

SYSTEMATIC REVIEW

Editor's Choice – Effect of Statins on Total Mortality in Abdominal Aortic Aneurysm Repair: A Systematic Review and Meta-analysisØyvind Risum ^{a,*}, Irene Sandven ^b, Jon O. Sundhagen ^a, Michael Abdelnoor ^c^a Department of Vascular Surgery, Oslo University Hospital, Aker, Oslo, Norway^b Oslo Centre of Biostatistics and Epidemiology, Oslo University Hospital, Sogn Arena, Oslo, Norway^c Epidemiology and Biological Statistics Unit, Independent Multidisciplinary Health Research Unit, Oslo, Norway**WHAT THIS PAPER ADDS**

The beneficial effect of statins on long term survival after operative treatment, both open surgery and endovascular aneurysm repair (EVAR) has been confirmed. Statin therapy after abdominal aneurysm repair should be included in the guidelines.

Objective: The aim was to summarise the evidence from published epidemiological studies investigating the efficacy of statin therapy on long term survival in patients after abdominal aortic aneurysm (AAA) repair.

Data sources: This study was a systematic review with critical appraisal and meta-analysis of observational studies.

Review methods: A systematic literature search was carried out throughout February 2020, revealing 14 eligible cohort studies of which 11 were judged to be of high quality. A random effects model was used to synthesise results, and heterogeneity between studies examined by subgroup and meta-regression analyses considering patient and study related variables. Small study effect was evaluated.

Results: The pooled estimate showed that statin treatment among 69 790 AAA patients with a median follow up of 3.1 years was associated with a 35% relative reduction in total mortality (rate ratio 0.65, 95% confidence interval 0.57–0.73) with moderate heterogeneity ($I^2 = 68%$) and no small study effect.

Conclusion: Evidence from this systematic review indicates a beneficial effect of statins on long term survival in patients treated by AAA repair.

Keywords: Abdominal aortic aneurysm, Endovascular aneurysm repair, Long term survival, Open surgical repair, Statin therapy

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INTRODUCTION

The prophylactic treatment with statins in cardiac and non-cardiac atherosclerotic disease is associated with improved survival and is well documented.¹ However, the same result in patients with abdominal aortic aneurysm (AAA) had not been clear previously. Later results, however, have shown that prophylactic treatment with statins should be included because of the effect on reduction in growth progression, rupture, and lower rates of peri-operative mortality.² Statins have also been shown to be independent predictors of decreased long term mortality after AAA.^{3–7}

The aim of the study was to search the literature to study the long term effects of statins after open surgical repair (OSR) and endovascular aneurysm repair (EVAR) in general and to search for possible trends in the choice of treatment. A systematic review and meta-analysis was conducted to clarify this issue.

METHODS

The review protocol has been registered at <https://www.crd.york.ac.uk/PROSPERO/>, ID: CRD42018107454. The Preferred reporting items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines for meta-analyses and systematic reviews of observational studies were followed in reporting the present study.⁸

Eligibility criteria

All types of epidemiological study designs comparing statin use with non-use in patients after AAA repair were

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considered. Eligible studies had to include data in extractable form for patients with OSR or EVAR or both, and long term survival as an endpoint.

Search strategy and selection process

A qualified medical librarian was consulted in the medical library at Oslo University Hospital. MEDLINE, EMBASE, and the Cochran Library were searched up to 1 March 2020 with no language restrictions. The Clinicaltrials.gov website was also searched. The following free text search terms were used: (“Aortic Aneurysm, Abdominal” [Mesh] OR (abdominal [Title] AND aortic [Title] AND aneurysm*[Title]) AND (“Hydroxymethylglutaryl-CoA Reductase Inhibitors”[Mesh] OR HMG-CoA [title] OR “Hydroxymethylglutaryl-CoA Reductase”[title] OR statin [title] OR statins [title])). All four authors (Ø.R., M.A., I.S., J.O.S.) were involved in the search and study selection of references of eligible studies. Reference lists were scrutinised in order to pick up articles of interest not included in the original search.

