Pilot study to validate a computer-based clinical decision support system for dyslipidemia treatment (HTE-DLP)

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1 The members of the Valida Group are listed in the Appendix section.

Atherosclerotic cardiovascular disease (CVD) is the leading cause of death and hospitalization in Spain [1]. There is strong evidence that reducing cholesterol can prevent CVD [2]. The results of the DARIOS-study show that in Spain less than 3% of high cardiovascular risk patients meet recommended lipid targets according to European Society of Atherosclerosis criteria [3]. The Reality Group showed that in Spain only 12.9% of patients attained the LDL-C goal on their initial lipid-lowering drugs and an additional 13.4% achieved the goal after a change of treatment [4]. There is a need for the design of initial strategies to meet goals in cholesterol reduction [5].

Computerized Decision Support Systems (CDSS) have been introduced into medical practice and may help physicians tailor recommendations for chronic disease management, while also obtaining savings in healthcare costs [6]. Electronic prescription of lipid-lowering medications increases the probability of achieving LDL-C goals [7,8]. On the other hand, a recent meta-analysis concluded that only around 60% of new technological processes succeed in improving clinical practice [9].

The aim of this pilot study was to validate the efficacy, safety, cost-effectiveness and feasibility of a CDSS for dyslipidemia...

1. Methods

This was a cluster-randomized trial comparing standard prescriptions with HTE-DLP assistance, conducted by 10 expert physicians (7 specialists and 3 general practitioners) in cardiovascular risk management from 5 different hospitals and primary care centers in Catalonia (Spain). Each physician was asked to recruit 10 patients. The study protocol was approved by local ethics committees. We enrolled consecutive eligible patients aged ≥18 years old with LDL-cholesterol (LDL-C) >100 mg/dl and attending participating centers from January to March 2010 and at least one of the following conditions: a) established cardiovascular disease b) 10-year risk of developing cardiovascular disease according to the Score low risk ≥5% or c) diabetes with other risk factors or target organ damage. The exclusion criteria were: a) Charlson Index ≥3 b) patient life expectancy <1 year b) Triglyceride level >400 mg/dl. Patients gave written informed consent. Included patients were randomly distributed into the intervention or control group by a computer program. HTE-DLP was blocked automatically if a patient was assigned to the control group. Primary end-points were: patients at LDL-C goal <70 mg/dl. Secondary end-points were: pharmacological side effects, cost for each mg/dl of LDL-C decreased and user satisfaction. The primary outcome was based on first LDL-C measurement at 12 weeks of follow-up. LDL-C was measured by enzymatic colorimetric method and participating laboratories used standardized calibration methods. High potency statin treatment was defined as at least 10 mg rosuvastatin, at least 20 mg atorvastatin and at least 40 mg simvastatin; all other statin treatments were defined as having low potency. Simvastatin 80 and rosuvastatin 40 were excluded because they are not available in Spain. Physicians were consulted regarding their degree of acceptance of the HTE-DLP’s first recommendation and its ease-of-use.

1.1. The CDSS system

HTE-DLP was written in Java using Open Source tools (OpenJDK, Netbeans, iText, POI). At this prototype stage it runs as a standalone desktop application. HTE-DLP performs a sequence of clinical decisions including all statins, ezetimibe and niacin/laropiprant and creates specific recommendations for each patient using efficiency, safety and cost criteria. It is based on European Guidelines for the Management of Dyslipidemia. Firstly, HTE-DLP applies selection criteria to discard statins which are contraindicated if renal or liver dysfunction or severe drug interactions exist. Secondly, treatments are selected with the necessary power to reduce LDL-C. LDL-C/HDL-C is a secondary target applicable only when user-specified. Following this, HTE-DLP applies order criteria to compare all treatment options in pairs. Drug interactions and market prices are parameterized, prioritizing first safer lipid-lowering therapy and then cheaper products. When HTE-DLP detects a difference, the comparison process ends and the program orders all selected treatments from best to worst. All of these processes are done with a single click on-screen. The system also provides a questionnaire on patients’ adherence to Mediterranean Diet. HTE-DLP allows on-line updating. http://www.udgmedicina.cat/web/pagina/66/sistema-de-apoyo-a-la-toma-de-decisiones-hte-dislipemia

1.2. Statistical analysis

Data were analyzed using SPSS 14.0. Descriptive statistics were used for comparison of the groups. Inter-group differences for continuous variables were evaluated using the t-test and Mann–Whitney test. A univariate analysis with categorical variables was performed using the chi-square test and Fisher’s exact test. All statistical tests were two-sided and a value of <0.05 was considered significant. The study was designed to have 95% power to detect at least a 40% difference between the intervention and the control group.

2. Results

The first 77 consecutive patients (43 and 34 with very high and high CVD risk, respectively) were recruited for the analysis. The average number of patients enrolled by each researcher was 8. Baseline characteristics of patients showed no differences between groups except a significantly higher proportion of diabetic patients in the intervention group (Table 1a). Primary study outcomes of intervention are shown in Table 1b. Patients in the intervention group achieved a significantly better lipid profile and a higher proportion of patients at LDL goal (Fig. 1). “High potency statins” and combined therapy (statin + ezetimibe or niacin/laropiprant) were used more frequently in the intervention group than the control group (74.6% vs 25.4% = 0.001 and 32.4% vs 23% = 0.01, respectively). In the control group, the LDL-C score was decreased more among specialists than general practitioners (38.11 mg/dl vs 18.66 mg/dl/p = 0.03). Seven adverse effects were documented in the intervention group and two in the control group (Table 1b). Inadequate prescription was recorded in two intervention group patients with severe adverse effects: one patient received atorvastatin 80 and nicotinic acid simultaneously and not gradually as suggested by HTE-DLP; in the other patient, who suffered from severe heart failure, the physician didn’t stop treatment with statins. The cost of reducing 1 mg/dl of LDL-C was less in the intervention group than in control group (0.89 EUR/day vs 1.10 EUR/day). 86.1% of first treatments offered by HTE-DLP were generic drugs. Physicians expressed good agreement with the 1st HTE-DLP recommendation in 86.1% of cases and use was described as comfortable in 85% of cases.

