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The Effect of ACE Inhibitors/ARBs Withdrawal on the Risk of Postoperative Complications in Abdominal Surgery

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Summary

A significant proportion of patients undergoing non-cardiac surgery receive therapy with angiotensin converting enzyme (ACE) inhibitors/angiotensin II receptor blockers (ARBs), which are usually prescribed for treatment of arterial hypertension and CHF. Current guidelines fail to provide clear consensus on whether it is worth discontinuing ACEi/ARBs before non-cardiac surgery.

The aim of this research was to assess the contribution of pre-op ACEi/ARBs withdrawal to the development of postoperative complications in patients after abdominal surgery using data from STOPRISK database.

Materials and methods. Data of 1945 patients from of the STOPRISK database was used for the analysis. Patients were retrospectively divided into two groups: first group (*N*=471, 24.2%) included patients subjected to ACEi/ARBs withdrawal 24 h before surgery, second group (*N*=1474, 75.8%) included patients continuing on ACEi/ARBs therapy. The 30-day outcomes were analyzed — postoperative complications (acute kidney injury, acute respiratory distress syndrome, anastomosis failure, arrhythmias, circulatory arrest, cardiogenic pulmonary edema, postoperative delirium, myocardial infarction, pneumonia, ileus, postoperative bleeding, pulmonary embolism, acute cerebrovascular accident, wound infection) and mortality. We were not evaluating intraoperative and postoperative arterial hypotension and hypertension, we analyzed the use of vasopressors as a surrogate marker. ACEi/ARBs re-initiation after surgery was not evaluated.

Results. One or more post-operative complications were documented in 113 patients (5.8%). Only postoperative delirium was more common in patients (1.06% vs. 0.27%, *P*=0.027) after ACEi/ARBs withdrawal 24 h before surgery, the difference reached statistical significance.

Sub-analysis in the group of patients with arterial hypertension as the only comorbidity showed no statistically significant differences in the outcomes. Sub-analysis in the group of patients with CFH showed higher incidence of postoperative delirium after ACEi/ARBs withdrawal (2.68% vs. 0.6%, *P*=0.023). The logistic regression analysis showed that the risk of developing postoperative delirium is influenced by age, vasopressor support, and ACEi/ARBs withdrawal (the area under the curve for the model was 0.92 (0.90–0.93).

Conclusion. Rates of pre-op ACEi/ARBs withdrawal (24.2%) are consistent with published data. In the entire cohort, ACEi/ARBs withdrawal resulted in higher incidence of postoperative delirium, as well as in the subgroup of patients with CHF, while ACEi/ARBs withdrawal in the subgroup of patients with arterial hypertension had no influence on postop complications.

ACEi/ARBs withdrawal, along with hemodynamic instability and older age, contributes to the development of postoperative delirium, which is the subject of future research.

Keywords: angiotensin converting enzyme inhibitors; angiotensin II receptor blockers; postoperative complications; abdominal surgery

Conflict of interest. The article presents the interim results of a multicenter study of the All-Russian public organization «Federation of Anesthesiologists and Reanimatologists (FAR) «Concomitant diseases and stratification of risks of postoperative complications in abdominal surgery — STOPRISK». Some authors of this paper head organizations conducting research: K. M. Lebedinsky — President of the FAR; I. B. Zabolotskikh — First Vice-President of the FAR; A. I. Gritsan — Vice-President of the FAR; A. N. Kuzovlev — Director of the V.A. Negovsky Research Institute of General Reanimatology, Federal Scientific and Clinical Center of Reanimatology and Rehabilitation (FSCC RR). The remaining authors declare no conflict of interest.

Author contribution. All authors meet all four ICMJE authorship criteria, and contributed to the conception of the article, acquisition and analysis of factual data, writing and editing the text of the article, revisiting and approving the final version for publication.

Registration of the study. The study was registered in the international database https://clinicaltrials.gov under the auspices of the All-Russian Public Organization «Federation of Anesthesiologists and Reanimatologists» (principal investigator I. B. Zabolotskikh), study number NCT03945968.

