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ORIGINAL RESEARCH ARTICLE

Risk Perceptions in Diabetic Patients Who Have Experienced Adverse Events: Implications for Patient Involvement in Regulatory Decisions

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Abstract

Background Increasingly, patients are expected to influence decisions previously reserved for regulatory agencies, pharmaceutical companies, and healthcare professionals. Individual patients have previously represented their patient population when rare, serious adverse events (AEs) were weighed as part of a benefit-risk assessment. However, the degree of heterogeneity of the patient population is critical for how accurately they can be represented by individuals.

Objectives This study aims to explore patients' risk perception of rare, serious adverse effects of medicines with regard to blood glucose-lowering antidiabetics used by the individual patient.

Methods Semi-structured interviews were conducted with 18 patients with diabetes with self-perceived serious, but not necessarily rare, AEs (e.g. stroke or valve or bypass surgery). The interviews explored the patients' history of disease, perceptions of the terms rare and serious, and overall levels of risk aversion. A thematic analysis of the interviews, including a consensus discussion, was carried out.

Results Interestingly, respondents rarely made a clear distinction between medicines-induced AEs and complications related to disease progression. Concerns regarding AEs were apparently diverse but were systematically related to the personal experiences of the respondents. Respondents routinely ignored information about possible rare, serious AEs, unless it could be related to personal experience. In the absence of experience, concerns were focused on common and less serious AEs, thus disregarding rare and more serious events.

Conclusion The study suggests that experience of AEs, related to either medicines or disease, constitutes an important factor of patient risk perception. We therefore propose that serious adverse experiences should be added to the traditional panel of socioeconomic factors that are accounted for when patients are invited to give input on regulatory decisions.

Key Points

The interviewed patients primarily described experienced events that had either obstructed everyday life or were particularly frightening as serious, and these were the focus of future concern.

Patients who seemed alike were not concerned with the same type of adverse events (AEs), suggesting attitudes towards AEs of diverse patient groups are not easily represented.

The study suggests that the personal experience of patients with AEs should be considered when authorities seek to include patients in developing regulatory decisions.

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1 Introduction

A favorable benefit-risk assessment (BRA) is pivotal to the approval of a new pharmaceutical product.[1] In pursuit of an 'explicit, consistent, transparent, and aggregate' [1] foundation for BRAs, considerable efforts have been dedicated to the development of numerous qualitative and quantitative methodologies [2–6]. To improve the tools of decision making, companies and patient organizations have recently encouraged the inclusion of patients in the decision making of market approval processes of medicines authorities [7–11]. Patients can be involved in different stages of regulatory decision making, including weighing the benefits of a medicine against risks to assess whether a final market approval should be granted. Patients are considered important in this process, first because they are the ones to receive the medicine and live with the consequences of the decisions taken and, second, because their views appear to be lacking in regulatory decision-making processes, as lay people's risk-assessment of medicines have been found to differ from those of experts [12–14]. Hence, recent studies conducted in the medical field of risk perception show that patients estimate benefits higher and risks lower than regulators and healthcare professionals, regardless of the intervention, clinical context, or patient population involved [15].

A particular difficulty in granting marketing authorizations of pharmaceutical products is determining the impact of rare, serious adverse events on decisions. One difficulty relates to the predictive power of clinical trials, as even sample sizes of 4000 participants are too small to detect rare events [16–18]. Hence, uncertainties about rare adverse events (AE) exist at the time of approval. The other challenge is defined by the perception of the seriousness of an event should it occur. Studies have shown that experts and patients weigh AEs differently. Patients weigh impact on everyday life higher compared with experts [19], and highest among adverse drug reactions [20]. The difficulty is further accentuated in case of the combination of rare and serious events because the basis for weighing is often inadequate.

Risk perception is the subjective judgment that people make about the characteristics and severity of a risk. This definition of risk perception proposed by Starr in 1969 is still widely used. Gierlach et al. narrow the definition and describe a subjective judgment about the felt likelihood of encountering hazards when objective information is minimal as an inherently psychological construct [21]. Factors that affect the psychological construct of risk perception are the matter of the theoretical framework of cognitive biases. Described as predictable deviations from rationality [22], descriptions of cognitive biases aim at, and often succeed in, characterizing factors affecting risk perception. A variety of biases have been proposed within the framework and several are relevant to risk perception regarding rare, serious AEs: events present in the memory (available) are assessed as having a larger perceived risk of occurring (Availability bias) [23, 24]; the tendency to avoid choices with unknown probabilities (Ambiguity effect) [25]; neglect of background incidence and focus on individual cases (Base rate neglect) [26]; the tendency to stick to an established belief in the face of new evidence (Belief revision) [27]; the tendency to prefer immediate payoffs as opposed to later payoffs (Current moment bias) [28]; and the tendency to focus on impact and disregard probability when making decisions under uncertainty (Probability neglect) [29].

