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The Quality Needed for Measuring Glycated Haemoglobin. An Application

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INTRODUCTION

The principles for estimation of the analytical quality needed in different screening and diagnostic strategies are well described. The models for bimodal distributions were outlined in a previous NORDKEM-PROJECT (5) where graphical as well as computer simulation methods were presented. Effects of both analytical bias and imprecision were studied in order to evaluate the effects of analytical variation and errors on the fractions of false negative and false positive individuals from the classification strategies. Models for estimation of the needed analytical quality in screening of unimodal biological distributions have been described based on computer simulations (4) and on statistical computations (7,8).

HbA_{1c}

The use of HbA_{1c}-measurements, however, is neither a screening nor a diagnostic procedure, but rather a monitoring of patients with diabetes. As the disease has been diagnosed earlier in the individual patient, the above mentioned models for estimation of the needed analytical quality cannot be used, and other models must be elaborated.

STRATEGIES

The clinicians' goal in monitoring of diabetics is to keep the HbA1c-concentration low and stable. The strategy for treatment of patients can be to get values below 9.0 in insulin-dependent

(3) and below 7.5 percent HbA_{1c} in non-insulin-dependent diabetics (1). Furthermore, an increase in percent HbA_{1c} of 1.0 will call the clinicians attention and an increase of 2.0 will lead to an intervention (6) comprising change-diet etc.

From the two strategies it is possible to evaluate the influence of analytical variation and errors and to define the maximum combination of analytical imprecision and bias (or systematic error), which will result in acceptable changes in the clinical outcome.

WITHIN SUBJECT VARIATION

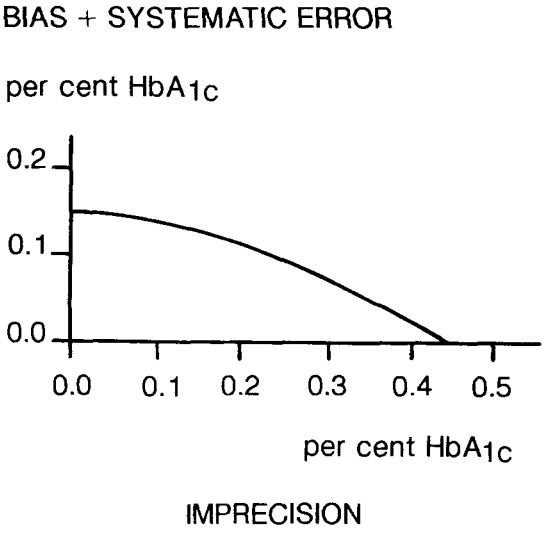
In both situations knowledge about the within- subject biological variation around the homeostatic setpoint is an indispensable prerequisite for the evaluation. But in constrast to within-subject biological variations for healthy individials (2) these patients are in medical treatment, so a natural balance in glucation of haemoglobin cannot be expected. For patients to be considered in stable conditions, however, a within-subject variation can be calculated, giving an estimate of appearent variation (6). This estimate is 0.41 percent HbA_{1c}.

INFLUENCE OF ANALYTICAL QUALITY ON THE STRATEGY OF KEEPING HbA_{1c} BELOW 7.5

For the evaluation of analytial influence on keeping the percent HbA_{1c} below a certain value, e.g. 7.5, the meaning of the clinical strategy must be clearified in more operational terms: How often should it be accepted that a well regulated patient shows HbA_{1c}-values above 7.5 without intervention? In the optimal situation and in the acceptable situation? These questions may be difficult to answer, but let us assume 10% for the optimal situation, which may be increased to 20% due to the analytical performance. This means that the limit for a well regulated patient in the optimal situation is a homeostatic setpoint which will allow only 10% of the results to exceed 7.5 percent HbA_{1c}. The one-tailed z-value for p = 10 % is 1.28 which gives a setpoint approx. 7.0 percent HbA_{1c} (assuming the within-subject biological variation $\approx$ 0.41 and negligible analytical

imprecision and bias). In reality the strategy of keeping HbA_{1c} below 7.5 is equivalent to keeping homestatic setpoint below 7.0.

