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ORIGINAL ARTICLE

The *NOS1AP* gene rs10494366 common genetic variant does not modify the risk of sudden cardiac death in users of digoxin

Negin Soroush[1] | Albert-Jan Aarnoudse[2] | Maryam Kavousi[1] | Jan A. Kors[3] | M. Arfan Ikram[1] | Bruno H. Stricker[1] | Fariba Ahmadizar[1,4]

[1]Department of Epidemiology, Erasmus MC, University Medical Center, Rotterdam, The Netherlands

[2]Department of Internal Medicine, Catharina Hospital, Eindhoven, The Netherlands

[3]Department of Medical Informatics, Erasmus MC, University Medical Center, Rotterdam, The Netherlands

[4]Department of Data Science & Biostatistics, Julius Global Health, University Medical Center Utrecht, Utrecht, The Netherlands

Correspondence
Prof. Dr. B.H. Stricker, Department of Epidemiology, Erasmus Medical Center, PO Box 2040, 3000 CA Rotterdam.
Email: b.stricker@erasmusmc.nl

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Abstract

Aims: Common genetic variations in the nitric oxide synthase-1 adaptor protein (*NOS1AP*) gene are associated with QT-interval prolongation. In a previous study, we observed an association between the rs10494366 variant of this gene and an increased QT-interval shortening in digoxin users. As QT-interval shortening is a risk factor for sudden cardiac death (SCD), in this study, we investigated whether the association between digoxin use and risk of SCD differs in participants with different *NOS1AP* rs10494366 genotypes.

Methods: We included 11 377 individuals from the prospective population-based cohort of the Rotterdam Study. We used Cox proportional hazard regression analysis with digoxin as time-dependent exposure to estimate the associations between current digoxin use and the risk of SCD among different rs10494366 genotype groups in the adjusted models. We also studied whether such an association was dose-dependent, comparing high dosage (≥ 0.250 mg), moderate dosage (0.125 mg ≤ dose< 0.250 mg) and low dosage (< 0.125 mg) digoxin users with non-users.

Results: The median baseline age of the total study population was 62 (interquartile range [IQR] 58–71) years. The cumulative incidence of SCD was 4.1% (469 cases), and among them, 74 (15.7%) individuals were current digoxin users at the time of death, during a median follow-up of 11.5 (IQR 6.5–17) years. Current digoxin users had an increased risk of SCD (multivariable adjusted model hazard ratio [HR]: 3.07; 95% confidence interval [CI]: 2.38–3.98), with no significant differences between the three genotype groups. The adjusted HRs were 4.03 [95% CI: 1.98–8.21] in the minor homozygous GG, 3.46 [95% CI: 2.37–5.04] in the heterozygous TG and 2.56 [95%CI: 1.70–3.86] in the homozygous TT genotype groups. Compared to low- and moderate-dose, high-dose digoxin users with GG genotype had the highest risk of SCD (HR: 5.61 [95% CI: 1.34–23.47]).

The Principal Investigator of this study is Prof. Dr. B.H. Stricker.

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Conclusions: Current use of digoxin is associated with a significantly increased risk of SCD. The *NOS1AP* gene rs10494366 variant did not modify the digoxin-associated risk of SCD in a population of European ancestry.

KEYWORDS
digoxin, genetic variants, *NOS1AP* gene, sudden cardiac death

1 | INTRODUCTION

Genome-wide association studies (GWAS) have identified common genetic variants in the nitric oxide synthase-1 adaptor protein (NOS1AP) gene as markers contributing to the differences in QT-interval duration in the general population.[1,2] Observational studies revealed the association of common variants of this gene and QT-interval prolongation within the large population-based cohort of the Rotterdam Study.[3,4] The QT interval with the variation heritability of 35% in the general population[5] is a measure of ventricular repolarization, and both its prolongation and shortening are risk factors for developing malignant ventricular arrhythmias.[6] Therefore, genes affecting the QT interval have been implied to be associated with sudden cardiac death (SCD).[7] A meta-analysis study reported that the rs10494366 variant of the *NOS1AP* gene might potentially influence SCD occurrence in a Caucasian population.[8]

