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Cardiovascular Toxicities Associated With Ibrutinib

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ABSTRACT

BACKGROUND Ibrutinib has revolutionized treatment for several B-cell malignancies. However, a recent clinical trial where ibrutinib was used in a front-line setting showed increased mortality during treatment compared with conventional chemotherapy. Cardiovascular toxicities were suspected as the culprit but not directly assessed in the study.

OBJECTIVES The purpose of this study was to identify and characterize cardiovascular adverse drug reactions (CV-ADR) associated with ibrutinib.

METHODS This study utilized VigiBase (International pharmacovigilance database) and performed a disproportionality analysis using reporting odds ratios (ROR) and information component (IC) to determine whether CV-ADR and CV-ADR deaths were associated with ibrutinib. IC compares observed and expected values to find associations between drugs and adverse drug reactions using disproportionate Bayesian-reporting; IC_{025} (lower end of the IC 95% credibility interval) >0 is significant.

RESULTS This study identified 303 ibrutinib-associated cardiovascular deaths. Ibrutinib was associated with higher reporting of supraventricular arrhythmias (SVAs) (ROR: 23.1; 95% confidence interval: 21.6 to 24.7; $p < 0.0001$; IC_{025}: 3.97), central nervous system (CNS) hemorrhagic events (ROR: 3.7; 95% confidence interval: 3.4 to 4.1; $p < 0.0001$; IC_{025}: 1.63), heart failure (ROR: 3.5; 95% confidence interval: 3.1 to 3.8; $p < 0.0001$; IC_{025}: 1.46), ventricular arrhythmias (ROR: 4.7; 95% confidence interval: 3.7 to 5.9; $p < 0.0001$; IC_{025}: 0.96), conduction disorders (ROR: 3.5; 95% confidence interval: 2.7 to 4.6; $p < 0.0001$; IC_{025}: 0.76), CNS ischemic events (ROR: 2.2; 95% confidence interval: 2.0 to 2.5; $p < 0.0001$; IC_{025}: 0.73), and hypertension (ROR: 1.7; 95% confidence interval: 1.5 to 1.9; $p < 0.0001$; IC_{025}: 0.4). CV-ADR often occurred early after ibrutinib administration. Importantly, CV-ADR were associated with fatalities that ranged from ~10% (SVAs and ventricular arrhythmias) to ~20% (CNS events, heart failure, and conduction disorders). Ibrutinib-associated SVA portends poor prognosis when CNS events occur concomitantly, with 28.8% deaths (15 of 52 cases).

CONCLUSIONS Severe and occasionally fatal cardiac events occur in patients exposed to ibrutinib. These events should be considered in patient care and in clinical trial designs. (Evaluation of Reporting of Cardio-vascular Adverse Events With Antineoplastic and Immunomodulating Agents [EROCA]; NCT03530215) (J Am Coll Cardiol 2019;74:1667–78) © 2019 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CD = conduction disorders

CNS = central nervous system

CV-ADR = cardiovascular adverse drug reactions

HF = heart failure

IC_{025} = information component (and its 95% credibility interval lower end)

ICSR = individual case safety report

ROR = reporting odds ratio

SVA = supraventricular arrhythmia

VA = ventricular arrhythmia

Ibrutinib, a Bruton tyrosine kinase inhibitor, is an effective treatment for hematological malignancies including chronic lymphocytic leukemia, Waldenstrom's macroglobulinemia, mantle cell lymphoma, marginal zone lymphoma, and chronic graft versus host disease (1-8). However, early data suggested ibrutinib was associated with atrial fibrillation and bleeding (1-9). More recently, reports of supraventricular arrhythmias (SVAs) and life threatening ventricular arrhythmias (VAs) associated with ibrutinib have emerged (10,11). As ibrutinib is being tested in a front line setting, it is important to assess its overall adverse risks on the cardiovascular system. A recent randomized trial with 2 ibrutinib-containing arms in the front-line setting reported death rates of 7% in each ibrutinib arm, compared with 1% in the control arm, with many of these deaths "unexplained/unwitnessed death" or cardiac in nature (12). Whether ibrutinib is associated with other cardiovascular adverse drug reactions (CV-ADR) and the extent of cardiovascular toxicities in a "real-world" population is also unclear, as are the characteristics, timing, and outcomes of ibrutinib-associated CV-ADR. Defining these ibrutinib-associated toxicities is critical, especially because ibrutinib is increasingly used in a front-line setting and combined with other agents. Here, we used VigiBase, the World Health Organization's (WHO) global database of individual case safety reports (ICSRs) to further characterize these CV-ADR (13).

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METHODS

STUDY DESIGN AND DATA SOURCES. The study is a disproportionality analysis based on adverse drug reactions (ADR) reported within VigiBase, the WHO global deduplicated database of ICSRs, originating from >130 countries (14). VigiBase is managed by the Uppsala Monitoring Centre (UMC) and contains more than 16 million ICSRs of suspected medication ADR (as of January 2018) submitted by national pharmacovigilance centers since 1967. These reports originate from different sources, such as physicians or other healthcare professionals, pharmaceutical companies, and patients, and generally occur post-marketing. The use of confidential electronically processed patient data was approved by the Vanderbilt University Medical Center institutional review board (#181337).

PROCEDURES. This observational retrospective study included all CV-ADR classified by group queries according to the Medical Dictionary for Drug Regulatory Activities (MedDRA) (Online Table 1) between inception in November 14, 1967, and January 2, 2018. CV-ADR specifically considered in the analysis were suspected to be induced by ibrutinib. Each report contains general administrative information (reporter qualification, date of reporting, country of origin), patient characteristics (age, sex), drugs (indication for the drug, dosage regimen, start and end dates, route of administration), and reactions/events (reported terms, MedDRA classification terms, onset date, end date, seriousness, and final outcome).

STATISTICAL ANALYSIS. VigiBase allows for case/noncase analysis (disproportionality analysis), which we utilized to study if suspected drug-induced CV events were differentially reported with ibrutinib compared with CV events reported in the entire database. Disproportionality analysis compares the proportion of selected specific ADR reported for a single or a group of drugs (e.g., ibrutinib) with the proportion of the same ADR for a control group of drugs (e.g., entire database). The denominator in these analyses is the overall ADR reported for each group of drugs. If the proportion of an ADR is greater in patients exposed to a group of drugs (cases) than in patients not exposed to this drug group (noncases), this suggests an association between the specific drug and the reaction and is a potential signal for safety. Disproportionality can be either calculated by the information component (IC) or reporting odds ratio (ROR) when using the entire database as comparator.

