Pregnancy Outcome Following Exposure to Angiotensin-Converting Enzyme Inhibitors or Angiotensin Receptor Antagonists
A Systematic Review

Marina Bullo; Sibylle Tschumi; Barbara S. Bucher; Mario G. Bianchetti; Giacomo D. Simonetti

Abstract—The objective was to analyze the outcome following prenatal exposure to angiotensin-converting enzyme inhibitors (ACE-Is) or angiotensin receptor antagonists (ARBs). For this purpose, a systematic review of published case reports and case series dealing with intrauterine exposure to ACE-Is or to ARBs using Medline as the source of data was performed. The publications retained for analysis included patients who were described individually, revealing, at minimum, the gestational age, substance used, period of medication intake, and the outcome. In total, 72 reports were included; 37 articles (118 well-documented cases) described the prenatal exposure to ACE-Is; and 35 articles (68 cases) described the prenatal exposure to ARBs. Overall, 52% of the newborns exposed to ACE-Is and 13% of the newborns exposed to ARBs did not exhibit any complications ($P<0.0001$). Neonatal complications were more frequent following exposure to ARBs and included renal failure, oligohydramnios, death, arterial hypotension, intrauterine growth retardation, respiratory distress syndrome, pulmonary hypoplasia, hypocalvaria, limb defects, persistent patent ductus arteriosus, or cerebral complications. The long-term outcome is described as positive in only 50% of the exposed children. Fetopathy caused by exposure to ACE-Is or ARBs has relevant neonatal and long-term complications. The outcome is poorer following exposure to ARBs. We propose the term “fetal renin-angiotensin system blockade syndrome” to describe the related clinical findings. Thirty years after the first description of ACE-I fetopathy, relevant complications are, at present, regularly described, indicating that the awareness of the deleterious effect of prenatal exposure to drugs inhibiting the renin-angiotensin system should be improved. (Hypertension. 2012;60:00-00.)

Key Words: pregnancy ■ angiotensin-converting enzyme inhibitors ■ angiotensin receptor blockers ■ fetopathy ■ prenatal exposure ■ systematic review

An undamaged renin-angiotensin system (RAS) is a prerequisite for normal prenatal renal development. Loss of function mutations in the genes encoding the RAS present with a disturbed renal development, characterized by reduced fetal diuresis, leading to oligohydramnios and, optionally, skull-ossification defects. At birth, blood pressure is reduced fetal diuresis, leading to oligohydramnios and, occasionally, skull-ossification defects. The long-term outcome is described as positive in only 50% of the exposed children. Fetopathy caused by exposure to ACE-Is or ARBs has relevant neonatal and long-term complications. The outcome is poorer following exposure to ARBs. We propose the term “fetal renin-angiotensin system blockade syndrome” to describe the related clinical findings. Thirty years after the first description of ACE-I fetopathy, relevant complications are, at present, regularly described, indicating that the awareness of the deleterious effect of prenatal exposure to drugs inhibiting the renin-angiotensin system should be improved. (Hypertension. 2012;60:00-00.)

Methods
Between April 2010 and August 2011, we performed a thorough computer-based search of the terms angiotensin receptor blocker.
angiotensin receptor antagonist, angiotensin converting enzyme inhibitor, ARB, ACE-I, or sartan, each combined with pregnancy, fetopathy, fetus, newborn, teratogen, fetal exposure, prenatal exposure, or toxicity in the US National Library of Medicine (Medline) for the period January 1980 through August 2011 as sources of data, using the Prisma Guidelines.4

Study Selection and Validity Assessment
Publications available as a full-length article or a letter in English, German, French, Portuguese, Spanish, or Italian, including patients who were described individually, were retained for analysis if the publication described, at minimum, the gestational age, substance used, period of medication intake (gestational trimester), and outcome of the single cases. If the same case was present in different publications, we retained the most complete description. Two authors (M.B. and G.D.S.) scanned the titles and abstracts for the initial selection. The selected articles were reviewed in full and independently assessed for eligibility by the same 2 reviewers.

Outcome Measures
Outcomes were neonatal and long-term (defined as present after 6 months of life) complications, following the exposure to medications inhibiting the RAS.

