

The impact of diabetes and coronary artery disease on mortality and morbidity in patients with hypertension

Hipertansiyonlu hastalarda diyabet ve koroner arter hastalığının mortalite ve morbidite üzerine etkisi

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Objectives: We evaluated the impact of diabetes mellitus (DM) and/or coronary artery disease (CAD) on cardiovascular endpoints in a cohort of hypertensive patients.

Study design: The Vascular Risk Study is a cross-sectional, multicenter, observational study conducted among 5,600 patients from various regions of Turkey. This analysis included 2,664 patients (1,643 women, 1,021 men; mean age 65.3 years; range 55-99 years) whose follow-up data were adequate among a population of 4,506 hypertensive subjects. Cardiovascular primary and secondary endpoints at the end of a five-year follow-up were assessed in patients who had hypertension alone, and in those having DM and/or CAD. Information on the cause of death was obtained from the relatives of the patients by follow-up phone calls.

Results: There were 1,171 patients (44%) with isolated hypertension, 631 (23.7%) with DM, 530 (19.9%) with CAD, and 332 (12.5%) with both DM and CAD. The presence of either DM or CAD was associated with significant increases in the incidences of all endpoints. The occurrences of primary and secondary endpoints, cardiovascular death, and all death were similar in hypertensive patients who had DM without CAD and in patients who had CAD without DM. In survival analysis, the incidence of cardiovascular death was lowest (5.7%) in hypertensive patients without DM and CAD, and highest (18.4%) in hypertensive patients with DM and CAD. The cumulative survival rates were similar in hypertensive patients with either DM or CAD alone ($p>0.05$).

Conclusion: This study demonstrated that the level of cardiovascular risk associated with DM was equal to the risk associated with CAD in hypertensive patients and that the coexistence of DM and CAD in these patients increases the risk geometrically.

Key words: Cardiovascular diseases/epidemiology; coronary artery disease/epidemiology; diabetes mellitus/epidemiology; hypertension/complications/epidemiology; risk factors.

Amaç: Hipertansif hastalarda diabetes mellitus (DM) ve/veya koroner arter hastalığının (KAH) kardiyovasküler sonlanım noktaları üzerine etkisi değerlendirildi.

Çalışma planı: Kesitsel, çokmerkezli, gözlemsel bir çalışma olan Vasküler Risk Çalışması, Türkiye'nin farklı bölgelerinden 5600 hasta ile yürütülmektedir. Bu çalışma grubunda yer alan hipertansiyonlu 4506 hastadan takipleri yapılan 2664'ü (1643 kadın, 1021 erkek; ortalama yaş: 65.3; dağılım 55-99) değerlendirildi. Beş yıllık takip sonundaki kardiyovasküler birincil ve ikincil sonlanım noktaları, sadece hipertansiyon bulunan hastalarda ve DM ve/veya KAH bulunan hastalarda araştırıldı. Ölüm nedeniyle ilgili bilgi hastaların yakınlarından takip telefonlarıyla elde edildi.

Bulgular: İncelenen hastaların 1171'inde (%44) sadece hipertansiyon, 631'inde (%23.7) DM, 530'unda (%19.9) KAH, 332'sinde (%12.5) DM ve KAH vardı. Diyabet ve KAH'den birinin olduğu hastalarda tüm sonlanım noktalarında anlamlı artış görüldü. Birincil ve ikincil sonlanım noktaları, kardiyovasküler ölüm ve tüm nedenli ölümlerin oranları, hipertansiyon yanında sadece DM olan ve sadece KAH olan hastalarda benzer bulundu. Sağkalım analizinde, en düşük kardiyovasküler ölüm oranı sadece hipertansiyon olan hastalarda (%5.7), en yüksek oran ise hem DM hem de KAH olan hastalarda (%18.4) görüldü. Hipertansif grupta sadece DM ve sadece KAH olan hastalarda kümülatif sağkalım oranları benzer bulundu ($p>0.05$).

