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Health Enterprise East

MANAGEMENT OF CARDIOVASCULAR DISEASE

THE JOURNEY TO PERSONALISED DISEASE MANAGEMENT

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EVELYNE PRIESTMAN
HEALTH ENTERPRISE EAST LTD

Medtech Navigator

The Medtech Navigator, part-funded by the European Regional Development Fund (ERDF), is a three-year programme, delivered by Health Enterprise East Ltd., to facilitate knowledge exchange between the medtech industry, many of whom are small and medium sized enterprises (SMEs), the NHS, and academia. The programme seeks to enable companies to identify potential market opportunities in a variety of specific disease areas and apply for Innovation Grant funding through the programme, thereby engaging SMEs in new R&D projects that are both customer-focussed and collaborative in nature. This will allow the creation of partnerships between clinicians, academics and industry to develop novel medical technologies which will improve healthcare and quality of life for patients and the healthcare market of the future.

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Report Summary

This report discusses the different strategies employed to manage the burden imposed by cardiovascular diseases on the population. Effecting changes requires a concerted approach of preventive, screening and treatment interventions which span across the spectrum from low-risk to high-risk individual. Digital health presents a unique opportunity to link up population- and individual-level strategies and make the identification of “at-risk” individuals a cost-effective undertaking.

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Contents

1. Abstract

Cardiovascular disease (CVD) remains one of the biggest challenges facing the developed world, with the UK spending an estimated £12.5 billion in healthcare costs in 2015. Furthermore, CVDs are responsible for some of the most significant healthcare inequalities seen in the UK and responsible for higher premature death rates in socio-economically deprived areas.

Bringing about reductions in CVD has become a national priority for the UK with the NHS Long Term Plan identifying cardiovascular disease as the single biggest risk area where lives can be saved in a decade.

Management of cardiovascular diseases at the national level requires a concerted approach combining a population strategy, aimed to reduce the determinants of disease in the population, with an individual strategy, which seeks to identify high-risk individuals susceptible to the disease to then offer specific treatment.

Population-level measures, though capable of effecting significant change in population health, tend to offer only small benefits to each individual. Identifying individuals deemed to be at high risk of developing cardiovascular disease to then target treatment yields high rewards as the relative risk reduction achievable is much higher than for people with a lower risk profile. However, the utility of this approach is limited in cases where the impact may only be small if the individuals identified as high risk contribute little to the overall CVD burden.

Without the population strategy, CVD events will continue to occur in a large number of people who each may have a low individual level of risk. Furthermore, eliminating some of the causes of disease by population-wide measures can cause a significant reduction in the incidence of CVD at the macro-level. Individual strategies targeted at “high risk” subjects act as an expedient to help protect susceptible individuals. The extent to which one strategy is emphasized over the other depends on achievable effectiveness, cost-effectiveness and resource considerations.

A significant barrier on the road to personalised disease management remains the cost of screening large swathes of the population to identify high-risk individuals. HEE expects to see the development of new medical technologies which harness existing data streams from both medical and non-medical sources to create a dynamic way of identifying and monitoring high-risk individuals. Furthermore, the uptake of digital technologies, accelerated by COVID-19, offers the chance to use personalised digital health interventions based on people’s individual data profiles and risk scores with the potential to bring about lasting behaviour change and reduce CVD risk at the individual as well as the population level.

2. Cardiovascular Diseases – A burden on society

Though we are still living in the midst of a pandemic, we must not forget that one of the biggest challenges facing the developed world, in the long run, is cardiovascular disease (CVD), brought on by sedentary lifestyles, a diet high in salts and saturated fats, smoking

and alcohol consumption, etc. Furthermore, pre-existing CVD appears to be linked with worse outcomes and increased risk of death in patients with Covid-19[2], and patients suffering from post-acute Covid-10 ("long Covid") are at higher risk of experiencing adverse cardiovascular events requiring hospitalisation[3].

CVD is estimated to affect over 6 million people in England[4] and includes many inter-related conditions such as coronary heart disease, cerebrovascular disease, peripheral artery disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis and pulmonary embolism. An evaluation by the British Heart Foundation calculated healthcare costs to amount to £12.5 billion in 2015[5]; the equivalent of £14.2 billion in 2020. Furthermore, CVDs are responsible for some of the most significant healthcare inequalities seen in the UK and responsible for higher premature death rates in socio-economically deprived areas.

