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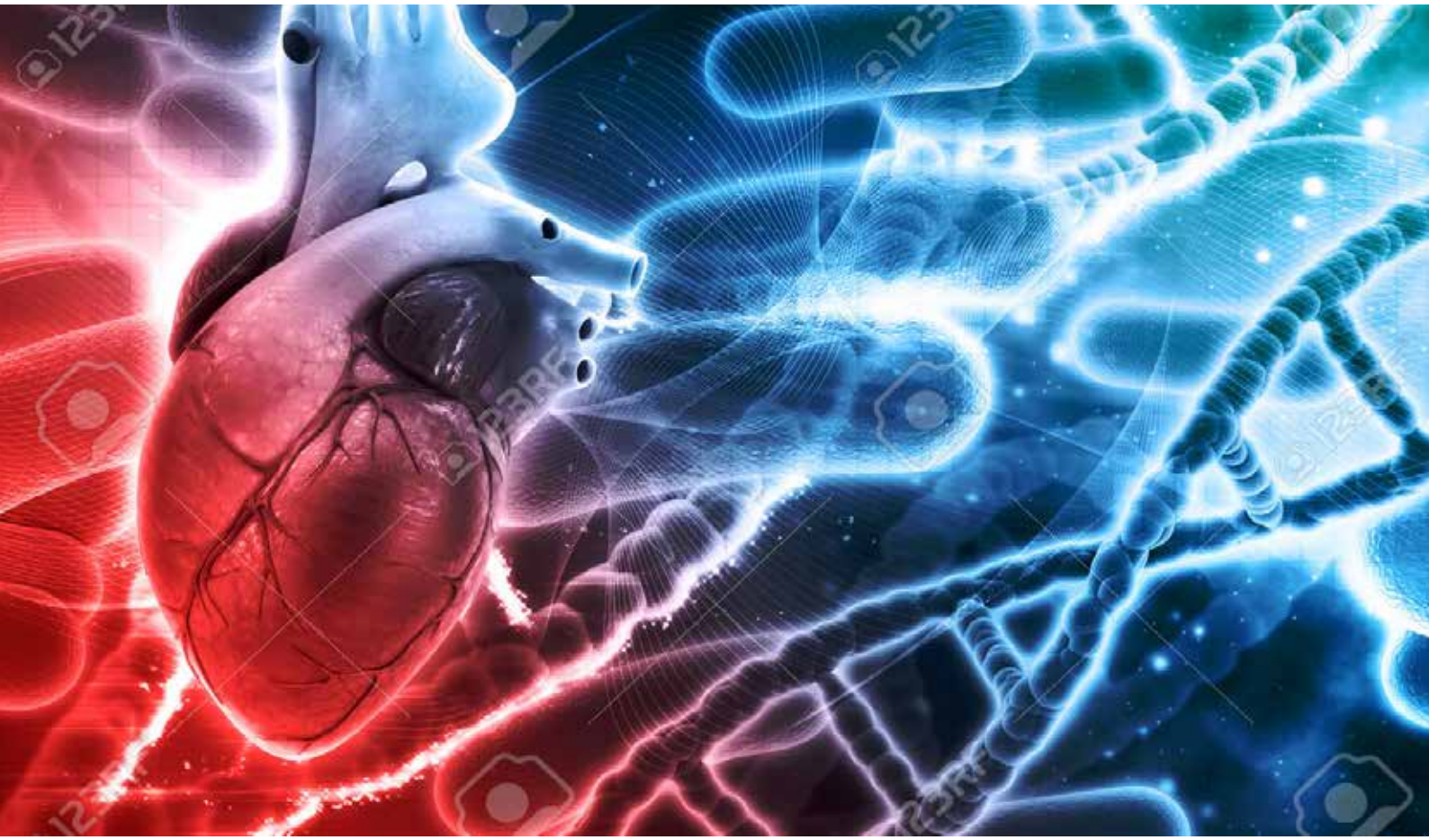
Heart Matters

Cardiology Newsletter



- Current practices in genetic testing to aid therapeutics and medical prescribing: A short guideline and synopsis
- NHI: Implications for cardiologists in the short-, medium- and long-term
- Artificial intelligence (AI): The heart of the matter
- Antihypertensive side-effects

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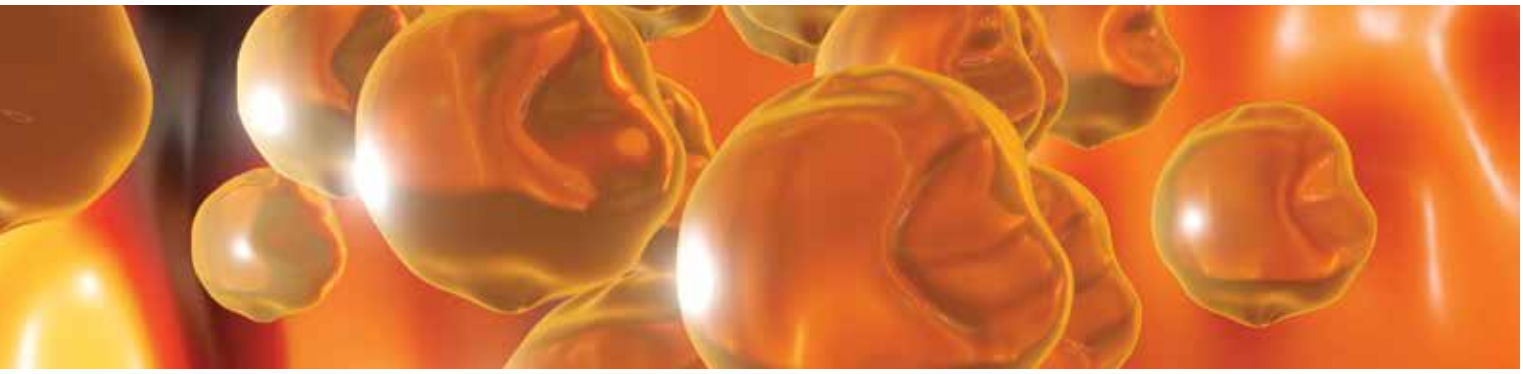

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HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol

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SUN PHARMA

Editorial

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Welcome to the second publication of the year of Heart Matters, a journal dedicated to the ever-evolving Cardiac environment. In this edition, we delve into a variety of topics ranging from the cutting-edge field of pharmacogenomics to the transformative potential of artificial intelligence. Our latest issue offers a wealth of insights to keep you informed.

We begin with an illuminating piece by Professor Monique Zaahl on the fascinating field of pharmacogenomics. This area of study focuses on how an individual's genetic makeup influences their response to drugs, offering the potential to tailor treatments for optimal efficacy and minimal side effects. In cardiology, where therapeutic strategies often need to be finely balanced to manage complex conditions, pharmacogenomics offers a new frontier.

Professor Zaahl's article explores how pharmacogenomics can be integrated into clinical practice to assess treatment response and predict adverse reactions. By identifying genetic markers associated with drug metabolism and sensitivity, clinicians can personalise therapy, improving outcomes and reducing the risk of complications. This precision approach not only enhances patient care but also paves the way for more efficient use of healthcare resources.

The introduction of National Health Insurance (NHI) represents a significant shift in healthcare delivery, with profound implications for both practitioners and patients. Our second article by Elsabe Klinck, a revered legal authority in the healthcare space provides a detailed analysis of how NHI will impact the field of cardiology. Key considerations include changes in funding models, access to care, and the potential for improved health outcomes through broader coverage, if rolled out correctly. The article discusses the practical challenges and opportunities that NHI presents, underscoring the importance for healthcare authorities, funders and practitioners to adapt to new administrative processes in the management of patients through integrated care networks. By examining these factors, the article offers valuable insights for practitioners navigating this transformative period.

