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Research Article

Association between Angiotensin II Type 1 Receptor Polymorphism and Sudden Cardiac Death in Myocardial Infarction

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Objective. The renin-angiotensin system is involved in the pathogenesis of coronary artery disease and myocardial infarction (MI). Angiotensin II (Ang II) has many adverse effects such as vasoconstriction and vascular remodeling, and these actions are mediated by the angiotensin II type 1 receptor (AT1R). *Patients and Methods*. A total of 1376 patients were recruited from January 2010 to April 2012. The study group consisted of 749 patients with ACS (317 females and 432 males) and of 627 healthy controls. *Results*. The ACS patients demonstrated a lower proportion of AA genotypes and AC genotypes but higher proportions of CC genotypes than the control population. The AT1R CC genotype conferred a 2.76-fold higher risk of MI compared with the genotype AC and AA. In addition, the CC genotype was also associated with a 4.08 times higher risk of left anterior descending artery infarction and a 3.07 times higher risk of anterior wall infarction. We also found that the CC genotype was independently associated with sudden cardiac death. *In Summary*. This study demonstrated that the AT1R CC genotype is an independent risk factor for ACS incidence, and this genotype is associated with a greater ACS severity and greater risk of sudden cardiac death.

1. Introduction

Acute myocardial infarction (MI) is defined as death or necrosis of myocardial cells due to an inadequate amount of oxygen supply to the heart. The classical symptoms of MI are shortness of breath, anxiety, chest pain typically radiating to the left arm or left side of the neck, vomiting, and palpitations. Important risk factors include previous history of vascular disease, such as atherosclerosis, angina, previous heart attack or stroke, and age—especially men over 40 and women over 50 years [1].

The renin-angiotensin system plays an important role in blood pressure regulation and homeostasis, and it is involved in the pathogenesis of coronary artery disease and MI [2–5]. Angiotensin II (Ang II) is a key component of the renin-angiotensin system formed by action of the angiotensin-converting enzyme on the precursor molecule angiotensin I. It has many adverse effects, such as vasoconstriction, cellular proliferation, vascular remodeling, and aldosterone secretion, and it contributes to endothelial dysfunction and atherosclerosis by promotion of oxidative stress [6, 7]. All these actions are mediated by the angiotensin II type 1 receptor (AT1R).

The *AT1R* gene is located on chromosome 3q21-q25, its length is >55 kb, and it is composed of five exons and four introns. It belongs to the superfamily of G-protein-coupled

receptors. The gene polymorphism in the present study was located at the untranslated 3′ region (A1166C), corresponding to an A → C transversion in the position of nucleotide 1166 of the mRNA sequence, resulting in an A/C polymorphism [8, 9].

Studies have been carried out to find an association between the A/C polymorphism of AT1R and MI. Some studies have revealed that the CC genotype is not associated with MI [10, 11], while others have observed that the CC homozygous genotype is associated with MI and coronary heart disease [12–14]. Tiret et al. found significant association between angiotensin type II receptor polymorphism and acute coronary syndrome. On the other hand, in the study by Gardemann et al. There was no detected association between angiotensin II type 1 receptor *A1166C* gene polymorphism and coronary artery disease. In view of these controversial reports, the present study was aimed at assessing the association of the A1166C polymorphism of the AT1 receptor gene with MI and sudden cardiac death.

2. Methods

The study was designed as a case-control study. Aim of this study was to determine the prevalence of polymorphisms of the gene for angiotensin II type 1 receptor and compare it with the healthy population.

A total of 1376 patients were recruited from January 2010 to April 2012 in the 5th Department of Internal Medicine, University Hospital Bratislava, Slovak Republic. The study conforms with the Declaration of Helsinki and Institutional Ethics Committee of the University Hospital Bratislava, and written informed consent was obtained from all the subjects.

