

LDL-cholesterol and the potential for coronary risk improvement

Evidence from a practice-based carotid imaging study

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Summary

Aim: To determine population-attributable predicted coronary risk for major coronary risk factors and derive potential for reduction of global coronary risk.

Methods: We obtained images of carotid atherosclerosis in practice-based subjects from self-referred CORDICARE (COR) and physician-referred KARDIOLAB (KAR) patients and calculated 10-year predicted coronary risk according to Swiss guidelines (AGLA) and via reclassification by post-test risk derived from ultrasound-measured total plaque area of the left and right carotid artery. We calculated predicted coronary risk reduction attributable to achievement of all AGLA goals, and for individual risk factors: smokers became nonsmokers, diabetic patients became nondiabetic patients, HDL level, if not already attained, was increased to 1.5 mmol/l, similarly, LDL level was lowered to 1.8 mmol/l, systolic blood pressure (BP) was lowered to 130 and then 10-year risk was recalculated for every subject.

Results: COR included N = 900 (48% female), mean age 59 ± 9 years, KAR included N = 600 (35% female), mean age 58 ± 9 years. COR vs KAR: fewer smokers (12% vs 28%), fewer diabetic patients (3% vs 9%), higher systolic BP (133 ± 15 vs 128 ± 19) and higher HDL (1.6 ± 0.4 vs 1.4 ± 0.4 mmol/l), lower AGLA coronary risk (6.6 ± 7.0 vs 8.1 ± 8.6%), lower post-test risk (13.4 ± 14.1 vs 16.2 ± 16.4%). Predicted percent risk reductions for COR and KAR were: all AGLA treatment goals reached (−46% vs −51%), AGLA LDL goals met (−29% vs −29%), LDL ≤1.8 mmol/l (−52% vs −49%), no smokers (−7% vs −12%), HDL 1.50 mmol/l (−13% vs −21%), blood pressure ≤130 (−7% vs −6%), no diabetes (−1% vs −3%).

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Conclusions: Achieving LDL ≤1.8 mmol/l would be the single most important intervention in lowering coronary risk by 50%. In reaching all AGLA goals, the predicted 10-year risk would fall from 13–7% in COR and from 16–8% in KAR. Subjects are predominantly at low risk according to AGLA, at intermediate risk after reclassification, and could become true low risk through intensified intervention.

Key words: cardiovascular prevention; lipid profile; carotid plaque imaging

Introduction

Assessment of coronary risk is performed by risk charts and usually, the predicted risk for the next ten years is calculated [1, 2]. According to Swiss guidelines, coronary risk is stratified since the year 2005 into low (<10%), intermediate (10–20%) and high coronary risk (>20%) and according to these risk strata, different lipid goals should be obtained, e.g., LDL <2.6 mmol/l in high-risk subjects [1]. However, at a population level, the same risk factor may have greater importance than at the individual level: certainly, having diabetes mellitus Type II may expose a subject to a

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high coronary risk, but when only relatively few subjects have diabetes mellitus type II (low prevalence), the ability to reduce coronary risk at the population level is small [3]: it is estimated, that by the year 2025, the prevalence of diabetes mellitus worldwide will be 5.4% [4]. At the world level, major causes of loss of life years are childhood and maternal underweight, unsafe sex, high blood pressure, tobacco, and alcohol [5]. For Switzerland, there exist virtually no data on population attributable risk due to coronary risk factors. A study comparing three surveys between 1984 and 1993 noticed that more beneficial life style changes could be observed, that average systolic blood pressure had decreased among women (to 124), that the percentage of smokers regressed from 32 to 28%, and that HDL increased during the observation time in both men and women [6]. In view of the high importance at the public health level for the prevention of atherosclerosis and atherothrombosis in an aging population, it appears appropriate to study coronary risk factors that may have the most impact on cardiovascular risk reduction at the population level.

The aim of this study was to estimate population attributable risk for the major independent cardiovascular risk factors by recalculating predefined goals of medical preventive intervention in two practice-based populations for their coronary risk. Based on many years of subjective impression in our patients, we hypothesised that LDL cholesterol would be the single most important independent coronary risk factor to still be undertreated at the population level. Further we used atherosclerosis imaging to measure carotid plaque (total plaque area, TPA) as an additional predictor for coronary risk, because coronary risk is largely underestimated by currently applied coronary risk charts [1].