Introduction

The challenge of safe anesthesia in abdominal surgery remains relevant despite continuous improvements in anesthetic techniques. The incidence of postoperative complications is 18–24% [1, 2].

Many patients undergoing non-cardiac surgery are treated with angiotensin converting enzyme inhibitors (ACEIs)/angiotensin II receptor blockers (ARBs), which are usually prescribed as first-line antihypertensive agents [3–5]. In addition, ACEIs/ARBs are also used to treat patients with chronic left ventricular dysfunction and patients with diabetic nephropathy and a very high risk of postoperative complications [6]. However, suppression of the renin-angiotensin-aldosterone system may cause hypotension during induction of anesthesia, as shown by meta-analyses [7, 8]. Data on the role of ACEIs/ARBs in lowering blood pressure after induction of anesthesia are contradictory, and some studies have failed to find this effect [9]. There are also conflicting data on the effect of ACEI/ARB administration on the development of postoperative complications, ranging from a significant increase in mortality and cardiac complications when ACEIs/ARBs are taken before surgery [3] to a lack of effect [8] and even a negative effect of drug withdrawal on the incidence of complications due to the development of postoperative hypertension [10]. The RAAS is also known to modulate the coagulation system, influence capillary leakage associated with inflammation, and be involved in the pathophysiology of coronary atherothrombosis [11–13], therefore its preoperative inhibition may have an unpredictable effect on the postoperative period. All this has led to a lack of consensus in national European and North American guidelines on the need to discontinue ACEIs/ARBs before non-cardiac surgery.

The aim of this study was to investigate the role of ACEI/ARB withdrawal in the development of postoperative complications in patients undergoing abdominal surgery according to the STOPRISK database.

Materials and methods

Data Collection. By the time of interim analysis, data on perioperative parameters of 6,283 patients who underwent abdominal and pelvic surgery were obtained from 32 centers in 21 cities representing 8 federal districts for the period from July 1, 2019 to March 1, 2022. 6,195 patients were selected; 88 patients were excluded due to missing data required for analysis (Fig. 1).

All centers received local ethics committee approval prior to the study. Patients signed an informed consent form to participate in the study.

According to the study protocol (available on the WIT website at https://goo.su/5vL6oBI) [14], information was collected on all patients who met the eligibility criteria on a selected day.

Inclusion criteria for the subanalysis were presence in the STOPRISK database, long-term history of treatment with ACEIs/ARBs (3 months or more).

Exclusion criteria were ACEI/ARB discontinuation less than 24 h prior to surgery.

The study cohort was retrospectively divided into a group of patients who discontinued ACEIs/ARBs 24 h before surgery and a group of patients who continued ACEIs/ARBs until surgery.

Secondary analysis. A group of patients with hypertension as the only comorbidity and a group of patients with chronic heart failure in combination with other comorbidities were chosen from all patients included in the final analysis. In each of the above groups, subgroups were selected according to the pattern of ACEI/ARB prescription, i.e., discontinuation 24 h before surgery and continuation (Fig. 1).

Study endpoints. 30-day mortality and postoperative complications were assessed according to the classification of the Working Group of the European Society of Anesthesiologists and the European Society of Intensive Care Medicine [15]:

- Acute kidney injury
- Acute Respiratory Distress Syndrome (ARDS)
- Anastomotic failure
- Cardiac arrhythmias
- Circulatory arrest
- Cardiogenic pulmonary edema
- Postoperative delirium (ICU-CAM scale)
- Myocardial infarction
- Pneumonia
- Paralytic ileus
- Postoperative bleeding
- Pulmonary Embolism (PE)
- Acute Cerebrovascular Accident (ACVA)
- Wound infection

Intraoperative vasopressor requirements were also assessed.

Statistical analysis of data was performed using MedCalc software version 19.1.3 (MedCalc Software Ltd).

Data with normal distribution (Kolmogorov–Smirnov test) were presented as mean ± standard deviation, and data with non-normal distribution were presented as median (25–75 percentiles).

