Canadian Journal of Cardiology 34 (2018) 532–535

Editorial

Type 2 Diabetes and the Reduction of Cardiovascular Risk: Sorting Out the Actors and the Roles

Ross D. Feldman, MD,[a] David Fitchett, MD,[b] Robert A. Hegele, MD,[c] and Neil R. Poulter, FMedSci[d]

[a] Cardiac Sciences Program, IH Asper Institute, St Boniface Hospital, Winnipeg, Manitoba, Canada

[b] Division of Cardiology, St Michael's Hospital, Toronto, Ontario, Canada

[c] Robarts Research Institute, Schulich School of Medicine and Dentistry, Western University, London, Ontario, Canada

[d] International Centre for Circulatory Health, Imperial College London, London, United Kingdom

Diabetes increases the risk of cardiovascular events, with a wide spectrum of absolute risk that extends from a low risk in the recently diagnosed younger patient with diabetes and no detected cardiovascular disease to very high risk in the older patient with long-standing diabetes and established cardiovascular disease. Among individuals with coronary heart disease almost half have type 2 diabetes, and up to two-thirds have abnormal glucose regulation.[1] Cardiac dysfunction is common and heart failure often unrecognized in the patient with diabetes. Heart failure is a more common reason for admission to hospital than either myocardial infarction or stroke in patients with diabetes especially for those with established cardiovascular disease or receiving insulin.[2] Furthermore, heart failure is a prognostically important outcome because patients admitted with heart failure have a higher subsequent mortality than those with myocardial infarction or stroke.

The determinants of the increased risk of cardiovascular disease in patients with diabetes are multifactorial. These include hyperglycemia, hypertension, and dyslipidemia (small dense atherogenic low-density lipoprotein [LDL], associated with low high-density lipoprotein [HDL] and elevated triglycerides), all of which cluster in patients with diabetes. Furthermore, cardiovascular risk has been shown to be reduced with a multifaceted approach to risk factor management[3] that includes lifestyle modifications (weight control, healthy diet, and increased physical activity), intensive cholesterol-lowering, and blood pressure (BP) control. A recent report from the Steno-2 trial indicates that intensive compared with usual risk factor management is associated with an increased life expectancy of 7.9 years.[4]

Although the effectiveness of global risk reduction in patients with diabetes is unquestioned, the effect of management of each of these isolated risk factors remains an ongoing area of controversy. In this article, we examine the effect of these individual risk factors on coronary artery disease in patients with diabetes and the effect of therapy for them.

Hyperglycemia

The development of microvascular disease (neuropathy, retinopathy, and nephropathy) is related to the severity of hyperglycemia, with a threshold of risk at the level of hyperglycemia that defines diabetes (fasting blood glucose $>$ 7.0 mmol/L and A1c $>$ 0.065).[5,6] In contrast, the development of macrovascular disease has a less robust relationship to hyperglycemia (beyond the long-recognized risk of severe hyperglycemia and cardiac disease)and is more closely associated with measures of insulin resistance.[7] The development of heart failure also relates to the degree of hyperglycemia.

Glucose control reduces the risk of development or progression of microvascular disease (although more effective in slowing nephropathy than retinopathy) in type 1 as well as type 2 diabetes. However, over the same time period in which the reduction of microvascular risk is observed, no individual study has shown a reduction of cardiovascular risk (myocardial infarction, stroke, or the development of heart failure) using tight vs usual glucose control. Further, concerns regarding the possibility of an increased cardiovascular risk with some of the older hypoglycemic agents including the sulfonylureas and subsequently the glitazones led several international drug regulatory agencies to mandate the incorporation of cardiovascular outcome trials as a prerequisite for drug approval. Subsequent meta-analyses indicate myocardial infarction is reduced by tight glycemic control yet cardiovascular mortality is not changed.[8] When patients are followed for longer periods (up to 15 years), the incidence of myocardial infarction as well as cardiovascular mortality are reduced in the intensively treated group in patients with type 1[9] as well as type 2[10]

Received for publication November 24, 2017. Accepted January 30, 2018.

Corresponding author: Dr Ross D. Feldman, IH Asper Institute-CR1056, St Boniface Hospital, 369 Tache Ave, Winnipeg, Manitoba 2RH 2A6, Canada. Tel.: +1-204-235-3324; fax: +1-204-233-8783.

