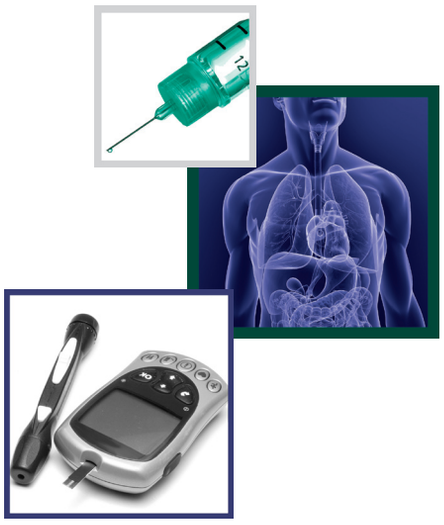

ACCORD microvascular and Eye substudy: should the results change our practice?

Alice YY Cheng[†] & Lawrence A Leiter[1]

Practice Points

- Intensive glycemic control in Type 2 diabetes reduces retinopathy, nephropathy and elements of peripheral neuropathy.
- There appears to be greater benefit when intensive glycemic control is instituted earlier in the disease spectrum.
- Glycemic targets should be individualized taking into consideration the overall risk:benefit ratio.

SUMMARY Microvascular complications of diabetes are potentially devastating and costly to both individuals and society. The United Kingdom Prospective Diabetes Study (UKPDS) and Steno-2 studies confirmed the benefits of glycemic control for reducing microvascular complications in Type 2 diabetes mellitus (T2DM) of short duration, but the benefits in people with T2DM of longer duration was not as clear. The Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) and Veterans Affairs Diabetes Trial (VADT) studies were designed to address the question of macrovascular risk reduction in people with a longer duration of T2DM, but also looked at microvascular complications. Although the microvascular primary composite outcomes were not reduced in the ACCORD trial, seven of the 13 prespecified secondary outcomes were significantly reduced, and when considering those results along with the ACCORD-Eye substudy, one can conclude that there is reduction in retinopathy with intensive glycemic control. Nephropathy was also reduced in both the ADVANCE and ACCORD studies. As for peripheral neuropathy, ADVANCE did not show a reduction, but the assessment method was unclear. The ACCORD study did demonstrate significant reduction in three of the four prespecified neuropathy elements – an important finding in an area with limited effective therapies. VADT was the only study to show no microvascular benefit at all, however, it had the smallest sample size, as well as the oldest and the most advanced population of all of the studies, which may account for the discrepancy. Therefore, the evidence to date supports that intensive glycemic control is effective in reducing microvascular complications among people with T2DM. However, although microvascular complication reduction is worthwhile, one must consider the patient as a whole and individualize the targets and consider the overall risk (including hypoglycemia):benefit ratio.

[1]Division of Endocrinology & Metabolism & Keenan Research Center in the Li Ka Shing Knowledge Institute of St Michael's Hospital, University of Toronto, Toronto, Canada

[†]Author for correspondence: Division of Endocrinology & Metabolism, St Michael's Hospital & Credit Valley Hospital, Assistant Professor, Department of Medicine, University of Toronto, 507–2300 Eglinton, Avenue West, Mississauga, ON L5M 2V8, Canada; Tel.: +1 905 828 7622; Fax: +1 905 828 7769; chenga@smh.ca

