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ORIGINAL ARTICLE – BREAST ONCOLOGY

Effects of Antihypertensive Drugs on Outcomes of Breast Reconstruction

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ABSTRACT

Background. Angiotensin receptor blocker (ARB), a commonly used antihypertensive drug, is reported to affect wound healing and flap survival in animal models. However, this has not been elucidated in a clinical series. This study aimed to investigate the impact that perioperative use of ARB has on outcomes after breast reconstruction.

Methods. Patients who underwent immediate breast reconstruction using a tissue expander or a deep inferior epigastric perforator (DIEP) flap were reviewed. The patients were categorized according to the types of antihypertensive medications as follows: the ARB group consisted of hypertensive patients treated with ARB alone or a combination of ARB and other drugs; the non-ARB group included those receiving drugs other than ARB; and the control group did not receive any medication. The effects of antihypertensive drugs on the development of complications were evaluated.

Results. The study analyzed 1390 cases including 999 cases of tissue-expander insertion and 391 cases of DIEP flap reconstruction. With regard to tissue-expander reconstruction, the rates of seroma, reoperation, reconstruction failure, and overall complications were significantly higher in the ARB group than in the other two groups. Compared with no medication, ARB use was an independent risk factor for these complications. With regard to DIEP flap reconstruction, the ARB group showed a significantly higher rate of fat necrosis and significantly greater odds for the development of overall perfusion-related complications and fat necrosis than the control group after adjustment for other variables.

Conclusions. Perioperative administration of ARB might be associated with adverse outcomes after breast reconstruction.

Breast reconstruction is crucial in the treatment of breast cancer.[1] Among the diverse reconstructive methods, the two predominant options are two-stage tissue-expander-implant reconstruction among those using prostheses and deep inferior epigastric perforator (DIEP) flap reconstruction among those using autologous flaps.[2,3]

Hypertension, a long-term medical condition with a very high global prevalence, can cause several life-threatening conditions. To prevent serious complications, a majority of patients with hypertension are treated with antihypertensive medications,[4] as recommended by the eighth Joint National Committee guidelines.[5] Accordingly surgeons are encountering more patients receiving antihypertensive drugs among those who require breast reconstruction.

The potential effects of antihypertensive drugs on postoperative outcomes have rarely been investigated. Several animal studies have demonstrated that administration of antihypertensive drugs could influence tissue perfusion and wound healing. In particular, angiotensin receptor blocker (ARB) is reported to decrease flap survival[6] and wound tensile strength after repair.[7] Previously, we compared the effects of various antihypertensive drugs on perfusion of a perforator flap in a rat model. Similar findings were observed in that the survival territory of a

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dorsal island flap differed according to the type of antihypertensive drug administered, being the lowest in ARB-treated rats.[8]

Despite existing experimental evidence suggesting detrimental effects of ARB on wound healing and tissue perfusion, this has not been elucidated in the clinical setting. We hypothesized that patients administered ARB could be at a higher risk for the development of postoperative complications associated with reduced healing potential and tissue perfusion. Breast reconstruction surgery can be a good model for investigating this issue.

In breast reconstructions, a large area of tissues is elevated and put under temporarily reduced perfusion with or without implanted foreign material. For such wounds with a high burden of healing, complications caused by insufficient tissue perfusion could be relatively common, resulting in serious adverse outcomes. Therefore, this study aimed to evaluate the effects of antihypertensive drugs, especially ARB, on the development of complications after breast reconstruction.

PATIENTS AND METHODS

After approval was obtained from the institutional review board, a retrospective chart review was conducted for patients who underwent immediate breast reconstruction between July 2009 and April 2017. Cases that involved the use of tissue-expander implants or DIEP flaps were included because those two were the most predominantly used approaches at our institution. Patients followed up for a minimum of 6 months postoperatively were included.

We identified all patients with hypertension who were receiving antihypertensive medication at the time of the operation. Patients were excluded if they had started with antihypertensive medication only a month before the surgery or had undergone a change in their treatment regimen within a month before the surgery. Patients who had a diagnosis of hypertension but did not take pertinent medications also were excluded.

