Evaluation of Cardiovascular Disease Risk in HIV-1–Infected Patients Treated with Darunavir

Magda Opsomer1 · Dessislava Dimitrova2 · Johan Verspeelt1 · Amy Purrington3 · Abdul Mehbob4 · Scott Chavers2 · Helen Pai5 · Simon Vanvegge1 · Donghan Luo2 · Kimberley Brown6 · Christiane Moecklinghoff7 · Richard E. Nettles6 · Katia Boven2

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Abstract

Introduction We evaluated cardiovascular disease (CVD) risk associated with darunavir treatment and examined the demographic/clinical characteristics of darunavir users based on data from Janssen-sponsored clinical trials, post-marketing pharmacovigilance databases, and administrative claims databases.

Methods First, selected CVD events [myocardial infarction, stroke, sudden death, invasive cardiovascular procedures (coronary artery angioplasty or bypass, or carotid endarterectomy)] were analyzed in 19 Janssen-sponsored phase 2–4 studies (incidence rates estimated from pooled data; 95% confidence intervals derived from Poisson distribution). Second, analyses were conducted to identify spontaneously reported CVD events in post-marketing pharmacovigilance databases and evaluate disproportional reporting of CVD events for darunavir (using Empirical Bayesian Geometric Mean scores). Third, baseline demographic/clinical characteristics of human immunodeficiency virus-1 (HIV-1)–infected patients in general and new users of darunavir and atazanavir were explored using three US administrative claims databases.

Results Among 19 Janssen-sponsored clinical trials (treatment durations ≤ 6 years), the CVD event rate (95% CI) per 1000 person-years (pooled population; n = 5713) was 6.15 (2.91–11.89), and was lower for patients who used once-daily darunavir/ritonavir 800/100 mg [0.71 (0.16–3.05); n = 1326] versus twice-daily darunavir/ritonavir 600/100 mg [9.21 (4.94–16.04); n = 3058]. Trend analysis of post-marketing pharmacovigilance data showed that cumulative CVD event reporting rates for darunavir users (any dose) generally declined over time. Spontaneously reported CVD events were not disproportionately reported with darunavir versus other protease inhibitors. Compared with the general HIV-1–infected population and atazanavir users, higher proportions of darunavir users were male, older, and had comorbidities associated with CVD risk based on results from US administrative claims databases.

Conclusions This comprehensive review of Janssen-sponsored clinical trial, post-marketing, and epidemiological data does not suggest that CVD should be considered an important risk for users of darunavir.

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Magda Opsomer
mopsomer@its.jnj.com

Extended author information available on the last page of the article
Key Points

People living with HIV-1 infection have an increased risk of developing cardiovascular disease (CVD).

Using 3 different approaches, we evaluated the CVD risk associated with use of the antiretroviral agent darunavir, and examined demographic and clinical characteristics of darunavir users.

This comprehensive review of Janssen-sponsored clinical trial, post-marketing, and epidemiological data does not suggest that CVD should be considered an important risk for users of darunavir.

Our findings are strengthened by the combination of analyses and, taken together, they offer important insights into the relationship between darunavir and CVD.

1 Introduction

Cardiovascular disease (CVD) is a leading cause of death in the USA and worldwide [1, 2] and individuals with human immunodeficiency virus (HIV)-1 infection are at increased risk of CVD [2–5]. As HIV-1–infected patients age, they are more likely than their non-infected peers to develop comorbidities such as hypertension, diabetes, dyslipidemia, and renal dysfunction [3, 5, 6]. There are multiple factors that can increase the risk of CVD in people living with HIV-1, including the HIV-1 infection itself as well as conventional CVD risk factors (e.g., tobacco use, alcohol consumption, other substance abuse, hypercholesterolemia, hypertension, elevated blood glucose, aging, male gender) [7, 8]. In HIV-1–infected individuals, continued use of antiretroviral therapy has been associated with decreased risk of fatal or nonfatal CVD events compared with episodic antiretroviral therapy (based on CD4+ cell count), although a more recent study suggests a complex relationship between antiretroviral therapy and CVD risk [9, 10]. In the case of protease inhibitors (PIs), the use of older PIs has been associated with an increased risk of CVD-related events due to these drugs causing metabolic abnormalities such as dyslipidemia and insulin resistance; however, newer PIs have demonstrated improved CVD risk profiles [11–18].

