CARDIOVASCULAR MEDICINE

Impact on cardiovascular events of increasing high density lipoprotein cholesterol with and without lipid lowering drugs

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Objective: To estimate the impact on cardiovascular events of changes in high density lipoprotein (HDL) adjusted for changes in total cholesterol.

Design: Cohort study based on a record linkage database.

Setting: Community study in Tayside, Scotland, UK.

Patients: 18 815 patients were identified for the study between 1989 and 2001.

Main outcome measures: Cardiovascular events.

Results: 5510 patients taking lipid lowering treatment who had not been hospitalised previously for cardiovascular disease had 314 cardiovascular events recorded (9407 person years of follow up). Patients whose HDL rose by > 20% were less likely to have an event (23.5/1000 person years, 95% confidence interval (CI) 17.3 to 29.6) compared with patients whose HDL did not rise (42.6/1000 person years, 95% CI 35.5 to 49.7, adjusted relative risk 0.60, 95% CI 0.44 to 0.83). HDL change and cardiovascular outcome were not significantly associated among patients who had been hospitalised previously for cardiovascular disease or among patients who were not taking lipid lowering drugs.

Conclusion: In this study a rise in HDL independently predicted reduced cardiovascular risk in patients taking lipid lowering treatment who had not been hospitalised previously for cardiovascular disease.

An inverse relation between the plasma concentration of high density lipoprotein (HDL) cholesterol and coronary heart disease (CHD) has long been recognised.¹ The findings in the Framingham cohort have been confirmed in subsequent epidemiological studies, in analyses of statin trial datasets, and in specific patient groups.²⁻⁷ The importance of HDL cholesterol in the prevention and treatment of CHD has been recognised formally.⁸ A major impetus for the recent guidelines came from the publication in 1999 of the report of the VA-HIT (Veterans Affairs high density lipoprotein cholesterol intervention trial) study group.⁹ This showed that treatment with the fibrate drug gemfibrozil, aimed primarily at raising HDL cholesterol (and lowering triglycerides), significantly reduced the incidence of death from CHD and non-fatal myocardial infarction among men with CHD. Since then, newer drugs have been developed that substantially raise HDL cholesterol.¹⁰ However, it remains unclear whether a rise in HDL cholesterol predicts a fall in cardiovascular events independently of total cholesterol. In the present study we aimed at establishing whether this is the case and, if so, whether it is influenced by lipid lowering treatment or by previous cardiovascular disease.

METHODS

The studies were carried out in Tayside, Scotland (population about 400 000) by using the Medicines Monitoring Unit record linkage database. The data collection methods for this database have previously been described.¹¹ Briefly, this database contains several datasets including all dispensed community prescriptions, hospital discharge data, biochemistry data, and other data that are linked by a unique patient identifier, the community health index number. These data are made anonymous for the purposes of research as approved by the government appointed guardians of patient confidentiality. The project was also approved by the Tayside committee on research medical ethics.

Study population

The study population consisted of residents of Tayside who were registered with a general practitioner in January 1989 and remained resident in Tayside until December 2001 or died during the study period.

Subjects

Study subjects were those who had at least two serum measurements of total and HDL cholesterol with a time interval between the two measurements of > 30 days. They entered the study on the date of second measurement. Subjects were categorised into four groups according to whether they were taking lipid lowering treatment and whether they had been hospitalised previously for cardiovascular disease. Patients were enrolled in the lipid lowering treated cohort if: (1) they were taking lipid lowering treatment within one month before the second measurement; (2) they were not taking lipid lowering treatment before the first measurement; and (3) they had at least 30 days of follow up time. Patients were stratified into primary and secondary prevention cohorts according to whether they had been hospitalised for cardiovascular disease at least once in the five years preceding entry to the study.

HDL measurements

Serum measurements of total cholesterol and HDL between 1989 and 2001 were recorded in the biochemistry database. All measurements throughout the study period were subject to rigorous internal and external quality control procedures. Measurements were excluded from the analysis if patients had been hospitalised for cardiovascular disease within the

Abbreviations: CHD, coronary heart disease; HDL, high density lipoprotein; ICD, *International classification of diseases*; SMR01, Scottish Morbidity Record; VA-HIT, Veterans Affairs high density lipoprotein cholesterol intervention trial

previous two months or if any of the following results had been obtained within the previous month: (1) serum thyroid stimulating hormone > 10 mU/l; (2) plasma glucose > 10 mmol/l; or (3) 24 hour urine protein > 300 mg/l.

