www.fmshk.org

THE HONG KONG MEDICAL DIARY

香 港 醫 訊

VOL.24 NO.12 December 2019

Evidence-based Medicine

OFFICIAL PUBLICATION FOR THE FEDERATION OF MEDICAL SOCIETIES OF HONG KONG ISSN 1812 - 1691

Teva Pharmaceutical Hong Kong Limited
Unit 2303, 23/F., Mira Place Tower A, 132 Nathan Road, Tsimshatsui, Kowloon, Hong Kong
Tel : +852 3188 4288 Fax : +852 3585 6220
Website: www.tevapharm.hk

FDA, U.S Food and Drug Administration.

References: 1. Lee WS, et al. *J Eur Acad Dermatol Venereol* 2013;27:1026–1034. 2. Adil A, Godwin M. *J Am Acad Dermatol* 2017;77:136–141.

FINAS-HK-00008

Contents

Scan the QR-code

To read more about The Federation of Medical Societies of Hong Kong

Disclaimer

The Cover Shot

Guidance and Mentorship

The definition of guidance given by the Cambridge Dictionary is "help and advice about how to do something or about how to deal with problems connected with your work, education, or personal relationships". In medicine, mentorship is a very important part of the training.

Mentorship is a relationship in which a more experienced or more knowledgeable person helps to guide a less experienced or less knowledgeable person. The role of the mentor is to provide guidance to the mentee.

Dr Hin-keung WONG
MBBS (HK), FHKCOS, FRCS Ed (Ortho), FHKAM (Ortho Surgery), MMedSc (HK)
President,
The Hong Kong Society for Surgery of the Hand
Specialist in Orthopaedics and Traumatology
Chief of Service and Consultant, Department of Orthopaedics amd Traumatology,
Princess Margaret Hospital and
North Lantau Hospital

Published by
The Federation of Medical Societies of Hong Kong

Design and Production
A-PRO MULTIMEDIA LTD www.apro.com.hk

Evidence-based Medicine

Prof Bernard M Y CHEUNG

FRCP, FHKAM (Medicine)

Division of Clinical Pharmacology, Department of Medicine, University of Hong Kong

Editor

Prof Bernard M Y CHEUNG

We are so used to the idea of evidence-based medicine (EBM) nowadays that we tend to forget that this is a fairly recent development in the history of medicine. For centuries, eastern and western doctors learn from textbooks and experienced practitioners. Expert opinion, consensus and 'experience of a lifetime' were sufficient to justify the clinical practice. In 1972, Archie Cochrane (1909-1988) published the book, 'Effectiveness and Efficiency', lamenting the lack of controlled trials supporting medical practices. His enthusiasm for randomised controlled trials (RCTs) led to the establishment of the Cochrane Library, a database of systemic reviews, the UK Cochrane Centre based in Oxford, and the international Cochrane Collaboration.

Cochrane was afflicted with porphyria, and his medical career was anything but smooth, interrupted by wars in Europe. Perhaps his chequered history led him to be sceptical of orthodoxy and question the effectiveness of commonly-accepted practices. He remarked that the prevalence of doctors in a country was positively associated with mortality! He thought that ineffective treatment can make the patient worse rather than better. To me, that is the raison d'etre of EBM. The movement inspired by Cochrane aims to distinguish between effective and ineffective or even harmful treatment, and amongst effective treatment, to find out which is the most effective and beneficial.

At McMaster University in the Canadian city of Hamilton and later at Oxford, David Sackett (1934-2015) founded the first department of Clinical Epidemiology and became another father of EBM. He was the one who said, 'half of what you learn in medical school is dead wrong'. He was instrumental in teaching clinicians critical appraisal of the medical literature and published extensively in journals read by family physicians. Critical appraisal of the medical literature involves the understanding of clinical trials, biostatistics and biases in research, all of which are not easy or intuitive concepts. Nevertheless, nearly all medical schools now expect graduates to have a working knowledge and basic understanding of these research tools. It is not good to put too much reliance on experts to tell you which treatments are good or bad, because the opinions of experts can be swayed by deep-rooted misconceptions, and conflicts of interest. Therefore, it is important that doctors can study the evidence and judge for themselves what is best for their patients.

It is in that optimistic spirit that the Medical Diary has taken the unprecedented step of devoting a whole issue not to a well-recognised subspeciality, but the brave new world of EBM. Lipid-lowering or lipid-modifying drugs is a good example of the need to review rigorously the benefits and risks of a therapy. In this issue, Prof Brian Tomlinson, who has studied the efficacy and safety of statins and other lipid influencing drugs for many years, gives us an up-to-date account of the latest evidence from randomised trials. In another article, Prof Cyrus Kumana, who worked at McMaster University at the time of Sackett, used statins as an example to illustrate the important concept of number-needed-to-treat. A treatment that is only slightly better than another treatment can be demonstrated to be superior in a clinical trial involving large numbers of patients, but the benefits may be

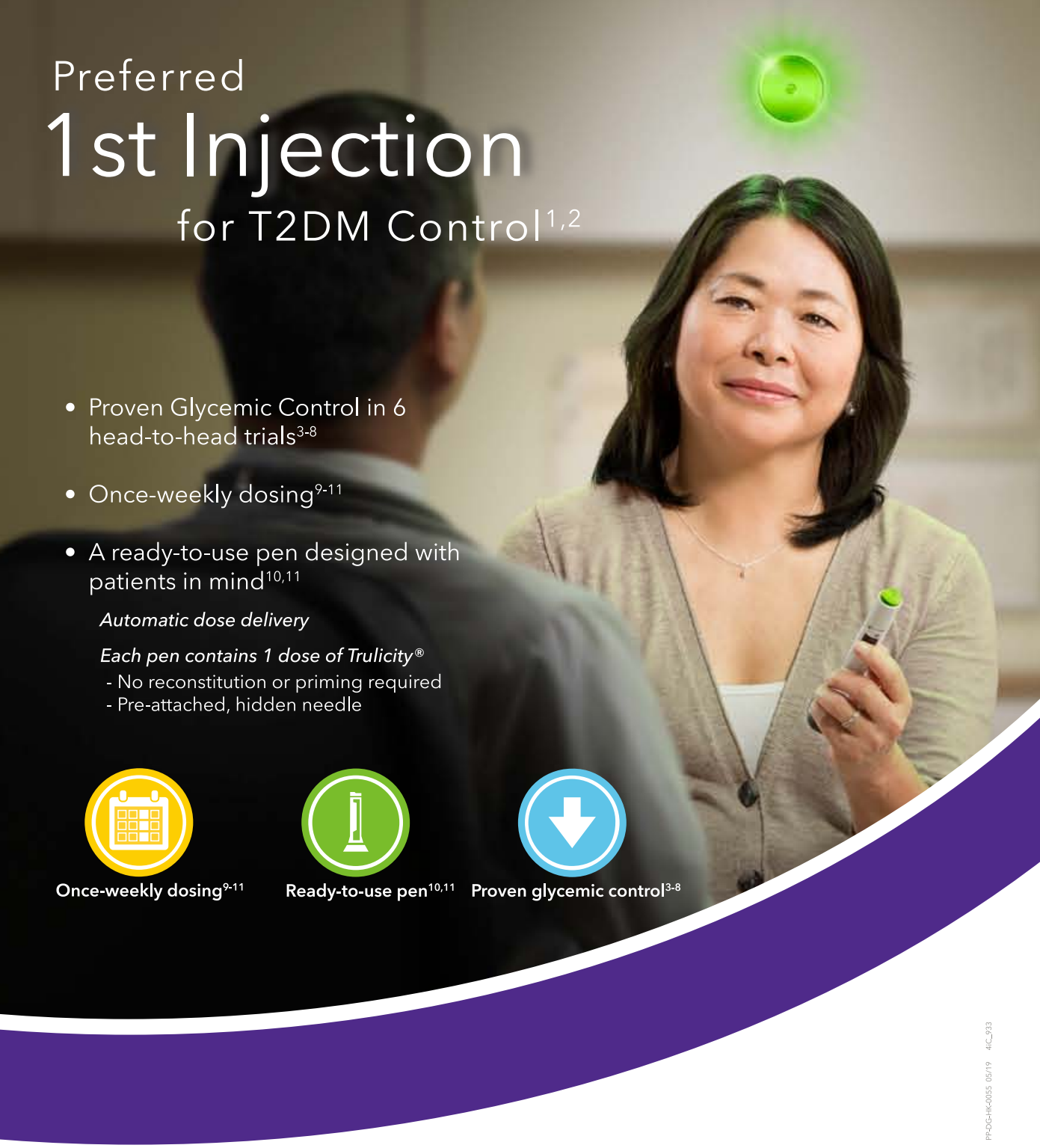
minimal. That is why apart from efficacy (the potential to produce a favourable effect), it is always important to consider effectiveness (the ability to achieve a favourable effect on those to whom it the treatment is offered), cost-effectiveness and utility when evaluating any therapeutic intervention.

The EBM movement has brought an increase in properly-designed and rigorously-conducted clinical trials to determine the effectiveness of new and old treatments. Robust clinical trial evidence is particularly important for biologics, which are expensive and have potentially serious adverse effects. Their efficacy and safety must, therefore, be clearly known. In this issue, Dr Tommy Cheung writes on biological treatments for rheumatoid arthritis. Advanced hepatocellular carcinoma used to be a disease associated with a poor prognosis, but Dr Thomas Yau describes recent advances and clinical trials that bring more than a glimmer of hope to these patients.

Although there are many established treatments for diabetes, it has been difficult to show that controlling blood glucose leads to lower cardiovascular disease risk. Dr Paul Lee describes the new generation of diabetic medications that begin to show a considerable reduction in cardiovascular risk.

Whilst the RCT as championed by Cochrane remains the gold standard of proof, in recent years, a lot of useful insights can be gained through examining 'big data'. This evidence does not replace, but adds to and complements, data from RCTs. As we all know, RCTs have limited duration, exclude many patients, and their participants may have closer monitoring and better compliance. Therefore, evidence from RCTs is supplemented by real-world data. In his article on application of big data in medical research, Dr Ka-Shing Cheung shares his impressive insights and experience in using the huge amount of computerised medical records in the Hong Kong Hospital Authority to address some of the most urgent questions in clinical medicine.

EBM is an evolving discipline. It never stays still and challenges us to move with it. It is also the least exclusive; you do not have to take an examination to practise it. It is universally available and accessible to anyone with an open mind.



Preferred 1st Injection for T2DM Control[1,2]

- Proven Glycemic Control in 6 head-to-head trials[3-8]
- Once-weekly dosing[9-11]
- A ready-to-use pen designed with patients in mind[10,11]

Automatic dose delivery

Each pen contains 1 dose of Trulicity®
- No reconstitution or priming required
- Pre-attached, hidden needle

Once-weekly dosing[9-11] **Ready-to-use pen[10,11]** **Proven glycemic control[3-8]**

PP-DG-HK-0055 05/19 4iC_933

T2DM = type 2 diabetes mellitus

References: 1. Gelhorn HL et al. Patient Prefer Adherence 2016;10:1337-48. 2. Gelhorn HL et al. Patient Prefer Adherence 2015;9:1611-22. 3. Wysham C et al. Diabetes Care 2014;37:2159-67. 4. Umpierrez G et al. Diabetes Care 2014;37:2168-76. 5. Nauck M et al. Diabetes Care 2014;37:2149-58. 6. Giorgino F et al. Diabetes Care 2015;38:2241-9. 7. Dungan KM et al. Lancet 2014;384:1349-57. 8. Blonde L et al. Lancet 2015;385:2057-66. 9. Trulicity® Instructions for Use. 10. Matfin G et al. J Diabetes Sci Technol 2015;9:1071-9. 11. Trulicity® 0.75mg and 1.5mg Prescribing Information.

Trulicity® Abbreviated Prescribing Information

Indication: Trulicity® is indicated in adults with type 2 diabetes mellitus to improve glycaemic control as: Monotherapy: When diet and exercise alone do not provide adequate glycaemic control in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications. Add-on therapy: In combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control. Dosage: Adult Monotherapy: 0.75 mg once weekly. Add-on therapy: 1.5 mg once weekly. Elderly ≥75 years old: Initially 0.75 mg once weekly. Renal impairment: No dosage adjustment is required in patients with mild, moderate or severe renal impairment (eGFR <90 to ≥15 mL/min/1.73m^2). **Administration:** To be injected subcutaneously in the abdomen, thigh or upper arm. It should not be administered intravenously or intramuscularly. The dose can be administered at any time of day, with or without meals. **Contraindications:** Hypersensitivity to dulaglutide or any of its excipients. **Special Precautions:** Do not use in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. Do not administer IV. Acute pancreatitis. Hypoglycaemia. Limited experience in patients with congestive heart failure. **Adverse Drug Reactions:** Hypoglycaemia, nausea, diarrhoea, vomiting, abdominal pain, decreased appetite, dyspepsia, constipation, flatulence, abdominal distention, gastroesophageal reflux disease, eructation, fatigue, injection site reactions, acute pancreatitis, sinus tachycardia, first-degree atrioventricular block.
Full prescribing information is available upon request

trulicity®
dulaglutide once-weekly injection

Eli Lilly Asia, Inc. Hong Kong
Unit 3203-3206, 32/F, Chubb Tower, Windsor House, 311 Gloucester Road, Causeway Bay, Hong Kong
Tel : (852) 2572 0160 Fax : (852) 2572 7893 Website : www.lilly.com.hk

Lilly

Evidence-based Biologic or Target Therapy for Rheumatoid Arthritis

Dr Tommy Tsang CHEUNG

MBBS(HK), MRCP(UK), FRCP(Edin, Glasg), FHKCP, FHKAM(Medicine), Dip Clin Tox (HKPIC & HKCEM)

Honorary Clinical Assistant Professor, The University of Hong Kong
Specialist in Rheumatology

Dr Tommy Tsang CHEUNG

INTRODUCTION

Rheumatoid arthritis (RA) is a common chronic inflammatory arthritis affecting approximately 1% of the general population worldwide. If effective treatment is delayed, chronic synovitis can cause permanent joint damage and progressive functional impairment. In addition, persistent systemic inflammation and immune dysregulation are associated with other comorbidities, such as cardiovascular diseases, interstitial lung disease, and malignancies.

Fortunately, our understanding of RA has evolved considerably during the past decade. One of the most important new discoveries is the recognition of key inflammatory cytokines in the pathogenesis of RA, which in turn has led to the development of biologic disease-modifying anti-rheumatic drugs (bDMARDs). The first bDMARD approved was a tumour necrosis factor (TNF) inhibitor, and after that many biologic agents targeting different cytokines and immune cells have become available. Furthermore, targeted synthetic disease-modifying anti-rheumatic drugs (tsDMARDs) inhibiting Janus kinase (JAK) have been available in the market recently. These effective therapies, together with treat-to-target approaches, have significantly improved the treatment outcomes and quality of life in patients with RA.

TYPES OF bDMARs AND tsDMARDs

To date, four different classes of bDMARDs have been commonly used for the treatment of RA, including TNF inhibition, interleukin 6 (IL-6) inhibition, B cell depletion and T cell co-stimulation blockade. Orally administered, small molecules that target and inhibit JAK-STAT pathway have recently been developed as an important alternative to biologic therapies. As a result, there are altogether 11 advanced therapeutic options available for the treatment of RA (Table 1).

Table 1. bDMARDs and tsDMARDs for RA (Developed by author)

TNF inhibitors	IL-6 inhibitors	B cell depletion	T cell co-stimulation blocker	JAK inhibitors
Infliximab Etanercept Adalimumab Certolizumab pegol Golimumab	Tocilizumab Sarilumab	Rituximab	Abatacept	Tofacitinib Baricitinib Upadacitinib* Filgotinib#

Abbreviation: TNF: Tumour necrosis factor; IL-6: Interleukin 6, JAK: Janus kinase
*Upadacitinib was just approved by the US FDA
#pending approval by the US FDA

USE OF bDMARDs OR tsDMARDs IN RA

bDMARDs or tsDMARDs should be used as the second-line agent in RA patients with poor prognostic factors.

According to the EULAR recommendations on RA[1], conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) should be commenced as soon as the diagnosis of RA is confirmed. However, a large proportion of patients cannot achieve remission or low disease activity with csDMARDs alone. Although the use of certain bDMARDs or tsDMARDs as first-line therapy is more effective than methotrexate monotherapy and may be a reasonable option for patients with contraindications or intolerance to methotrexate or other csDMARDs (Fig. 1). However, evidence suggests that first-line therapy involving bDMARDs could lead to overtreatment of approximately 25% of patients at high cost[2]. There is also evidence to suggest that addition of a bDMARD in patients with suboptimal response to methotrexate (MTX) monotherapy ultimately results in a similar response to initial combination therapy[3,4]. Taken together, bDMARDs or tsDMARDs should not be used as first-line therapy for RA.

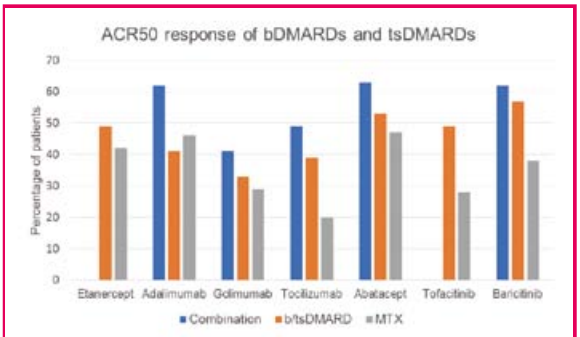


Fig. 1. Use of bDMARDs or tsDMARDs in patients with RA with no prior or limited exposure to csDMARDs

Genovese MC et al. Arthritis Rheum 2002; 46(6): 1443-50.
Breedveld FC et al. Arthritis Rheum 2006; 54(1): 26-37.
Emery P et al. Arthritis Rheum 2009; 60(8): 2272-83.
Emery P et al. Ann Rheum Dis 2015; 74: 19-26.
Burmester GR et al. Ann Rheum Dis 2016; 75: 1081-91.
Lee EB et al. N Engl J Med 2014; 370: 2377-86.
Fleischmann R et al. Arthritis Rheumatol 2017; 69(3): 506-17.

In general, a bDMARD or tsDMARD should be considered the second-line agents in a patient with poor prognostic factors, such as high disease activity at disease onset, presence of anti-citrullinated peptide antibody and early joint damage. However, the EULAR

recommendations do not favour the use of one specific bDMARD or tsDMARD or suggest a certain sequence of its use. It is because head-to-head studies directly comparing different bDMARDs or tsDMARDs are sparse. The AMPLE study investigated the clinical efficacy of abatacept versus adalimumab in RA patients with an inadequate response to MTX. Clinical efficacy and inhibition of radiographic progression were similar within these two agents[5]. The ORAL Standard compared tofacitinib both with placebo and with adalimumab in RA patients with an inadequate response to MTX. Although a formal non-inferiority comparison was not performed, tofacitinib appeared to be as effective as adalimumab[6]. The EXXELARATE trial investigated the clinical efficacy of adalimumab versus certolizumab pegol. Similarly, the efficacy of certolizumab pegol was not significantly different from that of adalimumab[7].

In addition, indirect comparisons between different bDMARDs and tsDMARDs in many network meta-analyses did not show any significant difference in clinical efficacy when used in combination with MTX[8-10].

As a result, choosing the best treatment option for an individual patient has become increasingly difficult for rheumatologists. Although many cellular and molecular markers have been tested for the prediction of treatment response, no clear and consistent patterns have yet emerged. As a result, none of them is widely adopted in clinical practice. Therefore, safety of bDMARDs and tsDMARDs remains to be the most important consideration. However, some bDMARDs or tsDMARDs may be preferred in some special situations, such as seronegative RA, intolerance to csDMARDs and pregnancy.

SERONEGATIVE RHEUMATOID ARTHRITIS

Rituximab and abatacept are not preferred in patients with seronegative RA.

Among patients with RA, serological status regarding anti-cyclic citrullinated peptide (anti-CCP) antibodies appears to influence the effectiveness of rituximab and abatacept. A meta-analysis of 4 randomised controlled trials of rituximab showed that seropositive patients had a better response to rituximab when compared to seronegative patients[11]. A post-hoc analysis of the AMPLE study evaluated the impact of anti-CCP antibody concentrations on clinical outcomes in patients treated with abatacept versus adalimumab. Similarly, patients with the highest baseline anti-CCP antibody concentrations had better response to abatacept than patients with lower concentrations, an association that was not observed with adalimumab[12].

INTOLERANCE TO MTX OR OTHER csDMARDs

Interleukin 6 inhibitors or JAK inhibitors are preferred.

As shown in Fig. 1, the efficacy of combination therapy is consistently superior to any bDMARD or tsDMARD monotherapy. Only tocilizumab and JAK inhibitors are more efficacious than MTX when used as monotherapy. There is, however, no evidence that TNF inhibitors are clinically superior to MTX monotherapy. ADACTA trial compared the efficacy of tocilizumab monotherapy versus adalimumab monotherapy in patients with RA who were intolerant or inappropriate candidates for MTX. The mean disease activity score 28 (DAS28) improvement was significantly higher in the tocilizumab (−3.3) than in the adalimumab group (−1.8) (difference −1.5, 95% CI −1.8 to −1.1; p<0.0001) from baseline to week 24[13].

As a result, IL-6 inhibitor or JAK inhibitor monotherapy may be preferred in patients who cannot use csDMARDs because of intolerance or contraindication.

PREGNANCY

Use of TNF inhibitors is generally safe in the first and second trimester.
Etanercept and Certolizumab pegol can be considered during the third trimester if indicated.

Available data indicate that TNF inhibitors, which are classified as pregnancy category B (no documented human toxicity) by the US FDA, do not increase the risk of miscarriage or congenital malformation[14,15]. However, transport of immunoglobulin (IgG) proteins across the placenta increase steadily after the second trimester of pregnancy, and neonatal exposure to monoclonal antibodies, which are mostly IgG1 subtype, would be expected to be highest in infants of mothers exposed in the third trimester. As IgG clearance is slower in neonates, prolonged exposure to monoclonal antibodies may potentially increase the risk of neonatal infection[16]. Etanercept and certolizumab pegol are fusion protein and pegylated Fab respectively, therefore, their placental transfer is relatively low and can be continued during the third trimester.

Compared with the TNF inhibitors, rituximab, tocilizumab, sarilumab and abatacept have comparatively limited documentation of safety in pregnancy. Except abatacept, placental transfer is expected for those bDMARDs because they are of IgG1 subtype. Therefore, they should be replaced by other medications before conception. These drugs should be used during pregnancy only when no other pregnancy-compatible drug can effectively control RA. Since tsDMARDs have insufficient documentation for use in pregnancy, these should also be avoided during pregnancy.

SAFETY ISSUES OF bDMARDs

Compared to csDMARDs, the use of bDMARDs is associated with an increased risk of serious infections (6 per 1000 patient-year) [17,18]. There was no significant difference between bDMARDs; however, increasing age, comorbidity, glucocorticoid use, and previous history of serious infections are associated with future infections in different databases and biologic registries.

