DES Reduce the Need for Repeat Revascularization: Results from the ISAR-CABG Trial

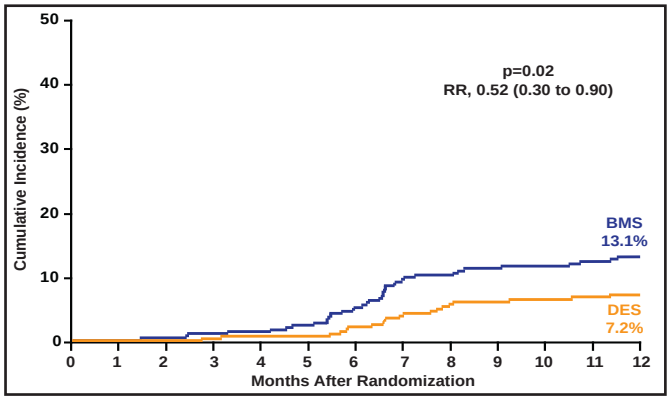
Investigators from the Efficacy Study of Drug-Eluting and Bare Metal Stents in Bypass Graft Lesions (ISAR-CABG; NCT00611910) report that treatment of saphenous vein graft (SVG) lesions with drug-eluting stents (DES) may decrease the long-term need for repeat target lesion revascularization (TLR) by approximately 50% compared with bare metal stents (BMS), making DES the preferred way to reduce restenosis in bypass grafts.

Only two published randomized controlled trials have compared DES with BMS for SVG lesions: the DELAYED RRISC (Reduction of Restenosis in Saphenous Vein Grafts With Sirolimus-Eluting Stent) trial [Vermeersch P et al. *J Am Coll Cardiol* 2007] and the SOS (Stenting of Saphenous Vein Grafts) trial, which compared paclitaxel-eluting stents (PES) with BMS [Brilakis ES. *J Am Coll Cardiol* 2009]. The results of these trials were mixed, and neither was powered to examine clinical endpoints (DELAYED RRISC trial n=75; SOS trial n=80).

In the ISAR-CABG trial, patients with *de novo* SVG lesions were randomized to receive either DES (sirolimus, paclitaxel, or biodegradable polymer-based sirolimus) or BMS. Participants had ischemic symptoms or evidence of myocardial ischemia in the presence of ≥50% *de novo* stenosis that was located in SVGs. Exclusion criteria included cardiogenic shock, target lesions in arterial grafts, malignancies with <1 year of life expectancy, and allergies to study medication. The primary endpoint of the prospective ISAR-CABG trial was a composite of death, myocardial infarction (MI), or ischemia-related TLR at 1-year postindex percutaneous coronary intervention (PCI). Secondary endpoints included all-cause mortality, MI, ischemia-related TLR, and incidence of definite or probable stent thrombosis. Patients were followed for 12 months, with a repeat angiogram that was encouraged at 6 to 8 months. After PCI, patients were treated with clopidogrel 150 mg per day until discharge, followed by 75 mg clopidogrel daily for at least 6 months and aspirin 200 mg daily indefinitely.

A total of 610 patients were randomized (DES=303, BMS=307) and baseline characteristics were balanced between groups. The primary composite endpoint of death, MI, or TLR at 12 months was significantly reduced with DES compared with BMS (15.4% vs 22.1%; RR 0.65; 95% CI, 0.45 to 0.96; p=0.03), driven primarily by a reduction in TLR (7.2% DES vs 13.1% BMS; RR, 0.52; 95% CI, 0.30 to 0.90; p=0.02 ; Figure 1). There was no significant difference in the rates of MI (p=0.27) or mortality (p=0.82). There was no difference in the rate of definite or probable stent thrombosis between groups (0.7% both groups; p=0.99).

Figure 1. Target Lesion Revascularization.



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The ISAR-CABG outcomes show that DES are associated with lower rates of MACE compared with BMS for SVG lesions. These results are driven largely by a reduced need for revascularization, and there were no significant differences in death or stent thrombosis between groups. These findings are supportive of those that are found in the long-term follow-up of the SOS trial, which showed that the use of paclitaxel-eluting stents was associated with significantly better clinical outcomes than BMS in SVG lesions (NCT00247208) [Emmanouil S et al. *J Am Coll Cardiol Cardiovasc Interv* 2011].

Preventing Contrast-Induced Acute Kidney Injury: Results from the REMEDIAL Trial II

Investigators from the Renal Insufficiency Following Contrast Media Administration Trial II (REMEDIAL II; NCT01098032) report that the RenalGuard™ automated hydration matching system is safe and effective in preventing contrast-induced acute kidney injury (CI-AKI) in high- and very-high-risk patients with chronic kidney disease (CKD) compared with the optimal strategy of sodium bicarbonate infusion plus N-acetylcysteine (NAC). Carlo Brigouri, MD, PhD, Clinica Mediterranea, Naples, Italy, presented the findings.

Contrast-induced acute kidney injury is strongly associated with unfavorable early and late clinical outcomes in

patients, which may be mitigated by maintaining a high urine flow. Prior strategies focused on forced diuretic regimens (typically with high-dose furosemide), which may be harmful due to a resulting negative fluid balance. The primary hypothesis of REMEDIAL II was that achieving a precise real-time high urine output and matched fluid balance using the RenalGuard™ hydration system would be noninferior to a control hydration strategy of prophylactic sodium bicarbonate plus NAC to prevent CI-AKI.

