International Journal of Cardiology 201 S1 (2015) S1–S7

Contents lists available at ScienceDirect

International Journal of Cardiology

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

Global burden of CVD: focus on secondary prevention of cardiovascular disease

Sameer Bansilal[a,b], José M. Castellano[a,b,c], Valentín Fuster[a,b,*]

[a] Mount Sinai Cardiovascular Institute, New York, USA
[b] Centro Nacional de Investigaciones Cardiovasculares (CNIC) Carlos III, Madrid, Spain
[c] HM Hospitales, Hospital Universitario Monteprícipe, Madrid, Spain

KEYWORDS

Global cardiovascular disease
Secondary prevention
Therapeutic adherence
Accessibility to drugs

ABSTRACT

Despite encouraging advances in prevention and treatment of atherothrombosis, cardiovascular disease (CVD) remains a major cause of deaths and disability worldwide and will continue to grow mainly due to the increase in incidence in low and middle income countries (LMIC). In Europe and the United States of America (USA), coronary heart disease (CHD) mortality rates have decreased since the mid-1990s due to improvements in acute care, however the prevalence of CHD is increasing largely in part due to the overall aging of the population, increased prevalence of cardiovascular (CV) risk factors, and improved survival of patients after a CV event. Data from clinical trials has consistently proven the efficacy of pharmacologic interventions with aspirin, statins, and blood pressure (BP)-lowering agents in reducing the risk of CV events and total mortality in the ever growing pool of patients in secondary prevention. However, large gaps between indicated therapy and prescribed medication can be observed worldwide, with very low rates of use of effective therapies in LMIC countries. Adherence to medication is very poor in chronic patients, especially those treated with multiple pharmacologic agents, and has been directly correlated to a greater incidence of recurrent CV events and increase in direct and indirect healthcare costs. In this article, we review the global burden of CV disease, status of secondary prevention therapy and major barriers for treatment adherence.

The global cardiovascular disease pandemic, current status and future projections

Despite encouraging advances in our knowledge of the prevention, diagnosis and treatment of atherothrombosis, cardiovascular disease (CVD) remains a major cause of disability and premature death throughout the world [1]. Globally an estimated 16.7 million deaths in the year 2010 were attributed to CVD; with projections showing a staggering 23.3 million by 2030. CVD mortality rates are considered equivalent to the combined number of deaths due to nutritional deficiencies, infectious diseases, and maternal and perinatal conditions [2]. This massive growth of CVD during the last decade is mainly due to the increasing incidence in low-and middle-income countries (LMICs) [2]. In 2012, the Developed and Caucasus and Central Asia regions had the highest CVD death rates in the world (>400 deaths per 100,000 population, in both genders). Lowest CVD death rates were estimated for the Oceania region (85 deaths per 100,000 population, in both genders) [3] (Fig. 1).

CVDs (including coronary heart disease (CHD), stroke and other CVD) cause more than 4 million deaths each year in the 53 countries of the World Health Organization (WHO) European Region and over 1.9 million deaths in the European Union (EU) countries [4]. Data from the Organisation for Economic Co-operation and Development (OECD) show that in 2010, coronary heart disease (CHD) alone was responsible for 13% of all deaths in EU member states. However, mortality from CHD varies considerably being generally higher in the countries of the former communist bloc. Rates are also relatively high in Finland and Malta, being several times higher than in France, Portugal, the Netherlands and Spain. Rates are generally lower in the southern countries, frequently considered to be a consequence of the Mediterranean diet. In all countries, death rates for CHD are higher for men than women in 2012 [4] (Fig. 2).

Since the mid-1990s, CHD mortality rates have declined in most European countries. Declining tobacco consumption contributed significantly to reducing mortality rates but improvements in medical care have also played a part. A recent study compared short-term outcomes in patients with acute myocardial infarction (MI) in the United Kingdom (UK) and Sweden. Unadjusted 30-day mortality was more than a third higher in the UK (10.5% [95% CI: 10.4–10.6]) than in Sweden (7.6% [95% CI: 7.4–7.7]) in 2004–2010. The authors suggest that the difference is mostly due to the more rapid adoption of new technologies and recommendations for practice in Sweden than in the UK despite similar spending on acute MI in both countries [5]. In the United States of America (USA), CHD alone caused 375,295 deaths. Each year an estimated 635,000 Americans have a new coronary attack (defined as first hospitalized MI or CHD death) [6].

* Corresponding author at: Mount Sinai Heart. One Gustave L. Levy Place, Box 1030 New York City, NY 10029. Tel.: +1212.241.3852; fax: +1212.423.9488.
E-mail address: valentin.fuster@mountsinai.org (V. Fuster).

