Prevalence, Recognition and Treatment of Cardiovascular Risk Factors in Outpatients with Atherothrombosis in Israel

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Abstract

Background: Cardiovascular disease remains the most common cause of death in the industrialized world. The REACH study is an international registry of outpatients from 44 countries, including Israel, with risk factors for cardiovascular morbidity or with stable atherosclerotic clinical syndromes.

Objectives: To compare the prevalence and treatment of cardiovascular risk factors between Israeli patients enrolled in REACH and international controls.

Methods: Consecutive eligible outpatients aged 45 years or older with established coronary artery disease, cerebrovascular disease, or peripheral arterial disease, or with at least three atherosclerosis risk factors were enrolled.

Results: Altogether, 381 Israeli patients were enrolled in the registry. The mean age of the Israeli participants was 70 years and 71% were men. Among the Israeli patients there was a higher percentage with hypercholesterolemia (86% vs. 72%) who were overweight (45% vs. 40%) and obese (69% vs. 47%), but fewer former smokers (33% vs. 42%). The percentage of patients with hypertension taking at least one medication was similar in the two groups, but there was a difference regarding which antihypertensive was used. Israeli patients took more beta-blockers (62% vs. 49%) and angiotensin-converting enzyme inhibitors (60% vs. 48%) but fewer angiotensin II receptor blockers (12% vs. 25%). A higher percentage of Israeli patients were taking at least one antiplatelet agent (88% vs. 79%) and a higher percentage of patients from Israel were on statins (85% vs. 69%).

Conclusions: Israeli patients with atherothrombotic disease had a higher prevalence of hypercholesterolemia and obesity than other patients and were treated appropriately compared to patients from other countries.

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Cardiovascular disease remains the most common cause of death in the industrialized world despite recent advances in its treatment. Primary [1] and secondary prevention [2] has been shown to be the most effective method to combat this epidemic. In order to best design appropriate prevention projects it is imperative to understand the risk pattern profile of the population at risk. The Reduction of Atherothrombosis for Continued Health (REACH) study is an international registry of 67,888 non-selected outpatients from 44 countries, including Israel, with risk factors for cardiovascular morbidity or with stable atherosclerotic clinical syndromes [3]. The patients were recruited from general physician and specialist-affiliated ambulatory care facilities worldwide. The aim of the present study was to compare the prevalence and treatment of cardiovascular risk factors between Israeli patients enrolled in REACH and international controls.

Patients and Methods

The design and methodology of the REACH Registry has been described elsewhere in detail [3]. Briefly, consecutive eligible outpatients aged 45 years or older with established coronary artery disease, cerebrovascular disease, or peripheral artery disease, or with at least three atherosclerosis risk factors were enrolled over an initial 7 month recruitment period on a worldwide basis between December 2003 and June 2004. Medical record documentation was required for establishment of the presence of CAD, CVD, or PAD. Forty randomly selected physicians (mostly general practitioners but also specialists) from a large health management organization representing all regions of Israel were invited to recruit eligible patients to the study.

Documented CAD consisted of one or more of the following criteria: stable angina with documented CAD, history of unstable angina with documented CAD, history of percutaneous coronary intervention, history of coronary artery bypass graft surgery, or previous myocardial infarction. Documented CVD consisted of a hospital or neurologist report with the diagnosis of transient ischemic attack or ischemic stroke. Documented PAD consisted of one or both criteria: current intermittent claudication with ankle-brachial index < 0.9 or a history of intermittent claudication together with a previous and related intervention, such as angioplasty, stenting, atherectomy, peripheral arterial bypass graft, or other vascular intervention including amputation. The risk factors were those that were documented in the medical record or for which patients were receiving treatment at the time of study enrollment: treated diabetes mellitus, diabetic nephropathy, ankle-brachial index < 0.9, asymptomatic carotid stenosis of ≥ 70%, carotid intima media thickness ≥ 2 times adjacent sites, systolic blood pressure ≥ 150 mmHg despite therapy for at least 3 months, hypercholesterolemia treated with medication, current smoking of at least 15 cigarettes per day, men aged ≥ 65 years, or women aged ≥ 70 years. Patients already in a clinical trial, hospitalized patients, or those who might have difficulty returning for a follow-up visit were excluded from enrollment. This protocol

CAD = coronary artery disease
CVD = cerebrovascular disease
PAD = peripheral artery disease

was submitted to the institutional review board in each country according to local requirements, and a signed informed consent was obtained for all patients.

