unfavorable association was consistent across clinical settings and was more pronounced as the indications for IABP use became less established.

Several limitations need to be acknowledged. Because of the observational design, we cannot assume a causal relationship between IABP use and mortality. Despite rigorous risk adjustment, the possibility of confounding by unmeasured covariates remains. However, the consistency of the association between IABP use and mortality in various subgroups is notable. Our registry does not capture reasons for IABP insertion. Some physicians or patients may have declined IABP based on institutional or personal preferences.

Using a contemporary multicenter Japanese PCI registry, we have shown a negative association between IABP use and mortality. Our findings are consistent with the meta-analysis by Ahmad et al[1] and suggest that it is time to reconsider the appropriate use of IABP therapy, a potentially life-saving but extremely costly and high-risk intervention for patients.

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Study concept and design: Inohara, Kohsaka.
Acquisition, analysis, or interpretation of data: All authors.
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Statistical analysis: Inohara, Miyata.
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Invited Commentary | LESS IS MORE

Is Increased Use of Mechanical Circulatory Support Devices Justified? A Cause for Concern

There has been a significant increase in the use of mechanical circulatory support devices in recent years.[1] This increase has been largely due to the availability of several new percutaneous ventricular assist devices (PVADs). Khera et al[1] documented in this journal a 30-fold increase in the use of PVADs based on National Inpatient Sample data from 2007 through 2012. In this issue of *JAMA Internal Medicine*, Inohara et al[2] identify frequent use of the intra-aortic balloon pump (IABP) in Japan among patients with guideline-based indications and other less established indications. However, increased implantation of IABPs or PVADs is not supported by any evidence of clinical benefit or by professional guidelines.

Related article page 1980

Both Khera et al[1] and Inohara et al[2] demonstrate that the use of mechanical circulatory support devices is associated with increased mortality. The latter is an observational study[2] from a multicenter Japanese registry of 13 253 patients undergoing angioplasty for various indications, with substantial heterogeneity among subgroups of the patients. Similar to some previous reports, the study by Inohara et al[2] also showed that the use of IABPs is associated with higher in-hospital mortality overall and among various subgroups, including those with less severe disease. These data are consistent with several randomized clinical trials that have not shown benefit from IABP implantation. For example, IABP use has been found to have no survival benefit in patients with myocardial infarction-related heart failure or shock who receive thrombolysis or angioplasty.[3] In hemodynamically stable patients undergoing high-risk angioplasty, there was no demonstrable difference in clinical outcomes or infarct size associated with the use of IABPs.[4] A recent meta-analysis by Ahmad et al[5] summarized data from major clinical trials and observational studies and concluded that IABP use did not improve mortality after myocardial infarction in patients with or without cardiogenic shock. Furthermore, IABP outcomes in those observational studies were better compared with controls only among lower-risk patients, questioning whether IABP use was ever indicated in those patients.[5]

With increasing evidence showing no benefit in hard outcomes, enthusiasm for IABP use in guidelines seems to be waning. Recent European Society of Cardiology guidelines[6] recommend against regular use of IABPs in patients with cardiogenic shock (class III). The guidelines also cite no mortality benefit of PVADs over IABPs in these patients and provide no definite

recommendation for their use. Despite the lack of guideline-based recommendations and little evidence to support IABP use, the study by Inohara et al[2] finds that IABPs continue to be used frequently and that their use is associated with increased in-hospital mortality.

Although there has been enthusiasm about newer PVADs (eg, Impella LP2.5 [Abiomed Europe GmbH] and TandemHeart [Cardiac Assist]), initial studies regarding their use to treat cardiogenic shock have not shown any significant survival benefit compared with IABPs and observed increased bleeding and a tendency toward more limb ischemia from the use of larger sheaths with PVADs.[7] Similar to IABPs, no net benefit was demonstrated in hemodynamically stable patients with an implanted PVAD undergoing high-risk angioplasty, another common clinical scenario for the use of PVADs.[8]

Why is there reluctance to abandon these invasive, expensive, and seemingly ineffective therapies? The answer might be multifactorial. Cardiogenic shock complicating myocardial infarction remains a formidable foe and is associated with 40% to 50% in-hospital mortality.[9] In this setting, only early revascularization has shown improved survival. In some of these critically ill patients, it may seem reasonable to use mechanical circulatory support devices as salvage therapy. However, they offer little benefit in reducing clinical events, and have high costs and significant complication rates. Inohara et al[2] confirm previous findings that IABPs and PVADs are being increasingly used in patients without indications for their use. Although the precise reasons for such excessive use remain to be established, misaligned financial incentives might have a role. Furthermore, continued use of IABPs may be due to established routines or treatment protocols, with commission bias tending toward action rather than inaction.[10]

Based on available data, the use of these invasive and expensive mechanical circulatory support devices should be critically appraised and limited because of significant complication rates associated with their use and a lack of evidence demonstrating any benefit. In the use of IABPs and PVADs, it seems appropriate to conclude that perhaps less is more.

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Disparities in Time Spent Seeking Medical Care in the United States

The Institute of Medicine identifies timeliness of care as a key aspect of quality. Racial and socioeconomic disparities exist in receipt of timely appointments and interventions.[1]

Editor's Note page 1986

Patient time burden (ie, time spent traveling to, waiting for, and receiving ambulatory medical care) is a separate domain of timeliness. Disparities in this domain have received less attention, although prior work has described inequalities in pediatric emergency department wait time[2] and racial disparities in the time adults spend seeking medical care.[3] In prior work, using survey data on time associated with medical visits, we estimated that patients incurred $52 billion in opportunity costs obtaining medical care in 2010.[4] In this article, we assessed how time associated with medical visits varied across socioeconomic variables and visit characteristics.

Methods | The American Time Use Survey data from 2005 to 2013 includes coded single-day 24-hour time diaries for 108 486 respondents 18 years and older.[5] We identified respondents reporting *clinic time*, or time waiting for or obtaining medical care, on their interview day. We excluded respondents reporting more than 6 hours of clinic time as extreme outliers (n = 99), and we also excluded respondents receiving care for multiple individuals on their interview day (n = 101). For the remaining respondents with clinic time (n = 3787), we determined associated *travel time*, or time spent traveling for care, and *total time*, or the sum of clinic time and travel time. We compared these time estimates with *face-to-face time*, or time spent with a physician, collected from 2006 to 2010 by the National Ambulatory Medical Care Survey, a nationally representative survey of office-based physician visits (n = 150 022).

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Changes in tumor expression of HER2 and hormone receptors status after neoadjuvant chemotherapy in 21 755 patients from the Japanese breast cancer registry

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Background: We investigate rates of pathologic complete response (pCR) and tumor expression of ER, PgR, HER2 discordance after neoadjuvant chemotherapy using Japanese breast cancer registry data.

Patients and methods: Records of more than 300 000 breast cancer cases treated at 800 hospitals from 2004 to 2013 were retrieved from the breast cancer registry. After data cleanup, we included 21 755 patients who received neoadjuvant chemotherapy and had no distant metastases. pCR was defined as no invasive tumor in the breast detected during surgery after neoadjuvant chemotherapy. HER2 overexpression was determined immunohistochemically and/or using fluorescence *in situ* hybridization.

Results: pCR was achieved in 5.7% of luminal tumors ($n = 8730$), 24.6% of HER2-positive tumors ($n = 4403$), and 18.9% of triple-negative tumors ($n = 3660$). Among HER2-positive tumors, pCR was achieved in 31.6% of ER-negative tumors ($n = 2252$), 17.0% of ER-positive ones ($n = 2132$), 31.4% of patients who received trastuzumab as neoadjuvant chemotherapy ($n = 2437$), and 16.2% of patients who did not receive trastuzumab ($n = 1966$). Of the 2811 patients who were HER2-positive before treatment, 601 (21.4%) had HER2-negative tumors after neoadjuvant chemotherapy, whereas 340 (3.4%) of the 9947 patients with HER2-negative tumors before treatment had HER2-positive tumors afterward. Of the 10 973 patients with ER-positive tumors before treatment, 499 (4.6%) had ER-negative tumors after neoadjuvant chemotherapy, whereas 519 (9.3%) of the 5607 patients who were ER-negative before treatment had ER-positive tumors afterward.

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Conclusion: We confirmed that loss of HER2-positive status can occur after neoadjuvant treatment in patients with primary HER2-positive breast cancer. We also confirmed that in practice, differences in pCR rates between breast cancer subtypes are the same as in clinical trials. Our data strongly support the need for retest ER, PgR, HER2 of surgical sample after neoadjuvant therapy in order to accurately determine appropriate use of targeted therapy.

Key words: breast cancer, chemotherapy, HER2, *in situ* hybridization, neoadjuvant therapy

introduction

In breast cancer patients, neoadjuvant chemotherapy (i.e. presurgical systemic chemotherapy) is associated with rates of disease-free survival and overall survival comparable with those for adjuvant (post-surgical) chemotherapy [1]. It is standard in locally advanced and operable breast cancer, being intended to shrink the tumor and improve the chance for breast-conserving surgery [2]. Pathologic complete response (pCR) is the best predictor of patient outcome after neoadjuvant chemotherapy [2–4]; it is generally defined as the absence of residual invasive cancer in the breast [5]. Clinical trials have found that different breast cancer subtypes have different rates of pCR and that patients who show pCR have a different prognosis in each subtype. However, in an attempt to improve pCR, clinical trial investigators may use more frequent or standard doses of chemotherapeutic agents than would be used in a routine clinical setting.

