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Five year follow-up of patients with high cardiovascular risk in the Turkish population. What are the predictors of highest cardiovascular risk?

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Summary
Background: Despite the overwhelming evidence from clinical trials showing that preventive measures recommended by recent guidelines significantly reduce mortality, the implementation rate in patients with high cardiovascular risk is still far from optimal.
Methods: A total of 5600 patients with a high cardiovascular risk were invited to participate however 3331 (59%) agreed to a five year follow-up in a multicenter, observational study. Primary end-points included death, myocardial infarction, stroke and optimal medication use over 5 years.
Results: Primary end-points including cardiovascular mortality were higher in patients with vascular disease (25.3% vs 15.1%, $p < 0.001$, and 13.5 vs 6.2%, $p < 0.001$, respectively) and it was doubled in 5 years. Presence of end organ damage further increased the incidence of primary end-point and cardiovascular mortality (30.6% vs 16.2%, $p < 0.001$ and 18.1% vs 6.8%, $p < 0.001$, respectively). The optimal preventive treatment (statin, renin-angiotensin system blocker, beta-

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blocker and antiplatelet) rate was low and did not change significantly in 5 years, although the consistent use of angiotensin-converting enzyme inhibitor seemed to be a protective predictor of cardiovascular mortality.
Conclusion: In this high risk Turkish population, mortality and morbidity in the medium to long term were high and the implementation rate of optimal preventive treatment unacceptably low. The highest risk subgroup was identified to be those with previous vascular disease/event and end organ damage requiring aggressive medical treatment.

Introduction

Cardiovascular disease is the leading cause of total mortality and morbidity in Turkey and is increasing consistently. In adults aged 20 years or older coronary deaths comprised 42% of all deaths, exceeding those due to cancer (20%), cerebrovascular accident (11%) and other causes [1]. Such a distribution is similar to that observed in developed countries for more than half a century and is in sharp contrast to that seen in developing regions of the world. Certain risk factors such as smoking, low HDL-cholesterol levels, increasing triglyceride levels, obesity, diabetes and hypertension appear to be the leading risk factors in the Turkish population. These factors constitute the major components of the cardiometabolic syndrome. There is considerable increase in the incidence of metabolic syndrome in Turkey in parallel to the increase seen all over the world [2].

The first aim of this study was to define patients with the highest cardiovascular risk among those known to have cardiovascular disease or a high risk profile. The second aim was to evaluate the event rate during a short and long term follow-up period and to determine the implementation rate of optimal medical treatment in these patients.

We previously reported our results from the first year follow-up of this study. A remarkably high rate of mortality and morbidity and inadequate optimal medical treatment were documented at the end of one year. The presence of end organ damage and previous vascular event were shown to be the strongest predictors of mortality and morbidity at the end of one year [3]. The mortality rate in patients with end organ damage was 5.8% vs 2.7% in those without end organ damage. Similarly, the mortality rate in patients with known vascular disease was higher in the presence of a previous vascular event (7.8% vs 5.3%). In this paper, we evaluated the event rate and the utilization of optimal treatment over a long term follow-up period of 5 years.

Materials and methods

The Vascular Risk Study was a multicenter, observational, follow-up study. A total of 5600 high risk patients from different geographical regions of the country were enrolled in the study. They were enrolled by 305 investigators from cardiology, internal medicine, endocrinology and primary care clinics. The inclusion criteria in this noninterventional study were age above 55 years and having a high risk of a cardiovascular event. High risk was defined as having vascular disease (coronary, cerebral, peripheral arterial) or diabetes. This concept is in accordance with the recent guidelines which accept that the presence of cardiovascular disease identifies a patient in a high risk group. Type 2 diabetes is also accepted as equivalent to having cardiovascular disease [4]. Hypertension, accompanied by other risk factors, also places a patient in a high risk group and was another inclusion criterion. The threshold for a diagnosis of hypertension was 140/90 mmHg or above, or being under antihypertensive treatment. A detailed medical history and physical examination along with laboratory measures were recorded at baseline. The details of the measurement methods were described previously [3].

Patients were divided into two major groups with regard to the presence of vascular disease and subgroups with regard to the presence of diabetes and/or hypertension.

- Vascular disease
  - Without diabetes and hypertension
  - With diabetes and/or hypertension
- No vascular disease
  - With diabetes or hypertension or both

Vascular disease was identified by either coronary, peripheral or carotid angiography or the presence of a well documented cardiovascular event in the past medical history. Primary end-points of the study were death, non-fatal myocardial infarction

(MI) or stroke. Secondary end-points were revascularization (percutaneous or surgical) and hospitalization due to cardiovascular causes.

