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The clinical reality of guidelines for primary prevention of cardiovascular disease in type 2 diabetes in Italy

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Abstract

Introduction and aim: Guidelines for cardiovascular prevention in diabetes have been issued by the national and international scientific societies. No audit as ever been performed to evaluate the implementation of these documents in clinical practice in Italy.

The study evaluates the prevalence, treatment, and control of major cardiovascular risk factors in type 2 diabetic patients, to assess the clinical practice of primary cardiovascular prevention in type 2 diabetes.

Patients and methods: Two thousand four hundred and sixty-five men and women with type 2 diabetes, aged 50–75 and free of cardiovascular events were recruited on a consecutive basis at 10 hospital based outpatients diabetes clinics. Clinical variables were measured by standard protocol. Biochemical parameters were evaluated at each centre. The laboratories were monitored by an external quality control assessment in order to reach and maintain a standard of quality and traceability among the participating centres.

Results: A minority of patients (5%) met the recommended targets for LDL cholesterol, blood pressure, glycated haemoglobin and smoking habits, whereas the vast majority (66%) had unsatisfactory control of three or more of the above. Achievement of desirable control of risk factors differed according to gender and known diabetes duration. Lipid lowering and, to a lesser extent, antihypertensive medications were under-used and their titration insufficiently target-driven. Prophylactic use of antiplatelet agents was scarce, only one out of five patients was treated independent of absolute cardiovascular risk.

Conclusion: In clinical practice there is poor adherence to national and international guidelines for primary cardiovascular prevention in type 2 diabetes in Italy. The study underlines the great potential for prevention, particularly in women and in high-risk patients.
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Keywords: Type 2 diabetes; Cardiovascular prevention; Guidelines; Clinical practice

1. Introduction

Compelling evidence from randomized intervention trials demonstrates that control of blood glucose, blood pressure and cholesterol levels can dramatically delay or prevent the micro and macrovascular complications of diabetes [1–5]. Therefore, one of the main objectives in the management of patients with diabetes is to reduce the risk of complica-

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tions, thus improving their chances of survival as well as their quality of life.

People with diabetes represent one of the highest priorities in the recommendations issued by the Joint European Societies for primary and secondary cardiovascular prevention; the aim of these recommendations is to raise the standard of preventive cardiology by stimulating the development and revision of national guidelines based on multidisciplinary consensus and their implementation in the community [6]. In agreement with these aims, the Italian Diabetes Society (SID) has issued guidelines for cardiovascular prevention in diabetes [7]. The document is based on a multidisciplinary consensus of the national societies of cardiology, hypertension, atherosclerosis, general practitioners and representatives of patient associations. Among other things, these guidelines define goals with regards to lifestyle related risk factors and therapy for the reduction of cardiovascular risk and prevention of cardiovascular events [8]. The goals are to stop smoking, reduce calorie and saturated fat intake, increase the level of physical activity, achieve and maintain a body mass index of 25 kg/m^2 or below, or a weight loss of 7–10%, glycated haemoglobin below 7%, serum LDL cholesterol below 115 mg/dl, blood pressure below 130/85 mmHg, and define rules for the use of appropriate prophylactic drugs such as aspirin. No audit survey has ever been performed since the publication of this document to evaluate its implementation in clinical practice. Available information on the physicians attitudes towards cardiovascular risk factors detection and correction in patients with diabetes comes from analyses of clinical records which often suffer from lack of uniformity in selection criteria between participating centres, and of standardization in the laboratory methods and instrumental procedures, in addition to the fact that available information mainly pertains to high-risk patients.

This study was designed to evaluate the prevalence, treatment, and control of major cardiovascular risk factors in a large sample of type 2 diabetic patients fairly representative of the generality of patients followed-up at diabetes clinics, and to assess the clinical practice of primary cardiovascular prevention in type 2 diabetes. This paper also incorporates recent evidence [8,9] on the need to modify the goals originally proposed by national guidelines for blood pressure (i.e. from 130/85 to 130/80 mmHg) and LDL cholesterol (i.e. from 115 to 100 mg/dl).

