SCREENING AND IDENTIFICATION
Carbohydrate Deficient Transferrin in a Driver’s License Regranting Program

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Abstract — Aims: Carbohydrate deficient transferrin (CDT) is a common diagnostic marker for detecting chronic alcohol abuse. For over 2.5 years, it has been used in traffic medicine among subjects applying for driver’s license renewal or regranting in Belgium. We report on data collected during the program and provide an estimation of an applicable cut-off point in forensic situations. Using this cut-off, the success of the driver’s license regranting program is evaluated. Methods: CDT was assayed at Ghent University Hospital by capillary zone electrophoresis, measured on the Capillaries 2™ system, in 3977 subjects applying for driver’s license regranting. Determination of a cut-off was done by using Bhattacharya statistics and by adding a measurement uncertainty interval. The outcome of the program was evaluated by monitoring CDT values for 163 subjects during one entire year. Results: In 3977 subjects (3481 males and 496 females), CDT values were significantly higher in men compared with women, but there is no need for a gender-specific cut-off value. Drunk drivers under the age of 30 have significantly lower CDT values than older subjects, and a separate cut-off could be calculated. A general cut-off of 2.3% CDT was calculated for the entire study population. Using this cut-off value for evaluating the outcome of the program for 163 subjects, the percentage offenders at the beginning (29%) decreased to 8% after 1 year. Conclusion: Applying a marker for chronic alcohol abuse such as CDT for driver’s license renewal or regranting is a powerful tool. Analysis of data collected over 2.5 years reveals a favorable outcome of the program and a useful cut-off point could be determined.

INTRODUCTION
Diagnosing chronic alcohol abuse is difficult because a majority of the subjects denies or minimizes alcohol abuse and because diagnostic parameters with both high sensitivity and specificity are lacking. From both a medical and from a social perspective, there is a need for early detection and correct judgment of the severity of alcoholism. Indications in the field of forensic medicine are identification of drunk drivers (Gjerde and Morland, 1987; Iffland and Grassnack, 1995; Bortolotti et al., 2007) and license reapplication (Morgan and Major, 1996). Carbohydrate deficient transferrin (CDT) is regarded as the laboratory parameter with the highest diagnostic efficiency (Delanghe and De Buyzere, 2009). Morgan and Major (1996) investigated and observed the potential impact of CDT values on the decision of license reapplication in ‘high-risk offenders’. Iffland and Grassnack (1995) investigated the significance of CDT values in drivers suspected of having driven drunk.

At least eight countries in Europe use biomarkers routinely as a part of the clinical evaluation of drunk drivers and to assess alcohol abstinence (Delanghe and De Buyzere, 2009). In Switzerland, Italy and Austria, repeat offenders are sent to therapy and biological markers, including CDT, are measured quarterly for an entire year to monitor alcohol abstinence. After 1 year, if treatment was successful and biomarkers were kept in check, the driver’s licence is reinstated.

CDT testing has been introduced in Belgium in 2008 within the framework of driver’s licence reinstatement. Drunk drivers are invited to participate in an alcohol contract program, in which regular blood controls are integrated. The subject is free to decide whether to participate or not. The blood samples are drawn bimonthly during a 1-year period. Among others, CDT is one of the biomarkers that are used to monitor the driver’s adherence to the abstinence program (Delanghe and De Buyzere, 2009). In view of the numerous caveats and especially for forensic applications, a well-balanced interpretation is needed. For these purposes, high performance liquid chromatography (HPLC) or capillary zone electrophoresis (CZE) are to be preferred for CDT analysis as their main advantage is the separation of different CDT isoforms. In problem cases, the use of additional alternative tests (e.g. ethyl glucuronide and fatty acid ethyl esters in hair) can be considered. In the present prospective study, the CDT data from this program are analyzed and the possibilities, limitations, the outcome and pitfalls regarding the use of CDT for evaluating driving ability are discussed.

MATERIALS AND METHODS
Subjects
A total of 8318 CDT analyses were carried out on a population of 3977 subjects: 3481 males (87.5%) and 496 females (12.5%). They were all included in a driver’s license regranting program under the control of the Belgian Institute of Road Safety [Belgisch Instituut voor Verkeersveiligheid (BIVV)-Institut Belge pour la Sécurité Routière (IBSR)]. The data were obtained over a period of 2.5 years (September 2008–March 2011). Not all data were available for every subject, because of teething problems of the project. No data were excluded from the analysis. The study was approved by the Ethics Committee of Ghent University Hospital (EC/008-2012).

