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Aspirin Therapy is Still Underutilized Among Patients With Type 2 Diabetes

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ABSTRACT

The daily use of aspirin in patients with type 2 diabetes mellitus (DM2) reduces significantly cardiovascular events (CVE). In the absence of contraindications, American Diabetes Association (ADA) recommends the use of aspirin to all DM2 patients older than 40 years of age. To evaluate aspirin use among 636 out patients with DM2 who participate in a regional multicenter study in Southern Brazil, a standard questionnaire was used. Patients also underwent a physical examination and laboratorial tests. All patients were older than 40 years (mean 58 ± 11 years old; 42% male) and by ADA guidelines most of them should be using aspirin. However, only 177 (27.5%) were on this medication. The use of aspirin was higher when any CVE were present. However, the percentage of users was still below the expected, not even reaching 50%. In conclusion, even though the use of aspirin is greater in patients with CVE, and its benefits are well documented, it is still underutilized. Strategies to enhance the use of aspirin should be developed to reduce the morbidity and mortality from cardiovascular diseases in patients with DM2. **(Arq Bras Endocrinol Metab 2006;50/6:1014-1019)**

Keywords: Aspirin; Type 2 diabetes mellitus; Cardiovascular disease; ADA guidelines

RESUMO

A Terapia com Aspirina Ainda é Subutilizada em Pacientes Com Diabetes Tipo 2.

O uso diário de aspirina em pacientes com diabetes mellitus do tipo 2 (DM2) reduz significantemente os eventos cardiovasculares (ECV). Na ausência de contraindicações, a ADA (American Diabetes Association) recomenda o uso de aspirina para todos os pacientes com DM2 maiores de 40 anos de idade. Para avaliar o uso de aspirina em 636 pacientes ambulatoriais com DM2 que participaram de um estudo multicêntrico na região Sul do Brasil, utilizamos um questionário padrão. Os pacientes foram também examinados e submetidos a testes laboratoriais. Todos eram maiores de 40 anos (média 58 ± 11 anos; 42% homens) e a maioria deles deveria estar usando aspirina, de acordo com as orientações da ADA. Entretanto, somente 177 (27,5%) estavam com esta medicação. O uso de aspirina era maior em presença de qualquer ECV. Contudo, a porcentagem dos que a usavam estava ainda abaixo do esperado, não atingindo 50%. Em conclusão, mesmo sendo o uso da aspirina maior em pacientes com ECV, e seus benefícios bem documentados, ela ainda é subutilizada. Assim, estratégias para aumentar o uso de aspirina devem ser desenvolvidas para reduzir a morbi-mortalidade decorrente da doença cardiovascular em pacientes com DM2. **(Arq Bras Endocrinol Metab 2006;50/6:1014-1019)**

Descritores: Aspirina; Diabetes mellitus tipo 2; Doença cardiovascular; Recomendações da ADA

CARDIOVASCULAR EVENTS (CVE) prevention should be an important goal in the management of patients with type 2 diabetes mellitus (DM2), since DM2 is associated with a two to fourfold increase in the risk of coronary heart disease (CHD) (1,2). Middle-aged individuals DM2 also require special attention since even without a prior CVE they have the same risk of developing a fatal or nonfatal myocardial infarction as a nondiabetic individual with prior history of myocardial infarction (3). This suggests that all individuals with DM2 should be treated as if they had prior CHD (3).

One of the major causes of acute coronary syndrome is the formation of thrombus on a disrupted atherosclerotic plaque (4). This process starts when a platelet is exposed to collagen and tissue factors that induce their activation and the release of thromboxane A2. Thromboxane A2 is one of the principal vasoactive substances and it is produced in excess in individuals with DM2 (5,6). Aspirin, in low doses, acts as an antiplatelet agent by binding irreversibly to the ciclooxygenase, which is responsible for thromboxane A2's synthesis, and consequently, inhibiting the thrombus formation.

Those reasons added to many trials which evaluated the use of aspirin and CHD, explain why, since 1997, the American Diabetes Association (ADA) (7) recommends the use of low doses of aspirin (81–325 mg / day) for primary and secondary prevention of CVE and has reestablished this guidelines in 2000 (8) and 2003 (9,10) with minor alterations. All patients with DM2 who have history of myocardial infarction, vascular bypass procedure, stroke or transient ischemic attack, peripheral vascular disease, claudication and / or angina should use aspirin as secondary prevention (evidence level A). Moreover, patients who have one or more risk factors for CHD such as family history of CHD, cigarette smoking, hypertension, obesity, age > 30 years, albuminuria or lipids abnormalities should use aspirin as a primary prevention. In 2004 ADA (10) reinforced these recommendations but increases the age to older than 40 years (evidence level A). The exception to these guidelines is patient with aspirin allergy, bleeding tendency, recent gastrointestinal bleeding or clinical hepatic disease.