The third topic presented by Dr David Jankelow focuses on the revolutionary impact of artificial intelligence (AI) in cardiology. AI, with its capabilities in big data analysis, diagnostics, and therapeutics, is poised to transform the way we approach cardiovascular care. This article, infused with an inspirational and cautionary tone, also highlights the incredible potential of AI in the cardiac catheterisation (Cath) lab.

AI's ability to analyse vast amounts of data quickly and accurately enables precise diagnostics and personalised treatment plans to be formulated and actioned. In the Cath lab, AI can assist in real-time decision-making (imaging analysis through machine learning), improving procedural outcomes and enhancing patient safety. The article explores recent advancements in AI applications, such as predictive analytics for identifying patients at risk of complications and machine learning algorithms that enhance imaging techniques.

By embracing AI, we stand on the brink of a new era in cardiology, where technology augments human expertise, leading to unprecedented levels of care and innovation. The future holds immense promise, with AI-driven tools that will not only streamline workflows but also unlock new possibilities in diagnostics and treatment.

Our final article addresses a critical issue in cardiology: The adverse effects of antihypertensive therapy. While these therapies are essential for controlling blood pressure and preventing cardiovascular events, they are not without risks, including potential side effects like electrolyte imbalances, renal dysfunction, and orthostatic hypotension. This comprehensive review explores current strategies to mitigate these risks and highlights future directions for safer therapeutic regimens. Emphasis is placed on the importance of individualised treatment plans, regular monitoring, and the development of novel agents with improved safety profiles. The article also discusses the role of patient education and adherence in minimising adverse effects, underscoring the collaborative effort required between healthcare providers and patients.

As you delve into this edition of Heart Matters, we hope you find the articles both informative and inspiring. The topics covered reflect the dynamic nature of cardiology, where continuous advancements drive improvements in patient care and outcomes. From the precision of pharmacogenomics to the preventive strategies for antihypertensive therapy, the implications of NHI, and the transformative power of AI, this issue encapsulates the future directions of our field.

We trust that these insights will enrich your practice and spark new ideas as we collectively navigate the evolving landscape of cardiovascular medicine. Enjoy this exciting edition, and best wishes for your continued journey in the field of cardiology.

Warm regards,
Chevaan Hendrickse

If you have any suggestions or topics you would like to see published or have articles and/or case studies for publishing, please email us at: lakeann@mweb.co.za.

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Current practices in genetic testing to aid therapeutics and medical prescribing: A short guideline and synopsis

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Pharmacogenomics (PGx) is a rapidly growing field that focuses on how genetic factors influence drug response and patient outcomes. This article provides a concise overview of PGx, its application in cardiovascular disease, and the clinical implementation of PGx testing. The benefits of pre-emptive testing and future directions in PGx are also discussed.

Introduction to PGx

PGx is focused on understanding how genetic factors influence drug response and patient outcomes. It has applications in various medical disciplines, providing a wealth of information as research continues to grow and more clinically validated data become available.

Known factors influencing drug response include age, weight, sex, comorbidities, renal and hepatic function, and drug-drug interactions. The role of genetics in drug response is now recognised, with interindividual differences due to variants in genes encoding drug-metabolising enzymes, drug transporters, or drug targets.[1,2] It is estimated that 99% of people have variants affecting drug response, carrying at least 1 to 3 clinically actionable genotypes. Increasingly, PGx is recommended before administering drugs.[3]

How Does It Work?

Cytochrome P450 (CYP) genes are one of the largest families of genes playing a major role in the detoxification of foreign chemicals and drug metabolism. Approximately 75 to 90% of all drugs are metabolised by CYP genes.[4] Variants in these genes can result in proteins with normal, increased (fast and ultrarapid metabolisers), decreased (slow or intermediate and poor metabolisers), or complete loss of function/expression. **Table 1** describes the differences in metabolising rates and their effects on standard drugs (active form when administered) and prodrugs (must be metabolised into active form).

Table 1. Description of Metabolising Rates

Description	Standard Drug	ProDrugs
Ultrarapid metaboliser	The drug is processed very rapidly and therefore leaves the body too quickly, often not having a chance to work properly. A different drug is recommended.	Drug is metabolised rapidly into active form, increasing activation and toxicity risk.
Fast metaboliser	**The drug is processed rapidly, often requiring a different dose (higher dosage) or a different drug. You may not benefit from the drug as it breaks down quickly.**	**Drug is rapidly metabolised into active form, increasing activation and toxicity risk.**
Normal metaboliser	Drugs are processed normally. The patient is likely to benefit from treatment and have fewer adverse drug reactions.	Processed normally and can be prescribed as on the label.
Slow metaboliser	**Drugs are processed less actively than for normal metabolisers, potentially causing adverse drug reactions. A lower than normal dosage is recommended.**	**Drug metabolised and eliminated slower, increasing risk of toxicity.**
Poor metaboliser	Drugs are processed more slowly than for slow metabolisers, likely causing adverse drug reactions. A different drug is recommended.	Drug activated slower, possibly reducing efficacy.

PGx in Cardiovascular Disease

The most common use of PGx is for cardiovascular drugs.[5] Several studies and clinical trials have demonstrated that PGx-guided cardiovascular drug therapy significantly improves patient outcomes.[6,7] PGx testing can enhance clinical outcomes by reducing adverse drug reactions and increasing therapeutic efficacy for commonly used drugs. The PGx of clopidogrel,[8] statins[9,10] and warfarin[11] has been extensively studied, with clinical implementation initially focused on these drugs. **Table 2** shows the genes involved in metabolising these drugs and the Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines and recommendations.

To date, several additional cardiovascular drugs have been included in PGx testing. These categories include antiarrhythmics, anticoagulants, antihypertensives, antiplatelets, beta-blockers, and calcium channel blockers.[12,13]

A consortium of scientists and medical practitioners who are experts in pharmacogenetics and clinical implementation was established to overcome the barrier of implementing pharmacogenetic testing in clinical practice. This consortium, CPIC (https://cpicpgx.org), aims to translate laboratory test results into actionable prescribing decisions for affected drugs. This guides laboratories to report pharmacogenetic results in a user-friendly manner and provides evidence-based pharmacogenetic test result interpretations and recommendations for select gene-drug pairs. The CPIC guidelines are the most comprehensive and up-to-date clinical PGx database, alongside the Pharmacogenetics Knowl-

edgebase (PharmGKB) (https://www.pharmgkb.org).

Future Directions

PGx tests could help reduce the burden of cardiovascular disease. Initially, pharmacogenetic testing was done reactively, i.e. the test was done after the patient experienced adverse drug reactions from a prescribed drug. However, testing has shifted in the last decade to pre-emptive pharmacogenetic testing, which is also driven by patients through direct-to-consumer (DTC) testing, becoming increasingly popular.

Pharmacogenetic testing assists clinicians in identifying how a patient will react to certain medications based on their genetic profile, aiming to identify the right drug at the right concentration for the right patient, thereby minimising adverse drug reactions and streamlining treatment. PGx testing should not be considered in isolation, as various clinical aspects can influence drug response. It is essential to view PGx testing as part of comprehensive patient management and care. Decades of PGx research have resulted in correlations between certain genotypes and the safety and effectiveness of numerous therapies, now being translated into clinical practice. The adoption of PGx testing in clinical practice has been slow despite strong evidence of the implications of specific genotypes on drug response. Including genetic testing strategies in clinical practice guidelines[14] might signal broader adoption of PGx testing, moving towards personalised medicine.

