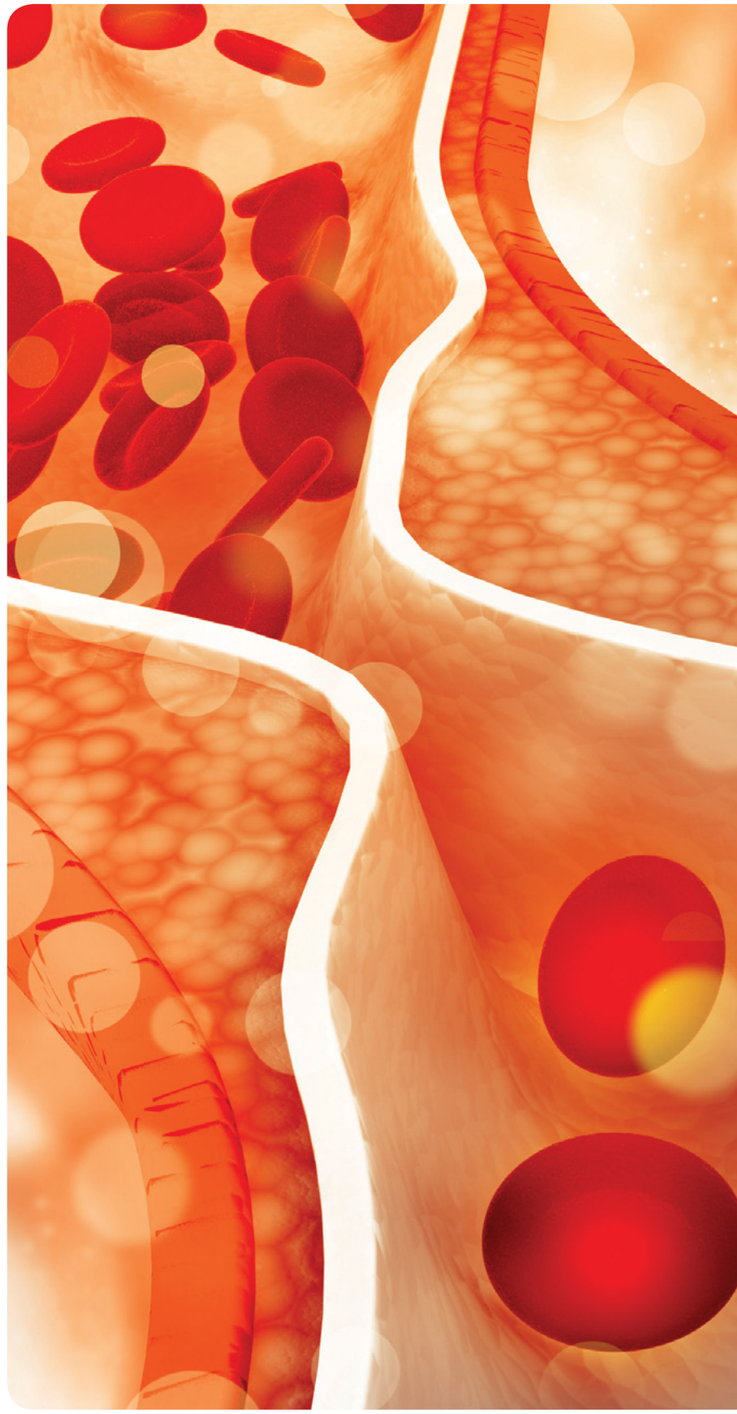
TAN TOCK SENG HOSPITAL

MEDICAL DIGEST

JANUARY - MARCH 2018



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Medical Digest is a quarterly publication of Tan Tock Seng Hospital written by healthcare providers for healthcare providers, as a service to the medical community.

FROM THE EDITOR

I am moved to remember my time in Houston, Texas because of the floods that devastated the city in October 2017. I lived in Houston from October 1996 to October 1997, a beneficiary of the Ministry's Health Manpower Development Plan. Besides Singapore, I have never stayed anywhere else longer.

Houston has a special place in my heart. I went there when Bill Clinton was gunning for a second term in office (before anyone had heard of Monica Lewinsky), when Leann Rimes was still a teenager, and when Enron was just another energy company. The hit song was Toni Braxton's Un-break My Heart and the blockbuster movie was The English Patient. Mother Theresa, Diana Princess of Wales and John Denver were alive at the start of my fellowship but were not by the time it ended. Some nurses in the Texas Children Hospital still remember the bubble boy (David Phillip Vetter 1971-84). My classmate Adela Tow was in Houston at the same time. While in the US, I caught up with other classmates Yeoh Khay Guan in San Antonio and Dennis Lim in New York City.

I loved the Half-Price Bookstores, the Menil Collection, Goode Company Texas Bar-B-Q, the Astrodome, Galleria at Westheimer, and Chinatown at west Bellaire. I attended talks by Leroy Hood (inventor of the automated DNA sequencer), David Roth (not the Van Halen band member but the expert on VDJ recombination) and Graham Hughes (a friend of Singapore Rheumatology, though I first met him in Houston).

Thank you, Dr David Huston, for welcoming me into the Immunology Section in Baylor College. I learnt many things. There are many ways to get the job done besides the Singapore way. Some duplication is not a waste if it improves efficiency. There is a strategy to writing a scientific paper. There is nothing we cannot do – we can always collaborate and discuss. IL-5 is important in asthma and rhinitis. And a mouse can be made asthmatic!

I was surprised that visitors have to go through a metal detector to enter the Ben Taub Hospital. But the Methodist Hospital is like a five-star hotel. Somehow I was invited to the dinner to send off Dr Anthony Gotto as he left Baylor College to go to Cornell University. Together with 1,000 other people..

The signatories on my fellowship certificate are American medical luminaries: Michael DeBakey (who needs no introduction), Ralph Feigin (author of the Textbook of Pediatric Infectious Diseases), William Shearer (paediatric immunologist and HIV expert), Edward Lynch (haematologist and prize-winning teacher), and William Butler (President of Baylor College).

Though political scandals, racial disharmony and sexual abuse dominate the headlines, America remains a great country. I have seen tolerance, generosity, innovation, hard work, and strive for excellence in American institutions and hospitals. Not everyone is happy with their overseas fellowship. But I was blessed to see a slice of a great city and a great medical institution.

Dr Leong Khai Pang
EDITOR
Medical Digest

MEDICAL DIGEST

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RESEARCH

TTSH RESEARCH NEWS

Every year, TTSH clinicians publish about 300 scientific papers. In this section, we selected a few reports and asked one of the authors of each to summarise and discuss the clinical relevance of their research. The theme this issue are the medical disciplines.

RESEARCH EXCERPT 1

Clinical characteristics, risk factors and outcomes of South-East Asian patients with acute pulmonary embolism

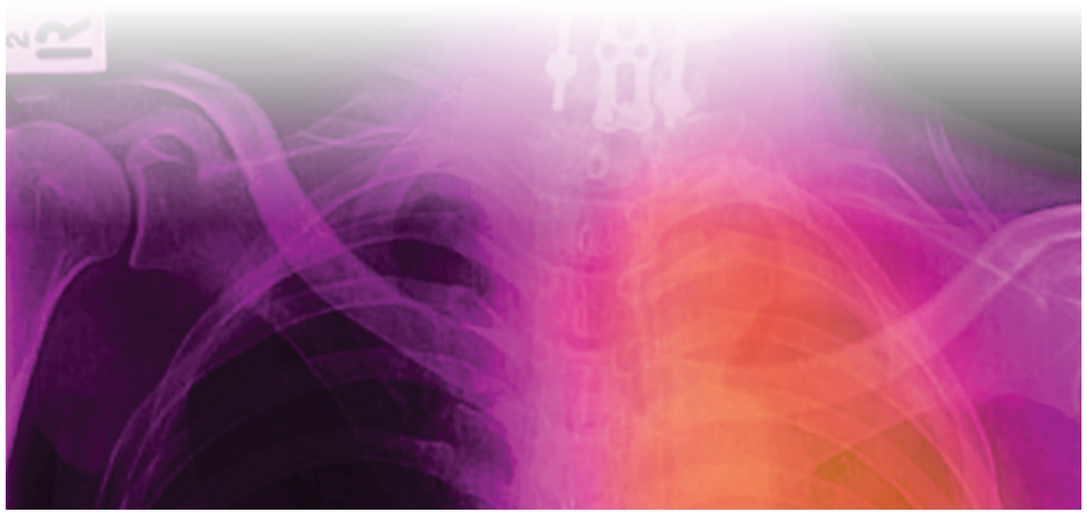
Mok KH, Wong SW, Wong YM, Foo D, Watson TJ, Ho HH. Int J Cardiol 2017; 249:431-3.

The diagnosis of pulmonary embolism (PE) depends on a high index of suspicion, but much of the literature on PE comes from Western populations with little data from our region. We aimed to study the clinical characteristics, risk factors and outcomes of patient diagnosed with PE in Tan Tock Seng Hospital. Between January 2008 and March 2013, we identified 343 patients admitted with a diagnosis of PE, of which 9% were massive PE and the rest submassive. Our data showed that the two most common precipitating causes of PE were immobilisation (21%) and deep vein thrombosis (37%), but one-third of patients had no apparent risk factors. The clinical presentation, similar to data from the West, was variable with dyspnoea being the most common symptom (72%). Eighty-three percent of our patients were treated with low-molecular-weight heparin and 7% were treated with lytics. Overall, 10% of patients suffered from bleeding complications of which 3.5% were major. This is consistent with prior literature which has shown that Asians have a higher tendency of bleeding.

IMPORTANCE IN CLINICAL PRACTICE

Having local data is invaluable especially for conditions that are hard to pick up. The fact that one-third of our patients had no apparent risk factor for PE underscores the importance of a high index of suspicion for this potentially life-threatening condition. Elucidating our own Asian data helps in weighing the risk versus benefit of our therapies and also in counselling patients and their families on the potential risks of bleeding complications.

This summary was prepared by Dr Mok Kwang How, an associate consultant in the Department of Cardiology, Tan Tock Seng Hospital.



RESEARCH EXCERPT 2

A randomised controlled trial evaluating the impact of targeted vitamin D supplementation on endothelial function in type 2 diabetes mellitus: The DIMENSION trial

Dalan R, Liew H, Assam PN, Chan ES, Siddiqui FJ, Tan AW, Chew DE, Boehm BO, Leow MK. Diab Vasc Dis Res 2016; 13(3):192-200.

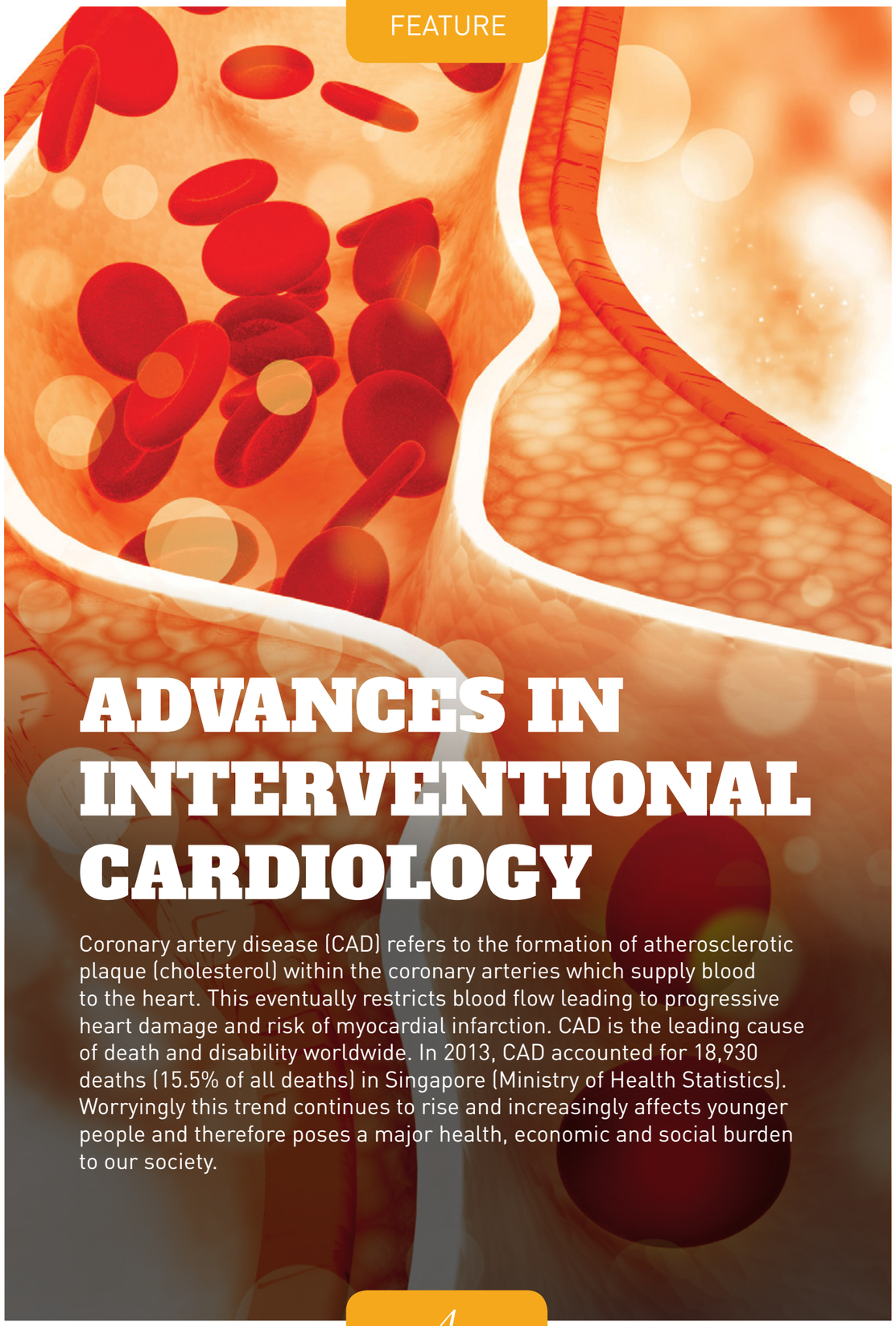
Patients with type 2 diabetes mellitus (T2DM) have a high risk for all cardiovascular events and cardiovascular deaths even in those without a history of prior myocardial infarction. Hence, it has been postulated that endothelial dysfunction is the precipitating factor for atherosclerosis which leads to vascular complications. Vitamin D protects the endothelium from the effects of advanced glycation end products in diabetes by reducing oxidative stress, modulating and attenuating the inflammatory response, attenuating platelet activation and reducing the expression of vascular adhesion markers on the endothelium.

In this study conducted in Tan Tock Seng Hospital, we evaluated the effect of 16 weeks of cholecalciferol supplementation on endothelial function in a multi-ethnic group of patients with T2DM and hypovitaminosis D, aiming for a target 25(OH)D concentration of 30–40 ng/mL. This randomised, double-blind, placebo-controlled, parallel group trial included 64 patients with T2DM, who had glycated haemoglobin (HbA1c) of 6.0%–10.0%, hypovitaminosis D, and were on stable medications for glycaemic, blood pressure and lipid control. Endothelial function was assessed by peripheral tonometry (reactive hyperaemia index–endothelial peripheral arterial tonometry) and vascular biomarkers: E-selectin, von-Willebrand factor and high-sensitivity C-reactive protein. Median reactive hyperaemia index in the vitamin D group increased from 0.65 (interquartile range, IQR: 0.42) to 0.73 (IQR: 0.36), whereas it decreased from 0.73 (IQR: 0.65) to 0.65 (IQR: 0.38) ($p = 0.02$) in the placebo group. After adjustment for baseline variables, the change was not statistically significant for reactive hyperaemia index ($p = 0.07$) and for other vascular biomarkers ($p > 0.05$). Targeted vitamin D supplementation for 16 weeks resulted in a small but non-statistically significant improvement in endothelial function in this T2DM cohort.

IMPORTANCE IN CLINICAL PRACTICE

Our study shows a high prevalence of hypovitaminosis D in this group of T2DM patients in Singapore. The target approach of daily oral supplementation of cholecalciferol at 2000–4000 IU was safe and effective in improving the vitamin D status in T2DM patients. Our study is similar to other trials which have failed to show improvement in endothelial function in the short term if patients with hypovitaminosis are chosen. We need to look at other methods of selecting patients for vitamin D supplementation for example patients with genetic polymorphisms which are associated with hypovitaminosis in the long term and a longer duration of cholecalciferol supplementation should be considered in future studies.

This was a principal investigator-initiated study conducted by Dr Rinkoo Dalan, a senior consultant in the Department of Endocrinology, Tan Tock Seng Hospital. The study was funded by the DUKE-NUS Tanoto Diabetes initiative and the National Healthcare Group.