Calculation of the IC (details in Online Appendix 1), using a Bayesian confidence propagation neural network, was specifically developed and validated by UMC as an automated, flexible indicator value for disproportionate reporting that compares expected

Abbvie, Acerta, Astellas, AstraZeneca, Beigene, Genentech/Roche, Gilead, Juno/Celgene, Kite, Loxo, Novartis, Octapharma, Pfizer, Pharmacyclics, Redx, Sun, Sunesis, TG Therapeutics, and Verastem; has received honoraria from Janssen and Teva; has received research funding from Gilead, Loxo, Sun, and Verastem; and has served on Data Safety Monitoring Committees for Morphosys and Invectys. Dr. Moslehi has served on Advisory Boards for Pharmacyclics, Bristol-Myers Squibb, Pfizer, Novartis, Regeneron, Takeda, Deciphera, and Myokardia; and has received research funding from Pfizer and Bristol-Myers Squibb. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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TABLE 1 Disproportionality Analysis in VigiBase

	Ibrutinib	Entire Database (Since Inception)	IC/IC_{025}	Entire Database (Since 2013)	ROR ($_{95}$CI)
Total number of ICSRs available	13,572	16,343,451		8,318,890	
Number of ICSRs and statistics by CV-ADR subgroups					
Cardiac supraventricular arrhythmias	**959 (7.07)**	**68,597 (0.42)**	**4.06/3.97**	**28,242 (0.34)**	**23.1 (21.6-24.7)**
CNS hemorrhagic events	**505 (3.72)**	**179,621 (1.10)**	**1.76/1.63**	**85,402 (1.03)**	**3.7 (3.4-4.1)**
Heart failure	**363 (2.67)**	**142,502 (0.87)**	**1.61/1.46**	**65,680 (0.79)**	**3.5 (3.1-3.8)**
Cardiac ventricular arrhythmias	**70 (0.52)**	**33,504 (0.20)**	**1.32/0.96**	**9,220 (0.11)**	**4.7 (3.7-5.9)**
Cardiac conduction disorders	**50 (0.37)**	**26,008 (0.16)**	**1.19/0.76**	**8,834 (0.11)**	**3.5 (2.7-4.6)**
CNS ischemic events	**254 (1.87)**	**161,618 (0.99)**	**0.92/0.73**	**70,529 (0.85)**	**2.2 (2.0-2.5)**
Hypertension and related end-organ damages	**295 (2.17)**	**239,232 (1.46)**	**0.57/0.40**	**109,148 (1.31)**	**1.7 (1.5-1.9)**
Cardiac valve disorders	30 (0.22)	25,500 (0.16)	0.49/−0.07	NA	NA
Myocardial infarction	149 (1.10)	163,908 (1.00)	0.13/−0.11	NA	NA
Cardiac death or shock	131 (0.97)	144,825 (0.89)	0.12/−0.13	NA	NA
Venous thrombo-embolic events	108 (0.80)	134,718 (0.82)	−0.05/−0.34	NA	NA
Vascular neoplasms	2 (0.01)	2,687 (0.02)	−0.13/−2.72	NA	NA
Pulmonary hypertension and cardiac involvements	19 (0.14)	30,718 (0.19)	−0.42/−1.14	NA	NA
Hyperglycemia, diabetes	112 (0.83)	233,007 (1.43)	−0.79/−1.07	NA	NA
Torsade de pointes/QT prolongation	9 (0.07)	20,938 (0.13)	−0.91/−2.01	NA	NA
Myocarditis	2 (0.01)	5,515 (0.03)	−1.02/−3.61	NA	NA
Dyslipidemia	14 (0.10)	64,555 (0.39)	−1.90/−2.75	NA	NA

Values are n (%) unless otherwise indicated. Information component (IC) and its 95% credibility interval lower endpoint (IC_{025}) comparing cardiovascular adverse drug reactions (CV-ADR) associated with ibrutinib versus entire database in VigiBase (from inception in November 14, 1967, to February 1, 2018). A positive IC_{025} value (>0) is the traditional threshold used for statistical signal detection **(in bold).** For significant signals, reporting odds ratio (ROR) and its 95% confidence ($_{95}$CI) interval were also calculated using entire database from January 1, 2013, to February 1, 2018 as comparator (contemporary control group for ibrutinib, first ibrutinib report in 2013).

ADR = adverse drug reaction; CNS = central nervous system; NA = not applicable.

and observed drug ADR associations to find new drug ADR signals with identification of probability difference from the background data (entire database since inception) (13,15,16). IC_{025} is the lower end of a 95% credibility interval for the IC. A positive IC_{025} value (>0) is the traditional threshold used in statistical signal detection at UMC (16,17). Compared with Bayesian statistics, disproportionality in VigiBase can also be assessed using a more classical frequentist approach by calculating the ROR Chi^2, described and used elsewhere (Online Table 2) (13,18-22). The lower end of ROR 95% confidence interval (CI) ≥1 is the threshold deemed significant. ROR was calculated taking as comparator of the entire database since 2013 to provide a contemporary control group for ibrutinib (first ICSR in VigiBase in 2013, the year of its first FDA approval) (6).