The *HER2/neu* gene is amplified in 10%–20% of primary breast cancer cases. In HER2-positive patients, HER2-targeting therapies such as neoadjuvant trastuzumab result in better rates of pCR than non-HER2-targeting therapies [6, 7], as might be expected, HER2-positive patients who show pCR have a better prognosis than those who do not. In the latter, HER2 status may be discordant between the primary breast tumor and those remaining after chemotherapy [8–12]. Some studies suggest that trastuzumab in particular can convert disease status from HER2-positive in a primary tumor to HER2-negative in residual tumors [13–15]. Mittendorf et al. found that according to fluorescence *in situ* hybridization (FISH) analysis, approximately one-third of their patients with sufficient residual disease to warrant repeat HER2 testing had lost *HER2* gene amplification. Furthermore, patients who have lost *HER2* gene amplification have significantly lower relapse-free survival than those whose tumors retain *HER2* gene amplification [15]. Patients with such HER2 status discordance between primary tumors and residual or metastatic ones may also have shorter survival than those without [15, 16]. However, the prevalence of such discordance in patients who have undergone neoadjuvant chemotherapy has not been conclusively established, and it is unclear if trastuzumab increases its likelihood; if so, the treatment may not be suitable for such patients. Using data from the Japanese national breast cancer registry, we aimed to investigate pCR and discordance rates after neoadjuvant chemotherapy in relation to positivity for estrogen receptor (ER), progesterone receptor (PgR), and HER2.

materials and methods

data collection

The Breast Cancer Registry (BCR) in Japan's National Clinical Database (NCD) contains records on more than 300 000 cases of breast cancer from more than 800 hospitals. Affiliated institutes voluntarily provide the BCR with data on newly diagnosed primary breast cancer patients through a Web-based system, covering more than 50 demographic and clinicopathological categories. TNM classification is registered according to the 6th edition of the Unio Internationalis Contra Cancrum (UICC) staging system [17].

The BCR was originally maintained by the Registration Committee of the Japanese Breast Cancer Society (JBCS) and supported by the Public Health Research Foundation (Tokyo). Until 2012, annual reports on this registry were published in Japanese and made accessible to active JBCS members through the JBCS homepage (http://www.jbcs.gr.jp/Member/tourokusyukei.html). Since 2012, this dataset has been part of the NCD, a nationwide project managed in cooperation with the certification board of the Japan Surgical Society [18]. For the year 2011 alone, data from more than 1.2 million surgical cases were collected from more than 3500 hospitals. The NCD is continuously updated by the data management departments of participating institutions and is evaluated annually using a Web-based data management system to ensure data traceability. All variables, definitions, and inclusion criteria for the NCD are accessible to participating institutions on its web site (http://www.ncd.or.jp); the database administrators also provide e-learning systems to teach participants how to input data consistently [18]. The administrators answer all inquiries regarding data entry, having taken ~80 000 inquiries in 2011, and a list of frequently asked questions is displayed on the web site.

For our study, we used the BCR to review 238 840 breast cancer cases treated between 2004 and 2011 and selected 21 755 patients who received neoadjuvant chemotherapy and had no distant metastases (Figure 1). Male patients, those with bilateral tumors, those who did not undergo surgery, and those with tumor stages of Tis or T0, were excluded. pCR was defined as no invasive tumor in the breast found during surgery after neoadjuvant chemotherapy. HER2 overexpression was defined as immunohistochemically 3+ and/or a positive FISH result. Hormone receptor positivity (ER or PgR positivity) was diagnosed if at least 1% of nuclei in the tumor were stained on immunohistochemical tests for ER or PgR. Immunohistochemical tests for ER, PgR, and HER on core biopsies were carried out before neoadjuvant therapy. Cases were categorized on the basis of their immunohistochemical status as follows: luminal (ER+ and HER2−); HER2-overexpressing (HER2+, regardless of ER status); and triple-negative (ER− and HER2−).

statistical analysis

The median and standard deviations were calculated for age at diagnosis. Associations between clinical categorical variables and HER2 status were analyzed using Pearson's χ^2. Fisher's exact test was also used to determine differences between patients who showed HER2 status discordance and those who did not. All analyses were carried out using SAS 9.3 (SAS Institute, Cary, NC).

results

A total of 21 755 patients who received neoadjuvant chemotherapy and developed no distant metastases were listed in Table 1. More than 80% of patients had a tumor of stage T2 or worse, and more than 60% were node-positive. Almost 70% received anthracyclines and taxanes as neoadjuvant chemotherapy.

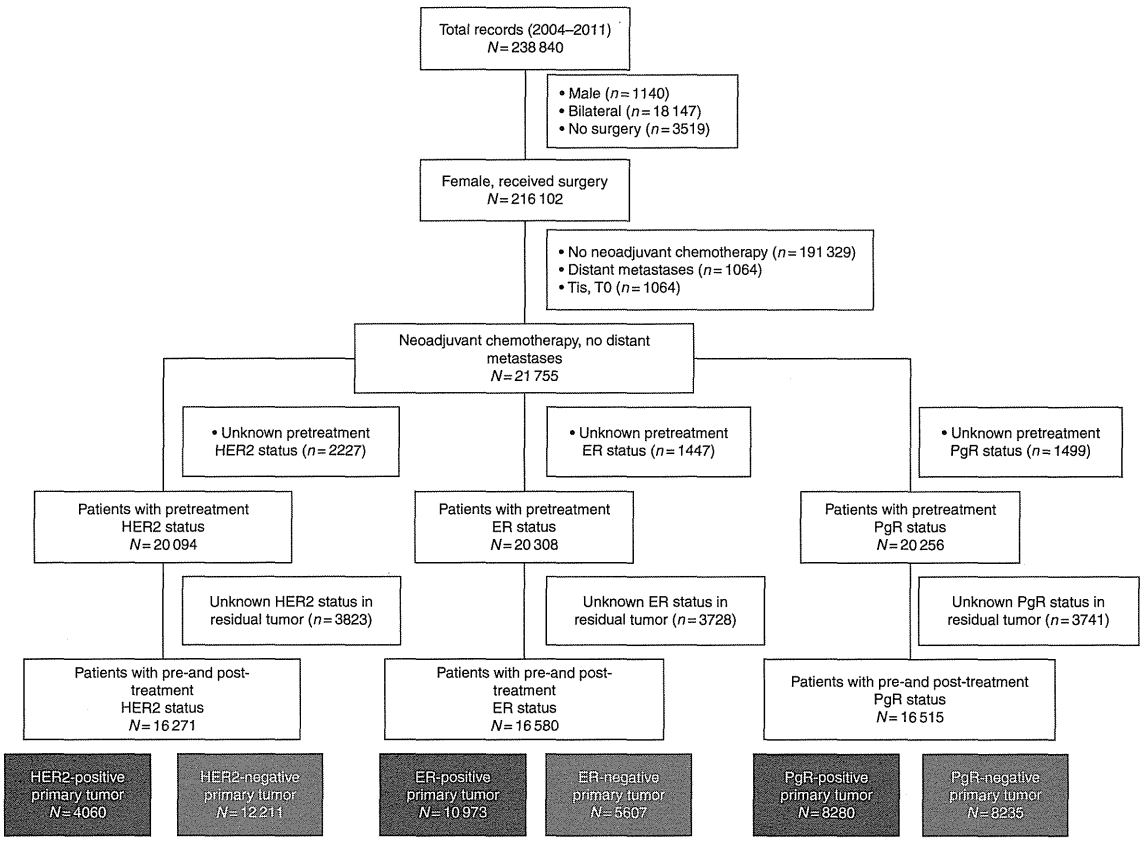

Figure 1. *Study flow.*

rate of pCR

The rate of pCR was 5.7% for luminal cancer ($n = 8730$), 24.6% for HER2-positive ($n = 4403$), and 18.9% for triple-negative ($n = 3660$) (Figure 2). Thus, HER2-overexpressing tumors had a higher rate of pCR than triple-negative or luminal ones; however, within this category, the rate was 31.6% for ER-negative tumors ($n = 2252$), 17.0% for ER-positive ones ($n = 2132$), 31.4% for those who received trastuzumab as neoadjuvant chemotherapy ($n = 2437$), and 16.2% for those who did not receive trastuzumab ($n = 1966$) (Figure 2). In addition, HER2-positive patients who were ER-negative had a higher rate of pCR than those who were ER-positive ($P < 0.0001$), and those treated with trastuzumab had a higher rate of pCR than those not so treated ($P < 0.0001$).

rate of discordance after chemotherapy

Of the 2811 patients who were HER2-positive before treatment, 601 (21.4%) had tumors that showed HER2 negativity after neoadjuvant chemotherapy, whereas only 340 (3.4%) of the 9947 patients with HER2-negative pretreatment tumors developed HER2-positive tumors after neoadjuvant chemotherapy (Table 2). According to immunohistochemical testing, 499 (20.4%) of the 2447 patients with HER2-positive tumors lost HER2 positivity after neoadjuvant chemotherapy; with FISH, the rate was 8.4% (17/203). Of 342 patients whose tumors converted from HER2-positive to HER2-negative, who received neoadjuvant trastuzumab, 96 (28%) did not receive adjuvant trastuzumab therapy. Conversely, of 340 patients whose tumors converted from HER2-negative to HER2-positive, 206 (60%) received adjuvant trastuzumab therapy.

Of the 10 973 patients with ER-positive tumors before treatment, 499 (4.6%) had ER-negative tumors after neoadjuvant chemotherapy, whereas 519 (9.3%) of the 5607 patients with ER-negative tumors before treatment had ER-positive ones after neoadjuvant chemotherapy. Of the 499 patients whose tumors converted from ER-positive to ER-negative, 280 (56%) did not receive adjuvant endocrine therapy. Conversely, of 519 patients whose tumors converted from ER-negative to ER-positive, 333 (64%) received adjuvant endocrine therapy.

