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CLINICAL UP-DATE

Clinical decisions in patients with diabetes and other cardiovascular risk factors. A statement of the Spanish Society of Internal Medicine



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Abstract Although the mortality associated to cardiovascular diseases (CVD) has been reduced in the last decades, CVD remains the main cause of mortality in Spain and they are associated with an important morbidity and a huge economic burden. The increasing prevalence of obesity and diabetes could be slowing down the mortality reduction in Spain. Clinicians have often difficulty making clinical decisions due to the multiple clinical guidelines available. Moreover, in the current context of economic crisis it is critical to promote an efficient use of diagnostic

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◇ The components of the SEMI Working Group are listed in Appendix A to the end of work.

Diabetes mellitus;
Obesity;
Hypertension;
Dyslipidemia;
Platelet aggregation

PALABRAS CLAVE

Enfermedades
cardiovasculares;
Prevención primaria;
Prevención
secundaria;
Diabetes mellitus;
Obesidad;
Hipertensión;
Dislipidemia;
Agregación
plaquetaria

and therapeutic proceedings to ensure the viability of public health care systems. The Spanish Society of Internal Medicine (SEMI) has coordinated a consensus document to answer questions of daily practice with the aim of facilitating physicians' decision-making in the management of diabetes and cardiovascular risk factors from a cost-efficiency point of view.

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Decisiones clínicas en pacientes con diabetes y otros factores de riesgo cardiovascular. Una declaración de la sociedad española de medicina interna

Resumen Aunque la mortalidad asociada a enfermedades cardiovasculares (ECV) se ha reducido en las últimas décadas, las ECV siguen siendo la causa principal de mortalidad en España y están asociadas a una morbilidad importante y una enorme carga económica.

La creciente prevalencia de obesidad y de diabetes podría estar frenando la reducción en la mortalidad en España. Los médicos suelen tener mucha dificultad en la toma de decisiones clínicas debido a las múltiples guías clínicas disponibles. Por otro lado, en el contexto actual de la crisis económica es imprescindible promover un uso eficaz de los procedimientos diagnósticos y terapéuticos para garantizar la viabilidad de los sistemas de salud pública. La Sociedad Española de Medicina Interna (SEMI) ha desarrollado un documento de consenso para responder a las dudas que surgen en la práctica rutinaria con el objetivo de facilitar a los médicos la toma de decisiones en el control de la diabetes y en los factores de riesgo cardiovascular desde el punto de vista de la rentabilidad.

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Introduction

Cardiovascular diseases (CVD) are still the leading cause of death worldwide,¹ being the first cause of death in the Spanish population.² In addition, CVD are responsible for high social and economical burden, including direct costs related to the use of health resources for the diagnosis and treatment of the various forms of CVD, and indirect cost derived from early mortality, absenteeism from work, family care or disability.³ Among the direct costs, and according to the Spanish Ministry of Health, CVD ranks first in drug consumption (considering the percentage of defined daily dose (DDD) over the total of therapeutic groups).⁴ Atorvastatin, enalapril and simvastatin are included among the ten top active ingredients in number of vials/packages prescribed.⁵

Cardiovascular mortality rates in Spain have decreased over the last decades. This reduction could be explained by a better control of risk factors and the use of evidence-based treatments.⁶ It is generally accepted that the prevention of CVD – and CVD related mortality – is based on the detection and control of modifiable risk factors, such as hypercholesterolemia, hypertension, diabetes mellitus (DM) or overweight.⁷ In Spain, the most important achievements contributing to mortality reduction have been the better control of cholesterol levels and blood pressure.^{8,9} However, other risk factors have not followed this beneficial trend. The increases in body mass index (BMI) in men, smoking in women, and diabetes mellitus (DM) in both sexes¹⁰ could be slowing down the mortality reduction in Spain.

