

Renal Impairment and Cardiovascular Disease in HIV-Positive Individuals: The D:A:D Study

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Background. While the association between renal impairment and cardiovascular disease (CVD) is well established in the general population, the association remains poorly understood in human immunodeficiency virus (HIV)-positive individuals.

Methods. Individuals with ≥ 2 estimated glomerular filtration rate (eGFR) measurements after 1 February 2004 were followed until CVD, death, last visit plus 6 months, or 1 February 2015. CVD was defined as the occurrence of centrally validated myocardial infarction, stroke, invasive cardiovascular procedures, or sudden cardiac death.

Results. During a median follow-up duration of 8.0 years (interquartile range, 5.4–8.9 years) 1357 of 35 357 individuals developed CVD (incidence rate, 5.2 cases/1000 person-years [95% confidence interval {CI}, 5.0–5.5]). Confirmed baseline eGFR and CVD were closely related with 1.8% of individuals (95% CI, 1.6%–2.0%) with an eGFR > 90 mL/minute/1.73 m² estimated to develop CVD at 5 years, increasing to 21.1% (95% CI, 6.6%–35.6%) among those with an eGFR ≤ 30 mL/minute/1.73 m². The strong univariate relationship between low current eGFR and CVD was primarily explained by increasing age in adjusted analyses, although all eGFRs ≤ 80 mL/minute/1.73 m² remained associated with 30%–40% increased CVD rates, and particularly high CVD rates among individuals with an eGFR ≤ 30 mL/minute/1.73 m² (incidence rate ratio, 3.08 [95% CI, 2.04–4.65]).

Conclusions. Among HIV-positive individuals in a large contemporary cohort, a strong relation between confirmed impaired eGFR and CVD was observed. This finding highlights the need for renal preventive measures and intensified monitoring for emerging CVD, particularly in older individuals with continuously low eGFRs.

Keywords. eGFR; renal impairment; kidney disease; cardiovascular disease; myocardial infarction; stroke; invasive cardiovascular procedures; sudden cardiac death; HIV.

The association between impaired renal function and cardiovascular disease (CVD) is well established in the general population, particularly for severe levels of renal impairment [1–6]. As such, $>50\%$ of all deaths among individuals with end-stage renal disease are related to a CVD event [7]. In contrast, most prior studies that have investigated the relation between renal impairment and CVD in human immunodeficiency virus (HIV)-positive individuals have been small, have used relatively broad definitions of CVD, or have focused on single measures of renal function, which are subjected to random variation and the transient effects of acute illness [8–13]. The influence of a more sustained impairment of the estimated glomerular

filtration rate (eGFR) on well-defined CVD events in HIV-positive individuals is less clear.

Renal impairment is projected to become more prevalent among HIV-positive individuals in future years owing to aging and an accumulating burden of comorbidities and lifestyle-related risk factors. CVD is furthermore now one of the leading causes of non-AIDS-defining death in HIV-positive individuals [14]. A better understanding of the rates of CVD among HIV-positive individuals with renal impairment is therefore warranted to assist identification of those at highest risk with a need for intensified monitoring and initiation of preventive measures [15].

The relationship between renal impairment and CVD is complex and may be mediated through a variety of different pathways [3, 6, 14]. These include accelerated coronary and cerebrovascular atherosclerosis (which may be mediated in part by increased inflammation and oxidative stress) atrial fibrillation, and ventricular hypertrophy, which are common at severe levels of renal impairment and may, similar to electrolyte abnormalities, promote dysrhythmias, resulting in stroke or sudden cardiac death [3, 15–20]. Finally, renal impairment and CVD are

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known to share a common underlying risk factor profile, which includes hypertension, diabetes, dyslipidemia, smoking, injection drug use, obesity, ongoing inflammation, and black African origin [20, 21]. CVD, renal impairment, and many of the underlying shared individual risk factors are more prevalent among HIV-positive individuals than in the general population, and, hence, the association between renal impairment and CVD may be stronger in HIV-positive individuals [22, 23]. The aim of this analysis is to investigate the nature and relationship of various levels of sustained eGFR impairment with centrally adjudicated CVD endpoints in a large heterogeneous and contemporary cohort of primarily white HIV-positive individuals.

METHODS

Study Population

The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study is a large, prospective cohort collaboration established in 1999 and following >49 000 HIV-positive persons from 11 cohorts in Europe, the United States, and Australia; details have been published previously [17]. Data on centrally validated clinical events, including myocardial infarction, sudden cardiac death, stroke, invasive cardiovascular procedures, end-stage renal disease, and death, is collected in real time during routine clinical care. Information on sociodemographic factors, antiretroviral treatment, HIV viral load, CD4⁺ T-cell counts, AIDS-defining events, viral hepatitis, levels of creatinine and other laboratory biomarkers, and cardiovascular risk factors is collected electronically at enrollment and every 6 months thereafter.

