Minimally invasive direct coronary artery bypass improves late survival compared with drug-eluting stents in isolated proximal left anterior descending artery disease: A 10-year follow-up, single-center, propensity score analysis

Umberto Benedetto, MD, PhD,[a] Shahzad G. Raja, MRCS, FRCS(C-Th),[a] Rafik F. B. Soliman, MD, FRCS(C-Th),[a] Alberto Albanese, MD,[a] Anand Jothidasan, MRCS,[a] Charles D. Ilsley, MD,[b] and Mohamed Amrani, MD, PhD, FECTS,[a] on behalf of the Harefield Cardiac Outcomes Research Group

Objectives: Minimally invasive direct coronary artery bypass (MIDCAB) has been proposed to reduce surgical morbidity and improve long-term outcomes compared with stenting in the treatment of isolated proximal left anterior descending artery. However, the survival benefit from MIDCAB still needs to be demonstrated, in particular, because percutaneous coronary intervention with drug-eluting stents (DES-PCI) continues to be considered the initial treatment strategy. We conducted a 10-year follow-up, single-center, propensity score-matched MIDCAB versus DES-PCI comparison.

Methods: A total of 1033 patients (303 MIDCAB and 730 DES-PCI) with isolated proximal left anterior descending disease were included. Propensity score matching was used to compare 303 pairs of MIDCAB and DES-PCI patients.

Results: MIDCAB and DES-PCI presented with comparable 30-day mortality (2 of 303 [0.6%] vs 1 of 303 [0.3%]; $P = 1.0$). At 10 years, DES-PCI was associated with a 2.19-fold increased risk of late death (95% confidence interval, 1.15-4.17), a 2.0-fold increased risk of repeat revascularization (95% confidence interval, 1.20-3.47), and a 2.14-fold increased risk of the composite of death and repeat revascularization (95% confidence interval, 1.41-3.24).

Conclusions: These findings strongly support a survival benefit from MIDCAB at long-term follow-up compared with DES-PCI in the treatment of isolated left anterior descending disease. (J Thorac Cardiovasc Surg 2014;148:1316-22)

Despite the introduction of drug-eluting stents (DESs), which have reduced the incidence of subsequent restenosis, coronary artery bypass grafting (CABG) remains associated with a decreased risk of repeat revascularization and potentially improved survival at long-term follow-up in patients with multivessel coronary disease.[1-4]

However, percutaneous coronary intervention with drug-eluting stents (DES-PCI) has continued to be widely accepted as the first-line treatment of isolated proximal left anterior descending (LAD) stenosis, and CABG is usually offered for lesions unsuitable for PCI only.[5,6]

The development of minimally invasive direct coronary artery bypass (MIDCAB) using the left internal mammary artery (LIMA) to the LAD has emerged as an attractive and less invasive approach than the conventional sternotomy procedure in patients with isolated LAD disease.[7]

Theoretically, arterial revascularization of the LAD has been expected to result in better late outcomes than DES-PCI. This advantage has largely resulted from the subsequent protection of the entire proximal and mid-LAD artery from future disease progression compared with focal treatment with PCI.[8]

However, the lack of evidence supporting a definitive survival benefit with MIDCAB compared with DES-PCI in the long term has led to even more widespread adoption of percutaneous techniques with concomitant limited MIDCAB popularity and uptake. We aimed to achieve insights into the role of MIDCAB compared with DES-PCI in the treatment of isolated proximal LAD disease by conducting a 10-year follow-up, single-center, propensity score-matched cohort comparison.

METHODS

Study Population

The present study was conducted in accordance with the principles of the Declaration of Helsinki. The local ethical committee approved the

From the Departments of Cardiac Surgery[a] and Cardiology,[b] Harefield Hospital, London, United Kingdom.

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Address for reprints: Umberto Benedetto, MD, PhD, Department of Cardiac Surgery, Harefield Hospital, London, United Kingdom (E-mail: umberto.benedetto@hotmail.com).

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Abbreviations and Acronyms

CABG = coronary artery bypass grafting
DES = drug-eluting stent
LAD = left anterior descending
LIMA = left internal mammary artery
MIDCAB = minimally invasive direct coronary artery bypass
PCI = percutaneous coronary intervention
PS = propensity score

present study, and the requirement for individual patient consent was waived.

We retrospectively analyzed prospectively collected data from the institutional surgical and interventional database (Patient Analysis and Tracking System [PATS]; Dendrite Clinical Systems, Ltd, Oxford, UK). The PATS database captures detailed information on a wide range of preoperative, intraoperative, and hospital postoperative variables (including complications and mortality) for all patients undergoing CABG or PCI at our institution. The data were collected and reported in accordance with the Society for Cardiothoracic Surgery in Great Britain and Ireland database criteria. The database is maintained by a team of full-time clinical information analysts, who are responsible for continuous prospective data collection as a part of a continuous audit process. The data collection is validated regularly. Information about death from any cause is regularly obtained from the General Register Office approximately 1 week after the event. Data on repeat revascularization were obtained from a network of institutional databases.

All patients with a nonemergency status with isolated proximal LAD disease undergoing first-time MIDCAB or DES-PCI from April 2001 to May 2013 were included in the present analysis. The exclusion criteria were admission for acute coronary syndrome and undergoing primary PCI, emergency or salvage CABG, and previous CABG.

