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**RESEARCH ARTICLE**

# Dementia-related adverse events in PARADIGM-HF and other trials in heart failure with reduced ejection fraction

**Jane A. Cannon[1†], Li Shen[1†], Pardeep S. Jhund[1], Søren L. Kristensen[2], Lars Køber[2], Fabian Chen[3], Jianjian Gong[3], Martin P. Lefkowitz[3], Jean L. Rouleau[4], Victor C. Shi[3], Karl Swedberg[5], Michael R. Zile[6], Scott D. Solomon[7], Milton Packer[8], and John J.V. McMurray[1]*, on behalf of the PARADIGM-HF Investigators and Committees**

[1]BHF Cardiovascular Research Centre, University of Glasgow, Glasgow, UK; [2]Rigshospitalet Copenhagen University Hospital, Copenhagen; [3]Novartis Pharmaceutical Corporation, East Hanover, NJ, USA; [4]Institut de Cardiologie, Université de Montréal, Montréal, Canada; [5]Department of Molecular and Clinical Medicine, University of Gothenburg, Gothenburg, Sweden and National Heart and Lung Institute, Imperial College, London; [6]Medical University of South Carolina and RHJ Department of Veterans Administration Medical Center, Charleston, SC, USA; [7]Cardiovascular Medicine, Brigham and Women's Hospital, Boston, MA, USA; and [8]Baylor Heart and Vascular Institute, Baylor University Medical Center, Dallas, TX, USA

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**Aims** Inhibition of neprilysin, an enzyme degrading natriuretic and other vasoactive peptides, is beneficial in heart failure with reduced ejection fraction (HFrEF), as shown in PARADIGM-HF which compared the angiotensin receptor–neprilysin inhibitor (ARNI) sacubitril/valsartan with enalapril. As neprilysin is also one of many enzymes clearing amyloid-$\beta$ peptides from the brain, there is a theoretical concern about the long-term effects of sacubitril/valsartan on cognition. Therefore, we have examined dementia-related adverse effects (AEs) in PARADIGM-HF and placed these findings in the context of other recently conducted HFrEF trials.

**Methods and results** In PARADIGM-HF, patients with symptomatic HFrEF were randomized to sacubitril/valsartan 97/103 mg b.i.d. or enalapril 10 mg b.i.d. in a 1:1 ratio. We systematically searched AE reports, coded using the Medical Dictionary for Regulatory Activities (MedDRA), using Standardized MedDRA Queries (SMQs) with 'broad' and 'narrow' preferred terms related to dementia. In PARADIGM-HF, 8399 patients aged 18–96 years were randomized and followed for a median of 2.25 years (up to 4.3 years). The narrow SMQ search identified 27 dementia-related AEs: 15 (0.36%) on enalapril and 12 (0.29%) on sacubitril/valsartan [hazard ratio (HR) 0.73, 95% confidence interval (CI) 0.33–1.59]. The broad search identified 97 (2.30%) and 104 (2.48%) AEs (HR 1.01, 95% CI 0.75–1.37), respectively. The rates of dementia-related AEs in both treatment groups in PARADIGM-HF were similar to those in three other recent trials in HFrEF.

**Conclusion** We found no evidence that sacubitril/valsartan, compared with enalapril, increased dementia-related AEs, although longer follow-up may be necessary to detect such a signal and more sensitive tools are needed to detect lesser degrees of cognitive impairment. Further studies to address this question are warranted.

**Keywords** Heart failure • ARNI • Dementia • Neprilysin inhibition

*Corresponding author. British Heart Foundation Cardiovascular Research Centre, University of Glasgow, 126 University Place, Glasgow, G12 8TA, UK. Tel: +44 141 330 3479, Fax: +44 141 330 6955, Email: john.mcmurray@glasgow.ac.uk
†These two authors contributed equally to this work.

# Introduction

The angiotensin receptor–neprilysin inhibitor sacubitril/valsartan (formerly known as LCZ696) reduces the risk of both death and hospitalization, compared with an ACE inhibitor, in patients with heart failure and reduced ejection fraction (HFrEF).[1,2] Decreased breakdown of vasoactive peptides with favourable actions in heart failure, including the natriuretic peptides, as a consequence of neprilysin inhibition is believed to explain the additional benefit of sacubitril/valsartan over renin–angiotensin blockade alone.[3,4] Neprilysin, however, has other substrates including amyloid-$\beta$ peptides in the central nervous system.[5,6] Accumulation of certain amyloid-$\beta$ peptides is a pathognomonic feature of Alzheimer's type dementia.[5,6] Although only one of many enzymatic and non-enzymatic amyloid-$\beta$ clearance pathways in the central nervous system, concern has been raised that inhibition of neprilysin could cause or accelerate amyloid-$\beta$-related cognitive decline in patients treated with sacubitril/valsartan.[5–7] We have, therefore, analysed relevant cognition- and memory-related adverse event (AE) reports in the Prospective comparison of ARNi with ACEi to Determine Impact on Global Mortailty and morbidity in Heart Failure (PARADIGM-HF) trial. [1,2] To place these findings in the context of available evidence, we have analysed cognitive-related events in three other trials in patients with HFrEF which recorded AEs in a similar fashion.

