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Suspected Causes of the Specific Intolerance Profile of Spike-Based Covid-19 Vaccines (Review/Analysis)

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ABSTRACT

The aim of this review is to provide explanations for many of the reported adverse reactions associated with spike-based Covid-19 vaccination and to draw appropriate conclusions.

Based on the comparatively disproportionate spectrum of adverse reactions of spike-based vaccines, an overwhelming body of evidence supports the consequences of the main mode of action of spike-based Covid-19 vaccines, namely the downregulation of angiotensin-converting enzyme 2 (ACE2) by spikes. This enzyme is a key protective counterregulator in the renin-angiotensin-aldosterone system. The renin-angiotensin-aldosterone system is not only responsible for cardiovascular homeostasis, but is also involved in pro-inflammatory, procoagulant, pro-fibrotic and immunological effects via its main vasoconstrictor effector, angiotensin II. This may explain the magnitude and diversity of the spectrum of side effects.

Other spike effects (cell fusion, binding to heparan sulphate, activation of Toll-like receptor 4), synergisms (increase in des-arg^9-bradykinin, catecholamines) and impairment of intestinal amino acid uptake complement and multiply the already adverse effects of spike-related downregulation of ACE2 on tolerability.

Spike-based Covid-19 vaccines are characterised by a class-specific profile of adverse reactions. A causal relationship between an activated renin-angiotensin-aldosterone system and vasoconstrictive and ischaemic sequelae can be considered to be proven. Therefore, stimulation of the renin-angiotensin-aldosterone system and co-medication with vasoconstrictive, catecholaminergic or TLR4- and DABK-activating and heparan sulphate-inhibiting drugs should be avoided for the duration of spike efficacy.

It has been shown that vaccine spikes are distributed systemically and are detectable in the body for longer than previously thought. According to current knowledge, the time window for assessing a causal relationship between vaccination and adverse reactions can be extended to up to six months.

The variability of adverse effects is likely to be comparatively high, especially for spike-inducing vaccines, as the occurrence and severity of adverse reactions can be influenced by numerous individual factors and counter-regulatory mechanisms. There are no findings on this.

The exceptionally wide range, frequency and severity of reported adverse reactions associated with spike-based Covid-19 vaccination exceeds the known level of conventional vaccination and is a cause for serious concern. From a pharmacological point of view, spikes are highly potent substances, but they are not innocuous antigens. Therefore, they do not appear to be suitable for preventive immunisation against comparatively harmless infections.

Keywords: Spike-based Covid-19 vaccination, spike induced adverse drug reactions, mode of action of spikes

Introduction

The benefits of vaccinating to prevent infectious diseases are undisputed. However, the safety requirements for vaccines are particularly high because they are administered to healthy people whose health status should not be affected.

The safety profile of Covid-19 vaccines should be especially favourable, as Covid-19 disease is in the vast majority of cases not life-threatening, but usually mild to moderate. The infectious fatality rate (IFR) has been calculated to be quite low at 0.27-0.36% [1, 2]. A representative mathematical analysis came to similar findings. The median IFR was 0.466% in April 2020 and fell by around 33% within 8 months to 0.314% (1 January 2021) before the vaccination campaigns began, with results varying greatly depending on age and country[3].

However, expectations associated with the novel spike-based vaccines, which were originally only conditionally authorised and developed in a very short time, have been disappointed. In Germany, for example, the number of PCR-confirmed infections surprisingly increased in 2021 compared with the previous year without vaccination. The expected decrease in Covid-19-related deaths did not occur [4]; in some countries, a surprising coincidence between vaccination rates and the number of excess deaths emerged [5].

In addition, since the start of the Covid-19 vaccination campaign, spontaneous reports of suspected adverse drug reactions (ADRs) and associated deaths have increased at an unusually high rate. The spectrum of adverse reactions is exceptionally broad compared to conventional vaccines and is very similar to the organ dysfunctions associated with Covid-19 [6].

The similarity of the systemic symptoms of Covid-19 disease in non-respiratory organs with the spectrum of ADRs of the vaccination suggested a common cause.

The most suspicious factor seems to be the efficacy of the spikes and their interactions, which could be causal for both the organ dysfunctions of Covid-19 and the class-specific side-effect spectrum of spike-based vaccines (mRNA-, adenovirus-vector, protein-based vaccines). Knowledge of these obvious, but so far ignored, backgrounds could help to improve diagnostic and therapeutic options.

The present analysis addresses the causation of selected important adverse reactions of spike-based vaccination and their consequences.

Methodology

The data analysed were taken from the publicly available EudraVigilance web reports of the European Medicines Agency (EMA). Reference was made to previously published data [6,7,8].

Numerous cases of thunderclap headache, reversible cerebral vasoconstriction syndrome (RCVS) and posterior reversible encephalopathy (PRES) related to Comirnaty® were added until 1 March 2024[9].

The scientific literature was reviewed for a possible association with the adverse effects of the spike-based Covid-19 vaccines.

Analysis and discussion

GENERAL FEATURES OF SPIKE-INDUCING AND SPIKE-BASED VACCINES

Spike-inducing vaccines (messenger ribonucleic acid mRNA- and adenovirus vector vaccines) have unique characteristics compared to conventional vaccines (live-attenuated/inactivated) and protein-based Covid-19 vaccines.

In the case of spike-inducing Covid-19 vaccines, the vaccine antigen is not administered in a defined, immunologically effective amount, but only the genetic code to induce intracellular production of the antigen. The spike glycoprotein selected from several possible candidates as an antigen must be produced by the recipient's organism itself. In this respect, spike-inducing vaccines could be described as precursor vaccines.

In principle, the receptor binding domain (RBD) of the subunit S1 of the spikes is responsible for the desired immune response. Spikes that are not neutralised by the immune system are available for interactions of the RBD of the S1 subunit particularly with its receptor angiotensin- converting-enzyme ACE2; the two reactions cannot be separated.

Moderna®, BioNTech® and Novavax® introduced some proline mutations into the spike protein with the aim of thereby keeping the spike protein produced in its prefusion conformation for longer[10]. Neither a more sustained antibody production nor a reduced side effect rate are proven. It is rather likely that the consequences of an undesirably prolonged functional ACE2 impairment will increase. Related results are not available.

To date, there is no knowledge of the dose-response relationship between the dose of the active substance and the full-lenght spike antigen production or concentration, including its duration. There are no reliable findings, for example, on the half-life of encoding mRNA, influence of endoplasmic reticulum (ER) activity and/or other important factors, on intracellular antigen transport, on spike antigen detachment from the outer cell membrane and on the proportion of non-neutralised spikes.

The unknown nature of these factors has implications for the efficacy and tolerability of these precursor vaccines, increasing the variability of responses and making them less predictable.

As systemic distribution of spikes is the precondition for direct spike-effects and interactions with receptors or co-receptors in different organs, their evidence is of eminent importance for spike-based vaccines (mRNA-, vector-, and protein-based vaccines). Sustained or prolonged bioavailability of spike protein may also be causally involved in the development of subacute to chronic organ dysfunctions.