3. Discussion

Our study demonstrates that in the “real-clinic-world” expert physicians in the cardiovascular field can improve cholesterol management by using a specific CDSS.

<table>
<thead>
<tr>
<th>Table 1a</th>
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<tr>
<td>Baseline characteristics of patients and primary study outcomes post-12 weeks intervention period.</td>
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<tr>
<td></td>
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<tr>
<td>Gender women (%)</td>
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<tr>
<td>Mean (range) age, years (SD)</td>
</tr>
<tr>
<td>Dyslipidemia (%)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
</tr>
<tr>
<td>Smoking (%)</td>
</tr>
<tr>
<td>Diabetes (%)</td>
</tr>
<tr>
<td>History of cardiovascular events (%)</td>
</tr>
<tr>
<td>Any lipid-lowering medication (%)</td>
</tr>
<tr>
<td>Mean total cholesterol (mg/dl)</td>
</tr>
<tr>
<td>Mean LDL cholesterol (mg/dl)</td>
</tr>
<tr>
<td>Mean HDL cholesterol (mg/dl)</td>
</tr>
<tr>
<td>Mean Non-HDL cholesterol (mg/dl)</td>
</tr>
<tr>
<td>Mean triglycerides (mg/dl)</td>
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<tr>
<td>Renal function (GFR) ml/min/1.73 m²</td>
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</tbody>
</table>

Data are n, means (±SD), range, or proportions as indicated. p-value <0.05 is considered statistically significant. (NS) GFR: glomerular, filtrate rate; AST aspartate aminotransferase.

Cardiovascular events include coronary artery disease, stroke or transient ischemic attack, Abdominal aortic aneurysm or peripheral vascular disease.
The results indicate a significant improvement in the initial planning of lipid-lowering therapy, with a high therapeutic success rate. The number of patients with LDL-C <70 mg/dl was 4.4-fold greater in the HTE-DLP group than in the control groups only 12 weeks after starting lipid-lowering therapy. These results may be even better in unselected general practitioners, with a theoretical 5.8-fold lower rate of patients at LDL-C goals [4]. It is possible that the alert version [12] and web-oriented-design [6] with automatic data collection from HTE-DLP electronic records and databases could improve recruitment and results. Four previous trials focusing primarily on dyslipidemia have evaluated CDSS, though none in European populations [13–16]. Only one showed reduced blood lipids levels, with a modest effect at 6 months of follow-up and a very low rate of drug-up titration [15]. Katz P et al. found that using a 26-week algorithm-based treatment strategy at 12 weeks of follow up, 36.6% of patients with high CVD risk reported an LDL-C<77 mg/dl [17], less than with the HTE-DLP.

We observed an increased occurrence of side effects in the intervention group. This could be due to more frequent use of high potency statins [18] or niacin/laropiprant plus statin in the intervention group [19]. We consider it necessary to improve warning systems. Further studies are needed with larger numbers of participants and long-term follow-up to determine clinical safety.

Our study shows that using the HTE-DLP can represent a cost-effective intervention. Previously, one study showed that patients receiving an e-prescription of lipid-lowering drugs were more likely to achieve the LDL goal with lower medication costs [20]. Gilutz H. et al. showed that using a CDSS to treat dyslipidemia in secondary prevention reduced the number of cardiovascular readmissions in a relatively short time [15]. Considering that a reduction of 39 mg/dl of LDL-C implies a 21% coronary event reduction [2], widespread use of the HTE-DLP would theoretically reduce coronary events by 16% and the coronary revascularization rate by 19% in our area.

User satisfaction plays a significant role in the success of implementing a CDSS within an organization [21]. Ease-of-use of CDSS for dyslipidemia treatment has not been previously assessed [13–16]. In our study, physicians’ overall level of satisfaction and agreement with the HTE-DLP recommendations were high.

The study has several limitations. Firstly, the limited number of patients at an initial intervention phase and a very short follow-up period. Also, the physicians in this study were trained in hypothesis testing. Despite this, we observed better prescription using the HTE-DLP. Another limitation of this study is that treatment adherence and patient opinion were not measured. In the future, it is very important to involve scientific associations in the development of relevant, useful and safe CDSS [6].

In conclusion, in clinical practice it is possible to improve the management of dyslipidemia in high-risk patients using a specific CDSS.

### Competing interests

The present project is a follow-up to the Observatory of Innovation Experiences in ICTs and Health in Catalonia (Fundació TicSalut, Health Department, Government of Catalonia). This work was presented at the 2011–2015 Health Plan of Catalonia Meeting. (http://www.ticsalut.cat/observatori/innova-tic-salut/79/hte-dislipemia)

The company Merck Sharp & Dohme (MSD) has contributed to centralized data collection. The sponsor played no role in CDSS design, study design, development of the paper or decision to publish.

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### Appendix

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