# Methods

## PARADIGM-HF

The design and primary results of the PARADIGM-HF trial have been previously described.[4,8]

### Study patients and trial procedures

Patients had NYHA class II–IV symptoms, a LVEF ≤40% (changed to ≤35% by amendment), and a plasma BNP ≥150 pg/mL (or NT-proBNP ≥600 pg/mL). Patients with lower levels of natriuretic peptides (BNP ≥100 pg/mL, NT-proBNP ≥400 pg/mL) were eligible if they had been hospitalized for heart failure within 12 months. Patients were required to tolerate the equivalent of enalapril 10 mg daily for at least 4 weeks before screening, along with a stable dose of a beta-blocker (unless contraindicated or not tolerated) and a mineralocorticoid receptor antagonist (if indicated).

### Cognition, memory, dementia-like and related events

In PARADIGM-HF, we systematically searched AE reports coded using the 17.0 version of the Medical Dictionary for Regulatory Activities (MedDRA) using Standardized MedDRA Queries (SMQs) with 'broad' and 'narrow' preferred terms (PTs) related to dementia-like AEs.[3] The precise terms used are detailed in Appendix 1.

The sponsor of PARADIGM-HF (Novartis) had two additional chronic heart failure databases [the Valsartan Heart Failure Trial (Val-HeFT) and the Aliskiren Trial to Minimize OutcomeS in Patients with HEart failure trial (ATMOSPHERE)] in which the same searches could be conducted and the other authors had an additional trial [the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA)] the AEs from which could also searched in the same fashion.

## Val-HeFT

Val-HeFT was a randomized placebo-controlled trial which enrolled 5010 patients with clinical heart failure (NYHA class II–IV) and an LVEF <40%.[9] Study patients were randomly assigned to receive either 160 mg of valsartan or placebo twice daily. The overall mean duration of follow-up was 23 months (range, 0–38 months). The target dose was achieved in 84% of patients receiving valsartan (mean dose, 254 mg). Dementia-related AEs were recorded as in PARADIGM-HF, using standardized MedDRA queries with broad and narrow PTs, and we analysed these in the same way as in PARADIGM-HF.

## ATMOSPHERE

ATMOSPHERE enrolled 7016 participants with symptomatic heart failure (NYHA class II–IV), a LVEF ≤35%, and a plasma BNP concentration of ≥150 pg/mL (or a NT-proBNP concentration ≥600 pg/mL) or, if they had been hospitalized for heart failure within the previous 12 months, a BNP concentration of ≥100 pg/mL (or a NT-proBNP concentration of ≥400 pg/mL).[10,11] The average age of participants was 63 years. Patients entered an open-label run-in period similar to that in PARADIGM-HF with an initial period of treatment with enalapril followed by treatment with the combination of enalapril and aliskiren. Patients completing both treatment periods were randomized to enalapril 5–10 mg twice daily, aliskiren 150–300 mg once daily, or the combination of both drugs. The median follow-up was 36.6 months. Dementia-related AEs were again documented as described in the trials above and analysed in the same way.

## CORONA

CORONA enrolled 5011 participants aged at least 60 years with heart failure (NYHA class II–IV) and a reduced LVEF (≤40% and ≤35% if NYHA class II).[12] The average age of participants was 73 years. Patients were randomized to placebo or rosuvastatin 10 mg daily. The median follow-up was 32.8 months. Dementia-related AEs were again documented in the same way as in PARADIGM-HF, Val-HeFT, and ATMOSPHERE, and analysed in the same way.

# Results

## PARADIGM-HF

### Broad Standardized Medical Dictionary for Regulatory Activities Queries

The broad SMQ PT analysis identified 104 cases in the sacubitril/valsartan group (2.48%) and 97 (2.30%) in the enalapril group. The most commonly reported dementia-related AEs in the sacubitril/valsartan group (vs. the enalapril group) were PTs of 'confusional state' (12 vs. 18), 'somnolence' (11 vs. 9), 'delirium' (10 vs. 8), and 'amnesia/amnestic disorder' (11 vs. 7) (*Tables 1* and *2*).

### Narrow Standardized Medical Dictionary for Regulatory Activities Queries

Using the narrow SMQ PTs, a total of 6 cases (0.14%) of unspecified dementia were identified in the sacubitril/valsartan group and 10 cases (0.24%) in the enalapril group. The number of reports of specific types of dementia in the sacubitril/valsartan group, compared with the enalapril group were, respectively: Alzheimer's