Recently, some results have shown a significant systemic and longer than expected distribution of spikes. The

production of S1 antigens was already detectable on the first day after the first vaccination and extends beyond the injection site and the associated regional lymph nodes[11-13]. Specific vaccine spike proteins could be detected up to 187 days after mRNA-vaccination[14]. This is consistent with objectively detectable vaccination effects in asymptomatic vaccinated individuals up to 180 days after the second dose (^{18}F-FDG uptake[15]). Spike protein was detected in the plasma of 96% of people shortly after vaccination, in 63% of vaccinees one week after the first dose and spike antigen and vaccine mRNA were present in the germinal centres of lymph nodes up to 8 weeks after vaccination[16]. In the plasma of some patients, partial or complete sequences of the vaccine mRNA could be detected up to 28 days after vaccination [17]. mRNA vaccine was detected in axillary lymh nodes and in myocardial tissue of a very small subset of patients (n=3) dying within 30 days after vaccination; apart from subtle microscopic lesions, the myocardium showed no signs of myocarditis[19].

In Ad26.COV2.S vaccinees (who were seronegative at baseline) spike-protein levels peaked after 3 days and decreased to near background levels 28 days after dosing[19].

Using fluorescently labelled spike-S1 protein, a multi-organ distribution was detected in intact mice, including a distribution in the prefrontal cortex. Spike-S1 accumulated strongly in the vicinity of blood vessels[20]. Very interestingly, individuals who developed post-vaccine myocarditis uniquely show elevated levels of free circulating spike protein, unbound by anti-spike antibodies[21].

In summary, the systemic detection of spikes and/or encoding mRNA after vaccination thus disproves the claimed regional and time-limited efficacy. The time window for the assessment of a possible link between suspected adverse reactions and spike-based vaccination must be extended.

THE KEY FUNCTION OF THE SPIKE-RECEPTOR-ENZYM ACE2

The angiotensin-converting enzyme 2 (ACE2) possess an important physiological function in the local and systemic renin-angiotensin-aldosterone system (RAAS), the main function of which is to regulate cardiovascular homeostasis.

ACE2 is present in membrane-bound and soluble circulating forms and is widely distributed throughout the body. The enzyme is expressed in different quantities in coronary artery endothelium, cardiomyocytes, fibroblasts, epicardial adipocytes, vascular endothelial and smooth cells, gut/enterocytes, brain, eye, tracheal and bronchial epithelial cells, type 2 pneumocytes, macrophages, kidneys, testes, placental throphoblastes and gall bladder[22-24]. The expression of ACE2 is essential for SARS-CoV-2 tropism and helps to understand the ACE2-dependent extrapulmonary side effect spectrum of spike-based vaccination.

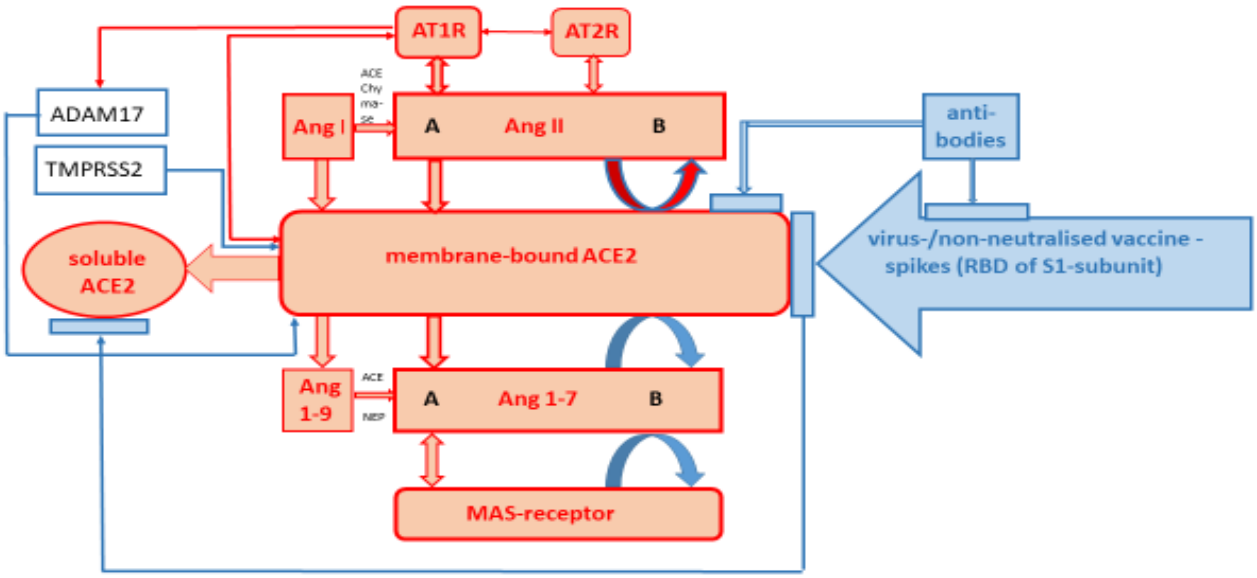

Figure 1*: *ACE2 function and impairment modes. *Note: A) ACE2 causes the conversion of Angiotensin I (Ang I) into Angiotensin 1-9 (Ang 1-9) and of Angiotensin II (Ang II) into Angiotensin 1-7 (Ang 1-7). Ang II acts via angiotensin 1 receptor (AT1R) and angiotenisn 2 receptor (AT2R) (physiological activities in red); B) Spikes and antibodies inhibit ACE2 with the consequence of increasing Ang II concentrations, decreasing Ang 1-7 concentrations and decreasing stimulation of the MAS receptor (pathophysiological activities in blue)*[25].
ACE: angiotensin converting enzyme; NEP: neutral endopeptidase; ADAM17: disintegrin and metalloproteinase domain-containing protein 17; TMPRSS2: transmembrane protease serine subtype 2

The most important effect of ACE2 is to reduce or eliminate the influence of the pathophysiologically potentially harmful vasoconstrictor octapeptide angiotenin II; Ang II is cleaved to the vasodilatory and antiproliferative Ang 1-7, providing cardiac and tissue protection (Figure 1).

Impairment of its physiological efficacy results in dysregulation of the RAAS, mainly through increased angiotensin II activity, and impairment of the anti-pathogenic ACE2/Ang1-7/MAS axis. Loss of the protective function of this enzyme opens the door to dysruption of homeostatic regulatory systems, as well as

defence and repair mechanisms, and can induce hyperinflammation, remodelling, thromboembolic or immunological dysfunction [25,26].

Pathogenic SARS-CoViruses use this enzyme as target receptor in competition with the natural ligands angiotensin I/II. Spike binding (subunit S1 with receptor binding domain-RBD) triggers a functional impairment of ACE2 with pathophysiologically relevant consequences already mentioned.

In a well-researched and comprehensive review, Gupta [23] already hypothesised a link between ACE2 impairment due to viral spikes and extrapulmonary manifestations of Covid-19 in July 2020. Osman[27] demonstrated lower ACE2 mRNA expression in circulating blood cells from Covid-19 patients and significant lower ACE2 gene expression in monocytes of prolonged viral Covid-19 shedders (PCR ≥10 days) who treated with antiviral drugs. The plasma concentration of soluble ACE2 was found to be significantly lower also in the prolonged viral shedders. The plasma concentrations of angiotensin metabolites were affected: consistent with evidence of lower ACE2 expression Covid-19 patients showed significantly higher Ang I and Ang II concentrations; Ang II was extremely high in two prolonged viral shedders. However, the Ang 1-7 concentrations remained surprisingly unchanged. This phenomenon should be investigated further.