In the CVD-related burden settings, multiple documents have been written to help clinicians in their daily clinical

decision making. These documents include clinical practice guidelines (CPG), recommendations and algorithms based on the available clinical evidence. In light of this wide amount of documentation, the difficulty for clinicians of being properly informed in their clinical practice is understandable. For this reason, the Spanish Society of Internal Medicine (SEMI) has coordinated an experience and knowledge exchange of experts, to help the clinicians to make decisions and solve questions of the daily practice, providing a practical approach to patients with potential cardiovascular risk (CVR). This document is not intended to increase the already available information. Considering the current situation of the health system, and in line with other similar initiatives from American scientific societies,^{11,12} this statement pretends to promote the effective use of procedures or medications in the management of CV risk factors, identifying practices that are not often necessary and which may cause detrimental effects.

Methodology

A panel of experts conducted a comprehensive analysis of the scientific literature related to diabetes and other CVR factors. This expert panel comprised 51 internal medicine physicians specialized in diabetes and CVD. Five of the 51 internists acted as coordinators and 8 as moderators. After reviewing the existing evidence each moderator proposed the key issues to be discussed by the experts. The 5 coordinators defined 21 relevant questions concerning diabetes and CVR factors, and proceeded to review and select the most pertinent bibliography which was sent to the experts

for their review. After this preliminary work, a consensus conference took place in Córdoba (Spain) on 23 November 2012. The whole-day conference was divided into three sessions: three moderators presented the key topics (diabetes and obesity, dyslipidemia, hypertension and platelet anti-aggregation) and formulated the questions to be discussed. Then, the members of the panel were distributed into 4 working groups to discuss and formulate precise answers to the questions being posed. Each working group had 2 moderators who conducted the discussions and summarized the conclusions. Finally, a plenary session took place, in which one moderator from each working group communicated the answers agreed upon by the groups and put to an anonymous vote by electronic system to reach a global agreement. Attendees had 3 vote options: "I agree", "I do not agree" and "I cannot define based on the evidence". A consensus agreement was considered when at least 75% of the votes were "I agree". When the cut-off point was not reached, the question was discussed by the whole panel, reworded accordingly, and then put to a vote again. After the vote and once a consensus were reached, the 5 coordinators supervised all the questions and answers to confirm its accuracy.

Results

A total of 21 questions were answered by a mean of 41 participants (range 32–44). Eleven (52%) questions were approved on the first ballot, and the rest underwent a second vote to achieve the minimum 75% of agreement. Some of the latest were reworded to better express the opinion of the experts. The result of this consensus is presented in the form of answers to the questions clustered under the four key topics (Figs. 1–4).

A. DM and obesity (Fig. 1)

1. Is it appropriate to test for myocardial ischemia in all DM2 asymptomatic patients?

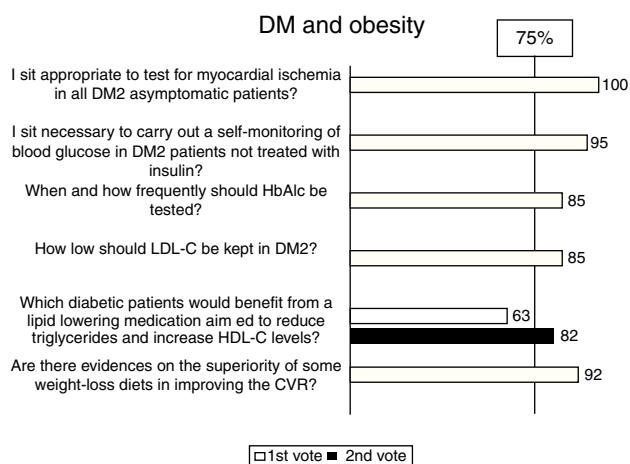


Figure 1 Diabetes and obesity. Percentage of participants agreeing with the answers proposed for each question. The answer to one question required a second vote to reach an agreement. The vertical line represents the minimum percentage (75%) of votes required to reach a consensus among participants.

