EDITORIAL

SECONDARY PREVENTION IN CORONARY ARTERY DISEASE IN 2012: ANALYSIS OF SOME ISSUES BEYOND DRUG PRESCRIPTION

PREVENCIÓN SECUNDARIA EN LA ENFERMEDAD CORONARIA EN 2012: ANÁLISIS DE ALGUNOS ASPECTOS MÁS ALLÁ DE LA PRESCRIPCIÓN DE FÁRMACOS

Eduardo F. Mele, MD

Ex President of the Argentine Society of Cardiology. Fellow American College of Cardiology. Fellow European Society of Cardiology. Sanatorio Güemes, Buenos Aires, Argentina.

Key words: Coronary artery disease, prevention & control, risk factors, atherosclerosis
Palabras clave: Enfermedad de la arteria coronaria, prevención & control, factores de riesgo, aterosclerosis

Este artículo también está disponible en español

By standards of secondary prevention in coronary heart disease, we mean those therapeutic, pharmacological measures or otherwise that are implemented in patients who have undergone coronary syndrome, with the aim of reducing the incidence of death and new events in its monitoring.

The main scientific societies of the world have published consensus and secondary prevention guidelines. We can mention the American College of Cardiology, American Heart Association (ACC/AHA), the European Society of Cardiology and the Argentine Society of Cardiology, among others[1-3].

In Table 1, the main indications shared by almost all of them are mentioned, with its kind of consensus and level of evidence that supports it.

Within secondary prevention measures, some relate to lifestyle, others to therapeutic aims and others to the

administration of drugs which have proved to prolong survival in different large multicenter randomized clinical trials.

Beyond what have been proven and is widely known regarding the beneficial effect of using these drugs, we are more concerned in emphasizing other aspects that are also crucial in terms of patient prognosis in secondary prevention.

For example, smoking cessation is the most potent intervention in the reduction of total death. It is known that quitting smoking is more effective than any other intervention to prevent the first coronary syndrome, the subsequent ones, and death after bypass surgery or another invasive treatment[3]. Therefore, smoking cessation strategies applied to patients after coronary syndrome are fully justified; measures that can begin to be implemented within the coronary care unit during hospitalization.

Regarding what is meant by control of risk factors, it is worthwhile to consider two conditions in which there are some peculiarities concerning control of coronary patients. They are diabetes and hypertension.

✉ *Eduardo F. Mele*
Sanatorio Güemes
Buenos Aires, Argentina.
Correo electrónico: efmele@gmail.com

Table 1. Major secondary prevention measures recommended by the current consensus (Class and level of evidence).

- Smoking cessation (IB)

- Control of BP <140/90 or 130/80 mmHg if diabetes or CRF (IA)

- Physical activity: 30 minutes, 7 days/week (minimum 5) (IB)

- Body weight: BMI 18.5 to 24.9 kg/m^2 (IB)

- LDL cholesterol <100 mg/dl (IA). Reasonable <70mg/dl (IIa A). Statins and others.

- Diabetes: HbA1c <7% (IA)

- Antiplatelet: ASA 75 to 162 mg / day (IA). Clopidogrel if stent or if post ACS (IB)

- ACEI: In all patients with EF <0.40, hypertension, diabetes, IR. (IA). Optional in others (IB)

- Beta blockers: Indefinitely (IA)

- Influenza vaccination (IB)

BP: blood pressure. CRF: chronic renal failure. BMI: body mass index. ASA: aspirin.
ACEI: angiotensin converting enzyme inhibitors.

HOW TO TREAT DIABETES?

Diabetes is one of the most important cardiovascular risk factors. It is known that the prognosis of non-diabetic patients with coronary artery disease is similar to the diabetic patient with no coronary artery disease, and in turn, diabetes is a negative prognostic factor in chronic coronary patients, as demonstrated in several population studies.

A strict control level with glycosylated hemoglobin less than 6.5 or 7% has been traditionally recommended, but recent studies such as ACCORD, VADT and ADVANCE[4-6] have clarified some aspects. They were designed to demonstrate whether the glycemic intensive treatment with goals of HbA 1c <6.5% in high-risk patients would result in reduction of microvascular and macrovascular complications.