Now that a systemic and prolonged distribution of spike protein has been demonstrated, the next question is whether vaccine spike antigens or the spike protein alone can affect ACE2 in the same way as the whole SARS-CoV-2 virus.

It has been known since 2006 that the SARS-CoV spike protein is capable of down-regulating ACE2 in vitro and in vivo in the absence of other viral components, leading to conditions resembling those of ace2-knock-out mice. The efficacy of Ang II increase in spike-treated mice was attenuated by AT_1R blockade [28,29]. In 2020, it was demonstrated[30] that spike protein (S1 region) expression alone in human lung epithelial cells was effective in inhibiting ACE2 expression, inducing increased Ang II levels and initiating the signalling cascade mediated after significantly increased AT_1R expression, including ADAM17 induction and inflammatory markers (IL-6 & other cytokines). Lei[31] later described damage to vascular endothelial cells in animal experiments by ACE2 downregulation, impaired NO bioavailability and inhibition of mitochondrial functions in response to spike proteins - preconditions for development of endothelitis. The spike protein may lead to ACE2 destabilisation via increased redox stress and deactivation of AMP kinases.

Furthermore, it could be confirmed that the S1 subunit of the spike glycoprotein is capable of causing systemic micro-endothelial cell damage[32]. Even before the authorisation of the first mRNA vaccines, it was known that SARS-CoV-2 and its spike protein directly enhance platelet aggregation and thus also thrombus formation through interaction with ACE2[33].

The RAAS is known to be closely interconnected with the bradykinin system. Bradykinin, which in principle is a vasodilator with an extremely short-term and localised efficacy, is degraded by kinase II = angiotensin-converting-enzyme (ACE) and its bioactive pro-inflammatory metabolite des-Arg^9-bradykinin (DABK) by ACE2[34]. Spike-triggered functional deficiency or lack of ACE2 not only favours the local accumulation of Ang II, but could also trigger a dysregulation of the closely linked bradykinin system, leading to an increase in des-arg^9-bradykinin (DABK, figure 2).

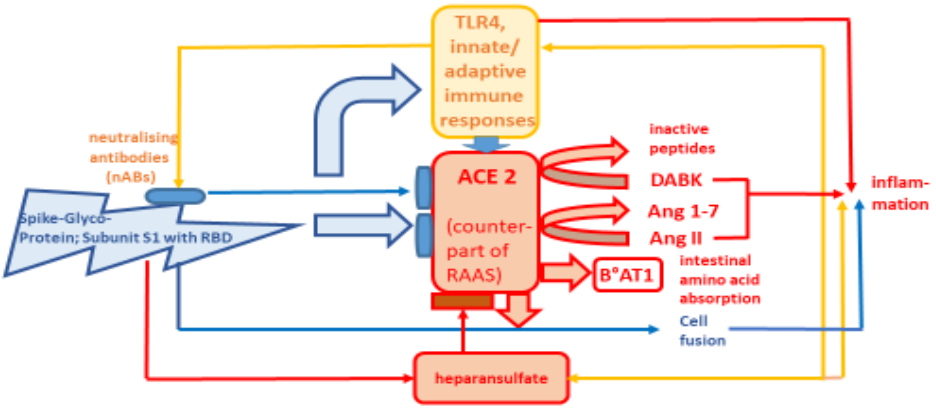

Figure 2: Basic mode of spike action[26]

As an antigen, the spike RBD of the S1 subunit triggers the cellular innate and adaptive immune response including the production of neutralising antibodies (nABs), and the Toll like receptor 4 (TLR4) activation.

The binding of the S1 spike subunit via its RBD (non-neutralised) to the receptor enzyme ACE2 leads to its downregulation and impairment of its most important physiological function: the degradation of the pathophysiologically harmful angiotensin II (Ang II) to the mainly protective angiotensin 1-7 (Ang 1-7).

In addition, the degradation of des-arg^9-bradykinin (DABK) is inhibited. Ang II, DABK and TLR4 act synergistically to stimulate inflammation.

The binding of S1 to the co-receptor heparan sulphate (HS) stabilises the interaction with ACE2. HS moreover interacts with the immune system and has a pro-inflammatory effect.

Spikes impair the co-operation of ACE2 with the amino acid transporter B°AT1 with regard to amino acid uptake in the intestine.

In addition, spike proteins can fuse cells equipped with the ACE2 receptor to form syncytia. Cell fusion contributes to tissue inflammation

Spike-triggered functional deficiency or lack of ACE2 not only favours the local accumulation of Ang II, but could also trigger a dysregulation of the closely linked bradykinin system, leading to an increase in des-arg^9-bradykinin (DABK, figure 2). The resulting synergism between Ang II and DABK, which can induce hyperactivation of the immune system, provides a plausible explanation for a variety of adverse spike-related reactions, in particular for the dangerousness of the cytokine storm observed in rare cases of Covid-19[35]. In a representative number of Covid-19 patients, it could be shown that DABK production was increased, especially in overweight people; the levels of Ang 1-7, on the other hand, were low as expected[36].

The causal role that DABK might play in triggering side effects of spike-based vaccination, such as cough and angioedema, has been ignored until now.

An important harmful property of SARS-CoV-2 spike proteins is their ability to fuse cells carrying the ACE2 receptor and form syncytia[37, 38]. Recently, the SARS-CoV-2 spike protein has been described as "enormously fusion active". Minimal amounts of spike protein on the cell surface or spiked virus particles are sufficient to initiate fusion, even if ACE2 is not overexpressed[39, 40]. In 2021, cell fusion was recognised as a trigger of the blood coagulation cascade. Viral fusogens are able to form large syncytia that tend to die, expose the thrombogenic basement membrane when detached and support platelet-dependent coagulation in this way. The fusion of neurons may lead to neurological manifestations, like cognitive disturbances. Due to chromosomal aberrations tumor progression seems to be also possible. In addition, cell fusion may contribute to an excessive inflammatory response, tissue damage or production of cytokines to SARS-CoViruses or their components[41].

Individuals with initially low ACE2 concentrations are particularly at risk when additional inhibitory influences are present. For example, in addition to spike-neutralising immunological reactions, it seems possible that antibodies, autoantibodies, anti-idiotype reactions and/or genetic conditions can impair the efficacy of the protective enzyme ACE2[42]. The latest findings following vaccination with Comirnaty^R (spike-inducing mRNA vaccine) and Sinovac^R (inactivated virus) are highly interesting. Both significantly increased ACE2 autoantibody IgG in 9.5-12.6% and 3.3-14.3% of individuals, respectively, on day 56 after vaccination. The values slowly decreased within 12 months[43]. However, due to the small number of cases and the lack of relevant data collection, no association with adverse vaccination events could be established; but involvement of ACE2-IgG antibodies in myo-/pericarditis according to Comirnaty^R (n=43) could be excluded.

Furthermore, specific antibodies against S1-RBD were shown to cross-react with ACE2, probably due to structural similarity[44].

