

Major determinants of myocardial infarction in diabetes

Baseline characteristics of Genetics, Outcomes and Lipids in type 2 Diabetes (GOLD) Study

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Received: 9.26.2006

Revision accepted: 11.06.2006

Abstract

Purpose: The Genetics, Outcomes and Lipids in type 2 Diabetes (GOLD) Study was aimed at identifying risk factors and polymorphisms affecting lipid metabolism related to myocardial infarction (MI) in patients with type 2 diabetes (DM2) and, prospectively, evaluating cardiovascular outcomes in this high-risk population. Here we report its baseline characteristics. In this publication, we present data of the GOLD Study on demography, risk factors and lipids. The genetic studies and the follow-up results will be addressed in future publications. **Methods:** A prospective, centrally coordinated study, evaluated risk factors in 990 consecutive DM2 outpatients with previous MI (n=386) or free of atherosclerosis (n=604), recruited from 27 university centers in 12 states of Brazil. Demography, risk factors and clinical examination were assessed. Twelve-hour fasting blood samples were collected, and shipped to the central laboratory of the Federal University of São Paulo. **Results:** Patients with DM2 presenting MI were older as compared to those without MI (62 ± 0.5 vs 59 ± 0.4 y, $p<0.001$), predominantly males (59 vs. 31%, $p<0.001$), had higher prevalence of current smoking (10 vs. 6%, $p=0.030$), left ventricle hypertrophy (35% vs 20%, $p<0.0001$), longer duration of diabetes (10.0 ± 0.4 vs 8.0 ± 0.3 y, $p=0.001$), lower HDL-cholesterol (35 ± 1 vs 38 ± 1 mg/dL, $p<0.001$), higher triglycerides (248 ± 14 vs 191 ± 6 mg/dL, $p<0.001$), and higher prevalence of metabolic syndrome (92 vs 86 %, $p=0.006$). In multiple logistic regression, male sex tripled, LVH doubled, smoking habit increased the risk of MI 1.8 times, whereas age, duration of diabetes, lower HDL-C and systolic blood pressure were modestly associated with MI ($p<0.05$). **Conclusions:** These aspects suggest a subgroup of diabetic patients at higher coronary risk. If confirmed in prospective studies, special policies to treat these patients may be proposed in the future.

Key words: Type 2 diabetes; Myocardial infarction; Risk factors; Left ventricle hypertrophy; Metabolic syndrome

Introduction

Diabetes mellitus is increasing worldwide and according to the World Health Organization, is likely to reach 366 million by 2030. In addition, the largest proportional and absolute increase will occur in developing countries^{1,2}. Brazil contributed with 4.5 million cases in 2000, considered one of the top ten in the world, and is expected to reach as much as 11.3 million subjects affected by the year 2030³.

According to the American Diabetes Association, cardiovascular disease is the cause of death in as many as 75-80% of subjects with diabetes mellitus⁴. About 90% of diabetes is type 2, initially recognized as adult-onset diabetes, but now emerging at all ages.

Patients with diabetes have a two- to four-fold increase in both cardiovascular mortality and risk of stroke⁴.

The direct cost of diabetes in the United States was US\$132 billion in 2002⁵, suggesting the need of great efforts in primary prevention of CHD, not only regarding the treatments, but also the identification of patients at higher cardiovascular risk.

According to the National Cholesterol Education Program Adult Treatment Panel (NCEP/ATP) III, patients with diabetes mellitus are considered at high coronary risk, independently of additional risk factors⁶. However, those

with metabolic syndrome were associated with the highest prevalence of coronary heart disease (CHD)^{7,8}. In addition, the metabolic syndrome and the aggregation of its components were significantly associated with macro- and microvascular complications in type 2 DM patients⁹, thus contributing to the increased attention to its components as well as the search for other risk factors and genetic alterations related to the occurrence of CHD in subjects with diabetes^{10,11}.

The Genetics, Outcomes and Lipids in type 2 Diabetes (GOLD) Study is a prospective, multicenter study, aimed at evaluating risk factors and genetic polymorphisms related to lipid metabolism and their association with myocardial infarction, cardiovascular death, and the need of hospitalization due to coronary syndromes, among patients with diabetes and previous myocardial infarction or free of atherosclerotic disease at baseline.

