Effect of lipid exposure on graft patency and clinical outcomes: arteries and veins are different†

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Abstract

OBJECTIVES: We evaluated the influence of lipid exposure upon conduit patency in long-term follow-up after primary CABG.

METHODS: From a prospectively compiled database, we identified 1207 grafts (436 SV and 771 mixed arterial grafts) among 413 CABG patients with 9.4 ± 2.4 years of follow-up (range 3–13). Surveillance angiography was performed as part of a randomized trial. All available lipid assays were collected from pathology laboratories, and from these, mean annualized lipid exposure was calculated for total cholesterol, HDL, LDL and triglycerides. Angiographical and clinical data were analysed against lipid exposure. Graft failure was defined as occlusion, string sign or >80% stenosis.

RESULTS: Six thousand and seventy-seven lipid measurements were obtained, and there were 154 failed grafts. Three hundred and eleven patients received at least one vein graft, and all 413 patients received at least one arterial graft. Overall, only HDL levels were inversely correlated with graft failure, with total cholesterol and LDL showing no associations in a mixed pool of arterial and venous grafts. To assess whether total/LDL cholesterol had no effect or were exerting competing effects in arteries and veins, separate multivariate analyses were performed. Venous graft failure was associated with increased total cholesterol/HDL (P = 0.006) and LDL/HDL (P = 0.032). By contrast, elevated total cholesterol was correlated with a reduced risk of arterial graft failure (OR for graft failure 0.705, P = 0.023) with increasing LDL cholesterol following a similar trend (OR for graft failure 0.729, P = 0.051).

CONCLUSION: Sub-fractions of dyslipidaemia known to be risk factors for native vessel disease appear to similarly influence vein grafts. Arterial conduits are at least more resistant to the effects of high lipid exposure, and appear to be protective. These results favour the use of arterial grafts in patients with poorly controlled dyslipidaemia.

Keywords: Coronary artery bypass grafting • Cholesterol exposure • Graft patency • Radial artery conduits

INTRODUCTION

Coronary artery bypass grafting (CABG) remains the gold standard therapy for ischaemic heart disease (IHD). Crucial to its long-term success is the ability to achieve durable effective revascularization. Graft patency is therefore a critical determinant of outcomes, and our understanding of the various factors influencing this continues to evolve.

Dyslipidaemia is an important risk factor for the development and progression of atherosclerotic disease within native coronary vessels, and the stringent management guidelines for high-risk patients with IHD reflect this [1]. Previous reports have demonstrated an association between elevated cholesterol and atherosclerosis in vein grafts, which is analogous to that of native coronary disease [2–4].

The past decade has also seen several reports favouring the use of multiple arterial conduits [5–8], and long-term studies suggest an overall superiority of arterial grafts over their venous counterparts [9]. Multiple mechanisms for this advantage have been proposed; these include differences in endothelial function and platelet adherence, production of vasodilators [10], hyperplastic response to changes in coronary circulation pressures [11] and flow rate. Given these distinct variations in histology and physiology, the response of arterial conduits to lipid exposure cannot simply be extrapolated from studies of vein grafts or of native vessels. We therefore sought to clarify the behaviour of arterial grafts under different lipid environments. Given that cholesterol control is likely to affect upon both native and grafted vessel diseases, we also examined for correlations between lipid exposure,
graft patency and clinical outcomes for a group of patients up to 10 years after primary CABG.

METHODS

Radial artery patency and clinical outcomes trial

The study derives from the Radial Artery Patency and Clinical Outcomes (RAPCO) Trial, the design of which has been previously published [12]. The primary aim of RAPCO is to assess the long-term patency and clinical outcomes of the radial artery (RA) compared with the right internal thoracic artery (RTA) or the saphenous vein (SV) when grafting to the largest non-left anterior descending (LAD) target. RAPCO enrolled 619 patients, and all received the gold standard in situ LITA to the LAD. Any third- or fourth-order grafts usually employed the SV or occasionally an RA.

