# Does radial use as a second arterial conduit for coronary artery bypass grafting improve long-term outcomes in diabetics?[☆],[☆☆]

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## Abstract

**Objectives:** The evidence supporting the survival benefit of multiple arterial grafts in the general coronary bypass surgery (CABG) population is compelling. Alternatively, results of studies comparing 2 versus 1 internal thoracic artery (ITA) grafts in diabetics have reported conflicting survival data. The use of radial versus ITA as the second arterial conduit has not been studied. **Methods:** We obtained complete death follow-up in 1516 consecutive diabetic [$64 \pm 10$ years (mean $\pm$ SD). *Insulin/no insulin*: There were 540 (36%)/976 (64%)] primary isolated CABG patients all with $\geq 1$ ITA grafts. The series included 626 ITA/radial (41%) and 890 ITA/vein (59%) patients. Using separate radial-use propensity models, we matched one-to-one 475 (76%) ITA/radial to 475 (53%) unique ITA/vein patients; each including 166 insulin and 309 no insulin patients. **Results:** Unadjusted survival was markedly better for (1) ITA/radial (94.3%, 86.7% and 70.4% at 1, 5 and 10 years, respectively) versus ITA/vein (91.8%, 74.5% and 53.8%; $p < 0.0001$) and (2) for no insulin (94.2%, 82.8% and 65.5%) versus insulin (90.4%, 73.1% and 49.2%; $p < 0.0001$). In matched patients, 11-year Kaplan—Meier analysis showed essentially identical ITA/radial and ITA/vein survival for all diabetics combined ($p = 0.53$; log rank) and for the no insulin ($p = 0.76$) cohort. Lastly, a trend for better ITA/radial survival in insulin dependent diabetics after the second postoperative year did not reach significance ($p = 0.13$). **Conclusions:** Using radial as a second arterial conduit as opposed to vein grafting did not confer a survival benefit in diabetics. This unexpected result is perhaps related to relatively diminished radial graft patency and/or the augmented radial vasoreactivity characteristic of diabetics. These findings indicate that the radial survival advantage demonstrated in the general CABG population lies primarily in non-diabetics in whom this advantage may be underestimated.
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*Keywords:* Coronary artery disease; Arterial grafting; Diabetes mellitus; Insulin; Kaplan—Meier survival; Outcomes

## 1. Introduction

The aim of coronary artery bypass grafting (CABG) is the durable relief of symptoms of myocardial ischemia and restored life expectancy of patients with coronary atherosclerosis to age-matched population without coronary disease. The current paradigm for this strategy is complete myocardial reconstruction with a maximum number of arterial grafts. Compared to vein-only grafting, use of the left internal thoracic artery (ITA) to revascularize the left anterior descending coronary artery has been, unambiguously, shown to improve survival and minimize recurrent symptoms requiring re-interventions postoperatively [1].

Also, increasing the number of arterial grafts via the use of bilateral ITA was shown to carry an incremental survival benefit, particularly in the second decade post-CABG [1,2]. Using the radial artery as opposed to another ITA as the second arterial conduit, we showed that a survival benefit may be realized as early as the third postoperative year, and this improved survival correlated with superior radial versus vein graft patency in the restudied symptomatic subcohort [3]. This clinical result is consistent with the reported favorable physiological characteristics, specifically relatively greater endothelial production and or/vessel sensitivity to nitric NO, of the radial artery versus vein conduits [4].

Diabetes is an increasingly common risk factor in the CABG population approaching 40% in some patient series, and increased morbidity and mortality in this CABG cohort is well established including diminished long-term survival [5—7]. The impact of multiple arterial grafts in the diabetic CABG population is less well defined with relatively few studies addressing this issue. Moreover, these investigations (e.g., [8—10]) were generally small, principally confined to bilateral versus single ITA configurations, have not distinguished

between insulin-requiring versus other types of diabetes and, in nearly all cases, have failed to prove a survival advantage of >1 arterial graft. Accordingly, we investigated in a large retrospective series of diabetic patients all with ≥1 ITA grafts whether a survival benefit is achieved by using radial artery as the primary second graft as opposed to saphenous vein.

## 2. Methods

### 2.1. Study population

This investigation was approved by the Saint Vincent Mercy Medical Center (Toledo, Ohio, USA) Institutional Review Board. The study population was derived from a total of 4639 primary isolated CABG patients at a single institution (Saint Vincent Mercy Medial Center, Toledo, Ohio, USA; January 1996–June 2005). Of these, 4343 (93.6%) received ≥1 ITA grafts; 131 ITA-only patients and 15 emergency salvage patients were excluded.

The diabetes study population was next drawn from the remaining 4197 consecutive isolated multi-graft CABG patients that included: 1851 patients with ≥1 radial (ITA/radial; 41.3%) versus 2346 patients with additional vein grafts only (ITA/vein; 58.7%). Grafting method choice changed substantially over the study period with radial use increasing from about 25% in 1996 to nearly 60% in 2005 (Fig. 1, top). The multi-graft inclusion requirement meant that 98% of patients had multivessel coronary disease (3168 triple vessel disease or 76%) compared to only 84 patients or 2% with single vessel disease. Incidence of diabetes increased over the study period especially between 2001 and 2005 (Fig. 1, top), and totaled 1516 (36%) diabetic patients overall.

Study patients were further categorized based on the type of diabetes; insulin dependent (insulin) or non-insulin dependent (no insulin), and based on the grafting method or treatment approach used: (1) patients receiving at least one radial graft (ITA/radial) and (2) patients receiving additional vein grafts only (ITA/vein). Note, ITA/radial patients may have received additional vein grafts as necessary. Aortocoronary grafting was used in the over-whelming majority of both groups (~99%) unless aorta quality was suboptimal. Sequential grafting was used to a similar extent in both diabetes groups.

