Biomedical Research 2017; 28 (20): 8862-8869 *ISSN 0970-938X*
www.biomedres.info

Usage rates of treatments for cardiovascular prevention in patients with type 2 diabetes mellitus without diagnosis of coronary artery disease.

Dilek Oztas[1], Mehmet Kayhan[2], Hüseyin Balcıoğlu[3], Yasemin Sağlan[4], Yunus Emre Sarı[3], Uğur Bilge[3*]

[1]Department of Public Health, Faculty of Medicine, Yildirim Beyazıt University, Ankara, Turkey

[2]Department of Family Medicine, Faculty of Medicine, Abant İzzet Baysal University, Bolu, Turkey

[3]Department of Family Medicine, Faculty of Medicine, Eskisehir Osmangazi University, Eskisehir, Turkey

[4]Eskişehir Public Health Directorate, Eskişehir, Turkey

Abstract

Aim: The aim of this study is to retrospectively investigate the usage rates of antidiabetic treatments, and statin, aspirin and angiotensin (angiotensin converting enzyme inhibitors and angiotensin receptor blockers) based treatments for cardiovascular prevention in patients with type 2 diabetes mellitus.
Material and methods: Drug exemption reports issued during 2015 and 2016 were evaluated from the hospital's digital database. Among these reports, files of patients with the DM diagnosis code (E11-E14) and without any diagnosis that could be associated with major cardiac events were scanned, and approximately 31685 records were obtained.
Results: A total of 11942 individuals were selected randomly according to simple random sampling method, and the active ingredients of the drugs listed in the drug exemption reports and used by the selected individuals were investigated. When usage in all groups was investigated, it was found that 21.3% of the patients used statin, 26.08% used ACE-I/ARB, and 9.8% used aspirin.
Discussion: In conclusion, the use of multiple treatments such as statins, angiotensinogen-dependent treatments, and aspirin in patients with DM2 is associated with a reduction in all-cause mortality. Secondary prevention, however, depends on the early selection of cases, and the initiation of appropriate preventive treatments; progression of the disease can only be stopped this way.

Keywords: Diabetes mellitus, Cardiovascular prevention.

Accepted on October 16, 2017

Introduction

Diabetes Mellitus (DM) is a chronic metabolic disease that occurs due to lack of effect and/or secretion or complete deficiency of insulin [1]. DM is a chronic disease that is very common all over the world, including Turkey. In TURDEP-II study in 2010, DM frequency in adults in Turkey was found to be 13.7% [2]. At present, there are more than 130 million adult DM patients all over the world, and it is estimated that this number will rise to 333 million by 2025 [3]. The main goals of treatment in diabetic patients are blood sugar regulation, control of hypertension, treatment of dyslipidemia and obesity [4]. For blood sugar regulation, proper diet, weight control, diabetes education, physical activity, oral antidiabetic drugs (OAD), and if necessary, insulin therapy are implemented. Hypertension, dyslipidemia and coronary artery diseases are frequently seen as comorbidities in patients with diabetes mellitus. Cardiovascular prevention is particularly important. Statins, ACE inhibitors (ACE-I)/angiotensin receptor blockers (ARB), and aspirin use is predominant in cardiovascular prevention [5-9].

The aim of this study is to retrospectively investigate the usage rates of antidiabetic treatments, and statin, aspirin and angiotensin (angiotensin converting enzyme inhibitors and angiotensin receptor blockers) based treatments for cardiovascular prevention in patients with type 2 diabetes mellitus who are not diagnosed with coronary artery disease, and to determine the distribution of these treatments according to age and gender.

Material and Methods

In Turkey, a report called “drug exemption report” is issued to individuals when a patient with DM diagnosis is thought to have reached the target values, and exemption is made for some payments to be made to the insurance institution, and when the patient report is issued, the doctor can prescribe the medicines again in the light of this report. These reports are prepared for 1 or 2 years. Ankara Atatürk Education and Research Hospital is a medical center located in the capital Ankara, where patients from neighboring cities can also apply. For this reason, it is thought that the data obtained from this

center can be generalized for all of Turkey. Drug exemption reports issued during 2015 and 2016 were evaluated from the hospital's digital database. Among these reports, files of patients with the DM diagnosis code (E11-E14) and without any diagnosis that could be associated with major cardiac events were scanned, and approximately 31685 records were obtained.