Digoxin is one of the oldest cardiovascular medications prescribed for ventricular rate control in chronic atrial fibrillation (AF).[9] It may reduce symptoms in patients with mild to moderate heart failure (HF). Its mechanism of action leads to a shortening of the QT interval. Due to its narrow therapeutic window, digoxin has been associated with intoxication, life-threatening arrhythmias and cardiac death since its introduction into medical practice.[10] Digoxin therapy revealed a neutral effect on mortality in HF in a large randomized controlled trial.[11] However, its relation with mortality has aroused widespread concern in observational studies in recent years.[12–15] Earlier, we observed a paradoxical association between the minor allele of the rs10494366 variant of the *NOS1AP* gene and an increased QT-interval duration shortening in patients who take digoxin.[16]

In this study, we further explored whether the association between digoxin use and the risk of SCD varies between different *NOS1AP* gene rs10494366 genotypes. Based on our previous findings,[16] we hypothesized that minor allele carriers of this variant might have a role in an increased risk of SCD in users of digoxin.

What is already known about this subject

- Genes affecting the QT interval might be associated with the occurrence of sudden cardiac death (SCD).
- Based on our previous finding, there is an association between the rs10494366 variant of the *NOS1AP* gene and an increased QT-interval shortening in digoxin users.
- The effect of the rs10494366 variant on the association between digoxin use and SCD is unknown.

What this study adds

- In this community-based prospective cohort study of 11 377 middle-aged and older adults, we found that the *NOS1AP* gene rs10494366 variant is not an effect modifier of the association between digoxin use and SCD event.
- High-dose digoxin users with GG genotype had the highest risk of SCD.

2 | METHODS

2.1 | Study population and setting

This prospective study was embedded within the Rotterdam Study, the population-based cohort that started in 1990 in the district of Ommoord, in the city of Rotterdam, The Netherlands.[17] The Rotterdam Study aims to assess the risk factors for chronic diseases in a middle-aged and older population of almost 15 000 participants ≥45 years old. The objectives, methods and the ongoing recruitment process of participants have been reported in detail.[18] We report on data collected from the starting point in 1990 until 1 January 2014. The study population consisted of 11 377 participants, who were followed from the baseline until their death or the end of the study period (Figure 1). The Medical Ethics Committee of the Erasmus MC (registration number MEC 02.1015), and the Ministry of Health, Welfare, and Sport of the Netherlands (Population Screening Act WBO, licence number 1071272–159521-PG) approved the Rotterdam Study. The Rotterdam Study has been entered into the Netherlands National Trial Register (NTR; www.trialregister.nl) and the WHO International Clinical Trials Registry Platform (ICTRP; www.who.int/ictrp/network/primary/en/) under shared catalogue number NTR6831. All participants included in this study provided written informed consent to participate and share their medical records and samples for scientific purposes.

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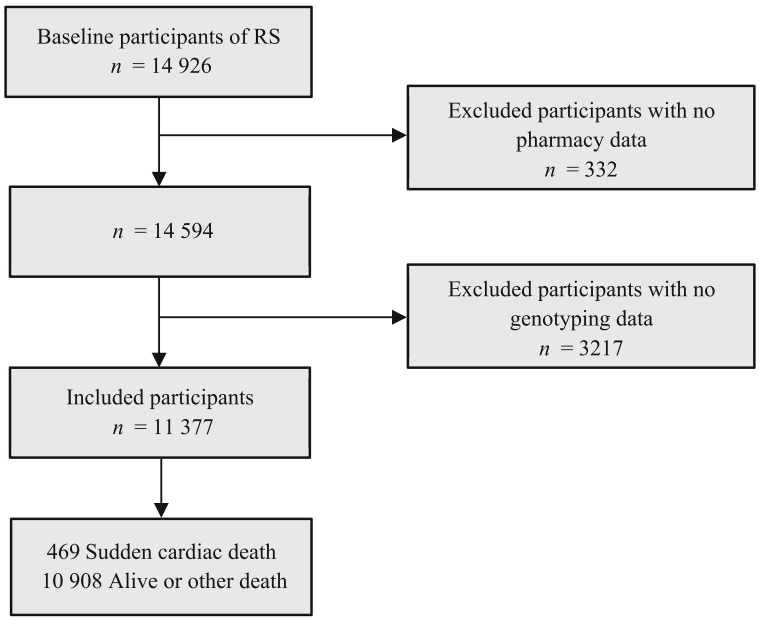

