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D:A:D

Relationship Between Confirmed eGFR and Cardiovascular Disease in HIV-positive Persons

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BACKGROUND

- While the association between various measures of impaired renal function and cardiovascular disease (CVD) is well established in the general population (1-3), this association remains more poorly elucidated in HIV-positive individuals
- As most prior studies in HIV have focused on unconfirmed measures of renal function (4-6), which are subject to random variation and acute illness, the influence of sustained estimated glomerular filtration rate (eGFR) impairment on CVD in a contemporary HIV cohort is less clear
- Renal impairment is projected to become more prevalent among HIV-positive individuals in future years due to an accumulating burden of risk factors, making investigation of possible related complications such as CVD urgently warranted
- The primary objective of this analysis was hence to investigate the relationship between confirmed eGFR impairment and development of centrally validated CVD events

METHODS

- The D:A:D Study is a large prospective cohort-collaboration including HIV-positive individuals from 11 cohorts across Europe, Australia and the United States
- Participants with ≥2 eGFRs (Cockcroft Gault, standardised for body surface area) after 1/1/2004 (baseline for systematic creatinine collection) were followed until the earliest of first CVD event, death, last visit plus 6 months or 1/2/2013
- CVD was defined as centrally validated (fatal and non-fatal) myocardial infarction (MI), stroke (STR), coronary angioplasty (ANG), bypass (BYP) and carotid endarterectomy (END)
- Kaplan-Meier estimation was used to investigate time to CVD stratified by confirmed baseline eGFR >90, >60-≤90, >30-≤60 and ≤30 ml/min/1.73m^2
- Poisson regression stratified according to confirmed current eGFR level was used to model the incidence rate ratios of CVD, while adjusting for demographics, antiretroviral treatment, traditional HIV, cardiovascular and renal risk factors

RESULTS

- 34,793 persons were included in analysis with a median follow-up of 6.3 years (IQR 4.1-7.9)
- A total of 1,033 persons developed 1,251 CVD events during follow-up, incidence 5.1 per 1000 PYFU [95% CI 4.8-5.4], **Figure 1**
- Baseline characteristics are shown in **Table 1**

FIGURE 1

Overview of Patient Inclusion

Included in D:A:D
N=47,717
↓
≥2 eGFRs after 1/1/2004
N=35,192
↓
With baseline CD4 count and HIV-VL
N=34,795
↓
With FU after baseline
N=34,793
↓
1,033 persons experienced 1251 CVD events*
during 203,394 PYFU

443 MI (12.4%)** **335 STR** (9.0%)
389 ANG (1.8%) **67 BYP** (1.5%) **17 END** (0%)

*213 persons experienced more than 1 CVD event on the same date, most commonly an MI and ANG (n=192)
** % of fatality in parenthesis

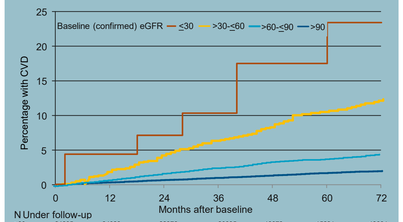
TABLE 1

Baseline Characteristics

		All		CVD	
		N	%	N	%
All		34,793	100	1,033	3.0
Gender	Male	25,701	73.9	905	87.6
Race	Caucasian	16,754	48.2	549	53.2
HIV Risk Group	MSM	15,954	45.8	552	53.4
HBV	Positive	4,051	11.6	112	10.8
HCV	Positive	465	13.3	124	12.0
cART	On	26,071	74.9	924	84.5
Prior AIDS		8,470	24.3	369	35.7
VL<400	Yes	20,623	59.3	741	71.7
Smoking	Current	14,322	41.2	524	50.7
BMI	>30	1,816	5.2	62	6.0
CVD Disposition	Yes	2,650	7.6	141	13.7
Prior CVD	Yes	235	0.7	63	6.1
Hypertension	Yes	3,150	9.1	215	20.8
Diabetes	Yes	1,376	4.0	134	13.0
eGFR	>90	24,350	70.0	485	47.0
	>30-≤90	10,376	29.8	540	52.3
	≤30	67	0.2	8	0.8
Age (median, IQR)	Years	41	35-48	51	44-59
CD4 (median, IQR)	/mm^3	440	290-623	440	288-639

FIGURE 2

Kaplan-Meier Progression to CVD by Confirmed Baseline eGFR



- The proportion of fatal CVD events (death ≤28 days of event) increased from 8.4% in individuals with a confirmed current eGFR >90 ml/min/1.73m^2 to 29.4% in individuals with a confirmed current eGFR ≤30 ml/min/1.73m^2
- There was a clear relationship between confirmed eGFR at baseline and incident CVD with 1.7% [95% CI 1.5-1.9%] estimated to have progressed to CVD at 5 years among those with eGFR >90 ml/min/1.73m^2, increasing to 23.4% [95% CI 6.9-39.8%] among those with eGFR ≤30 ml/min/1.73m^2, **Figure 2**
- No statistically significant difference in time to type of CVD event was observed in individuals with a confirmed baseline eGFR <60 ml/min/1.73m^2, with a median time to CVD of 31.5 months (IQR 17.9- 51.2), (test for trend, p=0.64)
- The strong relationship between a low confirmed current eGFR and CVD in unadjusted analyses was primarily explained by increasing age in adjusted analyses, although a strong trend for increased CVD rates with decreasing eGFR levels remained, largely driven by high rates in those with eGFR ≤30 ml/min/1.73m^2 (test for trend, p=0.0019), **Figure 3**
- This finding was consistent in different age groups (test for interaction, p=0.43), after accounting for death as possible a competing risk for CVD and further strengthened when analyses were restricted to include only fatal CVD events (data not shown)
- The confirmed eGFR level prior to the CVD event did not, with the exception of BYP, differ according to type of CVD event, **Figure 4**

CONCLUSIONS

- In a large contemporary cohort of HIV-positive individuals we observed a strong relationship between baseline and current confirmed impaired renal function and incident CVD
- Among those with the most severely impaired renal function by five years almost one in four were estimated to have developed CVD, with an increasing 28-day CVD fatality rate as eGFR declined
- These findings highlight the need for an intensified monitoring for all types of emerging CVD, in particular in older individuals with continuously low eGFR levels, and calls for an increased focus on applying different renal and cardiovascular preventive measures in HIV-positive individuals

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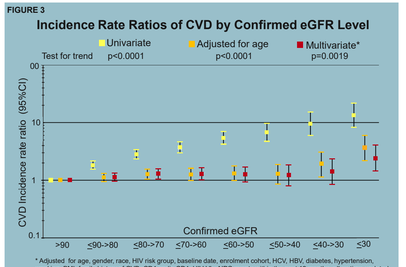
FIGURE 3

Incidence Rate Ratios of CVD by Confirmed eGFR Level



* Adjusted for age, gender, race, HIV risk group, baseline date, enrolment cohort, HCV, HBV, diabetes, hypertension, smoking, BMI, family history of CVD, CD4 nadir, CD4, HIV-VL, AIDS events within the past 12 months, all as time-updated variables. In addition time-updated exposure to antiretrovirals fitted as cumulative (AZT, ddI, ddC, d4T, 3TC, FTC, TDF, ABC, EFV, NVP, IDV, SQV, RTV, LPV, NFV, APV, ATV, DRV) and current (on and within last 6 months: AZT, ddI, ddC, 3TC, d4T, FTC, TDF, ABC) exposure according to former D:A:D analyses

FIGURE 4

Confirmed eGFR Level Prior to CVD Event

Acknowledgements

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