Atherosclerosis 251 (2016) 483–489

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Review article

Where to now in cardiovascular disease prevention☆

Osman Najam [a], Kausik K. Ray [b, *]

[a] Cardiovascular Sciences Research Centre, St George's University, Cranmer Terrace, London, SW17 0RE, United Kingdom
[b] Department of Primary Care and Public Health, The Reynolds Building, Imperial College London, St Dunstan's Road, London, W6 8RP, United Kingdom

ARTICLE INFO

Article history:
Received 12 October 2015
Received in revised form
16 May 2016
Accepted 17 June 2016
Available online 18 June 2016

Keywords:
Clinical trials
Population
Cardiometabolic risk
Registry-based randomised trials
Pharmacogenomics
Lipoprotein(a)
Triglyceride-rich lipoprotein cholesterol

ABSTRACT

Clinical trials have been instrumental in reducing the morbidity and mortality associated with cardiovascular disease, especially in the developed world. Recently however this improvement has plateaued, highlighting the importance of optimising current strategies and considering alternative practises. Inequalities in global healthcare, the changing patient profile as a result of an obesity and diabetes epidemic, and inadequate utilisation of evidence-based treatments are partly responsible. Despite pharmacotherapies such as statins having substantial evidence for cardiovascular benefit, patient response may be variable with genetic factors thought to be partly responsible. Although randomised controlled trials remain the backbone of clinical research, they have limitations including time taken to complete a trial and the financial costs associated with it. In this opinion-based paper, we discuss some of the key considerations for the future of cardiovascular disease prevention.

1. Addressing the inequalities in global healthcare

Despite advances in medical therapy, cardiovascular disease (CVD) remains the leading cause of death worldwide, with an estimated annual mortality of 18 million [1]. Significant region specific disparities however exist. Whilst CVD is the leading cause of death in high income countries, it is fourth and fifth in low income countries [1]. With escalating rates of obesity and diabetes globally, CVD is set to remain as the leading cause of death well into the latter half of this century. The growing healthcare burden of CVD continues to provide a significant challenge to healthcare systems worldwide. It has been estimated that no data on the precise cause of death is available in 89.8% of the population in sub-Saharan Africa, 48.1% in the Middle East and 24.2% in South Asia [2,3]. To date, most of the large-scale CVD prevention trials have been performed in the developed world, which form the basis of our guidelines. Therefore it surprising that 80% of all CV related deaths actually occur in low and middle income regions, and it is this patient population that has not been studied comprehensively [2,4]. The healthcare systems of developing countries already face a battle with excessive burden from communicable diseases and, maternal and child mortality. The rise in CVD has further led to a diversion of these scarce resources. Although projections of CVD burden in developing countries are worrying, there remains a great paucity of data about CVD and its risk factors from many of these regions [3]. Early identification of at-risk groups is therefore crucial, with risk prediction models potentially contributing to this decision making process. Despite the large number of algorithms developed, only a minority are eventually used in clinical practise [3]. Current models are based on data obtained from populations with differing economic and health burdens, and whether these models should be used universally is debatable. For these models to be of most clinical use, they should instead be developed from populations with similar risk profile or calibrated to the target population to help local practises. Future trials need to be conducted exploring patient populations from low and middle-income countries, where 10 million more CVD related deaths occur [2]. Availability of many interventions may be limited by financial restrictions or complexity, and in this context CV research in areas of primary prevention, clinical guidelines, health services and epidemiology is needed.

☆ Professor Ray has received honoraria (modest) for consulting and is a member of the speaker's bureaus and advisory committees from Pfizer Inc., AstraZeneca Pharmaceuticals LP, Merck Sharp & Dohme, Abbott Laboratories, Roche Therapeutics Inc., Regeneron Pharmaceuticals, Inc., Aegerion Pharmaceuticals, Inc., The Sanofi-Aventis Group, Novartis Pharmaceuticals Corporation, Novo Nordisk Inc., Eli Lilly and Co., Daiichi-Sankyo, Inc., Amgen Inc., and Bristol-Myers Squibb Co.

* Corresponding author.
E-mail address: k.ray@imperial.ac.uk (K.K. Ray).

http://dx.doi.org/10.1016/j.atherosclerosis.2016.06.036
0021-9150/

2. Improving uptake of existing therapies

Patients with established CVD remain at risk of recurrent events [5,6]. Benefit of many secondary prevention medications in reducing CV mortality, re-infarction or stroke is already well established. These evidence based preventative therapies although effective, are vastly underused globally. The WHO-PREMISE study was a cross-sectional survey of 10,000 CVD patients in three low-income and seven middle-income countries assessing secondary prevention of CVD [7]. In patients with coronary artery disease (CAD), 18.8% were noted not to receive aspirin, 51.9% did not receive beta-blockers, 60.2% did not receive ACE inhibitors and 79.2% did not receive statins. Quite alarmingly, 10% of patients with CAD were not receiving any medications. This is in comparison to European surveys that have noted better uptake. EUROASPIRE I-IV are cross sectional surveys which began in 1995–1996 to track lifestyle, risk factor control and cardioprotective drug use in Europe [8]. Although trends across the surveys have noted increased use of preventative medications, there has been a worsening of lifestyle with increased obesity and high prevalence of smoking, especially in young patients [8,9]. Despite increased use of anti-hypertensive and lipid-lowering drugs, target levels were still not being achieved. Reasons include inadequate dosing of the drug, failure to use a combination of drug therapies and poor adherence, with large variation amongst countries [8].

