Area-under-the-HbA1c-curve above the normal range and the prediction of microvascular outcomes
an analysis of data from the Diabetes Control and Complications Trial
Maple-Brown, Louise; Ye, C; Retnakaran, R

Published in:
Diabetic Medicine

DOI:
10.1111/dme.12004

Published: 01/01/2013

Document Version
Peer reviewed version

Citation for published version (APA):

General rights
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

• Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
• You may not further distribute the material or use it for any profit-making activity or commercial gain
• You may freely distribute the URL identifying the publication in the public portal

Take down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Download date: 11. Dec. 2018
"This is the peer reviewed version of the following article: Maple-Brown, L. J., Ye, C. and Retnakaran, R. (2013), Area-under-the-HbA1c-curve above the normal range and the prediction of microvascular outcomes: an analysis of data from the Diabetes Control and Complications Trial. Diabetic Medicine, 30: 95–99. doi:10.1111/dme.12004, which has been published in final form at https://doi.org/10.1111/dme.12004. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Self-Archiving."
Technical Editor DRH

Short Report: Complications

Area-under-the-HbA1c-curve above the normal range and the prediction of microvascular outcomes: an analysis of data from the Diabetes Control and Complications Trial

L. J. Maple-Brown1,2,3, C. Ye1 and R. Retnakaran1,4
1Leadership Sinai Centre for Diabetes, Mount Sinai Hospital, Toronto, ON, Canada, 2Menzies School of Health Research, Charles Darwin University, 3Division of Medicine, Royal Darwin Hospital, Darwin, NT, Australia and 4Division of Endocrinology, University of Toronto, Toronto, ON, Canada

Correspondence to: Ravi Retnakaran. E-mail: rretnakaran@mtsinai.on.ca

Running head: Area-under-the-HbA1c-curve in the DCCT • L. J. Maple-Brown et al.
Abstract

Aims In the Diabetes Control and Complications Trial, mean updated HbA1c accounted for most of the differential risk of microvascular complications between intensive and conventional insulin therapy. We hypothesized, however, that a more precise measure of chronic hyperglycaemic exposure may be the incremental area-under-the-HbA1c-curve above the Diabetes Control and Complications Trial-standardized normal range for HbA1c (iAUC_{HbA1c>norm}).

Methods Using the Principal Diabetes Control and Complications Trial data set, we compared the following three measures of chronic glycaemic exposure for their capacity to predict retinopathy, nephropathy and neuropathy during the Diabetes Control and Complications Trial: mean updated HbA1c, iAUC_{HbA1c>norm}, and total area-under-the-HbA1c-curve (tAUC_{HbA1c}). For each outcome, models using each of these three glycaemic measures were compared in the following three ways: hazard or odds ratio, $\chi^2$ statistic, and Akaike information criterion.

Results The three glycaemic measures did not differ in their prediction of neuropathy. iAUC_{HbA1c>norm} was modestly superior to mean updated HbA1c for predicting nephropathy ($\chi^2 P = 0.017$, Akaike $P = 0.032$). In contrast, for predicting retinopathy, both iAUC_{HbA1c>norm} ($\chi^2 P = 0.0005$, Akaike $P = 0.0005$) and tAUC_{HbA1c} ($\chi^2 P = 0.004$, Akaike $P = 0.0004$) were significantly better than mean updated HbA1c. Varying its HbA1c threshold incrementally between 37 and 53 mmol/mol (5.5–7.0%), inclusive, did not improve the prediction of retinopathy by iAUC_{HbA1c>threshold} beyond that of tAUC_{HbA1c}, consistent with the concept of a continuous relationship between glycaemia and retinopathy, with no glycaemic threshold.

Conclusions Both iAUC_{HbA1c>norm} and tAUC_{HbA1c} were superior to mean updated HbA1c for predicting retinopathy. Optimal assessment of chronic glycaemic exposure as a determinant of
retinopathic risk may require consideration of both the degree of hyperglycaemia and its duration.