**Table 1 Breakdown of cognition-related adverse events in trials analysed**

| | PARADIGM-HF | | Val-HeFT | | CORONA | | ATMOSPHERE | | |
|---|---|---|---|---|---|---|---|---|---|
| | Enalapril (*n* = 4212) | Sacub/val (*n* = 4187) | Placebo (*n* = 2494) | Valsartan (*n* = 2506) | Placebo (*n* = 2497) | Rosuvastatin (*n* = 2514) | Enalapril (*n* = 2336) | Aliskiren (*n* = 2340) | Combination (*n* = 2340) |
| Narrow SMQs | | | | | | | | | |
| Dementia | 10 | 6 | 4 | 5 | 11 | 14 | 13 | 11 | 11 |
| Dementia Alzheimer's type | 2 | 2 | 0 | 1 | 4 | 6 | 1 | 5 | 4 |
| Senile dementia | 2 | 0 | 0 | 0 | 1 | 4 | 0 | 0 | 2 |
| Vascular dementia | 1 | 2 | 1 | 0 | 3 | 4 | 3 | 4 | 0 |
| Pre-senile dementia | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Hippocampal sclerosis | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Frontotemporal dementia | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Broad SMQs | | | | | | | | | |
| Confusional state | 18 | 12 | 31 | 20 | 21 | 19 | 11 | 13 | 17 |
| Somnolence | 9 | 11 | 17 | 13 | 6 | 5 | 5 | 4 | 4 |
| Delirium | 8 | 10 | 0 | 0 | 7 | 10 | 5 | 11 | 6 |
| Amnesia/amnestic disorder | 7 | 11 | 10 | 12 | 11 | 4 | 1 | 3 | 2 |
| Memory impairment | 6 | 6 | 17 | 9 | 9 | 22 | 2 | 9 | 4 |
| Cognitive disorder | 5 | 4 | 1 | 1 | 3 | 8 | 1 | 4 | 9 |
| Hallucination/delusion/illusion | 5 | 3 | 3 | 5 | 10 | 2 | 1 | 4 | 6 |
| Aphasia | 4 | 5 | 7 | 5 | 1 | 4 | 1 | 3 | 4 |
| Disorientation | 4 | 5 | 18 | 5 | 3 | 1 | 6 | 3 | 1 |
| Agitation | 3 | 7 | 14 | 12 | 2 | 4 | 2 | 5 | 5 |
| Restlessness | 2 | 3 | 13 | 8 | 6 | 3 | 1 | 7 | 4 |
| Mental status changes | 1 | 5 | 8 | 9 | 0 | 0 | 1 | 0 | 2 |
| Affect lability | 1 | 0 | 0 | 4 | 1 | 2 | 0 | 1 | 0 |
| Feeling abnormal | 1 | 0 | 1 | 4 | 3 | 1 | 1 | 2 | 2 |
| Psychotic disorder | 2 | 1 | 3 | 0 | 1 | 1 | 0 | 3 | 2 |
| Mental impairment | 2 | 0 | 3 | 0 | 1 | 1 | 0 | 0 | 0 |
| Other[a] | 4 | 9 | 9 | 11 | 11 | 5 | 5 | 5 | 10 |

SMQ, Standardized Medical Dictionary for Regulatory Activities query.
[a]Fifteen additional terms (mental disorder, mood altered, mood swings, cerebral atrophy, speech disorder, initial insomnia, abnormal behaviour, aggression, apathy, apraxia, somnambulism, inappropriate affect, personality change, disturbance in social behaviour, abulia); see Supplementary material online, *Table S1* for breakdown by treatment group.

type dementia (2 vs. 2), senile dementia (0 vs. 2), vascular dementia (2 vs. 1), hippocampal sclerosis (1 vs. 0), and pre-senile dementia (1 vs. 0) (*Tables 1* and *2*).

### Annual rates of dementia-related adverse events

The crude annual rates of dementia-related AEs using both broad and narrow SMQ PTs are shown in *Table 2*. These did not differ significantly between sacubitril/valsartan and enalapril. Using the broad SMQ PTs, the age-adjusted annual rate of these AEs was 0.95 [95% confidence interval (CI) 0.75–1.15] per 100 patient-years in the sacubitril/valsartan group and 0.98 (95% CI 0.77–1.19) per 100 patient-years in the enalapril group.

## Val-HeFT

### Broad Standardized Medical Dictionary for Regulatory Activities Queries

Total dementia-related AEs were reported in 139 (5.57%) of the 2494 patients receiving placebo compared with 102 (4.07%) of the 2506 study patients receiving valsartan. Of the broad SMQ terms, confusional state was most commonly reported in the placebo group (31 in the placebo group vs. 20 in the valsartan group) followed by disorientation (18 vs. 5), memory impairment (17 vs. 9), and somnolence (17 vs. 13) (*Tables 1* and *2*).

### Narrow Standardized Medical Dictionary for Regulatory Activities Queries

Of the reported narrow SMQ terms, 'unspecified dementia' was the most commonly reported type in the placebo group (4 vs. 5 in the valsartan group). There was one case of vascular dementia in the placebo group and none in the valsartan group and two other reports of specific dementias in the valsartan group and none in the placebo group (*Tables 1* and *2*).