Of the 8280 patients with PgR-positive tumors before treatment, 1545 (18.7%) had PgR-negative ones after neoadjuvant chemotherapy, whereas 766 (9.3%) of the 8235 patients with PgR-negative tumors before treatment had PgR-positive tumors after neoadjuvant chemotherapy (Table 3).

clinicopathologic features associated with discordance

We evaluated HER2 concordance and discordance rates in relation to various clinical factors (Table 4). There were statistically significant differences in HER2 discordance rates between patients

Table 1. Patients Characteristic

		With pretreatment HER2 status ($n = 20\,094$)				With pretreatment ER status ($n = 20\,308$)				With pretreatment PgR status ($n = 20\,256$)			
		Positive ($n = 5535$)		Negative ($n = 14\,559$)		Positive ($n = 12\,938$)		Negative ($n = 7370$)		Positive ($n = 9720$)		Negative ($n = 10\,536$)	
		n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Age	Median		54		51		51		55		49		55
Menopausal status													
	Premenopausal	2079	37.6	6928	47.6	6429	49.7	2679	36.4	5302	54.6	3779	35.9
	Post-menopausal	3289	59.4	7260	49.9	6183	47.8	4468	60.6	4152	42.7	6472	61.4
	Unknown	167	3.0	371	2.6	326	2.5	223	3.0	266	2.7	285	2.7
T stage													
	T1	587	10.6	1772	12.2	1578	12.2	804	10.9	1222	12.6	1157	11.0
	T2	3197	57.8	8288	56.9	7472	57.8	4112	55.8	5673	58.4	5876	55.8
	T3	893	16.1	2071	14.2	1837	14.2	1173	15.9	1346	13.9	1660	15.8
	T4	858	15.5	2428	16.7	2051	15.9	1281	17.4	1479	15.2	1843	17.5
N stage													
	N0	1725	31.2	4793	32.9	4304	33.3	2288	31.0	3353	34.5	3217	30.5
	N1	2807	50.7	7513	51.6	6805	52.6	3631	49.3	5116	52.6	5296	50.3
	N2	582	10.5	1356	9.3	1100	8.5	849	11.5	779	8.0	1169	11.1
	N3	411	7.4	859	5.9	699	5.4	583	7.9	452	4.7	825	7.8
	Unknown	10	0.2	38	0.3	30	0.2	19	0.3	20	0.2	29	0.3
Neoadjuvant chemotherapy													
	CMF alone	2	0.0	12	0.1	9	0.1	5	0.1	7	0.1	7	0.1
	Anthracycline regimen alone	547	9.9	1765	12.1	1502	11.6	851	11.6	1106	11.4	1235	11.7
	TC alone	81	1.5	265	1.8	265	2.1	82	1.1	219	2.3	127	1.2
	Taxane alone	532	9.6	586	4.0	634	4.9	510	6.9	464	4.8	681	6.5
	Anthracycline regimen and taxane	3891	70.3	10 191	70.0	9118	70.5	5097	69.2	6856	70.5	7316	69.4
	Others	482	8.71	1740	11.95	1410	10.90	825	11.19	1068	10.99	1170	11.10

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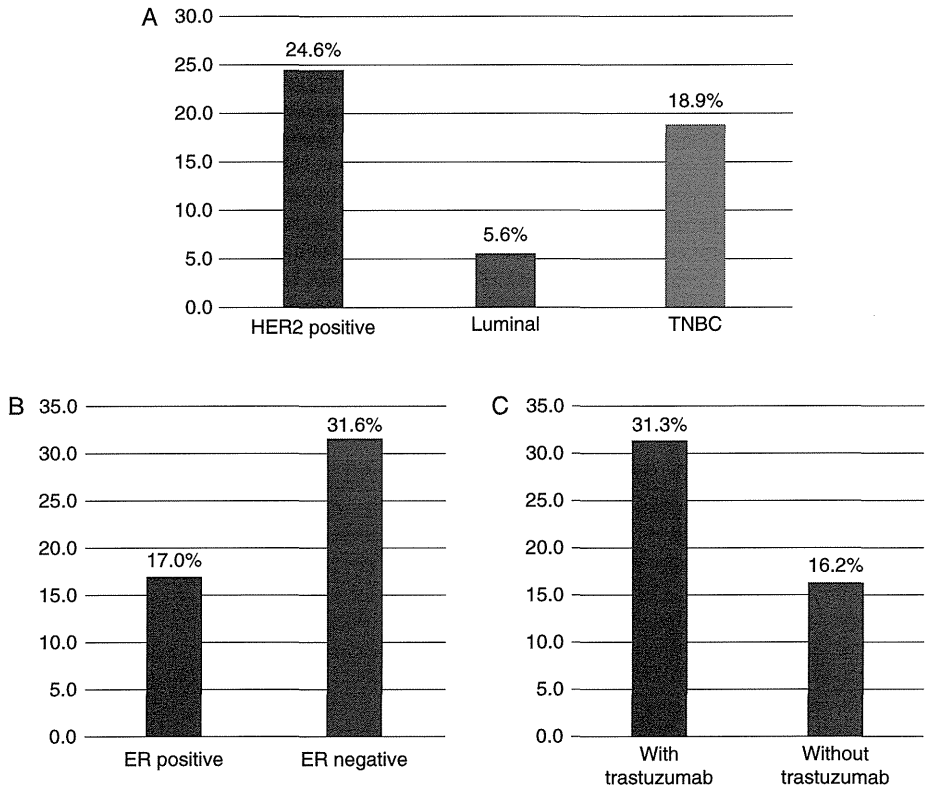

Figure 2. Rates of pathologic complete in response by (A) subtype (HER2-positive, luminal, triple-negative), (B) ER status (for HER2-positive tumors), and (C) treatment with trastuzumab as neoadjuvant therapy (HER2-positive tumors).

Table 2. Change in HER2 status of the primary tumor after neoadjuvant therapy

Primary tumor		Residual tumor	
HER2 status	n	HER2 status	n
Positive	2811	Positive	2210 (78.6%)
		Negative	601 (21.4%)
Negative	9947	Positive	340 (3.4%)
		Negative	9607 (96.6%)
Immunohistochemical analysis			
HER2 3+	2447	HER2 3+	1948 (79.6%)
		HER2 2+	203 (8.3%)
		HER2 1+	163 (6.6%)
		HER2 0	133 (5.4%)
HER2 2+	2077	HER2 3+	128 (6.2%)
		HER2 0, 1+, 2+	1949 (93.8%)
HER2 1+	3741	HER2 3+	68 (1.8%)
		HER2 0, 1+, 2+	3673 (98.2%)
HER2 0	4196	HER2 3+	45 (1.1%)
		HER2 0, 1+, 2+	4151 (98.9%)
FISH analysis			
Positive	203	Positive	186 (91.6%)
		Negative	17 (8.4%)
Negative	572	Positive	28 (4.9%)
		Negative	544 (95.1%)

who received trastuzumab and those who did not ($P < 0.0001$). Of the 1385 patients who received trastuzumab as neoadjuvant therapy, 342 (24.7%) showed HER2 discordance. Similarly, of the 1426 patients who did not receive trastuzumab as neoadjuvant therapy, 259 (18.2%) showed HER2 discordance. Furthermore, there were statistically significant differences in discordance rates in relation to pretreatment ER status ($P < 0.0001$) and PgR status ($P < 0.0001$). In contrast, there were no statistically significant differences in HER2 discordance rates between premenopausal and menopausal women ($P = 0.440$) or among patients with residual tumors of different volumes ($P = 0.345$).

discussion

To the best of our knowledge, we use largest dataset to compare tumor expression of ER, PgR, HER2 discordance after neoadjuvant chemotherapy. Our pCR rates, obtained in a setting of clinical practice, were lower than those reported in clinical trials. One reason may be that in our study, almost 70% of patients were treated with anthracyclines and taxanes, whereas in clinical trials with a focus on pCR, investigators often test new agents and higher doses, patients in the real world have higher age, and poor performance status than in clinical trials. Another may be that 44% of HER-positive patients did not receive trastuzumab as neoadjuvant therapy; it was not until 2008 that trastuzumab was approved as an adjuvant therapy by the Ministry of Health, Labour and Welfare in Japan. However, differences in pCR rates in our study with regard to cancer subtype and trastuzumab treatment were similar to those reported in clinical trials. For

instance, patients with luminal tumors had lower pCR rates than those with HER2-positive or triple-negative tumors. Among HER2-positive tumors, tumors negative for hormonal receptors had higher pCR rates after neoadjuvant chemotherapy than those positive for hormonal receptors. HER2-positive, tumors that are negative for hormonal receptors are highly dependent on the *HER2* gene and respond well to therapies targeted against HER2 such as trastuzumab and pertuzumab [19]. As might be expected, HER2-positive, ER-negative patients who show pCR have better prognosis than those who do not [3, 4]. A previous study found that the use of trastuzumab as a neoadjuvant increased pCR rate (43% with trastuzumab, 26% without) in HER2-positive cancer [6]. Our data also showed this.

Table 3. Change in ER and PgR status of the primary tumor after neoadjuvant therapy

Primary tumor		Residual tumor	
ER status	*n*	ER status	*n*
Positive	10 973	Positive	10 474 (95.5%)
		Negative	499 (4.5%)
Negative	5607	Positive	519 (9.3%)
		Negative	5088 (90.7%)
PgR status			
Positive	8280	Positive	6735 (81.3%)
		Negative	1545 (18.7%)
Negative	8235	Positive	766 (9.3%)
		Negative	7469 (90.7%)

Our results also showed that HER2 status does not necessarily carry over between the original tumor and residual tumors. In 21.4% of HER2-positive patients, the tumor converted to HER2-negative; further, according to immunohistochemistry, 635 (17.9%) of the 3548 patients with HER2-positive tumors before neoadjuvant chemotherapy had HER2-negative tumors afterward. However, inconsistencies in immunohistochemical testing, for example, in antigen retrieval methods, fixation, and observer analysis, may affect the results [20]. Another study [14, 15] using FISH found a loss of HER2 amplification in paired pre- and post-treatment specimens from patients treated with neoadjuvant trastuzumab. FISH data are more easily reproducible than immunohistochemical data [21, 22], and in our study, although the sample size for FISH analysis was small, FISH data were less likely to show discordance than immunohistochemical data.