End Point Definition

CVD events are reported using designated event forms (more information is available at: <http://www.chip.dk/Studies/DAD/Study-Documents>) and are defined as centrally validated fatal and nonfatal myocardial infarction, stroke, coronary angioplasty, coronary bypass, carotid endarterectomy, and sudden cardiac death. A fatal CVD event is defined as one of the above events leading to death within 28 days. Adjudication of CVD events is made in accordance with predefined algorithms, and only confirmed events are included in analysis. Sudden cardiac death is defined as a sudden death in which the underlying cause could not be established as a myocardial infarction, owing to the lack of data on symptoms, electrocardiogram findings, and changes in cardiac biomarkers, but in which cardiovascular risks were present at the time of death, according to the World Health Organization MONICA Dundee score [24], and without evidence of other nonatherosclerotic or noncardiovascular causes of death. All sudden cardiac deaths in the D:A:D study are reviewed by an external cardiologist.

Statistical Methods

D:A:D study participants with ≥ 2 eGFR measurements after 1 February 2004 (baseline for initiation of systematic creatinine

collection) were included and followed until the earliest of the following: first CVD event, death, 6 months after the last visit, or 1 February 2015. Persons with <3 months of follow-up from the first to the last eGFR measurement were excluded. The Cockcroft-Gault equation [25], standardized for body surface area [26], was used to estimate creatinine clearance, a surrogate for eGFR in this analysis [27, 28]. As several cohorts participating in D:A:D are prohibited from collecting ethnicity information, the Cockcroft-Gault equation was used, rather than an equation including ethnicity. Where eGFR measurements were performed more frequently than every 28 days, the median value was used and assigned to the median date. Confirmed baseline and time-updated (current) eGFRs were defined using 2 consecutive eGFR measurements, regardless of the time between measurements (per the definition minimum of 28 days). The confirmed baseline and current eGFRs were subsequently allocated to the following eGFR strata: >90, >60 to ≤ 90 , >30 to ≤ 60 , and ≤ 30 mL/minute/1.73 m². Where 2 consecutive eGFRs (<15% of all values) did not fall within the same eGFR strata, the mean of 2 eGFRs carried forward was used to assign an eGFR category.

Individuals with a prior CVD event were included, but only the first CVD event experienced during prospective follow-up after baseline was included as an event. Individuals could, however, experience ≥ 2 different types of CVD events on the same date.

Incidence rates were calculated per 1000 person-years of follow-up. Kaplan-Meier estimation was used to investigate time to CVD, stratified according to confirmed baseline eGFRs (>90, ≤ 90 to >60, ≤ 60 to >30, and ≤ 30 mL/minute/1.73 m²).

Poisson regression models stratified according to the confirmed current eGFR were used to model the CVD incidence rate ratios (IRRs), overall and stratified by individual CVD events. Potential confounders included in multivariate models were age (per 10 years older), sex, ethnicity, D:A:D enrollment cohort, nadir CD4⁺ T-cell count, HIV acquisition group, and family history of CVD. All remaining variables were adjusted for as time updated, including hepatitis B virus (HBV)/hepatitis C virus (HCV) coinfection, HIV RNA level (per log₁₀), CD4⁺ T-cell count, prior AIDS, hypertension (>150/>100 mm Hg or receipt of antihypertensive treatment), diabetes (confirmed diagnosis of diabetes mellitus or receipt of antidiabetic treatment), confirmed eGFR strata, smoking status (current, previous, never), dyslipidemia (total cholesterol level >6.2 mmol/L, high-density lipoprotein cholesterol level <0.9 mmol/L, triglyceride level >2.3 mmol/L, or receipt of lipid-level-lowering treatment), and prior CVD (confirmed diagnosis). Antiretroviral drug use was fitted as time-updated cumulative use (per 5 years; zidovudine, didanosine, zalcitabine, stavudine, lamivudine, emtricitabine, tenofovir disoproxil fumarate, abacavir, efavirenz, nevirapine, indinavir, saquinavir, ritonavir, nelfinavir, (fos)amprenavir, atazanavir, and darunavir) and current use

(currently receipt and use within the last 6 months; zidovudine, didanosine, zalcitabine, stavudine, lamivudine, emtricitabine, tenofovir disoproxil fumarate, and abacavir).

