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Lower Urinary Tract Symptoms

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*OAB: Overactive Bladder + LUTS: Lower Urinary Tract Symptoms
α_1-blockers are often considered the first line drug treatment of male LUTS[3]

Reference: **1.** Chapple C.R. et al. Neurourol Urodynam 2013 [doi 10.1002/nau22505] **2.** Chapple C.R. et al. Eur Urol Supp. 2005; 4:33-44
3. Gravas S, et al. EAU Guidelines on the Treatment of Non-neurogenic Male LUTS. European Association of Urology. 2017.

Abbreviated prescribing information of Harnal OCAS® 0.4 mg Tablets
Version: 002 PI version: Sep 2013. **Composition:** Tamsulosin HCl **Indication:** Lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH). **Dosage:** 1 tab daily, can be taken independently of food. **Administration:** Swallow whole, do not chew/crunch. **Contraindications:** Hypersensitivity to tamsulosin hydrochloride or to any of the excipients. **Special warnings and special precaution for use:** As with other α1-adrenoceptor antagonists, a reduction in blood pressure can occur in individual cases during treatment with Harnal OCAS® 0.4 mg Tablets, as a result of which, rarely, syncope can occur. At the first signs of orthostatic hypotension (dizziness, weakness), the patient should sit or lie down until the symptoms have disappeared. Before therapy with Harnal OCAS® 0.4 mg Tablets is initiated, the patient should be examined in order to exclude the presence of other conditions, which can cause the same symptoms as benign prostatic hyperplasia. Digital rectal examination and, when necessary, determination of prostate specific antigen (PSA) should be performed before treatment and at regular intervals afterwards. Treatment of patients with a history of orthostatic hypotension should be approached with caution. The treatment of patients with severe renal impairment (creatinine clearance of <10 ml/min) should be approached with caution, as these patients have not been studied. The treatment of patients with severe hepatic dysfunction should be approached with caution. The 'Intraoperative Floppy Iris Syndrome' (IFIS, a variant of small pupil syndrome) has been observed during cataract and glaucoma surgery in some patients on or previously treated with tamsulosin hydrochloride. IFIS may increase the risk of eye complications during and after the operation. Discontinuing tamsulosin hydrochloride 1-2 weeks prior to cataract or glaucoma surgery is anecdotally considered helpful, but the benefit of treatment discontinuation has not been established. IFIS has also been reported in patients who had discontinued tamsulosin for a longer period prior to the surgery. The initiation of therapy with tamsulosin hydrochloride in patients for whom cataract or glaucoma surgery is scheduled is not recommended. During pre-operative assessment, surgeons and ophthalmic teams should consider whether patients scheduled for cataract or glaucoma surgery are being or have been treated with tamsulosin in order to ensure that appropriate measures will be in place to manage the IFIS during surgery. Tamsulosin hydrochloride should not be given in combination with strong inhibitors of CYP3A4 in patients with poor metaboliser CYP2D6 phenotype. Tamsulosin hydrochloride should be used with caution in combination with strong and moderate inhibitors of CYP3A4. Cases of allergic reaction to tamsulosin in patients with a past history of sulfonamide allergy have been reported. If a patient reports a previously experienced sulfa allergy, caution is warranted when administrating tamsulosin hydrochloride. **Undesirable effects:** *Common (>1%, <10%), Uncommon (>0.1%, <1%), Rare (>0.01%, <0.1%), Very rare (<0.01%). Cardiac disorder: Uncommon:* Palpitations. *Gastrointestinal disorders: Uncommon:* Constipation, diarrhoea, nausea, vomiting. *General disorders and administration site conditions: Uncommon:* Asthenia. *Nervous systems disorders: Common:* Dizziness (1.3%). *Uncommon:* Headache. *Rare: Syncope. Reproductive system and breast disorders: Common:* Ejaculation disorders. *Very rare:* Priapism. *Respiratory, thoracic and mediastinal disorders: Uncommon:* Rhinitis. *Skin and subcutaneous tissue disorders: Uncommon:* Rash, pruritus, urticaria. *Rare:* Angioedema. *Vascular disorders: Uncommon:* Orthostatic hypotension. ***Post-marketing experience:*** The following events have also been reported during the post-marketing period. These events are reported voluntarily from a population of uncertain size, therefore it is not possible to reliably estimate their frequency: visual disorders (e.g. blurred vision, visual impairment), dermatitis exfoliative, erythema multiforme and epistaxis. During cataract and glaucoma surgery a small pupil situation, known as Intraoperative Floppy Iris Syndrome (IFIS), has been reported. **Full prescribing information is available upon request.**

Abbreviated prescribing information of Betmiga® prolonged-release tablets
Version: 003 PI version: Apr 2016. **Composition:** Mirabegron **Indication:** Symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with overactive bladder (OAB) syndrome. **Dosage:** Adult including elderly 50 mg once daily with or without food. **Administration:** Swallow whole with liquids. Do not chew/divide/crush. **Contraindications:** Mirabegron is contraindicated in patients with - Hypersensitivity to the active substance or to any of the excipients. - Severe uncontrolled hypertension defined as systolic blood pressure ≥ 180 mm Hg and/or diastolic blood pressure ≥ 110 mm Hg. **Special warnings and precautions for use:** Renal impairment: Betmiga has not been studied in patients with end stage renal disease (GFR < 15 mL/min/1.73 m^2 or patients requiring haemodialysis) and, therefore, it is not recommended for use in this patient population. Data are limited in patients with severe renal impairment (GFR 15 to 29 mL/min/1.73 m^2); based on a pharmacokinetic study a dose reduction to 25 mg is recommended in this population. Betmiga is not recommended for use in patients with severe renal impairment (GFR 15 to 29 mL/min/1.73 m^2) concomitantly receiving strong CYP3A inhibitors. Hepatic impairment: Betmiga has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) and, therefore, it is not recommended for use in this patient population. Betmiga is not recommended for use in patients with moderate hepatic impairment (Child-Pugh B) concomitantly receiving strong CYP3A inhibitors. Hypertension: Mirabegron can increase blood pressure. Blood pressure should be measured at baseline and periodically during treatment with Betmiga, especially in hypertensive patients. Data are limited in patients with stage 2 hypertension (systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 100 mm Hg). Patients with congenital or acquired QT prolongation: Betmiga, at therapeutic doses, has not demonstrated clinically relevant QT prolongation in clinical studies. However, since patients with a known history of QT prolongation or patients who are taking medicinal products known to prolong the QT interval were not included in these studies, the effects of mirabegron in these patients is unknown. Caution should be exercised when administering mirabegron in these patients. Patients with bladder outlet obstruction and patients taking antimuscarinics medications for OAB: Urinary retention in patients with bladder outlet obstruction (BOO) and in patients taking antimuscarinic medications for the treatment of OAB has been reported in postmarketing experience in patients taking mirabegron. A controlled clinical safety study in patients with BOO did not demonstrate increased urinary retention in patients treated with Betmiga; however, Betmiga should be administered with caution to patients with clinically significant BOO. Betmiga should also be administered with caution to patients taking antimuscarinic medications for the treatment of OAB. **Undesirable effects:** Summary of the safety profile: The safety of Betmiga was evaluated in 8,433 patients with OAB, of which 5,648 received at least one dose of mirabegron in the phase 2/3 clinical program, and 622 patients received Betmiga for at least 1 year (365 days). In the three 12-week phase 3 double blind, placebo controlled studies, 88% of the patients completed treatment with Betmiga, and 4% of the patients discontinued due to adverse events. Most adverse reactions were mild to moderate in severity. The most common adverse reactions reported for patients treated with Betmiga 50 mg during the three 12-week phase 3 double blind, placebo controlled studies are tachycardia and urinary tract infections. The frequency of tachycardia was 1.2% in patients receiving Betmiga 50 mg. Tachycardia led to discontinuation in 0.1% patients receiving Betmiga 50 mg. The frequency of urinary tract infections was 2.9% in patients receiving Betmiga 50 mg. Urinary tract infections led to discontinuation in none of the patients receiving Betmiga 50 mg. Serious adverse reactions included atrial fibrillation (0.2%). Adverse reactions observed during the 1-year (long term) active controlled (muscarinic antagonist) study were similar in type and severity to those observed in the three 12-week phase 3 double blind, placebo controlled studies. List of adverse reactions: The table below reflects the adverse reactions observed with mirabegron in the three 12-week phase 3 double blind, placebo controlled studies. The frequency of adverse reactions is defined as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Infections and infestations: Common: Urinary tract infection. Uncommon: Vaginal infection, Cystitis. Psychiatric disorders: Not known (cannot be estimated from the available data): Insomnia*. Eye disorders: Rare: Eyelid oedema. Cardiac disorders: Common: Tachycardia. Uncommon: Palpitation, Atrial fibrillation. Vascular disorders: Very rare: Hypertensive crisis*. Gastrointestinal disorders: Common: Nausea*, Constipation*, Diarrhoea*. Uncommon: Dyspepsia, Gastritis. Rare: Lip oedema. Skin and subcutaneous tissue disorders: Uncommon: Urticaria, Rash, Rash macular, Rash popular, Pruritus. Rare: Leukocytoclastic vasculitis, Purpura, Angioedema*. Musculoskeletal and connective tissue disorders: Uncommon: Joint swelling. Reproductive system and breast disorders: Uncommon: Vulvovaginal pruritus. Investigations: Uncommon: Blood pressure increased, GGT increased, AST increased, ALT increased. Renal and urinary disorders: Rare: Urinary retention*. Nervous system disorders: Common: Headache*, Dizziness*. *observed during post-marketing experience. **Full prescribing information is available upon request.**

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The Cover Shot

This December 2019 family photo shows Victoria Falls (VF) on the Zambezi River in southern Africa. VF is located on the border between Zambia and Zimbabwe, and is classified as the world's largest sheet of falling water (not highest nor widest) based on its combined width of 1,708 metres and height of 108 metres. The underlying basalt rock (玄武岩) is very dense and hard, resisting erosion; as such, the river removes the rock one block at a time, resulting in a rough hewn appearance rather than a smooth, water-torm surface. In the photo, the low rainfall has revealed the wrinkled rock surface normally hidden under torrential water flows.

Reference
https://en.wikipedia.org/wiki/Victoria_Falls

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LUTS: Introduction and Epidemiology

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Editor

Dr Siu-king MAK

HONG KONG POPULATION

Hong Kong's population will be a lot greyer in the next 20 years. The Census and Statistics Department has forecasted that our elderly population will increase from 1.32 million in 2019 to 2.52 million in 2039. This is the effect of post-war baby boomers entering old age.[1] The median age would increase from 45.5 in 2019 to 52.5 in 2039.

We would expect a steep rise in the number of elderly patients utilising our healthcare system. Lower urinary tract symptoms (LUTS) is a common medical condition in the elderly population with significant impact on the quality of life worldwide. LUTS incidence increases with age. LUTS can affect patients of both sexes and all ages. LUTS in the elderly is a common but long-neglected problem. Gacci has shown that a number of modifiable medical risk factors are associated with LUTS development. These risk factors are potential targets for modification.[2] In addition, men with moderate-to-severe LUTS may have an increased risk of major adverse cardiac events[3]. The associated costs and burdens of LUTS are therefore likely to increase[4]. LUTS, in particular nocturia, is also a risk factor for falls and fractures in the elderly. The elderly are also prone to the adverse effects of anti-cholinergic agents, which worsen physical and cognitive functions. As such healthcare professionals of various specialties would expect encountering a variety of clinical scenarios of LUTS patients in future.

In this issue of the Hong Kong Medical Diary, we have gathered a multi-disciplinary team of specialists with experience in LUTS management in their practice. Tips and tricks in the management of LUTS using patient-centric approaches in urology, gynaecology, cardiology, geriatrics and primary care settings are provided for ease of reference.

New technology is driving the advancement of medical practice. Targeted ultrasound examination of the urinary tract is considered an emerging non-invasive assessment tool for LUTS patient. In the last chapter, we have outlined the understanding of basic ultrasound concepts and instrumentation.

INTERNATIONAL CONTINENCE SOCIETY DEFINITION OF LUTS

International Continence Society (ICS) has classified LUTS into 3 groups for standardisation of reporting: 1. storage, 2. voiding, and 3. postmicturition symptoms.[5] Storage symptoms include urinary frequency and urgency, nocturia, incontinence as stress, urgency or mixed, nocturnal enuresis, leaking during sexual activity, and leaking for no reason. Voiding symptoms include weak stream, terminal dribble, hesitancy, straining, intermittency, and split stream. Postmicturition symptoms include incomplete emptying and postmicturition incontinence.

Berry et al. showed in a 1984 autopsy study that the prevalence of BPH in men increases with age.[6] Two subsequent studies reported

the prevalence of LUTS ranges from 15% to 60% in men in their 40s and 70s, respectively. [7,8]

EPIDEMIOLOGY OF LOWER URINARY TRACT SYMPTOMS STUDY

Epidemiology of Lower Urinary Tract Symptoms (EpiLUTS) Study is the first epidemiological study using ICS definition of LUTS. EpiLUTS is a population-based, cross-sectional survey conducted in the United States, the United Kingdom, and Sweden to evaluate the prevalence and symptom-specific bother of Overactive Bladder (OAB) and other lower urinary tract symptoms (LUTS) among adults age 40 or above. Participants were recruited from internet-based panels developed from consumer and voter databases. Potential respondents were sent an electronic mail invitation. The overall survey response rate was 59.2%. Thirty thousand subjects participated. There were 14,129 men and 15,861 women. Twenty thousand subjects were from the United States, 7,500 from the United Kingdom, and 2,500 from Sweden.[9]

This study demonstrated the prevalence of at least one LUTS was 72.3% for men and 76.3% for women. More women than men reported OAB symptoms (43% vs 27%) and more men than women reported LUTS without OAB symptoms (44% vs 33%). If a more stringent criteria is used as the cut-off, the percentage of men and women reporting OAB symptoms became 16% and 33% respectively, and LUTS without OAB was 31% and 24% respectively. There is a significantly greater percentage of women than men reported being bothered by their OAB symptoms (68% vs 60%).

CHINESE POPULATION STUDY

Liu from Taiwan reported in 2019 the prevalence of LUTS based on ICS definition increased with age in both genders.[10] The prevalence increased from 53.7% at age 40 to 49 to 70.1% at age equal or above 70. They also showed LUTS were more common in individuals with comorbidities than those without. The prevalence of LUTS is significantly higher in patients with diabetes, cardiac disease and hyperlipidemia than normal individuals.

A local telephone survey of subjects aged 40 and above was conducted on an Asian population in 2017. 77.8% of men and 77.3% of women aged 40 and above reported at least a mild degree of LUTS according to IPSS assessment. The age-adjusted prevalence of overactive bladder syndrome was 15.1%. The prevalence of storage and voiding symptoms increases with age. Nocturia was the most common symptom among patients who sought medical advice.[11]

WAY FORWARD

The Hong Kong Elderly Welfare Foundation was established in 2016. It is a tax-exempt charity. The Foundation aims at promoting the health and welfare of the elderly population by facilitating the exchange of knowledge amongst medical and other professionals. Its governing body is comprised of doctors, nurses and accountants. It is financed by grant and donations made by corporations and individuals. Dr Mak Siu-king is the Founding President. Dr Leong Che-hung GBM, OBE, JP, Dr Ko Wing-man, GBS, BBS, JP and Dr Lam Ching-choi, BBS, JP are the Founding Advisors.

The Hong Kong Elderly Welfare Foundation - Happy Ageing Secret is a task force driven by a team of multi-disciplinary specialists. Our aims are to promote public awareness of LUTS management and to enhance peers' continuous development. We are deeply indebted to our task force core members especially Dr Chak-lam Cho, Dr Franklin Kwok-leung Ho, Dr Wing-hong Chu, Dr Jennifer Ma-wai-wai Myint, Dr John Tai-hung Wong, Dr Cecilia Willy Cheon, Dr Yuen-mei Chan and Prof Michael Tin Cheung Ying for their contribution to this issue. We proudly ran our first online LUTS Crash Course in a local medical conference in September 2020. Materials presented in the crash course have been organised to develop this issue of the HK Medical Diary on LUTS. It is indeed exciting to see specialists from different branches of medicine coming together and working towards advances in the management of a LUTS. Let us come together and build a harmonious community free of disturbance from LUTS.

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Lower Urinary Tract Symptoms and Benign Prostatic Hyperplasia : Alpha Blockers

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INTRODUCTION

Lower urinary tract symptoms (LUTS) is highly prevalent in men, and the prevalence increases with age[1,2]. Storage symptoms, often attributed to overactive bladder (OAB) and involuntary detrusor contractions during bladder filling, were experienced by 74% of men aged >60 years[3]. In men, detrusor overactivity may coexist with bladder outlet obstruction (BOO) as a result of benign prostatic hyperplasia (BPH). Or detrusor overactivity may be secondary to obstruction, whereby the increased pressure required to void leads to structural changes in the bladder, which in turn, increases the excitability of detrusor smooth muscle cells[4]. The clinical presentation of OAB in men is often similar to BOO, and it can be difficult to distinguish between these conditions, or whether both conditions coexist[5].

For men with LUTS, alpha adrenergic receptor blockers (AARB), which reduce smooth muscle tone in the prostate and bladder neck and decrease bladder outlet resistance, are a logical first-line therapy[6]. However, patients with storage symptoms and OAB component are less likely to respond fully to alpha blockade, but may respond to therapy with an antimuscarinic drug[7]. Although antimuscarinic agents reduce detrusor overactivity and are indicated for the treatment of OAB symptoms, some clinicians may elect not to initiate the therapy in men because of concern that decreasing detrusor contractility could increase the risk of urinary retention in cases of potential outlet obstruction. Therefore, AARB is the most widely used medications in the management of patients with LUTS/BPH currently.

ALPHA BLOCKERS IN THE MANAGEMENT OF MALE LUTS

Clinical practice guidelines for male LUTS endorse the sequential use of antimuscarinics in combination with AARB for ongoing storage LUTS[8]. This recommendation is supported by the results of several studies which assessed whether there was any benefit of adding an antimuscarinic agent in combination with AARB in men with BOO but persistent OAB symptoms. These studies also allow a glimpse into the efficacy of AARB alone in the treatment of male LUTS.

In a prospective study, 144 men with BOO were included. All of them had a baseline pressure-flow urodynamic study and were then subdivided into those with BOO only or BOO + OAB based on absence or presence of involuntary detrusor contractions. All patients were treated with AARB (doxazosin 4 mg/day) for three months. After three months of treatment with AARB, 79% with BOO, and 35% with BOO + OAB reported symptomatic improvement. In those patients with no improvement, the majority of them responded to add-on antimuscarinic. Overall, 85% of men with BOO with or without OAB were helped with AARB alone or by adding an antimuscarinic[9]. The result supported the recommendations of starting AARB first in view of the significant proportion of responding patients in both groups to AARB alone.

