A comprehensive guidelines-based approach reduces cardiovascular risk in everyday practice: the VARO study

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Abstract

Introduction: The aim of study was to investigate the possibility of cardiovascular risk improvement through systematic identification of high-risk individuals and treatment in accordance with current guidelines using modern therapy in daily clinical practice.
Material and methods: Two hundred and sixty-three physicians participated in the study. The physicians were asked to screen for cardiovascular risk factors in patients presenting with unrelated problems and to re-evaluate the attainment of treatment goals in those with already known risk factors. Each physician enrolled up to 20 consecutive patients with hypertension and/or hyperlipidemia. A total of 3015 patients were included. Cardiovascular risk was assessed using the SCORE system. Risk factors were treated in accordance with current national guidelines. The therapy of hyperlipidemia and hypertension was preferentially based on rosuvastatin, amlodipine and valsartan. Further medication was at the discretion of the attending physician. Patients were examined at baseline and after 3 and 6 months.
Results: The principal result is that global cardiovascular risk decreased by 35% (from 8.9 ±6.4 to 5.9 ±4.4, $p < 0.001$). Systolic and diastolic blood pressure decreased by 12.5% (from 152 ±18 to 133 ±11, $p < 0.001$) and 11.4% (from 88 ±11 to 78 ±7, $p < 0.001$). The level of total cholesterol decreased 21% (from 6.3 ±1.2 to 5.0 ±0.9, $p < 0.001$) and the concentration of LDL-C decreased 28% (from 3.9 ±1.1 to 2.8 ±0.8, $p < 0.001$). HDL-C increased by 7% (from 1.43 ±0.58 to 1.53 ±0.56, $p < 0.001$) and triglycerides decreased by 25% (from 2.4 ±1.3 to 1.8 ±0.9, $p < 0.001$). Blood pressure and LDL-C target values were reached in 68% and 34%of patients, respectively.
Conclusions: The VARO study demonstrates that in daily practice settings, both individual risk factors and global cardiovascular risk are significantly improved through the systematic identification of high-risk individuals and their treatment in accordance with current guidelines using modern pharmacotherapy.

Key words: global cardiovascular risk, hypertension, dyslipidemia, cardiovascular risk reduction, guidelines implementation.

Introduction

Prevention of cardiovascular disease is crucial for reducing cardiovascular risk in the population. A number of studies have demonstrated the possibility of reducing cardiovascular risk (CVR) through the therapy of cardiovascular risk factors [1–11]. These results, however, may appear

difficult to apply to a wide range of patients who are often substantially different from carefully selected participants of the respective trials. Also, trial participants are treated with precisely defined therapies, while, in routine practice, patients typically receive multiple medications in diverse dosing regimens, raising the issues of side effects, drug interactions, and patient compliance with therapy [12]. In addition, there are other barriers to practical application of the scientific knowledge, including previous expertise of the doctor, personal preferences and attitudes of doctors and patients, insufficient knowledge, lack of time, and economic factors [13–17]. In line with this, control of cardiovascular risk factors in the general population is far from satisfactory, and therapies with proven efficacy are underused [18, 19].

Obviously, therefore, translating the knowledge gained in clinical trials into clinical practice is less self-evident than expected, and the problem of application of research knowledge deserves attention. However, compared to the large body of clinical trial data, there is a paucity of research addressing the issue of effectively translating scientific evidence into routine clinical practice [20–26]. The aim of the VARO study (Valsartan Amlodipine and ROsuvastatin for global cardiovascular risk decrease in daily practice) was to assess the possibility of CVR improvement through the systematic identification and subsequent treatment of high-risk individuals using guideline-based therapy in clinical practice.