FIGURE 1 Flowchart of the included study participants.

2.2 | Genotyping

Genotyping of DNA samples from the almost 12 000 participants of the Rotterdam Study cohort was performed using Illumina 550 K (single + duo format) and Illumina Human 610 K (Quattro format) arrays. The Rotterdam Study GWAS dataset was imputed with 1000 Genomes (version Iv3) reference dataset.[18] Data on the single nucleotide polymorphism (SNP) rs10494366 were extracted for this study. Imputation quality for this SNP was high (>0.99).

2.3 | Exposure definition

Digoxin dispensing data were obtained from all pharmacies in the study district, which use one collaborative computer system. Filled prescription data, including product name, Anatomical Therapeutic Chemical (ATC) code, dispensing date, prescribed daily dose and the amount prescribed were collected. The defined daily dose (DDD) of digoxin [ATC code: C01AA05] is equivalent to 0.25 mg.[19] The duration of dispensed digoxin prescription was calculated by dividing the number of tablets in the prescription by the daily prescribed number of units. Each subject was considered as currently exposed to digoxin if the index date of SCD occurrence fell within this duration. The exposure was assessed in that case and all the remaining participants as controls on that specific date.[20] Current digoxin use was categorized into three daily dose groups: 1 [dose < 0.125 mg (low dosage)], 2 [0.125 mg ≤ dose < 0.250 mg (moderate dosage)], and 3 [dose ≥ 0.250 mg (high dosage)].

2.4 | Definition of sudden cardiac death (SCD) outcome

According to Myerburg's definition, endorsed by the European Society of Cardiology (ESC), SCD is defined as 'a natural death due to cardiac causes, heralded by abrupt loss of consciousness within one hour of the onset of acute symptoms; pre-existing heart disease may have been known to be present, but the time and mode of death are unexpected'.[21] Information on vital status and cause of death was obtained from general practitioners and hospital records. If death was unwitnessed, the medical history was reviewed for evidence of cardiac or non-cardiac causes.[22] The adjudication of SCD cases in the Rotterdam Study was performed by two physicians and ascertained by a cardiologist.[23] This step was performed without knowledge of the current research question. We further restricted the event definition to only witnessed SCD events. The index date was defined as every date that an SCD case occurred.

2.5 | Covariables

Data on baseline covariables were collected through standardized home interviews and also physical examination and blood sampling during visits to the research centre.[18] Body mass index (BMI) was calculated as weight (kg) divided by height (m^2). Smoking status was categorized as current, past and never smoking. A systolic blood pressure of ≥140 mmHg or a diastolic pressure of ≥90 mmHg, measured by a random-zero sphygmomanometer from the right arm of the participants in a sitting position, or use of blood pressure-lowering drugs were defined as hypertension.[18] Cardiovascular disease (CVD) status at the study baseline was defined as a combination of HF, coronary heart disease (CHD) and stroke. The definitions and procedures of the adjudication have been described in detail previously.[22] HF was diagnosed in patients with typical symptoms according to the ESC guidelines and the presence of objective evidence of cardiac dysfunction.[22] CHD was defined as a combined outcome of surgical or percutaneous coronary revascularization (as a proxy for significant coronary artery disease), myocardial infarction (MI) (fatal and nonfatal) and fatal CHD. Patients with pathology outcomes of an acute MI within 28 days of death or