Of the 5600 patients, 3331(1842 females, 1489 males; mean age 65 ± 7) were reached at the end of the first year. Clinical end-points were evaluated in these patients at the end of first, second, third, fourth and fifth years. Data were obtained through telephone calls to the patients and/or family and follow-up questioning on cause of death, weight changes, diseases, hospitalizations, PTCA or CABG procedures and medication use.

The study was approved by the ethics committee of the coordinating center.

Statistical analysis

Analysis of variance with Tukey's HSD for post-hoc analysis, chi-square test or Student's *t*-test were used according to the type of variable and number of groups, in order to evaluate univariate demographics, clinical baseline characteristics and end-point results. After the univariate analysis of end-point events, all the major variables were included in a logistic regression analysis. Odds ratios and 95% confidence intervals were derived from this analysis. A *p*-value of less than 0.05 was set for statistical significance.

Results

Of the 5600 patients, 3331 (59.5%) consented to being followed for 5 years by telephone. Demographic characteristics and risk factors of these patients are shown in Table 1. It should be noted that risk factors such as hypertension, high body mass index (overweight and obese), and hyperlipidemia were present in more than 50% of the cases.

Primary end-points

The incidence of primary end-points in the entire population increased significantly from 7.2% at the end of the first year to 19.5% at the end of the fifth year. Higher rates were observed in males compared to females (15.9% vs 24.0% $p < 0.001$). Primary end-points were reached more frequently in patients with vascular disease and in those with end organ damage (Figs. 1 and 2). The presence of a prior vascular event was associated with a further increase in the rate of primary end-points (29.3% vs 16.6, $p < 0.001$%). Patients with diabetes also had a significantly higher rate of primary end-points (17.4% vs 22.8% $p < 0.001$) particularly when they had end organ damage (Figs. 3 and 4). The highest rate of primary end-points was observed in patients who had established disease in more than one vascular bed (43.7% vs 23.4% $p < 0.001$).

Table 1 Baseline demographics of cases.

	Percent	Frequency
Age y mean—(SD)	65 ± 7	
Men	44.7	1489
End organ damage	23.1	770
Vascular disease	43.5	1449
Diabetes	39.4	1312
Hypertension	80.0	2664
Total chol >200 mg/dl	51.8	1385
HDL chol <40 mg/dl	37.1	846
Smoker	21.8	726
Overweight (BMI 25—29.9)	43.6	1318
Obesity (BMI $\geqslant$ 30)	28.9	873

Secondary end-points

The incidence of secondary end-points was 13.6% at the end of the first year and 26.0% at the end of the fifth year. The incidence was higher in patients with vascular disease and end organ damage when compared to patients who did not have these features (37.8% vs 17.0%, $p < 0.001$ and 34.4% vs 23.5%, $p < 0.001$, respectively). Combined end-points were found in 36.6% of all patients at the end of the fifth year and were significantly higher than at the end of the first year (17.5%).

Cardiovascular mortality

The cardiovascular mortality rate was 9.4% in the entire group at the end of the fifth year. It was higher in males (11.6% vs 7.6%, $p < 0.001$) and in those who had vascular disease (13.5% vs 6.2%, $p < 0.001$) particularly when they had involvement in more than one vascular bed. It was also higher in patients with end organ damage (18.1% vs 6.8%, $p < 0.001$).

Adherence to medications

Major preventive agents such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, antiplatelets, statins and beta-blockers were used only in one third to a half of the patients at baseline. The term ''adherence to medication'' included both consistent prescribing of medications by physicians and patient compliance with medications. Therefore, any more specific explanation for this suboptimal usage could

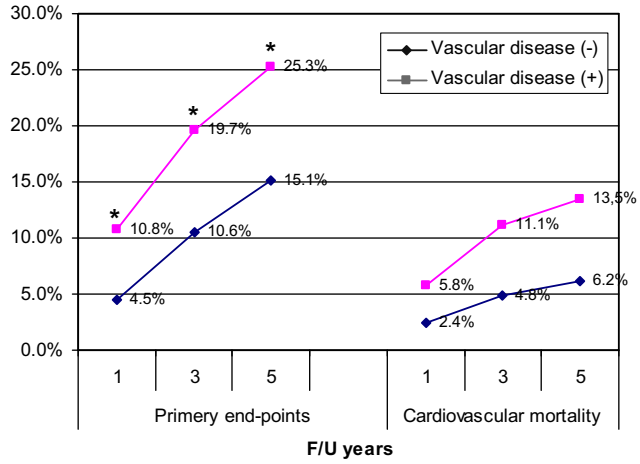

Figure 1 Relationship between vascular disease, primary end-points and cardiovascular mortality. Incidence of primary end-points and cardiovascular death rate is significantly higher in patients who have documented vascular disease (* = $p < 0.001$).

