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Pharmacogenetic polymorphisms affecting bisoprolol response

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ABSTRACT

β-blockers are commonly prescribed to treat multiple cardiovascular (CV) diseases, but, frequently, adverse drug reactions and intolerance limit their use in clinical practice. Interindividual variability in response to β-blockers may be explained by genetic differences. In fact, pharmacogenetic interactions for some of these drugs have been widely studied, such as metoprolol. But studies that explore genetic variants affecting bisoprolol response are inconclusive, limited or confusing because of mixed results with other β-Blockers, different genetic polymorphisms observed, endpoint studied etc. Because of this, we performed a systematic review in order to find relevant genetic variants affecting bisoprolol response. We have found genetic polymorphism in several genes, but most of the studies focused in *ADRB* variants. The *ADRB1* Arg389Gly (rs1801253) was the most studied genetic polymorphism and it seems to influence the response to bisoprolol, although studies are inconclusive. Even, we performed a meta-analysis about its influence on systolic/diastolic blood pressure in patients treated with bisoprolol, but this did not show statistically significant results. In conclusion, many genetic polymorphisms have been assessed about their influence on patients´ response to bisoprolol and the *ADRB1* Arg389Gly (rs1801253) seems the most relevant genetic polymorphism in this regard but results have not been confirmed with a meta-analysis. Our results support the need of further studies about the impact of genetic variants on bisoprolol response, considering different genetic polymorphisms and conducting single and multiple SNPs analysis, including other clinical parameters related to bisoprolol response in a multivariate study.

1. Introduction

Bisoprolol is a highly selective β1-blocker approved for the treatment of hypertension, heart failure (HF) and ischemic heart disease [1]. Beta-receptors are G-protein-coupled receptors (Gs alpha subunit) which action are mediated by the cyclic adenosine monophosphate (cAMP) and cAMP-dependent protein kinase that increases calcium ion concentration with an inotropic effect on cardiomyocytes. Bisoprolol and other β-blockers inhibit this process and exert their antiarrhythmic action (Fig. 1).

In the ESC EUROASPIRE V (European action on secondary and primary prevention by intervention to reduce events – European Society of Cardiology) registry of patients with coronary diseases, β-blockers were prescribed to 81% of patients [3]. Data from the CLARIFY registry (Prospective observational longitudinal registry of patients with stable coronary artery disease) show that β-blockers were prescribed in 77% of western/central Europe and 87% in eastern European population. Even though, heart rate control is not addressed adequately [4].

In the TRECE registry (Treatment of coronary artery disease in Spain), including patients with coronary artery disease (CAD) in Spain, atenolol (43.9%) was the most prescribed β-blocker followed by bisoprolol (30.9%) and both groups of patients had significantly higher prevalence of resting heart rate (RHR) < 70 bpm, compared to those with metoprolol, carvedilol or propranolol [5].

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In a recent study, Taborsky et al. analyzed the use of β-blockers in HF patients in the Czech Republic between 2012 and 2018. Thus, metoprolol and bisoprolol were the most prescribed β-blockers. In particular, bisoprolol prescription changed among those years, from 20.3% in 2012 to 28% in 2018 [6]. In particular in Spain and our hospital, bisoprolol is largely the most prescribed β-blocker.

Bisoprolol is administered orally with 90% of bioavailability and 50% of the dose is metabolized by hepatic clearance [1]. An in vitro study demonstrated that CYP3A4 and CYP2D6 enzymes are enrolled in the oxidation of both bisoprolol enantiomers [7].

Anyway, β-blockers are largely prescribed, its use has been widely studied since its discovery in 1960s, new mechanisms of action are still revealed [8] and they are well stablished for various cardiovascular (CV) diseases, but, adverse effects and patients´ intolerance lead to stop the treatment [9].

Interindividual differences about patients´ response to these drugs have been found. The cytochrome P450 (CYP) isoenzymes, especially CYP2D6, have shown to affect the metabolism of several drugs, thus genetic variants in the gene encoding this enzyme might affect the response to β -blockers, among other drugs [10].

Over the years, pharmacogenetics (PGx) studies have gained value in the management of CV diseases, especially for the purpose of achieving target dose of drugs, thus, avoiding adverse drug reactions [11]. Regarding β -blockers, finding single nucleotide polymorphisms (SNPs) that would predict responsiveness to treatment, and the study of its clinical impact on undesirable effects is determinant to optimize CV therapies. Regarding bisoprolol, many genetic variants have been assessed about their possible PGx association, some of them with inconclusive results [12].

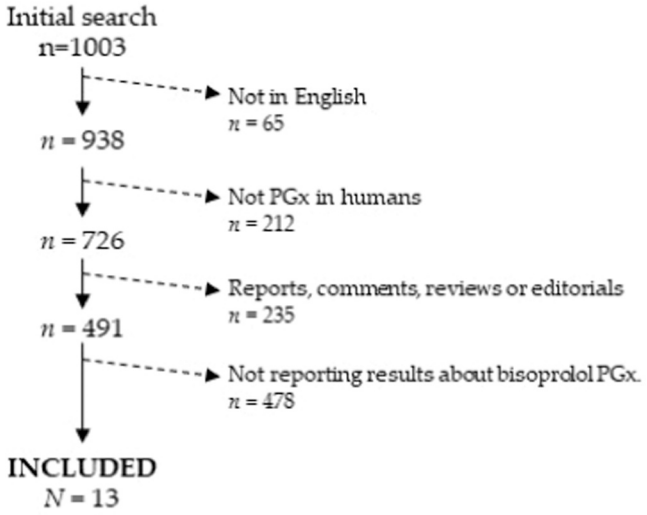

Fig. 2. Bibliography search strategy.