Data extraction

Data regarding publication status, study design, patient related characteristics, and results were extracted on a standardised form according to an *a priori* protocol. Patient related variables considered included mean age of the cohort, frequency of female gender, and frequency of EVAR or OSR. Study level variables considered included type of study design and timing of the study (prospective vs. retrospective). The endpoint considered was total mortality (hazard ratio or long term mortality). Three authors were involved in data extraction (Ø.R., M.A., I.S.). Disagreement was resolved by discussion and subsequent consensus.

Assessment of study quality

Only cohort studies were identified, and for the purpose of critically appraising these studies the Newcastle–Ottawa Scale (NOS) was used⁹ as a checklist, including core domains assessing (1) methods for selecting study participant; (2) appropriate control for confounding (comparability); and (3) methods assessing the outcome. The NOS consists of eight multiple choice questions, and high quality responses earned a star totalling up to nine stars whereof the comparability question earns up to two stars. Three review authors independently assessed the methodological quality of each study (Ø.R., I.S., M.A.), and disagreement was resolved by discussion and subsequent consensus.

Statistical analysis

Results from individual studies were combined considering both fixed and random effects model analyses. The DerSimonian Laird estimate¹⁰ was used in the random effects model. Mortality risk was quantified by the risk ratio (RR) with 95% confidence interval (CI). The information required from each study is an appropriate measure of RR and its variance, which can be calculated if the lower and upper confidence limits are given.¹¹

Sources of heterogeneity, evaluation, and quantification

Statistical heterogeneity among studies was assessed with Cochran’s Q test. The magnitude of heterogeneity was evaluated by the I^2 statistic, which describes the proportion of total variation due to heterogeneity rather than chance (I^2 values of 25%, 50%, and 75% indicate low, moderate, and high heterogeneity, respectively).¹² In order to investigate potential sources of heterogeneity, the data were stratified according to the study level variable prospective vs. retrospective timing of the study. The subgroup analysis was extended by a random effects meta-regression analysis that allowed the effect of the continuous variables to be investigated (such as in years: mean age, mean follow up time; and in percent: female gender, OSR, and EVAR) as well as the dichotomous variable used in the subgroup analysis. Meta-regression was performed to explore the influence of each covariable on the effect of statins on mortality. If the covariable decreased the between study variance, the source of heterogeneity was considered important. The estimate of τ^2 in the presence of a covariable when compared with that when the covariable is omitted allows the proportion of the heterogeneity variance explained by the covariable to be calculated.¹³ For power consideration a minimum of 10 studies per covariable in a single model of meta-regression was required.¹⁴

Evaluation of small study effect

Potential small study effect was assessed visually by the funnel plot and complemented by two established tests of bias: Begg and Mazumdar Rank correlation¹⁵ and Egger’s test of asymmetry.¹⁶

Adjusting for small study effect

To detect and control for small study effect, the “trim and fill” method was used.¹⁷ But since the method is known to perform poorly in the presence of substantial between study heterogeneity¹⁸ a regression based approach was also considered: the method of limit meta-analysis,¹⁹ which is robust against heterogeneity.²⁰

Additional analysis

An additional sensitivity analysis was undertaken to investigate the influence of each study by omitting each in turn from the meta-analysis and assessing the degree to which the size and significance of the statin therapy effect changes.²¹

Software for meta-analysis

All statistical analyses were performed with R Package Meta and Stata version 15.^{22,23}

RESULTS

After identifying 528 references, 511 were excluded due to irrelevant content and duplicate publications, leaving 17 potentially eligible studies. Three were not appropriate for inclusion because one reported early mortality only, one did

not include operation of the patients, and in the third the risk ratio (RR) could not be extracted. Finally, 14 studies^{3–6,24–33} were included in this systematic review (Fig. 1).

Study characteristics

The study characteristics are presented in Table 1. The entire cohort comprised 69 790 patients after AAA, of whom on average 48% were on statin therapy (median 48.1, range 12.4–76.4). The median age was 73 years (range 68.5–76), 15% were women (range 6.0–21.3), 30% had OSR (range 0–100), and 70% EVAR (range 0–100). Median follow up was 3.1 years (range 1–6.95). Nine studies were on European populations, and four on US populations.

All studies were cohort designs, with retrospective timing in eight. The majority of studies were judged to be high quality. As shown in Table 2, the selection procedure and control for confounding were adequate in 13 studies, and outcome assessment with long enough follow up in all 14 studies. In 13 studies there was no drop out. In summary, 11 studies achieved 8/9 stars, two 7/9 stars, and one 6/9 stars according to the NOS.

