Comparison of an effect-model-law-based method versus traditional clinical practice guidelines for optimal treatment decision-making: application to statin treatment in the French population

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Healthcare authorities make difficult decisions about how to spend limited budgets for interventions that guarantee the best cost-efficacy ratio. We propose a novel approach for treatment decision-making, OMES—in French: Objectif thérapeutique Modele Effet Seuil (in English: Therapeutic Objective–Threshold–Effect Model; TOTEM). This approach takes into consideration results from clinical trials, adjusted for the patients’ characteristics in treatment decision-making. We compared OMES with the French clinical practice guidelines (CPGs) for the management of dyslipidemia with statin in a computer-generated realistic virtual population, representing the adult French population, in terms of the number of all-cause deaths avoided (number of avoided events: NAEs) under treatment and the individual absolute benefit. The total budget was fixed at the annual amount reimbursed by the French social security for statins. With the CPGs, the NAEs was 292 for an annual cost of 122.54 M€ compared with 443 with OMES. For a fixed NAEs, OMES reduced costs by 50% (60.53 M€ yr−1). The results demonstrate that OMES is at least as good as, and even better than, the standard CPGs when applied to the same population. Hence the OMES approach is a practical, useful alternative which will help to overcome the limitations of treatment decision-making based uniquely on CPGs.

1. Background

In the current situation where healthcare budgets are increasingly limited, healthcare authorities are faced with difficult decisions on how to spend their budget. They need to be able to select interventions that guarantee the best cost-efficacy ratio while respecting the fundamentals of individual ethics. Medical decisions are frequently based on thresholds of one or more continuous or ordinal variables. For example, a person with a systolic blood pressure of more than 160 mm Hg will be diagnosed as having hypertension and will be treated for this. In an American study, it was found that doctors used thresholds for some of their therapeutic decisions instinctively [1]. Below a certain threshold, the expected benefit from a treatment does not seem to outweigh the potential inconveniences. The threshold can involve a synthetic variable such as the absolute benefit or one or more biomarkers, such as the systolic blood pressure...
or the cholesterol level. Considering a threshold is crucial because generally treatment benefit is represented as a continuous function, with no notable changes or breaks as a function of the patients’ characteristics.

Decision-making using clinical practice guidelines (CPGs) is based on thresholds of measurable variables, for example, blood pressure or cholesterol levels. These thresholds are not evidence-based; they are based on physicians’ experience, expert opinion or economic considerations in the absence of a natural threshold separating harmful and beneficial effects.

In cost-effectiveness studies, the monetary costs of a treatment strategy are evaluated against its efficacy, expressed as a direct effect. Using these methods the decision thresholds define the efficacy levels (poor, acceptable or high efficacy), risk or benefit groups (high, low) and values of biological variables (e.g. blood pressure or cholesterol levels). However, this approach does not allow the therapeutic target population to be clearly identified nor does it take into consideration the inter-subject variability in terms of the quantity of benefit or the individual characteristics of the target patients. In other words, it does not identify the benefit threshold that will characterize those patients who will respond better to the treatment and the characteristics of these responders.

Several methods for estimating treatment thresholds have been published but these have not been adopted by prescribers or healthcare decision-makers. Some of these methods are based on the analysis of uncertainty (uncertainty around the mean values) and robustness (identification of false positives and false negatives) in a classification model [2]. These methods involve a global decision and do not integrate the individual patient characteristics. Other methods involve using logistic regression models either taking into account the uncertainty in the decision-making process (ordered logistic regression: yes, no, unsure) [1] or without including uncertainty (simple logistic regression: yes, no) [3]. The disadvantage of this method is that it is based on analysis of physicians’ practice and does not integrate available evidence on treatment efficacy. The decision thresholds are difficult to determine and are not easily reproducible or justifiable. Finally, a method that takes into consideration economic constraints (costs) and the treatment efficacy to select a decision threshold was reported in 1998 [4]. This method models the relationship between the cost of an avoided event and a decision threshold based on a biological marker. An alternative to these methods has recently been reported [5]. With this alternative method it is possible to select the decision threshold, which is directly related to the treatment efficacy, transparently. This method, known as OMES—in French: Objectif thérapeutique Modèle Effet Seuil (in English: Therapeutic Objective–Threshold–Effect Model), can be used to estimate the efficacy of a treatment, and to select the decision threshold and thus the treatment target population. OMES not only considers the patients’ characteristics, which determine their baseline risk (distribution of risk factors in a given population) and their response to treatment (integrated in a mathematical model—the effect model) [6–10], but also considers other constraints, in particular, economic constraints.

