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ARTÍCULO DE REVISIÓN

Update in prevention of atherosclerotic heart disease: Management of major cardiovascular risk factors

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ABSTRACT

Cardiovascular disease (CVD) remains as the first cause of death worldwide. Scientific community works everyday trying to ameliorate this burden. Only in the year 2004 around 2,790 publications about the therapeutic use of antihypertensive agents can be found in MEDLINE. Despite this overwhelming effort and information, only a relatively short number of manuscripts have a real impact in clinical practice. For the busy clinician, it becomes almost impossible to screen and be updated with the landmark publications. The purpose of this article is to provide concise information related to prevention of CVD. We reviewed publications in the past 5 years regarding cardiovascular risk factors with special attention to dyslipidemia, hypertension, diabetes, smoking cessation and obesity, discussing some new findings and treatments. We also discuss obstructive sleep apnea (OSA) as a recently identified cardiovascular risk factor, and provide a general overview about its pathophysiology and treatment.

Key words. Cardiovascular disease. Update. Prevention. Risk factors. Atherosclerosis. Dyslipidemia. Hypertension. Diabetes. Smoking cessation. Obesity. Obstructive sleep apnea.

Actualización en la prevención de la enfermedad aterosclerótica: manejo de los principales factores de riesgo

RESUMEN

La enfermedad cardiovascular es la primera causa de muerte a nivel mundial. La comunidad científica trabaja diariamente con el fin de atenuar este problema. Sólo en el año 2004 cerca de 2,790 publicaciones acerca del manejo de hipertensión pueden ser encontradas en el servidor electrónico MEDLINE. A pesar de esta gran cantidad de información, sólo un pequeño número de publicaciones tiene impacto en la práctica clínica. Tomando en cuenta el trabajo del clínico hoy en día y la cantidad de material publicado, resulta casi imposible el mantenerse actualizado. El propósito de este artículo es el proveer información concisa y relevante relacionada con la prevención de la enfermedad cardiovascular aterosclerótica. Se revisaron publicaciones relevantes de los últimos cinco años concernientes a los principales factores de riesgo cardiovascular con especial énfasis en dislipidemia, hipertensión, diabetes, tabaquismo y obesidad. También se discute la apnea obstructiva del sueño, enfermedad descrita recientemente como un factor de riesgo cardiovascular, se comentan de manera general su patofisiología y tratamiento.

Palabras clave. *Enfermedad cardiovascular. Actualización. Prevención. Factores de riesgo. Aterosclerosis. Dislipidemia. Hipertensión. Diabetes. Tabaquismo. Obesidad. Apnea obstructiva del sueño.*

INTRODUCTION

In the past, cardiovascular disease (CVD) was considered an illness of industrialized countries. Annually, over 13 million cardiovascular deaths occur globally, 80% occurring in developing countries, becoming the first or second leading causes of death, and being responsible for one-third of total deaths.[1]

When compared to industrialized countries, developing countries experience twice as many fatalities from CVD.[2] US Hispanics suffer a high prevalence of conventional or modifiable CVD risk factors such as hypertension, smoking, low HDL cholesterol, diabe-

tes and obesity, which can explain at least 75-85% of new cases of CVD.[3] The high prevalence and increasing incidence of these risk factors in developing countries along with a high mortality makes CVD a great toll for society and a tremendous economical burden.[4,5]

Significant research advances have been reported during the past few years; with great impact on secondary cardiovascular prevention.[6] This article will introduce landmark publications in each of the modifiable risk factors and new promising therapies.

MODIFIABLE MAYOR RISK FACTORS

Dyslipidemia

Statins and Coronary heart disease

The Heart Protection Study is the largest lipid reduction study to date, involving participants at high risk for cardiac adverse events who were assigned to receive simvastatin 40 mg/day or placebo. Even tough significant cross over from treatment arms was present (18% by the 5th year of follow-up), when compared to placebo statin treatment was associated with significant reductions in adverse events, such as: total mortality 12.9% vs. 14.7%, coronary heart death 5.7 *vs.* 6.9% and a marginal reduction in other vascular deaths 5.3 *vs.* 5.6%.[7] Importantly, benefit was present even in patients with baseline cholesterol below 100 mg/dl opening the question of which is the "ideal" level for LDL reduction. Adverse events related to treatment were low in the statin group and were not related to irreversible damage. Mortality or morbidity for any non-cardiovascular events, including cancer was the same in treatment and placebo groups. The benefit of statin treatment was very consistent across age, sex, and baseline disease and nonlipid risk factor status. This study suggests that lowering LDL using statins provides an important benefit on cardiovascular outcomes in patients at high risk for cardiovascular events and they might be helpful in patient with "normal" LDL levels.