Once-daily darunavir 800 mg, boosted by ritonavir or cobicistat and in combination with two nucleos(t)ide reverse transcriptase inhibitors, is recommended by the US Department of Health and Human Services (DHHS) as an initial antiretroviral treatment option in certain clinical situations [17] and is also recommended by the European AIDS Clinical Society (EACS) as an initial regimen [19]. Once-daily darunavir 800 mg (boosted with ritonavir 100 mg) was approved for treatment-naive and treatment-experienced patients without darunavir resistance-associated mutations in 2009 (Europe; 2010 in the USA) [20]. Darunavir is also indicated for use in twice-daily dosing regimens in those patients with darunavir resistance-associated mutations. Twice-daily darunavir 600 mg (boosted with ritonavir 100 mg) was approved for treatment-experienced, HIV-1–infected patients, including patients with triple class experience, in 2006 (USA; 2007 in Europe).

There are limited data suggesting that darunavir use is associated with increased CVD risk, although a recent observational cohort study examined the association between CVD risk and use of the contemporary PIs darunavir and atazanavir [21, 22], and a recent longitudinal cohort study evaluated CVD risk among 119 antiretroviral-naïve, HIV-1–infected individuals starting their first therapy [23]. In the current analyses, we evaluated the CVD risk associated with darunavir use and, in addition, examined the demographic and clinical characteristics of darunavir users in clinical trials and the real world. Assessments were based on Janssen-sponsored clinical trials, post-marketing pharmacovigilance databases, and US administrative claims databases.

2 Methods

2.1 CVD Events in Janssen-Sponsored Clinical Trials

These analyses were based on pooled data from 19 Janssen-sponsored, international, phase 2/3/4 studies of darunavir/ritonavir (summarized in Supplementary Table S1; see the electronic supplementary material) [24–41]. Patient baseline demographic and clinical characteristics, including specific risk factors for CVD, were determined for the pooled population. Medical Dictionary for Regulatory Activities (MedDRA) preferred terms corresponding to the medical concepts of CVD events (myocardial infarction, stroke, sudden death, and invasive cardiovascular procedures such as coronary artery angioplasty or bypass or carotid endarterectomy) were retrieved.

The incidence of CVD events per 1000 person-years of exposure to darunavir/ritonavir was assessed as 1000 times the number of patients with a CVD event divided by the total person-years of exposure by patients “at risk”. Incidence rates overall and incidence rates over time in yearly exposure intervals for patients at risk in the pooled Janssen-sponsored clinical trial population were calculated for these CVD events. Results were also calculated by dosing regimen [once-daily darunavir/ritonavir 800/100 mg and twice-daily...
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darunavir/ritonavir 600/100 mg (with a total daily dose of
darunavir/ritonavir 1200/200 mg)], as this is an indicator of
a specific target population in terms of HIV-1 and general
disease characteristics. Descriptive statistics were used to
calculate incidence rates and corresponding 95% confidence
intervals (CIs) utilizing Poisson distribution.

2.2  CVD Events in Post-Marketing
Pharmacovigilance Databases

Spontaneously reported, post-marketing cases of CVD
events in patients treated with darunavir/ritonavir were
identified in the Janssen Global Safety Database during
the period from June 23, 2006 (international birth date)
to December 23, 2016. A trend evaluation was conducted
using the Standardized MedDRA Queries (SMQs) of central
nervous system hemorrhages and cerebrovascular conditions
(broad) and ischemic heart disease (broad), and the Med-
DRA preferred terms of carotid angioplasty, carotid artery
bypass, carotid artery stent insertion, carotid artery stent
removal, carotid endarterectomy, carotid revascularization,
coronary angioplasty, coronary arterial stent insertion, coro-
nary artery bypass, coronary artery stent removal, coronary
brachytherapy, and coronary endarterectomy.

Empirical Bayesian Geometric Mean (EBGM) scores
were derived using Multi-Item Gamma Poison Shrinker
disproportionality methodology, used to evaluate dispro-
portionality of reporting [42] of CVD events for darunavir
and other PIs (indinavir, nelfinavir, ritonavir, saquinavir,
atazanavir, fosamprenavir, and tipranavir) in the US Food
and Drug Administration Adverse Event Reporting System
(FAERS) (2016 quarter 2 [2016Q2]) and World Health
Organization VigiBase (2016Q4) databases. The thresh-
hold for disproportional reporting was \( n \geq 3 \), EBGM \( \geq 2 \),
and lower bound of the two-sided 90% CI around EBGM
(EB05) > 1.

2.3  Demographic and Clinical Characteristics
of Darunavir Users in US Administrative Claims
Databases

Baseline demographic characteristics, as well as clinical
characteristics (comorbidities considered to be CVD
risk factors), of HIV-1–infected patients, new users of
darunavir, and new users of atazanavir were explored
using three US administrative claims databases [Truven
Health MarketScan® Medicaid (MDCD), Truven Health
MarketScan® Commercial Claims and Encounters (CCAE),
and Optum Clinformatics™ Extended DataMart Socio-Eco-
nomic Status (Optum); all data collected through Septem-
ber 2016]. Additional analyses were conducted using data
from CCAE and Optum (January 2007–September 2016) to
evaluate the comparability of populations, with respect to
comorbidities prior to initiating darunavir and atazanavir,
using propensity score matching and cohort characteriza-
tion methods.

