UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS MÉDICAS:

ENDOCRINOLOGIA

CONTROLE GLICÊMICO DE PACIENTES COM DIABETES TIPO 2 NAS CINCO REGIÕES DO BRASIL E ANÁLISE DE EFETIVIDADE DE UM PROGRAMA DE CONTROLE DA GLICEMIA E DA HIPERTENSÃO ARTERIAL SISTÊMICA NA REDE PÚBLICA

TESE DE DOUTORADO

LUCIANA VERÇOZA VIANA

Porto Alegre, abril 2012.

UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS MÉDICAS:

ENDOCRINOLOGIA

CONTROLE GLICÊMICO DE PACIENTES COM DIABETES TIPO 2 NAS CINCO REGIÕES DO BRASIL E ANÁLISE DE EFETIVIDADE DE UM PROGRAMA DE CONTROLE DA GLICEMIA E DA HIPERTENSÃO ARTERIAL SISTÊMICA NA REDE PÚBLICA

Luciana Verçoza Viana

Orientadores: Profa. Dra. Cristiane Bauermann Leitão

Prof. Dr. Jorge Luiz Gross

Tese de Doutorado apresentada ao Programa de Pós-Graduação em Ciências Médicas: Endocrinologia da Universidade Federal do Rio Grande do Sul (UFRGS) como requisito parcial para obtenção do título de Doutor em Endocrinologia.

Porto Alegre, abril de 2012.

CIP - Catalogação na Publicação

Viana, Luciana Verçoza
CONTROLE GLICÊMICO DE PACIENTES COM DIABETES TIPO 2 NAS CINCO REGIÕES DO BRASIL E ANÁLISE DE EFETIVIDADE DE UM PROGRAMA DE CONTROLE DA GLICEMIA E DA HIPERTENSÃO ARTERIAL SISTÊMICA NA REDE PÚBLICA / Luciana Verçoza Viana. -- 2012.
84 f.

Orientador: Cristiane Bauermann Leitão.
Coorientador: Jorge Luiz Gross.

Tese (Doutorado) -- Universidade Federal do Rio Grande do Sul, Faculdade de Medicina, Programa de Pós-Graduação em Ciências Médicas: Endocrinologia, Porto Alegre, BR-RS, 2012.

1. diabetes tipo 2. 2. epidemiologia. 3. controle glicêmico. 4. hipertensão. I. Leitão, Cristiane Bauermann, orient. II. Gross, Jorge Luiz, coorient. III. Título.

Elaborada pelo Sistema de Geração Automática de Ficha Catalográfica da UFRGS com os dados fornecidos pelo(a) autor(a).

DEDICATÓRIA

A minha família.

AGRADECIMENTOS

A minha família pelo incentivo constante ao estudo e superação e ao exemplo de esforço e dedicação que recebo todos os dias dos meus pais e irmãos.

Aos orientadores (Dra. Cristiane e Dr. Gross) pela busca incansável da ciência e por nunca desistirem de se aperfeiçoarem no tratamento dos pacientes.

Aos pacientes que foram a "matéria-prima" do meu trabalho e à equipe da Unidade Básica Santa Cecília, que me receberam de braços abertos e muito me ajudaram com o encaminhamento e triagem dos pacientes, em especial ao Dr. Francisco Arsego e à Enfa. Maria de Fátima Grillo.

Aos colaboradores dos estudos: aos acadêmicos, hoje médicos, Ennio Paulo da Rocha e Juliana Brenner; aos pesquisadores de Belém e Manaus; à Dra Mirela, pela incessante correção dos detalhes, meu muito obrigado.

SUMÁRIO

Capítulo 2

Are diabetes management guidelines applicable in the 'real life'?

Capítulo 3

Hypertension management algorithm for type 2 diabetic patients applied in Primary Care

LISTA DE TABELAS E FIGURAS

Capítulo 1

Capítulo 2

Capítulo 3

LISTA DE ABREVIATURAS

ACE	*Angiotensin conversor enzime*
ADA	*American Diabetes Association*
ANOVA	*Analysis of Variance*
BMI	*Body mass index*
BP	*Blood pressure*
CI	*Confidence interval*
CNPq	Conselho Nacional de Desenvolvimento Científico e Tecnológico
DBP	*Diastolic Blood Pressure*
DM	Diabetes melito
EASD	*European Association for the Study of Diabetes*
EURIKA	*European Study on Cardiovascular Risk Prevention and Management in Daily Practice*
FIOCRUZ	Fundação Oswaldo Cruz
FIPE	Fundo de Incentivo à Pesquisa
HAS	Hipertensão arterial sistêmica
HbA1c	Hemoglobina glicada
HCPA	Hospital de Clínicas de Porto Alegre
HDL	*High Density Cholesterol*
HIPERDIA	Sistema de Cadastramento e Acompanhamento de Hipertensos e Diabéticos
HPLC	*High performance liquid chromatography*
IBGE	Instituto Brasileiro de Geografia e Estatística

JNC 7	*Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure*
LDL	*Low Density Cholesterol*
NHCS	*National Hospital Care Survey*
NGSP	*National Glycohemoglobin Standardization Program*
DCCT	*Diabetes Control and Complications Trial*
OR	*Odds ratio*
PA	Pressão arterial
SBD	Sociedade Brasileira de Diabetes
SBGM	*Self-Blood Glucose Monitorization*
SBP	*Systolic Blood Pressure*
SD	*Standard deviation*
SUS	Sistema Único de Saúde
UBS	Unidade Básica de Saúde
UNIFESP	Universidade Federal de São Paulo

INTRODUÇÃO

O Diabete Melito (DM) tipo 2 afeta 7,6% da população adulta brasileira (1) e está associado ao desenvolvimento de uma série de complicações crônicas (2). Em números absolutos, estima-se que nos países em desenvolvimento haverá um crescimento de 170% na prevalência de DM, com um aumento de 84 para 228 milhões de indivíduos afetados. O Brasil figura entre os dez países com maior prevalência de adultos com DM no mundo (3).

A hiperglicemia crônica é um dos principais fatores de risco para o desenvolvimento das complicações crônicas do DM (4) e seu tratamento foi capaz de reduzir as complicações associadas (4,5). Paralalelamente ao controle glicêmico, o controle da hipertensão arterial, que frequentemente co-existe nos pacientes com DM, demonstrou reduzir as complicações cardiovasculares e renais associadas à doença (6). Além disso, o controle de múltiplos fatores de risco foi capaz de reduzir mortalidade e eventos cardiovasculares em pacientes com DM tipo 2 intensivamente tratados (7).

Em 2006, a *American Diabetes Association* (ADA) e a *European Association for the Study of Diabetes* (EASD) publicaram um algoritmo com uma sugestão para manejo da hiperglicemia de pacientes com DM tipo 2 (8), aceito pela Sociedade Brasileira de Diabetes (SBD). Este algoritmo tinha como alvo uma HbA1c <7%. No entanto, este instrumento foi baseado na realidade de atendimento de pacientes com DM na Europa e na América do Norte, não levando em conta as características e necessidades da população brasileira atendidas pelo Sistema Unico de Saúde (SUS). Isto é particularmente importante, pois sendo o Brasil um país de dimensões continentais, com diversidades étnicas e culturais que potencialmente influenciam o controle da glicemia e a distribuição das complicações crônicas do DM, as peculiaridades de cada região do

país devem ser levadas em consideração durante o planejamento de uma proposta de tratamento do DM.

Considerando dados locais que mostravam média HbA1c acima das metas preconizadas (9) e que apenas 30% dos pacientes hipertensos tratados no estado (10) apresentam níveis pressóricos adequados, foi idealizado o projeto "Análise de efetividade de um programa de controle da glicemia e da hipertensão arterial sistêmica em pacientes diabéticos tipo 2 na rede pública". Este estudo teve como base o algoritmo lançado em 2006 e as evidências em relação ao controle pressórico dos pacientes com DM tipo 2**.** Seu objetivo principal era a avaliação da efetividade dos medicamentos distribuídos gratuitamente pelo SUS para tratamento de pacientes diabéticos tipo 2 e hipertensos, de acordo com as metas propostas pela ADA (glicemia jejum <130mg/dl; A1c <7%, pressão arterial <130/80 mmHg) (11). Originalmente o estudo foi projetado para ser realizado em dois centros: a Unidade Básica de Saúde (UBS) do Hospital de Clínicas de Porto Alegre (HCPA), inaugurada em 2004 e contando, na época, com um cadastro de 264 pacientes diabéticos e/ou hipertensos; e no Centro de Saúde Vila dos Comerciários - Pronto Atendimento Cruzeiro do Sul, gerenciado pela prefeitura de Porto Alegre. Infelizmente, por questões logísticas, não foi possível incluir o centro da prefeitura no estudo.

Paralelamente ao desenvolvimento do primeiro estudo, entre agosto de 2005 a abril de 2007, estava sendo realizada a "Pesquisa sobre a Epidemiologia do Diabetes no Brasil: Grau de Controle Glicêmico e Complicações", com o apoio da Sociedade Brasileira de Diabetes e coordenado pelo Dr. Antônio Roberto Chacra (UNIFESP), Dr. Edson Duarte Moreira (FIOCRUZ) e Dra. Ana Beatriz Valverde Mendes (UNIFESP). Este projeto recrutou 6671 indivíduos com DM (DM1: n = 979 e DM2: n = 5692; 15% e 85% da amostra, respectivamente) de 4 regiões do país, respeitando a distribuição

demográfica do País (12), porém não incluiu indivíduos da região Norte (13). Em 2009, visando obter uma visão mais completa do controle glicêmico no Brasil, o grupo do Serviço de Endocrinologia do HCPA foi contemplado junto ao CNPq com o projeto "Tratamento do Diabetes Melito no Brasil: Descrição da Situação Atual do Controle Glicêmico e das Complicações Crônicas nas Cinco Regiões do País e Análise Crítica das Intervenções Terapêuticas Disponíveis". Ao banco de dados já disponível, planejou-se adição dos dados da região Norte e reanálise dos dados do Brasil como um todo, a partir de uma amostra representativa da população brasileira e com medida do controle metabólico baseado em HbA1c analisada em laboratório central. Este projeto incluiu, também, a análises das diversas estratégias de tratamento do diabetes sob forma de revisões sistemáticas e meta-análises.

Esta tese sumariza os resultados dos dois projetos, descritos sob forma de 3 artigos científicos, e procura apresentar um panorama do tratamento do DM tipo 2 no Brasil, tanto do ponto de vista epidemiológico, quanto da aplicação dos recursos disponíveis pelo SUS. Como apêndice, está a meta-análise de inclusão da terceira droga no tratamento do DM tipo 2, publicada no Annals of Internal Medicine em 2011, da qual a autora participou ativamente (14).

Bibliografia

1. Marlebi D, Franco L. Multicenter study of the prevalence of diabetes mellitus and impaired glucose tolerance in the urban Brazilian population aged 30-69yr. Diabetes Care 15:1509-1516, 1992.

2. Gross, J. L., F. S. R. G., *et al.* Diagnóstico e classificação do diabetes melito e tratamento do diabetes melito tipo 2. Recomendações da Sociedade Brasileira de Diabetes. Arq Bras Endocrinol Metabol, v.44, Mar, p.S8-s35. 2000.

3. King H, Aubert RE, Herman WH. Global burden of diabetes, 1995-2025: prevalence, numerical estimates, and projections. Diabetes Care. 1998 Sep;21(9):1414-31.

4. Stratton, I. M., A. I. Adler, *et al.* Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ, v.321, n.7258, Aug 12, p.405-12. 2000.

5. UKPDS - 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, v.352, n.9131, Sep 12, p.854-65. 1998.

6. Standards of medical care in diabetes--2012. Diabetes Care. 2012 Jan;35 Suppl 1:S11-63.

7. Gaede P, Valentine WJ, Palmer AJ, Tucker DM, Lammert M, Parving HH, et al. Cost-effectiveness of intensified versus conventional multifactorial intervention in type 2 diabetes: results and projections from the Steno-2 study. Diabetes Care. 2008 Aug;31(8):1510-5.

8. Nathan, D. M., J. B. Buse, *et al.* Management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care, v.29, n.8, Aug, p.1963-72. 2006.

9. American Diabetes Association. Standards of Medical Care in Diabetes–2006. Diabetes Care 2006 29: S4-42.

10. Scheffel RS, Bortolanza D, *et al.* Prevalência de complicações micro e macrovasculares e seus fatores de risco em pacientes com diabetes melito tipo 2 em atendimento ambulatorial. Rev Assoc Med Bras 50(3): 233-7; 2004

11. Gus I, Harzheim E, Zavasky C, Medida C, Gus G. Prevalência, reconhecimento e controle da Hipertensão Arterial Sistêmica no Estado do Rio Grande do Sul. Arq Bras Cardiol 83(5): 424-8; 2005.

12. Site IBGE (Instituto Brasileiro de Geografia e Estatística), http://www.ibge.gov.br/home/estatistica/populacao/contagem2007/default.shtm, último acesso em 15 de outubro de 2008.

13. Mendes ABV, Fittipaldi JAS, Neves RCS, Chacra AR, Moreira-Jr ED. Prevalence and correlates of inadequate glycemic control: results from nationwide survey in 6,671 adults with diabetes in Brazil. Acta Diabetol. 2010 47: 137-145.

14. Gross JL, Kramer CK, Leitao CB, Hawkins N, Viana LV, Schaan BD, et al. Effect of antihyperglycemic agents added to metformin and a sulfonylurea on glycemic control and weight gain in type 2 diabetes: a network meta-analysis. Ann Intern Med. 2011 May 17;154(10):672-9.

Poor Glycemic Control in Brazilian Diabetic Patients Attending the Public Health System - What is Missing?

Luciana V. Viana*, MD[1]

Cristiane B. Leitão*, MD, PhD[1]

Caroline K. Kramer MD, PhD[1]

Alessandra T.N. Zucatti[1]

Deborah L. Jezini MD[2]

João Felício MD[3]

Ana B. Valverde, MD[4]

Antonio R. Chacra, MD, PhD[4]

Mirela J. Azevedo, MD, PhD[1]

Jorge L. Gross, MD, PhD[1]

[1]Endocrine Division of Hospital de Clínicas de Porto Alegre and Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil; [2]Endocrine Division of Hospital Getúlio Vargas and Universidade Federal do Amazonas, Manaus, Brazil; [3]Universidade Federal do Pará, Belém, Brazil; [4]Endocrine Division of Universidade Federal de São Paulo, São Paulo, Brazil.

Abstract word count: 262

Manuscript word count: 2.038

Tables: 5

Figures: 1

Corresponding author

Jorge Luiz Gross, Serviço de Endocrinologia do Hospital de Clínicas de Porto Alegre.

Rua Ramiro Barcelos 2350, Prédio 12, 4º andar, 90035-003, Porto Alegre, RS, Brazil.

E-mail: jorgeluizgross@gmail.com; Phone: + 55 51 3359 8127. Fax: + 55 51 3359 8777

Este artigo será enviado para publicação no British Medical Journal

Abstract:

Background and aim: Brazil is among the ten countries in the world with the highest prevalence of diabetes mellitus. Diabetes is the underlying cause of death of 2.5% of Brazilian population, which in part can be attributed to poor glycemic control. This study aimed to describe main characteristics of Brazilian type 2 diabetic patients attending Public Health Care System and identify factors associated with poor glycemic control.

Material and methods: A cross-sectional study was conducted in patients with type 2 diabetes attending outpatient clinics of Public Health System in the five regions of Brazil. Clinical variables were obtained by standardized questionnaire. HbA1c was centrally measured by HPLC (NGSP certified). Poor glycemic control was defined as HbA1c >8%.

Findings: A total of 5750 patients aged 61±10 years with 11±8 years of diabetes duration (66% female, 56% non-white, BMI: 28.0±5.3 kg/m²) were analyzed. The mean HbA1c was 8.6±2.2% and a HbA1c ≥7% was observed in 73.6% of patients. Subjects from the North and Northeast regions had higher mean HbA1c values (North: 9.0±2.6%, Northeast: 8.9±2.4%) than other regions (Center-West: 8.1±2.0, Southeast: 8.4±2.1, and South: 8.3±1.9; P <0.01). In adjusted Poison Regression analyses, prevalence of HbA1c ≥8% was higher with longer diabetes duration (in years), non-white ethnicity, use of insulin and living in Northeast regions. Younger age and living in the Mid-West region associated to a protection against HbA1c ≥8%.

Conclusion: In Brazilian type 2 diabetic patients attending the Public Health System, HbA1c values were far above recommended targets. The recognition of Northeast regions and non-white patients as vulnerable populations should guide governmental health care policies.

Funding: Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Fundo de Incentivo à Pesquisa (FIPE) of Hospital de Clínicas de Porto Alegre (HCPA), and Pfizer Pharmaceutical.

Introduction

Brazil is among the ten countries in the world with the highest prevalence of diabetes mellitus (DM) of about 7.6% (1,2). Diabetes is considered the fifth underlying cause of death occurring in 2.5% of Brazilian population (3) and in a preliminary publication of this study (4) only 24% of the Brazilian diabetic patients had an HbA1c lower than the recommended target (HbA1c <7%; 5). The Public Health Care System (Sistema único de Saúde-SUS) is entitled to provide free medical care for every Brazilian citizen (6). The medical assistance is provided by regional government and medications are free of charge all over the country. The available anti-hyperglycemic medication includes metformin, sulphonilureas, and insulin which are distributed in primary care units and specific drugstores around the country. Considering that poor diabetic control is an important factor associated with mortality in diabetic populations (7) it is important to analyse the possible factors associated with high levels of HbA1c. Therefore, the aim of this study was to characterize patients with type 2 diabetes attending Brazilian Public Health Care System in different regions and identify possible factors associated with poor glycemic control.

