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# Long-term benefits and risks of drug-eluting compared to bare-metal stents in patients with versus without chronic kidney disease☆

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ABSTRACT

*Aims:* Chronic kidney disease (CKD) is associated with worse outcomes in patients with coronary artery disease (CAD). How CKD influences the benefit-risk balance of drug-eluting stents (DES) versus bare-metal stents (BMS) is less known.

*Methods and results:* In the multicentre BASKET-PROVE trial, 2314 patients in need of large coronary stenting (≥3.0 mm) were randomised 2:1 to DES or BMS. In an a priori planned secondary analysis, outcomes were evaluated according to renal function defined by estimated glomerular filtration rates (eGFR; normal: eGFR≥60 ml/min/1.73 $m^2$; CKD: eGFR<60 ml/min/1.73 $m^2$). The primary endpoint was the first major adverse cardiac event (MACE: cardiac death, myocardial infarction, target vessel revascularisation) up to 2 years. A Cox proportional-hazard model was used to evaluate adjusted relative risks (hazard rates, HRs) for BMS versus DES. The interaction of stent type and renal function was tested.

CKD patients (189 (11.2%)/1681 with such data) had a 2-year MACE rate of 8.5% versus 7.4% in those without CKD [HR 0.98 (0.56–1.72), p=0.95] with cardiac mortalities of 5.3% and 1.5%, respectively (p=0.002, non-significant after baseline adjustments). The MACE rate was lower in CKD patients with DES than with BMS [4.9% versus 15.2%, p=0.017, HR 0.29(0.10–0.80)] as was the MACE rate in patients without CKD [5.6% with DES versus 11.1% with BMS, p<0.0001, HR 0.51(0.35–0.75)]. No significant interaction between stent type and renal function was found.

*Conclusions:* This analysis of patients needing large coronary artery stenting confirms the increased mortality of CKD patients and documents a long-term benefit of DES compared to BMS irrespective of kidney function.


## 1. Introduction

Chronic kidney disease (CKD) is associated with an increased risk of cardiovascular morbidity and mortality [1–4]. Since the coincidence of CKD and cardiovascular diseases affects millions of people worldwide [5], it seems important to ascertain if the benefit of drug-eluting stents (DES) over bare-metal stents (BMS) in current management of coronary artery disease (CAD) can be established also for all patients with CKD. Based on results of pivotal trials in highly selected groups of patients [6,7] guidelines on myocardial revascularisation recommend the use of DES rather than BMS also in patients with CKD [8]. However, these pivotal trials focused on "label" indications limiting their applicability to daily practice in the "real world". Since CKD has been identified as one potential predictor of restenosis after stent implantation [9,10] it seems of particular interest to test whether the value of DES versus BMS can be documented also in patients at low risk of restenosis such as those with large vessel stenting.

☆ The BASKET PROVE trial was registered with the Current Controlled Trial Number, ISRCTN72444640.

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A large number of "real-world" patients in need of large vessel coronary stent implantation has been studied in the multicentre Basel Stent Kosten-Effektivitäts Trial-PROspective Validation Examination (BASKET-PROVE) which included patients with acute and chronic CAD [11]. This dataset provided an excellent patient cohort to evaluate the benefits and risks of DES versus BMS in patients with or without CKD on long-term outcome. The present analysis was an a priori defined secondary aim of BASKET-PROVE and forms the basis for this study. Specifically, we intended to compare the efficacy and safety of DES versus BMS during a 2-year follow-up period in patients with CKD to those with normal renal function.