Quantitative data synthesis

The pooled estimate (Fig. 2) indicates a 35% relative risk (RR) mortality reduction in AAA patients on statin therapy compared with non-users (RR 0.65, 95% CI 0.57–0.73) with moderate between study heterogeneity ($I^2 = 68\%$). The funnel plot visually demonstrates non-presence of the small study effect (Fig. 3) confirmed by Egger's test ($p = .71$) and

Begg's test ($p = .25$). Results from limit meta-analysis indicate no missing studies and unchanged pooled effect.

Investigating sources of heterogeneity by subgroup analysis, the stratified pooled meta-analysis showed a stronger beneficial effect of statins on total mortality in prospective studies (RR 0.58, 95% CI 0.50–0.67, $I^2 = 0\%$) than in retrospective studies (RR 0.69, 95% CI 0.58–0.80, $I^2 = 81\%$) with a borderline statistically significant subgroup difference ($p = .12$). Extending the analysis with meta-regression this study related characteristic was not associated with the efficacy of statins ($p = .14$) and did not account for any heterogeneity. Similar results were shown for the patient related covariates considered.

The robustness of the primary result obtained from the 14 studies was supported by an influential analysis; when omitting one study at a time from the meta-analysis a stable pooled estimate was shown.

DISCUSSION

Results from this meta-analysis of cohort studies comparing statin therapy with no statins in patients after AAA repair showed a beneficial effect of statins on lowering total mortality.

Many patients have not been optimally treated with statins,^{2,5} a fact reflected in the results of the early trials. On average 48% of the patients included had received treatment with statins, but a stronger beneficial effect on total mortality was observed in prospective studies than in retrospective studies, suggesting that the patients included in the former were subject to closer medical follow up. The

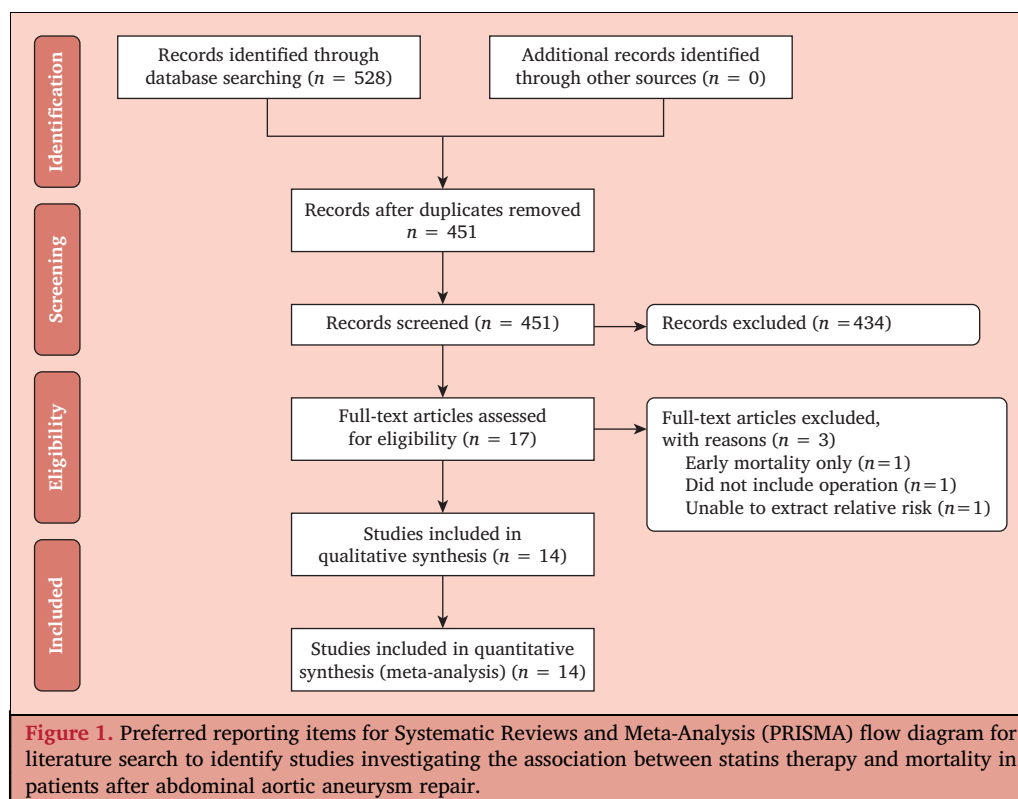


Table 1. Characteristics of the 14 cohort studies included in the meta-analysis of studies investigating the association between statin therapy and mortality after abdominal aortic aneurysm repair

