# Association between Withholding Angiotensin Receptor Blockers in the Early Postoperative Period and 30-day Mortality

## *A Cohort Study of the Veterans Affairs Healthcare System*

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## ABSTRACT

**Background:** Despite widespread use, there is limited information to guide perioperative management of angiotensin receptor blockers (ARBs).

**Methods:** In this retrospective cohort study, the authors evaluated the patterns of postoperative ARB use in veterans regularly prescribed ARBs admitted for noncardiac surgery at the Veterans Affairs Healthcare system between 1999 and 2011. Multivariable and propensity score–matched Cox proportional hazards models were used to determine the independent effect of failure to resume ARB by postoperative day 2 on the primary outcome of all-cause 30-day mortality.

**Results:** Out of 1,167,482 surgical admissions, 30,173 inpatient surgical admissions met inclusion criteria. Approximately 10,205 patients (33.8%) in the cohort did not resume ARB by day 2. Those that resumed ARB had a 30-day mortality rate of 1.3% (260 of 19,968), whereas 3.2% (323 of 10,205) died in the group that withheld ARB. The unadjusted hazard ratio (HR) for 30-day mortality was 2.45 (95% CI, 2.08 to 2.89; $P < 0.001$) for those that withheld ARB compared with those that resumed, whereas the multivariable adjusted HR was 1.74 (95% CI, 1.47 to 2.06; $P < 0.001$). When restricted to a propensity score–matched subset of 19,490, the HR was similar (1.47; 95% CI, 1.22 to 1.78; $P < 0.001$). Withholding ARB in younger patients increased mortality risk (HR = 2.52; 95% CI, 1.69 to 3.76; $P < 0.001$ for age <60 yr) compared with older patients (HR = 1.42; 95% CI, 1.09 to 1.85; $P = 0.01$ for age >75 yr).

**Conclusions:** Postoperative delay in resuming ARB is common, particularly in patients who are frail after surgery. Withholding ARB is strongly associated with increased 30-day mortality, especially in younger patients, although residual confounding may be present. **(Anesthesiology 2015; 123:288-306)**


ANGIOTENSIN receptor blockers (ARBs) are frequently prescribed for chronic hypertension, heart failure, and chronic renal failure as they help reduce the progression of cardiovascular and renal diseases.[1] However, both ARBs and angiotensin-converting enzyme inhibitors (ACEIs) impair the renin–angiotensin–aldosterone system, which plays an important role in maintaining blood pressure under anesthesia, and have frequently been associated with intraoperative hypotension after induction of general anesthesia.[2–6] This hypotension may be refractory to treatment with conventional adrenergic vasopressors and may respond better to vasopressinergic agonists.[7] According to one observational study, the hypotensive effects of ARBs under anesthesia may be even worse than ACEIs.[3] A randomized controlled trial showed that withholding the ARB on the morning of surgery reduces the episodes of intraoperative hypotension and improves responsiveness to ephedrine and phenylephrine.[4] Although controversial, some suggest that both ACEIs and ARBs be discontinued 10 to 24 h before surgery.[2,8,9]

### What We Already Know about This Topic

- Despite widespread use, there is limited information to guide perioperative management of angiotensin receptor blockers (ARBs)

### What This Article Tells Us That Is New

- In a review of over 30,000 inpatient surgical admissions of patients taking angiotensin receptor blockers (ARBs) in the Veterans Affairs Healthcare system between 1999 and 2011, ARBs were not resumed by day 2 after surgery in one third of subjects
- Thirty-day mortality was increased approximately 50% in those without resumption of ARBs, and this effect was even greater in younger patients under 60 yr of age

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Data about the longer-term postoperative effects of ACEIs and ARBs are conflicting. A retrospective cohort study of vascular surgery patients on ACEI/ARB compared with propensity score–matched controls showed an increased 30-day mortality in those on ACEI/ARB preoperatively,[10] whereas another study of major elective noncardiac surgery patients showed decreased need for postoperative dialysis among those on ACEI/ARB preoperatively.[11] A study of cardiac surgery patients showed that preoperative ACEI/ARB increased the risk of acute kidney injury postoperatively,[12] whereas another study found the converse—preoperative ACEI/ARB use lowered the rates of acute kidney injury.[13]

It is possible that physicians actively choose to restart an ARB postoperatively. However, another possibility, which has previously been observed in postsurgical patients,[14] is the inadvertent discontinuation of the drug during multiple transitions of care. Withdrawal of other classes of cardiovascular drugs in the perioperative period, including statins and β-blockers, has been shown to lead to worse outcomes.[15,16]

A recent cohort study among Veterans Health Administration (VHA) patients on chronic ACEI therapy showed that failure to resume ACEI therapy by 14 days postoperatively was associated with increased mortality.[17] It is unclear whether these associations are also true for ARBs. We therefore determined how often patients with regular preoperative ARB prescriptions, who presented for any inpatient surgery at the VHA between 1999 and 2011, had ARBs restarted within the first 2 days postoperatively. We then examined whether withholding ARBs in the early postoperative period was associated with postoperative morbidity and mortality.

## Materials and Methods

This retrospective cohort study was approved by the institutional research ethics board at the University of California, San Francisco, San Francisco, California, and the Research and Development Committee of the San Francisco Veterans Affairs (VA) Medical Center. Individual patient consent was waived. We analyzed patients regularly taking ARBs, presenting for surgery at the VHA between 1999 and 2011. Data were obtained from the Medical Statistical Analysis System and Corporate Data Warehouse files in the Veterans Affairs Informatics and Computing Infrastructure. The Corporate Data Warehouse is a national repository comprising data from several VHA clinical and administrative systems.* VHA data have been used to characterize the surgical risk on the basis of comorbidities in a variety of cohorts.[17–19] Multiple datasets within the VA Informatics and Computing Infrastructure were accessed, including Bar Code Medication Administration, Outpatient Pharmacy, Patient Demographics, Inpatient Encounters, Lab Chemistry, Vital signs, Outpatient Visits, and the Beneficiary Identification and Records Locator Subsystem. The datasets were merged using scrambled social security numbers.

### Subjects

Adults with recurring prescriptions for an ARB presenting for any noncardiac inpatient surgery at the VHA between 1999 and 2011 were included in the study. The VHA includes 130 surgical hospitals across the United States.

### Selection Criteria and Rationale

Inclusion criteria were adults undergoing any noncardiac surgery at a VA center with a hospital length-of-stay greater than 24 h, two or more preoperative outpatient prescription fills for an ARB (any of candesartan, irbesartan, losartan, olmesartan, or valsartan) within the preceding 6 months, and a prescription supply overlapping with the day of surgery.

### Exclusion Criteria

Patients with fewer than two refills of ARB preoperatively were excluded because chronic use of ARB could not be established. Patients with more than a 6-month gap between most recent outpatient prescription for ARB and date of surgery were excluded, as were those with a day supply that did not overlap with the day of surgery because these could have represented preoperative discontinuation or inconsistent use. For patients presenting for multiple surgeries, encounters with previous surgery in the prior 90 days were excluded. Patients with missing diagnosis codes were also excluded. Patients unable to take oral medications for the first 2 days postoperatively, as noted by medications administered intravenously only, were excluded. The exclusion of *nil per os* patients at postoperative day (POD) 2 removed those with significant postoperative ileus (*e.g.*, after major abdominal surgery) from the cohort. Patients who died on POD 0 to 2 were also excluded to minimize survivor bias because they may not have had the opportunity to be restarted on their ARB.

### Determination of Postoperative ARB Use

The *restarted* group is defined as patients having a record of inpatient ARB administration or a postdischarge outpatient ARB prescription within 2 days of the operative day. The *withheld* group is defined as patients with no record of inpatient ARB administration and no postdischarge outpatient ARB prescription within 2 days. The 2 days were chosen to be able to have at least one reliable inpatient medication administration record and to allow enough time to determine which early postoperative outcomes may have contributed to decisions to resume or withhold ARB (*e.g.*, early postoperative hypotension and acute kidney injury). Inpatient VA medication records have previously been shown to be highly reliable, with 99% sensitivity for administrative data *versus* medical record abstraction.[20]

* Further information on VA data sources found at the VA Information Resource Center Web site. Information about VA Data, 2014. Available at: http://www.virec.research.va.gov/Resources/Info-About-VA-Data.asp. Accessed October 9, 2014.

### Determination of Outcomes

**Mortality.** Date of postoperative deaths were determined from VA Vital Status files, which have previously been shown to be 98% sensitive and specific when compared with the National Death Index.[21]

**Postoperative Complications.** Complications were defined using newly incident International Classification of Diseases (ICD-9) diagnostic codes occurring after POD2 and up to 91 days after surgery (see Supplemental Digital Content 1, http://links.lww.com/ALN/B164, table 1, for ICD-9 codes used). Complications determined on the basis of these codes included cardiac complications (congestive heart failure, myocardial infarction, myocardial ischemia, elevated troponin [>0.1 ng/ml], arrhythmia, cardiac arrest, and cerebral ischemia) and noncardiac complications (renal failure, sepsis, deep vein thrombosis, pulmonary embolus, pneumonia, bleeding, urinary tract infection, and nonischemic stroke). If elevated troponin or creatinine was present before POD2, ICD-9 codes after POD2 of myocardial infarction/myocardial ischemia/elevated troponin, and renal failure, respectively, were not considered as complications.

### Measurement of and Adjustment for Confounders

Factors relating to the operation, such as surgical subspecialty (see Supplemental Digital Content 1, http://links.lww.com/ALN/B164, table 2, for procedural codes used to classify surgical type), duration of procedure (categorized into <2, 2 to 3, 3 to 4, and >4 h), and emergency *versus* elective surgery may have affected both prescribing patterns and mortality postoperatively. A number of patient demographics and comorbidities may also have acted as confounders. These include age, sex, and preoperative comorbidities, which were determined from ICD-9 codes present in at least one inpatient or two outpatient encounters in the 12 months preoperatively (see Supplemental Digital Content 1, http://links.lww.com/ALN/B164, table 3, for ICD-9 codes used). ICD-9 codes from VHA data repositories for outpatient comorbidities and postoperative complications have previously been shown to be accurate compared with chart reviews.[22,23]

Gagne scores, which combine the commonly used Charleson and Elixhauser measures, were determined on the basis of ICD-9 codes for the following comorbidities: metastatic cancer, congestive heart failure, dementia, renal failure, weight loss, hemiplegia, alcohol abuse, any tumor, cardiac arrhythmias, chronic pulmonary disease, coagulopathy, complicated diabetes, anemia, fluid and electrolyte disorders, liver disease, peripheral vascular disorder, psychosis, pulmonary circulation disorders, human immunodeficiency virus, and hypertension. The Gagne score has higher correlation to 30-day, 90-day, 180-day, and 1-yr mortality than the Charleson score.[24]

Immediate postoperative events, such as early postoperative hypotension, may also have contributed both to stopping the ARB and to mortality. The first blood pressure taken on POD 1 was determined from VA vital signs records and categorized into degree of hypotension, as measured by mean arterial blood pressure (MAP): severe hypotension: less than 65 mmHg, mild hypotension: 65 to 80 mmHg, normotensive: 80 to 110 mmHg, and hypertensive: more than 110 mmHg. Patients were placed into the severe hypotension category if they required vasopressor or inotropic support (epinephrine, norepinephrine, phyenylephrine, vasopressin, dopamine, or dobutamine). Severe hypotension (MAP <65 mmHg) on the day of surgery, when measured after surgical end time, was also included in the models. Acute kidney impairment was defined by categorized increases in first postoperative creatinine (if measured within 2 days) compared with baseline (lowest recorded in prior 3 months): unchanged (<10%), mild (10 to 50%), moderate (50 to 100%), and severe (>100%). Transfusion requirement was also recorded in the first 2 days postoperatively. Last, postoperative cardiac and noncardiac complications (as listed in Materials and Methods, Determination of Outcomes, Postoperative Complications), but occurring in the first 2 days postoperatively, were assessed for their possible role in confounding.

