

The 2008 Canadian Diabetes Association Clinical Practice Guidelines: Focus on Cardiovascular Disease

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The Canadian Diabetes Association (CDA) 2008 Clinical Practice Guidelines (CPGs) for the prevention and management of diabetes mellitus (DM) in Canada¹ were published in September. This set of guidelines represents an updated version and, when compared to its predecessor in 2003,² is greater in breadth, scope, and length. The 2008 version has 201 pages with almost 200 recommendations and 39 chapters. Many people were involved in the development of these guidelines, with over 100 healthcare professionals serving on various committees and many more external reviewers providing critical comments and suggestions. One of the major changes to the 2008 CPGs is the strong focus on cardiovascular disease (CVD). There are 5 new chapters on this topic:

- Identification of individuals at high risk of coronary events (p. S95-S98)
- Screening for the presence of coronary artery disease (p. S99-S101)
- Vascular protection in people with diabetes (p. S102-S106)
- Management of acute coronary syndromes (p. S119-S122)
- Treatment of diabetes in people with heart failure (p. S123-S125).

The majority of the concepts in these chapters are new, and this issue of *Endocrinology Rounds* discusses them and how they can impact your practice.

CVD and diabetes

The reasons for choosing CVD as one of the major themes of the 2008 CDA CPGs are well known by healthcare professionals, but perhaps underrecognized by the public. Coronary and cerebrovascular events account for the vast majority of deaths among people with DM³ and are 40 times more likely to occur than serious microvascular complications of DM. Therefore, efforts to reduce the risk of CV events among those with DM should be a priority.

Identifying patients at high risk of vascular events

The first step in reducing CV risk is identifying patients at high risk. Data suggest that the presence of DM is a "cardiovascular equivalent" and, therefore, its risk is similar to the risk of those who have already experienced a CV event.⁴ For a large proportion of people with DM, this is true; however, there are also data to suggest that not all people with DM carry the same risk.^{5,6} It is useful to recognize this fact so that vascular protection efforts can be targeted at patients who would benefit the most. The 2008 CPGs include a chapter addressing this issue and provides guidance on how to identify the high-risk individual.

Age: Age is the most powerful predictor of CVD risk and DM confers a risk that is equivalent to aging about 15 years. The transition from intermediate to high risk among those with DM is at 47.9 years in men and 54.3 years in women.⁷ At these ages, CVD risk begins to mirror that in patients with previous CVD and no DM (Figure 1). Therefore, it is recommended that men aged ≥ 45 years and women aged ≥ 50 years with DM be considered high risk (Grade B, Level 2).

Among those below the cut-off age, the presence of one or more of the following risk factors portends high risk for CVD (Grade D, consensus):

Macrovascular disease: The highest risk group comprises individuals with both CVD and DM (Figure 1).⁷ A history of any macrovascular disease (clinical or subclinical) significantly



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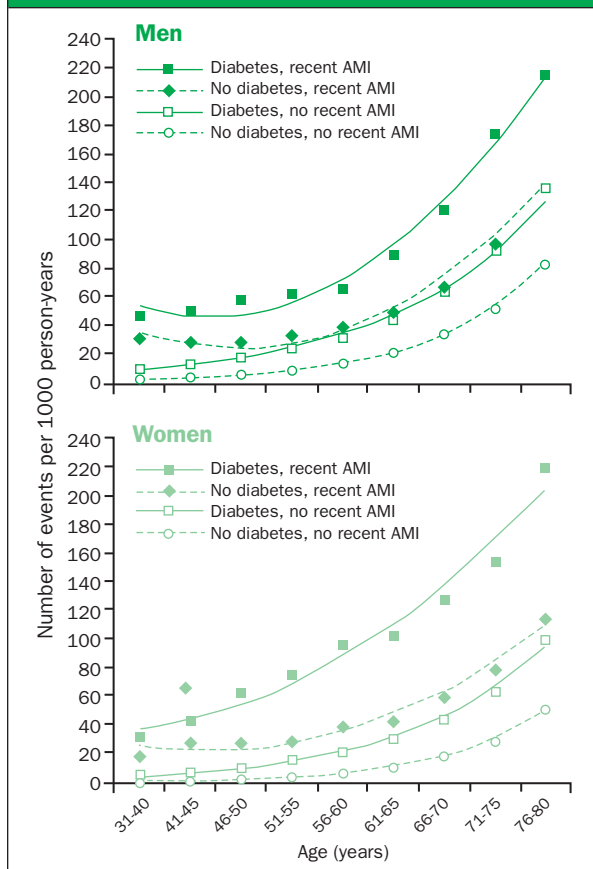
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Figure 1: Relationship between age and rates of AMI or death from any cause in men and women according to presence of DM and previous AMI⁷



