



Cardio- and Cerebrovascular Events (CVE) and Predicted Rates of Myocardial Infarction (MI) in the D:A:D Study

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BACKGROUND

Recent results from the D:A:D Study, a prospective observational cohort of 23,468 HIV-patients, indicated that the incidence of MI increased by 26% per year of exposure to combination antiretroviral treatment (CART). We investigated whether this risk was similar when including other cardiovascular disease events (I). We also compared the observed rate of MIs seen in D:A:D to that predicted by the Framingham risk equation (II).

I Composite endpoint of cardio- and cerebrovascular disease events (CVE)

OBJECTIVES (I)

- To describe the incidence of a composite CVE endpoint, including MI, stroke, invasive cardiovascular procedures and death from other cardiovascular disease
- To assess the association of CART exposure with the risk of CVE
- To identify other factors associated with the risk of CVE

METHODS (I)

- Rates of first CVE (either MI, invasive cardiovascular procedure, stroke or death from other cardiovascular disease) were calculated according to CART duration in intervals of: no CART, <1 year, 1-2 years, 2-3 years, 3-4 years and 4+ years
- The association between cumulative CART exposure and CVE was assessed using Poisson regression methods, by fitting CART exposure as a continuous variable
- The primary model included demographic and traditional risk factors that had been associated with the risk of CVE in univariable analyses
- Additional analyses tested metabolic and physiologic factors that could be on a causal pathway, such as total cholesterol, triglycerides, diabetes mellitus and hypertension
- Sensitivity analyses that included all (initial plus subsequent) events were performed

RESULTS (I)

- The prevalence of traditional risk factors for cardiovascular disease (CVD), in the D:A:D study population and stratified by CART exposure, is shown in Table 1
- Over 36,151 person-years of follow-up, 199 patients experienced at least one CVE, an incidence of 5.5 per 1000 person-years
- The 199 first events were :
 - 123 acute MI
 - 4 deaths from other CVD
 - 42 invasive cardiovascular procedures
 - 30 coronary artery angioplasty/stent
 - 11 coronary artery bypass
 - 1 carotid endarterectomy
 - 30 strokes

- The incidence of first CVE increased with longer exposure to CART (Figure 1)
- After adjusting for other factors significantly associated with CVE in the primary Poisson model, the relative rate (RR) of CVE per year of CART exposure was 1.26 (95% CI: 1.15-1.38). Other independent predictors of CVE were: age (RR 1.43 per 5 years older; 95% CI 1.33-1.53), male gender (1.92 ; 1.13 - 3.25), previous CVD (MI or stroke) (6.76 ; 4.61-9.91), smoking (ever vs. never) (1.82 ; 1.23 - 2.70) and family history of MI (1.72; 1.11- 2.65), Figure 2
- Additional factors associated with CVE were diabetes (RR 2.35; 95% CI 1.55-3.58), hypertension (1.76; 1.22-2.54), cholesterol (1.11 per mmol/L higher; 1.03-1.20), and triglycerides (1.33 per log₂ higher; 1.14-1.55)
- Sensitivity analyses including all events (initial plus subsequent) (n= 259) gave similar results for the association of CART with CVE: adjusted RR 1.27 (95% CI 1.15-1.41)

CONCLUSIONS (I)

- The increased risk of CVE with longer exposure to CART is similar to that found using MI as a single endpoint
- Other identified predictors of CVE are also very similar to those identified for MI
- These results confirm the previously reported association and suggest that the causal mechanism is similar for this composite endpoint