A similar finding has been reported in large-scale randomised, double-blind placebo-controlled studies. Patients in TIMES study were randomly assigned to receive placebo, AARB (tamsulosin 0.4 mg), antimuscarinics (tolterodine ER 4 mg), or both AARB and antimuscarinics for 12 weeks. The study recruited patients based on clinical findings without urodynamic study. Only patients presented with LUTS and documented features suggestive of significant OAB symptoms on bladder diary were included in the study. Although AARB monotherapy may be less effective than combination therapy, AARB alone demonstrated significant improvement in total and storage International Prostate Symptom Scores (IPSS) compared to placebo and may be more efficacious than antimuscarinics alone even in patients with bothersome storage symptoms[10].

NEPTUNE study involving 1,500 men with BPH and a substantial component of storage LUTS also reported a significant improvement in Total Urgency Score after AARB (tamsulosin oral controlled absorption system 0.4 mg) compared to placebo[11].

These studies provide a rationale for the sequential use of AARB and antimuscarinics. Although the use of AARB monotherapy may not provide effective symptom relief in all patients with LUTS associated with OAB, a substantial proportion of patient showed significant and potential satisfactory improvement. Therefore, the approach of AARB first may potentially avoid the side effects and cost implication of additional medication in a certain number of patients. The use of AARB first is probably a more rational approach in patients with LUTS/BPH and/or OAB symptoms compared to initial combination therapy.

CONCLUSION

LUTS, including both voiding and storage symptoms,

suggestive of BPH and OAB pathophysiology commonly coexist in the ageing male. Detrusor overactivity may be primary, or it can be secondary to prostatic obstruction. The differentiation between BPH and OAB is often difficult in view of similar clinical presentation, and urodynamic study may not be helpful. AARB is widely used and has demonstrated its efficacy and safety in patients with LUTS/BPH. The efficacy of the medication in relieving symptoms of patients with LUTS and substantial storage component suggestive of OAB has been reported. Although AARB monotherapy may not achieve sufficient symptom control in all patients with LUTS, it is rational to start the treatment first and consider combination therapy for non-responders.

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LUTS and Management of the Overactive Bladder in the Primary Care Setting

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INTRODUCTION: AN OPEN-MINDED APPROACH TO LUTS

According to the International Continence Society definition, lower urinary tract symptoms (LUTS) may originate from the bladder, urethra, prostate (in men), adjacent pelvic floor/organs, and/or similarly innervated anatomy (e.g. lower ureter)[1]. There appears to be a relatively common physician misconception that the majority of male LUTS are secondary to benign prostatic enlargement causing bladder outlet dysfunction and voiding symptoms. In fact, male LUTS patients may present with various combinations of voiding, storage and post-micturition symptoms. In the largescale EpiLUTS survey, among 14,139 men at and over the age of 40 from the USA, the UK and Sweden, 71% reported ≥1 symptom(s)[2], among whom 46% reported having storage symptoms (Fig. 1)[3].

Literature discussions in recent years converge toward a more "open-minded and holistic" approach to male LUTS diagnosis and management[4,5]. While the causes of male LUTS are many and varied, the general practice is a perfect place for making a well-rounded assessment, and for initiating lifestyle and medical therapies[5]. At specialist urologic clinics in Hong Kong, compared with other Southeast Asian countries, patients tended to be more highly symptomatic and bothered, and less likely to have received prior treatment[6]. The present article will explore feasible assessment and treatment strategies in the primary care setting.

ASSESSMENT STRATEGIES

Urologists have come to realise that LUTS are not only caused by prostatic obstruction but a diversity of factors including detrusor overactivity, detrusor underactivity during voiding, nocturnal polyuria and urethral strictures[3]. Because LUTS may arise from different causes, it is important to understand the underlying pathophysiology, differentiate among symptoms, and assess their levels of bothering to the patient.

For assessing LUTS, the general practitioner may begin with two relatively easy-to-use instruments that have been translated into Chinese and validated in Hong Kong: the International Prostate Symptom Score (IPSS) – Hong Kong Chinese version 2[7] and Overactive Bladder Symptom Score – Hong Kong Chinese (OABSS-HKC) questionnaire[8]. In addition, the use of a bladder diary or frequency-volume chart can help quantify urinary frequencies and volumes[3]. At initial assessment, the United Kingdom National Institute for Health and Care Excellence guideline also recommends a urine dipstick test for men to detect the presence of blood, glucose, protein, leucocytes and nitrites[9]. At the specialist setting, a uroflowmetry test may capture the voiding dynamics in more detail, for quantifying the severity and to rule out urinary retention.

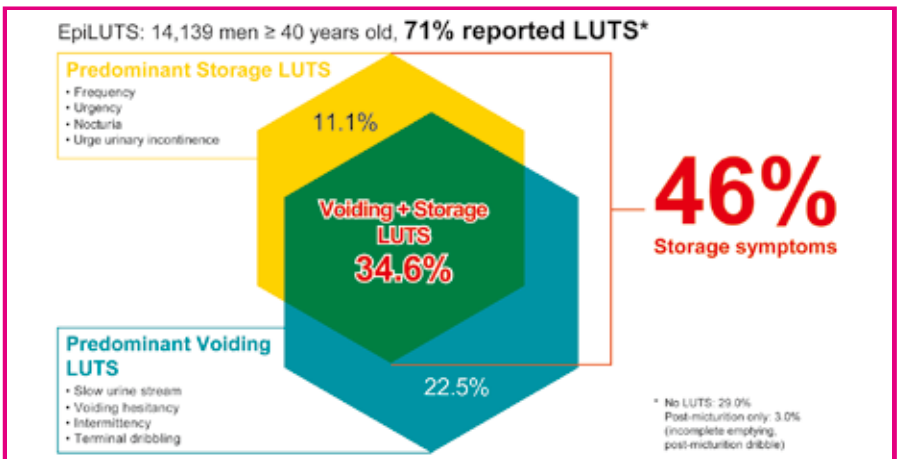

Fig. 1. The variety and combinations of male LUTS reported in the EpiLUTS survey.[2] Figure modified from: Sexton CC, Coyne KS, Kopp ZS, et al. The overlap of storage, voiding and postmicturition symptoms and implications for treatment seeking in the USA, UK and Sweden: EpiLUTS. BJU Int. 2009;103 Suppl 3:12-23. Copyright © 2009 The Authors.

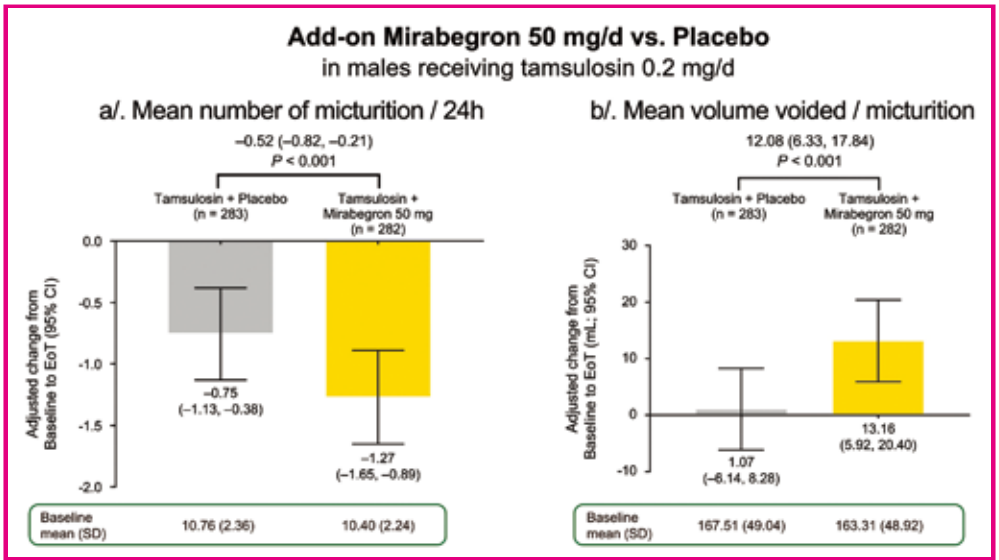

Fig. 2. Effects of add-on mirabegron to tamsulosin in male OAB patients: a) mean number of micturition episodes per 24 hours; b) mean volume voided per micturition.[12] CI, confidence interval; EoT, end of treatment; SD, standard deviation. Figure excerpted from: Kakizaki H, Lee KS, Yamamoto O, et al. Mirabegron Add-on Therapy to Tamsulosin for the Treatment of Overactive Bladder in Men with Lower Urinary Tract Symptoms: A Randomised, Placebo-controlled Study (MATCH). Eur Urol Focus. 2019. Copyright © 2019 European Association of Urology.

MEDICATION STRATEGIES FOR DIFFERENT SYMPTOM COMBINATIONS

The European Association of Urology guideline on the Management of Non-neurogenic Male LUTS was updated in 2019[10]. The updated guideline reported that add-on therapy using the β3-agonist mirabegron was effective for patients with persistent LUTS and OAB symptoms not controlled with α1-blocker monotherapy, without causing negative effects on voiding function. Moreover, there is also level 1a evidence that the α-blockers alfuzosin, terazosin and doxazosin significantly increased the risk of developing vascular-related events compared with placebo[10].

Nowadays, LUTS patients with predominant storage symptoms who require medical therapy may begin with β_3-agonist monotherapy, which is associated with fewer side effects (e.g. dry mouth or acute urinary retention)[11] as compared with using an anti-muscarinic agent. In patients receiving tamsulosin therapy with residual LUTS, adding mirabegron may further improve symptoms. The 12-week MATCH study[12] at 58 sites in Japan and Korea (565 male patients aged ≥ 40 years receiving tamsulosin) of add-on mirabegron vs. placebo demonstrated significantly improved mean number of micturition episodes per 24 hours (-1.27 vs. -0.75, $p < 0.001$; Fig. 2a), mean volume voided per micturition (+13.16 mL vs. +1.07, $p < 0.001$; Fig. 2b), and OABSS score (-2.78 vs. -2.13, $p = 0.001$).

STRATEGIES FOR IMPROVING LONG-TERM PERSISTENCE

Because non-neurogenic male LUTS usually involve certain physiological causes of dysfunction (e.g. an enlarged prostate or overactive bladder), medical therapies are often required on a long-term basis. Thus, as part of treatment planning, it would be advantageous if the medication is well-tolerated and can be used persistently. There have been long-standing concerns that the use of anti-muscarinic agents for treating LUTS contributes an additional cognitive burden on elderly patients[13], who may also be generally less tolerant of side effects. Indeed, Wang et al. reported that age was an independent predictor of drug persistence in OAB patients[14]. In an analysis of 21,966 records from the UK Clinical Practice Research Datalink database, mirabegron demonstrated significantly longer persistence than tolterodine or other anti-muscarinic agents (Fig. 3)[15]. Respectively, these correspond to a 55% (vs. tolterodine) and a 24% (vs. solifenacin) to 126% (vs. flavoxate) increase in treatment persistence when treated with mirabegron. Another Japan study reported a 3-year mirabegron persistence rate of 51% in male OAB patients from an academic hospital[16].

When combining mirabegron with tamsulosin, the MATCH study[12] reported similar treatment emergant adverse effect (TEAE) rates between the two arms of tamsulosin + mirabegron and tamsulosin + placebo (23.4% vs. 22.5% and 3.9% vs. 6.3%, respectively). Adverse events were consistent with those known individually for mirabegron and tamsulosin. No major concerns were noted in terms of urinary retention or cardiovascular events (Table 1). For the mirabegron + solifenacin combination, data from the phase 3b BESIDE study[17] (n = 2,174) showed that common TEAEs and drug-related TEAEs were similar across the three groups of solifenacin 5 mg, solifenacin 10 mg and solifenacin 5 mg + mirabegron (dose increased to 50 mg): 33.1% vs. 39.4% vs. 35.9%, and 17.2% vs. 22.4% vs. 19.4%, respectively.

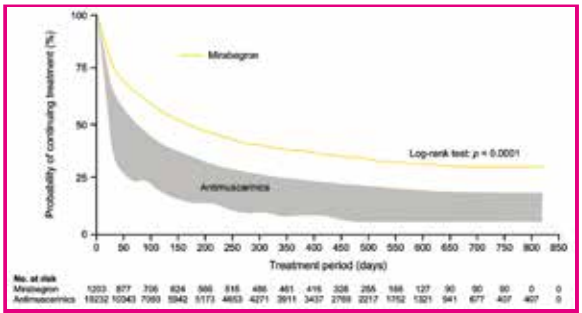

Fig. 3. A UK 2013-2014 database analysis is showing significantly longer median time-to-discontinuation of mirabegron vs. other anti-muscarinics (darifenacin, fesoterodine, flavoxate, oxybutynin ER, oxybutynin IR, propiverine, solifenacin, tolterodine and trospium).[15] Figure excerpted from: Chapple CR, Nazir J, Hakimi Z, et al. Persistence and adherence with mirabegron versus anti-muscarinic agents in patients with overactive bladder: A retrospective observational study in UK clinical practice. Eur Urol. 2017;72(3):389-399. Copyright ©2017 European Association of Urology.

System Organ Class TEAE, n (%)	Tamsulosin 0.2 mg/d + Placebo (n = 284)	Tamsulosin 0.2 mg/d + Mirabegron 50 mg (n = 282)
Cardiovascular events	3 (1.1)	3 (1.1)
Tachycardia	0	2 (0.7)
Angina unstable	1 (0.4)	1 (0.4)
Arrhythmia	1 (0.4)	0
Bradyarrhythmia	1 (0.4)	0
Blood pressure	3 (1.1)	0
Blood pressure increased	1 (0.4)	0
Hypertension	2 (0.7)	0
Urinary retention (urination related events)	1 (0.4)	4 (1.4)
Residual urine volume increased	1 (0.4)	3 (1.1)
Dysuria	0	1 (0.4)

Table 1. Treatment-emergent adverse events (TEAEs) of special interest in the MATCH study of mirabegron add-on to tamsulosin therapy for OAB patients.[12] Table excerpted from: Kakizaki H, Lee KS, Yamamoto O, et al. Mirabegron Add-on Therapy to Tamsulosin for the Treatment of Overactive Bladder in Men with Lower Urinary Tract Symptoms: A Randomised, Placebo-controlled Study (MATCH). Eur Urol Focus. 2019. Copyright © 2019 European Association of Urology

CONCLUSION

Adopting an open-minded and holistic approach in the primary care for LUTS could help facilitate appropriate treatment by correctly identifying the underlying pathophysiology of the condition and addressing the most bothersome symptoms. Symptoms may be assessed with validated instruments such as the IPSS and OABSS and a bladder diary. Nevertheless, neurogenic and/or more severe cases of LUTS should be referred to specialist care.

When compared with other existing LUTS medications, the newer class of β_3-agonist is associated with reduced side-effects and improved treatment persistence. It is suitable for use as monotherapy in initiating medical treatment, or in combination with an α-blocker or anti-muscarinic agent for treating residual symptoms, without any major concerns in toxicity. By tailoring medical therapy toward various symptom combinations and severities, the quality of life of LUTS patients can hopefully be improved early on and persistently in the long run.

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OAB: overactive bladder

Abbreviated prescribing information of Betmiga® prolonged-release tablets

Version: 003 PI version: Apr 2016. **Composition:** Mirabegron **Indication:** Symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with overactive bladder (OAB) syndrome. **Dosage:** Adult including elderly 50 mg once daily with or without food. **Administration:** Swallow whole with liquids. Do not chew/divide/crush. **Contraindications:** Mirabegron is contraindicated in patients with **-** Hypersensitivity to the active substance or to any of the excipients. **-** Severe uncontrolled hypertension defined as systolic blood pressure ≥ 180 mm Hg and/or diastolic blood pressure ≥ 110 mm Hg. **Special warnings and precautions for use:** Renal impairment: Betmiga has not been studied in patients with end stage renal disease (GFR < 15 mL/min/1.73 m2 or patients requiring haemodialysis) and, therefore, it is not recommended for use in this patient population. Data are limited in patients with severe renal impairment (GFR 15 to 29 mL/min/1.73 m2); based on a pharmacokinetic study a dose reduction to 25 mg is recommended in this population. Betmiga is not recommended for use in patients with severe renal impairment (GFR 15 to 29 mL/min/1.73 m2) concomitantly receiving strong CYP3A inhibitors. Hepatic impairment: Betmiga has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) and, therefore, it is not recommended for use in this patient population. Betmiga is not recommended for use in patients with moderate hepatic impairment (Child-Pugh B) concomitantly receiving strong CYP3A inhibitors. Hypertension: Mirabegron can increase blood pressure. Blood pressure should be measured at baseline and periodically during treatment with Betmiga, especially in hypertensive patients. Data are limited in patients with stage 2 hypertension (systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 100 mm Hg). Patients with congenital or acquired QT prolongation: Betmiga, at therapeutic doses, has not demonstrated clinically relevant QT prolongation in clinical studies. However, since patients with a known history of QT prolongation or patients who are taking medicinal products known to prolong the QT interval were not included in these studies, the effects of mirabegron in these patients is unknown. Caution should be exercised when administering mirabegron in these patients. Patients with bladder outlet obstruction and patients taking antimuscarinics medications for OAB: Urinary retention in patients with bladder outlet obstruction (BOO) and in patients taking antimuscarinic medications for the treatment of OAB has been reported in postmarketing experience in patients taking mirabegron. A controlled clinical safety study in patients with BOO did not demonstrate increased urinary retention in patients treated with Betmiga; however, Betmiga should be administered with caution to patients with clinically significant BOO. Betmiga should also be administered with caution to patients taking antimuscarinic medications for the treatment of OAB. **Undesirable effects:** Summary of the safety profile: The safety of Betmiga was evaluated in 8,433 patients with OAB, of which 5,648 received at least one dose of mirabegron in the phase 2/3 clinical program, and 622 patients received Betmiga for at least 1 year (365 days). In the three 12-week phase 3 double blind, placebo controlled studies, 88% of the patients completed treatment with Betmiga, and 4% of the patients discontinued due to adverse events. Most adverse reactions were mild to moderate in severity. The most common adverse reactions reported for patients treated with Betmiga 50 mg during the three 12-week phase 3 double blind, placebo controlled studies are tachycardia and urinary tract infections. The frequency of tachycardia was 1.2% in patients receiving Betmiga 50 mg. Tachycardia led to discontinuation in 0.1% patients receiving Betmiga 50 mg. The frequency of urinary tract infections was 2.9% in patients receiving Betmiga 50 mg. Urinary tract infections led to discontinuation in none of the patients receiving Betmiga 50 mg. Serious adverse reactions included atrial fibrillation (0.2%). Adverse reactions observed during the 1-year (long term) active controlled (muscarinic antagonist) study were similar in type and severity to those observed in the three 12-week phase 3 double blind, placebo controlled studies. List of adverse reactions: The table below reflects the adverse reactions observed with mirabegron in the three 12-week phase 3 double blind, placebo controlled studies. The frequency of adverse reactions is defined as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Infections and infestations: Common: Urinary tract infection. Uncommon: Vaginal infection, Cystitis. Psychiatric disorders: Not known (cannot be estimated from the available data): Insomnia*. Eye disorders: Rare: Eyelid oedema. Cardiac disorders: Common: Tachycardia. Uncommon: Palpitation, Atrial fibrillation. Vascular disorders: Very rare: Hypertensive crisis*. Gastrointestinal disorders: Common: Nausea*, Constipation*, Diarrhoea*. Uncommon: Dyspepsia, Gastritis. Rare: Lip oedema. Skin and subcutaneous tissue disorders: Uncommon: Urticaria, Rash, Rash macular, Rash popular, Pruritus. Rare: Leukocytoclastic vasculitis, Purpura, Angioedema*. Musculoskeletal and connective tissue disorders: Uncommon: Joint swelling. Reproductive system and breast disorders: Uncommon: Vulvovaginal pruritus. Investigations: Uncommon: Blood pressure increased, GGT increased, AST increased, ALT increased. Renal and urinary disorders: Rare: Urinary retention*. Nervous system disorders: Common: Headache*, Dizziness*. *observed during post-marketing experience. **Full prescribing information is available upon request.**

Reference: **1.** Chapple C.R. et al. Neurourol Urodynam 2014 Jan:33 (1):17-30 **2.** Hong Kong package insert of Betmiga® Apr 2016

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LUTS And Mortality : Falls And Fractures

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INTRODUCTION

Lower urinary tract symptoms (LUTS) as a group is one of the most common clusters of urinary symptoms encountered in the elderly. It consists of voiding symptoms (e.g. weak stream, hesitancy, sense of incomplete emptying) and storage symptoms (e.g. nocturia, frequency, urgency, incontinence). It is seen not only in gentlemen but also in ladies. From the epidemiological study, it is more prevalent in advanced age; yet many of them did not seek medical attention, even if their symptoms belong to moderate or severe group[1].

