

**16 DE ABRIL — SÁBADO**

# **SESSÃO TELEVOTER DIABETES**

**ANTÓNIO PEDRO MACHADO**

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**JÁCOME DE CASTRO**

**SIMÕES-PEREIRA**

# Objectivos glicémicos em adultos

(mulheres não grávidas)

**A1C < 7.0% - Objectivo global**

**Valores inferiores**

**Se não houver risco de hipoglicémias e**

- ♥ **Diabetes com poucos anos de evolução**
- ♥ **Expectativa de vida longa**
- ♥ **Ausência de doença cardiovascular**

# Objectivos glicémicos em adultos

(mulheres não grávidas)

**A1C < 7.0% - Objectivo global**

**Valores superiores**

- ♥ **Risco de hipoglicémias**
- ♥ **Expectativa de vida limitada**
- ♥ **Complicações micro ou macrovasculares avançadas**
- ♥ **Comorbilidades associadas importantes**
- ♥ **Diabetes de longa evolução**

# Objectivos glicémicos em adultos

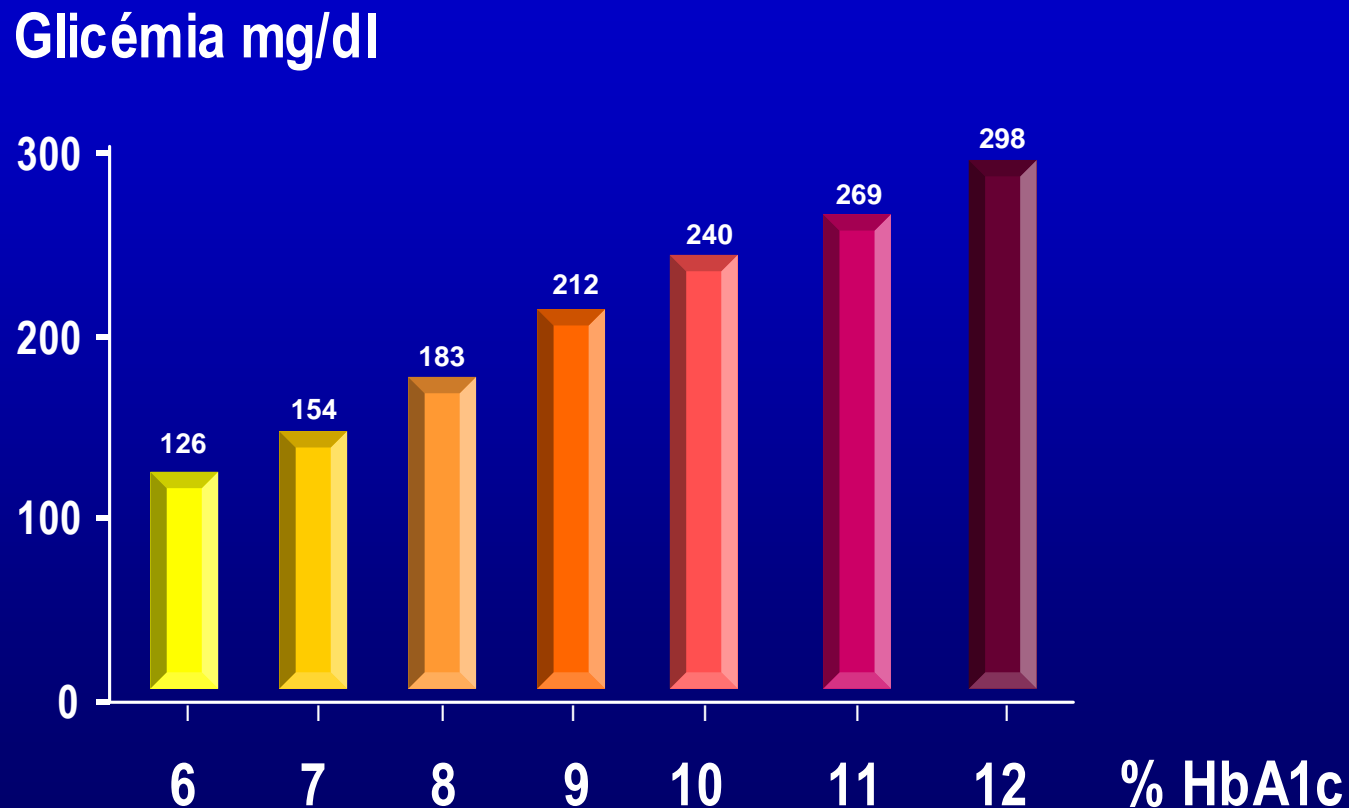
(mulheres não grávidas)

**A1C < 7.0% - Objectivo global**

**Valores superiores**

- ♥ **Risco de hipoglicémias**
- ♥ **Expectativa de vida limitada**
- ♥ **Complicações micro ou macrovasculares avançadas**
- ♥ **Comorbilidades associadas importantes**
- ♥ **Diabetes de longa evolução**

## Relação entre a HbA1C e a glicemia média



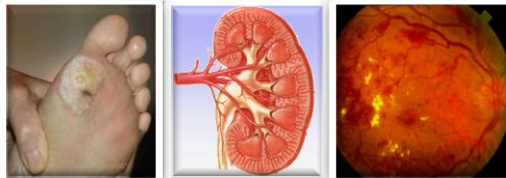
# Ensaio UKPDS

3867 diabéticos diagnosticados de novo  
Idade média de 54 anos

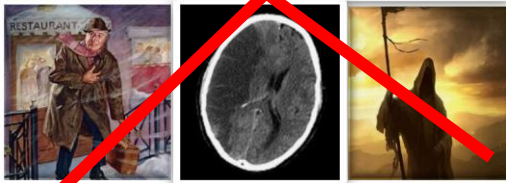
Sulfonilureias ou Insulina



↓ 25% eventos  
microvasculares



~~Sem redução eventos  
macrovasculares~~



Metformina nos obesos



	Redução de Risco	Valor do p
Qualquer end-point relacionado com a diabetes	↓ 32%	0.0023
Mortes relacionadas com a DM	↓ 42%	0.017
Mortalidade global	↓ 36%	0.001
Enfarte do Miocárdio	↓ 39%	0.01