We previously reported that trastuzumab therapy is not associated with an increased chance of loss of HER2 positivity in metastases, whereas chemotherapy is associated with an increase in the loss of such positivity [16]. Likewise, in a previous study of patients with residual disease treated with either chemotherapy alone or chemotherapy plus an anti-HER2 agent, HER2 expression loss was observed in 40% of the former group and 14.7% of the latter group [23]. We demonstrated that trastuzumab therapy is associated with increased odds of loss of HER2 positivity in residual tumors.

Nevertheless, it is unclear whether loss of HER2 amplification reflects response to therapy or a resistance mechanism and

Table 4. Discordance rates by clinical factors

	Post-treatment HER2 status ($N = 2811$)				*P*-value
	Negative (discordance)		Positive (concordance)		
	n	%	*n*	%	Pearson's χ^2
Pretreatment ER status					
Negative	169	13.0	1130	87.0	<0.0001
Positive	427	28.4	1075	71.6	
Pretreatment PgR status					
Negative	263	14.9	1501	85.1	<0.0001
Positive	330	32.0	701	68.0	
Menopausal status					
Pre	245	22.5	846	77.5	0.4626
Post	337	20.6	1301	79.4	
Unknown	19	23.2	63	76.8	
Neoadjuvant trastuzumab					
No	259	18.2	1167	81.8	<0.0001
Yes	342	24.7	1043	75.3	
Volume of residual tumor					
<50%	265	22.3	923	77.7	0.3436
>50%	313	20.8	1192	79.2	
Year of registration					
2004–2007	159	18.95	680	81.05	0.0405
2008–2011	442	22.41	1530	77.59	
Surgical cases at institution					
>100 cases/year	277	19.74	1126	80.26	0.0346
<100 cases/year	324	23.01	1084	76.99	

Volume of residual tumor: size of residual tumor divided by size of primary tumor.

whether chemotherapy can promote clonal selection of *HER2/neu*-amplified cancers. In our study, 28% of patients whose cancer lost HER2 expression after neoadjuvant therapy did not receive trastuzumab, and 60% patients whose cancer developed HER2 expression after therapy did receive it. Possible explanations include true biological change, treatment-induced clonal selection, pre-analytical and analytical pitfalls, sampling errors, and tumor heterogeneity [24]. It is unclear if patients with HER2-negative tumors after neoadjuvant chemotherapy should receive anti-HER2 treatment, as sampling by core needle biopsy in pretreatment settings may not be representative of the character of the whole tumor. If the core needle biopsy proves to be a false positive, discontinuing the drug will avoid risking unnecessary treatment after loss of HER2 amplification after neoadjuvant therapy. However, if the core needle biopsy gives a false-negative result, anti-HER2 treatment should be started as soon as post-therapy HER2 amplification is detected.

We acknowledge several important limitations of this study. First, this study is retrospective, incurring the possibility of selection bias and precluding the determination of causal relationships. However, Japanese BCR data cover more than 50% of patients diagnosed with breast cancer in Japan [25], and therefore, we do not feel that this possibility would have substantially affected our findings. Secondly, our data were obtained through a web database, with no centralized reassessment of ER, PgR or HER2 status. Thirdly, several studies reported discordance ER, PgR, HER2 status between core needle biopsy, and resection specimens without neoadjuvant chemotherapy [26]. Finally, our registry data did not include sufficient survival data to fully analyze the effects of pCR and tumor expression discordance on survival. However, the strength of our study is that it draws from more than 20 000 patients treated with neoadjuvant chemotherapy in a 'real-world' setting.

In conclusion, our findings demonstrate that although pCR rates in the real world have the same differences with regard to subtypes and trastuzumab treatment that are seen in clinical trials, they are also lower than those in clinical trials. Further, we have shown that HER2 status does not always carry over from the original tumor to residual tumors. In our study, more than 20% of patients with residual tumors after neoadjuvant therapy showed loss of HER2 expression. Our data strongly support the need for retest ER, PgR, HER2 of surgical sample after neoadjuvant therapy in order to accurately determine appropriate use of targeted therapy. Additional research should be conducted on biology and treatment in breast cancer patients whose tumors lose HER2 expression after neoadjuvant chemotherapy.

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disclosure

The authors have declared no conflicts of interest.

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Prospective phase II trial of trabectedin in BRCA-mutated and/or BRCAness phenotype recurrent ovarian cancer patients: the MITO 15 trial

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Background: Current evidence suggest that trabectedin is particularly effective in cells lacking functional homologous recombination repair mechanisms. A prospective phase II trial was designed to evaluate the activity of trabectedin in the treatment of recurrent ovarian cancer patients presenting BRCA mutation and/or BRCAness phenotype.

Patients and methods: A total of 100 patients with recurrent *BRCA*-mutated ovarian cancer and/or BRCAness phenotype (≥2 previous responses to platinum) were treated with trabectedin 1.3 mg/mq i.v. q 3 weeks. The activity of the drug with respect to BRCA mutational status and to a series of polymorphisms [single-nucleotide polymorphisms (SNPs)] involved in DNA gene repair was analyzed.

Results: Ninety-four were evaluable for response; in the whole population, 4 complete and 33 partial responses were registered for an overall response rate (ORR) of 39.4. In the platinum-resistant (PR) and -sensitive (PS) population, an ORR of 31.2% and 47.8%, and an overall clinical benefit of 54.2% and 73.9%, respectively, were registered. In the whole series, the median progression-free survival (PFS) was 18 weeks and the median overall survival (OS) was 72 weeks; PS patients showed a more favorable PFS and OS compared with PR patients. BRCA gene mutational status was available in 69 patients. There was no difference in ORR, PFS and OS according to BRCA 1–2 status nor any association between SNPs of genes involved in DNA repair and NER machinery and response to trabectedin was reported.

Conclusions: Our data prospectively confirmed that the signature of 'repeated platinum sensitivity' identifies patients highly responsive to trabectedin. In this setting, the activity of trabectedin seems comparable to what could be obtained using platinum compounds and the drug may represent a valuable alternative option in patients who present

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CRITICAL CARE MEDICINE

Effects of Preoperative β-Blocker Use on Clinical Outcomes after Coronary Artery Bypass Grafting

A Report from the Japanese Cardiovascular Surgery Database

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ABSTRACT

Background: The authors evaluated the effect of preoperative β-blocker use on early outcomes in patients undergoing coronary artery bypass grafting (CABG) in Japan.

Methods: The authors analyzed 34,980 cases of isolated CABGs, performed between 2008 and 2011, at the 333 sites recorded in the Japanese Cardiovascular Surgical Database. In addition to the use of multivariate models, a one-to-one matched analysis, based on estimated propensity scores for patients with or without preoperative β-blocker use, was performed.

Results: The study population (mean age, 68 yr) comprised 20% women, and β-blockers were used in 10,496 patients (30%), who were more likely to have risk factors and comorbidities than patients in whom β-blockers were not used. In the β-blocker and non-β-blocker groups, the crude in-hospital mortality rate was 1.7 *versus* 2.5%, whereas the composite complication rate was 9.7 *versus* 11.6%, respectively. However, after adjustment, preoperative β-blocker use was not a predictor of in-hospital mortality (odds ratio, 1.00; 95% CI, 0.82 to 1.21) or complications (odds ratio, 0.99; 95% CI, 0.91 to 1.08). When the outcomes of the two propensity-matched patient groups were compared, differences were not seen in the 30-day operative mortality (1.6 *vs.* 1.5%, respectively; $P = 0.49$) or postoperative complication (9.8 *vs.* 9.7%; $P = 1.00$) rates. The main findings were broadly consistent in a subgroup analysis of low-risk and high-risk groups.

Conclusion: In this nationwide registry, the use of preoperative β-blockers did not affect short-term mortality or morbidity in patients undergoing CABG. **(ANESTHESIOLOGY 2015; XXX:00-00)**

THERE are ample data in the literature regarding the perioperative risk reduction associated with β-blocker use in noncardiac surgery. However, data are limited for patients undergoing coronary artery bypass grafting (CABG), who may comprise the group with the highest risk of perioperative events.[1] Small, randomized trials did not find any clinical benefits when β-blocker usage was compared with placebo in patients undergoing CABG,[2] but studies were clearly underpowered, and the 95% CIs showed a wide variation in possible events. Sentinel investigation by Ferguson *et al.*[3] reported results from more than 600,000 patients from the Society of Thoracic Surgeons (STS) database. However, controversies still exist in the literature regarding the effectiveness of preoperative β-blocker use in providing survival and safety advantages. The most recent meta-analysis on the use of β-blocker in noncardiac surgery indicated that β-blocker use was associated with a reduction in nonfatal myocardial infarction (MI) and an increase in nonfatal stroke, hypotension, and bradycardia.[4] There also was a trend toward an increase in the rate of cardiovascular mortality. Accordingly, the use of β-blockers as a quality indicator has been questioned.[5]

What We Already Know about This Topic

- It remains unclear whether preoperative β-blocker use is protective in patients undergoing coronary artery bypass grafting

What This Article Tells Us That Is New

- Using a Japanese national cardiovascular surgical registry, the authors compared patients undergoing bypass grafting who were and who were not taking β-blockers preoperatively
- Unadjusted results favored chronic β-blocker use
- But after adjustment (the presumably more reliable results), β-blocker use did not alter complications, in-hospital mortality, or 30-day mortality

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Hence, the efficacy and safety of β-blocker use during the perioperative period of vascular surgery have not been adequately evaluated. Conducting sufficiently powered, prospective randomized clinical trials to investigate the effect of perioperative β-blocker use on cardiovascular patients is difficult. Also, there are ethical concerns regarding the design of such trials because a significant proportion of patients are already likely to be taking β-blockers and the withdrawal of this medication, before surgery, would entail an unacceptable risk.[6] There is some evidence that indicates that acute withdrawal of a β-blocker can lead to substantial morbidity and even mortality.[7–9]

To overcome these difficulties, large-scale registries may be used to support clinical decisions. According to a previous retrospective review of approximately 630,000 patients from the STS database who underwent CABG between 1996 and 1999, β-blocker use resulted in a slight reduction in mortality; however, this was of borderline significance after propensity matching.[3] The aim of the current study was to review the Japanese National Cardiovascular Surgical Database (JCVSD) to evaluate the immediate effects of preoperative β-blocker treatment on early clinical outcomes after CABG. We conducted a propensity-matched analysis to model the association of β-blocker use with the 30-day operative mortality and cardiac morbidity, using a robust set of clinical variables.

