Poster 815

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Presence of the metabolic syndrome (MS) is not a better predictor of cardiovascular disease (CVD) than the sum of its components; Data from the D:A:D Study

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BACKGROUND

Metabolic syndrome (MS) is a cluster of CVD risk factors associated with a 2-fold increased risk of CVD in the general population

- MS is usually defined as the presence of 3 or more risk factors from elevated triglycerides, low HDL, abdominal obesity, impaired fasting glucose and hypertension
- In HIV-infected persons, metabolic changes are often induced by medicine rather than by diet and lifestyle
- It is debated whether the MS, as an entity, contributes additional prognostic information about CVD over and above that provided by the individual risk factors alone

OBJECTIVE

We investigated whether the presence of MS in an HIV-infected individual constitutes an additional risk for CVD, over and above that, which would be expected in the individual given his/her known risk factors for CVD. In particular, we:

- studied whether any pair wise combinations of the risk factors included in the definition of MS were associated with an increased risk of CVD;
- investigated whether the presence of specific pairs of risk factors was associated with a higher risk of CVD than would be expected from combining the risk attributable to each risk factor; and
- investigated whether MS as an entity was predictive for CVD after adjusting for the individual risk factors making up the MS

METHODS

D:A:D is a prospective multi-national cohort study of 33,389 HIV-infected subjects, from 188 clinics in Europe, the US and Australia

- The 5 CVD risk factors encompassed in the definition of MS (modified NCEP criteria (1) are listed below.
  The abbreviations indicate the presence of the risk factor at levels above (and for HDL below) the threshold (see **Box 1** for conversion of units):
  - Elevated Triglycerides ≥1.7mmol/L (TG)
  - Low HDL cholesterol ≤1.0 mmol/L in men, ≤1.3 mmol/L in women (HDL)
  - Hypertension: Systolic blood pressure (BP) ≥130 or diastolic BP ≥85 mmHg (HYP)
  - Body mass index ≥ 25 kg/m2 (BMI)
  - Diagnosis of diabetes mellitus (DM)
- The incidence of a composite CVD endpoint of myocardial infarction [MI], stroke, invasive CV procedures [ICPs], or death from other CV cause was calculated by dividing the number of such events by the total person-years of follow-up (PYFU) in the cohort. Patient follow-up was counted from the time of enrolment in D:A:D until the date of first CVD event, 1st February, 2006 or 6 months after the patient's last clinic visit
- For each pair of factors considered, patients were grouped into four strata depending on their risk factor status at entry in D:A:D (neither risk factor present; one (or other) risk factor present; both risk factors present) and incidences were calculated for each strata
- Multivariable analyses further explored these relationships through Poisson regression models; these models allowed us to formally test whether the risk factors acted synergistically on the composite endpoint, by the incorporation of each pair of risk factors along with the interaction between them - any statistically significant interaction (p<0.05) with a rate ratio (RR) value greater than 1.00 would suggest a positive synergistic effect between the MS components
- Finally, we examined whether the presence of the MS as an entity was significantly associated with the risk of CVD, both before and after controlling for each of the 5 individual risk factors and other possible confounders (age, sex, family history of CVD, smoking status, calendar year, cohort and exposure to combination antiretroviral therapy [cART])
- Because of the potential for a high Type I error rate due to multiple testing, all pair wise effects and interactions were initially assessed in a random sample of 70% of the cohort (training sample; n=23,236) and were validated in the remaining 30% (n=10,153) of the cohort

(1)Executive summary of the third report of the national cholesterol educational program (NCEP) expert panel on detection, evaluation and treatment of high cholesterol in adults (Adult treatment III). JAMA 2005;285(19):2486-97

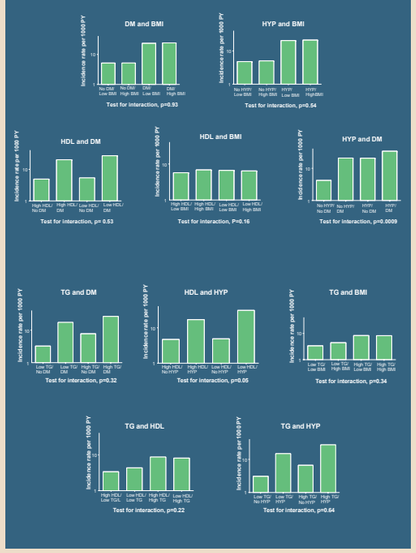
Table 1

Characteristics at baseline of patients included in D:A:D, training and validation samples

		Training sample	Validation sample
Number of patients		23,236	10,153
Male sex (No./%)		17,178 (73.9)	7,541 (74.3)
Age (years)		38 (32-44)	38 (32-45)
CD_4 count (cells/mm³)		407 (247-609)	410 (250-605)
HIV RNA (log_ copies/ml)		2.7 (1.7-4.3)	2.7 (1.7-4.2)
Current smoker (No./%)		7,708 (49.0)	3,383 (49.2)
Lipodystrophy (No./%)		4,351 (17.9)	1,901 (18.7)
Prior CVD (No./%)		178 (0.8)	85 (0.8)
Exposure to ARV therapy (years (med, IQR))			
	PI	0.7 (0.0-2.6)	0.6 (0.0-2.6)
	NNRTI	0.0 (0.0-0.4)	0.0 (0.0-0.4)
	NRTI	2.0 (0.0-4.0)	2.0 (0.0-4.0)
MS at enrolment in D:A:D			
	Number of patients with complete data	6,954	3,090
	MS at enrolment (No./%)	1,392 (20.0)	588 (19.0)
	MS components (No./%)		
	TG	1,265 (90.9)	526 (89.5)
	HDL	1,148 (82.5)	476 (81.0)
	HYP	1,031 (74.1)	424 (72.1)
	BMI	171 (12.3)	69 (11.7)
	DM	992 (71.3)	420 (71.4)