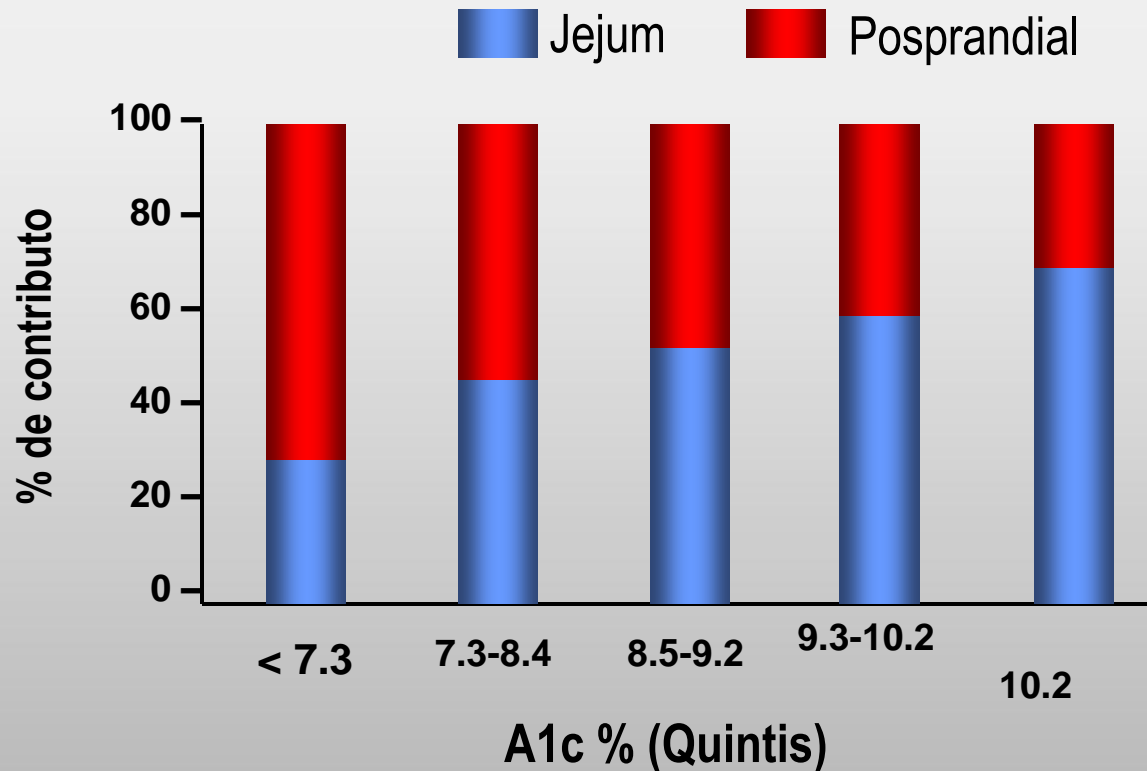
No UKPDS, o controlo intensivo com Metformina em DM tipo 2 com excesso de peso reduziu a HbA1c em 0.6% ao longo de 10 anos.

# Objectivos glicémicos em adultos

(mulheres não grávidas)

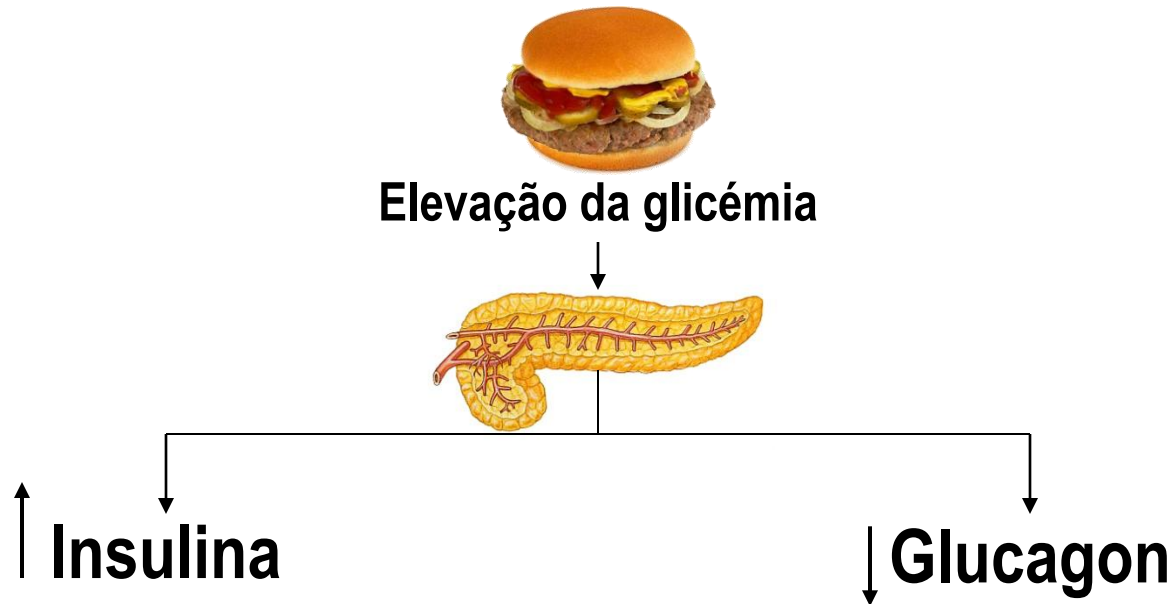
<b>A1C</b>	<b>&lt; 7.0%</b>
<b>Glicémia jj</b>	<b>70-130 mg/dl</b>
<b>Glicémia pp (1-2 h pp)</b>	<b>&lt; 180 mg/dl</b>

## Contributo da glicemia em jejum e posprandial para a HbA1C em diabéticos tipo 2





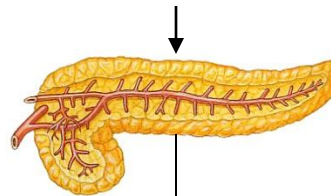
# Resposta fisiológica à ingestão de hidratos de carbono



# Resposta fisiológica à ingestão de hidratos de carbono



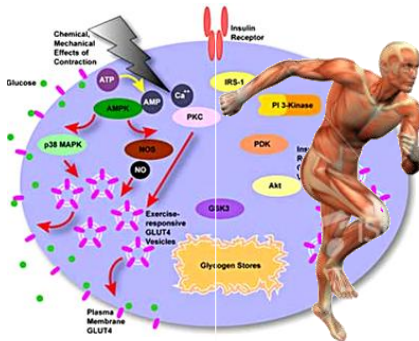
Elevação da glicémia



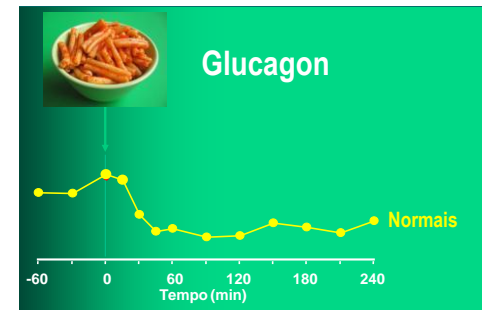
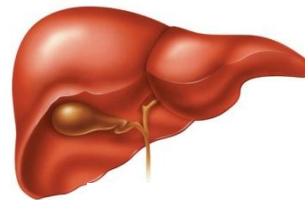
↑ **Insulina**