Data Extraction and Synthesis
From each case of prenatal exposure to medications blocking the RAS, we extracted the patients’ clinical characteristics, including information concerning the underlying cause of the antihypertensive treatment of the mother, maternal age, period of prenatal exposure (gestational trimester), gestational age at birth, birth weight, neonatal complications, and the period of follow-up with long-term consequences.

Statistical Analyses
The analyzed data were all extrapolated from case reports and case series and were homogenous in view of the clinical context; moreover, all of the retained studies presented the data of the single cases similarly, therefore, permitting estimation of the outcomes and comparison between the ACE-I and ARB subgroups. Continuous data are presented as the mean values with standard deviations (SDs), and categorical data are presented as frequencies and percentages calculated from the results reported in the original publications. The Fisher exact test was used to compare dichotomous variables, and the Student t test or the Mann-Whitney–Wilcoxon rank-sum test was used to compare continuous variables, as appropriate. All of the statistical analyses were performed with GraphPad Prism, version 5.01 for Windows (GraphPad Software). Statistical significance was assigned at P<0.05.

Results
Search Results
The initial search revealed 3639 publications, of which 1685 remained after excluding duplicates (ie, the same publications were found with different search terms). One hundred and seventeen of them were reviewed in detail, and 61 reports were retained for the final analysis (see online-only Data Supplement Figure S1). Eleven further pertinent reports were found in the references of the mentioned 117 reports. Hence, a total of 72 reports (64 in English, 6 in French, 1 in Portuguese, and 1 in Spanish) were used for the final analysis. The reports document 186 cases.35–75 Thirty-seven reports documented the prenatal exposure to ACE-Is, for a total of 118 well-documented cases (captopril: N = 59; enalapril: N = 42; lisinopril: N = 11; ramipril: N = 3; benazepril: N = 2; quinapril: N = 1), and 35 reports documented the prenatal exposure to ARBs, for a total of 68 cases (losartan: N = 20; candesartan: N = 17; valsartan: N = 17; irbesartan: N = 7, olmesartan: N = 6; telmisartan: N = 1).

Six articles were excluded from the analysis because the listed cases were not described in detail; however, these reports were further explored for the description of the prevalence and general aspects of fetal RAS-blockade syndrome (see the online-only Data Supplement Expanded Results section with Figure S2) and the analysis of the prevalence of major congenital malformations.

Intrauterine Exposure to ACE-Is
The mean maternal age of the 118 well-documented cases of intrauterine exposure to ACE-Is was 31.3±6.6 years. ACE-Is were generally taken by the mother only during the first trimester of the pregnancy (32 cases); however, occasionally, the medication was taken only during the second trimester (11 cases) or only during the third trimester (18 cases). In 15 cases, ACE-Is were taken during the first and second trimesters; in 11 cases, they were taken during the second and third trimesters; and in 31 cases, they were taken during the entire pregnancy (Figure 1).

The children were born at a mean gestational age of 34.7±3.7 weeks, with a mean birth weight of 2121±877 g.
Sixty-one newborns (52%) were described as not having fetal RAS-blockade syndrome (Figure 2, online-only Data Supplement Table S1). Significantly more newborns without fetal RAS-blockade syndrome were exposed at the beginning of the pregnancy only ($P < 0.05$, online-only Data Supplement Table S1). Thirty-six of these 61 newborns (59%) were exposed to captopril, 17 (28%) to enalapril, 6 (10%) to lisinopril, and 1 each (1.5%) to quinapril and ramipril. Interestingly, 24 of the 25 newborns who experienced no complications and were exposed at the end of the pregnancy or during the entire pregnancy had been exposed to captopril, a drug with a short elimination half-life. The remaining healthy newborns had been exposed to enalapril.

The most commonly observed complications were as follows: renal failure or need for dialysis (23%), anuria (20%), oligohydramnios (19%), death (intrauterine or after birth) or miscarriage (18%), arterial hypotension (17%), intrauterine growth retardation (15%), respiratory distress syndrome (14%), hypocalvaria (8%), limb defects (8%), persistent patent ductus arteriosus (6%), pulmonary hypoplasia (5%), or cerebral complications (4%), as depicted in Figure 2. These complications were more frequent if the ACE-Is were taken during the entire pregnancy or during the second and third trimesters (Figure 1, online-only Data Supplement Table S1; $P < 0.05$). Five cases were characterized by miscarriage, 1 case by voluntary abortion, 6 cases by intrauterine death (ie, after the 18th gestational week), 9 by postpartum death (8 preterm newborns and 1 term newborn), and 57 cases were characterized by premature births. In 40 cases, the neonates born at term were described as alive.