A theoretical demonstration suggested that OMES is always at least as efficient as CPGs, and often more efficient, both on a target population level as well as on an individual patient level [5]. Here, we report a comparison of OMES with an established approach, CPGs, for the treatment of patients with lipid-lowering treatment to prevent all-cause mortality. We addressed two questions: (i) how many events would each method prevent with a fixed budget? and (ii) how much would it cost to obtain a specified reduction in the all-cause mortality rate with each approach?

2. Material and methods

We used a four-step methodology involving:

1. generation of a realistic virtual population (RVP);
2. estimation of the number of events (all-cause mortality), using the cardiovascular risk and the all-cause mortality risk in the RVP;
3. integration of efficacy data from meta-analyses and economic data; and
4. comparison of the OMES and CPG approaches.

2.1. Generation of the realistic virtual population

The RVP was generated to be representative of the French population aged between 35 and 64 years old (26 million individuals).

For the research reported here, we worked with a sample of 1 004 217 individuals, which is about 4% of this population. The variables used to generate the RVP were: systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol (TC), HDL cholesterol (HDL-c), glycaemia (Glyc), serum creatinine (Creat), weight (Weight), height (Height), gender (Sex), age (Age), left ventricular hypertrophy (LVH) and smoker status (Smoking). The individuals from the RVP were randomly selected from a truncated multivariate normal distribution to avoid extreme values using the mean values of the variables and their covariance matrix as the parameters. The algorithm used, which has been reported previously, is represented in figure 1 [11–13]. The population was divided into 10-year age classes using the same distribution as that in the real French population, based on data for January 2010 from the French National Statistics Institute (INSEE) [14] (table 1; see appendix A for more details).

2.2. Estimation of the number of events (all-cause mortality), using the cardiovascular risk and the all-cause mortality risk in the realistic virtual population

The individual risks were estimated using the patients’ characteristics and the SCORE model for cardiovascular mortality risk in a low-risk area [15] (figure 2). Cardiovascular mortality as a percentage of the total mortality was estimated by age group, as the ratio of deaths due to any cardiovascular disease to deaths due to any cause (table 2) using exhaustive French national data for 2007 from the website of the Epidemiology Centre for Medical Causes of Death (in French: Centre d’épidémiologie sur les causes médicales de décès—CépiDC) [16].

As SCORE uses ICD9 codes and CépiDC uses ICD10 codes, we had to identify the correspondence between the ICD9 and ICD10 codes in order to calculate the cardiovascular mortality rates for the same diseases as those used in the SCORE model. In addition, SCORE predicts the individual risk for cardiovascular mortality rCVD, whereas the therapeutic objective for treatment with statins was total mortality rTM. Hence, we assumed that the risk of total mortality could be estimated by the simple addition of rCVD and the risk for non-cardiovascular mortality (rNCVD)

\[
\text{rTM} = r_{CVD} + r_{NCVD}. \tag{2.1}
\]
In order to estimate the risk of all-cause mortality for each individual risk of cardiovascular mortality in the same class, we estimated a mean cardiovascular mortality risk: $r_{CVD}$, and that the mean non-cardiovascular mortality risks $r_{NCVD}$ for each class are estimated as follows:

$$r_{CVD} = \frac{r_{NCVD}}{\bar{r}_{CVD}}$$

and

$$r_{TM} = \frac{r_{CVD}}{\bar{r}_{TM}}$$

and that the mean non-cardiovascular mortality risks $r_{NCVD}$ for each class are estimated as follows:

$$r_{NCVD} = r_{TM} - r_{CVD}$$

then

$$r_{NCVD} = \frac{r_{CVD}}{\bar{r}_{TM}} \times (1 - \bar{r}_{CVD}).$$

In order to estimate the risk of all-cause mortality for each individual $i$ for a given class $j$ ($r_{TMj}$), the mean risk of non-cardiovascular mortality for one class was added to the individual risk of cardiovascular mortality in the same class

$$r_{TMj} = r_{CVDj} + r_{NCVD}.$$ 

2.3. Integration of efficacy data from meta-analyses and economic data

The estimate of the efficacy for statins on the reduction of all-cause mortality comes from a meta-analysis carried out by our team for the French National Authority for Health (in French: Haute Autorité de Santé—HAS) [17]. In this meta-analysis, we assessed statin efficacy in terms of public health. To do this, we collected all-cause mortality data from all 91 publically available randomized clinical trials on the efficacy of statins used in primary prevention compared with placebo or no lipid-lowering treatment. We used the collected data to evaluate the dose–effect relationship and a potential class effect, i.e. differences between the various statins effects. The results from the meta-analysis showed that an ‘average’ statin could reduce the incidence of all-cause mortality with a relative risk (RR) of 0.901 [95% confidence interval (95% CI): 0.87, 0.93]. In addition, the results suggest the assumption of a linear effect model for all statins was acceptable. Using data from the French national health system in 2007 [18], the mean cost per patient was estimated at 415 € yr$^{-1}$. Thus, the average statin used in the simulations had a relative risk reduction of 0.901 and cost 415 € yr$^{-1}$.

2.4. Comparison of the OMES and clinical practice guideline approaches

We selected a CPG published in 2005 from the French agency AFSSaFS (Agence Française de Sécurité Sanitaire des Produits de Santé) [19]. The therapeutic objective in this guideline was the reduction of serum LDL cholesterol (LDL-c). The guideline recommends, if medical treatment is prescribed, five different target values for LDL-c, depending on the condition of the patient’s vascular system and their associated cardiovascular risk factors (table 3; appendix B: risk factors). When we transformed this guideline into an algorithm, some of the variables were not available in our RVP (microalbuminuria and family history of cardiovascular disease).

2.4.1. Calculations

We used the number of all-cause deaths avoided (number of avoided events: NAE) after 1 year of treatment in the target population to compare the two methods. The NAE was obtained by summing the individual absolute benefit (AB) for all the individuals in the target population. The estimation of the absolute benefit was based on the effect model, which for statins is assumed to be a multiplicative linear function, coherent with the meta-analysis [17]. Thus, for each subject, $i$, in the target population

$$AB_i = RR \times Re_i.$$ 

### Table 1. Age and gender distribution of the French population (data from INSEE [14]).

<table>
<thead>
<tr>
<th>age group</th>
<th>men</th>
<th>women</th>
</tr>
</thead>
<tbody>
<tr>
<td>percentage of the general</td>
<td>35–44</td>
<td>6.88</td>
</tr>
<tr>
<td>population on 1 Jan 2010</td>
<td>45–54</td>
<td>6.64</td>
</tr>
<tr>
<td>(62.8 million individuals)</td>
<td>55–64</td>
<td>6.10</td>
</tr>
</tbody>
</table>

Letting $j$ be the age–gender classes and $k_j$ the corresponding number of individuals, for each class, we estimated a mean cardiovascular mortality risk: $r_{CVDj}$, a mean all-cause mortality risk: $r_{TMj}$, and the number of deaths due to cardiovascular disease: $n_{CVDj}$. We also estimated the percentage of cardiovascular deaths among all deaths: $\tau_j$ [16] (table 2).