The study group consisted of 749 patients with acute coronary syndrome (ACS patients—317 females and 432 males) with a mean age of 61.4 ± 9.7 years. All patients were admitted with acute coronary syndrome, and on the basis of typical ECG changes, elevated cardiac markers, clinical history, and coronary angiography (50% stenosis affected at least one major coronary vessel) the diagnosis was confirmed as MI. Blood samples were collected from patients after 12 to 14 hours of fasting. Simultaneously, blood samples were collected from 627 healthy, age- and sex-matched controls (male : female = 354 : 273) with mean age 54 ± 10.3. All controls were nonhypertensive and nondiabetic. Information on height, weight, body mass index, cigarette smoking, hypertension, diabetes, family history of coronary artery disease, and diabetes was collected using a structured questionnaire. Acute coronary syndrome was diagnosed on the basis of recommendations of European Society of Cardiology (ESC) [15, 16]. Hypertension was defined according to ESC guidelines as systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg, based on the average of two blood pressure measurements, or a patient's self-reported history of hypertension [17]. Diabetes was diagnosed if fasting plasma glucose was >110 mg/100 mL or the patient was on antidiabetic medications [18]. The reference value for cholesterol was 200 mg/dL and for triglycerides 130–150 mg/dL. Dyslipidemia was diagnosed according to ESC guidelines [19]. Coronary angiography was used to confirm the presence or assess the extension of coronary artery disease, and patients with obstructive lesions greater than 50% were selected for the study. Total cholesterol and triglyceride plasma levels were performed on automated analyzer Hitachi 917 Germany, using commercial kits supplied by Roche diagnostics (Mannheim Germany). Demographic and clinical characteristics are in Table 1.

Table 1: Demographic and clinical characteristics of ACS patients and healthy controls.

	ACS patients (n = 749)	Healthy controls (n = 627)
Mean age (years)	61.4 ± 9.7	54 ± 10.3
Sex (male/female)	432/317	354/273
BMI (kg/m^2)	28.4 ± 4.6	27.3 ± 5.4
Smokers n (%)	328 (43.79%)	163 (25.99%)
Fasting glucose (mmol/L)	6.4 ± 1.4	4.9 ± 1.2
Diabetes mellitus (%)	329 (43.65%)	0 (0%)
HbA1c (%)	7.3 ± 2.4	3.4 ± 1.5
Arterial hypertension n (%)	377 (50.33%)	0 (0%)
Systolic blood pressure (mmHg)	154 ± 16.4	124 ± 8.6
Diastolic blood pressure (mmHg)	93.6 ± 10.4	82.3 ± 6.7
Dyslipidemia (%)	213 (28.43%)	49 (7.81%)
Total cholesterol (mmol/L)	8.2 ± 1.7	4.3 ± 0.9
HDL-cholesterol (mmol/L)	1.5 ± 0.2	1.3 ± 0.3
LDL-cholesterol (mmol/L)	5.9 ± 1.6	2.7 ± 0.9
Triglycerides (mmol/L)	2.1 ± 0.4	1.3 ± 0.2

2.1. Genotyping Methods. Blood was collected in ethylenediaminetetraacetic acid. DNA was isolated from leukocytes according to standard procedures using proteinase K. DNA segments were amplified by polymerase chain reaction (PCR) in a total volume of 15 μL containing 0.1 μL Taq, 1.5 μL buffer, 2.5 μL $MgCl_2$, 0.5 μL dNTP, 0.5 μL of each primer, and 7.4 μL H_2O. The primers used were 5′-AGAAGCCTGCACCATGTTTT-3′ (sense) and 5′-TGTGGCTTTGCTTTGTCTTG-3′ (antisense). The reaction conditions were as follows: initial denaturation 95°C 5 min, then 33 cycles of denaturation 94°C for 30 s, annealing 53°C for 25 s, elongation 72°C for 25 s, final elongation 72°C for 10 min, and cooling 10°C for 10 min. The PCR product (233 bp) was digested by 5 U of Dde I for 12 h. The fragments were separated by electrophoresis using 3% agarose gel at 85 V and visualized by ethidium bromide staining under UV light. The AA variant was detected as one fragment (233 bp), AC as three fragments (233, 118, 115 bp), and CC as two fragments (118 and 115 bp).

2.2. Statistical Methods. Patient's age at diagnosis was recorded as a continuous variable and shown as mean ± standard deviation. The odds ratios (ORs) and corresponding 95% confidence intervals (CIs) for assessing the effect of the AT1R A/C genotype distribution and allele frequencies on ACS were calculated by logistic regression analysis with adjustment for relevant significant variables (Tables 4 and 5). All the statistical analyses were performed using SPSS 16.0

and Excel 2007. All statistical tests were two sided, and the level of significance was set at 0.05.