**Abbreviations**  
iAUC$_{\text{HbA}1c}$, incremental area-under-the-HbA$_{1c}$-curve; iAUC$_{\text{HbA}1c>\text{norm}}$, incremental area-under-the-HbA$_{1c}$-curve above the normal range for the DCCT-standardized HbA$_{1c}$ assay; tAUC$_{\text{HbA}1c}$, total area-under-the-HbA$_{1c}$-curve; DCCT, Diabetes Control and Complications Trial; IFCC, International Federation of Clinical Chemistry and Laboratory Medicine

**Introduction**

The Diabetes Control and Complications Trial (DCCT) study group reported that intensive insulin therapy can reduce the development and progression of retinopathy, nephropathy and neuropathy in Type 1 diabetes, with glycaemic exposure (as determined by mean updated HbA$_{1c}$) explaining virtually all of the difference in risk of these complications between the intensive and conventional therapy groups [1–3]. These data highlight the central importance of chronic exposure to hyperglycaemia as a determinant of microvascular complications in patients with Type 1 diabetes. Although assessed by the mean updated HbA$_{1c}$ in the DCCT, we hypothesized that a more precise measure of chronic hyperglycaemic exposure would be the incremental area-under-the-HbA$_{1c}$-curve above the DCCT-standardized normal range for HbA$_{1c}$ (iAUC$_{\text{HbA}1c>\text{norm}}$). Indeed, this measure provides a way of integrating both the degree of glycaemia and the time spent above the normoglycaemic range, and hence could capture the cumulative exposure to hyperglycaemia. As such, by reflecting the presumed key biologic risk determinant relevant to the development of microvascular complications, it may be
a stronger predictor of these outcomes than mean updated HbA$_{1c}$. Thus, we sought to evaluate the predictive capacity of iAUC$_{HbA1c>\text{norm}}$ as a determinant of microvascular complications in the DCCT, as compared with mean updated HbA$_{1c}$.

**Methods**

The DCCT has been previously described in detail [4,5]. In brief, 1441 participants with Type 1 diabetes were randomized to intensive or conventional insulin therapy and followed for a mean 6.5 years, with quarterly measurement of HbA$_{1c}$ and regular assessment for microvascular complications. Using the publicly available Principal DCCT data set (National Technical Information Service, Alexandria, VA, USA), we evaluated the following three measures of chronic glycaemic exposure: mean updated HbA$_{1c}$, mean iAUC$_{HbA1c>\text{norm}}$ and mean total area-under-the-HbA$_{1c}$-curve (tAUC$_{HbA1c}$).

These measures were assessed because, while mean updated HbA$_{1c}$ will reflect the actual mean value for HbA$_{1c}$ over follow-up, it does not account for duration of time spent above a particular glycaemic threshold [such as the upper-limit-of-normal for the DCCT-standardized HbA$_{1c}$ assay (IFCC 42 mmol/mol or DCCT 6.0%)]. In contrast, iAUC$_{HbA1c>\text{norm}}$ provides a measure of glycaemic exposure that incorporates not only the degree of glycaemia, but also the time spent above the normal range. To illustrate this difference, consider the hypothetical example of two patients with the following quarterly HbA$_{1c}$ measurements: Patient A has measurements of 42 mmol/mol (6.0%), 42 mmol/mol, 42 mmol/mol and 42 mmol/mol, while patient B has measurements of 42 mmol/mol, 46 mmol/mol (6.4%), 38 mmol/mol (5.6%) and
42 mmol/mol. Mean updated HbA1c will be the same for both patients, but only iAUC_{HbA1c>norm} will capture the fact that patient B spent time with HbA1c over the normal range. Finally, we also assessed tAUC_{HbA1c}, as it is similar to iAUC_{HbA1c>norm} but does not assume that the upper-limit-of-normal for the DCCT-standardized assay (IFCC 42 mmol/mol or DCCT 6.0%) is an absolute threshold below which glycaemic exposure does not contribute to microvascular risk.

