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.

acknowledgments

We would like to thank Editage (www.editage.jp) for English language editing.

funding

This research was supported in part by MEXT KAKENHI grant number 26870597 (2014–2015) JSPS KAKENHI grant numbers 15H04796 and Tokai University School of Medicine Research Aid (2013–2015).

disclosure

The authors have declared no conflicts of interest.

references

1. Mauri D, Pavlidis N, Ioannidis JP. Neoadjuvant versus adjuvant systemic treatment in breast cancer: a meta-analysis. J Natl Cancer Inst 2005; 97: 188–194.
2. Bonadonna G, Valagussa P, Brambilla C, Ferrari L. Preoperative chemotherapy in operable breast cancer. Lancet 1993; 341: 1485.
3. Cortazar P, Zhang L, Untch M et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 2014; 384: 164–172.
4. von Minckwitz G, Untch M, Blohmer JU et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol 2012; 30: 1796–1804.
5. Berruti A, Brizzi MP, Generali D et al. Presurgical systemic treatment of nonmetastatic breast cancer: facts and open questions. Oncologist 2008; 13: 1137–1148.
6. Gianni L, Eiermann W, Semiglazov V et al. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort. Lancet 2010; 375: 377–384.
7. Buzdar AU, Ibrahim NK, Francis D et al. Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer. J Clin Oncol 2005; 23: 3676–3685.
8. Simon R, Nocito A, Hubscher T et al. Patterns of her-2/neu amplification and overexpression in primary and metastatic breast cancer. J Natl Cancer Inst 2001; 93: 1141–1146.
9. Gancberg D, Di Leo A, Cardoso F et al. Comparison of HER-2 status between primary breast cancer and corresponding distant metastatic sites. Ann Oncol 2002; 13: 1036–1043.
10. Simmons C, Miller N, Geddie W et al. Does confirmatory tumor biopsy alter the management of breast cancer patients with distant metastases? Ann Oncol 2009; 20: 1499–1504.
11. Thompson AM, Jordan LB, Quinlan P et al. Prospective comparison of switches in biomarker status between primary and recurrent breast cancer: the Breast Recurrence in Tissues Study (BRITS). Breast Cancer Res 2010; 12: R92.
12. Lower EE, Glass E, Blau R, Harman S. HER-2/neu expression in primary and metastatic breast cancer. Breast Cancer Res Treat 2008; 113: 301–306.
13. Burstein HJ, Harris LN, Gelman R et al. Preoperative therapy with trastuzumab and paclitaxel followed by sequential adjuvant doxorubicin/cyclophosphamide for HER2 overexpressing stage II or III breast cancer: a pilot study. J Clin Oncol 2003; 21: 46–53.
14. Hurley J, Doliny P, Reis I et al. Docetaxel, cisplatin, and trastuzumab as primary systemic therapy for human epidermal growth factor receptor 2-positive locally advanced breast cancer. J Clin Oncol 2006; 24: 1831–1838.
15. Mittendorf EA, Wu Y, Scaltriti M et al. Loss of HER2 amplification following trastuzumab-based neoadjuvant systemic therapy and survival outcomes. Clin Cancer Res 2009; 15: 7381–7388.
16. Niikura N, Liu J, Hayashi N et al. Loss of human epidermal growth factor receptor 2 (HER2) expression in metastatic sites of HER2-overexpressing primary breast tumors. J Clin Oncol 2012; 30: 593–599.
17. Fl G. TNM Classification of Malignant Tumours. 6th ed. New York: Wiley 2002; 131–141.
18. Miyata H, Gotoh M, Hashimoto H et al. Challenges and prospects of a clinical database linked to the board certification system. Surg Today 2014; 44: 1991–1999.
19. Nagayama A, Hayashida T, Jinno H et al. Comparative effectiveness of neoadjuvant therapy for HER2-positive breast cancer: a network meta-analysis. J Natl Cancer Inst 2014; 106.

20. Sauter G, Lee J, Bartlett JMS et al. Guidelines for human epidermal growth factor receptor 2 testing: biologic and methodologic considerations. J Clin Oncol 2009; 27: 1323–1333.
21. Press MF, Sauter G, Bernstein L et al. Diagnostic evaluation of HER-2 as a molecular target: an assessment of accuracy and reproducibility of laboratory testing in large, prospective, randomized clinical trials. Clin Cancer Res 2005; 11: 6598–6607.
22. Paik S, Bryant J, Tan-Chiu E et al. Real-world performance of HER2 testing—national surgical adjuvant breast and bowel project experience. J Natl Cancer Inst 2002; 94: 852–854.
23. Guarneri V, Dieci MV, Barbieri E et al. Loss of HER2 positivity and prognosis after neoadjuvant therapy in HER2-positive breast cancer patients. Ann Oncol 2013; 24: 2990–2994.
24. Pusztai L, Viale G, Kelly CM, Hudis CA. Estrogen and HER-2 receptor discordance between primary breast cancer and metastasis. Oncologist 2010; 15: 1164–1168.
25. Kurebayashi J, Miyoshi Y, Ishikawa T et al. Clinicopathological characteristics of breast cancer and trends in the management of breast cancer patients in Japan: based on the Breast Cancer Registry of the Japanese Breast Cancer Society between 2004 and 2011. Breast Cancer 2015; 22: 235–244.
26. Dekker TJ, Smit VT, Hooijer GK et al. Reliability of core needle biopsy for determining ER and HER2 status in breast cancer. Ann Oncol 2013; 24: 931–937.