Figure 1

Incidence of CVD according to pair wise combinations of the components in the MS



RESULTS

Overall 19.7% had MS at enrolment in D:A:D (20% of training set and 19% of validation set)**(Table 1);**

- Other characteristics at baseline are depicted in **Table 1**
- The most common components of the MS were elevated TG (91% of those with MS) and low HDL (83%)
- Over 47,185 person-years in the training set, a total of 554 patients experienced at least one CVD event (first event observed: 292 MIs, 158 strokes, 93 ICPs and 11 CV deaths)

The Incidence of CVD According to Pair Wise Combinations of MS Components

Figure 1 shows incidence rates of CVD stratified by the combination of each pair of MS components, ordered from lowest risk on the left (ie. both risk factors absent) to highest risk on the right (ie. both risk factors present).

- When exploring the incidence according to pair wise combinations, the highest CVD rates (per 1000 persons years) were seen in patients with
  - HYP and DM (34.0 versus 4.2 in patients without HYP and DM)
  - HDL and HYP (30.7 versus 4.8 in patients without HDL and HYP)
  - HYP and TG (27.7 versus 3.1 in patients without HYP and TG)
  - DM and HDL (27.1 versus 4.9 in patients without HDL and DM)

The Risk of CVD According to Number of MS Components

- The risk of CVD increased as the number of risk factors present increased **(Figure 2)**
- The risk of CVD increased by 70% (RR 1.70 [1.50-1.93]; p=0.0001) for each additional risk factor that was present

Multivariate Models Exploring Possible Synergistic Effects of MS Components

- 10 different Poisson regression models (one for each pair of factors shown in **Figure 1**) tested whether there were any possible synergistic effects between MS components
- In 9 out of the 10 models, the interaction term was non-significant (p>0.05), suggesting that the pair of MS components, when seen together in an individual patient, did not result in a higher CVD risk than would have been expected based on the risks attributable to each factor
- In only one model was the interaction term significant (RR 0.33, p=0.0009), although its direction was counter-intuitive. The estimated interaction term suggested that individuals with both HYP and DM had a *lower* risk of CVD than what would be expected based on the main effects of these risk factors alone
- We chose not to explore higher order interactions given the generally non-significant two-way interactions
- All findings were confirmed in the validation sample (156 events over 50,759 PYRS)

Final Model Testing Whether There is Any Independent Effect of the MS on CVD Risk after Adjusting for its Components

- In unadjusted analyses, individuals with the MS (≥3 of the factors) had a 4.6-fold higher risk of CVD (unadjusted rate ratio 4.60 [3.19-6.65]; p=0.0001) compared with individuals not fulfilling the MS definition **(Figure 3)**
- Importantly, however, after adjustment for the risk factors themselves, MS as an entity no longer predicted the risk of CVD (adjusted RR 0.93 [0.57-1.49]; p=0.75).
- After further adjustment for other potential confounding factors, this risk estimate was modified to 1.04 [0.64- 1.69]; p=0.89 **(Figure 3)**

CONCLUSIONS

- There is a strong positive correlation between an increasing number of the components of the MS in individual patients and CVD risk. In particular, patients with the MS had a 4.6 fold higher risk of CVD compared to patients without the MS
- However, this finding did not remain after controlling for each of the individual risk factors
- Furthermore, whilst the underlying concept of the MS as a specific entity would suggest, that the risk factors making up the MS act synergistically on an individual's risk of CVD, we found no significant positive interactio between any of the risk factors considered
- Thus, the presence of the MS in HIV appears not to increase the CVD risk over and above that conferred by the components of the syndrome separately

Figure 2

The relative risk (and 95% confidence intervals) for CVD associated with increasing numbers of components of the MS

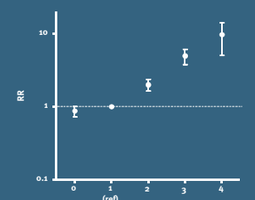
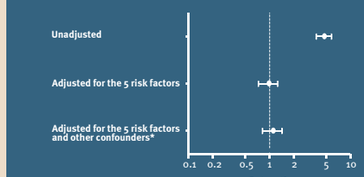


Figure 3

The rate ratio of CVD in individuals with versus without the MS



*adjusted for age, sex, family history of CVD, smoking status, calendar year, cohort and exposure to cART

Box 1. Converting units for cholesterol and triglycerides

Cholesterol	mmol/L to mg/dl: multiply by 38.5	mg/dl to mmol/L: divide by 38.5
Triglycerides	mmol/L to mg/dl:multiply by 87.7	mg/dl to mmol/L:divide by 87.7

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