First author	Year	Total – n	Statin – %	Design	Mean age – y	Female – %	OSR – %	EVAR – %	Mean follow up – y
Kertai ⁴	2004	510	30.2	RC	69.0	15.0	100	0	4.70
Leurs ⁵	2006	5 892	12.4	PC	72.3	6.0	0	100	1.40
Diehm ³	2008	731	43.6	PC	76.0	9.3	0	100	4.20
Schouten ²⁵	2008	124	63.0	PC	74.0	8.0	56	44	3.30
Winkel ²⁶	2009	220	58.0	PC	72.9	12.0	0	100	2.90
Ohrlander ²⁷	2011	304	35.0	RC	74.0	14.0	0	100	5.60
Parmar ²⁸	2013	2 063	35.0	PC	68.5	19.8	46	54	2.60
Lee ²⁹	2013	774	45.9	RC	73.6	16.0	35	65	6.95
De Bruin ²⁴	2014	351	38.5	RC	70.0	8.2	51	49	6.4
Grant ³⁰	2014	506	76.0	PC	73.4	17.4	35.4	64.6	2.16
Galiñanes ³¹	2014	19 323	50.3	RC	74.3	–	25	75	1.00
Mathisen ⁶	2017	640	58.0	RC	73.0	21.3	100	0	3.93
O'Donnell ³²	2018	37 950	69.0	RC	72.7	19.0	23	77	2.90
Young ³³	2019	402	76.4	RC	73.1	19.7	23	77	2.5

PC = prospective cohort study; RC = retrospective cohort study; OSR = open surgery repair; EVAR = endovascular repair.

studies consider treatment of statins in general, but do not specify which type of 3-hydroxy-3-methylglutaryl coenzyme-A reductase inhibitor has been used or the treatment dose. The exact effect of statins on mortality in AAA is not known, but several biological mechanisms of the prophylactic protective effect are known to be important.

The pathogenesis of AAA is closely related to chronic inflammatory atherosclerotic artery disease and to the same risk factors.³⁴ Severe coronary disease is present in 36% of patients with AAA and only 6% have normal coronary arteries.^{4,35} Protective treatment with statins is not only related to the decrease in low density lipoprotein levels, but also to its pleiotropic effects on endothelial function, smooth muscle cells, inflammatory response,

thrombus formation, and plaque stability.^{36,37} Metalloproteinases (MMPs) and their inhibitors, tissue inhibitors of metalloproteinases (TIMPs), are implicated in both aneurysmal and atherosclerotic disease.³⁸ MMPs are responsible for reducing the extracellular matrix in the AAA wall.³⁹ Statins have been shown to decrease the levels of MMP-9 and MMP-3. Reduction in MMP-9 is considered to be important since it is strongly implicated in all stages of AAA pathogenesis from inception to rupture. Furthermore, a total reduction in MMP-3 is observed.³⁹ The presence of a combination of macrophages and B lymphocytes indicate an extensive inflammatory response. To a certain extent, the reduction in MMP may be derived from the anti-inflammatory properties of statins.⁴⁰

Table 2. Review authors' assessment of study quality of studies investigating the association between statin therapy and mortality after abdominal aortic aneurysm repair according to the Newcastle–Ottawa Scale (NOS) for cohort studies*