β-Adrenoceptors (β-AR) are targets of endogenous catecholamines

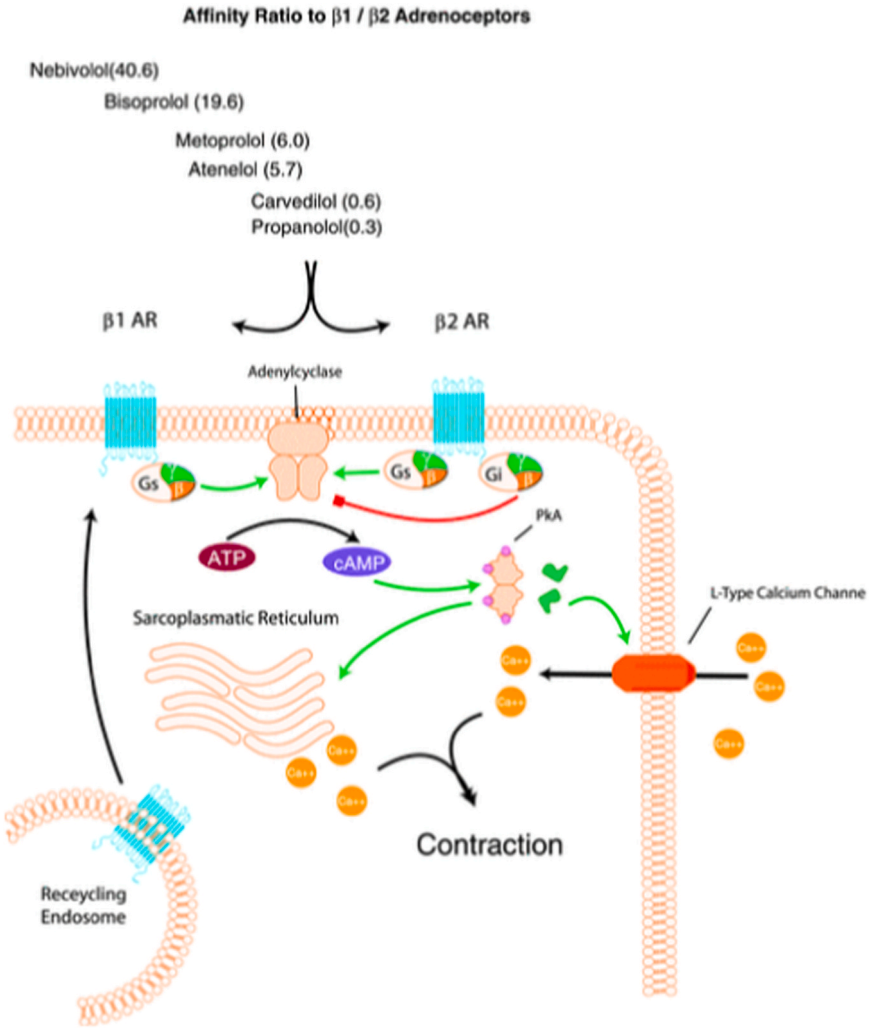

Fig. 1. Molecular mechanism of beta-receptors and β-blockers affinity [2].

and agonist or antagonist drugs. They are particularly polymorphic receptors extensively investigated to assess an association with interindividual variability in β -blockers response or risk of disease [13].

Most of the studies have focused on genes coding for β1 and β2-AR, especially two SNPs in β1-AR gene (*ADRB1*): rs1801252 (Ser49Gly) and rs1801253 (Arg389Gly); and rs1042713 (Gly16Arg), rs1042714 (Gln27Glu) in β2-AR gene (*ADRB2*) [11,13].

In the *ADRB1*, rs1801252 AG and GG genotypes are related to a higher risk of major adverse events (MACE) in patients treated with β-blockers [14]. As well, *ADRB1* (rs1801252) AA carriers have been described to response better to metoprolol than AG carriers, but this association might also be influenced by rs1801253(Arg389Gly) polymorphism [15]. In contrast, the AA genotype for this SNP was not related to blood pressure reduction in hypertensive patients treated with bisoprolol [16].

In patients with CAD, carrying the *ADRB1*(*rs1801253)* CC genotype is associated with lower catecholamines required doses compared with CG or GG genotype [17]. Johnson et al. also described better diastolic blood pressure (BP) response to metoprolol in patients with the CC genotype and Terra et al. found an association of this SNP with improvement in left ventricular ejection fraction (LVEF) [15,18]. Parvez et al. had reported contradictory results in patients with atrial fibrillation describing better response to atenolol, metoprolol or carvedilol in *ADRB1* (rs1801253) CG or GG carriers [19].

On the other hand, several studies concluded that CC genotype of this SNP is not associated with better response to β-blockers, including metoprolol, carvedilol and atenolol, in patients with essential hypertension or HF [20]. The average dose of bisoprolol did not differ between CC genotype and CG/GG genotype in patients with CAD [21]. Related to heart rate, Rau et al. associated CC genotype with a lower response in patients with HF treated with carvedilol and they found no genetic association in those patients treated with bisoprolol [22]. The absence of PGx interaction between *ADRB1* Arg389Gly genotype (rs1801253) and β-blockers was previously reported by de Groote et al. in patients with HF [23].

In the *ADRB2* gene, rs1042714GG genotype is associated with greater response to carvedilol in HF patients compared to CC or CG genotype but other studies did not find significant associations [23–25]. Recently, CC genotype has been related to increased heart rate lowering effect, so better response to atenolol or metoprolol in patients with European ancestry [26].

As mentioned before, variability in pharmacokinetics caused by impaired hepatic metabolism is of main interest to select the adequate β-blocker for each patient. In this regard, *CYP2D6**4 and *CYP2D6**10 are the most important studied alleles. *CYP2D6**3/*4/*5/*6 carriers are known of having reduced metabolism of metoprolol [27]. The *CYP2D6**4 (*rs3892097*) T allele has been associated with higher lowering effect of metoprolol on heart rate and BP compared to C allele [28]. *CYP2D6**10 (100C > T) (*rs1065852)* GG genotype was associated with lower heart rate in patients with HF and percutaneous coronary intervention after metoprolol treatment compared to AA or AG genotype [29]. It has also been described a reduced metabolism of carvedilol in patients with angina related to *CYP2D6**10 allele [30].

Another interesting studied gene linked to CYP metabolism is the *ACY3*, encoding the amino acylase 3 protein. The C allele (rs2514036) seems to be associated with better diastolic and systolic BP reduction in hypertensive patients treated with bisoprolol or atenolol compared to T allele [31], but Hiltunen et al. described contradictory results in hypertensive men with increased response to bisoprolol in T allele carriers compared to C allele [32].

