

Suspected cardiovascular side effects of two COVID-19 vaccines

Karla J. Lehmann

Retired

Current Address: Franz-Liszt-Str. 7a
D-01219 Dresden

Corresponding author:
Karla J. Lehmann
E-Mail: karla.lehmann@t-online.de

Abstract

Fatalities or cardiovascular side effects of vaccines were rather uncommon in the past. So far, numerous reports of side effects and deaths associated with Covid-19 vaccination have been accepted behind the background of the pandemic situation and the priority vaccinated elderly population at the beginning of the vaccination campaign. Cardiac and heart circulatory disturbances resp. cardiovascular side effects associated with the application of Covid-19 vaccines have not been recognized up to now with the exception of thrombotic/embolic side effects and cases of myo-/pericarditis. But the mechanism of action suggests that downregulation of ACE2 by non-neutralised spike proteins may have cardiovascular effects.

The objective of this analysis was to determine the total number of reported adverse events and fatalities and to record suspected important cardiovascular adverse events up to the cut-off date in European countries. Therefore, a current review/analysis of spontaneously reported fatalities as well as of adverse events after application of Covid-19 vaccines has been performed. Data were retrieved from the EudraVigilance web reports of the European Medicines Agency (EMA), partly also from the safety reports of the German PEI.

Covid-19 vaccine-associated suspected side effects and related deaths are alarming. Surprisingly, numerous cardiovascular reactions were reported, many of which were life-threatening. Cardiac and heart circulatory caused fatalities alone accounted for about 33% of all Comirnaty^R vaccine-related deaths.

The second most important side effects were vascular thrombotic/embolic side effects, often also associated with serious consequences. Based on their quality and quantity, these side effects seem to be characteristic for spike-producing vaccines and do not appear to be substance-specific. Further investigations are needed to clarify the approximately 3.5 times more frequent cases of sinus vein thrombosis and the some different frequent cases of thrombotic/embolic events after Vaxzevria^R.

The hypothesis could be confirmed. Because of their importance and their sometimes life-threatening consequences, cardiovascular side effects need to be better communicated.

Limitations of the investigation result from the individual reporting and recording procedure, the lack of detailed individual information and the lack of an appropriate comparison population.

Introduction

It is very well recognized that the coronavirus SARS-CoV-2 needs the membrane-bound aminopeptidase ACE2 (angiotensin-converting enzyme 2) for cell entry before replication will start. Responsible for binding to the receptor ACE2 is subunit S1 of the viral spikes with its receptor binding domain (RBD). The S1-protein–receptor interaction determines the tissue tropism of the virus. It is likely that one of the reasons for its specific dangerousness and multi-organ toxicity is the expression of ACE2 in numerous organ tissues, such as those of the lung, heart, vascular system, gastrointestinal tract, skin or central nervous system [1, 2, 3].

Since ACE2 plays a potent counterregulatory role in the RAAS pathway, its downregulation by SARS-CoV-2 or by isolated spikes can result in activation of the RAAS, particularly in an increase in Angiotensin II. Acute pathophysiologically harmful consequences might occur, such as acute blood pressure increase, hypertensive crisis, circulatory collaps, myocardial ischemia, infarcts, strokes etc. Numerous cardiovascular manifestations of Covid-19 disease have been reported [4,5], but these appear to be missing from the side effect profile of spike-producing vaccines summarized in the marketing authorization holder's product characteristics (SmPC).

Additionally, a recent letter to the Medicines and Healthcare Products Regulatory Agency drew attention to the high number of COVID-19 vaccine-attributed deaths (1,253) and adverse drug reactions (ADRs, 888,196 from 256,224 individual reports) that have been reported for all vaccines until May 26th 2021 via the Yellow Card system in the UK [6]. Also

in Germany, an unexpectedly high number of adverse reactions and of fatalities related to Covid-19 vaccination (n=79,106 resp. 873 [8]) were observed within the first 5 months since the start of vaccination. An explanation for this phenomenon does not exist to date.

We asked the following questions: 1. Can the high number of Covid-19 vaccine attributed side effects and deaths reported for the UK and Germany be confirmed for other European countries? 2. Is there an association between cardiovascular side effects and Covid vaccination?

I performed an analysis first for total individual cases suffering from any suspected side effects, as well as from related fatal outcomes, collected in the EudraVigilance database for the four vaccines that were granted the “Conditional Marketing Authorization” (CMA).

In a second step, I focused on suspected reported cardiovascular side effects of the mRNA-Vaccine Comirnaty^R and the vector vaccine Vaxzevria^R which can be potentially life-threatening.

