ACE Inhibitor and Angiotensin Receptor Blocker Use During Pregnancy: Data From the ESC Registry Of Pregnancy and Cardiac Disease (ROPAC)

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Angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (ARBs) are not recommended during the second and third trimester because of the significant risk of congenital anomalies associated with their use. However, data are scarce, especially regarding their use in the first trimester and about the impact of stopping just before pregnancy. Our study illustrates the profile of the women who used ACE-Is or ARBs during pregnancy and evaluates the impact on perinatal outcomes. The Registry of Pregnancy and Cardiac Disease is a prospective, global registry of pregnancies in women with structural heart disease. Outcomes were compared between women who used ACE-Is or ARBs and those who did not. Multivariable regression analysis was performed to assess the effect of ACE-I or ARB use on the occurrence of congenital anomalies. ACE-Is (n = 35) and/or ARBs (n = 8) were used in 42 (0.7%) of the 5,739 Registry of Pregnancy and Cardiac Disease pregnancies. Women who used ACE-Is or ARBs more often came from a low-or-middle-income country (57% vs 40%, p = 0.021), had chronic hypertension (31% vs 6%, p <0.001), or a left ventricular ejection fraction <40% (33% vs 4%, p <0.001). In the multivariable analysis, ACE-I use during the first trimester was associated with an increased risk of congenital anomaly (odds ratio 3.2, 95% confidence interval 1.0 to 9.6). Therefore, ACE-Is should be avoided during pregnancy, also in the first trimester, because of a higher risk of congenital anomalies. However, there is no need to stop long before pregnancy. Preconception counseling is crucial to discuss the potential risks of these medications, to evaluate the clinical condition and, if possible, to change or stop the medication. **(Am J Cardiol 2024;230:27−36)**

Keywords: ACE inhibitor, angiotensin receptor blocker, preconception, pregnancy

Angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (ARBs) are widely used in patients with cardiovascular diseases, and also in noncardiac diseases, including chronic kidney disease, hypertension, and diabetes mellitus.[1] Both ACE-Is and ARBs inhibit the renin-angiotensin-aldosterone system (RAAS) by blocking the conversion of angiotensin I to angiotensin II and antagonizing receptor binding of angiotensin II to angiotensin I receptors, respectively.[2] Previous studies showed an increased risk of neonatal harm after *in-utero* exposure to ACE-Is or ARBs during the second and third trimester.[3,4] The mechanism is probably through inhibition of the fetal RAAS, which reduces kidney function resulting in oligohydramnios and impaired lung development.

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Therefore, these medications are contra-indicated during the second and third trimester of pregnancy.[3,4] Although recent meta-analyses suggest an increased risk of adverse pregnancy outcomes after in utero ACE-I or ARB exposure during the first trimester, the quality of the results is debatable because of the lack of adjustment for confounders and most of the studies have a retrospective design.[5,6] As pregnant women are actively excluded from most clinical trials, prospective, observational studies with medication exposure data during pregnancy are crucial. We used prospective data from the Registry Of Pregnancy And Cardiac Disease (ROPAC) to describe the profile of the women who used an ACE-I or ARB during pregnancy and to investigate the perinatal outcomes after in utero ACE-I or ARB exposure, particularly during the first trimester.

Methods

The ROPAC is a prospective, global, observational registry that enrolled 5,739 pregnancies of women with structural heart disease. A detailed description of the rationale and design of the ROPAC has been reported previously.[7,8] In brief, women from 138 centers in 53 countries were enrolled between 2007 and 2018. Participating centers managed the approvals of national or regional ethics committees or Institutional Review Boards, according to local regulations.

Data regarding maternal diagnosis, obstetric history, medication use, events, and complications during pregnancy and delivery were collected. In this substudy, we analyzed the pregnancies in which ACE-Is and/or ARBs were used, which was defined as the use of an ACE-I and/or ARB at any point during pregnancy. Medication use was reported by the local investigators and defined as prescribed. The group of women in the ROPAC database who did not used ACE-Is or ARBs during pregnancy was defined as nonusers and women who did not used ACE-Is or ARBs before and during pregnancy were defined as never-users. The classification for a low-or-middle-income country (LMIC) was based on The International Monetary Classification. Stillbirth was defined as fetal death after 20 weeks' gestation[9] and neonatal mortality as death of a live-born baby within the first month of life. Small for gestational age was defined as birth weight <10 percentile. The maternal cardiac and pregnancy outcomes were studied. A major adverse cardiac event (MACE) was defined as a composite endpoint of maternal mortality (follow-up to 6 months postpartum), heart failure, arrhythmia, endocarditis, thromboembolic event, and aortic dissection. The outcome 'total congenital anomalies' was defined as composite endpoint of therapeutic abortion because of fetal anomalies, and congenital disease in the infant.

Categorical data are presented as frequencies (numbers) and percentages and were compared using chi-square tests. Normally distributed continuous data are described as mean values with SD and were compared using unpaired *t* tests or one-way analysis of variance. If skewed, continuous data are described as median with interquartile range and were compared using the Mann-Whitney *U* test. Missing values were handled using multiple imputation, and all relevant information regarding missing data was provided in the figure or table legends if applicable. For all analyses, a two-sided p value of <0.05 was considered statistically significant. IBM SPSS Statistics version 28.0 was used for all statistical tests and analyses.