Methods

We studied healthy, practice-based subjects from self-referred CORDICARE (COR) and physician-referred KARDIOLAB (KAR) patients for 10-year coronary risk determined by Swiss guidelines (AGLA) and through reclassification by post-test probability (PTP) derived from total plaque area of carotid arteries (TPA-PTP).

COR subjects were recruited prospectively between 2007–2011 from a primary prevention center (Kardiolab, Olten, Switzerland) by advertisements in local newspapers and radio broadcasts, then an assessment of risk was performed free of charge funded by the vascular risk foundation VARIFO. After written-informed consent, medical history and actual medication was reviewed, blood pressure measurements were done in a standard manner, measurement of total cholesterol, LDL, HDL cholesterol, triglycerides and blood glucose was performed and then the total plaque area of the carotid arteries was determined by ultrasound.

KAR subjects were retrospectively collected and all were referred from primary care physicians for an assessment of coronary risk between 2002 and 2011. Most laboratory variables were determined by the Medical Laboratory in Olten (www.mlo.ch).

All data were entered into an Excel® spreadsheet (Microsoft, Richmond, USA) and coronary risk was calculated using the PROCAM-Algorithm for men (Cox proportional hazards model extended to the age of maximally 70 years) adopted for Switzerland [1] (AGLA).

Because coronary risk calculations may lack sensitivity, we used carotid imaging to further stratify coronary risk for every single subject as described elsewhere [7]; in brief, any visible plaque defined by a thickness of over 1 mm on the ultrasound screen is

Table 1

Comparison of Cordicare and Kardiolab populations according to baseline characteristics.

| | CORDICARE | % | KARDIOLAB | % | P |
|------------------------------------|-------------|-----|-------------|-----|---------|
| | N | | N | | |
| Baseline Characteristics | 900 | 100 | 600 | 100 | |
| Age years ± SD | 59 ± 9 | | 58 ± 9 | | 0.0006 |
| Females | 430 | 48 | 212 | 35 | <0.0001 |
| Smoker (%) | 105 | 12 | 165 | 28 | <0.0001 |
| Family History (%) | 152 | 17 | 98 | 16 | 0.7773 |
| Diabetes Type II (%) | 24 | 3 | 54 | 9 | <0.0001 |
| Systolic Blood Pressure mm Hg ± SD | 133 ± 15 | | 128 ± 19 | | <0.0001 |
| TPA mm ² ± SD | 48 ± 48 | | 62 ± 55 | | <0.0001 |
| AGLA 10 year risk % ± SD | 6.6 ± 7.0 | | 8.1 ± 8.6 | | 0.0004 |
| TPA-PTP 10 year risk % ± SD | 13.4 ± 14.1 | | 16.2 ± 16.4 | | 0.0004 |

traced longitudinally, and the TPA is derived from the sum of all plaque areas detected during the imaging of both carotid arteries and reported in cm² or mm². For the purpose of post-test coronary risk calculations, we used a specifically designed sex-specific post-test risk calculator based on the total area of carotid plaque (TPA): PTP pos: $(PV \times SE) / [PV \times SE + (1 - PV) \times (1 - SP)]$. PTP pos is the post-test probability in subjects with plaques, PV is the prevalence or the pre-test probability, SE is the sensitivity and SP is the specificity of a given TPA value (table 3 outlines every sensitivity and specificity for every TPA value by sex, which then allows for the calculation of the post-test probability). For every TPA result, sensitivity and specificity (with the only modification that TPA was truncated for a sensitivity of 5% and a specificity of 95%) for fatal and nonfatal myocardial infarction was used to calculate post-test risk (with AGLA risk as the pretest probability) based on the results of the Tromso study [8] and using the Bayes formula [9] (TPA-PTP). A positive test was defined by a TPA >5 mm² in women and >10 mm² in men. In subjects without TPA >5 mm² post-test risk was calculated by the formula $[PV \times (1 - SE)] / [PV \times (1 - SE) + SP \times (1 - PV)]$ [9]. We validated our risk calculator externally in a cohort observing 684 healthy Canadian subjects who experienced 13 AMI over 3 years [10]. NCEP III area under the curve (AUC) was 0.68, for TPA-PTP-based on the Tromso cohort AUC was 0.76 ($p = 0.0133$).