Sonuç: Bu çalışmada, hipertansif hastalarda DM varlığının oluşturduğu kardiyovasküler riskin, KAH varlığının oluşturduğu riske eşit olduğu ve bunların ikisinin bir arada bulunduğu hipertansif hastalarda riskin geometrik olarak arttığı gösterilmiştir.

Anahtar sözcükler: Kardiyovasküler hastalık/epidemioloji; koroner arter hastalığı/epidemioloji; diabetes mellitus/epidemioloji; hipertansiyon/komplikasyon/epidemioloji; risk faktörü.

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Hypertension and diabetes mellitus (DM) are major independent risk factors for cardiovascular outcomes. The coexistence of hypertension and diabetes is a common condition and it doubles the risks associated with diabetes alone.^[1-3] The risk level of myocardial infarction (MI) in diabetic patients with no previous MI history was found to be similar to that of nondiabetic patients with MI history.^[4] Thus, in general population, diabetes and coronary artery disease (CAD) are accepted as equivalent risk factors.

The aim of this study was to estimate and compare the effect of the presence of diabetes and/or CAD on cardiovascular outcomes in a cohort of hypertensive patients.

PATIENTS AND METHODS

Study patients. The Vascular Risk Study is a multicenter observational cohort study conducted with 305 investigators among 5,600 patients from various regions of Turkey. The mortality and morbidity of a total of 3,331 patients were followed-up for five years. The patients enrolled in the study were >55 years old and had at least one of the following conditions: CAD, peripheral vascular disease, ischemic stroke, DM, and hypertension. Baseline demographic characteristics and comorbidities of the patients were recorded at the study entry. The details of the method were reported previously.^[5] The study protocol was approved by the Turkish Ministry of Health.

Out of the participants of the Vascular Risk Study, this analysis included 2,664 patients (1,643 women, 1,021 men; mean age 65.3 years; range 55-99 years) whose follow-up data were adequate among a population of 4,506 hypertensive subjects. The hypertensive patients were evaluated in four groups depending on the presence or absence of DM and CAD. Thus,

group 1 included nondiabetics without a history of CAD; group 2 included diabetics without a history of CAD; group 3 included nondiabetics with a history of CAD; and group 4 included diabetics with a history of CAD.

The primary endpoint of the study was a composite of death/cardiovascular death, MI, or stroke. The secondary endpoint was a composite of revascularization or hospitalization due to cardiovascular causes. Information on the cause of death was obtained from the relatives of the patients by follow-up phone calls.

Statistical analysis. The analysis of the data was performed using SPSS 11.5 software package. Numerical and categorical variables of descriptive statistics were expressed as mean±standard deviation (SD) and percentages, respectively. The groups were compared using the Student's t-test for numerical and chi-square test for categorical variables. Survival analysis was performed using the life table method. For all analyses, statistical significance level was set at <0.05.

RESULTS

In a total of 2,664 hypertensive cases, 1,171 patients (44.0%) had isolated hypertension, 631 (23.7%) had diabetes, 530 (19.9%) had CAD, and 332 (12.5%) had diabetes and CAD.

The characteristics of the study population in terms of the presence of diabetes and/or CAD are summarized in Table 1. Taking all cases into account, we found that patients with CAD were older (67.8 years vs. 65.1 years; $p=0.026$) and had a lower body mass index (27.7 kg/m² vs. 28.6 kg/m²; $p=0.001$) compared to those without CAD. Moreover, patients with CAD showed a male preponderance, had higher percentages of serum HDL-cholesterol levels of <40 mg/l