The obtained data were randomly selected in the IBM SPSS Statistics v21.0 package based on simple random sampling method. After the selection process, drug exemption reports of 11942 individuals were received. The sample used in this study comprises all drug exemption reports issued during this period and recorded in the electronic system.

Statistical analysis

The descriptive data are given in percentages (%). Pearson Chi Square, Yate's Exact Chi Square and Fisher's Exact Chi Square analyses were used in the analysis of the generated cross tables. The analysis was performed using IBM SPSS Statistics 21.0 software (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0, Armonk, NY: IBM Corp.). For statistical significance, $p<0.05$ was considered.

Results

Approximately 32 thousand individuals, who were diagnosed with DM2 with the determined criteria, applied to Ankara Atatürk Education Research Hospital between 2015-2016. A total of 11942 individuals were selected randomly according to simple random sampling method, and the active ingredients of the drugs listed in the drug exemption reports and used by the selected individuals were investigated. In the treatment of DM, since the use of single medication as well as the simultaneous use of different medications is often the case, the analysis was done accordingly. When gender distributions were analyzed, it was found that 6153 (51.5%) individuals were female and 5789 (48.5%) were male. The average age of the study group was 60.48 ± 11.35, with a minimum age of 18 and a maximum age of 107. The average age of women was 61.43 ± 11.43, and the average age of men was found to be 59.47 ± 11.18. It was found that the age of women participating in the study was significantly higher than that of men ($p<0.001$). When the accompanying diseases of 11942 individuals diagnosed with DM were examined, it was found that 3591 (30.1%) individuals had HT, 46 (0.4%) individuals had COPD and 54 (0.5%) individuals had Asthma.

Table 1. *Ingredients of the drugs used (anti-hypertensive, anti-diabetic drugs and others).*

Anti-diabetic drugs	(n)	Percentages in study population (n) (%)	Percentages in the ingredients (%)
Metformin	8332	69.77	42.10
Insulin glargine	2168	18.16	10.96
Insulin aspart and insulin protamine	1396	11.69	7.05
Sitagliptin	1211	10.14	6.12
Insulin aspart	1130	9.46	5.71
Repaglinide	766	6.41	3.87
Sitagliptin and metformin	727	6.09	3.67
Insulin lispro and insulin protamin	635	5.32	3.21
Vildagliptin ve metformin	477	3.99	2.41
Insulin detemir	450	3.77	2.27
Linagliptin	377	3.16	1.91
Insulin lispro	371	3.11	1.87
Nateglinide	322	2.70	1.63
Vildagliptin	303	2.54	1.53
Acarbose	289	2.42	1.46
Pioglitazone	253	2.12	1.28
Insulin glulisin	144	1.21	0.73
Saxagliptin	118	0.99	0.60
Insulin nph human	101	0.85	0.51