↓ **Glucagon**

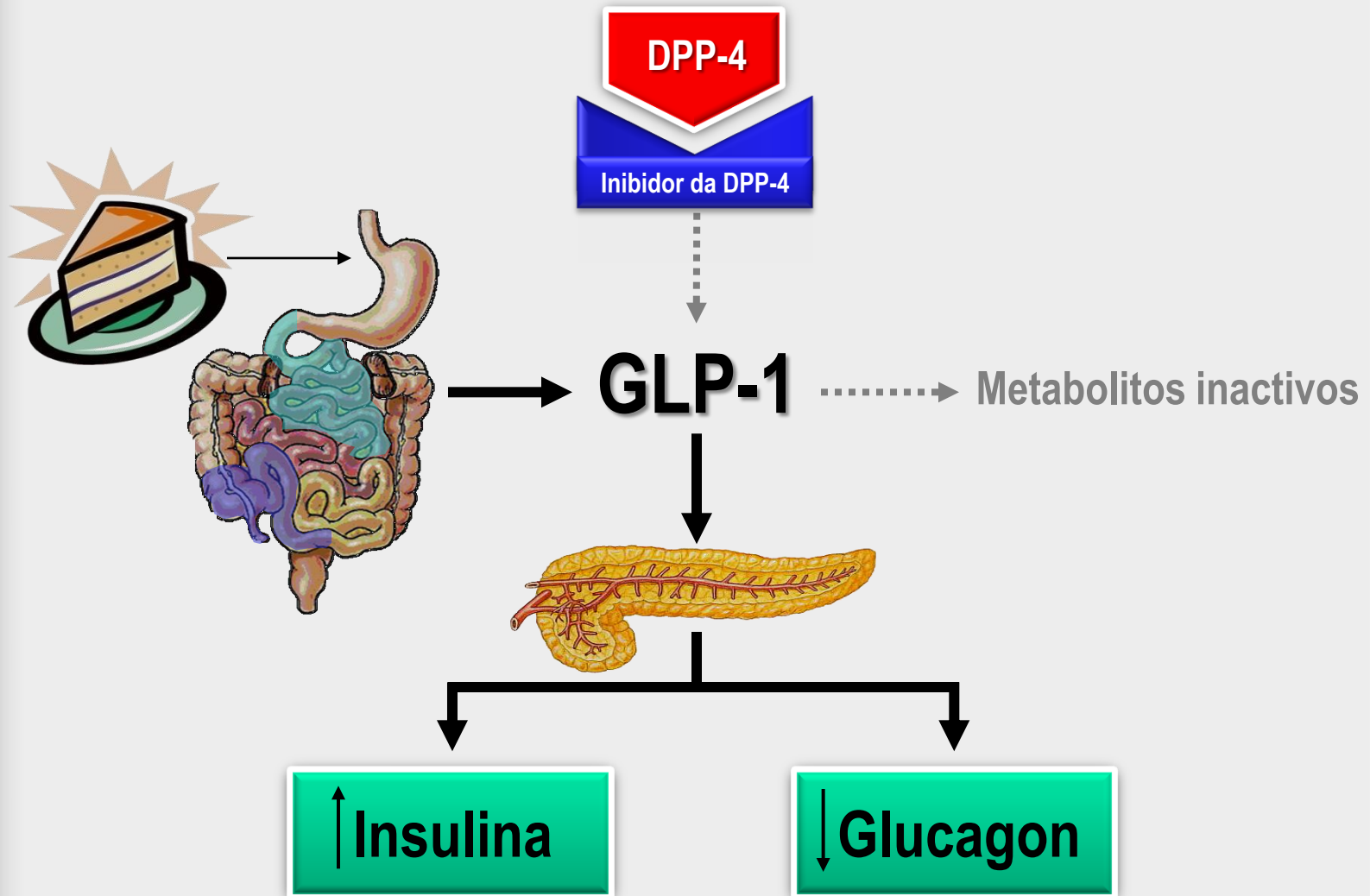
**Transporte de glucose**



**Síntese de glicogénio**



# Mecanismo de acção dos inibidores da DPP-4



# Terapêutica hipolipemiante em diabéticos

## Objetivos terapêuticos

### Em indivíduos sem evidência de DCV

#### Objectivo primário:

- LDL < 100 mg/dl (nível de recomendação A)

#### Com idade > 40 anos

- Estatina para conseguir uma redução de 30-40% das LDL independentemente do valor basal (nível de recomendação A).

#### Com idade < 40 anos (Mas com risco cardiovascular elevado)

- Adicionar uma estatina se não atingirem os valores lipídicos alvo com a modificação do estilo de vida (nível de evidência C)

## **Prevenção primária com antiagregantes plaquetários**

**AAS (75-150 mg/dia)**

- ♥ **Homens >50 anos**
- ♥ **Mulheres >60 anos**
- ♥ **Com um factor de risco major adicional**
  - História familiar de DCV
  - HTA
  - Tabagismo
  - Dislipidemia
  - Albuminúria

# Intervenção multifactorial na Diabetes

Modificação do  
estilo de vida

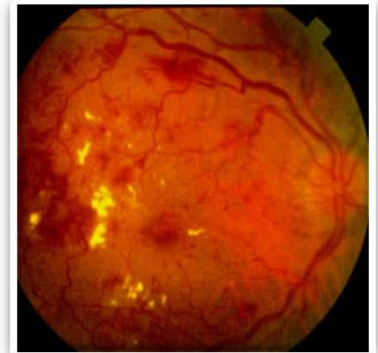
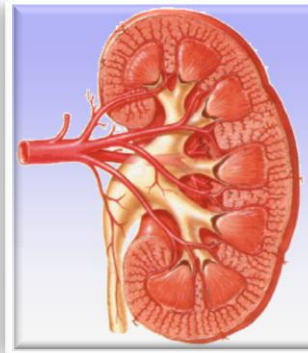
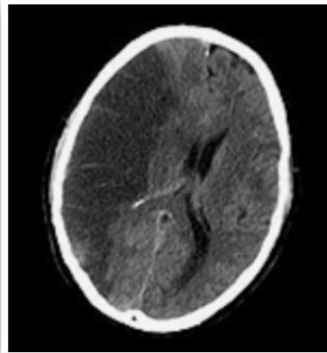
Controlo da  
Pressão arterial