### Statistical Analysis

**Multivariable Logistic Regression.** Multivariable logistic regression modeling was used to determine which hospital, operative, and patient-related factors were associated with ARB nonresumption. Prespecified predictors were divided into two groups (appendix 1): group A was made up of predictors that would be included in the model on the basis of the likely relation between each potential explanatory variable and the primary outcome based on prior studies[17] and clinical knowledge while group B included predictors that were plausible confounders, but not fully supported by the literature. Predictors from group B were included in the model only if a backward stepwise selection resulted in $P$ value less than 0.1.

**Cox Proportional Hazards Modeling.** Using a change-in-coefficient criterion approach, the same factors used in the multivariable logistic model for predicting ARB nonresumption were also used to develop a Cox proportional hazards model for postoperative mortality within 30 days. As with the logistic regression model, predictors from group A were included in the model. Predictors in group B were included in the model only if their inclusion resulted in a change-in-coefficient of the primary predictor (ARB nonresumption by day 2) of 5% or more. Interactions of each predictor in the Cox model with ARB nonresumption were evaluated.

**Model Diagnostics.** The logistic regression model was not tested for discrimination and calibration with *c*-statistic or goodness-of-fit tests because it has been shown that there is no association between these tests and the ability of a given propensity score to accurately balance important confounding predictors.[25] For the Cox proportional hazards model, the assumption of proportional hazards was confirmed both graphically and by testing scaled Schoenfeld residuals.

**Propensity Score Matching.** The resumption or withholding of ARB by POD2 was not randomly assigned in this study population, thus we used propensity score matching to reduce the risk of confounding by indication. A propensity score was calculated from the multivariable logistic regression model (described in Materials and Methods, Statistical Analysis, Multivariable logistic regression) to estimate the likelihood of the ARB being withheld at 2 days postoperatively. Matching was done by nearest-neighbor matching using a caliper distance of 0.005 without replacement. Each patient who resumed ARB by POD2 was matched to one patient who did not resume with a similar propensity score. The propensity score was then used to estimate the mortality risk, both by adjusting for propensity score in the full cohort and repeating the analysis in the propensity score–matched subset. The advantage of the analysis on the propensity-matched subset is that it removed patients from the cohort that had such extreme propensity scores that they were unlikely to ever resume ARB (or conversely, near-certain to resume ARB), allowing for more comparable groups to determine the treatment effect on the treated.[26] In addition, it allowed for an exploratory analysis of postoperative complications without developing multiple models for each complication because the covariates were likely to be similar for complications compared with mortality.

**Interactions and Sensitivity Analyses.** Interactions of each included group A predictor in the Cox model with ARB resumption status by day 2 were tested. The effect of withholding ARB at 2 days postoperatively was modeled in a variety of prespecified populations: those without disseminated cancer, those without postoperative elevated creatinine, American Society of Anesthesiologists (ASA) physical status 1 to 3 only and 4 to 5 only, those at high and low Gagne and cardiac risk scores, elective cases only, emergency cases only, various ARB restart cut-points, and those concurrently on β-blockers, ACEI, or statins, as described in the following paragraph. Further sensitivity analyses in several subgroups were added after examination of the data: those with hospital length-of-stay more than 7 days, those who resumed ARB before or upon hospital discharge only, those concurrently on antiplatelet agents, and cases in patients with and without diabetes.

To determine that the association between ARB resumption and mortality is not simply measuring the effect of failing to resume other important cardiovascular medications, such as β-blockers, statins, and ACEI, we defined each patient in the cohort as being a regular user of these other medications using a similar technique as that used for ARB use (more than two prescriptions in the 6 months before surgery). Similarly, we determined resumption by POD2 on the basis of inpatient medication administration and outpatient prescription records. We were then able to perform sensitivity analyses restricting the cohort to, for example, only those that resumed their usual β-blocker. The effect of ARB use would not be due to failure to resume β-blocker in any of the patients in the restricted cohort (because the cohort is restricted to only those that resumed). Because acetylsalicylic acid is often purchased over-the-counter, we were not confident in our definition of preoperative use of acetylsalicylic acid. However, we were able to determine postoperative antiplatelet use (acetylsalicylic acid, clopidogrel, and ticlopidine) and perform a sensitivity analysis on the basis of receiving or not receiving antiplatelet agents by POD2.

**Timing of ARB Resumption: Other Cut-points and Time-dependent Covariate Analysis.** The survival analysis was repeated using other cut-points (days 1, 7, and 14 excluding those who died before days 1, 7, and 14, respectively). Lastly, ARB resumption was treated as a time-dependent covariate, both in the cohort excluding and including those who died by day 2.

A two-tailed *P* value of less than 0.05 was considered significant for all analyses. Stata version 12 (StataCorp LP, USA) was used for all analyses.

## Results

Of the 1.2 million surgical admissions at the VA during the study period, 30,173 surgical admissions in 25,663 patients met inclusion criteria (fig. 1). By day 2, 10,205 (33.8%) had not yet restarted their ARB and by day 30, 20.1% (n = 6,071) were still not represcribed their ARB. Selected baseline characteristics of the cohort are shown in table 1, classified by POD of ARB resumption. The cohort consisted of 96% men, as is typical of the VA population. The patients had an average age of 66 yr (SD, 10.2), with a median Gagne score of 1 (interquartile range, 0 to 2). The most common comorbidity in the cohort was hypertension (37.3%), whereas diabetes (27.2%), dyslipidemia (20.4%), and ischemic heart disease (19.7%) were also common. A wide range of surgical subspecialties were represented in the cohort. ARBs were most often restarted by POD2 in orthopedic (76.1%) and neurosurgery (75.1%) patients, whereas thoracic and general surgery patients had the fewest patients resuming by day 2 (56.7 and 57.9%).

Logistic regression was used to identify the predictors of ARB withholding and resumption by POD2 (table 2). The following were predictive of ARB withholding: ASA physical status classification 4 to 5, emergency surgery, longer duration of surgery, preoperative history of heart failure, valvular heart disease, liver disease, morbid obesity and fluid/electrolyte disorder, POD1 hypotension, elevated troponin, and elevated creatinine. The following were predictive of ARB resumption: older age, surgery after the year 2004, having at least four ARB refills before surgery, having had previous surgery, nongeneral surgery, and early postoperative hypertension.

Propensity score matching in a 1:1 ratio by nearest-neighbor (n = 19,490) improved the balance of baseline characteristics (table 1). After matching, the strongest predictors of ARB nonresumption, such as duration of surgery, emergency surgery, and early postoperative elevated creatinine

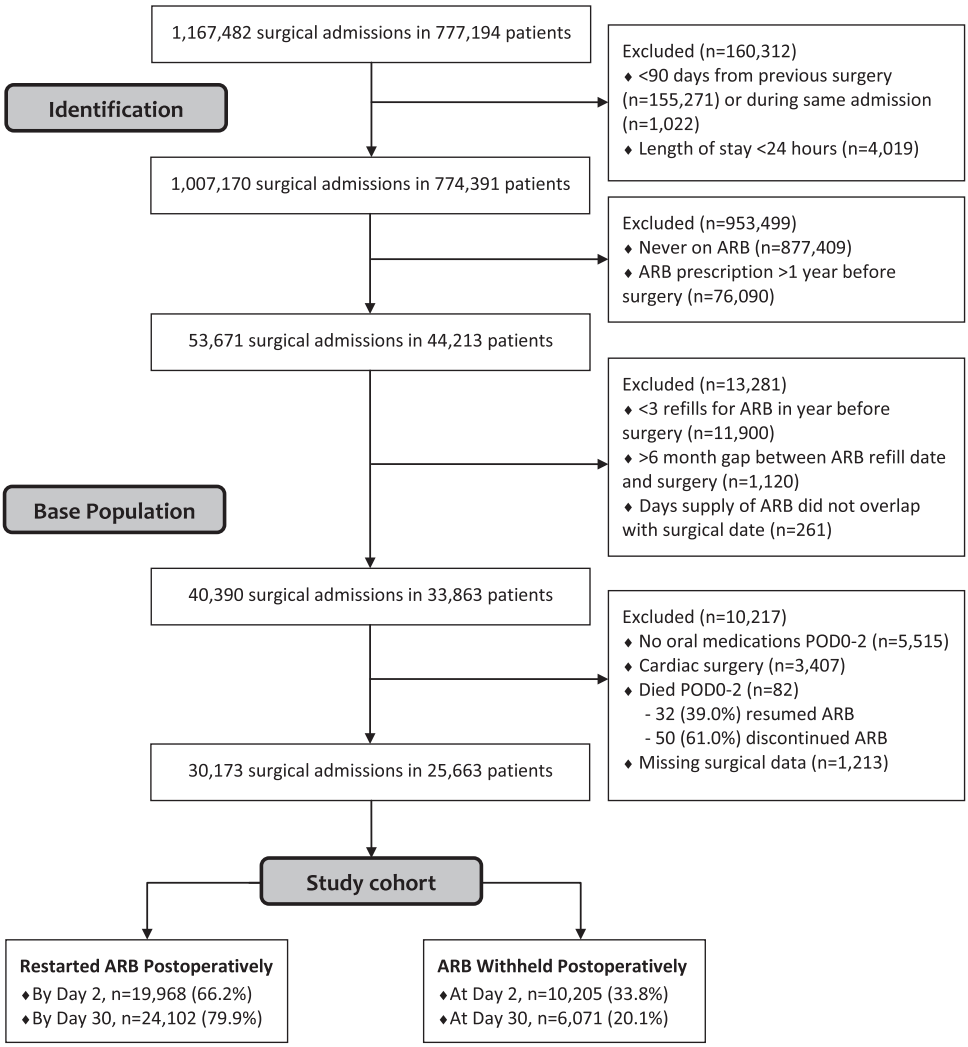


**Fig. 1.** Flowchart of included and excluded patients in the study cohort. ARB = angiotensin receptor blocker; POD = postoperative day.

and troponin elevation, were well balanced. Although early postoperative hypotension was statistically significantly different between groups ($P$ = 0.049), the absolute difference was small, and those that resumed ARB actually had slightly more hypotension than those that withheld. Before propensity score matching, the average MAP on POD1 was higher in the group that resumed ARB (90.4 mmHg compared with 88.5 mmHg, $P$ < 0.0001). After propensity score matching, the average MAP in the group that resumed ARB was 89.0 mmHg (SD, 14.4), which was not statistically different ($P$ = 0.14) than the average MAP in the group that had ARB withheld, which was 88.7 mmHg (SD, 13.9). When considering only moderate and severe hypotension, the groups were well balanced after propensity score matching: there were 2.5% with severe hypotension (MAP <65 mmHg) in both the ARB resumed group and in the ARB withheld group ($P$ = 0.96). There were 1,740 (17.9%) that had moderate hypotension (MAP 65 to 80 mmHg) in the ARB resumed group compared with 1,651 (16.9%) in the ARB withheld group ($P$ = 0.09).

