Five year clinical effect of coronary stenting and coronary artery bypass grafting in renal insufficient patients with multivessel coronary artery disease: insights from ARTS trial

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Introduction

Renal dysfunction is a well known risk factor for adverse cardiac events after coronary revascularization. Renal dysfunction, even the mild renal dysfunction, is associated with both restenosis and mortality after percutaneous coronary intervention.¹,² Coronary artery bypass grafting (CABG) is also associated with adverse outcome in patients with renal dysfunction.³ Renal dysfunction is an important factor for calculating CABG risk scores, according to ACC/AHA guidelines, Cleveland clinic score, and Euro scores.⁴⁻⁷ However, no randomized trial has compared the long-term clinical effect of coronary stenting vs. CABG in renal insufficient patients with multivessel coronary disease. Therefore, investigated the clinical outcomes of renal insufficient patients in the ARTS trial.

Aims To compare coronary stent implantation and bypass surgery for multivessel coronary disease in patients with renal insufficiency.

Methods and results In the ARTS trial, 142 moderate renal insufficient patients (Ccr < 60 mL/min) with multivessel coronary disease were randomly assigned to stent implantation (n = 69) or CABG (n = 73). At 5 years, there was no significant difference between the two groups in terms of mortality (14.5% in the stent group vs. 12.3% in the CABG group, P = 0.81), or combined endpoint of death, cerebrovascular accident (CVA), or myocardial infarction (MI) (30.4% in the stent group vs. 23.3% in the CABG group, P = 0.35). Among patients who survived without CVA or MI, 18.8% in the stent group underwent a second revascularization procedure when compared with 8.2% in the surgery group (P = 0.08). The event-free survival at 5 years was 50.7% in the stent group and 68.5% in the surgery group (P = 0.04).

Conclusion At 5 years, the differences in mortality and combined incidence of death, CVA, and MI between coronary stenting and surgery did not reach statistically significant level. However, the occurrence of MACCE in the stent group was higher than in the CABG group, mainly driven by the higher incidence of repeat revascularization in the stent group.

Keywords Stent; Coronary artery bypass; Renal insufficiency
in the ARTS trial. Renal dysfunction was classified by estimated creatinine clearance (Ccr) calculated by use of the Cockcroft-Gault formula: \[ \text{Ccr (mL/min)} = \left[ \frac{(140 - \text{age}) \times \text{weight (kg)}}{\text{serum creatinine (mg/dL)} \times 72} \right]. \] Patients who had Ccr < 60 mL/min comprised the moderate renal insufficient group and patients who had Ccr ≥ 60 mL/min comprised the mild renal dysfunction and normal renal function group, according to the definition of National Kidney Foundation. \(^{12}\) Patients with left main stem stenosis, impaired left ventricular function (left ventricular ejection fraction < 30%), previous cerebrovascular accident (CVA), myocardial infarction (MI) within the week preceding randomization, neutropaenia, or thrombocytopaenia, or an intolerance or contraindication to acetylsalicylic acid or ticlopidine and patients who needed concomitant major surgery and severe hepatic or renal disease (worst Ccr level is 27.3 mL/min in enrolled patients) were not included in the study. Among 1205 patients, 1062 patients (88.1%) had their Ccr level before the revascularization. Figure 1 shows the cumulative curve of Ccr in overall patients. Among 1062 patients, 142 patients had moderate renal dysfunction (Ccr < 60 mL/min), of which 69 were randomly assigned to undergo stenting and 73 to CABG. All patients gave written informed consent. Randomization did not take into account Ccr level. The aim of this study was to evaluate coronary stent implantation and bypass surgery for multivessel coronary disease in patients with renal insufficiency. To evaluate the interventional strategy in the renal insufficiency group more specifically, we also investigated the Ccr ≥ 60 mL/min group in the ARTS trial.

### Data collection and endpoints

Angiographic data were adjudicated by an independent core laboratory (Cardialysis BV, The Netherlands). The study protocol required all patients to have follow-up clinic visits with an electrocardiogram (ECG) at 1, 3, and 5 years. At each visit, physical examination, anginal status, and use of medications were assessed. Additional information was obtained by telephone interview or via the referring physician when needed. An independent committee adjudicated clinical events and ECGs. The clinical events were defined as any of the following major adverse cardiac or cerebrovascular events (MACCE) within 5 years after randomization, defined as death, stroke, transient ischaemic attack, reversible ischaemic neurologic deficits, documented non-fatal MI, and repeated revascularization by percutaneous intervention or surgery. Deaths from all causes were reported. In the first 7 days after the intervention, a definite diagnosis of MI was made if there was documentation of new abnormal Q waves (according to the Minnesota code\(^{13}\)) and either cardiac enzymes greater than five times the upper limit of normal or a ratio of peak serum creatinine kinase MB (CK-MB) to creatinine kinase (CK) greater than 0.1. From the eighth day onwards, either abnormal Q waves or enzymatic changes were sufficient for a diagnosis of MI.