### Annual rates of dementia-related adverse events

The crude annual rates of dementia-related AEs using both broad and narrow SMQ PTs are shown in *Table 2*. The rate of broad SMQ reports was lower in the valsartan than in the placebo group. Using

**Table 2 Number and rate of cognition-related adverse events in trials analysed**

| | Broad SMQ *n* (rate[a]) | Narrow SMQ *n* (rate[a]) |
|---|---|---|
| PARADIGM-HF | | |
| Enalapril (*n* = 4212) | 97 (0.91, 0.73–1.12) | 15 (0.16, 0.10–0.27) |
| Sacubitril/valsartan (*n* = 4187) | 104 (0.92, 0.75–1.14) | 12 (0.12, 0.07–0.21) |
| Hazard ratio (95% CI) | 1.01 (0.75–1.37) | 0.73 (0.33–1.59) |
| Val-HeFT | | |
| Placebo (*n* = 2494) | 139 (3.03, 2.57–3.56) | 5 (0.11, 0.04–0.26) |
| Valsartan (*n* = 2506) | 102 (2.20, 1.82–2.67) | 6 (0.13, 0.06–0.28) |
| Hazard ratio (95% CI) | 0.73 (0.56–0.94) | 1.12 (0.37–3.93) |
| CORONA | | |
| Placebo (*n* = 2497) | 115 (1.62, 1.33–1.97) | 19 (0.31, 0.20–0.48) |
| Rosuvastatin (*n* = 2514) | 120 (1.74, 1.44–2.10) | 28 (0.45, 0.31–0.65) |
| Hazard ratio (95% CI) | 1.07 (0.82–1.41) | 1.46 (0.82–2.62) |
| ATMOSPHERE | | |
| Enalapril (*n* = 2336) | 52 (0.65, 0.48–0.85) | 17 (0.21, 0.12–0.33) |
| Aliskiren (*n* = 2340) | 81 (1.01,0.81–1.26) | 20 (0.25, 0.15–0.38) |
| Combination (*n* = 2340) | 85 (1.05, 0.84–1.30) | 16 (0.20, 0.11–0.32) |
| Hazard ratio (95% CI)[b] | 1.57 (1.11–2.22) | 1.18 (0.62–2.26) |
| Hazard ratio (95% CI)[c] | 1.63 (1.15–2.30) | 0.93 (0.47–1.85) |

CI, confidence interval; SMQ, Standardized Medical Dictionary for Regulatory Activities Query.
[a]Rates were calculated per 100 patient-years (crude rate with 95% confidence interval). Rate for broad SMQ includes narrow SMQ terms.
[b]Aliskiren vs. enalapril.
[c]Combination vs. enalapril.

the broad SMQs, the age-adjusted annual rate of dementia-related AEs was 2.43 (95% 1.94–2.92) per 100 patient-years in the placebo group and 3.46 (95% CI 2.87–4.04) per 100 patient-years in the valsartan group.

## ATMOSPHERE

### Broad Standardized Medical Dictionary for Regulatory Activities Queries

The broad SMQ PT analysis of ATMOSPHERE identified 52 cases (2.23%) in the enalapril group, 81 cases (3.46%) in the aliskiren group, and 85 cases (3.63%) in the combination therapy group (*Tables 1* and *2*). As in the other trials, the most commonly reported PT in the enalapril group was confusional state (11 enalapril vs. 13 aliskiren vs. 17 combination) with delirium (5 vs. 11vs. 6) and memory impairment (2 vs. 9 vs. 4) the other most common terms (*Table 1*).

### Narrow Standardized Medical Dictionary for Regulatory Activities Queries

A total of 13 cases (0.56%) of unspecified dementia were identified in the enalapril group, 11 cases (0.47%) in the aliskiren group, and 11 cases (0.47%) in the combination therapy group, with an additional 4 cases of specific dementias in the enalapril group, 9 cases in the aliskiren group, and 6 cases in the combination treatment group, giving totals of 17, 20, and 16 cases, respectively (*Tables 1* and *2*).

### Annual rates of dementia-related adverse events

The crude annual rates of dementia-related AEs using both broad and narrow SMQ PTs are shown in *Table 2*. The rate of broad SMQ reports was lower in the enalapril group than in the aliskiren and combination therapy groups. Using the broad SMQs, the age-adjusted annual rate of dementia-related AEs was 0.71 (95% CI 0.52–0.91) per 100 patient-years in the enalapril group, 1.14 (95% 0.89–1.39) per 100 patient-years in the aliskiren group, and 1.17 (95% CI 0.92–1.42) per 100 patient-years in the combination therapy group.

## CORONA

### Broad Standardized Medical Dictionary for Regulatory Activities Queries

The broad SMQ PT analysis of CORONA identified 115 cases (4.61%) in the placebo group and 120 cases (4.77%) in the rosuvastatin group (*Tables 1* and *2*). As in the other trials, the most commonly reported PT in the placebo group was confusional state (21 placebo vs. 19 rosuvastatin), with amnesia/amnestic disorder (11 vs. 4) the next most common term (*Tables 1* and *2*).

### Narrow Standardized Medical Dictionary for Regulatory Activities Queries

A total of 11 cases (0.44%) of unspecified dementia were identified in the placebo group and 14 cases (0.56%) in the rosuvastatin group, with an additional 8 cases (0.32%) of specific dementias in the placebo group and 14 cases (0.56%) in the rosuvastatin group, giving totals of 19 and 28 cases, respectively (*Tables 1* and *2*).

### Annual rates of dementia-related adverse events

The crude annual rates of dementia-related AEs using both broad and narrow SMQ PTs are shown in *Table 2*. These did not differ significantly between placebo and rosuvastatin. Using the broad SMQs, the age-adjusted annual rate of dementia-related AEs was 1.03 (95% CI 0.8–1.24) per 100 patient-years in the placebo group and 1.06 (95% CI 0.86–1.27) per 100 patient-years in the rosuvastatin group.