ADVANCES IN INTERVENTIONAL CARDIOLOGY

Coronary artery disease (CAD) refers to the formation of atherosclerotic plaque (cholesterol) within the coronary arteries which supply blood to the heart. This eventually restricts blood flow leading to progressive heart damage and risk of myocardial infarction. CAD is the leading cause of death and disability worldwide. In 2013, CAD accounted for 18,930 deaths (15.5% of all deaths) in Singapore (Ministry of Health Statistics). Worryingly this trend continues to rise and increasingly affects younger people and therefore poses a major health, economic and social burden to our society.

Medical progress in the late 19th and early 20th centuries was largely limited to curious observation, anatomical dissection and description of disease processes. Consequently, little impact was made in improving disease outcomes, but this allowed us to appreciate that the atherosclerotic plaque and consequent restriction of blood flow with associated risk of myocardial infarction was a significant process which demanded a solution to improve outcomes. Initially the atherosclerotic plaque could only be managed surgically using coronary artery bypass grafting which itself only became possible with the advent of the mechanical heart-lung bypass circuit. This initially crude technique has been progressively refined over many decades and generally has excellent outcomes, but still is associated with a prolonged recovery phase and risk of complications.

Coronary balloon angioplasty was first performed in a human patient in 1977 by Dr Andreas Gruentzig in Switzerland, thereby opening a new chapter in cardiovascular medicine. Since then, the field of interventional cardiology has made significant strides with percutaneous coronary intervention (PCI) now established as the preferred method of revascularisation for patients with obstructive CAD. Over the past four decades, we have witnessed several important advances in devices, procedural techniques and adjunctive antithrombotic therapy in this exciting field. We summarise some of the latest developments and novel therapies in our review.

Transradial intervention

The first balloon angioplasty in human was performed in a patient undergoing coronary artery bypass surgery (CABG). Thus, it was performed in a relatively safe environment where the surgeon was able to immediately undertake grafting of the treated vessel should the procedure become complicated. The procedure was successful, demonstrating that balloon angioplasty has a clear potential to be an effective standalone treatment. Dr Gruentzig was driven to push the boundaries further to utilise an entirely percutaneous approach.

Without specific solutions available commercially, Dr Gruentzig was forced to design and manufacture most of his early equipment himself. Consequently, the equipment was relatively cumbersome and large in caliber. Initially coronary angiography was developed as a technique through the brachial artery. This required a surgical cut-down with catheter introduction directly into the artery and bleeding controlled by a series of sutures around the arteriotomy whilst the catheter was being manipulated into position. Naturally this led to risk of vascular injury, bleeding and distal thrombosis, and damage to adjacent structures. PCI requiring large caliber equipment had to be undertaken via the femoral artery.

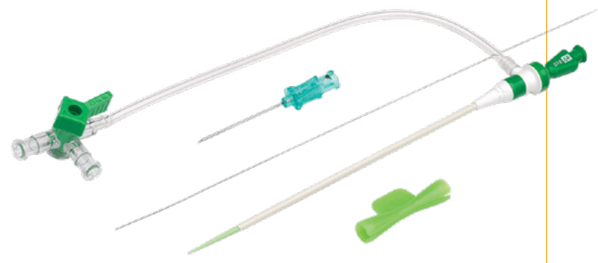


Figure 1. A percutaneous vascular sheath allowing access to the arterial system without significant blood loss.

The introduction of the percutaneous vascular sheath (figure 1) with a haemostatic valve allowed arterial access to become completely percutaneous using the Seldinger technique, without need for a surgical cut-down. This allowed the sheath to be left in situ during the procedure allowing for catheter manipulation and catheter switching with minimal blood loss. After the procedure was completed, the sheath could be removed by simple manual compression to achieve haemostasis. This combined with progressive miniaturisation of balloons allowed catheter size to be reduced, limiting the probability of vascular injury. Nonetheless, haemostasis in the femoral artery can be challenging with possibility of retroperitoneal bleeding, haematoma and potential for distal limb vascular compromise.

European efforts to further refine PCI and improve safety, particularly in France, led to the introduction of transradial access. This was possible largely because the necessary guide catheter caliber by this point had been reduced to 6 French (2 mm) or sometimes even 5 French. The majority of radial arteries can accommodate 6 French sheaths safely without risk of vascular damage, whilst the risk of hand ischaemia is precluded by the presence of the ulnar artery which ensures adequate perfusion. Importantly, the radial artery is readily accessible allowing easy access and readily compressible allowing haemostasis to be achieved quickly and safely with minimal risk of haematoma and bleeding.

Although the transradial approach is technically more demanding than the transfemoral route, its success has been greatly enhanced by technological improvement in equipment and increased operator experience. Importantly, patients find radial procedures more comfortable and there is an association with reduced length of hospital stay. Moreover, the ability to achieve haemostasis has allowed day case PCI services to be realised for selected patients.

Over the past five years in Tan Tock Seng Hospital, we have been performing invasive cardiac procedures [including primary PCI for acute myocardial infarction (AMI)] through the radial artery as the default choice (approximately 90% of all cases). We have achieved high procedural success with minimal complications.

Primary percutaneous coronary intervention

CAD can present in many guises, however the most dramatic is AMI. AMI is one of the top ten leading causes of death in Singapore with a 28-day case-fatality rate of 12.7% and therefore rightly merits aggressive and effective treatments to optimise outcomes for our patients.

AMI has a spectrum of presentations, but the most severe and dramatic form is an ST-segment elevation myocardial infarction (STEMI). This is a direct result of complete obstruction of the coronary artery by a ruptured atherosclerotic plaque and rapid formation of thrombus. This deprives the heart of its important blood supply and rapidly results in death of heart muscle. STEMI requires emergency treatment to remove the obstruction to blood flow as quickly and effectively as possible. This is best achieved using emergency PCI. This service is offered at all restructured hospitals in Singapore, including Tan Tock Seng Hospital on a 24-hours-a-day, 365-days-a-year basis.

Over the last 70 years though, the management of STEMI has changed dramatically. Early milestones include the introduction of the coronary care unit (1961) and the development of the cardiac defibrillator (1962), both of which have a major impact in improving outcomes. However, it is the 1980s which witnessed perhaps the most striking breakthroughs towards improving clinical outcomes for STEMI. A number of major mega-trials were conducted in this era, centred around the 'open artery' hypothesis – that key to improving outcomes for STEMI was rapid and timely reperfusion or restoration of blood flow through the occluded coronary artery. This led to the widespread adoption of aspirin (1997) and pharmacological thrombolysis (1986), both of which had vast impacts.

However, as effective as these strategies were, it was clear that further progress needed to be made. Major drawbacks to pharmacological approaches to achieving an open artery include risk of major or life-threatening bleeding (1%), and delay or failure to reperfuse. This is coupled with inherent difficulties in managing the patients' haemodynamic status – a factor which can even preclude use of pharmacological agents. Furthermore, pharmacological strategies have no impact on dealing with the underlying atherosclerotic plaque and even should reperfusion be successful, often the critically stenosed underlying plaque remains. This

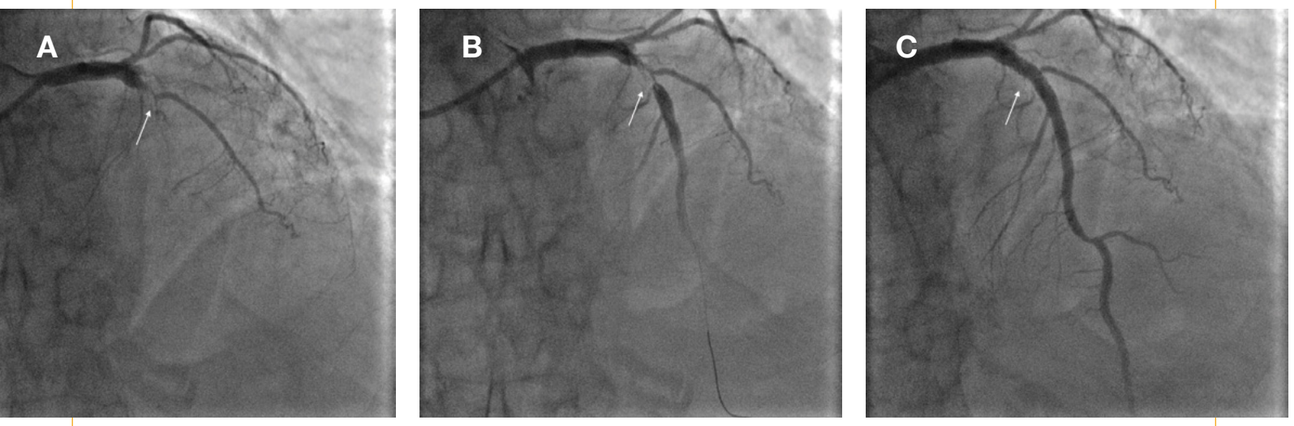
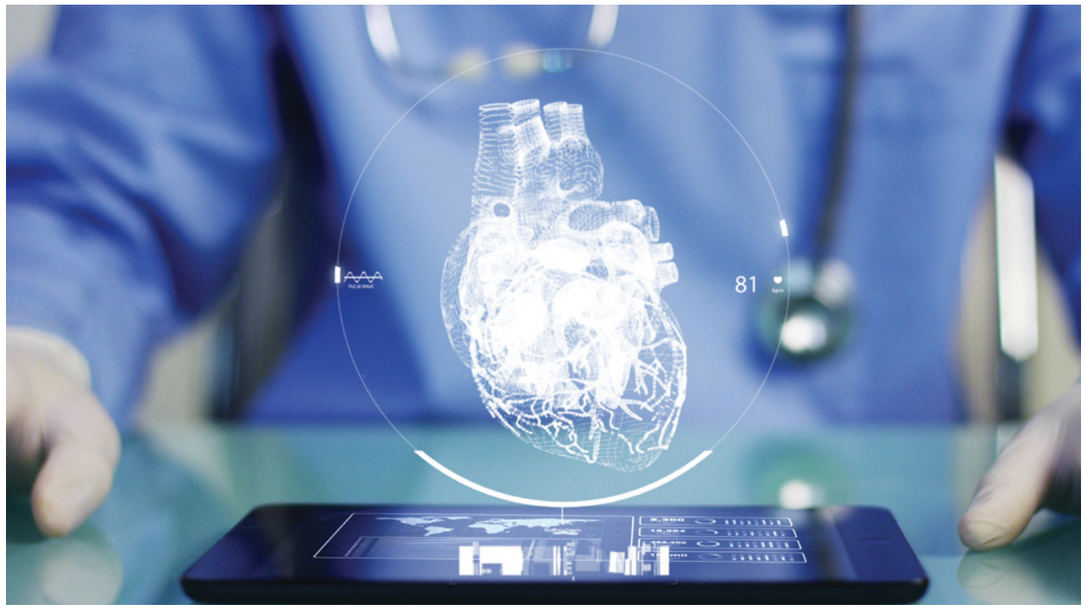


Figure 2. a) Occluded left anterior descending (LAD) coronary artery causing acute myocardial infarction (arrow); b) Wiring the LAD has allowed some flow to be restored but a critical stenosis remains (arrow); c) LAD after insertion of a drug eluting stent is now widely patent and with good flow (arrow).



threatens further adverse events and may generate exertional angina once the patient recovers from the index event.

With superior rates of reperfusion, lower rates of bleeding complications and subsequent adverse events, primary PCI has become the standard of care for patients presenting with STEMI (figure 2). Moreover, this procedure effectively manages the underlying atherosclerotic plaque (usually with a stent or use of a drug coated balloon) so that recurrent angina rates remain low. With marked improvements in outcome, significant resources have been directed towards developing the STEMI-care model and as one of the largest centres in Singapore, TTSH has been central in developing these frameworks. This includes a process of fast tracking STEMI patients from the emergency department directly to the invasive cardiac laboratory for emergency coronary angiography. We have an emergency STEMI team which includes immediate availability of the necessary medical and ancillary staff to facilitate rapid reperfusion. Moreover, we have worked hard towards ensuring community awareness and encouraging early presentation following symptom onset. All these factors have been shown to improve outcomes and we continue to aim for as rapid reperfusion as possible.

Coronary stents

The success of balloon angioplasty in clinical practice is limited by the risk of acute vessel closure, elastic recoil, negative vascular remodeling and restenosis. Thus, patients with obstructive CAD are often treated with balloon angioplasty followed by coronary stenting. Coronary stents (figure 3) were first introduced into clinical practice in 1986. They are essentially metallic scaffolding to keep the lumen of the artery open with preservation of flow as vessel recoil or dissection may occur after ballooning. Stent implantation, however, causes arterial injury triggering vascular smooth muscle proliferation and extracellular matrix formation leading to neointimal formation. Excessive tissue growth leads to in-stent restenosis (ISR) which remains a major Achilles heel in the bare metal stent era (restenosis rate around 20–30%). With the advent of drug-eluting stents (DES), the rate of ISR has been significantly reduced (<10%) compared to bare metal stents. DES are based on three components, a metallic stent platform, an anti-proliferative agent and a drug carrier (polymer coating). The anti-proliferative agent suppresses the excessive neointimal formation and reduces ISR. Nevertheless, the use of first-generation DES was associated with the phenomenon of late stent thrombosis with increase in cardiovascular mortality. This raised safety concerns and led to development of newer generation DES which are both efficacious and safer.

The presence of permanent polymers in the older generation DES has been blamed for the delayed healing and poor endothelialisation observed in patients presenting with late stent thrombosis. New-generation DES have successfully incorporated

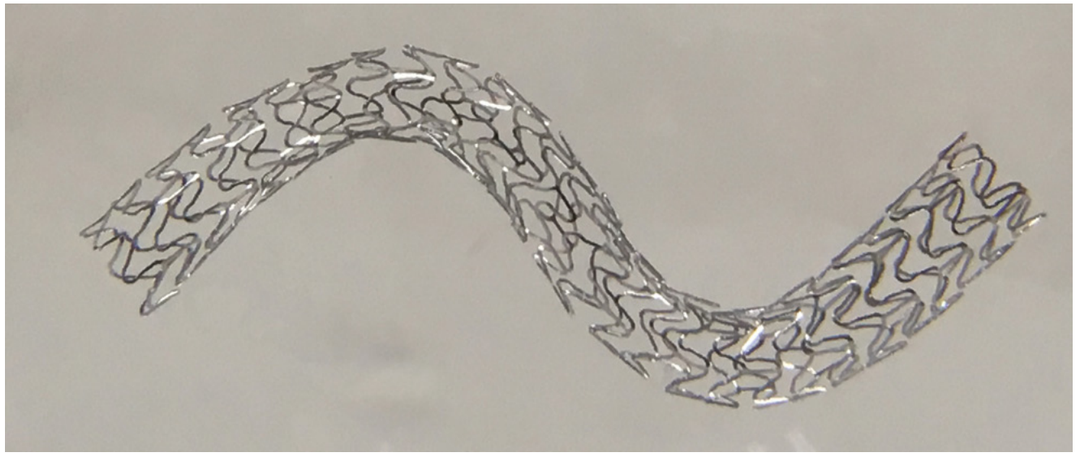


Figure 3. A modern coronary stent is low profile and able to traverse complicated anatomy.

bioabsorbable polymers into their stent platforms. This approach combines both *efficacy* (drug eluted from the polymers reduces neointimal hyperplasia within the stent) and *safety* (polymers disappear over time thus reducing the risk of late stent thrombosis). Although a number of current generation DES models still have a permanent polymer, these are still considered efficacious as manufacturers have worked towards increasing the polymer biocompatibility. This has consequently led to less inflammation whilst also allowing for enhanced endothelialisation ensuring that these devices continue to provide excellent efficacy.

The newer DES also have new metallic alloys and thinner stent struts making them more deliverable in challenging lesions. Further developments have led to the emergence of polymer-free DES which also release the anti-proliferative agent (sirolimus or its analogues) from the stent surface without application of the polymer coating. During the manufacturing process these devices are 'etched' to allow the limus agent to stick to the surface or the stent design incorporates micro-reservoirs to act as a depot for controlled drug release. Clinical results with these new stent platforms have been promising as they demonstrate improved biocompatibility and better healing profile. With some stent models, this has allowed significantly abbreviated dual anti-platelet therapy (DAPT) protocols to be prescribed rather than mandating this for the 12 months which was previously considered routine (see 'Optimal medical therapy' below).

Singapore is also waging a war against diabetes mellitus and with one of the highest rates of this condition in the world and an association with poor outcomes, this truly is a war rather than a battle. Worryingly, diabetic patients often have more complex multi-vessel CAD characterised by long lesions, calcified vessels and small coronary vessels. Based on the available clinical evidence, contemporary metallic DES represents the standard of care for patients undergoing PCI at this point of time. However, diabetes mellitus remains an independent predictor of adverse clinical outcomes in patients undergoing PCI.