Assays
CDT was assayed using CZE (Schellenberg et al., 2007), measured on the Capillaries 2™ system (Sebia, France). In this technique, after on-line iron saturation, samples are submitted to high voltage (8200 V) zone electrophoresis in alkaline buffer (pH 8.8). The transferrin glycoforms are
quantified by their peptide bond absorbance at 200 nm. Pheroğrams were validated using the manufacturer’s software. In case of heterozygous transferrin C-variants (TIC), the % CDT result was corrected for heterezygosity by a factor 2. It is possible to estimate the total amount of disialo-C- and trisialo-C-transferrin, using approximately twice the value of disialo-D- and trisialo-D-transferrin (Wuysts et al., 2001).

### Determination of a cut-off value for %CDT

Determination of a suitable cut-off limit for forensic use was carried out on a major subgroup of 8233 data points in which samples with distorted transferrin pheroğrams were excluded. The upper limit of normal (ULN) was calculated as the 99.9th percentile of the normal or gamma distribution extracted out of the population using Bhattacharya analysis (Bhattacharya, 1967) as modified by Naus et al. (1980). In order to interpret the result with certainty, ISO 15189 requires a method-dependent critical difference to the upper reference limit (Kristiansen, 2003). The ‘Guide to the expression of uncertainty in measurement’ (GUM) provides instructions for constructing uncertainty intervals for a measurement. The variances of the internal quality control (IQC) and the individual CDT values over time [\([u^2_{\text{IQC}}]\) and \([u^2_{\text{intra-individual}}]\)] are propagated and used to calculate a composite uncertainty. The latter is multiplied by a coverage factor \(k\) to obtain the expanded uncertainty (U). A coverage factor of 2 is used in order to define an interval giving a level of confidence greater than 95% (Helander et al., 1998; Kristiansen, 2003; Schellenberg and Wielders, 2010). The variance related to accuracy calculated from external quality control data (EQUALIS) is taken into account as a bias factor \(E\). The cut-off was calculated as follows:

\[
\text{cut-off} = \text{ULN} + E + U \text{ at 95% CI}
\]

### Outcome of the driver’s license regranting program evaluated only on %CDT

In order to evaluate the effectiveness of the driver’s license regranting program, we evaluated the absolute CDT change for a subgroup of 163 subjects (randomly selected from both genders and all age-groups) who participated in a 1 year program. The CDT result at the start of the program was considered as the baseline value. The latter was compared with the mean %CDT value obtained during the first 6 months and the last 6 months for each subject individually.

We also compared the results of the bimonthly measurements of these subjects with their baseline CDT. We considered two baseline situations: CDT >2.3% (positive) and CDT ≤2.3% (negative). According to their outcome, the subjects were divided into different subgroups. When a subject had a CDT >2.3% during the whole program, he was classified as refractory. When the CDT remained ≤2.3%, the driver was considered as an abstainer or moderate alcohol consumer. A subjects’ CDT decreasing from positive at the baseline to a CDT ≤2.3%, was considered as controlled. Inversely, when the CDT increased from negative at the baseline to a CDT >2.3%, this was considered as a relapse (exceeding the cut-off only once during the program, is considered as a relapse).

Additionally, the reference change value (RCV) was calculated based on analytical and biological variation. This value makes it possible to evaluate if a subject’s CDT change is clinically significant, meaning an effective alteration of the drinking behavior.

### Statistics

Non-parametric tests were used because of deviation of normality of all data, even after they were log-transformed. Mann–Whitney U-tests were used to compare median CDT values between different age-groups and between men and women. Differences between CDT values at the start of the program and 6-monthly intervals were evaluated by a Wilcoxon test for paired samples. Results are expressed as median and interquartile range (IQR). Statistical calculations were run using MedCalc® version 11.4.20 (MedCalc Software, Mariakerke, Belgium). Bhattacharya analysis was performed on a Microsoft Excel spreadsheet developed by Naus et al. (1980). Partitioning criteria were adapted from Harris and Boyd (1995) as proposed by the clinical and laboratory standards. This method takes into account the width of the distributions as well as the difference in means. Additionally, Sinton et al. (1986) suggest a partitioning of a population when the difference in means is greater than 25% of the normal range. The latter was calculated with the Bhattacharya method described above.