Data were collected centrally by means of a standardized international case report form, completed at the study visit. Baseline height, weight, waist circumference, seated systolic and diastolic blood pressure, and available fasting glucose and cholesterol levels were obtained. From these data, baseline demographic and risk factor characteristics were analyzed. Body mass index was defined as weight in kilograms divided by the square of height in meters. Participants were considered to be overweight if they had a BMI of between 25 and 29, or obese if their BMI was ≥ 30. Waist circumference was used to classify patients as obese if it was ≥ 40 inches (≥ 102 cm) in men or ≥ 35 inches or larger (≥ 88 cm) in women. Current smoking was defined as at least five cigarettes per day on average within the last month before entry into the REACH Registry; former smoking was defined as at least five cigarettes per day on average more than 1 month before entry. Polyvascular disease was defined as coexistent symptomatic (clinically recognized) arterial disease in two or three territories (coronary, cerebral, and/or peripheral) within each patient.

Statistical analysis

Bivariate hypotheses involving continuous variables were tested with a *t*-test for independent groups. To examine whether the distribution of categorical variables differed across study groups the chi-square test was used. Fisher's exact test was applied when appropriate. Continuous variables were expressed as mean ± SD, and categorical variables were expressed as percentages. All reported *P* values are two-sided and $P < 0.05$ was considered significant.

Results

A total of 69,055 patients were enrolled in the REACH registry. Baseline data were available for 67,888; 1109 did not meet the inclusion criteria and 58 withdrew their consent. Thus, 381 Israeli patients were enrolled in the registry. The percentage of symptomatic patients was similar in both groups.

As shown in Table 1, the mean age of the Israeli participants was 70 years and 71% were men. Among the Israeli patients there was a higher percentage with hypercholesterolemia (86% vs. 72%), who were overweight (45% vs. 40%) and obese (69% vs. 47%), but fewer former smokers (33% vs. 42%) compared to the total cohort.

Among the patients with more than three risk factors, Israeli patients had more hypertension (97% vs. 90%) [Table 1]. As shown in Table 2, the percentage of hypertension patients taking at least one medication was similar in the two groups but there was a difference regarding which antihypertensive was used. Israeli patients took more beta-blockers (62% vs. 49%) and ACE inhibitors (60% vs. 48%) but fewer angiotensin II receptor blockers (12% vs. 25%). A higher percentage of Israeli patients took at least one antiplatelet agent (88% vs. 79%) but there was less use of agents other than acetylsalicylic acid (7% vs. 25%). A higher percentage of patients from Israel took statins than patients from other countries (85% vs. 69%) and fewer patients received specific therapy for PAD (4% vs. 29%). Israeli patients also took fewer non-steroid anti-inflammatory drugs (2% vs.12%).

Discussion

The risk factor profile of Israeli patients with atherothrombotic disease is similar to patients from other countries, as determined by an international registry, with some important differences. Israeli patients are more overweight and are more frequently hypercholesterolemic. While genetic and environmental factors certainly play a role in these findings, it highlights the central role of obesity in the epidemic of cardiovascular disease in Israel. Sedentary lifestyle and a western-style diet are undoubtedly major risk factors for these findings. Previous studies have also documented a high rate of obesity in Israel [4].

