

Risk Factors in Severe Anaphylaxis: Which Matters the Most, Food or Cofactors?

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■ Abstract

Background: The prevalence of anaphylactic shock, the most severe manifestation of anaphylaxis, remains unknown. Risk factors and biomarkers have not been fully identified.

Objective: To identify risk factors in patients who experience anaphylactic shock.

Methods: Using lipid transfer protein (LTP) allergy as a model, we compared the characteristics of patients who developed anaphylaxis and anaphylactic shock. We recorded demographics, pollen sensitization, foods ingested up to 2 hours before onset of the reaction, and the presence of cofactors. Culprit foods were identified through a compatible clinical history and positive allergology work-up (skin prick test and/or sIgE).

Results: We evaluated 150 reactions in 55 patients with anaphylaxis (134 reactions) and 12 with anaphylactic shock (16 reactions). Patients in the anaphylaxis group experienced twice as many reactions (mean [SD], 2.4 [2.5] for anaphylaxis vs 1.3 [1.5] for anaphylactic shock; $P<.02$). No relationship was found between any food group and severity of the reaction. The most frequent food involved in both groups of patients was the combination of several plant-derived foods (plant food mix), followed by peach and nuts. Indeed, in the reactions caused by plant food mix, the presence of a cofactor was observed more often than in other food groups. On the other hand, cofactors were not present in peach- and nut-related reactions. Exercise was the most frequent cofactor in all groups.

Conclusion: In our series, the severity of the reactions was not determined by the kind of food or presence of a cofactor. Anaphylactic shock seems to be an infrequent presentation that may be associated with other individual-related factors requiring further evaluation.

Key words: Anaphylaxis. Anaphylactic shock. Cofactor. Food allergy.

■ Resumen

Antecedentes: La prevalencia del shock anafiláctico sigue siendo desconocida. Aún no se han identificado completamente factores de riesgo ni biomarcadores.

Objetivo: Identificar factores de riesgo de shock anafiláctico.

Método: Utilizando la alergia a proteína de transferencia de lípidos (LTP) como modelo, se han comparado características de pacientes que han presentado una anafilaxia (An) y pacientes que han desarrollado un shock anafiláctico (SAn). Se recopilaron datos demográficos, sensibilización a pólenes, alimentos ingeridos hasta 2 horas antes del inicio de la reacción y la presencia o no de cofactores. El alimento implicado se identificó mediante historia clínica compatible y estudio alérgico positivo (*prick test* y/o IgE).

Resultados: Se evaluaron un total de 150 reacciones; 55 pacientes del grupo An sufrieron 134 reacciones, y 12 pacientes del grupo SAn sufrieron 16 reacciones. El grupo An experimentó el doble de reacciones por paciente (media [DS] 2,4 [2,5] en An vs 1,3 [1,5] en SAn, $p<0,02$). No se observó relación entre el tipo de alimento y la gravedad de la reacción. El alimento implicado con más frecuencia en ambos grupos fue la combinación de varios vegetales ("mix de vegetales"), seguido por el melocotón y frutos secos. No hubo cofactores implicados en las reacciones con melocotón ni con frutos secos. En ambos grupos el ejercicio fue el cofactor involucrado con más frecuencia.

Conclusión: En nuestra serie, el alimento y la presencia de cofactor no determinan la gravedad de una reacción. Los shocks anafilácticos parecen ser una presentación infrecuente y podrían estar relacionados con factores individuales que precisarán una evaluación más extensa.

Palabras clave: Anafilaxia. Shock anafiláctico. Cofactor. Alergia alimentaria.

Introduction

Anaphylaxis is commonly defined as a severe and life-threatening hypersensitivity reaction [1-3]. However, since there is no universally accepted definition, it is difficult to compare epidemiological data worldwide. In anaphylaxis, the most frequently affected organs are the skin, followed by the gastrointestinal tract, respiratory tract, and cardiovascular system. As observed in the European Anaphylaxis Registry (NORA) [4], respiratory or cardiovascular collapse during anaphylaxis may be fatal owing to a situation of distributive shock in which hypoperfusion of vital organs and tissues can lead to dysfunction and cell death. Despite the importance of anaphylactic shock, no worldwide epidemiological data are available, and only local registries exist [5-7]. The presence of comorbidities, such as atopic eczema/dermatitis and asthma [8], or specific triggers, such as drugs, has been associated with more severe anaphylaxis [9,10]. Indeed, there is abundant evidence that the presence of cofactors, such as exercise, alcohol, and nonsteroidal anti-inflammatory drugs (NSAIDs), can increase the severity of the reactions and/or lower the reaction threshold [11-16]. However, the risk factors specifically linked to anaphylactic shock are still unknown.