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increases the risk of having another event. Therefore, aggressive treatment and risk-factor modification is particularly critical among this group. Individuals with any of the following must be treated aggressively:

- cerebrovascular disease (stroke, transient ischemic attack [TIA])
- carotid disease (carotid bruits)
- cardiac ischemia (silent or overt)
(see *Screening for coronary artery disease* below.)
- peripheral arterial disease (clinically evident or silent (eg, reduced ankle-brachial index))

Microvascular disease: The association between microvascular disease and risk of CVD is often under-appreciated. However, the association, particularly for nephropathy (micro- or macroalbuminuria and/or reduced renal function), is strong,⁸ as is retinopathy.⁹ Therefore, the presence of any microvascular disease, particularly retinopathy and nephropathy, places a patient at high risk.

Multiple cardiac risk factors: The presence of ≥ 2 of the following classic cardiac risk factors also places individuals at high risk:

- a family history of premature coronary artery disease (CAD) or CVD in a first-degree relative (man <55 years or woman <65 years)

Table 1: Components of vascular protection⁴

The first priority in the prevention of DM complications should be the reduction of CV risk by vascular protection through a comprehensive, multifaceted approach (Grade D, consensus for all people with DM; Grade A, Level 1A for people with type 2 (T2) DM, age >40 years with microalbuminuria):

For all patients with diabetes:

- Hemoglobin A_{1c} $\leq 7\%$
- Blood pressure <130/80 mm Hg
- Smoking cessation
- Regular physical activity
- Healthy body weight
- Healthy diet

For high-risk patients, include:

- ACE inhibitor or ARB (Grade A, Level 1A for people with vascular disease; Grade B, Level 1A for other high-risk groups).
- Lipid-lowering medication (primarily statins)*
- Antiplatelet therapy (as recommended)**

* Statin indicated for all high-risk patients. Dose change or additional lipid therapy warranted if lipid targets (low-density lipoprotein [LDL] cholesterol ≤ 2.0 mmol/L and total cholesterol: HDL ratio <4) not being met.

** Low-dose acetylsalicylic acid (ASA; 81-325 mg) may be considered in people with stable CVD (Grade D, consensus). Clopidogrel (75 mg) may be considered in people unable to tolerate ASA (Grade D, consensus). The decision to prescribe antiplatelet therapy for primary prevention of CV events, however, should be based on individual clinical judgment (Grade D, consensus).

CV = cardiovascular; ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker

- smoking
- hypertension (treated or untreated)
- dyslipidemia (treated or untreated).

An extreme single risk factor: The person with DM who has either of the following (extreme) risk factors (whether or not on treatment for it) should be considered at high risk.

- systolic blood pressure >180 mm Hg
- low-density lipoprotein (LDL) cholesterol >5.0 mmol/L

Duration of diabetes: Type 1 (T1) DM is an independent risk factor for premature CVD and mortality in young adults.¹⁰ Among younger people with DM and no other CV risk factors, the short-term risk of CVD may be relatively low, but their long-term risk is very high. Therefore, in the absence of firm data on this risk, it is recommended that individuals aged >30 years who have had DM for >15 years be considered at high risk.

Vascular protection – the “package” approach

The concept of vascular protection was introduced in the 2003 CPGs and recommended as the first priority in the management of DM.² This remains unchanged in the 2008 CPGs. However, the evidence supporting the use of this multifactorial approach to reduce CV risk has grown since 2003 and some of the evidence has been re-evaluated. It is now recognized that certain components of the vascular protection approach are best suited for those at high risk for CVD (Table 1), while others are suited for all patients with DM. Therefore, the 2008 CPGs provide more specific guidance on which components apply to all

people with DM, and which ones should be considered only in those at high risk (Table 1).