ASSESSMENT OF LUTS

The severity and bother of individual LUTS should be identified with a symptom score, supplemented by directed questioning if needed. A validated bladder diary is mandatory. The patient's medical history and medications, including directed evaluation for key conditions, such as renal failure, diabetes mellitus, cardiac failure, and obstructive sleep apnoea should be reviewed, since these diseases could aggravate LUTS. Therefore, LUTS not only represents the functionality of the bladder and prostate but also carries great importance in the overall well-being of patients. Here we will use nocturia as an example to elaborate how LUTS could impact on well-being of patients.

NOCTURIA AND ITS IMPACT

Nocturia is highly prevalent in older adults, and its prevalence increases with age. For the younger old, it is more common among women, but more men are affected in the older old. Nocturia is one of the most common and most bothersome symptoms among LUTS. A study among 1,198 men with benign prostatic hyperplasia (BPH) has shown that about 65% have nocturia[2]. Another local epidemiological study surveying 1,009 people aged 40 years or above using random telephone calls reported a nocturia prevalence of 63% (95% CI 60-66%) (unpublished data)[3].

Nocturia is a risk factor for falls and fractures, as well as for mortality, especially in the elderly[4,5]. In a study with population-based sample of community-dwelling elderlies followed up for three years, based on multivariable logistic regression, three or more episodes of nocturia were associated with an increased risk of falling (RR=1.28)[6]. In another study, nocturia is associated with a 20% increase in the risk of falls and a 30% increase in the risk of fractures[7]. The risk of falls also depends on the severity of symptoms. In a prospective cohort of 5,872 patients, the 1-year risk of fall increased by 11% for moderate symptoms while by 33% for severe symptoms. Furthermore, those with moderate symptoms had a 21% and those with severe symptoms a 63% increased risk of at least two falls[8]. According to WHO in 2018, falls are the second leading cause of accidental or unintentional injury deaths worldwide[9].

Since nocturia is a condition of high prevalence and with a wide range of aetiologies, a multi-disciplinary approach in both assessment and management is required. Among the wide-ranging causative disorders, increased diuresis during night time, i.e. nocturnal polyuria, is one of the most common conditions responsible for nocturia. It is estimated that up to 88% of nocturia patients suffer an underlying condition which has led to nocturnal polyuria[10,11]. Nocturia may be an early manifestation of heart failure occurring in the pre-oedematous stage 3. It affects the quality of life of heart failure patients and may prevent them from obtaining much-needed rest[12,13]. Nocturia is associated with multiple comorbidities, including not only urinary tract disorders but also cardiovascular diseases, gastro-intestinal problems, anxiety and depression etc[4,14].

Poor sleep quality is highly prevalent among the elderly[15], with nocturia being one of the causes[16]. Nocturia-related insomnia has been shown to cause impairment of quality of life, health and productivity[17]. Patients reporting two or more voids every night will feel disturbed and bothered by the nocturia, which in turn leads to mental disturbances[18]. Studies have shown that because of insufficient sleep, there is an increased risk of poor physical functioning, decreased cognitive function, and even mortality[15]. Although there are many other reasons for disturbed sleep, the sensation of a full bladder is a common reason for waking up patients at night. Real-life burden from nocturia-associated insomnia includes not only the impaired quality of life, but also the impairment of the cognitive and physical functions, hospitalisations, and even work absence[17]. Studies have shown that the quality of life has been much affected among patients who reported two or more voids at night. One's work performance is severely affected because of sick leave days taken. In the West, road traffic accidents and workplace accidents are common as a result of fatigue and a lack of refreshing sleep. Given the various medical conditions associated with nocturia, and resultant insomnia and functional impairment, it is understandable that nocturia poses an increased risk of depression in both men and women. It is, therefore, important to look out for comorbid

anxiety and depression symptoms among patients with nocturia[15].

Similar to frailty and cognitive impairment, nocturia and urinary disorder is one of the geriatric syndromes. Those syndromes interact with each other, and with other comorbidities. Nocturia not only disrupts their sleep, mood and cognitive function, but it also worsens the control of cardiovascular disease and diabetes. Cohort studies show that nocturia is associated with adverse survival outcome[19]. Although elderly share some common causes of nocturia as the younger adults, nocturia in the former group is more likely related to medical conditions, such as diabetes mellitus, chronic kidney disease, and neurodegenerative diseases.

CONCLUSION

In conclusion, lower urinary tract symptoms are frequent in older adults, and they carry a great burden to patients and the healthcare system. Multi-disciplinary and patient-centred care is the essence of management.

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LUTS Management in Primary Care: Alerts & Advice

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This article has been selected by the Editorial Board of the Hong Kong Medical Diary for participants in the CME programme of the Medical Council of Hong Kong (MCHK) to complete the following self-assessment questions in order to be awarded 1 CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 31 December 2020.

RELATIONSHIP BETWEEN LUTS, OAB AND BPH

There are two major classifications for lower urinary tract symptoms (LUTS): 1) irritative (storage) symptoms, e.g. urgency and frequency, which are frequently observed in overactive bladder (OAB); 2) obstructive (voiding) symptoms, e.g. poor and/or intermittent stream and hesitancy[1]. LUTS in males, voiding symptoms, in particular, are commonly associated with benign prostate hyperplasia (BPH), while OAB can also be the culprit or comorbidity, which may be attributable to prostate enlargement, overactivity of the detrusor muscle, or an ageing bladder[1]. Recently the American Urological Association (AUA) and the Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (SUFU) updated their guidelines on the management of non-neurogenic OAB[2].

MANAGEMENT OF OAB

OAB primarily refers to storage symptoms, including urgency and frequency, which are commonly diagnosed with a bladder diary, in which a patient will record his urination and drinking patterns for 3 days[3]. Alternatively, a locally validated questionnaire, the four-question Overactive Bladder Symptom Score (OABSS), can serve as a quick convenient diagnostic tool in the primary care setting[4]. Notably, as per the AUA/SUFU guidelines[2], urodynamics, cystoscopy, and renal/bladder ultrasound would not be used in the initial workup of uncomplicated cases.

Once OAB is diagnosed, education and cognitive behavioural therapies can be initiated[2]. If there are no improvements after 4-6 weeks, pharmacotherapy, i.e. antimuscarinics or β_3-agonists, should be prescribed[2]. Notably, in view of the chronic nature of OAB, patients should be informed of the long-term risks of these medical treatments. The AUA/SUFU guidelines[2] suggest that, in frail and elderly patients, antimuscarinics should be used cautiously, because they may affect the central nervous system by crossing the blood-brain barrier (BBB), increasing the risk of dementia, which may worsen treatment adherence and symptom control in the long term. β_3-agonists could be considered an alternative in older patients[5], because these drugs appear to have a low propensity to cross the BBB and to have no known association with dementia[5].

Furthermore, contrary to antimuscarinics, β_3-agonists are not contraindicated in patients with glaucoma (closed/open-angle) or acute urinary retention (AUR)[7,8], and have no impact on bladder contractility in patients with bladder outlet obstruction (BOO)[9]. While β3-agonists can serve as an alternative to antimuscarinics, they are contraindicated in patients with severe uncontrolled hypertension[3].

MANAGEMENT OF BPH

To evaluate BPH symptoms in the primary care setting, the International Prostate Symptom Score (IPSS), a universal and validated screening tool, can be used[10]. To further assess the prostate size and exclude the possibility of malignancy, digital rectal examination or ultrasound can be considered[1].

BPH can be managed based on the impacts and severity of symptoms[1]. In mild cases, the initial approach is often lifestyle modification, e.g. avoidance of stimulants. If prostate-related voiding symptoms become more bothersome, pharmacotherapy, i.e. α-blockers or 5-α-reductase inhibitors (5-ARIs), can be used.

ARIs are one of the treatment options for BPH, but some significant risks are worth considering in patients prescribed 5-ARIs. A US cohort study showed that, among > 80,000 patients with prostate cancer (PCa)[11], 5-ARIs users had a significantly greater risk of developing high-grade PCa than non-5-ARIs users (25% vs. 17%). Compared with α-blockers-alone users and patients who received neither of the drugs, 5-ARIs users had a significantly higher 12-year cumulative incidence of PCa-specific mortality (Fig. 1). 5-ARIs users had a 39% increased risk of PCa-specific mortality compared with non-5-ARIs users. These outcomes suggest that, as 5-ARIs would contribute to a 50% decline in the prostate-specific antigen (PSA) level, physicians may underestimate the patient's risk of PCa and delay the decision on biopsy. To monitor the risk of PCa in symptomatic patients receiving 5-ARIs, regular PSA testing (every 6 or 12 months) should be considered. Prostate health index (PHI) could be used for more accurate PCa diagnosis[12], but the impact of 5-ARIs on PHI remains uncertain.

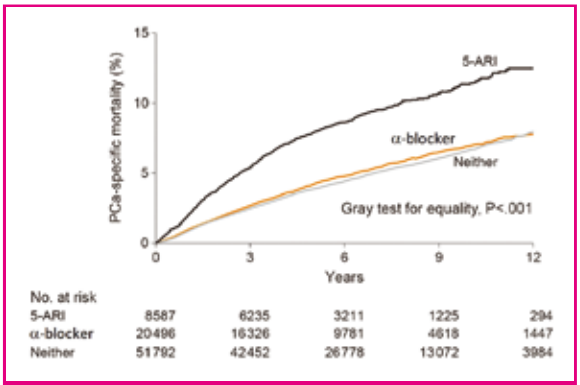

Fig. 1. Unadjusted cumulative prostate cancer-specific mortality in patients exposed to 5-ARIs, α -blockers, or neither. Excerpted from Sarkar RR, Parsons JK, Bryant AK, et al.[11]

In a registry study of men with LUTS secondary to BPH (N = 460; follow-up = 36-42 months) conducted by the Boston University, long-term 5-ARIs treatment was associated with increased glycated haemoglobin (HbA1c) levels and activities of liver enzymes compared with α-blockers treatment (Fig. 2)[13]. In the primary care setting, there are commonly LUTS patients with comorbid diabetes or poorly controlled HbA1c. Even in the absence of contraindications, 5-ARIs should be used cautiously in these patients, considering the risk of the long-term increase in HbA1c and subsequent diabetes. Clinicians could counsel the patient about the potential risk of long-term 5-ARIs treatment, or consider other lower-risk medications for BPH. While the impacts of 5-ARIs on the activities of liver enzymes remain to be confirmed, liver function monitoring could be considered in patients on long-term treatment.

The European Association of Urology (EAU) Male LUTS Treatment Guidelines recommend α-blockers as the first-line medication for men with predominant voiding symptoms, with an individualised treatment duration[3]. The IPSS can continually be used to evaluate the treatment response and symptom improvements in BPH. In select patients with co-existing BPH and OAB, the combination therapy of α-blockers and β_3-agonists can be considered to treat both voiding and storage symptoms by two different pathways[14]. If symptoms persist, further assessments should be conducted, e.g. post-void residual (PVR) urine testing with ultrasound[1]. If there is a high PVR (> 50 mL), an elevated PSA level, or the presence of recurrent complications such as urinary tract infection, the patient could be referred to a urologist for detailed examination[1].

SUMMARY

- OABSS and IPSS can be used to evaluate OAB and BPH symptoms, respectively.
- In frail and elderly patients with OAB, β_3-agonists could be considered an alternative to antimuscarinics, the former being without known associated risk of dementia.
- Contrary to antimuscarinics, β_3-agonists are not contraindicated in patients with glaucoma (closed/open-angle), AUR, or BOO.
- Physicians should discuss with patients about the risk of PCa-specific death and potential long-term impacts on the risks of diabetes and deranged liver function before starting 5-ARIs treatment for BPH.
- The EAU guidelines recommend α-blockers as the first-line medication for men with BPH.
- Combined use of α-blockers and β_3-agonists can be considered to treat patients with both BPH and OAB.

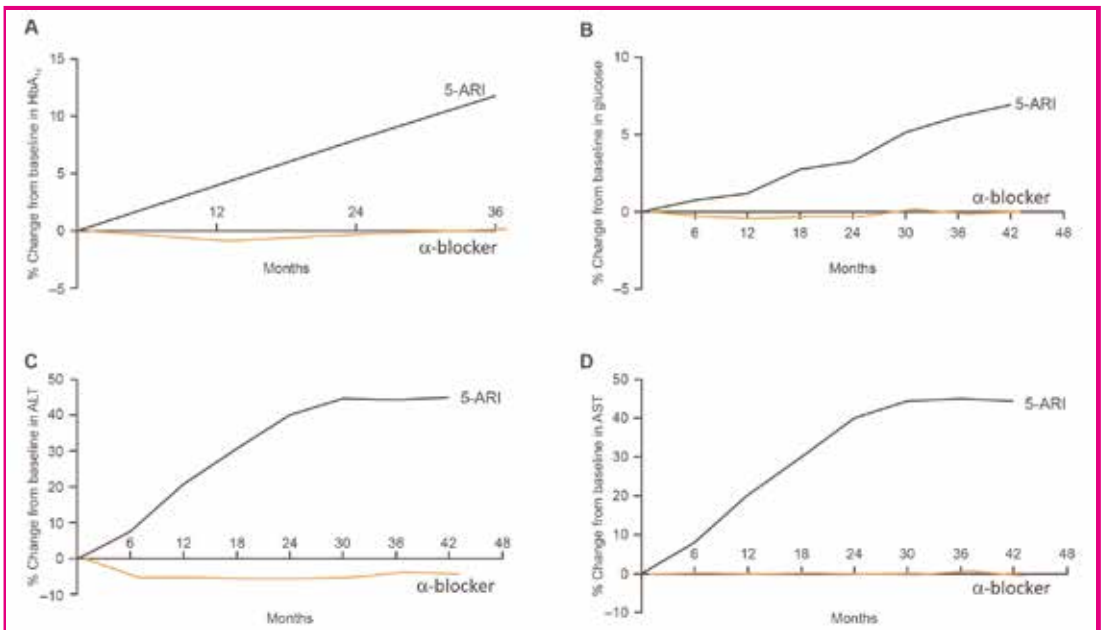

Fig. 2. Effects of α-blockers or long-term 5-ARIs on levels of HbA1c (A), fasting blood glucose (B), alanine transferase (ALT, C), and aspartate transferase (AST, D) in patients treated for BPH. Excerpted from Traish A, Haider KS, Doros G, Haider A[13] *.*

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Radiology Quiz

Dr Frank WONG

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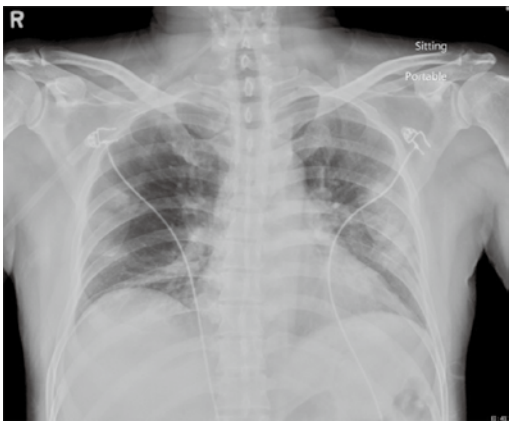

Questions

1. What are the findings on the CXR of this patient with respiratory symptoms?
2. What diagnosis should be included in the differential diagnosis in 2020?
3. What are the typical CXR findings in COVID-19?
4. Can a negative CXR rule out COVID-19?

(See P.36 for answers)

MCHK CME Programme Self-assessment Questions

Please read the article entitled "LUTS Management in Primary Care: Alerts & Advice" by Dr Siu-king MAK and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded CME credit under the Programme for returning completed answer sheets via fax (2865 0345) or by mail to the Federation Secretariat on or before 31 December 2020. Answers to questions will be provided in the next issue of The Hong Kong Medical Diary.