Table 1. Baseline characteristics of the study population

	Nondiabetic hypertensive patients			Diabetic hypertensive patients			All hypertensive patients	
	CAD (+) (n=530)	CAD (-) (n=1171)	<i>p</i>	CAD (+) (n=332)	CAD (-) (n=631)	<i>p</i>	<i>p</i> for CAD (+) vs. CAD (-)	<i>p</i> for DM (+) vs. DM (-)
Age (years)	65.55	65.02	0.168	66.07	65.2	0.068	0.026	0.287
Body mass index (kg/m ²)	27.05	28.4	0.001	28.76	29.11	0.065	0.001	0.001
Gender (Female/Male)	220/310	791/380	0.001	184/148	448/183	0.001	0.001	0.002
Total cholesterol >200 mg/dl (%)	48.5	52.3	0.198	54.5	56.3	0.624	0.205	0.037
HDL-cholesterol <40 mg/dl (%)	39.6	23.9	0.001	50.2	41.8	0.032	0.001	0.001
Family history of cardiovascular disease (%)	35.3	24.6	0.001	42.2	26.1	0.001	0.001	0.041
Smoking (%)	26.6	16.3	0.001	24.4	15.2	0.001	0.001	0.473

CAD: Coronary artery disease; DM: Diabetes mellitus.

Table 2. The outcomes of hypertensive patients with or without diabetes and/or coronary artery disease

	Nondiabetic hypertensive patients			Diabetic hypertensive patients			All hypertensive patients	
	CAD (+)	CAD (-)	<i>p</i>	CAD (+)	CAD (-)	<i>p</i>	<i>p</i> for CAD (+) vs. CAD (-)	<i>p</i> for DM (+) vs. DM (-)
	(n=530)	(n=1171)		(n=332)	(n=631)			
Primary endpoint (%)	20.2	13.9	0.001	29.2	19.7	0.001	0.001	0.001
Secondary endpoint (%)	40.9	15.5	0.001	39.5	22.0	0.001	0.001	0.009
Cardiovascular death (%)	9.8	5.7	0.002	18.4	8.7	0.001	0.001	0.001
All death (%)	14.3	10.2	0.012	24.1	14.9	0.001	0.001	0.001

Primary endpoint: The composite of death/cardiovascular death, MI or stroke; Secondary endpoint: The composite of revascularization or hospitalization due to cardiovascular causes; CAD: Coronary artery disease; DM: Diabetes mellitus.

dl and family history of cardiovascular disease, and included more smokers.

When the same comparisons were made between diabetic and nondiabetic patients, it was noted that diabetic patients had higher BMI values (30 kg/m² vs. 28 kg/m²; *p*=0.001), showed a female preponderance, and displayed higher percentages of serum total cholesterol levels of >200 mg/dl, serum HDL-cholesterol levels of <40 mg/dl, and family history of cardiovascular disease.

Table 2 demonstrates the incidences of endpoints according to the presence of diabetes and/or CAD. The analysis revealed that the presence of CAD increased the incidence of all endpoints in patients both with and without diabetes. The occurrences of primary and secondary endpoints, cardiovascular death, and all death were similar in diabetic hypertensive patients without a history of CAD (group 2) and hypertensive patients who had a history of CAD but not diabetes (group 3) (19.7% vs. 20.2%; 22% vs. 40.9%; 8.7% vs. 9.8%; and 14.9% vs. 14.3%, respectively). When all hypertensive patients were taken into account, it was observed that the presence of either diabetes or CAD was associated with a significant increase in the incidence of all endpoints.

Survival analysis (Fig. 1) revealed that the incidence of cardiovascular death was lowest in nondiabetic hypertensive patients who did not have CAD (group 1) and highest in diabetic hypertensive patients who had CAD (group 4). The cumulative survival curves based on cardiovascular mortality were similar in hypertensive patients with either diabetes or CAD alone (group 2 and 3) (*p*=0.8797).

The evaluation of the use of antihypertensive medications in hypertensive patients showed that the mean number of antihypertensive drugs was 1.5 at baseline and 0.8 at the end of 60 months. At baseline, 4.4% of

hypertensive patients were not using any antihypertensive medication, 53.6% were taking antihypertensive monotherapy, and 42% were on antihypertensive combination. At the end of 60 months, these ratios were 50.5%, 25.3%, and 24.1%, respectively.