The ADA recommendations for aspirin use in CHD primary prevention are not based in data as strong as the evidence existing for general secondary prevention. The majority of clinical trials were not designed to study specifically the DM2 population, and the conclusions are derived from subgroup analyses that show lower relative benefits in DM2 group (11). Nevertheless, the specialists position statements need to guide the physicians based in the best available evidence and, at least until now, it indicates that the DM patient is in high risk of CHD and needs to be treated in the same way as that group of patients.

The ADA recommendations were used to evaluate aspirin use among 636 out patients with DM2 who participate in a regional multicenter study in Southern Brazil.

MATERIAL AND METHODS

Patients

Six hundred thirty six patients with DM2 were identified from an ongoing multicentric study that investigates risk factors for chronic complications of DM2, being carried out in the South of Brazil. It includes 3 endocrinology centers located at general hospitals in Rio Grande do Sul State, namely: Hospital de Clínicas de Porto Alegre (n= 396); Hospital Independência (n= 94) and Hospital de Passo Fundo (n= 146). In these first two centers, patients with DM2 from the nephrology clinic and dialysis unit were also included. DM2 was defined by the diagnosis of diabetes after the age of 35, and with no use of insulin during the first two years after diagnosis.

A standard questionnaire was used to collect information about current age, age at DM2 diagnosis, drug treatment, smoking habits and prior CVE or symptoms. All patients underwent a complete physical examination and laboratorial tests. They were weighed without shoes, in light outdoor clothes, and had their height measured. Body mass index (BMI) was calculated as weight (kg) divided by square height (m^2). Waist circumference was measured at the narrowest part, as viewed from the front; hip circumference was measured at the widest part, and the waist to hip ratio (WHR) was calculated. Obesity was defined by BMI ≥ 30 kg / m^2 and / or high WHR (> 0.90 for men or > 0.85 for women). Blood pressure was measured twice in the sitting position after a 10-minute rest by means of a mercury sphygmomanometer (Korotkoff phases I and V). Hypertension was considered to be present when blood pressure was ≥ 140 / 90 mmHg, or if the patient was taking antihypertensive drugs. Diabetic nephropathy (DN) was defined when patients presented 24-hour timed urinary albumin excretion rate (UAER) > 20 µg / min or 17 mg / l in urine spot (12), confirmed at least two times, 3 to 6 months apart. Dyslipidemia was defined by a low HDL (< 35 mg / dl for men or < 39 mg / dl

for women), and/or high LDL (> 100 mg/dl) and/or high tryglicerides (> 150 mg/dl).

Peripheral vascular disease (PVD) was evaluated by the WHO questionnaire of cardiovascular disease for the presence of intermittent claudication and clinically by the presence or absence of posterior tibial and podal pulses. The presence of cerebrovascular disease was established by history of stroke and/or presence of compatible findings (sequeal). The diagnosis of CHD was based on the presence of angina or possible infarct according to the WHO questionnaire for cardiovascular disease and/or on the presence of resting ECG abnormalities (Minnesota Code) and/or on the presence of perfusion abnormalities (fixed or variable) upon myocardial scintigraphy at rest and after dipyridamole administration.

The protocol was approved by local Ethics Committee and all patients signed an informed consent form.

Laboratory analysis

UAER was measured in 24-h timed or spot sterile urine samples by immunoturbidimetry (Microalb, Ames-Bayer, Tarrytown, NY, intra- and inter-assay coefficients of variation: 4.5% and 11.0%, respectively). Glucose levels were determined by a glucose oxidase method; creatinine by the Jaffé reaction; HbA1c by an ion-exchange HPLC procedure (Merck-Hitachi L-9100 Glycated hemoglobin Analyser; reference range: 2.7–4.3%), and triglycerides and cholesterol levels by enzymatic methods. LDL-cholesterol was calculated using the Friedewald equation.