3  Results

3.1  CVD Events in Janssen-Sponsored Clinical Trials

3.1.1  Baseline Characteristics

A total of 5713 patients were enrolled across 19 Janssen-
sponsored clinical trials. Baseline characteristics are
summarized (Table 1). Overall, 3058 patients used twice-
daily darunavir/ritonavir 600/100 mg, 1326 used once-
daily darunavir/ritonavir 800/100 mg, and 5713 used
any darunavir/ritonavir dose (including doses other than
twice-daily darunavir/ritonavir 600/100 mg and once-daily
darunavir/ritonavir 800/100 mg). Among all patients (any
darunavir dose), the median (range) age was 43 (18–82)
years and most were male (77%), Caucasian (49%), and
had a body mass index of 18–26 kg/m² (69%). Evalua-
tion of clinical characteristics showed that compared
with patients who used once-daily darunavir/ritonavir
800/100 mg, those who used twice-daily darunavir/rito-
navir 600/100 mg had a higher median (range) HIV-1 RNA
viral load [3.74 (1.6–6.7) vs 4.7 (1.7–7.1) \log_{10} \text{copies/mL},
respectively] and a lower median (range) CD4+ cell
count [347 (4–1888) vs 140 (1–1193) cells/mm³, respec-
tively]. Other disease characteristics such as lipid levels,
blood pressure, renal function, and presence of diabetes
are shown in Table 1. Together, these results indicate
that patients who used twice-daily darunavir/ritonavir
600/100 mg tended to have more advanced HIV-1 disease
and comorbidities than those who used once-daily daru-
navir/ritonavir 800/100 mg.

3.1.2  CVD Event Incidence Rates

The treatment duration across the 19 Janssen-sponsored
clinical trials was up to 6 years (median 1.9 years; inter-
quartile range 0.94–2.75 years; range 0–6.1 years). The
incidence rate (95% CI) per 1000 person-years of CVD
events in the overall pooled population (any darunavir
dose) was 6.15 (2.91–11.89), and was lower for patients
using once-daily darunavir/ritonavir 800/100 mg [0.71
(0.16–3.05)] versus twice-daily darunavir/ritonavir
600/100 mg [9.21 (4.94–16.04); Fig. 1]. CVD incidence
rates did not increase with exposure to darunavir/ritonavir
over increasing yearly intervals, and there were no CVD
events in exposure intervals of more than 3 years (Fig. 1).
Table 1  Baseline characteristics of patients enrolled in Janssen-sponsored clinical trials

