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Adverse events with sacubitril/valsartan in the real world: emerging signals to target preventive strategies from the FDA Adverse Event Reporting System

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Abstract

Aims: To characterize clinical priority of adverse events (AEs) with sacubitril/valsartan for targeting preventive measures.

Methods: We used the FDA Adverse Event Reporting System (worldwide pharmacovigilance database) to compare AEs recording sacubitril/valsartan as suspect with other cardiovascular drugs. Disproportionality analyses were performed by calculating the reporting odds ratios (RORs), deemed significant when the lower limit of the 95% confidence interval (LL95%CI)>1. Clinical priority was assigned to AEs with significant disproportionality by scoring (range 0-10 points) five features (number of events, magnitude of LL95%CI, mortality rate, important/designated medical event, biological plausibility).

Results: Sacubitril/valsartan was recorded in 20,021 reports, with 178 AEs associated with significant disproportionality: 71.9%, 25.9% and 2.2% were classified as weak, moderate and strong clinical priorities, respectively. Increased reporting emerged for several cardiovascular AEs, including "renal failure" (N=388; LL95%CI 2.26), "hyperkalaemia" (314; 2.42), and "angioedema" (309; 1.56). Sudden cardiac death (SCD) (priority score=9 points) was the only designated medical event with strong clinical priority. Notably, SCD occurred early after sacubitril/valsartan administration (average onset 124 days), with concomitant drugs known for pro-arrhythmic potential (e.g., amiodarone, escitalopram, mirtazapine, loop diuretics) in 26.2% of records.

Conclusion: The increased cardiovascular reporting of sacubitril/valsartan in the real world was largely predictable from pre-approval evidence, underlying disease and likely patients' comorbidities. The unexpected reporting of SCD occurred well before the complete development of positive electrical remodelling induced by sacubitril/valsartan, and calls for stringent clinical monitoring (to reduce the pro-arrhythmic burden related to co-medications), and further investigation on appropriate combination with other preventive measures.

Keywords: sacubitril/valsartan; pharmacovigilance; disproportionality; sudden cardiac death.

Introduction

The combination of sacubitril, the first-in-class angiotensin receptor-neprilysin inhibitor (ARNI), and valsartan, a well-known angiotensin receptor antagonist [1], was approved by the Food and Drug Administration (FDA) in 2015 and the European Medicines Agency (EMA) in 2016 for the management of patients affected by heart failure with reduced ejection fraction, based on the pivotal phase III PARADIGM-HF trial [2], showing 20% relative risk reduction in the primary composite endpoint (cardiovascular death or hospitalization for heart failure), as compared to enalapril alone. Notably, the divergence of incidence in primary outcome became evident only at day 180, and even later for individual outcomes.

This new combination coupled the blockade of detrimental effects associated with upregulation of renin-angiotensin-aldosterone system promoted by valsartan, with beneficial effects on natriuretic peptide system due to neprilysin inhibition induced by sacubitril, overall resulting in increased natriuresis and diuresis, vasodilation, anti-proliferative effect and reduced sympathetic activity [1].

Overall, tolerability was predictable: symptomatic hypotension occurred more frequently in patients receiving the drug combination, whereas renal impairment (elevated creatinine ≥2.5 mg/dL), hyperkalemia and cough (despite being common side effects) were significantly recorded in the enalapril group [2]. Furthermore, concerns emerged regarding the theoretical possibility of an increased risk for cognition, memory, or dementia-related adverse events (AEs), given that neprilysin inhibition may affect the brain clearance of amyloid-beta peptide [3-4].

Considering the recognized limitations and the observed methodological bias of a single clinical trial in fully evaluating the safety profile of drugs, especially in the detection of rare, unexpected and delayed AEs, spontaneous reporting systems (SRSs) represent a valuable source for post-marketing surveillance, allowing early identification of possible safety signals. Additionally, analysis of SRSs provides a broader perspective by collecting unpublished reports of AEs occurring in the real world, including multifaceted scenario of patients with comorbidities and poly-pharmacotherapy [5-6].

Safety assessment of sacubitril/valsartan appears a neglected clinical issue and, to the best of our knowledge, only a few case reports/series have preliminary described specific toxicities, mainly limited to muscular-, renal- and cognition-related AEs [3, 7-11].