Plant foods are one of the most frequent causes of food allergy worldwide [17-20]. Thaumatin, 2S-albumins, and lipid transfer protein (LTP) have been associated with severe systemic reactions [21], although not particularly with anaphylactic shock. LTP is one of the most common allergens involved in plant food allergy in the Mediterranean area, although it is becoming more evident that this problem is not as geographically localized as once reported [22]. Several studies from northern Europe and Asia [23-25] have also shown LTP allergy to be a major concern. The severity of LTP allergy may vary widely [26], and risk factors for severe reactions have not been fully identified. Cofactors, as described for other allergens [27,28], may be associated with severe reactions in those patients [13]. However, no particular LTP-containing food has been linked to severity [26,29,30]. In any case, LTP allergy is a medical challenge owing to the potential severity of the reactions and the number of potential foodstuffs triggering the reactions, including vegetables, nuts, fruits, cereals, and legumes.

In this study we aimed to evaluate a group of patients with LTP allergy who had experienced anaphylaxis and to compare differences between those with anaphylaxis but no shock and those who experienced anaphylaxis and shock.

Patients and Methods

Patient Selection

We consecutively selected adult patients (>18 years) seen in the Allergy Department of Hospital Clinic, Barcelona, Spain who had a clinical diagnosis of anaphylaxis due to LTP allergy. Patients were classified into 2 groups according to clinical presentation. The anaphylaxis group, which included patients who had experienced anaphylactic reactions without manifestations of shock (grades 3 and 4), and the anaphylactic shock group (grade 5), which comprised patients who

presented only anaphylactic events with clinical signs of shock, such as respiratory or cardiovascular collapse, according to the definition of the Anaphylaxis Committee of the World Allergy Organization (WAO) [31,32].

We recorded demographic data, pollen sensitization, all foods ingested up to 2 hours before onset of the reaction, and the presence of a cofactor up to 4 hours before reaction onset, including NSAIDs, exercise, alcohol, menstrual cycle, and sleep deprivation.

Foods were grouped as follows: nuts, Prunoideae, legumes, cereals, vegetables, other fruits, and plant food mix. Plant food mix referred to a situation where more than 1 LTP-containing food was involved in the reaction (ingested at the same time, in the same meal) and the individual culprit could not be identified by the clinical history and/or allergology work-up (see supplementary table 1 for a breakdown of plant food mix).

All patients underwent skin prick testing (SPT) with a panel of aeroallergens and food allergens with commercial extracts and extracts used in the standard practice of our department following standard procedures. This included cypress, olive tree, plane tree, mugwort, wall pellitory, grass pollen, profilin, cow milk, egg, walnut, kiwi, peach, corn, wheat, chickpea, mustard, apple, hake, *Anisakis simplex*, shrimp, melon, green beans, peanut, hazelnut, lettuce, beef, and gliadin [33]. Prick-by-prick testing with the suspected culprit was performed when a commercial prick test was negative or not available. Total and specific IgE (sIgE) were measured in serum using ImmunoCAP (Phadia, Thermo Fisher Scientific) and values ≥ 0.1 kU/L were considered positive. sIgE for the suspected allergenic source and its LTP (when available) was determined. Microarray immunoassay using ImmunoCap ISAC (Phadia, Thermo Fisher Scientific) was also used to rule out sensitization to other panallergens and to confirm sensitization to LTP; values ≥ 0.30 kU_A/L were considered positive. A patient was considered to have LTP syndrome when LTPs from plant-food families other than peach or Rosaceae were recognized [26,34,35].

Oral challenge testing with suspect foods was ruled out owing to the severity of the reactions. The diagnosis was based on a compatible clinical history and confirmed sensitization to the culprit food by SPT and/or sIgE. In cases in which an NSAID was a suspected cofactor, an oral challenge test was performed under fasting conditions to rule out hypersensitivity to NSAIDs.

