

# Revisiting the Role of Intensive Glucose Control on Cardiovascular Outcomes

Written by Jill Shuman

Silvio E. Inzucchi, MD, Yale University School of Medicine, New Haven, Connecticut, USA, presented the second of 2 Presidential Plenary sessions and focused on evolving views of glucose control and its effect on cardiovascular (CV) outcomes.

He began the session by reviewing the epidemiologic and pathophysiologic links between HbA<sub>1c</sub> and microvascular complications, as noted in the UKPDS 35 trial [Stratton IM et al. *BMJ*. 2000]. However, a definitive link between HbA<sub>1c</sub> and myocardial infarction (MI) and mortality remains more elusive and controversial [Emerging Risk Factors Collaboration. *JAMA*. 2014; Brewer N et al. *Diabetes Care*. 2008].

According to Dr Inzucchi, this lack of an association is probably due to the fact that atherosclerosis occurs at the macrovascular level, which is influenced by a variety of factors, including genetics, blood lipids, inflammation, obesity, blood pressure (BP), and smoking, as well as hyperglycemia and probably insulin resistance. Microvascular complications, however, occur in a single epithelial layer within the capillaries, where the predominant risk factors are hyperglycemia, BP, and genetics.

Dr Inzucchi went on to highlight results from the 5 major clinical trials that have investigated the impact of intensive therapy for diabetes on CV outcomes: (1) UKPDS 33 [UK Prospective Diabetes Study. *Lancet*. 1998], (2) DCCT/EDIC [Holman RR et al. *N Engl J Med*. 2008; The Diabetes Control and Complications Trial Research Group. *N Engl J Med*. 1993], (3) ACCORD [Action to Control Cardiovascular Risk in Diabetes Study Group. *N Engl J Med*. 2008], (4) ADVANCE [Advance Collaborative Group. *N Engl J Med*. 2008], and (5) VADT [Duckworth W et al. *N Engl J Med*. 2009].

Dr Inzucchi emphasized that among all these aforementioned studies, microvascular complications were improved, but a neutral effect was seen on mortality and CV events. The exceptions are the trials with long-term components (UKPDS and DCCT/EDIC), where there was an improvement in both mortality and CV events, and the ACCORD trial, where there was an increase in mortality. Dr Inzucchi cautioned that the increase in mortality seen in ACCORD was likely driven by an older group of patients with a high risk of overt atherosclerosis at baseline. Further, data from the VADT study suggested that intensive glucose lowering reduced CV events only in those with no or little preexisting atherosclerosis in coronary arteries [Reaven PD et al. *Diabetes*. 2009]. Aside from these 5 trials, the ORIGIN Trial [ORIGIN Trial Investigators. *N Engl J Med*. 2012] showed that insulin glargine had a neutral effect on CV outcomes in patients with only mild hyperglycemia over a median follow-up of 6.2 years. Dr Inzucchi also observed that, based on meta-analyses, if there is a CV benefit from glucose lowering, it is on the order of a 15% relative risk reduction.

Dr Inzucchi then moved on to discuss CV issues associated with various therapies for type 2 diabetes mellitus (T2DM; Table 1). Metformin probably provides some CV advantage over diet and possibly sulfonylurea drugs. The TZD pioglitazone appeared to reduce major adverse CV events in 1 trial, but these data need to be confirmed. This specific class of insulin-sensitizing drugs remains highly controversial.

In 2008, the US Food and Drug Administration (FDA) issued an industry guidance that mandated manufacturers of diabetes medications to demonstrate that their therapy would not result in an unacceptable increase in CV risk [US Department of Health and Human Services. *Guidance for Industry*. 2008]. This guidance was issued as a direct result of the controversy surrounding rosiglitazone and its purported association with poor CV outcomes. Dr Inzucchi

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Table 1. Cardiovascular Issues Associated With Therapies for T2DM

Class	Potential CV Benefit	Potential CV Concern
SU		Hypoglycemia Blunted ischemic preconditioning
Metformin	↓ MI/MACE in UKPDS, HOME ↓ LDL-C ↓ CRP	Lactic acidosis in advanced HF
TZD	↓ MACE in PROACTIVE ↓ TG, ↑ HDL-C ↓ CRP ↓ Albuminuria	HF risk Weight gain ↑ LDL-C
DPP4i	? Indirect cardiac effects (via GLP-1) ? Direct vascular effects	? HF risk
GLP-1 RA	Weight loss ↓ BP ↓ TG ? Direct cardiac effects	↑ Heart rate
SGLT2i	Weight loss ↓ BP ↓ Albuminuria ↓ Uric acid	Volume contraction
Insulin	Anti-inflammatory ↓ Mortality in DIGAMI	Hypoglycemia Weight gain ? Mitogenicity

BP, blood pressure; CRP, C-reactive protein; CV, cardiovascular; DPP4i, dipeptidyl peptidase-4 inhibitor; GLP-1, glucagon-like peptide 1; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular event; MI, myocardial infarction; RA, receptor agonist; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SU, sulfonylurea; T2DM, type 2 diabetes mellitus; TG, triglyceride; TZD, thiazolidinedione.