Pre-pregnancy baseline characteristics and outcomes were compared between the women who used an ACE-I and/or ARB during pregnancy and nonusers. We performed a multivariable logistic regression analysis with backward selection to identify the key features associated with ACE-I and/or ARB use during pregnancy, including variables that were p <0.1 in the univariable analysis. To investigate an association between ACE-I and/or ARB use and congenital anomalies, we performed a multivariable logistic regression analysis with backward selection (except for ACE-I or ARB use) corrected for baseline characteristics with a p value <0.1 in the univariable analysis and factors associated with congenital anomalies (maternal age, smoking, diabetes mellitus, maternal diagnosis), based on previous literature.

Additionally, we performed several secondary analyses. First, we compared the outcomes between the women who used an ACE-I and/or ARB during the first trimester (the period of organogenesis) and nonusers, and examined the association between ACE-I and/or ARB use during the first trimester and the occurrence of congenital anomalies with a multivariable logistic regression analysis, corrected for baseline characteristics with a p value <0.1 in the univariable analysis and factors which are associated with congenital anomalies. Second, we compared the outcomes of women who only used an ACE-I during the first trimester with nonusers and performed a multivariable logistic regression analysis to examine an association between ACE-I during the first trimester and congenital anomalies, corrected for baseline characteristics with a p value <0.1 in the univariable analysis and factors associated with congenital anomalies. Lastly, we compared the outcomes of women who stopped ACE-Is or ARBs before pregnancy with never-users to examine if preconception use of ACE-Is or ARBs was associated with a higher incidence of congenital anomalies, and we compared the maternal outcomes of women who stopped ACE-Is or ARBs before pregnancy with the maternal outcomes of the women who continued.

Results

ACE-Is (n = 35) and/or ARBs (n = 8) were used in 42 (0.7%) of the 5,739 ROPAC pregnancies (Figure 1). The diagnostic details and pre-pregnancy baseline characteristics are listed in Table 1. Enalapril 49% and valsartan 38% were the most frequently used types of ACE-I and ARB, respectively (Figure 2). Most of the women who used an ACE-I and/or ARB had cardiomyopathy (CMP, 38%), the remainder had valvular heart disease (VHD, 33%), congenital heart disease (CHD, 14%), ischemic heart disease (IHD, 10%) or aortopathy (AOP, 5%), and nearly 70% of the women were classified as modified World Health Organization (Geneva, Switzerland) risk class II to III. Women who used an ACE-I and/or ARB during pregnancy more often came from an LMIC (57% vs 40%, p = 0.021), had chronic hypertension (31% vs 6%, p <0.001), or an estimated left ventricular ejection fraction (LVEF) <40% (33% vs 4%, p <0.001). Other cardiac medication use was associated with