Methods

This review/analysis is not based on a clinical trial. It deals with the evaluation of anonymously reported adverse events of vaccinated healthy individuals in publicly available databases or reports. Identification of individuals was not possible. According to the Ethics Committee of the Saxon State Medical Association (SLÄK), an ethics vote is not necessary for anonymised, non-personalised data.

The primary objective was to determine the total number of reported adverse events and deaths and to record suspected cardiovascular adverse events.

Data were retrieved from Web Reports of EudraVigilance [7] of the European Medicines Agency (EMA) and the Safety report from the German PEI [8].

EudraVigilance is a system designed for the reporting of suspected side effects. The EudraVigilance system allows the detection of signals of suspected side effects that were previously unknown and of new information on known side effects. Therefore, it seems to be suitable to help answer the questions raised.

The EudraVigilance database is updated weekly and the data is constantly growing. The cut-off dates were June 5th (all suspected adverse reactions and related fatalities as well as cardiac- and heart-circulatory system-ADRs after vaccination with Tozinameran/Comirnaty^R) and 12th June 2021 (CNS and peripheral suspected vascular adverse reactions after vaccination with Tozinameran/Comirnaty^R and Vaxzevria^R).

The total number of deaths was evaluated by summing the fatal outcomes in all 27 defined reaction groups (Table 6 of the EudraVigilance system).

The number of individual cases for a selected reaction resp. search term were retrieved from the reaction groups of Tab 6, which provides the most detailed level of information. Because several defined reaction groups of the EudraVigilance Web Reports contain information on relevant search terms/selected reactions (e.g. cardiac arrest, cardiac death, sudden cardiac death, sudden death), all reaction groups had to be systematically searched for these selected reactions.

The running total of individual cases available in Tab 1 of EudraVigilance was the value that I have used to quantify the total number of individual cases that have been reported to EudraVigilance for the selected vaccine.

All information on included suspected side effects should primarily not be considered or interpreted as meaning that the vaccine causes the observed effect or is unsafe to use.

Results

The global side effect profile of the COVID-19 vaccines in the EudraVigilance database is more comprehensive and differentiated compared to the German safety reports. Those

vaccinated were predominantly between the ages of 18-64 years (66-81.6%). Among them, 67–74% were women and 24-31% men.

From a total of 525,907 individual cases (approximately 0.2% of all vaccinations reported up to June 5th 2021) for all four vaccines associated with any suspected side effects, 13,867 were fatalities (2.64%) (Table 1).

Table 1: Total individual cases with any adverse reaction (a) and fatal outcomes (b) after vaccination up to June 5th 2021 (EudraVigilance, 7) and up to May 31st 2021(Germany, 8).

Vaccine	European countries	Germany
Comirnaty® (since December 8 th 2020 in the UK)	a) 212,053 / 180 days (1,178/day) b) 6,732	a) 34,735/156 days (223/day) b) 674
Moderna (available since approximately January 11 th 2021)	a) 40,712/146 days (279/day) b) 3,821	a) 8,319/141 days (59/day) b) 19
Vaxzevria® (available since approximately February, 1 st 2021)	a) 264,549/125 days (2,116/day) b) 2,848	a) 34,870/120 days (291/day) b) 162
Janssen (since about March 12 th 2021)	a) 8,593/86 days (100/day) b) 466	a) 733/80 days (0.9/day) b) 5
Total	a) 525,907 b) 13,867 (2.64 % of a, 77/day)	a) 79,106 (449 unspecified) (507/day) b) 873 (13 unspecified) (1.1 % of a; 5.6/day)

On average, 1.1% of vaccinated persons with ADRs in Germany and 2.64 % of Europeans died in connection with ADRs. The high number of individual cases with adverse reactions and related deaths, especially in connection with Vaxzevria®, is atypical for any vaccine. Compared to the 2014 annual total number of side effects of all vaccinations in Germany [9] (3,720 cases; 10.2/day with a total of only three deaths in adults and 9 in children; 0.03 cases/day) and to the average annual rate in Germany [10] (3.8 reports/day and 0.028 deaths/day for adults), there was a 50–133-fold increase in reported side effects in temporal relation to COVID-19 vaccinations and a 187–200-fold increase in vaccination ADR-related fatalities.

When reviewing the 27 reaction groups in the EudraVigilance database, many cardiac and heart-circulatory ADRs as well as CNS and peripheral cardiovascular reactions were noticed. That had not previously been the focus of attention. Suspected cardiovascular reactions and blood coagulation-related laboratory values are presented for Tozinameran/Comirnaty® (Tables 2 and 3) and the vaccine from AstraZeneca (Table 4). The search terms within the reaction groups are mentioned in Tables 2 to 4.

Suspected cardiac and heart circulatory side effects associated with Comirnaty^R

Of a total of 1719 cardiac arrests associated with Comirnaty^R vaccination (0.8% of individual cases), the majority of those affected could not be saved. 1575 (92%) died (see Tab. 2).

