

Editorial

# Multiple Risk Factor Intervention to Prevent Cardiovascular Disease. A High Powered and Evidence Based Approach

## Intervención sobre múltiples factores de riesgo para prevenir la enfermedad cardiovascular. Un enfoque basado en la evidencia

Thomas Guterbaum<sup>a</sup> and Peter Gæde<sup>b,\*</sup>

<sup>a</sup> Department of Cardiology, Copenhagen University Hospital Slagelse, Slagelse, Denmark

<sup>b</sup> Department of Endocrinology, Copenhagen University Hospital Slagelse, Slagelse, Denmark

### ARTICLE INFO

#### Article history:

Available online 16 February 2011

On a worldwide scale cardiovascular disease is estimated to be the leading cause of death and loss of disability-adjusted life expectancy in the next decade.<sup>1</sup> The INTERHEART study has demonstrated that classic risk factors such as abnormal lipids, smoking, hypertension, lack of regular physical activity, diabetes, abdominal obesity, psychosocial factors, excessive alcohol consumption, and inadequate intake of fruits and vegetables, account for most of the risk of myocardial infarction worldwide in both sexes and at all ages in all regions.<sup>2</sup> In total, risk factors accounted for 90% of the observed risk in men and 94% in women in this large case-control study of acute myocardial infarction in 52 countries, suggesting that approaches to prevention have the potential to prevent most premature cases of myocardial infarction.

In secondary prevention of cardiovascular disease, numerous clinical trials have tested the effects of single risk factor intervention in both myocardial infarction and stroke, leading to several sets of guidelines on both national and international levels. With this abundance of knowledge, the obvious question is: why does cardiovascular disease still account for around half of deaths in subjects below the age of 70 years?

Much of the gap between recommended and actual levels of chronic disease care is attributable to medication nonadherence.<sup>3</sup> The importance of this factor has been clearly demonstrated in a recent United States trial in myocardial infarction.<sup>4</sup> In a prospective registry of 1521 patients admitted with a myocardial infarction and discharged with treatment with acetylsalicylic acid, beta-blockers and statins, 184 discontinued use of all 3 medications, 56 discontinued use of 2 medications, 272 discontinued use of 1 medication, and 1009 continued taking all 3 medications at 1 month.

The consequences of discontinuing treatment were devastating. Patients who discontinued use of all medications at 1 month had lower 1-year survival (88.5% vs. 97.7%,  $P < .001$ ) compared with patients who continued to take 1 or more of the medications.

In multivariable survival analysis, medication therapy discontinuation was independently associated with an almost 4 times higher mortality rate.<sup>4</sup> In type 2 diabetes mellitus, the age-adjusted prevalence of coronary heart disease is twice as high among those with type 2 diabetes as among those without diabetes.<sup>5</sup> Despite this fact, surveys once again have demonstrated insufficient use of recommended treatments. Thus, in a Canadian registry trial the overall use of antiplatelet agents, statins or angiotensin-converting enzyme inhibitors inhibitors was suboptimal (37%, 29% and 60%, respectively) even in type 2 diabetic patients with known cardiovascular disease, with treatment with all 3 types of drugs in only 11% of patients.<sup>6</sup>

In the article published in *Revista Española de Cardiología* Moreno-Palanco et al<sup>7</sup> report the results from the MIRVAS Study. This hospital-based secondary intervention trial assessed the effect of intensive treatment of multiple cardiovascular risk factors in patients admitted for acute coronary syndrome or ischemic stroke as compared to standard treatment. Of 247 patients included in the study, 121 were randomized to intensive treatment. In this group, hospital visits were planned at 2, 5, 12, 24 and 36 months after discharge; at each visit, nursing intervention (health education, lifestyle modification, evaluation of adherence to treatment) and medical assessment (clinical evaluation and modification of treatment) took place. The standard group received follow-up in cardiology or neurology, or consultations at the family physician level. At 36 months the dietary pattern and physical exercise was significantly better in the intensive group, as was the level of low-density lipoprotein cholesterol and glucose control (around 30% of patients enrolled had diabetes at baseline). Use of statins and inhibitors of the renin-angiotensin system was higher in the intensive group. These differences translated into a marked risk reduction in mortality in group receiving intensive treatment. The risk of a combined endpoint for cardio-cerebrovascular disease also was significantly reduced.<sup>7</sup>

The MIRVAS Study once again clearly demonstrates the benefits of intensified multiple risk factor intervention, following guidelines with strict targets as secondary prevention in patients at high risk for cardiovascular disease. Unfortunately, the MIRVAS Study also underlines the infrequent use of well-established treatment modalities in routine care. In the control group, only 83% of

DOI OF RELATED ARTICLE: 10.1016/j.rec.2010.07.002

IN Rev Esp Cardiol. 2011;64:179–85.

\* Corresponding author: Department of Endocrinology, Copenhagen University Hospital Slagelse, Ingemanns Vej 18, 4200 Slagelse, Denmark.