E-mail: rfeldman@sbgh.mb.ca

See page 534 for disclosure information.

https://doi.org/10.1016/j.cjca.2018.01.091

diabetes. Glycemic control to a personalized target remains important to reduce microvascular disease. Furthermore, the **UK P**rospective **D**iabetes **S**tudy (UKPDS) long-term follow-up data[10] suggest that early good glycemic control in recently diagnosed patients with diabetes is associated with an improved long-term cardiovascular outcome.

Reduction of cardiovascular risk appears to be more related to the choice of glucose-lowering agent than to the reduction of blood glucose per se. A small substudy of the UKPDS with metformin in obese patients showed a reduction of cardiovascular events and mortality compared with treatment mainly on the basis of diet.[11] Pioglitazone, although it did not reduce a multicomponent primary end point, significantly reduced the more conventional 3-point major adverse cardiac events (MACE) end point.[12] Among diabetic patients with established cardiovascular disease in the Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes trial (EMPA-REG OUTCOME) and **Can**agliflozin Cardio**v**ascular **A**ssessment **S**tudy (CANVAS) Program, the sodium-glucose co-transporter 2 (SGLT2) inhibitors, empagliflozin and canagliflozin, respectively, reduced the triple MACE end point and heart failure admission compared with placebo.[13,14] Empagliflozin reduced cardiovascular mortality by 38%, whereas canagliflozin had no effect on mortality. Notably, for both SGLT2 inhibitors, their effect on cardiovascular risk reduction appeared to be independent of their hypoglycemic effects. The GLP-1 agonists liraglutide[15] and semaglutide[16] reduced triple MACE, compared with placebo—also among diabetic patients with established cardiovascular disease—with liraglutide significantly reducing cardiovascular mortality and semaglutide having no effect on cardiovascular mortality.

Hypertension

As in the general population, the risk of hypertensive complications in patients with type 2 diabetes increases with systolic BPs > 115-120 mm Hg.[17] On the basis of the overall increased risk of atherosclerotic disease in these patients and the demonstration primarily in observational studies that the relative risk reduction associated with effective antihypertensive therapy is constant across the range of BP elevations it had been widely suggested that those with diabetes should be treated to a lower target. That belief was supported by the **A**ction in **D**iabetes and **V**ascular Disease: Preterax and Diamicro**n** MR-**C**ontrolled **E**valuation (ADVANCE) trial[18] but challenged with the reporting of the **A**ction to **C**ontrol **C**ardi**o**vascular **R**isk in **D**iabetes **B**lood **P**ressure (ACCORD BP) study, which failed to show a significant superiority of a systolic BP target of 120 mm Hg over that of 140 mm Hg.[19] On the basis of that finding many national guidelines groups backed off their systolic BP targets for patients with diabetes—notwithstanding (as described by Leung and Padwal[20]) that the ACCORD BP study was underpowered to rule out a 20% risk reduction on the basis of a lower than expected event rate. Further subsequent meta-analyses have supported a further risk reduction to BPs approaching 130 mm Hg[21]—the target for systolic BP control still recommended by Hypertension Canada's guidelines.

The choice of therapy for antihypertensive treatment as recommended by Hypertension Canada includes all of the major classes of antihypertensive drugs with the exception of β-adrenergic antagonists.[22] Angiotensin converting enzyme inhibitor/calcium channel blocker combinations are recommended preferentially in all patients with diabetes. It is notable that this latter recommendation, on the basis of the **A**voiding **C**ardiovascular Events Through **Com**bination Therapy in **P**atients **Li**ving With **S**ystolic **H**ypertension (ACCOMPLISH) study[23] (and supported by the subgroup of patients with diabetes in the **A**nglo-**S**candinavian **C**ardiac **O**utcomes **T**rial—**B**lood **P**ressure **L**owering **A**rm [ASCOT-BPLA] trial[24]), was ratified before the adoption of single-pill combinations as first-line therapy in patients with hypertension, regardless of the extent of BP elevation. However, whether this will be interpreted as an endorsement of an angiotensin converting enzyme inhibitor/calcium channel blocker combination as the initial preferred first-line therapy of patients with diabetes and hypertension has yet to be clarified.