Intrauterine Exposure to ARBs

The mean maternal age of the 68 well-documented cases of intrauterine exposure to ARBs was 36.1 ± 5.8 years. ARBs were generally taken by the mother during the entire pregnancy (26 cases). In each of 18 cases, the medication was taken exclusively during the first trimester of pregnancy or during the first and second trimesters; however, the medication was rarely taken exclusively during the second trimester (1 case) or only during the third trimester (3 cases). In 2 cases, ARBs were taken during the second and third trimesters (Figure 1).

The children were born at a mean gestational age of 33.5 ± 3.9 weeks, with a mean body weight of 2140 ± 769 g.

Nine newborns (13%) were described as not having fetal RAS-blockade syndrome (Figure 2, online-only Data Supplement Table S1); 8 of these newborns had been exposed only during the first trimester, and 1 newborn had been exposed during the first and second trimesters. Five of these 9 newborns (56%) were exposed to losartan, 2 (22%) to valsartan, and 1 each (11%) to candesartan and irbesartan. The most commonly observed complications included the following: oligohydramnios (63%), renal failure or need for dialysis (51%), anuria (40%), respiratory distress syndrome (37%), death (intrauterine or after birth) or miscarriage (37%), hypocalvaria (32%), limb defects (32%), intrauterine growth retardation (16%), pulmonary hypoplasia (16%), arterial hypotension (15%), cerebral complications (10%), or persistent patent ductus arteriosus (9%), as depicted in Figure 2. These complications were more frequent if the ARB had been taken during the entire pregnancy (Figure 1, online-only Data Supplement Table S1; $P < 0.05$).
Two cases were characterized by miscarriage, 4 cases by voluntary abortion, 5 cases by intrain uterine death, and 14 cases were characterized by postpartum death (13 preterm and 1 term newborn). Twenty-eight premature neonates and 15 neonates born at term were described as alive.

Comparison Between Intrauterine Exposure to ACE-Is and ARBs

The mothers treated with ARBs were older by 4.8 years compared with the mothers treated with ACE-Is (P<0.0001). Pregnancy-induced hypertension was less frequently the indication for therapy in mothers treated with ARBs (P=0.02), and the gestational age of infants born alive was younger in newborns prenatally exposed to ARBs (P=0.04). Newborns prenatally exposed to ACE-Is were more frequently born without fetal RAS-blockade syndrome compared with the group of newborns exposed to ARBs (P<0.0001), independent of the exposure period (Figure 2, online-only Data Supplement Table S1). Moreover, preterm newborns exposed to ARBs more frequently died postnatally compared with the preterm newborns exposed to ACE-Is (P=0.02); this difference was not significant for newborns born at term. The prevalence of miscarriage or intrain uterine death was not different between the groups.

In general, complications were more frequent in children prenatally exposed to ARBs when compared with children exposed to ACE-Is (Figure 1, Figure 2, and online-only Data Supplement Table S1). Moreover, if the children were exposed only at the beginning of pregnancy, oligohydramnios, renal failure, hypocalvaria, and limb defects were also more frequently observed in children prenatally exposed to ARBs (Figure 1, online-only Data Supplement Table S1).

Follow-Up at 6 or More Months

Long-term outcomes with a follow-up of >6 months were only available for a total of 26 children.7–8,10,17,21,23,25,27,29,30,34,37,38,44,45,54–56,63,65,69. The mean age of the children described was 3.3±4.5 (range: 0.5 to 18) years. Fourteen children had prenatally been exposed to ACE-Is, and 12 had been exposed to ARBs. Four children were exposed only during the first or second trimesters (1, ACE-I; and 3, ARBs), and 22 were exposed during the second and third trimesters or during the entire pregnancy (13, ACE-Is; and 9, ARBs). The most frequently described complications of fetal RAS-blockade syndrome are depicted in Table. Complications were similar if the children had been exposed to ACE-Is or ARBs. In the 4 children exposed exclusively during the first or second trimester, the general outcome was good (ie, normal development and kidney function) in 3 and mild in 1 (ie, mild renal insufficiency, arterial hypertension, proteinuria, or developmental delay), whereas, in the 22 children exposed at the end or during the entire pregnancy, the outcome was good in 10, mild in 10, and bad in 2 (ie, need for dialysis or transplantation).