### RESULTS

Table 1 depicts the median and IQR of the CDT distribution and the number of analytical interferences according to age and gender. CDT patterns could be reliably quantified in 3953 (99.40%) individuals. Among them, in 61 pheroğrams (1.53%), a heterozygous TIC variant was encountered. In 24 (0.60%) subjects, the transferrin could not be properly quantified due to disturbance of the pheroğram, mainly caused by genetic transferrin BC or CD variants (n = 20). A disialo-transferrin (DST)-trisialotransferrin-bridging phenomenon (di-tri-bridge) was seen in two subjects (0.05%). In two (0.05%) cases, interference was due to high concentration of paraproteins characterized by a retention time within the zone of interest (Bergström and Helander, 2008a).

Males are overrepresented among the subgroups of drivers participating in the driver’s license regranting program. CDT values were significantly higher in men when compared with women (P < 0.0001). Translating this difference into the partitioning of reference values has been evaluated. Neither the Harris and Boyd, nor the Sinton method suggests a separate cut-off point for both genders. When comparing different age-groups, there is a statistically significant difference between the subjects below the age of 30 years and older subjects (P < 0.0001). A separate partition for subjects under the age of 30 years could be suggested based on the difference in median and IQR of CDT values (Harris and Boyd, 1995).

We studied the distribution of the CDT results in the group of drivers applying for driver’s license regranting over a period of 2.5 years. Figure 1 shows an absolute frequency plot of the data. Inspection of the CDT data set reveals a right skewed distribution. It does not follow a
normal distribution as indicated by the D’Agostino-Pearson test \( (P < 0.0001) \). The Bhattacharya calculation was made for a normal distribution and a gamma distribution in which a lambda coefficient of 10.38 was used for the Box-Cox transformation of the data. From a major subgroup of 8233 data points, the right-sided ULN was calculated using the 99.9th percentile. The %CDT ULN was 1.8% for the Gaussian distribution and 2.0% for the Gamma distribution. The gamma curve is preferred because it is the best fitting line in the Bhattacharya plot (Fig. 2A). The resolved gamma distribution out of the data is shown as a black line in Fig. 2B.

The variance of the internal quality control \( u^2 _{IQC} = 0.004534 \) was calculated from the cumulative standard

Table 1. Summary of results of the Belgian driver’s license regranting program over a period of 2.5 years for all subjects combined and for men and women separately

<table>
<thead>
<tr>
<th>Age</th>
<th>Number of subjects (samples)</th>
<th>Median (IQR)( ^a )</th>
<th>Subjects carrying heterozygous TIC variants</th>
<th>Subjects showing disturbed transferrin pherograms( ^c )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>( n )</td>
<td>%</td>
<td>( n )</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>507 (921)</td>
<td>0.9 (0.7–1.4)</td>
<td>7 0.20</td>
<td>2 0.06</td>
</tr>
<tr>
<td>30–40</td>
<td>755 (1501)</td>
<td>1.0 (0.7–1.7)**</td>
<td>4 0.11</td>
<td>2 0.06</td>
</tr>
<tr>
<td>41–50</td>
<td>1004 (2282)</td>
<td>1.0 (0.7–1.6)**</td>
<td>17 0.49</td>
<td>6 0.17</td>
</tr>
<tr>
<td>51–60</td>
<td>837 (1990)</td>
<td>1.1 (0.8–1.8)**</td>
<td>13 0.37</td>
<td>7 0.20</td>
</tr>
<tr>
<td>61–70</td>
<td>295 (620)</td>
<td>1.1 (0.8–1.7)**</td>
<td>5 0.14</td>
<td>1 0.03</td>
</tr>
<tr>
<td>&gt;70</td>
<td>83 (121)</td>
<td>1.1 (0.8–1.8)**</td>
<td>2 0.06</td>
<td>0 0.00</td>
</tr>
<tr>
<td>Total</td>
<td>3481 (7435)</td>
<td>1.0 (0.7–1.6)b</td>
<td>48 1.38</td>
<td>18 0.52</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>35 (66)</td>
<td>0.9 (0.7–1.1)</td>
<td>0 0.00</td>
<td>0 0.00</td>
</tr>
<tr>
<td>30–40</td>
<td>69 (119)</td>
<td>1.0 (0.8–1.4)**</td>
<td>1 0.20</td>
<td>0 0.00</td>
</tr>
<tr>
<td>41–50</td>
<td>143 (268)</td>
<td>1.0 (0.7–1.4)**</td>
<td>5 1.01</td>
<td>4 0.81</td>
</tr>
<tr>
<td>51–60</td>
<td>156 (304)</td>
<td>1.0 (0.7–1.3)**</td>
<td>4 0.81</td>
<td>1 0.20</td>
</tr>
<tr>
<td>61–70</td>
<td>57 (83)</td>
<td>1.0 (0.7–1.2)**</td>
<td>2 0.40</td>
<td>1 0.20</td>
</tr>
<tr>
<td>&gt;70</td>
<td>36 (43)</td>
<td>1.0 (0.6–1.3)**</td>
<td>1 0.20</td>
<td>0 0.00</td>
</tr>
<tr>
<td>Total</td>
<td>496 (883)</td>
<td>1.0 (0.7–1.3)</td>
<td>13 2.62</td>
<td>6 1.21</td>
</tr>
<tr>
<td>All</td>
<td>3977 (8318)</td>
<td>1.0 (0.7–1.6)</td>
<td>61 1.53</td>
<td>24 0.60</td>
</tr>
</tbody>
</table>