Abatacept appeared to be a safer option among bDMARDs. The ATTEST study compared the efficacy and safety of abatacept or infliximab versus placebo in RA patients with an inadequate response to MTX. Of

note, adverse events (89.1 vs 93.3%), serious adverse events (9.6 vs 18.2%), serious infections (1.9 vs 8.5%) and discontinuations due to adverse events (3.2 vs 7.3%) and serious adverse events (2.6 vs 3.6%) were significantly lower with abatacept than infliximab over 1 year[19].

SPECIFIC SIDE EFFECTS OF JAK INHIBITORS

Use of JAK inhibitors is associated with a higher risk of herpes zoster re-activation.
The lipid change is not associated with major cardiovascular events.

Risk of herpes zoster is apparently increased in patients treated with JAK inhibitors compared with that in the RA registries. Of 6192 patients who received tofacitinib in the clinical development programme, 636 patients developed herpes zoster with a crude incidence ratio of 4.0 (95% CI 3.7, 4.4) per 100 patient-year. Serious herpes zoster was reported in about 7% of patients, but no fatal case was reported[20]. A recent pooled analysis of integrated database of clinical development programme reported a similar incidence of 3.9 (95% CI 3.6, 4.2) per 100 patient-year[21]. With unknown reasons, the incidence ratio was higher in Asian countries, particularly in Japan and Korea (8.0 per 100 patient-year, 95% CI 6.6, 9.6) and India (8.4 per 100 patient-year, 95% CI 6.4, 10.9), than in the rest of the world (2.7–4.3 per 100 patient-year). Age at baseline, corticosteroid dose at baseline, regions of recruitment, smoking status and tofacitinib dose during treatment were significant risk factors of herpes zoster in the analysis.

Risks of herpes zoster were compared among tofacitinib and bDMARDs using data from an insurance claim database in the US. The crude incidence (95% CI) of herpes zoster in RA patients who initiated tofacitinib (n = 2526) was 3.87 (2.82, 5.32); for other bDMARDs, the crude incidence rate (95% CI) in RA patients ranged from 1.95 (1.65, 2.31; adalimumab) to 2.71 (2.33, 3.08; infliximab). Adjusted hazard ratio (95% CI) of tofacitinib versus abatacept was 2.01 (1.40, 2.88). No other bDMARDs showed a significant change in hazard ratio versus abatacept[22].

JAK inhibitors can cause anaemia and cytopenias, but this is rarely of clinical significance for either tofacitinib or baricitinib at the approved doses. Unexpectedly, mild thrombocytosis has been observed in patients treated with baricitinib but not with tofacitinib. Both tofacitinib and baricitinib treatment are associated with reductions in peripheral blood NK cell counts. In the case of tofacitinib, there is a dose-dependent decrease over the first two weeks of therapy while for baricitinib, there is a transient increase over the first four weeks of treatment before counts fall below baseline levels[23]. However, there have been no reported associations between baseline or nadir NK cell counts and the occurrence of serious infection, herpes zoster or malignancy.

Both tofacitinib and baricitinib are associated with increases in serum levels of low-density lipoprotein (LDL) and high-density lipoprotein (HDL) but without alteration in the LDL: HDL ratio. In pooled phase II tofacitinib studies, dose-dependent increases in total, HDL and LDL cholesterol of 16–30% were reported[24]. Similarly, dose-dependent increase in LDL, HDL and triglycerides was observed in baricitinib studies[25]. This may be related to modulation of signalling downstream of IL-6 given that similar changes have been observed with IL-6 inhibitors. Reviews of pooled data from late-phase trials of tofacitinib and baricitinib confirmed that like tocilizumab, this lipid change is not associated with any major cardiovascular events[26,27].

DOSE TAPERING OR DISCONTINUATION OF bDMARDs IN RA

The success rate of discontinuation of bDMARDs is higher among patients with early RA.
Dose tapering of bDMARDs is a better treatment strategy for patients with established RA.

The feasibility of bDMARD tapering has been demonstrated in patients with early RA. After achieving remission or low disease activity with bDMARD and MTX combination therapy, patients were randomised to continue full-dose bDMARD or to a dose reduction strategy[4,28,29]. Of note, most of the patients were naïve to MTX or csDMARDs and had a disease duration of less than one year. Treatment outcomes were comparable whether bDMARD was continued or withdrawn in patients who initially responded to bDMARD and MTX combination therapy. However, the implementation of this treatment strategy in clinical practice is challenging because the use of bDMARDs as the first-line therapy is not recommended by international guidelines.

Studies have also been conducted in patients with established RA who were in remission or had low disease activity while receiving bDMARD therapy. However, compared with studies in patients with early RA, the results of these studies showed that tapering bDMARDs is feasible only in a relatively small subset of patients in sustained remission. In HONOR trial, the decision to discontinue adalimumab was taken based on patients' agreement with the physician's judgment. After one year, 91% of patients on adalimumab remained in low disease activity versus 62% of patients on MTX monotherapy[30]. In the ACT-RAY study, 50.4% of patients discontinued tocilizumab following sustained clinical remission after one year. However, 84% of those patients experienced a flare up[31]. Instead of discontinuation of bDMARDs, dose tapering seems to be a better treatment strategy in patients with established RA. In the PRESERVE trial, RA patients with an inadequate response to MTX were pre-treated with etanercept. Patients who achieved sustained low disease activity were randomised to receive combination therapy (standard dose and reduced dose of etanercept) versus MTX monotherapy. After one year, a higher percentage of patients treated with combination therapy remained in low disease activity (82.6% and 79.1%) compared with MTX monotherapy (42.6%)[32].

CONCLUSION

Novel therapies including bDMARDs and tsDMARDs are increasingly used in patients with RA. Most of them

have a similar efficacy and safety profile; therefore, choosing the best treatment agent should be based on the drug profile and patient's characteristics.

References

1. Smolen, J.S., et al., EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis, 2017. 76(6): p. 960-977.
2. Kavanaugh, A., et al., Testing treat-to-target outcomes with initial methotrexate monotherapy compared with initial tumour necrosis factor inhibitor (adalimumab) plus methotrexate in early rheumatoid arthritis. Ann Rheum Dis, 2018. 77(2): p. 289-292.
3. Bijlsma, J.W.J., et al., Early rheumatoid arthritis treated with tocilizumab, methotrexate, or their combination (U-Act-Early): a multicentre, randomised, double-blind, double-dummy, strategy trial. Lancet, 2016. 388(10042): p. 343-355.
4. Smolen, J.S., et al., Adjustment of therapy in rheumatoid arthritis on the basis of achievement of stable low disease activity with adalimumab plus methotrexate or methotrexate alone: the randomised controlled OPTIMA trial. Lancet, 2014. 383(9914): p. 321-32.
5. Schiff, M., et al., Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: two-year efficacy and safety findings from AMPLE trial. Ann Rheum Dis, 2014. 73(1): p. 86-94.
6. van Vollenhoven, R.F., et al., Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. N Engl J Med, 2012. 367(6): p. 508-19.
7. Smolen, J.S., et al., Head-to-head comparison of certolizumab pegol versus adalimumab in rheumatoid arthritis: 2-year efficacy and safety results from the randomised EXXELERATE study. Lancet, 2016. 388(10061): p. 2763-2774.
8. Singh, J.A., et al., A network meta-analysis of randomized controlled trials of biologics for rheumatoid arthritis: a Cochrane overview. CMAJ, 2009. 181(11): p. 787-96.
9. Guyot, P., et al., Abatacept with methotrexate versus other biologic agents in treatment of patients with active rheumatoid arthritis despite methotrexate: a network meta-analysis. Arthritis Res Ther, 2011. 13(6): p. R204.
10. Singh, J.A., et al., Biologics or tofacitinib for rheumatoid arthritis in incomplete responders to methotrexate or other traditional disease-modifying anti-rheumatic drugs: a systematic review and network meta-analysis. Cochrane Database Syst Rev, 2016(5): p. CD012183.
11. Isaacs, J.D., et al., Effect of baseline rheumatoid factor and anticitrullinated peptide antibody serotype on rituximab clinical response: a meta-analysis. Ann Rheum Dis, 2013. 72(3): p. 329-36.
12. Sokolove, J., et al., Impact of baseline anti-cyclic citrullinated peptide-2 antibody concentration on efficacy outcomes following treatment with subcutaneous abatacept or adalimumab: 2-year results from the AMPLE trial. Ann Rheum Dis, 2016. 75(4): p. 709-14.
13. Gabay, C., et al., Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial. Lancet, 2013. 381(9877): p. 1541-50.
14. Gotestam Skorpen, C., et al., The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. Ann Rheum Dis, 2016. 75(5): p. 795-810.
15. Burmester, G.R., et al., Adalimumab long-term safety: infections, vaccination response and pregnancy outcomes in patients with rheumatoid arthritis. Ann Rheum Dis, 2017. 76(2): p. 414-417.
16. Julsgaard, M., et al., Concentrations of Adalimumab and Infliximab in Mothers and Newborns, and Effects on Infection. Gastroenterology, 2016. 151(1): p. 110-9.
17. Singh, J.A., et al., Risk of serious infection in biological treatment of patients with rheumatoid arthritis: a systematic review and meta-analysis. Lancet, 2015. 386(9990): p. 258-65.
18. Lahiri, M. and W.G. Dixon, Risk of infection with biologic antirheumatic therapies in patients with rheumatoid arthritis. Best Pract Res Clin Rheumatol, 2015. 29(2): p. 290-305.
19. Schiff, M., et al., Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. Ann Rheum Dis, 2008. 67(8): p. 1096-103.
20. Winthrop, K.L., et al., Herpes Zoster and Tofacitinib: Clinical Outcomes and the Risk of Concomitant Therapy. Arthritis Rheumatol, 2017. 69(10): p. 1960-1968.
21. Cohen, S.B., et al., Long-term safety of tofacitinib for the treatment of rheumatoid arthritis up to 8.5 years: integrated analysis of data from the global clinical trials. Ann Rheum Dis, 2017. 76(7): p. 1253-1262.
22. Curtis, J.R., et al., Real-world comparative risks of herpes virus infections in tofacitinib and biologic-treated patients with rheumatoid arthritis. Ann Rheum Dis, 2016. 75(10): p. 1843-7.
23. Tanaka, Y., et al., Characterization and Changes of Lymphocyte Subsets in Baricitinib-Treated Patients With Rheumatoid Arthritis: An Integrated Analysis. Arthritis Rheumatol, 2018. 70(12): p. 1923-1932.
24. McInnes, I.B., et al., Open-label tofacitinib and double-blind atorvastatin in rheumatoid arthritis patients: a randomised study. Ann Rheum Dis, 2014. 73(1): p. 124-31.
25. Kremer, J.M., et al., Effects of Baricitinib on Lipid, Apolipoprotein, and Lipoprotein Particle Profiles in a Phase IIb Study of Patients With Active Rheumatoid Arthritis. Arthritis Rheumatol, 2017. 69(5): p. 943-952.
26. Charles-Schoeman, C., et al., Cardiovascular safety findings in patients with rheumatoid arthritis treated with tofacitinib, an oral Janus kinase inhibitor. Semin Arthritis Rheum, 2016. 46(3): p. 261-271.
27. Taylor, P.C., et al., Lipid profile and effect of statin treatment in pooled phase II and phase III baricitinib studies. Ann Rheum Dis, 2018. 77(7): p. 988-995.
28. Emery, P., et al., Sustained remission with etanercept tapering in early rheumatoid arthritis. N Engl J Med, 2014. 371(19): p. 1781-92.
29. Westhovens, R., et al., Maintenance of remission following 2 years of standard treatment then dose reduction with abatacept in patients with early rheumatoid arthritis and poor prognosis. Ann Rheum Dis, 2015. 74(3): p. 564-8.
30. Tanaka, Y., et al., Discontinuation of adalimumab after achieving remission in patients with established rheumatoid arthritis: 1-year outcome of the HONOR study. Ann Rheum Dis, 2015. 74(2): p. 389-95.
31. Huizinga, T.W., et al., Clinical and radiographic outcomes at 2 years and the effect of tocilizumab discontinuation following sustained remission in the second and third year of the ACT-RAY study. Ann Rheum Dis, 2015. 74(1): p. 35-43.
32. Smolen, J.S., et al., Maintenance, reduction, or withdrawal of etanercept after treatment with etanercept and methotrexate in patients with moderate rheumatoid arthritis (PRESERVE): a randomised controlled trial. Lancet, 2013. 381(9870): p. 918-29.

monthly Simponi® golimumab

Four weeks of movement.
One injection subcutaneously.[1]

SIMPONI®
OPTIMIZE PATIENT JOURNEYS

Durable efficacy and established safety for up to 5 years

57% ASAS40 response in AS[2]

48% ACR50 response in PsA[4]

55% ACR50 response in RA[3]

Simponi® demonstrated high persistence rates in both RCTs and in real world experiences[2,4,7-9]

70%

5-year persistence rate in clinical trials[2,4,7]

Simponi® significantly improves patient-reported outcomes and experiences:[5,6]

- Relieves pain/ discomfort
- Improves functional ability
- Ease and confidence with autoinjector
- Reduce fatigue

Significantly higher persistence rates in real world evidence[8,9]

Abbreviations: ACR50=American College of Rheumatology 50% improvement; AS=ankylosing spondylitis; ASAS40= Assessment of SpondyloArthritis International Society 40% improvement; PsA=psoriatic arthritis; RA=rheumatoid arthritis; RCT=randomized controlled trial

References: 1. Simponi® Hong Kong Prescribing Information P06. **2.** Deodhar, A. A. *et al.* Golimumab administered subcutaneously every 4 weeks in ankylosing spondylitis: 5-year results of the GO-RAISE study. *Annals of the Rheumatic Diseases* 74, 757–761 (2015). **3.** Emery, P. *et al.* Efficacy and Safety of Subcutaneous Golimumab in Methotrexate-Naive Patients With Rheumatoid Arthritis: Five-Year Results of a Randomized Clinical Trial. *Arthritis Care & Research* 68, 744–752 (2016). **4.** Kavanaugh, A. *et al.* Clinical efficacy, radiographic and safety findings through 5 years of subcutaneous golimumab treatment in patients with active psoriatic arthritis: results from a long-term extension of a randomised, placebo-controlled trial (the GO-REVEAL study). *Ann Rheum Dis* 73, 1689–1694 (2014). **5.** Krüger, K. *et al.* Patient-reported outcomes with golimumab in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: non-interventional study GO-MICE in Germany. *Rheumatol Int* 39, 131–140 (2019). **6.** Schulze-Koops, H. *et al.* THU0198 Patient Evaluations of Autoinjectors for Delivery of Subcutaneous Golimumab for Treatment of Rheumatoid Arthritis. *Annals of the Rheumatic Diseases* 72, A230–A231 (2013). **7.** Keystone, E. C. *et al.* Safety and Efficacy of Subcutaneous Golimumab in Patients with Active Rheumatoid Arthritis despite Methotrexate Therapy: Final 5-year Results of the GO-FORWARD Trial. *J Rheumatol* 43, 298–306 (2016). **8.** Fasoli, E. G. *et al.* Two-year persistence of golimumab as second-line biologic agent in rheumatoid arthritis as compared to other subcutaneous tumor necrosis factor inhibitors: real-life data from the LORHEN registry. *Int J Rheum Dis* 21, 422–430 (2018). **9.** Dalén, J. *et al.* Treatment persistence among patients with immune-mediated rheumatic disease newly treated with subcutaneous TNF-alpha inhibitors and costs associated with non-persistence. *Rheumatol Int* 36, 987–995 (2016).

SIMPONI® Pre-filled Smartject Autoinjector 50mg/0.5ml ABBREVIATED PRESCRIBING INFORMATION

ACTIVE INGREDIENT(S): Golimumab. **INDICATION(S):** Rheumatoid Arthritis (RA) - SIMPONI, in combination with methotrexate (MTX), is indicated for reducing signs and symptoms and improving physical function in adult patients with moderately to severely active rheumatoid arthritis, and inhibiting the progression of structural damage in adult patients with moderately to severely active rheumatoid arthritis who had not previously been treated with MTX. Psoriatic Arthritis (PsA) - SIMPONI is indicated for reducing signs and symptoms, inhibiting the progression of structural damage and improving physical function in adult patients with moderately to severely active psoriatic arthritis. SIMPONI can be used in combination with MTX in patients who do not respond adequately to MTX alone. Ankylosing spondylitis (AS) - SIMPONI is indicated for reducing signs and symptoms in adult patients with active ankylosing spondylitis who have had an inadequate response to conventional therapies. Non-radiographic Axial Spondyloarthritis (nr-Ax SpA) - SIMPONI is indicated for the treatment of adults with severe active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs (NSAIDs). Ulcerative Colitis (UC) - SIMPONI is indicated in adult patients with moderately to severely active disease who have had an inadequate response to, or have medical contraindications for, conventional therapy including corticosteroids, amino salicylates, azathioprine (AZA), or 6-mercaptopurine (6-MP), for inducing and maintaining clinical response (reduction in signs and symptoms), inducing clinical remission, achieving sustained clinical remission in induction responders and improving endoscopic appearance of the mucosa during induction. **DOSAGE & ADMINISTRATION:** Rheumatoid Arthritis(RA), Psoriatic Arthritis(PsA), Ankylosing Spondylitis (AS) and Non-Radiographic Axial Spondyloarthritis(nr-Ax SpA) - 50 mg administered by subcutaneous injection once a month. Ulcerative Colitis(UC) - 200 mg initially administered by subcutaneous injection at Week 0, followed by 100 mg at Week 2 and then 50 mg every 4 weeks, thereafter. The maintenance dose of 100 mg every 4 weeks can be considered at the discretion of the treating physician. In addition to the clinical assessment, measurement of golimumab levels may be taken into account before considering dose optimization. **CONTRAINDICATIONS:** Severe infections. Moderate or severe (NYHA class III/IV) congestive heart failure. Hypersensitivity to golimumab or any other ingredients in the formulation or component of the container. **SPECIAL WARNINGS & PRECAUTIONS: Infections: Discontinue SIMPONI if patient develops a serious infection or sepsis. Treatment with SIMPONI should not be initiated in patients with active infections including chronic or localized infections. Caution in patients with a history of recurring or latent infections (including TB), or with underlying conditions predisposing patients with infections, who have resided in regions where TB and invasive fungal infections are endemic. Before starting treatment with SIMPONI, all patients should be evaluated for both active and latent tuberculosis. Patients should be monitored for signs and symptoms of active tuberculosis, including patients who tested negative for latent tuberculosis infection. Malignancies: Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, of which SIMPONI is a member.** Congestive Heart Failure: Stop SIMPONI if new or worsening symptoms of heart failure occur. Concurrent Administration with Abatacept or Anakinra: Combination of abatacept or anakinra with TNF-blockers, including SIMPONI, is not recommended. Concurrent administration with other Biological Therapeutics: Not recommended. Switching Between Biological Therapeutics: Continue to monitor patients since overlapping biological activity may further increase the risk of infection. Hematologic Reactions: Use with caution in patients who have a current or past history of significant cytopenias. Patients should seek immediate medical attention upon signs and symptoms suggestive of blood dyscrasias. Discontinue SIMPONI in patients with confirmed significant hematologic abnormalities. Immunizations: Patients treated with SIMPONI may receive concurrent vaccinations, except for live vaccines/ other therapeutic infectious agents. Hypersensitivity Reactions: If an anaphylactic or other serious allergic reaction occurs, discontinue SIMPONI immediately. Latex Sensitivity: The product contains dry natural rubber (a derivative of latex), which may cause allergic reactions in individuals sensitive to latex. Discontinue golimumab if patient develops symptoms of a lupus-like syndrome. Demyelinating Disorders: Use with caution in patients with central or peripheral nervous system demyelinating disorders. Discontinuation should be considered if these disorders develop. Surgery: Patients who require surgery while on SIMPONI should be closely monitored for infections. **SIDE EFFECTS:** Upper respiratory tract infection and nasopharyngitis. Refer to the full prescribing information for other side effects. **PREGNANCY & LACTATION:** SIMPONI should be given to a pregnant woman only if clearly needed. Women of child bearing potential must use adequate contraception to prevent pregnancy and continue its use for at least 6 months after the last golimumab treatment. It is not known whether golimumab is excreted in human milk or absorbed systemically after ingestion. **INTERACTIONS:** Other biological therapeutics including abatacept or anakinra. Live vaccines or therapeutic infectious agent. Cytochrome P450 Substrates. Simponi aRi ver.5.0.

PLEASE REFER TO FULL PRESCRIBING INFORMATION BEFORE PRESCRIBING.

janssen

Unit 1302-1307, Tower 1, Grand Century Place,
193 Prince Edward Road West, Mongkok, Kowloon, Hong Kong
Tel: 2736 1711 Fax: 2736 1926

CP-119045 Nov 2019

Practical Management of Immune-Related Adverse Events (irAEs) Associated with Immune Checkpoint Inhibition

Dr Yawen DONG
MD
Clinical Fellow in Medical Oncology, Department of Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong

Dr Thomas YAU
MBBS (HK), MD (HK), MRCP (UK), FRCP (London), FHKCP (Med Onc), FHKAM (Medicine)
Clinical Associate of Professor in Medical Oncology, Department of Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong


Dr Yawen DONG


Dr Thomas YAU

INTRODUCTION

With the breakthrough development of immune-based oncological therapies for multiple types of tumors, the cancer treatment landscape has been revolutionised tremendously. In particular, the administration of immune checkpoint inhibitors (ICI) has produced remarkable responses and durable clinical benefits leading to a significant improvement of prognosis for many patients with advanced cancer disease. Despite their promising efficacy and feasible tolerability, immune checkpoint inhibitors are also known to have their own distinctive "side effects", which are collectively termed as immune-related adverse events (irAEs). Since the inhibition of immune checkpoints can trigger the activation of auto-reactive T cells, auto-immune reactions are considered to be the most common adverse events. Therefore, it is crucial that clinicians and other healthcare professionals are familiar with the basic management of irAEs, which should be addressed differently from adverse events caused by conventional cancer therapeutic regimens such as cytotoxic chemotherapy.

IMMUNE CHECKPOINTS IN CANCER

Cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death 1 protein (PD-1) belong to the family of immune checkpoint proteins, which are receptor molecules expressed on the surface of cytotoxic T cells that interact with their ligands on antigen-presenting cells CD80/CD86 in the case of CTLA-4 and programmed death ligand-1 or 2 (PD-L1 or PD-L2) in the case of PD-1[1]. Under physiological circumstances, these immune checkpoints work as "brakes" on the immune system, with the primary aim to avoid excessive immune reactions (i.e. autoimmune reactions). However, in the context of cancer, immune checkpoints suppress antitumor immunity by disrupting the interaction between T cells and tumour antigens, resulting in inhibition of T cell proliferation and diminished cellular survival of T cells[1]. Additionally, tumour cells also express immune checkpoint proteins, such as PD-L1, on their cell surface, thereby exploiting this immunosuppressive mechanism to escape immune-surveillance. The use of immune checkpoint inhibitors aims at the reversal of this negative effect on the intrinsic immune system so as to restore tumour-specific immune responses[2]. On the downside, the inhibition of immune checkpoints can also trigger the activation of auto-reactive T cells, which in turn can result in the development of irAEs affecting the skin, endocrine system, gastrointestinal organs, amongst others[2].