Allowing that

$$n_{CVDj} = \sum_{i=1}^{k_j} r_{CVDij}$$

and

$$r_{CVDj} = \frac{n_{CVDj}}{k_j}$$

(2.2)

and

$$r_{TMj} = \frac{r_{CVDj}}{\tau_j},$$

and

$$r_{NCVDj} = r_{TMj} - r_{CVDj},$$

(2.3)

then

$$r_{NCVDj} = \frac{r_{CVDj}}{k_j} \times (1 - \tau_j).$$

(2.4)

Figure 1. Algorithm of the RVP based on the study of Marchant et al. [11]. The RVP was generated to be representative of the French population aged between 35 and 64 years old (26 million individuals). (Online version in colour.)
Rc was estimated using the SCORE equation. The relative risk (RR) and confidence interval (CI) were obtained from the meta-analysis. The variability of the RR allowed us to integrate uncertainty in the AB calculations with 95% CI. The calculation of the CI uses its logarithm (log RR), because the natural logarithm is normally distributed, so that the lower (log RR<sub>lower</sub>) and upper (log RR<sub>upper</sub>) 95% limits of log RR are calculated as follows:

\[
\log RR\text{lower} = \log RR - 1.96 \times \sigma_{\log RR} \\
\log RR\text{upper} = \log RR + 1.96 \times \sigma_{\log RR}
\]

(2.7)

Thus, from the value of RR and its CI we calculated the CI for log RR

\[
RR\text{lower} = e^{\log RR\text{lower}} \Leftrightarrow \log RR\text{lower} = \ln (RR\text{lower}) \\
\text{and}\quad RR\text{upper} = e^{\log RR\text{upper}} \Leftrightarrow \log RR\text{upper} = \ln (RR\text{upper})
\]

(2.8)

These estimations are based on the bootstrap method [20–22] which involves random sampling with replacement from the original population, re-estimating the value of interest \(K\) times (\(K = \text{number of bootstraps}\)) and then to calculate its parameters (mean, variance, distribution and CI). For each of the simulations of the \(K\) bootstraps, we calculated the individual AB using equation (2.6) by taking as many random samples from the distribution law of log RR around the values of log RR as there were individuals (Rc) in the population. The sum of the AB gives the NAE. The NAE for each of the two approaches is the mean of the \(K\) bootstraps and its CI, corresponding to 95% of the values calculated around this mean.

2.4.2. Target populations

The subjects in the sample with an AB above the decision threshold (OMES) or above the combination of the biomarker threshold values (AFSSaPS clinical practice guideline) form the target populations.

2.4.3. Computer programs and simulations

The development of the algorithms and the statistical analyses were done using R v. 2.11.1 (MacOs) software [23–25]. The estimations of NAE and their confidence intervals were done with
Table 3. Recommended target levels of LDL-c as a function of the presence of cardiovascular disease risk factors [19]. Patients with a high cardiovascular risk are those with a history of established cardiovascular disease, those with a high-risk type-2 diabetes (appendix B: high-risk diabetes) and those with an estimated more than 20% risk of having a coronary event within 10 years.

<table>
<thead>
<tr>
<th>therapeutic objective</th>
<th>high risk of cardiovascular disease</th>
<th>≥3 risk factors</th>
<th>2 risk factors</th>
<th>1 risk factor</th>
<th>no risk factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>for LDL-c (g l⁻¹)</td>
<td>&lt;1</td>
<td>&lt;1.3</td>
<td>&lt;1.6</td>
<td>&lt;1.9</td>
<td>&lt;2.2</td>
</tr>
</tbody>
</table>

1000 bootstraps (1000 samples of the same size as the original population) for both approaches. We used parallel calculation methods with the MPI (Message Passing Interface) standard, because of the large number of bootstraps and the size of the matrices of the patients’ descriptors (1 million patients, each with 12 variables). Two libraries, Rmpi and SNOW, were used [26–29]. The simulations were performed on a MacOS 8-processor calculation server. The parallel calculation method enabled us not to be limited by the sample size, and to be able to use the individual risks instead of the mean subgroup risks, thus removing the recurrent problem of the subdivision of the sample, known as the edge effect (i.e. results that are different depending on the limits of the risk classes). And last, but not least, the calculation time was substantially reduced, as it was divided by the number of nodes (CPU) used.