Statistical Analysis

The statistical analysis was performed using IBM SPSS 23 statistical software. Normally distributed quantitative variables were expressed as mean (SD); nonnormally distributed variables were expressed as median (IQR). Categorical variables were compared with continuous variables using the parametric *t* test and ANOVA together with the Tukey and Tamhane post hoc test. A *P* value < .05 was considered statistically significant.

Results

Population Characteristics

The study population comprised 67 patients with LTP-related anaphylaxis, who were divided into 2 groups according

Table 1. Demographic Data of Patients With Anaphylaxis and Anaphylactic Shock

	Anaphylaxis n=55	Anaphylactic shock n=12	P Value
Mean (SD) age, y	42.35 (12.41)	40.67 (11.68)	NS
Female sex, No. (%)	36 (65.45%)	9 (75%)	NS
Total IgE	144 (60.8-287.5)	108 (28.7-177)	NS
Peach sIgE	4.4 (1.5-11.7)	4.6 (0.8-10.8)	NS
Pru p 3 sIgE	5.8 (2-13.3)	3.7 (0.4-9.5)	NS
Ara h 9 sIgE	1.8 (0.5-4.8)	1.3 (0.3-5.4)	NS
Cor a 8 sIgE	0.9 (0.3-9.2)	0.8 (0.2-2.5)	NS
Jug r 3 sIgE	2.3 (0.5-1.7)	1 (0.4-3.6)	NS
Basal tryptase	4.1 (2.9-5.7)	3.8 (3-4.4)	NS

Abbreviation: NS, nonsignificant.

^aValues are expressed as median (IQR) unless otherwise stated. sIgE is expressed as kU/L.

to their clinical manifestations; the anaphylaxis group included 55 patients (82%), and the anaphylactic shock group included 12 patients (18%).

Table 1 shows demographic data, total IgE levels, tryptase, peach, Pru p 3 sIgE (as a marker of LTP allergy), and nut LTP sIgE (Ara h 9, Cor a 8, Jug r 3). There were no statistically significant differences in the study variables between the groups. LTP sIgE levels were lower in patients with shock, although the differences were not significant. In Supplementary Table 1, we specify all food sensitization identified through positive results in SPT (commercial and/or natural extracts) and/or sIgE and the food registered in the plant food mix group

Table 2. Sensitization Profile of LTP Syndrome Patients

	Anaphylaxis n=50	Anaphylactic shock n=11	P Value
	No. (%)	No. (%)	
Pru p 3 monosensitized	2 (4)	1 (9)	NS
Pru p 3 + 1 LTP	4 (8)	1 (9)	NS
Pru p 3 + 2 LTPs	8 (16)	3 (27)	NS
Pru p 3 + 3 LTPs	36 (72)	6 (55)	NS

Abbreviation: LTP, lipid transfer protein; NS, nonsignificant.

Table 3. Food and Cofactors Involved in the Reactions

Food group	Anaphylaxis n=134		Anaphylactic shock n=16		P Value
	No. of reactions, %	Food-disaggregated No. of reactions	No. of reactions, %	Food-disaggregated No. of reactions	
Prunoideae	16 (12) 2* (13)	Peach (14) Cherry (2*)	3 (19)	Peach (3)	NS
Plant food mix	77 (57) 51* (66)	-	8 (50) 3* (38)	-	NS
Nuts	15 (10)	Peanut (3) Walnut (5) Hazelnut (2) Several nuts (5)	2 (13) 2* (100)	Several nuts (2*)	NS
Other vegetables	9 (7) 5* (56)	Lettuce (3;1*) Tomato (2;1*) Cabbage (2*) Sunflower seed (2;1*)	2 (13)	Tomato (1) Sunflower seed (1)	NS
Cereals	3 (2)	Wheat (2) Corn (1)	1 (6)	Wheat (1*)	NS
Legumes	4 (3)	Chickpea (1) Lentil (1) Green bean (2)	-	-	NS
Other fruits	10 (7)	Banana (1) Apple (2) Orange (1) Pomegranate (1) Grape (2) Pear (2) Strawberry (1)	-	-	NS

Abbreviation: NS, nonsignificant.