ACCORD[4] included 10,251 patients with a history of diabetes, cardiovascular disease, and ages between 40 and 79. This study compared the results of a glycemic control strategy with HbA1c goals<6% *versus* the conventional strategy with HbA1c between 7 and 7.9%. This research had to be suspended due to an increase in mortality in the aggressive arm (regarding the invasive treatment used) and no differences between the two strategies in the incidence of vascular disease were found.

VADT[5] study, conducted in 1,791 patients, showed similar results to ACCORD, and although there was a mortality increase in the aggressive arm, it was not significant. In populations' analysis of this study, a significant benefit in patients with diabetes under 12 years of evolution was observed.

ADVANCE[6] study, that included 11,140 patients, showed no benefit either in establishing an HbA1c <6.5% for prevention of macrovascular complications, however, there was reduction of nephropathy and retinopathy; although no increased mortality from hypoglycemia in the aggressive arm was found. The population of this study had a history of diabetes of shorter duration (8 years).

The meta-analysis conducted by Ray et al.[7] which included VADT, ACCORD, ADVANCE, PROACTIV and UKPDS showed that an aggressive strategy on glycemia reduces nonfatal heart attacks by 17% , and coronary heart disease events by 15%, without changing the likelihood of stroke and death.

However, unlike what was observed in people without previous vascular changes, not all patients may need an aggressive strategy. Severe hypoglycemia - a complication more common in elderly patients with previous vascular disorders - and a history of poorly controlled and long-term (9 to 10 years) diabetes was a predictor of mortality.

In summary, for the diabetic population with a history of vascular disease, the aggressive strategy could be beneficial and acceptable only in the young population with diabetes of short duration, and evidence of its good control. In elderly patients with long-term diabetes (> 10 years) and evidence of poor glycemic control, less pretentious goals would be advisable.

WHAT BLOOD PRESSURE SHOULD HAVE A CHRONIC CORONARY PATIENT?

With respect to control of hypertension, the debate about what level of blood pressure should be main-

tained in a patient with coronary artery disease remains. The traditional guidelines recommend less than 140/90 or 130/80 mmHg in the case of those with diabetes or kidney failure, with the concept of "less is better." However, in recent years several studies have cast doubt on the latter concept. Boutitle[8] in a meta-analysis of over 40,000 patients describes that a decrease in blood pressure beyond certain limits increases mortality. Messerli[9] in 2006, confirmed these findings, and the INVEST[9] study with more than 22,000 patients, demonstrated that the mortality of those with coronary disease has a J-curve with respect to blood pressure levels, i.e. that both hypertension, and blood pressure below certain values increase risk.

ACCORD BP[10] study in diabetics showed no additional benefit in reducing systolic blood pressure to 120 mmHg compared to keeping it at 140 mmHg. Cooper[11] in a group of coronary patients found that the blood pressure level between 130 and 140 mmHg was the one correlated with the lowest immediate and long-term mortality. Mortality increased significantly beyond 140 mmHg, but also had a slight increase below 130. The INVEST group found that this assumption is also valid for patients with coronary artery disease after coronary artery bypass graft surgery, with peripheral arterial disease, and in the elderly[12-14].

A retrospective analysis of the TNT study, which was an intervention trial with statins in patients after acute coronary syndrome, followed for 5 years, found that the level of blood pressure with better prognosis was 146.3 / 81.4 mmHg and below 120/70 the risk is increased, except for stroke[15].

Several possible causes to explain the J curve have been described. First, diastolic hypotension may compromise coronary blood flow and cause myocardial ischemia. Furthermore, a low diastolic pressure may accompany an increase in pulse pressure, which is an arterial stiffness rate and a marker of advanced vascular disease. In INVEST study, both diastolic and pulse pressure had predictive values. The systolic pressure had a weaker association. Persistent hypotension may be due to more severe heart disease, in the same way, low blood pressure may be related to underlying medical comorbidities that increase morbidity and mortality.

The Consensus on Prevention of the Argentine Society of Cardiology recommends keeping blood pressure below 140/90 in hypertensive patients with coronary disease[3].

