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A retrospective study: Factors associated with the risk of abdominal aortic aneurysm rupture

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ABSTRACT

Introduction: Literature regarding pharmacological manipulation of aneurysm development and progression is abundant; however studies looking at preventing rupture are sparse. Moreover, best medical therapy is ill-instituted, and continued in this high-risk cohort. This paper aims to identify factors which affect the risk of AAA-rupture.

Materials & methods: A retrospective review of patients undergoing non-screen detected AAA-repair at a single tertiary-referral centre was performed. Age, cardiovascular history, medication use and the nature of surgical repair (elective or emergency) were converted to binary characteristics and a binomial logistic regression performed.

Results: We included 315 admissions for ruptured AAA, and 668 referrals for elective repair of large aneurysms ($n = 983$). Multifactorial analysis showed that the cohort which was prescribed statins experienced fewer ruptured AAA ([OR] 0.50, [95% CI] 0.32–0.77). Factors associated with increased risk of rupture include female gender (2.49, 1.63–3.80), history of hypertension (3.5, 1.6–3.8) or renal failure (8.08, 4.15–15.4), age over 80 (2.77, 1.79–4.27) and current smoking (1.80, 1.09–2.96).

Discussion and conclusions: This is the largest study, interrogating individual patient data, to suggest an association between statins and prevention of large AAA-rupture. As patients with AAA are at high risk of cardiovascular events, and statins may decrease the risk of the devastating consequence of the condition, healthcare teams should maintain pharmaco-vigilance in instituting and continuing best medical therapy, including a statin.

1. Introduction

Abdominal aortic aneurysm remains amongst the top 10 most common causes of death in the over 55 age group in the United Kingdom, with rupture accounting for a more than 85% of the 6300 AAA-related deaths in 2011 [1]. The only definitive treatment options continue to be open surgical or endovascular repair as exclusion of the aneurysmal sac from the circulation substantially reduces the risk of subsequent rupture. The holy grails of the stages of aneurysm management are the prevention of formation; and stabilisation of the developed aneurysm. Much work is directed towards the former; however, a paucity of knowledge prevails with respect to the latter.

It has been argued that medical management may have a role in stabilising the disease [2]. There is little in the literature regarding pharmacologically reducing the risk of AAA rupture, the usually lethal consequence of the condition. A number of agents have been investigated with the aim of pharmacologically manipulating the biology of the aortic wall [3], and a recent Cochrane review [4] has distilled the cocktail to beta-blockers, tetracycline antibiotics, and HMG-CoA reductase inhibitors (statins). This study aimed to identify factors, including statin use, which are associated with AAA rupture.

2. Materials and methods

2.1. Database

The study design comprised of a retrospective analysis of a prospectively maintained database of consecutive patients referred with AAA at a single vascular unit between January 2004 and December 2010 ($n = 1092$) in a single centre. The data have been collected as part of the group's submission to the National Vascular Database.

Demographic data including age, comorbidities, and operative outcomes were all prospectively entered into the database with the exception of preoperative renal function which was retrospectively retrieved from an electronic patient database. Baseline characteristics included age, gender, smoking history and obesity status. Comorbidities recorded included ischaemic heart disease (history of angina, any previous MI, prior percutaneous coronary intervention, or coronary artery bypass surgery), hypertension, cerebrovascular disease (previous transient ischemic attack or stroke), chronic obstructive pulmonary disease, chronic renal failure (creatinine levels more than 120 μmol/L) and

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diabetes mellitus. Statin therapy status was also recorded prospectively. Statin status information was obtained retrospectively for patients who were admitted with ruptured AAA and did not undergo repair.

2.2. Patient population

This study included 1) all patients with newly detected clinically intact (non-ruptured) aneurysms, which met criteria for surgical repair (larger than 55 mm or symptomatic), and 2) those who were admitted for ruptured AAA.

For the intact AAA group, those patients who had undergone a period of surveillance for a known aneurysm were excluded. This is due to the fact that the policy is to institute best medical therapy (aspirin, cessation of smoking, statin and blood pressure control) from the time of AAA diagnosis. This removed best medical therapy as a potential confounding factor for AAA rupture.