We hypothesized that among an unselected cohort of individuals with type 2 diabetes, consecutively evaluated in different regions of Brazil, the prevalence of some risk factors might differ in those with established MI, and by adding genetic study we would improve current stratification in subjects with DM2. The GOLD Study has addressed 9 common polymorphisms that affect lipids, regarding triglyceride-rich lipoprotein metabolism and re-

verse cholesterol transport, which are the main lipid alterations present in the subjects with type 2 diabetes. We assessed the Apo AI (Msp I, M1 and M2 alleles), Apo CIII (Sst I), LPL (D9N), CETP (Taq IB), Apo E (Hha I), PON-1 (Q192R) and two polymorphisms of LCAT (Mwo I and Avr II) in a sample of 1,000 subjects with type 2 diabetes. Follow-up study was scheduled to assess primary cardiovascular (myocardial infarction, coronary death, total mortality), and secondary endpoints (angina, the need for hospitalization due to coronary artery disease, and stroke) in the first five years after enrollment and to be repeated annually during ten years.

This report includes the baseline characteristics of the study population. The genetic studies and the follow-up results will be addressed in future publications.

Patients and methods

Subjects

Between 2001 and 2004, the Genetics, Outcomes and Lipids in type 2 Diabetes Study evaluated a sample of 1,002 subjects with DM2 aged 35-80 years in 27 medical centers of 12 states from five demographic regions of Brazil. Patients were eligible if they had confirmed diagnosis of diabetes mellitus, according to the American Diabetes Association¹². Myocardial infarction (MI) was considered when two of three criteria of the World Health Organization¹³ were present. Subjects with diabetes without any history of prior CHD, peripheral vascular disease or stroke formed the control group. Exclusion criteria included type 1 diabetes, recent major surgery, cerebrovascular or CHD event in the preceding three months. Patients with congestive heart failure (NYHA) classes III or IV, hepatic failure, uncontrolled hypothyroidism, as well as history of neoplasm were excluded. The protocol was in accordance with the Declaration of Helsinki, and was approved by the institution's review board of each center, and by a federal Ethics Committee, which is in agreement with the International Ethical Guidelines for Biomedical Research Involving Human Subjects. All eligible subjects provided written informed consent.

Clinical evaluation

Eligible patients with DM2 were classified according to the presence of prior myocardial infarction (MI group) or absence of CHD and non-coronary atherosclerotic disease (control group). A clinical questionnaire was applied in order to obtain demographic data and physical examination was performed at enrollment. Sitting blood pressure, body weight and height were obtained, and body

mass index was calculated (weight/height²). Clinical follow-up was scheduled to assess primary cardiovascular (myocardial infarction, coronary death, total mortality), and secondary endpoints (angina, the need for hospitalization due to coronary artery disease, and stroke) in the first five years after enrollment and to be repeated annually.

Blood sampling, shipment and laboratory assays

Twelve-hour fasting blood samples were drawn for lipid and genetic studies. The samples were refrigerated and shipped to the Central Laboratory of the Federal University of Sao Paulo for analysis.

Lipid analyses were performed in one single session. Total cholesterol and triglycerides were assayed by enzymatic methods (SERA-PAK, Bayer, Germany), and HDL-cholesterol was measured after removal of apo-B containing particles (Immuno FS, Diasys Diagnostic Systems, Germany) using the ADVIA 1650 (Bayer, Japan) analyzer. LDL-cholesterol was calculated using the Friedewald equation¹⁴, for triglycerides <400 mg/dL. Plasma samples for genetic studies were stored at -80°C for further analysis.

Standard 12-lead electrocardiograms were obtained locally, and sent to the coordinating center, where they were examined in a blinded manner by two independent investigators unaware of the patients' condition. The presence of left ventricle hypertrophy (LVH) was tested by Perugia's criteria¹⁵.

Statistical analysis

Categorical variables were compared by Cramèr's coefficient to minimize the sample size effect. Continuous variables were presented as mean \pm SEM and compared by Student's independent-sample *t* test. For the multiple logistic regression¹⁶, covariates associated with myocardial infarction were included in the equation. The variables included in the final regression model were gender, systolic blood pressure, age, duration of diabetes, smoking habit, HDL-C, and left ventricle hypertrophy. The goodness of fit (Hosmer and Lemeshow test) and residuals were examined. For all analysis a *p* value less than 0.05 was considered significant.