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reviewed the main points of the guidance, which mandates that manufacturers implement additional pre- and postmarketing CV outcome trials (CVOTs), using the following metrics:

- Premarketing analyses: HR for major adverse CV events (MACEs) to include an upper limit of the 95% CI < 1.8
- Postmarketing analyses: HR for MACEs to include an upper limit of the 95% CI < 1.3
- Meta-analysis strategy using phase 2/3 data
- Blinded central adjudication of CV events in phase 2/3
- Inclusion of high-risk patients
- Minimum exposure of 2 years
- Approximately 15 000 patient years

Dr Inzucchi then discussed the published results from 2 of these CVOTs—SAVOR-TIMI 53 [Scirica BM et al. *N Engl J Med.* 2013] and EXAMINE [White WB et al. *N Engl J Med.* 2013]. SAVOR-TIMI 53 followed >16 000 patients who had been randomized to either saxagliptin or placebo over a median of 2.1 years with a primary end point of cardiovascular death, nonfatal myocardial infarction or nonfatal ischemic stroke (saxagliptin, n = 613; placebo, n = 609). Although there was neither an increase nor a decrease in ischemic results among patients in the saxagliptin arm, the rate of hospitalization for heart failure was significantly increased ( $P = .007$ ). In the EXAMINE trial, 5380 patients who had T2DM and were hospitalized for either an MI or unstable angina were randomly assigned to alogliptin (n = 2701) or placebo (n = 2679). Patients were followed for up to 40 months (median, 18 months). There was no significant difference between the groups in mortality from CV causes, nonfatal MI, and nonfatal stroke ( $P_{\text{Noninferiority}} < .001$ ).



Table 2. Ongoing Cardiovascular Trials for Diabetes Drugs (Noninsulin)

Class	Study				
	SAVOR	EXAMINE	TECOS	CAROLINA	CARMELINA
DPP4i	Saxagliptin	Alogliptin	Sitagliptin	Linagliptin	Linagliptin
Comparator	Placebo	Placebo	Placebo	Sulfonylurea	Placebo
No.	16500	5400	14000	6000	8300
Results	2013	2013	2015	2017	2017
	LEADER	ELIXA	SUSTAIN6	EXSCEL	REWIND
GLP1-RA	Liraglutide	Lixisenatide	Semaglutide	Exenatide LR	Dulaglutide
Comparator	Placebo	Placebo	Placebo	Placebo	Placebo
No.	16500	14000	6000	5400	8300
Results	2016	2015	2016	2018	2019
	EMPA-REG	CANVAS	DECLARE	NCT01986881	
SGLT2i	Empagliflozin	Canagliflozin	Dapagliflozin	Ertugliflozin	
Comparator	Placebo	Placebo	Placebo	Placebo	
No.	7300	4300	22200	3900	
Results	2015	2017	2019	2020	

DPP4i, dipeptidyl peptidase-4 inhibitor; GLP-1 RA, glucagon-like peptide 1 receptor agonist; SGLT2i, sodium-glucose cotransporter-2 inhibitor. Reproduced with permission from SE Inzucchi, MD.