## Baseline characteristics associated with dementia-related adverse events

Because of their almost identical design, PARADIGM-HF and ATMOSPHERE were pooled in order to examine which baseline characteristics were associated with dementia-related AEs (*Table 3*). As can be seen, patients with dementia-related AEs were older, especially those with narrow SMQ PTs, and were more likely to have AF, coronary heart disease, chronic lung disease, and to have experienced a stroke than those without. Patients with dementia-related AEs had a higher NT-proBNP and lower estimated glomerular filtration rate (eGFR). These patients also reported greater alcohol intake.

**Table 3 Baseline characteristics of those with no dementia SMQ, those with the narrow SMQs, and those with the broad SMQs in PARADIGM-HF and ATMOSPHERE combined**

| | No dementia ($n = 15\,028$) | With dementia | | *P*-value | |
|---|---|---|---|---|---|
| | | Narrow SMQs ($n = 80$) | Broad SMQs ($n = 307$) | Narrow vs. none | Broad vs. none |
| Age, years | 63.4 ± 11.6 | 75.4 ± 7.2 | 68.4 ± 10.5 | <0.001 | <0.001 |
| Male sex, *n* (%) | 11748 (78.2) | 58 (72.5) | 252 (82.1) | 0.221 | 0.100 |
| Race, *n* (%) | | | | 0.002 | <0.001 |
| White | 9818 (65.6) | 68 (86.1) | 250 (82.0) | | |
| Black | 526 (3.5) | 1 (1.3) | 10 (3.3) | | |
| Asian | 3238 (21.6) | 8 (10.1) | 27 (8.9) | | |
| Other | 1395 (9.3) | 2 (2.5) | 18 (5.9) | | |
| Region, *n* (%) | | | | <0.001 | <0.001 |
| North America | 722 (4.8) | 5 (6.3) | 52 (16.9) | | |
| Latin America | 2512 (16.7) | 3 (3.8) | 37 (12.1) | | |
| Western Europe | 3725 (24.8) | 39 (48.8) | 138 (45.0) | | |
| Central Europe | 4700 (31.3) | 25 (31.3) | 45 (14.7) | | |
| Asia or Pacific region | 3369 (22.4) | 8 (10.0) | 35 (11.4) | | |
| BMI, kg/m$^2$ | 27.8 ± 5.4 | 27.2 ± 4.8 | 28.4 ± 6.1 | 0.296 | 0.041 |
| Blood pressure, mmHg | | | | | |
| Systolic | 122.4 ± 16.7 | 128.0 ± 16.9 | 122.6 ± 18.0 | 0.003 | 0.789 |
| Diastolic | 75.3 ± 10.7 | 75.6 ± 10.5 | 72.9 ± 10.9 | 0.798 | <0.001 |
| Heart rate, b.p.m. | 72.1 ± 12.3 | 71.8 ± 12.7 | 70.5 ± 11.8 | 0.823 | 0.026 |
| Left ventricular ejection fraction, % | 29.0 ± 6.0 | 30.4 ± 6.3 | 28.7 ± 6.4 | 0.042 | 0.322 |
| NYHA class, *n* (%) | | | | 0.321 | 0.609 |
| I | 554 (3.7) | 1 (1.3) | 7 (2.3) | | |
| II | 10 489 (69.9) | 53 (66.3) | 217 (70.7) | | |
| III | 3855 (25.7) | 26 (32.5) | 80 (26.1) | | |
| IV | 117 (0.8) | 0 (0.0) | 3 (1.0) | | |
| Ischaemic aetiology, *n* (%) | 8723 (58.0) | 55 (68.8) | 188 (61.2) | 0.053 | 0.262 |
| HF duration, *n* (%) | | | | 0.522 | <0.001 |
| ≤1 year | 4799 (31.9) | 21 (26.3) | 64 (20.8) | | |
| >1 year and ≤5 years | 5678 (37.8) | 34 (42.5) | 113 (36.8) | | |
| >5 years | 4547 (30.3) | 25 (31.3) | 130 (42.3) | | |
| Smoking habit, *n* (%) | | | | 0.255 | <0.001 |
| Never smoked | 7955 (52.9) | 47 (58.8) | 119 (38.8) | | |
| Ex-smoker | 5018 (33.4) | 27 (33.8) | 140 (45.6) | | |
| Current smoker | 2055 (13.7) | 6 (7.5) | 48 (15.6) | | |
| Alcohol habit[a], *n* (%) | | | | <0.001 | 0.010 |
| <1 drink per day | 13 226 (88.0) | 59 (73.8) | 257 (83.7) | | |
| 1–2 drinks per day | 1467 (9.8) | 18 (22.5) | 36 (11.7) | | |
| ≥3 drinks per day | 333 (2.2) | 3 (3.8) | 14 (4.6) | | |
| Medical history, *n* (%) | | | | | |
| Previous HF hospitalization | 9224 (61.4) | 42 (52.5) | 196 (63.8) | 0.104 | 0.380 |
| Myocardial infarction | 6283 (41.8) | 38 (47.5) | 160 (52.1) | 0.303 | <0.001 |
| Angina | 3908 (26.0) | 23 (28.7) | 92 (30.0) | 0.577 | 0.118 |
| Stable angina | 3031 (20.2) | 18 (22.5) | 58 (18.9) | 0.604 | 0.581 |
| Unstable angina | 1655 (11.0) | 7 (8.8) | 59 (19.2) | 0.519 | <0.001 |
| CABG | 2190 (14.6) | 17 (21.3) | 74 (24.1) | 0.092 | <0.001 |
| PCI | 3085 (20.5) | 20 (25.0) | 75 (24.4) | 0.324 | 0.094 |
| Hypertension | 9998 (66.5) | 64 (80.0) | 210 (68.4) | 0.011 | 0.491 |
| Diabetes | 4719 (31.4) | 13 (16.3) | 119 (38.8) | 0.004 | 0.006 |
| Atrial fibrillation | 5301 (35.3) | 45 (56.3) | 135 (44.0) | <0.001 | 0.002 |
| Stroke | 1166 (7.8) | 8 (10.0) | 43 (14.0) | 0.455 | <0.001 |
| Transient ischaemic attack | 446 (3.0) | 8 (10.0) | 24 (7.8) | <0.001 | <0.001 |
| Cancer | 628 (4.2) | 9 (11.3) | 21 (6.8) | 0.002 | 0.022 |