Other unbalanced comorbidities also tended to be more common in the group that restarted ARB (*e.g.*, cardiovascular comorbidities). Supplemental Digital Content 2, http://links.lww.com/ALN/B165, shows the absolute standardized differences in characteristics between those that did not resume and those that resumed ARB by POD2 in the full cohort and after propensity score matching. All variables were within 10% after propensity score matching. As expected, in the full cohort, the average propensity score, expressed as probability between 0 and 1 of resuming ARB by day 2, for those that resumed ARB (0.805; 95% CI, 0.798 to 0.812) was higher ($P$ < 0.001) than in those that did not resume by day 2 (0.53; 95% CI, 0.52 to 0.54). Once matched, the average propensity score in both groups did not differ (0.58; 95% CI, 0.57 to 0.59; $P$ = 0.57).

There were a total of 583 deaths between POD2 and POD30, and the average length of follow-up in the model was 29.7 days. As shown in table 3, using a Cox proportional hazards model, the crude hazard ratio (HR) for all-cause 30-day mortality in the group that failed to resume

**Table 1.** Demographics and Risk Factors, Stratified by Postoperative ARB Status in the Full Cohort and Propensity Score–matched Subset

| | | Full Cohort | | | Propensity-matched Cohort | | |
|---|---|---|---|---|---|---|---|
| | Parameters | ARB Restarted after Day 2 (or Never Restarted), n (%) | ARB Restarted Day 0–2, n (%) | *P* Value | ARB Restarted after Day 2 (or Never Restarted), n (%) | ARB Restarted Day 0–2, n (%) | *P* Value |
| Total surgeries | | 10,205 | 19,968 | | 9,745 | 9,745 | |
| Demographics | | | | | | | |
| Age | <60 yr | 3,000 (29.4) | 5,793 (29.0) | | 2,854 (29.3) | 2,915 (29.9) | |
| | 60–75 yr | 5,064 (49.6) | 9,849 (49.3) | | 4,830 (49.6) | 4,686 (48.1) | |
| | >75 yr | 2,141 (21.0) | 4,326 (21.7) | 0.38 | 2,061 (21.2) | 2,144 (22.0) | 0.11 |
| Sex | Female | 412 (4.0) | 783 (3.9) | | 396 (4.1) | 430 (4.4) | |
| | Male | 9,793 (96.0) | 19,185 (96.1) | 0.63 | 9,349 (95.9) | 9,315 (95.6) | 0.23 |
| Medication factors | | | | | | | |
| ARB prescription pattern | Two to three refills preoperatively | 2,123 (20.8) | 3,301 (16.5) | | 1,932 (19.8) | 2,023 (20.8) | |
| | More than three refills preoperatively | 8,082 (79.2) | 16,667 (83.5) | <0.001 | 7,813 (80.2) | 7,722 (79.2) | 0.11 |
| Surgical factors | | | | | | | |
| Surgery type | General | 2,831 (27.7) | 3,885 (19.5) | | 2,589 (26.6) | 2,541 (26.1) | |
| | Neurosurgery | 343 (3.4) | 1,034 (5.2) | | 341 (3.5) | 374 (3.8) | |
| | Orthopedic | 2,076 (20.3) | 6,617 (33.1) | | 2,060 (21.1) | 2,051 (21.1) | |
| | Ophthalmology, plastics, otolaryngology | 543 (5.3) | 1,256 (6.3) | | 536 (5.5) | 538 (5.5) | |
| | Thoracic | 505 (5.0) | 662 (3.3) | | 460 (4.7) | 493 (5.1) | |
| | Urology, gynecology | 1,892 (18.5) | 3,129 (15.7) | | 1,809 (18.6) | 1,735 (17.8) | |
| | Vascular | 2,015 (19.8) | 3,385 (17.0) | <0.001 | 1,950 (20.0) | 2,013 (20.7) | 0.46 |
| Surgery year | 1999–2004 | 2,580 (25.3) | 4,402 (22.1) | | 2,455 (25.2) | 2,314 (23.8) | |
| | 2005–2007 | 3,223 (31.6) | 6,310 (31.6) | | 3,067 (31.5) | 3,104 (31.9) | |
| | 2008–2009 | 2,445 (24.0) | 5,189 (26.0) | | 2,339 (24.0) | 2,397 (24.6) | |
| | 2010–2011 | 1,957 (19.2) | 4,067 (20.4) | <0.001 | 1,884 (19.3) | 1,930 (19.8) | 0.13 |
| Emergency *vs.* elective | Elective surgery | 9,196 (90.1) | 18,773 (94.0) | | 8,910 (91.4) | 8,863 (91.0) | |
| | Emergency surgery | 1,009 (9.9) | 1,195 (6.0) | <0.001 | 835 (8.6) | 882 (9.1) | 0.24 |
| Duration of surgery | <2 h | 2,699 (26.5) | 5,647 (28.3) | | 2,594 (26.6) | 2,697 (27.7) | |
| | 2–3 h | 2,533 (24.8) | 5,557 (27.8) | | 2,445 (25.1) | 2,412 (24.8) | |
| | 3–4 h | 2,162 (21.2) | 4,480 (22.4) | | 2,100 (21.6) | 2,028 (20.8) | |
| | >4 h | 2,811 (27.6) | 4,284 (21.5) | <0.001 | 2,606 (26.7) | 2,608 (26.8) | 0.32 |
| Comorbidities | | | | | | | |
| ASA physical status | 1–2 | 859 (8.4) | 1,946 (9.8) | | 849 (8.7) | 871 (8.9) | |
| | 3 | 7,249 (71.0) | 14,979 (75.0) | | 7,049 (72.3) | 6,868 (70.5) | |
| | 4–5 | 2,097 (20.6) | 3,043 (15.2) | <0.001 | 1,847 (19.0) | 2,006 (20.6) | 0.01 |

(*Continued*)

**Table 1.** Continued

| | Parameters | Full Cohort: ARB Restarted after Day 2 (or Never Restarted), n (%) | Full Cohort: ARB Restarted Day 0–2, n (%) | Full Cohort: *P* Value | Propensity-matched Cohort: ARB Restarted after Day 2 (or Never Restarted), n (%) | Propensity-matched Cohort: ARB Restarted Day 0–2, n (%) | Propensity-matched Cohort: *P* Value |
|---|---|---|---|---|---|---|---|
| Cardiovascular comorbidities | Hypertension | 4,130 (40.5) | 7,128 (35.7) | <0.001 | 3,843 (39.4) | 4,187 (43.0) | <0.001 |
| | Diabetes mellitus | 2,963 (29.0) | 5,259 (26.3) | <0.001 | 2,735 (28.1) | 3,084 (31.7) | <0.001 |
| | Ischemic heart disease | 2,244 (22.0) | 3,690 (18.5) | <0.001 | 2,065 (21.2) | 2,315 (23.8) | <0.001 |
| | Dyslipidemia | 2,238 (21.9) | 3,926 (19.7) | <0.001 | 2,072 (21.3) | 2,355 (24.2) | <0.001 |
| | Peripheral vascular disease | 1,523 (14.9) | 2,562 (12.8) | <0.001 | 1,419 (14.6) | 1,571 (16.1) | 0.003 |
| | Heart failure | 1,304 (12.8) | 1,894 (9.5) | <0.001 | 1,149 (11.8) | 1,266 (13.0) | 0.01 |
| | Valvular disease | 371 (3.6) | 482 (2.4) | <0.001 | 306 (3.1) | 333 (3.4) | 0.28 |
| | Stroke | 289 (2.8) | 522 (2.6) | 0.27 | 270 (2.8) | 320 (3.3) | 0.04 |
| | Chronic kidney disease | 320 (3.1) | 468 (2.3) | <0.001 | 286 (2.9) | 328 (3.4) | 0.09 |
| | Pulmonary circulatory disease | 184 (1.8) | 205 (1.0) | <0.001 | 148 (1.5) | 155 (1.6) | 0.69 |
| Cardiac risk factors* | >1 | 2,175 (21.3) | 3,559 (17.8) | <0.001 | 1,968 (20.2) | 2,271 (23.3) | <0.001 |
| Gagne comorbidity score | 0 | 3,845 (37.7) | 8,708 (43.6) | | 3,778 (38.8) | 3,405 (34.9) | |
| | 1 | 2,154 (21.1) | 4,518 (22.6) | | 2,098 (21.5) | 2,205 (22.6) | |
| | 2 to 4 | 2,719 (26.6) | 4,731 (23.7) | | 2,573 (26.4) | 2,750 (28.2) | |
| | >4 | 1,487 (14.6) | 2,011 (10.1) | <0.001 | 1,296 (13.3) | 1,385 (14.2) | <0.001 |
| Events on POD0-1 | | | | | | | |
| Mean arterial blood pressure on POD0 | <65 mmHg | | | | 110 (1.1) | 132 (1.4) | 0.16 |
| Mean arterial blood pressure on POD1 | 80–110 mmHg | 4,642 (45.5) | 10,981 (55.0) | | 4,592 (47.1) | 4,421 (45.4) | |
| | 65–80 mmHg | 1,695 (16.6) | 3,431 (17.2) | | 1,651 (16.9) | 1,740 (17.9) | |
| | <65 mmHg | 282 (2.8) | 355 (1.8) | | 246 (2.5) | 247 (2.5) | |
| | >110 mmHg | 484 (4.7) | 1,392 (7.0) | | 480 (4.9) | 543 (5.6) | |
| | Not recorded | 3,102 (30.4) | 3,809 (19.1) | <0.001 | 2,776 (28.5) | 2,794 (28.7) | 0.05 |
| Creatinine change by POD2 | <10% | 2,953 (28.9) | 5,829 (29.2) | | 2,816 (28.9) | 2,811 (28.9) | |
| | 10–50% increase | 1,495 (14.7) | 2,640 (13.2) | | 1,392 (14.3) | 1,510 (15.5) | |
| | 50–100% increase | 273 (2.7) | 385 (1.9) | | 250 (2.6) | 256 (2.6) | |
| | >100% increase | 148 (1.5) | 157 (0.8) | | 115 (1.2) | 129 (1.3) | |
| | Not measured | 5,336 (52.3) | 10,957 (54.9) | <0.001 | 5,172 (53.1) | 5,039 (51.7) | 0.12 |
| | Elevated troponin POD0–1 | 368 (3.6) | 386 (1.9) | <0.001 | 278 (2.9) | 294 (3.0) | 0.50 |
| | Transfusion POD0–2 | 115 (1.1) | 139 (0.7) | <0.001 | 106 (1.1) | 90 (0.9) | 0.25 |

*P* values were determined by chi-square tests. Percentages are column percentages. Of the 30,173 patients in the cohort, 19,968 (66.2%) restarted ARB by POD2 and 10,205 (33.8%) had their ARB withheld (see text for description of propensity score generation and table 2 for variables included in propensity score). All characteristics other than age, sex, and history of stroke were unbalanced in the full cohort. After propensity score matching, most variables showed improved balance. For comorbidities that remained unbalanced (ASA physical status, cardiac comorbidities, and risk scores), there was greater comorbidity burden in the group that restarted ARB (see Supplemental Digital Content 2, http://links.lww.com/ALN/B165,figure, for graphical presentation of absolute standardized differences before and after propensity score matching, showing improvement in previously unbalanced covariates).