We calculated coronary risk reduction attributable to achievement of all AGLA goals, and for single risk factors: smokers became nonsmokers, diabetic patients became nondiabetic patients, HDL level, if not already reached, was increased to 1.5 mmol/l, similarly, LDL level was decreased to 1.8 mmol/l, systolic blood pressure (BP) was decreased to 130 and then 10-year risk was recalculated for every subject using our Excel risk calculation tool.

The Cordicare II study was approved in December 2006 by the Cantonal Ethical committee of the Canton of Solothurn.

Calculations were performed with the analyse-it software tool for Excel® (Microsoft, Richmond, USA), with the level of significance set at <0.05. We used standard statistical procedures such as comparisons of groups with two tailed t-test, Chi² Pearson, and weighted kappa. For the external validation of TPA we compared ROC curves and assessed a statistical significance using the DeLong-DeLong method [11].

Results

COR included N = 900 (48% female), mean age 59 ± 9 years, KAR included N = 600 (35% female), mean age 58 ± 9 years (table 1).

COR compared to KAR showed less smokers (12% vs 28%), less diabetic patients (3% vs 9%), higher systolic BP (133 ± 15 vs 128 ± 19), higher HDL (1.6 ± 0.4 vs 1.4 ± 0.4 mmol/l), lower AGLA coronary risk (6.6 ± 7.0 vs 8.1 ± 8.6 %), lower post-test risk (13.4 ± 14.1 vs 16.2 ± 16.4%).

Coronary risk reclassification occurred in 39% of patients when using post-test risk based on TPA. For both groups, agreement was present for 60% of patients and the remaining 40% were almost all shifted into a higher risk category. As an example, of the 24% of low risk subjects defined by AGLA, 19% were shifted into the intermediate risk and the remaining 5% into the high-risk group, while 15% of the medium-risk subjects were shifted into the high-risk group. The weighted kappa statistic with an observed agreement of 0.607, an expected agreement of 0.455 was only moderate at 0.28 and a 95% CI from 0.25–0.31 ($p < 0.0001$).

Predicted risk reductions in COR and KAR for individual risk factors alone and combinations (in %) show that the largest difference from baseline can be

Table 2

Population attributable coronary risk reduction (estimates for various risk factors), mean percent values ± 1SD for absolute 10 year coronary risk estimates

| | 10-year risk Mean % ± SD | Difference from baseline (%) | 10-year risk Mean % ± SD | Difference from baseline (%) |
|---------------------------------|-----------------------------|---------------------------------|-----------------------------|---------------------------------|
| Baseline coronary risk | 13.4 ± 14.1 | | 16.2 ± 16.4 | |
| No Diabetes Mellitus | 13.2 ± 13.9 | -1.0 | 15.7 ± 16.0 | -0.5 |
| HDL ≥1.5 mmol/l | 11.6 ± 12.3 | -1.8 | 12.8 ± 13.7 | -3.4 |
| No Nicotine + BP sys ≤130 mm Hg | 11.5 ± 12.2 | -1.8 | 13.5 ± 14.3 | -2.8 |
| AGLA LDL Goal Achieved | 9.5 ± 9.1 | -3.9 | 11.6 ± 11.0 | -4.7 |
| LDL ≤1.8 mmol/l | 6.4 ± 7.4 | -7.0 | 8.3 ± 9.4 | -8.0 |
| AGLA ALL | 7.2 ± 6.5 | -6.2 | 7.9 ± 7.2 | -8.3 |

Note: percentages indicate the absolute predicted reduction of coronary risk from baseline individually and thus can not be added together.

Table 3

Sensitivities and specificities used for post-test risk calculations for myocardial infarction, personal communication from [8].
 TPA = total plaque area in mm².