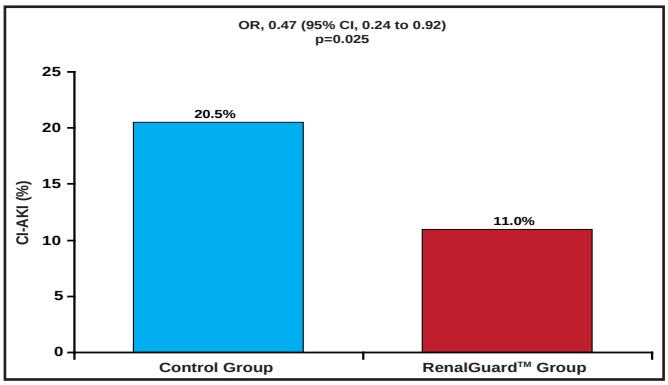
REMEDIAL II was a multicenter, prospective trial that included of 294 patients at elevated risk of contrast nephropathy, randomized to either hydration by the RenalGuard™ system (n=135; hydration with normal saline [target urine flow ≥300 ml/h]+1.5 g/L NAC+ 0.25 mg/kg furosemide) or hydration with sodium bicarbonate and acetylcysteine (n=145; hydration by 3 ml/kg of IV sodium bicarbonate for 1 hour before treatment and 1 ml/kg for 6 hours after, and 1200 mg NAC bid x 2 and 1.5 g during therapy). In all cases, the contrast media that was administered was iodixanol (an iso-osmolar, nonionic contrast agent).

The primary endpoint was the rate of CI-AKI, defined as an increase of ≥0.3 mg/dL in serum creatinine (sCr) concentration 48 hours after the procedure. Secondary endpoints included an increase in the sCr concentration ≥25% and ≥0.5 mg/dL at 48 hours after contrast exposure; changes in serum cystatin C (sCyC) concentration at 24 and 48 hours after contrast exposure; the rate of acute renal failure that required dialysis; the rate of in-hospital and 1-month major adverse events (composite of death, renal failure requiring dialysis, or acute pulmonary edema); and changes in serum and urine NGAL concentrations at 2, 6, 12, 24, and 48 hours postcontrast exposure.

The mean age of the 294 patients was 75 years, about one-third were women, almost all had hypertension, 70% had diabetes, half were on an ACE inhibitor, and the mean eGFR was 32 ml/min/1.73 m^2. The mean volume of contrast that was infused was about 135–140 ml.

The percentage primary endpoint occurred in 11% in the RenalGuard™ group and 20.5% in the control group (OR, 0.47; 95% CI, 0.24 to 0.92; p=0.025; Figure 1). This translated into an absolute risk difference of 8.5%, or a number needed to treat of 12 to prevent 1 patient with a 10% rise in creatinine after contrast exposure. The secondary endpoint of an increase in the sCr concentration ≥25% at 48 hours after contrast exposure occurred in 2.7% in the RenalGuard™ group and 13% in the control group (p=0.001). Similarly, changes in creatinine and cystatin C at 48 hours (secondary endpoints) were significantly reduced (Table 1) in the RenalGuard™ group. At 1 month, 0.7% of patients in the RenalGuard™ group versus 4.8% in the control group needed dialysis (number needed to treat of 25 to prevent 1 patient requiring dialysis; p=0.031). The cumulative secondary endpoint of major adverse events occurred in 6.8% in the RenalGuard™ group compared with 9.6% in the control group (p=0.52)

Figure 1. Primary Endpoint.



CI-AKI=Contrast-Induced Acute Kidney Failure

Table 1. Secondary Endpoints.

	Control Group (n=146)	RenalGuard™ Group (n=146)	p value
Changes in creatinine at 48 hours			
Increase ≥0.3 mg/dL	30 (20.7%)	16 (11%)	0.025
Increase ≥0.5 mg/dL	22 (15%)	9 (6%)	0.003
Increase ≥25%	19 (13%)	4 (2.7%)	0.001
Increase ≥50%	11 (7.5%)	1 (0.7%)	0.003
Changes in cystatin C at 24 hours			
Increase ≥0.3 mg/dL	21 (15.5%)	11 (8.5%)	0.07
Increase ≥10%	33 (24%)	22 (16%)	0.13
Increase ≥15%	23 (17%)	17 (12%)	0.29
Increase ≥25%	14 (10%)	5 (3.5%)	0.04
Changes in cystatin C at 48 hours			
Increase ≥0.3 mg/dL	29 (21%)	16 (12%)	0.045
Increase ≥10%	47 (34%)	29 (22%)	0.027
Increase ≥15%	35 (25.5%)	21 (16%)	0.050
Increase ≥25%	23 (17%)	11 (8.5%)	0.039

Data from REMEDIAL II demonstrate that among patients who are at high risk for contrast nephropathy, the aggressive hydration and matched fluid balanced that were achieved with the RenalGuard™ system (in conjunction with NAC and furosemide) were superior to hydration with sodium bicarbonate plus NAC in preventing contrast-induced sCr increases. Future trials should determine whether the automated closed-loop system that balances fluid management could be replicated simply with a routine aggressive hydration strategy.