

# The emergence of cardiometabolism

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## Introduction

Atherosclerotic cardiovascular disease (ASCVD) and its complications [i.e. heart attacks, strokes, peripheral arterial disease, chronic kidney disease (CKD), and heart failure (HF)] are the key causes of morbidity and mortality in patients with type 2 diabetes mellitus (T2DM) [1]. Cardiometabolism focuses on both the science and the clinical management strategies aimed to reduce the associated risks and treat the cardiovascular consequences in patients with diabetes. Cardiometabolism emphasizes a close collaboration between not only the clinical endocrinologist-diabetologist and cardiologist, but encompasses multidisciplinary diabetes treatment experts, including nephrologists, exercise physiologists, nutrition experts, podiatrists, cardio-thoracic and other vascular surgeons, primary care physicians, as well as the scientists involved in studying the connection between diabetes and ASCVD. In this very brief commentary, it is suggested that an interactive cardiometabolism collaboration, focusing on both scientific discoveries and clinical management strategies, can ultimately reduce risks, in the primary prevention, or delay, of chronic complications, or optimally treat the ASCVD consequences, to, ultimately, improve patient outcomes, quality of life, and longevity in persons with diabetes.

## Rationale for cardiometabolism

About one-third of cardiovascular patients already have T2DM, and about another third have either newly diagnosed T2DM or are prediabetic defined by the presence of dysglycemia (i.e. impaired glucose tolerance or impaired fasting glucose) [2], with many other characteristics of the insulin resistance (metabolic) syndrome [i.e. hypertension (HTN), abdominal obesity, dyslipidemia] that further increase cardiovascular risks. Of the remaining third, many of those may have the insulin resistance (metabolic) syndrome, but not yet the dysglycemia. Therefore, it is critical, in the primary prevention setting, but especially in the secondary prevention setting, where decisions become much more complex, that cardiologists and endocrinologists collaborate along with other providers in managing patients with prediabetes and diabetes. Cardiologists

must become accustomed to decisions made by the endocrinologist/diabetologist and/or take greater responsibility for the management of prediabetes and diabetes. It is important to understand that old and new therapies for glucose, cholesterol, and blood pressure (BP) control may have to be mutually coordinated for safety and efficacy (e.g. maximal reduction of cardiovascular outcomes), guided by information gleaned from clinical trial results. Furthermore, endocrinologists/diabetologists need be aware of the likelihood of subclinical, or clinical, ASCVD in these patients with T2DM and work together to reduce the risk of the first, or subsequent, clinical outcome(s), respectively.

Key to cardiometabolism is a focus on a multidisciplinary approach to ensure that the numerous ‘global’ ASCVD risk factors, often present in those with prediabetes and T2DM, be addressed adequately. It is not well appreciated that relatively few patients with diagnosed T2DM, even in the USA, despite its sophisticated healthcare systems, achieve guideline-directed goals for the major conventional cardiovascular risk factors, especially lipids, BP, blood glucose, and weight, which, when inadequately controlled, can lead to significant ASCVD residual risk. A report from the US National Health and Nutrition Examination Survey data shows that although ~50% of patients with T2DM may achieve targets for glycated hemoglobin (HbA1c), BP, or low-density lipoprotein-cholesterol (LDL-C), the likelihood that all three risk factors together are at target is only 25%. This report also showed only 10% of diabetics have a normal BMI below 25 kg/m<sup>2</sup> and only 4% achieved all four targeted goals [3]. The STENO-2 trial showed that controlling multiple modifiable cardiovascular risk factor measures can reduce CVD outcomes by nearly 60%, along with significant reductions in total and cardiovascular mortality [4], and more recently, at 21 years of follow-up, a nearly 8-year greater life expectancy was found [5]. Recently, Wong *et al.* [6] showed among a pooling of T2DM patients from three major prospective epidemiologic studies (MESA, ARIC, and Jackson) that those patients with diabetes achieving all three guideline-based goals for HbA1c, LDL-C, and BP had

60% lower CVD event risks compared with those who achieved none of those goals.