### 2.2. Surgical procedure

Radial artery utilization was at the discretion of the surgeon. Radial artery harvesting was initially performed via a full forearm incision, but has evolved more recently to a minimally invasive approach using the RadLITE system (Starion Inc. Sunnyvale, CA). The minimally invasive approach is accomplished through a small incision proximal to the wrist. Adequacy of collateral ulnar circulation was assessed preoperatively via an Allen's test. Intraoperative pulse oximetry and palmar arch Doppler assessment were carried out, following occlusion of the radial artery, to correlate the preoperative assessment. The non-dominant hand was used when possible. The radial artery utilization rate increased steadily during the study period. Radial artery was not utilized in patients with Raynaud's disease,
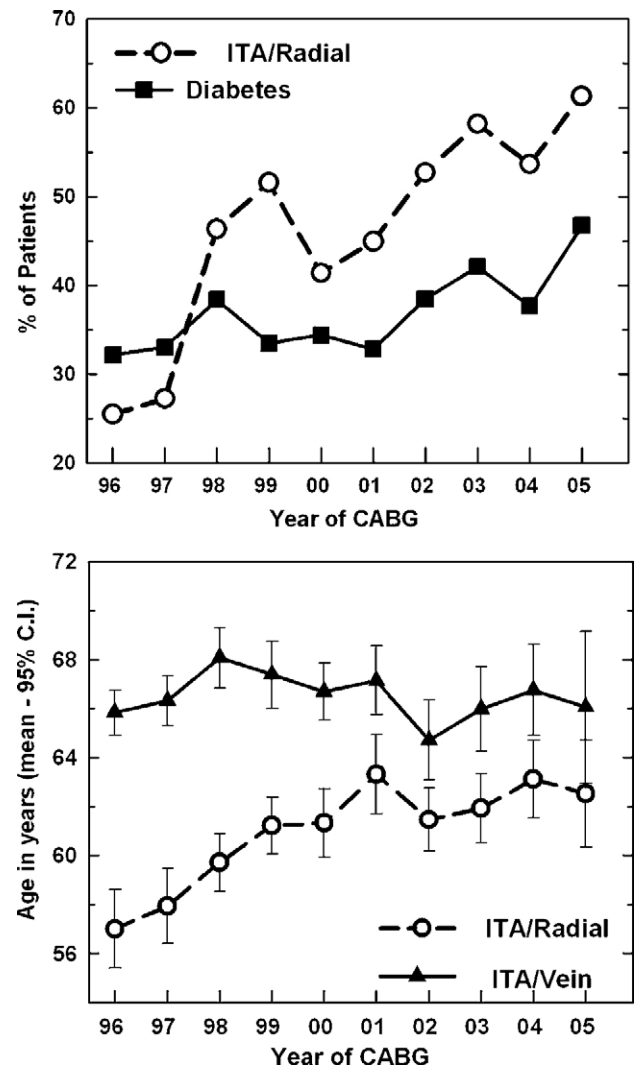


Fig. 1. *Top*: Annual incidence of ITA/radial and diabetic patients among the 4197 primary isolated CABG with ITA population at our institutions between 1996 and 2005. *Bottom*: The 1996–2005 age (mean ± 95% confidence interval) trends comparison of the ITA/radial and ITA/vein subcohorts of the 4197 CABG with ITA population.

equivocal/inadequate ulnar collateral flow, impending dialysis-dependent renal failure with imminent AVF construction, vasculitis, or presence of more than mild calcifications or atherosclerotic plaque within the radial artery. The radial artery was harvested atraumatically as a pedicle using a 'no-touch technique'. An ultrasonic scalpel (Ethicon Endo-Surgery, Inc., Cincinnati, OH) or the RadLITE system was utilized exclusively. The radial arteries were harvested concurrently with other conduits, with clamping only following adequate heparinization. Following extraction of the radial artery, the proximal end was cannulated and flushed gently with warm 'graft solution' (300 cc of lactated Ringer's solution with 5 mg of verapamil, 2.5 mg of NTG, 500 units of heparin and 0.2 cc of $NaHCO_3$). Saphenous vein grafts and radial artery grafts were stored ex vivo in the same 'graft solution' at 37 °C, while topical papaverine was placed on the IMA. Normothermic cardiopulmonary bypass was used in all on-pump patients (96%) while 4% of patients underwent off-pump coronary artery reconstruction. Aorto-coronary grafts

were constructed exclusively, unless aorta quality was poor or conduit length was inadequate. Sequential grafting of the radial artery was utilized with increasing frequency during the study period.

Operative radial artery utilization strategy evolved during the study period. Initially, radial artery utilization was restricted to patients that were younger and carried a reasonable long-term prognosis. Also, RA grafts were placed to both the right coronary artery and the left coronary artery systems. This practice reflected a philosophical bias towards a perceived superior radial artery patency that was extrapolated from ITA data. Progressively, with increasing experience with RA, such a highly selective RA utilization strategy evolved into the routine utilization of radial arteries in all possible patients that had adequate ulnar collateral flow and adequate left-sided targets. RA grafts have not been placed to the RCA system in the latter portion of the study, based on reports documenting suboptimal patency in this distribution [11]. Recently, we have also utilized RA grafts only to target vessels in the left coronary arterial system with greater than 70% proximal stenosis, due to the negative impact of collateral coronary flow on radial artery durability. There was no size restriction of the target vessel on radial artery graft placement. Initially, all patients received intravenous diltiazem drips in the perioperative period, which transitioned to oral diltiazem postoperatively, and was maintained for three to 6 months postoperatively. With increasingly convincing data of no substantial impact of vasodilators on radial artery durability, and the frequent interactions between calcium antagonists and beta-blockers resulting in negative inotropic and chronotropic effects, vasodilators have been progressively phased out.

All patients received aspirin, statins, beta-blockers and ACE inhibitors postoperatively, unless these were contra-indicated by allergies or clinical circumstances. All smokers were enrolled in a smoking cessation program. Tight glycemic control, with blood sugar target levels of 80–120 mg/dl, was implemented with aggressive utilization of intraoperative and postoperative insulin drips. The patients were transitioned to their preoperative antihyperglycemic regimen, which was not infrequently upgraded to produce the desired glycemic control.

### 2.3. Patient matching

Comparing treatment groups derived from observational data is often complicated by differing patient characteristics of the groups being compared [15,16]. The ITA/radial and ITA/vein subpopulations in both diabetes study groups were characterized by many significant demographic and risk factor differences (Table 1). Such differences can influence CABG outcomes substantially.

To overcome the confounding effects of between-group differences in patient data on outcome data, we used propensity score matching where use of radial grafting was considered as treatment [3]. Briefly, the probability that a patient received a radial graft was defined by a propensity score derived from a logistic multivariate model applied to the insulin and no insulin patient groups separately (or two models). A total of 47 preoperative risk factors, demo-

graphics and operative variables were entered into the model irrespective of their significance (see list of variables in Table 1 in addition to other variables, e.g., hyperlipidemia, time on cardiopulmonary bypass, cross-clamp time, New York Heart Association class, race, time of myocardial infarction, arrhythmias, preoperative medications including aspirin, beta-blockers, ACE inhibitors, anticoagulants). Also, time of surgery was entered into the model indicating the quarter of each year [i.e., values between 1 (Quarter 1 of 1996) up to 40 (Quarter 4 of 2005)] to account for the increasing use of radial over the study period. Highly redundant variables (e.g., weight, height and body surface area) were avoided. Expectedly, the resulting radial-use propensity score distributions derived for ITA/radial and ITA/vein patients were distinct ($p = 0.0000$).

A computer algorithm was next used to obtain one-to-one or greedy matching of the propensity scores for each ITA/radial patient with its closest possible unique ITA/vein match from the same diabetes subcohort. The maximal accepted propensity score difference during matching was always 1% (i.e., all matches were within ±1%).

### 2.4. Follow-up

Long-term all-cause mortality data were secured from our service patient follow-up and verified from individual patient queries of the United States Social Security Death Index database (http://ssdi.genealogy.rootsweb.com) in June 2007. Database records were updated for missing death information when necessary. Allowing for a 3-month lag in the SSDI database, this corresponds to a minimum of 21 (June 2005 patients) and a maximum of 135 (January 1996 patients) months follow-up.

