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CLINICAL RESEARCH
Coronary artery disease

Acute coronary syndromes in human immunodeficiency virus patients: a meta-analysis investigating adverse event rates and the role of antiretroviral therapy

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Aims Highly active antiretroviral therapy (HAART) dramatically reduces human immunodeficiency virus (HIV)-associated morbidity and mortality, but adverse effects of HAART are becoming an increasing challenge, especially in the setting of acute coronary syndromes (ACS). We thus performed a comprehensive review of studies focusing on ACS in HIV patients.

Methods and results MEDLINE/PubMed was systematically screened for studies reporting on ACS in HIV patients. Baseline, treatment, and outcome data were appraised and pooled with random-effect methods computing summary estimates [95% confidence intervals (CIs)]. A total of 11 studies including 2442 patients were identified, with a notably low prevalence of diabetes [10.86 (4.11, 17.60); 95% CI]. Rates of in-hospital death were 8.00% (2.8, 12.5; 95% CI), ascribable to cardiovascular events for 7.90% (2.43, 13.37; 95% CI), with 2.31% (0.60, 4.01; 95% CI) developing cardiogenic shock. At a median follow-up of 25.50 months (11.25, 42; 95% CI), no deaths were recorded, with an incidence of 9.42% of acute myocardial infarction (2.68, 16.17; 95% CI) and of 20.18% (9.84, 30.51; 95% CI) of percutaneous coronary revascularization. Moreover, pooled analysis of the studies reporting incidence of acute myocardial infarction in patients exposed to protease inhibitors showed an overall significant risk of 2.68 (odds ratio 1.89, 3.89; 95% CI).

Conclusion Human immunodeficiency virus patients admitted for ACS face a substantial short-term risk of death and a significant long-term risk of coronary revascularization and myocardial infarction, especially if receiving protease inhibitors.

Keywords Acute coronary syndromes • HIV • Mortality • Antiretroviral therapy; Meta-analysis • Observational registries

Introduction

Antiretroviral therapies dramatically reduced human immunodeficiency virus (HIV)-associated morbidity and mortality.[1] Consequently, detrimental effects of both disease progression and antiretroviral therapy are becoming an increasing challenge for physicians managing this high-risk subset of patients.[2]

In the USA, cardiovascular disease represents the third cause of death or hospitalization for these patients.[3] Coronary artery disease is an emerging complication, related both to traditional risk factors and to specific features of these patients. Actually smoking and hypertriglyceridaemia are more common than among non-HIV patients, while both the heightened proinflammatory state and antiretroviral drugs[4–8] offer a substrate for the development of premature atherosclerosis and atherothrombosis.[9–11]

Many studies have provided features and outcomes with acute coronary artery disease in HIV patients, and the influence of antiretroviral therapy in them, providing notable results, often limited

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by the small number of patients. Especially, some reports demonstrated a higher incidence of acute coronary syndromes (ACS) in patients under treatment with antiretroviral drugs, in particular protease inhibitors.[12,13]

Thus, a meta-analysis was performed to critically appraise risk factors and outcomes of these patients, and their relationship with antiretroviral drugs.

Methods

The present research was elaborated according to the current guidelines, including the recent Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) amendment to the Quality of Reporting of Meta-analyses (QUOROM) statement, and recommendations from The Cochrane Collaboration and Meta-analysis Of Observational Studies in Epidemiology (MOOSE).[14–17] No language restriction was applied.

Search strategy and study selection

Pertinent articles were searched in Medline, Cochrane Library, Biomed Central, and Google Scholar in keeping with established methods[15] with Mesh strategy and with terms related to HIV patients admitted with a diagnosis of ACS: (coronary AND (stent* OR ptca OR angioplasty OR cabg OR (bypass AND (graft* OR surgery)) AND (hiv OR aids OR (human AND immunodeficiency AND virus)). Studies appraising only HIV patients or HIV and non-HIV patients were included.

Two independent reviewers (G.B.-Z. and F.D.) first screened retrieved citations at the title and/or abstract level, with divergences resolved after consensus. If potentially pertinent, they were then appraised as complete reports according to the following explicit selection criteria. Studies were included if investigating HIV patients presenting with ACS, while exclusion criteria were (i) non-human setting, (ii) duplicate reporting (in which case the manuscript reporting the largest sample of patients with HIV was selected), or (iii) HIV patients undergoing cardiac surgical procedure other than for ACS.