The landmark Steno-2 trial demonstrated that a multifactorial approach, including glucose control, blood pressure control, lipid control, angiotensin-converting enzyme (ACE) inhibitor therapy, acetylsalicylic (ASA) therapy, and lifestyle modification, dramatically reduces micro- and macrovascular complications among those with T2DM and microalbuminuria.¹¹ The use of this approach in just 5 people with T2DM and microalbuminuria resulted in the prevention of 1 event in 8 years (number needed to treat = 5). The original cohorts were then passively observed for an additional 5 years.¹² Despite equalization of the various metabolic parameters among the 2 groups, the micro- and macrovascular benefits not only persisted, but continued to grow.

In addition to the updated data from Steno-2, the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET)¹³ and Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRANSCEND)¹⁴ trials allowed the inclusion of angiotensin-receptor blockers (ARBs) as an alternative to ACE inhibitors for vascular protection among those at high risk. The dose of ACE inhibitor or ARB used should have proven vascular benefit. The ASA recommendation was also changed to reflect re-evaluation of the evidence surrounding the use of ASA as primary prevention among those with DM.

A number of studies, including a meta-analysis of ASA trials, have demonstrated the CV benefit of ASA therapy in primary prevention in the general population.¹⁵⁻¹⁸ Each of these studies included subjects with DM and, when these subgroups were analyzed, the CV benefits observed in the whole study population were not demonstrated in the DM subgroups. Therefore, use of ASA among those with DM for primary-prevention purposes should only be based on individual clinical judgment, given the lack of proven benefit and the potential harm associated with long-term use.¹ However, given the strong benefit for secondary prevention in the general population¹⁸ and the trend towards benefit among those with DM and CAD,¹⁹ the use of ASA for secondary prevention among patients with DM is reasonable.¹

Screening for presence of CAD (Table 2)

Silent myocardial ischemia is particularly common among individuals with DM. Almost one-third of myocardial infarctions (MIs) are silent.²⁰ The goals of screening for CAD are to improve quality of life and life expectancy by preventing cardiac events through early detection of CAD. Although clinical symptoms of CAD (eg, chest pain, shortness of breath on exertion, etc) should certainly prompt further investigations, many individuals may not have such symptoms. The resting electrocardiogram (ECG) can be a useful screening tool to identify those who should proceed to further testing. A resting ECG

Table 2: Screening for the presence of coronary artery disease¹

A baseline resting electrocardiogram (ECG) should be performed (Grade D, consensus) in:

- All individuals >40 years of age
- All individuals with duration of diabetes >15 years
- All individuals (regardless of age) with hypertension, proteinuria, reduced pulses, vascular bruits

A repeat resting ECG should be performed every 2 years in those considered at high risk for CV events (Grade D, consensus)

Stress testing should be performed in the presence of any of the following (Grade D, consensus):

- Typical or atypical cardiac symptoms (eg, unexplained dyspnea, chest discomfort) (Grade C, level 3)
- Resting ECG abnormalities (eg, Q waves) (Grade D, consensus)
- Carotid bruits (Grade D, consensus)
- Transient ischemic attack (Grade D, consensus)
- Stroke (Grade D, consensus)

Exercise ECG stress testing should be the initial testing modality unless there are resting ECG abnormalities that preclude its use (eg, LBBB or ST-T abnormalities) or the individual is unable to exercise.

In that case, pharmacologic stress echocardiography or nuclear imaging should be performed (Grade D, consensus for ECG abnormalities; Grade C, Level 3 for inability to exercise).

People with DM who demonstrated ischemia at low exercise capacity (<5 METs) on stress testing should be referred to a cardiac specialist (Grade D, consensus)

LBBB = left bundle-branch block; MET = metabolic equivalent

should be performed (Grade D, consensus) in all those aged >40 years, with DM duration >15 years, or with other high-risk features such as hypertension, proteinuria, or signs of peripheral arterial disease (reduced pulses or vascular bruits). The ECG should be repeated every 2 years in those at high risk (Grade D, consensus). If the resting ECG is abnormal (Q waves, ST-T abnormalities), further testing should be performed (ie, stress testing) to evaluate the extent of disease.