Patients

A cross-sectional study was conducted in 7201 patients with type 1 and type 2 diabetes attending outpatient clinics of Public Health Care System (Sistema Único de Saúde-SUS) between February, 2006 and April, 2011 in the five regions of Brazil: North (n = 500; 7%), Northeast (n = 2184; 30%), Center-West (n= 461; 6%), Southeast (n = 3382; 47%), and South (n = 674; 9%). Patient's distribution over the five regions represents the population density as defined by 2000 Brazilian survey (*Instituto Brasileiro de Geografia e Estatística* – IBGE) (8). A preliminary data on characteristics

of Brazilian diabetic patients, both type 1 and type 2, and not including the North region, was already published (4). The protocol was approved by the Ethics Committee of the Hospital de Clínicas de Porto Alegre, as well as in each center Ethics Committee, and all patients provided written informed consent.

The current study reports data from 5750 type 2 diabetic patients of the five regions of Brazil who had HbA1c values available. Type 2 diabetes was defined as diabetes diagnosis after 30 years of age and not using insulin in the first five years after the diagnosis. Patients were from North (n = 312; 5%), Northeast (n = 1906, 33%), Center-West (n = 348, 6%), Southeast (n = 2642, 46%), and South (n = 542, 9%) regions.

Clinical Characteristics Assessment

Clinical variables (age, gender, ethnicity, DM duration, medication in use, body weight and height) were obtained by a standardized questionnaire. Briefly, ethnicity was self-reported as white or non-white (black, mixed, or other - including Asian and Native American Indian). Marital status was defined as living with or without a partner, and working status as being current active or not. Degree of literacy was classified as at least eight years of formal education or less than that. The DM treatment was classified as none; diet alone, oral agents, oral agents plus insulin, and insulin alone. Frequency of self-blood glucose monitorization (SBGM) and hypoglycemic episodes in the previous year were recorded. BMI was calculated (weight/height^2; kg/m^2). Data were collected in 14 cities (Porto Alegre, Curitiba, São Paulo, Cotia, Campinas, Taguatinga, Belo Horizonte Rio de Janeiro, Brasilia, Fortaleza, Recife, Salvador, Belém, Manaus) representing the 5 regions of Brazil.

HbA1c measurements

HbA1c was measured in a central laboratory by ion-exchange high performance liquid chromatography (HPLC) procedure (reference range 4.7-6.0%) certified by the National Glycohemoglobin Standardization Program (NGSP) and calibrated to Diabetes Control and Complications Trial (DCCT).

Statistical Analyses

Pearson correlation was used to identify demographic and clinical variables associated with HbA1c results. The differences in clinical variables and HbA1c results among the five regions were evaluated by One-way-ANOVA (with Bonferroni post-hoc test) and chi-squared testes. The characteristics of patients were compared according to glucose control (median HBA1c), region of origin, and self-referred ethnic background. Adjusted Poison Regression Analyses were performed in order to evaluate the factors associated with HbA1c >8% (dependent variable). Independent variables were selected based on their significance on univariate analyses and/or biological relevance.

Variables are expressed as mean ± SD, number of cases (%) and interquartile interval: P25-P75. HbA1c was also described as median. Statistical analyses were carried out using SSPS 18.0. P values less than 0.05 (two tailed) were considered significant. All patients

RESULTS

Sample description

Table 1 shows main patients characteristics. Patient's mean age was 61 years (53 to 68 years) and their diabetes duration was about 11 years (4 to 16 years). Most of the patients were female (66%), non-white (56%), and were living with a partner (59%).

About a third completed eight years of formal education, only 20% were active workers, and the mean BMI was 28.0%. Regarding treatment, 1% did not follow any kind of treatment for diabetes, 6% were on diet alone, 57% were taking oral agents, 22% used oral agents and insulin and 13% insulin alone.

The median HbA1c of the study population was 8.1% (interquartile interval: 6.9 – 9.9%) and the mean was 8.6 ± 2.2%. HbA1c values were associated with age ($r = -0.125$; $P < 0.01$) and diabetes duration ($r = 0.130$; $P < 0.01$). HbA1c<7% was found in only 26% of the patients.

Glycemic control

Since the majority of the included patients had a very poor glycemic control we decided to compare the characteristic of patients according to median HbA1c (8.0%) Table 2 shows data and prevalence of baseline characteristics in patients with HbA1c ≥8% and HbA1c<8%. Patients with HbA1c ≥8% were younger, with longer DM duration, more sedentary, and treated more frequently with insulin than patients with HbA1c<8%. Patients HbA1c ≥8% were mainly from North and Northeast regions and non-whites.

Geographic region and HbA1c

Patient's characteristics were stratified by region in order to identify possible reasons for the poorest glycemic control observed in the North and Northeast **(Table 3)**. The five regions differed in all evaluated characteristics. Regarding glycaemic control, patients from the North and Northeast regions had the worst glucose control, contrasting with HbA1c observed in the other regions. The North sample was composed mainly by younger non-white active working male subjects as compared with other regions.

Patients from North region also had a higher degree of education, higher BMI, and were more frequently living with a partner than patients from other regions. The Northeast region had also a high prevalence of non-whites, but had the lowest BMI and frequency of active workers.

Ethnicity and HbA1c

Characteristics of patients according self-reported ethnicity (whites and non-white) are described in **Table 4**. Non-white subjects had higher HbA1c values, were younger and thinner than white patients; they had also a higher prevalence of female sex and single status and more years of formal education.

Insulin users

A total of 2021 (35%) of the included patients were on insulin: once a day, 33% (n = 658); twice a day, 58% (n = 1154); and three times a day or more, 9% (n = 189). Eighty-one percent (n = 1630) of the insulin users performed SBGM, but only 421 (26%) did it in a daily basis. Patients complying with SBGM had lower values of HbA1c than non-compliers (no test: 9.7 ± 2.3%, eventually: 9.5 ± 2.2%, and at least once a day: 9.3 ± 2.1%; P = 0.008 for no test vs. at least once a day).

Hypoglycemic episodes

Twenty percent of patients (n = 1129) had at least one hypoglycemic episode in the previous year. These patients had longer diabetes duration were thinner, more frequently females and non-whites as compared with patients without hypoglycemia. They were also more frequently sedentary and less frequently actively workers than patients without hypoglycemia. Patients experiencing hypoglycemia were more

frequently insulin users and performed SBGM as part of their treatment more frequently than patients without hypoglycemic episodes. In addition, the number of daily SBGM tests was higher in patients with than without hypoglycemia. Among insulin users, patients with hypoglycemia performed more injections per day than patients without hypoglycemia.

Factors associated with poor metabolic control

Poison regression analysis was conducted with HbA1c ≥8% as the dependent variable. Adjusted prevalence ratio for age, DM duration, ethnicity, working status, insulin use, SBGM, and country region (using the South region as the reference) are shown in **Table 2**. Age and being treated in the Center-West region were inversely associated with poor glycemic control. In contrast, prevalence of HbA1c ≥8% was more frequently in longer DM duration, non-white ethnicity, use of insulin and being treated in Northeast regions.

Conclusions

In this sample of patients with type 2 diabetes attending public health system in Brazil, the majority had HbA1c above recommended targets. Mean HbA1c was 8.6 ± 2.2%. Non-white ethnicity and being from Northeast regions were associated with poor metabolic control, as well the longer diabetes duration, and insulin use. Young age and being from Center-West region were associated with HbA1c <8.0%. As far as we are aware this is the largest diabetes glycemic control surveillance performed in Brazil. In addition, this study probably truthfully characterize the profile of Brazilian diabetic patients attending by the Public Health System since it includes the five official country regions and the main outcome, HbA1c, was performed by a certified method for all included patients.

Diabetes control varies in different countries. In the Unites States of America, mean HbA1c among middle-aged adults was approximately 7.3% (9). In type 2 diabetic patients using oral agents to treat diabetes from seven European countries, the glycemic control was similar (mean HbA1c 7.2%) (10). However, in the EURIKA (11), a study performed in 12 European countries, only 36.7% of patients with type 2 diabetes achieved the goal of HbA1c <6.5%. In the present study, HbA1c mean is much higher than that observed in these countries and only 26% of our patients had HbA1c lower than the 7.0% goal.

In the current study HbA1c also varies broadly among different Brazilian regions. One explanation for the poorest glycemic control observed in North and Northeast regions can be the diversity in ethnic and economic background. According to the IBGE, white population represented 23.6% of the North region and 28.9% in Northeast. In the other hand, white subjects represent 41.7% of population in West-Center, 56.7% in the Southeast, and 78.5% in the South region (12). Numerous studies show ethnic disparities in HbA1c values. In a meta-analyses study, African-Americans had HbA1c absolute values 0.65% higher than non-Hispanic whites (13). In our study, the HbA1c difference between whites and non-whites was about 0.5%.

Regarding the possible role of economic background in glycemic control, the income per capita also differs among the five regions being almost twice higher in the South than Northeast states (14). In this sense, a European surveillance of socio-economic predictors of mortality had demonstrated that in type 2 diabetic males a low income (15) was associated with higher mortality.

Brazil has adopted a Public Health Care System (Sistema único de Saúde-SUS) since 1988, which ensures free medical care for every Brazilian citizen (6). The medical assistance is provided by regional government and medications are free of

charge all over the country. The available anti-diabetic medication includes metformin, sulphonilureas, and insulin which are distributed in primary care units and drugstores around the country. However, other classes of medications used to treat diabetes are not in the panel of free medications. Also, SBGM devices are not supplied for all patients. Therefore, although our Public Health System may represent an advance in health care, it has not been enough to reach glycemic control targets in diabetes care.

The current study has limitations. Firstly, the surveillance was based on self-reported answers, although medical records were consulted when available. Moreover, only patients attending Public Health system were evaluated. It is known that almost a quart of Brazilian population uses private health care insurances (16). Lastly, due to its cross section design, our study demonstrated associations with glycemic control, and not true risk factors. It is also important to clarify that reversal causality is always present in cross-section studies and poor glycemic control in patients using insulin can not be attributed to insulin prescription *per se*. Insulin in general is used patients with more severe diabetes and this is probably the cause of worse glycemic control found in such patients.

In conclusion, Brazilian patients with type 2 diabetes attending Public Heath System have poor glycemic control as demonstrated by HbA1c values far above the recommended targets. New strategies are necessary to improve glycemic control in type 2 diabetic patients all over the country. Furthermore, the recognition of North and Northeast regions and non-white patients as vulnerable populations should guide governmental health care policies.

References

1. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care. 2004 May;27(5):1047-53.
2. Marlebi DA, Franco LJ. Multicenter study of the prevalence of diabetes mellitus and impaired glucose tolerance in the urban Brazilian population aged 30-69 yr. The Brazilian Cooperative Group on the Study of Diabetes Prevalence. Diabetes Care 1992 Nov;15(11):1509-16.
3. Datasus – downloaded from http://tabnet.datasus.gov.br/cgi/deftohtm.exe?idb2009/c12.def
4. Mendes ABV, Fittipaldi JAS, Neves RCS, Chacra AR, Moreira-Jr ED. Prevalence and correlates of inadequante glycemic control: results from nationwide survey in 6,671adults with diabetes in Brazil. Acta Diabetol. 2010 47: 137-145.
5. American Diabetes Association. Standards of Medical Care in Diabetes - 2012. Diabetes Care. 2012. 35 Suppl 1:S11-S63.
6. Pustai OJ. O Sistema de Saúde no Brasil. *In*: Medicina ambulatorial: Condutas de Atenção Primária Baseadas em Evidências, ArtMed 2004.
7. UK Prospective Diabetes Study (UKPDS) Group. Lancet Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33).. 1998 Sep 12;352(9131):837-53.
8. IBGE - Instituto Brasileiro de Geografia e Estatística. Downloaded from www.ibge.gov.br.

9. Chiu C-J, Wray LA. Factors Predictiong Glycemic Control in Middle-Aged and Older Adults with Type 2 Diabetes. Prev Chronic Dis 2010; 7(1): A08.
10. Alvarez Guisasola F, Mavros P, Nocea G, Alemao E, Alexander CM, Yin D. Glycaemic control among patients with type 2 diabetes mellitus in seven European countries: findings from the Real-Life Effectiveness and Care Patterns of Diabetes Management (RECAP-DM) study. Diabetes Obes Metab. 2008 Jun;10 Suppl 1:8-15.
11. Banegas JR, Lopez-Garcia E, Dallongeville J, Guallar E, Halcox JP, Borghi C, et al. Achievement of treatment goals for primary prevention of cardiovascular disease in clinical practice across Europe: the EURIKA study. Eur Heart J. 2011 Sep;32(17):2143-52.
12. IBGE – dowloaded from seriesestatisticas.ibge.gov.br/series.aspx?vcodigo=PD336&sv=32&t=populacao-residente-por-cor-ou-raca.
13. Kirk JK, D'Agostino RB, Jr., Bell RA, Passmore LV, Bonds DE, Karter AJ, et al. Disparities in HbA1c levels between African-American and non-Hispanic white adults with diabetes: a meta-analysis. Diabetes Care. 2006 Sep;29(9):2130-6.
14. Download from: http://www.todospelaeducacao.org.br/educacao-no-brasil/busca-comparativa/resultado/resultado/?tipo=1&id_check_universo%5B%5D=10905&id_universo%5B%5D=10905&id_check_universo%5B%5D=10902&id_universo%5B%5D=10902&id_check_universo%5B%5D=10901&id_universo%5B%5D=10901&id_check_universo%5B%5D=10903&id_universo%5B%5D=10903&id_check_universo%5B%5D=10904&id_universo%5B%5D=10904&criterios

=157&id_check_criterio%5B%5D=157&id_criterio%5B%5D=157&comparar=Comparar.

15. Forssas E, Manderbacka K, Arffman M, Keskimaki I. Socio-economic predictors of mortality among diabetic people. Eur J Public Health. 2011 Apr 15.
16. Agencia Nacional de Saúde – downloaded from http://www.ans.gov.br/index.php/materiais-para-pesquisas/perfil-do-setor/dados-gerais.

Table 1. Characteristics of the 5750 patients with type 2 diabetes

N	5750
Age (years)	61 ± 10
Diabetes duration (years)	11 ± 8
Females (%)	3796 (66)
Ethnicity *	
White	2538 (44)
Mixed	1776 (31)
Black	722 (13)
Other	710 (12)
Living with a partner (%)	3375 (59)
At least 8 years of formal education	1900 (33)
Active worker	1136 (20)
Sedentary	2111 (37)
BMI (kg/m²)	28.0 ± 5.3
HbA1c (%)	8.6 ± 2.2
Diabetes treatment*	
None	71 (1)
Diet only	343 (6)
Oral agents	3295 (57)
Oral agents and insulin	1248 (22)
Insulin alone	773 (13)

Data are mean ± SD, number of patients with the characteristic (%).

*Data available for 5746 patients

**Data available for 5730 patients

Table 2 . Prevalence of patients characteristics according to HbA1c ≥8%

	HbA1c <8% n = 2791	HbA1c ≥8% n = 2959	PR (CI 95%)	P	Adjusted PR (CI95%)	P
Age (years)	62 ± 11	60 ± 10	0.991 (0.989-0.993)	0.000	0.986 (0.983-0.989)	0.000
Diabetes duration (years)	9 ± 8	12 ± 8	1.018 (1.015-1.021)	0.000	1.015 (1.012-1.018)	0.000
BMI (kg/m²)	28.0 ± 5.1	28. 0 ± 5.4	0.999 (0.994-1.004)	0.640	--	--
Females	1824 (65)	1972 (67)	0.972 (0.922-1.026)	0.304	--	--
White	1339 (48)	1199 (40)	0.862 (0.818-0.907)	0.000	0.931 (0.883-0.981)	0.007
Living with a partner	1613 (58)	1762 (59)	1.035 (0.983-1.089)	0.189	1.006 (0.959-1.057)	0.796
≥ 8 years of formal education	933 (41)	967 (48)	0.987 (0.932-1.044)	0.646	--	--
Active worker	527 (19)	609 (21)	0.949 (0.893-1.009)	0.094	1.053 (0.989-1.212)	0.109
Ever participate in a diabetes education program*	318 (11)	387 (13)	0.929 (0.865-0.999)	0.047	--	--
Diabetes treatment				0.000	--	--
None	48 (2)	23 (1)				
Diet only	285 (10)	58 (2)	0.522 (0.346-0.786)			
Oral agents	1905 (69)	1390 (47)	1.302 (0.928-1.827)			
Oral agents and insulin	318 (11)	930 (32)	2.300 (1.641-3.224)			
Insulin alone	228 (8)	545 (18)	2.176 (1.551-3.055)			

Insulin use	546 (20)	1475 (50)	1.834 (1.749-1.924)	0.000	1.710 (1.624-1.802)	0.000
SBMG	1838 (66)	2158 (73)	1.186 (1.118-1.1258)	0.000	1.061(1.001-1.1.23)	0.045
Geographic region				0.000		0.000
North	135 (43)	177 (57)	1.225 (1.073-1.399)		1.137 (0.996-1.298)	
Northeast	814 (43)	1092 (57)	1.212 (1.212-1.365)		1.197 (1.085-1.321)	
Center-West	194 (56)	154 (44)	0.956 (0.842-1.109)		0.858 (0.745-0.989)	
Southeast	1357 (51)	1285 (49)	1.050 (0.951-1.159)		0.959 (0.871-1.056)	
South	291 (54)	251 (46)				

*Data not available for North region (not included in the adjusted analysis)

Table 3. Characteristics of patients with type 2 diabetes according to the five geographic regions of Brazil

