# A meta-analysis of adjusted hazard ratios from 20 observational studies of bilateral versus single internal thoracic artery coronary artery bypass grafting

Hisato Takagi, MD, PhD, Shin-nosuke Goto, MD, Taku Watanabe, MD, Yusuke Mizuno, MD, Norikazu Kawai, MD, and Takuya Umemoto, MD, PhD

**Objective:** In 2001, a landmark meta-analysis of bilateral internal thoracic artery (BITA) versus single internal thoracic artery (SITA) coronary artery bypass grafting for long-term survival included 7 observational studies (only 3 of which reported adjusted hazard ratios [HRs]) enrolling approximately 16,000 patients. Updating the previous meta-analysis to determine whether BITA grafting reduces long-term mortality relative to SITA grafting, we exclusively abstracte, then combined in a meta-analysis, adjusted (not unadjusted) HRs from observational studies.

**Methods:** MEDLINE and EMBASE were searched until September 2013. Eligible studies were observational studies of BITA versus SITA grafting and reporting an adjusted HR for long-term (≥4 years) mortality as an outcome. Meta-regression analyses were performed to determine whether the effects of BITA grafting were modulated by the prespecified factors.

**Results:** Twenty observational studies enrolling 70,897 patients were identified and included. A pooled analysis suggested a significant reduction in long-term mortality with BITA relative to SITA grafting (HR, 0.80; 95% confidence interval, 0.77 to 0.84). When data from 6 pedicled and 6 skeletonized internal thoracic artery studies were separately pooled, BITA grafting was associated with a statistically significant 26% and 16% reduction in mortality relative to SITA grafting, respectively ($P$ for subgroup differences = .04). A meta-regression coefficient was significantly negative for the proportion of men (−0.00960; −0.01806 to −0.00114).

**Conclusions:** Based on an updated meta-analysis of exclusive adjusted HRs from 20 observational studies enrolling more than 70,000 patients, BITA grafting seems to significantly reduce long-term mortality. As the proportion of men increases, BITA grafting is more beneficial in reducing mortality. (J Thorac Cardiovasc Surg 2014;148:1282-90)

ACD

In 2001, a landmark meta-analysis by Taggart and colleagues[1] of bilateral internal thoracic artery (BITA) versus single internal thoracic artery (SITA) grafting in coronary artery bypass grafting (CABG) was published in the *Lancet*. The BITA group had significantly better long-term survival than the SITA group (hazard ratio [HR] for death, 0.81; 95% confidence interval [CI], 0.70 to 0.94). The meta-analysis,[1] however, included only 7 observational studies[2-8] that had enrolled 15,962 patients and were published in the 1990s. On the one hand, the Cox model was used in an attempt to adjust for the characteristics of the patients (eg, mean age, sex distribution, ventricular function, diabetic status, and so forth) that differed between the 2 groups in 3 reports[3,5,8]; on the other hand, no statistical attempts to adjust for the distribution of these variables were made in the other studies.[2,4,6,7] Furthermore, the largest (enrolling 10,124 patients) study by Lytle and colleagues[5] had the highest weight (40.4%) in the meta-analysis,[1] and we revealed that exclusion of that study[5] from the analysis substantively altered the overall result (statistically significant benefit in the BITA group than the SITA group for long-term mortality) to no statistically significant difference (HR, 0.85; 95% CI, 0.68 to 1.05; calculated by us) between the 2 groups. Since the previous meta-analysis[1] was performed, several studies on BITA versus SITA grafting in CABG have been published. In a recent large study published in 2013 by Parsa and colleagues,[9] which enrolled 17,609 patients (more than the 15,962 patients included in the meta-analysis[1]), adjusted mortality was similar (HR, 0.95; 95% CI, 0.83 to 1.08) between the BITA and SITA groups. To the best of our knowledge, only 2 randomized controlled trials[10,11] of BITA versus SITA grafting in CABG have been published until now. In a small trial by Myers and colleagues,[10] randomizing only 162 patients with a median 7.5-year follow-up, 5-year survival was not different (96.3% [95% CI, 92.0% to 98.7%] vs 93.8%

From the Shizuoka Medical Center, Department of Cardiovascular Surgery, Shizuoka, Japan.

Disclosures: Authors have nothing to disclose with regard to commercial support.
Received for publication Oct 29, 2013; revisions received Dec 23, 2013; accepted for publication Jan 10, 2014; available ahead of print Feb 9, 2014.

Address for reprints: Hisato Takagi, MD, PhD, Shizuoka Medical Center, Department of Cardiovascular Surgery, 762-1 Nagasawa, Shimizu-cho, Sunto-gun, Shizuoka 411-8611, Japan (E-mail: kfgth973@ybb.ne.jp).

0022-5223/$36.00



http://dx.doi.org/10.1016/j.jtcvs.2014.01.010

**Abbreviations and Acronyms**

BITA = bilateral internal thoracic artery
CABG = coronary artery bypass grafting
CI = confidence interval
ITA = internal thoracic artery
OR = odds ratio
RR = relative risk
SITA = single internal thoracic artery
SWI = sternal wound infection

[95% CI, 88.4% to 97.3%]; $P = .39$) between the BITA and SITA groups. Another relatively large trial randomizing 3102 patients, the Arterial Revascularization Trial,[11] also demonstrated similar mortality at only 1 year (2.5% for BITA vs 2.3% for SITA; relative risk [RR], 1.06; 95% CI, 0.68 to 1.67). Accordingly, evidence for long-term survival in BITA versus SITA grafting in CABG from randomized controlled trials remains insufficient.