| Demographic characteristics | Once-daily darunavir/ritonavir 800/100 mg (n=1326) | Twice-daily darunavir/ritonavir 600/100 mg (n=3058) | Any darunavir/ritonavir dose* (n=5713) |
|----------------------------|---------------------------------|---------------------------------|----------------------------------|
| Age, years, median (range) | 40 (18–82)                      | 43 (18–78)                      | 43 (18–82)                      |
| Gender, n (%)              |                                 |                                 |                                 |
| Female                     | 370 (28)                        | 709 (23)                        | 1323 (23)                       |
| Male                       | 956 (72)                        | 2349 (77)                       | 4390 (77)                       |
| Race, n (%)                |                                 |                                 |                                 |
| Black                      | 286 (22)                        | 653 (21)                        | 1007 (18)                       |
| Caucasian                  | 769 (58)                        | 1685 (55)                       | 2774 (49)                       |
| Hispanic                   | 146 (11)                        | 399 (13)                        | 592 (10)                        |
| Asian                      | 100 (8)                         | 95 (3)                          | 201 (4)                         |
| Other                      | 25 (2)                          | 226 (7)                         | 1139 (20)                       |
| BMI, kg/m², n (%)a,b       |                                 |                                 |                                 |
| < 18                       | 20 (2)                          | 162 (5)                         | 236 (4)                         |
| 18–26                      | 888 (67)                        | 2085 (68)                       | 3938 (69)                       |
| 26.1–30                    | 277 (21)                        | 515 (17)                        | 1012 (18)                       |
| > 30                       | 141 (11)                        | 295 (10)                        | 499 (9)                         |
| Smoking status, n (%)a     |                                 |                                 |                                 |
| Smoking                    | 217 (16)                        | 388 (13)                        | 1027 (18)                       |
| Nonsmoking                 | 447 (34)                        | 697 (23)                        | 1581 (28)                       |
| Missing                    | 662 (50)                        | 1973 (65)                       | 3105 (54)                       |
| HIV-1 disease characteristics |                                |                                 |                                 |
| HIV-1 RNA viral load, log_{10} copies/mL, median (range)c | 3.74 (1.6–6.7) | 4.7 (1.7–7.1) | 4.43 (1.2–7.5) |
| CD4+ cell count, cells/mm³, median (range)d | 347 (4–1888) | 140 (1–1193) | 212 (1–1888) |
| HIV-1 transmitted by IV drug use, n (%)e | 54 (4) | 209 (7) | 520 (9) |
| Other disease characteristics |                                |                                 |                                 |
| Lipid parameters, mg/dL, mean (SE)f |                  |                                 |                                 |
| Total cholesterol          | 175.79 (1.43)                   | 174.1 (0.855)                   | 177.07 (0.665)                  |
| HDL-C                      | 42.04 (0.51)                    | 38.38 (0.26)                    | 39.08 (0.201)                   |
| LDL-C                      | 97.79 (1.204)                   | 96.06 (0.727)                   | 98.22 (0.579)                   |
| Triglycerides              | 152.85 (3.828)                  | 249.64 (4.27)                   | 226.61 (2.984)                  |
| Blood pressure, mmHg, mean (SE)g |                      |                                 |                                 |
| Systolic                   | 122.17 (0.423)                  | 120.32 (0.285)                  | 121.1 (0.207)                   |
| Diastolic                  | 76.64 (0.288)                   | 76.03 (0.199)                   | 76.55 (0.143)                   |
| eGFRCG, mL/min, n (%)a,h   |                                 |                                 |                                 |
| Normal renal function (≥ 90) | 871 (83)                      | 2094 (69)                       | 3749 (72)                       |
| Mild renal impairment (≥ 60 to < 90) | 165 (16)                  | 782 (26)                       | 1240 (24)                       |
| Moderate renal impairment (≥ 30 to < 60) | 15 (1)                     | 172 (6)                        | 236 (5)                         |
| Severe renal impairment (≥ 15 to < 30) | 0 (0)                       | 5 (< 1)                        | 5 (< 1)                         |
| Renal failure (<15)        | 0 (0)                           | 1 (< 1)                        | 2 (< 1)                         |
| Intake of lipid-lowering drugs, n (%) | 74 (6)                        | 468 (15)                       | 651 (11)                        |
| Intake of antidiabetes drugs, n (%) | 27 (2)                        | 217 (7)                        | 283 (5)                         |
| Intake of antihypertensive drugs, n (%) | 131 (10)                      | 555 (18)                       | 775 (14)                        |
| Dyslipidemia, n (%)i       | 474 (36)                        | 1942 (64)                       | 3162 (55)                       |
| Diabetes, n (%)j          | 42 (3)                          | 285 (9)                         | 415 (7)                         |
| Hypertension, n (%)k       | 318 (24)                        | 906 (30)                        | 1499 (26)                       |

BMI body mass index, eGFRCG, estimated glomerular filtration rate calculated using the Cockcroft-Gault method, HDL-C high-density lipoprotein cholesterol, HIV-1 human immunodeficiency virus-1, IV intravenous, LDL-C low-density lipoprotein cholesterol, SE standard error

*aIncludes doses other than twice-daily darunavir/ritonavir 600/100 mg and once-daily darunavir/ritonavir 800/100 mg

*bPercentages may not total 100% due to rounding

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3.2 CVD Events in Post-Marketing Pharmacovigilance Databases

Trend analysis of post-marketing pharmacovigilance data showed that cumulative reporting rates of CVD events for darunavir users generally declined over time (Fig. 2). A higher reporting rate was observed during the period of 2006–2009 (when only twice-daily darunavir/ritonavir 600/100 mg was available) compared with the period of 2010–2016 (when both twice-daily darunavir/ritonavir 600/100 mg and once-daily darunavir/ritonavir 800/100 mg were available). During the first period (June 23, 2006–December 23, 2006), the CVD event reporting rate per 1000 person-years was 0.348; through December 23, 2009, the cumulative reporting rate per 1000 person-years had decreased to 0.124; and by December 23, 2016, it was 0.042.