	North	Northeast	Center-West	Southeast	South	P
N	312	1906	348	2642	542	-
HbA1c (%)	9.0 ± 2.6	8.9 ± 2.4	8.1 ± 2.0	8.4 ± 2.1	8.3 ± 1.9	<0.01[a]
Age (years)	58 ± 10	61 ± 11	60 ± 11	61 ± 10	62 ± 10	<0.01[bc]
Diabetes duration (years)	10 ± 8	10 ± 8	11 ± 8	11 ± 9	11 ± 9	0.029
BMI (kg/m²)	29.0 ± 5.5	27.2 ± 5.0	27.7 ± 5.2	28.2 ± 5.3	29.1 ± 5.3	<0.01[cde]
Females	193 (62)	1317 (69)	245 (70)	1726 (65)	315 (58)	<0.01[f]
White	71 (23)	560 (29)	131 (38)	1311 (50)	465 (86)	<0.01[f]
Living with a partner	199 (64)	1099 (58)	185 (53)	1537 (58)	355 (66)	<0.01[g]
≥ 8 years of formal education	140 (45)	521 (34)	106 (39)	1011 (47)	122 (27)	<0.01[h]
Active worker	112 (38)	341 (18)	65 (19)	482 (18)	136 (25)	<0.01[i]
Sedentary	134 (43)	670 (35)	147 (43)	1005 (38)	168 (31)	<0.01[j]
Diabetes treatment						
None	2 (1)	18 (1)	7 (2)	38 (1)	6 (1)	<0.01[f]
Diet only	14 (5)	145 (8)	31 (9)	138 (5)	15 (3)	
Oral agents	172 (59)	1172 (62)	180 (52)	1426 (54)	345 (64)	
Oral agents and insulin	67 (23)	332 (17)	64 (18)	660 (25)	125 (23)	
Insulin alone	37 (12)	239 (12)	66 (19)	380 (15)	51 (9)	

Data are mean ± SD or number of patients with the characteristic (%)

[a] North and Northeast vs. Center-West, Southeast and South

[b] North vs. Northeast, Southeast and South

[c] Center-West and Southeast vs. South

[d] North vs. Northeast and Center-West

[e] Northeast vs. Southeast and South

[f] Linear-by-linear association

[g] higher in North and South; lower in Center-West

[h] higher in Southeast; lower in Northeast and South

[i] higher in North and South; lower in Northeast and Southeast

[j] higher in North and Center-West; lower in Northeast and South

Table 4. Demographic and clinical characteristics of patients with type 2 diabetes according to ethnicity

	White n = 2538	Non-white n = 3208	P
HbA1c (%)	8.3 ± 2.1	8.8 ± 2.3	<0.01
Age (years)	62 ± 10	60 ± 10	<0.01
Diabetes duration (years)	11 ± 9	11 ± 8	0.06
BMI (kg/m²)	28.2 ± 5.2	27.8 ± 5.3	0.003
Females – n (%)	1615 (64)	2178 (68)	<0.01
Living with a partner - n (%)	1568 (62)	1805 (56)	<0.01
At least eight years of formal education - n (%)	803 (38)	1094 (41)	0.011
Active worker - n (%)	520 (21)	616 (19)	0.227
Sedentary – n (%)	904 (36)	1220 (38)	0.072
Diabetes treatment - n (%)			0.007
None	37 (2)	34 (1)	
Diet only	151 (6)	192 (6)	
Oral agents	1498 (59)	1794 (56)	
Oral agents and insulin	533 (21)	714 (22)	
Insulin alone	314 (12)	459 (15)	
Geographic region – n (%)			<0.01
North	71 (23)	241 (77)	
Northeast	560 (29)	1344 (71)	
Center-West	131 (38)	217 (62)	
Southeast	1311 (50)	1329 (50)	
South	465 (86)	77 (14)	

Data are mean ± SD, number of patients with the characteristic (%).

Figure 1. HbA1c Distribution Among the Five Brazilian Geographic Regions. (HbA1c higher in the North and Northeast regions vs South, Southeast, and Center-West Regions P<0.01).

ARE DIABETES MANAGEMENT GUIDELINES APPLICABLE IN THE 'REAL LIFE'?

Luciana V. Viana

Cristiane B. Leitão

Maria de Fátima Grillo

Ennio P. C. da Costa Rocha

Juliana Brenner

Rogério Friedman

Jorge L. Gross

Endocrine Division and Primary Care Unit of Hospital de Clinicas de Porto Alegre and Federal University of Rio Grande do Sul, Porto Alegre, Brazil.

Corresponding author:

Jorge L. Gross, MD

Endocrine Division - Hospital de Clínicas de Porto Alegre

Rua Ramiro Barcelos, 2350 – Prédio 12 – 4° andar.

90035-003 – Porto Alegre, RS – Brazil

Phone/Fax : +55 51 3332-5188/3330-9100

E-mail: jorgeluizgross@gmail.com

Word count: 1669

Number of figures 1; Table 1

Aim: To analyze the feasibility of reaching and/or maintaining HbA_{1c} <7.0% using current diabetes treatment guidelines and resources available in the Public Health System of Brazil.

Methods: A one-year, single-arm interventional study was conducted with type 2 diabetes patients in a primary care unit. Intervention consisted of intensification of lifestyle changes and sequential prescription of drugs based on ADA guidelines using the medications available in the Public Health System – Sistema Unico de Saúde (SUS).

Results: Ninety patients (age: 62.7±10.4 years; diabetes duration: 8.2±9.1 years) completed the trial. During the intervention period, an increment in number of anti-diabetic oral agents (ADO) classes/patient (1.50±0.74 vs. 1.67±0.7; p=0.015), ADOs pills/patient (2.64±1.89 vs. 3.33±2.23 pills/patient; p <0.001), insulin dosage (0.20±0.29 vs.0.50±0.36 UI/kg/day; p=0.008) and number of patients on insulin [19 (21%) to 31 (34%) (p <0.01)] were observed, but no improvement in HbA1c (7.2±1.6% vs. 7.3±1.5%; p=0.453) nor in frequency of patients on target defined as HbA1c<7% (53.3% vs. 48.9%; p=0.655) was detected. Patients with baseline HbA1c <7% had a increase HbA1c during the trial (6.3±0.4 vs. 6.7±0.9%; p=0.002) and no change was observed in those with HbA1c ≥7%.

Conclusions: In this group of patients with baseline mean HbA1c 7.2%, the implementation of ADA/EASD 2006/2009 guidelines was not able to prevent deterioration in glycemic control of type 2 diabetic patients with an HbA1c ~7% at baseline, and the goal of <7% was reached in a small proportion of patient.

Key words: type 2 diabetes; ADA guidelines; ‘real life’.

Introduction:

Both American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) have published algorithms for hyperglycemia management in patients with type 2 diabetes (1,2). According to these algorithms the first step in diabetes treatment consisted on lifestyle intervention plus meformin. If the optimal diabetes control is not achieved, the second step recommends either the association of suphonylureas or basal insulin. These recommendations have not, however, been tested in the 'real life' scenario. In Brazil, most type 2 diabetic patients are treated in primary care units and have free access to metformin, sulfonylurea, and NPH insulin, which are provided by public health care system – Sistema Unico de Saude (SUS). Therefore, the aim of this study was to analyze if it is possible to reach and maintain an HbA_{1c}<7.0% in patients with type 2 diabetes attending a primary care unit and following ADA/EASD guidelines.

Research Design and Methods

Consecutive adult (more than 18 years-old) patients with type 2 diabetes attending regularly the primary care unit in the previous 6 months before the screening visit were invited to participate in the study. Exclusion criteria were: history of active infection (eg. osteomyelitis, pulmonary tuberculosis, AIDS), chronic corticosteroids use, unstable angina or myocardial infarction in the last 3 months, advanced renal disease – defined as dyalises procedures, heart failure (New York Heart Association class III and IV), cirrhosis, alcohol or illicit drug use, dementia, actual pregnancy or lactation, current cancer or any disease that might affect survival in the next 5 years.

At baseline, patients underwent an evaluation consisting of anamnese and physical examination. Patients were considered as current smokers or non-smokers. Ethnic

definition was self-classified as white or non-white. Previous medical history was evaluated clinically. Microalbuminuria was defined by random spot urine sample higher than 17 mg/l (9,10). Cerebrovascular disease was established in the presence of a history of stroke and/or compatible findings (sequelae). The diagnosis of heart disease was based on previous history of myocardial infarction, angina or heart failure and when available myocardial scintigraphy and coronary angiography. Body mass index (BMI) was calculated [weight (kg)/ height^2 (m)].

Blood pressure was measured twice each visit in the sitting position after 10 minutes rest with OMRON Automatic Blood Pressure Monitor HEM- 720. Hypertension was defined as blood pressure levels ≥140/90 mmHg, or use of anti-hypertensive drugs.

This one-year, open-label, non-controlled, single-arm interventional study was conducted at a primary care unit located in the metropolitan area of the city of Porto Alegre, nearby the Hospital de Clínicas de Porto Alegre, a University Hospital and reference center. The primary care unit is responsible for the care of approximately 40.000 individuals. The study comprised 3 stages: a run-in (3 months), drug intervention period (6 months) and stabilization period (2-3 months) and was conducted by an endocrinologist (LVV) and a generalist nurse (MFG). Eligible patients underwent an interview, clinical examination and performed laboratory exams (glucose, HbA1c, lipid profile, hepatic tests, creatinine and albuminuria in spot urine). In the run-in period, patients received a glucose monitoring device and strips, and were oriented in using it and to record the results of measurements. They were asked to perform blood glucose monitoring in the fasting state, before the breakfast. Due to economic restrictions it was performed only three times a week. Patients visited the primary care unit monthly and received reinforcements about

diet, exercise and adherence to medication already in use. During the intervention period, participants visited the center at monthly intervals to check weight, blood pressure and results of their self monitoring blood glucose (SMBG). The goal was to obtain fasting capillary blood glucose by SMBG between 90 to 130 mg/dl. If the mean SMGB values were higher than 130 mg/dl medications were added following this sequence: metformin, glyburide and NPH insulin, initially at bedtime and if the goal were not met another shot was added before breakfast according to 2006 Diabetes Treatment Algorithm (1). Medication was started at the lower dose recommended by manufacturer and the dose was increased to the maximum tolerated at monthly intervals guided by SMBG. Another class of glucose lowering medication was added after the maximum dose was reached. HbA1c was also performed each 3-4 months to further adjust the diabetes medications. The last 2-3 months (stabilization period) of the study were used to observe if the participants had stabilized the HbA1c levels after the treatment modifications performed during the intervention period. During study period, patients received standard medical care in the primary care unit for intercurrences or other concomitant illness.

Study endpoints were the change in HbA1c after the intervention and the proportion of patients reaching and/or maintaining a HbA1c < 7% during a one-year follow-up. Sample was calculated taking in account a 0.5% reduction in the HbA1c with 1.5% SD.

Results are expressed as mean±SD, median (P25-P75) or number of cases (%). Comparisons were performed by Student's t test, Mann-Whitney U test or Chi-square test. Multivariate logistical analyses were performed in order to evaluate the factors associated with HbA1c >7% (dependent variable). Independent variables were selected based on their significance on univariate analyses and/or biological relevance. P values <0.05 (two-sided) were considered statistically significant. SPSS 15.0 (Chicago, IL, USA) was used. These

protocol was approved by the Ethics Committee of the Hospital de Clínicas de Porto Alegre and all patients provided written informed consent. This trial is registered in the Clinical Trials Protocol Registration System ID 06260.

Results

A total of 116 patients agreed to participate in the study, but 26 did not complete the trial [withdrawal of consent (n=3), follow-up lost (n=16), death (n=2), stroke with significant sequelae (n=1), and cancer (n=4)]. These participants did not differ from those who completed the trial regarding age, diabetes duration, proportion of females, ethnicity, and baseline HbA1c. Ninety patients (age: 62.7±10.4 years, females: 57.8%, whites: 78.9%, diabetes duration: 8.2±9.1 years, BMI: 29.8±4.9 kg/m^2, systolic blood pressure: 144.3±22.7 mmHg) completed the trial **(Table 1)**.

At enrollment, 10 (11%) patients were treated with diet, 30 (33%) with metformin alone, 3 (3%) with sulphonylurea alone, 28 (31%) with metformin and sulphonylurea combined, and 19 (21%) were on insulin (4 on insulin alone). During the intervention period, the number of oral agents employed rose (1.50±0.74 vs. 1.67±0.7; p=0.015), as well as the number of oral agents tablets (2.64±1.89 vs. 3.33±2.23 pills/patient; p <0.001). Several patients started insulin use, increasing the number of patients on insulin from 19 (21%) to 31 (34%) (p <0.01). There was also a significant increment in insulin dosage (0.20±0.29 vs.0.50±0.36 UI/kg/day; p=0.008) in patients on insulin since baseline, but no episode of severe hypoglycemia was reported. At baseline, mean HbA1c was 7.2±1.6%, and no change was observed during the follow-up (7.30±1.48%; p=0.453; Figure 1A). The number of patients with HbA1c within target values was 48 (53.3%) at baseline and 44 (48.9%) at the end of the study (p=0.655). No individual factor could predict final

HbA1c≥7%, except for age at diabetes onset (OR: 0.963; 95%CI 0.930–0.997; p=0.033) and insulin use at baseline (OR: 3.412; 95%CI 1.110–10.491; p=0.032).

Based on the mean of two initial HbA1c tests (baseline and end of run-in) patients were divided into two groups: HbA1c<7% (n=55, 61%) and HbA1c ≥7% (n=35, 39%). No differences regarding age, gender, diabetes duration, and BMI were seen between the two groups. Patients with HbA1c<7% had a significant increase in HbA1c (6.30±0.43 vs. 6.71±0.90%; p=0.002) during the study period, while those with HbA1c≥7% did not show changes (8.6±1.5% vs. 8.3±1.7%; p=0.64) (Figure 1B). At the end of the study, 39 (71%) out of 55 patients persisted with HbA1c <7% , and of the group with HbA1c≥7% at baseline, only 7 (20%) of 35 reached this goal.

Conclusions

In this sample of patients with type 2 diabetes attending a primary care unit, the recommendation of lifestyle changes and the intensification of treatment with traditional antihyperglycemic agents were not enough to decrease or maintain HbA1c to ADA/EASD goals. Its recognized that most therapies failure to control blood glucose as monotherapy as time goes by (3,4) and addition of more antihyperglycemic agents including insulin are able to reach HbA1c goal in approximately 50% of the patients (5,6). In our study, only 16% of the patients reached HbA1c <7% notwithstanding the increase in dosage and number of antihyperglycemic agents.

It should be noted that this cohort of patients was relatively well controlled (mean HbA1c 7.2%; 6.1–7.9%). It was surprising since in the last diabetes surveillance study in Brazil, median HbA1c was 8.1% (7). Baseline HbA1c might be a determinant of glucose

response to anti-hyperglycemic therapies (8,9), and a small reduction in HbA1c could be expected in this sample. Even so, a small increase in HbA1c in patients with HbA1c <7% was observed, whereas no improvement was found in those with higher HbA1c levels at baseline.

A limitation of this study is the absence of control group. In a French study with a similar standardized diabetes care, no improvement was observed in the interventional group along the trial (7.5±1.8 vs. 7.2±1.5; p=0.1) but a deterioration occurred in the control group, resulting in a difference of -0.87% between groups at the end of the trial (10). Recently ADA/EASD published a new patient center strategy to treat diabetes. This new protocol still uses the same principles applied to conduct this study (11). Based on the recent evidences about HbA1c targets (12, 13), even though HbA1c lower than 7% is not reached in all patients, in a more conservative HbA1c perspective it may be possible to obtain HbA1c around 7% with medications available in the Brazilian Public Health System.

In conclusion, the implementation of ADA/EASD 2006/2009 guidelines was not able to prevent deterioration in glycemic control of type 2 diabetic patients with an HbA1c ~7% at baseline, and the goal of <7% was reached in a small proportion of patient. Revision of anti-hyperglycemic treatment strategies, perhaps employing a more aggressive life-style intensification strategy (13) and/or including new classes of antidiabetic agents, is needed in order to guarantee an adequate blood glucose control in patients with type 2 diabetes.

Declaration of Competing Interesting: Nothing to declare

Author Contributions: LVV researched data and wrote manuscript. MFG, EPPCR and JKB

researched data. CBL, RF and JLG reviewed/edited the manuscript and contributed to discussion.

References

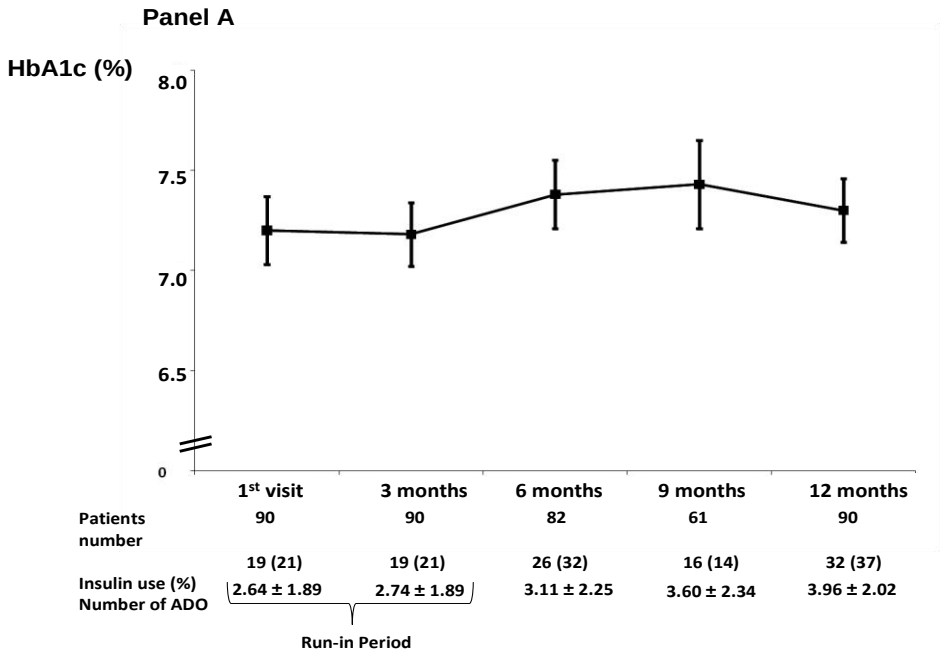
1. Nathan DM, Buse JB, Davison MB, Heine RJ, Holman RR, Sherwin R, Zinman B. Management of Hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy. Diabetes Care 2006; 49:1963 – 1972
2. Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, Zinman B. Management of Hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy. Diabetes Care 2009; 32:193-203
3. Turner RC, Cull CA, Frighi V, Holman RR. Glycemic Control with Diet, Sulfonylurea, Metformin, or Insulin in Patients with Type 2 Diabetes: Progressive Requirement for Multiple Therapies (UKPDS 49). JAMA 1999; 21: 2005-12
4. Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, et al. Glycemic Durability of Rosiglitazone, Metformin, or Glyburide Monotherapy. N Eng J Med 2006; 23: 2427-43
5. Riddle MC, Rosenstock J, Gerich J. The treat-to-target trial: Randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. Diabetes Care 2003; 26:3080–3086.
6. Bailey CJ, Kodack M. Patient adherence to medication requirements for therapy of type 2 diabetes. Int J Clin Pract 2011;65: 314-322
7. Viana LV. Tese de Doutorado: Controle Glicêmico de Pacientes com Diabetes Tipo 2 nas Cinco Regiões do Brasil e Análise de efetividade de um programa de controle da glicemia E da hipertensão arterial sistêmica na rede pública. Universidade Federal do Rio Grande do Sul, 2012.

