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Avogaro P, Bittolo Bon G, Cazzolato G & Quinci G B. Are apolipoproteins better discriminators than lipids for atherosclerosis? *Lancet* 1:901-3, 1979.
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The assay of plasma cholesterol and/or lipids has been for decades the only approach to the clinical discrimination between atherosclerotic patients and healthy people. This paper offered the first approach to the utilization of the protein part of lipoproteins, namely, apolipoproteins B and A-I. Our results have been confirmed nearly unanimously. The paper appears, therefore, to be a relevant contribution to the understanding of the clinical role of apolipoproteins. [The *SCI*® indicates that this paper has been cited in over 265 publications.]

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The exponential curve relating the prevalence of coronary heart attacks to the cholesterol plasma levels makes the epidemiologist happy. Clinicians, however, are faced with actually treating sick men rather than dealing with "large numbers." Working in a hospital, we were interested more in the events occurring in people belonging to the "low" segment of the curve than to the "high" segment. Why did so many coronary events occur in subjects having plasma cholesterol levels situated largely below what was then considered to be a "safety" cut-off point? We thought that we had to face three possible explanations: 1) the "low" segment of the curve is overcrowded, 2) the "cut-off" point for a normal cholesterol level is too high (at that time it was 260 mg/dl), or 3) in the lipoprotein particles, components other than lipids could be significant. We decided to focus on possibility number 3.

Why was the protein counterpart of lipoproteins so neglected despite its relevant role in lipoprotein structure and function? An explanation could be found in the technical difficulties in performing an assay of the protein part of lipoproteins. We were lucky that the electroimmunoassay,[1] which turned out to be easy to perform and reproduce, was introduced just at that time. We couldn't, however, readily acquire the necessary antisera. Gerhard Kostner from Graz kindly supplied us with the immune sera, so we could then start our work. We thought that the survivors of myocardial infarction would represent a good group to be tested; J.L. Goldstein and colleagues[2] previously had chosen a group of survivors of myocardial infarction to verify some clinical aspects of the lipid hypothesis.

After we collected and analyzed our data, it appeared that apoB was the best discriminator between survivors and controls and that the ratio apoB/apoA-I had the best absolute discriminating power. Our work received nearly unanimous confirmation, including results from groups studying patients whose disease was coronarographically proven. Our work contributed to the understanding of the clinical role of apolipoproteins.

In the following years, A. Sniderman and colleagues[3] described patients affected by ischemic heart disease (IHD) as characterized by an isolated increase of apoB (hyperapoprebetalipoproteinemia) and by a high ratio apoB/apoC. Later, C. Vergani and G. Bettale[4] described a family with higher than normal prevalence of IHD and characterized by the deficiency of apoA-I (hypoalphalipoproteinemia). It was also observed that there are patients affected by premature coronary heart disease whose plasma levels of low-density-lipoprotein cholesterol and apoB are normal but who show a synthetic rate of apoB that is significantly higher than normal.[5] How the high flux of apoB may be atherogenic is still unclear. A significant understanding of the clinical role of apolipoproteins, however, has been achieved.

1. **Curry M D, Alaupovic P & Suenram C A.** Determination of apolipoprotein A and its constitutive A-I and A-II polypeptides by separate electroimmunoassays. *Clin. Chem.* 22:315-22, 1976. (Cited 280 times.)
2. **Goldstein J L, Hazzard W R, Schrott H G, Bierman E L, Motulsky G, Levinski M J & Campbell E D.** Hyperlipidemia in coronary heart disease. I. Lipid levels in 500 survivors of myocardial infarction. *J. Clin. Invest.* 52:1533-43, 1973. (Cited 400 times.)
3. **Sniderman A, Shapiro S, Marpole D, Skinner B, Teng B & Kwiterovich P O.** Association of coronary atherosclerosis with hyperapobetalipoproteinemia (increased protein but normal cholesterol levels in human plasma low density (B) lipoproteins). *Proc. Nat. Acad. Sci. USA* 77:604-8, 1980. (Cited 195 times.)
4. **Vergani C & Bettale G.** Familial hypo-alpha-lipoproteinaemia. *Clin. Chim. Acta* 114:45-52, 1981. (Cited 40 times.)
5. **Kesaniemi Y A & Grundy S M.** Overproduction of low density lipoproteins associated with coronary heart disease. *Arteriosclerosis* 3:40-6, 1983. (Cited 25 times.)