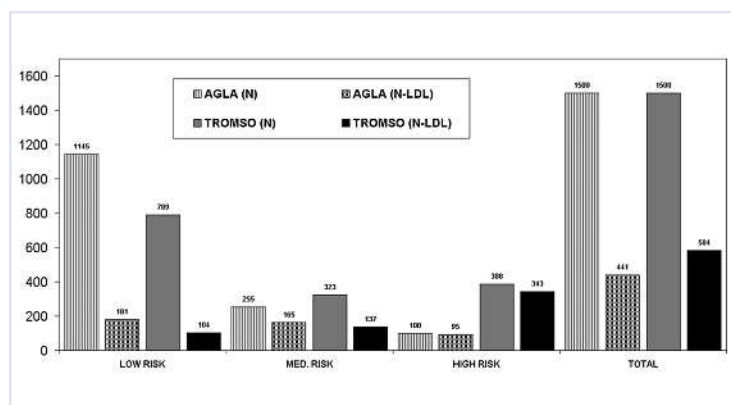
| Men | | | Woman | | | Men | | | Woman | | |
|-----|--------|--------|-------|--------|--------|-----|--------|--------|-------|--------|--------|
| TPA | SENS | SPEC | TPA | SENS | SPEC | TPA | SENS | SPEC | TPA | SENS | SPEC |
| 0 | 0.6868 | 0.5008 | 0 | 0.7938 | 0.5662 | 45 | 0.1162 | 0.9452 | 45 | 0.0825 | 0.9770 |
| 1 | 0.6869 | 0.5012 | 1 | 0.7939 | 0.5663 | 46 | 0.1162 | 0.9483 | 46 | 0.0825 | 0.9781 |
| 2 | 0.6869 | 0.5013 | 2 | 0.7939 | 0.5669 | 47 | 0.1112 | 0.9506 | 47 | 0.0825 | 0.9790 |
| 3 | 0.6869 | 0.5027 | 3 | 0.7939 | 0.5695 | 48 | 0.1112 | 0.9524 | 48 | 0.0825 | 0.9804 |
| 4 | 0.6819 | 0.5079 | 4 | 0.7629 | 0.5792 | 49 | 0.1112 | 0.9545 | 49 | 0.0722 | 0.9815 |
| 5 | 0.6768 | 0.5198 | 5 | 0.7526 | 0.5984 | 50 | 0.1061 | 0.9573 | 50 | 0.0619 | 0.9823 |
| 6 | 0.6667 | 0.5368 | 6 | 0.7320 | 0.6235 | 51 | 0.1011 | 0.9590 | 51 | 0.0619 | 0.9838 |
| 11 | 0.5859 | 0.6460 | 11 | 0.5980 | 0.7356 | 56 | 0.0910 | 0.9682 | 56 | 0.0619 | 0.9879 |
| 14 | 0.5051 | 0.7083 | 14 | 0.5155 | 0.7911 | 59 | 0.0859 | 0.9709 | 59 | 0.0619 | 0.9904 |
| 15 | 0.4950 | 0.7236 | 15 | 0.4743 | 0.8048 | 60 | 0.0859 | 0.9716 | 60 | 0.0516 | 0.9911 |
| 16 | 0.4798 | 0.7357 | 16 | 0.4640 | 0.8182 | 61 | 0.0859 | 0.9730 | 61 | 0.0516 | 0.9920 |
| 17 | 0.4647 | 0.7486 | 17 | 0.4433 | 0.8314 | 62 | 0.0859 | 0.9751 | 62 | 0.0516 | 0.9920 |
| 18 | 0.4495 | 0.7629 | 18 | 0.4227 | 0.8448 | 63 | 0.0809 | 0.9766 | 63 | 0.0516 | 0.9920 |
| 19 | 0.4142 | 0.7767 | 19 | 0.4124 | 0.8577 | 64 | 0.0758 | 0.9770 | 64 | 0.0516 | 0.9930 |
| 20 | 0.3990 | 0.7885 | 20 | 0.3918 | 0.8665 | 65 | 0.0708 | 0.9779 | 65 | 0.0516 | 0.9930 |
| 21 | 0.3788 | 0.7990 | 21 | 0.3609 | 0.8765 | 66 | 0.0657 | 0.9795 | 66 | 0.0516 | 0.9930 |
| 22 | 0.3637 | 0.8099 | 22 | 0.3403 | 0.8876 | 67 | 0.0607 | 0.9800 | ≥67 | 0.0500 | 0.9940 |
| 23 | 0.3485 | 0.8200 | 23 | 0.3196 | 0.8949 | 68 | 0.0607 | 0.9807 | | | |
| 24 | 0.3233 | 0.8297 | 24 | 0.2990 | 0.9027 | 69 | 0.0607 | 0.9823 | | | |
| 25 | 0.3081 | 0.8385 | 25 | 0.2887 | 0.9095 | 70 | 0.0607 | 0.9836 | | | |
| 26 | 0.2879 | 0.8447 | 26 | 0.2578 | 0.9155 | 71 | 0.0556 | 0.9836 | | | |
| 27 | 0.2778 | 0.8534 | 27 | 0.2372 | 0.9219 | 72 | 0.0556 | 0.9841 | | | |
| 28 | 0.2728 | 0.8630 | 28 | 0.2372 | 0.9275 | 73 | 0.0556 | 0.9848 | | | |
| 29 | 0.2576 | 0.8695 | 29 | 0.2165 | 0.9332 | ≥74 | 0.0500 | 0.9851 | | | |
| 30 | 0.2425 | 0.8764 | 30 | 0.2062 | 0.9380 | | | | | | |
| 31 | 0.2273 | 0.8816 | 31 | 0.2062 | 0.9419 | | | | | | |
| 32 | 0.2273 | 0.8863 | 32 | 0.1959 | 0.9447 | | | | | | |
| 33 | 0.2273 | 0.8927 | 33 | 0.1650 | 0.9473 | | | | | | |
| 34 | 0.2223 | 0.8988 | 34 | 0.1650 | 0.9510 | | | | | | |
| 35 | 0.2223 | 0.9044 | 35 | 0.1341 | 0.9555 | | | | | | |
| 36 | 0.2172 | 0.9090 | 36 | 0.1135 | 0.9585 | | | | | | |
| 37 | 0.2172 | 0.9137 | 37 | 0.1135 | 0.9609 | | | | | | |
| 38 | 0.1819 | 0.9180 | 38 | 0.1135 | 0.9635 | | | | | | |
| 39 | 0.1819 | 0.9223 | 39 | 0.1031 | 0.9657 | | | | | | |
| 40 | 0.1667 | 0.9266 | 40 | 0.0928 | 0.9673 | | | | | | |
| 41 | 0.1516 | 0.9304 | 41 | 0.0928 | 0.9693 | | | | | | |
| 42 | 0.1415 | 0.9331 | 42 | 0.0928 | 0.9717 | | | | | | |
| 43 | 0.1314 | 0.9378 | 43 | 0.0928 | 0.9738 | | | | | | |
| 44 | 0.1213 | 0.9422 | 44 | 0.0825 | 0.9755 | | | | | | |