Table 1. Cardiovascular risk factors by duration of CART¹

Risk factor	Duration of CART					
	0 years N=1,093	<1 year N=4,292	1-2 years N=4,806	2-3 years N=9,055	3-4 years N=10,076	4+ years N=8,886
Sex - % male	69.6%	74.4%	75.0%	76.7%	78.4%	80.6%
Age (yrs) Median (IQR)	37.0 (32.8 to 43.0)	38.1 (33.0 to 44.1)	38.8 (34.0 to 45.0)	39.1 (34.0 to 45.0)	40.0 (35.0 to 46.0)	41.2 (36.0 to 47.0)
Currently smoke - % yes	62.0%	59.4%	59.0%	58.0%	58.8%	56.5%
Previous cardiovascular disease - % yes	10.8%	1.5%	1.4%	1.3%	1.7%	2.0%
Systolic blood pressure (mmHg) Median (IQR)	120 (100 to 130)	120 (100 to 130)	120 (100 to 130)	120 (100 to 130)	120 (100 to 130)	120 (100 to 130)
Diabetes - % yes	1.0%	2.3%	2.4%	2.0%	3.0%	3.8%
Total cholesterol (mmol/L) Median (IQR)	6.8 (5.8 to 7.9)	6.8 (5.8 to 7.9)	5.1 (4.3 to 6.0)	5.0 (4.4 to 6.0)	5.4 (4.6 to 6.3)	5.5 (4.6 to 6.4)
HDL cholesterol (mmol/L) Median (IQR)	1.1 (0.8 to 1.4)	1.1 (0.8 to 1.4)	1.2 (0.9 to 1.4)	1.1 (0.9 to 1.4)	1.1 (0.9 to 1.4)	1.1 (0.9 to 1.4)
Total cholesterol/HDL ratio Median (IQR)	3.9 (3.1 to 5.1)	4.2 (3.1 to 5.1)	4.3 (3.1 to 5.1)	4.6 (3.1 to 5.1)	4.9 (3.1 to 5.1)	5.1 (3.1 to 5.1)
Triglycerides (mmol/L) Median (IQR)	1.3 (0.9 to 2.0)	1.5 (1.0 to 2.3)	1.6 (1.0 to 2.4)	1.8 (1.1 to 2.9)	2.0 (1.2 to 3.1)	2.2 (1.4 to 3.5)
Lipodystrophy - % reported	4.0%	6.1%	12.1%	20.0%	30.2%	36.8%

1. Risk factors summarized in Table are time updated values immediately prior to CART category change
 2. % of all patients with missing data before imputation of missing values. Figures in table did not include imputed data
 3. Numbers of patients seen to be greater than 23,468 patients in follow-up because patients contribute to more than one duration of CART group
 4. IQR = inter quartile range

Figure 1 Incidence of CVE according to duration of CART exposure

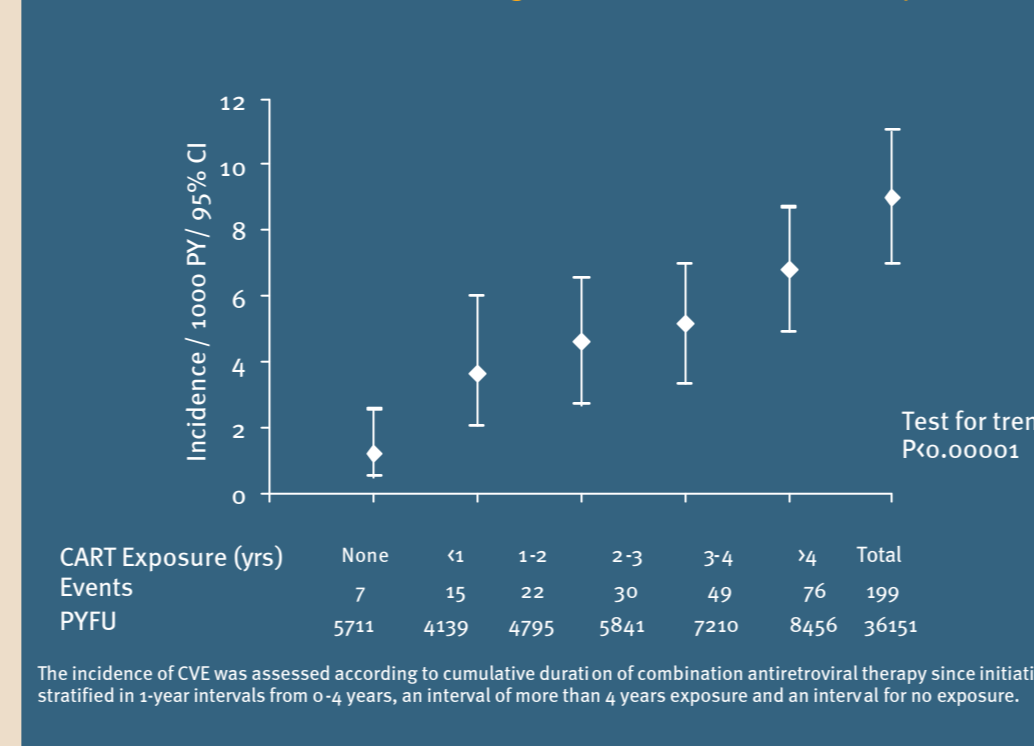
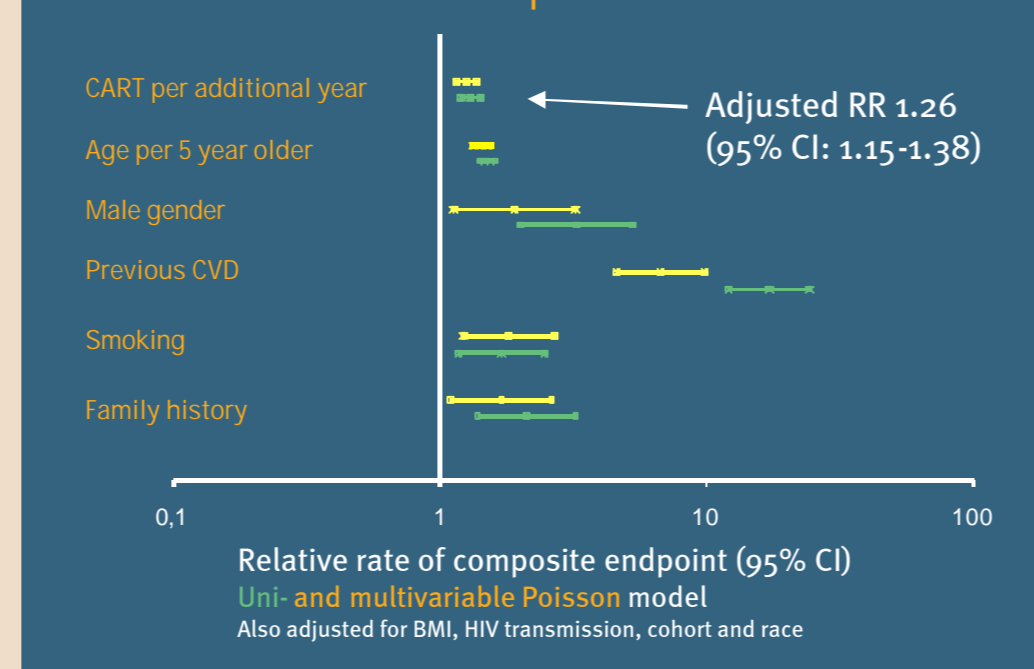