In addition to resting ECG abnormalities, other features that should prompt stress testing include typical (or atypical) symptoms of CAD or the presence of other vascular disease (peripheral arterial disease, carotid bruits, TIAs, or stroke). There is, however, no role for mass screening of all patients with DM with stress testing. The choice of stress testing modality depends on the individual's ability to exercise and the presence of resting ECG abnormalities. If exercise ability is limited, pharmacological forms of stress are preferred. If the resting ECG has abnormalities that limit the accuracy of stress ECG testing, then either echocardiography or nuclear imaging is preferred. If the stress test is abnormal, referral to a cardiac specialist is warranted.

Table 3: Recommendations for the management of acute coronary syndrome in patients with DM¹

- In patients with DM and acute ST-segment elevation MI, the presence of retinopathy should not be a contraindication to fibrinolysis (Grade B, Level 2).
- All patients with an AMI, regardless of whether or not they have a prior diagnosis of DM, should have their blood glucose level measured on admission (Grade D, consensus). Those with blood glucose >12.0 mmol/L should receive insulin-glucose infusion therapy to maintain blood glucose between 7.0–10.0 mmol/L for at least 24 hours, followed by multi-dose subcutaneous insulin for at least 3 months (Grade A, Level 1). An appropriate protocol should be developed and staff trained to ensure the safe and effective implementation of this therapy and to minimize the likelihood of hypoglycemia (Grade D, consensus).
- As beta-blockers provide similar or enhanced survival benefit in patients with DM and MI compared to patients without DM, they should not be withheld because of concern about the risks associated with hypoglycemia (Grade D, consensus).

Management of acute coronary syndromes (Table 3)

This topic constitutes another new chapter in the 2008 CPGs. Approximately one-third of hospital admissions for an acute MI (AMI) are in people with DM.²¹ DM is an independent predictor of short- and long-term mortality, recurrent MI, and heart failure among those with an AMI.^{4,22,23} Therefore, the proper management of patients with DM and an AMI is critical to try to reduce future risk. In addition, there are certain aspects of management that are unique to those with DM (eg, glycemic control) and others that are not unique to DM, but are more likely to be withheld from those with DM for a variety of reasons.²⁴⁻²⁷ All of the usual guideline recommendations for the management of an acute coronary syndrome developed by the American College of Cardiology/American Heart Association^{28,29} and the European Society of Cardiology³⁰ are applicable to those with DM. Subgroup analyses within trials have demonstrated either equal or greater benefit among diabetes subgroups. Aspects that are unique to DM are discussed below.

Glycemic control: Admission hyperglycemia is an independent predictor of survival after AMI.³¹ The Diabetes Mellitus, Insulin, Glucose Infusion in Acute Myocardial Infarction (DIGAMI 1) study,^{32,34} demonstrated that the use of intravenous (IV) insulin for the first 24 hours after presentation, followed by multiple daily injections of subcutaneous insulin for

at least 3 months after presentation, resulted in a significant reduction in mortality. The follow-up study, DIGAMI 2, attempted to differentiate whether it was the early use of IV insulin, the use of multiple daily injections of insulin for the subsequent 3 months, or the combination of the 2 modalities that resulted in the mortality benefit.³⁵ Unfortunately, the study had many problems, including recruitment issues, contamination of study arms, failure to follow protocol in certain arms, and failure to differentiate glycemic control. The study was unable to demonstrate any difference among the 3 arms; however, it did show that outcomes were closely related to glycemic control. Therefore, glycemic control is an important consideration among those with AMI and hyperglycemia.