### 2.5. Data analysis and statistical methods

Continuous data were expressed as mean ± standard deviation (SD) unless otherwise stated. Univariate comparisons were done with chi-square ($\chi^2$) or Fisher's exact test for categorical variables and either the unpaired $t$-test or the non-parametric Mann–Whitney rank sum test for continuous variables. Kaplan–Meier plots were determined for survival comparisons (log rank test). We determined the effects of explanatory variables on survival by multivariate Cox proportional hazard analysis. Model selection was first done with backward elimination (Wald statistic), and variables significant at the $p$ less than 0.05 level were retained as independent predictors and confirmed using forward and stepwise selection. Statistical analysis was conducted with SPSS version 15.0 software (SPSS Inc., Chicago, IL). A $p$ value less than 0.05 indicated significance.

## 3. Results

The study population consisted of 1516 consecutive primary isolated CABG patients with a presurgery diagnosis of diabetes including: 540 insulin-dependent (insulin: 35.6%) and 976 no insulin (64.4%) patients. The latter group were managed predominantly with oral medication (898/976; 92%)

Table 1
Demographics, risk factors, coronary disease/grafting and mortality data in ITA/radial and ITA/vein subcohorts of the overall *insulin* and *no insulin* diabetic population

| | All patients, mean ± SD/% | Insulin-dependent | | p value | No insulin | | p value |
|---|---|---|---|---|---|---|---|
| | | ITA/radial, mean ± SD/% | ITA/vein, mean ± SD/% | | ITA/radial, mean ± SD/% | ITA/vein, mean ± SD/% | |
| No. of patients | 1516 | 189 | 351 | | 437 | 539 | |
| Male | 61% | 54.0% | 50.1% | NS | 73% | 62% | 0.001 |
| Age (years) | 64 ± 10 | 62 ± 10 | 64 ± 10 | 0.046 | 62 ± 9 | 67 ± 10 | 0.000 |
| Weight (kg) | 90 ± 19 | 95 ± 20 | 88 ± 18 | 0.000 | 95 ± 19 | 87 ± 19 | 0.000 |
| Height (cm) | 170 ± 10 | 170 ± 10 | 168 ± 10 | 0.133 | 172 ± 9 | 170 ± 10 | 0.000 |
| Body surface area ($m^2$) | 2.06 ± 0.25 | 2.11 ± 0.24 | 2.02 ± 0.24 | 0.000 | 2.12 ± 0.25 | 2.02 ± 0.25 | 0.000 |
| Body mass index (kg/$m^2$) | 31.2 ± 6.2 | 33.3 ± 7.4 | 31.0 ± 6.2 | 0.000 | 31.8 ± 5.8 | 30.0 ± 5.7 | 0.000 |
| Smoker | 61% | 63% | 58% | NS | 65% | 59% | 0.054 |
| Current smoker | 19% | 15% | 19% | NS | 23% | 18% | 0.049 |
| Family history CAD | 61% | 60% | 60% | NS | 64% | 60% | 0.148 |
| Renal failure | 6.9% | 6.3% | 18.2% | 0.000 | 0.7% | 4.6% | 0.000 |
| Hypertension | 89% | 90% | 89% | NS | 88% | 89% | NS |
| Peripheral vascular disease | 21% | 21% | 32% | 0.004 | 13% | 21% | 0.001 |
| Cerebrovascular disease | 26% | 23% | 34% | 0.005 | 16% | 29% | 0.000 |
| Cerebrovascular accident | 10% | 10% | 15% | 0.084 | 6% | 9% | 0.030 |
| Chronic lung disease | 21% | 19% | 26% | 0.061 | 17% | 23% | 0.020 |
| Congestive heart failure | 19% | 21% | 32% | 0.006 | 10% | 18% | 0.000 |
| Myocardial infarction | 61% | 65% | 68% | NS | 57% | 58% | NS |
| Ejection fraction (%) | 47 ± 12 | 48 ± 11 | 46 ± 12 | 0.023 | 49 ± 11 | 47 ± 12 | 0.024 |
| Previous CV intervention | 28% | 27% | 30% | NS | 27% | 30% | NS |
| Status (1–4) | 1.73 ± 0.54 | 1.70 ± 0.50 | 1.77 ± 0.53 | 0.117 | 1.69 ± 0.52 | 1.75 ± 0.58 | NS |
| Emergency | 4.8% | 2.1% | 5.1% | 0.091 | 2.7% | 7.2% | 0.002 |
| Coronary disease/grafting | | | | | | | |
| Triple vessel disease | 79% | 80% | 80% | NS | 78% | 79% | NS |
| Vessel disease (1–3) | 2.77 ± 0.45 | 2.79 ± 0.43 | 2.79 ± 0.44 | NS | 2.76 ± 0.46 | 2.77 ± 0.46 | NS |
| Left main disease | 19% | 15% | 17% | NS | 18% | 22% | 0.112 |
| No. of grafts | 3.38 ± 0.87 | 3.48 ± 0.90 | 3.22 ± 0.76 | 0.000 | 3.60 ± 0.98 | 3.27 ± 0.78 | 0.000 |
| ITA grafts | 1.03 ± 0.17 | 1.02 ± 0.13 | 1.01 ± 0.12 | NS | 1.04 ± 0.21 | 1.03 ± 0.19 | NS |
| Radial grafts | 0.54 ± 0.74 | 1.30 ± 0.52 | 0.00 | 0.000 | 1.31 ± 0.58 | 0.00 | 0.000 |
| Vein grafts | 1.81 ± 0.97 | 1.16 ± 0.87 | 2.21 ± 0.75 | 0.000 | 1.26 ± 0.93 | 2.24 ± 0.79 | 0.000 |
| All arterial | 10% | 27% | 0% | 0.000 | 24% | 0% | 0.000 |
| ITA + radial + vein | 31% | 73% | 0% | 0.000 | 76% | 0% | 0.000 |
| Radial-use propensity score [a] | 0.41 ± 0.20 | 0.43 ± 0.16 | 0.31 ± 0.15 | 0.000 | 0.54 ± 0.18 | 0.37 ± 0.19 | 0.000 |
| Outcome data | | | | | | | |
| STS mortality risk (%) | 3.67 ± 4.50 | 3.02 ± 3.46 | 5.2 ± 5.64 | 0.000 | 2.03 ± 1.75 | 4.23 ± 5.06 | 0.000 |
| Operative death | 2.97% | 2.12% | 4.84% | 0.118 | 2.52% | 2.42% | NS |
| All deaths | 28.1% | 23.8% | 43.9% | 0.000 | 16.0% | 29.1% | 0.000 |
| Follow-up (days) | 2075 ± 1104 | 2033 ± 988 | 1934 ± 1163 | NS | 2007 ± 1049 | 2236 ± 1129 | 0.001 |

NS (not significant) = $p > 0.2$.
CAD: coronary artery disease; CV: cardiovascular; NYHA: New York Heart Association; ITA: internal thoracic artery; STS: Society of Thoracic Surgeons.
  [a] Propensity scores were based on separate multivariate models for insulin-dependent and no insulin patients.

with the remainder on diet control. The demographic, comorbidity, as well as their coronary disease and grafting data are summarized in Table 1. Radial grafting was used less frequently in insulin (189 of 540; 35%) compared to no insulin (437 of 976; 45%) patients, and in whom radial use approached that in non-diabetics (1225 of 2681; 46%). The characteristics and coronary disease and grafting data for the two diabetes subcohorts, each divided to their corresponding ITA/radial and ITA/vein subgroups are compared in Table 1. ITA/vein patients were generally older, contained more females, were smaller in size and had more comorbidities. Yet, over the 10-year study period, the age gap between ITA/vein and ITA/radial patients has narrowed substantially (Fig. 1, bottom) as did consequently the other characteristics, which reflected a change in radial-use practice pattern.