Questions 1-10: Please answer T (true) or F (false)

1. Irritative & obstructive symptoms are commonly seen in male patients with lower urinary tract symptoms (LUTS).
2. Both frequency and urgency are obstructive symptoms.
3. When prescribing 5-alpha reductase inhibitors for the treatment of benign prostatic hyperplasia (BPH), the risk of prostate cancer-specific mortality, and potential long-term impacts on the risks of diabetes and impaired liver function are worth considering.
4. In an United States cohort study of > 80,000 men with prostate cancer (PCa), 5-alpha reductase inhibitor (5-ARI) users had a 39% increase in the risk of PCa-specific mortality compared with patients without the use of 5-ARIs.
5. Prostate health index (PHI) could be used for more accurate prostate cancer (PCa) diagnosis, and the impact of 5-ARIs on PHI is very well defined.
6. Long-term use of 5-ARIs in treatment of BPH appears to be associated with increased glycated haemoglobin (HbA1c) levels and activities of liver enzymes (Aspartate transaminase(AST), Alanine transaminase (ALT)).
7. According to the European Association of Urology (EAU) Male LUTS Treatment Guidelines, alpha blockers are the first-line treatment option for men with predominant storage symptoms.
8. Overactive Bladder Symptom Score (OABSS) is a locally validated questionnaire for the diagnosis of overactive bladder in Hong Kong.
9. Anticholinergic agents are contraindicated in patients with closed-angle glaucoma, bladder outlet obstruction (BOO) or acute urinary retention (AUR).
10. Beta-3 agonist, when used to treat OAB, does not affect bladder contractility in patients with BOO, and is not contraindicated in patients with AUR.

ANSWER SHEET FOR DECEMBER 2020

Please return the completed answer sheet to the Federation Secretariat on or before 31 December 2020 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

LUTS Management in Primary Care: Alerts & Advice

Dr Siu-king MAK

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Specialist in Urology
President, Hong Kong Elderly Welfare Foundation Convener, Happy Ageing Secrets
Honorary Clinical Associate Professor , Department of Surgery, The Chinese University of Hong Kong

1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐

Name (block letters):_____ HKMA No.: _____ CDSHK No.: _____

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Contact Tel No.:_____ MCHK No. / DCHK No.: _____(must fill in)

Answers to November 2020 Issue

Appropriate Use of Antibiotics for Acute Uncomplicated Cystitis in Women in Primary Care Setting

1. T 2. F 3. T 4. T 5. T 6. T 7. T 8. F 9. T 10. T

Anticholinergic Burden in the Elderly

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MBBS(HK), MRCP (UK), MMed(Geriatrics)(New South Wales), FHKCP, FHKAM (Medicine), FRCP(Edin)

Specialist in Geriatric Medicine

Dr Jennifer Ma-wai-wai MYINT

Pharmacological management of overactive bladder (OAB) in the elderly in the past involved using antimuscarinic drugs. In combination with other drugs which older adults are already taking, there may be a substantial anticholinergic burden. These other drugs may be prescribed for their anticholinergic effect, as well as other medicines which can cause anticholinergic side effects but are not strictly classified as anticholinergics[1]. Commonly prescribed drugs with anticholinergic side effects in primary care and Geriatric practice are antihistamines, antihypertensives, antidepressants, sedatives, etc.

Older adults are more at risk of anticholinergic side effects than young people because of increased permeability of the blood-brain barrier, decreased drug metabolism and elimination, and age-related deficit in central cholinergic transmission[2]. Commonly reported peripheral side effects of anticholinergic medicines include dry mouth, dry eyes, constipation, urinary retention, blurred vision and increased heart rate, while central effects range from dizziness, sedation, confusion and delirium [1,2,3].

Multiple studies reported the impact of anticholinergic effects on cognitive function[1,3,4], increased risk of delirium[3], cognitive decline[5,6], hospitalisations[1,7,8], falls and fractures[1,3,9], and decline in physical function[1,10], especially in vulnerable populations such as the elderly[1] or patients with Parkinson's disease[11] or dementia. The risk of dementia is associated with total anticholinergic use over the previous years of life; so even the middle-aged and the younger old should avoid these drugs if possible[12].

The anticholinergic burden is the cumulative effect of taking one or more medications with anticholinergic properties. Various scoring systems have been published to help clinicians to refer to the high-risk drugs quickly and to modify medications accordingly. These are also used for research purposes for quantification of anticholinergic exposure. A user-friendly version is the Anticholinergic Cognitive Burden Scale (ACB) developed by the Aging Brain Program of the Indiana University Center for Aging Research[13] which is also the most frequently validated expert-based anticholinergic scale on adverse outcome[14]. A study using this scale has shown that each definite anticholinergic may increase the risk of cognitive impairment by 46% over six years[6]. For each one point increase in the ACB total score, a decline in Mini-mental state examination (MMSE) score of 0.3[3] points over 2 years has been suggested[3]. Additionally, each one point increase in the ACB total score has been correlated with a 26% increase in the risk of death[3].

Effective management of overactive bladder in the elderly involves a careful balance of patient profile, adverse drug reactions and economic factors. The total cholinergic load of the patient should be carefully considered before instituting long-term therapy for OAB. Beta 3 agonist Mirabegron is a newer alternative treatment without any anticholinergic adverse effects.

Examples of medications listed in Anticholinergic Cognitive Burden Scale[13,15].

Drugs with ACB Score of 1 (possible anticholinergic effect)	Drugs with ACB Score of 2 (definite anticholinergic effect)	Drugs with ACB Score of 3 (definite anticholinergic effect)
Alimemazine	Amantadine	Amitriptyline
Alverine	Belladonna	Amoxapine
Alprazolam	Carbamazepine	Atropine
Aripiprazole	Cyclobenzaprine	Benztropine
Asenapine	Cyproheptadine	Brompheniramine
Atenolol	Loxapine	Carbinoxamine
Bupropion	Meperidine	Chlorpheniramine
Captopril	Methotrimeprazine	Chlorpromazine
Cetirizine	Molindone	Clemastine
Chlorthalidone	Nefopam	Clomipramine
Cimetidine	Oxcarbazepine	Clozapine
Clidinium	Pimozide	Darifenacin
Clorazepate		Desipramine
Codeine		Dicyclomine
Colchicine		Dimenhydrinate
Desloratadine		Diphenhydramine
Diazepam		Doxepin
Digoxin		Doxylamine
Dipyridamole		Fesoterodine
Disopyramide		Flavoxate
Fentanyl		Hydroxyzine
Furosemide		Hyoscyamine
Fluvoxamine		Imipramine
Haloperidol		Meclizine
Hydralazine		Methocarbamol
Hydrocortisone		Nortriptyline
Iloperidone		Olanzapine
Isosorbide		Orphenadrine
Levocetirizine		Oxybutynin *
Loperamide		Paroxetine
Loratadine		Perphenazine
Metoprolol		Promethazine
Morphine		Propantheline
Nifedipine		Propiverine
Paliperidone		Quetiapine
Prednisone		Scopolamine
Quinidine		Solifenacin *
Ranitidine		Thioridazine
Risperidone		Tolterodine *
Theophylline		Trifluoperazine
Trazodone		Trihexyphenidyl
Triamterene		Trimipramine
Venlafaxine		Trospium *
Warfarin		* Common antimuscarinic drugs used for overactive bladder

Numerical Scoring:

- Add the score contributed to each selected medication in each scoring category
- Add the number of possible or definite Anticholinergic medications

A total ACB scale score of 3 or more is considered clinically relevant.

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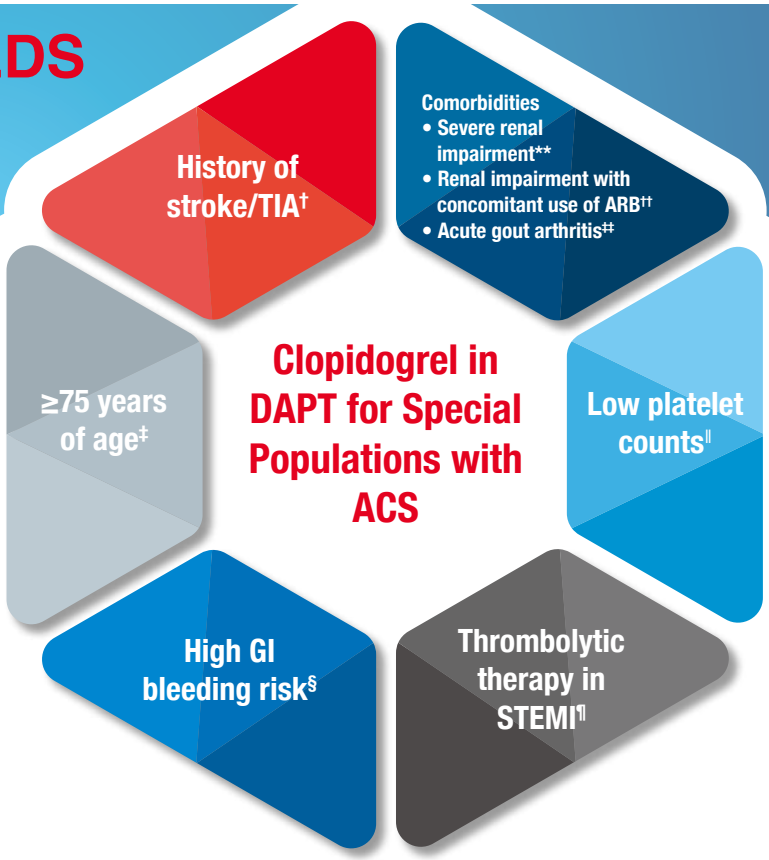
Preferred $P2Y_{12}$ inhibitor in 2018 Chinese Expert Consensus on Antiplatelet Therapy for Special Populations with ACS in the following populations:

For details of the recommendations and other recommendations stated in the consensus, please refer to the full publication in Chinese.



† For ACS patients with a history of ischaemic stroke or TIA, clopidogrel (75 mg/day) plus aspirin (100 mg/day) should be continued to 12 months.

‡ For patients with ACS ≥75 years of age, on top of using aspirin, clopidogrel is recommended as the first-choice $P2Y_{12}$ inhibitor.

§ For ACS patients with a high risk of GI bleeding (including the elderly and patients taking other medications such as warfarin, glucocorticoids or NSAIDs etc.), PPIs for 1-3 months are recommended on the basis of clopidogrel and aspirin.

¶ Patients with STEMI receiving thrombolytic therapy should initiate DAPT as soon as possible. Aspirin is given at a loading dose of 200-300 mg (chew and swallow) followed by 100 mg/day. For patients aged ≤75 years, clopidogrel at a loading dose of 300 mg followed by 75 mg/day should be given; No loading dose is given for patients aged >75 years. Ticagrelor is not recommended for patients with STEMI receiving thrombolytic therapy. In the case of patients undergoing PCI after thrombolytic therapy, taking into account both ischaemic and haemorrhagic risks, administration of ticagrelor can be considered 48 hours after thrombolytic therapy.

‖ If the ACS patient has a low platelet count of <100 x 10^9/L and >60 x 10^9/L, it is needed to carefully assess the safety of DAPT. For patients with low bleeding risk, clopidogrel plus aspirin is preferred. For patients with high bleeding risk, monotherapy (clopidogrel or aspirin) can be considered. The use of ticagrelor should be avoided. If the ACS patient has a platelet count of <60 x 10^9/L and >30 x 10^9/L, it is recommended to use monotherapy (clopidogrel or aspirin) as maintenance treatment. The use of ticagrelor should be avoided. If the ACS patients has a platelet count <30 x 10^9/L, it is recommended to stop antiplatelet therapy and to avoid PCI.

** For ACS patients with severe renal impairment (eGFR <30 mL/min), clopidogrel (75 mg/day) plus aspirin (100 mg/day) is preferred.

†† If a concomitant ARB is given to ACS patients with renal impairment, DAPT of clopidogrel plus aspirin is preferred.

‡‡ For ACS patients with comorbid acute gout arthritis flares, clopidogrel at 75-150 mg/day is preferred. Once symptoms are relieved, initiate clopidogrel at 75 mg/day plus aspirin at 75-100 mg/day. After 6-12 months, maintain with clopidogrel at 75 mg/day for long-term treatment. In case of acute gout during administration of DAPT following PCI, concomitant use of antigout agents with DAPT of clopidogrel plus aspirin can be considered taking into account of the risks for ischaemia and gout. Low-dose aspirin (75-325 mg/day) has a mild effect on increasing plasma uric acid, which raises the risk of gout. If the risk of gout has been increased by aspirin, stop using aspirin or replace with cilostazol plus clopidogrel.

ACS=acute coronary syndrome. ARB=angiotensin II receptor blocker. CHD=coronary heart disease. DAPT=dual antiplatelet therapy. eGFR=estimated glomerular filtration rate. GI=gastrointestinal. NOAC=novel oral anticoagulant. NSAID=non-steroidal anti-inflammatory drug. PCI=percutaneous coronary intervention. PPI=proton pump inhibitor. PTE=pulmonary thromboembolism. STEMI=ST-elevation myocardial infarction. TIA=temporary ischaemic attack.

Reference

Specialty Committee on Prevention and Treatment of Thrombosis of Chinese College of Cardiovascular Physicians, Interventional Cardiology Branch of Chinese Society of Cardiology of Chinese Medical Association and Editorial Board of Chinese Journal of Cardiology. Chinese expert consensus on antiplatelet therapy for special patients with acute coronary syndrome. Chin J Cardiol 2018;46:255-266.

Presentation: Clopidogrel film-coated tablets. **Indications:** Prevention of atherothrombotic events in (a) adult patients suffering from myocardial infarction (from a few days until less than 35 days), ischaemic stroke (from 7 days until less than 6 months) & established peripheral arterial disease (b) adult patients suffering from acute coronary syndrome: (i) Non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction), including patients undergoing a stent placement following percutaneous coronary intervention, in combination with acetylsalicylic acid (ASA) (ii) ST segment elevation acute myocardial infarction, in combination with ASA in medically treated patients eligible for thrombolytic therapy. Prevention of atherothrombotic and thromboembolic events, including stroke, in adult patients with atrial fibrillation who have at least one risk factor for vascular events, are not suitable for treatment with Vitamin K antagonists (VKA) and who have a low bleeding risk. **Dosage:** Adults and elderly: 75mg once daily. For patients with UA/NQWMI, loading dose 300mg, followed by 75mg once daily (with ASA 75mg-325mg daily). Since higher doses of ASA were associated with higher bleeding risk, recommended dose of ASA ≤100 mg. For patients with ST segment elevation myocardial infarction, 75mg once daily with a 300mg loading dose in combination with ASA and with or without thrombolytics. For patients ≥75 years, initiate clopidogrel without loading dose. For patients with atrial fibrillation, 75 mg daily with ASA (75-100 mg daily). Children and adolescents: not recommended under 18 years. **Contraindications:** Hypersensitivity to clopidogrel or excipients; severe hepatic impairment; active pathological bleeding such as peptic ulcer & intracranial haemorrhage. **Precautions:** If a patient is to undergo elective surgery and antiplatelet effect is not necessary, clopidogrel should be discontinued 7 days prior to surgery. Patients who may be at risk of increased bleeding from trauma, surgery or other pathological conditions; hypersensitivity to thienopyridines; patients with renal impairment; patients with moderate hepatic disease who may have bleeding diatheses. Not recommended during the first 7 days after an acute ischaemic stroke. Patients with genetically reduced CYP2C19 function. Patients treated concomitantly with clopidogrel and CYP2C8 substrates. **Interactions:** Not recommended with oral anticoagulants, caution with glycoprotein IIb/IIIa inhibitors, aspirin, heparin, thrombolytics or NSAIDs (including Cox-2 inhibitors), selective serotonin reuptake inhibitors (SSRIs). Drugs that inhibit CYP2C19, including proton pump inhibitors. CYP2C8 substrates such as rapaglinide and paclitaxel. **Undesirable effects:** haemorrhagic disorders; haematological including bleeding such as purpura, bruising, haematoma and epistaxis; gastrointestinal system disorders such as dyspepsia, abdominal pain and diarrhea. For uncommon, rare and very rare undesirable effects, please refer to the full prescribing information. **Preparations:** 75 mg x 14's; 300 mg x 30's. **Legal Classification:** Part 1, First & Third Schedules Poison ***Full prescribing information is available upon request.*** API-HK-CLO-18.04

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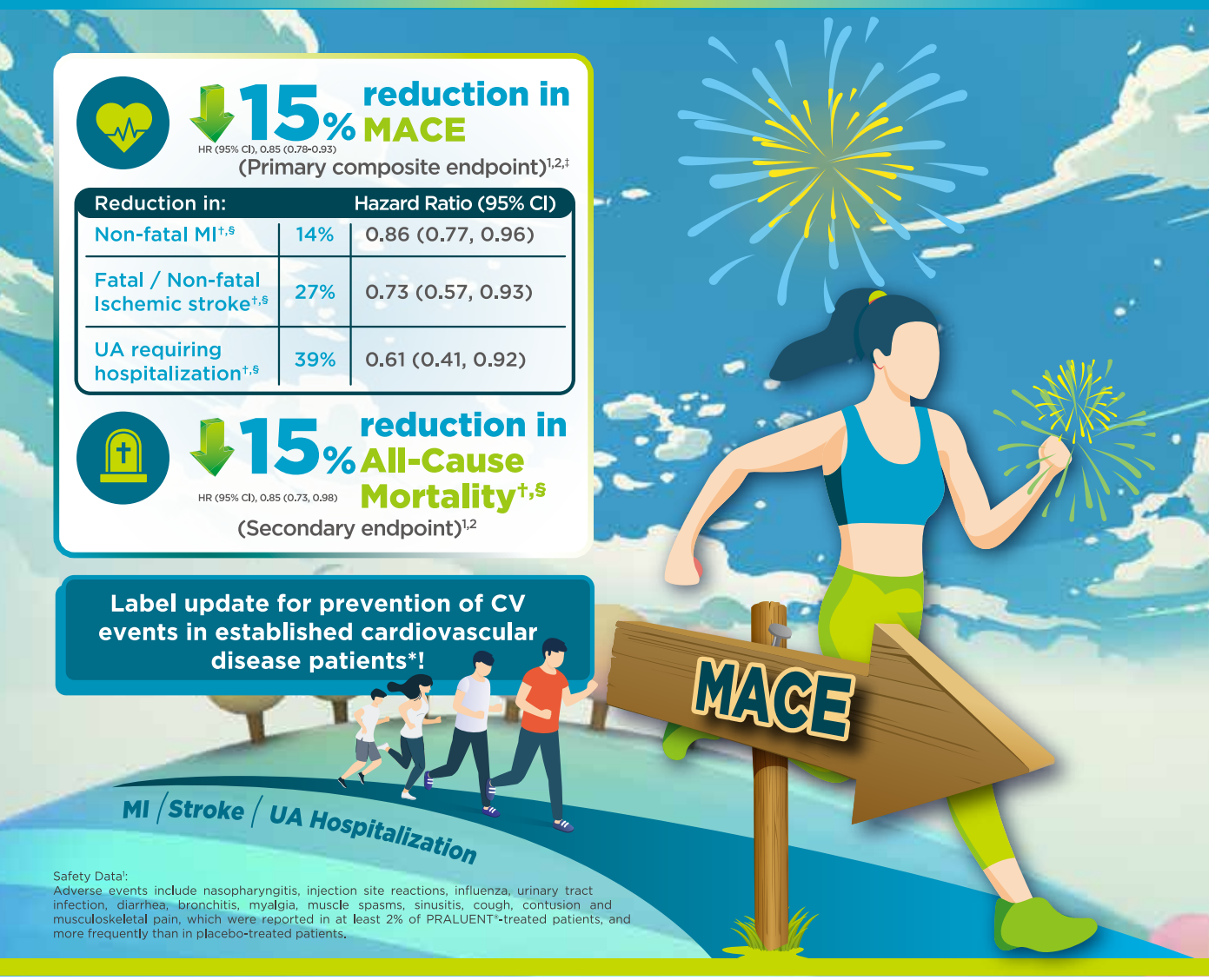
Fatal / Non-fatal Ischemic stroke[†,§]	27%	0.73 (0.57, 0.93)
UA requiring hospitalization[†,§]	39%	0.61 (0.41, 0.92)

15% reduction in All-Cause Mortality[†,§]

HR (95% CI), 0.85 (0.73, 0.98)

(Secondary endpoint)[1,2]

Label update for prevention of CV events in established cardiovascular disease patients*!