Thrombolysis and ocular hemorrhage: The presence of diabetic retinopathy should not be considered a contraindication to thrombolysis in patients with ST-segment elevation MI.³⁶ This was clearly demonstrated in the Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO 1) trial, in which >6000 patients with DM received thrombolytic therapy.³⁶

Long-term management: There is a therapeutic gap among those with DM. Despite the knowledge that the risk of a future CV event is particularly high among those with established CVD plus DM, studies have shown that people with DM are less likely to receive proven treatments such as revascularization, thrombolysis, beta-blockers, or ASA than people without DM.^{24,27} They are also less likely to be followed by a cardiologist.²⁴ The discharge prescription for a patient with AMI (with or without DM) should include dual antiplatelet therapy (ASA and clopidogrel), a beta-blocker, ACE inhibitor, or an ARB, and a statin.¹

Treatment of diabetes in patients with heart failure (Table 4)

Another new chapter in the 2008 CPGs addresses issues surrounding the management of DM in people with heart failure. The incidence of heart failure is 2- to 4-fold higher in people with DM as compared to those without DM.^{37,38} This increase in incidence is related to the strong association between DM and ischemic heart disease and the potential for diabetic cardiomyopathy.³⁹ Among individuals with heart failure, about one-third have DM.¹ The treatment for heart failure should be the same for those with or without DM.¹

Special considerations among those with DM have more to do with the choice of agents for glycemic control. Metformin should remain first-line therapy, even among those with heart failure. Current evidence suggests that patients with heart failure fare at least as well, if not better, with metformin than

Table 4: Recommendations for the treatment of DM in people with heart failure¹

- Individuals with DM and heart failure should receive the same heart failure therapies as those identified in the evidence-based Canadian Cardiovascular Society heart failure recommendations (<http://www.hfcc.ca>) (Grade D, consensus).
- Unless contraindicated, metformin may be used in people with T2DM and heart failure (Grade C, Level 3). Metformin should be temporarily withheld if renal function acutely worsens, and should be discontinued if renal function significantly and chronically worsens (Grade D, consensus).
- Physicians should be aware that people taking thiazolidinediones are at increased risk of heart failure and may present with symptoms such as increased dyspnea and peripheral edema (Grade B, Level 2).
- In people with diabetes and heart failure and an estimated glomerular filtration rate <60 mL/min:
 - Starting dose of ACE inhibitors or ARBs should be halved (Grade D, consensus)
 - Serum electrolytes and creatinine, blood pressure, body weight, heart failure symptoms and signs should be monitored more frequently (Grade D, consensus)
 - Dose uptitration should be more gradual with monitoring of blood pressure, serum potassium and creatinine (Grade D, consensus)
 - The target drug doses should be those identified in the Canadian Cardiovascular Society recommendations on heart failure.
- Beta-blockers should be prescribed when indicated for systolic heart failure, as they provide similar benefits in people with DM and in those without DM (Grade B, Level 2). Where hypoglycemia is a particular concern, a selective beta-blocker such as bisoprolol or metoprolol may be preferred (Grade D, consensus).

with other antihyperglycemic agents if they have only mild to moderate renal dysfunction (estimated glomerular filtration rate >30 mL/min). Thiazolidinediones (TZDs) are known to cause fluid retention and, therefore, there is an increased risk of heart failure symptoms. As a result, they should be discontinued or used cautiously in patients with stable heart failure and discontinued in those with unstable or acute heart failure. Beta-blockers should be utilized for systolic heart failure in the same fashion for those with or without DM. Finally, the increased prevalence of renal dysfunction among patients with DM should be taken into account when choosing doses of medications typically used for heart failure.

Conclusions

Cardiovascular disease is a major consideration in the management of DM and steps to identify, prevent, and manage CVD should be a priority. The CDA 2008 CPGs have made CVD a major focus and there are new chapters and recommendations to reflect this. The definition of the high-risk individual has been better outlined, the importance of vascular protection has been re-emphasized, and there is better guidance about how to stratify interventions to impact those who will benefit the most. Therefore, most of the components of vascular protection apply to all, but the use of an ACE inhibitor or an ARB, a lipid-lowering therapy (statin), and ASA should be reserved for those at high risk. Screening for CAD should be considered in everyone with DM. Resting ECGs are appropriate for many and the criteria for moving on to stress testing have been described. Generally, the management of an acute coronary syndrome and heart failure is the same in the presence

or absence of DM. However, certain special considerations have also been described. Overall, it is important to remember that when seeing a patient with DM to consider CVD. With the guidance of the CPGs, the next steps are to decide if the patient is at high risk, what tests to perform, and what should be done to reduce the risk of future events.