Genetic variants affecting the response to β-blockers have been identified. Even, for metoprolol, its drug label includes pharmacogenetic information reporting the association with *CYP2D6* variants. In this regard, patients carrying *CYP2D6* no function variants, translated into CYP2D6 intermediate/poor metabolizer phenotypes, have been related to a lower conversion of metoprolol to its inactive metabolites, thus with higher rates of bradycardia, and, pharmacogenetic dosing guidelines from the Dutch Pharmacogenomics Working Group (DPWG) recommend to increase the dose in smaller steps and/or prescribe no more than 25% of the standard dose if gradual reduction in heart rate is desired, or in the event of symptomatic bradycardia (Level of evidence 1 A: variant-drug combinations that have variant-specific prescribing guidance available). On the other hand, ultra-rapid metabolizers, carrying *CYP2D6* increased function alleles, have been associated with an increased conversion of metoprolol to inactive metabolites and DPWG guidelines recommend to use the maximum dose for the relevant indication as a target dose or, if the effectiveness is still insufficient, to increase the dose based on effectiveness and side effects to 2.5 times the standard dose or select an alternative.

Regarding bisoprolol, most of these drug-gene interactions have been reported as Level 3 of evidence (Variant-drug combinations with a low level of evidence supporting the association), as they are based on a single significant (not yet replicated) study or annotation evaluated in multiple studies but lacking clear evidence of an association [33]. Moreover, there is a wide heterogeneity in PGx studies of β-blockers. While some of them analyze genetic variants associated with response to various β-blockers, others have focused on a specific β-blocker in a single cohort of patients with a certain cardiovascular pathology, based on intrinsic and pharmacokinetic differences among β-blockers [34].

Thus, the aim of this study is to explore genetic variants affecting bisoprolol response, performing a systematic review and a meta-analysis.

2. Material and methods

2.1. Search strategy and inclusion/exclusion criteria

A systematic review about genetic variants affecting the response to bisoprolol was performed. In order to find relevant manuscripts about this topic we performed a search in Pubmed on 15th January 2021 using MESH terms in the following argument: (“Bisoprolol” OR “Metoprolol” OR “Adrenergic Beta antagonist”) AND (“Pharmacogenetic” OR “SNP” OR Polymorphism”).

The publications found in the initial search were included for review according to the following inclusion/exclusion criteria:

1. Manuscripts written in English (only) were included.
2. Manuscripts assessing the association of genetic variants with the illness and not related to bisoprolol response were excluded.
3. Manuscripts studying the association of any genetic variant with bisoprolol in vitro or non-humans were excluded.
4. Reports, comments and editorials were excluded.
5. Manuscripts about genetic variants affecting β -Blockers response without reporting results about bisoprolol treated patients were excluded.
6. Only manuscripts about genetic variants influencing bisoprolol response in human patients were included.

First, we checked all abstract titles looking for publications not written in English. Then, we extensively read abstracts and/or complete manuscripts in order to identify those publications meeting the inclusion/exclusion criteria. We also checked all the review articles found in the initial search with the aim of identifying other publications meeting the inclusion/exclusion criteria. Finally, we manually checked the provided literature on PharmGKB about genetic variants affecting bisoprolol response to verify that we had not excluded any relevant publication related to the topic of this systematic review.

2.2. Data extraction and quality assessment

Two different researchers carried out the search strategy. In case of discrepancies, another researcher blinded for the decision from these 2

researchers, performed an independent evaluation and took the final inclusion/exclusion decision.

Regarding those considered for inclusion manuscripts, we performed a quality assessment using the Newcastle–Ottawa quality assessment scale (NOS) [35]. About this, we judged each study on three categories (selection, comparability, and exposure) and eight items, up to nine "stars/points", as the top score. Finally, considered to inclusion manuscripts with NOS score below five points were excluded. We obtained the following information from the included studies: author, reference SNP (rs), gene, SNP, minor allele frequency (MAF), genotypes distribution, ethnicity, treatment strategy, diagnosis, follow-up time, study endpoint and results.

2.3. Meta-analysis

Among all the publications found, we included in the meta-analysis those patients treated with bisoprolol, without exclusions regarding diagnosis, treatment strategy or ethnicity. Every genetic variant assessed to be related to bisoprolol response was included, and all the efficacy or toxicity parameters used to evaluate the association between genetic variants and patients' drug response were recorded and considered for meta-analysis.

We conducted a random-effects meta-analysis in recessive, dominant, codominant and over-dominant models for the G risk allele in order to assess the association between the *ADRB1* A389G (rs1801253) and treatment response to bisoprolol, as it was the only genetic variant meeting the meta-analysis criteria.

For each primary study, we calculated the effect size as the standardized difference in means between the two groups being compared. A random-effects meta-analysis was chosen due to the variability in methods across the primary studies. Heterogeneity between primary studies was assessed using the I2 statistic [36]. We used R statistics software, version 3.6.2, with the package "meta" to conduct the meta-analysis (https://CRAN.R-project.org/package=meta).

We used Harbord's test in order to quantitatively assess publication bias, considering p-value < 0.1 as significant statistical publication bias.

3. Results

In the initial search we found 1003 publications. Based on their titles we excluded 65 not written in English. The abstracts of the remaining 938 publications were examined and 235 were excluded because of being reports, comments, editorials or reviews. We also excluded 212 publications because of being in vitro or no-human studies, or exploring genetic variants related to different pathologies and not to β -blockers response.

Finally, we found 491 publications studying the association between different SNPs and the response to β-blockers, but most of them ($n = 478$) exploring the association with different drugs to bisoprolol or doing this without reporting differentiated results about bisoprolol. After checking publications included in reviews found in the initial search and those included in PharmGKB as research articles about pharmacogenetics of bisoprolol, we did not find discrepancies, so we considered we had performed the bibliography search properly.

This way 13 research articles were selected as publications analyzing genetic variants associated with bisoprolol response (Tables 1 and 2). Among them, no one was scored below five points with the NOS scale, and we did not find evidence of publication bias after Harbord's test.

Table 1
Genetic variants and population characteristics of research articles studying genetic variants influencing bisoprolol response in human patients.