Table 2: Comirnaty®/Tozinameran vaccine - suspected adverse reactions related to cardiac and heart circulatory disorders from the EudraVigilance database up to June 5th 2021

Search terms	Number of individual cases with suspected adverse reactions (EudraVigilance) [7]	% from 212,053 total individual cases [7]	Number of fatal outcomes (% of cardiovascular suspected adverse reactions) [7]
Cardiac disorders			
Cardiac arrest, cardio-respiratory arrest, cardiac death, death, sudden cardiac death, sudden death (*1,*2)	1,719	0.8 %	1,575 (92 %)
Acute left ventricular failure, cardiac failure, acute congestive heart failure, left ventricular failure, right ventricular Failure (*2)	524	0.25 %	173 (33 %)
Acute myocardial infarction, myocardial infarction (*2)	703	0.33 %	206 (29.3 %)
Acute coronary syndrome, angina pectoris, coronary arteriospasm, cardiovascular disorder, cardiovascular insufficiency, coronary artery disease, occlusion, stenosis, myocardial ischemia (*2)	637	0.3 %	64 (10 %)
Myocarditis, pericarditis, pleuropericarditis, Autoimmune-myocarditis (*2)	562	0.27 %	9 (1.6 %)
Chest pain (*1)	3,008	1.42 %	35 (1.2 %)
Heart-circulatory disorders			
Tachycardia (*2, *3)	5,788	2.7 %	40 (0.69 %)
Arrhythmia, tachyarrhythmia, atrial and ventricular fibrillation and flutter (*2, *3)	1,809	0.85 %	74 (4.1 %)
Circulatory collaps, peripheral circulation failure (*4)	255	0,12 %	34 (13.3 %)
Hypertension, increased blood pressure (*3,*4) Hypertensive crisis, accelerated hypertension, hypertensive emergency, malignant hypertension (*4)	5,579 551 Σ = 6,130	2.9 %	29 (0.47 %)
Palpitations (*2)	2,726	1.3 %	1
Extrasystoles (*2)	335	0.16 %	0

*) Oracle BI interactive dashboard reported suspected reactions from the reaction groups: 1 -

general disorders and administration site conditions, 2 - cardiac disorders, 3 - investigations, 4 - vascular disorders

Acute heart failure (including 8 cases of right heart failure) occurred in 524 cases (0.25% of the total amount of adverse events). The severity of the disease resulted in 173 deaths (33%). Of 703 heart attacks, 206 were fatal (29.3%). Acute circulatory disturbances of the heart muscles in connection with the vaccination were suffered by 637 vaccinated persons, of whom approx. 10% (n=64) died. Chest pain (n=3008) with 35 fatal outcomes was most likely attributable to ischaemic myocardial disorders or damage. It can also be the first sign of myocarditis.

A total of 561 cases of myocarditis or pericarditis (0.27%) and one case of autoimmunmyocarditis were fatal in only 1.6% of cases.

With 6130 reports (2.9% of all Comirnaty^R individual case reports), hypertension and hypertensive crisis (including 29 deaths) ranked first among cardiovascular side effects (see Tab. 2), followed by 5788 cases of tachycardia with 40 fatal outcomes. A total of 1809 cases reported arrhythmia, tachyarrhythmia, atrial and ventricular fibrillation and flutter. 74 cases (4.1%) were fatal. No statement can be made about the exact increase in blood pressure in mmHg or the extent of the heart rate changes due to missing data. However, it can be assumed that the reporting physician only sends a report in case of considerable abnormality.

Blood pressure reductions were not included in the analysis, despite numerous reports (approx. 1% of all adverse experiences), because of their constitutional or secondary symptomatic character. Similarly, blood pressure changes that were not clearly defined (e.g. "abnormal blood pressure,") were not included.

A comparatively high rate of death (13.3%) was observed in association with circulatory collapse and cardiovascular failure in 255 vaccinated individuals.

The total number of cardiac and heart circulatory caused fatalities associated with Comirnaty^R was 2,240 (summarized from Table 2), representing approximately 33% of all reported vaccine-related deaths associated with Comirnaty^R vaccination (n=6,732, see Table 1).

Palpitations (n=2,726 with only one fatal outcome) and extrasystoles (n=335 without any fatality) were more likely to be subjective complaints.

CNS vascular side effects

Among the cardiovascular side effects of the CNS in association with Comirnaty^R vaccination, stroke dominated with 1003 cases, a high percentage of which were fatal (n=124, 12.4%, pl. see Table 3).

