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Multiple arterial grafting confers survival advantage compared to percutaneous intervention with drug-eluting stents in multivessel coronary artery disease: A propensity score adjusted analysis

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ABSTRACT

Background: The best revascularisation strategy for multivessel coronary artery disease (MVD) is still controversial. Percutaneous coronary intervention (PCI) utilising drug eluting stents (DES) has emerged as an acceptable alternative to conventional coronary artery bypass grafting (CABG) in the last decade. However, multiple arterial grafting (MAG) is superior revascularisation strategy compared with conventional CABG utilising single internal mammary artery and currently there is a paucity of comparison of DES and MAG. We aimed to investigate whether MAG offers advantage over DES-PCI in MVD.

Methods: A total of 6126 patients with MVD (≥2 vessel) underwent CABG (n = 4652) or PCI (n = 1474) at a single institution. MAG was performed in 1372 CABG cases and DES were implanted in 1222 PCI cases. Propensity score adjusted analysis was performed to investigate the potential survival advantage of MAG over PCI. Mean follow-up was 4.9 years.

Results: Risk for late death was comparable after DES-PCI and conventional CABG (HR 1.11; 95%CI 0.9 to 1.33; P = 0.25). However, DES-PCI was associated with an increased risk for late death compared to MAG (HR 1.53; 95%CI 1.08 to 2.91; P = 0.02). DES-PCI was also associated with a 3.51 fold increased risk for repeat revascularisation over MAG (95%CI 2.60 to 4.75; P < 0.0001) and 2.66 fold increased risk for repeat revascularisation over conventional CABG (95%CI 2.11 to 3.36; P < 0.0001).

Conclusions: MAG improved late survival and offered superior freedom from repeat revascularisation compared to DES-PCI. When feasible, MAG should be strongly recommended in patients with MVD.

1. Introduction

Coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) are well-established strategies for treatment of patients with significant obstructive coronary artery disease to relieve symptoms, improve survival or both [1]. The development of drug-eluting stents (DES) in the last decade has resulted in a significant rise in rates of PCI particularly utilising DES with a concomitant decline in CABG for multivessel disease (MVD) [1,2]. The emergence of encouraging short- and mid-term outcomes of DES from randomised controlled trials (RCTs) [3–6] and real world registries [7–9] accompanied by the notion that DES provide a less invasive and possibly superior alternative is the likely reason for these changing trends. However, irrespective of this shift away from CABG the best revascularisation strategy for MVD is still controversial.

Despite increasing recognition that CABG compared to PCI is associated with significantly reduced need for repeat revascularisation, available evidence form RCTs and meta-analyses suggests that overall late mortality is comparable for the two strategies [10–14]. This perception supports PCI as an acceptable alternative to conventional CABG utilising single internal mammary artery (SIMA) particularly when DES are used. On the other hand, multiple arterial grafting (MAG) confers improved patency and survival benefits compared with conventional CABG

Abbreviations: ATE, average treatment effect; BMS, bare metal stent; CABG, coronary artery bypass grafting; DES, drug eluting stents; ESS, effective sample size; ETA, experimental treatment assignment; GBM, generalised boosted model; HR, hazard ratio; IPTW, inverse probability of treatment weighting; KS, Kolmogorov–Smirnov; LAD, left anterior descending artery; MVD, multivessel coronary artery disease; NYHA, New York Heart Association; PATS, Patient Analysis and Tracking System; PCI, percutaneous coronary intervention; PSB_{1k}, population absolute standardised bias; RCTs, randomised controlled trials; SIMA, single internal mammary artery; SVGs, saphenous vein grafts; 95%CI, 95% confidence interval.

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utilising SIMA [15–18]. We aimed to investigate whether MAG offers survival benefit over DES-PCI in MVD.

2. Methods

2.1. Study population

The study was conducted in accordance with the principles of the Declaration of Helsinki.

We retrospectively analysed prospectively collected data from the institutional surgical and interventional database (PATS [Patient Analysis & Tracking System]; 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 in our institution. The data is collected and reported in accordance with the Society for Cardiothoracic Surgery in Great Britain & 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 part of a continuous audit process. 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.

All patients with multivessel coronary disease (≥2 vessels diseased) undergoing multivessel myocardial revascularisation from April 2003 to May 2013 were included in the present analysis. Exclusion criteria were: significant left main disease, admission for acute coronary syndrome receiving primary PCI and previous CABG.

In the PCI group, patients were divided into DES-PCI group when at least one DES was used or bare metal stent (BMS) group when PCI was performed with BMS only.

All PCI patients received aspirin (300 mg daily) before and after the procedure and a 300-mg loading dose of clopidogrel before the procedure and 75 mg daily for at least 6–12 months thereafter.