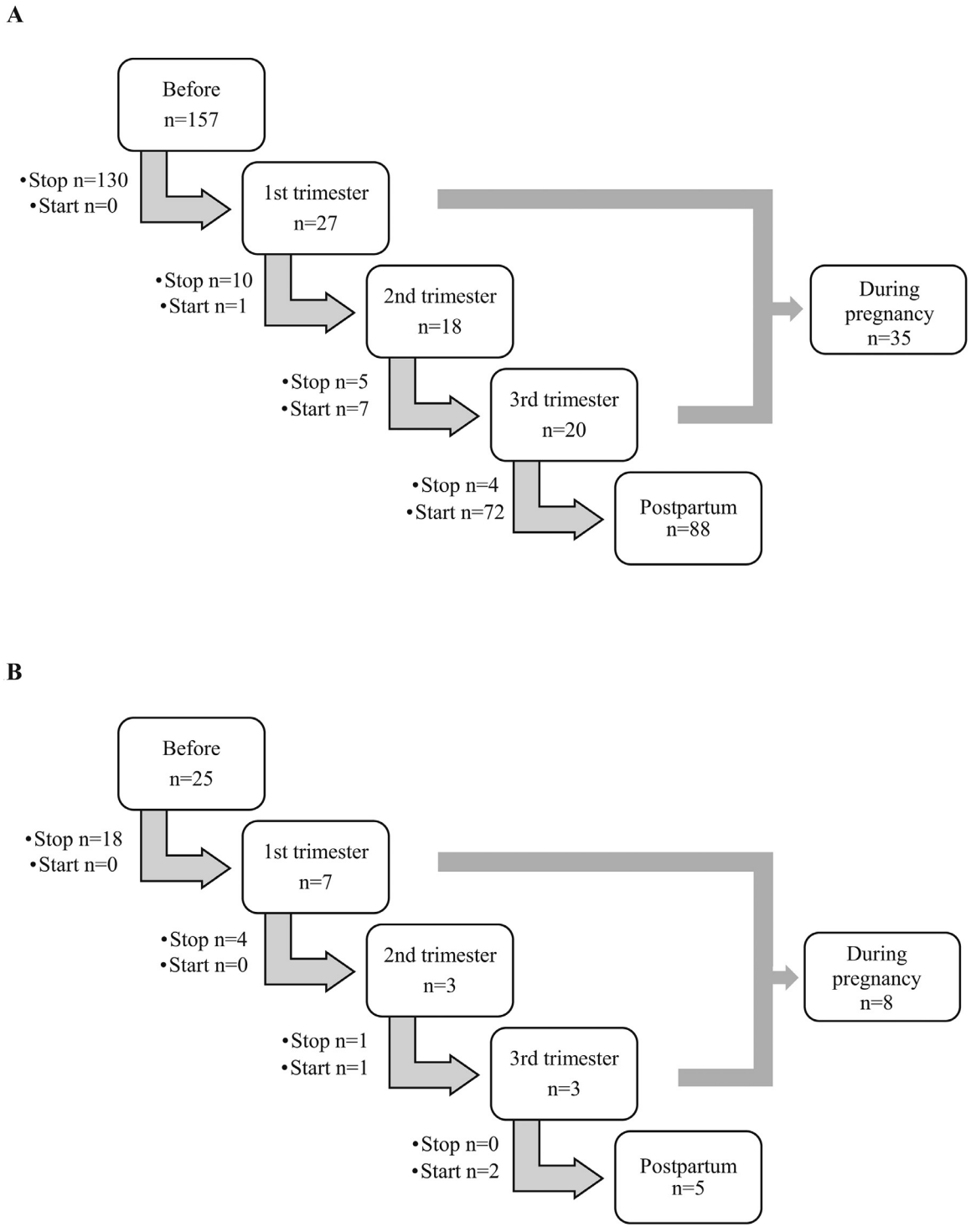

Figure 1. Number of pregnancies in which ACE-Is *(A)* or ARBs *(B)* were used, divided into before pregnancy, during the first trimester, during the second trimester, during the third trimester, and postpartum. One woman used an ACE-I and ARB during pregnancy, and therefore 42 pregnancies were included in our study.

ACE-I or ARB use (odds ratio [OR] 4.8, 95% confidence interval [CI] 2.4 to 9.7), as were chronic hypertension (OR 3.0, 95% CI 1.5 to 6.2), estimated LVEF <40% (OR 3.8, 95% CI 1.9 to 7.7), and VHD (OR 3.73, 95% CI 1.4 to 9.9), CMP (OR 7.3, 95% CI 2.5 to 20.8) and IHD (OR 7.9, 95% CI 2.0 to 30.6) using maternal diagnosis of CHD as the reference (Supplementary Table 1).

A MACE was more common in the women who used an ACE-I and/or ARB during pregnancy (41% vs 15%, p <0.001), especially heart failure (Table 2). Therapeutic termination of the pregnancy because of maternal health issues was more often seen in the women who used an ACE-I and/or ARB during pregnancy compared with the nonusers (12% vs 1%, p <0.001), whereas therapeutic termination

Table 1
Baseline characteristics of women who used an ACE-I and/or ARB during pregnancy compared with nonusers

	Users during pregnancy (n=42, 0.7%)	Nonusers (n=5697, 99.3%)	P-value
Diagnosis details			
Congenital heart disease	6 (14.3%)	3289 (57.7%)	**<0.001**
Valvular heart disease	14 (33.3%)	1635 (28.7%)	0.508
Cardiomyopathy	16 (38.1%)	422 (7.4%)	**<0.001**
Aortopathy	2 (4.8%)	215 (3.8%)	0.738
Ischaemic heart disease	4 (9.5%)	91 (1.6%)	**<0.001**
Pulmonary hypertension	0	45 (0.8%)	0.563
mWHO I	2 (4.8%)	1183 (20.8%)	**0.011**
mWHO II	0	828 (14.5%)	**0.008**
mWHO II-III	29 (69.0%)	2669 (46.8%)	**0.004**
mWHO III	4 (9.5%)	589 (10.3%)	0.863
mWHO IV	7 (16.7%)	400 (7.0%)	**0.015**
Pre-pregnancy characteristics			
Age, years, mean (±sd)	31.1 ± 6.1	29.5 ± 5.6	0.152
BMI, kg/m^2, median (Q1-Q3)	25.4 (21.7-30.9)	24.0 (21.5-27.5)	0.063
Nulliparity	13 (31.0%)	2560 (44.9%)	0.067
LMIC	24 (57.1%)	2257 (39.6%)	**0.021**
Current smoker	3 (7.1%)	225 (3.9%)	0.312
Chronic hypertension	13 (31.0%)	367 (6.4%)	**<0.001**
Diabetes mellitus	1 (2.4%)	89 (1.6%)	0.670
Atrial fibrillation/flutter	1 (2.4%)	105 (1.8%)	0.796
Signs of heart failure	6 (14.2%)	590 (10.4%)	0.356
Estimated LVEF <40%	14 (33.3%)	239 (4.2%)	**<0.001**
Cyanosis	1 (2.4%)	62 (1.1%)	0.423
NYHA class > II	2 (4.8%)	202 (3.5%)	0.671
Prior cardiac intervention	19 (45.2%)	3141 (55.1%)	0.322
Pre-pregnancy cardiac medication use			
ACE-I	27 (64.3%)	130 (2.3%)	**<0.001**
ARB	7 (16.7%)	18 (0.3%)	**<0.001**
Beta-blocker	18 (42.9%)	545 (9.6%)	**<0.001**
Diuretic	14 (33.3%)	203 (3.6%)	**<0.001**
Other cardiac medication	11 (26.2%)	188 (3.3%)	**<0.001**

Data are presented as n (%) unless otherwise specified. Bold values denote statistical significance at the p-level <0.005.

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; LMIC = low-or-middle-income country; LVEF = left ventricular ejection fraction; mWHO = modified World Health Organization classification for maternal cardiovascular risk; NYHA class = New York Heart Association Functional Classification; Q1-Q3 = interquartile range.

because of fetal anomalies was not reported in the women who used an ACE-I and/or ARB (Table 2). Women who used ACE-Is and/or ARBs delivered almost 2 weeks earlier than nonusers (37^{+0} vs 38^{+6} weeks, p <0.001), and were more likely to deliver by cesarean delivery (62% vs 47%, p = 0.021). Preterm birth was more common (33% vs 16%, p = 0.002). The mean birth weight of the infants was almost 400 g lower in the women who used an ACE-I and/or ARB (2,591 vs 2,974 g, p = 0.004), but the difference in small for gestational age infants between the women who used an ACE-I and/or ARB compared with nonusers (17% vs 10%, p = 0.163) was not significant. Four (10%) infants had a congenital anomaly and detailed information on these pregnancies are listed in Table 3. In our univariable and multivariable logistic regression analyses, we found no association between ACE-I and/or ARB use during pregnancy and congenital anomalies (OR 1.9, 95% CI 0.6 to 5.4) (Supplementary Table 2).