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The microvascular complications of diabetes are potentially devastating and costly to both individuals and society. Diabetes remains a leading cause of blindness, end stage renal disease and nontraumatic amputations [1,2]. Clinical practice guidelines from around the world have focused on strategies to manage diabetes to reduce the risk of these, as well as the macrovascular, complications [3–6]. In Type 1 diabetes, the Diabetes Control and Complications Trial (DCCT) [7] and the follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) trial [8] proved the benefit of intensive glycemic control to reduce the development and progression of all of the microvascular complications and, over time, macrovascular complications. By contrast, in Type 2 diabetes (T2DM), the story is somewhat more complex. The original United Kingdom Prospective Diabetes Study (UKPDS) [9] showed that intensive glycemic control was effective in reducing the risk of developing microvascular complications (retinopathy requiring photocoagulation, vitreous hemorrhage and/or renal failure) by 25% and subsequent analyses showed that there was a 37% reduction in microvascular end points for every 1% A1c reduction [10]. Furthermore, the landmark Steno-2 study [11,12], also demonstrated marked and sustained reductions in microvascular complications with a multifactorial, multidisciplinary management approach to T2DM, including not only glycemic but also blood pressure, lipids, and other preventative medications, as well as lifestyle. This further supported the notion of glycemia being a relevant prevention strategy for microvascular complications (retinopathy, nephropathy and autonomic neuropathy, but not peripheral neuropathy). However, in 2008, three major randomized controlled trials of glycemic control in T2DM and its effect on macrovascular and microvascular outcomes – Action to Control Cardiovascular Risk in Diabetes (ACCORD) [13], Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) [14] and Veterans Affairs Diabetes Trial (VADT) [15] questioned the role of glycemic control in T2DM. The studies were designed primarily to address macrovascular risk reduction and to that end, ADVANCE and VADT demonstrated no macrovascular risk reduction with intensive glycemic control and ACCORD was terminated early because of an unexpected and unexplained [16,17] increase in all-cause mortality. However, a meta-analysis [18] of these three studies, plus the UKPDS, demonstrated no increase in all-cause or cardiovascular mortality and showed a small, but statistically significant, decrease in major cardiovascular events (hazard ratio: 0.91; 95% CI: 0.84–0.99) and myocardial infarctions (hazard ratio: 0.85; 95% CI: 0.85–0.94). Focusing on the microvascular side, the ADVANCE trial showed that intensive glycemic control, defined as targeting an A1c <6.5% using a gliclazide-based regimen, was able to reduce new or worsening nephropathy by 21%, but not retinopathy or neuropathy. A small proportion (n = 1241) of the ADVANCE patients also participated in a substudy looking at eye-related changes with fundus photography and no difference was found in incidence or progression of retinopathy between intensive and standard glycemic control over 4.1 years [19]. In VADT, intensive glycemic control defined as targeting an A1c 1.5% lower than the standard group (achieved A1c 6.9% intensive vs 8.4% standard) did not result in a statistically significant reduction in any of the microvascular end points (retinopathy, nephropathy and neuropathy). The microvascular results of ACCORD were the most recent to be published.

ACCORD study

The Action to Control Cardiovascular Risk in Diabetes study was designed to determine the cardiovascular effects of strategies to achieve intensive (A1c target <6%, median achieved 6.4%) versus standard (A1c target 7–7.9%, median achieved 7.5%) glycemic control, intensive versus standard systolic blood pressure control (<120 mmHg versus <140 mmHg), and fenofibrate plus simvastatin versus simvastatin alone [13,20,21]. Predefined secondary outcomes included the effect of these interventions on incidence and progression of retinopathy, nephropathy and neuropathy [22] and there was also a predefined substudy of the effects on retinopathy as assessed by fundus photography [23]. The ACCORD trial enrolled people with longstanding T2DM either with established cardiovascular disease or deemed to be at high cardiovascular risk. A total of 10,251 participants were assigned to therapy in the glycemia arm with a median age of 62 years and duration of diabetes of 10 years. In February 2008, after a median of 3.7 years, the intensive glycemic control arm of the study was stopped because of an increase in all-cause mortality [13] and all participants were assigned to standard glycemia intervention for the originally planned duration of the study (median 5.0 years).

ACCORD microvascular findings

The results of the predefined secondary microvascular outcomes of retinopathy, nephropathy and neuropathy were reported at transition from intensive to standard therapy as well as for the full duration of the study [22]. The primary composite microvascular outcome was identical to the UKPDS and included retinopathy-requiring photocoagulation or vitreal hemorrhage or renal failure. The second composite outcome included the components of the primary composite outcome plus peripheral neuropathy. There were 13 additional prespecified secondary outcomes: five related to kidney function; four related to eye function; and four related to nerve function.