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changes in cardiac biomarker values and objective-indicative ECGs were considered as definite MI cases, confirmed by a medical specialist.[22]

2.6 | Statistical analysis

Descriptive statistics were performed by reporting median (interquartile range [IQR]) for continuous variables and numbers (percentage) for categorical variables. Differences in study population characteristics between digoxin users and non-users were estimated using the non-parametric Mann–Whitney U and chi-square tests. Hardy–Weinberg equilibrium *P*-value was calculated for genotype frequencies using the chi-square test.

We used a Cox proportional hazard regression model to calculate hazard ratios (HR) with 95% confidence intervals (CIs) to study the association between current digoxin use as a time-dependent exposure and the occurrence of SCD during follow-up time in the total population regardless of their genotype and also among *NOS1AP* gene rs10494366 genotype groups. We also studied whether such an association was dose-dependent, comparing high dosage (≥0.250 mg), moderate dosage (0.125 mg ≤ dose < 0.250 mg), and low dosage (<0.125 mg) digoxin users with non-users. All analyses were adjusted for age, sex, BMI, smoking behaviour, hypertension and prevalent CVD at baseline. We further adjusted the model with the QT-interval measurements at the baseline. We performed the analyses, restricted to witnessed SCD cases to minimize the potential misclassification of the SCD outcome. In a sensitivity analysis, we estimated the association between the rs10494366 variant as exposure and the risk of SCD in the total population and also digoxin users and non-users.

All analyses were performed at the significance level of 0.05 (two-tailed). Based on the sample size calculations, this study is 80% powered to detect the effect sizes of 1.93, 1.93 and 3.29 for the TT, TG and GG genotype groups, respectively, at the 95% significance level. Missing values in the covariables were handled by a multiple imputation algorithm. Data were analysed using IBM SPSS Statistics, version 25 (IBM Corp, Armonk, NY, USA) and R Survivalpwr packege.

3 | RESULTS

The median baseline age of the total study population ($n = 11\,377$) was 62 (IQR: 58–71) years, and 58% of the total population were women (Table 1). In total, 1147 participants used digoxin at any time during the study period. A total of 469 SCD cases with a cumulative incidence of 4.1% were identified by the end of the median follow-up period of 11.5 (IQR: 6.5–17) years. Among them, 74 (15.7%) patients were current digoxin users at the time of the event. The SCD event was recorded in current users of digoxin with TT, TG and GG genotypes of the rs10494366 variant in 29 (39.2%), 35 (47.3%) and 10 (13.5%) subjects, respectively.

The minor allele frequency (MAF) for the SNP rs10494366 was 35.8%, corresponding to the G allele, and the genotype distribution was in Hardy–Weinberg equilibrium ($\chi^2 = 0.08$, *P*-value = 0.77).

3.1 | Digoxin use, risk of sudden cardiac death and genetic influence

The interaction term of the gene variant with the current use of digoxin showed some indications of the association with an increased risk of SCD (*P*-value = 0.23).

We found that current use of digoxin was associated with an increased risk of SCD in the total population irrespective of their genotype (multivariable adjusted model HR: 3.07; 95% CI: 2.38–3.98). The results of the multivariable adjusted model showed the HRs of (3.74; 95% CI: 2.14–6.53) in high-dose digoxin users, and respectively (HR: 3.41; 95% CI: 2.49–4.68) and (HR: 2.15; 95% CI: 1.29–3.56) in moderate- and low-dose users.

TABLE 1 Baseline characteristics of the study populations.

