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CardioVascular Burden Of Narcolepsy Disease (CV-BOND): A Real-World Evidence Study

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Introduction

- Narcolepsy is a rare, lifelong central disorder of hypersomnolence that requires long-term treatment[1]
- Narcolepsy is associated with multiple comorbidities, including cardiovascular disorders and factors that increase cardiovascular risk[2]
  - In a previous large-scale, retrospective analysis of 5 years of United States (US) medical claims data (2006–2010) comparing adults with narcolepsy (n=9312) with matched controls (n=46,559), occurrence of stroke, myocardial infarction, cardiac arrest, and heart failure were significantly increased in people with narcolepsy[3]
- Many treatments prescribed for narcolepsy symptoms have cardiovascular-related warnings and precautions in their labels[2]
- Understanding the risk of new cardiovascular events in people with narcolepsy, specifically in those who have no history of such conditions, is important for optimising treatment

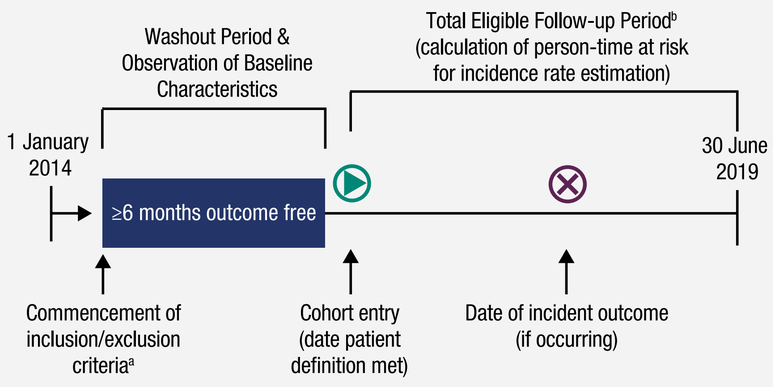
Objective

- The objective of this study was to compare the risk of new-onset cardiovascular events in adult patients with narcolepsy with matched non-narcolepsy patients in the US

Methods

- Retrospective analysis of the IBM® MarketScan® database (commercial and Medicare medical and prescription claims) conducted from 1 January 2014 to 30 June 2019, as shown in **Figure 1**
  - The IBM MarketScan database integrates de-identified patient-level health data (including medical and drug data, lab results, and hospitalisation records) contributed by large employers, managed care organisations, hospitals, electronic medical record providers, Medicare, and Medicaid; the database is nationally representative of Americans with employer-provided health insurance[4]

Figure 1. Study Design



[a]Inclusion criteria included ≥6 months of continuous enrolment.
[b]Patients were censored at discontinuation of insurance coverage, at the end of the study period (for those continuously enrolled), or at first qualifying diagnosis for the outcome of interest.

- Eligible patients were 18 years of age and older with continuous medical and prescription coverage (gaps ≤30 days allowed) during baseline and the follow-up period
  - The narcolepsy cohort was defined by the earliest available 2 outpatient claims containing a diagnosis of narcolepsy type 1 or type 2 on separate visits no more than 6 months apart, with ≥1 nondiagnostic (ie, not for diagnostic sleep testing) claim[5]
  - Non-narcolepsy patients were matched 3:1 to narcolepsy patients by calendar date of cohort entry, age, gender, US geographic region, and insurance type (commercial or Medicare)
  - Patients with a diagnosis of an outcome (comorbidity) of interest in the 6 months prior to cohort entry were excluded from the incidence analysis for that comorbidity
- The following outcomes were assessed: any stroke; atrial fibrillation; heart failure; ischaemic stroke; major adverse cardiac event (MACE; defined as grouped instances of myocardial infarction, ischaemic stroke, heart failure, acute coronary syndrome, coronary artery bypass grafting, and percutaneous coronary intervention); myocardial infarction; grouped instances of stroke, atrial fibrillation, or oedema; and cardiovascular disease (CVD; grouped instances of stroke, atrial fibrillation, heart failure, and myocardial infarction)
  - A hypertension analysis was included initially. However, it was removed from this presentation because patients in the hypertension analysis may have been on hypertension medications during baseline
- Patients were followed from 1 day after cohort entry until they experienced the outcome of interest for that analysis, or until the earliest day of insurance coverage discontinuation or end of the data collection period
- Differences between cohorts were evaluated using a Cox proportional hazard model adjusted for age, gender, region, insurance type, and relevant morbidities/comorbidities (anxiety disorders, cataplexy, history of CVD, coronary revascularisation, depressive disorders, diabetes, headache/migraine, hypersomnia, mood disorders, periodic limb movement disorder, pulmonary fibrosis or interstitial lung disease, rapid eye movement [REM] behaviour disorder, restless legs syndrome, sleep apnoea, hyperlipidaemia, renal impairment, and hyperuricaemia) and medications (diabetes medication, obesity medication, and antihypertensives) in the baseline period
  - Baseline included the 6-month period up to cohort entry date, during which washout criteria were applied and patient characteristics were measured
  - Due to no adjustments for multiplicity, the *P* values presented are nominal