2.4.4. Definition of the thresholds
In the CPG approach, the biomarker thresholds were defined by experts from AFSSaPS, who developed the guideline. For the OMES approach, the AB threshold was defined using the sum of money allocated for statin treatment calculated as the sum of ‘size of the target population’ × ‘annual cost of individual treatment’ which is a constraint in the function used to calculate the AB. The number of deaths avoided by OMES thus corresponds to the AB threshold below which treating patients would lead to overspending of the allocated budget.

2.4.5. Comparison of the approaches
The simulations were carried out using the same individuals for both methods to ensure similar conditions for the comparison, using an ‘average’ statin (RR = 0.901, cost = 415 € yr⁻¹). Initially, the allocated sum for the OMES approach was calculated by applying the CPG to the selected sample (comparison with a fixed sum: allocated sum = cost incurred by applying the CPG). Then, to assess the possible savings arising from the choice of one of the approaches compared with the other, we used the same NAE. This reference NAE was calculated using the guidelines and the comparison outcome was the cost.

3. Results
The individual characteristics and the risk factor values used for the RVP are summarized in table 4. In the population targeted by the CPGs, the average risk of all-cause mortality over 1 year was 1%, with the lowest risk being 0.022%. The average risk of cardiovascular mortality (SCORE) over 1 year was 0.16%. The number of average individuals varied slightly between simulations, owing to the variability of the bootstrap samples. On average, the guideline targeted 295 269 individuals, 26.83% of whom were women and 73.17% were men.

In the target population with an allocated sum of 122.54 M€ with the OMES approach, the treatment target population involved patients with an estimated absolute benefit of more than 0.0812% [95% CI: 0.0810, 0.0820] (AB threshold). The average risk of all-cause mortality over 1 year was 1.46%, with the lowest risk being 0.82%. The average risk of cardiovascular mortality over 1 year was 0.19%. This target population comprised 51% women and 49% men. In the comparison with a fixed cost, the OMES approach resulted in more deaths being avoided than the CPG approach; the NAE was 443 yr⁻² [95% CI: 442, 445] which is about 1.5 times more than that with the guideline approach (292 yr⁻²; [95% CI: 291, 293]; table 5). When using a constant NAE, the OMES approach reduced the cost for statin treatment by half, while avoiding the same number of deaths (table 6). The OMES approach would cost an average of 60.53 M€ to avoid 292 deaths annually, compared with 122.54 M€ with the CPG approach. The NAE is a linear function of RR: \( f(RR) = \text{sum}(\text{Rc}) \times (1 - RR) \) (we assumed a linear effect model for statin, see Material and methods) with a straight slope equal to the sum of the Rc (figure 3: NAE versus RR with fixed global and unit costs, 132.86 M€ and 450 € yr⁻¹, respectively). When we compared the simulated NAE from the OMES (NAEo) and guidelines (NAEg) approaches by varying the RR, the ratio NAEo/NAEg was always equal to 1.5.

The unit cost, which is another parameter that is used to define the threshold for the absolute benefit in the population, has a sigmoidal relationship with NAE, under conditions of a fixed budget and RR. The NAE is inversely proportional to the unit cost, with a saturation effect. We observed an initial plateau for the NAE for low unit cost and decrease in NAE as the unit cost increased. Figure 4 shows the relationship between NAE and unit cost with an RR of 0.8 and a budget of 132.86 M€. The analysis of the
relationship between NAE and unit cost also showed that increasing the RR shifted both the log and lag phases of the sigmoidal curve downwards (figure 5).

4. Discussion

Economic evaluation (cost-effectiveness studies) is central to healthcare decision-making as it helps determine whether, and by how much, medical treatments are ‘worth’ spending money on. Effectiveness research plays an increasingly important role in reimbursement decisions for therapeutic interventions. Its main purpose is to establish a link between an amount of public spending and the consequences expressed as a healthcare outcome or a direct effect. The benefits for the patients are expressed in terms of NAE or life-years gained or healthy life-years gained. This benefit is measured against how much money is needed to obtain it. Although widely used, the approach is of little help to identify the individual patients who will benefit most from the treatment, as it does not account for the patients’ characteristics or the inter-individual variability.