Annals of Oncology 27: 487–493, 2016
doi:10.1093/annonc/mdv608
Published online 17 December 2015

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

D. Lorusso[1*], G. Scambia[2], S. Pignata[3], R. Sorio[4], G. Amadio[2], S. Lepori[1], A. Mosconi[5], C. Pisano[3], G. Mangili[6], G. Maltese[1], R. Sabbatini[7], G. Artioli[8], T. Gamucci[9], M. Di Napoli[3], E. Capoluongo[10], V. Ludovini[11], F. Raspagliesi[1] & G. Ferrandina[2]

[1]*Gynecologic Oncology Unit, Fondazione IRCCS National Cancer Institute, Milan;* [2]*Department of Obstetrics and Gynecology, Catholic University of Rome;* [3]*Department of Gynecologic and Urologic Oncology, Fondazione Pascale, National Cancer Institute of Naples;* [4]*Department of Oncology, CRO Aviano, Aviano;* [5]*Medical Oncology Unit, University Hospital S. Maria della Misericordia, Perugia;* [6]*Department of Obstetrics and Gynecology, San Raffaele Hospital, Milan;* [7]*Department of Oncology Haematology and Respiratory Disease, AOU Policlinico di Modena, Modena;* [8]*Medical Oncology Unit, Hospital of Mirano, Mirano;* [9]*Medical Oncology Unit, Hospital 'SS. Trinità', Sora;* [10]*Department of Molecular Biology, Catholic University of Rome;* [11]*Molecular Biology Unit, University Hospital S. Maria della Misericordia, Perugia, Italy*

Received 5 August 2015; revised 7 December 2015; accepted 9 December 2015

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

*Correspondence to: Dr Domenica Lorusso, Gynecologic Oncology Unit, Fondazione IRCCS National Cancer Institute of Milan, Via Venezian 1, 20133 Milan, Italy. Tel: +39-0223903697; E-mail: domenica.lorusso@istitutotumori.mi.it

Asha	09/16/15	08:13	4 Color Fig(s):0	ART: ALN201412127

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

Shun Kohsaka, M.D., Hiroaki Miyata, Ph.D., Noboru Motomura, M.D., Kazuhito Imanaka, M.D., Keiichi Fukuda, M.D., Shunei Kyo, M.D., Shinichi Takamoto, M.D.

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

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org).

Submitted for publication December 29, 2014. Accepted for publication August 4, 2015. From the Japan Cardiovascular Surgery Database Organization, Tokyo, Japan (S.K., H.M., N.M., K.I., S.K., S.T.); and Department of Cardiology, Keio University School of Medicine, Tokyo, Japan (S.K., K.F.).

<zdoi;10.1097/ALN.0000000000000901>

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

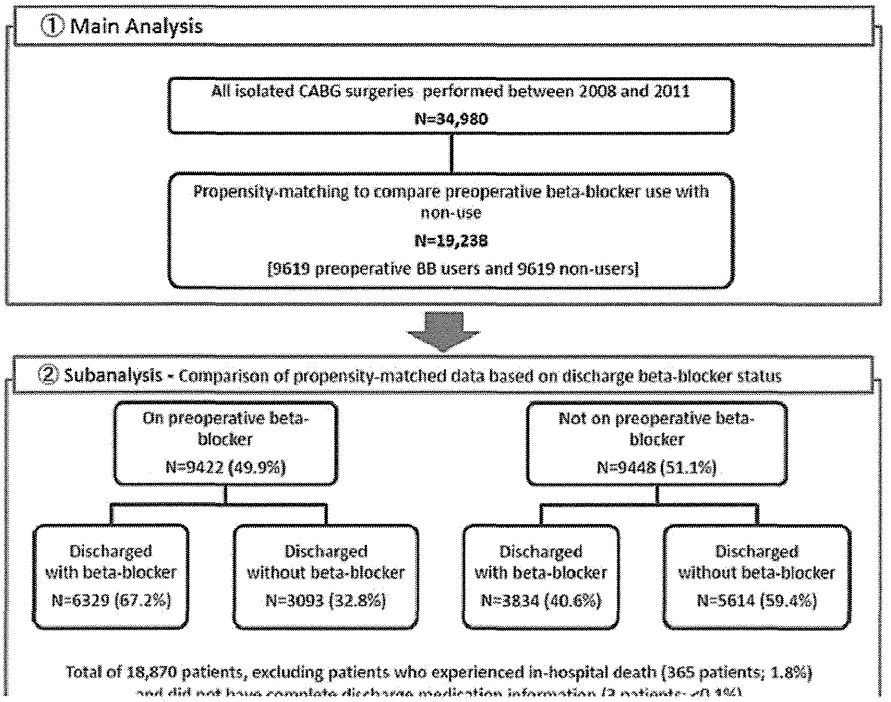
	All Patients				Propensity-matched Patients			
	β	Non-β	*P*	Standardized	β	Non-β	*P*	Standardized
No. of Patients	10,496	24,484	Value	Difference	9,619	9,619	Value	Difference
Digitalis, %	1.3	0.9	< 0.001	0.018	1.3	1.0	0.107	0.012
Intravenous nitrates, %	12.1	12.4	0.001	0.004	11.7	11.7	0.875	0.001
Aspirin, %	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 F1 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. AQ6

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



AQ1

AQ7 **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 AQ8 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). T3

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. F2 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.

