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BREAKING THE MYTHS OF CORONARY ARTERY DISEASE: WHAT YOU NEED TO KNOW ABOUT INOCA

Ischemia with no obstructive coronary artery disease (INOCA) is a clinical entity that has gained increasing attention in recent years due to its prevalence, clinical significance, and diagnostic challenges. Contrary to mainstream understanding, a large proportion of patients (up to 70%) undergoing coronary angiography because of stable angina and ischemia on stress tests do not have obstructive coronary artery disease in the major epicardial vessels (< 50% diameter stenosis). Intracoronary physiology of borderline lesions in these "large vessels" using pressure wire based hyperemic fractional flow reserve (FFR) or non-hyperemic resting indices are often normal. Unfortunately, in view of seemingly reassuring results, such patients are advised that their chest pains have a non-cardiac aetiology and do not receive the optimal tailored therapy that is required.

A failure to diagnose epicardial coronary artery disease in a patient with documented angina or ischemia on stress test should promote a subsequent search pathway to elucidate INOCA endotypes before a search for non-cardiac causes of chest discomfort is explored. The 3 main coronary epicardial vessels drain into an extensive microvascular reservoir (see Figure 1) and chronic microvascular dysfunction (CMD) is a key pathophysiology in INOCA. This is by way of structural remodelling of the microvasculature leading to fixed reduced microcirculatory conductance or vasomotor disorders affecting the coronary arterioles causing dynamic arteriolar obstruction. Coronary vasospasm is the other smaller contributor to the INOCA phenomenon. Figure 2 summarises the current concepts in the mechanisms of myocardial ischemia.

The risk factors for INOCA are nondescript and mirrors the traditional risk factors for obstructive coronary artery disease. These include diabetes, hypertension, dyslipidaemia, smoking, obesity and aging. There is a higher prevalence in women and it can present as nonspecific symptoms such as fatigue, weakness and sleep disorders. There needs to be a high index of suspicion and there are contemporary interventional pressure wire based technologies to measure the 'invisible' microcirculation.

The ability to measure adjunctive indices such as the coronary flow reserve (CRF) and index of microvascular resistance (IMR) has given patients and cardiologists another dimension in cardiovascular diagnostics. In the absence of epicardial disease (FFR ≥ 0.8), a CFR of < 2 and a IMR of ≥25 is suggestive of CMD.

INOCA is not a benign disease and a metanalysis by Gdowski M et all in 2020 showed that it is associated with a 4 fold increase in mortality and a 5 fold increase in major adverse cardiac events. While lifestyle and risk factor modification are necessary, antianginals (beta blockers, calcium channel blockers, ranolazine or trimetazidine) help with symptom management. To date, there are no disease modifying therapies specific to INOCA. The small vessel remodelling properties of ACE/ARBS and the pleiotropic effects of reduced vascular inflammation of statins are being studied in the ongoing WARRIOR trial.

Inoca's status is akin that of an emerging disease where it is underdiagnosed, undertreated and associated with poor prognosis. As research picks up pace to further shed light on improving management aspects, perhaps the best way forward now is for the medical community to recognise and evaluate its presence.

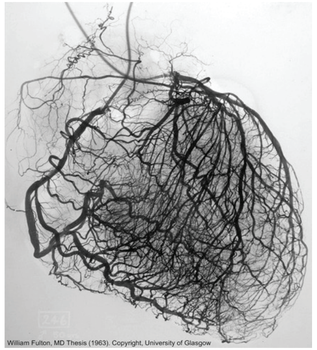

Figure 1.

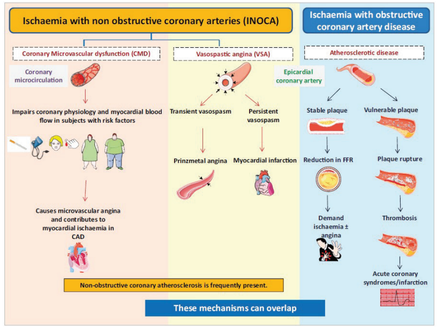

Figure 2. 2021 EAPCI expert consensus document on ischemia with non-obstructive coronary arteries

By **Dr. Pinakin V Parekh**
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STATIN INTOLERANCE

Statin intolerance is a challenge faced by many doctors when managing patients with hyperlipidemia. Statins are effective at lowering lipids and they reduce the risk of cardiovascular events. However, some patients experience adverse effects, which can lead to noncompliance and inadequate management of their cardiovascular risk. In this article we will explore what causes intolerance, its prevalence, and how to approach treatment in affected patients, including insights from the SAMSON trial.