PSYCHOSOCIAL ASPECTS

Coronary patients have personality features that have

been known for a long time. An acute coronary syndrome is capable of generating consequences on the psychological status of patients that should be considered in their rehabilitation. Moreover, the psychosocial aspects surrounding the patient should be taken into account. The psychological reactions that may occur after coronary syndrome are diverse. The most common is depression, which occurs in 20 to 45% of cases and is an independent prognostic factor. It may be accompanied by anxiety, hostility, isolation, sexual dysfunction, fatigue, decreased quality of life, work and family conflicts, and abandonment of treatment[16]. Therefore, the task of the health team is, in this regard, to provide patients suffering from acute coronary syndrome with counseling and support.

Different publications have acknowledged the influence of various social collective traumatic situations on cardiovascular mortality[17-21], such as wars, terrorist attacks, natural disasters, economic crises, among others.

In our country, this phenomenon in relation to the last two major economic crises that affected our society, in 1995 and 2001, have been investigated, hence the evolution of cardiovascular mortality is correlated with gross domestic product (GDP) since 1995 to 2005[22]. In the period analyzed, there was a steady decline in the rate of cardiovascular mortality. During the 2 crisis mentioned, which were accompanied by a fall in GDP, the rate of decline was less or even saw a rise that broke the global trend. The results of this analysis would support the hypothesis that economic and financial crisis, expressed through indicators like GDP, could have an impact on cardiovascular mortality. The close temporal relationship observed between increased cardiovascular mortality and declining GDP, suggests looking at such crises as a new psycho-social risk factor.

PHYSICAL ACTIVITY

Another aspect to be promoted in patients in secondary prevention is physical exercise as its beneficial effects are well known. Basically, they are: improvement of functional capacity, of lipid profile (increased high density lipoprotein, and decreased triglycerides), improvement of blood pressure, and a better glycemic control in diabetics. On the other hand, an effect of reduced inflammation, improvement in ischemic preconditioning, in endothelial function and in fibrinolysis, is attributed to it. In addition, physical activity helps patients psychologically[16]. Notwithstanding the aforesaid, it was discussed for a long time whether or not cardiac rehabilitation improved the prognosis of pa-

tients. The meta-analysis of Taylor[23] showed that this benefit exists. A decrease in cholesterol of 14.3 mg / dl, triglycerides of 20.4 mg / dl, blood pressure of 3.4 mmHg and a reduction in mortality with an odds ratio (OR) of 0.8 were found.

The ideal patient approach in secondary prevention is integral, and various plans that include or not exercise have been implemented. Likewise, in meta-analysis it has also been found that these plans can cause a slight decrease in long-term pathological events. These plans should compulsorily include adequate categorization of the patient, nutritional counseling and weight control, blood pressure and lipids monitoring, the treatment of diabetes according to the rules and, of course, smoking cessation, in case the patient maintains this habit, an exercise plan should be started and where necessary, psychosocial counselling[24,25].

Given the high prevalence of coronary heart disease, the patients that can be included in organized secondary prevention plans are a minority, but medical consultation can and should be the context where the professional give the guidelines to the patient. The limited time given to consultation, in most health systems, is often an obstacle to carrying out this task, which besides benefiting the patient, is cost-beneficial for the system as hospitalizations and expensive treatments can be prevented.

TREATMENT COMPLIANCE

One of the biggest challenges in secondary prevention is to achieve patient compliance to treatments. The lack of compliance is due to many causes, and it has been object of analysis[26,27]. It is known, for example, the small number of hypertensive patients who actually have their blood pressure below the maximum established values.

EUROASPIRE registries of the European Society of Cardiology reveal interesting facts. EUROASPIRE III registry[28], for example, conducted between 2006 and 2007 in a population of 8,966 patients with prior coronary syndromes showed that smoking rate was above 10%, overweight and obesity rates were above 30%, about 50% if we consider central obesity, hypertension greater than 50% and hypercholesterolemia close to that figure. When comparing this record with the EUROASPIRE I and II[29], conducted between 1995 and 1996 (EUROASPIRE I) and between 1999 and 2000 (EUROASPIRE II), it was found that only hypercholesterolemia had decreased progressively, whereas hypertension and smoking were stable, and an increase in the prevalence of diabetes and obesity in the

last report was noted. With regard to drugs, 80% of patients received antiplatelet effectively and about 70%, statins and beta blockers. The decline in cholesterol levels was attributed to the widespread use of statins over the periods analyzed, but it is clear that there was not a change of habits among secondary prevention patients over 10 years, but instead, the disorders attributable to the kind of food increased.

