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gSCIENCE

ORIGINAL RESEARCH

Trends in Secondary Prevention of Coronary Heart Disease in Tunisia: Prevention of Recurrences of MI and Stroke

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OBJECTIVES The survival benefits achieved by prescription of antiplatelet agents, B-adrenoreceptor antagonists (beta-blockers), angiotensin II receptor blockers (ARB), and lipid lowering agents in patients surviving the myocardial infarction (MI) have been well documented in large clinical trial. Despite well-established benefits, these pharmacological agents continue to be underutilized. The main objective of this study was to evaluate the progress of cardiovascular secondary prevention practices in Tunisia.

METHODS The PREMISE (Prevention of Recurrence of Myocardial Infarction and Stroke) is a descriptive, cross-sectional study conducted in Tunisia in two phases (2002 and 2009). Seven hundred eighty two patients were recruited. The recruitment criteria were: previous MI, stable angina, unstable angina, percutaneous transluminal coronary angioplasty (PTCA), coronary artery bypass graft (CABG), stroke, transient ischemic attack (TIA) or carotid endarterectomy. This analysis is limited to coronary heart disease (CHD) patients. Five hundred hospital patients were interviewed and their medical records were reviewed: 250 in 2002 and 250 in 2009. Patients were included if they had confirmed diagnosis of MI, angina, CABG or PTCA, and if their first cardiovascular event had occurred more than one month but not later than 3 years ago. We compared the total of both patient groups, using the prevalence of Cardio-Vascular Risk Factors (CVRF) and the treatment prescribed at hospital discharge.

RESULTS The proportion of patients with reported hypertension, diabetes, hypercholesterolemia and current smoker patients had decreased. Concerning pharmacological prescriptions, a significant increase was observed in prescribing statins (38.9% vs. 70.3%) and ACE inhibitors (49.3% vs. 69.9%), non pharmacological prescriptions as healthy diet or tobacco cessation had opposite trends. Adherence to treatment did not change substantially.

CONCLUSION Although the use of cardioprotective drugs had increased in CHD patients, there are still gaps in secondary prevention in Tunisia. The recommended strategies of secondary prevention need to be applied more intensively in clinical practice.

Tunisia is now facing a rapidly growing burden of chronic disease. The epidemiological transition has been compounded by powerful environmental and behavioral changes. In particular, the adoption of new dietary habits and a sedentary lifestyle and the stress of urbanization and of working conditions all lead to increases in major cardiovascular disease risk factors [1]. Cardiovascular diseases (CVD) are responsible for 30% of all deaths worldwide [2]. Mortality rates from CVD have declined in the

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past years among patients in the United States and in Europe [3,4]. This decline in mortality of CVD has been attributed to advances in the prevention and treatment of acute and chronic ischemic heart disease. In the Tunisian population, the age-standardized rate of myocardial infarction (MI) was 163 per 100,000 people [5]. It has been reported that in persons with a history of MI, cardiovascular mortality in absence of treatment was high, 5% per year after a first MI, and 10% per year after a subsequent MI, persisting for many years and probably for the rest of the patient's life. The high mortality rate emphasizes the need to ensure that everyone who had an MI, even in previous years, receives effective preventive treatment [6].

The survival benefits achieved by prescription of antiplatelet agents, beta-adrenoreceptor antagonists (beta-blockers), angiotensin-converting enzyme (ACE) inhibitors, and lipid-lowering agents in patients surviving MI have been well documented in large clinical trials. There is consensus that patients with a history of MI should be treated with a combination of these drugs [7]. When the potential benefits of quitting smoking and of lowering blood pressure in hypertensive patients are added to the 4-drug regime, it may be possible to lower the risk of future events in high-risk individuals by more than four-fifths [8]. Despite the positive findings of studies delineating the effectiveness of these therapies, findings of several previous studies suggest that these medications are underprescribed to patients at hospital discharge after MI even in developed countries [9].

In low- and middle-income countries, there is a scarcity of data related to the secondary prevention of CVD. In this context, the World Health Organization (WHO) has initiated the WHO-PREMISE (Prevention of Recurrences of MI and Stroke) program to provide technical cooperation to countries for assessing and scaling up secondary prevention of CVD [10]. In Tunisia, the PREMISE study was conducted in 2 phases (2002 and 2009). This study aimed to provide an opportunity to view time trends over almost a practice of secondary prevention in patients with CVD in Tunisia.