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* PRALUENT® is indicated to reduce the risk of myocardial infarction, stroke, and unstable angina requiring hospitalization in adults with established cardiovascular disease. PRALUENT® is also indicated as an adjunct to diet, alone or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe), for the treatment of adults with primary hyperlipidemia to reduce low-density lipoprotein cholesterol (LDL-C).

† Statistical testing performed outside hierarchy; therefore not considered statistically significant.

‡ Primary composite endpoint of death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization.

§ Major secondary end points (HR, 95% CI), in order of hierarchical testing, include any coronary heart disease event (0.88, 0.81-0.95), major coronary heart disease event (0.88, 0.80-0.96), any cardiovascular event (0.87, 0.81-0.94), composite of death from any cause, nonfatal myocardial infarction, or nonfatal ischemic stroke (0.86, 0.79-0.93), death from coronary heart disease (0.92, 0.76-1.11, the hierarchical analysis was stopped after the first nonsignificant P value was observed, in accordance with the hierarchical testing plan), death from cardiovascular causes (0.88, 0.74-1.05) and death from any cause (0.85, 0.73-0.98). To adjust for multiplicity, the results of the main secondary end points were to be tested in hierarchical fashion in the sequence listed above if the risk of the composite primary end point was found to be significantly lower in the alirocumab group than in the placebo group.

Study Design[1,2]
ODYSSEY OUTCOMES is a multicenter, randomized, double-blind, placebo-controlled trial involving 18,924 patients who had an acute coronary syndrome 1 to 12 months earlier, had a low-density lipoprotein (LDL) cholesterol level of at least 70 mg per deciliter (1.8 mmol per liter), a non–high-density lipoprotein cholesterol level of at least 100 mg per deciliter (2.6 mmol per liter), or an apolipoprotein B level of at least 80 mg per deciliter, and were receiving statin therapy at a high-intensity dose or at the maximum tolerated dose. Patients were randomly assigned to receive alirocumab subcutaneously at a dose of 75 mg (9462 patients) or matching placebo (9462 patients) every 2 weeks. The dose of alirocumab was adjusted under blinded conditions to target an LDL cholesterol level of 25 to 50 mg per deciliter (0.6 to 1.3 mmol per liter).

MACE=major adverse cardiovascular events. MI=myocardial infarction. UA=unstable angina. PCSK9=Proprotein convertase subtilisin/kexin type 9. CVD=cardiovascular disease. HeFH=Heterozygous Familial Hypercholesterolemia.

Reference:
1. Praluent® Prescribing Information. Mar 2020. 2. Schwartz GG, et al. N Engl J Med. 2018;379:2097-2107.

Presentation: Alirocumab solution for injection. Indications: Prevention of Cardiovascular Events: Reduce risk of myocardial infarction, stroke and unstable angina requiring hospitalization in adults with established cardiovascular disease. Primary Hyperlipidemia (incl. heterozygous familial hypercholesterolemia): As an adjunct to diet, alone or in combination with other lipid-lowering therapies, for the treatment of adults with primary hyperlipidemia to reduce LDL-C. Dosage: 75 mg once every 2 weeks administered subcutaneously. An alternative starting dosage for patients who prefer less frequent dosing is 300 mg once every 4 weeks. If the LDL-C response is inadequate, the dosage may be increased to the maximum dosage of 150 mg administered every 2 weeks. Contraindications: History of serious hypersensitivity reaction to alirocumab. Precautions: Hypersensitivity reactions. Pregnancy and Lactation: There are no available data on use of alirocumab in pregnant women to inform a drug-associated risk. There is no information regarding the presence of alirocumab in human milk, the effects on the breastfed infant, or the effects on milk production. Undesirable effects: Nasopharyngitis, injection site reactions, influenza, urinary tract infection, diarrhea, bronchitis, myalgia, muscle spasms, sinusitis, cough, contusion, musculoskeletal pain, flu-like illness, angioedema. For other undesirable effects, please refer to the full prescribing information. Preparation: 1 x 75mg/ml prefilled pen, 1 x 150mg/ml prefilled pen. Legal Classification: Part 1, First & Third Schedules Poison Full prescribing information is available upon request.
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Praluent® alirocumab

LUTS and Heart Diseases

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INTRODUCTION: LUTS IN PATIENTS WITH CVD

The presence of lower urinary tract symptoms (LUTS; e.g. frequency, urgency and/or incontinence) in a considerable portion of patients with cardiovascular diseases (CVDs) is a clinically relevant and interesting observation - one that can impact treatment planning and symptom management. This article will explore the prevalence, association and relationship of LUTS with CVDs, discuss the resulting clinical implications, and introduce therapies that have recently become available.

PREVALENCE AND ASSOCIATION

LUTS and CVDs appear to be closely associated. In a 2017 Internet survey of 8,284 men and women aged ≥ 40 (mean = 54) years from China, Taiwan and South Korea, the prevalence of overactive bladder (OAB) among those who also had diabetes mellitus (DM), cardiac disease, hypertension or hyperlipidemia was very high: 43.1%, 37.8%, 30% and 27.5%, respectively (Fig. 1)[1]. In another Australian survey of 106,435 men aged ≥ 45 years[2], those with any CVD scored significantly higher in storage and voiding symptoms versus those without (odds ratio [OR]= 1.45; 94% confidence interval [CI]: 1.36-1.56 and OR = 1.34; 95% CI: 1.24-1.44, respectively), as measured by the International Prostate Symptom Score.

For patients with LUTS, the risk of having CVD also seems higher. A meta-analysis of longitudinal trials[3] (25,494 men; mean age = 52.5 years) showed an association between moderate-to-severe LUTS and an increased risk of angina pectoris, acute myocardial infarction, other chronic ischemic heart diseases, congestive heart failure, transient ischemic attack and cerebrovascular accident (OR = 1.68, p = 0.01). In a 2013-2015 single urology centre survey of 996 men with LUTS in Hong Kong, LUTS severity was associated with an increased Framingham risk score for coronary heart disease (p = 0.008)[4]. In a prospective cohort of 308 Turkish patients aged > 65 years undergoing coronary angiography, those with comorbid OAB also had significantly higher Gensini scores (for plaque burden), and low-density lipoprotein and total cholesterol levels[5].

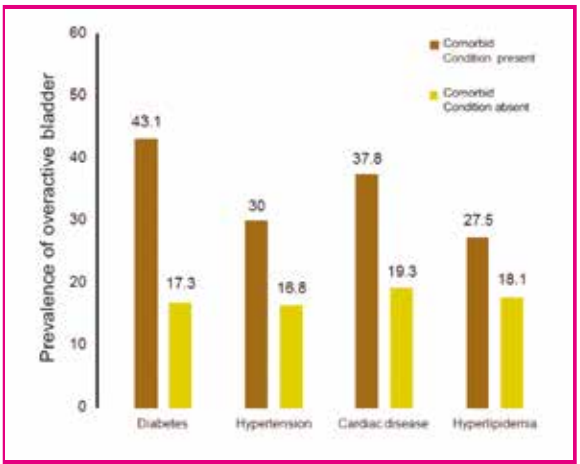

Fig. 1. Prevalence of OAB from an Internet-based study of men from China, Taiwan and South Korea (aged ≥ 40 years), with and without comorbid cardiovascular (CV) conditions1. Figure excerpted from: Chuang YC, Liu SP, Lee KS, et al. Prevalence of overactive bladder in China, Taiwan and South Korea: Results from a cross-sectional, population-based study. Low Urin Tract Symptoms. 2019;11(1):48-55. Copyright © 2017 The Authors.

RELATIONSHIP BETWEEN LUTS AND CVDS

The data described above prompt the question of what underlies the association between LUTS and CVDs. One possibility is that metabolic syndrome (MetS; i.e. metabolic abnormalities related to central obesity and insulin resistance) seems to overarch both phenomena[6]. Worldwide, 26.5%-55.6% of patients with LUTS also have MetS[6]. In a meta-analysis of 8 studies (5,403 patients)[7] on MetS and benign prostate enlargement, patients with MetS had a significantly larger prostate volume (+1.8 mL, p < 0.001), which was in turn significantly associated with lower high-density lipoprotein levels (p < 0.001), increased obesity (p < 0.005) and older age (p = 0.02).

Second, chronic ischemic damages associated with CVDs and DM may result in bladder overactivity[8,9]. Possible mechanisms include the production and release of adenosine triphosphate (ATP), prostaglandins and neural growth factors (NGF) in the urothelium and lamina propria, as well as partial denervation and increased sensitivity in muscle layers[9]. Patients with OAB have significantly higher insulin resistance levels, suggesting the likelihood of ischemic damages

Table 1: Cardiac safety data of the β_3-agonist (mirabegron) in a 4-week Japanese postmarketing study of CVD patients aged ≥ 75 years[21]. Table excerpted from: Katoh T, Kuwamoto K, Kato D, Kuroishi K. Real-world cardiovascular assessment of mirabegron treatment in patients with overactive bladder and concomitant cardiovascular disease: Results of a Japanese post-marketing study. Int J Urol. 2016;23(12):1009-1015. Copyright© 2016 The Japanese Urological Association.

	n	Baseline Mean (SD)	Week 4 Mean (SD)	Change from baseline to week 4 Mean (SD) [95% CI]	Wilcoxon signed-rank test (P)
HR (bpm)	179	68.27 (11.541)	69.51 (11.254)	1.24 (7.314) [0.2, 2.3]	0.010
QTcF (ms)	146	419.53 (20.410)	418.75 (20.172)	–0.78 (11.202) [–2.6, 1.1]	0.461 NS
RR (ms)	179	897.72 (152.686)	879.34 (141.181)	–18.38 (90.790) [–31.8, –5.0]	0.006
PR (ms)	179	180.07 (27.899)	181.02 (26.565)	0.95 (15.898) [–1.4, 3.3]	0.097 NS
QRS (ms)	179	97.77 (20.356)	98.14 (21.239)	0.38 (7.254) [–0.7, 1.4]	0.436 NS

bpm = beats per minute. CI = confidence interval. HR = heart rate. NS = non-significant. SD = standard deviation.

and reperfusion injury[10]. In healthy men, C-reactive protein, a well-known marker of inflammation, has been correlated with storage symptoms after adjusting for age, body mass index, prostate volume and metabolic risk factors[11]. In rats with arterial atherosclerosis, bladder ischemia resulted in detrusor overactivity, which progressed towards bladder underactivity[12]. The process involved neural–structural injuries, loss of nerve fibres and differential expression of muscarinic receptors[12].

In patients with DM, a condition well-known for its vascular complications, the presence of urinary symptoms is a relatively common clinical observation. An Italian study (n = 661) that compared diabetic patients with healthy controls reported significantly higher OAB questionnaire (OAB-q) scores ($p < 0.0001$), as well as per-24 hour episodes of micturition, urgency, urge urinary incontinence and nocturnal micturition (all $p < 0.001$)[13]. In a multivariate analysis of 457 DM patients with OAB from Mainland China, OAB severity was associated with age (OR = 1.59, $p = 0.036$), duration of diabetes (OR = 1.41, $p = 0.049$) and symptomatic diabetic peripheral neuropathy (OR = 2.39, $p = 0.012$)[14].

LUTS MANAGEMENT IN CVD PATIENTS

The management of patients with LUTS and CVDs requires attention to some potential overlap in behavioural and pharmacological treatment strategies. To improve urinary outcomes, a "golden rule" to begin with would be to avoid diuretic medication and fluid intake during the evening. Further strategies may include titrating diuretics and fluid restriction[15].

In terms of co-medications for patients with LUTS and CVDs, the following should be noted:

1. Traditional OAB Treatment – Anticholinergic Medications

Nowadays, anticholinergic medications are much less commonly used, as a result of concerns over the cumulative risks of cognitive impairment, falls and mortality – i.e. the "anticholinergic burden[16]." The EPIC-Norfolk study reported a class effect, as well as a dose-response relationship, between anticholinergic medications and the risks of mortality and CVDs[17]. Non-selective anticholinergic LUTS medications such as trospium chloride, tolterodine tartrate, fesoterodine fumarate and propiverine hydrochloride may potentially lead to an unfavourable increase in heart rate (HR)[18].

2. Common BPH Treatment – α-Blockers

The concomitant use of α-blockers and anti-hypertensive medication may increase the risk of developing hypotension[19]. In a retrospective evaluation of 9,242 Italian hypertensive patients aged ≥ 18, 10.4% experienced orthostatic hypotension (OH), and the use of α-blockers was associated with an increased risk of OH (OR = 1.6; 95% CI: 1.24–2.07),[20] which may result in fainting and falls during nocturia episodes. For patients who may be concerned with or prone to developing OH, using more selective α-blockers (e.g. tamsulosin), as well as evening after-meal dosing, may help reduce the risk[19]. In a meta-analysis of 25 studies of α-blocker use in benign prostate hyperplasia, alfuzosin, terazosin and doxazosin were associated with significantly increased odds of developing a vascular-related event: OR = 1.66 (95% CI: 1.17 – 2.36), OR = 3.71 (95% CI: 2.48 – 5.53) and OR = 3.32 (95% CI: 2.10 – 5.23), respectively[21]. However, tamsulosin, which is α1a- and α1d-selective, showed only a marginally significant increase (OR = 1.42, 95% CI: 0.99 – 2.05)[21].

3. Novel OAB Treatment –β_3-agonists

β_3-agonists appear to be well-tolerated in patients with CVD[15]. A real-world prospective study of the β_3-agonist (mirabegron) in 236 elderly Japanese patients with OAB and a history of/co-existing CVDs showed no unexpected CV safety concerns[22]. The mean HR increase after 4 weeks was 1.24 beats per minute, which was not clinically significant. There were no significant changes in PR, QRS or Fridericia's corrected QT intervals (Table 1)[22].

LATEST AVAILABLE CVD THERAPIES

SGLT-2i and CVDs

The sodium-glucose cotransporter-2 inhibitors (SGLT-2i) are a class of glucose-lowering agents that can induce glucosuria (Fig. 2) and have a diuretic effect that reduces extracellular fluid and plasma volume[23]. In both patients with and without pre-existing CVDs, large-scale trials of SGLT-2i (empagliflozin, canagliflozin and dapagliflozin) demonstrated significant reductions not only in HbA1c levels but also CV mortality and hospitalisation for heart failure (HHF)[24]. In the EMPA-REG OUTCOME trial[25] of 7,020 patients with established atherosclerotic disease, a statistically significant reduction was observed for empagliflozin versus placebo for the exploratory endpoint of HHF, with a relative risk reduction (RRR) of −35% and an absolute risk reduction (ARR) of −1.4% that

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Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)

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Elderly aged 65+ with chronic diseases are more likely to develop pneumococcal pneumonia:

DIABETES

2.8 folds[2*]

CHRONIC CVD†

3.8 folds[2*]

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7.7 folds[2*]

