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How many patients need statin treatment in a low-cardiovascular-risk country? Low-density lipoprotein-cholesterol target and distance from target distribution in an Italian cohort

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Abstract *Background and aim:* To assess cardiovascular risk distribution, distribution of individual low-density lipoprotein (LDL)-cholesterol target and distance of LDL cholesterol from the target in a representative sample of the Italian population.
Methods and results: Cross-sectional, population-based study of a representative sample of the Italian adult population, comprising 5458 individuals (from 40 to 79 years of age, both sexes) from general practices in Italy.

Of the subjects, 65.2% were in the low-cardiovascular-risk class, whereas 10.5%, 18.3% and 6.0% had moderate, high, and very high cardiovascular risk profiles, respectively; 8.2% of the subjects were treated with statins at enrolment. Of the cohort, 68.3% displayed LDL-cholesterol values below their LDL target, as calculated according to their individual risk profile. Among the 31.7% 'not at target', 42.3% were $\leq$15%, 44.3% were between 15% and 40% and 13.4% were $>$40% over their LDL target.
Conclusions: About two-thirds of adults in a low-cardiovascular-risk country, such as Italy, have LDL-cholesterol levels 'at target', as defined in current guidelines. Accordingly, the remaining subjects require a lifestyle or pharmacological intervention to reach their target; 24% of the

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total cohort, in detail, need to be treated with a statin (or to continue the prescribed statin treatment) to reach the proper LDL target. This type of data analysis might help to optimise resource allocation in preventive medicine.

International guidelines on cardiovascular prevention indicate that interventions to reduce plasma low-density lipoprotein (LDL)-cholesterol levels should be based on the global cardiovascular risk of patients. With increasing risk, specifically, most guidelines indicate that the therapeutic targets for LDL cholesterol should be more aggressive and achieved through non-pharmacological or, when necessary, through pharmacological interventions. Notably, these targets may be extremely different from person to person: for example, in the US National Cholesterol Education Program (Adult Treatment Panel III (ATP-III)) guidelines, published in 2001 and revised in 2004 [1,2], LDL-cholesterol targets range from 70 mg dl^{-1} for very-high-risk patients to 160 mg dl^{-1} for low-risk subjects. In Europe, the joint societies' guidelines suggest targets of 4.5 mmol l^{-1} ($\sim$115 mg dl^{-1}) for low-risk and 2.5 mmol l^{-1} ($\sim$80 mg dl^{-1}) for high-risk patients [3].

The distribution of cardiovascular risk in the population and, consequently, of LDL-cholesterol target values exerts a strong influence on therapeutic interventions to control plasma cholesterol levels. However, although several articles on the attainment of therapeutic goals in various countries have been published [4–7], information on cardiovascular risk distribution in the general population and, hence, on LDL-cholesterol targets distribution, is scanty.

In the present study, we used data from the Italian cohort enrolled in the Cholesterol: Education, Control and Knowledge (CHECK) study[8] to evaluate the distribution of cardiovascular risk in Italy. Then, we estimated individual LDL-cholesterol targets and calculated the difference between measured and target LDL-cholesterol values for each study participant. Finally, we hypothesised the interventions that theoretically would be needed to bring each subject to his or her individualised LDL target value.

Methods

CHECK is an ongoing observational study, started in 2001, jointly coordinated by the Epidemiology and Preventive Pharmacology Centre (SEFAP) of the University of Milan and the Italian Society of General Medicine (SIMG). A general description of this study has been reported elsewhere [8]. In brief, each of 425 general practitioners, distributed across the country, extracted 16 subjects between 40 and 79 years of age from their patients' database. The entire Italian population is listed in general practitioners' databases; moreover, the extraction was based on a software-assisted random-number selection generated by the coordinating centre, to ensure that the sample was representative of the Italian population in the age range 40–79 years. Following extraction, each patient was contacted by his or her physician and invited to participate in the study. Those who refused or were unable to participate were substituted according to a predefined standardised procedure, designed to maintain random selection of the cohort. Enrolled subjects were evaluated clinically by their physician and underwent blood sampling for routine biochemical analyses (plasma total and high-density lipoprotein (HDL) cholesterol, triglycerides, apolipoprotein B, glucose and fibrinogen; LDL cholesterol was calculated using the Friedewald formula). Blood samples were centrifuged and immediately shipped, in a package kept at 4 °C, to a centralised laboratory where the samples were received and analysed in the same day.

A preliminary analysis showed that the resulting sample cohort could be considered as representative of the Italian resident population, within the age range 40–79 years: gender and age distributions are, in fact, superimposable to those of the general population, published by the National Institute of Statistics (ISTAT) [9].

Based on the presence or absence of cardiovascular disease, as assessed by the responsible general practitioner, and on clinical and biochemical data, individual cardiovascular risk was estimated. When appropriate, calculations were made using the CUORE project's algorithm, developed by the National Health Institute (ISS) [10]. The capacity of CUORE to predict cardiovascular events in an Italian population, and its better performance compared with algorithms not derived from Italian cohorts, has been demonstrated [11].

Subjects were then stratified into various risk classes, based on the criteria reported in Table 1.

The therapeutic LDL-cholesterol target of each subject was determined as 70, 100, 130 and 160 mg dl^{-1} for very high, high, moderate, and low global cardiovascular risk, respectively, in accordance with the targets defined by ATP-III in the 2004 revised form [2]. For every subject, the (positive or negative) difference between the calculated plasma LDL-cholesterol levels and his or her therapeutic target (calculated as indicated in Table 1) was then computed. Subjects treated with statins at enrolment (2001–2004, based on data provided by the participating physicians), or those not statin-treated were analysed separately.

Subjects with LDL-cholesterol levels over their target were classified as needing a statin treatment if their LDL cholesterol exceeds their target by more than 15%; below this threshold, they were classified into the 'non-pharmacological treatment' group. The 15% cut-off for non-pharmacological treatment was arbitrarily defined based on the cumulative effect on LDL-cholesterol levels of an appropriate hypolipidaemic diet, of phytosterols, at a 1.5–2.0 g day^{-1} dosage, of soy proteins and of soluble fibre. This combination, in published studies, has, in fact, yielded LDL-cholesterol reductions between 15% and 30% [12].