Spontaneously reported CVD events were not disproportionately reported with darunavir in FAERS/VigiBase. First-generation PIs (indinavir, nelfinavir, ritonavir, and c any darunavir/ritonavir dose. CI confidence interval, CVD cardiovascular disease. *Includes doses other than twice-daily darunavir/ritonavir 600/100 mg and once-daily darunavir/ritonavir 800/100 mg

Table 1 (continued)

| A | B | C |
|---|---|---|
| Once-daily darunavir/ritonavir 800/100 mg, n = 1326 | Twice-daily darunavir/ritonavir 600/100 mg, n = 3055 | Any darunavir/ritonavir dose, n = 5650 |
| Once-daily darunavir/ritonavir 800/100 mg, n = 1311 | Twice-daily darunavir/ritonavir 600/100 mg, n = 3055 | Any darunavir/ritonavir dose, n = 5650 |
| Percentage calculated based on the total populations, which include patients categorized as having “missing data” for HIV mode of transmission. Patients with missing data were as follows: once-daily darunavir/ritonavir 800/100 mg, n = 415 (31%); twice-daily darunavir/ritonavir 600/100 mg, n = 331 (11%); any darunavir/ritonavir dose, n = 750 (13%) |

Dyslipidemia defined as elevated total cholesterol [> 6.2 mmol/L (240 mg/dL)], and/or decreased HDL-C [< 0.9 mmol/L (35 mg/dL)], and/or elevated triglycerides [> 2.3 mmol/L (200 mg/dL)]

Diabetes defined as fasting glucose ≥ 126 mg/dL (7 mmol/L)

Hypertension defined as elevated systolic blood pressure (≥ 140 mmHg) and/or elevated diastolic blood pressure (≥ 90 mmHg)

Fig. 1 Incidence rates of CVD events overall and over time in yearly exposure intervals for patients at risk using a once-daily darunavir/ritonavir 800/100 mg, b twice-daily darunavir/ritonavir 600/100 mg, and c any darunavir/ritonavir dose. CI confidence interval, CVD cardiovascular disease. *Includes doses other than twice-daily darunavir/ritonavir 600/100 mg and once-daily darunavir/ritonavir 800/100 mg.
Fig. 2 Cumulative reporting rate for spontaneous cases reporting CVD events identified with darunavir treatment by time interval (June 23, 2006–December 23, 2016). CVD cardiovascular disease. *Cumulative Periodic Benefit-Risk Evaluation Report (PBRER)-Periodic Safety Update Report (PSUR) reporting period

Table 2 Signal scores from FAERS (2016Q2): cardiovascular and cerebrovascular events

| Event | First-generation PIs | Second-generation PIs |
|-------|----------------------|-----------------------|
|       | Indinavir            | Nelfinavir            | Ritonavir            | Saquinavir            | Atazanavir            | Darunavir            | Fosamprenavir        | Tipranavir            |
| n     | EBGM                 | EB05                  | n                    | EBGM                 | EB05                  | n                    | EBGM                 | EB05                  |
|       |                      |                       |                      |                      |                       |                      |                      |                       |
| Carotid artery occlusion | 1 0.966 0.213 | 1 1.021 0.225 | 3 1.057 0.405 | 1 1.021 0.225 | 1 1.057 0.405 | 1 1.057 0.405 | 1 1.057 0.405 | 1 1.057 0.405 |
| Carotid artery stenosis | 9 3.523 2.003 | 9 3.523 2.003 | 2 1.097 0.347 | 4 1.008 0.436 | 1 0.765 0.169 | 1 0.765 0.169 | 1 0.765 0.169 | 1 0.765 0.169 |
| Carotid artery thrombosis | 2 1.535 0.486 | 2 1.535 0.486 | 2 1.535 0.486 | 2 1.535 0.486 | 2 1.535 0.486 | 2 1.535 0.486 | 2 1.535 0.486 | 2 1.535 0.486 |
| Coronary artery insufficiency | 1 1.23 0.271 | 1 1.23 0.271 | 1 1.23 0.271 | 1 1.23 0.271 | 1 1.23 0.271 | 1 1.23 0.271 | 1 1.23 0.271 | 1 1.23 0.271 |
| Coronary artery occlusion | 32 3.275 2.432 | 32 3.275 2.432 | 10 1.517 0.889 | 35 1.975 1.486 | 16 3.147 2.063 | 16 3.147 2.063 | 16 3.147 2.063 | 16 3.147 2.063 |
| Coronary artery thrombosis | 2 1.367 0.433 | 2 1.367 0.433 | 2 1.367 0.433 | 2 1.367 0.433 | 2 1.367 0.433 | 2 1.367 0.433 | 2 1.367 0.433 | 2 1.367 0.433 |
| Coronary artery stenosis | 5 1.959 0.922 | 11 3.415 1.933 | 11 3.415 1.933 | 11 3.415 1.933 | 11 3.415 1.933 | 11 3.415 1.933 | 11 3.415 1.933 | 11 3.415 1.933 |
| Ischemic stroke | 1 0.505 0.111 | 1 0.505 0.111 | 1 0.505 0.111 | 1 0.505 0.111 | 1 0.505 0.111 | 1 0.505 0.111 | 1 0.505 0.111 | 1 0.505 0.111 |
| Sudden cardiac death | NR NR NR NR NR NR NR NR NR | NR NR NR NR NR NR NR NR NR | NR NR NR NR NR NR NR NR NR | NR NR NR NR NR NR NR NR NR | NR NR NR NR NR NR NR NR NR | NR NR NR NR NR NR NR NR NR |
| Ischemic heart disease (SMQ) | 373 1.802 1.653 | 253 0.851 0.618 | 253 0.851 0.618 | 253 0.851 0.618 | 253 0.851 0.618 | 253 0.851 0.618 | 253 0.851 0.618 | 253 0.851 0.618 |
| Myocardial infarction (SMQ) | 325 1.912 1.744 | 229 2.016 1.806 | 229 2.016 1.806 | 229 2.016 1.806 | 229 2.016 1.806 | 229 2.016 1.806 | 229 2.016 1.806 | 229 2.016 1.806 |
| CNS hemorrhages and cerebrovascular conditions (SMQ) | 154 0.911 0.796 | 75 0.594 0.49 | 75 0.594 0.49 | 75 0.594 0.49 | 75 0.594 0.49 | 75 0.594 0.49 | 75 0.594 0.49 | 75 0.594 0.49 |