To complete the dataset for the ruptured AAA group, records were obtained from local death registries, to ensure that all patients whose cause of death was ruptured AAA, but may not be on the database, were included in this study. These ensured that all patients who were admitted with ruptured AAA, but were unsuitable for repair were also included.

2.3. Risk factor analysis

Risk factor analysis was performed for patients with intact AAA versus those with ruptured AAA (Table 1). A number of risk factors have been associated with altered AAA-rupture risk, including age, gender, diabetes status, ischaemic heart disease, hypertension, cerebrovascular incident, renal failure (known or previous creatinine >120 μmol/L), smoking, and AAA-size. These were all included in the analysis. Moreover, the concurrent use of statins was factored into analyses.

The database was greater than 94% complete, apart from the diameter of AAA in the rupture group, which was available in only 41% complete. AAA diameter data were unavailable for 1) patients that underwent emergency AAA-repair without pre-operative imaging, and 2) patients not wishing to undergo AAA repair or turned down for emergency AAA repair.

2.4. Statistics

All traits were transformed into binary characteristics and the Chi-squared test employed to perform significance tests between groups. Risk factors with $p < 0.05$ by univariate analysis were then taken forward to multivariate analysis to identify the final model of risk factors associated with AAA rupture, by means of binary logistic regression using SPSS version 20. Statistical significance was accepted at $p < 0.05$.

3. Results

We identified 983 patients who were referred for repair abdominal aortic aneurysm in the 7 year period between January 2004 and December 2010. Rupture was the indication for repair in 32% of these; the remainder were for elective repairs. Of the 315 in the rupture cohort, 134 (42.5%) were unsuitable for repair. As outlined in Table 2, of the patients who presented with rupture (32%), 12.4% were prescribed a statin, compared to the 28% who presented for elective repair and were prescribed a statin. Between the statin and no statin groups of patients, there was no significant difference in the mean age of patients; gender; presence of chronic renal failure or aneurysm size. At a significance level of $p = 0.05$, patients who took statins were less likely to suffer from diabetes (12.4% vs 7.0%), but more likely to have a history of hypertension (70.4% vs 30.3%), cerebrovascular accident (11.0% vs 5.0%), ischaemic heart disease (41.6% vs 13.2%), and be current smokers (18.1% vs 12.7%).

3.1. Rupture vs non-rupture group

As shown in Table 2, univariate analysis showed that male gender, statin use and diabetes were associated with decreased risk of aneurysm rupture, and that histories of ischaemic heart disease, hypertension, renal failure or cerebrovascular accident, age over 80, or current smoking status were associated with increased risk of AAA rupture.

3.2. Multivariate analysis

Multivariate analysis revealed that the use of a statin (OR 0.50, 95% CI 0.32–0.77; $p = 0.002$) was associated with protection against the risk of rupture. Female gender (OR 2.49, 95% CI 1.63–3.80, $p < 0.001$), a history of hypertension (OR 3.5 95% CI 1.6–3.8, $p < 0.001$) or renal failure (OR 8.08 95% CI 4.15–15.4, $p < 0.001$), age over 80 (OR 2.77 95% CI 1.79–4.27, $p < 0.001$) and current smoking (OR 1.80, 95% CI 1.09–2.96, $p = 0.021$) were associated with increased the risk of rupture of AAA. Taking into account all factors, diabetes status (OR 0.86, 95% CI 0.49–1.76) and a history of cerebrovascular accident (OR 1.10, 95% CI 0.63–2.77) did not have a statistically significant association with the risk of aneurysm rupture. This is summarised in Table 3.

4. Discussion

4.1. Statins

A number of groups have reported evidence supporting the use of statins in patients with AAA due their pleiotropic effects; however this is the largest study to examine individual patient data to support the theory that statins protect against large AAA rupture. The mechanism of this protection is uncertain. There is no clear association between AAA progression and lipid profile [7,8]; hence the lipid lowering effect of statins is unlikely to be relevant. A recent large mate-analysis showed that statins reduce the rate of progression of AAA [5].