The selected patients were categorized into three groups according to their treatment as follows: no medication, ARB treatment, and non-ARB treatment groups. The ARB group consisted of patients treated with ARB alone or ARB in combination with other antihypertensive drugs. The non-ARB group consisted of patients receiving a different class of drugs including calcium-channel blockers, beta-blockers, or diuretics. Patients who had been treated with ARBs in the past but had changed to another regimen without ARBs were excluded from the non-ARB group to reduce potential confounding effects.

Our protocol for administering antihypertensive drugs during the perioperative period involved discontinuation of the medication on the operation day and resumption in the early postoperative period.

Outcome Measures

Cases were divided according to the type of reconstruction. The outcome of interest was the development of postoperative complications. For cases of tissue-expander/implant reconstructions, complications that developed after the first-stage operation of tissue-expander insertion were analyzed, including infection, seroma, hematoma, mastectomy flap necrosis, wound breakdown, wound revision, reoperation, and reconstruction failure. Cases of wound dehiscence were defined as those showing wound breakdowns along the margin of the surgical incision, which were treated with conservative management or surgical intervention. Cases of wound revision were defined as those requiring re-operations to treat dehiscence of the incision wound or necrosis of the mastectomy flap.

For cases of DIEP flap reconstruction, the outcome measures were flap perfusion-related complications, including total or partial flap loss and fat necrosis, and donor-site complications, including wound breakdown, seroma, hematoma, and bulge/hernia. Fat necrosis in the DIEP flap was diagnosed by the detection of a persistent, palpable nodule larger than 2 cm in diameter through physical examinations by the attending surgeon 6 months after the operation and confirmed subsequently by ultrasonography.

Statistical Analysis

The complication rates in the three groups were compared using the Pearson Chi square test. Post hoc analysis was conducted to calculate the observed power of analyses. To evaluate the independent impact of antihypertensive drugs on the development of complications compared with no medication use, we performed multivariate analyses. Multiple logistic regression analyses were conducted by applying the backward model selection technique, starting with all the patients and operation-related variables. This method involves starting with all variables, removing a variable, observing the effect of the removal on a measure of the model complexity and repeating the process until no additional reduction is observed in the model complexity. A p value lower than 0.05 was considered statistically significant.

RESULTS

The study evaluated 1346 patients representing 1390 cases of breast reconstruction, including 999 tissue-expander/implant reconstruction cases (959 patients) and 391 DIEP flap reconstruction cases (386 patients). There were 45 patients undergoing bilateral reconstructions, including 40 using a tissue expander/implant and 5 using a DIEP flap. We identified 79 patients with hypertension who had received antihypertensive drugs. Of these patients, 55 were included in the ARB group, with the remaining 24 patients included in the non-ARB group (Table 1).

In the ARB group, the majority of the patients (49 of 55, 89.1%) had received an ARB for years, and six had the medication administered less than a year, including three for 2 months, two for 6 months and one for 9 months. Systolic and diastolic blood pressures were well controlled during the perioperative period in both groups.

Tissue Expander Reconstruction

The ARB patients were older, had a higher body mass index (BMI), a higher rate of bilateral reconstruction, larger breasts, a larger tissue expander inserted, and a greater volume of initial inflation (Table 2) than the control group. Postoperative complications developed in 204 patients (20.4%). The ARB group showed a significantly higher rate of seroma, wound revision, reoperation, reconstruction failure, and overall complications than the non-ARB and no medication groups. The rates of the other complications did not differ between the groups (Table 3).

In the ARB group, the patients treated with only ARB and those treated with a combination of ARB and other drugs showed similar overall complication rates (45% and 43.8%, respectively). Multivariate analyses showed that compared with no medication, treatment with ARB medication was an independent risk factor for overall postoperative complications. The type of mastectomy, tissue-expander size, and initial inflation volume also significantly influenced the development of overall complications (Table 4).

Administration of non-ARB treatment did not affect the development of overall complications. Other variables, including laterality, did not show significant influences. Similarly, antihypertensive medication (ARB vs no medication: odds ratio [OR] 3.584; 95% confidence interval [CI] 1.504–8.542; $p = 0.004$) and initial inflation volume (OR 1.006; 95% CI 1.004–1.008; $p < 0.001$) were significant predictors of reoperation. Developments of seroma (OR 3.599; 95% CI 1.151–11.258; $p = 0.028$) and reconstruction failure (OR 2.418; 95% CI 1.171–4.993; $p = 0.017$) also were shown to be significantly affected by ARB medication compared with no medication after adjustment for other variables. For predicting the occurrence of mastectomy flap necrosis, the mastectomy type and the initial inflation volume, but not the antihypertensive medications (compared with no medications), served as independent predictors.