2. Study population and methods

The study was undertaken in 2004–2006 at 10 large hospital-based out-patients diabetes clinics representing all those willing to participate and which met the eligibility criteria. To be eligible, centres had to provide medical care to at least 2000 patients, and have an internal or a reference laboratory willing to take part in a mandatory External Quality Assessment Service (EQAS) and which all patients participating in the study could be referred to for biochemical analyses. The distribution of the participating centres was fairly representative of the geographical distribution of diabetic clinics all over the country: four in Northern Italy (La Spezia, Torino, Pavia, Piacenza), four in the centre (Pisa, Perugia, Chieti, Carrara), and two in the South (Roma, Bari). Each centre was asked to recruit 250 consecutive patients (men and women) with type 2 diabetes diagnosed at least 2 years before, and who met the following additional inclusion criteria: age between 50 and 75 years, no history of prior cardiovascular events, and normal renal function defined as serum creatinine below 1.5 mg/dl. Exclusion criteria were liver cirrhosis, neoplasm, chronic use of steroids or substance abuse. The study was carried out according to an observational, cross sectional design.

Prior to enrolment (start-up phase) an External Quality Assessment Service (EQAS) was performed in all the laboratories to verify the comparability and reliability of analytical methods, and to reach a standard of quality and traceability among the participating centres. All EQAS data were pooled together and normalized to target values; the Bias% was calculated and a correction factor was applied for laboratories whose Bias% exceeded (±) the accuracy criteria set by the Centre for Disease Control (CDC, Atlanta, GA, USA). Quality control of the analytical variability was monitored thereafter during the whole study period. Quality control of laboratory data was provided by the laboratory of Clinical Chemistry Standardization of the San Raffaele Hospital (Milan, Italy) which takes part in an international laboratory network for the standardization of reference methods. Training sessions for the observers were also undertaken to standardise clinical measurements, use of questionnaires and data collection procedures, thus reducing the inter-observer variability within and between centres.

Venous blood samples were drawn in the morning, in the fasting state, to evaluate total cholesterol, HDL cholesterol, and triglycerides, by standard methods; LDL cholesterol was calculated according to Friedewald, glycated haemoglobin was measured by HPLC. Weight, height and waist circumference were measured according to a standard protocol. Sitting blood pressure was measured after a five-minute rest, on the right arm with a mercury sphygmomanometer of appropriate cuff size; the first and fifth Korotkoff sound were recorded, and the average of three readings taken two minutes apart was used in the analyses. Validated standard questionnaires (WHO) were used to assess prior MI or stroke [10]. Use of medications and smoking habits were recorded.

The study protocol was approved by the local ethics committees and informed consent was obtained from all participants; the study plan is available at www.SIDitalia.it/research projects.

3. Statistical analyses

Data is given as mean and standard deviation or percentages. For not normally distributed variables, the median and

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interquartile ranges are given. The sample size was calculated to be sufficient to estimate prevalence of risk factors with a precision of at least 5%. Analyses were conducted by gender and by known diabetes duration (i.e. above or below the median of the distribution). For analytical purposes 10 year CHD risk was calculated according to the UKPDS risk engine [11]. Proportions were compared by Chi square; to compare group means, the unpaired Student's *t*-test or analysis of variance were used, as appropriate. Non-parametric statistics were used for not normally distributed variables. The SPSS statistical software (version 12.0) was used; significance was set at a *p*-value of less than 0.05 (two tails).

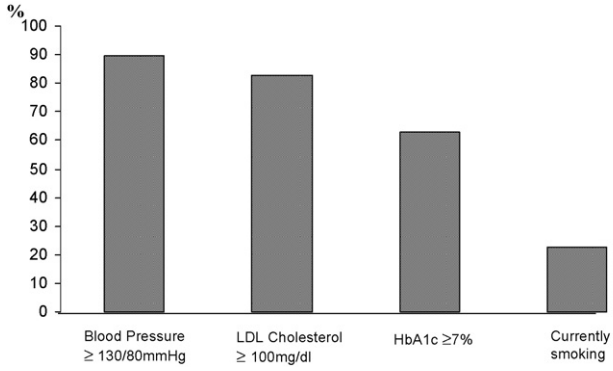


Fig. 1. Proportion (%) of patients not achieving the goals for major cardiovascular risk factors set by current guidelines.