3. Results

Comparisons of the distributions of demographic and relevant clinical risk factors between ACS patients and healthy controls and the estimated OR for each risk factor are listed in Table 2. There was no significant difference in either the age or gender distribution between the two groups included. The prevalence of arterial hypertension (AH), dyslipidemia, and diabetes mellitus (DM) was significantly increased in acute MI patients as compared to healthy controls. Diastolic blood pressure (DBP) and systolic blood pressure (SBP), total cholesterol, and LDL-cholesterol were also higher in MI patients than in healthy controls. In the univariate logistic regression model, older age, higher systolic blood pressure or diastolic blood pressure and the presence of diabetes mellitus were found to be significant risk factors for ACS.

The distribution of the AT1R genotypes was in agreement with the Hardy-Weinberg equilibrium. The frequency of the A1166C polymorphism was significantly different between patients and controls ($P = 0.024$). Table 3 illustrates that ACS patients demonstrated a lower proportion of AA genotypes (32.17%) but higher proportions of CC genotypes (23.79%) than the control population (AA 50.39%, AC 42.90%, CC 6.69%). The AT1R CC genotype conferred a 2.76-fold risk of ACS compared with the genotype AC and AA (95% CI: 1.07–6.49, $P = 0.004$, logistic regression). After controlling for other risk factors, the CC genotype was still significantly associated with ACS, conferring a 4 times higher risk (OR = 4.295; 95% CI: 1.436–12.851). To further evaluate the etiologic effects of ATR1 polymorphisms in ACS, we analyzed the association between AT1R genotypes and different ACS manifestations (UAP and acute MI), relevant clinical risk factors (hypertension, diabetes mellitus, hypercholesterolemia, systolic blood pressure, diastolic blood pressure, and body mass index), clinical history (heart failure, CAD, MI, and family history), and history of smoking.

As shown in Table 4, the CC genotype conferred a significant 3.35-fold risk of acute MI (Table 2. 95% CI: 1.111–10.115, $P = 0.032$, logistic regression); however, there was no significant association between A1166C polymorphism and any other risk factor among the recruited ACS group. Subsequent analyses evaluated the possible influence of A1166C polymorphism on final ACS clinical outcome. The association between AT1R A/C polymorphism and ACS severity and mortality was determined. Interestingly, ACS patients with the CC genotype had a significantly higher risk of presenting with a greater number of stenosed vessels, with a 3.87 times increased risk of stenosis in all three coronary arteries (Table 5, 95% CI: 1.09–13.81, $P = 0.037$, logistic regression). In addition, the CC genotype was also associated with a 4.08-fold risk of left anterior descending artery infarction (Table 5, 95% CI: 1.04–9.12, $P = 0.042$) and a 3.07-fold risk of anterior wall infarction (Table 5, 95% CI: 1.04–9.12, $P = 0.024$). The CC genotype was found to be independently associated with sudden cardiac death in patients with ACS (Table 5, OR = 6.48, 95% CI: 1.04–40.60, $P = 0.036$, logistic regression).

4. Discussion

The AT1R is a major component of the renin-angiotensin system. It mediates most of the classical and biological functions of angiotensin II [20]. It belongs to the G-protein-coupled receptor superfamily and is a peptide containing 360 amino acids. Binding of angiotensin II to the AT1R in vascular smooth muscle cells results in phospholipase C-mediated generation of inositol 1,4,5-trisphosphate and diacylglycerol. Inositol 1,4,5-trisphosphate mobilizes calcium from the endoplasmic reticulum, and calcium and diacylglycerol activate enzymes, including protein kinase C and calcium/calmodulin-activated kinases. Ang II acts as a mitogen in vascular smooth muscle cells by activating several signaling pathways, such as that of phospholipase C, phospholipase A2, and phospholipase D, as well as activating a large number of kinases, such as tyrosine kinases, mitogen-activated protein kinases (MAPKs), c-src kinase, Janus-associated tyrosine kinase, and receptors with tyrosine-kinase activity. Ang II also stimulates transcription factors, such as the activating protein, signal transduction and transcription activators (STATs), and the nuclear factor kappa B (NfκB) [6, 20–22]. The AT1R has been shown to be involved in the process of vascular hypertrophy, sodium retention, cardiac remodeling, hypertension and fibrinogenesis [23–25]. The AT2 receptor plays a counter-regulatory role [6, 26, 27].