Patients receive annual telephone and clinical follow-up for at least 10 years after surgery. Using a second random assignment, protocol-directed angiograms were allocated at intervals of 1, 2, 5, 7 and 10 years, with the bulk weighted to the second half of the follow-up as this was anticipated to coincide with the majority of graft occlusion events. In addition, elective angiograms at the 5- and 10-year mark were offered to all patients. A less invasive CT angiogram (CTA) was offered in cases where the protocol or elective angiograms were refused. Angiograms are reported by three independent specialists and any disputed findings were further assessed by a fourth independent observer. Graft failure as defined by occlusion, >80% stenosis or string sign was recorded along with any pathological findings at the proximal or distal anastomoses.

Patients

This study included all RAPCO patients who had undergone at least one elective, protocol- or symptom-directed angiogram or CTA and at least one postoperative lipid assay. The primary end-point was defined as graft failure, and clinical end-points included all-cause mortality, non-fatal AMI and repeat revascularization (either PCI or reoperative CABG). Repeat revascularizations were performed on both grafted and ungrafted coronary arteries. All patients consented to the surgery, angiograms, annual telephone follow-up and surgical reviews. The RAPCO protocol was approved by the Austin Hospital Human Research Ethics Committee (project no. H95/086). Further approval was gained for this project as a substudy within RAPCO (3 December 2008, project no H2006/02690).

Lipid exposure

Cholesterol measurements (total cholesterol, HDL-C, LDL-C and triglycerides) in mmol/l were obtained via retrospective review of pathology and general practitioner records. All results dating back to the operation date were acquired. All HDL-C assays were included in our analysis irrespective of fasting status [13], while only the fasting measurements for total cholesterol, LDL-C and triglycerides were assessed. LDL-C assays were further filtered to exclude values for which the corresponding triglyceride level exceeded 4.52 mmol/l [14].

A graph of cholesterol measurements against time was compiled and the area under the curve calculated. This was divided by the duration in years between the date of the first and the last reading to obtain annualized lipid exposures for total cholesterol, HDL-C, LDL-C and triglycerides. This calculation was repeated for each graft and for each patient. The date of the most recent lipid reading did not exceed the angiogram or clinical event date by more than 3 months, ensuring that only lipid measurements which may have influenced event occurrence were incorporated. Angiographic, demographic and clinical data were analysed against the annualized lipid exposures.

Statistics

All analyses were performed using SPSS statistical software (SPSS Inc. 2010, PASW Statistics 18, Chicago, IL, USA). Lipid status was compared between patients using Student’s t-test. Generalized linear models were used to derive odds ratios and 95% confidence limits for predictor variables of graft patency. The generalized linear model adjusts for the non-independent nature of the observations and potential clustering effects. All odds ratios were calculated based upon increments of lipid exposure equivalent to 1 standard deviation (SD). For the graft patency analysis, 1 SD was equivalent to 0.76, 0.32, 0.67, 0.88 and 0.76 mmol/l for total cholesterol, HDL, LDL, triglycerides and non-HDL cholesterol respectively and was 0.70, 0.36, 0.85, 0.77 and 0.71 mmol/l for the clinical outcomes analysis.

RESULTS

Study population

440 patients from RAPCO’s cohort of 619 had available lipid data and were included in the clinical end-points analysis. Of these, 27 were excluded from the graft patency analysis due to lack of angiographic data (angiogram not performed or not yet due). Among the remaining 413 patients, we assessed a total of 1207 grafts (408 LITAs, 436 SVGs, 226 RA and 137 RTAs). Mean duration of follow-up was 9.4 ± 2.4 years and patients received an average of 2.9 grafts. All 413 patients received at least one arterial graft (as per trial protocol) and 311 were grafted with at least one SV.