For the analysis of ACE-I and/or ARB use during the first trimester, 8 of 42 pregnancies with ACE-I (n = 8) and/or ARB (n = 1) exposure were excluded as these medications were only used during the second and/or third trimester. The diagnostic details, prepregnancy baseline characteristics and outcomes of the women who used an ACE-I and/or ARB during the first trimester are listed in Table 4, and were compared with nonusers. Neonatal CHD was more common in the women who used an ACE-I and/or ARB during the first trimester (9% vs 3%, p = 0.043), but the composite end point of congenital anomalies did not reach significance (12% vs 5%, p = 0.084). In the logistic regression analysis, ACE-I and/or ARB use during the first trimester was not associated with congenital anomalies (OR 2.3; 95% CI 0.8 to 6.9) (Supplementary Table 3). We reported no congenital anomalies after *in-utero* ARB exposure. In the sub analysis in which we compared the outcomes of only the ACE-I users during the first trimester and the outcomes of the nonusers, neonatal congenital disease was more commonly seen in the women who used an ACE-I during the first trimester (15% vs 5%, p = 0.018) (Supplementary Table 4), and ACE-I use during the first trimester was independently associated with congenital anomalies (OR 3.2, 95% CI 1.0 to 9.6), even as other cardiac medication use (OR 1.4, 95% CI 1.0 to 2.0), diabetes mellitus (OR 2.3, 95% CI 1.1 to 4.6), and maternal diagnosis (CHD [OR 1.8, 95% CI 1.3 to 2.6], CMP [OR 2.0, 95% CI 1.2 to 3.2] and AOP [OR 3.3, 95% CI 2.0 to 5.7]) (Table 5).

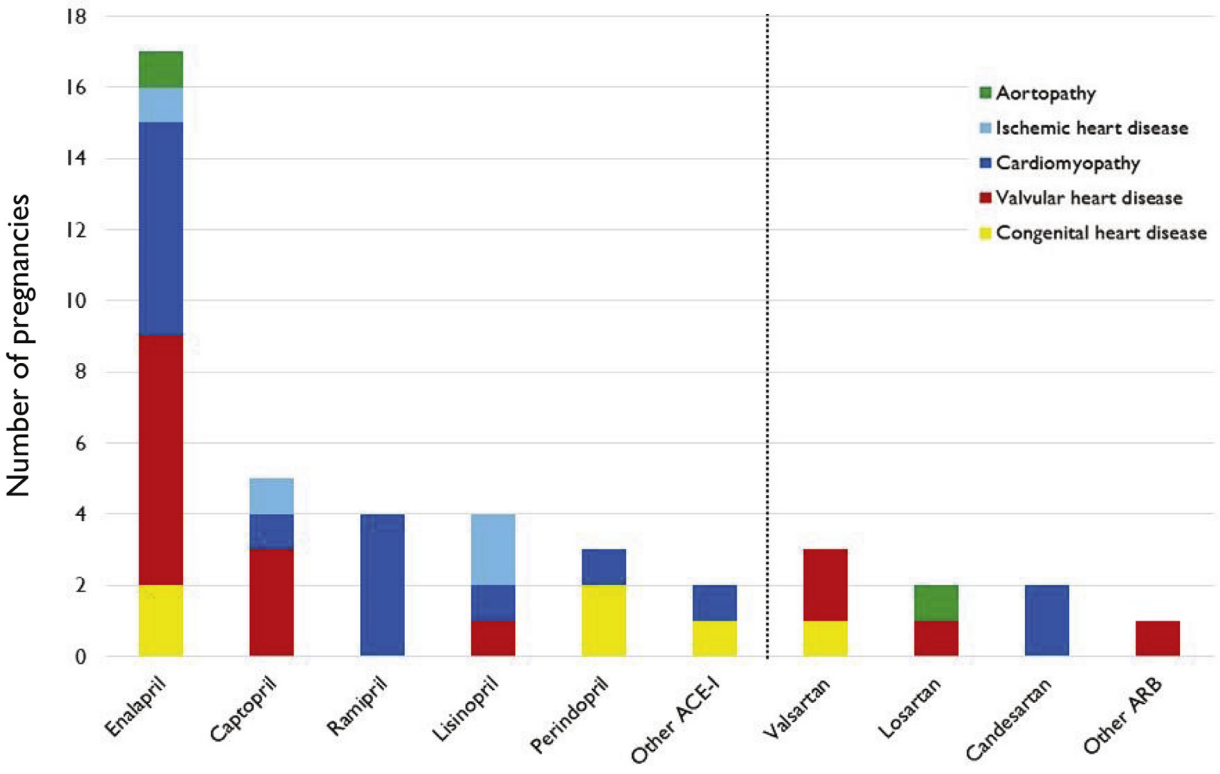

Figure 2. Type of ACE-I and ARB stratified by maternal diagnosis.