## 2. Methods

### 2.1. Study design, patients and definitions

The study design of the prospective, investigator-driven BASKET PROVE trial has been described previously [12]. In summary, 2314 patients in need of large coronary artery stenting (≥3.0 mm) were randomly assigned in a 1:1:1 fashion to receive either a first generation sirolimus-eluting stent (Cypher select™, Cordis), a second generation Everolimus-eluting stent (Xienxe V™, Abbott Vascular) or a new generation bare-metal stent (Multilink Vision™, Abbott Vascular). Randomisation was carried out in permuted blocks of 12 for each centre with the use of sealed envelopes. Patients, all-comers with chronic or acute CAD, were included at the participating centres in Switzerland, Denmark, Austria and Italy between March 5, 2007, and May 15, 2008. Exclusion criteria were cardiogenic shock, in-stent re-stenosis, stent thrombosis, unprotected left main disease, planned surgery <12 months, need for oral anticoagulation, increased bleeding risk and suspected non-compliance with long-term antiplatelet therapy. All patients were prescribed double antiplatelet therapy with aspirin and clopidogrel for 12 months irrespective of disease presentation or stent type. Clinical follow-up was obtained after one and two years during which angiography was allowed only for new ischemic symptoms. Each patient gave written informed consent. The protocol was approved by the ethics committees at each centre and the study complies with the Declaration of Helsinki. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

### 2.2. Renal function evaluation

Baseline renal function was determined based on creatinine values, age, sex and body surface area using the second Modification of Diet in Renal Disease formula (MDRD2) which estimates glomerular filtration rates (GFR) as follows: eGFR(ml/min/1,73 $m^2$) = 186xcreatinine$^{-1.154}$×Age$^{-0.203}$ [x0.742 if female] [13]. Baseline creatinine values were available in 1681 of 2314 patients (72.6%); lacking values for renal function were due to emergent or urgent interventions or logistic reasons in busy daily practice (for comparison of patients with and without known creatinine values see Appendix Tables 1a and 1b). In accordance with the guidelines of the National Kidney Foundation for staging chronic kidney disease based on eGFR, patients were categorised into 2 groups: patients with an eGFR≥60 ml/min/1.73 $m^2$ were defined as patients with a normal kidney function and patients with an eGFR below 60 ml/min/1.73 $m^2$ were those with CKD.

### 2.3. Clinical endpoints and definitions

An independent Critical Events Committee adjudicated all events according to definitions previously described [11]. The primary end point for the present analysis was the incidence of the first major adverse cardiac event (MACE) up to 2 years. MACE was defined as cardiac death, target vessel revascularisation (TVR) and non-fatal myocardial infarction (MI) up to 2 years. Secondary efficacy and safety endpoints were each of the components of the primary endpoint, stent thrombosis according to the Academic Research Consortium [14] and major bleeding events according to the Bleeding Academic Research Consortium (BARC) definitions [15,16] and the Thrombolysis In Myocardial Infarction (TIMI) [17] classifications.

The study was planned, conducted and analysed independently from industry. Financial support was given by the Basel Cardiovascular Research Foundation, the Swiss Heart Foundation in Berne and the Swiss National Foundation for Research. The authors have full access to the data and take responsibility for its integrity. All authors have read and approved the manuscript as written.

### 2.4. Statistical analyses

Baseline characteristics are reported as counts and percentages or means±SD. Student's *t*-test and Pearson $\chi 2$ test were used to compare categorical variables and quantitative variables, respectively. Kaplan Meier analyses were performed to evaluate univariately the effects of implanted stents and kidney function. Additionally, we estimated multivariate effects through Cox proportional hazard regression, thereby adjusting for age, sex and relevant covariates significantly different at baseline comparison. An interaction test of kidney function in relation to the effect of implanted stents on major cardiac adverse events was done. Since the main BASKET-PROVE trial showed no significant differences in baseline variables and 2-year outcomes between the two different DES used, they were grouped together for the present analysis. All statistical analyses were performed with SPSS for Windows version 19 (SPSS Inc., Chicago, Illinois, USA).

## 3. Results

### 3.1. Patient population

Baseline kidney function was known in 1681 patients (72.6% of all 2314 patients of BASKET-PROVE). Among those, 189 (11.2%) had impaired baseline renal function and were diagnosed as having CKD. Regarding stent treatment among patients with known kidney function, 1127 (67.0%) received DES and 554 (33%) BMS.

