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ORIGINAL ARTICLE

Incidence of heart failure following exposure to a protein kinase inhibitor, a French population-based study

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Aims: Pharmacovigilance signals of heart failure (HF) following exposure to protein kinase inhibitors (PKIs) have been detected in recent years. Our aim was to identify the PKIs most frequently associated with the development of HF.

Methods: Using the French National Healthcare Database, all patients newly exposed to a PKI between January 2011 and June 2014 were followed up for 18 months. Specific hospitalization diagnosis and long-term HF-related disease codes were used to identify HF patients. HF incidence rate ratios (IRRs) were measured and adjusted hazard ratios (aHRs) were estimated using a Cox model. Sensitivity analyses were performed to limit the potential indication and competitive risk bias.

Results: Thirteen PKIs were studied. Among the 49 714 new PKI users registered during the study period, the mean IRR of HF was 3.38 per 100 person-years, with a median time to onset of 155 days. We found a significant increase in the incidence of HF for six medicinal products: pazopanib (aHR = 2.42, 95% confidence interval [CI] 1.67-3.52), dasatinib (aHR = 2.22, 95% CI 1.42-3.44), ruxolitinib (aHR = 2.11, 95% CI 1.69-2.64), crizotinib (aHR = 1.71, 95% CI 1.07-2.72), everolimus (aHR = 1.45, 95% CI 1.26-1.67) and vemurafenib (aHR = 1.37, 95% CI 1.01-1.86). Sensitivity analyses were consistent with our primary analysis.

Conclusions: The current study provides knowledge on HF following exposure to a PKI. Additional studies could confirm these results for dasatinib, everolimus, pazopanib and ruxolitinib, and particularly for the two medicinal products with results slightly above the significance threshold, namely, crizotinib and vemurafenib, in our sensitivity analyses.

KEYWORDS
adverse drug reaction, heart failure, protein kinase inhibitor

1 | INTRODUCTION

The 2000s saw the advent of oral "targeted therapies", with the iconic arrival of the first protein kinase inhibitor (PKI), imatinib. Currently, there are more than 50 PKIs on the market, and nearly twice as many are still in late-stage clinical development.[1] These drugs have revolutionized the prognosis for certain types of cancer—what was nearly always a fatal short- to medium-term prognosis is being transformed into chronic outpatient cancer treatment.[2,3] The undeniable benefits of some of these drugs have contributed to an acceleration of premarketing clinical evaluations in the name of rapid access to innovation. Over the last decade, we have witnessed a reduction in the PKI clinical evaluation timeline, justifying the crucial need to complete the data with follow-up under "real-life" conditions using pharmacovigilance and pharmacoepidemiology.[3–6] Moreover, these PKIs represent a chemically heterogeneous family with complex affinity profiles.[7] In pharmacodynamic terms, this complexity sometimes induces unexpected and serious adverse drug reactions (ADRs) requiring specific management.

Heart failure (HF) is a major public health concern, with 2.3% of the French population being diagnosed, a 2-year survival rate of 60% and nearly 70 000 related deaths each year.[8,9] We previously conducted a disproportionality analysis using worldwide pharmacovigilance data.[10] Dasatinib, imatinib, bosutinib, sunitinib and nilotinib were found to be significantly associated with an increased risk of reporting HF among the 15 PKIs evaluated. However, this study suffers from typical limitations of pharmacovigilance studies such as under- and selective reporting. Other studies have shown an increased risk of HF in patients exposed to sunitinib and sorafenib, while some case reports describe the impact of pazopanib on HF occurrence among sarcoma patients.[11–16] In a scientific statement, the American Heart Association classified lapatinib, imatinib, sunitinib and sorafenib as carrying moderate to minor risks of HF.[17]

The primary objective of the current study was to identify the PKIs most frequently associated with an HF outcome. The secondary objectives were to identify the predictors associated with an HF outcome and to describe the characteristics of the patients exposed to PKIs and developing HF.

What is already known about this subject

- Some protein kinase inhibitors (PKIs) might increase the onset of heart failure.
- A large study reviewing more PKIs should be conducted to investigate this risk.

What this study adds

- Measurement of heart failure incidence rate after PKI exposure in France.
- Compared to other PKIs, dasatinib, ruxolitinib, everolimus, pazopanib, crizotinib and vemurafenib increase the risk of heart failure.

2 | METHODS

2.1 | Data source

All data were obtained from the French National Healthcare Data System (Système National des Données de Santé, SNDS), which gathers data on reimbursements received by beneficiaries of the main health insurance schemes, covering about 98% of the French population. This medical administrative database contains anonymized individual patient data. The diagnoses related to long-term conditions (LTC) and hospital stay diagnoses (including main, related and associated hospital diagnoses) are identified in specific SNDS tables using International Classification of Diseases – 10th revision (ICD-10) codes. Reimbursed medicinal products issued in the community are identified by their Anatomic Therapeutic Chemical (ATC) code.

2.2 | Study design and population

We used a retrolective cohort study design. All adult patients (≥18 years old) with no prior HF and newly exposed to only one marketed PKI approved for cancer therapies from 1 January 2011 to 30 June 2014 were included in our study population. A 12-month observation period before patient inclusion was introduced to ensure the absence of prior PKI reimbursement or prior HF. PKIs to which fewer than 100 patients were exposed were excluded from the study.

