5 µg as compared with tiotropium Handihaler at a once-daily dose of 18 µg. During a mean follow up of 2.3 years, Respimat was non-inferior to Handihaler with respect to risk of death (Respimat 5 µg vs Handihaler: hazard ratio [HR], 0.96; 95% CI, 0.84–1.09; Respimat 2.5 µg vs Handihaler: HR, 1.00; 95% CI, 0.87–1.14) and was not superior to Handihaler with respect to the risk of first exacerbation. Cause of death and incidence of major cardiovascular adverse events were similar in the three groups (Table 2 and 3, Figure 1).8

In conclusion, tiotropium Respimat at doses of 5 µg and 2.5 µg had a safety profile and exacerbation risk similar to tiotropium Handihaler at a dose of 18 µg in patients with COPD.

<table>
<thead>
<tr>
<th>Event</th>
<th>Tiotropium Respimat 2.5 µg (N=5,724)</th>
<th>Tiotropium Respimat 5 µg (N=5,705)</th>
<th>Tiotropium HandiHaler 18 µg (N=5,687)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any serious adverse event</td>
<td>1,937 (33.8)</td>
<td>1,846 (32.4)</td>
<td>1,842 (32.4)</td>
</tr>
<tr>
<td>Respiratory, thoracic, or mediastinal disorder</td>
<td>1,017 (17.8)</td>
<td>957 (16.8)</td>
<td>964 (17.0)</td>
</tr>
<tr>
<td>Infection or infestation</td>
<td>497 (8.7)</td>
<td>502 (8.8)</td>
<td>495 (8.7)</td>
</tr>
<tr>
<td>Cardiac disorder</td>
<td>293 (5.1)</td>
<td>273 (4.8)</td>
<td>270 (4.7)</td>
</tr>
<tr>
<td>Major adverse cardiovascular events</td>
<td>224 (3.9)</td>
<td>222 (3.9)</td>
<td>202 (3.6)</td>
</tr>
<tr>
<td>Stroke</td>
<td>56 (1.0)</td>
<td>52 (0.9)</td>
<td>57 (1.0)</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>25 (0.4)</td>
<td>30 (0.5)</td>
<td>20 (0.4)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>70 (1.2)</td>
<td>73 (1.3)</td>
<td>52 (0.9)</td>
</tr>
</tbody>
</table>

Table 3. Serious adverse events and major adverse cardiovascular events8

Tiotropium Respimat 2.5 µg vs Tiotropium HandiHaler

<table>
<thead>
<tr>
<th>Event</th>
<th>Tiotropium Respimat 2.5 µg vs Tiotropium HandiHaler (Hazard Ratio (95% CI))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major adverse cardiovascular events</td>
<td>1.11 (0.91–1.34)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.24 (0.89–2.24)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1.34 (0.94–1.92)</td>
</tr>
</tbody>
</table>
A friend?

The short-acting anticholinergic agent ipratropium is listed in the Global Initiative for Asthma (GINA) guideline as a reliever medication for acute exacerbations of asthma.9 According to a Cochrane Review, ipratropium may not be justified as a controller medication while the action of long-acting anticholinergic in this role is unknown.10 Currently, adults with inadequately controlled asthma have the treatment options of addition of:11

- leukotriene modifier
- sustained-release theophylline
- long-acting beta-agonist (LABA)
- increased dose of inhaled glucocorticoid

Peters et al have undertaken a three-way, double-blind, triple-dummy crossover trial involving 210 patients with uncontrolled asthma receiving only inhaled glucocorticoid. This trial evaluated the outcome of adding tiotropium bromide to these patients versus outcome of doubling the dose of inhaled glucocorticoid (primary superiority comparison) or adding LABA salmeterol (secondary non-inferiority comparison).12 The tiotropium treatment group had a superior outcome when compared with doubling the dose of glucocorticoid in the following categories: peak expiratory flow rate (mean difference of 25.8 L/min; p<0.001); evening peak expiratory flow rate (mean difference 35.5 L/min; p<0.001); proportion of asthma control days (difference of 0.079; p=0.01); forced expiratory volume in 1 second (FEV1) before bronchodilatation (a difference of 0.10 L; p=0.004) and daily symptom scores (with a difference of −0.11 points; p<0.001). The addition of tiotropium to treatment was non-inferior for all assessed outcomes with an increase in pre-bronchodilator FEV1, greater than salmeterol (with a difference of 0.11 L; p=0.003) (Figure 2).12

