HONG KONG PHARMACEUTICAL JOURNAL

VOL 28 NO 1 Jan - Apr 2021 ISSN 1727-2874

The Pharmaceutical Society of Hong Kong
The Practising Pharmacists Association of Hong Kong
The Society of Hospital Pharmacists of Hong Kong

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All communications and enquiries should be directed to:
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INSTRUCTIONS FOR AUTHORS

The Hong Kong Pharmaceutical Journal is a journal of the pharmacists, for the pharmacists and by the pharmacists. Submissions are welcome for the following sections:

- Pharmacy Education & Practice
- Drugs & Therapeutics
- Primary Care
- OTC & Health
- Pharmaceutical Techniques & Technology
- Medication Safety
- Herbal Medicines & Nutraceuticals
- Society Activities
- New Products

Comments on any aspects of the profession are also welcome as Letter to the Editor.

There is no restriction on the length of the articles to be submitted. They can be written in English or Chinese. The Editorial Committee may make editorial changes to the articles but major amendments will be communicated with the authors prior to publishing.

It is preferable to have original articles submitted as an electronic file, in Microsoft Word, typed in Arial 9pt. Files can be sent to the following address:

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For detail instructions for authors, please refer to the first issue of each volume of HKPJ.

Roles of Pharmacists

Starting in February 2021, COVID-19 vaccines have become available to all Hong Kong residents under the COVID-19 Vaccination Programme. In many Community Vaccination Centre (CVC), pharmacists are involved in the preparation and dilution of COVID-19 vaccines. For those who have attended the immunisation training programme, as mentioned by the Pharmaceutical Society of Hong Kong (p.39), and completed the supervised practice requirement, they can even be involved as an inoculator.

Figure: *Pharmacists preparing COVID-19 vaccines at CVC (Photo courtesy of Dr. Esther Chan)*

As being part of the healthcare team, pharmacists are fielding all sorts of questions related to COVID-19 vaccines. A common one is the differences among various vaccines. Currently there are 2 vaccines available in Hong Kong and they are made by different technologies. In the review article by Dr. Hon-Yeung Cheung (p. 28), a wide range of vaccine production platforms has been described and the pros and cons of these different approaches are systematically reviewed and compared.

Diabetes is a major cause of morbidity and mortality in Hong Kong. According to Department of Health, it was the ten commonest cause of deaths in Hong Kong.[1] Sodium-glucose co-transporter 2 inhibitors (SGLT-2i) are a new class of glucose-lowering drugs and have been studied vigorously for various health outcomes. Mr. Nath Sing-Yung Chu (page 11) provided a summary regarding the cardiovascular and renal outcomes of the four SGLT-2i that are available in Hong Kong. In addition, guideline recommendations (e.g. KDIGO 2020, European Society of Cardiology (ESC)) regarding the use of SGLT-2i in managing patients with diabetes or heart failure are discussed.

The introduction of non-vitamin K antagonist oral anticoagulants (NOACs) has significantly changed the landscape for stroke prevention in atrial fibrillation (AF). NOACs are now recommended over warfarin for reducing the risk of stroke associated with AF. In the article written by Mr. Andy HY Liu et al (page 23) reviewed the stroke prevention in patients with AF according to the latest guidelines of various international associations/ organizations.

Hong Kong is a melting pot of Eastern and Western cultures and this cultural melting pot extends to medicine as well. The interview with Dr. Warren Tsang (page 6) described the differences between manufacturing Chinese and western medicines as well as the roles played by pharmacists in the development of Traditional Chinese medicine.

Last but not the least, the theme speech delivered by Dr. Lam Ching-choi during The Hong Kong Pharmacy Conference 2019 was included (page 7) in this issue. In his speech, Dr. Lam shared his opinions on the roles and positions of pharmacists in the era of ageing population.

I hope you enjoy reading this issue. As always, you may provide suggestions and give feedbacks on any aspect of the Journal by contacting me or other members of the Editorial Committee.

May PS Lam
Editor-in-Chief
19 May 2021

References

1. Centre for Health Protection. Diabetes mellitus. [Cited 19 May 2021]. Available from: https://www.chp.gov.hk/en/healthtopics/content/25/59.html

Prepared by Howard Chan, Tsz Ching Chiu, Branson Fok and Chloe Ip.

US FDA Approves Trilaciclib to Reduce Myelosuppression Caused by Chemotherapy

Date: February 12, 2021

The US FDA approved Cosela (trilaciclib) to reduce the incidence of chemotherapy-induced myelosuppression in adult patients administered prior to a platinum/etoposide-containing regimen or topotecan-containing regimen for extensive-stage small cell lung cancer (ES-SCLC). Trilaciclib is the first cyclin-dependent kinase (CDK) 4/6 inhibitor approved for such indication.

The efficacy of Cosela was established in three randomized, double-blinded, placebo-controlled trials in patients with ES-SCLC. A combined total of 245 patients were randomly assigned to receive either Cosela IV infusion or placebo. In all three studies, patients who received Cosela had a lower incidence of severe neutropenia (defined as absolute neutrophil count [ANC] <0.5 × 10^9 cells/L) compared to those receiving placebo. The average duration of severe neutropenia was also statistically significantly shorter in patients who received Cosela compared to those receiving placebo in all three studies.

The recommended dose of Cosela is 240mg/m^2 as a 30-minute IV infusion completed within 4 hours prior to the start of chemotherapy on each day chemotherapy is administered. The most common adverse effects of Cosela were fatigue, hypocalcemia, hypokalemia, hypophosphatemia; increased aspartate aminotransferase (AST), headache, and pneumonia.

Source: www.fda.gov

Weekly Semaglutide Effective for Overweight or Obesity Management in Adults

Date: March 18, 2021

Weight management by lifestyle modifications has always been challenging for obese and overweight patients, while efficacy and safety of available medications is a major concern when considering adjunctive drug treatment. The STEP 1 trial was hence conducted to investigate on the new approach of using semaglutide for weight management in non-diabetic obese patients.

The STEP 1 trial was a randomized, double-blind, placebo-controlled trial which enrolled 1961 non-diabetic patients with body mass index ≥30 and at least one weight-related comorbidity. Participants were randomized in 2:1 ratio in which 1306 received semaglutide subcutaneous injection while 655 received placebo. Semaglutide was given at 0.25 mg weekly with dose titration at 4-week interval to reach 2.4mg weekly in the 16th to 68th week. Both semaglutide and placebo groups underwent low-calorie diet and increased exercising during the 68 weeks. The coprimary endpoints were the percentage weight reduction and the succession of reducing 5% weight after 68 weeks. Safety assessment was determined by the number of adverse events.

The average reduction in body weight from baseline to week 68 was 14.9% and 2.4% in the semaglutide and placebo groups respectively, with the estimated treatment difference being −12.4% (95% CI, −13.4 to −11.5; p<0.001). The semaglutide group also had a remarkably higher success rate of achieving weight reductions of ≥5% (86.4% vs. 31.5%), ≥10% (69.1% vs. 12.0%), and ≥15% (50.5% vs. 4.9%) at week 68 than the placebo group (p<0.001). The most commonly reported adverse events were mild-to-moderate transient gastrointestinal disorders, occurring in 74.2% and 47.9% of the semaglutide and placebo groups respectively.

2.4mg of semaglutide once weekly with modifications in diet and physical activity was proved to have clinically significant body weight reduction in overweight or obese adults.

Source: www.nejm.org

Trial of Upadacitinib and Adalimumab for Psoriatic Arthritis

Date: April 1, 2021

Upadacitinib, an oral and reversible Janus kinase (JAK) inhibitor, is an approved treatment for rheumatoid arthritis. On the other hand, adalimumab is a tumour necrosis factor α (TNF-α) inhibitor used to treat rheumatoid arthritis and psoriatic arthritis. The efficacy and safety of upadacitinib compared with adalimumab in patients with psoriatic arthritis have not been well-established. Hence, SELECT-PsA 1, a double-blind, phase 3 trial was conducted to compare upadacitinib with placebo and with adalimumab in patients with psoriatic arthritis who had an inadequate response with nonbiologic disease-modifying antirheumatic drugs (DMARDs).

In the 24-week trial, a total of 1704 patients were enrolled and randomly assigned in a 1:1:1:1 ratio to receive oral upadacitinib (15mg or 30mg once daily), placebo, or subcutaneous adalimumab (40mg every other week). The primary end point was an American College of Rheumatology 20 (ACR20) response (≥20% decrease in the number of tender and swollen joints and ≥20% improvement in at least three of five other domains) at week 12.

At week 12, the percentage of patients who had an ACR20 response was 70.6% with 15-mg upadacitinib, 78.5% with 30-mg upadacitinib, 36.2% with placebo (p<0.001 for both upadacitinib doses vs. placebo), and 65.0% with adalimumab. The difference in ACR20 response between 15-mg upadacitinib and adalimumab group was 5.6 percentage points (95% CI, −0.6 to 11.8) and 13.5 percentage points between 30-mg upadacitinib and adalimumab group (95% CI, 7.5 to 19.4). The incidence of adverse events through week 24 was 66.9%, 72.3%, 59.6%, and 64.8% for patients who received 15-mg upadacitinib, 30-mg upadacitinib, placebo, and adalimumab respectively.

Based on the ACR20 response at week 12, both doses of upadacitinib (15mg or 30mg once daily) was more effective than placebo and non-inferior to adalimumab. The 30-mg dose in particular, was superior to adalimumab. Adverse events were more frequent with either dose of upadacitinib than with placebo, but serious adverse events were commonly associated with the 30-mg dose.

Source: www.nejm.org

The Truly once-daily[1] mesalazine providing Efficacy on remission[2-3] with Freedom to discover the day

- Prolonged MMX* Release[4,5]
- Sustainable Remission[3]
- Low Pill Burden[1]

* MMX = Multi-Matrix System

References: **1.**Mezavant prescribing information Aug 2019. **2.**Lichtenstein GR, et al. Aliment Pharmacol Ther 2008;27(11):1094-1102. **3.**Kamm MA et al. Gut. 2008;57:893-902. **4.**Abinusawa A & Tenjarla S. AdvTher. 2015. 32: 477-484. **5.**Tenjarla S, et al. Adv Ther 2007 24:826-840.

Abbreviated Prescribing Information:
Presentation & Packing: Gastro-resistant PR tab 1200mg x 60's. **Contents:** Mesalazine. **Indication:** For the induction of clinical and endoscopic remission in patients with mild to moderate, active ulcerative colitis. For maintenance of remission. **Dosage:** Acute episode of ulcerative colitis Adult 2-4 tab once daily. Evaluate patient after 8 weeks treatment if taking max daily dose of 4.8g/day. **Administration:** Take at the same time each day. Swallow whole, do not crush/chew. **Contraindications:** Hypersensitivity to salicylates. Severe renal or hepatic impairment. **Special Precautions:** Renal or hepatic impairment. History of heart inflammation & allergic reation to sulphasalazine. Stomach/gut narrowing or blockage/ Lung problems. Pregnancy & lactation. **Adverse Reactions:** Cramping, severe stomach pain, diarrhea, fever, headache or rash; bruising, anaemia, sore throat or unusual bleeding; allergic swelling of tongue, lips & around eyes. Changes in BP, flatulence, nausea, bloated or painful stomach, indigestion, vomiting, abnormal liver function test, itching, joint & back pain, weakness fatigue. **Interactions:** Sulphalazine, NSAIDs, azathioprine or 6-mercaptopurine, coumarin-type anticoagulants

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An Industrial Perspective of Traditional Chinese Medicine Development - Interview with Dr. Warren Tsang Yuen Wo

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INTRODUCTION

Having obtained a Bachelor of Pharmacy from the Aston University, and a PhD from the University of Sydney, Dr. Warren Tsang Yuen Wo returned to Hong Kong to develop his career in 1996. Dr. Tsang first worked in the community pharmacy sector, then later worked in the Chief Pharmacist's Office of the Hospital Authority. In 2001, Dr. Tsang was recruited by Europharm Laboratoires Co. Ltd., where he worked as the Quality Assurance Manager and an Authorized Person for 12 years. Dr. Tsang subsequently moved to Hong Kong Lee Man Shan Medicine Manufacturing Limited. Currently, Dr. Tsang is the Technical Director at Wai Yuen Tong Medicine Co. Ltd. and Authorized Person at Luxembourg Medicine Co. Ltd.

Figure 1. *Portrait of Dr. Warren Tsang Yuen Wo*

PJ: Can you share with us why you are so passionate about the pharmaceutical industry?

Before the Good Manufacturing Practice (GMP) implementation, there were many pharmaceutical factories, and the manufacturing qualities were questionable. After the GMP implementation in 2002, the standards were raised and reached the international level, but the number of manufacturers dropped to around 20, as many left the industry reluctantly for falling short of the standards. In 2016, when the Pharmaceutical Inspection Co-operation Scheme (PIC/S) GMP was adopted, the number of pharmaceutical manufacturers remained similar, despite the even more stringent requirements. This manifested the flexibility, vibrancy and momentum of the industry, and how incredibly swift our industry can react to the ever-changing environment. This signifies that the industry is not stagnant and boring. It requires fast and broad learning, and you have to go beyond the textbooks most of the time.

PJ: What are the major differences between manufacturing Chinese and western medicines?

There is not much difference in the process, except Chinese medicines may involve a few more distinctive steps. However, there are differences in terms of regulation. In Hong Kong, the Chinese Medicine Council is responsible for implementing regulatory measures for Chinese medicine, while the Pharmacy and Poisons Board regulates the western medicines. Traditional Chinese Medicine (TCM) manufacturers follow GMP guidelines set by the Chinese Medicines Board of the Chinese Medicine Council, while manufacturers of western medicines follow the much more stringent PIC/S GMP guidelines. Although PIC/S is not a trade agreement, a membership in PIC/S may facilitate the export of pharmaceuticals. Some non-PIC/S authorities accept GMP Certificates from PIC/S Participating Authorities. This means that even non-PIC/S authorities and organisations have great confidence in medicines manufactured in countries where the Regulatory Authority is a PIC/S Participating Authority. Consequently, the pharmaceutical industry located in these countries indirectly benefits from PIC/S Membership. I hope one day Hong Kong will take steps to adopt a more updated PIC/S GMP standard for TCM manufacturers as well, but there are huge obstacles in front.

PJ: What roles can pharmacists play in the development of TCM?

Currently, the regulation for Chinese medicines is not optimal, but it is slowly taking its pace. Many local Chinese medicine manufacturers look for authorized persons who possess a pharmacy background as they want to recruit people of higher calibre, even though it is not required by law. Pharmacists who have gone through professional training in pharmaceutical science and quality control are capable of managing Chinese medicines manufacturing and assisting the process of bridging towards the more rigorous standards. Going one step further, having taken a course in Chinese medicine with a focus on manufacturing would benefit them even more, of course.

PJ: What are the advantages that Hong Kong holds in the Chinese Medicine development?

Firstly, the Hong Kong Government saw the potential and value of Chinese medicines and allocated five hundred million for promoting the development of Chinese medicines in the 2018 Government Budget. This resulted in the establishment of the Chinese Medicine Development Fund, which was launched in June 2019. With such support, it is foreseeable that this industry will flourish. Secondly, the high manufacturing standards and advanced technology of Hong Kong would be advantageous for entering other markets, namely, mainland China.

PJ: Regarding the concern for job shortage, do you have any suggestion for future pharmacists?

When I came back to Hong Kong, pharmacy graduates also faced job shortage. The fierce competition brought the salary down, but this did not persist for too long and the job market was open again. Pharmacists' job market goes up and down all the time, and you need to be optimistic, work hard and prepare for the future. Moreover, the government and universities should have better workforce planning for pharmacists.

Apart from optimism, I think graduates ought to have a more realistic expectation when they first enter the workforce. Without much working experience, pharmaceutical companies cannot offer a managerial grade position to a fresh graduate. Nonetheless, with years of training and learning, pharmacy graduates will eventually be equipped with solid knowledge and abundant experience, and all companies are willing to offer appealing salary and welfare to their competent employees.

Author's background

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Reinvigorating Pharmacists' Role to Rejuvenate our Elderly Population - Theme Speech from Dr. Lam Ching-choi

INTRODUCTION

The Hong Kong Pharmacy Conference 2019 invited Dr. Lam Ching-choi, BBS JP as the guest speaker. Dr. Lam is a specialist in paediatric and community medicine, and is now the CEO of Haven of Hope Christian Service. He is also the chairman of the Elderly Commission and advises the government on related policies. As an expert in policies related to the ageing population in Hong Kong, Dr. Lam shared his opinions on the roles and positions of pharmacists as part of the evolving healthcare system in the era of population ageing.

THE SPEECH

Thank you very much. Actually, this is my first time to be involved in a conference full of pharmacists. I am very glad that I have this opportunity to be invited to this conference, especially to share the stage with EK (Professor Yeoh Eng-kiong) since we share the same opinions and views on many aspects, no matter if they are on primary care or hospital services. You can see that why the government engages the Chinese University of Hong Kong to do various studies on our healthcare system including the health voucher. As you can see from my slide and as introduced by the MC, I am basically doing three jobs at the same time. The reason is because I am lucky enough to have a very capable CEO in my own organization. The CEO is a pharmacist, so I know that a pharmacist can do a lot of things, including managing the whole NGO for me. Thus, I can focus on other things for the government. Just a little bit of amendment for the role on elderly commission, it is actually not under the Social Welfare Department. It is a high-level commission for overseas delegates set up by the government to advise on various policies, no matter if they are about social welfare, healthcare, housing or transportation. So, it is a high-level advisory role.

Figure 1. *Dr. Lam Ching-choi delivering his speech in the HKPC 2019.*

Today I am trying to speak from my role as a frontline practitioner. We have hospitals, nursing homes, and various kinds of community care clinics in Haven of Hope. Of course, the Elderly Commission plays an important role in how our healthcare system is structured, especially with this ageing population. As EK just mentioned, we are facing an ageing population and it is my role to bring out this to the government to make sure that the whole society understands what an ageing population is. We have a golden foundation exhibition next door which is on how we harvest the golden age or the so-called silver hair market. As just mentioned yesterday in the opening ceremony, I said that Hong Kong is not ready for it because we are lagging behind. No matter from the angle of the government, the

government policies, the private sector, the business model or the HR policies, they are not conducive to our ageing population at all. Thus, we still have a huge gap to catch up. Even the NGO, subvented organizations or statutory bodies including Hospital Authority, they are well lagged behind in all strategies and policies concerning the ageing population. We do have quite a bit to catch up, and I believe pharmacists do have a major role to play. I would try to introduce a bit of district health centres, especially on some information which you might not be able to read from the government paper, as you all know that the government is usually more conservative and tries to be very safe especially on writings. I will talk a bit on technology which will be a big thing in the coming decades.

Speaking about elderly people, one of my utmost concern is polypharmacy. How heavy is our burden of the ageing population? Our secretary of Labour and Welfare once mentioned a term called ageing tsunami, which unfortunately was misinterpreted by the media. Obviously it is a negative term, but what he meant was a green portion of the ageing population that are below the age of 85. I think what we should do is to enable those "young elderly" from the age of 65 to 85 to still contribute to the society in whatever capacity they have. Since in Hong Kong we enjoy the longest life expectancy in the world, we should especially target this age bracket. This age bracket will be enlarged substantially as you can see from the green section of the bar chart. Apart from our famous quoting "one in six citizens being an elder", we will have the saying "one in three citizens being an elder" within 20 years' time. But what we should stress more is the age group beyond 85. Why? Because we are facing an entirely different disease burden. According to health statistics, those beyond age 85 do have quite a bit of problems and we need to accept it. Not only episodic diseases, there is also a prevalence of chronic diseases. More than 60% of those beyond 60 years old are suffering from chronic diseases. Adding on the burden, according to a research done by the Department of Health a couple of years ago, around half of our hypertension or diabetes patients are undiagnosed. By that, we should know that the trend is here, the writings are on the wall that we are facing a huge wave of chronic diseases, as we have more and more people beyond the age of 65 and also even more so beyond the age of 85. According to the Hospital Authority, diabetes, stroke, hypertension, and coronary heart disease will increase about 50% from the year of 2014 to 2024. So, it is really an issue for Hong Kong. The government does know that we are basically in short of a functioning primary care system.

As mentioned by our Chief Executive, she was the secretary drafting the paper called the Rainbow Document 30 years ago, which stresses the importance of primary care in our healthcare system. Unfortunately, the government did nothing during these 30 years and our Chief Executive was very disappointed with that. After she was elected two years ago, she immediately put in place the establishment of district health centres. Part of the reason why we did not have these centres 30 years ago is because Hong Kong people are pretty short-sighted. We do not like long-term planning. Apart from short-sighted, "seeing is believing" is too much of a thing in Hong Kong. When citizens walk along the streets, they will see a lot of general practitioners. There are clinics right in the heart of Mong Kok and everywhere else. In every estate, you can see one, two or even three general practitioner clinics right at the corner next to a 7-11. Therefore, Hong Kong people basically believe that we do have a primary care system. Because no elsewhere in China, America, and even in the UK where they have the NHS, you can see a clinic just across the street. Even in tourist areas, you can find general practitioners opening clinics. Thus, due to this "seeing is believing" phenomenon, Hong Kong people do believe that we have a primacy care system in place. But in fact, we do not. We do have a lot of general practitioners doing curative treatment for ordinary folks, but it does not mean we do have a functioning primary care system.

This has been an issue in Hong Kong for more than 30 years, and finally this October we will have our first district health centre in Kwai Ching district. Do not misinterpret that there is only one district health centre in one district; it will not work by so. If we do not have the scale, this kind of primary care system could not be rooted in local communities. A primary care system needs to be district-based and have a very good network in the community to make sure that they can reach those who are otherwise unreachable. In order to do that in the Kwai Ching district, we decided that apart from establishing one major centre, we are going to build five more satellite centres. This was decided after consulting with the Kwai Ching District Council, because only they know how the local communities move around, where they live, and how they can reach those district health centres nearby. Especially for the elderly, their mobility circle is less than one kilometer. We need to well situate our satellite centres to make sure that they can easily access them when needed. Another characteristic of this district health centre is that it is not run by doctors. It is run by a multidisciplinary team of nurses, physiotherapists, social workers, and pharmacists. This is the first time in Hong Kong that we put pharmacists in the centre of health system.

So I admire your decision to name the conference "the time is now". Really, the time is now to see how our pharmacists will function and expand their roles in these district health centres. Of course, you deserve to have skepticism in whatever the government runs, as we do not have the legislation yet and we still have a lot of barriers. During the design stage we put in a number of things to ensure that you will have some room to maneuver. If you are capable enough, you might expand your role. We designed it to be funded by the Government but run by NGOs or non-profit making private enterprises. As you read from the news, the district health center will be run by NGO in Kwai Ching. As NGO mandated to do it, they should be more flexible, more receptive to new ideas and more innovative. This will be a big thing for the pharmacists if you are going to expand your role in primary care. Our plan is to roll out this kind of district health centre to the other 17 districts as soon as possible.

As mentioned in the budget speech, we are not only willing to rent the office, we are willing to buy or build the office if needed. Another good thing that we put in this is that any programme funded by the government will be under very vigorous scrutinization by the community as well as the Elderly Commission, but we try to protect this district health centre to make sure that this NGO can grow. This means we are not giving contract as stated as that means nothing could be changed for the coming years. We are

trying to make sure that the Food and Health Bureau will work closely with the particular operator. We will ensure that they can invent and reinvent themselves to make sure that they can adjust really well to that district, and to build a network or even to change what it has been prescribed to do. For example, looking at the role of pharmacists in drug management - during the course of a particular contract, if they find that there is something that pharmacists can do more, we will allow them to adjust the contract to provide the services needed. Therefore, it is very much like a living organism, they will grow along the way.

We are trying to make sure that they have enough room to innovate and grow along. According to this design of district health centres (DHC), I believe there are a number of roles that pharmacists may contemplate, like apart from medication review, the pharmacists can focus on consultation. A good news is that the pharmacist consultation will be free of charge in the DHC. That means our citizens do not need to pay to see a pharmacist.