Results

Baseline characteristics, demography and laboratory findings of GOLD population are presented in Table 1. A preponderance of men was observed among patients with myocardial infarction and diabetes as compared to those without MI (59 vs 31%, *p*<0.001), and these individuals were slightly older (62 \pm 0.5 vs 59 \pm 0.4 y, *p*<0.001) and

Table 1. Baseline characteristics of GOLD population and risk factors for CHD and type 2 diabetes.

Characteristics	MI diabetics n=386	Control diabetics n=604	p
Age (y) ¹	62±0.5	59±0.4	<0.001
Men (%) ²	228 (59)	186 (31)	<0.001
Hypertension (%) ²	314 (81)	473 (78)	0.250
Age as risk factor (%) ²	351 (91)	492 (81)	<0.001
Current smokers (%) ²	38 (10)	37 (6)	0.030
BMI (kg/m ²) ¹	28.6±0.3	29.2±0.2	0.020
Obesity (%) ²	129 (33)	226 (37)	0.210
Overweight (%) ²	308 (80)	485 (80)	0.850
Diagnosis of type 2 diabetes (y) ¹	10.0±0.4	8.0±0.3	0.001
Family history of premature CHD (%) ²	112 (29)	153 (25)	0.200
Family history of diabetes mellitus (%) ²	220 (57)	333 (55)	0.560
Blood glucose (mg/dL) ¹	168±4	166±3	0.220
Total cholesterol (mg/dL) ^{1&}	212±4	204±2	0.130
LDL-C (mg/dL) ^{1&}	127±3	130±2	0.710
HDL-C (mg/dL) ^{1&}	35±1	38±1	<0.001
Triglycerides (mg/dL) ^{1&}	248±14	191±6	<0.001
SBP	137±1	140±1	0.022
DBP	82±1	86±1	<0.001
LVH (%) ²	137 (35)	123 (20)	<0.001

Data are presented as mean values ± SEM or percentage of patients.

LVH: left ventricle hypertrophy; ¹For lipid analysis only patients not taking lipid-lowering agents were considered. Obesity and overweight were defined as BMI ≥30 kg/m² and ≥25 kg/m², respectively. LVH was considered according to Perugia's criteria¹⁵.
p<0.05; ¹Student's t test, independent samples; ²Cramèr's coefficient.

Table 2. Distribution of patients according to medications at baseline.

Medications	MI with diabetes n=386 (%)	Controls with diabetes n=604 (%)	p
Metformin	141 (37)	260 (43)	0.042
Sulfonylurea compounds	206 (53)	292 (48)	0.123
Insulin	101 (26)	116 (19)	0.010
Other hypoglycemic agents	25 (6)	22 (4)	0.040
Statins	179 (46)	97 (16)	<0.001
Fibrates	19 (5)	27 (4)	0.742
Diuretics	136 (35)	192 (32)	0.261
Beta-blockers	172 (45)	61 (10)	<0.001
ACE inhibitors	276 (71)	323 (53)	<0.001
Calcium-channel blockers	72 (19)	103 (17)	0.520
AT1-Receptor blockers	8 (2)	15 (2)	0.670

Data are presented as percentage of patients; p<0.05; Cramèr's coefficient.

more frequently smokers than controls (10 vs 6%, p=0.030). Body mass index was lower in patients with MI (28.6±0.3 vs 29.2±0.2 kg/m², p=0.020), however, no differences in the prevalence of obesity or overweight, and

also in hypertension were observed between groups. Patients with MI were diagnosed for the presence of diabetes for a longer period (10.0±0.4 vs 8.0±0.3 y, p=0.001), and presented the risk factor age in a higher pro-

Table 3. Distribution of patients at baseline according to the presence of metabolic syndrome.