References: 1. Kornum BR, et al. *Nat Rev Dis Primers.* 2017;3:16100. **2.** Jennum PJ, et al. *Sleep Med Rev.* 2021;58:101440. **3.** Black J, et al. *Sleep Med.* 2017;33:13-8. **4.** IBM MarketScan Research Databases for life sciences researchers. 2021. Available at: https://www.ibm.com/downloads/cas/OWZWJ0QO. Accessed January 5, 2022. **5.** Carls G, et al. *Sleep Med.* 2020;66:110-8.

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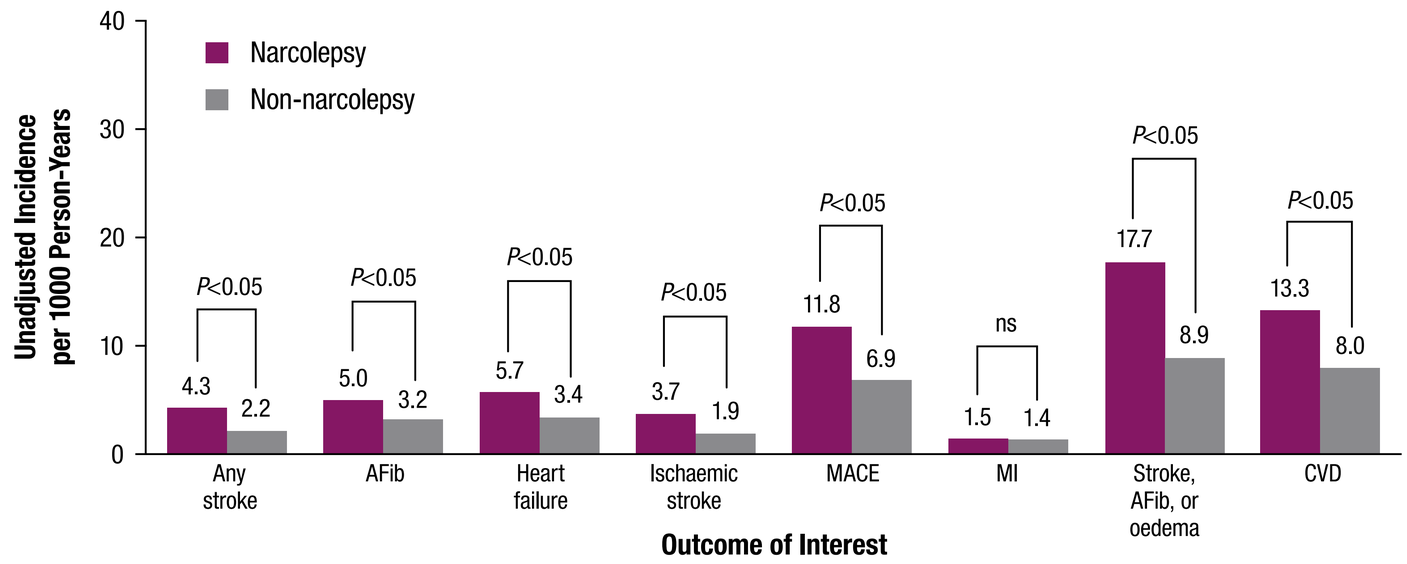
Disclosures: RH Ben-Joseph and **R Saad** are full-time employees of Jazz Pharmaceuticals who, in the course of this employment, have received stock options exercisable for, and other stock awards of, ordinary shares of Jazz Pharmaceuticals, plc. **J Black** is a part-time employee of Jazz Pharmaceuticals and shareholder of Jazz Pharmaceuticals plc. **EC Dabrowski, B Taylor,** and **S Gallucci** are full-time employees of Aetion, Inc. and hold stock options or equity in Aetion. **VK Somers** provides paid consulting services to Jazz Pharmaceuticals.