### 3.1. Effects of diabetes on CABG survival

Mean follow-up for the 1516 diabetic patients was 2075 ± 1104 days (mean ± SD) during which a total of 426 deaths were documented (28.1%). These deaths included 45 operative mortalities (O.M. = 2.97%, defined as in-hospital or out-of-hospital within 30 days of CABG surgery) versus 381 late deaths (25.1%). The corresponding Society of Thoracic Surgery predicted O.M. risk was calculated to be 3.67 ± 4.5 (%) indicating an observed-to-expected mortality rate of 0.81.

While the age distributions of the diabetic and non-diabetic (data not shown) patients are similar, the diabetes cohort was characterized by noticeably greater incidence of comorbidities (e.g., 6.9% renal failure, 26% cerebrovascular disease, 21% peripheral vascular disease, 19% congestive
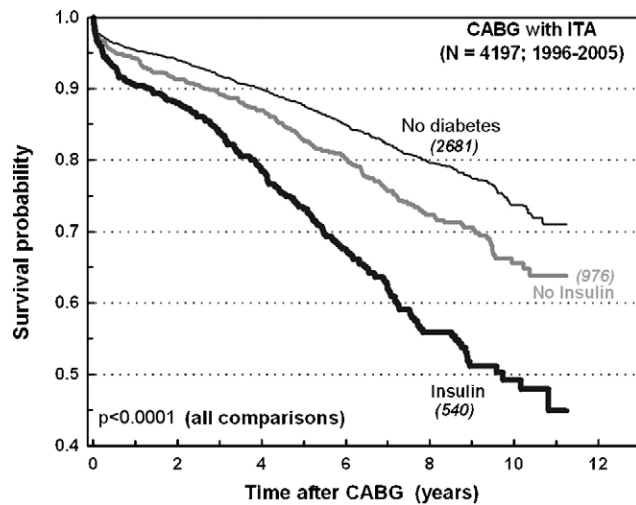
Fig. 2. Eleven-year unadjusted Kaplan–Meier survival reflecting all-cause mortality for the insulin (mean age = 63 ± 10 years; thick line, black) and non-insulin (mean age = 65 ± 10 years; thick line, gray) diabetic study patients that underwent primary isolated CABG with ≥1 ITA grafts. The corresponding non-diabetic (mean age = 64 ± 11 years) survival data are also shown (thin line, black) to reference the diabetes data.

heart failure). Expectedly, the substantially increased comorbidity in diabetics adversely affected 0–11-year survival in this study population as is clearly evident from the unadjusted Kaplan–Meier survival data comparisons shown in Fig. 2. Moreover, the diabetes survival data also suggested that survival trends following CABG are distinctly worse in the insulin-requiring cohort. Specifically, the 1-, 5- and 10-year survival for the no insulin cohort was 94.2%, 82.8% and 65.5%, respectively, compared to 90.4%, 73.1% and 49.2% for the insulin cohort ($p < 0.0001$).

## 3.2. Effect of graft conduit choice on survival

### 3.2.1. Unadjusted comparisons (all patients)

Fig. 3 shows the unadjusted 11-year ITA/radial versus ITA/vein survival comparisons for all (top), no insulin (middle) and insulin diabetics. All three unadjusted comparisons showed that ITA/radial survival was substantially and significantly (all $p < 0.0001$) better than the corresponding ITA/vein group. For all diabetics, the 1-, 5- and 10-year survival in ITA/radial patients was 94.3%, 86.7% and 70.4%, respectively, compared to 91.8%, 74.5% and 53.8% for the ITA/vein cohort ($p < 0.0001$). Interpretation of these significant survival differences is, however, hindered by the substantial differences in the patient characteristics of the grafting method compared groups.

### 3.2.2. Propensity-matched comparisons

A total of 475 ITA/radial were matched to 475 unique ITA/vein diabetic patients using separate propensity models for insulin and no insulin groups. These were divided as follows: (1) insulin patients: 166 of 189 (88%) ITA/radial patients were closely one-to-one matched to 166 of the 351 (47%) ITA/vein patients; and (2) insulin patients: 309 of 437 (71%) ITA/radial patients were closely one-to-one matched to 309 of the 539 (57%) ITA/vein patients. The corresponding demographics, risk factors and operative data of the
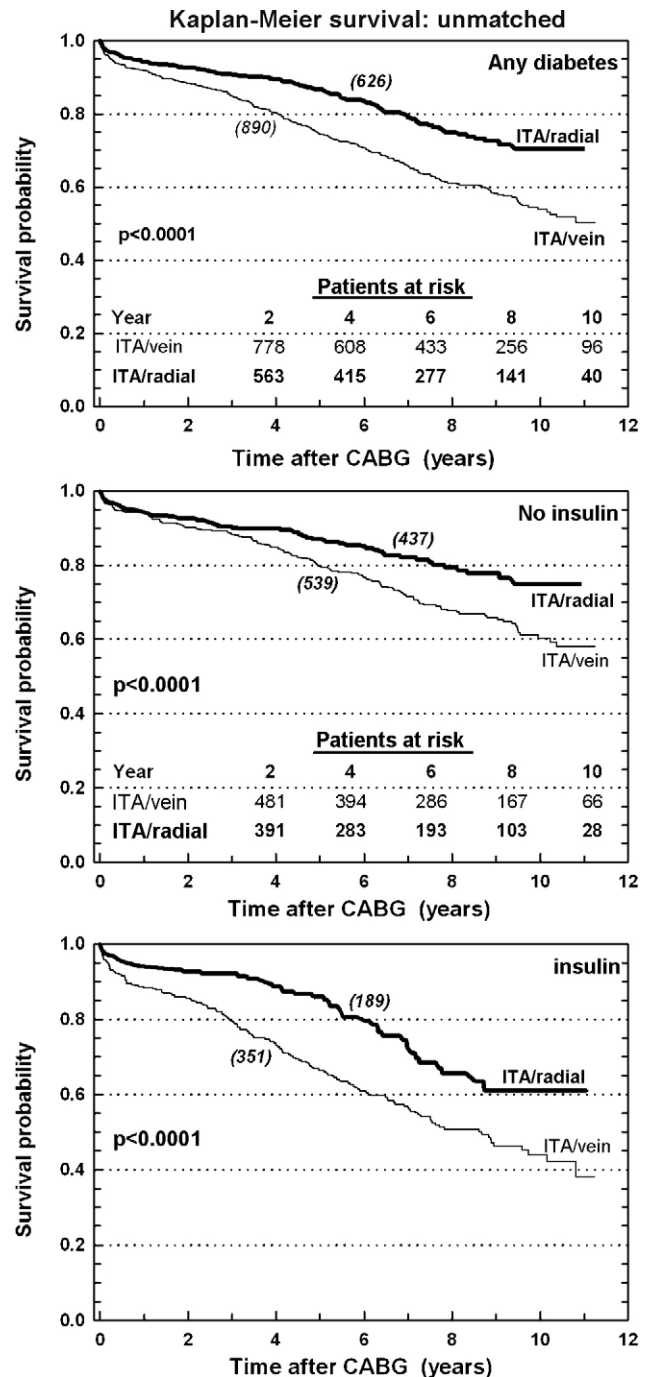