To date, several monoclonal antibodies targeting either CTLA-4, PD-1 or PD-L1 have been approved by the Food and Drug Administration (FDA) of the US in the treatment of certain cancer types, including metastatic melanoma, non-small cell lung carcinoma (NSCLC), renal cell carcinoma, urothelial carcinoma, and head and neck squamous cell carcinoma[3]. Table 1 summaries the currently approved immune checkpoint inhibitors in cancer treatments.

Table 1. Overview of the currently FDA approved immune checkpoint inhibitors in cancer treatment. (Adapted from https://www.drugs.com/history/)

Name	Target	Approved Indications
Pembrolizumab	PD-1	Metastatic melanoma, non-small cell lung cancer, small cell lung cancer, head and neck squamous cell carcinoma, classical Hodgkin's lymphoma, primary mediastinal large B-cell lymphoma, urothelial carcinoma, microsatellite instability-high cancer, gastric cancer, esophageal cancer, cervical cancer, hepatocellular carcinoma, Merkel cell carcinoma, renal cell carcinoma, and endometrial carcinoma
Nivolumab	PD-1	Advanced melanoma, advanced non-small cell lung cancer, advanced small cell lung cancer, advanced renal cell carcinoma, classical Hodgkin's lymphoma, advanced squamous cell carcinoma of the head and neck, urothelial carcinoma, microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer, and hepatocellular carcinoma
Cemiplimab	PD-1	Metastatic or locally advanced cutaneous squamous cell carcinoma
Ipilimumab	CTLA-4	Metastatic melanoma, advanced renal cell carcinoma, and microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer
Atezolizumab	PD-L1	Advanced urothelial carcinoma; metastatic non-small cell lung cancer (NSCLC); extensive-stage small cell lung cancer; and in combination with Abraxane for the treatment of metastatic triple-negative breast cancer
Avelumab	PD-L1	Metastatic Merkel cell carcinoma (MCC); advanced or metastatic urothelial carcinoma; and in combination with axitinib for treatment of advanced renal cell carcinoma.
Durvalumab	PD-L1	Metastatic urothelial carcinoma and for the treatment of unresectable non-small cell lung cancer that has not progressed after chemoradiation

Ipilimumab, a CTLA-4 inhibitor, was the first regimen granted FDA approval in 2014 for use in patients with advanced melanoma[4]. The approval for the anti-PD1 antibodies, pembrolizumab and nivolumab, soon followed afterwards, for the treatment of melanoma, metastatic NSCLC, head and neck squamous cancers,

urothelial carcinoma, gastric adencarcinoma and mismatch repair-deficient solid tumours as well as for Hodgkin's lymphoma[5,6]. Nivolumab is further approved for treating patients with hepatocellular carcinoma and renal cell carcinoma. In 2015, the combination of nivolumab and ipilimumab also received accelerated approval for first-line treatment of advanced melanoma. More recently, monoclonal antibodies targeting PD-L1 expressed on the tumour cell surface have been approved in clinical use as well, amongst others for the treatment of urothelial carcinoma (atezolizumab, durvalumab, avelumab), NSCLC (atezolizumab) and Merkel cell carcinoma (avelumab)[7-9]. As numerous large-scale clinical trials are presently ongoing, indications for immune checkpoint inhibitors and combination therapy are expanding at a rapid rate.

CHARATERISTICS OF irAEs IN ICI THERAPY

Despite the favourable tolerability and effectiveness of ICI therapy, the administration of immune checkpoints inhibitors is fraught with a range of adverse effects that are fundamentally different from other systemic therapies such as conventional chemotherapy. Based on the results from a meta-analysis investigating the adverse events in immune checkpoint blockade versus in cytotoxic chemotherapy, a better overall understanding of key differences between these two mainstays of therapy have been achieved[10]. In general, studies have proven that ICI therapy carries a better tolerability and toxicity profile when compared to standard chemotherapy. While more asthenia, fatigue, gastrointestinal symptoms such as nausea, diarrhoea and appetite loss are observed in patients undergoing immunotherapy with checkpoint inhibitors, chemotherapy is more often linked to the occurrence of neutropenia, anaemia, alopecia and stomatitis[10].

Table 2. List of most frequently reported irAEs categorised by organ systems. (Adapted from De Velasco G. et al. Comprehensive meta-analysis of key immune-related adverse events from CTLA-4 and PD-1/PD-L1 inhibitors in cancer patients.)

IrAEs sorted by organ system	% affected in the clinical trial cohort, based on meta-analysis
Fatigue	16-40%
Dermatologic adverse effects	30-50%
Endocrinopathy	10%
Hepatotoxicity	6.50%
Pneumonitis	2.60%
Gastrointestinal toxicity	2.30%
Renal toxicity	1-2%

Although the use of immune checkpoint inhibitors can cause toxic and auto-immune reactions in a variety of organs, a certain pattern in irAE development is described in the literature (Table 2). Common irAEs that are associated with the application of ICI therapy are skin rash, hypothyroidism, liver dysfunction and gastrointestinal side effects such as nausea, vomiting and diarrhoea. Furthermore, the onset of these irAEs may also vary and depends on the type of checkpoint inhibitors. In terms of the CTLA-4 antibody ipilimumab, cutaneous and mucous complications seem to arise relatively early in the course of treatment, followed by gastrointestinal symptoms, while for the PD-1 inhibitor nivolumab, most irAEs usually emerge few weeks after its administration. However, in particular cases a delayed manifestation of irAEs up to a year after the initiation of anti-PD-1 therapy has been reported[11].

It has also been postulated that autoimmune reactions afflicted by immune checkpoint blockade seem to be dependent on the signalling pathways that are being disrupted. For example, since CTLA-4 is expressed in the pituitary gland, manifestation of hypophysitis occurs more often under anti-CTLA4 therapy than under anti-PD-1/ anti-PD-L1 treatment. Furthermore, according to meta-analysis, CTLA-4 inhibitors cause higher rates of and more severe irAEs when compared to anti-PD-1/ anti-PD-L1 antibodies, affecting 90% and 70% of treated patients, respectively[12,13]. Fig. 1 illustrates a comparison between PD-1/PD-L1 inhibitors versus CTLA-4 inhibitors in terms of relative risk (%) of certain irAEs.

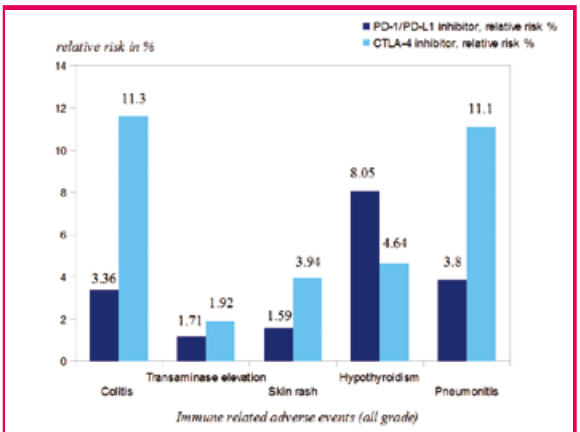


Fig. 1. Comparison between PD-1/PD-L1 and CTLA-4 inhibitors. (Adapted from De Velasco G. et al. Comprehensive meta-analysis of key immune-related adverse events from CTLA-4 and PD-1/PD-L1 inhibitors in cancer patients.)

A correlation between certain irAE manifestations and specific types of cancer has also been described in several studies. For example, vitiligo occurs much more often in melanoma patients or pneumonitis in NSCLC patients[11,12]. However, further investigations are needed to delineate the underlying mechanism(s).

GENERAL APPROACH FOR THE MANAGEMENT OF irAEs

With the incorporation of immune checkpoint blockade as a standard cancer treatment strategy, it is imperative to facilitate the implementation of a practical algorithm for the optimal management of irAEs. For this purpose, the American Society of Clinical Oncology (ASCO) has created organ-specific guidelines in cooperation with the National Comprehensive Cancer Network (NCCN)[15]:

As mentioned earlier, the use of immune checkpoint blockers can cause a wide spectrum of irAEs affecting multiple organ systems including the skin, gastrointestinal, hepatic and endocrine system. One fundamental obstacle when treating irAEs lies within the balance of achieving adequate irAE control without

compromising immunotherapy response. For a better assessment of irAEs, they are categorised according to the Common Terminology Criteria for Adverse Events grading system: In general, continuation of ICI therapy should be opted with close monitoring for grade 1 toxicities, with the exception of some neurologic, hematologic, and cardiac toxicities. In contrast, treatment with immune checkpoint inhibitors should be withheld for most grade 2 toxicities, and re-initiation should be considered as soon as symptoms and/ or laboratory values revert to grade 1 or less. For the low-severity irAEs (grade 1-2), corticosteroids may be administered with an initial dose of 0.5 to 1 mg/kg/d of prednisone or equivalent. In case of severe irAEs (grade 3-4), ICI therapy should be discontinued, and high dose corticosteroid treatment should be applied (prednisone at 1-2 mg/kg/d or methylprednisolone intravenously at 1-2 mg/kg/d). Once the irAEs have resolved, corticosteroids should be tapered over the course of at least 4 to 6 weeks. If proper symptom relief is not achieved within 48 to 72 hours of high-dose corticosteroids, other immunosuppressants such as infliximab, rituximab, methotrexate or mycophenolate mofetil may be offered for some toxicities. Currently, several studies are in progress, determining the efficacy of distinct approaches to diminish irAE occurrence while maintaining efficacy, such as prolonging the intervals between treatment administration. Until results from these studies become available, dose reductions are not recommended but instead, therapeutic adjustments by way of temporary or permanent discontinuation of ICI therapy should be preferred. Importantly, irAEs of grade 4 warrant permanent discontinuation of ICI therapy, with the exception of endocrinopathies that have been successfully managed by hormonal replacement (Table 3).

Table 3. A practical approach in the management of irAEs associated with immune checkpoint inhibitors. (Adapted from Trinh S. et al. Management of Immune-Related Adverse Events Associated with Immune Checkpoint Inhibitor Therapy: a Minireview of Current Clinical Guidelines.)

The basic algorithm for the management of immune-related adverse events (irAEs)		
irAE	ICI therapy	Treatment for irAE
Grade 1	• Discontinue in case of hypophysitis, pneumonitis, sarcoidosis • Consider withholding if renal irAE • Hold if neurologic, aplastic anaemia, acquired haemophilia • Continue for all other irAEs	Prednisone 0.5-1mg/kg/day if acquired hemophilia
Grade 2	• Consider holding if dermotologic, rheumatoilogic,or lymphopnie • Hold for all others	Prednisone 0.5-1mg/kg/day if gastrointestinal Prednisone 1-2mg/kg/day if hypophysitis Prednisone 2mg/kg/day if transverse myelitis
Grade 3	• Discontinue if hepatitis, renal, ocular, neurologic, cardiovascular, rheumatologic, and/ or hematologic • Hold for all others	Prednisone 1-2mg/kg/day Prednisone 2-4mg/kg/day if peripheral neuropathy or Guillain Barre Syndrome Consider plasmapheresis, intravenous immunoglobulin therapy, methotrexate, azathioprine, or mycophenolate mofetil through Grade 4 if myositis Consider methotrexate or tocilizumab through Grade 4 if refractory arthritis Consider rituximab or cyclophosphamide if acquired haemophilia
Grade 4	Discontinuation	Prednisone 2-4mg/kg/day

SPECIAL PATIENT GROUP WITH UNDERLYING AUTOIMMUNE DISEASES

In light of the characteristics of irAEs associated with ICI therapy, it seems plausible that patients with a history of autoimmune diseases such as ulcerative colitis, Crohn's disease, lupus and active rheumatoid arthritis, have been excluded from clinical trials using immune checkpoint inhibitors. However, increasing evidence has emerged indicating that even in this special patient cohort, the use of immune checkpoint antibodies is deemed feasible[16,17]. For example, a systemic review of case reports on patients suffering from autoimmune conditions treated with immune checkpoint inhibitors revealed that 40% of the patients did not experience an irAE or exacerbation of their underlying autoimmune disease[18]. Nevertheless, given the potential fatal outcome of certain severe irAEs, the application of immune checkpoint inhibitors to this patient group should be cautious.

CONCLUSION

With the expanding indications for immune checkpoint inhibitors in cancer treatment, the adequate management of irAEs plays a paramount role in the clinical routine of physicians and other medical professionals involved in the care of cancer patients. In general, immune-based cancer treatment are deemed to have a more favourable toxicity and tolerability profile when compared to other standard cancer regimens. However, since irAEs associated with immunotherapy differentiate themselves substantially from side effects caused by conventional cancer treatment such as cytotoxic chemotherapy, practical guidelines have been published by the ASCO in order to facilitate optimal symptom-orientated treatment of irAEs. While mild toxicities do not necessarily require discontinuation of ICI therapy, the use of corticosteroids and discontinuation of ICI therapy should be used promptly in patients with moderate and severe irAEs.

References

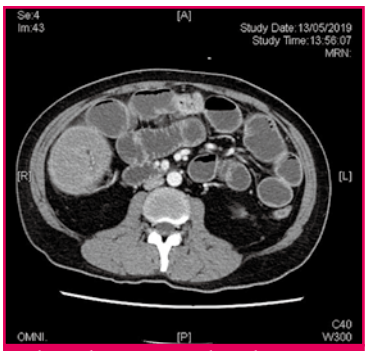
1. Buchbinder EI, Desai A. CTLA-4 and PD-1 pathways: Similarities, differences, and implications of their inhibition. Am J Clin Oncol 2016.;39:98-106.
2. La-Beck NM, Jean GW, Huynh C, Alzghari SK, Lowe DB. Immune checkpoint inhibitors: New insights and current place in cancer therapy. Pharmacotherapy 2015.; 35:963-76.
3. https://www.cancerresearch.org/immunotherapy/timeline-of-progress (last accessed on 2019 Oct 20)
4. Yervoy (ipilimumab) Package Insert. New York, USA: Bristol-Myers Squibb; July 2018. Available from: https://www.packageinserts.bms.com/pi/pi_yervoy.pdf. (last accessed on 2019 Oct 20)
5. Keytruda (pembrolizumab) Package Insert. Whitehouse Station, New Jersey, USA: Merck Sharp and Dohme Corp.; December 2018. Available from: https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf. (last accessed on 2019 Oct 20).
6. Opdivo (nivolumab) Package Insert. New York, USA: Bristol-Myers Squibb; November, 2018. Available from: https://www.packageinserts.bms.com/pi/pi_opdivo.pdf. (last accessed on 2019 Oct 20).

7. Tecentriq (atezolizumab) Package Insert. South San Francisco, California, USA: Genentech, Inc.; December, 2018. Available from: https://www.gene.com/download/pdf/tecentriq_prescribing.pdf. (last accessed on 2019 Oct 20).
8. Bavencio (avelumab) Package Insert. Rockland, Massachusetts, USA: EMD Serono, Inc.; October, 2018. Available from: https://www.emdserono.com/content/dam/web/corporate/non-images/country-specifics/us/pi/bavencio-pi.pdf. (last accessed on 2019 Oct 20).
9. Imfinzi (durvalumab) Package Insert. Wilmington, Delaware, USA: AstraZeneca Pharmaceuticals LP.; February, 2018. Available from: https://www.azpicentral.com/imfinzi/imfinzi.pdf#page=1. (last accessed on 2019 Oct 20)
10. Khan M, Lin J, Liao G, Tian Y, Liang Y, Li R, et al. Comparative analysis of immune checkpoint inhibitors and chemotherapy in the treatment of advanced non-small cell lung cancer: A meta-analysis of randomized controlled trials. Medicine (Baltimore) 2018;97:e11936
11. Michot JM, Bigenwald C, Champiat S, Collins M, Carbonnel F, Postel-Vinay S, et al. Immune-related adverse events with immune checkpoint blockade: A comprehensive review. Eur J Cancer 2016;54:139-48.
12. Nishino M, Giobbie-Hurder A, Hatabu H, et al: Incidence of programmed cell death 1 inhibitorrelated pneumonitis in patients with advanced cancer: A systematic review and meta-analysis. JAMA Oncol 2:1607-1616, 2016
13. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med 2018;378:158-68.
14. Baxi S, Yang A, Gennarelli RL, Khan N, Wang Z, Boyce L, et al. Immune-related adverse events for anti-PD-1 and anti-PD-L1 drugs: Systematic review and meta-analysis. BMJ 2018;360:k793.
15. Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2018;36:1714-68.
16. Johnson DB, Sullivan RJ, Ott PA: Ipilimumab therapy in patients with advanced melanoma and preexisting autoimmune conditions. JAMA Oncol 2: 234-240, 2016
17. Menzies AM, Johnson DB, Ramanujam S, et al: Anti-PD-1 therapy in patients with advanced melanoma and preexisting autoimmune disorders or major toxicity with ipilimumab. Ann Oncol 28: 368-376, 2017
18. Abdel-Wahab N, Shah M, Suarez-Almazor M: Use of immune checkpoint inhibitors in thetreatment of patients with cancer and preexisting autoimmune diseases: A systematic review of casereports. World Congress of Gastroenterology ACG2017 Annual Scientific Meeting Washington, DC, November 1116, 2016

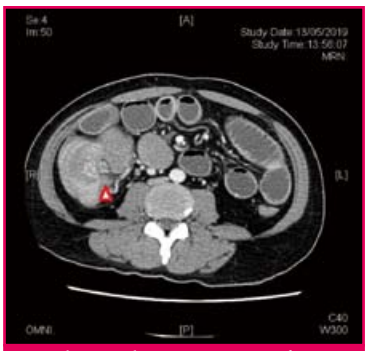
Radiology Quiz

Dr Jeremy Man-leung YU

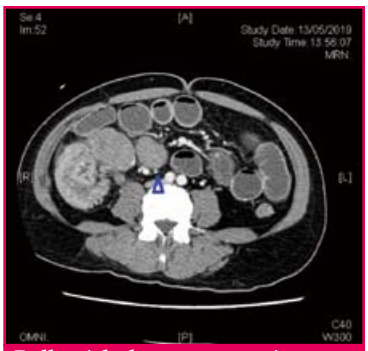
Dr Jeremy Man-leung YU



A large homogenously enhancing mass was noted in the right-sided colon.



Intraluminal invagination of terminal ileum mesentery suggested intussusception, indicated by a red arrowhead.



Bulky right lower mesenteric lymphadenopathies were present, indicated by a blue arrowhead.

A 49 year-old gentleman with good past health presented to AED with symptoms of intestinal obstruction. Abdominal X-ray revealed dilated small bowel. Blood test showed microcytic hypochromic anaemia. Contrast CT abdomen and pelvis was performed for intestinal obstruction in a patient with virgin abdomen to look for underlying cause.

Questions

1. What were the CT findings?
2. What is the possible differential diagnosis?
3. What imaging features suggest one differential diagnosis over others?
4. How common is intussusception in the adult patient?
5. What should be the next step of management for the patient?

(See P.36 for answers)

SGLT2 Inhibitors – More Clinical Data, More Patient Candidates?

Dr Paul Chi-Ho LEE

Dr Paul Chi-Ho LEE

MBBS (HK), MRCP (UK), FHKCP, FHKAM
Clinical Assistant Professor,
Department of Medicine, University of Hong Kong, Hong Kong

The advent of sodium-glucose co-transporter 2 (SGLT2) inhibitors has declared a new chapter in the management of type 2 diabetes. This new class of oral anti-diabetic agents, which introduces a novel strategy of glucose-lowering through decreased renal reabsorption of glucose, is certainly a welcome addition to the armamentarium for the treatment of type 2 diabetes. This is not only because of their accompanying blood-pressure lowering and weight-reducing properties, but also because of their cardio-renal benefits that were well demonstrated in multiple large-scale randomised controlled trials. In 2018, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) issued an updated consensus statement, which recommended the use of SGLT2 inhibitors in those with established atherosclerotic cardiovascular disease (ASCVD) or chronic kidney disease (CKD), especially with co-existing heart failure. Recently, the European Society of Cardiology (ESC), in collaboration with the EASD, further put forward the position of SGLT2 inhibitors, by recommending their use in drug-naïve patients, before metformin, who have ASCVD or target organ damage, including the presence of proteinuria, left ventricular hypertrophy, or retinopathy. Moreover, the ESC guidelines also recommended SGLT2 inhibitors in those with multiple risk factors of ASCVD and CKD, namely long duration of diabetes ≥10 years, old age, presence of hypertension, dyslipidaemia, smoking and obesity. While it is still too early to see how much clinicians agree and comply with these new recommendations, the ESC guidelines have indeed put a large emphasis on the positive cardio-renal outcomes brought about by SGLT2 inhibitors in various cardiovascular outcome trials (CVOTs).

In a meta-analysis of 34,322 patients from three main CVOTs of SGLT2 inhibitors: EMPA-REG OUTCOME for empagliflozin, CANVAS Program for canagliflozin, and DECLARE-TIMI 58 for dapagliflozin,[1] the benefits of SGLT2 inhibitors in the reduction of major adverse cardiovascular events, a composite of myocardial infarction, stroke, and cardiovascular death, were only demonstrable in those with established ASCVD. In contrast, SGLT2 inhibitors reduced the risk of hospitalisation for heart failure in both patients with and without established ASCVD. Moreover, SGLT2 inhibitors consistently reduced CKD progression in patients with type 2 diabetes regardless of the presence of ASCVD, or their renal function at baseline. These results were consolidated in two more recent trials, CREDENCE and DAPA-HF, which evaluated the use of SGLT2 inhibitors in two extended populations with type 2 diabetes. In CREDENCE,[2] the use of canagliflozin significantly reduced the risks of adverse renal outcomes, which included the doubling of serum creatinine, end-stage kidney disease, or renal death, as well as cardiovascular events, in 4,401 participants with type 2 diabetes and CKD. All of these participants had albuminuria on angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), with their eGFR levels between 30 and 90 ml/min/1.73 m^2. Their findings confirmed that the reno-protective effects of SGLT2 inhibitors were additive to ACEI/ARB and could be demonstrated across all levels of renal function at baseline. On the other hand, in the DAPA-HF trial,[3] which involved 4,744 participants with reduced left ventricular ejection fraction of ≤40% while on standard medical and/or device therapy for heart failure, the use of dapagliflozin significantly reduced the risks of worsening heart failure and cardiovascular deaths. Importantly, the benefits were achieved regardless of the presence of diabetes. Since the glucose-lowering effects through SGLT2 inhibition lessen as renal function worsens, collectively, the findings from CREDENCE and DAPA-HF suggested that SGLT2 inhibitors provide cardio-renal protection through mechanisms independent of glucose-lowering. Indeed, in the heart, mechanistic studies have proposed that SGLT2 inhibitors could improve ventricular loading, and exert beneficial effects on myocardial metabolism and cardiac fibrosis; whereas in the kidney, SGLT2 inhibitors restore normal tubulo-glomerular feedback, reverse vasodilation of the afferent arterioles and ameliorate glomerular hypertension.[4]

Given the multiple salutary metabolic effects of SGLT2 inhibition, the use of SGLT2 inhibitors in type 1 diabetes is appealing. Indeed, several phase 2 and phase 3 randomised trials have also examined the use of SGLT2 inhibitors in adults with type 1 diabetes, such as the EASE trials for empagliflozin and the DEPICT studies for dapagliflozin.[5] Overall, in these studies, SGLT2 inhibitors improved body weight, HbA1c levels and even glucose variability of the participants; however, at the expense of an increased rate of ketones-related adverse events. To date, although the European Commission has approved dapagliflozin in early 2019 as an adjunct to insulin therapy in adults with type 1 diabetes whose body mass index (BMI) is ≥27kg/m^2, none of the SGLT2 inhibitors are currently approved by the U.S. Food and Drug Administration (FDA).