The newer DES also have new metallic alloys and thinner stent struts making them more deliverable in challenging lesions.

The FREEDOM trial showed that for patients with diabetes and advanced CAD, CABG was superior to PCI as it significantly reduced rates of death and myocardial infarction, with a higher rate of stroke. Therefore, CABG remains the preferred method of revascularisation for diabetic patients with complex multi-vessel CAD. A dedicated polymer-free DES using amphilimus (sirolimus + fatty acid) has shown some promise in patients with diabetes but its preliminary results need to be validated in large-scale randomised controlled trials.

An inherent drawback of DES is the presence of a permanent metallic implant which can affect the natural vasomotion of the coronary artery and the potential for late inflammation. The concept of "leaving nothing behind" in the treatment of CAD subsequently led to the concept of a fully *biodegradable stent/scaffold*. The advantage of a biodegradable stent/scaffold is there will be no permanent metallic implant in the artery as the stent/scaffold resorbs naturally into the body. It can also allow repeated re-intervention on the same target vessel either by PCI or CABG without the technical difficulties posed by previous stent(s).

The use of first generation bioresorbable vascular scaffold was shown to be feasible and safe in initial studies. Preliminary evaluation has provided evidence of complete resorption, restoration of vasomotion as well as positive vessel remodeling. However, when used in complex coronary lesions and small vessels, its long-term outcomes were hampered by higher risk of late scaffold thrombosis. The first generation bioresorbable vascular scaffold had a longer resorption time of two to three years and was limited by thick strut and other mechanical shortcomings. The currently available bioresorbable stent/scaffold is regarded as an investigational device and clinical studies have indicated that additional modifications will be required for this novel technology to provide a safety and efficacy profile comparable to the contemporary metallic DES.

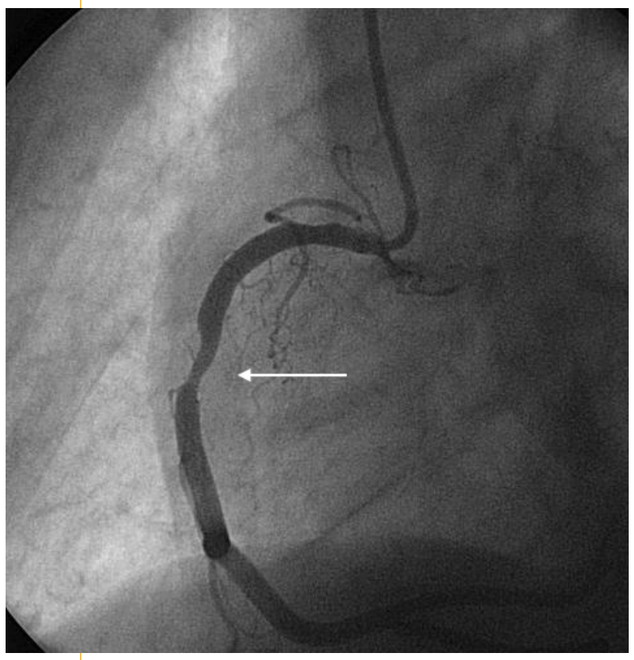


Figure 4. Coronary angiography showing moderate stenosis in the mid right coronary artery (arrow). The impact that moderate stenosis has on blood flow can be difficult to gauge visually.

The currently available bioresorbable stent/scaffold is regarded as an investigational device and clinical studies have indicated that additional modifications will be required for this novel technology to provide a safety and efficacy profile comparable to the contemporary metallic DES.

Intracoronary imaging

Development of invasive coronary imaging techniques in the cardiac catheterisation laboratory have allowed clinicians to "peek" inside the artery and better assess the underlying coronary plaque and its surrounding tissues. This has improved our understanding of the pathophysiology of atherosclerotic disease and also helped us to evaluate the effectiveness of new drugs and new intravascular devices. In clinical practice these tools are particularly helpful for grading disease which is angiographically moderate (figure 4), where there is extensive calcification or where vessel size is hard to determine due to diffuse disease.

Grey-scale *intravascular ultrasound* (IVUS) was first introduced 30 years ago and has been so far the most useful invasive imaging technique that has impacted clinical practice (figure 5). Using IVUS, lipid lowering drugs like statins have been shown to decrease size of plaque and as a result, these drugs have been approved for clinical use. During coronary angiography, IVUS is used as a diagnostic tool to assess the severity of left main lesion, to assess hazy lesions and to examine the geometry of complex coronary anatomy. In PCI, IVUS is also useful to optimise the stent, evaluate the efficacy of different stent designs and identify causes of restenosis and stent thrombosis. In addition, IVUS-guided PCI has been shown to decrease the rate of restenosis and stent thrombosis which translates into favourable long term outcomes. It is especially useful to guide DES implantation in long lesions, large vessels and left main lesions.

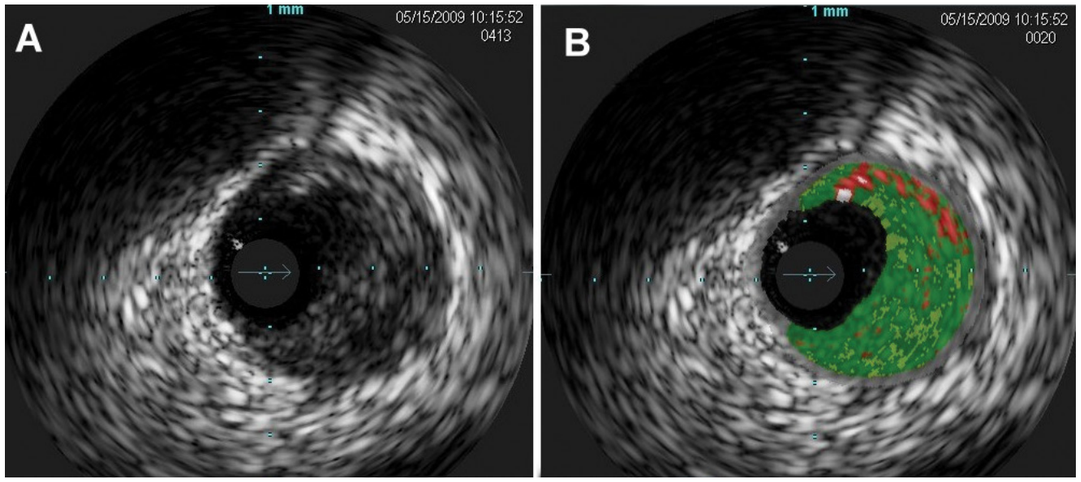


Figure 5. Grey-scale intravascular ultrasound of the mid right coronary artery (panel A) showing eccentric atherosclerotic plaque. Virtual histology analysis (panel B) showing the plaque was mainly composed of fibrous tissue with minimal necrotic core.

Subsequently, two new invasive coronary imaging techniques were developed: *virtual histology* (VH) and *optical coherence tomography* (OCT). VH (figure 5) offers a more detailed evaluation of the atherosclerotic plaque than grey-scale IVUS. Through radiofrequency analysis, it is able to classify plaque into four major components (fibrous, fibrofatty, necrotic core and dense calcium). It is especially useful in identifying a vulnerable plaque which is the main precursor lesion for plaque rupture in AMI. The PROSPECT study evaluated the potential value of IVUS-VH-derived plaque types in predicting adverse cardiac events and gave invaluable information on the natural history and features of high risk plaque types.

OCT is a near infra-red light-based imaging modality that can be used to study tissues in vivo with near histologic, ultra-high resolution (figure 6). Certain microstructures like thickness of the fibrous cap or stent strut coverage can be visualised much better than with grey-scale IVUS. This has provided new insights into the interaction between the vessel wall and the stent and has allowed more accurate characterisation of coronary plaques. Like IVUS, OCT is also useful in evaluating the efficacy of different stent designs and identifying causes of restenosis and stent thrombosis. OCT-guided PCI has been shown by several studies to be non-inferior to IVUS-guided PCI in terms of clinical outcomes. Further studies are required to indicate the most helpful technology in different lesion subsets and clinical settings.

Advances in the field of intracoronary imaging include development of hybrid intravascular catheters which allow more accurate evaluation of plaque morphology. It also allows assessment of plaque biology and local haemodynamic forces following PCI. These techniques will allow us to identify patients with vulnerable plaques (at high risk of developing major adverse cardiac events) and also to evaluate the benefits of local or systemic therapeutic interventions.

Physiological assessment of coronary artery disease

The focus of CAD has shifted from anatomical to physiological assessment with the development of the pressure wire in 1991. This led to the concept of *fractional flow reserve* (FFR) in coronary physiology. In normal coronary arteries, the highest possible FFR value is 1.0. An FFR value of 0.70 implies that the maximum flow to the distal myocardium only reaches 70% of what it should be if the artery were normal. It is especially useful for assessing moderate coronary lesions (stenosis of 50–70%) and deciding whether to treat these lesions with medical therapy or revascularisation (PCI/CABG). The three most important FFR trials were DEFER, FAME and FAME 2. The DEFER study showed that patients with FFR value ≥0.75 can be treated with optimal medical therapy and risk of cardiac death/myocardial infarction was <1% per year. The FAME studies adopted a higher FFR cut-off value of 0.80 and showed that FFR-guided PCI resulted in better clinical outcomes by avoiding unnecessary stent implantation.

The FFR model applies only when maximal hyperaemia is achieved by using intravenous/intracoronary adenosine or intracoronary papaverine. A new development is the instantaneous wave-free ratio (iFR) which is proposed as a vasodilator-free index of stenosis severity comparable to FFR. The effectiveness of iFR (figure 7) to guide revascularisation as compared to FFR was evaluated in two large randomised controlled trials and both showed that iFR produced non-inferior clinical outcomes.

With the advent of pressure wires (FFR, iFR), the clinical decision-making process of the interventional cardiologist has been markedly refined and allows clinicians to identify patients at high risk of adverse cardiovascular event with greater objectivity.

Optimal medical therapy

Optimal medical therapy (OMT) remains the cornerstone in the management of patients after PCI, as coronary atherosclerosis continues to progress after revascularisation. OMT can reduce the progression of atherosclerosis and prevent plaque rupture or thrombotic events. Anti-platelet agents and a lipid lowering drugs are indicated for all patients who have undergone PCI, unless they are contraindicated or not tolerated.

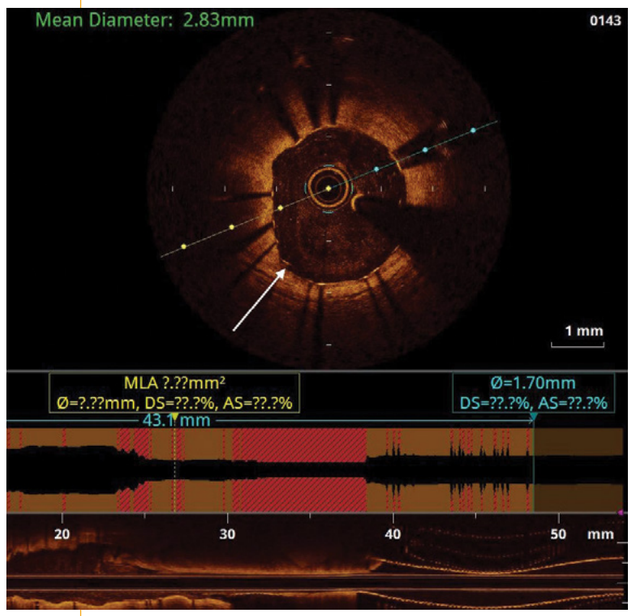


Figure 6. Optical coherence tomography of coronary artery after stenting; note its detailed near-field resolution to assess stent apposition. The arrow indicates the stent as visualised on optical coherence tomography with a shadow behind the struts.

Optimal medical therapy (OMT) remains the cornerstone in the management of patients after PCI, as coronary atherosclerosis continues to progress after revascularisation.

Dual anti-platelet therapy is recommended for all patients with CAD undergoing PCI with DES implantation. A DAPT regimen consists of aspirin 100 mg daily and a P2Y12 inhibitor (either clopidogrel 75 mg daily or ticagrelor 90 mg twice a day). Six to twelve months of DAPT is the general recommendation but the optimal duration of DAPT after stenting is still being debated. Extension of DAPT beyond 12 months involves a trade-off between reduced ischaemic events and increased bleeding risk. Doctors have to consider the risk-benefit ratio of DAPT for each patient. In Singapore, the local population is ageing rapidly and as a result, more elderly patients present with obstructive CAD. They often have multiple co-morbidities including an increased risk of bleeding. Such patients will benefit from a shorter duration of DAPT. The LEADERS FREE study has shown that the polymer-free biolimus DES is safe and efficacious in patients with high bleeding risk treated with one-month DAPT. Nonetheless, the duration of DAPT following stent implant is considered of critical importance to protect the patient from life-threatening stent thrombosis and should not be interrupted without consulting the managing cardiologist.

Statins are first-line lipid lowering therapy as their beneficial effect of reducing low density lipoprotein level and adverse cardiovascular outcomes are well proven in clinical studies. In addition, statins have pleiotropic effects on inflammation and endothelial function beyond their lipid lowering effect and are therefore beneficial for patients with established CAD. Alternative oral agents are available for patients who cannot tolerate statins. However, none of these have been shown to have the dramatic effect on clinical outcomes as statins. Also, some patients continue to have poorly controlled lipid profiles despite statin agents at appropriate doses. The recently introduced PCSK-9 inhibitor drug class may be an elegant solution for this and has been shown in early clinical trials to have marked efficacy for low density lipoprotein reduction. It is expected that in coming years these drugs will become more mainstream as further evidence emerges and as cost reduces.

Angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers are also recommended for all post-acute coronary syndrome patients and stable CAD patients with hypertension, diabetes mellitus, chronic kidney disease and left ventricular dysfunction. Beta-blockers are also indicated for all post-acute coronary syndrome patients (particularly where myocardial injury has been substantial) and should be used as first-line anti-anginal therapy in CAD. Further, OMT should also include control of other cardiovascular risk factors and life-style interventions such as healthy eating, exercise and smoking cessation.

Conclusion

The field of interventional cardiology has evolved tremendously since its inception in 1977. Advances in the past four decades have resulted in PCI being established as the preferred method of revascularisation for patients with obstructive CAD. With further developments in the pipeline, there is great excitement and anticipation that these novel therapies will lead to paradigm shifts in the treatment of CAD.

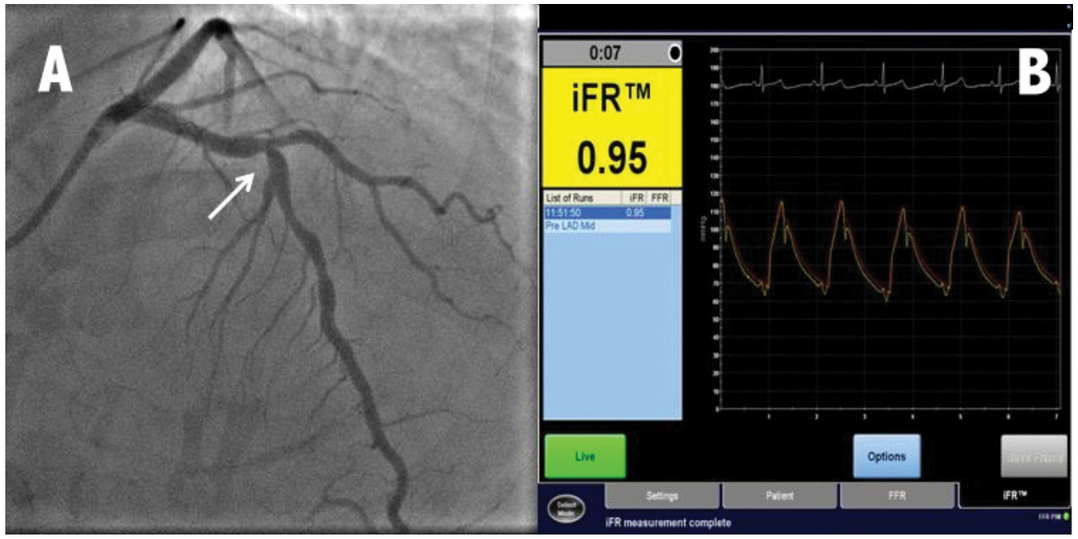


Figure 7. Instantaneous wave-free ratio evaluation of moderate stenosis in mid left anterior descending artery was 0.95, signifying a non-flow limiting lesion.