High blood pressure

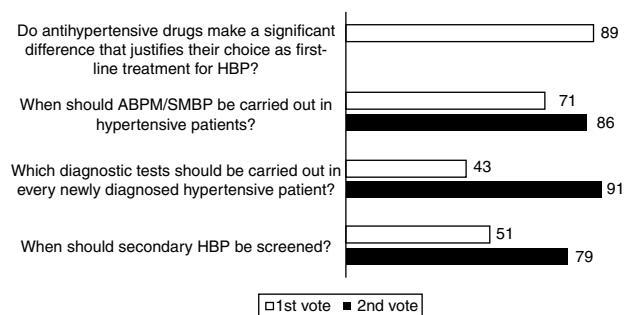


Figure 2 High blood pressure. Percentage of participants agreeing with the answers proposed for each question. The answers to three questions required a second vote to reach the agreement. The vertical line represents the minimum percentage (75%) of votes required to reach a consensus among participants.

- The detection of myocardial ischemia is not indicated as a routine practice.^{13,14} In DM2 asymptomatic patients, a comprehensive clinical history searching for CVR, including symptoms and signs of CVD, and an electrocardiogram obtained at rest should be enough.¹⁵
2. Is it necessary to carry out a self-monitoring of blood glucose (SMBG) in DM2 patients not treated with insulin?
- Routine SMBG is not needed in DM2 patients with a stable disease and a good glycemic control,¹⁶ particularly in those patients treated with anti-diabetics non-related to higher risk of hypoglycemia.
 - Patients treated with insulin secretagogues must have access to SMBG, to confirm hypoglycemia if it is suspected.¹⁷
 - In newly diagnosed patients, a SMBG during the first 2 months could be suggested as part of the patient diabetic education.¹⁸

Dyslipidemia

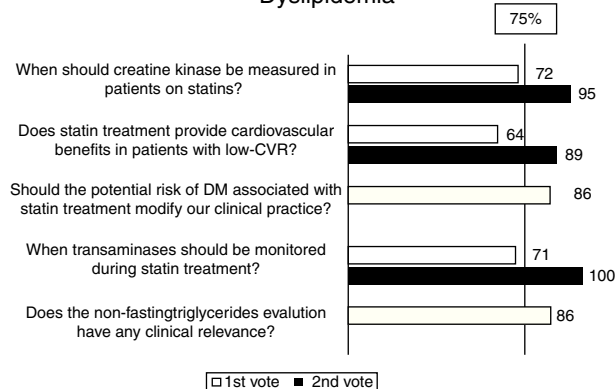


Figure 3 Dyslipidemia. Percentage of participants agreeing with the answers proposed for each question regarding. The answers to three questions required a second vote to reach the agreement. The vertical line represents the minimum percentage (75%) of votes required to reach a consensus among participants.

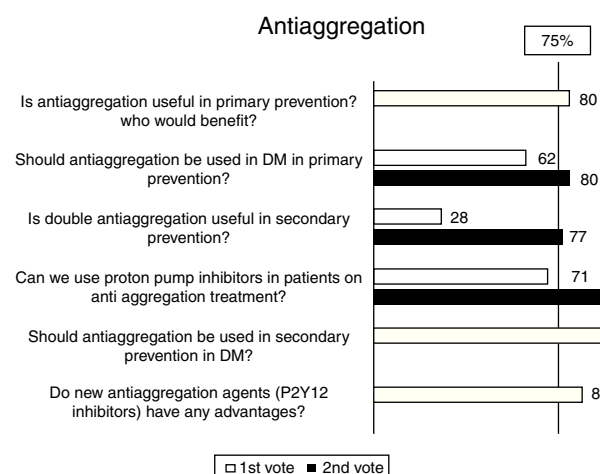


Figure 4 Antiaggregation. Percentage of participants agreeing with the answers proposed for each question regarding. The answers to three questions required a second vote to reach the agreement. The vertical line represents the minimum percentage (75%) of votes required to reach a consensus among participants.