Intensive vs. moderate lipid-lowering therapy

Since the results of the Heart Protection Study, the possibility of obtaining additional benefit by reducing LDL cholesterol below "normal values" has been investigated. Three randomized controlled trials assessing the potential benefit or high dose statins *vs.* usual dosage have been conducted and are showing interesting results.

Pravastatin or Atorvastatin Evaluation and Infection Therapy trial (PROVE-IT) compared high dose statins (atorvastatin 80 mg) versus usual statin dose (simvastatin 20mg) enrolled a large number of patients with acute coronary syndromes who were followed by a mean of 24 months to assess all-cause mortality and cardiovascular events. High dose therapy showed a 16% reduction in major cardiovascular events (except stroke), and a 28% reduction in total mortality when compared to moderate therapy.[8] These results are consistent with more recent studies, such as the ones reported in Treating to New Targets (TNT), using the same medications (atorvastatin 80 mg versus simvastatin 20-40 mg) reported a 22% risk reduction in major cardiovascular events, 20% reduction in Cardiac Heart Disease (CHD) a 22% reduction in nonfatal myocardial infarction, 25% reduction in fatal and nonfatal stroke in the intensive treatment arm when compared to usual dose therapy.[9] Recently, the Incremental Decrease in End points through Aggressive Lipid lowering (IDEAL) randomized controlled trial of high statin dosage versus normal dosage reported a nearly significant reduction of 11% ($p = 0.07$) in the intensive therapy group for major coronary event (primary outcome), but when using the same primary endpoint as the TNT trial (major cardiovascular events) the IDEAL trial showed a significant 13% risk reduction ($p = 0.02$) in the intensive therapy arm.[10] Important to mention, all 3 trials have reported a significant increase (around 5%, $p = < 0.001$) in drug related adverse events, being the most common liver enzyme elevations. However, none of the studies reported a difference in serious adverse events or a higher number of non-cardiovascular deaths. These studies suggest that high dose statins brings additional benefit in cardiovascular outcomes, but no benefits in total mortality. Recently National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) recommends a LDL < 70 mg/dl in patients at high risk for cardiovascular events (previous myocardial infarction or patients with coronary artery disease and multiple cardiovascular risk factors) supporting that lower is better.

Statins and acute coronary syndrome

A growing area of study has been the use of statins in the management of persons with acute coronary syndromes. The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) is a randomized controlled trial which assessed the potential impact of early (24-96 hours post admission) administration of high dose (80 mg/day) atorvastatin in patients hospitalized with unstable angina or non-Q-wave MI. After a 16-week follow-up period, fa-

tal and non-fatal stroke were reduced in the treatment arm as compared to the placebo arm (0.8% versus 1.6%, p=0.02).[11] Although a modest benefit, additional benefit of using statins and especially high dose statins appears to be consistent for preventing adverse cardiovascular events, even in patients with acute coronary syndromes.

Hypertension

Hypertension and dyslipidemia

The effect of cholesterol lowering therapy (especially statins) to prevent CVD in hypertensive patients has been contradictory. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial—Lipid Lowering Trial (ALLHAT-LLT), a multicenter randomized non blinded trial enrolled hypertensive patients to receive pravastatin (40 mg a day) versus usual care (diet and exercise). After a mean follow up of 4.8 years statin therapy did not reduce the primary outcome of all-cause mortality or cardiovascular events when compared with usual care. These results are not consistent with studies reporting benefit with statin treatment. A possible explanation for this result is that only a small difference in LDL levels was achieved between groups at 6 years follow up (104 mg/dl in statin group vs. 121 mg/dl in the control) and lower number of events than projected at follow up. This study suggest that statin use in hypertensive patients may not benefit or that hypertensive patients might have a limited benefit from statin treatment than patients without hypertension.[12] In contrast, the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA), a multicenter randomized trial [13] designed to compare two antihypertensive treatments to prevent CHD events, where 18,000 hypertensive subjects with no history of CHD were assigned to receive atorvastatin (10mg) vs. placebo. The study was stopped prematurely (after a median follow-up of 3.3 years instead of 5 years) by the data safety monitoring board, based in the clear benefit obtained in the lipid-lowering arm, a non-fatal infarction and fatal CHD was 36% lower at the statin group when compared to placebo and a 29% reduction for total coronary events. LDL reduction was 29% in the atorvastatin group vs. 19% in the placebo group (blood-pressure control was similar in both groups)[14] although women and diabetics did not show benefit from statin use. Even though these studies are contradictory, statins have been related to better outcomes across several studies and they should be encouraged in hypertensive patients when indicated.

