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If apoB is so good, why isn't everybody measuring it?

One reason why we need the Netherlands Journal of Medicine!

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INTRODUCTION

I recently had the privilege of giving a state-of-the-art lecture on the clinical value of apoB to the residents and staff of the Department of Internal Medicine of the Radboud University Nijmegen Medical Centre after which residents reviewed two recent key papers: the Northwick Park Heart Study[1] and the INTERHEART study.[2] One resident concluded his analysis with the question: if apoB is so good, why isn't everybody doing it?

All at once, I felt everyone's eyes on me: such a simple question, such a difficult answer. My answer was inadequate then and will almost certainly be inadequate now. But I know it is tied in some way to another question: Why do we need a journal such as the Netherlands Journal of Medicine?

I am going to try to answer both: the first by listing the relevant facts, the second by suggesting that we in modern academic medicine are less secure and less confident intellectually than we used to be. The remedy, I believe, is to rediscover our own strengths and by doing so to recover our independence. One way to do so is to encourage independent analyses of major issues in journals such as this.

APOLIPOPROTEIN B *VERSUS* CHOLESTEROL

What is plasma apoB?

Each atherogenic particle – that is to say, each VLDL, IDL, LDL and Lp(a) particle – contains one molecule of apoB100[3] Each chylomicron and chylomicron remnant particle contains one molecule of apoB48. All the standardised, automated assays that measure total plasma apoB recognise both apoB100 and apoB48. However, except in type III hyperlipoproteinaemia, there are so few apoB48 particles present in plasma, even during the peak postprandial period, that total apoB is not affected. This means that for clinical practice apoB does not have to be measured fasting, but can be determined at the patient's convenience. LDL, the most important of the atherogenic particles, account for more than 90% of total plasma apoB particles and so LDL particle number is the principal determinant of the atherogenic particle number.

What is the evidence that apoB is better than any of the other cholesterol indices for estimating the risk of vascular disease?

The evidence is overwhelming. To be sure, the initial generation of cross-sectional and nested case-control studies yielded mixed results, in part because the assays were not standardised, in part because the wrong question was asked (Did the indices being compared predict haemodynamically significant coronary disease – which is not the issue – *vs* just anatomic coronary disease – which is? Did apoB predict better than all the lipids combined including HDL – which is not the test? And finally, the initial types of studies – both cross-sectional and nested case-control studies – generate but do not establish hypotheses).

But time and knowledge have advanced. Multiple, large, prospective epidemiological studies are now in hand and the results are straightforward: apoB is superior to any of the cholesterol indices to predict the likelihood of vascular events. The Quebec Cardiovascular Study was the first of these,[4] followed by the THROMBO Study,[5] the AMORIS

Study,[6] the Northwick Park Heart Study,[1] the THROMBO Metabolic Syndrome Study[7] plus the placebo arms of a number of the statin clinical trials, including 4S,[8] AFCAPS/TexCAPS,[9] and LIPID.[10] Not only has apoB been shown to be better than any of the other cholesterol indices, the apoB/apoA-I ratio has also been shown to be superior to the other cholesterol indices – TC/HDL C, non-HDL C/HDL C, and LDL C/HDL .[5,9-11] The list of citations should be long enough and broad enough to justify the judgment at the beginning of this paragraph that the weight of evidence in favour of apoB as a predictor of vascular disease is, in fact, overwhelming.

What is the evidence that apoB is better than LDL C for judging the adequacy of statin therapy?

Depending on which analysis is examined, either LDL C or apoB was superior in the 4S study, the statin study in which cholesterol levels were highest.[12] However, there is no ambiguity in AFCAPS/TexCAPS[9] the Leiden Heart Study,[13] and LIPID.[10] On-treatment apoB was predictive of outcome, whereas on-treatment LDL cholesterol was not. Moreover, there is evidence for superiority of apoB over LDL cholesterol in CARE[14] and FATS.[15,16] Interestingly, a number of fibrate trials produced the same result. In the Bezafibrate trial, apoB was predictive of progression of coronary disease, whereas LDL cholesterol was not.[17] The same was observed in the DAIS trial.[18] Finally, when LDL particle number was estimated by nuclear magnetic resonance, a decrease in LDL particle number was shown to contribute to benefit in the VA-HIT trial, whereas there was no evidence that benefit correlated with a change in LDL cholesterol (Jim Otvos, personal communication). Non-HDL cholesterol has been proposed as a surrogate for apoB. However, while they are highly correlated, they are not highly concordant. That is, for any value of one, there is a considerable range of values for the other.[19] Moreover, the available evidence from epidemiological studies, noninvasive studies and clinical trials indicates that apoB is superior to non-HDL cholesterol as a marker of the risk of vascular disease and as an index of the adequacy of LDL-lowering therapy.[9-11,13,20-22] Finally, apoB is more closely associated with the other markers of the metabolic syndrome than either LDL or non-HDL cholesterol.[19, 23]

Why is apoB superior to any of the cholesterol indices for estimating risk and assess the adequacy of therapy?

Each atherogenic particle has one molecule of apoB; except for type III hyperlipoproteinaemia, LDL make up the vast majority of these, more than 90%.[24,25] Thus the first major advantage of apoB over LDL cholesterol is that it counts all the atherogenic particles, not just the majority of them. But the gain is much greater than this. The amount of cholesterol in LDL particles can vary substantially and so LDL cholesterol does not necessarily equal LDL particle number.[26-29] The discrepancy can be deadly in patients with predominantly small dense cholesterol-depleted LDL particles. In such patients, LDL cholesterol necessarily underestimates LDL particle number and the error is frequently substantial.[20]

Small dense LDL tend to be the rule with triglycerides >1.5 mmol/l, but the actual apoB cannot be guessed from the calculated LDL cholesterol.[27] Moreover, there is no triglyceride level that ensures small dense LDL are not present. Exceptions abound and no doctor should be confident the patient in front of him or her is not one more exception to a very porous rule. Indeed, the lipid profile may reveal normal plasma triglycerides and LDL cholesterol with low HDL cholesterol. But even in these patients, the apoB may be high or normal.[30] Skip apoB; miss the diagnosis. Skip apoB and therapy may be inadequate.