SGLT2 inhibitors increase the risk of ketoacidosis. Therefore, in patients with clinical features suspicious of latent autoimmune diabetes in adulthood (LADA), such as young age, low BMI <25 kg/m^2 and rapidly

Table 1 Dosing recommendations of SGLT2 inhibitors available in Hong Kong

	eGFR in ml/min/1.73m^2			
	≥ 60	≥45 and <60	<45	<30
Canagliflozin (INVOKANA®)	• 100mg daily • 300mg daily if tolerated	• 100mg daily	• 100mg daily if with albuminuria >300mg/day	• 100mg daily if already initiated on therapy and with albuminuria >300mg/day Contraindicated in those on dialysis
Dapagliflozin (FORXIGA®)	• 10mg daily	• 10mg daily	• Use is not recommended	• Contraindicated for use
Empagliflozin (JARDIANCE®)	• 10mg • 25mg daily if tolerated	• 10mg daily • 25mg daily if tolerated	• Initiation is not recommended • Discontinue if eGFR is persistently <45 ml/min/1.73m^2	• Contraindicated for use
Ertugliflozin (STEGLATRO®)	• 5mg • 15mg daily if tolerated	• Initiation is not recommended • Continued use not recommended	• Continued use not recommended	• Contraindicated for use

decompensating diabetes, clinicians should be very cautious before initiating SGLT2 inhibitors. Moreover, when prescribing for patients with type 2 diabetes, clinicians should follow dosing recommendations (Table 1) and be aware that some patient groups might not be perfect candidates for SGLT2 inhibitors, such as those with untreated prostatism, overactive bladder with bothersome urinary incontinence, poor personal hygiene with recurrent urogenital tract infections. Furthermore, patients who have been started on SGLT2 inhibitors should be clearly informed the need to withhold the medication during conditions that might precipitate ketoacidosis, such as acute illness, volume depletion, extensive exercise, excessive alcohol intake, or on a low-carbohydrate diet. In fact, it has been recommended by some guidelines to stop SGLT2 inhibitors three days prior to major surgical procedures.[6]

Over the years, driven by clinical evidence from several large-scale and well-conducted randomised controlled trials, we could see that SGLT2 inhibitors have gradually brought a paradigm shift in the pharmacological management of type 2 diabetes. While we eagerly await the results from more upcoming cardio-renal trials such as the DAPA-CKD, EMPA-Kidney and EMPEROR-HF trials, we should also look forward to further studies that are underway to evaluate the role of SGLT2 inhibitors in other diabetic complications, such as retinopathy, cancers and non-alcoholic fatty liver disease. Indeed, SGLT2 inhibitors have already been shown to reduce non-alcoholic steatohepatitis and liver fibrosis in humans, as well as the proliferation of hepatocellular carcinoma in preclinical studies.[7] On the other hand, good scientific evidence can only be translated to improved clinical care if patients comply and adhere to the treatment. In this regard, it should also be emphasised that patient education and counselling on the anticipated side effects, sick day management, etc., are equally important, and should be given during prescription of SGLT2 inhibitors. Only then will we make the best use of this new class of anti-diabetic agents and ultimately improve the overall standard of care in patients with diabetes.

References

1. Zelniker, TA, Wiviott, SD, Raz, I, Im, K, Goodrich, EL, Bonaca, MP, Mosenzon, O, Kato, ET, Cahn, A, Furtado, RHM, Bhatt, DL, Leiter, LA, McGuire, DK, Wilding, JPH, Sabatine, MS: SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet, 393: 31-39, 2019.
2. Perkovic, V, Jardine, MJ, Neal, B, Bompoint, S, Heerspink, HJL, Charytan, DM, Edwards, R, Agarwal, R, Bakris, G, Bull, S, Cannon, CP, Capuano, G, Chu, PL, de Zeeuw, D, Greene, T, Levin, A, Pollock, C, Wheeler, DC, Yavin, Y, Zhang, H, Zinman, B, Meininger, G, Brenner, BM, Mahaffey, KW, Investigators, CT: Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. N Engl J Med, 380: 2295-2306, 2019.
3. McMurray, JJV, Solomon, SD, Inzucchi, SE, Kober, L, Kosiborod, MN, Martinez, FA, Ponikowski, P, Sabatine, MS, Anand, IS, Belohlavek, J, Bohm, M, Chiang, CE, Chopra, VK, de Boer, RA, Desai, AS, Diez, M, Drozdz, J, Dukat, A, Ge, J, Howlett, JG, Katova, T, Kitakaze, M, Ljungman, CEA, Merkely, B, Nicolau, JC, O'Meara, E, Petrie, MC, Vinh, PN, Schou, M, Tereshchenko, S, Verma, S, Held, C, DeMets, DL, Docherty, KF, Jhund, PS, Bengtsson, O, Sjostrand, M, Langkilde, AM, Committees, D-HT, Investigators: Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med, 2019.
4. Verma, S, McMurray, JJV: SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review. Diabetologia, 61: 2108-2117, 2018.
5. Danne, T, Garg, S, Peters, AL, Buse, JB, Mathieu, C, Pettus, JH, Alexander, CM, Battelino, T, Ampudia-Blasco, FJ, Bode, BW, Cariou, B, Close, KL, Dandona, P, Dutta, S, Ferrannini, E, Fourlanos, S, Grunberger, G, Heller, SR, Henry, RR, Kurian, MJ, Kushner, JA, Oron, T, Parkin, CG, Pieber, TR, Rodbard, HW, Schatz, D, Skyler, JS, Tamborlane, WV, Yokote, K, Phillip, M: International Consensus on Risk Management of Diabetic Ketoacidosis in Patients With Type 1 Diabetes Treated With Sodium-Glucose Cotransporter (SGLT) Inhibitors. Diabetes Care, 42: 1147-1154, 2019.
6. Goldenberg, RM, Berard, LD, Cheng, AYY, Gilbert, JD, Verma, S, Woo, VC, Yale, JF: SGLT2 Inhibitor-associated Diabetic Ketoacidosis: Clinical Review and Recommendations for Prevention and Diagnosis. Clin Ther, 38: 2654-2664 e2651, 2016.
7. Dokmak, A, Almeqdadi, M, Trivedi, H, Krishnan, S: Rise of sodium-glucose cotransporter 2 inhibitors in the management of nonalcoholic fatty liver disease. World J Hepatol, 11: 562-573, 2019.

Number Needed to Treat: A Means of Comprehending the Impact of Medical Interventions in Terms of Absolute Benefit and/or Harm

Dr Cyrus KUMANA

Dr Cyrus KUMANA

BSc; MBBS; FRCP (London, Edinburgh, Glasgow, Canada), FHKAM(Medicine)
Founding Chair Professor & Emeritus Professor of Clinical Pharmacology & Therapeutics, Department of Medicine, The University of Hong Kong

This article focuses on the appropriate application of the parameter known as 'Number Needed to Treat' (**NNT**) and related issues used to describe the impact of interventions resorted to in clinical medicine, and provides a personal perspective on the topic. The term was first introduced in 1988,[1] to highlight the importance of considering clinical significance in terms of Absolute Risk (**AR**) rather than Relative Risk (**RR**), as only the former can enable clinicians to make genuinely well-informed decisions. Mathematically, NNT is the reciprocal of the 'Absolute Risk Reduction' (**ARR**); the smaller the number, the greater the perceived effect, and is regarded as statistically significant only if its 95% confidence interval does not traverse infinity (i.e. does not yield positive and negative values).‡

Just as meta-analysis should not be regarded as the infallible holy grail for arriving at critical treatment decisions, similar cautions should apply to unreserved reliance on NNTs.[2] For example, comparing NNT values derived from in an older trial to those in a very new one could well invalidate the exercise. This is because, in the newest trial, both actively treated and control patients are more liable to be in receipt of supplementary efficacious co-treatments, making the differences in outcomes in those on active treatment and the controls less marked and thus liable to yield larger NNTs. In long-term trials moreover, the NNT is inextricably time-dependent. Yet in the medical literature, NNTs continue to be cited without referring to relevant periods. So when it comes to comparing NNTs derived from treatments of different duration, it is convenient to overcome this anomaly by various adjustments. Expressing values as NNT/year is one such method, but this makes the implicit assumption that any differences in treatment efficacy are evenly distributed over the duration of corresponding treatment periods. It should also be appreciated that taken in isolation, and the NNT cannot inform on whether a treatment is worthwhile. Thus, a value of 100 could be regarded as worth pursuing so long as the treatment in question was not costly and safe. On the contrary and depending on the patient's circumstances, if the desired outcome entailed only minimal benefit, was very costly or associated with significant risk of serious toxicity - even a value of 10 could be regarded as unacceptable.

Generally, physicians (and to some extent patients too) appreciate the meaning of the terms 'Relative Risk Reduction' (RRR) and its converse RR, both of which are often expressed as percentages. However, even doctors are not adept at coming to terms with figures such as 0.086%, which is the ARR for myocardial infarction or coronary heart disease death applicable to the 4S study of high-risk patients treated with simvastatin for an average of 5.4 years.[3] By contrast, they find it easier to comprehend an NNT of 12 (i.e. one additional patient avoiding such an event for every 12 who are treated), which is another way of expressing the absolute risk reduction over the same period.[4] Another advantage of resorting to NNTs rather than RRRs is that they convey a fair idea of an intervention's overall cost-effectiveness. The later entails preventing event-related losses in longevity and/or quality of life, likely monetary costs, as well as patient numbers necessarily exposed to the adverse effects of the intervention (e.g. the side/adverse effects and inconvenience of taking long-term medication), just to prevent one individual from enduring an event. After the 2015 Supreme Court Montgomery judgement, the ability to communicate such ideas effectively has acquired added importance.[5] The latter ruling mandated that doctors give patients comprehendible, personally relevant information about all reasonable treatment options, for which the NNT would appear to be a suitable tool.

This article addresses several of the above mentioned diverse issues in relation to the application of the NNTs, all of which are discussed with reference to examples. These include: 1) describing an intervention's absolute benefits over finite periods of treatment, 2) expressing an intervention's harm (NNH) over finite periods of treatment, 3) expressing absolute benefit (or harm) attributable to once-off interventions, 4) meta-analysis by NNT and 5) Use of NNTs to develop treatment/prevention guidelines.

NNT TO DESCRIBE AN INTERVENTION'S ABSOLUTE BENEFITS, OVER FINITE PERIODS OF TIME

Table 1 is reproduced from a Contempo article in JAMA,[4] and shows a comparison of unadjusted RRR, NNT, and NNT/year values applicable to several iconic large-scale, long-term, randomised double blind clinical trials of therapy with different statins. Though not necessarily true, for the purpose of comparing results detailed in different trials the authors assumed that the effects of these drugs were evenly distributed over the corresponding intended follow-up treatment duration in each study. They also inferred that meaningful comparison could only apply to the specific statin

‡ Any NNT value of infinity corresponds to no effect

Table 1. Results of Long-term Studies of Statins (Excerpted from Kumana CR, Cheung BMY, Lauder IJ 1999. JAMA 282:1899-901 (Contempo Update) Gauging the Impact of Statins using Number Needed to Treat.)

	4S,* 1994	WOSCOPS,* 1995	CARE,[13,14] 1996, 1999	AFCAPS/TexCAPS,[12] 1998
Statin, dose per day	Simvastatin 10-40 mg	Pravastatin 40 mg	Pravastatin 40 mg	Lovastatin 20-40 mg
Average follow-up duration, y	5.4†	4.9	5.0†	5.2
Eligibility criteria				
Coronary heart disease	Present	Absent	Present	Absent
Hyperlipidemia	Present	Present	Absent	Absent
Mean cholesterol level, mmol/L (mg/dL)	6.8 (262.5)	7.0 (270.3)	5.4 (208.5)	5.7 (220.1)
Subject characteristics				
Mean age, y	54	59	59	58
Men	3617	6595	3583	5608
Women	827	0	576	987
All end point deaths				
RRR (95% CI)	30 (15-42)	22 (0-40)	9 (−12 to 26)	−4‡
NNT (95% CI)	30 (20-65)	112 (55 to NA)	128 (30 to NA)	NA
NNT per year	163	551	639	NA
Fatal and nonfatal coronary events§				
RRR (95% CI)	34 (25-41)	31 (17-43)	24 (9-36)	37 (21-50)
NNT (95% CI)	12 (9-17)	44 (29-95)	33 (20-99)	49 (33-99)
NNT per year	63	217	167	256
Fatal and nonfatal strokes				
RRR (95% CI)	30 (4-48)‖	11 (−33 to 40)	27 (4-44)‖	NA
NNT (95% CI)	80 (42-885)	642 (134 to NA)	65 (34-586)	NA

*4S indicates Scandinavian Simvastin Survival; WOSCOPS, West of Scotland Coronary Prevention; CARE, Cholesterol and Recurrent Events; AFCAPS/TexCAPS, Air Force/Texas Coronary Artery. RRR indicates relative risk reduction; CI, confidence interval; NNT, number needed to treat; NA, not available. The values for RRR (95% CI) are from previous publications. Whenever an RRR (95% CI) was negative, no upper limit was quoted for the corresponding NNT (95% CI). On average, reduction in total cholesterol achieved in these trials was 17% to 25%. In contrast to the RRR (95% CI) values for coronary events, corresponding NNT (95% CI) values in the trials do not overlap, indicating a statistically significant difference.
†Median duration treated as a mean.
‡Negative value denotes increased mortality in the treatment group rendering further analysis inappropriate.
§Excludes uncomplicated coronary artery bypass grafting or coronary angioplasty.
‖Inclusive of transient ischemic attacts (TIAs): in CARE, if TIAs are excluded, the corresponding values become RRR, 32 (95% CI, 4-52), and NNT, 86 (95% CI, 55-1140).

and dosages actually used in each trial; there being no specific information on the relative efficacy/potency of each agent (other than roughly comparable cholesterol-lowering effects).

Interestingly, the table shows that all four trials yielded a limited range of RRR values (e.g. 24-37 for fatal and nonfatal coronary events. Whereas the corresponding NNT values differed markedly; when annualised for treatment duration, they ranged from 63 to 256. Thus, assuming that the statin treatments used in each trial conferred comparable efficacy on lipid metabolism - it appeared that patients at highest risk (those having prior coronary heart disease [CHD] and hypercholesterolaemia) derived the greatest benefit. By contrast, patients in AFCAPS/TexCaps who lacked both of these risk factors enjoyed the least benefit. Moreover, though by no means statistically significant, this was the only trial in which active treatment was associated with a slight increase in overall mortality. Not surprisingly, some authorities are of the opinion that statins do not improve the length or quality of life when used solely for primary prevention in the absence of risk factors, which may also be consistent with the very high rates of non-adherence to these drugs due to side effects, particularly in the elderly.[6] It, therefore, seems that worthwhile cardiovascular benefits from taking statins are largely confined to patients with recognised risk factors. Analysis of the NNTs detailed in Table 1 also reveals that recourse to statins reveals a much greater impact (yields smaller NNTs) on preventing CHD events than strokes, which is in marked contrast to the known impact of treatment of hypertension (with different classes of drugs).

Table 2 was derived by analysing the results of the so-called the Heart Protection study in high-risk individuals treated with a statin.[7,8] This analysis also emphasises the critical importance of clinical rather than soft risk factors. It shows that in the presence of accepted risk factors (CHD or diabetes), the absolute benefits of simvastatin are scarcely influenced by the serum/plasma cholesterol level or age, corresponding NNT values being virtually the same. Thus, in terms of preventing CHD events with statins, having an established clinical risk factor (CHD or diabetes) was of crucial importance, regardless of prevailing cholesterol values or age.

Table 2: First Major Vascular Event over 5 years (Adapted from Heart Protection Study Collaborative Group 2002. Lancet; 360:7–22. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo controlled trial Kumana CR, Cheung BM, Lauder IJ 2003. Evidence Based Medicine; 8:10-11. Commentary on MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet)*

Risk Category		NNT (95% CI)
Cholesterol (mM/L)	< 5.0	19 (13 to 35)
	≥ 5.0 to < 6	18 (13 to 27)
	≥ 6	19 (14 to 30)
Age (years)	< 65	19 (15 to 28)
	≤ 65 to < 70	16 (11 to 26)
	> 70	20 (14 to 36)
Prior CHD only		18 (13 to 26)
Prior diabetes only		21 (14 to 40)

* Non-fatal MI, CHD death, Stroke, or Revascularisation procedure (coronary or non-coronary)

NNT USED TO EXPRESS HARM (NNH), OVER FINITE PERIODS OF TIME

Numerous publications have reported therapeutic and/or prophylactic long-term interventions associated with specific unfavourable effects/harm. When assessing desirable outcomes, unfavourable impacts result in negative RRRs (or RR values less than unity). Correspondingly, NNTs become negative, but can be referred to with a positive value and termed 'number need to harm' or **NNH**. Moreover, just as positive NNTs provide a genuine reflection of absolute benefit, in contrast to RR and RRR values, they represent an easily understood parameter to describe absolute harm.

NOW FOR ADULT **PSORIATIC ARTHRITIS (PsA)** AND **ANKYLOSING SPONDYLITIS (AS)**[1]

WATCH ME

ENJOY THE FINER THINGS IN LIFE

DISCOVER A NEW WAY TO TREAT PsA AND AS

AND WATCH YOUR PATIENTS FIND A NEW OUTLOOK ON LIFE

INTRODUCING COSENTYX®:

THE FIRST AND **ONLY FULLY HUMAN IL-17A** INHIBITOR[1]

Cosentyx®
secukinumab

LIFE IN MOTION

Reference:

1. Cosentyx® Hong Kong Product Insert (Ref: EMA Apr 2016)

Cosentyx®

Important note: Before prescribing, consult full prescribing information. **Presentation:** Secukinumab. Powder for solution for subcutaneous injection, solution for subcutaneous injection in pre-filled syringe or pre-filled pen contain 150 mg of secukinumab. **Indications: Plaque psoriasis** Cosentyx is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy. **Psoriatic arthritis** Cosentyx, alone or in combination with methotrexate (MTX), is indicated for the treatment of active psoriatic arthritis in adult patients when the response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate. **Ankylosing spondylitis** Cosentyx is indicated for the treatment of active ankylosing spondylitis in adults who have responded inadequately to conventional therapy. **Dosage and administration:** ***Dosage*** **Plaque psoriasis:** The recommended dose is 300 mg by subcutaneous injection with initial dosing at weeks 0, 1, 2 and 3, followed by monthly maintenance dosing starting at week 4. Each 300 mg dose is given as two subcutaneous injections of 150 mg. **Psoriatic arthritis:** The recommended dose is 150 mg by subcutaneous injection with initial dosing at Weeks 0, 1, 2 and 3, followed by monthly maintenance dosing starting at Week 4. For patients who are anti-TNFα inadequate responders or patients with concomitant moderate to severe plaque psoriasis, the recommended dose is 300 mg by subcutaneous injection with initial dosing at Weeks 0, 1, 2 and 3, followed by monthly maintenance dosing starting at Week 4. Each 300 mg dose is given as two subcutaneous injections of 150 mg. **Ankylosing spondylitis:** The recommended dose is 150 mg by subcutaneous injection with initial dosing at Weeks 0, 1, 2 and 3, followed by monthly maintenance dosing starting at Week 4. For all of the above indications, available data suggest that a clinical response is usually achieved within 16 weeks of treatment. Consideration should be given to discontinuing treatment in patients who have shown no response by 16 weeks of treatment. Some patients with an initial partial response may subsequently improve with continued treatment beyond 16 weeks. **♦Paediatric population (aged below 18 years):** The safety and efficacy of Cosentyx in children below the age of 18 years have not yet been established. No data are available. **♦Renal impairment / hepatic impairment:** Cosentyx has not been studied in these patient populations. No dose recommendations can be made. ***Administration*** Cosentyx is to be administered by subcutaneous injection. If possible, areas of the skin that show psoriasis should be avoided as injection sites. **Contraindications:** ♦Cosentyx is contraindicated in patients who have/had severe hypersensitivity reactions reaction to the active substance or to any of the excipients. ♦Clinically important, active infection (e.g. active tuberculosis) **Warnings and precautions: ♦Infections:** Cosentyx has the potential to increase the risk of infections. Caution in patients with chronic or history of recurrent infection. If a patient develops a serious infection, the patient should be closely monitored and Cosentyx should not be administered until the infection resolves. Anti-tuberculosis therapy should be considered prior to initiation of Cosentyx in patients with latent tuberculosis. Cosentyx should not be given to patients with active tuberculosis. **♦Crohn's disease:** Patients with active Crohn's disease treated with Cosentyx should be followed closely. **♦Hypersensitivity reactions:** In clinical studies, rare cases of anaphylactic reactions have been observed in patients receiving Cosentyx. Administration of Cosentyx should be discontinued immediately and appropriate therapy initiated if an anaphylactic or other serious allergic reaction occurs. **♦Latex-sensitive individuals:** The removable cap of the Cosentyx pre-filled syringes/pen contains a derivative of natural rubber latex. **♦Vaccinations:** Cosentyx should not be given concurrently with live vaccines. Patients receiving Cosentyx may receive concurrent inactivated or non-live vaccinations. **♦Concomitant immunosuppressive therapy:** In psoriasis studies, the safety and efficacy of Cosentyx in combination with immunosuppressants, including biologics, or phototherapy have not been evaluated. **Women of childbearing potential:** Effective method of contraception during treatment and for at least 20 weeks after treatment should be used. **Pregnancy:** There are no adequate data from the use of secukinumab in pregnant women. As a precautionary measure, it is preferable to avoid the use of Cosentyx in pregnancy. **Breast-feeding:** It is not known whether secukinumab is excreted in human milk. Because of the potential for adverse reactions in nursing infants from secukinumab, a decision on whether to discontinue breast-feeding during treatment and up to 20 weeks after treatment or to discontinue therapy with Cosentyx must be made taking into account the benefit of breast-feeding to the child and the benefit of Cosentyx therapy to the woman. **Adverse drug reactions: Very common (≥10%):** Upper respiratory tract infections. **Common (1 to <10%):** Oral herpes, diarrhea, rhinorrhea. **Uncommon (0.1 to <1%):** Oral candidiasis, neutropenia, otitis externa, tinea pedis, conjunctivitis, urticaria. **Rare (0.01 to <0.1%):** Anaphylactic reactions. **Interactions:** Live vaccines should not be given concurrently with Cosentyx. Therapeutic monitoring should be considered when using Cosentyx with CYP450 substrates with a narrow therapeutic index, where the dose is individually adjusted (e.g. warfarin). No interaction was seen when Cosentyx was administered concomitantly with methotrexate (MTX) and/or corticosteroids in arthritis studies (including in patients with psoriatic arthritis and ankylosing spondylitis). **Packs and prices:** Powder in Vial: 1's. Solution in pre-filled syringe: 1's or 2's. Solution in pre-filled pen; 1's or 2's. Not all pack sizes are marketed. **Legal classification:** P1S1S3

Ref: EMA Apr 2016

NOVARTIS

Novartis Pharmaceuticals (HK) Ltd

7/F, Citi Tower, One Bay East, 83 Hoi Bun Road,
Kwun Tong, Kowloon, Hong Kong
Tel: (852) 2882 5222 Fax: (852) 2577 0274

HK1907705870

Entresto®
sacubitril/valsartan

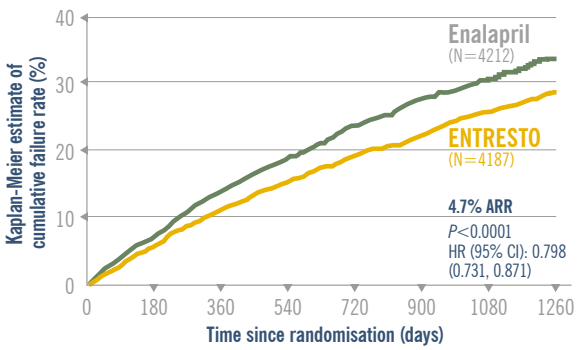
THE SOONER, THE BETTER.