A number of sensitivity analyses were performed to test the robustness of the results. One analysis investigated death as a potential competing risk of CVD. Another analysis excluded all with a prior CVD event. Other analyses adjusted for the D:A:D chronic kidney disease (CKD) risk score [29] and the predicted CVD risk based on the Framingham CVD prediction model [30] to estimate how much of the CVD risk is explained through common renal and CVD risk factors. The D:A:D CKD risk score is a 9-variable prediction score estimating the 5-year risk of developing CKD in HIV-positive individuals. Individuals in the low CKD risk group (score, <0) have a 1 in 393 (0.3%) 5-year CKD risk, rising to 1 in 47 (2.1%) in the medium-risk group (score, 0–4) and 1 in 6 (16.7%) in the high-risk group (score ≥5) [29]. A final analysis investigated the association between current nadir eGFR and the percentage of follow-up time spent with an eGFR of ≤ 60 mL/minute/1.73 m² and CVD.

RESULTS

Study Population

A total of 35 357 persons with follow-up after 2004 and at least 2 eGFR measurement were included in analysis, [Supplementary Figure 1](#). Included individuals were predominantly white (48.1%) and male (73.9%), and the median age was 41 years (interquartile range [IQR], 35–48 years; [Table 1](#)). While 41.6% were smokers, 4.0% had diabetes, 8.9% had hypertension, and 0.7% had experienced a prior CVD event. At baseline, the median estimated 5-year risk of CKD was low overall (–1 [IQR –3 to 4]; corresponding to 0.3%) and medium in those developing a CVD event (4 [IQR, –1 to 9], corresponding to 2.1%; [Table 1](#)). A total of 558 persons were excluded from analysis because of missing CD4⁺ T-cell counts or viral load at baseline or because of insufficient follow-up. Excluded persons were more likely to be young, to be white, to be naive to combination antiretroviral therapy, to be positive for HCV, to have no family history of CVD, and to have experienced a prior AIDS event.

Age and eGFR

Among individuals younger than 40 years, 87.0% (13 660) had normal baseline renal function (confirmed eGFR, > 90 mL/minute/1.73 m²), and only 0.04% (7) had advanced renal impairment (confirmed eGFR, ≤ 30 mL/minute/1.73 m²). In contrast, among individuals older than 60 years, only 15.8% (321) had a confirmed baseline eGFR > 90 mL/minute/1.73 m², and 0.8% (17) had a confirmed baseline eGFR ≤ 30 mL/minute/1.73 m².

CVD Events

Over a median follow-up time of 8.0 years (IQR, 5.4–8.9 years; total person-years of follow-up, 258 480), 1357 persons developed 1646 CVD events (incidence rate, 5.2 events per 1000

Table 1. Baseline Characteristics

Characteristic	All Persons (n = 35 357)	Persons Developing CVD (n = 1357)
Male sex	26 124 (73.9)	1181 (87.3)
Ethnicity		
White	17 016 (48.1)	697 (51.4)
Black	2450 (6.9)	40 (3.0)
Other	716 (2.0)	12 (0.9)
Unknown	15 175 (42.9)	608 (44.8)
HIV acquisition group		
MSM	16 234 (45.9)	728 (53.7)
IDU	4529 (12.8)	154 (11.4)
Heterosexual	12 436 (35.2)	386 (28.4)
Other	2158 (6.1)	89 (6.6)
HBV ^a		
Positive	1597 (4.5)	46 (3.4)
Negative	31 169 (88.2)	1 213 (89.4)
Unknown	2591 (7.3)	98 (7.2)
HCV ^b		
Positive	6479 (18.3)	236 (17.4)
Negative	25 535 (72.2)	973 (71.7)
Unknown	3343 (9.5)	148 (10.9)
cART use	26 425 (74.7)	1 197 (88.2)
Prior AIDS event	8768 (24.8)	462 (34.1)
HIV RNA load < 400 copies/mL	20 828 (58.9)	956 (70.4)
Current smoker	14 715 (41.6)	688 (50.7)
BMI >30 ^c	1830 (5.2)	78 (5.7)
Family history of CVD	2712 (7.7)	179 (13.2)
Prior CVD ^d	240 (0.7)	72 (5.3)
Hypertension ^e	3133 (8.9)	264 (19.5)
Diabetes ^f	1425 (4.0)	163 (12.0)
eGFR, mL/min/1.73 m ^{2g}		
>90	24 937 (70.5)	656 (48.3)
>60 to ≤90	9378 (26.5)	559 (41.2)
>30 to ≤60	999 (2.8)	13.5 (10.0)
≤30	43 (0.1)	7 (0.5)
Framingham risk score (%)		
Low (0–5)	24 111 (68.2)	275 (18.9)
Moderate (5–10)	5821 (16.5)	290 (21.4)
High (>10)	5425 (15.3)	810 (59.7)
D:A:D study CKD risk score median (IQR) ^h	–1 (–3 to 4)	4 (–1 to 9)
Age, median (IQR)	41 (35–48)	50 (44–59)
CD4 ⁺ T-cell count, cells/mm ³ median (IQR)	44 (290–625)	441 (289–640)

Data are no. (%) of subjects or median value (interquartile range). Baseline was defined as 1 February 2004.