\( ^a \)P-value of Mann–Whitney U-test (data are compared with age-group ‘<30’ within the same gender): \( P > 0.05 \), no asterisk; \( * P < 0.05 \); \( ** P < 0.0001 \).

\( ^b \)P-value of Mann–Whitney U-test <0.0001 when comparing with men.

\( ^c \) %CDT could not be quantified correctly due to interference of co-migrating paraprotein, di-tri-bridging, genetic BC/CD transferrin variants.

Fig. 1. Distribution of %CDT values measured in samples analyzed for the BIVV-IBSR driver’s license regranting program \( (n = 8233; \) samples with disturbed pherograms were excluded). The dotted line is the calculated cut-off at 2.3% CDT.
deviation over a period of 6 months at the ULN of 2.0%. This includes analytical and lot-to-lot variability. The variance of the individual CDT values over time $\sigma^2_{\text{intra-individual}} = 0.00846$ was based on the results in seven abstinent patients with at least five CDT determinations each over a period of >1 year (Schellenberg and Wielders, 2010). The mean difference between the laboratory and the true value (EQUALIS EQC) was included as a bias factor ($E = 0.0808$) and added to the composite uncertainty. Adding the measurement uncertainty to the ULN of the resolved gamma distribution (2.0% CDT) gives rise to a calculated cut-off of 2.3% CDT.

In order to evaluate the cut-off point, indicators of diagnostic performance such as specificity and sensitivity were calculated. The calculated gamma distribution was considered as the true negative population. We calculated specificity and sensitivity for cut-off points ranging from the 97.5th percentile of the gamma distribution (1.6% CDT) to the proposed cut-off of 2.3% CDT (Table 2).

A separate cut-off was calculated for drivers under the age of 30 years, based on a subgroup of 533 subjects (970 samples). Using the 99.9th percentile in the Bhattacharya calculation, a CDT ULN of 1.7% was found. Adding a 95% measurement uncertainty gives rise to a cut-off value of 2.0% CDT.

Overall evaluation of the driver’s license regranting program based on the follow up of 163 subjects during one entire year showed a significant reduction of %CDT. When performing a pairwise comparison of %CDT values during a 1 year program, there is a statistically significant decrease in %CDT during the first 6 months ($P = 0.0126$) compared with the %CDT at the start of the program. During the second semester, median %CDT decreased from 1.3 to 1.2% ($P < 0.0001$) and the right skew of the initial distribution at the start of the program tends to disappear (Fig. 3).

The outcome of the 163 participants is listed in Table 3. Sixty percent ($n = 98$) of the subjects did not exceed the cut-off once during the program, meaning they do not show a chronic abusive drinking behavior (this number could be overestimated by the relatively low sensitivity of the used cut-off). The program has an obvious success in 23% ($n = 37$) of the participants lowering their %CDT level below the proposed cut-off of 2.3% CDT. Ten percent ($n = 17$) initially had an acceptable %CDT level, but relapsed into an abusive drinking pattern while being admitted to the program. Finally, the program seems not to have any impact on 7% ($n = 11$) of the participants. Their level of CDT never decreases below the cut-off point.