As described by Duncan et al. (2001), many polymorphisms of the *AT1R* gene have been identified, but the A1166C polymorphism has been the most extensively studied. The physiological significance of this polymorphism is uncertain because of its location in the 3′-untranslated region of the gene [28].

There are controversial reports regarding the role of *AT1R* gene A/C polymorphism as a risk factor for MI. Some studies have reported a positive association [12–14], while others could not find any association [10, 11, 28, 29].

In the study by Berge et al. (1997), 247 survivors of myocardial infarction (MI) were compared to 384 controls with respect to distribution of genotypes and gene frequencies in the A1166C polymorphism at the AT1R locus. No differences in allele frequencies or genotype distribution were observed when all patients were compared with all controls. When they compared CC homozygotes with the combined group of CA heterozygotes and AA homozygotes (CA/AA), a difference in borderline significance between the MI group and controls was observed ($P = 0.05$). In males alone, this difference was much more pronounced because of the larger proportion of males with the CC genotype in MI cases than in male controls ($P = 0.01$). No significant differences were observed between female cases and controls. When was the subjects subdivided into a "low-risk" and a "high-risk" group, based on levels of apolipoprotein B (apoB) and body mass index (BMI), and whether or not the person used lipid-lowering drugs, the frequency of CC homozygotes in male cases of the "low-risk" group differed significantly compared to the frequency in male controls of the "low-risk" group

Table 2: Distributions of demographic and relevant clinical risk factors between ACS patients and healthy controls and the estimated OR for each risk factor.

Subject characteristics	ACS patients ($n = 749$)	Controls ($n = 627$)	Univariate analysis OR (95% CI)	P	Multivariate analysis OR (95% CI)	P
AT1R-genotypes						
AA	241	316	1 (ref.)		1 (ref.)	
AC	329	269	1.17 (0.79–2.1)	0.603	1.284 (0.595–2.773)	0.524
CC	179	42	2.76 (1.07–6.49)	0.004	4.295 (1.436–12.851)	0.009
Mean age	61.4 ± 9.7	54 ± 10.3	0.75 (0.24–2.76)	0.98	1.25 (0.46–2.96)	0.425
Sex—male	432	354	1.53 (0.89–2.62)	0.123	—	—
Systolic blood pressure ≥ 140 mmHg	327	97	9.73 (3.44–17.16)	<0.001	6.97 (2.53–14.37)	0.003
Diastolic blood pressure ≥ 90 mmHg	94	23	5.92 (1.47–9.81)	0.002	3.65 (1.45–10.40)	0.004
Diabetes mellitus	329	0	14.22 (4.98–25.26)	<0.001	12.75 (3.41–23.58)	0.001

Table 3: Distribution of AT1R A/C gene polymorphisms.

ATR1 A1166C Polymorphism	ACS patients ($n = 749$)	Healthy controls ($n = 627$)	OR
CC (%)	179 (23.89%)	42 (6.69%)	OR = 2.76 (1.07–6.49), $P = 0.004$
AC (%)	329 (43.92%)	269 (42.90%)	OR = 1.17 (0.79–2.1), $P = 0.603$
AA (%)	241 (32.17%)	316 (50.39%)	OR = 0.43 (0.23–0.76), $P = 0.015$
C (%)	508 (67.82%)	311 (49.60%)	OR = 1.68 (1.17–2.41), $P = 0.004$
A (%)	570 (76.10%)	585 (93.30%)	OR = 0.59 (0.41–0.85), $P = 0.004$

($P < 0.001$). No interaction between the insertion/deletion (I/D) polymorphism at the angiotensin I-converting enzyme (ACE) locus and the polymorphism at the AT1R locus was detected [13].

Tiret et al. (1994) described a synergic association of DD (I/D) homozygotes of the *ACE* and *CC* gene of the A1166C polymorphism of the *AT1R* gene. For these authors, this gene interaction of risk for myocardial infarction might suggest a possible epistatic effect of the two genes, assuming that the C allele of *AT1R* is associated with a modified response of the angiotensin II receptor, thus modulating the possible risk conferred by the D allele of the *ACE* gene [14]. Álvarez et al. (1998) in a young Spanish population developed a case-control study to determine the I/D genotypes of the *ACE* gene and A1166C of the gene of receptor 1 of angiotensin II. Separately, no association was observed; but the ACE-DD and AT1R-CC genotypes interacting synergically were associated with coronary artery disease (OR = 5.32; 95% CI, 1.45–19.51) [30].

