Paolo Maggi, Chiara Bellacosa, Francesca Lenoci, Gioacchino Angarano, Giovanna Trillo

HAART and Cardiovascular Toxicity: a Chapter to Rewrite?

Institute of Infectious Disease - University of Bari Policlinico

Corresponding author: Paolo Maggi, MD
Institute of Infectious Disease - University of Bari Policlinico
Piazza Giulio Cesare 11, 70124 Bari (BA) Italy
Tel.: +39 080 5592134 - E-mail: P_maggi@yahoo.com

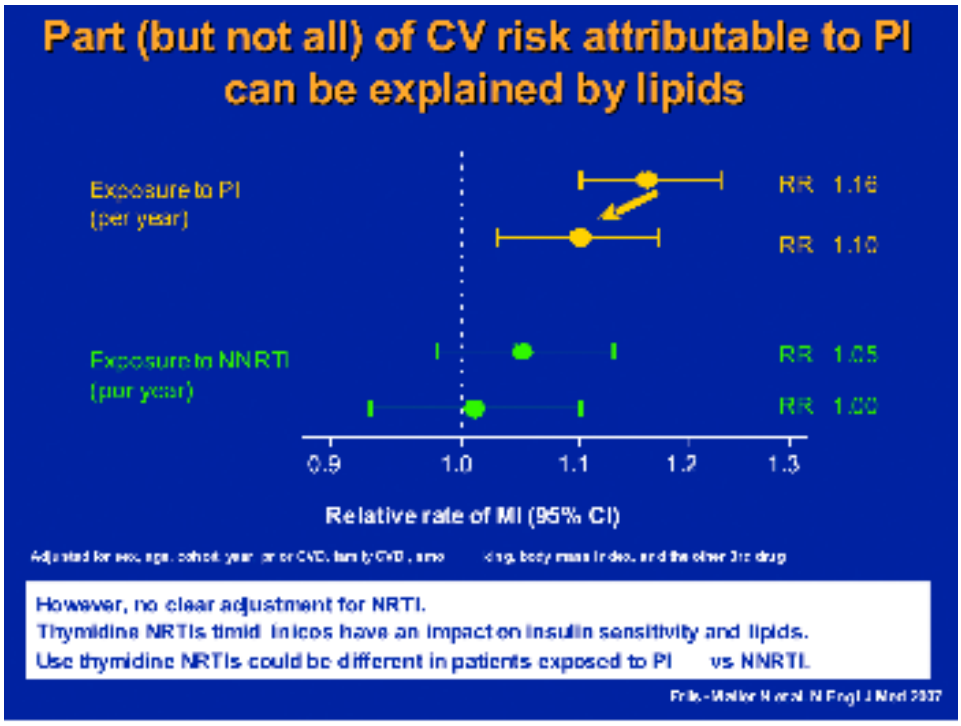
HAART currently springs to mind when cardiovascular problems arise in HIV infection. In actual fact, cardiovascular diseases were encountered in HIV patients well before the advent of antiretroviral drugs, but prior to the HAART era they were mainly opportunistic infections or AIDS-related tumours involving cardiac tissues [1,2].

Twelve years have gone by since the first warning at the outset of HAART in a letter published in the *Lancet* [3]. But how could HAART give rise to coronary artery disease? At the time it was already clear that PI could raise total cholesterol, LDL, and diminish HDL [4]. So the initial equation was: *drug-induced dyslipidemia equals an increased risk of acute coronary artery disease*. In fact, the cardiovascular risk is typically multifactorial: if raised blood cholesterol levels play an important role, other factors have recently emerged as "new" risk factors, first and foremost chronic inflammatory diseases.

Disregarding the fact that the problem is likely to be complex and articulated, infectivologists have long pursued to initial hypothesis: given their effect on blood lipids potential, are PIs directly correlated to the increased cardiovascular risk? For many years results have been contradictory. Although data emerged from megacohorts like the Kaiser Permanent, Veteran Affairs, HOOPS and other studies, it wasn't until the results of the D:A:D study, a megacohort specifically designed in 1999, that solid reference data became available in 2007 [5]. It appeared from the D:A:D study that the risk of coronary artery disease was proportional to the period of exposure to protease inhibitors. Subsequent issues of D:A:D has identified certain PIs like indinavir, or lopinavi/ritonavir as carrying a greater risk [6].

But, again, what is the mechanism underlying this increased coronary risk? Can a few score milligrams more or less cholesterol explains this event in the context of a disease like a heart attack which has such a complex pathogenesis? There is no doubt that the D:A:D findings yield major doubts. In particular, correcting the data for traditional risk factors we note

Figure 1



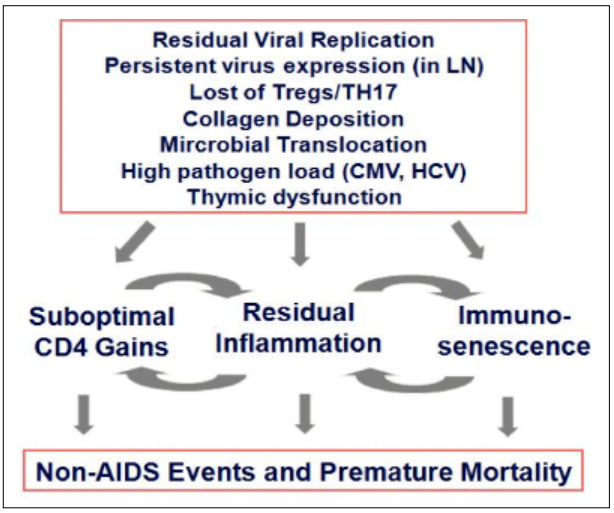
that the incriminated drugs carry an independent risk not predicted by either the raised cholesterol or triglyceride levels they cause, nor by traditional risk factors [5] that nonetheless play a major role in the genesis of coronary disease in these patients.