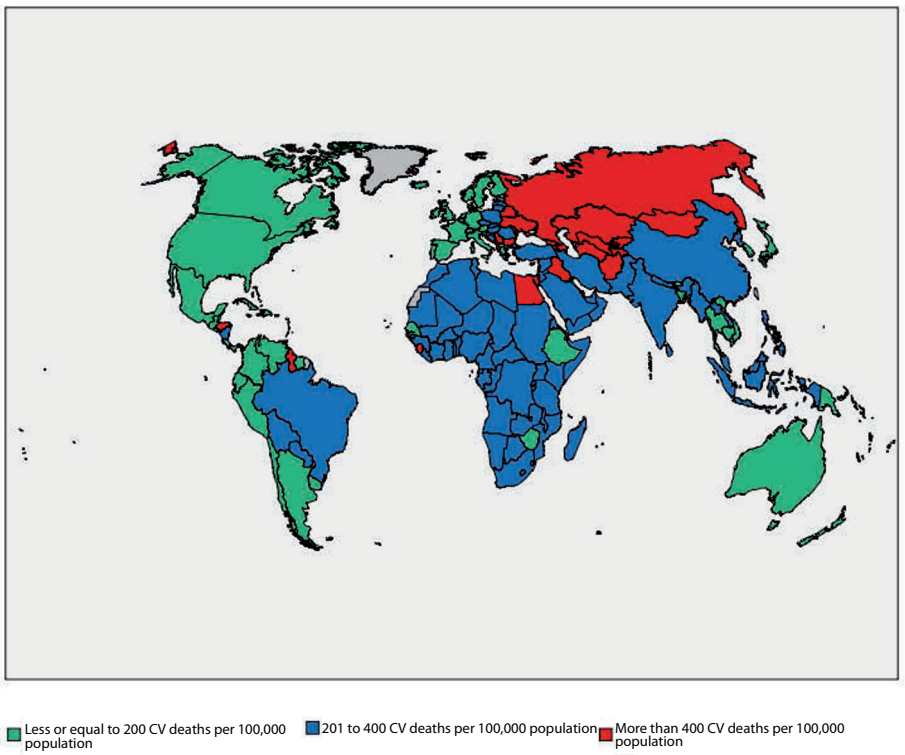

Fig. 1. CV death rates per 100,000 population (age-standardized rates), the World Health Organization 2012 [3].

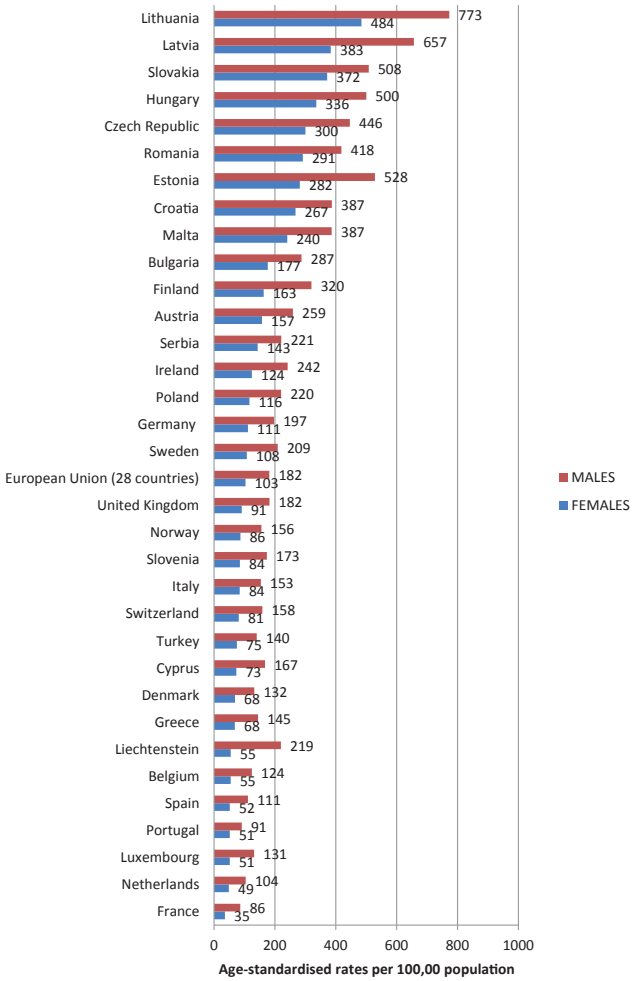

Fig. 2. Ischaemic heart disease mortality rates 2012 (or nearest year) from the Eurostat Statistics Database [60].

Several studies in Europe have demonstrated that due to stabilisation of the incidence of MI and the case-fatality decrease, the prevalence of CHD is increasing. Recurrent CVD events are common in people who have already had a MI. Various studies have found a recurrence rate of close to 50% for any CVD event [7,8] or for subsequent revascularisation [9] in the year after an MI, and up to 75% of patients have a recurrent event within 3 years [8,10] (Fig. 3). A recent report from Denmark showed increasing prevalence of CHD associated with a decline in mortality and ageing of the population. The number of prevalent cases of CHD in Denmark increased from 125,000 in 2000 to 150,000 in 2009 and the number of people having survived an acute MI increased from 67,000 to 72,000. This study showed that about 3% of the Danish population has CHD [11]. A recent study sought to characterise the incidence for first and recurrent acute MI in England in 2010 by means of a population based national-linked database study. Overall, the annual age-standardised event rate of all acute MI (first and recurrent) per 100,000 was 174 (95% CI: 173–176) in men and 73.7 (95% CI: 72.9–74.5) in women. Of all the events that occurred: 83% were first acute MIs and 13% were re-infarctions. One-third (32%) of all acute MIs were fatal, with about two-thirds of deaths being sudden acute MI deaths. Similar proportions of all events were first and recurrent acute MI deaths (23% and 21%, respectively) [12]. In the USA, an estimated 300,000 have a recurrent attack [6]. In addition, 17.1% of acute MI were followed by a readmission within 30 days in 2009. For 1.6% of the index admissions the reason for readmission was a new MI, while for 2.0% the reason was a scheduled revascularization, for 2.3% it was heart failure or shock and the remaining 11.2% of index admissions were readmitted for other conditions and procedures [10].

As short-term survival in acute MI hospitalised patients improves, it becomes more important to understand the implications for longer-term prognosis, both with respect to survival and the risk of recurrence [13]. Factors associated with higher risk of recurrence include: older age, socioeconomic status, no revascularization procedures, presence of co-

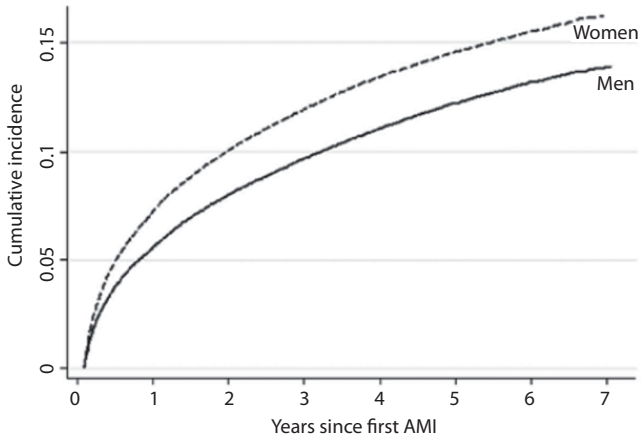

Fig. 3. Risk of a second acute myocardial infarction (AMI) over 7 years among 30-day survivors of first acute MI by gender, 2004 to 2010, England [13].

