The clinical benefit of implementing guidelines in cardiovascular disease prevention in real world settings

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In the current issue of the *Archives of Medical Science* two studies from the same group, an academic community cardiology practice [1, 2], address the issue of the impact of the implementation of secondary cardiovascular disease (CVD) prevention guidelines on the long-term clinical outcome in patients with established coronary artery disease (CAD).

In the 1st study [1] the differences in medication usage and in CVD event rates are reported. From the early era (before 2002) to the later era (2005-2008), there was an increase in the use of β-blockers (from 66% to 83%, $p < 0.0001$), angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARBs) (from 34% to 80%, $p < 0.0001$), and statins (from 40% to 90%, $p < 0.0001$). This resulted in a substantial CAD rate reduction (9.2% vs. 29.1% in the later vs. early time period; $p < 0.0001$) [1]. In the second study that included a different population [2], CAD patients were not initially treated with statins during the first year of being seen in an outpatient cardiology practice but subsequently treated with statins (100%) for a mean period of 66 months. Myocardial infarction (MI) occurred in 10% of patients before statins, and in 4% after statins ($p < 0.01$), percutaneous coronary intervention (PCI) had been performed in 22% of patients before statins and in 13% after statins ($p < 0.01$), and coronary artery bypass graft (CABG) surgery had been performed in 18% of patients before statins and in 7% after statins ($p < 0.001$) [2]. These two studies point out that the implementation of secondary CVD prevention guidelines in a "real world" setting have a considerable positive impact on subsequent CVD morbidity and mortality [1, 2].

Several studies have demonstrated improved clinical outcomes when key quality-of-care indicators are implemented in the management of patients with acute coronary syndromes (ACS) or stable CAD [3]. However, secondary prevention guidelines can be poorly implemented [4, 5]. Particularly, in regard to statins, which have to be taken indefinitely, there is a concern that poor compliance may compromise their benefit [4-7]. Patients with dyslipidaemia do not experience symptoms and they need motivation to adhere to their medication. Clinical trials are performed at a controlled environment and data reported by them may vary from "real

life data" [6, 7]. For example a US study that reported the 2-year adherence of a non-selected MEDICAID cohort showed that only < 40% of patients were on a statin > 80% of the time [8]. The large US registry CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines), the EUROASPIRE I, II, III real world data on effective treatment of stable CAD, and the international Global Registry of Acute Coronary Events (GRACE) study demonstrated a world-wide underuse of proven medical therapies, including statins, among patients with either ACS or stable CAD [4, 9, 10]. Therefore, the gap between guidelines and routine clinical practice seems to have persisted during the decade 2000 to 2010 [11] and is a universal phenomenon [12-18]. Bridging the care gap in secondary CVD prevention remains a significant challenge. The lost benefit due to undertreatment contributes to the CVD burden. In addition to diet, exercise and lifestyle interventions new strategies are urgently needed to optimize vascular disease management in secondary prevention.

There have been prospective attempts to improve this situation, but mainly focused on the time after the acute event. A simplified treatment algorithm that initiated secondary CVD protection measures before hospital discharge in patients with an ACS was tested in the Cardiac Hospitalization Atherosclerosis Management Program (CHAMP) during the 90's [19]. CHAMP was associated with a significant increase in use of medications that had been demonstrated to reduce mortality after ACS. Comparison of the pre- and post-CHAMP patient groups showed that aspirin use at discharge improved from 68% to 92% ($p < 0.01$), β-blocker use from 12% to 62% ($p < 0.01$), ACE-I use increased from 6% to 58% ($p < 0.01$), and statin use increased from 6% to 86% ($p < 0.01$). This increased use of treatment persisted during subsequent follow-up. During this programme a high percentage of patients achieved secondary CVD prevention targets including low density lipoprotein cholesterol (LDL-C) goal (< 100 mg/dl) (58% in post-CHAMP vs. 6% pre-CHAMP, $p < 0.001$). This translated in an improvement in clinical outcome; the incidence of non-fatal MI and cardiac death was cut by half in the 1-year follow-up [19]. Another major attempt to improve implementation of guidelines was the real-time American College of Cardiology Guidelines Applied in Practice (GAP) programme. The GAP tools also resulted in higher discharge rates of secondary prevention medication (aspirin, β-blockers, ACE I and statins) [20]. The GAP tools were associated with fewer rehospitalizations for CAD, MI, and combined death/cerebrovascular event/MI in the first 1-year of follow-up. The CVD mortality substantially declined during the post-GAP period [20]. The Swedish Quality Control Programme [21] is the first attempt to assess implementation of CVD treatment guidelines on a national level. After 1 year a large proportion of patients were still on preventive drugs: aspirin (96%), β-blockers (78%) and lipid-lowering drugs (83%), but no actual clinical results have been reported yet [21].