Mean updated HbA1c was calculated as the mean of all quarterly HbA1c measures up to the visit under study, computed at 6-monthly intervals [3]. Mean AUC_{HbA1c} was calculated by trapezoidal rule as a mean of the number of visits under study. For example, AUC_{HbA1c} at year 3 (12 visits) was calculated as:

\[
0.5 \times [H_0 + (2 \times H_1) + (2 \times H_2) + (2 \times H_3) + (2 \times H_4) + (2 \times H_5) + (2 \times H_6) + (2 \times H_7) + (2 \times H_8) + (2 \times H_9) + (2 \times H_{10}) + (2 \times H_{11}) + H_{12}] / 12,
\]

where H_0 is baseline HbA1c, H_1 is first-quarterly visit HbA1c, H_2 is second-quarterly visit HbA1c, etc. Calculations for each 6-monthly or annual interval included all preceding quarterly HbA1c measurements since the start of the DCCT.

For each measure of glycaemic exposure, we determined its predictive capacity for incidence of the following DCCT-defined [3] microvascular outcomes: persistent 3-step change in retinopathy, microalbuminuria and neuropathy. Retinopathy and nephropathy were analysed by time-dependent proportional hazards models and neuropathy by logistic regression model. For each outcome, models using each of the three HbA1c measures were compared in three ways: hazard or odds ratio, χ² statistic, and Akaike information criterion (Table 1). For both the χ² and Akaike information criterion statistics, pairwise comparisons were conducted using bootstrap
methods (2000 bootstrap samples were drawn from the original data set with replacement). The pairwise differences of the estimated $\chi^2$ and Akaike information criterion statistics were obtained for each bootstrap sample. The bootstrap method made it possible to estimate the sampling distribution of the pairwise difference of the $\chi^2$ or Akaike information criterion statistic. Based on this non-parametric method, and the observed pairwise differences, we calculated bootstrap $P$-values to control type I error and determine the significance of pairwise differences. The bootstrap $P$-values were estimated by the proportion of those bootstrapped $\chi^2$ or Akaike values at greater than or equal to the observed pairwise difference from the original data.

Models for the prediction of retinopathy were repeated at different HbA1c thresholds between 37 and 53 mmol/mol (5.5–7.0%) for comparison of $iAUC_{HbA1c>threshold}$ vs. $tAUC_{HbA1c}$ (Table 2). The purpose of this analysis was to see if there was a particular HbA1c threshold where $iAUC_{HbA1c>threshold}$ was superior to $tAUC_{HbA1c}$ for predicting retinopathy by both $\chi^2$ and Akaike information criterion. All statistical analyses were performed using Stata 10.0 (StataCorp., College Station, TX, USA) and SAS 9.2 (SSA Institute, Cary, NC, USA).

Results

All three HbA1c measures (mean updated HbA1c, $tAUC_{HbA1c}$, $iAUC_{HbA1c>norm}$) were significantly associated with each microvascular outcome (Table 1). However, their comparative predictive capacities differed for each complication. While the three measures did not differ in their prediction of neuropathy, $iAUC_{HbA1c>norm}$ (but not $tAUC_{HbA1c}$) was superior to mean updated HbA1c for prediction of nephropathy ($\chi^2$ bootstrap $P = 0.017$, Akaike bootstrap $P = 0.032$). In contrast, both $iAUC_{HbA1c>norm}$ ($\chi^2$ bootstrap $P = 0.0005$, Akaike bootstrap...
P = 0.0005) and tAUC\textsubscript{HbA1c} (\chi^2\ bootstrap \ P = 0.004, Akaike bootstrap \ P = 0.0004) were superior to mean updated HbA\textsubscript{1c} for the prediction of retinopathy, with no significant difference between iAUC\textsubscript{HbA1c>norm} and tAUC\textsubscript{HbA1c}. Varying its HbA\textsubscript{1c} threshold above or below 42 mmol/mol (6.0%) from 37–53 mmol/mol (5.5–7.0%) did not improve the prediction of retinopathy by iAUC\textsubscript{HbA1c>threshold} beyond that of tAUC\textsubscript{HbA1c} (Table 2). Specifically, the \chi^2 statistic did not reveal a significant difference between these two measures at any threshold, although the Akaike information criterion statistic found tAUC\textsubscript{HbA1c} to be superior to iAUC\textsubscript{HbA1c>threshold} at HbA\textsubscript{1c} thresholds > 48 mmol/mol (6.5%). Lastly, after adjustment for covariates (baseline HbA\textsubscript{1c}, age, gender, BMI, duration of diabetes, treatment group and baseline value of the outcome variable), both iAUC\textsubscript{HbA1c>norm} and tAUC\textsubscript{HbA1c} remained superior to mean updated HbA\textsubscript{1c} for the prediction of retinopathy but not nephropathy or neuropathy (see also Supporting Information, Table S1).