Both of the composite outcomes were no different between the groups at transition or at study end. Of the 13 prespecified secondary outcomes, seven were in favor of intensive glycemic control at study end **(Table 1)** and included microalbuminuria, macroalbuminuria, loss of pressure sensation, new loss of ankle jerk, new neuropathy, eye surgery for cataract extraction and three-line change in visual acuity. One of the secondary outcomes was unfavorable with the intensive glycemia group having more adverse renal outcomes (estimated glomerular filtration rate decrease by >20 ml/min/1.73 m^2 or doubling of serum creatinine or macroalbuminuria or renal failure) with a hazard ratio of 1.07 (95% CI: 1.02, 1.13; p = 0.016). However, this outcome was largely driven by the transient increases in creatinine observed in the first 2 years of the study that were reversed as the study progressed.

Table 1. Secondary outcomes that were reduced by intensive glycemic control in the ACCORD study (seven of 13 prespecified secondary outcomes).

Outcome	Until transition	Study end
Nephropathy		
Microalbuminuria (urine ACR >3.4 mg/mmol)	HR = 0.79 (95% CI: 0.69–0.90), p = 0.0005 NNT = 35	HR = 0.85 (95% CI: 0.77–0.94), p = 0.0012 NNT = 32
Macroalbuminuria (urine ACR >33.9 mg/mmol)	HR = 0.69 (95% CI: 0.54–0.86), p = 0.0013 NNT = 82	HR = 0.71 (95% CI: 0.59–0.86), p = 0.0003 NNT = 58
Renal failure	NS	NS
Doubling of serum creatinine or >20 ml/min per 1.73 m^2 eGFR decrease	HR = 1.07 (95% CI: 1.01–1.13), p = 0.0160 NNT = -69	NS
Neuropathy		
Loss of light touch (10 g force monofilament)	HR = 0.88 (95% CI: 0.77–1.00), p = 0.0451 NNT = 78	HR = 0.85 (95% CI: 0.75–0.95), p = 0.0043 NNT = 49
New score of >2 on MNSI	NS	HR = 0.92 (95% CI: 0.86–0.99), p = 0.0265 NNT = 33
New loss of ankle jerk during Jendrassik maneuver	NS	HR = 0.90 (95% CI: 0.84–0.97), p = 0.005 NNT = 28
New loss of vibratory sensation (tested with 128 Hz tuning fork)	NS	NS
Retinopathy		
Eye surgery for cataract extraction	NS	HR = 0.89 (95% CI: 0.80–0.99), p = 0.0265 NNT = 65
Three-line change in visual acuity	HR = 0.84 (95% CI: 0.73– 0.97), p = 0.0163 NNT = 83	HR = 0.91 (95% CI: 0.83–1.00), p = 0.05 NNT = 60
Retinal photocoagulation or vitrectomy to treat retinopathy	NS	NS
Severe vision loss (Snellen fraction <20/200)	NS	NS

ACR: Albumin:creatinine ratio; eGFR: Estimated glomerular filtration rate; HR: Hazard ratio; MNSI: Michigan neuropathy screening instrument; NNT: Number needed to treat; NS: Not significant.
Data taken from [22].

ACCORD-Eye substudy

A subgroup of 2856 participants were also included in the ACCORD-Eye substudy evaluating the effects of the three interventions (glycemia, blood pressure and lipids) on the primary outcome of the composite of progression of diabetic retinopathy by three or more steps on the Early Treatment Diabetic Retinopathy Study Severity Scale (using seven-field stereoscopic fundus photographs) or the development of diabetic retinopathy necessitating laser photocoagulation or vitrectomy over 4 years [23]. At baseline, 50.8% of the participants had no retinopathy, 18.1% had mild retinopathy and 29.6% had moderate nonproliferative diabetic retinopathy. The results of the study are shown in **Table 2**. Intensive glycemic control was able to reduce the primary outcome by 33% (7.5 vs 10.4%) while the use of fenofibrate plus a statin was able to reduce the primary outcome by 40% (6.5 vs 10.2%). The intensive systolic blood pressure intervention had no effect on retinopathy.