The calculated RCV for %CDT is 28%, meaning that a decrease or increase of 28% in %CDT is clinically significant. The number of persons with a significant increase or decrease in CDT is depicted for each subgroup and for all 163 subjects in Table 3. Only 16% ($n = 27$) of the participants has a positive RCV, while 39% ($n = 63$) shows a significant decrease of their CDT level. When considering the refractory group (7% of total subjects), there is a significant decrease in %CDT in 6 of the 11 participants, but the CDT level never declines beneath the cut-off.

### Table 2. Sensitivity and specifically calculated using different cut-off values for CDT measured on Capillaries 2

<table>
<thead>
<tr>
<th>Cut-off (%CDT)</th>
<th>&gt;1.6</th>
<th>&gt;1.7</th>
<th>&gt;1.8</th>
<th>&gt;1.9</th>
<th>&gt;2.0</th>
<th>&gt;2.1</th>
<th>&gt;2.2</th>
<th>&gt;2.3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (%) ± CI</td>
<td>79.8 ± 1.8</td>
<td>74.6 ± 2.0</td>
<td>68.9 ± 2.2</td>
<td>63.8 ± 2.4</td>
<td>59.3 ± 2.5</td>
<td>55.9 ± 2.7</td>
<td>52.2 ± 2.8</td>
<td>48.8 ± 2.9</td>
</tr>
<tr>
<td>Specificity (%) ± CI</td>
<td>98.7 ± 0.3</td>
<td>99.3 ± 0.2</td>
<td>99.6 ± 0.1</td>
<td>99.8 ± 0.1</td>
<td>99.9 ± 0.1</td>
<td>99.9 ± 0.0</td>
<td>99.9 ± 0.0</td>
<td>100.0 ± 0.0</td>
</tr>
</tbody>
</table>

![Fig. 2. (A) Bhattacharya plot constructed for 8233 data points acquired from the Belgian (BIVV-IBSR) driver’s license regranting program (dotted line: straight best line of fit (Gaussian); thick black line: gamma function best line of fit (Gamma)). (B) Resolved gamma distribution extracted out of same data [plots constructed with Microsoft Excel® Spreadsheet provided by Naus et al. (1980)].](image)
CZE provides high-resolution separation of serum transferrin isoforms and includes the detection of genetic variants and disorders of glycosylation. In only 2.13% \( (n = 85) \) of all investigated drivers, analytical problems were encountered. In 72% \( (n = 61) \) of the latter, a heterozygous TfC variant was detected and a quantitative result could still be calculated.

**DISCUSSION**

Fig. 3. Distribution of %CDT values of 163 subjects participating in the Belgian driver’s license regranting program at the start (A), during the first 6 months (B) and during the last 6 months (C) of the program. \( (P\)-values are for Wilcoxon test for paired samples compared with %CDT at start of the program: \*\( P < 0.05 \); **\( P < 0.0001 \); dotted line: cut-off at 2.3% CDT).
Next to TfC, the most frequent variants are the D variant (cathodal) and the B variant (anodal) (Arndt et al., 2008a). BC and CD variants were easily recognized because of doubling of the major tetrasialotransferrin peak. In these variants, %CDT cannot be measured accurately by CZE. The allele frequency of the transferrin subtypes varies between different ethnic origins (Wuyts et al., 2001). The observed transferrin allele frequencies are in agreement with data reported in literature (Cavalli-Sforza et al., 1994). A di-tri-bridge appears with high prevalence in serum from liver cirrhosis patients (Arndt et al., 2008b) and was seen in 0.05% (n = 2) of the subjects. Its presence could lead to the inability of correctly quantifying CDT. Interference by complement C3 has also been described. This interference is detected by the software and a treatment solution can prevent complement C3 from interfering (Beisler et al., 2000). Congenital disorders of glycosylation (CDG) were not encountered, but can give rise to false positive results concerning chronic alcohol abuse (Helander et al., 2004).

Differences have been reported in basal and alcohol-related CDT levels in relation to factors such as age and gender (Whitfield et al., 1998). In the cohort, significant differences were found between young drivers (aged 30 or less) and older drivers, as previously confirmed by another group (Szabó et al., 2009). This could be partly explained by the different drinking behavior in younger subjects. Drinking frequency and intensity are mediators when analyzing the data for partitioning. Young subjects more frequently show an intermittent (binge) drinking pattern which can raise carbohydrate deficient transferrin, but the extent to which this occurs is dependent on the frequency of drinking and the amount of alcohol consumed on each occasion. Older subjects show a more continuous drinking behavior, which has a larger impact on CDT (Anton et al., 1998). Therefore, serum CDT has a lower sensitivity in detecting heavy drinkers under the age of 30 years (Bisson and Milford-Ward, 1994).