The threshold in the OMES approach is determined using the estimation of the consequences of the therapeutic effect in terms of efficacy on the whole population. Using this paradigm for the impact on public health, patient management

Table 5. Results from the comparison of both approaches with fixed cost.

<table>
<thead>
<tr>
<th></th>
<th>annual cost (M€)</th>
<th>no. patients</th>
<th>NAE (95% CI)</th>
<th>cost/event avoided (€)</th>
</tr>
</thead>
<tbody>
<tr>
<td>'average' statin</td>
<td>CPG</td>
<td>122.54</td>
<td>295 269</td>
<td>291.88 (290.69, 293.08)</td>
</tr>
<tr>
<td></td>
<td>OMES</td>
<td></td>
<td></td>
<td>443.48 (442.26, 444.71)</td>
</tr>
</tbody>
</table>

Table 6. Results from the comparison of both approaches with fixed NAE.

<table>
<thead>
<tr>
<th></th>
<th>NAE</th>
<th>no. patients</th>
<th>annual cost (M€) (95% CI)</th>
<th>cost/event avoided (€)</th>
</tr>
</thead>
<tbody>
<tr>
<td>'average' statin</td>
<td>CPG</td>
<td>292</td>
<td>295 269</td>
<td>122.5384 (122.1802, 122.9204)</td>
</tr>
<tr>
<td></td>
<td>OMES</td>
<td></td>
<td>145 862</td>
<td>60.52831 (60.24976, 60.80786)</td>
</tr>
</tbody>
</table>

Figure 3. Effect of increasing RR and unit cost on the number of avoided events (NAE) with a fixed budget of 132.86 M€.

Figure 4. The relationship between number of avoided events (NAE) and unit cost with a fixed RR of 0.8 and a fixed budget of 132.86 M€.

Figure 5. The impact of increasing RR on the relationship between number of avoided events (NAE) and unit cost with a fixed budget of 132.86 M€. (Online version in colour.)
characteristics are taken into consideration (effect model), as well as the economic constraints, here represented by treatment cost and annual reimbursement. Furthermore, the uncertainty of the data used is also accounted for. The critical advantage of this approach is its unbiased and measurable nature. Thus, this modelling approach enables other constraints to be readily included, as needed.

In this analysis, we have considered only the medical treatment and have not included hygiene–dietetic advice, which would have brought up the problem of follow-up, assessment of the real effect of this advice and of adherence. The OMES method theoretically can take into consideration these aspects if evidence on their impact is available. We based our analysis on the hypothesis that the treatment effect was constant over time, adherence was 100% and that there were no treatment side effects that would have led to treatment withdrawal. The short treatment time used helped to minimize the impact of these hypotheses. In particular, the assumption of 100% adherence avoided the bias of a possible interaction between the cardiovascular risk and adherence, although this risk does not have the same distribution in the populations targeted by the two approaches.

We can justify the selection of all-cause mortality as the efficacy outcome for interventions aimed at preventing cardiovascular diseases because of the advantages this outcome has over others. Reduction of mortality is a priority for individual medical decisions and for public health decisions. It is also an integrative outcome combining the expected beneficial effects, i.e. a reduction of cardiovascular morbidity and mortality for statins, and the possible serious harmful effects. The diagnosis of death is unbiased, unlike outcomes involving morbidity or specific causes of death; the definitions in the cardiovascular area vary over time and validation processes in clinical trials are not standardized or unbiased. Data on mortality are often collected in clinical trials, even those with biological primary outcomes, whereas the other, more specific outcomes are recorded in about 50% of the trials, at best. Hence the efficacy data used in our comparison, i.e. estimation of RR and its 95% CI, are robust. On the other hand, this choice involved extrapolating from the cardiovascular risk estimated using the SCORE equation. The validity of the simulation results requires that the non-cardiovascular mortality is independent from the cardiovascular mortality. This seems to be an acceptable hypothesis, even if we know that some cardiovascular risk factors, for example smoking, are also risk factors for other diseases such as cancer. Hence the choice of outcome should not have had a particular influence on the results of the comparison, because even if the extrapolation is erroneous, the error will be the same for the two methods.