2.3 | Exposure definition

Exposure was defined by the dispensing of at least one marketed PKI during the study period. The PKIs were identified by the L01XE codes of the ATC classification system (Supporting Information Table S1). Because HF is a condition that may take several months to develop and because of a potential persistent effect of PKIs even after discontinuation of treatment, the patients were followed up from the initial dispensation of a PKI up to 18 months, even if PKI treatment had been stopped. This follow-up period was defined according to the occurrence time for HF as described in the literature.[15–18] Defined daily dose (DDD) is described by the World Health Organization (WHO) as the assumed average maintenance dose per day for a medicinal product used for its main indication in adults. As the WHO has not established a DDD for PKIs, we estimated the cumulative PKI exposure by calculating a defined daily dose equivalent (DDDe), dividing cumulative PKI exposure by the recommended daily dosage for their main indications in adults described in the Summary of Product Characteristics

(SmPC) (Supporting Information Table S1). Two groups of patients were thus formed depending on whether their DDDe was lower or higher than an equivalence of 6 months with a standard dosage.

$$\text{DDDe(day)} = \frac{\sum(\text{number of packages dispensed} \times \text{packaging} \times \text{dose})}{\text{daily recommended dosage of PKI for its main indication in adults in its SmPC}}$$

2.4 | Event of interest and covariates

The event of interest, namely "heart failure", was identified using existing acute and chronic HF algorithms.[19] This identification methodology, established by a group of experts from the French National Healthcare Insurance Fund, is based on data from the LTC and hospitalization diagnoses through the identification of specific ICD-10 codes and is described in Supporting Information Table S2. The first date identified in relation to HF was considered as the date of onset.

Several potential confounding factors already described in the literature were considered.[17,18,20] These were socio-demographic characteristics (age at initiation of PKI, gender, Social Deprivation Index, classifying individuals according to the level of deprivation/privilege based on geographic areas of residence),[21] comorbidities identified during the 1-year period before PKI onset (diabetes, stroke, acute coronary syndrome, chronic coronary disease, cardiac rhythm or conduction disorder, valvular disease, pulmonary embolism, obliterative arterial disease of the lower limbs, addictive disorder) and consumption of medicinal products in the year preceding PKI initiation (hospitalization for a chemotherapy session, outpatient use of HF-related medicinal products (antihypertensive drugs, thyroid-related drugs, antidepressants and nonsteroidal anti-inflammatory drugs [NSAIDs]). These confounders were identified with the National Health Insurance Fund algorithm using LTC and hospitalization diagnosis codes.[19] A combined covariate related to "cardiovascular history" was created considering the following covariates: acute coronary syndrome, chronic coronary artery disease, obliterative arterial disease of the lower limbs, cardiac rhythm or conduction disorder, valvular disease and hypertension estimated from antihypertensive drug use.

2.5 | Analyses

For descriptive analyses, the quantitative variables were described according to their mean ± standard deviation, or median and interquartile range if their distributions were not normal. The categorical variables were described according to the number of patients in each category and their respective percentages.

2.5.1 | Cumulative incidence rate

We calculated the crude cumulative incidence rate (CIR) of HF following PKI exposure for each PKI as the number of new HF cases for this PKI divided by the total number of patients exposed to this PKI and during the 18 months of follow-up.

2.5.2 | Hazard ratio estimates

The hazard ratios (HRs) of each confounder were estimated using univariate regression to identify the covariates significantly associated with the HF outcome. The censoring events were death, identification of an HF event or end of the follow-up period. For our multivariate Cox regression model, we preselected covariates with a *P* value lower than .25. We then retained only the significant covariates in our final model by eliminating covariates with a *P* value higher than .05 using backward selection. We stratified our final model based on the treatment duration group, as described above. Finally, we estimated the adjusted hazard ratios (aHRs) of each PKI compared to the others.

2.5.3 | Incidence rate ratio

The crude incidence rate ratio (IRR) of HF occurrence was measured for each PKI, taking into account the duration of the respective exposure. The standardized rate ratio (SRR) was then calculated according to gender and age groups (18-55, 55-65, 65-75, 75+ years old) using an indirect method. Our reference population was the general population from a 1/97th permanent representative sample of the SNDS during 2012 to be concurrent with the study period.[22] The same algorithm was used to identify HF events. The 95% confidence intervals (95% CIs) were calculated using normal distribution.

2.5.4 | Sensitivity analyses

To limit any potential indication bias, a subgroup analysis was performed for each group of at least three PKIs sharing the same indication. The three groups of indications were "haematological malignancies", "nonsmall-cell lung cancer" and "metastatic kidney cancer". Patients with another indication that was identified by a long-term condition or hospitalization (main or related diagnosis) within 12 months before or 18 months after initiation of the PKI in accordance with the marketing authorization indications of the PKI in question were excluded. Lapatinib and vemurafenib could not be included in this sensitivity analysis as they were alone in their indication group. An adjusted Fine-Gray competing risk model was then used to calculate the subdistribution hazard ratio (sHR) of each PKI compared to others, considering death as a competing risk.[23]

2.5.5 | Description of drug management in HF

The management of HF occurring in patients after exposure to PKIs was described, specifying the overall and cardiovascular drugs

dispensed (using ATC codes) from 1 year prior to the onset of heart failure to 1 year after, divided by the number of patients.

All analyses were conducted using SAS statistical software (version 9.4; SAS Institute, Cary, NC, USA) and R Studio software (CRAN version 1.3).