Materials and Methods

Database

The JCVSD was established in 1998 to assess adult cardiac surgery outcomes. Data for the JCVSD are collected annually from the majority of Japanese hospitals that perform cardiovascular surgeries. Data were collected between January 2008 and December 2011 from 333 centers in the current analysis; this accounts for 73.8% of the sites performing open-heart bypass surgeries in Japan. Data completeness also was high; the overall preoperative risk factors were missing from less than 2% of the entire assembled data set. The accuracy of submitted data was maintained by data auditing conducted by administrative office members making monthly, random hospital visits and checking the data against clinical records. The ratio of JCVSD-registered data to the actual number of cases at the hospital also was confirmed in advance through a comparison with data reported to the Japanese Association for Thoracic Surgery Registry.[10]

Clinical data were entered at the sites using uniform definitions and certified software systems. The JCVSD variables and their definitions[11] are identical, for the most part, to those of the STS National Adult Cardiac Database.[12] For the current analysis, the use of β-blockers was defined as the use of any β-blocker during the 24-h period before cardiac surgery. This definition was set to assess the direct effect of β-blocker use on cardiac surgery. The definition also was consistent with that used in most previous studies that evaluated the preoperative use of β-blockers (*e.g.*, in most studies, β-blocker therapy was started on the day of surgery). Data quality standards have to be met before a local data set can be entered into the aggregate national data set. Data were maintained by the Department of Healthcare Quality Assessment, Tokyo University, Tokyo, Japan, which produces annual site-specific reports to JCVSD participants for outcome analyses and quality improvement. All available information must be registered in this national database. Therefore, all information regarding medications is required, and none of the registered patients had missing β-blocker information.

The study population for the current analysis was derived from patients in the JCVSD who underwent isolated CABG (*i.e.*, did not undergo concomitant valve surgery or other cardiac procedures) between 2008 and 2011 (n = 34,980). AQ4

Endpoints

The JCVSD outcome measures included operative mortality, defined as death within 30 days of the date of surgery, which is equivalent to "the 30-day operative mortality" defined in the STS National Adult Cardiac Database. A composite major complication was defined as any of the five postoperative, in-hospital complications: stroke, reoperation for any reason, need for postoperative mechanical ventilation for more than 24 h, renal failure with newly required dialysis, or deep sternal wound infection. In this analysis, we used postoperative stroke and prolonged mechanical ventilation as individual endpoints, in addition to major morbidity and operative mortality. This was done because of the association of postoperative stroke with β-blocker use in the Perioperative Ischemic Evaluation (POISE) study,[13] and the fact that β-blockers are associated with side effects, including bronchospasms and heart failure.[14,15] Other in-hospital outcomes included bleeding complications that warranted surgical intervention within 30 days of the original surgery, postoperative MI, postoperative renal failure (creatinine level increases to more than twice the preoperative value, an absolute value > 2.0 mg/dl, or newly initiated dialysis), cardiac tamponade that required percutaneous or operative drainage, gastrointestinal bleeding that required blood transfusion or surgical intervention, postoperative pneumonia, rehospitalization within 30 days, and an intensive care unit stay of more than 7 days.

Quality Assurance

To perform routine audits, we created the site visit working group (SV-WG). The WG members consisted of one SV-WG chief (selected from the administrative office members) and six data managers from six areas in Japan. Each month, one hospital was randomly chosen, and the SV-WG chief listed all the deceased patients and drew up printed tables showing all the entered variables for the deceased patients. The chief also created another table that included randomly picked cases from among the living patients.

Statistical Analysis

We compared baseline demographics for patients who received β-blockers with those for patients who did not. Differences between treated and nontreated patients were determined by using a chi-square test for categorical variables and the Wilcoxon rank sum test for continuous variables. The impact of preoperative β-blocker use was examined using a multiple logistic regression model that set previously identified clinical risk factors as fixed effects. For adjustment of surgical volume, we first determined the average number of procedures that each surgeon performed during the study period. We then created categorical variables for volume by ranking surgeons in order of increasing estimated total volume and selecting cutoff points that most closely sorted patients into four evenly sized groups (low, low medium, high medium, and high volume).

The modeling was also performed for subgroups of patients with relative contraindications for β-blocker use, such as respiratory disability (1-s forced expiratory volume < 75% and/or use of bronchodilators), symptoms of congestive heart failure within 2 weeks of surgery, cardiopulmonary arrest within 24 h of surgery, cardiogenic shock at the time of surgery (n = 7,787), documented left ventricular dysfunction (defined as a preoperative left ventricular ejection fraction [LVEF] < 50% [n = 4,869]), and for those who underwent CABG for urgent indications (n = 6,531).

Because treatment assignment was nonrandom, we performed a one-to-one matched analysis, based on estimated propensity scores for patients with or without preoperative β-blocker use. The log of the estimated probability that a patient received a β-blocker was calculated as the log of the odds p/(1-p), where p was the estimated propensity score (the logit). By using the estimated logits, each patient treated with a β-blocker was matched, without replacement, to the "closest" non-β-blocker patient. "Close" was defined based on the SD of the estimated logits, using calipers of width equal to 0.2 of the SD. We selected 0.2 because this value AQ5 has been shown to eliminate approximately 90% of the bias due to the observed confounders.[13] If several non-β-blocker users were successfully matched using these criteria, then one of them was chosen randomly as the match. To ensure that the results were not driven by the major difference between the groups, *c*-scores for discrimination were calculated for the present propensity model and for the propensity model that forced entry of all variables in tables 1 and 2, other than T1,T2 intraoperative variables such as total operative time, perfusion time, or cross-clamp time. The *c*-scores from two models were virtually identical (0.722 and 0.721, respectively). Furthermore, we also calculated the standardized differences for each of the covariates to provide insight into how effectively the propensity score controlled for observed confounders. We compared early outcomes, including 30-day operative mortality and details of postoperative complications, between

Table 1. Baseline Characteristics of the Study Population before and after Propensity Score Matching

	All Patients				Propensity-matched Patients			
	β	Non-β	*P*	Standardized	β	Non-β	*P*	Standardized
No. of Patients	10,496	24,484	Value	Difference	9,619	9,619	Value	Difference
Age, yr	68.0±9.6	68.7±9.6	< 0.001	0.070	68.1±9.5	68.2±9.6	0.53	0.010
Male, %	77.8	78	0.73	0.002	77.7	78.1	0.49	0.005
Body mass index	23.8±3.5	23.6±3.4	< 0.001	0.060	23.7±3.5	23.7±3.4	0.13	0.001
Smoker, %	58.0	55.4	< 0.001	0.024	57.7	56.9	0.31	0.007
Diabetes mellitus, %	52.7	49.8	< 0.001	0.027	52.7	52.7	1.00	0.000
Diabetes mellitus, on treatment, %	43.1	40.7	< 0.001	0.023	43.3	43.4	0.83	0.002
Chronic kidney disease, %	14.1	13.1	0.018	0.013	14.0	13.9	0.92	0.001
Hyperlipidemia, %	66.9	56.5	< 0.001	0.097	65.4	64.2	0.066	0.013
Hypertension, %	82.4	73.9	< 0.001	0.092	81.2	81.1	0.85	0.001
Cerebrovascular disease, %	13.1	13.2	0.84	0.001	12.8	13.3	0.27	0.008
Carotid stenosis, %	9.4	7.8	< 0.001	0.026	9.2	8.6	0.20	0.009
Atrial fibrillation, %	4.6	3.5	< 0.001	0.026	4.2	4.0	0.47	0.005
Respiratory disability, %	9.6	9.4	0.45	0.004	9.5	9.3	0.64	0.003
Peripheral arterial disease, %	16.1	16.6	0.30	0.006	16.4	16.7	0.52	0.005
Previous PCI, %	31.1	23.8	< 0.001	0.076	28.8	28.5	0.61	0.004
Previous myocardial infarct, %	39.1	35	< 0.001	0.039	36.8	35.2	0.022	0.017
Unstable angina at the time of surgery, %	26.9	33.8	< 0.001	0.068	27.4	27.1	0.60	0.004
CCS class 3 or 4, %	28.7	34.3	< 0.001	0.054	28.9	27.9	0.12	0.011
LVEF ≤ 50%, %	53.1	49.9	< 0.001	0.029	51.2	50.0	0.081	0.013
Congestive heart failure within 2 weeks of surgery, %	11.4	13.4	< 0.001	0.027	11.2	10.9	0.46	0.005
Cardiogenic shock at the time of surgery, %	1.6	5	< 0.001	0.08	1.7	1.3	0.030	0.015

CCS = Canadian Cardiovascular Society; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention.

