A REVIEW OF RESEARCH ON THE USE OF
DESK-TOP ANALYSERS FOR CHOLESTEROL SCREENING

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Introduction

The association between an elevated total serum cholesterol and an increased risk of coronary heart disease is well established and there has been much recent interest in cholesterol screening as a public health measure to identify high-risk individuals and refer them for appropriate treatment. Concurrent with this interest has been the development of portable desk-top analyzers which can rapidly measure total cholesterol in blood taken by means of a simple finger prick. This new technology offers the advantages of minimal patient discomfort, more convenient testing sites due to instrument portability, and the availability of test results within minutes which obviates the need for a return visit to discuss test results. A number of authors have suggested the use of of such analyzers to implement recommendations for general cholesterol screening, although the implications of this suggestion have not been fully discussed.[1-3]

This paper will examine the use of desk-top cholesterol measurement with respect to the reliability and validity of the results as well as the implications of this new technology for cholesterol screening in general.

1. Diagnostic test characteristics of cholesterol desk-top analyzers

There are two desk-top cholesterol analyzers available on the market for which information on their performance characteristics could be located: the Boehringer Mannheim Reflotron and the Abbott Vision analyzer.[1] Most of the published information refers to the Reflotron analyzer, and so this model will be examined in further detail.

Proponents of desk-top analyzers emphasize their practicality compared to laboratory testing where it is usually necessary for the patients to make a special visit to have their blood drawn. It is appropriate, therefore, to compare the total cholesterol results obtained using capillary blood in the Reflotron analyzer with results obtained from venous blood drawn at the same time and analyzed in a quality-controlled lipid laboratory. A number of

studies have carried out this comparison and found the correlation coefficients (r) between the two data sets to range from 0.92 - 0.99.[1,2,4] Reliability was assessed by calculating the coefficient of variation (100 x standard deviation/mean) for repeated analyses on the same sample; values for the Reflotron were 1-2% for trained technical personnel and 2-6% for untrained-personnel (such as medical office clerks and secretaries).[5] Few papers have examined the direction of any bias inherent in the Reflotron results and those that have report inconsistent results: Bachorik et al.[4] found the Reflotron values to be 1-4% lower than the laboratory values in two cities studied (with sample sizes of 107 and 275) , Jones et al.[7] found them to be 8% higher (but based on only nine samples), and another study by Bachorik's group found them to be 6% higher (sample size of 290).[6] No adequate explanation of this variation has been offered, but it may be due to the relatively small sample sizes involved in the studies and/or the variability that has been observed between reference laboratories (see later).

The above estimates of reliability and validity do not address the question of interest here which is the extent to which the Reflotron results misclassify people compared to the laboratory results. This is of particular importance since proposals for cholesterol screening call for certain cut-off values below which the individual is reassured and above which the individual is referred for further investigation and possible treatment. Only two studies permit an estimation of the sensitivity and specificity of the Reflotron measurement relative to the laboratory analysis of venous blood. Bachorik et al.[4] compared results from two Lipid Research Center laboratories that used Centers for Disease Control (CDC)-standardized methods with Reflotron desk-top results, and found the sensitivity of the Reflotron analyzer to range from 0.93 to 0.99 and specificity to range from 0.80 to 0.93 (using a cut-off of 5.2 mmol/L or 200 mg/dL). This particular cut-off was chosen since the National Cholesterol Education Program in the United States stated that desirable total cholesterol levels were those below 5.2 mmol/L, which is approximately the mean for the adult US population.[8] In a later study using the same cut-off level and a similar group of patients (those volunteering for cholesterol measurements as a result of community publicity), these same authors estimated the sensitivity to be 0.95 and the specificity to be 0.73.[6] The authors were not able

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to explain this difference in specificity, but it is likely related to the reasons mentioned above for the difference in the direction of bias.