The cognitive biases presented above show that the perceived risk can be very different from an objective risk, supported by Klein and Stefanek [30]. When experience and information are abundant, this difference reduced. Considerations regarding rare, serious AEs are therefore particularly vulnerable to cognitive biases. Furthermore, little is known about how patients consider the risk of future rare, serious AEs in relation to treatment for one or more chronic diseases that have not progressed to an invalidating stage, such as diabetes, and cardiovascular and pulmonary disease.

Patients affected by chronic disease have been described as heterogeneous (diabetes [31], chronic obstructive pulmonary disease [COPD] [32], rheumatoid arthritis [33], and asthma [34]). Such heterogeneity is a challenge for patient involvement since representability is greatly influenced by intervariability. Patients have previously been involved in, and subsequently impacted, regulatory decisions [35–37], a canonical example being involvement of patients severely affected by relapsing late-stage multiple sclerosis contributing to the BRA of the medicine Tysabri®. No assessment of the heterogeneity of the involved patients could be found but it stands as an example of patient homogeneity that is probably not reflected in the large groups of chronic diseases. Knowledge about how patients perceive rare, serious risks is crucial in order to qualify patient input in future regulatory decisions for the treatment of diseases that are among the most prevalent globally.

The aim of the study was to explore patients' risk perception of possible rare, serious adverse effects of

[1] In this study, pharmaceutical products will be termed *medicines* according to European convention; however, the term *drug* is standard in the US. The difference in terminology is apparent in the names of the respective regulatory agencies: US FDA versus European Medicines Agency. The term *drug* encompasses substances that exert an effect in the organism, whereas the term *medicines* is given as the subset of drugs used to treat or prevent a disease or an unwanted condition.

medicines with regard to blood glucose-lowering antidiabetics used by the individual patient.

2 Methods

To explore patients' risk perception of rare, serious adverse effects of medicines with regard to blood glucose-lowering antidiabetics used by the individual patient, a semi-structured interview study was conducted. This method was chosen to explore the often very personal, even intimate perceptions, attitudes and experiences that patients consider important in relation to AEs [38].

Diabetes was found to be suitable to study rare, serious AEs in a heterogeneous patient population. A long timeframe from diagnosis to death, as well as multiple treatment options, could potentially result in multifaceted perceptions of risks and benefits with respect to treatment and disease progression [39]. In addition, antidiabetic treatment has been subject to long-standing regulatory attention, with specific regard to the occurrence of rare, severe cardiovascular events [40, 41].

2.1 Interview Guide

The purpose of the interview guide was to expose the reasoning behind the concern, if present, for future rare, serious AEs. The themes and questions of the interview guide were based on a literature review of risk perception [42–45] and burden of diabetes [39, 46–49]. These reviews suggested that risk should be expected to be perceived differently between individuals. The interview guide accommodated this by posing open questions, with the opportunity for the researcher to follow-up.

The first part of the interview guide explored patients' medical histories, with a focus on their positive and negative experiences with diabetes medicines as previous experiences have been described to be important for individual risk assessments [23].

The second part focused on how participants understood and used the terms rare and serious. Participants were asked to describe the meaning of the terms in the context of AEs and, if possible, to give examples of both rare and serious events.

The third part of the interview guide was designed to let respondents express how prevalence and seriousness contributed to the perceived risk of specific AEs. To obtain this, patients were presented with a slightly modified table of AEs (AE table) from the relevant glucose-lowering pharmaceutical product that each individual patient had been treated with. The participant was asked to think out loud while reading through the entire table. Information about manufacturer, brand name and dosing are not part of the results, analysis, and discussion. The table was taken from the Summary of Product Characteristics (SmPC) on the website of the European Medicines Agency, and supplemented with numerical prevalence intervals from common to very rare (1:10–1:10000).

The initial intention of presenting participants with the AE table was for them to rank the AEs in the AE table from most to least dreaded. The first three respondents were unable to provide such ranking of AEs based on the AE table; however, instead, they gave rich details related to the listed AEs they had themselves experienced. The interview guide was therefore changed to investigate which AEs on the list were given attention and why.

2.2 Sample

Inclusion criteria were diagnosed with type 2 diabetes, undergoing treatment with a blood glucose-lowering pharmaceutical, and experience of a cardiovascular, nephrotic, or peripheral nerve complication that patients themselves judged as serious. This strategy enabled the recruitment of respondents who could give anecdotal rather than hypothetical responses. Recruitment of patients having experienced a rare event with a confirmed relation to an antidiabetic was considered not feasible.