**Table 3 continued**

| | No dementia (*n* = 15 028) | With dementia | | *P*-value | |
|---|---|---|---|---|---|
| | | Narrow SMQs (n = 80) | Broad SMQs (*n* = 307) | Narrow vs. none | Broad vs. none |
| Asthma | 504 (3.4) | 5 (6.3) | 18 (5.9) | 0.152 | 0.016 |
| COPD | 1787 (11.9) | 17 (21.3) | 63 (20.5) | 0.010 | <0.001 |
| Abdominal aortic aneurysm | 190 (1.3) | 2 (2.5) | 6 (2.0) | 0.325 | 0.287 |
| Medication, *n* (%) | | | | | |
| Digitalis | 4687 (31.2) | 21 (26.3) | 73 (23.8) | 0.342 | 0.006 |
| Diuretic | 12 026 (80.0) | 64 (80.0) | 246 (80.1) | 0.996 | 0.963 |
| ACE inhibitor/ARB before entry | 12 781 (85.0) | 60 (75.0) | 248 (80.8) | 0.012 | 0.038 |
| Beta-blocker | 13 886 (92.4) | 69 (86.3) | 288 (93.8) | 0.039 | 0.355 |
| Aldosterone antagonist | 7128 (47.4) | 23 (28.7) | 122 (39.7) | 0.001 | 0.008 |
| Antiplatelet agent | 8380 (55.8) | 34 (42.5) | 189 (61.6) | 0.017 | 0.043 |
| Aspirin | 7747 (51.6) | 29 (36.3) | 174 (56.7) | 0.006 | 0.075 |
| Anticoagulant | 4644 (30.9) | 38 (47.5) | 121 (39.4) | 0.001 | 0.001 |
| Lipid-lowering agent | 8202 (54.6) | 45 (56.3) | 201 (65.5) | 0.765 | <0.001 |
| Pacemaker | 1718 (11.4) | 14 (17.5) | 68 (22.1) | 0.089 | <0.001 |
| CRT | 920 (6.1) | 5 (6.3) | 42 (13.7) | 0.962 | <0.001 |
| ICD | 2181 (14.5) | 17 (21.3) | 93 (30.3) | 0.088 | <0.001 |
| 12-lead ECG, *n* (%) | | | | | |
| QRS duration | 116.9 ± 35.1 | 112.2 ± 33.1 | 129.7 ± 47.1 | 0.237 | <0.001 |
| Atrial fibrillation | 3538 (23.7) | 29 (36.7) | 70 (23.0) | 0.007 | 0.769 |
| Left bundle branch block | 2987 (20.0) | 12 (15.2) | 83 (27.2) | 0.288 | 0.002 |
| Right bundle branch block | 1114 (7.5) | 2 (2.5) | 22 (7.2) | 0.096 | 0.874 |
| Q waves | 2636 (17.6) | 15 (19.0) | 49 (16.1) | 0.754 | 0.476 |
| Left ventricular hypertrophy | 2706 (18.1) | 10 (12.7) | 39 (12.8) | 0.210 | 0.017 |
| Paced rhythm | 1624 (10.9) | 14 (17.7) | 65 (21.3) | 0.051 | <0.001 |
| Laboratory measures | | | | | |
| eGFR, mL/min/1.73 $m^2$ | 70.7 ± 22.2 | 63.4 ± 16.6 | 66.9 ± 21.9 | 0.004 | 0.003 |
| eGFR <60 mL/min/1.73 $m^2$, *n* (%) | 4759 (31.7) | 34 (42.5) | 117 (38.2) | 0.262 | 0.001 |
| Serum creatinine, mg/dL | 1.08 ± 0.29 | 1.12 ± 0.29 | 1.14 ± 0.32 | 0.038 | 0.017 |
| NT-proBNP, pg/mL[b] | 1410 (768–2770) | 1595 (910–3003) | 1679 (859–3201) | 0.421 | 0.019 |

BMI, body mass index; CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter defibrillator; PCI, percutaneous coronary intervention; SMQ, Standardized Medical Dictionary for Regulatory Activities Query.
[a]One drink equals 12 fluid ounces of beer, 8 fluid ounces of malt liquor, 5 fluid ounces of wine, or 1.5 fluid ounces or a 'shot' of 80-proof distilled spirits or liquor (e.g. gin, rum, vodka, or whiskey).
[b]NT-proBNP was reported as median and interquartile range.