Table 3: Comirnaty®/Tozinameran vaccine - CNS and peripheral suspected vascular adverse reactions from the EudraVigilance database up to June 12th 2021 [7]

Search terms	Number of individual cases with suspected adverse reactions (EudraVigilance) [7]	% from 223,594 total individual cases [7]	Number of fatal outcomes (% of suspected adverse reactions) [7]
CNS vascular disorders			
Stroke (ischemic, embolic, haemorrhagic) , infarction, microinfarction, lacunar infarction or stroke (*5)	1,003	0.45	124 (12.4 %)
CNS haemorrhage (*5)	328	0.15	139 (42.4 %)
CNS ischemia, vascular	110	0.05	14 (12.7 %)

occlusion, stenosis (*5)			
CNS thrombosis, embolism, among them: venous sinus thrombosis (*5)	254	0.11	26 (10.2 %)
	90	0.04	7 (7.8 %)
Transient ischemic attack (*5)	455	0.2	5 (1.1 %)
CNS vasculitis (*5)	10	0.004	0
Peripheral vascular disorders			
Thrombosis, embolism, microembolism among them: pulmonary embolism Total(*4, *6-9)	2778 1786 1639	0.73	84 (3 %) 155 (8.7 %) 146 (8.9 %)
	4564	2.04	239 (5.24 %)
haemorrhage (*4, *6-9)	523	0.23	39 (7.5 %)
vasculitis, phlebitis, arteritis, vascular disorder (*4, *8, *9)	431	0.19	10 (2.3 %)
ischaemia, vascular occlusion, stenosis (*4, *6-9)	161	0.07	29 (18 %)
Lab-values			
A) indicating increased bleeding (total): among them: - immune-thrombocytopenia, - thrombozytopenia, thrombozytopenia purpura, thromb. thrombocytopenic purpura (*3, *6)	983	0.44	56 (5.7 %)
	165	0,07	2 (1.2 %)
	497	0,22	34 (6.84 %)
B) indicating activated blood coagulation (total): among them: - D-dimer increased, - disseminated intravascular coagulation, (*3, *6)	221	0.1 %	20 (9.0 %)
	131	0.06	5 (3.8 %)
	13		6 (46 %)

*Oracle BI interactive dash board: reported suspected reactions from the reaction groups 1-general disorders and administration site conditions, 2-cardiac disorders, 3-investigations, 4-vascular disorders, 5-nervous system disorders, 6-blood and lymphatic system disorders, 7-gastrointestinal disorders, 8-renal and urinary disorders, 9-respiratory, thoracic and mediastinal disorders.

All without exactly defined values like ,abnormal', undefined disorder etc.

A: bleeding/coagulation time prolonged, activated partial thromboplastin time prolonged, blood fibrinogen decreased, factor 8 decreased, coagulation factor decr, platelet count decr., prothrombin level decr., prothrombin time prolonged, heparin induced thrombocytopenia, coagulopathy, hypocoagulable state

B: activated partial thromboplastin time shortened, blood fibrinogen/coagulation factor increased, fibrin, platelet count incr., prothrombin level incr., prothrombin time shortened, hypercoagulation, hyperfibrinogenaemia, pl. anisocytosis, thrombocytosis.

Life-threatening intracerebral haemorrhages (n=328) were fatal in 139 vaccinated persons (42.4%). Transient ischaemic attacks were comparatively frequent (n=455) but usually not fatal. In the context of thrombotic-embolic events (n=254), 90 cases of venous sinus thrombosis were registered, of which 7 vaccinated persons died (7.8%). Overall, 10.2% died.

Vascular occlusion, stenosis and ischemia (n=110) were rarer but still serious events (12.7% fatal). Vasculitides (n=10) occurred very rarely; no deaths were reported.

Those vaccinated with Vaxzevria^R (pl. see Table 4) suffered strokes slightly less frequently (n=848 or 0.3% of individual cases) than those vaccinated with Tozinameran (n=1003 or 0.45% of individual cases). The resulting deaths were also less frequent (n=67 vs. 124). Transient ischaemic attacks, on the other hand, were relatively common (0.2% of all individual cases) and remained without serious consequences in most cases (only 0.35% fatal outcomes). Life-threatening central haemorrhages were equally frequent after Tozinameran (n=429 vs. 328 corresponds to 0.15%); they were fatal in about 30% of those affected (n=130).