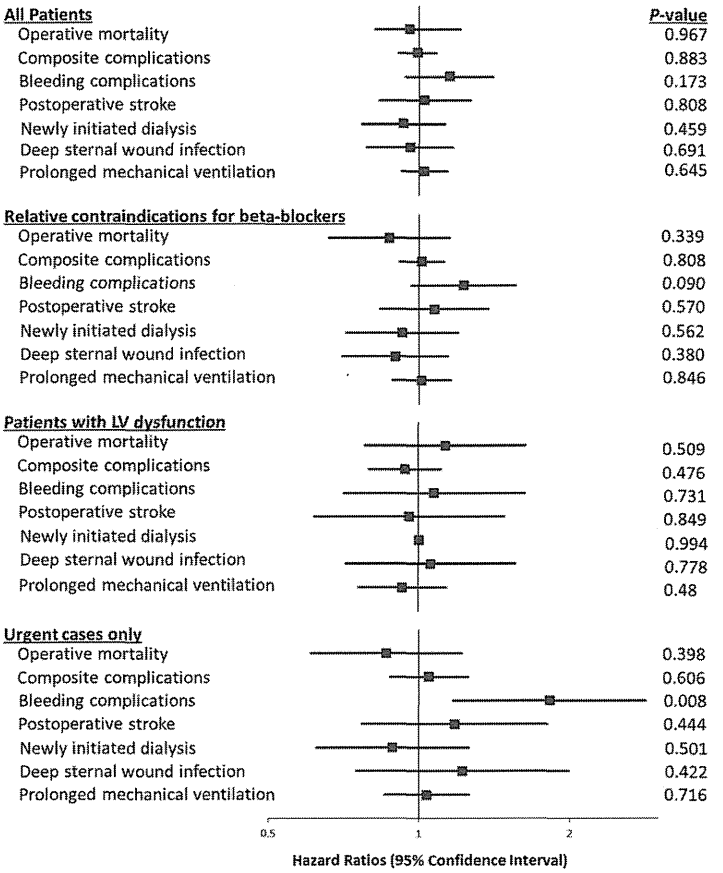


Fig. 2. Adjusted risk of various in-hospital outcomes among all patients and the subgroups of patients with relative contraindications for β-blocker, such as respiratory disability, congestive heart failure within 2 weeks of surgery, cardiopulmonary arrest within 24 h of surgery, cardiogenic shock at 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			
No. of Patients	β 1,810	Non-β 1,815	Odds Ratio (95% CI)	*P* Value	β 2,439	Non-β 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.

Acknowledgments

This research was supported by the Grants-in-Aid for Scientific Research from the Japan Society for the Promotion of Science from the Japanese Ministry of Education, Culture, Sports, Science and Technology (Tokyo, Japan; grant no. 30528659) and Health Labour Sciences Research Grant from the Japanese Ministry of Health Labour and Welfare (Tokyo, Japan; grant no. H26-014).

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.

Correspondence

Address correspondence to Dr. Kohsaka: Department of Cardiology, Keio University, 35 Shinanomachi, Shinjuku,

Tokyo, Japan. kohsaka@cpnet.med.keio.ac.jp.