Dyslipidemia

Abnormal plasma lipids are seen in half and two-thirds of patients who have had type 2 diabetes for 2 and 15 years' duration, respectively.[25] As mentioned previously, the typical dyslipidemia pattern in diabetes features hypertriglyceridemia and depressed HDL cholesterol, with elevated non-HDL cholesterol and high apolipoprotein B levels in the face of relatively normal LDL cholesterol (LDL-C) levels, providing a clinical clue that the LDL particles are qualitatively small and dense, making them more susceptible to oxidation and thus more atherogenic.[26] The elevated triglycerides are also an indirect marker for numerous other unmeasured proatherogenic metabolic changes.[27]

Although LDL-C is quantitatively relatively normal in diabetes, several studies confirm that the cardiovascular benefits derived from lowering LDL-C apply equally well to people with and without diabetes.[28-31] Statin therapy reduces the relative risk of outcomes across all patient groups, with greater absolute benefit seen with higher absolute risk, such as in diabetic patients. Subgroup analyses of statin trials showed benefits of LDL-C-lowering, irrespective of baseline LDL-C levels.[28-31]

Although the evidence is most voluminous for statins, the benefit of lipid-lowering in diabetes encompasses at least 2 other classes of LDL-lowering medications. First, the **Imp**roved **R**eduction of **O**utcomes: **V**ytorin **E**fficacy **I**nternational **T**rial (IMPROVE-IT) showed that after an acute coronary syndrome, ezetimibe used in addition to 40 mg of simvastatin reduced LDL-C as well as the risk of subsequent cardiovascular events significantly more than statin alone; a subgroup analysis showed that patients with diabetes had the greatest risk reduction.[32] Second, a prespecified subanalysis of the **F**urther Cardiovascular **Ou**tcomes **R**esearch With PCSK9 **I**nhibition in Subjects With **E**levated **R**isk (FOURIER) study showed that inhibition of proprotein convertase subtilisin kexin 9 using the monoclonal antibody evolocumab significantly reduced cardiovascular risk in patients with and without diabetes; relative risk reduction was similar, but absolute risk reduction was greater in the patients with diabetes, because of their higher baseline risk.[33]

In contrast, other lipid-lowering therapies in diabetes do not appear to reduce events. For instance, in the **A**ction to **C**ontrol **C**ardi**o**vascular **R**isk in **D**iabetes (ACCORD) trial of diabetic patients, fenofibrate added to statin therapy did not reduce cardiovascular events.[34] Similarly, when niacin was used in addition

to background statin therapy in the **A**therothrombosis **I**ntervention in **M**etabolic Syndrome With Low **H**DL/High Triglycerides and **I**mpact on **G**lobal **H**ealth Outcomes (AIM-HIGH) trial, and the **H**eart **P**rotection **S**tudy **2**-**T**reatment of **H**DL to **R**educe the **I**ncidence of **V**ascular **E**vents (HPS2-THRIVE) trial, there was no incremental benefit of niacin.[35,36] Although a possible benefit cannot be ruled out in specific subgroups, such as those with very high triglycerides, niacin and fibrates are not currently recommended to reduce cardiovascular risk in diabetic patients who already take a statin. The role of bile acid sequestrants is less well studied in randomized trials, but these agents also reduce LDL-C by approximately 20% and might also secondarily improve glycemic control.[37]

Thus, in the management of dyslipidemia in diabetes: (1) consider diabetes as a statin-indicated condition; (2) consider ezetimibe as an additional treatment with any maximally tolerated dose of statin when treatment goals are not achieved; (3) use PCSK9 inhibitors when a statin used in addition to ezetimibe are insufficient; (4) avoid niacin and avoid fibrates (except for the prevention of systemic complications of hypertriglyceridemia—ie, pancreatitis); and (5) possibly consider bile acid sequestrants to further lower LDL-C if necessary. Finally, patients taking high-dose statins, but not ezetimibe or PCSK9 inhibitors, have a small increased risk of developing diabetes.[38] This theoretical diabetes risk should not delay initiation of statin therapy for a patient at risk of cardiovascular events.

