Effects of Bisoprolol Transdermal Patches for Prevention of Perioperative Myocardial Injury in High-Risk Patients Undergoing Non-Cardiac Surgery — Multicenter Randomized Controlled Study —

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Background: The aim of this study was to evaluate the efficacy and safety of transdermal β-blocker patches, which offer stable blood concentration and easy availability during operation, for prevention of perioperative myocardial injury (PMI) in high-risk patients.

Methods and Results: In this randomized controlled trial, patients aged >60 years with hypertension and high revised cardiac risk index (≥2) undergoing non-cardiac surgery were randomly assigned to a bisoprolol patch or control group. Primary efficacy outcome was incidence of PMI, defined as postoperative high-sensitivity cardiac troponin T (hs-cTnT) >0.014ng/mL and relative hs-cTnT change ≥20%. Secondary efficacy outcomes were number of cardiovascular events and 30-day mortality. From November 2014 to February 2019, 240 patients from 5 hospitals were enrolled in this study. The incidence of PMI was 35.7% in the bisoprolol patch group and 44.5% in the control group (P=0.18). Incidence of major adverse cardiac events including non-critical myocardial infarction, strokes, decompensated heart failure and tachyarrhythmia was similar between the 2 groups. Tachyarrhythmia tended to be higher in the control group. There were no significant differences in safety outcomes including significant hypotension and bradycardia requiring any treatment between the 2 groups.

Conclusions: Bisoprolol patches do not influence the incidence of PMI and cardiovascular events in high-risk patients undergoing non-cardiac surgery, but perioperative use of these patches is safe.

Key Words: Bisoprolol transdermal patch; High-sensitivity cardiac troponin T; Perioperative myocardial injury

Perioperative myocardial injury (PMI), which is defined as an increase in cardiac troponin after surgery, is increasingly recognized as being associated with a higher risk of morbidity and mortality after non-cardiac surgery. It occurs in 8–52% of patients who undergo non-cardiac surgery and has received considerable attention since it was reported to be associated with an increased risk of morbidity and mortality.1–6 The main pathology of PMI is thought to be myocardial ischemia, possibly attributable to pre-existing coronary artery disease (CAD), plaque rupture, or imbalance between myocardial oxygen supply and demand. Interestingly, the incidence of coronary artery stenosis is poorly correlated with postoperative myocardial infarction; and revascularization before high-risk surgery does not improve the long-term outcome.8 Indeed, it was recently reported that non-ischemic factors, such as sepsis, tachyarrhythmia, and hypotension, play a greater role than does ischemia.11–13 Beta-blocker treatment has been expected to reduce cardiovascular events after surgery, but a meta-analysis of randomized controlled trials (RCT) suggested that β-blockers reduce non-fatal myocardial infarction but increase stroke and hypotension.14 The efficacy of perioperative β-blockers, even in high-risk patients, is therefore controversial and current guidelines do not recommend routine use of perioperative β-blockers. Bisoprolol patches,
a newly developed form of \( \beta \)-blocker in Japan, are designed to deliver bisoprolol through the skin to produce stable blood concentration.\(^{15}\) The safety and efficacy of bisoprolol patches in patients with heart failure have recently been demonstrated.\(^{16}\) We therefore designed this RCT to evaluate the safety and efficacy of bisoprolol patches in high-risk patients undergoing non-cardiac surgery.

**Methods**

**Study Design**

This study (MAMACARI study; UMIN000016908) was a multicenter, prospective randomized controlled, open-label study designed to evaluate the efficacy and safety of \( \beta \)-blocker patches for prevention of PMI in high-risk patients undergoing non-cardiac surgery. An outline of the study protocol is shown in **Figure 1**. The study was approved by the local medical ethics committee (application number of Ethics Committee of Okayama University m07015) and all patients provided written informed consent. This trial was conducted in compliance with the Declaration of Helsinki.