Table 2. CPIC Guidelines and Recommendations for Clopidogrel, Statins, and Warfarin

Drug(s)	Gene(s)	CPIC Guidelines and Recommendations
Clopidogrel	**CYP2C19**	For CYP2C19 slow and poor metabolisers: Avoid clopidogrel if possible due to the risk of therapeutic failure. Use alternative antiplatelet agents (ticagrelor, prasugrel, or ticlopidine) at standard dose if no contraindication.
Statins	**SLCO1B1**	For SLCO1B1 slow and poor metabolisers: Avoid statin if possible due to the increased risk for developing statin-induced myopathy. Prescribe an alternative statin depending on the desired potency. This is relevant to atorvastatin, lovastatin (prodrug), pitavastatin, pravastatin, and simvastatin (prodrug).
	CYP2C9	In addition to SLCO1B1, CYP2C9 also plays a role in dosage recommendations for fluvastatin.
	ABCG2	ABCG2 also plays a role in dosage recommendations for rosuvastatin.
Warfarin	**CYP2C9**	A dosing table calculator is provided based on CYP2C9 and VKORC1 genotype. (https://files.cpicpgx.org/data/guideline/publication/warfarin/2011/IWPC_dose_calculator.xls)
	VKORC1	

Take home messages

- Pharmacogenetics (PGx) is a tool to assist clinicians to identify the right drug at the right dosage for the right patient.
- PGx focuses on how genetic factors influence drug response and patient outcomes.
- 99% of people have variants affecting drug response with at least 1 to 3 clinically actionable genotypes.
- PGx is increasingly being recommended before administering drugs.
- Pre-emptive PGx testing is recommended and not reactive testing to improve patient outcomes (safety and efficacy).
- Direct to Consumer (DTC) testing becoming increasingly popular.

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NHI: Implications for cardiologists in the short-, medium- and long-term

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The NHI Act was signed into law on 15 May 2024. This is in spite of hopes that the President would refer the Bill back to parliament, due to various concerns raised in relation to its constitutionality.

A long road...

The proponents of the NHI Act argues that the Bill has been in the making for some 13 years, after an NHI Green Paper was published for comment in 2011,[1] and two White Papers published, one in 2015,[2] and another in 2017.[3] This makes the finalisation of the concept, as law, long overdue.

Opponents of the NHI Act argue that their comments have not been duly considered, and that even state-linked panels and committees, such as the Davis Tax Committee[4] and the Motlanthe Report of The High Level Panel on The Assessment of Key Legislation and The Acceleration of Fundamental Change[5] pointed to respectively the fiscal difficulties of implementation of the NHI as it had been proposed, and that other models would need to be considered, urging Parliament to "consider the substantive inputs that have been submitted through the Panel process when it deliberates on the NHI Bill".

Below in part 2, there are three significant opportunities posed by these developments that, irrespective of how the NHI debate and legal action plays out, will add value to cardiology.

Part 1: about the law

Not yet in law or capable of being implemented

The signing of the NHI Act has led to fears that the South African public, and healthcare providers and suppliers, may take rash action. The Council for Medical Schemes[6] and various medical schemes[7] have urged their members to not resign their membership.

The law, although now on the statute books, is not in effect. It is possible in South African law to bring laws into effect section-by-section. For example, bringing sections into effect that create the NHI Fund and its structures, could be done first. Politicians have repeatedly stated that the NHI would be implemented in phases. Which phases are not clear – only two are mentioned in the NHI Act, with "selected" contracting only taking place in the phase from 2026 to 2028. It seems unlikely that the first "selected" contracting would include specialists.

Consensus on the end-goal

All stakeholders support the objective of "universal health coverage". In the South African Constitution, that is the right of access to healthcare, entrenched in section 27 thereof. But section 27 sets criteria for any law, or other measure, aimed at implementing access to healthcare. These criteria include that the measures must be "reasonable", and subject to "available resources".

It is within the interpretation of these criteria that disputes arise. For example, are measures that would require of cardiologists to contract through private hospitals with the NHI, "reasonable"? Is the rolling of the Compensation Fund and all provincial health budgets into one massive Fund, ensuring one is making (better) use of "available reasources?"? And in the absence of being able to, at least in the medium term, increase taxes, facilitating "progressive realisation of healthcare"?

Part 2: Opportunities

These matters are bound to play out in the political space if the NHI Act goes back to Parliament, when regulations are drafted and through litigation in the courts. However, in the meantime, what could cardiologists do?

Opportunity 1: restructuring healthcare businesses

NHI or no NHI, the most recent changes to the HPCSA Ethical Rules,[8] provide an opportunity to increase efficiencies in healthcare delivery models and freeing up valuable time for cardiologists. The amended ethical rule 8 now provides for multi-disciplinary practices, subject to the conditions stipulated in the rule.

This means that a cardiologist, or a group of cardiologists, could work together, and include in a multidisciplinary practice an anaesthesiologist for an interventional cardiology team, a specialist physician to look after patients in intensive care units or high care, general practitioners to do follow-ups or routine investigations, nursing professionals to do screening, biokenticists on exercise, and dieticians on nutrition. These models would also enable easier contracting in a future NHI, which, hopefully be amended to not require contracting through a hospital.

One should just note that the HPCSA rules in relation to the private sector employment of practitioners still in training, and employment of those in the public sector without so-called RWOPS (remunerated work outside of the public sector) permissions, are still prohibited. The same applies to prohibitions relating to pathology and radiology, and rules around clinical technology. One should also ensure that, where the practitioners are from different statutory councils – that all councils permit the specific envisaged structure.

The Practice Code Numbering System has re-issued the multi-disciplinary practice code application form, enabling the system of billing and fee-sharing under the multi-disciplinary practice.

Opportunity 2: Reimbursement models and pricing

The Minister of Finance announced as part of his budget speech that one of the current NHI interventions is work relating to the implementation of a reference pricing model.[9]

The current system of free pricing has led to various issues. Patients complain about the unpredictability of fees and co-payments. Practitioners are concerned about reimbursement levels that vary from scheme option to scheme option - there being some 239 options[10] - and the resulting issues with bad debt or co-payment management. In some cases, these varying levels of reimbursement may be grounds for claw-backs by funders, where they have billed above levels set by scheme rules applied to a specific option.

The HPCSA has also amended ethical rule 7[11] to allow fee-sharing within multi-disciplinary practices. This opens space for innovative reimbursement models. The latest version of the Business Practices Policy,[12] released in May 2024, confirms opportunities for outcomes- or performance-based reimbursement models, including the provision of incentives for practitioners.

Alternative Reimbursement Models (ARMs) have also been raised by the Minister of Finance during the budget speech as one of the NHI-related areas that will be given attention to in this year. During the recent Board of Healthcare Funders Conference, sessions were dedicated to value-based contracting and reimbursement models.[13] At this event, Shivani Ranchod of Percept Actuaries listed options for practices as:, amongst others:

- capitation (a per patient fee per population),
- bundled team fees (also called global fees),
- bundled episode fees (also called fixed fees per health episode),

Incentivising good healthcare (as the HPCSA allows in the new version of the Business Practices Policy), could link fees such as bundled fees, with agreed outcomes, performance and/or value measurements.

The NHI Act states that it would fund healthcare on DRGs – diagnosis-related groups, which however requires data sets not yet in existence.

Whereas models in the cardiology space have focused on specific technologies and specific procedures, there is room for the development of contracting and reimbursement models that benefit practices and patients.

Opportunity 3: Quality and health outcomes improvements

The Office of Health Standards Compliance (OHSC) has been accrediting public- and private hospitals for compliance with the Norms and Standards Regulations of 2018,[14] issued under the National Health Act, 2003.