2.6 | Funding and ethical statement

For this study, Yoann Zelmat received a grant from the Fondation ARC for cancer research as part of a research year. The observational study declaration with the Institute of Health Data was obtained on 24 November 2015 and validated by the French Data Protection Authority (CNIL).

3 | RESULTS

Of the 116 378 patients exposed to 13 different PKIs, 49 714 were included in the analysis after applying the selection process (Figure 1). The cohort characteristics are shown in Table 1. The current study population was predominantly male (55.1%, N = 27 394), with a median age of 64.8 years (interquartile range [IQR] = 56.6, 73.5). The number of patients with at least one comorbidity of interest was 28 104 (56.5%). Nearly 50% of patients had a cardiovascular history and 18% had diabetes. The distribution classes from the social deprivation index scores were homogeneous. The three most frequently used PKIs were erlotinib (n = 18 648, 37.5%), sorafenib (n = 7085, 14.3%) and everolimus (n = 5470, 11.0%). During the 18-month follow-up period, 19 111 patients died (38.4%).

The proportion of patients who developed HF during the 18-month follow-up period was 3.7% (N = 1852). These patients had a median age of 71.8 years (IQR = 62.9, 79.2) and were predominantly male (n = 1119, 60.4%). A cardiovascular history was reported in 74.2% of patients and diabetes in 26.6%. During the 18-month follow-up period, 960 patients died (51.8%) (Table 1).

Figure 2 shows the monthly distribution of HF events during the 18-month follow-up period. The number of events peaked at 2 months and decreased afterwards up to the end of follow-up. More than half of the events occurred within the first 6 months (970, 52.4%).

Figure 3 shows the CIR of HF during follow-up. Pazopanib and ruxolitinib had the highest CIRs and nilotinib the lowest, with 10.5% (95% CI = 6.7, 14.3), 9.1% (95% CI = 7.2, 11.0) and 1.2% (95% CI = 0.4, 2.0), respectively.

We performed a univariate analysis of the predictors associated with the occurrence of HF. A history of cardiovascular disease, use of lipid-lowering drugs, presence of type 2 diabetes, male gender and over 65 years of age were significantly associated with an increased incidence of HF (Figure 4).

The multivariate analysis adjusted for age, gender, diabetes and cardiovascular history and stratified by DDDe showed that six PKIs carried a significantly increased incidence of HF compared to the others (Figure 5). Pazopanib had the highest aHR of 2.42 (95% CI = 1.67, 3.52), followed by dasatinib 2.22 (95% CI = 1.42, 3.44), ruxolitinib 2.11 (95% CI = 1.69, 2.64), crizotinib 1.45 (95% CI = 1.26, 1.67), everolimus 1.71 (95% CI = 1.07, 2.72) and vemurafenib 1.37 (95% CI = 1.01, 1.86).

We compared the IRRs of the occurrence of HF with a sample from the general population (Table 2). The mean incidence rate of HF was 3.38 in the study populaiton versus 0.42 in the sample of the general population, per 100 person-years. The IRRs of patients exposed to PKI were always higher than the mean of the general population sample with equivalent age category and gender. Figure 6 shows the standardized incidence rate of HF per 100 person-years compared to the general population and for each of the PKIs studied. All PKIs except nilotinib carried a significantly increased incidence of HF.

Sensitivity analyses were also performed (Supporting Information Table S3). In the subgroups of PKIs sharing the same indication, pazopanib and everolimus showed a significantly increased incidence of HF in the metastatic kidney cancer subgroup. Among the PKIs indicated for haematological malignancies, dasatinib and ruxolitinib also displayed statistical significance with an increased incidence of

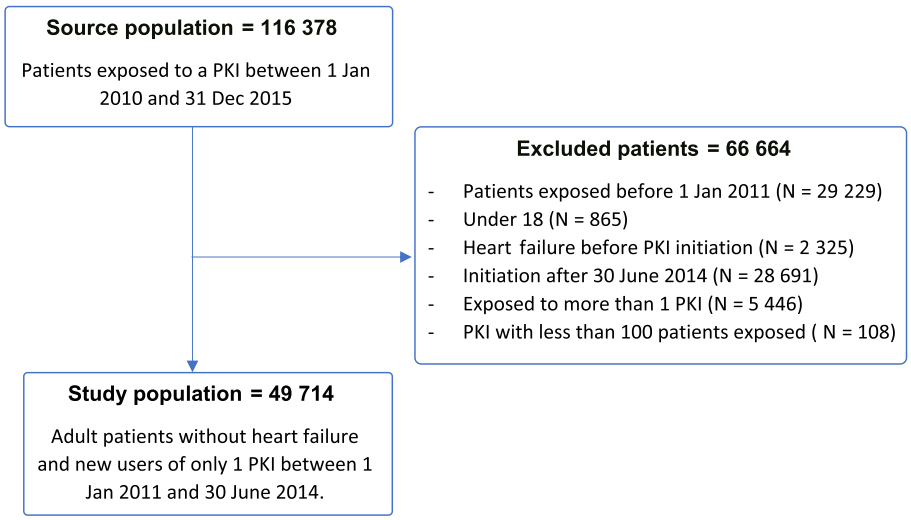

FIGURE 1 Flowchart of the study. PKI, protein kinase inhibitor

TABLE 1 Baseline characteristics of the overall population and heart failure patients