Criteria for metabolic syndrome (MS)*	MI diabetics n=381 (%)	Control diabetics n=599 (%)	p
Metabolic syndrome	350 (92)	516 (86)	0.006
3 criteria for MS	105 (30)	178 (35)	
4 criteria for MS	157 (45)	212 (41)	0.360
5 criteria for MS	88 (25)	126 (24)	
Individual criteria			
BMI ≥ 30 kg/m ²	133 (38)	235 (45)	0.028
SBP ≥ 130 or DBP ≥ 85 , or treatment for hypertension	347 (99)	472 (91)	<0.001
Blood glucose ≥ 110 mg/dL or treatment for diabetes	381 (100)	599 (100)	–
HDL-C <40 for men or <50 for women	317 (90)	463 (89)	0.680
Triglycerides ≥ 150 mg/dL	236 (67)	326 (63)	0.130

*For metabolic syndrome 980 patients had data regarding the five criteria. [§]BMI ≥ 30 kg/m² was used as a substitute for waist circumference. Data are presented as percentage of patients; p<0.05; [†]Cramèr's coefficient.

portion than non-MI patients (91 vs 81%, p<0.001). We found a more severe dyslipidemia in those with prior myocardial infarction, with higher triglycerides (248±14 vs 191±6 mg/dL, p<0.001) and lower HDL-C (35±1 vs 38±1 mg/dL, p<0.001) when compared to controls. Blood glucose levels were similar in both groups and showed suboptimal control of this parameter in both groups (172±4 vs 167±3 mg/dL).

Systolic and diastolic blood pressure were lower in patients with MI, compared to non-MI individuals (137±1 vs 140±1, p=0.022, for SBP, and 82±1 vs 86±1, p<0.0001, for DBP). However, patients with MI had a higher prevalence of left ventricle hypertrophy when compared to non-MI patients (35% vs 20%, p<0.0001) (Table 1).

A higher proportion of subjects with MI were treated with insulin (26 vs 19%, p=0.010), ACE inhibitors (71 vs 53%, p<0.0001), and beta-blockers (45 vs 10%, p<0.0001), and a lower proportion was taking metformin (37 vs 43%, p=0.042) (Table 2).

The prevalence of metabolic syndrome (MS) was evaluated, based on the NCEP/ATP III guidelines [7], using body mass index ≥ 30 kg/m² as a substitute for the waist circumference, as previously reported¹⁷ (Table 3).

A higher prevalence of MS was observed among patients with MI and DM2 when compared with non-MI subjects (92 vs 86%, p=0.006), but the number of MS components did not differ. Among the criteria for MS, hypertension was more prevalent in individuals with MI (99 vs 91%, p<0.001), who also presented lower rates of obesity. Gender differences in the number of criteria for MS were seen in patients with DM2 and MI, where females had a higher prevalence of more components than males (Table

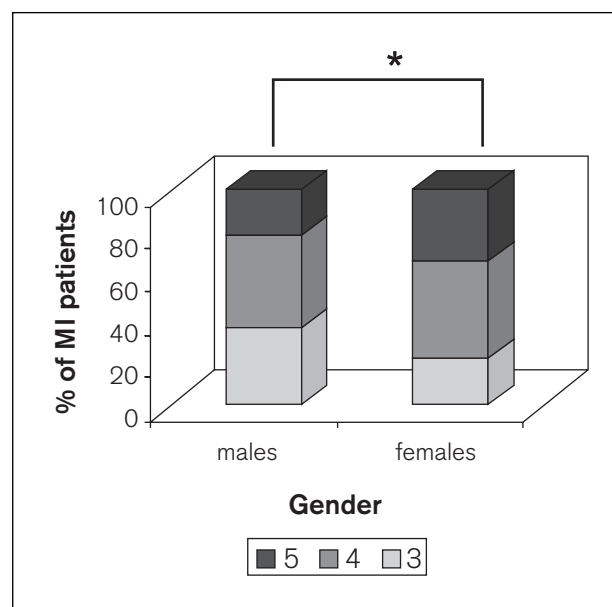


Figure 1. Prevalence of number of criteria for metabolic syndrome according to gender in patients with type 2 diabetes and myocardial infarction.
*p<0.001 (males vs females)

4). Figure 1 shows the inverse relationship between the prevalence of number of criteria for MS and gender.

Cardiovascular risk factors associated with myocardial infarction

Our final model of multiple logistic regression identified the variables independently associated with MI in patients with DM2. Their corresponding odds ratios and 95% CI are shown in Table 5. Myocardial infarction in pa-

Table 4. Gender differences in the prevalence of metabolic syndrome in patients with type 2 diabetes.