* Cardiac risk factors include ischemic heart disease, cerebrovascular disease, heart failure, diabetes mellitus, and chronic kidney disease.

ARB = angiotensin receptor blocker; ASA = American Society of Anesthesiologists; POD = postoperative day.

**Table 2.** Factors Associated with Restarting ARB by POD2

| Parameters | Reference | Univariable Odds Ratio | 95% CI | *P* Value | Multivariable Odds Ratio | 95% CI | *P* Value |
|---|---|---|---|---|---|---|---|
| Demographics | | | | | | | |
| Male sex | Female | 1.03 | 0.91–1.16 | 0.63 | 1.00 | 0.88–1.13 | 0.96 |
| Age 60–75 | Age <60 | 1.01 | 0.95–1.06 | 0.80 | 1.04 | 0.98–1.10 | 0.18 |
| Age >75 | Age <60 | 1.05 | 0.98–1.12 | 0.19 | 1.16 | 1.08–1.25 | <0.001 |
| Cardiac comorbidities* | | | | | | | |
| Valvular disease | No valvular disease | 0.66 | 0.57–0.75 | <0.001 | 0.83 | 0.72–0.97 | 0.02 |
| Heart failure | No heart failure | 0.72 | 0.66–0.77 | <0.001 | 0.89 | 0.82–0.98 | 0.02 |
| Peripheral vascular disease | No peripheral vascular disease | 0.84 | 0.78–0.90 | <0.001 | 0.92 | 0.85–1.00 | 0.05 |
| Chronic kidney disease | No chronic kidney disease | 0.74 | 0.64–0.86 | <0.001 | 0.90 | 0.77–1.06 | 0.20 |
| Dyslipidemia | No dyslipidemia | 0.87 | 0.82–0.92 | <0.001 | 1.04 | 0.97–1.12 | 0.28 |
| Diabetes mellitus | No diabetes mellitus | 0.87 | 0.83–0.92 | <0.001 | 0.96 | 0.90–1.03 | 0.29 |
| Ischemic heart disease | No ischemic heart disease | 0.80 | 0.76–0.85 | <0.001 | 1.01 | 0.93–1.09 | 0.84 |
| History of cerebral ischemia | No history of cerebral ischemia | 0.92 | 0.80–1.07 | 0.27 | 1.00 | 0.85–1.17 | 0.96 |
| Other comorbidities* | | | | | | | |
| Fluid or electrolyte disorder | No fluid or electrolyte disorder | 0.67 | 0.62–0.73 | <0.001 | 0.80 | 0.73–0.88 | <0.001 |
| Morbid obesity | Not morbidly obese | 0.62 | 0.53–0.73 | <0.001 | 0.72 | 0.61–0.86 | <0.001 |
| Liver disease | No liver disease | 0.68 | 0.57–0.82 | <0.001 | 0.81 | 0.67–0.98 | 0.03 |
| Lymphoma | No lymphoma | 0.56 | 0.40–0.78 | 0.001 | 0.70 | 0.49–0.99 | 0.05 |
| Pulmonary circulatory disorder | No pulmonary circulatory disorder | 0.56 | 0.46–0.69 | <0.001 | 0.81 | 0.65–1.01 | 0.06 |
| Drug abuse | No drug abuse | 1.15 | 0.88–1.51 | 0.31 | 1.30 | 0.97–1.72 | 0.08 |
| Neurologic disease | No neurologic disease | 0.78 | 0.67–0.90 | 0.001 | 0.87 | 0.74–1.01 | 0.07 |
| Metastatic cancer | No metastatic cancer | 0.63 | 0.53–0.74 | <0.001 | 0.87 | 0.72–1.03 | 0.11 |
| Nonmetastatic cancer | No localized cancer | 0.71 | 0.66–0.76 | <0.001 | 0.95 | 0.87–1.03 | 0.18 |
| Medication and institution factors | | | | | | | |
| Few ARB preoperative refills (two to three) | Four or more preoperative ARB refills | 1.33 | 1.25–1.41 | <0.001 | 1.33 | 1.25–1.42 | <0.001 |
| Surgery year quartile | | | | | | | |
| 2004–2007 | 1999–2004 | 1.15 | 1.08–1.22 | <0.001 | 1.17 | 1.09–1.26 | <0.001 |
| 2007–2009 | 1999–2004 | 1.24 | 1.16–1.33 | <0.001 | 1.30 | 1.20–1.41 | <0.001 |
| 2009–2011 | 1999–2004 | 1.22 | 1.13–1.31 | <0.001 | 1.30 | 1.20–1.42 | <0.001 |
| Subsequent surgery | First surgery | 1.39 | 1.30–1.49 | <0.001 | 1.30 | 1.21–1.40 | <0.001 |
| Surgical factors | | | | | | | |
| ASA physical status 3 | ASA physical status 1 and 2 | 0.91 | 0.84–0.99 | 0.03 | 1.00 | 0.91–1.09 | 0.99 |
| ASA physical status 4 and 5 | ASA physical status 1 and 2 | 0.64 | 0.58–0.71 | <0.001 | 0.85 | 0.76–0.95 | 0.003 |
| Emergency surgery | Nonemergency surgery | 0.58 | 0.53–0.63 | <0.001 | 0.69 | 0.63–0.76 | <0.001 |
| Surgery type | | | | | | | |
| Neurosurgery | General surgery | 2.20 | 1.93–2.51 | <0.001 | 2.04 | 1.78–2.34 | <0.001 |
| Orthopedic | General surgery | 2.32 | 2.17–2.49 | <0.001 | 2.03 | 1.89–2.19 | <0.001 |
| Ophthalmology, plastics, otolaryngology | General surgery | 1.69 | 1.51–1.88 | <0.001 | 1.52 | 1.35–1.70 | <0.001 |
| Thoracic | General surgery | 0.96 | 0.84–1.08 | 0.48 | 1.09 | 0.96–1.25 | 0.19 |
| Urology, gynecology | General surgery | 1.21 | 1.12–1.30 | <0.001 | 1.09 | 1.00–1.17 | 0.04 |
| Vascular | General surgery | 1.22 | 1.14–1.32 | <0.001 | 1.29 | 1.18–1.41 | <0.001 |
| Duration of surgery | | | | | | | |
| 2–3 h | <2 h | 1.05 | 0.98–1.12 | 0.16 | 0.93 | 0.87–1.00 | 0.04 |
| 3–4 h | <2 h | 0.99 | 0.92–1.06 | 0.78 | 0.88 | 0.81–0.95 | 0.001 |
| <4 h | <2 h | 0.73 | 0.68–0.78 | <0.001 | 0.75 | 0.70–0.81 | <0.001 |
| Early postoperative factors | | | | | | | |
| Blood pressure POD0 | | | | | | | |
| MAP <65 mmHg | MAP not <65 mmHg | 0.71 | 0.57–0.89 | 0.003 | 0.85 | 0.67–1.08 | 0.17 |
| Blood pressure POD1 | | | | | | | |
| MAP 65–80 mmHg | MAP 80–110 mmHg | 0.86 | 0.80–0.92 | <0.001 | 0.89 | 0.83–0.95 | 0.001 |
| MAP <65 mmHg† | MAP 80–110 mmHg | 0.53 | 0.45–0.62 | <0.001 | 0.60 | 0.51–0.71 | <0.001 |
| MAP >110 mmHg | MAP 80–110 mmHg | 1.22 | 1.09–1.36 | <0.001 | 1.26 | 1.13–1.41 | <0.001 |

(*Continued*)

**Table 2.** Continued

| Parameters | Reference | Univariable Odds Ratio | 95% CI | *P* Value | Multivariable Odds Ratio | 95% CI | *P* Value |
|---|---|---|---|---|---|---|---|
| Creatinine change POD0–2 | | | | | | | |
| Increased 10–50% | Within 10% or less than baseline | 0.89 | 0.83–0.97 | 0.005 | 0.99 | 0.91–1.07 | 0.72 |
| Increased 50–100% | Within 10% or less than baseline | 0.71 | 0.61–0.84 | <0.001 | 0.87 | 0.74–1.03 | 0.12 |
| Increased >100% | Within 10% or less than baseline | 0.54 | 0.43–0.68 | <0.001 | 0.69 | 0.55–0.88 | 0.003 |
| Creatinine not measured | Within 10% or less than baseline | 1.04 | 0.98–1.10 | 0.16 | 1.03 | 0.97–1.10 | 0.37 |
| New cerebral ischemia POD0–1 | No cerebral ischemia POD1 | 1.13 | 1.00–1.28 | 0.05 | 1.21 | 1.05–1.40 | 0.01 |
| Elevated troponin POD0–1 | No elevated troponin POD0–1 | 0.53 | 0.46–0.61 | <0.001 | 0.75 | 0.64–0.87 | <0.001 |
| New renal failure POD0–1 | No renal failure POD0–1 | 0.27 | 0.19–0.38 | <0.001 | 0.34 | 0.24–0.49 | <0.001 |
| New sepsis diagnosis POD0–1 | No sepsis diagnosis POD0–1 | 0.21 | 0.07–0.60 | 0.004 | 0.37 | 0.12–1.14 | 0.08 |

Odds ratios are derived from univariable and multivariable logistic regression analyses. The multivariable model includes all variables in the table (see Materials and Methods, Statistical Analysis, Multivariable Logistic Regression and appendix 1 for predictor selection procedures). This model was used to develop a propensity score to estimate the likelihood, on the basis of preoperative and early postoperative comorbidities, of resuming ARB by POD2. After adjustment, statistically significant predictors for ARB resumption include older than 75 yr, surgery year after 2004, subsequent surgery, nongeneral surgery, and early postoperative hypertension or stroke. Statistically significant predictors for ARB nonresumption include preoperative history of heart failure, valvular disease, fluid or electrolyte disorder, morbid obesity, liver disease, fewer preoperative ARB refills, ASA physical status 4–5, emergency surgery, surgical duration >2 h, and POD1 hypotension, renal failure, and elevated troponin.

* Comorbidities defined by preoperative International Classification of Diseases (ninth revision) codes, † or requiring inotropic or vasopressor support.

ARB = angiotensin receptor blocker; ASA = American Society of Anesthesiologists; MAP = mean arterial blood pressure; POD = postoperative day.