The larger Prospective Urban Rural Epidemiological (PURE) study was established to investigate associations between social, behavioural, genetic and environmental factors, and CVD in 17 countries [10]. Individuals with CVD from communities in countries at various stages of economic development were recruited to assess the use of proven effective secondary preventative drugs [10]. Vast differences in uptake were noted with less than 20% of patients in low-income countries using any blood pressure lowering agent, compared to 75% in high-income regions [10]. Of additional concern was that only 3% were on statin therapy, with a 20-fold difference between low-income and high-income countries despite the well-established benefits and low costs [11]. Even the use of aspirin varied by seven-fold. 80% of those at risk in these developing regions did not receive any treatment at all, compared to 11% in developed countries. These wide-ranging inequalities in healthcare underline the urgency of improving the availability and uptake of these inexpensive treatments. Although the reason for the poor uptake of these evidence-based therapies is unclear, it may include unaffordability of the drug or of visiting a practitioner, limited drug availability in low and middle-income countries, transportation difficulties, absence of a national healthcare preventative programme and lack of awareness of the importance of lifelong therapy [10,12–14]. Prospective multi-national studies are needed to explore this with qualitative research and surveys, and assessment of existing national and community databases. Many of the evidence-based therapies, such as statins are affordable and readily available. An increase in global exposure to those with unmet needs would have a greater absolute risk reduction in CVD than any new treatment, which may be expensive and available to a select few.

3. Absolute risk is what really counts

Whilst the projected increase in CVD prevalence is alarming, it need not become a reality [15]. CVD is preventable. Absolute CVD risk is the probability of a CV event occurring within a defined time period [16]. It is dependent on a combination of modifiable risk factors such as smoking, blood pressure, lipid levels, and non-modifiable risk factors such as age, gender and family history [16]. The cumulative effects of these are synergistic and more accurate in predicting absolute risk than any individual risk factor alone [17]. For trial results to be of most clinical use, the level of global risk needs to be taken into account. Five and ten year risk estimates have been adopted in recent guidelines [18,19]. It would be reasonable to expect a CVD prevention strategy based on estimated absolute lifetime risk (including the total number of events and not just the first event) to be a more effective and efficient use of resources, rather than the traditional method of identifying and managing individual risk factors. Despite the prognostic value of using cardiometabolic risk prediction, it is yet to be widely utilised in trials for patient selection. Trial population selection is usually rigid and often does not directly translate into a real-life clinical setting. With escalating cardiometabolic risk in low to middle income countries, this is clearly relevant. Absolute risk may vary by more than 20-fold in patients with the same blood pressure or cholesterol levels [20,21]. Post hoc analysis of the Treating to New Targets (TNT) study demonstrated increased CV risk with features of metabolic syndrome. Patients with one to two features of metabolic syndrome receiving a potent dose of atorvastatin had a residual CV risk of 5–18%, whilst those with all five features had a residual risk of 32% [22]. This emphasises the limitations of categorising patients as simply having hypertension or hypercholesterolemia. Therefore an individual with low cholesterol or blood pressure may in fact have higher absolute CV risk than someone with a high level of one of these risk factors. In clinical practise, accurate risk assessment is vital to effective clinical management. Whilst the Framingham Risk Score is one of the most validated and widely used predictive scores, other multivariable risk models have also been developed in an attempt to improve prediction of major clinic outcomes [23].

Whilst scores such as ASSIGN, Reynolds Risk Score, PROCAM Risk Score and QRISK all have advantages and disadvantages, not one model can be used universally and this is reflected in different recommendations across nations [24–26]. Analysis of relative prognostic performance has shown inconsistencies across studies with potential biases and methodological variation making direct comparisons difficult [24]. Although randomised controlled trials comparing different predictive models would be ideal in assessing their clinical effectiveness, in reality this may prove difficult due to costs and complexity. Whilst comparing models, future studies should attempt to standardise performance measures such as discrimination and calibration and perform consistent statistical analysis. Head to head comparisons are needed to further our understanding. The performance of a risk prediction model is dependent on its population characteristics and although ideally developed locally, they should at least be validated in their local populations [17]. With improvements in information technologies and medical record keeping, it may be possible to obtain data on risk factor and disease event to allow development of scores appropriate for a specific population [17,27]. With our increased understanding of CVD, physicians should move away from treating individual risk factors and instead focus on absolute risk.

4. Utilisation of cardiac imaging

Advances in imaging have provided a range of diagnostic tools to identify high-risk atherosclerotic coronary plaques. When combined with conventional screening measures such as lipid and non-lipid variables, CVD risk assessment algorithms and clinical judgement, the likelihood of identifying individuals deemed to be at higher risk of future clinical events is increased [28]. In trials however, use of traditional and emerging atherosclerosis imaging platforms to select patients is largely limited. This is partly due to the complexities of recruiting large number of patients and having appropriate resources to allow these imaging facilities to be