Updating the meta-analysis by Taggart and colleagues[1] to determine whether BITA grafting reduces long-term mortality relative to SITA grafting in CABG, we exclusively abstracted, then combined in a meta-analysis, adjusted (not unadjusted [crude]) risk estimates for long-term mortality from 20 observational studies (more than 70,000 patients were enrolled, which was more than quadruple the number of patients included in the previous meta-analysis[1]). Moreover, meta-regression analyses were performed to determine whether the effects of BITA grafting were modulated by prespecified factors.

## METHODS

### Search Strategy and Study Selection

All observational studies of BITA versus SITA grafting that enrolled patients undergoing isolated CABG and reported adjusted risk estimates for long-term mortality were identified using the same search strategy as in the previous meta-analysis by Taggart and colleagues.[1] The MEDLINE and EMBASE databases were searched for publications containing the words "internal," "mammary," "thoracic," "single," "unilateral," "bilateral," "multiple," "artery," "arteries," "singly" and in combination, between 1972 (MEDLINE) or 1980 (EMBASE) and September 2013. Two of us (H.T. and S.G.) independently inspected the electronic reports identified by the searches. We included published studies that had at least 100 patients in each group, and had a median (or mean) follow-up of at least 4 years. Only data from the last publication of centers that had produced sequential reports were included. We inspected the references of all studies to identify further studies.

### Data Abstraction and Statistical Analysis

Data regarding detailed inclusion criteria, duration of follow-up, and all-cause long-term mortality (adjusted HRs for BITA vs SITA grafting and 95% CIs) were abstracted from each individual study. All study-specific estimates were combined using inverse variance-weighted averages of logarithmic HRs in both fixed- and random-effects models (primary meta-analysis). Between-study heterogeneity was analyzed by means of standard $\chi^2$ tests. Where nonsignificant statistical heterogeneity was identified, the fixed-effects estimate was used preferentially as the summary measure. Sensitivity analyses were performed to assess the contribution of each study to the pooled estimate by excluding individual studies 1 at a time and recalculating the pooled HR estimates for the remaining studies (1-study-removed meta-analysis). To assess the impact of differential internal thoracic artery (ITA) harvesting techniques among the studies on the pooled estimate, the effects of BITA grafting on long-term mortality were explored separately in studies using the pedicled and skeletonized ITA. Publication bias was assessed graphically using a funnel plot and mathematically using adjusted rank correlation and linear regression tests. Mixed-effects (unrestricted maximum likelihood) meta-regression analyses were performed to determine whether the effects of BITA grafting were modulated by prespecified factors: that is, the mean length of follow-up or age (years), and proportion of men or diabetes (%). Meta-regression graphs depict the effect of BITA grafting on the outcome (plotted as logHR on the y-axis) as a function of a given factor (plotted as a mean or proportion of that factor on the x-axis). Meta-regression coefficients (slopes of the meta-regression line) show the estimated increase in logHR per unit increase in the covariate. Because logHR >0 corresponds to HR >1 and log HR <0 corresponds to HR <1, a negative coefficient indicates that as a given factor increases, the HR decreases; that is, BITA grafting is more beneficial in reducing the outcome of interest. All analyses were conducted using Review Manager version 5.2 (Nordic Cochrane Centre, Copenhagen, Denmark) and Comprehensive Meta-Analysis version 2 (Biostat, Englewood, NJ).

## RESULTS

### Search Results

Our comprehensive search identified 20 observational studies[3,8,9,12-28] of BITA versus SITA grafting that enrolled patients undergoing CABG and reported adjusted risk estimates for long-term mortality. In total, our meta-analysis included data on 70,897 patients undergoing CABG assigned to BITA or SITA grafting. The baseline characteristics for the patients enrolled in each study are summarized in Table 1. The most notable difference in some studies[13,19,28] from the others was the criteria for enrollment of patients. The studies by Bonacchi and colleagues,[13] Di Mauro and colleagues,[15] Joo and colleagues,[19] Kinoshita and colleagues,[21] Navia and colleagues,[25] and Toumpoulis and colleagues[28] exclusively enrolled patients undergoing nonelective CABG,[13] those aged less than 70 years,[15] those undergoing off-pump CABG,[19] those aged more than 70 years,[21] those undergoing total arterial off-pump CABG,[25] and those with diabetes,[28] respectively. Despite the noted heterogeneity in design among studies, there was sufficient similarity between the populations and the hypotheses to merit inclusion of all 20 studies in the quantitative meta-analysis. The most dissimilar studies (Bonacchi and colleagues, 2006,[13] Di Mauro and colleagues, 2005,[15] Joo and colleagues, 2012,[19] Kinoshita and colleagues, 2012,[21] Navia and colleagues, 2013,[25] and Toumpoulis and colleagues, 2006[28]) were sequentially eliminated in sensitivity analyses to assess their impact on the pooled effect estimate.

### Primary Meta-Analysis

A pooled analysis of all 20 studies demonstrated a statistically significant 20% reduction in long-term mortality

ACD