4. Results

All together 2465 patients (1297 men and 1168 women) were recruited: 1021 in Northern Italy, 961 in Central Italy and 483 in the South. Study participants were on average middle aged and markedly overweight, as one would expect for type 2 diabetic patients. Mean values of lipids and blood pressure were substantially higher than recommended by current national and international cardiovascular prevention guidelines. Some gender differences were observed: women were slightly, but significantly older and significantly more obese than men, had significantly higher glycated haemoglobin, LDL cholesterol and systolic blood pressure, but smoked significantly less than men (Table 1). Differences were also observed in terms of diabetes duration (below or above the median of the distribution); besides being older, patients with longer diabetes duration had higher HbA1c and systolic blood pressure ($p<0.01$), but were less obese, had significantly lower diastolic blood pressure and smoked less (all $p<0.01$) than patients with shorter diabetes duration (Table 1).

Only a minority of patients (5%) met the goals set by guidelines for glycated haemoglobin, lipids and blood pressure, whereas the large majority (66%) had a combination of two or more conditions among glycated haemoglobin >7%, blood pressure >130/80 mmHg, LDL cholesterol >100 mg/dl. The proportion of patients off target for each end point is given in Fig. 1. The least achieved goals were those for blood pressure (10.3% of all participants) and LDL cholesterol (16.5% of all participants); instead, 37% of patients achieved goals for glycated haemoglobin and more than 70% were not smoking. Women were off target more frequently than men for HbA1c and LDL cholesterol (59.8% vs. 40.2%, $p<0.001$ and 85% vs. 81%, $p<0.02$, respectively), although insulin treatment was significantly more common in women (11.7% vs. 16.6%, $p<0.01$) and there was no difference between men and women in the use of lipid lowering medications (Table 2). Furthermore, notwithstanding a generally more adverse cardiovascular risk factor profile, women were on antiplatelet agents significantly less frequently than men (Table 2). As for diabetes duration the target for HbA1c was less frequently met by patients with longer diabetes duration (27% vs. 46%, $p<0.001$), despite a much larger use of insulin treatment in this group (24.0% vs. 4.4%, $p<0.001$) (Table 2). No differences were observed, instead, in the proportion of patients not achieving the targets for blood pressure, LDL cholesterol and smoking (89.7% vs. 89.3%; 84.4% vs. 81.5%; 23.4% vs. 21.4% respectively for patients with short or long diabetes

Table 1
Clinical characteristics of study participants by gender and diabetes duration

	Gender		Diabetes duration		All ($n=2465$)
	Men ($n=1297$)	Women ($n=1168$)	≤7 years ($n=1283$)	>7 years ($n=1182$)	
Age (years)	60 ± 5	61 ± 5*	60 ± 5	62 ± 5#	61 ± 5
Diabetes duration (years)†	7 (8)	7 (8)	4 (3)	12 (7)	7 (8)
BMI (kg/m^2)	28.6 ± 4.1	30.7 ± 5.7*	30.0 ± 5.0	29.2 ± 5.0#	29.6 ± 5.0
Waist (cm)	101 ± 10	100 ± 13	101 ± 12	100 ± 12	101 ± 12
Systolic BP (mmHg)	141 ± 16	142 ± 17*	140 ± 16	143 ± 17#	141 ± 16
Diastolic BP (mmHg)	85 ± 9	84 ± 8*	85 ± 9	84 ± 9#	84 ± 9
HbA1c (%)	7.5 ± 1.4	7.7 ± 1.4*	7.3 ± 1.3	7.9 ± 1.4#	7.6 ± 1.4
Total cholesterol (mg/dl)	208 ± 7	219 ± 9*	214 ± 38	212 ± 37	213 ± 37
HDL cholesterol (mg/dl)	46 ± 11	53 ± 13*	49 ± 12	50 ± 13#	49 ± 12
LDL cholesterol (mg/dl)	130 ± 34	135 ± 34*	134 ± 34	132 ± 34	133 ± 34
Triglycerides (mg/dl)	164 ± 97	158 ± 89	163 ± 94	158 ± 92	161 ± 93
Current smokers (%)	27.5	16.0*	23.4	21.4#	22.5

Data is given as $M \pm S$ or †median and interquartile range ( ); *$p<0.01$ vs. men; #$p<0.01$ vs. diabetes duration ≤7 years.