Statistical analysis

Continuous data were expressed as means ± standard deviation. Categorical data were expressed as number of cases and percent of individuals affected. Chi-square, Student's t-test or one-way analysis of variance (ANOVA) was used to compare the groups in terms of clinical and laboratorial characteristics. The Tukey test was used for post-hoc multiple comparisons. Variables without normal distribution where log-transformed. P value (two sided) < 0.05 was considered to be significant.

RESULTS

A total of 636 patients with DM2 were evaluated. All patients were older than 35 years of age and, by ADA guidelines, most of them should be been using aspirin. However only 175 (27.5%) were on medication. There were no differences between the group that was taking aspirin and that which was not when considering sex, ethnics and presence of obesity (table 1). Patients using aspirin were older and had longer DM2 duration than patients without aspirin. The aspirin users also had higher frequency of systemic arterial hypertension, lower fasting plasma glucose, higher total cholesterol and lower HDL cholesterol.

The distribution of aspirin use according to the presence of cardiovascular disease (secondary prevention) is depicted in table 2. CHD was present in 241 (37.9%) patients; 44 (6.9%) had had stroke and 249 (39.2%) had PVD. The use of aspirin was higher when any of the cardiovascular diseases was present. Forty three percent of patients with CHD were on aspirin compared to 17.7% of patients without CHD (P< 0.001). Among patients who had had a stroke, 52% were using aspirin in contrast to 28% among those without a history of stroke (P< 0.001). The same pattern was observed for the presence of PVD (32.9 vs. 24.0%, P= 0.014).

Table 1. Clinical and laboratorial characteristics according to the use of aspirin.

	Aspirin Use		
	YES (n= 175)	NO (n= 461)	P
Sex (% male)	46	41	0.239
Ethnics (% Caucasians)	70	62	0.163
Age (years)	60.8 ± 8.91	57.6 ± 10.3	< 0.001
Diabetes duration (years)	14.0 ± 9.0	10.6 ± 7.7	< 0.001
Body Mass Indedx (kg/m^2)	28.9 ± 5.1	28.8 ± 5.2	0.957
Waist/hip ratio	0.946	0.940	0.519
Systemic arterial hypertension (%)	92.1	76.3	< 0.001
Smoking habit (%)	20.3	25.0	0.308
Fasting plasma glucose (mg/dl)	164 ± 64.9	189 ± 86.1	< 0.001
Total cholesterol (mg/dl)	221.4 ± 44.1	211.5 ± 47	0.047
HDL cholesterol (mg/dl)	44.2 ± 11.4	45.7 ± 12.9	0.033
LDL cholesterol (mg/dl)	145.5 ± 39.7	142.4 ± 41.2	0.575

Data are mean ± standard deviation or (%) of cases.

Table 2. Aspirin use for secondary prevention according to the presence of secondary risk factors for cardiovascular disease.

	Aspirin Use		
	YES (n= 175)	NO (n= 461)	P
Coronary artery disease			
Present (n= 241)	105 (43.6)	136 (56.4)	
Absent (n= 395)	70 (17.7)	325 (82.3)	< 0.001
Stroke			
Present (n= 44)	23 (52.3)	21 (47.7)	
Absent (n= 592)	152 (28.0)	440 (79.9)	< 0.001
Peripheral vascular disease			
Present (n= 249)	82 (32.9)	167 (67.1)	
Absent (n= 387)	93 (24.0)	294 (76.0)	0.014

Among patients without cardiovascular disease (primary prevention), systemic arterial hypertension was present in 70.2%; obesity in 85.9%; smoking habit in 10.7%; dyslipidemia in 58.8% and DN in 41.2% (table 3). Patients with DM2 and hypertension used aspirin more often than normotensive patients (21.8 vs. 7.5%, P= 0.022). For all the other risk factors, the aspirin use was similar in the presence or absence of the risk factor.

CONCLUSION

In this sample of patients with DM2 attending endocrine clinics in general hospitals, the use of aspirin was lower than recommended. Following ADA recommendations almost all patients should be on aspirin therapy. Its use was significantly increased among those patients with established cardiovascular disease (CVD) or systemic arterial hypertension, but even so bellow the expected.