Table 2. Concomitant Medical Therapy of the Study Population before and after Propensity Score Matching

	All Patients				Propensity-matched Patients			
	β	Non-β			β	Non-β		
No. of Patients	10,496	24,484	*P* Value	Standardized Difference	9,619	9,619	*P* Value	Standardized Difference
Digitalis, %	1.3	0.9	< 0.001	0.018	1.3	1.0	0.107	0.012
Intravenous nitrates, %	12.1	12.4	0.001	0.004	11.7	11.7	0.875	0.001
Aspirin, %	46.3	34.6	0.455	0.11	43.4	44.6	0.089	0.012
Anticoagulants, %	14.3	15.3	< 0.001	0.014	14.1	14.4	0.536	0.005
Statins, %	55.7	29.9	0.001	0.244	52.0	52.3	0.708	0.003
ACE inhibitors, %	17.5	7.2	< 0.001	0.155	13.4	12.0	0.004	0.021
Angiotensin receptor blockers, %	39.6	23.0	< 0.001	0.169	38.5	39.0	0.564	0.004
Calcium channel blockers, %	36.4	25.7	< 0.001	0.105	35.4	37.4	0.005	0.021

ACE = angiotensin-converting enzyme.

the groups using the Pearson chi-square test, with *P* value less than 0.05 being the criterion of statistical significance.

We also performed an additional analysis, based on information available at the time of discharge, in our propensity-matched group. For this additional analysis, 365 patients (1.8%) who died during hospitalization and 3 patients who did not have discharge medication information (< 0.1%) were excluded. The remainder of the patients (n = 18,870) were further subcategorized by the presence or absence of discharge β-blocker prescriptions, as presented in figure 1. In this subgroup of patients, we compared the rate of postoperative MI and heart block, 30-day readmission, and prolonged stay in the intensive care unit (> 8 days). Postoperative MI was defined when any two of the following four criteria were met: (1) chest discomfort lasting more than 20 min, not responsive to nitrates and/or rest, (2) increase in levels of cardiac biomarkers, (3) newly developed myocardial wall motion abnormality, or (4) ST-T changes in more than two anatomically continuous leads.

Finally, given the results of a recent analysis of "non-cardiac" surgeries in the Veterans Health Administration database that showed the benefit of perioperative β-blocker use among patients with intermediate to high risk,[16] we performed an additional matching analysis in the low-risk

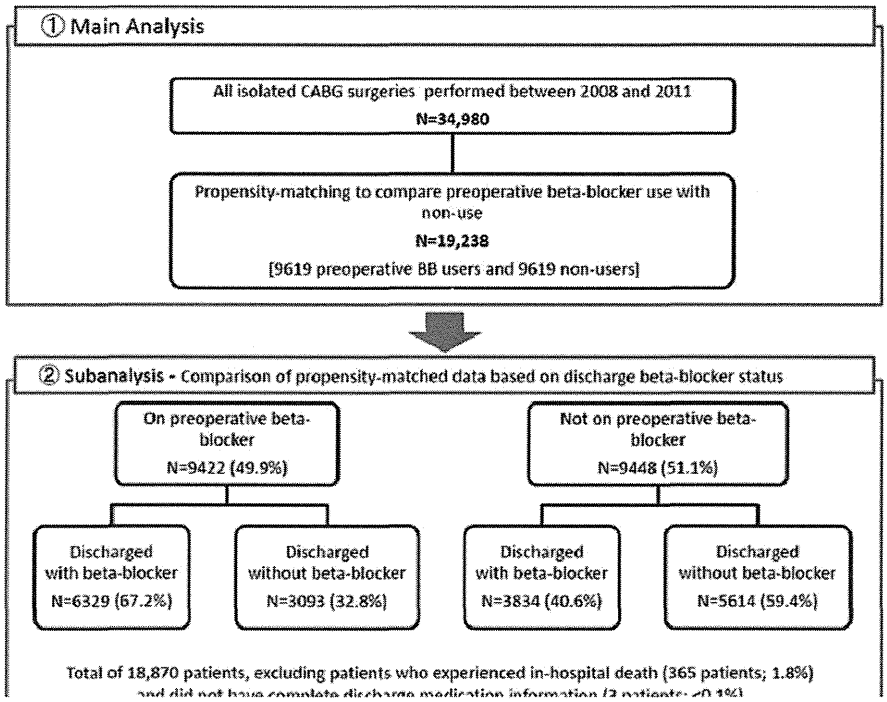

Fig. 1. β-Blocker (BB) use at the time of discharge in the propensity score-matched patients and data comparison and analysis steps. CABG = coronary artery bypass grafting.

and high-risk subgroups, based on risk estimations made using the Japan Score system.[17] The current Japan Score was calculated from an 80% development sample derived from 24,704 cases of isolated CABG surgery performed between January 2006 and December 2009 and validated in the remainder of the patient data (20% validation data). Final logistic models and model performance metrics are presented in Supplemental Digital Content 1, http://links.lww.com/ALN/B199, Table S1. All analyses were performed using SPSS Version 20 (SPSS, USA).

Results

According to the preoperative profiles, women accounted for 20% of the patients, and 50% of the overall patient population had diabetes mellitus; the mean patient age was 68 yr. Off-pump CABG was performed 65% of the time, with the mean number of anastomoses being 3.0. Preoperative β-blockers were used in 10,496 patients (30%). Patients receiving β-blockers were younger (68.0 *vs.* 68.7 yr old; $P < 0.001$) than those not receiving β-blockers, but they were more likely to have risk factors or other comorbidities, such as diabetes mellitus, chronic kidney disease, or left ventricular dysfunction (tables 1–3).

The crude 30-day operative mortality rate was 1.7 and 2.7% and the crude, in-hospital major complication rate was 9.7 and 11.6% for patients receiving or not receiving preoperative β-blockers, respectively. However, after adjusting for differences in the patient characteristics (such as younger age), the use of preoperative β-blockers was not associated with 30-day mortality (odds ratio [OR] associated with β-blocker use, 1.00; 95% CI, 0.82 to 1.21) or major in-hospital complications (adjusted OR associated with β-blocker use, 0.99; 95% CI, 0.91 to 1.08).

The adjusted prematch associations of β-blocker use with individual in-hospital outcomes are presented in figure 2. There was no significant association between β-blocker and short-term outcomes, and this was consistent across all subgroups, including the relative contraindications for β-blocker use (*e.g.*, respiratory disability, n = 7,787), patients with left ventricular dysfunction (n = 4,869), and those who underwent CABG for urgent indications (n = 6,531). Of note, use of β-blocker was not associated with either improved or impaired outcome, even after adjustment for surgical case volume (Supplemental Digital Content 1, http://links.lww.com/ALN/B199, Table S2).

After propensity matching, baseline differences were balanced between users and nonusers of preoperative β-blockers; all of our demographic and operative characteristics had postmatching standard reference values less than 0.1; standardized differences of 0.2, 0.5, and 0.8 represent small, medium, and large effect sizes, respectively. In addition, the overall expected mortality rates (calculated from Japan Score) were 0.0182 ± 0.00042 and 0.0253 ± 0.00038 for β-blocker and non-β-blocker, respectively, before matching ($P < 0.001$); after matching, the rates were 0.0186 ± 0.00045 and 0.0176 ± 0.00038 ($P = 0.10$). Details of the patients' medical and operative backgrounds are given in tables 1 and 2.

Table 3. Operative Characteristics of the Study Population before and after Propensity Score Matching

	All Patients				Propensity-matched Patients			
	β	Non-β			β	Non-β		
No. of Patients	10,496	24,484	*P* Value	Standardized Difference	9,619	9,619	*P* Value	Standardized Difference
Multivessel disease, %	94.3	93.1	< 0.001	0.023	94.2	93.8	0.30	0.008
Triple-vessel disease, %	71.8	68.6	< 0.001	0.032	71.4	70.5	0.16	0.010
Left main disease, %	37.5	42.1	< 0.001	0.044	38.3	38.6	0.65	0.003
Surgery status, urgent, %	7.4	13	< 0.001	0.082	7.9	7.8	0.77	0.002
Surgery status, emergent, %	3.0	9.2	< 0.001	0.11	3.2	2.7	0.056	0.014
Reoperation, %	2.2	1.6	< 0.001	0.023	2.0	2.1	0.58	0.004
Total operative time, min	328.4 ± 103.3	316.8 ± 101.7	< 0.001	0.11	326.9 ± 103.2	320.4 ± 102.5	< 0.001	0.06
Perfusion time, min	143.0 ± 56.7	137.7 ± 54.6	< 0.001	0.10	142.3 ± 56.6	139.1 ± 54.6	0.027	0.06
Cross-clamp time, min	97.3 ± 40.0	89.9 ± 38.6	< 0.001	0.19	97.0 ± 40.2	93.6 ± 39.4	0.009	0.09
Number of anastomoses, %	3.14 ± 1.17	3.02 ± 1.18	< 0.001	0.10	3.11 ± 1.16	3.10 ± 1.19	0.32	0.01
< 2	28.8	32.7	< 0.001	0.038	29.7	30.0	0.71	0.003
3	35.2	35.8	0.24	0.006	35.3	35.5	0.87	0.001
4–5	33.5	29.6	< 0.001	0.039	32.6	32.4	0.85	0.001
> 6	2.4	1.9	< 0.001	0.018	2.3	2.1	0.24	0.008
Off-pump surgery, %	69.6	62.9	< 0.001	0.065	68.3	69.1	0.26	0.008
Off-pump surgery converted to on-pump, %	2.1	2.2	0.60	0.003	2.0	2.3	0.14	0.011
Left IMA use, %	92.0	90.8	< 0.001	0.019	91.9	91.7	0.53	0.005
Right IMA use, %	36.6	31.2	< 0.001	0.053	35.4	35.9	0.42	0.006
Blood transfusion, %	66.6	66.9	0.54	0.003	66.6	64.4	0.001	0.024

IMA = internal mammary artery.