# Discussion

We examined the incidence of dementia-related AEs in PARADIGM-HF because of a theoretical concern about the potential effect of neprilysin inhibition on amyloid-$\beta$ clearance from the central nervous system. We have also carried out the same analysis in three other trials, Val-HeFT, CORONA, and ATMOSPHERE, which used a similar method to record AEs and which were available to the authors. We are not aware of any prior reports of this type.

We found, using the broadest collection of terms related to dementia, that the annual rate of AEs was ~1 per 100 patient-years in PARADIGM-HF and ATMOSPHERE, and ~70% higher in the older patients enrolled in CORONA. The prevalence of cognitive impairment increases with age, and we found that patients with dementia-related AEs were significantly older than patients without these AEs. However, the age-adjusted rates were similar in all three trials. For unknown reasons, the crude and age-adjusted rates of these AEs were higher in Val-HeFT than in the three other trials. This was not the case when the more specific SMQs were examined, with rates of dementia-related AEs of ~0.1–0.2 per 100 patient-years in each of PARADIGM-HF, Val-HeFT, and ATMOSPHERE (and a higher rate of 0.3–0.4 per 100 patient-years in the older patients aged ≥60 years in CORONA). It is difficult to place these findings in context because dementia-related AEs have not been published in any clinical trial in heart failure. Examining epidemiological data, the Framingham Heart Study, for its latest epoch (2004–2008), reported an annual incidence of dementia

of 0.44 (95% CI 0.36–0.56) per 100 person-years in individuals with a mean age at entry of 72 years (range 60–101 years).[13] In the most recent report from the Cognitive Function and Ageing Study (CFAS), the incidence of dementia in men in the UK aged 65–69 years was 0.50 (95% CI 0.25–1.02) per 100 person-years and in men aged 70–74 years it was 0.87 (95% 0.51–1.51) per 100 person-years; in women, the corresponding rates were 0.46 (95% CI 0.22–0.96) and 0.64 (95% CI 0.33–1.23), respectively.[14] The rates in these two epidemiological studies are not dissimilar to those identified in CORONA which enrolled the oldest patients among the trials we analysed. However, it is still likely that spontaneous AE reporting underestimated the true rate of dementia, especially as it is thought that patients with heart failure have a higher risk of cognitive dysfunction than healthy individuals.

We identified two studies reporting the incidence of dementia in patients with heart failure. One used ICD-9 (International Classification of Diseases, 9th revision) codes to identify diagnoses of both heart failure and dementia in a Medicare data set in the USA. Over a median follow-up of 22 months, 1135 of 8062 patients with heart failure (mean age 74.5 years; 53% women) developed dementia. This equated to an incidence rate of ~7.55 per 100 patient-years (ranging from ~3.8 in those <65 years and 5.0 in those aged 65–74 years to 26 per 100 patient-years in those >85 years).[15] A Swedish study used a similarly broad diagnosis of heart failure. Using detailed clinical and cognitive testing at each study follow-up visit, the investigators identified 205 subjects aged 83.3 years of age on average at baseline (80% were female). After a mean follow-up of 5 years, the investigators reported an incidence rate of dementia of 8.46 per 100 patient-years.[16] It is very hard to compare these studies with ours given the broad diagnosis of heart failure, the much more advanced age of included subjects, and quite different gender balance. Our trial patients were also selected, with just the consenting process alone likely to exclude patients with cognitive impairment. However, the broad SMQ AE rate in CORONA and Val-HeFT was not far off the rate of incident dementia among similarly aged patients in the US study.

In PARADIGM-HF, compared with enalapril, sacubitril/valsartan did not lead to any increase in dementia-related AEs whether defined using broad or narrow SMQs. Unpublished data from the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE) study report show similar findings with respect to omapatrilat (a neprilysin–ACE inhibitor) compared with enalapril, although details of how this analysis was conducted are not available.[17] Specifically, 5 of 2886 patients (0.2%) treated with omapatrilat had an AE related to memory impairment, compared with 13 of 2884 (0.5%) patients treated with enalapril. The corresponding figures of dementia were 1 (<0.1%) and 6 (0.2%). While these findings provide some reassurance, the median duration of follow-up in PARADIGM-HF was 2.7 years with a maximum of 4.3 years; the median follow-up in OVERTURE was only 1.2 years. Detectable effects of a treatment on cognitive decline might take much longer to occur, although this concern is less relevant in a condition such as heart failure with limited life expectancy, compared with conditions such as hypertension where treatment might be given for decades. On the other hand, the concern about an effect of neprilysin inhibition on amyloid-$\beta$ peptides in the brain is theoretical and without any supporting experimental or clinical evidence. Sacubitril/valsartan did not increase the concentration of amyloidogenic species in the cerebrospinal fluid of healthy volunteers or brain tissue in cynomolgus monkeys.[6,18] Moreover, human genetic data do not provide consistent support for a relationship between neprilysin and Alzheimer's disease.[19–21] Moreover, cognitive decline in heart failure may not be wholly related to Alzheimer's type pathology and may also be associated with declining cardiac function and vascular abnormalities. [22–24] In keeping with this, we found that patients with dementia-related AEs had more evidence of cardiovascular disease including coronary disease, stroke, and AF, as well as a higher NT-proBNP level and lower eGFR. Effective treatments that improve cardiac function might have a favourable effect on cognition, and ARBs in particular have been postulated to have such a benefit.[22–24] Another related and important contributor to cognitive decline in heart failure may be unplanned admission to hospital with decompensation as episodes of critical illness are associated with marked cognitive decline over the subsequent 12 months.[25] It is plausible, therefore, that long-term sacubitril/valsartan treatment, by improving cardiovascular function and preventing hospitalization, may have a favourable effect on cognitive function in patients with heart failure.