First author	Selection				Comparability		Outcome	
	Representativeness of the exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Demonstration that outcome was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow up long enough for outcome to occur	Adequacy of follow up of cohorts
Kertai ⁴	*	*	*	*	*	*	*	*
Leurs ⁵	*	*	*	*	*	*	*	*
Diehm ³	*	*	*	*	*	*	*	*
Schouten ²⁵	*	*	*	*	*	*	*	*
Winkel ²⁶	*	*	*	*	*	*	*	*
Ohrlander ²⁷	*	*	*	*	*	*	*	*
Parmar ²⁸	*	*	*	*	*	*	*	*
Lee ²⁹	*	*	*	*	*	*	*	*
De Bruin ²⁴	*	*	*	*	**	*	*	*
Grant ³⁰	*	*	*	*	*	*	*	*
Galiñanes ³¹	*	*	*	*	*	*	*	*
Mathisen ⁶	*	*	*	*	*	*	*	*
O'Donnell ³²	*	*	*	*	*	*	*	*
Young ³³	*	*	*	*	*	*	*	*

* A study can be awarded a maximum of one star for each numbered item within the selection and outcome categories. A maximum of two stars can be given for comparability.

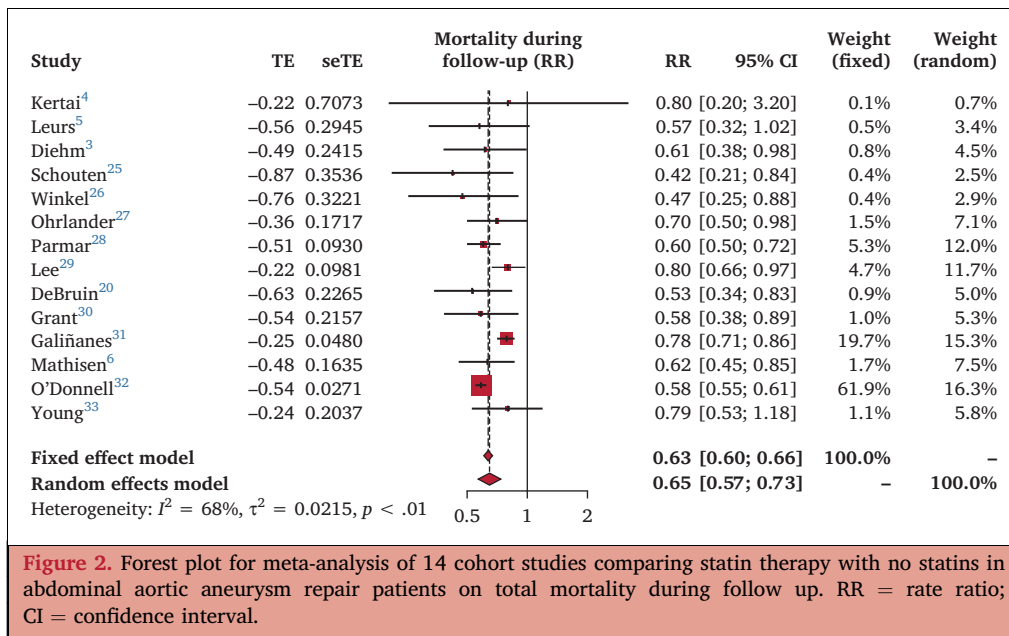


Figure 2. Forest plot for meta-analysis of 14 cohort studies comparing statin therapy with no statins in abdominal aortic aneurysm repair patients on total mortality during follow up. RR = rate ratio; CI = confidence interval.

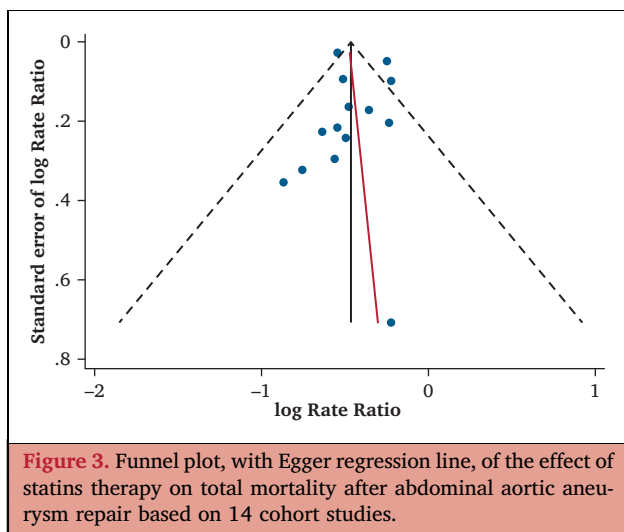


Figure 3. Funnel plot, with Egger regression line, of the effect of statins therapy on total mortality after abdominal aortic aneurysm repair based on 14 cohort studies.