We characterized the safety profile of sacubitril/valsartan, by analysing spontaneous reports submitted to the US FDA Adverse Event Reporting System (FAERS) database. The extracted AEs, potentially emerging as safety signals, were ranked in term of clinical priority level in order to identify and prioritize potential preventive measures.

Methods

Study design and data source

The study was conceived as an observational, retrospective disproportionality analysis, a validated concept in pharmacovigilance to assess whether an association is likely to exist between sacubitril/valsartan and a given AE based on a differential reporting [12].

All reports recorded in FAERS between the second quarter (Q2) of 2015 (considering the US marketing approval of sacubitril/valsartan) and 2018Q2, in which the drug was considered the primary or secondary suspect, and reaching a pre-defined quality level, were included in our analysis. Other cardiovascular drugs were considered as control.

Disproportionality analysis was performed by calculating the reporting odds ratio (ROR) with relevant 95% confidence interval (CI), and considered statistically significant when the lower limit of the 95% CI of the ROR exceeds 1. Disproportionality was calculated according to the traditional signalling criterion (when at least three cases of interest were reported) [12-14], and performed at the system organ class (SOC) and preferred term (PT) level to describe the spectrum of toxicities. Details concerning study design and disproportionality analysis are shown in Supplementary material – 1.

Classification and prioritization of relevant disproportionality signals

AEs emerging with significant disproportionality were ranked in terms of clinical priority as follows.

First, important medical events (IMEs) and designated medical events (DMEs) were selected among disproportionality signals using public lists developed and updated by the EMA [15-16]. IMEs are any AE showing seriousness features (death, life-threatening, hospitalization, disability or congenital anomaly). DMEs are rare, serious AEs associated with a high drug-attributable risk, which may constitute a safety issue under certain circumstances (e.g., high quality reports).

Second, IMEs and DMEs were prioritized according to three levels of clinical importance, by creating a semi-quantitative score assessing five different features: number of events reported, magnitude of the lower limit of the 95% CI of ROR, mortality rate, characterization as IMEs or DMEs, biological plausibility (Table 1). A score between 0-4, 5-7 or 8-10 identified respectively AEs with weak (green light), moderate (yellow light) or strong (red light) clinical priority.

No matter clinical relevance/priority, these findings were classified into four broad categories, according to the predictability of AEs:

Expected AEs: predictable events on the basis of sacubitril/valsartan mechanism of action, or anticipated from pre-marketing pivotal trials;

<u>Disease-related AEs</u>: events for which underlying heart failure represents *per se* a risk factor (i.e. heart failure may increase the risk of supraventricular or ventricular arrhythmia);

<u>Comorbidities-related AEs</u>: events for which concomitant diseases or co-administered drugs represent risk factors (i.e. patients with heart failure are commonly affected by diabetes, or concomitant therapy with loop diuretics may lead to deafness or electrolyte abnormalities);

<u>Unexpected AEs</u>: unpredictable and previously unknown events.

Results

Descriptive analysis

During the 3-year study period, a total of 16,331,098 FAERS reports were initially processed for drug codification and duplicate removal: 9,354,225 reports were finally retained, of which 1,149,398 included at least one cardiovascular drug; 20,021 reports (1.74%; cases) mentioned sacubitril/valsartan as suspect agent, while 1,128,887 were non-cases (Supplementary Figure 1).

Demographic data are reported in Table 2. The reported country was US in 40.9% of records. Subjects aged > 60 years old were the most represented, with male preponderance (60.5%). Hospitalization and death occurred respectively in 14.4% and 12.1%. Consumers represented the main source of reports in at least half of cases (52.8%), followed by clinicians (28%) and other health care professionals (17.8%). The majority of reports was submitted during the 2017Q3-2018Q2 period (55.6%).

Disproportionality analysis

The disproportionality analysis identified five areas of toxicity with statistically significant ROR: *cardiac disorders* (N = 2559; adjROR = 1.33; 95% CI 1.27-1.39), *ear and labyrinth disorders* (328; 1.15; 1.02-1.28), *investigations* (3655; 1.33; 1.29-1.39), *renal and urinary disorders* (1569; 1.40; 1.33-1.48) and *vascular disorders* (3368; 2.29; 2.20-2.38), with consistent results for both crude and adjusted disproportionality (Supplementary Table 1, Supplementary Figure 2).