References

1. Goldman L, Caldera DL, Nussbaum SR, Southwick FS, Krogstad D, Murray B, Burke DS, O'Malley TA, Goroll AH, Caplan CH, Nolan J, Carabello B, Slater EE: Multifactorial index of cardiac risk in noncardiac surgical procedures. N Engl J Med 1977; 297:845–50
2. Effect of metoprolol on death and cardiac events during a 2-year period after coronary artery bypass grafting. The MACB Study Group. Eur Heart J 1995; 16:1825–32
3. Ferguson TB Jr, Coombs LP, Peterson ED; Society of Thoracic Surgeons National Adult Cardiac Surgery Database: Preoperative β-blocker use and mortality and morbidity following CABG surgery in North America. JAMA 2002; 287:2221–7
4. Wijeysundera DN, Duncan D, Nkonde-Price C, Virani SS, Washam JB, Fleischmann KE, Fleisher LA: Perioperative β blockade in noncardiac surgery: A systematic review for the 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. J Am Coll Cardiol 2014; 64:2406–25
5. Brinkman WT, Herbert MA, Prince SL, Magee MJ, Dewey TM, Smith RL, Edgerton JR, Head SJ, Ryan WH, Mack MJ: Preoperative β-blocker usage: Is it really worthy of being a quality indicator? Ann Thorac Surg 2011; 92:788–95; discussion 795–6
6. Wallace AW, Au S, Cason BA: Association of the pattern of use of perioperative β-blockade and postoperative mortality. ANESTHESIOLOGY 2010; 113:794–805
7. Miller RR, Olson HG, Amsterdam EA, Mason DT: Propranolol-withdrawal rebound phenomenon. Exacerbation of coronary events after abrupt cessation of antianginal therapy. N Engl J Med 1975; 293:416–8
8. Psaty BM, Koepsell TD, Wagner EH, LoGerfo JP, Inui TS: The relative risk of incident coronary heart disease associated with recently stopping the use of β-blockers. JAMA 1990; 263:1653–7
9. Rangno RE, Nattel S, Lutterodt A: Prevention of propranolol withdrawal mechanism by prolonged small dose propranolol schedule. Am J Cardiol 1982; 49:828–33
10. Kazui T, Osada H, Fujita H; Japanese Association for Thoracic Surgery Committee for Scientific Affairs: Thoracic and cardiovascular surgery in Japan during 2004. Jpn J Thorac Cardiovasc Surg 2006; 54:363–85
11. Available at: http://jacvsd.umin.jp. Accessed August 5, 2015
12. Available at: http://sts.org. Accessed August 5, 2015
13. Devereaux PJ, Yang H, Yusuf S, Guyatt G, Leslie K, Villar JC, Xavier D, Chrolavicius S, Greenspan L, Pogue J, Pais P, Liu L, Xu S, Málaga G, Avezum A, Chan M, Montori VM, Jacka M, Choi P; POISE Study Group: Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): A randomised controlled trial. Lancet 2008; 371:1839–47
14. Hawkins NM, Petrie MC, Macdonald MR, Jhund PS, Fabbri LM, Wikstrand J, McMurray JJ: Heart failure and chronic obstructive pulmonary disease the quandary of β-blockers and β-agonists. J Am Coll Cardiol 2011; 57:2127–38
15. Mentz RJ, Wojdyla D, Fiuzat M, Chiswell K, Fonarow GC, O'Connor CM: Association of β-blocker use and selectivity with outcomes in patients with heart failure and chronic obstructive pulmonary disease (from OPTIMIZE-HF). Am J Cardiol 2013; 111:582–7
16. London MJ, Hur K, Schwartz GG, Henderson WG: Association of perioperative β-blockade with mortality and cardiovascular morbidity following major noncardiac surgery. JAMA 2013; 309:1704–13
17. Motomura N, Miyata H, Tsukihara H, Okada M, Takamoto S; Japan Cardiovascular Surgery Database Organization: First report on 30-day and operative mortality in risk model of isolated coronary artery bypass grafting in Japan. Ann Thorac Surg 2008; 86:1866–72
18. Hillis LD, Smith PK, Anderson JL, Bittl JA, Bridges CR, Byrne JG, Cigarroa JE, Disesa VJ, Hiratzka LF, Hutter AM Jr, Jessen ME, Keeley EC, Lahey SJ, Lange RA, London MJ, Mack MJ, Patel MR, Puskas JD, Sabik JF, Selnes O, Shahian DM, Trost JC, Winniford MD; American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines; American Association for Thoracic Surgery; Society of Cardiovascular Anesthesiologists; Society of Thoracic Surgeons: 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the American Association for Thoracic Surgery, Society of Cardiovascular Anesthesiologists, and Society of Thoracic Surgeons. J Am Coll Cardiol 2011; 58:e123–210
19. Task Force on Myocardial Revascularization of the European Society of Cardiology, the European Association for Cardio-Thoracic Surgery, European Association for Percutaneous Cardiovascular Interventions, Wijns W, Kolh P, Danchin N, Di Mario C, Falk V, Folliguet T, Garg S, Huber K, James S, Knuuti J, Lopez-Sendon J, Marco J, Menicanti L, Ostojic M, Piepoli MF, Pirlet C, Pomar JL, Reifart N, Ribichini FL, Schalij MJ, Sergeant P, Serruys PW, Silber S, Sousa Uva M, Taggart D: Guidelines on myocardial revascularization. Eur Heart J 2010; 31:2501–55
20. Devereaux PJ, Yusuf S, Yang H, Choi PT, Guyatt GH: Are the recommendations to use perioperative β-blocker therapy in patients undergoing noncardiac surgery based on reliable evidence? CMAJ 2004; 171:245–7
21. Boersma E, Poldermans D, Bax JJ, Steyerberg EW, Thomson IR, Banga JD, van De Ven LL, van Urk H, Roelandt JR; DECREASE Study Group (Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiogrpahy): Predictors of cardiac events after major vascular surgery: Role of clinical characteristics, dobutamine echocardiography, and β-blocker therapy. JAMA 2001; 285:1865–73
22. Bangalore S, Steg G, Deedwania P, Crowley K, Eagle KA, Goto S, Ohman EM, Cannon CP, Smith SC, Zeymer U, Hoffman EB, Messerli FH, Bhatt DL; REACH Registry Investigators: β-Blocker use and clinical outcomes in stable outpatients with and without coronary artery disease. JAMA 2012; 308:1340–9
23. Chen ZM, Pan HC, Chen YP, Peto R, Collins R, Jiang LX, Xie JX, Liu LS; COMMIT (ClOpidogrel and Metoprolol in Myocardial Infarction Trial) Collaborative Group: Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: Randomised placebo-controlled trial. Lancet 2005; 366:1622–32
24. Ozasa N, Kimura T, Morimoto T, Hou H, Tamura T, Shizuta S, Nakagawa Y, Furukawa Y, Hayashi Y, Nakao K, Matsuzaki M, Nobuyoshi M, Mitsudo K; j-Cypher Registry Investigators: Lack of effect of oral β-blocker therapy at discharge on long-term clinical outcomes of ST-segment elevation acute myocardial infarction after primary percutaneous coronary intervention. Am J Cardiol 2010; 106:1225–33
25. Wood AJ: Racial differences in the response to drugs—Pointers to genetic differences. N Engl J Med 2001; 344:1394–6
26. Zhou HH, Koshakji RP, Silberstein DJ, Wilkinson GR, Wood AJ: Altered sensitivity to and clearance of propranolol in men

of Chinese descent as compared with American whites. N Engl J Med 1989; 320:565–70