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TYPE 2 DIABETES MELLITUS AND NUTRITION

Dietary management is key to living well with type 2 diabetes mellitus (T2DM). Many aspects of the diet have been studied extensively in the literature to aid long term management of diabetes and prevention of macrovascular and microvascular complications of diabetes.

In summary, the key dietary principles for diabetes management are:

1. Regular timings of three main meals;
2. Maintenance of consistent carbohydrate portion throughout the day;
3. Having two servings of fruits and at least two servings of vegetables daily;
4. Reduction of refined sugar intake;
5. Reduction of saturated fat intake;
6. Avoidance of alcohol; and
7. Choosing of foods that are rich in fibre by switching at least 50% of carbohydrates consumed to whole grains.

The rationale behind some advice like reducing refined sugar is self-evident. This article elaborates on carbohydrate counting skill, considerations when using the glycaemic index to educate individuals about food choices and the role of fibre in managing diabetes.

Nutrition Facts

Serving Size 1 cup (228g)
Servings Per Container 2

Amount Per Serving

Calories 250	Calories from Fat 110
	% Daily Value*
Total Fat 12g	**18%**
Saturated Fat 3g	**15%**
Trans Fat 3g	
Cholesterol 30mg	**10%**
Sodium 470mg	**20%**
Total Carbohydrate 31g	**10%**
Dietary Fiber 0g	**0%**
Sugars 5g	
Protein 5g	
Vitamin A	4%
Vitamin C	2%
Calcium	20%
Iron	4%

* Percent Daily Values are based on a 2,000 calorie diet. Your Daily Values may be higher or lower depending on your calorie needs.

	Calories	2,000	2,500
Total Fat	Less than	65g	80g
Sat Fat	Less than	20g	25g
Cholesterol	Less than	300mg	300mg
Sodium	Less than	2,400mg	2,400mg
Total Carbohydrate		300g	375g
Dietary Fiber		25g	30g

Figure 1. Sample of a nutrition facts food label.

Carbohydrate counting

In order to achieve a consistent carbohydrate intake, basic carbohydrate counting skills are essential. First, identifying the sources of carbohydrate is important. Not all foods contain carbohydrate; some food contains minimal carbohydrates, with their main macronutrient being fat or protein. Second, it is useful to understand serving sizes of carbohydrate food, in which one portion of carbohydrate refers to the quantity of food containing approximately 15 g of carbohydrates (table 1).[1]

The recommended macronutrient distribution is 50-60% carbohydrates, 10-20% protein and 25-30% fat.[2] The amount of carbohydrates each person requires is based on his or her height, weight, physical activity, age, and health status, etc. As a general guide, women require three to four servings of carbohydrates per meal (45-60 g) while men require four to five servings of carbohydrates per meal (60-75 g). Between-meal snacks usually provide one to two servings of carbohydrates (15-30 g).[1] The amount of carbohydrates in each dish must then be estimated and portion sizes adjusted to meet carbohydrate needs. Food labels (figure 1) also provide information on carbohydrate content and other macronutrients in food products. Reading food labels is an essential skill for deciding portion sizes when consuming packaged food.

Glycaemic index

The glycaemic index (GI) is based on the grounds that not all carbohydrate food elicit the same glycaemic response (figure 2). It is defined as the "incremental area under the blood glucose response curve after consumption of 50 g carbohydrate from a test food divided by area under the curve after consumption of 50 g of a reference food (either glucose or white bread over a two-hour period)".[3] This is not a measure of how quickly foods are digested and absorbed. The glycaemic response to an ingested food is also affected by the total intake of carbohydrates, giving rise to the concept of glycaemic load (GL) (figure 2).

Food	Quantity
Corn tortilla, 6 inches	1 piece
Flour tortilla, 10 inches	⅓ piece
Cooked rice	⅓ cup
Cooked beans	½ cup
Whole or skim milk	1 cup
Evaporated whole milk	½ cup
Cooked pasta	½ cup
Cooked lentils	½ cup
Small apple	1 piece
Papaya	1 cup
Banana	½ piece
Cereal without sugar	1 cup
Cereal with sugar	¾ cup

Table 1. Examples of food equivalent to one portion of carbohydrates.[1]

$$\text{Glycaemic Index} = \frac{\text{Blood Glucose Response to 50g}_{\text{test}}\text{ food} \times 100}{\text{Blood Glucose Response to 50g}_{\text{reference}}\text{ food}}$$

$$\text{Glycaemic Load}_{\text{food}} = \text{Glycaemic Index}_{\text{food}} \times \frac{\text{Amount (g) of available carbohydrate}}{100}$$

Figure 2. Formulae for calculating glycaemic index[4] and glycaemic load.[5]

A glycaemic index ≤55 is considered low, between 56 and 69 is considered medium and ≥70 is considered high (figure 3).[1,7] The higher the GI of foods, the greater the impact on blood glucose levels. A glycaemic load between 1 and 10 is considered low, between 11 and 19 is considered medium and ≥20 is considered high.[1,7] GI is typically determined for single-item foods, however the GI values of mixed meals can also be assessed via direct measurement.

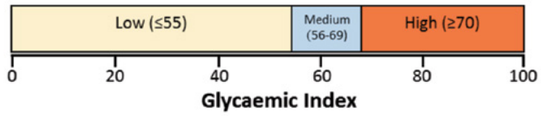

Figure 3. Categorising glycaemic index.

The methodology for measuring GI of foods and categorising them accordingly has been established and published,[8] and it is known that certain factors affect GI values.

First, there is inter-individual variability. GI measurement of small groups of 10 made up of predominantly white subjects may not yield similar estimates when carried out in another population. One group postulated that differences in baseline haemoglobin A1c (HbA1c) and insulin index suggest that longer-term glycaemic control and insulin response even in non-diabetic individuals affect the GI values.[9]

Second, the species and ripeness of the food, and time taken for an individual to consume the food affects the GI of the food. The GI value of an Australian potato may vary greatly from the GI value of a USA potato. An undercooked potato will have a lower GI value than the same potato cooked till soft.[1,7] Products higher in fibre tend to be lower in GI than refined counterparts.

Additionally, intake of carbohydrates along with protein or fat may yield a different glycaemic response compared to consuming it alone. Fat and protein increases the time taken for food to move from the stomach to the intestine. This slows the rate of carbohydrates digested in the small intestine, giving rise to a lower GI value than its equivalent without fat. Therefore, preparation methods of the food comparatively alter GI values. Roasted, baked or fried sweet potatoes have lower GI values than boiled sweet potatoes.[10]

For the layman, food products with low GI values may be interpreted as being healthier than others. Opting for low GI food products yet compensating with larger portion sizes may result in minimal or even negative impact on glycaemic control. Also, high fat food choices like ice cream (GI=~37) may have low GI values but is energy dense[6] and contradict key principles of DM management – to aim for weight loss and to reduce saturated fat and refined sugar intake.

Furthermore, GI of foods can be manipulated by food manufacturers by substituting sucrose (GI=58) with fructose (GI=~15) as a sweetener to lower GI values. This gives rise to situations where food that is higher in sugars can have lower GI values than wholegrain or unprocessed starches.[11] This is potentially confusing and may mislead the consumer.

The American Diabetes Association (ADA) stated that the literature concerning glycaemic index and glycaemic load in individuals with diabetes is complex but lowering the glycaemic index of consumed carbohydrates has demonstrated HbA1C reductions of –0.2% to –0.5% in studies.[12]

The Evidence Analysis Library suggested that lowering GI or glycaemic load may or may not have a significant effect on glycaemic control. Studies spanning durations longer than 12 weeks showed no significant influence of GI or glycaemic load, independent of weight loss, on HbA1c. There were mixed results regarding fasting glucose levels and endogenous insulin levels. Most individuals with diabetes already appear to consume a moderate-GI diet. There is insufficient evidence to show that reducing the GI in the diet by a few units will meaningfully improve glycaemic control.[13]

There are too many confounders that affect the accuracy of GI to be used as a basis for making food-based recommendations. Also, they may not reflect the nutritional quality of the food.

Instead, in line with key principles (3) and (7), ADA recommends that individuals with diabetes should be encouraged to consume fruits and vegetables instead of juices and purees and choose wholegrain products

over refined options[12] rather than solely depending on GI values.

Fibre

Fibre content in food can promote satiety in individuals. They also tend to be lower in calories while high in minerals and vitamins. By displacing other macronutrient intake, this can prevent excessive weight gain and excessive intake of carbohydrates. Theories have also attributed to the ability of fibre to increase the gastrointestinal content viscosity, decrease the gastric-emptying rate, thereby slowing glucose-absorption rates.[14,15]

The effect of dietary fibre on glycaemic control in individuals with diabetes is controversial. The Evidence Analysis Library 2017[13] and Franz et al.[16] showed that dietary fibre has mixed results on HbA1c and no significant effects on exogenous insulin levels. Instead, it suggested that adults with diabetes consume dietary fibre from foods (like fruits, vegetables, legumes and wholegrains) at the levels recommended by the Dietary Reference Intakes (21 to 25 g/day for adult women; 30 to 38 g/day for adult men)[17] with special emphasis on soluble fibre sources (7 to 13 g) due to positive effects on lipid profile. This can be roughly achieved by aiming for two servings of fruits and at least two servings of vegetables daily and switching at least 50% of carbohydrates consumed to wholegrains.

Conclusion

Imparting knowledge on carbohydrate counting, food label reading, considering the GI when making food choices and increasing fibre intake from vegetables, fruit, legumes and whole grains can guide individuals towards good diabetes management. Educating individuals on misconceptions and food knowledge gaps form the basis of the initial counselling sessions. While the key principles may appear straightforward, the management of diabetes is complex as nutrition advice has to be tailored to an individual's lifestyle and preferences for the lifestyle changes to be sustained. The ability of healthcare professionals to employ various counselling strategies such as motivational interviewing, health belief model and cognitive behavioural theory to empower individuals to change their behaviour is important.[18,19]

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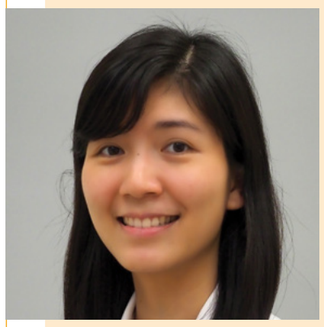

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LEAPP CLINIC: A LEAP IN THE DARK OR A LEAP OF FAITH?

Foot ulceration in diabetes mellitus is common. Foot problems remain the commonest cause of hospital admission. The lifetime risk of a patient with diabetes developing an ulcer is 25%, and up to 85% of all lower limb amputations in diabetes are preceded by foot ulcers.

Singapore has a high burden of diabetes-related complications and one of the highest rates of major lower extremity amputations among the developed countries. Unfortunately, the trend appears to be rising, creating a healthcare crisis of substantial significance. Treatment within the hospitals is focussed on taking care of acute foot emergencies which is often very challenging. Patients present late, usually with advanced infection and tissue loss. Even with the best treatment and the concerted effort of several disciplines in the hospital, the results are not always good. What can be done to change this? How can we bring about a paradigm shift in the way we approach this problem?

Around 50% of patients with diabetes have risk factors for foot problems that can be identified by regular screening and careful clinical examination. Ideally, this should be community-based, in a primary care setting. Those found to be at risk should attend more regular follow-up together with education in foot self-care, appropriate footwear and caregiver education where appropriate.

However, once ulceration has occurred, one of the key principles in reducing eventual amputation is prompt multidisciplinary management of the ulcer. This is outlined in the National Institute for Clinical Excellence guideline: 'Diabetic foot problems: prevention and management'. One of its principal recommendations is the provision of 'a multidisciplinary foot care service for managing diabetic foot problems in hospital and in the community that cannot be managed by the foot protection service. This may also be known as an interdisciplinary foot care service'. In many countries in Europe and in the United States, such multidisciplinary diabetic foot clinics have a long and established history of serving as the key link between primary care screening and the treatment of patients with foot ulcers. Audited results on the efficacy of these clinics have provided solid evidence that they are cost-effective in reducing lower extremity amputations.

In Tan Tock Seng Hospital we have, according to Ministry of Health statistics, the highest number of admissions of patients with diabetic foot ulcers. Once admitted, patients benefit from the care provided by several disciplines including vascular surgery, orthopaedics, endocrinology, vascular laboratory, radiology (both diagnostic and interventional), podiatry, wound nursing, and rehabilitation services.

It is almost intuitive that one of the best ways of approaching the prevention of lower extremity amputation is to move this multidisciplinary team to an outpatient setting. Thus, the concept of the LEAPP (Lower Extremity Amputation Prevention Programme) clinic was born (figure 1).

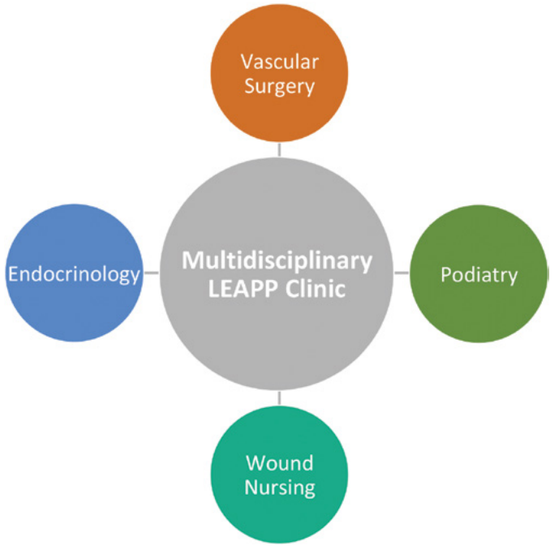

Figure 1. The LEAPP (Lower Extremity Amputation Prevention Programme) clinic is conceptualised around a multidisciplinary approach in the prevention of lower extremity amputation.

The blueprint for the LEAPP clinic has been drawn to reflect best practice guidelines on the management of diabetic foot ulcers from established world literature and evidence-based reviews. The key principle of the clinic is ease of access of a patient with a "hot foot" or a "foot at risk". The multidisciplinary team includes experts from vascular surgery, endocrinology, podiatry, and wound nursing (figure 2).

Around 50% of patients with diabetes have risk factors for foot problems that can be identified by regular screening and careful clinical examination.

2.

3.

Figure 2. The dedicated team members of the LEAPP clinic. The clinic is made up of experts from vascular surgery, endocrinology, podiatry, and wound nursing. In the future, we hope to include orthopaedics, plastic surgery, prosthetics and orthotics, rehabilitation services, and on-site diabetic nurse educators.

Figure 3. A patient undergoing a foot evaluation by a vascular surgeon and podiatrist (foreground) while her clinical investigations are being assessed by an endocrinologist (background).

The clinic allows fast tracking of patients so that they can be seen by a dedicated specialist team as soon as possible. This enables rapid assessment in a holistic manner, where the patient with an established foot ulcer will undergo detailed evaluation (figure 3). The cause of the ulcer can be assessed and established in the shortest possible time. The risk of limb loss is stratified using currently available scoring systems. Intervention can be initiated immediately, including the control of blood sugar levels, relief of pressure on the foot, debridement, wound care, vascular investigations and revascularisation. For patients, it is a "one-stop shop" for care and treatment, minimising multiple visits to different specialist services. The LEAPP clinic essentially facilitates on-the-spot communication between the specialists and the patient, thus enabling them to jointly devise a customised strategy for each patient.

For patients who have been admitted with foot ulcer-related problems, access to the LEAPP clinic will allow for early discharge as they can be followed up in the LEAPP clinic for surveillance, till their wounds heal. In the future, we hope that the clinic can expand to include orthopaedics for patients with complex foot deformities, plastic surgery for patients needing complex tissue cover, prosthetics and orthotics, rehabilitation services, and on-site diabetic nurse educators.

Ultimately, the outcomes we aim to achieve with this clinic are the tangible goals of improved limb salvage. Secondary goals are the reduction in length of stay of inpatients and increased patient satisfaction. It will provide our multidisciplinary team with an opportunity to extend our inpatient services to an outpatient setting, hopefully with as good or better results in terms of limb salvage.