HDL change

HDL change was calculated as $(\text{HDL2} - \text{HDL1})/\text{HDL1}$, where HDL1 and HDL2 were the first and second HDL measurements, respectively. Patients were categorised into four groups: group 1, HDL did not change or fell; group 2, HDL rose by < 7%; group 3, HDL rose by between 7–20%; and group 4, HDL rose by > 20%.

Drug utilisation

For each dispensed lipid lowering prescription and other drugs, we knew the date prescribed, strength, amount, and instructions on how medication should be taken. Thus, the daily dose and the number of days of treatment dispensed (duration) were calculated.

Outcome variables

The outcome of the study was a cardiovascular event. This was defined as the composite end point of hospitalisation with a primary diagnosis of myocardial infarction, angina, angioplasty or coronary revascularisation, stroke, transient ischaemic attack, congestive cardiac failure, and cardiovascular death during the follow up period. These diagnoses were ascertained from the hospital discharge diagnosis data in the Scottish Morbidity Record (SMR01) coded by primary *International classification of diseases* (ICD), ninth revision (ICD-9) or ICD-10

codes and, in the case of angioplasty and coronary revascularisation, by the code of classification of surgical operations and procedures. We also obtained the certified cause of death data from the General Register Office for Scotland.

Statistical analysis

A prespecified test for heterogeneity was used to assess consistency of treatment effect in both primary and secondary prevention cohorts. This was done because we expected primary and secondary prevention cohorts to behave differently. Cardiovascular event rates were compared between the categories of HDL change defined above. Adjustments for potential confounders were calculated by the Poisson regression model. The covariates were age at entry to the study, sex, social deprivation category, concentrations of total and HDL cholesterol, changes in total cholesterol, and use of angiotensin converting enzyme inhibitors, anticoagulants, antiplatelet agents, α blockers, β blockers, calcium channel blockers, cardiac glycosides, diuretics, nitrates, and hypoglycaemic drugs during the follow up period. To avoid confounding by adherence with lipid lowering drug treatment, an adherence index was calculated as the number of days dispensed lipid lowering drugs were supplied divided by the total number of days from the first prescription for a lipid lowering drug to the end of the study. This index was then adjusted for in the multivariate analysis in the treated cohort. All analyses were carried out with SAS version 8.2 (SAS Institute, Cary, North Carolina, USA). All p values were two sided.

Figure 1 Procedure for identification of patients in the lipid lowering treated and untreated cohorts. HDL, high density lipoprotein; TC, total cholesterol.

RESULTS

Figure 1 shows the course of the patients in the study. There were 7079 patients in the treated cohort (5510 primary prevention and 1569 secondary prevention) and 11 736 patients in the untreated cohort (10 897 primary prevention and 839 secondary prevention). Table 1 shows that in all patients HDL change had no independent effect when adjusted for total cholesterol in any patient. The heterogeneity test showed that lipid lowering treatment effects varied significantly between the primary and secondary prevention patients ($\chi^2 = 51$, $p < 0.001$).

Treated cohort

Primary prevention group

Of 5510 patients, 5251 (95.3%) were taking lipid lowering treatment during the follow up period. The overall distribution of lipid lowering drug use was similar across the HDL groups. However, statin and fibrate use differed significantly between group 4 and the other groups. Patients in group 4 used statins less and fibrates more than did patients in the other groups (87.7% v 94.6%, 10.7% v 4.3%, respectively). Table 2 shows the characteristics of patients within the categories of HDL changes defined above (groups 1 to 4). Use of β blockers, calcium channel blockers, and diabetic drugs differed significantly between these four groups.

In 9407 person years of follow up, 314 cardiovascular events were recorded. The rate of events was 42.6/1000 person years (95% confidence interval 35.5 to 49.7) in group 1 and 31.0, 32.5, and 23.5 in groups 2, 3, and 4, respectively.

Compared with group 1, in the other groups the risk of cardiovascular events was reduced (significantly for group 4) (table 1).