**Participants**

The key inclusion and exclusion criteria are detailed in **Table 1**. Patients were eligible if they were aged \( \geq 60 \) years, had hypertension and revised cardiac risk index (RCRI) \( \geq 2 \), and were scheduled to undergo elective non-cardiac surgery under general anestheisa. RCRI assigns 1 point for each of 6 criteria (high-risk type of surgery; history of isch-
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Baseline clinical data were obtained in the preoperative period before randomization and consisted of patient characteristics, physical status, comorbidities, all perioperative medication, and type of surgery. American Society of Anesthesiologists (ASA) class and RCRI were also determined for all patients. All patients underwent electrocardiography, chest radiography, transthoracic echocardiography, and pulmonary function test in the preoperative period.

The anesthesia route, surgical status, and duration of surgery were recorded.

Serum concentration of fifth-generation high-sensitivity cardiac troponin T (hs-cTnT) was measured before and 24 h (postoperative day 1) and 72 h (postoperative day 3) after non-cardiac surgery. All plasma samples were frozen and stored at −20°C in the hospital's laboratory until analysis. hs-cTnT concentration was measured using a commercially available Electrochemiluminescence Immunoassay and a Cobas® 8000 modular analyzer (Roche Diagnostics, Rotkreuz, Switzerland). hs-cTnT concentration >0.014 ng/mL was considered to be high, in accordance with the hospital laboratory’s normal range.

Outcomes

The primary efficacy outcome was the incidence of PMI, for which there is currently no generally accepted definition. In previous studies, hs-cTnT has been shown to be a more reliable marker for predicting adverse short-term and long-term outcomes in a perioperative setting. Therefore in our study we used fifth-generation hs-cTnT to improve the accuracy of diagnosis of PMI. In accordance with our previous study, PMI was defined as postoperative hs-cTnT >0.014 ng/mL and relative hs-cTnT change.
| Table 2. Baseline Characteristics of All Randomized Patients |
|-----------------|-----------------|-----------------|
|                  | Bisoprolol patch (n=120) | Control (n=120) |
| Age (years)      | 76 (67–85)       | 76 (66–86)      |
| Female sex       | 28 (23)          | 28 (23)         |
| BMI (kg/m²)      | 22.8 (20.6–24.7) | 22.8 (21.2–25.3) |
| RCRI score       | 2 (2–2)          | 2 (2–2)         |
| RCRI factors     |                  |                 |
| High-risk procedure | 98 (82)      | 103 (86)         |
| History of IHD   | 73 (61)          | 65 (54)          |
| History of heart failure | 34 (28) | 29 (24)         |
| History of CVD   | 37 (31)          | 36 (30)          |
| Renal failure (creatinine ≥2.0 mg/dL) | 5 (4) | 6 (5) |
| Preoperative insulin use | 19 (16) | 22 (18) |
| ASA class        |                  |                 |
| 2                | 82 (68)          | 82 (68)         |
| 3                | 38 (32)          | 38 (32)         |
| History          |                  |                 |
| Hypertension     | 120 (100)        | 120 (100)       |
| Diabetes mellitus| 53 (44)          | 62 (52)         |
| Dyslipidemia     | 62 (52)          | 62 (52)         |
| Smoker           | 77 (64)          | 72 (60)         |
| PAF              | 5 (4.2)          | 9 (8)           |
| Peripheral artery disease | 11 (9) | 9 (8) |
| Obstructive lung disease | 30 (25) | 35 (29) |
| Asthma           | 2 (2)            | 3 (3)           |
| Previous treatment |                |                 |
| PCI              | 16 (13)          | 19 (16)         |
| CABG             | 1 (1)            | 5 (4)           |
| Pacemaker        | 4 (3)            | 2 (2)           |
| Bisoprolol patch dose (mg) | 2 (2–4) |                |
| SBP (mmHg)       | 140 (128–149)    | 140 (127–151)   |
| DBP (mmHg)       | 74 (66–83)       | 76 (65–83)      |
| Pulse (beats/min)| 71 (64–80)       | 72 (62–82)      |
| LVEF (%)         | 66 (61–69)       | 66 (62–69)      |
| LAD (mm)         | 37 (34–40)       | 36 (32–40)      |
| E/e'             | 11.4 (8.6–14.8)  | 12.3 (9.3–14.9) |
| eGFR (mL/min/1.73 m²) | 58.4 (47–70) | 57.2 (47.4–71.2) |
| Medication       |                  |                 |
| Calcium blocker  | 71 (59)          | 70 (58)         |
| ACEI             | 9 (8)            | 12 (10)         |
| ARB              | 62 (52)          | 53 (44)         |
| Diuretics        | 18 (15)          | 11 (9)          |
| Antiplatelet therapy | 37 (31) | 49 (41)       |
| OAC              | 16 (13)          | 16 (13)         |
| Statin           | 44 (37)          | 49 (41)         |
| Vital capacity (L) | 2.96 (2.3–3.41) | 2.78 (2.47–3.29) |
| FEV1.0 (%)       | 75 (68–79)       | 75 (68–80)      |
| Surgical specialty |                |                 |
| General          | 31 (26)          | 34 (28)         |
| Thoracic         | 45 (38)          | 57 (48)         |
| Vascular         | 26 (22)          | 20 (17)         |
| Neurosurgery     | 5 (4)            | 0 (0)           |
| Orthopedic       | 3 (3)            | 2 (2)           |
| Otolaryngology   | 2 (2)            | 2 (2)           |
| Urology          | 3 (3)            | 4 (3)           |
| Others           | 5 (4)            | 1 (1)           |
| Anesthesia       |                  |                 |
| Inhalation anesthesia | 78 (65) | 73 (61)     |
| Duration of surgery (min) | 249 (187–374) | 250 (180–385) |