**Table 3.** Unadjusted and Adjusted 30-day Mortality by Cox Proportional Hazards Model

| Parameters | Reference | Hazard Ratio | 95% CI | *P* Value |
|---|---|---|---|---|
| ARB nonresumption at day 2 (unadjusted) | ARB resumed by POD2 | 2.45 | 2.08–2.89 | <0.001 |
| ARB nonresumption at day 2 (adjusted for decile of propensity score) | ARB resumed by POD2 | 1.74 | 1.47–2.05 | <0.001 |
| ARB nonresumption at day 2 (propensity-matched cohort only, n = 19,490) | ARB resumed by POD2 | 1.47 | 1.22–1.78 | <0.001 |
| ARB nonresumption at day 2 (multivariable adjusted—no interactions) | ARB resumed by POD2 | 1.74 | 1.47–2.06 | <0.001 |

Cox proportional hazards models: unadjusted, adjusted for propensity score, in propensity-matched subset only, and multivariable adjusted. Variables included in the development of the propensity score are found in table 2. Multivariable-adjusted model includes all variables in table 4, except the interaction with age. As expected, adjustment of confounders by each method reduces the estimated hazard ratio for death by 30 days. Propensity score adjustment in the full cohort produces similar results as multivariable adjustment. However, when analysis is restricted to only those matched on propensity score, the result more closely estimates the treatment effect on the treated because it eliminates those with extreme propensity scores.

ARB = angiotensin receptor blocker; POD = postoperative day.

ARB compared with those that resumed by POD2 was 2.45 (95% CI, 2.08 to 2.89; $P < 0.001$). After adjusting for predictors of ARB nonresumption, the HR for mortality was 1.74 (95% CI, 1.47 to 2.06; $P < 0.001$) and 1.74 (95% CI, 1.47 to 2.05; $P < 0.001$) when adjusted for deciles of propensity score. When only cases in the propensity score–matched subset of 19,490 were considered, the HR was 1.47 (95% CI, 1.22 to 1.78; $P < 0.001$).

### *Adjusted 30-day Mortality Cox Proportional Hazards Model Including Interaction with Age*

Interactions of all predictors in the Cox model with ARB resumption status by day 2 were tested. There was a statistically significant interaction with age more than 75 yr (*P* value for interaction 0.018). The effect of withholding ARB appeared to be greater in those of younger age. The HR for those younger than 60 yr was 2.52 (95% CI, 1.69 to 3.76; $P < 0.001$), whereas it was 1.42 (95% CI, 1.09 to 1.85; $P = 0.01$) for those older than 75 yr, as shown in table 4. Table 4 also shows the full multivariable Cox proportional hazards model. The strongest predictors of 30-day mortality, other than ARB withholding, included older age, history of cancer, high ASA physical status, and emergency surgery. Early postoperative hypotension and creatinine rise were also predictive of death.

The adjusted Cox regression curves, for each age group, are shown in figure 2. When age was modeled as a continuous variable, the HR for 30-day mortality in those that failed to resume ARB compared with those that restarted within 2 days at the mean age in our cohort (67 yr) is 1.89 (95% CI, 1.56 to 2.28) and decreases 0.85 times for each decade increase in age, such that the HR is 2.22 (95% CI, 1.65 to 2.99) at age 57 yr and only 1.60 (95% CI, 1.33 to 1.94) at age 77 yr.

Statistically significant interactions were also found with a history of diabetes and nonmetastatic cancer (*P* values for interaction = 0.02 and 0.03). However, once stratified by age, the interactions were no longer statistically significant at any age group. Analyses were repeated with and without excluding patients with diabetes and nonmetatstatic cancer, and the results did not appreciably change. Therefore, the analysis was carried out including all patients, stratified by age group, with diabetes and cancer patients excluded in sensitivity analyses.

**Table 4.** Factors Associated with 30-day Mortality by Cox Proportional Hazards Model: Final Model Including Interaction with Age

| Parameters | Reference | Hazard Ratio | 95% CI | *P* Value |
|---|---|---|---|---|
| ARB nonresumption at day 2—stratified by categorized age group | | | | |
| ARB nonresumption at day 2 (age <60 yr) | ARB resumed by POD2 | 2.52 | 1.69–3.76 | <0.001 |
| ARB nonresumption at day 2 (age 60–75 yr) | ARB resumed by POD2 | 1.79 | 1.39–2.31 | <0.001 |
| ARB nonresumption at day 2 (age >75 yr) | ARB resumed by POD2 | 1.42 | 1.09–1.85 | 0.01 |
| Interaction between age and ARB nonresumption at day 2 | | | | |
| Age 60–75 yr and ARB nonresumption | Age <60 and ARB nonresumption | 0.71 | 0.44–1.13 | 0.15 |
| Age >75 yr and ARB nonresumption | Age <60 and ARB nonresumption | 0.56 | 0.35–0.90 | 0.02 |
| Demographics | | | | |
| Male sex | Female | 1.23 | 0.71–2.15 | 0.47 |
| Age 60–75 yr | Age <60 | 1.45 | 1.00–2.10 | 0.05 |
| Age >75 yr | Age <60 | 2.68 | 1.84–3.89 | <0.001 |
| Few ARB preoperative refills (two to three) | Four or more preoperative ARB refills | 0.92 | 0.75–1.13 | 0.45 |
| Cardiac comorbidities* | | | | |
| Heart failure | No heart failure | 1.57 | 1.26–1.96 | <0.001 |
| Peripheral vascular disease | No peripheral vascular disease | 1.45 | 1.17–1.80 | 0.001 |
| Valvular disease | No valvular disease | 1.37 | 1.01–1.86 | 0.04 |
| Chronic kidney disease | No chronic kidney disease | 1.33 | 0.94–1.89 | 0.11 |
| Dyslipidemia | No dyslipidemia | 0.87 | 0.70–1.07 | 0.18 |
| Ischemic heart disease | No ischemic heart disease | 1.07 | 0.86–1.33 | 0.53 |
| Diabetes mellitus | No diabetes mellitus | 0.94 | 0.77–1.15 | 0.55 |
| History of cerebral ischemia | No cerebral ischemia | 0.99 | 0.66–1.50 | 0.97 |
| Other comorbidities* | | | | |
| Metastatic cancer | No metastatic cancer | 2.30 | 1.63–3.24 | <0.001 |
| Nonmetastatic cancer | No localized cancer | 1.41 | 1.10–1.80 | 0.006 |
| Lymphoma | No lymphoma | 2.23 | 1.21–4.10 | 0.01 |
| Fluid or electrolyte disorder | No fluid/electrolyte disorder | 1.23 | 0.98–1.54 | 0.08 |
| Hypothyroidism | No hypothyroidism | 1.53 | 0.97–2.42 | 0.07 |
| Neurologic disease | No neurologic disease | 1.38 | 0.97–1.95 | 0.07 |
| Drug abuse | No drug abuse | 0.16 | 0.02–1.19 | 0.07 |
| Weight loss | No weight loss | 1.43 | 0.90–2.26 | 0.13 |
| Obesity | Not obese | 0.76 | 0.48–1.22 | 0.26 |
| Pulmonary circulatory disorder | No pulmonary circulatory disorder | 0.85 | 0.53–1.35 | 0.49 |
| Alcohol abuse | No alcohol abuse | 0.86 | 0.54–1.35 | 0.51 |
| Liver disease | No liver disease | 0.89 | 0.52–1.54 | 0.69 |
| Morbid obesity | Not morbidly obese | 0.91 | 0.52–1.62 | 0.76 |
| Peptic ulcer disease | No peptic ulcer disease | 1.09 | 0.59–2.02 | 0.79 |
| Chronic pulmonary disease | No pulmonary disease | 0.85 | 0.53–1.35 | 0.49 |
| Paralysis | No paralysis | 0.98 | 0.61–1.60 | 0.95 |
| Surgical factors | | | | |
| ASA physical status 3 | ASA physical status 1 and 2 | 3.04 | 1.50–6.17 | 0.002 |
| ASA physical status 4 and 5 | ASA physical status 1 and 2 | 7.26 | 3.55–14.85 | <0.001 |
| Emergency surgery | Nonemergency surgery | 2.36 | 1.92–2.89 | <0.001 |
| Surgery type | | | | |
| Neurosurgery | General surgery | 0.98 | 0.63–1.52 | 0.9 |
| Orthopedic | General surgery | 0.85 | 0.68–1.07 | 0.17 |
| Ophthalmology, plastics, ENT | General surgery | 0.38 | 0.22–0.65 | <0.001 |
| Thoracic | General surgery | 1.13 | 0.81–1.57 | 0.47 |
| Urology, gynecology | General surgery | 0.42 | 0.30–0.57 | <0.001 |
| Vascular | General surgery | 0.49 | 0.36–0.66 | <0.001 |
| Duration of surgery | | | | |
| 2–3 h | <2 h | 0.72 | 0.58–0.89 | 0.002 |
| 3–4 h | <2 h | 0.57 | 0.44–0.74 | <0.001 |
| >4 h | <2 h | 0.68 | 0.53–0.87 | 0.002 |
| Surgery year quartile | | | | |
| 2005–2007 | 1999–2004 | 0.70 | 0.54–0.91 | 0.007 |
| 2008–2009 | 1999–2004 | 0.64 | 0.49–0.85 | 0.002 |
| 2010–2011 | 1999–2004 | 0.37 | 0.26–0.51 | <0.001 |

(*Continued*)

**Table 4.** Continued

| Parameters | Reference | Hazard Ratio | 95% CI | *P* Value |
|---|---|---|---|---|
| Early postoperative events | | | | |
| Blood pressure POD0 | | | | |
| MAP <65 mmHg | MAP not <65 mmHg | 1.23 | 0.71–2.10 | 0.46 |
| Blood pressure POD1 | | | | |
| MAP 65–80 mmHg | MAP 80–110 mmHg | 1.36 | 1.08–1.71 | 0.009 |
| MAP <65 mmHg† | MAP 80–110 mmHg | 2.07 | 1.41–3.03 | <0.001 |
| MAP >110 mmHg | MAP 80–110 mmHg | 0.82 | 0.51–1.32 | 0.42 |
| Creatinine change POD0–2 | | | | |
| 10–50% increase | Within 10% or less than baseline | 1.34 | 1.06–1.70 | 0.01 |
| 50–100% increase | Within 10% or less than baseline | 2.06 | 1.42–3.00 | <0.001 |
| >100% increase | Within 10% or less than baseline | 2.60 | 1.57–4.32 | <0.001 |
| Not measured | Within 10% or less than baseline | 0.75 | 0.59–0.95 | 0.02 |
| Transfusion POD0–2 | No transfusion POD0–2 | 1.11 | 0.57–2.18 | 0.75 |

The final multivariable model included the interaction of ARB resumption status with categorized age group, so age-specific hazard ratios are reported. Although nonresumption of ARB by POD2 is associated with increased mortality in all age groups, the hazard ratio is lowest in those >75 yr. The strongest predictors of death at 30 days other than ARB nonresumption include older age, preoperative history of heart failure, peripheral vascular disease, cancer, high ASA physical status, emergency surgery, surgery before 2005, POD1 hypotension, and postoperative creatinine elevation.

* Comorbidities defined by preoperative International Classification of Diseases (ninth revision) codes. † Included in this category if patient was on inotropic or vasopressor support on POD0–1.

ARB = angiotensin receptor blocker; ASA = American Society of Anesthesiologists; ENT = otolaryngology; MAP = mean arterial blood pressure; POD = postoperative day.

