Sub-optimal drug treatment of diabetes and cardiovascular risk in diabetic patients in Turkey. A countrywide survey

T Damci¹, H Kultursay², A Oguz³, S Pehlivanoglu⁴, L Tokgozoglu⁵, The Vascular Risk Study Group

SUMMARY

Objectives: The present study is a snapshot of how diabetic patients are treated for diabetes and coexisting cardiovascular risk factors in Turkey. We also addressed the question of what percentage of these patients are treated appropriately according to the current guidelines. Next step will be to determine which pharmacological treatment strategies affect mortality and morbidity in these patients and whether there are regional differences in these outcomes.

Methods: To get a representative picture, Turkey was split into four parts with different ethnic and socioeconomic features and centers were randomized within each of these parts. Number of the centers in a region were calculated according to the population of that region. 305 physicians in 11 cities participated in data collection during a period of 3 months.

Consecutive 2226 diabetic patients patients who were above 55 years of age were included. Detailed information was obtained about the demographic features and the cardiovascular risk factor and diabetes status of the patients together with relevant drug treatment. Laboratory analyses were done locally and recorded if performed during the last 3 months.

Results: Most patients were treated with oral antidiabetic monotherapy regardless of diabetes duration, metabolic control and complication and cardiovascular risk factor status. There was a trend among physicians except for endocrinologists to underprescribe insulin. Monotherapy also was the main mode of treatment for hypertension. Angiotensin converting enzyme inhibitors were generally not used as first line treatment contrary to the recommendations and angiotensin converting enzyme inhibitors and angiotensin receptor blockers are not prescribed for renoprotection in microalbuminuric patients. Statins, fibrates, metformin and aspirin were largely underused.

Conclusion: The present study indicates that diabetic patients are undertreated in Turkey. Therefore every effort should be spent to implement current guidelines in diabetic patients in order to prevent macro and microvascular complications of diabetes.

Key-words: Diabetes · Cardiovascular risk factors · Drug treatment · Turkey.

RéSUMÉ

Traitement médicamenteux sub-optimal du diabète et du risque cardiovasculaire chez les diabétiques en Turquie. Une enquête nationale

Objectifs: La présente étude est une photographie de la prise en charge thérapeutique du diabétique et des facteurs de risque coexsis-tants en Turquie. Nous avons également abordé la question du pourcentage parmi ces patients traité de façon appropriée par rapport aux recommandations actuelles. La prochaine étape sera de déterminer quelle stratégie pharmacologique affecte la mortalité et la morbidité de ces patients et s’il existe des disparités régionales.

Méthodes: Afin d’avoir une idée représentative, la Turquie a été divisée en quatre partie avec caractéristiques ethniques et socioécono-miques distinctes, puis des centres ont été randomisés au sein de ces parties. Le nombre de centres dans une région a été calculé en fonction de la population de cette région. 305 praticiens dans 11 villes ont participé à la collecte des données pendant 3 mois. L’étude a inclus 2 226 patients diabétiques consécutifs âgés de plus de 55 ans. Une information détaillée portant sur les caractéristiques démographiques, les facteurs de risque cardiovasculaire, le statut diabétique et le traitement médicamenteux a été obtenue. Les analyses de laboratoire ont été réalisées localement et retenues si effectuées au cours des 3 derniers mois.

Résultats: La plupart des patients étaient traités par monothérapie antidiabétique orale quelle que soit la durée du diabète, le contrôle métabolique, le statut des complications ou des facteurs de risque cardiovasculaire. Une tendance était notée parmi les praticiens à l’exception des endocrinologues de sous-prescrire l’insuline. Une monothérapie était également le principal mode de traitement de l’hypertension. Les inhibiteurs de l’enzyme de conversion n’étaient généralement pas utilisés en première ligne contrairement aux recommandations et les inhibiteurs de l’enzyme de conversion et les bloqueurs du récepteur de l’angiotensine n’étaient pas prescrits pour la néphroprotection des patients microalbuminuriques. Statines, fibrates, metformine et aspirine étaient largement sous-utilisés.