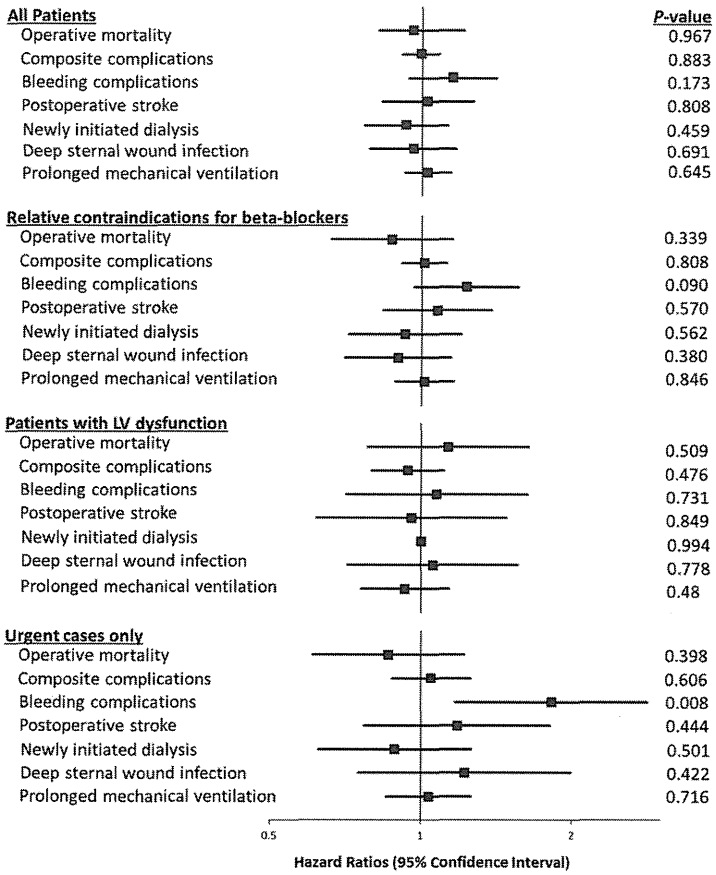

Fig. 2. Adjusted risk of various in-hospital outcomes among all patients and the subgroups of patients with relative contraindications for β-blocker, such as respiratory disability, congestive heart failure within 2 weeks of surgery, cardiopulmonary arrest within 24 h of surgery, cardiogenic shock at the time of surgery (n = 7,787), left ventricular (LV) dysfunction (n = 4,869), and those undergoing coronary artery bypass grafting for urgent indications (n = 6,531). AQ9

In terms of immediate outcomes for the matched patients, the 30-day operative mortalities were 1.6 and 1.5% for the β-blocker and non-β-blocker groups, respectively ($P = 0.49$). The overall incidence of postoperative complications, such as stroke (1.3 and 1.4%; $P = 0.66$), prolonged mechanical ventilation (6.0 and 5.6%; $P = 0.43$), or perioperative MI (0.8 and 0.7%; $P = 0.37$), was also similar between patients using and not using β-blockers, respectively (table 4). T4

Among patients who were using preoperative β-blockers, more patients were discharged without β-blockers when they also had newly initiated dialysis, prolonged mechanical ventilation, or postoperative heart block requiring permanent pacemaker placement. However, in this subgroup analysis, there was no significant difference in the rate of postoperative MI, prolonged intensive care unit stay, or 30-day readmission between those who were discharged with β-blockers and those who were not (table 5). Among those who were not on preoperative β-blockers, more patients were discharged with β-blockers if they experienced postoperative atrial fibrillation (POAF, 50.6% discharged on β-blocker; no POAF, 38.2% discharged on β-blocker; $P < 0.001$). There were no significant differences in the rate of postoperative MI, prolonged intensive care unit stay, or 30-day readmission between those who were discharged on β-blockers and those who were not. T5

The immediate outcomes from the use of preoperative β-blocker were compared in two different risk groups (low and high risk). These patients were matched separately, based on a preoperative risk estimation derived from their Japan Scores. The low-risk groups of patients with and without β-blocker included 1,810 and 1,815 patients, and the high-risk groups included 2,439 and 2,418 patients, respectively. The operative mortalities were 0.1 and 0.3% ($P = 0.10$), respectively, in low-risk patients and 4.7 and 4.5% ($P = 0.67$) in high-risk patients. β-Blocker use was not associated with a difference in any of the postoperative complication rates, including stroke, prolonged mechanical ventilation, or perioperative MI, in either of these patient subgroups (table 6). T6

Discussion

The findings from the current study demonstrated that preoperative β-blocker use was not associated with a significant

Table 4. Early Postoperative Outcomes of the Study Population before and after Propensity Score Matching

	All Patients				Propensity-matched Patients			
	β	Non-β	Odds Ratio	*P*	β	Non-β	Odds Ratio	*P*
No. of Patients	10,496	24,484	(95% CI)	Value	9,619	9,616	(95% CI)	Value
Operative mortality, %	1.7	2.7	0.607 (0.512–0.719)	< 0.001	1.6	1.5	1.085 (0.885–1.361)	0.49
Composite complications, %	9.7	11.6	0.823 (0.763–0.888)	< 0.001	9.8	9.7	1.001 (0.910–1.101)	1.00
Bleeding complications, %	1.6	1.5	1.046 (0.869–1.074)	0.64	1.6	1.4	1.120 (0.887–1.416)	0.37
Postoperative stroke, %	1.3	1.5	0.873 (0.718–1.061)	0.18	1.3	1.4	0.940 (0.736–1.200)	0.66
Newly initiated dialysis, %	1.7	2.2	0.765 (0.644–0.908)	0.020	1.7	1.7	0.994 (0.799–1.237)	0.96
Deep sternal wound infection, %	1.5	1.6	0.942 (0.782–1.134)	0.54	1.5	1.5	0.952 (0.754–1.202)	0.68
Prolonged mechanical ventilation, %	6.0	7.6	0.771 (0.702–0.846)	< 0.001	6.0	5.8	1.050 (0.931–1.184)	0.43
Postoperative myocardial infarction, %	0.8	0.9	0.946 (0.735–1.216)	0.70	0.8	0.7	1.158 (0.840–1.597)	0.37
Postoperative renal failure, %	4.0	4.5	0.902 (0.805–1.012)	0.81	4.1	3.9	1.033 (0.894–1.194)	0.66
Tamponade, %	0.9	0.9	0.932 (0.731–1.189)	0.62	0.9	0.8	1.087 (0.803–1.472)	0.59
Gastrointestinal bleeding, %	1.2	1.4	0.885 (0.721–1.086)	0.26	1.2	1.3	0.967 (0.750–1.246)	0.80
Postoperative pneumonia, %	1.9	2.5	0.772 (0.657–0.907)	0.020	1.9	1.9	1.006 (0.818–1.236)	1.00
Prolonged stay in intensive care unit (> 8 days), %	5.1	7.6	0.657 (0.595–0.725)	< 0.001	5.2	5.3	0.973 (0.857–1.105)	0.67
Rehospitalization within 30 days, %	2.1	2.1	1.023 (0.871–1.200)	0.78	2.1	2.3	0.930 (0.767–1.128)	0.46

decrease in 30-day operative mortality or in in-hospital complications, such as stroke, prolonged ventilation, or perioperative MI. These findings were consistent among the various subgroups, such as the group without relative contraindications for β-blocker or the group that included urgent procedures only. In addition, when the outcomes of the two propensity-matched patient groups were compared, differences were not seen in the aforementioned outcomes. The main findings were broadly consistent in the analysis of low-risk and high-risk groups, according to preoperative background information. Although there were some alterations in the use of β-blockers during the perioperative period, they did not seem to alter the main outcomes of the study.

At present, clinical guidelines for CABG surgery recommend preoperative β-blockers for patients without specific contraindications.[18,19] However, the magnitude of the

Table 5. Incidence of Perioperative Events, According to β-Blocker Usage at the Time of Discharge

	Patients on Preoperative β-Blockers, n = 9,422 (49.9%)				Patients Not on Preoperative β-Blockers, n = 9,448 (51.1%)			
	Discharged with β-Blockers	Discharged without β-Blockers			Discharged with β-Blockers	Discharged without β-Blockers		
No. of Patients	6,329 (67.2%)	3,093 (32.8%)	Odds Ratio (95% CI)	*P* Value	3,834 (40.6%)	5,614 (59.4%)	Odds Ratio (95% CI)	*P* Value
Bleeding complications, %	1.4	1.4	1.012 (0.699–1.467)	1.000	1.1	1.4	0.766 (0.526–1.116)	0.194
Postoperative stroke, %	1.0	1.4	0.742 (0.502–1.098)	0.145	1.3	1.1	1.207 (0.832–1.753)	0.336
Newly initiated dialysis, %	1.1	1.6	0.648 (0.449–0.934)	0.023	1.4	1.2	1.205 (0.841–1.725)	0.309
Deep sternal wound infection, %	1.2	1.4	0.871 (0.596–1.274)	0.489	1.2	1.4	0.830 (0.576–1.194)	0.363
Prolonged mechanical ventilation, %	4.6	6.8	0.662 (0.551–0.794)	< 0.001	5.2	4.8	1.089 (0.903–1.314)	0.386
Postoperative myocardial infarction, %	0.6	0.7	0.742 (0.438–1.258)	0.265	0.6	0.6	0.894 (0.525–1.522)	0.789
Postoperative heart block, %	0.3	0.6	0.487 (0.262–0.907)	0.027	0.2	0.4	0.487 (0.207–1.147)	0.122
Prolonged stay in intensive care unit (> 8 days), %	4.2	5.0	0.820 (0.669–1.004)	0.056	5.1	4.4	1.153 (0.951–1.398)	0.150
Rehospitalization within 30 days, %	2.2	2.0	1.122 (0.830–1.517)	0.498	2.3	2.3	1.030 (0.784–1.353)	0.834

Table 6. Postoperative Outcomes in Matched Patients, Risk Stratified Based on Baseline Background Characteristics