### Sensitivity Analyses

The HRs for postoperative mortality in predetermined subpopulations, stratified by age group, are shown in figure 3 and tabulated in appendix 2. The results are generally consistent across subgroups.

The HRs for postoperative mortality were consistent even when excluding patients on other cardiac medications preoperatively, such as β-blockers, statins, and ACEIs. Only a small number of patients were on both ACEIs and ARBs preoperatively, so the sensitivity analysis in this subgroup was inconclusive, although the point estimate was consistent with the other analyses. When the analyses are restricted to patients on β-blockers and statins, who resumed these medications in the first 2 days postoperatively, the HRs are consistent with the whole cohort. Together, these findings indicate that the effect of ARB nonresumption is unlikely to be simply a measure of the effect of the withdrawal of some other important cardiac medication, but rather specific to ARB withdrawal.

### Timing of ARB Resumption: Other Cut-points and Time-dependent Covariate Analysis

The effect of withholding ARB appears to be important at multiple time points, not just at POD2, as exemplified by the similar HRs obtained when using different cut-points and treating ARB nonresumption as a time-dependent covariate shown in figure 3. For example, failure to resume ARB by POD1 increases 30-day mortality risk in all age groups, but less prominently in those older than 75 yr (HR = 2.33; 95% CI, 1.58 to 3.45; $P < 0.001$ for age <60 yr; HR = 1.73; 95% CI, 1.33 to 2.23; $P < 0.001$ for age 60 to 75 yr; and HR = 1.39; 95% CI, 1.07 to 1.81; $P = 0.01$ for age >75 yr). Similarly, when ARB resumption is used as a time-dependent covariate starting on the operative day, 30-day mortality risk has the same pattern (HR = 2.49; 95% CI, 1.74 to 3.57; $P < 0.001$ for age <60 yr; HR = 1.83; 95% CI, 1.43 to 2.34; $P \leq 0.001$ for age 60 to 75 yr; and HR = 1.42; 95% CI, 1.09 to 1.84; $P = 0.01$ for age >75 yr).

### Complications by Propensity Score–matched Cohort

Postoperative complications recorded after POD2 in the full and propensity score–matched cohorts are shown in table 5. In the full cohort, most complications occurred at higher rates in the group that failed to resume ARB, likely due to confounding. In the propensity score–matched cohort, there are more noncardiac complications in the group that failed to resume ARB ($P < 0.001$). The increased rate of noncardiac complications was driven by increased rates of renal failure, pneumonia, and sepsis in the group that failed to resume ARB, although absolute differences were less than 1 to 2%. Although heart failure occurred more commonly in those that did not resume ARB ($P = 0.02$), there was no statistically significant difference in overall cardiac complications.

### Model Diagnostics

Model diagnostics were performed to test the assumption of proportional hazards. On the model without interactions and three models stratified by categorized age groups, the Kaplan–Meier estimates, predicted survival plots, log-minus-log plots, and smoothed scaled Schoenfeld residuals were graphed by ARB resumption status, and there were no obvious departures from proportionality. The Schoenfeld test for proportional hazards for ARB resumption status on the model without interactions ($P = 0.14$) and the models stratified by age group ($P = 0.82$, 0.47, and 0.16 for ages <60, 60 to 75, and >75 yr) similarly did not indicate any departures from the proportional hazards assumption.

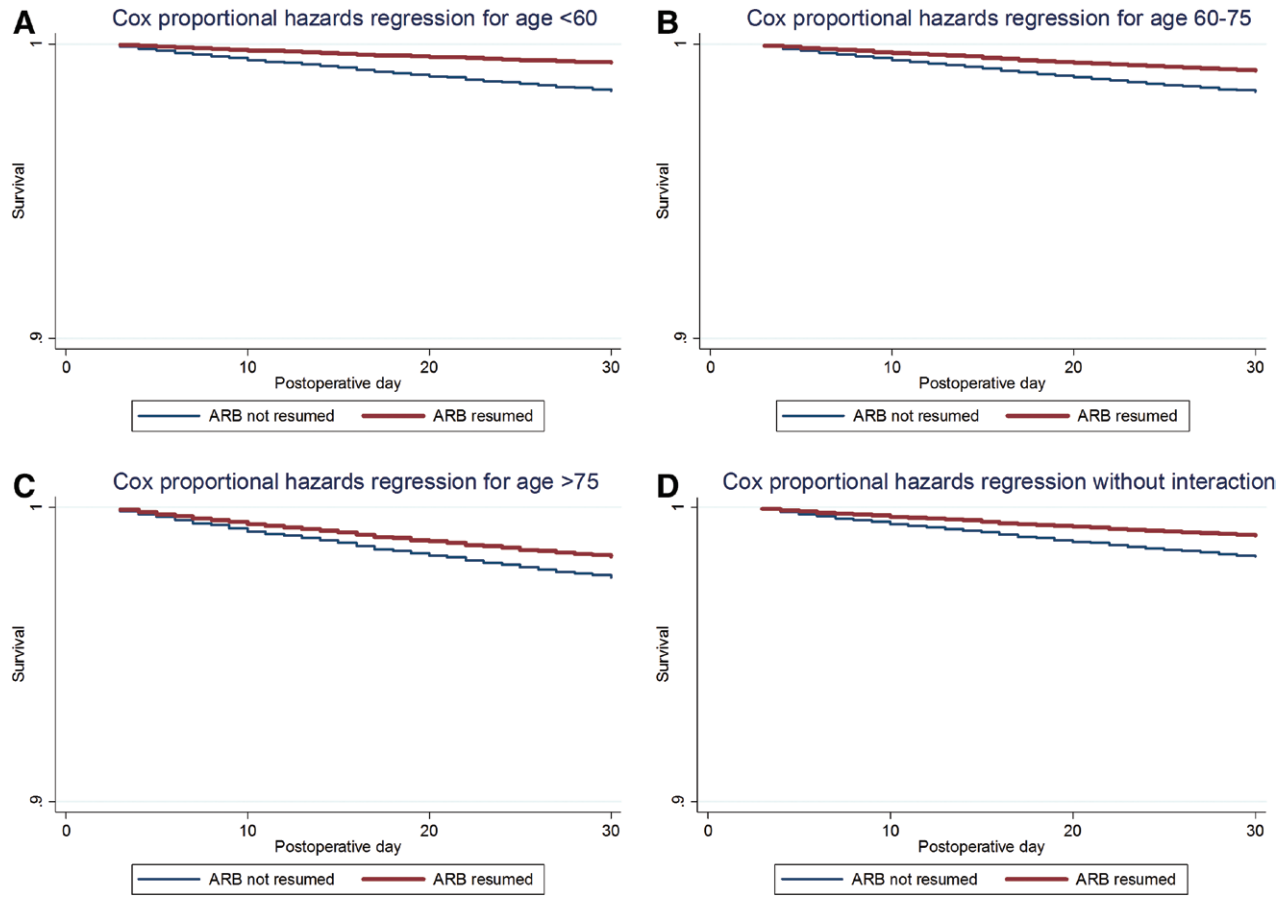


**Fig. 2.** Adjusted Cox proportional hazards regression curves comparing 30-day postoperative mortality in those resuming angiotensin receptor blocker (ARB) by day 2 and those that failed to resume. The model is as specified in table 4. For the purpose of graphical display, covariates have been set for absence of comorbidities, American Society of Anesthesiologists physical status 3 in elective male general surgery patients with surgical duration 2 to 3 h during the year quartile 2008–2009. (*A–C*) Stratified by categorized age group. (*D*) The full cohort without interactions, where age is modeled as a continuous predictor and set at the mean age (67 yr). The risk of mortality is increased by failure to resume ARB in all age groups. Although the overall risk of death increases with age, the relative hazard between those resuming and failing to resume ARB is greatest in younger patients.

## Discussion

In summary, failure to resume ARB by POD2 is common, occurring in 33.8% of patients in this national VA cohort. Nonresumption of ARB by POD2 was independently associated with increased 30-day mortality (adjusted HR = 1.74; 95% CI, 1.47 to 2.06; $P < 0.001$). The increased risk is consistent even when restricting the cohort to those with matched propensity for restarting ARB within the first 2 days postoperatively (HR = 1.47; 95% CI, 1.22 to 1.78; $P < 0.001$).

The frequency of ARBs being withheld at POD2 (around one third of the cohort) is higher than inadvertent drug discontinuation seen in previous studies, which has been closer to 10%.[14] One reason could be that ARBs are not seen as a priority for restarting early in the postoperative period, perhaps due to apprehension over hypotension and renal function. This is supported by the fact that the restart rate by POD2 was 85% for β-blockers in this cohort (15,361 of the 18,044 concurrently on β-blockers), perhaps because there is more awareness of the harms of β-blocker withdrawal in the perioperative period.[16]

Postoperative day 2 was selected as a convenient time point to enable assessment of ARB resumption during the inpatient stay, when medication administration records are most accurate, and also allow for measurement of early postoperative confounders, such as hypotension and acute kidney impairment. However, when sensitivity analyses were done at different time points, such as POD1, 7, and 14, the results remained consistent. When ARB resumption was treated as a time-dependent covariate, which rather than assigning an arbitrary cut-point, allowed ARB resumption status to change with time, the HRs were also similar (HR = 2.49; 95% CI, 1.74 to 3.57; $P < 0.001$ for age <60 yr; HR = 1.83; 95% CI, 1.43 to 2.34; $P \leq 0.001$ for age 60 to 75 yr; and HR = 1.42; 95% CI, 1.09 to 1.84; $P = 0.01$ for age >75 yr), indicating that withholding ARB at all time points postoperatively is associated with increased mortality.