This design is also good to expand the roles of the pharmacist. Apart from taking care of the medication problems and the polypharmacy issues, I believe pharmacists obviously can be involved in disease screening, public education or even self-management. One of the main objectives of this district health centre is to make sure that ordinary people, especially our old folks, are being empowered to manage their own chronic diseases. So obviously drug management is an important element of that.

At the same time, the government has come up with a new thing called Innovation and Technology Fund for Application in Elderly and Rehabilitation Care. This is something new for the government because of the initiatives of the Greater Bay Area and also for our ageing population since the Elderly Commission published the Elderly Service Programme Plan. It is not a very sexy name but is a very important paper, because it will guide the government in the coming 20 years on how to deliver our social services to the elderly population. One important aspect is the adoption of technology.

For the initial funding, the government has given out 1 billion dollars for various service units to procure technology. I was promised by the Development Secretary from the government that this money is not one-off. When the money is used up, it will be given more by the government if the utilization is proven to be effective. I encourage you to use more technology and I believe some speakers will speak on various aspects on the adoption of technology in the field of pharmacy. Obviously there are a lot of technologies can help in the field of pharmacy. I just want to cite an example that I believe pharmacists can use technology to solve it. For our elderly care homes and residential care for elderly, most of the residents are getting drugs from the Hospital Authority. The elderly people visit various clinics and there are lots of overlapping in the follow-up dates. In these settings, there is a huge wastage of drugs and more than 50% of the drugs are redundant. Because of various reasons, I visit the pharmacies and elderly homes and their huge problem is how to dispose the huge amount of drugs. There were kilos of drugs being dumped and it is expensive to dump the drugs now because of the law. So there is huge amount of wastage, even for those inhalers and very expensive drugs. We neither have a good system nor a good technology on how to recycle those drugs. How to develop a system to track the drugs well to make sure that the wastage will be kept to the minimum would be what we need. In recent years, we are talking about rare diseases, and those drugs are very expensive. If we can save this 50% of the wasted drugs, then maybe we can solve the problem of those rare diseases from the saved medicine cost. So this is a huge area for the pharmacists to explore on how to use technology to help.

EK has just mentioned about the functions of community pharmacists. We do not have community pharmacists in our district health centres as we are trying to keep it simple at this stage, but we are not excluding them. The centres are not touching on the existing public-private partnership (PPP) programme and operations of our network doctors. When the time comes, this will become a sticky issue as drug cost will be a major concern for the success of our PPP. Thus, the possibility of setting up a community pharmacy is still there. Currently, we already have more than six hundred community pharmacists. Apart from the traditional dispensing, we can do more medication review, medication counselling, and at least to teach our old folks how to use inhalers. A lot of studies have shown that more than half of our patients do not know how to use a simple inhaler. So if I am the operator of the DHC, I will be very keen to collaborate with the local existing community pharmacists to make sure those prescribed with inhalers would know exactly how to use them. The operator of DHC is mandated to build a network with the community doctors, community groups, NGOs and elderly centres, and I believe they should extend their collaborations with the community pharmacists too.

Now I change the topic a little bit. You all know that polypharmacy among our elderly is a huge problem. How can we solve that problem? We have a scheme called Pilot Scheme on Visiting Pharmacists Service. Based on this scheme, none of our old age homes are hiring pharmacists. Obviously, they know the benefits of having a pharmacist apart from having dispensers in the nursing homes and in the care and attention homes. The question is why. Why are they not hiring? Every single one of the residents in those old age homes have the polypharmacy and drug compliance problems. We very much rely on the Hospital Authority to sort out the problem of polypharmacy. For the old age home operators, they only care about dispensing the correct drugs in the correct time. If the polypharmacy issue fell between the gap of the Hospital Authority and the old age home operators, the sufferers are those residents. So I think it is good question to ask how various professional bodies of pharmacists could make sure that this is no longer a gap. Maybe one day we will see more pharmacists not only working in the district health centres and the community pharmacies. They should work in our old age homes too, just like nurses, physiotherapists and occupational therapists.

Thank you.

ACKNOWLEDGEMENTS

The editorial committee is grateful to Ms. Ngai Tsz Chun and Mr. Choi Yiu-Ting Angus for their help in transcribing and editing the manuscript.

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University of Sunderland

Application Code: 1950-HS073A
Programme Code: HS073A

Application Deadline: 30 June 2021

Enquiries
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BSc (Hons) Pharmaceutical Science*

This programme is a 2-year top-up degree offered in part-time mode of study in Hong Kong. The BSc (Hons) Pharmaceutical Science is to be awarded by the University of Wolverhampton, UK. The programme aims to produce high quality pharmaceutical science graduates with the generic, subject-specific and transferable knowledge and skills suited to a career in the pharmaceutical industry or other related laboratory based scientific discipline.

Programme Features:

- a 24-month part-time undergraduate programme
- it covers the area of pharmaceutical science including pharmacology, pharmaceutical design and manufacture, biopharmaceutical, methods of analysis, quality assurance and delivery of pharmaceutical substances

Entry Requirements:

Applicants should hold either:

- Associate of Health Science (Biomedical Sciences)/ Advanced Diploma in Pharmaceutical Science (HKU SPACE); or
- Higher Diploma in Medical and Health Products Management (HPSHCC); or
- Higher Diploma in Pharmaceutical Technology (Western Medicine)/ Dispensing Studies/ Pharmaceutical Science/ Hospital Dispensing Studies (HKIVE); or
- Higher Diploma in Pharmaceutical Dispensing (CBCC)

UNIVERSITY OF WOLVERHAMPTON

Application Code: 1950-HS072A
Programme Code: HS072A

Application Deadline: 30 June 2021

Enquiries
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Professional Diploma in Marketing for Pharmaceutical Industries

The objectives of the programme are to equip the practitioners of pharmaceutical industry or medical devices business or those who intend to develop their career in marketing in these two industries with solid knowledge and practical skills in marketing, selling, tender planning and pitching, market knowledge and the latest trends in product development. The graduates of this programme will be able to develop marketing strategies, prepare tender proposal and manage business pitching abiding by regulations and code of practice of the industry concerned.

Programme Features:

- Students can choose to focus on either the pharmaceutical market / the medical device business
- Emphasis on practicality and the curriculum responds to the business needs of the pharmaceutical and medical device industries
- Interactive learning with lots of case studies, discussion and sharing by guest speakers
- Experienced and well-qualified lecturers
- Strong connection with the industries

Entry Requirements:

Applicants shall hold:

- A Diploma/ Advanced Diploma awarded by a recognized institution; or
- A Professional Certificate in Marketing awarded within the HKU system through HKU SPACE or equivalent.

Applicants with a science background are preferred.
Applicants with other equivalent qualifications and relevant work experience will be considered on individual merit.

資歷架構 Qualifications Framework
Level 4
Registration Number:19/001296/L4
Valid From:01 Feb 2020 - on-going

Application Code: 1940-MK075A
Programme Code: MK075A

Application Deadline: 17 July 2021

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* These are exempted courses under the Non-Local Higher and Professional Education (Regulation) Ordinance. It is a matter of discretion for individual employers to recognize any qualification to which these courses may lead.

Cardiovascular and Renal Benefits of SGLT-2 Inhibitors – Is It a Class Effect?

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ABSTRACT

Diabetes increases the risk of cardiovascular events and nephropathy, which motivates researchers to study if anti-diabetic medications can impact the incidence of cardiovascular and renal events. Sodium-glucose co-transporter 2 inhibitors (SGLT-2i) is a class of anti-diabetic medication being vigorously studied for its cardiovascular and renal outcomes. This review summarises and compares the cardiorenal benefits of SGLT-2i available in the Hong Kong market in the diabetic and heart failure with reduced ejection fraction (HFrEF) population, and examines if the benefits are indeed class effects. All SGLT-2i were able to slow down decline in renal function in patients with type 2 diabetes, and reduce the risk of hospitalisation due to heart failure in patients with type 2 diabetes and a high risk of or established cardiovascular disease. Dapagliflozin and empagliflozin were shown to reduce the combined risk of cardiovascular death and heart-failure hospitalization. Last but not least, guideline recommendations regarding the use of SGLT-2i in managing patients with diabetes or heart failure are also discussed.

Keywords: *SGLT-2 Inhibitors, Cardiovascular, Renal, Heart Failure, Diabetes*

INTRODUCTION

Following the discovery of increased risk of myocardial infarction with the use of rosiglitazone, all novel type 2 diabetic medications are required to conduct large-scale cardiovascular outcome trials (CVOTs) prior to market authorization.[1] Sodium-glucose co-transporter 2 inhibitors (SGLT-2i) is a new class of anti-diabetic medication that inhibits the reabsorption of filtered glucose by sodium-glucose cotransporter 2 (SGLT-2) in the proximal renal tubules, thus increasing urinary excretion of glucose and reducing plasma glucose concentration.[2]

In recent years, SGLT-2i have been under active investigation of its cardiovascular (CVS) and renal outcomes in patients with type 2 diabetes (T2DM). Among all SGLT-2i, Empagliflozin (Jardiance®) was the first to demonstrate a significant risk reduction in CVS death, all-cause mortality, and heart failure-related hospitalization,[3] in patients with T2DM and existing CVS disease. Subsequently, CVS and renal outcomes of other members of SGLT-2i, including Canagliflozin (Invokana®), Dapagliflozin (Forxiga®), and Ertugliflozin (Steglatro®), have been published. In the trials, substantial benefits on heart failure-related hospitalization were seen, which has instigated further trials in dapagliflozin and empagliflozin to see if their benefits are reproducible in non-diabetic patients with heart failure.

This review serves to provide an update on the available data regarding the CVS and renal outcomes of four SGLT-2i available in Hong Kong market: Canagliflozin, Dapagliflozin, Empagliflozin, and Ertugliflozin. The CVS and renal benefits brought by SGLT-2i have led to a paradigm shift in the management of patients with diabetes. Thus, the position of SGLT-2i in the treatment algorithm of diabetes recommended by guidelines published by American Diabetes Association (ADA), and International Society of Nephrology (ISN) will be addressed respectively in this discourse.

CANAGLIFOZIN – CANVAS Programme & CREDENCE Trial

CANVAS Programme and CREDENCE Trial are the two main trial series assessing the CVS and renal outcomes of canagliflozin in patients with T2DM. CANVAS Programme, comprised of two double-blind, randomized, placebo-controlled trials, namely Canagliflozin Cardiovascular Assessment Study (CANVAS) and CANVAS-Renal (CANVAS-R), evaluated the CVS and renal outcomes in patients with T2DM and a high cardiovascular risk. On the other hand, CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) is a double-blind, randomized, placebo-controlled trial, assessing the outcomes in patients with T2DM and established albuminuric chronic kidney disease (CKD).

1. CANVAS Programme[4]

The programme followed a total of 10,142 subjects, 4330 in CANVAS and 5812 in CANVAS-R, with a mean

follow-up of 3.62 years. Participants in CANVAS were randomly assigned to receive canagliflozin (100mg or 300mg) or placebo; while subjects in CANVAS-R received canagliflozin at a starting dose of 100mg, with an optional increase to 300mg starting from week 13, or placebo. The primary outcome was a composite of CVS death, nonfatal myocardial infarction (MI), or nonfatal stroke. The secondary outcomes included (1) all-cause mortality, (2) CVS death, (3) the composite of CVS death and hospitalization for heart failure (HHF), (4) progression of albuminuria. An exploratory renal outcome was a composite of renal outcomes including a 40% reduction in eGFR, the need for renal-replacement therapy, or death from renal causes.

Overall Outcome

In CANVAS programme, canagliflozin significantly reduced the occurrence of primary outcome (HR, 0.86; 95% CI, 0.75 to 0.97; P<0.001 for noninferiority; P = 0.02 for superiority). However, canagliflozin failed to reduce the occurrence of any component in the composite primary outcome in a statistically significant manner. In terms of secondary outcomes, subjects in canagliflozin arm were observed to have a lower risk of HF hospitalization (HR, 0.67; 95% CI, 0.52 to 0.87) and a composite of CVS death or HHF (HR, 0.78, 95% CI, 0.67 to 0.91). Canagliflozin also significantly reduced the incidence of albuminuria progression (HR, 0.73; 95% CI, 0.67 to 0.79). In addition, canagliflozin was also found to promote regression of albuminuria (HR, 1.70; 95% CI, 1.51 to 1.91) and reduce the occurrence of composite renal outcome (HR, 0.60; 95% CI, 0.47 to 0.77).

Extending from the data of CANVAS Programme, subgroup analyses were performed to assess the effect of canagliflozin on (i) prespecified outcomes according to baseline kidney function; (ii) primary and secondary prevention of CVS events; and (iii) outcomes of heart failure, with either reduced ejection fraction (HFrEF) or preserved ejection fraction (HFpEF).

(i) Outcomes with reference to baseline renal function[5]

In this subgroup analysis, subjects were analyzed based on the presence of CKD, defined as having eGFR <60mL/min/1.73m^2, and further stratified into 4 categories (i.e., eGFR <45, 45 to <60, 60 to <90, and ≥ 90mL/min/1.73m^2). From the analysis, with a progressively lower categories of renal function, subjects were found to be older; white; more likely to be female; have a longer history of diabetes; have established atherosclerotic vascular disease (ASCVD) and microvascular disease; have a history of heart failure (HF) and macro- or microalbuminuria (all *P*<0.0001).

The effects of canagliflozin on significantly reducing MACE, HHF and occurrence of renal composite were consistent across 4 eGFR subgroups (*P* heterogeneity; 0.33, 0.62 and 0.59, respectively), suggesting benefits at all levels of kidney function. However, despite a lack of heterogeneity, the benefit of reducing HHF may be more prominent in participants with poorer baseline renal function (i.e., eGFR <45mL/min/1.73m^2), while the benefit of reducing incidence of renal composite may be greater in subgroups without CKD (i.e., eGFR ≥60mL/min/1.73m^2). On the contrary, heterogeneity was detected in the effect on fatal or non-fatal stroke (HR, 0.87; 95% CI, 0.69 to 1.09; P heterogeneity, 0.01), postulating a clinically significant benefit on stroke may be observed in patients with a more declined renal function. Moreover, this analysis also showed that, although patients on canagliflozin arm experienced a decline in eGFR within the first 13 weeks of trial, canagliflozin was able to, compared to placebo, significantly decelerate the annual decline of renal function in all subgroups from week 13 until the end of follow-up.

(ii) Effect of canagliflozin on primary and secondary prevention of CVS events[6]

In another subgroup analysis, participants from CANVAS programme were divided into 2 cohorts, namely primary prevention cohort and secondary prevention cohort. Subjects in the primary prevention cohort, accounting for 34% of the total cohort, aged 50 years or older, didn't experience a prior CVS event but have ≥2 risk factors. On the other hand, patients in the secondary prevention cohort aged 30 years or older and experienced a CVS event.

From the analysis, patients with a history of CVS events (i.e., the secondary prevention cohort) were more susceptible to all primary and secondary outcomes (all *P* < 0.001, except 0.002 for renal composite). Also, although heterogeneity was not detected between two cohorts in reducing the occurrence of primary endpoint, HHF and renal composite (*P* heterogeneity, 0.18, 0.91 and 0.73, respectively), the benefits may be more observable in the secondary prevention cohort. Nonetheless, additional studies with sufficient statistical power are needed to validate this observation.

(iii) Outcomes on Heart Failure[7,8]

From the total cohort, it is observed that canagliflozin can significantly reduce the risk of a composite of CVS death or HHF, and HHF alone. Another subgroup analysis examined the prespecified outcomes of canagliflozin on patients with a history of HF, accounting for 14.4% (n = 1461) of the total cohort, compared to those without. It revealed that the beneficial effects of canagliflozin on the composite outcome of CVS death and HHF is marginally greater in patients with a history of HF at baseline (HR, 0.61; 95% CI, 0.46 to 0.80; *P* heterogeneity, 0.02). The same study also reported canagliflozin also significantly lowered the risk of a composite of fatal HF or HHF (HR, 0.70; 95% CI, 0.55 to 0.89), but not fatal HF alone (HR, 0.89; 95% CI, 0.49–1.60).

Another study further analysed the benefit of canagliflozin on reducing the risk of a composite of fatal or hospitalised HF by stratifying patients based on preserved or reduced ejection fraction (HFpEF or HFrEF), with HFrEF defined as EF <50% upon HF admission. The study concluded canagliflozin was able to reduce overall risk of HF events, without significant differences between HFpEF and HFrEF. However, this analysis is substantially limited by a significant proportion of subjects with unknown EF status and the fact that EF was measured at the time of event instead of baseline.

2. CREDENCE Trial[9,10]

CREDENCE randomised 4401 patients with T2DM and established albuminuric chronic kidney disease, with a urinary albumin-to-creatinine ratio (UACR, in mg/g) >300-5000, to receive canagliflozin (100mg once daily) or placebo, and a median follow-up period of 2.62 years. The primary outcome was a composite of end-stage renal disease (ESRD), doubling of serum creatinine level (SCr) from baseline sustained for ≥ 30 days, or death from renal or CVS causes. The secondary outcomes included (1) a composite of CVS death or HHF; (2) a composite of CVS death, MI, or stroke; (3) HF hospitalization; (4) a renal outcome composite of ESRD, doubling of the SCr, or death from renal cause; (5) CVS death; (6) death from any cause; and (7) a composite of CVS death, MI, stroke, or HHF or for unstable angina.

In CREDENCE trial, canagliflozin significantly reduced the occurrence of primary outcome event (HR, 0.70; 95% CI, 0.59 to 0.82; P = 0.00001). Canagliflozin also reduced the risks of doubling SCr (HR, 0.60; 95% CI, 0.48 to 0.76; P < 0.001), and ESRD (HR, 0.68; 95% CI, 0.54 to 0.86; P = 0.002). In CREDENCE, echoing the findings of CANVAS, canagliflozin reduced the risks of a composite of CVS death or HHF (HR, 0.69; 95% CI, 0.57 to 0.83; P < 0.001), and HHF alone (HR, 0.61; 95% CI, 0.47 to 0.80; P < 0.001). However, contrary to CANVAS, canagliflozin produced a marginal benefit on CVS death in CREDENCE (HR, 0.78; 95% CI, 0.61 to 1.00; P = 0.05).

The primary outcome and the renal-specific composite outcome were further examined according to patients' baseline renal function, including eGFR and UACR. The outcomes appeared to be consistent across all subgroups, while patients with a poorer renal function at baseline (i.e. eGFR <60mL/min/1.73m^2 and UACR > 1000) may benefit from canagliflozin to a greater extent.

The effect of canagliflozin on primary prevention and secondary prevention of CVS events was studied. In CREDENCE, 49.6% of patients were enrolled in the primary prevention cohort. The effect of canagliflozin on primary and secondary outcomes were consistent in both primary prevention and secondary prevention cohorts. However, different from the observations in CANVAS which suggested the reduction of CVS events was more apparent in the secondary prevention cohort, CREDENCE established robust efficacy of canagliflozin in both primary and secondary prevention of HHF, CVS composite (CVS death, non-fatal MI, non-fatal stroke, HHF, or hospitalization for unstable angina) and renal composite, in patients with T2DM and albuminuric CKD.

DAPAGLIFLOZIN – DECLARE-TIMI 58, DAPA-HF & DAPA-CKD

DECLARE–TIMI 58 (Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58), DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) and DAPA-CKD (Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease) are three key trials studying the CVS and renal outcomes of dapagliflozin in patients with T2DM who had or were at risk of ASCVD, patients with heart failure with reduced ejection fraction, and patients with chronic kidney disease, respectively.

1. DECLARE-TIMI 58[11,12]

In DECLARE–TIMI 58, 17,160 subjects with T2DM (including 6974 who had ASCVD and 10,186 at risk of ASCVD), were randomized to receive either dapagliflozin 10mg or placebo, and followed for a median period of 4.2 years. The primary outcomes were (1) major adverse cardiovascular events (MACE), defined as CVS death, MI, or ischemic stroke; and (2) a composite of CVS death or HHF. The secondary outcomes included (1) all-cause mortality; (2) a renal outcome composite, including ≥40% reduction in eGFR to <60 mL/min/1.73m^2, newly diagnosed ESRD, or death from renal cause; and (3) a cardiorenal outcome composite, comprised of the renal outcome composite and death from CVS causes.

In DECLARE-TIMI 58, compared with placebo arm, dapagliflozin failed to lower the incidence of MACE (HR, 0.93; 95% CI, 0.84 to 1.03; P = 0.17). However, a significant reduction in the composite primary outcome of CVS death or HHF was observed in dapagliflozin arm (HR, 0.83; 95% CI, 0.73 to 0.95; P = 0.005), regardless of the presence of HF at baseline (*P* heterogeneity, 0.60). Yet, when the components of the composite outcome were individually assessed, dapagliflozin was able to lower the incidence of HHF (HR, 0.73; 95% CI, 0.61 to 0.88) but not CVS death (HR, 0.98; 95% CI, 0.82 to 1.17).

In a focused analysis of the secondary outcomes, dapagliflozin significantly reduced the incidence of both the composite renal outcome (HR, 0.53; 95% CI, 0.43 to 0.66), and the composite cardiorenal outcome (HR, 0.76; 95% CI, 0.67 to 0.87) but not all-cause mortality (HR, 0.93; 95% CI, 0.82 to 1.04). When the components of the secondary outcomes were assessed independently, it is revealed that the risk of sustained ≥40% reduction in eGFR to <60 mL/min/1.73m^2 was significantly reduced

in dapagliflozin arm (HR, 0.54; 95% CI, 0.43 to 0.67, P < 0.0001). Besides, a subgroup analyses indicated the effects of both renal and cardiorenal composite outcomes were consistent, regardless of gender, age, baseline HbA1c and renal function.[12]

Despite a lower risk of renal outcome composite, similar to canagliflozin, patients experienced a significant decrease in eGFR after the initiation of dapagliflozin, compared to placebo group. In dapagliflozin, the drop in eGFR equalized after 2 years, and significantly slowed down thereafter in the dapagliflozin arm, compared with placebo arm. The pattern of the phenomenon was similar in all subgroups defined by renal function (i.e. eGFR ≥90; eGFR 60 to <90; or eGFR <60 mL/min/1.73m^2).[12]

With reference to the data from DECLARE-TIMI 58, sub-analyses were performed to assess the CVS outcomes in patients with or without a history of (i) myocardial infarction, and (ii) heart failure.

(i) CVS outcomes with respect to history of MI[13]

In the total cohort of DECLARE-TIMI 58 trial, 20.9% (n = 3584) had a previous diagnosis of MI at baseline. Subjects with MI were more like to be male, younger, a higher body-mass-index (BMI), more likely to have dyslipidaemia, and a history of HF (all P < 0.001). The analysis revealed that patients with T2DM and a history of MI are more prone to the prespecified primary outcomes, i.e. MACE (adjusted HR, 2.28; 95% CI, 1.96 to 2.65, P < 0.001) and a composite of CVS death or HHF (adjusted HR, 1.77; 95% CI, 1.46 to 2.14, P < 0.001).

The effect of dapagliflozin on reducing the incidence of a composite of CVS death or HHF was consistent in both patient population (*P* heterogeneity, 0.69). On the contrary, in terms of MACE reduction, although dapagliflozin didn't produce statistically significant benefit in total population, this subgroup analysis detected a marginal benefit in patients with a previous MI (HR, 0.84; 95% CI, 0.72 to 0.99, P = 0.039) with an absolute risk reduction (ARR) of 2.6% (95% CI, 0.1 to 5.0), compared to patients without a previous MI (HR, 1.00; 95% CI, 0.88 to 1.13; P=0.97; ARR, 0%; 95% CI, −0.9 to 0.8). In addition, when the patient population with previous MI was stratified by the time from last MI, heterogeneity on efficacy of dapagliflozin on MACE reduction was identified (*P* heterogeneity, 0.007). This suggests the benefit of dapagliflozin on MACE reduction may be greater, the earlier it is initiated after an acute coronary event.

(ii) CVS outcomes with respect to history of heart failure [14]

This subgroup analysis explored the CVS outcomes of dapagliflozin in patients with HFrEF, defined as EF <45%, which accounted for 3.9% (n = 671) of the total cohort. Patients with HFrEF were more likely to be male, and have a history of ASCVD, especially coronary artery disease.