Conclusion: Cette étude montre que les diabétiques sont sous-traités en Turquie. Ainsi des efforts doivent être entrepris pour appliquer les recommandations diabétologiques actuelles afin de prévenir les complications macro et microvasculaires du diabète.

Mots-clés : Diabète · Facteurs de risque cardiovasculaire · Traitement médicamenteux · Turquie.

1 Department of Internal Medicine, Professor of Medicine, Istanbul University Cerrahpaşa Medical Faculty, Division of Endocrinology, Diabetes and Metabolism, Istanbul, Turkey
2 Department of Cardiology, Professor of Cardiology, Ege University, Izmir, Turkey
3 Professor of Medicine, SSK Goztepe Hospital, Istanbul Turkey
4 Department of Cardiology, Professor of Cardiology, Istanbul University Cerrahpaşa Medical Faculty, Istanbul Turkey
5 Department of Cardiology, Professor of Cardiology, Hacettepe University Medical Faculty, Ankara, Turkey.

Address correspondence and reprint requests to: T Damci, Ataöy 4, Kism, O-67, D-7, 34750, Ataöy, Istanbul Turkey. tdamci@superonline.com
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Diabetes Metab 2004,30,327-33 • © 2004 Masson, all rights reserved 327
he prevalence of diabetes is high in all countries which is 7.2% in adult population living in Turkey [1]. Figures are increasing exponentially and diabetes prevalence in the forthcoming decades is expected to reach enormous proportions [2].

Cardiovascular events are encountered 2-4 times more frequently in diabetic men and women respectively than in nondiabetic people [3, 4]. Furthermore, cardiovascular event mortality is higher in diabetic patients than in those without diabetes [5]. The cardiovascular event risk is equivalent in a diabetic patient without history of cardiovascular disease and a nondiabetic patient who previously had a myocardial infarction [6]. Mortality in a diabetic patient who previously had a vascular event is even higher [6].

Lowering blood pressure [7] and LDL cholesterol levels are associated with greater reduction in the cardiovascular events rate and mortality in diabetic patients than in nondiabetic people [8, 9]. Thus, current guidelines have set lower targets for blood pressure [10] and LDL cholesterol specifically for diabetic patients [11]. To achieve these goals higher doses of drugs and combination therapy are required in this group of patients. Moreover, some antihypertensive agents namely angiotensin converting enzyme (ACE) inhibitors [12] and angiotensin receptor blockers (ARB’s) [13, 14] have renoprotective effects in addition to blood pressure lowering; therefore recommended as first line treatment in hypertensive diabetic patients [15].

The UKPDS study showed that intensive treatment of type 2 diabetes is associated with a significantly lower rate of microvascular complications and lower but marginally non-significant rate of myocardial infarction [16]. If a greater reduction than the actual level of 0.9% in HbA1c had been achieved in the intensively treated group, the difference would probably have been significant. Some other trials have shown that increased blood glucose and HbA1c levels are associated with higher cardiovascular mortality in both diabetic and nondiabetic people [17]. These findings have led physicians to use early combination treatment with oral hypoglycemic agents and insulin to achieve as low HbA1c as possible.

Low dose aspirin therapy is associated with decreased cardiovascular mortality and morbidity in patients with diabetes [7, 18]. The American Diabetes Association (ADA) recommended that all diabetic patients with one of the following cardiovascular risk factors should use aspirin: previous vascular event, family history of heart attack, smoking, overweight or obesity, hypertension, micro- or macroalbuminuria or dyslipidemia [19].

Knowledge favoring aggressive treatment of hypertension, dyslipidemia and hyperglycemia in diabetic patients is rapidly accumulating and treatment targets are lowered in every guideline compared with the previous one. It has recently been shown that targeting multiple risk factors in patients with type 2 diabetes and microalbuminuria reduces the risk of macrovascular and microvascular complications by about 50% [20]. With the aid of sophisticated information technology; widespread access to the internet in particular, latest advances in every field of science can be reached quite readily almost anywhere in the world. However, implementation of this knowledge to routine practice is not that fast and widespread. Even when limited resources are excluded, millions of patients all over the world are probably still undertreated according to the current guidelines.