■ Implications for clinical practice

The microvascular findings of the UKPDS, ADVANCE, VADT, ACCORD and Steno-2 trials/studies are summarized in **Table 3**. All of the studies, with the exception of VADT, demonstrated some reduction in at least one major microvascular outcome. Examining VADT in greater detail reveals that its participants had the highest A1c at baseline (mean 9.4%), as well as the longest duration of diabetes (mean

Table 2. Effects of intensive glycemic control, fenofibrate use and intensive blood pressure control on progression of diabetic retinopathy from the ACCORD study.

Intervention	Progression of diabetic retinopathy (%)	Adjusted odds ratio	95% CI	p-value
Glycemia				
Intensive Standard	7.3 10.4	0.67	0.51–0.87	0.0025
Dyslipidemia				
With fenofibrate With placebo	6.5 10.2	0.60	0.42–0.86	0.0056
Blood pressure				
Intensive Standard	10.4 8.8	1.23	0.84–1.79	0.29

Data taken from [23].

11.5 years), the most pre-existing cardiovascular disease (mean 40%), the highest body weight (mean 97.3 kg) and proportion of men (97% men) and the smallest sample size (n = 1791) with a median duration of follow-up of only 5.6 years. In contrast, the participants in the other studies, particularly UKPDS and Steno-2, were considerably younger, earlier in their diabetes, and had fewer comorbidities. Perhaps all of these factors contribute to the discrepancy in the results on the primary composite outcome of retinopathy requiring photocoagulation, vitreal hemorrhage or renal failure between UKPDS and ACCORD. Therefore, it would seem that the growing understanding that the benefits of glycemic control are best realized in people that are earlier in their diabetes course and that these benefits may also take a long time to manifest, applies not only to macrovascular, but also to microvascular, disease.

In addition, the potential benefits on the various microvascular complications are not the same. For example, microalbuminuria and macroalbuminuria were consistently reduced by better glycemic control across the studies (even almost achieving statistical significant reduction in VADT). This finding was independent of blood pressure control and certainly justifies the recommendation for better glycemic control for renal protection.

The beneficial effects on retinopathy were less consistent but that may be related to differences in the studies' duration and statistical power. UKPDS was able to demonstrate a difference in the requirement for photocoagulation and the composite retinal end point but ACCORD was not able to show such a difference. However, these outcomes represent more advanced stages of retinopathy that take a longer time to develop. When examining for earlier and more subtle changes with fundus photography, ACCORD was able to demonstrate benefit. Perhaps ADVANCE was not able to demonstrate a similar finding because of the smaller sample size of only 1241 compared with the ACCORD-Eye substudy with 2856 and UKPDS with 3827 subjects. Therefore, glycemic control does have benefit for reducing incidence and progression of retinopathy throughout the spectrum of T2DM duration.

However, beneficial effects on neuropathy have remained more difficult to demonstrate. In Type 1 diabetes, there is good evidence that glycemic control reduces the risk for neuropathy [7]. By contrast, there is less evidence of benefit in T2DM. The UKPDS did not include neuropathy in their composite microvascular end point. Neuropathy was assessed by ankle and knee jerk reflexes and by biothesiometer readings and no differences were found. Steno-2 was only able to demonstrate reductions in autonomic neuropathy (as defined by measurement of the relative risk (RR) interval on an ECG during paced breathing and on an orthostatic-hypotension test by a blinded laboratory technician), but not peripheral neuropathy, as assessed by biothesiometer readings. ADVANCE demonstrated no difference in neuropathy. Only ACCORD has now provided some evidence of benefit of intensive glycemic control with three of the four prespecified secondary outcomes assessing peripheral neuropathy achieving statistical significance. The benefits were reductions in loss of light touch with a 10 g monofilament, new loss of ankle jerk during the Jendrassik manoevre, and new neuropathy with a score >2 on the Michigan Neuropathy Screening Instrument with low numbers-needed-to-treat of 49, 33 and 28, respectively. Loss of vibration sense was not significantly improved. Although not all of the neuropathy outcomes were improved, this is still clinically relevant in that loss of 10 g monofilament sensation has been associated with high risk of development of diabetic ulcers and amputation. This is an important finding in a population that had previously lacked proof of benefit. The apparent discrepancies in effect on peripheral neuropathy between the studies may be explained by the assessment methods. Both UKDPS and Steno-2 utilized the biothesiometer reading to assess for peripheral neuropathy. The biothesiometer measures vibration sense – the one secondary outcome of neuropathy that

Table 3. Characteristics and findings of the ACCORD, ADVANCE, VADT, UKPDS, UKPDS-PTM, Steno-2 and Steno-2 OBS trials.

