Electronic health records to facilitate continuous detection of familial hypercholesterolemia

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ABSTRACT

Background and aims: Familial hypercholesterolaemia (FH) is an inherited disorder associated with increased risk of coronary heart disease as a result of high LDL-cholesterol (LDL-C). The clinical diagnosis can be made with the Dutch Lipid Clinic Network criteria (DLCN criteria). FH is an underdiagnosed disorder, possibly due to false negative LDL-C interpretation during lipid lowering therapy (LLT). We hypothesized that automated health record-based integration of data can provide a signal to facilitate identification of FH patients.

Methods: We included patients with LDL-C ≥6.5 mmol/l after correction for LLT in all patients testing LDL-C in Northwest Clinics, The Netherlands. Patients previously diagnosed with FH were excluded. The primary endpoint was the additional number of patients with DLCN criteria ≥6 points after correction for LLT. Secondary endpoints were the additional number of patients with DLCN criteria ≥6 points after also adding data on patient- and family history, and LDL-C before and after correction for LLT. Analysis was performed in a daily automated routine (HiX ChipSoft).

Results: In a total of 41,937 individual LDL-C measurements during 26 weeks, we found 351 patients with LDL-C ≥6.5 mmol/l after automated correction for LLT. FH had previously been diagnosed in 42 patients. In the remaining 309 patients (58.3% female; age: 66 ± 11 yrs (mean ± SD); 85.8% on LLT), the number of patients with DLCN criteria ≥6 points increased from 9 to 95 after correction for LLT, and to 127 after also adding patient and family history. The mean LDL-C before and after correction for LLT was 4.69 ± 1.42 mmol/l and 8.16 ± 1.68 mmol/l, respectively (mean ± SD; p < 0.001).

Conclusions: We conclude that automated medical record-based integration of LDL-C, LLT and patient- and family history can provide a crucial signal to facilitate identification of FH. Whether this signal results in subsequent genetic identification of FH patients and their relatives requires further study.

1. Introduction

Familial hypercholesterolemia (FH) is an autosomal dominant inherited disorder caused by alterations in the low-density lipoprotein cholesterol (LDL-C) receptor clearance pathway, resulting in high plasma levels of LDL-C starting from birth onwards. The prolonged exposure to elevated LDL-C for many years leads to early and accelerated atherogenesis as attested by a more than 10-fold increased risk of coronary heart disease (CHD) [1,2]. The prevalence of heterozygous FH, previously thought to be 1 in 500 [2], has now been estimated at 1 : 250 subjects worldwide [3,4]. When detected and treated early in life, the risk of premature CHD can be virtually abolished [5]. Unfortunately, the majority of patients with FH remain undetected. Whereas in the Netherlands detection rates may approach 71% of cases, detection rates below 5% hallmark the majority of countries worldwide [1].

Among the available diagnostic frameworks such as the Simon Broome criteria [6], Make Early Diagnosis to Prevent Early Deaths (MEDPED) [7], NICE and the Familial Hypercholesterolaemia Case
Ascertainment Tool (FAMCAT) [8], the Dutch Lipid Clinical Network (DLCN) criteria [9] is a widely used algorithm because of its validation with genetic testing for FH with a sensitivity of 67% for ‘definite’ (>8 points) or ‘probable’ (6–8 points) FH [10]. A score ≥6 points in the DLCN criteria indicates the need for genetic testing. Currently, the DLCN criteria are recommended by the European Atherosclerosis Society Guidelines 2019 [9].

In an outpatient setting, failure to recognize FH is often due to the ongoing use of lipid lowering therapy (LLT), which leads to misclassification due to reduced LDL-C levels [11]. In fact, this may well be one of the major reasons that previous efforts to improve FH-detection using electronic screening algorithms in electronic health records (EHR) have only provided modest results [8,12–15]. Since LDL-C is one of the strongest discriminatory factors in the clinical diagnosis of FH using the DLCN criteria, it is essential to use untreated LDL-C values in patients already using LLT [16]. To date, exact calculation of untreated LDL-C levels is however not routinely performed [12,13,15].

In the present study we investigated whether an automated EHR-based algorithm, including correction of LDL-C for specific type and dose of LLT, can facilitate the detection of the FH phenotype in a single teaching hospital in the Netherlands.

2. Patients and methods

2.1. Study design and population

We conducted a prospective cohort study. All patients were evaluated in whom an LDL-C result was assessed between April 15th and October 15th, 2019 in the Northwest Clinics Laboratory. This laboratory serves an area with approximately 465,000 residents. LDL-C measurements were requested by general practitioners or hospital physicians. Individual patients were evaluated at first measurement only when a second LDL-C result was obtained between April 15th and October 15th, 2019.