Figure 2 CART and other predictors of CVE



II Comparison of predicted versus observed rates of MI

OBJECTIVES (II)

- To use the Framingham equation to predict the rate of MI that would have been expected during the D:A:D study follow-up
- To determine whether the increased risk of MI that was seen with greater duration of CART can be explained by changes in conventional cardiovascular risk factors. If the increase can be explained in this way, it would be expected that the predicted rates of MI by duration of CART would parallel the increased rates observed during follow-up

METHODS (II)

- The Framingham equation was used to predict MI rates by duration of CART in the same intervals as in (I)
- Analyses were based on individual patient data; CVD risk factors were time-updated for patients who contributed follow-up to more than one CART category
- Missing values were imputed using best subsets regression
- Predicted numbers of events were adjusted for different baseline cardiovascular event rates in different countries based on WHO myocardial infarction mortality rates, using USA as a reference country
- Best predictions of MI rates were based on data from all patients and assumed a 5-fold increased risk of MI in patients with prior CVD; upper and lower limits were placed around these (Figure 3)
 - Upper limits: obtained by assuming that features of the metabolic syndrome associated with CART, in the presence of either:
 - lipodystrophy,
 - body mass index >30 kg/m² (height²), or
 - elevated triglycerides (>2.3 mmol/L)
 carried an increased risk of MI equivalent to that of pre-existing diabetes in the background population
 - Lower limits: derived assuming that the induced metabolic alterations are not immediately clinically relevant, and do not increase an individual's risk of MI over the medium 5-10 year period
- Sensitivity analyses were performed to assess the effect of model and data assumptions