Abbreviations: cART, combination antiretroviral therapy; CKD, chronic kidney disease; CVD, cardiovascular disease; D:A:D, Data Collection on Adverse Events of Anti-HIV Drugs; eGFR, estimated glomerular filtration rate; HIV, human immunodeficiency virus; IDU, injection drug use; IQR, interquartile range; MSM, men who have sex with men.

^a Positivity was defined as detection of hepatitis B virus (HBV) surface antigen, HBV e antigen, or HBV DNA.

^b Positivity was defined as detection of anti-hepatitis C virus (HCV) antibody and either detection or unknown status of HCV RNA.

^c Body mass index (BMI) was calculated as the weight in kilograms divided by the height in meters squared.

^d As diagnosed on a D:A:D study CVD event form.

^e Defined as a blood pressure of >150/>100 mm Hg or receipt of antihypertensive treatment.

^f Defined as the recording of a diagnosis of diabetes on a D:A:D study event form or receipt of antidiabetic treatment.

^g Calculated using the Cockcroft-Gault equation.

^h A score of <0 indicated a low 5-year CKD risk (0.3%); 0–4, a medium risk (2.1%); and ≥5, a high risk (16.7%).

person-years of follow-up [95% confidence interval, CI, 5.0–5.5]). The CVD events included 586 myocardial infarctions (11.1% fatal), 430 strokes (8.6% fatal), 510 coronary angioplasties (1.6% fatal), 96 coronary bypasses (2.1% fatal), 19 carotid endarterectomies (0% fatal), and 5 sudden cardiac deaths. A total of 284 persons (21.0%) experienced >1 CVD event on the same date, most commonly a myocardial infarction and coronary angioplasty (n = 259).

Median eGFRs and Incident CVD

The median eGFR measured in individuals prior to their CVD event was significantly lower (85 mL/minute/1.73 m² [IQR, 69–102 mL/minute/1.73 m²]) than the median eGFR measured during follow-up in individuals not experiencing a CVD event (94 mL/minute/1.73 m² [IQR, 79–110 mL/minute/1.73 m²]; *P* < .0001). Likewise, a greater proportion of individuals experiencing a CVD event had some level of confirmed reduced eGFR, compared with individuals not experiencing an event (Figure 1). When comparing the individual types of CVD events, those experiencing a coronary bypass event had significantly lower confirmed eGFRs as compared to those with all other CVD event types (*P* = .018). When excluding coronary bypass events, there were no statistically significant differences in confirmed eGFR levels prior to a CVD event (*P* = .068). Likewise, when comparing those with an invasive cardiovascular procedure (coronary angioplasty, carotid endarterectomy, or coronary bypass) to those with a myocardial infarction and/or

stroke, there was no statistically significant difference (*P* = .55; Figure 1).

Confirmed Baseline eGFRs and Incident CVD

We observed a clear inverse relationship between confirmed eGFRs at baseline and incident CVD, with 1.8% (95% CI, 1.6%–2.0%) estimated to have progressed to CVD at 5 years among those with a confirmed baseline eGFR > 90 mL/minute/1.73 m², increasing to 4.1% (95% CI, 3.5%–4.6%) for those with a baseline eGFR of 60–90 mL/minute/1.73 m², 10.8% (95% CI, 8.7%–12.9%) for those with a baseline eGFR of 30–60 mL/minute/1.73 m², and 21.1% (95% CI, 6.6%–35.6%) for those with confirmed baseline eGFR ≤ 30 mL/minute/1.73 m² (Figure 2).

Among individuals with moderately impaired baseline eGFR (confirmed eGFR ≤ 60 mL/minute/1.73 m²) who developed a CVD event, we did not observe a statistically significant differences (*P* = .63) in the time to different CVD events, with a median time to CVD event of 45 months (IQR, 21–76 months).