- An efficient use of self-checks would decrease the cost of the management of DM patients.¹⁷

3. When and how frequently should HbA1c be tested?

- For diagnostic purposes, HbA1c should be tested in patients with altered basal glycemia, in those with high CVR, and in patients with overt CVD.
- For metabolic control, in diabetic patients: at least every 6 months when the disease is stable; every 3 months in non-stable patients or after treatment modifications.
- HbA1c interpretation has to take into account some limitations, including hemoglobinopathy, pregnancy, chronic kidney disease, etc.

4. How low should LDL-cholesterol (LDL-C) be kept in DM2?

- The primary goal is an LDL-C < 100 mg/dl in all diabetic patients.^{13,19}
- A further target of LDL-C below 70 mg/dL has been proposed in patients:
 - With a very high CVR: atherogenic dyslipidemia (defined as decreased HDL cholesterol [HDL-C] and increased triglycerides [TG]),²⁰ chronic renal impairment (glomerular filtration rate < 45 ml/min) with proteinuria,²¹ or peripheral artery disease.²²
 - With overt CVD.^{13,19}

5. Which diabetic patients would benefit from a lipid lowering medication aimed to reduce TG and increase HDL-C levels?

- Once the LDL-C target is achieved (as stated in question 4), patients with HDL-C < 35 mg/dl and TG > 200 mg/dl would benefit from additional lipid lowering medication.²³

6. Is there any evidence on the superiority of certain weight-loss diets in improving the CVR?

- There is no consistent evidence supporting the superiority of any particular diet in terms of weight loss.²⁴ However, the Mediterranean diet improves the cardio-metabolic profile over the long term in obese patients²⁵ and it has shown to reduce the incidence of CV events among people at high CVR.²⁶
- Clinical studies are needed to establish the cardiovascular safety of dissociated diets.

B. High blood pressure (HBP) Fig. 2

1. Do antihypertensive drugs make a significant difference that justify their choice as first-line treatment for HBP?²⁷

- First of all, changes in lifestyle, such as diet or exercise, should not be overlooked as an essential first step in the treatment of HBP.
- First-line drugs should include angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers and diuretics.
- Treatment must be tailored according to the degree of CVR, co-morbidities, age, ethnicity, tolerance, blood pressure level, therapeutic purposes and cost/effectiveness profile.
- Renin-angiotensin system inhibitors are the right choice for patients with DM and metabolic syndrome.

2. When should ambulatory blood pressure monitoring (ABPM)/Self Monitoring of Blood Pressure (SMBP) be carried out in hypertensive patients?²⁷

- We should optimize the arterial blood pressure measure at the doctor's office.
- It would be advisable to generalize the SMBP records for a better control of blood pressure values.
- In case of doubt on HBP diagnosis or degree of therapeutic control, SMBP or preferably ABMP (when available) must be preformed.
- It would be desirable that all hypertensive patients had at least one ABPM record (when available).

3. Which diagnostic tests should be carried out in every newly diagnosed hypertensive patient?²⁷

- A proper clinical history together with a comprehensive physical examination is essential.
- Every patient should undergo the following:
 - Laboratory tests (including plasma glucose, lipid profile, glomerular filtration rate (GFR), and albumin-creatinine ratio in a fresh urine sample).
 - Electrocardiogram.

4. When should secondary HBP be screened?²⁸

- It is advisable in newly diagnosed patients aged <20 and >65 years.
- In patients with resistant hypertension.

- When physical or complementary examinations show alterations suggesting secondary HBP.

C. Dyslipidemia

1. When should creatine kinase (CK) be measured in patients on statins?

- We do not believe that CK levels should be determined systematically, due to its low specificity and sensibility; thus it should be reserved for symptomatic patients.²⁹⁻³²

2. Does statin treatment provide cardiovascular benefits in patients with low-CVR?

- Statins are beneficial in patients at low-CVR,³³ although the decision of starting treatment with those drugs must take into account efficiency criteria.