Other real life studies reveal even more discouraging results. For example, Ho et al.[30] in a population of postinfarction patients found that 34% of those who were prescribed statins, beta blockers and aspirin, interrupted at least one medication, and 12% the three of them a month after hospital discharge, while at 12 months only half of them continued to receive the 3 medications. This finding had its clinical correlation: each drug suspended implied an increased risk of death between 1.82 and 2.86, which could quintuple in the case of complete abandonment of treatment.

The lack of treatment compliance is due to various causes. Many of them have to do with the limited knowledge on the part of the patient of the real benefits provided by changes in habits and medication compliance in the clinical evolution. Medical consultation, through an appropriate doctor-patient relationship is the most important time for that purpose, either during hospitalization or in ambulatory monitoring. Public outreach campaigns are also very useful, and particularly important in primary prevention.

The patients' social, educational, cultural and economic status is determinant in medication compliance. Niu and al.[31] in China, described how the use of aspirin, beta blockers, statins, angiotensin converting enzyme (ACE) inhibitors and clopidogrel have a different correlation with socioeconomic status of patients. Although there was a small difference between the lowest and highest social stratum, regarding compliance with beta-blockers, ACE inhibitors and aspirin, this difference was bigger in the case of more expensive drugs such as clopidogrel and statins. In the highest socioeconomic level, the use of statins doubled that of the lowest level, while the use of clopidogrel was 6 times greater.

Accessibility to medication is crucial. Population studies have shown that patients who have restrictions or quotas for the provision of drugs have lower compliance with treatment for hypertension, hyperlipidemia and diabetes. Furthermore, patients, in systems with limits on the provision of medicines, have worse control of their variables (e.g., low density lipoprotein and hypertension) and more visits to emergency services and unplanned hospitalizations. In some cases,

changes in coverage or copayment increases were associated with up to twice the incidence of statins abandonment[32].

It has been proposed that compliance with treatment leads to increased spending on medications, but lower medical costs in evolution. A recent evaluation found that high compliance with statins was associated with higher pharmacy costs and lower medical costs, but after several years of monitoring, the final cost to the system was the same, with or without compliance. Anyway, compliance is cost-beneficial or neutral for health systems[26].

The prospective urban and rural epidemiological study (PURE)[33], published recently, enrolled 153,996 adults, between 35 to 70 years old, belonging to 608 communities in high, medium-high, medium-low and low developing countries, between 2003 and 2007. Of these, 4.9% reported having had coronary syndrome or a previous stroke. In this population in secondary prevention, compliance with recommended treatment guidelines and consensus was analyzed. The worrying results show how far we are from meeting the recommendations. Overall, only 25.3% of patients were taking antiplatelet, 17.4% beta blockers, 19.5% ACE inhibitors or angiotensin receptor antagonists, and 14.6% were taking statins. There were huge differences between countries according to their development level and socioeconomic status. The respective percentages for each type of drug were in countries of higher economic level, 62%, 40%, 49.8% and 66.5%, while for lower level countries it was 8.8%; 9.7%, 5.2% and 3.3%, respectively. The percentage of patients who did not receive any of the evidence-based medications was 11.2% in countries with the highest level, 45.1% in medium-high level, 69.3% in the mid-low level and 80.2% in the lowest socioeconomic level countries. In turn, urban populations were more compliant than rural areas and also a correlation with educational level, age and other variables was observed.

As shown, the difference of high level countries with respect to others is very important and the highest correlation variable with treatment compliance was the population socioeconomic level. Nevertheless, the analysis of compliance level in populations with the highest purchasing power is far from ideal, which shows the influence of other reasons, mainly education, lack of government campaigns, among other factors.

CONCLUSIONS

In summary, we could conclude that secondary preven-

tion guidelines exist, and they are consensual and evidence-based, however, compliance with recommendations and treatments is unsatisfactory. It is influenced by medical, cultural, psychological, social and economic factors. These aspects should be considered in plans for secondary prevention and rehabilitation.

