Canadian Journal of Cardiology 29 (2013) 1616–1622

Clinical Research

Time Dependency of Outcomes for Drug-Eluting vs Bare-Metal Stents

Alexander A. Leung, MD, MPH,[a] Danielle A. Southern, MSc,[b] P. Diane Galbraith, RN, BN,[c] Merril L. Knudtson, MD,[c] Andrew C. Philpott, MBBS,[d] and William A. Ghali, MD, MPH;[a,b] for the APPROACH Investigators

[a] *Department of Medicine, University of Calgary, Alberta, Canada*

[b] *Department of Community Health Sciences, University of Calgary, Alberta, Canada*

[c] *Libin Cardiovascular Institute of Alberta, Calgary, Alberta, Canada*

[d] *Lyell McEwin Hospital, Adelaide, South Australia*

ABSTRACT

Background: Previous research suggests that the early benefit from revascularization with drug-eluting stents might diminish over time.

Methods: We performed an extended analysis of a previously identified cohort of 6440 patients who underwent percutaneous coronary intervention between April 1, 2003 and March 31, 2005 using a prospective provincial clinical registry in Alberta, Canada. We compared rates of death, and of death or repeat revascularization among the 6440 patients receiving either drug-eluting (sirolimus- and paclitaxel) stents or bare-metal stents. We determined risk-adjusted hazard ratios at moments in time with a spline analysis using Cox proportional hazards modelling.

RÉSUMÉ

Introduction : Des recherches antérieures montrent que l'avantage de la revascularisation précoce au moyen d'endoprothèses médicamentées pourrait diminuer avec le temps.

Méthodes : Nous avons réalisé une analyse approfondie d'une cohorte précédemment identifiée de 6440 patients ayant subi une intervention coronarienne percutanée entre le 1er avril 2003 et le 31 mars 2005 en utilisant un registre clinique provincial prospectif en Alberta, au Canada. Nous avons comparé les taux de mortalité, et de mortalité ou de revascularisation répétée parmi les 6440 patients ayant reçu soit des endoprothèses médicamentées (sirolimus et paclitaxel) ou des endoprothèses non médicamentées. Nous avons déterminé les

Although the use of drug-eluting stents (DESs) has become widespread as the result of trials demonstrating significant reduction in stent restenosis and subsequent repeat revascularization compared with bare-metal stents (BMSs),[1-5] concerns have been raised regarding the possible increased risk of late complications and mortality with DESs.[4-9]

Accordingly, we previously reported results from a prospective cohort of patients receiving either DESs or BMSs from the **A**lberta **P**rovincial **Pr**oject for **O**utcome **A**ssessment in **C**oronary **H**eart Disease (APPROACH) registry with 3 years of follow-up, and demonstrated an initial suggestion of benefit among patients receiving DESs, followed by a shifting of relative risk over time toward worse outcomes in DES patients for the combined outcome of death or repeat revascularization.[10] Our findings suggested that the pace of occurrence of adverse events among patients receiving DESs was not uniform, and that insufficient follow-up duration might lead to underestimation of late events.

Existing reports of the long-term safety of DESs have been conflicting. Considering the concerns about the safety of DESs, especially with the growing awareness of long-term complications relating to the stent itself and the associated bleeding risk from dual antiplatelet therapy, we present a follow-up analysis with 8-year post-stent data to extend our understanding of whether the use of DESs is associated with a significantly greater long-term risk of death or repeat revascularization compared with BMSs.

Methods

Study design and patient population

A prospective cohort of all patients undergoing percutaneous coronary intervention with BMSs or DESs in the province of Alberta between April 1, 2003 and March 31,

Received for publication April 12, 2013. Accepted September 3, 2013.

Corresponding author: Dr William A. Ghali, Departments of Medicine and Community Health Sciences, University of Calgary, 3330 Hospital Drive NW, Calgary, Alberta T2N 4N1, Canada. Tel.: +1-403-210-9317; fax: +1-403-210-3818.

E-mail: wghali@ucalgary.ca

See page 1621 for disclosure information.

0828-282X/$ - see front matter
http://dx.doi.org/10.1016/j.cjca.2013.09.003

Results: During the 8 years of observation, the relative risks for death or the composite outcome of death or repeat revascularization varied over time. There was an early finding of better outcomes associated with drug-eluting stents in the first year after implantation. Thereafter, there was no significant benefit associated with drug-eluting stents compared with bare-metal stents with 8 years of follow-up. At 30 days, the adjusted hazard ratio was 0.38 (95% confidence interval [CI], 0.18-0.81) for death and 0.27 (95% CI, 0.14-0.54) for the composite outcome of death or repeat revascularization. By 8 years, the adjusted hazard ratio of death or the composite outcome was 1.15 (95% CI, 0.97-1.36) and 1.01 (95% CI, 0.87-1.17), respectively.