DIEP Flap Reconstruction

Patient- and operation-related variables including BMI, laterality, weight of the elevated flap and inset flap, and number of harvested perforators were similar across the groups. The mean inset ratio, defined as the weight ratio of the inset flap to the harvested flap, differed significantly

TABLE 1 Specific regimens of antihypertensive drugs in ARB and non-ARB groups

	Tissue expander reconstruction *n* (%)	DIEP reconstruction *n* (%)	Overall *n* (%)
Entire cohort	999	391	1390
Antihypertensive medication group	49	30	79
ARB group	36	19	55
ARB only	20 (61.1)	14 (73.7)	34 (61.8)
ARB and CCB	8 (22.2)	5 (26.3)	13 (23.6)
ARB and BB	2 (5.6)	0	2 (3.6)
ARB and diuretics	2 (5.6)	0	2 (3.6)
ARB, CCB and diuretics	4 (11.1)	0	4 (7.2)
Non-ARB group	13	11	24
CCB only	10 (76.9)	10 (90.9)	20 (83.3)
BB only	1 (7.7)	1 (9.1)	2 (8.3)
CCB and diuretics	2 (15.4)	0	1 (8.3)
Control group	950	361	1311

DIEP deep inferior epigastric artery perforator, *ARB* angiotensin receptor blocker, *CCB* calcium-channel blocker, *BB* beta-blocker

TABLE 2 Patient- and operation-related characteristics of the three groups

Variables	Overall	No medication	ARB	Non-ARB	*p* value
Tissue expander reconstruction					
Case no.	999	950	36	13	
Mean age (years)	43.6	43.1	52.6	50.5	< 0.001
Mean BMI (kg/m^2)	22.2	22.0	25.5	22.7	< 0.001
Active smoking: *n* (%)	30 (3.0)	30 (3.2)	0	0	0.450
Diabetes: *n* (%)	9 (0.9)	9 (0.9)	0	0	0.791
Prior radiotherapy: *n* (%)	36 (3.5)	39 (4.1)	1 (2.8)	0	0.702
Prior chemotherapy: *n* (%)	80 (7.7)	47 (4.9)	0	0	0.280
Laterality: *n* (%)					0.044
Unilateral	919 (95.8)	878 (96.1)	28 (87.5)	13 (100.0)	
Bilateral	40 (4.2)	36 (3.9)	4 (12.5)	0	
Type of mastectomy: *n* (%)					0.718
Nipple-sparing	300 (30.0)	283 (29.8)	13 (36.1)	4 (30.8)	
Skin-sparing	699 (70.0)	667 (70.2)	23 (63.9)	9 (69.2)	
Weight of mastectomy specimen (g)	362.8	356.6	517.7	464.7	< 0.001
Size of inserted tissue expander (ml)	393.1	389.7	472.9	425.0	< 0.001
Initial inflation volume (ml)	141.8	142.5	197.8	120.2	0.013
Use of acellular dermal matrix: *n* (%)	566 (54.3)	547 (67.6)	27 (75.0)	7 (53.8)	0.069
DIEP flap reconstruction					
Case no.	391	361	19	11	
Mean age (years)	46.6	46.0	51.6	54.8	< 0.001
Mean BMI (kg/m^2)	23.4	23.3	24.5	24.0	0.101
Active smoking: *n* (%)	9 (2.3)	8 (2.2)	1 (5.3)	0	0.603
Diabetes: *n* (%)	5 (1.4)	5 (1.4)	0	0	0.810
Prior radiotherapy, n (%)	32 (8.2)	31 (8.6)	0	1 (9.1)	0.410
Prior chemotherapy: *n* (%)	72 (18.4)	69 (19.1)	1 (5.3)	2 (18.2)	0.316
Laterality: *n* (%)					0.808
Unilateral	381 (98.7)	351 (98.6)	19 (100.0)	11 (100.0)	
Bilateral	5 (1.3)	5 (1.4)	0	0	
Abdominal scars d/t previous operation: *n* (%)					
Vertical midline scars	34 (8.7)	27 (7.5)	6 (31.6)	1 (9.1)	0.001
Pfannenstiel scars	77 (19.7)	71 (19.7)	4 (21.1)	2 (18.2)	0.981
Type of mastectomy: *n* (%)					0.838
Nipple-sparing	52 (13.3)	48 (13.3)	2 (10.5)	2 (18.2)	
Skin-sparing	339 (86.7)	313 (86.7)	17 (89.5)	9 (81.8)	
Weight of mastectomy specimen (g)	450.4	440.3	415.6	459.7	0.549
Weight of elevated flap (g)	691.2	660.9	788.0	751.3	0.224
Weight of inset flap (g)	468.9	457.6	470.2	511.0	0.445
Inset ratio[a]	0.72	0.72	0.62	0.72	0.032
No. of harvested perforators	3.0	3.1	2.5	3.2	0.161
Bipedicled flap harvest: *n* (%)	87 (22.3)	79 (21.9)	5 (26.3)	3 (27.3)	0.831