Recently, a positive correlation between ACE2 expression and anti-tumour signatures was found in various tumour types. Unimpaired function of ACE2 may protect against cancer progression, possibly by inhibiting tumour angiogenesis[45]. Further, especially tumour-specific studies in vaccinated patients are required.

The most important result of ACE2 activity (fig. 1) is the regulation of the concentration of the multifaceted, multipotent octapeptide angiotensin II (Ang II), the main effector of the RAAS.

In principle, Ang II concentrations are controlled by the balance between ACE and ACE2 activity, alternatively to ACE in cardiac, vascular and renal tissues by chymase produced by mast cells[46]. Diagnostically/therapeutically, the presence of chymase instead of ACE in the heart tissue of elderly people must be taken into account. In these patients, significantly elevated Ang II concentrations do not respond adequately to ACE inhibition[47]. In contrast, chymase inhibitors have been shown to have a protective effect on cardiac tissue in experimental studies.

Angiotensin II effects are mediated by both AT_1 and AT_2 receptors, with AT_1R implicated in classically physiological but also pathophysiologically deleterious, and AT_2R in mediating vasodilation and further protective effects[48-50]. High AT_1R expression is particularly present in vascular smooth muscles. Of importance is the presence of AT_1R in macrophages, bronchial epithelium, zona glomerulosa of the adrenal glands, endometrium and dopaminergic brain regions.

It should be noted that AT_1R is subject to a genetic polymorphism associated with increased development of cardiovascular risk factors, such as increased sensitivity to the vasoconstrictor effects of Ang II. The genetic variation A1166C has been observed in hypertension, myocardial infarction/coronary artery disease, hyperlipidaemia or aortic vascular disease[51].

The physiological ligand of ACE2, Ang II, influences the function of almost all organs, including the heart, kidney, vascular system and brain[51]. It is well accepted that Ang II is involved in vasoconstriction, increase in blood pressure, hypertension and associated end-organ injuries; vasopressin release; noradrenaline increase (elevated release, reuptake-inhibition); disturbance of the electrical conductivity of the heart; inducing of tachycardia and/or arrhythmia; increased oxidative stress; inducing deficient NO bioavailability; aldosterone-caused increase of sodium and water reabsorption; endothelial dysfunction; ADAM 17 increase; promoting (pro)-inflammatory (NF-kB) and pro-coagulant processes; microthrombus inducing; pro-arteriosclerotic, pro-fibrotic effects; promoting of hypertrophic and proliferative reactions; cardiac remodelling; proteolysis of skeletal muscles; affecting glucose/cellular metabolism; severe Covid-19 courses; beta-amyloid increase; downregulation of survival genes.

Increased Ang II levels are significantly associated with depression, anxiety, hypothalamic-pituitary-adrenal (HPA) axis hyperactivity, neuroinflammation, enhanced plasma cytokine levels and nitro-oxydative stress. AT_1 receptor blockers have been shown to be superior to the neuroprotective properties of ACE inhibitors. Anxiolytic/antidepressant effects of RAAS blockers may be mediated by their anti-inflammatory and/or anti-oxydative stress effects[52].

A large number of findings suggest that the RAAS/ACE2/Ang II system is fundamentally involved in inflammatory processes and in disorders of both the innate and acquired immune systems[53]. The RAAS signalling cascade interacts with the immune system on several levels, both systemically and tissue-specifically.

Angiotensin II triggered an inflammatory response by promoting the expression of pro-inflammatory cytokines/chemokines responsible for the accumulation of immunocompetent cells in the tissue. Vascular endothelial growth factor (VEGF) and adhesion factor expression were increased. Cox-2 activation has been implicated in mediating endothelial dysfunction, activation of dendritic cells in pro-inflammatory activities. TLR4 expression is mediated via activation of AT_1R. In contrast, AT_1R blockade or ACE inhibition reduced inflammatory processes and protected tissues from oxidative lesions independently of blood pressure reduction[46,54]. Local Ang II formation can modulate inflammatory responses by altering blood flow, vascular permeability and granulomatous reactions[55].

It has been known for decades that immune cells (e.g. macrophages in granulomas or circulating leukocytes) can generate and release Ang II[55, 56], that AT_1 receptors are present in T cells, macrophages and in lymphoid organs and that Ang II can therefore act directly on immune cells and have a proliferative effect[57].

Stressed Covid-19 sufferers or those vaccinated with spike-based vaccines are exposed to dual RAAS activation, namely stress-induced by increased sympathetic tone/Ang II concentrations and spike-induced activation of the RAAS with increasing Ang II concentrations, which may not only trigger acute haemodynamic consequences, but may furthermore result in an inflammatory process or thrombo-embolic consequences. Post-mortem reports from Covid-19 patients indeed demonstrated severe vascular damage and alveolar microthrombi; microcirculatory lesions with pro-coagulatory consequences are of considerable clinical relevance[47].

In contrast, unimpaired ACE2 function, presumably by enhancing Ang II degradation and increasing Ang 1-7 concentration, ameliorates inflammatory lesions in the kidney and vasculature and limits the production of pro-inflammatory cytokines (TNF-alpha, IL-6) by macrophages. An interesting finding in recent years is that the AT_1-receptor is more strongly expressed than AT_2R in cells of the immune system in adults. It is thought that the AT_1-receptors of the immune system modulate pathogenic renal and vascular AT_1R effects to limit tissue injuries in hypertension. Independently, the AT_2-receptor is considered to counteract AT_1R effects and thus possesses a broad spectrum of anti-inflammatory properties. The development of Ang 1-7 analogues and specific AT_2R-agonists is thought to have therapeutic potential[54].

Inhibition of AT_1R with anti-inflammatory and immunosuppressive consequences, e.g. in immunologically caused myocarditis, to suppress pathogenic Ang II effects, was already considered therapeutically useful at that time. The favourable effects on the vascular musculature and the inhibition of the production of inflammatory mediators have been attributed a significant role[57].

RAAS activity and AT_1R activity are additionally counter-balanced by the components of the anti-pathogenic, anti-inflammatory ACE2/Ang 1-7/MAS axis and AT_2R activity mentioned above. It is considered beyond doubt that the vasoconstrictor Ang II/ AT_1R effects are antagonised and AT_2R-mediated vasodilation in resistance and capacitance vessels or hypotension prevails, which is not only acutely detectable but also longer lasting; desensitisation is not known[46]. In particular, when AT_1R/RAAS is overstimulated (e.g. during salt restriction or Ang II infusion), the protective vasodilatory effect of AT_2R comes into play; an inverse relationship exists between AT_1R and AT_2R[48,58.] Independent of agonist activation, AT_2R can directly trigger inhibition of AT_1R[51].

Activation of the AT_2-receptor reduces ROS formation and inflammatory cytokine activity, increases NO formation, modulates NF-κB, increases apoptosis and tissue repair mechanisms (including neuronal), inhibits renin formation, cell growth and proliferation, influences cell differentiation, reduces sympathetic activity, induces natriuresis and participates in blood pressure regulation, can improve contractile function after myocardial infarction and thus counteracts the development of cardiac hypertrophy. In addition, some protection against ageing processes and related chronic diseases is conceivable.