Risk Reduction in Patients With Diabetes: By the Numbers

Reducing the atherosclerotic risk of patients with diabetes requires a multipronged approach including healthy behaviours as well as aggressive treatment of modifiable risk factors. Notwithstanding, it is still useful to consider how the effectiveness of each risk reduction strategy in patients with type 2 diabetes mellitus, if only to better understand the relative benefit of each individual approach. As noted previously a treatment strategy on the basis of the primary focus of more aggressive treatment of hyperglycemia in patients with diabetes has not been shown to be generally effective. (However, as also noted previously, the recent evidence supporting cardioprotective effects of specific hypoglycemics, ie, the SGLT2 inhibitors empagliflozin and canagliflozin and the GLP-1 agonists liraglutide and semaglutide would support their greater utility.) Using an arbitrary 10-year Framingham risk of 28% (such as in a 64-year-old woman with diabetes with a fasting blood sugar of 7.4 mmol/L, smoker, LDL-C 3.6 mmol/L, HDL cholesterol 0.8 mmol/L, and BP 145/85 mm Hg) and assuming a relative risk reduction for risk factor treatment equivalent to that in a general population: (1) effective smoking cessation would result in approximately a 50% risk reduction; (2) effective BP reduction (to a target of $< 130/80$ mm Hg) would be expected to accrue a 40% risk reduction for stroke and approximately a 25% risk reduction for coronary artery disease; and (3) LDL-C reduction to < 2.0 mmol/L each would be expected to accrue approximately a 30% risk reduction for coronary artery disease complications.

Conclusion

The reduction in macrovascular risk in patients with diabetes requires a multifactorial approach. This strategy includes the assumption of healthy behaviours especially smoking cessation as well as aggressive pharmacological reduction of BP and LDL-C. More aggressive blood sugar-lowering is probably the least effective means of reducing atherosclerotic risk in these patients (although remaining important in the prevention of microvascular disease). Notwithstanding, there is emerging evidence that specific hypoglycemic agents might have additional cardioprotective effects beyond blood sugar control. In this context for patients with established atherosclerotic disease or at very high risk, the use of an SGLT2 inhibitor or a GLP-1 agonist with proven benefit should be viewed as important additions to recommended therapeutic regimens on the basis of their cardioprotective effects, independent of their hypoglycemic actions.

Disclosures

R.D.F. has been supported for continuing professional development programs (CPD) by Servier and has served on advisory boards for GSK and Valeant. D.F. has been a consultant or received CPD support from Boehringer Ingelheim, Lilly, Astra Zeneca, Janssen, Merck, and Novartis. R.A.H. has received honoraria for membership on advisory boards and speakers' bureaus for Akcea/Ionis, Aegerion, Amgen, Boston Heart Diagnostics, Gemphire, Regeneron, and Sanofi. N.R.P. has received personal speaker fees from AstraZeneca, LriTherapharma, Napi, Novo Nordisk, Pfizer, Servier, and Takeda, and support for consultancy/advisory board activities from Amgen, AstraZeneca, Novo Nordisk, and Pfizer, and research grants for his research group from Pfizer, Diabetes UK, National Institute for Health Research Efficacy and Mechanism Evaluation Programme, Julius Clinical, and the British Heart Foundation.

References

1. Bartnik M, Ryden L, Ferrari R, et al. The prevalence of abnormal glucose regulation in patients with coronary artery disease across Europe. The Euro Heart Survey on diabetes and the heart. Eur Heart J 2004;25:1880-90.
2. McMurray JJ, Gerstein HC, Holman RR, Pfeffer MA. Heart failure: a cardiovascular outcome in diabetes that can no longer be ignored. Lancet Diabetes Endocrinol 2014;2:843-51.
3. Gaede P, Vedel P, Larsen N, et al. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med 2003;348:383-93.
4. Gaede P, Oellgaard J, Carstensen B, et al. Years of life gained by multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: 21 years follow-up on the Steno-2 randomised trial. Diabetologia 2016;59:2298-307.
5. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;321:405-12.
6. Coutinho M, Gerstein HC, Wang Y, Yusuf S. The relationship between glucose and incident cardiovascular events: a metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. Diabetes Care 1999;22:233-40.
7. Gast KB, Tjeerdema N, Stijnen T, Smit JW, Dekkers OM. Insulin resistance and risk of incident cardiovascular events in adults without diabetes: meta-analysis. PLoS One 2012;7:e52036.