The OHSC is currently working with General Practitioner groups on the standards to be applied to general practice,[15] and other professional groupings would follow. This is as the NHI Act requires all service providers to be accredited by the NHI Fund, which includes accreditation by the OHSC, amongst other criteria.

Working within the general norms set by the 2018-regulations, quality metrices and tools can be developed that are specific to cardiology practices, and, with reference to the HPCSA rules changes, cardiology-driven multi-disciplinary practices.

Conclusion

The Deputy-Director General: NHI in the National Department of Health is reported as stating that the NHI implementation will take "decades",[16] or at least "years".[17] More recently there have been mixed message on free care within four years,[18] or that the NHI Fund will only be implemented in four years.

For cardiologists, these time periods are opportunities to address challenges in the current health system, both in the public and private sectors, and to, for the short-term work on practice models, reimbursement and fee systems, and to enhance quality of care.

In the longer term, the issues relating to the role of medical schemes, funding of healthcare and cross-subsidisation will be more prominent.

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Artificial intelligence (AI): The heart of the matter

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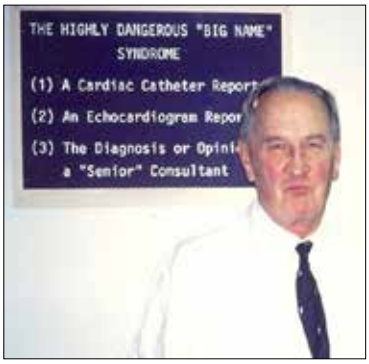
Could disruptive technologies, such as AI pose a threat to doctors. Could we eventually be replaced?

To answer this question - let's first go back several years.



Professor John Brereton Barlow
Photograph courtesy of Dr Tsung O. Cheng

This is Professor John Brereton Barlow, who many of us had the privilege to train under. He was one of the most accomplished cardiologists of his generation and his greatest legacy is the discovery of the most common heart valve disease, the billowing mitral valve leaflet syndrome, known as the "Barlow's Syndrome".

He was regarded as the ultimate clinician in the interpretation of symptoms and signs of heart disease. If you ever watched him with a patient, his clinical examination was painstaking. He never took shortcuts; he never reached a quick decision; he would carefully consider the problem.[1] John Barlow's research culminated in his book, "Perspectives of the Mitral Valve", which he dedicated "to all students of medicine who listen, look, touch, and reflect: May they hear, see, feel, and comprehend".[2] **I assure you that no technology could ever serve as a substitute for such clinical intuition and human touch. Rather than replacing doctors, AI has made the consideration of human values, as reflected by the guidance of a thoughtful physician, more essential than ever.[3]**

To further put this into perspective, imagine you woke up in the early hours of the morning with severe retrosternal chest pain due to a myocardial infarction. Who will you call? The emergency services to take you to the nearest tertiary care hospital, where a cardiologist can rapidly perform a percutaneous intervention to open up your occluded coronary artery? Will you rather refer to Chat-GPT? I know what I would do and have no doubt that you would do the same.

But what is Chat-GPT?

It stands for generalised pre-transformer, a powerful natural language tool that is taking the world by storm. It allows for a personalised conversation with an AI-bot, with rapid detailed responses to any question. It draws on a data store of knowledge that has been uploaded to the internet through 2021. Released to the public in November 2022, its global uptake (by a hundred million users) has been faster than any previous technology in the history of mankind. Open-AI (it's creator) believes that their ongoing research will eventually lead to a system to solve human-level problems. There is a new flagship model, GPT-4o, which can reason across audio, vision, and text in real time.[4] Not quite perfect, Chat-GPT was able to pass both the US Medical Licensing Examination and the European Exam in Core Cardiology (EECC). The EECC is required for completion of specialty training in cardiology in many countries.[5] We are certainly coming to an era where AI and large language models are reaching a maturity level that will gradually have an impact in healthcare. The ability to effectively process massive amounts of information with uncanny speed, could lead to a transformation in medical training and education. It is important that these systems are not a replacement for specialised knowledge, critical thinking, innovation, creativity, as well as the ethical considerations that are essential to the practice of medicine.[5] Despite these concerns, we face exciting times with the upscaling of concepts and technologies.

AI: where will it take us or rather where will we take it?

An important symposium was held at the 2022 European Society of Cardiology (ESC) Congress - Digital Cardiology and AI in 2033, Where will it take us? Martin Cowie (past chair of the ESC's Digital Committee) rather asked, where will we take it? This is most apt, because we as physicians will have to be engaged in the conversation as to the value of these technologies.[6] I assure you that AI is developing faster than we all think. We will need to use these tools to our advantage in the future - to augment expertise, improve patient care and outcomes. Many of us spend our time in healthcare consumed with repetitive redundant tasks, but unfortunately with very little return. Surely these tasks can be automated? AI has the potential to free us up so that we can work at the top of our competence and not at the bottom.[6]

So what is artificial intelligence?

It is the science of making machines smart; a system that is capable of learning directly from the data. Much of this comes from a process called machine learning (ML), which is different to traditional computer programming, in which you give exact and detailed commands. It is more like you feed it a huge bunch of data and by churning through it all, it will then come up with its own hypotheses and discover relationships that were not previously obvious. This is called unsupervised learning. We are trying to find naturally occurring patterns within the data. Supervised learning starts with the goal of predicting a known target, such as automated detection of an abnormality on a X-ray or ECG. You have the clinician saying this is normal and this is not. The computer will then build the algorithm depending on how you trained it.

Reinforcement learning is where the algorithm learns to react to an environment. Imagine you're a child in a living room. You see a fireplace, and you approach it, it warms you. That is positive. But then you touch the fire. It burns you. We obviously

learn through negative and positive experiences. Reinforcement learning is merely a computational way of learning through interaction.[7,8] Supervised learning is just like didactic teaching of medical students, whereas reinforcement and to a certain extent unsupervised learning is analogous to allow the students to clerk and assess patients by themselves, and to learn from their own mistakes.

Alan Fraser (Cardiff University, Wales) brings us back to reality, in that that AI is an umbrella term and the mention of "intelligence" may be inappropriate. There are multiple definitions and types. Programs with the ability to learn and reason like humans. ML within AI, and deep learning within ML.[9] There is a viewpoint that AI or ML, is really statistical analysis, with a different vocabulary. The differences in approach are only superficial and caused more by terminology and scientific culture.[10] AI is therefore an advanced tool to effectively handle large volumes of big data. We may have no other ways of making sense of massive amounts of information. It is not some form of voodoo magic that can spin data into gold.[11]

Is AI the next frontier?

Paul Friedman (Chair of the Mayo Clinic, Department of Cardiovascular Medicine) calls AI the next frontier. I agree, so why? He explains that in traditional medicine you have a person happily living their life, then lightning strikes and they develop symptoms and signs of disease. There is a fundamental problem with the way we physicians approach this, because we then start ordering a battery of investigations to formulate a treatment plan. Sounds quite reasonable, but as you well know, in cardiovascular medicine it may be too late. The first event might have been a devastating stroke, heart attack or even sudden cardiac death. The crux is that the underlying pathophysiological abnormality, may well have been developing for years. So, if we could have detected this earlier on, we may have been able to intervene to prevent a catastrophic event.[12]

AI for the ECG

The application of AI to the standard electrocardiogram (AI-ECG) has enabled the diagnosis of conditions with greater accuracy than previously possible. This includes the detection of episodic atrial fibrillation while in sinus rhythm, the presence of left ventricular dysfunction (LVD), valvular heart disease, channelopathies and even hypertrophic cardiomyopathy.[13]