The present study is a snapshot of how diabetic patients are treated for diabetes along with coexisting cardiovascular risk factors in Turkey. A total of 5600 patients who were above 55 years of age with at least one of previous myocardial infarction, stroke, stable or unstable angina pectoris, percutaneous transluminal coronary angioplasty (PTCA) or coronary artery by-pass grafting (CABG), peripheral vascular disease, diabetes mellitus and hypertension were included, hereby we present the results of the diabetes subgroup of 2226 patients.

Research design and methods

Vascular Risk Study is a prospective observatory prognosis survey which addresses the question of which pharmacological treatment strategies affect mortality and morbidity in patients bearing high cardiovascular risk and whether there are regional differences in these outcomes. Also some other interventional trials are planned to be done in special subgroups of patients in this population. In the first step, to get a representative picture of Turkey, country was splited into four parts as northwest, southwest, northeast and southeast with different ethnic and socioeconomic features and centers were randomized within each of these parts. Number of the centers in a region were calculated according to the population of that region.

87.3% percent of people living in Turkey are covered by social insurance that is provided by the government. 92% of patients that are included in this study had social insurance. Diabetic patients as well as other patients who bear high cardiovascular risk are mainly followed up by internists, general practitioners, cardiologists and less commonly by other specialists such as endocrinologists and family physicians. Family physicians have an education of totally four years after medical school in internal medicine, general surgery, pediatrics and obstetrics clinics, one year for each. On the other hand internists are specialists who had a more specific and comprehensive education in internal medicine for four years. Ratio of specialties of participating physicians reflected their relative roles in the care of diabetic patients. 389 physicians were participated in the study. 305 physicians (response rate: 78.4%) in 11 cities participated in data collection during a period of about three months. 94 physicians were general practitioners, 92 were internists, 79 were cardiologists, 16 were endocrinologists, 11 were family physicians and 13 were of other specialties. Consecutive patients who were above 55 years of age and had at least one of the fol-
lowing features were included: previous myocardial infarction, stroke, stable or unstable angina pectoris, percutaneous transluminal coronary angioplasty (PTCA) or coronary artery by-pass grafting (CABG), peripheral vascular disease, diabetes mellitus and hypertension. Detailed information was obtained about the cardiovascular and antidiabetic treatment of the patients along with the demographic features. Laboratory analyses were done locally and recorded if performed during the last 3 months.

Of the 2226 diabetic patients 1376 (61.8%) were female and 850 (38.2%) were male. 1813 (81.4%) patients had lipid results, 1472 (66.1%) had ECG, 406 (18.2%) had echocardiography, 689 (30.9%) patients had HbA1c results. HbA1c measurement has not been standardized in Turkey but most laboratories give their normal values between 4.5-6%. Written informed consent was taken from all patients. 5600 patients fulfilling the criteria were included. The present study is a subgroup analysis of 2226 diabetic patients who were previously diagnosed to have diabetes. We have not made a distinction between type 1 and type 2 diabetic patients in data collection to make the procedure easier.

Electronic medical record systems were used for data collection. Random source data verification with hospital records and case record forms in 112 (5%) cases was performed. In only 2 (< 2%) cases minor corrections were required.

Statistical analyses were done in SPSS 10. for Windows, frequency analysis, chi square statistics were performed as required.

Results

The mean age of the included patients was 64.7 ± 6.9 (55-95) and diabetes duration was 9.7 ± 7.6 (0-42) years. 1376 (61.8%) patients were female and 850 (38.2%) were male. Mean BMI was 28.4 ± 4.7 kg/m² and HbA1c was 8.15 ± 2.3%. Seventy seven percent of patients were overweight or obese (BMI > 25 kg/m²). 14.4% had previous myocardial infarction, 18.4% had stable or unstable angina, 4.4% had previous stroke and 4.5% had peripheral vascular disease. 6.6% had previously undergone PTCA and 6.7% CABG. 73.4% of patients were hypertensive, 54.4% had total cholesterol levels above 200 mg/dl, 43.4% had lower than 40 mg/dl HDL concentrations, 11.6% were microalbuminuria and 20% were current smokers. Coronary angiography had been performed in 373 patients and 80% had coronary artery stenosis at least in one vessel. Family history of cardiovascular disease in the first degree relatives was present in 27.4% of patients, 28.4% had left ventricular hypertrophy (>11 mm) and 36.2% had ejection fraction less than 50% on echocardiography, 11.6% had microalbuminuria, 6.9% had macroalbuminuria, 8.2% had serum creatinine levels above 1.4 mg/dl.