If one assumes these test characteristics are constant for different cut-off levels (different prevalences of "high" total cholesterol), then the predictive value of this desk-top analyzer may be assessed relative to the laboratory. For example, the Canadian Consensus Conference on Cholesterol[9] recommended intervention when cholesterol values exceed 6.2 mmol/L, which is approximately the 75th percentile for the adult Canadian population.[8,10] Using a sensitivity of 0.95 and a specificity of 0.8 (the approximate means of the estimates in Bachorik's two papers[4,6]), one may calculate a positive predictive value of 61.3% and a negative predictive value of 98% (since the prevalence of "high" cholesterol is about 25%). That is, 61% of the results judged to be high by desk-top analysis would be judged high on laboratory analysis, and conversely 98% of the low desk-top results would also be low on laboratory analysis. Furthermore, 39% of the adult population would be identified as having "high" total cholesterol rather then the laboratory-determined prevalence of 25%.

2. Cholesterol screening programs in general

There are a variety of current recommendations for the implementation of cholesterol screening. For example, the National Cholesterol Education Program (NCEP) in the USA recommends screening for all adults over the age of 20 and drug therapy for those with LDL cholesterol above 4.9 mmol/L (approximately above a total cholesterol of 6.2 mmol/L).[8] The Canadian Consensus Conference on Cholesterol (CCCC) recommends screening for all adults over the age of 18 as resources permit, and recommends drug therapy for those with cholesterol levels persisting above 6.2 mmol/L after six months of intensive dietary therapy.[9]

However, before one can consider the impact of desk-top analyzers on these recommendations for cholesterol screening programs, it is necessary to first address the issues involved in cholesterol screening when laboratory measurements are used to determine total serum cholesterol. A recent

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review of asymptomatic hypercholesterolemia by the Toronto Working Group on Cholesterol Policy[10] examined this question in detail and the main issues may be summarized as follows:

a. There are recognized difficulties in standardization and quality control between laboratories regarding the measurement of total serum cholesterol. For example, a 1988 survey of laboratories in Ontario found a range of measurements of 4.64-7.72 mmol/L for a reference value of 6.67 mmol/L.[10] It was further estimated that for a patient with a total serum cholesterol of 6.5 mmol/L, the range required to encompass 95% of the results from the different laboratories would be 6.0-7.0 mmol/L.

Such sources of inaccuracy may be due to imprecision or bias. The precision in Ontario laboratories appears fairly good; a 1984 survey found a mean coefficient of variation of 4% (the suggested "acceptable" level is ≤5% and "ideal" is ≤3%).[10] Bias, on the other hand, is more variable and depends not only on the type of analytic machine used, but also on the particular laboratory using the machine. For example, American labs using the Dupont-ACA machine reported values ranging from 15% below to 3% above the value obtained by a Lipid Research Centre reference laboratory, and Technicon-SMAC results varied from 5% below to 12% above the reference value.[10] As a result, the Toronto group recommended the establishment of a number of lipid reference laboratories to improve standards and quality control to reduce the problems associated with misclassification. In addition, it is important to note that for any given degree of imprecision and bias, the lower the threshold value for diagnosing "high" cholesterol, the greater the absolute number of persons who will be misclassified since a larger proportion of the population will have cholesterol values close to the the cut-off level.

b. Even assuming no laboratory error, there is still a great deal of variation in the relationship between total serum cholesterol and subsequent coronary heart disease (CHD). Data from the MRFIT trial indicate that middle-aged men in the top 20% of the serum cholesterol range (approximately greater

than 6.7 mmol/L) have a 0.7-2.2% chance of dying from a CHD event over the next six years, which is approximately double the chance for those in the lower 80% of the range.[10] If one then uses 6.7 mmol/L to divide men into high- and low-risk categories, the sensitivity would be 0.35-0.40 and the specificity 0.72-0.83 for predicting CHD mortality over the next six years.[10] Assuming from the above that the cumulative incidence of coronary mortality over a six-year period for a group of middle-aged men is 1%, then an individual with a positive test (serum cholesterol greater than 6.7 mmol/L) would have about a 1.7% chance of experiencing such mortality (1.7% positive predictive value). A person with a negative test would have approximately a 0.8% chance (99.2% negative predictive value).