Participants were recruited from all parts of Denmark between September 2015 and May 2016. As the recruitment of participants for the study proved difficult, participants were recruited from several recruitment channels: the website of the Danish Diabetics Association (DDA), through chairpersons of the 92 local chapters of the DDA, Danish diabetes Facebook groups, and relevant staff of nursing units of 130 municipal health centers, along with diabetic/metabolic/endocrinological/cardiovascular clinics of 13 public hospitals across the country.

2.3 Data Collection

Each respondent was given information about his or her participation, both orally and in writing. Participants signed an informed consent form prior to the start of each interview. The interviews were held in the patients' homes.

Parts 1, 2, and 3 of the interview guide were addressed in this order in the interview setting. During each interview, the researcher gave summaries and brief interpretations when possible, thereby allowing respondents to verify the initial interpretations of the researcher. This incorporated the initial phases of the analysis in the interview, and not only simplifies these early analytical steps but also places the analysis on firmer ground, as described by both Morse et al. and Kvale and Brinkmann [50, 51]. As most respondents had difficulties explaining their perceptions,

reformulations of questions and extensive probing were carried out [51, 52].

A debriefing routine was completed after each interview, with the first author conducting all interviews. The interviews were audio recorded and transcribed verbatim. No financial incentives were offered or transacted.

2.4 Data Analysis

The analytical approach used was based on the six phases of thematic analysis described by Braun and Clarke [53]. The analytical process enabled the authors to explore risk perception regarding rare, serious AEs in patients despite varying degrees of preconceptions. The first six interviews were analyzed in parallel by the first and second authors. After initial coding and theme identification [54], the researchers aligned inductive outcomes through discussion. The established themes were presented, discussed, merged, and adjusted. The remaining 12 interviews were deductively analyzed by the first author and added to the analytical corpus. The third author independently evaluated the coherence between the previously established themes and the analytical output after reading all interviews.

The analytical process gave rise to three themes. The first two showed, as planned, how respondents defined rare AEs and serious AEs, respectively, whereas the last theme inductively emerged from the interviews. It demonstrated how respondents handled rare versus serious AEs based on prior experience.

Qualitative studies aim to achieve saturation, the threshold where further interviews reveal no new significant aspects of the research topic. The last three respondents did not present considerations that had not been previously expressed by other participants and it was concluded that the most prevalent themes had been captured. However, it should be noted that one of the last three respondents presented a unique example of how to consider rare AEs, and this parameter is not claimed as saturated (see Fig. 2, right).

3 Results

3.1 Participant Demographics

Eighteen interviews were included in the study. The interviews took between 30 and 130 min, with an average of 70 min.

Participants were 55–83 years of age, with a median age of 72 years, and had been diagnosed with type 2 diabetes between 1 and 28 years prior to the study, with a median of 16 years. Thirteen of the 18 respondents were male and all were Caucasian. The following channels of recruitment were employed (successful contacts in brackets). Chairpersons of the 92 local chapters of the DDA were personally contacted via mail (n = 4), and personal indirect contact (n = 1) and contact directly via Danish diabetes Facebook groups (n = 1) was employed. Phone calls were placed with relevant staff, often the Nursing Head of Unit, to increase attention to leaflets sent to the 130 Municipal Health Centers (n = 5) and to the diabetic/metabolic/endocrinological/cardiovascular clinics of the public hospitals across the country (n = 9).

Reported experienced AEs that were considered serious included impaired vision, kidney failure, neuropathy, sexual dysfunction, and cardiovascular disease. See Table 1 for respondent composition in terms of sex, age, duration of diabetes mellitus type 2, medication, and the adverse experiences mentioned during the interviews.

3.2 Characterization of Serious Adverse Events (AEs)

When respondents described the term serious, they gave examples of events related to both disease progression and medical products. Hence, respondents consistently referred to personal experience when describing the term serious (see Fig. 1, left). In other words, when reflecting about seriousness, only a few respondents recalled information about potential serious AEs related to medicines or disease progression that was not related to personal experience (see Fig. 1, right).

Participants often did not distinguish between medicines and disease progression as the cause for serious AEs.

> Interviewer: *"Regarding side effects, what would be serious to you?"*
> Patient 02: *"The eyes. If I couldn't see any more, that would be terrifying. And the eyes are a typical side effect."*

In this example, Patient 02 seems to be mistaking the term side effects for the term complications. Other examples include Patients 04–09, 16 and 17 who initially, during the interview, specifically stated that they had not experienced any medicines-related AEs, but later in the respective interviews respondents described AEs as linked to the ingestion of a medicine. Two participants specifically stated that they did not know whether experienced AEs were due to medication or due to disease.