In contrast, Gardemann et al. (1998) found no synergic interaction between the polymorphic variants of the *ACE* and *AT1R* genes and coronary artery disease in 2244 Caucasian men [31].

In this study no association was detected between angiotensin II type 1 receptor *A1166C* gene polymorphism and coronary artery disease. Similarly, there was no link to myocardial infarction. Rice et al. (1999) demonstrated the absence of a synergic association with myocardial infarction, although they found a weak association between some genotypes (AC/II and CC/DD) and coronary stenosis [32].

de Araújo et al. (2004) found no association between A1166C polymorphism of the *AT1R* gene and the severity of the coronary lesions, when comparing the genotypes CC versus AC versus AA [11]. It was a prospective cross-sectional study with 110 consecutive patients (66.6% of the male sex and 36.4% of the female sex, mean age = 61.82 ± 10.81 years) diagnosed with acute myocardial infarction based on clinical, electrocardiographic, and enzymatic data and confirmed through coronary angiography. The control group comprised 104 patients (57.7% of the female sex and 42.3% of the male sex, mean age = 56.69 ± 11.52 years) who were renal transplant donors or had valvular heart disease or atypical chest pain but had no lesions in the coronary arteries on coronary angiography. The genotypic frequency in the infarcted patients was as follows: AA = 54.5%; AC = 35.5%; and CC = 10%, which was similar and nonsignificant in regard to that in the control group without myocardial infarction ($P = 0.83$). No risk increase occurred for acute myocardial infarction when comparing the genotypes as follows: CC versus AA (OR = 1.35; 95% CI = 0.50–3.59); AC versus AA (OR = 1.03; 95% CI = 0.58–1.84); and AA + AC versus AA (OR = 1.33; 95% CI = 0.51–3.45).

Based on these discrepancies, we decided to study the association between AT1R A/C polymorphism and myocardial infarction in the Slovak population. To our knowledge, no study dealing with the relationship between the AT1R A/C polymorphism and sudden cardiac death has as yet been published. For this reason we intended to determine whether AT1R A/C polymorphism was an independent risk factor for sudden cardiac death.

This study demonstrated that the CC genotype acted as an independent risk factor for ACS and in particular for

Table 4: Association between AT1R A/C polymorphism and ACS risk factors.

ATR1 genotypes ACS risk factors	AA (n = 241) n	AC (n = 329) n	Univariate OR (95% CI)	P	CC (n = 179) n	Univariate OR (95% CI)	P
UAP	145	214	1.37 (0.31–2.18)	0.273	66	1.24 (0.73–2.98)	0.148
AMI	96	115	1.21 (0.51–2.834)	0.670	113	3.35 (1.11–0.12)	0.032
Age (mean)	65.7 ± 11.1	61.2 ± 13.5	0.98 (0.95–1.01)	0.232	60.3 ± 14.1	0.97 (0.94–1.01)	0.149
Sex—male	137	146	1.35 (0.43–7.54)	0.450	149	1.18 (0.38–3.72)	0.776
Hypertension	131	143	0.57 (0.23–1.44)	0.236	103	0.40 (0.14–1.21)	0.104
Diabetes mellitus	117	137	0.88 (0.36–2.16)	0.780	75	1.36 (0.43–4.33)	0.603
Hypercholesterolemia	54	107	0.63 (0.21–1.87)	0.403	52	0.92 (0.23–3.68)	0.905
BMI (kg/m^2) ≥ 27	17	26	2.16 (0.65–9.33)	0.151	13	1.67 (0.22–9.73)	0.622
Systolic blood pressure ≥ 140 mmHg	109	131	0.50 (0.20–1.25)	0.137	87	1.13 (0.39–3.24)	0.822
Diastolic blood pressure ≥ 90 mmHg	28	40	0.36 (0.12–1.10)	0.143	26	1.18 (0.38–3.72)	0.776
Heart failure history	21	32	0.88 (0.31–2.51)	0.817	16	1.59 (0.49–5.18)	0.445
CAD history	143	204	1.67 (0.37–2.07)	0.755	107	0.95 (0.17–3.62)	0.257
MI history	36	42	1.23 (0.28–5.51)	0.785	27	1.08 (0.17–7.00)	0.936
Family history of ACS	12	17	0.35 (0.03–4.01)	0.399	9	0.80 (0.07–9.30)	0.855
Family history of diabetes	21	33	0.47 (0.07–2.03)	0.576	17	0.97 (0.25–2.46)	0.767
Smoking	105	136	0.89 (0.38–2.09)	0.793	87	1.28 (0.45–3.64)	0.639