Baseline characteristics of patients in different groups and outcomes were compared using the χ^2 criterion for binary variables (or Fisher's exact test when the expected frequency of an event was less than 10) and the independent samples *t*-test for continuous variables with normal distribution and the Mann–Whitney test for variables with non-normal distribution. Repeated measures analysis of variance (RMANOVA) was used to compare the values of a variable at different stages of the study.

Multivariate logistic regression analysis was also performed to assess the contribution of multiple independent variables to the outcome.

Study registration. The study was registered in the international database https://clinicaltrials.gov under the auspices of the Russian Federation of Anesthesiologists and Reanimatologists (principal investigator I. Zabolotskikh), study number NCT03945968.

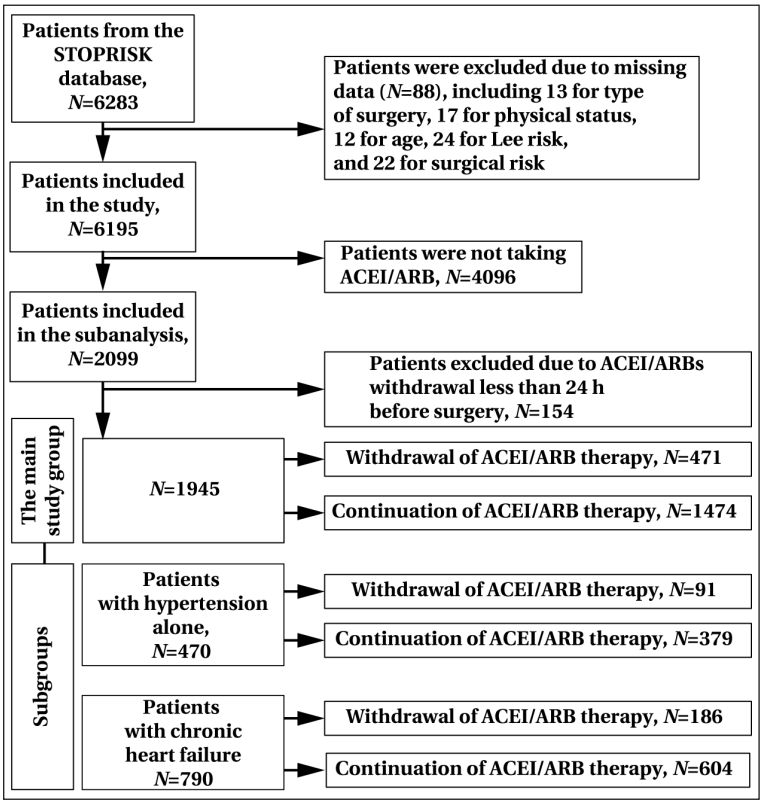

Fig. 1. Study flowchart.

Results

Among all patients in the STOPRISK database (6195 patients), comorbidities were registered in 3492 patients (56.4%), with a single condition observed in 1394 patients (22.5%), a combination of two conditions in 1052 patients (17.0%), three conditions in 606 patients (9.8%), four conditions in 308 patients (5.0%), and more than 4 comorbidities in 132 patients (2.1%) (Fig. 2).

Among patients with one comorbidity, hypertension was the most common (78%), diabetes mellitus (DM) was observed in 6%, CHD in 4%, COPD and arrhythmias in 3%, asthma and CKD in 2%, history of ACVA in 1%, and other diseases represented 6%. In patients with two comorbidities, the combination of hypertension with CHF, CHD, or DM was predominant (more than 80%); in patients with three comorbidities, the combination of hypertension and CHF with CHD or DM was most common (more than 75%); whereas in patients with four or more comorbidities, the combination of hypertension, CHF, and CHD with DM, arrhythmia, COPD, CKD, and ACVA was seen (more than 70%).

The results of 1945 patients were included in the analysis (Fig. 1). 471 patients were taking ARBs and 1474 patients were on ACE inhibitors.