27. Beltrame JF, Sasayama S, Maseri A: Racial heterogeneity in coronary artery vasomotor reactivity: Differences between Japanese and Caucasian patients. J Am Coll Cardiol 1999; 33:1442–52
28. Pristipino C, Beltrame JF, Finocchiaro ML, Hattori R, Fujita M, Mongiardo R, Cianflone D, Sanna T, Sasayama S, Maseri A: Major racial differences in coronary constrictor response between Japanese and caucasians with recent myocardial infarction. Circulation 2000; 101:1102–8
29. Japanese Beta-Blockers and Calcium Antagonists Myocardial Infarction (JBCMI) Investigators: Comparison of the effects of β blockers and calcium antagonists on cardiovascular events after acute myocardial infarction in Japanese subjects. Am J Cardiol 2004; 93:969–73
30. Kohsaka S, Kimura T, Goto M, Lee VV, Elayda M, Furukawa Y, Fukushima M, Komeda M, Sakata R, Willerson JT, Wilson JM, Kita T: Difference in patient profiles and outcomes in Japanese *versus* American patients undergoing coronary revascularization (collaborative study by CREDO-Kyoto and the Texas Heart Institute Research Database). Am J Cardiol 2010; 105:1698–704
31. Shimohama T, Ako J, Yamasaki M, Otake H, Tsujino I, Hasegawa T, Nakatani D, Sakurai R, Chang H, Kusano H, Waseda K, Honda Y, Stone GW, Saito S, Fitzgerald PJ, Sudhir K: SPIRIT III JAPAN *versus* SPIRIT III USA: A comparative intravascular ultrasound analysis of the everolimus-eluting stent. Am J Cardiol 2010; 106:13–7
32. Cohen J: Statistical Power Analysis for Behavioral Sciences, 2nd edition. Hillsdale: Lawrence Erlbaum Associates Publishers, 1988 AQ15
33. Kohro T, Hayashi D, Yamazaki T, Nagai R; JCAD Investigators: β-Blocker prescription among Japanese cardiologists and its effect on various outcomes. Circ J 2010; 74:962–9

AUTHOR QUERIES

AUTHOR PLEASE ANSWER FOR ALL QUERIES

AQ1—The bottom of the supplied figure 1 file is cut off. Please provide a replacement version that displays the full bottom portion of the figure.

AQ2—Please provide department name (if any) for the authors "H.M., N.M., K.I., S.K., and S.T."

AQ3—Kindly check and confirm the edits made to the summary box text.

AQ4—Please note that the paragraph starting "This research was ..... Tokyo Japan.)" has been deleted since it has already been given under funding section. Kindly approve.

AQ5—Kindly check and confirm if the number "13" in the sentence starting "We selected 0.2 because this ..." has been set correctly.

AQ6—Kindly check and confirm if the term "continuous" in the sentence starting "Postoperative MI was defined ..." should be changed to "contiguous" if appropriate.

AQ7—Please note that "β-blocker" has been taken as the expansion for "BB" in Fig. 1 legend. Kindly confirm.

AQ8—Kindly check and correct the phrase "development sample" if appropriate.

AQ9—Please note that "left ventricular" has been taken as the expansion for "LV" in Fig. 2 legend. Kindly confirm.

AQ10—Kindly approve edits to the sentence beginning "This rate is considerably lower ..."

AQ11—Please provide expansion of "JACVSD."

AQ12—Please check the sentence starting "In the current study, ..." for clarity, if appropriate.

AQ13—Please confirm that the "Acknowledgments" section text is correct as presented.

AQ14—Kindly check and correct the URL given in Ref. 11.

AQ15—Kindly provide chapter title, editors' names, and page range for Ref. 32.

Surg Today (2016) 46:38–47
DOI 10.1007/s00595-015-1146-y

REVIEW ARTICLE

National Clinical Database feedback implementation for quality improvement of cancer treatment in Japan: from good to great through transparency

Mitsukazu Gotoh[1,2] · Hiroaki Miyata[1,2] · Hideki Hashimoto[1,2] · Go Wakabayashi[2] · Hiroyuki Konno[1,2] · Shuichi Miyakawa[3] · Kenichi Sugihara[1] · Masaki Mori[1] · Susumu Satomi[1] · Norihiro Kokudo[1] · Tadashi Iwanaka[1]

Received: 13 January 2015 / Accepted: 26 January 2015 / Published online: 24 March 2015

Abstract The National Clinical Database (NCD) of Japan was established in April, 2010 with ten surgical subspecialty societies on the platform of the Japan Surgical Society. Registrations began in 2011 and over 4,000,000 cases from more than 4100 facilities were registered over a 3-year period. The gastroenterological section of the NCD collaborates with the American College of Surgeons' National Surgical Quality Improvement Program, which shares a similar goal of developing a standardized surgical database for surgical quality improvement, with similar variables for risk adjustment. Risk models of mortality for eight procedures; namely, esophagectomy, partial/total gastrectomy, right hemicolectomy, low anterior resection, hepatectomy, pancreaticoduodenectomy, and surgery for acute diffuse peritonitis, have been established, and feedback reports to participants will be implemented. The outcome measures of this study were 30-day mortality and operative mortality. In this review, we examine the eight risk models, compare the procedural outcomes, outline the feedback reporting, and discuss the future evolution of the NCD.