Author	refSNP (rs)	Gen	SNP (Location)	MAF	Genotype mm/Mm/MM	Ethnicity	Patients	Follow-up
Zaugg et al. [21]	rs1801252	ADRB1	Ser49Gly	0111	1/41/147	Switzerland	CAD	12 m
	rs1801253	ADRB1	Arg389Gly	0198	27/47/112	Switzerland	CAD	12 m
	rs1042713	ADRB2	Gly16Arg	0251	25/70/94	Switzerland	CAD	12 m
	rs1042714	ADRB2	Gln27Glu	0243	26/66/97	Switzerland	CAD	12 m
Mohammed Alkreathy et al. [37]	rs1080985	CYP2D6	C1496G	0257	18/19/70	South Arabia	CD	–
	rs1065852	CYP2D6	C100T	0,00	0/0/99	South Arabia	CD	
Fedorinov et al. [38]	rs3892097	CYP2D6	G1846A	0,09	0/6/26	Russian/Yakut	CAD	–
	rs1065852	CYP2D6	C100T	0,15	0/10/22	Russian/Yakut	CAD	
Lee et al. [39]	rs1801253	ADRB1	Arg389Gly	0,18	5/25/53	Korea	HF	12 m
	rs1042713	ADRB2	Gly16Arg	0,33	14/41/28	Korea	HF	12 m
	rs1042714	ADRB2	Gln27Glu	0,09	1/15/67	Korea	HF	12 m
Rau et al. [22]	rs1801252	ADRB1	Ser49Gly	–	–	Caucasian	HF (SR/AF)	4 weeks
	–	CYP2D6	–	–	–	Caucasian	HF (SR/AF)	4 weeks
	rs1801253	ADRB1	Arg389Gly	0,23	23/101/140	Caucasian	HF (SR/AF)	4 weeks
Suonsyrja et al. [40]	rs4961	ADD1	Gly460Trp	0,21	13/78/117	Finnish	EH	4 weeks
	–	ACE	ACE I/D	0,34	37/105/66	Finnish	EH	4 weeks
	rs699	AGT	Met235Thr	0,31	35/78/95	Finnish	EH	4 weeks
	rs5186	AGTR1	1166A/C	0,13	5/52/151	Finnish	EH	4 weeks
Donner et al.* [41]	rs17367504	MTHFR	236 + 160T > C	0,14	3/51/152	Finnish	EH	4 weeks
	rs9815354	ULK4	750 + 12715C > T	0,24	18/83/143	Finnish	EH	4 weeks
Hiltunen et al. [32]	^	ACY3	^	–	–	Finnish	EH	4 weeks
de Groote et al. [23]	rs1801252	ADRB1	Ser49Gly	0,14	3/34/93	Caucasian	Stable HF	30 m
	rs1801253	ADRB1	Arg389Gly	0,24	15/48/67	Caucasian	Stable HF	30 m
	rs1042713	ADRB2	Gly16Arg	0,29	20/57/53	Caucasian	Stable HF	30 m
	rs1042714	ADRB2	Gln27Glu	0,31	25/57/48	Caucasian	Stable HF	30 m
	rs1800888	ADRB2	Thr164Ile	0,02	0/5/125	Caucasian	Stable HF	30 m
Bruck et al. [42] †	rs1801253	ADRB1	Arg389Gly	0,2	8/0/10	UK	Normal health	2 days
de Groote et al. [43]	–	ACE	ACE I/D	0,28	20/53/57	Caucasian	HF	30 m
Gong et al. [44]	rs12346562	PTPRD	11018077C > A	0.27	–	Finnish	EH	–
	rs7640608	OTOL1	161760608A > G	0.05	–	Finnish	EH	–
Suonsyrja et al. [16]	rs1801252	ADRB1	Ser49Gly	0,14	7/58/143	Finnish	EH	4 weeks
	rs1801253	ADRB1	Arg389Gly	0,2	13/73/122	Finnish	EH	4 weeks
	rs1042713	ADRB2	Gly16Arg	0,34	39/103/66	Finnish	EH	4 weeks
	rs1042714	ADRB2	Gln27Glu	0,3	30/95/83	Finnish	EH	4 weeks

refSNP: Reference single nucleotide polymorphism; MAF: Minor Allele Frequency; mm: number of patients with recessive homozygous genotype; Mm: Heterozygous genotype; MM: Dominant homozygous genotype; CAD: Coronary Artery Disease; CD: Cardiac Disease; HF (SR/AF): Heart Failure (Sinus rhythm/Atrial fibrillation); EH: Essential hypertension; "- "means "Data not shown in the original article". *Only shows genes with statistically significant related results, see the original publication to know all the studied genes and variants. ^ Several SNPs were studied, see the original publication; † Patients treated with bisoprolol and dobutamine.

Table 2
Genetic variants, related bisoprolol efficacy endpoints and resulting p-values of included articles.

Study	n	Gen	SNP (Location)	Related endpoint	p-valor
Zaugg et al. [21]	189	*ADRB1*	Ser49Gly	Combined: CV mortality/Nonfatal myocardial infarction/Unstable angina/HF/Cerebrovascular insult	Data not shown
	186	*ADRB1*	Arg389Gly		p = 0,01
	189	*ADRB2*	Gly16Arg		Data not shown
	189	*ADRB2*	Gln27Glu		Data not shown
Mohammed Alkreathy et al. [37]	107	*CYP2D6*	C1496G	Blood pressure/Heart rate/[Bisoprolol]	Data not shown
	107	*CYP2D6*	C100T		Data not shown
Fedorinov et al. [38]	32	*CYP2D6*	G1846A	Dose titrated bisoprolol	p = 0029
	32	*CYP2D6*	C100T		p = 0244
	32	*CYP2D6*	G1846A/C100T		p = 0,03
Lee et al. [39]+	83	*ADRB1*	Arg389Gly	Heart rate change (6 months)	p = 0,43
				Systolic BP	P = 0,41
				Diastolic BP	P = 0,90
				Dose of bisoprolol needed	p = 0022
				Left ventricular volume	p = 0,26
				B-natriuretic peptide	p = 0005
				Readmission/mortality (1 year)	p = 0162
	83	*ADRB2*	Gly16Arg	Data not shown	Data not shown
	83	*ADRB2*	Gln27Glu	Data not shown	Data not shown
Rau et al. [22]	264	*ADRB1*	Ser49Gly	Heart rate lowering difference	Data not shown
	264	*CYP2D6*	–		Data not shown
	264	*ADRB1*	Arg389Gly		p > 0,08
Suonsyrja et al. [40]	208	*ADD1*	Gly460Trp	Ambulatory BP (Systolic/diastolic)	p = 0,03/ p = 0,13
				Office BP (Systolic/diastolic)	p = 0,61/ p = 0,49
	208	*ACE*	ACE I/D	Ambulatory BP (Systolic/diastolic)	p = 0,56/ p = 0,36
				Office BP (Systolic/diastolic)	p = 0,33/ p = 0,29
	208	*AGT*	Met235Thr	Ambulatory BP (Systolic/diastolic)	p = 0,98/ p = 0,48
				Office BP (Systolic/diastolic)	p = 0,72/ p = 0,94
	208	*AGTR1*	1166A/C	Ambulatory BP (Systolic/diastolic)	p = 0,82/ p = 0,71
				Office BP (Systolic/diastolic)	p = 0,82/ p = 0,38
Donner et al. [41]*	208	*MTHFR*	rs2514036	Systolic BP (multivariate/univariate)	
Diastolic (multivariate/ univariate)	p = 0.21/0.002, p = 0.17/0.001				
	208	*ULK4*	750 + 12715C > T	Systolic BP (multivariate/univariate)	
Diastolic (multivariate/ univariate)	p = 0.46/0.08, p = 0.55/0.04				
Hiltunen et al. [32]	207	*ACY3*	^	Systolic BP	^
de Groote et al. [23]	130	*ADRB1*	Ser49Gly	ΔLVEF (%)	Data not shown
	130	*ADRB1*	Arg389Gly		Data not shown
	130	*ADRB2*	Gly16Arg		Data not shown
	130	*ADRB2*	Gln27Glu		Data not shown
	130	*ADRB2*	Thr164Ile		Data not shown
Bruck et al. [42]	18	*ADRB1*	Arg389Gly	ΔHR (BEATS/MIN)	p < 0.05
				ΔSystolic BP (mmHg)	p < 0.05
				ΔDiastolic BP (mmHg)	p > 0,05
				ΔPRA (plasma renin activity)	p < 0.05
de Groote et al. [43]	130	*ACE*	ACE I/D	ΔLVEF	Data not shown
Gong et al. [44]	207	*PTPRD*	11018077C > A	Ambulatory diastolic BP	p = 0095
	207	*OTOL1*	161760608A > G	BP response	p = 0,65
Suonsyrja et al. [16]	208	*ADRB1*	Ser49Gly	Ambulatory BP (Systolic/diastolic)	p = 0,10/ p = 0,18
				Office BP (Systolic/diastolic)	