*Number of cofactor-dependent reactions.

reactions. Sensitization to at least 1 LTP other than Pru p 3 was recorded in 96% in the anaphylaxis group and in 91% of the anaphylactic shock group. These patients fulfilled the definition of LTP syndrome definition. The median (IQR) number of sensitizations was 2 (3), with no statistically significant differences between the groups (Table 2). Only 10 patients were sensitized to profilin (8 in the anaphylaxis group). No sensitization to other panallergens was identified.

Food and Cofactors Involved in Anaphylaxis

A total of 150 reactions were observed in 67 patients: 134 (89%) were anaphylaxis and 16 (11%) anaphylactic shock (Table 3). Patients in the anaphylaxis group had significantly more reactions per patient than the shock group (mean [SD] 2.4 [2.5] vs 1.3 [1.5], respectively; $P=.02$).

In both severity groups, the food most frequently involved in the reactions was plant food mix, followed by Prunoideae fruits and nuts. Peach and walnut were the most frequent single foods identified as a culprit in the reactions in both groups.

Interestingly, legumes and fruits other than peach were never involved in anaphylactic shock. Peach was never observed in cofactor-dependent reactions in either of the groups. Nuts were only involved in anaphylactic shock when

associated with a cofactor or when several nuts were taken (Table 3).

Cofactors were involved in 43% (58/134) and 38% (6/16) of the reactions in the anaphylaxis group and anaphylactic shock group, respectively, with no statistically significant differences between them. Plant food mix was the food group most frequently involved in cofactor-dependent reactions and was significantly more common in the anaphylaxis group than in the anaphylactic shock group (88% [51/58] vs 50% [3/6]; $P=.04$). Exercise was the most frequent cofactor in both groups (33/58 [57%] for anaphylaxis and 3/6 [50%] for anaphylactic shock), with no statistically significant differences between them. Remarkably, more than 1 cofactor was involved in 9 reactions (8 anaphylaxis and 1 anaphylactic shock), with no differences between the groups (Table 4).

No differences in the kind of food or presence of a cofactor were observed between the groups in the subanalysis of patients sensitized to both LTP and profilin and subsequent comparison with the group that were sensitized only to LTP.

Pollen Sensitization

We found sensitization to at least 1 of the LTP-containing pollens tested in our routine panel (olive tree, plane tree, mugwort, and wall pellitory) in 57/66 (86%) patients; most patients (80% [51/64]) had pollinosis. Although no significant differences in pollen sensitization or pollinosis were observed between the groups, sensitization to olive and plane tree was more frequent in the anaphylactic shock group, and sensitization to mugwort was more common in the anaphylaxis group. Sensitization to plane tree was the most frequent type in both groups, with no differences between them (Table 5).

Discussion

The prevalence of anaphylactic shock, the most severe manifestation of anaphylaxis, is still unknown, and the risk factors associated with this entity are poorly defined. Using LTP allergy as a model, we compared the characteristics of 2 sets of patients who developed anaphylaxis and anaphylactic shock. According to the sensitization pattern, we observed that

Table 4. Cofactors Involved in the Reactions

	Anaphylaxis n=58	Anaphylactic shock n=6	P Value
	No. of reactions (%)	No. of reactions (%)	
NSAID	15 (26)	2 (33)	NS
Exercise	33 (57)	3 (50)	NS
Alcohol	2 (3)	0 (0)	NS
Several cofactors	8 (15)	1 (17)	NS

Abbreviation: NS, nonsignificant; NSAID, nonsteroidal anti-inflammatory drug.

Table 5. Pollen Sensitization Profile

	Anaphylaxis n=52	Anaphylactic shock n=12	P Value
	No. of reactions (%)	No. of reactions (%)	
Pollen sensitization			
Olive tree	16 (31)	5 (42)	NS
Plane tree	33 (63)	10 (83)	NS
Mugwort	29 (56)	4 (33)	NS
Wall pellitory	15 (29)	3 (25)	NS
Profilin	8 (15)	2 (17)	NS
Pollinosis	42 (81)	9 (75)	NS

more than 90% of patients were sensitized to different LTPs, in line with the results of other Spanish series [36,37], thus underlining the burden of LTP syndrome in Spain.