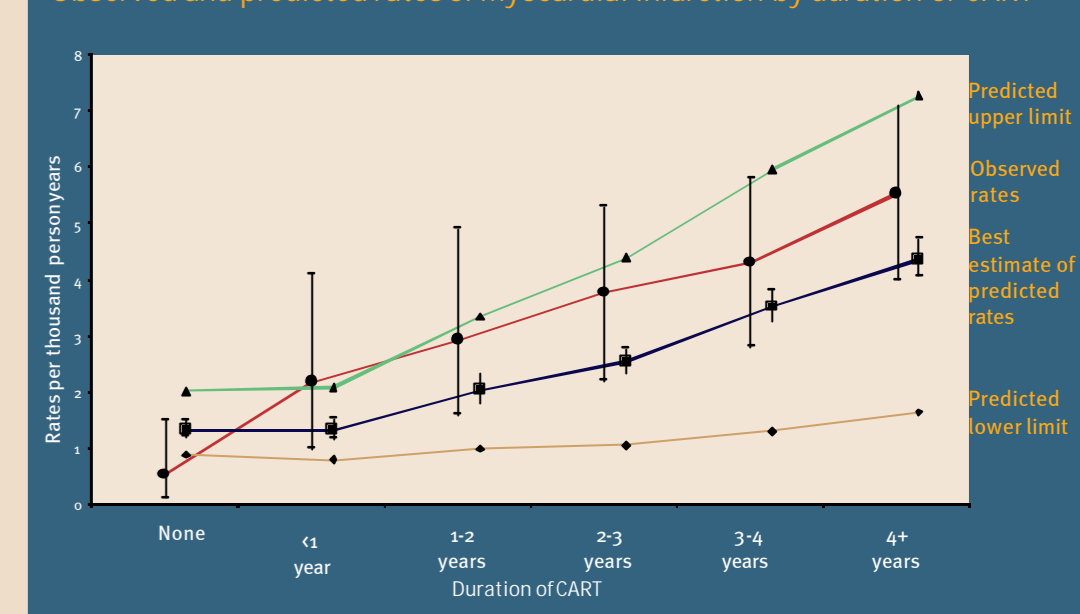
RESULTS (II)

- In patients not receiving CART, the observed number of MIs was fewer than the predicted (3 observed vs. 7.6 predicted)
- In patients receiving CART, the numbers of MI observed during D:A:D follow-up were slightly higher than the best predicted rates, but were generally lower than the upper limit predictions (Figure 3 and Table 2). The trends seen, however, with increasing rates of MI with longer duration of CART, were similar to those that would have been expected on the basis of changes in known risk factors for CVD
- Predicted MI rates were within the 95% confidence interval of observed rates
- Sensitivity analyses consistently showed that in patients receiving CART the observed and predicted rates of MI increased in a parallel fashion with greater CART duration (table 2)

CONCLUSIONS (II)

- The observed rate of MI in the D:A:D Study was of a similar magnitude to, or somewhat higher than, that predicted by the Framingham risk equation
- The fact that observed and predicted rates of MI increased in a parallel fashion with increased CART duration suggests that the observed increase in risk of MI may largely be explained through CART-induced changes in conventional CVD risk factors
- These findings provide pertinent guidance in terms of choosing lifestyle or therapeutic interventions to decrease these risk factors in much the same way as in persons without HIV infection

Figure 3 Observed and predicted rates of myocardial infarction by duration of CART



Error bars are 95% confidence intervals, based on Poisson distribution for observed rates and bootstrap resampling for the best estimate of the predicted rates.

Table 2. Predicted rates of myocardial infarction by duration of CART – sensitivity analyses

Country	0 years	<1 year	1-2 years	2-3 years	3-4 years	4+ years	Total
Observed events	7	15	22	30	49	76	199
Number MI	7	15	22	30	49	76	199
Person-years follow-up	5711	4139	4795	5841	7210	8456	36551
Rate / 1000 person years	1.2	3.6	4.6	5.1	6.8	8.9	5.5
Best predicted estimates (all data, adjusted for different countries, patients with previous cardiovascular disease taken to have 5-fold risk of MI)	1.3	3.3	4.0	4.5	5.5	6.4	4.4
Number MI	7	14	19	27	38	57	164
Rate / 1000 person years	1.2	3.4	4.0	4.6	5.3	6.7	4.5
Best predicted estimates (all data, with no adjustment according to country, with patients with any previous CVD taken to have 5-fold risk of MI)	1.2	3.6	4.3	4.9	5.9	6.9	4.8
Number MI	7	15	22	30	49	76	199
Rate / 1000 person years	1.2	3.6	4.6	5.1	6.8	8.9	5.5
Best predicted estimates (country, with patients with missing cholesterol, HDL or systolic BP omitted (note: different numbers of observed for comparison))	1.2	3.5	4.2	4.7	5.7	6.7	4.7
Number MI	7	14	20	27	37	56	161
Person-years follow-up	5711	4139	4795	5841	7210	8456	36551
Rate / 1000 person years	1.2	3.4	4.2	4.6	5.1	6.6	4.7
Best predicted estimates (all data, with no adjustment according to country, with patients with any previous CVD taken to have 5-fold risk of MI)	1.2	3.4	4.1	4.6	5.6	6.6	4.6
Number MI	7	14	20	27	37	56	161
Rate / 1000 person years	1.2	3.4	4.1	4.6	5.1	6.6	4.6

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