In the DES-PCI group, paclitaxel-eluting stents and sirolimus-eluting stents were used. All DES-PCI patients received aspirin (325 mg daily) before and after the procedure and a 300-mg loading dose of clopidogrel the day before the procedure and 75 mg daily for $\geq$3 months thereafter.

All MIDCAB patients underwent surgery without extracorporeal circulation, and all surgical procedures included implantation of the LIMA to the LAD. In brief, a limited left anterolateral thoracotomy was performed through the fourth intercostal space. The LIMA was harvested either under direct vision or using thoracoscopic assistance. After administration of heparin (200 U/kg), the activated clotting time was kept at $\geq$400 seconds by repeated application of heparin, if needed. The LIMA was divided distally. Local immobilization of the anastomotic site was achieved with mechanical stabilizers. Anastomosis was performed using 1 running 8-0 polypropylene suture on the beating heart. Protamine was applied to partially neutralize the dose of heparin. The wounds were closed in a standard fashion. In the present cohort, MIDCAB was performed only when the LAD lesions were judged unsuitable for PCI. In most cases, the MIDCAB patients received aspirin 75 mg daily. Dual antiplatelet therapy was not recommended after MIDCAB. Clopidogrel was prescribed for patients with aspirin intolerance. Most MIDCAB procedures (225 of 303 [74.2%]) were performed by a single surgeon (M.A.) fully experienced in off-pump CABG.

Study Endpoints

The primary study endpoint was all-cause 10-year mortality; this represented the most robust and unbiased index event because no adjudication was required, thus avoiding inaccurate or biased documentation and clinical assessments. The secondary endpoints were target vessel revascularization, the need for repeat revascularization (PCI or CABG), and the composite of death or repeat revascularization.

Early outcomes were also investigated, including 30-day mortality, hospital length of stay, the incidence of perioperative stroke, and the need for renal replacement therapy. The incidence of local complications was also investigated, including wound infections and arterial complications for MIDCAB and DES-PCI, respectively.

Statistical Analysis

For baseline characteristics, the variables are summarized as the mean $\pm$ standard deviation for continuous variables and numbers and percentages for categorical variables.

The risk factors investigated were age $\geq$ 70 years, gender, hypertension, hypercholesterolemia, New York Heart Association functional class, diabetes mellitus, obesity (defined as a body mass index $\geq$30 kg/m^2), serum creatinine $\geq$ 200 mmol/L, previous myocardial infarction, previous PCI, functional New York Heart Association class III or IV, reduced left ventricular ejection fraction (<50%) poor left ventricular function (<30%), current smoking, history of cerebrovascular accident, peripheral vascular disease, an elective indication, and the prevalence of chronic total occlusion.

Because of the significant imbalances in baseline covariates between the 2 groups, we used propensity score (PS) matching. A PS representing the probability of undergoing MIDCAB versus DES-PCI was calculated for each patient using nonparsimonious logistic regression model that included all baseline risk factors. The pairs of patients treated by MIDCAB and DES-PCI were derived using greedy 1:1 matching with a caliper width of 0.2 standard deviations of the logit of the PS. A covariate balance was measured using the standardized differences, by which an absolute standardized difference of >10% has been suggested to represent a meaningful covariate imbalance.

Generalized linear mixed models, as appropriate, were used to estimate the effect of MIDCAB compared with DES-PCI on the early outcomes.

Kaplan-Meier estimates were used to plot the rates of long-term adverse events (all-cause death, repeat revascularization, and the composite of death or repeat revascularization), and differences between the risk curves were assessed using the Klein-Moeschberger test for matched pairs.[9] For each adverse outcome, the hazard ratio of MIDCAB versus DES-PCI was estimated using Cox proportional hazard models with robust standard errors to account for clustering in the matched pairs. The consistency of treatment effects across patient characteristics was investigated using a prespecified subgroup analysis (age $\geq$ 70 vs < 70 years; DES-PCI with sirolimus-eluting stents vs paclitaxel-eluting stents; and diabetes mellitus status) for all outcomes of interest. In addition, the covariate interactions, including age, diabetes, and baseline serum creatinine $\geq$ 200 mmol/L, on the effect estimate for the primary outcomes were tested to identify the subgroup of patients most likely to benefit from MIDCAB. All statistical analyses were performed using R, version 2.15.2 (R Core Team, R: A Language and Environment for Statistical Computing, Vienna, Austria: R Foundation for Statistical Computing; 2012, available at: http://www.R-project.org; "nonrandom": Susanne Stampf, nonrandom: Stratification and Matching by the Propensity Score, R Package, version 1.4, 2012. Q3, available at: http://CRAN.R-project.org/package=nonrandom;"survival": Terry Therneau 2012, A Package for Survival Analysis in S, R package, version 2.36-14; and "rms": Frank E. Harrell, Jr, 2013; rms: Regression Modeling Strategies, R package, version 4.0-0, available at: http://CRAN.R-project.org/package=rms) packages were used.

RESULTS

A total of 1033 patients (303 MIDCAB and 730 DES-PCI) for isolated proximal LAD disease were