**Discussion**

In this analysis, all three HbA\textsubscript{1c} indices yielded comparable hazard or odds ratios for the prediction of each microvascular outcome, and the overall benefits of the AUC\textsubscript{HbA1c} measures over mean updated HbA\textsubscript{1c} were modest. Furthermore, it is recognized that neither the AUC\textsubscript{HbA1c} indices nor mean updated HbA\textsubscript{1c} are practical measures for calculation in clinical practice. Instead, however, these indices are more relevant as research tools in clinical studies. Indeed, as shown in this analysis, AUC\textsubscript{HbA1c} measures can provide insight on the impact of glycaemic exposure on risk of microvascular complications and, potentially, the biology underlying these relationships. In this context, three key findings emerge from the current data.
First, the demonstration that both iAUC_{HbA1c>norm} and tAUC_{HbA1c} were superior to mean updated HbA1c for the prediction of retinopathy supports the concept that optimal assessment of chronic glycaemic exposure as a determinant of microvascular risk may require consideration of both the degree of hyperglycaemia and its duration. Interestingly, Orchard and colleagues previously explored this general concept with their construct of A1months, defined as the product of HbA1c above the normal range and months of exposure, as determined from biennial assessment in the Pittsburgh Epidemiology of Diabetes Complications study [6]. While they found that this measure was not a better predictor of microvascular complications than its components (duration and mean HbA1c), it should be noted that its calculation from biennial HbA1c assessments would have rendered A1months a less precise measure of chronic glycaemic exposure than the AUC_{HbA1c} indices obtained from the more frequent HbA1c measurements in the DCCT. Thus, the AUC_{HbA1c} measures in the current study may have been better able to demonstrate the predictive capacity of a cumulative glycaemic exposure variable that incorporates both duration and degree of glycaemia.

Secondly, it is noted that iAUC_{HbA1c>norm} and tAUC_{HbA1c} were both consistently superior to mean updated HbA1c for the prediction of retinopathy, but not nephropathy and neuropathy. This difference may relate to methodologic features (e.g. neuropathy was assessed only at 5 years, while retinopathy was assessed every 6 months) or limitations in the measurement of nephropathy and neuropathy outcomes, but also may reflect a comparatively greater influence of glycaemic exposure on risk of retinopathy, as compared with the other outcomes. Thirdly, we did not detect an HbA1c level above which iAUC_{HbA1c} surpasses tAUC_{HbA1c} for predicting retinopathy, consistent with the concept of a continuous relationship between glycaemia and retinopathy, with no glycaemic threshold [3].
Finally, it should be noted that, although non-glycaemic factors may also be relevant [7],
the unmeasured effect of glycaemic exposure in the years prior to the DCCT may have limited
the achievable predictive capacity of all three HbA1c-based measures obtained during the trial.
Thus, iAUC_{HbA1c>norm} and tAUC_{HbA1c} from the time of diagnosis ultimately warrant study for the
evaluation of total cumulative glycaemic exposure as a determinant of microvascular risk in
Type 1 diabetes.

**Competing interests**

Nothing to declare.

**Acknowledgements**

The authors thank Dr Bernard Zinman (University of Toronto and Leadership Sinai Centre for
Diabetes, Toronto, Canada) for advice and helpful discussion. The authors thank DCCT
Investigators and participants for their landmark contributions to the understanding of diabetes
control and complications. LMB is supported by an Australian National Health and Medical
Research Council Early Career Fellowship no. 605837. RR is supported by a Canadian Institutes
of Health Research New Investigator award, Canadian Diabetes Association Clinician Scientist
incentive funding, and an Ontario Ministry of Research and Innovation Early Researcher Award.