From the analysis, dapagliflozin was able to provide a greater benefit in reducing the outcome composite of CVS death or HHF in patients with HFrEF (HR, 0.62; 95% CI, 0.45 to 0.86; P heterogeneity = 0.046). More importantly, dapagliflozin was also found to significantly reduce CVS death (HR, 0.55; 95% CI 0.34 to 0.90; P = 0.02) and all-cause mortality (HR, 0.59; 95% CI, 0.40 to 0.88; P = 0.01) in patients with HFrEF, but not those without. These findings highlighted the potential benefits of dapagliflozin on mortality in patients with HFrEF. However, since DECLARE-TIMI 58 is not dedicated to HFrEF patients, such favourable outcomes shall be cautiously interpreted due to a small sample size.

2. DAPA-HF[15]

Contrary to DECLARE-TIMI 58, DAPA-HF is dedicated to investigate the CVS outcomes of dapagliflozin in patients with HFrEF, who may or may not have T2DM. This phase 3, placebo-controlled trial randomised 4744 subjects with New York Heart Association (NYHA) class II to IV HF and LVEF ≤40% to receive dapagliflozin (10mg once daily) or placebo. The primary outcome was a composite of CVS death or worsening HF, defined as HHF or urgent visits in which intravenous (IV) therapy for HF is required. The secondary outcomes included (1) a composite of HHF or CVS death; (2) the total number of HHF and CVS deaths; (3) a composite of worsening renal function; and (4) all-cause mortality.

In DAPA-HF, dapagliflozin significantly reduced the incidence of primary outcome composite (16.3% vs. 21.2%; HR, 0.74; 95% CI, 0.65 to 0.85; P<0.001), with all three components in the composite being statistically significant. In other words, dapagliflozin can significantly reduce HHF (HR, 0.70; 95% CI, 0.59 to 0.83), urgent visit for HF (HR, 0.43; 95% CI, 0.20 to 0.90) and cardiovascular death (HR, 0.82; 95% CI, 0.69 to 0.98). The subgroup analysis revealed the effect of dapagliflozin on primary outcome composite was broadly consistent among prespecified subgroups, including age, the presence of multiple CVS risk factors, the presence of T2DM, cause of HF, BMI and baseline renal function, although patients with NYHA class II HF appeared to benefit more than those with class III or IV symptoms. Nonetheless, DAPA-HF has demonstrated the superior efficacy of dapagliflozin in reducing the risk of worsening HF or CVS death in patients with HFrEF, without increasing the risk of major hypoglycaemia, regardless of the presence of T2DM.

3. DAPA-CKD[16]

DAPA-CKD aimed to study the renal outcomes of dapagliflozin in patients with CKD, with or without T2DM. This multicentre, double-blinded trial randomised 4304 subjects with eGFR of 25-75 mL/min/1.73m^2 and UACR between 200-5000mg/g, to receive dapagliflozin (10mg once daily) or placebo. The primary outcome was a composite of the first occurrence of ≥ 50% decline in

eGFR, ESRD, kidney transplantation, death from renal cause, or CVS death. The secondary outcomes included (1) a renal composite of ≥ 50% decline in eGFR, ESRD, or renal death; (2) a CVS outcome composite HHF or CVS death; and (3) all-cause mortality.

In DAPA-CKD, dapagliflozin significantly prevented the incidence of primary outcome (HR, 0.61; 95% CI, 0.51 to 0.72; P < 0.001). Subsequent subgroup analysis also revealed its efficacy on preventing primary outcome was found to be consistent across subgroups, regardless of age, gender, race, the presence of T2DM, eGFR higher or lower than 45mL/min/1.73m^2, and UACR higher or lower than 1000mg/g. Moreover, dapagliflozin also substantially reduced all-cause mortality (HR, 0.69; 95% CI,0.53 to 0.88; P = 0.004), and other prespecified secondary composite outcomes. In renal outcomes, echoing the findings in DECLARE-TIMI 58, dapagliflozin was able to slow down eGFR decline, following an initial dip which equalised within 16 months after randomisation.

EMPAGLIFLOZIN – EMPA-REG OUTCOME & EMPEROR-Reduced

EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients – Removing Excess Glucose) and EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure With Reduced Ejection Fraction) are two landmark trials, studying the CVS and renal outcomes in patients with T2DM with a high CVS risk, and patients with HFrEF, respectively.

(1) EMPA-REG OUTCOME[3,17]

EMPA-REG OUTCOME is a double-blinded and placebo-controlled trial, randomising 7028 patients with T2DM and pre-existing cardiovascular diseases to receive either empagliflozin 10mg once daily, 25mg once daily, or placebo, with a median follow-up period of 3.1 years. The primary outcome was a composite of CVS death, non-fatal MI, or non-fatal stroke. The secondary outcomes were (1) a composite of primary outcome, or hospitalisation for unstable angina; and (2) a composite of microvascular events, including incident or worsening nephropathy.

Overall Outcome

Compared to placebo arm, empagliflozin significantly reduced the incidence of primary outcome (HR, 0.86; 95.02% CI, 0.74-0.99; P <0.001 for non-inferiority; P = 0.04 for superiority). Such difference was largely driven by a reduced risk CVS death (HR, 0.62; 95% CI, 0.49 to 0.77; P <0.001) since no significant differences were observed in the occurrence of MI and stroke between empagliflozin and placebo groups. Moreover, empagliflozin was able to reduce the risk of HHF (HR, 0.65; 95% CI, 0.50 to 0.85; P = 0.002), and all-cause mortality (HR, 0.68; 95% CI, 0.57 to 0.82, P <0.001).

In terms of renal outcomes, empagliflozin reduced the incidence of newly onset or worsening nephropathy (HR, 0.61; 95% CI, 0.53 to 0.70; P <0.001), defined as a composite of progression to macroalbuminuria (UACR >300mg/g), doubling of SCr which leads to eGFR ≤ 45mL/min/1.73m^2, initiation of renal replacement therapy, or death from renal causes. All the components in the renal composite were of statistical significance upon individual assessment.

Similar to canagliflozin and dapagliflozin, compared to placebo group, a significant initial reduction in eGFR was observed in patients taking empagliflozin (P < 0.001).[18] However, the drop stabilised after 4 weeks and by the end of the follow up (i.e. a median of 3.1 years), eGFR was more significantly preserved in patients in empagliflozin arm than those in the placebo arm (P < 0.001). More importantly, the effect sustained for up to 3 weeks after cessation of empagliflozin. In a subgroup analysis, the observation was consistent in subgroups with or without risk factors of CKD progression, including pre-existing CKD, presence of microalbuminuria, race, high blood pressure, age and HbA1c at baseline.

Subgroup analyses according to the presence of pre-existing diseases and stratified CVS risks were performed to examine the coherence of CVS and renal benefits in patient population with various comorbidities. The parameters of interest included (i) peripheral artery disease (PAD), (ii) atrial fibrillation (AF), (iii) CKD, (iv) MI or stroke, and (v) risk of HF development at baseline.

(i) CVS and renal outcomes in patients with pre-existing PAD[19]

PAD is a common complication of T2DM and reported as a predictor of CVS death. In EMPA-REG OUTCOME, 20.8% (n = 1461) of the total cohort had PAD at baseline. When the cohort was categorised by a history of PAD, patients with pre-existing PAD shared the CVS and renal benefits of empagliflozin, including HHF, CVS death, all-cause mortality, and incident or worsening nephropathy, to the same extent, with those without PAD at baseline (P heterogeneity, 0.53, 0.67, 0.56, and 0.33, respectively).

(ii) CVS and renal outcomes in patients with pre-existing AF[20]

In EMPA-REG OUTCOME, only 5.5% (n = 389) of the total cohort had AF at baseline. The subgroup with pre-existing AF was more likely to be older, male, and have a higher BMI. Also, they were at a higher risk of previous stroke, HF, PAD, and had lower renal function. Patients with and without AF at baseline were equally benefited with the CVS and renal outcomes of empagliflozin, including CVS death, all-cause mortality, and incident

or worsening nephropathy (*P* heterogeneity, 0.56, 0.19, and 0.20, respectively).

(iii) CVS outcomes in patients with pre-existing CKD[21]

In the total cohort of EMPA-REG OUTCOME, 32% of subjects had pre-existing CKD, defined by eGFR <60mL/min/1.73m^2 or the presence of macroalbuminuria. The cohort with CKD at baseline was more likely to be older, have a T2DM diagnosis for >10 years, and a greater proportion with multi-vessel CAD, and HF. In this subgroup analysis, benefits on reducing CVS death, and all-cause mortality (*P* heterogeneity, 0.19, and 0.22, respectively), were consistent across patient groups with or without CKD, while renal outcomes were not reported. The EMPA-KIDNEY trial is ongoing to investigate the cardio-renal outcomes in patients with chronic kidney disease (ClinicalTrials.gov number, NCT03594110).

(iv) CVS outcomes in patients with a history of MI or stroke[22]

In EMPA-REG OUTCOME, 65% (n = 4566) of the total cohort experienced a prior atherothrombotic event (i.e. MI or stroke). Patients with prior MI or stroke were found more likely to experience HHF, CVS death, death from any cause than patients without a history of these events. Yet, empagliflozin was able to lower the these outcomes as effectively as in the cohort without prior MI or stroke. Furthermore, in this analysis, CVS risks of the population with a history of atherothrombotic event at baseline were computed based on 10-point TIMI Risk Score for secondary prevention, and subsequently stratified into low (12%), intermediate (40%), high (30%), or highest risk (18%) group. The CVS outcomes of empagliflozin in all sub-population categorised with CVS risks were free from significant heterogeneity. However, the favourable outcomes appeared to be prominent in the subgroups with higher CVS risks.

(v) CVS outcomes in patients with or without a history of HF[23,24]

At baseline, 10.1% (n = 706) of the total cohort had a diagnosis of HF, who was found to be slightly older, had a higher BMI, and more likely to have a declined renal function, history of MI, and atrial fibrillation. The outcomes of empagliflozin on HHF, CVS death, and all-cause mortality were homogenous in patient population with or without HF at baseline.

Another analysis extracted patients without HF, and derived their 5-year risk of developing HF using a 9-variable Health ABC HF Risk Score. 67.2% of the population had low to average risk (< 10%), 24.2% high (10-20%), and 5.1% very high (≥ 20%). Empagliflozin produced the greatest benefit of reducing CVS death in the subgroup of "very high risk" and HHF in the subgroup of "high risk", although no heterogeneity of the CVS outcomes across different risk groups was detected.

(2) EMPEROR-Reduced[25]

Similar to DAPA-HF, EMPEROR-Reduced is a trial dedicated to examine the CVS and renal outcomes of empagliflozin in patients with HFrEF, regardless of the presence of T2DM. This double-blind, placebo-controlled trial randomised 3730 patients with HFrEF (defined as EF < 40%) to receive either empagliflozin (10mg daily) or placebo, with a median follow up of 16 months. The primary outcome was a composite of CVS death or time to first HHF. The secondary outcomes were the total number of HHF episodes, and rate of eGFR decline.

In EMPEROR-Reduced, empagliflozin significantly reduced the incidence of primary composite outcome (HR, 0.75; 95% CI, 0.65 to 0.86; P <0.001). However, unlike dapagliflozin, empagliflozin achieved a statistically significant reduction of HHF (HR, 0.69; 95% CI, 0.59 to 0.81), but not CVS death (HR, 0.92; 95% CI, 0.75 to 1.12). Nonetheless, empagliflozin was able to reduce the total number of HHF (HR, 0.70; 95% CI, 0.58 to 0.85; P < 0.001) and slow down eGFR decline in patients with HF (mean slope of change in eGFR -0.55 mL/min/1.73m^2 per year vs. -2.28 mL/min/1.73m^2 per year, respectively, p<0.001).

ERTUGLIFLOZIN – VERTIS-CV

VERTIS-CV (Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial) is a double-blinded, placebo-controlled trial, studying the CVS and renal outcomes in patients with T2DM and ASCVD. This study randomised 8246 subjects to receive either placebo, ertugliflozin 5mg once daily, or 15mg once daily, with a median follow-up of 3.0 years. The primary outcome was major adverse cardiovascular event, defined as a composite of CVS death, nonfatal MI, or nonfatal stroke. Key secondary outcomes include (1) a composite of CVS death or HHF; (2) CVS death; (3) a composite of renal outcomes, including renal death, renal replacement therapy, or doubling SCr.

Cardiovascular Outcomes[26,27]

In VERTIS-CV, despite being non-inferior to placebo, ertugliflozin failed to significantly reduce the incidence of primary outcome (HR, 0.97; 95.6% CI, 0.85 to 1.11; P < 0.001 for non-inferiority). Ertugliflozin also failed to produce statistically significant improvement in all key secondary outcomes. However, it is noteworthy that, when the components of secondary outcomes were assessed independently, ertugliflozin appeared to reduce the incidence of HHF (HR, 0.70; 95% CI, 0.54 to 0.90). Nonetheless, the statistical significance of this secondary outcome was not tested.[26]

In view of the potential benefit of ertugliflozin on heart failure, a secondary time-to-event analysis was performed to examine the effect of ertugliflozin on time

to first HHF and time to first composite of HHF and CVS death, in patients with T2DM and ASCVD. In the total VERTIS-CV cohort, ertugliflozin failed to reduce the risk of the composite of HHF and CVS death (HR, 0.88; 95% CI, 0.75 to 1.03, P = 0.109). However, echoing the effects of other SGLT-2i, ertugliflozin significantly reduced the risk of first HHF (HR, 0.70; 95% CI, 0.54 to 0.90, P = 0.006), regardless of dosage, a previous HF diagnosis, and LVEF status; and the cumulative incidence of total HHF events (HR, 0.70; 95% CI, 0.56 to 0.87, P = 0.001). A subgroup analysis subsequently revealed that the favourable effect of ertugliflozin on time to first HHF was more prominent in patients with eGFR <60mL/min/1.73m^2, micro- and macro-albuminuria, taking any diuretics, and specifically loop diuretics, respectively.

Despite the effort to demonstrate CVS benefits of ertugliflozin, these are results of prespecified secondary analyses that require validation in further studies of sufficient statistical power.

Renal Outcomes [28-30]

In VERTIS-CV, benefits on composite renal outcome was not observed (HR, 0.81; 95.8% CI, 0.63 to 1.04). On the other hand, a post-hoc analysis on the effect of ertugliflozin on renal function over 104 weeks of treatment was performed by pooling data from two phase 3 trials from VERTIS programme, namely VERTIS-SU and VERTIS-MET. VERTIS SU is a head-to-head study comparing the safety and efficacy of ertugliflozin with glimepiride, while VERTIS-MET evaluated the safety and efficacy of ertugliflozin, compared with placebo and glycemic rescue therapy with glimepiride +/- basal insulin, in patients with T2DM insufficiently controlled by metformin monotherapy. The exploratory analysis included a total of 1936 randomised subjects, among which 644 did not receive ertugliflozin, 652 received 5mg ertugliflozin, and 640 received 15mg ertugliflozin.

This exploratory study analysed the effect on renal function with respect to the change of eGFR and UACR over time, respectively. Subgroup analysis was also performed by stratifying patients with the presence of albuminuria, defined as UACR ≥ 30mg/g. Similar to other SGLT-2i, subjects receiving ertugliflozin experienced an significant initial drop of eGFR in the first 6 weeks of treatment. At week 104, eGFR of ertugliflozin arms, both 5mg and 15mg, was significantly preserved compared to non-ertugliflozin treatment groups. On the other hand, in terms of the UACR change from baseline, ertugliflozin was able to produce a significant reduction in UACR only in the subgroup with pre-existing albuminuria.

DISCUSSION

With promising results from clinical trials, SGLT-2i has outgrown itself from being a drug of endocrinology, and entered the arena of nephrology and cardiology. **Table 1** has summarised the outcomes of trials studying the CVS and renal benefits of SGLT-2i in patients with T2DM and, a high CVS risk or established ASCVD.

In terms of renal benefits, the effect on slowing eGFR decline was generally consistent among all SGLT-2i. In trials, all SGLT-2i inhibitors produced the same phenomenon that, following an initial drop, the eGFR decline was decelerated. It is postulated the initial drop was a result of acute haemodynamic response, and the preservation of kidney function in latter phase was reversal of renal haemodynamic effect.[17] On the other hand, more discrepancy was observed in terms of the benefits on albuminuria prevention or progression. In patients with T2DM, canagliflozin, empagliflozin and ertugliflozin could slow down the progression of albuminuria to different extent, while data was not available for dapagliflozin. However, dapagliflozin is currently the only SGLT-2i with proven favourable renal outcomes on patients with CKD, with or without T2DM.

In terms of CVS outcomes, in patients with T2DM and a high risk or established ASCVD, canagliflozin, dapagliflozin and empagliflozin significantly prevented the occurrence of primary outcomes in their respective trials; while ertugliflozin was only proven non-inferior to placebo. This observation gave rise to questions on underlying reasons accounting for such discrepancy. Indeed, EMPA-REG OUTCOME and VERTIS-CV studied the same primary outcome, and shared a highly similar subject population, in terms of age, gender, history of CAD, PAD and cerebrovascular diseases, baseline eGFR and pre-existing albuminuria, and baseline MACE risk (Ertugliflozin vs. Empagliflozin: 4.0% per year vs. 3.7% per year) **(Table 2)**. Therefore, we cannot exclude the possibility that the discrepancy observed on primary outcomes was due to pharmacological differences of individual SGLT-2i agents. It is also notable that, among all SGLT-2i, only empagliflozin was shown to prevent CVS death and all-cause mortality in such patient population.

Nonetheless, current available data showed that all SGLT-2i appeared to be significantly reducing the risk of HHF in patients with T2DM and a high risk or established ASCVD. This finding has aroused interests in studying their efficacy in patients with HFrEF, regardless of the presence or absence of T2DM. Unsurprisingly, both DAPA-HF and EMPEROR-Reduced have further validated the efficacy of dapagliflozin and empagliflozin in reducing the risk of HHF **(Table 3)** in patients with HFrEF, the majority of whom are on guideline-directed medical therapy for HFrEF **(Table 4)**. Yet, contrary to the findings in EMPA-REG OUTCOME and DECLARE-TIMI 58, dapagliflozin was found to significantly reduce CVS death and all-cause mortality while empagliflozin was not. Unlike dapagliflozin and empagliflozin, no evidence is currently available to demonstrate improved cardiovascular outcomes with

the use of canagliflozin or ertugliflozin in patients with HFrEF, with or without T2DM.

In trials, SGLT-2i demonstrated a wide variety of cardiac protective effects, in patients with T2DM or HFrEF. In May 2020, the ground-breaking results from DAPA-HF has earned dapagliflozin a new indication of the treatment of HFrEF in adults with and without T2DM. Following the release of result from EMPEROR-Reduced, it is believed that empagliflozin will be soon licensed for the same indication. Currently, in addition to HFrEF, clinical trials have been completed or are ongoing to examine if the benefits are reproducible in patients with HFpEF, including DELIVER (NCT03619213) and DETERMINE-preserved (NCT03877224) for dapagliflozin, and EMPEROR-PRESERVED (NCT03057951) for empagliflozin. The impact of the results of these trials on the future of HFpEF management is highly anticipated.

To explain the cardiac benefits of SGLT-2i, the mechanism of action has been actively investigated, yet not precisely developed. Some postulations were made, including the diuretic effect leading to a reduction in ventricular overload;[31] improving heart fuel energetics;[32] decreasing myocardial calcium overload;[33] and attenuating renin-angiotensin-aldosterone system.[34] Real life evidence has shown canagliflozin halted the rise in cardiac biomarkers, including troponin and NT-proBNP.[35] Also, EMPA-HEART (Effects of Empagliflozin on Cardiac Structure in Patients With Type 2 Diabetes) showed that empagliflozin reduced left ventricular mass in patients with T2DM and either a history of MI or previous coronary revascularisation.[36]

Table 1. CVS and Renal Outcomes of SGLT-2i in Patients with T2DM and a high CVS risk or established ASCVD[3,4,11,12,17,26,30]

	Canagliflozin (CANVAS Programme)[3,4]		**Dapagliflozin (DECLARE-TIMI 58)[11,12]**		**Empagliflozin (EMPA-REG OUTCOME)[17]**		**Ertugliflozin (VERTIS-CV)[26,30]**	
Median follow-up period, yrs	2.4		4.2		3.1		3.0	
	HR (95% CI); *P* value (if any)	NNT	HR (95% CI); *P* value (if any)	NNT	HR (95% CI); *P* value (if any)	NNT	HR (95% CI); *P* value (if any)	NNT
CVS Outcomes								
A Composite of CVS death, nonfatal MI, or nonfatal stroke	**0.86 (0.75 to 0.97); *P* < 0.001 for noninferiority; *P* = 0.02 for superiority**	Not calculable	-	-	**0.86; (0.74-0.99); *P* < 0.001 for non-inferiority; *P* = 0.04 for superiority**	63	0.97 (0.85 to 1.11); *P* < 0.001 for non-inferiority	-
A Composite of CVS death, MI, or ischemic stroke	-	-	0.93 (0.84 to 1.03); *P* = 0.17	-	-	-	-	-
A Composite of CVS death or HHF	-	-	**0.83 (0.73 to 0.95); *P* = 0.005**	112	-	-	-	-
HHF	**0.67 (0.52–0.87)**	-	**0.73 (0.61−0.88)**	-	**0.65 (0.50–0.85); *P* = 0.002**	-	**0.70 (0.54–0.90)**	-
CVS Death	0.87 (0.72–1.06)	-	0.98 (0.82−1.17)	-	**0.62 (0.49–0.77); *P* <0.001**	-	0.92 (0.77–1.11)	-
Fatal or nonfatal MI	0.89 (0.73–1.09)	-	0.89 (0.77−1.01)	-	0.87 (0.70–1.09)	-	1.04 (0.86–1.26)	-
Fatal or nonfatal Stroke	0.87 (0.69–1.09)	-	1.01 (0.84−1.21)** Ischaemic stroke only	-	1.18 (0.89–1.56)	-	1.06 (0.82–1.37)	-
All-cause mortality	0.87 (0.74–1.01)	-	0.93 (0.82−1.04)	-	**0.68 (0.57–0.82); *P* <0.001**	-	0.93 (0.80–1.08)	-
Renal Outcomes								
Composite Outcome	Doubling of SCr, ESRD, or Renal death		≥40% decrease in eGFR to<60mL/min/1.73m^2, ESRD, or Renal death		Doubling of SCr to eGFR ≤45mL/min/1.73m^2, RRT, or Renal death		Doubling of SCr, RRT, or Renal death	
	0.66 (0.53–0.81) *P* <0.001	-						
	40% reduction in eGFR, RRT, or Renal death		**0.53 (0.43−0.66) *P* <0.0001**	-	**0.54 (0.40–0.75) *P* <0.001**	-	0.81 (0.63–1.04)	-
	0.60 (0.47–0.77)	-						
Progression of albuminuria	**0.73 (0.67–0.79)**	-	-	-	-	-	-	-
Incident or worsening nephropathy	**-**	-	-	-	**0.61 (0.53–0.70) <0.001**	-	-	-
Progression to macroalbuminuria	**-**	-	-	-	**0.62 (0.54–0.72) <0.001**	-	-	-
Doubling of serum creatinine level	**-**	-	**To eGFR <60 mL: 0.54 (0.43–0.67) *P* <0·0001**	-	**To eGFR ≤45mL/min/1.73m^2: 0.56 (0.39–0.79) *P* <0.001**	-	-	-
ESRD	**-**	-	**0.31 (0.13–0.79) *P* = 0.013**	-	-	-	-	-

Table 2. Baseline Characteristics of Trials Studying the CVS and Renal Outcomes of SGLT-2i in Patients with T2DM and, a high CVS risk or established ASCVD[3,4,11,12,17,26]