Fig. 3. Comparison of unadjusted 0–11-year Kaplan–Meier survival data in all ITA/*radial* (thick lines) *versus* all ITA/*vein* (thin lines) diabetic patients. *Top*: All diabetes patients with 626 ITA/*radial* and 890 ITA/*vein* patients ($p < 0.0001$, log rank test). *Middle*: No insulin subcohort with 437 ITA/*radial* and 539 ITA/*vein* ($p < 0.0001$). *Bottom*: Insulin-dependent subcohort with 189 ITA/*radial* and 351 ITA/*vein* ($p < 0.0001$). Inserted tables in each panel provide the patient at risk in each of the comparison groups at fixed time points.

matched ITA/radial and ITA/vein subcohorts were similar as detailed in Table 2.

For the overall 950 matched diabetic patients, a total of 11 (1.16%) operative deaths were documented including 9 of 475 (1.89%) among ITA/radial versus 2 of 475 (0.42%) among

ITA/vein patients ($p$ = 0.019; chi-square). The total number of documented deaths in the propensity-matched population was 220 of the 950 patients (23.2%), and this showed an opposite trend favoring ITA/radial patients. Specifically, the combined early and late deaths in ITA/radial patients totaled 98 of 475 (20.6%) versus 122 of 475 (25.7%) for ITA/vein patients ($p$ = 0.065; chi-square). Note, this difference was particularly evident in the insulin patient comparison where all deaths were 24.7% and 34.9% of ITA/radial and ITA/vein, respectively ($p$ = 0.042; chi-square; see Table 2).

For the combined propensity-matched diabetic patients (475 patient each), Kaplan—Meier analysis showed that the 0—11-year cumulative survival was essentially identical for the ITA/radial and ITA/vein cohorts ($p$ = 0.53 (log rank test); Fig. 4, top). This result was also true for the matched no insulin ($p$ = 0.76 (log rank test); Fig. 4, middle) and insulin ($p$ = 0.13 (log rank test); Fig. 4, bottom) subgroup compar-

isons. However, for the insulin comparison, the survival differences favoring ITA/radial did approach significance with an evident separation in the survival trends after the second postoperative year.

### 3.2.3. Survival in unmatched patients

A total of 151 (17 deaths) of 626 ITA/radial and 415 (189 deaths) of 890 ITA/vein diabetic patients were not matched based on the propensity score model. Fig. 5 (top) shows the corresponding un-adjusted Kaplan—Meier survival with the ITA/radial patients showing substantially better results ($p$ = 0.0000) with an estimated 10-year survival of 81% compared to about 40% for ITA/vein. However, these unmatched cohorts were distinctly different populations as is implicit from consideration of the risk factors and demographics in the overall populations (Table 1) versus the matched cohorts (Table 2). These unmatched cohorts

Table 2
Demographics, risk factors, coronary disease/grafting and mortality data in ITA/radial and ITA/vein propensity-matched insulin and no insulin diabetic population

| | Insulin-dependent | | $p$ value | No insulin | | $p$ value |
|---|---|---|---|---|---|---|
| | ITA/radial, mean ± SD/% | ITA/vein, mean ± SD/% | | ITA/radial, mean ± SD/% | ITA/vein, mean ± SD/% | |
| No. of patients | 166 | 166 | | 309 | 309 | |
| Male | 52% | 53% | NS | 66% | 66% | |
| Age (years) | 63 ± 10 | 63 ± 10 | NS | 64 ± 10 | 64 ± 10 | NS |
| Weight (kg) | 94 ± 18 | 92 ± 20 | NS | 91 ± 18 | 91 ± 19 | NS |
| Height (cm) | 169 ± 10 | 170 ± 10 | NS | 171 ± 10 | 171 ± 10 | NS |
| Body surface area (m$^2$) | 2.09 ± 0.23 | 2.08 ± 0.25 | NS | 2.08 ± 0.24 | 2.08 ± 0.25 | NS |
| Body mass index (kg/m$^2$) | 32.9 ± 7.0 | 32.1 ± 6.7 | NS | 31.1 ± 5.7 | 31.0 ± 5.5 | NS |
| Smoker | 64% | 59% | NS | 65% | 61% | NS |
| Current smoker | 15% | 19% | NS | 24% | 21% | NS |
| Family history CAD | 58% | 61% | NS | 65% | 61% | NS |
| Renal failure | 7.2% | 7.2% | NS | 1.0% | 0.3% | NS |
| Hypertension | 92% | 89% | NS | 87% | 88% | NS |
| Peripheral vascular disease | 23% | 24% | NS | 18% | 15% | NS |
| Cerebrovascular disease | 26% | 21% | NS | 22% | 20% | NS |
| Cerebrovascular accident | 11% | 8% | NS | 8% | 7% | NS |
| Chronic lung disease | 20% | 19% | NS | 19% | 20% | NS |
| Congestive heart failure | 23% | 21% | NS | 11% | 12% | NS |
| Myocardial infarction | 65% | 64% | NS | 56% | 56% | NS |
| Ejection fraction (%) | 48 ± 11 | 48 ± 11 | NS | 48 ± 11 | 48 ± 11 | NS |
| Previous CV intervention | 28% | 33% | NS | 28% | 29% | NS |
| Status (1—4) | 1.72 ± 0.50 | 1.74 ± 0.50 | NS | 1.70 ± 0.52 | 1.70 ± 0.51 | NS |
| Emergency | 2.4% | 3.0% | NS | 2.9% | 2.6% | NS |
| Coronary disease/grafting | | | | | | |
| Triple vessel disease | 79% | 79% | NS | 75% | 76% | NS |
| Vessel disease (1—3) | 2.78 ± 0.45 | 2.78 ± 0.45 | NS | 2.73 ± 0.48 | 2.75 ± 0.46 | NS |
| Left main disease | 16% | 18% | NS | 20% | 17% | NS |
| No. of grafts | 3.37 ± 0.84 | 3.38 ± 0.77 | NS | 3.35 ± 0.83 | 3.41 ± 0.82 | NS |
| ITA grafts | 1.01 ± 0.08 | 1.01 ± 0.11 | NS | 1.04 ± 0.19 | 1.04 ± 0.21 | NS |
| Radial grafts | 1.27 ± 0.50 | 0.00 | 0.000 | 1.22 ± 0.49 | 0.00 | NS |
| Vein grafts | 1.10 ± 0.85 | 2.37 ± 0.75 | 0.000 | 1.09 ± 0.84 | 2.37 ± 0.82 | 0.000 |
| All arterial | 28% | 0% | 0.000 | 26% | 0% | 0.000 |
| ITA + radial + vein | 72% | 0% | 0.000 | 74% | 0% | 0.000 |
| Radial-use propensity score[a] | 0.40 ± 0.14 | 0.40 ± 0.14 | NS | 0.47 ± 0.17 | 0.47 ± 0.17 | 0.000 |
| Outcome data | | | | | | |
| STS mortality risk (%) | 3.27 ± 3.61 | 3.49 ± 3.65 | NS | 2.37 ± 1.94 | 2.69 ± 2.56 | 0.080 |
| Operative death | 2.41% | 0.60% | 0.187 | 1.62% | 0.32 | 0.056 |
| All deaths | 24.7% | 34.9% | 0.042 | 18.4% | 20.7% | NS |
| Follow-up (days) | 2027 ± 984 | 2083 ± 1064 | NS | 2010 ± 1064 | 2361 ± 1090 | 0.000 |