WHY DO WE NEED THE NETHERLANDS JOURNAL OF INTERNAL MEDICINE?

Listing the evidence that apoB is superior to any of the cholesterol indices is the easy part. Now I must turn to the difficult part: the resident's question, the audience's question, my question. If apoB is so much better, why isn't everybody doing it – or more accurately, why are so few doing it? The answer, if there is one, lies in understanding what governs modern medical decision-making. Many would say that the mark of modern medicine is that what we do is evidence based, by which they mean that what we do is the outcome, so far as possible, of the results of rigorously conducted clinical studies and clinical trials. It is the facts that direct us, nothing more, nothing less.

But is that the real sequence or is there another step that is decisive? Is it the bare and unadorned results from the studies that govern us or is it the interpretation and authorisation by 'expert' groups that really counts? How many of us have read the actual results of a study as opposed to the minimalist summary contained in a review by an 'expert'? For that matter, how many 'experts' really understand all the methods in the studies they review so often and so glibly? How many 'reviews' analyse methods and results, critique design and statistics, discuss opposing interpretations as opposed to merely presenting lists of positive *vs* negative?

Our present is different from our past.

As a young doctor, what I was taught and what we did in the hospital where I trained was based on my teachers' interpretation of the evidence which, in turn, was the

outcome of the interplay between the evidence of others and their own scholarly work. The academic faculty was made up of clinician-researchers. They were doers, analysers, innovators as well as appliers. They had the confidence to fulfil their responsibility as academics to measure the strengths and the weaknesses of new proposals. They could do so largely because they were integrally connected to the world from which change came.

Over the past 40 years, the clinician-researcher model – at least in North America – has been largely torn apart and discarded. Now clinicians may do some research, but they are not confident, and they do not love it. Their greatest commitment is to clinical trials, designed by others, organised by others, and interpreted by others. This is not to diminish the value of clinical trials, but in my opinion, except for the leadership, participation does not equal academic work.

There are clinician-scientists, although in ever-diminishing numbers. Their work is mainly fundamental. Such physician-researchers may do some clinical work, but often only when they must and frequently as little as possible. Research is now almost blind to the insights into biological regulation and dysregulation that can only come from clinical experience.

This loss of expertise has another critical consequence. We have surrendered the right my teachers had – the right to analyse and judge for ourselves. The rate at which medical knowledge has expanded has far outpaced the rate at which we have converted these facts to useful medical knowledge. This second step – conversion of facts to knowledge – is why I believe we need journals such as the Netherlands Journal of Medicine, which represent the broader rather than the narrower medical community.

Cholesterol is the most scientifically decorated word in modern medicine in that more Nobel prizes have been awarded for the study of this molecule than any other. Just as the one word 'penicillin' encompasses the transformation of infectious disease, so cholesterol, for both the profession and the public, has become the symbol of our mastery of vascular disease. But cholesterol is only a word and words have only assigned meanings and not intrinsic values. Cholesterol does not have to remain pre-eminent for order to exist in the universe. Which patient or physician would not choose change if change represents life rather than death?

What conclusion do I hope the reader will draw from this article? Only this: that perhaps we should not leave the evaluation of evidence entirely to the 'experts'. The 'experts' are not always right. We have innumerable examples in areas other than medicine (don't weapons of mass destruction and Iraq immediately come to mind?) when the 'experts' were absolutely confident, but utterly – and tragically – wrong. There is nothing so unique about our discipline that immunises it against similar error. As more and more issues come on the table, the competence and breadth of the expert, both intellectually and clinically, too often becomes more and more miniaturised and the result can be an awful gap between their conclusions and reality.

Is there an alternative? I think I saw one in Nijmegen: local analysis by a general internal medicine group that had the expertise and confidence to assess the merits of specific claims. They were a good and fair jury of the facts. Could the Netherlands Journal of Medicine be a formal multiplier of these values? Why not? The scientific process must be pluralistic to operate effectively.

Our best-known medical journals do much well. But intentionally or not, they have become high-earning vehicles competing for our attention. Profit is a major, sometimes perhaps a dominant, objective. Growing brand names are unquestionably a major objective. Our top line medical journals compete to publish the latest, largest clinical trials and their issues are replete with advertising. They assail others such as the pharmaceutical industry for their errors – as they should – but how developed are their processes to deal with errors that appear in the articles they publish? If we absolutely need post-marketing surveillance for medications, don't we also absolutely need post-publication surveillance for scientific articles? How confident are we that our best journals have made this commitment and that they are acting on it. Moreover, at least in cardiology, most of the major journals are controlled by the major professional societies. The guidelines from these societies appear automatically in their journals. How often do any critiques of these guidelines appear beside them? Given that guidelines often become public policy, how healthy is that relationship?

Globalisation of science should not – must not – mean homogenisation of opinion. The only antidote is to enlarge the presentation of reasoned opinion. The problems we face are difficult. The solutions – if there are such things – are not easy to find. That is why I am convinced that we need more, not fewer, avenues of medical expression. That is why I am proud to have the opportunity to publish my answer to the resident in Nijmegen in the Netherlands Journal of Medicine.

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