Characteristic		Total ($N = 11\,377$)	Digoxin users ($n = 1147$)	Digoxin non-users ($n = 10\,230$)	*P*-value
Age (years), median (IQR)		62 (58–71)	72 (66–79)	62 (57–70)	**<0.001**
Sex (Female), *n* (%)		6582 (57.9)	643 (56.1)	5939 (58.1)	0.19
BMI (kg/m^2), median (IQR)		26.4 (24.2–29.0)	26.6 (24–29)	26.4 (24.1–29)	0.98
Ever smokers, *n* (%) (current or past)		8430 (74.1)	926 (80.7)	7504 (73.4)	**<0.001**
Hypertension, *n* (%)		6768 (59.5)	899 (78.4)	5869 (57.4)	**<0.001**
Prevalent CVD, *n* (%)		1377 (12.1)	322 (28.1)	1055 (10.3)	**<0.001**
HDL cholesterol (mmol/L), median (IQR)		1.3 (1.1–1.6)	1.2 (1–1.5)	1.3 (1.1–1.6)	**<0.001**
Total cholesterol (mmol/L), median (IQR)		6.1 (5.3–6.9)	6.3 (5.4–7.1)	6.1 (5.3–6.9)	**0.001**
rs10494366 variant genotypes, *n* (%)	TT	4702 (41.3)	494 (43.1)	4208 (41.1)	0.45
	TG	5213 (45.8)	510 (44.5)	4703 (45.9)	
	GG	1462 (12.9)	143 (12.4)	1319 (12.9)	

Abbreviations: BMI, body mass index; CVD, cardiovascular diseases; HDL, high-density lipoprotein; IQR, interquartile range.

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The results of the association of digoxin use and total SCD and witnessed SCD events occurrence among patients with different rs10494366 genotypes are shown in Figure 2. Current use of digoxin resulted in a statistically significant increased risk of total SCD events in homozygous minor allele carriers with GG genotype (HR: 4.03; 95% CI: 1.98–8.21), in heterozygous TG genotype (HR: 3.46; 95% CI: 2.37–5.04) and homozygous TT genotype (HR: 2.56; 95% CI: 1.70–3.86).

Furthermore, the analysis with the outcome restricted to only witnessed SCD cases ($n = 238$) showed a significantly increased risk of SCD in the GG genotype group (HR: 5.16; 95% CI: 2.23–11.91) compared to the non-user reference group, which was higher than the other genotypic groups, albiet not statistically significant (Figure 2).

As shown in Figure 3, high-dose digoxin users with GG genotype had the highest risk of total SCD event compared to non-users in the multivariable adjusted model (HR: 5.61; 95% CI: 1.34–23.47). The event risk in the TG genotype group was (HR: 2.73; 95% CI: 1.00–7.43) and (HR: 4.42; 95% CI: 2.05–9.52) in the TT genotype group.

The results of sensitivity analyses revealed that the *NOS1AP* gene rs10494366 variant was not associated with SCD in the total population (HR: 1.04; 95% CI: 0.91–1.19) independent of whether subjects were exposed to digoxin, nor among non-users of digoxin (HR: 1.02; 95% CI: 0.88–1.18), in the adjusted model.

4 | DISCUSSION

In this study, we found that current digoxin users had an increased risk of SCD with no significant differences between the three genotype groups of the *NOS1AP* gene rs10494366 variant. We further observed that the rs10494366 variant was not associated with the outcome irrespective of digoxin use status in the total population or only among non-users. Observing no significant association between the *NOS1AP* gene rs10494366 variant and SCD risk in the total population was in line with previous findings in the Rotterdam Study population.[3,24] In a similar set of the Rotterdam Study, the minor G allele of the rs10494366 variant has shown an association with increased risk of all-cause and cardiovascular mortality in participants taking dihydropyridine calcium channel blockers,[24] indicating that the association between the rs10494366 variant and mortality is present when the medication is prescribed.