Secondary prevention

Of 1569 patients, 1499 (95.5%) were taking lipid lowering treatment during the follow up period. Table 3 shows characteristics of patients in groups 1 to 4. Use of β blockers and diabetic drugs differed significantly between the four groups.

There were 87 cardiovascular events in 2790 person years of follow up. The rate of events was 30.5/1000 person years (95% confidence interval 19.4 to 41.6) in group 1 compared with 30.7, 22.8, and 39.8 in groups 2, 3, and 4, respectively. The risk of cardiovascular events was similar in each group (table 1).

Untreated cohort

In the primary prevention cohort (5079, 1997, 2258, and 1563 patients in groups 1 to 4, respectively), sex, deprivation category, and use of β blockers, cardiac glycoside drugs, anticoagulant drugs, and diabetic drugs differed significantly between the HDL groups (data not shown). HDL group 4 contained more men and more deprived patients, and had more diabetic drug use than group 1; cardiovascular drug use was less in group 4 than in group 1. In the secondary prevention cohort (380, 161, 160, and 138 patients in groups 1 to 4, respectively), use of diuretics, cardiac glycoside drugs, anticoagulant drugs, and diabetic drugs differed significantly between the HDL groups. More use of diuretics, cardiac

Table 1 Association between high density lipoprotein (HDL) groups and all cardiovascular events in patients with or without prior cardiovascular events

HDL change by group	No of events	Event rate/1000 PY	Univariate		Multivariate*	
			RR	95% CI	RR	95% CI
Total patients						
+0.1 mmol/l	873	27.6	0.96	0.94 to 1.00	0.98	0.95 to 1.01
Lipid lowering treated patients						
+0.1 mmol/l	401	33.2	0.96	0.92 to 1.01	0.98	0.93 to 1.02
Lipid lowering untreated patients						
+0.1 mmol/l	472	24.2	0.95	0.91 to 1.00	0.98	0.94 to 1.03
Lipid lowering treated patients						
Primary prevention†						
+0.1 mmol/l	314	33.7	0.94	0.89 to 0.99	0.96	0.90 to 1.01
Group 1	134	42.6	1.00		1.00	
Group 2	49	31.0	0.73	0.52 to 1.01	0.75	0.54 to 1.05
Group 3	76	32.5	0.76	0.58 to 1.01	0.80	0.60 to 1.06
Group 4	55	23.5	0.55	0.40 to 0.75	0.60	0.44 to 0.83
Secondary prevention†						
+0.1 mmol/l	87	31.4	1.02	0.95 to 1.08	1.00	0.92 to 1.08
Group 1	28	30.5	1.00		1.00	
Group 2	12	30.7	1.01	0.51 to 1.98	0.90	0.45 to 1.78
Group 3	16	22.8	0.75	0.40 to 1.38	0.64	0.34 to 1.19
Group 4	31	39.8	1.31	0.78 to 2.18	1.07	0.62 to 1.86
Lipid lowering untreated patients						
Primary prevention						
+0.1 mmol/l	389	21.4	0.95	0.91 to 1.00	0.97	0.93 to 1.02
Group 1	176	22.7	1.00		1.00	
Group 2	62	19.0	0.84	0.63 to 1.12	0.89	0.66 to 1.19
Group 3	85	21.2	0.93	0.72 to 1.21	1.02	0.78 to 1.33
Group 4	66	21.0	0.92	0.69 to 1.22	1.04	0.78 to 1.40
Secondary prevention						
+0.1 mmol/l	83	63.3	0.93	0.84 to 1.02	1.04	0.94 to 1.14
Group 1	35	64.5	1.00		1.00	
Group 2	19	83.8	1.30	0.74 to 2.27	1.50	0.84 to 2.67
Group 3	13	45.9	0.71	0.38 to 1.35	0.94	0.48 to 1.83
Group 4	16	62.0	0.96	0.53 to 1.74	1.61	0.85 to 3.03

*Adjusted for changes in total cholesterol, concentrations of total cholesterol and HDL at entry to the study, age, sex, social deprivation, and use of angiotensin converting enzyme (ACE) inhibitors, anticoagulants, antiplatelet, α blocker, β blocker, calcium channel blocker, cardiac glycosides, diuretics, nitrates, and diabetic drugs during the follow up; †also adjusted for adherence to lipid lowering drugs in the multivariate analysis.
CI, confidence interval; PY, person years; RR, relative risk.