Medications in hypertension

To establish which specific antihypertensive therapy results in greater benefit becomes more complex every day. In the last few years many randomized clinical trials comparing antihypertensive therapies have shown contradictory data. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), a randomized, double-blind controlled trial was designed to compare the efficacy of calcium channel blocker therapy, angiotensin-converting enzyme inhibitor therapy and diuretic therapy as first-step therapy for hypertension. Participants with at least one other coronary heart disease risk factor besides hypertension were randomly assigned to one of three treatment arms: (1) chlorthalidone, 12.5 to 25 mg/day, amlodipine, 2.5-10 mg/day, or lisinopril, 10 to 40 mg/day. Mean follow-up was 4.9 years. The study did not find a difference in fatal cardiac heart disease and nonfatal MI (primary outcome) by treatment group, and found no difference in blood pressure reduction across treatment groups. This finding suggests, that reduction in blood therapy is the most important goal to achieve rather than the type of medication used.[15]

Recently, a meta-analysis including data from 42 randomized clinical trials with 192,478 patients assigned to receive the following treatments: placebo, angiotensin converting enzyme inhibitors, calcium channel blockers, beta blockers, angiotensin receptor blockers and low-dose diuretics. Low-dose diuretics showed the better outcome compared to placebo and other medications for almost every outcome, such as coronary heart disease (RR, 0.79; 95% CI, 0.69-0.92); congestive heart failure (RR, 0.51; 95% CI, 0.42-0.62); stroke (RR, 0.71; 0.63-0.81); cardiovascular mortality (RR, 0.81; 95% CI, 0.73-0.92); and total mortality (RR, 0.90; 95% CI, 0.84-0.96).[16] This meta-analysis suggests that low-dose diuretics are an effective and affordable treatment in hypertensive patients to prevent total mortality and adverse cardiovascular events, with similar or better results than other antihypertensive medications.

Diabetes

Diabetes and atherosclerosis

Diabetes is considered as a coronary risk equivalent. Both, diabetic men and women without clinical coronary disease and diabetes had shown extensive atherosclerosis at autopsy which was equal to that of those with clinical coronary disease.[17] Therefore, diabetes has to be considered a high risk factor for adverse Cardiovascular (CV) events and should re-

ceive aggressive treatment and special consideration when treating additional risk factors for secondary prevention of CVD.

Lifestyle modification in type 2 diabetes

The Diabetes Prevention Program Research Group conducted a randomized trial designed to compare the impact of usual care versus therapeutic lifestyle change (7% weight loss and 150 minutes/wk of exercise) and medical therapy with metformin (850 mg twice a day) in the prevention of type 2 diabetes in persons at high risk body mass index (BMI) (of 34 and impaired glucose tolerance) for developing the disease. The trial was stopped early (3 years) because due to a lower incidence (14%) of diabetes in lifestyle changes group compared to a 22% incidence in the treatment arm with metformin and 29% incidence in the control group. The lifestyle change group was significantly better than either the control group or the metformin group despite the fact that only 50% achieved the treatment goals in that group. The number needed to treat in order to prevent one case of diabetes was 14 for the metformin group and 7 for the therapeutic lifestyle change group. These findings were similar in all age, sex, race, and ethnic groups studied.[18] Lifestyle modifications with diet had also been studied; The Health Professionals Study and Nurses Health study showed that consuming a western diet (red meat, refined grains, French fries, sugary drinks, high fat dairy, sweets & desserts) is more related to develop diabetes, than those consuming a diet high in whole grains.[19-21] This findings suggest that a proper diet and exercise to maintain a healthy weight are the most effective therapies to reduce the development of type 2 diabetes.

Diabetes and vascular complications

Vascular complications are the first cause of mortality in patients with diabetes mellitus. A clinical randomized trial conducted to asses if patients that monitor their risk factors were more likely to retard vascular complications in patients with type 2 diabetes when compared to the standard care.[22] Patients were given written targets for blood pressure, LDL cholesterol, glycosylated hemoglobin and weight; instructions specified that they as patients were responsible for reaching and maintaining these parameters; instructions to record these parameters and request therapeutic changes if they were not at target. At four years, the patient participation group had significantly lower mean blood pressure, LDL cholesterol, glycosylated hemoglobin, and number of cardiovascular events. Every patient in the patient participation group was on angiotensin converting enzyme inhibitors or angiotensin receptor blockers and statin therapy; whereas, only 50% of the standard groups were on these drugs.[23] These findings are consistent with a previous report from Greenfield[24] that found that persons with diabetes who were involved in their own care had better clinical outcomes than those individuals who were not actively involved in their own health management. Patient-oriented education aimed at increasing self-management skills helps improve the use of appropriate preventive medications and the control of cardiovascular risk factors in persons with diabetes. Given the traditional physician-directed care results in suboptimal cardiovascular disease (CVD) risk factor control and use of preventive medication, self-management training should be considered for all patients at risk for CVD, particularly those with diabetes.