Lipid influence on graft performance

Table 1 shows the baseline demographics of patients receiving arterial and venous conduits. More vein grafts were used in older patients. This is an effect of the RAPCO study design [12] as patients ≥70 years were randomized to either a RA or SV as the study graft, while those <70 received only arteries (either RA or RTA) as the study graft. Although veins were more frequently employed in older patients, the patency of these grafts at 5 and 10 years are similar between the older (≥70 years) and younger (<70 years) population.

As expected, lipid exposures were similar between the two conduit types given that these grafts were derived from the same study population (Table 1). In the overall cohort of mixed arterial and venous grafts (Table 2), only HDL-C was correlated with graft patency (1 SD increase in HDL decreased the risk of overall graft
failure by 20.5%, \( P = 0.048 \). There were no significant associations with either total cholesterol or LDL-C.

After an average of 9.4 years, 88/436 or 20% of SV grafts failed. In multivariate analysis (Table 2), the LDL-C to HDL-C ratio and total cholesterol to HDL-C ratio were the most significant predictors of vein graft failure. A one-unit increase in LDL-C/HDL-C increased the risk of vein graft failure by 43% \( (P = 0.032) \) and one-unit increase in total cholesterol/HDL-C conferred a 46% increase in vein graft failure rates \( (P = 0.006) \).

In comparison, only 66 of 771 (8.6%) arterial grafts failed (Table 2). In contrast to the vein grafts, multivariate analysis showed that elevated total cholesterol was protective against arterial graft failure (a 0.76-mmol/l increase in total cholesterol reduced the risk of arterial graft failure by 29.5%, \( P = 0.023 \)) and increasing LDL cholesterol tended towards a similar effect, reducing the risk of arterial failure by 27.1% \( (P = 0.051) \). The opposing influence of cholesterol on these arterial conduits compared with vein grafts explains the lack of association seen in the pooled graft population.

Patients who experienced any graft failure, either arterial or venous, had significantly lower HDL and higher triglyceride exposure than those who had entirely patent grafts (Table 3). This effect is largely driven by vein graft failure; patients with SV failure had lower HDL and higher triglyceride levels than those with patent SVs \( (P = 0.025 \) and \( P = 0.037 \), respectively), but lipid sub-fractions were not different between patients with and without arterial graft failure. These findings mirror our patency findings in Table 2.

### Lipid influence on clinical outcomes

There were 56 deceased patients (17 from cardiac-related causes), 16 non-fatal AMIs and 62 patients who required repeat revascularization (Table 4). Elevated HDL-C exposure favourably influenced survival in the whole population \( (0.36 \text{ mmol/l increase conferred a 45% reduction in mortality, } P = 0.010) \). Elevated total cholesterol was associated with non-fatal clinical events in the whole population \( (63\% \text{ and } 28\% \text{ increases in risk of AMI and revascularization, } P = 0.007 \text{ and } 0.028, \text{ respectively}) \). In a similar fashion, increased LDL-C/HDL-C ratio and total cholesterol/HDL-C ratio were both correlated with higher rates of revascularization and death in the whole study population, who received a mixture of artery and vein grafts.

While elevated lipid exposure was detrimental towards clinical outcomes in the overall cohort of patients, we performed a separate analysis of patients who received total arterial revascularization \( (n = 101) \) to isolate the influence of lipids on arterial grafts and subsequent clinical events (Table 5). Interestingly, repeat revascularization rates were favourably correlated with increased levels of LDL-C \( (0.67 \text{ mmol/l increase in LDL actually reduced reintervention rates by } 46\% \ (P = 0.049)), \text{ consistent with the seemingly protective influence of LDL-C on arterial graft patency described earlier. Survival was unaffected by any of the lipid parameters in patients with only arterial grafts. The duration of follow-up and the number of patients}
were inadequate for the detection of a survival difference between those receiving total arterial revascularization and those receiving mixed conduits based on previous reports of the influence of bilateral internal thoracic artery grafting [15]. AMI occurred in 16 patients overall and in only 3 of 101 patients with total arterial revascularization, which was inadequate for assessment.