There have been only a few attempts to improve adherence in secondary CVD prevention drugs away from the acute event, taking into account "real word data". This is why the 2 studies [1, 2] published in this issue are valuable, despite their retrospective design.

From 1998 to 2002 the prospective, randomised, and controlled GReek Atorvastatin on Coronary-heart-disease Evaluation (GRACE) study was carried out [22]. This was the first target based study, aiming to assess the clinical benefit from attaining the LDL-C goal (< 100 mg/dl) in 1,600 consecutive patients with established CAD. Patients were randomised either to "structured care" ($n = 800$) with dose titrating of atorvastatin (from 10 to 80 mg/day) in order to achieve the LDL-C target or to "usual" medical care ($n = 800$). All patients were followed for a mean period of 3 years [22]. There was an orchestrated effort to keep the "structured care" patients on atorvastatin and the LDL-C < 100 mg/dl (mean dosage of atorvastatin: 24 mg/day). This was achieved in 95% of patients, at a level much higher than "usual care" (12 on statins, 3% on LDL-C target). Other secondary CVD prevention therapies had no difference between the 2 treatment groups [22]. During the study 196 (24.5%) CAD patients on "usual" care had a CAD recurrent event or died vs. 96 (12%) CAD patients on "structured care"; risk ratio (RR) 0.49, confidence interval (CI) 0.27-0.73, $p < 0.0001$. In detail, structured care reduced, in comparison to "usual care", total mortality (RR 0.57, 95% CI 0.39-0.78, $p = 0.002$), coronary mortality (RR 0.53, 95% CI 0.29-0.74, $p = 0.0016$), coronary morbidity (RR 0.46, 95 % CI 0.25-0.71, $p < 0.0001$), and stroke (RR 0.53, 95% CI 0.30-0.82, $p = 0.0018$) [22]. All subgroups of patients (women, those with diabetes mellitus, arterial hypertension, age 60 to 75 years, congestive heart failure or prior revascularization) benefited from treatment with atorvastatin. Withdrawal of patients because of side effects from the atorvastatin group was low (0.75%), similar to that of the "usual" care group (0.4%) [22]. Similar were the results of the Aggressive Lipid-Lowering Initiation Abates New Cardiac Events (ALLIANCE) study, published 2 years later [23]. In ALLIANCE an aggressive, focused statin therapy management strategy outperformed "usual care" in health maintenance organization and Veterans Administration clinic patients with CAD. The "structured care" patients experienced a pri-

mary outcome (time to first CVD event: HR, 0.83; 95% CI 0.71 to 0.97, $p = 0.02$). This reduction in morbidity was largely due to fewer non-fatal myocardial infarctions (47% reduction, $p = 0.0002$) [23]. This benefit was less than that reported by GREACE, but this study came 2 years later (secondary prevention improves with time) and was performed in US, where "usual care" was better than that in Greece.

Very recent data on primary CVD prevention are very encouraging. These show that first MI (within primary CVD prevention) and subsequent short term (30 day) mortality halved over the last 10-25 years in at least 3 European countries [24-26].