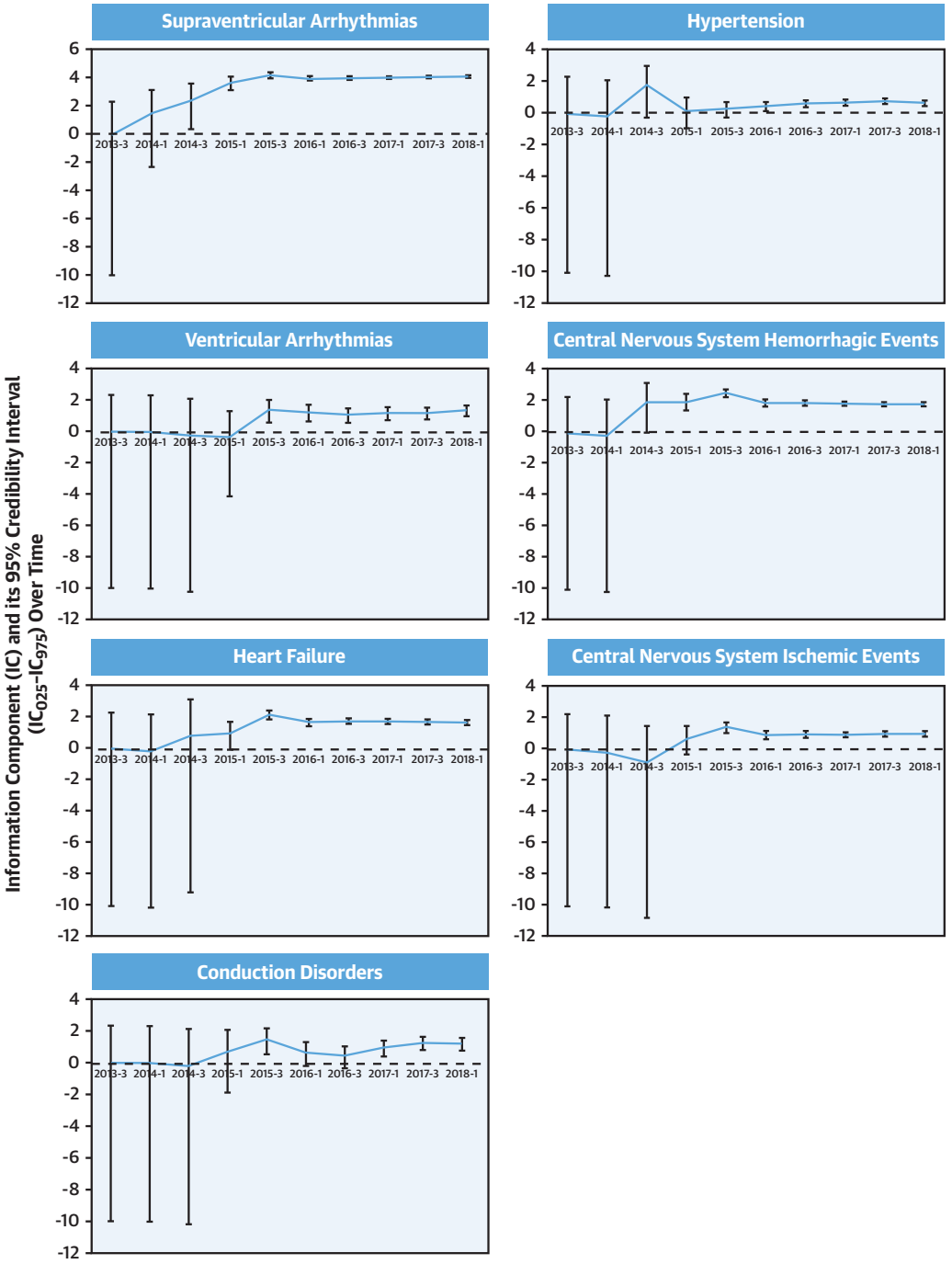
Characteristics of cases were described in terms of mean ± SD or median (interquartile range) for quantitative variables, and in terms of effective and proportion for qualitative ones. Comparison of qualitative and quantitative variables (non-normally distributed) were performed by chi-square test and Kruskal-Wallis with Dunn's post-tests, respectively (Prism version 7, GraphPad, La Jolla, California). A p value <0.05 was deemed significant.

RESULTS

CV-ADR SIGNAL DETECTED USING WHO's GLOBAL DATABASE OF ICSRs. Given the considerable overlap of symptoms for various cardiovascular disease etiologies as well as redundancies in reporting cardiac complications associated with oncologic therapies, we broadly categorized cardiovascular disease entities in the MedDRA Classification (version 20.1) based on underlying pathophysiology (Online Table 1). The total ADR (rate) in the ibrutinib subgroup (n = 13,572) versus the entire database (n = 16,343,451 since inception; n = 8,318,890 since 2013—date of the first ICSR with ibrutinib) was compared. Details concerning number of CV-ADR by cardiovascular grouping categories are available in **Table 1**.

Using this approach, we identified 7 broad CV entities where CV reporting was significantly increased in ibrutinib compared with the entire database. Ibrutinib was associated with higher reporting of SVAs (ROR: 23.1; 95% CI: 21.6 to 24.7; p < 0.0001; $IC_{025:}$ 3.97), central nervous system (CNS) hemorrhagic events (ROR: 3.7; 95% CI: 3.4 to 4.1; p < 0.0001; $IC_{025:}$ 1.63), heart failure (HF) (ROR: 3.5; 95% CI: 3.1 to 3.8; p < 0.0001; $IC_{025:}$ 1.46), VAs (ROR: 4.7;

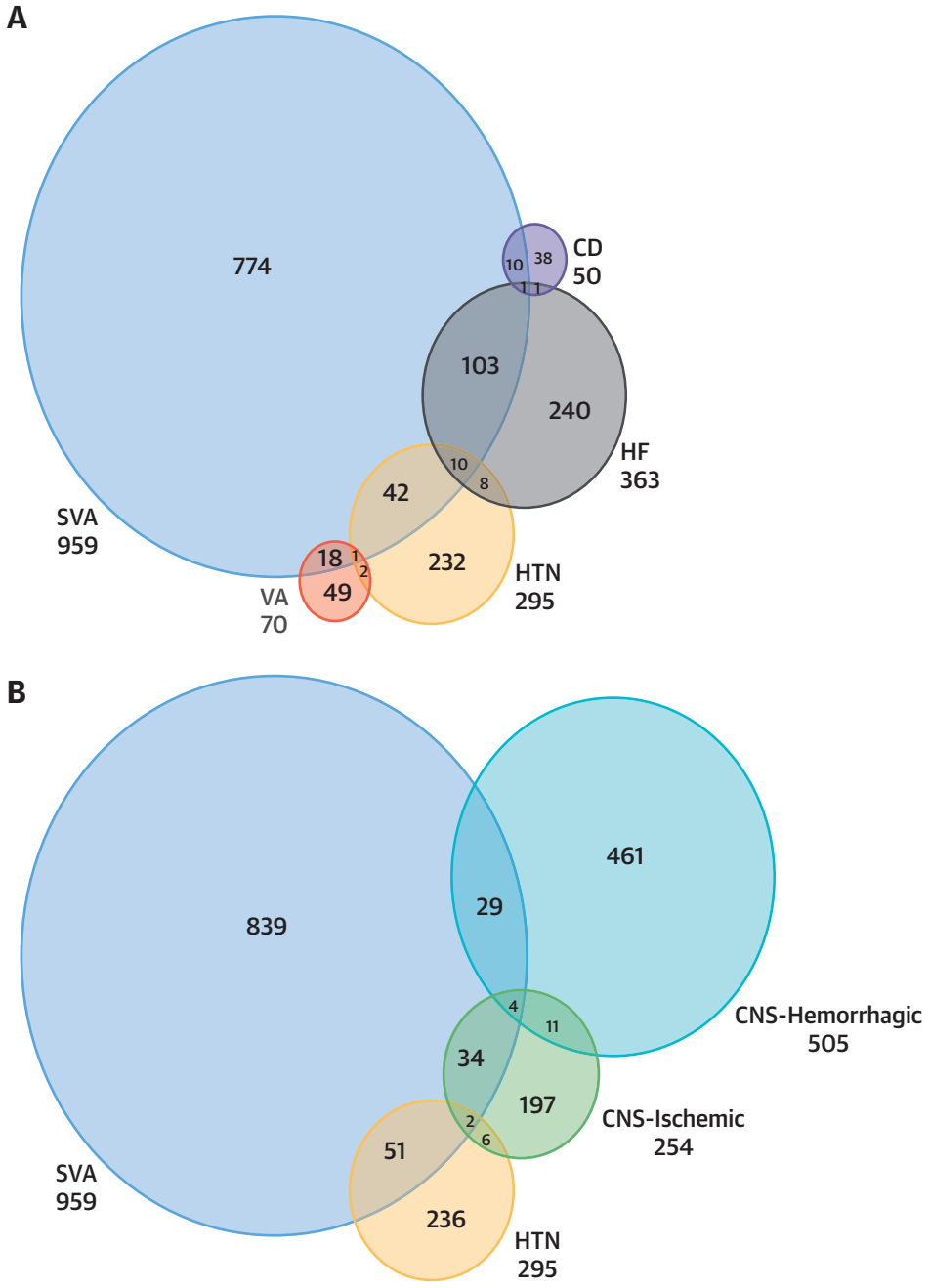
CENTRAL ILLUSTRATION Cardiovascular Fatalities Associated With Ibrutinib