Prevalence of Statin Intolerance
The prevalence of statin intolerance is estimated to be around 5-10% in clinical trials, but the real-world incidence may be higher, ranging from 10-15%. This variation is partly due to the underreporting of side effects in clinical trials and differences in patient populations. Furthermore, definitions of statin intolerance can vary, which may also contribute to discrepancies in reported rates.

Causes of Statin Intolerance
Myalgia and Myopathy: The most common cause of statin intolerance is muscle-related symptoms. The exact mechanism underlying statin-induced muscle symptoms remains unclear.

Liver Dysfunction: Statins can, in rare cases, cause elevations in liver enzymes, which can progress to liver injury. However, severe liver injury is infrequent, and mild elevations in liver enzymes often resolve with continued statin therapy or dose adjustment.

Drug Interactions: Statin intolerance can result from interactions with other medications that inhibit statin metabolism, such as certain antifungal agents, antibiotics, and immunosuppressants. These interactions can lead to increased plasma statin concentrations and a higher risk of side effects.
Genetic Factors: Genetic predisposition can influence individual susceptibility to statin intolerance.

Nocebo Effect: The SAMSON Trial was published in 2020 and aimed to investigate the role of the nocebo effect in patients reporting statin intolerance. The nocebo effect refers to the phenomenon where a patient experiences adverse side effects from a treatment due to negative expectations, rather than the treatment itself.

It was a randomized, placebo-controlled, and crossover study that included 60 participants who had previously reported statin intolerance. The participants were given three different sets of treatments in a random order: statin (atorvastatin 20 mg), placebo, and no treatment. Each treatment period lasted for one month, and there was a washout period between treatments. Participants were asked to rate their symptom intensity on a visual analogue scale (VAS) daily.

The study found that participants reported an increase in symptom intensity during both statin and placebo treatments compared to the no-treatment periods. However, 90% of the symptom intensity during the statin treatment was also experienced during the placebo treatment, suggesting that the nocebo effect played a significant role in patients' perceived intolerance to statins. The trial also found that 50% of the participants were able to tolerate the statin treatment without significant symptoms, and only 10% of the symptoms were attributable to the statin itself.

The findings of the SAMSON trial have important implications for physicians managing patients with statin intolerance. It highlights the need to consider the nocebo effect as a possible contributor to patients' reported side effects, and it emphasizes the importance of patient education and communication in managing expectations and perceptions of statin therapy. By addressing patients' concerns and providing reassurance, healthcare providers may help to mitigate the nocebo effect and improve statin adherence and tolerability.

Approaching Treatment in Statin-Intolerant Patients
Rule out other causes: Before attributing symptoms to statin intolerance, rule out other potential causes and consider whether any concurrent medications could be contributing to the adverse effects.

Re-challenge with a lower dose or different statin: Temporarily discontinuing the statin and re-challenging the patient with a lower dose or a different statin may help identify if the symptoms are indeed statin-related.

Non-statin lipid-lowering agents: In patients who remain intolerant to multiple statins, consider using non-statin lipid-lowering medications. Such as ezetimibe, bempedoic acid, PCSK9 inhibitors or Inclisiran.

Nutraceuticals and lifestyle modifications: Encourage patients to adopt a heart-healthy diet, increase physical activity, and maintain a healthy weight. Some nutraceuticals may be considered as adjunctive therapy in statin-intolerant patients. Red Yeast Rice can lead to a 25% reduction in LDL-C and is generally very well tolerated.

Address the nocebo effect: Based on the findings of the SAMSON trial, it is crucial to address patients' concerns and provide reassurance to mitigate the nocebo effect and improve statin adherence and tolerability.

Close monitoring and reassessment: Regularly monitor patients' lipid levels, liver function tests, and muscle symptoms to assess the efficacy and safety of the chosen therapy.

Conclusion
Statin intolerance is a significant challenge faced by physicians in managing patients with hyperlipidemia. Identifying statin intolerance, understanding its causes, including the nocebo effect as highlighted by the SAMSON trial, and employing a patient-centered approach to treatment are crucial to ensuring optimal cardiovascular risk reduction. Regular monitoring and adjusting treatment strategies as needed can help patients overcome statin intolerance and reduce their risk of cardiovascular events.