The threshold for disproportional reporting was \( n \geq 3 \), \( EBGM \geq 2 \), and \( EB05 > 1 \). Events that met the disproportionality threshold are in bold. 2016Q2, 2016 quarter 2, CI confidence interval, CNS central nervous system, FAERS US Food and Drug Administration Adverse Event Reporting System, \( EBGM \) Empirical Bayesian Geometric Mean, \( EB05 \) lower bound of the 2-sided 90% CI around \( EBGM \), MedDRA Medical Dictionary for Regulatory Activities, NR not reported, PIs protease inhibitors, SMQ Standardized MedDRA Query

*Events based on MedDRA preferred terms or SMQs (as noted)

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saquinavir) displayed a higher number of drug-event pairs that met the threshold for disproportionate reporting compared with second-generation PIs (atazanavir, darunavir, fosamprenavir, tipranavir) in FAERS (Table 2).

### 3.3 Demographic and Clinical Characteristics of Darunavir Users in US Administrative Claims Databases

Across the MDCD, CCAE, and Optum databases, higher proportions of darunavir users were male (56, 82, and 83%, respectively) compared with the general HIV-1–infected population (55, 76, and 73%) and atazanavir users (49, 78, and 81%) (Table 3). Darunavir users also tended to be older than the other populations, with mean (standard deviation) ages in the three databases ranging from 42.6 (11.9) to 47.2 (11.1) years for darunavir users, 41.0 (14.3) to 42.3 (13.2) years for the general HIV-1–infected population, and 40.8 (12.0) to 43.6 (10.2) years for atazanavir users; correspondingly, higher percentages of darunavir users, versus the general HIV-1–infected population and atazanavir users, were ≥ 50 years of age. Higher percentages of darunavir users had comorbidities considered to be CVD risk factors compared with the general HIV-1–infected population and atazanavir users. For example, the percentage of darunavir users who had a cardiovascular disorder ranged from 50 to 64% across the three databases, compared with 23–30% of the general HIV-1–infected population and 38–52% of atazanavir users. Similar results were seen for metabolic disorder, hypertension, hyperlipidemia, and diabetes.

Clinical variables that are known or are likely risk factors for CVD events were more prevalent among patients initiating darunavir versus those initiating atazanavir in the Optum database; the 13 conditions with a prevalence ratio (darunavir vs atazanavir) of ≥ 5 are shown in Table 4. The conditions with the highest prevalence ratio were diabetes without complication (18.550), type 2 diabetes without complication (18.219), hyperglycemia (15.017), chronic heart failure (7.589), and chronic systolic heart failure (7.214).