Controlo da  
dislipidemia

Antiagregação  
plaquetária



**Macrovasculares**

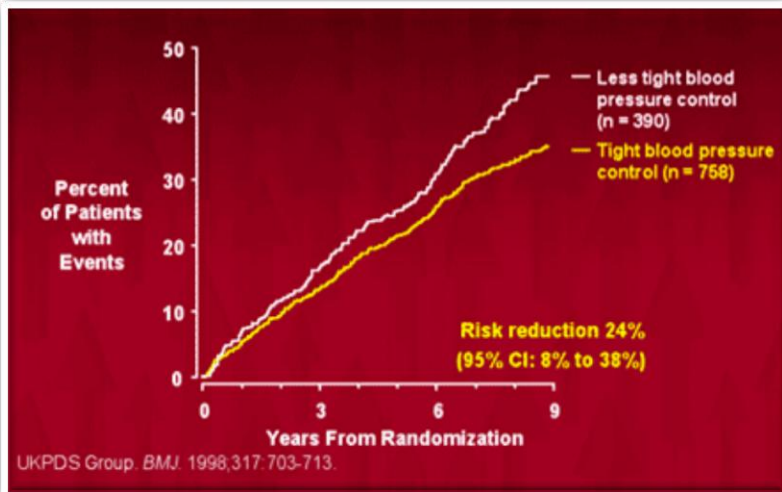


**Microvasculares**

# Redução de todos os end-points relacionados com a Diabetes



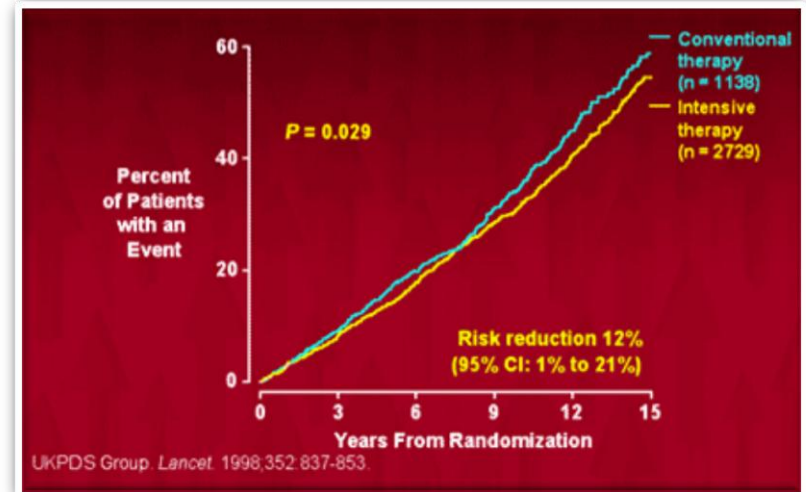
## Controlo tensional



↓ 23%



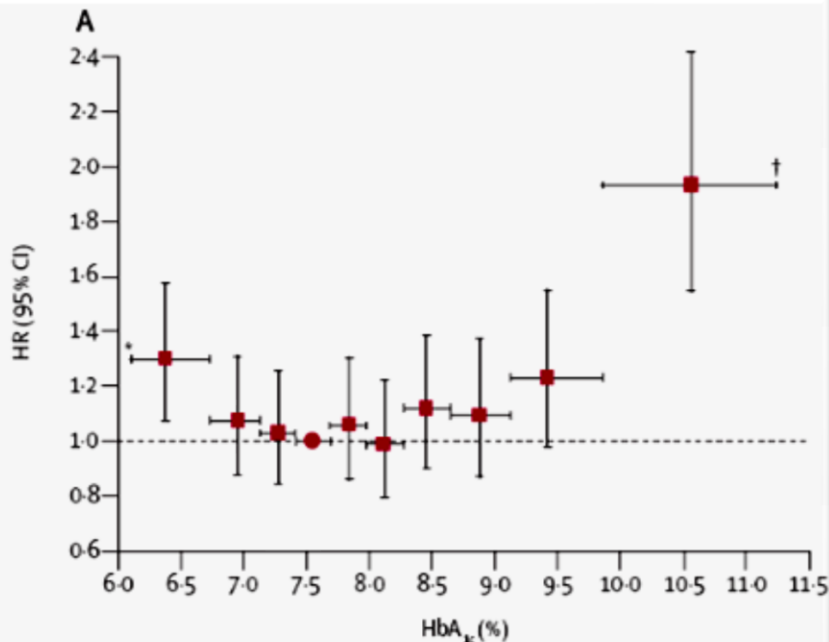
## Controlo glicémico



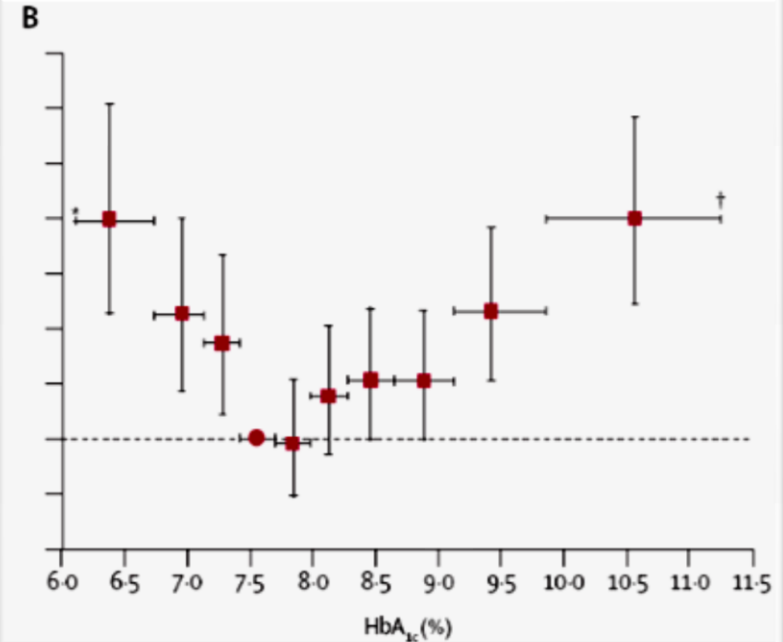
↓ 12%

# Mortalidade global e HbA1c por decis em diabéticos em função do regime terapêutico (Metanálise)

## Sulfonilureias e Metformina



## Insulina





## ORIGINAL ARTICLE

## Glucose Control and Vascular Complications in Veterans with Type 2 Diabetes

William Duckworth, M.D., Carlos Abaira, M.D., Thomas Moritz, M.S., Domenic Reda, Ph.D., Nicholas Emanuele, M.D., Peter D. Reaven, M.D., Franklin J. Zieve, M.D., Ph.D., Jennifer Marks, M.D., Stephen N. Davis, M.D., Rodney Hayward, M.D., Stuart R. Warren, J.D., Pharm.D., Steven Goldman, M.D., Madeline McCarren, Ph.D., M.P.H., Mary Ellen Vitek, William G. Henderson, Ph.D., and Grant D. Huang, M.P.H., Ph.D., for the VADT Investigators\*

## ABSTRACT

## BACKGROUND

The effects of intensive glucose control on cardiovascular events in patients with long-standing type 2 diabetes mellitus remain uncertain.

## METHODS

We randomly assigned 1791 military veterans (mean age, 60.4 years) who had a sub-optimal response to therapy for type 2 diabetes to receive either intensive or standard glucose control. Other cardiovascular risk factors were treated uniformly. The mean number of years since the diagnosis of diabetes was 11.5, and 40% of the patients had already had a cardiovascular event. The goal in the intensive-therapy group was an absolute reduction of 1.5 percentage points in the glycated hemoglobin level, as compared with the standard-therapy group. The primary outcome was the time from randomization to the first occurrence of a major cardiovascular event, a composite of myocardial infarction, stroke, death from cardiovascular causes, congestive heart failure, surgery for vascular disease, inoperable coronary disease, and amputation for ischemic gangrene.

## RESULTS

The median follow-up was 5.6 years. Median glycated hemoglobin levels were 8.4% in the standard-therapy group and 6.9% in the intensive-therapy group. The primary outcome occurred in 264 patients in the standard-therapy group and 235 patients in the intensive-therapy group (hazard ratio in the intensive-therapy group, 0.88; 95% confidence interval [CI], 0.74 to 1.05;  $P=0.14$ ). There was no significant difference between the two groups in any component of the primary outcome or in the rate of death from any cause (hazard ratio, 1.07; 95% CI, 0.81 to 1.42;  $P=0.62$ ). No differences between the two groups were observed for microvascular complications. The rates of adverse events, predominantly hypoglycemia, were 17.6% in the standard-therapy group and 24.1% in the intensive-therapy group.