In 471 (24.2%) patients, RAAS-inhibiting drugs were discontinued 24 hours before surgery, and in the remaining patients, the drugs were continued.

Comparison of baseline characteristics in the group of patients with ACEI/ARB withdrawal and in the group with continued administration is shown in Table 1. Patients with ACEI/ARB withdrawal had a lower Lee score.

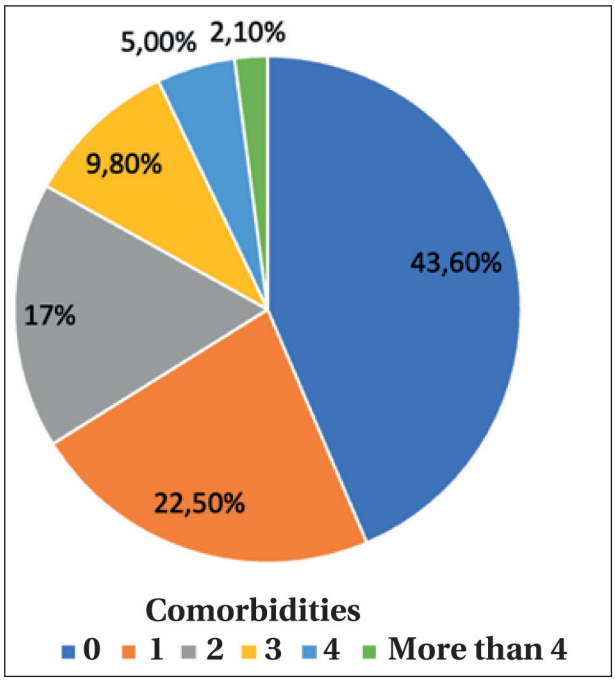

Fig. 2. Number of comorbidities in the studied cohort.

Complications were documented in 113 patients (5.8%). The frequency of complications is shown in Table 2.

Subanalysis in the subgroup of patients with hypertension alone showed that patients who continued to take ACEIs/ARBs were older, had a higher

Table 1. Parameters of the main study group.

Parameter	Values			*P*
	Total (*N*=1945)	Treatment withdrawal, *N*=471	Treatment continuation, *N*=1474	
Age, years	63 (57–70)	64 (57–70)	63 (57–70)	0.94
Surgical risk, %				
Low	26.7	25.9	26.9	0.65
Moderate	56.8	57.9	56.4	0.5
High	13.1	14.6	12.6	0.25
ASA class	2 (2–3)	2 (2–3)	2 (2–3)	0.15
Lee score, points	**1 (0–2)**	**1 (0–1)**	**1 (0–2)**	**0.0141**
Frequency of vasopressor support, %	5.45	7.22	4.88	0.05

Table 2. Complications in the main study group.

Parameter	Values			*P*
	Total (*N*=1945)	Treatment withdrawal, *N*=471	Treatment continuation, *N*=1474	
Complications	5.8	7.4	5.3	0.09
AKI	0.57	0.64	0.54	0.73
ARDS	0.31	0.42	0.27	0.63
Anastomotic failure	1.03	0.64	1.15	0.43
Cardiac arrhythmias	0.62	1.06	0.47	0.17
Circulatory arrest	0.26	0.21	0.27	1.0
Postoperative delirium	**0.46**	**1.06**	**0.27**	**0.042***
Pneumonia	1.39	1.27	1.42	1.0
Paralytic ileus	1.7	2.34	1.49	0.22
Postoperative bleeding	0.57	0.64	0.54	0.73
Pulmonary embolism	0.1	0	0.14	1.0
Cerebrovascular accident	0.21	0.21	0.20	1.0
Wound infection	0.87	1.27	0.75	0.26

Note. Here and in Tables 3, 4, 6: * — significant differences (Fisher's exact test).

Table 3. Parameters of patients with hypertension.