### Barriers to goal attainment

There are numerous barriers that keep many of our T2DM patients from achieving targeted goals. Far from a comprehensive look at the barriers issue, two issues stand out in a discussion of cardiometabolic collaboration. One includes a perceived lack of unifying recommendations among stakeholder organizations on the actual goals and the methods for their achievement and even the perceived necessity of achieving those goals. A second issue pertains to the many available numbers and classes/types of pharmaceutical agents to control lipids, BP, blood glucose, and weight, complicated by the complexity of deciding which are the most appropriate choice(s) for a given patient. In this respect, these decisions become particularly difficult, in more complicated patients, who often have additional comorbidities (i.e. CKD, heart failure, liver abnormalities) that often limit the choice(s) or dose(s) of many agents, within multiple classes, that may be required for control of modifiable risks.

### Targeting hyperglycemia for reduction of atherosclerotic cardiovascular disease

The association of hyperglycemia with microvascular complications [i.e. retinopathy, neuropathy, nephropathy (CKD)] and with ASCVD events has been shown in many epidemiologic studies. Randomized clinical trials have clearly reported that reducing hyperglycemia reduces onset and progression of microvascular disease. However, although the multifactorial role of hyperglycemia, in unfavorably modifying the atherosclerotic environment, has been recognized for decades, large randomized clinical trials, historically, have failed to show that glycemic control reduces ASCVD events significantly. As with lipid-lowering trials, statistically significant ASCVD risk reduction has depended on achieving between-group atherogenic cholesterol differences and negative trials are often a 'design issue' or 'in-trial mishap' such as a drug-drop out or placebo-drop-in issue. Compared with lipid-lowering trials, very few studies have been carried out to adequately assess the effects of glycemia on ASCVD and none of the large trials had an adequate between-group A1C difference (0.9–1.8%), perhaps an ethically driven design decision. In only one very small ( $n=110$ ) successful trial of lean patients with T2DM [7], Kumamoto study, was there likely an adequate (2.3%) A1C between-group difference and relative risk reductions of macrovascular complications and diabetes-related death by 54% (2–78%) and 81% (28–95%), respectively. Although falling short of the desired evidence-based medicine requirements, post-hoc analyses of the large studies, however, do support an ~14–16% risk reduction in ASCVD events for each 1% reduction of A1C. Furthermore, a legacy or a memory

effect has been noted, similar to that observed long after the completion of monotherapy trials with lipid-lowering agents (i.e. niacin, fibrate, statins), suggesting that early treatment can lead to long-term positive effects.

### Searching for special properties beyond glycemic control

Metformin showed a hint of special cardiovascular risk-reduction properties, beyond glucose control, in a very small group of obese participants, in the UK Prospective Diabetes Study [8], relative to conventional therapy, that is, initially diet only, and intensive therapy with insulin or sulfonylurea; this effect was attributed, at that time, to a proposed modest reduction in insulin resistance, likely a nominal effect, or inhibition of advanced glycation end-products formation. Although metformin is considered extremely safe and is the first-line agent of choice, recommended by global guidelines, its use becomes more complex in the settings of progressive CKD, heart failure, or chronic atrial fibrillation. In a multicenter, RCT, patients ( $n=1364$ ) with IGT who received the alpha-glucosidase inhibitor, acarbose, had a 49% RRR in the development of CV events, and a 91% RRR in MI compared to controls, suggesting that targeting postprandial hyperglycemia has ASCVD benefit [9]. To meet FDA requirements for post-marketing CV analysis of new diabetes, in the Cycloset Safety Trial in T2DM patients ( $n=3095$ ) the quick-release dopamine D2 receptor agonist, bromocriptine-QR, versus placebo, at 52 weeks, had a significant 40% risk reduction in a composite CVD end-point, and 39% and 52% relative risk reductions in the CV death-inclusive composite cardiovascular and MACE end points suggesting that targeting hypothalamic aberrations that precipitate multiple parallel pathophysiological, i.e., 'central' insulin resistance, events known to potentiate CV disease [10].