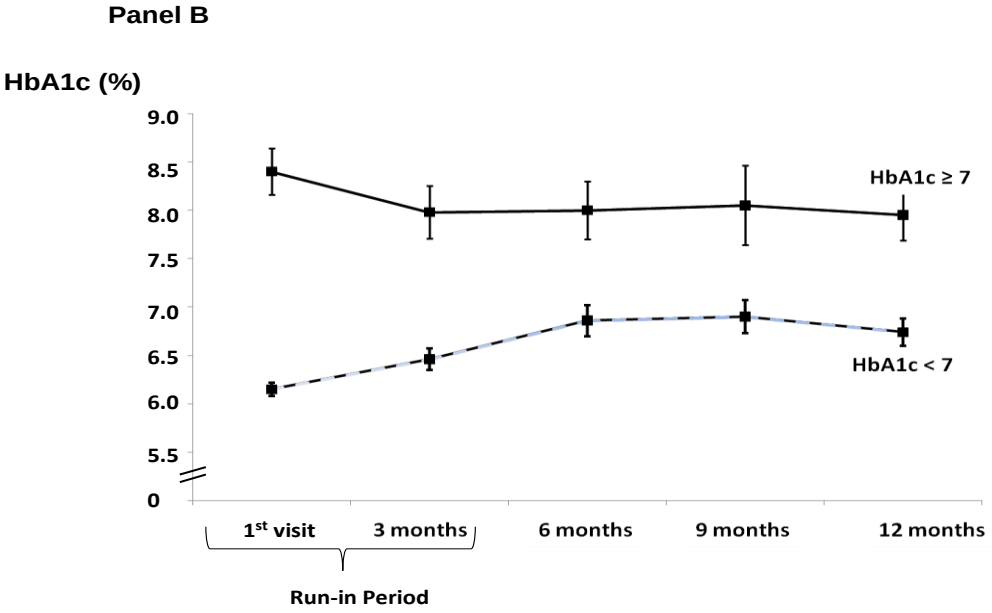
8. Monnier L, Lapinski H, Collete C. Contributions of fasting and post-prandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients. Diabetes Care 2003; 26: 881-5
9. Sherifali D, Nerenberg K, Pullenayegum E, Cheng JE, Gerstein HC. The Effect of Oral Antidiabetic Agents on A1c Levels. Diabetes Care 2010; 8: 1859-64
10. Varroud-Vial M, Simon D, Attali J, Durand-Zaleski I, Bera L, Attali C, et al. Improving glycemic control of patient with type 2 diabetes in primary care setting: a French application of the Staged Diabetes Management programme. Diabetic Medicine 2004; 21: 592-8
11. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach: Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2012 Jun;35(6):1364-79.
12. Currie CJ, Peters JR, Tynan A, Evans M, Heine RJ, Bracco OL, et al. Survival as a function of HbA(1c) in people with type 2 diabetes: a retrospective cohort study. Lancet. 2010 Feb 6;375(9713):481-9.
13. Del Prato S. Megatrials in type 2 diabetes. From excitement to frustration? Diabetologia. 2009 Jul;52(7):1219-26.
14. Coppell KJ, Katoaka M, Williams SM, Chisholm AW, Vorgers SM, Mann JI. Nutritional intervention in patients with type 2 diabetes who are hyperglycemic despite optimized drug treatment – Lifestyle Over and Above Drugs in Diabtes (LOADD) study: randomized controlled trial. BMJ 2010;341:c3337

Table 1. Baseline clinical and laboratory characteristics of type 2 diabetic patients included in the study

Baseline	
N	90
Age (years)	62.7 ± 10.4
White ethnicity	71 (78.9%)
Female sex	52 (57.8%)
Diabetes duration (years)	8.2 ± 9.1
Primary care unit attendance (years)	2.1 ± 2.5
Previous cardiovascular event	21 (23.3%)
Current Smoking	13 (14.4%)
Hypertension	79 (89.8%)
SBP (mmHg)	144.3 ± 22.7
DBP (mmHg)	79.4 ± 10.7
BMI (kg/m^2)	29.8 ± 4.9
Using statin	45 (50%)
Using aspirin	55 (61.1%)
Microalbuminuria	20 (23.8%)
Treatment Type	
Diet only	10 (11.1%)
One oral agent	33 (36.6%)
Metformin	30
Glybenclamide	3

Two oral agents	28 (31.1%)
Insulin use	19 (21.1%)
NPH alone	4
NPH + Metformin	14
NPH + Glybenclamide	0
NPH + Metformin + Glybenclamide	1
Total cholesterol (mg/dl)	179.1 ± 41.2
HDL cholesterol (mg/dl)	47.5 ± 11.8
Triglycerides (mg/dl)	153 (109.0 -216.5)
LDL cholesterol (mg/dl)	94.9 ± 33.0
HbA1c (%)	7.2 ± 1.6


Panel A
HbA1c (%)
8.0
7.5
7.0
6.5
0
1st visit
3 months
6 months
9 months
12 months
Patients number
90
90
82
61
90
Insulin use (%)
19 (21)
19 (21)
26 (32)
16 (14)
32 (37)
Number of ADO
2.64 ± 1.89
2.74 ± 1.89
3.11 ± 2.25
3.60 ± 2.34
3.96 ± 2.02
Run-in Period


Panel B
HbA1c (%)
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
0
HbA1c ≥ 7
HbA1c < 7
1st visit
3 months
6 months
9 months
12 months
Run-in Period

Legend Figure 1 – HbA1c values during the study: Panel A – General view of the HbA1c in the 90 patients and medication prescribed during the study. Panel B – HbA1c ≥7% and HbA1c <7% behavior throughout the study.

HYPERTENSION MANAGEMENT ALGORITHM FOR TYPE 2 DIABETIC PATIENTS APPLIED IN PRIMARY CARE

Luciana V. Viana

Cristiane B. Leitão

Maria de Fátima Grillo

Ennio P. C. da Costa Rocha

Juliana Brenner

Rogério Friedman

Jorge L. Gross

Endocrine Division and Primary Care Unit of Hospital de Clinicas de Porto Alegre and Federal University of Rio Grande do Sul, Porto Alegre, Brazil.

Corresponding author:

Jorge L. Gross, MD

Endocrine Division - Hospital de Clínicas de Porto Alegre

Rua Ramiro Barcelos, 2350 – Prédio 12 – 4° andar.

90035-003 – Porto Alegre, RS – Brazil

Phone/Fax : +55 51 3332-5188/3330-9100

E-mail: jorgeluizgross@gmail.com

Word count: 2052

Number of figures 1

Table: 1

Este artigo será enviado para publicação no American Journal of Hypertension

Abstract (349)

Aim: Hypertension frequently coexist with type 2 diabetes, and patients with this combination are at higher risk of cardiovascular outcomes. The aim of this study was to analyze if it is possible to obtain and maintain blood pressure (BP) goals (ADA/ JNC 7) with an aggressive BP lowering strategy, based on a stepwise active BP algorithm using the medication supplied by Brazilian Government (HiperDia System).

Methods: A one-year, single-arm interventional study was conducted with type 2 diabetes patients. Intervention consisted of intensification of lifestyle changes and sequential prescription of drugs: diuretic (hydrochlorothiazide); angiotensin converting enzyme (ACE) inhibitors (captopril or enalapril); β-adrenergic blocking agent (propranolol) and calcium channel blocking agent (amlopidine) if BP was >130/80 mmHg in order to reach ADA/ JNC 7 goals.

Results: A total of 107 patients with diabetes and hypertension were included in the study (age 62.6 ± 11.2 years; white 82.2%; females 64.5%; hypertension duration 10.7 ±10.4 years). Mean systolic BP (SBP) and diastolic BP (DBP) were 145.3 ± 21.6 mmHg and 79.0 ± 11.4 mmHg, respectively, and BP lower than 130/80 mmHg was observed in 16 (15%) patients at baseline. Seventy-eight patients completed the trial. From baseline to the end of run-in, both SBP and DBP decreased (145.0±22.8 vs. 138.8±21.2 mmHg; p=0.002 and 79.4±11.5 vs. 76.5 ±10.9; p=0.026). During the intervention period, the number of anti-hypertension agents tablets rose (3.6±3.5 vs. 5.9±3.5 pills/patient; p <0.001), as the number of antihypertensive classes increased (1.8±1.0 vs. 2.70±1.2; p<0.01) and the overall drop of BP was 11 mm Hg for SBP (145.0±22.8 vs. 133.7±20.9 mmHg; p<0.01) and 5 mmHg for DBP (78.7±11.5 vs. 73.7±10.5 mmHg; p=0.001). Although the number of patients with BP

values lower than 130/80mmHg almost doubled from the first visit to the end of the study [14 (18.7%) vs. 30 (38.5%) p = 0.008], less than 40% of the patients achieved the proposed goals.

Conclusions: A BP algorithm applied to type 2 diabetic and hypertensive patients is able to lower BP, however more than half of the patients did not achieved the ADA/JNC 7 targets, demonstrating the complexity of BP control in this population.

Key words: type 2 diabetes; hypertension; JNC 7; ADA guidelines; 'real life'.

Introduction:

Type 2 diabetes and hypertension frequently coexist, and patients with this combination are at higher risk for cardiovascular events (1). United Kingdom Prospective Diabetes Study (UKPDS) conclude that tight blood pressure (BP) control in patients with type 2 diabetes and hypertension is able to reduce micro and macrovascular diabetic complications (2). However, strict BP control in this population, as advised by The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7) and American Diabetes Association (ADA), aiming a BP lower than 130/80 mmHg, is difficult to obtain and multiple medications are often required (3,4,5).

In Brazil, hypertension was present in 81% of the patients with diabetes participating in the HiperDia System - a program developed to provide antihypertensive and antidiabetic medication in the primary care units around the country (6). The aim of this study was to analyze if it is possible to obtain and maintain BP goals (ADA/ JNC 7) with an aggressive BP lowering strategy, based on a stepwise active BP algorithm using the medication supplied by Brazilian Government (HiperDia System).

Patients and Methods

Consecutive adult (more than 18 years-old) patients with type 2 diabetes attending regularly a primary care unit in the previous 6 months before the screening visit were invited to participate in the study. Exclusion criteria were: history of active infection (eg. osteomyelitis, pulmonary tuberculosis, AIDS), chronic corticosteroids use, unstable angina or myocardial infarction in the last 3 months, advanced renal disease – defined as dialysis

procedures, heart failure (New York Heart Association class III and IV), cirrhosis, alcohol or illicit drug use, dementia, actual pregnancy or lactation, current cancer or any disease that might affect survival in the next 5 years.

At baseline, patients underwent an evaluation consisting of anamnesis and physical examination. Patients were considered as current smokers or non-smokers. Ethnic definition was self-classified as white or non-white. Previous medical history was evaluated clinically. Cerebrovascular disease was established in the presence of a history of stroke and/or compatible findings (sequelae). The diagnosis of heart disease was based on previous history of myocardial infarction, angina or heart failure and when available myocardial scintigraphy and coronary angiography. Body mass index (BMI) was calculated [weight (kg)/ height^2 (m)].

Blood pressure (BP) was measured twice each visit in the sitting position after 10 minutes rest with OMRON Automatic Blood Pressure Monitor HEM- 720. Hypertension was defined as blood pressure levels ≥140/90 mmHg or use of anti-hypertensive drugs. The protocol was approved by the Ethics Committee of the Hospital de Clínicas de Porto Alegre and all patients provided written informed consent.

Study Design and Interventions

This one-year, open-label, non-controlled, single-arm interventional study was conducted at a primary care unit located in the metropolitan area of the city of Porto Alegre, nearby the Hospital de Clínicas de Porto Alegre, a University Hospital and reference center.

The study comprised 3 stages: a run-in (3 months), drug intervention period (6 months) and stabilization period (2-3 months) and was conducted by an endocrinologist

(LVV) and a generalist nurse (MFG). During the run-in period patients were advised to maintain a healthy diet, to exercise and to take all the medications prescribed by their primary care physicians. Patients visited the primary care unit monthly and received reinforcements about diet, exercise and adherence to medication already in use. During the intervention period, participants visited the center at monthly intervals to check weight, BP and glucose. The goal was to obtain systolic and diastolic BP ≤130/80 mmHg. If the mean systolic or diastolic BP values were higher than 130/80 mmHg, medications were added following this sequence: diuretic (hydrochlorothiazide); angiotensin converting enzyme (ACE) inhibitors (captopril or enalapril); β-adrenergic blocking agent (propranolol) and calcium channel blocking agent (amlopidine). These drugs are provided by the Brazilian health care system. The patients requiring more than four anti-hypertensive medications used hydralazine and/or clonidine (not available in the primary care unit). Medication was started with the lower dose recommended by manufacturer, with increments to the maximum tolerated dose at monthly intervals guided by BP measurements. Another class of antihypertensive drug was added after the maximum tolerated dose was reached. During study period, patients received standard medical care in the primary care unit for intercurrences or other concomitant illness.

Endpoints

Study endpoints were the change in systolic and diastolic BP after the intervention and the proportion of patients reaching and/or maintaining a BP ≤130/80 mmHg during the one-year follow-up.

Laboratory Methods

Fasting plasma glucose was measured by the glucose oxidase ultraviolet (UV) enzymatic method. Total cholesterol, HDL and triglycerides were measured by enzymatic

methods. Low-density lipoprotein cholesterol (LDL) was calculated using the Friedewald equation. Serum creatinine was measured by a kinetic alkaline picrate Jaffe reaction and converted to the standardized Jaffe Roche (CREA), traceable method, by linear regression equation (traceable Jaffe creatinine = – 0.236 + 1.061 × non-compensated Jaffe creatinine). Urinary albumin was measured in duplicate by immunoturbidimetric method (Microalb; Ames-Bayer, Tarrytown NY). Microalbuminuria was defined by a random spot urine sample higher than 17 mg/l (9,10). All chemistry parameters were analyzed in a Modular P (Roche® (Basel, Switzerland). The HbA1c test measurements (%) were performed by HPLC.

Statistical analysis

Results are expressed as mean ± SD, median (P25-P75) or number of cases with the characteristic (%). Comparisons were performed by Student's t test, Mann-Whitney U test or Chi-square test, as appropriate. Paired t-test was used to compare BP variation before and after the intervention. P values <0.05 (two-sided) were considered to be statistically significant. SPSS 18.0 - Professional Statistics™ (SPSS Inc., Chicago, IL, USA) was used.

Results:

Baseline Characteristics:

The original cohort comprised 116 diabetic patients and 107 (92%) had the diagnosis of hypertension. Mean hypertension duration was 10.7 ±10.4 years. The baseline characteristics of the hypertensive patients are shown in Table 1. Most patients were white (82.2%), 9 (8.4%) patients were current smokers, and the mean BMI was 30.2 ± 5.9 kg/m^2. At enrollment, diabetes treatment was diet alone in 11 patients, one oral agent in 46, two oral agents in 42, and three medications in 8; insulin was used in 23 (4 patients on insulin

alone). Forty four percent the patients were on statins and mean LDL was 100.6 ± 28.4 mg/dl. Twenty one patients (19.2%) had a previous cardiovascular event (stroke n=4; ischemic heart disease n=17; heart failure n=3; lower limb amputation n=1) and 25 patients (23.4%) were microalbuminuric. Mean systolic BP (SBP) and diastolic BP (DBP) were 145.3 ± 21.6 mmHg and 79.0 ± 11.4 mmHg, respectively, and BP lower than 130/80 mmHg was observed in 16 (15%) patients in the first visit. Hypertension medication previously prescribed by the primary care physician was as follows: no medication in 11 (10.3%) patients; one agent in 28 (26.2%); two agents in 46 (43%); three agents in 16 (15%) and four agents in 6 (5.5%) (69 patients on diuretics, 76 on ACE inhibitor, 36 on beta-blocker agent and 15 patients were using calcium channel blocking agents).

Follow-up results:

Of the 107 hypertensive patients that agreed to participate in the study, 29 (27%) were lost to follow-up and were not included in the final analysis [withdrawal of consent form (n=3), lost to follow up (n=19), death (n=2), stroke with important physical limitation (n=1), and cancer (n=4)]. Therefore, the results of the 78 patients (73%) that completed the trial are presented bellow. There was no difference between missing patients and those who completed the follow-up regarding age, sex, duration of hypertension and diabetes, and BP levels.