ARB angiotensin receptor blocker, *BMI* body mass index, *DIEP* deep inferior epigastric artery perforator

[a]Defined as the weight ratio of the inset flap to the harvested flap

between the groups, with the ratio in the ARB group being the lowest (Table 2).

No significant differences were observed in flap perfusion-related and donor-site complications between the groups. A higher rate of fat necrosis in the transferred flap was observed in the ARB and non-ARB groups than in the no medication group, with marginal significance (Table 3).

In a head-to-head comparison between the ARB-treated and no medication groups, the fat necrosis rate was significantly higher in the ARB group (21.1% vs 8.0%;

TABLE 3 Comparison of complication profiles among the three groups

Complications	Overall *n* (%)	No medication *n* (%)	ARB *n* (%)	Non-ARB *n* (%)	*p* value	Power (1 − *β*)
Tissue expander reconstruction						
Infection	29 (2.9)	27 (2.8)	2 (5.6)	0	0.522	0.16
Seroma	38 (3.8)	33 (3.5)	4 (11.1)	1 (7.7)	0.048	0.59
Hematoma	11 (1.1)	11 (1.2)	0	0	0.751	0.10
Mastectomy flap necrosis	94 (9.4)	88 (9.3)	6 (16.7)	0	0.165	0.38
Wound dehiscence	49 (4.9)	44 (4.6)	4 (11.1)	1 (7.7)	0.188	0.35
Wound revision	62 (6.2)	55 (5.8)	6 (16.7)	1 (7.7)	0.029	0.66
Reoperation	87 (8.7)	77 (8.1)	9 (25.0)	1 (7.7)	0.002	0.90
Reconstruction failure	18 (1.8)	14 (1.5)	4 (11.1)	0	< 0.001	0.98
Overall complication	204 (20.4)	186 (19.6)	16 (44.4)	2 (15.4)	0.001	0.92
DIEP flap reconstruction						
Flap perfusion-related	39 (10.0)	34 (9.4)	4 (21.1)	2 (18.2)	0.157	0.38
Total flap loss	2 (0.5)	2 (0.5)	0	0	0.920	0.06
Partial flap loss	3 (0.8)	3 (0.8)	0	0	0.882	0.07
Fat necrosis	35 (9.0)	29 (8.0)	4 (21.1)	2 (18.2)	0.085	0.50
Donor site-related	39 (10.0)	36 (10.0)	3 (15.8)	0	0.380	0.22
Dehiscence	10 (2.6)	9 (2.5)	1 (5.3)	0	0.653	0.12
Seroma	6 (1.5)	6 (1.7)	0	0	0.776	0.09
Hematoma	4 (1.0)	4 (1.1)	0	0	0.845	0.08
Bulge/hernia	11 (2.8)	10 (2.8)	1 (5.3)	0	0.691	0.11

ARB angiotensin receptor blocker; *DIEP* deep inferior epigastric artery perforator

TABLE 4 Multivariate analyses of predictors for the development of overall complications (using backward selection models)

Variables	*p* value	OR (95% CI)
Antihypertensive medication		
No medication	Reference	Reference
ARB	0.017	2.418 (1.171–4.993)
Non-ARB	0.767	0.793 (0.171–3.673)
Mastectomy type		
NSM	Reference	Reference
Non-NSM	0.001	0.569 (0.404–0.801)
Size of inserted tissue expander	0.074	1.002 (1.000–1.004)
Initial inflation volume	< 0.001	1.004 (1.002–1.006)