Table 2 Characteristics of patients in each HDL change group with no prior cardiovascular events in the lipid lowering treated cohort

	Group 1	Group 2	Group 3	Group 4
Number of patients	2023 (36.7%)	989 (18.0%)	1337 (24.3%)	1161 (21.1%)
Sex				
Women	1054 (52.1%)	513 (51.9%)	663 (49.6%)	599 (52.0%)
Men	969 (47.9%)	476 (48.1%)	674 (50.4%)	562 (48.4%)
Age (years)	63.5 (10.4)	63.8 (10.2)	63.4 (9.9)	62.6 (10.2)
Deprivation category				
1 (least deprived)	172 (8.5%)	76 (7.7%)	103 (7.7%)	72 (6.2%)
2	396 (19.6%)	177 (17.9%)	237 (17.8%)	204 (17.6%)
3	509 (25.2%)	225 (22.8%)	339 (25.4%)	296 (25.5%)
4	369 (18.2%)	181 (18.3%)	253 (19.0%)	209 (18.0%)
5	229 (11.3%)	129 (13.0%)	158 (11.8%)	133 (11.5%)
6 (most deprived)	348 (17.2%)	201 (20.3%)	245 (18.4%)	245 (21.1%)
Use of any cardiovascular drugs during the follow up				
ACE inhibitors	522 (25.8%)	271 (27.4%)	358 (26.8%)	331 (28.5%)
Anticoagulants	92 (4.6%)	45 (4.6%)	54 (4.0%)	53 (4.6%)
Antiplatelets	925 (45.7%)	462 (46.7%)	587 (43.9%)	508 (43.8%)
α Blockers	104 (5.1%)	43 (4.4%)	72 (5.4%)	63 (5.4%)
β Blockers**	720 (35.6%)	331 (33.5%)	410 (30.7%)	322 (27.7%)
CCBs*	674 (33.3%)	328 (33.2%)	500 (37.4%)	424 (36.5%)
Cardiac glycosides	70 (3.5%)	26 (2.6%)	47 (3.5%)	26 (2.2%)
Diuretics	743 (36.7%)	370 (37.4%)	508 (38.0%)	404 (34.8%)
Nitrates	491 (24.3%)	233 (23.6%)	306 (22.9%)	290 (25.0%)
Lipid lowering drugs	1917 (94.8%)	934 (94.4%)	1274 (95.3%)	1114 (96.0%)
Use of diabetic drugs during the follow up**	347 (17.2%)	189 (19.1%)	290 (21.7%)	289 (24.9%)

Data are mean (SD) or number of patients (%).

*Comparison of all four groups, $p < 0.05$; ** $p < 0.001$.

Group 1, HDL did not change or fell; group 2, HDL rose by $< 7\%$; group 3, HDL rose by between 7% and 20% ; group 4, HDL rose by $> 20\%$.

CCB, calcium channel blocker.

glycoside drugs, and diabetic drugs and less use of anticoagulant drugs were seen in group 4 than in group 1. The risk of cardiovascular events was similar in groups 1 to 4, irrespective of previous hospitalisation for cardiovascular disease (table 1). The primary prevention cohort of patients untreated with lipid lowering drug had lower event rates than did patients who received lipid lowering treatment. This

is likely to reflect the guidelines for treatment that targeted treatment towards those at high cardiovascular risk.

DISCUSSION

In this study we have examined the impact on cardiovascular events of changes over time in HDL cholesterol concentration,

Table 3 Characteristics of patients in each HDL group with prior cardiovascular events in the lipid lowering treated cohort