Keep HFrEF patients alive, out of the hospital, and on the right path

The path to slowing disease progression starts with ENTRESTO. Improve survival by reducing the risk of HF events, and give them more time to keep doing what they love.

In the PARADIGM-HF study,

ENTRESTO reduced the risk of CV death or HF hospitalisation as a first event by 20% vs enalapril (primary end point)[1*]



70% of patients were NYHA Class II[2]

In post hoc analyses of the PARADIGM-HF study,

ENTRESTO reduced the risk of sudden cardiac death in HF patients by 20% vs enalapril ($P=0.0082$)[1†]

ENTRESTO reduced the risk of a primary end point event in both the most and least stable HF patients[3‡]

ENTRESTO helped slow the clinical progression of HF vs enalapril[4§]

- ⬇ **16%** fewer CV hospitalisations ($P<0.001$)
- ⬇ **30%** lower rate of ED visits ($P=0.017$)
- ⬇ **16%** less likely to require intensification of outpatient HF therapy

By slowing disease progression, ENTRESTO helps keep HF patients out of the hospital and living longer.

ARR = absolute risk reduction; EF = ejection fraction; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; HF = heart failure; HFrEF = heart failure with reduced ejection fraction

*PARADIGM-HF was a multinational, randomised, double-blind, active-controlled, 2-arm event-driven trial comparing the long-term efficacy and safety of enalapril and ENTRESTO in 8442 patients in NYHA classes II-IV with chronic symptomatic HF and reduced EF (LVEF ≤40%. This was changed to ≤35% by an amendment to the protocol on 15 December, 2010). Patients were required to discontinue their existing ACE inhibitor or ARB therapy and entered a sequential single-blind run-in period during which patients received treatment with enalapril 10 mg twice daily, followed by treatment with ENTRESTO 49 mg/51 mg twice daily, increasing to 97 mg/103 mg twice daily. Patients were then randomised to the double-blind period of the study to receive either ENTRESTO 97 mg/103 mg (n=4209) or enalapril 10 mg twice daily (n=4233). Patients received treatment for up to 4.3 years, with a median duration of follow-up of 27 months; 3271 ENTRESTO patients were treated for more than 1 year.[1] †This post hoc analysis of PARADIGM-HF examined the effect of ENTRESTO compared with enalapril on mode of death in HF patients (a total of 1546 patients died, including 711 in the ENTRESTO group and 835 in the enalapril group [17% and 19.8% of total patients, respectively]). The majority of deaths were cardiovascular (80.9%; n=1251), and the majority of these CV deaths were categorised as sudden (44.8%) or HF related (26.5%).[1] ‡This post hoc analysis of PARADIGM-HF examined the risk of the primary outcome based on presence of and time from a prior HF hospitalisation as a measure of clinical stability. Patients having their most recent HF hospitalisation within 3 months of screening (n=1611) were defined as least stable, while patients who had no prior HF hospitalisation (n=3125) were defined as the most stable. Compared to patients in the enalapril group, patients in the ENTRESTO group, regardless of presence of and time from a prior HF hospitalisation, had a reduction of at least 19% in the risk of a primary end point event.[1,3] §This post hoc analysis of PARADIGM-HF focused on prespecified measure of nonfatal clinical deterioration. In comparison with the enalapril group, fewer ENTRESTO patients required intensification of medical treatment for HF (520 for ENTRESTO vs 604 for enalapril; HR, 0.84; 95% CI, 0.74-0.94; P=0.003) or an ED visit for worsening HF (HR, 0.66; 95% CI, 0.52-0.85; P=0.001).[1,4]

References: 1. ENTRESTO Core Data Sheet, Version 1.2. Novartis Pharmaceuticals, July 2017. **2.** McMurray JJ, et al. *N Engl J Med*. 2014;371(11):993-1004. **3.** Solomon SD, et al. *JACC Heart Fail*. 2016;4(10):816-822. **4.** Packer M, et al. [Abstract P1705]. *Circulation*. 2015;131(1):54-61.

ENTRESTO tablets Important note: Before prescribing, consult full prescribing information. **Presentation: ENTRESTO 50 mg film-coated tablets** Each film-coated tablet contains 24.3 mg sacubitril and 25.7 mg valsartan (as sacubitril valsartan sodium salt complex). **ENTRESTO 100 mg film-coated tablets** Each film-coated tablet contains 48.6 mg sacubitril and 51.4 mg valsartan (as sacubitril valsartan sodium salt complex). **ENTRESTO 200 mg film-coated tablets** Each film-coated tablet contains 97.2 mg sacubitril and 102.8 mg valsartan (as sacubitril valsartan sodium salt complex). **Indications:** Treatment of symptomatic chronic heart failure (NYHA class II-IV) in adult patients with reduced ejection fraction to reduce the risk of cardiovascular death and hospitalization due to heart failure. **Dosage and administration: Adults:** •The recommended starting dose of ENTRESTO is 100 mg twice daily. The dose should be doubled at 2-4 weeks to the target dose of one tablet of 200 mg twice daily, as tolerated by the patient. •A starting dose of 50 mg twice daily is recommended for patients not currently taking an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB), and should be considered for patients previously taking low doses of these agents. **•Geriatric patients:** The dose should be in line with the renal function. **•Pediatric patients:** ENTRESTO has not been studied. Use of ENTRESTO is not recommended. **•Renal impairment:** No dose adjustment is required in patients with mild renal impairment(Estimated Glomerular Filtration Rate (eGFR) 60-90 ml/min/1.73 m2); A starting dose of 50 mg twice daily is recommended in patients with moderate renal impairment(eGFR 30-60 ml/min/1.73 m2); A starting dose of 50 mg twice daily and caution is recommended in patients with severe renal impairment (eGFR <30 ml/min/1.73 m2). Not recommended for patients with end-stage renal disease. **•Hepatic impairment:** No dose adjustment is required in patients with mild hepatic impairment (Child-Pugh A classification). A starting dose of 50 mg twice daily is recommended in patients with moderate hepatic impairment (Child-Pugh B classification) or with AST/ALT values more than twice the upper limit of the normal range. In patients with severe hepatic impairment use of ENTRESTO is not recommended. **•Method of administration** For oral use. May be administered with or without food. **Contraindications: •**Hypersensitivity to the active substance, sacubitril, valsartan, or to any of the excipients. •Concomitant use with ACE inhibitors. ENTRESTO must not be administered until 36 hours after discontinuing ACE inhibitor therapy. •Known history of angioedema related to previous ACE inhibitor or ARB therapy. •Concomitant use with aliskiren in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m2). • Second and third trimester of pregnancy. •Hereditary or idiopathic angioedema •Severe hepatic impairment, biliary cirrhosis and cholestasis **Warnings and precautions: •Dual blockade of the Renin-Angiotensin-Aldosterone System (RAAS):** ENTRESTO must not be administered with an ACE inhibitor due to the risk of angioedema. ENTRESTO must not be initiated until 36 hours after taking the last dose of ACE inhibitor therapy. If treatment with ENTRESTO is stopped, ACE inhibitor therapy must not be initiated until 36 hours after the last dose of ENTRESTO. • The combination of ENTRESTO with direct renin inhibitors such as aliskiren is not recommended. The combination of ENTRESTO with aliskiren-containing products is contraindicated in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m2). • ENTRESTO contains valsartan, and therefore should not be co-administered with another ARB containing product. **•Hypotension:** If hypotension occurs, temporary down-titration or discontinuation of ENTRESTO is recommended. Dose adjustment of diuretics, concomitant antihypertensive drugs, and treatment of other causes of hypotension (e.g. hypovolemia) should be considered. Sodium and/or volume depletion should be corrected before starting treatment with ENTRESTO. **•Impaired renal function:** • Evaluation of patients with heart failure should always include assessment of renal function. Down titration of ENTRESTO should be considered in patients who develop a clinically significant decrease in renal function. Caution should be exercised when administering ENTRESTO in patients with severe renal impairment (eGFR <30 ml/min/1.73 m2). **•Hyperkalaemia:** Treatment should not be initiated if the serum potassium level is >5.4 mmol/l. Medications known to raise potassium levels (e.g. potassium-sparing diuretics, potassium supplements) should be used with caution. If clinically significant hyperkalemia occurs, measures such as adjustment of concomitant medicinal products, temporary down-titration or discontinuation should be considered. Monitoring of serum potassium is recommended especially in patients with risk factors such as renal impairment, diabetes mellitus, hypoaldosteronism, receiving a high potassium diet or mineralocorticoid antagonists. If serum potassium level is >5.4 mmol/l discontinuation should be considered. **•Angioedema:** If angioedema occurs, ENTRESTO should be immediately discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. ENTRESTO must not be re-administered. Patients with a prior history of angioedema were not studied. As they may be at higher risk for angioedema, caution is recommended if ENTRESTO is used in these patients. ENTRESTO must not be used in patients with a known history of angioedema related to previous ACE inhibitor or ARB therapy. Black patients may have increased susceptibility to develop angioedema. **•Patients with renal artery stenosis:** Caution is required in patients with renal artery stenosis and monitoring of the renal function is recommended. **•Patients with NYHA functional classification IV:** Caution should be exercised. **•B-type natriuretic peptide (BNP):** BNP is not a suitable biomarker of heart failure in patients treated with ENTRESTO. **•Hepatic impairment:** Caution is recommended when using ENTRESTO in patients with moderate hepatic impairment (Child-Pugh B classification) or with AST/ALT values more than twice the upper limit of the normal range. ENTRESTO is contraindicated in patients with severe hepatic impairment, biliary cirrhosis or cholestasis (Child-Pugh C classification). **Pregnancy:** The use of ENTRESTO is not recommended during the first trimester of pregnancy and is contraindicated during the second and third trimesters of pregnancy. **Breast-feeding:** It is not known whether ENTRESTO is excreted in human milk. Because of the potential risk for adverse drug reactions in breastfed newborns/infants, ENTRESTO is not recommended during breastfeeding. **Adverse drug reactions:** ***Very common (≥1/10):*** Hyperkalaemia, hypotension, renal impairment. ***Common (≥1/100 to <1/10):*** Anaemia, hypokalaemia, Hypoglycaemia, Dizziness, Cough, Headache, Syncope, Vertigo, Orthostatic hypotension, Diarrhoea, Nausea, Gastritis, Renal failure (renal failure, acute renal failure), Fatigue, Asthenia ***Uncommon (≥1/1,000 to <1/100):*** Hypersensitivity, Dizziness postural, Pruritis, Rash, Angioedema. **Interactions:** ***•Concomitant use contraindicated:*** aliskiren in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m2); Use with ACE inhibitors: ENTRESTO must not be started until 36 hours after taking the last dose of ACE inhibitor therapy. ACE inhibitor therapy must not be started until 36 hours after the last dose of ENTRESTO. ***•Concomitant use not recommended:*** ARB containing products ***•Caution when used concomitantly*** with OAT1B1 and OATP1B3 substrates(e.g. statins), PDE5 inhibitors (e.g. sildenafil), lithium, potassium-sparing diuretics (tramterene, amiloride) , mineral corticod antagonists (e.g. spironolactone, eplerenone), potassium supplements, salt substitutes containing potassium, other agents that may lead to increased serum potassium level (e.g. heparin), non-steroidal anti-inflammatory agents (NSAIDs) including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors), inhibitors of OATP1B1, OATP1B3, OAT3 (e.g. rifampin, cyclosporine),OAT1 (e.g. tenofovir, cidofovir) or MPR2 (e.g. ritonavir), furosemide, nitrates (e.g. nitroglycerine), metformin. **Packs:** 50mg: 28's; 100mg: 28's and 56's; 200mg: 56's. Not all pack sizes may be marketed. **Legal classification:** P.I.S.I.S3. **Ref:** EMA Nov 2015. **FULL PRESCRIBING INFORMATION IS AVAILABLE UPON REQUEST.**

HK1907/0264

NOVARTIS
Novartis Pharmaceuticals (HK) Ltd
7/F, Citi Tower, One Bay East, 83 Hoi Bun Road, Kwun Tong, Kowloon, Hong Kong
Tel: 2882 5222 Fax: 2577 0274

Table 3: Benefits vs Harms of Statins (Excerpted from Hippisley-Cox J, Coupland C 2010. BMJ; 340:c2197 doi:10.1136/bmj.c2197. Unintended effects of statins in men and women in England and Wales: population based cohort study using the QResearch database.)

Estimated 5 year NNT & NNH values (based on 368 UK General Practices; about 1 million men aged 30-84 years); findings for women were similar

Outcome	NNT (95% CI)	NNH (95%CI)
Benefits		
Cardiovascular Event Prevention	33 (24 to 57)	
Oesophageal Cancer Prevention	1082 (711 to 2807)	
Harms		
Acute RF		346 (245 to 539)
Cataract		52 (44 to 63)
Liver Dysfunction		142 (115 to 180)
Myopathy (sometimes symptomatic)		92 (74 to 112)

Table 4: RR and NNH/year values for rhythm control of AF derived from raw data published in the AFFIRM trial (4060 patients; mean follow-up duration 3.5 years) (Excerpted from Wyse DG, Waldo AL, DiMarco JP, et al 2002. NEJM; 347: 1825–33. Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation.)

Event	RR (95% CI)	NNH/year (95% CI)
Hospitalisation	1.12 (1.04 to 1.21)	47 (34 to 79)
Torsade	5.98 (1.30 to 27.58)	712 (411 to 2659)

For example, apart from their favourable impact on several cardiovascular outcomes – long-term treatment with statins has been associated with several unintended effects. This is amply exemplified by the five years NNH and NNT values for different endpoints shown in table 3, which was adapted from a comprehensive epidemiologic study published in 2010.[9] The table shows the substantial absolute benefits of statin therapy (NNT 33) for cardiovascular event prevention (a beneficial critical endpoint). Whereas the absolute harms attributable (admittedly to less serious deleterious outcomes) were relatively minor; corresponding NNH values ranged from 52 to 246. Among the latter, the only somewhat troubling NNH of 52 was for cataracts. This association does not prove causation by statin therapy, as on average non-users were about three years younger and differences in smoking history (a possible risk for cataracts) could also have been relevant. A recent case-control study and a meta-analysis looked into this somewhat bizarre finding,[10,11] and inferred some support but no clear evidence for the association with cataracts. The authors of these studies, therefore, recommend that due to the considerable cardiovascular benefits from statin therapy - this issue should not deter their use.

Recourse to NNTs (including negative values expressed as 'NNH') to describe adversity, provides much more relevant clinical information about the absolute liability to harms than RRs. Parameters shown in table 4 derived from the published findings in the AFFIRM trial of rhythm versus rate control for atrial fibrillation (AF),[12] illustrate this point. Notably, the RR for Torsade (a potentially dangerous cardiac arrhythmia) indicates that rhythm control patients endured almost six times the risk for that endpoint than controls. For hospitalisation, however, the RR was only 1.12. Thus, for Torsade that was a much less frequent outcome than hospitalisation - there was a comparatively trivial AR; respective NNH/year values for these outcomes were 712 versus 47.

NNT USED TO EXPRESS ABSOLUTE BENEFIT (OR HARM) ATTRIBUTABLE TO ONCE-OFF INTERVENTIONS

Absolute benefit from once-off surgical interventions: Absolute benefits often ensue after surgical interventions, Bariatric Surgery (BS) being one example. Whilst BS to combat obesity confers risks, apart from other benefits, it can also result in remission of diabetes mellitus (DM). Surgeons performing BS, therefore, need to appreciate and communicate the relative and absolute extent of any benefits (or harm) that they confer. One study, therefore, set out to derive Relative Chance (RC)† and NNT values for such an effect,[13] based on the results of two non-blinded, randomised clinical trials in severely obese diabetic patients having BS or intensive conventional therapy that was published in the New England Journal of Medicine. At least in the short term (1-2 years), none of the small number of patients in these trials suffered any serious complications and the NNTs for DM remission were very low, indicating very high efficacy in absolute terms.

Table 5: adapted from Kumana et al 2010. (Excerpted from Wyse DG, Waldo AL, DiMarco JP, et al 2002. NEJM; 347: 1825–33. Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation.)

Trial (Patient Nos)	Primary Endpoint	Active Treatment	RR (95% CI)	NNT (95% CI)
Mingrone G, et al (n = 60)†	HBA_1C <6.5% at 2 years	GB & PD	8.5 (2.0 to 36.4)	1.33 (1.08 to 1.74)
		GB	7.5 (1.7 to 32.8)	1.54 (1.13 to 2.41)
		PBD	9,5 (2.1 to 42.0)	1.18 (0.98 to 1.46)
Schauer PR, et al (n = 150)§	HBA_1C <6.0% at 1 year*	GB & SG	3.2 (3.2 to 8.4)	3.68 (2.42 to 7.68)
		GB	3.4 (1.3 to 9.3)	3.36 (2.12 to 8.00)
		SG	3.0 (1.1 to 8,3)	4.08 (4.08 to 13.54)

† Assuming no DM in 2 controls lost to follow-up;
§ No intention to treat analysis;
* With additional criteria; RR = Relative Risk; NNT = Number Need to Treat; GB = gastric bypass; PBD = biliopancreatic diversion; SG = sleeve gastrectomy
Mingrone G et al, 2012. NEJM 366:1577-85; Schauer PR et al, 2012. NEJM 366:1567-75

Once off Medical interventions conferring absolute benefit: A once-off intervention study assessed the prevention of Leprosy in nearly 19,000 close contacts of confirmed cases given a single tablet of rifampicin (600 – 300mg depending on body weight and age) or a placebo.[14] At two years after taking the tablet, the NNT for leprosy prevention in rifampicin recipients was 297 (95%CI 176 to 537). It therefore appeared that over the two study years, one out of approximately 300 recipients given this simple and cheap once-off intervention could avoid the disease, indicating an absolute worthwhile effect.

† Relative Chance (RC) is another term corresponding to the RR for achieving Diabetes remission.

Balancing absolute benefit versus absolute harm after one-off medical interventions: Since its inception, intravenous thrombolytic therapy after acute ischaemic stroke has generated considerable controversy and confusion and continues to do so.[15-21] Proposed/possible reasons include an uncertain window of opportunity, relatively meagre anticipated net benefits, being a very costly and logistically challenging intervention, devastating adversity in some patients, recourse to 'adjusted' analysis, and possible conflicts of interest. Furthermore, it is difficult to adequately inform potential recipients about its risks with any confidence (as mandated by the Montgomery judgement), as the mental status of potential targeted patients was liable to be compromised due to the acute stroke. For all of these reasons, due consideration and honest communication of the absolute benefits and harms stemming from this particular once-off intervention can be problematic.

Out of all the studies that investigated thrombolytic therapy in stroke, only the so-called NINDS (National Institute of Neurological Disorders and Stroke) trial published in199515 was acknowledged to be reasonably rigorous and of high quality. It entailed administration intravenous recombinant tissue plasminogen activator (rt-PA) or placebo within 3 hours of stroke onset. By contrast, the rigour of many of the studies in often cited meta-analyses justifying this strategy has been repeatedly questioned, especially because of the possible clinical heterogeneity of their constituent trials. The so-called IST-3 trial published in 2012,[19] embraced a six-hour treatment window and recruited approximately 3,000 considerably older patients, but in this study, rt-PA treatment allocation was not blinded. Consequently, the NINDS trial appears to be the most reliable and unbiased information resource for assessing the risks and benefits of this intervention strategy and is therefore worthy of most scrutiny.

Table 6: Parameters derived from part 2 of the NINDS trial findings after once-off intravenous injections of rt-PA in patients having acute ischaemic strokes (Excerpted from Kumana CR, Cheung BMY 2011. Hong Kong Med J: 17:83. Thrombolytic therapy for acute ischaemic stroke: is the hype justified)

	RR (95% CI)	NNH (95% CI)
Symptomatic or Fatal ICH within 36 hours	5.9 (1.3 to 27.2)	17 (10 to 62)
Outcome at 3 months		
Favourable BI	**1.3** (0.9 to 1.8)	**8** (4 to 99)
Favourable MRS	**1.5** (1.0 to 2.2)	**8** (4 to 33)
Favourable GCS	**1.4** (0.9 to 2.0)	**8** (4 to 73)
Favourable NIHSS	**1.5** (1.0 to 2.4)	**9** (5 to 67)

rt-PA = recombinant tissue Plasminogen Activator; ICH = Intracranial Haemorrage; BI = Barthel Index; MRS = Modified Rankin Score; GCS = Glasgow Coma Scale; NIHSS = NIH Stroke Score

Table 6 is an analysis of the seminal findings pertaining to part 2 of the NINDS trial published in a Hong Kong Medical Journal publication,[20] all the parameters having been derived from the corresponding unadjusted raw data. That part of the trial was double-blind and randomised, enrolled 333 eligible patients (giving 'informed' consent and having no contraindication) from 45 tertiary centres. The trial was designed to assess the risk of death or severe disability after three months, the primary outcome being a so-called 'Global Statistic' (based on the Barthel Index, modified Rankin Score, Glasgow Coma Scale, and the NIH Stroke Scale). The table shows that within 36 hours, patients receiving active treatment experienced clinically and statistically significant harm; there is a nearly six fold excess of symptomatic or fatal intracranial bleeds, for which the NNH was 17.