Keywords Gastrointestinal surgery · National Clinical Database · Nationwide web-based database · Mortality · Risk model

✉ Mitsukazu Gotoh
mgotoh@fmu.ac.jp

[1] National Clinical Database, 1-8-3 Marunouchi, Chiyoda-ku, Tokyo, Japan

[2] The Japanese Society of Gastroenterological Surgery (JSGS), Database Committee, 1-14-1-501 Shintomi, Chuo-ku, Tokyo 104-0041, Japan

[3] Board Certification Committee of JSGS, Tokyo, Japan

Abbreviations

NCD	National Clinical Database
ACS NSQIP	The American College of Surgeons National Surgical Quality Improvement Program
ASA	American Society of Anesthesiologists
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
DIC	Disseminated intravascular coagulation
JSS	The Japan Surgical Society
JSGS	The Japanese Society of Gastroenterological Surgery
ROC	Receiver operating characteristic
SIRS	Systemic inflammatory response syndrome
SSI	Surgical site infection

Introduction

Until recently, no nationwide data on cancer were available in the field of gastroenterological surgery in Japan. In 2006, the Japanese Society of Gastroenterological Surgery (JSGS) formed a committee to devise a database to track surgical patients treated in Japan over the 3 years from 2006 to 2008, and reported relatively low mortality rates for the major surgical procedures [1, 2]. The JSGS acknowledged the importance of risk-adjusted surgical outcomes for accurate comparisons and quality improvement; thus, in April, 2010, it created the database as a subset of the National Clinical Database (NCD) of Japan with major support from the Japan Surgical Society (JSS). Eight other surgical professional societies, including the Japanese Society for Cardiovascular Surgery, the Japanese Society for Vascular Surgery, the Japanese Association for Thoracic Surgery, the Japanese Association for Chest Surgery, the Japanese Society of Pediatric Surgeons, the Japanese Breast Cancer

Society, the Japan Association of Endocrine Surgeons, and the Japanese Society of Thyroid Surgery, joined the NCD. Registrations began in 2011, since when more than 4100 facilities have enrolled and over 4,000,000 cases have been registered over a 3-year period.

The gastroenterological section of the NCD collaborates with the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) [3], which shares a similar goal of developing a standardized surgical database for quality improvement. The NSQIP was originally developed in the 1990s by the United States Veterans' Health Administration and led to marked improvement in surgical quality [4]. The American College of Surgeons (ACS) initiated the ACS-NSQIP in 2006 and demonstrated improved surgical outcomes across all participating hospitals in the private sector [5]. The core members of the NCD joined the meetings and seminars of the ACS-NSQIP and debated various aspects of clinical databases, such as data collection methods and public relations [3]. In addition, the NCD implemented the same items as those of the ACS-NSQIP to conduct international cooperative studies. Reliable 30-day outcomes, including mortality and morbidity, serve as a quality improvement catalyst for ACS-NSQIP-participating institutions. Risk adjustment is a key component of the ACS-NSQIP and most variables included in risk adjustment models focus on patient factors and comorbidities. In this article, we focused on the gastrointestinal surgery subset of the NCD. All cases are input with items representing the surgical performance in each specialty for the following eight procedures: esophagectomy (Eso), total/distal gastrectomy (TG/DG), right hemicolectomy (RHC), low anterior resection (LAR), hepatectomy performed for more than one segment apart from the lateral segment (Hx), pancreaticoduodenectomy (PD), and surgery for acute diffuse peritonitis (ADP). Risk models of mortality for each procedure were created using approximately 120,000 cases registered in 2011, and each model has been accepted and published in peer-reviewed journals [6–13]. We review the results and discuss the future evolution of the NCD using these risk models in terms of the surgical quality improvement program in Japan.

NCD data entry system

Submitting cases to the NCD is a prerequisite for all member institutions of the JSS and JSGS, and only registered cases can be used for board certification [3]. To assure the traceability of data, the NCD continuously tracks persons who approve data, persons in departments who are in charge of annual cases, and persons responsible for data entry, through its web-based data management system. The NCD also continuously validates data consistency through random site visits.

The NCD variables are almost identical to those applied in the ACS-NSQIP (http://www.site.acsnsqip.org/wp-content/uploads/2013/10/ACSNSQIP.PUF_.UserGuide.2012.pdf#search='user+guide+for+the+2012+ACS+NSQIP). The potential independent variables include patient demographics, pre-existing comorbidities, preoperative laboratory values, and perioperative data. The demographic variables include age, sex, smoking status, and drinking status. Patients were categorized according to whether they were brought to hospital directly, by ambulance. General factors such as the patient's body mass index (BMI) and preoperative functional status, defined as independent, partially dependent, or totally dependent, according to their ability to perform activities of daily living (ADL) in the 30 days prior to surgery and immediately before surgery, were also considered. We evaluated the physical status classification by the American Society of Anesthesiologists (ASA) and considered pre-existing comorbidities, including the cardiovascular status, respiratory status, renal status, hematological status, oncological status, preoperative blood transfusion, chronic steroid use, ascites, sepsis, diabetes, open wound, and pregnancy. The laboratory parameters included in the analysis were the white blood cell count, hemoglobin level, hematocrit, platelet count, prothrombin time, and activated partial thromboplastin time, as well as the serum levels of albumin, total bilirubin, aspartate amino transferase, alanine aminotransferase, alkaline phosphatase, urea nitrogen, creatinine, sodium, hemoglobin A1c, and C-reactive protein. The length of surgery, intraoperative blood loss, amount of transfusion, and any accident during the operation were also considered.

Postoperative outcomes evaluated 30 days after surgery were categorized according to the Clavien and Dindo classification [14]. The outcomes included relaparotomy within 30 days after surgery, wound events, anastomotic leak, respiratory events, urinary tract events, central nervous system events, cardiac events, other events, systemic sepsis, sepsis, systemic inflammatory response syndrome, and 24 other complications added by the NCD. For Hx procedures, the indications for surgery and resected subsegments (S1–S8) were included as preoperative variables to create risk models [9].