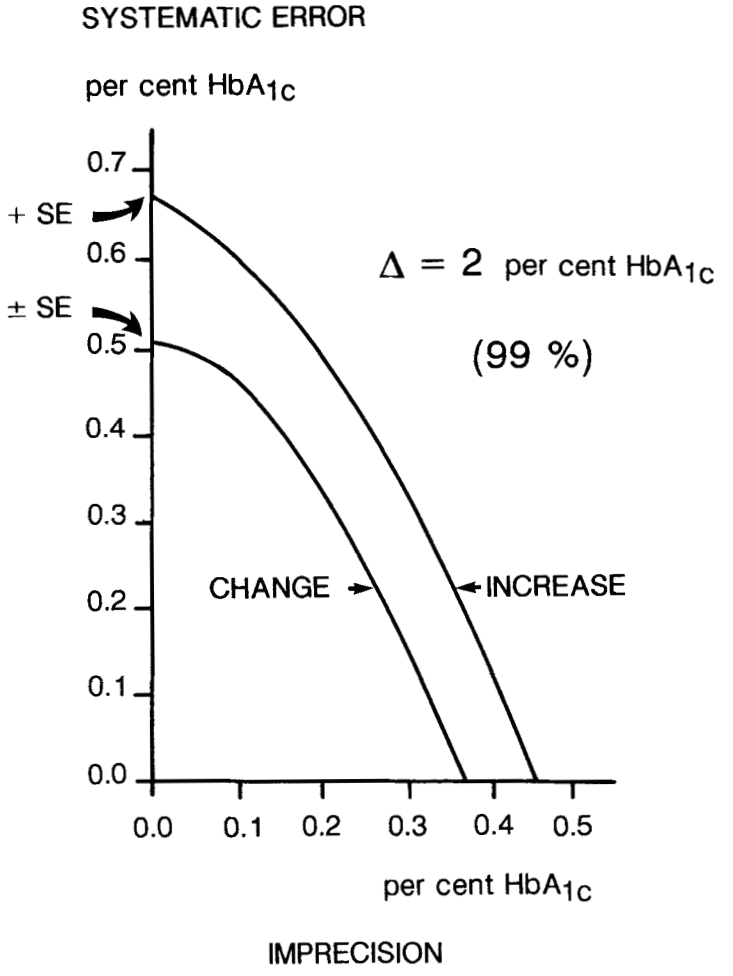
We can now assume that the analytical performance may increase the percentage of measured values above 7.5 percent HbA_{1c} from 10 to 20%. The one-tailed z- value is 0.84 and thus the maximum acceptable positive bias is 0.16 percent HbA_{1c} (from (1.28 - 0.84)* 0.41). Imprecision alone may be as large as 0.43 percent HbA_{1c} (from 0.84 $(0.41 + s2_A)^{\frac{1}{2}} = 0.50$). This gives us the maximum allowable bias (when $s_A = 0$) and the maximum allowable imprecision (when bias = 0). The maximum allowable combination has been elaborated.



INFLUENCE OF ANALYTICAL QUALITY ON MEASUREMENTS OF AN INCREASE IN PERCENT HbA_{1c} of 2.0

In evaluation at an increase between two measurements, the analytical bias may be considered insignificant, as long as analyses are performed in the same laboratory. Systematic error in the analytical performace in one of two measurements will influence on the measured difference. Therefore, both analytical imprecision and systematic error must be taken into consideration in the evaluation of the effects of analytical quality on the increase.

The clinician will react on a increase of 2.0 percent HbA_{1c}, so the probability of making mistakes due to analytical variation should be low, e.g. 1% (which gives a one-tailed z = 2.33).



When within-subject biological variation is 0.41 percent HbA_{1c}, s_A can be calculated from difference = 2.0 = 2.33 (2 * $(0.41^2 + S_{A2}))^{\frac{1}{2}}$, which gives a maximum allowable S_A = 0.44 percent HbA_{1c}. If the decrease in HbA_{1c} of 2.0 percent has a comparable consequence the z-value should be 2.58 (two-tailed) and here s_A would be 0.37 percent HbA_{1c}. The maximum combined analytical imprecision and systematic error has been elaborated,

and shows for the two-tailed situation and negligble imprecision a maximum acceptable systematic error of ± 0.51 percent HbA_{1c}.

DISCUSSION

The present evaluation illustrates the effects of analytical quality on the outcome of clinical strategies based on measurements of HbA_{1c}, and stress the need for specifications of analytical quality if optimal decisions should be achieved according to the clinical strategy.

However, each strategy should be analyzed in details as the needs for analytical quality are different in various situations. We found that the analytical bias was insignificant in the 'increase strategy' where imprecision and systematic error were the determining factors. In the other strategy, however, analytical bias was most demanding, only allowing a bias of 0.16 percent HbA_{1c}; a goal which is very difficult to fulfil (9, 10). It should be mentioned that in the latter situation as systematic error will have the same effect as bias as long as it persists.

Our assumption and our analysis of clinicians strategies may be questioned - and should be discussed. But the general approaches to evaluation of the needed analytical quality from clinical strategies are tools which can be used for analytical goalsetting, and when several different goals for analytical quality are obtained the most demanding should be used.

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