achieved by lowering LDL ≤ 1.8 mmol/l (table 2). The relative attributable coronary risk reductions are: all AGLA treatment goals achieved (–46% vs –51%), AGLA LDL goals met (–29% vs –29%), LDL ≤ 1.8 mmol/l (–52% vs –49%), no smokers (–7% vs –12%), HDL ≥ 1.50 mmol/l (–13% vs –21%), blood pressure ≤ 130 (–7% vs –6%), no diabetes (–1% vs –3%).

Implications of atherosclerosis imaging (TPA) on the number of subjects having an indication for LDL lowering, e.g., with statins, was assessed for AGLA and TPA-PTP (post-test probability calculations). Looking at both groups with $N = 1500$, AGLA would treat 441 and TPA-PTP would treat 584 subjects for their LDL, which corresponds to an increase from 29 to 39% (fig. 1).

Figure 1

Number (N) of subjects according to level of coronary risk (low, intermediate, high) showing an indication for LDL-lowering intervention (LDL), e.g., with statins, by Swiss guidelines for AGLA pretest (AGLA) and post-test risk (TPA-PTP).



Discussion

The main finding of this study is that predicted coronary risk at the population level of our two populations is largely attributable to LDL cholesterol and could be reduced by about 50% if all subjects had their LDL lowered to 1.8 mmol/l or less.

The effect of atherosclerosis imaging in both populations was a doubling of coronary risk from an average of 7% ten-year risk (AGLA) to an average of 15% ten-year risk (TPA-PTP), exhibiting an expected substantial underestimation of risk by AGLA standards.

When we looked at the main risk factors causing myocardial infarction in our two populations with a total of 1500 subjects, we found the population attributable risk of LDL to be by far the most prevalent coronary risk factor when compared with ongoing cigarette smoking, blood pressure, HDL-cholesterol and diabetes.