Nevertheless, based on the favourable 3-month 'Global Statistic' odds ratio of 1.7 (95% CI 1.2 to 2.6) - it was inferred that rt-PA treatment resulted in an overall benefit. The latter somewhat subjective and arbitrary prioritisation of benefit versus harm needs viewing in the context of several inherent biases evident in the NINDS study. Notably, compared to the controls - fewer actively treated recipients were smokers or had experienced prior transient ischaemic attacks, whilst a greater proportion of them had been receiving aspirin and had endured less severe/smaller cerebral infarcts. Moreover, prolonged bleeding times may well have un-blinded the investigators. Crucially, all the patients were off aspirin in the first 24 hours, which means that the controls were not on optimal standard therapy; unless contraindicated, recourse to aspirin at the earliest opportunity has been identified as a key beneficial treatment for acute ischaemic stroke.[21] To overcome possible excessive risks of bleeding due to co-treatment with aspirin, a double-dummy strategy could have been employed. Lastly, the so-called 'Global Statistic' score was a composite of 4 overlapping and inevitably inter-related soft endpoints. Furthermore, though the percentages of rt-PA recipients attaining favourable results for each score were always greater than in the controls, using unadjusted raw data none of the differences was statistically significant. By contrast, symptomatic or fatal intracranial haemorrhage within 36 hours was an unambiguous hard endpoint, analysis of which yielded incontrovertible statistically and clinically significant serious harm. For all of the above-mentioned reasons, intravenous thrombolysis for acute ischaemic stroke should be viewed with a degree of healthy scepticism.

META-ANALYSIS BY NNT

Systematic reviews and meta-analyses entail collection and scrutiny of research data in defined areas of interest and are frequently undertaken to address clinical studies with drugs. So long as their constituent trials are large and acceptable (in term of not being clinically or statistically heterogeneous and biased in other respects), conventional meta-analyses can be used to derive composite odds ratios, RRs, or RRRs and their corresponding 95% confidence intervals. The composite mean effects may then be regarded as more reliable and precise measures of the effects under investigation. Similarly (and with the same cautions), the meta-analysis by NNT can also be applied to derive more reliable and precise measures of composite absolute benefits and harm from a collection of trials.

Such a meta-analysis was performed on the earliest iconic trials of rhythm versus rate control in patients with atrial fibrillation.[22] The latter investigation revealed that for all critical endpoints (death, ischaemic stroke, and 'non-CNS' bleeding) as well as the quality of life, there was no significant difference between the

two strategies. In all 5 of its constituent trials moreover, the RRs for hospitalisation were invariably significantly higher in the rhythm group than in the controls. The corresponding NNH/year values in these trials ranged from 2 to 47, and the composite meta-analysed NNH/year value came to 35.

USE OF NNTS TO DEVELOP TREATMENT/PREVENTION GUIDELINES

Due to escalating medical treatment costs as well as the need to properly inform patients about the likelihood and extent of possible benefits, harms, and inconvenience - whom to treat, and when have become important issues for health care providers. In this context, for any given patient group, ARRs and the absolute liability to confer harm have become increasingly important considerations. Not surprisingly, therefore, for any given set of outcomes - a given treatment's anticipated ARR and AR (and their description as NNT and NNH values) have become key instruments for drawing up treatment and/or prevention guidelines.

Nevertheless, some researchers have urged a re-examination of unfettered reliance on this proposition,[23] since it often depends on the premise that all individuals with a given AR should have equal access to beneficial interventions, regardless of their circumstances (e.g. age and comorbidity). This is because, for any given outcome, treatment contingent on a predefined AR does not necessarily equate to conferring of equal benefit. For example, an elderly person commonly achieves the required degree of AR for many age-related untoward events. On the contrary, a young individual with multiple risk factors may not reach the same annualised AR that mandates treatment. Thus, whilst having a stroke may be equally devastating in a 30 year-old and 70-year-old man, prevention of such an event in the younger individual (with a greater remaining average life-expectancy and family responsibilities) is likely to accrue much more benefit in the long run, though ironically he or she may not qualify for the preventive treatment. To overcome this dilemma, it may be feasible to calculate the NNT for different patient age (and other) categories required to gain one QUALY (one year of quality-adjusted life). Thus, treating to benefit rather than risk could entail setting a threshold NNT per QUALY, below which an intervention could be designated as justified.

References

1. Laupacis A, Sackett DL, Roberts RS. An assessment of clinically useful measures of the consequences of treatment. N Engl J Med 1988;318:1728-33.
2. McAlister FA 2008. CMAJ;179:549-53. The "number needed to treat" turns 20 — and continues to be used and misused
3. Scandinavian Simvastatin Survival Study Group 1994. Lancet;334:1383-9. Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease.
4. Kumana CR, Cheung BMY, Lauder IJ 1999. JAMA 282:1899-901 (Contempo Update) Gauging the Impact of Statins using Number Needed to Treat.
5. Freeman ALJ Freeman ALJ 2019. ALJ. Drug and Therapeutics Bulletin 57:119-24. How to communicate evidence to patients
6. Diamond DM, de Lorgeril M, Kendrick M, Ravnskov U, Rosch PJ 2019. Formal comment on "Systematic review of the predictors of statin adherence for the primary prevention of cardiovascular disease". PLoS ONE 14(1): e0205138. https://doi.org/10.1371/journal. pone.0205138
7. Heart Protection Study Collaborative Group 2002. Lancet; 360:7–22. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo controlled trial
8. Kumana CR, Cheung BM, Lauder IJ 2003. Evidence Based Medicine; 8:10-11. Commentary on MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet
9. Hippisley-Cox J, Coupland C 2010. BMJ; 340:c2197 doi:10.1136/bmj.c2197. Unintended effects of statins in men and women in England and Wales: population based cohort study using the QResearch database
10. Case control study on incident cataracts Erie JC, Pueringer, MR, Brue M et al,2016. Ophthalmic Epidemiol; 23: 40–5. doi:10.3109/09286586.2015.1077258. STATIN USE AND INCIDENT CATARACT SURGERY: A CASE CONTROL STUDY
11. Yu s, Chu Y, Li G et al 2017 J Am Heart Assoc; 6:e004180. DOI: 10.1161/JAHA.116.004180. Statin Use and the Risk of Cataracts: A Systematic Review and Meta-Analysis
12. Wyse DG, Waldo AL, DiMarco JP, et al 2002. NEJM; 347: 1825–33. Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation.
13. Kumana CR, Cheung BMY, K Tan 2013. Clinical Therapeutics; 35: Issue 8 Suppl, August 2013, Pages e71-e72. Short-Term Impact of Bariatric Surgery on Obesity Associated Diabetes Mellitus
14. Moet FJ et al 2008. BMJ; 33:761-8. Moet FJ, Pahan D, Oskam L et al 2008. BMJ 33:761-8. Effectiveness of single dose rifampicin in preventing leprosy in close contacts of patients with newly diagnosed leprosy: cluster randomised controlled trial
15. NINDS study group 1995. NEJM; 333:1581-7. Tissue Plasminogen Activator (TPA) for Acute Ischaemic Stroke
16. Kumana CR 1999. Journal of the American Medical Association SE Asia; 15:5-6. Déjà vu (an Editorial)
17. Radecki RP 2011. West J Emerg Med; 12:435–441. Pharmaceutical Sponsorship Bias Influences Thrombolytic Literature in Acute Ischemic Stroke
18. Alpers B and colleagues 2015. BMJ; 350:h1075. Thrombolysis in acute ischaemic stroke; time for a rethink?
19. The IST-3 collaborative group 2012. Lancet; 379:2352–63. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial
20. Kumana CR, Cheung BMY 2011. Hong Kong Med J: 17:83. Thrombolytic therapy for acute ischaemic stroke: is the hype justified
21. Rothwell P, Algra A, Chen Z, et al, 2016. Lancet 388:365-75. Effects of aspirin on risk and severity of early recurrent stroke after transient ischaemic attack and ischaemic stroke: time-course analysis of randomised trials
22. Kumana CR, Cheung BMY , Cheung GTY, et al 2005. Brit J Clin Pharmacol; 60:347–54. Rhythm vs. rate control of atrial fibrillation meta-analysed by number needed to treat
23. Cheung BMY, Kumana CR 2001. New Zealand Med J; 114:214-5. Should decisions on treatment be based on absolute benefit rather than absolute risk?

Community Doctor Consultation Program for Gastroesophageal Reflux Disease (GERD)

GERD has become more prevalent in Hong Kong.[1] GERD symptoms not only impair patient's quality of life, its nocturnal symptoms also deteriorate sleep quality and productivity at work.[2] Despite its severity, study demonstrated that current routine clinical care helps most patients remain stable or improve over a 5-year period.[3]

In order to support proper diagnosis and disease management for suspected GERD patients, you are cordially invited to join the Community Doctor Consultation Program for GERD.

Recruitment Target:

Private practice doctors actively managing GERD patients and willing to offer free initial consultation to potential patients.

Program Detail:

1. Potential GERD patients can register through program hotline or website, and will be randomly assigned to one participating medical practitioner based on their selected district.
2. Participating medical practitioners will provide free initial consultation for enrolled potential GERD patients (for medication and diagnostic test if needed, the cost can be charged to patients according to the practitioner's decision.)
3. GERD education materials will be provided to participating medical practitioners.

Please note that your participation in the program does not constitute an inducement or award to you to, either directly or indirectly, influence, prescribe, recommend and/or promote a Takeda product. Takeda fully supports your independent and professional judgment on the selection of treatment and/or medicine that best suits your patient's condition.

Join Now! 2133 9831 TPHK-info@takeda.com

Reference: 1.Tan VP et al. J Clin Gastroenterol. 2016 ;50:e1-e7 2.Fass R, et al. Am J Gastroenterol 2011; 106:421-31 3.Malfertheiner P, et al. Aliment Pharmacol Ther 2012; 35: 154-164

Takeda Pharmaceuticals (HK) Ltd.
23/F & 24/F, East Exchange Tower, 38 Leighton Road, Causeway Bay, Hong Kong
Tel: 2133 9800 Fax: 2856 2728

HK-GLD2019-00007

Evidence-based Medicine for Lipid-modifying Medications

Dr Brian TOMLINSON

MBBS (Lond), MD (Lond), FRCP (Lond), FRCP (Edin), FRCP (Glasg), FACP, FHKCP, FHKAM (Medicine)

Professor, Faculty of Medicine, Macau University of Science & Technology, Taipa, Macau.
President, Hong Kong Pharmacology Society

Dr Brian TOMLINSON

This article has been selected by the Editorial Board of the Hong Kong Medical Diary for participants in the CME programme of the Medical Council of Hong Kong (MCHK) to complete the following self-assessment questions in order to be awarded 1 CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 31 December 2019.

INTRODUCTION

The clinical trials with the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors or statins probably represent the largest body of evidence-based medicine with any single group of drugs in pharmacotherapy. The first studies with statins were published in 1980,[1] but it was not until 1994 that the landmark 4S (Scandinavian Simvastatin Survival Study) study convinced the medical profession, or most of them, of the benefits of statins in reducing cardiovascular morbidity and mortality in patients at high cardiovascular risk. Over a median follow-up of 5.4 years, the 4S study showed a remarkable reduction in all-cause mortality of 30% with simvastatin 20 mg or 40 mg daily, which reduced low-density lipoprotein (LDL) cholesterol by 35% (Fig. 1).[2]

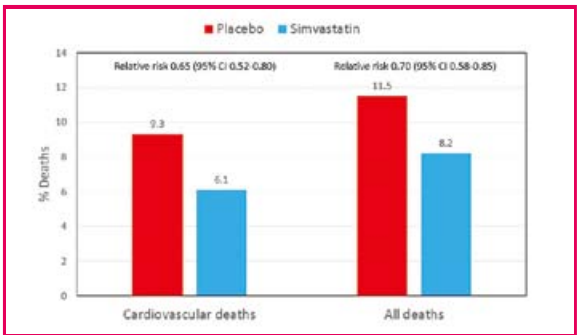


Fig. 1. The Scandinavian Simvastatin Survival Study. (Adapted from The Scandinavian Simvastatin Survival Study (4S) Group. Lancet 1994;344:1383-9.)

ACCUMULATING EVIDENCE

This study was followed by a series of trials comparing different statins against placebo in groups of patients at various levels of cardiovascular risk in primary and secondary prevention. By 2005, the Cholesterol Treatment Trialists' (CTT) Collaboration was able to analyse data from 90,056 participants in 14 randomised trials of statins.[3] This analysis showed a 21% reduction in the 5-year incidence of major vascular events for an absolute reduction in LDL cholesterol of 1 mmol/L and significant reductions in coronary mortality (Fig. 2). There was a non-significant 5% increase in haemorrhagic stroke with statin compared to placebo, but the number of events in these trials was very small. Notably, the absolute benefit of statin treatment was related chiefly to an individual's absolute risk of such events and to the absolute reduction in LDL cholesterol achieved.

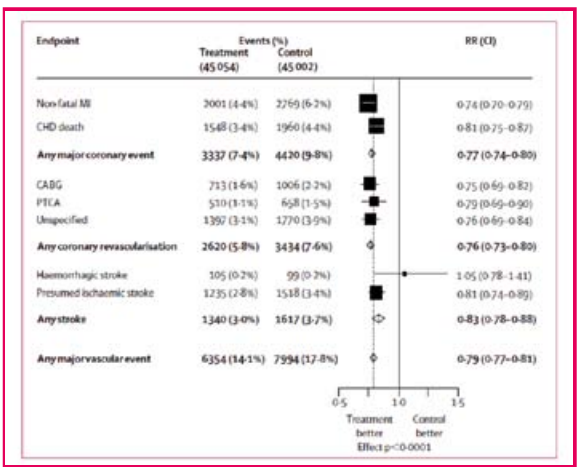


Fig. 2. Proportional effects on major vascular events per mmol/L LDL cholesterol reduction. (Excerpted from the Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent C, et al. Lancet 2005;366:1267-78.)

OCCASIONAL SETBACKS

There was competition between pharmaceutical companies marketing different statins with varying pharmacological properties, which might influence benefit and risk. Cerivastatin was launched in 1997 and hailed as a very potent drug with a better safety profile than competitors because of its dual pathway of metabolism. It turned out that compared with other statins, higher doses of cerivastatin were associated with an increased risk of severe myopathy and sometimes fatal rhabdomyolysis, especially when used in combination with gemfibrozil. Cerivastatin was withdrawn from the market in 2001.[4]

The PROVE IT–TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22) study sponsored by Bristol-Myers Squibb set out to prove that pravastatin 40 mg was "as good as it gets", and that 80 mg of the more potent atorvastatin would have no greater benefit.[5] It ended up proving the opposite, at least

for the composite cardiovascular primary end-point. The median LDL cholesterol during treatment with pravastatin 40 mg was 95 mg/dl (2.46 mmol/L), and with atorvastatin 80 mg it was 62 mg/dl (1.60 mmol/L). There was a 16% relative reduction or 3.9% absolute reduction in the primary composite end-point with atorvastatin compared to pravastatin over two years of follow up. There was no significant reduction in mortality or in stroke events comparing the two treatments. PROVE IT–TIMI 22 paved the way for a series of studies comparing more intensive with less intensive reduction in LDL cholesterol. It was not all plain sailing!

In the SEARCH (Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine) trial, the 6% proportional reduction in major vascular events with the additional 0.35 mmol/L reduction in LDL cholesterol with 80 mg simvastatin compared to 20 mg was not significant and there were 0.9% cases of severe myopathy in the 80 mg group.[6] Following this, regulatory authorities made recommendations to avoid the use of 80 mg simvastatin and to avoid combinations of other doses of simvastatin with interacting drugs that may result in plasma concentrations similar to the 80 mg dose.

EFFECTS ON INFLAMMATION

The JUPITER (Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) trial was another landmark study which recruited apparently healthy people with relatively low LDL cholesterol (<130 mg/dL or 3.4 mmol/L) but raised high-sensitivity C-reactive protein (hs-CRP) at ≥2.0 mg/L.[7] This showed an impressive 44% reduction in combined cardiovascular events with rosuvastatin 20 mg daily compared to placebo over a median follow-up of 1.9 years. There was some controversy over whether the results could be attributed entirely to the 50% reduction in LDL cholesterol levels or to the additional reduction in the inflammatory marker hs-CRP, as claimed by the investigators. The later CANTOS (Canakinumab Antiinflammatory Thrombosis Outcome Study) trial with canakinumab targeting interleukin-1β (IL-1β) showed a 15% reduction in 3-point major adverse cardiovascular events (MACE) with the 150-mg dose of canakinumab, which reduced IL-1β and hs-CRP without changing LDL cholesterol, confirming that inflammation contributes to residual cardiovascular risk beyond LDL cholesterol levels.[8]

NEW ONSET DIABETES MELLITUS

The JUPITER trial was the first study to clearly show that statin treatment increases the risk for new onset diabetes mellitus (NODM).[7] It was subsequently shown in several meta-analyses that other statins have the same effect and the risk is related to the intensity of statin treatment and to predisposing factors in individuals such as having prediabetes or the metabolic syndrome.[9] Overall, any increase in cardiovascular risk from NODM is far outweighed from the benefits in reduction of LDL cholesterol.[10]

HAEMORRHAGIC STROKE

The SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) study in patients with a previous stroke or transient ischaemic attack (TIA) who were randomised to atorvastatin 80 mg daily or placebo showed 16% reduction in fatal or nonfatal stroke but there was a small increase in the incidence of haemorrhagic stroke (2.3% vs 1.4%; p=0.02) with atorvastatin compared to placebo.[11]

The CTT meta-analysis in 2010 included data from 170,000 participants in 26 randomised trials which involved five trials of more versus less intensive statin regimens and 21 trials of statin versus control.[12] This meta-analysis confirmed that further reductions in LDL cholesterol produce further significant reductions in cardiovascular events (Fig. 3) but no significant reductions in CHD death. As in the earlier meta-analysis, there was a non-significant increase in haemorrhagic stroke, this time of 12% with each 1 mmol/L reduction in LDL cholesterol. In a subsequent analysis, the increase in haemorrhagic stroke was 21% (95% CI 5–41; p=0.01) for each 1 mmol/L reduction in LDL cholesterol.[13]

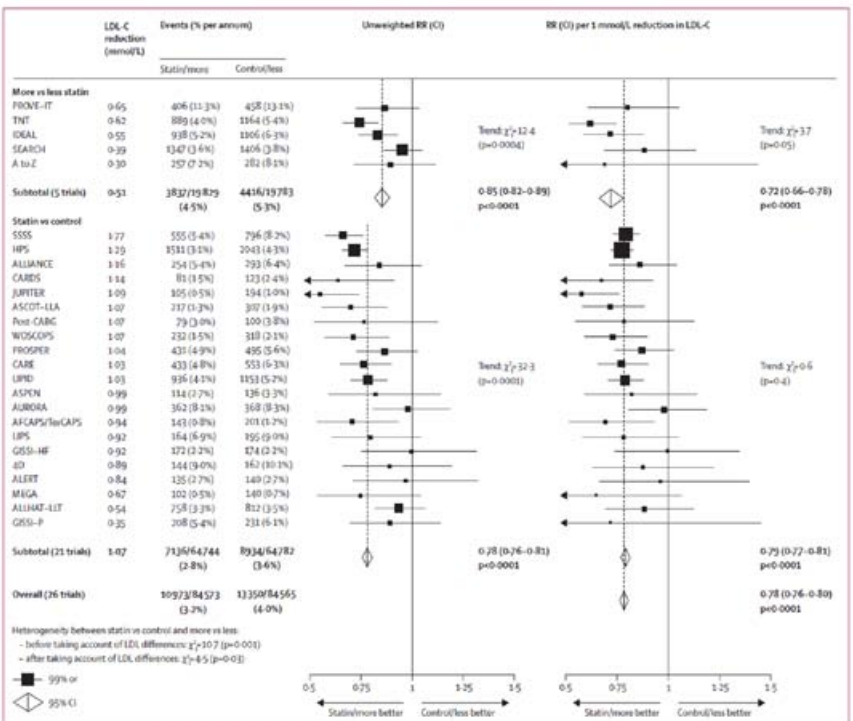


Fig. 3. Effects on any major vascular event in each study of more versus less intensive statin regimens and trials of statin versus control.
(Excerpted from Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent C, et al. Lancet 2010;376:1670-81.)

Table 1. Maximum doses (mg) of statins approved in Japan and the United States. (Excerpted from Naito R, Miyauchi K, Daida H. Racial Differences in the Cholesterol-Lowering Effect of Statin. J Atheroscler Thromb 2017;24:19-25.)

	Simvastatin	Pravastatin	Fluvastatin	Atorvastatin	Rosuvastatin	Pitavastatin
Japan	20	20	60	40	20	4
United States	80	80	80	80	40	4

This finding of an increase in haemorrhagic stroke may be alarming in East Asian countries where haemorrhagic stroke is considerably more common than western countries. Many observational studies have reported that low LDL cholesterol levels are associated with an increased risk of haemorrhagic stroke. A recent large long-term epidemiologic study in China found there was an excess risk of haemorrhagic stroke in people with uncontrolled hypertension and LDL cholesterol <70 mg/dL but not with LDL cholesterol in the 70-99 mg/dL range, and in people with normal blood pressure (BP), with systolic BP <140 mm Hg and diastolic BP <90 mm Hg, the risk of haemorrhagic stroke with LDL cholesterol <70 mg/dL was not increased compared with higher LDL cholesterol levels. The association between low LDL cholesterol levels and haemorrhagic stroke in observational studies would suggest that the risk of haemorrhagic stroke is related to lower levels of LDL cholesterol per se rather than statin treatment and that any increased risk with low LDL cholesterol related to treatment with statins or other lipid lowering drugs may be abrogated by effective treatment of hypertension.[14]

In the clinical trials with the proprotein convertase subtilisin/kexin type-9 (PCSK9) inhibitors discussed below, there was no significant increase in haemorrhagic stroke with the very low levels of LDL cholesterol achieved in the trials. It has been suggested this may be related to the very effective treatment of BP in these more recent trials.

STATIN PHARMACOGENETICS

A genome-wide association study (GWAS) from the SEARCH trial looking for genetic associations of severe myopathy with high dose simvastatin identified one single nucleotide polymorphism (SNP) in the SLCO1B1 gene encoding the organic anion-transporting polypeptide 1B1 (OATP1B1) liver uptake transporter, which was in nearly complete linkage disequilibrium with the functional c.521T>C (rs4149056) SNP, known to influence the liver uptake of simvastatin acid.[15] This finding of a gentic marker for the risk of myopathy with simvastatin was a major breakthrough in understanding the pharmacogenetics of statins.

A GWAS from the JUPITER trial identified that a SNP in the gene for the ATP binding cassette G2 (ABCG2) efflux transporter was related to the LDL cholesterol reduction with rosuvastatin.[16] The functional c.421C>A (rs2231142) polymorphism in ABCG2 had been shown to influence the LDL cholesterol response to rosuvastatin earlier in a study in Chinese patients using a candidate gene approach.[17]

Plasma concentrations of some statins are higher in Chinese and Japanese people than in Caucasians, particularly for rosuvastatin. This finding is probably related in part to the increased frequency of the ABCG2 c.421C>A polymorphism in East Asian populations. There is also some evidence that Chinese and Japanese patients may show a greater reduction in LDL cholesterol than Caucasians with doses of some statins.[18] It has been suggested that the maximum dose of statins for Chinese people should be the same as the maximum dose approved in Japan rather than that in the United States (Table 1) or Hong Kong to avoid an increased risk of severe myopathy related to increased systemic exposure to the drug.[19]

Milder forms of statin-associated muscle symptoms (SAMS), such as myalgia, are the most common reason for statin intolerance,[20] although it is disputed whether these are really caused by the drug and some authorities consider they are largely a nocebo effect.