	CANVAS Programme[3,4]	DECLARE-TIMI 58[11,12]	EMPA-REG OUTCOME[17]	VERTIS-CV[26,30]
Trial design				
Randomised treatment	Canagliflozin vs. Placebo	Dapagliflozin vs. Placebo	Empagliflozin vs. Placebo	Ertugliflozin vs. Placebo
SGLT-2 inhibitor dose	100mg or 300mg	10mg	10mg or 25mg	5mg or 15mg
Participants, n	10142	17160	7020	8246
Median follow-up period, years	2.4	4.2	3.1	3.0
Subject Characteristics				
Age, mean (SD), years	63.3 (8.3)	63.9 (6.8)	63.1 (8.7)	64.4 (8.1)
Male, n (%)	6509 (64.2)	10738 (62.6)	5016 (71.5)	5769 (70.0)
BMI, mean (SD), kg/m2	32.0 (5.9)	32.1 (6.0)	30.6 (5.3)	32.0 (5.4)
Race, n (%)				
White	7944 (78.3)	13653 (79.6)	5081 (72.4)	7240 (87.8)
Asian	1284 (12.7)	2303 (13.4)	1517 (21.6)	498 (6.0)
African American or Black	336 (3.3)	603 (3.5)	357 (5.1)	235 (2.8)
Others/unknown	578 (5.7)	601 (3.5)	65 (0.9)	273 (3.3)
HbA1c, mean (SD), %	8.2 (0.9)	8.3 (1.2)	8.1 (0.8)	8.3 (0.9)
Duration of diabetes, mean (SD), years	13.5 (7.8)	11.8 (7.8)	> 10 years - 4011 patients (57%)	12.9 (8.3)
History of coronary artery disease, n (%)	5721 (56.4)	5658 (33.0)	5308 (75.6)	6256 (75.9)
History of peripheral artery disease, n (%)	2113 (20.8)	1025 (5.9)	1461 (20.8)	1541 (18.7)
History of cerebrovascular disease, n (%)	1958 (19.3)	1301 (7.6)	1637 (23.3)	1889 (22.9)
History of heart failure, n (%)	1461 (14.4)	1724 (10.0)	706 (10.1)	1958 (23.7)
eGFR, mean (SD), mL/min/1.73m^2	76.5 (20.5)	86.1 (21.8)	74.0 (21.0)	76.0 ± 20.9
Albuminuria, n (%)	3026/10033 (30.2)	5192 (30.2)	2782 (39.7)	3244 (39.3)
Microalbuminuria, n (%)	2266/10033 (22.6)	4023 (23.4)	2013 (28.7)	2490 (30.2)
Macroalbuminuria, n (%)	760/10033 (7.6)	1169 (6.8)	769 (11.0)	754 (9.1)

Table 3. CVS Outcomes of Dapagliflozin and Empagliflozin in Patients with Heart Failure with Reduced Ejection Fraction[15,25]

	DAPA-HF (Median follow-up = 18.2 months)[15]		EMPEROR-Reduced (Median follow-up = 16 months)[25]	
	HR (95% CI); *P* value	NNT	HR (95% CI); *P* value	NNT
Cardiovascular death, heart-failure hospitalization or urgent visit resulting in IV therapy for HF	**0.74 (0.65 to 0.85); *P* <0.001**	21	-	-
Cardiovascular death or heart-failure hospitalization	0.75 (0.65 to 0.85); *P* <0.001	-	**0.75 (0.65 to 0.86) ; *P* <0.001**	19
Hospitalization for heart failure	0.70 (0.59 to 0.83)	-	0.69 (0.59 to 0.81)	-
Cardiovascular death	0.82 (0.69 to 0.98)	-	0.92 (0.75 to 1.12)	-
Death from any cause	0.83 (0.71 to 0.97)	-	0.92 (0.77 to 1.10)	-

(The primary outcome of the trials is bolded)

Guideline Update[37-41]

Cardiac and renal benefits brought by anti-diabetic medications have led a paradigm shift in the management of patients with T2DM and CKD. Since 2019, "Standards of Medical Care in Diabetes" guideline published by ADA has placed stress on taking comorbidities, including ASCVD, HF and CKD, into account when considering add-on therapy after failing 1st line medication (i.e. metformin).[37-39,41] The use of SGLT-2 inhibitors with established CVS or renal outcome benefits is favoured as add-on therapy in patients with a high risk of or established ASCVD, HF, or CKD whose renal function is sufficient for initiating SGLT-2 inhibitors.

KDIGO 2020 "Guideline for Diabetes Management in Chronic Kidney Disease" also favours the use of SGLT-2i in patients with T2DM and CKD.[40] In the guideline, SGLT-2i, along with metformin, is recommended as the first-line therapy, in patients with eGFR ≥30 mL/min/1.73m^2. The guideline also acknowledges the initial decrease in eGFR following the commencement of SGLT-2i therapy, which generally does not indicate discontinuation of treatment. Last but not least, in patients already receiving SGLT-2i, continuation of treatment is justified even if eGFR falls below 30 mL/min/1.73m^2, unless it is not tolerated or renal replacement therapy is required.

Since the favourable outcomes of SGLT-2i on non-diabetic patients with HFrEF were recently evidenced, the position of SGLT-2i has not yet been elucidated in the treatment guideline. However, in view of the substantial benefits demonstrated by clinical trials, particularly DAPA-HF and EMPEROR-Reduced, European Society of Cardiology (ESC) has published a position paper on the use of SGLT-2i in HF patients. ESC has acknowledged that favourable outcomes demonstrated by DAPA-HF have a fast onset, are able to improve patients' quality of life, and are broadly consistent across a wide patient demographic.[42] Therefore, after reviewing available evidence, the paper recommends, in patients with T2DM with a high risk of or established CVS diseases, canagliflozin, dapagliflozin, empagliflozin, or ertugliflozin are recommended to prevent HHF.[43] Moreover, dapagliflozin and empagliflozin are recommended to reduce the total risk of HHF and CVS death in symptomatic HF patients receiving guideline-directed therapy.[43]

CONCLUSION

SGLT-2i has exhibited significant cardiovascular and renal benefits in patients with T2DM and established or at a high risk of CVS diseases. While its favourable outcome on slowing down eGFR decline and reducing the incidence of heart failure-related hospitalisation appeared to be a class effect, discrepancies were observed in other outcomes, such as cardiovascular death and all-cause mortality. Nevertheless, further meta-analysis is warranted to statistically study this observation.

On the other hand, in patients with heart failure with reduced ejection fraction who may or may not have T2DM, clinical data is currently only available for dapagliflozin and empagliflozin. Both were shown to significantly reduce heart failure-related hospitalisation, while only dapagliflozin was proven to reduce cardiovascular death. Still, this ground-breaking discovery has provided patients with HFrEF with an alternative therapeutic option which is likely to improve their clinical outcomes.

Author's background

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Table 4. Baseline Characteristics of Trials Studying CVS Outcomes of Dapagliflozin and Empagliflozin in Patients with Heart Failure with Reduced Ejection Fraction[15,25]

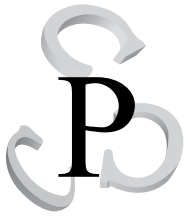
	DAPA-HF[15]		EMPEROR-Reduced[25]	
	Dapagliflozin 10mg po daily (n = 2373)	Placebo (n = 2371)	Empagliflozin 10mg po daily (n = 1863)	Placebo arm (n = 1867)
Subject Characteristics				
Age, mean (SD), years	66.2 (11.0)	66.5 (10.8)	67.2 (10.8)	66.5 (11.2)
Male, n (%)	1809 (76.2)	1826 (77.0)	1426 (76.5)	1411 (75.6)
BMI, mean (SD), kg/m^2	28.2 (6.0)	28.1 (5.9)	28.0 (5.5)	27.8 (5.3)
Race, n (%)				
White	1662 (70.0)	1671 (70.5)	1325 (71.1)	1304 (69.8)
Asian	552 (23.3)	564 (23.8)	337 (18.1)	335 (17.9)
African American or Black	122 (5.1)	104 (4.4)	123 (6.6)	134 (7.2)
Others/unknown	37 (1.6)	32 (1.3)	78 (4.2)	94 (5.0)
eGFR, mL/min/1.73 m^2				
Mean value (SD)	66.0 (19.6)	65.5 (19.3)	61.8 (21.7)	62.2 (21.5)
<60 ml/min/1.73 m^2, no./total no. (%)	962/2372 (40.6)	964/2371 (40.7)	893/1862 (48.0)	906/1866 (48.6)
NYHA functional class, n (%)				
II	1606 (67.7)	1597 (67.4)	1399 (75.1)	1401 (75.0)
III	747 (31.5)	751 (31.7)	455 (24.4)	455 (24.4)
IV	20 (0.8)	23 (1.0)	9 (0.5)	11 (0.6)
Mean LVEF (SD), %	31.2 (6.7)	30.9 (6.9)	27.7 (6.0)	27.2 (6.1)
Median NT-proBNP (IQR), pg/ml	1428 (857–2655)	1446 (857–2641)	1887 (1077–3429)	1926 (1153–3525)
Medical History, n (%)				
Atrial fibrillation	916 (38.6)	902 (38.0)	664 (35.6)	705 (37.8)
Diabetes mellitus	993 (41.8)	990 (41.8)	927 (49.8)	929 (49.8)
Heart Failure Medication, n (%)				
Renin–angiotensin inhibitor	2257 (95.1)	2219 (93.6)	1654 (88.8)	1673 (89.6)
Neprilysin inhibitor	250 (10.5)	258 (10.9)	340 (18.3)	387 (20.7)
Mineralocorticoid receptor antagonist	1696 (71.5)	1674 (70.6)	1306 (70.1)	1355 (72.6)
Beta-blocker	2278 (96.0)	2280 (96.2)	1765 (94.7)	1768 (94.7)

References

1. Regier, E. E., Venkat, M. V. & Close, K. L. More Than 7 Years of Hindsight: Revisiting the FDA's 2008 Guidance on Cardiovascular Outcomes Trials for Type 2 Diabetes Medications. *Clin Diabetes* 34, 173-180, doi:10.2337/cd16-0005 (2016).
2. Verma, S. & McMurray, J. J. V. SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review. *Diabetologia* 61, 2108-2117, doi:10.1007/s00125-018-4670-7 (2018).
3. Zinman, B. *et al*. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med* 373, 2117-2128, doi:10.1056/NEJMoa1504720 (2015).
4. Neal, B. *et al.* Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Engl J Med* 377, 644-657, doi:10.1056/NEJMoa1611925 (2017).
5. Neuen, B. L. *et al.* Cardiovascular and Renal Outcomes With Canagliflozin According to Baseline Kidney Function. *Circulation* 138, 1537-1550, doi:10.1161/CIRCULATIONAHA.118.035901 (2018).
6. Mahaffey, K. W. *et al.* Canagliflozin for Primary and Secondary Prevention of Cardiovascular Events: Results From the CANVAS Program (Canagliflozin Cardiovascular Assessment Study). *Circulation* 137, 323-334, doi:10.1161/CIRCULATIONAHA.117.032038 (2018).
7. Radholm, K. *et al.* Canagliflozin and Heart Failure in Type 2 Diabetes Mellitus: Results From the CANVAS Program. *Circulation* 138, 458-468, doi:10.1161/CIRCULATIONAHA.118.034222 (2018).
8. Figtree, G. A. *et al.* Effects of Canagliflozin on Heart Failure Outcomes Associated With Preserved and Reduced Ejection Fraction in Type 2 Diabetes Mellitus. *Circulation* 139, 2591-2593, doi:10.1161/CIRCULATIONAHA.119.040057 (2019).
9. Mahaffey, K. W. *et al.* Canagliflozin and Cardiovascular and Renal Outcomes in Type 2 Diabetes Mellitus and Chronic Kidney Disease in Primary and Secondary Cardiovascular Prevention Groups. *Circulation* 140, 739-750, doi:10.1161/CIRCULATIONAHA.119.042007 (2019).
10. Perkovic, V. *et al.* Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. *N Engl J Med* 380, 2295-2306, doi:10.1056/NEJMoa1811744 (2019).
11. Wiviott, S. D. *et al.* Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med* 380, 347-357, doi:10.1056/NEJMoa1812389 (2019).
12. Mosenzon, O. *et al.* Effects of dapagliflozin on development and progression of kidney disease in patients with type 2 diabetes: an analysis from the DECLARE–TIMI 58 randomised trial. *The Lancet Diabetes & Endocrinology* 7, 606-617, doi:10.1016/s2213-8587(19)30180-9 (2019).
13. Furtado, R. H. M. *et al.* Dapagliflozin and Cardiovascular Outcomes in Patients With Type 2 Diabetes Mellitus and Previous Myocardial Infarction. *Circulation* 139, 2516-2527, doi:10.1161/CIRCULATIONAHA.119.039996 (2019).
14. Kato, E. T. *et al.* Effect of Dapagliflozin on Heart Failure and Mortality in Type 2 Diabetes Mellitus. *Circulation* 139, 2528-2536, doi:10.1161/CIRCULATIONAHA.119.040130 (2019).
15. McMurray, J. J. V. *et al.* Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med* 381, 1995-2008, doi:10.1056/NEJMoa1911303 (2019).
16. Heerspink, H. J. L. *et al.* Dapagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med* 383, 1436-1446, doi:10.1056/NEJMoa2024816 (2020).
17. Wanner, C. *et al.* Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. *N Engl J Med* 375, 323-334, doi:10.1056/NEJMoa1515920 (2016).
18. Wanner, C. *et al.* Empagliflozin and Kidney Function Decline in Patients with Type 2 Diabetes: A Slope Analysis from the EMPA-REG OUTCOME Trial. *J Am Soc Nephrol* 29, 2755-2769, doi:10.1681/ASN.2018010103 (2018).
19. Verma, S. *et al.* Cardiovascular Outcomes and Safety of Empagliflozin in Patients With Type 2 Diabetes Mellitus and Peripheral Artery Disease: A Subanalysis of EMPA-REG OUTCOME. *Circulation* 137, 405-407, doi:10.1161/CIRCULATIONAHA.117.032031 (2018).
20. Bohm, M. *et al.* Efficacy of empagliflozin on heart failure and renal outcomes in patients with atrial fibrillation: data from the EMPA-REG OUTCOME trial. *Eur J Heart Fail* 22, 126-135, doi:10.1002/ejhf.1663 (2020).
21. Wanner, C. *et al.* Empagliflozin and Clinical Outcomes in Patients With Type 2 Diabetes Mellitus, Established Cardiovascular Disease, and Chronic Kidney Disease. *Circulation* 137, 119-129, doi:10.1161/CIRCULATIONAHA.117.028268 (2018).
22. Fitchett, D. *et al.* Empagliflozin Reduced Mortality and Hospitalization for Heart Failure Across the Spectrum of Cardiovascular Risk in the EMPA-REG OUTCOME Trial. *Circulation* 139, 1384-1395, doi:10.1161/CIRCULATIONAHA.118.037778 (2019).
23. Fitchett, D. *et al.* Effects of empagliflozin on risk for cardiovascular death and heart failure hospitalization across the spectrum of heart failure risk in the EMPA-REG OUTCOME(R) trial. *Eur Heart J* 39, 363-370, doi:10.1093/eurheartj/ehx511 (2018).
24. Fitchett, D. *et al.* Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME(R) trial. *Eur Heart J* 37, 1526-1534, doi:10.1093/eurheartj/ehv728 (2016).
25. Packer, M. *et al.* Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. *New England Journal of Medicine*, doi:10.1056/NEJMoa2022190 (2020).
26. Cannon, C. P. *et al.* Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes. *N Engl J Med* 383, 1425-1435, doi:10.1056/NEJMoa2004967 (2020).
27. Cosentino, F. *et al.* Efficacy of Ertugliflozin on Heart Failure-Related Events in Patients With Type 2 Diabetes Mellitus and Established Atherosclerotic Cardiovascular Disease: Results of the VERTIS CV Trial. *Circulation* 142, 2205-2215, doi:10.1161/CIRCULATIONAHA.120.050255 (2020).
28. Gallo, S. *et al.* Long-term efficacy and safety of ertugliflozin in patients with type 2 diabetes mellitus inadequately controlled with metformin monotherapy: 104-week VERTIS MET trial. *Diabetes Obes Metab* 21, 1027-1036, doi:10.1111/dom.13631 (2019).
29. Hollander, P. *et al.* Results of VERTIS SU extension study: safety and efficacy of ertugliflozin treatment over 104 weeks compared to glimepiride in patients with type 2 diabetes mellitus inadequately controlled on metformin. *Curr Med Res Opin* 35, 1335-1343, doi:10.1080/03007995.2019.1583450 (2019).
30. Cherney, D. Z. I. *et al.* Effects of ertugliflozin on renal function over 104 weeks of treatment: a post hoc analysis of two randomised controlled trials. *Diabetologia* 63, 1128-1140, doi:10.1007/s00125-020-05133-4 (2020).
31. Inzucchi, S. E. *et al.* How Does Empagliflozin Reduce Cardiovascular Mortality? Insights From a Mediation Analysis of the EMPA-REG OUTCOME Trial. *Diabetes Care* 41, 356-363, doi:10.2337/dc17-1096 (2018).
32. Verma, S. *et al.* Empagliflozin Increases Cardiac Energy Production in Diabetes: Novel Translational Insights Into the Heart Failure Benefits of SGLT2 Inhibitors. *JACC Basic Transl Sci* 3, 575-587, doi:10.1016/j.jacbts.2018.07.006 (2018).
33. Packer, M., Anker, S. D., Butler, J., Filippatos, G. & Zannad, F. Effects of Sodium-Glucose Cotransporter 2 Inhibitors for the Treatment of Patients With Heart Failure: Proposal of a Novel Mechanism of Action. *JAMA Cardiol* 2, 1025-1029, doi:10.1001/jamacardio.2017.2275 (2017).
34. Heerspink, H. J., Perkins, B. A., Fitchett, D. H., Husain, M. & Cherney, D. Z. Sodium Glucose Cotransporter 2 Inhibitors in the Treatment of Diabetes Mellitus: Cardiovascular and Kidney Effects, Potential Mechanisms, and Clinical Applications. *Circulation* 134, 752-772, doi:10.1161/CIRCULATIONAHA.116.021887 (2016).
35. Januzzi, J. L., Jr. *et al.* Effects of Canagliflozin on Cardiovascular Biomarkers in Older Adults With Type 2 Diabetes. *J Am Coll Cardiol* 70, 704-712, doi:10.1016/j.jacc.2017.06.016 (2017).
36. Verma, S. *et al.* Effect of Empagliflozin on Left Ventricular Mass in Patients With Type 2 Diabetes Mellitus and Coronary Artery Disease: The EMPA-HEART CardioLink-6 Randomized Clinical Trial. *Circulation* 140, 1693-1702, doi:10.1161/CIRCULATIONAHA.119.042375 (2019).
37. American Diabetes, A. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2019. *Diabetes Care* 42, S90-S102, doi:10.2337/dc19-S009 (2019).
38. American Diabetes, A. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2020. *Diabetes Care* 43, S98-S110, doi:10.2337/dc20-S009 (2020).
39. American Diabetes, A. 10. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes-2020. *Diabetes Care* 43, S111-S134, doi:10.2337/dc20-S010 (2020).
40. Kidney Disease: Improving Global Outcomes Diabetes Work, G. KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. *Kidney Int* 98, S1-S115, doi:10.1016/j.kint.2020.06.019 (2020).
41. American Diabetes, A. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2021. *Diabetes Care* 44, S111-S124, doi:10.2337/dc21-S009 (2021).
42. Seferovic, P. M. *et al.* Sodium-glucose co-transporter 2 inhibitors in heart failure: beyond glycaemic control. A position paper of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 22, 1495-1503, doi:10.1002/ejhf.1954 (2020).
43. Seferovic, P. M. *et al.* Heart Failure Association of the European Society of Cardiology update on sodium-glucose co-transporter 2 inhibitors in heart failure. *Eur J Heart Fail* 22, 1984-1986, doi:10.1002/ejhf.2026 (2020).

Questions for Pharmacy Central Continuing Education Committee Program

(Please be informed that this article and answer sheet will be available on PCCC website concurrently. Members may go to PCCC website (www.pccchk.com) to fill in their answers there.)



2 CE Units

Cardiovascular and Renal Benefits of SGLT-2 Inhibitors – Is It a Class Effect?

1. ***Which of the following is FALSE regarding SGLT-2 inhibitors?***
   - A. It inhibits the reabsorption of filtered glucose facilitated by sodium-glucose-cotransporter 2 in the proximal renal tubules.
   - B. It is recommended to be used in patients with diabetes receiving renal-replacement therapy.
   - C. This class has been recommended as add-on therapy to metformin for type 2 diabetes in patients with established CKD whose eGFR is above 30ml/min/1.73m^2.
   - D. It is expected that eGFR will initially drop when starting SGLT-2 inhibitor.

2. ***Which of the following is TRUE regarding CANVAS and CREDENCE trials?***
   - A. Canagliflozin significantly reduces hospitalization due to heart failure in CANVAS, but not in CREDENCE.
   - B. The benefit of canagliflozin on reducing CVS events may be more observable in patients who have already had a CVS event in the past than those who are at risk of CVS events but have not experienced these in the past.
   - C. Canagliflozin may reduce the incidence of renal outcomes to a greater extent in patients with a more preserved renal function.
   - D. Canagliflozin produced a marginal benefit on reducing CVS death in CREDENCE, but not in CANVAS.

3. ***Which of the following is TRUE regarding DECLARE-TIMI 58 trial?***
   - A. The primary outcome, major adverse cardiovascular events (MACE), is defined as cardiovascular death, myocardial infarction, or acute decompensated heart failure.
   - B. A marginal benefit on MACE reduction was detected in the subgroup of patients with a previous stroke.
   - C. Dapagliflozin significantly reduces cardiovascular death and all-cause mortality in patients with HFpEF.
   - D. A subgroup analysis postulated the effect of dapagliflozin on MACE may be greater when it is initiated earlier after an acute coronary event.

4. ***Which of the following is TRUE regarding DAPA-HF trial?***
   - A. DAPA-HF recruited subjects with New York Heart Association (NYHA) class I to IV heart failure.
   - B. Dapagliflozin appears to produce a greater benefit in patients with NYHA class III or IV HF than those with NYHA class II HF.
   - C. Dapagliflozin does not significantly increase the risk of major hypoglycemia in patients with HFrEF regardless of diabetes status.
   - D. Dapagliflozin only reduces the risk of hospitalization due to heart failure but not CVS mortality.

5. ***Which of the following is TRUE regarding EMPA-REG OUTCOME trial?***
   - A. Empagliflozin significantly reduces all-cause mortality in patients without diabetes.
   - B. Empagliflozin significantly reduces the incidence of nonfatal MI and stroke.
   - C. The benefit of empagliflozin on slowing downing the decline of eGFR was sustained for up to 3 weeks after cessation of the drug.
   - D. Empagliflozin can significantly preserve renal function in patients with diabetes at any time point of the study.

6. ***Which of the following is TRUE regarding Ertugliflozin?***
   - A. Ertugliflozin significantly reduces the risk of CVS death.
   - B. Ertugliflozin significantly reduces the risk of first hospitalization for heart failure.
   - C. Ertugliflozin significantly reduces the risk of renal death.
   - D. Ertugliflozin significantly slows down albuminuria progression, regardless of the presence of pre-existing albuminuria.

7. ***Which of the following is true regarding the effect of SGLT-2 inhibitors on renal function?***
   - A. All SGLT-2i discussed in the article have demonstrated a significant reduction in the initiation of renal replacement therapy.
   - B. Compared to placebo, it generally slows down eGFR decline in patients with diabetes.
   - C. It demonstrates a significant increase in death from renal causes.
   - D. All of the above

8. ***As of April 2021, which of the following has been licensed by FDA to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure with reduced ejection fraction?***
   - A. Canagliflozin
   - B. Dapagliflozin
   - C. Empagliflozin
   - D. Ertugliflozin

9. ***Which of the following trial(s) studied the cardiac benefits of SGLT-2 inhibitors in patients with heart failure with reduced ejection fraction regardless of the presence of diabetes?***
   - (i) CREDENCE Trial
   - (ii) DECLARE-TIMI 58
   - (iii) DAPA-HF
   - (iv) EMPA-REG Outcome
   - (v) EMPEROR-Reduced
   - A. (ii) and (iv)
   - B. (i) and (iii)
   - C. (iii) and (v)
   - D. (iii) (iv) and (v)

10. ***Which of the following is true regarding the possible mechanism of action explaining the cardiac benefits of SGLT-2 inhibitors?***
    - A. Diuretic effect leading to a decrease in ventricular overload
    - B. Activation of renin-angiotensin-aldosterone system
    - C. Decreasing myocardial potassium overload
    - D. All of the above

Answers will be released in the next issue of HKPJ.