	ACCORD	ADVANCE	VADT	UKPDS	UKPDS-PTM	Steno-2	Steno-2 OBS
Population							
Participants (n)	10,251	11,140	1791	4209	3277	160	130
Mean age (years)	62	66	60	54	62	55	62
Mean duration of diabetes (years)	10.0	8.0	11.5	Newly diagnosed	10.0	6.0	13.0
Median HbA_{1c}	8.1	7.2	9.4	7.08	7.9 vs 8.5	8.6	7.9 vs 9.0
History of macrovascular disease (%)	35	32	40	†	†	29	†
Mean weight (kg)	93.5	78.3	97.3	77.5	81.0	BMI 29–31	BMI 30–33
Intervention							
Target HbA_{1c} (intensive vs standard), %	<6.0 vs 7.0–7.9	≤6.5 vs standard care	<6.0 vs 8.0–9.0	FPG <6.0 mmol/l vs FPG <15 mmol/l	None	HbA_{1c} <6.5% vs <7.5% plus lipid, blood pressure, medication and lifestyle intervention	None
Median follow-up (years)	3.4	5.0	6.0	10.0	17.0	7.8	13.3
Treatment intervention (intensive vs standard)	Investigator's discretion	Gliclazide MR-based therapy vs nongliclazide MR-based therapy (additions at investigator's discretion)	Metformin + rosiglitazone to start, then stepwise addition	SU or insulin or metformin vs 'standard care'	Investigator's discretion	Metformin ± SU ± insulin	Investigator's discretion
Outcome (intensive vs standard)							
Median HbA_{1c} at study end (%)	6.4 vs 7.5	6.4 vs 7.0	6.9 vs 8.4	7.0 vs 7.9	7.8 vs 7.8	7.9 vs 9.0	7.7 vs 8.0
Primary microvascular outcome (if applicable)	Renal failure or photocoagulation or vitrectomy	New or worsening nephropathy or retinopathy	Retinopathy or nephropathy or neuropathy	Renal failure or photocoagulation or vitrectomy	Renal failure or photocoagulation or vitrectomy	Retinopathy or nephropathy or neuropathy	Retinopathy or nephropathy or neuropathy
Result	NS	HR: 0.86	NS	0.75	0.76	HR: 0.42 (retinopathy), HR: 0.39 (nephropathy), HR: 0.37 (autonomic neuropathy)	HR: 0.57 (retinopathy), HR: 0.44 (nephropathy), HR: 0.53 (autonomic neuropathy)

†Data unavailable in the public domain at the time of preparation of this article.
ACCORD: Action to Control Cardiovascular Risk in Diabetes Study Group; ADVANCE: Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; FPG: Fasting plasma glucose; HbA_{1c}: Hemoglobin A_{1c}; HR: Hazard ratio; MR: Modified release; NS: Not significant; Steno-2 OBS: Steno-2 observation trial; SU: Sulfonylurea; UKPDS: United Kingdom Prospective Diabetes Study; UKPDS-PTM: United Kingdom Prospective Diabetes Study 10-Year Post-Trial Monitoring; VADT: Veterans Affairs Diabetes Trial.

Table 3. Characteristics and findings of the ACCORD, ADVANCE, VADT, UKPDS, UKPDS-PTM, Steno-2 and Steno-2 OBS trials.