Baseline characteristics		Overall N = 49 714	Heart failure patients N = 1 852 (3.7%)
Age			
	Median (IQR)	64.8 (56.6, 73.5)	71.8 (62.9, 79.2)
	18-55	10 657 (21.4%)	180 (9.7%)
	55-65	14 646 (29.5%)	397 (21.4%)
	65-75	13 905 (28.0%)	535 (28.9%)
	75+	10 506 (21.1%)	740 (40.0%)
Sex	Male	27 394 (55.1%)	1 119 (60.4%)
Comorbidity			
	Diabetes	8964 (18.0%)	494 (26.6%)
	Stroke	470 (0.9%)	27 (1.5%)
	Pulmonary embolism	977 (2.0%)	30 (1.6%)
	Addictive disorder	482 (1.0%)	10 (0.5%)
	Cardiovascular history	25 214 (50.7%)	1 375 (74.2%)
	Acute coronary syndrome	391 (0.8%)	36 (1.9%)
	Chronic coronary disease	4527 (9.1%)	375 (20.2%)
	Obliterative arterial disease of the lower limb	2465 (5.0%)	146 (7.9%)
	Cardiac rhythm disorder	4453 (9.0%)	389 (21.0%)
	Valvular disease	946 (1.9%)	98 (5.3%)
Social deprivation index			
	1	8310 (16.7%)	282 (15.2%)
	2	8416 (16.9%)	316 (17.1%)
	3	9268 (18.6%)	312 (16.8%)
	4	9252 (18.6%)	390 (21.1%)
	5	9375 (18.9%)	384 (20.7%)
	Unknown	5093 (10.2%)	168 (9.1%)
Protein kinase inhibitor			
	Crizotinib	410 (0.8%)	18 (1.0%)
	Dasatinib	339 (0.7%)	20 (1.1%)
	Erlotinib	18 648 (37.5%)	653 (35.3%)
	Everolimus	5470 (11.0%)	259 (14.0%)
	Gefitinib	2475 (5.0%)	67 (3.6%)
	Imatinib	4666 (9.4%)	166 (9.0%)
	Lapatinib	3048 (6.1%)	88 (4.8%)
	Nilotinib	690 (1.4%)	8 (0.4%)
	Pazopanib	357 (0.7%)	28 (1.5%)
	Ruxolitinib	1000 (2.0%)	83(4.5%)
	Sorafenib	7085 (14.3%)	253 (13.7%)
	Sunitinib	4435 (8.9%)	167 (9.0%)
	Vemurafenib	1091 (2.2%)	42 (2.3%)
DDDe			
	Median (IQR)	100.0 (56.0, 225.0)	90.0 (56.0, 180.0)
	≤6 months	34 062 (68.5%)	1413 (76.3%)
	>6 months	15 652 (31.5%)	439 (23.7%)
Medicine consumption in the year prior to initiation of protein kinase inhibitor			
	Antihypertensive	22 725 (45.7%)	1244 (67.1%)
	Chemotherapy	26 227 (52.8%)	902 (48.7%)

(Continues)

TABLE 1 (Continued)

Baseline characteristics	Overall N = 49 714	Heart failure patients N = 1 852 (3.7%)
Thyroid	4148 (8.3%)	194 (10.5%)
Lipid-lowering	11 926 (24.0%)	675 (36.4%)
Antidepressant	6368 (12.8%)	253 (13.6%)
NSAID	5182 (10.4%)	163 (8.8%)
Death during 18 months of follow-up, n (%)	19 111 (38.4%)	960 (51.8%)

Abbreviations: DDDe, daily defined dose equivalent; IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drug.