Material and methods

Design of the study

Physicians who are routinely involved in treatment of cardiovascular risk factors on an outpatient basis (general practitioners, internists, cardiologists and diabetologists) were offered to participate in the study. The information about the study was disseminated through e-mail and during seminars and symposia. Two hundred and sixty-three physicians, of whom 68% were general practitioners, 26% internists, 5% cardiologists, and 1% diabetologists, participated in the study. The study was approved by the State Institute for Drug Control.

The physicians were asked to screen for cardiovascular risk factors in all patients who sought their consultation, regardless of the presenting problem. Individuals with hypertension and/or dyslipidemia (either established or newly diagnosed during the initial visit) were enrolled in the study. Each physician enrolled up to 20 consecutive patients. Dyslipidemia was defined as total cholesterol (TC) > 5.0 mmol/l or triglycerides (TG) > 1.7 mmol/l or high-density lipoprotein cholesterol (HDL-C) < 1.0 mmol/l (males)/ < 1.2 mmol/l (females) or use of lipid-lowering drugs. Hypertension was defined as systolic blood pressure > 140 mm Hg or diastolic blood pressure > 90 mm Hg or use of antihypertensive drugs. History of cardiovascular disease (CVD) was defined as a history of coronary heart disease, heart failure, stroke, or peripheral vascular disease. Smoking was defined as having smoked within the last 4 weeks.

Patients were examined at baseline and again after 3 and 6 months. During each visit, clinical and laboratory examinations were performed and global CVR was assessed. Based on these examinations, the attainment of treatment goals was evaluated and the therapy for risk factors was adjusted accordingly.

Examinations

Biochemical tests were performed at local laboratories using automated analyzer methods. All patients were examined for total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), triglycerides (TG), glycemia and safety laboratory tests, including serum transaminases, creatinine and creatine kinase. A subgroup of patients was examined for apolipoproteins apo A-I, apo B and lipoprotein(a) (Lp(a)). Global CVR (expressed as a 10-year risk of fatal cardiovascular disease) was assessed using the SCORE risk charts (charts specific for the Czech Republic were used) [27].

Treatments

Risk factors were treated in accordance with current national guidelines, which are based on European guidelines on cardiovascular disease prevention [28]. In addition, lifestyle measures were recommended to all patients. Hyperlipidemia and hypertension therapy was preferentially based on rosuvastatin, amlodipine and valsartan, but other drugs prescribed by the attending physician were considered to be acceptable. Any further medication was at the discretion of the attending physician.

End points

The primary outcome was change in cardiovascular risk. Secondary outcomes included changes in serum lipids and blood pressure. In addition, changes in blood glucose, apolipoproteins, body mass index (BMI) and waist circumference were evaluated.

Statistical analysis

Continuous variables were described by mean and standard deviation and discrete ones by ab-

solute and relative frequencies. Time changes for continuous variables were evaluated by ANOVA with repeated measures and pairwise comparisons performed by the contrast method. McNemar's test, with Bonferroni correction for significance levels, was used for discrete variables. All tests were two-sided and $p < 0.05$ was considered to be significant. All calculations were done by SYSTAT software version 13 (Systat Software, Inc, USA).

Results

A total of 3015 patients were included and 2932 completed the study. Baseline characteristics of the patients are shown in Table I and the main outcomes of the study are shown in Table II. Patients who dropped out did not differ from those who completed the study. The most significant result is the profound decrease in global CV risk which became evident after the second visit and a further drop by the third visit (by 21% and 35%, respectively). The improvement in the SCORE risk estimate was driven by the simultaneous decrease in systolic blood pressure and total cholesterol concentration. In addition, a highly significant improvement in diastolic blood pressure and in other lipid values was attained. The decrease in LDL-C was paralleled by a decrease in apoB concentration. ApoA concentrations also decreased, despite an increase in HDL-C, while concentrations of Lp(a) remained unchanged. Concerning other variables, there was a decrease in blood glucose and a small, but still significant, decrease in body weight, BMI and waist circumference.