Confirmed Current eGFR and Incident CKD

There was a strong and inverse linear relationship between confirmed current eGFR and CVD in univariate analysis: IRRs increased from 1.00 at eGFR > 90 mL/minute/1.73 m² to 14.09 (95% CI, 9.58–20.74) at eGFR ≤ 30 mL/minute/1.73 m² (Figure 3). Adjustment for increasing age explained most of the relationship between eGFR and CVD at eGFRs >30 mL/minute/

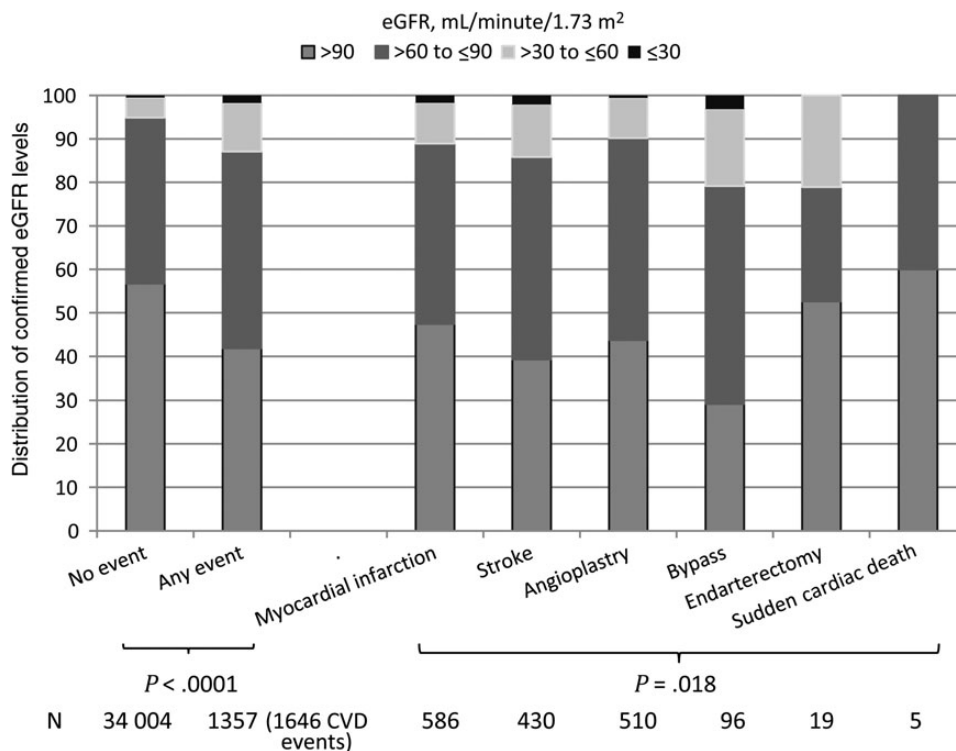


Figure 1. Confirmed current estimated glomerular filtration rate (eGFR) levels prior to cardiovascular disease (CVD) event. Confirmed current eGFR for those with a CVD event is the last measured median eGFR prior to the event. For those without a CVD event, confirmed current eGFR is the last measured median eGFR during follow-up.

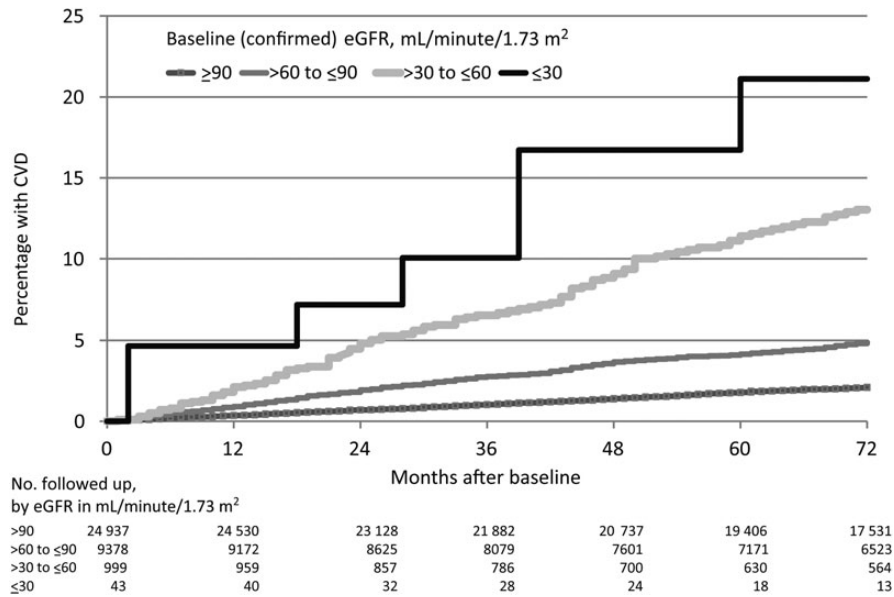


Figure 2. Kaplan–Meier progression to cardiovascular disease (CVD), by confirmed baseline estimated glomerular filtration rate (eGFR).