2.2. Data collection

HiX is an electronic health record (EHR) developed by ChipSoft, Amsterdam, the Netherlands, used by Northwest Clinics in the Netherlands since 2018. HiX is classified as a medical device, class IIb, certified for ISO 13485:2016 and complies with the European Medical Device Directive 93/42/EEC MDD. HiX EHR contains data of patients from Northwest Clinics and of 465,000 people residing in the Northwest Clinics and Northwest Clinics Laboratory adherence, most of whom are cared for by general practitioners in the area. The EHR combines registration of name, address, residence, date of birth, medical history (preferably encoded since 2018), encoded current and previous medication, clinical notes, several numerical measurements of blood pressure, weight etc., a full array of automatically downloaded laboratory, radiology, pathology and microbiology data, financial and logistic administration, and more.

In the EHR, an algorithm was constructed in the clinical decision rule module, which continuously evaluated LDL-C results of the previous day. LDL-C without LLT was calculated using correction factors based on 71 original papers [16]. The measured LDL-C was automatically multiplied by the applicable correction factor (for instance 20 mg rosvastatin requires LDL-C correction by factor 2.1; 80 mg atorvastatin plus ezetimibe 10 mg requires LDL-C correction by factor 2.5). In order not to correct for LLT with only very recent patient exposure, medication had to be registered as active in the EHR for at least 3 weeks. When LDL-C was higher than or equal to the prespecified cut-off value (6.5 mmol/l), patients were included. Patients under 18 years of age were excluded [17]. Patients previously diagnosed with FH or other previously diagnosed inherited lipid disorders were also excluded. A cut-off of 6.5 mmol/l was selected, corresponding to a minimal DLCN criterion score of 5 points. For the purpose of the current study, individual records of patients were checked manually to verify the algorithm and to collect other DLCN criteria if documented. Only sufficiently specific DLCN-related information about family members was taken into account, i.e. specific details of FH-related physical examination and family LDL-C levels and the specific age at which premature coronary heart disease had occurred in family members. For the patients included in the study, the DLCN criteria score was calculated before correction for LLT, after correction for LLT and also after adding data on family history, clinical history and physical examination. The primary endpoint of the study was the additional number of patients with DLCN criteria ≥6 points after also adding data on patient- and family history and LDL-C before and after correction for LLT (mmol/l).

2.3. Ethics

This project was approved by the institutional review board. There was no need for informed consent as only de-identified laboratory results and documented data were analysed. The data were de-identified in such a way that patients could be re-identified if this was necessary for clinically required follow-up. In these cases, the treating physician was informed, providing information on the possibility to perform genetic testing in consultation with the patient.

2.4. Statistics

Statistical analysis was carried out by using SPSS statistics version 25. Normally distributed variables were described as means with standard deviations (SD). Non-normally distributed variables were described as medians with interquartile range (IQR). Normality was assessed using the Kolmogorov–Smirnoff test and Shapiro Wilk test and using QQ plots. For the comparison between continuous variables with normal distribution, the paired sample T-test was used and the Wilcoxon signed-rank test was used for non-normally distributed variables.

3. Results

41,937 LDL-C measurements were collected in 41,937 individual patients from April 15th until October 15th, 2019. The automated algorithm extracted 357 patients with an LDL-C ≥6.5 mmol/l after correction for LLT. In these 357 patients, FH had already been diagnosed in 42 patients who were excluded from further analysis. In 6 patients, the LLT-correction factor was used incorrectly, since medication was temporarily on hold in the EHR. These patients were also excluded (Fig. 1). In the remaining 309 patients (0.74% of 41,937 LDL-C measurements or 1 : 136 patients) the mean age was 66 ± 11 yrs (mean ± SD), 58.3% were female, 85.8% used LLT, of which 84.8% statins (Table 1). In 54 patients, LDL-C was ≥6.5 mmol/l before correction for LLT. Of these 54 patients, 44 did not use LLT. In 2 of the 309 included patients, a combination of LLT was used that did not have a correction factor in the current literature (rosvastatin 2.5 mg and the combination of rosvastatin 5 mg and ezetimibe 10 mg). In those two patients, the correction factor closest to the dosage or combination of LLT was selected. The automated algorithm would extract 2760 patients out of 41,937 LDL-C measurements when applying a cut-off value of LDL-C ≥5 mmol/l after correction for LLT.