Targeting insulin resistance (metabolic) syndrome is vital because of its higher prevalence in prediabetes, diabetes, and ASCVD. The thiazolidinedione class of glucose-lowering agents, including rosiglitazone and pioglitazone, significantly reduces insulin resistance and has  $\beta$ -cell preservation properties. The Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive), a secondary prevention, moderately sized ( $n=5238$ ) trial [11] utilizing pioglitazone in high-risk patients, was event driven and completed after 3 years. Although the primary endpoint showed a positive effect trend, it failed to reach statistical significance and was, therefore, considered a negative trial. However, a secondary major adverse cardiovascular events endpoint that included nonfatal myocardial infarction (MI), stroke, and all-cause death did show a statistically significant 16% decrease, as well as an impressive subgroup analysis showing a 47% risk reduction for recurrent stroke. These benefits occurred in the absence of significant between-group blood glucose differences, consistent with the concept that special

properties beyond glycemic control, such as insulin sensitization, likely explained the benefits. On the basis of the results of those analyses, pioglitazone was added to the 2008 European Stroke Organization [12] recommended agents for secondary stroke prevention in patients with T2DM who do not need insulin (class III, level B). Pioglitazone also showed benefit in the Carotid Intima-Media tHICKness in Atherosclerosis using pioglitazone (CHICAGO) [13] and Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation (PERISCOPE) studies [14], where it was shown to reduce carotid intimal medial thickness and coronary plaque atheroma volume, respectively. In the Insulin Resistance Intervention after Stroke (IRIS) trial [15], 3876 patients with insulin resistance and recent ischemic stroke or TIA receiving pioglitazone (target dose, 45 mg daily) or placebo, by 4.8 years, had a 24% reduction ( $P=0.007$ ) in the primary outcome, (fatal or nonfatal stroke or myocardial infarction), 52% reduction. Clinicians are often faced with the challenge of deciding in whom and when to use thiazolidinediones as these agents are known to have potential side effects such as subcutaneous fat weight gain, despite visceral fat loss, and heart failure, in susceptible patients, that is, with pre-existing ventricular dysfunction. In addition, an increased risk of distal limb bone fractures has been documented.

Importantly, over the past 15 months, several outcome trials of two more classes of antihyperglycemic agents have shown reduced cardiovascular outcomes in patients with T2DM beyond glucose control. In the EMPA-REG trial [16], the sodium glucose transporter-2 inhibitor, empagliflozin, significantly reduced the primary outcome of nonfatal MI, or nonfatal stroke and death from CV causes by 14%. There were no significant between-group differences in the rates of MI or stroke, but significantly lower rates of death from CV causes by 38%. Furthermore, there were significant risk reduction for hospitalization for heart failure (35%), and death from any cause (32%). The benefits of empagliflozin are likely multifactorial. Empagliflozin is also the first glucose-lowering drug now FDA-indicated to “reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease”. Other sodium glucose transporter-2 inhibitor cardiovascular trials, CANVAS with canagliflozin (<https://clinicaltrials.gov/ct2/show/NCT01032629>), DECLARE with dapagliflozin (<https://clinicaltrials.gov/ct2/show/NCT01730534>), and VERTIS CV with ertugliflozin (<https://clinicaltrials.gov/ct2/show/NCT01986881>), are underway to evaluate the potential for a class effect.

In the ELIXA trial [17], the glucagon-like peptide-1 receptor antagonist (GLP-1RA), lixisenatide, a derivative of exenatide, showed neither benefit nor harm for major adverse cardiovascular events during a relatively short median follow-up duration of 25 months. Exenatide and

its derivative have a 50% homology to human GLP-1. However, more recently, the LEADER [18] trial, after 3.8 years of median follow-up, showed a significant 13% reduction in the composite cardiovascular events (cardiovascular death, nonfatal MI, and stroke) and a reduction of cardiovascular mortality with the GLP-1RA, liraglutide, that has nearly 100% homology to human GLP-1. In the short SUSTAIN-6 trial [19], the use of semaglutide reduced a composite of cardiovascular events by 23%. Trials with the first oral GLP-1RA, oral semaglutide, are just underway. Other ongoing GLP-1RA cardiovascular trials, EXSCCEL with exenatide once weekly (<https://www.clinicaltrials.gov/ct2/show/NCT01144338>), and REWIND with dulaglutide (<https://clinicaltrials.gov/ct2/show/NCT01394952>), are due to report in 2018 and 2019. These trials will hopefully clarify the mechanisms for the positive cardiovascular benefits and determine whether or not they are unique or the result of a class effect.