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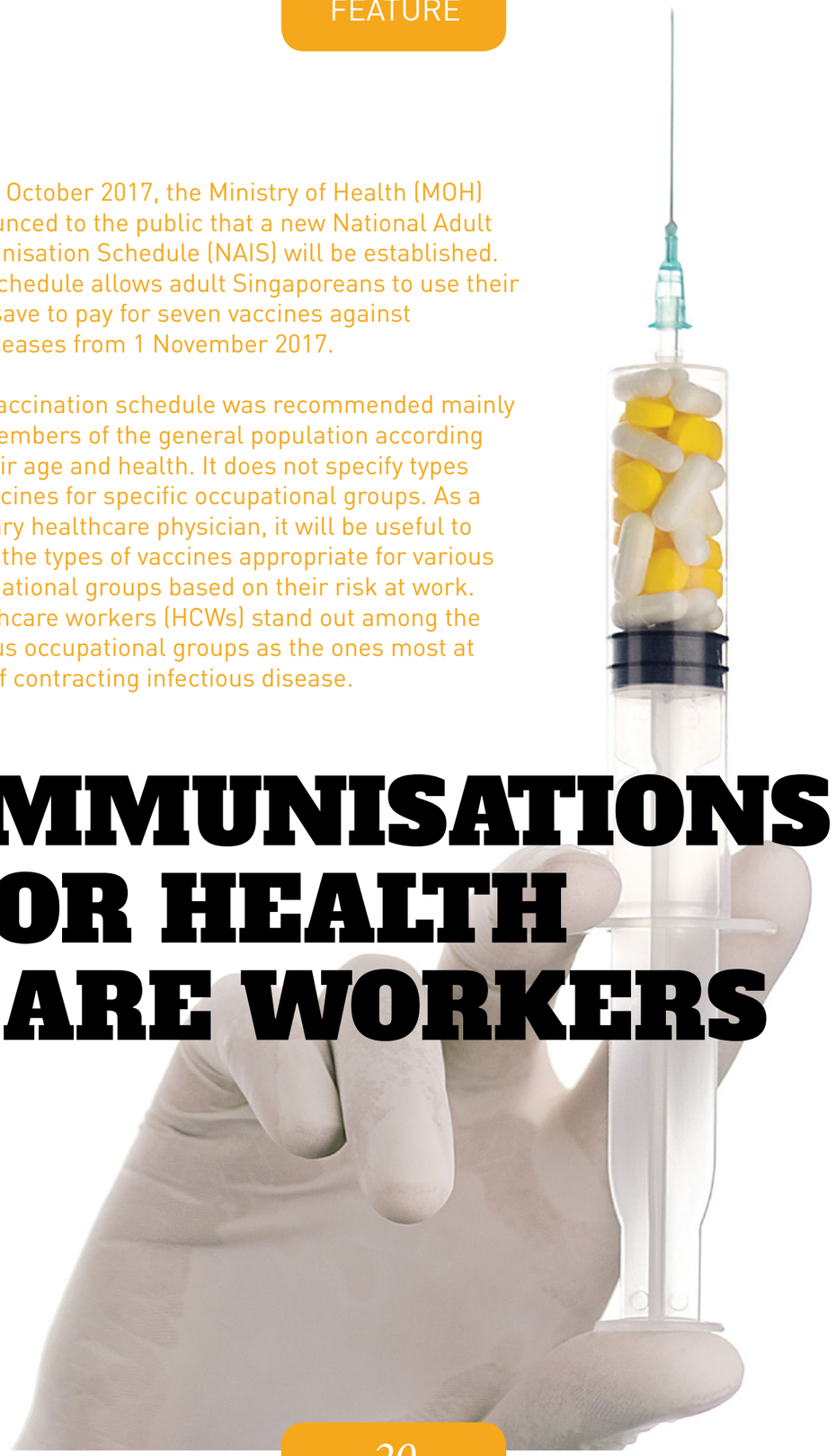
On 21 October 2017, the Ministry of Health (MOH) announced to the public that a new National Adult Immunisation Schedule (NAIS) will be established. The schedule allows adult Singaporeans to use their Medisave to pay for seven vaccines against 11 diseases from 1 November 2017.

The vaccination schedule was recommended mainly for members of the general population according to their age and health. It does not specify types of vaccines for specific occupational groups. As a primary healthcare physician, it will be useful to know the types of vaccines appropriate for various occupational groups based on their risk at work. Healthcare workers (HCWs) stand out among the various occupational groups as the ones most at risk of contracting infectious disease.



IMMUNISATIONS FOR HEALTH CARE WORKERS

Hence besides complying with standard precautions against infection such as wearing appropriate personal protective equipment (PPE), hand hygiene etc., HCWs should also be immunised against diseases that are vaccine-preventable. Optimal use of recommended vaccines helps maintain immunity and safeguards them from infection, thereby also protecting patients, their co-workers and even family members from becoming infected.

From the national and institutional point of view, a vigorous vaccination programme for HCWs will reduce sickness absence and disruption of work routines. There will also be cost savings as resources need not be deployed to evaluate and contain exposures and outbreaks especially if there are no readily available data on the HCWs' immunity.

Who is a healthcare worker?

The term 'healthcare worker' usually brings to mind doctors and nurses involved in direct care of patients. However from the occupational risk assessment point of view, any person who may be potentially at risk of exposure to infectious agents that can be transmitted from hospital or clinic staff to patients or vice versa would be considered one. In recent years many health authorities including the US Communicable Disease Centre (CDC) and locally MOH have broadened the definition of an HCW. A person will be considered an HCW if he or she belongs to any these groups:

1. Clinical and other staff who have regular, clinical contact with patients e.g. doctors, dentists, nurses, paramedical professionals (occupational therapists, physiotherapists, radiographers, pharmacists), ambulance workers, and porters.
2. Laboratory and other staff (including mortuary staff) who have direct contact with potentially infectious clinical specimens and may additionally be exposed to pathogens in the laboratory.
3. Non-clinical staff who may have social contact with patients and clinical staff e.g. receptionists, ward clerks and other administrative staff working in hospitals and primary care settings. This also includes support and maintenance service staff such as technicians, gardeners, cleaners, and security guards.

The above list is not exhaustive and is not confined to those working in acute-care hospitals. The list may also include those working in long-term care facilities (e.g. community hospitals and nursing homes), physician's offices, rehabilitation centres, and outpatient clinics as well as persons who provide home health care and emergency medical service.

Type of infections	Examples of pathogens
Airborne/droplet-borne infections	1. Respiratory viruses: e.g. **chicken pox, influenza, pertussis, diphtheria, measles, mumps and rubella** (MMR), SARS, MERS CoV, rhinoviruses 2. Bacteria: e.g. *Neisseria meningitidis* or **meningococcus, pneumococcus**, *Mycoplasma haemophilus* 3. Mycobacteria: e.g. **tuberculosis**
Contact-borne infections	1. Viruses: adenovirus (conjunctivitis), **herpes simplex** (e.g. herpetic whitlow and zoster) 2. Bacteria: e.g. Methicillin-resistant Staphylococcus aureus, Carbapenem-resistant enterobacteriacea and vancomycin-resistant enterococci, Ebola 3. Enteropathogens which cause diarrhoeal diseases: e.g. *salmonella* and rotavirus 4. Parasites: e.g. scabies (especially Norwegian scabies)
Blood-borne infections	1. Viruses: e.g. **hepatitis B, hepatitis C**, HIV through contact with blood and body fluids 2. Bacteria spores: e.g. *Clostridium tetani* through contact with soil, dust and animal faeces/bites.

Table 1. Common pathogens and pathogens with serious public health consequences, and their main transmission route. In bold are diseases where vaccines are available for prevention.

In addition, a person may also be considered an HCW if he or she is not an employee, but needs to enter healthcare facilities for work or attachments such as a contractor, student, trainee and volunteer.

What are the infectious risks to healthcare workers and patients?

Pathogens and main transmission route

Some common pathogens and their main route of transmission are listed in table 1. Also listed are those not currently prevalent in the population but can have serious public health consequences because of a high mortality rate for infected individuals and adverse socio-economic impact.

High risk procedures and contact

There are several procedures and types of contact that are considered high risk for transmission for pathogens.

Exposure prone procedures

There has been some confusion about the definition of exposure prone procedures (EPP). A clear understanding is important when considering whether there is significant risk of transmission from patient to HCW and vice versa. HCWs who are carriers of blood-borne pathogens are not allowed to do such procedures under MOH's recommendations. The definition used by MOH which is also used internationally is as follows: "Exposure prone procedures are those invasive procedures where there is a risk that injury to the worker may result in exposure of the patient's open tissues to the blood of the worker. These procedures include those where the worker's gloved hands may be in contact with sharp instruments, needle tips or sharp tissues (e.g. spicules of bone or teeth) inside a patient's confined anatomical space where the hands or fingertips may not be completely visible at all times, open body cavity, or wound".

Hence procedures such as giving injections, phlebotomy, general wound dressing, superficial skin suturing, and simple endoscopy will not be considered as EPP.

Procedures involving generation of aerosols

Procedures which generate aerosols should be minimised to reduce environmental contamination with infectious material. These include:

- Cough-inducing procedures e.g. endotracheal intubation and suctioning, sputum induction and bronchoscopy
- Aerosol generating procedures e.g. aerosol treatments, irrigation of abscesses, centrifuging, homogenising or lyophilising tissue.

Handling of potentially infected body fluids, specimens, instruments and sharps

Body fluids that can be highly infectious include blood, serum and wound exudates. Those of moderate infectious risk are semen, vaginal fluids and saliva. Those of lowest risk are urine, faeces and breast milk.

Sharps include any device with sharp points or edges that can puncture or cut skin and is not limited to needles, surgical blades or instruments but also contaminated broken glass, for example.

What are the common vaccines recommended for healthcare workers?

A number of vaccines are recommended for overseas health agencies and MOH (see table 2 for MOH's recommendations). These are general recommendations given taking into consideration factors which include prevalence of disease in the community, herd immunity, likelihood of exposure for the HCW based on the pathogen's route of transmission and the HCW's route of exposure, and procedures and practices.

When evaluating the type of vaccine to be provided for individual HCWs or implementing a vaccination programme for a healthcare facility, a similar rationale and risk assessment approach should also apply.

It is also useful to know the immune status of the HCW prior to vaccination. Singapore has a comprehensive Childhood Immunisation Programme. The immunisation coverage is extensive and includes some of those required for HCWs such as hepatitis B, measles, mumps and rubella (MMR) and pertussis (see table 3). Some of these vaccines are also included in NAIS. Coverage for HCWs who are born in foreign countries may not be so extensive or is uncertain.

Immune status of HCWs whether acquired through infection or immunisation should be based on documentary evidence and not on memory recall. Verbal declaration of immunity by HCWs is no longer acceptable in many of our local healthcare institutions including Tan Tock Seng Hospital.

Infectious Disease	Recommended Group	Recommendations for Vaccination	Acceptable Evidence of Immunity
Hepatitis B	All HCWs and HCWs who perform exposure prone procedures	• Primary vaccination consists of 3 doses at 0, 1 and 6 months • HCWs with anti-HBs concentrations of <10 mIU/mL should be revaccinated with a second 3-dose series, followed by anti-HBs testing	• Documented proof of vaccination; **and** post-vaccination serological evidence of immunity (anti-HBs concentrations of ≥10 mIU/mL
Influenza	All HCWs	• Annual (in accordance with MOH recommendations on seasonal influenza vaccination)	• *Not applicable*
Varicella	All HCWs, particularly susceptible HCWs	• 2 doses; minimum interval of 4–8 weeks apart	• Serological evidence of immunity; **or** • Laboratory confirmation of disease; **or** • Documented proof of vaccination
Measles, Mumps and Rubella	All HCWs, particularly susceptible HCWs	• 2 doses; minimum interval of at least 4 weeks apart	• Serological evidence of immunity against **all** three diseases; **or** • Laboratory confirmation of **all** three diseases; **or** • Documented proof of vaccination
Pertussis	All HCWs who come into contact with newborns and infants	• 1 dose of Tdap, irrespective of interval since last dose of tetanus or diphtheria-containing vaccine	• Documented proof of vaccination with Tdap
Others	*Where applicable, healthcare institutions and establishments should also consider other vaccinations for their HCWs depending on the unique communicable disease risks in their work duties and environments. These may include, but are not limited to vaccinations against meningococcal disease, particularly those with high risk of exposure such as laboratory personnel.*		

HCW, healthcare worker; anti-HBs, Hepatitis B surface antibody

Table 2. Summary of the Ministry of Health recommendations for immunisation of healthcare workers.

National Childhood Immunisation Schedule, Singapore										
Vaccination against	**Birth**	**1 Month**	**3 Months**	**4 Months**	**5 Months**	**6 Months**	**12 Months**	**15 Months**	**18 Months**	**10-11 Years**
Tuberculosis	BCG									
Hepatitis B	HepB (D1)	HepB (D2)			HepB (D3)#					
Diphtheria, Tetanus, Pertussis			DTap (D1)	DTap (D2)	DTap (D3)				DTap (B1)	Tdap (B2)
Poliovirus			IPV (D1)	IPV (D2)	IPV (D3)				IPV (B1)	OPV (B2)
Haemophilus influenza type b			Hib (D1)	Hib (D2)	Hib (D3)				Hib (B1)	
Measles, Mumps, Rubella							MMR (D1)	MMR (D2)##		
Pneumococcal Disease			PCV (D1)		PCV (D2)		PCV (B1)			
Human Papilomavirus	Recommended for females 9 to 26 years, three doses are required at intervals of 0, 2, 6 months									

BCG	Bacillus Calmette–Guérin
HepB	Hepatitis B vaccine
DTaP	Paediatric diphtheria and tetanus toxoids and acellular pertussis vaccine
Hib	*Haemophilus influenza* type b vaccine
Tdap	Tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine
MMR	Measles, mumps and rubella vaccine
IPV	Inactivated polio vaccine
OPV	Oral polio vaccine
PCV	Pneumococcal conjugate vaccine
D1/D2/D3	1st dose, 2nd dose, 3rd dose
B1/B2	1st booster, 2nd booster
^	Primary 5
#	3rd dose of HepB can be given with 3rd dose of DTaP, IPV and Hib for the convenience of parents
##	2nd dose of MMR can be given between 15-18 months

Table 3. National Childhood Immunisation Schedule, Singapore. (Reproduced with permission from the National Immunisation Registry)

Types of vaccines recommended

Hepatitis B

Currently the hepatitis B vaccine is the only available vaccine against the blood-borne virus. Hepatitis B is highly infectious, especially for non-immune persons. Disease transmission from a needlestick injury is up to 100 times more likely following exposure to hepatitis B e–antigen-positive blood than to HIV-positive blood. The virus is also environmentally stable, remaining infectious on environmental surfaces for at least seven days.

After three intramuscular doses of hepatitis B vaccine, more than 90% of healthy adults and more than 95% of infants, children and adolescents (from birth to 19 years of age) develop adequate antibody responses. Hepatitis B surface antibody (anti-HBs) concentrations of ≥10 mIU/mL after pre-exposure vaccination is protective. Though anti-HBs levels decline over time, responders continue to be protected against infection and the majority will show an anamnestic response to vaccine challenge. There is no need to give booster doses if there is evidence of past response to the three-dose vaccination.

Those who do not respond to the primary 3-dose vaccine series may respond with a 3-dose revaccination series using standard or high dosage vaccine. If they do not have protective levels of anti-HBs one to two months after revaccination, there is a possibility that they may have previously been infected with hepatitis B or are primary non-responders (if their total hepatitis B core antibody is negative).

Primary non-responders will need to take special precautions when involved in high-risk behaviour or EPP. They will require hepatitis B immune globulin post-exposure prophylaxis (passive immunisation). Those who are suspected to be previously infected will need further evaluation by a gastroenterologist.

Measles

Measles is a highly contagious disease which might result in pneumonia, encephalitis and death. It is spread through air droplets and direct contact with nasal and throat secretions. The measles virus can live on surfaces for several hours. As the infected particles enter the air and settle on surfaces, anyone within close proximity can also become infected.

Measles vaccination was made compulsory in Singapore in 1985. The one-dose immunisation was found to have inadequate protection and a two-dose regimen of the MMR vaccine was introduced in 1998.

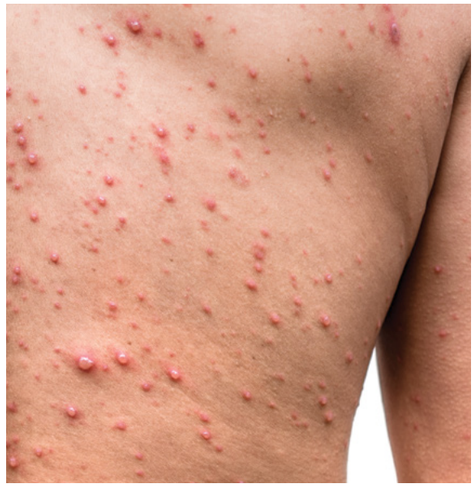
The MMR vaccine is highly effective in preventing measles with a one-dose vaccine effectiveness of 95% when administered on or after age 12 months and a two-dose vaccine effectiveness of 99%. Two doses of live measles vaccine are required to provide long-lasting immunity.