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Table 2
Use of medications by gender and diabetes duration

Treatment	Gender		Diabetes duration		All ($n=2465$)
	Men ($n=1297$)	Women ($n=1168$)	≤7 years ($n=1283$)	>7 years ($n=1182$)	
Hypoglycemic treatment					
Diet only	211 (16.3)	172 (14.7)	291 (22.7)	92 (7.8)	383 (15.5)
Oral agents	933 (72.0)	802 (68.7)	935 (72.9)	800 (67.7)	1735 (70.4)
Insulin	74 (5.7)	90 (7.7)	28 (2.2)	136 (11.5)	164 (6.7)
Orals + insulin	78 (6.0)	104 (8.9)	28 (2.2)	154 (13.0)	182 (7.4)
p	<0.006		<0.001		
Antihypertensive	701 (54.0)	772 (66.1)*	749 (58.4)	724 (61.3)	1473 (59.8)
Lipid-lowering	345 (26.6)	316 (27.1)	338 (26.3)	323 (27.3)	661 (26.8)
Antiplatelets	298 (23.0)	225 (19.3)*	242 (18.9)	281 (23.8)#	523 (21.2)

Data is given as number and % ( ) of non-missing values. *$p<0.01$ vs. men; #$p<0.01$ vs. diabetes duration ≤7 years.

duration). The use of antiplatelet medications was more frequent in patients with longer diabetes duration probably due to their older age (Table 2).

To further evaluate the physician's attitude in regard to correction of cardiovascular risk factors, the use of lipid lowering and antihypertensive medications was analysed according to attained values of LDL cholesterol or blood pressure (Fig. 2). The proportion of patients on lipid lowering agents did not change with increasing LDL cholesterol levels (Fig. 2); furthermore a very large proportion (71%) of patients with markedly elevated LDL cholesterol (i.e. >160 mg/dl) was not being treated for hyperlipidemia (Fig. 2). Conversely, the proportion of patients on antihypertensive medications increased in parallel with blood pressure values ($p<0.001$ for linear trend), although 27% of patients with clearly elevated BP (i.e. systolic above 160 mmHg and/or diastolic above 95 mmHg) were not treated. In addition to these analyses absolute 10 year CHD risk was calculated with the UKPDS risk engine, and the use of lipid lowering, antihypertensive, and antiplatelet drugs was analysed across risk strata (Fig. 3). No changes in the use of lipid lowering treatment was observed with increasing CHD risk, whereas the proportion of patients on antihypertensive and antiplatelet agents increased slightly, albeit significantly, across increasing risk strata, remaining however generally below desirable levels, particularly in high-risk patients.

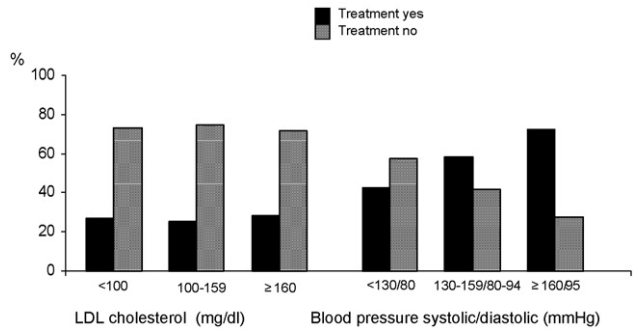


Fig. 2. Proportion (%) of patients on lipid lowering or antihypertensive medications by attained levels of LDL cholesterol or blood pressure.