OTHER LIPID MODIFYING TREATMENTS

The benefit of adding ezetimibe to statin treatment in patients with an acute coronary syndrome (ACS) within the preceding ten days was shown in the IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) study.[21] The benefit was much greater in patients with diabetes and in high-risk patients without diabetes and became non-significant in those patients who had suffered ACS but did not have these additional cardiovascular risks.[22]

The outcome studies with the proprotein convertase subtilisin/kexin type-9 (PCSK9) inhibitors evolocumab and alirocumab have also shown increasing benefits in cardiovascular outcomes with lower LDL cholesterol levels in patients with stable, established cardiovascular disease or after ACS.[23,24] Even with the very low levels of LDL cholesterol achieved in these studies, there was no increase in adverse events including cognitive impairment, muscle symptoms, NODM, and haemorrhagic stroke.

Several subgroup analyses from the PCSK9 inhibitor studies show that those patients with established cardiovascular disease and higher levels of cardiovascular risk, such as those with diabetes, more recent myocardial infarction (MI), multiple MIs, peripheral vascular disease, chronic kidney disease, and higher-baseline levels of lipoprotein(a) or hs-CRP, have higher absolute risk of cardiovascular events and greater reductions in events with intensive lowering of LDL cholesterol.

In contrast to the clinical trials of new drugs lowering LDL cholesterol, the trials with drugs targeting elevated triglycerides or low levels of high-density lipoprotein (HDL) cholesterol have been disappointing. The two major studies with fenofibrate were only positive in subgroups of patients with high triglycerides and low HDL cholesterol,[25,26] so this was considered as less compelling evidence to support the use of fibrates by the lipid guidelines.[27]

The two studies with niacin to increase levels of HDL cholesterol in patients with well-controlled LDL cholesterol showed no additional benefit of niacin alone or combined with laropiprant in combination with intensive statin treatment.[28,29] In retrospect, the notion that increasing the amount of HDL cholesterol would reduce cardiovascular events is now considered incorrect, the patients included in those studies were already well treated in terms of their non-HDL cholesterol levels, which might reduce any potential benefits of niacin, and laropiprant may have contributed to adverse effects in the HPS2-THRIVE study. Nevertheless, nowadays, niacin is not recommended in lipid guidelines and is no longer available in many countries.

Previously, recommendations for the use of the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have focused on their benefits in reducing the risk of pancreatitis with very high triglyceride levels. The REDUCE-IT study with high dose icosapent ethyl, a highly purified EPA ethyl ester, showed a significant 25% reduction in the primary end-point events in patients with established cardiovascular disease or with diabetes and other risk factors on statin therapy with moderately increased fasting triglyceride (135-499 mg/dL or 1.52 to 5.63 mmol/L) and LDL cholesterol level of 41-100 mg/dL (1.06 to 2.59 mmol/L) compared to a mineral oil control group.[30] In recent guidelines, icosapent ethyl is now given priority over fibrates as a treatment in addition to statins when triglyceride levels remain elevated in high-risk patients, although this product is not available in many countries.[27]

LIPID GUIDELINES

Guidelines for lipid management are based on the evidence from the cardiovascular outcome trials with lipid-modifying drugs, usually with additional interpretation from expert opinion to cover some areas that have not been addressed by clinical trials. As the evidence has accumulated for benefits of more aggressive lowering of LDL cholesterol, the target levels for treatment have gradually become lower. In the most recent 2019 ESC/EAS Guidelines for the management of dyslipidaemias, the recommended LDL cholesterol goal for patients at very high risk in secondary prevention is <1.4 mmol/L (<55 mg/dL) and for those with established atherosclerotic cardiovascular disease who experience a second vascular event within 2 years while taking maximally tolerated statin-based therapy, an LDL cholesterol goal as low as <1.0 mmol/L (<40 mg/dL) may be considered.[27]

Imaging tests to detect arterial plaque or coronary artery calcium may be useful as a risk modifier in the cardiovascular risk assessment of asymptomatic individuals at low or moderate risk, and therapy could be avoided or discontinued in some people without evidence of arterial disease.[27] It is important to remember that cardiovascular disease is largely related to lifestyle and therefore lifestyle modification should be the first-line intervention before pharmacotherapy and should always be continued in combination with any drug treatment.

CONCLUSION

The extensive evidence base of cardiovascular outcome trials with statins and other LDL cholesterol-lowering drugs supports the guidelines to reduce LDL cholesterol to prevent cardiovascular events. Lower levels of LDL cholesterol are associated with lower rates of cardiovascular events, and the effect is greater the longer the period of exposure to lower LDL cholesterol levels. Adverse effects with statins used in appropriate doses are very uncommon, but the maximum dose of a statin should be chosen carefully for the individual patient. Ezetimibe and the PCSK9 inhibitors appear free of any serious adverse effects in the studies to date, and very low levels of LDL cholesterol achieved with these drugs have not been associated with any obvious risks with the proviso that concomitant hypertension should be treated aggressively to avoid any increased risk of haemorrhagic stroke. The cost-effectiveness of treatments is influenced by the baseline level of cardiovascular risk and the absolute reduction in LDL cholesterol, which in turn depends on the baseline LDL cholesterol level. Whilst in theory all patients may benefit from more aggressive LDL cholesterol-lowering, the benefits in some patients with lower cardiovascular risk may be minimal so it is important to make a judicious assessment of risk before intensifying therapy and data from evidence-based medicine should be interpreted with a personalised medicine approach for individual patients.

References

1. Yamamoto A, Sudo H, Endo A. Therapeutic effects of ML-236B in primary hypercholesterolemia. Atherosclerosis 1980;35:259-66.
2. The Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344:1383-9.
3. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005;366:1267-78.
4. Farmer JA. Learning from the cerivastatin experience. Lancet 2001;358:1383-5.
5. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 2004;350:1495-504.
6. Armitage J, Bowman L, Wallendszus K, et al. Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12,064 survivors of myocardial infarction: a double-blind randomised trial. Lancet 2010;376:1658-69.
7. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008;359:2195-207.
8. Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. N Engl J Med 2017;377:1119-31.
9. Mach F, Ray KK, Wiklund O, et al. Adverse effects of statin therapy: perception vs. the evidence - focus on glucose homeostasis, cognitive, renal and hepatic function, haemorrhagic stroke and cataract. Eur Heart J 2018.
10. Sattar N, Preiss D, Murray HM, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. Lancet 2010;375:735-42.
11. Amarenco P, Bogousslavsky J, Callahan A, 3rd, et al. High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med 2006;355:549-59.
12. Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet 2010;376:1670-81.
13. Collins R, Reith C, Emberson J, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. Lancet 2016;388:2532-61.
14. Zhang X, Liu J, Wang M, et al. Twenty-year epidemiologic study on LDL-C levels in relation to the risks of atherosclerotic event, hemorrhagic stroke, and cancer death among young and middle-aged population in China. J Clin Lipidol 2018;12:1179-89 e4.

15. Link E, Parish S, Armitage J, et al. SLCO1B1 variants and statin-induced myopathy--a genomewide study. N Engl J Med 2008;359:789-99.
16. Chasman DI, Giulianini F, MacFadyen J, Barratt BJ, Nyberg F, Ridker PM. Genetic determinants of statin-induced low-density lipoprotein cholesterol reduction: the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial. Circ Cardiovasc Genet 2012;5:257-64.
17. Tomlinson B, Hu M, Lee VWY, et al. ABCG2 Polymorphism Is Associated With the Low-Density Lipoprotein Cholesterol Response to Rosuvastatin. Clin Pharmacol Ther 2010;87:558-62.
18. Naito R, Miyauchi K, Daida H. Racial Differences in the Cholesterol-Lowering Effect of Statin. J Atheroscler Thromb 2017;24:19-25.
19. Tomlinson B, Chan P, Liu ZM. Statin Responses in Chinese Patients. J Atheroscler Thromb 2018;25:199-202.
20. Stroes ES, Thompson PD, Corsini A, et al. Statin-associated muscle symptoms: impact on statin therapy-European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management. Eur Heart J 2015;36:1012-22.
21. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. N Engl J Med 2015;372:2387-97.
22. Giugliano RP, Cannon CP, Blazing MA, et al. Benefit of Adding Ezetimibe to Statin Therapy on Cardiovascular Outcomes and Safety in Patients With Versus Without Diabetes Mellitus: Results From IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial). Circulation 2018;137:1571-82.
23. Sabatine MS, Giugliano RP, Keech AC et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. N Engl J Med 2017;376:1713-22.
24. Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. N Engl J Med 2018;379:2097-107.
25. Ginsberg HN, Elam MB, Lovato LC, et al. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med 2010;362:1563-74.
26. Keech A, Simes RJ, Barter P, et al. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet 2005;366:1849-61.
27. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J 2019.
28. Boden WE, Probstfield JL, Anderson T, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med 2011;365:2255-67.
29. Landray MJ, Haynes R, Hopewell JC, et al. Effects of extended-release niacin with laropiprant in high-risk patients. N Engl J Med 2014;371:203-12.
30. Bhatt DL, Steg PG, Miller M, et al. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. N Engl J Med 2019;380:11-22.

MCHK CME Programme Self-assessment Questions

Please read the article entitled "Evidence-based Medicine for Lipid-modifying Medications" by Dr Brian TOMLINSON and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded CME credit under the Programme for returning completed answer sheets via fax (2865 0345) or by mail to the Federation Secretariat on or before 31 December 2019 Answers to questions will be provided in the next issue of The Hong Kong Medical Diary.

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

1. In the 4S (Scandinavian Simvastatin Survival Study) trial, there was no significant reduction in all-cause mortality with simvastatin treatment compared to placebo.
2. The analysis of the randomised trials of statins by the Cholesterol Treatment Trialists' (CTT) Collaboration in 2005 showed that for an absolute reduction in LDL cholesterol of 1 mmol/L the reduction in the 5-year incidence of major vascular events was about 21%.
3. Cerivastatin was withdrawn from the market because it was associated with an increased risk of haemorrhagic stroke compared with other statins.
4. In the PROVE IT–TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22) study, treatment with pravastatin 40 mg was equally effective as atorvastatin 80 mg for the composite cardiovascular primary end-point.
5. In the SEARCH (Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine) trial, the incidence of severe myopathy with 80 mg simvastatin was so high that regulatory authorities subsequently recommended avoiding that dose.
6. The CANTOS (Canakinumab Antiinflammatory Thrombosis Outcome Study) trial showed that treatment with canakinumab reduced major adverse cardiovascular events without reducing LDL cholesterol levels.
7. The SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) study showed an increase in the incidence of haemorrhagic stroke with atorvastatin compared to placebo in patients with a previous stroke or transient ischaemic attack.
8. A genetic variant in the ATP binding cassette G2 (ABCG2) efflux transporter influences the plasma concentrations and the LDL cholesterol response to rosuvastatin.
9. The very low levels of LDL cholesterol achieved with the proprotein convertase subtilisin/kexin type-9 (PCSK9) inhibitors evolocumab and alirocumab in cardiovascular outcome trials resulted in a significant increase in haemorrhagic stroke.
10. Imaging tests to detect arterial plaque or coronary artery calcium are not useful to modify the cardiovascular risk assessment in people without symptoms at low or moderate risk.

ANSWER SHEET FOR DECEMBER 2019

Please return the completed answer sheet to the Federation Secretariat on or before 31 December 2019 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

Evidence-based Medicine for Lipid-modifying Medications

Dr Brian TOMLINSON

MBBS (Lond), MD (Lond), FRCP (Lond), FRCP (Edin), FRCP (Glasg), FACP, FHKCP, FHKAM (Medicine)

Professor, Faculty of Medicine, Macau University of Science & Technology, Taipa, Macau.
President, Hong Kong Pharmacology Society

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

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

HKID No.: __ __ - __ __ __ __ X X (X) HKDU No.: _____ HKAM No.: _____

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

Answers to November 2019 Issue

Update on Surgical Management of End- Stage Ankle Arthritis

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

The Application of Big Data Analysis in Medical Research

Dr Ka-shing CHEUNG

MBBS, MPH

Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong
Department of Medicine, The University of Hong Kong-Shenzhen Hospital, Shenzhen 518053, China

Dr Ka-shing CHEUNG

INTRODUCTION

The etymology of 'Big Data' dates from the 1990s, with the term being popularised by John Mashey, the then chief scientist at Silicon Graphics[1]. Fed with a wealth of sources (including mobile communications, websites, social media/crowdsourcing, sensors, cameras/lasers, transaction process generated data, administrative, scientific experiments, science computing and industrial manufacturing), datasets are exponentially expanding every day.[2] While there is no consensus on the definition of Big Data, certain characteristics related to the process of collection, storage, processing and analysis of data forges Big Data a more tangible term. Doug Laney, a leading figure in the field of data and analytics, first identified three main features of Big Data: the 3Vs – volume (large storage space required for data storage), velocity (high speed of data generation and transformation) and variety (a wide array of data sources)[3]. Thereafter, other traits of Big Data have been characterised, including veracity, value, exhaustivity (n=all), fine-grained resolution, indexicality, relationality, extensionality, scalability and variability[2].

BIG DATA RESEARCH IN MEDICAL RESEARCH

The field of health care is no exception to the digitalisation of daily life. The importance of Big Data application in medical research is increasingly being recognised in recent years. The definition of Big Data in Health was proposed in the third Health Programme (2014–2020) from the Consumer, Health, Agriculture and Food Executive Agency (Chafea) mandated by the European Commission[4]. Big Data in Health is defined as reusable large datasets that are collected routinely or automatically and stored electronically, with combination of existing databases. Big Data are considered reusable because these are multipurpose data not dedicated to a specific study, but for improving health and health system performance. The large volume of Big Data comes from the number of included subjects as well as the diversity of variables of various domains (including clinical, lifestyle, socioeconomic, environmental, biological and omics) at different time points. The healthcare data volume in 2014 is estimated at 153 exabytes (1018) and expected to hit 2,300 exabytes by 2020[5, 6].

Big Data in medical research relies on a wide array of sources: administrative databases, insurance claims, electronic health records, cohort study data, clinical trial data, pharmaceutical data, medical images, biometric data, biomarker data, omics data (e.g. genomics, proteomics, metabolomics, microbiomics), social media (e.g. Facebook, Twitter), income statistics, environmental databases, mobile applications, e-Health tools, telemedicine (diagnosis and management at a distance, particularly by means of the internet, mobile phone applications and wearable devices)[6]. 'Data fusion' systematically links datasets from different sources to add new insights, enabling analysis of health data from different perspectives (individual, group, social, economic and environmental factors) across different regions or nations.

While disease entities are often heterogeneous (e.g. malignancy, autoimmune diseases) with a broad range of phenotypes (e.g. age of onset, severity, natural course of disease, association with other diseases, treatment response), Big Data approach enables phenotype mapping of a disease entity (i.e. subclassification into distinct subgroups), through which disease pathogenesis can be better understood, and more precise predictive models of outcomes be developed.

Using merely clinical and laboratory data to predict disease course, outcome and treatment response may not achieve a high degree of accuracy[6], which in turn leads to untargeted use of therapeutics which may incur undesirable side effects and costs in non-responsive patients. Big data approach considers the complex interplay between clinical, lifestyle, genetic, environmental and previously unconsidered factors (e.g. omics) to establish a more accurate prognostic model, and to guide a targeted approach in treatment regimens on an individual basis (i.e. precision or personalised medicine)[6, 7, 8].

Other important aspects of the Big Data approach are drug discovery and safety. Drug research and development (R&D) is an expensive and lengthy process, with each drug approval costing US$ 3.2 to 32.3 billion[9]. Many trial drugs have been proven futile or harmful in early or even late stages of the development. For those proven beneficial, they may only work in certain subgroups. Precision medicine from Big Data approach helps pharmaceutical companies to prioritise drug targets on a specific group of patients[10], ensuring cost-effectiveness of developing new therapeutics with a higher odds of success. Another way of drug discovery is 'drug repositioning' or 'drug repurposing', wherein currently approved drugs are explored for other

indications. New indications of existing medications constituted 20% of 84 drugs products introduced to the market in 2013[11]. Pertinent disease areas include oncology (e.g. hepatocellular carcinoma)[12, 13], infectious diseases, and inflammatory bowel disease, to name a few.

Traditionally, monitoring of drug safety depends on data from randomised controlled trials (RCTs) or post-marketing studies. However, RCTs may fail to detect rare but important adverse effects, some of which may only surface beyond the prespecified follow-up time (e.g. malignancy). Post-marketing studies based on registries are resource-intensive, and safety profile of drugs can only be determined years after marketing. Big Data approach makes use of text mining (i.e. computational process of extracting meaningful information from unstructured text) to enhance pharmacovigilance (e.g. arthralgia in vedolizumab users with inflammatory bowel disease[14]) from sources not limited to medical literature and clinical notes, which include product labelling, social media and web search logs[15, 16].

ADVANTAGES AND SHORTCOMINGS OF BIG DATA APPROACH IN MEDICAL RESEARCH

The advent of Big Data has revolutionised medical research approach, usually in the form of either retrospective cohort study or nested case-control study. As data can be easily retrieved from the electronic storage system, a multitude of variables can be explored to analyse various outcomes. Studying rare exposures, rare events and long-term effects within a relatively short period of time is no longer a problem for observational study designs. Resources required are minimal, except for dedicated manpower and the aid of high-performance computers and software for more complex statistical analysis. Therefore, Big Data approach retains most of the advantages and circumvents some of the disadvantages of traditional observational studies. Unlike RCTs, it reflects the real-world data, and studies patients who are often under-represented in RCTs (e.g. the elderly, pregnant women).

In an ideal situation of n=all when the whole population in the territory or nation is included, selection bias does not exist. A huge sample size ensures adequate statistical power for subgroup analysis to study the interaction effect of different variables on the outcome of interest. By observing a large number of patients for a sufficiently long period (in terms of years or decades), researchers can explore how the time factor (i.e. division of the follow-up duration into different segments) affects the association between exposure and outcome. Robustness of study results is strengthened using multiple sensitivity analyses on various sub-cohorts, by modification of exposure definition (e.g. duration of drug usage), or by different statistical methods.

That being said, residual/unmeasured confounding is inherent to all types of observational studies, and hence definite conclusion on causality still cannot be established. Some clinical data may not be recorded[17] (e.g. lifestyle factors, dietary pattern, exercises) or incompletely recorded (e.g. smoking, alcohol use, body mass index, family history). This may be partially addressed by using other variables as proxies for unmeasured variables. Possible causality can be fortified by fulfilling the Bradford Hill criteria. Linkage with other data sources (e.g. RCT datasets) may partly address this issue[18]. Big Data usually contain a sufficient set of measured surrogate variables that are representative of relevant unmeasured confounding. The use of propensity score (PS) methodology[19] has facilitated Big Data approach in medical research. Interestingly, free-text searches (e.g. natural language processing [NLP]) by analysing unstructured data in the electronic health records can further increase the precision of data[20].

A few other limitations should be noted. First, accuracy of diagnosis codes in electronic databases has been challenged[17]. This limItation, however, can be tackled by cross-validating with the medical records in a subset of patients. Second, bias can arise from missing data due to failure of entering certain diagnosis codes by healthcare professionals or unavailability of laboratory information. However, differential misclassification bias is unlikely, as there is no patient involvement in revelation of their particulars and laboratory information are automatically uploaded. Multiple imputations can also be applied to impute missing variables[21]. Lastly, ethics concerns over privacy and confidentiality are still under debate[22]. De-identification of individuals using anonymous identifiers can largely address this issue.

Table 1 lists the advantages and shortcomings of the Big Data approach in medical research and proposed solutions for the latter.

CONCLUSION

The advent of Big Data in medical research has revolutionised traditional clinical research approach. With digitalization of medical research, resource issue is no longer a hindrance to production of high-quality clinical studies in a cost-effective manner. By continuously merging data from different sources across different regions, Big Data approach provides an invaluable opportunity to improve health, in terms of phenotype mapping, precision medicine, drug discovery and pharmacovigilance.

Table 1. Advantages and shortcomings of Big Data approach and its proposed solutions (Developed by author)

Advantages	
Minimal resources	
Can study rare exposures, rare events and long-term effects	
Real-world data	
Large sample size	
- subgroup analysis - sensitivity analysis - interaction of different variables - adjustment of outcome to a multitude of risk factors - precise estimation of effect size	
No selection bias if n=all	
Shortcomings specific of Big Data analysis	**Solutions**
Diagnosis coding accuracy	Cross-validation of diagnosis codes with medical records
Missing data	Multiple imputations Text mining or natural language processing
Incomplete capture of variables or unavailability of certain diagnosis codes	Inclusion of a large set of measured variables and surrogate markers Text mining or natural language processing
Privacy	De-identification of individuals
Shortcomings of all observational study including Big Data analysis	**Solutions**
Residual/unmeasured confounding	Inclusion of a large set of measured variables and surrogate markers Fulfilment of Bradford Hill criteria Inclusion of RCT datasets
Reverse causality (the outcome of interest leads to exposure of interest)	Cohort study design instead of a case-control study design
Selection bias	Recruitment of entire study population (n=all)
Indication bias in the pharmacoepidemiological study	Balance of patient characteristics (e.g. propensity score matching of a large set of measured variables) Adjustment for indication Negative control exposure
Healthy user bias/adherer bias	Adjustment for other lifestyle factors Text mining or natural language processing
Ascertainment bias/surveillance bias	Selection of an unexposed group with a similar likelihood of screening/testing Adjustment for the surveillance rate
Access to healthcare	Stratified analysis concerning residential regions (e.g. rural vs urban), socioeconomic status, immigration status, race/ethnicity, institutional factors (e.g. restrictive formularies)

References

1. Lohr S. The Origins of 'Big Data': An Etymological Detective Story. Avaiable at: https://bits.blogs.nytimes.com/2013/02/01/the-origins-of-big-data-an-etymological-detective-story/ (accessed 25 September 2019).
2. Kitchin R, McArdle G. What makes Big Data, Big Data? Exploring the ontological characteristics of 26 datasets. Big Data and Society 2016:1-10.
3. Laney D. 3D data management: controlling data volume, velocity and variety. META Group Research Note, 6. Available at: https://blogs.gartner.com/doug-laney/files/2012/01/ad949-3D-Data-Management-Controlling-Data-Volume-Velocity-and-Variety.pdf (accessed 25 September 2019).
4. Consumer, Health and Food Executive Agency (Chafea), European Comission. Study on Big Data in Public Health, Telemedicine and Healthcare. December 2016 [DOI: 10.2875/734795]. Available at: https://ec.europa.eu/health/sites/health/files/ehealth/docs/bigdata_report_en.pdf (accessed 25 September 2019).
5. Bellazzi R. Big data and biomedical informatics: a challenging opportunity. Yearb Med Inform 2014;9:8-13.
6. Olivera P, Danese S, Jay N, et al. Big data in IBD: a look into the future. Nat Rev Gastroenterol Hepatol 2019.
7. Shivade C, Raghavan P, Fosler-Lussier E, et al. A review of approaches to identifying patient phenotype cohorts using electronic health records. J Am Med Inform Assoc 2014;21:221-30.
8. Zuo T, Kamm MA, Colombel JF, et al. Urbanization and the gut microbiota in health and inflammatory bowel disease. Nat Rev Gastroenterol Hepatol 2018;15:440-452.
9. Schuhmacher A, Gassmann O, Hinder M. Changing R&D models in research-based pharmaceutical companies. J Transl Med 2016;14:105.
10. Denny JC, Van Driest SL, Wei WQ, et al. The Influence of Big (Clinical) Data and Genomics on Precision Medicine and Drug Development. Clin Pharmacol Ther 2018;103:409-418.
11. Graul AI, Cruces E, Stringer M. The year's new drugs & biologics, 2013: Part I. Drugs Today (Barc) 2014;50:51-100.
12. Chen MH, Yang WL, Lin KT, et al. Gene expression-based chemical genomics identifies potential therapeutic drugs in hepatocellular carcinoma. PLoS One 2011;6:e27186.
13. Wang J, Li M, Wang Y, et al. Integrating subpathway analysis to identify candidate agents for hepatocellular carcinoma. Onco Targets Ther 2016;9:1221-30.
14. Cai T, Lin TC, Bond A, et al. The Association Between Arthralgia and Vedolizumab Using Natural Language Processing. Inflamm Bowel Dis 2018;24:2242-2246.
15. Harpaz R, Callahan A, Tamang S, et al. Text mining for adverse drug events: the promise, challenges, and state of the art. Drug Saf 2014;37:777-90.
16. Wang G, Jung K, Winnenburg R, et al. A method for systematic discovery of adverse drug events from clinical notes. J Am Med Inform Assoc 2015;22:1196-204.
17. Schneeweiss S, Avorn J. A review of uses of health care utilization databases for epidemiologic research on therapeutics. J Clin Epidemiol 2005;58:323-37.
18. Hsing AW, Ioannidis JP. Nationwide Population Science: Lessons From the Taiwan National Health Insurance Research Database. JAMA Intern Med 2015;175:1527-9.
19. D'Agostino RB, Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. Stat Med 1998;17:2265-81.
20. Murdoch TB, Detsky AS. The inevitable application of big data to health care. JAMA 2013;309:1351-2.
21. White IR, Royston P. Imputing missing covariate values for the Cox model. Stat Med 2009;28:1982-98.
22. Vayena E, Salathe M, Madoff LC, et al. Ethical challenges of big data in public health. PLoS Comput Biol 2015;11:e1003904.