Zacchi Attia and the Mayo Clinic team engineered a convolutional network to screen for asymptomatic LVD that affects 2 to 3% of the global population.[14] What is important, is that if you knew that you had a weak heart, there are guideline directed treatments that all lower mortality and prevent hospitalisation. The key point is that we should know that the condition is there beforehand.[12] LVD was defined as an ejection fraction (EF) of < 35%, as this is the generally accepted threshold for implantation of an internal cardiac defibrillator.[14] They trained the network by feeding in paired ECG and echocardiogram reports. The system will then process the information and through a process of back-propagation, it then modifies the weights of biases of these mathematical neurons; and just as a child learns that a ball is round and it bounces, so too does the computer learn over time that a specific ECG is associated with a low EF.[12] To test how well the algorithm performed, they then presented it with a different 53 000 dataset of ECG's. Performance was measured by the area under the receiver operating curve (AUC), which depicts the trade-off between sensitivity and specificity across a series of continuous cut-off points (a perfect score would be 1). This was a powerful result (with an AUC of 0.93) for the computers ability to read an ECG and to detect the presence of LVD. The most striking finding was the long-term outcome of those with a false positive AI ECG. In those with structurally normal hearts, subjects with a positive AI screen, were four times more likely (HR 4.1; P<0.001) to develop a dilated cardiomyopathy, as compared to those with a truly negative AI screen.[14] The network amazingly identified ECG abnormalities before overt LVD became clinically evident, and this could be important for example, patients receiving cardiotoxic chemotherapy. Those with an abnormal AI-ECG can be followed-up more carefully with echocardiography.[12]

How this will all work when integrated into the workflow of primary care practice?

Yao et al conducted a prospective randomised clinical trial (in primary care clinics) to screen for a low EF in patients without a prior history of heart failure.[15] The primary outcome was a new diagnosis of low EF (< 50%) within three-months of a routine ECG. All tracings in the intervention arm were analysed by the AI. The control group had no access to this information. The AI-ECG increased the detection a low EF by almost a third (1.6% vs 2.1%, P=0.007). The test performance was nearly identical to the initial retrospective study, with an AUC of 0.92.

The overall image utilisation was similar between the two groups, but more studies were performed in those with a positive AI-ECG. It therefore led to better selection of who should receive an echocardiogram, and this is important to eventually direct the resources to those that need it the most. These results indicate that use of an AI algorithm, based on ECG's can enable the early diagnosis of low EF in the setting of routine primary care.[15]

Can we screen patients using their wearable devices such as their smart watch?

In a prospective, digital remote study, AI was applied to ECG's that were recorded by subjects with their own Apple watches.[16] The algorithm detected a low EF (≤ 40%) with an AUC of 0.885, which suggests that consumer watch ECG's, acquired in non-clinical environments can be used to successfully identify patients with cardiac dysfunction. It offers the opportunity to use AI in geographically dispersed populations.[16] It would have important implications for screening in underserved communities and certainly resonates for Southern Africa. These results will however require further clinical validation and regulation, particularly as medical software is superimposed into a commercial device.[17]

Atrial fibrillation (AF) and valvular heart disease

The AI-ECG can now detect hidden AF when in sinus rhythm.[18] It can identify patients with moderate to severe aortic stenosis.[19] In a different multicentre cohort, deep learning analysis of the ECG accurately detected both aortic valve disease and mitral regurgitation.[20] In the future it could serve as a powerful screening tool for the development of a valvular heart disease screening program.[19,20]

You surely get the notion that the basic ECG, enhanced with automated AI interpretation, can be upscaled to what has always required an echocardiogram, which is costly, time consuming and takes years of training to master.[17] And recognising that ultrasonography is undergoing a transformation with point of care devices, can AI teach you to how to do an echocardiogram? With platforms such as from Caption Health's solution, any healthcare professional can record diagnostic-quality

images, with AI guiding them in real time, through every step of the scanning and acquisition process. It will even provide for intelligent interpretation, with calculation of EF to assess cardiac function.[21]

Eric Topol: "We still use dumb algorithms (rules-based, heuristic, univariate) in medicine, developed decades ago. Eagerly await validated smart ones with deep neural networks #AI"
This is a 2018 social media post from Eric Topol,[22] a prominent cardiologist and executive vice president of Scripps Research. His latest book is called Deep Medicine, How Artificial Intelligence can make Healthcare Human Again. So why don't we simply outsource to a machine? Because, there will have to be thousands of algorithms to even come close to replicating what any physician (or radiologist) can do on any day. Its' not going to be all solved tomorrow.[23,24]

AI for interventional cardiology

Artificial intelligence, in the future, will have a major impact on interventional cardiology, the unique nature of which, makes it ripe for AI-based systems to improve real-time clinical decision support and workflow in the catheterisation laboratory. It could standardise angiography procedures through advanced robotics; and augmented reality for real time viewing, measurement and manipulation of anatomy in a holographic display, could well and better guide structural heart procedures.[25]

A machine-learning analysis reports that an algorithm can offer a decision on the appropriateness of coronary revascularisation during pressure-wire pullback, at least as well as expert consensus.[26] Du et al have reported the performance of a novel AI solution (called DeepDiscern) that uses a neural network for automated analysis of coronary angiograms. Two unique deep neural networks were trained, validated and then tested for coronary segment recognition and lesion morphology. The success offers the ability to extract features at a pixel scale that may be difficult to discern by the human eye. It recognises all coronary segments and then detects the lesions in the angiogram. It could in the future assist us to rapidly help highlight coronary anatomy and severity, before us making a treatment decision.[27] Despite these interesting results, it must be noted that this remains a single-centre study and, as yet, no system has been able to harness the rich temporal data that can be gleaned from angiographic videos. Instead, angiograms are interpreted as still images.[28]

Whilst Du et al are tackling the automated analysis of coronary angiograms, others are working on similar technology for aortic waveforms and coronary physiology.[28] On this basis, can AI improve the safety of these procedures? An AI-based algorithm with pressure monitoring during angiography accurately detected pressure damping, which is important to avoid complications due to deep intubation of a coronary artery.[29] Damping will also hinder accurate physiological metrics, such as fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR). Strikingly, the time taken to process a single beat was less than one second.[29] There are currently no automated methods to do this and the recognition of damping is dependent on operator training, experience, and attentiveness. You will all agree that ten eyes rule when performing a coronary angiogram[30] The study of Howard et al has shown that real-time waveform analysis with ML in the catheterisation laboratory is possible; it may have implications for both patient safety and diagnostics.[29,30]

What could the future look like?

Could AI be used to recommend a patient-, vessel-, and lesion-specific revascularisation strategy? Perhaps in the future, but sound clinical judgement will always remain central to caring and treating our patients. Specifically these algorithms will need to be shown to be superior to human expert consensus, before many in the field will want to use them.[31] They will require external validation in randomised control trials, just like a pharmaceutical drug or a device.

A word of caution

AI has demonstrated great promise in cardiology with numerous examples of powerful AI models and positive published results. We however cannot assume that an algorithm trained in one population, may predict the same end-point in other clinical settings (not represented in the training set). External validation is the key for any intervention intended for patient care; and this includes AI tools that are becoming increasingly popular in commercially available consumer products.[32]

Regulation of AI

My friend Alan Fraser, who I mentioned earlier, is the Scientific Director CORE-MD, which is a European Union (EU) Horizon project. It is evaluating high-risk medical devices, including software for AI. The aim is to translate evidence into advice for EU regulators, and to strike a balance between innovation, safety and clinical effectiveness.[33] He says that the regulatory approach needs to define the function of the algorithm and not the technology specifically, which people focus on. If we are using it to measure ejection fraction, there is not much controversy, but if we use it to make recommendations about coronary revascularisation – we need higher standards and more transparency.[9] Despite these concerns, there is much excitement regarding the development of AI in cardiovascular medicine. I ask you to consider a recent editorial entitled, "a window into the cath lab of the future", which provocatively concluded, "Given these advances, it may be that in two decades we won't be asking about AI's role in the cath lab, but rather the cardiologist's".[28] Do you agree with this prediction?