5. Discussion

This study provides updated information on cardiovascular risk management in patients with type 2 diabetes in clinical practice in Italy. The results clearly indicate poor adherence to national and international guideline recommendations for primary cardiovascular prevention in type 2 diabetes [6–9]. Only a minority of patients (5%) meets the targets set for optimal LDL cholesterol, blood pressure, glycated haemoglobin and smoking cessation, whereas the vast majority (66%) has unsatisfactory control of three or more of these factors. Furthermore, lipid lowering and, to a lesser extent, antihypertensive medications are under-used and their titration is insufficiently target-driven. Prophylactic use of aspirin is scarce, particularly in women and in high-risk patients. An additional finding of this study is a gender gap in the achievement of desirable control of cardiovascular risk factors.

To our knowledge this is the first report on the clinical reality of the implementation of guidelines for primary cardiovascular prevention in diabetes in Italy, based on a standardised data set collection; moreover it is one of the few available reports on the implementation of cardiovascular prevention guidelines in diabetic women [12,13]. There

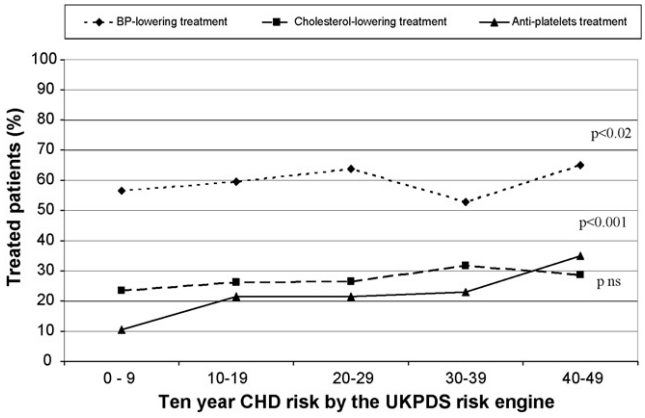


Fig. 3. Proportion (%) of patients on antihypertensive, lipid lowering or antiplatelets treatment according to estimated 10 year CHD risk.

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is abundant evidence that diabetes has a particularly negative effect on cardiovascular risk in women, partly due to a more adverse cardiovascular risk factors profile in diabetic women as compared to men. Nonetheless cardiovascular disease is often perceived as a disease of men also among diabetic patients; this may interfere with both the physician's attitude and patient compliance [13], thus leading to a less intensive correction of risk factors and under-use of antiplatelet drugs in women. Our findings further document this gender gap thus stimulating physicians to recognize sub-optimal management of cardiovascular risk in diabetic women in every-day clinical practice.

Previous studies, based on questionnaire surveys or analysis of clinical records, have documented under-use of aspirin in high-risk patients as well as under-use of statins and β blockers for secondary cardiovascular prevention in general practice in Italy [14–16], although there is some evidence that prescription of antiplatelet treatment may be increasing over time [16]. Reports examining care in various clinical settings in different countries have also found that medical practice is generally not achieving goals for appropriate management of cardiovascular risk in both primary and secondary prevention in diabetic and non diabetic people alike [17–20].

As for the likely barriers to guideline implementation, we can only make speculations. Economic cost and physicians' conviction may influence clinical practice [21,22], but the slow incorporation of guidelines in clinical practice not only in Italy but also in other countries, raises, among other things, the question of patient compliance. Adherence to lifelong treatments requires that patients clearly understand their level of risk, the progressive nature of atherosclerotic disease and the need to take drugs for the rest of their lives [13,23]. Lack of adequate time devoted by physicians to routine office visits and a limited training in counselling techniques may likely affect patient compliance, and are therefore among the possible barriers to guideline implementation [24].