The proportion of regularly used antihypertensive medications (confirmed by at least three phone calls) for 60 months was 32.5% for angiotensin converting enzyme inhibitors, 23.1% for calcium channel blockers, 20% for beta-blockers, and 20.3% for angiotensin receptor blockers. When the ratios of concomitant medications at baseline and at the end of 60 months were compared, it was noted that the use of almost all medications showed a gradual decrease by time (Fig. 2).

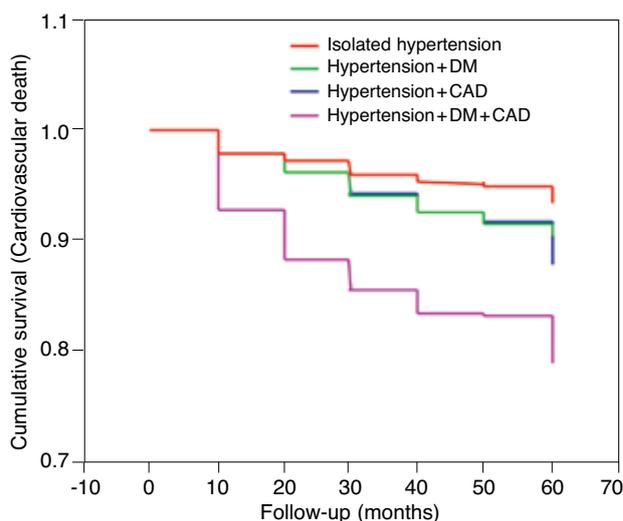


Figure 1. The survival curves for cardiovascular deaths in four risk groups of hypertensive patients. Comparisons by Wilcoxon test were as follows: Isolated HT vs. HT+DM, *p*=0.011; Isolated HT vs. HT+CAD, *p*=0.022; Isolated HT vs. HT+CAD+DM, *p*=0.001; HT+DM vs. HT+CAD, *p*=0.901; HT+DM vs. HT+CAD+DM, *p*=0.001; HT+CAD vs. HT+CAD+DM, *p*=0.001. HT: Hypertension; CAD: Coronary artery disease; DM: Diabetes mellitus.

