Controle Glicêmico Intensivo e Prevenção de Eventos Cardiovasculares: Implicações do ACCORD, ADVANCE e VA

Apresentado pelo Residente Igor Denizarde Bacelar Marques

na reunião da Unidade de Hipertensão
do Hospital das Clínicas da Faculdade de Medicina
da Universidade de São Paulo
em 05 de Março de 2009

EXPERT CONSENSUS DOCUMENT

Intensive Glycemic Control and the Prevention of Cardiovascular Events: Implications of the ACCORD, ADVANCE, and VA Diabetes Trials

A Position Statement of the American Diabetes Association and a Scientific Statement of the American College of Cardiology Foundation and the American Heart Association

Jay S. Skyler, MD, MACP*
Richard Bergenstal, MD†
Robert O. Bonow, MD, MACC, FAHA‡
John Buse, MD, PHD§
Prakash Deedwania, MD, FACC, FAHA‖
Edwin A.M. Gale, MD¶
Barbara V. Howard, PHD¶#
M. Sue Kirkman, MD**
Mikhail Kosiborod, MD, FACC††
Peter Reaven, MD‡‡
Robert S. Sherwin, MD§§

J. Am. Coll. Cardiol. published online Dec 17, 2008;

Intensive Glycemic Control and the Prevention of Cardiovascular Events: Implications of the ACCORD, ADVANCE, and VA Diabetes Trials

A Position Statement of the American Diabetes Association and a Scientific Statement of the American College of Cardiology Foundation and the American Heart Association

Jay S. Skyler, MD, MACP*
Richard Bergenstal, MD†
Robert O. Bonow, MD, MACC, FAHA‡
John Buse, MD, PHD§
Prakash Deedwania, MD, FACC, FAHA‖
Edwin A.M. Gale, MD¶
Barbara V. Howard, PHD¶#
M. Sue Kirkman, MD**
Mikhail Kosiborod, MD, FACC††
Peter Reaven, MD‡‡
Robert S. Sherwin, MD§§

Diabetes is defined by its association with hyperglycemia-specific microvascular complications; however, it also imparts a two- to fourfold risk of cardiovascular disease (CVD). Although microvascular complications can lead to significant morbidity and premature mortality, by far the greatest cause of death in people with diabetes is CVD.

Results from randomized controlled trials have demonstrated conclusively that the risk of microvascular complications can be reduced by intensive glycemic control in patients with type 1 (1,2) and type 2 diabetes (3–5). In the Diabetes Control and Complications Trial (DCCT), there was an ≈60% reduction in development or progression of diabetic retinopathy, nephropathy, and neuropathy between the intensively treated group (goal A1C <6.05%, mean achieved A1C ≈7%) and the standard group (A1C ≈9%) over an average of 6.5 years. The relationship between glucose control (as reflected by the mean on-study A1C value) and risk of complications was log-linear and extended down to the normal A1C range (<6%) with no threshold noted.

In the UK Prospective Diabetes Study (UKPDS), participants newly diagnosed with type 2 diabetes were followed for 10 years, and intensive control (median A1C 7.0%) was found to reduce the overall microvascular complication rate by 25% compared with conventional treatment (median A1C 7.9%). Here, too, secondary analyses showed a continuous relationship between the risk of microvascular complications and glycemia extending into the normal range of A1C, with no glycemic threshold.

On the basis of these two large controlled trials, along with smaller studies and numerous epidemiologic reports, the consistent findings related to microvascular risk reduction with intensive glycemic control have led the American Diabetes Association (ADA) to recommend an A1C goal of <7% for most adults with diabetes (6), recognizing that more or less stringent goals may be appropriate for certain patients. Whereas many epidemiologic studies and meta-analyses (7,8) have clearly shown a direct relationship between A1C and CVD, the potential of intensive glycemic control to reduce CVD events has been less clearly defined.

From the *University of Miami, Miami, Florida; the †International Diabetes Center at Park Nicollet, Minneapolis, Minnesota; the ‡Northwestern University Feinberg School of Medicine, Chicago, Illinois; the §University of North Carolina, Chapel Hill, North Carolina; the ‖VA Central California Healthcare System, University of California San Francisco, Fresno, California; the ¶University of Bristol, Bristol, U.K.; #MedStar Research Institute, Hyattsville, Maryland; the **American Diabetes Association, Alexandria, Virginia; the ††Mid America Heart Institute of Saint Luke's Hospital and the University of Missouri-Kansas City, Kansas City, Missouri; the ‡‡Carl T. Hayden VA Medical Center, Phoenix, Arizona; and §§Yale University School of Medicine, New Haven, Connecticut.

The American College of Cardiology Foundation requests that this document be cited as follows: Skyler JS, Bergenstal R, Bonow RO, Buse J, Deedwania P, Gale EAM, Howard BV, Kirkman MS, Kosiborod M, Reaven P, Sherwin RS. Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA Diabetes trials. J Am Coll Cardiol 2009;53:298–304.

Simultaneous publication: This article is being simultaneously published in 2009 in *Diabetes Care*, the *Journal of the American College of Cardiology*, and *Circulation* by the American Diabetes Association, the American College of Cardiology Foundation, and the American Heart Association.