In 148 (3%) of the 5,739 ROPAC pregnancies, women stopped using an ACE-I and/or ARB before pregnancy. We compared the diagnostic details, prepregnancy baseline characteristics, and outcomes between the women who stopped the use of an ACE-I or ARB before they became pregnant with the outcomes of never-users (Supplementary Table 5). There were no differences in the number of miscarriages (3% vs 4%, p = 0.514), therapeutic abortions (1.4% vs 1.1%, p = 0.772), and the incidence of congenital anomalies (4% vs 5%, p = 0.538) between both groups. However, MACE was more common in the women who stopped an ACE-I or ARB before pregnancy compared with the never-users (23% vs 15%, p = 0.010). We found no differences in the occurrence of MACE between the women who stopped before pregnancy and the women who continued the ACE-I or ARB (23% vs 29%, p = 0.429) (Supplementary Table 6).

Discussion

Our data from the large multicenter ROPAC study with prospective design showed that ACE-Is and ARBs are seldom used during pregnancy. Women who used ACE-Is or ARBs during pregnancy more often came from an LMIC and had chronic hypertension or LVEF <40% compared with the nonusers. There were several differences in maternal and neonatal outcomes between both groups, including a higher rate of MACE, pre-eclampsia and hemolysis elevated liver enzymes and low platelets syndrome syndrome, and preterm birth in the ACE-I and/or ARB users. Our secondary analysis showed that ACE-I use during the first trimester was independently associated with an increased risk of congenital anomalies (adjusted OR 3.2).

Women who used ACE-Is or ARBs during pregnancy were typically more sick, as shown by the higher proportion who had an LVEF <40% before pregnancy and the occurrence of MACE during pregnancy in 40%. This emphasizes the importance of a preconception assessment in this high-risk population when the ACE-I or ARB can be stopped, the impact on the clinical state observed, and new analyses (including echocardiography and exercise testing) be performed without medication to ensure that the cardiac function is good enough to embark on pregnancy. It is interesting to speculate whether the outcomes would have been worse if their medication had been stopped before pregnancy. Compared with the never-users, women who stopped the ACE-I or ARB before pregnancy had more MACE, especially heart failure. However, these women probably have a higher risk for cardiac events in advance as these women were more frequently classified as modified World Health Organization classification for maternal cardiovascular risk (mWHO) class IV and used cardiac medication before pregnancy more frequently. In addition, we found no differences in the occurrence of MACE between the women who stopped before pregnancy and the women who continued the ACE-I or ARB, and the severity of disease (mWHO class, New York Heart Association class) did not differ between both groups. Based on these results, we can speculate that women who stopped with ACE-Is or ARBs would not have worse pregnancy outcomes. However, women who are taking ACE-Is or ARBs are a high-risk population, as stated before, who need careful, thorough evaluation before pregnancy.

Table 2
Maternal, obstetric, and perinatal outcomes in women who used an ACE-I and/or ARB during pregnancy compared with nonusers

	Users during pregnancy (n=42, 0.7%)	Nonusers (n=5697, 99.3%)	p-value
Maternal outcomes			
MACE	17 (40.5%)	878 (15.4%)	**<0.001**
Maternal mortality*	1 (2.4%)	39 (0.7%)	0.188
Heart failure	12 (28.6%)	599 (10.5%)	**<0.001**
Pre-existent heart failure	3 (7.1%)	250 (4.4%)	0.386
Arrhythmia	3 (7.1%)	178 (3.1%)	0.138
Supraventricular	1 (2.4%)	94 (1.6%)	0.711
Ventricular	2 (4.8%)	88 (1.5%)	0.095
Endocarditis	2 (4.8%)	31 (0.5%)	**<0.001**
Thromboembolic event	0	87 (1.5%)	0.420
Aortic dissection	1 (2.4%)	4 (0.1%)	**<0.001**
Obstetric and fetal outcomes			
Reported miscarriage	3 (7.1%)	211 (3.7%)	0.241
Therapeutic termination of pregnancy	5 (11.9%)	63 (1.1%)	**<0.001**
For fetal abnormalities	0	15 (0.3%)	0.739
For maternal health	5 (11.9%)	43 (0.8%)	**<0.001**
Multiple gestation	1 (2.4%)	95 (1.7%)	0.719
Pregnancy-induced hypertension	1 (2.4%)	149 (2.6%)	0.949
(Pre-)eclampsia and HELLP syndrome	4 (9.5%)	155 (2.7%)	**0.006**
Gestational diabetes mellitus	1 (2.4%)	159 (2.8%)	0.882
Stillbirth	1 (2.4%)	71 (1.2%)	0.510
Delivery			
Gestational age at delivery, median, weeks (Q1-Q3)	37.0 (35.5-38.6)	38.6 (37.3-39.7)	**<0.001**
Caesarean section	26 (61.9%)	2655 (46.6%)	**0.021**
Planned Caesarean section	14 (33.3%)	1901 (33.4%)	0.996
For cardiac reason	7 (16.7%)	723 (12.7%)	0.441
Postpartum hemorrhage	0	170 (3.0%)	0.256
Neonatal outcomes			
Preterm birth	14 (33.3%)	886 (15.6%)	**0.002**
Extremely preterm (24-28 weeks)	0	35 (0.6%)	0.610
Very preterm (28-32 weeks)	3 (7.1%)	126 (2.2%)	**0.032**
Moderate to late preterm (32-37 weeks)	11 (26.2%)	725 (12.7%)	**0.009**
Apgar score <7 at 5 minutes	2 (4.8%)	395 (6.9%)	0.581
Birth weight, grams, mean (±sd)	2591 ± 724	2974 ± 637	**0.004**
Small for gestational age	7 (16.7%)	577 (10.1%)	0.163
Neonatal congenital disease	4 (9.5%)	279 (4.9%)	0.168
Neonatal congenital heart disease	3 (7.1%)	167 (2.9%)	0.109
Other neonatal congenital disease	1 (2.4%)	125 (2.2%)	0.934
Neonatal mortality	1 (2.4%)	32 (0.6%)	0.120
Total congenital anomalies†	4 (9.5%)	294 (5.2%)	0.204