Data extraction

Two unblinded independent reviewers (G.B.-Z. and F.D.) abstracted the following data on pre-specified forms: authors, journal, and year of publication, location of the study group, baseline features, death, myocardial infarction, and revascularization. Endpoints of interest were incidence of adverse outcomes and their relationship to antiretroviral therapies. Rates of death, of cardiovascular death, and of cardiogenic shock were appraised. Moreover, at follow-up, rates of myocardial infarction, evaluated according to European Guidelines,[16] and of percutaneous coronary revascularization (both repeat revascularization on the target vessel/lesion and on *de novo* stenosis) were evaluated.

Internal validity and quality appraisal

Unblinded independent reviewers (G.B.-Z. and F.D.) evaluated the quality of included studies on pre-specified forms. Modifying the MOOSE items to take into account the specific features of included studies,[17] we separately abstracted and appraised study design, setting, data source, as well as risk of analytical, selection, adjudication, detection, and attrition bias (expressed as low, moderate, or high risk of bias, as well as incomplete reporting leading to inability to ascertain the underlying risk of bias). Moreover, we awarded overall credibility of studies included to summarized previous features. Zero points were assigned for retrospective design and one-centre study, and one for prospective arrangement and for a multicentre setting. Moreover, two points were ascribed for low risk of bias, one for moderate risk, and zero for high risk or unclear. If the sum of these scores was 10, a very high credibility was granted, if it was between 7 and 9 high, between 4 and 6 moderate, between 1 and 3 low, and 0 very low.

Data analysis and synthesis

Continuous variables are reported as mean (standard deviation) or median (range). Categorical variables are expressed as *n/N* (%). Statistical pooling was performed according to a random-effect model with generic inverse-variance weighting, computing risk estimates with 95% confidence intervals (CIs), using RevMan 5 (The Cochrane Collaboration, The Nordic Cochrane Centre, and Copenhagen, Denmark). A small study bias was appraised by graphical inspection of funnel plots. Standard hypothesis testing was set at the two-tailed 0.05 level.

Results

A total of 236 citations were first screened and appraised at the abstract level; 19 articles were selected, among which 4 were excluded because of investigating also non-coronary cardiac surgery,[18–21] three because of including HIV patients undergoing percutaneous coronary intervention also in stable clinical settings,[1,22,23] and 2 because of investigating baseline features of HIV patients.[4,24] Finally, 11 studies were included in our review[2,12,13,19,25–31] (*Figure 1*).

The methodological assessment is reported in *Table 1*, showing an overall good quality of the selected studies, most of them being prospective, half of them multicentre, without a high risk of analysed bias. Moreover, for each study, definitions of adverse events and single follow-up were evaluated (see Supplementary material online, Appendix *Table SA*).

A total of 2442 patients were included, showing at pooled analysis an overall average incidence of traditional cardiovascular risk factors, except for diabetes [10.86 (4.11, 17.60); 95% CI] (*Table 2*).

Pooled analysis of HIV disease characteristics are reported in *Table 3*, showing a time from HIV diagnosis to ACS of 7.45 years (2.38, 12.51; 95% CI), with most of the patients exposed to nucleoside reverse-transcriptase inhibitors [84.23% (74.15, 94.3; 95% CI)] and protease inhibitors [66.21% (59.77, 72.65; 95% CI)].

At admission, most patients presented with ST-segment elevation myocardial infarction (STEMI) [57.19% (47.64, 66.75; 95% CI)], with one-vessel disease as the most angiographic presentation [52.83% (34.83, 70.83; 95% CI)], and percutaneous transluminal coronary angioplasty as the most exploited revascularization strategy [54.23% (38.97, 69.49; 95% CI)] (*Table 4*).

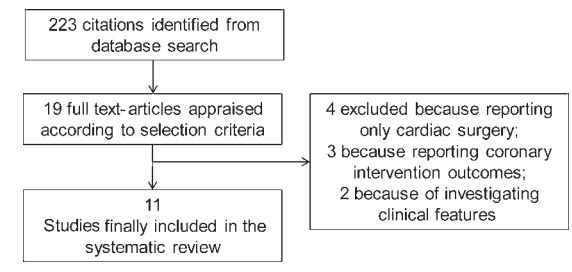

Figure 1 Review profile.