Mumps

Mumps is characterised by fever and inflammation of the salivary glands. The spectrum of illness ranges from subclinical infection to non-specific respiratory illness, sialadenitis including classic parotitis, deafness, orchitis, and meningoencephalitis. Severity of infection increases with age. MMR vaccine has a one-dose vaccine effectiveness in preventing mumps of 80%–85% (range 75%–91%) and a two-dose vaccine effectiveness of 79%–95%. Antibody levels induced by the MMR vaccine wane over time following the first or second dose of vaccination, but the correlates of immunity to mumps are poorly understood and the significance of these waning antibody levels is unclear.

Rubella

Rubella (German measles) is characterised by rash, fever, lymphadenopathy, and malaise. Although rubella is considered a benign disease, transient arthralgia and arthritis are observed commonly in infected adults, particularly among post-pubertal females. Of primary concern are the effects that rubella can have when a pregnant woman becomes infected, especially during the first trimester, which can result in miscarriages, stillbirths, therapeutic abortions, and congenital rubella syndrome.



In clinical trials, 97%–99% of susceptible persons who received a single dose of the rubella vaccine above the age of 12 months developed antibodies. Studies have demonstrated that vaccine-induced rubella antibodies might wane after 12–15 years. However, rubella surveillance data do not indicate that rubella and congenital rubella syndrome are increasing among vaccinated persons.

Varicella

Varicella (chicken pox) is highly infectious and is caused by primary infection with the varicella-zoster virus. The virus is transmitted from person to person by direct contact, inhalation of aerosols from vesicular fluid of skin lesions of varicella or herpes zoster (shingles) or infected respiratory tract secretions that might be aerosolised. Varicella vaccination is not covered under the Childhood Immunisation Programme and hence many new HCWs have unknown immune status regarding the disease.

A single dose of the varicella vaccine is 85% effective at preventing any form of varicella infection and almost 100% effective against severe infection. Two doses will be 88–98% effective at preventing all varicella infections and 100% effective against severe infections.

Studies have demonstrated that though 25–31% of adult vaccine recipients who seroconverted lost detectable antibodies one to eleven years after vaccination, vaccine-induced T-cell response remained in 94% of adults one and five years post-vaccination.

Pertussis

Pertussis is a highly contagious bacterial infection. Secondary attack rates among susceptible household contacts exceed 80%. Transmission occurs by direct contact with respiratory secretions or aerosolised droplets from the respiratory tract of infected persons. Infants too young to be vaccinated are at greatest risk for severe pertussis, including hospitalisation and death. MOH recommends that all HCWs who come into contact with newborn infants to be vaccinated with a single dose of Tdap (tetanus toxoid, reduced diphtheria toxoid and acellular pertussis) regardless of the interval since last dose of tetanus or diphtheria-containing vaccine. The Advisory Committee on Immunisation Practices recommends that HCWs who work in hospitals or ambulatory care settings and have direct patient contact should receive a single dose of Tdap as soon as feasible if they have not previously received it.

Protection from pertussis is not life-long, but restricted to a period of five to eight years, after natural infection, as well as after vaccination.

All healthcare facilities should put in place a vaccination programme for their HCWs... Elements that should be within the programme are pre-employment screening, job placement, vaccination, database of immune status of HCWs, and communication.

Overseas and local studies have shown that the current dosing schedule for pertussis immunisation may not be adequate to attain herd immunity level of 90–95%.

Diphtheria and tetanus
HCWs are not at greater risk for diphtheria or tetanus than the general population. Diphtheria vaccination was made compulsory in Singapore since 1962. Coverage is over 90% and a study showed that 99.4% of subjects were immune in the population aged one to seventeen years old. HCWs who handle animals, e.g. for research, and waste should however be vaccinated against tetanus.

In randomised controlled trials, virtually all adolescent and adult recipients of Tdap developed antibody levels of tetanus and diphtheria antitoxin correlated with protection. Booster response rates to these antigens were achieved in ≥90%.

Influenza
Influenza may be a mild illness for most people, but not everyone. Those with underlying conditions (e.g. diabetes, heart diseases, kidney failure, lung diseases, and neuromuscular disorders) and low immunity may be at higher risk of complications like respiratory and heart failure from pneumonia.

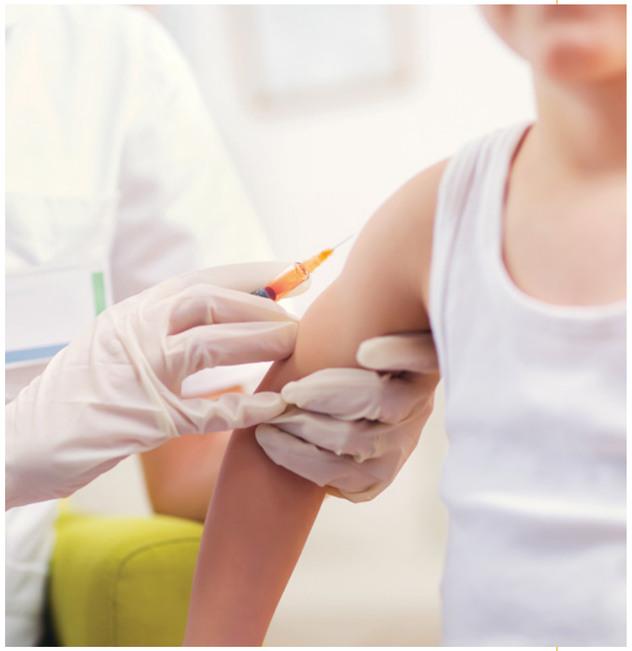
In tropical countries like Singapore where there are no seasons, influenza cases peak during the months of April to July and November to January (roughly corresponding to the peaks in influenza activities in the Northern and Southern Hemispheres). During an influenza season, infected but pre-symptomatic HCWs may continue to work, shedding the virus and infecting others. Vaccination of HCWs can enhance patient safety, reducing all-cause mortality by 29% amongst long-term patients. It is also associated with reduced influenza and/or pneumonia in hospital patients. Flu vaccination is also associated with reduced hospitalisations among people with diabetes (79%) and chronic lung disease (52%).

Effectiveness of influenza vaccines varies from year to year and depends on the age and health status of the person receiving the vaccine and the similarity or "match" between the viruses or virus in the vaccine and those in circulation. The strains of virus to be included in the vaccine each year is recommended by World Health Organisation and MOH. Annual vaccination is recommended because the predominant circulating influenza viruses typically change from season to season and because immunity declines over time post-vaccination.

Other vaccines
Other vaccines against vaccine-preventable disease should be given depending on the types of patients cared for or clinical specimens handled.

What should be included in a vaccination programme for healthcare workers?

All healthcare facilities should put in place a vaccination programme for their HCWs. In many of the hospitals the vaccination service is provided free for staff as a staff benefit. Non-employees who are classified as HCWs are also required to provide evidence of immune status. Elements that should be within the programme are pre-employment screening, job placement, vaccination, database of immune status of HCWs, and communication.



Pre-employment screening
The pre-employment medical examination serves a few purposes:

a. To detect any pre-existing medical condition that will put the candidate or the patients at risk.
b. To obtain history of allergy or adverse reaction to previous vaccination and components of vaccine such as egg protein, yeast, chicken and certain drugs.
c. To screen for immune status of staff for the recommended vaccine-preventable diseases. The candidate will be required to produce documentary evidence of past infection, vaccination or serological results. Their vaccination records and serology test results may be available through the National Electronic Medical Records or the National Immunisation Registry (for Singaporeans who are born around the late 80s).
d. Serology testing:
   - Screening for hepatitis B antigen and antibodies for those in EPP jobs or at risk of hepatitis B exposure
   - Screening for varicella antibodies for all HCWs with unknown immune status.

   Screening is not recommended for those unable to show evidence of immunity against MMR vaccination as it is not cost effective. They should receive the two-dose regime if there are no records or one more dose if there is a single record of MMR vaccination.

Job placement
HCWs who are carriers of blood-borne viruses should be reassigned to non-EPP jobs. Those who are not immune (e.g. non-responders) or not vaccinated because of medical conditions should be advised to take appropriate precautions. They may also not be allowed to have contact with susceptible patients such as those who are immune-compromised or pregnant and are required to wear appropriate PPE in situations where there is risk of exposure or disease outbreaks.

Vaccination
At the national and institutional level, the aim of vaccination is to achieve the highest rate as possible to build up herd immunity so that those who are susceptible or not vaccinated are protected and also do not become sources of spread.

Proper storage, handling of vaccines and good immunisation techniques, etc. need to be ensured but will not be discussed here in detail.

HCWs should be informed of likely adverse reactions before vaccination. There should also be proper record of vaccination details such as date of vaccination, vaccine batch number, etc. A vaccination certificate should be given to the HCW if it is not loaded online in a shared portal. Any adverse reaction should be reported to the vaccinating clinic and also notified to the Health Sciences Authority. All vaccinations should also be notified to the National Immunisation Registry.

Mass vaccination exercises such as flu vaccination and catch-up vaccination should be planned for and implemented at the institutional level especially when there is likelihood of outbreaks or emergent disease.

Database of immune status of HCWs
MOH is in the process of setting up a comprehensive national database of medical records (including vaccination details) which will be accessible to all healthcare institutions and healthcare practitioners. Until then, healthcare facilities should have a database system to track

and record the immunisation details of HCWs who work in their premises. The database system is useful during a vaccination exercise to track defaulters and success rates of vaccination. In the event of an outbreak, it can be used for contact tracing purposes such as finding those who are not immune and hence susceptible to infection. It is also useful for management of individual staff who are inadvertently exposed and do not know their own immune status.

Communication

As part of a complete immunisation programme, communication efforts by vaccination providers play a significant role. Those who provide vaccination should be knowledgeable about the vaccination that they provide and able to explain to the HCW about the different aspects of the vaccine including its efficacy and adverse effects and how to manage them. Vaccination providers who are themselves HCWs should be able to counter anti-vaccination sentiments and safety concerns with concrete scientific evidence.

Conclusion

HCWs face risk of infection at work. As HCWs, we have a duty to protect ourselves in order to protect our patients and the community at large in our course of work. Besides taking standard precautions such as hand hygiene and wearing PPE, we should also be vaccinated if there are effective vaccines available. We also have a role to encourage fellow HCWs to be vaccinated and to educate the public on the importance of vaccination as an important tool to prevent spread of diseases.

HCWs face risk of infection at work. As HCWs, we have a duty to protect ourselves in order to protect our patients and the community at large in our course of work.

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CLINICAL PEARLS FOR DIRECT-ACTING ANTIVIRALS USED IN CHRONIC HEPATITIS C

The main 'silent killers' that come to mind are hypertension, hyperlipidaemia or the lurking cardiovascular disease which many people (patients and healthcare professionals alike) have but are unaware of. Chronic hepatitis C infection though deserves a place in this group of silent killers, as patients are largely asymptomatic and are unaware of their condition until significant liver damage has occurred.

The hepatitis C virus was formally isolated in 1989, before which it was referred to as 'non-A and non-B'.[1] Over time, increased understanding of the pathophysiology and viral replication mechanisms has resulted in significant progress in drug therapies. With the availability of interferon-free direct-acting antiviral (DAA) regimens, novel sustained virological response (SVR) rates of >90% and better tolerability profiles, the horizon of chronic hepatitis C has never looked brighter, in spite of the currently elephantine price tag.

Overview of DAAs

DAAs are recommended in all patients with chronic hepatitis C, except for those with short life expectancy that cannot be altered with therapy or transplant. The target of therapy in most trials is to attain SVR, which has not been directly validated with mortality and morbidity outcomes, but has been associated with improved liver function, extrahepatic outcomes and all-cause mortality.[2] Treatment regimes of DAAs usually last 12 weeks or longer, but recent studies in carefully selected patient populations allow for 8-week regimens to be used, with significant cost savings.

DAAs can be classified according to their mechanism of action (table 1). DAAs from different classes are combined in various regimens to target the virus in a multi-pronged approach (figure 1). Of the DAAs registered in Singapore, combination products include sofosbuvir/ledipasvir (Harvoni®, Gilead Sciences Singapore Pte Ltd), dasabuvir/ombitasvir/paritaprevir/ritonavir (Viekira Pak®, Abbvie Pte Ltd) and sofosbuvir/velpatisvir (Epclusa®, Gilead Sciences Singapore Pte Ltd). Asunaprevir (Sunvepra®, Bristol-Myers Squibb (Singapore) Pte Ltd), daclatasvir (Daklinza®, Bristol-Myers Squibb (Singapore) Pte Ltd) and simeprevir (Olysio®, Johnson & Johnson Pte Ltd) are used in combination with sofosbuvir (Sovaldi®, Gilead Sciences Singapore Pte Ltd).

With the availability of these DAAs and an ever-expanding arsenal, the approach to choosing an appropriate regimen for the patient should be guided by viral genotyping. The virus can be categorised into six major genotypes from 1 to 6, with genotype 1 further divided into 1a and 1b. Some regimens are pan-genotypic while others have poorer efficacy in a certain genotype, or have not been studied in a particular genotype. Some may require further resistance testing which may lead to modification of the regimen (such as adding ribavirin) or prolonging the duration of therapy.

From there, depending on whether the patient has been treated before and whether he has compensated or decompensated cirrhosis, the most appropriate regimen can selected for the patient. Regimens containing NS3/4A protease inhibitors are not recommended in individuals with decompensated cirrhosis because of the potential for worsening decompensation.[3] In particular, paritaprevir/ritonavir/ombitasvir with or without dasabuvir should be used with caution even in compensated cirrhosis. Co-existing renal impairment narrows the options but new regimens such as elbasvir/grazoprevir and glecaprevir/pibrentasvir are now approved in patients with stage 4-5 chronic kidney disease as more safety data on existing regimens have come to light.[4] This is encouraging given the high prevalence and risk of transmission of hepatitis C in dialysis patients.

Adverse effects or drug interactions of individual agents in a regimen should be taken into account. Compared to the previous interferon-based regimens which cause side effects such as the flu-like syndrome and neuropsychiatric disturbances, tolerability is markedly improved with the DAAs.

Therapeutic Target	Examples
Nonstructural proteins 3/4A (NS3/4A) protease inhibitors (PIs) - "previr" **can be boosted with ritonavir*	Paritaprevir, simeprevir, grazoprevir, teleprevir, boceprevir, asunaprevir
NS5B nucleoside polymerase inhibitors (NPIs) - "buvir"	Sofosbuvir
NS5B non-nucleoside polymerase inhibitors (NNPIs) - "buvir"	Dasabuvir
NS5A inhibitors - "asvir"	Ledipasvir, daclatasvir, velpatasvir, elbasvir, ombitasvir

Table 1. Therapeutic targets according to the hepatitis C virus inhibition sites and some examples of currently available therapy.