The hypothesis that the statin effect model is linear is based on the results from the meta-analysis we used [17]. The fitting of a straight line to the results of clinical trials comparing a statin with placebo or no treatment was robust, i.e. did not vary when the trials used varied. In addition, the confidence interval for the intercept of the lines with the y-axis included zero, supporting the hypothesis of a multiplicative model. Equation (2.6) is, therefore, valid, in the light of available data. The shape of this effect model suggests that the variance of the AB is equal to the variance obtained by multiplying the two random variables (\(AB = Re \times (1 - RR)\)), which makes the mathematical estimation of the variance difficult. Some authors have developed mathematical methods to estimate this variance [30–33], but the use of these formulae is not simple. The approximation methods that use simulation, i.e. Monte Carlo simulation, also enable this type of variance to be estimated with the advantage of not being based on parametric hypotheses about the distributions of the parameters to be predicted, and therefore can be used in situations where these distributions are unknown. Although the choice of using an ‘average’ statin, defined by the average RR calculated in the meta-analysis and an ‘average’ treatment cost did not introduce bias into either one of the comparisons, the results in terms of NAE or cost for any given NAE cannot be extrapolated to a specific statin.

The French CPGs from AFFSAPS [19] for the management of dyslipidemia consider two variables that were not available in our RVP: microalbuminuria and family history of cardiovascular disease. The calculation algorithm used for translating the guidelines, therefore, could not include these two variables. This has probably resulted in an underestimation of the mean risk in the guideline target population compared with the real risk. However, this did not introduce any bias in the comparisons as the estimation of the AB in the target populations was derived from the same risk equation and the same variables.

OMES could be used at two different levels as a clinical decision support tool. In our research presented here we have illustrated its use at the physician–patient level but it would be possible to use this tool at a higher level to make decisions, for example, what to include in a formulary, how to use a fixed budget to maximize the NAEs for given cost or what should be reimbursed using absolute benefit thresholds. At the physician–patient level, it would be possible to predict adverse events with a treatment, using a similar approach. Although in this paper we have explored this approach in France, using French data, it would be possible to use this approach elsewhere. An essential requirement is the virtual population, which can be created using census data which are available in many countries and other large databases such as those in the large healthcare management organization in the USA or by merging information from smaller, less extensive databases. Cost data can be integrated into the model, so that local prices can be used in the model. It would be possible for pharmacy benefit managers to set up using parameters from their managed care organization. These different settings could be explored in future research projects to validate the generalizability and adaptability of the OMES tool. The next step before clinical use is to implement a randomized clinical trial to assess the benefits of OMES over guidelines, in a real-life setting; this will enable barriers and facilitators to be identified for both the patient and the physician.

5. Conclusion

Previously, in a theoretical approach we were able to demonstrate that the OMES was better than the CPG approach. Here we have reported the results from a practical application of the two approaches in the same population which demonstrate that the OMES approach is at least as good as, and is often superior to, the CPGs approach in terms of impact on public health, i.e. the NAE over a given time. This superiority can be explained by the different methods used to develop these approaches. In any decision algorithm the threshold value is essential; in the OMES approach this threshold has
a clear meaning through the method used to define. When the same constraints are used, the threshold value obtained is the same, and therefore it is important to funnel efforts into deciding the constraints to be used. This process can and should be consensual, but it can also be evidence-based. The OMES approach is therefore an interesting, practical alternative to CPGs. It provides a means of overcoming the inadequacies of guideline-based approaches because the treatment decision takes into consideration the impact on public health calculated using results from clinical trials, the individual expected benefit and societal constraints such as healthcare costs.