CABG patients were divided into two groups: SIMA group receiving one IMA to left anterior descending (LAD) graft and saphenous vein grafts (SVGs) to complete surgical revascularisation and MAG patients who received at least two arterial conduits of which one was IMA on LAD. In MAG group additional SVGs were used when required to complete revascularisation.

2.2. Risk factors and study end-points

Risk factors investigated were: age, female gender, diabetes mellitus, renal impairment defined as a baseline serum creatinine ≥ 200 mmol/l, previous myocardial infarction, previous PCI, current smoking, functional NYHA class III/IV, obesity defined as a body mass index ≥ 30, reduced left ventricular ejection fraction (<50%), non elective indication, and number of vessels treated.

The primary study end point was all-cause late mortality; this represents the most robust and unbiased index event because no adjudication is required, thus avoiding inaccurate or biased documentation and clinical assessments. Secondary endpoint was the need for repeat revascularization (PCI or CABG).

2.3. Statistical analysis

For baseline characteristics, variables are summarised as mean for continuous variables and fraction for categorical variables. Multiple imputations using bootstrapping-based expectation–maximization algorithm was used to address missing data. Over dispersed starting algorithm was used to check global maximum likelihood in the imputation model.

Average treatment effect (ATE) was used to summarise the treatment effect: the ATE for treatment t_1 relative to other treatment is the comparison of mean outcomes had the *entire* population received t1 versus had the entire population received another treatment.

Inverse probability of treatment weighting (IPTW) for modelling causal effects from multiple treatments was used to assess the effect of treatments. To reweight a treatment sample to make the distribution of covariates match that of any of the other treatment groups, individual weights were calculated as the reciprocal of the probability that a study participant received the treatment he or she received. For this purpose, generalised boosted model (GBM) was implemented to estimate multinomial propensity scores for treatment indicator adjusting for all pretreatment covariates and the *propensity score* was assumed as the probability that an individual with pretreatment characteristics X receives treatment *t*. Two different stopping rules for selecting the optimal GBM iteration were used: mean standardised bias and mean Kolmogorov–Smirnov (KS) statistic across the pretreatment covariates. The key assumption that each unit had a non-zero probability of belonging to each group was assessed by the overlap of the empirical propensity score distributions.

Population absolute standardised bias (PSB_{1k}) also referred to as the absolute standardised mean difference was used to directly assess how similar each treatment group is to the population in terms of covariate means both before and after weighting. Standardised mean differences of less than 0.20 were considered small, 0.40 were considered moderate, and 0.60 were considered large. KS statistics greater than 0.20 was used as indication of imbalance. Effective sample size (ESS) was calculated to account for disparity in the weights for a treatment group's sample and the potential loss in precision from weighting. The ratio of the ESSt to the number of observations in a treatment group sample equals the loss in precision because of weighting. If two alternative GBM fits yield essentially equal balance but one yields a larger ESSt than the other, then the fit yielding the larger ESSt was preferred.

"Diagnostic for experimental treatment assignment (ETA) Bias" (DEB) was used to estimate the extent of relative and absolute bias in the IPTW estimator due to ETA violations [19]. The sensitivity of IPTW estimators to unmeasured confounding was investigated by using a marginal structural model for repeated measures [20]. Finally, weighted Cox regression analysis was used to estimate the treatment effect on outcomes for all treatment comparisons. 'Doubly robust' estimation through weighted regression on treatment indicators and covariates remained unbalanced after weighting was used.

R version 2.15.2 (R Core Team (2012). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL http://www.R-project.org), *VIM package* (Matthias Templ, Andreas Alfons, Alexander Kowarik and Bernd Prantner (2013). VIM: Visualization and Imputation of Missing Values. R package version 4.0.0. http://CRAN.R-project.org/package=VIM), *Amelia package* (James Honaker, Gary King, Matthew Blackwell (2011). Amelia II: A Program for Missing Data. Journal of Statistical Software, 45(7), 1–47. URL http://www.jstatsoft.org/v45/i07/.), *gbm package* (Greg Ridgeway with contributions from others (2013). gbm: Generalized Boosted Regression Models. R package version 2.0-8. http://CRAN.R-project.org/package=gbm), *twang package* (Greg Ridgeway, Dan McCaffrey, Andrew Morral, Beth Ann Griffin and Lane Burgette (2013). twang: Toolkit for Weighting and Analysis of Nonequivalent Groups. R package version 1.3-18. http://CRAN.R-project.org/package=twang) and *survey package* (T. Lumley (2004) Analysis of complex survey samples. Journal of Statistical Software 9(1): 1–19) were used for statistical analysis.

The study was approved by the Institutional Ethics Committee, and informed consent was waived for this study due to its retrospective nature. The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

3. Results

The study population consisted of 6126 MVD patients treated by MAG (n = 1372), SIMA (n = 3280), DES-PCI (n = 1222) and BMS-PCI