Smoking

Smoking and cardiovascular mortality

Smoking is the leading cause of preventable death in developed countries, it is estimated that 1 of every 5 deaths can be attributed to cigarette smoking and 43% of those are related to CVD.[25] Long-term smoking is known to account as a major risk factor for CVD the relative risk for smokers is estimated to be from 1.5 to 3.[26-27]

Several studies have proven benefit of smoking cessation on mortality and cardiovascular outcomes in patients with coronary disease. There are two major meta-analyses assessing the effect of smoking cessation in patients with established coronary disease. A reduction from 36 to 46 % was reported in total mortality in patients who quitted smoking.[28-29] Both studies showed consistent results regardless of age, sex, country and year of study.

Smoking cessation

While smoking cessation interventions are generally more successful in persons with CVD than in those who don't have CVD, smoking cessation is a significant challenge in both groups.[30] Wiggers, et al,[31] reported a meta-analysis of several studies assessing different strategies (nicotine replacement therapy, antidepressants, behavioral council, and medical advice) to quit smoking in patients with coronary disease, none of these interventions is reliable and all of them have very high percentage of failure. Nicotine replacement therapy, the most frequently pharmacological intervention did not show any benefit from placebo, besides nicotine may have some cardiotoxic

effects and therefore should not be used in patients with unstable cardiac disease.

Rimonabant, a new drug that works as a selective cannabinoid channel blocker has been used in Phase III studies for smoking cessation. The Studies with Rimonabant and Tobacco Use (STRATUS-US) trial randomized smokers who had previously failed to quit smoking to placebo or rimonabant. Rimonabant arm had a 36.2% tobacco cessation versus 20.6% treated with placebo at 10 weeks with no weight gain. Smoking cessation can reduce adverse cardiovascular events as much as other therapies, such as: statins (29% reduction), aspirin (15% reduction) beta blockers and angiotensin converting enzyme inhibitors (23% reduction) and must be a cornerstone for CVD prevention.

Obesity

Obesity and cardiovascular disease

Overweight and obesity have reached epidemic proportions in the United States and many other countries. The actual prevalence of overweight and extreme obesity in US population is estimated to be 64.5% and 4.7% respectively in the general population.[32] This increase has occurred among men, women, all age groups and different races. The obesity epidemic is not limited to developed countries. About 1/3 of some Mexican samples have obesity, and more than 50% of Mexican women have central obesity (unpublished data provided by FLJ).

Overweight and obesity have been reported to be associated with an increased risk for cardiovascular disease, and is the most prevalent cardiovascular risk factor in patients with previous myocardial infarction.[33] Most of this association, however, has been traditionally attributed to the causal effect of obesity on dyslipidemia, hypertension, and insulin resistance. The possibility that excess body fat itself plays a major, direct role in the pathogenesis of CVD has been a matter of considerable debate. Several lines of evidence suggest that adipose tissue exhibits independent and potentially harmful effects on cardiovascular health and the distribution of obesity (central/visceral adiposity) might be more important to assess risk rather that other measures of obesity.[34]

Bariatric surgery and cardiovascular risk factors

Bariatric surgery has proven to be the most effective treatment for morbid and complicated obesity. One study explores the benefits in lifestyle, diabetes and cardiovascular risk factors of bariatric surgery (banding, vertical banded gastroplasty and gastric bypass) at 10 years follow-up versus contemporaneously treated obese control subjects. After 2 years the weight had increased 0.1% in the control group and had decreased 23.4% in the surgery group ($p<0.001$) by 10 years the weight had increased by 1.6% in the control and decreased by 16.1% at the intervention group ($p<0.001$). The incidence rates of hypertriglyceridemia, diabetes, and hyperuricemia were markedly lower in the surgically treated group than in the control at 10 years, but the incidence of hypertension and hypercholesterolemia did not differ between the groups.[35] This data suggest that bariatric surgery is a favorable option in the treatment of severe obesity, but not all obesity-associated risk factors can be improved by sustained weight loss. Risk prediction models suggest that bariatric surgery may actually reduce mortality;[36] nevertheless, long term effect of bariatric surgery on total mortality, cardiovascular even and cancer remains unknown.