**Effects of graft performance on clinical outcomes**

Table 6 shows the relationship between graft performance and clinical outcomes (Table 5). Any graft failure (artery or vein) increased the risk of repeat revascularization but not death or MI. Arterial graft failure was significantly predictive of revascularization, while vein graft failure (among the 311 patients who received at least one vein graft) tended towards the same end-point (P = 0.086).

**DISCUSSION**

**Graft patency**

Our study indicates that the long-term fate of vein grafts is significantly influenced by their lipid environment in a pattern familiar to us from native vessel disease. The ratio of total cholesterol-to-HDL cholesterol and ratio of LDL cholesterol-to-HDL cholesterol conferred the greatest risk of graft failure. Our findings are consistent with previous studies of lipid effect on vein graft patency [2] and observations that SV grafts have a propensity for developing accelerated atherosclerosis in their later years [16].

Although the response of vein grafts to lipids has been well documented, less is known about the effect of cholesterol on arterial grafts. Arterial conduits (a mixture of RA, LITA and RITA) in our analysis were more resistant to the effects of lipid exposure when compared with their SV equivalents. Given that these grafts are located differently from veins when exposed to the same lipid risk. This may partially explain why arterial grafts are observed to have superior long-term patency [17] in real world experience where perhaps only a minority of patients have optimally controlled lipid profiles [18].

The relative resistance of arteries to lipid exposure and subsequent atherosclerosis may be due to a combination of factors already described in the literature. There are a number of differences between the structure and function of arteries and veins; arteries undergo less lipid synthesis, slower lipid uptake and more rapid lipolysis [19]. Arteries also tend to maintain their endothelial

**Table 3: Comparison of lipid status between patients with and without graft failure**

<table>
<thead>
<tr>
<th>Lipid Parameter</th>
<th>Patients with any graft failure (n = 135)</th>
<th>Patients with no graft failure (n = 278)</th>
<th>P-value</th>
<th>Patients with ≥1 arterial graft failure (n = 61)</th>
<th>Patients with no arterial graft failure (n = 351)</th>
<th>P-value</th>
<th>Patients with ≥1 vein graft failure (n = 81)</th>
<th>No vein graft failure (n = 230)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>4.47</td>
<td>4.45</td>
<td>0.794</td>
<td>4.36</td>
<td>4.47</td>
<td>0.253</td>
<td>4.53</td>
<td>4.40</td>
<td>0.146</td>
</tr>
<tr>
<td>HDL</td>
<td>1.28</td>
<td>1.28</td>
<td>0.019</td>
<td>1.23</td>
<td>1.26</td>
<td>0.347</td>
<td>1.20</td>
<td>1.27</td>
<td>0.025</td>
</tr>
<tr>
<td>LDL</td>
<td>2.48</td>
<td>2.48</td>
<td>0.779</td>
<td>2.36</td>
<td>2.49</td>
<td>0.254</td>
<td>2.51</td>
<td>2.45</td>
<td>0.607</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>1.74</td>
<td>1.58</td>
<td>0.040</td>
<td>1.62</td>
<td>1.63</td>
<td>0.896</td>
<td>1.83</td>
<td>1.56</td>
<td>0.037</td>
</tr>
</tbody>
</table>