3. Should the potential risk of DM associated with statin treatment modify our clinical practice?

- The low risk of incident diabetes showed with statins in clinical trials should not modify the indication of those drugs in non-diabetic patients meeting the criteria for statin treatment.³⁴

4. When should serum transaminases be monitored during statin therapy?

- We recommend to measure transaminases levels at the beginning of treatment, when new symptoms or signs appear (e.g. jaundice), in patients with liver disease and when the treatment pattern is changed (e.g. changes in dosage, new drug combination, etc.)

5. Does the non-fasting TG evaluation have any clinical relevance?

- Although recent epidemiological studies remark the higher value of non-fasting (as compared to fasting) TG as predictors of CVD,³⁰ due to the lack of clear recommendations in current CPG, together with the difficulty in interpreting laboratory results under non-fasting conditions, including glycemia or calculated LDL-C, we strongly discourage its use for clinical decision making.

D. Antiaggregation

1. Is antiaggregation useful in primary prevention? Who would benefit?

- Antiaggregation is not useful in primary prevention on a general basis.^{13,35,36}
- It can be considered in high CVR patients, balancing the risk of bleeding in each patient.^{13,37}
- Although antiaggregation could be considered in cancer prevention, currently there is not enough evidence to support this recommendation.³⁸

2. Should antiaggregation be used in DM as primary prevention?

- Antiaggregation in DM is associated to higher pharmacologic resistance and higher risk of bleeding.³⁹
- The scientific evidence has not proven net clinical benefit in DM, and there are discrepancies among CPG.³⁵
- Thus, antiaggregation in primary prevention is only justified in patients with DM and high CVR.⁴⁰

3. Is double antiaggregation useful in secondary prevention?

- Except in the case of acute coronary syndrome (ACS), double antiaggregation has not demonstrated clear net clinical benefit.⁴¹
- In ACS not under percutaneous coronary intervention (PCI), we recommend double antiaggregation after balancing the risk of bleeding.⁴²
- In ACS undergoing PCI, we recommend double antiaggregation, with a minimum of 1 month for metallic-stents and 3-6 months for pharmacological-stents.⁴¹

4. Can we use proton pump inhibitors (PPI) in patients on antiaggregation treatment?

- There is not enough evidence supporting a potential increased risk of cardiovascular events with the concomitant use of clopidogrel and PPI.⁴³
- We recommend the use of PPI in antiaggregated patients after considering the risk of gastrointestinal bleeding.

5. Should antiaggregation be used in secondary prevention in DM?

- Unless contraindicated, antiaggregation is mandatory in secondary prevention in DM patients.⁴⁴

6. Do new antiaggregation agents (P2Y12 inhibitors) have any advantages?

- At present, the indication for the new P2Y12 inhibitors is for secondary prevention after ACS.

Discussion

This study shows that there is an extensive agreement among Spanish internal medicine physicians concerning crucial issues on diabetes and CVR factors. In addition, it shows the SEMI position related to 21 measures to implement an efficient use of available recommendations.

Among the 6 questions on DM and obesity, only one (A-5) was controversial. Initially, the working group proposed to recommend the specific use of fibrates and omega-3 agents to reduce triglycerides and increase HDL-C levels. However, it was not accepted by the majority of the whole panel; thus the agreement was to avoid the specific mention of these drugs, keeping the recommendation in a more generic level.

Regarding HBP, three out of the four questions required further revision by the whole panel: question B-2: although the usefulness of both ABPM and SMBP are fully recognized, the first is not always available in the medical practice. For this reason, the panel agreed to recommend spreading the use of SMBP, although stressing that it would be desirable to have at least one ABMP per patient (conditioned

to its availability). Question B-3: considering the diagnostic tests to be carried out in newly diagnosed hypertensive patients, the panel questioned the need of a routine chest X-ray and finally decided not to include this complementary test unless clinically indicated. Question B-4: After discussion, the panel decided to focus the screening for secondary HBP on three key points: age at diagnosis, resistance to treatment and a suspected secondary HBP.

