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Improvements in short-term mortality following myocardial infarction (MI): the D:A:D Study

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BACKGROUND

- Mortality after a first myocardial infarction (MI) in the general population has improved over the past 25 years; much of this improvement can be attributed to better management of cardiovascular disease (CVD) risk factors.[1,2]
- In-hospital mortality after MI shows an inverse association with the number of CVD risk factors that are present at the time of MI[3], with in-hospital mortality rates being increased by 54% in those with no risk factors present compared to those with 5 risk factors; it is speculated that individuals with no risk factors present may have other, as yet unidentified, factors that may contribute to progressive disease.
- To our knowledge, no study has described clinical outcomes after an MI in the HIV-positive population nor examined changes in such outcomes over time.

STUDY OBJECTIVE

To evaluate changes over time in short-term mortality post-MI in the D:A:D Study and to investigate possible reasons for these changes.

METHODS

- The D:A:D Study is an observational study of >49,000 HIV-positive patients from 11 cohorts in Europe, Australia, and the United States. The primary study aim is to investigate associations between the use of antiretroviral drugs and risk of CVD and other major disease events.
- Data are collected prospectively during routine clinic visits; the standardised dataset includes information on socio-demographic factors, AIDS events and deaths, known risk factors for CVD, laboratory markers for monitoring HIV (including CD4 count and HIV RNA) and CVD (including total/HDL cholesterol and triglycerides), antiretroviral treatment and treatments that influence CVD risk.
- All incident cases of MI and stroke are reported to the study co-ordinating centre for validation and coding using criteria from the WHO MONICA Study[4]; reported MIs are classified as definite, possible, or unclassifiable, strokes are classified as definitive or possible.

STATISTICAL METHODS

- Patients with an MI that occurred during prospective D:A:D follow-up were identified; post-MI mortality trends are described using Kaplan-Meier plots
- Associations between calendar year and short-term mortality (death in first month after diagnosis of MI) were identified using logistic regression with adjustment for the following factors:

  Age, gender, mode of HIV acquisition, ethnic/racial group, cohort, current/cumulative exposure to PIs/NNRTIs, AIDS, latest CD4 count and HIV RNA, smoking status, body mass index (BMI), family history of CVD, prior hypertension, dyslipidaemia, diabetes, MI or stroke, Framingham risk and haemoglobin.
- Associations were then additionally adjusted for interventions received in the first month after MI (in the 703 patients surviving for >1 day).
- Interventions considered for the present analysis were invasive procedures (angioplasties, coronary artery bypass grafts or cardiac endarterectomies) or the use of medications to reduce the risk of CVD (lipid-lowering drugs, anti-platelet drugs, ACE inhibitors or other anti-hypertensive medication).

Table 1: Characteristics of 844 patients at time of first MI during prospective follow-up

		n	(%)
Number of patients		844	(100.0)
Dundee classification, n (%)	Definite	501	(59.4)
	Possible	200	(23.7)
	Unclassifiable	143	(16.9)
Year of MI, n (%)	1999-2002	212	(25.1)
	2003-2004	194	(23.0)
	2005-2006	157	(18.6)
	2007-2008	171	(20.3)
	2009-2011	110	(13.0)
Male gender, n (%)		770	(91.2)
Age (years)	Median (IQR)	50	(43, 58)
White race, n (%)		482	(57.1)
Acquired HIV through IDU, n (%)		134	(15.9)
BMI >30 kg/m², n (%)		45	(5.3)
Prior AIDS, n (%)		334	(39.6)
CD4 count (cells/mm³)	Median (IQR)	444	(297, 666)
HIV RNA ≤50 copies/ml, n (%)		517	(61.3)
Prior receipt of cART, n (%)		806	(95.5)
Current smoker, n (%)		445	(52.7)
Family history of CVD, n (%)		121	(14.3)
Previous MI, n (%)		66	(7.8)
Previous stroke, n (%)		34	(4.0)
Previous diabetes, n (%)		113	(13.4)
Previous invasive procedure, n (%)		71	(8.4)
Any dyslipidaemia, n (%)		550	(65.2)
Any hypertension, n (%)		326	(38.6)
Framingham score (%)	Median (IQR)	13.9	(8.7, 20.5)

Table 2: Change in characteristics of individuals with an MI according to year of occurrence