**Table 4: Multivariate analysis of factors affecting clinical outcomes**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Hazard ratio (95% CI)</th>
<th>P-value</th>
<th>Hazard ratio (95% CI)</th>
<th>P-value</th>
<th>Hazard ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (decades)</td>
<td>1.01 (0.740, 1.372)</td>
<td>0.963</td>
<td>0.706 (0.403, 1.236)</td>
<td>0.223</td>
<td>2.302 (1.589, 3.336)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>0.540 (0.263, 1.109)</td>
<td>0.093</td>
<td>0.794 (0.164, 3.843)</td>
<td>0.775</td>
<td>1.074 (0.413, 2.790)</td>
<td>0.884</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.976 (0.549, 1.735)</td>
<td>0.934</td>
<td>2.073 (0.733, 5.860)</td>
<td>0.169</td>
<td>1.589 (0.899, 2.808)</td>
<td>0.111</td>
</tr>
<tr>
<td>Preoperative hypertension</td>
<td>1.475 (0.856, 2.541)</td>
<td>0.162</td>
<td>1.130 (0.402, 3.178)</td>
<td>0.817</td>
<td>1.300 (0.742, 2.276)</td>
<td>0.359</td>
</tr>
<tr>
<td>Smoking (previous)</td>
<td>0.923 (0.516, 1.651)</td>
<td>0.787</td>
<td>1.495 (0.399, 5.597)</td>
<td>0.550</td>
<td>0.741 (0.402, 1.366)</td>
<td>0.336</td>
</tr>
<tr>
<td>Smoking (current)</td>
<td>0.122 (0.016, 0.960)</td>
<td>0.046</td>
<td>1.561 (0.223, 10.91)</td>
<td>0.654</td>
<td>1.044 (0.316, 3.451)</td>
<td>0.944</td>
</tr>
<tr>
<td>Surgical urgency</td>
<td>0.814 (0.417, 1.590)</td>
<td>0.547</td>
<td>0.809 (0.221, 2.964)</td>
<td>0.750</td>
<td>1.210 (0.656, 2.231)</td>
<td>0.542</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>1.282 (1.028, 1.600)</td>
<td>0.028</td>
<td>1.631 (1.145, 2.323)</td>
<td>0.007</td>
<td>1.000 (0.734, 1.363)</td>
<td>1.000</td>
</tr>
<tr>
<td>HDL-C</td>
<td>0.872 (0.619, 1.229)</td>
<td>0.435</td>
<td>0.989 (0.569, 1.717)</td>
<td>0.967</td>
<td>0.553 (0.353, 0.869)</td>
<td>0.010</td>
</tr>
<tr>
<td>LDL-C</td>
<td>1.233 (0.902, 1.658)</td>
<td>0.195</td>
<td>1.130 (0.833, 1.535)</td>
<td>0.432</td>
<td>1.098 (0.836, 1.444)</td>
<td>0.501</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>1.213 (0.954, 1.542)</td>
<td>0.115</td>
<td>1.117 (0.748, 1.666)</td>
<td>0.589</td>
<td>1.025 (0.735, 1.429)</td>
<td>0.884</td>
</tr>
<tr>
<td>LDL-C/HDL-C ratio</td>
<td>1.366 (0.997, 1.873)</td>
<td>0.052</td>
<td>1.131 (0.774, 1.652)</td>
<td>0.525</td>
<td>1.288 (1.042, 1.592)</td>
<td>0.019</td>
</tr>
<tr>
<td>Total-C/HDL-C ratio</td>
<td>1.418 (1.103, 1.823)</td>
<td>0.006</td>
<td>1.428 (0.912, 2.236)</td>
<td>0.119</td>
<td>1.551 (1.150, 2.093)</td>
<td>0.004</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>1.502 (1.121, 2.013)</td>
<td>0.006</td>
<td>1.612 (1.136, 2.288)</td>
<td>0.007</td>
<td>1.223 (0.914, 1.637)</td>
<td>0.176</td>
</tr>
</tbody>
</table>

Hazard ratios are calculated based upon 1 SD increases in lipid parameters (1 SD = 0.70, 0.36, 0.85, 0.77 and 0.71 mmol/l for TC, HDL, LDL, triglycerides and non-HDL cholesterol, respectively).

aHRs for previous and current smoking are calculated against patients who have never smoked.
show that increased total cholesterol and LDL-C were associated with a 30% decrease in the hazards of arterial graft failure. Several hypotheses can be proposed to explain this apparent paradox. One theory is that more aggressive lipid therapy (with its plethora of anti-inflammatory, antioxidative and plaque stabilizing properties) in patients with higher cholesterol levels may prove protective via pleiotropic pathways, even if increased dosing fails to effectively lower lipids, thus translating into an apparent protective influence for LDL-C. The primary limitation in the interpretation of these results is the incomplete data regarding type and dosing of lipid-lowering therapy such that this could not be reliably incorporated into the analysis.