As mentioned above, the present analyses were limited as they relied on AE reporting and not formal, systematic, cognitive function testing which is likely to be more sensitive in detecting any effect of treatment. Serial assessment of cognitive function using the Mini Mental State Examination is being conducted in the Prospective comparison of ARni with Arb Global Outcomes in heart failure with preserved ejectioN fraction (PARAGON-HF, ClinicalTrials.gov, ID NCT01920711) trial which is comparing sacubitril/valsartan with valsartan in ~4300 patients with heart failure and preserved EF. In a new study, the Prospective Evaluation of cognitive function in heart failure: A Randomized double-blind Study in Patients with Preserved Ejection fraction Cardiac failure Treated wIth Valsartan or Entresto (PERSPECTIVE, ClinicalTrials.gov, ID NCT02884206), a battery of more sensitive cognitive function tests will be utilized and the effects of sacubitril/valsartan on amyloid-$\beta$ within the brain will be examined using positron emission tomography imaging. Patients with clinically obvious cognitive decline were excluded from the trials analysed. Longer term follow-up might identify effects not seen over the maximum 4.3 years of follow-up in PARADIGM-HF.

In summary, we found that the incidence of dementia-related AEs in patients treated with sacubitril/valsartan was similar to that in patients treated with enalapril in PARADIGM-HF and in patients enrolled in other recent heart trials. Our findings do not support the theoretical concerns about adverse cognitive effects of sacubitril/valsartan which has been shown definitively to reduce morbidity and mortality in patients with HFrEF.

## Supplementary Information

Additional Supporting Information may be found in the online version of this article:

**Table S1.** Additional broad SMQs.

**Conflict of interest:** F.C., M.P.L., J.G., and V.C.S. are employees of Novartis. J.A.C., L.S., and S.L.K. have no conflict of interest to report. All other authors or their institutions have received financial support from Novartis for involvement in the PARADIGM-HF trial, ATMOSPHERE, or both.

# Appendix 1. Cognition, memory, dementia-like and related events

In PARADIGM-HF, we systematically searched adverse event (AE) reports coded using the 17.0 version of the Medical Dictionary for Regulatory Activities (MedDRA) using Standardized MedDRA Queries (SMQs) with 'broad' and 'narrow' preferred terms (PTs) related to dementia-like AEs.[3]

The broad PTs used were: abnormal behaviour, abulia, activities of daily living impaired, affect lability, aggression, agitation, agnosia, amnesia, amnestic disorder, anterograde amnesia, apathy, aphasia, apraxia, borderline mental impairment, cerebral atrophy, cerebral atrophy congenital, change in sustained attention, cognitive disorder, confusional state, delirium, delusion, delusional disorder (jealous type), delusional disorder (unspecified type), disinhibition, disorientation, disturbance in social behaviour, executive dysfunction, feeling abnormal, flat affect, hallucination, hostility, hypomania, illusion, impaired reasoning, inappropriate affect, initial insomnia, intelligence test abnormal, irritability post-vaccinal, judgement impaired, learning disability, learning disorder, memory impairment, mental status changes, mood altered, mood swings, morose, negativism, neuropsychological test abnormal, personality change, prodromal Alzheimer's disease, psychotic behaviour, psychotic disorder, restlessness, sexually inappropriate behaviour, social avoidant behaviour, somnambulism, somnolence, sopor, speech disorder, suspiciousness, symbolic dysfunction, thinking abnormal, transient global amnesia, vascular cognitive impairment and visual cortex atrophy.

The narrow PTs were: behavioural and psychiatric symptoms of dementia, Creutzfeldt–Jakob disease, dementia, dementia of Alzheimer's type, dementia of Alzheimer's type (uncomplicated), dementia of Alzheimer's type (with delirium), dementia of Alzheimer's type (with delusions), dementia of Alzheimer's type (with depressed mood), dementia with Lewy bodies, frontotemporal dementia, hippocampal sclerosis, Korsakoff's syndrome, Mini Mental State Examination abnormal, pre-senile dementia, progressive supranuclear palsy, senile dementia, variant Creutzfeldt–Jakob disease, and vascular dementia.

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