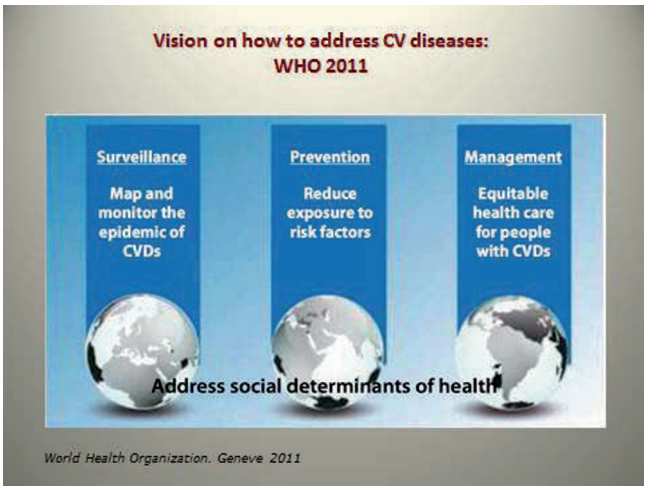

Fig. 4. Vision on how to address cardiovascular disease (CVD): World Health Organization 2011 [1].

morbidities, and lack of adherence to secondary prevention medication [12]. Both clinical care and secondary prevention are important in improving the long-term outcome of hospitalized patients with acute MI.

Current status of secondary prevention, accessibility and adherence to cardiovascular drugs

According to a WHO report, effective reduction of CV mortality should be based on three key points: surveillance (mapping and monitoring the epidemic of CVDs), prevention (reducing exposure to risk factors) and management (equitable health care for people with CVD) [14] (Fig. 4).

Overwhelming data from clinical trials show that pharmacologic interventions with aspirin, statins, and BP (BP)-lowering agents considerably reduce the risk of vascular events and total mortality [15–17]. Current European Cardiovascular Prevention Guidelines in patients with established coronary artery disease recommend the use of antiplatelet therapy, lipid-lowering agents when low-density lipoprotein (LDL) cholesterol ≥2.5 mmol/L, a beta-blocker, and additional BP-lowering agents in the case of a systolic BP ≥140 mm Hg, unless contraindicated [18,19]. The American Heart Association and the American College of Cardiology Foundation (AHA/ACCF) Guidelines promote the standard use of cholesterol-and BP-lowering agents, regardless of the initial levels of LDL cholesterol or BP in patients with established vascular disease [20,21].

In clinical practice, a substantial proportion of CHD patients should be treated with aspirin, a statin, and BP-lowering agents as a result of tailored and/or step-up therapy. However, large gaps between indicated therapy and prescribed medication can be observed worldwide, with very low rates of use of effective therapies in LMICs countries [22,23]. In the secondary prevention setting in high-income countries, around 60% of patients are prescribed anti-platelet therapy, 50% beta-blockers, 40% angiotensin converting enzyme inhibitor (ACEI) or angiotensin-receptor blocker (ARB) and almost 70% statins [23]. An analysis of data from the Antiplatelet Treatment Observational Registry (APTOR) in 14 European countries showed that only 43% of patients who had an acute coronary syndrome (ACS) event between 2007-2009 were receiving optimal secondary prevention (defined as use of aspirin and clopidogrel as well as three or more of the following post-discharge medications: statins, beta-blockers, ARB/ACEI, exercise or diet) at baseline and 1-year post-discharge. There was considerable variation by country in prescription of optimal therapy with highest rates reported for Austria/Hungary and lowest rates for the Czech Republic [24] (Fig. 5). The results of a prospective epidemiological registry conducted in Europe showed that the overall use of combination therapy with aspirin, statin, and ≥1 BP-lowering agent increased substantially from 9% in 1996 to 66% in 2009. Except for CHD, the trend to use combination therapy addressed to different risk factors increases very slowly and that means that there are still a high proportion of high risk patients not achieving a complete protection [25]. In the USA, Muntner et al. estimated that among patients with a history of CV disease, only 44.5% received aspirin, 87.8% received antihypertensive medication, and 64.6% received statins [26]. The WHO study on Prevention of Recurrences of Myocardial Infarction and StrokE (WHO-PREMISE) study found that in some LMICs fewer than 40% of acute MI patients received ACEIs, and only 20% received statins [27]. The Prospective Urban Rural Epidemiological (PURE) study of individuals from rural and urban communities in countries at various stages of economic development aged 35–70 years confirmed that adherence with drugs for secondary prevention in patients with CVD was generally low and worst in the low income countries; with over 80% receiving none of the effective drug treatments in South Asia [23].

Another fact that might affect the therapy of patients with CVD is the accessibility to medication, which is highly different among the different regions and countries of the world. In the EU, although there are differences between countries in relationship to healthcare systems the availability of drugs is very high compared to the LMICs. Cameron et al. assessed the availability of a basket of 15 medicines in the public and private sectors of 36 LMICs. Overall, generic medicines were not adequately available in both the public and private sectors (median availability of 38% and 64%, respectively) [29]. An analysis performed by Commonwealth Fund survey revealed that in the USA, particularly the relatively young and healthy, are more likely to use prescription drugs than are the residents of Australia, Canada, Germany, the Netherlands, New Zealand, and the UK, but they also experience more financial barriers in accessing medications and spend more out-of-pocket for prescriptions. In the USA, there are also larger income-related inequities in pharmaceutical use [28].