(*continued on next page*)

Table 2 (*continued*)

Study	n	Gen	SNP (Location)	Related endpoint	p-valor
					p = 0,45/ p = 0,86
	208	*ADRB1*	Arg389Gly	ABP (Systolic/diastolic)	p = 0,07/ p = 0,02
				Office BP (Systolic/diastolic)	p = 0,78/ p = 0,80
	208	*ADRB2*	Gly16Arg	Ambulatory BP (Systolic/diastolic)	p = 0,42/ p = 0,43
				Office BP (Systolic/diastolic)	p = 0,49/ p = 0,50
	208	*ADRB2*	Gln27Glu	Ambulatory BP (Systolic/diastolic)	p = 0,96/ p = 0,94
				Office BP (Systolic/diastolic)	P = 0,75/ P = 0,49

refSNP: Reference single nucleotide polymorphism; MAF: Minor Allele Frequency; mm: number of patients with recessive homozygous genotype; Mm: Heterozygous genotype; MM: Dominant homozygous genotype; CD: Cardiac Disease. +Only shows parameters with p-value < 0.5 for the association with the genetic variant or included in the meta-analysis. *Only shows genes with statistically significant related results, see the original publication to know all the studied genes and variants. ^Several SNPs were studied, see results in the original publication.

Four of them [16,32,40,41] are derived from the study "GENRES (Genetic of drug responsiveness in essential hypertension study): A randomized, double-blind, crossover, placebo-controlled trial based on a population of hypertensive Finnish men". Another one replicates the results obtained from a previous genome-wide association study (GWAS) of atenolol, in the Finnish population of GENRES treated with bisoprolol [32]. One article reports the results of a double-blinded, placebo-controlled, multi-center clinical trial of a CAD population undergoing surgery with neuraxial blockade, with the aim to explore the benefits of perioperative bisoprolol administration on MACE [21]. Two articles are from a prospective single center study of HF patients that started β-blocker therapy in the period of time selected by authors [23,43]. Another one is based on a sample of patients from the "Cardiac Insufficiency Bisoprolol Study in Elderly study (CIBIS-ELD): a randomized double-blinded study of bisoprolol and carvedilol in HF patients" [22]. One more article is also based on HF patients with bisoprolol in Korean population [39]. One of the two articles left is a single-center study in Yakutsk (Russia) of patients with CAD treated with various β-blockers and the last one is a single-center study of patients with any cardiovascular disease treated with bisoprolol [37,38].

3.1. Research articles about bisoprolol association with genetic polymorphisms in ADRB genes

Zaugg et al. [21] explored whether bisoprolol would protect patients at risk of cardiovascular complications undergoing surgery with spinal block in Swiss patients with CAD after 12 months follow-up, including genetic polymorphisms in the *ADRB1/ADRB2* genes as possible determinants of bisoprolol efficacy. These authors found that bisoprolol is not useful in terms of security in these patients, but they found that *ADRB1* Arg389Gly SNP is predictor of better response to bisoprolol (p = 0,01; see Table 2).

Lee et al. [39] studied in patients with chronic HF the same variants in *ADRB2* and *ADRB1* than Zaugg et al. except the *ADRB1* (rs1801252). Their results showed that *ADRB1* Arg389Arg genotype group needed higher doses of bisoprolol compared to Gly carriers (Arg389Gly, Gly389Gly genotypes) without differences in heart rates across genotypes after treatment, suggesting the potential of individually tailoring β-blocker therapy according to *ADRB1* genotype.

Rau et al. as well, searched for associations within *ADRB1* variants (rs1801252, rs1801253) in elderly HF patients treated with bisoprolol or carvedilol [22], but no association was observed about the influence of these genetic variants on heart lowering in patients treated with bisoprolol. They also genotyped the nine most frequent SNPs in *CYP2D6* but none of them were associated with response to both drugs and neither with the effect in HR [28].

De Groote et al. studied the association of 5 SNPs in *ADRB1* (rs1801252, rs1801253) and *ADRB2* (rs1042713, rs1042714, rs1800888) with bisoprolol effect on LVEF, HR and BP in chronic HF patients [23]. There were no differences by genotype in those outcomes. They also searched for any association in those patients treated with carvedilol without success [43].

Bruck et al. [42] studied the *ADRB1 rs1801253* variant in a small cohort of patients to explore the effects of bisoprolol in HR, BP and plasma-renin activity (PRA) after an infusion of dobutamine and its relationship with the genetic polymorphism. They found this variant as a determinant not only of hemodynamic effects but also of PRA, concluding that *ADRB1* polymorphisms may be useful for predicting therapeutic responses to β-blocker treatment.