## CONCLUSIONS

Intensive glucose control in patients with poorly controlled type 2 diabetes had no significant effect on the rates of major cardiovascular events, death, or microvascular complications, with the exception of progression of albuminuria ( $P=0.01$ ). (ClinicalTrials.gov number, NCT00032487.)

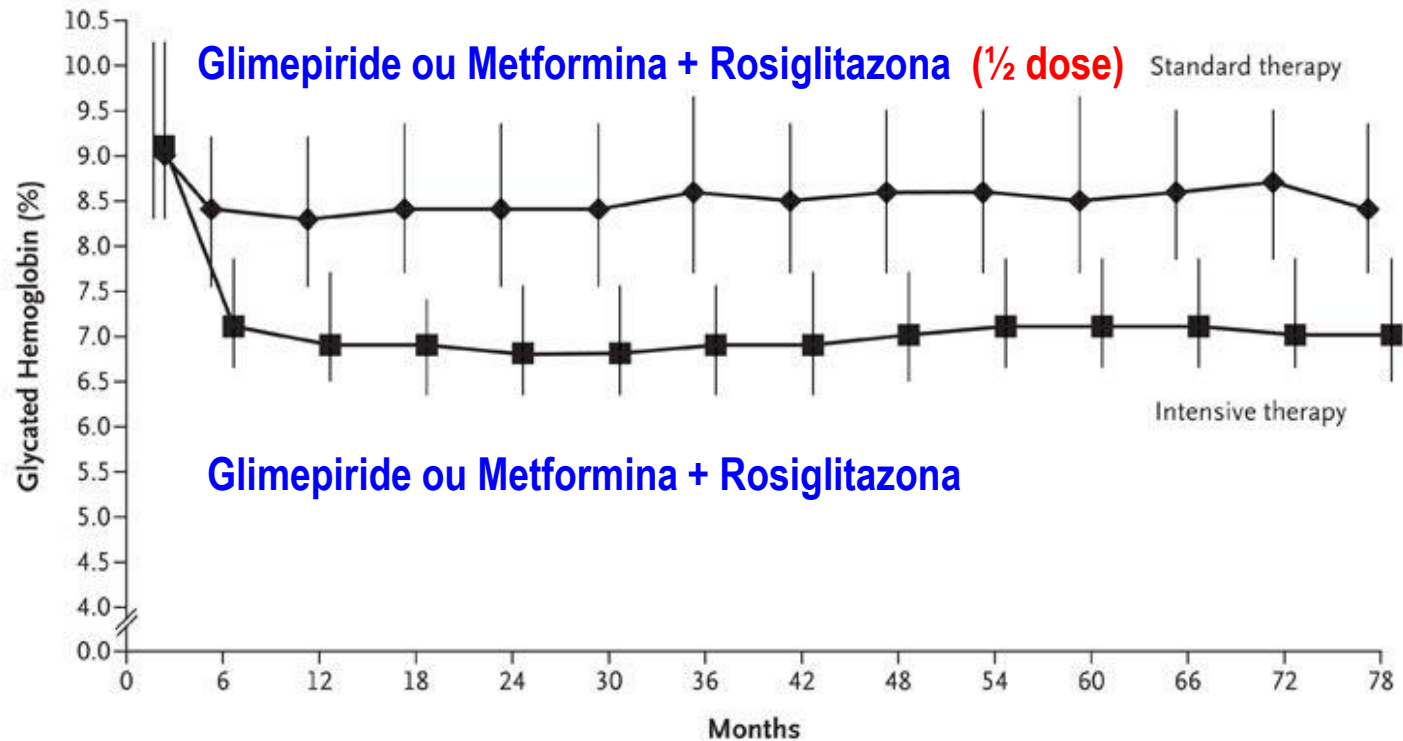
From the Phoenix Veterans Affairs (VA) Health Care Center, Phoenix, AZ (W.D., P.D.R.); Miami VA Medical Center, Miami (C.A., J.M.); Hines VA Cooperative Studies Program Coordinating Center (T.M., D.R., M.M., M.E.V., W.G.H.) and Hines VA Hospital (N.E.) — both in Hines, IL; Hunter Holmes McGuire VA Medical Center, Richmond, VA (F.J.Z.); Tennessee Valley Health Care System, Nashville (S.N.D.); VA Ann Arbor Healthcare System, Ann Arbor, MI (R.H.); VA Cooperative Studies Program Clinical Research Pharmacy Coordinating Center, Albuquerque, NM (S.R.W.); Southern Arizona VA Health Care System, Tucson (S.G.); and the Cooperative Studies Program Central Office, VA Office of Research and Development, Washington, DC (G.D.H.). Address reprint requests to Dr. Duckworth at the Phoenix VA Health Care System, 650 E. Indian School Rd., Phoenix, AZ 85012, or at [william.duckworth@va.gov](mailto:william.duckworth@va.gov).

\*Investigators in the Veterans Affairs Diabetes Trial (VADT) are listed in the Appendix.

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# Evolução da HbA1c média ao longo do estudo

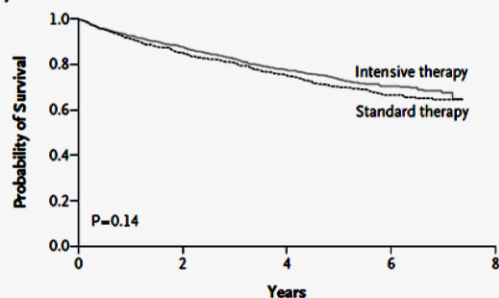


## No. at Risk

Standard therapy	899	811	812	759	760	727	727	707	688	667	644	472	329	225
Intensive therapy	892	801	805	763	754	729	706	692	668	661	639	489	340	223

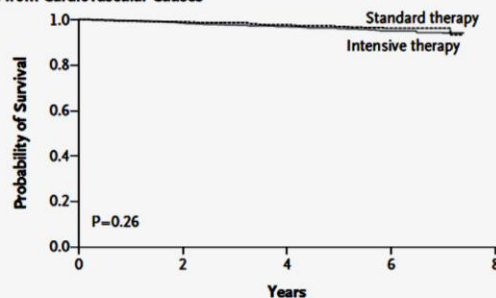
O início tardio de tratamento intensivo em diabéticos tipo 2 mal controlados não influenciou as taxas de eventos CV major, morte ou complicações microvasculares, à exceção da progressão da albuminúria

**A Primary Outcome**



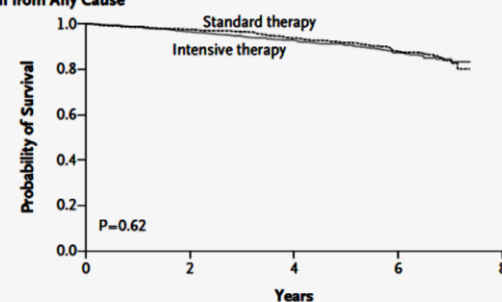
No. at Risk										
Standard therapy	899	770	693	637	570	471	240	55	0	
Intensive therapy	892	774	707	639	582	510	252	62	0	

**B Death from Cardiovascular Causes**



No. at Risk										
Standard therapy	899	833	797	767	724	635	320	75	0	
Intensive therapy	892	828	786	746	713	646	337	85	0	

**C Death from Any Cause**



No. at Risk										
Standard therapy	899	836	801	772	727	637	322	76	0	
Intensive therapy	892	832	791	752	720	650	341	86	0	

## Effects of Intensive Glucose Lowering in Type 2 Diabetes

The Action to Control Cardiovascular Risk in Diabetes Study Group\*

### ABSTRACT

#### BACKGROUND

Epidemiologic studies have shown a relationship between glycated hemoglobin levels and cardiovascular events in patients with type 2 diabetes. We investigated whether intensive therapy to target normal glycated hemoglobin levels would reduce cardiovascular events in patients with type 2 diabetes who had either established cardiovascular disease or additional cardiovascular risk factors.