Salem, J.-E. et al. J Am Coll Cardiol. 2019;74(13):1667-78.

Information component and its 95% credibility interval over time for supraventricular arrhythmias, ventricular arrhythmias, conduction disorders, heart failure, hypertension, and central nervous system hemorrhagic and ischemic events. The **error bars** show the 95% credibility interval of the information component (IC_{025}–IC_{975}). An IC_{025} value of >0 is deemed significant **(dotted line)**. Data are shown for the first and third trimester of each year (year-1; year-3).

FIGURE 1 Overlap of Cardiovascular Adverse Drug Reactions Associated With Ibrutinib in VigiBase



(A) Overlap between supraventricular arrhythmias (SVA), ventricular arrhythmias (VA), conduction disorders (CD), heart failure (HF) and hypertension (HTN). **(B)** Overlap between SVA, HTN and central nervous system (CNS) ischemic and hemorrhagic events. **(A)** Due to diagram limitation, the overlap between VA and CD (n = 1) or VA and HF (n = 7) groups are not displayed. **(B)** Due to diagram limitation, the overlap between HTN and CNS-Hemorrhagic (n = 11) groups is not displayed.

95% CI: 3.7 to 5.9; $p < 0.0001$; IC_{025}: 0.96), conduction disorders (CD) (ROR: 3.5; 95% CI: 2.7 to 4.6; $p < 0.0001$; IC_{025}: 0.76), CNS ischemic events (ROR: 2.2; 95% CI: 2.0 to 2.5; $p < 0.0001$; IC_{025}: 0.73), and hypertension (ROR: 1.7; 95% CI: 1.5 to 1.9; $p < 0.0001$; IC_{025}: 0.4). IC values and their 95% credibility interval over time are found in the **Central Illustration**. Other cardiovascular disease conditions, including

TABLE 2 Characteristics of Reported ICSRs With Cardiovascular ADRs Associated With Ibrutinib in VigiBase (Last Accessed February 1, 2018)