Most respondents' characterization of events included two aspects: lasting negative influence on everyday life (e.g. sexual dysfunction, immobilization, heart failure) and/or an alarming event (anaphylactic reaction, myocardial infarction, amputation). Furthermore, respondents often related ongoing events to their description of the term serious (see Fig. 1, lower right). However, particularly

Table 1 Overview of respondent demographics

ID[a]	Sex	Age, years	DM2[b]	Treatment[c]	Health issues experienced, and self-reported during interviews
Pt01	M	68	21	A, B, C	Cardiac valve replacement, cardiac output, gastroparesis, vision, kidney failure
Pt02	M	73	16	A, C1, C3	Cardiac valve replacement, double coronary bypass surgery, familial hypercholesterolemia
Pt03	F	72	1	A	Pacemaker, cardiac output, thrombosis (site unknown), vision, shortness of breath, cough, bilateral hip–single knee joint replacement, arthritis
Pt04	M	74	20	A, B, C2	Myocardial infarction, heart failure, sexual dysfunction
Pt05	M	71	24	A, B, C, E	Hypertension, arthritis, neuropathy
Pt06	M	55	8	A	High blood pressure, acute cerebral thrombosis, nephropathy, gout, kidney function
Pt07	M	66	4	A, B	2× acute myocardial infarction, automated implantable cardioverter defibrillator, cardiac output, vision, atherosclerosis of lower extremities
Pt08	M	65	15	A, B	2× acute myocardial infarction, triple coronary bypass surgery, cardiac valve replacement, hearing, sleep apnea
Pt09	M	74	16	A, C1, C3	Distorted nerve signaling from lower extremities, vision
Pt10	M	83	20	A, B, C2, D	Quadruple coronary bypass surgery, pacemaker, shortness of breath
Pt11	F	72	6	A	Cardiac output, two cardioversions, cough, vision
Pt12	M	70	16	A, C	No perceived additional health issues
Pt13	M	75	8	A	Myocardial infarction, hypertension, hypercholesterolemia
Pt14	M	80	20	A, B, C	Triple coronary bypass surgery
Pt15	M	76	27	A, C2	Nephropathy, hypertension, hypercholesterolemia
Pt16	F	78	10	A, E	No perceived additional health issues
Pt17	F	71	28	A	Acute cerebral thrombosis, acute medicine-induced allergic reaction, hypertension
Pt18	F	55	16	C2	Pacemaker, respiratory function, thoracic pain, left-sided heart failure

M male, *F* female, *A* oral metformin, *B* glucagon-like peptide-1 agonist, *C* insulin (1: fast; 2: intermediate; 3: prolonged), *D* Selective sodium glucose co-transporter-2 (SGLT-2) inhibitor, *Pt* patient

[a] Respondent identifier

[b] Years since diagnosis of diabetes mellitus type 2

[c] Blood glucose-lowering treatment reported to have been received since diagnosis

alarming events stayed with the respondents and were a part of their risk perception.

Divergent views of the term serious were observed. Patients reported experiences as diverse as coughing, severe muscle pain, and thrombotic events as both serious and not serious.

> Patient 08: *"In the spring of 2016 I experienced two thrombotic events, one in the heart and one in the brain. Nothing serious – not at all. However, I was rushed to the hospital. I highly doubt if that was necessary."*

The diversity illustrates that events were perceived as either negligible or serious depending on the individual and the conditions surrounding the event.

Events were considered serious when they were associated with adverse impacts on quality of life. An example was Patient 04, who was treated for chronic heart failure, myocardial infarction, and a perforated colon. However, when describing the term serious, he described three conditions with little resemblance to these previous life-threatening experiences: sexual dysfunction, neurological changes (fearing amputation), and cataracts/decreasing visual function (fearing blindness). The neurological concern related to an experience in 1989 where, as a patient at a hospital, the amputation of the foot of another patient had made a lasting impression. The experience of both cataracts and retinal detachment had likewise made the respondent concerned for loss of vision.

3.3 Characterization of Rare AEs

Respondents often struggled when asked to describe the term 'rare' and often left the term unexplained, either because it was difficult for them to relate to the term 'rare' or because they did not find rare events to be relevant when considering personal risk. In particular, it was difficult to express if they had no previous experience considered as rare (see Fig. 2, left).