	ACCORD	ADVANCE	VADT	UKPDS	UKPDS-PTM	Steno-2	Steno-2 OBS
Outcome (intensive vs standard) (cont.)							
Relevant secondary microvascular outcomes	Reduction in two renal outcomes, three neuropathy outcomes, two retinopathy outcomes and progression of retinopathy	New or worsening nephropathy (HR: 0.79)	None	None	Not studied	No difference for peripheral neuropathy	No difference in peripheral neuropathy
Other	No significant reduction in primary microvascular outcome						

[†]Data unavailable in the public domain at the time of preparation of this article.
ACCORD: Action to Control Cardiovascular Risk in Diabetes Study Group; ADVANCE: Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; FPG: Fasting plasma glucose; HbA_{1c}: Hemoglobin A_{1c}; HR: Hazard ratio; MR: Modified release; NS: Not significant; Steno-2 OBS: Steno-2 observation trial; SU: Sulfonylurea; UKPDS: United Kingdom Prospective Diabetes Study; UKPDS-PTM: United Kingdom Prospective Diabetes Study 10-Year Post-Trial Monitoring; VADT: Veterans Affairs Diabetes Trial.

was not significantly reduced in ACCORD. The publications on ADVANCE do not discuss their assessment method for peripheral neuropathy. So perhaps the peripheral neuropathy benefits of glycemic control in T2DM are detected better using assessments of light touch, ankle jerk reflex and a validated neuropathy assessment instrument. Steno-2 did not show a peripheral neuropathy benefit but did show reduction in autonomic neuropathy. This was not assessed in the other studies so it is difficult to comment any further. Taking into account all of the evidence to date, one can conclude that glycemic control appears to have benefit in reducing certain components of peripheral neuropathy in T2DM.

There is also the issue of fenofibrate use and reduction in microvascular complications. An interesting finding of the ACCORD-Eye substudy was the benefit seen with fenofibrate use. The magnitude of benefit was fairly impressive with an absolute risk reduction of 3.7%. This is consistent with the results of the Fenofibrate in Event Lowering in Diabetes (FIELD) study [24,25]. In the FIELD study, 9795 participants with T2DM were randomized to receive fenofibrate or placebo with the primary outcome of interest being cardiovascular. Despite not demonstrating overall cardiovascular benefit (similar to ACCORD), there were microvascular benefits. A prespecified tertiary outcome was the need for laser photocoagulation therapy for retinopathy. The fenofibrate group had significantly less laser treatment with a hazard ratio of 0.69 (95% CI: 0.56–0.84; p = 0.0002). A fundus photography substudy of only 1012 participants showed reduction in two-step progression using the Early Treatment Diabetic Retinopathy Study (ETDRS) for those with pre-existing retinopathy (3.1% fenofibrate vs 4.6% placebo; p = 0.004), but not for those without pre-existing retinopathy [25]. In addition, in the FIELD study, similar to in ACCORD lipid, the microvascular benefits were not only seen with retinopathy but there was also a reduction in albuminuria with 24% reduction in albumin:creatinine ratio in the fenofibrate group, compared with only 11% reduction with placebo (p < 0.001) [26]. There was also 14% less albuminuria progression and 18% more regression compared with placebo over the 5 years of the study and also less decline of renal function. In addition, there was a reduction in risk of first amputation and, in particular, minor amputations with no known large-vessel disease, which is more suggestive of a microvascular etiology [27].

These are all interesting findings and the exact mechanisms through which fenofibrate can reduce complications are not fully understood. Potential mechanisms include the effects of PPARα agonist on inflammation, angiogenesis and cell migration [25,28].