Although the increased risk of mortality is seen across all age groups, there appears to be an interaction of the effect of ARB nonresumption and age on mortality. The HR for all-cause mortality is 2.52 in patients younger than 60 yr

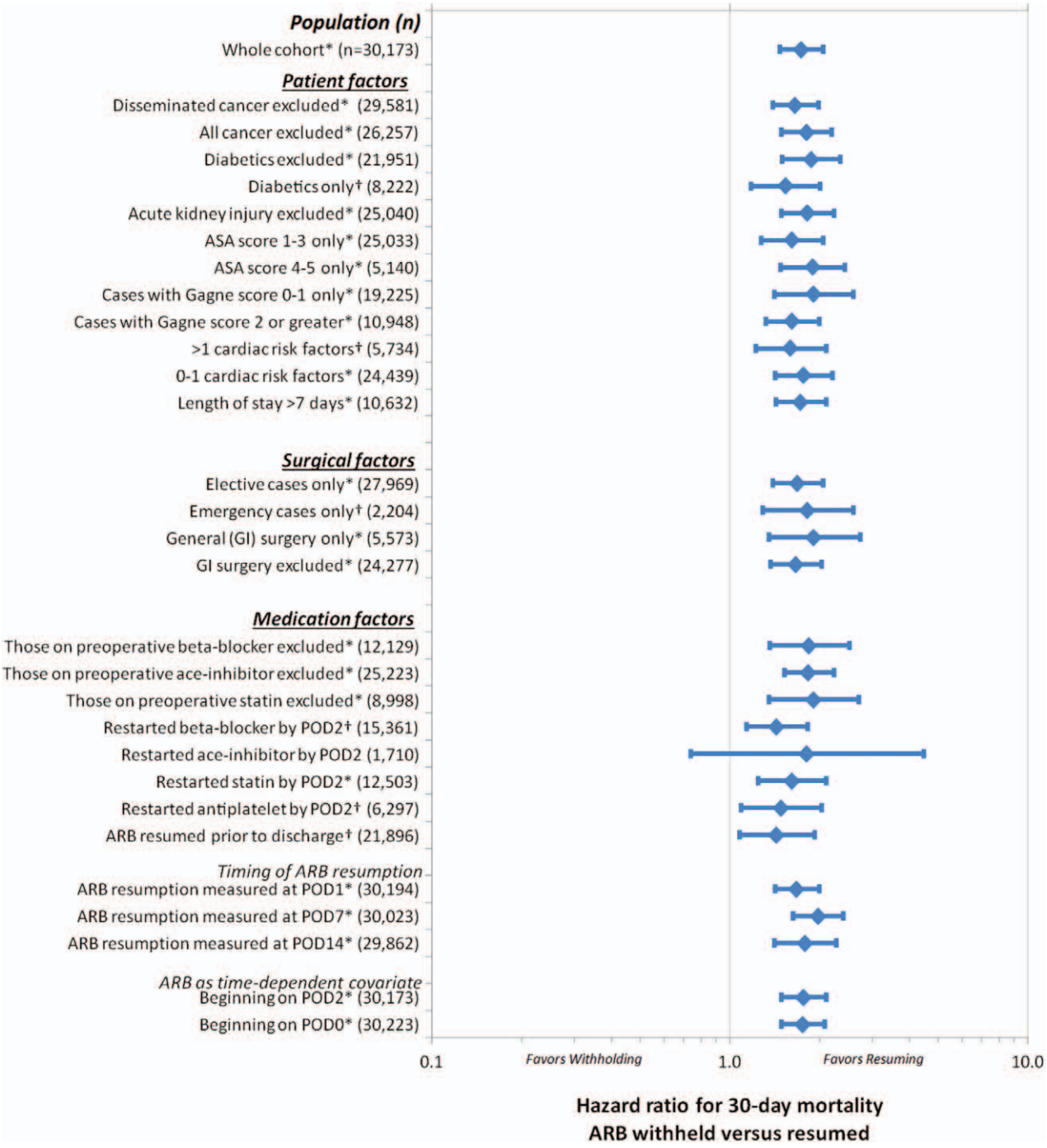


**Fig. 3.** Sensitivity analyses in selected prespecified populations. Models included all variables in table 4 except the interaction with age. Hazard ratios and 95% CIs are plotted on a logarithmic scale. Source data are given in appendix 2. Hazard ratios in sensitivity analyses were generally consistent with those found in the whole cohort. Severity of patient illness, surgical factors, concurrent medication use, and angiotensin receptor blocker (ARB) resumption timing did not seem to greatly affect the hazard ratios. All estimates were statistically significant except when analysis was restricted to those that resumed angiotensin-converting enzyme inhibitor, which resulted in a small sample size and wide CI. *$P < 0.001$, †$P < 0.01$. ASA = American Society of Anesthesiologists; GI = gastrointestinal; POD = postoperative day.

(95% CI, 1.69 to 3.76) and only 1.42 in those older than 75 yr (95% CI, 1.09 to 1.85). Although this study was not designed to determine the mechanism for this interaction, previous studies have shown that ACEIs are effective in preventing major cardiovascular events (myocardial infarction, stroke, and death) in both the elderly and in those younger than 65 yr.[27] Not only might younger patients be more dependent on medical control of risk factors, but they

**Table 5.** Postoperative Outcomes Stratified by Postoperative ARB Resumption Status

| | | Unmatched Full Cohort (n = 30,173) | | | | Propensity-matched Cohort (n = 19,490) | | | |
|---|---|---|---|---|---|---|---|---|---|
| Parameters | | ARB Restarted after Day 2 (or Never Restarted), n (%) | ARB Restarted Day 0–2, n (%) | *P* Value | Relative Risk (95% CI) | ARB Restarted after Day 2 (or Never Restarted), n (%) | ARB Restarted Day 0–2, n (%) | *P* Value | Relative Risk (95% CI) |
| Complications | Any cardiac | 2,654 (26.0) | 4,540 (22.7) | <0.001 | 1.14 (1.10–1.19) | 2,477 (25.4) | 2,442 (25.1) | 0.56 | 1.01 (0.97–1.06) |
| | Any noncardiac | 1,656 (16.2) | 2,321 (11.6) | <0.001 | 1.40 (1.32–1.48) | 1,515 (15.6) | 1,284 (13.2) | <0.001 | 1.18 (1.10–1.26) |
| Specific cardiac complications | Heart failure | 451 (4.4) | 705 (3.5) | <0.001 | 1.25 (1.11–1.41) | 422 (4.3) | 359 (3.7) | 0.02 | 1.18 (1.02–1.35) |
| | Cerebral ischemia | 60 (0.6) | 80 (0.4) | 0.002 | 1.35 (1.12–1.62) | 172 (1.8) | 146 (1.5) | 0.14 | 1.18 (0.95–1.47) |
| | Arrhythmia | 574 (5.6) | 897 (4.5) | <0.001 | 1.25 (1.13–1.39) | 521 (5.4) | 483 (5.0) | 0.22 | 1.08 (0.96–1.22) |
| | Elevated troponin | 1,837 (18.0) | 3,244 (16.3) | <0.001 | 1.11 (1.05–1.17) | 1,730 (17.8) | 1,769 (18.2) | 0.47 | 0.98 (0.92–1.04) |
| | Cardiac arrest | 60 (0.6) | 80 (0.4) | 0.02 | 1.47 (1.05–2.05) | 48 (0.5) | 55 (0.6) | 0.49 | 0.87 (0.59–1.28) |
| | Myocardial ischemia | 79 (0.8) | 139 (0.7) | 0.45 | 1.11 (0.84–1.46) | 74 (0.8) | 73 (0.8) | 0.93 | 1.01 (0.73–1.40) |
| | Myocardial infarction | 59 (0.6) | 78 (0.4) | 0.02 | 1.48 (1.06–2.07) | 52 (0.5) | 52 (0.5) | 1.0 | 1.00 (0.68–1.47) |
| Specific noncardiac complications | Renal failure | 439 (4.3) | 606 (3.0) | <0.001 | 1.42 (1.26–1.60) | 406 (4.2) | 313 (3.2) | <0.001 | 1.30 (1.12–1.50) |
| | Pneumonia | 443 (4.3) | 487 (2.4) | <0.001 | 1.78 (1.57–2.02) | 404 (4.2) | 295 (3.0) | <0.001 | 1.37 (1.18–1.59) |
| | Sepsis | 270 (2.7) | 218 (1.1) | <0.001 | 2.42 (2.03–2.89) | 230 (2.4) | 137 (1.4) | <0.001 | 1.68 (1.36–2.07) |
| | UTI | 645 (6.3) | 930 (4.7) | <0.001 | 1.36 (1.23–1.50) | 597 (6.1) | 515 (5.3) | 0.01 | 1.16 (1.03–1.30) |
| | Deep vein thrombosis | 84 (0.8) | 126 (0.6) | 0.06 | 1.30 (0.99–1.72) | 76 (0.8) | 56 (0.6) | 0.08 | 1.36 (0.96–1.91) |
| | Bleeding | 266 (2.6) | 417 (2.1) | 0.004 | 1.25 (1.07–1.45) | 252 (2.6) | 221 (2.3) | 0.15 | 1.14 (0.95–1.36) |
| | Nonischemic cerebral event | 19 (0.2) | 47 (0.2) | 0.39 | 0.79 (0.46–1.35) | 19 (0.2) | 29 (0.3) | 0.15 | 0.66 (0.37–1.17) |
| | Pulmonary embolus | 72 (0.7) | 104 (0.5) | <0.001 | 1.35 (1.00–1.83) | 67 (0.7) | 57 (0.6) | 0.37 | 1.18 (0.83–1.67) |
| Length-of-stay | >7 days | 3,590 (35.2) | 5,373 (26.9) | <0.001 | 1.31 (1.26–1.35) | 3,283 (33.7) | 2,950 (30.3) | <0.001 | 1.11 (1.07–1.16) |
| | >21 days | 1,081 (10.6) | 1,113 (5.6) | <0.001 | 1.90 (1.75–2.06) | 948 (9.7) | 656 (6.7) | <0.001 | 1.45 (1.31–1.59) |
| Death | Within 7 days | 68 (0.7) | 69 (0.4) | <0.001 | 1.93 (1.38–2.69) | 53 (0.5) | 54 (0.6) | 0.92 | 0.98 (0.67–1.43) |
| | Within 30 days | 323 (3.2) | 260 (1.3) | <0.001 | 2.43 (2.07–2.86) | 270 (2.8) | 186 (1.9) | <0.001 | 1.45 (1.21–1.75) |
| | In-hospital | 326 (3.2) | 214 (1.1) | <0.001 | 2.98 (2.51–3.54) | 267 (2.7) | 157 (1.6) | <0.001 | 1.70 (1.40–2.07) |

Percentages are column percentages. *P* values by chi-square test. Complications were determined by newly incident International Classification of Diseases (ninth revision) codes occurring after POD2 and up to 91 days postoperatively. In the full cohort, most complications occurred at higher rates in those that did not resume ARB, likely partially due to confounding. However, even after matching on propensity score, overall complications were seen at higher rates in those that failed to resume ARB by POD2. This was driven by increased rates of renal failure, sepsis, and pneumonia in the group that had ARB withheld.

ARB = angiotensin receptor blocker; POD = postoperative day; UTI = urinary tract infection.

may also mount a greater inflammatory response to stress,[28] which can be attenuated by ARB, resulting in reduced microvascular injury and organ dysfunction with ARB resumption.[11,29,30] We also suspect that the oldest age group, which had the highest mortality rate, had causes of death that were more multifactorial and may have obscured the association between ARB withholding and death.

Our results are consistent with the increased mortality found in a previous study of ACEI withdrawal[17] in a similar population, suggesting that abrupt withdrawal of agents acting on the renin–angiotensin–aldosterone system may be harmful. The HR we found was lower than that found in the study of ACEI, which might be because we adjusted for more confounders, examined a shorter time to resumption (and thus reduced survivor bias), ACEIs and ARBs act differently, or because the population under study differed.

Although it is difficult to determine from the available data whether withholding ARB is intentional or not, previous studies have suggested that unintentional discontinuation of regularly prescribed medications can occur perioperatively, likely related to transitions of care.[17] If intentional nonresumption occurred, our study may have been subject to confounding by indication; for example, if the sickest patients had their ARB withheld intentionally, they are also likely the ones to suffer mortality. However, our models adjust for more major confounders (*e.g.*, early postoperative hypotension and acute kidney injury) than previous studies.[17] Our measurement for outpatient prescription renewal as a marker for ARB resumption may have underestimated the true rate of ARB resumption. However, by excluding outpatient surgery, all patients had at least 1 day of reliable inpatient medication administration records. In addition, if patients were resuming their previous prescriptions as outpatients and misclassified as having ARB withheld, these patients would be, on average, healthier than inpatients and would be more likely to cause bias toward the null. This is most apparent in the increased HRs found when the analysis was restricted to those with hospital length-of-stay more than 7 days (HR = 1.73; 95% CI, 1.43 to 2.10; $P < 0.001$), a subset where reliable medication administration records are available for a longer duration compared with those with length-of-stay less than 7 days (HR = 1.34; 95% CI, 0.89 to 2.00; $P = 0.16$).