Table 1
Differences between groups of patients prescribed a statin, and not prescribed a statin. * = $p < 0.05$.

	Statin ($n = 226$)	No statin ($n = 757$)
Median age	73.6	74.2
Male	193 (85.4%)	650 (85.9%)
Diabetes	28 (12.4%)	53 (7.0%)*
History of MI	94 (41.6%)	100 (13.2%)*
Age over the age of 80	54 (23.9%)	191 (25.2%)
Hypertensive	159 (70.4%)	229 (30.3%)*
CVA	25 (11.1%)	38 (5.0%)*
Renal failure	39 (17.3%)	125 (16.5%)
Rupture	39 (17.3%)	276 (36.5%)*
Current smoker	41 (18.1%)	96 (12.7%)*
Aneurysm size (mm)	67	68

Table 2
Differences between rupture versus non-rupture cohort. * = $p < 0.05$.

	Rupture ($n = 315$)	Non-rupture ($n = 668$)
Median age	77.6	73.0*
Male	238 (75.5%)	605 (90.6%)*
Diabetes	16 (5.1%)	65 (9.7%)*
History of MI	27 (8.6%)	167 (25%)*
Age over the age of 80	127 (40.3%)	188 (28.1%) *
Hypertensive	55 (17.5%)	260 (38.9%)*
CVA	10 (3.2%)	53 (7.9%)*
Renal failure	11 (3.5%)	153 (22.9%)*
Statin	39 (12.4%)	187 (28.0%)*
Current smoker	26 (8.3%)	111 (16.6%)*
Aneurysm size (mm)	78	67*

Table 3
Odds ratio of analysed factors.

Variable	*p*	OR	95 % CI for OR	
			Lower	Upper
Statin	0.002	0.50	0.32	0.77
Hypertension	<0.001	3.46	2.34	5.11
Female gender	<0.001	2.49	1.63	3.80
Age over 80	<0.001	2.77	1.79	4.27
Renal failure	<0.001	8.08	4.15	15.37
Current smoker	0.021	1.80	1.09	2.96
DM	0.661	0.86	0.49	1.76
CVA	0.798	1.10	0.63	2.77

AAA is thought to be an inflammatory disease. Indeed, patients with AAA exhibit increased levels of the non-specific inflammatory marker, C-reactive protein [9], and various cytokines markers of the inflammatory cascade such as TNF-α [10], both of which statins reduce [11]. There is evidence that collagen and elastin in the aneurysmal aortic wall may be degraded by matrix-metalloproteases which are actively secreted by aortic-wall infiltrating macrophages [12]. Statins have been shown to inhibit these proteases by various mechanisms [13]. The aneurysmal aorta exhibits evidence of increased oxidative damage, and an abundance of pro-oxidative enzymes. Oxidative stress may therefore play a role in the destruction of the aneurysmal wall. One recent study in humans showed that simvastatin decreased the rate of free radical formation in the aneurysmal wall [11], thus protection of the AAA-wall from reactive oxygen species may be an important factor in the reduced AAA-rupture risk observed.

Although statins may even prevent aneurysm formation (as shown in an experimental model) [6], and observational studies in humans have reported a reduction in AAA expansion rate in patients taking lipid-lowering doses of statins [14,15], this study is the largest to report an effect on AAA-rupture. A sub-analysis of the data from EVAR-2 [16] showed similar results in terms of statin use and AAA rupture; however, the numbers were considerably smaller than this study.

The recently published European Society of Cardiology guidelines advise the use of statins in patients with AAA, citing data that the use of these agents is associated with threefold reduction in cardiovascular death following elective surgical repair [17]. Data from EVAR-2 [16] found that less than 18% of patients with a large AAA were taking a statin; our own data suggest that only 23% AAA of patients in the screening programme are prescribed a statin. Such findings must remind us that those patients with known cardiovascular disease (including AAA) are, and have been, poorly pharmacologically managed. Of note, one large recent study found that with focused cardiovascular risk reduction, fewer than 5% of 107 835 patients who were prescribed a statin had discontinued the medication after 12 months [18]. The authors of this paper discovered techniques to increase statin-compliance including a one-month-statin break on onset of side-effects, prior to recommencing the same statin at the same dose; and changing the statin type.