An inverse relationship between compliance and complications in the evolution after coronary syndrome has also been shown, the better compliance, the better evolution.

Increased compliance with treatment requires a joint effort of physicians and public health authorities for the dissemination of guidelines and awareness of the population. In this sense, Scientific Societies have a predominant role in the preparation and dissemination of these recommendations to physicians, government and community.

REFERENCES

1. Smith S, Benjamin E, Bonow R, Braun L, Creager M, Barry F, Franklin A, *et al*. AHA/ACCF Secondary Prevention and Risk Reduction Therapy for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2011 Update. JACC. 2011;58(23):2432-46.
2. Graham I, Atar D, Borch-Johnsen K, Boysen G, Burell G, Cifkova R. European Guidelines on Cardiovascular Diseases in Clinical Practice. Eur J Cardiovasc Prev Rehabil. 2007;14(Suppl2):S1-S113.
3. Consenso de Prevención de la Sociedad Argentina de Cardiología. Rev Argent Cardiol. 2012 (In press).
4. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008;358(24):2545-59.
5. Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, *et al*. Intensive glucose control and complications in American veterans with type 2 diabetes. N Engl J Med. 2009;360(2):129-39.
6. ADVANCE Collaborative Group, Patel A, MacMahon S, Chalmers J, Neal B, Billot L, *et al*. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008; 358(24):2560-72.
7. Ray KK, Seshasai SR, Wijesuriya S, Sivakumaran R, Nethercott S, Preiss D, *et al*. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: A meta-analysis of randomised controlled trials. Lancet. 2009;373(9677):1765-72.
8. Boutitie F, Gueyffier F, Pocock S, Fagard R, Boissel JP; INDANA Project Steering Committee. INdividual

Data ANalysis of Antihypertensive intervention. J-Shaped Relationship between Blood Pressure and Mortality in Hypertensive Patients: New Insights from a Meta-Analysis of Individual-Patient Data. Ann Intern Med. 2002;136(6):438-48.

9. Messerli FH, Mancia G, Conti CR, Hewkin AC, Kupfer S, Champion A, *et al.* Dogma Disputed: Can Aggressively Lowering Blood Pressure in Hypertensive Patients with Coronary Artery Disease Be Dangerous? Ann Intern Med. 2006;144(12):884-93.

10. ACCORD Study Group, Cushman WC, Evans GW, Byington RP, Goff DC, Grimm RH, *et al.* Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus. N Engl J Med. 2010;362(17):1575-85.

11. Cooper-DeHoff RM, Gong Y, Handberg EM, Bavry AA, Denardo SJ, Bakris GL, *et al.* Tight blood Pressure Control and Cardiovascular Outcomes Among Hypertensive Patients with Diabetes and Coronary Heart Disease. JAMA. 2010;304(1):61-8.

12. Denardo SJ, Messerli FH, Gaxiola E, Aranda JM, Cooper-Dehoff RM, Handberg EM, *et al.* Characteristics and Outcomes of Revascularized Patients With Hypertension: An International Verapamil SR-Trandolapril Substudy. Hypertension. 2009;53(4): 624-30.

13. Bavry AA, Anderson RD, Gong Y, Denardo SJ, Cooper-Dehoff RM, Handberg EM, *et al.* Outcomes Among Hypertensive Patients With Concomitant Peripheral and Coronary Artery Disease: Findings From the INternationalVErapamil-SR/Trandolapril Study. Hypertension. 2010;55(1);48-53.

14. Denardo SJ, Messerli FH, Gaxiola E, Aranda JM Jr, Cooper-Dehoff RM, Handberg EM. Coronary Revascularization Strategy and Outcomes According to Blood Pressure (from the International Verapamil SR-Trandolapril Study [INVEST]). Am J Cardiol. 2010;106(4):498-503.

15. Bangalore S, Messerli FH, Wun CC, Zuckerman AL, DeMicco D, Kostis JB, *et al.* J-curve revisited: An analysis of blood pressure and cardiovascular events in the Treating to New Targets (TNT) Trial. Eur Heart J. 2010;31(23):2897-908.

16. Wenger NK, MACP, FACC, FAHA. Current Status of Cardiac Rehabilitation. J Am Coll Cardiol. 2008; 51:1619-31.

17. Spiegel PB, Salama P. War and mortality in Kosovo, 1998-99: an epidemiological testimony. Lancet. 2000;355 (9222):2204-09.