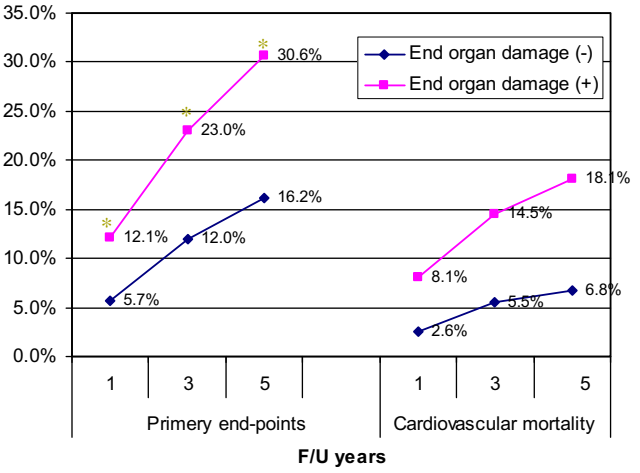

Figure 2 Relationship between end organ damage, primary end-points and cardiovascular mortality. Incidence of primary end-points and cardiovascular death rate is significantly higher in patients who have end organ damage (* = $p < 0.001$).

not be documented. This low utilization rate even decreased significantly at the end of 5 years (Table 2).

The effect of medication use on end-points and mortality

Renin-angiotensin system blockers (angiotensin-converting enzyme inihibitor or angiotensin receptor blocker) and statin usage were associated with a lower primary end-point rate. Cardiovascular mortality was significantly lower with consistent use of a RAS (renin-angiotensin system) blocker, aspirin, a statin and a beta-blocker (Fig. 5). Optimal therapy variable was created by establishing ordinal data with four agents, assigning the highest rank to the concomitant utilization of all four agents. Cardiovascular mortality was lowest in patients when all these agents were used.

Predictors of cardiovascular mortality

A multivariate analysis was performed in order to determine the predictors of cardiovascular mortality at the end of 5 years of follow-up in this high risk patient group. The most important predictors of cardiovascular mortality were the presence of cardiovascular disease, any vascular event, end or-

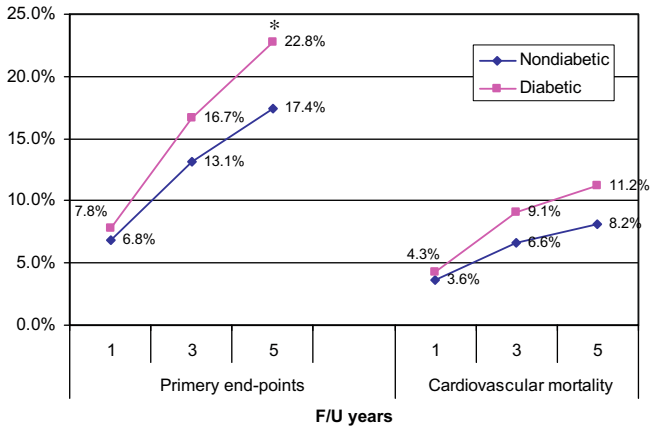

Figure 3 Primary end-points and cardiovascular mortality in non-diabetic and diabetic patients ($^{*}p < 0.001$).

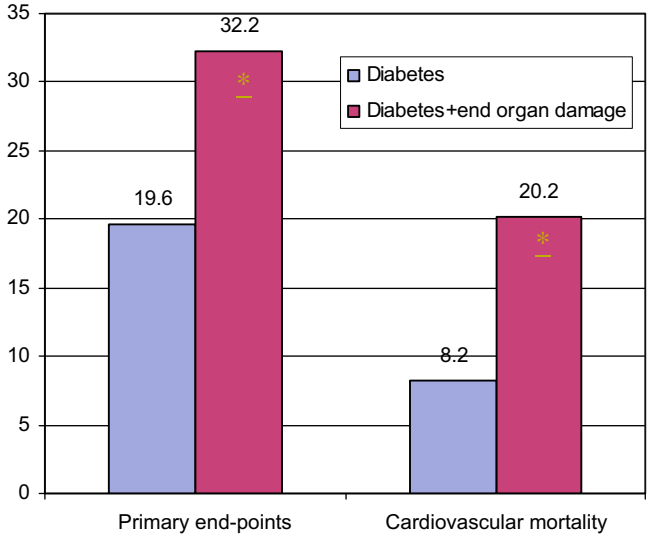

Figure 4 Primary end-points and cardiovascular mortality in diabetic patients with and without end organ damage ($^{*}p < 0.001$).

gan damage, and a low HDL-cholesterol level. On the other hand, consistent RAS blocker therapy predicted a lower rate of end-points (Fig. 5).