Conclusions: Revascularization with first-generation drug-eluting stents is associated with better outcomes within the first year only. Thereafter, the risk of death or repeat revascularization is similar between drug-eluting stents and bare-metal stents.

Résultats : Durant les 8 années d'observation, les risques relatifs de mortalité, ou de critère de jugement combiné de mortalité ou de revascularisation répétée ont varié avec le temps. Une conclusion préliminaire sur les meilleurs résultats associés aux endoprothèses médicamentées a été obtenue dans la première année après l'implantation. Par la suite, il n'y a eu aucun avantage significatif associé aux endoprothèses médicamentées comparativement aux endoprothèses non médicamentées après 8 ans de suivi. À 30 jours, le rapport de risque ajusté a été de 0,38 (intervalle de confiance [IC] à 95 %, 0,18-0,81) pour la mortalité et de 0,27 (IC à 95 %, 0,14-0,54) pour le critère de jugement combiné de mortalité ou de revascularisation répétée. Après 8 ans, le rapport de risque ajusté de mortalité ou du critère de jugement combiné a été respectivement de 1,15 (IC à 95 %, 0,97-1,36) et de 1,01 (IC à 95 %, 0,87-1,17).

Conclusions : La revascularisation au moyen d'endoprothèses médicamentées de première génération est associée à de meilleurs résultats dès la première année seulement. Par la suite, le risque de mortalité ou de revascularisation répétée est similaire entre les endoprothèses médicamentées et les endoprothèses non médicamentées.

2005 was assembled using the APPROACH database. Enrollment began on April 1, 2003 because this was the date that DESs (ie, the sirolimus-eluting Cypher and paclitaxel-eluting TAXUS stents) were first approved for use in Canada. Preliminary outcome data based on 3 years of follow-up were previously reported.[10] Herein, we present an extended analysis with outcome data compiled to March 31, 2011, allowing for a follow-up period of up to 8 years.

APPROACH is a geographically-defined prospective clinical registry of all patients undergoing cardiac catheterization in Alberta (population approximately 3.7 million) with longitudinal assessment for clinical, health-related quality of life, and economic outcomes since 1995.[11] Validation and enhancement of data (and completion of missing data) are performed using a validated methodology.[12,13] Data were not imputed. We documented the following variables at the time of catheterization: patient age and sex, history of congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, renal disease, diabetes mellitus, dialysis status, hyperlipidemia, hypertension, liver or gastrointestinal disease, malignant disease, smoking status, previous myocardial infarction, previous coronary artery bypass graft surgery, previous percutaneous coronary intervention, and use of glycoprotein IIb/IIIa inhibitors. Overall disease severity was determined using a modified Duke Myocardial Jeopardy score (expressed as a percentage after dividing the score by 12) which is an estimate of the percentage of myocardium at risk in consideration of the extent of coronary disease.[14] Left ventricular ejection fraction was categorized as $< 20\%$, 20%-34%, 35%-50%, $> 50\%$, and 'ventriculogram not done.' Details of the percutaneous coronary intervention such as type of stent, length of stent, and number of stents were recorded. Details on the duration of dual antiplatelet therapy was not available. This study was approved by the ethics review boards at the University of Calgary and University of Alberta. These review boards annually approve the APPROACH study protocol.

Outcomes

The main outcome measures were death and the composite of death or repeat revascularization of any coronary vessel. For our present analyses, relinkage of data from the Alberta Bureau of Vital Statistics was performed for ascertainment of death among patients in the cohort. Information on subsequent revascularization (ie, percutaneous coronary intervention or coronary artery bypass graft surgery) was obtained using the APPROACH database. Of note, APPROACH was integrated with the provincial personal health record and was present in all facilities performing revascularization procedures in Alberta, ensuring complete capture of all revascularization attempts during the study interval within the province.

Analysis

Baseline clinical and demographic characteristics of patients with DESs were compared with those with BMSs using the χ^2 test for categorical variables and Student t test for continuous variables. To address potential confounding by treatment indication, we used a propensity score and multivariable regression modelling to account for baseline differences between recipients of BMSs and DESs.[15] The propensity score also helped to reduce the dimensionality of the large number of potentially important covariates compared with the relatively few outcomes before modelling to improve parameter estimations.[16] Variables incorporated into the propensity score were selected based on discrimination (determined using the c-statistic) and clinical reasoning (Supplemental Table S1). Continuous variables (eg, ejection fraction, Duke Myocardial Jeopardy score, and stent length) were categorized according to clinically relevant cutoff values as used in previous studies.[10] For our primary analysis, the propensity score was incorporated as a covariate in our regression model. Outcomes were compared for the entire cohort, and for the 2 prespecified subgroups according to the primary indication for catheterization: acute