Your Role Is Key

PREVENAR 13® ABBREVIATED PACKAGE INSERT **1. TRADE NAME:** PREVENAR 13® **2. PRESENTATION:** A homogeneous white suspension for injection (0.5ml) supplied as a pre-filled syringe. **3. INDICATIONS:** Active immunisation for the prevention of pneumococcal disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F in adults and children aged more than 6 weeks of age. The use of Prevenar 13 should be guided by official recommendations. **4. DOSE & ADMINISTRATION:** Intramuscular administration only. The immunisation schedules should be based on official recommendations. Infants aged 6 weeks - 6 months: The primary infant series consists of three doses, with the first dose usually given at 2 months of age and with an interval of at least 1 month between doses. The first dose may be given as early as six weeks of age. A fourth (booster) dose is recommended after 12 months of age, and at least 2 months after the third dose. Unvaccinated children aged 7–11 months: 3 doses. Unvaccinated children aged 12–23 months: 2 doses. Unvaccinated children aged 24 months to 17 years: One single dose. Adults: One single dose. For more dosage information, please refer to the full Prescribing Information. **5. CONTRAINDICATIONS:** Hypersensitivity to the active substances or to any of the excipients, or to diphtheria toxoid. Allergic reaction or anaphylactic reaction following prior administration of Prevenar (7-valent). **6. WARNINGS & PRECAUTIONS:** Not for intravenous or intravascular administration; as with other vaccines, the administration should be postponed in subjects suffering from acute moderate or severe febrile illness; should not be given to individuals with thrombocytopenia or any coagulation disorder that would contraindicate intramuscular injection unless the potential benefit clearly outweighs the risk of administration; will not protect against *Streptococcus pneumoniae* serotypes other than those included in the vaccine nor other microorganisms that cause invasive disease, pneumonia, or otitis media; may not protect all individuals receiving the vaccine from pneumococcal disease. Individuals with impaired immune responsiveness may have reduced antibody response to active immunisation. Safety and immunogenicity data for Prevenar 13 are available for certain high-risk groups such as children and adolescents with sickle cell disease and children and adults with HIV infection or with a haematopoietic stem cell transplant. Data are not currently available for individuals in other immunocompromised groups (e.g., malignancy, or nephrotic syndrome) and vaccination should be considered on an individual basis. Children below 2 years old should receive the appropriate-for-age Prevenar 13 vaccination series. The potential risk of apnoea and the need for respiratory monitoring for 48–72h should be considered when administering the primary immunisation series to very premature infants (born ≤ 30 weeks of gestation), and particularly for those with a previous history of respiratory immaturity. Antipyretic treatment should be initiated according to local treatment guidelines. Prophylactic antipyretic medication is recommended for children with seizure disorders or with a prior history of febrile seizures and for all children receiving Prevenar 13 simultaneously with vaccines containing whole cell pertussis. **7. INTERACTIONS:** Infants and children aged 6 weeks to 5 years: Can be given with any of the following vaccine antigens, either as monovalent or combination vaccines: diphtheria, tetanus, acellular or whole-cell pertussis, *Haemophilus influenzae* type b, inactivated poliomyelitis, hepatitis B, meningococcal serogroup C, measles, mumps, rubella and varicella. Can also be given concomitantly between 12–23 months with the tetanus toxoid conjugated meningococcal polysaccharide serogroup A, C, W and Y vaccine. In clinical trials, where there was concomitant administration of Prevenar 13 and rotavirus vaccine, no change in the safety profiles of these vaccines was observed. When Prevenar 13 is administered concomitantly with Infanrix hexa (DTaP-HBV-IPV/Hib), the rates of febrile reactions are similar to those seen with concomitant administration of Prevenar (7-valent) and Infanrix hexa. Children 6 to 17 years of age and adults 18 to 49 years of age: No data are currently available regarding concomitant use with other vaccines. Adults aged 50 years and older: May be administered concomitantly with seasonal trivalent or quadrivalent inactivated influenza vaccine. Different injectable vaccines should always be given at different injection sites. **8. PREGNANCY AND LACTATION:** Prevenar 13 is not indicated or recommended for use in pregnant women and has not been evaluated for potential harmful effects during pregnancy in humans. Safety during lactation has not been established. **9. SIDE EFFECTS:** Children: Decreased appetite; fever; irritability; drowsiness/increased sleep; restless sleep/decreased sleep; any vaccination-site erythema, induration/swelling or pain/tenderness; vaccination-site pain/tenderness interfering with movement; diarrhoea, vomiting; rash. Children and adolescents aged 5 to 17 years of age: Decreased appetite; irritability; any vaccination-site erythema; induration/swelling or pain/tenderness; drowsiness/increased sleep; restless sleep/decreased sleep; vaccination-site tenderness (including impaired movement); fever; headache; rash; urticaria/urticaria-like rash; vomiting; diarrhoea. Adults: decreased appetite; headache; diarrhoea; vomiting; rash; chills; fatigue; vaccination-site erythema; vaccination-site induration/swelling; vaccination-site pain/tenderness; limitation of arm movement; joint pain; muscle pain; fever. **(Please refer to the full Prescribing Information for details)** **Reference:** HK LPD version July 2018 **Date of preparation:** APR 2019 **Identifier number:** PR13-0419 **FULL PRESCRIBING INFORMATION IS AVAILABLE UPON REQUEST.**

PP-PNA-HKG-0075 Feb/2020

† Cardiovascular disease

* Relative to the healthy counterparts

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was independent of renal function and glucose levels. In the CANVAS trial[26] of patients with established CVDs (n = 6,656) and of patients who were at high risk of having CVDs (n = 3,486), canagliflozin versus placebo significantly reduced the exploratory endpoint of HHF (−33% RRR; −3.2% AAR). In the DECLARE trial[27] of 17,160 patients, including 59.4% of patients who were without CVDs, treatment with dapagliflozin resulted in a lower rate of CV death or HHF versus placebo (−27% RRR; −0.8% ARR).

In view of these results, SGLT-2i appear to be particularly suitable for DM patients with heart failure[24]. Many hypotheses concerning the CV effects of SGLT-2i have been proposed, most of which involve improved metabolic processes and reduced inflammation. Clinical studies reported that SGLT-2i reduced leptin and increased adiponectin levels (which may counteract insulin resistance); increased levels were also observed for the inflammatory markers tumour necrosis factor-α and interleukin-6[28]. Preclinical studies support the hypothesis that SGLT-2i improve cardiac metabolism and bioenergetics, including reducing necrosis and cardiac fibrosis[29]. The overall effect of SGLT-2i may include weight loss, increased ketone bodies, reduced adipose tissue inflammation, uric acid levels and oxidative stress[28].

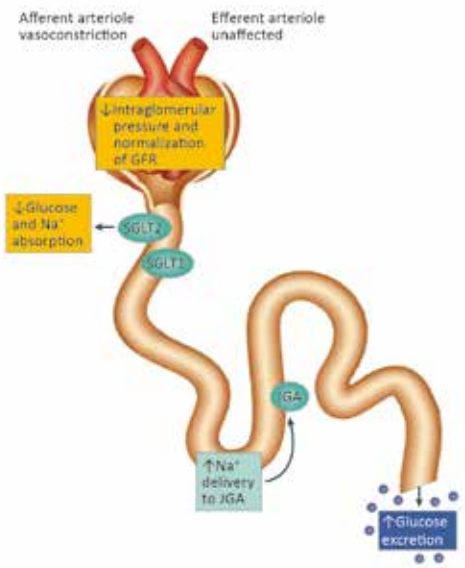

Fig. 2. Schematic diagram of the mechanism by which SGLT-2i promotes glucose and sodium excretion in the renal proximal tubule[23]. GFR, glomerular filtration rate; JGA, juxtaglomerular apparatus; SGLT, sodium-glucose co-transporter protein. Figure excerpted from: DeFronzo RA, Norton L, Abdul-Ghani M. Renal, metabolic and cardiovascular considerations of SGLT2 inhibition. Nat Rev Nephrol. 2017;13(1):11-26. Copyright © 2016 Macmillan Publishers Limited, part of Springer Nature.

Current diabetes guidelines recommend incorporating considerations of geriatric syndromes when individualising therapies[30]. In patients with LUTS, physicians may need to pay additional attention when prescribing SGLT-2i because of their diuretic effect and the increased risk of genitourinary infections reported in clinical trials[30].

Angiotensin Receptor Blockers/ Diuretic Fixed-dose Combinations

In patients with heart failure and/or hypertension, diuretics are often prescribed for more immediate symptomatic relief[15]. Combination therapy of an angiotensin receptor blocker (ARB) with a diuretic has become popular in recent years. In a population-based retrospective cohort of 13,350 hypertensive patients aged ≥ 66 years from Canada, fixed-dose combination therapy was associated with a significantly lower risk of composite clinical outcomes vs. multi-pill therapy[31]. Another systematic review of 14 randomised controlled trials (n = 5,120) of two-drug fixed-dose combinations (FDCs) versus monotherapy showed a 27% improvement in blood pressure control without increased withdrawals from side effects[32]. The combination therapy also tends to improve tolerability, because the dose of each component can be lowered[33]. In July 2019, the World Health Organization added FDC anti-hypertensive medications to their Essential Medicines List[34].

Diuretic effect may sometimes lead to urinary symptoms[15]. In the Boston Area Community Health Survey[35], positive associations were observed in men (n = 821; aged 30–79 years) for thiazide monotherapy and voiding symptoms (OR = 2.90, 95% CI: 1.17–7.19), as well as loop diuretic when used in combination therapy and nocturia (OR = 2.55; 95% CI: 1.26–5.14). Thus, similarly with the case of SGLT-2i, attention to urinary symptoms may be needed when diuretics are prescribed[15].

CONCLUSION

Current international and regional data suggest that LUTS are prevalent among CVD patients. Contributing pathophysiological factors may include MetS and vascular dysfunction. Fluid and diuretics should be avoided in the evening. The patient's total anticholinergic burden should be considered (if prescribing anticholinergic medications), as should the risk of hypotension that is associated with certain α-blockers. For patients with CVDs and BPH, highly (e.g. α1a- and α1d-) selective α-blockers (e.g. tamsulosin) should be considered. As novel OAB treatment agents, β_3-agonists (e.g. mirabegron) are well-tolerated in CVD patients: no clinically significant changes in cardiac parameters have been observed. While the use of a diuretic is often needed in patients with CVD, the presence of urinary symptoms should be considered and monitored.

In Hong Kong, studies on LUTS and CVDs appear lacking. It is conceivable that many LUTS cases remain undetected and untreated in the everyday clinic. Physician and patient awareness on the intimate association between LUTS and CVDs would be helpful for case identification, and for initiating individualised treatment planning and behavioural modifications.

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Female LUTS and Incontinence

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INTRODUCTION

Female Lower Urinary Tract Symptoms (LUTS) include symptoms of incontinence, storage problems, voiding problems, post micturition problems and nocturia.

PREVALENCE

Urinary incontinence (UI) is the commonest LUTS in female. UI is the complaint of any involuntary leaking of urine[1]. Prevalence of female urinary incontinence varies with the population sampled and definition used. Current data provide very disparate estimates of population prevalence for UI in women. Approximately 10% of all adult women report leakage at least weekly. Occasional leakage is much more common, affecting 25-45% of all adult women. This variation is seen both within and between countries. It is due to cultural differences in the perception of UI and willingness to report UI as well as methodological differences[2,3,4]. However, the distribution of UI subtypes is consistent. Isolated stress incontinence accounts for approximately half of all incontinence. With few exceptions, mixed incontinence is found to be the next most common, with most studies reporting 7.5-25%. Isolated urgency incontinence is 1-7%, while other causes of incontinence occur with approximately 0.5-1%[5]. The study by Wong et al. in Hong Kong revealed similar results[6]. Although UI is considered a benign situation, there is much impact on the quality of life for the affected individuals with reduced self esteem, impaired emotional/psychological well-being and poor social relationships with others[7]. The prevalence is estimated to grow as the life expectancy of women in the developed world increases[8].

COST

When a person with incontinence decides to seek medical care, there will have already increased costs, related to pads or laundry, and to managing the condition at home. She will then have a consultation, tests will probably be ordered, and treatment may be initiated. These are the costs of treatment. The incontinence may increase the risk of a urinary tract infection, or the person may slip and fall on the way to the toilet. These are the costs associated with treating the consequences of incontinence. Therefore, UI definitely creates much economic burden on the affected individuals and the society[9,10].

CAUSES

Common causes for female UI include stress urinary incontinence (SUI), overactive bladder syndrome (OAB), functional incontinence, overflow incontinence, obstetrics or surgical fistulae, congenital anomalies and neurological/metabolic diseases. Evaluations are important to assess the types of UI; severity of incontinence; impact on the quality of life; the presence of concomitant gynaecological problems like pelvic organ prolapse or uterine/ovarian abnormalities; the presence of neurological deficits; the presence of urinary tract infection and bladder pathology.

DIAGNOSIS

The diagnostic rationale for urodynamic study (UDS) in women with UI in association with the currently changing management paradigm has been debated for some time. The think tanks of the International Consultation of Incontinence Research Society (ICI-RS) have suggested that the patient's presentation can be more precisely delineated as syndromes e.g. stress urinary incontinence syndrome (SUI-S), the overactive bladder syndrome (OAB-S) and the neurogenic LUT dysfunction syndrome (NLUTD-S)[11]. Therefore, UDS are not always indicated before treatment can be initiated. It is recommended only when a patient presents with LUTS that are not typically SUI-S or OAB-S and when a patient presents with new or persisting symptoms and signs of LUTS after initial management or when a patient expresses the wish for alternative management (more invasive or more irreversible ones).

TREATMENT

Treatment depends on the respective cause of UI and the presence/absence of other concomitant gynaecological causes. Conservative treatment is always the first-line treatment, and entails pelvic floor exercise (PFMT), bladder retraining, lifestyle modification, etc. Many studies are showing that PFMT is effective as a stand-alone therapy, as part of the multi-component therapies embedding PFMT with concomitant behavioural strategies, lifestyle changes, and as part of more general physical exercise programs to improve physical function in older women. Benefits are shown across age cohorts and UI types, in various cultural contexts, using several different training regimes and assessed by multiple outcome measures. Level 1 evidence confirms that supervised PFMT should be offered as first-line

conservative therapy for women of all ages with urinary incontinence[12].

Surgical treatment can be used to treat stress urinary incontinence (SUI), concomitant gynaecological problems like pelvic organ prolapse (POP), uterine fibroids, fistulae, etc. SUI represents the most common type of female UI. Several surgical procedures, both vaginal and abdominal have been proposed over the years for treating SUI. Current evidence suggests that mid-urethral slings (MUS), such as retropubic MUS and transobturator MUS have become the treatment of choice and are considered the gold standard[13,14]. There are grade A evidence showing that retropubic MUS is an effective and durable treatment for SUI, and is comparable to autologous fascial sling (AFS) achieving 85-90% objective and subjective long-term success. Transobturator MUS may be offered as an effective treatment for SUI with appropriate counselling regarding its current limitations on long-term randomised clinical trial data regarding durability[12]. With regard to complications, bladder or vaginal perforations and postoperative haematoma were significantly more common following retropubic MUS. There was no significant difference between the 2 groups in need for repeating incontinence surgery; postoperative detrusor overactivity, de novo urgency and urge incontinence[12,15]. There was a significantly higher occurrence of groin pain (12%) in women, with the transobturator approach. However, postoperative voiding dysfunction occurred significantly less frequent in the transobturator groups[15]. Both approaches (outside-in vs inside-out) in transobturator MUS are associated with similar short/medium term outcomes. However, vaginal wall perforation is higher with the outside-in approach and voiding dysfunction is higher with inside-out approach[12].

The incidence of pelvic organ prolapse (POP) or urinary incontinence (UI) in women grows in parallel with the increase of life expectancy. According to the integral theory, UI and POP may be often related[16], and their coexistence is reported in 15-80% of women with POP[17]. This range depends on different ways of evaluating UI and by the fact that UI can be asymptomatic or occult. Therefore, it is important to cure the underlying concomitant POP to resolve both problems at one go. Studies have shown that combined procedures of MUS and POP surgeries are effective and safe to treat concomitant SUI and POP[18].

Pharmacological agents can be offered for treating OAB. New drugs are available in the market like Mirabegron and Botox, which are having encouraging results[12]. Proper patient selection for antimuscurinic and other drug treatment requires careful assessment of underlying physical status including cognitive function, mobility and comorbidities.

CONCLUSION

In conclusion, female LUTS and incontinence is a common condition affecting 1 in 3 women. Many advances have been made in the care of patients with those problems. Many effective treatment modalities are available thus enabling significantl improvement in the quality of life of our female population.

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Ultrasonography Assisting Management of LUTS

Prof Michael Tin-cheung YING

PDDR, MPhil, PhD, FHKCRRT

Professor,
Department of Health Technology and Informatics, The Hong Kong Polytechnic University

Prof Michael Tin-cheung YING

BASIC ULTRASOUND CONCEPTS AND INSTRUMENTATION

Ultrasound is high frequency sound wave. The frequency of ultrasound waves ranges from 1 to 30 MHz which is much higher than the frequency of audible sound waves (20 – 20,000 Hz). Ultrasound is a longitudinal wave. Unlike the electromagnetic radiation, ultrasound (& other kinds of sound wave) requires a medium for propagation. Therefore, coupling gels are required in ultrasound examination to ensure good transmission of ultrasound from the ultrasound transducer to the patient's body.

Each ultrasound unit is connected to at least one ultrasound transducer. Different transducers are designed for different clinical applications, such as curved transducers for an abdominal ultrasound scan, linear transducers for ultrasound scan of superficial structures, and endocavity transducers for transvaginal and transrectal ultrasound scans. Ultrasound transducer is an important component of an ultrasound unit because it generates ultrasound waves and receives ultrasound echoes for the formation of ultrasound image.

Ultrasound imaging (also known as ultrasonography) is to use ultrasound, based on its physical characteristics, to produce an image. Clinically, grey scale (also known as Brightness-mode, B-mode) ultrasound is commonly used.

When ultrasound waves propagate through a medium (e.g. a kind of soft tissue), it travels in its original direction until it meets an acoustic interface. Two media with different acoustic impedance (Z) form an acoustic interface. Acoustic impedance is the characteristic of a medium related to the density and elastic properties of the medium, and is a measure of resistance to sound waves passing through the medium. When ultrasound waves meet an acoustic interface, some of the ultrasound energy reflected as echoes while the remaining energy of the incident ultrasound beam is moving to the deeper region (Fig. 1). The amount of incident ultrasound energy reflected by an acoustic interface is expressed by the intensity reflection coefficient (α_R):

$$\alpha_R = \frac{(Z_2 - Z_1)^2}{(Z_2 + Z_1)^2}$$

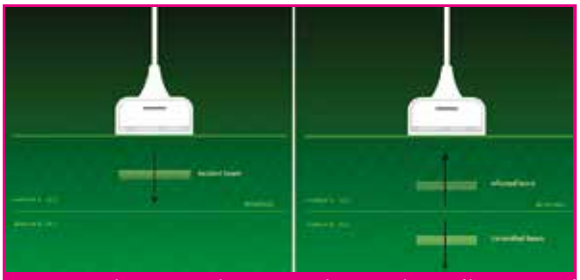

Fig. 1. Schematic diagram shows the reflection of ultrasound wave at an acoustic interface which is formed by two media with different acoustic impedance. (Personal collection)

where Z_1 and Z_2 are the acoustic impedance of two media that form the acoustic interface (Fig. 1). According to the equation, the larger the difference between Z_1 and Z_2 the larger the value of α_R , and thus more ultrasound energy is reflected by the acoustic interface.

Pulse wave ultrasound is common in grey scale ultrasound. In pulse wave ultrasound, the transducer sends a short pulse of ultrasound waves followed by a period of silence in order to receive the returning echoes before another ultrasound pulse is sent. The time of returning echoes provides information about the depth of the acoustic interface. The amplitude (i.e. the energy level) of the echoes determines the brightness of the bright spots in greyscale ultrasound image[1].

Several parameters should be considered when performing an ultrasound scan in order to optimise image quality:

1. Gain – adjust the overall echogenicity (i.e. brightness) of the ultrasound image
2. Time-gain compensation (TGC) – adjust the echogenicity at different levels of depth of ultrasound image so that the image has a uniform brightness
3. Lateral resolution – highest lateral resolution is at the focal zone, and therefore the focal zone should be adjusted and placed at the region of interest
4. Axial resolution – higher ultrasound frequency provides a higher axial resolution of the image but has lower ultrasound beam penetration. Therefore, high frequency ultrasound is used in scanning of superficial structures such as neck ultrasound and musculoskeletal ultrasound, whereas low frequency ultrasound is used in scanning of deeper structures such as abdominal ultrasound.

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MENARINI

ULTRASOUND ANATOMY OF URINARY TRACT

Kidneys and filled urinary bladder are clearly seen on ultrasound. A non-dilated ureter may be impossible to see on ultrasound because of the presence of overlying bowel gas. However, a dilated ureter may be seen as a hypoechoic tubular structure. The proximal ureter would be easier to visualise than other parts of the ureter when using the kidney as the acoustic window. The visualisation of dilated ureters can be improved by using transducer compression to displace overlying bowel gas.