From baseline to the end of run-in period there was a significant reduction in both systolic (145.0±22.8 vs. 138.8±21.2 mmHg; p=0.002) and diastolic BP (79.4±11.5 vs. 76.5 ±10.9; p=0.026) yet no increase in the number of pills taken in this first part of the study was observed (3.4±3.5 vs. 3.8±3.5; p=0.137). In the intervention period, the number of anti-hypertension agents tablets rose (3.6±3.5 vs. 5.9±3.5 pills/patient; p <0.001), as the number

of antihypertensive classes increased (1.8±1.0 vs. 2.70±1.2; p<0.01). During this period, a further decline in SBP and DBP was observed and the overall drop of BP was 11 mm Hg for SBP (145.0±22.8 vs. 133.7±20.9 mmHg; p<0.01) and 5 mmHg for DBP (78.7±11.5 vs. 73.7±10.5 mmHg; p=0.001); the number of patients with BP values lower than 130/80mmHg almost doubled [14 (18.7%) vs. 30 (38.5%) p = 0.008] from the first visit to the end of the study. During the stabilization period there was neither decline in BP nor increase in medication taken.

In order to identify baseline characteristics associated with better responses to the intervention, patients were stratified based on BP values at the end of the study. No differences regarding age, gender, and hypertension duration were seen between patients reaching BP goals, with the exception of a higher SBP at baseline in those with BP higher than 130 mmHg at the end of the study.

Conclusion:

In this cohort of type 2 diabetic and hypertensive patients, mean initial BP was 145/79 mmHg and only 15% of patients had BP levels at ADA/ JNC 7 targets. Along this one year study, the number of patients in the goal increased to 39%, with a mean drop of 11 mmHg in the SBP and 5 mmHg in DBP. The end-of-study BP was ~134/ 74 mmHg in the expense of an important increase in the number of pills taken by these patients. Noteworthy less than half the study participants ended the follow-up with a BP <130/80 mmHg.

Our baseline data is in agreement with previous results from a cross-sectional study preformed on an outpatient diabetes clinic from an University Hospital of Porto Alegre, were 83% of the treated patients had BP levels above ADA goals (5). A survey of NCHS examined hypertension management in diabetic patients and demonstrated that 66% of the

diabetic patients visiting outpatient clinics had BP higher than the goals, with a mean BP of 139/78 mmHg; despite the use of antihypertensive agents in 71% of patients with nearly half involving prescription of 2 or more hypertensive medications (9).

Therapeutic inertia is an important factor contributing to persistent elevated BP among these patients. In a cross-sectional study, researchers from Colorado found that more than 60% of type 2 diabetic patients were out of hypertension goals and action to lower BP were taken only in 35% of the cases (10). In our study, an aggressive BP lowering strategy, consisting in monthly evaluations and forced medication titration, doubled the number of patients with BP below the target. Two other strategies were tested in recent published trials to control BP in diabetic population (11, 12).The addition of a pharmacist and a nurse management of cardiovascular risk in primary care resulted in BP reductions similar to those observed in the present study (11, 12).

Another important factor that could contribute to the low number of patients on target is patient´s non-adherence to lifestyle modification strategies. The decrease in BP observed in the run-in period probably reflects an improvement in patient's adherence to behavior modification reinforcements (lifestyle intervention) in the first 3 months of the study. Although, there was no significant weight loss along the study despite reinforcements about diet and exercise at each consultation. Modifying diabetic patients diet is another important way to reduce BP. DASH diet applied to diabetic population was able to reduce both systolic BP and diastolic blood pressure (-13.6 ± 3.5mmHg; -9.5 ± 2.6mmHg, respectively) (13).

Recently, BP targets in patients with diabetes and hypertension have been debated (14,15), since only one intervention study testing different BP goals was able to lower patients BP levels to ADA/JNC 7 recommendations (16). In this scenario, a less strict blood

pressure control (BP <140/80mmHg) may be considered a more adequate target. Even when analyzed from this perspective, only 31% of our patients were initially well controlled and after the study intervention this number increased to 54%, leaving 46% of the patients at higher risk for diabetic complications.

In conclusion, a BP algorithm applied to type 2 diabetic and hypertensive patients is able to lower BP, however more than half of the patients did not achieved the ADA/JNC 7 targets, demonstrating the complexity of BP control in this population. Revision of anti-hypertensive treatment strategies, perhaps employing a more aggressive life-style intensification strategy and/or including new classes of agents, is needed in order to guarantee an adequate BP control in patients with type 2 diabetes.

References:

1. Mancia G. The association of hypertension and diabetes: prevalence, cardiovascular risk and protection by blood pressure reduction. Acta Diabetol 42:S17-S25, 2005.
2. UK Prospective Diabetes Study Group. Tight blood pressure control and the risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 317;703-713,1998.
3. Chobanian AV, Bakris GL, Black HR et al. The Seventh Report of the Joint Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. JAMA 289: 2560-72, 2003.
4. American Diabetes Association: Standards of medical care in diabetes, 2010. Diabetes Care 34:S11-S61, 2010.
5. Pinto LC, Ricardo DE, Leitão CB et al. Control Inadecuado de la Presion Arterial en Pacientes con Diabetes Melito tipo 2. Arq Bras Cardiol 94: 633-637, 2010.
6. Ferreira CLRA, Ferreira MG. Características epidemiológicas de pacientes diabéticos da rede pública de saúde: análise a partir do sistema HiperDia. Arq Bras Endocrinol Metab 53/1, 2009.
7. Zelmanovitz T, Gross JL, Oliveira JR, Paggi A, Tatsch M, Azevedo MJ. The receiver operating characteristics curve in the evaluation of a random urine specimen as a screening test for diabetic nephropathy. Diabetes Care 20:516-519, 1997.

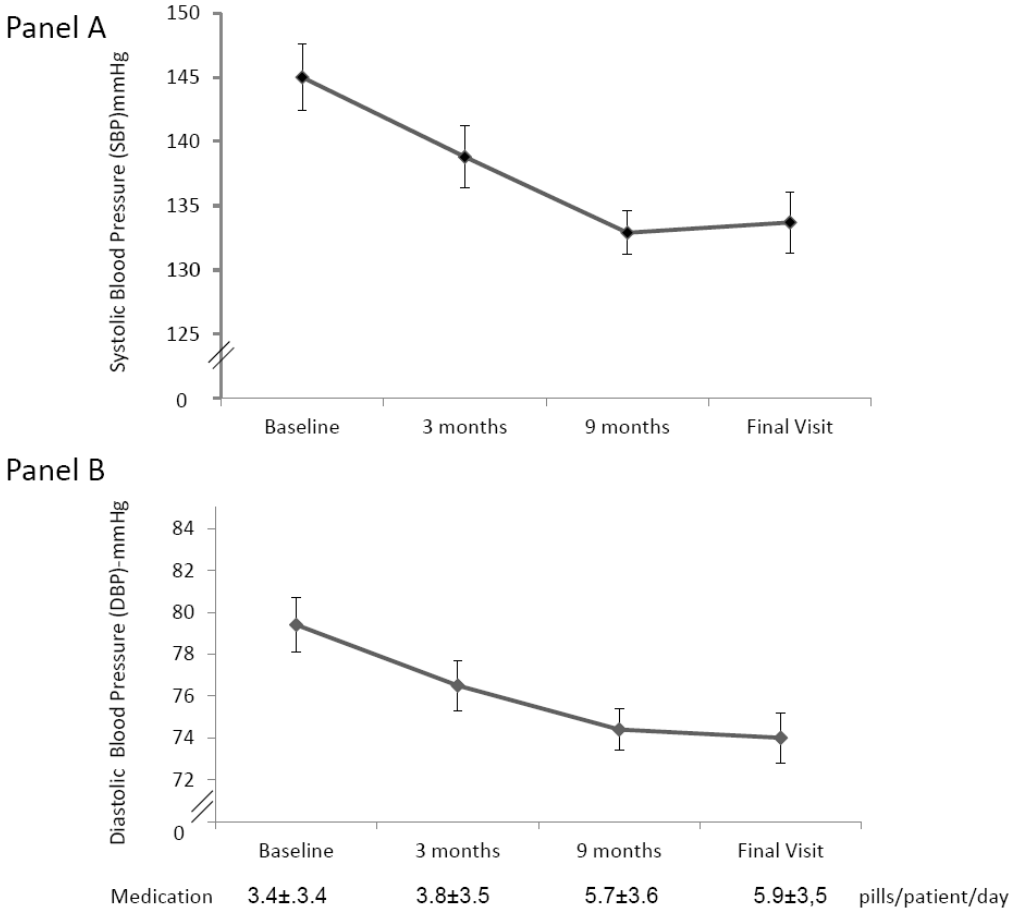
8. Sociedade Brasileira de Diabetes. Diretrizes da Sociedade Brasileira de Diabetes 2009.
9. Aparasu RR, Aparasu A. Hypertension management in outpatient visit by diabetic patients. Research in Social and Administrative Pharmacy4: 284-291, 2008.
10. Hicks PC, Westfall JM, Van Vorst RC et al. Action or Inaction? Decision Making in Patients with Diabetes and Elevated Blood Pressure in Primary Care. Diabetes Care 29: 2580-2585, 2006.
11. Simpson SH, Majumdar SR, Tsuyuki RT et al. Effect of adding pharmacists to primary care teams on blood pressure control in patients with type 2 diabetes: a randomized controlled trial. Diabetes Care 34(1):20-6, 2011.
12. Ishani A, Greer N, Taylor BC et al. Effect of Nurse Case Management Compared With Usual Care on Controlling Cardiovascular Risk Factors in Patients With Diabetes: A randomized controlled trial. Diabetes Care. 2011.
13. Azadbakht L, Fard NR, Karimi M et al. Effects of the Dietary Approaches to Stop Hypertension (DASH) eating plan on cardiovascular risks among type 2 diabetic patients: a randomized crossover clinical trial. Diabetes Care 34(1):55-7, 2011
14. MaciaG, Grassi G, Zanchetti A. Antihypertensive Treatment and Blood Pressure in Diabetic and Nondiabetic Patients. Diabetes Care 34 S304 – S307, 2011.
15. Grossman E. Blood Pressure: The Lower, the Better. Diabetes Care 34 S308 – S312, 2011
16. The ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med 362(17):1575–1582, 2010

Table 1. Baseline clinical and laboratory characteristics 107 hypertensive type 2 diabetic patients

Baseline	
N	107
Age (years)	62.6 ± 11.2
White ethnicity – n (%)	88 (82.2%)
Female sex– n (%)	69 (64.5%)
Diabetes duration (years)	8.3 ± 9.2
Primary care unit attendance (years)	2.3 ± 2.7
Previous cardiovascular event – n (%)	21 (19.2%)
Current Smoking – n (%)	9 (8.4%)
SBP (mmHg)	145.3 ± 21.6
DBP (mmHg)	79.0 ± 11.4
BMI (kg/m^2)	30.2 ± 5.9
Using statin – n (%)	47 (44%)
Using aspirin– n (%)	66 (61.8%)
Microalbuminuria– n (%)	25 (23.4%)
Diabetes Treatment - n (%)	
Diet only	11 (10.3%)
One agent	46 (43%)
Two agents	42(39.2)
Three agents	8 (7.5%)
Insulin use	23 (21.5%)

Hypertension Treatment	
No drugs	11 (10.3%)
One agent	28 (26.2%)
Two agents	46 (43%)
Three agents	16 (15%)
Four agents	6 (5.5%)
Diuretic	69
ACE inhibitor	76
B-blocker	36
Calcium channel blocking	15
Total cholesterol (mg/dl)	179.9 ± 39.7
HDL cholesterol (mg/dl)	48.0 ± 11.3
Triglycerides (mg/dl)	152 (107.3 -368.7)
LDL cholesterol (mg/dl)	100.6 ± 28.4
HbA1c (%)	7.3 ± 1.6

Data are mean ± SD, number of patients with the characteristic (%).



Legend Figure 1 –Blood Pressure decrease and Medication Tablets increase along the study: Panel A – Systolic Blood Pressure (mean±SE); Panel B – Diastolic Blood Pressure (mean ±SE).

CONSIDERAÇÕES FINAIS

O tratamento do diabetes, nos seus aspectos de controle glicêmico e pressórico, é um desafio na prática diária, tanto pelas características heterogêneas dos pacientes com DM tipo 2, quanto por fatores geopolíticos particularmente relevantes no Brasil. De fato, a observação realizada mostra a existência de variações regionais no controle glicêmico (HbA1c: Norte 9±2% vs Centro-Oeste: 8±2%) provavelmente relacionadas não apenas a diversidade socioeconômica e étnica da população brasileira, mas também às diferentes políticas de saúde adotadas em cada estado para o tratamento da doença.

Embora as medicações estejam disponíveis universalmente em todo o país, a facilidade de acesso dos pacientes ao tratamento medicamentoso e aos profissionais da saúde capacitados certamente é diferente. Além disso, as leis regionais para distribuição de insumos terapêuticos tampouco são iguais. O Distrito Federal, por exemplo, possui, desde 1994, uma lei que garante a distribuição de tiras reagentes, seringas e adoçantes aos pacientes cadastrados em seu programa de tratamento para diabetes. Por outro lado, em outras regiões, a conscientização dos pacientes quanto à necessidade de realizar consultas e exames de controle parece ser limitada, o que se verificou pela dificuldade em fazer com que pacientes da região Norte comparecessem as coleta de sangue agendadas.

Os centros de referência e universitários também parecem apresentar um controle glicêmico menos efetivo quando comparado ao controle na Unidade Básica de Saúde (UBS) estudada (média controle no Brasil: 8.6±2.2% vs controle UBS: 7,2±1,6%), refletindo a maior gravidade dos pacientes encaminhados ao serviço terciário. Nesta UBS, atrelada a um hospital universitário, o controle glicêmico prévio a qualquer intervenção

encontrava-se ao redor de 7%; contudo, apesar dos esforços empregados, houve uma deterioração progressiva do controle glicêmico ao longo do tempo.

Face aos novos paradigmas de controle glicêmico e ao possível aumento de mortalidade relacionado às tentativas de controle mais estrito da glicose, é possível se chegar a um controle glicêmico razoável com as medicações disponíveis pelo SUS (média final HbA1c: 7.30±1.48%), embora as metas das sociedades internacionais não sejam alcançadas. O mesmo se dá em relação ao controle pressórico: embora o alvo não tenha sido atingido, a média da pressão arterial foi de 134/79 mmHg ao final do estudo.

A intensificação do tratamento do paciente diabético em postos de saúde diminuiria a necessidade de encaminhamento a centros terciários e, no longo prazo, o melhor controle pressórico e glicêmico poderia se refletir na diminuição das complicações crônicas do diabetes. Para o grupo de pacientes que não atingiram os alvos, a disponibilização de novas drogas, visando um tratamento mais individualizado do diabetes, surge como uma opção e necessita ser avaliada através de análises de custo-benefício. Estratégias de educação poderiam ser aplicadas, especialmente na região Norte e Nordeste do pais e a grupos étnicos minoritários, uma vez que, em estudos prévios, se mostraram bastante eficazes na obtenção de um melhor controle glicêmico com redução significativa na HbA1c.

Em resumo, o controle glicêmico no Brasil esta muito aquém das metas estabelecidas pela America Diabetes Association (ADA). É imprescindível a busca pela implantação de modelos de tratamento do DM nas regiões com pior controle metabólico, possivelmente espelhado nas regiões com maior sucesso no tratamento da doença. Recursos financeiros e de pessoal qualificado devem ser destinado ao tratamento do diabetes tipo 2 no Norte e Nordeste do país. Além disso, a replicação do protocolo de tratamento do

diabetes e hipertensão nas unidades básicas de saúde, aplicada fora do contexto acadêmico, surge como uma alternativa no âmbito de saúde pública.

APÊNDICE

Effect of Antihyperglycemic Agents Added to Metformin and a Sulfonylurea on Glycemic Control and Weight Gain in Type 2 Diabetes: A Network Meta-analysis

Jorge L. Gross, MD, PhD; Caroline K. Kramer, MD, PhD; Cristiane B. Leitão, MD, PhD; Neil Hawkins; Luciana V. Viana, MD, PhD; Beatriz D. Schaan, MD, PhD; Lana C. Pinto, MD; Ticiana C. Rodrigues, MD, PhD; and Mirela J. Azevedo, MD, PhD, for the Diabetes and Endocrinology Meta-analysis Group (DEMA)*

Background: Few studies have examined the effect of adding a third antihyperglycemic drug when blood glucose control is not achieved by using metformin and a sulfonylurea.

Purpose: To compare the efficacy of add-on antihyperglycemic drugs in patients with type 2 diabetes that is not controlled with metformin and a sulfonylurea.

Data Sources: MEDLINE, EMBASE, Cochrane Library, LILACS, and ClinicalTrials.gov electronic databases.

Study Selection: Randomized trials at least 24 weeks in duration. Studies evaluated the effects of adding a third antihyperglycemic drug to treatment of adults aged 18 years or older with type 2 diabetes and a hemoglobin A_{1c} (HbA_{1c}) level greater than 7.0% who were already receiving a combination of metformin and a sulfonylurea.

Data Extraction: Primary end points were change in HbA_{1c} level, change in weight, and frequency of severe hypoglycemia.

Data Synthesis: Eighteen trials involving 4535 participants that lasted a mean of 31.3 weeks (24 to 52 weeks) were included. Compared with placebo, drug classes did not differ in effect on HbA_{1c} level (reduction ranging from −0.70% [95% credible interval {CrI}, −1.33% to −0.08%] for acarbose to −1.08% [CrI, −1.41% to −0.77%] for insulin). Weight increase was seen with insulins (2.84 kg [CrI, 1.76 to 3.90 kg]) and thiazolidinediones (4.25 kg [CrI, 2.76 to 5.66 kg]), and weight loss was seen with glucagon-like peptide-1 agonists (−1.63 kg [CrI, −2.71 to −0.60 kg]). Insulins caused twice the absolute number of severe hypoglycemic episodes than noninsulin antihyperglycemic agents.

Limitations: Most of the trials were short term, and trial quality varied. With so few trials relative to antihyperglycemic agents, investigators relied on indirect comparisons, which increased the uncertainty of the findings and conclusions.

Conclusion: There is no clear difference in benefit between drug classes when adding a third agent to treatment of patients with type 2 diabetes who are already receiving metformin and a sulfonylurea. The most appropriate option should depend on each patient's clinical characteristics.