METHODS

Study population. The WHO-PREMISE study is a descriptive, cross-sectional investigation. In Tunisia, the PREMISE study was conducted in 2 phases (2002 and 2009) on patients followed in the outpatient cardiology departments of university hospitals in the district of Tunis. The first study took place in 5 centers and the second in 4 centers. For the analysis, only common hospitals were considered.

A total of 782 patients were recruited (279 in 2002 and 503 in 2009). The recruitment criteria were: previous MI, stable angina, unstable angina, percutaneous transluminal coronary angioplasty (PTCA), coronary artery bypass graft (CABG), stroke, transient ischemic attack, or carotid endarterectomy. This study dealt with 500 coronary heart disease (CHD) patients. The recruitment criteria were patients (both sexes) with confirmed diagnosis of CHD defined by 1 or more of the following conditions: MI, angina, CABG, or PTCA. Patients were included if their first cardiovascular event had occurred more than 1 month but not later than 3 years earlier.

During a period of 6 months (in 2002–2009), and after obtaining informed consent from the patients, interviews were conducted by trained doctors using a standardized questionnaire. The following data were collected: demographic and personal details, exposure to risk factors (except obesity), treatments prescribed and adherence to treatment, perceived barriers, access to care, and availability and affordability of drugs.

The presence of MI, angina, CABG, or PTCA was self-reported but also confirmed by checking physician hospital discharge reports. Risk factors were self-reported too; neither measurements of blood pressure nor blood tests were carried out. Patients reporting being hypertensive, dyslipidemic, diabetics or who were receiving antihypertensive drugs, lipid-lowering agents, and antidiabetic medication (oral antidiabetic drugs or insulin) were classified as having hypertension, dyslipidemia, and diabetes, respectively. All the participants were asked if a healthy diet had been prescribed to them. The prescription of tobacco cessation was asked only to patients who still smoked (at least 1 cigarette daily) after CHD occurred. The status of "physically active" was considered to be 30 min or more of physical activity daily. The drug prescription was verified by inspecting tablets, past prescriptions, and medical records. Patients with prescriptions were asked whether they had adhered (over the last month) to the prescribed drugs.

Statistical analysis. All statistical analyses were conducted using the SPSS statistical package (version 15.0, SPSS Inc., Chicago, Illinois). The significance threshold was set at $P < 0.05$. Continuous variables are presented as mean ± SD. Relative frequencies were derived for qualitative variables. Differences

Table 1. Diagnosis and risk-factors prevalence (2002–2009)

	2002 (%)	2009 (%)	*P* Value	OR (95% CI)
Diagnosis				
MI	49.6	59.2	0.019	1.47 (1.03–2.10)
UA	49.6	44.4	<0.001	0.49 (0.34–0.71)
CABG or PTCA	28.4	48.0	<0.001	2.32 (1.60–3.37)
Risk factors				
Hypertension	59.3	51.4	0.08	0.72 (0.50–1.04)
Diabetes	54.8	46.0	0.05	0.70 (0.49–1)
Dyslipidemia	50.6	31.2	<0.001	0.44 (0.30–0.63)
Current smokers[a]	17.0	12.9	0.201	0.43 (0.29–0.62)
Physical activity[b]	43.5	30.4	0.003	0.56 (0.39–0.82)
Three or more RF[c]	61.4	59.6	0.70	0.92 (0.63–1.34)

CABG, coronary artery bypass graft; CI, confidence interval; MI, myocardial infarction; OR, odds ratio; PTCA, percutaneous transluminal coronary angioplasty; RF, risk factor(s); UA, unstable angina.
[a] One cigarette or more daily.
[b] Thirty min or more of physical activity daily.
[c] Association of 3 or more of the risk factors already cited.

in baseline characteristics between groups were analyzed by Student *t* test and chi-squared test for continuous variables and categorical variables, respectively.

Multivariate analysis using logistic regression was performed to adjust for potential confounding factors.