3.1. DLCN criteria outcome

We calculated DLCN criteria scores for all patients included with an LDL-C ≥6.5 mmol/l after correction for LLT. Prior to correction for LLT (mandatory when calculating DLCN criteria score), 80 patients would erroneously have been classified as ‘possible FH’ (DLCN criteria 3–5 points), 9 patients as ‘probable FH’ (DLCN criteria 6–8 points) and 0 patients as ‘definite FH’ (DLCN criteria ≥8 points). After appropriate
correction for LLT, 214 patients were classified as ‘possible FH’ (DLCN criteria 3–5 points), 95 as ‘probable FH’ (DLCN criteria 6–8 points) and 0 as ‘definite FH’ (DLCN criteria ≥ 8 points). Thus, the mandatory correction for LLT increased the number of patients with a DLCN criteria ≥ 6 points by 86 patients. In 59 of 309 included patients, the addition of patient- and family history resulted in an increase of DLCN-score. Four patients had both DLCN-relevant family history and clinical history. When adding available patient- and family history to correction for LLT, the number of patients with ‘probable’ or ‘definite’ FH (DLCN criteria ≥ 6 points) increased from 95 to 127 (Table 2).

### 4. Discussion

This study demonstrates the potential strength and robustness of a continuous automated screening algorithm alerting for likelihood of the clinical diagnosis of FH. In particular, the automated correction for LLT increased the signal for the phenotypic diagnosis of FH after measuring LDL-C in large numbers of patients.

The clinical diagnosis of FH is most often made by applying an algorithm of clinical criteria of which the Dutch Lipid Clinic Network criteria are used frequently. Other algorithms are the Simon Broome criteria, Make Early Diagnosis to Prevent Early Deaths (MEDPED) and NICE criteria, and the recently developed Familial Hypercholesterolaemia Case Ascertainment Tool (FAMCAT) [8]. FAMCAT was validated for use in primary care, specifically, and showed better discrimination when compared to the other algorithms for the diagnosis of FH. However, the DLCN criteria algorithm was validated in concordance with genetic testing, with a sensitivity of 67% for “definite” or “probable” FH (≥ 6 points) and is recommended by the European Atherosclerosis Society Guidelines 2019, and was therefore used in the current study [10]. If FAMCAT turned out to correlate better with genetic testing than the DLCN criteria algorithm, adjustment to these criteria for the phenotypic diagnosis of FH would likely increase the signal for the diagnosis of FH even further. Whether machine learning will ultimately find its way in screening for FH, independent of LDL-C values, is unknown, and further studies are needed to show general applicability [19].

This is not the first study to analyse an EHR-based algorithm to facilitate detection of FH [8,13,15,19]. Previous studies also screened large numbers of patients and assisted in the identification of new index cases of FH. However, previous studies were often unable to correct for specific type and dose of LLT. Moreover, previous studies were retrospective cohort studies. We prospectively studied the application of an

#### Table 1

Characteristics of patients with LDL-C ≥ 6.5 mmol/l after correction for lipid lowering therapy (LLT).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n = 309</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD)</td>
<td>66 ± 11 yrs.</td>
</tr>
<tr>
<td>Women (% (n))</td>
<td>58.3 (180)</td>
</tr>
<tr>
<td>Median [IQR] DLCN criteria points before correction for LLT (mmol/l)</td>
<td>1.0 [0–3]</td>
</tr>
<tr>
<td>Median [IQR] DLCN criteria points after correction for LLT (mmol/l)</td>
<td>5.0 [5–8]</td>
</tr>
<tr>
<td>Use of LLT (%) (n)</td>
<td>85.8 (265)</td>
</tr>
<tr>
<td>Statin use (%) (n)</td>
<td>84.8 (262)</td>
</tr>
<tr>
<td>High intensity statin (%) (n)</td>
<td>52.4 (162)</td>
</tr>
<tr>
<td>Moderate intensity statin (%) (n)</td>
<td>32.0 (99)</td>
</tr>
<tr>
<td>Low intensity statin (%) (n)</td>
<td>0.30 (1)</td>
</tr>
<tr>
<td>Ezetimibe alone (%) (n)</td>
<td>0.97 (3)</td>
</tr>
<tr>
<td>Ezetimibe in combination with (n)</td>
<td>4.20 (13)</td>
</tr>
<tr>
<td>Ezetimibe use (%) (n)</td>
<td>5.18 (16)</td>
</tr>
<tr>
<td>First degree relative with known premature coronary artery disease (%) (n)</td>
<td>5.20 (16)</td>
</tr>
<tr>
<td>First degree relative with known LDL-C above the 95th percentile (%) (n)</td>
<td>0.30 (1)</td>
</tr>
<tr>
<td>Children &lt; 18 years of age with LDL-C above the 95th percentile (%) (n)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Physical examination (%) (n)</td>
<td>9.70 (30)</td>
</tr>
<tr>
<td>Tendinous xanthomata (%) (n)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Arcus cornealis (%) before the age 45 years (%)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