Primary Funding Source: Conselho Nacional de Desenvolvimento Científico e Tecnológico and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior.

Ann Intern Med. 2011;154:672-679. www.annals.org

For author affiliations, see end of text.

* Group members are listed in **Appendix 1** (available at www.annals.org).

There is consensus that lifestyle changes and metformin should be first-line treatment of patients with type 2 diabetes (1). However, 55% to 70% of patients who initially achieve their glycemic targets with metformin therapy have a progressive deterioration of glucose control in 2 to 3 years (2). Sulfonylureas are a commonly used second medication (3) on the basis of efficacy (4), availability, and cost (5). However, adding a sulfonylurea to metformin therapy usually does not maintain long-term control, and deterioration develops in as early as 6 months (6). Options for third agents include insulin, α-glucosidase inhibitors (acarbose), thiazolidinediones, glucagon-like peptide-1 (GLP-1) agonists, and dipeptidyl peptidase-4 inhibitors (5, 7).

We report the findings of a meta-analysis to assess the comparative efficacy of these drug classes in the reduction of hemoglobin A_{1c} (HbA_{1c}) level, change in body weight, and the frequency of severe hypoglycemic events when added as a third agent to the treatment of patients with uncontrolled type 2 diabetes who are already receiving metformin and a sulfonylurea. We did a conventional meta-analysis, but because the number of randomized trials directly comparing antihyperglycemic agents is limited, we also used indirect comparisons and network meta-analysis.

See also:

Print
Editors' Notes 673

Web-Only
Appendixes
Appendix Table
Appendix Figures
CME quiz
Conversion of graphics into slides

METHODS

The review protocol was registered at the Conselho Nacional de Desenvolvimento Científico e Tecnológico Web site (www.cnpq.br).

Identification of Trials

We searched MEDLINE, EMBASE, Cochrane Library, LILACS, and ClinicalTrials.gov from 1950 to De-

cember 2010 by using the Medical Subject Heading terms *type 2 diabetes*, *noninsulin antihyperglycemic agents* and *insulins*, and by using a validated filter (8) to identify randomized, controlled trials reporting the effect on HbA_{1c} level of adding a third noninsulin antihyperglycemic agent or insulin to metformin and sulfonylurea in patients with type 2 diabetes. The MEDLINE search strategy is detailed in **Appendix 2** (available at www.annals.org). All potentially eligible trials were considered for review, regardless of the primary outcome or language. A manual search was also done by using references of key articles published in English. The data of 1 study identified in ClinicalTrials.gov (but not published) obtained directly from the authors.

Studies were considered eligible for inclusion if they were conducted in adults aged 18 years or older with type 2 diabetes and an HbA_{1c} level greater than 7.0% while receiving metformin (≥1000 mg/d or maximum tolerated dose) and a sulfonylurea (≥50% of the maximum labeled dose) for at least 3 months before the screening visit, compared the effects of adding a third noninsulin antihyperglycemic agent or insulin to another agent or placebo in patients who were already receiving metformin and a sulfonylurea, had at least 24 weeks of follow-up, and reported changes in HbA_{1c} level and weight and numbers of patients with severe hypoglycemic reactions as defined by the investigator or as reactions requiring third-party assistance or blood glucose levels of 1.9 mmol/L (35 mg/dL) or less. Insulins were considered as a class and included human as well as analogue insulins. Studies comparing 2 formulations of insulins as a third agent in both groups were excluded.

Study Selection, Data Extraction, and Quality Assessment

Two independent investigators reviewed study titles and abstracts, and studies that satisfied the inclusion criteria were retrieved for full-text evaluation. Trials selected for detailed analysis and data extraction were analyzed by 2 investigators with an agreement value (κ) of 98%; disagreements were resolved by a third investigator.

We extracted data on the first author's name; year of trial publication; participant number, age, and sex; trial duration; drug class of the third antihyperglycemic agent added; change in HbA_{1c} level (mean [SD]); change in body weight; and number of severe hypoglycemic reactions. Two independent and blinded reviewers evaluated risk for bias according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) recommendations (9).

Data Synthesis and Analysis

Direct Meta-analysis

We analyzed HbA_{1c} level and weight as continuous variables and reported absolute differences between arithmetic means before and after interventions. We reported the absolute number of severe hypoglycemic episodes because the occurrence of 0 events in both groups of some studies precluded the calculation of an overall odds ratio (10).

We used the Cochran Q test to evaluate heterogeneity between studies and considered a threshold P value less than 0.1 as statistically significant. We also did I^2 testing to evaluate the magnitude of the heterogeneity between studies (11). We calculated pooled estimates of the mean differences in HbA_{1c} level and weight between intervention groups by using a random-effects model (DerSimonian–Laird method) to adequately account for the additional uncertainty associated with study–study variability in the effect of different agents. We used random-effects meta-regression analyses to assess whether diabetes duration, baseline HbA_{1c} level, baseline body mass index (BMI), and industry funding were potential sources of heterogeneity by using the restricted maximum likelihood estimator. We chose variables on the basis of previous data (12, 13) or biological relevance before the meta-analysis was undertaken. We assessed the possibility of publication bias by using a funnel plot of each trial's effect size against the SE. We evaluated funnel plot asymmetry by using Begg and Egger tests and defined significant publication bias as a P value less than 0.1 (14). The direct meta-analysis was done by using Stata statistical software, version 11.0 (StataCorp, College Station, Texas).

Network Meta-analysis

We also used network meta-analyses because no trials compared the effect of all antihyperglycemic agents used as a third drug with each other. This approach makes use of direct comparisons from existing trials comparing 2 treat-

Context

Metformin and sulfonylureas are inexpensive, first-line therapies for type 2 diabetes but are often insufficient to control blood glucose levels.

Contribution

This analysis of 18 trials found that all other available drugs decreased hemoglobin A_{1c} levels about equally when added to metformin and a sulfonylurea, without any clear between-drug differences. Insulin was associated with more weight gain and hypoglycemia.

Caution

Most trials were short, trial quality varied, and many comparisons of effect were indirect.

Implication

Available evidence suggests no clear differences in benefit between drugs when adding a third agent to metformin and a sulfonylurea. The choice should be based on patient preferences and characteristics.

—The Editors

ment strategies and indirect comparisons constructed from 2 trials that have at least 1 treatment in common (15). This statistical tool preserves the within-trial, randomized comparison of each study. Network analyses were conducted by using a Bayesian Markov-chain Monte Carlo method and fitted in the freely available Bayesian software WinBUGS (Medical Research Council Biostatistics Unit, Cambridge, United Kingdom; www.mrc-bsu.cam.ac.uk/bugs). Results are expressed as mean differences with 95% credible intervals (CrIs) (the Bayesian equivalent of CIs). The estimated uncertainties in the ranking of treatments were calculated directly from the simulated posterior distribution generated by using the Markov-chain Monte Carlo analysis. The WinBUGS code is available from the authors on request.

Role of the Funding Source

The study was supported by Conselho Nacional de Desenvolvimento Científico e Tecnológico and the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior Projeto Nacional de Pós-Doutorado no País. The funding sources had no role in the study design, data collection, data analyses, data interpretation, or writing of the report. The corresponding author had full access to all of the data in the study and was responsible for making the final decision to submit the manuscript for publication.

RESULTS

Literature Search Results and Study Characteristics

We identified 23 921 studies through electronic searches and 42 through manual searches (**Appendix Figure 1**, available at www.annals.org). Of these, 23 843 were excluded on the basis of the title and abstract, leaving 120 studies for further evaluation. Eighteen studies fulfilled our inclusion criteria, providing data on 4535 participants (16–32). We obtained data directly from the authors for 1 unpublished trial. Because another trial compared 2 classes of noninsulin antihyperglycemic agents with placebo, 19 sets of comparisons were available for analyses.

Table 1 summarizes the randomized, controlled trials. The trials were published from 1998 to 2009 and varied in sample size. Trial duration ranged from 24 to 52 weeks (mean, 31.3 weeks). The 4535 patients had a mean baseline HbA_{1c} level of 8.8% (7.5% to 10.6%), a mean baseline BMI of 28.8 kg/m^2 (24.0 kg/m^2 to 34.2 kg/m^2), and diabetes duration of 8.9 years (8.1 to 13.6 years). Nine reports compared active drugs (noninsulin antihyperglycemic agents or insulins) with placebo, and 10 trials compared noninsulin antihyperglycemic agents with insulins.

The **Appendix Table** (available at www.annals.org) shows the risk for bias in the trials. Nine studies reported adequate randomization, 0 were stopped early, and 15 did not specify whether data collectors and outcome assessors were blinded to study data. There was no evidence of publication bias when HbA_{1c} level was used as an outcome (**Appendix Figure 2**, available at www.annals.org).

Direct Meta-analysis

All classes of antihyperglycemic agents were associated with statistically significant reductions in HbA_{1c} level compared with placebo. In a pooled analysis (9 trials), the addition of a third agent led to a mean reduction of −0.96% (95% CI, −1.11% to −0.81%) in HbA_{1c} level (**Table 2**), with statistically significant between-study heterogeneity ($I^2 = 63.7\%$; $P = 0.005$). Change in HbA_{1c} level was seen with each antihyperglycemic class, varying from −0.60% (CI, −1.16% to −0.04%) for acarbose to −1.15% (CI, −1.35% to −0.95%) for thiazolidinediones. In meta-regression analysis, baseline HbA_{1c} level, diabetes duration, and baseline BMI were not associated with a change in HbA_{1c} level ($P = 0.19$).

In a pooled analysis of trials comparing noninsulin antihyperglycemic agents with insulin (10 trials), treatment with noninsulin antihyperglycemic agents led to a mean 0.29% increase in HbA_{1c} level (CI, 0.06% to 0.51%) compared with insulins, with statistically significant between-study heterogeneity ($I^2 = 73.4\%$; $P < 0.001$). In meta-regression analysis, baseline HbA_{1c} level, diabetes duration, baseline BMI, and industry funding were not associated with a change in HbA_{1c} level ($P = 0.08$).

Weight change varied by drug class. Compared with placebo, insulin led to a statistically significant increase in weight (2.31 kg [CI, 0.13 to 4.48 kg]), whereas acarbose led to a statistically significant decrease in weight (−0.96 kg [CI, −1.80 to −0.12 kg]) (**Table 2**). Compared with insulins, thiazolidinediones were associated with weight increase (1.67 kg [CI, 0.98 to 2.36 kg]), and GLP-1 agonists led to a weight decrease (−4.99 kg [CI, −5.80 to −4.18 kg]).

We could not meta-analyze the frequency of hypoglycemic episodes because severe hypoglycemia was not reported in either study group in several trials. As expected, insulins doubled the risk for severe hypoglycemic episodes when compared with noninsulin antihyperglycemic agents (**Table 2**).

Network Meta-analysis

Figure 1 shows the network of comparisons, and **Table 3** estimates HbA_{1c} level and weight change for each comparison. The change in HbA_{1c} level ranged from −0.7% (95% CrI, −1.33% to −0.08%) for acarbose to −1.08% (CrI, −1.41% to −0.77%) for insulin compared with placebo. There were no statistically significant differences between agents in pairwise comparisons. Weight loss was statistically significant for GLP-1 agonists compared with placebo (−1.63 kg [CrI, −2.71 to −0.06 kg]) and for acarbose compared with insulin (−3.79 kg [CrI, −5.91 to −1.88 kg]) and thiazolidinediones (−5.21 kg [CrI, −7.53 to −2.98 kg]). Weight gain was statistically significant for insulin compared with placebo and GLP-1 agonists and for thiazolidinediones compared with placebo, GLP-1 agonists, and insulin.

Table 1. **Summary of Randomized, Controlled Trials of Antihyperglycemic Drugs Added as a Third Agent in the Treatment of Patients With Type 2 Diabetes Who Are Receiving Metformin and a Sulfonylurea**

Study, Year (Reference), by Drug Type	Follow-up, *wk*	Group	Patients, *n*	Mean Age (SD), *y*	Men, %	Mean Diabetes Duration (SD), *y*	Mean Baseline HbA_{1c} Level (SD), %	Mean Baseline BMI (SD), *kg/m²*	Mean Change in HbA_{1c} Level (SD), %	Mean Change in Weight (SD), *kg*	Severe Hypoglycemia, *n*
Acarbose											
Lam et al, 1998 (16)	24	Placebo	40	56.9 (1.3)	56.8	10.1 (0.8)	9.4 (0.1)	24.1 (0.4)	0.1 (1.3)	0.4 (1.8)	0
		Acarbose	41	57.8 (1.3)	55.5	10.1 (0.7)	9.5 (0.1)	24.8 (0.5)	−0.5 (1.3)	−0.5 (2.0)	1
Ko et al, 2001 (17)	52	NPH insulin	30	59.1 (12.5)	30.0	13.3 (6.1)	10.0 (0.8)	24.9 (3.4)	−1.7 (1.3)	NA	NA
		Acarbose	27	58.5 (9.9)	37.0	9.7 (6.2)	10.6 (1.7)	24.3 (3.8)	−1.5 (1.8)	NA	NA
Thiazolidinediones											
Yale et al, 2001 (18)	24	Placebo	99	60 (0.9)	58.0	10.8 (0.6)	9.7 (0.1)	30.0 (0.4)	0 (1.0)	−0.1 (15.2)	0
		Troglitazone	101	58 (0.9)	55.0	11.9 (0.8)	9.6 (0.1)	30.1 (0.5)	−1.4 (2.0)	2.3 (14.0)	0
Dailey et al, 2004 (19)	24	Placebo	184	57 (10)	61.0	9.0 (6.0)	8.1 (0.8)	32.0 (5.0)	0.1 (1.0)	0.1	0
		Rosiglitazone	181	57 (9)	58.0	9.0 (7.0)	8.1 (0.9)	32.0 (5.0)	−0.9 (1.2)	3.0	0
Kadoglou et al, 2008 (28)	26	Placebo	35	66.7 (9.6)	45.7	7.5 (5.9)	8.0 (0.8)	29.9 (4.3)	0.3 (0.6)	NA	NA
		Rosiglitazone	35	63.8 (7.3)	40.0	8.5 (4.6)	8.2 (1.2)	29.5 (3.8)	−0.9 (0.4)	NA	NA
Ko et al, 2006 (22)	48	NPH insulin	56	59.8 (11.2)	42.9	13.6 (7.5)	9.6 (0.9)	24.0 (2.7)	−1.3 (1.7)	NA	0
		Rosiglitazone	56	56.6 (10.7)	57.1	11.8 (7.7)	10.1 (1.0)	25.3 (3.8)	−1.1 (1.6)	NA	0
Rosenstock et al, 2006 (23)	24	Glargine insulin	104	55.9 (10.5)	45.0	8.5 (5.8)	8.8 (1.0)	34.6 (7.0)	−1.7 (0.9)	1.7 (4.0)	3
		Rosiglitazone	112	55.3 (11.4)	58.0	8.1 (5.1)	8.7 (1.0)	33.6 (6.3)	−1.5 (0.9)	3.0 (4.2)	6
Reynolds et al, 2007 (26)	24	Glargine insulin	20	NA	NA	NA	8.9 (0.9)	32.4 (5.3)	−1.4 (1.3)	0.9 (1.0)	0
		Rosiglitazone	20	NA	NA	NA	9.1 (0.9)	30.7 (5.1)	−1.5 (1.4)	3.2 (2.2)	0
Dorkhan et al, 2008 (27)	26	Glargine insulin	19	61.9 (7.7)	68.4	9.5 (6.8)	8.2 (1.3)	31.4 (5.7)	−2.2 (1.5)	2.4 (20.0)	0
		Pioglitazone	17	60.8 (7.1)	76.4	11.5 (6.1)	8.1 (1.4)	30.6 (5.3)	−1.3 (1.4)	3.3 (11.9)	0
Hartemann-Heurtier et al, 2009 (31)	24	NPH insulin	13	58 (10)	64.2	12.0 (6.0)	8.6 (0.5)	32.0 (4.0)	−1.6 (0.5)	2.4 (1.7)	0
		Pioglitazone	14	62 (10)	53.8	12.0 (4.5)	8.3 (0.5)	30.0 (5.0)	−1.2 (0.7)	3.7 (3.5)	0
Rosenstock et al*	48	Exubera†	203	54.2 (9.5)	57.6	10.2	9.2 (1.0)	31.3 (4.7)	−1.7 (1.3)	5.0 (18.0)	3
		Rosiglitazone	202	55.0 (9.4)	55.0	10.0	9.0 (1.1)	31.3 (4.5)	−1.5 (1.2)	5.2 (19.0)	0
GLP-1 agonists											
Kendall et al, 2005 (21)	30	Placebo	247	56 (10)	55.9	9.4 (6.2)	8.5 (1.0)	34.0 (5.0)	0.2 (1.6)	−0.9 (3.1)	0
		Exenatide	241	55 (10)	59.3	8.7 (6.4)	8.5 (1.1)	34.0 (6.0)	−0.8 (1.5)	−1.6 (3.1)	0
Heine et al, 2005 (20)	26	Glargine insulin	267	58 (9.5)	56.6	9.2 (5.7)	8.3 (1.0)	31.3 (4.6)	−1.1 (1.6)	1.8 (3.2)	4
		Exenatide	282	59.8 (8.8)	55.0	9.9 (6.0)	8.2 (1.0)	31.4 (4.4)	−1.1 (1.6)	−2.3 (3.3)	4
Nauck et al, 2007 (25)	52	Premixed aspart (30%)	248	58 (9)	51.0	10 (6.2)	8.6 (1.1)	30.2 (4.2)	−0.9 (0.9)	2.9 (3.1)	0
		Exenatide	253	59 (9)	47.0	9.8 (6.3)	8.6 (1.0)	30.6 (4.0)	−1.0 (1.1)	−2.5 (3.2)	0
Bergenstal et al, 2009 (29)	24	Premixed aspart (30%) once daily	124	51.8 (10.9)	48.4	8.4 (6.3)	10.1 (1.8)	33.7 (7.1)	−2.3 (1.5)	2.8 (3.6)	4
		Premixed aspart (30%) twice daily	124	53.4 (9.96)	47.6	9.9 (5.6)	10.3 (1.9)	33.5 (7.4)	−2.8 (1.8)	4.1 (5.4)	6
		Exenatide	124	52.5 (10.62)	48.4	8.6 (5.9)	10.2 (1.5)	34.2 (7.1)	−1.7 (1.6)	−1.9 (3.8)	0
Russell-Jones et al, 2009 (32)	26	Placebo	114	57.5 (9.6)	49.0	9.4 (6.2)	8.3 (0.9)	31.3 (5.0)	−0.2 (1.2)	0.4 (4.2)	0
		Glargine insulin	232	57.5 (10.5)	60.0	9.7 (6.4)	8.2 (0.9)	30.3 (5.3)	−1.1 (1.4)	1.6 (5.0)	0
		Liraglutide	230	57.6 (9.5)	57.0	9.2 (5.8)	8.3 (0.9)	30.4 (5.3)	−1.3 (1.4)	−1.8 (5.0)	5
DPP-4 inhibitors											
Hermansen et al, 2007 (24)	24	Placebo	116	57.7 (8.9)	52.2	10.6 (6.8)	8.3 (0.7)	30.7 (6.2)	0.3 (0.9)	NA	0
		Sitagliptin	113	56.6 (8.8)	52.6	9.3 (5.7)	8.3 (0.7)	31.3 (5.9)	−0.6 (0.8)	NA	0
Insulins											
Blicklé et al, 2009 (30)	36	Lifestyle changes	108	60.7 (8.1)	50.0	10.1 (6.9)	7.5 (0.4)	29.9 (3.4)	−0.2 (0.9)	−2.5 (3.2)	0
		Glargine insulin	103	60.6 (7.7)	55.0	10.0 (6.2)	7.6 (0.7)	30.1 (3.5)	−0.8 (0.7)	0.9 (2.9)	2

BMI = body mass index; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; HbA_{1c} = hemoglobin A_{1c}; NA = not available; NPH = neutral protamine Hagedorn.
* Unpublished report (in preparation).
† Pfizer (New York, New York); no longer on the market.