Overall, sacubitril/valsartan was recorded as suspect agent in 2288 PTs, of which 197 (8.6%) showed a statistically significant ROR, representing 55.7% of cases. After accounting for indication bias and removal of medication errors, 178 PTs with significant disproportionality were finally retained. Sacubitril/valsartan was associated with higher reporting of renal failure (N = 388; adjROR = 2.52; 95% CI 2.26-2.8), hyperkalaemia (314; 2.74; 2.42-3.08), and angioedema (309; 1.76; 1.56-1.98). Disease-related, expected and comorbidities-related AEs amounting respectively for 41.6%, 28.7% and 28.1% of PTs. Only three PTs (1.6%) were classified as unexpected AEs, just including 31 cases (0.1%) (Figure 1).

Clinical prioritization of relevant clinical signals

Overall, 44 out of 178 PTs (24.7%) showing statistically significant disproportionality were classified as IMEs (Table 3; Figure 1). Only four significant PTs (2.2%) were identified as DMEs (Table 4; Figure 1), and none of these represented unexpected AEs. Collectively, 33 out of 62 DMEs (53.2%) were recorded at least once with sacubitril/valsartan (Supplementary Table 2), with renal failure (N = 388), acute kidney injury (N = 345) and angioedema (N = 309) being the most common.

Based on clinical priority score, 128 (71.9%), 46 (25.9%) and 4 (2.2%) PTs were classified as weak, moderate and strong clinical priority, respectively (Tables 3 and 4, Supplementary Table 3). *Sudden cardiac*

death (SCD) (points = 9), *sudden death* (points = 8), *death* (points = 8) and *ischaemic cardiomyopathy* (points = 8) emerged as strong clinical priorities.

Unexpected AEs showing statistically significant RORs (but not fulfilling criteria for strong prioritization) were: *nipple pain* (N = 16; adjROR = 5.59; 95% CI 3.01-9.84), *hepatic cyst* (11; 2.27; 1.14-4.08) and *pyoderma gangrenosum* (4; 22.23; 5.86-65.48).

Discussion

To the best of our knowledge, this is the first real world study describing the worldwide reporting of AEs with sacubitril/valsartan, and one of its key findings is a major over-reporting of cardiovascular AEs. Previous studies were limited to local/national experiences [7-8] or focused on specific AEs such as dementia [3], thus providing only a narrow view of potential safety concerns emerging from post-marketing use of sacubitril/valsartan.

Disproportionality approaches are exponentially increasing in the recent literature, especially to investigate cardiovascular safety [17]. In our study, we attempted to move forward the application of statistical techniques by proposing a priority score based on well-defined criteria. Our score was developed to assign clinical relevance on signals and avoid unnecessary alarm. It may also be useful to assist clinicians to define toxicities emerging in daily practice that warrant further investigation to target preventive strategies, and support pharmacovigilance experts and regulatory agencies in routine signal detection activity to prioritize safety signals.

Overall, sacubitril/valsartan showed a predictable safety profile based on the known mechanism of action [1], anticipated common AEs found in PARADIGM-HF trial [2, 4], expected clinical complications, comorbidities and co-medications likely overlapping in patients with chronic cardiac insufficiency [18]. We interpreted the vast majority of cardiovascular AEs with significant disproportionality as strictly associated with heart failure *per se* (disease-related AEs) or with comorbidities and co-administered medications (comorbidities-related AEs), rather than with inherent toxicity of sacubitril/valsartan. In fact, considering therapeutic indication and the European Society of Cardiology (ESC) guidelines' recommendations, it is likely that patients eligible to sacubitril/valsartan are affected by advanced stages of cardiac insufficiency, thus being at higher risk of major cardiovascular events [18], a phenomenon known as "channeling" to be verified through pharmaco-epidemiological research.

Our score identified four AEs with strong clinical priority. These AEs, through expected and most likely related to the underlying heart failure, should not be overlooked considering the limited uptake of the drug in clinical practice coupled with the observed increasing reporting over time, as well as the observed discrepancy between patients enrolled in PARADIGM-HF trial and real-world use in the post-marketing registry [19-20].