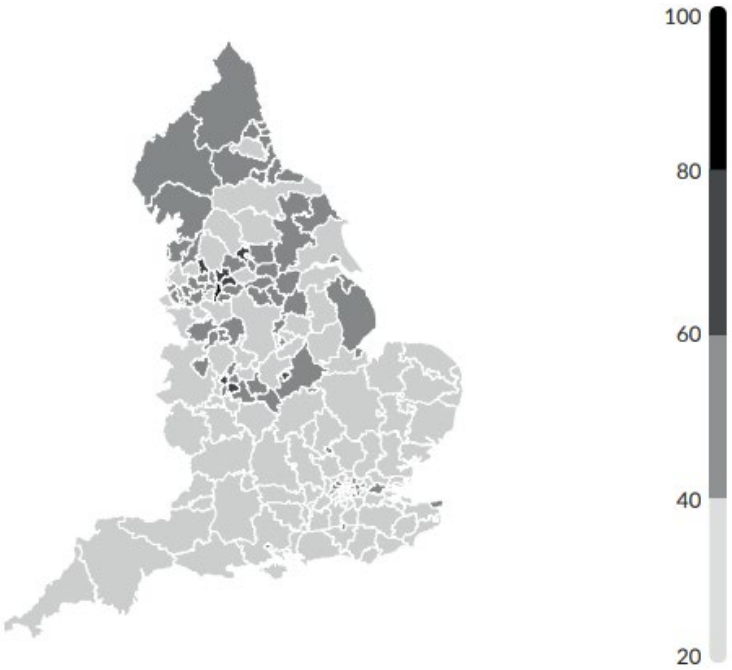


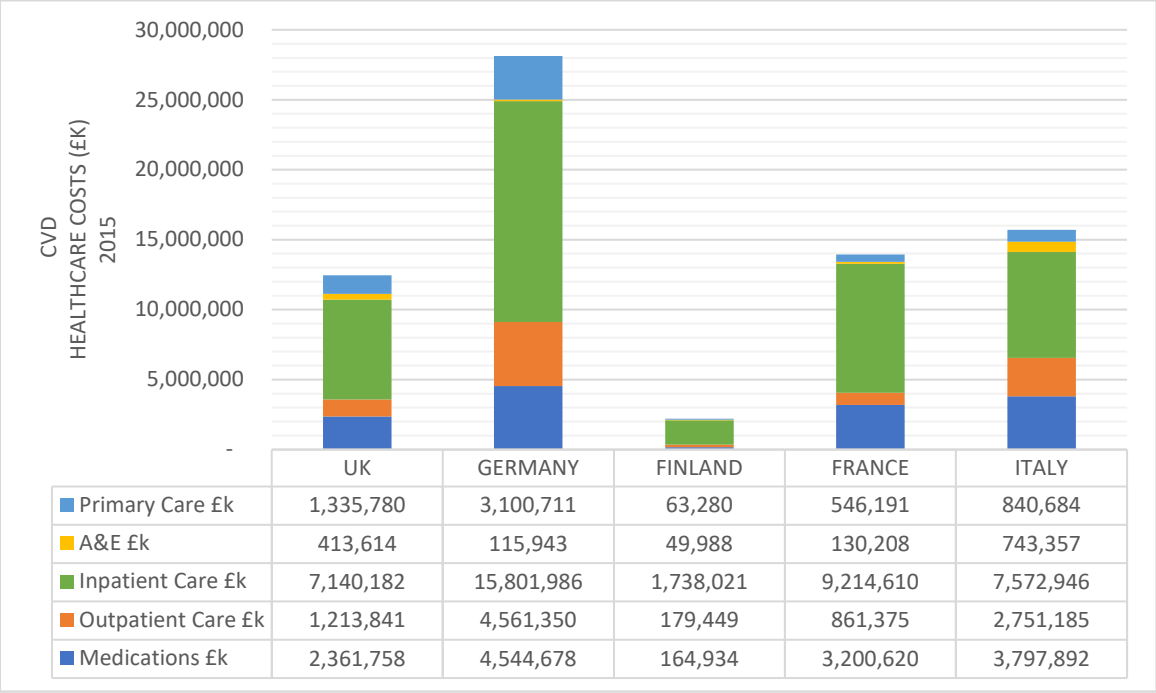
Figure 1 – Geographical variation in deaths from coronary heart disease in people under 75 in England (directly standardised rate per 100,000 people) Source: Public Health England (2016 to 2018)

The National Health Service (NHS) and the National Institute for Clinical Excellence (NICE) remain committed to the guiding principle of reducing health inequalities within the UK, which includes the support for strategies offering benefits that focus on the most disadvantaged as a way of improving population health as a whole[6].