NS (not significant) = $p$ > 0.2.
CAD: coronary artery disease; CV: cardiovascular; NYHA: New York Heart Association; ITA: internal thoracic artery; STS: Society of Thoracic Surgeons.
[a] Propensity scores were based on separate multivariate models for insulin-dependent and no insulin patients.
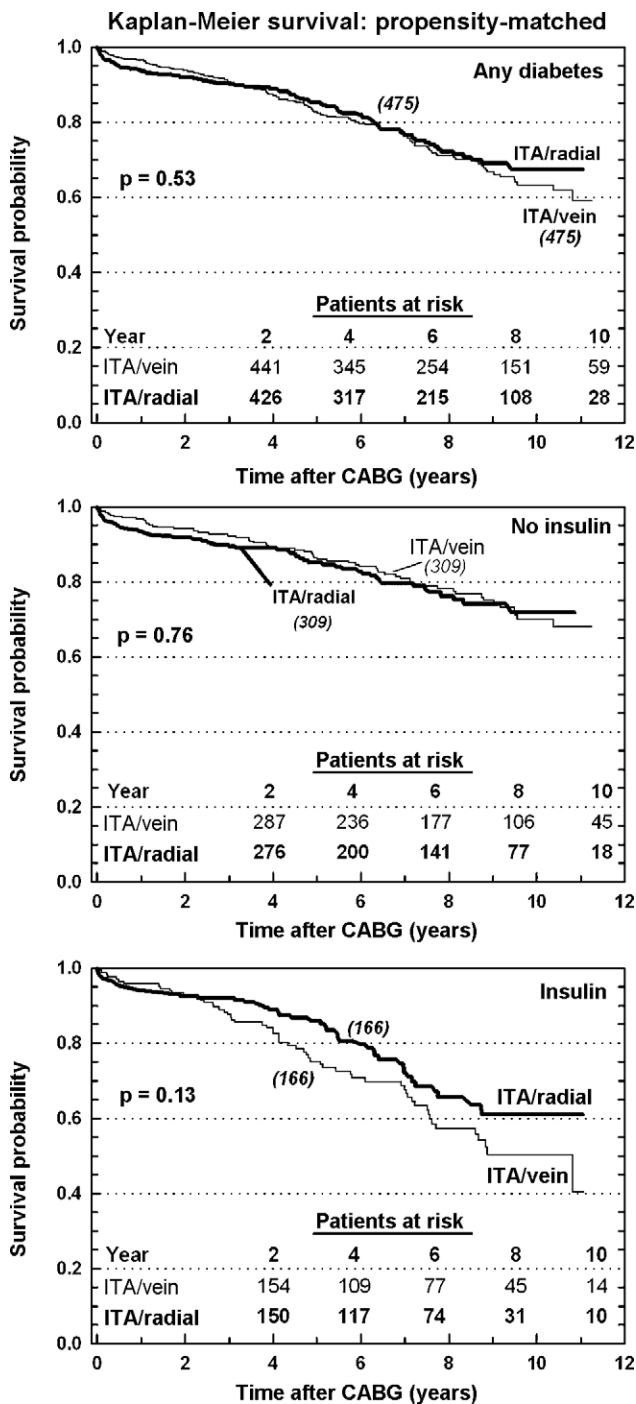
Fig. 4. Comparison of 0—11-year Kaplan—Meier survival data in propensity-matched ITA/*radial* (thick lines) *versus* ITA/*vein* (*thin lines*) diabetic CABG patients. *Top*: All diabetes patients with 475 ITA/*radial* and 475 ITA/*vein* patients (*p* = 0.53; log rank test). *Middle*: No insulin subcohort with 309ITA/*radial* and 309 ITA/*vein* (*p* = 0.76). *Bottom*: Insulin-dependent subcohort with 166 ITA/*radial* and 166 ITA/*vein* (*p* = 0.13). Inserted tables in each panel provide the patient at risk in each of the comparison groups at fixed time points.

were: (1) generally younger/low risk ITA/radial patients and (2) disproportionately older and higher risk ITA/vein patients. Adjusting for the other risk factors (Fig. 5, bottom; see legend for details), this observed radial versus vein survival difference, estimated at the mean of covariates, was greatly
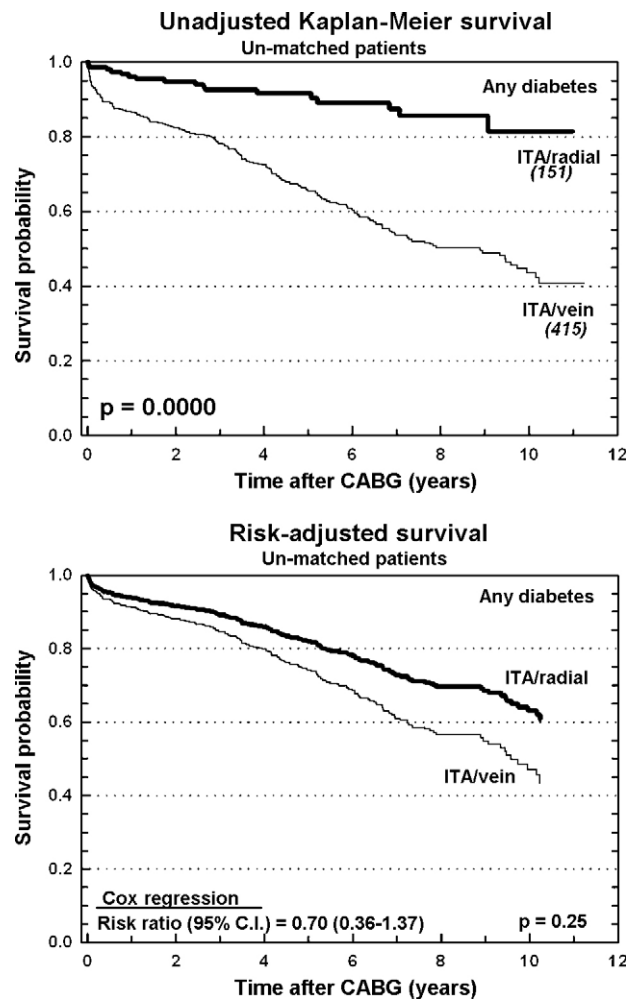