Pharmacological treatment in obesity

Despite many attempts to create an effective medication to treat obesity results are far from being satisfactory. New treatments for obesity are now being developed that appear to be promissory. Ghrelin, a recently discovered a hormone that increases food intake in humans is secreted primarily in the stomach and the duodenum. Ghrelin has been related to mealtime hunger and long-term regulation of body weight. Cummings, et al, assessed the effect of plasma levels of ghrelin in patients with normal diet versus gastric bypass. Diet-induced weight loss was associated with 24% increase for the 24-hour ghrelin profile, while patients with weight loss after gastric bypass had and absent diurnal rhythm of the ghrelin.[37] This discovery opens the possibility of developing ghrelin antagonists that might someday be considered as a "pharmacological bypass" for treating obesity.

The endocannabinoid system is a newly discovered, physiological system believed to play a role in maintaining energy balance through the regulation of food intake and energy expenditure.[38] An overactive endocannabinoid system has been found in overweight/obese people and might be one of the reasons of weight gain.[39-40] Rimonabant is the first in a new class of drugs called cannabinoid type1 (CB_1) blockers which can help to modulate the disrupted endocannabinoid system found in overweight and obese population. The Rimonabant in Obesity trial (RIO-Lipids) was an international, multi-center, do-

uble blind, placebo-controlled phase III study aimed to assess weight loss in 1,036 patients with dyslipidemia and BMI between 27 and 40 kg/m^2 and its association with major cardiovascular risk factors. Patients were randomized to receive rimonabant (5 and 20 mg) or placebo along with a reduced calorie diet for one year. Patients treated with rimonabant 20 mg per day lost 8.6 kg *vs.* 2.3 kg on placebo ($p < 0.001$), HDL-cholesterol increase by 23% ($p < 0.001$ *vs.* placebo); 15% reduction in triglycerides ($p < 0.001$ *vs.* placebo), blood glucose was reduced by 9% *versus* 4% in the placebo ($p < 0.001$).[41] Rimonabant was well tolerated and has proven to prevent weight regain after two years. This new CB1 blockers may be one of the most important therapies for overweight and obesity in the years to come.

Obstructive sleep apnea

Obstructive sleep apnea and CVD

Obstructive sleep apnea (OSA) has been recently identified as an independent and highly prevalent cardiovascular risk factor. OSA can be found in 1 of 5 adults and its prevalence increases as the BMI does.[42] Diagnose of sleep apnea is clinically suggested by daytime sleepiness and nocturnal snoring but the diagnosis is confirmed with an overnight polisomnography study.[43] Several pathophysiological factors found in OSA are closely related to CVD: (1) Altered peripheral chemoreflex sensitivity, leading faster heart rates, blunted heart rate variability, and increased blood pressure.[44] This impairment of peripheral chemoreceptors predisposes to severe bradyarrhythmias during apneic events and had been related to an increase of fatal outcomes.[45] (2) Endothelial dysfunction is found in patients with OSA, an increase of endothelin (an endogenous vasoactive substance produced in the endothelial cells) is deeply related to nitric oxide, resulting on increased endothelin and low levels of nitric oxide which have also been found in patients with CVD.[46-48] (3) Inflammatory markers such as C-reactive protein and serum amyloid A are also increased in patients with OSA, this makers are associated to the development and progression of CVD.[49-51] (4) Insulin resistance and diabetes mellitus have a higher prevalence in patients with OSA (adjusting for body weight)[52] The adipocyte-derived protein leptin also appears to be abnormal in OSA individuals,[53] leptin is known to act in the central nervous system as an appetite suppressant in lean patients, and its blood concentrations correlate with overall adipocyte mass, suggesting leptin-resistance in obese patients.

With all these pathophysiologic findings is not surprise that OSA has been related to hypertension, cardiac heart failure, arrhythmias, coronary artery disease and stroke.[54-55]

Effective treatments for OSA include: loosing weight (10% weight loss improves significantly severity of OSA), continuous positive airway pressure (eliminates upper-airway flow limitation in almost every patient) has been associated with improvement of most pathophysiological mechanisms, other treatments like uvulopalatopharyngoplasty and mandibular devices needs further studies,[56-57] if actual treatments for OSA improve mortality is not known.

Given the high prevalence of OSA in the population and its association with CVD, a more aggressive screening approach is guaranteed, particularly in patients with hypertension or at high risk for CVD.

ACKNOWLEDGMENTS

Dr. Somers is supported by NIH grants HL65176, HL61560, HL 70302, and M01-RR00585.

Dr. Lopez-Jimenez is a recipient of a Clinical Scientist Development Award from the American Heart Association.

Dr. Korinek is supported by grant MSM 00216 20817.

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Recibido el 9 de agosto de 2005.
Aceptado el 27 de febrero de 2006.