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IRON DEFICIENCY IN CARDIOVASCULAR DISEASE

Iron is needed in all organ systems for various metabolic processes, e.g. erythropoiesis, mitochondrial function, oxygen transport, myocardial and skeletal muscle metabolism, immune and nervous systems, inflammatory response, lipid metabolism and many others. Iron deficiency (ID) is common in patients with cardiovascular (CV) disease. The definition of ID is a serum ferritin concentration <100 ng/mL, or a ferritin concentration 100–299 ng/mL in combination with a transferrin saturation (TSAT) <20%.

ID can be characterized by:
1. Absolute ID = Depleted iron stores linked with a decrease in the total body iron supply due to insufficient nutritional iron intake, impaired absorption or chronic blood loss
2. Functional ID = Reduced circulating iron, which can be linked to a persistent inflammatory state as in many CV diseases

Inflammation leads to an **increased release** of **hepcidin**, a liver- expressed type II acute phase protein and a major player in iron homeostasis. Hepcidin regulates the degradation of ferroportin, a transmembrane protein which transports iron absorbed after dietary intake from the inside of the mucosal cells in the small intestine to the bloodstream, and also mediates the release of recycled iron from macrophages in the spleen and the liver. Therefore, ID observed with CV diseases may be due to the increased levels of hepcidin linked with a chronic inflammatory status, which leads to decreased iron absorption and mobilization from the reticuloendothelial system. In severe heart failure, In severe HF, a contributing cause of ID might be the reduction in iron absorption in the bowel due to an HF-related generalized bowel wall oedema.

Serum ferritin alone is a poor guide to ID in patients with Heart failure (HF) or atherosclerotic heart disease. Both conditions are associated with chronic inflammation, which increases hepcidin secretion, thus reducing iron absorption but provoking release of ferritin from cells (akin to troponin release from damaged cardiac myocytes), and therefore uncoupling ferritin from its usual relationship with ID.

ID across the spectrum of cardiovascular disease is summarized in Figure 1.

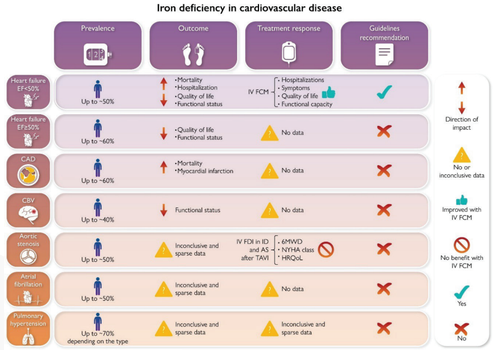

Figure 1. (taken from European Heart Journal (2023) 44, 14–27)

ID in HF is common regardless of ejection fraction (EF), i.e. up to 60%, more likely observed in women, older patients, and with increasing disease severity and symptoms. The association with clinical events varies based on the specific ID definition, but may be more closely related to low serum iron and TSAT than to low ferritin, which may be confounded by increases in inflammatory markers with advancing HF. However, ID is associated with an increased risk of hospitalizations across the EF spectrum and all-cause mortality in HFrEF/HFmrEF, even in the absence of anaemia. Current evidence from randomized controlled trials does not support the use of oral iron for ID in patients with HF, but highlights that IV ferric carboxymaltose reduces hospitalizations, improves quality of life, symptoms and functional capacity in ID patients with stable HFrEF and in those hospitalized for decompensated HF with an EF <50%.

There is a high prevalence of ID, up to 60%, in coronary artery disease (CAD). Overall, the evidence suggests that ID is associated with higher risk of ischaemic heart events and CV mortality in people with and without CAD, and adverse remodelling after a myocardial infarction. Evidence supporting iron supplementation for treating ID regardless of anaemia in patients with CAD is currently missing.

There is currently no data to treat ID without anaemia in patients with aortic stenosis, atrial fibrillation and pulmonary hypertension. Since ID can be easily treated, future research should aim for a full characterization of patients with CV diseases for ID, to identify those phenotypes who are more likely to benefit from iron supplementation.