Results

Figure 2. Unadjusted Incidence Rates for New-Onset Cardiovascular Events[a]

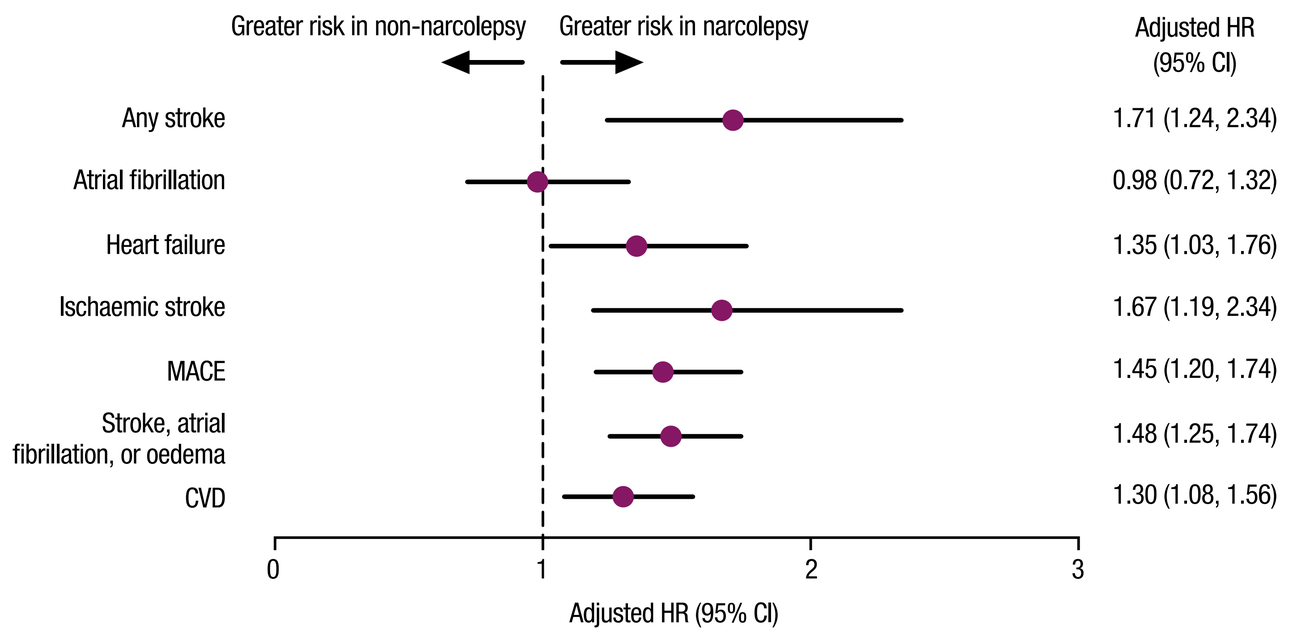


	Any stroke	AFib	Heart failure	Ischaemic stroke	MACE	MI	Stroke, AFib, or oedema	CVD
Narcolepsy n=	12,768	12,746	12,752	12,770	12,680	12,807	12,610	12,635
Non-narcolepsy n=	38,391	38,275	38,318	38,398	38,224	38,415	38,121	38,109

AFib, atrial fibrillation; CVD, cardiovascular disease; MACE, major adverse cardiac event; MI, myocardial infarction; ns, *P*≥0.05.
[a]*P* values are nominal.

- Unadjusted incidence rates (per 1000 person-years) for all outcomes, except myocardial infarction, were higher in narcolepsy compared with non-narcolepsy

Figure 3. Adjusted Hazard Ratios (95% CI) for Incidence of New-Onset Events



CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; MACE, major adverse cardiac event.
[a]Insufficient events to derive hazard ratio for myocardial infarction.