Finally, Sounsyrja et al. [16] studied the four same variants as Zaugg et al. [21] in the *ADRB1* and *ADRB2* genes in hypertensive men. Regarding rs1801253 *ADRB1* Arg389Gly, their results showed that patients with Gly389Gly genotype had a tendency in better BP response to bisoprolol compared with those Arg389Arg genotypes, but their results were not statistically significant [16].

3.2. Research articles about bisoprolol association with genetic polymorphisms in CYP2D6

Regarding polymorphisms in *CYP2D6*, Rau et al. [22] genotyped the nine most frequent SNPs in *CYP2D6* but none of them were associated with response to both drugs and neither with the effect in HR.

On the other hand, Alkreathy et al. [37] investigated the rs1080985 (*CYP2D6*2A*) and rs1065852 (*CYP2D6*10*) measuring bisoprolol plasma levels and blood pressure. They reported that *CYP2D6*2A* CC genotype carriers had higher BP (systolic and diastolic) and lower bisoprolol concentration (ng/mL) compared to GG or GC. They also reported higher frequencies of side effects such as tiredness, chest pain or troubled breathing in GG allele carriers. For the rs1065852 (*CYP2D6*10*) all patients were homozygous (GG) [37].

Also, Fedorinov et al. studied the rs3892097 (*CYP2D6*4*) and rs1065852 (*CYP2D6*10*) in patients with CAD titrating dose of bisoprolol [38]. For both SNPs, none of the patients carried the homozygous recessive genotypes. Their results showed that patients heterozygous for both variants received statistically significant lower dose of bisoprolol than those patients carrying the wildtype genotype for both SNPs. Also, the dose titrated of bisoprolol was lower in patients carrying the heterozygote genotype of rs3892097 (*CYP2D6*4*) [38].

3.3. Research articles about bisoprolol association with polymorphisms in non-ADRB genes

Sounsyrja et al. have also studied other genetic variants in genes related to cardiovascular diseases. In the same cohort of hypertensive men, they explored the effect of angiotensin gene (*AGT*) Met235Thr (rs699), angiotensin converting enzyme (*ACE*) insertion/deletion (I/D), angiotensin II type I receptor (*AGTR1*) 1166A/C (3 prime UTR variant) (rs5186), and α-adducin (*ADD1*) Gly460Trp (rs4961) polymorphism on BP response to bisoprolol. There were no association between these polymorphisms with BP responses, just for *ADD1* Gly460Trp (rs4961) the ambulatory systolic BP was barely lower in patients carrying the Trp allele, but the difference was not statistically significant [40]. *De* Groote et al. also analyzed the impact of *ACE* gene deletion in LVEF in HF patients, but they did not found differences between genotypes [43].

Donner et al. tried to identify more SNPs that could affect the BP response to four antihypertensive treatments including bisoprolol in the population of hypertensive men of GENRES. None of these gene variants reached a significant level of association stablished ($p < 0.0007$), but two of them (rs17367504 and rs11014166) showed a tendency in genotype-related differences ($p < 0.05$). Only the rs6749447 variant in *STK39* gene was associated with BP response to losartan [41].

For the same population of GENRES, Hiltunen et al., conducted a GWAS to identify SNPs affecting the response to four antihypertensive drugs. They identified the 20 different genetic loci with the lowest P values for BP response for each drug, considering significant values P values $< 5 \times 10^{-8}$. Three SNPs (rs2514036, rs948445 and rs2514037) showed evidence for association with ambulatory systolic BP changes after bisoprolol. These SNPs are related with the *ACY3* gene coding for aminoacylase III. They also performed a meta-analysis of the 20 SNPs associated with bisoprolol response, in the population of the PEAR study, treated with atenolol, to asses any association with this β-blocker. Only one out of two SNPs with suggestive evidence of association for both drugs, the rs7268800, is located close to a protein-coding gene, the SPATA13 gene, which codes for a protein associated with spermatogenesis [32]. Finally, Gong et al. explored the association of two SNPs (intergenic variants) in *PTPRD* (rs12346562) and *OTOL1* genes (rs7640608), previously associated with response to atenolol in PEAR patients, in GENRES patients. Only the *PTPRD* SNP showed some indication of genotype differences in diastolic BP response to bisoprolol ($p = 0.095$) in trend with findings for atenolol (A allele carriers respond better to the β-blocker effect) [44].

3.4. Meta-analysis

Among the considered publications after systematic review, the *ADRB1* A389G (rs1801253) was the only variant assessed for the association with bisoprolol response in at least two publications and it was the only one related to an endpoint feasible enough to be compared (see Tables 1 and 2). We performed a meta-analysis about the association of *ADRB1* A389G with bisoprolol response, considering as endpoint, first, the mean systolic BP, and second, the mean diastolic BP. Systolic and diastolic BP were recorded in baseline and follow-up time for each of the included publications, and, mean change and SD were calculated. We included in the meta-analysis 3 publications among all those found in the systematic review.

About the influence of *ADRB1* A389G variant on systolic BP in patients treated with bisoprolol we did not find statistically significant results for both the dominant model (SMD = 0.02; 95% CI = −0.13 to 0.17; p-value = 0.98) and the recessive genetic model (SMD = 0.05; 95% CI = −0.31 to 0.41; p-value = 0.98). This also happened for the association with diastolic BP for both the dominant (SMD = 0.04; 95% CI = −0.15 to 0.23; p-value = 0.97) and recessive genetic model (SMD = 0.10; 95% CI = −0.69 to 0.89; p-value = 0.91). As we can see (Figs. 3 to 6), our results show a high statistical homogeneity ($I^2 = 0\%$).

4. Discussion

To our knowledge, this is the first systematic review performed about genetic variants affecting bisoprolol response. Clearly, the most genetic variants assessed to be associated with bisoprolol response are in *ADRB1* and *ADRB2*.

The main limitation of this systematic review and meta-analysis is related to main results. We found only 13 articles after systematic review and three of them only were available to be included in the meta-analysis. Also, related to the methodology, we excluded publications not written in English (n = 65; see Fig. 2), since it would be difficult to find official translators to several languages in those manuscripts and all of them were published in low impact factor scientific journals. Furthermore, research articles from Suonsyrja et al. [16] Rau et al. [22] included in the meta-analysis, provided not combinable results so they were contacted in order to provide means values and SD by genotype in baseline and follow-up time in order to perform the meta-analysis. In this regard, it is important to highlight the heterogeneity of populations recruited in included publications (see Tables 1 and 2). As we can see, different ethnicities, indication of use, follow-up times and endpoints were considered.