Table 1 Methodological evaluation and quality appraisal of selected studies

	11 studies (%)
Region of origin	1 Africa (10%) 4 Europe (36%) 5 North America (45%) 1 worldwide (10%)
Location of the study	
One centre	5 (45%)
Multicentre	6 (55%)
Organization of the study	
Retrospective	4 (30%)
Prospective	7 (70%)
Source of data	
Clinical database	10 (91%)
Organizational database	1 (9%)
Risk of analytical bias	
Low	3 (28%)
Medium	8 (72%)
Risk of selection bias	
Low	7 (72%)
Medium	4 (28%)
Risk of attrition bias	
Low	6 (54%)
Medium	3 (27%)
Unclear	2 (28%)
Risk of adjudication bias	
Low	1 (10%)
Medium	6 (54%)
Unclear	4 (36%)
Overall credibility	
Low	1 (10%)
Medium	5 (45%)
High	4 (32%)
Very high	1 (10%)

Table 2 Cardiovascular evaluation

	Pooled analysis (95% CI)[a]
Age (years)	61 (58, 64)
Male gender	80.45 (77.22, 83.69)
Hypertensive patients	22.29 (14.23, 30.34)
Dyslipidaemic patients	42.50 (33.35, 51.64)
Patients with hypertriglyceridaemia	45.03 (23.68, 66.38)
Diabetic mellitus type 2 patients	10.86 (4.11, 17.60)
Patients actual or previous smoker	60.30 (56.62, 63.99)

[a]All data reported as mean or percentages.

Rates of in-hospital death (*Figure 2*) were 8.00% (2.8, 12.5; 95% CI), ascribable to cardiovascular events for 7.90% (2.43, 13.37; 95% CI), with 2.31% (0.60, 4.01; 95% CI) developing cardiogenic shock.

Table 3 Human immunodeficiency virus disease characteristics

	Pooled analysis (95% CI)[a]
Time from diagnosis of HIV infection (years)	7.45 (2.38, 12.51)
Median CD4+ cell count per mm^3	382.71 (309.34, 456.09)
Patients exposed to protease inhibitors (previous and current)	66.21 (59.77, 72.65)
Duration of therapy (years)	4.01 (0.95, 7.07)
Patients exposed to non-nucleoside reverse-transcriptase inhibitors (previous and current)	29.81 (8.36, 51.26)
Patients exposed to nucleoside reverse-transcriptase inhibitors	84.23 (74.15, 94.31)

[a]All data reported as mean or percentages.

Table 4 Acute coronary syndrome presentation, angiographic findings, and revascularization strategies

	Pooled analysis (95% CI)[a]
Patients admitted with unstable angina/ non-segment elevation myocardial infarction	46.08 (38.13, 54.02)
Patients admitted with segment elevation myocardial infarction	57.19 (47.64, 66.75)
Angiographic findings	
One-vessel disease	52.83 (34.83, 70.83)
Multivessel disease	46.27 (36.30, 56.24)
Percutaneous transluminal coronary angioplasty	54.23 (38.97, 69.49)
Coronary artery bypass graft	11.80 (4.32, 19.28)

[a]All data reported as mean or percentages.

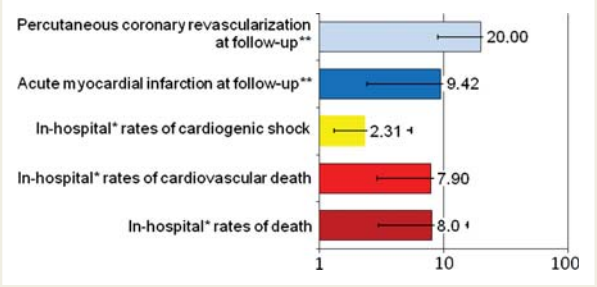

Figure 2 In-hospital and long-term outcomes. *Up to 30 days. **Follow-up of 25.50 (11.25, 42 months, 95% CI).

At a median follow-up of 25.50 months (11.25, 42; 95% CI), no deaths were recorded, with an incidence of 9.42% of acute myocardial infarction (2.68, 16.17; 95% CI) and of 20.18% (9.84, 30.51; 95% CI) of percutaneous coronary revascularization.

Moreover, pooled analysis of two[25,28] studies reporting the incidence of acute myocardial infarction in patients exposed to protease inhibitors showed an overall significant risk of 2.68 (odds ratio 1.89, 3.89; 95% CI).