* Maternal mortality up to 6 months postpartum.
† Combined endpoint of therapeutic abortion because of fetal anomalies, and congenital disease in the infant.
Data are n (%) unless otherwise specified. Bold values denote statistical significance at the p-level <0.005.
ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; HELLP syndrome = hemolysis, elevated liver enzymes and low platelets syndrome; MACE = major adverse cardiac event (the combined end point of maternal mortality: heart failure, arrhythmia, endocarditis, thromboembolic event, and dissection).

It is striking that ACE-Is and ARBs were still used during the second and/or third trimester of 29 pregnancies, despite the clear advice to avoid ACE-Is or ARBs in this period of pregnancy, because of the high risk of fetal renal dysfunction and the development of pulmonary hypoplasia.[3,4] Given the high rates of MACE in this population, the decision to use ACE-Is or ARBs was probably made on the basis of clinical need. Cardiac event rates during pregnancy are higher in LMIC compared with developed countries because of differences in access to medical care, travel distances and barriers in the underlying social-cultural environment.[10] It is therefore plausible that pregnant women in LMIC are more affected and therefore need to use such cardiac medications more often.

Regarding the impact of the medications on the baby, the results are more elusive. Most results suggest a negative effect on neonatal outcomes after ACE-I or ARB exposure, but probably also because of low numbers, the results are not always statistically significant. We found no congenital anomalies after *in-utero* ARB exposure (n = 8). In the event that the adverse outcomes of ACE-I use during the first trimester are attributable to RAAS system blockage, it makes sense to also avoid ARBs during the first trimester, considering similar mechanisms of action. ARBs may even carry a higher fetopathy risk than exposure to ACE-Is, concludes Weber-Schoendorfer et al.[11]

Recently, two meta-analyses of studies on the use of ACE-I or ARB during the first trimester of pregnancy have

Table 3
Neonatal congenital disease (n = 4) after *in-utero* ACE-I or ARB exposure

	Maternal diagnostic group	Maternal diagnosis	Maternal age, years	Timing of ACE-I exposure	ACE-I type and dose	Neonatal diagnosis
1.	CHD	Tetralogy of Fallot with pulmonary atresia	31	Before pregnancy + all trimesters	Enalapril 10 mg	VSD
2.	CMP	Non-compaction cardiomyopathy + (secondary) pulmonary hypertension	39	Before pregnancy + 1st trimester	Fosinopril 40 mg	TAPVR + ASD
3.	VHD	Aortic regurgitation	30	Before pregnancy + all trimesters	Enalapril (dose unknown)	Hypoplastic left heart syndrome
4.	VHD	Mitral regurgitation and stenosis + (secondary) pulmonary hypertension	31	Before pregnancy + 1st trimester	Lisinopril 12.5 mg	Trisomy 21

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ASD = atrial septal defect; CHD = congenital heart disease; CMP = cardiomyopathy; TAPVR = total anomalous pulmonary venous return; VHD = valvular heart disease; VSD = ventricular septal defect.

been published.[5,6] Buawangpong et al[5] included 13 studies and showed a significant association between overall congenital malformations and first-trimester-only exposure to ACE-Is or ARBs (OR 1.94, 95% CI 1.71 to 2.21), and significant relation between cardiovascular malformations, miscarriage and stillbirth with ACE-I or ARB exposure. Fu et al[6] included 6,234 pregnancies exposed to ACE-Is or ARBs and found a higher risk of major congenital malformations, cardiovascular malformations and stillbirths in the ACE-I or ARB exposed pregnancies compared with the nonexposed controls. Although both meta-analyses showed adverse fetal or neonatal outcomes after ACE-I or ARB exposure during the first trimester, no clear consensus on the use of these medications during the first trimester has been reached. An important limitation of these meta-analyses is the quality of the included studies. Most studies were retrospective and did not adjust the data for factors that might contribute to a higher risk of congenital anomalies. In contrast, our study contains prospective data and adjusts for several important confounding factors, such as maternal diagnosis, maternal age, and the use of other cardiac medications, making our study relatively high-quality evidence in the field of safety of medication use during pregnancy. As pregnant women are usually excluded from pharmaceutical trials, most of the data on the safety of medication use during pregnancy will have to be based on observational registry studies.

We found congenital anomalies in 4 infants: 3 with a CHD and one trisomy 21. Whether in utero ACE-I exposure and trisomy 21 are linked can be debated. Although environmental factors, such as tobacco use, maternal weight, socioeconomic conditions, and radiation exposure have been linked to an increased risk of trisomy 21 in the offspring,[12] an association of medication use during embryogenesis and trisomy 21 is not completely inconceivable. Biological and epigenetic processes in the preconception period are influenced by an interplay of genetic factors and environmental exposures, including medication use.[13,14] We found no increase in the number of congenital anomalies between women who used ACE-Is or ARBs preconceptionally and discontinued them before they became pregnant and the women who did not use these medications at all. Therefore, for reason of fetal toxicity, it does not seem necessary to discontinue these drugs earlier than a few days before conception, also taking into account the half-life. Notwithstanding, as already mentioned, to monitor the clinical condition of women it is advisable to stop earlier or change medications earlier and follow the patients before conception.