The commonest complaints are fatigue, headache and nausea. One outstanding side effect of sofosbuvir, which is commonly employed across multiple regimens, is the potentially life-threatening bradycardia that may occur in patients also receiving amiodarone.[5] For regimens containing ribavirin, severe haematological abnormalities may develop. Ribavirin is contraindicated in pregnancy or in male patients with pregnant partners in view of potential teratogenicity.[6]

Controversially, reactivation of hepatitis B has been associated with DAAs and appropriate monitoring and pre-screening should be carried out.[7]

Drug interactions with DAAs are many, and a good tool to check for interactions can be found at http://www.hep-druginteractions.org/checker. These interactions arise primarily due to their effect on CYP450 enzymes, OATP1B1/3,

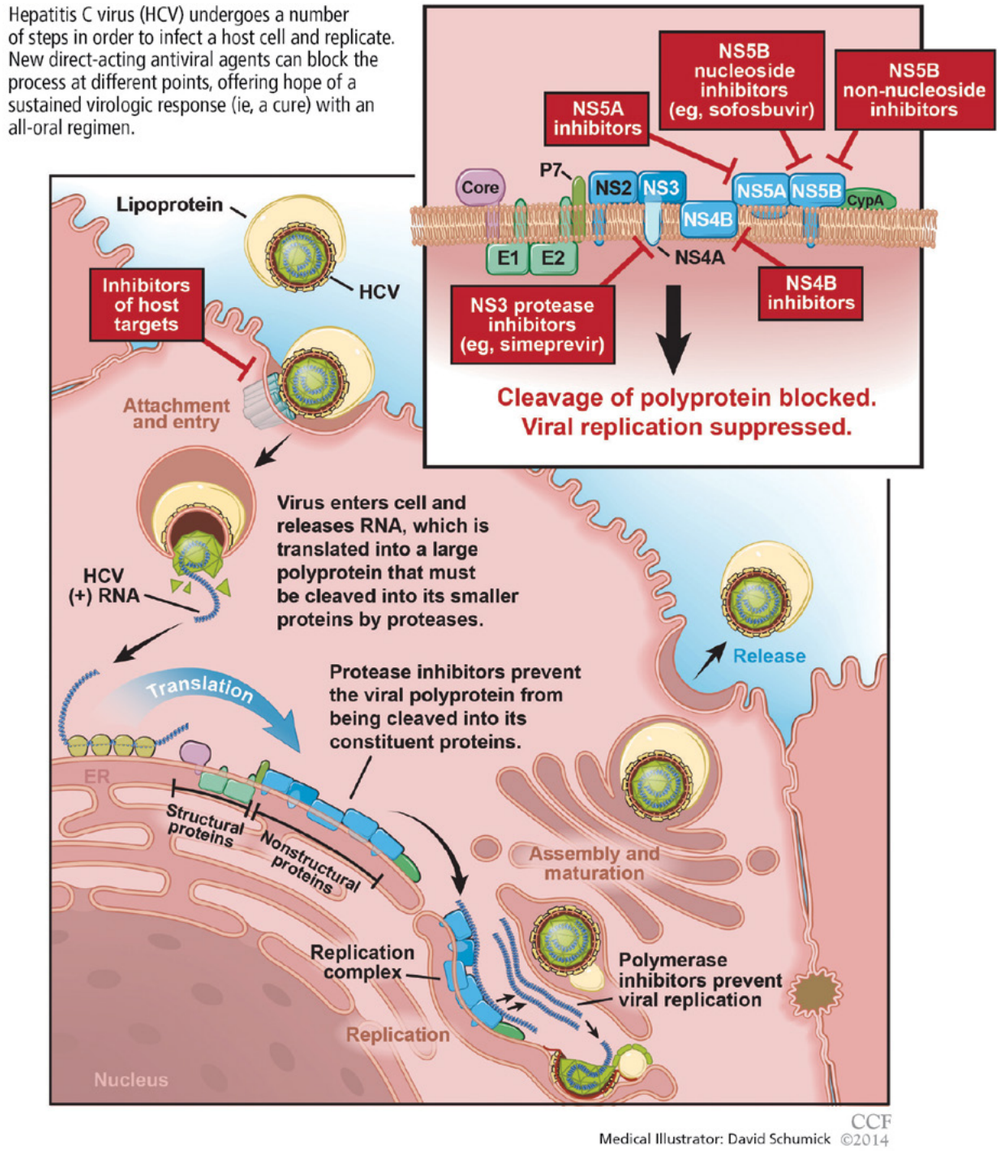

Figure 1. Blocking the HCV life cycle. (Reprinted with permission from Dugum M, O'Shea R. Hepatitis C virus: Here comes all-oral treatment. Cleve Clin J Med 2014; 81:159-172. Copyright © 2014 Cleveland Clinic. All rights reserved.)

- Genotype and resistance testing where indicated
- History of prior antiviral treatment
- Hepatic function
  - Stage of hepatic fibrosis e.g. presence of cirrhosis, decompensation
  - Prior hepatic transplantation
  - Other coexistent hepatic disease e.g. hepatitis B infection
- Renal function
  - Prior renal transplant
- Special populations, i.e. pregnancy, children, HIV coinfection
- Potential adverse effects
- Potential drug-drug interactions
- Pill burden, compliance issues
- Cost and duration
- Prognosis

Box 1. Factors affecting hepatitis treatment choice and management

p-glycoproteins and BCRP.[8] It is important to check for interactions as many common drugs, for examples, alfuzosin, calcium channel blockers and statins, may either induce, inhibit or be substrates of these proteins. Some manufacturers recommend avoiding concurrent administration of DAAs when significant drug interactions occur because of the potential for viral resistance with sub-therapeutic levels and toxicity with supratherapeutic drug levels. Some recommend dosage reductions as a means to ameliorate toxicity, such as for daclatasvir. In the case of patients with HIV coinfection, particular care needs to be taken to ensure that their HIV therapy is never compromised.[8] The factors that affect hepatitis C treatment and management are summarised in box 1.

Conclusion

All in all, these new regimens offer the prospect of eradicating hepatitis C infection. It is crucial to identify those infected with hepatitis C efficiently and to improve accessibility of treatment. The World Health Organisation advocates hepatitis elimination and encourages nations to approach hepatitis C with the same priority as other communicable diseases like HIV/AIDS and tuberculosis.[9] In the words of John Ward, M.D., director of CDC's Division of Viral Hepatitis, "Stopping hepatitis C will eliminate an enormous disease and economic burden for all (people). We have a cure for this disease and the tools to prevent new infections. Now we need a substantial, focused, and concerted (national) effort to implement…and make effective prevention tools and curative treatment available to (those) in need."[10]

Useful readings

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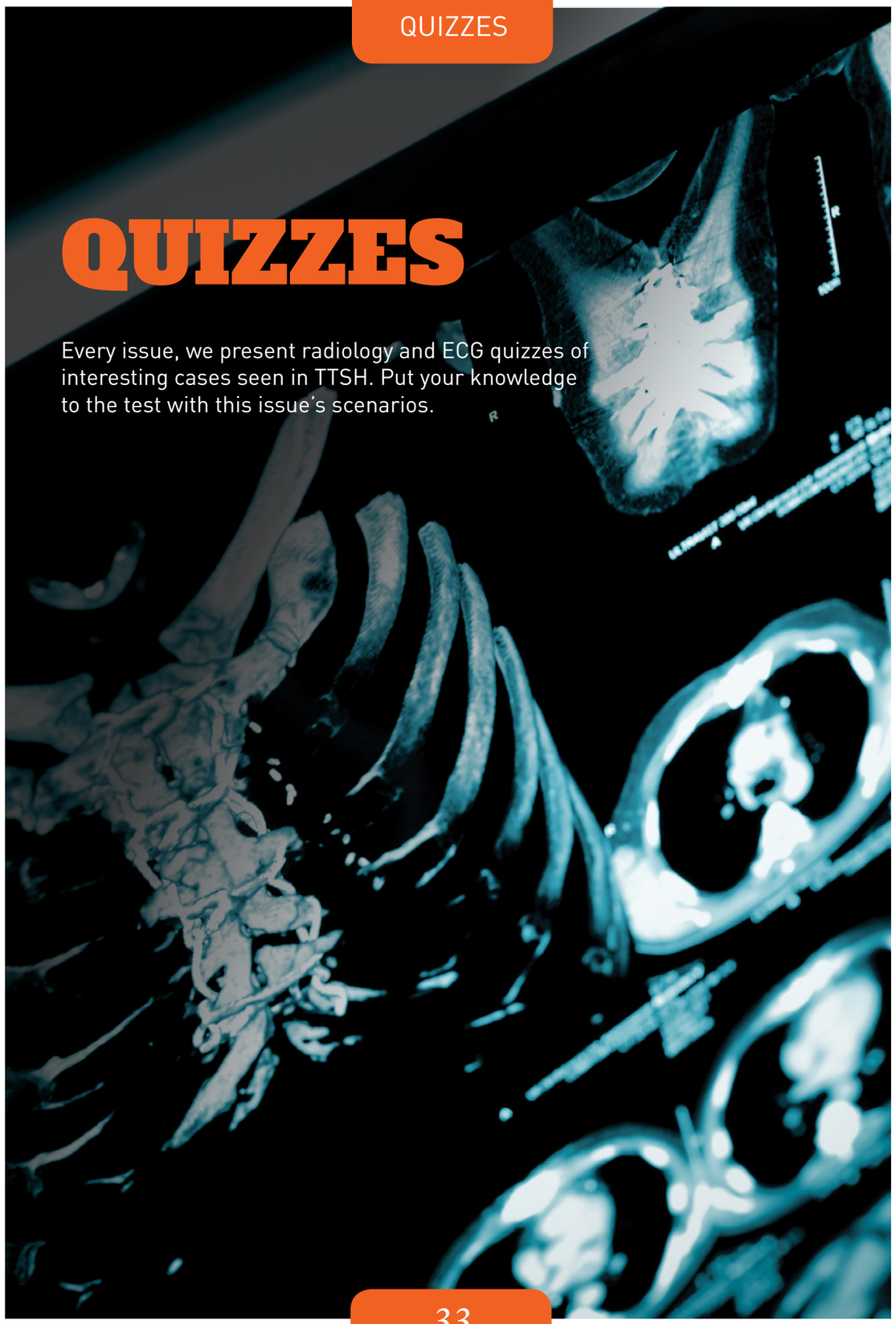


RADIOLOGY QUIZ

A 44-year-old lady with no known past medical history presented to the general practitioner with generalised weakness for one day which was more pronounced on the left. She appeared slightly confused. Blood tests showed low potassium level of 1.3 mmol/L and raised creatinine level of 145 µmol/L. She was immediately referred to the emergency department (ED) for further treatment.

Plain radiographs and subsequent ultrasound imaging of the urinary system were ordered in the ED (figures 1 and 2).

QUESTION

What do the radiograph and ultrasound images show?

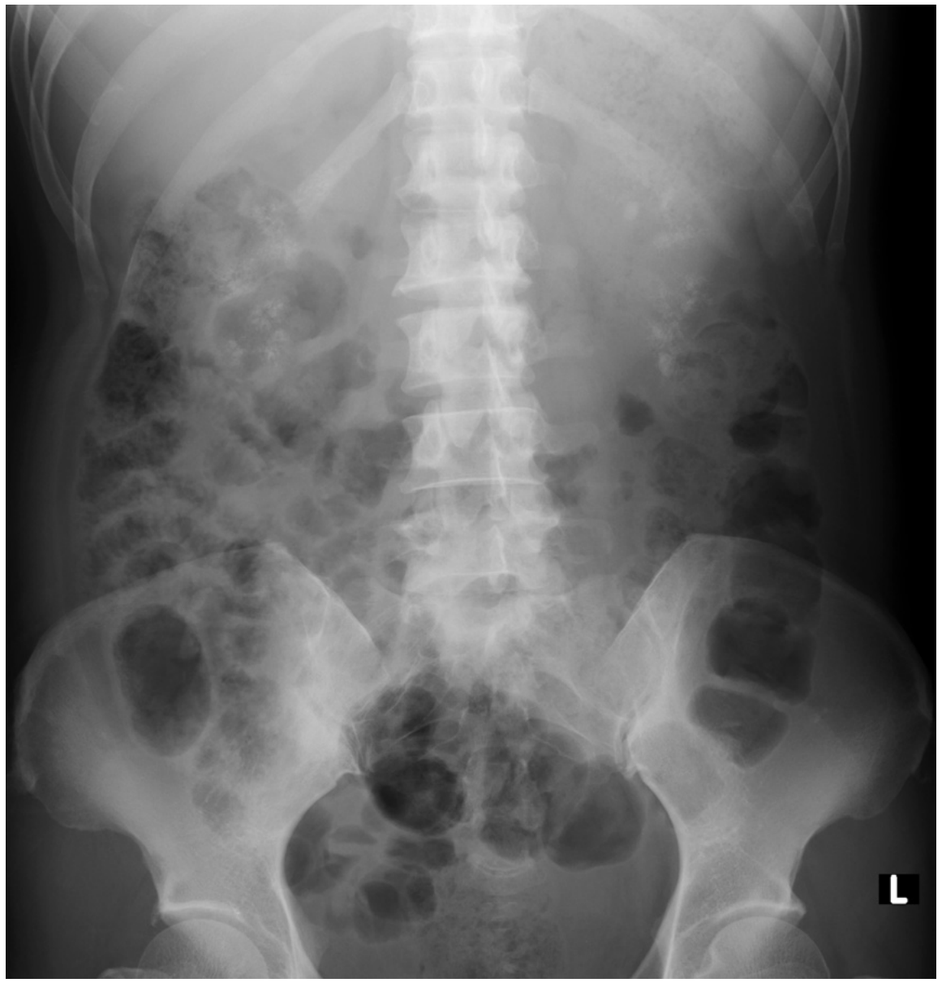
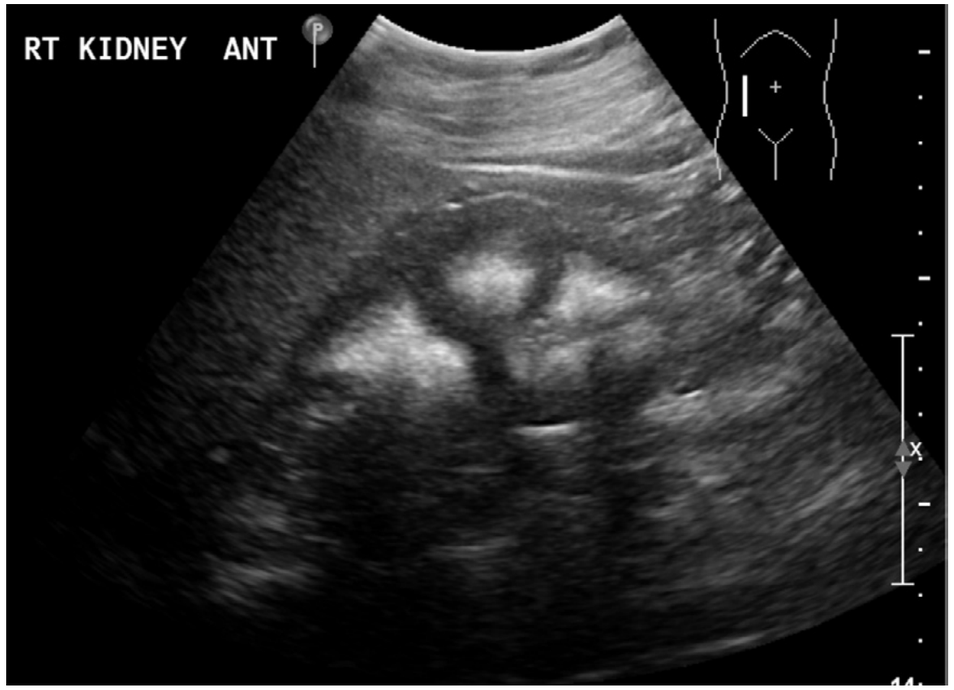


Figure 1. Plain radiograph of the kidneys, ureters and bladder (KUB).



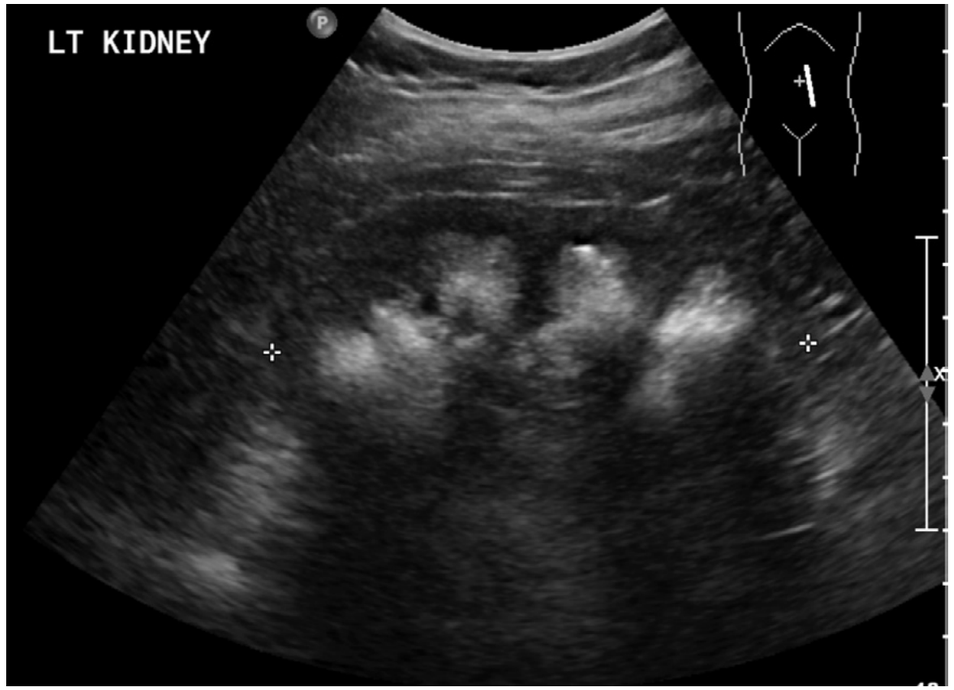


Figure 2. Ultrasound imaging of the right (top) and left (bottom) kidneys.

ANSWER

Plain KUB radiograph findings:

The radiograph reveals fluffly, cloud-like calcifications projected over the renal shadows bilaterally which appear to be mainly distributed in a medullary location. This finding raises the possibility of medullary nephrocalcinosis. No obvious radio-opaque urinary calculus is seen along the courses of the ureters or within the urinary bladder. Bowel gas pattern is unremarkable.

Ultrasound findings:

The ultrasound confirms the presence of calcification within the expected locations of the renal medulla in both kidneys in a symmetrical fashion. This is evident by the increased echogenicity with areas of posterior acoustic shadowing. No hydronephrosis is seen.