Bringing about reductions in CVD has thus become a national priority with the potential to improve population health, reduce the cost burden to the NHS and decrease health inequalities within the UK. This is why the NHS Long Term Plan[7] (NHSLTP) identifies

cardiovascular diseases as a clinical priority and the single biggest risk area where lives can be saved in a decade.

Narrowing down and stratifying the assortment of clinical risk areas associated with CVD underpins the NHS' approach in achieving the goals laid out in the Long-Term Plan. The NHS is shifting efforts towards strategies allowing for earlier detection and treatment that have great potential at curbing serious downstream effects for those with CVD – conditions the NHS are dubbing as a patient's "ABC's", i.e., atrial fibrillation (AF), (high) blood pressure, and cholesterol (namely high cholesterol, and those with familial hypercholesterolaemia)[7]. Please reference Figure 2 below for an insight into the associated healthcare costs, estimated by the British Heart Foundation in 2015, for the management of CVD in the UK and prominent EU member countries[5]. In the UK, Healthcare costs in 2015 totalled £12.5 billion, which would be the equivalent of £14.2 billion in 2020 using Bank of England inflation rates[8].



	UK	GERMANY	FINLAND	FRANCE	ITALY
Primary Care £k	1,335,780	3,100,711	63,280	546,191	840,684
A&E £k	413,614	115,943	49,988	130,208	743,357
Inpatient Care £k	7,140,182	15,801,986	1,738,021	9,214,610	7,572,946
Outpatient Care £k	1,213,841	4,561,350	179,449	861,375	2,751,185
Medications £k	2,361,758	4,544,678	164,934	3,200,620	3,797,892

Figure 2 – Direct healthcare costs associated with the management of CVD (including stroke and coronary heart disease) in 2015 for the UK and prominent EU member nations[5]

3. Strategies for management of cardiovascular diseases in the UK

Management of cardiovascular diseases at the national level requires a concerted approach combining a population strategy, aimed to reduce the determinants of disease in the population, with an individual strategy, which seeks to identify high-risk individuals susceptible to the disease to then offer a specific treatment[9,10]. The combination of these two approaches requires the risk-stratification of individuals at the intersection; a screening strategy to identify high-risk individuals as well as diagnose individuals who suffer from a cardiovascular disease. This enables the prescription of targeted interventions and

treatments (both preventative and curative) to those individuals who are most likely to benefit (see Figure 3).

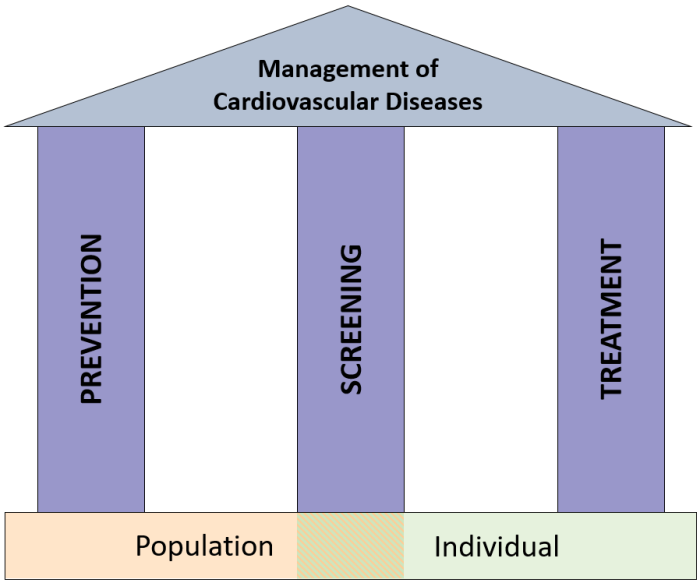


Figure 3 - Strategies for the management of cardiovascular diseases

A successful national management approach requires an interplay of all three strategies, the relative emphasis and resources spent on each depends on achievable effectiveness, cost-effectiveness, and resource considerations.

3.1 Prevention

The NICE impact report on CVD prevention published in 2018[4] identified six high-risk conditions on which to focus prevention activities[11]; high blood pressure, high cholesterol, atrial fibrillation, chronic kidney disease, high blood sugar (pre-diabetes), and diabetes. This report is due to be updated this year (2021) with more emphasis on addressing health inequalities.

Prevention of cardiovascular disease can be done at two levels; the population level by targeting the whole of the UK population and the individual level by targeting an intervention at a specific sub-group of the population deemed to be high risk.

3.1.1 Population-level approach

The NHS prevention programme outlined in The NHS Long Term Plan defines the top five risk factors associated with early mortality as high blood pressure, obesity, alcohol and drug use, smoking, and poor diet – all of which have serious implications for CVD disease[12].