Permanent Congenital Malformations, Other Than Those Described Above, Following Prenatal Exposure to Drugs Inhibiting the Renin-Angiotensin System

Major permanent congenital malformations following prenatal exposure to drugs inhibiting the RAS has been debated in several studies. The analysis performed by Cooper et al demonstrates that exposure to ACE-Is during the first trimester of pregnancy is a risk factor for major congenital malformations.76 Other reports could not confirm these results and suggest that ACE-Is or ARBs are not major teratogens when used in the first trimester only.79–81

Discussion

Drugs that block the RAS, either ACE-Is or ARBs, are effective agents, with few side effects, which are often prescribed to women of reproductive age.82 This systematic review confirms that fetal RAS-blockade syndrome is frequent. Moreover, this survey demonstrates that fetal RAS-blockade syndrome also occurs following first-trimester exposure to ACE-Is or ARBs, although it occurs significantly less frequently when compared with exposure during the second and third trimesters of pregnancy or during the entire pregnancy. Finally, the review surprisingly demonstrates that fetal RAS-blockade syndrome is more frequent and severe in newborns exposed to ARBs than in newborns prenatally exposed to ACE-Is. This review largely supports the current recommendations stating that women of childbearing age should be treated with ACE-Is or ARBs only if absolutely indicated; women taking these drugs should be warned about the consequences of prenatal exposure, and effective contraception must be assured. These warnings are important because 5% of the women of childbearing age have to be treated with antihypertensive medication.83 Furthermore, ACE-Is or ARBs should never be started during pregnancy.

The RAS promotes cellular proliferation and cellular growth via angiotensin II and the angiotensin II type 1 receptor, which is blocked by ARBs. Angiotensin II is crucial for fetal kidney development, especially at the end of pregnancy, and is less important at the beginning of fetal development. This finding may explain the better outcomes in newborns exposed only during the first trimester of preg-
Moreover, angiotensin II maintains adequate renal perfusion and glomerular filtration in the low-perfusion pressure system of the fetal kidney. The consequences of the inhibition of the RAS are renal hypoperfusion and ischemia, leading to reduced glomerular filtration (and oligohydramnios) and impaired tubular development.

There exists some difference between ACE-Is and ARBs in their mechanism of action that could explain the divergent outcomes following in utero exposure to these drugs. By decreasing angiotensin II production, ACE-Is reduce the activation of both type 1 and type 2 angiotensin II receptors, whereas only the former is inhibited by the ARBs. Furthermore, in some tissues, the production of angiotensin II is catalyzed by enzymes other than angiotensin-converting enzymes, an effect that can be inhibited by ARBs but not by ACE-Is. Finally, ARBs usually have a longer elimination half-life than ACE-Is. Taken together, these data suggest that the less favorable outcomes following in utero exposure to ARBs compared with ACE-Is might result from a more profound and longer blockade of the angiotensin II action on its type 1 receptor. This hypothesis is supported by Hanssens et al. These authors noted a better outcome following in utero exposure to captopril, an ACE-I with a very short elimination half-life, compared with enalapril, an ACE-I with a slightly longer elimination half-time.

Few reports address the long-term follow-up after fetal exposure to drugs inhibiting the RAS. Renal complications were the most frequently encountered long-term complications of fetal RAS-blockade syndrome, followed by neurodevelopmental delay and failure to thrive. Approximately half of the children exposed to RAS inhibitors had favorable long-term outcomes without sequelae, and half of the children developed some chronic condition. Ten percent of children exposed experienced a bad outcome, such as end-stage renal disease. Long-term multidisciplinary follow-up is indicated in these children.

Major permanent congenital malformations following exposure to drugs inhibiting the RAS during the first trimester of pregnancy is a matter of discussion, and the results of differently designed surveys are not uniform. It is worthy of mention that the congenital malformations that occur following in utero exposure to a blocker of the RAS may result either directly from the drug as well as from the underlying maternal illness. It is well-recognized, for example, that pregestational diabetes mellitus is associated with a 2- to 3-fold increase in risk of malformations.