The primary endpoint was defined as the absence of any of the following MACCE within 5 years after randomization: death, CVA, documented non-fatal MI adjudicated by either new abnormal Q wave or pre-defined enzymatic changes, or repeat revascularization by coronary stenting or CABG.

### Statistical analysis

Statistical analysis was performed with SAS 6.12 software (SAS Institute Inc.). Continuous variables were expressed as mean ± SD and compared with the unpaired Student’s t-test. The Fisher exact test was used for categorical variables. Discrete variables were expressed as counts and per cent values and compared in terms of relative risks (RRs) with 95% confidence intervals (CI) calculated by the formula of Greenland and Robins. \(^{14}\) All analyses were based on the intention-to-treat principle, and statistical tests were two-tailed. Cumulative event-free survival was calculated according to the Kaplan-Meier method and differences were assessed using the log-rank test. Ccr was analysed as a continuous value for the prediction of MACCE in univariate analysis. P-values < 0.05 were considered statistically significant.

### Results

#### Patient characteristics

Baseline and procedural characteristics were similar between patients assigned to stenting (stent arm) or CABG (CABG arm) within each group (Table 1). In the moderate renal insufficiency group (Ccr < 60 mL/min group), all patients allocated to stent implantation were treated with stents, whereas five patients allocated to bypass surgery were instead treated with stent implantation or medical treatment. In total, 100% of renal insufficient patients in the stent arm and 93.2% of those in the CABG arm received the assigned treatment.

#### Five year clinical outcome

Comparison between moderate renal dysfunction (the Ccr < 60 mL/min group) vs. mild renal dysfunction and normal renal function (the Ccr ≥ 60 mL/min group)

In the Ccr < 60 mL/min group, complete follow-up during 5 years was obtained in 100% patients assigned to stenting (stent arm) and in 97% assigned to CABG (CABG arm). In the Ccr ≥ 60 mL/min group, complete follow-up during 5 years was obtained in 99% patients assigned to stenting and in 98% assigned to CABG. Table 2 displays the 5 year clinical results with respect to comparison between patients assigned to stent and CABG within each group. Five year mortality rate of the moderate renal insufficient group was 14.5% in the stent arm and 12.3% in the CABG arm. Those rates were higher than the group with mild renal dysfunction and normal renal function (7.6% in the stent arm and 7.1% in the CABG arm), but did not achieve significant differences in both arms: RR, 1.90; 95% CI 0.98–3.65; \( P = 0.07 \) in the stent arm and RR, 1.73; 95% CI 0.86–3.46; \( P = 0.16 \) in the CABG arm. However, the combined incidence of death, CVA, or MI was higher in patients with moderate renal impairment in both arms, stenting and CABG, when compared with patients with mild renal dysfunction and normal renal function (30.4 vs. 16.6% in the stent arm: (RR, 1.83; 95% CI, 1.22–2.77; \( P = 0.01 \) and 23.3 vs. 14.3% in the CABG arm: RR, 1.63; 95% CI, 1.02–2.62; \( P = 0.05 \)). Regardless of the revascularization strategies, the occurrence of repeat revascularization was similar between the Ccr < 60 mL/min

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[Figure 1](#) The cumulative curve of Ccr in the ARTS trial.
group and the Ccr ≥ 60 mL/min group with a higher repeat
revascularization rate in the stent arms than that in the
CABG arms (29.0% vs. 29.7% in the stent arm; RR, 0.98; 95%
CI, 0.66 – 1.50; P = 1.00 and 9.6 vs. 8.0% in the CABG arm:
RR, 1.20; 95% CI, 0.56 – 2.58; P = 0.65). The MACCE rate in
the stent arms was higher than that in the CABG arm,
mainly due to the higher incidence of repeat revasculari-
zation in both the Ccr < 60 mL/min group and the Ccr ≥ 60
mL/min group. However, the difference in rates of MACCE
between the stenting and the surgery in the Ccr < 60 mL/
min group was similar to the Ccr ≥ 60 mL/min group
(Δ17.8 vs. Δ19.6%, respectively).

To assess the effect of renal insufficiency on outcome, Ccr
was analysed as a continuous valuable for the prediction in
MACCE. Ccr was a significant predictor for MACCE in the
CABG group, but not in the stent group (RR, 0.986; 95% CI,
0.978–0.995; P = 0.0015 in the surgery group and RR,
0.996; 95% CI, 0.990–1.001; P = 0.1288 in the stent group).

Comparison of intervention in renal insufficient patients
In the moderate renal insufficient group, the overall 5 year
mortality rate and the incidence of cardiac death were
not statistically different between the stent and the CABG
arms (RR of total death, 1.18; 95% CI, 0.51–2.72; RR of cardiac
death, 0.64; 95% CI, 0.15–2.69; P = 0.1288 in the stent group).
The combined incidence of death, stroke, or MI was also
not statistically different between patients in the stent
arm and in the CABG arm, although the actual rates were
higher in the stent arm than in the CABG arm (30.4% in
the stent arm vs. 23.3% in the CABG arm: RR, 1.31; 95%
CI, 0.76–2.26; P = 0.35). However, the incidence of repeat
revascularization was significantly higher in the stent arm
when compared with the CABG arm (29.0 vs. 9.6% RR, 3.02; 95% CI, 1.37–6.70; \( P = 0.005 \)). Overall, MACCE occurred in 34 patients (49.3%) assigned to stent implantation when compared with 23 of patients (31.5%) assigned to bypass surgery (RR, 1.56; 95% CI, 1.03–2.37; \( P = 0.04 \)). The different incidence of MACCE rate was driven by the higher incidence of repeat revascularization in the stent arm. The different clinical outcomes are illustrated by the Kaplan–Meier estimates of event-free survival in the stent and CABG arm within each group (Figure 2).