#### METHODS

In this randomized study, 10,251 patients (mean age, 62.2 years) with a median glycated hemoglobin level of 8.1% were assigned to receive intensive therapy (targeting a glycated hemoglobin level below 6.0%) or standard therapy (targeting a level from 7.0 to 7.9%). Of these patients, 38% were women, and 35% had had a previous cardiovascular event. The primary outcome was a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. The finding of higher mortality in the intensive-therapy group led to a discontinuation of intensive therapy after a mean of 3.5 years of follow-up.

#### RESULTS

At 1 year, stable median glycated hemoglobin levels of 6.4% and 7.5% were achieved in the intensive-therapy group and the standard-therapy group, respectively. During follow-up, the primary outcome occurred in 352 patients in the intensive-therapy group, as compared with 371 in the standard-therapy group (hazard ratio, 0.90; 95% confidence interval [CI], 0.78 to 1.04;  $P=0.16$ ). At the same time, 257 patients in the intensive-therapy group died, as compared with 203 patients in the standard-therapy group (hazard ratio, 1.22; 95% CI, 1.01 to 1.46;  $P=0.04$ ). Hypoglycemia requiring assistance and weight gain of more than 10 kg were more frequent in the intensive-therapy group ( $P<0.001$ ).

#### CONCLUSIONS

As compared with standard therapy, the use of intensive therapy to target normal glycated hemoglobin levels for 3.5 years increased mortality and did not significantly reduce major cardiovascular events. These findings identify a previously unrecognized harm of intensive glucose lowering in high-risk patients with type 2 diabetes. (ClinicalTrials.gov number, NCT00000620.)

The members of the writing group (Hertzel C. Gerstein, M.D., M.Sc., McMaster University and Hamilton Health Sciences, Population Health Research Institute, Hamilton, ON, Canada; Michael E. Miller, Ph.D., Robert P. Byington, Ph.D., and David C. Goff, Jr., M.D., Ph.D., Wake Forest University School of Medicine, Winston-Salem, NC; J. Thomas Bigger, M.D., Columbia University College of Physicians and Surgeons, New York; John B. Buse, M.D., Ph.D., University of North Carolina School of Medicine, Chapel Hill; William C. Cushman, M.D., Memphis Veterans Affairs Medical Center, Memphis, TN; Saul Genuth, M.D., and Faramarz Ismail-Beigi, M.D., Ph.D., Case Western Reserve University, Cleveland; Richard H. Grimm, Jr., M.D., Ph.D., Berman Center for Outcomes and Clinical Research, Minneapolis; Jeffrey L. Probstfield, M.D., University of Washington, Seattle; Denise G. Simons-Morton, M.D., Ph.D., National Heart, Lung, and Blood Institute, Bethesda, MD; and William T. Friedewald, M.D., Columbia University Mailman School of Public Health, New York) assume responsibility for the overall content and integrity of this article. Address reprint requests to Dr. Byington at the Division of Public Health Sciences, Wake Forest University School of Medicine, Medical Center Blvd., Winston-Salem, NC 27157, or at [bybingto@wfubmc.edu](mailto:bybingto@wfubmc.edu).

\*Members of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study Group are listed in the Appendix.

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**Table 2. Prescribed Glucose-Lowering Drugs.\***

Drug Class and Name	Intensive Therapy (N=5128)		Standard Therapy (N=5123)	
	<i>no. of patients (%)</i>	<i>person-years</i>	<i>no. of patients (%)</i>	<i>person-years</i>
<b>Single class</b>				
Metformin	4856 (94.7)	14,444	4452 (86.9)	12,693
Secretagogue†	4443 (86.6)	12,021	3779 (73.8)	10,059
Glimepiride	4010 (78.2)	9,142	3465 (67.6)	8,955
Repaglinide	2574 (50.2)	4,447	908 (17.7)	1,293
Thiazolidinedione‡	4702 (91.7)	12,844	2986 (58.3)	6,719
Rosiglitazone	4677 (91.2)	12,639	2946 (57.5)	6,563
α-Glucosidase inhibitor§	1191 (23.2)	941	263 (5.1)	200
Incretin¶	911 (17.8)	566	251 (4.9)	175
Exenatide	622 (12.1)	415	204 (4.0)	155
Any insulin	3965 (77.3)	11,902	2837 (55.4)	7,842
Any bolus insulin	2834 (55.3)	6,806	1794 (35.0)	4,336
<b>Combination of classes</b>				
No. of classes without insulin				
1 or 2	2798 (54.6)	2,011	3224 (62.9)	6,612
3	3030 (59.1)	3,681	1681 (32.8)	2,545
4 or 5	539 (10.5)	332	109 (2.1)	67
No. of classes with insulin				
0	916 (17.9)	829	892 (17.4)	1,495
1 or 2	3311 (64.6)	6,603	2375 (46.4)	5,284
3	2668 (52.0)	4,126	834 (16.3)	1,027
4 or 5	526 (10.3)	344	64 (1.2)	36

\* Metformin, glimepiride, repaglinide, rosiglitazone, acarbose, and exenatide were provided by a study-supervised formulary. Patients could receive more than one medication or combination of medications and may therefore be counted in more than one category. All individual medications that are listed were prescribed to at least 10% of patients in either group.