RESULTS

In the PREMISE studies, 500 hospital patients were interviewed and their medical records were reviewed: 250 in PREMISE I and 250 in PREMISE II. The distribution of patients by the 4 considered university hospitals was statistically different between the 2 periods. Patients followed in centers 1 and 2, respectively (32.0% vs. 42.4%) and (27.2% vs. 35.6%), are over-represented in 2009 to the detriment of the others.

A significant increase in the average age (61.5 ± 10.2 years vs. 63.7 ± 10.3 years) was found between the 2 studies, but the difference did not persist when dividing the variable age in 3 classes (<50, $\geqslant 50$ and $\leqslant 60$, >60). The percentage of women significantly increased (27.2% vs. 46.4%). The proportion of patients who paid all of the costs of their health care increased (1.2% vs. 17.8%). The mean of total number of schooling years did not vary (4.14 years vs. 4.77 years).

The diagnosis and the cardiovascular risk factors, by year of study, are illustrated in Table 1. The increases in the percentage of patients with MI (49.6% vs. 59.3%) and those with a history of CABG or PTCA (28.4% vs. 48.0%) were significant. Surprisingly, the proportion of patients with unstable angina decreased over time. Concerning the prevalence of risk factors, the proportion of patients reported as hypertensive, diabetic, hypercholesterolemic, and current-smoker decreased. However, inactive patients were more frequent (56.5% vs. 69.6%). Almost 60% of patients (in both studies) had 3 or more of these associated risk factors in both studies.

The prevalence of the 4 different treatments (aspirin, beta-blockers, ACE inhibitors, statins) prescribed independently is presented by year of study in Figure 1. The prescription of ACE inhibitors and

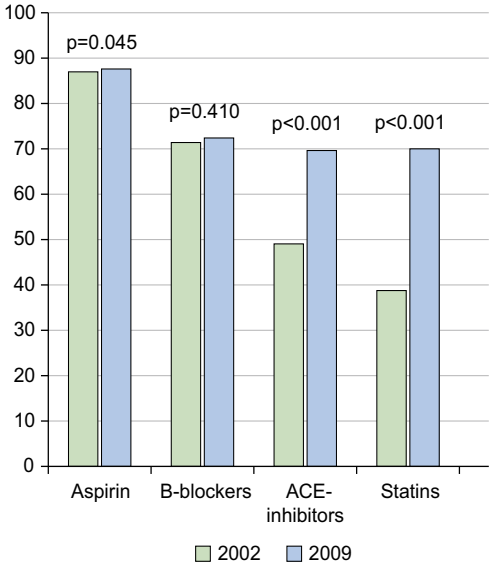

Fig. 1. The prevalence of treatments prescribed independently. ACE, angiotensin-converting enzyme.

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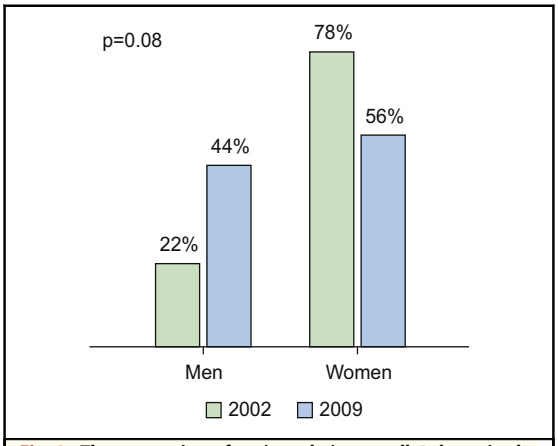

Fig. 2. The proportion of patients being on all 4 therapies by sex.