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IS OPEN BYPASS SURGERY BETTER THAN MINIMALLY INVASIVE ENDOVASCULAR THERAPY IN PERIPHERAL ARTERIAL DISEASE – CONFUCIUS WHERE ART THOU?

Confucius said, "We have two lives, and the second begins when we realize we have only one".

The world of vascular surgery has been thrown into a Confucian conundrum over the last few months. This article is to help us all navigate the hot-off-the-press but conflicting data from two major trials on managing peripheral arterial disease (PAD) in our patients.

As new devices like drug-coated angioplasty balloons, atherectomy devices to remove calcified atherosclerotic plaques and stents of various shapes and sizes have developed, an increase has also occurred in the incidence of limb threatening ischemia. Amputation rates have continued to rise world-wide, largely due to the increase in diabetic PAD. Toe amputations progress to below-knee and then above-knee amputations, with a 5-year mortality that is poorer than that of breast or colonic cancer.

Two basic approaches exist to try to re-establish blood flow to the ischemic foot.

The traditional open bypass surgery using the patient's own great saphenous vein or other veins from the lower limb or even the arm is a major undertaking under general anaesthesia and days of in-patient stay. Major morbidity and wound related complications in limb bypass surgery are not rare. However, a successful vein bypass has significant longevity – if the patient survives the procedure itself.

The minimally invasive image guided endovascular procedures with fancy new catheters and balloons are the current fashion, but expensive equipment, variable levels of skills and training and the need for re-intervention on a regular basis are an issue. Most patients today with limb threatening PAD are, however, diabetic - with some impairment of renal function, which increases the risk of permanent renal damage from the use of angiographic contrast during such procedures.

Real world trial data was therefore desperately needed to answer the question of which was the better approach for chronic limb threatening ischemia to save limbs and lives. The now outdated BASIL trial published in 2005 (and the only trial with a head-to-head comparison of open and endovascular approaches for many years) showed that in patients with a life expectancy of over 2 years, open surgery had better survival and lower rates of amputation. However, most of these patients (some 75%) only had an above-the knee intervention in the femoral-popliteal segment. Disease today, especially in Singapore, is extensive in its distribution of plaque both above and below the knee – an unfortunate result of diabetes.

The first piece of major trial data on the subject for almost 20 years appeared in November 2022 in the BEST-CLI trial. BEST-CLI enrolled more than 1,800 patients from sites in the U.S. and abroad. Patients enrolled in the trial were randomized to receive a Bypass with an available, good-quality single segment great saphenous vein (SSGSV), or Endovascular intervention. As not all patients have an ideal vein conduit available, the trial also compared bypass and endo treatment among patients with only alternative conduit options, like a prosthetic bypass graft.

The main finding of BEST-CLI was that patients who had good quality SSGSV available and a bypass, had a 32 percent reduction in Major Adverse Limb Events (MALE) or death compared to endovascular treatment. This included 65 percent fewer major re-interventions and 27 percent fewer amputations. For patients who had only an alternative bypass conduit available, there was no difference in these outcome measures. The message seemed clear – open surgery is better if a good vein for bypass is available.

And then, on the 25th of April this year, the BASIL-2 trial data from the UK, Sweden and Denmark was simultaneously presented in London and published in the Lancet. BASIL-2 is the only randomised trial to compare a vein bypass to endovascular treatment in patients with chronic limb threatening ischaemia who specifically required a below knee intervention, with or without an additional more proximal infra-inguinal, revascularisation procedure to restore limb perfusion. The key trial finding is that an endovascular treatment first strategy is associated with a better amputation-free survival. This is mainly because endovascular treatment resulted in fewer deaths. Limb-related outcomes i.e. amputation rates, were similar between both groups.

So, which of the two trials is to be followed in Singapore – BEST-CLI that suggests open bypass surgery first if a good vein is available, or BASIL-2 that says go endovascular first because it gives better results for amputation free survival? Well, a finer analysis of the data, the outcome measures, the statistical assumptions in both trials etc is already feverishly underway in the vascular world as we speak. But some aspects are clear.

PAD today is difficult to treat, predominantly diabetic in origin, and allowing it to progress to limb threatening ischemia from extensive combined below and above the knee atherosclerotic disease leads to poorer outcomes regardless of the method applied. And that means regular PAD screening, and screening early. Ankle brachial index (ABI), toe brachial index (TBI), and segmental pressure studies (figure 1) are simple hemodynamic studies that identify subclinical disease early. The real solution would be to recognise and treat the disease early – with lifestyle measures, aggressive optimised medical therapy at primary care level and yes, early, simpler interventions.