CE Questions Answer for 273(D&T)

Pharmacokinetic drug interaction of protein kinase inhibitors

1. B 2. C 3. D 4. C 5. C 6. D 7. D 8. C 9. D 10. C

Stroke Prevention in Atrial Fibrillation – A Review of International Clinical Guidelines

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ABSTRACT

Atrial fibrillation (AF) is a common yet debilitating heart condition. Patients with AF are at higher risk for stroke and thus effective stroke prevention is the cornerstone of management of patients with AF. This review article discusses the use of oral anticoagulants (OACs) for stroke prevention in patients with AF according to the international clinical guidelines.

Keywords: *atrial fibrillation, stroke prevention, warfarin, non-vitamin K antagonist oral anticoagulants (NOACs), antiplatelets*

INTRODUCTION

Atrial fibrillation (AF) is a common heart condition which poses significant risk to patients by causing stroke, heart failure and other complications.[1] Patients with AF have four to six folds higher risk of stroke than the general population.[2] The consequences of AF-associated stroke have been debilitating, such as paralysis, loss of motor control, aphasia, which cause patients to lose their ability to take care of their daily lives. Therefore, stroke prevention therapy is crucial to patients with AF. In recent years, the use of oral anticoagulants (OACs) has been increasing gradually[3] with emerging evidence of better clinical outcomes and safety profiles compared to antiplatelets.[4,5]

This review article outlines the stroke prevention in patients with AF according to the latest versions of European Society of Cardiology (ESC),[6] American College of Cardiology (ACC) and American Heart Association (AHA),[7] National Institute for Health and Care Excellence (NICE),[8] National Heart Foundation of Australia (NHFA) and Cardiac Society of Australia and New Zealand (CSANZ)[9] and highlights the evolution of anticoagulation management in AF over the past few years following the launch of non-vitamin K antagonist oral anticoagulants (NOACs). Stroke prevention management has been optimized to reduce the risk and improved patients' clinical outcome.

STROKE PREVENTION MANAGEMENT

The risk of stroke can be assessed by CHA_2DS_2-VASc score.[10] CHA_2DS_2-VASc score positively correlates with the risk of ischemic stroke, transient ischemic attack[9] and systemic embolism and is used to identify high-risk patients.[11] When stratifying by genders, women aged below 65 years old without any risk factors have a relatively lower risk of stroke when compared with men.[12] However, with one or more risk factors apart from genders, women are at a higher risk of stroke than men.[13] International clinical guidelines have suggested that OACs can be considered when CHA_2DS_2-VASc score of 1 (men) or score of 2 (women) and OACs are recommended as compulsory when CHA_2DS_2-VASc score ≥2 (men) or score ≥3 (women) unless contraindicated.[6-9] Patients who have a CHA_2DS_2-VASc score of 0 (male) or score of 1 (female) are classified as low risk (stroke risk of 0.2%-0.9% per year) and stroke prevention therapy can reasonably be omitted. However, the risk factors of stroke could change over time due to aging and development of new diseases. It is highly recommended to conduct stroke risk assessment and review the CHA_2DS_2-VASc score annually.[9]

Before initiation of stroke prevention therapy, it is also important to evaluate bleeding risk as the incidence of any type of bleeding and major bleeding during OAC therapy ranged from 10%-17% and 2%-5% per year respectively.[14] Various risk factors have been found to increase the risks of bleeding events during stroke prevention therapy. There are three types of risk factors: 1) non-modifiable (e.g. age >65 years, prior bleeding events, comorbidities), 2) potentially modifiable (e.g. fragility, risk of falls) and 3) modifiable risk factors (e.g. adherence to OACs, excessive alcohol intake). Different bleeding risk prediction scores were developed based on the risk factors and biomarkers. HAS-BLED score has been commonly applied in clinical practice for many years. Recent studies in 2018 suggested that HAS-BLED score has the highest sensitivity and specificity for predicting bleeding risk compared to other prediction tools.[15,16] The NICE guideline published in 2021 recommended the use of ORBIT bleeding risk score as it

could accurately predict patients' absolute bleeding risk but it has not been fully embedded into clinical practice yet.[8]

ESC and NHFA guidelines have recommended that high bleeding risk score should not lead to the cessation of anticoagulation therapy, as the benefit of stroke risk reduction outweighs risk of bleeding among the high-risk patients.[6,9] Bleeding risk score should be used to identify any non-modifiable risk factors and manage modifiable risk factors to minimize the occurrence of potential bleeding events. High-risk patients should be scheduled for more frequent follow-up of 4 weeks instead of 4-6 months as previous study showed the follow-up HAS-BLED score was more accurate in predicting the risk of major bleeding when compared with baseline score.[17] More regular reviews should be conducted to reduce the possibility of severe bleeding, especially for patients with increasing bleeding risk.[8]

Vitamin K antagonists (e.g. warfarin) and NOACs (e.g. dabigatran, rivaroxaban, apixaban and edoxaban) are the currently available OACs in clinical practice. Before the introduction of NOACs, warfarin and aspirin were the two only available options for stroke prevention in the market. In recent years, there have been concerns raised by clinicians and researchers on the under-prescribing of OACs in patients with AF. Previous studies in Denmark and the UK reported the prescribing of OACs in patients with AF decreased before the introduction of NOACs, then increased rapidly afterwards while the use of antiplatelet reduced concurrently.[18,19] In Hong Kong, the proportion of AF patients receiving antiplatelet therapy was almost twice as those receiving OACs (43% vs 26%) in 2016.[20] With increasing evidence of superior efficacy on stroke reduction of NOACs and lower or comparable risks of major bleeding compared to warfarin,[21] recent international clinical guidelines commonly suggested to prescribe NOACs over warfarin in patients with AF unless contraindicated.[6,7,8,9]

Choice of therapy - Warfarin

Warfarin is an anticoagulant with well-established efficacy and safety profiles. It could reduce the risk of stroke and mortality in patients with AF by 60-70% and 26% respectively.[22,23] Warfarin has been indicated for patients with both AF and rheumatic mitral valve disease and/or mechanical heart valve.

However, narrow therapeutic index of warfarin limits its use as it is difficult to determine the appropriate dosage in order to strike a balance between achieving optimal anticoagulation effect and minimizing the risk of bleeding. Patients are less likely to adhere to treatment due to complex dosing regimen. Regular monitoring (6-8 weeks) of international normalized ratio (INR) with aim of INR = 2-3 are required after warfarin initiation.[24] Time in therapeutic range (TTR) of INR is one of the most frequently used measuring tools for assessing the safety and efficacy of warfarin. Benefits of warfarin is maximized when TTR is greater than 70%.[25] Nonetheless, several studies reported that most patients with AF had a suboptimal TTR of warfarin. From the US Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF), mean TTR among 5210 patients with AF was 65%.[26] In Hong Kong, INR control was also suboptimal as the TTR was 40.2% and 49.1% using European therapeutic range and Japanese therapeutic range respectively.[27] Risk factors for poor control of TTR include younger age, underweight, smoking, renal dysfunction, advanced heart failure and frailty.[26,28] For stroke reduction, warfarin users with high TTR showed no statistically significant difference in terms of efficacy when compared with NOACs.[29] However, NOACs were associated with lower risk of major bleeding and mortality compared with warfarin.[20,29,30]

TTR is positively correlated with the efficacy and safety of warfarin. Compared to patients with poor control of TTR (i.e. ≤50%), NOACs were associated with significantly lower risk of stroke or systemic embolism.[31] Similarly, the benefits of reduced risk of bleeding events of NOACs over warfarin was the most pronounced when TTR lied between 51-64%.[31] An increase in overall treatment cost was observed for patient group with a TTR ≤70% compared with that of >70%, suggesting warfarin is only cost-effective when achieving a TTR of 70%.[32] Accordingly, the ESC AF guideline published in 2020 had a new recommendation for patients with TTR <70%. It suggested this group of patients should either switch to a NOAC but ensuring good adherence and persistence with therapy, or provide efforts to improve TTR (e.g. education, counselling and more frequent INR checking).[6] NHFA AF guideline has also recommended patients with TTR of <60% to consider switching to NOAC.[9]

Choices of therapy – NOACs

NOACs were launched since 2009, with the indication of stroke prevention in patients with AF. Over the years, there have been more studies showing that they are superior or non-inferior to warfarin in terms of efficacy and bleeding complications. All NOACs were shown to be at least as effective as warfarin in AF populations from their individual pivotal trials.[33-36] From a meta-analysis of the randomized controlled trials, NOACs were reported to reduce the risk of hemorrhagic stroke by 52% and the risk of all-cause mortality by 10% compared to warfarin.[37] From the safety perspective, NOACs have comparatively better safety profiles compared to warfarin. The use of NOACs was associated with reduced risk of major bleeding and risk of intracranial hemorrhage compared with warfarin.[38,39]

Additional advantages of NOACs include simple dosing regimen, lower susceptibility to drug and

food interactions and no therapeutic drug monitoring required. NOACs can also be used cautiously in patients with stage 3 of chronic kidney disease (CKD) and dose reduction is required in those with stage 4 and 5 CKD although the current evidence is not yet well-established.[41,42] Therefore, NOACs are recommended preferentially over warfarin for stroke prevention in patients with AF except for those with mechanical heart valves or moderate-to-severe mitral stenosis.[6,7,8,9]

Use of antiplatelet drugs

Several randomized controlled trials and observational studies have investigated the efficacy and safety on antiplatelet drugs in patients with AF. Prior study reported that the use of warfarin was associated with a 52% risk reduction of stroke or systemic embolism, compared to aspirin in the elderly aged over 75 years.[43] Previous studies using electronic healthcare databases also reported similar findings. Compared with antiplatelet monotherapy, both warfarin and NOACs were associated with a lower risk of ischemic stroke and all-cause mortality and additionally a similar risk of intracranial haemorrhage and gastrointestinal bleeding was observed in clinical practice.[20, 44]

The combination of aspirin and clopidogrel was also studied for stroke prevention in AF. Warfarin was found to be superior to dual antiplatelet therapy (DAPT) as the annual risks of primary outcomes including stroke, systemic embolism, myocardial infarction and vascular death were significantly lower than DAPT group (3.93% vs 5.60%).[45] In the ACTIVE-W trial, patients who were not prescribed OACs received either DAPT or aspirin alone. The DAPT caused a significant reduction in the annual risk of primary outcomes over aspirin alone (6.8% vs 7.6%).[46] However, DAPT posed a comparable risk of major bleeding compared to aspirin alone (2% vs 1.3%/year).

Thus, antiplatelet monotherapy (aspirin and/or clopidogrel) is no longer recommended regardless of risk of stroke in the international clinical guidelines.[6,7,8,9]

CLINICAL INTERPRETATIONS

Several epidemiological studies have been conducted over the years to observe the changes of the prescribing pattern of OACs and the findings commonly reflected the problem of under-prescribing of OACs among patients with AF. These findings have been alarming to the healthcare professionals, researchers and patients. In spite of the latest recommendation by the international clinical guidelines supported by emerging evidence on the superiority of OACs compared to antiplatelets, there seems to be difficulties of clinicians translating the theoretical recommendations into clinical competency and also patients' willingness to uptake OACs. A recently published study revealed that the major factor of refusing anticoagulation from patients' perspective is the lack of knowledge on AF and its management, which often leads to the misunderstanding because of peer influence and hearsays.[47] Another concern from both clinicians and patients is the risk of bleeding.[47,48] Further studies will be warranted to investigate the solutions on resolving the barriers of using OACs among patients with AF.

Pharmacists, as the first point of contact of healthcare system, play a key role in promoting the importance of taking OACs for stroke prevention to both clinicians and patients. Undoubtedly, both ischemic stroke and bleeding complications are associated with a higher risk of mortality. However, stroke can be more detrimental as the subsequent damage to the patients' physical health and quality of life could be irreversible and poses significant burden to the patients, caregivers and the society as a whole. More importantly, current findings revealed that aspirin is not just unsafe compared to OACs in terms of bleeding complications but the efficacy has found to be less superior to OACs. Therefore, risk of bleeding should not be a concern that clinicians are worried about and stopped prescribing. Pharmacists should be actively educating the public on raising the awareness and enhancing the understanding of the importance of stroke prevention therapy in community and hospital settings; and more importantly resolving communication barriers between the clinicians and patients by acting as a channel to allow transparent exchange of correct information in order to produce an appropriate treatment regimen plan to patients.

CONCLUSION

This review outlines the recommendations of stroke prevention as part of the AF management and highlights the importance of the stroke prevention to patients. Pharmacists are recommended to actively raise the public awareness and enhance the understanding of the efficacy and safety of OACs; and collaborate with clinicians to provide patient-centred care.

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References

1. Benjamin EJ, Muntner P, Alonso A, et al. Heart disease and stroke statistics - 2019 update: a report from the American Heart Association. *Circulation*. 2019; 139: e56-e528.
2. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke*. 1991; 22: 983-8.
3. Birkinshaw A, Fly C, Fluck D, et al. Changing trends in the use of novel oral anticoagulants and warfarin for treating non-valvular atrial fibrillation. *JRSM Cardiovasc Dis. 2020;* 9: 2048004020915406.
4. Shroff GR, Solid CA, Herzog CA. Atrial fibrillation, stroke, and anticoagulation in Medicare beneficiaries: trends by age, sex, and race, 1992-2010. *J Am Heart Assoc.* 2014; 3: e000756.
5. Suzuki S, Otsuka T, Sagara K, et al. Nine-year trend of anticoagulation use, thromboembolic events, and major bleeding in patients with non-valvular atrial fibrillation - shinken database analysis. *Circ J.* 2016; 80: 639-49.
6. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J.* 2021; 42: 373-498.
7. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines and the Heart Rhythm Society. *J Am Coll Cardiol.* 2019; 74: 104-32.
8. National Institute for Health and Care Excellence. Atrial fibrillation: diagonsis and management [NICE Guideline No. NG196]. 2021. https://www.nice.org.uk/guidance/ng196/chapter/Recommendations [Accessed 3 May, 2021].
9. Brieger D, Amerena J, Attia JR, et al. National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand: Australian clinical guidelines for the diagnosis and management of atrial fibrillation 2018. *Med J Aust.* 2018; 209: 356-62.
10. Pamukcu B, Lip GY, Lane DA. Simplifying stroke risk stratification in atrial fibrillation patients: implications of the CHA2DS2-VASc risk stratification scores. *Age Ageing*. 2010; 39: 533-5.
11. Lip GY, Nieuwlaat R, Pisters R, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest*. 2010; 137: 263-72.
12. Friberg L, Benson L, Rosenqvist M, et al. Assessment of female sex as a risk factor in atrial fibrillation in Sweden: nationwide retrospective cohort study. *BMJ*. 2012; 344: e3522.
13. Poli D, Antonucci E, Grifoni E, et al. Gender differences in stroke risk of atrial fibrillation patients on oral anticoagulant treatment. *Thromb Haemost*. 2009; 101: 938-42.
14. Rubboli A, Becattini C, Verheugt FW. Incidence, clinical impact and risk of bleeding during oral anticoagulation therapy. *World J Cardiol.* 2011; 3: 351-8.
15. Borre ED, Goode A, Raitz G, et al. Predicting thromboembolic and bleeding event risk in patients with non-valvular atrial fibrillation: a systematic review. *Thromb Haemost*. 2018; 118: 2171-87.
16. Chang G, Xie Q, Ma L, et al. Accuracy of HAS-BLED and other bleeding risk assessment tools in predicting major bleeding events in atrial fibrillation: a network meta-analysis. *J Thromb Haemost*. 2020; 18: 791-801.
17. Chao TF, Lip GYH, Lin YJ, et al. Incident risk factors and major bleeding in patients with atrial fibrillation treated with oral anticoagulants: a comparison of baseline, follow-up and delta HAS-BLED scores with an approach focused on modifiable bleeding risk factors. *Thromb Haemost*. 2018; 118: 768-77.
18. Gadsbøll K, Staerk L, Fosbøl EL, et al. Increased use of oral anticoagulants in patients with atrial fibrillation: temporal trends from 2005 to 2015 in Denmark. *Eur Heart J*. 2017; 38: 899–906.
19. Apenteng PN, Gao H, Hobbs FR, et al. Temporal trends in antithrombotic treatment of real-world UK patients with newly diagnosed atrial fibrillation: findings from the GARFIELD-AF registry. *BMJ Open*. 2018; 8: e018905.
20. Li X, Pathadka S, Man KKC, et al. Comparative outcomes between direct oral anticoagulants, warfarin, and antiplatelet monotherapy among Chinese patients with atrial fibrillation: a population based cohort study. *Drug Saf*. 2020; 43: 1023-33.
21. Yao X, Abraham NS, Sangaralingham LR, et al. Effectiveness and safety of dabigatran, rivaroxaban, and apixaban versus warfarin in nonvalvular atrial fibrillation. *J Am Heart Assoc.* 2016; 5: e003725.
22. Amin A. Oral anticoagulation to reduce risk of stroke in patients with atrial fibrillation: current and future therapies. *Clin Interv Aging.* 2013; 8: 75-84.
23. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med*. 2007; 146: 857-67.
24. Gallus AS, Baker RI, Chong BH, et al. Consensus guidelines for warfarin therapy. Recommendations from the Australasian Society of Thrombosis and Haemostasis. *Med J Aust.* 2000; 172: 600-5.
25. Schmitt L, Speckman J, Ansell J. Quality assessment of anticoagulation dose management: comparative evaluation of measures of time-in-therapeutic range. *J Thromb Thrombolysis.* 2003; 15: 213-6.
26. Pokorney SD, Simon DN, Thomas L, et al. Patients' time in therapeutic range on warfarin among US patients with atrial fibrillation: results from ORBIT-AF registry. *Am Heart J*. 2015; 170: 141-8.
27. Lam ASM, Lee IMH, Mak SKS, et al. Warfarin control in Hong Kong clinical practice: a single-centre observational study. *Hong Kong Med J*. 2020; 26: 294-303.
28. Macedo AF, Bell J, McCarron C, et al. Determinants of oral anticoagulation control in new warfarin patients: analysis using data from Clinical Practice Research Datalink. *Thromb Res*. 2015; 136: 250-60.
29. Sjalander S, Sjogren V, Renlund H, et al. Dabigatran, rivaroxaban and apixaban vs. high TTR warfarin in atrial fibrillation. *Thromb Res*. 2018; 167: 113-8.
30. Chan YH, See LC, Tu HT, et al. Efficacy and safety of apixaban, dabigatran, rivaroxaban, and warfarin in Asians with nonvalvular atrial fibrillation. *J Am Heart Assoc.* 2018; 7: e008150.
31. Mitsuntisuk P, Nathisuwan S, Junpanichjaroen A, et al. Real-world comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants vs. warfarin in a developing country. *Clin Pharmacol Ther.* 2020; 109: 1282-92.
32. Hospodar AR, Smith KJ, Zhang Y, et al. Comparing the Cost Effectiveness of Non-vitamin K Antagonist Oral Anticoagulants with Well-Managed Warfarin for Stroke Prevention in Atrial Fibrillation Patients at High Risk of Bleeding. *Am J Cardiovasc Drugs.* 2018; 18: 317-25.
33. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2009; 361: 1139-51.
34. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2013; 369: 2093-2104.
35. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2011; 365: 981-92.
36. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med.* 2011; 365: 883-91.
37. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet*. 2014; 383: 955-62.
38. Adeboyeje G, Sylwestrzak G, Barron JJ, et al. Major bleeding risk during anticoagulation with warfarin, dabigatran, apixaban, or rivaroxaban in patients with nonvalvular atrial fibrillation. *J Manag Care Spec Pharm.* 2017; 23: 968-78.
39. Vinogradova Y, Coupland C, Hill T, et al. Risks and benefits of direct oral anticoagulants versus warfarin in a real world setting: cohort study in primary care. *BMJ*. 2018; 362: k2505.
40. Ha JT, Neuen BL, Cheng LP, et al. Benefits and harms of oral anticoagulant therapy in chronic kidney disease: a systematic review and meta-analysis. *Ann Intern Med.* 2019; 171: 181-9.
41. Lutz J, Jurk K, Schinzel H. Direct oral anticoagulants in patients with chronic kidney disease: patient selection and special considerations. *Int J Nephrol Renovasc Dis.* 2017; 10: 135-43.
42. Tereshchenko LG, Henrikson CA, Cigarroa J, et al. Comparative effectiveness of interventions for stroke prevention in atrial fibrillation: a network meta-analysis. *J Am Heart Assoc.* 2016; 5: e003206.
43. Mant J, Hobbs FD, Fletcher K, et al. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. *Lancet*. 2007; 370: 493-503.
44. Fanning L, Wong ICK, Li X, et al. Gastrointestinal bleeding risk with rivaroxaban vs aspirin in atrial fibrillation: A multinational study. *Pharmacoepidemiol Drug Saf.* 2020; 29:1550-61.
45. Connolly S, Pogue J, Hart R, et al. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet*. 2006; 367: 1903-12.
46. Connolly SJ, Pogue J, Hart RG, et al. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. *N Engl J Med.* 2009; 360: 2066-78.
47. Ng VWS, Siu CW, Chiu PKC, et al. Understanding the barriers to using oral anticoagulants among long-term aspirin users with atrial fibrillation – a qualitative study. *BMC Health Serv Res.* 2020; 20: 1084.
48. Decker C, Garavalia L, Garavalia B, et al. Exploring barriers to optimal anticoagulation for atrial fibrillation: interviews with clinicians. *J Multidiscip Healthc.* 2012; 5:129-35.

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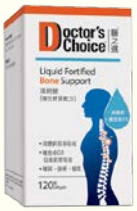

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A Brief Review of Contemporary Technology Platforms Being Used for Production of the SARS-CoV-2 Vaccines

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ABSTRACT

The outbreak of the severe acute respiratory syndrome-2 virus (SARS-CoV-2), which is responsible for the rapid spread of coronavirus disease (COVID-19) to more than two hundred countries in 2020 has created a widespread global health concerns as well as economic disruption. To cope with this pandemic problem, an array of products has been swiftly developed and introduced to meet the world's need. A comprehensive survey reveals different approaches have been applied for vaccine design and production depending on the availability of resource, trained manpower and know-how techniques. In this review article, a wide range of vaccine production platforms, namely, conventional attenuation of the virus, subunit expression of the spike protein molecule via recombinant vectors, non-replicating viral vector, synthetic nucleotides as means to produce COVID-19 vaccine are described. Pros and cons of these different approaches are systematically reviewed and compared. Never prompt availability of a vaccine for immunization against a pathogen in the past provides biomedical students and scientist with such an opportunity to acquaint these knowledges and technologies relevant to the design, production, and safety pitfalls of the launch of a vaccine.

Keywords: *Covid-19 pandemic, Vaccine design, Vaccine production, technology platform, recombinant subunit products, synthetic nucleotides, attenuated vaccine, adjuvant*

INTRODUCTION

Coronaviruses are contagious pathogen of the respiratory and gastrointestinal tracts. They are responsible for the eruption of severe acute respiratory syndrome, Middle East respiratory syndrome and many other influenzas in the past.[1-3] In December 2019, a few cases of death due to pneumonia were first reported in Wuhan, Hubei province of China. They were subsequently diagnosed to have coronavirus infection of SARS-CoV-2.[4] Within couple of months after its outbreak, the infectious disease (COVID-19) rapidly spread to other cities and caused 2788 deaths in China.[5] By 17 April 2021, transmission of this novel coronavirus (SARS-CoV-2), have already been found worldwide, with 139,501,934 confirmed cases and 2,992,193 death.[6] As a result of its severe threat to health, distance of social engagement and knockdown of international travel have been imposed. Because borders of many country are closed to prevent further transmission, global economic activities have been disrupted and shut down.[7-9]

Although social restriction was implemented and different drugs have been considered, there is no sign for people back to normal life up to now.[7] Instead, more cities have been reported to have another wave of outbreak. Consequently, restriction and lockdown are highly likely to be imposed. Unlike many other infectious diseases, this coronavirus infection does not have an effective drug to choose.[7,10,11] Furthermore, to identify, design and produce an effective drug for treatment of coronaviruses, which frequently mutate, is not an easy task and may take 10 to 15 years' effort before a pharmaceutical product could be used in clinic **(Figure 1a)**.[12,13] At present, a better solution to stop its transmission is by means of wearing protective clothes and mask. Alternatively, buildup personal immune strength to eliminate the pathogen is also important. Hence, injection of an impeccably design vaccine should be considered.[7,12,14]

Because of this scenario, all developed countries have committed, and injected lots of resource, manpower and supports to develop an effective vaccine for immunization of the SARS-CoV-2 virus. Hence, global vaccine R&D effort in response to the need of COVID-19 pandemic is unprecedentedly fueled in terms of scale and speed. As a result of these consorted efforts, some vaccine products have already been produced and launched on the market after a year of exploration and investigation, which otherwise, would take many years to develop **(Figure 1b & C)**.