Table 4: Vaxzevria® vaccine – CNS and peripheral suspected vascular adverse reactions from the EudraVigilance database up to June 12th 2021 [7]

Search terms	Number of individual cases with suspected adverse reactions (EudraVigilance) [7]	% from 282 643 total individual cases [7]	Number of fatal outcomes (% of suspected adverse reactions) [7]
CNS vascular disorders			
Stroke (ischemic, embolic, haemorrhagic), infarction, microinfarction, lacunar infarction or stroke (*5)	848	0.3	67 (7.9 %)
CNS haemorrhage (*5)	429	0.15	130 (30.3 %)
CNS ischemia, vascular occlusion, stenosis (*5)	76	0.03	7 (9.2 %)
CNS thrombosis, embolism, among them: venous sinus thrombosis (*5)	739 405 (54.8 %)	0.26 0.14	111 (15 %) 54 (13.3 %)
Transient ischemic attack (*5)	576	0.2	2 (0.35 %)
CNS vasculitis (*5)	7		0
Peripheral vascular disorders			
Thrombosis, embolism, microembolism among them: pulmonary embolism Total(*4, *6-9)	5,312 (64.8 %) 2,882 (35.2 %) 2,495	2.9	155 (2.9 %) 182 (6.3 %) 169 (6.8 %) 337 (4.1 %)
haemorrhage (*4, *6-9)	8,194 916	0.23	22 (2.4 %)
vasculitis, phlebitis, arteritis, vascular disorder (*4, *8, *9)	702	0.19	4 (0.6 %)
ischaemia, vascular occlusion, stenosis (*4, *6-9)	188	0.07	18 (9.6 %)
Lab-values			
A) indicating increased bleeding (total): among them:	2,861	0.44	123 (4.3 %)
- immune-thrombocytopenia,	366 (12.8 %)	0.13	11 (3 %)
- thrombozytopenia, thrombozytopenia purpura, thrombotic thrombocytopenic	1,656 (57.9 %)	0.59	93 (5.5 %)

purpura (*3, *6)			
B) indicating activated blood coagulation (total): among them:	562	0.2	32 (5.7%)
- D-dimer increased,			13 (3.4%)
- disseminated intravascular coagulation, (*3, *6)	387 (68.9 %) 53 (9.4 %)		15 (28.3%)

*Oracle BI interactive dash board: reported suspected reactions from the reaction groups 1-general disorders and administration site conditions, 2-cardiac disorders, 3-investigations, 4-vascular disorders, 5-nervous system disorders, 6-blood and lymphatic system disorders, 7-gastrointestinal disorders, 8-renal and urinary disorders, 9-respiratory, thoracic and mediastinal disorders

All without exactly defined values like ,abnormal‘, undefined disorder etc.

A: bleeding/coagulation time prolonged, activated partial thromboplastin time prolonged, blood fibrinogen decreased, factor 8 decreased, coagulation factor decr, platelet count decr., prothrombin level decr., prothrombin time prolonged, heparin induced thrombocytopenia, coagulopathy, hypocoagulable state

B: activated partial thromboplastin time shortened, blood fibrinogen/coagulation factor increased, fibrin, platelet count incr., prothrombin level incr., prothrombin time shortened, hypercoagulation, hyperfibrinogenemia, pl. anisocytosis, thrombocytosis.

CNS thromboses and embolisms were observed significantly more frequently than tozinameran (0.26% vs. 0.11%). In particular, the high proportion of venous sinus thrombosis with 405 cases (54.8% of central thrombosis cases) and 54 fatalities (13.3%) was striking.

Rarely, cerebral ischaemia or vascular occlusion (n=76) were reported, although these were associated with considerable lethality (9.2%) when they occurred. Central vasculitides were very rare (n=7) and did not seem to have any particular relevance for the central side effect profile.

Peripheral vascular side effects

A total of 4564 cases of thrombotic/embolic events (2.04% of all individual cases) were reported after vaccination with Tozinameran (pl. see tab. 3). These include 2778 thrombosis cases with 84 deaths (3%) and 1786 embolism cases, which were fatal in 155 (8.7%) vaccinated persons. Most of the embolism cases (91.8%) involved the lungs (n=1639). Of these affected, 8.9% (n=146) died.

Peripheral hemorrhages were slightly more common than central hemorrhages (n=523), but less dangerous (7.5% fatal). Inflammatory changes in the vessels were observed more frequently than in the CNS. They resulted in a comparatively low fatality rate (2.3%).

Ischaemic conditions, vascular occlusions and stenoses occurred approximately equally often compared to central disorders (0.05-0.07%) and were also similarly serious (13-18% fatalities).

Increased blood coagulation was reported in 221 individual laboratory reports (0.1% of all individual cases); 9% were fatal. The proportion of increased D-dimer was only 131 cases associated with a 3.8% fatal outcome.

The frequency of laboratory values indicating delayed or inhibited coagulation exceeded the total number of hemorrhages (n=851), with 983 individual reports. The death rate associated with the laboratory values was 5.7%. The number of immune thrombocytopenias was 165, and the number of related deaths was 1.2%. A total of 497 thrombocytopenias, including 34 deaths (6.84%), were reported.