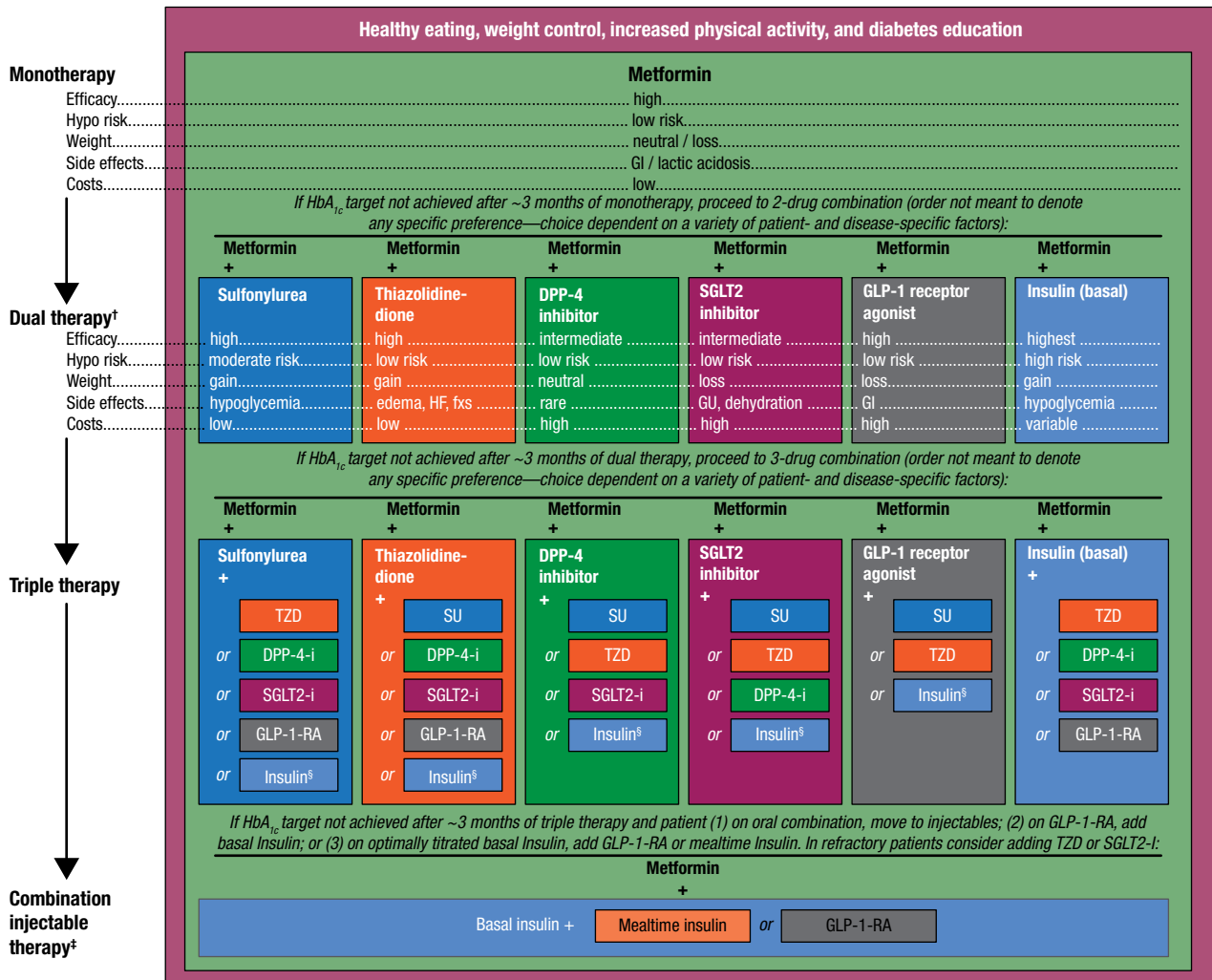
A number of other trials are ongoing, with results due over the next few years (Table 2). Dr Inzucchi emphasized that although these preliminary studies may report effects on CV markers and surrogates, these effects do not necessarily predict what will happen to patients in terms of actual clinical events in the CVOTs. In addition, while the drugs may present no CV safety signals during these trials, it may be overly optimistic to think that they will show any differences in effectiveness on CV end points over a period of just 2 to 4 years. And because the FDA has demanded the recruitment of high-risk patients into these CVOTs, there is some concern that the presence of advanced CV disease and an underlying predilection for further overt macrovascular complications will outweigh any possible CV benefits of a glucose-lowering drug.

Dr Inzucchi then reviewed the updated 2015 American Diabetes Association/European Association

for the Study of Diabetes treatment algorithm for managing hypertension in T2DM (Figure 1). He noted that if any of the compounds included in 1 of the ongoing CVOTs were to show a CV benefit, the current treatment algorithm would likely be updated to reflect that benefit.

In closing, Dr Inzucchi emphasized that although diabetes confers additional CV disease risk, glycemic control itself appears to only modestly reduce nonfatal MI. Any benefit from glycemic control will likely have to accrue over many years and may be negated by progressive atherosclerosis. The ideal glucose-lowering agent will reduce CV events as well as maintain glycemic control. For now, however, glycemic control should be used mainly to prevent microvascular complications, while control of lipids and BP is the best means for preventing macrovascular complications.

Figure 1. General Recommendations for Antihyperglycemic Therapy, T2DM



GLP-1 RA, glucagon-like peptide 1 receptor agonist; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SU, sulfonylurea; T2DM, type 2 diabetes mellitus; TZD, thiazolidinedione.

†Consider initial therapy at this stage when HbA<sub>1c</sub> is 9% (75 mmol/mol).

‡Consider initial therapy at this stage when blood glucose is 300–350 mg/dL (16.7–19.4 mmol/L) and/or HbA<sub>1c</sub> 10–12% (86–108 mmol/mol), especially if patient is symptomatic or if catabolic features (weight loss, ketosis) are present, in which case basal insulin 1 mealtime insulin is the preferred initial regimen.

§Usually a basal insulin (eg, NPH, glargine, detemir, degludec).

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