In our study, individuals who experienced anaphylaxis had almost twice as many reactions per patient than those experiencing anaphylactic shock. This finding was as expected, because after having experienced an extremely severe reaction such as anaphylactic shock, patients are probably more careful with their diet and/or are referred to an allergist faster than individuals with milder anaphylaxis (grade 3 according to the WAO definition [32]), who are frequently overlooked [38]. Another hypothesis is that the occurrence of anaphylactic shock may be linked to predisposition associated with yet-to-be-identified factors that are present only in specific individuals. Predisposing factors in patients who develop life-threatening anaphylaxis may include genetic mutations (as observed in patients with systemic mastocytosis), the KARS gene mutation (recently described in one patient with extremely severe hymenoptera allergy [39]), and defects in compensatory mechanisms [40], such as prostaglandin E2 (as recently observed in patients with hymenoptera venom [41] and LTP allergy [42]).

We did not find any obvious relationship between food type and severity, although we were able to make some interesting observations. When all reactions were pooled, most patients (54%) needed several LTP-containing foods in the same meal to develop a reaction. This observation is in line with the everyday habits of our population, which follows a Mediterranean diet, where it is usual to mix vegetables, fruits, legumes, and cereals, all containing LTP, in the same meal. Thus, in some cases it was not possible to identify whether the trigger was a single plant food, or the cumulative dose of LTPs from various sources, considering that the patients were sensitized to all of them. Interestingly, plant food mix was also the most frequent food group in cofactor-dependent reactions overall (anaphylaxis, 88%; anaphylactic shock, 50%), with significant differences irrespective of severity. In a series of cofactor-dependent food allergy patients [13,15], lettuce and wheat were the plant foods most frequently involved in the reactions.

Peach was the food most often involved in both anaphylaxis and anaphylactic shock in our study. This is unsurprising, given that peach is the most common cause of food allergy in Spain, Italy, and Portugal, mainly owing to sensitization to LTP [43]. Indeed, peach is considered the primary sensitizer in LTP allergy in southern Europe and, for this reason, the prototypic marker of sensitization to LTP [44]. Interestingly, all peach-related reactions in our study were cofactor-independent. Similarly, some series of cofactor-dependent LTP-related reactions have shown almost no peach-related reactions [13,15].

Walnut was the second most frequently involved food in the anaphylaxis group, with no cases of anaphylactic shock reported. Tree nut allergy accounts for up to 40% of deaths from food-induced anaphylaxis, and in some cases, tree nut reactions have been reported to be more severe than reactions to peanut [45]. In a recent study by Ballmer-Weber et al [46] comparing patients with walnut allergy from Spain, Germany, and Switzerland, sensitization to Jug r 1 but not to Jug r 3

(walnut LTP) was significantly associated with systemic reactions. Interestingly, in our series, nuts were only involved in anaphylactic shock when associated with a cofactor or when several nuts were consumed together.

Legumes were only associated with cases of anaphylaxis without shock, and no cofactors were involved. Legumes, excluding peanut, are an important cause of allergy in some geographical areas, mainly in children [47], and several allergens have been described, including LTP [48]. Some of these allergens, such as 2S albumins, have been associated with severe reactions [49,50], although almost no data are available on the characteristics of LTP-dependent reactions in legume-allergic patients.

Taking these observations together, we could speculate whether the LTPs from different allergenic sources might have different capacities for inducing an allergic reaction. Consequently, we might also ask why some allergenic sources usually “need” a cofactor, whereas others, such as peach, are able to induce severe reactions by themselves. Another interesting observation, as yet unresolved, is the amount of LTP needed to develop a severe reaction. This may be associated with the specific allergenic source, the way it is consumed (cooked or raw), and, perhaps, personal predisposition [50]. However, the studies performed by Christensen et al [52] and Brockow et al [53] in wheat-dependent exercise-induced anaphylaxis (WDEIA) would suggest that increasing the amount of allergen may suffice both to decrease the threshold level and to increase the severity of the reaction in the absence of a cofactor and regardless of the characteristic of the original reaction. For this reason, although other studies are needed, it may be important to identify all types of food sensitization in LTP-allergic patients, even if they are apparently asymptomatic [54,55]. Although these foods themselves may not induce a reaction, they may contribute to the onset of the final reaction when ingested with a sufficient amount of other LTP-containing allergenic sources.