More than a century ago, the father of modern medicine, Sir William Osler said, "Medicine is a science of uncertainty and an art of probability". Perhaps all these exponential advances and innovations, will render this highly relevant statement redundant in the coming decades.

The South African Heart Association (SA Heart) mission is cardiovascular care for all of our citizens

I was the President of SA Heart from 2018 to 2020. In 2016, a position statement was published for cardiology-cardiothoracic subspecialty training in South Africa. At that time the number of registered cardiologists was approximately 200 for 52 million South Africans (1 per 260 000). How does that compare with Brazil or one of the other BRICs countries with similar health issues? Brazil has tenfold more cardiologists (8000) for a population of 185 million (1 per 23 000), and even with that number, it is not adequately equipped for the enormous cardiovascular challenges.[34]

It is my hope that leveraging technology such as AI, could solve disease detection earlier and help to democratise healthcare in our beautiful country.

References available on request.

Antihypertensive side-effects

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The increased utilisation of antihypertensive medications worldwide are driven by various factors including an aging global population, urbanisation, sedentary lifestyles, and dietary shifts (processed foods, 'hidden salts', hormones) leading to higher rates of hypertension.

As the understanding of hypertension management evolves, there has been a trend towards polypharmacy resulting in adverse effects, especially in aged populations who are often on treatment for other comorbidities.

There has been a global shift toward the use of combination therapies (reduced pill burden and efficacious combinations) offering better blood pressure control and a reduction in adverse effects. Fixed-dose combination medications that contain two or more antihypertensive agents in a single pill are therefore becoming more popular due to their convenience and improved adherence.

Healthcare providers are also placing greater emphasis on evidence-based guidelines and step wise protocols to standardise therapy, such as those provided by organisations like the American College of Cardiology (ACC) and the American Heart Association (AHA), the European Society of Cardiology (ESC), and the World Health Organization (WHO). These guidelines help inform treatment decisions and promote standardised approaches to hypertension management globally.

There is a growing awareness of the importance of individualised treatment approaches based on factors such as age, sex, race, comorbidities, pharmacogenetics, and lifestyle factors. Tailoring treatment to the specific needs of each patient can lead to better outcomes and improved medication adherence. For example, patients of African enthogegraphical ancestry tend to respond more effectively to calcium channel blockers and diuretics but less so to renin angiotensin blockers and B adrenergic blockers. Possible mechanisms include lower clearance of the drug (Nifedipine), relating to cytochrome P450 polymorphisms and vascular smooth muscle physiology. These observations highlight the complexity of blood pressure physiology and the challenges that may be encountered in the treatment process.

Non-pharmacological interventions, including lifestyle modifications such as dietary changes, exercise, weight loss, and stress reduction techniques, are increasingly being incorporated into hypertension management protocols either as adjuncts to pharmacotherapy or as standalone treatments, particularly in patients with mild to moderate hypertension. The concept of renal denervation will also be introduced later on.

Over the last 4 years, the COVID-19 pandemic has accelerated the adoption of telemedicine and digital health solutions for hypertension management, have enabled remote blood pressure monitoring, virtual consultation with healthcare providers, the use of mobile reminder apps, the reporting of adverse effects and lifestyle tracking. These technologies have the potential to improve access to care, enhance patient engagement, and optimise treatment outcomes by amplifying compliance and lifestyle adherence, indirectly, minimising adverse events and optimising prognosis.

Overall, the global trend in antihypertensive use reflects a shift towards comprehensive, patient-centered care involving a combined pharmacological and non-pharmacological approaches to individual patient management.

Adverse effects linked to hypertensive treatment are a common problem, effecting compliance and treatment efficacy. Common adverse effects and possible practical solutions are outlined below.

ACE Inhibitors (ACEI)

ACE Inhibitors (ACEI) are well-tolerated by most individuals but are known for certain common adverse effects including a dry, persistent cough, on the basis of complex neurohumoral mechanisms, but mainly due to increased levels of bradykinin due to decreased ACE activity (most widely accepted hypothesis). The incidence is quoted in the region of 3.9% (B. Pinto et al) and may vary between ACE inhibitors. An ACE cough may be more common in patients with cardiac failure compared to arterial hypertension. Data are largely available from to Perindopril studies (PAINT, PIANIST, PROOF and PETRA).

Enalapril has an approximately 2-3 fold incidence of 'cough' when compared to perindopril. Interesting, perindopril also has higher bradykinin/angiotensin selectivity when compared to enalapril, but has the lowest incidence of cough (Ceconi C et al). The incidence, in general, is low and only 3.1 % of patients stopped treatment due to cough.

Angioedoema is a rare, but serious adverse effect, characterised by swelling of the face, lips, tongue, or throat requiring immediate cessation of the drug. An alternative strategy should then be explored for further management.

Hyperkalemia: Due to inhibition of aldosterone secretion, leading to potassium retention. Potassium levels should be monitored and lifestyle adjusted. Note concomitant treatments such as mineralocorticoid antagonists, non-steroidals, herbal supplements etc. Hypotension and dizziness is another side effect which should be cautioned to patients and often settled within 2 weeks.

Prevention

Cough Management: Switching to an alternative class of antihypertensive drug such as an ARBs can alleviate cough (see

below). Angioedema awareness should be created when prescribing ACE inhibitors. Patients should be educated on recognising symptoms and seeking immediate medical attention when it occurs. An alternative strategy should then be explored for further management.

Regular monitoring of serum potassium levels can help prevent hyperkalemia and adjust treatment strategy where needed.

Angiotensin receptor blockers (ARB)

Angiotensin receptor blockers (ARB) are usually selected when patients are intolerant to ACEI therapy. Although data for head to head comparisons of ACEI and ARB is scarce, the available evidence suggests that both are equally effective in reducing adverse outcomes in hypertensive patients at risk of CV events.

Adverse Effects

- **Hyperkalemia:** Similar to ACE inhibitors, due to inhibition of aldosterone.
- **Hypotension:** Especially pronounced in elderly patients or those on diuretics.
- **Renal dysfunction:** May impair renal function, particularly in patients with pre-existing renal impairment.

Prevention

- **Dose adjustment:** Initiate therapy at lower doses, especially in patients at risk of hypotension such as the elderly or renal dysfunction.
- **Monitoring:** Regular monitoring of renal function and potassium levels.
- **Hydration:** Encourage adequate hydration, particularly in patients on diuretics.

Diuretics

- **Electrolyte imbalance:** Particularly hypokalemia, hyponatremia, and hypomagnesemia.
- **Volume depletion:** Hypotension, dizziness, and syncope due to reduced intravascular volume.
- **Hyperuricemia:** Increased risk of gout attacks due to elevated serum uric acid levels.

Prevention

- **Electrolyte monitoring:** Regular monitoring of electrolyte levels, especially potassium and particularly if additional medications such as Digoxin are being taken.
- **Potassium supplementation:** Supplementing with potassium or prescribing potassium-sparing diuretics in patients at risk of hypokalemia.
- **Patient education:** Educate patients on the importance of maintaining adequate fluid intake.

Beta blockers

Adverse effects

- **Bradycardia:** Especially in patients with pre-existing conduction abnormalities.
- **Fatigue:** Non-specific fatigue or lethargy may occur. Nightmares. Erectile dysfunction.
- Beta blockers may precipitate **asthma**. They are therefore relatively contraindicated, however, cardio-selective beta blockers may be well tolerated in suitable patients.
- ***Masking of hypoglycemia:*** Particularly in diabetic patients, as beta blockers can blunt the adrenergic symptoms of hypoglycemia.