Gender	Metabolic syndrome (%)&		p-value
	Men	Women	
Group	N=350	N=516	
MI with diabetes	202 (58)	148 (29)	<0.001
Non-MI with diabetes	148 (42)	368 (71)	
Criteria for MS			
MI with diabetes	N=202	N=148	
3 criteria	73 (36)	32 (22)	0.034
4 criteria	89 (44)	68 (46)	
5 criteria	40 (20)	48 (32)	
Non- MI with diabetes	N=148	N=368	
3 criteria	61 (41)	117 (32)	0.100
4 criteria	49 (33)	163 (44)	
5 criteria	38 (26)	88 (24)	

Data are presented as percentage of patients. ⁸BMI ≥ 30 kg/m² was used as a substitute for waist circumference. MS, metabolic syndrome; p<0.05; Cramèr's coefficient.

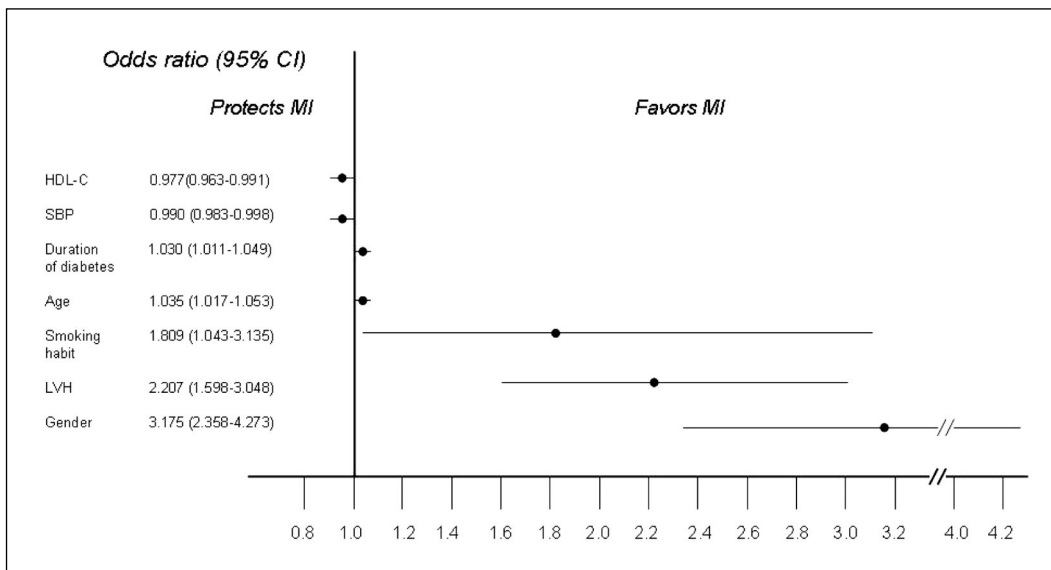


Figure 2. Odds ratios and 95% CI for myocardial infarction among patients with type 2 diabetes, according to risk factors. SBP, systolic blood pressure; LVH, left ventricle hypertrophy.

Table 5. Association of cardiovascular risk factors with myocardial infarction among patients with type 2 diabetes.

Independent variable	Coefficient	SEM	p-value	Odds ratio	Lower 95% CI	Upper 95% CI
HDL-C	-0.023	0.007	0.002	0.977	0.963	0.991
SBP	-0.100	0.004	0.010	0.990	0.983	0.998
Duration of diabetes	0.029	0.010	0.002	1.030	1.011	1.049
Age	0.034	0.009	<0.001	1.035	1.017	1.053
Smoking habit	0.593	0.281	0.035	1.809	1.043	3.135
LVH	0.791	0.165	<0.001	2.207	1.598	3.048
Gender	1.154	0.152	<0.001	3.175	2.358	4.273

Goodness of fit was examined by Hosmer and Lemeshow test (p=0.872).

tients with DM2 was positively associated with male sex, LVH, smoking habit, age, duration of diabetes, and inversely associated with SBP and HDL-C. Male sex tripled the chance of MI, LVH doubled and smoking habit increased the risk 1.8 times among subjects with DM2 (Figure 2).