3.2. LDL-C concentrations

The mean LDL-C before and after correction for LLT was 4.69 ± 1.42 mmol/l and 8.16 ± 1.68 mmol/l, respectively (mean ± SD; p < 0.001; Fig. 2). The mean LDL-C in women was 4.84 ± 1.47 mmol/l before correction and 8.25 ± 1.82 mmol/l after correction for LLT (mean ± SD). The mean LDL-C in men was 4.49 ± 1.33 mmol/l before correction and 8.04 ± 1.48 mmol/l after correction for LLT (mean ± SD). In 255 of the 309 patients included (82.5%), LDL-C was ≥ 6.5 mmol/l before correction for LLT. In the youngest age group (29–50 years), the untreated LDL-C values were significantly higher (p = 0.032) compared to the older age groups (> 50 years) (Table 3). Of all patients included, 52.4% used high intensity statin therapy [18].

**Fig. 1.** Number of patients evaluated (A); number of patients with LDL-C ≥ 6.5 mmol/l after correction for lipid-lowering therapy (B); number of patients after applying exclusion criteria (C).

[*After genetic testing or by a lipid specialist.*]
Table 2
Number of patients per DLCN criteria score.

<table>
<thead>
<tr>
<th>DLCN criteria score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>&gt;8</th>
<th>Median DLCN criteria score [IQR]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncorrected LDL-C</td>
<td>114</td>
<td>106</td>
<td>35</td>
<td>45</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.0 [0.0–3.0]</td>
</tr>
<tr>
<td>LDL-C corrected for LLT</td>
<td>214</td>
<td>95</td>
<td>5.0 [5.0–8.0]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After adding family- and clinical history and physical examination</td>
<td>182</td>
<td>17</td>
<td>13</td>
<td>69</td>
<td>28</td>
<td>5.0 [5.0–8.0]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fig. 2. Number of patients before (blue) and after (red) correction for lipid-lowering therapy according to LDL-C.
X-axis: 4–5 refers to ≥4.00 mmol/l to <5.00 mmol/l; 5–6 refers to ≥5.00 mmol/l to <6.00 mmol/l; etc.

Table 3
LDL-C (mmol/l) for men and women and different age categories, before and after lipid-lowering therapy (LLT).

<table>
<thead>
<tr>
<th>Gender</th>
<th>N</th>
<th>N (%) using LLT</th>
<th>LDL-C (mmol/l), mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>180</td>
<td>148 (82%)</td>
<td>4.84 ± 1.47</td>
</tr>
<tr>
<td>Before correction for LLT</td>
<td></td>
<td></td>
<td>8.25 ± 1.82</td>
</tr>
<tr>
<td>Men</td>
<td>129</td>
<td>114 (88%)</td>
<td>4.49 ± 1.33</td>
</tr>
<tr>
<td>Before correction for LLT</td>
<td></td>
<td></td>
<td>8.04 ± 1.48</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>29–50</td>
<td>25</td>
<td>12 (48%)</td>
<td>6.07 ± 2.54</td>
</tr>
<tr>
<td>Before correction for LLT</td>
<td></td>
<td></td>
<td>7.92 ± 1.58</td>
</tr>
<tr>
<td>51–70</td>
<td>169</td>
<td>147 (87%)</td>
<td>4.69 ± 1.31</td>
</tr>
<tr>
<td>Before correction for LLT</td>
<td></td>
<td></td>
<td>8.19 ± 1.66</td>
</tr>
<tr>
<td>71–90</td>
<td>115</td>
<td>106 (92%)</td>
<td>4.40 ± 1.03</td>
</tr>
<tr>
<td>Before correction for LLT</td>
<td></td>
<td></td>
<td>8.17 ± 1.75</td>
</tr>
</tbody>
</table>

being a strong discriminatory factor in the clinical diagnosis of FH using the DLCN criteria [16], Bell et al. searched for all DLCN-related criteria. They found that clinical history relevant to the DLCN criteria was present in 1.1% of individuals, and that statin therapy was reported in 51.18 out of 84,823 individuals. Where the current algorithm is likely to include more patients based on LLT-corrected LDL-C, the retrospective expert system by Bell et al. is perhaps more likely to include patients on the basis of history relevant to DLCN criteria. Efficacy of different algorithms is difficult to compare since the only relevant endpoint for that would be the number of patients testing positive at genetic confirmation.