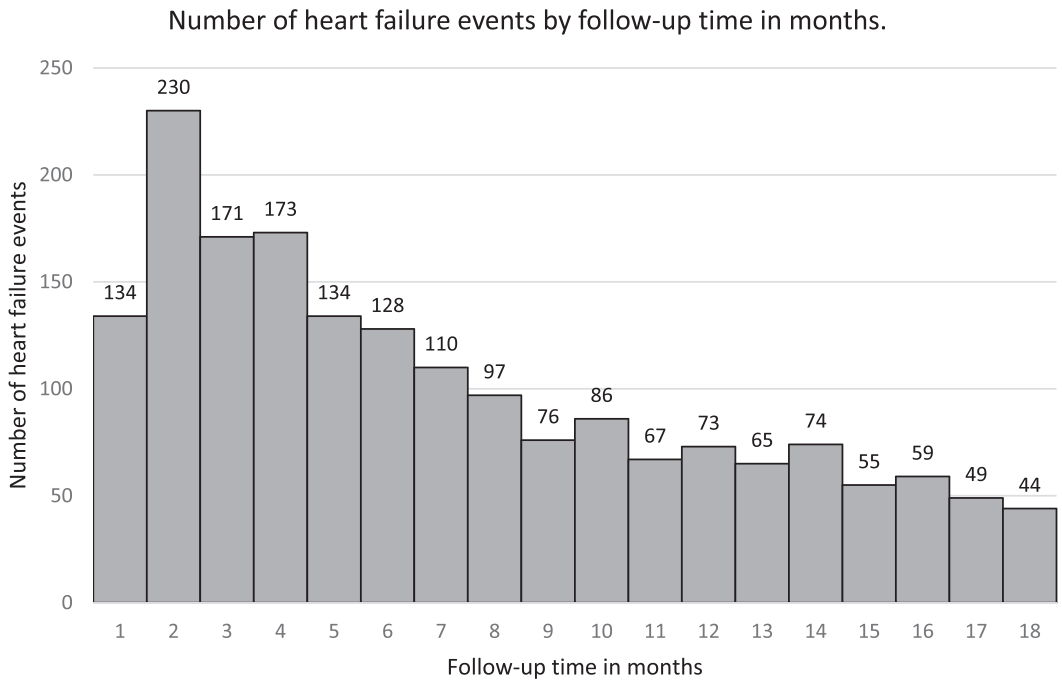

FIGURE 2 Number of heart failure events by follow-up time in months

HF. The same applies to crizotinib among the PKIs indicated for nonsmall-cell lung cancer. The second sensitivity analysis took into account the competing risk of death. The results of the Fine-Gray model are consistent with our primary analysis, except for vemurafenib and crizotinib.

The consumption of cardiovascular medicine increased after the onset of HF, especially beta-blocking agents and diuretics (Supporting Information Figure S1).

4 | DISCUSSION

The current study investigates the occurrence of HF following exposure to PKIs using data from a medical administrative database (SNDS). Of the 13 PKIs studied, six were found to be significantly associated with an increased incidence of HF: dasatinib, ruxolitinib, crizotinib, everolimus, pazopanib and vemurafenib. The onset of HF appeared to occur relatively early, with more than half of the events occurring within 6 months of introducing the PKI. The incidence rate ratio of HF in our study population was increased compared to the general population. The predictors associated with the occurrence of HF corresponded with the main predictors described in the literature: age, male gender, diabetes, cardiovascular history and use of antihypertensive and lipid-lowering drugs.[24,25] Our sensitivity analyses confirmed this risk for dasatinib, ruxolitinib, pazopanib and everolimus.

Current data regarding the risk of HF occurrence following PKI exposure are sparse. Some case reports describe the relevance of pazopanib in the occurrence of HF in patients with sarcoma.[11–14] The American Heart Association classified certain PKIs according to their ability to induce or precipitate HF based on published clinical trials.[17] Among these PKIs, lapatinib was classified as "moderate and major", imatinib as "moderate" and sunitinib and sorafenib as "minor". These data are difficult to compare with our own because few patients took part in these clinical trials, hence their representativeness in terms of the actual population using these PKIs may be questionable. However, this ranking is consistent with the decreasing trend found in the

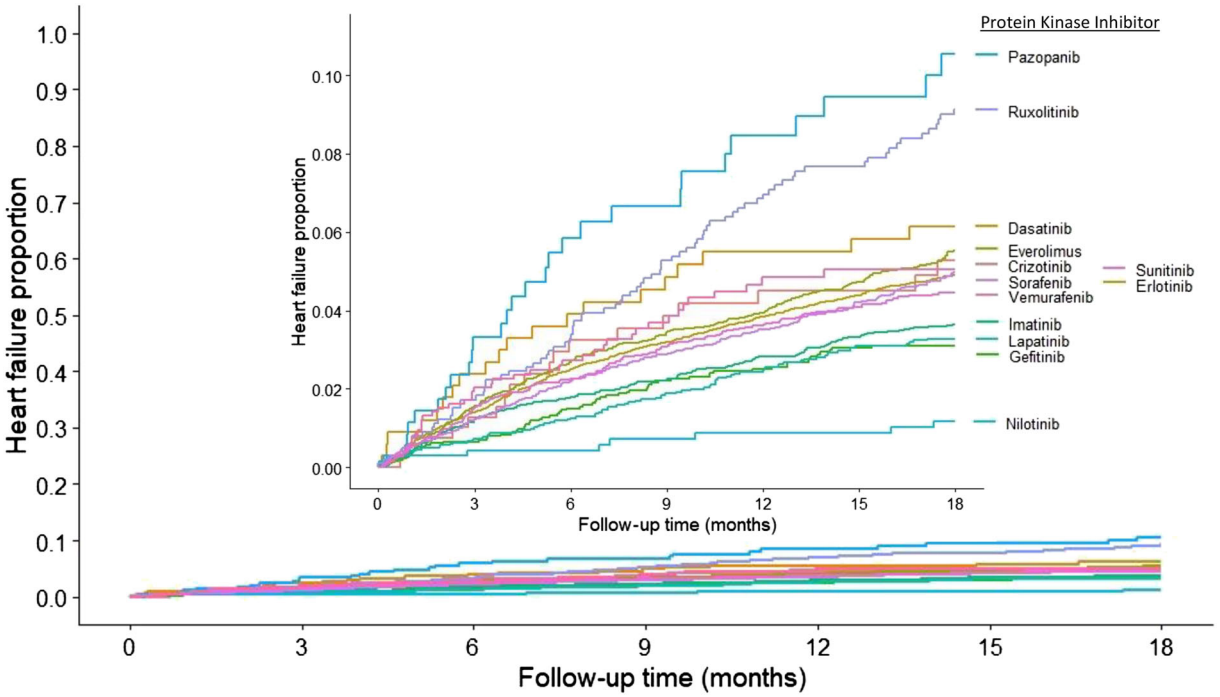

FIGURE 3 Cumulative incidence rate of heart failure by follow-up time in months after PKI exposure. PKI, protein kinase inhibitor