So considering the totality of evidence as it currently exists, what are the exact benefits of improved glycemic control in T2DM? Although microvascular complication reduction is obviously worthwhile, one must consider the patient as a whole. The primary cause of death among those with diabetes remains cardiovascular disease. In those patients who are younger and/or earlier in their course of diabetes, aggressive glycemic control to target an A1c of at least <7% remains warranted to reduce both microvascular and macrovascular complications in the long term. However, for those who are older and have had diabetes for longer duration, the potential microvascular benefits of intensive glycemic control must be balanced against the overall effects of intensive glycemic management which included negative effects such as weight gain and increased risk of severe hypoglycemia. It should be noted that although an increased risk of mortality associated with intensive therapy was also seen in ACCORD, this was not observed in the other recent trials nor in the meta-analyses of the UKPDS, ACCORD, ADVANCE, and VADT studies [18], and an explanation for the ACCORD results remains elusive [16,17]. Further analyses of the ACCORD data suggest that severe hypoglycemia is a marker of those at higher risk of mortality, especially if in the intensive arm, and that those who were able to achieve better glycemic control with no severe hypoglycemia, benefitted the most. It would thus seem appropriate to conclude that the approach to consider for glycemic control is not a 'one size fits all' approach, but rather one of individualization and consideration of the overall risk (including hypoglycemia) benefit ratio. However, it is critical that this approach not be interpreted as permission to be lax with glycemic control, but more as a reminder that in the vast majority of those with T2DM, aggressive glycemic management is warranted but as the risk benefit status changes, it may be prudent to be less aggressive. Furthermore, the Steno-2 study reminds us that glycemic control is not the sole important factor in the management of T2DM, but rather one of many. A multifactorial, multidisciplinary approach is the most effective to reduce both micro- and macro-vascular complications. The role of fenofibrate is evolving and may be a consideration for those with T2DM, not for its lipid-lowering properties, but rather for its ability to reduce some microvascular complications. However, a recommendation for its widespread use for this purpose remains premature at this time.

Conclusion & future perspective

Intensive glycemic control in T2DM reduces the risk of nephropathy, retinopathy and elements of peripheral neuropathy and although benefit was seen throughout the spectrum of disease duration, the benefit appears to be greater when applied earlier in the disease. Although reduction of microvascular complications is worthwhile, one must consider the patient as a whole. Therefore, glycemic targets should be individualzed and the overall risk:benefit ratio must be considered.

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Bibliography

Papers of special note have been highlighted as:

- ▪ of interest
- ▪▪ of considerable interest

1 Canadian Institute for Health Information. *Treatment of End-Stage Organ Failure in Canada, 1999–2008: CORR 2010 Annual Report.* CIHI, Ottawa, Canada (2010).

2 Public Health Agency of Canada. *Report from the National Diabetes Surveillance System: Diabetes in Canada 2009*. Public Health Agency of Canada, Ottawa, Canada (2009).

3 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* 32(Suppl. 1), S1–S201 (2008).

4 American Diabetes Association. Standards of Medical Care in Diabetes – 2010. *Diabetes Care* 33(Suppl. 1), S11–S61 (2010).

5 IDF Clinical Guidelines Task Force. *Global guideline for Type 2 diabetes.* International Diabetes Federation, Brussels (2005).

6 National Collaborating Centre for Chronic Conditions and the Centre for Clinical Practice at NICE. *NICE Clinical Guideline 87 – Type 2 diabetes: The management of type 2 diabetes.* National Institute for Health and Clinical Excellence, London, UK (2009).

7 The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N. Engl. J. Med.* 329(14), 977–986 (1993).

8 Nathan DM, Cleary PA, Backlund JY *et al.* Diabetes Control and Complications Trial/ Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with Type 1 diabetes. *N. Engl. J. Med.* 353(25), 2643–2653 (2003).

9 UK Prospective Diabetes Study (UKPDS) Group. Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with Type 2 diabetes (UKPDS 33). *Lancet* 352(9131), 837–853 (1998).

10 Stratton IM, Adler AI, Neil AW *et al.* Association of glycaemia with macrovascular and microvascular complications of Type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 321, 405–412 (2000).

11 Gaede P, Vedel P, Larsen N *et al.* Multifactorial intervention and cardiovascular disease in patients with Type 2 diabetes. *N. Engl. J. Med.* 348(5), 383–393 (2003).

■ **Impressive microvascular and macrovascular benefits of multifactorial management for Type 2 diabetes are shown in this landmark study.**

12 Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in Type 2 diabetes. *N. Engl. J. Med.* 358(6), 580–591 (2008).