Normal kidney appears as a bean-shaped structure with smooth outlines. The renal cortex is slightly hypoechoic when compared to the liver parenchyma. In adults, the normal kidney is about 8-13 cm in length, and the renal cortex, medullary pyramids and sinus echo complex (also known as renal hilum) are demonstrated (Fig. 2). The visualisation of renal cortex and medullary pyramids indicates good corticomedullary differentiation. A well-defined echogenic line surrounding the kidney represents the renal capsule with perinephric fat[2].

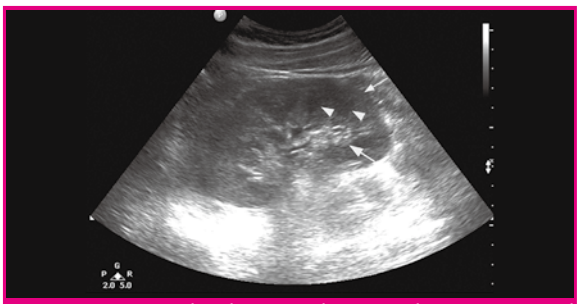

Fig. 2. A grey scale ultrasound image shows a coronal scan of a normal kidney. The renal cortex (small arrow), medullary pyramids (arrowheads) and sinus echo complex (large arrow) of the kidney are demonstrated. (Personal collection)

In an ultrasound examination of kidney, the following renal sonographic features should be assessed:

1. Renal size/length
2. Renal outline
3. Renal cortex
4. Renal echogenicity
5. Corticomedullary differentiation
6. Evidence of renal stone/calcification
7. Evidence of space occupying lesion

Filled urinary bladder appears as a homogeneous, hypoechoic structure with well-defined bladder walls (Fig. 3). In an ultrasound examination of urinary bladder, the following sonographic features should be assessed:

1. Bladder outline
2. Bladder wall thickness
3. Evidence of bladder stone
4. Evidence of space occupying lesion

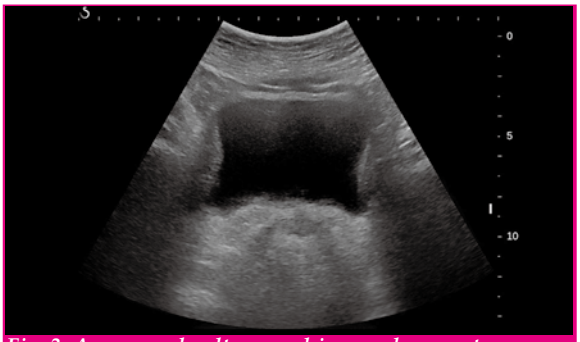

Fig. 3. A grey scale ultrasound image shows a transverse scan of a normal filled urinary bladder with well-defined bladder walls. (Personal collection)

COMMON APPLICATIONS OF ULTRASOUND IN LUTS

Benign prostate hyperplasia (BPH) can be assessed using ultrasound. Transabdominal ultrasound is performed by scanning over the patient's pelvic region transversely and longitudinally. Ultrasound is commonly used to estimate the size of the prostate gland and the amount of residual urine after urination. Transrectal ultrasound may be conducted for precise measurement of prostate size and in suspected cases of prostate cancer in which ultrasound-guided biopsy of the tumour is performed. The prostate volume and amount of residual urine are commonly estimated using the ellipsoid equation (0.52 x width x height x length) [3,4].

Ultrasound can help in the assessment of bladder outlet obstruction (BOO) and detrusor underactivity (DU). Using high frequency ultrasound (7.5 MHz or higher) and scanning transversely over the suprapubic region, the anterior bladder wall can be demonstrated in which the hypoechoic detrusor is sandwiched between the hyperechoic adventitia and mucosa. Detrusor wall thickness (DWT) is the distance between the inner border of the adventitia and that of the mucosa[5]. It has been reported that the DWT increases in patients with BOO. About 95% of men with DWT ≥ 2 mm had BOO. In addition, ultrasound measurement of DWT can help the detection of DU. DWT ≤ 1.23 mm in combination with bladder capacity > 445 ml is a significant predictor of DU with a positive predictive value of 100% and a negative predictive value of 85%[6,7].

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HKSH SYMPOSIUM ON ADVANCES IN CANCER MANAGEMENT 2020

Precision Medicine in Oncology Treatment

WEBINAR

Date: Wednesday, 9 December 2020

Time: 19:00 – 22:00 HKT

Programme

19:00 - 19:05	**Welcome Speech**	 **Mr. Wyman LI** Chief Operating Officer, HKSH Medical Group Manager (Administration), Hong Kong Sanatorium & Hospital
19:05 - 19:10	**Introduction**	
19:10 - 19:40	**MRI-Guided Radiotherapy – Paradigm Shift in Precision Radiotherapy**	 **Dr. Darren POON** Honorary Consultant in Clinical Oncology Hong Kong Sanatorium & Hospital
19:40 - 19:50	**Q&A**	
19:50 - 20:20	**How Could Urologists "Salvage" the Rectum for Patients with Pelvic SBRT**	 **Dr. Ka Lun CHUI** Private Specialist in Urology Honorary Clinical Assistant Professor, Department of Surgery The Chinese University of Hong Kong
20:20 - 20:30	**Q&A**	
20:30 - 21:00	**The Bio-Molecular Basis & Challenges of PET/CT in Radiation Treatment Planning**	 **Dr. Garrett HO** Head, Department of Nuclear Medicine and Positron Emission Tomography Honorary Consultant in Nuclear Medicine Hong Kong Sanatorium & Hospital
21:00 - 21:10	**Q&A**	
21:10 - 21:40	**Radixact Synchrony: Preliminary Clinical Experience from University of Turin**	 **Prof. Umberto RICARDI, MD** Full Professor and Chairman of Radiation Oncology Dean of School of Medicine, University of Turin, Italy Director, Department of Oncology Health and Science Academic Hospital, Italy
21:40 - 21:50	**Q&A**	
21:50 - 22:00	**Closing Remarks**	 **Dr. Walton LI** Chief Executive Officer, HKSH Medical Group Medical Superintendent, Hong Kong Sanatorium & Hospital
22:00	**End of Symposium**	

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Moderators

Dr. Wing Hong KWAN
Director, Department of Radiotherapy
Associate Director, Comprehensive Oncology Centre
Honorary Consultant in Clinical Oncology
Hong Kong Sanatorium & Hospital

Dr. Chun Key LAW
President, Hong Kong College of Radiologists
Honorary Consultant in Clinical Oncology
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		* Certificate Course in Cardiology 2020 (Video Lectures) **1**	* Facebook Live Update on Acne Management * Short Course in Clinical Toxicology 2020 (Video Lectures) **2**	* Facebook Live Advanced Technologies and Application of Early Nasopharyngeal Carcinoma Screening **3**	* Facebook Live Management of Hypertension with Vasodilating Beta-blockers **4**	* 2020 Paediatric Update No. 2 - aediatric Endocrine Emergencies Organiser: Hong Kong College of Paediatricians **5**
6	**7**	* Certificate Course in Cardiology 2020 (Video Lectures) **8**	* The Hong Kong Neurosurgical Society Monthly Academic Meeting –Intraoperative Neurophysiology in Glioma Surgery **9**	**10**	**11**	**12**
13	**14**	* Certificate Course in Cardiology 2020 (Video Lectures) **15**	* Facebook Live Personalized Treatment for Childhood Asthma Advent of a New Age **16**	* Facebook Live Sarcopenia Diagnosis and Management **17**	**18**	**19**
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A LOT CAN HAPPEN IN EXTRA TIME

FIRMAGON®
degarelix

- THANKS TO ITS DISTINCT MOA[1-5], COMPARED WITH LHRH AGONISTS, FIRMAGON®:
  - *Provides significantly faster suppression of testosterone and PSA levels*[5-7]
  - *Demonstrates improved and long-lasting disease control from the start*[6,8]
  - *Delivers significantly improved overall survival during the 1st year of treatment*[8]
  - *Significantly improves QoL and reduces prostate size compared with LHRH agonist + antiandrogen treatment*[10]
- PATIENTS WITH HIGH-RISK PROSTATE CANCER
  - *Fast and lasting testosterone and PSA control over time*[6]
- PATIENTS WITH A HISTORY OF CVD
  - *56% relative risk reduction in cardiac events or death during the 1st year of treatment compared with LHRH agonists*[9]
- EAU RECOMMENDS LHRH ANTAGONISTS FOR PROSTATE CANCER PATIENTS WITH BLADDER OUTLET OBSTRUCTION[11]

CVD: cardiovascular disease; LHRH: luteinising hormone-releasing hormone; MOA: mechanism of action; PSA: prostate-specific antigen; QoL: quality of life

FOR PATIENTS WITH ADVANCED HORMONE-DEPENDENT PROSTATE CANCER[1,2]

START STRONG.
STAY IN CONTROL.

REFERENCES: 1) Hong Kong Product Package Insert of FIRMAGON 80mg (Date of revision: May 2015); 2). Hong Kong Product Package Insert of FIRMAGON 120mg (Date of revision: May 2015); 3) Van Poppel H, et al. *Int J Urol.* 2012;19:594–601; 4) Drudge-Coates L. *Int J Urol Nurs.* 2009;3:85–92; 5) Crawford ED, et al. *J Urol.* 2011;186:889–97; 6) Crawford ED, et al. *Urology.* 2014;83:1122–8; 7) Klotz L, et al. *BJU Int.* 2008;102:1531–8; 8) Klotz L, et al. *Eur Urol.* 2014;66:1101–8; 9) Albertsen PC, et al. *Eur Urol.* 2014;65:565–73; 10) Anderson J, et al. *Urol Int.* 2013;90(3):321–328; 11) EAU Guidelines. Edn. presented at the EAU Annual Congress Amsterdam 2020.

Abbreviated Prescribing Information of FIRMAGON
Active Ingredient: Degarelix. **Indications:** Treatment of advanced hormone-dependent prostate cancer in adult males. **Dosage and Administration:** Initially: 240 mg administered as 2 SC inj of 120 mg each. Maintenance: 80 mg administered as 1 SC inj (mthly administration). The first maintenance dose should be given one mth after the starting dose. **Contraindications:** Hypersensitivity. **Special Warnings and Precautions:** The vials should not be shaken. Long-term androgen deprivation therapy may prolong QT interval. Use w/ caution in patients with Hx of QTc interval >450 msec, Hx or having risk factors of torsades de pointes or CVD, Hx of severe untreated asthma, anaphylactic reactions or severe urticaria or angioedema. May decrease bone density. May reduce in glucose tolerance, diabetic patients may require more frequent monitoring of blood glucose. Use w/ caution in patients w/ severe renal & hepatic impairment. May impair ability to drive or operate machinery. May inhibit male fertility as long as the testosterone is suppressed. No relevant indication for use in women, children and adolescents. Must not be mixed with other medicinal products. **Side Effects:** Hot flushes, inj site reactions, anaemia, increased wt, insomnia, dizziness, headache, diarrhoea, nausea, increased liver transaminases, hyperhidrosis (incl. night sweats), rash, musculoskeletal pain & discomfort, gynaecomastia, testicular atrophy, erectile dysfunction, chills, pyrexia, fatigue, flu-like illness. **Interactions:** Medicinal products known to prolong the QTc interval or able to induce torsades de pointes such as Class IA (eg, quinidine, disopyramide) or Class III (amiodarone, sotalol, dofetilide, ibutilide) antiarrhythmics, methadone, cisapride, moxifloxacin, antipsychotics.

For additional information, please consult the product package insert before prescribing.

FERRING PHARMACEUTICALS

Ferring Pharmaceuticals Ltd.
Suites 2604-05, 26/F, AXA Tower, Landmark East,
100 How Ming Street,
Kwun Tong, Kowloon, Hong Kong
Tel.: +852 2622 8000 Fax: +852 2622 8001 www.ferring.com

UR008/20/Sep/HK

Date / Time	Function	Enquiry / Remarks
1 TUE 7:00 PM	**Certificate Course in Cardiology 2020 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Dr YUNG Tak-cheung	Ms. Vienna LAM Tel: 2527 8898
2 WED 2:00 PM	**Facebook Live** **Update on Acne Management** Organiser: HKMA-Kowloon West Community Network Speaker: Dr LAM Yuk-keung	Miss Antonia Lee 3108 2514 1 CME Point
7:00 PM	**Short Course in Clinical Toxicology 2020 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr WONG Oi-fung	Ms. Vienna LAM Tel: 2527 8898
3 THU 2:00 PM	**Facebook Live** **Advanced Technologies and Application of Early Nasopharyngeal Carcinoma Screening** Organiser: HKMA-Kowloon East Community Network Speaker: Dr Julian Kay-chung YAU	Miss Antonia Lee 3108 2514 1 CME Point
4 FRI 2:00 PM	**Facebook Live** **Management of Hypertension with Vasodilating Beta-blockers** Organiser: HKMA-Kowloon West Community Network Speaker: Dr Gary Shing-him CHEUNG	Miss Antonia Lee 3108 2514 1 CME Point
5 SAT 3:00-6:05 PM	**2020 Paediatric Update No. 2 - aediatric Endocrine Emergencies** **Organiser: Hong Kong College of Paediatricians** On-site Venue: Lim Por Yen Lecture Theatre, Hong Kong Academy of Medicine Jockey Club Building On-line: ZOOM Teleconference (ZOOM Meeting ID:99654291445) Chairpersons: Prof LEUNG Ting-fan, Dr Betty BUT; Speakers: Dr Queenie SEE, Dr Grace POON, Dr Sarah POON, Dr Anita TSANG, Dr Sharon TO, Dr Antony FU, Dr Catherine WONG, Dr Jasmine CHOW	Miss Antonia Lee 3108 2514 1 CME Point
8 TUE 7:00 PM	**Certificate Course in Cardiology 2020 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr TAN Guang-ming	Ms. Vienna LAM Tel: 2527 8898
9 WED 7:30 AM	**The Hong Kong Neurosurgical Society Monthly Academic Meeting –Intraoperative Neurophysiology in Glioma Surgery** Organiser: Hong Kong Neurosurgical Society Speaker(s): Dr Victor Ka-ho HUI Chairman: Dr Michael Wing-yan LEE Venue: Conference Room, F2, Department of Neurosurgery, Queen Elizabeth Hospital; or via Zoom meeting	CME Accreditation College: 1.5 points Enquiry: Dr Calvin MAK Tel: 2595 6456 Fax. No.: 2965 4061
15 TUE 7:00 PM	**Certificate Course in Cardiology 2020 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr Victor Yue-hong CHEUNG	Ms. Vienna LAM Tel: 2527 8898
16 WED 2:00 PM	**Facebook Live** **Personalized Treatment for Childhood Asthma Advent of a New Age** Organiser: HKMA-Shatin Community Network Speaker: Dr TAM Yat-cheung;	Miss Antonia Lee 3108 2514 1 CME Point
17 THU 2:00 PM	**Facebook Live** **Sarcopenia Diagnosis and Management** Organiser: HKMA-Hong Kong East Community Network Speaker: Dr Ray Chun-chung CHAN	Ms. Candice Tong 3108 2513 1 CME Point

Answers to Radiology Quiz

Answers:

1. There are bilateral peripheral ill-defined opacities. No lung nodules or pleural effusion.

2. Coronavirus disease 2019 (COVID-19).

3. The most common findings are consolidation and ground-glass opacities. Distribution is variable, but there is a propensity towards bilateral, peripheral, and lower zone distribution. Pleural effusion is not common on initial presentation. Lung nodules are atypical.

4. No. CXR has limited sensitivity of ~33-69% in recent reports, while CT has a higher sensitivity of over 90%. The gold standard for diagnosis remains RT-PCR of upper respiratory tract specimens such as nasopharyngeal swabs. Initial experience suggests that the value of CXR lies in the triage of suspected cases in settings where RT-PCR is not immediately available, and in monitoring disease course and complications, and in raising the alarm in patients with no prior suspicion for COVID-19.