Table I. Baseline characteristics of study subjects

Parameter	Value
Number	2932
Male/female (%)	52/48
Age [years]	61 ±10.5
BMI [kg/m^2]	29.4 ±4.3
History of CVD	48.2%
Hypertension	69.5%
Diabetes mellitus	20%
Smoking (%)	17

BMI – body mass index, CVD – cardiovascular disease.

In terms of target values, significantly more patients attained target values for blood pressure and LDL-C during the second and third visits compared to the baseline (19.5%, 44.6% and 67.8% for blood pressure and 10.6%, 25.6%, 34.3% for LDL-C, at the first, second and third visits respectively). The study treatments were well tolerated. Creatine kinase levels increased moderately, and there was no increase in liver or renal tests (Table II).

Table II. Main outcomes of study

Parameter	Visit 1	Visit 2	%	Visit 3	%
Global CVR*	8.9 ±6.4	6.7 ±4.8	–24.7	5.9 ±4.4	–33.7
SBP [mm Hg]	152 ±18	139 ±13	–8.6	133 ±11	–12.5
DBP [mm Hg]	88 ±11	81 ±8	–8.0	78 ±7	–11.4
TC [mmol/l]	6.3 ±1.2	5.4 ±1.0	–14.3	5.0 ±0.9	–20.6
LDL-C [mmol/l]	3.9 ±1.1	3.1 ±0.9	–20.5	2.8 ±0.8	–28.2
HDL-C [mmol/l]	1.43 ±0.58	1.49 ±0.53	+4.2	1.53 ±0.56	+7.0
TG [mmol/l]	2.4 ±1.3	1.9 ±0.9	–20.8	1.8 ±0.9	–25.0
ApoB [g/l]**	1.21 ±0.43	1.02 ±0.30	–15.7	0.97 ±0.38	–19.8
ApoA-I [g/l]**	1.44 ±0.43	1.30 ±0.40	–9.7	1.23 ±0.34	–14.6
Lp(a) [g/l]**	0.23 ±0.15	0.22 ±0.12†	–4.3	0.21 ±0.09††	–8.7
Weight [kg]	86 ±15	85 ±14	–1.2	84 ±14	–2.3
BMI [kg/m^2]	29.4 ±4.3	29.0 ±4.2	–1.4	28.7 ±4.2	–2.4
Waist circumference [cm]***	97 ±14	96 ±13	–0.8	96 ±13	–1.6
Glucose [mmol/l]	6.1 ±1.6	5.9 ±1.3	–3.3	5.7 ±1.3	–6.6
CK [µkat/l]	2.05 ±1.08	2.26 ±1.20	+10.2	2.33 ±1.20	+13.7

*Global CVR is expressed as the 10-year risk of fatal cardiovascular disease. CVR – cardiovascular risk, SBP – systolic blood pressure, DBP – diastolic blood pressure, BMI – body mass index, CK – creatine kinase. *Global CVR was calculated only in subjects without a history of cardiovascular disease (1518 patients); **apolipoprotein and Lp(a) concentrations were examined in a subgroup of 236 subjects; ***waist circumference was measured standing, just above the upper hip bone, at the end of normal expiration. †non-significant visit 2 vs. visit 1; ††non-significant visit 2 vs. visit 1; all remaining differences between visit 2/visit 1 and visit 3/visit 1 were significant at p < 0.001.*

Discussion

The VARO study demonstrated substantial improvement of the global cardiovascular risk estimate and several individual risk factors in the daily clinical practice settings. The global CVR, as assessed using the SCORE risk prediction model, decreased by one third. This goal was achieved through the improved identification of high-risk individuals and greater adherence to current treatment guidelines and modern drug therapy.