	Group 1	Group 2	Group 3	Group 4
Number of patients	543 (34.6%)	224 (14.3%)	393 (25.1%)	409 (26.1%)
Sex				
Women	232 (42.7%)	89 (39.7%)	151 (38.4%)	168 (41.1%)
Men	311 (57.3%)	135 (60.3%)	242 (61.6%)	241 (58.9%)
Age (years)	64.6 (10.0)	65.7 (8.9)	65.5 (9.6)	64.7 (10.4)
Deprivation category				
1 (least deprived)	43 (8.0%)	14 (6.3%)	26 (6.6%)	36 (8.8%)
2	97 (17.9%)	36 (16.1%)	57 (14.5%)	65 (15.9%)
3	129 (23.8%)	52 (23.2%)	95 (24.2%)	85 (20.8%)
4	93 (17.2%)	50 (22.3%)	76 (19.3%)	70 (17.1%)
5	61 (11.3%)	23 (10.3%)	40 (10.2%)	39 (9.5%)
6 (most deprived)	118 (21.8%)	49 (21.9%)	99 (26.1%)	114 (27.9%)
Use of any cardiovascular drugs during the follow up				
ACE inhibitors	210 (38.7%)	101 (45.1%)	144 (36.6%)	167 (40.8%)
Anticoagulants	49 (9.0%)	26 (11.6%)	39 (9.9%)	33 (8.1%)
Antiplatelets	387 (71.3%)	165 (73.7%)	282 (71.8%)	299 (73.1%)
α Blockers	21 (3.9%)	14 (6.3%)	27 (6.9%)	21 (5.1%)
β Blockers**	271 (49.9%)	99 (44.2%)	155 (39.4%)	148 (36.2%)
CCBs*	201 (37.0%)	87 (38.8%)	163 (41.5%)	159 (38.9%)
Cardiac glycosides	32 (5.9%)	14 (6.3%)	15 (3.8%)	28 (6.9%)
Diuretics	230 (42.4%)	89 (39.7%)	153 (38.9%)	189 (46.2%)
Nitrates	248 (45.7%)	103 (46.0%)	200 (50.9%)	196 (47.9%)
Lipid lowering drugs	515 (94.8%)	215 (96.0%)	370 (94.2%)	399 (97.6%)
Use of diabetic drugs during the follow up**	97 (17.9%)	43 (19.2%)	81 (20.6%)	104 (25.4%)

Data are mean (SD) or number of patients (%).

*Comparison of all four groups, $p < 0.05$; ** $p < 0.001$.

Group 1, HDL did not change or fell; group 2, HDL rose by $< 7\%$; group 3, HDL rose by between 7% and 20% ; group 4, HDL rose by $> 20\%$.

adjusted for total cholesterol. We found that in patients taking lipid lowering treatment who had not previously been hospitalised for cardiovascular disease a rise in HDL predicted reduced cardiovascular risk independently of total cholesterol. However, we did not find this relation between HDL change and cardiovascular outcome in patients who had been hospitalised previously for cardiovascular disease, or in patients who were not taking lipid lowering drug treatment. A recent systematic review of statin trials reported a weak link between HDL increases and risk of CHD mortality.¹² Those authors concluded that the narrow range of HDL increases seen may have reduced the ability to detect a beneficial HDL effect, if present. Our study results are consistent with this (we found that only substantial increases in HDL (> 20%) were associated with a reduced risk of cardiovascular outcome).

The finding that a rise in HDL cholesterol over time independently predicted reduced cardiovascular risk in patients taking lipid lowering treatment who have not previously been hospitalised for cardiovascular disease is not surprising. This observation extends the findings of prospective studies that have shown that HDL predicts CHD independently of both low density lipoprotein cholesterol and triglycerides.²⁻³ It is also consistent with the findings of the VA-HIT study, which reported that CHD events were reduced by 11% with gemfibrozil for every 0.13 mmol/l increase in HDL.⁹ But why should the impact of HDL change on cardiovascular risk be confined to patients given lipid lowering treatment who had not previously been hospitalised for cardiovascular disease? There are two separate questions, which we will address in turn.

Firstly, why did we not observe a similar effect in the secondary prevention cohort (patients who had been hospitalised previously for cardiovascular disease)? Cardiovascular drug use was significantly greater in this cohort, and this may have masked a relation between HDL change and cardiovascular risk we might otherwise have observed. Another consideration is that the relation between HDL concentration and CHD is curvilinear.² The relation observed between HDL change and coronary risk depends on where on the curve the patients starts; this in turn depends on the baseline HDL and the global coronary risk. This may help to explain the apparent discrepancy between the findings in our secondary prevention cohort (no impact of HDL change on cardiovascular events) and those of the VA-HIT trial (inverse relation between HDL change and CHD events). The mean baseline HDL concentration in VA-HIT was 0.83 mmol/l compared with 1.28 mmol/l in our study. However, comparisons between the present study and VA-HIT should be made with caution; apart from lipid parameters, demography, study design, and outcome measures also differed.