Outcome measures and statistical analysis

The outcome measures of this study were 30-day mortality and operative mortality. The former was defined as death within 30 days of surgery, regardless of the patient's geographical location, even if the patient had been discharged from hospital. The latter was defined as death within the index hospitalization period, regardless of the length of hospital stay (up to 90 days), as well as any death after discharge, up to 30 days after surgery. Data were randomly

Table 1 Registered cases used to create risk models for 8 surgical procedures [6–13]

	Eso	TG	DG	RHC	LAR	Hx	PD	ADP
Registered cases	5354	20,011	33,917	19,070	16,695	7732	8575	8482
Participating hospitals	713	1623	1737	1689	1620	987	1167	1285
(%)	34.9	79.4	84.9	82.6	79.2	48.3	57.1	62.8
30-day mortality (%)	1.2	0.9	0.5	1.1	0.4	2.0	1.2	9.0
Operative mortality (%)	3.4	2.3	1.2	2.3	0.9	4.0	2.8	14.1
Cancer surgery (%)	98.4	98.5	99.9	92.6	98.5	94.5	91.4	10.8
Emergent case (%)	0.8	2.0	0.9	8.4	1.1	0.8	0.9	92.9

Esophagectomy (Eso), total/distal gastrectomy (TG/DG), right hemicolectomy (RHC), low anterior resection (LAR), hepatectomy performed for >1 segment except for the lateral segment (Hx), pancreaticoduodenectomy (PD), and operation for acute diffuse peritonitis (ADP)

assigned into two subsets that were split 80/20: the first, for model development, and the second, for validation. The two sets of logistic models (30-day mortality and operative mortality) were constructed for dataset development using step-wise selection of the predictors with a probability (p) value for inclusion of 0.05. A "goodness-of-fit" test was performed to assess how well the model could discriminate between patient survival and death. The receiver operating characteristic (ROC) curves for the 30-day and operative mortalities were created for the validation dataset. An ROC curve is a plot of a test's true-positive rate (sensitivity) versus its false-positive rate (1—specificity). Model calibration, being the degree to which the observed outcomes matched the predicted outcomes from the model across a group of patients, was examined by comparing the observed and predicted averages with each of 10 equally sized subgroups, arranged in the order of increasing patient risk.

Case number and participating hospitals for each procedure and mortality rates

The NCD is a nationwide project in cooperation with Japan's board certification system in surgery, for which more than 1,200,000 surgical cases from over 3500 hospitals were collected in 2011. The number of participating hospitals in the gastroenterological section was 2045 at the time of the analysis (July, 2012). Among these cases, approximately 120,000 were used to create the risk models. Table 1 lists the number of cases for each procedure and the number of hospitals performing the respective procedure with its ratio to the total number of hospitals (%). Most procedures, except for ADP, were performed for cancer. Emergency surgery was most common for ADP (93 %). The 30-day mortality and operative mortality rates for the eight procedures were as follows: Eso, 1.2/3.4; TG, 0.9/2.3; DG, 0.5/1.2; RHC, 1.1/2.3; LAR, 0.4/0.9; HX, 2.0/4.0; PD, 1.2/2.8; and ADP, 9.0/14.1 %, respectively (Table 1). The operative mortality for each procedure, apart from ADP, was more than twice that of the 30-day mortality.

Risk models in the eight procedures

The 30-day mortality and operative mortality risk models for the eight procedures were created, and the C-index for those in the validation data sets was as follows: Eso, 0.767/0.742; TG, 0.811/0.824; DG, 0.785/0.798; RHC, 0.836/0.854; LAR, 0.75/0.766; HX, 0.714/0.761; PD, 0.675/0.725; and ADP, 0.851/0.852, respectively (Tables 2, 3). The final logistic models for the 30-day mortality with odds ratios for the eight procedures are listed in Table 2. Age; sex; emergency surgery; ADL; ASA class; BMI; cardiovascular, pulmonary, and renal comorbidities; and other patient conditions such as disseminated cancer, ascites, preoperative transfusion, bleeding disorder, diabetes, weight loss, sepsis, and chronic steroid use, including 121 variables, were found to be risk factors for certain procedures. Age, ADL ASA, BMI, disseminated cancer, bleeding disorder, and weight loss appeared to be common risk factors in most of the procedures. Table 3 lists the final logistic models for the operative mortality with odds ratios for the eight procedures, including 159 variables. New and additional 38 variables were captured for these models.

Feedback implementation (risk calculator)

A risk-adjusted analysis based on nationwide data allows personnel to establish and provide feedback on the risks that patients face before undergoing a procedure. On the basis of these objective data, healthcare professionals can then determine the treatment indicators and obtain informed consent. The risk calculator for all eight procedures will be available soon, on the websites of the hospitals that are a part of NCD, although the calculators for TG, PD, Hx, Eso, RHC, and LAR are currently available (February, 2015). The real-time feedback system gives the predicted mortality of patients simultaneously with data input. Standardized information on patient risk and predicted mortality can be reformulated as case reports and shared at conferences.