Discussion

This study is the first to prospectively evaluate risk factors and genetic markers associated with myocardial infarction among patients with DM2 presenting prior MI or free of atherosclerotic disease. Here we report the baseline characteristics of the Genetics, Outcomes and Lipids in type 2 Diabetes (GOLD) Study. Our major findings were that some, but not all risk factors for CHD and diabetes were associated with myocardial infarction in subjects with DM2. Male sex, LVH, smoking habit, age, duration of diabetes, were the major determinants of MI in subjects with type 2 diabetes. Lower systolic blood pressure and higher levels of HDL-C were protective in this subset of patients.

Interestingly, the prevalence of hypertension was similar in subjects with MI and controls, however a very high proportion of patients with high blood pressure were observed in both groups (81 and 78% respectively). For individuals with established diabetes, risk factor management must be intensified to reduce their higher cardiovascular risk including achievement of optimal blood pressure control¹⁸.

The typical dyslipidemia present in subjects with DM2 include hypertriglyceridemia, low HDL-cholesterol levels and small and dense LDL particles. In the GOLD Study, the LDL particle size was not measured, but low HDL-C and high triglyceride serum levels were observed in this population. In addition, these lipid abnormalities were more severe among those DM2 individuals with prior MI.

Metabolic syndrome was also highly prevalent, with the highest rates among MI patients. This finding is in agreement with the report of Carr and Brunzell⁸.

The Framingham Heart Study reported the importance of LVH in the coronary risk¹⁹. Our results suggest that, among patients with diabetes, the relevance of this risk factor could be higher than in the general population, especially when we observe the same rate of hypertension in DM2 with or without MI. Increased LV mass has been associated with insulin resistance and renin-angiotensin aldosterone system (RAAS) activation²⁰⁻²². In this scenario, by increasing pro-inflammatory cytokines, changes in insulin-mediated signaling pathways may cause endothelial dysfunction and cell proliferation²³. In addition, LVH was more common in MI subjects, whose blood pres-

sure levels were lower, and were treated with ACE inhibitors in a higher proportion, to prevent adverse left ventricle remodeling.

On a 7-y follow up, the United Kingdom Prospective Diabetes Study (UKPDS) has identified the association of the time of diabetes mellitus diagnosis with increased risk of myocardial infarction²⁴. Our study also found the same association, suggesting that usual diabetes control appears insufficient to avoid the whole impact of several mechanisms related to the atherothrombotic disease.

Some studies have shown for different populations that subjects with DM2 are at high CHD and mortality risk, including the female sex at impressive rates^{8,25,26}. In our study, patients with MI were predominantly males. A possible explanation for this marked difference could be related to the relatively low mean age for MI in the GOLD population, a characteristic of developing countries. However, a progressive rate of MI should be expected among women with diabetes at higher ages.

According to the NCEP III definition, MS is common in the Adult US population²⁷. In contrast, diabetes without MS seems to be uncommon, and considered a condition associated with lower coronary risk⁷. In fact, the prevalence of CHD is markedly increased in the presence of MS, and those with both DM2 and MS (14.8%), had the highest prevalence of CHD (19.2%)⁷. In the Atherosclerosis Risk In Communities (ARIC) Study, individuals without diabetes or cardiovascular disease, but presenting MS, were at increased risk for cardiovascular events. Of the MS components, elevated blood pressure and low HDL-C levels showed the strongest associations with CHD²⁸. Recently, definitions of MS and their relevance for the clinical practice are under debate²⁹⁻³¹. In our study, MS was very frequent among patients with DM2, with a prevalence of 92% in MI patients and 86% in non-MI individuals, twice that observed for the NHANES III study population. We also observed a greater number of components for MS among females with MI. Juutilainen et al. reported a stronger effect of type 2 diabetes on the risk of CHD in women as compared with men, and this excess of risk was in part explained by a heavier risk factor burden and a greater effect of blood pressure and atherogenic dyslipidemia in women with diabetes³².

Summarizing, among patients with DM2 living in a developing country, the risk of myocardial infarction was associated with male sex, dyslipidemia, smoking and LVH. Metabolic syndrome was also highly prevalent in these patients. These aspects suggest a subgroup of diabetic patients at higher coronary risk. If confirmed in prospective studies, special policies to treat these patients may be proposed in the future.

Acknowledgments: This study was supported by Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) grant 00/14333-1 and in part by a grant from the Sociedade Brasileira de Cardiologia - Departamento de Aterosclerose (SBC-DA).

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