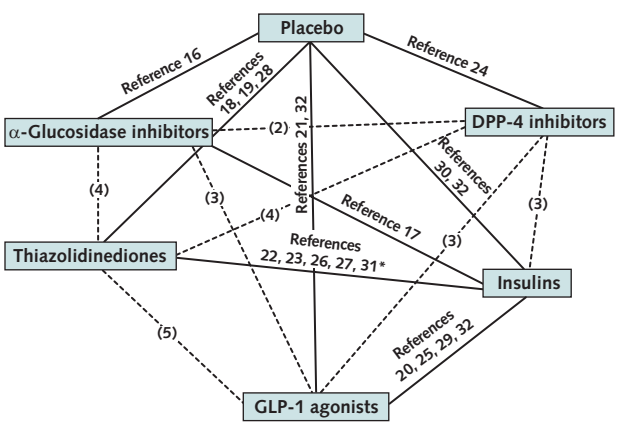
Table 2. **Direct Meta-analysis Comparing Noninsulin Antihyperglycemic Agents or Insulins With Placebo and Noninsulin Antihyperglycemic Agents With Insulins: Effects on Change in HbA_{1c} Level and Weight and Severe Hypoglycemic Episodes**

Reports, *n*	Intervention	Weighted Mean Difference (95% CI) in HbA_{1c} Level, %	Weighted Mean Difference (95% CI) in Weight, *kg*	Severe Hypoglycemic Episodes (Events/Total), *n/n*	
				Intervention	Placebo or Insulin
Noninsulin antihyperglycemic agents or insulins vs. placebo					
9*	All agents	−0.96 (−1.11 to −0.81)	0.37 (−1.46 to 2.20)	8/1233	0/1016
2	Insulin	−0.71 (−0.95 to −0.47)	2.31 (0.13 to 4.48)	2/335	0/222
3†	Thiazolidinediones	−1.15 (−1.35 to −0.95)	2.40 (−1.65 to 6.45)	0/278	0/277
1	Acarbose	−0.60 (−1.16 to −0.04)	−0.96 (−1.80 to −0.12)	1/41	0/40
2	GLP-1 agonists	−1.04 (−1.24 to −0.85)	−1.40 (−2.90 to 0.08)	5/466	0/361
1	DPP-4 inhibitors	−0.89 (−1.11 to −0.67)	NA	0/113	0/116
Noninsulin antihyperglycemic agents vs. insulins					
10‡	All agents	0.29 (0.06 to 0.51)	−1.90 (−3.73 to −0.06)	6/553	15/566
6§	Thiazolidinediones	0.22 (0.07 to 0.37)	1.67 (0.98 to 2.36)	3/415	9/421
1	Acarbose	0.20 (−0.60 to 1.00)	NA	NA	NA
3	GLP-1 agonists	0.10 (−0.28 to 0.42)	−4.99 (−5.80 to −4.18)	3/138	6/145

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; HbA_{1c} = hemoglobin A_{1c}; NA = not available.
* Six studies reported a change in body weight.
† One study reported a change in body weight, and 2 studies reported hypoglycemic episodes.
‡ Nine studies reported a change in body weight.
§ Five studies reported a change in body weight.

Figure 2 summarizes the estimated probability that a given drug class is the next best one to reduce levels of HbA_{1c} (*left*) or to avoid weight gain (*right*), given available trial data.

Figure 1. **Network of clinical trials of antihyperglycemic agents in addition to metformin and a sulfonylurea in patients with type 2 diabetes.**



Solid lines represent direct comparison trials, and dashed lines represent indirect comparisons having placebo as the reference agent. Reference numbers indicate the trials contributing to direct comparisons. The number of studies that contribute for the indirect effect estimates are shown in parentheses. DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1.
* These references also include an unpublished report by Rosenstock and colleagues (in preparation).

DISCUSSION

In this meta-analysis of trials evaluating the effects of adding a third antihyperglycemic agent to metformin and sulfonylurea therapy for patients with type 2 diabetes, we report an overall reduction of HbA_{1c} level of −0.96%, a finding similar to that of a recent network meta-analysis (7) that reported an overall reduction of HbA_{1c} level of −0.62% to −1.00% when a second drug was added to metformin therapy. We found no clear statistically significant differences in the degree of reduction of HbA_{1c} level by drug class in direct and indirect comparisons, also confirming findings from the previous analysis, although it did not evaluate insulin efficacy (7). A similar decrease (−0.5% to −1.25%) was seen in a meta-analysis comparing the effect of adding a single oral antidiabetic agent (GLP-1 agonists and insulins were not evaluated) versus placebo in participants who either were drug-naive or were receiving background therapy with an oral antidiabetic agent with or without insulin (13). Taken together, these findings suggest that addition of a third antihyperglycemic agent provides useful additional glycemic control for patients who are already receiving metformin and a sulfonylurea. The available limited evidence does not clearly identify a preferred antihyperglycemic drug class among drugs represented in clinical trials (thiazolidinediones, GLP-1 agonists, dipeptidyl peptidase-4 inhibitors, insulins, and acarbose). Glucagon-like peptide-1 agonists led to more weight loss than other agents and might be chosen as a third agent on that basis, but they also were associated

Table 3. **Network Meta-analysis Comparing All Noninsulin Antihyperglycemic Agents and Insulins: Mean Changes in HbA_{1c} Level and Weight**

Treatment	Change in HbA_{1c} Level (95% CrI), %					
	Placebo	GLP-1 Agonists	Insulin	Thiazolidinediones	DPP-4 Inhibitors	Acarbose
Placebo	–	–	–	–	–	–
GLP-1 agonists	−1.01 (−1.38 to −0.66)	–	–	–	–	–
Insulin	−1.08 (−1.41 to −0.77)	−0.07 (−0.41 to 0.25)	–	–	–	–
Thiazolidinediones	−0.95 (−1.27 to −0.65)	0.05 (−0.35 to 0.5)	0.12 (−0.16 to 0.41)	–	–	–
DPP-4 inhibitors	−0.94 (−1.58 to −0.36)	0.07 (−0.6 to 0.67)	0.14 (−0.51 to 0.77)	0.01 (−0.67 to 0.69)	–	–
Acarbose	−0.70 (−1.33 to −0.08)	0.31 (−0.4 to 1.03)	0.38 (−0.28 to 1.06)	0.25 (−0.39 to 0.93)	0.24 (−0.56 to 1.13)	–
	Change in Weight (95% CrI), *kg*					
	Placebo	GLP-1 Agonists	Insulin	Thiazolidinediones	DPP-4 Inhibitors	Acarbose
Placebo	–	–	–	–	–	–
GLP-1 agonists	−1.63 (−2.71 to −0.60)	–	–	–	–	–
Insulin	2.84 (1.76 to 3.90)	4.47 (3.71 to 5.26)	–	–	–	–
Thiazolidinediones	4.25 (2.76 to 5.66)	5.89 (4.54 to 7.2)	1.42 (0.29 to 2.55)	–	–	–
DPP-4 inhibitors	NA	NA	NA	NA	–	–
Acarbose	−0.96 (−2.77 to 0.73)	0.67 (−1.37 to 2.63)	−3.79 (−5.91 to −1.88)	−5.21 (−7.53 to −2.98)	NA	–

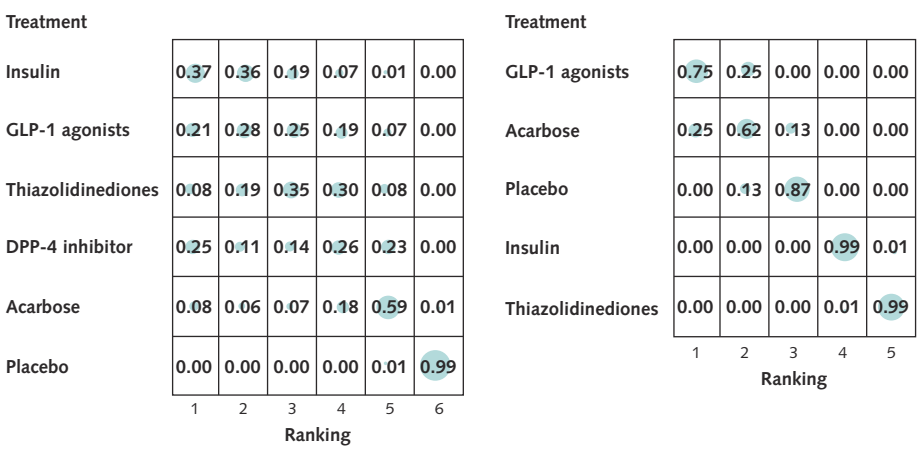
CrI = credible interval; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; HbA_{1c} = hemoglobin A_{1c}; NA = not available.

with more severe hypoglycemic reactions than any other drug class except insulin.

It is common in clinical practice to initiate insulin therapy after failure of therapies of 2 oral antihyperglycemic agents. In direct and network comparisons, insulins did not differ from other drug classes in their ability to decrease HbA_{1c} levels, although the point estimate of effect was slightly greater for insulins in our analysis of trials directly comparing insulins with other drug classes (difference in HbA_{1c}, 0.29% [CI, 0.06% to 0.51%]) (**Table 2**). In network meta-analysis, insulin ranked first in the probability of being the most effective. This apparent lack of superiority of insulin over other agents could be explained by the few trials comparing insulin with other agents (limited statistical power) and by the use of lower doses of insulin (about 20 IU/d) in trials comparing insulin with placebo, which may have contributed to an overall underestimation of the effect of insulin on HbA_{1c} level. Also, insulin-induced weight gain in these trials could have blunted the apparent benefits of the drugs.

There were statistically and clinically significant differences between drug classes in weight changes and incidence of severe hypoglycemia. Patients receiving GLP-1 agonists had the greatest weight reduction, a finding noted in a previous meta-analysis (7). Thiazolidinediones seemed to cause more weight gain (4.25 kg [CrI, 2.76 to 5.66 kg])

Figure 2. **Network meta-analysis of antihyperglycemic agents.**



Green dots account for the estimated probability (the higher the probability, the larger the dot). DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1. **Left.** The estimated probability that each treatment is ranked first, second, or third as the most effective for changing hemoglobin A_{1c} levels. **Right.** The estimated probability that each treatment is ranked first, second, or third as the most effective for avoiding an increase in weight.

than insulins (2.84 kg [CrI, 1.76 to 3.90 kg]), although the findings were not significantly different. Insulin doubled the frequency of severe hypoglycemic episodes. Other adverse events potentially related to the antihyperglycemic agents in this review (bone fracture; pancreatitis; and cardiovascular, gastrointestinal, and renal dysfunction) were not evaluated because of the lack of reporting data in most of the trials included in our meta-analysis.

Our analysis has many limitations. Most of the trials were short term, generally lasting less than 1 year, and none evaluated important clinical outcomes, such as cardiovascular events and death. The quality of trial conduct and reporting varied; only 5 of 18 studies included in the analyses were double-blind, and details of allocation were noted in only 9 of 18 studies, suggesting that other potential biases may have been introduced. Treatment regimens and patient populations varied, and we documented statistical heterogeneity that is unexplained by our meta-regression model, a reflection of unmeasured factors influencing the findings and the many different agents and classes of agents included in the trials.

Perhaps most important, the need to rely on indirect comparisons for most antihyperglycemic agents makes our conclusions tentative, and the fact that so few studies contributed evidence for so many of the indirect comparisons adds uncertainty about the relative effectiveness of these agents. For example, the evidence for the indirect comparison between α-glucosidase inhibitors and dipeptidyl peptidase-4 inhibitors comes from pairing only 2 studies that each used a placebo control as a comparator, whereas the indirect comparison of α-glucosidase inhibitors with thiazolidinediones used data from 1 study comparing α-glucosidase inhibitors with placebo and 3 studies that compare thiazolidinediones with placebo for this estimate. More trials would therefore be required before the indirect evidence about many of the comparisons could be considered robust.

Notwithstanding these important limitations, it is unlikely that the head-to-head trials necessary to address this clinical question will be conducted. There would need to be at least 13 trials to compare all classes of antihyperglycemic agents, and in their absence, our network meta-analysis seems a reasonable tool to ask and attempt to answer the question.

In summary, we conclude that there is no apparent difference in benefit between drug classes in patients with type 2 diabetes who are receiving metformin and a sulfonylurea and require a third antihyperglycemic agent. When choosing a third drug to be added to metformin and sulfonylurea therapy in patients requiring additional glycemic control, the patient's clinical features, such as importance of weight changes and incidence of hypoglycemia, should be taken into account. The most appropriate drug option should be individualized to each patient's clinical characteristics.

From Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil.

Acknowledgment: The authors thank Solomon Klioze and Neville Jackson from Pfizer for providing unpublished data, John Stewart and Maria Isabel Vergani from Sanofi-Aventis for making supplemental data available, and Edison Gonçalves for his technical revision and useful suggestions.

Grant Support: From Conselho Nacional de Desenvolvimento Científico e Tecnológico grant A576627/2008-9 and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior Programa Nacional de Pós-Doutorado no País 03021/09-2.

Potential Conflicts of Interest: Dr. Gross: *Board membership:* Bristol-Myers Squibb, GlaxoSmithKline, Novo Nordisk, Sanofi-Aventis, Eli Lilly; *Payment for development of educational presentations:* Bristol-Myers Squibb, Novo Nordisk, Eli Lilly. Disclosures can also be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M10-2318.

Requests for Single Reprints: Jorge L. Gross, MD, PhD, Division of Endocrinology of Hospital de Clínicas de Porto Alegre, Rua Ramiro Barcelos 2350, Prédio 12, 4th Floor, 90035-003, Porto Alegre-RS, Brazil; e-mail, jorgeluizgross@gmail.com.

Current author addresses and author contributions are available at www.annals.org.

References

1. 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;352:854-65. [PMID: 9742977]

2. **Cook MN, Girman CJ, Stein PP, Alexander CM.** Initial monotherapy with either metformin or sulphonylureas often fails to achieve or maintain current glycaemic goals in patients with type 2 diabetes in UK primary care. Diabet Med. 2007;24:350-8. [PMID: 17335466]

3. **Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, et al; American Diabetes Association.** Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2009;32:193-203. [PMID: 18945920]

4. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998;352:837-53. [PMID: 9742976]

5. **International Diabetes Federation.** Global Guideline for Type 2 Diabetes. Accessed at www.idf.org/node/1285?unode=B7462CCB-3A4C-472C-80E4-710074D74AD3 on 3 April 2011.

6. **Cook MN, Girman CJ, Stein PP, Alexander CM, Holman RR.** Glycemic control continues to deteriorate after sulfonylureas are added to metformin among patients with type 2 diabetes. Diabetes Care. 2005;28:995-1000. [PMID: 15855556]

7. **Phung OJ, Scholle JM, Talwar M, Coleman CI.** Effect of noninsulin antidiabetic drugs added to metformin therapy on glycemic control, weight gain, and hypoglycemia in type 2 diabetes. JAMA. 2010;303:1410-8. [PMID: 20388897]

8. **Robinson KA, Dickersin K.** Development of a highly sensitive search strategy for the retrieval of reports of controlled trials using PubMed. Int J Epidemiol. 2002;31:150-3. [PMID: 11914311]

9. **Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al.** The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med. 2009;151:W65-94. [PMID: 19622512]

10. **Sweeting MJ, Sutton AJ, Lambert PC.** What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. Stat Med.