Another possible confounder that we accounted for with sensitivity analyses includes the possibility that the effect of nonresumption of ARB on mortality is actually due to other cardiac medications being withheld. However, this is unlikely, given that the effect of ARB nonresumption is still seen when analyses are restricted to patients who resumed their other cardiac medications.

Our study did not address the biological mechanism by which failure to restart ARB might contribute to mortality. Long-term ARB usage has been shown to reduce inflammation indices,[30] so it is possible that the associated reduction in mortality among those that resumed ARB may be related to the inhibitory role of ARBs on postoperative inflammation. The lower rate of pneumonia in patients who resumed ARB in the propensity score–matched cohort (3.0% for ARB resumed compared with 4.2% for ARB withheld, $P < 0.001$) is consistent with previous studies[29,31] that have found that ACEI and ARB curb the incidence of pneumonia, perhaps by reducing the inflammatory response. Postoperative withdrawal of ACEI has previously been shown to result in increased renal complications,[32] a finding supported by our propensity score matched–analysis of complications, which showed that a new diagnosis of renal failure after POD2 occurred in 4.2% of those that had ARB withheld and only 3.2% of those that had resumed ($P < 0.001$). Our finding is also congruent with a previous large population-based study showing decreased risk of acute kidney injury requiring dialysis and mortality in those prescribed ACEI or ARB preoperatively, suggesting a possible renal protective effect of ACEI/ARB,[11] perhaps by improving renal blood flow and reducing oxidative stress and tubular injury associated with angiotensin II.[33] Hypertensive rebound and associated cardiac decompensation has also been suggested as a potential contributor to perioperative morbidity after withdrawal of ACEI,[17] a finding supported by the increased heart failure in the propensity-matched group that did not resume ARB (4.3 *vs.* 3.7%, $P = 0.02$). However, because complication ICD-9 codes were bundled with admissions, discharges, and procedures, it was difficult to determine precisely whether complications occurred after POD2 or were merely coded after POD2. This is a major limitation of the complication analysis, and the complication analysis should therefore be considered exploratory.

Although multivariable regression techniques and propensity score matching were used to minimize overt biases, the limitations of a nonrandomized study remain. The statistical models presented are unable to account for unmeasured variables, and there is still the possibility of residual confounding. One such unmeasured variable includes intraoperative vital signs, which are not currently available in the VA national data repository. Nevertheless, because it is most often surgeons and hospitalists that choose to resume medications postoperatively, we feel the inclusion of early postoperative vital signs reduces much of the confounding related to hypotension. The study of medication management is particularly susceptible to confounding by indication[34,35] because physicians prescribe or withhold drug treatments based on a rich variety of diagnostic and prognostic information available at the time, not all of which may be accurately captured in an electronic database. It is possible that failure to restart ARB and mortality are common effects of unmeasured aspects of being frail or sick. Therefore, although we were able to find strong associations between ARB withholding and 30-day postoperative mortality, given the retrospective observational nature of the data, we are unable to make statements of causality. Future prospective randomized studies will be helpful in furthering our understanding of this association.

In conclusion, failure to resume ARB in the early postoperative period is common and is associated with increased 30-day postoperative mortality, even after adjusting for likely confounders. Careful attention to resuming regularly prescribed medications in the postoperative period may reduce mortality, particularly in younger patients.

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## Competing Interests

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## Appendix 1. Predictors of ARB Nonresumption

- Group A: Likely confounders for 30-day mortality
  - Demographics and period
    - Age
    - Sex
    - Year of surgery quartile (1999–2004, 2005–2007, 2008–2009, and 2010–2011)
  - Comorbidities
    - Cerebral ischemia (stroke/transient ischemic attack)
    - Chronic kidney disease
    - Diabetes mellitus
    - Dyslipidemia
    - Heart failure
    - Ischemic heart disease
    - Lymphoma
    - Metastatic cancer
    - Nonmetastatic cancer
    - Peripheral vascular disease
    - Valvular disease
  - Surgical and early postoperative factors
    - ASA physical status
    - Emergency *vs.* elective surgery
    - Duration of surgery
    - Surgery type (general, plastic, vascular, orthopedic, urologic, neurosurgery, thoracic, and gynecology)
    - Acute renal impairment POD0–2
      - Creatinine unchanged (<10%) or increased mildly (10–50%), moderately (50–100%), or severely (>100%)
    - Hypotension POD0 (MAP <65 mmHg)
    - MAP POD1
      - Severe hypotension <65 mmHg, mild hypotension 65–80 mmHg, normal 80–110 mmHg, and hypertensive >110 mmHg
- Group B: Possible confounders for 30-day mortality
  - Comorbidities
    - Alcohol abuse*
    - Chronic peptic ulcer disease*
    - Chronic pulmonary disease*†
    - Depression
    - Drug abuse*
    - Fluid or electrolyte disorder*†
    - Hepatitis C
    - HIV
    - Hypertension
    - Hypothyroidism*
    - Liver disease*†
    - Morbid obesity*†
    - Neurologic disease*†
    - Obesity*
    - Paralysis*
    - Psychosis
    - Pulmonary circulatory disease*†
    - Tobacco use
    - Weight loss*
  - Medication factors
    - Few ARB preoperative refills (two to three)*†

(*Continued*)

## Appendix 1. Continued

- Surgical factors and early postoperative factors
  - First *vs.* subsequent surgery†
  - Elevated troponin POD0–1†
  - Transfusion requirement POD0–2*
  - New diagnoses POD0–1: arrhythmia, cardiac arrest, myocardial ischemia, myocardial infarction, heart failure, renal failure,† cerebral ischemia,† nonischemic stroke, venous thromboembolism, pneumonia, sepsis, and urinary tract infection

Group A predictors were included in multivariable logistic regression and Cox proportional hazards models, whereas group B predictors included only if they met predetermined criteria. For the multivariable logistic regression model predicting ARB resumption, variables from group B were included by backward stepwise selection for $P < 0.1$. For the Cox proportional hazards model for 30-day postoperative mortality, a change-in-coefficient approach was used. Predictors from group B were only selected into the final model if their inclusion resulted in a change-in-coefficient of the primary predictor (ARB nonresumption by day 2) of 5% or more.

* The predictors selected using the change-in-coefficient approach for the Cox proportional hazards model. † The predictors selected using backward stepwise selection for the multivariable logistic regression model.

ARB = angiotensin receptor blocker; ASA = American Society of Anesthesiologists; HIV = human immunodeficiency virus; MAP = mean arterial blood pressure; POD = postoperative day.

## Appendix 2. Sensitivity Analyses: 30-day Mortality Risk Associated with ARB Nonresumption (Source Data for Figure 3)

| Population | n | Hazard Ratio | 95% CI | *P* Value |
|---|---|---|---|---|
| Whole cohort | 30,173 | 1.74 | 1.47–2.06 | <0.001 |
| Patient factors | | | | |
| Disseminated cancer excluded | 29,581 | 1.66 | 1.39–1.99 | <0.001 |
| All cancer excluded | 26,257 | 1.81 | 1.49–2.20 | <0.001 |
| Diabetes patients excluded | 21,951 | 1.88 | 1.51–2.35 | <0.001 |
| Diabetes patients only | 8,222 | 1.54 | 1.18–2.01 | 0.002 |
| Acute kidney injury excluded* | 25,040 | 1.83 | 1.49–2.24 | <0.001 |
| ASA physical status 1–3 only | 25,033 | 1.62 | 1.28–2.06 | <0.001 |
| ASA physical status 4–5 only | 5,140 | 1.90 | 1.49–2.43 | <0.001 |
| Gagne score 0–1 only | 19,225 | 1.91 | 1.40–2.59 | <0.001 |
| Gagne score 2 or greater | 10,948 | 1.62 | 1.32–1.99 | <0.001 |
| >1 cardiac risk factors | 5,734 | 1.60 | 1.22–2.11 | 0.001 |
| 0 to 1 cardiac risk factors | 24,439 | 1.77 | 1.42–2.21 | <0.001 |
| Length-of-stay >7 days | 10,632 | 1.73 | 1.43–2.10 | <0.001 |
| Surgical factors | | | | |
| Elective cases only | 27,969 | 1.69 | 1.39–2.06 | <0.001 |
| Emergency cases only | 2,204 | 1.83 | 1.29–2.60 | 0.001 |
| Gastrointestinal surgery only | 5,573 | 1.92 | 1.34–2.74 | <0.001 |
| Gastrointestinal surgery excluded | 24,277 | 1.67 | 1.37–2.03 | <0.001 |
| Medication factors | | | | |
| On preoperative β-blocker excluded | 12,129 | 1.85 | 1.36–2.52 | <0.001 |
| On preoperative angiotensin-converting enzyme inhibitor excluded | 25,223 | 1.84 | 1.52–2.23 | <0.001 |
| On preoperative statin excluded | 8,998 | 1.91 | 1.35–2.70 | <0.001 |
| Restarted β-blocker by POD2 | 15,361 | 1.44 | 1.14–1.82 | 0.002 |
| Restarted angiotensin-converting enzyme inhibitor by POD2 | 1,710 | 1.82 | 0.74–4.46 | 0.19 |
| Restarted statin by POD2 | 12,503 | 1.62 | 1.24–2.11 | <0.001 |
| Restarted antiplatelet by POD2 | 6,297 | 1.49 | 1.09–2.03 | 0.01 |
| ARB resumed before discharge | 21,896 | 1.44 | 1.08–1.93 | 0.01 |
| ARB timing | | | | |
| ARB nonresumption at POD1 | 30,194 | 1.68 | 1.42–1.99 | <0.001 |
| ARB nonresumption at POD7 | 30,023 | 1.98 | 1.63–2.40 | <0.001 |
| ARB nonresumption at POD14 | 29,862 | 1.79 | 1.41–2.27 | <0.001 |
| ARB resumption as time-dependent covariate | | | | |
| Beginning on POD2 | 30,173 | 1.77 | 1.50–2.10 | <0.001 |
| Beginning on operative day | 30,223 | 1.76 | 1.50–2.08 | <0.001 |

All analyses adjusted for factors in table 4, without interaction for age, compare resumption *vs.* nonresumption of ARB by POD2 unless otherwise indicated. Hazard ratios in sensitivity analyses were generally consistent with those found in the whole cohort. Severity of patient illness, surgical factors, concurrent medication use, and ARB resumption timing did not seem to greatly affect the hazard ratios. For analyses with time points of POD1, POD7, and POD14, those who died before the cut-point are excluded from the analysis to minimize immortal time bias.

* Acute kidney injury defined by increased creatinine POD0–2 >10% or new diagnosis of renal failure POD0–2.

ARB = angiotensin receptor blocker; ASA = American Society of Anesthesiologists; POD = postoperative day.