In a clinical setting, a recent meta-analysis has stated that statin therapy may be associated with reduction in AAA progression, rupture, and lower rates of peri-operative mortality following elective AAA repair.² Also, in post-deployment of EVAR, it has been documented that statin therapy can be predictive of AAA sac diameter reduction.⁴¹

Although optimisation with best medical treatment is recommended, evidence of the effect of single drugs has been conflicting⁴² and further research is required.⁴³ However, the results of this study suggest that there is a beneficial effect of statins on long term survival after AAA repair for both methods of repair. The mean follow up time of the cohorts in this study is relatively short; 3.1 years ranging from one to 6.95 years. Whether this equal effect subsides or alters in longer long term survival results, can only be described in further follow up studies.

Strengths and limitations

This meta-analysis was based on cohort studies and the majority were considered to be of high quality. For the hard endpoint mortality there was no misclassification, and no losses of follow up. Of methodological concern was their potential for selection and confounding bias due to the non-random allocation of statin therapy, and the retrospective timing in some. Although confounding was dealt with using multivariable techniques, the possibility of unmeasured confounding cannot be excluded, especially in retrospective studies where the accuracy of important potential confounding factors recorded is variable. This might explain the difference in magnitude of the pooled effect of statins between prospective and retrospective studies with no observed heterogeneity in the subgroup of prospective studies. Heterogeneity was explored by meta-regression considering potential moderators specified *a priori* in the protocol, but because of power concern no more than one variable at a time could be addressed in the model, and none accounted for any observed heterogeneity between the studies.

Conclusion

The beneficial effect of statins on total survival suggests routine prescription to all patients with AAA, together with aggressive treatment of known risk factors. Since less than 50% of the actual patients had been treated with statins previously, a potential benefit on long term survival should be expected if they are treated optimally.

CONFLICT OF INTEREST

None.

FUNDING

None.

AUTHOR CONTRIBUTIONS

All review authors made substantial contributions to concept and design, acquisition of data, or analysis and interpretation of data. All participated in drafting of the article or revising it critically for important intellectual content and gave final approval to the version to be published. All are accountable for all aspects of the work, including ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

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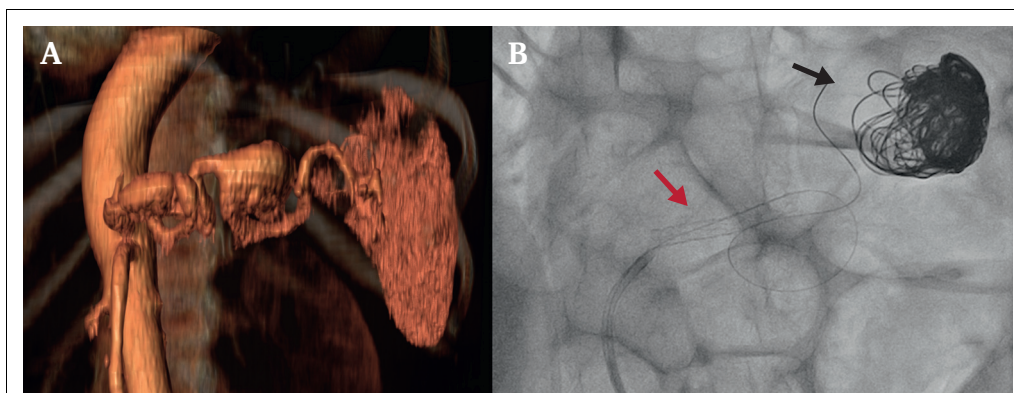
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COUP D'OEIL

Coil Embolisation and Stent Grafting for Splenic Artery Aneurysms

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A 66 year old male was admitted with left upper abdominal pain for one month. As an incidental finding, two aneurysms of the splenic artery measuring 4.8 cm and 1.9 cm were diagnosed using computed tomography angiography (A). The larger of the two aneurysms was embolised with 10 coils (32 mm × 60 cm, Penumbra, Alameda, CA, USA; black arrow) and a 5 × 26 mm stent graft (Lifestream, Bard Inc., Tempe, AZ, USA; red arrow) was successfully deployed across the smaller one (B). The patient made an excellent recovery with no complications at six month follow up.

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