2004;23:1351-75. [PMID: 15116347]
11. **Higgins JP, Thompson SG.** Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21:1539-58. [PMID: 12111919]
12. **Bekelman JE, Li Y, Gross CP.** Scope and impact of financial conflicts of interest in biomedical research: a systematic review. JAMA. 2003;289:454-65. [PMID: 12533125]
13. **Sherifali D, Nerenberg K, Pullenayegum E, Cheng JE, Gerstein HC.** The effect of oral antidiabetic agents on A1C levels: a systematic review and meta-analysis. Diabetes Care. 2010;33:1859-64. [PMID: 20484130]
14. **Begg CB, Mazumdar M.** Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994;50:1088-101. [PMID: 7786990]
15. **Lu G, Ades AE.** Combination of direct and indirect evidence in mixed treatment comparisons. Stat Med. 2004;23(20):3105-24.
16. **Lam KS, Tiu SC, Tsang MW, Ip TP, Tam SC.** Acarbose in NIDDM patients with poor control on conventional oral agents. A 24-week placebo-controlled study. Diabetes Care. 1998;21:1154-8. [PMID: 9653611]
17. **Ko GT, Tsang CC, Ng CW, Wai HP, Kan EC.** Use of acarbose or bedtime insulin after failure of treatment with conventional oral antidiabetics: a one-year randomised clinical trial. Clin Drug Investig. 2001;21:401-8.
18. **Yale JF, Valiquett TR, Ghazzi MN, Owens-Grillo JK, Whitcomb RW, Foyt HL.** The effect of a thiazolidinedione drug, troglitazone, on glycemia in patients with type 2 diabetes mellitus poorly controlled with sulfonylurea and metformin. A multicenter, randomized, double-blind, placebo-controlled trial. Ann Intern Med. 2001;134:737-45. [PMID: 11329231]
19. **Dailey GE 3rd, Noor MA, Park JS, Bruce S, Fiedorek FT.** Glycemic control with glyburide/metformin tablets in combination with rosiglitazone in patients with type 2 diabetes: a randomized, double-blind trial. Am J Med. 2004;116:223-9. [PMID: 14969649]
20. **Heine RJ, Van Gaal LF, Johns D, Mihm MJ, Widel MH, Brodows RG; GWAA Study Group.** Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: a randomized trial. Ann Intern Med. 2005;143:559-69. [PMID: 16230722]
21. **Kendall DM, Riddle MC, Rosenstock J, Zhuang D, Kim DD, Fineman MS, et al.** Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. Diabetes Care. 2005;28:1083-91. [PMID: 15855571]
22. **Ko GT, Tsang PC, Wai HP, Kan EC, Chan HC.** Rosiglitazone versus bedtime insulin in the treatment of patients with conventional oral antidiabetic drug failure: a 1-year randomized clinical trial. Adv Ther. 2006;23:799-808. [PMID: 17142216]
23. **Rosenstock J, Sugimoto D, Strange P, Stewart JA, Soltes-Rak E, Dailey G.** Triple therapy in type 2 diabetes: insulin glargine or rosiglitazone added to combination therapy of sulfonylurea plus metformin in insulin-naive patients. Diabetes Care. 2006;29:554-9. [PMID: 16505505]
24. **Hermansen K, Kipnes M, Luo E, Fanurik D, Khatami H, Stein P; Sitagliptin Study 035 Group.** Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, in patients with type 2 diabetes mellitus inadequately controlled on glimepiride alone or on glimepiride and metformin. Diabetes Obes Metab. 2007;9:733-45. [PMID: 17593236]
25. **Nauck MA, Duran S, Kim D, Johns D, Northrup J, Festa A, et al.** A comparison of twice-daily exenatide and biphasic insulin aspart in patients with type 2 diabetes who were suboptimally controlled with sulfonylurea and metformin: a non-inferiority study. Diabetologia. 2007;50:259-67. [PMID: 17160407]
26. **Reynolds LR, Kingsley FJ, Karounos DG, Tannock LR.** Differential effects of rosiglitazone and insulin glargine on inflammatory markers, glycemic control, and lipids in type 2 diabetes. Diabetes Res Clin Pract. 2007;77:180-7. [PMID: 17239474]
27. **Dorkhan M, Frid A, Groop L.** Differences in effects of insulin glargine or pioglitazone added to oral anti-diabetic therapy in patients with type 2 diabetes: what to add—insulin glargine or pioglitazone? Diabetes Res Clin Pract. 2008;82:340-5. [PMID: 18926586]
28. **Kadoglou NP, Iliadis F, Angelopoulou N, Perrea D, Liapis CD, Alevizos M.** Beneficial effects of rosiglitazone on novel cardiovascular risk factors in patients with type 2 diabetes mellitus. Diabet Med. 2008;25:333-40. [PMID: 18307460]
29. **Bergenstal R, Lewin A, Bailey T, Chang D, Gylvin T, Roberts V; NovoLog Mix-vs. Exenatide Study Group.** Efficacy and safety of biphasic insulin aspart 70/30 versus exenatide in subjects with type 2 diabetes failing to achieve glycemic control with metformin and a sulfonylurea. Curr Med Res Opin. 2009;25:65-75. [PMID: 19210140]
30. **Blicklé JF, Hancu N, Piletic M, Profozic V, Shestakova M, Dain MP, et al.** Insulin glargine provides greater improvements in glycaemic control vs. intensifying lifestyle management for people with type 2 diabetes treated with OADs and 7-8% A1c levels. The TULIP study. Diabetes Obes Metab. 2009;11:379-86. [PMID: 19087105]
31. **Hartemann-Heurtier A, Halbron M, Golmard JL, Jacqueminet S, Bastard JP, Rouault C, et al.** Effects of bed-time insulin versus pioglitazone on abdominal fat accumulation, inflammation and gene expression in adipose tissue in patients with type 2 diabetes. Diabetes Res Clin Pract. 2009;86:37-43. [PMID: 19683825]
32. **Russell-Jones D, Vaag A, Schmitz O, Sethi BK, Lalic N, Antic S, et al; Liraglutide Effect and Action in Diabetes 5 (LEAD-5) met+SU Study Group.** Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): a randomised controlled trial. Diabetologia. 2009;52:2046-55. [PMID: 19688338]

Current Author Addresses: Drs. Gross, Kramer, Leitão, Viana, Schaan, Pinto, Rodrigues, and Azevedo and Mr. Hawkins: Division of Endocrinology, Hospital de Clínicas de Porto Alegre, Rua Ramiro Barcelos 2350, Prédio 12, 4th Floor, 90035-003, Porto Alegre-RS, Brazil.

Author Contributions: Conception and design: J.L. Gross, C.B. Leitão, M.J. Azevedo.
Analysis and interpretation of the data: J.L. Gross, C.K. Kramer, C.B. Leitão, N. Hawkins.
Drafting of the article: J.L. Gross, C.K. Kramer, C.B. Leitão, M.J. Azevedo.
Critical revision of the article for important intellectual content: J.L. Gross, C.K. Kramer, C.B. Leitão, M.J. Azevedo.
Final approval of the article: J.L. Gross, C.K. Kramer, C.B. Leitão, L.V. Viana, B.D. Schaan, T.C. Rodrigues, M.J. Azevedo.
Provision of study materials or patients: L.C. Pinto.
Statistical expertise: C.K. Kramer, N. Hawkins.
Obtaining of funding: M.J. Azevedo.
Collection and assembly of data: C.B. Leitão, T.C. Rodrigues, L.C. Pinto, L.V. Viana, C.K. Kramer.

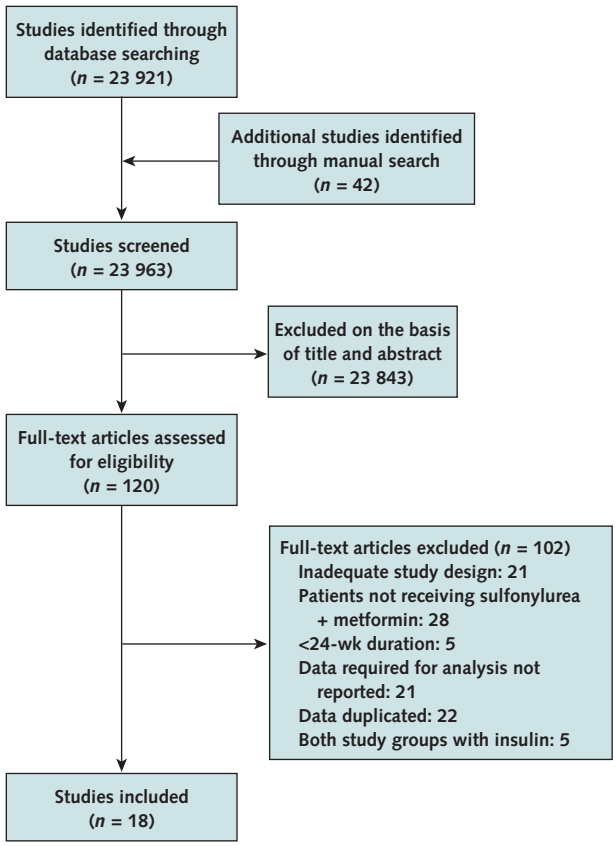
Appendix 1: Diabetes and Endocrinology Meta-analysis Group (DEMA)

Sandra P. Silveiro, MD, PhD; Rogério Friedman, MD, PhD; Luís H. Canani, MD, PhD; Themis Zelmanovitz, MD, PhD; Joíza L. Camargo, BC, PhD; Daisy C. Moreira, PhD; Fernando Gerchman, MD, PhD; Gabriele C. Ghisleni, PhD; Denise Sortica; Alessandra Zucatti; Thais Steemburgo, RD, PhD; João S. Felício, MD; Flávia Santos, MD; Ana R. Motta; Hermelinda C. Pedrosa, MD; Flaviene A. Prado, MD; Leonardo G. Miranda, MD; Monica T. Felix; Antonio R. Chacra, MD, PhD; Ana B. Valverde, MD; Marcelo A. Alvarenga, MD; William R. Komatsu, MD; Deborah L. Jezini, MD; Tatiane P. Oliveira, MD; Adriana C. Forti, MD; Ana L. Leitão Ramos, MD; Mirela C. Miranda; Marília B. Gomes, MD; Carisi A. Polanczyk, MD, PhD; Cristina Neumann, MD, PhD; and Otávio Berwanger, MD, PhD.

Appendix 2: MEDLINE Search Strategy

#1 "Diabetes Mellitus, Type 2"[Mesh] AND #2 ((((“Acarbose”[Mesh] OR “acarbose byproduct, component C” [Substance Name] OR “acarbose 7-phosphotransferase” [Substance Name] OR “acarbose 7-phosphate” [Substance Name])) OR “pramlintide” [Substance Name]) OR “3-hydroxyadamantylglycine-4,5-methanoprolinenitrile” [Substance Name]) OR “alogliptin” [Substance Name] OR ((((((((((((((((((“Metformin”[Mesh] OR “tetrachloro(metformin)platinum(IV)” [Substance Name])) OR “Sulfonylurea Compounds”[Mesh]) OR (“Glyburide”[Mesh] OR “4-transhydroxy glyburide” [Substance Name])) OR (“glimepiride” [Substance Name] OR “hydroxyglimepiride” [Substance Name])) OR (“Tolbutamide”[Mesh] OR “tolbutamide 4-hydroxylase” [Substance Name] OR “carboxytolbutamide” [Substance Name])) OR “Gliclazide”[Mesh]) OR “Chlorpropamide”[Mesh]) OR (“rosiglitazone” [Substance Name] OR “rosiglitazone-metformin combination” [Substance Name])) OR “pioglitazone” [Substance Name]) OR “Thiazolidinediones-”[Mesh]) OR (“troglitazone” [Substance Name] OR “5-(4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl)-2,4-dioxothiazollidine, troglitazone dihydrate” [Substance Name])) OR “exenatide” [Substance Name]) OR “liraglutide” [Substance Name]) OR “vildagliptin” [Substance Name]) OR “sitagliptin” [Substance Name]) OR (“repaglinide” [Substance Name] OR “2-methoxy-4-(3-methyl-1-(2-piperidin-1-ylphenyl)butylcarbamoyl) benzoic acid” [Substance Name])) OR “nateglinide” [Substance Name]) OR “meglitinide” [Substance Name]) OR “Insulin-”[Mesh] AND #3 (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR (“clinical trial”[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR (“latin square”[tw]) OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR follow-up studies[mh] OR prospective studies[mh] OR cross-over studies[mh] OR control*[tw] OR prospectiv*[tw] OR volunteer*[tw]) NOT (animal[mh] NOT human[mh])

Appendix Figure 1. **Summary of evidence search and selection.**

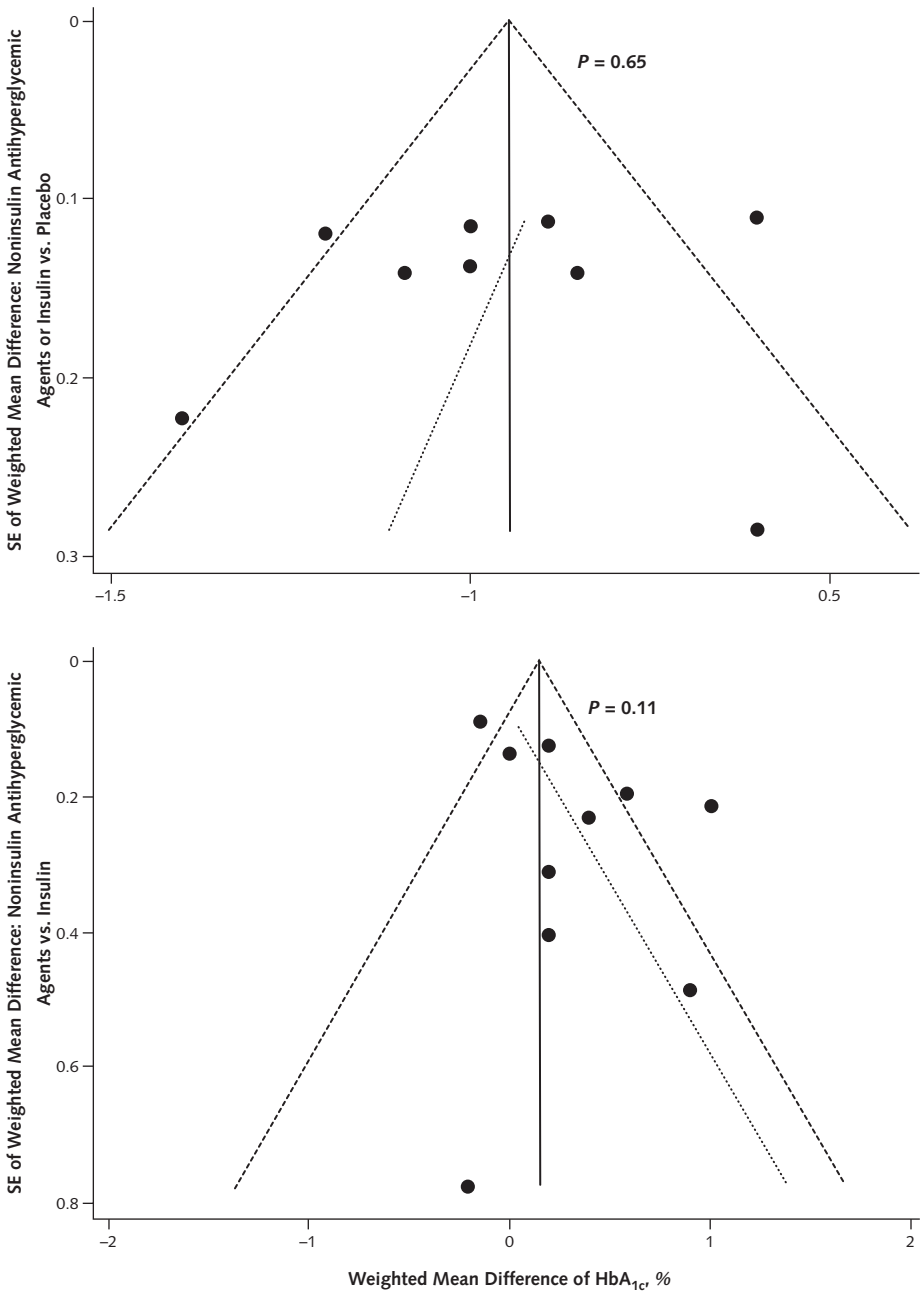


Appendix Table. **Risk for Bias Assessment in Randomized, Clinical Trials**

Study, Year (Reference)	Concealment of Randomization	Stopped Early	Patients Blinded	Health Care Providers Blinded	Data Collectors Blinded	Outcome Assessors Blinded
Lam et al, 1998 (16)	Not informed	No	Yes	Yes	Not informed	Not informed
Ko et al, 2001 (17)	Not informed	No	No	No	Not informed	Not informed
Yale et al, 2001 (18)	Yes	No	Yes	Yes	Yes	Yes
Dailey et al, 2004 (19)	Not informed	No	Yes	Yes	Not informed	Not informed
Heine et al, 2005 (20)	Yes	No	No	No	Not informed	Not informed
Kendall et al, 2005 (21)	Not informed	No	Yes	Yes	Not informed	Not informed
Ko et al, 2006 (22)	Not informed	No	No	No	Not informed	Not informed
Rosenstock et al, 2006 (23)	Not informed	No	No	No	Not informed	Not informed
Hermansen et al, 2007 (24)	Yes	No	Yes	Yes	Not informed	Not informed
Nauck et al, 2007 (25)	Yes	No	No	No	Not informed	Not informed
Reynolds et al, 2007 (26)	Not informed	No	No	No	Not informed	Not informed
Dorkhan et al, 2008 (27)	Not informed	No	No	No	Not informed	Not informed
Kadoglou et al, 2008 (28)	Not informed	No	No	No	Not informed	Not informed
Bergenstal et al, 2009 (29)	Yes	No	No	No	Not informed	Not informed
Blicklé et al, 2009 (30)	Yes	No	No	No	Not informed	Not informed
Hartemann-Heurtier et al, 2009 (31)	Yes	No	No	No	Not informed	Not informed
Russell-Jones et al, 2009 (32)	Yes	No	No	No	No	No
Rosenstock et al*	Yes	No	No	No	No	No

* Unpublished report (in preparation).

Appendix Figure 2. **Funnel plots of change in HbA_{1c} level with Egger regression line.**



HbA_{1c} = hemoglobin A_{1c}.