OR odds ratio, *CI* confidence interval, *ARB* angiotensin receptor blocker, *NSM* nipple-sparing mastectomy

$p = 0.049$). The patients in the ARB group who received ARB alone and those who received a combination of ARB and other drugs showed similar rates of overall flap perfusion-related complications (21.4% vs 20.0%). Multivariate analyses demonstrated that antihypertensive medication, inset ratio, vertical midline scars, bipedicled flap harvest, and prior irradiation history significantly influenced the development of fat necrosis. The ARB group had approximately six times higher odds of experiencing fat necrosis than the no medication group (Table 5). Administration of non-ARB treatment did not significantly influence the development of fat necrosis. Analysis of the development of overall flap perfusion-related complications also showed that compared with no medication, administration of ARB was an independent risk factor (OR 4.646; 95% CI 1.165–18.290; $p = 0.029$).

DISCUSSION

The current study evaluated the impact of antihypertensive medication on the outcomes of breast reconstruction using tissue-expander and DIEP flaps and demonstrated that administration of ARB was associated with an increased risk for the development of complications. To our knowledge, this is the first clinical study to report the effect of antihypertensive medication on surgical complications in breast reconstruction.

According to a large-scale national person-level study,[9] compared with that of other classes of antihypertensive drugs, the use of ARB increased the most between 2001 and 2010, accounting for more than 20% of all antihypertensive medications in the United States. Accordingly,

TABLE 5 Multivariate analyses of predictors for fat necrosis developed in the transferred DIEP flap

Variables	*p* value	OR (95% CI)
Antihypertensive medication		
No medication	Reference	Reference
ARB	0.014	5.870 (1.439–23.951)
Non-ARB	0.123	3.986 (0.688–23.100)
Inset ratio[a]	< 0.001	713.374 (28.958–17,573.683)
Vertical midline scars	0.004	4.996 (1.667–14.975)
Bipedicled flap harvest	0.003	0.186 (0.062–0.560)
Prior irradiation	0.020	3.916 (1.246–12.310)

DIEP deep inferior epigastric artery perforator, *OR* odds ratio, *CI* confidence interval, *ARB* angiotensin receptor blocker

[a]Defined as the weight ratio of the inset flap to the harvested flap

ARB use could be prevalent and even greater among patients with hypertension who require breast reconstruction. Nonetheless, to date, no consensus exists regarding the potential impact of perioperative use of ARBs. The latest guidelines have posed conflicting recommendations in that the 2014 American College of Cardiology/American Heart Association guidelines suggest perioperative continuation of ARBs,[10] whereas the 2017 Canadian Cardiovascular Society guidelines recommend withholding ARBs from 24 h before non-cardiac surgery.[11]

Angiotensin receptor blockers are selective angiotensin 2 type 1 receptor blockers.[12] Recently, angiotensin 2 has been shown to have a novel role as a growth factor. Binding of angiotensin 2 to angiotensin 2 type 1 receptor induces cell proliferation and angiogenesis.[13–15] Several experimental studies have shown that endogenous production of angiotensin 2 and its receptors is increased at sites of injury[16] and that topical administration of angiotensin 2 accelerates dermal tissue repair.[16,17] In addition, angiotensin 2 has been shown to increase angiogenesis in rat skin and rabbit corneas.[18,19]

Several fundamental studies have reported consistent results that support the aforementioned findings.[18,20] Takeda et al.[18] demonstrated that administration of ARB suppressed wound healing in rat skins by inhibiting re-epithelization, dermal repair, and angiogenesis. Our outcomes showing significantly increased risks of complications among ARB-treated patients can be interpreted as corroborating experimental studies, suggesting that ARB medications might affect postoperative wound healing. However, the development of postoperative complications, including reconstruction failure, is a multifactorial phenomenon. Therefore, further studies are required for definitive conclusions to be drawn.

In breast reconstruction using a DIEP flap, deterioration of angiogenesis from the adjacent soft tissue caused by ARBs might result in decreased blood supply to the marginal soft tissue of flaps, eventually leading to the development of fat necrosis, especially where blood flow is insufficient for tissue survival. Future experimental studies also are warranted to confirm the hypothesis that the anti-angiogenic effects of ARBs contribute to fat necrosis.