Discussion

Nowadays, HIV-infected patients live longer owing to more effective antiretroviral therapy. At the same time, while this population becomes older, the cardiovascular risk of morbidity and death increases, and also the prevalence of chronic conditions related to this disease. With our systematic review and meta-analysis, we intended to summarize available data about risk factors, angiographic and clinical presentation at admission, and safety of antiretroviral therapy, reporting the current knowledge about the physiopathology of HIV infection.

The risk of coronary heart disease in HIV patients is influenced both from traditional risk factors and from specific features of this disease. Our meta-analysis shows an overall average incidence of traditional cardiovascular risk factors, except for diabetes, as can be expected in a young population. In contrast, in some studies, cigarette smoking was more prevalent in HIV patients.[32] Moreover, lack of data makes it not possible to analyse the burden of illicit drug users, which was reported more frequently among HIV-infected patients and which i's known to confer a higher thrombotic risk.[33] Nonetheless, as confirmed in the present work, in various large cohorts, HIV-infected patients showed high percentages of hypertriglyceridaemia, also related to their young age.[34,35] Many authors[36–38] suggest virus involvement in the atherosclerosis process through direct effects on cholesterol processing and transport, attraction and activation of monocytes at the intimal wall, inducing inflammatory response and endothelial proliferation.

In our meta-analysis, high rates of in-hospital death were recorded, probably because of STEMI being the most common presentation and of frequent occurrence of multivessel. ST-segment elevation myocardial infarction rates were higher than in contemporary ACS registries of non-HIV patients,[39,40] and similar differences were found for multivessel involvement. These two factors combined together could easily explain high rates of in-hospital events in HIV patients.[41] The peculiar type of coronary disease in HIV patients derived both from cardiovascular risk factors and enhanced from viral pathological process and side effects of antiretroviral drugs could explain such findings.

Furthermore, our report confirms an important risk of non-fatal reinfarction after ACS. This finding could be in part explained considering the young age of the population. Also the prothrombotic state may be involved in the higher incidence of thrombo-embolic events and in-stent thrombosis as reported in some studies.[19] The whole mechanisms underlying the disease are probably not completely clear, but again the HIV infection by itself and the antiretroviral therapy associated with chronic inflammation could play a role in the risk of plaque rupture and atherothrombosis.[42,43] As reported previously,[44,45] HIV infection has a direct toxic effect upon the endothelium and increases interleukin-6 production that is implicated in the pathogenesis of ACS. Moreover, the prothrombotic tendency increases proportionally to the viral load and the CD4 cell count.

No deaths were recorded in the follow-up. This could be due to many reasons. First, HIV patients may benefit from the use of more recent therapies and/or aggressive risk factor modification. Moreover, the present meta-analysis included studies obtained from centres with great experience and expertise in managing patients with HIV and coronary artery disease.

Finally, we observe that most of the patients presenting with coronary artery disease are exposed to protease inhibitors or nucleoside reverse-transcriptase inhibitors. In the pooled analysis, we are able to include only the protease inhibitors therapy, whereas incomplete data about other therapies are available in the selected articles. The metabolic syndrome consisting of lipid abnormalities and insulin resistance induced by the protease inhibitors certainly plays a role as a cofactor promoting the progression of underlying coronary lesions eliciting plaque inflammation and rupture. Anyway, as reported from many authors,[46,47] a clear dose–effect relationship has not been found. The better way to manage these patients is addressing the modifiable risk factor, keeping close attention to drug interactions in the presence of a high cardiovascular risk profile.

Limitations

Our work shares several important limitations. First, data about the odds ratio for myocardial infarction after proton-pump inhibitors use derived neither from randomized clinical trial nor from multivariate adjustment, thus being generating hypothesis only, without the aim of inference. Moreover, we appraised infrequent events, with all the limits about reporting uncommon outcomes.[47] Secondly, no data were pooled about the influence of nucleoside and non-reverse-transcriptase inhibitors on outcomes, because of the absence in the included original researches, Thirdly, data about illicit drugs used, especially cocaine, were present in only one study,[2] and thus, it was not possible to address their influence on outcomes. Furthermore, in the selected articles, data about chemokines receptor CCR5 inhibitors[48] (entry inhibitors) therapy were not reported probably because of its recent approval by the Food and Drug Administration.[45] These classes of drugs could provide new insights because of the critical role of chemokines and their receptors in the pathology of atherosclerosis. Moreover, no data on cardiac rupture and reperfusion success were obtained, thus limiting the exploration of mechanisms of in-hospital death.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Conflict of interest: none declared.

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