**References**

1. DCCT Research Group. The effect of intensive treatment of diabetes on the development
and progression of long-term complications in insulin-dependent diabetes mellitus. N


Supporting Information

Additional Supporting Information may be found in the online version of this article;

Table S1. Comparative performance of each measure of glycaemic exposure for the prediction of microvascular outcomes, adjusted for baseline HbA1c, age, gender, BMI, duration of diabetes, treatment group and baseline value of the outcome variable.

Please note: Wiley-Blackwell are not responsible for the content or functionality of any supporting materials supplied by the authors. Any queries (other than for missing material) should be directed to the corresponding author for the article.
Table 1 Comparative performance of each measure of glycaemic exposure for the prediction of microvascular outcomes

<table>
<thead>
<tr>
<th></th>
<th>Mean updated HbA1c</th>
<th>tAUC\textsubscript{HbA1c}</th>
<th>iAUC\textsubscript{HbA1c&gt;norm}</th>
<th>(P)-values for pairwise comparisons§</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean updated HbA1c vs. tAUC\textsubscript{HbA1c}</td>
</tr>
<tr>
<td>Retinopathy* (n = 1440)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>1.64 (1.52–1.77)</td>
<td>1.69 (1.57–1.83)</td>
<td>1.68 (1.56–1.82)</td>
<td>N/A</td>
</tr>
<tr>
<td>(\chi^2)†</td>
<td>161.65</td>
<td>174.54</td>
<td>171.71</td>
<td>0.004</td>
</tr>
<tr>
<td>Akaike information criterion‡</td>
<td>2847.83</td>
<td>2837.39</td>
<td>2839.22</td>
<td>0.004</td>
</tr>
<tr>
<td>Nephropathy* (n = 1365)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>1.31 (1.22–1.41)</td>
<td>1.33 (1.23–1.43)</td>
<td>1.33 (1.23–1.44)</td>
<td>N/A</td>
</tr>
<tr>
<td>(\chi^2)†</td>
<td>50.18</td>
<td>52.18</td>
<td>53.21</td>
<td>0.068</td>
</tr>
<tr>
<td>Akaike information criterion‡</td>
<td>3517.83</td>
<td>3516.15</td>
<td>3515.45</td>
<td>0.076</td>
</tr>
<tr>
<td>Neuropathy* (n = 1161)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>1.53 (1.34–1.74)</td>
<td>1.53 (1.35–1.75)</td>
<td>1.54 (1.35–1.75)</td>
<td>N/A</td>
</tr>
<tr>
<td>(\chi^2)†</td>
<td>41.91</td>
<td>42.05</td>
<td>42.17</td>
<td>0.368</td>
</tr>
<tr>
<td>Akaike information criterion‡</td>
<td>662.35</td>
<td>662.26</td>
<td>662.31</td>
<td>0.412</td>
</tr>
</tbody>
</table>

© 2012 The Authors. Diabetic Medicine © 2012 Diabetes UK
Retinopathy was defined as persistent 3-step change from baseline, graded according to the Early Treatment Diabetic Retinopathy Study scale. Nephropathy was defined as urine albumin excretion rate ≥ 40 mg/24 h. Neuropathy was defined on clinical examination at 5 years with concurrent/prior abnormalities in nerve conduction or autonomic nervous system testing. Retinopathy and nephropathy were analysed by time-dependent proportional hazards models as they were assessed regularly during the DCCT. Neuropathy was analysed by logistic regression model because it was assessed only at 5 years. Patients with urine albumin excretion rate > 40 mg/24 h at baseline were excluded from nephropathy models and those with neuropathy at baseline were excluded from neuropathy models.

†A larger \( \chi^2 \) statistic indicates stronger evidence of an increasing trend over time in the effect of a measure of glycaemic exposure on the hazard or risk of an outcome.

‡The Akaike information criterion offers a measure of the information lost when a statistical model is used to describe reality. Thus, in this study, given a set of models using three measures of glycaemic exposure for each outcome, the preferred model is the one with the minimum Akaike information criterion value, as least information is lost.