	Supraventricular Arrhythmias*	Ventricular Arrhythmias	Conduction Disorders	Heart Failure	Hypertension	CNS Ischemic Events	CNS Hemorrhagic Events†
Region reporting	**959 (100.0)**	**70 (100.0)**	**50 (100.0)**	**363 (100.0)**	**295 (100.0)**	**254 (100.0)**	**505 (100.0)**
Americas	629/959 (65.7)	48/70 (68.6)	36/50 (72.0)	307/363 (84.6)	254/295 (86.1)	209/254 (82.3)	395/505 (78.2)
Europe	317/959 (33.0)	19/70 (27.1)	14/50 (28.0)	54/363 (14.8)	39/295 (13.2)	42/254 (16.5)	100/505 (19.8)
Australia	12/959 (1.2)	2/70 (2.9)	0/50 (0.0)	1/363 (0.3)	2/295 (0.7)	2/254 (0.8)	4/505 (0.8)
Asia	1/959 (0.1)	1/70 (1.4)	0/50 (0.0)	1/363 (0.3)	0/295 (0.0)	1/254 (0.4)	6/505 (1.2)
Africa	0/959 (0.0)	0/70 (0.0)	0/50 (0.0)	0/363 (0.0)	0/295 (0.0)	0/254 (0.0)	0/505 (0.0)
Clinical trial reporting	129/959 (13.5)	6/70 (8.6)	1/50 (2.0)	29/363 (8.0)	36/295 (12.2)	19/254 (7.5)	43/505 (8.5)
Reporting year	**959 (100.0)**	**70 (100.0)**	**50 (100.0)**	**363 (100.0)**	**295 (100.0)**	**254 (100.0)**	**505 (100.0)**
2018 (thru February 2018)	27/959 (2.8)	2/70 (2.9)	3/50 (6.0)	2/363 (0.6)	3/295 (1.0)	4/254 (1.6)	10/505 (2.0)
2017	394/959 (41.1)	34/70 (48.6)	25/50 (50.0)	124/363 (34.1)	128/295 (43.4)	100/254 (39.4)	177/505 (35.0)
2016	300/959 (31.3)	15/70 (21.4)	10/50 (20.0)	118/363 (32.5)	122/295 (41.4)	66/254 (25.9)	125/505 (24.8)
2015	231/959 (24.1)	19/70 (27.1)	11/50 (22.0)	114/363 (31.4)	39/295 (13.2)	82/254 (32.3)	182/505 (36.0)
2014	7/959 (0.7)	0/70 (0.0)	1/50 (2.0)	5/363 (1.4)	3/295 (1.0)	2/254 (0.8)	11/505 (2.2)
Reporter	**942 (98.2)**	**67 (95.7)**	**50 (100.0)**	**361 (99.4)**	**289 (98.0)**	**251 (98.8)**	**481 (95.2)**
Health care professional	609/942 (64.6)	49/67 (73.1)	39/50 (78.0)	174/361 (48.2)	116/289 (40.1)	115/251 (45.8)	263/481 (54.7)
Nonhealth care professional	333/942 (35.4)	18/67 (26.9)	11/50 (22.0)	187/361 (51.8)	173/289 (59.9)	136/251 (54.2)	218/481 (45.3)
Sex	**904 (94.7)**	**67 (95.7)**	**49 (98.0)**	**354 (97.5)**	**288 (97.6)**	**249 (98.0)**	**475 (94.1)**
Male	631/904 (69.8)	49/67 (73.1)	32/49 (65.3)	236/354 (66.7)	166/288 (57.6)	164/249 (65.9)	306/475 (64.4)
Female	273/904 (30.2)	18/67 (26.9)	17/49 (34.7)	118/354 (33.3)	122/288 (42.4)	85/249 (34.1)	169/475 (35.6)
Age at onset, yrs	**731 (76.2)**	**54 (77.1)**	**35 (70.0)**	**263 (72.5)**	**236 (80.0)**	**194 (76.4)**	**378 (74.9)**
Mean ± SD	70.1 ± 9.1	65.3 ± 12.4	72.7 ± 13.6	75.45 ± 9.8	71.6 ± 29.8	73.9 ± 10.3	73.1 ± 32.8
Min-max	23-94	8-85	9-91	45-97	35-93	41-97	46-94
Suspected drugs	**959 (100.0)**	**70 (100.0)**	**50 (100.0)**	**363 (100.0)**	**295 (100.0)**	**254 (100.0)**	**505 (100.0)**
Only Ibrutinib	817/959 (85.2)	57/70 (81.4)	45/50 (90.0)	323/363 (89.0)	251/295 (85.1)	219/254 (86.2)	415/505 (82.2)
Ibrutinib + 1 other drug	100/959 (10.4)	7/70 (10.0)	2/50 (4.0)	32/363 (8.8)	27/295 (9.1)	21/254 (8.3)	69/505 (13.7)
Ibrutinib + ≥2 other drugs	42/959 (4.4)	6/70 (8.6)	3/50 (6.0)	8/363 (2.2)	17/295 (5.8)	14/254 (5.5)	21/505 (4.1)
Ibrutinib dose, mg/day, oral	**758 (79.0)**	**56 (80.0)**	**43 (86.0)**	**320 (88.2)**	**271 (91.9)**	**229 (90.2)**	**395 (78.2)**
140	31/758 (4.1)	2/56 (3.6)	5/43 (11.6)	13/320 (4.1)	7/271 (2.6)	11/229 (4.8)	31/395 (7.8)
280	51/758 (6.7)	3/56 (5.4)	6/43 (14.0)	23/320 (7.2)	13/271 (4.8)	23/229 (10.1)	34/395 (8.6)
420	534/758 (70.4)	40/56 (71.4)	25/43 (58.1)	231/320 (72.2)	217/271 (80.1)	163/229 (71.2)	273/395 (69.1)
560	133/758 (17.6)	10/56 (17.8)	7/43 (16.3)	53/320 (16.5)	34/271 (12.5)	28/229 (12.2)	52/395 (13.2)
>560	9/758 (1.2)	1/56 (1.8)	0/43 (0.0)	0/320 (0.0)	0/295 (0.0)	4/229 (1.7)	5/395 (1.3)
Time to ADR onset, days	**381 (39.7)**	**39 (55.7)**	**34 (68.0)**	**154 (42.4)**	**21 (7.1)**	**84 (33.1)**	**74 (14.7)**
Median	74	70	27.5	54	164	51	53.5
IQR	29.5-196.5	28.5-152.5	1-138.5	20.3-142.8	20-274	17.5-160	20.3-183.3
Min-max	1-1,299	1-1,002	1-318	1 - 929	1-806	1-902	1-741
Severe ADR‡	**862 (89.9)**	**64 (91.4)**	**45 (90.0)**	**357 (98.3)**	**226 (76.6)**	**248 (97.6)**	**495 (98.0)**
	591/862 (68.6)	64/64 (100.0)	45/45 (100.0)	357/357 (100.0)	226/226 (100)	248/248 (100.0)	495/495 (100)
Outcome	**959 (100.0)**	**70 (100.0)**	**50 (100.0)**	**363 (100.0)**	**295 (100.0)**	**254 (100.0)**	**505 (100.0)**
Death	103/959 (10.7)	7/70 (10.0)	9/50 (18.0)	76/363 (20.9)	0/295 (0.0)	48/254 (18.9)	90/505 (17.8)
Indications	**867 (90.4)**	**62 (88.6)**	**47 (94.0)**	**348 (95.9)**	**288 (97.6)**	**237 (93.3)**	**474 (93.9)**
Chronic lymphocytic leukemia	608/867 (70.1)	37/62 (59.7)	29/47 (61.7)	232/348 (66.7)	209/278 (72.6)	177/237 (74.7)	337/474 (71.1)
Lymphoma (all types)	190/867 (21.9)	14/62 (22.6)	9/47 (19.1)	83/348 (23.9)	42/278 (14.6)	41/237 (17.3)	97/474 (20.5)
Waldenstrom's macroglobulinemia	53/867 (6.2)	9/62 (14.5)	2/47 (4.3)	24/348 (6.9)	31/278 (10.7)	15/237 (6.4)	28/474 (5.9)
Myeloma/myelodysplasia	8/867 (0.9)	1/62 (1.6)	0/47 (0.0)	3/348 (0.9)	0/278 (0.0)	1/237 (0.4)	4/474 (0.8)
Acute lymphoblastic leukemia	3/867 (0.3)	1/62 (1.6)	7/47 (14.9)	3/348 (0.9)	2/278 (0.7)	2/237 (0.8)	5/474 (1.1)
Other	5/867 (0.6)	0/62 (0.0)	0/47 (0.0)	3/348 (0.9)	4/278 (1.4)	1/237 (0.4)	3/474 (0.6)

Values are n (%) or n/N (%), unless otherwise indicated. Availability of data is mentioned in **bold** and top rows. *Supraventricular arrhythmia cases were reported on class I: 24/959 (2.5%), class II: 230/959 (24%), class III: 58/959 (6%), class IV: 42/959 (4.4%), other class: 9/959 (3%) antiarrhythmic drugs according to Vaughan-Williams classification. †CNS hemorrhagic events were reported on antiplatelets: 69/505 (13.7%), vitamin K antagonists: 38/505 (7.5%), heparins: 6/505 (1.2%), direct factor Xa: 24/505 (4.8%), and factor IIa: 4/505 (0.8%) inhibitors. ‡A severe ADR was defined as such when being life-threatening, leading to persistent or significant disability, birth defect, congenital anomaly, or to any other medically important conditions, requiring hospitalization (initial or prolonged) or when causing death.