Prevention

- **Heart rate monitoring:** Regular monitoring of heart rate, especially in patients prone to bradycardia.
- **Caution in diabetics:** Use cardio-selective beta blockers in diabetic patients to minimise the risk of masking hypoglycemia.
- **Gradual withdrawal:** Avoid abrupt withdrawal, especially in patients with ischemic heart disease.

Mineralocorticoid receptor antagonists

Adverse effects

- **Hyperkalemia:** Due to inhibition of aldosterone, leading to potassium retention.
- **Renal dysfunction:** May exacerbate renal impairment, particularly in patients with pre-existing renal disease.
- **Gynecomastia:** Rare, but can occur due to anti-androgenic effects.

Prevention

- **Potassium monitoring:** Regular monitoring of serum potassium levels.
- **Dose adjustment:** Initiate therapy at lower doses, especially in patients at risk of hyperkalemia or renal dysfunction.
- **Patient education:** Educate patients on recognising symptoms of hyperkalemia and the importance of adherence to dietary restrictions.

Alpha blockers

Adverse effects

- **Orthostatic hypotension:** Particularly during initiation of therapy or dose escalation.
- **Dizziness:** Non-specific dizziness or lightheadedness may occur.
- **Reflex tachycardia:** Due to alpha blockade, leading to compensatory increase in heart rate.

Prevention

- **Slow titration:** Gradual dose titration can minimise the risk of orthostatic hypotension.
- **Patient education:** Advise patients to rise slowly from a sitting or lying position to prevent orthostatic hypotension.
- **Combination therapy:** Consider combining with other antihypertensive agents to mitigate reflex tachycardia.

Calcium channel blockers

Adverse events

- **Oedema,** mainly involving the lower limbs, hypotension and constipation are often side effects most reported. Centrally acting calcium channel blockers also predispose bradycardia, especially coupled with beta blockers and other rate-slowing agents.
- Other common adverse effects include **headache due to vasodilatory effects**, **flushing** due to **vasodilatation involving the face including gingival hyperplasia.** Occasionally, patients report **irregular or forceful heartbeat including fatigue and abdominal discomfort.**
- **Rare side effects include hepatic toxicity, skin reactions and severe hypertension.**
- Long acting calcium channel blockers (for example verapamil or Diltiazem) should not be used in patients with left ventricular dysfunction to prevent further deterioration in LV function.

Pathogenesis of dihydropyridine calcium channel blocker (DH PCCB) induced oedemaa

According to a large systematic review (3312 publications) and network meta-analysis of randomised controlled trials (71 studies; total number of patient= 56 283), the estimated rate of oedema to be highest with Nifedipine (81 %) and the

lowest with Lacidipine (12%). The average rate varies significantly from 5% to 60 %with higher doses and vary among different formulations.

It's aetiology is related to imbalance between pre and post capillary tone causing intracapillary hypertension and extravasation often prompting dose reduction, reduced efficacy or non-compliance.

Management options

The combination of Renin angiotensin system blockers have been shown to decrease the incidence of DH PCCB induced oedema compared to monotherapy. The net reduction depends on the combination. The effect has also been noted with ACE inhibitors (ACE I) and the combination of amlodipine + ACE I (perindopril, enalapril and ramipril) ranked the lowest risk of developing oedema (Ling, Liang et al; J Clin Hypertesnion (Greenwich) 2022 May; 24 (5): 436-554).

DH PCCB-induced oedema remains a clinical challenge, however exploring different combination preparations could reduce the rate significantly.

Renal denervation: Resistant hypertension

Renal denervation is an evolving strategy of BP control in cases where severe or multiple adverse effects have occured on traditional antihypertensive therapy.

This innovative procedure targets the sympathetic nerve plexus in the renal arteries, disrupting their activity and thereby reducing blood pressure. The sympathetic nervous system plays a crucial role in regulating blood pressure by influencing renal blood flow, sodium handling, and renin release. In patients with hypertension, there is often overactivity of the

General prevention of adverse effects

In addition to the specific preventive measures outlined for each class of antihypertensive medication, it's essential to emphasise the importance of regular follow-up appointments, medication adherence, lifestyle modifications (such as salt restriction, weight loss, and exercise), and individualised therapy based on patient characteristics and comorbidities. Close monitoring and collaboration between patients and healthcare providers are key to optimising the management of hypertension while minimising adverse effects. Clinical guidelines for the prevention of antihypertensive side effects focus on several key principles:

- **Individualised therapy selection:** Healthcare providers should select antihypertensive medications based on individual patient characteristics, including age, sex, race (African population and CCB+= diuretics, hydralazine), comorbidities, and medication tolerability. Tailoring therapy to the specific needs of each patient can help minimise the risk of adverse effects.
- **Start low, go slow:** Initiate antihypertensive therapy at low doses and gradually titrate upward as needed to achieve target blood pressure goals. Slow titration allows for better tolerability and reduces the risk of side effects, particularly hypotension and electrolyte abnormalities.
- **Regular monitoring:** Monitor patients regularly for signs of adverse effects, including laboratory monitoring of electrolytes (e.g., potassium, sodium), renal function, and other relevant parameters based on the specific medication being used. Close monitoring allows for early detection and management of side effects.
- **Patient education:** Educate patients about the potential side effects of their antihypertensive medications and the importance of adherence to treatment. Patients should be aware of signs and symptoms to watch for and when to seek medical attention if side effects occur.
- **Combination therapy considerations:** When using combination therapy, consider the potential for additive or synergistic side effects. Combination products containing multiple antihypertensive agents may increase the risk of adverse effects compared to monotherapy and should be used judiciously.
- **Hydration and electrolyte balance:** Encourage adequate hydration and monitor electrolyte levels, particularly potassium and sodium, in patients receiving diuretics or medications that affect the renin-angiotensin-aldosterone system (RAAS). Adjustments to fluid intake and electrolyte supplementation may be necessary to prevent imbalances.
- **Dose adjustment in special populations:** Adjust medication doses in special populations such as elderly patients, patients with renal impairment, or those with hepatic dysfunction to minimise the risk of side effects. Lower starting doses and slower titration schedules may be required in these populations.
- **Avoidance of drug interactions:** Be mindful of potential drug interactions that can increase the risk of side effects or reduce the efficacy of antihypertensive therapy. Considerations should be given to concomitant medications that may affect blood pressure or electrolyte balance.
- **Shared decision-making:** Involve patients in shared decision-making regarding their antihypertensive therapy, discussing the potential benefits and risks of treatment options. Patients should feel empowered to voice concerns about side effects and work collaboratively with their healthcare providers to find the most suitable treatment regimen.
- **Exercise, weight loss, OSA, lifestyle management. May be able to down-titrate doses or stop meds.**

By following these clinical guidelines, healthcare providers can minimize the occurrence of antihypertensive side effects while optimizing blood pressure control and reducing the risk of cardiovascular complications in patients with hypertension.

sympathetic nerve plexus, contributing to elevated blood pressure levels.

Renal denervation involves the use of minimally invasive techniques to ablate or modulate the sympathetic nerves that surround the renal arteries.

The procedure typically involves the insertion of a catheter into the renal arteries under fluoroscopic guidance adhering to strict protocols and industry standards. Once in position, various energy modalities such as radiofrequency or ultrasound are used to deliver targeted energy to the renal artery wall, disrupting sympathetic nerve function. This leads to a reduction in sympathetic outflow and subsequent vasodilation of the renal arteries, ultimately lowering blood pressure.