89.6% of patients had at least one cardiovascular risk factor other than diabetes (Tab I).

Antidiabetic treatment

Of the 2226 diabetic patients 332 (14.9%) were on non pharmacological antidiabetic treatment (diet and exercise), 1040 (46.7%) were on monotherapy with oral antidiabetic drugs (OAD) (Tab II). 737 patients were treated with sulphonylureas (33.1%), 161 (7.2%) with metformin, 91 (4.1%) with acarbose, 23 (1.0%) with nateglinide, 21 (0.9%) with repaglinide, 7 (0.3%) with rosiglitazone monotherapy. Single most commonly used drug was gliclazide (28.9%).

444 (20.0%) patients were taking OAD combination therapy. Most commonly used combination was sulphonylurea-metformin which was used in 275 (12.3%) patients. Sulphonylurea-acarbose combination was used in 118 patients (5.3%), metformin-acarbose in 45 patients (2%), sulphonylurea-rosiglitazone in 6 (0.3%).

30% of patients with HbA1c levels above 8% were still treated with OAD monotherapy (not combination of OAD's or insulin). 182 patients had serum creatinine > 1.4 mg/dl, 77 (42.3%) of them were still on OADs (not insulin).

410 (18.4%) patients were treated with insulin. 294 (13.2%) were on insulin monotherapy, 116 (5.2%) on combination of

| Table II | Antidiabetic and antihypertensive treatment modalities used in diabetic patients. |

<table>
<thead>
<tr>
<th>Antidiabetic treatment (n: 2226)</th>
<th>Nonpharmacological treatment</th>
<th>Monotherapy</th>
<th>Combination therapy</th>
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<tr>
<td>Antihypertensive treatment (n: 1633)</td>
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insulin and OAD's. Insulin was combined with metformin in 61 (2.7%) patients, with acarbose in 35 (1.5%), with sulphonylureas in 13 (0.5%), with nateglinide in 3, repaglinide in 3 and rosiglitazone in 1 patients.

In 313 patients with poor metabolic control (HbA1c > 8%) insulin was used in 102 (32.6%).

525 patients had previous myocardial infarction, stroke, PTCA or CABG. Of these only 101 (19.2%) were treated with insulin. 320 patients had previous myocardial infarction with 26 of whom had it during the preceding one year. Insulin treatment rate in these groups were 20% and 23% respectively.

Endocrinologists prescribed insulin more commonly than other specialists and general practitioners (chi-square statistics, p < 0.0001).

**Antihypertensive treatment**

1633 (73.4%) patients were hypertensive. 1420 (87.0%) patients were on pharmacological treatment (Tab II). 954 (58.4% of hypertensive patients) patients were on monotherapy with antihypertensives, 386 (23.6%) were taking two agents, 66 (4.0%) three agents, 13 (0.8%) four agents and only 1 five agents.

329 (20.1% of all hypertensive patients) patients were treated with ACE inhibitor monotherapy, 298 (18.2%) with calcium channel blocker, 104 (6.4%) with ARB, 102 (6.2%) with diuretic, 95 (5.8%) with beta blocker, 26 (1.6%) with alpha adrenergic blocker monotherapy. Single most commonly prescribed antihypertensive drug for monotherapy was ramipril which was used in 9.2% of diabetic and hypertensive patients.

ACE inhibitor-diuretic combination was the most commonly prescribed combination of antihypertensives which was used in 191 (11.7% of all hypertensive patients) patients followed by ARB-diuretic combination in 57 (3.5%) and calcium channel blocker-ACE inhibitor in 21 (1.3%) patients.