It is likely that some major tool allowing us to interpret the events we observe is missing. The inadequacy of our interpretative tools became plain when data emerged implicating abacavir in coronary disease. As is known, a study within the D:A:D cohort unexpectedly disclosed that abacavir increased the risk of heart attack 1.9 times[7]. This finding was subsequently scaled down in a breakdown of the same patient cohort [6]. Moreover, beyond certain hypotheses, no evidence has yet emerged of how this molecule can lead to coronary damage.

Returning to the main problem: If it is not dyslipidaemia that creates the damage, then what does? In recent years cardiologists have radically reviewed the mechanism responsible for atheromasic plaque formation, the histological damage underlying coronary disease.

In actual fact, the literature had already disclosed much indirect evidence implicating the important role of pro-inflammatory factors in the pathogenesis of myocardial infarction. Some of the findings

Figure 2



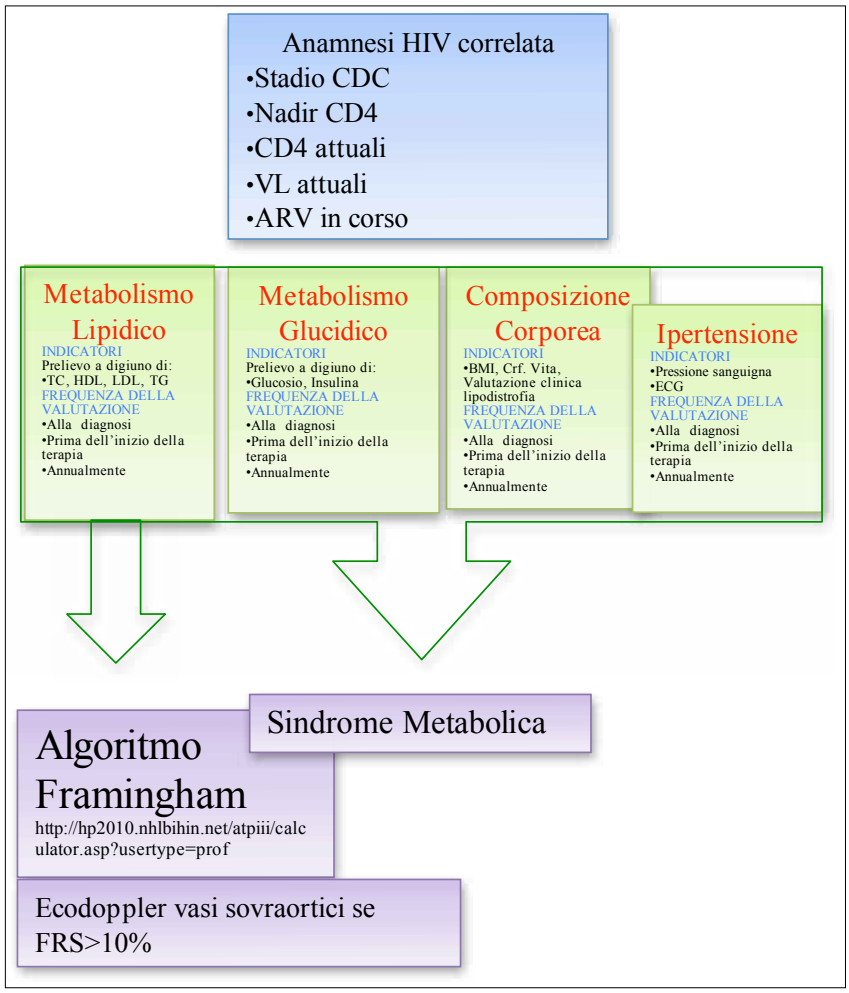
reported in the D:A:D study showed that a low level of CD4 is a major causative factor not only for AIDS-related disease, but also for coronary disease [8]. Subsequently, the SMART trial examining structured treatment interruption showed a dramatic increase in the percentage of coronary disease among patients with low CD4 levels [9]. Another treatment interruption trial (STACCATO) found peak circulating levels of pro-inflammatory cytokines in patients suspending treatment [10].

Our own histological and morphological studies on atheromasic plaque had already implicated the key role of inflammatory events [11,12]. However, the largest number of scientific studies on the relations between inflammation and endothelial damage emerged at CROI 2010. Hsue[13] had noted that "elite controllers" present significantly more subclinical atheromasic lesions than other patients, and subsequently showed that lesions tend to arise at the carotid bifurcation in the presence of a raised hsPCR [14].

Kaplan showed in a female cohort that t-cell activation and senescence is correlated with carotid artery damage [15]. Moreover, early administration of treatment seems to be associated with reduced arterial stiffness measured by pulse wave velocity [16].

The SUN study reported that the true protective factor against myo-intimal damage is the ability to suppress viral load [17]. According to Hsue, residual - perhaps even subliminal - viral replication could

Figure 3



SIMIT diagnostic management algorithm of cardiovascular risk (Borderi, Guaraldi, Maggi)

be responsible for a series of immune and other events, including bacterial translocation, which would account for residual inflammation responsible for non AIDS-related injury such as cardiovascular damage.

In conclusion, it appears increasingly plain that the complex phenomenon of coronary damage in HIV-positive patients cannot find a trivial explanation in hyperlipidaemia alone. Instead it should be viewed in a framework of inflammatory events in which residual viral loads play an increasingly decisive role in the risk of myocardial infarction.

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