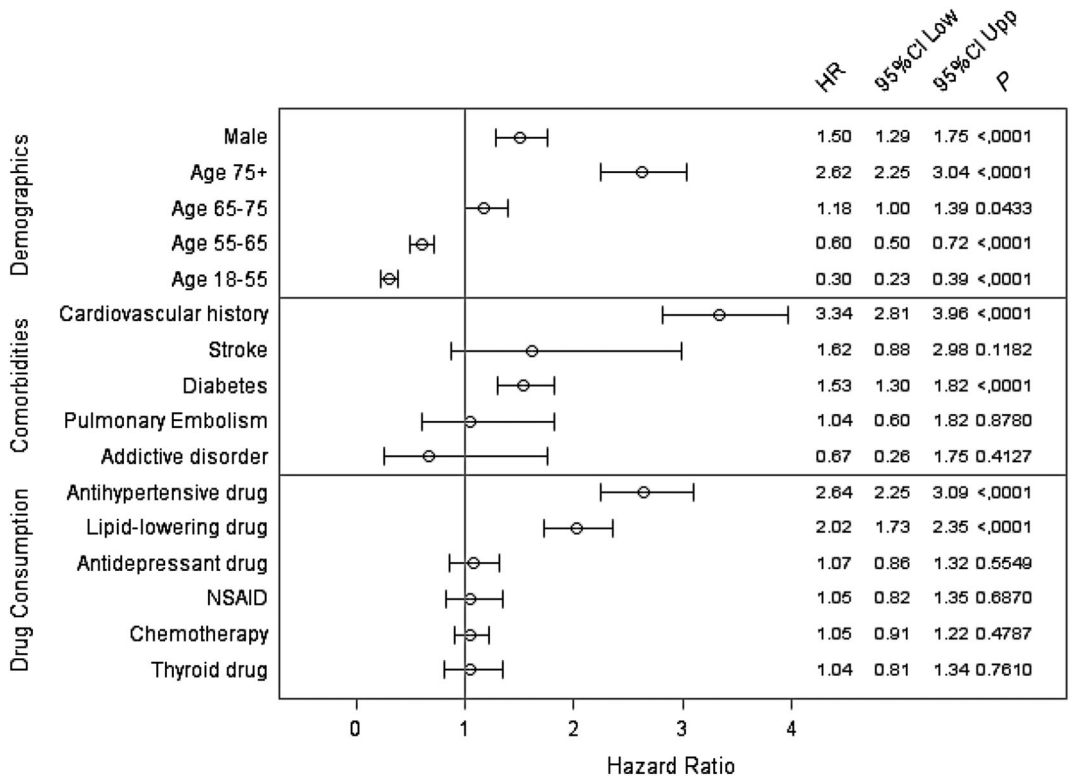

FIGURE 4 Predicted heart failure hazard ratio estimates by category. 95% CI Low, 95% confidence interval, lower limit; 95% CI Upp, 95% confidence interval, upper limit; HR, hazard ratio; NSAID, nonsteroidal anti-inflammatory drug

current study where the HRs of the above-mentioned PKIs were 1.08 (95% CI = 0.86, 1.34), 1.05 (95% CI = 0.89, 1.24), 0.86 (95% CI = 0.73, 1.01) and 0.72 (95% CI = 0.63, 0.82), respectively. The incidence of HF in Europe and the United States is estimated to be between 0.1 and 0.9 cases per 100 person-years, but is highly dependent on the study population.[24] In the current study, the mean

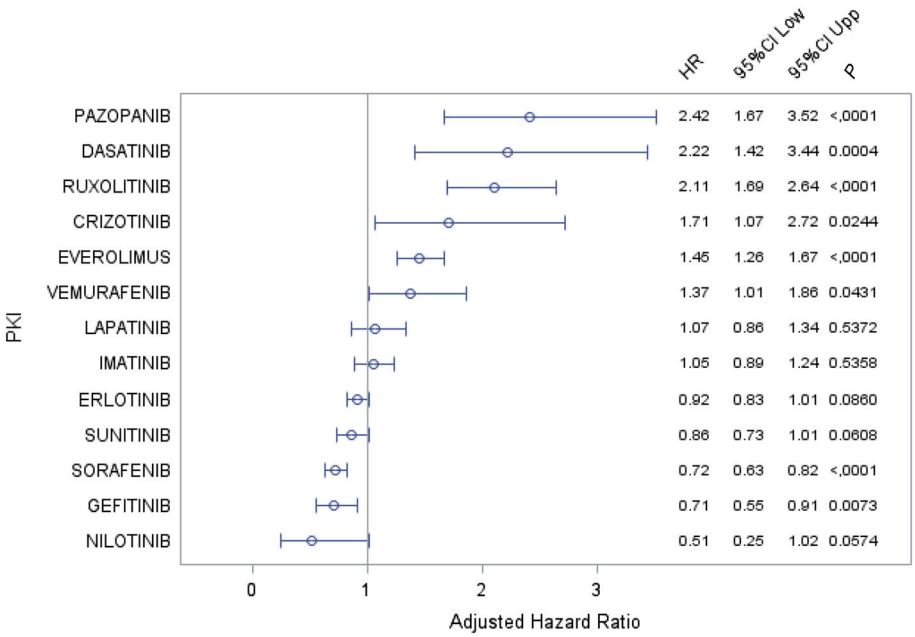

FIGURE 5 Hazard ratio estimates of the risk of heart failure of protein kinase inhibitors (PKIs) adjusted for age, sex, diabetes and cardiovascular history and stratified by defined daily dose equivalent. 95% CI Low, 95% confidence interval, lower limit; 95% CI Upp, 95% confidence interval, upper limit; HR, hazard ratio