ADR = adverse drug reactions; CNS = central nervous system; ICSR = individual case safety report; IQR = interquartile range; min-max = minimum-maximum.

cardiac ischemia, myocarditis, venous thromboembolic events, QT prolongation, and valvular disorders, were not overreported in this population (**Table 1**).

CHARACTERISTICS OF PATIENTS. Given that ibrutinib-associated cardiovascular toxicities are novel clinical entities and represent new challenges for the clinician, we extracted additional data to better characterize clinical features of ibrutinib-associated CV-ADR in 2,093 patients. A total of 90.6% (1,896 of 2,093) were reported from "real-world" settings compared with 9.4% (197 of 2,093) from clinical trials. CV-ADR included SVA (n = 959; of which 900 of 959, 93.8% were atrial fibrillation) (Online Table 3), CNS hemorrhagic events (n = 505; of which 275 of 505, 54.5% were intracerebral hemorrhage and 156 of 505, 30.9% were extracerebral hemorrhage) (Online Table 4), HF (n = 363) (Online Table 5), hypertension (n = 295) (Online Table 6), CNS ischemic events (n = 254) (Online Table 7), VA (n = 70; of which 31 of 70, 44.3% were ventricular tachycardias and 20 of 70, 28.6% were ventricular fibrillations) (Online Table 8), and CD (n = 50; of which 33 of 50, 64% were atrioventricular block and 14 of 50, 28.0% were bundle branch block) (Online Table 9). Overlap among these conditions is shown in **Figure 1** and Online Table 10. Main clinical and demographical characteristics, concurrent conditions, concomitant drugs (including antiarrhythmic agents), and CV-ADR diagnosis details (i.e., type of SVA, VA, CNS events, or CD) are displayed in **Table 2** and Online Tables 3 to 9. Diagnosis of each was reported worldwide with an increasing rate over time, with most of the cases reported in 2017. CV-ADR affected mostly men (58% to 73%), with a wide age range (8 to 97 years), but generally older than 70 years. All cancer types where ibrutinib has been utilized were affected, with chronic lymphocytic leukemia (60% to 76%), lymphomas (20% to 24%), and Waldenstrom's macroglobulinemia (4% to 15%) being the most common (**Table 2**). The indication of ibrutinib for Waldenstrom's macroglobulinemia was more frequent among VA cases versus SVA cases (9 of 62, 14.5% vs. 53 of 867, 6.2%; p = 0.01).

TIMING. CV-ADR occurred early after ibrutinib administration (**Figure 1**), as soon as after the first dose, with a shorter median time to onset of 27.5 days (IQR: 1 to 138.5 days) for CD (p < 0.01, Kruskal-Wallis) as compared with CNS ischemic events (51 days; IQR: 17.5 to 160 days; p = 0.05 vs. CD), CNS hemorrhagic events (53.5 days; IQR: 20.3 to 183.3 days; p = 0.03 vs. CD), HF (54 days; IQR: 20.3 to 142.8 days; p = 0.05 vs. CD), VA (70 days; IQR: 28.5 to 152.5 days; p = 0.03 vs. CD), SVA (74 days; IQR: 29.5 to 196.5 days; p = 0.0004 vs. CD), and hypertension (164 days; IQR: 20 to 274 days; p = 0.04 vs. CD).

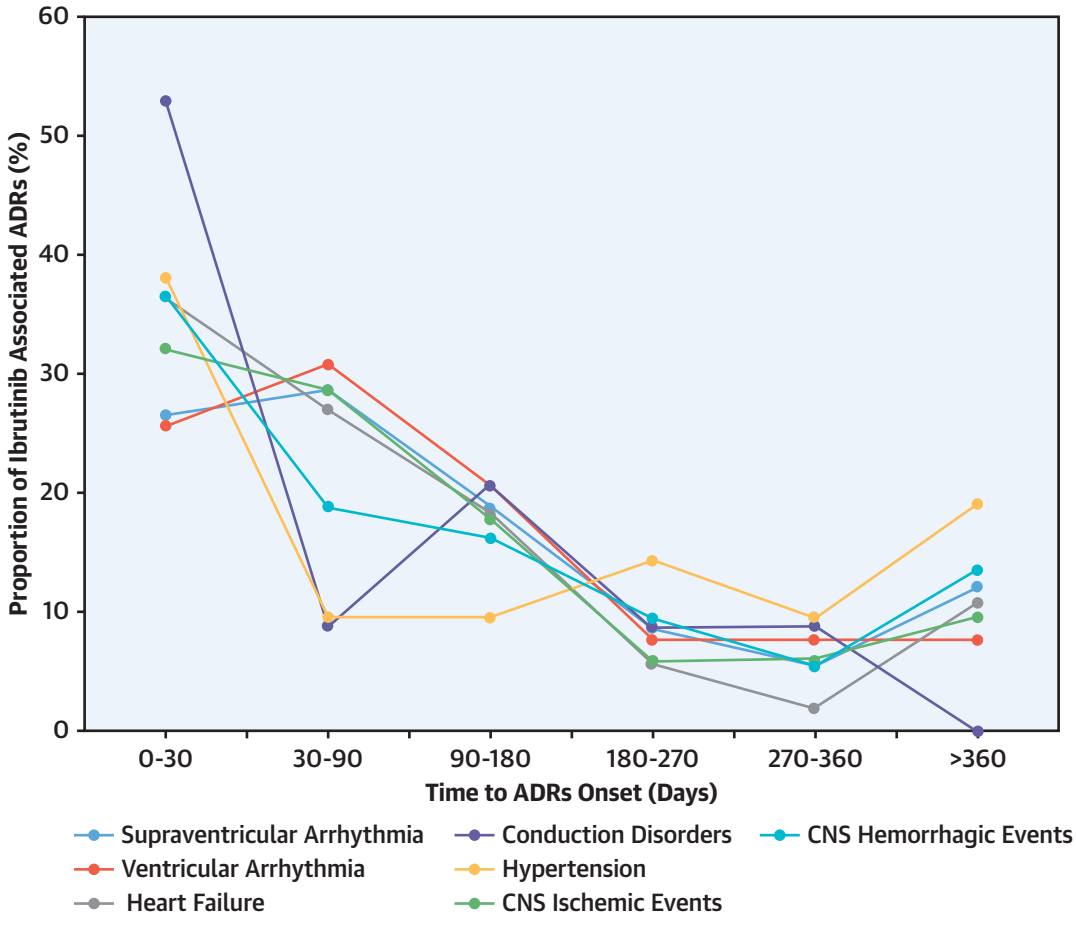
OUTCOMES. CV-ADR were almost always considered severe (77% to 98%) and were associated with fatalities ranging from ~10% (SVA and VA) to ~20% (CNS events, HF, and CD) with the exception of ibrutinib-associated hypertension being nonfatal (**Table 2**). SVA were associated with HF in 11.9% of SVA cases (114 of 959), with CNS ischemic events in 4.2% (40 of 959) and with CNS hemorrhagic events in 3.4% (33 of 959). There were more deaths when SVA cases were associated with CNS hemorrhagic and/or ischemic events compared with their absence (15 of 52, 28.8% vs. 88 of 907, 9.7%; p < 0.0001, respectively). HF cases were frequently associated with concurrent contributing conditions (**Figure 2**), such as SVA (114 of 363, 31.4%) and, more rarely, hypertension (18 of 363, 5%). CD were often associated with SVA (11 of 50, 22%).

