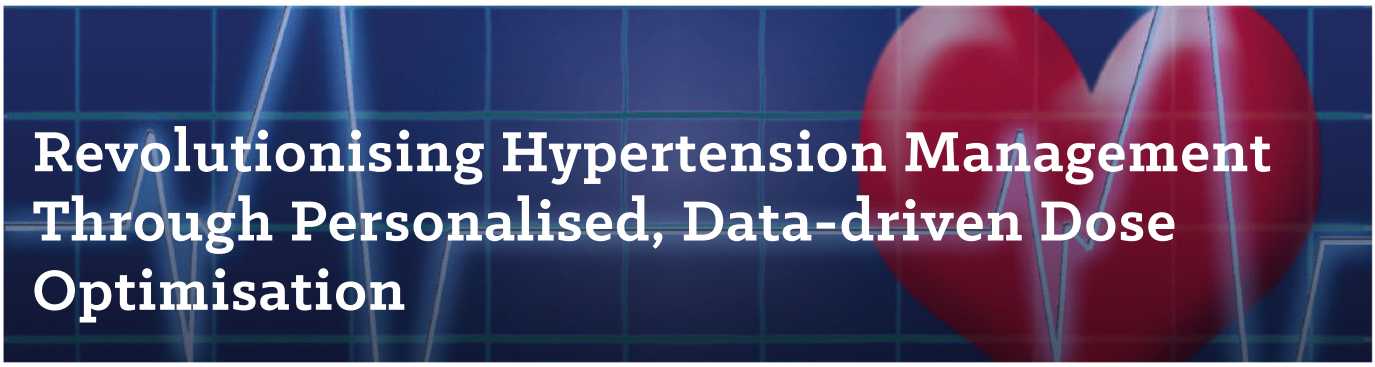

Revolutionising Hypertension Management Through Personalised, Data-driven Dose Optimisation

In the late 1990s, Pfizer's revenue stream was predominantly fuelled from the sales of antihypertensive drugs. The climax, so to speak, of its rigorous anti-hypertensive research efforts was the discovery of Viagra's unanticipated vascular system consequences. When the team at the Pfizer European Research centre, where the cardiovascular work was undertaken, proposed closing it all down, to move on to the next big thing, it was met with surprise and resistance from the commercial teams. The argument was, we've found the drugs to treat hypertension, our job is done. This poses the pivotal question: how has hypertension, despite decades of medical leaps, persisted as one of the world's biggest healthcare challenges?

Indeed in 2020, the first year of the COVID-19 global pandemic and before vaccine rollout, SARS-CoV-2 was only the third biggest killer in the Western world's leading causes of death; behind cancer and hypertension at number one. And it is not just the deaths from heart disease and strokes, for which hypertension is responsible for over half, but also the disease's core role in accelerating dementia.[1] There would be far more impact from rigorous control of blood pressure at a population level on dementia rates and outcomes than any of the anti-amyloid forerunners.

The scope of this challenge becomes apparent when considering approximately 1.28 billion adults between the ages of 30 and 79 are grappling with hypertension worldwide.[2] Notably, two-thirds of these individuals reside in low- and middle-income countries, highlighting the complex interplay between health and socio-economic factors. Adding to the complexity is the fact that an estimated 46% of affected adults are unaware of their condition. Moreover, less than half (42%) of those diagnosed receive appropriate treatment, and only around 1 in 5 (21%) maintain disease control. In response, a global target has been set by the World Health Organisation to reduce the prevalence of hypertension by 33% between 2010 and 2030, calling for innovative strategies to enhance personalised treatment and comprehensive management approaches.

Decoding the Complexities of Precise Dosing

What then has gone wrong in the effective management of hypertension, globally? There are two key issues, dose and process failure.

The words of Paracelsus, the father of pharmacology, resonate profoundly to this day: the only thing separating a drug from a poison is dose. Or in modern day parlance, concentration of drug at its effector site critically determines both benefit and side effects. Yet, amidst the pressures of clinical practice, this is not always at the forefront of clinicians' minds when reviewing a disease management plan. Partly this is due to the time and resource constraints in the modern healthcare system, but most critically, because of how clinical trials have historically been conducted to determine drug dose, based on average populations, paired with the simplified marketing narratives that pharmaceutical companies would ideally promote.

It is surprising that in today's consumer-driven societies, healthcare systems impose, and patients accept, a 'one size fits all' mentality. Patients now display an increasing array of critical pharmacokinetic and pharmacodynamic variables, influenced by factors ranging from obesity to numerous co-morbidities associated with an ever-increasing older population. Clothing retailers accommodate diversity by offering multiple sizes; should the pharmaceutical and healthcare industry not follow suit? Encouragingly, it is beginning to happen in some areas, most notably with continuous insulin infusions and glucose monitoring, with sophisticated software linking the two. This transformative approach begs the question: can the same philosophy be taken to other drugs, particularly solid dosage forms or injectables, and can this approach be used to manage other chronic diseases such as hypertension?

Blood pressure varies naturally during the day, as part of diurnal rhythms, as well as in response to current or anticipated bodily need. One-off readings at the clinic can be misleading as they often present a distorted image, contributing to clinician inertia and delay in treatment initiation or dose adjustments until there is a more convincing data set. Home measurements have emerged as a promising alternative, although there are challenges with the validity of measurements and data transmission. Nevertheless, these can be mitigated by undertaking a thorough assessment of an individual's response to medication through real-time feedback and using this information to dose optimise.