Afterall, our legs should last us that only lifetime we have.

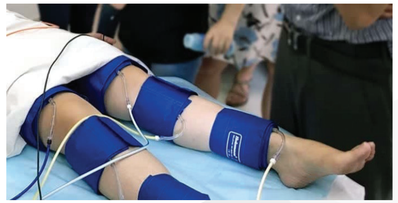

Figure 1. Segmental pressure measurements for PAD as done at the Harley Street Vascular laboratory.

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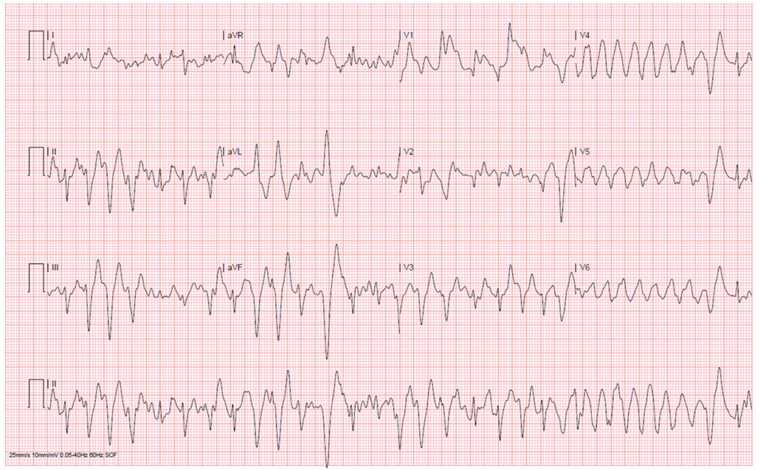
QUIZ



The ECG is taken from stage 4 of an exercise treadmill test performed in a 44-year-old man who presented with occasional dizziness when exercising. He was previously well with no significant medical history or cardiovascular risk factors. He was not on any medication and did not smoke or take any alcohol. His father and brother both had palpitations which was managed medically.

Investigations- his resting ECG and baseline echocardiogram were normal. Blood tests, including renal function, thyroid function and lipid profile, were normal. He was referred for a CT coronary angiogram which showed normal coronary arteries and a mild myocardial muscle bridge in his mid- left anterior descending artery.

Questions:

1. What does the treadmill test ECG show?
2. What other investigations would be helpful?
3. How should this patient be managed?

Answer is available on our website:
http://www.harleystreet.sg/quiz - answers/medbulletin-may-2023/

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MEDBULLETIN
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THE HARLEY STREET
HEART & VASCULAR CENTRE

INTRODUCTION

Greetings from the Harley Street Heart and Vascular Centre! As always, we are keen to provide our primary care colleagues with the most up-to-date information and practical tips in helping you manage your patients with cardiovascular disease. We would like to take this opportunity to inform you of a new addition to our team, Dr. Pinakin V Parekh, who is an experienced interventional cardiologist and senior consultant cardiologist. Dr. Pinakin brings a wealth of experience and expertise to our team and see patients at our Mount Elizabeth Orchard clinic.

In the current newsletter, Dr Pinakin provides a succinct overview of the increasingly recognised clinical condition- Ischemia with no obstructive coronary artery disease (INOCA) and outlines how it can be diagnosed and treated. Dr MacDonald has written a useful article on statin intolerance and provides practical advice on how it can be identified and managed. Dr Khurana highlights the importance in detecting and treating iron deficiency in patients with cardiovascular disease in his article. Dr Narayanan has written an interesting and thought-provoking article on the optimal treatment of patients with peripheral arterial disease in light of the latest trial data. As usual, the newsletter ends with an interesting but practical medical quiz. Dr. Liew's case tests your ECG skills with a challenging case he recently managed. The answer to the quiz will be posted on our website (https://www.harleystreet.sg/medbulletin/).

We hope these articles will be useful to your daily practice and help challenge and improve your management of patients with cardiovascular disease. Please feel free to contact us (at enquiries@harleystreet.sg) if you would like to provide any feedback or request a specific topic in future editions.

From The Harley Street Heart and Vascular Centre

From left to right:
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