An alternative explanation is that increasing lipid exposure promotes progression of proximal native vessel disease, which then reduces competition between native flow and graft flow. Competitive flow has been shown to decrease the patency of ITAs and RAs [21, 22], and a reduction of competitive flow may therefore enhance the patency of arterial grafts. This assumes that arterial conduits are more resistant to atherosclerosis than native coronary arteries (or the SV), and this has been previously described for the ITA [23]. It is also possible that this may be a spurious result related to random effect or measurement error, although the results for SV grafts in this cohort are acceptable.

### Clinical outcomes

Lipid therapy trials of revascularized patients have shown clinical benefits, including decreased rates of repeat revascularization, AMI, cardiac death and cerebrovascular events [3, 24, 25]. In our series, elevated cholesterol worsened clinical outcomes of death, non-fatal MI and repeat revascularization, consistent with these reports. That these outcomes do not match up with the favourable arterial graft patency in high lipid exposure likely reflects the opposing effects of lipids on arteries and veins in a population with mixed grafting. This is confirmed by the subset of patients with total arterial revascularization (Table 4) in whom elevated LDL-C appears to be protective against repeat revascularization, mirroring our patency findings.

Failure of any graft, and in particular an arterial graft, is significantly predictive of the need for revascularization, but is not associated with death or MI occurrence (Table 5). The pathogenesis of death or MI occurrence is multifactorial and involves more than isolated graft occlusion. The location of a failed graft is an important determinant of outcomes, as is progression of native vessel disease, both directly through limiting blood flow and indirectly via influencing graft patency. The lack of a clear correlation between graft performance and MI or mortality may indicate that native vessel or other systemic pathways for lipid action may have relatively greater impact on clinical events than graft failure alone.

### Limitations

Although lipid parameters were derived from reliable laboratory sources and analysed in a time-averaged manner, we were unable to obtain similar time-averaged estimates for other risk factors such as cigarette exposure, blood pressure and HbA1c during almost a decade of follow-up. In addition, we could not consistently obtain type, duration and dosing of lipid therapy and other potentially relevant treatments. The lack of pharmaceutical data does not alter the findings regarding lipid exposure and graft

| Table 5: Subset of patients with total arterial revascularization |
|-----------------|-----------|-------------|----------------|||-----------|-----------|-------------|
| N = 101         | Hazard ratio (death) | P-value | Hazard ratio (repeat revascularization) | P-value |
| Total cholesterol | 0.85     | 0.741       | 0.66 (0.36, 1.21) | 0.180 |
| HDL-C           | 1.02     | 0.973       | 0.53 (0.25, 1.13) | 0.100 |
| LDL-C           | 0.866    | 0.745       | 0.54 (0.29, 0.99) | 0.049 |
| Triglycerides   | 0.413    | 0.408       | 1.13 (0.71, 1.78) | 0.614 |

All hazard ratios are calculated using Cox proportional hazards regression after adjustment for age (in decades), sex, diabetes, hypertension, smoking and surgical status.

| Table 6: Influence of graft performance on clinical outcomes |
|-----------------|-------------|-------------|----------------|||-----------|-------------|
| Hazard ratio: (P-value) | Hazard ratio (P-value) | Hazard ratio (P-value): repeat revascularization |
| Any graft failure | 0.785 (0.420) | 0.279 (0.097) | 1.919 (0.012) |
| Arterial graft failure | 1.076 (0.859) | 0.397 (0.376) | 2.035 (0.019) |
| Vein graft failure | 0.698 (0.329) | 0.583 (0.502) | 1.757 (0.086) |

All hazard ratios are calculated using Cox proportional hazards regression after adjustment for age (in decades), sex, diabetes, hypertension, smoking and surgical status.
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