Low adherence: prevalence, causes and burden of disease of non-adherence

On the other hand, adherence to prescribed medication – the extent to which patients take their medications as prescribed –

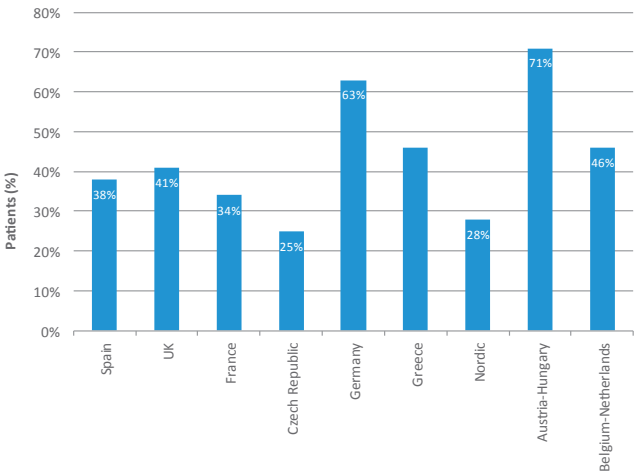

Fig. 5. Use of optimal therapy by country cluster after hospital discharge [24].

is generally poor for all diseases but especially poor for chronic conditions requiring long-term drug treatment such as CVD [29,30]. A systematic review of studies in adherence among patients with CVD showed that overall adherence was 57% over a median of 24 months [31]. In a systematic review and meta-analysis of 44 unique prospective studies (cohort, nested case–control, or clinical trial) comprising 1,978,919 non-overlapping participants at high CV risk, showed that 60% of included participants had good adherence (adherence ≥80%) to CV medications [32].

WHO has categorized potential barriers for medication non-adherence into five groups, including patient, condition, treatment, socioeconomic, and health system related factors [33,34]. The most common barriers for medication non-adherence have been the focus of numerous investigations of adherence [35,36]. The cross-sectional Phase 1 of the FOCUS (Fixed-Dose Combination Drug for Secondary Cardiovascular Prevention) study showed that the risk of being non-adherent was associated with younger age, depression, being on a complex medication regimen, poorer health insurance coverage, and a lower level of social support [37]. The concern about medication side effects and patient's lack of confidence in the benefit of treatment all play a role in the lack of adherence. Poor provider-patient relationship and difficulties accessing physicians or pharmacies are, among other, relevant socioeconomic factors [38]. Choudhry et al. conducted a retrospective study in a cohort of lower income post-MI retired patients in the USA. Results showed that only 38.6% of patients receiving a statin after discharge were fully adherent [39]. Finally, Akincigil et al. examined the duration of CV treatment within 24 months after a MI. 7% of patients receiving ACEI prescription discontinued treatment within 1 month, 22% at 6 months, 32% at 1 year and 50% at 2 years [40]. Finally, suboptimal medication adherence is associated with racial/ethnic minority groups. Ens et al. literature review examining factors contributing non-adherence to CV medications in South Asian´s (India and Pakistan) showed that medication side-effects, cost, forgetfulness and higher frequency of dosing contributed to non-adherence. South Asian immigrants also faced language barriers, which contributed to non-adherence [41].

Many studies have evaluated the effect of adherence with prescribed medications on outcomes in patients with existing CVD who need secondary prevention therapy [42–44]. These studies show that good adherence (generally defined as >80% adherence) to the combined therapy with aspirin, ACEI, beta-blockers and statins is associated with improved outcomes (reduction in CV events, all-cause mortality or CVD mortality, and reduced medical or pharmacy costs) [42–44]. So, in the previously cited systematic review and meta-analysis conducted by Chowduhry et al. of participants at high CV risk (≥18 years old), risk estimates of CVD (defined as any fatal or non-fatal CHD, stroke or sudden cardiac death) and/or all-cause mortality (defined as mortality from any cause) outcomes were reported. Overall, 60% (95% CI: 52–68%) of included participants had good adherence (adherence ≥80%) to CV medications. The relative risk reduction (RRR) of any CV disease in the adherent patients was of a 20% when compared to patients with poor adherence (RR 0.80 [95% CI: 0.77–0.84]) Corresponding RRR in all-cause mortality was of a 38% in good vs. poor adherers (RR 0.62 [95% CI: 0.57–0.67]. These associations remained consistent across subgroups representing different study characteristics. According to these results, a considerable proportion of all CVD events (approximately a 9% in Europe) could be attributed to poor adherence to vascular medications alone [32]. In the USA, Newby et al analyzed the use of evidence based therapies during the period from 1995 to 2002 for patients with documented CHD in the Duke Databank for Cardiovascular Disease. They showed that consistent use of CV medication in patients with CHD was associated with statistically significant lower adjusted mortality [45].

The burden of acute coronary syndromes (ACS) to healthcare services in five European countries (UK, France, Germany, Italy and Spain) was determined including medications prescribed, intervention rates and hospital utilisation as well as health outcomes during the first year following a diagnosis of ACS. All costs were reported in 2004 Euros. Overall, the major contributors to total costs were hospital stay and revascularisation procedures. The total cost of ACS was estimated to be €1.9 billion in the UK, €1.3 billion in France, €3.3 billion in Germany, €3.1 billion in Italy and €1.0 billion in Spain. The cost per ACS patient ranged from €7,009 in the UK to €12,086 in Italy [46]. The results of a systematic review studying the impact of medication adherence on CHD costs and outcomes found that the annual cost of treating an adherent compared to a non-adherent patient was significantly different ($4,040 versus $4,940 respectively, $p<0.01$) [47]. A systematic review concluded that the overall costs of care are lower in patients who are adherent to secondary prevention, although medication costs are higher in adherent patients than those who do not take their prescribed medications [47]. Finally, out-of-pocket payments for the treatment of CV diseases lead to significant costs for households in LMICs. Up to 71% of patients who had an acute stroke were found to face catastrophic health expenditure in China, and 37% of them fell below the poverty line (1 USD per day) after paying for healthcare bills [48]. This evidence shows the potential of strategies that increase adherence to cut direct healthcare costs.