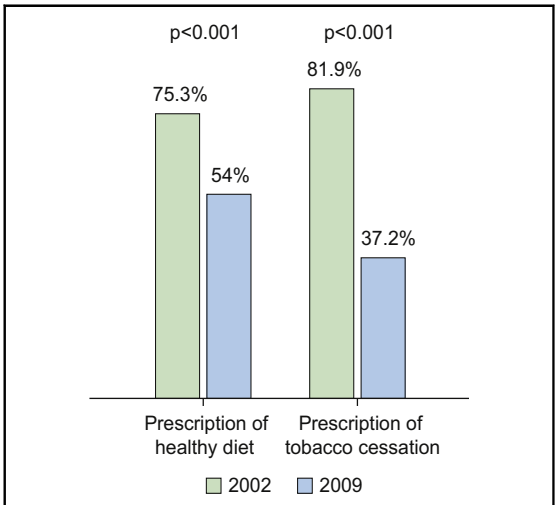

Fig. 4. The prevalence of nonpharmacological prescriptions.

statins had increased ($P < 0.001$), the odds ratios (OR) showed strong associations (OR: 2.38, 95% confidence interval [CI]: 1.63–3.47 for ACE inhibitors; OR: 3.72, 95% CI: 2.52–5.48 for statins), this increase concerned men as well as women. The prevalence of being on all 4 recommended therapies also changed widely for the better (7.2% in 2002 vs. 38% in 2009 [$P < 0.001$], OR: 7.89, 95% CI: 6.04–10.17), but because of the sex-related opposite trends of prescription and the decreased proportion of men in 2009, the association was no longer significant ($P = 0.08$) after stratifying by sex (Fig. 2). Despite the increase of prescriptions, adherence to treatments did not change substantially (Fig. 3). Concerning nonpharmacological prescriptions, such as healthy diet and tobacco cessation, an unexpected decrease ($P < 0.001$) is shown in Figure 4.

Multivariate analysis of data from PREMISE I showed only hypercholesterolemia as a predictor of better adherence to statins (OR: 4.8, 95% CI: 1.29–17.87).

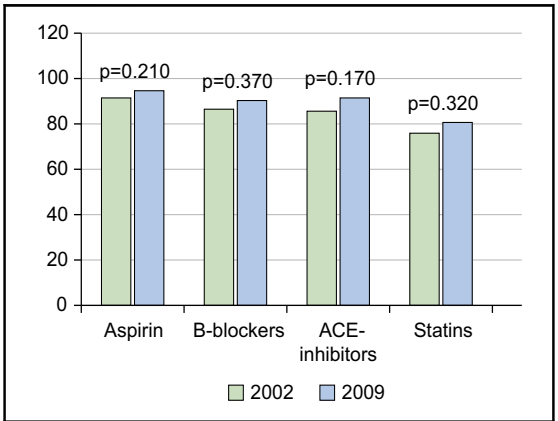

Fig. 3. The prevalence of adherence to treatments. Abbreviation as in Figure 1.

DISCUSSION

Though numerous randomized trials and observational surveys have shown the efficacy of several classes of drugs in secondary prevention for CHD, little is known about the way current recommendations translate into real-life clinical practice [11].

This study is the first conducted in Tunisia, in which we aimed to gain an overview of how the recommendations are implemented in university hospitals and to evaluate both the progress and the barriers to the secondary prevention of CHD in this country.

Mortality associated with a recurrent acute MI is appreciably higher than that associated with a first MI, and this is in spite of the existence of several medications that have been shown to reduce the likelihood of recurrent MI and death in patients who have had an established MI [12].

The effectiveness of therapy with aspirin, beta-blockers, ACE inhibitors, and lipid-lowering medications in the secondary prevention of MI has been well established in large, randomized clinical trials and/or meta-analyses of the published literature. It has been estimated that use of these medications can reduce the risk of cardiovascular death and nonfatal reinfarction, respectively, by 13% and 31% for aspirin, by 22% and 27% for beta-blockers, 21% and 25% for ACE inhibitors, and 14% and 25% for all lipid-lowering medications

combined. Statins prescribed alone reduce the risk of recurrence by 24% [12,13]. According to these results, the prescription of cardioprotective drugs had increased in the last decade. For example, the French PREVENIR (Prevent) study revealed increased prescription rates for MI patients on discharge for treatment with beta-blockers, ACE inhibitors, and hypolipidemics [11]. In the Spanish PREVESE (Prevención Secundaria del Infarto de Miocardio en España) study, conducted in 1998 and 2002, despite the decrease in beta-blockers prescription, an increase in the prescription of hypolipidemics was observed [14].