Diabetes (B:0.379, 95% CI:1.022—2.087), organ damage (B:0.915, 95% CI:1.739—3.587), vascular disease (B:0.719, 95% CI:1.267—3.329) and a baseline vascular event (B:0.732, 95% CI:1.321—3.275) were significant predictors of deaths due to cardiovascular causes. The same factors were also significant predictors of other primary end-points.

Discussion

In this five year follow-up study of high risk patients, we found that the early morbidity and mortality due to cardiovascular events were unacceptably high and medical treatment inadequate. There was a progressive increase in the incidence of primary and secondary end-points and cardiovascular death within 5 years.

In our already high risk population, the significant features characterizing the highest risk subgroup of patients with regard to cardiovascular events were the presence of an established vascular disease where a quarter of the patients suffered an event within 5 years, presence of a vascular event in the past and end organ damage. The highest rate of primary end-points was observed in patients who had established disease in more than one vascular bed. Low HDL-cholesterol was also found to be a determinant of cardiovascular end-

points. This is important since low HDL is an important prevalent risk factor in our country [1].

Diabetes was also a significant predictor for the development of primary and secondary end-points. Diabetic patients with end organ damage had the highest rate of primary end-points and cardiovascular mortality (32.2% and 20.2%). These findings support the recommendations of the recently published guidelines of the European Society of Cardiology on diabetes [5]. In the INTERHEART study [6] the presence of diabetes was also found to be an important risk factor for myocardial infarction (odds ratio 3.37, $p < 0.0001$). The relation between diabetes and MI was shown to be present in the study independent of age, sex, and regional differences.

In our multivariate analysis, increased total cholesterol level at baseline seemed to be associated with a reduced risk. This was an unexpected finding and could not be explained. Cholesterol levels were not rechecked during follow-up. These patients may have been treated more aggressively with a statin leading to a better prognosis.

We know that risk stratification is important to determine priorities. But even within the high risk group, there is a subgroup of patients who do worse and have an unacceptably high event rate. Treatment should be extremely aggressive in this subgroup. The National Cholesterol Education Program update recommends more aggressive LDL goals as a treatment choice in patients with the highest risk. In this recommendation, patients with known vascular disease and multiple, uncontrolled risk factors as well as acute coronary syndromes are defined as those with the highest risk. Findings from our study confirm that patients with known vascular disease are at highest risk. Additionally, patients with end organ damage and previous vascular events should also be added to this category according to our findings.

In a recent study, the lifetime risk for atherosclerotic cardiovascular disease for men and women at age 50 was found to be 51.7% and 39.2% respectively [7]. However, those with $\geqslant 2$ major risk factors had a strikingly greater risk when compared to those with optimal risk factor levels (68.9% vs 5.2% in men, 50.2% vs 8.2% in women, respectively) and they had a shorter survival. In our high risk group, the prevalence of conventional risk factors particularly the ones comprising the components of the cardiometabolic syndrome was high explaining our high event rates.

Although, there has been significant progress in knowledge, detection and treatment of atherosclerotic cardiovascular disease in recent years, the mortality and morbidity remain high and are even increasing in developing countries. This is partly due to inadequate identification of high risk patients and suboptimal implementation of medical treatment and preventive measures. All the recently updated prevention guidelines recommend more aggressive targets. However, the availability of practice guidelines and efficacious treatments do not necessarily mean that these are automatically implemented and recommended to patients. Our high risk patient group did not receive optimal care, once more highlighting the differences between real-life application and medical knowledge.

On the other hand, consistent use of optimal medical treatment, which consisted of a renin-angiotensin system blocker, a statin, aspirin and a beta-blocker resulted in significantly lower primary and secondary end-points and cardiovascular mortality in the high risk group. Despite this fact, the implementation rate of optimal medical treatment which was already low in the short term further decreased during long term follow-up. Similar findings were observed in the EuroAspire II study [7]. Likewise, the REACH study [8] demonstrated that in many countries statins, antiplatelet agents and other evidence based risk reducing therapies were used much below the suggestions proposed in guidelines. However, consistent use of medical treatment in our study was even lower than that reported in the REACH registry. The prevention guidelines of the ESC are well accepted in this country but a treatment gap is apparent necessitating extensive educational efforts to physicians and the public. Therefore, efforts aimed at prevention and treatment of risk factors should be intensified with special attention to those at highest risk.