Data given as n (%) or median (IQR). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ASA class, American Society of Anesthesiologists; BMI, body mass index; CVD, cerebrovascular disease; DBP, diastolic blood pressure; E/e’, ratio of transmural early filling velocity to early diastolic tissue velocity; FEV1.0, forced expiratory volume in 1 s; IHD, ischemic heart disease; LAD, left atrial dimension; LVEF, left ventricular ejection fraction; OAC, oral anticoagulants; PAF, paroxysmal atrial fibrillation; RCRI, Revised Cardiac Risk Index. Other abbreviations as in Table 1.
Bisoprolol Patches for Prevention of PMI

received at least 1 dose of study drug. Safety outcomes (significant hypotension and bradycardia, requiring discontinuation of bisoprolol patch, or any treatment with continuous infusion of catecholamines) were analyzed using the Pearson’s chi-squared test with the same stratification factors as for primary outcome. Subgroup analysis for primary efficacy outcome, including age, sex, previous heart disease, coronary risk factors, risk of operation, and preoperative hemodynamic variables, was also performed. P<0.05 was considered to indicate significance. Statistical analysis was performed using IBM SPSS 24.0 for Windows (IBM, Armonk, NY, USA).

Results

Patient Characteristics
This study started on 1st November 2014 and ended on 28th February 2019 and involved 5 institutions in Japan. A total of 240 patients undergoing non-cardiac surgery were randomly assigned to a bisoprolol patch or control group. Some patients were excluded because of cancellation or postponement of surgery. ITT analysis was performed on 112 patients in the bisoprolol patch group and 110 in the control group. The trial protocol is shown in Figure 2.

Baseline patient characteristics are presented in Table 2; none differed significantly between the 2 groups. The mean age was 76 years and 28% were women. Median RCRI was 2 points and the rate of high-risk procedures was >80%. The incidence of concomitant diseases did not differ significantly between the 2 groups. There were no significant differences in blood pressure, heart rate, ejection fraction, or medication during the preoperative period between the 2 groups. Lung function, surgical specialty, and duration of surgery also did not differ significantly between the 2 groups.

Bisoprolol Patch Dose
The initial dose was set to 4mg, and the dose could be reduced to 2mg or use of the patch could be stopped (at the discretion of the attending physician) if this low dose was not tolerated. Bisoprolol patch dose at the time of surgery was 4mg for 34 patients, 2mg for 65 patients, 1mg for 6 patients, and 0mg for 7 patients.
Efficacy

In the whole study cohort, 37% of patients were diagnosed with PMI. The primary efficacy outcome, the incidence of PMI, was 35.7% in the bisoprolol patch group and 44.5% in the control group (P=0.18; Figure 3); thus, the difference was not statistically significant. The incidence of major adverse cardiac events including non-critical myocardial infarction, strokes, decompensated heart failure and tachyarrhythmia was similar between the 2 groups.