This report reviews the technology platforms that have a successful launch of a COVID-19 vaccine product and compares the pros and cons of each approach to produce the vaccine. Never prompt availability of a vaccine for immunization against a pandemic in the past provides biomedical students and scientist with such an opportunity to acquaint these knowledges and

technologies relevant to the design and production strategy of a vaccine.

NIL AVAILABLE OF DRUG TREATMENT FOR COVID-19

The search of candidate drug therapies for COVID-19 is on-going and answer seems to change all the time. BioWorld has listed a total of some 511 candidate compounds, many of these candidate drugs remain at exploratory stage although a few have been chosen and proceeded to phase II-III trials. Hydroxychloroquine (Plaquenil) and chloroquine, which are anti-malarial and anti-arthritis, were the two candidate drugs that hit the headlines about 6 month ago as a good choice for COVID-19 treatment because President Trump strongly recommended their use. But a few small clinical studies immediately observed that they were helpful only for treating hospitalized patients with mild cases of COVID-19. Through a comprehensive investigation, the current consensus from the NIH and

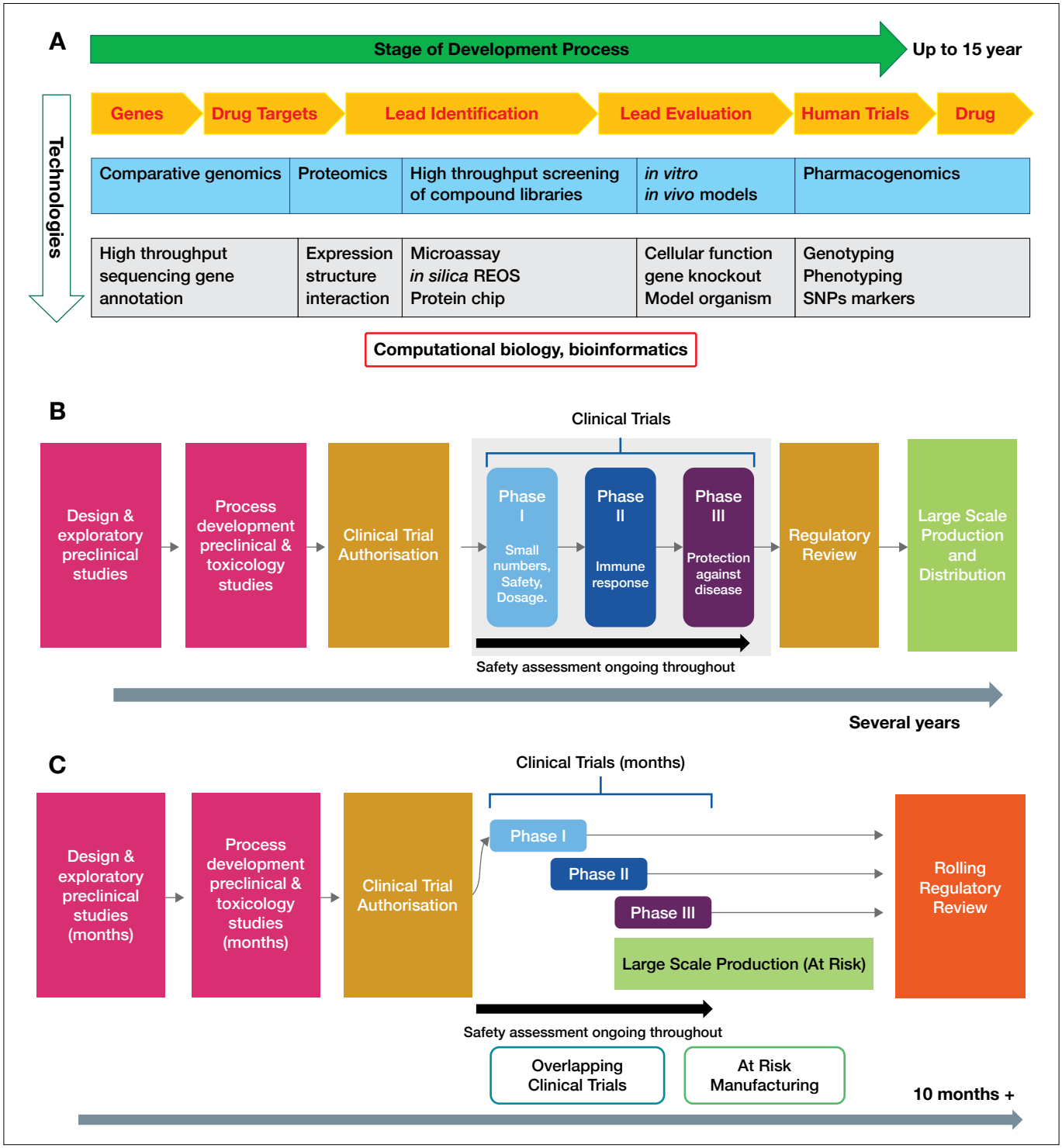

Figure 1. A snapshot of innovative pharmaceutical development through different stages and resources required for the development. ***A:*** *From gene to a drug;* ***B:*** *Traditional timeline for developing a vaccine;* ***C:*** *Speed process for developing new vaccine to cope with need in pandemic time.*[12,13]

the FDA is that hydroxychloroquine and chloroquine do not work for preventing or treating COVID-19. Clinical guidelines from the NIH recommend against their use for COVID-19.

Table 1 is a list of candidate drugs claimed by more people for treatment of COVID-19 in the past 2 years. Except remdesivir (Veklury) and baricitinib (Olumiant), many of them do not receive unanimous support from all national health authorities partly because the claim do not have enough evidence, no matter from in-situ computational[12] or from clinical study.[15] Even some, which have been approved by a health regulatory authory, are restricted to be used only either in clinic trials or in hospitals for hospitalized patient. Thus, they are not really a cure for the disease. Among many clinical trials conducted to identify a suitable therapy for COVID-19, remdesivir (Veklury) is the only medication warranted by the US FDA and the EMA for conditional treatment of COVID-19 patient who are admitted to hospital. The approval was based merely on findings that hospitalized patients who received this drug recovered faster.[16] But robust data from safety and efficacy studies have not been done. The World Health Organization's (WHO) solidarity trial, on the other hand, showed that it does not reduce mortality, or the time COVID-19 patients take to recover. Hence, use of remdesivir for COVID-19 was suspended based on a decision drawn by expert panel.[17]

VACCINATION: AN ALTERNATIVE TO BLOCK TRANSMISSION OF COVID-19

In view of no medication available today for effective treatment of COVID-19, it is necessary to consider another strategy, *i.e.*, to immunize people against inflection of the pathogen via giving them man-make antigens,[7] which work by exposing the body to molecules from the target pathogen in advance to trigger an immune response before getting contact with the pathogen. The artificially man-make antigen given to a person, normally through injection to trigger immunization responses, is called vaccine.

Vaccine can be grouped according to either biochemical nature of its constituents or technology platform of its production. The former type of grouping includes whole virus, protein or subunit protein, RNA, DNA, and viral vector while the other type of grouping focus on how innovative and advance a technology platform is. Upon this aspect of consideration, technology platforms are classified according to traditional inactivation, genetic engineering and functional lead identification and design.**(Figure 1)**[12]

Table 1. Drugs that have been considered for emergency treatment of COVID-19

Drug Name	Indications	Endorsed by (Yes / No / Inconclusive)			
		FDA	NIH	EMA	WHO
Remdesivir®	antiviral	Y	Y	Y	N
Baricitinib®	antiviral	Y	Y	N	N
Dexamethasone	A corticosteroid for antoimmune disorders and allergic reactions	Y	Y	Y	-
Hydoxychloroquine		N	N	N	N
Chloroquine		N	N	N	N
Convalescent plasma	Antibodies in the plasma help fight the coronavirus infection.	N	Y	Y	–
Bamlanivimab (LY-CoV555, VIR-7831, AZD7442, BRII-196, BRII-198)	Monoclonal antibodies to destroy foreign pathogens	Y	N	Y	–
Casirivimab & imdevimab (REGN-COV2)	Cocktail of monoclonal antibodies to destroy foreign pathogens	Y	–	Y	–
Azithromycin	Antibiotic used to treat bronchitis and pneumonia due to bacterial infection	N	N	–	N
Tocilizumab (Actemra), Kevzara (Sarilmab)	an IL-6 inhibitor approved for rheumatoid arthritis and juvenile idiopathic arthritis	N	N	–	–
Kinase Inhibitors (Acalabrutinib, Baricitinib, Ruxolitinib, Tofacitinib)	similar to IL-6 inhibitors in that they also affect the body's immune response	N	N	–	–
Kaletra (lopinavir, ritonavir)	HIV medication containing a combination of two antivirals called lopinavir and ritonavir	–	N	–	–
Ivermectin	oral medication used to treat infections caused by parasites, such as lice and rosacea	N	I	N	–
Tamiflu (oseltamivir)	antiviral medication used for influenza (flu)	–	–	–	–
Avigan (favipiravir)	Antiviral medication for flu & Ebola	–	I	–	–
Molnupirvir (Eidd-2801)	Antiviral medication for flu	Y	–	Y	–
Colchinine (Colcrys)	Medication for gout; activating anti-inflammatory processes	–	–	N	–

Y = Yes; N = No; I = Inconclusive; – = No comment

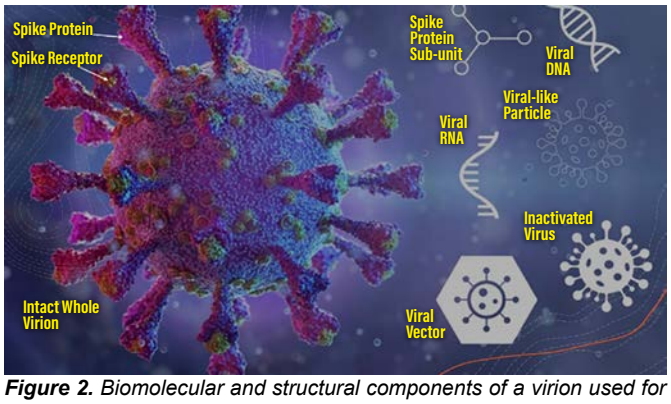

Figure 2. *Biomolecular and structural components of a virion used for the design and production of a COVID-19 vaccine.*

Whether a vaccine is effective or not, and safe or not safe for use depends very much on its design, formulation, and manufacturing facilities[5] as well as its inventory control before use. Adopting some technology platforms for vaccine production certainly might have a higher risk than the others.[13] At this moment of writing the review, there are at least 10 COVID-19 vaccines being rolling out across six continents to slow the global pandemic, and more are expected in pipe after completion of their late-stage testing. Nevertheless, these shots use different technologies to help people mount the molecular defenses that can fend off the disease.

GROUPING COVID-19 VACCINES BASED ON BIOMOLECULAR NATURE[18]

Companies and research institutes are working towards different types of COVID-19 vaccines.[7,13,14,18] According to biomolecular nature of the viral component used for vaccine development **(Figure 2)**, it could be the whole virion, spike protein, the viral genetic materials and viral vector. A COVID-19 vaccine, thus, could be classified to one of the following category:

Inactivated Whole or Defanged Viral Vaccine

Inactivated whole viral vaccine is produced by killing or inactivating the virion with chemical or physical treatment to make them unable to replicate anymore. For SARS-CoV-2 vaccine created by this way, it contains the whole material or part of the inactivated virion. In some ways, the virion has been denatured but some antigenic properties may still be preserved. It is not difficult to apprehend that quality of this type of the treated virion are more variable from each other and from batch to batch. Incomplete inactivation may occur and background of the inactivated whole or the defanged viral materials are in general more complex. Products made by Sinopharm/Beijing Institute of Biological Products or by Sinovac Biotech are belongs to this type.

Viral Vector Vaccine

Several projects use well-known viruses as a starting point, for example the “Modified Vaccinia Virus Ankara” (MVA), the adenovirus serotype 26 or the virus from measles vaccine. Such so-called vector viruses can multiply in humans assuming they do not cause disease. These vector viruses are well known to be produced abundantly in cell cultures. Now researchers are inserting one or more genes for surface proteins of SARS-CoV-2 to these replicating virus. Some vector viruses are “disguised” in this way because they then carry these proteins themselves on their surface and can thus fool the immune system into thinking they have a Covid-19 infection. Other vector viruses do not look like SARS-CoV-2 but induce the production of the SARS-CoV-2 proteins in cells they have invaded. In both cases, this leads to the build-up of immune protection that can also fight off a real infection - or so the plan goes. Based on each case on a vector virus, the first licensed Ebola vaccines, the first dengue vaccine and other experimental vaccines have been developed.

Recombinant vector virus vaccines are now being developed by, for example, Janssen (a branch of Johnson & Johnson), the German Centre for Infection Research (DZIF), the University of Oxford with AstraZeneca, the IAVI / MSD collaboration and the ReiThera / Leukocare / Univercells consortium.

Recombinant Protein Vaccine

Proteaceous structure of the pathogen that induces an immune response is used to make the vaccine. For the SARS-CoV-2 virion, it is the spike protein of its proteaceous capsid. Purified whole structure or fragments of the proteaceous structure or a subunit of the spike protein expressed via genetic engineering could be used to constitute a vaccine. Recombinant protein is a well-established technology today and could be easily applied to produce the protein in large quantities. Like any active protein, which requires the right conformation, whether the cloned product is effective depends on many parameters, such as the expression vectors, the host system, the downstream processing conditions and finally, the formulation step. These vaccines, such as those made by Novavax, Greffex, UMN Pharma, and Sanofi/GSK, contain selected viral spike proteins or subunit of the spike protein of the SARS-CoV-2 virus.

Synthetic Nucleotide Vaccine

These vaccines contain a selected gene of the virus in the form of RNA, or more precisely, the form of messenger RNA (mRNA) in which transcripts of individual genes that are required for protein production are produced in all living cells. After injection into muscle, the mRNA from the vaccine is supposed to induce the production of harmless viral protein in the body, which then in turn causes the build-up of immune protection, just as with a conventional vaccine. mRNA vaccines have the advantage that many injection doses can be produced from them very quickly. However, no such vaccine against any disease has been produced yet on the

market and it is totally a new attempt. Companies and institutes developing such vaccines against Covid-19 include BioNTech/Pfizer, Moderna, CureVac, Arcturus Therapeutics and eTheRNA.

Similarly, vaccines that contain a piece of DNA with a viral gene instead of mRNA have been explored; the companies working on this include Inovio, the Genexine consortium and the OpenCorona consortium led by the Swedish Karolinska Institute and with the participation of the University of Giessen. So far, however, no DNA-based Covid-19 vaccine has progressed beyond Phase I.

GROUPING COVID-19 VACCINES BASED ON PRODUCTION TECHNOLOGY PLATFORM[7,13,14,18]

Technological wise, current COVID-19 vaccines can be classified as one of the following three types; (1) **Conventional attenuated vaccine:** inactivated whole or broken cells of the pathogen; (2) **Genetic engineered non-pathogenic live vector or DNA** carrying some genes of the pathogen; (3) **Recombinant subunit protein of the pathogen by inserting** the correct coding gene into a vector via genetic engineering or (4) **biochemically or chemically synthesized molecules** directly or indirectly resemble the structure and conformation of an antigen on a pathogen.

(1) Chemically or Physically Inactivated Viral Vaccine

Two brands of China's COVID-19 vaccines belong to the traditional attenuation treatment of the virion during vaccine production, much like the technology behind shots for the flu or polio. Duck eggs[19] or Vero cell culture are seeded with the virus to allow propagation inside the eggs or cells. Once mature and plaque are formed and observed, virions are harvested and inactivated chemically or physically. Chemicals or physical treatment of the virions have been applied to kill or weaken the targeted virus after purified. The chemical also serves as a sterilant. The purified and attenuated viruses are subsequently formulated and used for injection to individual to generate an immune response that can protect against the pathogen. Formalin or β-propiolactone[19] and heat are the common treatment frequently used to inactivate the virion.

This is a long-proven technology; many approved vaccines are produced in this way; for example, those against hepatitis B or influenza. So far, studies on the effectiveness of Covid-19 vaccines using the traditional technology have shown them to have an efficacy rates comparatively lower than other shots with late-stage study results.

In these classic vaccines, such as those against measles and polio, patient is inoculated with weakened or inactivated versions of the virus to trigger the immune system and to produce specialized antibodies that are adapted to recognize the virus. After vaccination, the antibodies remain in the body. If the patient later becomes infected with the actual virus, the antibodies can identify and help neutralize it. Overall, attenuated vaccine is a weakened viral vaccine. It may have chances to be infected if some viruses survive the inactivation treatment or because of the presence of some tough virus. Nevertheless, vaccine produced by attenuation, in general, can stimulate our body to produce antibodies and get immune.

A Beijing-based drug-development unit of China National Pharmaceutical Group Co., known commonly as Sinopharm, relies on this traditional vaccine approach to produce a defanged version of the pathogen as vaccine.

China's state-owned Sinopharm adopts this conventional technology to produce the COVID-19 vaccine. Their products are available in: China, Bahrain, Serbia, U.A.E. and Seychelles.

- Doses: 2
- Efficacy: 11-79.4%, interim Phase 3 results
- Most common side effects: Injection-site pain, headache, muscle pain, fever

Sinovac Biotech Ltd. Also applies this technology platform to produce their attenuated vaccine. Their products are available in: China, Brazil, Indonesia and Turkey

- Doses: 2
- Efficacy: 50.3-95% (based on clinical trials in Brazil)
- Most common side effects: Unknown, a few cases of blood clotting reported.

(2) Genetic Engineered Non-replicating Viral Vector Vaccine

Several vaccines use what is known as a viral-vector approach, a reference to how the shots deliver immune-mobilization orders. The technology behind although relatively new, know how technic is well established and it has been used to produce vaccines protecting against another deadly infectious disease, such as Ebola. Whether it is safe to use Adenovirus as a live vector remains not sure.

Among the viral-vector Covid-19 vaccines are AstraZeneca's, developed with the University of Oxford and in use in the U.K. and across Europe; Russia's Sputnik V; a vaccine from China's CanSino Biologics Inc. working with the Chinese military. The shots use a modified virus—like the virus responsible for common colds—to carry genetic instructions teaching cells to make a protein from the coronavirus. A fourth viral-vector vaccine, from Johnson & Johnson, has completed its late-stage testing and has been authorized for use in the U.S. in March 2021. Vaccine relies on the modified virus vector, which is assumed non-pathogenic and easily manipulated. Vaccine produced by companies or institute mentioned above, whoever adopt the Adenovirus as the

recombinant viral vector, has been reported to cause blood clotting in some people after a week receiving the injection. Consequently quite a few brands have already been suspended or called to temporary withdrawn their uses until the cause of blood clotting is unveiled.

Companies adopted this approach include:

AstraZeneca
- Available in: U.K.
- Doses: 2
- Efficacy: 62% (with two doses)
- Most common side effects: blood clotting.

Johnson & Johnson
- Just approved for distribution
- Doses: 1
- Efficacy: 85-100% in the U.S., 66% in Latin America and 57% in South Africa
- Most common side effects: Fatigue, headache, muscle pain, injection-site pain & blood clotting

Sputnik-V
- Available in: Russia, Serbia, Argentina
- Doses: 2 (Russia is also offering to foreign customers who want to speed up vaccinations a one-dose version, Sputnik Light, consisting of the first dose of the regular Sputnik vaccine.)
- Efficacy: 91.4%, in an interim analysis
- Most common side effects: Injection-site pain and flu-like symptoms including fever, weakness, fatigue and headache

CanSino Biologics, working with the Chinese military
- Available in: China
- Doses: 1
- Efficacy: Unknown
- Most common side effects: Unknown

(3) Genetic Engineered Vaccine

Researchers designed these vaccines to generate an immune response to the coronavirus by introducing one of its proteins, like the spike protein jutting from its surface into a baculovirus vector, which require insect cells as host for propagation. Through this approach, the expressed recombinant subunit protein has been found to retain the right conformation and post-translation modifications and produce a correct protein identical to the native spike protein of the SARS-CoV-2. The presence of the protein, or something resembling it, can provoke the immune system to develop defenses against the virus. Covid-19 vaccines based on this technology have just been disclosed and to be available on market. Because recombinant protein produced in insect cell but not other host systems, are properly folded, glycosylated and methylated. Because the protein could be posttranslational modified, they retain a conformation similar to the native protein; thus, they are not only antigenic but also immunogenic albeit production cost is much higher. Novavax's approach is a typical example of this type and their shot, which is in final-stage testing, has been rolled out in the U.S. in March and has been proved to work safely.

Novavax
- Just announced its approval for distribution in March, 2021
- Doses: 2
- Efficacy: 89% effective (based on results released from a late-stage study in UK), with 49% in South Africa (based on a mid-stage trial)
- Most common side effects: Injection-site pain, fatigue, headache, muscle pain

(4) Synthetic mRNA Coding the Spike Protein of COVID-19 Vaccine

Since the genome composition of the novel Coronavirus (SARS-CoV-2) had been characterized and sequenced,[20,21] functional and pathogenic sequences of the corresponding genes could be identified and cloned.[22] Nucleotide coding the spike protein of COVID-19 has been identified and sequenced, it is now possible to biochemically isolate, characterize,[23] and chemically synthesize these genes.[24] With the help of high throughput screening, it is now possible to properly reconstitute each domain of the spike proteins.[24] Unlike DNA, the mRNA move only from the cell's nucleus to the cytoplasm. Once inside the cell's cytoplasm, the machinery responsible for building proteins, called the ribosome, reads the mRNA and gets to work making proteins. After mRNA is read and the building process begins, the mRNA is quickly destroyed by the cell. Destruction of the mRNA ensures that the cell does not make too much of one type of protein.

The idea behind mRNA vaccines, like the kind developed by Moderna Inc. and Pfizer Inc. for COVID-19, is to insert an mRNA into a cell. The cell would then turn this mRNA into a viral protein. A single viral protein would not be enough to cause the cell harm or the host to become sick. Given the right mRNA and the right protein, however, it may activate the immune response. In this case, the immune system could begin mounting a response and deploying antibodies against the virus without being infected. The body would then be able to easily fight off any subsequent infections quickly because antibodies are already present.

Both Moderna and Pfizer apply the high mobilize immune defenses using mRNA molecules encapsulated in fat envelopes, which they called them lipid nanoparticles (LNP). When LNP injected into a patient, the mRNA is released and enters healthy cells where it helps orchestrate the production of coronavirus spike proteins. Once exported from the cells, the spike proteins prompt the immune system to mount a defense, just as with traditional vaccines.

Contrary to the Pfizer and Modena's approach, AstraZeneca Inc., Russia's Sputnik-V[25] and John & Johnson choose to insert the spike gene of SARS-CoV-2 into the Adenoviral vector, which is initially assumed unharmful and was success in other applications. However, created the COVID-19 vaccine by this platform has turned out to be unfavorable as blood clotting was noted in some people.