	Low-risk Patients, Matched				High-risk Patients, Matched			
	β	Non-β			β	Non-β		
No. of Patients	1,810	1,815	Odds Ratio (95% CI)	*P* Value	2,439	2,418	Odds Ratio (95% CI)	*P* Value
Operative mortality, %	0.1	0.3	0.200 (0.023–1.717)	0.103	4.7	4.5	1.058 (0.809–1.385)	0.679
Composite complications, %	4.9	4.4	1.121 (0.823–1.527)	0.469	18.3	19.2	0.941 (0.815–1.087)	0.411
Bleeding complications, %	0.9	0.9	0.943 (0.475–1.872)	0.886	2.4	2.2	1.122 (0.772–1.630)	0.547
Postoperative stroke, %	0.9	0.8	1.147 (0.558–2.356)	0.709	2.5	2.1	1.187 (0.815–1.729)	0.372
Newly initiated dialysis, %	0.3	0.4	0.625 (0.204–1.915)	0.407	4.4	4.5	0.988 (0.753–1.296)	0.928
Deep sternal wound infection, %	1.0	1.2	0.858 (0.455–1.615)	0.634	2.4	2.3	1.062 (0.732–1.539)	0.753
Prolonged mechanical ventilation, %	2.1	1.9	1.119 (0.706–1.775)	0.632	12.9	13.1	0.979 (0.829–1.157)	0.806
Postoperative myocardial infarction, %	0.6	0.7	0.847 (0.379–1.896)	0.686	1.0	0.9	1.178 (0.658–2.110)	0.581
Postoperative renal failure, %	1.5	1.4	1.081 (0.631–1.850)	0.778	8.4	8.4	1.003 (0.819–1.228)	0.977
Tamponade, %	0.4	0.7	0.538 (0.214–1.351)	0.999	1.6	1.0	1.616 (0.963–2.695)	0.318
Gastrointestinal bleeding, %	0.5	0.8	0.714 (0.316–1.612)	0.180	2.2	2.6	0.846 (0.587–1.218)	0.640
Postoperative pneumonia, %	0.5	0.4	1.128 (0.434–2.930)	0.416	4.8	4.4	1.105 (0.845–1.445)	0.368
Rehospitalization within 30 days, %	2.0	1.6	1.249 (0.763–2.046)	0.804	2.2	2.8	0.765 (0.532–1.101)	0.466
Prolonged stay in intensive care unit (> 8 days), %	1.5	1.5	0.966 (0.567–1.645)	0.376	12.3	11.9	1.037 (0.873–1.232)	0.148

effect varies considerably across studies, with the literature supporting the use of β-blockers being modest, at best; the supportive literature is based on a few small, nonblinded studies with a focused patient population.[13,20] The study by Ferguson *et al.*,[3] upon which preoperative β-blocker use rests, showed only a slight reduction in mortality, which was of borderline significance after propensity matching (OR, 0.97; 95% CI, 0.93 to 1.00). Furthermore, the procedures in the previous study were performed in the 1990s and were predominantly on-pump. Reflecting the current practice of cardiovascular surgery, over half of our patients underwent off-pump surgery. Finally, the study reported a trend toward increased mortality in a subgroup of patients with an LVEF of less than 30%. We also performed a subanalysis in the patients with a mildly reduced ejection fraction (defined as a preoperative LVEF < 50%; N = 6,531) and severely reduced ejection fraction (LVEF < 30%; N = 1,039); this showed no association between the use of β-blocker and outcome. The present data, from the Japanese national registry, reflect the practical use of β-blockers in the "real world" and seem scientifically sound, with the analyses showing consistent results.

The effects of β-blocker use may vary depending on the preoperative risks of the patients.[18,21,22] Therefore, we analyzed the association of β-blocker use with perioperative outcomes in various subgroups, but the results were similar in all cases. The effect of β-blockers was neutral, even when patients with left ventricular dysfunction were analyzed separately, and when low-risk and high-risk patients, based on preoperative variables, were matched separately. Several authors postulated that the preoperative administration of β-blockers in these patients could contribute to a profound lowering of heart rates and blood pressures in the early postoperative phase, resulting in shock and renal dysfunction.

Implementation of patient care under stringent guidelines might have led to the neutral effect of β-blocker use. The beneficial effects of β-blockers seem less pronounced under the modern application of evidence-based medications and appropriate preoperative evaluations.[23] Current recommendations typically include aspirin or lipid-lowering agents, and approximately 50% of these patients used an angiotensin-converting enzyme inhibitor. These medications for secondary prevention further decrease the risk of perioperative events. Reflecting modern, real-world, cardiovascular surgical practice, we observed a relatively low rate of 30-day operative mortality and in-hospital complications.

In addition, international differences in the patterns of practice, as well as the ethnic background of the patients, may also have influenced the observed magnitude of the effects of β-blocker treatment. The rate of β-blocker use varies in international registries compared with the rates reported in clinical studies. In the current analysis, only 30% of patients received preoperative β-blockers. This rate is considerably lower than the β-blocker prescription rate reported from North America (50 to 60%),[3] but it is similar to the rate reported from other studies conducted in Japan.[24] Genetic variants strongly alter the responsiveness to β-blockade, and increased responsiveness to β-blockade, among Asians, has been noted previously.[25] In an early pharmacokinetic/pharmacodynamic study, Chinese subjects had at least a two-fold greater sensitivity to the β-blocking effects of propranolol than did white subjects.[26] Furthermore, concern over the use of β-blockers has emerged in Japan because Japanese patients with coronary artery disease (CAD) have higher incidences of coronary spasms compared with patients in other ethnic

AQ10

groups.[27,28] In the Japanese Beta-Blockers and Calcium Antagonist Myocardial Infarction study, the incidence of coronary spasms was significantly higher in the β-blocker group than in the calcium antagonist group (1.2 and 0.1%; $P = 0.027$), without any difference in the incidence of cardiovascular death (1.2 and 1.1%; $P = 0.37$).[29] These differences may have contributed to the lower rate of β-blocker use in this population.

Clinical guidelines suggest that the perioperative β-blocker dose should be titrated to achieve adequate heart rate control and increase the likelihood that patients will benefit from the medication. However, the relation between the magnitude of heart rate reduction and the efficacy of β-blockers has not been confirmed. In a recent meta-analysis, no significant relation was observed between β-blocker dose and improvement in all-cause mortality. In addition, the results from the POISE trial indicate that routine administration of high-dose β-blockers, in the absence of dose titration, is not useful and may be harmful.[13] Therefore, the preoperative use of β-blockers may have a limited role in reducing the risk of perioperative events.

The low 30-day operative mortality and in-hospital complication rates are also consistent with other large-scale cardiovascular registry studies conducted in East Asia.[30,31] A previously published study had an unadjusted operative mortality rate of 2.8 to 3.4%,[3] whereas the 30-day operative mortality rate was 1.7 to 2.7%. Therefore, insufficient statistical power may have played a role in the current study. Other potential explanations for the lack of a significant association of β-blocker use with improved outcomes include selection bias and/or the close monitoring associated with prolonged hospital stays under the national insurance coverage system in Japan.

The use of statins and aspirin, which reduce mortality in patients with CAD, was low in our patients; approximately 50% received preprocedural statins (within 24 h of surgery) and aspirin (within 5 days of surgery). This finding suggests that obstacles persist in the identification of ideal patients and in balancing the risks and benefits of treatment. The increasing proportion of patients with comorbidities in the modern era of CABG surgery may render treatment more challenging. Gaps in care might also result from inadequate provider knowledge and structural inadequacies in the systems of care. Our findings underscore the need for national initiatives to understand the reasons for persistent gaps in care and to improve the use of evidence-based care for CABG patients.

Our study has several important limitations. First, selection bias regarding the use of β-blockers is unavoidable in observational studies. Although we used a propensity score to adjust for baseline β-blocker use, we could not exclude the influence of unmeasured confounders on clinical outcomes. However, as listed in our tables (tables 1–3), all of our demographic and operative characteristics had postmatching standard reference values less than 0.1; standardized differences of 0.2, 0.5, and 0.8 represent small, medium, and large effect sizes, respectively.[32] Second, we did not have clarification of MI history (recent *vs.* nonrecent or description of time since MI). This might have been useful in identifying the role of β-blockers, particularly because the benefit of β-blockers observed in early studies may been driven by those with recent MIs, a cohort known to benefit from aggressive β-blockade. Third, our analyses of β-blocker use were limited to class effects and categorical/qualitative effects because we did not monitor the use of individual drugs or their dosages. Kohro *et al.*[33] have described these data previously in 13,812 Japanese patients with angiographically confirmed CAD (with ≥ 75% stenosis). The study was performed during approximately the same time period as our study, and the most frequently used β-blocker was carvedilol (1,421 of 4,160, 34.1%), followed by metoprolol tartrate (913 of 4,160, 9.3%), atenolol (774 of 4,160, 14.8%), and bisoprolol (547 of 4,160, 8.8%). Finally, the incidence of β-blocker therapy withdrawal in the non-β-blocker group could have affected our result. Because the reason for β-blocker discontinuation was not recorded in JACVSD, it remains unclear whether β-blocker discontinuation influenced the occurrence of POAF or *vice versa* (POAF occurrence might have led to the use of β-blockers postoperatively). In the current study, β-blocker-naive patients who experienced POAF, 50.6% were discharged on β-blockers (*vs.* 38.2% of patients who did not experience POAF); therefore, latter scenario seemed to have occurred rather frequently. Whether the timing of β-blocker initiation or discontinuation or other unrecorded covariates may contribute to this observation warrants further investigation.

In conclusion, in a propensity-matched, balanced cohort of CABG patients, the use of β-blockers was not associated with decreased mortality or in-hospital complications, regardless of the patient's preoperative risk profile. The present findings suggest that preoperative β-blocker use in patients undergoing CABG is not associated with improved short-term outcomes.

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Competing Interests

Dr. Kohsaka received unrestricted research grants for the Department of Cardiology, Keio University School of Medicine, Tokyo, Japan, from Pfizer Japan Inc. (Tokyo, Japan) and Bayer Pharmaceutical Co., Ltd. (Osaka, Japan). The other authors declare no competing interests.

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Tokyo, Japan. kohsaka@cpnet.med.keio.ac.jp. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. ANESTHESIOLOGY's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

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