Strategies to improve adherence to medications: an integrated approach

Different disease specific, patient, provider and health system barriers have already been identified as key players to be addressed in order to increase adherence across populations [38,49]. Measures to enhance adherence to help maximize the potentials of effective cardiac therapies in the clinical setting are urgently required. This is reflected in the ESC Cardiovascular prevention Guidelines, where adherence assessment in secondary prevention is a Class 1A recommendation stating that physicians must assess adherence to medication, and identify reasons for non-adherence in order to tailor further interventions to fulfill the individual needs of the patient or person at risk [19].

Patient-targeted strategies

Strategies to address therapy-related barriers to medication adherence in patients with CV disease have primarily focused on reducing the complexity of the prescribed medical regimen. Polypharmacy is a potentially modifiable and important component of adherence to medical therapy for patients with chronic conditions. Different ad-hoc tools such as electronic medication aid caps have been developed to be delivered directly to the patient to enhance use of CV medications as prescribed. In addition, technology based strategies such as cutting edge-technology in pill bottles which communicate with a health-coach [50] are being studied at this time. As a matter of fact, the Randomized Evaluation to Measure Improvements in Non-adherence from Low-Cost Devices (REMIND) trial is currently evaluating the impact on medication adherence of three different pill-box devices [51]. Data showing the efficiency of these approaches is still lacking. Another novel strategy that attempts to address the adherence issue is the use of a CV polypill as evidence suggests that reducing dosage demands is the most effective single approach to enhancing medication adherence [19]. Including the key medications necessary to reduce CV risk into a single, once daily dose pill improves treatment adherence, and could reduce CV events, hospitalizations and therefore lower costs [52,53]. The Heart Outcomes Prevention Evaluation (HOPE-4) trial [34] and the Secondary prevention of CardiovascUlaR disease in the Elderly (SECURE) trial are large CV outcomes-based randomized controlled trials testing the polypill concept.

Provider-targeted strategies

Strategies aimed at improving patient´s knowledge towards CV disease and use of medication as prescribed have increasingly focused on the role of highly labor intensive multidisciplinary care teams. These programs involve, between others, strategies such as individual counseling, medication education, pharmacy post-discharge programs and visiting nurse or nurse-practitioner based services. Berben et al. evaluated which strategies CV nurses and allied health professional utilize to enhance medication adherence. Results showed that educational interventions were the most frequently used tools. As a matter of fact, participants reported using a higher proportion of educational/cognitive interventions (36%) than counseling/behavioral (32%) or psychological/effective interventions (23%). Reading materials about CV care was the most used adherence-enhancing specific intervention, with 66% of respondents using it frequently. Only the half of the participants (48%) reported that they frequently trained patients on how to properly take their medications as prescribed during their inpatient recovery [54]. Nieuwkerk et al. examined the effect of nurse-led counseling program regarding CV risk on adherence to statins. Patients taking statins for either primary or secondary prevention of CV disease were randomized to routine care or to the intervention arm. The intervention consisted of nurse-led individualized counseling regarding CV risk and subsequent regular visits to assess the degree of control of dyslipidemia and other CV risk factors. At the completion of the trial, self-reported adherence to statins was significantly higher in the intervention arm as compared to those who received routine care (100% vs. 95%; $p<0.05$) [55]. The addition of a clinical pharmacist to monitor patients with CVD can lead to an improvement in CVD patients in many areas, including patient improvement of adherence medications and preventing potential drug-related problems. Hohmann et al evaluated the adherence to hospital discharge medication in patients with ischemic stroke before and after implementing a program provided by a clinical pharmacist. In the intervention group, the clinical pharmacist listed the medication at discharge and gave detailed information for all medication changes during hospital stay. Significant differences between the control group and intervention group were established with regard to adherence to both antithrombotic medications (83.8% control group vs. 91.9% intervention group, $p=0.033$) and to statin therapy (69.8% control group vs. 87.7% intervention group; $p<0.001$) [56]. None of these studies mentioned before reported economic outcomes.

Health system-targeted strategies

Medication non-adherence is increasingly recognized to be associated with socioeconomic adversity. Factors such as poverty and in particular food insufficiency and hunger [57], and unstable housing [58] have been associated with medication non-adherence in other chronic conditions such as human immunodeficiency virus and acquired immune deficiency syndrome (HIV/AIDS). In relation to CVD, low socioeconomic status has been found to be associated with low adherence in a number of different environments. Pharmacy benefit programs have a direct influence on adherence to medicines. Higher copays and restricted benefits lead to a reduction in use of medicines as prescribed. The Rand study performed in the USA found that doubling copays for commonly used drug classes reduced adherence by 25% to 45% [57].

Strategies may be more effective if they: 1) are designed for specific groups; 2) take into account behavioral patterns; and 3) are based on evidence-based specific tools or programs. Multifaced strategies simultaneously directed at patients, physicians/practices, and healthcare or social systems targeting physician prescribing behavior as well as interventions to reduce social, financial and treatment-related barriers to enable patients to adhere to prescribed therapy have been found to be most effective in low income groups. Moreover, complex multifactorial strategies, addressing different barriers have been mostly assessed without previous evaluation of their individual components [59]. Individual interventions such as simplifying dosage regimens and fixed combination pills appear to be the most effective tool. The European Guidelines on CVD prevention recommend all the physicians to reduce dosage demands of their patients to the lowest feasible level and additionally, to provide clear advice regarding the benefits and possible adverse effects of the medication as well as of the duration and timing of dosing. It is recommended to consider patients' habits and preferences and to ask patients in a non-judgmental way how the medication works for them, discussing possible reasons for non-adherence (e.g. side effects, worries). After the assessment of adherence it is important to implement repetitive monitoring and feedback, offering multisession or combined behavioral interventions in the case of persistent non-adherence through physicians assistants and/or trained nurses [19].