Of the 259 patients with microalbuminuria 81 (31.3%) were taking ACE inhibitors and 29 (11.2%) were on ARB’s; total of 42.5% for these two drugs.

56 normotensive patients had microalbuminuria. Of these 13 (23.2%) were on ACE inhibitor therapy, 4 (7.1%) were taking ARB’s.

In 50% of patients with elevated creatinine levels and hypertension ACE inhibitors were used. ARB’s were used in 16.7% of such patients.

26 patients had myocardial infarction during the preceding year only 6 (23.1%) of whom were using beta blocker treatment.

**Antidyslipidemic treatment**

In 1813 patients total serum cholesterol was measured; 989 (54.5%) had total cholesterol levels above 200 mg/dl.

<table>
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<tr>
<th>No of patients used (Total: 2226)</th>
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<tbody>
<tr>
<td>Statins</td>
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<td>Fibrates</td>
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<tr>
<td>Aspirin</td>
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Statins were used in 439 (19.7% of total) patients. 319 out of 989 patients who had total cholesterol levels higher than 200 mg/dl used statins (32.2% ) (Tab III).

Only 25 (1.1%) of patients were treated with fibrates.

**Antiplatelet treatment**

673 (30.2%) diabetic patients were using aspirin. Of the 525 patients who previously had myocardial infarction, stroke, PTCA or CABG only 286 (54.5%) were on aspirin.

**Conclusion**

In this study we have included 2226 diabetic patients. 62% of the patients were female, 38% were male. This gender difference probably reflects higher diabetes prevalence in women in Turkey [1]. Diabetes prevalence is 8% in women and 6.2% in men in Turkey. This feature must be genetic in origin because Turks living in Germany have diabetes prevalence of 10% in women and 8% in men [21].

There is no doubt that good glycemic control reduces diabetic microvascular complications [16] Although the association of better glycemic control with lowered cardiovascular risk has not been unequivocally demonstrated so far, there is evidence that increased fasting and postprandial blood glucose and HbA1c levels are associated with higher cardiovascular events and mortality rates even in nondiabetic people [17]. Moreover intensive glucose control during and after myocardial infarction with insulin in diabetic patients decreases 1 year mortality along with fatal reinfarctions [22].

Thus earlier combinations of oral antidiabetic drugs and/or insulin are advocated in the treatment of type 2 diabetic patients to achieve better glycemic control. Monotherapy with OAD’s should therefore be restricted to a relatively small number of patients during the first years after diagnosis. Nearly half of the patients who participated in this study were on OAD monotherapy regardless of diabetes duration.

The American Diabetes Association has spotted HbA1c 7% as target and 8% as action levels [23]. In our patients 30% of diabetic patients with HbA1c > 8% were still on monotherapy with OAD’s.

Insulin treatment is recommended in type 2 diabetic patients with diabetic nephropathy [24]. It is well docu-
mented that good glycemic control slows the progression of diabetic nephropathy [16, 25]. Moreover patients with decreased renal function are more prone to development of severe hypoglycemia. So oral insulin secretagogues must probably be avoided in such patients since they have the potential to cause severe and prolonged hypoglycemia. However 42% of our patients with elevated creatinine levels were still using OAD’s.

In type 2 diabetic patients diet or OAD’s gradually lose their effects [16] and indication for insulin treatment ensues eventually. Secondary OAD failure rate is around % 5 per year (26). Mean duration of diabetes in our patients is 9.7 years but only 18% of them were using insulin. Insulin undertreatment in type 2 diabetes is almost a global problem (27) which also seems to be the case in Turkey.

DIGAMI study clearly demonstrated that potassium-glu-
cose-insulin infusion during the acute phase of myocardial infarction followed by intensive insulin treatment for 1 year decrease mortality and morbidity in diabetic patients [22]. Only about 20% of the patients who had myocardial infarction during the preceding one year were using insulin in our study.

What are the barriers for insulin treatment in this country? Surely factors arising from the patients or financial constraints play important roles but it seems that there are also barriers originating from physicians. The speciality of the physician affects the prescription rate of insulin in Turkey. Physicians other than endocrinologists tend to under-prescribe insulin although this finding should be interpreted cautiously because of a potential referral bias as endocrinologists generally care for more complicated diabetic patients.