TABLE 2 Number of heart failures newly diagnosed after a protein kinase inhibitor among the general and study populations, categorized by age and sex

		General population					Study population				
Age	Sex	N	HF	Cumulated follow-up time (years)	Mean follow-up time (years)	HF risk (100 PY)	N	HF	Cumulated follow-up time (years)	Mean follow-up time (years)	HF risk (100 PY)
18-55	F	141 522	55	211 361	1.49	0.03	5667	84	6708	1.18	1.25
18-55	M	140 787	136	210 034	1.49	0.06	4990	96	5414	1.08	1.77
55-65	F	33 466	107	49 788	1.49	0.21	6221	142	7279	1.17	1.95
55-65	M	30 589	184	45 251	1.48	0.41	8425	255	8728	1.04	2.92
65-75	F	20 151	162	29 827	1.48	0.54	5574	186	6642	1.19	2.80
65-75	M	17 864	270	26 135	1.46	1.03	8331	349	8722	1.05	4.00
>75	F	25 288	1064	35 860	1.42	2.97	4858	321	5537	1.14	5.80
>75	M	14 501	688	20 384	1.41	3.38	5648	419	5783	1.02	7.25
Total		424 168	2666	628 639	1.48	0.42	49 714	1852	54 813	1.10	3.38

Abbreviations: F, female; M, male; HF, heart failure; PY, person-years.

incidence rate was 3.38 per 100 person-years and it was 0.42 in our reference population (General sample of beneficiaries, "Échantillon Généraliste des Bénéficiaires", EGB). This net increase in incidence can be explained by the specific nature of the current study population, with its relatively advanced age (median age of 64.8 years), the frequent presence of significant comorbidities (50.7% of patients had a history of cardiac disease, 18.0% had diabetes and 52.8% underwent chemotherapy in the year preceding PKI onset) and PKI exposure. Our results are noticeably different from those documented in the study previously conducted by our team using the global pharmacovigilance database, VigiBase. Dasatinib is the only PKI to be significantly associated with an increased risk of HF in this study and the previous one.[10] This may be explained by the differences in the medicinal products studied, the methodology applied (case/noncase analysis versus survival analysis) and the data sources used (reporting versus medical administrative data). Indeed, data based on spontaneous reports are subject to an under-reporting bias and cannot be used to estimate the incidence of an adverse drug reaction. A nested case-control study conducted in Israel using medical administrative data showed that among the 13 PKIs studied, four were found to be significantly associated with an increased risk of HF: trastuzumab, cetuximab, panitumumab and sunitinib.[26] This study did not focus on the same PKIs as ours, and the presence of some drugs in this study—such as monoclonal antibodies—might be questionable. Therefore, the comparator group used in their analyses is significantly different from ours, including a large proportion of medicinal products administered intravenously, unlike the current study, which focused solely on oral PKIs. The nonsignificance of dasatinib and pazopanib in their analyses

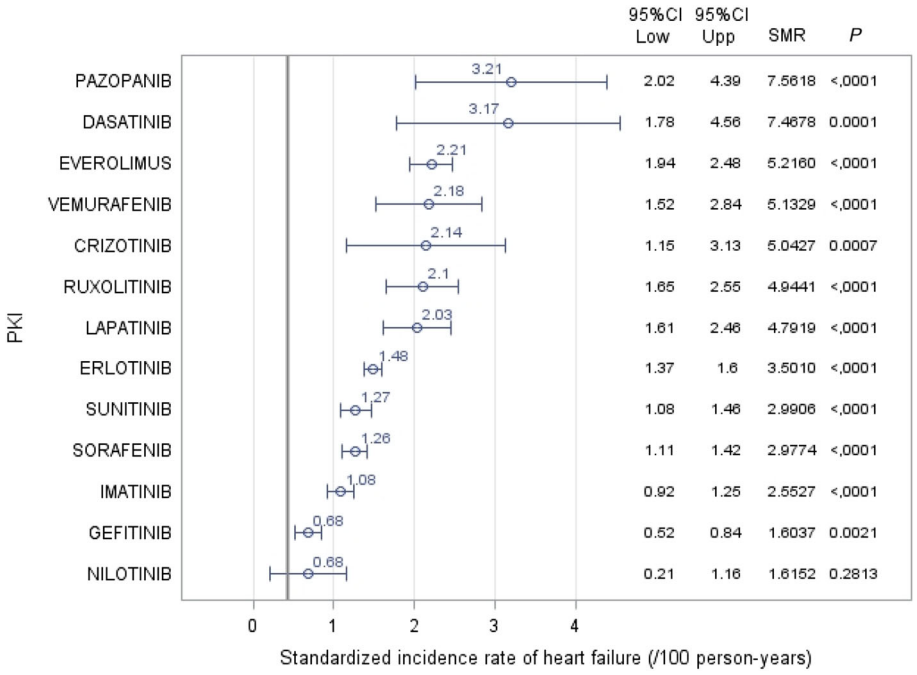

FIGURE 6 Age- and sex-standardized incidence rate of heart failure occurring within 18 months of the onset of exposure to a protein kinase inhibitor (PKI) and per 100 person-years. The baseline mean rate is 0.42 per 100 person-years in the reference population, which is from the generalist sample of beneficiaries. 95% CI Low, 95% confidence interval, lower limit; 95% CI Upp, 95% confidence interval, upper limit; SMR, standardized morbidity ratio