SANDOZ IS A GLOBAL LEADER IN GENERIC AND BIOSIMILAR MEDICINES

Our mission is to discover new ways to improve and extend people's lives

A BROAD PORTFOLIO[1]

We cover major therapeutic areas and geographic areas worldwide, with a strong focus on biosimilars and differentiated, value-added medicines

Biosimilars

Value-added Medicines

A GLOBAL LEADER[1]

We have leading positions in biosimilars, antibiotics and generic oncology and are pioneering the new area of PDT

Therapeutic areas

#1 in Gx antiobiotics
In Gx oncology

A NOVARTIS DIVISION[1]

We are uniquely positioned as one of the divisions of Novartis

One global quality standard

across Novartis Group

- Product development and manufacturing
- Pharmacovigilance system
- Quality management

A TRUE PARTNER[1]

We work closely with commercial and scientific partners to maximize our collective contribution to society

Driving Scientific Collaboration

* Multiple sites ▲ Sandoz presence ▲ Production and development - major sites ▲ Production - major sites ▲ Development

Sandoz is also recognized as part of the Novartis contribution in the Access to Medicines Index (ATMI) where Novartis was ranked number 2 globally in 2018[2]

PDT=prescription digital therapeutics

Reference: **1.** Data on file **2.** Access to Medicine Index. 2018 Ranking. Available at: https://accesstomedicinefoundation.org/access-to-medicine-index/2018-ranking

10-2019-HK-COMB-PRL-632-V1

SANDOZ A Novartis Division 山德士®

Novartis Pharmaceuticals (HK) Ltd
7/F, Citi Tower, One Bay East, 83 Hoi Bun Road, Kwun Tong, Kowloon, Hong Kong
Tel: (852) 2882 5222 Fax: (852) 2577 0274

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
1	2 * Certificate Course in Ophthalmology 2019	3 * HKMA-HKS&H CME Programme 2019-2020 - Update on Geriatric Medicine * FMSHK Officers' Meeting * HKMA Council Meeting	4 * HKMA & Hong Kong Society of Biological Psychiatry - Certificate Course in Psychiatry for Community Primary Care Doctors (Session 12) - Question and Discussion/ Course Wrap-up/Participants' Comment * HKMA New Territories West Community Network: Common Peripheral Nerve Problem * Certificate Course on Pain Management in Geriatric Patients 2019	5	6	7 * Refresher Course for Health Care Providers 2019/2020 - Dental management of patients with medical diseases
8	9 * Certificate Course in Ophthalmology 2019	10 * HKMA Kowloon West Community Network - Treatment of External Genital Wart	11 * HKMA Central, Western & Southern Community Network - Lipid Lowering: to Aim Super Low? * Certificate Course on Pain Management in Geriatric Patients 2019 * The Hong Kong Neurosurgical Society Monthly Academic Meeting –To be confirmed	12	13 * HKMA Kowloon City Community Network - Antiplatelet Therapy after PCI	14
15	16 * Certificate Course in Ophthalmology 2019	17	18	19 * HKMA Hong Kong East Community Network - Update on Lipid and Heart Failure Management * FMSHK Executive Committee Meeting	20	21
22	23 * Certificate Course in Ophthalmology 2019	24	25	26	27	28
29	30 * Certificate Course in Ophthalmology 2019	31 * FMSHK Annual Dinner 2019				

Date / Time	Function	Enquiry / Remarks
2 MON 7:00 PM	**Certificate Course in Ophthalmology 2019** Assessments 2019 Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Vienna LAM Tel: 2527 8898
3 TUE 1:00 PM	**HKMA-HKS&H CME Programme 2019-2020 - Update on Geriatric Medicine** Organiser: Hong Kong Medical Association & Hong Kong Sanatorium & Hospital; Speaker: Dr. LEUNG Man Fuk, Edward; Venue: HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, HK	HKMA CME Dept Tel: 2527 8285 1 CME Point
8:00 PM	**FMSHK Officers' Meeting** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Gallop, 2/F, Hong Kong Jockey Club Club House, Shan Kwong Road, Happy Valley, Hong Kong	Ms. Nancy CHAN Tel: 2527 8898
9:00 PM	**HKMA Council Meeting** Organiser: The Hong Kong Medical Association; Venue: HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, HK	Ms. Christine WONG Tel: 2527 8285
4 WED 1:00 PM	**HKMA & Hong Kong Society of Biological Psychiatry - Certificate Course in Psychiatry for Community Primary Care Doctors (Session 12) - Question and Discussion/ Course Wrap-up/Participants' Comment** Organiser: Hong Kong Medical Association & Hong Kong Society of Biological Psychiatry; Speaker: Dr. MAK Kai Lok / Dr. PAO Sze Yuan/ Prof. TANG Siu Wa, Dr. HO Chung Ping, MH, JP/ Dr. WONG Yee Him; Venue: Tang Room, 3/F, Sheraton Hong Kong Hotel & Towers, 20 Nathan Road, Kowloon	Ms. Candice TONG Tel: 2527 8285 2 CME Point
1:00 PM	**HKMA New Territories West Community Network: Common Peripheral Nerve Problem** Organiser: HKMA New Territories West Community Network; Speaker: Dr. LAM Chor Yin; Venue: SB 1036, Tuen Mun Hospital, Tsing Chung Koon Rd, Tuen Mun	Miss Antonia LEE Tel: 2527 8285 1 CME Point
7:00 PM	**Certificate Course on Pain Management in Geriatric Patients 2019** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Vienna LAM Tel: 2527 8898
7 SAT 2:15 PM	**Refresher Course for Health Care Providers 2019/2020 - Dental management of patients with medical diseases** Organiser: Hong Kong Medical Association, HK College of Family Physicians & HA-Our Lady of Maryknoll Hospital; Speaker: Dr. KUM Chun Sing; Venue: Lecture Halls A&B, 4/F, Block G, Wong Tai Sin Hospital	Ms. Clara TSANG Tel: 2354 2440 2 CME Point
9 MON 7:00 PM	**Certificate Course in Ophthalmology 2019** Assessments 2019 Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Vienna LAM Tel: 2527 8898
10 TUE 1:00 PM	**HKMA Kowloon West Community Network - Treatment of External Genital Wart** Organiser: HKMA Kowloon West Community Network; Speaker: Dr. WU Wai Fuk; Venue: Fulum Palace, Shop C, G/F, 85 Broadway Street, Mei Foo Sun Chuen	Ms. Candice TONG Tel: 2527 8285 1 CME Point
11 WED 1:00 PM	**HKMA Central, Western & Southern Community Network - Lipid Lowering: to Aim Super Low?** Organiser: HKMA Central, Western & Southern Community Network; Speaker: Dr. CHAN Ki Wan, Kelvin; Venue: The Chinese Banks' Association Ltd, 5/F, South China Building, 1 Wydham Street, Central	Miss Antonia LEE Tel: 2527 8285 1 CME Point
7:00 PM	**Certificate Course on Pain Management in Geriatric Patients 2019** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Vienna LAM Tel: 2527 8898
7:30 PM	**The Hong Kong Neurosurgical Society Monthly Academic Meeting –To be confirmed** Organiser: Hong Kong Neurosurgical Society; Speaker: Dr LI Ronald; Chairperson Dr CHEUNG Fung Ching; Venue: Seminar Room, G/F, Block A, Queen Elizabeth Hospital	1.5 points College of Surgeons of Hong Kong Dr WONG Sui To Tel: 2595 6456 Fax. No.: 2965 4061
13 FRI 1:00 PM	**HKMA Kowloon City Community Network - Antiplatelet Therapy after PCI** Organiser: HKMA Kowloon City Community Network; Speaker: Dr. TAM Kin Ming, Stephen; Venue: President's Room, Spotlight Recreation Club, 4/F, Screen World, Site 8, Whampoa Garden, Hunghom, Kowloon	Ms. Candice TONG Tel: 2527 8285 1 CME Point
16 MON 7:00 PM	**Certificate Course in Ophthalmology 2019** Assessments 2019 Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Vienna LAM Tel: 2527 8898
19 THU 1:00 PM	**HKMA Hong Kong East Community Network - Update on Lipid and Heart Failure Management** Organiser: HKMA Hong Kong East Community Network; Speaker: Dr. MIU Kin Man; Venue: HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, HK	Ms. Candice TONG Tel: 2527 8285 1 CME Point
8:00 PM	**FMSHK Executive Committee Meeting** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Nancy CHAN Tel: 2527 8898
23 MON 7:00 PM	**Certificate Course in Ophthalmology 2019** Assessments 2019 Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Vienna LAM Tel: 2527 8898
30 MON 7:00 PM	**Certificate Course in Ophthalmology 2019** Assessments 2019 Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Vienna LAM Tel: 2527 8898
31 TUE	**FMSHK Annual Dinner 2019** Venue: Run Run Shaw Hall, The Hong Kong Acadmy of Medicine Jockey Club Building	Ms. Gloria CHEUNG Tel: 2527 8898

Answers to Radiology Quiz

Answers:

1. A large homogenously enhancing mass was noted in the right-sided colon. Invagination of the terminal ileum mesentery into the right-sided colonic lumen was demonstrated. Small bowels were dilated. Features were in line with ileocolic intussusception with a caecal/terminal ileal mass acting as the pathological lead point, causing small bowel obstruction. Bulky adjacent lymphadenopathies were evident.

2. Caecal/terminal ileal lymphoma versus adenocarcinoma.

3. The homogenous texture of the mass and bulky lymphadenopathies point towards lymphoma.

4. Intussusception is rare in adult. 90% of these patients present in the paediatric population. While the cause of this condition in most paediatric patients is idiopathic, the majority of intussusception in the adult population is associated with pathological lead points.

5. The patient was at imminent risk of complications such as bowel strangulation/perforation. Urgent surgical reduction/relief of the intussusception was warranted. Right hemicolectomy was performed for the patient. Pathology came back to be diffuse large B-cell lymphoma.

Dr Jeremy Man-leung YU

enough already.

It's time to prevent migraine.

aimovig™
erenumab

Release the grip of migraine[1-3]

First and only therapy of its kind, specifically designed to prevent migraine by targeting the CGRP receptor[1]

Consistent and sustained efficacy across the migraine spectrum[1-3]

Placebo-like safety and tolerability profile[2-3]

Simple, once monthly administration with no loading dose[1]

Aimovig Important note: Before prescribing, consult full prescribing information. **Presentation:** Solution for injection, subcutaneous use: 1 mL prefilled pen contains 70 mg of erenumab. **Indications:** Aimovig is indicated for prophylaxis of migraine in adults who have at least 4 migraine days per month. **Dosage and administration: Adults:** The recommended dose of Aimovig is 70 mg administered subcutaneously every 4 weeks. Some patients may benefit from a dosage of 140 mg every 4 weeks. Aimovig is intended for patient self-administration in the abdomen, thigh, or, if someone else is giving the injection, also into the outer area of the upper arm. Administration should be performed by an individual who has been trained to administer the product. The needle cover of Aimovig pre-filled pen contains dry natural rubber, which may cause allergic reactions in individuals sensitive to latex. Consideration should be given to discontinuing treatment in patients who have shown no response after 3 months of treatment. Evaluation of the need to continue treatment is recommended regularly thereafter. The entire contents of the Aimovig pre-filled pen should be injected. **Special populations Pediatric patients:** The safety and effectiveness of Aimovig has not been studied in pediatric patients. **Geriatric patients:** No dose adjustment is necessary as the pharmacokinetics of erenumab are not affected by age. **Renal impairment/hepatic impairment:** No dose adjustment is necessary in patients with mild to moderate renal impairment. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. **Warnings and precautions:** Patients with certain major cardiovascular diseases were excluded from clinical studies. No safety data are available in these patients. **Pregnancy, lactation, females and males of reproductive potential: Pregnancy:** Safety has not been established. As a precautionary measure, it is preferable to avoid the use of Aimovig during pregnancy. **Lactation:** It is not known whether erenumab is present in human milk. Human IgGs are known to be excreted in breast milk during the first few days after birth, which is decreasing to low concentrations soon afterwards; consequently, a risk to the breast-fed infant cannot be excluded during this short period. Afterwards, use of Aimovig could be considered during breast-feeding only if clinically needed. **Females and males of reproductive potential:** Animal studies showed no impact on female and male fertility. **Adverse drug reactions: Common (1/100 to <1/10):** Injection site reactions, constipation, muscle spasm, pruritus. **Description of selected adverse reactions:** Injections site reactions include injection site pain, injection site erythema and injection site pruritus. A majority of injection site reactions were mild and transient. **Immunogenicity:** In pivotal studies the incidence of anti-erenumab antibody was 6.3% for the 70 mg dose (in-vitro neutralizing activity in 3 patients) and 2.6% for the 140 mg dose (no patients with in-vitro neutralizing activity). There was no impact of anti-erenumab antibody development on efficacy or safety of erenumab. **Interactions:** No effect on exposure of co-administered medicinal products is expected based on the metabolic pathways of monoclonal antibodies. No interaction with oral contraceptives (ethinyl estradiol/norgestimate) or sumatriptan was observed in studies with healthy volunteers. **Packs:** 1 mL prefilled pen contains 70 mg of erenumab. **Legal classification:** P1S1S3 Ref: EMA Aug 2018

References: 1. Aimovig™ Local Prescription Information 2019 . **2.** Goadsby PJ, Reuter U, Hallström Y, et al. A controlled trial of erenumab for episodic migraine. N Engl J Med. 2017;377(22):2123-2132. **3.** Tepper S, Ashina M, Reuter U, et al. Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial. Lancet Neurol. 2017;16(6):425-434

HK1910747530

NOVARTIS
Novartis Pharmaceuticals (HK) Limited
7/F, Citi Tower, One Bay East, 83 Hoi Bun Road, Kwun Tong, Kowloon, Hong Kong Tel: 2882 5222 Fax: 2577 0274

REDUCE YOUR PATIENTS' RISK OF HYPOGLYCAEMIA WITH TRESIBA®

VS GLARGINE U100[1-3]

Once-daily TRESIBA®: Ultra-long duration of action[4,5]

Severe hypoglycaemia — 40% significant rate reduction (p<0.001) — -40%

Nocturnal severe hypoglycaemia — 53% significant rate reduction (p<0.001) — -53%

Tresiba® OD* VS Glargine U100 OD*

* Plus additional antidiabetic treatments in accordance with standard of care.

DEVOTE Trial[1]

In **7,637** patients with type 2 diabetes at high risk of CV events[1]

At baseline: mean age was 65 years, diabetes duration was 16.4 years, HbA_{1c} was 8.4%, and 83.9% were on insulin therapy[1]

Abbreviated prescribing information
Tresiba® (insulin degludec) 100U (100 units/mL insulin solution for injection) in a prefilled pen (FlexTouch®). Consult Summary of Product Characteristics before prescribing.

Presentation: Tresiba® FlexTouch®. All presentations contain insulin degludec; Tresiba® 100 units/mL – 1 mL of solution contains 100 units insulin degludec (equivalent to 3.66 mg). One pre-filled device contains 300 units of insulin degludec in 3 mL solution. **Indications:** Treatment of diabetes mellitus in adults, adolescents and children from the age of 1 year. **Posology and administration:** Tresiba® is a basal insulin for once-daily subcutaneous administration any time of the day, preferably at the same time of day. On occasions when administration at the same time of the day is not possible, Tresiba® allows for flexibility in the timing of insulin administration. A minimum of 8 hours between injections should be ensured. In patients with type 2 diabetes mellitus, Tresiba® can be administered alone, or in any combination with oral antidiabetic medicinal products, GLP-1 receptor agonists and bolus insulin. In type 1 diabetes mellitus, Tresiba® must be used with short-/rapid-acting insulin. Administration by subcutaneous injection only. Tresiba® is available in 100 units/mL. For Tresiba® 100 units/mL a dose of 1–80 units per injection, in steps of 1 unit, can be administered. When initiating patients with type 2 diabetes mellitus the recommended daily starting dose is 10 units. Transferring from other insulins; in type 2 diabetes changing the basal insulin to Tresiba® can be done unit-to-unit, based on the previous basal insulin component; in type 1 diabetes the same applies apart from where transferring from twice-daily basal insulin or patients with an HbA1c <8.0%, the Tresiba® dose needs to be determined on an individual basis with a dose reduction considered. Doses and timing of concomitant treatment may require adjustment. Using Tresiba® in combination with GLP-1 receptor agonists in patients with type 2 diabetes mellitus; when adding Tresiba® to GLP-1 receptor agonists, the recommended daily starting dose is 10 units; when adding GLP-1 receptor agonists to Tresiba®, it is recommended to reduce the dose of Tresiba® by 20% to minimize the risk of hypoglycaemia. In all cases doses should be adjusted based on individual patients' needs; fasting plasma glucose is recommended to be used for optimising basal insulin doses. In elderly patients, and patients with renal/hepatic impairment glucose monitoring should be intensified and the dose adjusted on an individual basis. In paediatric population, when changing basal insulin to Tresiba®, dose reduction of basal and bolus insulin needs to be considered on an individual basis in order to minimise the risk of hypoglycaemia. Tresiba® comes in a pre-filled pen, FlexTouch®, designed to be used with NovoFine®. **Contraindications:** Hypersensitivity to the active substance or any of the excipients. **Special warnings and precautions:** Too high insulin dose; omission of a meal or unplanned strenuous physical exercise may lead to hypoglycaemia. In children care should be taken to match insulin doses (especially in basal-bolus regimens) with food intake and physical activities in order to minimize the risk of hypoglycaemia. Reduction of warning symptoms of hypoglycaemia may be seen upon tightening control and also in patients with long-standing diabetes. Administration of rapid-acting insulin is recommended in situations with severe hyperglycaemia. Inadequate dosing and/or discontinuation of treatment in patients requiring insulin may lead to hyperglycaemia and potentially to diabetic ketoacidosis. Concomitant illness; especially infections, may lead to hyperglycaemia and thereby cause an increased insulin requirement. Transferring to a new type, brand or manufacturer of insulin should be done under medical supervision and may result in a change in dosage. When using insulin in combination with pioglitazone, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs. Patients must be instructed to always check the insulin label before each injection to avoid accidental mix-ups with other insulins. Hypoglycaemia may constitute a risk when driving or operating machinery. **Pregnancy and lactation:** There is no clinical experience with use of Tresiba® in pregnant women and during breastfeeding. Animal reproduction studies have not revealed any difference between insulin degludec and human insulin regarding embryotoxicity and teratogenicity. **Undesirable effects:** Refer to SmPC for complete information on side effects. Very common (≥1/10); common (≥1/100 to < 1/10); uncommon (≥1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data). Very common: Hypoglycaemia. Common: Injection site reaction. Uncommon: Lipodystrophy and peripheral oedema. Rare: Hypersensitivity and urticaria. With insulin preparations, allergic reaction may occur; immediate-type allergic reactions may potentially be life threatening. Injection site reactions are usually mild, transitory and normally disappear during continued treatment.

FlexTouch®, NovoPen Echo®, NovoFine®, Penfill®, and Tresiba® are registered trademarks of Novo Nordisk A/S.

References: 1. Marso SP, McGuire DK, Zinman B, et al, for the DEVOTE Study Group; Efficacy and safety of degludec versus glargine in type 2 diabetes. New England Journal of Medicine 2017; 377:723–732. **2.** Wysham C, Bhargava A, Chaykin L, et al; Effect of Insulin Degludec vs Insulin Glargine U100 on Hypoglycemia in Patients With Type 2 Diabetes: The SWITCH 2 Randomized Clinical Trial, JAMA 2017; 318(1):45–56. **3.** Lane W, Bailey TS, Gerety G, et al, Effect of Insulin Degludec vs Insulin Glargine U100 on Hypoglycemia in Patients With Type 1 Diabetes: The SWITCH 1 Randomized Clinical Trial, JAMA 2017; 318(1):33–44. **4.** Tresiba® Packing Insert. **5.** Jonassen I, Havelund S, Hoeg-Jensen T, et al, Design of the novel protraction mechanism of insulin degludec, an ultra-long-acting basal insulin. Pharmaceutical Research 2012;29(8):2104-14

novo nordisk®

Further information is avaliable from
Novo Nordisk Hong Kong Ltd.
Unit 519, 5/F, Trade Square, 681 Cheung Sha Wan Road, Kowloon, Hong Kong
Tel: (852) 2387 8555 Fax: (852) 2386 0800 www.novonordisk.com

TRESIBA®
insulin degludec [rDNA origin] injection

TRE-D-20190101