In the dyslipidemia section, when monitoring patients on statins for dyslipidemia (question C-1), the working group initially recommended the systematic evaluation of CK levels in all patients on statin treatment. However, after discussing and evaluating the clinical evidence, the whole panel acknowledged that it was not cost-efficient to systematically test CK levels during statin treatment. Thus, we recommend conducting the test only in symptomatic patients. The other 2 questions requiring a second vote were approved after a slight modification of the answer or the question.

Finally, there was controversy regarding the minimum time of double antiaggregation (question D-3) in patients with ACS and PCI; this point was discussed and agreed upon according to the available evidence. The other 2 questions requiring a second vote reached the consensus by modifying the answers.

Conclusion

In spite of the multiple available guidelines on CVR and diabetes, there are practical questions needing simple answers. Routine clinical practices should be reconsidered according to clinical evidence and experience. Customary practices should be adapted to individual patients' characteristics. A rational use of diagnostic and management procedures leads to improved cost-effectiveness. Upon this consensus, SEMI recommends 21 measures to promote the efficient use of medical CV procedures.

Conflict of interest

This initiative has been supported by the Spanish Society of Internal Medicine (SEMI) and funded by Boehringer Ingelheim and Lilly. The authors declare no conflicts of interest.

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Appendix A.

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References

1. The World Health Organization (WHO). Cardiovascular diseases (CVDs), Fact sheet no. 317. March; 2013. Available from: <http://www.who.int/mediacentre/factsheets/fs317/en/index.html>
2. Estrategia en cardiopatía isquémica del sistema nacional de salud. Madrid: Ministerio de Sanidad, Política social e igualdad; 2011. Available from: <http://www.mspsi.gob.es/organizacion/sns/planCalidadSNS/docs/cardiopatia.isquemica/Estrategia.Cardiopatia.Isquemica.pdf>
3. Capewell S, Allender S, Critchley J, Lloyd-Williams F, O'Flaherty M, Rayner M, et al. Modelling the UK burden of Cardiovascular Disease to 2020. A research report for the Cardio & Vascular Coalition and the British Heart Foundation. London: British Heart Foundation; 2008. Available from: <http://www.bhf.org.uk/plugins/PublicationsSearchResults/DownloadFile.aspx?docid=ad18e5a0-7da6-4c7c-8142-f68f27cde451&version=-1&title=Modelling+the+Burden+of+Cardiovascular+Disease+to+2020&resource=Z154>
4. Instituto de Información Sanitaria. Consumo farmacéutico por grupos terapéuticos, edad y sexo. Indicadores. Madrid: Ministerio de Sanidad y Consumo; 2005. Available from: http://www.msc.es/estadEstudios/estadisticas/docs/Consumo_farmacaceutico_por_tramos.edad_ysexoII.Final.pdf
5. Villar F, Banegas JR, Donado JM, Rodríguez Artalejo F. Las enfermedades cardiovasculares y sus factores de riesgo en España: hechos y cifras. Informe SEA 2007. Madrid: Sociedad Española de Arterioesclerosis (SEA); 2004. Available from: http://www.searterioesclerosis.org/resources/archivosbd/clinica_investigacion/4d34a5f3ab9cb226e076bb3b11abf587.pdf
6. Graciani A, Leon-Munoz LM, Guallar-Castillon P, Rodríguez-Artalejo F, Banegas JR. Cardiovascular health in a southern Mediterranean European country: a nationwide population-based study. *Circ Cardiovasc Qual Outcomes*. 2013;6:90–8.
7. Guilbert JJ. The world health report 2002 – reducing risks, promoting healthy life. *Educ Health (Abington)*. 2003;16:230.
8. Gil M, Martí H, Elosua R, Grau M, Sala J, Masia R, et al. Análisis de la tendencia en la letalidad, incidencia y mortalidad por infarto de miocardio en Girona entre 1990 y 1999. *Rev Esp Cardiol*. 2007;60:349–56.
9. Flores-Mateo G, Grau M, O'Flaherty M, Ramos R, Elosua R, Violan-Fors C, et al. Análisis de la disminución de la mortalidad por enfermedad coronaria en una población mediterránea: España 1988–2005. *Rev Esp Cardiol*. 2011;64:988–96.
10. Franco M, Cooper R, Bilal U, Fuster V. Control de los factores de riesgo coronarios y terapias basadas en la evidencia: esfuerzos coordinados para la prevención cardiovascular en España. *Rev Esp Cardiol*. 2011;64:962–4.
11. Cassel CK, Guest JA. Choosing wisely: helping physicians and patients make smart decisions about their care. *JAMA*. 2012;307:1801–2.
12. de Boer MJ, van der Wall EE. Choosing wisely or beyond the guidelines. *Neth Heart J*. 2013;21:1–2.
13. American Diabetes Association. Standards of medical care in diabetes—2013. *Diabetes Care*. 2013;36 Suppl. 1:S11–66.
14. Lievre MM, Moulin P, Thivolet C, Rodier M, Rigalleau V, Penfornis A, et al. Detection of silent myocardial ischemia in