Our study has several limitations. First, the number of pregnancies analyzed in this study is limited which may cast doubt on the statistical power of the analyses. However, this only applies to the low number of pregnancies in which ARBs were used, because we did find an association between ACE-I use and congenital anomalies, despite the limited number of pregnancies. As with other registry-based studies, we had to deal with missing data. We do not have detailed information on the exact timing of exposure, as our information was limited to the trimester level. We do not know for sure if the women took the prescribed medication. Furthermore, the specific indication for the use of ACE-I or ARB was not reported and can only be based on assumptions. However, this does not affect our results considering the purpose of our study. ACE-Is and ARBs are known to decrease renal function in the fetus if used in the second and third trimester and to subsequently cause oligohydramnios,[3,4] but we have no data on the amniotic fluid. However, we do have information on neonatal congenital disease that can be secondary to oligohydramnios, such as pulmonary hypoplasia, limb contractures, and birth defects because of compression of fetal parts.[15] None of these congenital diseases were reported in our registry. Our study included only women with structural heart disease, so the generalizability to other groups of pregnant women could be discussed, as some types of structural heart diseases (i.e., CHD, some forms of CMP, etc.) are associated with a higher risk of congenital disease in the infant. Although we adjusted for maternal diagnosis in our analyses, a similar study including women with and without structural heart disease should be performed to totally exclude this confounding factor. Selection bias cannot be excluded, as the data was collected by different ROPAC investigators worldwide. Data on the safety of medication use during pregnancy are based on observational data, as randomized controlled trials are not feasible in this field, and therefore we believe that our study represents the best available data, despite these limitations.

In conclusion, based on our data on women with structural heart disease, ACE-Is should be avoided during

Table 4
Baseline characteristics and pregnancy outcomes of women who used an ACE-I or ARB during at least the first trimester compared with women who did not use an ACE-I or ARB during pregnancy

	Users during first trimester (n=34, 0.6%)	Nonusers (n=5697, 99.4%)	p-value
Pre-pregnancy baseline characteristics			
Diagnosis details			
Congenital heart disease	5 (14.7%)	3289 (57.7%)	**<0.001**
Valvular heart disease	11 (32.4%)	1635 (28.7%)	0.639
Cardiomyopathy	13 (38.2%)	422 (7.4%)	**<0.001**
Aortopathy	1 (2.9%)	215 (3.8%)	0.799
Ischaemic heart disease	4 (11.8%)	91 (1.6%)	**<0.001**
Pulmonary hypertension	0	45 (0.8%)	0.603
mWHO I	2 (5.9%)	1183 (20.8%)	**0.033**
mWHO II	0	828 (14.5%)	**0.016**
mWHO II-III	23 (67.6%)	2669 (46.8%)	**0.015**
mWHO III	4 (11.8%)	589 (10.3%)	0.785
mWHO IV	5 (14.7%)	400 (7.0%)	0.081
Pre-pregnancy characteristics			
Age, years, mean (±sd)	30.4 ± 6.4	29.5 ± 5.6	0.497
BMI, kg/m^2, median (Q1-Q3)	27.9 (23.1-32.0)	24.0 (21.5-27.5)	**0.007**
Nulliparity	10 (29.4%)	2560 (44.9%)	0.067
LMIC	21 (61.8%)	2257 (39.6%)	**0.009**
Current smoker	3 (8.8%)	225 (3.9%)	0.180
Chronic hypertension	12 (36.4%)	367 (6.4%)	**<0.001**
Diabetes mellitus	1 (2.9%)	89 (1.6%)	0.535
Atrial fibrillation/flutter	0	105 (1.8%)	0.424
Signs of heart failure	2 (5.9%)	590 (10.4%)	0.380
Estimated LVEF <40%	12 (35.3%)	239 (4.2%)	**<0.001**
Cyanosis	1 (2.9%)	62 (1.1%)	0.302
NYHA class > II	0	202 (3.5%)	0.264
Prior cardiac intervention	16 (48.5%)	3141 (55.1%)	0.432
Pre-pregnancy cardiac medication use			
ACE-I	27 (79.4%)	130 (2.3%)	**<0.001**
ARBs	7 (20.6%)	18 (0.3%)	**<0.001**
Beta-blockers	18 (52.9%)	545 (9.6%)	**<0.001**
Diuretics	14 (41.2%)	203 (3.6%)	**<0.001**
Other cardiac medication	10 (29.4%)	188 (3.3%)	**<0.001**
Pregnancy outcomes			
Maternal outcomes			
MACE*	10 (29.4%)	878 (15.4%)	**0.024**
Maternal mortality	1 (2.9%)	39 (0.7%)	0.115
Fetal outcomes			
Reported miscarriage	3 (8.8%)	211 (3.7%)	0.116
Therapeutic termination of pregnancy	5 (14.7%)	63 (1.1%)	**<0.001**
For fetal anomalies	0	15 (0.3%)	0.764
For maternal health	5 (14.7%)	43 (0.8%)	**<0.001**
Stillbirth	1 (2.9%)	71 (1.2%)	0.376
Neonatal outcomes			
Gestational age at delivery, median, weeks (Q1-Q3)	37.1 (36.3-39.0)	38.6 (37.3-39.7)	**0.003**
Preterm birth	9 (26.5%)	886 (15.6%)	0.080
Birth weight, grams, mean (±sd)	2661 ± 753	2974 ± 637	**0.045**
Small for gestational age	4 (11.8%)	577 (10.1%)	0.753
Neonatal congenital disease	4 (11.8%)	279 (4.9%)	0.065
Neonatal congenital heart disease	3 (8.8%)	167 (2.9%)	**0.043**
Other neonatal congenital disease	1 (2.9%)	125 (2.2%)	0.767
Neonatal mortality	0	32 (0.6%)	0.661
Total congenital anomalies†	4 (11.8%)	294 (5.2%)	0.084