There are limitations to the current study. First, we cannot be certain of the completeness of documented clinical history, physical examination and family history. It appears that increasing the use of coded content will reduce this limitation in the future [21]. Second, we were unable to correct for secondary causes of elevated LDL-C. Others found secondary causes for dyslipidemia in 11.7% of patients with an LDL-cholesterol ≥6.5 mmol/l. However, upfront exclusion of patients with secondary dyslipidemia could also exclude FH patients with concomitant secondary causes for dyslipidemia [22]. Furthermore, compliance to LLT is not taken into account in the present analysis. These limitations may have resulted in false positive interpretation and an overestimation of the corrected LDL-C values and the DLCN criteria scores. Lastly, we must acknowledge a limited accuracy of ‘calculation’ of untreated LDL-C levels. Indeed, considerable interindividual variation in LDL-C response to rosuvastatin 20 mg was observed in the JUPITER Trial, even among compliant patients. This may be due to genetic polymorphisms related to pharmacokinetics of statins and the LDL-C receptor clearance pathway [23].

The current study applied a somewhat arbitrary cut-off value for the primary endpoint of LDL-C ≥6.5 mmol/l, primarily because LDL-C ≥6.5 mmol/l results in 5 points in the DLCN criteria algorithm. The chosen cut-off value resulted in inclusion of 309 patients with LDL-C ≥6.5 mmol/l after correction for LLT and a resulting DLCN criteria ≥5 points (0.74%, or one in every 136 patients). By doing so, we also identified 42 patients that had genetically been diagnosed with FH. If we had applied a cut-off value of LDL-C ≥5 mmol/l after correction for LLT, this would have resulted in the inclusion of 2760 patients after correction for LLT, or one in every 15 LDL-C measurements. At this moment, it seems that one in 15 measurements is better in line with the estimated prevalence of FH. Bell et al. also suggested that a serum LDL-C cut-off point ≥6.5 mmol/l provided a result in line with the estimated prevalence of FH [22]. On the other hand, FH can be found in patients with LDL-C ≤6.5 mmol/l [10,24] and regional differences in prevalence have been described, also specifically in the northern part of the Netherlands, where this study was conducted [25]. We must also acknowledge that patients were selected for lipid testing, which may have resulted in an ascertainment bias and an increased likelihood of high LDL-C. Lastly, we emphasize that the number of patients with LDL-C ≥6.5 mmol/l after correction for LLT in the current study does not necessarily relate to the number of patients that will undergo actual genetic testing. This was not investigated in the current study and may be subject to regional differences in the organisation of healthcare and cost. In the Netherlands, genetic testing is generally available, funded by mandatory basic health insurance and performed at the discretion of the treating physician with no specific entry criteria. After identification of an index patient, a cascade testing program is available at similar financial conditions that can be coordinated by a national centre of FH expertise (www.LEEFH.nl) [26].
In conclusion, the current study shows that continuous automated electronic health record-based integration of LDL-C corrected for lipid lowering therapy can provide a signal to facilitate identification of familial hypercholesterolemia. Addition of family history, clinical history and physical examination can increase the signal even further. The tool is currently being installed in HiX ChipSoft electronic health record systems, which covers approximately 40% of hospitals in the Netherlands. Whether this automated algorithm results in subsequent genetic identification of FH in patients and their relatives, and perhaps even in better outcome, requires further study. Interpretative comments in response to the LDL-C-requesting physician specifically suggesting specialist referral have been shown to increase genetic diagnostic yields [27]. With the opportunity to identify large numbers of patients with phenotypic FH that may undergo genetic testing, the sensitivity and cost-effectiveness of different FH screening algorithms should also be investigated in further detail in future research.

CRediT authorship contribution statement

Shari Pepplinkhuizen: Methodology, Formal analysis, Writing - original draft. Shirin Ibrahim: Formal analysis, Writing - original draft. Rutger Vink: Methodology, Formal analysis, Writing - original draft. Bas Groot: Methodology, Formal analysis, Writing - original draft. Erik S.G. Stroes: Formal analysis, Writing - original draft. Willem A. Bax: Methodology, Formal analysis, Writing - original draft. Jan H. Cornel: Methodology, Formal analysis, Writing - original draft.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Rutger Vink and Bas Groot are employed by ChipSoft, The Netherlands, manufacturer of the electronic health record. All other authors have no competing financial interests or personal relationships that could influence the work reported in this paper.

References


87