In our series, exercise was the most frequent cofactor involved in both the anaphylaxis and the anaphylactic shock groups (57% and 50%, respectively), followed by NSAIDs. Using data from the European Anaphylaxis Registry [56], Worm et al [57] observed that vigorous but not mild or moderate exercise was a risk factor for more severe food-dependent reactions (OR, 2.06; $P < .0001$). Christensen et al [58] showed that NSAIDs are the most powerful cofactor in WDEIA patients, decreasing the threshold by 83%, compared with 63% observed for exercise or 36% for alcohol. Interestingly, we observed a nonnegligible rate of 14% in patients requiring more than 1 cofactor. Such a situation could arise quite easily in everyday life, for instance in women taking an NSAID for menstrual cramps or people drinking alcohol and dancing after dinner. Although we did not find that several cofactors were associated with severity, in WDEIA patients, NSAIDs and exercise together decreased the allergen threshold by 87%, thus indicating a partially additive effect [58].

Most patients in both groups were women. Previous studies have suggested that estrogens were associated with more severe reactions in mice [59] and that male sex was associated mainly with insect venom-related anaphylaxis [60]. Conversely, in a study based on the NORA registry, Worm

et al [57] found male sex to be associated with a higher risk of severe anaphylaxis, irrespective of the elicitor, including food, drugs, and hymenoptera venom. Our study is limited not only to foods, but to LTP-related reactions. In previous series of LTP-allergic patients, mostly with anaphylaxis, a slightly higher prevalence of females (around 60%) was recorded [22,61,62]. Together with our findings, these observations suggest that LTP allergy is more prevalent in females, rather than that severity is sex-related.

We found that patients were sensitized to all plant foods involved in the reactions owing to recognition of LTP. No panallergens other than profilin were identified in a small number of our patients. Although profilin has been associated with food-induced anaphylaxis [63,64], we believe that in double-sensitized patients (LTP and profilin), reactions were induced by LTP or both LTP and profilin; however, it is unlikely that symptoms were only related to sensitization to profilin. Furthermore, in contrast with other authors, we did not find any relationship between severity of the reaction and sensitization to profilin. In a series of more than 250 Spanish LTP-allergic patients from 2 geographical areas that include Barcelona, Bogas et al [37] found that double-sensitized (profilin and LTP) patients less frequently had peach anaphylaxis than those sensitized to LTP only. However, these authors did not compare the impact of profilin on the severity of anaphylaxis. In our sample, 13 of 55 patients from the anaphylaxis group experienced a reaction to peach, whereas only 2 (2/13 [15%]) were sensitized to profilin. In the anaphylactic shock group, on the other hand, none of the 3 patients who reacted to peach (3/12) had double sensitization. Therefore, consistent with Bogas et al, we found a low proportion of cases with double sensitization, although we would need a larger sample to draw conclusions on the “protective role” of profilin in different degrees of severity of anaphylaxis.

In contrast with other series [65], we found that pollinosis neither increased nor decreased the severity of the reactions. Sensitization to plane tree was the most common type, as expected, for 2 main reasons. Plane tree pollen is the most frequent sensitizer in respiratory allergy patients in Barcelona (37%) [66]. However, its prevalence in LTP-allergic patients is even higher, as previously shown by Enrique et al [67] in 2002, when plane tree sensitization was observed in 8% of patients with respiratory allergy and in 55% of those with LTP allergy. Cross-reactivity due to LTP in plane tree pollen and plant foods may account for this observation. The second most frequent type of sensitization was to mugwort pollen, which has no clinical relevance in our area and is related to LTP cross-reactivity, as previously described [68].

Our study is limited by recall bias. The particularities of the reaction, including food and cofactors, were collected some time after the acute reaction, with the result that relevant information may be missing. However, this is a real-life situation, in which avoidance recommendations and advice are based on the information offered by the patients. Our results may also be limited by the small number of cases of anaphylactic shock and other important factors that may be associated with severity, such as delay in seeking medical attention and administration of epinephrine, which were not evaluated in this study.

In conclusion, we did not find any risk factors for anaphylactic shock in the study variables, and neither individual foods nor cofactors seem to be associated with severity, although further studies with larger samples are needed to confirm these observations. In any case, our results suggest that different LTP sources may have different capacities for inducing severe reactions. For this reason, the risk of LTP-dependent anaphylaxis may be based on a particular combination of factors that are patient-dependent, including the allergenic source, the amount of allergen (cumulative dose), the presence of cofactors, and personal predisposition.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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