Peripheral thrombosis and embolisms dominated the side effects associated with blood coagulation disorders after vaccination with Vaxzevria^R, with a total of 8,194 cases (2.9% of individual cases, pl. see tab. 4). This is slightly higher than after Tozinameran (2.04%). 337 cases (4.1%) were fatal. Most of the embolism cases (86.6%) involved the lungs (n=2495). Of these affected, 6.8% (n=169) died.

There was no difference in the percentage of peripheral haemorrhages between the AstraZeneca vaccine and tozinameran (0.23% of all individual cases) or in cases with peripheral inflammatory vascular diseases (0.19%) and in cases suffering from ischaemia and vascular occlusion (0.07%). It should be noted, however, that lethal outcomes in these three categories were significantly less frequent in connection with the AstraZeneca vaccination than after tozinameran.

Laboratory findings of increased blood clotting were reported in 562 individual cases (0.2%); 5.7% (n=32) were fatal. These values are out of proportion to the 8,933 cases of central and peripheral thrombosis/embolism observed, unless considered an add-on. The same applies to the detection of elevated D-dimer (n=387 cases associated with 3.4% fatal outcomes).

The incidence of laboratory values indicating delayed or inhibited blood coagulation was higher (n=2,861 individual cases) than the total number of reported cases of haemorrhages (n=1,345). The case fatality rate associated with the laboratory values was 4.3%.

The number of immune thrombocytopenias was 366, and the number of related deaths was 3%. A total of 1656 thrombocytopenias, including 93 deaths (5.5%), were reported.

Discussion

Covid-19 vaccine-associated suspected side effects and related deaths are alarming in European countries and in Germany, as already reported by Lawrie for UK [6]. It is 50 to 200 times the number of any vaccinations during recent years in Germany. Presumably, the reporting rates would be even higher if the known underreporting could be reduced.

One of several reasons for underreporting is ignorance of possible side effects. In the clinical trials that led to the approval of, e.g., Comirnaty^R, predominantly local reactions were identified [11]. Pain, swelling and redness at the injection site, chills, fever, fatigue, headache, muscle and joint pain and/or nausea occurred in 10% to approx. 84% of cases. Few cases of anaphylaxis, facial paresis and appendicitis have been described. These comparatively harmless side effects are well communicated to the public and medical profession alike.

Some important cardiovascular side effects after COVID-10 vaccination were recently reported for the first time [19]. Over a comparatively short period of time (between December 15, 2020 and January 24, 2021), 4,863 (out of a total of 103,954 side effects = 4.7%) cardiovascular adverse events have been analysed. The most common events were tachy-/arrhythmias and increases in blood pressure. Myocardial infarctions, cardiac arrests and circulatory collapses were more common in the elderly (> 75 years), while blood pressure increases and arrhythmias were common in all age groups. No case of acute heart failure, stroke, sinus vein thrombosis or embolism has been reported.

However, after only a few months of pharmacovigilance more, the spectrum of reported ADRs has been expanded considerably. This report does not claim to be a complete analysis of all collected individual cases after vaccination, but focuses on acute important cardiovascular adverse reactions that have not been considered so far, but for which there exists a plausible hypothesis.

1. Cardiac arrests reported in association with Comirnaty^R vaccination, cases of acute heart failure, of acute myocardial infarction and cases of acute cardiovascular disorders/myocardial ischemia as well as many cases of chest pain are a matter of concern. Some of these disorders occur much more frequently, at least as frequently as the cases of myocarditis/pericarditis (n=562), and, moreover, are much more serious (fatal outcome between 10-92% vs. 1.6% in cases of myocarditis/pericarditis). In contrast to myocarditis/pericarditis, in which the European pharmacovigilance authority PRAC has recently identified as a possible side effect of mRNA vaccines [18], the other more serious side effects have not yet received any attention.

The spectrum of suspected ADRs is dominated by 6,130 reports of acute elevated blood pressure (2.9% of all reported individual cases), including cases of hypertensive crisis followed by cases suffering from tachycardia (n= 5,788, 0.7% fatal outcome) and arrhythmias (n=1,809, 4.1% fatal outcome). These cases of blood pressure increase are more than anecdotal events reported by Zappa [12] and should create a strong signal.

Interestingly, this spectrum is qualitatively quite similar to the cardiovascular symptomatology of Covid-19 disease [4, 5].

