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PROMOTING HDL FUNCTION VIA INTRAVENOUS INFUSION - THE REBIRTH OF APOA-I MILANO?

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Abstract:	

**PROMOTING HDL FUNCTION VIA INTRAVENOUS INFUSION – THE REBIRTH OF APOA-I
MILANO?**

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attending advisory boards and giving lectures.

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1 The apolipoprotein A-I (apoA-I) is the major protein component of the high-density
2 lipoprotein (HDL) particles. Higher levels of apoA-I have been associated with a lower
3 cardiovascular risk even among subjects with reduced low-density lipoprotein cholesterol
4 (LDL-C) levels^{1,2}; but, unlike HDL-C, an increase in apoA-I levels in individuals treated with
5 statins has been associated with a lower risk of major cardiovascular events². These and
6 other data have encouraged investigations of apoA-I mimetic compounds or reconstituted
7 HDL particles as a potential therapeutic strategy. The ApoA-I Milano (apoA-IM) is a natural
8 variant of human apoA-I identified in individuals in northern Italy that results from the
9 replacement of arginine by cysteine at position 173 of the apoA-I amino acid sequence³; this
10 variation introduces structural changes in apoA-I, allows the formation of apoA-I
11 homodimers (A-IM/A-IM) and heterodimers with apoA-II, and alters the apoA-I properties,
12 which ultimately may affect HDL function³. The carriers of this variant usually exhibit a lipid
13 phenotype consistent of low HDL-C, low apoA-I and moderate hypertriglyceridemia;
14 however, despite a lipid profile which may be considered to be pro-atherogenic, apoA-IM
15 seems to confer the carriers protection against the development of atherosclerosis and
16 cardiovascular disease (CVD)³.
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42 These observations have been supported by studies in animals, where the
43 intravenous administration of recombinant apoA-IM has been associated with an
44 improvement of endothelial dysfunction⁴, reduction of vascular lesions⁵, prevention of
45 atherosclerosis progression⁶, plaque regression and stabilisation⁷ and antithrombotic
46 effects⁸, among others. In humans, a randomized controlled trial in patients with acute
47 coronary syndrome (ACS) found a significant regression of coronary atherosclerosis after
48 treatment with intravenous infusions of apoA-IM/phospholipid complex (ETC-216, 5 once-
49 weekly infusions), as measured by intravascular ultrasound⁹. In animals, the intramural
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1 administration of the same compound (ETC-216) in coronary arteries before stent
2 placement (injury-induced luminal narrowing) significantly inhibited in-stent stenosis
3 through reduction of intimal hyperplasia¹⁰.
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8 Interestingly, apoA-IM has been associated with an increased capacity of HDL
9 particles to act as extracellular acceptors of cholesterol efflux from cells, which represents
10 one of the first steps in the reverse cholesterol transport. In this way, apoA-IM may enhance
11 the removal of excess cholesterol from the arterial wall and this may explain, at least partly,
12 the protective effect of apoA-IM. Early studies found that cholesterol efflux to sera from
13 apoA-IM carriers was as efficient as sera from control subjects (despite the large reduction
14 of apoA-I and HDL levels in the former), thus suggesting a higher relative apoA-I efflux
15 potential in those carrying the apoA-IM variant¹¹. Calabresi et al further showed that small
16 A-IM/A-IM reconstituted HDL particles were more efficient than the corresponding apoA-I
17 particles as acceptors of membrane cholesterol³. Similarly, a single intravenous high-dose of
18 recombinant apoA-IM in high cholesterol-fed apoE-deficient mice rapidly induced a nearly 2-
19 fold increase in cholesterol efflux capacity compared to controls¹². And Cimmino et al
20 described a decrease in cholesterol content associated with an up-regulation of the arterial
21 wall transporters ABCA1 and SR-R1 in aortas from rabbits treated with recombinant apoA-
22 IM¹³.
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48 In the present issue, Kallend et al report the results of a phase I randomized trial
49 using a single 2-hour infusion of highly purified apoA-IM (MDCO-216, apoA-IM/POPC) vs.
50 placebo in 24 healthy volunteers (mean age 26 years, n=10 males) and 24 stable coronary
51 artery disease (CAD) patients (mean age 62 years, n=23 males). The administration of
52 MDCO-216 rapidly increased apoA-I levels in a dose-dependent manner and was followed
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1 by a change in the lipid profile resembling that previously described in apoA-IM carriers: a
2 decrease in HDL-C and endogenous apoA-I (both more pronounced at higher doses and in
3 CAD patients) and a dose-dependent increase in triglycerides. Additionally, LDL-C decreased
4 in CAD patients with the higher doses, and apoB increased and apoE decreased in both
5 healthy volunteers and CAD patients. Importantly, the markers of HDL function were
6 enhanced with MDCO-216; in agreement with the previous findings, MDCO-216 significantly
7 increased (up to 4-fold with the highest doses) the ABCA1-mediated cholesterol efflux
8 capacity (CEC) in a dose-dependent manner in both groups; this increase was independent
9 of the baseline values, was maximal at the end of the infusion and decreased over time to
10 reach baseline levels at day 7. SR-BI-mediated CEC also increased dose-dependently but
11 modestly, and returned to baseline 24 hours after the infusion. ABCG1-mediated CEC
12 slightly increased without a clear dose-dependency. Finally, pre β 1-HDL (lipid-poor very small
13 HDL particles, acceptors of cholesterol effluxed by ABCA1) significantly increased in a dose-
14 dependent manner and returned to baseline levels at 24 hours. MDCO-216 was well
15 tolerated and considered safe.

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These results support (1) the enhancement of cholesterol efflux and cholesterol reverse transport as the mechanisms by which apoA-IM may exert its protective effect, (2) the importance of HDL function rather than HDL-C levels, and (3) the potential role of apoA-IM as a therapeutic strategy to reduce cardiovascular risk.

Whilst CEC has been inversely associated with the incidence of cardiovascular events in population based-studies^{14,15}, it is still uncertain whether pharmacologically mediated increases can be translated into a reduction in cardiovascular risk. In fact, therapy with another class of compound which inhibits cholesteryl ester transfer protein (CETPi) have all

1 led to significant increases in CEC (together with significant increases in apparently
2 functional HDL levels); however, this has not resulted in a reduction of cardiovascular
3 events¹⁶: in ILLUMINATE trial, with most participants having CVD, torcetrapib was associated
4 with an increased morbi-mortality; the dal-OUTCOMES trial in patients with ACS was
5 stopped for clinical futility of dalcetrapib; and very recently, the ACCELERATE trial with
6 evacetrapib for high-risk atherosclerotic CVD has been discontinued due to insufficient
7 efficacy¹⁷. Whether increases in cholesterol efflux mediated mostly by ABCA1 after the
8 administration of apoA-IM might exhibit different cardiovascular effects rather than the
9 increased CEC resulting from CETPi (mostly mediated via non-ABCA1) is unknown.
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24 The results reported by Kallend et al are preliminary but promising and should
25 encourage further confirmation in larger randomized trials assessing the effects of MDCO-
26 216 on atherosclerosis and cardiovascular outcomes. Its intravenous administration and the
27 duration of the effects suggest that it might be more suitable for patients with acute or
28 unstable CVD (rather than giving repeated infusions over time in subjects who are otherwise
29 stable).
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