References:

1. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2008 clinical practice guidelines for the prevention and management of diabetes in Canada. *Can J Diabetes*. 2008;32(suppl 1):S1-S201. Available at: <http://www.diabetes.ca/for-professionals/resources/2008-cpg>. Accessed: November 11, 2008.
2. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2003 clinical practice guidelines for the prevention and management of diabetes in Canada. *Can J Diabetes*. 2003;27(suppl 2):S1-S152.
3. Gu K, Cowie CC, Harris MI. Mortality in adults with and without diabetes in a national cohort of the US population, 1971-1993. *Diabetes Care*. 1998; 21(7):1138-1145.
4. Haffner SM, Lehto S, Ronnemaa T, et al. Mortality for coronary heart disease in subjects with type 2 diabetes and in non-diabetic subjects with and without prior myocardial infarction. *N Engl J Med*. 1998;339(4):229-234.
5. Evans JMM, Wang J, Morris AD. Comparison of cardiovascular risk between patients with type 2 diabetes and those who had had a myocardial infarction: cross sectional and cohort studies. *BMI*. 2002;324(7343):939-942.
6. Wannamethee SG, Shaper AG, Lennon L. Cardiovascular disease incidence and mortality in older men with diabetes and in men with coronary heart disease. *Heart*. 2004;90(12):1398-1403.
7. Booth GL, Kapral MK, Fung K, et al. Relation between age and cardiovascular disease in men and women with diabetes compared with non-diabetic people: a population-based retrospective cohort study. *Lancet*. 2006; 368(9529):29-36.
8. Dinneen SF, Gerstein HC. The association of microalbuminuria and mortality in non-insulin-dependent diabetes mellitus: a systemic overview of the literature. *Arch Intern Med*. 1997;157(13):1413-1418.
9. Faglia E, Favales F, Calia P, et al. Cardiac events in 735 type 2 diabetic patients who underwent screening for unknown asymptomatic coronary heart disease: 5-year follow-up report from the Milan Study on Atherosclerosis and Diabetes (MiSAD). *Diabetes Care*. 2002;25(11):2032-2036.
10. Laing SP, Swerdlow AJ, Slater SD, et al. The British Diabetic Association Cohort Study, II: cause-specific mortality in patients with insulin-treated diabetes mellitus. *Diabet Med*. 1999;16(6):466-471.
11. Gaede P, Vedel P, Larsen N, et al. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med*. 2003;348: 383-393.