Four respondents considered rare events relevant. Among these, three different subjective definitions of the term emerged. More are speculated to exist. According to

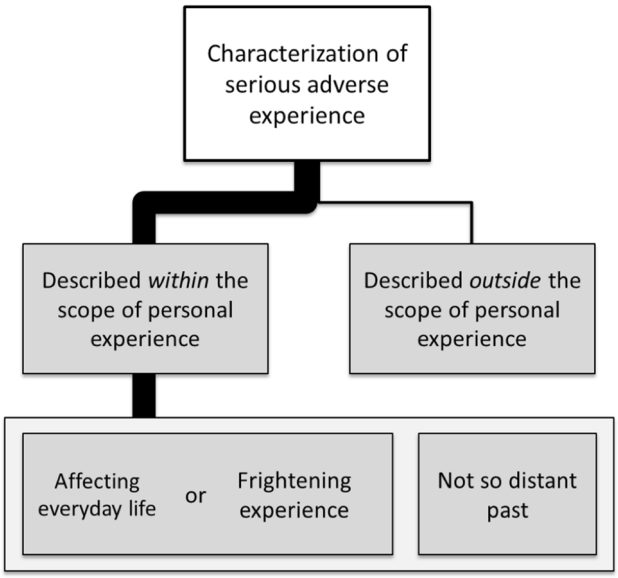

Fig. 1 Differences and similarities: how patients characterized serious. The *thickness* of the *line* indicates the frequency of statement. Schematic representation of what respondents drew upon when describing a serious experience. One respondent described the term serious using an example that did not relate to a personal experience. The *bottom box* represents characteristics of descriptions given within the scope of personal experience

these respondents, 'rare' could refer to (1) a regulatory construct, (2) events in an individual, or simply (3) events experienced once (see description below and Fig. 2, lower right).

First, when Patient 10 was asked if 'rare' was a threshold determined by authorities, i.e. related to the prevalence of an AE in a population of patients, the respondent explained that he had not paid attention to prevalence, rare or common, to the AE of shortness of breath, which he experienced chronically. However, he understood from the product information leaflet that the specific event was indeed rare.

> Patient 10: *They [the authorities] are the ones that establish that something is rare. They say this [chronic shortness of breath] can happen to 1 in 10,000 patients, but then I say well that one, that's me. I'm the 1 in 10,000."*

Second, 'rare' was described in relation to the ratio between experienced and potential events experienced by an individual. This was based on the following experience: over 16 years with diabetes, with between three to four blood glucose measurements per day, a participant had experienced hypoglycemic events only twice.

> Patient 09: *"Rare in my case – that must be something like low blood sugar."*

Third, one patient only took into account events that she had experienced *once* when describing what could be viewed as rare. After an event of 'three small blood clots in the neck', the respondent was administered antihypertensive treatment, resulting in a generalized anaphylactic reaction.

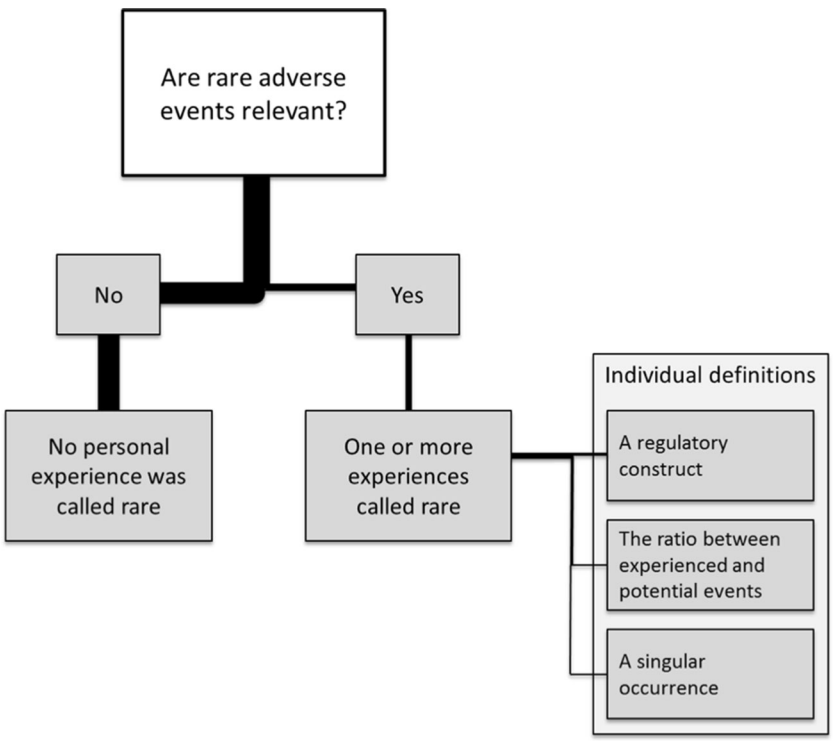

Fig. 2 Differences and similarities: relevance of rare adverse events to patient concern. The *thickness* of the *line* indicates the frequency of the statement

Patient 17: "One *time, you know, that is rare."*

Rare was described in terms of absolute occurrence, thus disregarding considerations of the occurrence of an event in relation to a population.