Only apparently the finding of SCD is paradoxical, and an underlying drug-induced torsadogenic component cannot be excluded [21]. While there are no data on direct QT-prolonging potential sacubitril/valsartan at crediblemeds.org, the medication is likely to possess anti-arrhythmic properties considering the potential impact on reverse remodelling. In PARADIGM-HF trial, 20% reduction in cardiovascular death was attributable to SCD and death due to progressive heart failure, but became apparent only after day 180 and even later [2, 22]. These findings have been reinforced by the results of a single centre study on implantable cardioverter defibrillator (ICD) carriers showing a reduction on anti-tachycardia interventions after 9 months

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of therapy with sacubitril/valsartan [23]. Furthermore, a positive electrical remodelling after switching from ACE-inhibitors to ARNI were reported, as documented by a reduction in QTc, T peak-T end interval and other measures of dispersion of ventricular repolarization [24].

Therefore, three main determinants may explain the possible occurrence of SCD with the use of sacubitril/valsartan: 1. late-onset of left ventricular reverse remodelling induced by ARNI; 2. concomitant ischaemic cardiomyopathy; 3. ethnicity. Different reports showed a clear temporal association between initiation of ARNI and early occurrence of ventricular arrhythmias [25-26]. Furthermore, an increased incidence of ventricular arrhythmias was recently reported in the first 12 months after initiation of sacubitril/valsartan, particularly in patients with ischaemic cardiomyopathy (11% versus 37%, p = 0.04) [27]. Notably, most of these events were recorded in the first 180 days after the shift in drug therapy. It is possible that neuro-hormonal and/or haemodynamic modification might be proarrhythmic in the acute phase, while after the occurrence of left ventricular reverse remodelling the outcome might improve. Evidence of a parallel behaviour between occurrence of reverse remodelling and reduction in the burden of ventricular arrhythmias may support this hypothesis [28].

In the 42 cases of SCD recorded in FAERS, the event occurred after a mean of 124 days, when left ventricular reverse remodelling induced by sacubitril/valsartan is still incompletely developed. We also recorded in a considerable proportion of cases different patient- and drug-related risk factors increasing the risk of torsade de pointes (TdP): use of antiplatelet/ anticoagulant agents, proxies of potential underlying ischaemic cardiomyopathy and atrial fibrillation, were reported in 42.9% of SCDs, while in 26.2% of cases, concomitant drugs known to increase directly (amiodarone, mirtazapine, escitalopram) or indirectly (loop diuretics via hypokalaemia) the pro-arrhythmic risk were recorded. Notably, cardiomyopathy/heart failure/acute myocardial ischemia represent *per se* risk factors for TdP.

In PARADIGM-HF trial [2], a higher prevalence of sudden death was reported in the Asia-Pacific region compared to remaining population (51.3% vs. 33.0%; p< 0.00001), representing 25.5% of the overall SCDs recorded during the study period. Our data are aligned to this trend: cases of SCD, largely reported in men, accounted for 1.3% of overall records from Asia-Pacific region as compared to 0.3% in remaining population (6/453 vs. 36/10.561; p< 0.001). Consequently, an underlying genetic susceptibility to ventricular arrhythmias strictly related to ethnicity cannot be excluded. Notably, the recently published PARAGON-HF trial [29] assessed the efficacy of sacubitril/valsartan in patients with heart failure and preserved ejection fraction, a scenario characterized by challenging management [30]: although in the overall population the study drug failed to reach a significant improvement, a better outcome was found in pre-specified subgroup analyses on Caucasian, female, and patients from Western Europe, thus reinforcing our hypothesis [31].

Although the prevalence of CRT (cardiac resynchronisation therapy) and ICD devices in PARADIGM-HF trial [2] was limited (respectively 6.8% and 14.8%) compared to the relatively high prevalence of severe left ventricular dysfunction (two thirds of the patients presented a left-ventricular ejection fraction <33%),

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several authors are claiming the use of sacubitril/valsartan before or even in spite of ICD [32-33], given the significant reduction in cardiovascular and sudden death. In the wake of our data, there is an urgent need for high-quality data before replacing ICD implementation with sacubitril/valsartan administration: patients at high risk of SCD should be identified, and careful benefit-risk and cost-effectiveness assessment should be implemented [34]. In this regard, the results from the Improvement of Left Ventricular Ejection Fraction in ICD Patients Undergoing Therapy With Sacubitril/Valsartan (SAVE-ICD) prospective registry (NCT03935087) are strongly awaited.