Table 2 Medication use over 5 years, $N = 3331$.

	Baseline (%)	1st year	2nd year	3rd year	4th year	5th year
RAS blocker	63.9	48.3	49.5	48.7	42.9	44.9
ASA	44.7	40.7	38.4	40.8	35.9	35.0
Statin	27.4	22.3	22.4	26.0	19.5	18.9
Beta-blocker	23.0	20.1	19.8	21.4	20.1	18.3

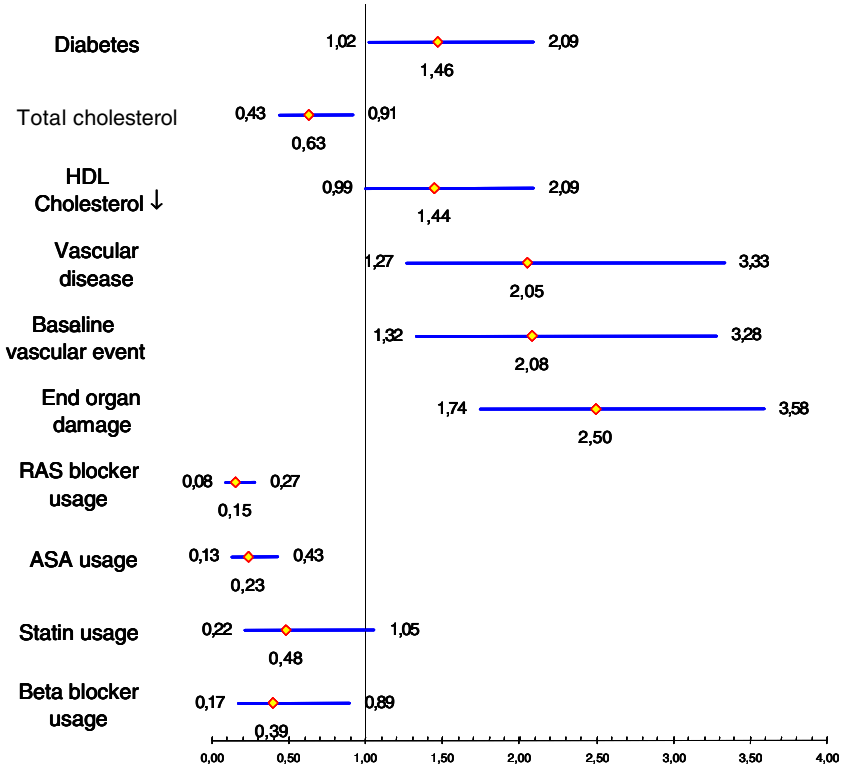

Figure 5 Significant predictors of cardiovascular mortality in multivariate analysis.

Limitations of the study

The follow-up information was obtained through calls based on a standard questionnaire, not by examination of the patient or direct contact with the responsible physician. The follow-up calls were initially made once every three months for one year and once each year after the first year. The questions were short and explicit e.g. ''Have you been hospitalized within the year 2007?", ''Please read the names of medications you are receiving at this time". Therefore, we do not expect significant recall bias in this study. A number of patients were lost to follow-up, due to a change of address, and no forwarding address/telephone number. We had no reason to anticipate that these patients had different outcomes than those who were followed up.

Clinical implications

Patients with a high cardiovascular risk can be graded according to their clinical features. Mortality and morbidity is highest in the subset of patients with vascular disease, previous events or end organ damage. Optimal preventive medical therapy is remarkably beneficial in these patients.

In conclusion, despite many advances in treatment, cardiovascular disease remains the primary cause of mortality and morbidity in the Turkish population. The rate of recurrent events and death is unacceptably high both in the short and long term. The presence of end organ damage and previous cardiovascular disease or event seem to increase mortality and morbidity further. These high risk patients need to be tracked for effective prevention. We need to intensify our efforts in order to close the gap between evidence based practice guidelines and implementation. Interventions supporting treatment compliance in real-life settings should be encouraged. Transformation of health services in Turkey in the near future, with the establishment of a family practitioner system is expected to improve secondary prevention in these patients.

Acknowledgement

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