Parameter	Value		*P*
	Treatment withdrawal, *N*=91	Treatment continuation, *N*=379	
Age, years	58 (48–63)	61 (54–66)	0.0027
	Surgical risk, %		
Low	40.6	39.8	0.8
Moderate	57.1	54.6	0.6
High	1.1	0.8	0.7
ASA class	2 (2–2)	2 (2–3)	0.0162
Lee score, points	**0 (0–1)**	**1 (0–1)**	**0.003***
Frequency of vasopressor support, %	3.3	1.8	0.41

Table 4. Complications in the hypertensive patient group.

Parameter	Value		*P*
	Treatment withdrawal, *N*=91	Treatment continuation, *N*=379	
Complications	2.2	1.3	0.62
Anastomotic failure	0	0.5	1.0
Circulatory arrest	0	0.26	1.0
Paralytic ileus	0	0.52	1.0
Wound infection	**2.2**	**0**	**0.007***

Table 5. Parameters of patients with chronic heart failure.

Parameter	Value		*P*
	Treatment withdrawal, *N*=186	Treatment continuation, *N*=604	
Age, years	68 (60–72)	66 (60–72)	0.5
	Surgical risk, %		
Low	23.1	19.2	0.24
Moderate	60.2	55.1	0.22
High	16.1	21.02	0.14
ASA class	3 (2–3)	3 (2–3)	0.9
Lee score, points	1 (1–2)	1 (1–2)	0.57
Frequency of vasopressor support, %	11.3	6.8	0.06

Table 6. Complications in patients with chronic heart failure.

Parameter	Value		*P*
	Treatment withdrawal, *N*=186	Treatment continuation, *N*=604	
Complications	10.2	7.6	0.22
AKI	1.07	1.32	1.0
ARDS	1.07	0.66	0.63
Anastomotic failure	1.07	1.32	1.0
Cardiac arrhythmia	1.07	0.66	0.63
Circulatory arrest	0.53	0.5	1.0
Postoperative delirium	**2.68**	**0.6**	**0.037***
Pneumonia	2.15	1.8	0.76
Paralytic ileus	3.8	2.3	0.29
Postoperative bleeding	0	0.8	0.59
Pulmonary embolism	0	0.3	1.0
Cerebrovascular accident	0	0.5	1.0
Wound infection, %	1.07	1.3	1.0

ASA score, and were at higher cardiovascular risk (Table 3).

Drug discontinuation occurred in one in five patients. Nevertheless, no significant differences in outcomes were observed, except for the incidence of wound infection, which was not documented in the group of patients who continued ACEIs/ARBs (Table 4). Notably, the incidence of postoperative complications in this group was 1.2%.

Subanalysis in patients with comorbid chronic heart failure showed that ACEI/ARB withdrawal occurred in 23.5% of cases. The subgroups with drug withdrawal and with treatment continuation did not differ in their characteristics (Table 5).

As for the outcomes, a higher incidence of postoperative delirium was found in the ACEI/ARB withdrawal group (Table 6). In total, complications were observed in 65 patients (8.2%).

Logistic regression analysis showed that the risk of postoperative delirium was associated with age, vasopressor support, and ACEI/ARB withdrawal. The equation coefficients are shown in Table 7 ($P<0.0001$, $R^2=0.25$, Hosmer-Lemeshow test, $\chi^2=4.39$, $P=0.82$).

Table 7. Parameters of the logistic regression equation.

Variable	Coefficient	Standard error	*P*
Vasopressor support (yes/no)	2.03364	0.71632	0.0045
Age, years	0.075098	0.027042	0.0055
ACEI/ARB withdrawal (yes/no)	1.52839	0.70570	0.0303
Constant	–16.33507	4.08762	0.0001

The odds ratios for the identified factors are shown in Table 8.

The area under the curve for the model was 0.92 (0.90–0.93) (Fig. 3). The cut-off point was >–5.04 (sensitivity 100% (66.4–100%), specificity 73.62% (70.4–76.7%)). The odds ratio was 159.2 (95% CI 9.2–2745.8, *P*=0.0005), and the incidence of postoperative delirium was 4.1% in the high-risk group (according to the identified cut-off point) and 0% in the low-risk group.