Fig. 5. *Top*: Unadjusted 0—11-year Kaplan—Meier survival for the 151 unmatched ITA/*radial* (thick lines) *and* the unmatched ITA/*vein* (*thin Lines*) diabetic patients (*p* < 0.0001, log rank test). *Bottom*: The ITA/*radial* versus ITA/*vein* risk-adjusted survival estimated via Cox regression analysis for the same 566 unmatched patients in the top panel. The model covariates were: *radial, insulin, BSA, BMI, age, male, chronic lung disease, current smoker, renal failure, hypertension, peripheral vascular disease, cerebrovascular disease, history of myocardial infarction, congestive heart failure, triple vessel disease, left main disease, ejection fraction (category), emergency, number of grafts* and *ITA use*.

reduced with an estimated radial-use risk ratio of 0.70 (95% C.I. = 0.36—1.37; *p* = 0.29). Note, this lack of statistical significance despite the 30% less mortality risk ratio should be considered with caution as it may be due to the small ITA/radial cohort with a relatively few total deaths (*n* = 17).

## 4. Discussion

Diabetes mellitus is an increasingly prevalent risk factor in coronary artery bypass surgery patients, with an incidence of anywhere between 20 and 49% [3—7]. Patients with diabetes have a clearly increased incidence of coronary artery occlusive disease and, indeed, 80% of deaths in diabetics are due to atherosclerosis. Diabetes has been shown to be a risk factor for graft failure and suboptimal long-term post-

CABG outcomes [5—7]. The specific factors behind the increased cardiac risks in diabetes are unclear, but most likely are diverse and multiple. Among these are extensive lipid abnormalities, endothelial dysfunction characterized by decreased nitric oxide production and increased endothelin production [12], inflammatory changes with supernormal production of interleukins [13], tumor necrosis factors and CRP, as well as augmented superoxide and NADPH oxidase activity [14]. Finally, but significantly, patients with diabetes also exhibit hemostatic aberrations such as increased platelet aggregation, increased platelet adhesion, and increased thrombogenesis, potentially accounting for premature graft failure and increased myocardial ischemic events noted in the postoperative period [15].

Given these substantial abnormalities seen in diabetics, perhaps it should not be surprising that any and all revascularization strategies, be they operative or percutaneous, are less effective in diabetics than their non-diabetic counterparts [5]. Yet, even within this milieu, arterial conduits have been found to be beneficial. Hirotani et al. [16], found that saphenous vein grafting only, exclusive of mammary artery grafts, conveys a significantly less 7-year survival benefit. In addition, the BARI study documented an 83.2% 7-year survival in diabetic patients receiving LIMA, as compared to a 54% survival in saphenous vein grafts only [7].

Encouraged by the above and the seminal studies of Lytle et al. [1], and Rankin et al. [2], establishing improved two-decade survival with multiple ITAs in the general CABG population (12—22% incidence of diabetes), a number of investigators evaluated whether multiple arterial grafting carries a similar survival benefit in diabetic CABG patients. Unfortunately, such a relationship has been difficult to establish. Hirotani et al. [10] found no difference in survival or MACE at 10 years in diabetic patients with single ITA as opposed to bilateral ITA grafting. Endo et al. [9] found that long-term mortality (up to 8 years) was not affected by bilateral internal ITA grafting. A positive impact on survival was seen in a subgroup of diabetic patients with an ejection fraction of greater than 40%. Tomupoulis et al. [8] found no incremental 10-year survival benefit in diabetic patients with bilateral versus single ITA grafting. It must be remembered that bilateral ITA grafting advantages become only apparent 7—10 years after surgery, and so perhaps the follow-up in the above studies may be too short to notice any substantial benefits.

In contrast to the above studies, Stevens et al. [17] found that bilateral ITA grafting decreased the risk of death. Interestingly, bilateral ITA grafting decreased the incidence of postoperative MI in non-diabetics while a similar benefit was not seen in diabetics. Bilateral ITA improved survival in patients who suffered an MI in the postoperative period, both in diabetics and non-diabetics. Similarly, Lev-Ran et al. documented a 7-year improved survival and a diminished rate of MACE in a group of patients with non-insulin-dependent diabetes mellitus undergoing left-sided bilateral ITA utilization [18].

The current study was motivated by two facts. First, the ambiguity of the results vis a vis the benefits of using two versus one ITA grafts in diabetic patients. Second, we are unaware of any studies that specifically addressed this question when radial is the preferred second arterial conduit as opposed to a second ITA. The primary finding in this study is that use of radial as a second arterial grafting conduit in CABG with ≥1 ITA grafts is not associated with improved 0—10-year CABG survival compared to well-matched diabetic patients where all additional grafts were constructed using saphenous vein. Moreover, this finding was particularly evident in patients with diet or oral controlled diabetes. It is unclear whether the observed trend of a radial grafting benefit in case of insulin-dependence that did not reach statistical significance ($p = 0.13$) is due to lack of statistical power, and that it may be confirmed using a larger patient series.

Unfortunately, our results add to a growing body of literature failing to substantiate a clear positive long-term survival benefit from utilization of multiple arterial grafts in the diabetic surgical population. Because the study spanned a decade, our selection criteria for patients revascularized with radial arteries resulted in a younger population with substantially less comorbidities. To compensate for this selection bias, propensity matching was utilized to offset this selection bias. Importantly, the findings in this study are counter to those we previously reported demonstrating improved 0—6-year survival with radial versus vein utilization in the context of LITA-to-LAD grafting in the general CABG population [3]. The prevalence of diabetes mellitus in that study was 34%. The lack of benefit in terms of survival in diabetic patients with radial arteries specifically, and multiple arterial grafts in general, is perplexing given the number of studies supporting superior patency of radial versus vein grafts and/or superior clinical outcomes in the general CABG population [3,19—22]. The notable exception to this trend is the study of Khot et al. documenting a significantly worse durability of radial conduits [23]. Paradoxically, in a multivariate analysis, absence of diabetes was a significant predictor of RA failure [23]. Clearly, regardless of the encouraging patency data in the overall CABG population, it is possible that radial durability strictly in a diabetic population may be equivalent to SVG grafts. In this case, long-term survival would be expected to be similar. Conversely, if the pattern of better radial patency is preserved in diabetics, other mechanisms may overwhelm the graft patency benefit on survival. Among these may be systemic, metabolic, inflammatory and hemostatic derangements coupled to myocardial endothelial abnormalities. The significance of increased radial artery atherosclerotic changes in patients with diabetes on clinical outcomes is unclear [24]. Finally, the intriguing recent report by Choudhary et al. documented augmented radial vasoreactivity in diabetic versus non-diabetics, and this may also adversely affect survival without necessarily leading to worse radial graft patency [25].