	Year of MI				
	99-02	03-04	05-06	07-08	09-11
Number of MIs	212	194	157	171	110
Definite MI (%)	59.9	64.4	61.8	55.0	52.7
Male gender (%)	91.0	92.8	90.5	89.5	92.7
Median age (years)	48	49	49	51	51
White race (%)	68.9	52.1	49.7	56.1	55.5
Acquired HIV through IDU (%)	18.9	15.0	13.4	17.5	12.7
BMI >30 kg/m² (%)	5.2	5.7	7.0	5.9	1.8
AIDS (%)	38.2	36.1	40.1	40.9	45.5
Median CD4 (cells/mm³)	398	444	454	436	546
HIV RNA ≤50 copies/ml	43.6	54.1	66.9	74.0	80.6
On cART (%)	86.3	90.7	88.5	86.6	96.4
Current smoker (%)	49.5	46.9	55.4	57.3	58.2
Family history (%)	14.2	13.9	14.7	15.2	13.6
Prior stroke (%)	5.7	3.6	3.8	3.5	2.7
High Framingham risk (%)	28.8	23.2	22.3	26.9	32.7

RESULTS

- Patient characteristics at the time of MI are shown in **Table 1**; changes in the key demographic and clinical characteristics, and CVD risk factors, over time are shown in **Table 2**. Whilst there was a tendency for some of these factors to change over time (e.g. a drop in age at the time of MI, a reduction in the proportion of individuals of white race, an increase in the proportion of individuals on combination antiretroviral therapy (cART) with a suppressed viral load, and an increase in the average CD4 count), these changes generally reflect those seen in the population of HIV-positive individuals in participating clinics over the same period. Overall, the proportion with a high Framingham risk (>20% 10-year risk) did not change over the period.
- Over a median (IQR) follow-up of 33.0 (6.5, 65.1) months, 88 (10%) of the 844 patients experienced a further MI and 281 patients (33.3%) died. 172 (61.2% of deaths) deaths occurred in the first month after MI, leading to a short-term mortality rate of 20.4%. In total, 91% of the deaths in the first month were due to CVD compared to only 39% of deaths that occurred after the first month.
- An increasing proportion of individuals with an MI have undergone either an invasive procedure (**Figure 1**) or have received medication to reduce their risk of CVD (**Figure 2**).
- The proportion of patients with MI dying in the first month dropped from 26.4% in 1999-2002 to 8.2% in 2009-2011 (unadjusted odds ratio [OR] /later year 0.88 [95% confidence interval 0.83, 0.94]) (**Table 3**).
- This reduction in short-term mortality did not appear to be due to changes in the characteristics of patients (injection drug use (IDU), CD4 count at time of MI, family history of CVD, BMI or prior stroke) over time. However, further adjustment for the increased use of invasive procedures and medications in the first month post-MI led to a complete attenuation of the odds ratio (aOR 1.02 [0.94, 1.10]), suggesting that the use of these interventions may have played a role in the increased survival rate.

SUMMARY AND FURTHER ANALYSES

- The improvement in short-term survival post-MI that we have seen since 1999 appears to be largely driven by improved patient management post-MI.
- Although an increased proportion of patients now receive an intervention post-MI, there are still some patients who do not appear to receive these interventions. Several questions therefore remain:
  - Is this due to under- or delayed ascertainment of information on the receipt of invasive procedures/drug therapy within study databases?
  - Is this a similar rate to that seen in the general (HIV-negative) population, i.e. Is this a general problem common to all individuals with an MI?
  - Have patients received other interventions (e.g. dietary advice, interventions to increase smoking cessation or exercise) that are not captured in the D:A:D dataset?
- Further analyses of the D:A:D dataset will consider longer-term outcomes, as well as associations between the pre-MI CD4 count and mortality.

Figure 1: Use of invasive procedure before and in the first month after MI

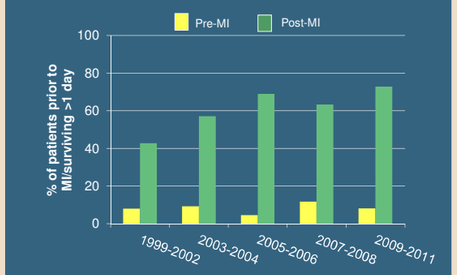

Figure 2: Use of drug interventions before and in the first month after MI

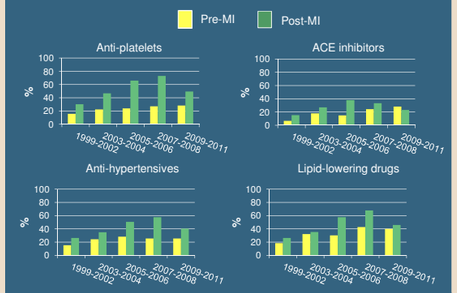

Table 3: Short-term mortality rate, and results from unadjusted and adjusted logistic regression analyses to investigate the association with calendar year

	Year of MI				
	99-02	03-04	05-06	07-08	09-11
Number of MIs	212	194	157	171	110
% dying in first month	26.4	24.7	19.8	16.4	8.2
OR (/later year) (95% CI)					
Unadjusted	0.88 [0.83, 0.94]				
Adjusted for baseline characteristics	0.88 [0.83, 0.94]				
Additionally adjusted for use of invasive procedures and/or medications in the first month post-MI	1.02 [0.94, 1.10]				

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