Table 8. Odds ratio (OR) of identified risk factors for postoperative delirium.

Variable	OR	95% CI
Use of vasopressors	7.6419	1.8770–31.1128
Age	1.0780	1.0223–1.1367
Withdrawal of ACEIs/ARBs	4.6107	1.1563–18.3856

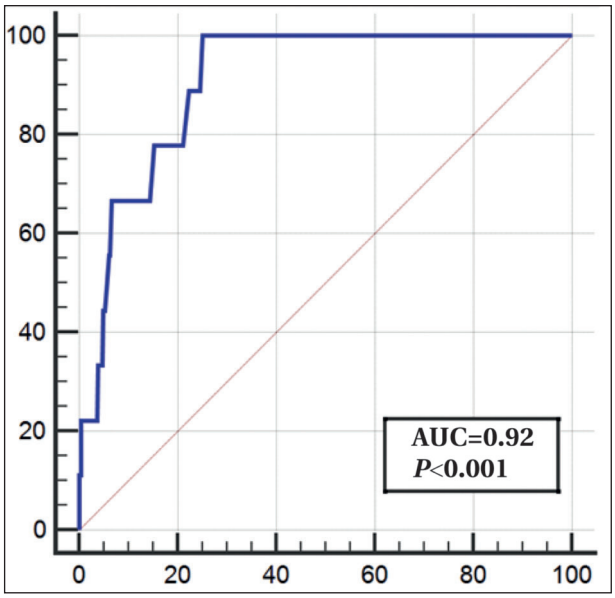

Fig. 3. ROC curve for the logistic regression equation showing its predictive value in assessing the risk of postoperative delirium.

Discussion

Of all patients (615) in the study cohort, ACEIs/ARBs were used in 33.9%, with 24.2% of preoperative 24 h withdrawals. Similar data were obtained in the VISION study, one of the largest studies to evaluate the impact of ACEI/ARB withdrawal on postoperative complications: ACEIs/ARBs were used in 32.6% of patients and withdrawn in 25.9% of cases [3].

We found no significant differences in the incidence of complications in the overall cohort of patients, except for postoperative delirium. Surprisingly, the frequency of vasopressor use was higher when ACEIs/ARBs were discontinued, despite the fact that such patients had a lower cardiovascular risk, whereas literature data suggest that hypotension is more common when drugs are continued [8], although this has not necessarily been confirmed [9]. The subanalysis showed that the findings were due to the patterns obtained in the subgroup of patients with chronic heart failure, since no significant differences were found in the subgroup with hypertension, and the complication rate was very low.

The finding of a lower incidence of postoperative delirium in the group of patients receiving preoperative ACEIs/ARBs (OR 4.6 with 95% CI 1.15–18.38) is interesting. Farag E. et al (2020) compared the incidence of postoperative delirium in non-cardiac surgery and found no effect of withdrawal of ACEIs/ARBs on its development. However, the use of these drugs in the postoperative period was associated with a lower incidence of delirium [16], even after adjustment for baseline and intraoperative factors. In addition, not only was the incidence of delirium higher, but the onset of delirium was earlier (19 h versus 64 h) in the group that did not receive the drug postoperatively. Therefore, the authors suggested that ACEIs/ARBs should be present at biologically relevant concentrations to prevent delirium.

The suggestion of a protective effect of ACEIs/ARBs in the prevention of delirium can be explained by the unique characteristics of the renin-angiotensin system. In particular, angiotensin II has neurotoxic effects mediated by its action on the angiotensin type 1 receptor. On the other hand, there is evidence in the literature for neuroprotective effects of the alternative renin-angiotensin system mediated by angiotensin, angiotensin III, and angiotensin IV [17]. Angiotensin-converting enzyme inhibitors increase brain levels of substance P, which is normally degraded by angiotensin-converting enzyme, which in turn increases the activity of neprilysin [18], an enzyme that breaks down β-amyloid [19]. In addition, ACEIs increase the production of angiotensin, which has neuroprotective and anti-inflammatory effects and leads to cerebral vasodilation [17]. The adverse effects of angiotensin II on the brain are mainly due to its action on the angiotensin 1A subtype receptor and include hypertension, inflammation, increased oxidative stress, blood-brain barrier disruption, and neurotoxicity.