The pathophysiology underlying cardiovascular manifestations is probably multifactorial involving pre-existing comorbidities and may be exaggerated by downregulation of ACE2, the physiological counterpart of an activated renin-angiotensin-aldosterone-system pathway. ACE2 is expressed in the endothelium of coronary arteries, myocytes, fibroblasts, epicardial adipocytes, vascular endothelial and smooth cells, the gut, tracheal and bronchial epithelial cells, type 2 pneumocytes, macrophages, the kidney, testis and brain [5, 13]. Therefore, it is not surprising that infection with SARS-Cov 2 or induced spike protein production trigger symptoms in organs equipped with ACE2 receptors.

The findings of this analysis confirm the hypothesis that isolated spikes may be able to trigger serious, sometimes life-threatening cardiovascular reactions. The reason for this could be the dysregulation of the RAAS initiated by ACE2 downregulation. Subjects with pre-existing ACE2-deficiency may be particularly at risk. Whether ACE2 upregulation by ACEIs/ARBs [14] counteracts these effects is unclear up to date and should be the subject of further investigation.

In any case, more attention should be paid to cardiac and heart circulatory side effects associated with Covid-19 vaccination. After all, they accounted for about 33% of the total fatalities associated to Comirnaty^R.

2. Thrombotic/embolic complications in the CNS and periphery that have been reported after vaccination have also been observed in critically ill COVID-19 patients [5]. Because of their frequency and dangerousness, they require special attention and knowledge.

Strokes and intracerebral haemorrhages were observed after the application of both vaccines. However, venous sinus thrombosis associated with Vaxzevria^R was approximately 3.5 times more frequent than after tozinameran (405 cases=0.14% vs. 90 cases= 0.04%) and more dangerous (13.3% fatal after Vaxzevria^R vs. 7.8%). In this context, a yet unknown reinforcing influence of the adenoviral vector should be considered. In some cases, a similarity to autoimmune heparin-induced thrombocytopenia (aHIT) has been postulated [8, 15].

Peripheral thrombosis or embolism is one of the dominant cardiovascular adverse reaction profile of the spike-producing vaccines. Related reports occurred slightly more frequently after Vaxzevria^R (2.9 %) than after Comirnaty^R (2.04 %). Embolism primarily affected the lungs (87-92% of all embolic cases) and was fatal in 7-9%. Mesenteric artery occlusions occurred, which is why peripheral vascular occlusions should be considered when an ileus occurs in connection with vaccination. Based on the ADR profile of Comirnaty^R, it appears

that the thrombotic/embolic risk is not exclusively vector vaccine-related. It may be a class-specific phenomenon of spike-producing vaccines.

Reports of increased blood coagulation (0.1-0.2%) are much fewer than the numerous cases of peripheral and CNS thrombosis/embolisms (2.15-3.16%). A cascade of different causes related to vaccination seems to be responsible for this phenomenon. Triggering by immunological processes or Ang II overactivation induced by ACE2 downregulation resulting in stimulation of coagulation and downregulation of NO, enhancement of sympathetic activity and vascular dysfunction are worthy of discussion. Platelet activation and aggregation triggered by SARS-Cov-2 and spike protein (involving ACE2) were already demonstrated in 2020 in COVID-19 patients [16]. This important finding should be included in the explanation of thrombosis cases after vaccination.

Numerous cases of immune thrombocytopenia (ITP) were reported more frequently after application of the AstraZeneca vaccine (0.13% = 130/100 000 vaccinated subjects) than after Comirnaty^R (0.074% = 74/100 000). Their proportion of blood clotting disorders was 16.8% after Comirnaty^R compared to 12.8% after Vaxzevria^R. Compared to the ITP prevalence in Germany (9-26/100 000 [17]), the proportion of affected persons among the vaccinated is high and points to a possible additional triggering factor by the vaccines.

The number of thrombocytopenias clearly exceeded that of ITP. The phenomenological recording does not allow any conclusions to be drawn about the causation or correlations with the extent of the thrombotic-embolic events. However, the twice as high values according to Vaxzevria^R (0.59% vs. 0.22% according to Comirnaty^R) require further research.

Limitations of the investigation result from the individual reporting and recording procedure, the lack of detailed individual information and the lack of an appropriate comparison population.

Conclusions

The quantity and quality of the analysed general side effects of COVID-19 vaccines and the specific cardiovascular side effects of Comirnaty^R and Vaxzevria^R are a matter of concern.

Most of the reported cardiovascular, sometimes life-threatening, side effects might be related to an increase in activity and/or dysregulation of the RAAS by ACE2 downregulation. Their share in the fatal side effects is considerable at approx. 33%.

Because of their frequency and importance, they should exert a signaling function and need to be better communicated. It is incomprehensible why cardiovascular adverse reactions, with the exception of myocarditis, have remained unconsidered thus far.

Furthermore, it is not plausible why thrombosis/thrombocytopenia provoked a signal effect only for vector-based vaccines and not for mRNA-based vaccines with essentially similar reported ADRs.