- asymptomatic patients with diabetes: results of a randomized trial and meta-analysis assessing the effectiveness of systematic screening. *Trials*. 2011;12:23.
15. Goh LG, Chua T, Kang V, Kwong KH, Lim WY, Low LP, et al. Ministry of health clinical practice guidelines: screening of cardiovascular disease and risk factors. *Singapore Med J*. 2011;52:220–5 [quiz 6–7].
 16. Simon J, Gray A, Clarke P, Wade A, Neil A, Farmer A, et al. Cost effectiveness of self monitoring of blood glucose in patients with non-insulin treated type 2 diabetes: economic evaluation of data from the DiGEM trial. *BMJ*. 2008;336:1177–80.
 17. Klonoff DC, Blonde L, Cembrowski G, Chacra AR, Charpentier G, Colagiuri S, et al. Consensus report: the current role of self-monitoring of blood glucose in non-insulin-treated type 2 diabetes. *J Diabetes Sci Technol*. 2011;5:1529–48.
 18. Duran A, Martin P, Runkle I, Perez N, Abad R, Fernandez M, et al. Benefits of self-monitoring blood glucose in the management of new-onset Type 2 diabetes mellitus: the St Carlos Study, a prospective randomized clinic-based interventional study with parallel groups. *J Diabetes*. 2010;2:203–11.
 19. Eldor R, Raz I. American Diabetes Association indications for statins in diabetes: is there evidence? *Diabetes Care*. 2009;32 Suppl. 2:S384–91.
 20. National Cholesterol Education Program Expert Panel on Detection E, Treatment of High Blood Cholesterol in A. Third report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report. *Circulation*. 2002;106:3143–421.
 21. Tonelli M, Muntner P, Lloyd A, Manns BJ, Klarenbach S, Pannu N, et al. Risk of coronary events in people with chronic kidney disease compared with those with diabetes: a population-level cohort study. *Lancet*. 2012;380:807–14.
 22. Scherthaner G, Scherthaner GH. Aktuelle Therapie des Typ-2-Diabetes. *Internist (Berl)*. 2012;53:1399–410.
 23. Ginsberg HN. The ACCORD (Action to Control Cardiovascular Risk in Diabetes) lipid trial: what we learn from subgroup analyses. *Diabetes Care*. 2011;34 Suppl. 2:S107–8.
 24. Dansinger ML, Gleason JA, Griffith JL, Selker HP, Schaefer EJ. Comparison of the Atkins, Ornish, Weight Watchers, and Zone diets for weight loss and heart disease risk reduction: a randomized trial. *JAMA*. 2005;293:43–53.
 25. Kastorini CM, Milionis HJ, Goudevenos JA, Panagiotakos DB. Mediterranean diet and coronary heart disease: is obesity a link? *Nutr Metab Cardiovasc Dis*. 2010;20:536–51.
 26. Estruch R, Ros E, Salas-Salvado J, Covas MI, Corella D, Aros F, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. *N Engl J Med*. 2013;368:1279–90.
 27. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens*. 2013;31:1281–357.
 28. Calhoun DA, Jones D, Textor S, Goff DC, Murphy TP, Toto RD, et al. Resistant hypertension: diagnosis, evaluation, and treatment. A scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. *Hypertension*. 2008;51:1403–19.
 29. Sathisvram S, Lecky B. Statin induced myopathy. *BMJ*. 2008;337:a2286.