The prevalence of hypertension in diabetic patients is very high that is 1.5-3 times more than that of nondiabetic people [28]. It has been clearly shown that aggressive treatment of hypertension in diabetic patients reduces microvascular and macrovascular diabetic complications [29]. Based on UKPDS [29] and HOT [19] results the ADA has lowered the target blood pressure to 130/80 [15]. To achieve this target blood pressure level combinations of antihypertensive agents are required. In the HOT study in 20% of diabetic patients combination of 3 antihypertensive drugs were required [19]. In our study 58.4% of patient were on monotherapy with antihypertensives, 23.6% were using two agents, 4.0% three agents and less than 1% four or five agents.

ACE inhibitors are generally recommended as the first line agents in treating diabetic hypertension [15] since they improve both micro and macrovascular outcomes in diabetic patients [12, 29]. 34% of diabetic and hypertensive patients in our study were treated with ACE inhibitors as monotherapy or combination therapy. Two thirds of the patients are not treated with ACE inhibitors which is a recommended class of antihypertensive drugs.

There is evidence that in patients with microalbumi-
uria and clinical nephropathy ACE inhibitors [12] and ARB’s [13, 14] prevent the progression of renal disease. 42.5% of our patients with microalbuminuria were treated either with ACE inhibitors or ARB’s. Only 30% of those with normotensive microalbuminuria were on one of ACE inhibitors or ARB’s. In patients with elevated creatinine levels ACE inhibitors or ARB’s were used in 67%.

The safety and efficacy of beta adrenergic blockers in diabetic patients after myocardial infarction is well documented. In a large study beta blocker therapy after myocardial infarction is associated with 40% reduction in two-year mortality [30]. In the same study only 31% of eligible diabetic patients received beta-blocker treatment which is slightly higher than the rate found in our patients. 23% of diabetic patients who had had a myocardial infarction during the preceding year were taking these drugs despite the presence of a clear indication.

Secondary prevention with LDL cholesterol lowering decreases the cardiovascular events rate and mortality in diabetic patients as well as in nondiabetic people [8, 9]. The latest Heart Protection Study not only have confirmed these results but also shown that in diabetic patients without previous coronary heart disease simvastatin therapy reduced cardiovascular events rate and mortality [31]. National Cholesterol Education Program Adult Treatment Panel III accepted diabetes as cardiovascular event equivalent and spotted the LDL target as 100 mg/dl for diabetic patients [11]. For practical purposes we recorded only total cholesterol and HDL levels in this study. The recommended level for total cholesterol for diabetic patients is 186-232 mg/dl [32]. Thus many patients with diabetes should be on statins. In our patient group only 19.7% were using statins and those who had total cholesterol levels above 200 mg/dl this ratio was 32% which is a very low rate according to the current recommendations. Moreover HDL cholesterol concentrations in Turkish people are lower than most of the other ethnic groups [33] which makes the levels of LDL or total cholesterol even more important. Fibrate treatment is also effective in reducing secondary cardiovascular events in diabetic patients with low HDL as in our study group [34]. But unfortunately only 1.1% of them were treated with this group of drugs.

In diabetic patients aspirin treatment is associated with a significant reduction in cardiovascular events rate [7, 18]. Therefore ADA recommends aspirin for secondary prevention of cardiovascular events in diabetic patients [19]. Aspirin is also recommended for those diabetic patients who have another cardiovascular risk factor. According to this criteria 90% of the patients included in our study were eligible for aspirin only 30% of whom were taking the drug.

In conclusion diabetes is associated with very high cardiovascualr risk both because of the diabetic state per se and also coexisting cardiovascular risk factors. Diabetes also has specific microvascular complications. There is convincing evidence that it is potentially possible to reduce macro and
microvascular complications risk considerably through appropriate use of antidiabetic, antihypertensive, antilipidemic and antiplatelet treatments. However the results of the present study indicate that diabetic patients are largely undertreated in Turkey. Therefore every effort should be spent to implement current guidelines in diabetic patients to prevent macro and microvascular complications of diabetes.

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