Preventative interventions aimed at the population level include public health interventions, such as public health campaigns to increase exercise levels and healthy eating, and legislative interventions, such as reducing the amount of salt in processed food.

The population-based approach aims to reduce the burden of disease across the entire population by shifting the distribution of risk factors and associated CVD risk in the whole population towards an optimal distribution of CVD risk[13]. (Figure 4)

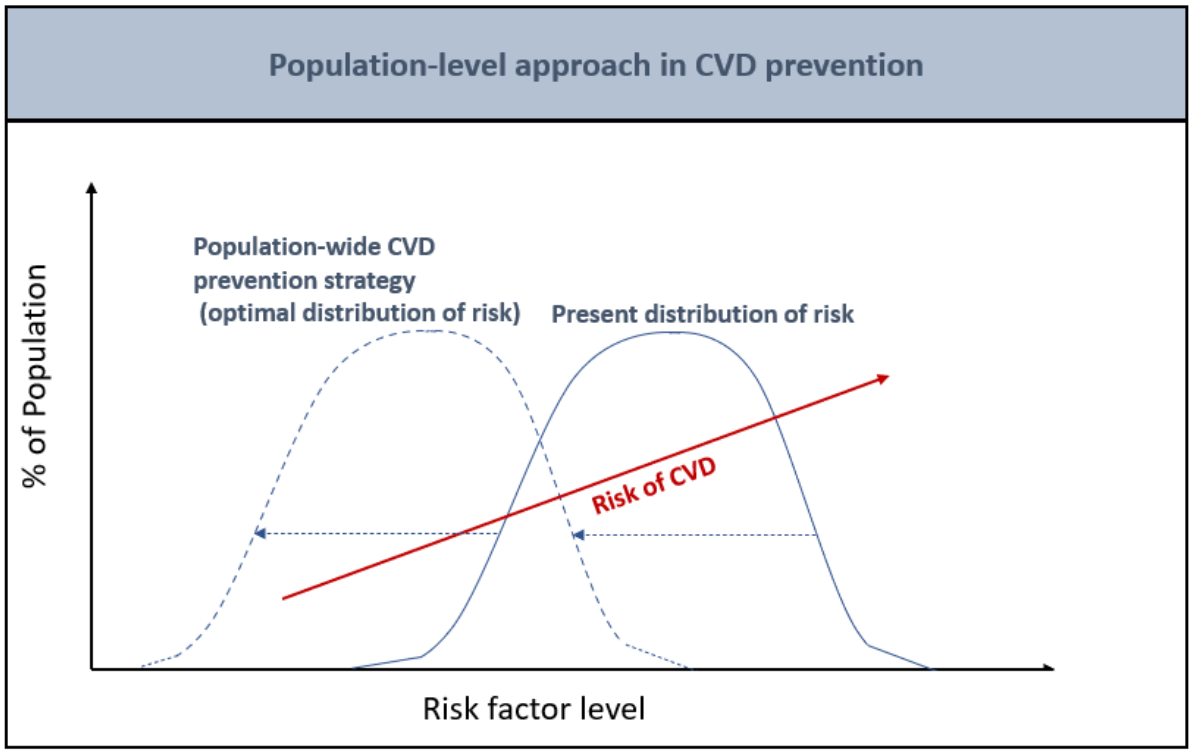


Figure 4-Population-based prevention strategy aimed at shifting the distribution of risk in the whole population

Legislative measures, such as regulation of dietary salts and fatty acids, require low levels of resource input to administer and yield high increments in improved health outcomes[14]. Public Health England (PHE) has made the reduction of salt intake a priority in a report published in 2020, which set out salt reduction targets to achieve by 2024 for retailers and manufacturers, as well as the eating out, takeaway, and delivery sector. Examples of suggested new salt targets for 2024 include a 22% reduction in breakfast cereals and a 5% reduction in all standard potato crisps[15]. Furthermore, financial incentives have been actioned for hospitals that provide healthy food options to their staff and actively hinder the promotion of high fat, salt, and sugar (HFSS) foods.

Public health interventions using mass media campaigns to bring about behaviour change show mixed results in terms of the relative benefits achieved as compared to the cost[16]. Though of enormous potential, any measure seeking to shape a change in social norms and behaviour requires a significant investment of time and money and can suffer from poor motivation from the subjects whose behaviour they seek to change. Furthermore, the time lag between exposure of the population to a particular primary prevention measure and the outcome can make it difficult to accurately measure the results achieved.