Secondly, why did we not observe a similar effect in patients who were not given lipid lowering drug treatment? The curvilinear nature of the relation between HDL concentration and CHD may once again provide part of the explanation. Although the mean baseline HDL cholesterol concentration in each group was similar (1.34 mmol/l *v* 1.35 mmol/l), the global coronary risk is unlikely to have been the same. In addition, it is widely recognised that lipid lowering drugs do more than just alter lipid concentrations, and that the additional effects both of statins and of fibrates contribute significantly to their clinical benefit.¹³⁻¹⁴ Thus, the HDL changes seen in patients taking lipid lowering treatment may simply have acted as a marker for additional clinical benefit.

We did not adjust for smoking, obesity, or exercise, all of which may have influenced CHD outcomes. However, we did use the Carstairs socioeconomic deprivation score as a surrogate, which adjusts for at least some of these factors.¹⁵⁻¹⁶

Our previous sensitivity analyses of unmeasured risk factors indicate that such unmeasured risk factors are unlikely to have a large impact on cardiovascular outcomes.¹⁷ Similarly, while we had triglyceride data when it was measured, not everyone had it measured and we could not determine whether it was done fasting. However, we did carry out a post hoc analysis that assumed that all triglycerides were measured fasting and calculated low density lipoprotein cholesterol. When we used this in the analysis the results were very similar to those obtained with total cholesterol.

We have taken account of adherence to lipid lowering drugs in our final analysis, as patients in group 4 had better adherence than patients in group 1 (44.0% good adherence *v* 47.3%), and we have previously shown that good adherence to statin treatment is associated with a lower risk of cardiovascular or mortality outcomes.¹⁸ These differences in adherence did not explain the differences in cardiovascular outcomes between group 1 and group 4.

Overall, statins accounted for 93% of prescriptions for lipid lowering drugs in our study. However, patients in group 4 (in whom HDL increased most) used fibrates more and statins less than did patients in group 1 (in whom HDL either did not change or fell). In addition, group 1 patients used more β blockers, which are known to lower HDL.¹⁹ We also did not consider drug dose in this study. The large increases in HDL seen in group 4 may have been related to drug dose, and recent studies have shown that aggressive lipid lowering treatment reduces cardiovascular outcomes more than less intense treatment does.²⁰⁻²¹

Although we have used multivariate analyses, observational studies cannot exclude residual confounding. However, balancing this, a major strength of our study is the population based cohort design, with complete follow up over the study period. This approach allows a real world population to be studied representing all socioeconomic groups and within a universal health care coverage scheme.²²

In conclusion, this is the first study to show that a rise in HDL cholesterol over time predicts reduced cardiovascular risk independently of total cholesterol. This relation was confined to patients taking lipid lowering treatment who had not previously been hospitalised for cardiovascular disease. Greater use of cardiovascular drugs by way of secondary prevention may have masked this relation in patients who had been hospitalised previously for cardiovascular disease, and the HDL changes may have acted as a marker for the additional pleiotropic effects of lipid lowering drugs.

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Conflicts of interest: TMM has received honoraria for lectures and advisory boards from Pfizer, Novartis, and Sankyo. MJM has received honoraria for lectures and advisory boards from AstraZeneca, Bristol Myers Squibb, Fournier, Novartis, and Pfizer.

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IMAGES IN CARDIOLOGY

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Angiographic appearance of “tumour blush” produced by a large right atrial myxoma

A 76 year old woman presented to the hospital with shortness of breath. The initial evaluation included a computed tomographic scan to exclude pulmonary embolism. However, this instead demonstrated a large right atrial mass which was confirmed on echocardiography. The patient was referred for coronary angiography before the resection of this mass. Right atrial angiogram showed a large mobile filling defect measuring 6 cm in diameter in the right atrium going into the right ventricle with each diastole. Coronary angiography showed no significant coronary artery disease. The right coronary artery injection showed an atrial branch of the right coronary artery supplying this tumour producing a “tumour blush” (panel). The patient underwent surgical excision of the mass with patch reconstruction of the atrial septum. The final pathological diagnosis was atrial myxoma.

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Right coronary artery injection showing the mass being supplied by an atrial branch of the right coronary artery producing a “tumour blush” (arrows).