Moderna:
- Available in: U.S., Canada, parts of Europe, Israel
- Doses: 2
- Efficacy: 94%
- Most common side effects: Injection-site pain, fatigue, headache, muscle pain

Pfizer-BioNtech:
- Available in: U.S., Canada, Mexico, U.K., parts of Europe and the Middle East, Ecuador and Singapore
- Doses: 2
- Efficacy: 95%
- Most common side effects: Injection-site pain, fatigue, headache, muscle pain

EVOLUTION OF THE VACCINE DESIGN AND PRODUCTION

In general, any vaccine designed and produced requires a bund of considerations and basic inputs, which include the availability of facilities, basic biochemical knowledge of the pathogen, trained manpower, know how skills and techniques of manipulating the pathogen. Depending on the availability of these different supports, a vaccine could be appropriately designed and produced even though all serve the same purpose. Nevertheless, their efficacy, specificity, and production cost could be different. **Figure 3** illustrate the evolution pattern of the design and production from simple method to innovative approach to produce a vaccine. Basically, it follows the path from (A) conventional, (B, C) biotechnological inputs including improvement of culture propagation, harvesting, purification and optimization of biomolecules to be used to mimic antigenic properties and (D, E) the antigens could be bioengineered or chemically synthesized to trim down the molecular size so that only an essential domain is used to trigger immunization. From conventional to synthetic vaccine, whether they are peptide- or nucleic acid-based, increasing weighting on basic biochemical knowledge of the pathogen, know how knowledge and trained personnel are proportionally increased while the production cost at final stage would be reduced. Whatever platform is used, some prerequisite conditions should be ready and available; otherwise, difficulties of vaccine production would be encountered.

ENHANCEMENT OF IMMUNE RESPONSE BY ADDING ADJUVANT TO VACCINE

It has been noted a century ago that the addition of some compounds, subsequently cloned as adjuvants, to a vaccine could boost the prophylactic and therapeutic efficacy of a vaccine by reducing the amount of antigens needed to trigger a durable immune response, eliciting an inflammatory cytokine and chemokine milieu, and polarizing the helper T-cell response along type 1 vs type 2 differentiation pathways. They are mostly required components of both protein subunit and certain inactivated vaccines. Many diverse classes of compounds have been used as adjuvants. These include mineral salts, microbial products, emulsions, saponins, cytokines, polymers, microparticles, and liposomes. Although the mechanisms by which they play are not yet understood, it is generally believed to facilitate uptake and delivery of antigens (e.g., emulsions, microparticles, mineral salts) or an increase in antigen presentation, acquisition of immune cells, and stimulation of the innate immune system via Toll-like receptors (TLR) that function as a warning system against pathogen. Addition of compounds to play these roles are regarded immunostimulant (e.g., saponins, Toll-like receptor agonists, cytokines). The adjuvants utilized in most vaccines, including COVID-19 vaccines, are shown in **Table 2.** From the table, it could be concluded that all sorts of COVID-19 vaccines, except the nonreplicating viral vector type, do have one or a cocktail adjuvant added to enhance their immune response.

PROS AND CONS OF EACH TYPE OF VACCINE

Table 3 is a list of all technology platforms regardless of the platform has been applied successfully or not to develop the COVID-19 vaccines. Except the DNA

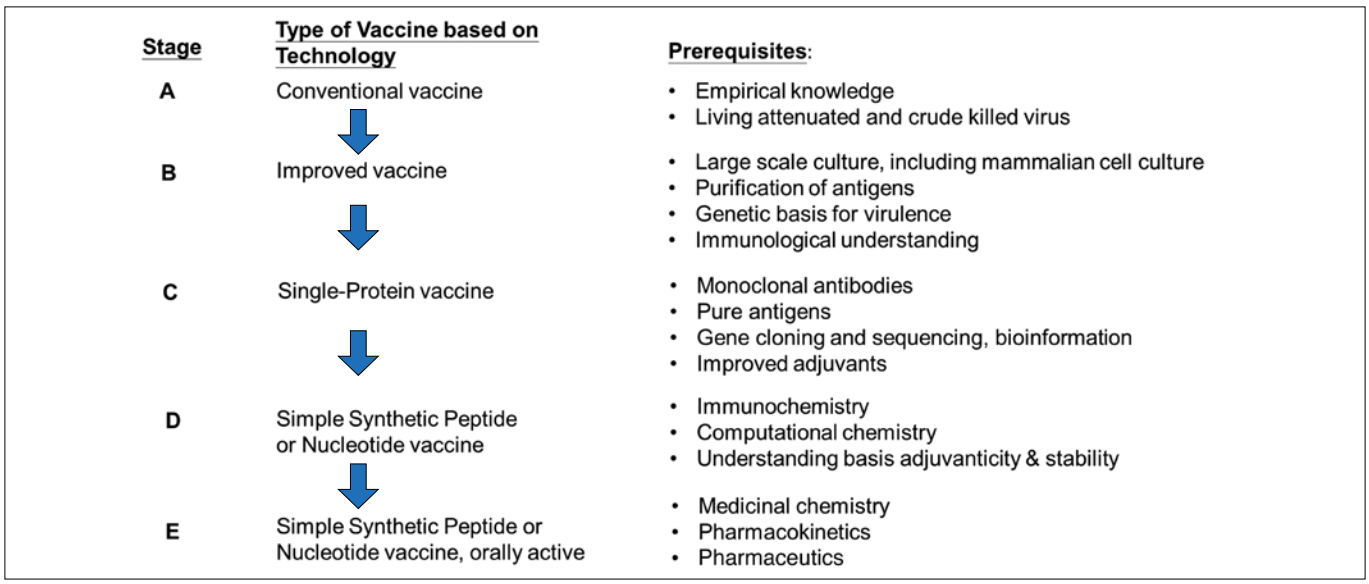

Figure 3. *The evolution path of production of an innovative vaccine*

Table 2. List of compounds used as adjuvant in vaccine[26-28]

Substance	Trade Name	CAS Number	Vaccine	Role Plays in Vaccine
Aluminum hydroxide	Alhydrogel	21645-51-2	Infanrix (DTP), Havrix (Hepatitis A)	--
Aluminum phosphate	AdjuPhos	7784-30-7	Tenivac (tetanus, diphtheria), UB-612 (COVID-19)	--
Aluminum hydroxy-phosphate sulfate	--	150828-31-2	PedvaxHIB (Haemophilus) Gardasil (HPV)	--
Oil-in water emulsion of squalene	MF59	172889-84-8	Fluad (influenza)	Mediate recruitment of immune cells at the injection site. Enhance the release of chemo-attractant like CCL2, CCL3 and CXCL8
Monophosphoryl lipid A and QS-21 saponin	AS01	807365-66-8	Shingrix (herpes zoster)	Promotes both antigen-specific antibodies and CD4 + T cells. CD4 + T cells express many cytokines such as IL-2, TNFα and IFNɣ
Squalene/α-tocopherol/ Tween 80 mixture	AS03	880261-17-6	Pandemrix (influenza), SCB-2019 (COVID-19)	Enhanced recruitment of neutrophils, eosinophils, and monocytes at the site of injection. Antigen trafficking and draining in the lymph node.
Oil-in-water emulsion of squalene	AF03	1244029-44-4	Humenza (influenza)	--
Mixture of saponin	Matrix M	1235341-17-9	NVX-CoV373 (COVID-19)	--
Monophosphoryl lipid A + Aluminum hydroxide	AS04	832690-19-4	Cervarix (HPV)	Induces transient local NFkβ activity and upregulate cytokine production. Up-regulates the pro-inflammatory genes and protein expression (IL-1, IL-6, IL-12, IL-18, and TNF-a)
Glucopyranosyl Lipid A	GLA-SE	1246298-63-4	ID93 (tuberculosis)	--
Phosphorothioate oligodeoxyribonucleotide	CpG 1018	937402-51-2	Heplisav-B (hepatitis B), SCB-2019 (COVID-19), MVC-COV1901 (COVID-19)	Targets TLR9, stimulate CD4 + and CD8 + T cells, Th1 helper T cells.
Inulin	Advax	9005-80-5	COVAX-19 (COVID-19)	--
Potaaium aluminum sulfate	Alum	10043-67-1	N.A.	Promote Th2 type immune responses. Robust antibody production and β-cell differentiation.
Imidazoquinoline derivatives	3M-052	1359993-59-1	N.A. (HIV, tumor)	--
Squalane-in-water emilsion of sucrose fatty acid sulfate ester	CoVaccine HT	872176-43-7	CiVax (COVID-19)	--
Water-in-oil emulsion of mannide monooleate surfactant	Montanide ISA-51	190396-06-6	Galinpepimut-S (mesothelioma)	--

big-data computation, simple molecules or epitopes of protein could be synthesized. The table also summarizes the pros and cons of each technology.

and the nonreplicating viral vector platform, all other platforms have been successfully applied in COVID-19 vaccine production. It should be highlighted that live-attenuated technique is the longest well established and easy method to produce vaccine, while synthetic method to produce simple biomolecules requires some prerequisite knowledge and conditions. Nevertheless, the latter one is fast and flexible to produce once background information is available. With helps of bioinformatics and big data computation, simple molecules or epitopes of protein could be synthesized. Details of pros and cons of each production technology could be found in the table .

Table 4 summarizes the key features of ten selected COVID-19 vaccine candidates that have been conditionally approved by at least one country. It displays all pharmaceutical and biochemical aspects of each vaccine. As some of them have not completed Phase-III clinical studies, information is extracted from press or major media instead from official source. Hence, they could be revised subsequently when time pass. As revealed in the table, vaccines produced by different technology platforms have different levels of effectiveness during testing, and different side effect risks. Among the Covid-19 vaccines currently produced, mRNA vaccines seem to display the highest efficacy rates during late-stage testing.

It must point out that mRNA molecules are very unstable at room temperature and subjected to enzymatic degradation, they have to be kept at very low temperature before use. They are packaged in nanoparticles or protected by a lipid coating to give a longer shelve life and good uptake by the body after intra-muscular injection. The requirement to keep the vaccine prior for use cause some financial burden and inflexible to some underdeveloped countries.

Table 3. Production platforms of vaccine based on biomolecular nature of their content*			
Platform Based on Molecular Nature	**Advantages**	**Disadvantages**	**Successfully Developed Vaccine**
Live-attenuated	• Strong and long-lasting immune response • Broad antigenic profile	• Potential risk of disease • Requirement for biosafety facilities	Measles, Polio (OPV), Smallpox, Tuberculosis (BCG)
Inactivated	• Broad antigenic profile	• Reduced immune response • Requirement of biosafety facilities • Lower purity	Hepatitis A, Influenza, Polio, Rabies
Viral lipid protein	• Noninfectious • Broad antigenic profile	• Limited immunogenicity • Lower purity	Hepatitis B (HBV), Papillomavirus (HPV)
Replicating viral vector	• Fast to produce • Lower doses/single dose • Reusable platform • Strong in both cell- and antibody-mediated immune response • Less infectious	• Pre-existing against the vector • Risk of adverse reactions	Ebola (EUA)
Nonreplicating viral vector	• Fast to produce • Reusable platform • Strong in both cell- and antibody-mediated immune response	• Pre-existing immunity against the vector • Risk of adverse reactions	N.A.
DNA	• Fast to produce • Scalable • Noninfectious • Reusable platform • Stable at room temperature	• May need special delivery devices	N.A.
Protein subunit	• Noninfectious • Targeting key antigens	• Limited capability in inducing cell-mediated immunity • Challenges in large-scale production • Adjuvant often needed	Hepatitis B (HBV), DTP (diphtheria, tetanus, and pertussis)
mRNA	• Fast to produce • Noninfectious • No genome integration risk • Reusable platform • Stimulates strong T cell response • Simple formulations	• May need extremely low temperature for storage and transportation • May need special delivery system	COVID-10 (EUA)

* Adopted and modified from Li et al[28]

Both recombinant subunit protein and RNA are macromolecules albeit non-pathogenic and safe. Contrary, non-replicating viral vaccines designed by all three companies are reported to cause cerebral venous sinus thrombosis or blood clotting and even incidence of death for one brand ten days after receiving this type of vaccine.

CONCLUSION

Since the beginning of the COVID-19 pandemic caused by SARS-CoV-2 sixteen months ago, this world has taken significant efforts to cope with the disease, from increasing personal protection equipment production and emphasizing the important of social distancing and masking to the limited approval of emergency use of remdesivir. However, the disease is still spreading in a relentless mode and has caused widespread health, social, and economic disruption. Therefore, effective vaccines are urgently needed to end this pandemic and help the society return to normal. Indeed, many COVID-19 candidate vaccines have been designed, developed, tested and evaluated at an unprecedented speed. As of the end of March 2021, at least ten of them have been conditionally approved, and used for immunization **(Table 4)**.

The fact that around a dozen of COVID-19 vaccines entered phase III clinical trials in less than a year and have been conditionally approved for use is a record-breaking speed in vaccine development history. This unprecedented speed is facilitated by the timely release of the viral genomic sequence from helps of next-generation sequencing technology, the availability of various vaccine technology platforms,[29] concert efforts among the scientific community, great financial supports from government as well as the huge and urgent demand. Of all the COVID-19 vaccines explored, only those have been granted approval for use are mentioned and described **(Table 3)**, whereas a candidate not proceeded beyond phase I are not included. As shown in the table, candidate vaccines are listed from top to bottom according to the order of technological evolution; i.e. the lower in the table the more innovative. For more detail description of the whole array of technology platform, two review articles written by Krammer[13] and by Li et al[28] are, in particular, recommended. Although not all these platforms offer a candidate vaccine equal success opportunity to come to the final stage of approved use, the exploration of COVID-19 vaccine has already covered most of these different technology applications. Hence, it is a good learning model for comprehension of the different approaches; each of them has some advantages and disadvantages.

Table 4. List of COVID-19 vaccine candidates with conditional approval granted or in phase-III clinical trials

Technology Platform	Vaccine Name	Storage (ºC)	Efficacy (%)	Reported Death after Vaccination[b] (Death per Million Vaccination)	Lead Developer
Inactivated viral	CoronaVac[a]	2-8	50.7	20 in HK (N.A.)	Sinovac
	BBIBP-CorV	2-8	79.3	(N.A.)	Sinopharm
	BBV152	2-8	N.A.	(N.A.)	Bharat Biotech
Nonreplicating viral vector	AZD1222	2-8	70.4	813, most due to blood clotting (8.8)	AstraZeneca/Oxford University
	Convidecia	2-8	65.3	(N.A.)	CanSino Biologics
	JNJ-78436735	2-8	66	54 (U.S alone), most due to blood clotting (7.5)	Johnson & Johnson
	Sputnik-V	-20 (liquid) 2-8 (powder)	91.6	(N.A.)	Gamaleya Research Institute
Protein subunit	NVX-CoV2373	2-8	89.7	(N.A.)	Novavax
Synthetic mRNA	BNT162b2[a]	-70	95	2485, 3 in Hong Kong (16)	Pfizer/BioNTech
	mRNA-1273[a]	-20 to -70	94.1	1275 (13.6)	Moderna

[a] Phase IV clinical trial in progress; [b] data up to 19 April, 2021 based on global reported death after vaccination in 12 countries (Source: CDC); N.A. = not available

Author's background

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References

1. Coronavirus. Human coronavirus types. CDC. https://www.cdc.gov/coronavirus/types.html. Accessed on 20210418.
2. Weiss SR, Leibowitz JL. (2011). Coronavirus pathogenesis. *Advance in Virus Research,* 81:85-164.
3. Masters PS, Perlman S. (2013). Coronaviridae. In: Knipe DM, Howley PM, eds. *Fields virology*. 6th ed. Lippincott Williams & Wilkins, p825-58.
4. Zhu N, Zhang DY, Wang WL, Li X, Yang B, et al (2020). A novel coronavirus from patients with pneumonia in China, 2019. *New England Journal of Medicine,* 382:727-733.
5. Wang HH, Li XM, Li T, Zhang SB, et al. (2020). The genetic sequence, origin, and diagnosis of SARS-CoV-2. European Journal of Clinical Microbiology & Infectious Diseases, https://doi.org/10.1007/s10096-020-03899-4.
6. WHO, COVID-19 Weekly Epidemiological Update. https://www.who.int/emergencies/diseases/novel-coronavirus-2019. Accessed on 20210418.
7. ElBagoury M, Tolba MM, Nasser HA, Jabbar A, et al. (2021). The find of COVID-19 vaccine: challenges and opportunities. *Journal of Infection and Public Health,* 14:389-416.
8. Vitenu-Sackey A, Barfi R. (2021). The impact of COVID-19 pandemic on the global economy: emphasis on poverty alleviation and economic growth. *The Economics and Finance Letters,* 8(1):32-43.
9. Research Office of Legislative Council Secretariat of Hong Kong. (2020). Challenges and economic impacts arising from coronavirus disease 2019. *Research Brief,* 2020-2021(1):1-39.
10. WHO, Coronavirus disease (COVID-19) Advice for the public: Mythbusters. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/advice-for-public/myth-busters. Accessed on 20210418.
11. Kuleshov MV, Stein DJ, Clarke DJB, Kropiwnicki E, et al. (2020). The COVID-18 drug and gene set library. *Patterns*, 1:100090.
12. Flaherty KT, Hodi FS, Fisher DE. (2012). From genes to drugs: targeted strategies for melanoma. *Nature Review of Cancer,* 12(5):349-361.
13. Krammer F. (2020). SARS-CoV-2 vaccines in development. *Nature*, 586:516-527.
14. Shin MD, Shukla S, Chung YH, Beiss V, et al. (2020). COVID-19 vaccine development and a potential nanomaterial path forward. *Nature Nanotechnology*, 15:646-655.
15. Wang Y, Zhang D, Du G, et al.(2020). Remdesivir in adults with severe COVID-19: a randomized, double-blind, multicentre, controlled trial. *Lancet*,395(10236):1569–1578.
16. Saint-Raymond A, Sato J, Kishioka Y, Teixeira T, et al. (2020). Remdesivir emergency approvals: a comparison of the U.S., Japaneses, and EU systems. *Expert Review of Clinical Pharmacology,* 13(10):1095-1101.
17. Cohen J, Kupferschmidt K. (2020). The "very, very bad look" of remdesivir, the first FDA-approve3d COVID-19 drug. *Science*, October 28. doi:10.1126/science.abf4549.
18. Grigoryan L, Pulendran B. (2020). The immunology of SARS-CoV-2 infections and vaccines. *Seminars in Immunology,* 50:101422.
19. Peck FB, Powell HM,Culbertson CG. (1956). Duck-embryo rabies vaccine: Study of fixed virus vaccine grown in embryonated duck eggs and killed with beta-propiolactone (BPL). *Journal of America Medical Association,* 162 (15):1373-1376.
20. Wu AP, Peng YS, Huang BY, Ding X, et al. (2020). Genome composition and divergence of the novel Coronavirus (2019-nCoV) originating in China. *Cell Host & Microbe,* 27:1-4.
21. Pfefferle S, Huang JB, Nörz D, Indenbirken D., et al. (2020). Complete genome sequence of a SARS-CoV-2 strain isolated in Northern Germany. *Microbiology*, 9(23):e00520-20.
22. Verma J, Subbarao N. (2021). A comparative study of human betacoronavirus spike proteins: structure, function and therapeutics. *Archives of Virology,* 166:697-714.
23. Lu J, Lu GL, Tan SD, Xia J., et al. (2020). A Covid-19 mRNA vaccine encoding SARS-CoV-2 virus-like particles induces a strong antiviral-like immune response in mice. *Cell Reseaarch*, 30:936-939.
24. Nagata S, Hamasaki T, Uetake K, Masuda H, et al. (2010). Synthesis and biological activity of artificial mRNA prepared with novel phosphorylating reagents. *Nucleic Acids Research,* 38(21):7845-7857.
25. Baraniuk C. (2021). Covid-19: What do we know about Sputnik V and other Russian vaccines? British Medical Journal, 372:n743.
26. Sharma R, Palanisamy A, Dhama K, Mal G, et al. (2020). Exploring the possible use of saponin adjuvants in COVID-19 vaccine. *Human Vaccines & Immunotherapeutics,* https://doi.org/10.1080/21645515.2020.1833579
27. Liang ZH, Zhu HR, Wang X, Jing B, et al. (2020). Adjuvants for coronavirus vaccines. *Frontiers in Immunology,* 11:589833.
28. Li YZ, Tenchov R, Smoot J, Liu C, et al. (2021). A comprehensive review of the global efforts on COCID-19 vaccine development. ACS Central Science, https:///doi.org/10.1021/acscentrsci.1c00120.
29. Le TT, Andreadakis Z, Kumar A, Román RG. (2020). The COVID-19 vaccine development landscape. Nature Reviews, 19:305-306.

The Society of Hospital Pharmacists of Hong Kong (SHPHK) – To vaccinate or not to vaccinate?

Happy New Year of the Ox!

The roll out of the COVID-19 Vaccination Programme in Hong Kong gives us hope of return to normal life. Although we still need to wear the face mask for a certain period of time after vaccination, we are at least one step closer to the end of this devastating pandemic.

Debunking COVID-19 Vaccine Myths - The Importance of Education

In the past few months, there have been quite a lot of myths regarding different types of COVID-19 vaccines going around on the internet. Some citizens have seemed hesitant about getting vaccinated against COVID-19 due to the fear of experiencing serious side effects after vaccination. In view of this, the Drug Education Resources Centre (DERC) has recently launched a brand-new column namely 「新冠肺炎疫苗最新資訊」in its website. In the column, different fact sheets regarding COVID-19 vaccines in both Chinese and English could be found and downloaded for further dissemination.

The Society hopes that the COVID-19 Vaccine Fact Sheets could help empower the general public to have sufficient vaccine literacy, so that they are able to make the right decision regarding COVID-19 vaccination to safeguard their own health.

To download the fact sheets, please follow the instructions below: www.derc.org.hk > 新醫藥透視 > 新冠肺炎疫苗最新資訊

Press Conference: Sharing of Frontline Experience by Specialist Pharmacists in Immunisations and Travel Medicine from the United Kingdom (U.K.)

On 21 February 2021, just about a week before the official commencement of the Hong Kong COVID-19 Vaccination Programme, SHPHK and the Hong Kong Society for Immunisations and Travel Medicine (HKSITM) jointly organised a press conference to analyse the difference between the arrangements of the Hong Kong and the U.K. Community Vaccination Centres, and make recommendations for the Hong Kong COVID-19 Vaccination Programme.

In the long run, both societies suggested that the Hong Kong Government could make reference to the practice in the U.K., to allow trained community pharmacists to provide vaccination service to the general public. This not only improves public access to vaccination, but also helps increase the overall vaccination rate in the community.

SHPHK Educational Events

A webinar on Migraine and Secondary Progressive Multiple Sclerosis was successfully held on 29 January 2021. More than 80 pharmacists from the public and private hospitals joined us in the webinar!

In the coming months, the Society will continue to organise different online educational events on various topics, including asthma, chronic obstructive pulmonary disease, biotechnology, age-related macular degeneration etc. Please stay tuned!

SHPHK Website Revamp

The new SHPHK website is coming soon!

The working group of the SHPHK website revamp project is pleased to announced that the first phase of the SHPHK website revamp will be completed by Q2 2021.

The whole website revamp project consists of two phases. The first phase of the project focuses on the development of the following webpages and subpages: About Us, Society News, Events and Resources; whereas the second phase of the project focuses on the development of the membership database.

In the future, members can enroll for SHPHK activities online. All previous SHPHK educational events will also be available on the new website for members' archive. In addition, members may renew their membership with SHPHK online and track their progress of continuing

professional development through logging into their own SHPHK account.

More information regarding the new SHPHK website will be announced in due course!

You are most welcome to follow the Society's Facebook page (@SHPHK) to know more about the Society's development and activities. You may also visit the Drug Education Resources Centre (DERC) Website: www.derc.org.hk to keep abreast of the latest news and development of pharmaceutical services in Hong Kong. Join us now as new member or renew your membership at the Society's website: www.shphk.org.hk.

Activities of the Pharmaceutical Society of Hong Kong

Immunisation Training Programme for Registered Pharmacists

PSHK always strives to provide the best training to equip the pharmacists ready for opportunities. This year PSHK has organized vaccination training for pharmacists in order to let the profession be well prepared for COVID-19 and flu vaccine administration. We had the pleasure to invite the Department of Pharmacology and Pharmacy of the University of Hong Kong for organising the Immunisation Training Programme for Registered Pharmacists between the period of January to March 2021, with 4 training workshops in total.