Tachyarrhythmia including new-onset AF, atrial tachycardia, inappropriate sinus tachycardia and ventricular tachycardia requiring any treatment ≤30 days after surgery occurred more often in the control group (Table 3), but the difference between the 2 groups was not statistically significant. The incidence of AF, however, was significantly higher in the bisoprolol group than in the control group (P<0.035).

The incidence of decompensated heart failure was also similar between the 2 groups. In this study, there were 3 cases of decompensated heart failure after surgery: 2 patients were in the bisoprolol patch group and 1 was in the control group. In 1 of those 2 patients assigned to the bisoprolol patch group, bradycardia occurred before surgery and use of the bisoprolol patch was discontinued. That patient, however, had a tachycardia attack that led to decompensated heart failure 1 day after surgery, and continuous i.v. infusion of landiolol, a β-blocker, had to be started. The other patient with bisoprolol patch and the 1

Table 3. Secondary Efficacy and Safety Outcomes

| Events                              | Bisoprolol group | Control group | P-value |
|-------------------------------------|------------------|---------------|---------|
| 30-day mortality                    | 0 (0)            | 0 (0)         | n.s.    |
| Major cardiovascular events         | 12 (10.7)        | 19 (17.2)     | 0.16    |
| Non-fatal myocardial infarction     | 2 (1.8)          | 1 (0.9)       | 0.57    |
| Non-fatal stroke                     | 1 (0.9)          | 2 (1.8)       | 0.55    |
| Decompensated heart failure         | 2 (1.8)          | 1 (0.9)       | 0.57    |
| Tachyarrhythmia                     | 7 (6.3)          | 15 (13.6)     | 0.07    |
| Atrial fibrillation                 | 4 (3.6)          | 12 (10.9)     | 0.035   |
| Atrial tachycardia                  | 2 (1.8)          | 1 (0.9)       | 0.57    |
| Inappropriate sinus tachycardia     | 1 (0.9)          | 1 (0.9)       | 0.99    |
| Ventricular tachycardia             | 0 (0)            | 1 (0.9)       | 0.31    |
| Bradycardia                         | 8 (7.1)          | 2 (1.8)       | 0.06    |
| Hypotension                         | 13 (11.6)        | 7 (6.4)       | 0.17    |

Figure 4. Subgroup analysis for primary efficacy outcome: forest plot of odds ratios (bisoprolol patch group vs. control group) for incidence of perioperative myocardial injury. eGFR, estimated glomerular filtration rate; RCRI, revised cardiac risk index.
patient without bisoprolol patch had decompensated heart failure because of volume overload and increasing blood pressure after surgery.

On subgroup analysis, age, sex, previous heart disease, coronary risk factors, risk of operation, and preoperative hemodynamic variables were not significantly different between the 2 groups with regard to the primary efficacy outcome (Figure 4).

Safety

Safety outcomes, including hypotension and bradycardia, did not differ significantly between the bisoprolol patch and control groups (hypotension, 11.6% vs. 6.4%, \(P=0.17\); bradycardia, 7.1% vs. 1.8%, \(P=0.06\); Table 3). Use of the bisoprolol patch was discontinued in 9 patients due to bradycardia (n=3), hypotension (n=3), and bradycardia and hypotension (n=3).

Discussion

The safety and efficacy of bisoprolol patches in high-risk patients undergoing non-cardiac surgery were evaluated in this RCT, and it was found that bisoprolol patches do not influence the occurrence of PMI as defined by cTnT elevation and major cardiovascular events, including non-critical myocardial infarction and stroke. There were no significant differences in safety outcomes, such as in hypotension and bradycardia, between the bisoprolol patch and control groups. Therefore, the safety of bisoprolol patches in the perioperative period has been demonstrated in this trial.

PMI is recognized as an important surrogate for short- and long-term mortality after non-cardiac surgery.1 4 The main pathology of PMI is myocardial ischemia, possibly caused by pre-existing CAD, plaque rupture, or imbalance between myocardial oxygen supply and demand. Anemia and hemodynamic instability caused by major bleeding during surgery may accelerate myocardial ischemia. Non-ischemic causes, such as hypotension, sepsis, and AF, have also been shown to be more common than ischemic causes.11 13 We previously reported that left ventricular diastolic dysfunction and intraoperative tachycardia are predictors of PMI, and that AF is a common complication after surgery.21 Therefore, the use of prophylactic \(\beta\)-blockers before surgery was expected to prevent PMI and associated adverse events.