1.73 m², although all eGFRs <80 mL/minute/1.73 m² were associated with an increased incidence of CVD of approximately 30%–40%. At a confirmed current eGFR ≤30 mL/minute/1.73 m², a significantly increased incidence of CVD remained

independent of age (IRR, 4.21 [95% CI, 2.81–6.30]; Figure 3). Further adjustment for other potential confounders, including individual antiretroviral drugs, had relatively limited impact on the overall association (IRR, 3.08 [95% CI, 2.04–4.65] at

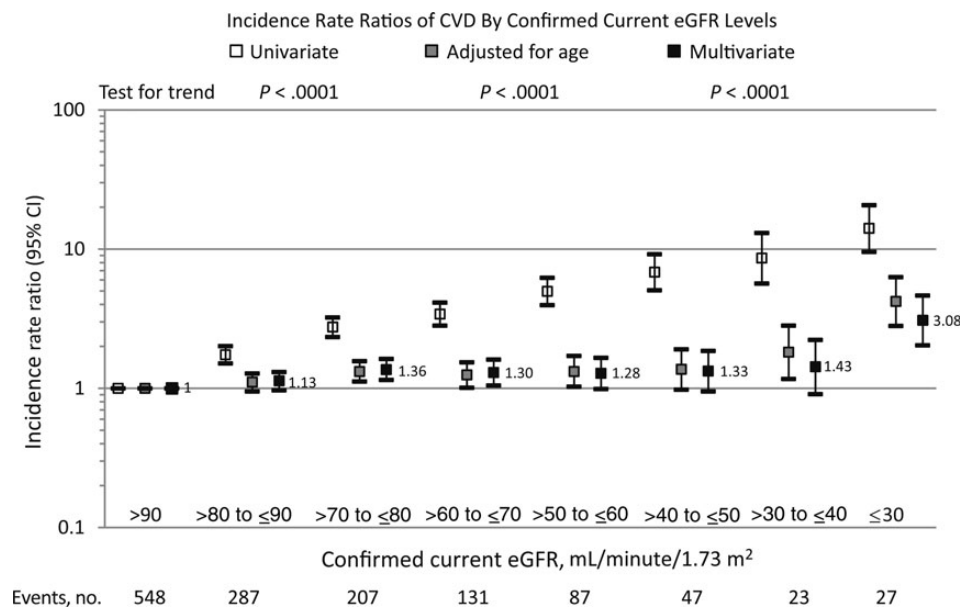


Figure 3. Cardiovascular disease (CVD) incidence rate ratios by confirmed current estimated glomerular filtration rate (eGFR). Multivariate analysis adjusted for age, sex, ethnicity, Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study enrollment cohort, nadir CD4⁺ T-cell count, mode of human immunodeficiency virus (HIV) acquisition group, and family history of CVD at baseline. Time-updated variables include hepatitis B virus/hepatitis C virus coinfection, HIV RNA level, CD4⁺ T-cell count, prior AIDS, hypertension, diabetes, confirmed eGFR strata, smoking status, dyslipidemia, prior CVD, exposure to antiretroviral drugs fitted as cumulative use (to zidovudine, didanosine, zalcitabine, stavudine, lamivudine, emtricitabine, tenofovir disoproxil fumarate, abacavir, efavirenz, nevirapine, indinavir, saquinavir, ritonavir, nelfinavir, (fos)ampreavir, atazanavir, and darunavir) and current use (zidovudine, didanosine, zalcitabine, lamivudine, stavudine, emtricitabine, tenofovir disoproxil fumarate, and abacavir). Abbreviation: CI, confidence interval.

confirmed eGFR ≤ 30 mL/minute/1.73 m² as compared to confirmed eGFR ≥ 90 mL/minute/1.73 m²; Figure 3). The exclusion of the 240 individuals with a CVD event prior to baseline led to entirely consistent results (data not shown).

In a bivariate analysis, adjustment for the Framingham score (as a continuous variable) explained some of the association between confirmed current eGFR and CVD, but not to the same extent as age alone (data not shown). In another analysis, which adjusted for the estimated 5-year D:A:D CKD risk score, individuals with a medium CKD risk (ie, a score of 0–4) had a 2.56-fold increased incidence of CVD (IRR, 2.56 [95% CI, 2.22–2.95]), and individuals with a high CKD risk (ie, a score of ≥ 5) had an almost 5-fold increased incidence of CVD (IRR, 4.98 [95% CI, 4.37–5.68]) as compared to persons with a low estimated CKD risk (ie, a score of <0). After adjustment for other potential confounders (as shown in Figure 3) not included in the D:A:D CKD risk score (with the exception of age), those with a medium or high CKD risk score continued to have a significantly higher risk of CVD (IRR, 1.29 [95% CI, 1.10–1.50] and 1.43 [95% CI, 1.19–1.71], respectively).