4.2. Hypertension

The UKSAT found an association with hypertension and increased rupture risk in small aneurysms, hypothesising that the biomechanical forces acting on the aneurysmal aortic wall might contribute to rupture [19]. Although our work was unable to identify patterns of hypertension, early work suggests that diastolic hypertension may be of more importance than systolic [20]. Bearing in mind that this cohort of patient is at elevated increased cardiovascular risk, The European Society of Cardiology advises that blood pressure is controlled in this population [17].

4.3. Gender

Consistent with previous work, the current study found that women are at increased risk of AAA-rupture by almost 2.5 times. In their recent large meta-analysis Sweeting, Thompson, Brown *et al.* reported a fourfold increased risk of rupture of small aneurysms in women as opposed to men [21]. Data from a cohort study supports this finding in large aneurysms also, reporting a fourfold increase in risk of AAA rupture [22].

4.4. Age

Our analysis showed that age over 80 was associated with an increased risk of AAA rupture. These data support extra-vigilance in this high risk group, potentially with an increased threshold for achieving optimal medical therapy despite relative contra-indications.

4.5. Current smoking

In their 2009 paper, Powell et al., reported data from EVAR 2 which supports our finding that current smoking increases the risk of large-AAA rupture [23]. The results of the UKSAT were similar, however in small aneurysms [18]. The mechanism of this remains illusive: the exact compound(s) which result in AAA-formation, potentiation, and/or rupture are unknown. The intake of benzo(a)pyrene, a by-product of combustion tobacco and a potential causative agent, is thought to be 10× higher than that required to cause aneurysms in people who smoke 20 cigarettes per day. This molecule has been shown to trigger up-regulation of MMP-expression [24], reactive oxygen species [25], and increase the inflammatory cellular load [26]in experimental and animal models. More recent work in rats suggested that continued exposure to this hydrocarbon increases the risk of rupture of the aorta [27]. Another important question to which there is no current answer is whether prolonged exposure or level of exposure to cigarette smoke is more significant.

5. Limitations

This study suffers from a number of limitations:

- Its retrospective nature. However, as statins are indicated in all patients with AAA, a prospective study would be difficult to implement.
- It was assumed that if a drug was prescribed, it was administered as prescribed.
- The diameter of the aneurysm was not available for all patients. Many presenting with a ruptured aneurysm were diagnosed clinically and the diagnosis was confirmed operatively; however preoperative imaging was not performed due to the emergent nature of the treatment. The size of aneurysm was unavailable in 18 (out of 668) patients with a non-ruptured aneurysm and 187/315 patients with a ruptured aneurysm. The mean diameter of the AAA is therefore heavily skewed towards that of patients who presented with non-ruptured aneurysms, which may arguably be smaller. Furthermore as not all aneurysms rupture at a critical limit, this suggests that other factors are likely to be important also.
- We do not have data on the type, duration, and dose of statin used or circulating cholesterol levels and whether changes in these can be associated with AAA stability.
- We do not have data on the concomitant use of other agents such as antibiotics and beta-blockers. Other pharmacological agents common in this population may be important to aneurysm biology; however a recent meta-analysis found that the only three agents which have any convincing evidence of effect on AAA are statins, beta-blockers and macrolide antibiotics. We feel that the magnitude and statistical significance of the potential protective effect of statins on risk of aneurysm rupture are strong (OR 2.01, 95% CI 1.3–3.1; $p =$

0.002); therefore the effect of other agents, although not implausible, is unlikely. Other groups have reported growth rates to be important in terms of risk of aneurysm rupture [17]; however, we report data derived from a cohort of unscreened patients in whom growth rates are unavailable.

6. Conclusion

The current data suggest that the highest risk of AAA rupture is posed to the female patient aged 80 or over who is a current smoker with a history of renal failure, hypertension and who does not take a statin. Although limited, the retrospective data presented in this paper suggest an association (as opposed to a causal link) between statin therapy and risk of AAA-rupture, and highlight the importance of one arm of best-medical therapy which AAA-patients should be offered.

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