8. Turnbull FM, Abraira C, Anderson RJ, et al. Intensive glucose control and macrovascular outcomes in type 2 diabetes. Diabetologia 2009;52:2288-98.

9. Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Sustained effect of intensive treatment of type 1 diabetes mellitus on development and progression of diabetic nephropathy: the Epidemiology of Diabetes Interventions and Complications (EDIC) study. JAMA 2003;290:2159-67.

10. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-Year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577-89.

11. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998;352:854-65.

12. Dormandy JA, Charbonnel B, Eckland DJ, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet 2005;366:1279-89.

13. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117-28.

14. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377:644-57.

15. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;375:311-22.

16. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016;375:1834-44.

17. Neaton JD, Wentworth D. Serum cholesterol, blood pressure, cigarette smoking, and death from coronary heart disease. Overall findings and differences by age for 316,099 white men. Multiple Risk Factor Intervention Trial Research Group. Arch Intern Med 1992;152:56-64.

18. Patel A, ADVANCE Collaborative Group, MacMahon S, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet 2007;370:829-40.

19. ACCORD Study Group, Cushman WC, Evans GW, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med 2010;362:1575-85.

20. Leung AA, Padwal RS. Blood pressure-lowering targets in patients with diabetes mellitus. Can J Cardiol 2018;34:644-52.

21. Bangalore S, Kumar S, Lobach I, Messerli FH. Blood pressure targets in subjects with type 2 diabetes mellitus/impaired fasting glucose: observations from traditional and bayesian random-effects meta-analyses of randomized trials. Circulation 2011;123:2799-810. 9 p following 810.

22. Leung AA, Daskalopoulou SS, Dasgupta K, et al. Hypertension Canada's 2017 guidelines for diagnosis, risk assessment, prevention, and treatment of hypertension in adults. Can J Cardiol 2017;33:557-76.

23. Jamerson K, Weber MA, Bakris GL, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. N Engl J Med 2008;359:2417-28.

24. Dahlof B, Sever PS, Poulter NR, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. Lancet 2005;366:895-906.

25. Harris SB, Ekoe JM, Zdanowicz Y, Webster-Bogaert S. Glycemic control and morbidity in the Canadian primary care setting (results of the diabetes in Canada evaluation study). Diabetes Res Clin Pract 2005;70:90-7.

26. Rana JS, Liu JY, Moffet HH, et al. Metabolic dyslipidemia and risk of coronary heart disease in 28,318 adults with diabetes mellitus and low-density lipoprotein cholesterol <100 mg/dl. Am J Cardiol 2015;116:1700-4.

27. Fruchart JC, Sacks FM, Hermans MP, et al. The Residual Risk Reduction Initiative: a call to action to reduce residual vascular risk in dyslipidaemic patient. Diab Vasc Dis Res 2008;5:319-35.

28. Colhoun HM, Betteridge DJ, Durrington PN, 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.

29. 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.

30. Collins R, Armitage J, Parish S, et al. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. Lancet 2003;361:2005-16.

31. Collins R, Reith C, Emberson J, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. Lancet 2016;388:2532-61.

32. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med 2015;372:2387-97.

33. Sabatine MS, Leiter LA, Wiviott SD, et al. Cardiovascular safety and efficacy of the PCSK9 inhibitor evolocumab in patients with and without diabetes and the effect of evolocumab on glycaemia and risk of new-onset diabetes: a prespecified analysis of the FOURIER randomised controlled trial. Lancet Diabetes Endocrinol 2017;5:941-50.

34. ACCORD Study Group, Ginsberg HN, Elam MB, et al. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med 2010;362:1563-74.

35. HPS2-THRIVE Collaborative Group, Landray MJ, Haynes R, et al. Effects of extended-release niacin with laropiprant in high-risk patients. N Engl J Med 2014;371:203-12.

36. AIM-HIGH Investigators, Boden WE, Probstfield JL, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med 2011;365:2255-67.

37. Brunetti L, Hermes-Desantis ER. The role of colesevelam hydrochloride in hypercholesterolemia and type 2 diabetes mellitus. Ann Pharmacother 2010;44:1196-206.

38. Mancini GB, Baker S, Bergeron J, et al. Diagnosis, prevention, and management of statin adverse effects and intolerance: Canadian Consensus Working Group Update (2016). Can J Cardiol 2016;32:S35-65.