In addition to modification of other risk factors such as blood pressure control and smoking cessation, major efforts to combat obesity and hypercholesterolemia need to be initiated. First-line therapy for hypercholesterolemia is diet therapy, followed by medical therapy [5]. Israeli patients receive drug therapy for

BMI = body mass index
ACE = angiotensin-converting enzyme

Table 1. Baseline population in REACH Registry and Israel (percentage of population)

	Total			Symptomatic			≥ 3 risk factors		
	All countries (n=67,888)	Israel (n=381)	*P*	All countries (n=55,499)	Israel (n=307)	*P*	All countries (n=12,389)	Israel (n=74)	*P*
Age, mean (SD) (yrs)	68.5 (10.1)	70.3 (9.3)	< 0.001	68.4 (10.1)	70.2 (9.2)	0.002	69.0 (9.8)	71.0 (9.4)	0.08
Men	63.7	70.8	0.004	66.9	75.0	0.003	49.5	53.4	0.50
Diabetes*	44.3	43.0	0.61	37.5	37.1	0.89	74.9	67.6	0.15
Hypertension**	81.8	84.0	0.27	80.0	80.7	0.76	90.3	97.3	0.04
Hypercholesterolemia	72.4	85.8	< 0.001	70.2	85.7	< 0.001	82.2	86.5	0.34
Obesity***	46.6	68.6	< 0.001	44.0	57.3	< 0.001	58.4	65.5	0.22
Overweight (BMI 25–30)	39.8	45.3	0.03	40.9	47.7	0.02	35.0	35.6	0.91
Smoker									
Former	41.6	32.9	0.001	44.6	36.7	0.01	28.4	21.9	0.22
Current	15.3	14.8	0.78	14.4	14.0	0.84	19.2	17.8	0.76

* Patients with type 1 or 2 diabetes currently treated with hypoglycemic agents or history of diabetes.
** Patients currently treated with medication.
*** Waist circumference: men ≥ 102 cm, women ≥ 88 cm.
Body mass index (calculated as weight in kilograms divided by the square of height in meters)

Table 2. Medication use among patients at the REACH registry and Israel (percentage of population)

	All countries (n=67,888)	Israel (n=381)	*P*
No. of patients with diagnosed hypertension or elevated blood pressure at initial examination (%)	58,920 (86.8)	320 (83.9)	0.10
At least one antihypertensive	95.8	96.3	0.66
Beta-blockers	48.9	61.6	< 0.001
ACE inhibitors	48.2	60.2	< 0.001
Diuretics	44.0	43.0	0.72
Calcium channel blockers	37.2	42.1	0.07
Angiotensin II receptor blockers	25.4	12.0	< 0.001
Other antihypertensives	10.6	18.4	< 0.001
Antiplatelet therapy (all patients)			
At least one antiplatelet agent	78.6	88.2	< 0.001
Acetylsalycilic acid	67.4	85.6	< 0.001
Other antiplatelet agents	24.7	6.7	< 0.001
Any two antiplatelet agents	13.2	4.0	< 0.001
No. of patients with history of diabetes or elevated blood glucose at initial examination (%)	31,424 (46.2)	164 (43.0)	0.21
At least one diabetes medication	85.9	84.1	0.51
Sulfonylurea	42.7	41.5	0.76

hypercholesterolemia, as documented by the high percentage taking stains but it is unclear how many are taking appropriate non-pharmacological therapy, which is much more difficult to comply with. In addition, the primary therapy for obesity is non-pharmacological, namely, a change in dietary habits and increased physical exercise. Obesity needs to be at the forefront of Israeli efforts to prevent cardiovascular disease, and this effort must begin at an early age since data suggest that obesity is emerging at younger ages in the western world [6]. Programs that encourage healthy diets and physical exercise need to be implemented and developed. Programs such as these have been developed [7] and it is time to consider whether they should be added to the healthcare basket.

The treatment of risk factors also differs between Israel and other countries. Similar to other countries, a very high percentage of patients with hypertension are treated with medication, but the drugs selected in Israel are different. Israeli physicians use more beta-blockers and ACE inhibitors and fewer ARBs than physicians from other countries. This is probably due to the fact that ARBs are not in the healthcare basket as first-line treatment of hypertension. There is also no evidence that ARBs are better than ACE inhibitors for the treatment of hypertension and they are more expensive since they are not yet available in generic form. The most common drug used for hypertension in Israel is beta-blockers. While they are certainly appropriate for patients with ischemic heart disease, there is some preliminary evidence that they might not be as effective as other medications for primary prevention of cardiovascular disease [8]. However, it is still acceptable therapy for hypertension according to guidelines [9]. According to the REACH data, physicians in Israel and across the world under-prescribe diuretics for the treatment of hypertension. Recent guidelines recommend diuretics as first-line therapy unless there is compelling reason not to [9]. For reasons that are not clear, physicians have been reluctant to fully follow this recommendation.