A similar picture results if one examines prediction of CHD morbidity. Using a cut-off of 6.7 mmol/L to predict morbidity over the next six years, total serum cholesterol has a sensitivity of approximately 0.35 and specificity of 0.85 [10] Assuming the cumulative incidence of coronary morbidity over a six-year period for middle-aged men is about 5% (value estimated from MRFIT data and data from UK Heart Disease Prevention Project presented in Naylor et al[10]), then an individual with a positive test would have an 8.4% chance of experiencing such morbidity. A negative test would confer a risk of about 4% (96% negative predictive value).

It is clear from these calculations that using a cut-off value of 6.7 mmol/L for serum cholesterol does not differentiate well between those who will and those who will not experience CHD morbidity and/or mortality. This problem of poor predictive value is not solved by changing the cut-off level: a higher cut-off would improve specificity but reduce sensitivity (more false negatives) and a lower cut-off would do the reverse (more false positives). Furthermore, the main problem with a high cut-off is that it would have little impact on the population burden of coronary heart disease, while a low cut-off would involve further diagnostic work-up and possibly treatment of many people never destined to get coronary heart disease.

It is evident, therefore, that even with a perfect laboratory test for total serum cholesterol, there are many problems associated with using such measurements as guides to further work-up and treatment in an attempt to reduce CHD mortality and morbidity. Extensive research efforts are currently underway on other serum lipids (most notably high density lipoprotein or HDL) to find measurements that are more predictive of CHD events.

c. Even if coronary morbidity could be accurately predicted using total cholesterol measurements, there is still the question of whether treatment is effective. A number of studies have convincingly shown that cholesterol-lowering drug therapy (and to a lesser extent dietary therapy) in middle-aged men with high cholesterol levels (e.g. above 6.85 mmol/L) can lower subsequent CHD morbidity and mortality. However, there are several important caveats here. Firstly, because of the above-mentioned misclassification and prediction problems, many men will have to be treated for many years in order to prevent one CHD event. Men treated unnecessarily will likely experience inconvenience, treatment side-effects and "labelling" which means they may feel and/or act unwell simply because they have been told they have high cholesterol. Secondly, the same studies which demonstrated a reduction in CHD mortality did not show a reduction in all-cause mortality. While the explanation for this is still not agreed upon, the experimental data available at present indicates that cholesterol-lowering therapy does not reduce overall mortality, at least in the short-term (five years). Thirdly, the effect of cholesterol-lowering therapy on overall morbidity cannot be assessed since these studies did not ascertain non-CHD morbidity. And finally, no studies have examined the effectiveness of treatment in women, younger men or older men.

In summary, a minority of the middle-aged treated for hypercholesterolemia will benefit in terms of reduced CHD morbidity and/or mortality , but even these individuals may not experience reduced overall morbidity or mortality.

d. Even if one could solve the above problems, there still remains cost and feasibility problems associated with any proposed program. Cost-effectiveness analyses of using drugs to treat all Canadian men in the 90th percentile for total serum cholesterol (>7.75 mmol/L) indicate that the costs would be $100,000-200,000 per life-year saved (assuming overall mortality reduction is similar to CHD mortality reduction).[10] This is extremely high compared to other CHD interventions: $20,000 per life-year for treatment of moderate and severe hypertension and $14,000 for coronary bypass graft surgery for 3-vessel disease.[10] Furthermore, implementing the screening programs suggested by NCEP or CCCC would overwhelm practitioners and laboratory facilities with the demand for counselling and blood analyses.