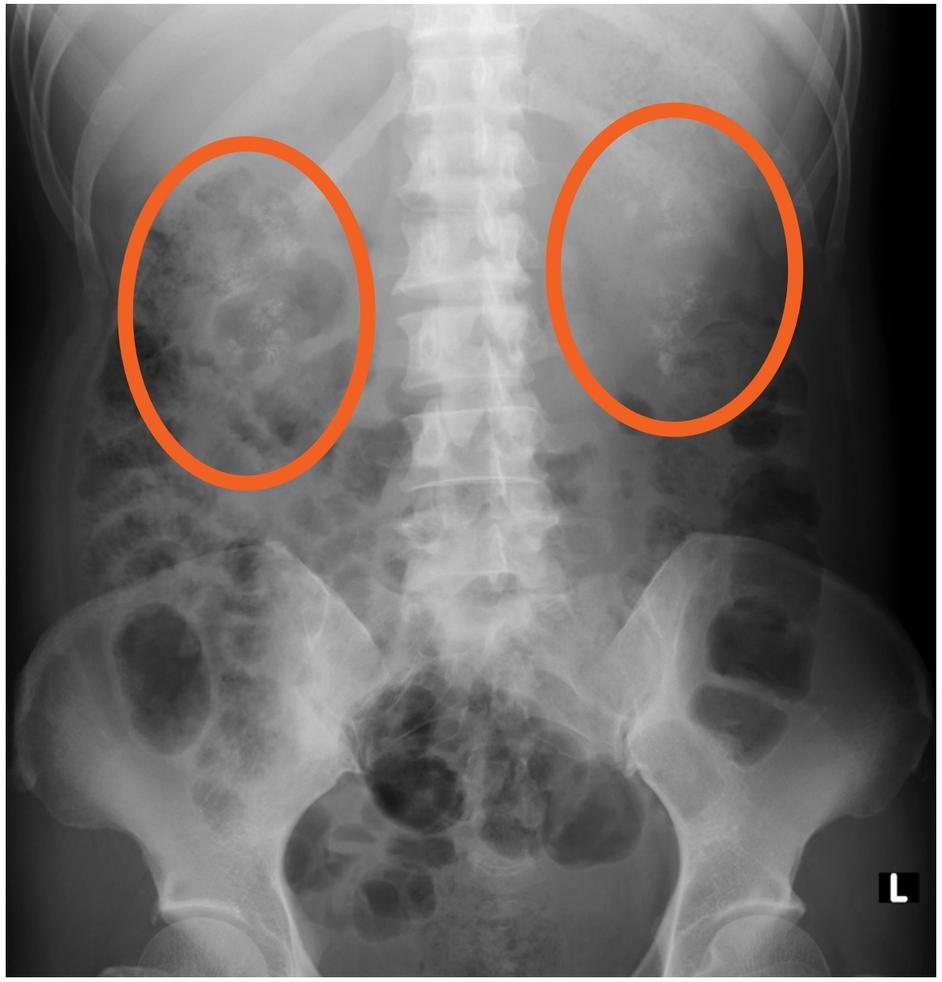
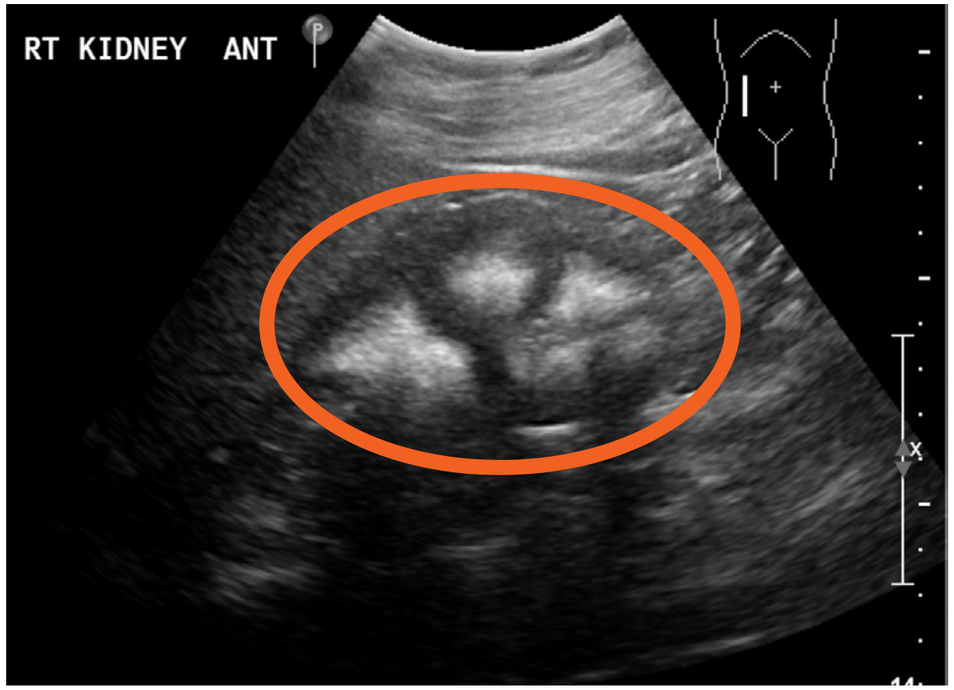


Figure 3. Radiograph showing bilateral cloud-like calcifications (circled) projected over the renal shadows.



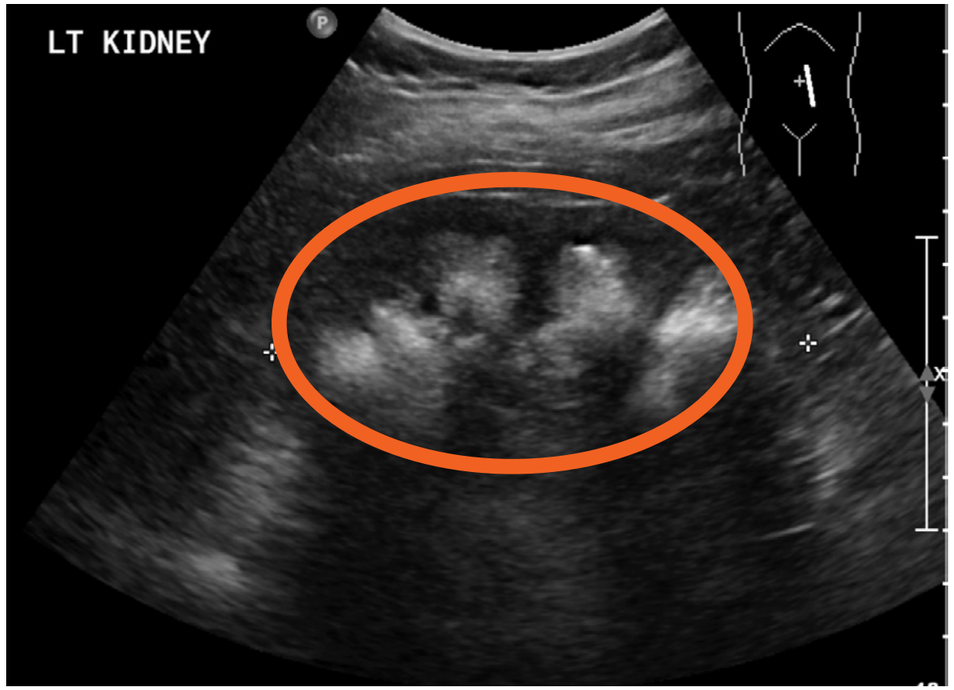


Figure 4. Presence of calcification (circled) seen within the expected locations of the renal medulla in both kidneys in a symmetrical fashion.

Discussion

Renal medullary nephrocalcinosis is the commonest form of nephrocalcinosis and refers to an excess deposition of calcium salts in the medulla of the kidney. Due to the concentrating effects of the loops of Henle and the biochemical milieu of the medulla, compared to the cortex, it is 20 times more common than cortical nephrocalcinosis. The main cause is an increase in the concentration of calcium in the blood which then deposits within the renal collecting systems. The commonest causes of nephrocalcinosis include primary hyperparathyroidism (which this patient was eventually diagnosed with), sarcoidosis, hypervitaminosis D, renal tubular acidosis, hyperoxaluria or hypercalcaemia, and medullary sponge kidney.

Clinically, most patients are asymptomatic and are commonly diagnosed through an incidental radiographic finding. Hence it is important for the reporting radiologist to recognise this entity and not consider it synonymous with urinary stone disease as the latter signifies underlying metabolic derangement which has broader implications (even though medullary calcification will lead to the same spectrum of complications related to stone disease). Some patients do present with renal colic, haematuria, renal metabolic derangement, repetitive episodes of urinary tract infection or even end-stage renal failure.

The prognosis and treatment of medullary nephrocalcinosis depend mainly on the underlying aetiology. Laboratory and biochemical investigations need to be performed to establish the underlying cause. The major long-term complication is renal failure. Early treatment of reversible causes of renal deterioration, such as urinary infections, calculus obstruction and hypertension, is essential. Once renal failure is established, it must be treated accordingly. Patients with idiopathic hypercalcuria and medullary sponge kidney have the lowest risk of renal failure, whereas patients with primary type 1 hyperoxaluria have the worst prognosis.

FURTHER READING

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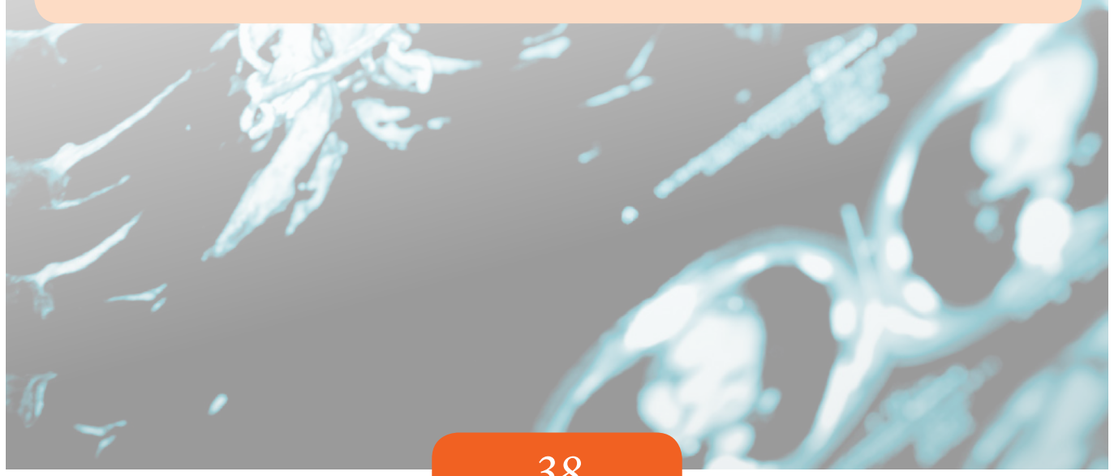

ECG QUIZ

A middle-aged Chinese lady with diabetes, hypertension, dyslipidaemia and stroke presented to the Polyclinic for routine follow-up. A screening 12-lead resting electrocardiogram (ECG) was performed (figure 1). She was asymptomatic and denied chest pain, dyspnoea, palpitations or episodes of loss of consciousness. She has no known cardiac problems and her last screening ECG was normal.

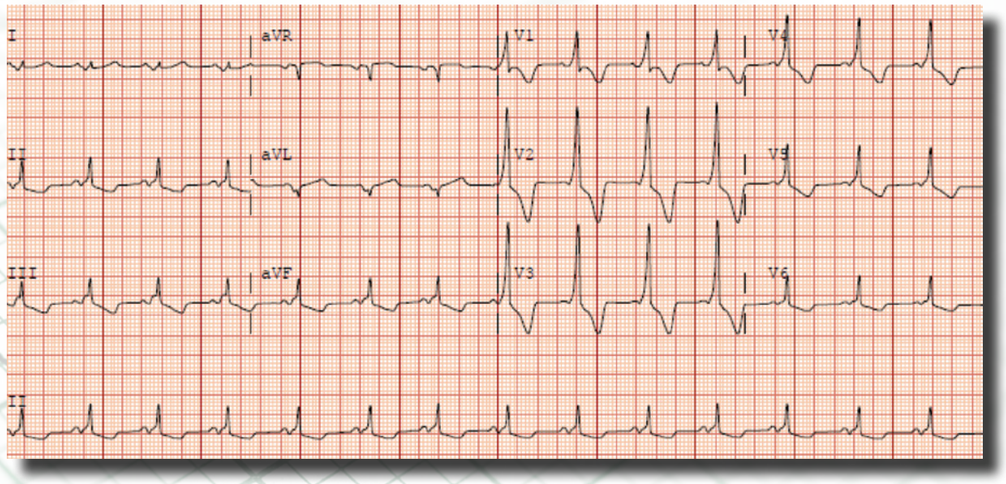

Figure 1. Resting 12-lead ECG of an asymptomatic middle-aged woman performed in the Polyclinic.

In view of the abnormalities seen on the ECG, the patient was rushed to the Emergency Department. She remained asymptomatic and her vital signs were normal. A repeat resting 12-lead ECG was performed in the hospital (figure 2).

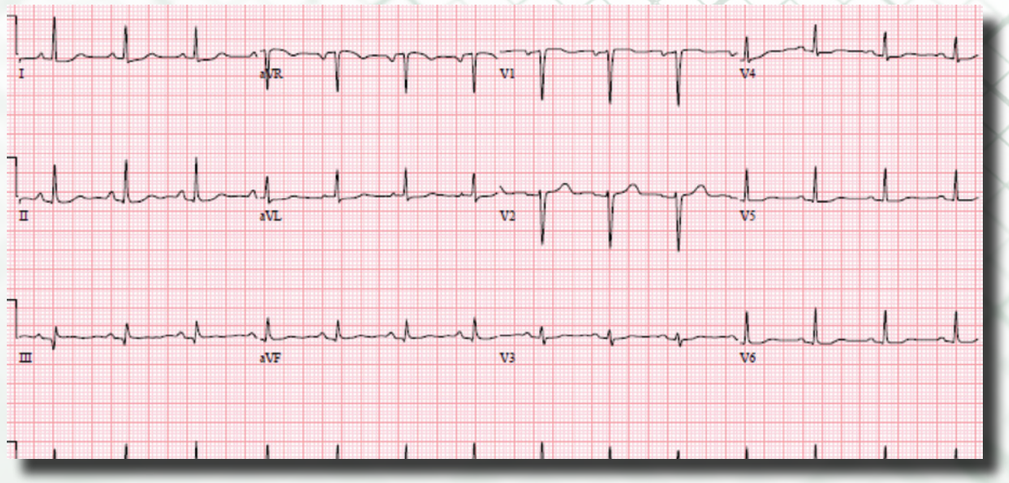

Figure 2. Resting 12-lead ECG performed in the Emergency Department.

QUESTION

What is the underlying cardiac diagnosis?

ANSWER

Intermittent ventricular pre-excitation (Wolff-Parkinson-White Syndrome).

Discussion

The patient was sent immediately to the hospital from the Polyclinic in view of the striking diffuse ST changes and T-wave inversions on the ECG. Given a history of multiple cardiovascular risk factors in the patient, the polyclinic doctor was understandably concerned about myocardial ischaemia. On closer examination, the QRS complex also appears abnormal. Specifically, the QRS complex is widened due to a slurred initial upstroke (delta wave) and accompanied by a short PR interval. These classical ECG manifestations of the Wolff-Parkinson-White (WPW) syndrome represent ventricular pre-excitation due to abnormal conduction through an accessory pathway. What is less well known is that the accompanying ST segment and T wave are often abnormal and generally directed opposite the delta wave and QRS complex, reflecting altered repolarisation.

How can we then explain the normal ECG that was acquired in the Emergency Department? In patients with WPW, electrical impulses from the atrium can conduct to the ventricle either through the 'normal' pathway (atrium-atrioventricular node) or the accessory pathway. When the accessory pathway enters a refractory period because the rate of conduction of impulses exceeds its capacity, electrical signals are re-directed down the 'normal' route instead, resulting in the disappearance of the classic WPW ECG changes.

WPW is associated with tachyarrhythmias such as atrioventricular reentrant tachycardia, which is a form of supraventricular tachycardia. More importantly, the presence of an accessory pathway in a patient with atrial fibrillation or atrial flutter allows very rapid conduction of the atrial impulses to the ventricles, which can provoke ventricular fibrillation and sudden death. A detailed review on risk stratification for sudden cardiac death in asymptomatic WPW patients is beyond the scope of this article. Specific to this patient, that the preexcitation is intermittent suggests failure of the accessory pathway to conduct at rapid rates and therefore confer a more favourable prognosis.

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