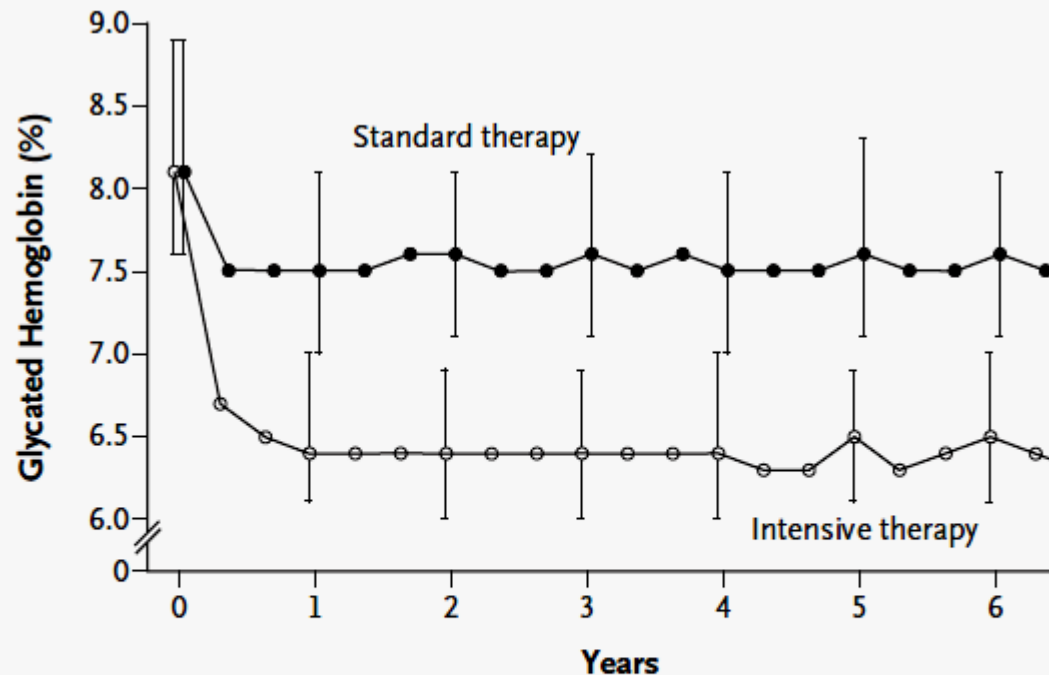
† Patients received glimepiride, glyburide, gliclazide, repaglinide, or nateglinide.

‡ Patients received rosiglitazone or pioglitazone.

§ All the patients in this category received acarbose except one who received miglitol.

¶ Patients received exenatide or sitagliptin.

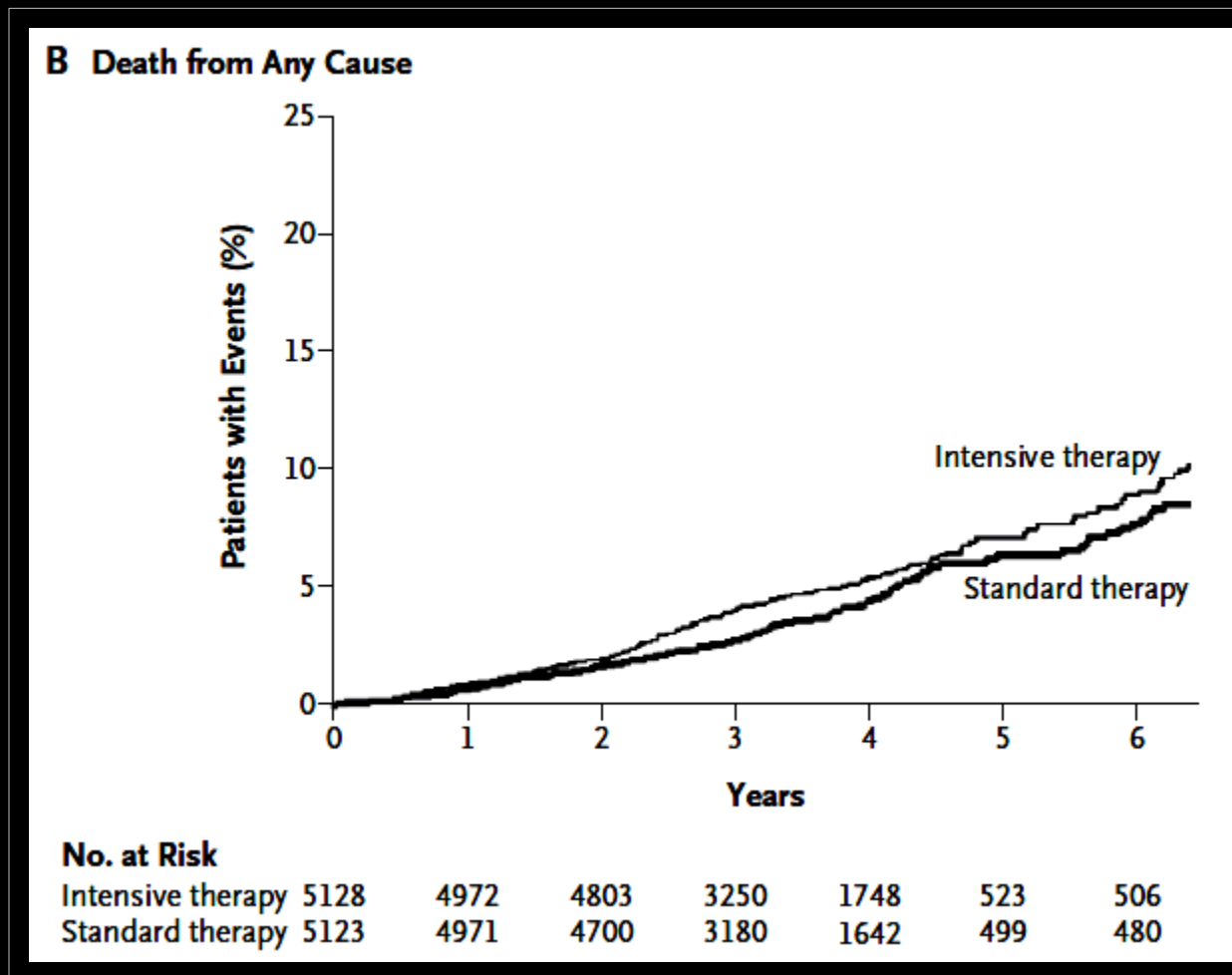
# Evolução da HbA1c nos dois grupos de intervenção



## No. at Risk

Standard therapy	5109	4774	4588	3186	1744	455	436
Intensive therapy	5119	4768	4585	3165	1706	476	471

# A terapêutica intensiva aumentou a mortalidade





# Metformin, Sulfonylureas, or Other Antidiabetes Drugs and the Risk of Lactic Acidosis or Hypoglycemia

A nested case-control analysis

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CHRISTIAN MEIER, MD<sup>2</sup>  
STEPHAN KRÄHENBÜHL, MD, PhD<sup>1</sup>

SUSAN S. JICK, DSc<sup>3,4</sup>  
CHRISTOPH R. MEIER, PhD, MSc<sup>3,4,5</sup>

**OBJECTIVE** — Lactic acidosis has been associated with use of metformin. Hypoglycemia is a major concern using sulfonylureas. The aim of this study was to compare the risk of lactic acidosis and hypoglycemia among patients with type 2 diabetes using oral antidiabetes drugs.

**RESEARCH DESIGN AND METHODS** — This study is a nested case-control analysis using the U.K.-based General Practice Research Database to identify patients with type 2 diabetes who used oral antidiabetes drugs. Within the study population, all incident cases of lactic acidosis and hypoglycemia were identified, and hypoglycemia case subjects were matched to up to four control patients based on age, sex, practice, and calendar time.