Adhering to AGLA LDL guidelines would reduce coronary risk by 29% in both groups, while a reduction of LDL to ≤ 1.8 mmol/l resulted in a coronary risk reduction of about 50% in both groups. If all AGLA goals were met, risk reduction would be 46% in the CORDICARE group and 51% in the KARDIOLAB group. This difference shows that patients referred for TPA by their physicians had a higher coronary risk and thus the possibilities of risk lowering were more substantial.

The concept of LDL “the lower the better” could be well shown in our two patient groups and is in line with a recent metaanalysis in the *Lancet*, encompassing more than 170 000 randomised subjects: “Further reductions in LDL cholesterol safely produce definite further reductions in the incidence of heart attack, of revascularisation, and of ischaemic stroke, with each 1.0 mmol/l reduction reducing the annual rate of these major vascular events by just over a fifth. There was no evidence of any threshold within the cholesterol range studied, suggesting that reduction of LDL cholesterol by 2–3 mmol/l would reduce risk by about 40–50%” [12].

Further, several surveys point to the fact, that LDL as a risk-lowering target is frequently undertreated at the population level, both in primary [13, 14] and secondary prevention or for patients with diabetes mellitus [15].

TPA may increase the numbers of subjects, in whom e.g., LDL should be treated: according to AGLA, LDL should be lowered < 4.1 mmol/l in low-risk (and one other risk factor), < 3.4 mmol/l in intermediate-risk and < 2.6 mmol/l in high-risk patients. Applying this rule (with the exception that all subjects at low risk should have their LDL below 4.1 mmol/l) to risk strata defined by pretest AGLA and post-test TPA-PTP we found the following results: AGLA would treat 441 subjects (29%) while TPA-PTP would treat only 10% more, which corresponds to 584 subjects (fig. 1). Therefore, TPA did increase the indication for LDL treatment in these subjects aged 45–75 years in only 10% and it can be assumed that the allocation of treatment (e.g., LDL lowering with statins) is more precise, since it is based upon a treatment decision that incorporates the presence of biologically proven atherosclerosis.

Limitations

Since, we do not present real outcome data in this work, but just risk estimates based upon observations made in non Swiss populations (PROCAM, Germany; TROMSO, Norway), we have to keep in mind, that PROCAM is validated for men only. However, atherosclerosis imaging may correct for such shortcomings especially in women, for which TPA has been shown to predict coronary risk even better than for men [8].

A further limitation is the assumption that by reducing the amount of risk factors, e.g., LDL from the

actual level to 1.8 mmol/l might not reflect the same future risk as would be observed in an untreated person with an LDL of 1.8 mmol/l. However, it has been shown that the reduction of LDL to such low levels using statins reduces coronary risk by about 50%, which corresponds almost exactly to our findings [12].

A certain proportion of subjects were under lipid lowering or antihypertensive drugs. In COR, 8% were under statin treatment and 20% used blood pressure lowering medications (combination: 4%); in KAR, 26% used statins and 38% used blood pressure lowering drugs (combination: 15%).

Conclusions

We observed that lowering of LDL ≤ 1.8 mmol/l would achieve the most prominent reduction in predicted coronary risk at the population level. Our results suggest, that current guidelines should be revised answering the question, whether LDL should not be lowered with more vigour in the population, also keeping the fact in mind, that risk for fatal or nonfatal myocardial infarction is just one expression of coronary atherosclerosis and that nonobstructing coronary artery disease shows about a five times higher event rate for composite endpoints such as unstable angina, chronic angina and need for coronary revascularisation [16]. Therefore, more extensive efforts may be undertaken to improve LDL lowering in primary care, but cost-efficiency of such intervention remains an important issue needing further comprehensive assessment. Further, we found, that physician-referred patients would benefit more from a global risk reduction strategy, including therapies that influence risk from LDL, HDL, systolic blood pressure and smoking cessation in comparison to the self-referred group. Doing so, their coronary risk could be reduced by 51%. But also in patients, primarily seeking medical attention within a nonreferral setting, important lowering of LDL would reduce coronary risk by 46%. In view of the increasing age of the Swiss population and the correlated increase of chronic cardiovascular diseases (including vascular cognitive impairment), our study might help to better allocate risk lowering activities by estimates of which risk factor treatment might be more cost-effective at the population level, helping therefore in reducing unnecessary costs, intervening early in the process of developing atherosclerosis and bringing us closer to the ultimate goal of disease compression.

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