### Other risk factor management to reduce atherosclerotic cardiovascular disease risks

Addressing HTN management may also be considered complex, by many clinicians, because of the varied opinions among organizations making recommendations, in both the primary and the secondary prevention settings. The American Society of Hypertension has enhanced the level of education of healthcare providers with state-of-the-art scientific principles and evidence-based clinical practice to prevent ASCVD (coronary heart disease, stroke) (<http://www.ash-us.org/>). Organizations, such as Kidney Disease: Improving Global Outcomes [20] and the National Kidney Foundation (<https://www.kidney.org/>), address its guidelines toward the prevention and management of CKD, where the metabolic syndrome (i.e. HTN) as well as lipid abnormalities, progressively worsen with progression of CKD and/or proteinuria [21].

The issues related to dyslipidemia management are becoming increasingly more complex, and barriers to adequate control also exist, possibly also fueled by a perceived lack of harmony among global organizations making recommendations. Many of the recommendations are more alike than different, but there is also increasing complexity and opinions in terms of approaches, even though all agree on first-line maximally tolerated statin use. The sources of controversies are related to goals of therapy, the inadequacy of statins among many patients, and the role of nonstatins for LDL-C lowering; that is, ezetimibe, bile acid sequestrants, niacin, and newer agents such as mipomersen, lomitapide, and PCSK9 inhibitors, as well as the need, in hypertriglyceride states, for triglyceride-lowering agents – that is omega-3 fatty acid, fibrates, and niacin. The National Lipid Association (<https://www.lipid.org/>) serves as a training ground with several educational opportunities and increasing numbers of clinicians – that is, endocrinologists, cardiologists, primary care physicians – as well

as registered dietitians, and pharmacists are receiving specialty training or/and board certification from the Board of Clinical Lipidology. Both the American Association of Clinical Endocrinologists (<https://www.aace.com>) and the American Diabetes Association (<http://www.diabetes.org>) have annualized updated guidelines for the management of dyslipidemia that lacks complete harmony, but have more agreement than disagreement. In an effort to reduce the confusion associated with a variety of recommendations for the prevention of ASCVD, the National Lipid Association, American Heart Association (<http://www.heart.org>), and American College of Cardiology (<http://www.acc.org>) are in pursuit of harmonious guidelines.

### Quality improvement efforts

In a major effort to promote continuous quality improvement efforts involving diabetes, the American College of Cardiology, in partnership with the American Diabetes Association, the American College of Physicians, the American Association of Clinical Endocrinologists, and the Joslin Diabetes Center, has launched the Diabetes Collaborative Registry (<https://www.ncdr.com/WebNCDR/Diabetes/publicpage>). This is the first worldwide collaborative diabetes registry and is designed to track and improve the quality of care of diabetes and those with the metabolic syndrome across the continuum of primary and specialty care. It encourages the participation of primary care physicians, endocrinologists, cardiologists, and other healthcare providers managing diabetes. Hundreds of practices representing over one million patients are already enrolled. In addition, the American College of Cardiology seeks to promote physician education through article reviews, clinical cases, and images through its clinical topic collection on diabetes and cardiometabolic disease ([http://www.acc.org/clinical-topics/diabetes-and-cardiometabolic-disease?w\\_nav=MN#sort=%40foriginalz32xpostedz32xdate86069%20descending](http://www.acc.org/clinical-topics/diabetes-and-cardiometabolic-disease?w_nav=MN#sort=%40foriginalz32xpostedz32xdate86069%20descending)).

### Conclusion

Cardiometabolic and promoting greater collaboration between cardiologists, diabetologists, and other healthcare providers caring for patients with prediabetes and diabetes are imperatives for optimizing quality of care to ensure the best possible outcomes in the settings of cardiometabolic disorders. Such collaboration fostering coordinated care and improved systems approaches for quality improvement is necessary to tackle the global epidemics of diabetes and CVD.

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### Conflicts of interest

There are no conflicts of interest.