could be explained by the lack of power due to the small number of patients exposed, with 27 and 37 patients followed up, respectively. Thus, their confidence intervals were particularly wide, ranging from 0.37 to 11.92 and from 0.77 to 7.93, respectively. The lack of patients exposed to vemurafenib resulted in a lack of power, and vemurafenib was the only PKI indicated for melanoma. We were therefore unable to estimate an aHR in subgroups by indication and thus we cannot exclude an indication bias for this PKI. Several potential mechanisms of cardiotoxicity have been suggested, but they remain unclear.[15,27,28]

The main strength of this initial study in France is the near-exhaustive nature of the data analysed at national level using data from the SNDS. These data include the healthcare consumption data of more than 65 million French people, that is, 98% of the French population, thus reflecting the entire French population and constituting one of the largest healthcare databases in the world.[29] The study design is well suited for pharmacoepidemiologic studies using longitudinal data, with advantages in the adjustment of confounders and consideration of exposure time. We were also able to adjust for major covariates in the occurrence of HF: age, gender, diabetes and cardiovascular history. The data identifying and quantifying the onset of exposure are precise, hence the healthcare pathway of patients can be traced over several years without attrition. In addition, although we were considering patients at risk of HF after discontinuation of treatment, we also considered duration in our analyses by stratifying according to the DDDe received by each patient. Finally, the consistency of our sensitivity analyses in relation to our main analysis, considering the indication bias and the competing risk of death, attests to the robustness of our results.

The main limitations of the current study concern the identification of the event, which is based on an algorithm that is not fully validated in the scientific literature. Nevertheless, this algorithm is approved by expert agreement and is used by the National Healthcare Insurance Fund ("Caisse Nationale d'Assurance Maladie", CNAM) to calculate the various follow-up statistics for HF patients in France. Moreover, a study assessing the accuracy of identifying HF diagnosis via ICD-10 hospitalization codes showed a positive predictive value ranging from 60.5% to 88.0%, depending on the codes used.[30] The identification algorithm used in the current study is also based on specific LTC codes. We can therefore assume that the positive predictive values of this algorithm are higher. Nevertheless, this algorithm could not identify patients with HF who were not registered with a corresponding LTC, those who were not hospitalized during the study period or those who had a preserved ejection fraction. Thus, our analyses tend to underestimate the occurrence of HF. Event identification via this algorithm may occur remotely from the clinical reporting of HF, thus overestimating the time to occurrence, and therefore we took a wide identification interval of 18 months post-onset in our analyses. We were not able to adjust for all covariates not recorded in the SNDS and involved in the occurrence of HF, such as smoking or obesity, but we were able to adjust for the major covariates. There are inherent limitations to the use of data from medical administrative databases, such as patient compliance, which cannot be verified, or the presence of potentially unobservable periods of drug intake, such as during hospitalization. A competing risk of death was present in our analyses and might overestimate the occurrence of the event of interest. However, we have taken this risk into account by performing a Fine-Gray model, which was consistent with our primary analysis. Moreover, a significant patient loss was recorded for everolimus and pazopanib in the metastatic kidney cancer subgroup (29.5% and 23.5% of remaining patients, respectively). This might be due to the fact that metastatic

kidney cancer is not their main indication. Indeed, pazopanib is mostly indicated in sarcoma and everolimus is also indicated in breast cancer and neuroendocrine tumours. Nonetheless, the results of this sensitivity analysis are consistent with the primary analysis in terms of significance and ratio, and generate confidence in the results of our primary analysis. Finally, the current study was only carried out on a limited number of PKIs. The results observed could therefore vary in a new analysis including other medicinal products. Additional studies could validate or refute our results and provide additional knowledge on the occurrence of HF following PKI exposure.

In summary, the current study is the first to estimate the nationwide incidence of HF following PKI exposure. Further studies may confirm these results for dasatinib, everolimus, pazopanib, ruxolitinib and more particularly for those PKIs with results slightly above the significance threshold, namely crizotinib and vemurafenib. The predictors significantly associated with this risk are cardiovascular history, diabetes, age, male gender and the use of antihypertensive and lipid-lowering agents. HF appears to be of relatively early onset as more than half of the events (55.2%) occurred in the first 6 months of follow-up. Early cardiac monitoring would appear advisable in patients starting one of these PKIs.

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COMPETING INTEREST

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CONTRIBUTORS

Yoann Zelmat, Maryse Lapeyre-Mestre and Fabien Despas were responsible for formulating the research question, designing and carrying out the study, and analysing the data. Yoann Zelmat wrote the article with Fabien Despas, and Cécile Conte, Pernelle Noize, Clémentine Vabre, Marie Pajiep and Margaux Lafaurie revised it.

DATA AVAILABILITY STATEMENT

According to data protection and French legislation, the authors cannot publicly share SNDS data. However, any person or organization, whether public or private, for-profit or non-profit, is able to access SNDS data with CNIL authorization to carry out a study, research or an evaluation of public interest (https://www.snds.gouv.fr).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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