Many studies on the means of preventing PMI have recently been performed. Coronary artery revascularization before elective surgery does not reduce the incidence of cardiac events after surgery.18 Clinical studies on the ability of various drugs to reduce perioperative cardiovascular events have been reported,24 but none has shown positive effects. Of these, \(\beta\)-blockers were the only drugs expected to reduce cardiovascular events. The POISE trial was a large and well-known RCT on the efficacy of \(\beta\)-blockers.25 Fewer patients in the metoprolol group than in the placebo group had myocardial infarction, but the rates of stroke and death were higher in the metoprolol than in the placebo group.25 The problem with that trial was that the use of a relatively high dose of the long-acting metoprolol just before surgery, without titration, caused serious hypotension and stroke. The advantages and disadvantages of \(\beta\)-blockers in the perioperative period need to be recognized.

To overcome the limitations of previous studies of perioperative \(\beta\)-blockers, several points, including trial design and dosage and route, require consideration. Bisoprolol transdermal patch, a newly developed form of \(\beta\)-blocker in Japan, is designed to deliver the drug through the skin. Using bisoprolol transdermal patches has several benefits. First, it enables stabilization of bisoprolol blood concentration, making hemodynamic instability less likely. Second, bisoprolol patch can be used in patients with gastrointestinal disease undergoing abdominal surgery, for whom perioperative oral treatment would be difficult. Third, bisoprolol patches can be safely and effectively used in patients with AF and heart failure.16 26 27 In the perioperative setting, it is important to introduce a \(\beta\)-blocker over several days before surgery. In this study, the use of bisoprolol patches from 7 days before surgery resulted in lower frequencies of intraoperative and postoperative hypotension and bradycardia than in previous studies.11 28

This does not prove that using bisoprolol patches in high-risk patients prevents PMI. We think that these negative results may be attributable to heterogeneity in factors such as patient background, surgical procedures, intraoperative and postoperative hemodynamics, and postoperative inflammation. We did, however, show that bisoprolol patches have the potential to prevent ischemia- and tachycardia-related events without causing hemodynamic instability.

In the whole study cohort, 37% of patients were diagnosed as having PMI; this is similar to that in other trials.1 4 19 20 In the present study, approximately one-third of patients diagnosed with PMI had some type of event after surgery; and tachyarrhythmia-related events occurred in half of those who had any events.

We have previously reported that intraoperative tachycardia is an independent predictive factor for cardiovascular events.21 In the present study, however, baseline heart rate at rest was not associated with the incidence of PMI or with cardiovascular events. Distribution of PMI by type of surgical procedure is an important consideration, but the incidence of PMI did not differ significantly by surgical procedure in this trial. Further studies are recommended to determine the indications for bisoprolol patch, to achieve reduction in the incidence of PMI and of cardiovascular events.

Study Limitations

This study had several limitations. First, there is no universally accepted definition of PMI. Second, we calculated that we required a sample of 240 patients for this study, this calculation being based on a previous cohort trial in which use of \(\beta\)-blockers was associated with approximately 50% risk reduction, but a 50% reduction may have been too high for this study. A third limitation is patient selection. We enrolled patients with relatively low risk in this study and excluded those with absolute or relative indications for bisoprolol. Fourth, the bisoprolol patch dose may not have been sufficient to prevent PMI. The median bisoprolol dose used was 2 mg in the bisoprolol patch group, and this dose may have been too low for prevention of PMI and cardiovascular events. If, however, the dose is increased further, the incidence of side-effects such as bradycardia and hypotension may increase. Based on the present results, we consider that 2 mg bisoprolol in the patch is the optimal dose for Japanese high-risk patients undergoing non-cardiac surgery. A further large-scale study is needed.
Conclusions

In this prospective, multicenter randomized controlled, open-label trial the use of bisoprolol patches moderately reduced the incidence of PMI in high-risk patients undergoing non-cardiac surgery, but this was not statistically significant, possibly because the study was underpowered. Conversely, this trial did establish the safety of bisoprolol patches in the perioperative period in such patients.

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Appendix

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