Whenever broad, population-wide measures are used in the management of conditions such as cardiovascular disease, the gains to be achieved by targeting the wider population, need to be balanced carefully against the significant cost of rolling out a national public health intervention and the opportunity cost this represents. An opportunity cost represents that which is foregone as a consequence of implementing a certain intervention; this can be measured in terms of health outcomes that may be lost as a result of displacement of activities to fund the selected intervention[17]. Population-level measures, though capable of effecting significant change in population health, tend to offer only small benefits to each individual[9]. This is known as the Prevention Paradox; "A preventive measure which brings many benefits to the population offers little to each participating individual"[1].

Successful management of cardiovascular diseases thus requires a combination of prevention measures applied at the population level with an individual approach, which specifically targets those individuals identified to be at high risk of developing a CVD.

3.1.2 Individual-level approach

This approach, also described as the "high risk" approach to prevention, is needed to protect susceptible individuals; once identified, individuals at high risk of developing CVD can be targeted to move them to a lower risk level. (Figure 5)

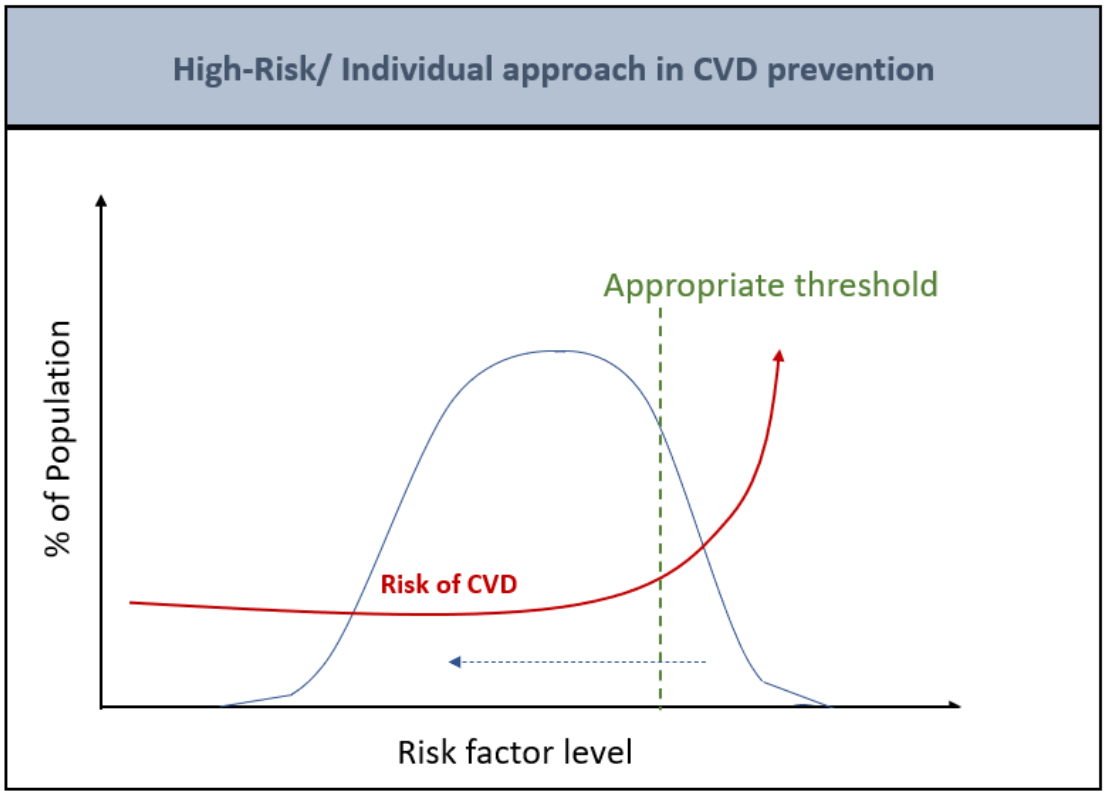


Figure 5 - Individual/High-Risk prevention strategy aimed at shifting individual risk scores from high to low

Identifying individuals deemed to be at high risk of developing cardiovascular disease to then target preventative lifestyle interventions to bring about behaviour changes and, if needed, preventative treatments, yields high rewards as the relative risk reduction achievable is much higher than for people with a lower risk profile. This approach tends to be more cost-effective as investments are targeted at individuals in worse health and thus the gains in terms of health improvements tend to be higher[18,19]. Furthermore, it allows for a preventative healthcare intervention that is appropriate to the individual, thus both subject and physician will be motivated to comply with the intervention and implement behaviour change. However, the utility of this approach is limited in cases where the impact may only be small if the individuals identified as high risk contribute little to the overall CVD burden[1].