Further, propensity score density plots were generated from the Optum and CCAE databases to show the treatment preference between darunavir and atazanavir (Fig. 3). The plots indicate the probability of receiving darunavir or atazanavir based on a patient’s clinical characteristics prior to receiving treatment. The area of overlap represents the patients in both groups who are similar with respect to clinical characteristics. Consistent results were observed in the Optum and CCAE databases, showing < 30% overlap between the two treatment groups and thus indicating that approximately 70% of patients treated with darunavir have no comparator in the atazanavir group with respect to comorbidities, drug exposures, procedures, and laboratory measures.
4 Discussion

CVD is an important clinical concern for HIV-1–infected individuals because of the many factors linking these conditions; HIV-1 infection increases the risk of developing CVD, while some CVD risk factors are more common in HIV-1–infected patients relative to their peers [2–5]. While antiretroviral therapy has been associated with decreased risk of CVD events, the connection is complex [9, 10]. Given the association between older PIs and CVD events [11–17], we examined the relationship between darunavir and CVD events using multiple approaches and datasets.

Analyses of pooled data from 19 Janssen-sponsored clinical trials did not indicate an increased risk of CVD events with exposure to darunavir/ritonavir over increasing yearly intervals (Fig. 1). Notably, the CVD event incidence rate

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Table 4 Pre-exposure conditions and cardiac risk factors

| Condition                                      | Darunavir users | Atazanavir users | Absolute difference | Prevalence ratio (darunavir vs atazanavir) |
|------------------------------------------------|-----------------|------------------|---------------------|------------------------------------------|
| Diabetes without complication                  | 56              | 0.011            | 4                   | 0.001                                    | 0.140 | 18.550 |
| Type 2 diabetes without complication            | 55              | 0.011            | 4                   | 0.001                                    | 0.138 | 18.219 |
| Hyperglycemia                                   | 34              | 0.007            | 3                   | 0.000                                    | 0.106 | 15.017 |
| Chronic heart failure                           | 63              | 0.013            | 11                  | 0.002                                    | 0.131 | 7.589  |
| Chronic systolic heart failure                  | 49              | 0.010            | 9                   | 0.001                                    | 0.114 | 7.214  |
| Acute systolic heart failure                    | 41              | 0.008            | 8                   | 0.001                                    | 0.103 | 6.791  |
| Acute heart failure                              | 58              | 0.012            | 12                  | 0.002                                    | 0.121 | 6.404  |
| Venous hypertension                             | 51              | 0.010            | 11                  | 0.002                                    | 0.112 | 6.143  |
| Dilation of aorta                               | 53              | 0.011            | 13                  | 0.002                                    | 0.110 | 5.402  |
| Peripheral circulatory disorder associated with type 2 diabetes | 48              | 0.010            | 12                  | 0.002                                    | 0.104 | 5.300  |
| Chronic kidney disease stage 2                  | 111             | 0.022            | 28                  | 0.004                                    | 0.159 | 5.253  |
| Deep venous thrombosis of lower extremity       | 84              | 0.017            | 22                  | 0.003                                    | 0.136 | 5.059  |
| Chronic kidney disease stage 1                  | 57              | 0.012            | 15                  | 0.002                                    | 0.112 | 5.035  |

Conditions with a prevalence ratio of ≥ 5 are reported (Optum Clinformatics™ Extended DataMart Socio-Economic Status database)

Fig. 3 Comparison of darunavir and atazanavir user baseline characteristics and comorbidities in the a Optum and b CCAE databases. CCAE Truven Health MarketScan® Commercial Claims and Encounters database, Optum Optum Clinformatics™ Extended DataMart Socio-Economic Status database
was lower for patients who used once-daily darunavir/ritonavir 800/100 mg versus twice-daily darunavir/ritonavir 600/100 mg. The relatively higher CVD event rate for twice-daily darunavir/ritonavir 600/100 mg may reflect differences in the patient populations, as this dosing regimen was developed for treatment-experienced, HIV-1–infected patients with advanced disease who may be at high risk of experiencing a CVD event. This hypothesis is supported by an analysis of the baseline characteristics of these patients. Compared with patients who used once-daily darunavir/ritonavir 800/100 mg, which included both treatment-experienced and treatment-naive individuals, those who used twice-daily darunavir/ritonavir 600/100 mg had higher baseline HIV-1 RNA levels and lower CD4+ cell counts; moreover, higher percentages of patients who used twice-daily darunavir/ritonavir 600/100 mg were being treated at baseline for, or diagnosed with, elevated lipid levels, diabetes, and hypertension. In addition to the more advanced disease and comorbidities for patients who used twice-daily darunavir/ritonavir 600/100 mg versus once-daily darunavir/ritonavir 800/100 mg, another possible factor leading to a higher CVD event rate with the twice-daily regimen is the higher ritonavir dose with the twice-daily versus once-daily regimen. As indicated in Table 2, as a first-generation PI, ritonavir itself may contribute to increased cardiovascular risk.