E-mail address: peter.gaede@dadlnet.dk (P. Gæde).

patients are treated with statins despite a previous cardiovascular event. Based on results from newer trials such as the Heart Protection Study, treatment with statins prevents both myocardial infarctions in ischemic strokes as secondary prevention even at very low levels of total cholesterol ( $>3.5$  mmol/L).<sup>8</sup> In type 2 diabetes, statin treatment should be prescribed as primary prevention unless contraindicated.<sup>9</sup>

The success of a treatment strategy depends both on the patient's ability or will to adhere to the treatment prescribed and on possible physician barriers. Studies have shown that only 50% to 70% of the prescribed medication is actually taken by patients.<sup>10</sup> Several factors are believed to be important to drug adherence. Many of the therapies given in an intensified multifactorial intervention approach are given as preventive treatments irrespective of the presence of symptoms, and therefore patients without symptoms may find that the treatment interferes more with daily life than the disease itself. In this respect, it is worth noting that patients may find that a change in lifestyle and diet greatly reduces their quality of life and thus reduces a barrier for adherence to drug therapy.<sup>10</sup> Even in case of symptoms, the start of a treatment may not relieve these, which in itself may be a risk factor for non-adherence to treatment.<sup>11</sup> The complexity of the drug regimen also seems to be of importance, especially the number of dosages per day: adherence decreases as the number of doses increases.<sup>12</sup> Of course, side effects including drug interactions will also influence drug adherence, and cost of treatment may be of importance for the patient.

Finally, it should be recalled that physician barriers also might be an important issue in following treatment guidelines. Failure to follow recommendations has been shown to be related to the physician's knowledge of the disease.<sup>13</sup>

Given the vast number of patients with cardiovascular disease, it is unrealistic to believe that all patients can be followed at specialized centers with specialist nurses and physicians. Most patients must be followed at the family physician level; as a consequence, simple daily practices must be implemented to ensure that treatment proceeds according to guidelines. The Danish National Indicator Project was established in 2000 as a nationwide multidisciplinary quality improvement project.<sup>14</sup> From 2000 to 2002, disease-specific clinical indicators and standards were developed for six diseases, including heart failure. Indicators and standards have been implemented in all clinical units and hospital departments in Denmark treating these six diseases, and participation is mandatory. National and regional audit processes are organized to explain the results and to prepare for implementation of improvements. All results are published, to inform the public and to give patients and relatives the opportunity to make informed choices. Recently, treatment of diabetes at the family physician level has been included in the program in selected areas, thus improving care for these patients. In the future, more common diseases, as for example coronary heart disease and chronic obstructive pulmonary disease, will be included in the program.

Multiple risk factor intervention has proven its efficiency as secondary prevention of cardiovascular disease in the MIRVAS Study. Other multiple risk factor intervention studies (eg, the Steno-2 Study) have proven the benefits of a similar approach in patients with type 2 diabetes.<sup>15</sup> Today's challenge is how to implement the treatment programs used in these studies. It would be a shame if patients could not harvest the benefits from well planned and long-running clinical trials.

## CONFLICTS OF INTEREST

None declared.

## REFERENCES

1. Murray CJL, Lopez AD, editors. The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020. Boston: Harvard School of Public Health; 1996.
2. Yusuf S, Hawken S, Ôunpuu S, Dans T, Avezum A, Lanas F, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004;364:937–52.
3. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med*. 2005;353:487–97.
4. Ho PM, Spertus JA, Masoudi FA, Reid KJ, Peterson ED, Magid DJ, et al. Impact of medication therapy discontinuation on mortality after myocardial infarction. *Arch Intern Med*. 2006;166:1842–7.
5. Wingard DL, Barrett-Connor E. Heart disease and diabetes. In: Harris MI, Cowie CC, Stern MP, Boyko EJ, Rieber GE, Bennett PH, editors. *Diabetes in America*. 2nd ed. (NIH publication n°. 95-1468). Bethesda: National Institutes of Health; 1995. p. 429–48.
6. Brown LC, Johnson JA, Majumdar SR, Tsuyuki RT, McAlister FA. Evidence of suboptimal management of cardiovascular risk in patients with type 2 diabetes mellitus and symptomatic atherosclerosis. *CMAJ*. 2004;171:1189–92.
7. Moreno-Palanco MA, Ibáñez Sanza P, Ciria De Pablo C, Pizarro Portillo A, Rodríguez Salvañés F, Suárez Fernández C. Impacto de un tratamiento integral e intensivo de factores de riesgo sobre la mortalidad cardiovascular en prevención secundaria: estudio MIRVAS. *Rev Esp Cardiol*. 2011;64:179–85.
8. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. 2002;360:7–22.
9. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet*. 2004;364:685–96.
10. Glasgow RE, McCaul KD, Schafer LC. Barriers to regimen adherence among persons with insulin-dependent diabetes. *J Behav Med*. 1986;9:65–77.
11. Johansen J, Claudi T, Holte Dahl K. Insulin treatment for poorly regulated diabetic patients in general practice. Better regulation and symptom relief? *Scand J Prim Health Care*. 1999;17:244–9.
12. Eisen SA, Miller DK, Woodward RS, Spitznagel E, Przybeck TR. The effect of prescribed daily dose frequency on patient medication compliance. *Arch Intern Med*. 1990;150:1881–4.
13. Kenny SJ, Smith PJ, Goldschmid MG, Newman JM, Herman WH. Survey of physician practice behaviors related to diabetes mellitus in the U.S. Physician adherence to consensus recommendations. *Diabetes Care*. 1993;16:1507–10.
14. Mainz J, Krog BR, Bjørnshave B, Bartels P. Nationwide continuous quality improvement using clinical indicators: the Danish National Indicator Project. *Int J Qual Health Care*. 2004;16 Suppl 1:i45–50.
15. Gæde P, Lund-Andersen H, Parving H-H, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med*. 2008;358:580–91.