The careful standardization and quality monitoring of laboratory measurements and clinical investigation procedures, are major strengths of this study. Furthermore, unlike previous reports, which mainly address cardiovascular risk factors management in high-risk patients, this study focuses on less selected patients more representative of the majority of patients with type 2 diabetes. As to its limitations, we must acknowledge that this work was performed at diabetes clinics, and therefore the extrapolation of the results to diabetic patients receiving care in different settings (i.e. private specialists, general practitioners) may not be straightforward. Unlike other countries in Italy a key role in the management of diabetic patients is played by a network of outpatient clinics that provide specialised and comprehensive diabetes care; access to the clinics is free of charge and it has been estimated that between 60 and 80% of patients with known diabetes in Italy mainly refer to these diabetes care units. We cannot exclude that patients followed at diabetes clinics may be selected in many ways [25–27] (i.e. they may have more "severe" disease, or be more health conscious than patients not attending); nonetheless the quality of diabetes health care provided in these units supposedly represents a high standard nation-wide. Available data show that all cause and CVD mortality may be lower in patients followed at diabetes clinics as compared to those cared for by GPs only [27]; therefore, if anything, this report may be an optimistic estimate of the gap between guideline recommendations and actual care. On the other hand, in keeping with our results a considerable gap between guidelines and clinical practice is reported in several other countries, thus conferring external consistency to our data and further stressing the evidence of a great potential for primary CVD prevention in type 2 diabetes.

In conclusion major implications emerge from this study. First, there is a need for physicians to recognise the modifiable risk factors in men and women with type 2 diabetes. Second, this information should be to stratify patients according to level of cardiovascular risk so as to identify targeted preventive strategies during routine office visits. Third, a better understanding of the barriers to guideline implementation is in order to improve the quality of preventive cardiology for diabetic patients.

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Appendix A

See Figs. A.1–A.3.

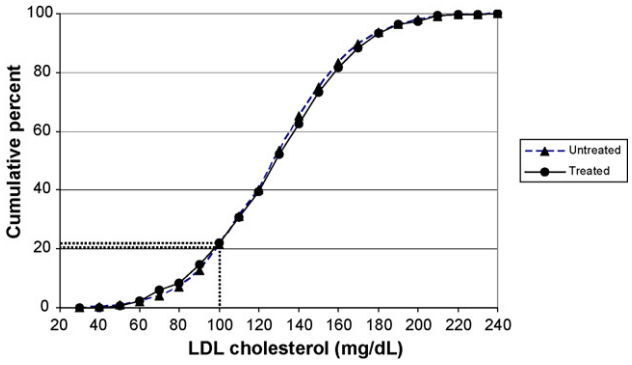


Fig. A.1. Cumulative frequency distribution of LDL cholesterol in participants taking or not taking cholesterol lowering drugs.

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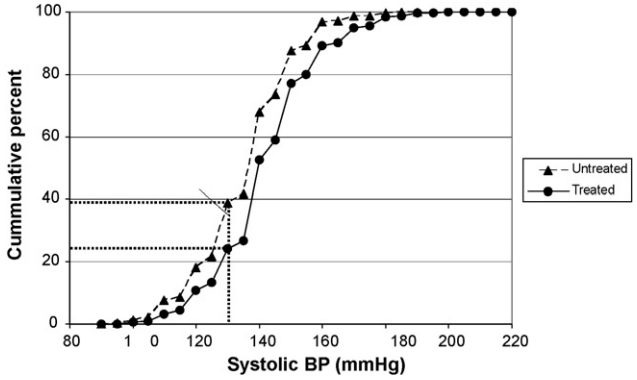


Fig. A.2. Cumulative frequency distribution of systolic blood pressure values for participants taking or not taking antyhypertensive drugs.

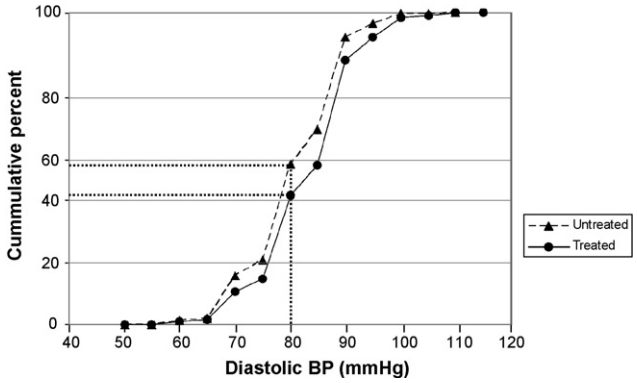


Fig. A.3. Cumulative frequency distribution of diastolic blood pressure values for participants taking or not taking antyhypertensive drugs.

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