**Discussion**

Renal insufficiency is associated with an increase in mortality and major adverse cardiac events after revascularization in a dose-dependent fashion.\(^1\)\(^3\)\(^15\) In the present study, at 5 years after revascularization, patients with moderate renal insufficiency (Ccr < 60 mL/min) and multivessel coronary disease had poor clinical outcomes for composite events of death, CVA, or MI when compared with mild renal dysfunction and normal renal function patients (Ccr ≥ 60 mL/min). Nevertheless, the rate of clinically driven repeat revascularization was similar between patients with moderate renal dysfunction and patients with normal renal function and mild renal dysfunction, regardless of the allocated strategy of revascularization. These results are comparable to those reported in previous retrospective studies.\(^1\)\(^2\)\(^15\) However, in these studies and the present study, no follow-up angiographic assessment was performed. High angiographic in-stent restenosis rates have been documented in patients with end stage renal function, but the actual rate of restenosis in moderate renal insufficiency is still unknown.\(^16\)\(^17\) In the present study, the rate of clinically driven repeat revascularization was comparable in patients with normal renal function and those with moderate renal dysfunction, despite a higher incidence of late cardiac events in this latter group, although we suspect that the patients with altered renal function are more prone to restenosis. Two factors may have contributed to this unexpected relatively low rate of intervention; First, as mentioned earlier, angiographic follow-up was not mandated by protocol. Secondly, a high incidence of silent ischaemia has been documented in those patients with renal dysfunction, a fact that may also explain the relatively low incidence of clinically driven intervention, particularly in the absence of mandated angiographic follow-up. It could be hypothesized that a high prevalence of silent ischaemia in renal insufficient patients may contribute to the comparable clinically driven repeat revascularization rate in spite of the high incidence of subsequent cardiac events when compared with patients with normal renal function.

This study also highlights that the 5 year mortality and composite rate of death, CVA, or MI did not reach a significantly statistical level between patients allocated to stenting or CABG in the moderate renal insufficiency group, although actual incidence of this rate in the stent arm was higher than that in the CABG arm. There are no precious reports comparing the clinical results of stenting vs. CABG for moderate renal insufficiency patients. However, some reports have compared outcomes after stenting and CABG in dialysis patients.\(^18\)\(^20\) All these studies showed that patients with dialysis or severe renal insufficiency had better long-term survival after CABG than PCI. However, these results did not apply to our study. Dialysis and moderate renal insufficient patients are different medical...
conditions. The limitations of coronary stenting for renal insufficient patients with multivessel disease are two-fold: a high incidence of repeat revascularization and the likelihood of renal function deterioration due to extensive use of contrast media in multivessel treatment. The ARTS trial was initiated in April 1997. It is relevant to consider the differences between the techniques used in this study and newly developed techniques for coronary revascularization such as off-pump CABG and new, minimally invasive approaches. Similarly, important developments in percutaneous coronary intervention have taken place since the completion of recruitment in the ARTS trial. Drug-eluting stents have definitively been shown to dramatically reduce restenosis rates and the different incidence of repeat revascularization (surgery and coronary intervention) are likely to narrow with the advent of drug-eluting stents. In addition, iso-osmolar, non-ionic contrast medium, acetylcysteine, and pre-hydration may potentially prevent the renal dysfunction induced by contrast media.

This study is a post-hoc sub-study of ARTS trial. The moderate number of patients may limit conclusions due to the lack of statistical power. We had several restrictive inclusion criteria, including lesion characteristics which had to be suitable for both percutaneous and surgical revascularization, so that the tentative conclusion may be restricted to the population initially included in the trial. In addition, the exact aetiology of renal dysfunction and renal function at follow-up period were not evaluated in this study. However, this is the first randomized prospective study to compare the 5 years clinical outcomes of the stenting vs. CABG in moderate renal insufficient patients with multivessel coronary disease.

Conclusions

In this 142 moderate renal insufficient patients (Cr < 60 mL/min) prospective cohort, the difference in 5 year mortality and combined incidence of death, CVA, and MI between stent coronary and surgery did not reach a statistically significant level, although the actual event rates in the stent group were higher than in the CABG group. The occurrence of MACCE in the stent group was statistically higher than in the CABG group, mainly due to the higher incidence of repeat revascularization in the stent group. However, the difference of MACCE rate between the stent and the CABG in the Cr < 60 mL/min group was similar as compared to the Cr ≥ 60 mL/min group.

References