There was no strong evidence suggesting that the observed association between confirmed current eGFRs and CVD differed among the individual types of CVD events. When restricting the analysis to fatal CVD events only, all observed associations were further strengthened (data not shown). Our findings were furthermore consistent in different age groups (test for interaction, $P = .88$) and after accounting for death as a possible competing risk for CVD (data not shown). The association between CVD and confirmed eGFR seen in the primary analyses was largely unchanged by fitting renal function as the current nadir eGFR and as the percentage of follow-up spent with a moderately impaired eGFR (eGFR ≤ 60 mL/minute/1.73 m²; data not shown).

Confirmed Current eGFRs and Number of CVD Events

Individuals with higher confirmed current eGFRs experienced ≥ 2 CVD events (at the same date) more frequently than those with lower eGFR levels (24.7% at eGFRs > 90 mL/minute/1.73 m² vs 4.2% at eGFRs ≤ 30 mL/minute/1.73 m²; $P = .0034$), most commonly myocardial infarction and coronary angioplasty. Furthermore, the proportion of individuals experiencing a fatal CVD event (with death occurring ≤ 28 days following the event) was strongly related to the confirmed current eGFR, increasing from 4.4% in individuals with a confirmed current eGFR > 90 mL/minute/1.73 m² to 25.0% in individuals with a confirmed current eGFR ≤ 30 mL/minute/1.73 m² ($P < .0001$).

DISCUSSION

In this large heterogeneous cohort of HIV-positive individuals, we found a strong association between centrally adjudicated CVD events and advanced levels of renal impairment

(confirmed eGFR ≤ 30 mL/minute/1.73 m²). Almost 60% of all individuals experiencing a CVD event had an eGFR ≤ 90 mL/minute/1.73 m², based on the latest median eGFR before the event, compared with $<40\%$ of those without an event. We further showed that development of a CVD event was considerably faster among those with a severely impaired eGFR at baseline. Among HIV-positive individuals with a confirmed baseline eGFR ≤ 30 mL/minute/1.73 m², $>20\%$ were estimated to have developed CVD after 5 years.

In previous studies from D:A:D, we investigated the inverse relation between CVD events and eGFR, focusing on CVD as a risk factor for various levels of chronic renal impairment [28, 29, 31]. Interestingly, these previous data also supported a strong association between CVD and renal function, which significantly diminished after accounting for other risk factors, suggesting an underlying biological mechanism at least partly mediated by other factors. We have also previously showed an association between the use of certain antiretroviral drugs and CVD and renal impairment [28, 30, 32]. The results of this analysis are entirely consistent with these prior findings, and adjustment for the use of individual antiretroviral drugs did not have any major impact on the association between impaired eGFR and CVD. Data from this analysis point toward increasing age as the main underlying driver of the inverse relationship between eGFR and CVD, in particular at mild to moderately impaired eGFR levels [14]. At more advanced levels of renal impairment (eGFR ≤ 30 mL/minute/1.73 m²), there are additional pathways between renal impairment and CVD that are not immediately related to any of the known common risk factors on the shared causal pathway, such as diabetes, hypertension, and immunosuppression. Regardless of the underlying pathology, the high rates of CVD observed in older individuals with mild to moderate renal impairment highlight the need for intensified monitoring and a search for effective prophylactic measures for impaired renal function and CVD in the aging HIV-population.

In other studies of HIV-positive individuals, a smaller cross-sectional analysis in the FRAM study did not confirm an association between carotid intima-media thickness and eGFR after accounting for older age, sex, and ethnicity [13]. Likewise, a British study did not find an association between eGFR as a continuous variable and coronary heart disease, although those with an eGFR < 75 mL/minute/1.73 m² already had a >4 -fold increased incidence [9]. In a recent EuroSIDA study, both the follow-up time with a low eGFR and an eGFR ≤ 30 mL/minute/1.73 m² were predictive of non-AIDS-defining events, including CVD, but power was limited [12]. An older large cohort study among HIV-positive US veterans showed an almost 6-fold higher association between an eGFR ≤ 30 mL/minute/1.73 m², albuminuria, and CVD, although this study also included peripheral artery disease and heart failure [10].