In view of all of the above, the basic recommendations of the Toronto Working Group were twofold. Firstly, instead of general screening, a case-finding approach in physicians' offices should be adopted where cholesterol testing is done only on those with CHD risk factors (such as smoking, elevated blood pressure, diabetes, etc). Those remaining in the 90th percentile after intensive dietary therapy should be considered for drug therapy only after they are fully informed regarding the benefits and risks of such therapy. And secondly, to reduce the population burden of CHD a population strategy is recommended whereby public health campaigns reinforce appropriate diet and lifestyle changes.

3. The effect of desk-top analyzers on recommendations for cholesterol screening

The main advantage of desk-top cholesterol analyzers is the provision of quick, convenient results in the physicians office. This advantage may help address some of the concerns regarding the overloading of laboratory facilities that were raised with respect to general screening. However, this advantage comes at the cost of increased misclassification. On top of the poor predictive value of a truly high cholesterol value, there is the problem of the accurate

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measurement and classification of this value. Even in large laboratories staffed by professionals there are difficulties in obtaining reliable, valid cholesterol results. Together these two facts lead to a very low positive predictive value (8.4%) and a relatively low negative predictive value (96%) when trying to predict future CHD events using a cut-off of 6.7 mmol/L for total cholesterol measured in quality-controlled laboratories (see section 2b). Furthermore, there is the additional problem with desk-top analyzers of the extra misclassification caused by using these devices to estimate laboratory measurements. At present, there is insufficient data in the literature to allow the combination of these two sets of diagnostic characteristics to estimate the accuracy of prediction of future CHD events based on desk-top results (especially need data on the degree of independence of the two tests). One may estimate, however, that using a cut-off of 6.7 mmol/L for desk-top measurements to predict future CHD events, the sensitivity would be approximately 0.30-0.35 and the specificity 0.70-0.80. The resulting predictive value of a positive test would be 6.4% and the predictive value of a negative test would be 95.5%. Thus, in exchange for patient convenience, the use of desk-top analyzers would worsen an already significant misclassification problem.

Proponents of desk-top analyzers argue that they are useful for general cholesterol screening if used as a preliminary screening tool. Since their misclassification errors appear to be primarily false positives rather than false negatives (low specificity, high sensitivity), few people with high cholesterol would be missed and the false positives could be detected at follow-up laboratory testing. Using figures presented in section 1 of this report and a cut-off of 6.2 mmol/L (75th percentile), for every 100 people presenting for general cholesterol screening the use of desk-top analyzers would send 39 for laboratory testing and reassure 61 that there cholesterol was not high enough to warrant further testing. Compared to general screening using laboratory measurements from the start, the desk-top approach would have certain advantages and disadvantages. The advantage is that 61 people would be reassured with the use of a more convenient and probably less expensive test. The disadvantages are that one or two of these 61 people would be falsely reassured (they would have high cholesterol values on laboratory testing) and that 39 people have had an unnecessary finger-prick blood test done (since

they would have gone for laboratory testing anyway in the scheme using laboratory testing initially). Which choice is preferable will depend on the relative cost of the two tests and the value to the patients of an office test which may obviate the need for a laboratory test.

Note, however, that this presupposes the bias in desk-top analyzers leads to consistent overestimation of total cholesterol, and insufficient studies of these analyzers have been done to confirm this. In addition, the question of quality control still remains: how would the analyzers be standardized and maintained, and what level of training would the operators have?

Whichever cholesterol screening program one prefers, there may be a place for desk-top analyzers to perform a convenient, preliminary test. Additional data is needed, however, before such a recommendation can be made with any confidence. In particular, information is needed in the following areas: (1) the costs of desk-top versus laboratory analysis; (2) the value to patients of having a convenient test that may mean they do not require a more inconvenient, invasive test; (3) the precise diagnostic test characteristics of desk-top analyzers relative to laboratory testing; and (4) how quality control issues will be addressed for desk-top analyzers. Clinicians would also have to be careful that the ease and availability of desk-top cholesterol analysis does not influence them to screen people who are not eligible for the screening program.

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