3.4 Concern for Future Rare, Serious Events

In general, participants were concerned about a gradual worsening of their health, but not with new types of AEs. If concerned about AEs, the concern was based on previous experience of the respondents, and only events considered serious were the cause of concern for future AEs. Presented information about events that had not been experienced did not give rise to concern. Participants had different strategies to cope with concern for serious events.

Seriousness, described as limitations to everyday life or recent frightening events, was a requirement for an experience to cause future concern.

Patient 18 illustrated how concerns for future serious, rare events were considered in the scope of current experience. Earlier in the interview, Patient 18 had described both heart and lung complications.

> Interviewer: *If this list had presented heart issues – would that have caused concern for you?*
> P18: *Yes.*
> Interviewer: *If this list had presented respiratory issues – would that have caused concern for you?*
> P18: *Yes, it would – because I'm both a heart patient and a lung patient.*
> Interviewer: *If it had also been very rare – 1 in 10.000?*
> P18: *Yes – I would have to consider it. I would, because I have enough issues with my current conditions. So, you do not want to add to that, right? Not if you can avoid it.*

The events that were the focus of concern for participants varied greatly but were related to prior adverse experiences. Patient 03 illustrated this finding when she was asked what type of AEs would make her reconsider a medicinal treatment:

> P03: *"That could be a very small adverse event, like headache. I have suffered from migraine in the past and it is among the most horrible conditions."*

In contrast to experienced serious events, which could elicit concern, participants clearly indicated that information alone did not cause concern (Fig. 3, lower left). Hence, the AE table was generally read as a checklist that confirmed experienced events rather than a source of information for future possible events.

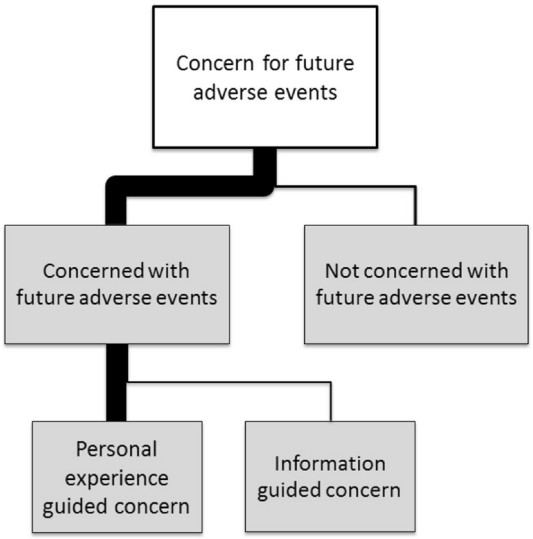

Fig. 3 Differences and similarities: patient concerns regarding future adverse events in relation to previous experience. The *thickness* of the *line* indicates the frequency of statement

> P07: *"I would only react to something I have experienced."*
> P17: *"Well, if I experienced new symptoms I would definitely check with this paper. I would. Otherwise, I wouldn't."*

Furthermore, when respondents read through the AE tables, they focused on the less serious, prevalent events, for example hypoglycemia, itching and constipation, rather than seemingly more serious, rare events, such as anaphylactic reactions, renal failure, and neuropathy. Patient 05 illustrated this tendency:

> Patient 05: *"Well, there is no doubt that I would always focus on the very common, the ones seen the most, however common they are. I become less and less interested the more we approach rare. I do not belong in the very rare category."*

Concerns were handled differently. Three approaches were observed, all consciously or subconsciously neglecting risks.

Respondents with close and positive relations with their healthcare professionals (both nurses and doctors were mentioned) deliberately placed confidence in the ability of the professionals to assess the possibility for future AEs.

> Interviewer: *"Do you lose interest when we discuss the rare and very rare?"*
> Patient 13: "*No, no. It's just that somebody else will deal with this if it appears. I think that they have it under control."*

Similarly, these patients also trusted the healthcare professionals to detect and act on AEs should they occur in the future.

Another conscious approach was to acknowledge but disregard the risk. These respondents considered future risk as insignificant and hypothetical in comparison with their experienced severely affected health.