 30. Jellinger PS, Smith DA, Mehta AE, Ganda O, Handelsman Y, Rodbard HW, et al. American Association of Clinical Endocrinologists' Guidelines for management of dyslipidemia and prevention of atherosclerosis. *Endocr Pract*. 2012;18 Suppl. 1:1–78.
 31. Thompson PD, Clarkson PM, Rosenson RS, National Lipid Association Statin Safety Task Force Muscle Safety Expert Panel. An assessment of statin safety by muscle experts. *Am J Cardiol*. 2006;97:69C–76C.
 32. Pasternak RC, Smith Jr SC, Bairey-Merz CN, Grundy SM, Cleeman Jr JI, Lenfant C, et al. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *Stroke*. 2002;33:2337–41.
 33. Tonelli M, Lloyd A, Clement F, Conly J, Huserneau D, Hemmelgarn B, et al. Efficacy of statins for primary prevention in people at low cardiovascular risk: a meta-analysis. *CMAJ*. 2011;183:E1189–202.
 34. Sattar N, Preiss D, Murray HM, Welsh P, Buckley BM, de Craen AJ, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet*. 2010;375:735–42.
 35. Pignone M, Alberts MJ, Colwell JA, Cushman M, Inzucchi SE, Mukherjee D, et al. Aspirin for primary prevention of cardiovascular events in people with diabetes. *J Am Coll Cardiol*. 2010;55:2878–86.
 36. Nicolucci A, De Berardis G, Sacco M, Tognoni G. AHA/ADA vs ESC/EASD recommendations on aspirin as a primary prevention strategy in people with diabetes: how the same data generate divergent conclusions. *Eur Heart J*. 2007;28:5–7.
 37. Belch J, MacCuish A, Campbell I, Cobbe S, Taylor R, Prescott R, et al. The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. *BMJ*. 2008;337:a1840.
 38. Rothwell PM, Price JF, Fowkes FG, Zanchetti A, Roncaglioni MC, Tognoni G, et al. Short-term effects of daily aspirin on cancer incidence, mortality, and non-vascular death: analysis of the time course of risks and benefits in 51 randomised controlled trials. *Lancet*. 2012;379:1602–12.
 39. Nemerovski CW, Salinitri FD, Morbitzer KA, Moser LR. Aspirin for primary prevention of cardiovascular disease events. *Pharmacotherapy*. 2012;32:1020–35.
 40. Bell AD, Roussin A, Cartier R, Chan WS, Douketis JD, Gupta A, et al. The use of antiplatelet therapy in the outpatient setting: Canadian Cardiovascular Society Guidelines Executive Summary. *Can J Cardiol*. 2011;27:208–21.
 41. Andersson C, Lyngbaek S, Nguyen CD, Nielsen M, Gislason GH, Kober L, et al. Association of clopidogrel treatment with risk of mortality and cardiovascular events following myocardial infarction in patients with and without diabetes. *JAMA*. 2012;308:882–9.
 42. Vandvik PO, Lincoff AM, Gore JM, Gutterman DD, Sonnenberg FA, Alonso-Coello P, et al. Primary and secondary prevention of cardiovascular disease: antithrombotic therapy and prevention of thrombosis, 9th ed.: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141:e637S–68S.
 43. Goodman SG, Clare R, Pieper KS, Nicolau JC, Storey RF, Cantor WJ, et al. Association of proton pump inhibitor use on cardiovascular outcomes with clopidogrel and ticagrelor: insights from the platelet inhibition and patient outcomes trial. *Circulation*. 2012;125:978–86.
 44. Antithrombotic Trialists Collaboration, Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet*. 2009;373:1849–60.