Prospective investigations should clarify in detail the causality between the reported suspected cardiovascular adverse events and the spike-producing COVID-19 vaccines.

Conflict of interest: no

Acknowledgement: For constructive discussions, critical comments and technical support, I am grateful to Em. O. Univ. Professor Dr. med. Hartmut Glossmann, Inst. f. Biochemical Pharmacology of the Medical. Faculty of the University of Innsbruck

References

1. Maier H J, Bickerton E and Britton P: Coronaviruses: An Overview of Their replication and Pathogenesis. *Coronaviruses*. 2015; 1282:1-23. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4369385/>
2. Donoghue M, Hsieh F, Baronas E, Godbout K, Gosselin M, Stagliano N et al.: A Novel Angiotensin-Converting Enzyme-related Carboxypeptidase (ACE2) Converts Angiotensin I to Angiotensin 1-9. *Circulation Research*. 2000: e1-e9 <https://doi.org/10.1161/01.RES.87.5.e1>
3. Lehmann, K J: Rezeptorvermittelte Wirkungen von SARS-CoV-2 und Spike-Proteinen, 26.2.2021; DOI:10.13140/RG.2.2.13081.13928; www.karla-lehmann.de
4. Zheng Y Y, Ma Y T, Zhang J Y, Xie X: Covid-19 and the cardiovascular system. *Nature Reviews cardiology* 2020: 17, 259-260
5. Gupta A, Madhavan M V, Sehgal K, Nair N, Mahajan S, Sehrawat T S et al. Extrapulmonary manifestations of COVID-19. *Nature Medicine* 2020 July (Vol.26), 1017-1032
6. Lawrie T: Letter to Dr. Raine/Medicines and Healthcare Products Regulatory Agency; 9 June 2021: Urgent preliminary report of Yellow Card data up to 26th May 2021
7. https://www.adrreports.eu/en/search_subst.html
8. Verdachtsfälle von Nebenwirkungen und Impfkomplicationen nach Impfung zum Schutz vor Covid-19, Sicherheitsbericht PEI vom 10.06.2021
9. PEI: Auswertung der Verdachtsmeldungen von Impfkomplicationen (01.01.2014-31.12.2014) liste-impfreaktionen-bewertung-2014.pdf
10. <http://52625146fm.pei.de/fmi/webd/#UAWDB>
11. Lehmann K: Was man zum Covid-19-Impfstoff Comirnaty^R wissen sollte! 7.1.2021; www.karla-lehmann.de
12. Zappa M, *European Journal of Internal Medicine*, <https://doi.org/10.1016/j.ejim.2021.06.013>
13. Verdecchia P, Cavallini C, Spanavello A and Angeli F: The pivotal link between ACE2 deficiency and SARS-Cov-2 infection. *Eur J Intern Med*. 2020 Jun; 76:14-20.
14. Bauer A, Schreinlechner M, Sappler N, Dolejsi Th, Tilg H, Aulinger B A et al. Discontinuation versus continuation of renin-angiotensinsystem inhibitors in COVID-

- 19 (ACEI-COVID): a prospective, parallel group, randomised, controlled, open-label trial *Lancet Respir Med* 2021 Jun 11;S2213-2600(21)00214-9. doi: 10.1016/S2213-2600(21)00214-9.
15. Greinacher A, Thiele Th, Warkentin Th E, Weisser K, Kyrle P A, Eichinger S.: Thrombotic thrombocytopenia after ChAdOx1 nCov-19 vaccination. *N Engl J Med.*: 2021 Jun 3;384 (22):2092-2101. doi: 10.1056/NEJMoa2104840. Epub 2021 Apr 9.
16. Si Zhang, Liu Y, Wang X, Yang L, Li H, Wang Y et al.: SARS-CoV-2 binds platelet ACE2 to enhance thrombosis in Covid-19. *J Hematol Oncol* 2020: 13: 120.
17. Matzdorff A, Meyer O, Ostermann H, Kiefel V, Eberl W, Kühne T, Pabinger H et al.: Immune Thrombocytopenia - Current Diagnostics and Therapy: Recommendations of a Joint Working Group of DGHO, ÖGHO, SGH, GPOH, and DGTI *Oncol Res Treat* 2018;41(suppl 5):1-30; <https://doi.org/10.1159/000492187>
18. blitz-a-t 12.07.2021: Myokarditis unter mRNA-Impfstoffen: Warnhinweise jetzt auch in Europa
19. Kaur, R J, Dutta S, Charan J, Bhardwaj P, Tandon A, Yadav D et al.: Cardiovascular Adverse Events Reported from COVID-19 Vaccines: A Study Based on WHO Database. *International Journal of General Medicine* 2021:14 3909–3927