Under pathological conditions, such as tissue and vascular damage, myocardial infarction, heart failure, renal failure or brain ischaemia/peripheral nerve damage, an activation of AT_2R expression has been described. In 2017, it was found for the first time that AT_2R is markedly expressed in the inflamed synovial tissue and in cells of the innate and adaptive immune system of patients with rheumatoid arthritis[59].

Angiotensin 1-7 is thought to have vasodilatory and anti-thrombotic effects (through NO activation), as well as anti-fibrotic and anti-inflammatory effects[47]. Its effects are mediated via the MAS receptor, which, like the AT_2R, produces tissue-protective and regenerative effects[60]. It attenuates fibrosis, proliferation and remodelling processes; pro-inflammatory effects are partially prevented[53]. ACE2 and MAS complement each other in their protective efficacy against Ang II-mediated outcomes[61].

SPIKE EFFECTS IN THE GASTROINTESTINAL TRACT

In addition to the known consequences of ACE2 downregulation triggered by SARS-CoV-2 spikes (increase in Ang II and AT_1R activation, which can lead to leaky gut syndrome, for example), this enzyme plays an important physiological role in the gastrointestinal tract that is independent of RAAS consequences. ACE2 is involved in the regulation of dietary amino acid homeostasis, intestinal inflammation, gut microbiota composition, innate immunity, and glucose absorption[62-64], all of which are affected by spikes.

The sodium-dependent uptake of neutral amino acids requires the presence of the amino acid transporter

B°AT1 (figure 2), whose expression on the luminal surface of intestinal epithelial cells is stimulated by ACE2. Structural analysis revealed that the S1-RBD components of two spike protein trimers interact with a complex of ACE2 and B°AT1[65]. In the absence of intestinal B°AT1 protein expression due to lack or functional impairment of ACE2 enzyme, serum levels of the neutral amino acids valine, threonine and tyrosine as well as of the essential amino acid tryptophan were significantly reduced; the mTOR activity, which is involved in cell proliferation and protein synthesis and which is activated by dietary tryptophan, is also reduced [64, 66, 67].

Tryptophan as a precursor of serotonin is of great importance for central nervous transmission processes, which are disturbed in depression, for example. Between Ang II and serotonin exist an interaction; Ang II regulates stress-related effects by modulating serotonin synthesis and release[52]. An involvement of low circulating serotonin levels in Long-COVID is discussed[68] and could also be a cause of post-VAC syndrome.

Recently, it could be shown, that the gut micro-biome reflects immunogenicity and was associated with vaccine related adverse events. Vaccinated individuals with a higher content of beneficial bacteria may have an optimal immune response and stronger protection. A higher content of *P. copri* and *Megamonas* species was associated with less adverse events. BNT162b2 vaccinees who reported any adverse reaction had a significant decrease in observed bacterial species richness[69]. Further investigations are required to verify these initial results.

SUPPORTING SPIKE EFFECTS

The spike glycoprotein of SARS-CoV-2, which acts as a Pathogen-Associated Molecular Pattern (PAMP), can directly bind and activate the Toll-Like Receptor 4 (TLR4) with high affinity, independent of ACE2[70, 71], resulting in NF-kB-activation and induction of proinflammatory cytokine expression (MyD88-dependent signaling pathway). This is very similar to inflammatory reactions caused by an activated RAAS with enhanced Ang II concentrations.

It could be shown, that decreased expression of ACE2 was associated with lung pathology and inflammatory injury resulted in abnormal activation of TLR4 in an experimental acute lung injury model[72]. TLR4 deficiency prevented Ang II-induced vascular remodeling without affecting blood pressure, abolished Ang II-induced vascular ROS, inhibited Ang II induced NADPH oxidase activity, and enhanced upregulation of anti-oxidative ecSOD[73]. Cardiomyocyte-specific TLR4 deletion attenuates angiotensin II-induced hypertension, reduced cardiac hypertrophy, fibrosis, and dysfunction as well as cardiac inflammation. Conversely, Ang II significantly increased TLR4 gene expression in hypertensive mice[74].

In recent years, inflammatory processes involving the innate immune system and the RAAS have been demonstrated to play an important role in the development of various chronic diseases such as hypertension[74,75], diabetic nephropathy[76], vascular remodeling and cardiovascular disease[73]. In addition, dysregulation of TLR4 signaling has been implicated in the development and/or progression of atherosclerosis, myocarditis, cancer, neuropsychiatric and neurodegenerative diseases[77].

The spike S1 subunit could trigger neuroinflammatory effects in the CNS and behavioral consequences in rats (reduced exploratory and social behavior - "behavioral sickness response"). S1 also activated TLR2 and TLR4 receptor signaling in vitro[78]. Furthermore, TLR4 has been identified as key mediator in longterm, specific and reversible cognitive dysfunction, microgliosis and loss of synapses after a single experimental brain infusion with spikes[79].

The involvement of the same effector molecules in initiation and maintenance of inflammation, proliferation and fibrosis supports the synergism between TLR4 activation and increased Ang II/ AT1R activity. In cases of overstimulated TLR4 potentiated by a dysregulated RAAS, the synergism can intensify to severe inflammatory consequences (e.g. cytokine storm) or even contribute to a fatal outcome.

SPIKE INTERACTION WITH THE CO-RECEPTOR HEPARAN SULFATE (HS)

Consequences of spike protein interactions with cells that have no detectable or low ACE2 activity suggest the presence of additional receptors. In contrast to the impressive body of evidence for the causal role of the spike/ACE2 interaction in triggering organ symptoms caused by SARS-CoV-2 infection or vaccination, there is much less evidence for the involvement of spike protein co-receptors.

However, there are relevant interactions for heparan sulphate (figure 2). Heparan Sulfate (HS) is ubiquitously expressed on the surface of almost all mammalian cells, in the extracellular matrix and basement membrane. HS plays several important roles in the immune system; it regulates the cell adhesion, the development of leukocytes, and their migration, activates the immune system and inflammatory processes. HS interacts with TLR4 and other TLRs. HS seems to be a major modulator of the complement system[80,81]. HS is used by many viruses as a cofactor for attachment to host cells[82]. For SARS-CoV-2 infections, for example, it has been shown that the S1 subunit of the spikes can bind with its RBD to Heparan Sulfate (HS) on the cell surface in the sense of a co-receptor function, thereby stabilising or enhancing the interaction with ACE2 [83].

As a component of the endothelial glycocalyx, heparan sulphate is also involved in the regulation of blood coagulation; it increases the activity of anticoagulation factors such as Anti-Thrombin (AT) and Heparin Cofactor II (HCII). But, after binding of HS by the spike-protein, HS could no longer interact with AT/HC II, resulting in a rapid coagulation reaction and suggesting a direct effect of the spike-protein on development of thrombosis. Heparin lost its anticoagulation-regulating ability in a spikeprotein concentration-dependent manner[84].

Furthermore, a synergism may be assumed between procoagulatory Ang II effects and direct spike-induced thrombotic effects with dramatic consequences for blood coagulation.

However, neither the involvement of the co-receptor HS in the blood coagulation disorders after spike-based vaccination nor the obvious synergism between binding of spikes to HS and the spike-induced downregulation of ACE2 or increase in Ang II has been investigated so far, although the frequency of corresponding relevant adverse effects is worrying.