Insulin human regular	87	0.73	0.44
Insulin human regular ve insulin Nph human	67	0.56	0.34
Pioglitazone and Metformin	57	0.48	0.29
Metformin and Repaglinide	5	0.04	0.03
Metformin and Gliclazide	3	0.03	0.02
Anti-hypertensive drugs			
Metoprolol	682	5.71	12.22
Amlodipine	620	5.19	11.11
Valsartan and hydrochlorothiazide	435	3.64	7.80
Ramipril	430	3.60	7.71
Candesartan and hydrochlorothiazide	266	2.23	4.77
Losartan and hydrochlorothiazide	211	1.77	3.78
Irbesartan and hydrochlorothiazide	200	1.67	3.58
Carvedilol	161	1.35	2.89
Perindopril and indapamid	155	1.30	2.78
Lercanidipine	134	1.12	2.40
Telmisartan and hydrochlorothiazide	134	1.12	2.40
Ramipril and hydrochlorothiazide	133	1.11	2.38
Nifedipine	132	1.11	2.37
Doxazosin	131	1.10	2.35
Perindopril	131	1.10	2.35
Olmesartan and hydrochlorothiazide	129	1.08	2.31
Valsartan	126	1.06	2.26
Amlodipin and Valsartan	118	0.99	2.12
Losartan	104	0.87	1.86
Indapamid	84	0.70	1.51
Olmesartan	83	0.70	1.49
Candesartan	81	0.68	1.45
Perindopril and Amlodipin	78	0.65	1.40
Furosemide	61	0.51	1.09
Lacidipin	58	0.49	1.04
Cilazapril and hydrochlorothiazide	56	0.47	1.00
Diltiazem	53	0.44	0.95
Irbesartan	49	0.41	0.88
Lisinopril and hydrochlorothiazide	48	0.40	0.86
Verapamil and trandolapril	48	0.40	0.86
Bisoprolol fumarat	45	0.38	0.81
Telmisartan	42	0.35	0.75

Cilazapril	39	0.33	0.70
Benidipin	38	0.32	0.68
Atenolol	36	0.30	0.65
Lisinopril	27	0.23	0.48
Atenolol and chlorthalidone	24	0.20	0.43
Spironolactone	24	0.20	0.43
Fosinopril and hydrochlorothiazide	22	0.18	0.39
Quinapril and hydrochlorothiazide	18	0.15	0.32
Verapamil	18	0.15	0.32
Zofenopril Kalsiyum ve hydrochlorothiazide	18	0.15	0.32
Enalapril maleat	14	0.12	0.25
Zofenopril kalsiyum	13	0.11	0.23
Spironolakton and Hydrochlorothiazide	12	0.10	0.22
Enalapril and nitrendipin	10	0.08	0.18
Captopril	10	0.08	0.18
Quinapril	9	0.08	0.16
Trandolapril	9	0.08	0.16
Amlodipin and atorvastatin	5	0.04	0.09
Benazepril and hydrochlorothiazide	5	0.04	0.09
Enalapril and lercanidipin	5	0.04	0.09
Fosinopril	3	0.03	0.05
Amlodipin and Valsartan and hidroklorotiazit	2	0.02	0.04
Other drugs			
Atorvastatin	2182	18.27	54.04
Rosuvastatin	455	3.81	11.27
Pravastatin	15	0.13	0.37
Fluvastatin	4	0.03	0.10
Pitavastatin	3	0.03	0.07
Acetylsalicylic acid	1096	9.18	27.14
Alpha lipoic acid	283	2.37	7.01

In Table 1, in which the frequency distributions of active ingredients are defined, two different percentages are given as percentage among the number of individuals and percentage among the active ingredient. The table is presented in three sections; including diabetes medicines, hypertension medicines, and other medicines (Statins, Acetylsalicylic Acid and Alpha Lipoic Acid). While percentage among the number of individuals indicates percent usage in all units participating in the study, percentage of the active ingredient indicates the percentage of which the active substance is used or not. Metformin was the most commonly used active ingredient in DM medicines, used by 8332 people and in 69.77% of individuals. Insulin Glargine used by 2168 people (18.16%), and Insulin Aspart and Insulin Aspart Protamine combination, used by 1396 people (11.69%) were found to be the 2nd and 3rd most commonly used active ingredients in diabetes medication. The least used active ingredient was a combination of Metformin and Gliclazide with only 3 people. Among HT medicines, Metoprolol was the most commonly used active ingredient and was used by 682 people (5.71%). The least used active ingredient was a combination of Amlodipine and Valsartan and Hydrochlorothiazide with 2 people. Among other medicines, 1096 (9.15%) individuals were found to use Acetylsalicylic Acid. The most commonly used active

ingredient in Statins was Atorvastatin Calcium with 2182 people (18.27%).

Table 2. *Distributions of the drugs among sexes.*

	Sex		p*
	Male	Female	
Statin	1133 (19.6%)	1406 (22.9%)	19.157 <0.001
ACE-Inhibitor	589 (10.2%)	638 (10.4%)	0.122 0.727
Angiotensin Receptor Blocker	686 (11.9%)	1202 (19.5%)	132.351 <0.001
Calcium Chanel Blocker	475 (8.2%)	809 (13.1%)	75.942 <0.001
Beta Blocker	409 (7.1%)	531 (8.6%)	10.071 0.002
Insulin	2364 (40.8%)	2200 (35.8%)	32.614 <0.001
Oral Anti-Diabetic Agents	4829 (83.4%)	5363 (87.2%)	33.429 <0.001
*Pearson Chi-Square test			

Table 3. *Distributions of the drugs according to adult and elderly population (65 older and other population).*

	Age		p*
	<65	≥ 65	
Statin	1509 (59.43%)	1030 (40.56%)	38.213 <0.001
ACE-Inhibitor	705 (57.45%)	522 (42.54%)	30.844 <0.001
Angiotensin Receptor Blocker	921 (48.78%)	967 (51.21%)	246.649 <0.001
Calcium Chanel Blocker	605 (47.11%)	679 (52.88%)	193.178 <0.001
Beta Blocker	377 (40.10%)	563 (59.89%)	268.619 <0.001
Insulin	2853 (62.51%)	1711 (37.48%)	14.614 <0.001
Oral Anti-Diabetic Agents	6765 (66.37%)	3427 (33.62%)	91.930 <0.001
*Pearson chi-square test			

In Table 2, differences between the distributions of active ingredients according to gender were examined. Acetylsalicylic Acid, an active ingredient listed under other medicines, was found to be used by 551 male individuals (9.57%), and 545 female individuals (8.86%). Acetylsalicylic Acid was not found to be significantly different between men and women (p=0.211). It was found that Atorvastatin Calcium, the most commonly used active ingredient in Statins, was used by 944 male individuals (16.39%), and 1139 female individuals (18.51%). Use of Atorvastatin Calcium was found to be significantly different between men and women (p=0.002). When the distributions of medication groups according to gender in Table 2 were examined, it was found that female individuals with 1406 people (%22.9) were significantly higher than male individuals with 1133 people (%19.6) among people who used medication with Statin as an active ingredient (p<0.001). Similarly, active ingredients ARB, CCB, Beta Blocker (BB) and OAD were found to be significantly higher in women (p<0.001 for each). However, it was found that the use of insulin by men with 2364 people (40.8%) was significantly higher compared to women with 2200 people (35.8%) (p<0.001). Unlike these groups, no significant difference was found between genders in the use of ACE-I (p=0.727).

Table 4. *Total number of the drugs and their percentages.*

	Patients' total drug numbers used (n)	Percentages of the Patients' total drug numbers used (%)
1	3679	30.807
2	3693	30.924
3	2140	17.919
4	1210	10.132
5	652	5.459
6	326	2.729
7	146	1.222
8	52	0.435
9	29	0.242
10	5	0.041
11	6	0.050
12	2	0.016
13	2	0.016

Acetylsalicylic Acid was found to be used by 498 (6.00%) patients under 65 years of age, and by 598 patients (14.00%) at 65 years of age and above. Acetylsalicylic Acid was found to be significantly different for patients at 65 years of age and above (p<0.001). Atorvastatin Calcium, the most commonly used active ingredient in Statins, was found to be used by 1261 patients (16.00%) under 65 years of age, and by 822 patients (19.00%) at 65 years of age and above. Atorvastatin Calcium was found to be significantly different for patients under 65 years of age (p<0.001). When the distributions of medication groups with respect to the age of 65 were examined in Table 3, it was found that statin, ACE-I, insulin and OAD groups within active ingredients were significantly over-used in patients under 65 years of age compared to patients at the age of 65 and

above ($p<0.001$ for each). However, ARB, CCB, and BB groups were found to be significantly over-used in patients at the age of 65 and above compared to patients under years of age ($p<0.001$ for each).

In Table 4, distribution frequencies according to the number of active ingredients from different medications simultaneously used by patients are given. It was found that the highest number of active ingredients simultaneously used by individuals participating in the study was 13. 3679 patients (30.807%) used a single active ingredient, 3693 patients (30.924%) used 2 active ingredients, 2140 patients (17.919%) used 3 active ingredients, 1210 patients (10.132%) used 4 active ingredients, 652 patients (5.459%) used 5 active ingredients, 326 patients (2.729%) used 6 active ingredients, 146 patients (1.222%) used 7 active ingredients, 52 patients (0.435%) used 8 active ingredients, 29 patients (0.242%) used 9 active ingredients, and 15 patients (0.131%) used 10 or more active ingredients.

It was determined that 420 of the patients included in the study (3.5%) used ACE-I/ARB, ASA, and Statin treatment together as preventive treatment. Of these patients, 216 (51.4%) were male and 204 (48.6%) were female. No significant difference was found in use of preventive treatment between genders ($p=0.218$). When the use of preventive treatment with respect to age was investigated, it was found that 237 of the patients (56.4%) aged 65 and above were using preventive treatment, whereas 183 of the patients (43.6%) under 65 years of age were using preventive treatment. Prevalence of preventive treatment over 65 years of age was found to be significantly higher than under 65 years of age ($p<0.001$). When usage in all groups was investigated, it was found that 21.3% of the patients used the statin, 26.08% used ACE-I/ARB, and 9.8% used aspirin.

Discussion

Cardiovascular Disease (CVD) is the most important cause of morbidity and mortality in diabetic patients. In type 2 diabetes patients, the risk of coronary artery disease (CAD) in particular is 2-4 times higher than in non-diabetics. 60-75% of these patients are lost due to macrovascular events. In diabetic patients, atherosclerosis occurs at an earlier age and is more common. Prevalence of acute diabetic complications has decreased considerably with increasing awareness and improvement of treatment efficacy and possibilities, and mortality frequency has decreased. Development of late complications is mostly related to duration of diabetes (10). 26.08% of patients were using ACE-I/ARB. ACE inhibitors (ACE-I), angiotensin receptor blockers (ARB), low dose thiazide group diuretics, and calcium channel blockers (CCB) are agents with positive effects that are indicated in clinically controlled studies in the pharmacological treatment of diabetic hypertension (HT) cases. In all guidelines, modification of life style is recommended as initial therapy, followed by selection of one of the ACE-I or ARB group of drugs that block the renin-angiotensin system (RAS) in patients with albuminuria. In type 2 diabetes however, in the presence of HT, it is known that the progression of microalbuminuria may be delayed with ACE-I or ARB [6]. Diabetic nephropathy displays increased albuminuria and decreased glomerular filtration rate. Both of these are independent risk factors for CVD. Especially in patients with type 2 diabetes, renal function should be assessed at the time of diagnosis. Angiotensin converting enzyme inhibitor therapy should be initiated if albumin excretion is over 300 mg per day or if the glomerular filtration rate is <60 mL/min/1.73 m^2. This treatment has a role in renal function as well as prevention of CVD development [10].

The first step in the treatment of dyslipidemia in diabetic patients is lifestyle changes. These changes are regulating the diet, weight loss if necessary, and increasing physical activity. However, if LDL cholesterol level>100 mg/dL despite the change in life style for those with proven cardiovascular disease (CVD), those with microvascular and macrovascular complications of diabetes, those over 40 and with one or more other cardiovascular risk factors (CVD family history, hypertension, smoking, dyslipidemia or albuminuria), those under 40 and with no CVD, statin should be added to the treatment regardless of baseline lipid levels [7]. In dyslipidemia, the primary goal should be lowering LDL-cholesterol. Target level of LDL-cholesterol should be <100 mg/dL in patients without proven cardiovascular disease and <70 mg/dl in patients with cardiovascular disease. If the desired values are not reached despite maximal statin therapy, a 50% reduction of baseline LDL cholesterol levels should be aimed [8].

21.3% of the patients were using statin, and this percentage was significantly higher (59.43%) for patients under 65 years of age as compared with patients over 65 years of age (40.56%). Morbidity and mortality in type 2 diabetes patients is due to major cardiovascular events. For this reason, the main goal of treatment in these patients is to reduce vascular risks. Dyslipidemia is the most important risk factor for atherosclerotic events and deaths, and must definitely be investigated and treated. As with other diseases, it is essential to lower LDL-cholesterol primarily to prevent vascular complications related to diabetes. Effective treatment of diabetic dyslipidemia is important in reducing cardiovascular risk. Lowering LDL-cholesterol with statins is the most effective treatment option. However, it should be kept in mind that LDL cholesterol levels are a significant residual risk in diabetic patients, even if they are maintained within safe limits. ADA suggests lifestyle changes to diabetic patients over 40 years of age, independent of lipid levels. American Heart Association and American College of Cardiology guidelines recommend statin therapy independent of cardiovascular risk for diabetic patients aged 40-75 years with LDL-C $\geq$ 70 mg/dL.

In another guideline, statin therapy is recommended for diabetic patients aged 40-75 years, even if there is no additional cardiovascular risk. Our results indicate that the use of statin remains relatively low and is an indication that these patients do not fully benefit from primary prevention [11]. Following American Heart Association's 2013 guideline, there

has been an increase in the use of statins, but there is insufficient evidence of the effects of statin use in primary prevention in patients who are older than 75 years of age. It should not be forgotten that there might be an increase in muscle symptoms and risks of side effects due to drug interactions due to the use of statin in the elderly [12-15].

Aspirin was used by 9.8% of our patients. The risk of coronary artery disease (CAD) is increased in DM patients, even more so in type 2 DM patients. Low-dose aspirin (75-150 mg/day) may be administered to diabetic patients with stable cardiovascular disease (CVD). Aspirin (75-150 mg) may be administered with the purpose of primary prevention to diabetic patients with a 10-year CV event risk>10% [9]. It should be noted that the use of aspirin in older patients, even with low doses, increases the risk of gastrointestinal bleeding, therefore cardiovascular risks and possible side effects should be carefully questioned when using aspirin in elderly diabetic patients [16,17].

Routine cardiac control is necessary for asymptomatic diabetic patients. Exercise stress test is recommended for both symptomatic and asymptomatic diabetics with certain criteria (those with typical or atypical cardiac symptoms, those with findings of ischemia or infections in resting ECG, those with peripheral artery and/or carotid obstruction). In addition, exercise stress test may be recommended in type 1 diabetic patients with more than 15 years of diabetes, type 2 diabetics with more than 10 years of diabetes, and type 2 diabetic patients older than 35 years [18]. Clinicians should be on the alert for diabetic patients who describe atypical symptoms (resting tachycardia, postural hypotension, erectile dysfunction, peripheral arterial disease, etc.).

In conclusion, the use of multiple treatments such as statins, angiotensinogen-dependent treatments, and aspirin in patients with DM2 is associated with a reduction in all-cause mortality. Secondary prevention, however, depends on the early selection of cases, and the initiation of appropriate preventive treatments; progression of the disease can only be stopped this way. Nephropathy and other complications should be investigated in patients with known diabetes mellitus with CAD, and the goal of glycemic control that is most appropriate to the patient should be ensured without increasing the risk of hypoglycemia. In addition to mild glycemic control to reduce the risk of CAD in type 2 diabetes, a multifactorial approach (change in lifestyle, lipid and BP control and antiaggregant use, as well as avoidance of harmful agents such as smoking) should be adopted.

References

1. American Diabetes Association. Diagnosis and classification of diabetes melitus. Diabetics Care 2010; 33: S62-S69.
2. Satman I, Omer B, Tutuncu Y, Kalaca S, Gedik S, Dinccag N, Karsidag K, Genc S, Telci A, Canbaz B, Turker F, Yilmaz T, Cakir B, Tuomilehto J. TURDEP-II Study Group. Twelve-year trends in the prevalence and risk factors of diabetes and prediabetes in Turkish adults. Eur J Epidemiol 2013; 28: 169-180.
3. International Diabetes Federation Clinical Guidelines Task Force. Global Guideline for Type 2 Diabetes. International Diabetes Federation, Brussels, 2012.
4. Mamur A, Bilge U, Kebapci MN, Unluoglu I. Achieving the target level of glycated haemoglobin in type 2 diabetes mellitus patients: method of treatment and body mass index in question. Biomed Res 2017; 28: 447-454.
5. Adler AI, Stratton IM, Neil HA. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. BMJ 2000; 321: 412-419.
6. James PA, Oparil S, Carter BL. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC8). JAMA 2014; 311: 507-520.
7. American Diabetes Association. Standards of medical care on diabetes. J Clin Appl Res Edu 2015; 38: 37.
8. Shepherd J, Barter P, Carmena R. Effect of lowering LDL-cholesterol substantially below currently recommended levels in patients with coronary heart disease and diabetes: the Treating to New Targets (TNT) study. Diabetes Care 2006; 29: 1220-1226.
9. Pignone M, Alberts MJ, Colwell JA, Cushman M, Inzucchi SE, Mukherjee D, Rosenson RS, Williams CD, Wilson PW, Kirkman MS. Aspirin for primary prevention of cardiovascular events in people with diabetes: a position statement of the American Diabetes Association, a scientific statement of the American Heart Association, and an expert consensus document of the American College of Cardiology Foundation. Circulation 2010; 121: 2694-2701.
10. Stahrenberg R, Edelmann F, Mende M, Kockskämper A, Düngen HD, Scherer M, Kochen MM, Binder L, Herrmann-Lingen C, Schönbrunn L, Gelbrich G, Hasenfuss G, Pieske B, Wachter R. Association of glucose metabolism with diastolic function along the diabetic continuum. Diabetologia 2010; 53: 1331-1340.
11. American Diabetes Association. Cardiovascular Disease and risk management. Sec. 8. In Standards of MedicalCare in Diabetes-2016. Diabetes Care 2016; 39: S60-S71.
12. American Diabetes Association. Standards of medical care in diabetes-2014. Diabetes Care 2014; 37 Suppl 1: S14-80.
13. Stone NJ, Robinson JG, Lichtenstein AH. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014; 63: 2889-2934.
14. Han BH, Sutin D, Williamson JD. ALLHAT Collaborative Research Group. Effect of statin treatment vs. usual care on primary cardiovascular prevention among older adults: the ALLHAT-LLT randomized clinical trial. JAMA Int Med 2017; 177: 955-965.

15. Ridker PM, Lonn E, Paynter NP, Glynn R, Yusuf S. Primary prevention with statin therapy in the elderly: new meta-analyses from the contemporary JUPITER and HOPE-3 randomized trials. Circulation 2017; 135: 1979-1981.
16. Higuchi T, Iwakiri R, Hara M. Low-dose aspirin and comorbidities are significantly related to bleeding peptic ulcers in elderly patients compared with nonelderly patients in Japan. Int Med 2014; 53: 367-373.
17. Sirois C, Moisan J, Poirier P, Grégoire JP. Myocardial infarction and gastro-intestinal bleeding risks associated with aspirin use among elderly individuals with type 2 diabetes. Ann Med 2014; 46: 335-340.
18. Harris GD, White RD. Exercise StressTesting in PatientsWithType 2 Diabetes: When are Asymptomatic Patients Screened? Clin Diabetes 2007; 25: 126-130.

***Correspondence to**

Uğur Bilge

Department of Family Medicine

Faculty of Medicine

Eskisehir Osmangazi University

Turkey