### References

- Boulos N, Wong ND. Epidemiology of diabetes and cardiovascular disease. In: Wong ND, Malik S, editors. *Diabetes and cardiovascular disease*. New Delhi, India: Jaypee Brothers Medical Publishers; 2014. pp. 1–13.
- Anselmino M, Mellbin L, Wallander M, Rydén L. Early detection and integrated management of dysglycemia in cardiovascular disease: a key factor for decreasing the likelihood of future events. *Rev Cardiovasc Med* 2008; **9**:29–38.
- Wong ND, Patao C, Wong K, Malik S, Franklin SS, Iloeje U. Trends in control of cardiovascular risk factors among US adults with type 2 diabetes 1999–2010: comparison by prevalent cardiovascular disease status. *Diab Vasc Dis Res* 2013; **10**:505–513.
- Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med* 2008; **358**:580–591.
- Gaede P, Oellegaard J, Carstensen B, Rossing P, Lund-Andersen H, Parving HH, Pedersen O. 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**: 2298–2307.
- Wong ND, Zhao Y, Patel R, Patao C, Malik S, Bertoni AG, et al. Cardiovascular risk factor targets and cardiovascular disease event risk in diabetes mellitus, a pooling project of the Atherosclerosis Risk in Communities Study, Multiethnic Study of Atherosclerosis, and Jackson Heart Study. *Diabetes Care* 2016; **39**:668–676.
- Wake N, Hisashige A, Katayama T, Kishikawa H, Ohkubo Y, Sakai M, et al. Cost-effectiveness of intensive insulin therapy for type 2 diabetes: a 10-year follow-up of the Kumamoto study. *Diabetes Res Clin Pract* 2000; **48**:201–10.
- [No authors listed]. 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**:854–865.
- Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M, et al. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. *JAMA* 2003; **290**:486–94.
- Gaziano JM, Cincotta AH, O'Connor CM, Ezrokhi M, Rutty D, Ma ZJ, et al. Randomized clinical trial of quick-release bromocriptine among patients with type 2 diabetes on overall safety and cardiovascular outcomes. *Diabetes Care* 2010; **33**:1503–8.
- Dormandy JA, Charbonnel B, Eckland DJA, on behalf of the PROactive investigators. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive study (Prospective Pioglitazone Clinical Trial in Macrovascular Events): a randomized controlled trial. *Lancet* 2005; **366**:1279–1289.
- European Stroke Organisation (ESO) Executive Committee; ESO Writing Committee. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. *Cerebrovasc Dis* 2008; **25**:457–507.
- Mazzone T, Meyer PM, Feinstein SB, Davidson MH, Kondos GT, D'Agostino RB Sr, et al. Effect of pioglitazone compared with glimepiride on carotid intima-media thickness in type 2 diabetes: a randomized trial. *JAMA* 2006; **296**:2572–2581.
- Nissen SE, Nicholls SJ, Wolski K, Nesto R, Kupfer R, Perez A, et al. Comparison of pioglitazone vs glimepiride on Progression of coronary atherosclerosis in patients with type 2 diabetes: the PERISCOPE randomized controlled trial. *JAMA* 2008; **299**:1561–1573.

- 15 Kernan WN, Viscoli CM, Furie KL, Young LH, Inzucchi SE, Gorman M, *et al.* for the IRIS Trial Investigators. Pioglitazone after ischemic stroke or transient ischemic attack. *N Engl J Med* 2016; **374**:1321–1331.
- 16 Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, *et al.* EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015; **373**: 2117–2128.
- 17 Pfeffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, Køber LV, *et al.* ELIXA Investigators. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *N Engl J Med* 2015; **373**:2247–2257.
- 18 Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, *et al.* LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2016; **375**:311–322.
- 19 Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, *et al.* for the SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2016; **375**: 1834–1844.
- 20 Kidney Disease: Improving Global Outcomes (KDIGO) Lipid Work Group. KDIGO clinical practice guideline for lipid management in chronic kidney disease. *Kidney Int Suppl* 2013; **3**:259–305.
- 21 Van der Velde M, Matsushita K, Coresh J, Astor BC, Woodward M, Levey AS, *et al.* Chronic Kidney Disease Prognosis. Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality. A collaborative meta-analysis of high-risk population cohorts. *Kidney Int* 2011; **79**:1341–1352.