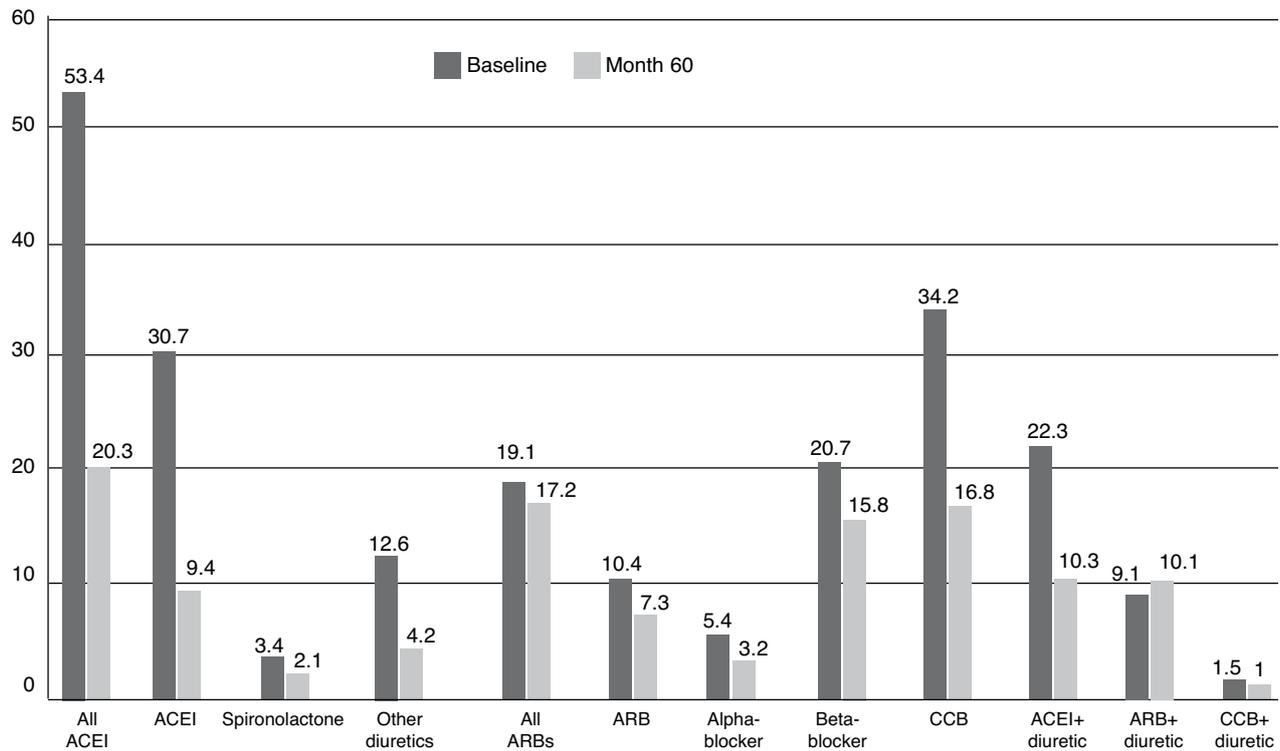


Figure 2. Changes in the use of antihypertensive medication over time. ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; CCB: Calcium channel blocker.

DISCUSSION

The results of this study showed that the coexistence of hypertension with DM or CAD equally raised the cardiovascular risk and that the coexistence of both diabetes and CAD in hypertensive patients increased the risk geometrically.

Increased cardiovascular mortality has been demonstrated in hypertensive patients. In particular, the coexistence of diabetes and hypertension has been observed to increase cardiovascular mortality, MI, and stroke.^[2] In our cohort, the presence of DM in hypertensive patients increased the relative risk for cardiovascular mortality by 64%. Lloyd-Jones et al.^[6] demonstrated that, among recently diagnosed hypertensive patients, the most commonly seen major cardiovascular events in males and females were CAD (8.2%) and stroke (5.2%), respectively. For any cardiovascular endpoint, the cumulative 12-year incidence of the first event was 24.7% in males. Interestingly, however, there was no significant difference between CAD and DM in terms of cardiovascular risk in hypertensive patients.

In a population-based study by Haffner et al.,^[4] the risk level of diabetic patients without a previous history of MI was similar to that of nondiabetics who

previously experienced MI. It was also shown that the coexistence of DM and CAD was associated with a 3-fold increase in cardiovascular risk when compared to the presence of either of them alone.^[4] Thus, diabetes and CAD are considered to be equivalent risk factors in the updated guidelines.^[7-9]

Our study demonstrated that the data of the general population could be valid for hypertensive patients. In hypertensive patients with a history of DM and CAD, the risk for cardiovascular disease showed a 3-fold increase in comparison to that of patients who did not have DM or CAD. The increase in relative risk was more than 100 percent in the presence of both DM and CAD in comparison to the presence of either of them alone.

The regular use of antihypertensive medications in this cohort was low. Even ACE inhibitors -most commonly used drugs- were regularly used only in one out of four patients. We surmised that the reason for this improper drug use was poor compliance.

The presence of hypertension in patients with diabetes is considered particularly pernicious because of the strong linkage of the two conditions with all cardiovascular diseases, stroke, progression of renal disease, and diabetic retinopathy.^[10] To our knowledge,

there is no report comparing the long-term effects of the presence of diabetes or CAD on cardiovascular risk in hypertensive population. This study provided supportive data on the importance of DM as a coronary artery disease risk equivalent in hypertensive patients.

This study has several limitations to be addressed. First of all, the interviews with patients or their relatives were based only on phone calls. The precise clinical conditions of the patients, such as glycated hemoglobin levels and all concurrent complications were not recorded. The correlation between the metabolic control and the cardiovascular risk was not evaluated.

In conclusion, this study demonstrated that DM and CAD were equivalent as cardiovascular risk factors in hypertensive patients. These results support the aggressive treatment approaches for global cardiovascular risk reduction in hypertensive patients with DM as being done for those with CAD.

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