Our analysis demonstrates that, despite the first warnings in 1980 (animal data presented by Broughton-Pipkin et al) and 1981 (human data reported by Guignard et al and Duminy et al), several cases of fetal exposure to ACE-Is and ARBs have been reported thereafter without any decrease of the reported cases. The reasons for this trend are most likely multifactorial: The ignorance of the treating physicians and the scarce information available to the women of a childbearing age who consequently do not discontinue the chronic antihypertensive therapy during pregnancy or because self-medication was not communicated to the treating obstetrician. With the development of aliskiren, a drug that directly inhibits the activity of renin, blockade of the RAS at a third level has become a reality. No information concerning its teratogenicity is currently available. Nonetheless, similar to ACE-Is and ARBs, aliskiren should not be used during pregnancy.

The results of this systematic review must be viewed with an understanding of the inherent limitations of the analysis process, which incorporated data exclusively from single-case reports or case series published between 1981 and 2011, permitting comparison between groups only as estimates.

**Perspectives**

Fetal exposure to ACE-Is or ARBs has relevant neonatal and long-term complications. The neonatal outcome appears to be poorer following prenatal exposure to ARBs compared with ACE-Is. Thirty years after the first description of ACE-I fetopathy, relevant complications are regularly described, indicating that the awareness of the deleterious effects of prenatal exposure to drugs inhibiting the RAS should be addressed.

**Disclosures**

None.

**References**

19. Cunniff C, Jones KL, Phillipson J, Benirschke K, Short S, Wujek J. Fetal diabetes and congenital anomalies associated with maternal use of angiotensin II type I receptor antag-
Fetal Renin-Angiotensin System Blockade Syndrome


Novelty and Significance

What Is New?

- Fetal exposure to ACE-Is or ARBs carries the risk for relevant neonatal and long-term complications, termed fetal renin-angiotensin system blockade syndrome.
- The neonatal outcome is poorer following prenatal exposure to ARBs.

What Is Relevant?

- The awareness of the deleterious effect of prenatal exposure to drugs inhibiting the renin-angiotensin system should be improved.
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ONLINE SUPPLEMENT

Pregnancy outcome following exposure to angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists: a systematic review

Short title
Fetal renin-angiotensin system blockade syndrome

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Expanded Results

General aspects and prevalence
The first case of suspected ACE-Is fetopathy was published in 1981. The same year, another case characterized by the voluntary termination of the pregnancy was described in South Africa by Duminy et al, although this case was excluded from our analysis because it did not fulfill the inclusion criteria. The first case of ARB fetopathy was reported nearly 20 years later in 1999. The number of publications over the years concerning the consequences of intrauterine exposure to ACE-Is or ARBs is depicted on Figure S2A. Interestingly, the number of published cases of ACE-Is fetopathy has declined during the most recent years (Figure S2B) despite the increased prenatal exposure to these drugs over the years. Pharmacovigilance studies dealing with the post-marketing safety of ARBs (losartan and valsartan) during the late 90s demonstrate that approximately three pregnancies will occur in 10,000 treated individuals. In contrast, the prenatal exposure to ACE-Is is between 2 and 70 per 10,000 pregnant women and increased between 1984 and 2003. The prevalence of exposure during the first trimester was considerably higher than the exposure at the end or during the entire pregnancy.

Intrauterine exposure to ACE-Is
The mean maternal age of the 118 well-documented cases of intrauterine exposure to ACE-Is was 31.3 ± 6.6 years, and the indications for maternal antihypertensive treatment mainly included essential hypertension (58 cases), followed by secondary causes for hypertension (mainly renal diseases; 28 cases), pregnancy-induced hypertension (15 cases) and diabetes mellitus (11 cases). In six cases, no corresponding information was available.