DISCUSSION

We report the largest and most extensive clinical characterization of CV-ADR associated with ibrutinib through analysis of individualized reportable events from the WHO pharmacovigilance database. The results show significant incidence of SVA, VA, CD, HF, hypertension, CNS ischemic, and hemorrhagic events with ibrutinib, with numbers high enough to suggest that some of these CV-ADR may be under-represented in the published data. SVA, VA, hemorrhage, and hypertension induced by ibrutinib have already been demonstrated, are listed on the U.S. Food and Drug Administration label, and represent positive controls for our analysis strategy (6); however, our findings of association with HF and CD (mainly high-grade atrioventricular block) are new findings. Importantly, a number of other CV-ADR, including cardiac ischemia and QT prolongation, were not overreported with ibrutinib, which is consistent with the antiplatelet effects of ibrutinib and studies showing no QT prolonging effects of ibrutinib (23-26). The lack of association with these and other CV-ADR serve as negative controls for our analysis. Moreover, our study describes the differential spectrum of time to onset with each CV-ADR. In our study, the median time from initiation of treatment with ibrutinib to onset for SVA was ~2 to 3 months and for hypertension was ~4 to 5 months. On the other hand, CD occurred mainly within the first month of ibrutinib start, contrasting with CNS events, HF and VA occurring around ~2 to 3 months (**Figure 2**) (27).

The association of SVA (and specifically atrial fibrillation) with ibrutinib was identified early in

FIGURE 2 Time to ADR Onset Associated With Ibrutinib



ADR = adverse drug reactions; CNS = central nervous system.

human studies with ibrutinib, and emerged in our analysis as the first CV-ADR significantly over-reported in VigiBase since 2014 (the year after U.S. approval, **Central Illustration**) (1-6,9). This signal is consistent with meta-analyses of clinical trials where atrial fibrillation was significantly more commonly observed in ibrutinib-treated arms (4% to 16%) compared with control arms, leading to increased vigilance by clinicians and regulatory authorities (1-6,28). In these studies, risk factors for developing SVA on ibrutinib included older age, male sex, a history of SVA, hypertension, and pre-existing cardiac diseases (7,29). Our study reports the data on almost 1,000 cases of SVA suspected to be induced by ibrutinib, with most of these occurring in the "real world" population, which is by far the largest case-series reported to date (<100 cases by other groups, mostly from clinical trials) (7,9,28-30). We show that SVA cases occurred mainly in men and in patients >70 years of age, and were frequently associated with other cardiovascular complications, including HF (11.9%) and CNS events (5.4%). Patients with ibrutinib-associated SVA were mainly taking beta-blockers (24%) and less often other types of antiarrhythmic drugs (≤6%) (**Table 1**), which is consistent with current proposed management by experts favoring lenient rate control (rather than rhythm control) with drugs at lower risk of interaction with ibrutinib metabolism (i.e., beta-blockers favored over amiodarone, digoxin, verapamil, and diltiazem) (28,31). Due to the frequent need for coprescriptions of drugs for rate control, anticoagulant stroke prophylaxis, and bleeding risk complicated by multiple drug interactions (Ibrutinib being a cytochrome 3A4 substrate and a P-glycoprotein inhibitor), there is a clear and pressing need to improve management of

these patients, requiring a better understanding of pathophysiology of SVA induced by ibrutinib (28). Current data are emerging and suggest that a drug-induced blockade of phosphoinositide 3-kinase-protein kinase B (PI3K-AKT) pathway, leading to activation of the late sodium current ($I_{Na\text{-}L}$) in atrial cells, may play a role (28,32–34). For patients with thromboembolic risks outwaiting hemorrhagic risks, possible choices for long-term anticoagulation include vitamin K antagonists, heparins, and factor Xa inhibitors based on individual patient profile and preference, as recently summarized (28,35).

Our report identified CD as a new complication with ibrutinib, which carries a high mortality, 18% (9 of 50) cases of atrioventricular block in VigiBase. Only a single case report was found by a PubMed/Embase literature review, in contrast with the 50 ICSRs documented in VigiBase (36). Ibrutinib prolongs PR in a concentration-dependent manner (<5 ms at therapeutic concentration) in healthy volunteers, in patients with B-cell malignancies, and in dogs (37). Ibrutinib-associated CD occurred early after initiation of ibrutinib and prior to other CV-ADRs. CD were often associated with SVA, suggesting a possible interplay between CD and SVA on ibrutinib, consistent with other data where PR prolongation is associated with increased risk of atrial fibrillation (38–40).

VA on ibrutinib (and not long QT) have been increasingly recognized as an emerging concern (6,10,11,41). Our pharmacovigilance query has captured this increasing trend for VA reporting over time in VigiBase (**Central Illustration**). This is unlikely to be mediated by QT prolongation, given that ibrutinib has been shown to reduce QT duration (corrected for heart rate) in multiple settings including preclinical data in dogs, in clinical trials, and in a thorough-QT study in healthy volunteers (37). Notably, an extreme shortening of QTc can be a risk factor for VA and SVA (37,42). Interestingly, 3 independent groups published several case reports of polymorphic ventricular tachycardia induced by ibrutinib with normal QTc interval, and no short-long-short coupling pattern before the VA (11,43,44). This electrocardiography description corresponds to the rare short-coupled variant of polymorphic ventricular tachycardia (45). This peculiar form of VA has a specific pathophysiology thought to involve alteration in cardiac sarcoplasmic reticulum Ca^{2+} homeostasis associated with cardiac ryanodine receptor (RyR2)-calmodulin-dependent protein kinase (CaMKII) pathways (46). CaMKII-RyR2 and PI3K-AKT signaling cascades have been shown to crosstalk (47), and cardiac PI3K-AKT signaling is inhibited by ibrutinib leading to increased $I_{Na\text{-}L}$, a trigger of VA (33,34). The exact mechanism of this observed association between ibrutinib and VA needs further investigation. Specifically, prospective studies of patients on ibrutinib with detailed electrophysiological studies may elucidate new mechanisms involved in VA in general. Clinical risk factors for developing VA on ibrutinib appear to be a history of SVA and male sex from 1 small retrospective study (10). Notably, our study reveals a significant overlap between SVA and VA reports among VA cases (~30%), with most cases occurring in male patients (~75%) (**Table 2**). Men are associated with shorter QTc than women (48–50), and this may contribute to sex dimorphism in ibrutinib-induced VA.