> Patient 03: *"I couldn't worry about something that I'm not experiencing. It's as simple as that. I've got too much on my plate. Remember – I've got three chronic diseases."*

Since, the concern for future medicine-related AEs was exceeded by the concern for present-day disease and complications, respondents did not let a potential risk affect their current concern.

Third, one respondent subconsciously neglected AEs of drugs if they overlapped with known diabetic complications.

> Patient 12: *I see retinopathy as a known problem in relation to diabetes. Therefore, I don't interpret this information as if retinopathy is related to this treatment.*

When a potential AE caused by a medicine is instead allocated to the disease progression, the perceived risk related to the medicine is lowered. If interpreted as an additional risk for an already likely complication, the perceived risk related to the medicine would be increased.

4 Discussion

In summary, this study places personal serious adverse experiences as a central factor impacting the perception of risk and a driver for future concern in the context of health. The results of this study also describe unexperienced events as not evoking concern. Only respondents who recalled an event that was considered as rare expressed concern for future rare AEs. These associations are, for the first time, proposed as relevant for patient involvement in regulatory decisions.

Respondents had, if any, different definitions of the term rare. The term serious was defined according to their own experience, leading them to focus their concern on less serious, more prevalent events instead of more serious, less prevalent events.

Respondents had very different concerns, and had these formative previous experiences not been first described by the patients and connected by the analysis of this study, their concerns would have seemed completely unrelated.

It was found that past personal experiences were the main determinant of risk perception. However, not all respondents with previous adverse experiences reported increased levels of concern. These respondents had outsourced or projected their concerns to healthcare professionals. This observation mitigates the apparent difference between respondents reporting concern and a lack of concern for future AEs.

The Social Amplification of Risk Framework (SARF) describes the process of individual risk assessment as highly influenced by previous experiences [55]. This theoretical suggestion is aligned with the subset of respondents described here who report heightened concerns about AEs that overlap with previous experiences.

4.1 Future AEs

Respondents related the risk of future AEs to previously experienced similar events. This complements prior research by Knuth et al. where personal experiences with an AE was shown to increase the perceived risk of that event occurring again [56]. The findings are also in accordance with the availability bias described by cognitive bias theory, stating that "events that can be more easily brought to mind or imagined are judged to be more likely than events that could not easily be imagined" [23, 24].

Patients with no recalled adverse experiences largely ignored the risk of a rare and serious event. Conversely, an event recalled as frightening triggered the aversion of risk factors for a similar event. The theory of probability neglect [29, 57, 58] predicts that "Affect-rich outcomes yield pronounced overweighting of small probabilities" [59]. In the present study, the concerns of the respondents were focused on even minor events that could worsen their present condition, rather than rare serious events.

4.2 Rare or Serious Events

Patients gave contradicting descriptions of the term 'rare'. One patient explained that his adverse experience was listed in the AE table as rare but he did not feel the rarity since he felt the effect every day. This underpins the binary nature of an experience. From this perspective, an event is either experienced or not, and, therefore, never considered rare.

Another patient described thousands of repeated actions (blood glucose measurements) as a reference for a rare event (two cases of hypoglycemia). Under the regulatory approach, one or multiple events experienced by the same individual are counted as one occurrence [60]. However, in the case of hypoglycemia, more than 10% of patients treated with sugar-lowering medicine will experience the event. This demonstrates an extreme difference between respondents' perception of hypoglycemia as rare, while

health professionals consider hypoglycemia to be one of the most prevalent AEs of antidiabetic treatment.

The framework of cognitive biases provides common deviances from rationality. The alternative perspectives regarding relevance of prevalence and the term rare proposed by respondents do not fit a certain type of cognitive bias and do not present as deviances from rationality.

Regarding serious events, there was a common theme in the respondents' descriptions. The term serious was mainly related to previous personal experience and was often related to the effects of such experiences on daily life. For the patients interviewed, a recent life-changing event was often considered to be more serious than a singular life-threatening event that occurred a long time ago and that had only a minor influence on daily life.

Respondents did not align with regulatory criteria for seriousness. While the regulatory criteria all relate to the consequences of an event [61], the observed patient criteria also relate seriousness to perceived likelihood, to whether the events have been experienced, and, if so, how far back in time such an experience took place. The results confirm and add detail to the existence of a certain mismatch in the dimensions of risk assessment between patients and regulatory decision makers [62].