Our findings do not suggest that the association between declining renal function and CVD is stronger or starts at higher eGFR levels in HIV-positive persons than in the general population, as was hypothesized on the basis of the higher occurrence of common renal and CVD risk factors and increased immune activation [1, 4, 33, 34]. There is, however, ongoing ambiguity in the general population with regard to the strength of the association between impaired renal function and CVD. Some studies report only an association with CVD at advanced levels of renal impairment (eGFRs ≤ 30 mL/minute/1.73 m²), while others report associations already at higher eGFR levels [1, 4, 5, 9, 10, 14, 33, 34]. However, the definitions of CVD differ considerably in these studies, ranging from subclinical imaging-verified diagnoses of atherosclerosis to various clinical events ascertained with different levels of certainty. The differences in the incidence of common risk factors and of CVD and renal impairment may also partly explain the conflicting results. Importantly, the D:A:D study focuses on hard clinical CVD events exclusively, and information on nonfatal heart failure or milder forms of ischemic CVD such as angina pectoris is not collected. This methodology may explain why more severe levels of renal impairment are necessary to establish an association with CVD. Interestingly, none of the widely accepted CVD risk prediction models currently include renal impairment in the estimates [30, 32], but the proportion of individuals with advanced renal impairment may be too limited to date.

We also found that fatal outcomes of a CVD event were more common at lower as compared to higher eGFR levels, which may be related to a more severe clinical event or to the fact that those with advanced levels of renal impairment provide a more fragile phenotype with less ability to cope with CVD complications. Likewise, fewer multiple CVD events occurred on the same date among those with lower eGFRs. This finding may be related to the increased fatality rate at lower eGFRs or to the possibility that those with lower eGFRs are less likely to undergo invasive cardiovascular procedures as secondary prophylaxis, owing to concerns about radiocontrast-induced nephrotoxicity. Interestingly, there was no evidence of a relation between the eGFR level and type of CVD outcome (ie, a myocardial infarction did not seem to occur at different eGFRs levels as compared to other CVD events), with the exception of coronary bypass. Coronary bypass was more commonly performed at lower eGFRs, compared with other CVD events, which may suggest more-advanced atherosclerosis with multiple vessel disease in this population.

The potential limitations of the analysis should be acknowledged. We may have underestimated the proportion of individuals with an impaired eGFR, as those excluded from analysis were more likely to have common renal risk factors; hence, the provided relation between eGFR and CVD is of a conservative nature. Proteinuria is a potential source of unmeasured confounding because it not measured systematically in the D:

A:D study and may also have moderating effects, as it is a strong independent risk factor for both CVD and CKD [35]. Furthermore, renal impairment may have developed secondary to a CVD event as part of a cardiorenal syndrome, with potential for reverse causality. However, in this analysis, eGFR impairment preceded all prospectively investigated CVD events [36]. Finally, nonischemic events such as cardiac arrhythmias and ventricular hypertrophy were not directly included in the CVD definition but may have contributed more indirectly via stroke and sudden cardiac death events.

In summary, in a large, contemporary cohort of HIV-positive individuals, we observed a strong relationship between confirmed impaired renal function and incident CVD. More than 1 in 5 of those with advanced levels of renal impairment were estimated to have developed CVD by 5 years, with an increasing 28-day CVD fatality rate as the eGFR declined. Our findings highlight the need for intensified monitoring for emerging CVD, in particular in older individuals with continuously low eGFRs levels. Our findings also call for an increased focus on applying different renal and cardiovascular preventive measures in HIV-positive individuals.

STUDY GROUP COHORTS AND MEMBERS

D:A:D participating cohorts (locations): the Australian HIV Observational Database (AHOD; Australia), Aquitaine (France), Athena (the Netherlands), the Barcelona Antiretroviral Surveillance Study (BASS; Spain), the Terry Bein Community Programs for Clinical Research on AIDS (CPCRA; United States), EuroSIDA (multinational), HivBivus (Sweden), the Italian Cohort Naive to Antiretrovirals (ICONA; Italy), Nice (France), the Swis HIV Cohort Study (SHCS; Switzerland), and St. Pierre (Belgium). D:A:D steering committee: W. El-Sadr, G. Calvo, F. Dabis, O. Kirk, M. Law, A. d'Arminio Monforte, L. Morfeldt, C. Pradier, P. Reiss, R. Weber, S. De Wit, B. Powderly, N. Shortman, C. Moecklinghoff, G. Reilly, X. Franquet, C. A. Sabin, A. Phillips, A. Mocroft, L. Ryom, and J. D. Lundgren (chair).

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Supplementary Data

[Supplementary materials](#) are available at <http://jid.oxfordjournals.org>. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes

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