* Combined endpoint of maternal mortality (up to 6 months postpartum), heart failure, arrhythmia, endocarditis, thromboembolic event, and dissection.
† Combined endpoint of therapeutic abortion because of fetal anomalies, and congenital disease in the infant.
Data are n (%) unless otherwise specified. Bold values denote statistical significance at the p <0.05 level.
ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; HELLP syndrome = hemolysis, elevated liver enzymes and low platelets syndrome; LMIC = low/middle-income country; LVEF = left ventricular ejection fraction; MACE = major adverse cardiac event; mWHO = modified World Health Organization classification for maternal cardiovascular risk; NYHA class = New York Heart Association Functional Classification.

Table 5
Univariable and multivariable logistic regression analysis for associations between ACE-I use during the first trimester and congenital anomalies*

	Univariable			Multivariable (final model)		
	OR	95% CI	p-value	OR	95% CI	p-value
ACE-I use during 1st trimester†	3.21	1.10-9.33	**0.033**	3.15	1.04-9.56	**0.043**
Age >35 y†	1.19	0.87-1.61	0.277			
Nulliparity†	1.27	1.01-1.61	**0.043**	1.20	0.94-1.52	0.139
BMI	0.99	0.96-1.01	0.259			
LMIC†	0.79	0.62-1.01	0.061	0.95	0.73-1.23	0.695
Twin pregnancy†	0.79	0.29-2.17	0.649			
Other cardiac medication use†	1.34	0.98-1.84	0.069	1.41	1.01-1.99	**0.046**
Current smoker†	1.13	0.64-2.01	0.665			
Chronic hypertension	0.95	0.59-1.53	0.828			
Diabetes mellitus†	1.64	0.73-3.66	0.229	2.25	1.11-4.57	**0.024**
Atrial fibrillation/flutter	0.35	0.09-1.41	0.139			
Signs of heart failure	0.96	0.65-1.41	0.816			
Estimated LVEF<40%	0.66	0.34-1.30	0.234			
NYHA class >II	0.84	0.43-1.65	0.609			
mWHO >II†	0.73	0.58-0.93	**0.009**			
CHD†	1.45	1.14-1.86	**0.003**	1.82	1.28-2.59	**<0.001**
CMP†	1.22	0.81-1.83	0.341	1.96	1.21-3.19	**0.007**
AOP†	2.03	1.27-3.23	**0.003**	3.34	1.95-5.73	**<0.001**

* Combined endpoint of therapeutic abortion because of fetal anomalies, and congenital disease in the infant.

† Variables included in the full model of the multivariable logistic regression analysis with backward selection.

After multiple imputation for age (9.5%); BMI (36.2%); parity (0.3%); smoking (14.2%); previous hypertension (1.7%); previous diabetes mellitus (2.3%), previous heart failure (1.4%) and gestational diabetes mellitus (1.2%). Bold script denotes p <0.05.

AOP = aortopathy; BMI = body mass index; CHD = congenital heart disease; CMP = cardiomyopathy; LMIC = low-or-middle-income country; LVEF = left ventricular ejection fraction; mWHO = modified World Health Organization risk classification; NYHA = New York Heart Association Functional Classification; VHD = valvular heart disease.

pregnancy, and also in the first trimester. Given the similar mechanism of action on RAAS and previous literature, ARBs should likewise be avoided, although we found no conclusive evidence to support this. In women with structural heart disease who wish to become pregnant, ACE-Is and ARBs can be temporarily discontinued to monitor the woman's clinical condition without these medications. If the clinical condition worsens or if the woman presents for the first time during pregnancy, the potential risks associated with the use of these medications should be discussed. If deemed necessary, such risks may be necessary to accept, taking into account both the woman's desire for pregnancy and her clinical condition. This emphasizes the importance of preconception counseling and management of these women by a pregnancy heart team.

Declaration of competing interest

The authors have no competing interests to declare.

CRediT authorship contribution statement

Johanna A. van der Zande: Writing – original draft, Investigation, Formal analysis. **Karishma P. Ramlakhan:** Writing – review & editing, Supervision. **Katja Prokselj:** Writing – review & editing. **Edison Muñoz-Ortiz:** Writing – review & editing. **Amalia Baroutidou:** Writing – review & editing. **Magdalena Lipczynska:** Writing – review & editing. **Edit Nagy:** Writing – review & editing. **Tobias Rutz:** Writing – review & editing. **Arie Franx:** Writing – review & editing, Supervision. **Roger Hall:** Writing – review & editing, Data curation, Conceptualization. **Mark R. Johnson:** Writing – review & editing, Supervision. **Jolien W. Roos-Hesselink:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization.

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Data Availability

The de-identified participant data that support the findings of this study are available from the corresponding author on reasonable request.

Ethical Approval

This study complies with the Declaration of Helsinki. Participating centers in the ROPAC managed the approvals of national or regional ethics committees or Institutional Review Boards, according to local regulations.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2024.08.004.

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