A higher percentage of Israeli patients take antiplatelet therapy compared to patients from other countries. It is not clear why, but it testifies to the good job that Israeli physicians are doing with the use of aspirin for primary and secondary prevention. This might reflect recent Israeli quality-improvement initiatives targeting the appropriate use of aspirin. Israeli physicians use less of other antiplatelet agents, presumably clopidegrol, than do other physicians. Again this is probably explained by its limited availability in the healthcare basket.

A higher percentage of patients from Israel are on statin therapy but this probably reflects the higher prevalence of hypercholesterolemia in Israel. Again, this demonstrates the effective job Israeli physicians are doing with the pharmacological treatment of hypercholesterolemia.

Very few patients are receiving specific drug therapy for PAD, which probably reflects the limiting efficacy of these drugs on morbidity and mortality [10] and the strict controls on their use in Israel. It would be far more effective for physicians to focus on global risk factor reduction for cardiovascular disease, such as smoking cessation, control of blood pressure and lipid reduction [10].

The lower percentage of Israeli patients receiving NSAID therapy should also be noted. Concern has been raised about the safety of this class of medications in patients with cardiovascular disease [11] and recent recommendations advocate limiting their use.

Study limitations

The study was limited by that fact that we were not able to sub-analyze the Israeli patients by demographic factors and socioeconomic status, and the number of Israeli patients compared to the large international cohort was small. The strengths of the study are the large number of patients in the registry to which the Israeli patients were compared, and the international nature of the study.

Conclusions

Israeli patients with atherothrombotic disease had a higher prevalence of hypercholesterolemia and obesity than other patients and were treated appropriately compared to patients from other countries. Efforts at providing high quality cost-effective care by avoiding the inappropriate use of more expensive medications seem to be working. This is accomplished through a national drug review committee and local efforts in mandating preferential therapies and physician education. A sophisticated information technology system helps keep track of medication usage and costs. Primary and secondary prevention of established risk fac-

ARB = angiotensin II receptor blockers

NSAID = non-steroidal anti-inflammatory drug

tors for cardiovascular disease is of the utmost importance, and further research, like the REACH registry, is needed both in Israel and worldwide.

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Capsule

Motility in bacteria

Motility in bacteria is important for pathogenesis and for bacterial chemotaxis. So-called gliding motility in the bacterium *Myxococcus xanthus* is powered by two distinct engines: S motility (powered by type IV pili) and A motility, of unknown mechanism. By following the localization pattern of an A motility-specific protein, Mignot and fellow workers discovered that the most popular hypothesis for A motility, directed slime secretion, is likely to be incorrect and that intracellular motor-coupled adhesion complexes power movement. Thus, bacteria and eukaryotic cells may use a similar transient adhesion-based mechanism for motility.

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Eitan Israeli

Capsule

Tumor gene on X chromosome

Wilms tumor is a pediatric kidney cancer that can be inherited or arise sporadically. A small fraction of sporadic cases are caused by mutations in the *WT1* gene on chromosome 11, which codes for a transcription factor regulating kidney development. Rivera et al. show that sporadic forms of Wilms tumor can also arise from mutations in a gene on the X chromosome, WTX. The function of the WTX protein is not yet known, but the gene's location on the X chromosome is of particular interest. Inactivation of most tumor suppressor genes requires two separate events or hits. Because humans carry only one functional allele of all X chromosome genes (in females one allele of each gene is silenced), the *WTX* gene presumably can be disabled by a single hit. The discovery of *WTX* suggests that X chromosome genes may play underappreciated roles in human cancer.

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