**RESULTS** — Among the study population of 50,048 type 2 diabetic subjects, six cases of lactic acidosis during current use of oral antidiabetes drugs were identified, yielding a crude incidence rate of 3.3 cases per 100,000 person-years among metformin users and 4.8 cases per 100,000 person-years among users of sulfonylureas. Relevant comorbidities known as risk factors for lactic acidosis could be identified in all case subjects. A total of 2,025 case subjects with hypoglycemia and 7,278 matched control subjects were identified. Use of sulfonylureas was associated with a materially elevated risk of hypoglycemia. The adjusted odds ratio for current use of sulfonylureas was 2.79 (95% CI 2.23–3.50) compared with current metformin use.

**CONCLUSIONS** — Lactic acidosis during current use of oral antidiabetes drugs was very rare and was associated with concurrent comorbidity. Hypoglycemic episodes were substantially more common among sulfonylurea users than among users of metformin.

*Diabetes Care* 31:2086–2091, 2008

Metformin plays a pivotal role in the treatment of patients with type 2 diabetes (1). Metformin decreases basal glucose output by suppressing gluconeogenesis and glycogenolysis in liver and increasing glucose disposal in muscle tissue. As the most worrisome complication, lactic acidosis (pH <7.37 and/or plasma lactate levels >4 mmol/l) continues to be discussed in the literature (2)

even though the absolute risk appears to be low, with incidence rates of lactic acidosis associated with metformin use ranging from 1 to 16.7 cases per 100,000 patient-years (3,4). Salpeter et al. (5) identified all trials and cohort studies conducted between 1959 and 2002 and did not find a single case of lactic acidosis in 36,893 person-years of metformin exposure. Lalau and Race (6)

analyzed 49 cases of lactic acidosis associated with metformin use; overall mortality was not correlated with plasma lactate concentrations. Interestingly, plasma metformin concentrations were, on average, three times higher in patients who survived. All case subjects with lactic acidosis had, in addition to metformin use, acute or chronic comorbidities predisposing to lactic acidosis. These data suggest that lactic acidosis may be coincidental rather than causally associated with metformin use.

Metformin alone is not (7,8) or only rarely (1) associated with hypoglycemia (defined as symptoms and signs of hypoglycemia and/or plasma glucose levels <3.3 mmol/l and clinical response to glucose administration). According to a recent review (9), the reported risks of hypoglycemia for metformin users varied between 0 and 21%. Since metformin does not directly stimulate insulin secretion, hypoglycemia risk may be lower than for that of other oral antidiabetes drugs. However, hypoglycemia in patients using metformin may occur in association with strenuous physical activity or fasting.

Hypoglycemia is a major concern for users of sulfonylureas. Magnitude and severity of sulfonylurea-induced hypoglycemia range widely across studies (1,9,10). In an observational study (11), the annual risk for a first hypoglycemia diagnosis associated with sulfonylurea use was 1.8% (1,800 per 100,000 person-years); long-acting formulations, renal impairment, older age, and incidental use of sulfonylureas were associated with a higher hypoglycemia risk. Despite many reports on the risk of hypoglycemia in patients using oral antidiabetes drugs, direct comparisons between drug classes in the same study population are rare (9). Furthermore, the definition of hypoglycemia varies considerably across previous studies, and a comparison of their results is therefore difficult (7). Additionally, no previous study quantified both the risk of developing lactic acidosis and hypoglycemia.

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A nested case-control analysis

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**OBJECTIVE** — Lactic acidosis has been associated with use of metformin. Hypoglycemia is a major concern using sulfonylureas. The aim of this study was to compare the risk of lactic acidosis and hypoglycemia among patients with type 2 diabetes using oral antidiabetes drugs.

**RESEARCH DESIGN AND METHODS** — This study is a nested case-control analysis using the U.K.-based General Practice Research Database to identify patients with type 2 diabetes who used oral antidiabetes drugs. Within the study population, all incident cases of lactic acidosis and hypoglycemia were identified, and hypoglycemia case subjects were matched to up to four control patients based on age, sex, practice, and calendar time.

**RESULTS** — Among the study population of 50,048 type 2 diabetic subjects, six cases of lactic acidosis during current use of oral antidiabetes drugs were identified, yielding a crude incidence rate of 3.3 cases per 100,000 person-years among metformin users and 4.8 cases per 100,000

analyzed 49 cases of lactic acidosis associated with metformin use; overall mortality was not correlated with plasma lactate concentrations. Interestingly, plasma metformin concentrations were, on average, three times higher in patients who survived. All case subjects with lactic acidosis had, in addition to metformin use, acute or chronic comorbidities predisposing to lactic acidosis. These data suggest that lactic acidosis may be coincidental rather than causally associated with metformin use.

Metformin alone is not (7,8) or only rarely (1) associated with hypoglycemia (defined as symptoms and signs of hypoglycemia and/or plasma glucose levels

rate of 3.3 cases per 100,000 person-years among metformin users and 4.8 cases per 100,000 person-years among users of sulfonylureas.

Metformin plays a pivotal role in the treatment of patients with type 2 diabetes (1). Metformin decreases basal glucose output by suppressing gluconeogenesis and glycogenolysis in liver and increasing glucose disposal in muscle tissue. As the most worrisome complication, lactic acidosis (pH <7.37 and/or plasma lactate levels >4 mmol/l) continues to be discussed in the literature (2)

even though the absolute risk appears to be low, with incidence rates of lactic acidosis associated with metformin use ranging from 1 to 16.7 cases per 100,000 patient-years (3,4). Salpeter et al. (5) identified all trials and cohort studies conducted between 1939 and 2002 and did not find a single case of lactic acidosis in 36,893 person-years of metformin exposure. Lalau and Race (6)

or fasting.

Hypoglycemia is a major concern for users of sulfonylureas. Magnitude and severity of sulfonylurea-induced hypoglycemia range widely across studies (1,9,10). In an observational study (11), the annual risk for a first hypoglycemia diagnosis associated with sulfonylurea use was 1.8% (1,800 per 100,000 person-years); long-acting formulations, renal impairment, older age, and incidental use of sulfonylureas were associated with a higher hypoglycemia risk. Despite many reports on the risk of hypoglycemia in patients using oral antidiabetes drugs, direct comparisons between drug classes in the same study population are rare (9). Furthermore, the definition of hypoglycemia varies considerably across previous studies, and a comparison of their results is therefore difficult (7). Additionally, no previous study quantified both the risk of developing lactic acidosis and hypoglycemia.

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# Métodos de avaliação da função renal

**Tabela 5.** Métodos para avaliar função renal

<b>Método</b>	<b>Situação para uso</b>
Equação do MDRD study	Nefropatia diabética IRC em pacientes de meia-idade Negros com nefrosclerose Transplantados renais
Cockcroft-Gault	Idosos
DCE em urina de 24 horas	Extremos de idade e tamanho Desnutrição ou obesidade Doenças musculoesqueléticas Paraplegia e quadriplegia Dieta vegetariana Modificação rápida de função renal Gestação

# Cálculo da Clearance da creatinina

## Fórmula de Cockcroft-Gault

$$\text{Clear Cr} = \frac{(140 - \text{idade}) \times \text{peso(Kg)}}{72 \times \text{creatininemia (mg/dl)}} \times 0,85 \text{ se mulher}$$