These limitations mean the need of perform further studies assessing the influence of genetic variants on bisoprolol response, including multivariant analysis considering different populations, indications of use, other clinical parameters and/or previously known genetic polymorphisms influencing bisoprolol response. Even, it would be interesting to look for new or low frequency genetic variants that may be influencing the response to the drug using newer methodologies as "Next Generation Sequencing" (NGS) technologies or "Genome Wide Association Studies" (GWAS).

Among genetic variants assessed to be associated with bisoprolol response, the *ADRB1* Arg389Gly polymorphism is by large the most studied among polymorphism related with β-blockers but its influence on bisoprolol response remains unclear.

Bibliography suggests an association between this variant and bisoprolol response regardless of the illness, but in our meta-analysis we did not find an association about *ADRB1* Arg389Gly and change in systolic BP or diastolic BP. This may be explained by multiple circumstances as

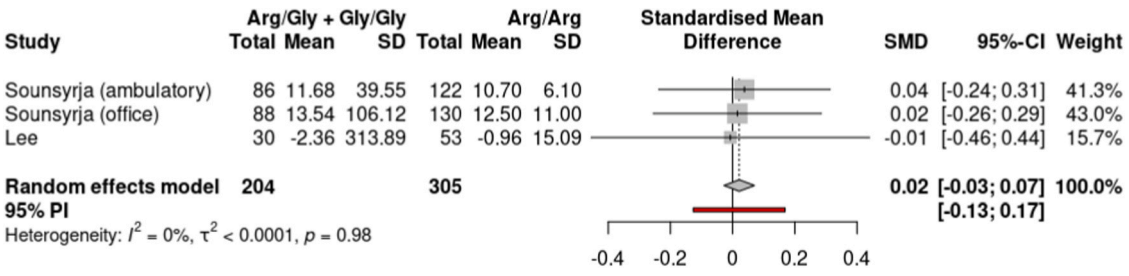

Fig. 3. Forest plot of the meta-analysis showing the association between ADRB1 A389G (rs1801253) and treatment response to bisoprolol (systolic blood pressure) using random-effects models. Dominant model.

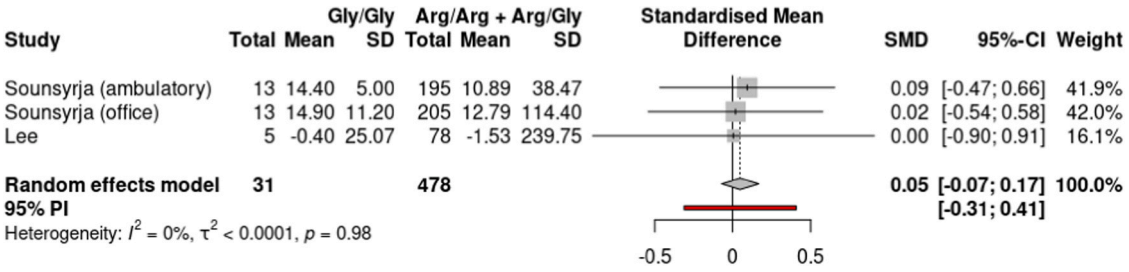

Fig. 4. Forest plot of the meta-analysis showing the association between ADRB1 A389G (rs1801253) and treatment response to bisoprolol (systolic blood pressure) using random-effects models. Recessive model.

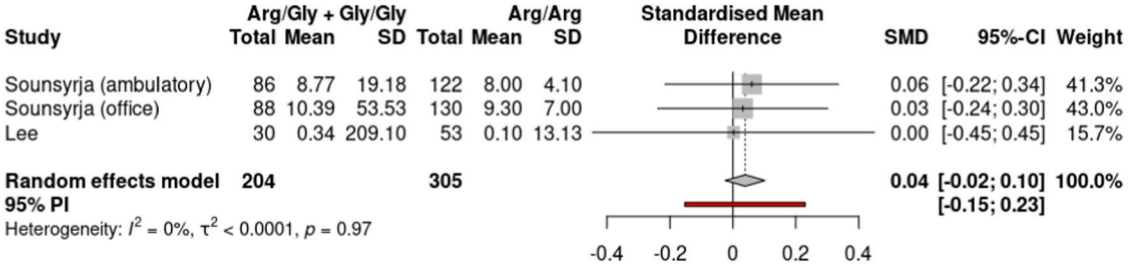

Fig. 5. Forest plot of the meta-analysis showing the association between ADRB1 A389G (rs1801253) and treatment response to bisoprolol (Diastolic blood pressure) using random-effects models. Dominant model.

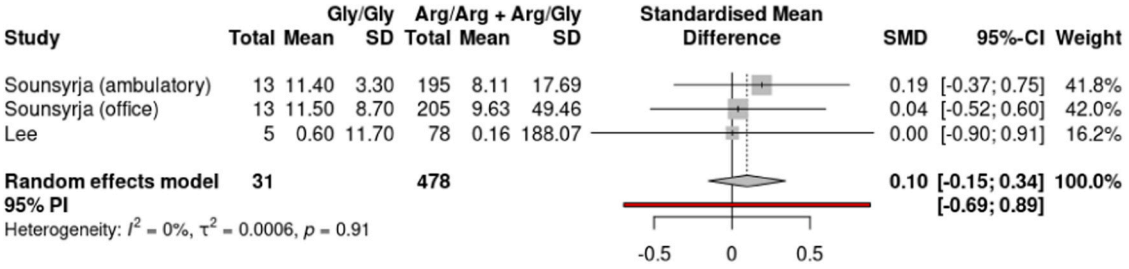

Fig. 6. Forest plot of the meta-analysis showing the association between ADRB1 A389G (rs1801253) and treatment response to bisoprolol (Diastolic blood pressure) using random-effects models. Recessive model.

the heterogeneity in the studied population by publication, the specific effect of bisoprolol on systolic BP and diastolic BP etc.

This probes the need of further studies in this regard.