The data of this cohort suggest that adapting different cut-off values according to gender is not feasible. CDT elevations are less significant in females with high long-term alcohol consumption, compared with males (Figlie et al., 2002). However, Sillanaukee et al. (1998) reported a comparable sensitivity for CDT in female and male heavy drinkers. As previously stated, adjustment of reference intervals for CDT in relation to ethnic origin, gender, body mass index and smoking is not required (Bergström and Helander, 2008b).

The IFCC-Working group on CDT states that the ULN is the 97.5th percentile of a group of non-drinkers or drinkers of maximum 20 g/day (Whitfield et al., 1998). Because of the high number of caveats in the analysis of %CDT, this ULN can give rise to legal consequences. Additionally, it is difficult to establish reference values for CDT in the classical manner. By definition, reference values are values obtained by measurement of a particular type of quantity of reference individuals. A reference individual is an individual selected for comparison using defined criteria including age, gender, conditions of specimen collection and whether they are healthy or have a certain disease. It is impossible to determine whether a person is completely abstinent or drinks at maximum 20 g (two consumptions) of alcohol per day. Difficulties in establishing a reliable reference population, given the problem of defining a healthy subject, have led to the exploration of alternative statistical methods to determine a cut-off value.

The studied population consists of normal individuals (social drinkers) and abnormal individuals (pathological drinkers). If a large database is available, preferably with abnormal results on one side of the distribution, the use of a Bhattacharya plot can be considered (Bhattacharya, 1967; Van den Bossche, 2007). By this method, a mixture of normal values polluted with abnormal results can be resolved and the Gaussian or gamma distribution can be reconstructed. The choice of a cut-off value depends partly on the intended use of the parameter. If CDT is used beyond a medical purpose in forensic affairs where an erroneous abnormal result may have rigorous consequences for the subject, special attention has to be paid to the risk of false positive values. The main objective of the driver’s license regranting program is to keep heavy offenders out of traffic.

Test results much more unusual than the 99th percentile of non-alcoholics should be required before they can be labeled ‘unfit’ (Berry, 2008). Analysis of our data by Bhattacharya analysis reveals a 99.9% UNL of 2.0% CDT. When evaluating different cut-off points, sensitivity decreases by increasing the cut-off point, as expected. Inversely there is only a slight gain in specificity. Schellenberg and Wielders (2010) calculated a 95% UNL of 1.6% CDT with a specificity of 99% and a sensitivity of 78%, which is in line with our findings. However, given the fact that the cut-off is implemented in a legal context, it is important to have a specificity as high as possible. The loss in sensitivity is of minor importance in this setting.

### Table 3. Subclassification of 163 subjects based on the outcome of the individual drivers license regranting programs

<table>
<thead>
<tr>
<th>Groups*</th>
<th>Refactory</th>
<th>Relapse</th>
<th>Controlled</th>
<th>Abstinent/moderate</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects in group (% of total)</td>
<td>11 (7%)</td>
<td>17 (10%)</td>
<td>37 (23%)</td>
<td>98 (60%)</td>
<td>163</td>
</tr>
<tr>
<td>Subjects with significant increase in %CDT (+RCV&lt;sub&gt;9&lt;/sub&gt;CDT)</td>
<td>1</td>
<td>10</td>
<td>0</td>
<td>16</td>
<td>27 (16%)</td>
</tr>
<tr>
<td>Subjects with no significant change in %CDT</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>64</td>
<td>73 (45%)</td>
</tr>
<tr>
<td>Subjects with significant decrease in %CDT (−RCV&lt;sub&gt;9&lt;/sub&gt;CDT)</td>
<td>6</td>
<td>4</td>
<td>35</td>
<td>18</td>
<td>63 (39%)</td>
</tr>
</tbody>
</table>

Classification was based on the course of the individual %CDT values in respective to the calculated cut-off of 2.3% CDT. Additionally, baseline CDT was compared with %CDT after 12 months by using the reference change value (RCV). Plus or minus RCV<sub>9</sub>CDT is defined as a relative increase/decrease in CDT of 28% compared with baseline CDT.