Introdução

- DCCT
  - ~60% de redução de complicações microvasculares entre o grupo de controle intensivo (HbA1c ~7%) e o grupo padrão (HbA1c ~9%).
  - Seguimento de 6,5 anos.
- UKPDS
  - ~25% de redução de complicações microvasculares entre o grupo de controle intensivo (HbA1c ~7%) e o grupo padrão (HbA1c ~7,9%).
  - Seguimento de 10 anos.

Introdução

- DCCT – EDIC
  - 9 anos de seguimento da coorte.
  - 57% de redução no risco de IAM não fatal, AVE ou morte por doenças CV no grupo de tratamento intensivo em relação ao padrão.
- ACCORD, ADVANCE E VADT

	ACCORD	ADVANCE	VADT
Participant characteristics			
n	10,251	11,140	1,791
Mean age (years)	62	66	60
Duration of diabetes (years)	10	8	11.5
Sex (% male/female)	39/61	42/58	97/3
History of CVD (%)	35	32	40
BMI (kg/m^2)	32	28	31
Median baseline A1C (%)	8.1	7.2	9.4
On insulin at baseline (%)	35	1.5	52
Protocol characteristics			
A1C goals (%) (I vs. S)*	<6.0 vs. 7.0–7.9	≤6.5 vs. "based on local guidelines"	<6.0 (action if >6.5) vs. planned separation of 1.5
Protocol for glycemic control (I vs. S)*	Multiple drugs in both arms	Multiple drugs added to gliclizide vs. multiple drugs with no gliclizide	Multiple drugs in both arms
Management of other risk factors	Embedded blood pressure and lipid trials	Embedded blood pressure trial	Protocol for intensive treatment in both arms
On-study characteristics			
Median duration of follow-up (years)	3.5 (terminated early)	5	5.6
Achieved median A1C (%) (I vs. S)*	6.4 vs. 7.5	6.3 vs. 7.0	6.9 vs. 8.5
On insulin at study end (%) (I vs. S)*	77 vs. 55*	40 vs. 24	89 vs. 74
On TZD at study end (%) (I vs. S)*	91 vs. 58*	17 vs. 11	53 vs. 42
On statin at study end (%) (I vs. S)*	88 vs. 88*	46 vs. 48	85 vs. 83
On aspirin at study end (%) (I vs. S)*	76 vs. 76*	57 vs. 55	88 vs. 86
Smokers at study end (%)	10	8	8
Mean blood pressure at study end (mm Hg)			
Intensive glycemic control arm	126/67	136/74	127/68
Standard glycemic control arm	127/68	138/74	125/69
Weight changes (kg)			
Intensive glycemic control arm	+3.5	−0.1	+7.8
Standard glycemic control arm	+0.4	−1.0	+3.4

CONT	ACCORD	ADVANCE	VADT
Severe hypoglycemia (participants with one or more episodes during study) (%)			
Intensive glycemic control arm	16.2	2.7	21.2
Standard glycemic control arm	5.1	1.5	9.9
Outcomes			
Definition of primary outcome	Nonfatal MI, nonfatal stroke, CVD death	Microvascular plus macrovascular (nonfatal MI, nonfatal stroke, CVD death) outcomes	Nonfatal MI, nonfatal stroke, CVD death, hospitalization for heart failure, revascularization
HR for primary outcome (95% CI)	0.90 (0.78–1.04)	0.9 (0.82–0.98); macrovascular 0.94 (0.84–1.06)	0.88 (0.74–1.05)
HR for mortality findings (95% CI)	1.22 (1.01–1.46)	0.93 (0.83–1.06)	1.07 (0.81–1.42)

Quais São as Potenciais Explicações para o Aumento da Mortalidade CV no Grupo de Controle Glicêmico Intensivo no Estudo ACCORD?

- Hipoglicemia
- Ganho de peso
- Efeitos adversos ou interações medicamentosas
- “Intensidade” da intervenção

Porque Nenhum destes *Trials* Consegue Mostrar Benefício do Controle Glicêmico Intensivo em Relação a Desfechos CV em DM Tipo 2 – em Contraste a Muitos Estudos Epidemiológicos e o DCCT – EDIC?

- Os outros fatores de risco
- Os níveis de HbA1c
- A duração do DM e a doença CV estabelecida
- Efeitos colaterais
  - Hipoglicemia
  - Ganho de peso
  - Outras alterações metabólicas

Implicações para a Prática Clínica

- Doença microvascular
  - HbA1c < 7%, para DM tipos 1 e 2.
- Doença macrovascular
  - HbA1c < 7%, nos anos logo após o diagnóstico de DM.

Implicações para a Prática Clínica

- Grupos individualizados
  - Benefício microvascular com valores de HbA1c mais baixos, próximos do normal, para indivíduos com menor duração do DM, maior expectativa de vida e doença CV de pequena importância.
  - Metas glicêmicas mais flexíveis para pacientes com história de hipoglicemia severa, baixa expectativa de vida, complicações micro e macrovasculares avançadas, múltiplas comorbidades ou DM de longa duração, nos quais as metas são difíceis de ser atingidas.
- Controle da PA, estatinas, AAS, cessação do tabagismo e mudanças no estilo de vida.