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Appendix A
The virtual population was composed of ‘individuals’ generated using simulation (in silico). Each individual was represented by a set of variables that correspond to the characteristics of a real population, based on their statistical distribution. The information can be obtained from one or more databases. This population can represent one or more groups of individuals, living in a given region or country, studied at a single time point or followed over a given period, healthy or with a given disease, being treated or not, with or without medical history, etc. The population was considered as a representative virtual population as it was based on real data. The structure of our virtual population, i.e. the number of individuals by age and sex, was selected to be representative of the French population aged between 35 and 64 years old. The information was obtained from the website of the National Institute for Statistics and Economic Studies (in French: Institut National de la Statistique et des Etudes Economiques—INSEE) [34]. INSEE collects, produces, analyses and disseminates economic and population information. The choice of the variables in the virtual population is usually guided by the specific objectives and analyses to be performed. In our case, to explore the risk of cardiovascular events in the French population, we used a risk prediction equation recommended in 2004 and SCORE [15,35]. Thus we had to include, at least, the variables in the risk prediction equation. The next step is to identify sources of data, a step that is very important to guarantee the representativity of the virtual population. For our project we used French data from a WHO study which was the most representative source of the cardiovascular risk in the French population [36]. The data were supplied as summary data (mean, standard deviation, quartiles) for each variable for each 10-year age group (from 35 to 64 years) and by gender. It was important to know the co-distribution to take into account the inter-dependency of the variables (risk factors) for correlated variables with a normal distribution or that had been normalized. For these variables, there was a multivariate normal distribution, characterized by a vector of the means and a matrix of the variances and co-variances. Variables with no known correlation, e.g. smoking, were modelled using a binomial distribution, where the probability that an individual in a given age and gender group was a smoker was represented by the percentage of smokers in the same age and gender group in the original population. For variables for which information was not available in the database, it is possible to infer the missing information from other variables using validated prediction algorithms, for example, a logistic regression model that was developed and validated for the French population. It is also possible to transform a continuous variable to a binary variable, for example, by using a clinical threshold. The final step after the generation of the virtual population is the validation step, in which the representativity and coherence of the population are verified.

Appendix B
Cardiovascular risk factors to be considered in the selection of the target value of LDL-c as a therapeutic objective.

(1) Risk factors
Age:
— men aged 50 years or above;
— women aged 60 years or above.

Family history of early coronary disease:
— myocardial infarction or sudden death of father or other first degree male relative before the age of 55;
— myocardial infarction or sudden death of mother or other first degree female relative before the age of 65.

Current smoker or stopped in the last 3 years.

Current high blood pressure, treated or not.

Type-2 diabetes, treated or not (refer to specific guideline).

HDL-c < 0.40 g l\(^{-1}\) (1 mmol l\(^{-1}\)) irrespective of gender.

(2) Protective factor
HDL-c > 0.60 g l\(^{-1}\) (1.5 mmol l\(^{-1}\)): subtract 1 from the risk factor score.

Appendix C
The three categories of high cardiovascular risk patients for whom LDL-c should be less than 1 g l\(^{-1}\).

(1) Patients with history of:
— established coronary disease (stable and unstable angina, revascularization, myocardial infarction, documented silent myocardial infarction),
— established vascular diseases (ischaemic stroke, stage II or higher peripheral arterial diseases).

(2) Patients with type-2 diabetes, without history of vascular disease but with a high cardiovascular risk, defined as
— renal impairment (proteinuria more than 300 mg 24 h\(^{-1}\) or creatinine clearance less than 60 ml min\(^{-1}\), estimated using the Cockcroft–Gault equation: creatinine clearance = (140 – Age(years)) × Weight(kg) ÷ K in ml min\(^{-1}\) per 1.73 m\(^2\), creatininaemia in μmol l\(^{-1}\), K = 1.23 for men and 1.04 for women),
— or at least two of the following risk factors (defined in appendix B): age, family history of early coronary diseases, current smoker or stopped with last 3 years, treated or untreated permanent blood (refer to specific guidelines), HDL-c < 0.40 g l\(^{-1}\) (1.0 mmol l\(^{-1}\)) irrespective of gender, microalbuminuria (more than 30 mg 24 h\(^{-1}\)).

(3) Patients with more than 20% risk of having a coronary event within 10 years (risk calculated using a risk equation).
References