- Adjusted hazard ratios, derived from incidence rates, demonstrated increased risk for incidence of new-onset cardiovascular events (any stroke; heart failure; ischaemic stroke; MACE; grouped instances of stroke, atrial fibrillation, or oedema; or CVD) in narcolepsy compared with non-narcolepsy
  - Hazard ratios could not be derived for myocardial infarction, for which there were insufficient events

Table 1. Demographic Characteristics

Characteristic	Narcolepsy (n=12,816)	Non-narcolepsy (n=38,441)
Age, y, mean (SD)	38.09 (14.17)	38.46 (14.18)
Female, n (%)	8598 (67.1)	25,797 (67.1)
US region, n (%)		
Northeast	1692 (13.2)	5074 (13.2)
North Central	3426 (26.7)	10,273 (26.7)
South	6283 (49.0)	18,849 (49.0)
West	1289 (10.1)	3867 (10.1)
Unknown	126 (1.0)	378 (1.0)
Insurance type, n (%)		
Commercial	12,355 (96.4)	37,060 (96.4)
Medicare	461 (3.6)	1381 (3.6)

There were 12,836 patients with narcolepsy in the database, but for 10 of them, 3 matched non-narcolepsy patients could not be identified; hence, there were 12,826 patients with narcolepsy (12,836 – 10 = 12,826) and 38,478 non-narcolepsy patients (12,826 × 3 = 38,478). Patients who entered the cohort but had no enrolment on the first day of follow-up were not eligible for the analysis; this included 10 patients with narcolepsy and 37 non-narcolepsy patients, leading to cohort counts of 12,816 (12,826 – 10 = 12,816) and 38,441 (38,478 – 37 = 38,441), respectively.
CI, confidence interval; SD, standard deviation.

- Of 54,239,110 adults in the database, 12,816 and 38,441 were included in the narcolepsy and non-narcolepsy cohorts, respectively
- In these 2 matched cohorts, demographic characteristics were similar; approximately 67% were female and mean age was approximately 38 years in each cohort

Table 2. Baseline Comorbidities

Comorbidities, n (%)	Narcolepsy (n=12,816)	Non-narcolepsy (n=38,441)	Difference (95% CI)
Sleep apnoea	4328 (33.8)	843 (2.2)	–31.6% (–32.4%, –30.7%)
Hypersomnia	4067 (31.7)	88 (0.2)	–31.5% (–32.3%, –30.7%)
Mood disorders	3282 (25.6)	2368 (6.2)	–19.4% (–20.2%, –18.7%)
Anxiety disorders	2780 (21.7)	2762 (7.2)	–14.5% (–15.3%, –13.7%)
Headache/ Migraine	2212 (17.3)	1896 (4.9)	–12.3% (–13.0%, –11.6%)
Hyperlipidaemia	1978 (15.4)	4084 (10.6)	–4.8% (–5.5%, –4.1%)
Diabetes or diabetes/obesity medication	1406 (11.0)	3183 (8.3)	–2.7% (–3.3%, –2.1%)
Prior CVD[a]	994 (7.8)	1547 (4.0)	–3.7% (–4.2%, –3.2%)
Restless legs syndrome	647 (5.0)	102 (0.3)	–4.8% (–5.2%, –4.4%)
Periodic limb movement disorder	566 (4.4)	25 (0.1)	–4.4% (–4.7%, –4.0%)
Renal impairment	170 (1.3)	307 (0.8)	–0.5% (–0.8%, –0.3%)
Pulmonary fibrosis or interstitial lung disease	34 (0.3)	35 (0.1)	–0.2% (–0.3%, –0.1%)

CI, confidence interval; CVD, cardiovascular disease. [a]Patients with prior CVD were excluded from the CVD incidence analyses.

- People in the narcolepsy cohort were more likely to have baseline comorbidities compared with the non-narcolepsy cohort

Conclusions

- Prior research showed that higher rates of comorbidities occur with narcolepsy. CV-BOND builds upon the known associations between narcolepsy and cardiovascular events by demonstrating that the risk of new onset of cardiovascular events is also higher among patients without a history of cardiovascular conditions
- Physicians should not only consider current cardiovascular comorbidities, but also the risk of future cardiovascular events in patients when considering treatment options for narcolepsy symptoms

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