4.3 Participant Causality Assessment

From the interviews, it emerged that respondents linked AEs to both disease progression (complications) and medicines (side effects). The interviews detailed three underlying reasons. First, a misunderstanding of terms such as complications, AE, and side effect was observed. Second, participants revealed that they did not have the immediate impression of being exposed to medicines-related AEs. Such relations came to the respondents' attention later and after probing as a result of other relevant information given in the interview by the respondent. Third, when the terminology was understood, and events were remembered, it was still unclear for respondents whether to link disease or medicine to an AE. These are known problems inherent to the discipline of causality assessment, the methodology of which was described in the early 1980s by Naranjo et al [63]. The divergences among respondents emphasize that elicitation and categorization of adverse experiences could be influenced by at least the observed factors. A recent study proposed a methodology for self-assessment of adverse drug reactions [64]. The authors also present literature on patient causality assessment.

4.4 Strengths and Limitations

The inclusion criteria were selected to recruit patients with experienced AEs to the study. These criteria ensured that the interviews were not set in a hypothetical frame of risk perceptions. However, this inclusion criterion did not ensure that all participants had experienced a confirmed medicine-related AE. Within the frame of the inclusion criteria, it was sought to increase heterogeneity via the described multiple recruitment routes. The resulting sample is not heterogeneous regarding age, time since initial diagnosis, and sex, but, despite this homogeny, respondents were highly diverse in relation to perceptions of risk related to rare serious AEs.

Self-perceived serious AEs permitted inclusion to this study. However, during the interviews, two patients stated that their experienced AEs were not considered serious. These respondents confirmed the relevance of the inclusion criteria by stating that questions on seriousness felt irrelevant due to their lack of experience.

The authors consider the following instances of bias related to responder composition. Recruitment via local DDA chapters tended to favor the participation of more community-engaged patients. The community orientation of the chairs of local DDA chapters indicated that events experienced by patients that respondents felt some degree of responsibility towards impacted risk perception in addition to their personal experiences. Recruitment via diabetes clinics was staff-mediated and favored the participation of those with good relations to staff members, while recruitment via health centers favored the participation of patients with curiosity towards research, initiative, and enough confidence to respond to the invitations distributed.

A majority of respondents were male. Although a more balanced composition was desired, there was no indication that prior experience was more or less formative of the risk perception of either male or female participants. However, men are reported to be more permissive of risk than females [65].

The age of 72 years (median) and time since diabetes diagnosis of 16 years (median) indicate a group of participants who have had a long time to consider health-related risks. The findings of this study should be explored in a broader spectrum of patients to investigate the degree of impact from personal experience on risk perception.

A registry-based approach to recruitment could have been feasible, but was considered disadvantageous due to a lack of self-perceived seriousness criteria. The employment of a multi-track parallel recruitment strategy increased diversity, but not to a level where this sample could be considered representative for patients with diabetes in Denmark.

Nonetheless, there was no indication among respondents that risk perception was tied to the specific disease. Had the focus of respondents been on the development of complications through disease progression, or specifically related to a barrier for invasive treatment, for example, this conclusion might have been the opposite. The findings are therefore not considered

to be restricted to patients with diabetes; however, alignment to other disease groups should be investigated specifically.

5 Conclusions

This study adds to the understanding of individual risk perception by proposing that concern for future AEs is driven by personal adverse experience. Events that were either recalled as frightening or chronically impacted quality of life were considered serious and, as such, qualified as a driver for future concern. Therefore, patient experiences should be investigated as a potentially pivotal stratification variable when eliciting risk perceptions.

The authors propose that prior adverse experiences of patients involved in regulatory decisions be documented and presented, preferably with an indication of what events were subjectively considered as serious. On this basis, the authors advise that, when regulatory decision makers find it relevant to qualify a decision with the input of patients, a multitude of patients with representative adverse experiences (including none) are included.

While this exploratory study identified prior experience as a potentially important factor in risk perception in the context of patient involvement, further research should determine its extent and magnitude.

Compliance with Ethical Standards

Ethical approval The confidentiality and anonymity of the data were ensured according to acting law. The study and the related data management was approved by the Head of Faculty and the Data Management Unit of the University of Copenhagen, Faculty of Health and Medicines. The Danish Data Protection Agency approved the study (Reference: SUND-2016-47). The study was conducted with the ethical standards of the Declaration of Helsinki. This includes adherence to the use of informed consent specified in the declaration.

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Conflict of interest Mikkel Lindskov Sachs is currently employed as a full-time industrial PhD student at the University of Copenhagen and Novo Nordisk A/S. Morten Colding-Jørgensen is a consultant and shareholder, Novo Nordisk A/S. Katarina Jelic, full-time employee and shareholder, Novo Nordisk A/S. Per Helboe, Sven Frokjaer, Sofia Kälvemark Sporrong, and Susanne Kaae have no conflicts of interest to declare.

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