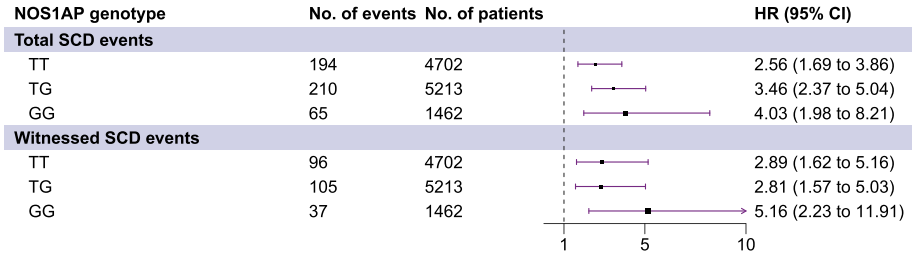

FIGURE 2 Digoxin use effects on total SCD events and witnessed SCD risk among different genotypes of the *NOS1AP* gene rs10494366 variant. A multivariable model adjusted for age, sex, body mass index (BMI), smoking behaviour, hypertension and prevalent cardiovascular disease (CVD) at baseline. SCD, sudden cardiac death; HR, hazard ratio; CI, confidence interval.

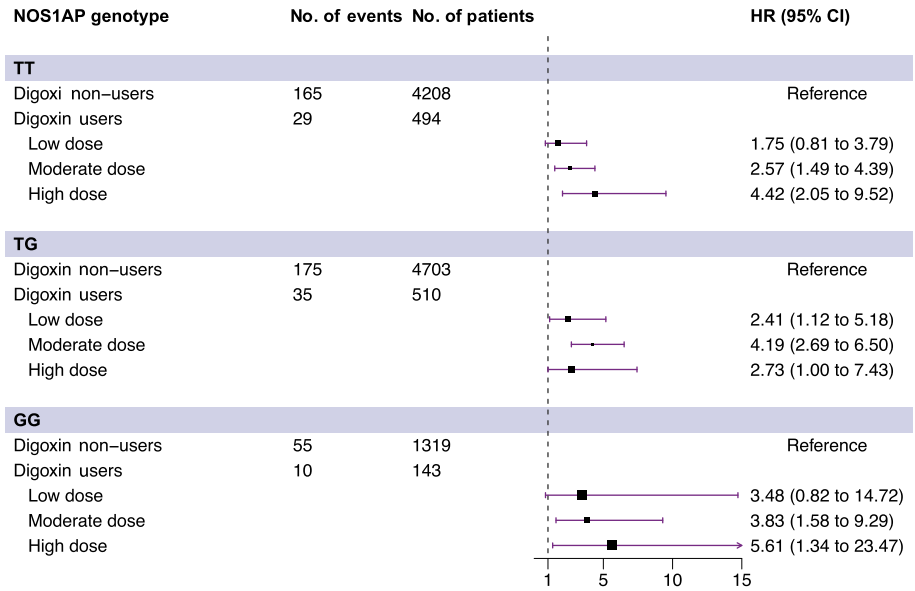

FIGURE 3 The association between digoxin dose categories and SCD events, stratified on *NOS1AP* gene rs10494366 variant genotypes. A multivariable model adjusted for age, sex, body mass index (BMI), smoking behaviour, hypertension and prevalent cardiovascular disease (CVD) at baseline. Defined daily dose categories in digoxin users: low dose: dose < 0.125 mg, moderate dose: 0.125 mg ≤ dose < 0.250 mg, and high dose: dose ≥ 0.250 mg. SCD, sudden cardiac death; HR, hazard ratio; CI, confidence interval.