It can be argued that the potential adverse effects of hypertension itself might contribute to increasing risks of complications. In fact, hypertension has been regarded as a risk factor for complications after breast reconstruction.[21,22] Underlying atherosclerosis and/or other morbidities including diabetes that frequently accompany hypertension were suggested as potential causes. However, very few patients from our study population had other morbidities. Furthermore, the mean age of the entire cohort was relatively younger, even that of hypertensive patients, than that in the previous reports. Besides, in contrast to the ARB group, the non-ARB group showed rates of complications similar to those observed in the control group in both tissue-expander and DIEP flap reconstructions. The increased risks of complications in the ARB-treated group might be attributable to the adverse effects of the ARB itself, and the effects of hypertension might not have a significant influence on the results.

The findings of the current study and previous experimental studies could raise doubts about the perioperative use of ARB. Clinicians might consider replacing ARB with other classes of antihypertensive medications during the perioperative period to prevent potentially adverse effects of ARB. However, further studies would be necessary to demonstrate validity of these clinical applications.

The current study had several limitations. Although several potential confounders were considered, risks for omission of other variables that can affect the outcomes still exist due to the retrospective study design. For instance, in tissue-expander-based reconstruction, the preoperative breast volume, shape, and ptosis could have influenced the development of complications.[23]

With regard to DIEP flap reconstruction, patient parity or size and spacing of the harvested perforators also could have affected the development of perfusion-related complications, including fat necrosis.[24,25] Besides, potential healthy-user bias also needs to be considered because patients in the no medication group may tend to have a more favorable physiology for wound healing, such as healthy microvascular structure and more vigorous hemodynamic status, than those in the ARB group. However, these factors could not be controlled in the current study. The patients who received ARB alone and those who received a combination of ARB and other drugs were combined into a single ARB group due to the small sample size of each subgroup. This heterogeneous composition could have hindered unbiased analyses for evaluating the effects of ARB medication compared with no medication. However, considering that the complication rates in the two subgroups were similar but higher than in the control and non-ARB groups, the confounding effects of the heterogeneity might have been limited in the current study.

Another limitation was the small sample of patients with hypertension. This could raise an issue about the power of the current study. However, analyses of rates for reoperation, reconstruction failure, and overall complication in the tissue-expander reconstruction group, which were significantly affected by the ARB medication in this study, had a relatively high power (≥ 0.9). Other analyses comparing complication rates among the three groups showed insufficient power. Therefore, substantive conclusions could not be made regarding the latter comparisons. To overcome these limitations, well-controlled prospective, multicenter large-scale studies are warranted.

CONCLUSIONS

Our results suggest that the type of antihypertensive drugs used might influence the postoperative outcomes of breast reconstruction. Careful preoperative consideration of patient comorbidity and associated medications might help to reduce morbidity and achieve optimal results. Despite its several limitations, the current study might provide a useful basis for future clinical studies.

DISCLOSURE There are no conflict of interest.