At first glance, the VARO study may resemble conventional trials of the efficacy of antihypertensive and hypolipidemic drugs, but the focus and importance of our study are quite different. The efficacy of neither drugs nor drug combinations was studied, but instead the effect of a complex approach to the identification and treatment of high-risk individuals in daily practice was explored. Doctors were simply asked to assess CVR, check for the attainment of blood pressure and lipid targets, and treat patients accordingly. For therapy, modern drugs were recommended but were not obligatory. No supervision or feedback was provided to doctors, and no aspects of patient assessment and treatment were evaluated or commented on during the study. The VARO study did not measure the effect of any therapy under controlled condition; instead it explored the feasibility and effect of the implementation of a guidelines-based approach in real-life settings.

Putting best practices into practice is crucial for reducing cardiovascular risk in the population. There are, at present, a variety of effective drugs available to achieve target values in most patients; however, there remains the problem that the available treatment options are underused [18, 28–30]. EUROASPIRE studies have shown that even in patients with a history of cardiovascular disease, who are at the highest risk of future events, appropriate blood pressure and cholesterol levels are achieved in less than half of all patients [18]. Therefore, the issue of implementing guidelines for cardiovascular disease prevention demands attention. Nevertheless, there are only a few studies that examine the effectiveness of various methods to improve adherence to the guidelines [20–25, 31, 32]. In this context, the VARO study demonstrates that a relatively simple approach may translate into an unexpectedly large reduction in cardiovascular risk. Our results parallel those obtained by Greek authors, who evaluated strategies to improve therapy of hyperlipidemia [24] or hypertension [25]. Compared to our study, those studies used a more stringent treatment protocol and demonstrated even greater reduction in the cardiovascular risk score.

It may seem difficult to identify the factors contributing to the favorable results of our study. Generally speaking, the doctors were asked to do what they should have done anyway, and what they would really have done in many patients. There was little new information in the simple risk evaluation and treatment recommendations. The most important and seemingly simple point is to remind doctors to do what they are already used to doing more consistently. However, reminding itself may not necessarily result in better outcomes. In a study by German authors, education of primary care physicians in cardiovascular prevention did not improve prescription of statins when compared to a group receiving no education [20], while education of physicians in hospitals resulted in improvement in cardiovascular risk prevention [33]. It would be therefore a step forward to identify specific factors that could have contributed most to the improvement observed in our study.

Most important, in our opinion, appears to be consistently evaluating and re-evaluating cardiovascular risk in all patients. It is clear that, in current practice, this evaluation is not routinely performed for people who have visited a doctor for something other than cardiovascular disease. The fact that the data associated with cardiovascular risk, blood pressure and serum lipids had to be recorded on the patient charts and explicitly compared with the desired target values lowered the likelihood of the doctor overlooking or underestimating the result. Also, a method of cardiovascular risk assessment could play a role. Physicians often use subjective assessment rather than risk charts or calculators [14], which often results in underestimating the risk in patients of older age groups. Consistent use of SCORE risk charts in our study could help to identify more patients at risk who require treatment. Finally, recommending the use of modern drugs to treat hypertension and dyslipidemia could eventually support the change in therapy in patients who have been treated with older, less effective therapies.

Obviously, our study has many limitations, especially if compared to conventional clinical trials. The lack of a control group appears most important. On the other hand, the design of the study precludes including a control group, because the screening itself (i.e. systematic assessment of CVR) was considered an important part of the complex approach to risk reduction. Also, there is no detailed information about the quality of dietary and lifestyle intervention or the changes achieved by the patients, which are all difficult to assess reliably. However, as noted above, the VARO study did not measure the effect of any particular therapy under controlled conditions, but rather assessed the overall effect of the complex approach to cardiovascular disease prevention.

The question remains whether the changes demonstrated in our study will persist even after

treatment. If we assume that the primary reason for the improved treatment was the attention given to patients, it is likely that the transition to normal controls, without the prescribed frequency and scope of the visits, will lead to some degree of worsening of results. An evaluation of the effects more than a year following the end of the study will be the subject of further research.

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Conflict of interests

RC and MV have received consultation honoraria from Teva Pharmaceuticals CR.

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