Tolerability of spike-based Covid-19 vaccination demonstrated using selected adverse reactions

Knowledge of the spike interactions with their receptor enzyme ACE2, direct spike effects, synergisms, the involvement of co-receptors and RAAS-independent responses is the key to understanding the unusually broad spectrum of adverse reactions associated with spike-based Covid-19 vaccination. In principle, analyses of reported suspected adverse reactions (ADRs) reflect this causative spike efficacy.

In 2022, a comprehensive analysis[8] provided a first insight into the spectrum and frequency of many specific adverse events associated with Covid-19 vaccination, as well as those that had previously received little attention and often remained unexplained, but which nevertheless had a very negative impact on overall health status.

Among the non-infectious, extrapulmonary organ-related ADRs spontaneously reported within just over a year of the start of the vaccination campaign, those affecting the nervous system were the most common (16.2-20.2%), followed in descending order by those affecting the musculoskeletal system (11.7-14.5%), the gastrointestinal system (7.5-9.3%), the skin (3.0-5.1%), the reproductive system (1.5-4.2%), cardiac disorders (1.8-3.4%), vascular disorders (2.2-2.9%) and the blood and lymph system (0.97-2.8%), according to the EudraVigilance WebReport reaction groups. The average lethality of adverse events ranged from 1.81 (Vaxzevria®), 2.34 (Comirnaty®), 4.75 (SpikeVax®) to 4.9% (Janssen vaccine). Surprisingly, almost equal numbers of adverse events ended fatally in the cardiac (8.4-14.5%), and nervous system (9.4-14.7%) reaction groups, suggesting a similar severity of events.[8]

The most common neurological adverse events reported by early February 2022 were headache (21.6-37.9% of cases) and dizziness (6.35-8.3%). Unusually for vaccines but relatively common were balance disorders (0.38-0.41% of individual cases). Dizziness/vertigo can also be secondary to orthostatic hypotension, blood pressure fluctuations or cardiac arrhythmia/tachycardia and could therefore be associated with sensorimotor/vegetative neuropathies.

Although headache/migraine is usually a common everyday phenomenon that occurs in response to various systemic, regional or local events, the character of the reported headache - sometimes stinging, flash-like - appears to be typical of Covid-19 vaccination. The relatively common reversible cerebral vasoconstriction syndrome[85] (RCVS) produces very similar symptoms - an attack of thunderclap headache with a subliminal persistent dull headache. Triggers include vasoactive substances such as catecholamines and angiotensin II. RCVS has been repeatedly reported as a complication of SARS-CoV-2 infections[86]. Recently, some cases of RCVS and PRES (posterior reversible encephalopathy syndrome) have been reported following SARS-CoV-2 vaccination[87-90]. It is assumed that the spikes generated by the vaccination or the viral spikes interact directly with the ACE2 receptor present in the brain tissue. The development of specific symptoms can be rapid, but can also take days, as the following cases show. A woman affected by RCVS did not suffer from scotomas and thunderclap headaches until 18 days after the second administration of Moderna® vaccine. MRI revealed an acute cortical ischaemic lesion; cerebral vasculitis was excluded. Nimodipine was therapeutically effective. In another woman, neurological symptoms developed very rapidly within 24 hours of the third Moderna® booster.

As of 1 March 2024, 35 cases of RCVS, 59 cases of thunderclap headache and 19 cases of PRES had been reported in the Eudravigilance pharmacovigilance system for Comirnaty® alone[9]. Spike-based vaccine-induced vasoconstriction with subsequent tissue ischaemia is very likely to trigger these phenomena and may be complemented by immunological-inflammatory and hypercoagulatory sequelae, as known from SARS-CoV-2 infections[86].

Ischaemia and hypoxia are also known to be contributory to central nervous function deficits, such as dizziness, balance disorders, transient memory loss or impairment (approximately 0.13%-0.25% of vaccinees with ADRs), impaired attention or consciousness (0.04%-0.46%), brain fog (5.9%) or blood-brain barrier dysfunction. In each case it should be considered that dizziness may also be secondary to orthostatic hypotension, blood pressure fluctuations or cardiac arrhythmias/tachycardia and could therefore be associated with heart-circulation dysfunctions or sensorimotor/vegetative neuropathies.

Other causative factors may include: spike-induced neuroinflammation, microgliosis, loss of synapses and/or neuronal fusion. It is known that increased Ang II concentrations are significantly associated with central dysfunction and neuroinflammation. Ang II modulate serotonin synthesis and release. RAAS blockers exert therapeutically relevant effects[52]. The impairment of amino acid absorption in the gut, especially of tryptophan, can cause a deficiency of transmitters in the CNS and thus initiate the development of mood disorders or contribute to long-lasting behavioral changes.

Changes in the sense of taste and smell, and facial nerve palsy are common sequelae of Covid-19 infection[23], but as is now known, are also sequelae of Covid-19 vaccination. The remarkable frequency of facial paralysis (0.2-0.4%) among vaccinated individuals with ADRs supports a causal relationship between spike-based vaccination and facial paralysis. Patone[91] reported that facial paralysis occurred simultaneously with GBS after Vaxzevria®. Autoimmune processes, such as a mononeuritic variant of GBS, have been implicated as causative factors for facial nerve palsy. However, the mechanism underlying the impairment of function of N. facialis and N. glossopharyngeus is unknown. Transient microvascular supply disturbances after vasoconstriction, similar to those described in the peripheral nervous

system, should be included in the discussion of the causation.

Paraesthesias and sensitivity disorders were relatively common (2.63-3.42%), diagnosed polyneuropathies (PNP) were rarely recognized (0.03-0.07%). Symptoms of sharp pain, burning sensation, disturbed pain, and temperature sensation (hyperesthesia) are characteristic of impairment of low-myelinated and unmyelinated fibers of the peripheral nervous system. If blood supply via the vasa nervorum to these fibers is interrupted or disturbed after vasculopathy, for example, vasoconstriction or vasculitis, peripheral symptomatic nerve dysfunction may occur. Unfortunately, the microvascular supply and markers of activated RAAS have not been systematically studied in this context. However, in some cases of neuropathy (n=5), auto-antibodies against AT_1R/ACE2 were found[8]. Together with the findings of antibodies against the MAS receptor (n=6), there is compelling evidence of the causal involvement of a disturbed ACE2/MasR axis in triggering neuropathic symptoms.

Demyelination or damage to the myelin sheath and/or axonopathy characterize Guillain-Barre syndrome, which may be the most common acquired inflammatory neuropathy, a consequence of an exaggerated auto-immune reaction with antibody formation against glycolipids of the myelin sheaths or T-cell activation. GBS has been observed relatively frequently in European countries (n=3373; 0.15 up to 0.87% of all individual cases[8]) and regardless of the type of Covid-19 vaccine (mRNA, vector). In the final report[92] of the German authority PEI on the safety profile of Covid-19 vaccines, significantly fewer GBS cases were mentioned by 31 March 2023, namely a total of only 214 (0.063%); these have been declared exclusively as characteristics of vector vaccines without any plausible justification.