### 3.2. Baseline characteristics of patients with versus without CKD

Table 1 displays baseline clinical and procedural characteristics of patients with and without CKD which differed in many aspects: patients with CKD were on average older, had more often hypertension, diabetes, a previous MI or peripheral artery occlusive disease. They were less likely to be male and smokers. No significant differences were observed for multivessel disease or number of stents implanted, whereby patients with a normal kidney function presented more often with chronic total occlusion and were more frequently treated with glycoprotein IIb/IIIa inhibitors.

**Table 1**
Baseline clinical and procedural characteristics of patients with CKD compared to those with normal kidney function.

| | eGFR <60 | eGFR ≥60 | p-Value |
|---|---|---|---|
| n | 189 | 1492 | |
| Age — years | 74.4±9.8 | 61.8±10.6 | <0.001 |
| Male | 106 (56.1) | 1188 (79.6) | <0.001 |
| eGFR (ml/min/kg) | 47.9±10.2 | 91.9±20.4 | <0.001 |
| Cardiac risk factors | | | |
| Diabetes | 50 (26.5) | 209 (14.0) | <0.001 |
| Hypertension | 147 (77.8) | 866 (58.0) | <0.001 |
| Hyperlipidemia | 113 (59.8) | 940 (63.0) | 0.43 |
| Current smoker | 37 (19.6) | 541 (36.3) | <0.001 |
| Family history | 54 (28.6) | 571 (38.3) | 0.010 |
| Past medical history | | | |
| Creatinine (mg/dl±SD) | 1.47±0.6 | 0.88±0.2 | <0.001 |
| TIA/stroke | 13 (6.9) | 46 (3.1) | 0.018 |
| Heart Failure | 17 (9.0) | 80 (5.4) | 0.07 |
| PAOD | 17 (9.0) | 59 (4.0) | 0.004 |
| Prior MI | 16 (8.5) | 65 (4.4) | 0.018 |
| Prior PCI | 31 (16.4) | 168 (11.3) | 0.043 |
| Clinical presentation | | | |
| Stable angina | 51 (27.0) | 538 (36.1) | 0.015 |
| NSTE-ACS | 68 (36.0) | 453 (30.4) | 0.13 |
| STEMI | 70 (37.0) | 501 (33.6) | 0.37 |
| Complexity of CAD | | | |
| Multivessel disease | 89 (47.1) | 667 (44.7) | 0.29 |
| Bifurcation lesions | 13 (6.9) | 137 (9.2) | 0.18 |
| CTO | 4 (2.1) | 89 (6.0) | 0.015 |
| Use of GP IIb/IIIa inhibitor | 35 (18.5) | 391 (26.2) | 0.02 |
| Procedural Characteristics | | | |
| DES | 123 (65.1) | 1004 (67.3) | 0.57 |
| BMS | 66 (34.9) | 488 (32.7) | 0.57 |
| Sirolimus-eluting DES | 64 (33.9) | 511 (34.2) | 0.94 |
| Everolimus-eluting DES | 59 (31.2) | 493 (33.0) | 0.68 |
| No. of treated segments per patient | 1.37±0.81 | 1.47±0.78 | 0.09 |
| No. of stents per patient | 1.60±1.0 | 1.74±1.0 | 0.09 |
| Total stent length per patient — mm | 29.8±22.1 | 33.0±23.3 | 0.07 |

n (%); MI = non fatal myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; NSTE-ACS = non-ST-elevation acute coronary syndrome; STEMI = ST-elevation myocardial infarction; CAD = coronary artery disease; CTO = chronic total occlusions; GP = glycoprotein; PAOD = peripheral arterial occlusive disease; TIA = transitory ischemic attack; BMS = bare-metal stents; DES = drug-eluting stents; eGFR = glomerular filtration rate.