Several publications suggest that angiotensin

II also induces nitric oxide production and promotes axon growth through activation of the angiotensin type 2 receptor and is an important factor in central nervous system development [17, 20]. The use of angiotensin type 1 receptor blockers enhances angiotensin II stimulation of the neuroprotective angiotensin type 2 receptor. In addition to blocking the angiotensin type 1 receptor, angiotensin receptor blockers also induce microglial polarization, which has anti-inflammatory and neuroprotective effects [21–23]. These effects have also been demonstrated in clinical trials. Therapy with losartan compared to atenolol in elderly hypertensive patients significantly improves cognitive functions, especially immediate and delayed memory [24]. In addition, the use of losartan in patients with hypertension improves cognitive functions, including memory, attention/concentration, comprehension, anxiety/depression, and interpersonal relationships [25]. Thus, the available evidence suggests that inhibition of the classical renin-angiotensin system pathway and simultaneous stimulation of alternative renin-angiotensin system pathways by ACEIs/ARBs have neuroprotective and anti-inflammatory effects, which may explain the reduced incidence of postoperative delirium.

Another possible mechanism influencing the risk of postoperative delirium is the potential neuroprotective effect of bradykinin [26], whose levels increase with the use of ACEIs.

The role of age and hemodynamic instability in the development of postoperative delirium has also been reported in the literature [27, 28].

The data on the lower incidence of wound infection in the ACEI/ARB withdrawal group are intriguing. The effects of ACEIs on the immune system and the anti-inflammatory properties of ACEIs are well-known [29] and may contribute to the risk of infectious complications. However, it is not clear how significant this impact is with short-term withdrawal, and this pattern we obtained requires further investigation.

Invasiveness of surgery may be an important factor associated with outcomes after non-cardiac surgery in patients taking ACEIs/ARBs and should be considered before their withdrawal or continuation. Previous prospective studies [30–32] and retrospective reviews [33, 34] have reported outcomes for a wide range of surgical procedures, from minimally invasive to major vascular surgery. Their results indicate that the use of ACEIs/ARBs is associated with an increased incidence of hypotension [30] and AKI in low-risk surgery [33, 34], but no effect on mortality was found [31]. In contrast, researchers found a 5-fold increased risk of mortality in major vascular surgery [32]. In the cited study, the invasiveness of the surgery had no effect on outcome, although preliminary outcome data have shown that this factor may have an impact, but is far from being decisive [35].

Study limitations. The current study is an observational study, which does not allow to exclude the influence of the reasons behind the decision to discontinue ACEIs/ARBs.

The study analyzed the effect of ACEI and ARB withdrawal in the same group because their effects on the risk of hemodynamic events during anesthesia are similar and are most often studied together. Because unexpected patterns were found, the final analysis should also be performed separately in each group.

The study did not evaluate intra- and postoperative hypo- and hypertension, and a surrogate parameter, the frequency of vasopressor use, was used. Re-initiation of ACEIs/ARBs in the postoperative period was not evaluated.

The data presented are preliminary.

The data obtained on the potential impact of ACEI/ARB withdrawal on the risk of postoperative delirium need validation and randomized trials.

Conclusion

The rate of ACEI/ARB withdrawal in patients undergoing abdominal and pelvic surgery was 24.2%, which correlates with literature data.

In the overall cohort, ACEI/ARB withdrawal was associated with a higher incidence of postoperative delirium. Subanalysis in the group of patients with chronic heart failure confirmed this pattern, whereas in the group of patients with hypertension, ACEI/ARB withdrawal did not affect outcome.

Together with hemodynamic instability and advanced age, ACEI/ARB withdrawal contributed to the development of postoperative delirium, which requires further investigation.

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