In the second set of analyses, based on real-world data, a trend analysis of post-marketing pharmacovigilance data for darunavir users showed a decline in the cumulative reporting rate of cases with CVD events from June 23, 2006 to December 23, 2016. Consistent with the pooled analysis of Janssen-sponsored clinical trials, higher CVD event reporting rates were observed during the period 2006–2009, when only twice-daily darunavir/ritonavir 600/100 mg was available, compared with the reporting rates for 2010–2016, when both twice-daily darunavir/ritonavir 600/100 mg and once-daily darunavir/ritonavir 800/100 mg were available. Overall, CVD event reporting rates with darunavir were significantly lower than the observed rates of CVD events in the general HIV-1–infected population [43, 44]. The data mining analysis of post-marketing pharmacovigilance databases [FAERS (2016 Q2) and VigiBase (2016 Q4)] exhibited disproportionality of CVD events mainly for first-generation PIs (e.g., indinavir, nelfinavir, ritonavir, saquinavir). Based on the results, there is no indication that use of darunavir is associated with increased reporting of CVD events over time.

The third set of analyses, an examination of baseline characteristics from three US claims databases, enabled assessment of the demographic and clinical characteristics of new users of darunavir or the contemporary PI atazanavir, as well as the general HIV-1–infected population, in the real world. These analyses demonstrated that HIV-1–infected patients who are prescribed darunavir tend to be sicker than the general HIV-1–infected population and those who are prescribed atazanavir, with more factors that could increase the risk of having a CVD event, including male gender, older age, and known CVD risk factors. The observed imbalance between populations suggests the possibility that patients with higher rates of comorbidities, and specifically cardiovascular conditions, may be channeled into darunavir treatment rather than other antiretroviral treatment. This scenario could occur if, for example, clinicians choose to treat more treatment-experienced patients or those who are medically more complex with darunavir, instead of alternative antiretroviral therapies. Darunavir was initially approved for use only in treatment-experienced patients because of its high genetic barrier to resistance and it is often selected for individuals with uncertain adherence, who can be medically more complex than those who are highly adherent to treatment [17, 45]. These results underscore the importance of carefully accounting for baseline characteristics when comparing outcomes between treatment groups so that confounding is minimized.

There were limitations associated with these analyses. The Janssen-sponsored clinical trials had limited durations (of up to 6 years; median duration approximately 2 years), there were gaps in data availability, few of the studies included a control arm with other PIs (precluding comparison with a reference), and the patients enrolled in these studies may not be reflective of real-world populations. The potential effect of antiretroviral therapy itself on CVD risk was also not assessed (e.g., by comparing darunavir users with untreated naive patients) [23]. Notably, a randomized study powered to definitively evaluate the association between darunavir and CVD events over time in a time-to-event analysis has not been conducted. In addition, CVD risk data were not evaluated adjusting for age and gender, which are known to be associated with CVD risk [7, 8]. In the case of the post-marketing pharmacovigilance data mining analysis, the results cannot be used to confirm or refute a causal association between drug and event; rather, these results are a measure of statistical association and need to be placed in a medical context. Moreover, underreporting of post-marketing adverse drug reactions over time, a limitation seen with a passive or voluntary reporting system, could have affected the evaluation. Results of the epidemiological analyses were based on three US claims databases and, thus, may not be generalizable to a global population. Finally, the epidemiological analysis focused only on demographics and baseline clinical characteristics, as no outcomes were analyzed. Collectively, these limitations illustrate the challenge of determining the true risk of CVD events associated with use of darunavir (and antiretroviral agents in general) [21–23]. Despite these limitations, our findings are strengthened by the combination of analyses, and taken together they offer important insights into the relationship between darunavir and CVD.
5 Conclusion

Overall, this comprehensive review of clinical, post-marketing, and epidemiological data does not suggest that CVD should be considered an important risk for patients who use darunavir.

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Compliance with Ethical Standards

Research Involving Human Participants and/or Animals This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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Data Availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Affiliations

Magda Opsomer¹ · Dessislava Dimitrova² · Johan Verspeelt¹ · Amy Purrington³ · Abdul Mehbob⁴ · Scott Chavers² · Helen Pai⁵ · Simon Vanveggel¹ · Donghan Luo² · Kimberley Brown⁶ · Christiane Moecklinghoff⁷ · Richard E. Nettles⁶ · Katia Boven²

¹ Janssen Research and Development, Beerse, Belgium
² Janssen Research and Development, LLC, Titusville, NJ, USA
³ Janssen Research and Development, LLC, Horsham, PA, USA
⁴ Janssen-Cilag Ltd, High Wycombe, UK
⁵ Janssen Research and Development, LLC, Raritan, NJ, USA
⁶ Janssen Scientific Affairs, LLC, Titusville, NJ, USA
⁷ Janssen EMEA, Neuss, Germany