From 2002 to 2010 in England, the age standardised total mortality rate fell by about half, whereas the age standardised CVD event and case fatality rates both declined by about one third. This was reported from the analysis of the data that included 840,175 people of all ages who were admitted to hospital for acute MI or died suddenly from acute MI. Half of the decline in deaths from acute MI during the 2000s in England can be attributed to a decline in event rate and half to improved survival at 30 days. Both prevention of first acute MI by addressing CVD risk factors and medical treatment during the acute phase hospitalization have contributed to the decline in deaths from acute MI over the past decade [24].

In addition, over half of the recent fall in mortality from CAD in Poland can be attributed to reductions in major risk factors and about one third to evidence based medical treatments. The CAD deaths in Poland plummeted after the socioeconomic reform in 1989. From 1991 to 2005, the death rate from CAD in Poland halved in people aged 25-74 years [25]. About 54% of the fall was attributed to changes in risk factors, mainly reductions in total cholesterol (39%) and an increase in physical activity (10%). These benefits were partially offset by increases in body mass index (–4%) and diabetes (–2%). Blood pressure fell in women, explaining about 29% of their decrease in mortality, but rose in men generating a negative influence (–8%). About 15% of the observed decrease in mortality was attributable to reduced smoking in men but this effect was negligible in women [25].

Finally, a study that included ≈250,000 Danish people and followed them up for 25 years showed that the rate of first MI and subsequent short-term mortality declined by nearly half between 1984 and 2008. The reduction in mortality occurred for all patients, independent of sex and comorbidity. However, comorbidity burden was a strong prognostic factor for short and long-term mortality, while gender was not. It was estimated that half of the decline in mortality since 1980 is attributable to primary prevention of MI (reduction in the prevalence of major CVD risk factors such as smoking, sedentary lifestyle, and uncontrolled high blood pressure) [26]. The other half is attributable to the introduction of thrombolysis, CABG, PCI, and antiplatelet regimens, β-blockers, ACE-I, and statins. It is relevant that the incidence of MI has continued to decline despite increased prevalence of obesity and diabetes [26].

Thus, the effort to address any excess CVD risk (though lower now in absolute terms than in the past) related to comorbidies has an outstanding place in primary CVD prevention and can further reduce CVD events and mortality. This was the reason that we carried out 4 "best practice" studies (aiming in attending international guidelines for CVD prevention) in order to deal with major comorbidities in a primary care setting, mainly in primary prevention patients [27-30]. The results of these studies suggest that the estimated risk for a fatal or non-fatal CVD event was nearly halved at 6 months of treatment, by multifactorial intervention in patients with at least one major CVD risk factor (arterial hypertension, dyslipidaemia, diabetes, and metabolic syndrome) [27-30]. Another best practice study showed that this was the case for long-term morbidity and mortality also in patients with metabolic syndrome [31]. Other comorbidies, increasing CVD risk, such as chronic kidney disease [32-34] and non-alcoholic fatty liver disease [35-37] should be diagnosed and treated accordingly. Also, in patients with metabolic syndrome, multifactorial intervention resulted in elimination of new cases of diabetes [38, 39], which is considered to be as harmful as pre-existing diabetes [40]. In any case statin treatment plays a great role in primary CVD prevention. A recent meta-analysis [41] showed that statins were found to be efficacious in preventing death and CVD morbidity in people at low CVD risk (without CAD or diabetes), within primary prevention. Reductions in RR were similar to those seen in patients with a history of CAD [41].

The data suggest that there is plenty of room in real world settings for a better implementation of guidelines in secondary CVD prevention (bridging the gap between guidelines and everyday clinical practice) with substantial clinical gains. Efforts like the ones in the 2 Studies in this issue of the journal [1, 2] are welcomed. On the other hand, effective risk factor control in primary CVD prevention leads to fewer MIs, while effective treatment measures during the acute phase of MI results in halving short- and long-term CVD mortality. However, there is still room for further improvement by addressing major comorbidities (especially the forthcoming epidemic of diabetes), which shape acute- and long-term mortality in men and women [42]. Interventions both in primary and secondary

CVD prevention will finally lead to substantial reduction of the human cost of this disease.

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