Table 2 Risk models for 30-day mortality after 8 gastrointestinal procedures (refs 6–13)

Variables	Eso	TG	DG	RHC	LAR	Hx	PD	ADP
Age category	1.5	1.2	1.2		1.3	1.4	1.3	1.2
Male sex						1.6	2.0	
Ambulance transport								1.4
Emergent surgery				1.9		3.8	4.3	
ADL within 30 days before surgery								
Any assistance	4.2					2.1		
Total			3.0					
ADL immediately before surgery								
Any assistance		2.1		2.8				
Total								1.4
ASA								
Class 3				2.3				2.7
Class 4								4.3
Class 5								8.7
Class 3, 4, 5			2.0			2.0	2.2	
Class 4, 5		9.4		4.0				
BMI								
>25 kg/m^2							2.4	
>30 kg/m^2					7.0			
Congestive heart failure				2.3				
Previous cardiac surgery		2.3						
Myocardial infarction			3.1					
Previous PCI								2.0
Previous PVD surgery					6.2			2.5
Cerebrovascular disease			2.1					
COPD							2.4	
Preoperative pneumonia			2.8					
Respiratory distress								1.6
Acute renal failure				3.2				
Preoperative dialysis		3.9						
Cancer with multiple metastases				2.2				
Disseminated cancer		2.6			4.9			2.2
Preoperative transfusion		1.9			5.4			1.6
Bleeding disorder without treatment			3.2		5.2			1.6
Bleeding disorder							4.4	
Diabetes		2.2						
Smoking within 1 year	2.6							
Ascites		2.0				2.1		
Without control			3.0					
Chronic steroid use								1.7
Weight loss	2.4		2.3					
Sepsis				2.0				
Habitual alcohol consumption			1.6					
WBC								
>12,000/μl	3.7		3.7					
>9000/μl				1.5				
<4000/μl	2.8							1.4

Table 2 continued

Variables	Eso	TG	DG	RHC	LAR	Hx	PD	ADP
Hemoglobin								
M < 13.5 g/dl, F < 12.5 g/dl		1.7	1.8					
<10.0 g/dl								1.3
Platelet								
>400,000/μl	2.5							
<150,000/μl								1.5
<120,000/μl				1.9	5.0	1.7		
<80,000/μl		3.1						1.5
<50,000/μl				5.6				
Albumin								
<4.0 g/dl				2.0	3.4			
<3.5 g/dl		1.7	1.5			2.0		
<2.0 g/dl								1.7
Total bilirubin								
>3.0 mg/dl				3.1				1.7
>2.0 mg/dl		2.9						
AST								
>35 U/l		2.3		3.1		2.3		1.4
ALP								
>600 U/l		2.5						1.7
>340 U/l		1.7	2.2					
BUN								
>25 mg/dl		1.9			2.5			1.4
>20 mg/dl								1.8
<8.0 mg/dl							2.3	
Creatinine								
>2.0 mg/dl						3.9		
>1.2 mg/dl			1.8					
Serum Na								
>145 mEq/l								1.7
<138 mEq/l				2.1	3.6			
<135 mEq/l	3.6		2.5					
<130 mEq/l								1.7
CRP								
<10.0 mg/dl								1.5
APTT								
>40 s							3.2	
PT-INR								
>1.25		2.2	2.0					
>1.1	2.0			1.5		1.7		
Non-tumor bearing								0.6
Surgical procedures						#1		
Indication for surgery						#2		

#1 Hepatectomy with S8 (2.2), hepatectomy with revascularization (3.8)

#2 Hilar bile duct carcinoma (2.5), gallbladder cancer (4.1)

ADL, Activities of daily living, PT-INR Prothrombin time-international normalized ratio, *WBC* white blood cells, *ASA* American society of anesthesiologists, *ADL* activities of daily living, *PCI* percutaneous coronary intervention, *COPD* chronic obstructive pulmonary disease, *AST* aspartate amino transferase, *ALP* alkaline phosphatase, *APTT* activated partial thromboplastin time

Table 3 Risk models for operative mortality after 8 gastrointestinal procedures [6–13]

Variables	Eso	TG	DG	RHC	LAR	Hx	PD	ADP
Age category	1.4	1.3	1.3	1.1	1.4	1.4	1.3	1.3
Male sex	2.3				1.9	1.5		
Emergent surgery		1.7	1.9	1.9		2.8		
ADL within 30 days before surgery								
Any assistance	4.7					2.8	2.5	
Total								1.6
ADL immediately before surgery								
Any assistance		2.0		2.5	2.5			1.4
Total			3.0		2.9			
ASA								
Class 3		1.8		1.6				2.3
Class 4								4.7
Class 5								6.5
Class 3, 4, 5			1.9			2.0	2.1	
Class 4, 5		5.2		2.9				
BMI								
>25 kg/m^2							1.9	
>30 kg/m^2					4.6			
Congestive heart failure				2.2				
Angina							2.6	
Previous PVD surgery				3.1	5.8			
Cerebrovascular disease			1.8					
Cerebrovascular accident		1.9						
Respiratory distress								
Any		1.7	2.4		2.9		2.4	
COPD	2.1					2.0		
Preoperative pneumonia						3.8		1.4
Preoperative dialysis		2.6		2.1				
Cancer metastasis/relapse	4.5			1.6				
Disseminated cancer		3.5	2.9	3.1	2.8			2.1
Preoperative transfusion					2.6			1.8
Bleeding disorder without therapy								1.6
Brinkman index							1.6	
Ascites								
Any		1.8		1.6	4.0	1.9		
Without control			2.8					
Chronic steroid use			2.8	2.0				1.9
Weight loss	2.0	1.6	2.2	1.6			2.1	1.4
Sepsis				1.7				
WBC								
>11,000/μl		2.0	2.5				3.1	
>9000/μl				1.6				
<4500/μl	1.8							1.5
<3500/μl		1.6						
Hemoglobin								
M < 13.5 g/dl, F < 12.5 g/dl					2.6			1.3
<10 g/dl						1.8		
Hematocrit								
M > 48 %, F > 42 %					3.6			