The individual approach requires screening of individuals to establish their risk level and imposing of an appropriate threshold above which these individuals will be considered as high risk.

3.2 Screening

Systematic screening of large swathes of the population can be an expensive undertaking and tends to have disappointing cost-benefit outcomes[20]. Consequently, the approach of "opportunistic screening" tends to be taken in the identification of individuals at high risk of CVD.

Opportunistic screening tends to happen in primary care, where healthcare professionals assess patients attending primary care for another reason. General Practitioners (GPs) in the UK are encouraged to opportunistically assess patients' risk using a combination of a rudimentary software tool (QRISK®2) to assess their level of risk as well as a full formal risk assessment for those patients identified as "high risk"[21].
The act of screening itself can often result in apparent improvements in recorded health outcomes due to two phenomena: administering a scientific test to an individual can act as a powerful psychological motivator driving behaviour change in the patient[9], and earlier detection of CVD at pre-clinical stages can result in apparent improvement in survival even in the absence of changes to treatments or therapies ("lead-time bias")[22].

With the screening of sub-groups of the population and subsequent risk-stratification comes the question of what constitutes an appropriate threshold of an individual's risk at which treatment is initiated[23]. The question of where this threshold should be set is a difficult decision taken at the national level by Ministries of Health, which requires a delicate balancing of cost of interventions, resources available, clinical concerns, as well as expectations of the public[18,23]. The threshold value set needs to reflect the opportunity cost of what health improvements would be sacrificed elsewhere in the system to improve the health of the sub-group of the population identified to be at high risk of CVD.

A combination of population-wide and individual disease management strategies is required to reduce the cardiovascular disease risk distribution of the population (See Figure 6)[24,13]. Without the population strategy, CVD events will continue to occur in a large number of people who each may have a low individual level of risk. Furthermore, eliminating some of

the causes of disease by population-wide measures can cause a significant reduction in the incidence of CVD itself. Individual strategies targeted at “high risk” subjects act an expedient to help protect susceptible individuals.

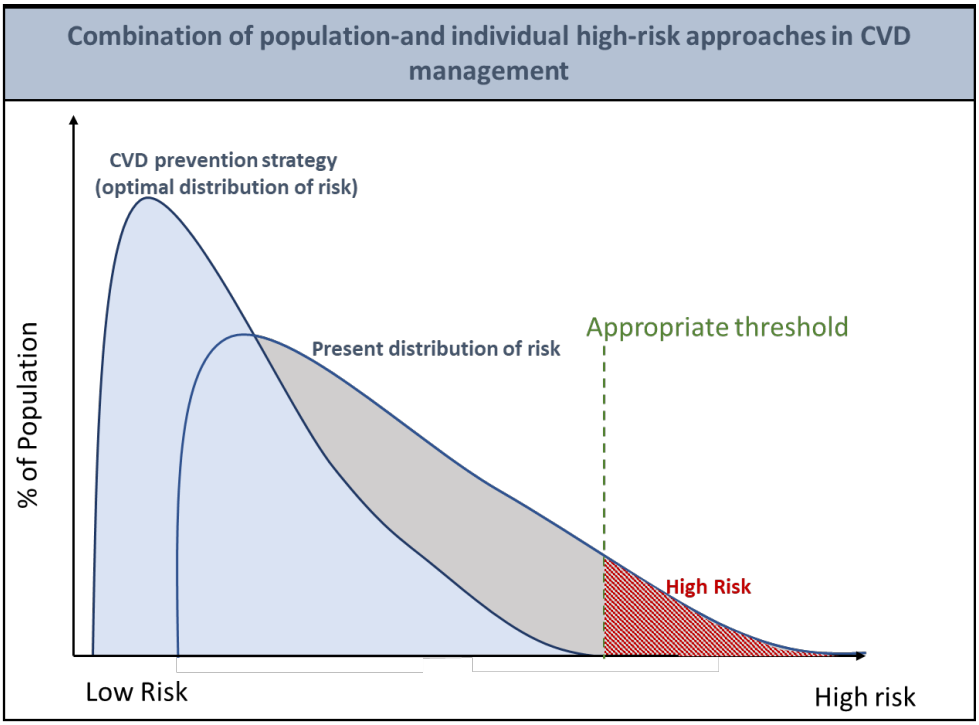


Figure 6 - Combinatorial approach of population and individual approach to managing CVD[10]

The extent to which one strategy is emphasized over the other depends on achievable effectiveness, cost-effectiveness and resource considerations[23].