In conclusion, for patients with poorly controlled asthma receiving inhaled glucocorticoid treatment, the...
addition of tiotropium greatly improved symptoms and lung functions compared with doubling the dose of inhaled glucocorticoid. Tiotropium’s efficacy appeared to be equivalent to that of salmeterol.12

In further studies by Kerstjens et al, 912 patients with poorly controlled asthma receiving inhaled steroid and LABA were randomized to receive either tiotropium (5 μg) or placebo treatment for 48 weeks in two replica, controlled trials.13 Tiotropium was delivered by a soft-mist inhaler. FEV1 and risk of acute exacerbations were end points for comparison. At 24 weeks, the mean change in peak FEV1 from baseline was greater with tiotropium than with placebo in the two trials (a difference of 86±34 ml in trial 1; p=0.01 and 154±32 ml in trial 2; p<0.001). The pre-dose FEV1, also showed improvement in trial 1 and 2 in the tiotropium treatment arm as compared with placebo. The tiotropium treatment arm showed increased time to first severe exacerbation (282 days vs 226 days), overall reduction of 21% in risk of severe exacerbation (hazard ratio, 0.79; p=0.03). The safety profile of death and adverse events were similar between the placebo and tiotropium groups (Figure 3).13

In conclusion, for patients with poorly controlled asthma receiving inhaled glucocorticoid and LABA, the addition of tiotropium significantly increased the time to the first severe exacerbation and reduced the risk of severe exacerbation by 21%.

However, in view of the small number of patients involved in these studies, we cannot yet include tiotropium as a standard therapy in asthma control. Large-scale randomized studies will be required to test the efficacy, safety profile and long-term outcomes of this long-acting anticholinergic in patients with poorly controlled asthma.

Discussion

Until now, evidence provided by both UPLIFT and TIOSPIR trials has supported tiotropium as a safe medication via both delivery systems in COPD patients. Therefore, it should not be withheld as treatment for patients with a history of CV disease, particularly as previous studies have demonstrated that COPD patients are more prone to CV morbidity and mortality.

Recent evidence has suggested that tiotropium improves peak flow rates, FEV1, symptom control and decreases risk of acute exacerbations in poorly controlled asthmatic patients already on a moderate dose of inhaled steroid. Further studies are needed to evaluate its role in long-term maintenance therapy for patients with poorly controlled asthma.

References
**SPIRIVA®** Your first choice for COPD maintenance therapy

- Prompt\(^1\) and sustained reduction of breathlessness\(^3,4,12\)
- Reduced risk of COPD exacerbations and hospitalisations\(^5,6,10,11\)**\(^\#\)
- Improved quality of life\(^6-8,10\)**\(^\#\)
- Reduced mortality\(^6,9,11\)**\(^\#\)

SPIRIVA\(^\circledR\) is indicated for the maintenance treatment of patients with COPD (including chronic bronchitis and emphysema), the maintenance treatment of associated dyspnoea and for prevention of exacerbations. In long-term studies of SPIRIVA\(^\circledR\), the most commonly reported anticholinergic adverse reaction was dry mouth (4%). Dry mouth was usually mild and often resolved with continued treatment.

COPD: Chronic Obstructive Pulmonary Disease.

---

**References:**
1. SPIRIVA\(^\circledR\) Respimat® Prescribing Information. Hong Kong.
2. SPIRIVA\(^\circledR\) HandiHaler® Prescribing Information. Hong Kong.

Please consult full prescribing information before prescribing.
References: