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Are patients, who were previously diagnosed with coronary artery disease by coronary angiography, on optimal medical treatment?

Önceden koroner anjiyografi ile koroner arter hastalığı tanısı konulmuş hastalar uygun medikal tedavi altında mı?

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ABSTRACT

Background: This study aims to detect the drug usage rate of patients who had coronary artery disease (CAD) diagnosis by coronary angiogram (CAG).

Methods: Reports of 1,549 patients (993 males, 556 females; mean age 62.9±10.9 years; range 20 to 87 years) (184 normal CAG, 1,365 CAD) who were performed CAG between October 2009 and February 2012 were retrospectively analyzed. Medication data were collected between August 2013 and November 2013 from patients' pharmacy refill data. Usage of aspirin, tienopiridine, statin, angiotensin converting enzyme inhibitor, beta blocker (BB), warfarin, angiotensinogen receptor blocker, nitrate, trimetazidine, calcium channel blocker, and diuretic were recorded.

Results: Usage rates of angiotensinogen receptor blocker, trimetazidine, calcium channel blocker, warfarin, diuretic, and fibrate were not statistically different between patients with CAD and normal CAG. Rates of using aspirin (50.3% vs. 39.1%, p=0.005), tienopiridine (25.6% vs. 9.8%, p<0.001), angiotensin converting enzyme inhibitor (38.0% vs. 21.7%, p<0.001), statin (48.5% vs. 30.6%, p<0.001), BB (56.8% vs. 40.2%, p<0.001) and nitrate (15.1% vs. 6.0%, p<0.001) were higher in patients with CAD. Rate of patients using all four drugs, antiplatelet agent, statin, angiotensin converting enzyme inhibitor, and BB was only 13.1% in CAD group. Only 25.8% of patients with CAD used all three of antiplatelet agent, statin, and BB.

Conclusion: Patients with CAD are not on optimal medical treatment. These patients should be questioned in every visit in terms of the status of their treatment to administer the optimum medications to reduce cardiovascular mortality and morbidity.

Keywords: Coronary angiography; coronary artery disease; medication adherence.

ÖZ

Amaç: Bu çalışmada koroner anjiyografi (KAG) ile koroner arter hastalığı (KAH) tanısı konulmuş hastaların ilaç kullanımı oranlarının saptanması amaçlandı.

Çalışma planı: Ekim 2009 - Şubat 2012 tarihleri arasında KAG yapılmış 1549 hastanın (993 erkek, 556 kadın; ort. yaş 62.9±10.9 yıl; dağılım 20-87 yıl) raporları (184 normal KAG, 1365 KAH) geriye dönük olarak incelendi. İlaç kullanım bilgileri Ağustos 2013 - Kasım 2013 tarihleri arasında hastaların eczane ilaç kayıt bilgilerinden edinildi. Aspirin, tienopiridin, statin, anjiyotensin dönüştürücü enzim inhibitörü, beta bloker (BB), varfarin, anjiyotensinojen reseptör blokeri, nitrat, trimetazidin, kalsiyum kanal blokeri ve diüretik kullanımları kaydedildi.

Bulgular: Anjiyotensinojen reseptör blokeri, trimetazidin, kalsiyum kanal blokeri, varfarin, diüretik ve fibrat kullanımı oranları KAH'li ve normal KAG'li hastalar arasında istatistiksel olarak farklı değildi. Aspirin (%50.3'e karşı %39.1, p=0.005), tienopiridin (%25.6'ya karşı %9.8, p<0.001), anjiyotensin dönüştürücü enzim inhibitörü (%38.0'a karşı %21.7, p<0.001), statin (%48.5'e karşı %30.6, p<0.001), BB (%56.8'e karşı %40.2, p<0.001) ve nitrat (%15.1'e karşı %6.0, p<0.001) kullanımı oranları KAH'li hastalarda daha yüksekti. KAH grubunda dört ilacın tamamını ve antitrombosit ajan, statin, anjiyotensin dönüştürücü enzim inhibitörü ve BB kullanan hasta oranı sadece %13.1 idi. KAH'li hastaların sadece %25.8'i antitrombosit ajan, statin ve BB'nin üçünü birden kullanıyordu.

Sonuç: Koroner arter hastalığı olan hastalar uygun tedavi altında değildir. Kardiyovasküler mortalite ve morbiditesini azaltmak için en uygun ilaçları uygulamak amacıyla bu hastalar her başvurularında tedavi durumları açısından sorgulanmalıdır.

Anahtar sözcükler: Koroner anjiyografi; koroner arter hastalığı; ilaç bağımlılığı.

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Coronary artery disease (CAD) is a worldwide problem and the number one cause of mortality in high and middle income countries.[1,2] It is also the most common cause of mortality in Turkey, with nearly half of all deaths being attributed to this disease.[3] Medications, percutaneous coronary angioplasty (PTCA), and coronary artery bypass graft (CABG) surgery are used to treat patients with CAD, but optimal medical treatment is the cornerstone for managing CAD patients, regardless of which procedure is used.[4] Coronary angiography (CAG) is the gold standard for diagnosing CAD, and once the diagnosis is made, secondary prevention should be a primary goal.

Certain drugs, for example acetylsalicylic acid (ASA), statins, beta blockers, and angiotensin-coverting enzyme (ACE) inhibitors, are strongly recommended for the management of CAD.[4] Adherence to medication is related to mortality and morbidity and is influenced by many factors, including socioeconomic status, comorbidities, drug side effects, insurance status, and pricing policies.[5-8] In addition, some patients stop taking their medications of their own accord and do not continue their follow-up visits. Our observations in daily practice suggest that adherence to medication is still inadequate despite better insurance policies and the greater availability of beneficial drugs. In this study, we aimed to evaluate whether or not CAD patients in Turkey who underwent CAG were adhering to their recommended medications.

PATIENTS AND METHODS

This retrospective study was composed of 1,549 patients (993 males, 556 females; mean age 62.9±10.9 years; range 20 to 87 years) who underwent CAG at our institution between October 2009 and February 2012. We analyzed the handwritten reports of the CAG results with regard to the patients' age and gender and also included those patients with normal CAG results to serve as the control group. The data related to their medications was collected between August 2013 and November 2013 from the patients' pharmacy refill data, which showed the drugs that had been used by the patients at least for the past year. We recorded the use of ASA, thienopyridine, statins, ACE inhibitors, beta blockers, warfarin, angiotensin receptor blockers (ARBs), nitrates, trimetazidine (TMZ), calcium channel blockers (CCBs), and diuretics. If the patient was prescribed a drug but had not taken it in the previous six months, we accepted that it was not being used by the patient. We also looked for the use of insulin and oral antidiabetics to identify diabetic patients and we recorded the drugs that are commonly used in the treatment of peripheral artery disease (PAD), such as pentoxifylline and cilostazol, in order to identify patients with this disease. Because the CAG results were handwritten, some patients' names were incorrect, so patients who were unmatched because of recording errors or those with the same name were excluded from the study. We also looked at the drug lists, and anyone who was taking medicine at a time that corresponded with the available data was accepted as alive. The patients with no drug information on file could have been dead or were deemed to not be adherent to their medication. For these patients, the Central Civil Registration System (MERNIS) was utilized to try to identify them before beginning the study. Those who had died at least one year after the CAG was performed were included in the study, and we analyzed the data for the year prior to their death.

The patients were divided into the following four groups: group 1 was composed of the patients with normal CAG results (control), group 2 was made up of those with nonobstructive CAD (<50% stenosis of the major epicardial coronary arteries, medically treated small side branch disease in which the degree of stenosis was unimportant, slow coronary flow, coronary ectasia without obstructive CAD, and medically managed myocardial bridges), group 3 was comprised of patients who had undergone percutaneous coronary intervention (PCI) (i.e., those with previous stents, ad hoc PCI, or planned PCI), and group 4 was made up of CAGB patients (i.e., those who had undergone previous CABG or who planned to undergo CABG). In addition, we added six patients with diffuse CAD to group 4 who were not suitable for revascularization. We then compared group 1 with the other groups to evaluate the differences between their primary and secondary prevention status. This study was approved by the local ethics committee.

Statistical analyses

All statistical analyses were carried out using the SPPS version 15.0 for Windows software program (SPSS Inc., Chicago, IL, USA). The quantitative variables were expressed as medians (minimum-maximum) while the qualitative variables were expressed as percentages (%). Furthermore, all of the measurements were evaluated using the Kolmogorov-Smirnov test. A comparison of the continuous values between the four groups was performed using the Kruskal-Wallis test, whereas the Mann-Whitney U test was used for comparisons between two groups. In addition, the categorical variables were compared using a chi-square test. A p value of <0.05 was considered to be statistically significant.

RESULTS

The comparison between group 1 (primary prevention group; n=184) and the CAD patients (secondary prevention group; n=1365) is shown in Table 1. The baseline characteristics and drug use rates of the patients are given based on the presence of CAD. However, this information is given based on CAD severity in Table 2. The combination therapy rates are presented in Table 3. In the group 1, 20.2% of the patients used both an antiplatelet agent and a statin while 38.9% of the CAD patients (groups 2, 3, and 4 combined) utilized this type of therapy. In addition, 22.3% of the patients in group 1 used an antiplatelet agent and a beta blocker, whereas the rate was 44.5% for the CAD patients. Furthermore, 12.5% of the patients in group 1 used an antiplatelet agent, a beta blocker, and a statin while 25.8% of the CAD patients used this combination. Finally, 3.8% of the patients in group 1 used the four-drug combination of an antiplatelet, a beta blocker, a statin, and an ACE inhibitor, whereas the rate was 13.1% for the CAD group.

The drug use rates did not differ according to age, except for the statins and nitrates. The patients over the age of 70 were significantly less likely be on statin therapy (43.7% <50 years old, 47.0% between 50 and 70 years old, and 33.2% >70 years old; p<0.001). However, the rates for the use of nitrates gradually increased by age (7.6% <50 years old, 12.5% between 50 and 70 years old, and 17.2% >70 years old; p=0.015).

DISCUSSION

Our study had several implications. First, certain drugs, such as ASA, statins, beta blockers, and ACE inhibitors, which are strongly recommended for both primary and secondary prevention of CAD, were underused. We found that roughly half of the patients were not taking any of these drugs. In addition, the primary prevention group was significantly undertreated compared with the secondary prevention group. Furthermore, some drugs, for example TMZ and nitrates, may be inadvertently used to treat CAD patients.

Table 1. Patient characteristics and the number of participants using each drug

	Primary prevention (Normal CAG) (n=184)			Secondary prevention (CAG-proven CAD) (n=1,365)			
	n	%	Range	n	%	Range	*p*
Age	57		20-80	65		27-88	<0.001
Gender							
Males		46.7			66.5		<0.001
Females		53.3			33.5		
Comorbidities							
Diabetes mellitus	39	21.2		399	29.2		0.023
Peripheral artery disease	20	10.9		116	8.5		0.287
Drugs							
Acetylsalicylic acid	72	39.1		686	50.3		0.005
Only acetylsalicylic acid	69	37.5		557	40.8		0.391
Only tienopiridine	15	8.2		220	16.1		0.005
Acetylsalicylic acid + tienopiridine	3	1.6		129	9.5		<0.001
Warfarin	13	7.1		68	5.0		0.235
Tienopiridine	18	9.8		349	25.6		<0.001
Statins	56	30.6		662	48.5		<0.001
Fibrates	6	3.3		43	3.2		0.928
Beta blockers	74	40.2		775	56.8		<0.001
Angiotensin-converting enzyme inhibitors	40	21.7		519	38.0		<0.001
Angiotensin receptor blockers	56	30.4		372	27.3		0.368
Nitrates	11	6.0		206	15.1		<0.001
Trimetazidine	25	13.6		204	14.9		0.626
Calcium channel blockers	50	27.2		290	21.3		0.069
Diuretics	81	44.0		635	46.5		0.523

CAG: Coronary angiography; CAD: Coronary artery disease.

Table 2. Patient characteristics by coronary artery disease subgroups and the number of patients using each drug

	Normal (n=184)			Non-obstructive			PCI			CABG			
	n	%	Range	n	%	Range	n	%	Range	n	%	Range	*p*
Age	57		20-80	62		32-87	65		27-87	67		41-88	<0.001
Gender													
Males		46.7			51.6			72.7			75		
Females		53.3			48.4			27.3			25		<0.001
Comorbidities													
Diabetes mellitus	39	21.2		110	25.1		186	30.4		103	32.6		0.012
Peripheral artery disease	20	10.9		46	10.5		39	6.4		31	9.8		0.059
Drugs													
Acetylsalicylic acid	72	39.1		190	43.4		312	51.1		184	58.2		<0.001
Only acetylsalicylic acid	69	37.5		181	41.3		215	35.2		161	50.9		<0.001
Only tienopiridine	15	8.2		29	6.6		137	22.4		54	17.1		<0.001
Acetylsalicylic acid + TP	3	1.6		9	2.1		97	15.9		23	7.3		<0.001
Warfarin	13	7.1		23	5.1		25	4.1		20	6.4		0.309
Tienopiridine	18	9.8		38	8.7		233	38.3		77	24.4		<0.001
Statins	56	30.6		132	30.1		359	58.9		171	54.1		<0.001
Fibrates	6	3.3		9	2.1		22	3.6		12	3.8		0.460
Beta blockers	74	40.2		179	40.9		386	63.2		210	66.5		<0.001
ACE inhibitors	40	21.7		118	26.9		261	42.7		140	44.3		<0.001
Angiotensin receptor blockers	56	30.4		137	31.3		162	26.5		73	23.2		0.067
Nitrates	11	6.0		28	6.4		103	17.0		75	23.7		<0.001
Trimetazidine	25	13.6		60	13.7		95	15.5		49	15.5		0.793
Calcium channel blockers	50	27.2		115	26.3		109	17.9		66	20.9		<0.001
Diuretics	81	44.0		202	46.1		285	46.6		148	46.8		0.929

PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass grafting; TP: Tienopiridine; ACE: Angiotensin-converting enzyme.

Adherence to medication is a multifactorial issue and is related to mortality.[5-8] Some studies have even shown that adherence to placebos is associated with decreased mortality.[9] In general, between 20 and 50% of patients do not adhere to their medications.[5-8] Jackevicius et al.[10] determined that 25% of the patients in their study were not taking their drugs seventh day after the index discharge from the hospital for treatment of acute myocardial infraction (AMI). The time interval between the initial diagnosis and the rate of adherence to medication is very important because longer intervals lead to decreased adherence. Newby et al.[11] found that six to 12 months after being diagnosed with CAD by CAG, only 21% of the patients in their study were still taking the three-drug combination of ASA, beta blockers, and statins. Similarly, only 25.8% of the CAD patients were taking these drugs in our study, and when an ACE inhibitor was added as a fourth drug, the rate declined even more to 13.1%.

For both primary and secondary prevention, antiplatelet therapy is one of the cornerstones of medical treatment for CAD.[12] In our study, 50.3% of the CAD patients and 39.1% of the control group were taking ASA. When agents like tienopiridine and warfarin were added, 28.6% of the CAD patients still did not use any antiplatelet agent or warfarin. When we investigated the subgroups of CAD patients, we found significant in ASA usage rates. The CABG patients in group 4 were more likely to be taking ASA, but even in this group, the usage rate was only 58.2%. In the European Action on Secondary and Primary

Table 3. Combination therapy rates in the study populations

	Normal CAG (n=184)		CAD (n=1365)		
	n	%	n	%	*p*
APA and statins	37	20.2	530	38.9	<0.001
APA and beta blockers	41	20.3	608	44.5	<0.001
APA, beta blockers, and statins	23	12.5	399	25.8	<0.001
APA, beta blockers, statins, and ACE inhibitors	7	3.8	179	13.1	<0.001

CAG: Coronary angiography; CAD: Coronary artery disease; APA: Antiplatelet agent; ACE: Angiotensin-converting enzyme.

Prevention through Intervention to Reduce Events III (EUROASPIRE III) survey, the trial rate of antiplatelet use for CAD patients six months after being discharged was 90.5%.[13] Tokgözoğlu et al.[14] performed an analysis of the Turkish patients who participated in this trial and discovered that 91.4% were on antiplatelet therapy in the sixth month of index evaluation. Since our study included patients who had been diagnosed with CAD one to three years previously, our findings support the fact that more patients eventually stop taking their medication.

Another therapy of choice for CAD is statin treatment for both primary and secondary prevention.[12,15] Statins lower cardiovascular morbidity and mortality and also reduce the need for PCI.[16] Furthermore, they may slow the progression of atherosclerosis and might even cause a regression in atherosclerotic plaques.[17] Because of this, statins are recommended for CAD patients regardless of their cholesterol levels.[18] Our study results were disappointing because nearly half (48.5%) of the patients were on statin therapy in the CAD group and nearly a third of the patients (30.6%) in the primary prevention group were on this therapy. In the EUROASPIRE III trial,[13] 78.1% of the patients were using statings six months after being discharged, but the rate was only 65.9% for the Turkish subgroup.[14] In our study, the rate of statin usage also differed as only a third of the patients in groups 1 and 2 were using statins while nearly 60% of patients in groups 3 and 4 were taking this medication.

Beta blockers are the firstline therapy for patients suffering from MI.[4,12] Although their role in stable CAD is questioned nowadays,[19] it has been shown that beta blockers may reduce the progression of atherosclerosis[20] and that they might possibly even reduce mortality in stable CAD patients.[21] The six-month rate for the use of beta blockers after discharge in the EUROASPIRE III survey was 83.1%, but just 69.0% in the Turkish subgroup. In our study, the rate was 56.8% in the CAD group and 40.2% in group 1. We also found differences between the CAD subgroups in our study. While 66.5% of the patients in group 4 and 63.2% of the patients in group 3 were using beta blockers, only 40.9% of group 2 were taking this medication. This is interesting because although ASA and statins are recommended more than beta blockers, our patients actually used them less frequently for both primary and secondary prevention.

The role of ACE inhibitors for the treatment of systolic dysfunction has been thoroughly studied, and they have been found to clearly reduce mortality and morbidity.[12] Additionally, lower mortality and morbidity rates have been reported in atherosclerotic patients with normal left ventricular function who take ACE inhibitors.[22] Furthermore, although they are not anti-anginal drugs, ACE inhibitors may also cause a reduction in future ischemic events.[23] In cases of intolerance or when the use of ACE inhibitors is contraindicated, ARBs can be used. In the EUROASPIRE III study, their rate of ACE inhibitor or ARB usage was 70.9% six months after being discharged,[13] and in the Turkish subgroup, the rate was 69.0%.[14] In our study, the cumulative usage rate for ACE inhibitors and ARBs was 65.3% (38.0% for ACE inhibitors and 27.3% for ARBs) in the CAD group and 52.1% (21.7% ACE inhibitors and 30.4% for ARBs) in the control group. Differences among the four groups were also observed. While groups 3 and 4 preferred ACE inhibitors, groups 1 and 2 preferred ARBs, and our usage rates (70.9% in our study and 69% in the mentioned study) were nearly the same as those of the Turkish participants in the EUROASPIRE III survey.[14]

Nitrates are effective for relieving acute anginal attacks, but chronic use should be avoided due to tolerance problems and associated side effects. In addition, they have not been shown to decrease mortality.[24] No data is available regarding nitrate usage rates among CAD patients in Europe or Turkey. In our study, we found that 6% of the control group and 15.1% of the CAD patients were on nitrate therapy. Furthermore, in the CAD subgroups, 6.8% of the patients in group 2, 17.0% of the patients in group 3, and 23.7% of the patients in group 4 were using nitrates. We also think groups 1 and 2 were using nitrates inadvertently. Additionally, complete revascularization is more possible with CABG, which reduces the need for nitrates. However, our findings showed higher nitrate usage among the CABG patients (group 4) than the PCI patients (group 3).

Calcium channel blockers are used as an anti-anginal agent for beta blocker-intolerant patients or in combination with beta blockers for refractory angina. They also they play a favorable role in cardioprotection.[4,25] In the EUROASPIRE III trial, 24.5% of the patients were found to be using CCBs six months after being discharged,[13] and 14.2% of the Turkish participants were receiving CCB therapy.[14] In our study, the rates (27.2% for group 1 and 21.3% for the CAD patients) were higher than for the EUROASPIRE III Turkish patients and nearly the same as the European participants. Recent guideline[26] has also recommended a combination

of renin angiotensin system blockers and CCBs for cardiovascular protection. Since the EUROASPIRE III trial was conducted in 2006-2007, the use of CCBs has become more popular in Turkey perhaps because of the increased implementation of new guidelines.

Diuretics have no special role in the treatment of CAD, but they are commonly used for patients with heart failure (HF) and hypertension (HT). The diuretic usage rate in our study was very high (nearly 50%) regardless of CAD severity. In contrast, the rate was 30.2% in the EUROASPIRE III trial and 27.6% in the Turkish subgroup in that survey. This may indicate the inadvertent use of diuretics or it might have stemmed from the higher numbers of HF and HT patients. Unfortunately, we did not determine the number of patients with HT and HF in our study.

Interestingly, the TMZ usage rates did not differ between the CAD subgroups in our study as nearly 15% of the participants (including group 1) were using this drug. Trimetazidine should be used as a secondline therapy for stable CAD with a weak level of indication (Class IIb, level B), but there is no rationale for using it for normal CAD or nonobstructive CAD.[4]

Our study had some limitations. First of all, it was retrospective and cross- sectional in nature, but the method used for defining the drug use status (pharmacy refill data) is well-known;[5-8] hence, we do not think that our findings would have differed significantly if we had conducted a prospective study. We also used handwritten forms to record the CAG results and a simple classification system for determining CAD severity based on the suggested therapy option. It would have been better to use Gensini or SYNTAX scores for defining CAD severity, but this was not feasible because it's time consuming for us. In addition, we were able to evaluate the diabetic patients in our study based on their medications, but we could not do the same for those with HF and HT because the same drugs may be used for both conditions. Furthermore, we did not include any laboratory measurements to show the rate of achieved lipid goals or data regarding the patients' lifestyles, such as their smoking status, exercise status, dietary adherence, and obesity status, all of which account for nearly half of the secondary prevention goals. Another limitation was that some of the patients may have lived abroad; thus, they could have been placed in the nonadherent category. However, if we had done this, we think that it would have had a negligible effect on our results because a number of immigrants live in our city. Finally, some of the patients may have used the drugs without a prescription; therefore, their information would not have been included in the pharmacy refill data. However, since we took our patients' socioeconomic status into consideration, we do not believer that this would have significantly affected our results.

Conclusion

We found that nearly half of the patients with CAD in our study were not using evidence-based medications to reduce morbidity and mortality. Therefore, patients must be constantly questioned with regard to their medications at every doctor's visit, and the medications should be optimized for every patient.

Declaration of conflicting interests

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