Renal denervation has shown promise as a therapeutic option for patients with treatment-resistant hypertension, defined as persistently elevated blood pressure despite adherence to a three-drug antihypertensive regimen, including a diuretic. For these patients, the addition of multiple antihypertensive agents often leads to intolerable side effects, such as electrolyte disturbances, orthostatic hypotension, and renal dysfunction.

By targeting the underlying cause of hypertension—the over-activation of the sympathetic nervous system—renal denervation offers a novel approach to blood pressure management. Clinical studies evaluating the efficacy of renal denervation have demonstrated significant reductions in both systolic and diastolic blood pressure levels, with some patients achieving normalisation of blood pressure without the need for additional antihypertensive medications.

One of the key advantages of renal denervation is its potential to reduce the pill burden and adverse effects associated with multiple antihypertensive medications. For patients experiencing significant side effects from their current antihypertensive regimen, renal denervation offers a welcomed alternative that can prevent target organ damage and improve quality of life.

In addition to its role in treatment-resistant hypertension, renal denervation has also shown promise in other hypertensive populations, including those with isolated systolic hypertension, obesity-related hypertension, and renal dysfunction. Ongoing research is exploring the broader applicability of renal denervation across various patient populations and its potential to prevent cardiovascular events and target organ damage associated with hypertension. Recent studies also explored is roll in the management of paroxysmal atrial fibrillation.

Conclusion

Advancing hypertensive management involves proactive measures to minimise adverse effects and enhance patient adherence. Future management will focus on personalised treatment protocols, pharmacogenomics, and digital technologies aimed at boosting compliance and treatment efficacy thereby reducing the global burden of hypertension.

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Therapeutic indications
Replacement therapy
AMTELIP® is indicated for the treatment of essential hypertension in patients who have been stabilised on the two component medicines used at the same dose.[5]
Add-on therapy
AMTELIP® is indicated in patients whose blood pressure is not adequately controlled on amlodipine monotherapy.[5]

References: 1. Data on file. Generics Dictionary. **2.** Neldam S, Lang M, Jones R [on behalf of the TEAMSTA-5 Investigators]. Telmisartan and amlodipine single-pill combinations vs. amlodipine monotherapy for superior blood pressure lowering and improved tolerability in patients with uncontrolled hypertension: Results of the TEAMSTA-5 study. *J Clin Hypertens* 2011;13:459-466. **3.** South African Medicine Price Registry [Internet]. Database of Medicine Prices. Dec 23, 2022. [cited Feb 23, 2023]. Available from http://www.mpr.gov.za/PublishedDocuments.aspx#DocCatId=21 **4.** Data on file. Bioequivalence of Amtelip. **5.** Amtelip tablets professional information, March 29, 2022.

S3 **AMTELIP® 40/5.** Each tablet contains telmisartan 40 mg and amlodipine 5 mg (as besylate salt). Contains sugar: mannitol 169,94 mg per tablet. Reg. No.: 50/7.1.3/0155. S3 **AMTELIP® 40/10.** Each tablet contains telmisartan 40 mg and amlodipine 10 mg (as besylate salt). Contains sugar: mannitol 169,94 mg per tablet. Reg. No.: 50/7.1.3/0156. S3 **AMTELIP® 80/5.** Each tablet contains telmisartan 80 mg and amlodipine 5 mg (as besylate salt). Contains sugar: mannitol 339,88 mg per tablet. Reg. No.: 50/7.1.3/0157. S3 **AMTELIP® 80/10.** Each tablet contains telmisartan 80 mg and amlodipine 10 mg (as besylate salt). Contains sugar: mannitol 339,88 mg per tablet. Reg. No.: 50/7.1.3/0158.

For full prescribing information please refer to the professional information approved by the South African Health Products Regulatory Authority. **Applicant:** Ranbaxy Pharmaceuticals (Pty) Ltd., a Sun Pharma company. 14 Lautre Road, Stormill Ext.1, Roodepoort, 1724. Tel: +27 11 495 0100. Fax: +27 11 495 0150. www.sunpharma.com.

SUN PHARMA

S4 Mezibe® 10
Ezetimibe

S4 Mezibe® Plus
Ezetimibe + Simvastatin

Mezibe® (ezetimibe) added to statin therapy.

- Offers a dual mechanism for LDL-cholesterol lowering[1]
- Reduced LDL-cholesterol by an additional 21-27 % vs. placebo[2]
- Dual strategy achieved greater coronary plaque reduction vs. statin monotherapy[1]
- Provides well-tolerated lipid-lowering therapy with a safety profile similar to statin monotherapy[3]

A fixed-dose combination[4] with cardiovascular benefits[5]

- Synergistic lowering effects on LDL-cholestrol, apolipoprotein B and triglycerides[6]
- Significantly lower risk of CV events vs. simvastatin alone[5]
- Reduced pill burden improves medication adherence[7]
  - 87 % greater odds of high adherence vs. two-pill combination[7]
- Single-tablet formulation for patients not at LDL-C goal with a statin alone[7]

LDL = low-density lipoprotein
CV = cardiovascular
LDL-C = low-density lipoprotein cholesterol

References: 1. Vavlukis M, Vavlukis A. Adding ezetimibe to statin therapy: latest evidence and clinical implications. Drugs Context. 2018;7:212534. **2.** Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41(1):111-188. **3.** Foody JM, Toth PP, Tershakovec AM, et al. (2014) Efficacy and safety of ezetimibe plus atorvastatin therapy. Clinical Lipidology. 2014;9:(4):441-470. **4.** Mezibe Plus professional information, March 2021. **5.** Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med 2015;372(25):2387-2397. **6.** Kater A-L,A, Batista MC, Ferreira SRG. Synergistic effect of simvastatin and ezetimibe on lipid and pro-inflammatory profiles in pre-diabetic patients. Diabetology & Metabolic Syndrome 2010;2:34 **7.** Rea F, Savaré L, Corrao G, et al. Adherence to lipid-lowering treatment by single-pill combination of statin and ezetimibe. Adv Ther 2021;38:5270–5285.

For full prescribing information refer to the professional information approved by the medicines regulatory authority.

S4 **MEZIBE® 10** Tablets. **Reg. No.:** 48/7.5/0637. Each tablet contains 10 mg ezetimibe. Contains sugar: 63 mg lactose monohydrate. **Pharmacological classification:** A 7.5 Serum-cholesterol reducers. **Applicant:** Ranbaxy Pharmaceuticals (Pty) Ltd., a Sun Pharma company. 14 Lautre Road, Stormill Ext.1, Roodepoort, 1724. Tel: +27 11 495 0100. Fax: +27 11 495 0150. www.sunpharma.com.

S4 **MEZIBE® PLUS 10/10** Tablets. **Reg. No.:** 50/7.5/0640. Each tablet contains 10 mg ezetimibe and 10 mg simvastatin. Contains sugar: lactose monohydrate 57,23 mg per tablet. S4 **MEZIBE® PLUS 10/20** Tablets. **Reg. No.:** 50/7.5/0641. Each tablet contains 10 mg ezetimibe and 20 mg simvastatin. Contains sugar: lactose monohydrate 124,45 mg per tablet. S4 **MEZIBE® PLUS 10/40** Tablets. **Reg. No.:** 50/7.5/0642. Each tablet contains 10 mg ezetimibe and 40 mg simvastatin. Contains sugar: lactose monohydrate 258,90 mg per tablet. **Pharmacological classification:** A 7.5 Serum-cholesterol reducers. **Applicant:** Ranbaxy Pharmaceuticals (Pty) Ltd., a Sun Pharma company. 14 Lautre Road, Stormill Ext.1, Roodepoort, 1724. Tel: +27 11 495 0100. Fax: +27 11 495 0150. www.sunpharma.com.

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