A limitation of our analysis was that it was performed on a retrospective observational CABG series. The question of whether radial versus vein grafting improves CABG outcome in diabetic patients is best addressed via specifically designed prospective multi-center randomized trials. This, however, is a rather expensive and impractical approach that may require well over a decade of multi-center effort to compile data equivalent to what is reported in this retrospective study. Fortunately, advances in statistical

methods have overcome many of the known shortcomings of observational data analyses, e.g., [3]. Here, we used propensity-matched radial and vein comparison groups. First, with radial use considered as treatment, we derived a comprehensive non-parsimonious radial-use propensity model that included all major demographic, risk factor/comorbidity and intraoperative variables. Next, we applied a strict matching criteria of ±1% maximum propensity score difference, and matching was done on a restricted one-to-one basis where patients were always matched to the same diabetes type (insulin and no insulin). This approach yielded an equal number of unique patients in well-matched comparison groups, and avoiding population-size bias that may plague other propensity matching approaches (e.g., decile groups). Other limitations of our study included: (1) unknown cause of death and hence the death rate may be in part independent of cardiac factors; (2) lack of preoperative or post-discharge glycemic control data in these patients which may impact outcomes; (3) unavailability of graft patency data and (4) potential effects of evolving techniques including the recent practice of avoiding radial grafting to RCA targets and to moderately diseased targets have not been considered.

In conclusion, we were unable to document a survival benefit to using radial artery versus saphenous vein grafting in diabetic patients whom receive ≥1 ITA grafts. Alternatively, our data does suggest that use of radial is a safe and a viable alternative to the traditional LITA/vein configuration when considering grafting strategy in insulin and no insulin diabetic patients. Furthermore, results of this study, considered in relation to our earlier report which included a relatively high incidence of diabetes [3], indicates that the reported survival benefit of radial artery grafting in the general CABG population probably underestimates the actual realizable radial benefit of radial in non-diabetic patients. We speculate that the lack of a radial grafting survival advantage may be due to (a) radial graft patency approximating that of saphenous vein in diabetics, (b) reduced radial patency in diabetics relative to their non-diabetic counterparts and (c) augmented radial artery vasoreactivity in diabetics. This speculation should be addressed in future investigations exploring the effects of diabetes on arterial and vein graft failure.

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## Appendix A. Conference discussion

*Dr A. Wechsler* (*Philadelphia, PA*): I have a couple of short questions for you. First, in the propensity matching, did you also match for surgeon?

*Dr Schwann*: No.

*Dr Wechsler*: It is just a minor point and it is an analysis that can be done at a later time.

Did you match for the percent of stenosis in the vessel to which the radial artery was grafted?

*Dr Schwann*: That is an excellent point and obviously reflects on the convergence of data, suggesting that indeed the radial artery patency is a substantial function of proximal stenosis. We found in our database to have a difficult time with the specific coronary anatomy and the upstream stenosis. So no, we did not match that.

Our approach to radial artery grafting evolved during the study period, and certainly over the latter portion of the study period we were a lot more hesitant to put radial arteries to patients who had disease in the right coronary arterial system because of the well described incidence of increased graft failure in that system versus the left system. We also have been very sensitive to placing radial arteries to target vessels that would minimize competitive flow and consequently minimize the premature graft failure. This represented a shift, a gradual shift, corresponding to the data that became available during the study period of over a decade.

*Dr Wechsler*: I think these are very important observations, so it leads to my next question. The strength of the study is that this is a beautiful use of propensity matching to try and neutralize unknown bias in patient selection for one or another treatment. It is also the weakness of the study in the sense that when you did propensity matching, you took 47 guesses as to what might influence the outcome of the study and included use of the radial artery as one of the guesses. That ended up with great matching, but what it also did was it eliminated 50% of the patients in the ITA vein graft group from the analysis, and we don't know, but perhaps that might have been the 50% who would have most benefited from the use of a radial artery as the other arterial conduit. Maybe you could just discuss that a little bit. And it is the difference between propensity matching and a randomized study.

*Dr Schwann*: Your comments are very insightful and obviously very well thought out and they hit at the heart of what we can potentially conclude from a propensity-matched analysis versus a prospective randomized study, and clearly those are the shortcomings of our study.

We tried to include in our analysis patient specific parameters which we thought would impact on long-term survival. I think that your point is extremely well taken and our conclusions have to be implemented into clinical practice with that contextual warning.

I think that there are two pieces of information that would be helpful to us to try to close the loop in terms of how to best incorporate this into clinical practice. The first would be to try to correlate survival with graft patency data, and we are in the process of doing that. The second element which I think is also important to consider is this. By virtue of propensity matching we have selected a patient population between the two study groups that is equivalent in everything that we could possibly think of except for the presence of a radial artery. The question that has to be answered is: does the advantage of a radial artery graft or multiple arterial grafting, become diluted by the other comorbidities, which are pretty substantial in both of our study populations, and is the survival of our two study populations based on noncardiac factors, i.e., do these patients die because of their noncardiac comorbidities and consequently by virtue of the propensity matching their outcomes are necessarily exactly the same? Thus, I think it would be helpful to ascertain the cause of death in both groups of patients, and we are trying to get our hands around that.

*Dr M. Sewielam* (*Cairo, Egypt*): I have one short question. Why did you abandon using the calcium channel blockers after the year 2000, and what kind of a vasodilator do you use to avoid spasm of the radial artery?

*Dr Schwann*: The approach to calcium channel blockers has evolved. Initially we started using calcium channel blockers routinely. We have also been sensitive to the fact that utilization of beta-blockers preoperatively, intraoperatively and postoperatively has a positive effect on long-term outcomes in CABG patients, and we have frequently encountered substantial interactions between calcium channel blockers and beta-blockers with negative chronotropic or inotropic effects. Consequently, frequently we would find ourselves in situations whereby sometimes the calcium channel blocker would be held and then the beta-blocker would be held and the patients would be discharged on various combinations of both of these. We also have found that in follow-up our cardiologists routinely stop the calcium channel blockers on their first two-week visit. Finally, we also feel that the calcium channel blockers have not been shown to be convincingly helpful in preventing vasospasm of the radial artery.