Significant room for improvement exists in the harnessing of data for more accurate identification of high-risk individuals; the approach currently employed by the NHS using QRISK® presents but a blunt tool which may only identify those people who present to a healthcare professional. Total CVD risk is a result of the combined effect of a multitude of risk factors, many of which coexist and act multiplicatively. Future developments are expected in the incorporation of user-generated data such as lifestyle, cultural and geographic data together with digital biomarkers and genetic profiling to the patient data routinely collected for electronic health records and the emergence of more accurate, dynamic scales for the identification and monitoring of patient risk scores over time. The use of data provided by consumer wearables, personal devices and smart homes would allow for cost-effective screening of a wider part of the population to identify those individuals most at risk. An algorithm-based approach harnessing and combining multiple data streams to provide individual risk scores systematically will offer a dynamic way of monitoring and identifying high-risk individuals and allow to bridge the gap in the population-wide and individual prevention strategy.

3.3 Treatment

The NHS considers both detection and treatment of CVDs as management of the disease. Treatment includes the preventative administration of a clinically effective intervention to individuals identified at early, or pre-clinical stages of the disease to modify disease progression (secondary prevention), as well as the administration of interventions to limit the damage in patients with the manifest disease (tertiary prevention).

The use of pharmacological treatments such as anti-hypertensives and lipid-lowering agents as secondary prevention has been shown to be clinically effective [25,26]. However, whether providing medication to high-risk patients is cost-effective depends on the threshold of what is considered to be "high risk", and the cost of each type of medication itself. A patchwork of cost-effectiveness of treatment approaches emerges, depending on patient characteristics (age, sex, blood pressure, body-mass index (BMI), co-morbidities) and the cost of treatment[27].

Non-pharmacological treatments at the manifest stages of CVD include percutaneous coronary intervention (PCI), coronary artery bypass grafts (CABG), heart valve surgery and artificial pacemaker surgery. Though high in cost, the incremental improvements to be had for patients who have to undergo surgery for CVD can potentially be high as long as adverse events can be minimised.

As the cost of preventative and curative treatment declines, threshold values for who is considered "high risk" may well need re-adjusting to account for the lower cost of treatment, which should allow a widening of the people eligible for treatment. This happened in the UK when NICE lowered the threshold for an estimated 10-year risk of CVD from 20% to 10% or more according to the QRISK®2 assessment tool[28] . This is estimated to have benefited an additional 4.5 million people[29] and prevented 28,000 heart attacks and 16,000 strokes each year[30]. However, one must not fail to take account of the fact that, as the threshold is lowered, the overall cost to the healthcare system increases, as well as the number of adverse events which may be associated with the intervention.

Treatments for CVD tend to be more cost-effective for younger patients even at lower risk threshold as these live longer and accrue more life-years overall; therefore, they had more time to be at risk of cardiovascular events such as stroke or myocardial infarction. The events avoided from treatment, therefore, lead to larger gains in quality-adjusted life-years (QALYs), a quantitative single-index measure used to quantify health outcomes for health economic evaluations. The cost-effectiveness of CVD treatments in older patients tends to require a higher risk threshold to be applied due to a shorter life expectancy and competing risk of all-cause mortality.

This skew of the cost-effectiveness distribution towards the younger sub-set of the population motivates the pivoting approach to the management of CVD towards identifying individuals at risk earlier on and score their risk from a lifetime perspective to manage Cardiovascular Diseases in the population at an earlier stage[31].

The NHS' Long term plan for improving access to screening in primary care and genetic testing for Familial Hypercholesterolaemia (FH) shows the emphasis on the detection and management of CVD[7] at an earlier stage by combining population and individual strategies to shift the population curve towards the low-risk end of the scale (see Figure 6) and thus reduce the volume of patients who develop a manifest CVD condition (such as coronary heart disease or peripheral vascular disease) and experience a CVD event (such as stroke).

4. Opportunities for MedTech innovators

The opportunities for medical technologies lie in the prevention of the initial development of CVD as well as in the screening of the population to detect CVD at the pre-clinical stage. As healthcare systems emphasize the prevention of CVD by improving the identification of high-risk individuals and managing their long-term risks, opportunities arise for the harnessing of multiple data streams from medical and non-medical sources as well as user-generated data to generate individualised dynamic risk scales which will enable the accurate identification and monitoring of high-risk individuals by systematically targeting large swathes of the population.