UAP: unstable angina pectoris, AMI: acute myocardial infarction, BMI: Body mass index, and CAD: coronary artery disease.

Table 5: Association between AT1R A/C polymorphism and ACS severity and myocardial infarct related sudden cardiac death.

ACE genotypes Clinical symptoms	AA (n = 241) n	AC (n = 329) n	Univariate OR (95% CI)	P	CC (n = 179) n	Univariate OR (95% CI)	P
Stenosis numbers							
0 or 1 vessel	97	149	1.384 (0.679–3.243)	0.665	51	2.154 (0.821–4027)	0.294
2 vessels	76	107	1.267 (0.435–3.686)	0.665	49	2.006 (0.729–5.515)	0.178
3 vessels	68	73	2.111 (0.530–8.407)	0.289	79	3.870 (1.085–13.812)	0.037
Infarcted left anterior descending artery	109	154	2.166 (0.912–5.144)	0.080	117	4.080 (1.041–9.118)	0.024
Infarcted left circumflex	93	124	1.477 (0.630–3.460)	0.370	76	1.744 (0.292–2.436)	0.753
Infarcted right coronary	98	137	1.174 (0.498–2.764)	0.714	74	0.779 (0.275–2.211)	0.639
Anterior infarction wall	113	157	1.727 (0.279–3.893)	0.514	119	3.073 (1.039–9.091)	0.043
Inferior infarction wall	97	126	2.429 (0.609–9.679)	0.208	81	2.386 (0.482–11.803)	0.286
Sudden cardiac death	4	6	1.489 (0.258–8.595)	0.656	13	6.484 (1.036–40.598)	0.036

acute MI (Table 2). In addition, the CC genotype was also found to be associated with greater ACS severity, including more stenosed vessels, greater occlusion of the left anterior descending branch, and a greater risk of anterior wall myocardial infarction (Table 5).

Other studies reported that CC genotype is to be associated with atherosclerosis [25], arterial hypertension [27], and coronary artery disease [12, 33].

Positive associations between A1166C polymorphism and disease may be the result of linkage disequilibrium with another polymorphism of functional importance, either within the *AT1R* gene or within a nearby one [34]. The A/C transversion per se does not characterize any functional diversity. Although there is no evidence to support this hypothesis, this polymorphism can be considered as a possible marker, in linkage disequilibrium with other functionally relevant genetic variants, affecting the structure or expression of the AT1R.

Finally, we focused this study on the effect of AT1R A/C polymorphisms on sudden cardiac death within 24 hours of ACS patients registered in the emergency room. AT1R CC genotype carriers had a higher mortality risk than AC or AA carriers. Genetic polymorphisms in AT1R-related genes have been independently associated with higher risk of MI-related sudden cardiac arrest.

5. Conclusions

In summary, this case-control study showed that the AT1R CC genotype was an independent risk factor for ACS incidence and especially for acute MI. In addition, the AT1R CC genotype was associated with greater ACS severity and

a greater risk of sudden cardiac death. This experience of patients requiring urgent ACS treatment suggests that AT1R CC genotype carriers should be followed up and treated especially carefully because of the higher relative risk of more severe ACS and sudden cardiac death. Further studies are necessary to evaluate the personal pharmacogenomic and pharmacogenetic effects of AT1R A/C polymorphisms to improve ACS therapeutic strategies and prognosis. In future, examination of this polymorphism could become a part of the risk stratification of patients with acute coronary syndromes and predictor of sudden cardiac death.

Disclosure

This study was elaborated within the projects.

Conflict of Interests

The authors declare that they have no conflict of interests.

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