12. Gaede P, Lund-Andersen H, Parving H, et al. Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med.* 2008;358(6):580-591.
13. The ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med.* 2008;385(15):1547-1559.
14. The TRANSCEND Investigators. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomized controlled trial. *Lancet.* 2008;372(9644):1174-1183.
15. Final report on the aspirin component of the ongoing Physicians' Health Study. Steering Committee of the Physicians' Health Study Research Group. *N Engl J Med.* 1989;321(3):129-135.
16. Sacco M, Pellegrini F, Roncaglioni MC, et al. PPP Collaborative Group. Primary prevention of cardiovascular events with low-dose aspirin and vitamin E in type 2 diabetic patients: results of the Primary Prevention Project (PPP) trial. *Diabetes Care.* 2003;26(12):3264-3272.
17. Hansson L, Zanchetti AIK, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomized trial. HOT Study Group. *Lancet.* 1998;351(9118):1755-1762.
18. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomized trials of antiplatelet therapy for prevention of death, myocardial infarction and stroke in high risk patients. *BMJ.* 2002;324(7329):71-86.
19. Aspirin effects on mortality and morbidity in patients with diabetes mellitus. Early Treatment Diabetic Retinopathy Study report 14. ETDRS Investigators. *JAMA.* 1992;268(10):1292-1300.
20. Cohn PF, Fox KM, Daly C. Silent myocardial ischemia. *Circulation.* 2003;108(10):1263-1277.
21. Hochman JS, McCabe CH, Stone PH, et al., for the TIMI Investigators. Outcome and profile of women and men presenting with acute coronary syndromes: a report from TIMI IIIb. Thrombolysis in Myocardial Infarction. *J Am Coll Cardiol.* 1997;30(1):141-148.
22. Sprafka JM, Burke GL, Folsom AR, et al. Trends in prevalence of diabetes mellitus in patients with myocardial infarction and effect of diabetes on survival. The Minnesota Heart Survey. *Diabetes Care.* 1991;14(7):537-543.
23. Fuller JH, Stevens LK, Wang SL. Risk factors for cardiovascular mortality and morbidity: the WHO Multinational Study of Vascular Disease in Diabetes. *Diabetologia.* 2001;44(suppl 2):S54-S64.
24. Alter DA, Khaykin T, Austin PC, et al. Processes and outcomes of care for diabetic acute myocardial infarction patients in Ontario: do physicians undertreat? *Diabetes Care.* 2003;26(5):1427-1434.
25. Eagle KA, Goodman SG, Avezum A, et al. Practice variation and missed opportunities for reperfusion in ST-segment elevation myocardial infarction: findings from the Global Registry of Acute Coronary Events (GRACE). *Lancet.* 2002;359(9304):373-377.
26. Norhammar A, Malmberg K, Ryden L, et al. Under utilisation of evidence-based treatment partially explains for the unfavourable prognosis in diabetic patients with acute myocardial infarction. *Eur Heart J.* 2003;24(9):838-844.
27. Yan RT, Yan AT, Tan M, et al. Canadian Acute Coronary Syndrome Registry Investigators. Underuse of evidence-based treatment partly explains the worse clinical outcomes in diabetic patients with acute coronary syndromes. *Am Heart J.* 2006;152(4):676-683.
28. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST elevation myocardial infarction – executive summary: a report of the American College of Cardiology / American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). *Circulation.* 2004;110(5):588-636.
29. Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction – summary article: a report of the American College of Cardiology / American Heart Association task force on practice guidelines (Committee on the Management of Patients with Unstable Angina). *J Am Coll Cardiol.* 2002;40(7):1366-1374.
30. Bertrand ME, Simoons ML, Fox KA, et al. Management of acute coronary syndromes: acute coronary syndromes without persistent ST segment elevation. Recommendations for the Task Force of the European Society of Cardiology. *Eur Heart J.* 2000;21(17):1406-1432.
31. Hadjadj S, Coisne D, Mauco G, et al. Prognostic value of admission plasma glucose and HbA1c in acute myocardial infarction. *Diabet Med.* 2004;21(4):305-310.
32. Malmberg K. Prospective randomized study of intensive insulin treatment on long term survival after acute myocardial infarction in patients with diabetes mellitus. DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) Study Group. *BMJ.* 1997;314(7093):1512-1515.
33. Malmberg K, Ryden L, Hamsten A, et al. Effects of insulin treatment on cause-specific one-year mortality and morbidity in diabetic patients with acute myocardial infarction. DIGAMI Study Group. *Diabetes Insulin-Glucose in Acute Myocardial Infarction.* *Eur Heart J.* 1996;17(9):1337-1344.
34. Malmberg K, Ryden L, Efendic S, et al. Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. *J Am Coll Cardiol.* 1995;26(1):57-65.
35. Malmberg K, Ryden L, Wedel H, et al, DIGAMI Investigators. Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. *Eur Heart J.* 2005;26(7):650-661.
36. Mahaffey KW, Granger CB, Toth CA, et al. Diabetic retinopathy should not be a contraindication to thrombolytic therapy for acute myocardial infarction: a review of ocular hemorrhage incidence and location in the GUSTO-1 trial. Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries. *J Am Coll Cardiol.* 1997;30(7):1606-1610.
37. Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: the Framingham Study. *Am J Cardiol.* 1974;34(1):29-34.
38. He J, Ogden LG, Bazzano LA, et al. Risk factors for congestive heart failure in US men and women: NHANES I epidemiologic follow-up study. *Arch Intern Med.* 2001;161(7):996-1002.
39. Bell DS. Heart failure: the frequent, forgotten, and often fatal complication of diabetes. *Diabetes Care.* 2003;26(8):2433-2441.

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