Advancing Hong Kong Pharmacy Profession Development – Local Continuing Education Programme

PSHK launched a Continuing Education (CE) programme. This programme is funded by the Professional Services Advancement Support Scheme, the Commerce and Economic Development Bureau, the Government of HKSAR. Pharmacists practicing in all sectors can expect to gain fruitful knowledge. This programme consists of 12 training sessions of different topics, focusing on pharmacotherapy for elderly.

The 5th training session of the programme has been successfully held, the following are the finished training sessions:

Training Session	Speaker
Osteoporosis screening and management	Dr. Tai-Pang IP
Endocrine disorders in the older adults	Dr. Tai-Pang IP
Ophthalmologic disorders	Dr. YUEN Kwok Lai Hunter Dr. Dexter Yu-lung LEUNG Dr. PONG Chiu Fai, Jeffrey
Introduction of Chinese Medicine's Treatment on Common Skin Diseases in Hong Kong	Dr. Csaryne Wan
Gastrointestinal diseases	Dr. Fok Ka Lung Dr. But Yiu Kuen, David

PSHK would like to take this opportunity to express our sincere gratitude to the above speakers for spending their precious time and the excellent sharing of their knowledge in the programme. Moreover, we would like to thank all pharmacists who participated and supported our programme. More and more interesting topics are coming soon this year, please stay tuned!

2021 General Council of the Pharmaceutical Society of Hong Kong and the Pharmaceutical Society Charitable Foundation Limited

We are pleased to announce that the Annual General Meeting of The Pharmaceutical Society of Hong Kong (PSHK) and The Pharmaceutical Society Charitable Foundation Limited (PSCF) has been held at PSHK Clubhouse on 17th December 2020. The following members were elected for the tenure from 17th December, 2020 onwards for 2020-2021 term.

President:	Mr. Dick SUNG (PPB member)		
Vice-presidents:	Ms. Beverley TAM (PPB member)	Mr. Edward YAU	
Hon. Secretary:	Mr. Jonathan NG		
Hon. Treasurer:	Mr. Paul LAM		
Council Members:	Mr. CHEUNG Wai Keung	Ms. Kathleen KUNG	Ms. PONG Scarlett Oi Lan, BBS, JP
	Ms. CHEW Leng Leng	Mr. Vincent LAU	Ms. Sandra TSANG
	Ms. Carmen FONG	Mr. Rex NG	Mr. Edwin WONG
Pharmacy & Poisons Board Members:	Mr. Rico YAU (till 16th August 2021)		

Active Ingredient:
lisdexamfetamine dimesylate

Pharmacological Properties:
Lisdexamfetamine is a prodrug of dextroamphetamine. Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. The exact mode of therapeutic action in ADHD is not known.

Amphetamines block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space. The parent drug, lisdexamfetamine, does not bind to the sites responsible for the reuptake of norepinephrine and dopamine *in vitro*.

Indications:
VYVANSE™ is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

Limitation of Use:
VYVANSE is not indicated or recommended for weight loss. Use of other sympathomimetic drugs for weight loss has been associated with serious cardiovascular adverse events. The safety and effectiveness of VYVANSE for the treatment of obesity have not been established.

Contraindication:
Known hypersensitivity to amphetamine products or other ingredients of VYVANSE.Anaphylactic reactions, Stevens-Johnson Syndrome, angioedema, and urticaria have been observed in post-marketing reports.

Patients taking monoamine oxidase inhibitors (MAOIs), or within 14 days of stopping MAOIs (including MAOIs such as linezolid or intravenous methylene blue), because of an increased risk of hypertensive crisis.

Dosage Forms and Strengths:
- Capsules 20 mg: ivory body/ivory cap (imprinted with S489 and 20 mg)
- Capsules 30 mg: white body/pink cap (imprinted with S489 and 30 mg)
- Capsules 50 mg: white body/blue cap (imprinted with S489 and 50 mg)

Dosage for Treatment of ADHD:
The recommended starting dose is 30 mg once daily in the morning in patients ages 6 and above. Dosage may be adjusted in increments of 10 mg or 20 mg at approximately weekly intervals up to maximum dose of 70 mg/day.

Dosage in Patients with Renal Impairment:
In patients with severe renal impairment (GFR 15 to < 30 mL/min/1.73 m2), the maximum dose should not exceed 50 mg/day. In patients with end stage renal disease (ESRD, GFR < 15 mL/min/1.73 m2), the maximum recommended dose is 30 mg/day.

Dosage Modifications due to Drug Interactions:
Agents that alter urinary pH can impact urinary excretion and alter blood levels of amphetamine. Acidifying agents (e.g., ascorbic acid) decrease blood levels, while alkalinizing agents (e.g., sodium bicarbonate) increase blood levels. Adjust VYVANSE dosage accordingly.

Pediatric Use
Safety and effectiveness have been established in pediatric patients with ADHD ages 6 to 17 years.

Safety and efficacy in pediatric patients below the age of 6 years have not been established.

Geriatric Use
Clinical studies of VYVANSE did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Administration
Swallow VYVANSE capsules whole, or

Open capsules, empty and mix the entire contents with yogurt, water, or orange juice.

Do not take anything less than one capsule per day. A single dose should not be divided.

Forensic Classification:
P1S1S3

Hong Kong Pharmaceutical Journal: For Detailed Instructions for Authors

INTRODUCTION

Hong Kong Pharmaceutical Journal (HKPJ) is the official publication of the Pharmaceutical Society of Hong Kong, the Practising Pharmacists Association of Hong Kong and the Society of Hospital Pharmacists of Hong Kong. It is a journal of the pharmacists, for the pharmacists and by the pharmacists. The Journal is currently divided into several sections: ***Editorial Comment; News & Short Communications; Pharmacy Practice; Over-the-Counter & Health; Drugs & Therapeutics; Primary Care; Herbal Medicines & Nutraceuticals; Pharmaceutical Technology*** and ***New Products***. It publishes review articles or original papers relevant to these different fields of pharmacy. In addition to the regular four issues of the Journal per year, there are issues dedicated solely to reports on special function of the society. The Aims and Scope of the Journal are published on the inside back cover of each issue.

Submission of Manuscript

Submission of a paper implies that it has not been published previously, that it is not under consideration for publication elsewhere, and that if accepted it will not be published elsewhere in the same form, in English or in any other language, without the written consent of the publisher. Authors are specifically discouraged from submitting papers as fragmented studies of a particular topic. A manuscript must be indicated which section it is belonged. Upon received, it will be screened by a **Sectional Editor** of HKPJ for initial consideration before it is sent out for further review or comment.

For online submission:
Authors are encouraged to submit manuscripts using the online submission system. Access to the system, and full instructions on its use, can be found on the HKPS website at: http://www.HKPS.org/HKPJ/Guidelines. In creating the electronic version of their manuscript, authors are requested to follow the guidelines for submitting files. The paper should be submitted as a single file, prepared with a standard word-processor such as Microsoft Word, with embedded tables and graphics. Please note that any embedded graphics must also be submitted as separate, original files. The preferred formats for graphics files are tiff or postscript. All correspondence between Editor and author is performed by email. Authors are reminded that the copyright of their article or paper is automatically transferred to HKPJ once it is accepted for publication in the journal.

For hardcopy submission:
Three copies of the manuscript are required on either 8.5"x11" or A4 paper (two copies are used for review purposes and the original is kept on file at the Section Editor). Copies must be produced on a high-quality printer, and originals and copies of all Figures and Schemes must be fully legible. Initially only send hard copies of the paper; when it has been refereed, revised if necessary, and accepted, you will be requested to send a disk containing the final version with the final hard copy to the appropriate Editor. Make sure that the disk and the hard copy match exactly. The revised manuscript must be returned to the Editors within one month, otherwise it may be deemed to be new and subject to further review. When submitting the final version with a disk please label all disks with "HKPJ", your name, software (e.g. word 2000), hardware used (e.g. PC or Macintosh) and file names with the correct extension (e.g. Fig 1.cdx, Table 1-6. xls). Save text on a separate disk from the graphics, include the text and tables in one file, and provide graphics and structures in separate numbered files. Please remember to keep a backup copy of both the electronic files and original manuscript for reference and safety since we cannot accept responsibility for damage or loss of papers. Original manuscripts are discarded three months after publication unless the Publisher is asked to return original material after use.

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Please submit, with your manuscript, the names and addresses of 2 potential referees. You may also mention persons who you would prefer not to review your paper.

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The Editors of HKPJ reserve the right to make alterations to manuscripts submitted for publication. Such alterations will be made if manuscripts do not conform with accepted scientific standards or if they contain matter which in the opinion of the Editors is unnecessarily verbose or unclear. Alterations may be queried, but this will inevitably delay publication.

Preparation of manuscript

The manuscript is required to be written in English, with numbered pages, single-spaced, using Arial 9 point font, and in a suitable word-processing format. Each page should have adequate margins (4 cm) and liberal spaces at top and bottom of the manuscript. All textual elements should begin flush left, with the second paragraphs onwards indent, and should use the wrap-around end-of-line feature, i.e. no returns at the end of each line. Place two returns after every element such as title, headings, paragraphs, figure and table call-outs. Most formatting codes will be removed or replaced on processing your article. Please do not use options such as automatic word breaking, justified layout, double columns or automatic paragraph numbering (especially for numbered references). However do use bold face, italic, subscripts, superscripts etc. The Editors reserve the right to adjust style to certain standards of uniformity. If authors are unfamiliar with HKPJ, they should consult a recent copy (or the free online sample copy available from www.HKPS.com/HKPJ) to see the conventions currently followed for guidance in preparing submissions.

The content of manuscripts must be arranged as follows: (1) a Title Page with authors name(s) and address(es); (2) an Abstract, in which contents are briefly stated; (3) a 4 to 6 Key Word Index, (4) Introduction, and (5) the Results and Discussion (preferably combined). Although each section may be separated by headings, they should form one continuous narrative and only include details essential to the arguments presented. If a discussion is separately provided, it should not include a repetition of the results, but only indicate conclusions reached on the basis of them, and those from other referred works; (6) Conclusions or Concluding Remarks; (7) the Experimental should include brief details of the methods used such that a competent researcher in the field may be able to repeat the work; (8) Acknowledgments; (9) References; (10) Legends, Formulae, Tables and Figures.

Title Page and Author Names: Titles must be as brief as possible, consistent with clarity, and should not exceed 10 words in length. Uninformative phrases such as "Chemical examination of", "Studies on", "Survey of", "New", "Novel" etc. will be deleted. If a paper is part of a series, this must not be given in the heading, but referred to in a footnote in the form: *Part 9 in the series "The Role of Pharmacists in Medical Care of Patients" followed by a numbered reference to the previous part. Author names should be typed right underneath the article title. Each author should identify himself or herself with Surname in capital letters, followed by the first name. All names are separated by a semicolon (;). An asterisk should be placed following the name of the author to whom correspondence inquiries should be made. Full postal addresses must be given for all co-authors. Superscript letters; a, b, c should be used to identify authors located at different addresses.

An **Author's background box** at the end of each article is mandatory to include the author's job title and the affiliated institutle or organization. Full details of telephone, fax numbers and e-mail address should also be indicated for the corresponding authors. No academic or professional membership title is allowed.

ABSTRACT: The abstract should be on a separate page and briefly describe the results obtained and conclusions reached, not the methods used, or speculations on any other matter. They are not expected to be a complete summary but only an outline of the main findings. The abstract should be contained within 250 words and should be readable without reference to the rest of the paper.

Key Words: Authors must give four to six "key words" or phrases, which identify the most important subjects covered by the paper.

INTRODUCTION should give the minimum historical data needed to give appropriate context to the author's investigation and its relationship to other similar research previously or currently being conducted. Only information essential to the arguments should be presented. Much data can be taken for granted or quoted in abbreviated form. Specific term (genus, species, authority) of all experimental works must be given at first mention and preferably be in the form adopted by the International Scientific Community.

RESULTS AND DISCUSSION: These sections should be carefully prepared with discussions of the results being compared with existing and/or previous knowledge within the field. Authors are, however, encouraged to combine the Results and Discussion sections wherever possible.

EXPERIMENTAL: Subsections on the Experimental Procedures should be italicized and inserted as part of the first line of the text to which they apply. HKPJ encourages an extensive use of abbreviations (these are listed at the back of the Instructions to Authors, or the reader is referred to other sources). The Experimental should begin with a subsection entitled General Experimental Procedures. This subsection will typically contain brief details of instruments used, and identification of sources of specialized chemicals, biochemicals and molecular biology kits. The next subsection describes the source(s) and documentation of biological materials used, whether in reference to whole plants or parts there from, crude drugs, or any other plant material from which identifiable chemical substances are obtained for the first time. Documentation must also include a reference to voucher specimen(s) and voucher number(s) of the compounds, plants or other material examined. If available, authors should quote the name and address of the authority who identified each sample investigated. Specimens should preferentially be deposited in a major regional herbarium where the collection is maintained by state or private institution and which permits loan of such materials. With other microorganisms, the culture collection from which they were either accessed and/or deposited should be included, together with identification of the strain designation code. The Experimental Procedures employed should be concise but sufficiently detailed that a qualified researcher will be able to repeat the studies undertaken, and these should emphasize either truly new procedures or essential modifications of existing procedures. Experimental details normally omitted include: (I) method of preparation of common chemical and biochemical derivatives, (2) excessive details of separation of compounds, proteins and enzymes, e.g. preparation of columns, TLC plates, column and fraction size. Compound Characterization: Physical and spectroscopic data for new compounds must be comprehensive, and follow the order shown below: compound name (and assigned number in text); physical state of compound (e.g. oil, crystal, liquid, etc.), melting and/or boiling point; optical rotation and/or circular dichroism measurements, if optically active; UV; JR, IH NMR; 13C NMR; MS. For all new compounds, either high-resolution mass spectral or elemental analysis data is required. See later section for method of data presentation.

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ACKNOWLEDGMENTS: This section is used to provide brief credit for scientific and technical assistance, and in recognition of sponsorship through financial support and any other appropriate form of recognition.

References: All publications cited in the text should be presented in a list of references following the text of the manuscript. In the text refer to the author's name (without initials) and year of publication (e.g. "Since Peterson (1993) has shown that ..." or "This is in agreement with results obtained later by Kramer.[4]" For two authors both authors are to be listed, with "and" separating the two authors. For more than two authors, use the first author's surname followed by et al. The list of references should be arranged according to the order of their appearance in the text with no more than three authors listed. If number of authors of a reference exceeds three, "et al" is used followed by year of publication in bracket after the first author. Journal titles should be completely shown followed by the volume, issue number in bracket if included, colon and start – final page number. The manuscript should be carefully checked to ensure that the spelling of authors' names and dates are exactly the same in the text as in the reference list. Some examples of references are shown below:

(1) Cabello-Hurtado F, Durst F, Jorrin JV, Werck-Reichhart D. et al. (1998). Coumarins in Helianthus tuberosus: characterization, induced accumulation and biosynthesis. *Biochemistry,* 49(1):1029-1036.

(2) Mabry T, Markham KR, Thomas MB. (1970). *The Systematic Identification of Flavonoids.* 2nd Ed, pp. 79-105. Springer Verlag, New York.

(3) Harborne JB. (1999). Plant chemical ecology. In: Barton D, Nakanishi K, Meth-Cohn 0, (Eds.), *Comprehensive Natural Products Chemistry,* Vol. 8. pp. 137-196. Pergamon, Oxford.

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Errata and Corrigenda to publish articles will be included, at the discretion of the Section Editors and the publisher.

Abbreviations
About, approximately: ca.
Anhydrous: dry (not anhyd.)
Aqueous: aq.
Circular dichroism: CD
Concentrated (or mineral acids): conc.
Concentrations: ppm (or ppb), μM, mM, M, %, mol
Dry weight: dry wt; fresh weight: fr. wt
Electricity: V, mA, eV
Force due to gravity (centrifugation): g; rpm (revolutions min^{-1})
Gas chromatography: GC
Gas chromatography-mass spectrometry: GC-MS Trimethylsilyl derivative: TMSi (TMS cannot be used as this refers to the internal standard tetramethylsilane used in ^{1}H NMR)
High performance liquid chromatography: HPLC
Infrared spectrophotometry: IR
Length: nm, μm, mm, cm, m
Literature: lit.
Mass spectrometry: m/z $[M]^{+}$ (molecular ion, parent ion)
Melting points: uncorr. (uncorrected)
Molecular mass: Da (daltons), kDa
Molecular weight: M_r
Nuclear magnetic resonance: ^{1}H NMR, ^{13}C NMR, Hz, δ
Numbers: e.g. 1, 10, 100, 1000, 10000; per or $^{-1}$
Optical rotatory dispersion: ORD
Paper chromatography: PC
Precipitate: ppt.
Preparative thin-layer chromatography: prep. TLC
Radioactivity: dpm (disintegrations per min), Ci (Curie), sp. act (specific activity), Bq (1 becquerel = 1 nuclear transformation sec^{-1})
Repetitive manipulations: once, twice, x3, x4, etc.
RR_t (relative retention time), R_1 (Kovat's retention index), ECL (equivalent chain length- term frequently used in fatty acid work)
Saturated: satd.
Solution: soln.
Solvent mixtures including chromatographic solvents: abbreviate as follows n-BuOH-HOAc-H_2O (4:1:5)
Statistics: LSD (least significant difference), s.d. (standard deviation), s.e. (standard error)
Temperature: (with centigrade), mp, mps, mmp, bp
Temperature: temp.
Thin-layer chromatography: TLC, R_f
Time: s, min, h, day, week, month, year
Ultraviolet spectrophotometry: UV, A (absorbance, not aD-optical density)
Volume: 1, (litre), μ1, ml
Weight: wt, pg, ng, μg, mg, g, kg

Inorganics, e.g. $AlCl_3$ (aluminum chloride), BF_3 (boron trifluoride), Cl., CO_3, H_2, HCl, $HClO_4$ (perchloric acid), HNO_3. H_2O, H_2O_2, H_2SO_4, H_3B0_3 (boric acid), He, $KHCO_3$ (potassium bicarbonate), $KMn0_4$ (potassium permanganate;), KOH, K-Pi buffer (potassium phosphate buffer), $LiAlH_4$ (lithium aluminium hydride), Mg^{2+}, $MgCl_2$, N_2, NH_3, $(NH_4)_2S0_4$, Na^{+}, $NaBH_4$ (sodium borohydride), NaCl, $NaI0_4$ (sodium periodate), NaOH, Na_2S0_3 (sodium sulphite), Na_2S0_4 (sodium sulphate), $Na_2S_20_3$ (sodium thiosulphate), 0_3, PPi (inorganic phosphate), SO_4^{2-}., Tris (buffer).

Organics, e.g. Ac_20 (acetic anhydride), n-BuOH (butanol), C_6H_6 (benzene), CCl_4 (carbon tetrachloride), CH_2Cl_2 (methylene chloride), $CHCl_3$ (chloroform), CH_2N_2 (diazo-methane), CM (carboxymethyl), DEAE (diethylaminoethyl), DMF (dimethylformamide), DMSO (dimethyl sulphoxide), EDTA (ethylene-diaminetetra-acetic acid), Et_20 (diethyl ether), EtOAc (ethyl acetate), EtOH (ethanol), $HC0_2H$ (formic acid), HOAc (acetic acid), iso-PrOH (iso-propanol), Me_2CO (acetone), MeCOEt (methyl ethyl ketone), MeOH (methanol), NaOAc (sodium acetate), NaOMe (sodium methoxide), petrol (not light-petroleum or petroleum ether), PhOH (phenol), PrOH (propanol), PVP (polyvinylpyrrolidone), TCA (trichloroacetic acid), TFA (trifluoroacetic acid), THF (tetrahydrofuran). ^{1}H NMR solvents and standards: $CDCl_3$ (deutero-chloroform), D_2O, DMSO-d_6 [deuterodimethylsulphoxide not $(CD_3)_2S0$], pyridine-d_5 (deuteropyridine), TMS (tetramethylsilane).

For further terms used in biochemistry and molecular biology the authors should see the websites of the nomenclature committees (www.chem.qmul.ac.uk/iubmb/).

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(lisdexamfetamine dimesylate)

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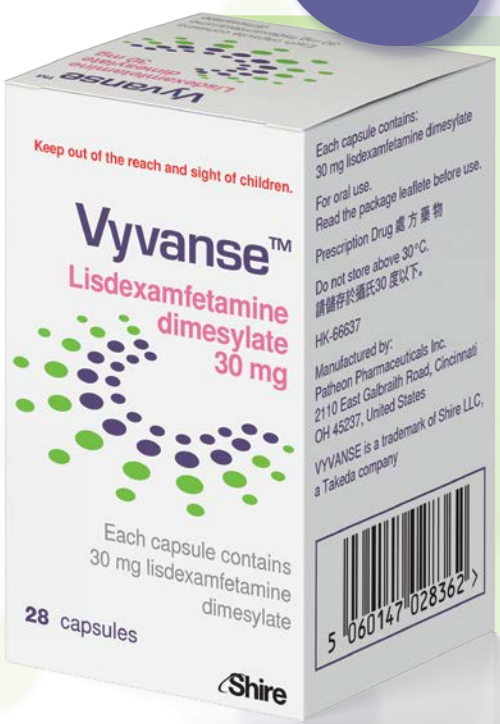

No.1 ADHD MEDICATION[2] IN THE WORLD

Bring Novelty* to
ADHD TREATMENT
in Children, Adolescents & Adults[1]

* Actual size

- **Novel Prodrug formulation** in ADHD treatment[1]
- **Once daily, Capsule or Capsule free administration**[1]
- Long acting efficacy **for up to 13 Hours in children 6-12 year old**[3] **& up to 14 hours in adults**[4]
- **The safety and tolerability profile** is similar to that of other stimulants[5]
- Rate of non-medical use was lower than or equivalent to **other long acting stimulant formulation**[5]

Visit **Vyvanse virtual booth "www.adhdsupport.com.hk"** for more information

* Vyvanse is the first and only prodrug available for the treatment of ADHD with a novel delivery mechanism , in contrast to formulation-based delivery system of other long-acting stimulants[6,7]

Abbreviated Prescribing Information (HKPI Nov 2019) - VYVANSE® (lisdexamfetamine dimesylate) Capsules 20 mg, 30 mg, 50 mg
Indication: VYVANSE is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) **Dosage:** The recommended starting dose is 30 mg once daily in the morning in patients ages 6 and above. Dosage may be adjusted in increments of 10 mg or 20 mg at approximately weekly intervals up to maximum dose of 70 mg/day. **Administration:** Take VYVANSE by mouth in the morning with or without food; avoid afternoon doses because of the potential for insomnia. Swallow VYVANSE capsules whole, or open capsules, empty and mix the entire contents with yogurt, water, or orange juice. Do not take anything less than one capsule per day. A single dose should not be divided. **Contraindications:** Known hypersensitivity to amphetamine products or other ingredients of Vyvanse. Patients taking monoamine oxidase inhibitors (MAOIs), or within 14 days of stopping MAOIs. **Warnings & Precautions:** Potential for abuse and dependence, serious cardiovascular reactions, blood pressure and heart rate increases, psychiatric adverse reactions, suppression of growth, peripheral vasculopathy including Raynaud's phenomenon, serotonin syndrome. **Adverse Reactions (incidence ≥5% and at a rate at least twice placebo):** reported in children, adolescents, and/or adults were anorexia, anxiety, decreased appetite, decreased weight, diarrhea, dizziness, dry mouth, irritability, insomnia, nausea, upper abdominal pain, and vomiting.
Full prescribing information is available upon request.

References: 1. Vyvanse (lisdexamfetamine dimesylate) capsules Hong Kong Prescribing information Nov 2019 version **2.** IQVIA worldwide sales data MAT 12/2019 **3.** Wigal SB et al. Child Adolesc Psychiatry Ment Health 2009;3:17. **4.** Wigal T et al. 316 study group. Behav Brain Funct 2010;6 :34 **5.** Coghill DR et al. CNS Drugs 2014 28:497–511 **6.** Pennick M. Neuropsychiatr Dis Treat. 2010;6:317-327 **7.** Roncero C. Alvarez FJ. Expert Rev Neurother 2014 ;14 :849-865

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C-APROM/HK/Vyv/0007 (11/2020)