However, this vision of "Big Data" to generate dynamic risk scores brings with it some ethical conundrums; should individuals with higher risk scores contribute more to the financing of the healthcare system by paying higher premiums or taxes? Misuse of this information could risk excluding some people from healthcare coverage altogether as they may be deemed "uninsurable". A disconnect is required separating clinical from economic use of healthcare data. Furthermore, sensitive data such as this is highly valuable and would need adequate encryption and data security walls for protection against data breaches and malicious programs.

Targeting "high risk" individuals with personalised lifestyle advice using digital avenues (such as applications on people's smartphones) is seen as a significant growth area with mobile health apps forecast to grow at a 17.7% compound annual growth rate (CAGR) from 2021 to 2028[32]. (Figure 7)

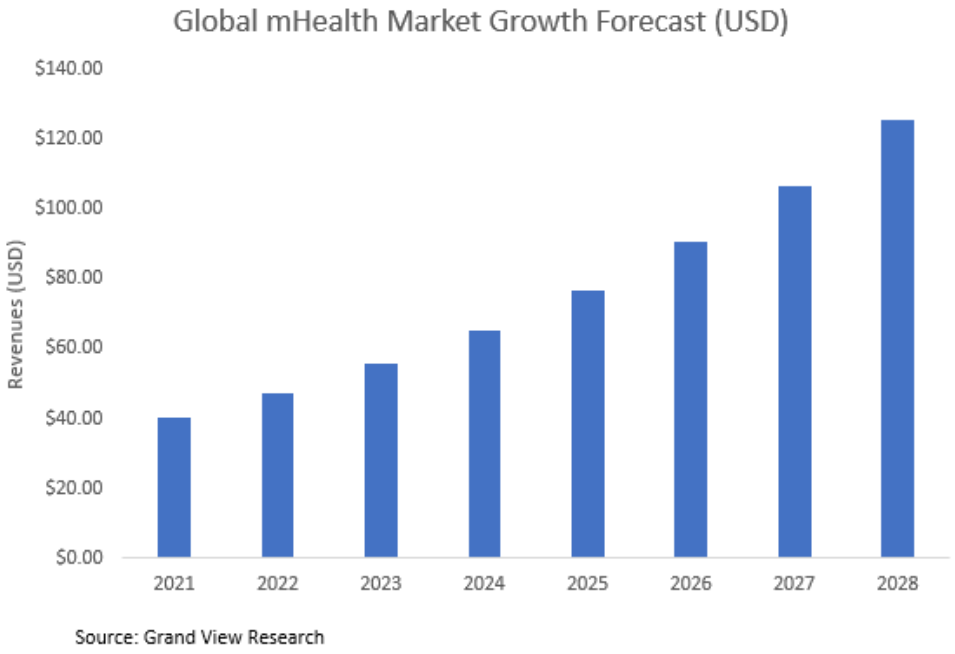


Figure 7 - Global mHealth market growth forecast according to Grand View research

In surgical treatment for CVD, the personalised 3D printing of aortic valves promises an exciting future for the way future heart surgery may be performed[33]. The use of living tissue to generate personalised grafts for CVD interventions may still be in its exploratory phase but could bring significant changes to heart surgery in the future[34].

There is an abundance of investment earmarked for CVD; for instance, of the £2.8 million in funding provided to companies by the SBRI (an NHS England backed/funded innovation scheme) for advances in CVD, £2.4 million of it has been allocated to novel medical devices, examples of which include an implantable adaptable neuronal pacer by Ceryx Medical Ltd., and imPulse, a handheld electrocardiogram (ECG) developed by Plessey Semiconductors.

The shift to digital, accelerated by the COVID-19 pandemic, presents significant opportunities for healthcare technologies that can bridge the gap between the population and individual approach by tracking cardiovascular risk over time and alerting healthcare professionals of the optimal time to start treatment. Data streams harnessed for these purposes are expected to include polygenic risk scoring, user-generated data from wearables (medical and consumer), smartphones, smart homes, as well as patient self-monitoring via at-home devices such as mobile ECG and blood-glucose monitoring (BGM).

Digital health interventions to bring about behaviour change can have a remarkable impact on reducing adverse health outcomes and reduce risk factors for CVD[35]. Before the pandemic, the elderly CVD population at the highest risk tended to have the lowest digital adoption rate[36]. However, the consecutive lock-downs of 2020 and 2021 have propelled the adoption of digital technologies amongst people aged 65 and over[37], though internet access still restricts access for some. A historical opportunity thus presents itself to deliver digital healthcare interventions to individuals by providing personalised advice based on people's

individual data profiles and risk scores with the potential to bring about lasting behaviour change and reduce CVD risk at the individual as well as the population level.

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