An association between HF and ibrutinib has been described in case reports (51,52). However, our study reports 363 cases of ibrutinib-associated AF. Even though SVA, HTN, and VA are risk factors for HF, most cases (66%) occurred without these concurrent conditions, suggesting a possible direct role for ibrutinib. This might be explained by the multiple off-target kinases blocked by ibrutinib at clinically relevant concentrations, including HER2 (Erb-B2 receptor tyrosine kinase 2) and/or PI3K-AKT pathways, which are critical for cardiac myocyte homeostasis and may lead to HF (32,33,53–55).

CNS hemorrhagic events signal over-reporting is concordant with ibrutinib's inhibition of platelet function resulting in hemorrhagic risk in a subset of patients. As with other CV-ADR signals, it remains to be seen whether this is due to on-target inhibition of Bruton tyrosine kinase or off-target effects (from effects on other kinase targets). Antiplatelet effects of ibrutinib are thought to be mediated by targeting platelets' von Willebrand factor-glycoprotein Ib and collagen-glycoprotein VI signals transduction (23–25,56). This phenomenon is more frequently observed early on ibrutinib therapy start, and it appeared to decrease beyond 6 months (23), compatible with the observation we have seen in VigiBase that most CNS hemorrhagic events were observed within 3 months of ibrutinib initiation (**Table 2**). In published clinical trials, subdural (extracerebral) hematoma was the most commonly reported form of CNS bleeding and occurred in 1% to 2% of ibrutinib-treated patients, although hemorrhagic conversion of ischemic stroke, subarachnoid hemorrhage after a fall, and vitreous hemorrhage have also been reported (6,25). Interestingly, in our series, we identified that most CNS hemorrhage reported were intracranial, in contrast with clinical trial findings. Overlap between ischemic stroke and

hemorrhage was modest (≤5%) in VigiBase. Considering the expected antiplatelet effects of ibrutinib and its propensity to induce SVA, the CNS ischemic over-reporting signal might be more driven by embolic events secondary to thromboembolism rather than by atherothrombosis (28). In the current series, ~20% of stroke had a coreported SVA event, but data concerning differential temporality of onset were rarely available in the same case.

While the incidence of ibrutinib-associated CV-ADR events cannot be determined using VigiBase, the following data have been published previously (1-6). U.S FDA labels and meta-analyses issued from randomized clinical trials evaluation of ibrutinib efficacy estimate rate of any grade SVA ~5% to 6% after 18 months on therapy and up to 16% with longer follow-up (3% to 12% grade 3 to 4 CTCAE, Common Terminology Criteria for Adverse Events). Any grade hypertension occurred ~11% to 29% (4% to 13% grades 3 to 4) and VA occurred ~0.2% for grade ≥3, depending on hematological indications and total duration of ibrutinib exposure (1-6). Other CV-ADR identified in this work have been sporadically reported, and thus the incidence is essentially unknown.

STUDY LIMITATIONS. Several limitations need to be recognized for VigiBase analysis. Some cases of suspected drug-induced CV-ADR are likely not reported to the national drug authorities, and therefore not submitted to VigiBase. However, a major strength is that VigiBase aggregates ICSRs collected from over 130 countries, which enables better identification of rare ADR and broader generalization of our findings. Importantly, another limitation of VigiBase is that sources of reports are nonhomogeneous, and there is limited possibility of verification of the clinical, laboratory tests, or radiological findings justifying the reported diagnosis, nor completeness of reporting for age, drug dosing, time to onset, comorbid conditions, and concomitant drugs. The exact denominator of patients exposed to ibrutinib cannot be evaluated. Instead, the total number of ICSRs for each drug is used as a denominator for this kind of disproportionality analysis in pharmacovigilance databases for signal detection (18,19). The volume of reports for a particular medicinal product may be influenced by the extent of use of the product, publicity, the nature of the reactions, and other factors such as competition bias. The value of disproportionality reporting (as the ROR) for several CV-ADR and culprit anticancer or endocrine drugs has already been demonstrated in various settings (13,20,21,49); nevertheless, there is still a risk that comparisons of disproportionality between medicinal products in pharmacovigilance databases may be misleading. Any hypotheses generated require validation by prospective studies.

Clinical trials are mandatory to establish efficacy but may not allow definitive conclusions on drug safety in part due to selected populations and limited power to detect imbalances in rare ADR. However, clinical trials in oncology often do not reflect the "real-world" population, which often has a higher prevalence of cardiovascular diseases and risk factors (57). Spontaneous notifications remain the cornerstone for ADR evaluation despite their limitations. Disproportionality analysis in pharmacovigilance databases is an important method to detect signals in drug safety research and post-marketing surveillance. Herein, we used this analysis to identify several new cardiovascular complications with ibrutinib.

CONCLUSIONS

Severe and occasionally fatal cardiac events related to cardiac SVA, VA, CD, HF, hypertension, CNS hemorrhagic, and ischemic events occur in patients exposed to ibrutinib. These events should be considered in patient care and in clinical trial designs.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In a clinical trial of therapy for B-cell malignancies, ibrutinib was associated with increased mortality compared to conventional chemotherapy. Among the observed toxicities were severe and occasionally fatal cardiac events, including SVAs and VAs, CD, HF, hypertension, and hemorrhagic or ischemic stroke.

TRANSLATIONAL OUTLOOK: In future clinical trials of ibrutinib, cardiovascular events should be carefully adjudicated so that patients at risk of these complications can be more accurately identified and preventive strategies can be developed.

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KEY WORDS atrial fibrillation, cardiac failure, cardiology, cardio-oncology, ibrutinib, oncology, ventricular tachycardia

APPENDIX For an expanded Methods section and supplemental tables, please see the online version of this paper.