The higher reporting of renal, ear and cognitive disorders (though partially expected) should not be overlooked. The considerable vasodilator effects exhibited by sacubitril/valsartan might impair renal perfusion, leading to clinically important rise in the serum creatinine level and acute renal injury. Clinicians should close monitor sacubitril/valsartan treated patients for the occurrence of acute kidney injury, considering that it represents a life-threatening DME. Moreover, chronic kidney disease (CKD) is commonly associated with heart failure, given that patients with CKD have greater prevalence of traditional heart failure risk factors as well as unique kidney-specific risk factors [35-37]. The significant disproportion for ear disorders may be likely associated with well-known AEs of loop diuretics (namely hypoacusis) used in the management of congestive heart failure [18].

Our analysis found that unexpected AEs only accounted for less than 2% of PTs showing statistically significant disproportionality. *Hepatic cyst* and *nipple pain* exhibit weak clinical relevance and may be likely considered incidental findings in patients treated with sacubitril/valsartan. On the other hand, clinicians should be aware that *pyoderma gangrenosum*, although rare (only four cases recorded), might be a non-negligible AE associated with sacubitril/valsartan. *Pyoderma gangrenosum* is an autoinflammatory neutrophilic dermatosis, which may progress to disabling complications, and was associated with certain medications (mainly colony-stimulating factors and small-molecule tyrosine kinase inhibitors) [38]. However, in our cases, concomitant drugs known to be associated with *pyoderma gangrenosum* were not found.

We acknowledge the limitations of our study, mainly related to the inherent nature of FAERS data, which do not allow to establish a causal relationship between drug exposure and occurrence of AE [12]. Given the lack of a denominator and the under-reporting phenomenon, the ROR and its magnitude cannot quantify the real risk in clinical practice, informing only an increased risk of AE reporting and not of AE occurrence. Consequently, incidence cannot be provided by spontaneous reports. Moreover, verification of events through clinical features, including laboratory and instrumental tests, comorbidities and adjustment of therapeutic regimens is limited.

However, FAERS is representative of the worldwide real-life use of drugs, which cannot be fully captured by clinical trials. Our attempt to control for main confounders (adjustment for co-medications and dataset restriction to cardiovascular area) and major bias (notoriety bias is not expected considering that no

regulatory warnings were issued) strengthened the clinical implications of these findings. Finally, we applied an original score to assess the clinical impact of relevant disproportionality signals. Although its accuracy cannot be determined (and was not the aim of the work), our score is based on well-established criteria showing unquestionable clinical relevance (i.e. mortality rate, classification as DME or IME), including biological plausibility in order to prioritize AEs of clinical interest, thus also supporting identification of preventive strategies.

In conclusion, this real life safety assessment of sacubitril/valsartan found increased reporting of cardiovascular and renal AEs, although largely predictable and expected. Early occurrence of SCD is likely to reflect the underlying arrhythmogenic substrate and calls for careful monitoring, including therapy reconciliation strategies to minimize the pro-arrhythmic burden related to co-medications, particularly in the first weeks after the initiation of sacubitril/valsartan awaiting for delayed anti-arrhythmic effect of reverse remodelling.

Further investigations are warranted on appropriate preventive strategies: until differently demonstrated, initiation of sacubitril/valsartan should not preclude the use of implantable or external defibrillators to obtain the proper level of reverse remodelling, especially in high-risk patients.

In the meantime, considering the evolving use of sacubitril/valsartan, pharmacovigilance plays a key role in promoting risk-benefit assessment through active clinical surveillance, especially for unexpected AEs.

Author contributions

MG contributed to the design of the work, analysis, interpretation of data, and drafted the manuscript. ICA contributed to the design, acquisition, analysis and interpretation of data, and critically revised the manuscript. ID and FDP contributed to the conception of the work, interpretation of data, and critically revised the manuscript. ER contributed to the conception and design of the work, analysis and interpretation

of data, and critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Figure legend

Figure 1 - Flowchart of disproportionality analysis performed at preferred term (PT) level. Green light: weak clinical priority; Yellow light: moderate clinical priority; Red light: strong clinical priority. AEs: adverse events; PTs: preferred terms.