4.1. Bisoprolol and ADRB genetic polymorphisms

About the studied SNPs in *ADRB1* gene, Zaugg et al. [21] found an association between the *ADRB1* arg389gly and the composed primary outcome of cardiovascular mortality/nonfatal myocardial infarction/unstable angina/congestive HF/cerebrovascular accident (CVA) (H. R. = 1,87; 95%CI = 1,04–3,35; p-value = 0,04), concluding that *ADRB1* genotype, but not perioperative bisoprolol, may determine cardiovascular outcome in at-risk patients undergoing surgery with spinal block. Looking carefully at these results we found that considering patients treated with bisoprolol only, these results remain statistically significant. Zaugg et al. reported the following primary outcome distribution among patients treated with bisoprolol: 8 of 55 [14.5%] with *ADRB1* wildtype genotype, and 14 of 37 [37.8%] patients carrying the *ADRB1* arg389gly SNP; this means O.R. = 3.58; 95% CI = 1.18–11.21; p-value = 0.01). This might mean a significant association between the *ADRB1* Arg389Gly variant and bisoprolol response. Also, Lee et al. [39] suggested that tailoring bisoprolol dose depending on *ADRB1* genotype may lead to less adverse events such as bradycardia [39].

On the other hand, results from Rau et al. [22] did not find a statistically significance about the influence of *ADRB1* polymorphisms and bisoprolol response, and highly suggest that the clinical effect of these polymorphisms varies between β-blockers, this way among Arg389Arg genotype patients with atrial fibrillation, Rau et al. described differences in HR lowering effect comparing carvedilol vs. bisoprolol. A limitation of their study is that 60% of the patients had been previously treated with a β-blocker, thus, they might be resistant to carvedilol or bisoprolol. And, as well, they could not explore the combined effects of different *ADRB* variants. In an in vitro study authors described that the arginine form in *ADRB1* had enhanced coupling to Gs, producing more cAMP signal mediated by the adenylyl cyclase, which leads to more active receptors available. This suggests that physiologic differences in the polymorphism may be the basis of the huge interindividual variation in response to β-blockers [45].

As commented above, results from Sounsyrja et al. showed a tendency in better BP response in patients Ser49Ser homozygotes (rs1801252) compared with Ser49Gly heterozygotes, but results were inconclusive [16].

About *ADRB2* gene polymorphisms, previous studies revealed that Glu27 polymorphism (rs1042714) and Arg16 (rs1042713) are more resistant to down-regulation and, in consequence, these variants might be more sensible to the effect of β-blockers. Even though, none of the authors found associations with response to bisoprolol and variants in *ADRB2* gene [25].

Anyway, as we can see, there is an important heterogeneity about how genetic polymorphisms in *ADBR* genes influence the response to

bisoprolol. Based on results from research articles found in this systematic review, the *ADRB1* Arg389Gly variant seems to be the most relevant on the influence over bisoprolol response regardless of the pathology. But we can find contradictory results depending on the clinical parameter considered as endpoint, population etc. Also, when we performed a meta-analysis, we did not find either significant results.

4.2. Bisoprolol and other genetic polymorphisms

Mohammed Alkreathy et al. [37] and Fedorinov et al. [38], explored genetic variants in gene enconding CYP2D6 isozyme but we cannot consider their results consistent as in both samples of patients for the SNPs analyzed the heterozygote or homozygote allele was not present. Other limitation of their studies is that they did not analyze the influence of variants in *CYP3A4*, while bisoprolol is principally metabolized by this CYP isoform.

The *ACE* insertion/deletion (I/D) genetic polymorphism has been investigated in PGx studies of antihypertensive drugs but, as described by Sounsyrja et al. [40] and de Groote et al. [43] it has not been associated with BP response to different classes of drugs such as β-blockers, thiazides or ACE inhibitors and it does not seem to be determinant in response or safety of β-blockers.

Results reported by Donner et al. suggest that other SNPs (rs17367504, rs6749447) may be implicated in the action of bisoprolol in hypertensive men, that need to be studied profoundly in large population studies to determine their connotation [41]. One of these SNPs, rs6749447 in *STK39* gene, is notably associated with response to losartan in this study. This gene encodes a serine threonine kinase that regulates the activity and expression of various renal ions co-transporters that modulate the homeostasis; thus, it has a relevant function in hypertension [46,47]. More SNPs possibly associated with BP regulation in hypertension are located in *ACY3*, *ALDH3B2*, *PTPRD* and *OTOL1,* that need to be studied profoundly to really asses any relevant PGx association in response to bisoprolol [32,44].

5. Conclusions

In conclusion, most of β-blockers such as bisoprolol, metoprolol, atenolol, carvedilol etc.; share indication of use, have similar pathways and mechanisms of action, and bisoprolol use is even more frequent depending on the sanitary system. Despite these similarities, for metoprolol, several pharmacogenetic studies have been performed, its drug label includes pharmacogenetic information, there are available pharmacogenetic dossing guidelines and there are warnings from sanitary authorities in this regard.

By contrast, there is an important lack of studies about the influence of genetic polymorphisms on other β-blockers (bisoprolol, atenolol, carvedilol etc.) response.

Regarding bisoprolol, we found only 13 publications studying the association of genetic polymorphisms with patients´ response to treatment, and even though the *ADRB1* Arg389Gly variant seems to have an influence on bisoprolol efficacy, published results are inconclusive and our meta-analysis did not find a statistically significant results in this regard.

This systematic review supports the need of research in this field, assessing how different genetic variants, especially in *ADRB* and *CYP2D6* genes may influence bisoprolol response. This should be studied considering different indications of use, interactions between genetic variants and multiple clinical parameters, use of co-medications and other co-morbidities.

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Celia Castaño-Amores: Conceptualization, Methodology, Writing – original draft, Investigation, Resources, Visualization. **Xando Díaz-Villamarín:** Conceptualization, Methodology, Writing – original draft, Investigation, Resources, Visualization. **Ana María Pérez-Gutiérrez:** Formal analysis, Data curation. **Alba Antúnez-Rodríguez:** Writing – review & editing, Formal analysis, Data curation. **Ana Pozo-Agundo:** Writing – review & editing, Data curation. **Eduardo Moreno-Escobar:** Validation, Writing – review & editing. **Jesús Gabriel Sánchez-Ramos:** Validation, Writing – review & editing. **Luis Javier Martínez-González:** Validation, Writing – review & editing, Supervision. **Cristina Lucía Dávila-Fajardo:** Conceptualization, Methodology, Writing – review & editing, Supervision, Project administration.

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Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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