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The association of prolonged QT interval and its components as risk factors for SCD has been well established in previous studies.[25,26] Using some of the non-cardiac QT-interval prolonging medications such as antithyroid drugs is associated with increased risk of SCD.[27] There is evidence showing that current users of chloroquine and hydroxychloroquine medications have significantly longer QT-interval duration, and use of these medications significantly increases the risk of SCD in the Rotterdam Study population.[28] A recent study using the Mendelian randomization approach has demonstrated that this cardiac electrophysiological factor is causally associated with sudden cardiac arrest (SCA) in the general population.[29] Also, a short QT interval is considered a risk factor for SCD as a congenital syndrome or in the general population.[30,31] In our previous study, we observed that the rs10494366 variant of the *NOS1AP* gene is associated with QT-interval duration and digoxin use in the population of the Rotterdam Study.[16] Current digoxin users with minor homozygous GG genotype showed a more pronounced QT-interval shortening effect.[16] Although, in the present study, the differences in genotype-stratified association analyses were not statistically significant, the direction of the findings is consistent with our primary hypothesis where the G minor allele carriers of this variant are expected to have an increased risk of SCD. We also observed that high-dose digoxin users with GG genotype had the highest increased risk of SCD compared to non-users with similar genotype.

From the existing data, it is difficult to determine the mechanism by which this genetic variant might affect SCD risk, whether it is through modulation of the QT interval or via other mechanisms. In this study, we investigated the total effect of digoxin use on SCD and its association with the gene variant without considering the mediation effect of QT interval since the baseline QT-interval durations, which is a dynamic phenotype, were measured well before the event. However, the estimates of the direct effect of digoxin use in the model adjusted for the baseline QT interval were similar to the multivariable model analysis findings (results not shown).

SCD is an major health issue globally. The pathophysiology of its occurrence is not sufficiently known. Identifying at-risk individuals is required as most affected patients would not even make it to hospital for medical intervention. In non-witnessed SCD case identification, some non-differential misclassification was expected; therefore, we performed a sensitivity analysis with restricted outcome definition to only witnessed SCD cases. Despite the lower number of events ($n = 238$), we observed a larger effect estimate in the digoxin users with minor homozygous genotype.

The strengths and limitations of this study should be noted. Access to the detailed pharmacy data of the Rotterdam Study participants enabled us to determine the history of digoxin use at the time of death. The SCD cases were determined without prior knowledge of this study hypothesis; the prospective design of the Rotterdam Study limits the risk of information bias. Furthermore, we could perform a sensitivity analysis with ascertained witnessed SCD cases. Our study also had several limitations that should be acknowledged. First, the Rotterdam Study cohort consists of a homogeneous population; thus, our findings are not directly applicable to other populations considering that the frequency of the rs10494366 G allele varies in populations with different ethnic backgrounds.[32] Also, this variant of the *NOS1AP* is probably in linkage disequilibrium with other causal genetic variants associated with the SCD outcome; their association with digoxin use is required to be explored with further research. Our study was underpowered to detect significant interactions and perform sex-stratified analyses. The current study would be underpowered to confirm significant associations in increased risks lower than the reported thresholds in our power analysis for each genotype group. Future studies with additional samples are necessary to confirm our results. The current findings imply a more exploratory or hypothesis-generating approach that could lay the groundwork for more comprehensive predictive approaches such as genetic risk score studies in future research where broader phenotypic variations need to be explained.

5 | CONCLUSIONS

In conclusion, we found no evidence to support the notion that the *NOS1AP* gene rs10494366 variant modifies the relationship between digoxin exposure and the risk of sudden cardiac death in our study population. While genetic factors may not have played a significant role in this association, our findings highlight the complexity of medication response and the need for continued research into other potential determinants. By understanding these factors more comprehensively, we can develop more personalized and effective approaches to cardiovascular therapeutics and patient care.

AUTHOR CONTRIBUTION

Bruno H. Stricker, Fariba Ahmadizar and Albert-Jan Aarnoudse are responsible for the study concept and design; Negin Soroush performed the statistical analyses, data interpretation and prepared the manuscript/revision; Albert-Jan Aarnoudse, Maryam Kavousi, Jan A. Kors, M. Arfan Ikram, Fariba Ahmadizar and Bruno H. Stricker critically edited the manuscript for intellectual content. Bruno H. Stricker and Fariba Ahmadizar are responsible for the final content and interpretation of the results.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Negin Soroush https://orcid.org/0000-0003-3110-9896

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