Conclusion

It is clear that the current CVD pandemic calls for a revision of the way we implement healthcare worldwide, as well as new simple, efficacious and efficient strategies to contain the growth of the disease worldwide.

The scenario in LMIC is especially worrisome, as many regions suffer what has been called the double burden of disease (that is, developing regions where communicable diseases are highly prevalent are also suffering the health toll from chronic, non-communicable diseases). In high income countries the higher survival rate after a CV event, the aging of the population and the increase in prevalence of CV risk factors has increased the

cost of treating CVD to a degree that will not be sustainable even in the wealthiest economies. Even in high income European countries where medication accessibility is guaranteed the efficacy of proven treatments is severely hampered due to poor adherence rates to pharmacologic therapy (consistently shown to be about 45–60% in secondary prevention). Hence, interventions toward improving adherence rates could have a far greater impact on public health than any individual treatment. Barriers to medication adherence might be surpassed through programs delivered through the healthcare system, through multidisciplinary care teams or directly by the patient by reducing the dosage demands which could include the intake of CV polypills. Hence, from a public health perspective, it is of highest importance implement existing and innovative strategies to achieve adequate adherence to secondary CV prevention medication in order to ensure efficacy of treatment.

Conflict of Interest Statement

Nothing to declare.

References

[1] Writing C, Smith SC, Jr., Collins A, Ferrari R, Holmes DR, Jr., Logstrup S, McGhie DV, Ralston J, Sacco RL, Stam H, Taubert K, Wood DA and Zoghbi WA. Our time: a call to save preventable death from cardiovascular disease (heart disease and stroke). Glob Heart. 2012;7:297-305.

[2] Organization WH and UNAIDS. Prevention of cardiovascular disease: World Health Organization; 2007.

[3] WHO. WHO. Data and statistics.

[4] Nichols M, Townsend N, Scarborough P and Rayner M. Cardiovascular disease in Europe: epidemiological update. Eur Heart J. 2013;34:3028-34.

[5] Chung SC, Gedeborg R, Nicholas O, James S, Jeppsson A, Wolfe C, Heuschmann P, Wallentin L, Deanfield J, Timmis A, Jernberg T and Hemingway H. Acute myocardial infarction: a comparison of short-term survival in national outcome registries in Sweden and the UK. Lancet. 2014;383:1305-12.

[6] Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, de Ferranti S, Despres JP, Fullerton HJ, Howard VJ, Huffman MD, Judd SE, Kissela BM, Lackland DT, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Matchar DB, McGuire DK, Mohler ER, 3rd, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Willey JZ, Woo D, Yeh RW, Turner MB, American Heart Association Statistics C and Stroke Statistics S. Heart disease and stroke statistics--2015 update: a report from the American Heart Association. Circulation. 2015;131:e29-322.

[7] Tuppin P, Neumann A, Danchin N, Weill A, Ricordeau P, de Peretti C and Allemand H. Combined secondary prevention after hospitalization for myocardial infarction in France: analysis from a large administrative database. Arch Cardiovasc Dis. 2009;102:279-92.

[8] Andres E, Cordero A, Magan P, Alegria E, Leon M, Luengo E, Botaya RM, Garcia Ortiz L and Casasnovas JA. Long-term mortality and hospital readmission after acute myocardial infarction: an eight-year follow-up study. Rev Esp Cardiol (Engl Ed). 2012;65:414-20.

[9] Bischoff B, Silber S, Richartz BM, Pieper L, Klotsche J, Wittchen HU and Study-Group D. Inadequate medical treatment of patients with coronary artery disease by primary care physicians in Germany. Clin Res Cardiol. 2006;95:405-12.

[10] Stranges E, Barrett M, Wier LM and Andrews RM. Readmissions for heart attack, 2009. 2012.

[11] Koch MB, Davidsen M, Andersen LV, Juel K and Jensen GB. Increasing prevalence despite decreasing incidence of ischaemic heart disease and myocardial infarction. A national register based perspective in Denmark, 1980-2009. Eur J Prev Cardiol. 2015;22:189-95.

[12] Smolina K, Wright FL, Rayner M and Goldacre MJ. Incidence and 30-day case fatality for acute myocardial infarction in England in 2010: national-linked database study. Eur J Public Health. 2012;22:848-53.

[13] Smolina K, Wright FL, Rayner M and Goldacre MJ. Long-term survival and recurrence after acute myocardial infarction in England, 2004 to 2010. Circ Cardiovasc Qual Outcomes. 2012;5:532-40.

[14] Alwan A. Global status report on noncommunicable diseases 2010: World Health Organization; 2011.

[15] Law M, Morris J and Wald N. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. Bmj. 2009;338.

[16] Antithrombotic Trialists C, Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, Buring J, Hennekens C, Kearney P, Meade T, Patrono C, Roncaglioni MC and Zanchetti A. Aspirin in the primary and secondary prevention of vascular disease: collaborative metaanalysis of individual participant data from randomised trials. Lancet. 2009;373:1849-60.

[17] Cholesterol Treatment Trialists C, Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, Peto R, Barnes EH, Keech A, Simes J and Collins R. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet. 2010;376:1670-81.

[18] Graham I, Atar D, Borch-Johnsen K, Boysen G, Burell G, Cifkova R, Dallongeville J, De Backer G, Ebrahim S, Gjelsvik B, Herrmann-Lingen C, Hoes A, Humphries S, Knapton M, Perk J, Priori SG, Pyorala K, Reiner Z, Ruilope L, Sans-Menendez S, Op Reimer WS, Weissberg P, Wood D, Yarnell J, Zamorano JL, Walma E, Fitzgerald T, Cooney MT, Dudina A, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Funck-Brentano C, Filippatos G, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Altiner A, Bonora E, Durrington PN, Fagard R, Giampaoli S, Hemingway H, Hakansson J, Kjeldsen SE, Larsen m L, Mancia G, Manolis AJ, Orth-Gomer K, Pedersen T, Rayner M, Ryden L, Sammut M, Schneiderman N, Stalenhoef AF, Tokgozoglu L, Wiklund O, Zampelas A, European Society of C, European Association for Cardiovascular P, Rehabilitation, Council on Cardiovascular N, European Association for Study of D, International Diabetes Federation E, European Stroke I, Society of Behavioural M, European Society of H, Europe W, European Heart N and European Atherosclerosis S. European guidelines on cardiovascular disease prevention in clinical practice: full text. Fourth Joint Task Force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts). Eur J Cardiovasc Prev Rehabil. 2007;14 Suppl 2:S1-113.