Subjects in group (% of total): Subjects with significant increase in %CDT (+RCV<sub>9</sub>CDT): 11 (7%), Subjects with no significant change in %CDT: 4 (2%), Subjects with significant decrease in %CDT (−RCV<sub>9</sub>CDT): 6 (4%).

Subjects in group (% of total): 1 (1%), 17 (10%), 37 (23%), 98 (60%), 163 (100%).
An important drawback of diagnostic performance indicators is the influence of analytical error. Systematic and random errors can deteriorate the test accuracy. A confidence interval (CI) has been calculated, but this does not cover measurement uncertainty. In order to interpret a result with certainty, the Dutch guideline adds a method-dependent critical difference to the upper reference limit. Both inter-laboratory variation and the biological variation contribute to the critical difference. This addition leads to their cut-off limits. In this study, uncertainty intervals were calculated according to GUM. This method is usually reserved for reference materials, but the use in cut-off calculations has been proposed (Schellenberg and Wielders, 2010). Calculation of the cut-off then results in a %CDT value of 2.3 with a sensitivity of 49% and a specificity of 100%. Taking into account all sources of imprecision, this cut-off value should be considered as the highest numerical value of %CDT to be expected in abstainers or occasional drinkers.

Bortolotti et al. (2007) proposed a cut-off set at 2.0% in the fitness evaluation for obtaining a driver’s license, based on a CZE method. A cut-off of 1.6% CDT is proposed by Schellenberg and Wielders (2010) to be used in forensic medicine. The HPLC upper reference limit applied in Sweden is 1.9% DST, corresponding to the mean value + 3 SD for control populations (Delanghe and De Buyzere, 2009). For younger drivers (18–30 years), a cut-off of 2.0% CDT was calculated as a useful decision point in legal cases such as driver’s license reinstatement. Given the fact that death risk in traffic is significantly higher in the 15–24 years age group when compared with older subjects, a more stringent cut-off point could be suggested for young drivers (Van den Bossche, 2007).

It has to be kept in mind that subjects are admitting themselves to a program which could lead to the important decision of granting a driver’s license. The final decision is, however, not made solely on the result of the CDT analysis, other parameters have to be also kept in check. The laboratory results have to confirm the results of other medical and psychological examinations. CDT analysis has an important additional value in monitoring abstinence. It has a high sensitivity in detecting relapse (Bergström and Helander, 2008a). CDT has a half-life of normalization of ~2 weeks, which makes it an ideal parameter to be used in a program where individuals are monitored every 2 months. During long-term monitoring the use of individualized cut-off points has been suggested, based on intra-individual variation in CDT (Borg et al., 1995). In this proper study, we used a RCV, which is comparable to the individualized cut-off point, to evaluate the outcome for each subject separately.

When considering the outcome of the program over one entire year, there is a significant decrease in %CDT and the number of offenders. There is a small subgroup of 10% that relapses into abusive drinking behavior. The program has a positive effect on 83% of the participants, meaning that their alcohol drinking behavior is controlled or moderate. Seven percent of the participants are refractory to the program, but also in this subgroup we see a significant decrease in %CDT. This suggests that an alcohol contract program, followed up by bimonthly control of the subjects’ CDT, can significantly alter the drinking behavior concerning drunk driving. Monitoring CDT in the framework of an alcohol contract program apparently has a therapeutic effect.

CONCLUSION

The main objective of the driver’s license regranting program is to keep heavy offenders out of traffic. Detection of CDT values is just one means of elucidating suspected alcohol abuse (Guidelines NVKC Working Group on CDT, 2008; Delanghe and De Buyzere, 2009). Confounding factors have to be taken into account when interpreting CDT results. We propose a cut-off for %CDT that is statistically well founded, making it applicable in legal situations. The data suggest adapting a more stringent cut-off for drivers younger than 30 years of age. Evaluation of the data shows a favorable outcome of the driver’s license regranting program after one entire year. The high validity of self-reported alcohol consumption in alcoholics may be due to the announcement of CDT determination (Fleming et al., 2004). The psychological pressure on the subjects being told that long-term alcohol consumption biomarker will be applied should not be underestimated. The data suggest that follow-up of drunk drivers by bimonthly CDT analyses apparently has a therapeutic effect.

REFERENCES