Drug + Software Solutions

Disruptive innovations in technology and data acquisition have led to the development of novel platforms set to address this challenge of effective patient monitoring, increase the effectiveness of existing medicines and transform how chronic diseases are managed. The effectiveness of any treatment relies on both its efficacy, safety / tolerability and patient adherence. Integrating traditional therapeutics and medical devices that enable real-time monitoring of patients can support tailored dose optimisation and improve outcomes for patients.

An illustrative example of the technology's potential is the PERSONAL COVID-BP trial, conducted in the UK, which was designed to evaluate a single-label combination product linking a medical device software product with a first-line anti-hypertensive, amlodipine, one of Pfizer's old blockbusters.[4] Nearly 20% of patients prescribed amlodipine discontinue its use after only the first prescription due to unwanted side effects, such as peripheral oedema, resulting in overall poor medication adherence and undermining the disease management plan.[4,5] Taking place during the COVID-19 pandemic, the aim of the PERSONAL COVID-BP trial was to evaluate the ability of the integrated precision care solution to optimise patient care, whilst also monitoring COVID-19 symptoms to allow better understanding of the links between the disease and high blood pressure.

Specifically, 205 participants aged 18 years and over with known hypertension and poor blood pressure control were enrolled in a community-based 14-week trial with remote monitoring and medical management, including patients shielding from COVID-19. Here, the technology closed the loop on blood pressure management by using processed data on both desired and undesired effects to precisely adjust the dose of amlodipine and deliver a personalised dosing regimen, without the patient ever needing to attend clinic. The study has shown promising preliminary results; demonstrating even low (novel) doses of 1 mg or 2 mg amlodipine reduced blood pressure, as did small 1 mg increments between 1mg–10 mg, allowing an individualised dosing sweet spot to be reached for each patient. Importantly, patient adherence to medication was found to be over 90%, perhaps in part because of the patient's active role in establishing their personal optimal dosage and seeing their personalised dose response curve. Encouragingly, the adherence rate of older participants was actually higher than their younger peers, which is fortunate as the cardiovascular events in outcome trials using amlodipine are dominated by those over 65 years of age.[3] Final findings are anticipated to be published shortly. (in press; Journal of the American Heart Association)

These preliminary findings have huge significance when considering the possibilities of software integration in disease management; suggesting that remote monitoring of blood pressure and side effects could revolutionise hypertension management. Tailoring dosages to the individual holds the potential to minimise side effects and significantly improve patient adherence for crucial cardiovascular medications, maximising overall effectiveness. Using this technology, the data also demonstrates how care can be maintained in unprecedented situations where face-to-face contact is not possible or desirable.

The Path to Process Refinement

The initial discussion highlighted two primary reasons behind the persistent poor control of blood pressure: dose selection and process failure. These process failures often stem from issues such as clinician availability, time constraints and lack of reimbursement incentives. The optimal system, akin to what we currently have for insulin, involves prescriptions of drugs coupled with software that automatically adjusts and optimises dose, based on collected data. This is paired with direct feedback communication to the patient. In regulatory terms, this marks a transition from clinician-in-the-loop, to clinician-on-the-loop, where the product operates automatically, but allows clinicians to intervene if necessary, ultimately aiming for a fully autonomous, clinician-out-of-the-loop system.

A key question then becomes how to conduct trials and evaluations to reach this nirvana. These evaluations should also incorporate health economics outcomes to facilitate uptake by payers. With blood pressure control being tightly linked to long term health outcomes, there is a compelling case. Furthermore, applying such a platform to other drugs can help achieve the outcomes-based reimbursement health care model so long called for by payers and governments.

Similar to insulin and diabetes, the algorithm's performance improves as more patients are treated and outcomes data assimilated. However, there's a need to generate evidence and assure regulators as the dose optimisation process becomes automated; in reality, policy-makers cannot simply follow the science. There are also the broader challenges seen with any Software-as-a-Medical-Device (SaMD) interacting with other components, in terms of maintaining integrity and safety when other components are upgraded. Incorporating safety features into the software platform from the beginning and understanding the ultimate goals are critical considerations, including the inevitable integration of AI. Acquiring data on effects as part of the product helps provide the regulatory assurance, along with approaches such as regulatory sandboxed deployments and conditional approvals of certain aspects of software.

The UK's Medicines and Healthcare products Regulatory Agency (MHRA) is at the forefront of these innovative ideas with the Innovation Access Pathways – involving collaboration between MHRA, The National Institute for Health and Care Excellence (NICE) and their Health Technology Assessments who lead on health economics for the UK government, as well as the NHS itself, the principal payor and healthcare provider in the UK. The aim of these collaborative pathways is to think about how innovative technologies can be deployed. There are also multi-agency collaborative support efforts for AI, which can then be fed into the Innovative Access Pathways, as well as multi-national discussions, with the MHRA co-chairing an International Medical Device Regulators Forum (IMDRF) group looking at AI SaMD group looking at AI SaMD.

Precision medicine has tended to equate to cancer genomics and an individual's chemotherapy selection, for which care has been revolutionised. But there's a growing recognition of its potential impact on the broader population with common diseases and in the not-too-distant future we will see similar impact on many other conditions. By minimising the need for clinician involvement in the optimisation and monitoring process as much as possible, we have the opportunity to address one of the biggest challenges in modern healthcare, besides funding – the lack of availability of health care professionals. This presents a future where better patient outcomes are delivered by the synergy of pharmaceuticals and technology, whilst reducing process costs for the payers.

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