Vaccinations of various kinds or infections are known triggers for GBS. Autoimmune reactions of the spike glycoprotein against ganglioside components of peripheral nerves are also discussed as possible triggers of the syndrome, presumably due to structural similarities [93]. In a patient with tetraparesis, autoanti-bodies against gangliosides were detected, confirming this hypothesis.

There is no doubt about a rational relationship between the efficacy of spikes and cardiovascular health burden[6,7].

A recent analysis[6] of cardiovascular reactions after vaccination with Tozinameran (reported from European authorities to the EudraVigilance of EMA) in 2023 showed the following frequencies of unexpected and adverse cardiovascular reactions for vaccines, in descending order

- 56,611 cases of tachycardia, arrhythmia, atrial fibrillation/flatter, bradyarrhythmia
- 32,358 cases of chest pain
- 27,123 cases with palpitations
- 25,907 reports of blood pressure increase/ hypertension
- 23,775 cases of myo-/pericarditis
- 9,912 times coronary ischaemia and myocardial infarction
- 8,799 cases of hypotension
- 6,496 cases of heart failure, decreased contractility
- 5,424 times cardiac arrest, sudden cardiac death and death
- 3,094 cases with extrasystoles
- 1,986 times circulatory collapse, shock
- 1,753 cases of cardiac/ventricular fibrillation/flatter
- 1,119 cases of cardiomyopathy
- 827 times impaired stimulus formation and conduction
- 325 times multiorgan dysfunction/failure.

Although diagnostic details are lacking, this pattern of cardiovascular adverse effects is in principle consistent with the consequences of the spikes' mode of action – the downregulation of the cardioprotective, antipathogenic enzyme ACE2 and subsequent dysregulation/activation of the RAAS with increasing Ang II concentrations.

The most commonly reported adverse events - chest pain, palpitations/extrasystoles - are subjectively striking, may be harmless, but may also be pathognomonic and therefore require diagnostic evaluation. The high number of reports alone indicates clinical relevance.

The most significant effect of Ang II is undoubtedly the vasoconstriction, which can manifest itself acutely as blood pressure increase, hypertensive crisis, tachycardia/arrhythmia, acute left heart failure, ischaemia-related cardiac or CNS-symptoms, myocardial infarction, sudden (cardiac) death or stroke. Central and peripheral catecholaminergic activities can amplify Ang II effects. Experimentally, the influence of AT_1R activation on the electrical conductivity of myocytes proved to be relevant with regard to the triggering of ventricular arrhythmias[48].

In addition to the peripheral dependence of blood pressure regulation on the RAAS elevated blood pressure can also be caused by central regulatory derailment in brain regions responsible for it, such as the brainstem or hypothalamus, in a complex interaction system involving multiple local and systemic components[95]. The MAS receptor, which is highly expressed in the brain, may be considered as one of the regulating links. ACE2 appears to be more important than ACE in normal brain function and acts as a compensatory limiting mechanism of RAAS hyperactivity. Absence or dysfunction of ACE2 results in increased sympathetic tone and decreased parasympathetic tone, which may manifest in the periphery, for example, by tachycardia and elevated blood pressure. Initial experimental attempts to selectively stimulate ACE2, thereby enhancing its RAAS-attenuating effect, resulted in lowered blood pressure and improved cardiac function, as expected. The availability of spikes in the CNS suggests that spike-based vaccines may also be causally involved in blood pressure regulation by affecting ACE2 function in the CNS.

Reports of hypotension are surprising. However, hypotension can occur in the context of neuropathic symptom complexes with neurovegetative components, but also in most severe disease processes, such as multi-organ failure/dysfunction, in which the response to Ang II declines. But, an immediate onset of symptoms within a few minutes after vaccination suggests allergic genesis.

Ischaemic heart disease and myocardial infarction were frequently reported. The increased vasoconstrictive and platelet activating and/or tachyarrhythmic effects of Ang II may lead to coronary and microvascular circulatory disturbances with thrombus formation and ischaemic sequelae. Comorbidities and stress-induced catecholaminergic amplification may exacerbate the condition.

With regard to the causation of long-term organ disturbances, it is important to consider that Ang II controls cell growth (hypertrophy, proliferation), adhesion, migration and intracellular matrix deposition, and thus influences chronic adaptation processes in blood vessels and heart muscle, such as remodelling, tissue repair and the development of atherosclerosis. In addition, the adaptive immune system and inflammatory responses, together with the local renin-angiotensin-system, are involved in Ang II-induced organ injury caused by spikes[94].

Multiorgan dysfunction/failure, associated with high lethality (61.85%), was reported infrequently compared to other spike-induced adverse events. It is more likely to be associated with severe Covid-19 disease, which can occur despite vaccination.

The high number of cardiac arrests, sudden cardiac deaths and deaths associated with Tozinameran (n=5,424) is characteristic and alarming regarding the severity of the cardio-vascular burden of heart failure, cardiomyopathy, cardiovascular collapse and ventricular fibrillation or flutter. The deaths caused by them accounted for at least one third (35%) of all deaths associated with Tozinameran's side effects. The cardiac adverse events with the most fatal outcomes were cardiac arrest (86%), multiorgan dysfunction (approximately 62%), myocardial infarction (21.4%), heart failure (14.6%) and circulatory collapse (10.44%). Acute/subacute spike-induced ACE2 downregulation with subsequent activation of the RAAS and pathogenetically harmful increases in Ang II levels and possible catecholaminergic amplification should be considered as causative of sudden and unexpected deaths until proven otherwise.

So far, only myo-/pericarditis from this spectrum (23,775 reports; 5th in terms of frequency and 13th in terms of cardiovascular hazard) and thrombo-embolic ADRs have been attributed a Covid-19-vaccine-related signalling effect by the EMA.

The focus of attention on myo-/pericarditis has certainly contributed to the fact that reports have increased more than 8-fold within about 2 years in European countries. Although the course of myocarditis is usually characterised as mild, severe courses and fatalities have also been reported. Recently, it has been shown that myocarditis after vaccination is associated with normal adaptive and T-cell immunity, but modest innate inflammatory activation with increased cytokine levels, an increase in neutrophil granulocytes and a decreased platelet count. Furthermore, individuals who developed myocarditis had markedly higher levels of free full-length spike protein in circulation, unbound by anti-spike antibodies, than control subjects[21]. Consequently, cytotoxic and ACE2 downregulation-mediated spike effects cannot be prevented in the absence of antigen neutralisation and can thus contribute to development of myocarditis. It is therefore extremely important to clarify the pathogenesis and consequences of high concentrations of non-neutralised spikes in the plasma of vaccinated patients with myocarditis. Neither the special distribution of ACE2 in the pericytes of the capillaries and small blood vessels of the myocardial tissue, in cardiomyocytes and endothelial cells, nor a possible pre-existing low ACE2 level linked to high Ang II concentrations, as in the multiple stressed older age (increased chymase and TMPRSS2 activity), was discussed regarding the pathogenesis of the globally declared "myocarditis"[96]. Direct spike damage potential[31], genetically fixed low ACE2 activity or a situation additionally aggravated by stress were also not considered. Specific investigations failed to materialise[25]. Even an alarming signal - the sudden cardiac death of two adolescents - was not used to clarify further "myocarditis" cases, despite resolute references by the authors to the suspected underlying stress cardiomyopathy caused by catecholamines (one could also say: toxic Ang II/Noradrenaline storm)[97].