Routine aspirin use is probably the easiest and less expensive therapy available to prevent CVE in patients with DM2. Use of low doses of aspirin (less than 325 mg / day) is associated with very few adverse events and, as demonstrated by the Hypertension Optimal Treatment trial (HOT) (13), the use of small doses as 75 mg might decrease the risk of myocardial infarction in about 36% in patients with DM2 and systemic hypertension. A meta-analysis of 145 prospective controlled trials of antiplatelet therapy after myocardial infarction, stroke or transient ischemic attack, or positive cardiovascular history (secondary prevention) showed significant reduction in vascular events for individuals with DM2 as well as non-diabetic individuals (14). It was estimated that 38 ± 12 vascular events per 1,000 diabetic patients would be prevented if they were treated with aspirin as a secondary prevention strategy. For primary prevention, The U.S. Physicians' Health Study (15) examined the effect of aspirin in primary prevention and demonstrated a 61% risk reduction for myocardial infarct among diabetic men using 325 mg every other day compared to placebo.

Rolka et al. reviewed the Third National Health and Nutrition Examination Study (NHANES III) data, and showed that aspirin was regularly used by 37% of patients with established CVD and only by 13% of those with one risk factor but no CVD (16). This study was performed before the ADA recommendations for aspirin use and the results were similar to our findings (43% and 17%, respectively).

Probably the most important factor influencing the aspirin use by the patients is the physician's prescription. In a random sample of patients with DM2, receiving care at the Department of Veterans Affairs health care, 66% out 71% counseled by the physician to use aspirin were actually taking it (17). Also, a large health care organization, Kaiser Permanent, reported that 78% of their patients were on aspirin a year after they started a multidisciplinary program (18). This reinforces how simple procedures can be employed to prevent the development of cardiovascular events.

The Brazilian Diabetic Society (www.diabetes.org.br) has not published specific guidelines in aspirin use. In this way, the low aspirin prescriptions found in this sample may reflect the unaware of ADA guidelines by the physicians studied. However, all the centers studied were specialized in providing care to patients with DM2 and most of these physicians have access to ADA guidelines, since it is published online once a year and it is free of charge (19). In addition, the higher prescriptions among CVD patients reflect more consistent data and increase in absolute benefit available for aspirin use in this group.

Table 3. Aspirin use according to the presence of risk factors among patients without cardiovascular disease (n= 177).

	Aspirin Use		
	YES	NO	P
Systemic arterial hypertension			
Present (n= 124)	27 (21.8)	97 (78.2)	
Absent (n= 53)	4 (7.5)	49 (92.5)	0.022
Obesity			
Present (n= 152)	25 (16.4)	127 (83.6)	0.357
Absent (n= 25)	6 (25.0)	19 (75.0)	
Smoking habit			
Present (n= 19)	3 (15.8)	16 (84.2)	0.834
Absent (n= 158)	28 (17.7)	130 (82.3)	
Dyslipidaemia			
Present (n= 104)	18 (17.3)	86 (82.7)	0.931
Absent (n= 73)	13 (17.8)	60 (82.2)	
Nephropathy			
Present (n= 73)	9 (12.3)	64 (87.7)	0.128
Absent (n= 104)	22 (21.2)	82 (78.8)	

Data are numbers and (%) of cases.

However, in a small number of subjects, aspirin may not be a good option. As ADA states (10), the use of aspirin by subjects under 21 years old is not recommended because of the risk of Reye's disease. The use before 30 years has not been completely studied. Gastric mucosal injury and gastrointestinal hemorrhage are real concerns when aspirin is prescribed. Aspirin increases the relative risk of major gastrointestinal bleeding around twofold (20). The risk of one episode of hemorrhagic stroke is approximately 1 event per 1,000 users over 3–5 years (15). Other situations where aspirin should be avoided are history of aspirin allergy, bleeding tendency, concurrent anticoagulant therapy, recent gastrointestinal bleeding, and clinically active hepatic disease. In this situation other antiplatelet agents are possible options for patients with high risk.

A limitation of the current study is the lack of information concerning other concomitant illnesses. Therefore, the proportion of patients with aspirin contraindication could not be assessed. Only three patients were on other antiplatelet therapy, and they were included as aspirin users in the analysis. In all three cases, there was history of aspirin gastrointestinal intolerance.

In addition to aspirin, other classes of drugs, such as angiotensin inhibitors (21) and statins (22) should be considered as standard therapy in patients with DM2. Based on this information, it becomes clear that a multiple intervention approach should be employed to treat and prevent the CVE in these patients (23).

In conclusion, the use of a well established, safe and inexpensive therapy to prevent major CV events is still underutilized among patients attending endocrine clinics of general hospitals. This profile can be changed by simple procedures, where the physician prescription has a pivotal role.

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