Recent data from studies in Europe and the United States suggest that there are still significant gaps in secondary prevention even in developed countries [9,10,14]. Data from REACH (Reduction of Atherothrombosis for Continued Health Registry), which collected its data during 2003 and 2004 [15], underlie a gap between recommendations and practices especially for statins. Despite an overwhelming amount of data in support of statins, the use of this class of medicine was suboptimal (69.4%). In the EUROSPIRE III (European action on secondary prevention through intervention to reduce events) survey carried out in 2006 and 2007, 93.2% of patients with atherosclerotic manifestations were using antiplatelet treatment, 85.5% beta-blockers, and 88.8% lipid-lowering drugs [9]. Data from a Finnish countrywide study showed that in 2003 about 28% and 15% of the patients did not receive hypolipidemic medications or beta-blockers, respectively, after their first cardiovascular event [16].

Our results were generally in line with these large international studies and showed that the use of evidence-based medications in 2009 in Tunisia was comparable to Western capitalist countries in the beginning of the decade. Despite the significant increase in prescription of ACE inhibitors and statins during the study period, in 2009, about 30.1% and 29.7% of the patients did not receive ACE inhibitors and statins, respectively, after CHD occurred. Although prescription of all medications after CHD had increased over time, surprisingly nonpharmacological prescriptions such as a healthy diet or tobacco cessation had opposite trends. It is clear now that drug treatments alone are not sufficient and must be combined with a professional lifestyle intervention. Therapeutic lifestyle changes in conjunction with an aggressive multidrug regimen targeted toward the normalization of the major risk factors will reduce vascular inflammation and markedly decrease the risk of adverse cardiovascular events and the need for revascularization procedures. Effectively, a physician's advice to stop smoking is the most important first step in the cessation process, but this advice should be reiterated and reinforced by all health professionals [17].

Concerning the prevalence of risk factors, atherothrombotic patients worldwide had similar risk-factor profiles: hypertension (81.8%); hypercholesterolemia (72.4%); diabetes (44.3%); smoking (14.4%); overweight (37.1%); obesity (26.6%); morbid obesity (30.6%). Furthermore, 53.9% have 3 or more risk factors [15].

Study limitations. Our findings seem to be different, particularly inferior to those of REACH registry, concerning hypertension, diabetes, and hypercholesterolemia. This may be due to one of the limitations of this study: we counted only self-reported risk factors, so we have omitted the unknown ones. Fewer patients also reported being smokers (12.9%) than in the REACH registry, and this may be related to a generally lower prevalence of smoking in our country, but the comparison is difficult because we did not adjust for sex and age. It should be recognized also that the study had some other limitations in terms of its generalizability. In fact, the data do not represent national profiles and therefore should not be used for comparison between different countries. Sampling patients from outpatient cardiology of university hospitals in the district of Tunis introduces a selection bias. The situation regarding secondary prevention of CHD in the general population and among patients who attend primary care facilities is likely to be far worse than in our sample. Furthermore, the increase of the prescription of ACE inhibitors and statins must be considered with caution, because of the over-representation in 2009 of patients followed in 2 hospitals to the detriment of the other patients. The improvement could be partly explained by a better application of recommendations in these centers of care.

Despite these limitations, the study provides a useful insight into current practice with regard to secondary prevention.

Although the use of cardioprotective drugs had increased in CHD patients, there are still gaps in secondary prevention in Tunisia. This could have several causes, such as lack of implementation of evidence-based clinical practice by healthcare providers [18], unaffordability and unavailability of medications, and selective prescription of drugs to certain categories of patients among others [19]. However, a more systematic and widespread application of proven medical therapies, reaching 80% of eligible patients, would

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probably double the number of deaths prevented [20]. Audit resources are limited, and prioritization is essential. Future local audit activity should therefore initially focus on secondary prevention.

CONCLUSIONS

There is a clear need to increase access to preventive drug therapy through the development of effective national drug policies, rational- and evidence-based selection of medicines, and affordable prices. Providing continuing medical education to healthcare providers could also ensure that patients benefit fully from available knowledge regarding secondary prevention. An effective information system such as a coronary heart registry is crucial for evaluating the performance of secondary prevention programs.

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