■ **The extension of Steno-2 demonstrated that the microvascular and macrovascular benefits of multifactorial management persist over time, even after the active intervention is stopped.**

13 The Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in Type 2 diabetes. *N. Engl. J. Med.* 358(24), 2545–2559 (2008).

■ **Randomized controlled trial of intensive glycemic control strategy versus conventional glycemic control strategy demonstrating lack of macrovascular benefit and potential harm.**

14 The ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with Type 2 diabetes. *N. Engl. J. Med.* 358(24), 2560–2572 (2008).

■ **Randomized controlled trial of intensive glycemic control using a gliclazide-based strategy compared to less intensive glycemic control strategy demonstrating lack of macrovascular benefit but presence of nephropathy reduction.**

15 Duckworth W, Abraira C, Moritz T *et al.* Glucose control and vascular complications in veterans with Type 2 diabetes. *N. Engl. J. Med.* 360(2), 129–139 (2009).

■ **Randomized controlled trial of intensive glycemic control compared to conventional glycemic control demonstrating lack of both microvascular and macrovascular benefit.**

16 Riddle MC. Counterpoint: intensive glucose control and mortality in ACCORD – still looking for clues. *Diabetes Care* 33, 2722–2724 (2010).

17 Lachin JM. Point: intensive glycemic control and mortality in ACCORD – a chance finding? *Diabetes Care* 33, 2719–2721 (2010).

18 Turnbull FM, Abraira C, Anderson RJ *et al.* Intensive glucose control and macrovacular outcomes in Type 2 diabetes. *Diabetologia* 52, 2288–2298 (2009).

19 Beulens JWJ, Patel A, Vingerling R *et al.* Effects of blood pressure lowering and intensive glucose control on the incidence and progression of retinopathy in patients with Type 2 diabetes mellitus: a randomized controlled trial. *Diabetologia* 52, 2027–2036 (2009).

20 The ACCORD Study Group, Ginsberg HN, Elam MB *et al.* Effect of combination lipid therapy in Type 2 diabetes. *N. Engl. J. Med.* 362, 1563–1574 (2010).

21 Cushman WC, Evans GW *et al.*; The ACCORD Study Group. Effects of intensive blood-pressure control in Type 2 diabetes mellitus. *N. Engl. J. Med.* 362, 1575–1585 (2010).

22 Ismail-Beigi F, Craven T, Banerji MA *et al.* Effect of intensive treatment of hyperglycaemia on microvascular outcomes in Type 2 diabetes: an analysis of the ACCORD randomized trial. *Lancet* 376, 419–430 (2010).

■ **The microvascular results of the ACCORD study demonstrating benefit in some of the secondary outcomes for retinopathy, nephropathy and neuropathy.**

23 The ACCORD Study Group, ACCORD Eye Study Group, Chew EY, Ambrosius WT, Davis MD *et al.* Effects of medical therapies on retinopathy progression in Type 2 diabetes. *N. Engl. J. Med.* 363, 233–244 (2010).

■■ **The ACCORD-Eye substudy demonstrating retinopathy benefits of intensive glycemic control, use of fenofibrate plus statin and lack of benefit with blood pressure control.**

24 The FIELD Study Investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with Type 2 diabetes mellitus (the FIELD study): randomized controlled trial. *Lancet* 366, 1849–1861 (2005).

25 Keech AC Mitchell P, Summanen PA *et al.* Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomized controlled trial. *Lancet* 370, 1687–1697 (2007).

26 Davis TM, Ting R, Best JD *et al.* Effects of fenofibrate on renal function in patients with Type 2 diabetes mellitus: the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Study. *Diabetologia* 54(2) 280–290 (2011).

27 Rajamani K, Colman PG, Li LP *et al.* Effect of fenofibrate on amputation events in people with Type 2 diabetes mellitus (FIELD study): a prespecified analysis of a randomized controlled trial. *Lancet* 373, 1780–1788 (2009).

28 Leiter LA. The prevention of diabetic microvascular complications of diabetes: is there a role for lipid-lowering therapy? *Diab. Res. Clin. Prac.* 68(S2), S3–S14 (2005).