Dr Frank WONG
MBBS (HK), FRCR (UK)
Resident, Department of Radiology, Queen Mary Hospital

DUODART
(dutasteride/tamsulosin HCl) Capsules

gsk

*The **ONLY** fixed-dose combination in relieving BPH symptoms and reduce risk of AUR or BPH-related surgery*

DUAL ACTION:

- **Superior symptoms improvement**[1]
  (adjusted mean change in IPSS from baseline to year 4 was **-6.3** points for combination therapy versus **-3.8** points for tamsulosin)
- Reduce prostate size up to **27%**#

DUAL PROTECTION:

Reduce relative risk of

- AUR by **68%**
- BPH related surgery by **71%**

vs tamsulosin monotherapy[1]

BPH: Benign Prostatic Hyperplasia
AUR: Acute Urinary Retention

DUODART (Dutasteride-tamsulosin) abbreviated prescribing information[2]

Indications Treatment of moderate to severe symptoms of benign prostatic hyperplasia (BPH). Reduction in the risk of acute urinary retention (AUR) and surgery in patients with moderate to severe symptoms of BPH. Limitations of use: Dutasteride-containing products, including DUODART, are not approved for the prevention of prostate cancer. **Dosage and Administration** The recommended dose of DUODART (Dutasteride-tamsulosin) is one capsule (0,5 mg/ 0,4 mg) taken once daily. The capsules should be swallowed whole and not chewed or opened. Contact with the contents of the dutasteride capsule contained within the hard-shell capsule may result in irritation of the oropharyngeal mucosa. **Contraindications** Patients with known hypersensitivity to dutasteride, other 5 alphareductase inhibitors, tamsulosin (including tamsulosin- induced angio-edema), soya, peanut or any of the excipients; history of orthostatic hypotension; with severe hepatic impairment; women and children and adolescents. **Warnings and Precautions** *Cardiac Failure* In two 4-year clinical study, the incidence of cardiac failure (a composite term of reported events, primarily cardiac failure and congestive cardiac failure) was higher among subjects taking the combination of dutasteride and an alpha1- adrenoceptor antagonist, primarily tamsulosin, than it was among subjects not taking the combination. In these two trials, the incidence of cardiac failure was low (≤1%) and variable between the studies. *Effect on prostate-specific antigen (PSA) and prostate cancer detection* Serum prostate-specific antigen (PSA) concentration is an important component in the detection of prostate cancer. DUODART causes a decrease in mean serum PSA levels by approximately 50%, after 6 months of treatment. Patients receiving DUODART should have a new PSA baseline established after 6 months of treatment with DUODART, It is recommended to monitor PSA values regularly thereafter. Any confirmed increase from lowest PSA level while on DUODART may signal the presence of prostate cancer or noncompliance to therapy with DUODART and should be carefully evaluated, even if those values are still within the normal range for men not taking a 5-alpha reductase inhibitor. In the interpretation of a PSA value for a patient taking dutasteride, previous PSA values should be sought for comparison. Treatment with DUODART does not interfere with the use of PSA as a tool to assist in the diagnosis of prostate cancer after a new baseline has been established, Total serum PSA levels return to baseline within 6 months of discontinuing treatment. The ratio of free to total PSA remains constant even under the influence of DUODART. If clinicians elect to use percent free PSA as an aid in the detection of prostate cancer in men undergoing DUODART therapy, no adjustment to its value appears necessary. Digital rectal examination, as well as other evaluations for prostate cancer or other conditions which can cause the same symptoms as BPH, must be performed on patients prior to initiating therapy with DUODART and periodically thereafter. *Prostate cancer and high grade tumours* The REDUCE study, a 4-year, multicentre, randomised, double-blind, placebo controlled study investigated the effect of dutasteride 0,5 mg daily on patients with a high risk for prostate cancer (including men 50 to 75 years of age with PSA levels of 2.5 to 10 ng/ml and a negative prostate biopsy 6 months before study enrolment) compared to placebo, Results of this study revealed a higher incidence of Gleason 8 – 10 prostate cancers in dutasteride treated men (n=29, 0,9%) compared to placebo (n=19, 0,6%), The relationship between dutasteride and Gleason 8 - 10 prostate cancers is not clear. Thus, men taking Avodart should be regularly evaluated for prostate cancer. *Renal impairment* The treatment of patients with severe renal impairment (creatinine clearance of less than 10 ml/min) should be approached with caution as these patients have not been studied. *Hypotension* Orthostatic: As with other alpha1-adrenoceptor antagonists, a reduction in blood pressure can occur during treatment with tamsulosin, as a result of which, rarely, syncope can occur. Patients beginning treatment with DUODART should be cautioned to sit or lie down at the first signs of orthostatic hypotension (dizziness, weakness) until the symptoms have resolved. Symptomatic: Caution is advised when alpha adrenergic blocking agents including tamsulosin are co-administered with PDE5 inhibitors. Alpha1-adrenoceptor antagonists and PDE5 inhibitors are both vasodilators that can lower blood pressure. Concomitant use of these two drug classes can potentially cause symptomatic hypotension. *Intraoperative Floppy Iris Syndrome* (IFIS, a variant of small pupil syndrome) has been observed during cataract surgery in some patients on or previously treated with tamsulosin. IFIS may increase the risk of eye complications during and after the operation. The initiation of therapy with DUODART in patients for whom cataract surgery is scheduled is therefore not recommended. During pre-operative assessment, cataract surgeons and ophthalmic teams should consider whether patients scheduled for cataract surgery are being or have been treated with DUODART in order to ensure that appropriate measures will be in place to manage the IFIS during surgery. Discontinuing tamsulosin 1 – 2 weeks prior to cataract surgery is anecdotally considered helpful, but the benefit and duration of stopping therapy prior to cataract surgery has not yet been established, *Leaking Capsule* Dutasteride is absorbed through the skin. therefore women and children and adolescents must avoid contact with leaking capsules. If contact is made with leaking capsules, the contact area should be washed immediately with soap and water. *Inhibitors of CYP3A4 and CYP2D6* Concomitant administration of tamsulosin hydrochloride with strong inhibitors of CYP3A4, or to a lesser extent, with strong inhibitors of CYP2D6 can increase tamsulosin exposure. Tamsulosin hydrochloride is therefore not recommended in patients taking a strong CYP3A4 inhibitor and should be used with caution in patients taking a moderate CYP3A4 inhibitor, a strong or moderate CYP2D6 inhibitor, a combination of both CYP3A4 and CYP2D6 inhibitors, or in patients known to be poor metabolisers of CYP2D6. *Hepatic Impairment* DUODART has not been studied in patients with liver disease Caution should be used in the administration of DUODART to patients with mild to moderate hepatic impairment. *Excipients* This medicinal product contains the colouring agent Sunset Yellow (E110), which may cause allergic reactions. *Breast neoplasia* There have been rare reports of male breast cancer reported in men taking dutasteride in clinical trials and during the post-marketing period. However, epidemiological studies showed no increase in the risk of developing male breast cancer with the use of 5-alpha reductase inhibitors. Physicians should instruct their patients to promptly report any changes in their breast tissue such as lumps or nipple discharge. **Interactions** *Tamsulosin* Concomitant administration of tamsulosin hydrochloride with drugs which can reduce blood pressure, including anaesthetic agents, PDE5 inhibitors and other alpha1- adrenoceptor antagonists could lead to enhanced hypotensive effects. Dutasteride-tamsulosin should not be used in combination with other alpha1- adrenoceptor antagonists, Concomitant administration of tamsulosin hydrochloride and ketoconazole (a strong CYP3A4 inhibitor) resulted in an increase of the Cmax and AUC of tamsulosin hydrochloride by a factor of 2.2 and 2.8 respectively. Concomitant administration of tamsulosin hydrochloride and paroxetine (a strong CYP2D6 inhibitor) resulted in an increase of the Cmax and AUC of tamsulosin hydrochloride by a factor of 1.3 and 1.6 respectively. A similar increase in exposure is expected in CYP2D6 poor metabolisers as compared to extensive metabolisers when co-administered with a strong CYP3A4 inhibitor, The effects of co-administration of both CYP3A4 and CYP2D6 inhibitors with tamsulosin hydrochloride have not been evaluated clinically, however there is a potential for significant increase in tamsulosin exposure. Concomitant administration of tamsulosin hydrochloride (0.4 mg) and cimetidine (400 mg every six hours for six days) resulted in a decrease in the clearance (26%) and an increase in the AUC (44%) of tamsulosin hydrochloride. Caution should be used when dutasteride-tamsulosin is used in combination with cimetidine, A definitive drug-drug interaction study between tamsulosin hydrochloride and warfarin has not been conducted. Results from limited in vitro and in vivo studies are inconclusive. Diclofenac and warfarin, however, may increase the elimination rate of tamsulosin. Caution should be exercised with concomitant administration of warfarin and tamsulosin hydrochloride. **Fertility, pregnancy and lactation** DUODART is contraindicated for use by women. There have been no studies to investigate the effect of DUODART on pregnancy, lactation and fertility. As with all 5 alpha reductase inhibitors, when the patient's partner is or may potentially be pregnant it is recommended that the patient avoids exposure of his partner to semen by use of a condom. As with other 5 alpha reductase inhibitors, dutasteride inhibits the conversion of testosterone to dihydrotestosterone and may, if administered to a woman carrying a male foetus, inhibit the development of the external genitalia of the foetus. Dutasteride has been reported to affect semen characteristics (reduction in sperm count, semen volume, and sperm motility) in healthy men. The possibility of reduced male fertility cannot be excluded. Effects of tamsulosin hydrochloride on sperm counts or sperm function have not been evaluated. The effects of dutasteride 0.5 mg/day on semen characteristics were evaluated in healthy volunteers aged 18 to 52 (n=27 dutasteride, n=23 placebo) throughout 52 weeks of treatment and 24 weeks of post-treatment follow-up. At 52 weeks, the mean percent reduction from baseline in total sperm count, semen volume and sperm motility were 23%, 26% and 18%, respectively, in the dutasteride group when adjusted for changes from baseline in the placebo group. Sperm concentration and sperm morphology were unaffected. After 24 weeks of follow-up, the mean percent change in total sperm count in the dutasteride group remained 23% lower than baseline. While mean values for all parameters at all time points remained within the normal ranges and did not meet the predefined criteria for a clinically significant change (30%), two subjects in the dutasteride group had decreases in sperm count of greater than 90% from baseline at 52 weeks, with partial recovery at the 24 week follow-up. The possibility of reduced male fertility cannot be excluded. It is not known whether dutasteride or tamsulosin are excreted in human milk. **Adverse Reactions** *Clinical Trial Data* ((Dutasteride and tamsulosin co-administration): Impotence, altered (decreased) libido, ejaculation disorders, breast disorders (includes breast tenderness and breast enlargement), dizziness and cardiac failure, (Dutasteride monotherapy): Impotence, altered (decreased) libido, ejaculation disorders, breast disorders (includes breast tenderness and breast enlargement), alopecia (primarily body hair loss), hypertrichosis. (Tamsulosin Monotherapy): Dizziness, abnormal ejaculation, palpitations, constipation, diarrhoea, vomiting, asthenia, rhinitis, rash, pruritis, urticaria, orthostatic hypotension, syncope, headache, nausea, angioedema, priapism, Stevens-Johnson syndrome, During postmarketing surveillance, reports of Intraoperative Floppy Iris Syndrome (IFIS), a variant of small pupil syndrome, during cataract surgery have been associated with alpha1- adrenoceptor antagonists, including tamsulosin. In addition atrial fibrillation, arrhythmia, tachycardia, dyspnoea, epistaxis, vision blurred, visual impairment, erythema multiforme, dermatitis exfoliative, ejaculation disorder, retrograde ejaculation, ejaculation failure and dry mouth have been reported in association with tamsulosin use. The frequency of events and the role of tamsulosin in their causation cannot be reliably determined. Abbreviated PI based on HK0720 17/GDS15v1/eMC20170628). Please refer to the full prescribing information before prescribing. Full prescribing information is available upon request.

At month 48, the adjusted mean percentage change from baseline in total prostate volume was -27,3% for combination therapy, +4.6% (p<0,001) for tamsulosin, and -28,0% (p=0,42) for dutasteride.

References: 1. Roehrborn CG, *et al. Eur Urol* 2010;57(1):123–31 **2.** DUODART Hong Kong Full Prescribing Information. Version number: HK072017(GDS15v1/eMC20170628).

For adverse events report, please call GlaxoSmithKline Limited at (HK) 852 9046 2498 Full prescribing information is available on request from GlaxoSmithKline Ltd. 23/F, Tower 6, The Gateway, 9 Canton Road, Tsimshatsui, Kowloon, Hong Kong.
Please read the full prescribing information prior to administration. This material is for the reference and use by healthcare professionals only.

GlaxoSmithKline Limited 23/F, Tower 6, The Gateway, 9 Canton Road, TsimShaTsui, Kowloon, Hong Kong Tel. (852) 3189 8989 Fax.(852) 3189 8931

HKRX/DUTT/0015/18b (11/2020)
Date of preparation: 01/12/2018

Patients with type 2 diabetes
should expect more after metformin

REALISE THE POTENTIAL

UP TO

80%

ACHIEVED ADA TARGET OF HbA_{1c}

<7%

VS OTHER DIABETES TREATMENT[1,2,7,8,9#]

OZEMPIC®

The only once-weekly treatment unifying superior efficacy and CV benefits[1-5]

SUPERIOR GLYCAEMIC CONTROL[1,2*]
Up to 1.8% HbA_{1c} reduction[2]

SUPERIOR AND SUSTAINED WEIGHT LOSS[1-3*]
Up to 6.5kg weight reduction[2]

PROVEN CV BENEFITS[1,3 †]
26% CV risk reduction[1,3§]

§ When added to SOC, which included oral antidiabetic treatment, insulin, antihypertensives, diuretics and lipid-lowering therapies.[3]

Other diabetes treatments refer to sitagliptin, dulaglutide, exenatide ER, liraglutide, canagliflozin and glargine U100. Target refers to American Diabetes Association target of HbA_{1c} <7%.

† In SUSTAIN 6, Ozempic® reduced CV risk (CV death, nonfatal myocardial infarction [MI] or nonfatal stroke) versus placebo in patients with type 2 diabetes at high CV risk treated with standard of care.[1]

* Results apply to Ozempic® across SUSTAIN trials, which included placebo, DPP-4I, SGLT-2I, GLP-1 RA and basal insulin.[1,2]

For adults with type 2 diabetes with established ASCVD or indicators of high ASCVD risk
2019 ADA/EASD consensus report recommends a GLP-1 RA therapy with proven CV benefit[6]

CV=cardiovascular; CVD=cardiovascular disease; ADA=American Diabetes Association; EASD=European Association for the Study of Diabetes;
GLP-1 RA=glucagon-like peptide-1 receptor agonist.

Abbreviated prescribing information Ozempic® (semaglutide), Ozempic 0,25 mg solution for injection in pre-filled pen; Ozempic 0,5 mg solution for injection in pre-filled pen; Ozempic 1 mg solution for injection in pre-filled pen, **Consult Summary of Product Characteristics before prescribing. Presentation:** Ozempic 0,25 mg & 0,5 mg solution for injection: Each pre-filled pen contains 2 mg semaglutide in 1,5 ml solution. Ozempic 1 mg solution for injection: One pre-filled pen contains 4 mg semaglutide in 3,0 ml solution. **Uses:** Ozempic® is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise as Monotherapy: when metformin is considered inappropriate due to intolerance or contraindications, Combination therapy: in addition to other medicinal products for the treatment of diabetes, For study results with respect to combinations, effects on glycaemic control and cardiovascular events, and the populations studied, see the full Summary of Product Characteristics. **Dosage and administration:** The starting dose is 0.25 mg Ozempic® once weekly. After 4 weeks the dose should be increased to 0.5 mg once weekly. After at least 4 weeks with a dose of 0.5 mg once weekly, the dose can be increased to 1 mg once weekly to further improve glycaemic control. Ozempic® is to be administered once weekly at any time of the day, with or without meals. Ozempic® is to be injected subcutaneously in the abdomen, in the thigh or in the upper arm. Ozempic® should not be administered intravenously or intramuscularly. When Ozempic® is added to existing metformin and/or thiazolidinedione therapy, the current dose of metformin and/or thiazolidinedione can be continued unchanged. When Ozempic® is added to existing therapy of sulfonylurea or insulin, a reduction in the dose of sulfonylurea or insulin should be considered to reduce the risk of hypoglycaemia, **Elderly:** No dose adjustment is required based on age, Therapeutic experience in patients aged ≥75 years of age is limited, **Renal impairment:** No dose adjustment is required for patients with mild, moderate or severe renal impairment, Experience in patients with severe renal impairment is limited. Not recommended for use in patients with end-stage renal disease. **Hepatic impairment:** No dose adjustment is required for patients with hepatic impairment. Experience in patients with severe hepatic impairment is limited. Caution should be exercised when treating these patients with Ozempic®. **Paediatric population:** The safety and efficacy of Ozempic® in children and adolescents below 18 years have not yet been established, No data are available, **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. **Special warnings and precautions for use:** Ozempic® should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. Ozempic® is not a substitute for insulin. There is no experience in patients with congestive heart failure NYHA class IV and Ozempic® is therefore not recommended in these patients. The possibility of gastrointestinal adverse reactions should be considered when treating patients with impaired renal function as nausea, vomiting, and diarrhoea may cause dehydration, which could cause a deterioration of renal function. Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, Ozempic® should be discontinued; if confirmed, Ozempic® should not be restarted. Caution should be exercised in patients with a history of pancreatitis. Patients treated with Ozempic® in combination with a sulfonylurea or insulin may have an increased risk of hypoglycaemia, Consider reducing the dose of sulfonylurea or insulin when initiating treatment with Ozempic®, In patients with diabetic retinopathy treated with insulin and Ozempic®, an increased risk of developing diabetic retinopathy complications has been observed, Caution should be exercised when using Ozempic® in patients with diabetic retinopathy treated with insulin. These patients should be monitored closely and treated according to clinical guidelines. Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy, but other mechanisms cannot be excluded. **Interactions:** Ozempic® delays gastric emptying and has the potential to impact the rate of absorption of concomitantly administered oral medicinal products, Ozempic® should be used with caution in patients receiving oral medicinal products that require rapid gastrointestinal absorption, No dose adjustment of paracetamol, oral contraceptives (ethinylestradiol and levonorgestrel), atorvastatin, warfarin, digoxin or metformin is necessary when administered with Ozempic®, For further details of these interaction studies, please see the Summary of Product Characteristics. **Pregnancy and lactation:** Ozempic® should not be used during pregnancy, If a patient wishes to become pregnant, or pregnancy occurs during treatment, Ozempic® should be discontinued, Ozempic® should not be used during breast-feeding. Effect of Ozempic® on fertility in humans is unknown. **Driving or using machines:** When Ozempic® is used in combination with a sulfonylurea or insulin, patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines. **Undesirable effects:** The most frequently reported adverse reactions with Ozempic® in clinical trials were gastrointestinal disorders, including nausea, diarrhoea and vomiting, Adverse reactions by system organ class and absolute frequencies identified in all phase 3a trials listed here as Very common (≥1/10): Hypoglycaemia when used with insulin or sulfonylurea, nausea, diarrhoea; Common (≥1/100 to <1/10): Hypoglycaemia when used with other OADs, decreased appetite, dizziness, diabetic retinopathy complications, vomiting, abdominal pain, abdominal distension, constipation, dyspepsia, gastritis, gastro-oesophageal reflux disease, eructation, flatulence, cholelithiasis, fatigue, increased lipase, increased amylase, weight decreased; Uncommon (≥1/1,000 to <1/100): Dysgeusia, increased heart rate, injection site reactions; Rare (≥1/10,000 to <1/1,000): Anaphylactic reaction.

References: 1. Ozempic® packing insert. **2.** Pratley RE, Aroda VR, Lingvay I, et al. Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial. Lancet Diabetes Endocrinol. 2018;6(4):275-286. **3.** Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2016;375:1834-1844. **4.** Bydureon® [summary of product characteristics]. Sodertalje Sweden: AstraZeneca AB, http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002020/WC500108241.pdf, Accessed October 10, 2017. **5.** Trulicity® [summary of product characteristics]. Utrecht, The Netherlands: Eli Lilly Nederland B.V., http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002825/WC500179470.pdf, Accessed October 10, 2017. **6.** Buse JB, Wexler DJ, Tsapas A, et al, 2019 update to: management of hyperglycemia in type 2 diabetes, 2018, A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2020;43(2):487-493. **7.** American Diabetes Association. Standards of medical care in diabetes—2018. Diabetes Care. 2018;41(suppl 1):S1-S159. **8.** Lingvay I, Catarig AM, Frias JP, et al. Efficacy and Safety of once-weekly Semaglutide versus daily canagliflozin as add-on to metformin in patients with type 2 diabetes (SUSTAIN 8): a double-blind, phase 3b, randomised controlled trial. Lancet Diabetes Endocrinol. 2019;7(11):834-844. **9.** Capehorn MS, Catarig AM, Furberg JK, et al. Efficacy and safety of once-weekly Semaglutide 1.0mg Vs once-daily liraglutide 1.2mg as add-on to 1-3 oral antidiabetic drugs in subjects with type 2 diabetes (SUSTAIN 10). 10). Diabetes Metab. 2020;46(2):100-109.

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