[19] Perk J, De Backer G, Gohlke H, Graham I, Reiner Ž, Verschuren M, Albus C, Benlian P, Boysen G and Cifkova R. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). European heart journal. 2012;33:1635-1701.

[20] Stone N, Robinson J, Lichtenstein A, Goff Jr D, Lloyd-Jones D, Smith Jr S, Blum C and Schwartz J. ACC/AHA Cholesterol Guideline Panel. Treatment of blood cholesterol to reduce atherosclerotic cardiovascular disease risk in adults: synopsis of the 2013 American College of Cardiology/American Heart Association cholesterol guideline. Ann Intern Med. 2014;160:339-43.

[21] Smith SC, Jr., Benjamin EJ, Bonow RO, Braun LT, Creager MA, Franklin BA, Gibbons RJ, Grundy SM, Hiratzka LF, Jones DW, Lloyd-Jones DM, Minissian M, Mosca L, Peterson ED, Sacco RL, Spertus J, Stein JH, Taubert KA, World Heart F and the Preventive Cardiovascular Nurses A. AHA/ACCF Secondary Prevention and Risk Reduction Therapy for Patients with Coronary and other Atherosclerotic Vascular Disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation. Circulation. 2011;124:2458-73.

[22] Kotseva K, Wood D, De Backer G, De Bacquer D, Pyorala K, Keil U and Group ES. Cardiovascular prevention guidelines in daily practice: a comparison of EUROASPIRE I, II, and III surveys in eight European countries. Lancet. 2009;373:929-40.

[23] Yusuf S, Islam S, Chow CK, Rangarajan S, Dagenais G, Diaz R, Gupta R, Kelishadi R, Iqbal R, Avezum A, Kruger A, Kutty R, Lanas F, Lisheng L, Wei L, Lopez-Jaramillo P, Oguz A, Rahman O, Swidan H, Yusoff K, Zatonski W, Rosengren A, Teo KK and Prospective Urban Rural Epidemiology Study I. Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE Study): a prospective epidemiological survey. Lancet. 2011;378:1231-43.

[24] Zeymer U, Berkenboom G, Coufal Z, Belger M, Sartral M, Norrbacka K, Bakhai A and investigators A. Predictors, cost, and outcomes of patients with acute coronary syndrome who receive optimal secondary prevention therapy: results from the antiplatelet treatment observational registries (APTOR). Int J Cardiol. 2013;170:239-45.

[25] Lafeber M, Grobbee DE, Spiering W, van der Graaf Y, Bots ML, Visseren FL and Group SS. The combined use of aspirin, a statin, and blood pressure-lowering agents (polypill components) in clinical practice in patients with vascular diseases or type 2 diabetes mellitus. Eur J Prev Cardiol. 2013;20:771-8.

[26] Muntner P, Mann D, Wildman RP, Shimbo D, Fuster V and Woodward M. Projected impact of polypill use among US adults: medication use, cardiovascular risk reduction, and side effects. American heart journal. 2011;161:719-725.

[27] Mendis S, Abegunde D, Yusuf S, Ebrahim S, Shaper G, Ghannem H and Shengelia B. WHO study on Prevention of REcurrences of Myocardial Infarction and StrokE (WHOPREMISE). Bull World Health Organ. 2005;83:820-9.

[28] Accessibility PD. Issues in International Health Policy. 2010.

[29] Haynes RB, McKibbon KA and Kanani R. Systematic review of randomised trials of interventions to assist patients to follow prescriptions for medications. Lancet. 1996;348:383-6.

[30] O'Flaherty M, Buchan I and Capewell S. Contributions of treatment and lifestyle to declining CVD mortality: why have CVD mortality rates declined so much since the 1960s? Heart. 2013;99:159-62.

[31] Naderi SH, Bestwick JP and Wald DS. Adherence to drugs that prevent cardiovascular disease: meta-analysis on 376,162 patients. Am J Med. 2012;125:882-7 e1.