Table 1 – Semi-quantitative score assessing clinical priority of adverse events showing statistically significant disproportionality. A score between 0-4, 5-7 or 8-10 identifies respectively relevant signals with weak (green light), moderate (yellow light) or strong (red light) clinical priority.

Clinical priority features	2 points	1 point	0 points
No. of events	> 50	10-50	< 10
Magnitude of the lower limit of the 95% CI of the ROR	> 5	2-5	1-2
Mortality rate	> 50%	25-50%	< 25%
Important or designated medical events	Designated medical event	Important medical event	None
Biological plausibility	Established on the basis of mechanism of action of sacubitril/valsartan or heart failure-related	Supposed on the basis of preclinical evidence or presumed comorbidities or concomitant drugs	No clear biological plausibility can be retrieved

ROR: reporting odds ratio; CI: confidence interval.

Table 2 – Demographic data.

	Cases	Non-cases
Overall number of reports	20.021	1.128.887
Sex		
F	5.738 (28.7%)	612.911 (54.3%)
M	12.103 (60.5%)	427.585 (37.9%)
Missing	2.180 (10.8%)	88.391 (7.8%)
Age (years)		
<10	2 (0.0%)	12.627 (1.1%)
10-19	4 (0.0%)	13.857 (1.2%)
20-29	28 (0.1%)	19.254 (1.7%)
30-39	103 (0.5%)	34.655 (3.1%)
40-49	277 (1.4%)	67.497 (6.0%)
50-59	760 (3.7%)	140.178 (12.4%)
60-69	1.513 (7.6%)	203.267 (18.0%)
70-79	1.674 (8.4%)	179.412 (15.9%)
≥80	1.232 (6.2%)	96.720 (8.6%)
Missing	14.428 (72.1%)	361.420 (32.0%)
Reporter Country		
North America	8.194 (40.9%)	806.116 (71.4%)
South America	228 (1.1%)	18.507 (1.6%)
Europe	2.096 (10.5%)	195.309 (17.4%)
Asia	275 (1.4%)	66.020 (5.8%)
Oceania	178 (0.9%)	7.865 (0.7%)
Africa	43 (0.2%)	2.416 (0.2%)
Missing	9.007 (45.0%)	32.654 (2.9%)
Reporter Type		
Consumer	10.578 (52.8%)	507.281 (44.9%)
Lawyer	0 (0.0%)	14.685 (1.3%)
Medical Doctor	5.600 (28.0%)	272.891 (24.2%)
Pharmacist	232 (1.2%)	77.466 (6.9%)
Other healthcare professionals	3.572 (17.8%)	213.875 (18.9%)
Missing	39 (0.2%)	42.689 (3.8%)
Role code		
Primary Suspect	19.869 (99.2%)	NA
Secondary Suspect	152 (0.8%)	NA
N. of co-reported drugs*		
<5	16.325 (79.6%)	NA
≥5	4.186 (20.4%)	NA
Outcome		
Congenital Anomaly	0 (0.0%)	1.324 (0.1%)
Death	2.425 (12.1%)	90.882 (8.1%)
Disability	122 (0.6%)	16.148 (1.4%)
Hospitalization	2.878 (14.4%)	281.194 (24.9%)
Life-Threatening	359 (1.8%)	34.697 (3.1%)
Other	3.253 (16.2%)	244.253 (21.6%)
Missing	10.984 (54.9%)	460.389 (40.8%)

NA: not applicable due to inability to identify an index drug.

* excluding uncodified medications and substances not formally considered as medications.

Table 3 - Designated medical events showing statistically significant disproportionality.

Designated medical events	No. cases	ROR adj	Death	Biological plausibility	Priority level (score)
RENAL FAILURE	388	2,52 (2,26-2,8)	92	Expected	Moderate (7)
ANGIOEDEMA	309	1,76 (1,56-1,98)	10	Expected	Moderate (6)
VENTRICULAR FIBRILLATION	46	1,78 (1,29-2,38)	22	Disease-related	Moderate (6)
SUDDEN CARDIAC DEATH	42	12,82 (8,53-19,13)	42	Disease-related	Strong (9)

ROR adj: adjusted reporting odds ratio (see text for details).