18. Oosterhoff P, Zwanikken P, Ketting E. Sexual torture of men in Croatia and other conflict situations: an open secret. Reprod Health Matters. 2004;

12(23):68-77.

19. Phillips DP, Jarvinen JR, Abramson IS, Phillips RR. Cardiac mortality is higher around Christmas and New Years´ than at any other time. The holidays as a risk factor for death. Circulation 2004;110(25): 3781-88.

20. Goldberg RJ, Spencer F, Leesard D, Yarzebsky J, Lareau C, Gore JM. Occurrence of acute myocardial infarction in Worcester Massachusetts before, during, and after the terrorist attacks in New York City and Washington, DC, on September 11 2001. Am J Cardiol. 2005;95(2):258-60.

21. Stalnikowicz R, Tsafrir A. Acute psychosocial stress and cardiovascular events. American Journal of Emergency Medicine. 2002;20(5):488-91.

22. Sosa Liprandi MI, Racki M, Khoury M, Villarreal R, Cestari G, Mele E, Sosa Liprandi A. Crisis económico-financieras en Argentina: ¿Un nuevo factor de riesgo de mortalidad cardiovascular? Rev Argent Cardiol. 2012 (In press).

23. Taylor RS, Brown A, Ebrahim S, Jolliffe J, Noorani H, Rees K, *et al.* Exercise-Based Rehabilitation for Patients with Coronary Heart Disease: Systematic Review and Meta-analysis of Randomized Controlled Trials. Am J Med. 2004;116(10):682-692.

24. Clark AM, Hartling L, Vandermeer B, McAlister FA. Meta-Analysis: Secondary Prevention Programs for Patients with Coronary Artery Disease. Ann Intern Med. 2005;143(9):659-72.

25. Balady GJ, Williams MA, Ades PA, Bittner V, Comoss P, Foody JM, *et al.* Core Components of Cardiac Rehabilitation/Secondary Prevention Programs: 2007 Update. Circulation. 2007;115(20): 2675-82.

26. Ho PM, Bryson CL, Rumsfeld JS. Medication Adherence: Its Importance in Cardiovascular Outcomes. Circulation. 2009;119(23):3028-35.

27. Newby LK, La Pointe NM, Chen AY, Kramer JM, Hammill BG, De Long ER, *et al.* Long-Term Adherence to Evidence-Based Secondary Prevention Therapies in Coronary Artery Disease. Circulation. 2006;113(2);203-12.

28. Kotseva K, Wood D, De Backer G, De Bacquer D, Pyörälä K, Keil U, *et al.* EUROASPIRE III: a survey on the lifestyle, risk factors and use of cardioprotective drug therapies in coronary patients from 22 European countries. Eur J Cardiovasc Prev Rehabil. 2009;16(2):121-37.

29. Kotseva K, Wood D, De Backer G, De Bacquer D, Pyörälä K, Keil U, *et al.* Cardiovascular prevention guidelines in daily practice: a comparison of EUROASPIRE I, II, and III surveys in eight Euro-

pean countries. Lancet. 2009;373 (9667):929-40.

30. Ho PM, Spertus JA, Masoudi FA, Reid KJ, Peterson ED, Magid DJ. Impact of Medication Therapy Discontinuation on Mortality After Myocardial Infarction. Arch Intern Med. 2006;166(17):1842-47.

31. Niu S, Zhao D, Zhu J, Liu J, Liu Q, Liu J, *et al.* The association between socioeconomic status of high-risk patients with coronary heart disease and the treatment rates of evidence-based medicine for coronary heart disease secondary prevention in China:Results from the Bridging the Gap on CHD Secondary Prevention in China (BRIG) Project. Am Heart J. 2009;157(4):709-15.

32. Hsu J, Price M, Huang J, Brand R, Fung V, Hui R, *et al.* Unintended Consequences of Caps on Medicare Drug Benefits. N Engl J Med. 2006; 354(22):2349-59.

33. Yusuf S, Islam S, Chow C, Rangarajan S, Dagenais G, Diaz R, *et al.* 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 (9798):1231-43.