REFERENCES

1. Heneghan HM, Prichard RS, Lyons R, et al. Quality of life after immediate breast reconstruction and skin-sparing mastectomy: a comparison with patients undergoing breast conserving surgery. *Eur J Surg Oncol*. 2011;37:937–43.
2. Tran BNN, Fadayomi A, Lin SJ, et al. Cost analysis of postmastectomy reconstruction: a comparison of two-staged implant reconstruction using tissue expander and acellular dermal matrix with abdominal based perforator free flaps. *J Surg Oncol*. 2017;116:448–9.
3. Chang DW. Breast reconstruction with microvascular MS-TRAM and DIEP flaps. *Arch Plast Surg*. 2012;39:3–10.
4. Mills KT, Bundy JD, Kelly TN, et al. Global disparities of hypertension prevalence and control: a systematic analysis of population-based studies from 90 countries. *Circulation*. 2016;134:441–50.
5. James PA, Oparil S, Carter BL, et al. 2014 Evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014;311:507–20.
6. Pazoki-Toroudi H, Ajami M, Habibey R, Hajiaboli E, Firooz A. The effect of enalapril on skin flap viability is independent of angiotensin II AT1 receptors. *Ann Plast Surg*. 2009;62:699–702.
7. Criss CN, Gao Y, De Silva G, et al. The effects of losartan on abdominal wall fascial healing. *Hernia*. 2015;19:645–50.
8. Park JW, Mun GH. Comparative analysis of the effect of antihypertensive drugs on the survival of perforator flaps in a rat model. *Microsurgery*. 2018;38:310–17.
9. Gu Q, Burt VL, Dillon CF, Yoon S. Trends in antihypertensive medication use and blood pressure control among United States adults with hypertension: the National Health And Nutrition Examination Survey, 2001 to 2010. *Circulation*. 2012;126:2105–14.
10. Fleisher LA, Fleischmann KE, Auerbach AD, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. Developed in collaboration with the American College of Surgeons, American Society of Anesthesiologists, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Anesthesiologists, and Society of Vascular Medicine Endorsed by the Society of Hospital Medicine. *J Nucl Cardiol*. 2015;22:162–215.
11. Duceppe E, Parlow J, MacDonald P, et al. Canadian Cardiovascular Society guidelines on perioperative cardiac risk assessment and management for patients who undergo noncardiac surgery. *Can J Cardiol*. 2017;33:17–32.
12. Schmieder RE. Mechanisms for the clinical benefits of angiotensin II receptor blockers. *Am J Hypertens*. 2005;18:720–30.
13. Shibasaki Y, Matsubara H, Nozawa Y, et al. Angiotensin II type 2 receptor inhibits epidermal growth factor receptor transactivation by increasing association of SHP-1 tyrosine phosphatase. *Hypertension*. 2001;38:367–72.
14. Murasawa S, Mori Y, Nozawa Y, et al. Angiotensin II type 1 receptor-induced extracellular signal-regulated protein kinase activation is mediated by Ca2 +/calmodulin-dependent transactivation of epidermal growth factor receptor. *Circ Res*. 1998;82:1338–48.
15. Eguchi S, Numaguchi K, Iwasaki H, et al. Calcium-dependent epidermal growth factor receptor transactivation mediates the angiotensin II-induced mitogen-activated protein kinase activation in vascular smooth muscle cells. *J Biol Chem*. 1998;273:8890–6.
16. Rodgers K, Abiko M, Girgis W, St Amand K, Campeau J, diZerega G. Acceleration of dermal tissue repair by angiotensin II. *Wound Repair Regen*. 1997;5:175–83.
17. Rodgers K, Xiong S, Felix J, et al. Development of angiotensin (1–7) as an agent to accelerate dermal repair. *Wound Repair Regen*. 2001;9:238–47.
18. Takeda H, Katagata Y, Hozumi Y, Kondo S. Effects of angiotensin II receptor signaling during skin wound healing. *Am J Pathol*. 2004;165:1653–62.

19. Fernandez LA, Twickler J, Mead A. Neovascularization produced by angiotensin II. *J Lab Clin Med*. 1985;105:141–5.
20. Biondo-Simoes Mde L, Zazula AD, Gomes AB, Poncio C, Torres LF, Borsato KS. Influence of arterial hypertension treated with losartan on skin healing in rats. *Acta Cir Bras*. 2006;21:144–50.
21. Fischer JP, Nelson JA, Serletti JM, Wu LC. Perioperative risk factors associated with early tissue expander (TE) loss following immediate breast reconstruction (IBR): a review of 9305 patients from the 2005–2010 ACS-NSQIP datasets. *J Plast Reconstr Aesthet Surg*. 2013;66:1504–12.
22. Gill PS, Hunt JP, Guerra AB, et al. A 10-year retrospective review of 758 DIEP flaps for breast reconstruction. *Plast Reconstr Surg*. 2004;113:1153–60.
23. Santanelli F, Longo B, Sorotos M, Farcomeni A, Paolini G. Flap survival of skin-sparing mastectomy type IV: a retrospective cohort study of 75 consecutive cases. *Ann Surg Oncol*. 2013;20:981–9.
24. Lee KT, Eom Y, Jeon BJ, Mun GH. Vertical spacing of perforators in deep inferior epigastric perforator flap breast reconstruction can affect the outcomes. *Plast Reconstr Surg*. 2018;142:319–29.
25. Santanelli F, Longo B, Cagli B, Pugliese P, Sorotos M, Paolini G. Predictive and protective factors for partial necrosis in DIEP flap breast reconstruction: does nulliparity bias flap viability? *Ann Plast Surg*. 2015;74:47–51.