Soon after the start of the Covid-19 vaccination campaign, it became apparent that thromboembolic complications in the periphery and CNS were frequently reported in connection with these vaccinations; they are a characteristic marker of the cardiovascular adverse reaction profile of spike-based vaccines.

In just under 5 months (until 12 June 2021)[7] since the start of the vaccination campaign,

- 2,778 cases of thrombosis, 1,786 cases of embolism/microembolism (including 1,639 cases of pulmonary embolism), 90 cases of central sinus vein thrombosis (CVST/CVT) and 983 cases of increased bleeding (including 165 cases of immune thrombocytopenia) were reported to the European Medicines Agency (EMA) following vaccination with Comirnaty®/Tozinameran.
- The absolute numbers associated with Vaxzevria® were higher (5,312 cases of thrombosis, 2,882 cases of embolism/microembolism including 2,495 cases of pulmonary embolism, 405 cases of central sinus vein thrombosis, and 2,861 cases of increased bleeding including 366 cases of immune thrombocytopenia).

Embolism primarily affected the lungs (87-92% of all embolic cases) and were fatal in 7-9%. Mesenteric artery occlusions occurred, which is why peripheral vascular occlusions should be considered when an ileus happens in connection with vaccination.

Phenomenologically, cases of thrombosis associated with thrombocytopenia were named vaccine-induced immune thrombotic thrombocytopenia (VITT) or thrombosis with thrombocytopenia syndrome (TTS). In some cases, antibodies (IgG) against platelet factor 4 (PF4) were detected; an increase in D-dimer was also described [92]. Many cases of immune thrombocytopenia (ITP) were reported, more frequently associated with Vaxzevria® (0.13% = 130/100 000 vaccinated subjects) than with Comirnaty® (0.074% = 74/100 000). Their percentage of increased blood coagulation was 16.8% after Comirnaty® compared to 12.8% after Vaxzevria®.

Compared to the ITP prevalence in Germany (9-26/100 000 [99]), the proportion of affected persons among the vaccinated is high and points to a possible additional triggering factor by spike-based vaccines.

The very rare but all the more serious cases of CVT/CVST attracted particular attention. Within one month of the start of the vaccination campaign, AstraZeneca reported 4 cases of CVST and 2 cases of cerebral thrombosis to EMA[100]. On 11 March 2021, Denmark and Norway suspended this vaccination. Shocking case reports followed [101, 102].

Numerous life-threatening strokes (848 cases after Vaxzevria® with 7.9% fatal outcomes; 1,003 cases after Comirnaty® with 12.4% fatal outcomes) and intracerebral haemorrhages (429 cases with 30.3% fatal outcomes after Vaxzevria®; 328 cases with 42.4% fatal outcomes after Comirnaty®) were observed.

Despite some numerical differences, however, the spectra were qualitatively consistent, which is why, contrary to other surveys[98], no particular specificity can be assumed for Vaxzevria®; the side-effect spectrum of spike-inducing vaccines exhibits class specificity[7].

Incomprehensibly, the consequences of the efficacy of the spike glycoprotein and Ang II have been ignored in clinical pathophysiological research. However, there is evidence that the formation of microthrombi/thrombi is influenced by Ang II-induced procoagulatory effects, increased thrombin formation, enhanced production of fibrinolysis-inhibiting plasminogen activator inhibitor 1 (PAI-1) in endothelial cells and vascular smooth muscle cells, sensitised platelets, promoted superoxide radical production and induced tissue factor expression[25], by loss of the vasodilatory, antithrombotic Ang 1-7 effects, by spike-induced direct enhancement of platelet aggregation, cell fusion and microendothelial cell damage. The inhibition of the anticoagulant heparan sulphate (HS) by spikes has particularly dramatic consequences and can contribute to the potentiation of the factors mentioned[26].

The involvement of spike-induced deleterious Ang II activity is also plausible in triggering immunological/ inflammatory diseases, muscle disorders, renal and gastrointestinal symptoms.

Macrovascular and microvascular changes in the blood vessels and the development of endothelial dysfunction may contribute to the development of organ dysfunctions.

The increasing total number of individual cases suffering from adverse effects (n=2,256,506 cases in European countries up to 31 July 2023) and their fatal outcome (n=51,740) associated with COVID-19 spike-based vaccines is more than alarming. With an average of 2,338 people affected per day in European countries, of whom an average of 54 per day died from adverse effects by 31 July 2023 (2.3% of vaccinated people with adverse effects), the decades of experience with conventional vaccines were far exceeded[6] as was the Covid-19 fatality rate[1-3].

Conclusions

The preconditions for spike effects, their systemic distribution as well as their prolonged detection after vaccination, are given, thus contradicting the claimed only regional and time-limited efficacy. The time window for assessing a possible association between suspected adverse effects and spike vaccinations must therefore be extended to the maximum duration of spike detection.

The spectrum of adverse reactions associated with spike-based vaccination is inappropriately broad, affecting almost all essential vital functions of the human organism. The severity of adverse reactions is alarming. The unique class-specific ADR profile of spike-based Covid-19 vaccines reflects their mode of action - downregulation of the cardioprotective enzyme ACE2 with subsequent dysregulation and activation of the RAAS, increase in Ang II influences, restriction of the antipathogenic ACE2/Ang1-7/MAS/AT_2R axis, direct spike effects and cell fusion, RAAS independent responses, synergismen with catecholamines, DABK and/or TLR4, interactions with the co-receptor heparan sulphate. Galenic details of the finished vaccines can only modulate this harmful basic mode of action. The occurrence and severity of an adverse reaction in each individual case is influenced by many individual factors such as health status, stress-situation, co-morbidity, genetic characteristics, gender, age, presence of anti-/autoantibodies, etc.

Knowledge and assessment of the influence of these relevant factors are the basis for successful therapeutic intervention. An individualised approach depending on symptoms and differentiated diagnosis is essential. Any stimulation of the RAAS as welll as comedication with vasoconstrictive, catecholaminergic or TLR4 and DABK activating and heparan sulphate inhibiting drugs should be avoided for the duration of spike efficacy.

Due to the special properties of the spike-inducing Covid-19 vaccines and the presumably numerous influencing factors to which spike production in the organism of the vaccinee is subject, both the predictability of efficacy and that of ADRs is considerably limited; in principle, the variability of spike-induced reactions is multiplied.

In any case, it must be taken into account that the informative value of the adverse event figures documented by established pharmacovigilance systems is significantly impaired by under-reporting due to lack of knowledge of the mode of action or ignorance of possible correlations, lack of willingness to report and provide information on the part of healthcare providers or a focus on other necessities. In order to avoid wrong decisions, the authorities are urged to analyse in detail not only a few suspicious adverse drug reactions (e.g. only 1.59% of all reported cases[92]), but the whole spectrum.

From a pharmacological point of view, spikes are highly active substances, but not tolerable simple antigens. Due to their uniquely broad, intolerable spectrum of adverse reactions, spike-based vaccines are therefore not suitable for immunisation to avoid comparatively harmless infections. Preventing harmful influences on the health of every person should be a top priority.

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