Intrauterine exposure to ARBs
The mean maternal age of the 68 well-documented cases of intrauterine exposure to ARBs was 36.1 ± 5.8 years, and the indications for maternal antihypertensive treatment were mainly essential hypertension (38 cases). Other indications included secondary causes for hypertension (largely renal diseases; 7 cases) and diabetes mellitus (5 cases). In 17 mothers, the indication for antihypertensive treatment was not known. Only one mother was treated with an ARB because of pregnancy-induced hypertension.
Literature


Table S1: Outcome following exposition during pregnancy to drugs that inhibit the renin-angiotensin system

<table>
<thead>
<tr>
<th>Fetal RAS-blockade syndrome</th>
<th>Angiotensin-Converting Enzyme Inhibitors (Total 58 infants)</th>
<th>Angiotensin-Receptor Blockers (Total 37 infants)</th>
<th>Angiotensin-Converting Enzyme Inhibitors (Total 60 infants)</th>
<th>Angiotensin-Receptor Blockers (Total 31 infants)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oligohydramnion</td>
<td>6 (10%)</td>
<td>16 (43%)*</td>
<td>16 (27%) †</td>
<td>27 (87%) *†</td>
</tr>
<tr>
<td>Anuria</td>
<td>2 (3%)</td>
<td>3 (8%)</td>
<td>22 (37%) †</td>
<td>24 (77%) *†</td>
</tr>
<tr>
<td>Renal failure or need for dialysis</td>
<td>1 (2%)</td>
<td>11 (30%) *</td>
<td>26 (43%) †</td>
<td>24 (77%) *†</td>
</tr>
<tr>
<td>Arterial hypotension</td>
<td>2 (3%)</td>
<td>0 (0%)</td>
<td>18 (30%) †</td>
<td>10 (32%) †</td>
</tr>
<tr>
<td>Pulmonary hypoplasia</td>
<td>0 (0%)</td>
<td>2 (5%)</td>
<td>6 (10%) †</td>
<td>9 (29%) *†</td>
</tr>
<tr>
<td>Respiratory distress syndrome</td>
<td>3 (5%)</td>
<td>4 (13%)</td>
<td>13 (22%) †</td>
<td>21 (68%) *†</td>
</tr>
<tr>
<td>Persistent patent ductus arteriosus</td>
<td>0 (0%)</td>
<td>2 (5%)</td>
<td>7 (12%) †</td>
<td>4 (13%)</td>
</tr>
<tr>
<td>Hypocalvaria</td>
<td>1 (2%)</td>
<td>6 (16%) *</td>
<td>9 (15%) †</td>
<td>16 (52%) *†</td>
</tr>
<tr>
<td>Limbs defect</td>
<td>0 (0%)</td>
<td>9 (24%) *</td>
<td>9 (15%) †</td>
<td>13 (42%) *</td>
</tr>
<tr>
<td>Intrauterine growth retardation</td>
<td>6 (10%)</td>
<td>8 (22%)</td>
<td>12 (20%)</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Cerebral complications</td>
<td>1 (2%)</td>
<td>4 (13%)</td>
<td>4 (7%)</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Death, miscarriage or intrauterine fetal death</td>
<td>15 (26%)</td>
<td>12 (32%)</td>
<td>6 (10%) †</td>
<td>13 (42%) *</td>
</tr>
<tr>
<td>Newborns without fetal RAS-blockade syndrome</td>
<td>36 (62%)</td>
<td>9 (24%) *</td>
<td>25 (42%) †</td>
<td>0 (0%) *†</td>
</tr>
</tbody>
</table>

* significantly (p<0.05) different from the respective value of Angiotensin-Converting Enzyme Inhibitors; † significantly different (p<0.05) when compared to the exposition during the first and second trimester (Fisher exact test)
Records identified through database search (n=3639)

Records searched after duplicates removed (n=1685)

Studies excluded after abstract or title review (n=1568)

Citations assessed in detail for eligibility (n=117)

Article excluded (n=56)
  language (n=8)
  duplicate cases of other reports (n=3)
  articles without cases or not described in detail (n=45)

Reports found in reference lists (n=11)

Eligible reports (n=72)

The flow of the studies through the review
The number of the considered publications dealing with exposure during pregnancy to drugs that inhibit the renin-angiotensin system. Angiotensin converting enzyme inhibitors: Black bar; angiotensin receptor blockers: Grey bar.
The number of the considered newborns per year of publication. Angiotensin converting enzyme inhibitors: Black bar; angiotensin receptor blockers: Grey bar.