[32] Chowdhury R, Khan H, Heydon E, Shroufi A, Fahimi S, Moore C, Stricker B, Mendis S, Hofman A, Mant J and Franco OH. Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences. Eur Heart J. 2013;34:2940-8.
[33] Sabaté E. Adherence to long-term therapies: evidence for action: World Health Organization; 2003.
[34] Castellano JM, Sanz G, Fernandez Ortiz A, Garrido E, Bansilal S and Fuster V. A polypill strategy to improve global secondary cardiovascular prevention: from concept to reality. J Am Coll Cardiol. 2014;64:613-21.
[35] Perreault S, Blais L, Lamarre D, Dragomir A, Berbiche D, Lalonde L, Laurier C, St-Maurice F and Collin J. Persistence and determinants of statin therapy among middle-aged patients for primary and secondary prevention. Br J Clin Pharmacol. 2005;59:564-73.
[36] Kassab Y, Hassan Y, Abd Aziz N, Ismail O and AbdulRazzaq H. Patients' adherence to secondary prevention pharmacotherapy after acute coronary syndromes. Int J Clin Pharm. 2013;35:275-80.
[37] Castellano JM, Sanz G, Penalvo JL, Bansilal S, Fernandez-Ortiz A, Alvarez L, Guzman L, Linares JC, Garcia F, D'Aniello F, Arnaiz JA, Varea S, Martinez F, Lorenzatti A, Imaz I, Sanchez-Gomez LM, Roncaglioni MC, Baviera M, Smith SC, Jr., Taubert K, Pocock S, Brotons C, Farkouh ME and Fuster V. A polypill strategy to improve adherence: results from the FOCUS project. J Am Coll Cardiol. 2014;64:2071-82.
[38] Osterberg L and Blaschke T. Adherence to medication. N Engl J Med. 2005;353:487-97.
[39] Choudhry NK, Setoguchi S, Levin R, Winkelmayer WC and Shrank WH. Trends in adherence to secondary prevention medications in elderly post-myocardial infarction patients. Pharmacoepidem Dr S. 2008;17:1189-1196.
[40] Akincigil A, Bowblis JR, Levin C, Jan S, Patel M and Crystal S. Long-term adherence to evidence based secondary prevention therapies after acute myocardial infarction. J Gen Intern Med. 2008;23:115-121.
[41] Ens TA, Seneviratne CC, Jones C, Green TL and King-Shier KM. South Asians' cardiac medication adherence. Eur J Cardiovasc Nurs. 2014;13:357-68.
[42] Ho PM, Magid DJ, Shetterly SM, Olson KL, Maddox TM, Peterson PN, Masoudi FA and Rumsfeld JS. Medication nonadherence is associated with a broad range of adverse outcomes in patients with coronary artery disease. American heart journal. 2008;155:772-779.
[43] Dagenais GR, Pogue J, Fox K, Simoons ML and Yusuf S. Angiotensin-converting-enzyme inhibitors in stable vascular disease without left ventricular systolic dysfunction or heart failure: a combined analysis of three trials. The Lancet. 2006;368:581-588.
[44] Mukherjee D, Fang J, Chetcuti S, Moscucci M, Kline-Rogers E and Eagle KA. Impact of combination evidence-based medical therapy on mortality in patients with acute coronary syndromes. Circulation. 2004;109:745-749.
[45] Newby LK, LaPointe NM, Chen AY, Kramer JM, Hammill BG, DeLong ER, Muhlbaier LH and Califf RM. Long-term adherence to evidence-based secondary prevention therapies in coronary artery disease. Circulation. 2006;113:203-12.
[46] Taylor MJ, Scuffham PA, McCollam PL and Newby DE. Acute coronary syndromes in Europe: 1-year costs and outcomes. Current Medical Research and Opinion®. 2007;23:495-503.
[47] Bitton A, Choudhry NK, Matlin OS, Swanton K and Shrank WH. The impact of medication adherence on coronary artery disease costs and outcomes: a systematic review. Am J Med. 2013;126:357 e7-357 e27.
[48] Heeley E, Anderson CS, Huang Y, Jan S, Li Y, Liu M, Sun J, Xu E, Wu Y, Yang Q, Zhang J, Zhang S, Wang J and China QI. Role of health insurance in averting economic hardship in families after acute stroke in China. Stroke. 2009;40:2149-56.
[49] Marcum ZA, Sevick MA and Handler SM. Medication nonadherence: a diagnosable and treatable medical condition. JAMA. 2013;309:2105-6.
[50] Mwaka AD, Wabinga HR and Mayanja-Kizza H. Mind the gaps: a qualitative study of perceptions of healthcare professionals on challenges and proposed remedies for cervical cancer help-seeking in post conflict northern Uganda. BMC family practice. 2013;14:193.
[51] Choudhry NK, Krumme AA, Ercole PM, Girdish C, Isaman DL, Matlin OS, Brennan TA, Shrank WH and Franklin JM. Rationale and design of the Randomized Evaluation to Measure Improvements in Non-adherence from Low-Cost Devices (REMIND) trial. Contemporary clinical trials. 2015;43:53-59.
[52] Castellano JM, Sanz G and Fuster V. Evolution of the polypill concept and ongoing clinical trials. Canadian Journal of Cardiology. 2014;30:520-526.
[53] Castellano JM, Sanz G, Peñalvo JL, Bansilal S, Fernández-Ortiz A, Alvarez L, Guzmán L, Linares JC, García F and D'Aniello F. A polypill strategy to improve adherence: results from the FOCUS project. Journal of the American College of Cardiology. 2014;64:2071-2082.
[54] Berben L, Bogert L, Leventhal ME, Fridlund B, Jaarsma T, Norekvål TM, Smith K, Strömberg A, Thompson DR and De Geest S. Which interventions are used by health care professionals to enhance medication adherence in cardiovascular patients? A survey of current clinical practice. European Journal of Cardiovascular Nursing. 2011;10:14-21.
[55] Nieuwkerk PT, Nierman MC, Vissers MN, Locadia M, Greggers-Peusch P, Knape LP, Kastelein JJ, Sprangers MA, de Haes HC and Stroes ES. Intervention to improve adherence to lipid-lowering medication and lipid-levels in patients with an increased cardiovascular risk. The American journal of cardiology. 2012;110:666-672.
[56] Hohmann C, Neumann-Haefelin T, Klotz JM, Freidank A and Radziwill R. Adherence to hospital discharge medication in patients with ischemic stroke A prospective, interventional 2phase study. Stroke. 2013;44:522-524.
[57] Kalichman SC and Grebler T. Stress and poverty predictors of treatment adherence among people with low-literacy living with HIV/AIDS. Psychosomatic medicine. 2010;72:810.
[58] Parashar S, Palmer AK, O'Brien N, Chan K, Shen A, Coulter S, Montaner JS and Hogg RS. Sticking to it: the effect of maximally assisted therapy on antiretroviral treatment adherence among individuals living with HIV who are unstably housed. AIDS and Behavior. 2011;15:1612-1622.
[59] Nieuwlaat R, Wilczynski N, Navarro T, Hobson N, Jeffery R, Keepanasseril A, Agoritsas T, Mistry N, Iorio A and Jack S. Interventions for enhancing medication adherence. Cochrane Database Syst Rev. 2014;11.
[60] Eurostat. Database -Eurostat.