§The pairwise comparisons were conducted using bootstrap methods (2000 bootstrap samples were drawn from the original data set with replacement). The pairwise differences of the estimated \( \chi^2 \) and Akaike information criterion statistics were obtained for each bootstrap sample. The bootstrap P-values were estimated by the proportion of those bootstrapped \( \chi^2 \) or Akaike values at greater than or equal to the observed pairwise difference from the original data.

<table>
<thead>
<tr>
<th>HbA1c threshold (T)</th>
<th>IFCC (mmol/mol)</th>
<th>DCCT (%)</th>
<th>Hazard ratio</th>
<th>Value</th>
<th>( \chi^2)-test</th>
<th>Akaike information criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P-value for iAUC(<em>{HbA1c&gt;T}) vs. tAUC(</em>{HbA1c})</td>
<td>Value</td>
</tr>
<tr>
<td>37</td>
<td>5.5</td>
<td>1.682</td>
<td>171.50</td>
<td>0.166</td>
<td>2838.74</td>
<td>0.316</td>
</tr>
<tr>
<td>38</td>
<td>5.6</td>
<td>1.682</td>
<td>171.55</td>
<td>0.169</td>
<td>2838.77</td>
<td>0.313</td>
</tr>
<tr>
<td>39</td>
<td>5.7</td>
<td>1.682</td>
<td>171.58</td>
<td>0.171</td>
<td>2838.85</td>
<td>0.293</td>
</tr>
<tr>
<td>40</td>
<td>5.8</td>
<td>1.683</td>
<td>171.64</td>
<td>0.175</td>
<td>2838.93</td>
<td>0.294</td>
</tr>
<tr>
<td>41</td>
<td>5.9</td>
<td>1.683</td>
<td>171.62</td>
<td>0.163</td>
<td>2839.05</td>
<td>0.278</td>
</tr>
<tr>
<td>42</td>
<td>6.1</td>
<td>1.684</td>
<td>171.81</td>
<td>0.180</td>
<td>2839.44</td>
<td>0.240</td>
</tr>
<tr>
<td>44</td>
<td>6.2</td>
<td>1.686</td>
<td>171.90</td>
<td>0.190</td>
<td>2839.74</td>
<td>0.205</td>
</tr>
<tr>
<td>45</td>
<td>6.3</td>
<td>1.687</td>
<td>171.95</td>
<td>0.200</td>
<td>2840.15</td>
<td>0.158</td>
</tr>
<tr>
<td>46</td>
<td>6.4</td>
<td>1.689</td>
<td>171.98</td>
<td>0.204</td>
<td>2840.70</td>
<td>0.109</td>
</tr>
<tr>
<td>48</td>
<td>6.5</td>
<td>1.690</td>
<td>171.94</td>
<td>0.202</td>
<td>2841.36</td>
<td>0.078</td>
</tr>
<tr>
<td>49</td>
<td>6.6</td>
<td>1.693</td>
<td>171.96</td>
<td>0.211</td>
<td>2842.08</td>
<td>0.047</td>
</tr>
<tr>
<td>50</td>
<td>6.7</td>
<td>1.696</td>
<td>172.05</td>
<td>0.225</td>
<td>2842.86</td>
<td>0.024</td>
</tr>
<tr>
<td>51</td>
<td>6.8</td>
<td>1.700</td>
<td>172.06</td>
<td>0.237</td>
<td>2843.76</td>
<td>0.014</td>
</tr>
<tr>
<td>52</td>
<td>6.9</td>
<td>1.705</td>
<td>172.29</td>
<td>0.264</td>
<td>2844.59</td>
<td>0.008</td>
</tr>
<tr>
<td>53</td>
<td>7.0</td>
<td>1.710</td>
<td>172.40</td>
<td>0.281</td>
<td>2845.56</td>
<td>0.005</td>
</tr>
</tbody>
</table>

iAUC\(_{HbA1c=T}\) incremental area-under-the-HbA1c-curve; tAUC\(_{HbA1c}\) total area-under-the-HbA1c-curve; DCCT, Diabetes Control and Complications Trial; IFCC, International Federation of Clinical Chemistry and Laboratory Medicine.

© 2012 The Authors. Diabetic Medicine © 2012 Diabetes UK